Microwaves in Organic Synthesis

Edited by
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Dr. André Loupy
Laboratoire des Réactions Sélectives
sur Supports
Université Paris-Sud
bat. 410
91405 Orsay cedex
France

Library of Congress Card No.: applied for
A catalogue record for this book is available from the British Library

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the internet at http://dnb.ddb.de.

Printed in the Federal Republic of Germany.
Printed on acid-free paper.

Composition ProSatz Unger, Weinheim
Printing Strauss Offsetdruck GmbH, Mörlenbach
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

ISBN 3-527-30514-9

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Preface

The domestic microwave oven is a serendipitous invention. Percy Spencer was working for Raytheon, a company heavily involved with radar during World War II, when he noticed the heat generated by a radar antenna. In 1947 an appliance called a Radarange appeared on the market for food processing. The first kitchen microwave oven was introduced by Tappan in 1955. Sales of inexpensive domestic ovens now represent a multibillion-dollar (euro) annual market.

Numerous other uses of microwaves have appeared in the recent years – essentially drying of different types of material (paper, rubber, tobacco, leather ...), treatment of elastomers and vulcanization, extraction, polymerization, and many applications in the food-processing industry.

The field of microwave-assisted organic chemistry is therefore quite young. The first two pioneering publications from the groups of R. Gedye and R.J. Giguere appeared in 1986. These authors described several reactions completed within a few minutes when conducted in sealed vessels (glass or Teflon) in domestic ovens. If the feasibility of the procedure was thus apparent, a few explosions caused by the rapid development of high pressure in closed systems were also reported. To prevent such drawbacks safer techniques were developed – reactions in open beakers or flasks or solvent-free reactions, as developed essentially since 1987 in France – in Caen (D. Villemin), Orsay (G. Bram and A. Loupy), and Rennes (J. Hamelin and F. Texier-Boullet). Combination of solvent-free procedures with microwave irradiation constitutes an interesting and well-admitted approach within the concepts of Green Chemistry. This coupling takes advantage both of the absence of solvent and of microwave technology under economical, efficient, and safe conditions with minimization of waste and pollution.

The goal of this book is to focus on the different fields of application of this technology in different aspects of organic synthesis. The chapters, which complement each other, were written by the most eminent scientists well-recognized in their own field.

After essential revision, and description of wave–material interactions, microwave technology, and equipment (Chapt. 1) the concepts of microwave-assisted organic chemistry in pressurized reactors are described (Chapt. 2). Special emphasis on the possible intervention of a specific (non-purely thermal) microwave effect is discussed in Chapt. 3 and this is followed by up-to-date reviews of microwave-assisted organic

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synthesis in homogeneous media (Chapt. 4), under the action of phase-transfer catalysis (Chapt. 5), using mineral solid supports under "dry media" conditions (Chapt. 6), and more specifically on graphite (Chapt. 7). Applications in which microwave-assisted technology has afforded spectacular results and applications are discussed extensively in Chapt. 8 (heterocyclic chemistry) and Chapt. 9 (on cycloadditions). Finally, the techniques have led to fruitful advances in microwave catalysis (Chapt. 10) and when applied to organometallic chemistry using transition metal complexes (Chapt. 11) and new, very promising, techniques are now under development as a result of applying microwave irradiation to combinatorial chemistry (Chapt. 12), radiochemistry (Chapt. 13), and photochemistry (Chapt. 14).

I wish to thank sincerely all my colleagues and, nevertheless, (essentially) friends involved in the realization of this book. I hope to express to all of them my friendly and scientific gratitude as eminent specialists who agreed to devote their competence and time to submitting and reviewing papers to ensure the success of this book.

Orsay, March 25th, 2002 André Loupy

List of Authors

Editor

Prof. Dr. André Loupy
Laboratoire des Réactions Sélectives sur Supports
Institut de Chimie Moléculaire d'Orsay
Université Paris-Sud
Bât 410
91405 Orsay Cedex
France
Phone: 33-1-69-15-76-50
Fax: 33-1-69-15-46-79
e-mail: aloupy@icmo.u-psud.fr

List of Authors

Jean-Pierre Bazureau
Université de Rennes 1
Institut de Chimie, Synthèse and Electrosynthèse Organiques 3
UMR 6510, Bât. 10A
Campus de Beaulieu
Avenue du général Leclerc
CS 74205
35042 Rennes Cedex
France

Dariusz Bogdal
Department of Chemistry
Politechnika Krakowska
ul. Warszawska 24
31-155 Krakow
Poland
e-mail: pcbogdal@cyf-ka.edu.pl

Vladimír Církva
Institute of Chemical Process Fundamentals
Academy of Sciences of the Czech Republic
Rozvojova 135
165 02 Prague
Czech Republic

Michel Delmotte
LM3/ENSAM 151
Bd. de l'Hopital
75013 Paris
France
e-mail: michel.delmotte@paris.ensam.fr

Angel Díaz-Ortiz
Departamento de Química Orgánica
Facultad de Química
Universidad de Castilla-La Mancha
14071 Ciudad Real
Spain
Fax: 34-926295418
e-mail: Angel.Diaz@uclm.es

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

Jacques Dubac
Université Paul-Sabatier
Laboratoire Hétérochimie Fondamentale
et Appliquée
UMR-CNRS 5069
118 route de Narbonne
31062-Toulouse Cedex
France
Fax: 33-561558204
e-mail: dubac@iris.ups-tlse.fr

Richard N. Gedye
Department of Chemistry and
Biochemistry
Laurentian University
Sudbury
Ontario
Canada
e-mail: rgedye@nickel.laurentian.ca

Milan Hájek
Institute of Chemical Process
Fundamentals
Academy of Sciences of the Czech
Republic
Rozvojová 135
165 02 Prague 6 – Suchdol
Czech Republic
e-mail: hajek@icpf.cas.cz

Anders Hallberg
Department of Organic Pharmaceutical
Chemistry
BMC
Uppsala University
Box 574
751 23 Uppsala
Sweden

Jack Hamelin
Université de Rennes 1
Institut de Chimie, Synthèse and Electrosynthèse Organiques 3
UMR 6510, Bât. 10A
Campus de Beaulieu
Avenue du général Leclerc
CS 74205
35042 Rennes Cedex
France
e-mail:
jhamelin@mailhost.univ.rennes1.fr

Antonio de la Hoz
Departamento de Química Orgánica
Facultad de Química
Universidad de Castilla-La Mancha
14071 Ciudad Real
Spain
Fax: 34-926295418
e-mail: Antonio.Hoz@uclm.es

John R. Jones
Department of Chemistry
School of Physics and Chemistry
University of Surrey, Guildford
Surrey, GU2 7XH
United Kingdom
e-mail: chs1jj@pop.surrey.ac.uk

C. Oliver Kappe
Institute of Chemistry
Karl-Franzens-University Graz
Heinrichstrasse 28
8010 Graz
Austria
e-mail: oliver.kappe@kfunigraz.ac.at

Petr Klán
Department of Organic Chemistry
Faculty of Science
Masaryk University
Kotlarska 2
611 37 Brno
Czech Republic
e-mail: klan@sci.muni.cz

Fernando Langa
Departamento de Química Orgánica
Facultad de Ciencias del Medio Ambiente
45071 Toledo
Spain
Fax: 34-925268840
e-mail: Fernando.LPuente@uclm.es

André Laporterie
Université Paul-Sabatier
Laboratoire Hétérochimie Fondamentale
et Appliquée
UMR-CNRS 5069
118 route de Narbonne
31062-Toulouse Cedex
France
Fax: 33-561-55-8204
e-mail: laporter@chimie.ups-tlse.fr

Mats Larhed
Department of Organic Pharmaceutical
Chemistry
BMC
Uppsala University
Box 574
751 23 Uppsala
Sweden
e-mail: mats@org.farm.uu.se

Shui-Yu Lu
Department of Chemistry
School of Physics and Chemistry
University of Surrey, Guildford
Surrey, GU2 7XH
United Kingdom

Julien Marquié
Université Paul-Sabatier
Laboratoire Hétérochimie Fondamentale
et Appliquée
UMR-CNRS 5069
118 route de Narbonne
31062-Toulouse Cedex
France
Fax: 33-561558204

Kristofer Olofsson
Harvey W Peters Center
Department of Chemistry
Virginia Tech
Blacksburg, VA 24061
USA

Laurence Perreux
Laboratoire des Réactions Sélectives sur
Supports
ICMO
Université Paris-Sud
Bât 410
91405 Orsay Cedex
France

Alain Petit
Laboratoire des Réactions Sélectives Sur
Supports
ICMO
Université Paris-Sud
Bât 410
91405 Orsay
France
e-mail: apetit@icmo.u.psud.fr

Alexander Stadler
Institute of Chemistry
Karl-Franzens-University Graz
Heinrichstrasse 28
8010 Graz
Austria

Christopher R. Strauss
Centre for Green Chemistry
Monash University
Clayton
3800 Victoria
Australia
and CSIRO Molecular Science
Private Bag 10
Clayton South
3169 Victoria
Australia
e-mail: chris.strauss@sci.monash.edu.au

Didier Stuerga
GERM/LRRS BP 47870
21078 Dijon cedex
France
e-mail: stuerga@u-bourgogne.fr

Françoise Texier-Boullet
Institut de Chimie, Synthèse and Electrosynthèse Organiques 3
UMR 6510
Université de Rennes 1
Bât. 10A
Avenue du général Leclerc
35042 Rennes Cedex
France

Rajender S. Varma
Clean Processes Branch
National Risk Management Research Laboratory
U. S. Environmental Protection Agency
26 West Martin Luther King Drive
MS 443
Cincinnati, Ohio, 45268
USA
Fax: 1-513-569-7677
e-mail: Varma.Rajender@epa.gov

1

Wave–Material Interactions, Microwave Technology and Equipment

Didier Stuerga and Michel Delmotte

1.1

Fundamentals of Microwave–Matter Interactions

The objective of this first part of the book is to explain in a chemically intelligible fashion the physical origin of microwave–matter interactions. After consideration of the history of microwaves, and their position in the electromagnetic spectrum, we will examine the notions of polarization and dielectric loss. The orienting effects of the electric field, and the physical origin of dielectric loss will be analyzed, as will transfers between rotational states and vibrational states within condensed phases. A brief overview of thermodynamic and athermal effects will also be given.

1.1.1

Introduction

According to the famous chemistry dictionary of N. Macquer edited in 1775, "*All the chemistry operations could be reduced to decomposition and combination; hence, the fire appears as an universal agent in chemistry as in nature*" [1]. Heating has remained the primary means of stimulating chemical reactions which proceed slowly under ambient conditions, although several other techniques have been used, e. g. photochemical, ultrasonic, high pressure, and plasma. In this book, we describe results obtained with the help of microwave heating. Microwave heating or dielectric heating, an alternative to conventional conductive heating, uses the property of some products (liquids and solids) to transform electromagnetic energy into heat. This "in situ" mode of energy conversion is very attractive for applications in chemistry and material processing.

If the effect of the temperature on reaction rate is well known, and is very easy to express, the problem is very different for effects of electromagnetic waves. What can be expected from the orienting action of electromagnetic fields at molecular levels? Are electromagnetic fields able to enhance or modify collisions between reagents? All these questions are raised by the use of microwaves energy in chemistry.

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1.1.1.1 History

The first announcement of a microwave oven was probably a magazine article about a newly developed Radarange for airline use [2, 3]. This device, it was claimed, could bake biscuits in 29 s, cook hamburgers in 35 s, and grill frankfurters in 10 s. The first commercial microwave oven was developed by P. Spencer, of a company called Raytheon, in 1952 [4]. There is a legend that P. Spencer, who studied high-power microwave sources for radar applications, observed the melting of a chocolate bar in his pocket. Another story says that Spencer had some popping corn in his pocket that began to pop as he was standing alongside a live microwave source [5]. This idea led to the microwave oven in 1961 and the generation of the mass market. The widespread domestic use of microwave ovens occurred during 1970s and 1980s as a result of Japanese technology transfer and global marketing. Curiously, industrial applications were initiated by the domestic oven.

Originally, microwaves played a leading role during the World War II, especially in the battle of Britain which, thanks to radar, English planes won despite being outnumbered three-to-one. The first generator of microwave power for radar, called the magnetron, was designed by Randall and Booth at the University of Birmingham during the 1940s. They were mass produced in the United States by companies such as Raytheon.

1.1.1.2 The Electromagnetic Spectrum

In the electromagnetic spectrum, microwave radiation occurs in an area of transition between infrared radiation and radiofrequency waves, as shown in Fig. 1.1. The wavelengths are between 1 cm and 1 m and frequencies between 30 GHz and 300 MHz.

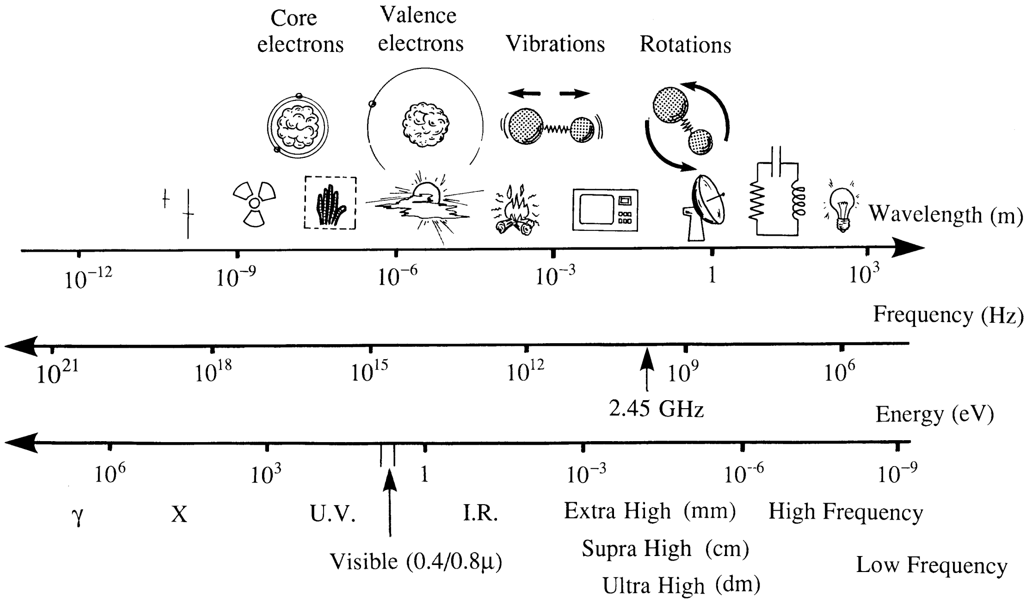

Fig. 1.1 The electromagnetic spectrum.

The fundamental relationship between energy, E, frequency, ν, wavelength, λ, and circular frequency, ω, is given by Eq. (1):

$$E = \hbar\omega = h\nu = \frac{hc}{\lambda} \tag{1}$$

To avoid interference with telecommunications and cellular phone frequencies, heating applications must use ISM bands (Industrial Scientific and Medical frequencies) which are 27.12 915 MHz and 2.45 GHz, (wavelengths 11.05 m, 37.24 cm, and 12.24 cm, respectively). Domestic ovens and laboratory systems generally work at 2.45 GHz. At frequencies below 100 MHz, where conventional open wire circuits are used, the technique will be referred to as radio-frequency heating. The object to be heated is placed between the two electrodes of a condenser. At frequencies above 500 MHz, however, wired circuits cannot be used and the power is transferred to the microwave applicator – a metallic box in which the object to be heated is placed. These operating conditions will be referred as microwave heating processes. In the microwave band the wavelength is of order of the size of production and transmission elements. Elements cannot, therefore, be considered as points in comparison with the wavelength, as is usual in circuit theory. In the same way, it is impossible to consider them as far bigger than the wavelength, as in geometrical optics. Hence, because of the position of microwaves in the electromagnetic spectrum, we will use both quantum mechanics (corpuscular aspect) and Maxwell equations (wavelike aspect). Detailed analysis of these phenomena is beyond the scope of this work.

1.1.1.3 **Energetics**

It is well known that γ or X photons have energies suitable for excitation of inner electrons. We can use ultraviolet and visible radiation to initiate chemical reactions (photochemistry). Infrared radiation excites bond vibrations only whereas hyperfrequencies excite molecular rotation. In Tab. 1.1 the energies associated with chemical bonds and Brownian motion are compared with the microwave photon corresponding to the frequency used in microwave heating systems such as domestic and industrial ovens (2.45 GHz, 12.22 cm).

Tab. 1.1 Brownian motion and bonds energies.

	Brownian motion	***Hydrogen bonds***	***Covalent bonds***	***Ionic bonds***
Energy (eV)	0.017 (200 K)	0.04 to 0.44	4.51 (C–H) 3.82 (C–C)	7.6
Energy (kJ mol^{-1})	1.64	3.8 to 42	435 (C–H) 368 (C–C)	730

According to these values, the microwave photon is not sufficiently energetic to break hydrogen bonds. Its energy is, furthermore, much smaller than that of Brownian motion, and it obviously cannot induce chemical reactions. If no bond breaking can occur by direct absorption of electromagnetic energy, then what can be expected from the orienting effects of electromagnetic fields at molecular levels? Are electromagnetic fields able to enhance or to modify collisions between reagents? Do reactions proceed with the same reaction rate with and without electromagnetic irradiation at the same bulk temperature? In the following discussion the orienting effects of the electric field, the physical origin of the dielectric loss, transfers between rotational and vibrational states in condensed phases, and thermodynamic effects of electric fields on chemical equilibrium will be analyzed.

1.1.2
The Complex Dielectric Permittivity

Insulating materials can be heated by applying high-frequency electromagnetic energy. The physical origin of this heating conversion lies with the ability of the electric field to induce polarization of charges within the heated product. This polarization cannot follow the extremely rapid reversals of the electric field and induce heating of the irradiated media.

The interaction between electromagnetic waves and matter is quantified by two complex physical quantities – the dielectric permittivity $\tilde{\varepsilon}$ and the magnetic susceptibility $\tilde{\mu}$. The electric components of electromagnetic waves can induce currents of free charges (electric conduction that could be of electronic or ionic origin). It can, however, also induce local reorganization of linked charges (dipole moments) and the magnetic component can induce structuring of magnetic moments. The local reorganization of linked and free charges is the physical origin of polarization phenomena. The storage of electromagnetic energy within the irradiated medium and thermal conversion in relation to the frequency of the electromagnetic stimulation appear as the two main aspects of polarization phenomena induced by the interaction between electromagnetic waves and dielectric media. These two main aspects of wave–matter interactions are expressed by the complex formula for the dielectric permittivity as described by Eq. (2):

$$\tilde{\varepsilon} = \varepsilon' - j\varepsilon'' = \varepsilon_0 \varepsilon'_r - j\varepsilon_0 \varepsilon''_r \tag{2}$$

where ε_0 is the dielectric permittivity of vacuum, ε' and ε'' are the real and imaginary parts of the complex dielectric permittivity, and ε'_r and ε''_r are the real and imaginary parts of the relative complex dielectric permittivity. The storage of electromagnetic energy is expressed by the real part whereas the thermal conversion is proportional to the imaginary part.

1.1.2.1 Polarization and Storage of Electromagnetic Energy

The physical origin of polarization

Polarization phenomena are expressed by the polarization, $\vec{P}$, which denotes the contribution by matter compared with that of vacuum. The electric field and the polarization are linked by Maxwell's equations. The constitutive equation for vacuum is given by Eq. (3):

$$\vec{D} = \varepsilon_0 \vec{E} \tag{3}$$

where $\vec{D}$ is the electric displacement and $\vec{E}$ the electric field. For a dielectric medium characterized by $\tilde{\varepsilon}$, the constitutive equation is given by Eq. (4):

$$\vec{D} = \tilde{\varepsilon}\vec{E} = \varepsilon_0 \vec{E} + \vec{P} \tag{4}$$

In the global formulation of Eq. (4), we can express the term corresponding to vacuum and given by Eq. (3). The second and complementary term then defines the contribution of matter to polarization processes, or polarization $\vec{P}$. The higher the dielectric permittivity of a material, the greater the polarization processes. The polarization process described by $\vec{P}$ has its physical origin in the response of dipoles and charges to the applied field. Depending on the frequency, electromagnetic fields put one or more types of charge association under oscillation. In any material there is a variety of types of charge association:

- inner electrons tightly bound to the nuclei,
- valence electrons,
- free or conduction electrons,
- bound ions in crystals,
- free ions as in electrolytes and nonstoichiometric ionic crystals (for example, ionic dipoles such as OH^- have both ionic and dipolar characteristics), and
- finally the multipole (mainly the quadrupole or an antiparallel association of two dipoles).

Depending on the frequency the electromagnetic field can induce one or more types of charge association under oscillation. Each configuration has its own critical frequency above which interaction with the field becomes vanishingly small, and the lower the frequency and the more configurations are excited. For electrons of the inner atomic shells the critical frequency is of the order of that of X-rays. Consequently an electromagnetic field of wavelength more than 10^{-10} m cannot excite any vibrations, but rather induces ionization of these atoms. There is no polarizing effect on the material, which for this frequency has the same dielectric permittivity as vacuum. For ultraviolet radiation the energy of photons is sufficient to induce transitions of valence electrons. In the optical range an electromagnetic field can induce distortion of inner and valence electronic shells. Polarization processes result from a dipole moment induced by distortion of electron shells and are called electronic polarizability. In the infrared range electromagnetic fields induce atomic vibrations in molecules and crystals and polarization processes result from the dipole moment induced by distortion of nuclei positions. These polarization processes are called atomic polarization. In all the processes mentioned so far, the charges affected by the field can be considered to be attracted towards their central position by forces which are proportional to their displacement by linear elastic forces. This mechanical approach of electronic resonance is only an approximation, because electrons cannot be properly treated by classical mechanics. Quantitative treatment of these processes requires the formalism of quantum mechanics. The two types of polarization process described above can be connected in distortion polarization.

The characteristic material response times for molecular reorientation are 10^{-12} s. Then, in the microwave band, electromagnetic fields lead to rotation of polar molecules or charge redistribution. The corresponding polarization processes are denoted orientation polarization.

Orienting effect of a static electric field

The general problem of the orienting effect of a static electric field (orientation of polar molecules) was first considered by Debye [6, 7], Frölich [8], and more recently Böttcher [9, 10].

We consider a collection of molecular dipoles in thermal equilibrium. It is assumed that all the molecules are identical and they can take on any orientation. Because of thermal energy each molecule undergoes successive collisions with the surrounding molecules. In the absence of an applied electric field, the collisions tend to maintain a perfectly isotropic statistical orientation of the molecules. This means that for each dipole pointing in one direction there is statistically a corresponding dipole pointing in the opposite direction, as described by Fig. 1.2.

In the presence of an applied electric field, $\vec{E}$, the dipole moment, $\vec{\mu}$, of a molecule undergoes a torque, $\vec{\Gamma}$. This torque tends to orientate the dipole moment parallel to the electric field. The corresponding potential energy (for a permanent or induced dipole) becomes minimal when the angle θ between the dipole and the electric field tends to zero. The dipole moment thus takes the same direction as the electric field. This is the same phenomenon as the orientation of the compass needle in the earthly magnetic field. For molecular dipoles, however, the thermal energy counteracts this tendency, and the system finally reaches a new statistical equilibrium which is represented schematically by Fig. 1.2. In this configuration more dipoles are pointing along the field than before and the medium becomes slightly anisotropic.

The likelihood of the medium being frozen by the electric field is given by the Langevin function resulting from statistical theories which quantify competition between the orienting effect of electric field and disorienting effects resulting from

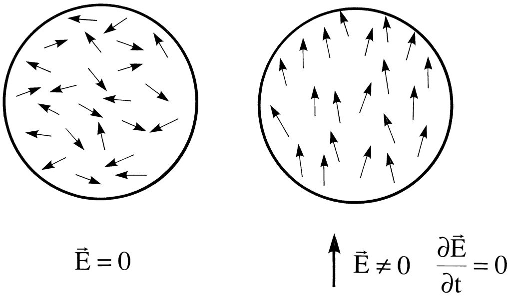

Fig. 1.2 A distribution of dipoles undergoing the effect of a static electric field.

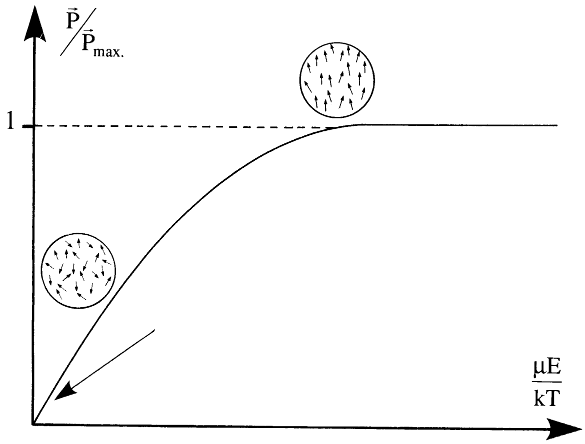

Fig. 1.3 The Langevin function.

thermal agitation. The relationship between the ratio of effective to maximum polarization and the ratio of the potential interaction energy to the thermal agitation is described by Fig. 1.3.

We can see that the Langevin function increases from 0 to 1 as the strength of the electric field is increased and/or the temperature is reduced. The molecules tend to align with the field direction. For high values of the field orientation dominates over the disorientation induced by temperature, and all the dipoles tend to become parallel to the applied field. The complete alignment corresponds to saturation of the induced polarization. In many practical situations field strengths are well below their saturation values. The arrow in Fig. 1.3 corresponds to the usual conditions of microwave heating (temperature close to room temperature, 25 °C, and electric field strength close to 10^5 V m^{-1}). According to these results, the electric field strength commonly used in microwave heating is not sufficient to induce a consequent freezing of the media.

1.1.2.2 **Thermal Conversion of Electromagnetic Energy**

Physical origin of dielectric loss

The foregoing conclusions correspond to a static description, or cases for which the polarization can perfectly follow the oscillation of the electric field. Indeed, the electric field orientation depends on time with a frequency equal to 2.45 GHz (the electric field vector switches its orientation approximately every 10^{-12} s). The torque exercised by the electric field induces rotation of polar molecules, but they cannot always orient at this rate. The motions of the particles will not be sufficiently rapid to build up time-dependent polarization $\vec{P}(t)$ that is in equilibrium with the electric field at any moment. This delay between electromagnetic stimulation and the molecular response is the physical origin of dielectric loss. The polarization given by Eq. (4) becomes a complex quantity with the real part in phase with the excitation and an imaginary part for which there is a phase lag with the excitation. The latter is the origin of the thermal conversion of electromagnetic energy within the irradiated dielectric.

Relaxation processes are probably the most important of the interactions between electric fields and matter. Debye [6] extended the Langevin theory of dipole orientation in a constant field to the case of a varying field. He showed that the Boltzmann factor of the Langevin theory becomes a time-dependent weighting factor. When a steady electric field is applied to a dielectric the distortion polarization, $\vec{P}_{\mathrm{Distor}}$, will be established very quickly – we can say "instantaneously" compared with time intervals of interest. But the remaining dipolar part of the polarization (orientation polarization, $\vec{P}_{\mathrm{Orient}}$) takes time to reach its equilibrium value. When the polarization becomes complex, the permittivity must also become complex, as shown by Eq. (5):

$$\tilde{\varepsilon} = \varepsilon' - j\varepsilon'' = n^2 + \frac{\varepsilon_s - n^2}{1 + j\omega\tau} \tag{5}$$

where n is the refractive index and τ the relaxation time. All polar substances have a characteristic time τ called the relaxation time (the characteristic time of reorientation of the dipole moments in the direction of the electric field). The refractive index corresponding to optical frequencies or very high frequencies is given by Eq. (6):

$$\varepsilon = n^2 \tag{6}$$

whereas static permittivity, or permittivity for static fields, corresponds to ε_{s}.

The real and imaginary parts of the dielectric permittivity are given by Eqs. (7) and (8):

$$\varepsilon' = n^2 + \frac{\varepsilon_s - n^2}{1 + \omega^2\tau^2} \tag{7}$$

$$\varepsilon'' = \frac{\varepsilon_s - n^2}{1 + \omega^2\tau^2}\,\omega\tau \tag{8}$$

Changes of ε' and ε'' with frequency are shown in Fig. 1.4. The frequency is displayed on a logarithmic scale. The dielectric dispersion covers a wide range of frequencies.

The dielectric loss reaches a maximum given by Eq. (9):

$$\varepsilon''_{\max} = \frac{\varepsilon_s - n^2}{2} \tag{9}$$

at a frequency given by Eq. (10):

$$\omega_{\max} = \frac{1}{\tau} \tag{10}$$

This macroscopic theory justifies the complex nature of the dielectric permittivity for media with dielectric loss. The real part of the dielectric permittivity expresses the orienting effect of the electric field with the component of polarization which fol-

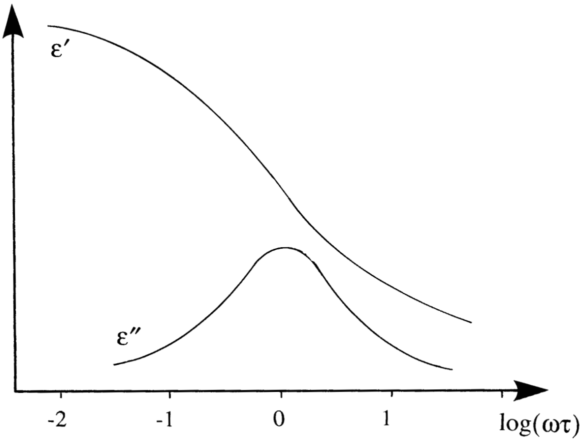

Fig. 1.4 Dependence of the complex dielectric permittivity on frequency (ε is the real part and ε is the imaginary part, or the dielectric loss).

lows the electric field, whereas the other component of the polarization undergoes chaotic motion leading to thermal dissipation of the electromagnetic energy. This description is well adapted to gases (low particle density). In fact, for a liquid we must take into account the effect of collisions with the surroundings and the equilibrium distribution function is no longer applicable. The Debye theory can define a distribution function which obeys a rotational diffusion equation. Debye [6, 7] based his theory of dispersion on Einstein's theory of the Brownian motion. He supposed that the rotation of a molecule caused by an applied field is constantly interrupted by collisions with neighbors, and the effect of these collisions can be described by a resistive couple proportional to the angular velocity of the molecule. This description is well adapted to liquids, but not to gases.

The general equation for complex dielectric permittivity is then given by Eq. (11):

$$\frac{\tilde{\varepsilon}_r - 1}{\tilde{\varepsilon}_r + 2} = \frac{\rho N}{3\varepsilon_0 M}\left(\alpha + \frac{\mu^2}{3kT(1 + j\omega\tau)}\right) \tag{11}$$

where N is Avogadro number, M is the molar mass, ρ the specific mass, and α the atomic polarizability. The relaxation time, τ, is a microscopic relaxation time that depends on the average resistive force experienced by the individual molecules. In the limit of low frequency the Debye expression is obtained for the static permittivity whereas in the high frequency limit the permittivity will fall to a value which can be written as the square of the optical index. The first term of the left side corresponds to the distortion polarization whereas the other term corresponds to the orientation polarization. For apolar molecules, we obtain the famous Clausius–Mosotti–Lorentz equation.

Relaxation times

Debye [6] suggested that a spherical or nearly spherical molecule can be treated as a sphere (radius r) rotating in a continuous viscous medium with the viscosity, η, of the bulk liquid. The relaxation time is given by Eq. (12):

$$\tau = \frac{8\pi\eta r^3}{2kT} \tag{12}$$

For a given molecular system it is, in fact, better to use a formula containing $\tau_{\text{inter}}(T)$, a part which depends on the temperature, and a part totally independent of the temperature, τ_{Steric}, as described by Eq. (13):

$$\tau(T) = \tau_{\text{Steric}} + \tau_{\text{Inter}}(T) \tag{13}$$

Relaxation times for dipole orientation at room temperature are between 10^{-10} s for small dipoles diluted in a solvent of low viscosity and more than 10^{-4} s for large dipoles in a viscous medium such as polymers (polyethylene), or dipole relaxation in crystals (the relaxation associated with pairs of lattice vacancies). The relaxation time of ordinary organic molecules are close to a few picoseconds. Thus for a frequency of 2.45 GHz these molecules can follow electric field oscillations, unlike substances which are strongly associated, e. g. water and alcohols, and therefore are subject to dielectric loss at 2.45 GHz. Consequently, the solvents for which dielectric loss is observed are water, MeOH, EtOH, DMF, DMSO, and CH_2Cl_2. For nonpolar solvents such as C_6H_6, CCl_4, and ethers dielectric loss is negligible, although addition of small amounts of alcohols can strongly increase dielectric loss and microwave coupling of these solvents.

It is clear that for a substance with dielectric loss, e. g. water and the alcohols, the molecules do not perfectly follow the oscillations of the electric field. For media without dielectric loss, and for the same reasons as under static conditions, the strength of the electric field cannot induce rotation of all polar molecules but, statistically, for a small part only (less than 1%). This means that all the molecules oscillate around an average direction (precession motion), as shown by Fig. 1.5.

The principal axis of the cone represents the component of the dipole under the influence of the thermal agitation. The component of the dipole in the cone results from the field that oscillates in its polarization plane. In this way, in the absence of Brownian motion the dipole follows a conical orbit. In fact the direction of the cone changes continuously (because of the Brownian movement) faster than the oscillation of the electric field; this leads to chaotic motion. Hence the structuring effect of electric field is always negligible, because of the value of the electric field strength, and even more so for lossy media.

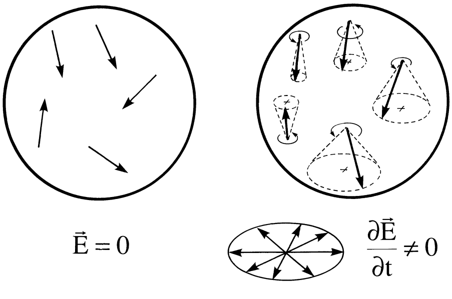

Fig. 1.5 Precession motion of the dipole of a distribution of molecules undergoing irradiation by a time dependent electric field.

It is well known that in condensed phases energy transfer can occur between rotational and vibrational states. Indeed, molecular rotation does not actually occur in liquids; rotational states turn into vibrational states because of an increase in collisions.

For liquids, the collision rate is close to 10^{30} collisions s^{-1}. Microwave spectroscopy, which studies molecular rotation, only uses dilute gases to obtain pure rotational states of sufficient lifetime. Rotational transitions are broadened by molecular collisions, because the pressure is close to a few tenths of a bar, as shown in Fig. 1.6.

In conclusion, for condensed phases molecular rotations have quite a short lifetime, because of collisions. The eventual oscillations induced by the electric field are then dissipated in the liquid state leading to vibration. At collision densities corresponding to liquids the frequency of the collisions become comparable with the frequency of a single rotation, and because the probability of a change in rotational state on collision is high, the time a molecule exists in a given state is small. It is, therefore, obvious that the electric field cannot induce organization in condensed phases such as in the liquid state.

Consequences of the thermal changes of the dielectric permittivity

In contrast with Eq. (5), Eq. (11) gives the frequency behavior in relation to the microscopic properties of the studied medium (polarizability, dipole moment, temperature, frequency of the field, etc). Thus for a given change of relaxation time with temperature we can determine the change with frequency and temperature of the dielectric properties – the real and imaginary parts of the dielectric permittivity.

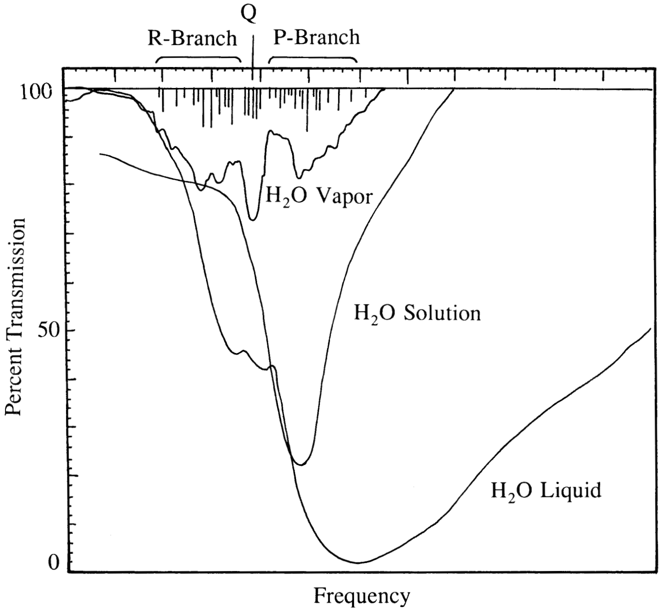

Fig. 1.6 Absorption spectrum for water (gaseous, solution, and liquid). Above the vapor band is Mecke's rotational analysis [11, 12].

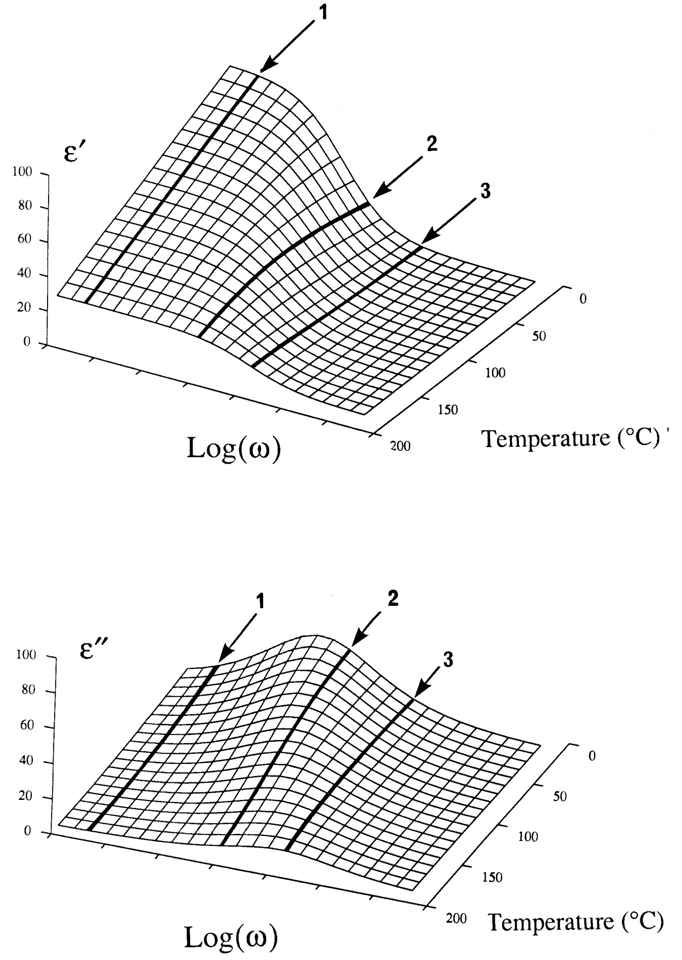

Fig. 1.7 Effect of frequency and temperature on the complex dielectric permittivity (ε is the real part and ε the imaginary part or the dielectric loss) [12].

According to the value of the frequency of the field, and the relaxation time band in relation to the temperature considered, one can find the three general changes with temperature of the dielectric properties. Fig. 1.7 gives the three-dimensional curves describing the dielectric properties in relation to frequency and temperature.

According to the value of the working frequency compared with the relaxation frequency, three general cases could be found:

1. the real and imaginary parts of the dielectric permittivity decrease with temperature (working frequency lower than relaxation frequency);
2. the real and/or imaginary parts of the dielectric pass through a maximum (working frequency very close to relaxation frequency).

3. the real and imaginary parts of the dielectric permittivity increase with temperature (working frequency higher than relaxation frequency).

The two solvents most commonly used in microwave heating are ethanol and water. Values for water are given by Kaatze [13] and those for ethanol by Chahine et al. [14]. Water is close to case 1 because both values decrease with temperature. In contrast, for ethanol the real part increases and the dielectric loss reaches a maximum at 45 °C (case 2). For ethanol, in fact, the working frequency is higher than relaxation frequency at room temperature. Ethanol has a single relaxation frequency, close to 1 GHz at 25 °C, and, furthermore, its relaxation frequency increases fairly rapidly with temperature (3 GHz at 65 °C). For water the working frequency is smaller than the relaxation frequency at all temperature (17 GHz at 20 °C and 53 GHz at 80 °C).

The pioneering work of Von Hippel [15] and his coworkers, who obtained dielectric data for organic and inorganic materials, still remains a solid basis. Study of dielectric permittivity as a function of temperature is, however, less well developed, particularly for solids.

Conduction losses

For highly conductive liquids and solids the loss term not only results from a single relaxation term, as given by Eq. (8), but also from term resulting from ionic conductivity, σ, as described by Eq. (14):

$$\varepsilon'' = \frac{\varepsilon_s - n^2}{1 + \omega^2 \tau^2}\,\omega\tau + \frac{\sigma}{\omega} \tag{14}$$

The hydroxide ion is the typical example of ionic species with both ionic and dipolar characteristics. For solutions containing large amount of ionic salts this conductive loss effect can become larger than dipolar relaxation. For solids conduction losses are usually very slight at room temperature but can change substantially with temperature. A typical example is alumina, for which dielectric losses are very small (~10^{-3}) at room temperature but which can reach fusion in several minutes in a microwave cavity [16]. This effect is because of a strong increase of conduction losses associated with the thermal activation of the electrons which pass from the oxygen 2p valence band to the 3s3p conduction band. In solids, moreover, conduction losses are usually enhanced by material defects which sharply reduce the energy gap between the valence and conduction bands.

Because conduction losses are high for carbon black powder it can be used as lossy impurities or additives to induce losses within solids for which dielectric losses are too small.

Magnetic losses

Chemical reagents are primarily concerned with dielectric liquids or solids. For metal oxides such as ferrites, however, magnetic losses occur in the microwave region. As for a dielectric material, a complex magnetic permeability is defined as given by Eq. (16):

$$\tilde{\mu} = \mu' - j\mu'' \tag{15}$$

The real part is the magnetic permeability whereas the imaginary part is the magnetic loss. These losses are quite different from hysteresis or eddy current losses, because they are induced by domain wall and electron-spin resonance. These materials should be placed at position of magnetic field maxima for optimum absorption of microwave energy. For transition metal oxides such as iron, nickel, and cobalt magnetic losses are high. These powders can, therefore, be used as lossy impurities or additives to induce losses within solids for which dielectric loss is too small.

Parameters of the thermal conversion

According to the Poynting formula, the time-averaged dissipated power density $P_{\text{diss}}(r)$ at any position r within a lossy material is given by Eq. (15):

$$P_{\text{Diss}}(r) = \frac{\omega\,\varepsilon_0\,\varepsilon_r''}{2}\,\vec{E}(r)^2 \tag{16}$$

where ω is the angular frequency, ε_0 the dielectric permittivity of vacuum, $\varepsilon(r)$ the dielectric loss, and $\vec{E}(r)$ the electric field amplitude. Depending on the dielectric loss and electric field strength, the dissipation of electromagnetic energy leads to heating of the irradiated medium. Hence estimation of dissipated power density within the heated object depends directly on the electric field distribution within the heated object and on the dielectric loss. Maxwell's equations can be used to describe the electromagnetic fields in a lossy medium and an energy balance can be solved to provide the temperature profiles within the heated reactor. The specificity of microwave heating results from the thermal dependence of dielectric properties. The complex dielectric permittivity is highly dependent on temperature and the dynamic behavior of microwave heating is governed by this thermal change. The electric field amplitude depends, moreover, on the real and imaginary parts of the dielectric permittivity, which themselves depend on temperature, as described by Eq. (17):

$$P_{\text{Diss}}(r, T) = \frac{\omega\,\varepsilon_0\,\varepsilon_r''(T)}{2}\,\vec{E}\left(r, \varepsilon_r''(T), \varepsilon_r''(T)\right)^2 \tag{17}$$

Consequently, this thermal change of dielectric properties causes changes in the dissipated energy during heating, in contrast with conventional heating modes. Depending on the nature on the thermal changes this can result in thermal runaway, occasionally, even, reduced material heating.

The author has studied the hydrodynamic behavior of water and ethanol, two classical solvents for chemistry [17–19]. Fig. 1.8 compares heating rate expected for water and ethanol for conventional and microwave heating.

For identical energy density or conventional heating the ratio of the induced heating rate for water and ethanol does not change during heating. If no significant changes are observed for the temperature range, a significant difference appears if the dielectric loss effect is taken into account. In a third step, with electric field cor-

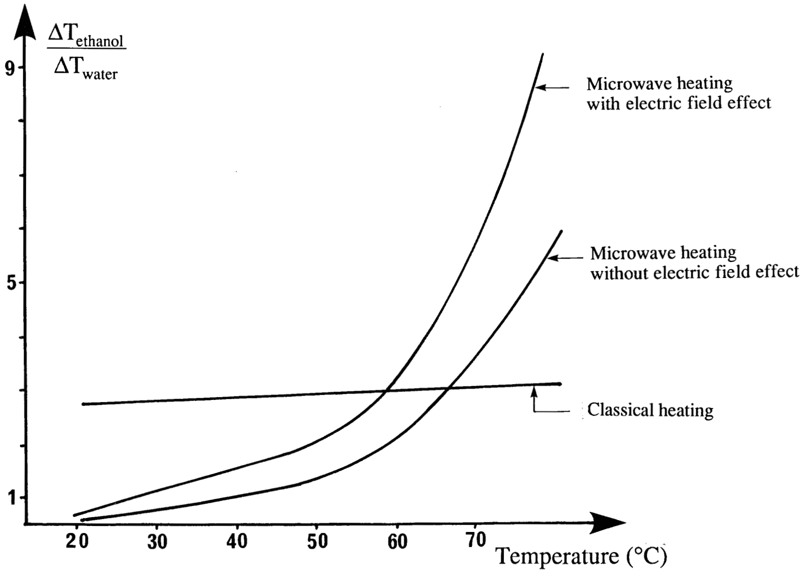

Fig. 1.8 Dependence on temperature of the heating expected with conventional and microwave heating (with and without the electric field effect) for water and ethanol [19].

rection, the difference is significantly amplified. Hence, we observe for temperatures below 50 °C that microwave heating is preponderant in water, and for temperature above 50 °C microwave heating is preponderant in ethanol compared with water. This clearly shows the selectivity difference between the classical heating and the microwave heating in relation to the thermal dependency of the real and imaginary parts of the dielectric permittivity.

1.1.3
Thermodynamic and other Effects of Electric Fields

The thermodynamic effects of electric fields and are well known. Application of an electric field to a solution can affect the chemical equilibrium. For example, in Eq. (18) where C has a large dipole moment and B has a small dipole moment the equilibrium is shifted toward C under the action of an electric field.

$$A + B \rightleftharpoons C \tag{18}$$

Typical examples are the conversion of the neutral form of an amino acid into its zwitterionic form, the helix–coil transitions in polypeptides and polynucleotides, and other conformational changes in biopolymers. Reactions of higher molecularity in which reactants and products have different dipole moments are subject to the same effect (association of the carboxylic acids to form hydrogen-bonded dimers). Equilibrium involving ions are often more sensitive to the application of an electric field;

the field induces a shift toward producing more ions. This is known as the dissociation field effect (DFE) or the “second Wien’s effect“ [20].

In principle the effect of an electric field on chemical equilibria can be described by the thermodynamic relationship described by Eq. (19):

$$\left(\frac{\partial \ln K_{\mathrm{Eq.}}}{\partial |\vec{E}|}\right)_{P,T} = \frac{\Delta\mu}{RT} \tag{19}$$

where $K_{\mathrm{eq.}}$ is the equilibrium constant, $|\vec{E}|$ the field strength (V m^{-1}), and $\Delta\mu$ the molar change of the macroscopic electric moment or the molar polarization for nonionic systems. For ionic equilibria it must be pointed out that a true thermodynamic equilibrium can never be reached, because of the field-induced flow of the ions. The DFE theory was been developed by Onsager [21]. The most notable result is that $\Delta\mu$ is proportional to the field strength, E. Hence, according to Eq. (20):

$$\int_0^E \mathrm{d}\ln K_{\mathrm{Eq.}} = \frac{1}{RT}\int_0^E \Delta\mu\,\mathrm{d}E \propto E^2 \tag{20}$$

which is the integration of Eq. (19), the change in equilibrium constant is proportional to the square of the electric field strength and the effect on equilibrium constant is noticeable only at high field strengths. In practice electric field strengths up to 10^7 V m^{-1} are required to produce a measurable effect upon normal chemical reactions. For water at 25 °C, K changes by about 14% if a field of 100 kV m^{-1} is applied. Smaller fields are required to achieve a comparable shift in less polar solvents. Nonionic equilibria can also be perturbed by the DFE if they are coupled to a rapid ionic equilibrium. A possible scheme is described by Eq. (21):

$$\mathrm{A^- + H^+ \rightleftharpoons AH \rightleftharpoons BH} \tag{21}$$

in which the slow equilibrium is coupled with an acid–base equilibrium. This is the same principle as coupling a temperature-independent equilibrium to a strongly dependent equilibrium. Such a scheme has been studied in the helix–coil transition of poly-α-L-glutamic acid by Yasunaga et al. [22] – dissociation of protons from the side chains increases the electric charge of the polypeptide, which in turn induces a transition from the helix to the coil form, in the dissociation of acetic acids by Eigen and DeMayer [23], and in the dissociation of water by Eigen and DeMayer [24].

Hence, if thermodynamic effects of electric effect occur, the electric field strengths necessary are too high compared with ordinary operating conditions of microwave heating.

1.1.4
The Athermal and Specific Effects of Electric Fields

A chemical reaction is characterized by the difference between the free energy of the reagents and products. According to thermodynamics the reaction is feasible only if the free energy change is negative. The more negative the free energy change, the more feasible the reaction. This free energy change for the reaction is the balance between broken and created chemical bonds. This thermodynamic condition is not, however, sufficient to ensure the chemical reaction occurs rapidly (i.e. with a significant rate of reaction). Kinetic conditions must also be verified to achieve the reaction. The free energy of activation depends on the enthalpy of activation which expresses the height of the energy barrier which must be surmounted. This energy condition is only a necessary condition but not sufficient to ensure the transformation of the reagents. The relative orientation of the molecules which react is crucial, and this condition is expressed by the entropy of activation. This entropic term expresses the need for a geometrical approach to ensure the effectiveness of collisions between reagents.

The essential questions raised by the assumption of "athermal" or "specific" effects of microwaves are, then, the change of these characteristic terms (free energy of reaction and of activation) of the reaction studied. Hence, in relation to previous conclusions, five criteria or arguments (in a mathematical sense) relating to the occurrence of microwave athermal effects have been formulated by the author [25]. More details can be found in comprehensive papers which analyze and quantify the likelihood of nonthermal effects of microwaves. This paper provides guidelines which clearly define the character of nonthermal effects.

Hence, according to these five criteria there can be no doubt that an electric field cannot have any molecular effect for solutions. First, the orienting effect of electric field is small compared with thermal agitation, which results from the weakness of the electric field amplitude. Even if the electric field amplitude were sufficient, the presence of dielectric loss results in a delay between dipole moment oscillations and electric field oscillations. Heating of the medium reveals the stochastic character of molecular motion induced by dissipation of the electromagnetic wave. The third limitation is the annihilation of molecular rotation in liquid state condensed phases. According to our demonstration, under normal operating conditions, it will be proved that the frequently propounded idea that microwaves rotates dipolar groups is, mildly speaking, misleading.

If the molecular effects of the electric field are irrelevant to microwave heating of solutions, this assumption could be envisaged in the use of operating conditions very far from current conditions. On one hand, it will be necessary to use an electric field of higher amplitude, or to reduce the temperature according to the Langevin function. This last solution is obviously antinomic with conventional chemical kinetics, and the first solution is, currently, technologically impossible. It will, on the other hand, be necessary to avoid reaction media with dielectric loss. The molecular effects of the microwave electric field could, paradoxically, be observed for a medium which is not heated by the action of microwave irradiation.

1.1.5
Conclusions

The interaction between a dipole and an electric field is clearly interpreted by quantum theory. Coupling is weaker than with magnetic fields, and when a dipole population is subjected to an electric field there is such a demultiplication of quantum levels that they are very close to each other. The interaction energy is continuous, and we have to use Boltzmann or Langevin theories. Because of the weak coupling between the dipole and electric field, and the lack of quantified orientations, the study of electric dipole behavior gives less information about the dipole itself than about its surroundings. Indeed electric dipoles are associated with molecular bonds (the electric dipole moment results from the distribution of positive and negative charges on the studied molecule; if they are centered at different points then the molecule has a permanent dipole and the molecule is polar). Any motion of electric dipoles induced, for example, by interaction with an electric field, lead to correlative motion of molecular bonds, whereas motion of magnetic moments is totally independent of any molecular motion. Consequently, studies of dielectric properties must be those of “group properties“. Those properties cannot be modeled by a single dipole; a group of dipoles interacting among themselves would be a key ingredient for these models. The origin of confusion between the behavior of a single dipole and a collection of dipoles (in other words differences between dilute and condensed phases) is the most important problem, and the source of the confusion of those who claim that microwave effect results from orienting effect of the electric field.

In conclusion, is it necessary to obtain a microwave athermal effect to justify microwave chemistry? Obviously not – it is not necessary to present microwaves effects in a scientific disguise. There are many examples in which microwave heating results in specific time–temperature histories and gradients which cannot be achieved by other means especially for solid materials. Hence, rather than claiming nonthermal effects it is better to claim a means or a tool which induces a specific thermal history.

1.2
Overview of Microwave Reactor Design and Laboratory and Industrial Equipment

The objective of this section is to provide the reader with a basic knowledge of microwave techniques used in the design and the construction of microwave ovens.

After some considerations relating to microwave technology, we will examine microwave ovens and reactor background. The limits of domestic ovens and temperature measurements will be analyzed, as well as design principles of microwave applicators. Next, a brief overview of laboratory, experimental and industrial equipment will be given.

1.2.1
Microwave Ovens and Reactors – Background

This part has been designed by the authors as a practical tool for people interesting by using laboratory or industrial equipment. An overall coverage of microwave ovens design would require more space than is available in this chapter. An excellent coverage of applicator theory can be found in [5, 26] and basis of electromagnetic waveguides and cavities can be found elsewhere [27].

1.2.1.1 Applicators, Waveguides, and Cavities

The microwave applicator is the component of a processing system in which energy is applied to the product to be heated. The equipment designer's objective is to insure that this is accomplished in the most efficient possible manner. The reagents packaging (powder, liquids, pellets) coupled with dielectric characteristics allow the designer to mold literally a process in terms of applying energy where it is needed and with the requested quantity. A wide variety of applicators are available or have been patented to cover almost any conceivable applications of microwave power [5]. In chemistry applications, the goal is to achieve the desirable reaction or products.

High power microwaves are generated by vacuum tubes. The magnetron and klystron are the most commonly used tubes for the generation of continuous waves power for microwave processing. Power is normally launched from the microwave tube into a transmission line or waveguide, where it travels to a load or termination such an antenna or a microwave heating applicator.

Lumped circuits with capacitors and inductors used at lower radiofrequencies are not usable at microwave frequencies. Open transmission lines are not used at microwave frequencies because radiation would be excessive. This has led to the use of waveguide as transmission media and to the use of resonant cavities as applicators. Waveguides are metallic tubes with circular or rectangular cross-section. Resonant cavities are metallic boxes (parallelepiped or circular). Voltage and currents are not the fundamental concerns. In fact, power is considered to travel in the transmission line by means of electromagnetic waves which consist of alternating electric and magnetic fields. When energy is launched into waveguide, many modes may be excited. For a waveguide, an infinite number of modes or wave configurations can exist. Only those modes above cutoff will attenuate in a short distance. Cutoff conditions are defined by dimensions of waveguide cross section. Discontinuities within the waveguide may excite higher order modes, resulting in higher energy storage at the discontinuity. As for waveguides, an infinite number of modes or wave configurations can exist for microwave cavities. According to geometry and dimensions of the boxes, single-mode or multimode cavities can be obtained. Domestic ovens belong to this last category. The empty domestic ovens have approximately two hundred of modes [28].

When microwaves travel along a waveguide terminated by the microwave heating application (for example a resonant cavity loaded by the object to be heated) a reflected wave travels back towards the source. The wave traveling towards the termination is called the incident wave and the wave traveling back to the magnetron is the reflected waves. The goal of microwave oven designer is to ensure that all the incident power is absorbed by the load. In other words, the resonant frequency of the loaded oven (and not the empty oven) should be close to frequency of the magnetron (i.e. 2.45 GHz). If too much energy is reflected back to the source, the magnetron may be damaged. That is the reason why it is not advised to run empty domestic ovens. However, most commercial ovens are protected by a thermal automatic cutoff in case of poor matching between magnetron and oven.

1.2.1.2 **Single-mode or Multimode?**

The electric field pattern produced by the standing waves within the cavity may be extremely complex. Some areas may receive large amounts of energy while others may receive slight energy [29–31]. In order to minimize this fact, domestic ovens use mode stirrers or fan-shaped paddles and turntables. These devices are designed for typical domestic loads. Consequently, the use of domestic ovens for laboratory purpose with small loads, poorly lossy media can lead to bad operating conditions, specially difficult to reproduce. The use of single-mode or quasi-single-mode cavities allow to define precise positions within the cavities where the electric field strength is maximum. Moreover, the electric field strength is much higher than those obtained in multimode devices. The effective cavity power is three orders of magnitude higher.

However, the use of single-mode cavities is more complex because of the insertion of the lossy sample changes the frequency resonance of the device. A multimode cavity is more versatile than a single-mode device because of the modes number. A movable plunger can allow a tuning of the cavity in order to ensure a good matching to the source. As the dielectric properties of materials strongly depend on temperature, a real-time tuning is necessary during the heating process. It was usually ensured by a computer. The use of a circulator which directs the reflected energy into a dummy water load is needed to avoid damage of the magnetron for poor matching situations. Another unfavorable argument against domestic oven for reproducible operating conditions is the problem of the variable power. The variable power of domestic ovens is produced by periodic switching of the magnetron power. Large switching periods are undesirable for chemistry processes because of the cooling period between switching steps.

In conclusion, the use of multimode system for laboratory purpose with reproducible operating conditions implies the same geometry, volume and position for the samples to be heated and switching cycle smaller than characteristic time of chemical kinetic of the studied reaction. The use of single-mode cavities seems to be of particular importance for allowing an efficient application of microwave energy. One of the mistake is to believe that single-mode cavities imply small operating volume close to several cubic centimeters. An efficient temperature control system allowing feedback control during heating would be an asset in case of thermal runaway and/or exothermic reactions. The thermal runaway is induced by thermal dependency of dielectric losses. Above a threshold value of temperature, the magnitude of heating rate becomes very high. The typical example is the heating of alumina (see the previous part on microwave–matter interaction).

1.2.1.3 Limits of Domestic Ovens

The majority of microwave promoted organic synthesis has been performed in multimode domestic ovens. In these ovens, despite the power level which commonly fluctuates as a result of the on–off cycles and heterogeneous energy, there are other problems dealing with safety. Heating organic solvents with open vessels can lead to violent explosion induced by electric arcs inside cavity or sparking resulting from the switching of magnetron. The conventional chemical reflux system could be used if the water condenser is outside the microwave cavity. In this case, it is necessary to connect the reaction vessel to the condenser through a port that ensures microwave leakage to safe limit. Mingos et al. [32] has described this kind of domestic oven modification for atmospheric pressure operating conditions.

High pressure operating conditions induced by microwave heating are very attractive for chemists. Microwave heating leads to core heating, then microwave heating of autoclaves has advantages compared to conventional heating modes. The closed vessel could be transparent to electromagnetic waves and can sustain the pressures induced by vaporization of solvents. The vessel material should have very slight dielectric losses. Moreover, this material must be chemically inert and able to accommodate the pressure rate induced by microwave heating. The pressure rate obtained depends on the microwave power level and also on media heated. The Parr instrument company [33] has designed this kind of vessels. They are made with Teflon and polyetherimide and they can support pressures up to 80 atm and temperature up to 250 °C [34]. The reagents volume is close to 20 cm^3. Obviously, in order to use safely this system, a pressure release system permits to avoid strong explosion of the vessels. However, for safety and reproducible operating conditions we recommend to use pressure systems with real time monitoring of pressure.

1.2.1.4 Temperature-measurement Limits

The other limit is the problem of temperature measurements. Classical temperature sensors could be avoided in relation to power level. Hence, temperature measurements will be distorted by strong electric currents induced inside the metallic wires insuring connection of temperature sensor. The technological solution is the optical fiber thermometers [35–39]. However, measurements are limited below 250 °C. For higher values, surface temperature can be estimated by infrared camera or pyrometer [38, 40]. However, due to volumic character of microwave heating, surface temperatures are often inferior to core temperatures.

1.2.1.5 The Design Principles of Microwave Applicators

The classical industrial design of microwave applicators and specifically the choice of the geometrical shape is based on a simple similarity principle between the wave propagation and spatial distribution within the empty and the loaded microwave applicator. The dielectric load is the reactor defined by chemical vessels and the reactants to be transformed. This theoretical approach is approximate. The spatial distribution of electromagnetic fields within applicators strongly depends on geometrical shape and dielectric properties of the load [41–43]. Hence, this design method will be only valid if the dielectric perturbation induced by the reactor is negligible. In fact, the magnitude of the perturbation is proportional to reactor to applicator volume ratio. The perturbation could be negligible if this ratio is close to 10^{-4} and most of laboratory and industrial devices have higher ratio [44].

Hence, it is more efficient but also more complicated to be guided by a geometrical matching principle. According to this geometrical matching principle the microwave applicator designer want to ensure a good match between electric field spatial distribution and geometrical shape of the chemical vessel used. This geometrical matching principle is easier to apply for monomodes applicators because of the knowledge of the waves propagation directions and spatial distribution. The limit of this design method is that it requires the knowledge of the empty applicator modes, but also the of the loaded applicator modes.

In the following text the different laboratory, experimental and industrial devices will be described according to the geometric shape of microwave applicators and reactors. Two fundamental transverse cross-section of microwave applicator will be distinguished: rectangular and circular whereas reactor geometrical shape will be cylindrical or egg-shaped. The microwave applicators and chemical reactors geometrical shape, and the physical nature of the reactant phases (solid, liquid or gas) are the most important points of the following description of laboratory, experimental and industrial microwave reactors..

First, laboratory and experimental reactors will be described. The vessel containing reactants or their supports are made of convenient dielectric materials (cylindrical or egg-shaped reactor). Original microwave reactors will be described. The first one is a metallic cylindrical reactor which is also the microwave applicator. It allow to reaches high pressures. The other one is a egg-shaped microwave reactor leading to high focusing level of microwave power.

Second, industrial microwave reactors will be described. Most of industrial applicators are made of rectangular wave guides. Reactants are contained within pipe or put on a simple conveyer belt.

1.2.2
Commercial Laboratory Microwave Reactors

Only a few microwave reactors equipped with efficient temperature control systems for safe microwave synthesis at laboratory scale are currently available on the market. These systems lead to reproducible operating conditions.

1.2.2.1 The Prolabo Products

This first family of laboratory equipment was no more commercial since the closing down of the Prolabo French company. The support is made by CEM [45]. However, we describe these system because many laboratories use these devices [46]. The Synthewave 402 and 1000 are systems devoted to laboratory synthesis [47, 48]. They are constituted by a closed rectangular waveguide section playing the role of cavity. The magnitude of microwave power available is 300 W. They can use cylindrical tubes with several diameters. A condenser could be connected to the tube. The originality of this setup is to allow measurements of temperature by an infrared pyrom-

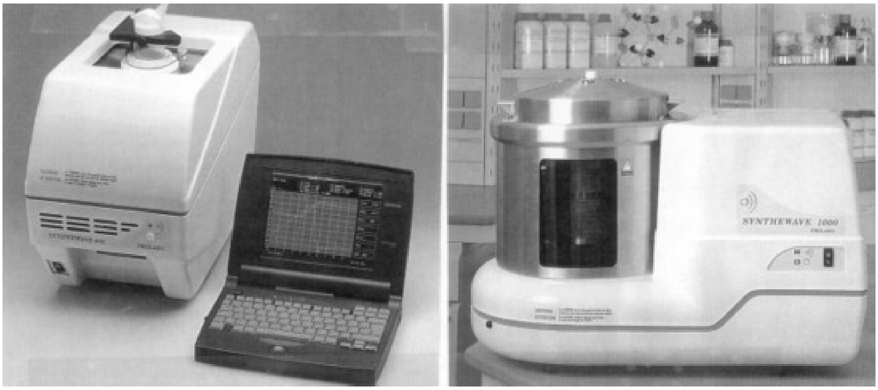

Fig. 1.9 General view of the Synthewave 402 (left) and the Synthewave 1000 (right) (courtesy of A. Loupy).

eter [49]. This system allow measurements on the bottom of the heated tube. This system was a good solution for laboratory experiments. Users should be aware of the problem of temperature measurements. It is better to calibrate the system for each media to be tested [50]. This setup could be associated with a computer in order to regulate reagents temperature. The Synthewave 402 and Synthewave 1000 are described by Fig. 1.9.

The Soxwave 100 is a variant which has been designed for extractions such as Soxhlet which are laborious. The extraction tube is capped with a cooling column. Optional temperature control during extraction was available. Maxidigest (one microwave unit 15 W to 250 W) and Microdigest (3 up to 6 independent digestions at one time with integrated magnetic stirrers) are other variants for digestion.

1.2.2.2 **The CEM Products** [45, 51–53]

The MARS-S is constituted of a multimode cavity very close to domestic oven with safety precautions (15 mL vessels up to 0.5 L round-bottomed flasks, magnetic stirring, temperature control). The magnitude of microwave power available is 300 W. The optical temperature sensor is immersed in the reaction vessel for quick response up to 250 °C. A ceiling mounted is available in order to make connection with a conventional reflux system located outside the cavity or to ensure addition of reactants. These ports are provided with a ground choke to prevent microwave leakage. It is also possible to use a turntable for small vessels with volumes close to 0.1 mL to 15 mL vessels (120 positions for 15 mL vessels). Pressure vessels are available (33 bar monitored, 20 controlled).

The Discover system is a new device designed for synthesis. CEM company claims a single-mode applicator and focused microwave. According to technical data, the applicator is constituted with two concentric cavity with aperture insuring the coupling. It can operate at atmospheric conditions using open vessels and standard glassware (1 mL to 125 mL)or at elevated pressure and temperature using sealed vessels (0.5 mL to 10 mL sealed with a septum). In situ pressure control, infrared tem-

Fig. 1.10 General view of MARS-S (courtesy of A. Loupy).

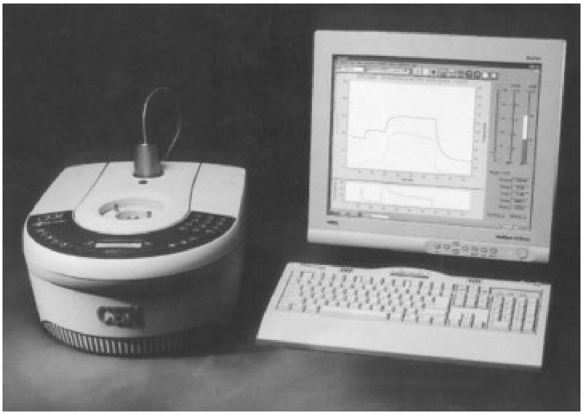

Fig. 1.11 General view of Discover (courtesy of A. Loupy and D. Conseil).

perature control and variable speed stirring are available. The MARS-S is described by Fig. 1.10 whereas the Discover system is described by Fig. 1.11.

The Star Systems 100 is device designed for digestions and extractions such as Soxhlet which are laborious

1.2.2.3 **The Milestone Products** [54–56]

The ETHOS MR is constituted of a multimode cavity very close to domestic oven with safety precautions. It can use standard glassware or glass (420 mL up to 2.5 bar) and polymer reactors (375 mL up to 200 °C and 30 bar) with magnetic stirring. The magnitude of microwave power available is 1 kW. The optical temperature sensor is immersed in the reaction vessel for quick response up to 250 °C. An infrared sensor is also available. A ceiling mounted is available in order to make connection with a conventional reflux system located outside the cavity or to ensure addition of reactants.

The ETHOS CFR is shown in Fig. 1.12. It is a continuous flow variant of the ETHOS MR.

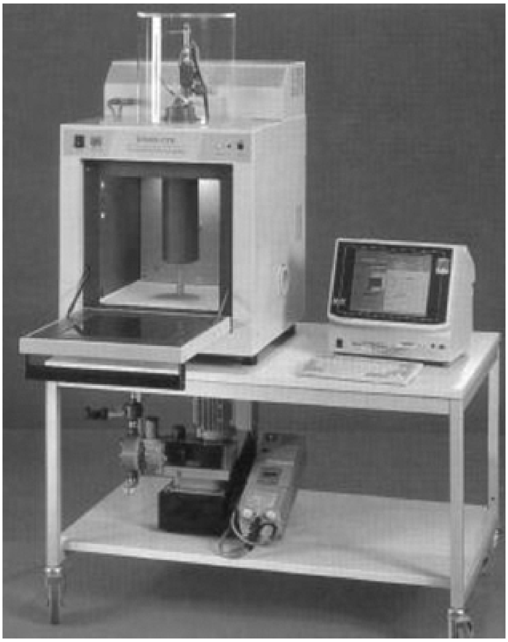

Fig. 1.12 General View of ETHOS CFR (courtesy of A. Loupy).

1.2.2.4 **The Personal Chemistry Products [57]**

The SmithSynthesizer and SmithCreator are systems devoted to laboratory synthesis. They are constituted by a closed rectangular waveguide section playing the role of cavity. They can use specific cylindrical tubes. Pressure and temperature sensors allow real-time monitoring and control of operating conditions. This system was a good solution for laboratory experiments. The SmithSynthesizer is described by Fig. 1.13. More details about the SmithSynthesizer could be found in Sect. 12.7 in Chapt. 12.

Fig. 1.13 General View of the SmithSynthesizer.

1.2.2.5 Plazmatronika Products [58]

Plazmatronika microwave reactor appears similar to multimodal microwave oven. It has been equipped with strong magnetic stirrer which can mix liquids even with some granulates. Field stirrer with metal rotating wings working was applied underneath the reaction vessel. Infrared thermography with fine beam focusing has been applied to measure temperature at the bottom of the reaction chamber and feed back loop-controlled temperature regulation is built in standard.

1.2.3
Experimental Microwave Reactors

Experimental systems are devices designed by research laboratory. Up to now, they are not commercial devices.

1.2.3.1 The RAMO System

Since seven years, D. Stuerga have designed an original microwave reactor the RAMO system (French acronym – Reacteur Autoclave MicroOnde). This microwave applicator and the reactor are original. The resonant frequency of the cavity can be controlled by varying the position of a plunger. The effective cavity power could be increased by three orders of magnitude. The autoclave is made with polymer materials which are microwave transparent, chemically inert and sufficiently strong to accommodate the pressures induced. The reactants are placed in a Teflon flask inserted within a polyetherimide flask. A fiber-optic thermometry system, a pressure transducer and a manometer allow to measure simultaneously temperature and pressure within the reactor. The system is controlled by pressure. The reactor is described by Fig. 1.14.

Fig. 1.14 General view of the RAMO system (courtesy of D. Stuerga).

The microwave power could be adjusted in order to allow constant pressure within the vessel. A incorporated pressure release valve permits to use this experimental device routinely and safely. Furthermore, an inert gas as argon could be introduced within the reactor to avoid sparking risk with flammable solvents. This experimental device is able to raise temperature from ambient to 200 °C in less than 20 s (pressure is close to 1.2 Mpa and heating rate is close to $7^\circ \mathrm{s}^{-1}$). The RAMO system has been designed for nanoparticles growing and elaboration [59–62]. The RAMO system is a batch system. It could be easily transpose to continuous process with industrial scale (several hundred kilograms by seconds).

1.2.3.2 The Supercritical Microwave Reactor

For several years M. Delmotte et al. have designed a microwave reactor for high pressure chemistry [63]. The microwave applicator and reactor are identical in order to accommodate the mechanical constraints induced by high pressure within liquids. This is the main interest of this device. The metallic cylindrical pipe is simultaneously a waveguide and the reactor. The device is described by Fig. 1.15.

The cylindrical reactor–applicator has steel wall with thickness close to 30 mm. This thickness permits to reach internal pressures above 30 Mpa. These operating pressure conditions are above the critical point of water. The internal diameter of the reactor is 50 mm and its length is 500 mm. The system is powered simultaneously with two 6-kW generators placed at the both ends of the reactor. This simultaneous supply is necessary to overcome the penetration depth within water. The penetration depth of waves is defined as the distance from the surface of the material at which the power drops to $1/e$ from its value at the surface. The penetration depth of microwaves is equal to 15 mm for water at 20 °C. The electromagnetic energy transfer is ensured by matched alumina windows. The propagated mode within the reactor is theoretically the TE_{11} mode. The interest of this system is to make very specific chemical reaction such as oxidation in aqueous medium under critical conditions.

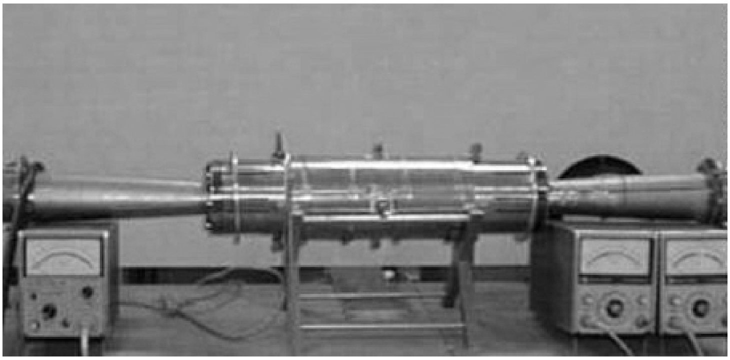

Fig. 1.15 The supercritical microwave reactor applicator The two cones are cylindrical waveguides for microwave power supply (courtesy of M. Delmotte).

Fig. 1.16 General view of the coconut reactor (courtesy of D. Stuerga).

1.2.3.3 The Coconut Reactor

D. Stuerga and P. Pribetich have designed an egg-shaped microwave reactor. Its name has been chosen in relation to its appearance (a black egg which reveals, after opening, a white core). The coconut reactor is described by Fig. 1.16.

The origin of this project is the classical observation of egg explosion during microwave cooking. Spheroidal objects act as dielectric lenses focusing electromagnetic energy. The difference between sphere and egg is the level of focusing. The authors don't want to focus all the microwave power within a small area. The most important point is to control the shape and volume of the focusing spot. This focusing spot is named caustic in geometrical optic. The focusing effect obtained allows heating rates five times higher than those obtained with the RAMO system (close to 35 ° s^{-1}).

1.2.4
Industrial Equipment – Batch or Continuous Flow?

Industrial equipment is classically divided into batch reactor and continuous flow systems. The typical sizes of batch reactor for industrial heterogeneous or homogeneous reactions are close to several cubic meters of liquids reagents. The design of microwave applicators able to heat these volumes meets scientific and technological limits of microwave penetration within high lossy media. The penetration depth of microwaves are beneath decimeter for classical solvents as water, alcohols, etc... So, the microwave treatment of a cubic meter of solvents is generally technologically impossible. Moreover, several cubic meters of liquids reagents inside batch reactors should need microwave power close to one megawatt power. This microwave power is out of range of the classical devices of microwave technology, generally close to one hundred kilowatts at 915 MHz or 2.45 GHz frequencies.

Consequently, we consider that the industrial scale technological management of microwave assisted chemical reaction is no compatible with batch reactors coupled with multimode applicators. Some typical processes with a systematic decrease of the dielectric losses of the concerned reactant, such as filtration and drying of mineral or pharmaceutical powders are compatible with multimode applicators. To our knowledge, the only industrial batch microwave device is the microwave variant of the Turbosphere ("all in one solution" mixer/granulator/dryer designed by Moritz

Fig. 1.17 General view of the microwave variant of Turbosphere (courtesy of A. Loupy).

company) described by Fig. 1.17. This industrial equipment is sold by the Pierre Guerin company, well known in the pharmaceutical industry [64].

In contrast, several industrial continuous flows systems are commercially available. The continuous flow systems permit the spatial localization of a small quantity of matter (between grams and one kilogram) in front of a microwave source with power magnitude close to several kilowatts (typically close to 2 or 6 kW). According to the flow and heating rates expected, several modular power units should be associated and microwave power magnitude could be typically about ten kW. The industrial continuous flows systems described in the following have been designed for food industries and drying and not specially for chemistry industry. However, these devices could be used for chemical processes.

1.2.4.1 **The Pulsar System**

This first industrial device has been designed by MES company [65] for drying. It could be used for solid state reactions with powder reactants. Consequently, the reactor cannot be a classical chemical vessel or a classical chemical reactor with stirrer and others associated technical devices but a container able to enclose a reactant powder layer. The geometrical shape of the microwave applicator is parallelepiped box and the reactants are supported by a dielectric conveyor belt with edges as described by the Fig. 1.18.

This conveyor belt passes through several open parallelepiped applicators such as oversized applicators. The geometrical structure of these waveguides is derived from a standard waveguide adjusted to the TE_{01} mode at frequency equal to 2450 MHz [66]. Each opened applicators is connected to one or two microwave generators set in both side parts of the equipment. If the interface matching of the matter layer is conveniently performed, each opened parallelepiped applicator transfers the electromagnetic power supplied by generators inside reactive bed. The power is dissipated in heat and the temperature of reactant gradually increases.

Fig. 1.18 General view of the Pulsar system. Each applicator is connected to one or two microwave generators set in both side parts of the equipment (courtesy of MES company).

This equipment could be used for chemical reactions based on a strong solid–gas interaction with gas adsorbed on powder such as limited air oxidation or with gas release (water, ammonia) such as esterification. The oversized applicator structure permits the design of dielectric pipe to manage such matter transfers. This equipment can be also used for many reactions on solid supports. A typical unit is powered with microwave generators units of 2 or 6 kW for a total microwave power close to 20 or 60 kW.

1.2.4.2 **The Thermostar System**

This industrial equipment has been designed by MES company [67]. The Thermostar system is constituted by cylindrical vessel associated with parallelepiped applicator. Circular pipes are very classical geometrical shape for industrial reactors. The Thermostar device is constituted of parallelepiped microwave applicators crossing by a dielectric pipe. Two variants of this device have been designed in relation to reactants state (liquid or solid).

The first variant is designed for liquid phases. The Fig. 1.19 describes the microwave applicator with the vertical or horizontal pipes according to nature of the product to be treated.

Six successive units are visible on the Fig. 1.19 (left) and they are set to obtain the heating of reactants in a vertical glass pipe. Each applicator is constituted by a parallelepiped metallic box ($200 \times 200 \times 300\ \mathrm{mm}^3$). The reactor is a dielectric pipe with diameter between 70 and 100 mm. This pipe passes through the box following the electric field direction within the excitation waveguide. This waveguide can be seen

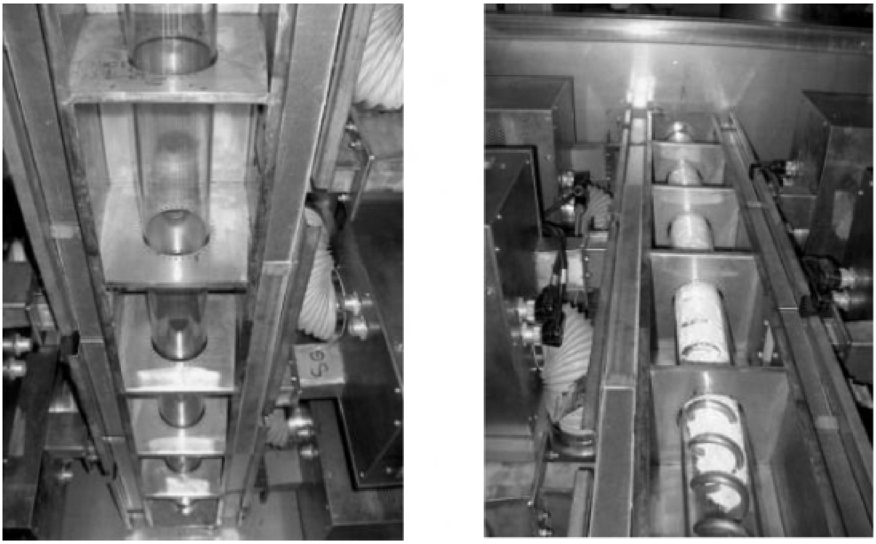

Fig. 1.19 General view of the Thermostar system. Six successive parallelepiped applicators crossing by a vertical pipe (left) or horizontal pipe with screw (right) (courtesy of MES Company).

on the Fig. 1.19 (left). This applicator–generator connection suggests a theoretical TE_{033} propagation mode when the pipe is empty. This equipment is specified for liquid phases heating. The liquid moving from bottom to top with the higher temperature in the high part of the pipe. The reactants can be only a liquid phases or a gas and liquid phases with a gas release system in the bottom part of the pipe (for example a bubble blowing system).

The second variant is designed for solid state reactants to the exclusion of liquid or gas. This powder variant of Thermostar is described by the Fig. 1.19 (right). The microwave applicator is the same as for the device for liquids heating but the reactant transport is ensured by a metallic screw set within the dielectric pipe. This specific traveling metallic screw crosses all the microwave applicators. The coexistence of this metallic screw with the electric field is ensured by the fact that the major electric field direction is parallel to the major direction and perpendicular to the local curving of the screw. A typical industrial unit for solid or liquid reactants is powered with microwave generators units of 2 or 6 kW for a total microwave power close to 20 or 60 kW.

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2

Microwave-assisted Organic Chemistry in Pressurized Reactors

Christopher R. Strauss

2.1

Introduction

The highest priorities for the chemical industry now are process and product safety and the environment [1–5]. New technologies and methods for “green” and sustainable chemistry are subjects of intense activity [6]. In that regard, the potential of microwave heating for organic synthesis attracted interest soon after the first reports [7, 8] appeared in 1986. Early reactions were performed with domestic microwave ovens and relatively primitive containers. Rate enhancement of up to three orders of magnitude was observed, but the time savings were offset by hazards such as deformation of the vessels and explosions.

Thus, the major challenge confronting the early microwave chemists was to retain or enhance the benefits of the technology while concurrently avoiding the risks. Several groups concluded that microwave heating was incompatible with organic solvents and investigated solvent-free conditions including “dry” media, usually with open vessels in domestic microwave ovens [9–12]. That area expanded rapidly, aided by the ready availability of inexpensive microwave equipment and encouraged by a diverse range of reactions awaiting exploration.

Synthetic chemists desire well defined reaction conditions. Process chemists demand them. Nonuniform heating and difficulties with mixing and temperature measurement are technical constraints that initially limited the scale of microwave chemistry with “dry” media and have not yet been overcome. Poor reproducibility also has been reported, probably resulting from differences in performance and operation of individual domestic microwave ovens [13–15]. Consequently, most, if not all, of the disclosed applications of “dry” media are laboratory-scale preparations. However, as discussed in other chapters, this does not prevent their being interesting and useful.

An alternative approach, developed by Bose [16–19] and termed “microwave-induced organic reaction enhancement” (MORE) chemistry, employed polar, high-boiling solvents with open vessels in unmodified domestic microwave ovens. The solvents had dielectric properties suitable for efficient coupling of microwave energy and rapid heating to temperatures that although high, were typically some 20–30 °C

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

below boiling. Apparent disadvantages were the need for high boiling polar solvents such as dimethylsulfoxide, ethylene glycol, diglyme, triglyme, *N*-methylmorpholine, *N,N*-dimethylformamide and 1,2-dichlorobenzene that have relatively similar boiling points and present difficulties for recycling and for isolation of liquid products.

The above strategies were pursued concurrently with our approach, its objective being to interface microwave technology with conventional organic chemistry including the use of low boiling organic solvents. Consequently, dedicated reactors were required that could operate reliably, safely and routinely in the presence of flammable compounds. When we began, such equipment was not available and apparently not contemplated for manufacture by others.

Our first tasks were first to design and fabricate appropriate systems and then to apply them to a diverse range of organic reactions. The following features were considered essential:

- measurement and control of reaction conditions in "real" time;
- immediate, automatic shutdown of microwave systems if reactions become uncontrollable;
- advantages that were unavailable with pre-existing laboratory equipment; and
- potential for scaling-up and scaling-down chemical processes.

2.2
Rationale for Pressurized Microwave Reactors

A practical approximation for chemists is that an increase of 10 °C in reaction temperature can lead to a halving of the time required. If a reaction taking 18 h at 80 °C could be performed at 200 °C, the time expected would be in the order of 2^{12} faster i. e. approximately 16 s. Thus, higher temperatures than normal offer opportunities for efficiencies in time and energy. An obvious extension is that lengthy batch processes could be transformed into continuous operations merely by raising the temperature.

However, at 200 °C or above, at atmospheric pressure, the choice of solvents is limited. High-boiling solvents are inconvenient to remove and to repurify. These disadvantages can be avoided by heating low-boiling solvents in closed systems that can withstand the increased internal pressure. After cooling and opening the vessel, concentration of products can be achieved readily by evaporation of the solvent, which usually can be redistilled for reuse.

Increases in boiling points of many common solvents are significant with modest rises in pressure. The temperature versus pressure curves have points of inflection beyond which considerable increases in pressure afford relatively modest elevations in the boiling point [20]. These properties indicate that reaction pressures of 2–3 MPa would facilitate temperatures in the order of 200 °C for common solvents such as EtOAc, MeOH, EtOH, MeCN and Me_2CO, all of which boil below 85 °C at atmospheric pressure.

These benefits can be obtained with traditional, conductively heated autoclaves, but heat losses increase with rises in temperature. Also, in the respective heating and cooling steps, the rates of temperature increase and decrease are usually low and thermal gradients are difficult to avoid.

It was surmised that with appropriate vessels, microwaves would be absorbed predominantly throughout the sample. In addition, the energy could be applied or withdrawn instantaneously and the input could be adjusted readily to match that required. Thus, it appeared likely that direct, bulk heating, combined with efficient stirring of the sample would diminish temperature gradients, particularly near the walls of the vessel.

2.2.1
The Continuous Microwave Reactor (CMR)

Two years after the 1986 reports of Gedye [7] and Giguere [8], a prototype continuous microwave reactor (CMR) was produced [21, 22]. It was the first microwave system designed to cope with organic solvents. Patents were obtained. Commercial systems developed under license, typically comprised a microwave cavity fitted with a vessel of microwave-transparent, inert material (Fig. 2.1). Plumbing in the microwave zone was connected to a metering pump and pressure gauge at the inlet end and to a heat exchanger and a pressure-regulating valve at the effluent end. The heat exchanger enabled rapid cooling of the effluent, under pressure, immediately after it exited the irradiation zone. Temperature was monitored immediately before and after cooling. Variables such as internal volume of the plumbing within the microwave zone, flow rate and control of the applied microwave power allowed flexible operation. To withstand corrosive acids and bases within the plumbing, contact was avoided between metal surfaces and reaction mixtures. Feedback microprocessor control allowed setting of pump rates and temperatures for heating and cooling of reactions. Failsafe measures were instituted to shut down the system if the tem-

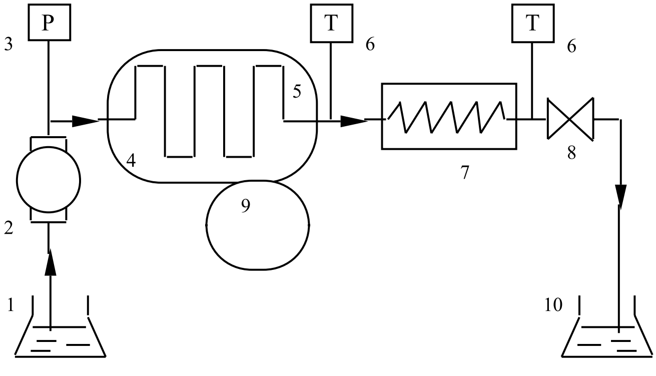


Fig. 2.1 Schematic diagram of the CMR [22]. 1, reactants for processing; 2, metering pump; 3, pressure transducer; 4, microwave cavity; 5, reaction coil; 6, temperature sensor; 7, heat exchanger; 8, pressure regulator; 9, microprocessor controller; 10, product vessel.

perature exceeded the maximum allowable by 10 °C, or in the event of blockage, leakage or rupture.

Commercial units [23–25] had volumes up to 120 mL within the microwave zone, 80 mL within the cooling zone and could be operated at flow rates up to 100 mL min^{-1}. Under such conditions residence times in the microwave zone were typically 2–10 min.

2.2.2
The Microwave Batch Reactor (MBR)

A complementary laboratory-scale microwave batch reactor (MBR) was developed for synthesis or kinetics studies (Fig. 2.2) [26]. It has a capacity of up to 200 mL and reactions can be heated to 260 °C and 10 MPa (100 atmospheres). In practice, pressures exceeding 5 MPa have been required only rarely. The main features include: rapid heating capability (1.2 kW microwave output); infinitely variable control of microwave power; measurement of absorbed and reflected microwave energy; a load matching device to maximize heating efficiency; direct measurement of the reaction temperature and pressure; a stirrer for mixing and to ensure uniform temperature within the sample; valving and plumbing to facilitate sample introduction and withdrawal during the heating period; chemically inert wettable surfaces and fittings; rapid cooling postreaction and a facility for conducting reactions under an atmosphere of inert gas.

Microwave power input is computer controlled. Heating can be performed at high or low rates as required and designated temperatures can be retained for hours if desired. A robotically operated microwave batch reactor designed along the lines of the MBR, but with a capacity low enough (1–5 mL) to accommodate postreaction cooling from outside the vessel, has been introduced for rapid synthesis of candidates for drug discovery [27].

Fig. 2.2 Dr Ulf Kreher at work with the MBR.

2.2.3
Transfer of Microwave Energy

Microwave energy is not transferred primarily by conduction or convection as with conventional heating, but by dielectric loss [28]. The dielectric loss factor (loss factor, ε'') and the dielectric constant (ε') of a material are two determinants of the efficiency of heat transfer to the sample. Their quotient ($\varepsilon''/\varepsilon'$) is the dissipation factor ($\tan\delta$), high values of which indicate ready susceptibility to microwave energy. Important parameters relevant to microwave dielectric heating have been discussed and reviewed [29].

The two main mechanisms by which materials dissipate microwave energy are dipole rotation and ionic conduction [30]. Dipole rotation refers to the alignment of molecules that have permanent or induced dipoles, with the electric field component of the radiation. At 2450 MHz, the field oscillates 4.9×10^9 times s^{-1}. Sympathetic agitation of the molecules generates heat. The efficacy of heat production through dipole rotation depends upon the characteristic dielectric relaxation time of the sample, which in turn, is dependent on temperature and viscosity. The second main dissipation mechanism, ionic conduction, is the migration of dissolved ions with the oscillating electric field. Heat generation is due to frictional losses, which depend on the size, charge and conductivity of the ions as well as on their interactions with the solvent.

Compounds with high dielectric constants such as water, ethanol and acetonitrile, tend to heat readily. Less polar substances like aromatic and aliphatic hydrocarbons or compounds with no net dipole moment (e.g. carbon dioxide, dioxane, and carbon tetrachloride) and highly ordered crystalline materials, are poorly absorbing.

Changes to the physical properties of a compound or material can have a dramatic influence on the susceptibility to microwave radiation. For example, ice has dielectric properties (ε', 3.2; $\tan\delta$, 0.0009; ε'', 0.0029) that differ significantly from those of liquid water at 25 °C (ε', 78; $\tan\delta$, 0.16; ε'', 12.48) [31], rendering it essentially microwave-transparent. Although liquid water absorbs microwave energy efficiently, the dielectric constant decreases with increasing temperature and supercritical water (T_C 374 °C) is also microwave-transparent.

Differences in sample size, shape and composition can also affect heating rates. The last case particularly applies when ionic conduction becomes possible through the addition or formation of salts. For compounds of low molecular weight, the dielectric loss contributed by dipole rotation decreases with rising temperature, but that due to ionic conduction increases. Therefore as an ionic sample is microwave-irradiated, the heating results predominantly from dielectric loss by dipole rotation initially, but the contribution from ionic conduction becomes more significant with temperature rise.

2.4
Contrasts between Synthesis and Digestion

Before the advent of the MBR and CMR for synthesis, microwave heating with pressure vessels had been used in analytical laboratories, to speed the rate of digestion and dissolution of solid samples, such as ores, hair and foodstuffs [32]. Digestion is a degradative process, typically involving treatment of a small sample with an excess of a strong oxidizing acid such as nitric, perchloric or sulfuric. The objective is to obtain a clear solution usually for quantitative analysis of mineral components, without charring and physical loss of material. Although it is essential that digestions be standardized for high precision, parameters such as temperature, reaction time, sample stirring and cooling rate are not essential to the outcome and so are not actively controlled.

As technologies for microwave-assisted digestion gained favor over slower, traditional heating methods, microwave equipment manufacturers emerged during the 1970s and 1980s to satisfy these analytical applications. The field of microwave-assisted organic chemistry developed after microwave digestion had become an accepted analytical tool. Not surprisingly, some manufacturers attempted to employ digestion technologies for synthesis. However, they did not appear to fully appreciate the differences between the applications. This probably slowed the introduction of appropriate equipment for synthesis, rather than assisting it.

In contrast with digestion, synthesis is a constructive process. Reactants that are not particularly stable to strong acids and bases may be required and in much larger amounts than those used for digestion. They may be expensive and highly reactive, even on the laboratory-scale. The ability to define and control conditions including temperature, time, sample stirring, addition or withdrawal of materials and postreaction cooling, is almost always vital for satisfactory outcomes and for reproducibility. Digestion techniques are unsatisfactory for these tasks.

2.5
Advantages of the MBR and CMR

The MBR and CMR have the following advantages for synthesis:

- the reaction conditions can be measured and reproduced;
- response is rapid in comparison with conventional heating;
- microwave energy is adsorbed directly by the sample and not via the vessel;
- when the power is turned on or off, energy input starts or stops immediately; an important safety consideration;
- thermally unstable products can be cooled rapidly, after the heating step;
- stirring of the sample limits thermal gradients: the temperature of the material on the inner walls of the reaction vessel is not significantly different from that in the body of the mixture, hence unwanted pyrolysis can be minimized;

- reactions that are known to require high temperatures and higher boiling solvents can be performed under pressure at these temperatures, but in lower boiling solvents, facilitating workup;
- the available temperature range for many solvents is increased dramatically;
- low boiling reactants can be heated to high temperatures and rapidly cooled under pressure; losses of volatile compounds are minimized;
- reactions can be sampled for analysis while material is being processed; with the CMR, reaction mixtures can be subjected to multiple passes if required, or the conditions can be altered during a run;
- reactions performed on a laboratory scale are amenable to scale up, because the conditions are defined;
- moderate to high temperature reactions can be performed in vessels fabricated from inert materials such as PFA Teflon, PTFE, or quartz; this is beneficial where strongly acidic or basic reactants or products are incompatible with metals or borosilicate glass; and
- in multiphase systems, selective heating is possible.

2.6
Applications of the MBR and CMR

The CMR and MBR are enabling technologies that can stand alone. They also can be integrated with other technologies and methodologies for processes that utilize renewable resources, limit waste and afford useful, recyclable products [6, 33]. They lie at the heart of an approach toward development of new tools for preparative organic chemistry, the aim being to be able to select appropriate combinations to solve specific problems in environmentally acceptable ways [6, 34]. This strategy has some similarity with combinatorial chemistry, which revolutionized approaches to drug discovery in the mid-1990s. However, it was designed more to establish multiple chemical processes than to accomplish many reactions by parallel applications of the same process. Downstream processing is a key element, as environmental damage can destroy the viability of chemical manufacturing practices.

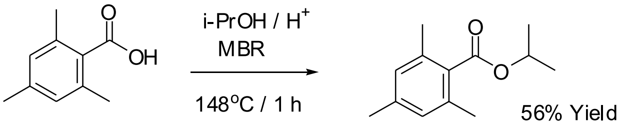
To complement the reactors, a catalytic membrane of Pd on porous glass tubing was produced [35]. As mentioned in Sect. 2.8, this has been used to perform various thermal reactions including Heck arylative coupling and to develop new reactions including a novel coupling–dehydrogenation and a new concerted process incorporating an oxidation–dehydrogenation–double-Heck coupling [36]. Both reactions proceeded well in the MBR.

Other methodologies feature solvent-free conditions with “neat” starting material, tandem or cascade, catalyzed or uncatalyzed reactions, the use of aqueous media at high temperature and nonextractive techniques for product isolation. Examples appear among the following microwave-assisted applications.

2.6.1
Reactions with Sterically Constrained Molecules

Reactions that are unfavored through steric constraints are difficult to achieve conventionally, but often proceed at higher than normal temperatures in the CMR or MBR.

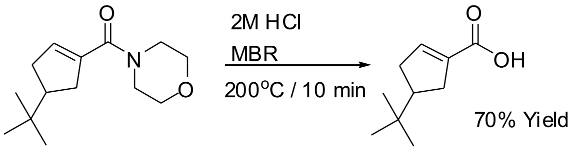
Heating of isopropanol under conventional reflux conditions, with 2,4,6-trimethylbenzoic acid and a catalytic amount of sulfuric acid, afforded the corresponding isopropyl ester in only 2% conversion after 28 h. With the MBR, the product was isolated in 56% yield after 1 h at 148 °C [26] (Scheme 2.1 – please note that in all schemes herein, the use of a double headed arrow does not imply a balanced equation).



Scheme 2.1 Preparation of isopropyl 2,4,6-trimethylbenzoate.

In the CMR, a yield of 81% was obtained after four passes (total residence time, 6.4 min) at 155–164 °C [22]. As indicated by the pressure, these reactions were performed at temperatures below those enabling esterification by elimination of the alcohol to propene, followed by addition of the acid to the olefin. Kinetics studies demonstrated that the significantly enhanced yields obtained under the microwave conditions, resulted from the higher temperatures employed and not from any intrinsic microwave "effects" [37, 38].

Similarly, hydrolysis of tertiary amides of carboxylic acids is usually slow under conventional conditions. Hydrolysis of a morpholide occurred in only 48% yield with 2M HCl at reflux after 4 h, yet proceeded in 70% yield after only 10 min at 200 °C in the MBR (Scheme 2.2) [26]. The convenience of operation and the rapid throughput enabled preparation of multiple batches of the corresponding acid in a few hours.



Scheme 2.2 Hydrolysis of a tertiary amide.

2.6.2
Preparation of Thermally Labile Products

Vessels for microwave-assisted chemistry are usually made from thermal insulators such as PEEK, quartz, borosilicate glass or PTFE. Thus, the benefits of rapid heating can be diminished if the opportunity for workup is delayed by slow cooling. Decomposition of thermally unstable products also can occur.

In the CMR, rapid cooling takes place through an in-line heat exchanger adjacent to the microwave zone. Mixtures can be cooled immediately, while still under pressure, to prevent losses of volatile compounds and to minimize decomposition of thermally labile products [22]. The MBR has a cold-finger that contacts the reaction mixture directly. Cooling can be initiated at any time during operation and is efficient because it is not via the container [26]. Temperature and pressure monitoring, as well as stirring, can be maintained during the process, allowing access to the vessel at the earliest opportunity.

2.6.2.1 **Depolymerization of Cellulose**

In the exploration of technologies based on renewable resources, a key challenge is the depolymerization of cellulose to produce glucose or its oligomers from biomass. These products may then be used as feedstock for fermentation to energy sources and synthetic building blocks such as ethanol, acetic acid and lactic acid [39]. Although high temperatures and acidic conditions are required to cleave the glycosidic bonds, the monosaccharide and oligosaccharides are more labile than the starting material and readily decompose to 5-hydroxymethylfurfural and other undesired compounds including polymeric tars. Thus, rapid heating and cooling are beneficial.

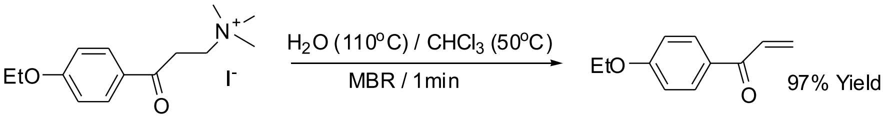
A method developed in the MBR involved heating the cellulose with 1% sulfuric acid, from ambient to 215 °C within 2 min, maintaining this temperature for 30 s and cooling. The entire operation was completed within 4 min and afforded glucose in nearly 40% yield, along with fermentable oligomers [26].

2.6.2.2 **Hofmann Elimination**

Aryl vinyl ketones are produced thermally from the corresponding quaternary ammonium salts via Hofmann elimination. However, the conjugated ketones are heat-sensitive and polymerization is difficult to avoid. Traditional preparations afforded only moderate yields. Microwave conditions were established for Hofmann eliminations, performed essentially quantitatively, by batch or continuous processes.

With the CMR, phenyl vinyl ketone was prepared by passage of a 5% aqueous slurry of *N*-(2-benzoylethyl)-*N*,*N*,*N*-trimethylammonium iodide through the microwave zone. The product was immediately extracted from the cooled aqueous effluent into chilled Et_2O, avoiding polymerization of the monomer and giving near quantitative yields [22].

With the MBR, individual components of multiphase systems can be heated at different rates according to differences in their dielectric properties. We have termed this, differential heating. For example, the aqueous phase of a water/chloroform system (1 : 1 by volume), heated more rapidly than did the organic layer and a temperature difference of 50 centigrade degrees or more, could be maintained for several minutes. Differential heating was employed advantageously in Hofmann eliminations. A mixture of *N*-[2-(4-ethoxybenzoyl)ethyl]-*N,N,N*-trimethylammonium iodide, water and chloroform was heated, with stirring for 1 min at 110 °C (temperature of the aqueous phase). During the reaction, 4-ethoxyphenyl vinyl ketone was formed, extracted and diluted into the cooler organic phase. The isolated yield was 97% (Scheme 2.3) [26].

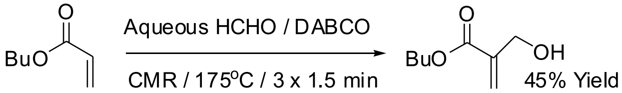


Scheme 2.3 Hofmann elimination by differential heating.

Differential heating is more easily achieved with microwave technology than by conventional conductive methods and as Cundy suggested in his excellent review, could well account for apparent rate enhancements obtained by others with organic reactions on "dry" media [40].

2.6.2.3 Alkyl 2-(hydroxymethyl)acrylates

Alkyl 2-(hydroxymethyl)acrylates are versatile functionalized monomers and synthetic building blocks. Conventional preparations employ the Baylis–Hillman reaction which involves the addition of formaldehyde to the parent acrylate ester, catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO). These reactions typically take several days at room temperature, but can be achieved within minutes in the CMR and MBR (Scheme 2.4). Rapid heating under pressure prevents loss of formaldehyde. Subsequent cooling limits hydrolysis of the product, as well as dimerization and polymerization [33].



Scheme 2.4 Baylis–Hillman reaction with formalin.

2.6.3
New Reactions that Require High Temperature

2.6.3.1 Etherification

Conditions employing elevated temperatures with less catalyst, a milder catalyst or without addition of catalyst, can supplant those utilizing aggressive reagents at lower temperatures. A recent example concerns a catalytic, thermal etherification that can be performed near neutrality and that produces minimal waste [41]. This represents a cleaner alternative to the traditional Williamson synthesis, in which the ether is produced through substitution of an alkyl halide (RX) by a strongly basic alkoxide or phenoxide. A stoichiometric amount of waste salt is generated and in some cases, base catalyzed elimination of hydrogen halide can compete.

The new process is suited to production by MBR or CMR and is shown in Scheme 2.5 for a symmetrical ether. An excess of alcohol (ROH) and a catalytic amount of RX are heated. A solvolytic displacement reaction between RX and ROH affords R_2O along with HX or its elements (hereafter referred to as HX; Scheme 2.5, Eq. 1). The liberated HX attacks another molecule of ROH to form water and to regenerate RX (Scheme 2.5, Eq. 2). If the rates of both reactions are comparable, the concentration of HX will be low throughout and that of RX will remain relatively constant. Although HX and RX are stoichiometric reactants or products in Eqs. (1) and (2), they do not appear in the sum, Eq. (3). The net procedure involves condensation of two molecules of ROH to give R_2O plus water. The process has been demonstrated with primary and secondary alcohols, including compounds labile to base and acid. Advantages for clean production are high atom economy, that salts are not formed, RX often is recoverable, the reaction does not require addition of strong acids or bases and that water is the major byproduct.

$$\mathrm{RX + ROH} \rightleftharpoons \mathrm{R_2O + HX} \qquad \text{Equation 1}$$

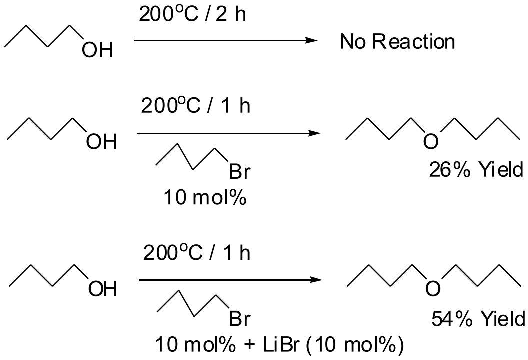
$$\mathrm{HX + ROH} \rightleftharpoons \mathrm{RX + H_2O} \qquad \text{Equation 2}$$

$$\mathrm{2\,ROH} \rightleftharpoons \mathrm{R_2O + H_2O} \qquad \text{Equation 3}$$

Scheme 2.5 Pathway for the etherification catalyzed by RX.

The preparation of di-*n*-butyl ether is illustrative (Scheme 2.6). No reaction occurred with *n*-butanol alone for 2 h at 200 °C. However, in the presence of 10 mol % *n*-butyl bromide, 26% conversion of the alcohol to the ether was obtained after 1 h, without apparent depletion of the catalyst. It is known that addition of alkaline metal salts can accelerate solvolytic processes, including the rate of ionization of RX [41]. This was confirmed when the introduction of LiBr (10 mol %) along with *n*-butyl bromide, afforded a conversion of 54% after 1 h at 200 °C. Ethers incorporating a secondary butyl moiety were not detected, precluding mechanisms involving elimination followed by Markovnikov addition.

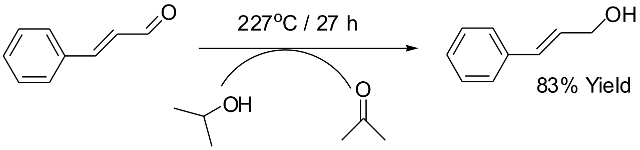
Hydroxy and alkoxy groups are not readily displaced from carbon atoms. Protonation with strong acids greatly facilitates their leaving. As demonstrated through the inefficacy of tetrabutylammonium bromide, the presence of the halide ion alone was insufficient to drive the reaction. HBr was required. Conversely, HBr and HI are commonly employed as cleavage agents for ethers. This suggests that etherification catalyzed by RX or HX is achieved through a shift in the position of equilibrium. The microwave reactors facilitate the process through their ability to cope with and retain HX at elevated temperature. Several reactions have been performed in the MBR. The CMR has been employed to produce not only dibutyl ether, but also dibenzyl ether from benzyl alcohol and a catalytic amount of benzyl bromide.



Scheme 2.6 Preparation of di-*n*-butyl ether.

2.6.3.2 Uncatalyzed Hydrogen-transfer Reduction

We recently reported a modified Meerwein–Ponndorf–Verley reduction in which low-boiling alcohols such as EtOH and *n*-PrOH, but preferably *i*-PrOH, were used at temperatures near 225 °C in the absence of aluminum alkoxides [42]. The carbonyl moiety of an olefinic aldehyde such as cinnamaldehyde was reduced selectively to the alcohol without the carbon–carbon double bond being affected (Scheme 2.7). Since base was not present, aldol and Claisen–Schmidt condensations were avoided.



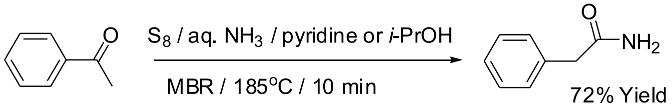
Scheme 2.7 Uncatalyzed thermal hydrogen transfer reduction of cinnamaldehyde.

This work elaborated upon that of Malwitz and Metzger [43] (who conducted the majority of their investigations at 400 °C) and was performed by conventional heating. It further emphasizes opportunities for the discovery of new, clean reactions that require high temperature.

2.6.4
Reactions Known to Require High Temperatures

2.6.4.1 Willgerodt Reactions

Phenylacetamides were prepared in the MBR from the corresponding styrene or acetophenone derivatives by Willgerodt reactions (Scheme 2.8) [44]. Yields were comparable with those obtained by others with conventional heating. At similar temperatures, the microwave-heated reactions were completed within minutes rather than hours. Optimization was readily accomplished through the capabilities of the MBR for rapid heating and cooling. The substantially shorter reaction times probably re-



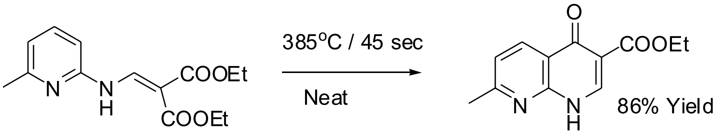
Scheme 2.8 Willgerodt reaction under microwave conditions.

sulted from the convenience in the operation of the reactor in comparison with a standard autoclave, indicating broader opportunities for microwave heating to improve the conditions for established reactions that require high temperatures.

2.6.4.2 Jacobs–Gould Reactions under Solvent-free Conditions

The Jacobs–Gould intramolecular cyclization of diethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate to 3-ethoxycarbonyl-7-methyl-1,8-naphthyrid-4-one is another reaction ideally suited to microwave heating, although conductively heated equipment was employed for laboratory-scale experiments [45]. The product is a key intermediate in the synthesis of nalidixic acid, the first of the quinolone antibacterials. The process usually is conducted at temperatures of 200–250 °C and in high dilution, with heat transfer oils such as the eutectic mixture of diphenyl ether and biphenyl. However, it proceeded rapidly, predictably and controllably under solvent-free conditions.

The findings contrasted with common conceptions that intramolecular reactions require dilution to restrict competing intermolecular processes. Indeed, under the optimal conditions, the temperature (385 °C) was nearly 150 °C higher than that normally employed and the reaction time was less than 1 min instead of many minutes. The yield was 86% and the process was performed continuously under the newly established conditions (Scheme 2.9) [45].



Scheme 2.9 Jacobs–Gould reaction in the absence of heat-transfer oil.

2.6.5
Viscous Reaction Mixtures

Typically, viscous materials transfer energy poorly. With conductively heated vessels, pyrolytic degradation on the walls can co-occur with incomplete reaction towards the center of the container. Large thermal gradients can result in suboptimum conversions, loss of product and laborious cleanup procedures. Also, when high temperatures are required, heat losses increase and conductive heating becomes inefficient. Under microwave conditions these problems are diminished. This accounts for the numerous applications for curing of polymers by microwave heating.

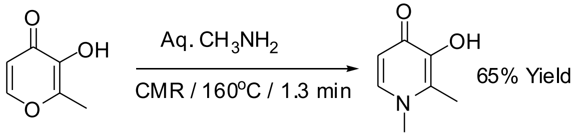
Reactions such as the acid catalyzed preparation of isopropylideneglycerol proceeded well in the CMR. A yield of 84% was obtained after a residence time of

1.2 min, the exit temperature being 133 °C. A conventional literature method in which the upper temperature was limited by the boiling point of acetone, required one day for a comparable result [22].

2.6.6
Reaction Vessels

Being microwave-transparent, the reaction vessels will be no hotter than their contents. As mentioned above, they usually are made from insulating polymeric materials like polytetrafluoroethylene (PTFE), which have inherent advantages for cleaner processing. In contrast with other materials, PTFE is resistant to attack by strong bases or HF and is not corroded by halide ions.

This was significant in the preparation of 1,2-dimethyl-3-hydroxy-4-pyridone, employed clinically as an iron chelating agent. The aminoreductone is obtained by reaction of methylamine with maltol. Traces of metal within the system readily form highly colored complexes with reactant or product and these are difficult to remove. With the CMR, the preparation was achieved in 65 % yield without the need for decolorizing charcoal and the product was crystallized by collecting the effluent in acetone (Scheme 2.10) [22].



Scheme 2.10 Microwave preparation of 1,2-dimethyl-3-hydroxy-4-pyridone.

Another advantage of PTFE vessels is low adhesivity, which can help to reduce detergent and organic solvent usage during cleaning operations that would otherwise generate considerable effluent [6].

2.6.7
Reactions with a Distillation Step

With conductive heating, several factors militate against efficient distillation. Transferal of heat to the liquid usually occurs from the inner surfaces of the vessel. Vaporization from the surface and convection preclude a uniform temperature within the liquid. To achieve distillation under those circumstances, the pot temperature must be considerably higher than that of the distillate. With microwaves, energy is absorbed more uniformly, a larger volume of the sample in the pot is heated simultaneously, convection is reduced and distillation is more rapid.

The MBR can accommodate distillation through an outlet tube connected to a port on the top flange. With that arrangement, a monodehydrobromination of 1,6-dibromohexane was performed in which the product 6-bromohex-1-ene was removed from the mixture before a second molecule of HBr could be eliminated [26, 33].

2.6.8
Miscellaneous Reactions

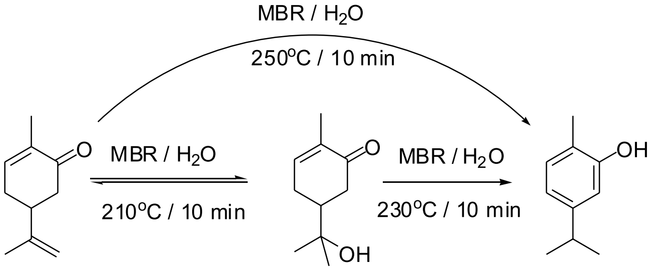
The MBR and CMR have been instrumental for transformations including nucleophilic substitution, oxidation, addition, elimination, isomerization, esterification, transesterification, hydrolysis, oximation, acetalization, amidation, decarboxylation and coupling. Most of the common organic solvents have been employed. “Name” reactions include Michael, Diels–Alder and aza Diels–Alder additions, Williamson etherification, Claisen and Rupe rearrangements, Finkelstein, Knoevenagel, Claisen–Schmidt, Mannich, Baylis–Hillman, Willgerodt, Meyer–Schuster, reactions, Heck arylative coupling and Hofmann elimination. Improved conditions obtained in comparison with literature methods, typically involved one or more of the following: increased convenience, savings in time, higher yields, greater selectivity, the need for less catalyst, or employment of a more environmentally benign solvent or reaction medium.

2.6.9
Kinetic Products

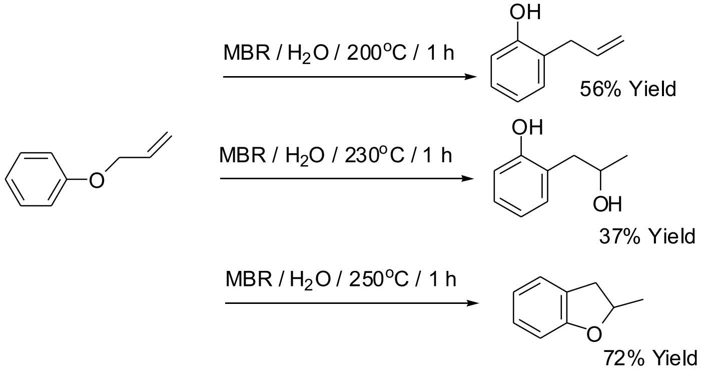
If a reaction can give multiple products, that obtained first (the kinetic product) is not necessarily the most stable (the thermodynamic product). The kinetic product will be in equilibrium with the starting materials but not necessarily with the thermodynamic product.

Where multiple products are possible, the CMR and MBR have been employed to optimize conditions for formation of specific components of a reaction sequence. Examples discussed below, were obtained by heating organic substrates such as allyl phenyl ether [46] and carvone [47] in water. Rearrangements, addition or elimination of water and isomerizations occurred, with each transformation favored under tightly defined conditions.

Heating of carvone in water at 210 °C for 10 min afforded 8-hydroxy-*p*-menth-6-en-2-one, the equilibrium position favoring the starting material by a factor of 4 : 1. The hydroxymenthenone, although in equilibrium with the starting material, also underwent elimination of water and isomerization to carvacrol, giving a 1 : 1:1 mixture of these three substances at 230 °C after 10 min. At 250 °C, for 10 min, carvone isomerized to carvacrol almost quantitatively (Scheme 2.11) [47].



Scheme 2.11 Kinetic and thermodynamic products from carvone in water.



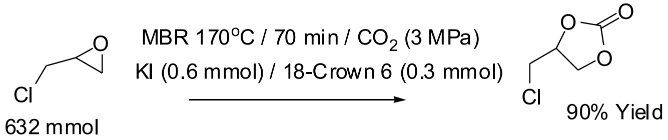
Scheme 2.12 Kinetic and thermodynamic products from allyl phenyl ether in water.

Allyl phenyl ether was heated with water in the MBR for 1 h at different temperatures [46]. It underwent Claisen rearrangement to 2-allylphenol (56% yield) at 200 °C, 2-(2-hydroxyprop-1-yl)phenol (37% yield) at 230 °C and 2-methyl-2,3-dihydrofuran (72% yield) at 250 °C (Scheme 2.12). Support for the reaction sequence was obtained through experiments with authentic intermediates.

2.6.10
Gaseous Reactants and Media

Even though the CMR and MBR operate under conditions in which pressure is developed, gaseous reactants or media often can be handled in these systems without problems arising through over-pressure. Mannich reactions with dimethylamine, Baylis–Hillman reactions with formaldehyde, aminoreductone formation with ammonia, all proceeded without difficulty, as did Willgerodt reactions in which gases are formed during the process.

In an extension, we recently reported the formation of cyclic carbonates respectively from epichlorohydrin (Scheme 2.13) and styrene oxide, with carbon dioxide under catalysis by KI in the presence of a crown ether [48].



Scheme 2.13 Preparation of the carbonate from epichlorohydrin in the MBR.

2.7
High-temperature Water as a Medium or Solvent for Microwave-assisted Organic Synthesis

At ambient temperature water is a poor solvent for most organic compounds. However, its ionic product increases one thousandfold between 25 °C and 240 °C, making it a stronger acid and base. The dielectric constant decreases from 78 at 25 °C to 20 at 300 °C, indicating that the polarity is lowered with temperature increase. These properties suggest that in organic reactions, water could have a role that varied with temperature. The MBR and CMR were ideally suited to investigations into organic synthesis in high-temperature water [6, 33, 47].

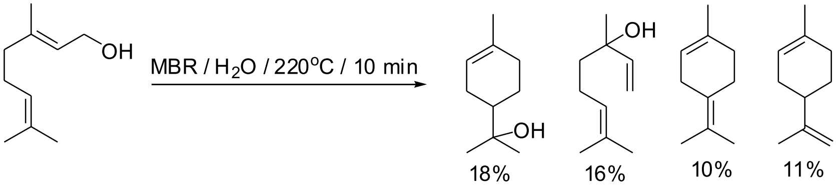
A diversity of reactions and high selectivities was obtained with seemingly minor variations in the conditions. Scaleup also was achieved, including to continuous operation with the CMR, confirming the potential of aqueous high-temperature media for the development of clean processes [49]. Obvious advantages of water include low-waste workup, low cost, negligible toxicity and safe handling and disposal. Some examples have already been discussed and additional ones appear below.

2.7.1
Biomimetic Reactions

Naturally occurring monoterpene alcohols were heated in water without prior derivatization with typical biological water-solubilizing groups such as phosphates or glycosidic units. Biomimetic reactions that normally would be acid-catalyzed, proceeded on the underivatized compounds in the absence of added acidulant. Cooling of the mixtures rendered the products insoluble, readily isolable and the aqueous phase did not require neutralization before workup.

Geraniol, nerol and linalool are practically insoluble in water at ambient temperature. Although acid labile, they do not readily react in water at moderate temperature and neutral pH. In unacidified water at 220 °C in the MBR, they reacted within minutes. Geraniol rearranged to α-terpineol (18%) and linalool (16%) predominantly. Lesser amounts of the monoterpene hydrocarbons were also obtained, including myrcene, α-terpinene (10%), limonene (11%), γ-terpinene, the ocimenes, α-terpinolene and alloocimenes (Scheme 2.14) [50].

Nerol and linalool underwent considerably more elimination than did geraniol, to give the same hydrocarbons. The major products and their relative proportions were



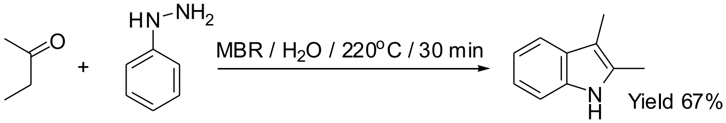
Scheme 2.14 Reaction of geraniol in water at 220 °C in the MBR.

consistent with those for carbocationic rearrangement of derivatives of linalool, nerol and geraniol under acidic conditions.

By a traditional method, α- and β-ionones can be converted to ionene, catalyzed by HI along with small amounts of phosphorus. A cleaner cyclization occurred by heating β-ionone in water at 250 °C in the MBR [50]. In the workup the usual exhaustive washing procedures were unnecessary. Similarly, as mentioned above, carvacrol was prepared almost quantitatively, by isoaromatization of carvone in water at 250 °C for 10 min [47]. A conventional, literature method utilized acidic conditions, took a longer time and proceeded in lower conversion. The above examples show that elevated temperatures under neutral pH conditions can offer advantages over acidic (or basic) reagents at lower temperatures.

2.7.2
Indoles

In the first example of water as the reaction medium for Fischer indole synthesis, 2,3-dimethylindole was obtained in 67% yield from phenylhydrazine and butan-2-one, at 220 °C for 30 min (Scheme 2.15). Neither a preformed hydrazone nor addition of acid was required [33].

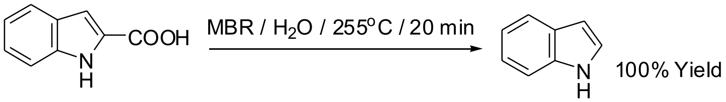


Scheme 2.15 Fischer indole synthesis in water.

Interestingly, the Fischer indole synthesis does not easily proceed from acetaldehyde to afford indole. Usually, indole-2-carboxylic acid is prepared from phenylhydrazine with a pyruvate ester followed by hydrolysis. Traditional methods for decarboxylation of indole-2-carboxylic acid to form indole are not environmentally benign. They include pyrolysis or heating with copper–bronze powder, copper(I) chloride, “copper” chromite, “copper” acetate or copper(II) oxide, in for example, heat-transfer oils, glycerol, quinoline or 2-benzylpyridine. Decomposition of the product during lengthy thermolysis or purification affects the yields.

In water at 255 °C, decarboxylation of indole-2-carboxylic acid was quantitative within 20 min in the MBR (Scheme 2.16) [33].

A semisystematic study into the hydrolysis of ethyl indole-2-carboxylate in aqueous media at high temperature, indicated that decarboxylation of the resultant acid proceeded by an arenium ion mechanism and was inhibited by base. As base pro-



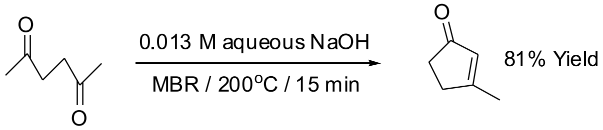
Scheme 2.16 Decarboxylation in water.

moted hydrolysis of the ester, it was possible to obtain either the acid or indole from the ester merely by manipulating the equivalents of base present [51].

2.7.3
Reactions in Aqueous Acid and Base

3-Methylcyclopent-2-enone typically is prepared by an intramolecular Claisen–Schmidt condensation from 2,5-hexanedione. The product is usually required free from traces of starting material but these substances co-distil. Accordingly, literature methods have employed strong aqueous base in 2–3% concentration at reflux and have been continued until all of the starting material has been consumed. Under those circumstances, the product also has undergone aldol and Claisen–Schmidt condensations severely lowering the yield.

In a method with microwave heating at 200 °C, two orders of magnitude less concentrated base was employed [49]. Competing reactions were suppressed, salt formation was lowered and the enone was obtained in conversions of about 94% and in isolated yields of over 80% depending on the scale (Scheme 2.17). The preparation was readily scaled up by conversion to a continuous process with the CMR.



Scheme 2.17 Intramolecular Claisen–Schmidt condensation.

2.7.4
Avoiding Salt Formation

The manufacture of fine chemicals and pharmaceuticals generates in the order of 25–100 times more waste than product [52]. Inorganic salts account for the bulk of the waste and are most often produced by neutralization of acidic or basic solutions [53]. Salts can pollute soil and ground water, lower the pH of atmospheric moisture and they may contribute to acid dew or acid rain [6]. For cleaner production, their minimization is essential and hence our concentration on new processes, such as the etherification (discussed in Sect. 2.6.3.1) and hydrogen transfer reduction (Sect. 2.6.3.2), that avoid salt formation and the use of salts.

The use of high-temperature water as a reaction medium can be beneficial in that regard. For reactions necessitating addition of acid or base, less agent is usually required for high temperature processes than for those at and below 100 °C and the reactions often proceed more selectively. At the end of the process, the requirement for less neutralizing agent lowers the formation of salt [6].

2.7.5
Resin-based Adsorption Processes

From the foregoing, microwave heating in pressurized systems facilitates organic reactions in aqueous media. Normally, the products would be recovered by extraction with organic solvent. The aqueous phase would become saturated with the organic solvent (and the solvent with water), complicating disposal and offsetting environmental benefits gained through the use of water as the reaction medium in the first place.

To avoid this, we have employed hydrophobic resins for concentration and isolation of the products from aqueous media [49]. Organics are retained on the resin and subsequently can be desorbed with solvents such as ethanol, which is useful for "green" chemistry as it is readily recyclable, renewable and biodegradable. Nonextractive processes offer convenience, can be conducted with high throughput and afford low waste owing to ready disposal of the spent water, recyclability of the resin and the solvent used for desorption.

2.8
Metal-catalyzed Processes

The first reports of the use of microwave heating to accelerate Heck, Suzuki and Stille reactions on the solid phase [54] and in solution did not appear until 1996 [55]. Since then, many metal-catalyzed reactions have been performed within minutes by microwave heating in pressurized systems, sometimes with high regio- and enantioselectivity [56, 57].

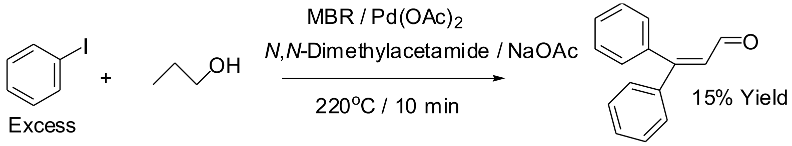
Palladium, its complexes and salts can catalyze transformations including oxidation, hydrogenation and rearrangement. One of the most useful applications of the metal though, is for activation of C–H bonds towards coupling reactions. The Heck reaction, which involves C–C coupling of an aryl or vinyl halide with an alkene in the presence of palladium derivatives has been the subject of intensive study [58]. Synthetic transformations of terminal alkynes via homo- or heterocouplings of the Glaser, Eglington, or Chodkiewicz–Cadiot type have also attracted interest.

Stille coupling involves the use of tin reactants. Tin is both toxic and difficult to remove. In an elegant extension of the pioneering work of Horvath [59], Curran and his coworkers prepared fluorous tin reactants that facilitated Stille reactions and enabled the convenient isolation and separation of products afterwards [60]. Probably owing to low solubility of fluorine-containing compounds in organic solvents, the reactions normally required about one day at 80 °C. With microwave heating, they were completed within minutes [61].

Typically, the Pd species for Heck couplings are homogeneous catalysts, stabilized by air-sensitive ligands. They present economic and environmental problems regarding separation, regeneration and reuse. These difficulties can be diminished with heterogeneous catalysts that are more easily recoverable from the reaction mixture. As mentioned in Sect. 2.6, a catalyst consisting of palladium metal deposited on porous glass tubing was developed for C–C coupling reactions [35]. It was used for reactions conducted continuously or batchwise and could be reused for repeat or different reactions. Reactions were performed in the presence of air, with either conventional heating or under microwave irradiation in the MBR.

Coupling of aryl halides with terminal acetylenes affords internal alkynes. Typically, high amounts of catalyst (1–5 mol % Pd) and coaddition of copper salts (also 1–5 mol % in Cu) are needed, thus reducing the industrial viability of such procedures. With palladium on porous glass, copper salts or activating ligands were not necessary. In contrast with Heck reactions involving halogen-containing reactants (usually aryl bromides or iodides), homocoupling of terminal acetylenes occurred readily and with excellent atom economy [35].

A new oxidation–dehydrogenation–Heck coupling catalyzed by Pd on porous glass or $Pd(OAc)_2$ also proceeded under microwave heating in the MBR (Scheme 2.18) [36]. With an excess of PhI, saturated alcohols including 1-propanol and 3-phenylpropanol afforded 3,3-diphenylpropenal as the major product, and *trans*-2,3-diphenylpropenal by a concerted process taking 10 min at 220 °C. The yields of this remarkable transformation were low, however, and further work into several aspects is required to make them more respectable.



Scheme 2.18 New cascade oxidation–dehydrogenation–double-Heck reaction.

Advantages of palladium on porous glass included ease of manufacture, mechanical strength and obviation of air-sensitive and temperature-sensitive ligands. Depending on the specific application, the catalyst also showed thermal stability and resistance to organic solvents. On occasions it was reused for repeat or different reactions. Turnover numbers in the order of 15,000 were achieved for Heck reactions in high-temperature water (with either Et_3N or NaOAc as base). However, some of the support dissolved and an alternative material may be advantageous for such conditions [35].

2.9
Pressurized Microwave Systems Developed by Others for Organic and Organometallic Chemistry

This account has been written from a personal perspective and thus has focused almost exclusively on the development and applications of the CMR and MBR. In that context, the numerous significant contributions of others are beyond the present scope and have been discussed comprehensively by the author elsewhere [6, 33, 34]. Nonetheless, they shall not be allowed to pass here without mention.

In their pioneering work, Gedye et al. used a domestic oven and commercially available screw cap pressure vessels [7, 62]. The pressure was measured and temperature was estimated through an infrared sensor, immediately after the power had been turned off. The reactor of Baghurst and Mingos [63] employed a glass vessel with a pressure-controlling device in a modified domestic oven. Pougnet and his coworkers constructed a range of equipment mainly for analytical applications. Among their developments was a pressure vessel [64] and a cylindrical microwave cavity that housed containers for chemical reactions and distillation [65]. Abramovitch et al. performed organic synthesis in a batch unit that incorporated a stirrer and temperature control, but the details were not disclosed [66]. Majetich and Hicks employed digestion bombs for 45 organic reactions in which a baristat was used to indirectly maintain the temperature below 200 °C [67].

Chemat et al. have reported several microwave reactors, including systems that can be used in tandem with other techniques such as sonication [68], and ultraviolet radiation [69]. With the microwave–ultrasound reactor, the esterification of acetic acid with *n*-propanol was studied along with the pyrolysis of urea. Improved results were claimed compared with those from conventional and microwave heating [68]. The efficacy of the microwave–UV reactor was demonstrated through the rearrangement of 2-benzoyloxyacetophenone to 1-(2-hydroxyphenyl)-3-phenylpropan-1,3-dione [69].

A specialized application of microwave-assisted organic synthesis involves the preparation of radiopharmaceuticals labeled with short-lived radionuclides, particularly for use in positron emission tomography [70–72]. This represented an excellent application of microwave technology, where the products must be prepared quickly and in high radiochemical yield, on a small scale.

Recent studies by Mingos and Whittacker into the optimum conditions have confirmed the benefits of pressurized systems for microwave chemistry [73].

2.10
Technical Considerations and Safety

As demonstrated above with examples, the CMR and MBR offer many advantages for synthetic processes that benefit from rapid heating and cooling. These systems are less useful and may be inappropriate when the reaction requires low temperature conditions throughout, when materials or reactions that are incompatible with microwave energy (e. g. reactions involving predominantly nonpolar organics) are to be employed or for reactions with “dry” media.

With microwaves, high rates of heating are usually desired. A difficulty can arise, however, when a material undergoing irradiation, possesses a dissipation factor that *increases* with temperature. In contrast with conventional heating, microwave energy is then absorbed more efficiently with temperature and the rate of temperature rise accelerates. Although, this phenomenon can be beneficial for maintaining high temperatures for catalysts, a thermal runaway can result unless the temperature is carefully monitored and the power controlled.

On the other hand, solvents usually show a *decrease* in dielectric constant with temperature. Efficiency of microwave absorption diminishes with temperature rise and can lead to poor matching of the microwave load, particularly as fluids approach the supercritical state. Solvents and reaction temperatures should be selected with these considerations in mind, as excess input microwave energy can lead to arcing. If allowed to continue unchecked, arcing could result in vessel rupture or perhaps an explosion, if flammable compounds are involved. Therefore it is important in microwave-assisted organic reactions, that the forward and reverse power can be monitored and the energy input be reduced (or the load matching device adjusted) if the reflected power becomes appreciable.

In the MBR, the applicator of plate steel was an important safety feature in the possible event of vessel rupture or explosion. Temperature and pressure measurements, stirring, infinitely variable control of microwave power input, the cold-finger, as well as a pressure relief valve, have all contributed significantly to the safety and reliability of the system.

Safety issues have been discussed comprehensively, in an earlier review [33]. At time of writing, more than two thousand reactions have been conducted with a range of solvents, times and temperatures in the CMR and MBR without accident or injury.

2.11
Conclusion

From tentative beginnings, microwave-assisted organic chemistry has become a field, experiencing exponential growth and commanding its own dedicated, international conferences. The number of papers in peer-reviewed journals stood at two in 1986, 220 in mid-1995 [33] and was well over 1000 by 2002. Commercial microwave reactors have been introduced, which have found applications for research and manufacture of high-value low-volume chemicals. They meet the objectives set out in Sect. 2.1, regarding measurement and control of reaction conditions, failsafe procedures, advantages unavailable with conventional equipment and capabilities for scaling up and scaling down chemical processes.

The CMR and MBR are capable of operation in the presence of organic solvents. They have extended the useful operating temperature range for low-boiling organic solvents and have facilitated the development of new chemical processes that require moderate temperatures. Although debate continues to rage on the existence or otherwise of so-called “nonthermal microwave effects” [74–76], the principles of microwave chemistry now are well understood [33, 34].

Economic and safety considerations encourage minimal stockpiling of chemicals and avoiding transportation of hazardous substances. These increasing demands offer many opportunities for microwave chemistry in the development of environmentally benign methods for the preparation of intermediates, specialty chemicals and pharmaceuticals [6]. It appears likely that within the next few years, individual chemical reactors will be required for diverse tasks and will need to be easily relocated as community pressure mounts to restrict movement of chemicals by road. Advantages sought will include quick start up and shut down, high yield, low holding capacity, almost complete elimination of waste, with the potential for accidents during transportation and storage being avoided by just-in-time, point-of-use production.

The MBR and CMR are portable, multipurpose and self-contained, features that could become increasingly important in this regard. Their capabilities for rapid throughput and the materials of construction enable easy cleaning for reuse and promote short turnaround times. Safety advantages include control and method of energy input, low volumes undergoing reaction at one time and opportunities for remote, programmable operation.

Acknowledgments

The author is particularly indebted to the following dedicated coworkers, whose efforts have helped to convert dreams into reality: A. F. Faux, T. Cablewski, R. W. Trainor, K. D. Raner, J. S. Thorn, L. Bagnell, U. Kreher, L. Mokbel and F. Vyskoc.

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3
Nonthermal Effects of Microwaves in Organic Synthesis

Laurence Perreux and André Loupy

Microwave (MW) activation as an unconventional energy source has become very popular and useful technology in organic chemistry, as shown recently in an exhaustive review [1]. The annual number of publications on microwave-assisted organic chemistry is growing rapidly with more than thousand publications in print since the pioneering work of Gedye [2] in 1986 (Fig. 3.1).

Most of these publications describe important accelerations of a wide range of organic reactions especially when performed under solvent-free conditions. The combination of solvent-free reaction conditions and microwave irradiation leads to large reductions in reaction times, enhancement of yield, and, sometimes [3, 4] in selectivity with several advantages of an eco-friendly approach, termed “green chemistry”.

Many of these reports are, however, based on inaccurate or unfounded comparisons with classical conditions which do not enable unequivocal conclusions to be drawn about the effects of microwaves. For this reason, apparent contradictions and controversies have appeared in the literature [5–7]. To try to rationalize all of these results it is necessary to propose a plausible interpretation of effects based on accurate

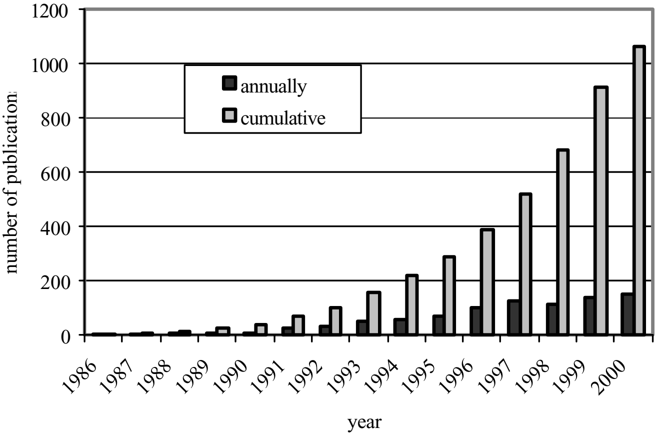


Fig. 3.1 The number of publications dealing with microwave irradiation in organic synthesis during the period 1986–2000.

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

and reliable data resulting from strict comparisons of reactions performed under similar conditions (reaction medium, temperature, time, pressure) except for microwave irradiation or conventional heating [3, 8, 9]. A monomode microwave reactor should preferably be used, because this enables wave focusing (reliable homogeneity of the electric field) and accurate control of the temperature (by use of optical fiber or infrared detection) throughout the reaction [3, 9]. This makes it possible to use both types of activation with similar temperature-profile increases. On the basis of such strict comparisons it becomes possible to make an educated judgment about the suitability, or otherwise, of microwave irradiation depending on reaction type and experimental conditions.

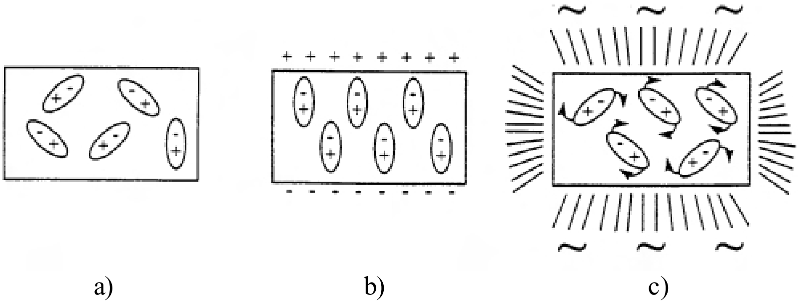
3.1
Origin of Microwave Effects

The acceleration of reactions by exposure to microwaves results from material–wave interactions leading to thermal effects (which can easily be estimated by temperature measurement) and specific (not purely thermal) effects. Clearly, a combination of these two contributions can be responsible for the effects observed.

Thermal effects (dielectric heating) can result from dipolar polarization as a consequence of dipole–dipole interactions of polar molecules with the electromagnetic field. They originate in dissipation of energy as heat, as an outcome of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at each alternation of the electric field at a very high frequency ($\nu = 2450$ MHz) [10, 11] (Scheme 3.1).

This energy dissipation in the core of materials results in a much more uniform temperature than classical heating. Classical thermal phenomena (conduction, convection, radiation, etc.) only play a secondary role in the *a posteriori* equilibration of temperature.

In this range of frequency charge–space polarization [12] can also occur and can be of prime importance with semiconductors, because it affects materials which con-



Scheme 3.1 Effects of the surrounding electric field on the mutual orientation of dipoles: (a) without constraint; (b) submitted to a continuous electric field; and (c) submitted to an alternating high frequency electric field.

tain free conduction electrons. This phenomenon is essential for heating of solid particles, more or less magnetic, such as a variety of mineral oxides or metallic species.

For liquid products (solvents), only polar molecules selectively absorb microwaves, because nonpolar molecules are inert to microwave dielectric loss. In this context of efficient microwave absorption it has also been shown that boiling points can be higher when solvents are subjected to microwave irradiation rather than conventional heating. This effect, called the "superheating effect" [13, 14] has been attributed to retardation of nucleation during microwave heating (Tab. 3.1).

Tab. 3.1 Boiling points (°C) of some polar solvents under the action of MW irradiation in the absence or presence of a nucleation regulator.

Solvent	*Boiling point*	*Microwave exposure*		
		Multimode [11, 12]	*Monomode (100 W)*	*Monomode + boiling chips*
Water	100	105	100	100
1-Heptanol	176	208	180	176
Ethyl acetate	77	102	92	77
Chloroform	61	89	85	62
Cyclohexanone	155	186	168	155

It is clearly connected with the effect of stirring and the presence of a nucleation regulator [15]. It is also related to the microwave power. It has been shown that the effect is eliminated when the experiments are performed on well-stirred mixtures [16, 17] using low microwave power. It could be essentially a consequence of the absence of stirring, i. e. in closed vessels inside a domestic microwave oven.

3.2
Specific Microwave Effects

The origin of specific microwave effects is twofold – those which are not purely thermal and a special thermal effect connected with possible intervention of "hot spots".

One of the few theoretical papers trying to explain acceleration under the action of microwaves has recently been published by A. Miklavc [18]. He stated that large increases in the rates of chemical reactions occur because of the effects of rotational excitation on collision geometry. This could be cautiously considered when one has knowledge of the quasi-nil energy involved by microwave interaction according to Planck's law [$E = hc/\lambda = 0.3$ cal/mol].

Non-purely thermal effects (other than simple dielectric heating) can be foreseen to have multiple origins. These effects can be rationalized by consideration in terms of the Arrhenius law [19, 20] and can result from modification of each of the terms of this equation.

$$k = A\exp(-\Delta G^{\ddagger}/RT)$$

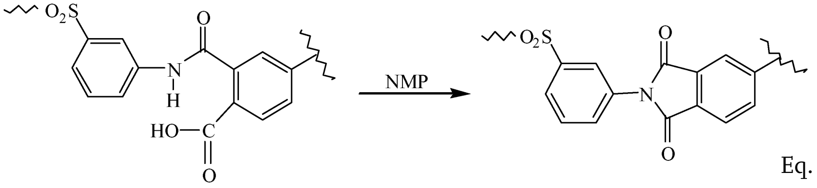
The first possibility is an increase in the pre-exponential factor, *A*, which represents the probability of molecular impacts. The collision efficiency can be effectively influenced by mutual orientation of polar molecules involved in the reaction. Because this factor depends on the frequency of vibration of the atoms at the reaction interface, it could be postulated that the microwave field might affect this. Binner et al. [21] explained the increased reaction rates observed during the microwave synthesis of titanium carbide in this way:

$$\mathrm{TiO_2} + 3\mathrm{C} \longrightarrow \mathrm{TiC} + 2\mathrm{CO}\uparrow$$

Calculations have shown that faster diffusion rates might be explained by an increase in the factor *A* with no change in activation energy.

A decrease in the activation energy $\Delta G^{\neq}$ is certainly a major effect. Because of the contribution of enthalpy and entropy to the value of $\Delta G^{\neq}$ (= $\Delta H^{\neq} - T\Delta S^{\neq}$), it might be predicted that the magnitude of the $-T\Delta S^{\neq}$ term would increase in a microwave-induced reaction, because organization is greater than with classical heating, as a consequence of dipolar polarization.

Lewis et al. [22] presented experimental evidence for such an assumption after measurements of rate constants at different temperatures for the unimolecular imidization of a polyamic acid (Eq. (1), Fig. 3.2, and Tab. 3.2).



Eq. (1)

NMP = N-methylpyrrolidinone

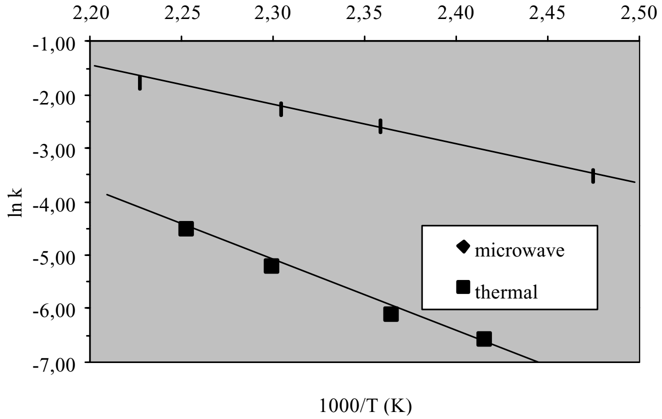


Fig. 3.2 First-order kinetic plots for microwave (MW) and thermal (Δ) activation of the imidization reaction.

Tab. 3.2 Results from the Arrhenius plots in Fig. 3.2.

Activation mode	*ΔH (kJ mol^{-1})*	*log A*
MW	57 ± 5	13 ± 1
Δ	105 ± 14	24 ± 4

The apparent activation energy is evidently substantially reduced. The same explanation, i.e. a decrease in $\Delta G^{\neq}$, was also proposed for the decomposition of sodium hydrogen carbonate in aqueous solution [23].

Intervention of localized microscopic high temperatures is possible [8, 14, 24], as advocated in sonochemistry to justify the sonochemical effect. There is an inevitable lack of experimental evidence, because we can necessarily have access to macroscopic temperature only. It has been suggested [6, 19] that, in some examples, MW activation could originate from hot spots generated by dielectric relaxation on a molecular scale.

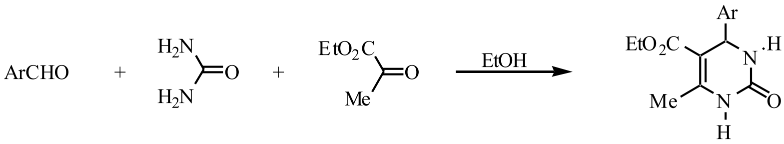
3.3
Effects of the Medium

Microwave effects should also be treated according to the reaction medium. Solvent effects are of particular importance [25, 26].

If polar solvents are used, either protic (e.g. alcohols) or aprotic (e.g. DMF, CH_3CN, DMSO etc), the main interaction might occur between MW and polar molecules of the solvent. Energy transfer is from the solvent molecules (present in large excess) to the reaction mixtures and the reactants, and it would be expected that any specific MW effects on the reactants would be masked by solvent absorption of the field. The reaction rates should, therefore, be nearly the same as those observed under the action of conventional heating (Δ).

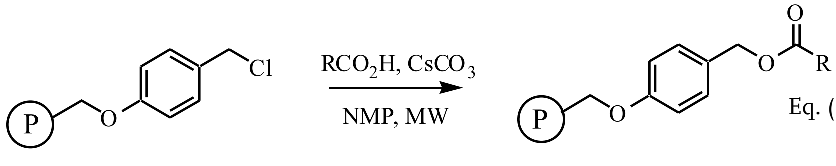
This is essentially true, as is evidenced by the rates of esterification in alcoholic media of propan-1-ol with ethanoic acid [27] or of propan-2-ol with mesitoic acid [28]. The absence of a specific microwave effect became apparent from several experiments carefully conducted in alcohols or in DMF under similar conditions but with microwave or classical heating [7].

More recently [29] the microwave-mediated Biginelli dihydropyrimidine synthesis (Eq. 2) was reinvestigated using a purpose-built commercial microwave reactor with on-line temperature, pressure, and microwave power control. Transformations performed with microwave heating at atmospheric pressure in ethanol solution resulted in neither a rate increase nor an increase in yield when the temperature was identical to that used for conventional thermal heating. The only significant rate and yield enhancements were found when the reaction was performed under solvent-free conditions in an open system.



Eq. (2)

A rapid and efficient procedure for flash heating by microwave irradiation has been described for attachment of aromatic and aliphatic carboxylic acids to chloromethylated polystyrene resins via their cesium salts (Eq. 3) [17].



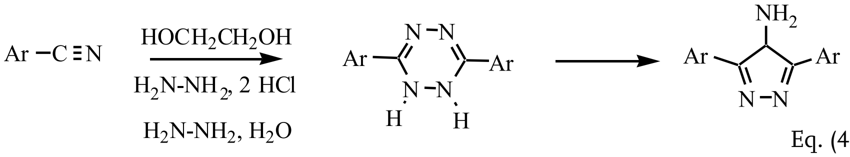
Eq. (3)

Significant rate accelerations and higher loadings are observed when the microwave-assisted and conventional thermal procedures are compared. Reactions times are reduced from 12–48 h with conventional heating at 80 °C to 5–15 min with microwave flash heating in NMP at temperatures up to 200 °C. Finally, kinetic comparison studies have shown that the observed rate enhancements can be attributed to the rapid direct heating of the solvent (NMP) rather than to a specific nonthermal microwave effect [17].

The synthesis of β-lactams from diazoketones and imines can be realized not only by using photochemical reaction conditions but also under the action of microwave irradiation. When the reaction was performed in *o*-dichlorobenzene at 180 °C, however, the rates of thermal and microwave-assisted formations of β-lactams were shown to be identical within the limits of experimental error (80–85 % conversion after 5 min) [30].

As described above, however, some rather small differences could be observed, taking into account the superheating effect of the solvent under the action of microwaves in the absence of any stirring. This probably occurs in the isomerization of safrole and eugenol in ethanol under reflux [31] (MW 1 h, Δ 5 h to obtain equivalent yields).

Superheating of the solvent was believed to be responsible of the observed rate enhancement under microwave irradiation in the synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles when conducted in 1,2-ethylene glycol as (polar) solvent (Eq. 4) [32].



Eq. (4)

The yields obtained by use of MW and Δ were clearly different for very short reaction times and became similar after 15 min at 130 °C (Fig. 3.3).

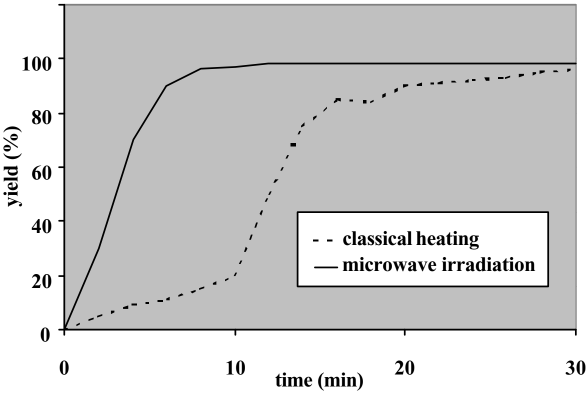


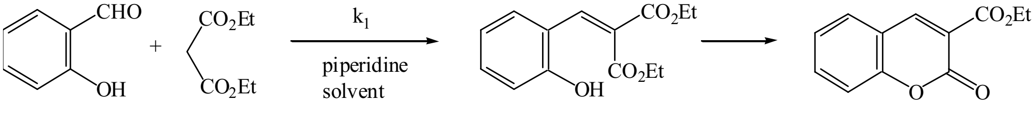
Fig. 3.3 Dependence of yield on time for 3,5-diphenyl-4-aminotriazole at 130 °C.

More interesting is the use of nonpolar solvents (e.g. xylene, toluene, carbon tetrachloride, hydrocarbons), because these are transparent to MW and absorb them only weakly. They therefore enable specific absorption by the reactants. If these reactants are polar, energy transfer occurs from the reactants to the solvent and the results might be different under the action of MW and Δ. This effect seems to be clearly dependent on the reaction and is, therefore, the subject of controversy. In xylene under reflux, for example, no MW-specific effects were observed for the Diels–Alder reaction [5] whereas important specific effects were described for aryldiazepinone synthesis [33].

These examples will be discussed and explained later, during discussion of the dependence of MW effects on reaction mechanisms.

Clearly, the effect of the solvent seems to be of great importance to the possibility of MW-specific effects. These could decrease when the polarity of the solvent is increased. This effect was shown in at least two studies by Berlan et al. [19] and, more recently, by Bogdal [34]. In the first study acceleration of a nonsymmetric Diels–Alder reaction under the action of MW was much more apparent in xylene than in the more polar dibutyl ether (Fig. 3.4).

In the second investigation [34], involving a coumarin synthesis by Knoevenagel condensation, supported by rate constant measurements and activation energy calculations, it was found that the effect of MW was more important when the reaction was conducted in xylene – it was noticeably reduced in ethanol (Eq. (5) and Tab. 3.3).



Eq. (5)

Microwave effects are most likely to be observed under solvent-free reactions [3]. In addition to the preparative interest of these methods in terms of use, separation, and economical, safe and clean procedures, absorption of microwave radiation

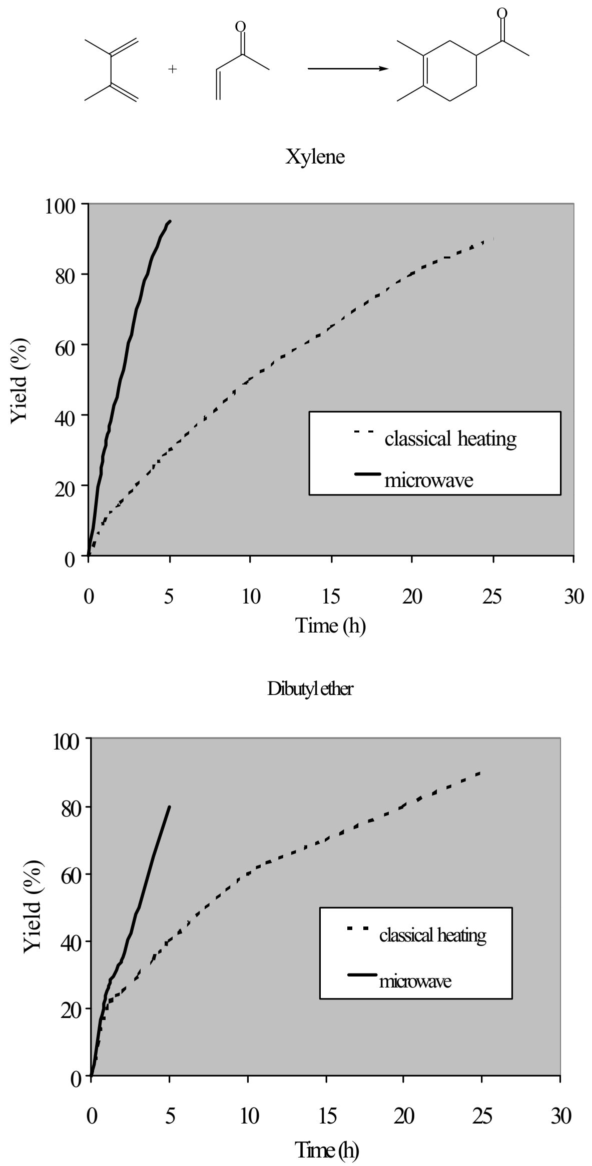
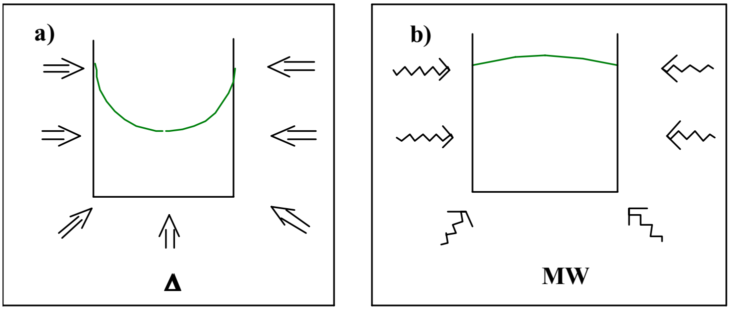


Fig. 3.4 Dependence of yields on time for a nonsymmetric Diels–Alder reaction at 95 °C.

Tab. 3.3 Rate constants (× 10^3) for the reaction depicted in Eq. (5).

T (°C)	*Xylene k_1 (mol L s^{-1})*		*Ethanol k_1 (mol L s^{-1})*	
	MW	Δ	*MW*	Δ
60	5.7	2.2	6.9	4.9
80	12.2	3.7	12.9	8.6



Scheme 3.2 Temperature gradients for materials subjected either to traditional heating (a) or to microwave irradiation (b).

should now be limited only to the reactive species. The possible specific effects will therefore be optimum, because they are not moderated or impeded by solvents.

They can be accomplished by three methods [3, 35]:

1. reactions between the neat reagents in quasi-equivalent amounts, requiring, preferably, at least one liquid phase in heterogeneous media and leading to interfacial reactions [36, 37]. Kinetic considerations for the reaction between two solids have been explained by considering the formation of a eutectic melt during the reaction [37];
2. solid–liquid phase-transfer catalysis (PTC) conditions for anionic reactions using the liquid electrophile as both reactant and organic phase and a catalytic amount of tetraalkylammonium salts as the transfer agent [38]; and
3. reactions using impregnated reagents on solid mineral supports (aluminas, silicas, clays) in dry media [3, 4, 39].

These procedures coupled with microwave activation have proven beneficial and have led to many success stories which are described in several reviews [3, 4, 39–42].

Some apparently specific effects can, however, arise from the supports. Mineral supports are usually poor heat conductors, i. e. significant temperature gradients can develop inside the vessels under the action of conventional heating, whereas they behave as efficient absorbers of microwave energy with consequently more temperature homogeneity (Scheme 3.2).

3.4
Effects of Reaction Mechanisms

Microwave effects result from material–wave interactions and, because of the dipolar polarization phenomenon, the greater the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature [43] is considered. In terms of reactivity and kinetics the specific effect has therefore to be considered according to the reaction mechanism and, particularly, with regard to how the

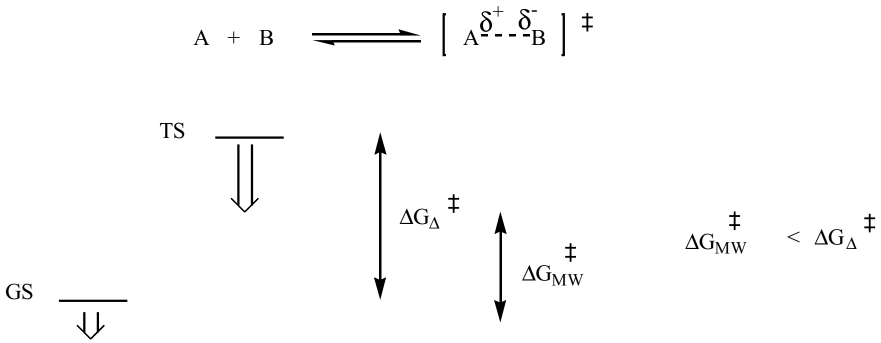


Fig. 3.5 Relative stabilization of a more polar TS when compared with the GS (polar mechanism).

polarity of the system is altered during the progress of the reaction. These assumptions are evidently connected to the Hughes–Ingold model [44] universally adopted to explain solvent effects [45] and especially the intervention of aprotic dipolar solvents.

Specific microwave effects can be expected for polar mechanisms, when the polarity is increased during the reaction from the ground state towards the transition state (as more or less implied by Abramovich in the conclusion of his review in 1991 [42]). The outcome is essentially dependent on the medium and the reaction mechanism.

If stabilization of the transition state (TS) is more effective than that of the ground state (GS), this results in enhancement of reactivity as a result of a decrease in the activation energy (Fig. 3.5), because of electrostatic (dipole–dipole type) interactions of polar molecules with the electric field.

3.4.1
Isopolar Transition-state Reactions

Isopolar activated complexes differ very little or not at all in charge separation or charge distribution from the corresponding initial reactants. These complexes are formed in pericyclic reactions such as Diels–Alder cycloadditions and the Cope rearrangement.

The polarity of ground and transition states are *a priori* identical, because no charges are developed during the reaction path. Following this rule, specific microwave effects would not be expected for these reactions, as has been verified when the reactions were performed in a nonpolar solvent [5, 6]. Solvent effects in these reactions are also small, or negligible, for the same reasons (Fig. 3.6) [46].

Such a conclusion is, nevertheless, connected with the synchronous character of the mechanism. If a stepwise process is involved (nonsimultaneous formation of the two new bonds), as for unsymmetric dienes and/or dienophiles or in hetero Diels–Alder reactions, a specific microwave effect could intervene, because charges are developed in the transition state. This could certainly be so for several cycloadditions [47, 48] and particularly for 1,3-dipolar cycloadditions [49]. Such an assumption has

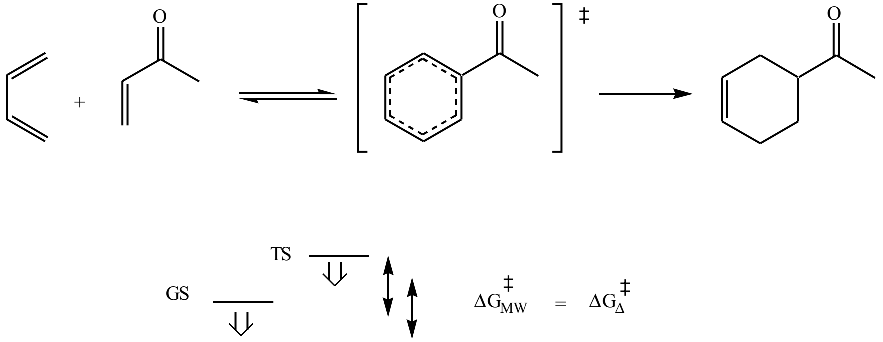
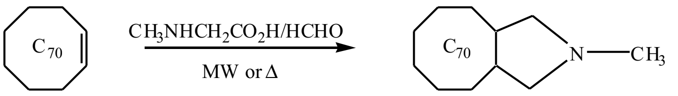


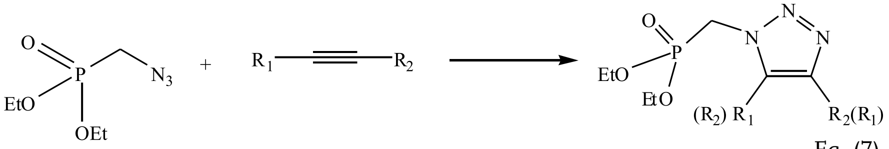
Fig. 3.6 Similar stabilization of isopolar TS and GS (concerted synchronous mechanism).

been verified experimentally and justified by considering theoretical calculations predicting an asynchronous mechanism in the cycloaddition of *N*-methylazomethine ylide to C_{70} fullerene [25] (Eq. 6).



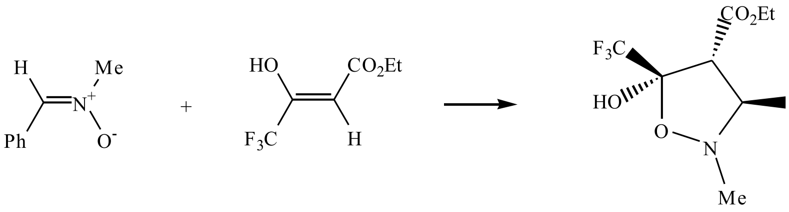
Eq. (6)

During the course of a study of the cycloaddition of azidomethyldiethylphosphonate with acetylenes and enamines leading to alkyltriazoles under solvent-free conditions we observed that specific effects can be involved, depending on the nature of the substituents on the dipolarophiles [50] (Eq. (7) and Tab. 3.4).



Eq. (7)

The synthesis of biologically significant fluorinated heterocyclic compounds has been accomplished by 1,3-dipolar cycloaddition of nitrones to fluorinated dipolarophiles [51]. This reaction was noticeably improved under solvent-free conditions and using microwave irradiation (Eq. (8) and Tab. 3.5).



Eq. (8)

Tab. 3.4 Thermal or microwave activation for the cycloaddition depicted in Eq. (7).

R_1	*R_2*	*Activation*	*Conditions* *t (min)*	 *T (°C)*	*Yield (%)*[a]
CH_3	$P(O)(OEt)_2$	Δ	20	90	5
		MW	20	90	78
H	CO_2Et	Δ	5	100	70
		MW	5	100	92
C_6H_5	CO_2Et	Δ	10	160	>98
		MW	10	160	>98
H	C_6H_5	Δ	30	120	40
		MW	30	120	>98
H	CH_2OH	Δ	30	100	40
		MW	30	100	>98

[a] The ratio of the amounts of the two isomers formed was identical for both activation conditions.

Tab 3.5 Thermal or microwave activation for the cycloaddition depicted in Eq. (8).

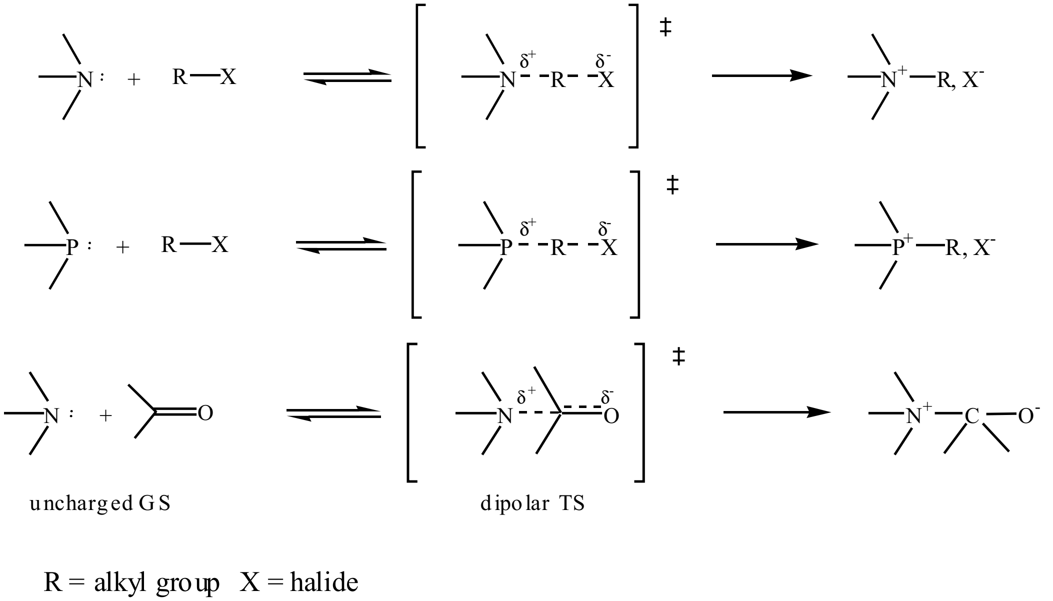
Activation	*Conditions* *Solvent*	 *Time*	 *Temp (°C)*	*Yield (%)*
Δ	Toluene	24 h	110	65
MW	None	3 min	119	98
Δ	None	3 min	119	64
Δ	None	30 min	119	98

It is apparent there is a definite advantage to operating under solvent-free conditions. The specific microwave effect is here of low magnitude, but evident, because after 3 min the yield increases from 64 to 98%. Prolongation of the reaction time with classical heating led to an equivalent result. The microwave effect is rather limited here, because of a near-synchronous mechanism.

3.4.2
Bimolecular Reactions between Neutral Reactants Leading to Charged Products

Typical reactions are amine or phosphine alkylation or addition to a carbonyl group (Scheme 3.3). In these examples, because of the development of dipoles in the TS, we are concerned with a polarity increase during the course of the reaction starting from the GS towards the TS. Favorable microwave effects are, consequently, expected.

The magnitude of these effects might be related to the nature of substituents α to N or P and to the structure of the leaving group, as exemplified by several observations that will be described and discussed below.

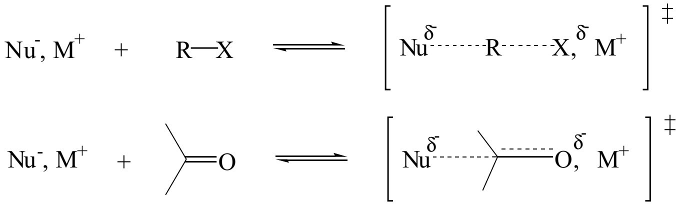


Scheme 3.3

3.4.3
Anionic Bimolecular Reactions Involving Neutral Electrophiles

These reactions comprise nucleophilic S_N2 substitutions, β-eliminations, and nucleophilic additions to carbonyl compounds or activated double bonds, etc. They involve the reactivity of anionic species Nu^- associated with counterions M^+ to form ion-pairs with several possible structures [52] (Scheme 3.4).

The transition states are composed of loose ion pairs in so far as they involve a charge-delocalized anion, thereby enhancing polarity compared with the ground states (in which the ion pairs are tighter), because of an increase in anionic dissociation as the more bulky product anion is formed. As a consequence, specific microwave effects, directly connected to polarity enhancement, should depend on the structure of reactive ion pairs in the GS:



Scheme 3.4

- If tight ion pairs (between two hard ions) are involved in the reaction the microwave-accelerating effect then becomes more important, because of enhancement of ionic dissociation during the course of the reaction as tight ion pairs (GS) are transformed into more polar loose ion pairs (TS).
- If, on the other hand, loose ion pairs (between soft ions) are involved, microwave acceleration is limited, because ionic interactions are only slightly modified from GS to TS.

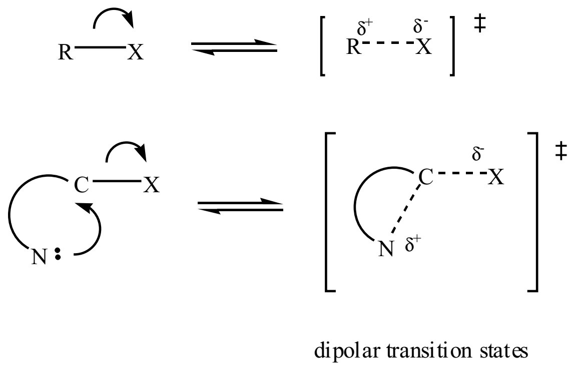
This duality in behavior of some S_N2 reactions can be foreseen and observed (*vide infra*) by comparing reactions involving hard or soft nucleophilic anionic reagents according to the cation and the leaving group.

3.4.4
Unimolecular Reactions

Entropic contributions to the acceleration of first-order reactions by microwaves should be negligible ($\Delta S^{\neq} = 0$). When ionization (S_N1 or E_1) or intramolecular addition (cyclizations) processes are involved a microwave effect could be viewed as resulting from a polarity increase from GS to TS, because of the development of dipolar intermediates (Scheme 3.5).

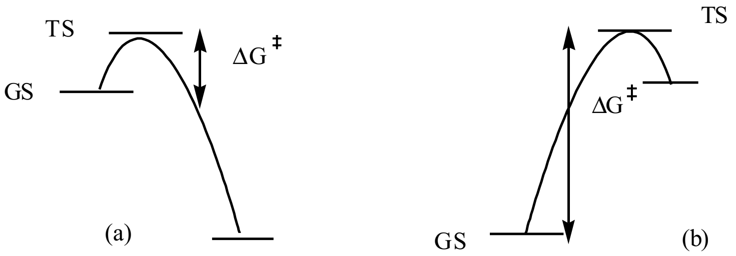
3.5
Effect of the Position of the Transition State Along the Reaction Coordinates

The position of the transition state along the reaction coordinates in relation to the well-known Hammond postulate [53] will now be considered. If the activation energy, $\Delta G^{\neq}$, of a reaction is only small the TS looks like the GS (it is depicted as a "reactant-like transition state"). Consequently, the polarity is only slightly modified between the GS and TS during the course of the reaction and only weak specific microwave effects can be foreseen under these conditions.



R = alkyl group X = halide

Scheme 3.5



Scheme 3.6 (a) Small $\Delta G \Rightarrow$ early TS $\Rightarrow$ little change in polarity TS/GS $\Rightarrow$ weak microwave effect. (b) Large $\Delta G \Rightarrow$ late TS $\Rightarrow$ important change in polarity TS/GS $\Rightarrow$ large microwave effect.

By way of contrast, a more difficult reaction implies a higher activation energy. The TS therefore occurs later along the reaction path and, consequently, the influence of polarity effects might be significantly larger. It might be assumed that a microwave effect should be more pronounced when the TS occurs later along the reaction coordinates (depicted more as a "product-like transition state") and is, therefore, likely to become more polar (Scheme 3.6).

This conclusion is in agreement with Lewis who stated that "slower reacting systems tend to show a greater effect under microwave radiation than faster reacting ones [54]".

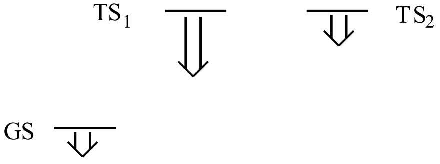
Consequently, a microwave effect can be important when steric effects are involved in a reaction, as exemplified by the increased magnitude of the effect for saponification of hindered mesitoic esters relative to benzoic esters [55] (*vide supra*).

3.6
Effect on Selectivity

The literature contains a few examples of increased selectivity [56–58] in which the steric course and the chemo- or regioselectivity of reactions can be altered under the action of microwave irradiation compared with conventional heating.

As a further consequence of these assumptions, it might be foreseen that microwave effects could be important in determining the selectivity of some reactions. When competitive reactions are involved, the GS is common for both processes. The mechanism occurring via the more polar TS could, therefore, be favored under the action of microwave radiation (Scheme 3.7).

Scheme 3.7 The more polar TS_1 is more stabilized by dipole–dipole interactions with the electric field and therefore more prone to microwave effects.



Langa et al. [26, 59, 60], while conducting the cycloaddition of *N*-methylazomethine ylide with C_{70} fullerene, proposed a rather similar approach. Theoretical calculations predict an asynchronous mechanism, suggesting that this phenomenon can be explained by considering that, under kinetic control, "microwave irradiation will favor the more polar path corresponding to the hardest transition state".

3.7
Some Illustrative Examples

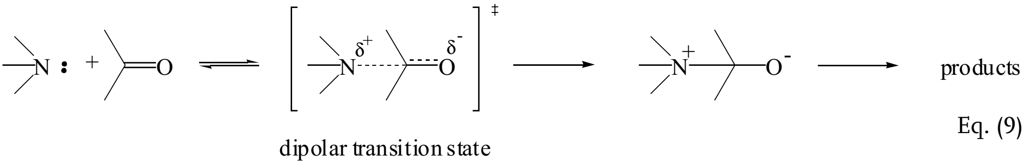
To illustrate these trends, we now present some typical illustrative examples. These have been selected because strict comparisons of microwave and classical heating activation were made under similar conditions (time, temperature, pressure, etc. ...) for the same reaction medium and using, preferably, a monomode system equipped with stirring. They mostly involve reactions performed under solvent-free conditions or, occasionally, in a nonpolar solvent, because these conditions are also favorable for observation of microwave effects.

3.7.1
Bimolecular Reactions between Neutral Reactants

These reactions are among the most propitious for revealing specific microwave effects, because the polarity is evidently increased during the course of the reaction from a neutral ground state to a dipolar transition state.

3.7.1.1 Nucleophilic Additions to Carbonyl Compounds

The most typical situation can be depicted for amine additions to a carbonyl group (Eq. 9)



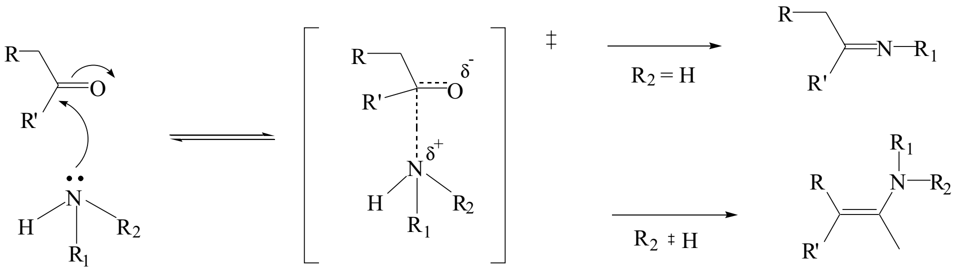
Eq. (9)

This example covers very classical processes such as syntheses of a wide variety of compounds including imines, enamines, amides, oxazolines, hydrazones, etc ...

Amines

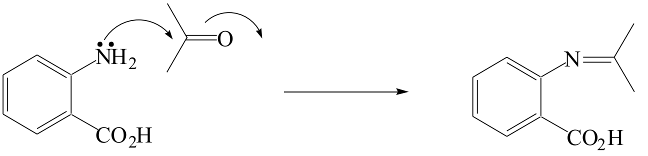
Imine or enamine synthesis

It has been shown by Varma et al. [61] that reaction of primary and secondary amines with aldehydes and ketones is substantially accelerated by microwaves under solvent-free conditions in the presence of montmorillonite K10 clay, affording high yields of imines and enamines (Eq. 10).



Eq. (10)

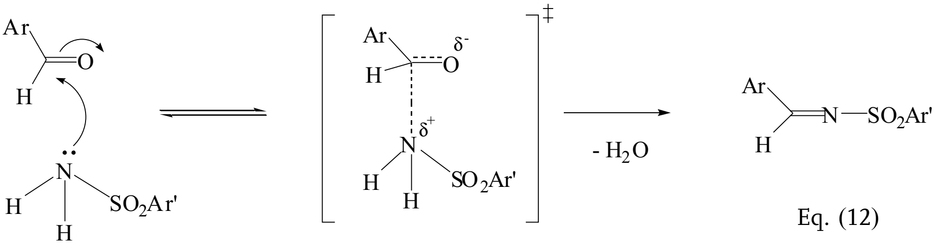
A more elaborate example is the Niementowski reaction to give access to quinazolinones and quinolines [62]. The determining step consists in the reaction of anthranilic acid with some amides or ketones (Eq. 11).



Eq. (11)

It has been shown that a mixture of an indoloquinazoline and anthranilic acid, adsorbed on graphite, led to cyclization in good yields after 30 min at 140 °C, in less time than for the purely thermal procedure under similar conditions, when a very poor yield is obtained even after 24 h [63].

A large specific microwave effect was observed in the solvent-free synthesis of *N*-sulfonylimines, a similar type of reaction [64] (Eq. 12).

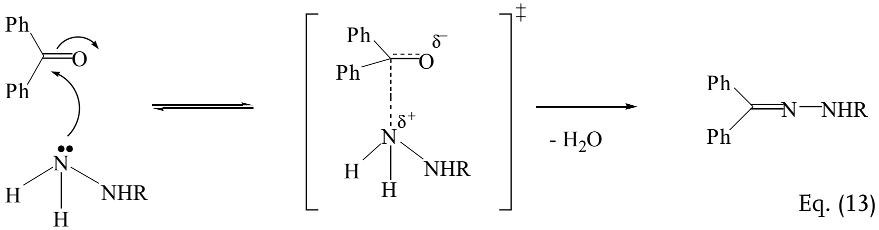


Eq. (12)

$Ar = C_6H_5$ $Ar' = p CH_3\text{-}C_6H_4$ 6 min 190 °C MW 91 % Δ 40 %

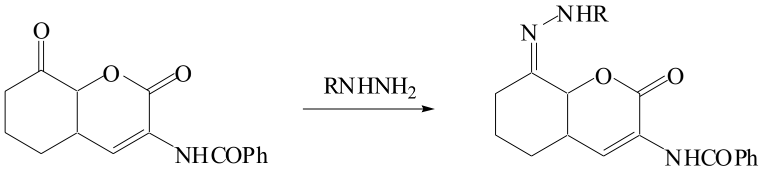
Hydrazone synthesis

In a typical example, a mixture of benzophenone and hydrazine hydrate in toluene resulted in 95% yield of the hydrazone within 20 min [65] (Eq. 13).



Eq. (13)

The hydrazone was subsequently treated with KOH under the action of MW to undergo Wolff–Kishner reduction (leading to $PhCH_2Ph$) within 25–30 min in excellent yields (95 %). As an extension, the reaction of neat 5- or 8-oxobenzopyran-2(1*H*)-ones with a variety of aromatic and heteroaromatic hydrazines is substantially accelerated by irradiation in the absence of any catalyst, solid support, or solvent [66] (Eq. 14).



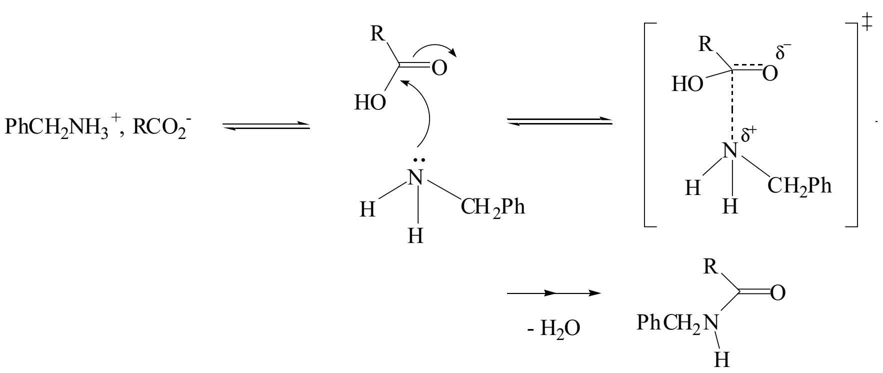
Eq. (14)

Ex: R = 4-nitrophenyl

MW	9min	130°C	98%
Δ	1h	130°C	80%

Amidation of carboxylic acids

Uncatalyzed amidations of acids have been realized under solvent-free conditions and with a very important microwave effect [67 a]. The best results were obtained by use of a slight excess of either amine or acid (1.5 equiv.). The reaction involves thermolysis of the previously formed ammonium salt (acid–base equilibrium) and is promoted by nucleophilic attack of the amine on the carbonyl moiety of the acid and removal of water at high temperature. The large difference in yields (MW ≫ Δ) might be a consequence of interaction of the polar TS with the electric field (Eq. (15 a) and Tab. 3.6).



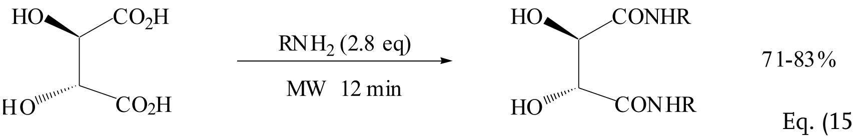
Eq. (15 a)

Tab. 3.6 Reaction of benzylamine with carboxylic acids at 150 °C for 30 min.

R	*Amine/acid*	*Yield (%)*	
		MW	Δ
Ph	1:1	10	10
	1.5:1	75	17
	1:1.5	80	8
$PhCH_2$	1:1	80	63
	1.5:1	93	40
	1:1.5	92	72
$CH_3(CH_2)_8$	1:1	85	49

If it is considered that at 150 °C water can be removed equally under both types of activation, the noticeable difference in yields is clearly indicative of an improvement in the nucleophilic addition of the amine to the carbonyl group when performed under the action of microwave irradiation, with important specific effects.

The preparation of aliphatic, aromatic, or functionalized tartramides directly from tartaric acid and amines under solvent-free conditions and microwave activation was very recently described [67 b].

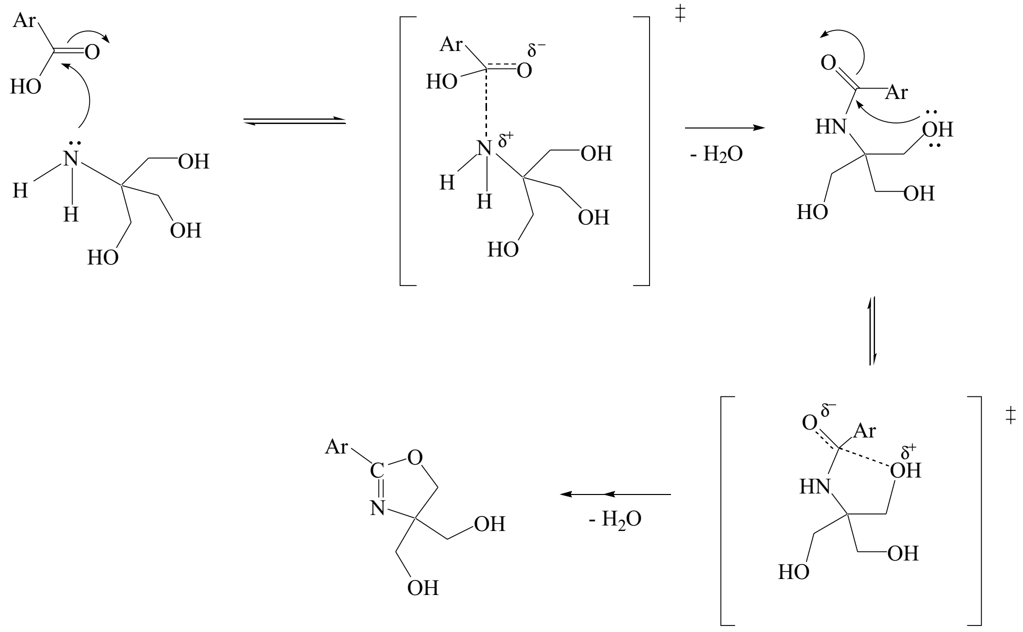


Eq. (15 b)

R = $PhCH_2$, n-$C_{10}H_{21}$, n-C_6H_{13}, n-C_4H_9, Ph

Synthesis of 2-oxazolines

Oxazolines can be readily synthesized by means of a noncatalyzed solvent-free procedure by two successive nucleophilic additions on a carbonyl group with the formation of an amide as an intermediate [68] (Eq. 16).

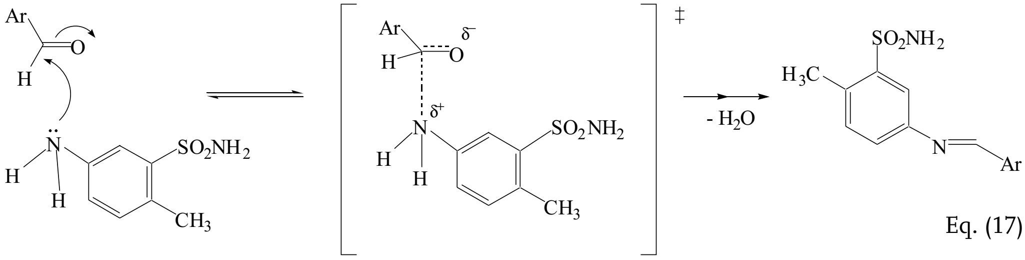


10 min 200 °C MW 80-95% Δ < 5%

Eq. (16)

Synthesis of aminotoluenesulfonamides

These compounds were prepared by reacting aromatic aldehydes with sulfonamides under the action of microwaves in the presence of a few drops of DMF to enable better energy transfer [69] (Eq. (17) and Tab. 3.7).



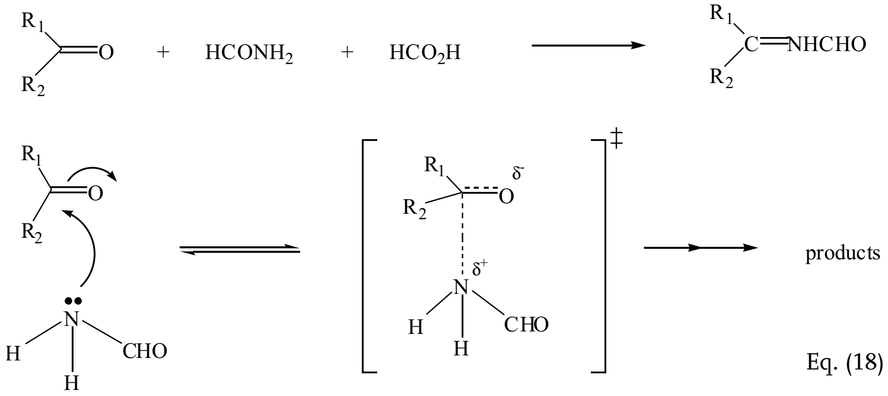
Eq. (17)

Tab. 3.7 Reaction of 5-amino-2-toluenesulfonamide with aromatic aldehydes.

Ar	*Time (min)*	*Yield (%)* *MW (no DMF)*	*MW (ε DMF)*	*Δ (ε DMF)*
p-$NO_2C_6H_4$	1	40	98	5
o-ClC_6H_4	2	22	90	6
5-NO_2-2-furyl	2	20	96	5

Leuckart reductive amination of carbonyl compounds

This reaction is well known but, unfortunately, using classical procedures is only possible under very harsh conditions (temperature 240 °C, sealed containers, long reaction times) and gives modest yields [70] (30%). Its difficulty constitutes a good challenge to check the effectiveness of microwave irradiation, because the mechanism involves a dipolar transition state [71] (Eq. (18) and Tab. 3.8) and this should also favor the involvement of a microwave effect.



Eq. (18)

Tab. 3.8 Microwave-mediated Leuckart reductive amination of carbonyl compounds in 30 min.

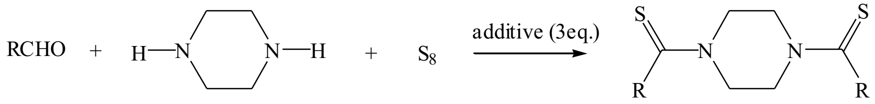
R_1	R_2	T (°C)	Activation	Yield (%)
Ph	Ph	202	MW	>98
		202	Δ	2
p-CH_3OPh	*p*-CH_3OPh	193	MW	95
		193	Δ	3
Ph	CH_2Ph	210	MW	95
		210	Δ	12

This study is a distinctive example of a pronounced microwave effect for a reaction occurring with a very late dipolar transition state.

Synthesis of 1,4-dithiocarbonyl piperazines

A series of 1,4-dithiocarbonyl piperazines has been synthesized from aldehydes, piperazine, and elemental sulfur under the action of microwave irradiation and solvent-free conditions. An important nonthermal effect of the radiation was revealed [72] (Eq. 19).

This is consistent with nucleophilic attack of neutral molecule (amine or sulfur) on the carbonyl compound, leading to a dipolar TS.



Eq. (19)

DMF	5min	100-102°C	MW 85%	Δ 48%
EG	5min	105-107°C	MW 80%	Δ 40%

Alcohols

Solvent-free esterification of fusel oil

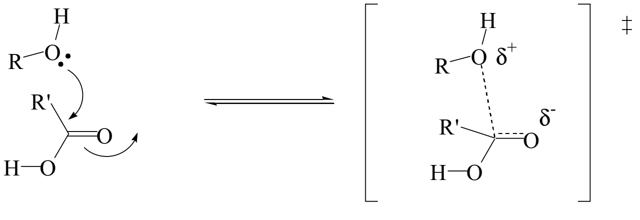
Fusel oil basically comprises a mixture of alcohols such as isopentanol and isobutanol. The synthesis of isopentyl stearate has been performed using both microwave irradiation and conventional heating under solvent-free conditions (Eq. 20) [73].

$$H_{35}C_{17}CO_2H + HO\text{-}(CH_2)_2\text{—}CH(CH_3)_2 \xrightarrow{\text{HOTs (10\%)}} C_{17}H_{35}CO_2\text{-}(CH_2)_2\text{—}CH(CH_3)_2$$

Eq. (20)

1min 20	90°C	MW	98%
1min 20	120°C	Δ	13%
10min	120°C	Δ	57%

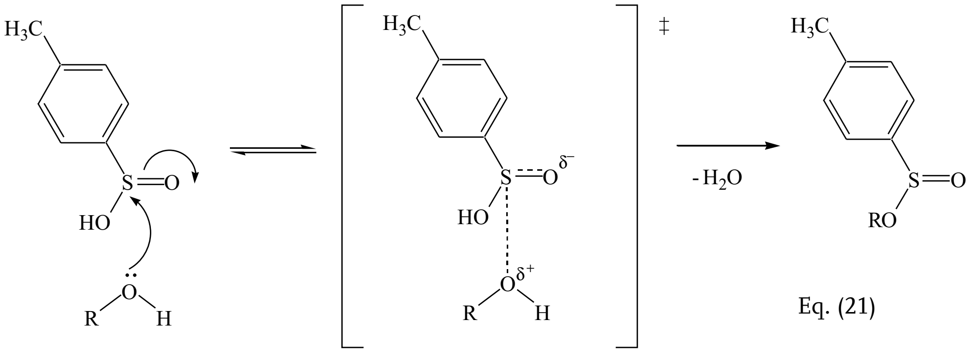
The very important specific microwave effect is consistent with the mechanism which involves the formation of a dipolar TS from neutral molecules (Scheme 3.8).



Scheme 3.8

Synthesis of alkyl *p*-toluenesulfinates

The reactions of aliphatic alcohols with *p*-toluenesulfinic acid are accelerated by microwave irradiation under solvent-free conditions in the presence of silica gel, to afford a high-yielding synthesis of *p*-toluenesulfinate esters [74] (Eq. 21).

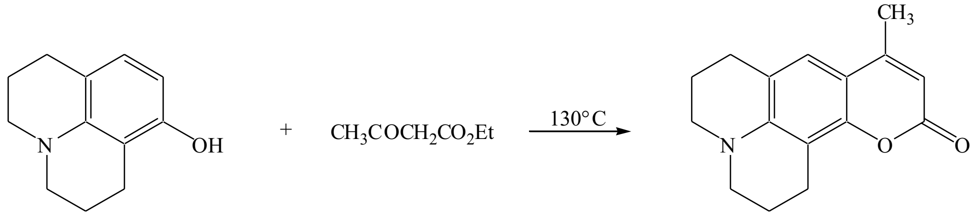


Eq. (21)

R = $(CH_3)_2CHCH_2$	70 °C	MW	1.5 min	95%	Δ	30 min	10%

Synthesis of aminocoumarins by the Pechmann reaction

Efficient synthesis of 7-aminocoumarins has been performed via the Pechmann reaction between *m*-aminophenols and *β*-ketonic esters. A comparative study of this procedure showed that use of microwave irradiation reduced the reaction time from several hours, if conventional heating was used, to a few minutes only (Eq. 22) [75].

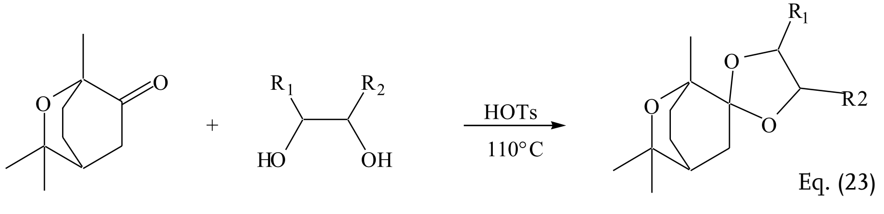


MW	12 min	62%
Δ	390 min	62%

Eq. (22)

Synthesis of cyclic acetals

Cyclic ketals (potential cosmetic ingredients) were obtained in excellent yields from a cineole ketone under the action of microwaves in solvent-free conditions or in toluene. The results reported compared very favorably with those obtained by use of conventional heating (Eq. (23) and Tab. 3.9) [76].



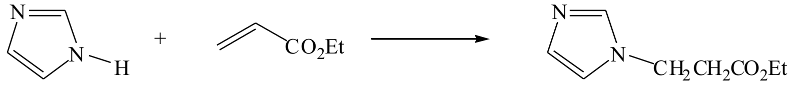
Eq. (23)

Tab. 3.9 Synthesis of ketal from cineole ketone and propylene glycol ($R_1 = CH_3$ $R_2 = H$).

Method	*Activation*	*Time (min)*	*Yield (%)*
Alumina	MW	30	78
	Δ	300	27
Toluene	MW	15	90
	Δ	360	30

3.7.1.2 **Michael Additions**

Imidazole has been condensed via a 1,4 Michael addition with ethyl acrylate by use of basic clays (Li^+ and Cs^+ montmorillonites) under solvent-free conditions with microwave irradiation [77] (Eq. 24).

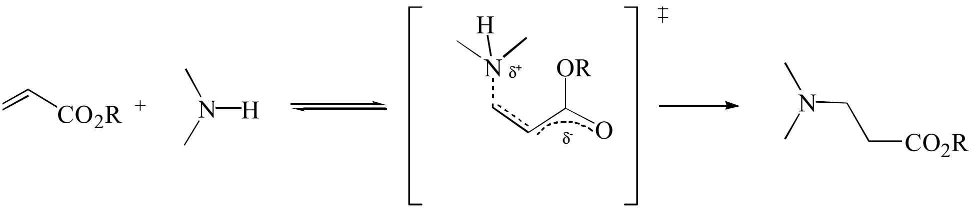


Eq. (24)

montmorillonite Li^+ 1 min 40 °C MW 40% Δ 0%

5 min 75 °C MW 72% Δ 27%

It was shown that microwave irradiation accelerated the 1,4 Michael addition of primary and cyclic secondary amines to acrylic esters, leading to several β-amino acid derivatives in good yields within short reaction times [78] (Eq. 25).



R = Me, Bu

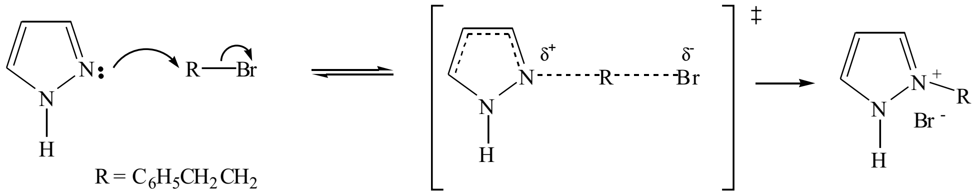
Eq. (25)

1,2 asymmetric induction of up to 76% diastereoisomeric excess was observed in reactions of several amines with β-substituted acrylic acid esters from d-(+)-mannitol, in the absence of solvent, after exposure to microwaves for 12 min [79].

3.7.1.3 **S_N2 Reactions**

Reaction of pyrazole with phenethyl bromide

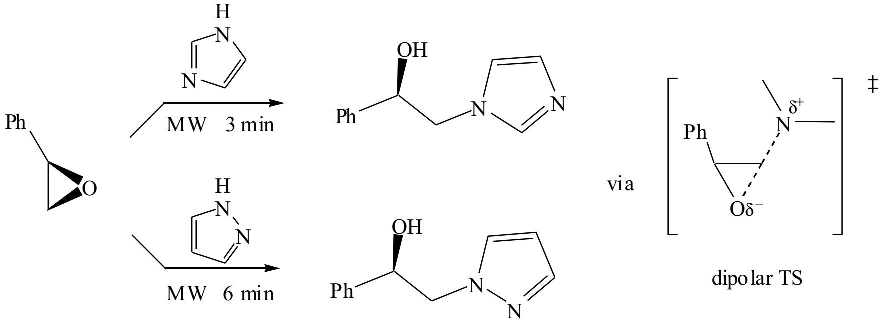
In the absence of base the phenethylation of pyrazole under solvent-free conditions is more rapid by far under the action of microwaves (8 min at 145 °C) when compared with Δ, which requires 48 h [80] (Eq. 26).



Eq. (26)

Ring opening of an epoxide by amines

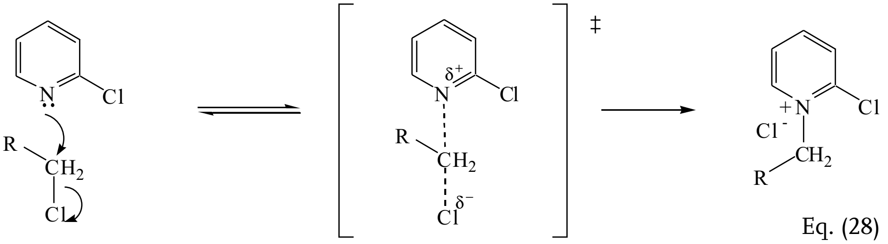
Microwave-assisted ring opening of (*R*)-styrene oxide by pyrazole and imidazole leads to the corresponding (*R*)-1-phenyl-2-azolylethanols. With pyrazole, use of microwave irradiation increases both chemo- and regioselectivity compared with the conventional heating [81] (Eq. 27).



Eq. (27)

N-alkylation of 2-halopyridines

A microwave- (focused waves) assisted procedure for *N*-alkylation of 2-halopyridines has been described; the noticeable microwave effect was indicative of a polar TS [82] (Eq. 28).

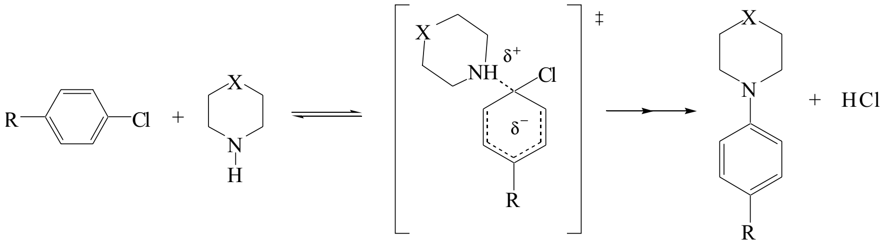


Eq. (28)

R = CO_2Et	165 - 170 °C	MW	40 min	80%
		Δ	23 h	46%
R = CN	165 - 170 °C	MW	40 min	56%
		Δ	50 h	10%

Nucleophilic aromatic substitutions

An expeditious microwave assisted S_NAr reaction with cyclic amines has been reported for activated aromatic substrates [83] (Eq. 29).



Eq. (29)

$R = CHO, NO_2$ $X = CH_2, O$

The reactions were performed in a heterogeneous medium using K_2CO_3 in ethanol (MW or Δ) or basic alumina in dry media to trap the hydrochloric acid formed. Because of the formation of a dipole in the TS, the microwave effect depicted in Tab. 3.10 was observed.

Tab. 3.10 S_NAr reaction between *p*-chlorotoluene and piperidine ($X = CH_2$, $R = CH_3$).

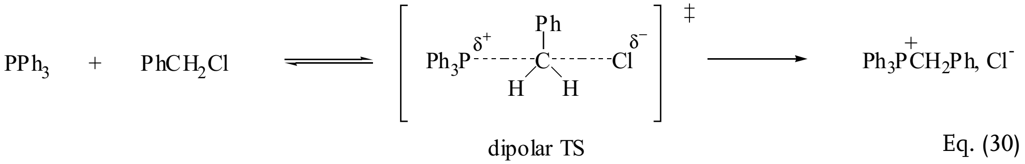
	Activation mode	*Conditions*		*Yields (%)*
K_2CO_3–EtOH	Δ	16 h	Reflux	60
	MW	6 min	Reflux	70
Basic alumina	MW	75 s	–[a]	92

[a] Undetermined, but certainly a very high temperature because the vessel was placed inside an alumina bath (prone to microwave absorption).

Synthesis of phosphonium salts

Using a domestic oven it was shown that reaction of triphenylphosphine with an organic halide is very rapid under the action of microwave irradiation. Reaction times were reduced to a few minutes only, compared with 30 min to 14 days when conventional heating is used [84].

Nucleophilic substitutions of benzyl chloride or benzyltrimethylammonium chloride as electrophiles with Ph_3P or Bu_3P as nucleophiles have been performed with accurate control of the power and temperature by use of a monomode reactor. The results were carefully compared under similar conditions with microwave or Δ activation [85] (Eq. (30) and Tab. 3.11).



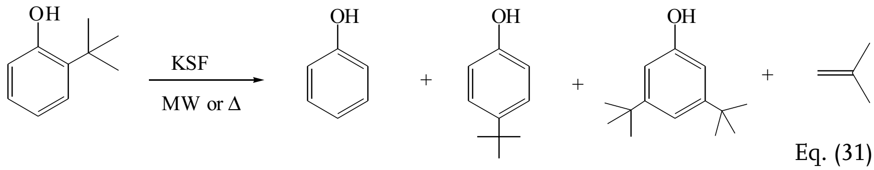
Eq. (30)

Tab. 3.11 Solvent-free benzylation of triphenylphosphine in 10 min.

Temp (°C)	*Yield (%)*	
	MW	Δ
100	78	24
150	94	91

Although the microwave effect is not appreciable at 150 °C, it becomes clearly apparent when the temperature is decreased to 100 °C. When delineating microwave effects, careful attention needs to be paid to the temperature level. If this is too high, the microwave effect will be masked and the temperature has to be minimized in order to start from a low yield under the action of Δ and therefore have the possibility of observing microwave enhancements.

This conclusion is in agreement with the kinetic results from Radoiu et al. [86] obtained for the transformation of 2- and 4-^{t}butyl phenols in the liquid phase in the presence of montmorillonite KSF as catalyst either under the action of MW or Δ (Eq. (31) and Tab. 3.12).



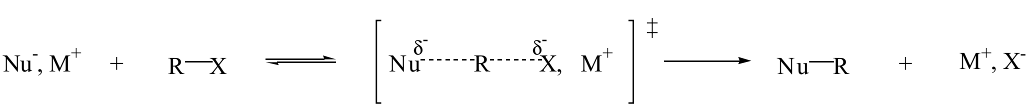
Eq. (31)

Tab. 3.12 Rate constants ($r°$) for the transformation of 2-^{t}butyl phenols under the action of MW or Δ according to temperature.

Temp (°C)	r°_{MW} *(10^3 s^{-1})*	r°_{Δ} *(10^3 s^{-1})*	$r^{\circ}_{MW/\Delta}$
22	1.5	0.07	21.6
75	3.2	1.2	2.7
105	10.3	7.1	1.5
198	21.0	20.0	1.1

3.7.2
Bimolecular Reactions with One Charged Reactant

The TS for anionic S_N2 reactions involves loose ion pairs as in a charge delocalized (soft) anion. On the another hand, the GS could involve a neutral electrophile and either tight or loose ion pairs depending on the anion structure (hard or soft) (Eq. 32).



$$\mathrm{Nu^-, M^+} + \mathrm{R{-}X} \rightleftharpoons \left[\overset{\delta^-}{\mathrm{Nu}}\cdots\cdots\mathrm{R}\cdots\cdots\overset{\delta^-}{\mathrm{X}},\ \mathrm{M^+}\right]^{\ddagger} \longrightarrow \mathrm{Nu{-}R} + \mathrm{M^+, X^-}$$

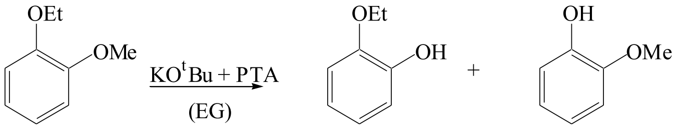
Eq. (32)

3.7.2.1 Anionic S_N2 Reactions Involving Charge-localized Anions

In this case, the anion being hard and with a high charge density, the reactions are concerned with tight ion pairs. During the course of the reaction, ionic dissociation is increased and hence polarity is enhanced from the GS towards the TS. Specific microwave effects should be expected.

Selective dealkylation of aromatic alkoxylated compounds

Selective de-ethylation of 2-ethoxyanisole is observed using KO^{t}Bu as the reagent in the presence of 18-crown-6 as the phase transfer agent (PTA). With the addition of ethylene glycol (E.G.), the selectivity is reversed and demethylation occurs (Eq. (33) and Tab. 3.13). If the involvement of microwaves is favorable in both examples, the second reaction should be more strongly accelerated than the first [87].



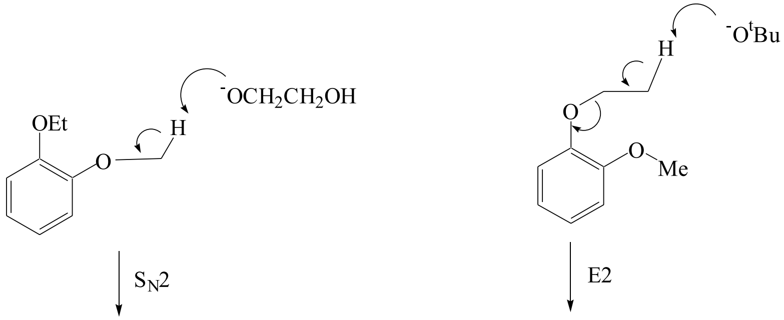
1 2 3

Eq. (33)

Tab. 3.13 Reaction of KO^{t}Bu with 2-ethoxyanisole in the presence of 18-crown-6 and, optionally, ethylene glycol.

Additive	*Time*	*Activation*	*Temp (°C)*	*1 (%)*	*2 (%)*	*3 (%)*
–	20 min	MW	120	7	0	90
–	20 min	Δ	120	48	0	50
E.G.	1 h	MW	180	0	72	23
E.G.	1 h	Δ	180	98	0	0

Demethylation results from the S_N2 reaction whereas de-ethylation occurred via the E2 mechanism (Scheme 3.9).

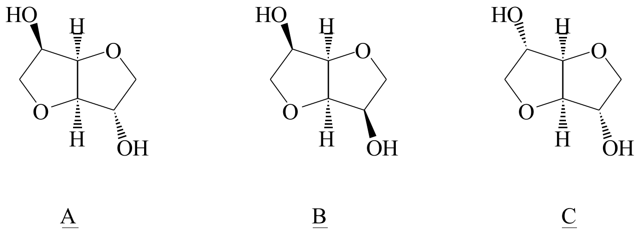


2 3

Scheme 3.9 Mechanisms for demethylation and de-ethylation of ethoxyanisole.

The microwave-specific effect is more apparent in the case of demethylation (S_N2). The microwave acceleration clearly is more pronounced with the difficulty of the reaction, thus constituting a clear example of an increased microwave effect with a more difficult reaction, indicative of a later TS position along the reaction coordinate. The microwave effect may also be connected to the more localized charge in the S_N2 transition state (three centers) when compared to that of β-E_2 (charge developed over five centers).

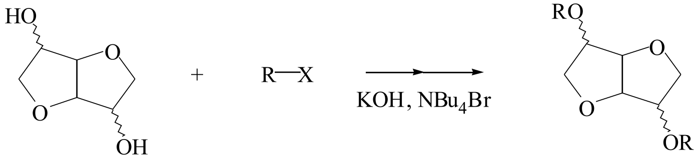
Alkylation of dianhydrohexitols under phase-transfer catalysis (PTC) conditions
Dianhydrohexitols, important by-products of biomass (Scheme 3.10), were dialkylated under PTC conditions in the presence of a small amount of xylene.



A B C

Scheme 3.10 Structure of 1,4 : 3,6-dianhydrohexitols. (A = isosorbide, B = isomannide, C = isoidide).

Dialkylations were attempted as model reactions before subsequent polymerizations and revealed very important specific microwave effects [88] (Eq. (34) and Tab. 3.14).

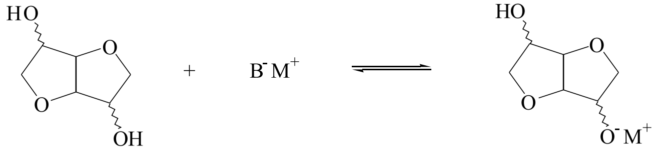


Eq. (34)

Tab. 3.14 Yield (%) from dialkylation of dianhydrohexitols under PTC conditions.

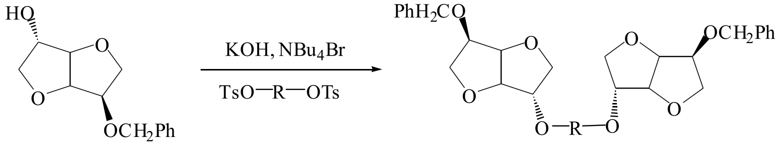
RX	*t (min), T (°C)*	*A*		*B*		*C*	
		MW	Δ	*MW*	Δ	*MW*	Δ
$PhCH_2Cl$	5, 125	98	13	98	15	97	20
$nC_8H_{17}Br$	5, 140	96	10	74	10	95	10

These observations are consistent with the reactive species being constituted from tight ion pairs between cations and the alkoxide anions resulting from abstraction of hydrogen atoms in A, B and C (Scheme 3.11).



Scheme 3.11

The reaction of monobenzylated isosorbide D with ditosylates (Eq. 35) is more subtle; the microwave-specific effect (Tab. 3.15) appeared when the temperature was lowered to 80 °C (modulated by the presence of cyclohexane) whereas it was masked by a higher temperature of 110 °C (maintained by the use of toluene) [89].



D E

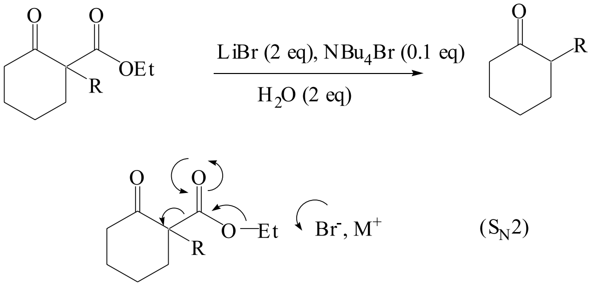
Eq. (35)

Tab. 3.15 Yield (% E) from reaction of monobenzylated isosorbide (D) with ditosylates for 15 min.

R	*T 110 °C (xylene)*		*T 80 °C (cyclohexane)*	
	MW	Δ	*MW*	Δ
$(CH_2)_8$	95	91	96	39
$(CH_2)_6$	91	90	96	45
$CH_2CH_2OCH_2CH_2$	92	92	91	36

The Krapcho reaction

Dealkoxycarbonylation of activated esters occurs classically under drastic thermal conditions [90]. It constitutes a typical example of a very slow-reacting system (with a late TS along the reaction coordinates) and is therefore prone to a microwave effect. The rate determining step involves a nucleophilic attack by halide anion and requires anionic activation, which can be provided by solvent-free PTC conditions under the action of microwave irradiation [91]. The above results illustrate the difficult example of cyclic *β*-ketoesters with a quaternary carbon atom in the *α* position relative to each carbonyl group (Eq. 36).



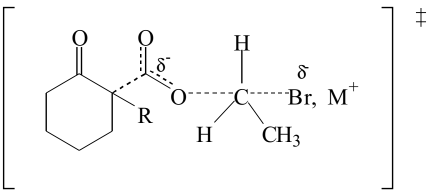
Eq. (36)

Some typical results are summarized in Tab. 3.16.

Tab. 3.16 The Krapcho reaction under solvent-free PTC conditions.

R	*Reaction conditions*		*Yields (%)*	
	t (min)	*Temp (°C)*	*MW*	Δ
H	8	138	96	<2
Et	15	160	94	<2
n-Bu	20	167	89	<2
n-Hex	20	186	87	<2
n-Hex	60	186	–	22
n-Hex	180	186	–	60

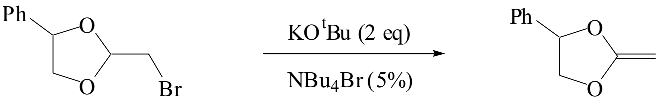
A definite microwave effect is involved when strict comparisons of MW and Δ activation are considered and is compatible with the mechanistic assumption that a very polar TS is developed (Scheme 3.12).



Scheme 3.12 Transition state for the Krapcho reaction.

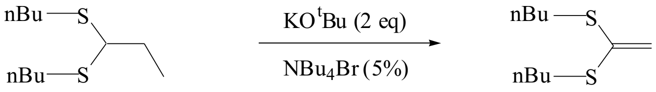
Anionic *β*-elimination

Ketene acetal synthesis by *β*-elimination of haloacids from halogenated acetals under well controlled conditions using thermal activation (Δ), ultrasound (US) or microwave irradiation [92] (MW) has been described. From a mechanistic point of view, as the TS is more charge delocalized than the GS and the polarity is enhanced during the course of the reaction, a favorable microwave effect can therefore be observed (Eqs. (37) and (38) and Scheme 3.13).



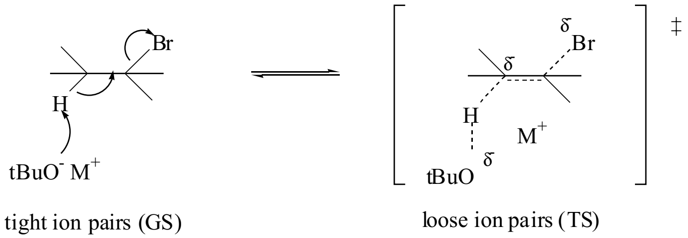
Eq. (37)

5 min 75 °C Δ: 36% US: 55% MW: 87%



Eq. (38)

25 min 90 °C Δ: 15% US: 45% MW: 79%



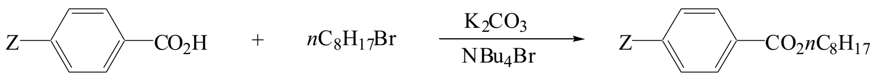
Scheme 3.13 Evolution of polarity in β-elimination.

3.7.2.2 Anionic S_N2 Reactions Involving Charge-delocalized Anions

Weak or nonexistent microwave effects are expected for these reactions as the GS and TS exhibit rather similar polarities since they both involve loose ion pairs.

Alkylation of potassium benzoate

Alkylation of several substituted benzoic acid salts with *n*-octyl bromide was performed under solvent-free PTC with excellent yields (95%) within a very short reaction time [93] (2–7 min). Oil bath heating (Δ) led to yields equivalent to those produced under the action of microwave irradiation, which thus revealed only thermal effects in the range of temperature used (145–202 °C) (Eq. 39).



Eq. (39)

Z = H	2.5 min	145 °C	Δ = MW	99 %
Z = OCH_3	2 min	145 °C		98 %
Z = CN	2 min	202 °C		95 %

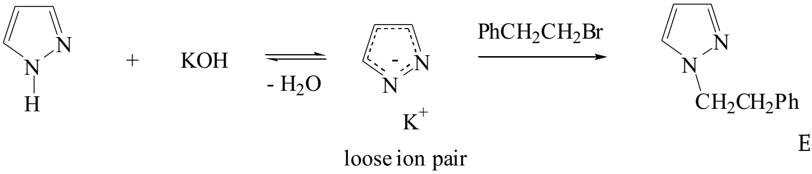
Conversely, when *n*-octyl bromide was used with the less reactive terephthalate species, which constitutes a “slow-reacting system”, the yield was raised from 20 to 84% under the action of microwaves compared with Δ, which can be attributed to a later TS along the reaction coordinates (Eq. 40).

Eq. (40)

R = nC_8H_{17} 6 min 175 °C MW 84% Δ 20%

Pyrazole alkylation in basic media [80]

A very important microwave-specific effect was evidenced in the absence of a base for the reaction of pyrazole with phenethyl bromide (reaction times: MW = 8 min, Δ = 48 h, Eq. 41). When the same reaction was performed in the presence of KOH, the microwave effect disappeared (*vide supra*, Eq. 26).



Eq. (41)

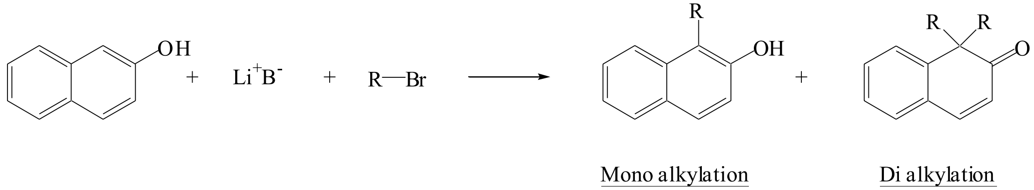
8 min 145 °C MW 64 % Δ 61 %

This effect could be predicted when considering the weak evolution of polarity between the GS and TS as the reactive species consist of loose ion pairs (involving a soft anion).

Selective alkylation of *β*-naphthol in basic media

Alkylations in dry media of the ambident 2-naphthoxide anion were performed under the action of focused microwave activation. Whereas the yields were identical to those obtained under the action of Δ for benzylation, they were significantly improved under microwave irradiation conditions for the more difficult *n*-octylation (a less reactive electrophilic reagent). No change in selectivity was observed, however, indicating the lack of influence of ionic polarization [94].

The absence or weakness of the microwave effect was assumed to be related to loose ion pairs involving the soft naphthoxide anion in the GS and a small change in polarity in an early TS. When the TS occurred later along the reaction coordinates (e.g. for *n*-octylation requiring a higher temperature), more polarity is developed and, consequently, the microwave effect could appear (Eq. (42) and Tab. 3.17 limited here to the lithiated base).



Eq. (42)

Tab. 3.17 C-alkylation of β-naphthol in the presence of lithiated base under solvent-free conditions.

RX	*Li^+ B^-*	*t (min)*	*Temp (°C)*	*Yield (%)*			
				MW		Δ	
				Mono C	*Di C*	*Mono C*	*Di C*
$PhCH_2Br$	LiOH	4	190	98	2	97	2
	LiO^tBu	4	137	9	91	8	88
$nC_8H_{17}Br$	LiOH	9	240	92	1	62	–
	LiO^tBu	10	200	27	56	7	20

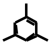
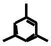
3.7.2.3 **Nucleophilic Additions to Carbonyl Compounds**

Saponification of hindered aromatic esters

This is a typical representative example of an enhanced microwave-specific effect related to the difficulty of the reaction, which presumably proceeds via a later and later TS. Whereas essentially thermal effects are observed (around 200 °C) with methyl and octyl benzoate, a microwave-specific effect is increasingly apparent with hindered esters and becomes optimal with mesitoyl octanoate (Eq. (43) and Tab. 3.18) [95].

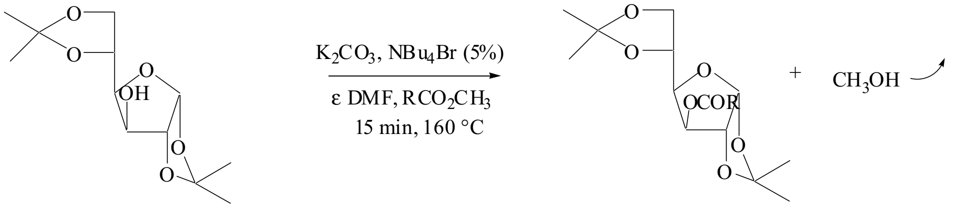
$$RCO_2R' \xrightarrow[\substack{\text{1) NaOH (2 eq), Aliquat 336 (10\%)} \\ \text{2) HCl (2N)}}]{\text{200 °C, 5 min}} RCO_2H \qquad \text{Eq. (43)}$$

Tab. 3.18 Solvent-free PTC saponification of aromatic esters.

R	*R*	*Yield (%)*	
		MW	Δ
Ph	Me	92	73
Ph	*n*-Oct	98	86
	Me	90	48
	*n*-Oct	97	39

PTC transesterification in basic medium

The microwave-assisted PTC transesterification of several carbohydrates in basic medium with methyl benzoate or laurate has been studied [96]. Small amounts of DMF were necessary to provide good yields within 15 min at 160 °C. Rate enhancements were compared to conventional heating (Δ) under the same conditions and specific microwave activation was mostly seen when the less reactive fatty compounds were involved (Eq. (44) and Tab. 3.19)



Eq. (44)

Tab. 3.19 Transesterification in 15 min at 160 °C in basic medium with methyl benzoate and laurate (monomode reactor, relative amounts 1 : 2 : 2).

R	***Yield (%)***	
	MW	**Δ**
Ph	96	21
$CH_3(CH_2)_{10}$	88	0

The reactive species under these conditions consist of tight ion pairs involving the alkoxide anion from the carbohydrate (charge localized anion). The less reactive long chain methyl laurate leads to a later TS along the reaction coordinates and the magnitude of the microwave effect is therefore increased.

Ester aminolysis in basic medium

Ester aminolysis, in general, occurs under harsh conditions that require high temperatures and extended reaction periods or the use of strong alkali metal catalysts. An efficient solid state synthesis of amides from nonenolizable esters and amines using KO^tBu under the action of microwave irradiation [97] has been described. The reaction of esters with octylamine was extensively studied to identify possible microwave effects [98] (Eq. (45) and Tab. 3.20).

$$RCO_2Et \;+\; CH_3(CH_2)_7NH_2 \xrightarrow[150\ °C]{10\ min} RCONH(CH_2)_7CH_3 \;+\; EtOH \nearrow$$

Eq. (45)

Tab. 3.20 Ester aminolysis with *n*-octylamine at 150 °C for 10 min.

R	***Base***	***Yield (%)***	
		MW	**Δ**
Ph	–	0	0
	KO^tBu	80	22
	KO^tBu	87	70
	336	87	70
$PhCH_2$	–	63	6
	KO^tBu + Aliquat 336	63	36

The microwave-specific effect is increased when the reaction is performed in the absence of a phase transfer catalyst, showing that the nature of the reactive species is of great importance in connection with ionic dissociation (Eq. 46).

$$CH_3(CH_2)_7NH_2 + KO^tBu \rightleftharpoons \underset{\text{tighter ion pair}}{CH_3(CH_2)_7NH^-, K^+} + {}^tBuOH\uparrow$$

$$CH_3(CH_2)_7NH^-, K^+ + R_4N^+, Cl^- \rightleftharpoons \underset{\text{looser ion pair}}{CH_3(CH_2)_7NH^-, R_4N^+} + K^+, Cl^- \qquad \text{Eq. (46)}$$

As expected, the tighter ion pair (RNH^-, K^+) exhibits the larger microwave effect. As an extension of this work, and in order to gain further insight, the effect of amine substituents was studied [99] in the reaction with ethyl benzoate (Eq. (47) and Tab. 3.21).

$$PhCO_2Et + RNH_2 \xrightarrow[10\ \text{min}/150\ °C]{{}^tBuOK} PhCONHR + EtOH\uparrow \qquad \text{Eq. (47)}$$

Tab. 3.21 Ethyl benzoate aminolysis with different amines at 150 °C for 10 min (relative amounts $PhCO_2Et : RNH_2 : KO^tBu = 1.5 : 1 : 2$).

R	*Yield (%)*			
	Without NR_4Cl		*With NR_4Cl*	
	MW	Δ	*MW*	Δ
Ph	88	73	90	83
$PhCH_2$	84	42	98	85
n-Oct	80	22	87	70

The microwave effects are clearly substituent dependent and, as in the former example, disappear by adding a phase transfer agent. When the substituent R is able to delocalize the negative charge on the amide anion (R = Ph), the ion pairs RNH^-, M^+ exist in a looser association. Consequently, a decrease in microwave effect is expected as the evolution from the GS ↔ TS occurs with only a slight modification of polarity in the ion pairs. Conversely, the microwave effect is optimal with the tighter ion pair (*n*$OctN^-$, K^+).

In a parallel study [100], it was shown that formamide, primary and secondary amines react with esters in the presence of potassium *tert*-butoxide under the action of microwave irradiation. Substituted amides are formed in yields (generally more than 70%) much higher than under the action of conventional heating (Eq. (48) and Tab. 3.22).

$$\begin{array}{l} RCO_2R' + HCONH_2 \xrightarrow[\text{MW}]{\text{tBuOK}} RCONH_2 + R'CO_2H \\ RCO_2R' + R_1R_2NH_2 \xrightarrow[\text{MW}]{\text{tBuOK}} RCONR_1R_2 \end{array}$$

Eq. (48)

Tab. 3.22 Ester aminolysis with different amines under the action of microwave irradiation during 3 min and with conventional heating.

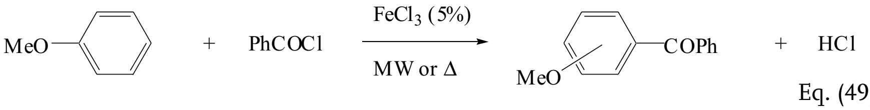
Ester	*Amine*	*T (°C)*	*Yield (%)*	
			MW	Δ
CH_3CO_2Et	$BuNH_2$	95	70	25 (2 day)
	Et_2NH	129	74	30 (1 day)
$C_6H_3CH_2CO_2Me$	$BuNH_2$	105	97	36 (1 day)
	Et_2NH	204	70	25 (6 h)

3.7.2.4 **Reactions Involving Positively Charged Reactants**

Relatively few comparative MW/Δ studies are presently available in this area.

Friedel–Crafts acylation of aromatic ethers

Solvent-free benzoylation of aromatic ethers has been performed under the action of microwave irradiation in the presence of a metallic catalyst, $FeCl_3$ being one of the most efficient [101]. With careful control of the temperature and other parameters, nonthermal microwave effects have not been observed either in terms of yields or isomeric ratios of the obtained products (Eq. 49).



Eq. (49)

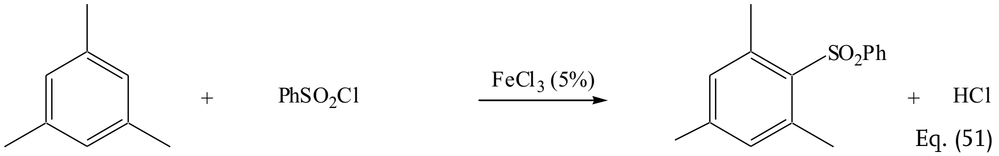
1 min   165 °C   yield = 95%   para/ortho = 94/6

The reactive species is the acylium ion resulting from abstraction of a chloride anion from benzoyl chloride (Eq. 50). This reagent comprises an ion pair formed between two large (soft) ions which are therefore associated as loose ion pairs. According to these assumptions, the absence of a microwave effect should be expected as the polarity evolution is very weak between the GS and TS (two loose ion pairs of similar polarities).

$$PhCOCl + FeCl_3 \rightleftharpoons \left\{ \begin{array}{c} Ph\overset{+}{C}{=}O,\ FeCl_4^- \\ \updownarrow \\ PhC{\equiv}O^+,\ FeCl_4^- \end{array} \right\}$$

Eq. (50)

This conclusion is also in agreement with the results obtained for the sulfonylation of mesitylene in the presence of metallic catalysts such as $FeCl_3$ [102] (5%) (Eq. 51)



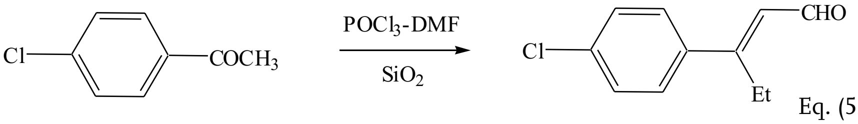
Eq. (51)

30 min 110 °C MW = 80% Δ = 78%

A nonthermal microwave effect was not observed when identical temperature gradients were produced by classical heating and microwave irradiation and if the reaction temperature was strictly controlled.

Formylation using Vilsmeier reagent [103]

Substituted acetophenones were irradiated in a domestic microwave oven with $POCl_3$–DMF/SiO_2 to give β-chlorovinylaldehydes in 2 min with yields of 75–88%. Under the same conditions, conventional heating lead to only 30–40% (Eq. 52).

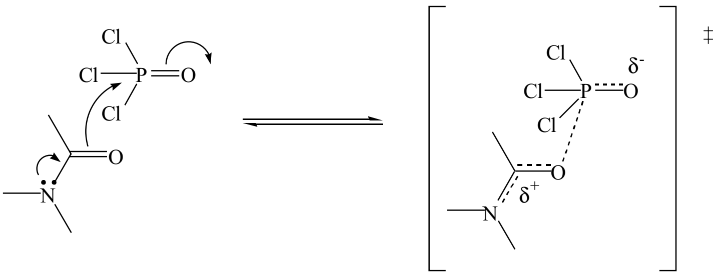


Eq. (52)

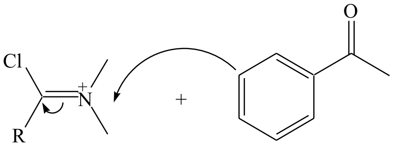
2min 75-78°C MW = 79% Δ = 35%

The specific microwave effect can be attributed to two different facts:

- improvement in the formation of chloroiminium species (so-called Vilsmeier reagent)

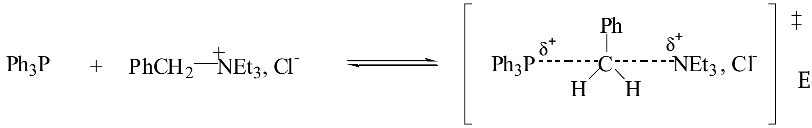


- enhancement of subsequent electrophilic aromatic substitution.



S_N2 reactions with tetralkylammonium salts

The S_N2 reaction of triphenylphosphine with triethylbenzylammonium chloride (the tertiary amine is thus the leaving group) was studied under solvent-free microwave conditions. The reaction occurred only under the action of MW [83] irradiation (Eq. 53).



$$Ph_3P + PhCH_2-\overset{+}{N}Et_3, Cl^- \rightleftharpoons \left[Ph_3\overset{\delta^+}{P}\cdots\cdots\overset{Ph}{\underset{H\ \ H}{C}}\cdots\cdots\overset{\delta^+}{N}Et_3, Cl^- \right]^{\ddagger}$$

Eq. (53)

tight ion pair very loose ion pairs

150 °C 10 min MW = 70% Δ = 0%

This effect is readily attributable to the very loose structure of the ion pairs in the TS (additionally involving delocalization in the phenyl groups of the phosphine) and which are therefore far more polar than the initial ion pairs in the GS.

3.7.3
Unimolecular Reactions

3.7.3.1 Imidization Reaction of a Polyamic Acid [22]

The polyamic acid (Fig. 3.7) precursor was prepared by adding stoichiometric amounts of 3,3,4,4-benzophenonetetracarboxylic acid dianhydride (BTDA) and diaminodiphenylsulfone (DDS). The solution in NMP was then submitted to either thermal or MW activation with accurate monitoring of the temperature (Scheme 3.14).

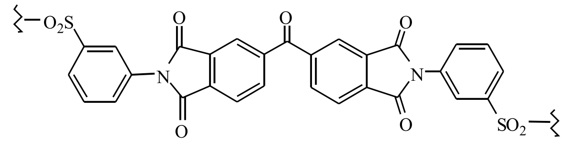
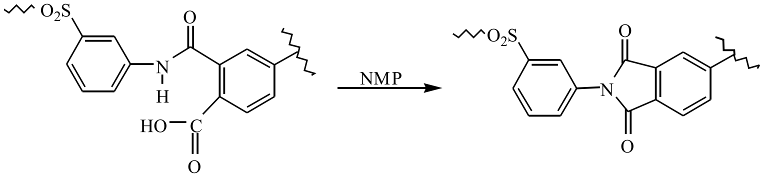


Fig. 3.7 Polyamic acid structure.



Scheme 3.14

Analysis of the kinetic parameters showed that the apparent activation energy for the reaction was reduced from 105 to 57 kJ mol^{-1} (Tab. 3.2). This observation is consistent with the polar mechanism of this reaction implying the development of a dipole in the transition state (Fig. 3.8) even when the reaction was performed in a polar solvent.

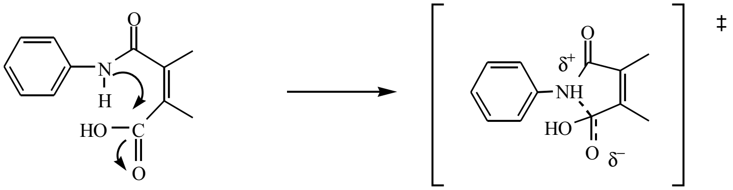
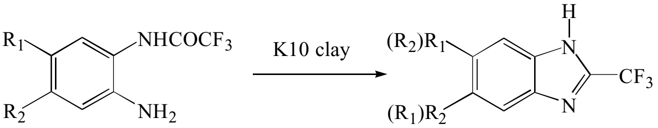


Fig. 3.8 Mechanism for the imidization reaction.

3.7.3.2 Cyclization of Monotrifluoroacetylated o-Arylenediamines

Cyclocondensation of *N*-(trifluoroacetamido)-*o*-arylenediamines leads to a series of 2-trifluoromethylarylimidazoles with good yields on montmorillonite K10 in dry media under the action of microwave irradiation within 2 min. Using conventional heating under the same conditions, no reaction was observed [104] (Eq. (54) and Tab. 3.23).

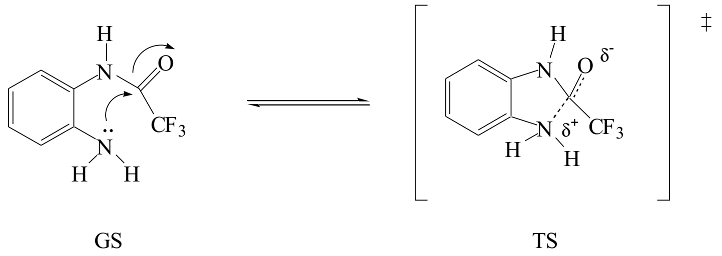


Eq. (54)

Tab. 3.23 Cyclization of monotrifluoroacetylated *o*-arylenediamines.

R₁	*R₂*	*Temp (°C)*	*Yield (%)* *MW (2 min)*	 *Δ (20 h)*
H	H	125	87	23
H	CH_3	127	84	19
NO_2	H	134	95	28

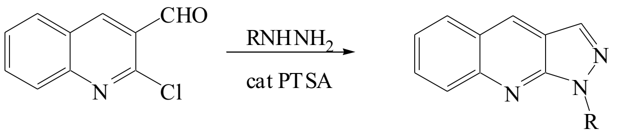
This observation is consistent with the assumptions of the authors predicting microwave effects when the polarity is enhanced in a dipolar TS. The kinetic rate-determining step consists of an intramolecular attack of the nitrogen lone pair on the carbon atom of the carbonyl moiety (Scheme 3.15).



Scheme 3.15 Mechanism of cyclocondensation.

3.7.3.3 Intramolecular Nucleophilic Aromatic Substitution

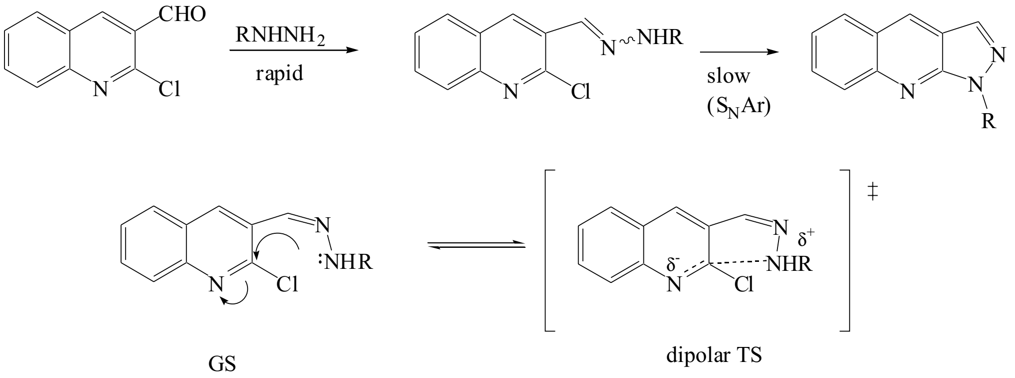
Pyrazolo-[3,4*b*]-quinolines and -pyrazoles have been synthesized by reacting *β*-chlorovinylaldehydes and hydrazine or phenyl hydrazine using a catalytic amount of *p*-toluenesulfonic acid (PTSA) under the action of microwave irradiation. The yields are much better than under the action of Δ using the same conditions [105] (Eq. 55).



Eq. (55)

R = H 1.5 min 127-130 °C MW = 97% Δ = 30%

The noticeable rate enhancement due to a microwave-specific effect is consistent with a reaction mechanism in which the kinetic rate-determining step is nucleophilic attack of an amino group on the chloroquinoline ring (Scheme 3.16).

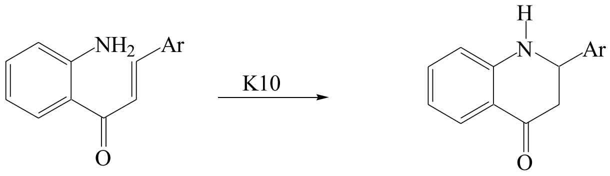


R = H, Ph

Scheme 3.16 Mechanism of internal S_NAr.

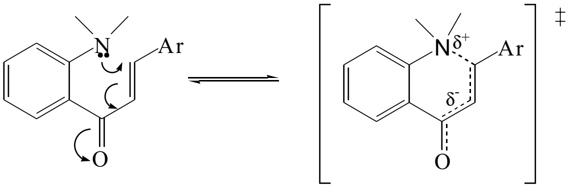
3.7.3.4 Intramolecular Michael Additions

ortho-Aminochalcones were cyclized to tetrahydroquinolones in dry media using K10 clay as the support under the action of microwave irradiation. The role of microwaves in accelerating the process was evidenced as a relatively extended reaction time was required under the action of conventional heating to obtain similar yields [106] (Eq. (56) and Scheme 3.17).



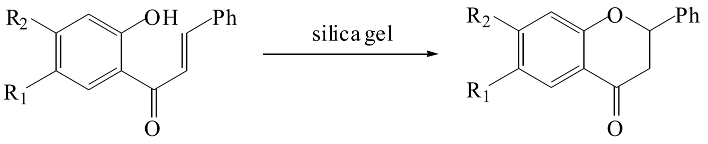
Eq. (56)

MW 1.5-2 min 110 °C 70-80%



Scheme 3.17 Mechanism of intramolecular Michael addition of an amino group.

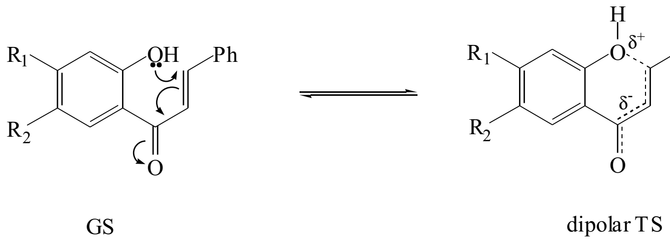
A similar study has been reported with *ortho*-hydroxychalcones in dry media on silica gel [107]. Conventional thermal cyclization, under the same conditions as for microwave irradiation, required a much longer reaction period (Eq. (57), Tab. 3.24, and Scheme 3.18).



Eq. (57)

Tab. 3.24 Intramolecular Michael addition of *o*-hydroxychalcones during 20 min at 140 °C.

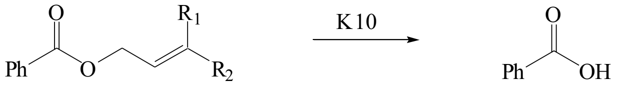
R_1	*R_2*	*Mode*	*Yield (%)*
H	H	MW	82
		Δ	44
CH_3O	H	MW	61
		Δ	22



Scheme 3.18 Mechanism of intramolecular Michael addition of an hydroxy group.

3.7.3.5 Deprotection of Allyl Esters

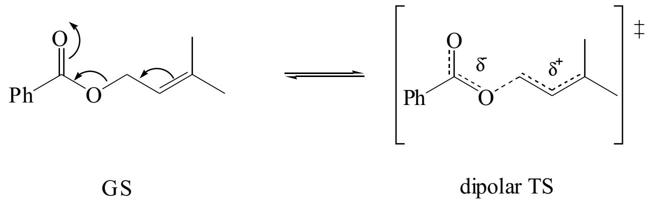
Carboxylic acids are regenerated from their corresponding substituted allyl esters on montmorillonite K10 using microwave irradiation under solvent-free conditions to afford enhanced yields and reduced reaction times when compared to thermal conditions [108] (Eq. 58).



Eq. (58)

$R_1 = H$ $R_2 = Ph$	110 °C	MW : 20 min	96%	Δ : 6 h	96%
$R_1 = R_2 = H$	110 °C	MW : 20 min	98%	Δ : 5 h	94%

This effect can also get again be rationalized via a mechanism with the intervention of a dipolar TS (Scheme 3.19).



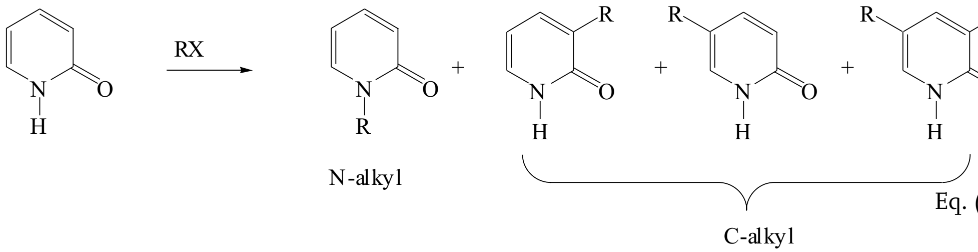
Scheme 3.19 Mechanism of deprotection of allyl esters.

3.8
Illustrative Examples of the Effects of Selectivity

Very few results on selectivity effects are available due to a lack of strict comparisons between microwave and Δ activation and in which kinetic details of reactions have been described. Reports of the effect of microwaves on selectivity up to 1997 have been reviewed by Langa et al. [57].

3.8.1
Benzylation of 2-Pyridone

Regiospecific *N*- or *C*-benzylations of 2-pyridone were observed under solvent-free conditions in the absence of base. The regioselectivity was controlled by the activation method (MW or Δ) or, when using microwaves, by the emitted power level or the leaving group of the benzyl halides [58] (Eq. 59).



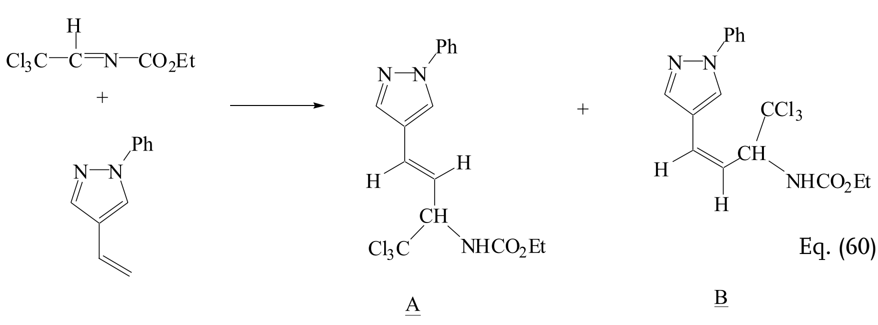
Eq. (59)

$PhCH_2Br$	5 min	196 °C	MW : > 98% C-alkyl	Δ : > 98% N-alkyl
$PhCH_2I$	5 min	180 °C	MW : > 98% C-alkyl	Δ : traces

To justify these results, it may be assumed that the TS leading to C-alkylation will be more polar than that responsible for *N*-alkylation. This assumption, however, presumes the existence of kinetic control (which is not ensured in this case).

3.8.2
Addition of Vinylpyrazoles to Imine Systems

Upon microwave irradiation, vinylpyrazoles react with *N*-trichloroethylidene carbamate to undergo addition to the imine system through the conjugated vinyl group [109] (Eq. 60).

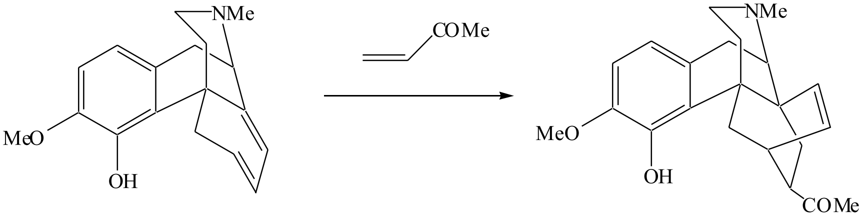


Eq. (60)

MW	15 min	125 °C	A : 70%	B : 15%

The use of microwave irradiation as an energy source is crucial to conduct the reaction and to avoid the decomposition or dimerization of the starting pyrazole, which are observed in the absence of microwave irradiation.

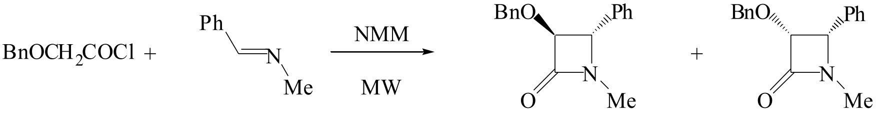
A similar conclusion has been drawn during an examination of the Diels–Alder reaction of 6-demethoxy-*β*-dihydrothebaine with methylvinylketone using microwave irradiation [110]. When performed under conventional heating conditions, extensive polymerization of the dienophile was observed whereas reaction is much more cleaner under microwave activation (Eq. 61).



Eq. (61)

3.8.3
Stereo Control of *β*-Lactam Formation [111, 112]

Formation of *β*-lactams by the reaction of an acid chloride, a Schiff base and a tertiary amine (Eq. 62) appears to involve multiple pathways, some of which are very fast at higher temperatures. When conducted in open vessels in unmodified microwave ovens, high level irradiation leads to preferential formation of the *trans* *β*-lactams (55%) whereas, at low power, the *cis* isomer was obtained as the only product (84%). The failure of the *cis* isomer to isomerize to the *trans* compounds is an example of induced selectivity.



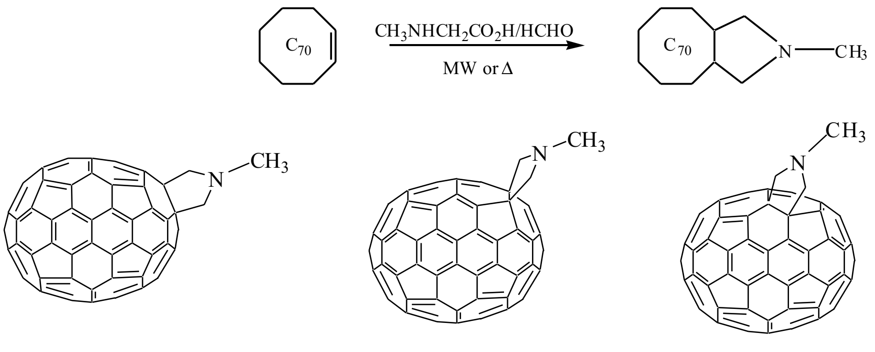
Eq. (62)

NMM= *N*-methylmorpholine

This effect has recently been explained by considering that under the action of microwave irradiation the route involving direct reaction between the acyl chloride and the imine competes efficiently with the ketone–imine reaction pathway, a situation highlighted by theoretical calculations [113]. In the other words and according to our assumptions, it can be stated that the transition state leading to the *trans* isomer therefore seems to be more polar than that leading to the *cis* compound.

3.8.4
Cycloaddition to C_{70} Fullerene

The regioselectivity of the cycloaddition of *N*-methylazomethine ylide to C_{70} was claimed to be slightly affected using microwave irradiation as the source. By choosing an appropriate solvent (*o*-dichlorobenzene, ODCB) and the emitted microwave power, the ratio 1a:1b is modified from 50:50 to 45:55 [26, 59] (Eq. (63) and Tab. 3.25).



1a (1-2 isomer) 1b (5-6) 1c (7-21)

Eq. (63)

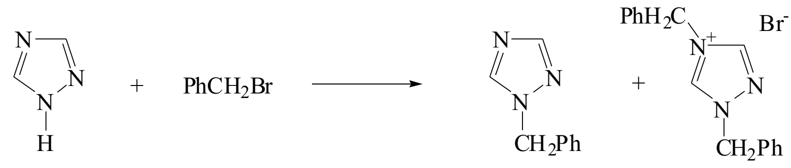
Tab. 3.25 Yields of monoadducts and isomer distribution for cycloaddition (Eq. 63) in ODCB at 180 °C.

Mode		*Time (min)*	*Yields (%)*	*% 1a*	*% 1b*	*% 1c*
MW	120 W	30	39	50	50	–
	180 W	30	37	45	55	–
	300 W	15	37	47	53	–
Δ		120	32	46	46	8

Theoretical calculations predict an asynchronous mechanism and suggest that the modification of the regiochemical outcome is related to the energies and hardness of the TS involved. Perhaps, in other words, the more polar TS are favored under the action of MW.

3.8.5
Selective Alkylation of 1,2,4-Triazole

Using MW irradiation under solvent-free conditions, it was possible to obtain regiospecific benzylation in position 1 of 1,2,4-triazole whereas only the 1,4-dialkylated product was obtained in poor yields under the action of conventional heating [114] (Eq. 64).



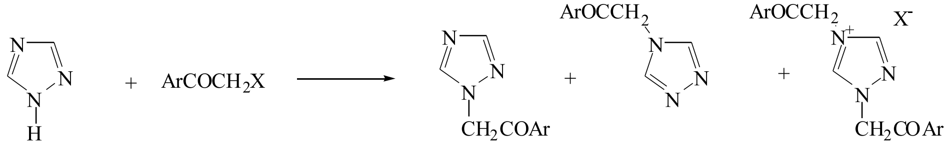
Eq. (64)

molar ratio 1:1 N_1 $N_{1,4}$

5 min 165 °C MW: yield 70% 100% N_1
Δ: yield 14% 100% $N_{1,4}$

This observation may be explained by the increased efficiency of the first benzylation (S_N2 reaction between two neutral reagents proceeding via a dipolar TS) under microwave conditions.

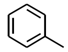
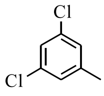
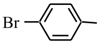
As an extension towards azolic fungicides, phenacylation was next examined. Under the action of microwave irradiation, exclusive reaction in position 1 (or equivalent 2) occurred whereas mixtures of N_1, N_4 and $N_{1,4}$ products were obtained by Δ under the same conditions [115] (Eq. (65) and Tab. 3.26).



N_1 N_4 $N_{1,4}$

Eq. (65)

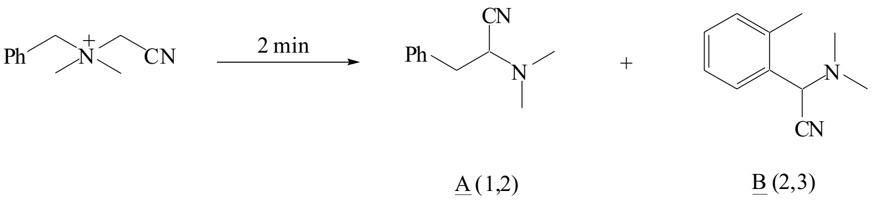
Tab. 3.26 Phenacylations of 1,2,4-triazole.

Ar	*X*	*Time (min)*	*Temp. (°C)*	*Mode*	*Global yield (%)*	*N_1*	*N_4*	*$N_{1,4}$*
	Cl	25	140	MW	90	100	–	–
				Δ	98	33	29	38
	Cl	20	140	MW	95	100	–	–
				Δ	98	38	27	37
	Br	24	170	MW	90	100	–	–
				Δ	98	38	28	34

As kinetic control was ensured, this clear microwave effect could possibly be due to a difference in polarity of the transition states, with apparently a more polar TS being formed when π attack by the nitrogen atom in position 2 is concerned. Theoretical calculations are in progress at the present time to try to confirm this assumption.

3.8.6
Rearrangement of Ammonium Ylides

Ammonium ylides can isomerize to (1,2) rearrangement products (Stevens rearrangement) or to (2,3) shift products (Sommelet–Hauser sigmatropic rearrangement) when allyl or benzyl are located on the nitrogen atom. A strong microwave effect is noticed (Eq. 66) [116].



A (1,2)

B (2,3)

Eq. (66)

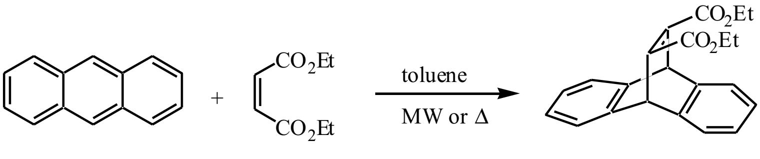
MW	yield 69%	A : B = 70 : 30
Δ	yield 56%	A : B = 10 : 90

Under similar profiles of raising in temperature, it was shown that the selectivity favoring 1,2 Stevens rearrangement is exemplified under the action of microwaves. A tentative explanation can be to consider that, under the action of radiation, the more polar mechanism (1,2 ionic shift) is favored when compared to less polar one (2,3 radical shift). Maybe this result is indicative of a competition between ionic and radical pathways.

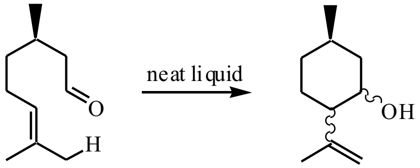
3.9
Concerning the Absence of Microwave Effects

The absence of a microwave effect can result from at least three different origins:

(a) a similar polarity of the transition state when compared to the ground state. This is the situation for synchronous mechanisms in some pericyclic reactions when performed in nonpolar solvents [5, 6] or in neat liquids (Eqs. 67 and 68).



Eq. (67)



Eq. (68)

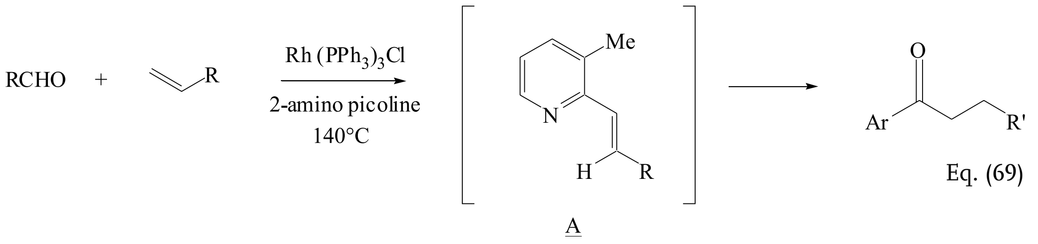
(b) a very early transition state along the reaction coordinates (cf. Hammond postulate) which cannot allow the development of polarity between the GS and TS (reactant-like). This will occur when the reactions are rather easy and do not require classically harsh conditions. This would be true for phthalimide syntheses by reacting phthalic anhydride and amino compounds [117], and chalcone syntheses by reacting aromatic aldehydes and acetophenones [118], etc. ... Slight differences can appear when performing the reaction in the presence of a solvent due to a superheating effect if no stirring is used.

(c) a too high temperature level, which may produce good yields in short reaction times under the action of conventional heating. In order to find evidence of microwave effects, it is necessary to reduce the temperature under conventional conditions in order to start from a rather poor yield (< 30–40%) to appreciate possible microwave activation. These cases have been revealed in some studies where a microwave effect appeared at relatively low temperatures but are masked at higher temperatures where yields of conventionally heated reactions are elevated [85, 86, 89].

3.10
Conclusions

We have proposed in this review a rationalization of microwave effects in organic synthesis based on medium effects and mechanistic considerations. If the polarity of a system is enhanced from the ground state to the transition state, it can result in an acceleration due to an increase in material–wave interactions during the course of the reaction. The most frequently encountered cases concern unimolecular or bimolecular reactions between neutral molecules (as dipoles are developed in the TS) and anionic reactions of tight ion pairs i.e. involving charge localized anions (leading to ionic dissociation in TS). They could be more important in the cases of a product-like TS in agreement with the Hammond postulate. By far the most useful situation is related to solvent-free conditions (green chemistry procedures) as microwave effects are not masked or limited by solvent effects, although of course, nonpolar solvents can always be used. Many types of carefully controlled experiments need to be performed, however, to evaluate the reality and limitations of this approach in order to make valid comparisons.

Finally, the magnitude of a specific microwave effect could be indicative of a polar mechanism or to access the rate-determining step in a procedure involving several steps. For instance, during the study of microwave effect in the solvent-free synthesis of ketones from aldehydes and terminal alkenes by Wilkinson complex [Rh (I) complex], a serious improvement was evidenced under the action of microwave when compared to classical heating (Eq. (69) and Tab. 3.27).



Eq. (69)

Tab. 3.27 Solvent-free hydroacylation of 1-alkenes with aldehyde.

R	*R*	*Time (min)*	*Yield (%)*	
			MW	Δ
C_6H_5	n-C_8H_{17}	30	95	30
C_6H_5	$CH_2C_6H_5$	10	84	30
n-C_6H_{13}	n-C_8H_{17}	10	61	30

This microwave effect is consistent with the fact that the rate-determining step may be certainly the generation of aldimine A from aldehydes and 2-amino 3-picoline. It is in agreement with the transition state develops a dipole and, consequently more polar than the ground state. To ascertain this hypothesis, it was effectively next shown that the reaction involving reaction with preformed aldimine A, no revealed any microwave effect [119].

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4

Organic Synthesis using Microwaves in Homogeneous Media

RICHARD N. GEDYE

4.1

Introduction

Although the ability of microwaves (MW) to heat water and other polar materials has been known for half a century or more, it was not until 1986 that two groups of researchers independently reported the application of MW heating to organic synthesis. Gedye et al. [1] found that several organic reactions in polar solvents could be performed rapidly and conveniently in closed Teflon vessels in a domestic MW oven. These reactions included the hydrolysis of amides and esters to carboxylic acids, esterification of carboxylic acids with alcohols, oxidation of alkyl benzenes to aromatic carboxylic acids and the conversion of alkyl halides to ethers.

Most of these reactions occurred much faster using MW irradiation (at increased pressure and temperature) than under conventional heating (ambient pressure, reflux), with rate enhancements ranging from 5 to 1200 times.

Shortly after these results were published, Giguere and coworkers reported dramatic reductions in reaction times in other MW-assisted syntheses, including Diels–Alder, Claisen rearrangements and ene reactions [2]. These reactions were also performed at elevated pressures, but sealed glass vessels (inside a bath packed with vermiculite) were used rather than Teflon.

It is to be noted that the reactions mentioned so far were performed under homogeneous conditions and, in most cases, using polar solvents, which are efficient absorbers of MW energy. Rate enhancements were attributed to the superheating of the solvent due to the elevated pressures generated in the closed vessels.

During the 15 years since these reports, a large number of synthetic applications of MW in organic. synthesis have been reported and these have been summarized in a number of reviews [3–10].

The use of dry media (solvent-free) conditions, in which the reactants are absorbed on inert solid supports, in MW-heated reactions, has received a considerable amount of attention recently and has been used in the synthesis of a wide range of compounds [11–16]. These reactions generally occur rapidly and the method avoids hazards, such as explosions, associated with reactions in solvents in sealed vessels in which high pressures may be generated. Also the removal of

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

solvents and their disposal are not required making the technique more environmentally friendly.

MW heated reactions in homogeneous media, using either neat reagents or in the presence of solvents, may also be performed at atmospheric pressure. This approach has been used particularly by Bose et al. [17]. (MORE Chemistry), who reported, for example, the rapid synthesis of heterocycles [18] in open vessels. Another approach, which avoids hazards due to the flammability of solvents, is to perform the reactions under reflux in a MW oven, which is modified to allow the reaction vessel to be attached to a reflux condenser outside the MW oven [7, 19]. It should be pointed out, however, that most of the available evidence shows that rate enhancements of MW heated reactions in homogeneous media at atmospheric pressure are small or nonexistent [19]. This will be discussed in more detail later in this review (see also Chapt. 5 of this book).

4.2
Reactions at Elevated Pressures

As mentioned previously, most of the earlier work on MW-assisted synthesis involved homogeneous reactions in closed Teflon or glass vessels [1–3, 20]. The obvious advantage of this technique is that reactions can be performed much more rapidly than under conventional heating (reflux), due to elevation of the boiling point of the solvent (or of the reactants in the absence of solvent) at increased pressures. The technique is particularly suitable for reactions which are normally very slow, requiring several hours, and in some cases days, of reflux under conventional conditions. Although slow reactions can also be accelerated by heating in conventional ovens or furnaces in sealed glass or stainless steel vessels, the rate of heating of the reaction mixture is slower than under microwave heating and temperatures and pressures are more difficult to control. Also, in conventional autoclaves heating is conductive and this results in substantial thermal gradients near the walls of the reaction vessel, which may result in decomposition or the formation of unwanted byproducts.

Teflon vessels are particularly suitable since they are transparent to MW and are resistant to attack by chemicals or solvents (both organic and aqueous). The high melting point of Teflon (320 °C) enables reactions to be performed relatively safely, although vessels have been known to expand or explode at high pressures, particularly when the temperature is also high [1, 7].

Until recently, the pressures used in MW reactions in sealed Teflon containers have been restricted to 600–700 kPa (6–7 atm) for safety reasons. However CEM [21] have developed computerized systems with pressure and temperature control using vessels capable of withstanding pressures of 1500 kPa or more. Teflon bombs produced by Parr [22] can accommodate pressures up to 8 MPa (80 atm) and temperatures up to 250 °C. However it has been reported that repeated use of the vessels above 150 °C can lead to distortions which reduce the safe pressure level [7]. For safety reasons, the vessels used in these higher pressure reactions are equipped with pressure release valves, designed to vent when the pressure approaches an unsafe level.

A continuous MW reactor (CMR), which operates by passing a reaction mixture through a pressurized tubular microwave-transparent coil and a MW batch reactor (MBR), have been developed by CSIRO in Australia and are used for organic synthesis on the laboratory scale [8]. The CMR can be operated at pressures up to 1400 kPa and temperatures up to 200 °C and the MBR at pressures and temperatures up to 10 MPa and 260 °C.

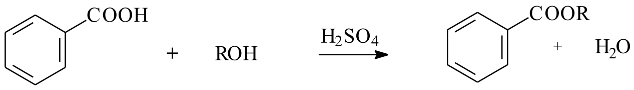
Milestone [23] have produced a range of MW reactor systems for organic synthesis, including a quartz or ceramic MW reactor (MRS) for high pressure (up to 4 MPa) and temperature reactions, designed for large volume batch synthesis and a multiple batch reactor MPR/HPR for up to 12 vessels, with volumes 2–270 mL for operation at 3.5–10 MPa.

These instruments, designed by CSIRO and Milestone, include, in addition to pressure and temperature measurement and control, a number of other features allowing for greater safety and reproducibility of reaction conditions, such as stirring to minimize temperature gradients, rapid cool-down at the end of the heating period and energy shut-down if temperatures or pressures exceed safe levels.

The pressure generated in a reaction vessel, and hence the rate enhancement, depends on a number of factors including the MW power level, the volatility of the solvent, the dielectric loss of the reaction mixture, the size of the vessel and the volume of the reaction mixture [7, 20]. Gedye et al. [20] found that, in the esterification of benzoic acid with a series of aliphatic alcohols (Scheme 4.1) in closed Teflon vessels, the most dramatic rate enhancements were observed with methanol (the most volatile solvent).

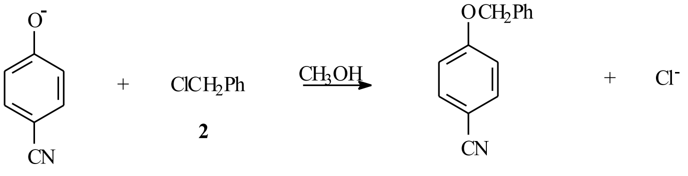
The rate enhancement for the esterification of benzoic acid with methanol was close to 100, when compared with the classical heating under reflux. On the other hand, the rate enhancement for the esterification with *n*-pentanol, using the same power level (560 W) was only 1.3. The approximate reaction temperature was almost the same for the two alcohols (134 °C and 137 °C respectively). It should be noted, however, that the rate enhancement for the esterification in pentanol increased to 6 times when a higher power level (630 W) was used, the reaction temperature being higher (162 °C).

It is interesting to note that in the case of the reaction with pentanol (boiling point 138 °C), when the temperature of the MW reaction and the conventional reflux reaction were about the same, there was very little difference in the reaction rates, suggesting that the reaction rate depends on the reaction temperature rather than the method of heating.



(R = CH_3, n-C_3H_7, n-C_4H_9, n-C_5H_{12})

Scheme 4.1 Microwave-assisted esterification of benzoic acid.



1 **2**

Scheme 4.2 S_N2 reaction of the 4-cyanophenoxide ion with benzyl chloride.

The effect of the size of the reaction vessel on the rate of MW-heated S_N2 reaction of 4-cyanophenoxide ion **1** and benzyl chloride **2** in methanol (Scheme 4.2) was investigated by reacting identical amounts of reagents in Teflon vessels of different sizes.

It was found that there was an inverse relationship between the size of the vessel and the reaction rate. In each case the time required for the reaction to go to 65 % completion was determined. It was shown that the rate of the reaction increases as the pressure increases, since the pressure is inversely related to the volume of the vessel.

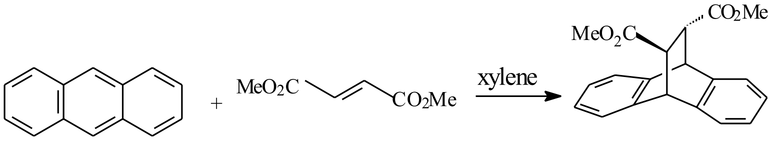
The heating rate, and hence the rate of pressure increase, also depends on the volume of the reaction mixture [20]. When the volume is small, the pressure increases as the volume of the reaction mixture increases. However at a certain volume this trend is reversed and a larger volume heats more slowly. For example when water was heated in a 150-mL Teflon vessel, the greatest rate of pressure increase occurs when 15 mL water are heated using a power of 560 W. The volume at which this maximum heating rate, however, varies for different solvents. For example it occurs at 20 mL for 1-propanol.

Using this information, it was possible to optimize the reaction conditions to achieve a particularly high rate enhancement. The rate enhancement of the esterification of benzoic acid with 1-propanol (Scheme 4.1) was increased from 18 to 60 times when the volume was increased from 10 mL to 20 mL at 560 W and increased further to 180 times by increasing the power level to 630 W.

In this early work, pressure was measured by connecting the cap of a pressure-release Savillex [24] Teflon vessel to a pressure gauge outside the MW oven and the final temperature estimated by pointing an infrared sensor at the mixture in the vessel immediately after the heating was completed.

MW heating under pressure has been used to accelerate the rates of a wide variety of reactions, which occur only slowly under conventional heating. This technique has been particularly useful in accelerating Diels–Alder and related reactions. For example the reaction of anthracene **3** with dimethyl fumarate **4** in *p*-xylene (Scheme 4.3), gave an 87% yield of the adduct in only 10 min by MW heating using a sealed tube as the reaction vessel [2]. In contrast, the control reaction, performed under reflux in *p*-xylene (bp 138 °C required 4 h to give a 67% yield. It is to be noted that the reaction temperature of the MW heated reaction was estimated to be in the range 325–361 °C, approximately 200 °C higher than the control reaction.

Dimethyl formamide (DMF) has been found to be a particularly useful solvent in these reactions because it absorbs MW irradiation strongly, has a relatively high boil-



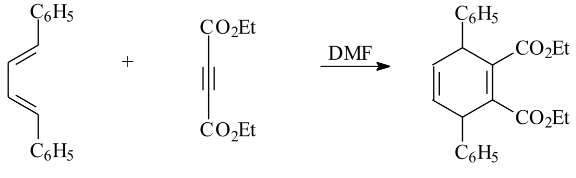
3 **4**

Scheme 4.3 Diels–Alder reaction of anthracene with diethyl fumarate.

ing point and is miscible with water, making it relatively easy to remove from the reaction mixture. Majetich and Hicks [6] showed that the reaction of 1,4-diphenylbutadiene **5** with diethyl acetylenedicarboxylate **6** under reflux in DMF (Scheme 4.4) at 153 °C gave a 67% yield of the Diels–Alder adduct **7** in 6 h. When the same reaction was performed by use of MW heating in a CEM microwave system using Teflon vessels with pressure and temperature monitoring (196 °C and 200 kPa), a comparable yield of **7** was obtained in only 20 min.

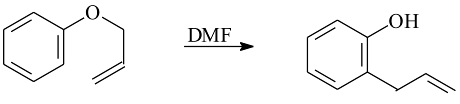
The *ortho*-Claisen rearrangement of phenyl vinyl ether **8** to 2-vinylphenol **9** (Scheme 4.5) is a very slow reaction, requiring 80 h of reflux in DMF to give a yield of only 34%. Using the CEM microwave system an 80% yield was obtained in 5 h at 196 °C and 200 kPa [6].

The Alder–Bong reaction of cyclohexene with diethyl acetylenedicarboxylate **6** in DMF under reflux (Scheme 4.6) gives a 14% yield of the tricyclic compound **10** in



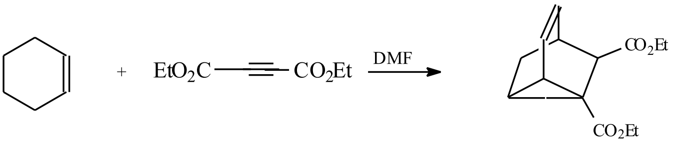
5 **6** **7**

Scheme 4.4 Reaction of 1,4-diphenylbutadiene with diethyl acetylenedicarboxylate



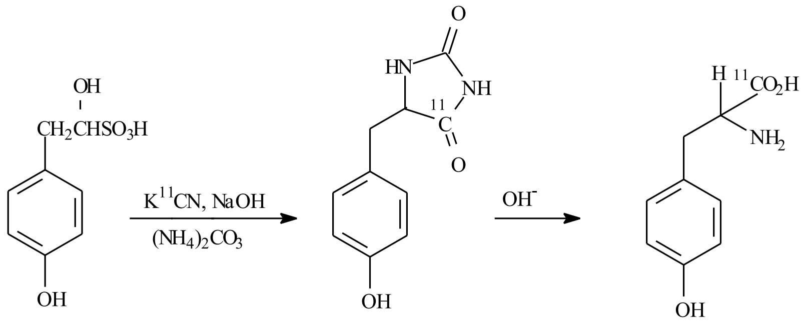
8 **9**

Scheme 4.5 Rearrangement of phenyl vinyl ether to 2-allylphenol.



6 **10**

Scheme 4.6 Reaction of cyclohexane with diethyl acetylene dicarboxylate.



11 **12**

Scheme 4.7 Synthesis of [1-^{11}C]tyrosine.

40 h, whereas a 50% yield was obtained by MW heating in DMF at 182 °C and 650 kPa for only 20 min [6].

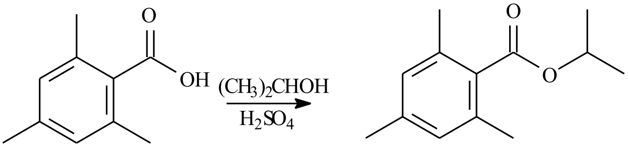
Mingos and coworkers have synthesized a number of organometallic compounds by MW heating in Teflon autoclave vessels [7]. The synthesis of rhodium(I) and iridium(I) dimers [M_2Cl_2(diolefin)$_2$], from $MCl_3.xH_2O$ and the diene requires several hours under reflux in alcohol–water mixtures. Using MW heating in a Parr bomb the same syntheses can be performed in good yield in less than 1 min.

A particularly useful application of MW-assisted synthesis at elevated pressure has been in the preparation of radiopharmaceuticals containing isotopes with short half-lives, such as C-11 (half-life 20 min) and F-18 (half-life 110 min) [25–27]. Clearly, these compounds have to be synthesized very rapidly in order to give products with high radiochemical yield. For example, [1-^{11}C] tyrosine **12** was synthesized using the two step Bucher–Strecker method by the reaction of *p*-hydroxyphenylacetaldehyde bisulfite adduct **11** with $K^{11}CN$ and $(NH_4)_2CO_3$ followed by hydrolysis with aqueous NaOH (Scheme 4.7)

Using conventional heating each step involved heating at 170 °C for 10 min, giving an overall radiochemical yield of 40–60%. In contrast, MW heating in a closed Pyrex tube gave a radioactivity gain of 91% in a total reaction time of 1 min.

In some cases, MW heating at elevated pressures makes feasible reactions which give negligible yields even after prolonged reflux in lower boiling solvents. The choice of high boiling solvents (>150 °C) is limited and these solvents may be difficult to remove by distillation. Strauss and Trainor [8] showed that the reaction of the sterically hindered mesitoic acid **13** with excess 2-propanol (bp 83 °C) in the presence of sulfuric acid (Scheme 4.8) gives less than 3% isopropyl mesitoate **14** after reflux for 28 h. Using a MW batch reactor (MBR) at 148 °C, however, a 56% yield of the ester was obtained after only 1 h [8].

Another example is the preparation of methyl 2-phenylethyl ether **16** by the reaction of 2-phenylethylbromide **15** with methanol (Scheme 4.9). This reaction is too slow to give an appreciable yield of the ether at the boiling point of methanol. An alternative approach is to use the reaction of sodium methoxide with the bromide, but this causes elimination of HBr, giving styrene as the main product. In contrast, re-



13

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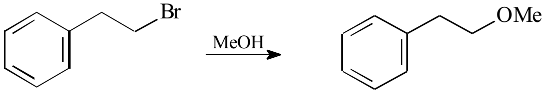
Scheme 4.8 Synthesis of isopropyl mesitoate.



Scheme 4.9 Preparation of methyl 2-phenylethyl ether.

15

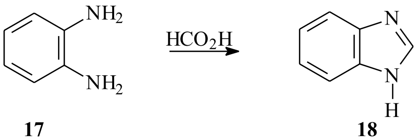
16

acting the bromide with methanol using the MBR at 170 °C gave a 75% yield of **16** in 20 min [8].

4.3
Reactions at Atmospheric Pressure

MW-assisted organic synthesis in homogeneous media at atmospheric pressure has recently received a considerable amount of attention [7, 17, 19]. This might seem surprising, since rate enhancements would be expected to be much smaller than in MW heating at higher pressures. In fact, acceleration of reactions by MW compared with conventional heating at the same temperature would not be expected unless the participation of a specific or nonthermal MW effect was involved [19, 28]. The existence of such effects is still a matter of debate among researchers in the MW chemistry area and will be discussed in this review, as they pertain to MW heated reactions in homogeneous media (see Chapt. 5 for a more general discussion).

The advantages of performing MW-heated reactions at atmospheric pressure are that the danger of explosions due to pressure increases are eliminated and that the equipment required is much less expensive. Reactions may be performed in open vessels, such as Erlenmeyer flasks, with a funnel as a loose top, in domestic MW ovens. This approach has been used particularly by Bose [17, 18] and has been termed MORE (microwave-organic reaction enhancement) chemistry. Reactions are usually performed in polar, relatively high boiling solvents. DMF is often the solvent of choice and other solvents include chlorinated benzenes, ethylene glycol and diglyme. These solvents heat rapidly and the MW power is adjusted so that the temperatures reach about 20–30 °C below their boiling points. Reactions are usually complete within minutes when performed on a small scale (ranging from a few milligrams to up to 5 grams of product). Some reactions have been scaled up to a hundred grams or more, but this requires longer reaction times, since larger quantities of materials heat up more slowly.


17 **18**

Scheme 4.10 Synthesis of benzimidazole.

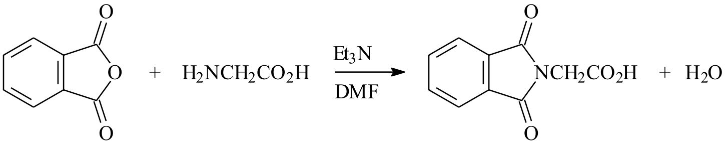
A number of syntheses of heterocycles were performed using the MORE technique [17, 18]. While most of these reactions had been reported in Organic Synthesis to require reflux times of an hour or more, Bose et al. were able to obtain comparable yields in a matter of minutes. For example, benzimidazole **18** was synthesized from 1,2-diaminobenzene **17** and formic acid, which served as both reagent and solvent, in 70% yield in 3 min (Scheme 4.10), compared with the recommended heating time of 2 h [17].

In some of these syntheses the original reaction conditions were modified and this might partly account for the much shorter reaction times. The synthesis of phthalimidoacetic acid **20** from phthalic anhydride **18** and glycine in the presence of triethylamine (Scheme 4.11) gives a yield of 83–90% when the reagents are heated under reflux in toluene for 1.5 h [29]. Bose found that good yields of the product could be obtained in 1–3 min when the reaction was performed in DMF in a MW oven [18].

This reaction was later re-examined by Westaway and Gedye [30], who showed that the rate of the reaction was actually the same whether performed by MW heating or conventional heating in DMF at the same temperature. Thus the rate increase observed by Bose was due to an increase in polarity and temperature when DMF was substituted for toluene.

The advantages of the MORE technique are that the apparatus required is simple and inexpensive and that reactions can be performed rapidly and conveniently. It has been used in teaching laboratories, making it feasible for the student to perform syntheses which would normally require long reflux times, in a 2 or 3 h laboratory period [31]. Disadvantages of the technique are that rate enhancements are smaller than those of reactions performed under pressure and that high boiling solvents are required to achieve fast reactions, leading to difficulties in separation of the products from these solvents. Although lower boiling solvents can be used, reaction rates are lower and fire hazards, due to the ready vaporization of the solvent, are significant.

Reactions at atmospheric pressure may also be performed using MW ovens modified so that a reflux condenser can be attached outside the oven [7, 19]. Since volatile solvents are contained in MW reflux, the fire hazard is minimized. Mingos has re-


19 **20**

Scheme 4.11 Synthesis of phthalimidoacetic acid.

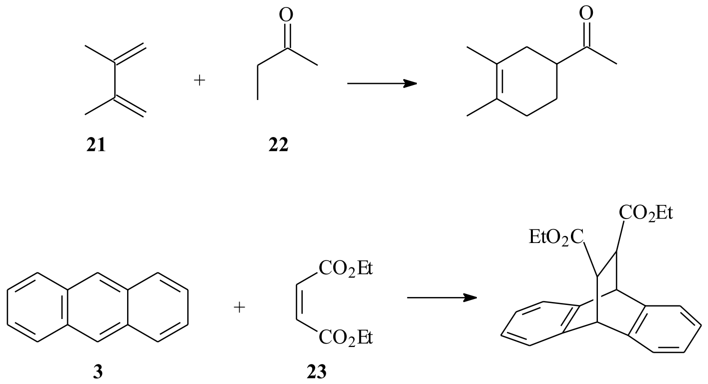
ported the synthesis of a number of organometallic compounds using this technique. For example, the rhodium dimer Rh(cod)Cl_2 (cod is 1,5-cyclohexadiene) was synthesized in 87% yield by MW reflux in a reaction time of 25 min. compared with a reported time of 18 h using conventional heating [7]. Although it is likely that the conventional heating time to give a comparable yield could be reduced considerably, an appreciable MW-induced rate enhancement of this reaction is probable. Mingos has noted that many solvents can superheat by 10–30 °C when reacted under reflux using MW heating [7]. It is well known that a temperature increase of 10 °C usually doubles the reaction rate and so an increase in temperature of 30 °C would be expected to result in a rate enhancement of 8 times. It should be noted that this superheating effect largely disappears on stirring or on addition of boiling chips [44]. However, stirring is not feasible in an unmodified domestic MW oven and boiling chips soon lose their effectiveness unless continuous MW power is supplied. For these reasons it is likely that many reported rate enhancements of reactions performed in solvents are due primarily to the superheating effect. There is also the possibility of nonthermal effects contributing to the rate enhancement, but this will be discussed in the next section. In any case, much larger rate enhancements can be achieved using high pressure conditions. The rhodium dimer referred to above was synthesized in 91% yield in only 50 s under MW irradiation using a Parr bomb [22].

4.4
Effect of Microwaves on the Rates of Homogeneous Reactions in Open Vessels

There have been a number of reports which claim that MW heating causes significant rate increases in some reactions in homogeneous media in open vessels, based on comparisons between rates of reactions performed by MW heating and conventional heating at the same temperature. This has led to the suggestion that specific or nonthermal activating effects are responsible for these rate enhancements. However, some of these reactions have been re-examined and shown to occur at the same rate, or only slightly faster, under MW irradiation.

4.4.1
Diels–Alder reactions

The first report suggesting specific activation of an organic reaction by MW was that of Berlan et al. [28] who observed that some Diels–Alder reactions occurred more rapidly on MW heating than under conventional heating at the same temperature (95 °C). The reactions were performed in two different solvents, xylene and dibutyl ether and the rate enhancements were slightly higher in xylene, the less polar solvent. For example the rate enhancement of the reaction of 2,3-dimethyl-1,3-butadiene **21** with methyl vinyl ketone **22** was 8 times in xylene and 2.3 times in dibutyl ether, based on the half lives of the reactions. Reaction of anthracene **3** with diethyl maleate **23** in xylene (Scheme 4.12) resulted in an approximately fourfold rate increase.



Scheme 4.12 Diels–Alder reactions reported to show a specific microwave effect.

In a subsequent paper [32], however, Berlan himself cast doubt on the existence of nonthermal effects, attributing the observed rate increases to localized hot-spots in the reaction mixture or to superheating of the solvent above its boiling point. He also mentioned the difficulty of measuring the temperature accurately in MW cavities. Furthermore, kinetic studies by Raner et al. [33], showed that the Diels–Alder reaction of **3** with **23** (Scheme 4.12) occurred at virtually the same rate under MW and conventional heating at the same temperature.

4.4.2
Reactions of Biologically Important Molecules

Sun et al. [34] reported that the rate of hydrolysis of the biomolecule ATP under MW irradiation was 25 times faster than under classical heating at similar temperatures. However, the same research group [35] later observed that, with more accurate temperature control, the hydrolysis rates were in fact almost identical.

There have also been reports [36, 37] that racemization of amino acids occurs more rapidly using MW heating than conventional heating at the same temperature. Chen et al. [36] observed that racemization of amino acids in acetic acid the presence of benzaldehyde was accelerated by MW heating. Lubec et al. [37] reported that some D-proline and *cis*-4-hydroxy-D-proline were found in samples of infant milk formula when they were heated in a MW oven. On the other hand, conventionally heated samples did not contain these unnatural D-amino acids. This report caused concern, and received media attention because D-proline is neurotoxic and suggested that MW heating of some foods could have deleterious effects on their nutritional value and the health of the consumer.

However, Marchelli et al. [38]. were unable to detect any D-proline when milk formula containing l-proline was heated in open vessels in a MW oven. Westaway and Gedye [30] showed that very small amounts of D-proline (0.1–0.2%) were produced when an aqueous solution of L-proline was heated under reflux in a MW oven for

15 min. Although D-proline was not detected when the same solution was heated under reflux conventionally for the same time, approximately 1% of D-proline was produced after 24 h of conventional reflux. MW did not have a significant effect on the rate of racemization of L-proline in acetic acid in the presence of benzaldehyde [30]. The small increase in racemization rate observed when an aqueous solution of L-proline was heated under reflux on a MW oven at atmospheric pressure could be attributed to localized superheating or a generalized superheating of the solvent. It is known that water superheats by 4–10 °C when boiled in a MW oven [39, 40].

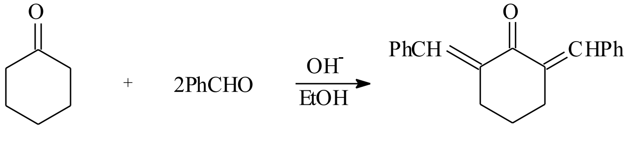
4.4.3
Other Reactions in Polar Solvents

We have investigated a number of reactions in polar solvents, most of which had been previously reported to occur more rapidly under microwave heating than classical heating in open vessels, to see if there are any significant MW rate enhancements, which could suggest to the involvement of a specific MW effect [19, 20].

It should be pointed out that many of these reports compared reaction times of MW heated reactions with times previously reported in the literature for the same reactions under conventional heating. Unfortunately the conventionally heated reactions are often complete in times which are much shorter than those quoted and it is important to perform direct and careful comparisons between MW and thermal reactions, using the same quantities of reagents and solvents and the same reaction temperature.

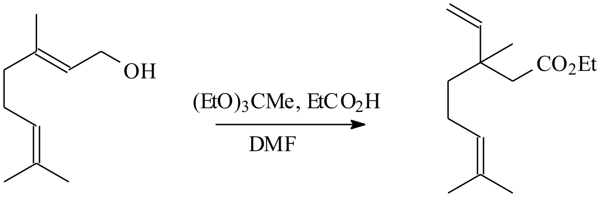
For example, large rate enhancements have been reported in the synthesis of chalcones by crossed-aldol condensations in open vessels, suggesting the participation of specific MW effects [41]. The chalcone **24** was synthesized from cyclohexanone and benzaldehyde in ethanol, in the presence of a catalytic amount of sodium hydroxide (Scheme 4.13), in a MW oven in 90% yield in only 1 min.

This was compared to a time, quoted previously, of 2 h of conventional heating to obtain a 72% yield, indicating a time saving of at least 120 times. We performed the same reaction under MW and conventional heating (heating mantle) in open vessels using the same proportions of reactants, catalyst and solvent. The conventionally heated reaction was found to give a high yield of the product in a time much shorter than 2 h at the boiling point of ethanol, and initial experiments showed only a two to five fold rate increase under microwave heating. In fact, when the reactions were performed under reflux to avoid evaporation of the solvent, an even smaller rate enhancement of 1.5 times was observed. When the reaction was performed in an open



24

Scheme 4.13 Microwave-assisted synthesis of chalcones.



25 **26**

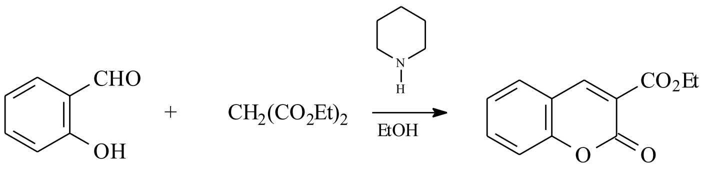
Scheme 4.14 *ortho*-Ester Claisen rearrangement of geraniol.

vessel in the MW oven, substantial evaporation of the solvent occurred, resulting in a more concentrated solution and a higher reaction temperature. The amount of evaporation in the conventionally heated reaction tended to be less, due to a slower heating rate, and so this reaction occurred more slowly.

Substantial rate enhancements of over 100 times have been reported in *ortho*-ester Claisen rearrangements of allylic alcohols in DMF in open vessels [42]. For example, geraniol **25** gave an 87% yield of the ester **26** in 12 min in a domestic MW oven, whereas the same reaction required 48 h of conventional heating to give a comparable yield (Scheme 4.14). In our laboratory, identical reaction mixtures of geraniol, triethyl orthoacetate, propanoic acid and DMF were heated both conventionally and with MW at the boiling point of DMF for 10 min, but in contrast to the previous report, no significant rate enhancement was observed [19]. It should be pointed out that it is not clear whether identical reaction mixtures or the same temperatures had been used for the two heating methods in the previous report [42].

A major problem in performing meaningful comparisons between the rates of MW and conventionally heated reactions is that the reaction temperature is difficult to control and to measure accurately in a domestic MW oven. In MW heated reactions, the temperature typically rises faster than in conventionally heated reactions and so even if the final temperatures are the same, the average temperature of the MW reaction is likely to be higher, resulting in an apparently faster reaction. Also, the MW fields are nonhomogeneous, making it difficult to obtain reproducible results. These drawbacks can be overcome by using monomode reactors with focused waves, producing a homogeneous electromagnetic field, with temperature monitoring using fiber optic probes or infrared detectors [43]. These systems are computerized giving accurate control of required conditions, including temperature, allowing one to match closely temperature profiles of MW and conventionally heated reactions [13, 44, 45]. The main limitation of these systems is their relatively high cost

We have found it convenient to compare MW and conventional reactions using reflux conditions, since the temperatures are constant at the boiling point of the solvent. To eliminate the problem of the time required to reach the reflux temperature, reaction mixtures without one of the reactants or catalyst are heated to reflux and then the other reactant or catalyst quickly added. The reflux times required to give similar yields for a reaction, taken only partially to completion by MW and classical heating, are then compared. Small rate enhancements might still be expected merely because of superheating by up to 40 °C by the MW [39, 40, 46], and localized heating



27 **28** **29**

Scheme 4.15 Knoevenagel reaction of salicylaldehyde with diethyl malonate.

(hot spots) may also contribute. For this reason, these modest rate enhancements should not necessarily be taken as evidence for nonthermal effects since rate increases of less up to about 20 times can be explained by superheating, assuming reaction rates double for every 10 ° rise in temperature. Mingos [47] has suggested that rate enhancements should only be taken as evidence for nonthermal effects if they are 100 times or more, but this includes the longer time required to reach the reaction temperature by conventional heating.

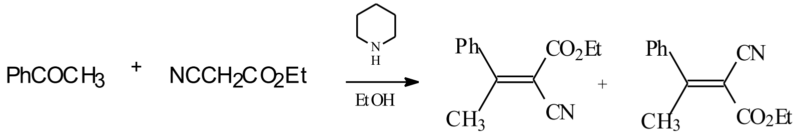
Comparison between reaction rates using MW and conventional heating should preferably be performed using kinetic studies [19, 33, 48], where rate constants can be evaluated or plots of yield of product versus reaction time for the conventional and MW reactions can be compared.

Bose et al. [18] reported that the Knoevenagel reaction between salicylaldehyde **27** and ethyl malonate **28** in the presence of piperidine gave a high yield of 3-carbethoxycoumarin **29** in 3 min in an open vessel in a MW oven (Scheme 4.15).

In their initial studies on this reaction, Westaway and Gedye [30] observed slightly increased rates both in the presence of ethanol and in the absence of a solvent, when MW heating was used in an open vessel. Since it was difficult to measure the temperature accurately in the MW experiment, the reaction in ethanol was later performed under reflux [19]. The yield of the product was found to be 73% in 8 min using MW reflux compared with a yield of 71% in 20 min under conventional reflux, representing a rate enhancement of approximately 2.5 times.

The rate of the Knoevenagel reaction of acetophenone **30** with ethyl cyanoacetate **31** (Scheme 4.16) was observed to be considerably slower and it was therefore found to be more suitable for rate studies [19].

A mixture of **30** and **31** and a small amount of acetic acid in ethanol was heated to reflux in a domestic MW oven. A catalytic amount of piperidine was then added and



30 **31** **32** **33**

Scheme 4.16 Knoevenagel reaction of acetophenone with ethyl cyanoacetate.

the mixture heated under reflux at low power (180 W). Heating was interrupted at regular time intervals and aliquots taken for G.C. analysis. A plot of yield of the product versus reaction time showed that the same yield of the mixture of isomers **32** and **33** (17%) was obtained after heating under reflux for 120 min in the MW oven and 320 min of conventional reflux, and hence the rate enhancement was 2.5–3.0 times.

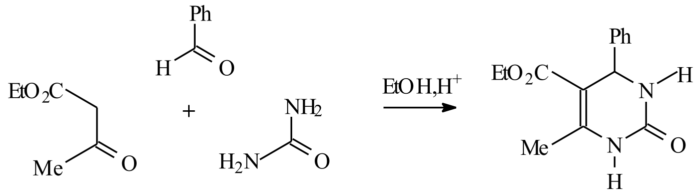
The isomer ratio E : Z (**33** : **32**) was 1.2–1.6 over the course of the reaction and was not affected by the heating method, so it was concluded that MW irradiation did not affect the stereochemical outcome of this reaction, presumably due to the reaction being under thermodynamic control.

It is interesting to note that when the same reaction was performed using a variable frequency MW system [49] with temperature control at 80 °C in the absence of a solvent, it occurred at the same rate as a similar reaction heated conventionally at the same temperature. The use of variable frequency provides very uniform heating, minimizing the possibility of hot spots. Thus it can be concluded that the modest rate enhancement observed in ethanol under reflux was because of hot spots or to a general superheating of the solvent. Again, it should be emphasized that these modest MW rate enhancements should not be taken as hard evidence for nonthermal MW effects.

Substantial MW rate enhancements have been reported in the Biginelli synthesis of dihydropyrimidines [50, 51] under homogeneous conditions. The synthesis involves a one-pot cyclocondensation of a β-ketoester with an aryl aldehyde and urea or thiourea in the presence of a catalytic amount of HCl in ethanol solution. An example of this synthesis is shown in Scheme 4.17.

The reactions were performed in an open beaker using a domestic MW oven, and reaction times were reduced from 2–24 h of conventional reflux to 3–11 min under MW irradiation.

Stadler and Kappe [52] re-examined this synthesis using a Milestone ETHOS 1600 series MW reactor [23] with on-line temperature and pressure control in order to investigate the existence of a nonthermal MW effect. They found, however, that when the reactions were performed under the action of MW heating using a reflux condenser no significant rate increase occurred over conventional reflux at the same temperature (80 °C). They confirmed that there was an increase in rate and yield when the reaction was performed in an open beaker, but this could readily be explained by evaporation of the solvent, causing an increase in temperature and concentration solution. It is to be noted that the same explanation applies for the appar-



Scheme 4.17 Biginelli synthesis of a dihydropyrimidine.

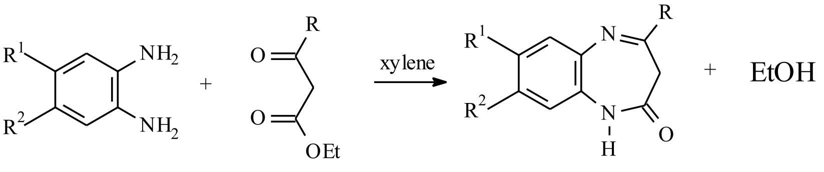
ent rate enhancement in the MW-assisted synthesis of chalcones (*vide supra*, Scheme 4.13). Thus there was no evidence for the participation of a nonthermal MW effect.

4.4.4
Reactions in Nonpolar Solvents

There have been a few reports recently of substantial MW rate enhancements of reactions of polar reactants in nonpolar solvents [53, 54]. Soufiaoui et al. [53] have synthesized a series of 1,5-aryldiazepin-2-ones **36** in high yield in only 10 min by the condensation of *o*-aryldiamines **34** with *β*-ketoesters **35** in xylene under MW irradiation in open vessels (Scheme 4.18). The temperature at the end of these reactions was shown to be 136–139 °C. Surprisingly, they observed that no reaction occurred when the same reactions were heated conventionally for 10 min at the same temperature. These results could be taken as evidence for a specific MW effect.

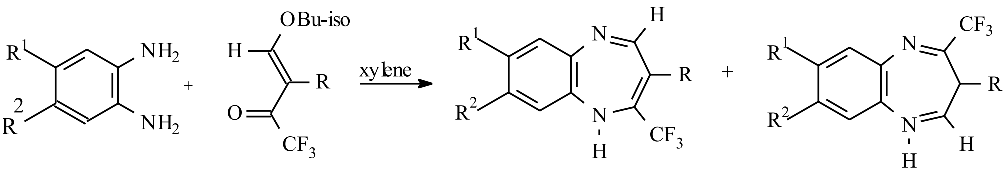
Reddy et al. [54] performed a rather similar synthesis of trifluoromethyl aryldiazepines **38** and **39** by the reaction of *o*-aryldiamines **35** with the synthon **37** (Scheme 4.19).

Under MW irradiation (980 W) in xylene yields of 73–93% were obtained in 10–20 min, whereas under conventional conditions a complex mixture of products was obtained, which was unsuitable for preparative work. Thus it would appear that these reactions not only occur much faster under microwaves but also give cleaner products, indicating greater selectivity. Loupy [44, 45] has speculated that these reactions, among others performed in nonpolar solvents or in the absence of solvent, might be accelerated under MW irradiation due to the involvement of relatively polar



34 **35** **36**

Scheme 4.18 Microwave-assisted synthesis of 1,5-aryldiazepines-2-ones.



35 **37** **38** **39**

Scheme 4.19 Microwave-assisted synthesis of trifluoromethyl aryldiazepines.

transition states, leading to lower activation energies. Specific effects would be more likely when nonpolar solvents are used, since only the reactants would absorb MW energy, whereas in polar solvents any such effects would be masked due to absorption of MW by the solvent.

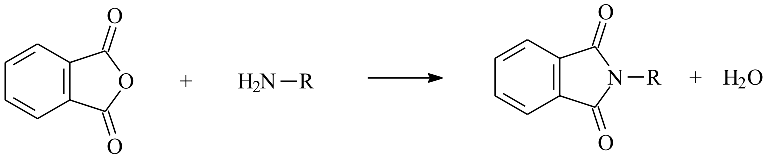
Since there appeared to be strong evidence for a nonthermal effect in this type of reaction, we repeated the reaction of *o*-phenylenediamine **34** (Scheme 4.13, $R_1 = R_2 = H$) with ethyl acetoacetate **35** ($R = CH_3$) [19], which was one of the reactions reported by Soufiaoui [53] to give the diazepine only on MW heating. However, when the same reaction mixtures were heated for10 min with the same temperature profile, almost identical yields of the diazepines were obtained by MW and classical heating. Later, this was also found to be the case in the reaction of **34** with ethyl benzoylacetate **35** (R = Ph).

However, the possibility of the participation of nonthermal effects in MW-assisted reactions in nonpolar solvents is still an open question. Loupy et al. [55] observed an increase in yield and purity of the diazepine **36**, in the reaction of ethyl acetoacetate with *o*-phenylenediamine using monomode MW reactor with focused MW heating, when compared with conventional heating with the same temperature profile.

Recently Bogdal [48] observed, using kinetic studies, greater MW rate enhancements when the Knoevenagel reaction of salicylaldehyde with ethyl malonate (*vide supra,* Scheme 4.15) was performed in toluene than when ethanol was used as the solvent. The calculated rate constants in toluene solution were more than three times higher under MW irradiation than under conventional conditions, whereas the rate constants of the reaction in ethanol were the same, within experimental error, under both heating methods.

In a joint paper, Loupy and Gedye [45] reported an investigation of the influence of MW activation on the synthesis of phthalimides by the reaction of phthalic anhydride with several amino compounds (Scheme 4.20) both in the absence of solvent and in the presence of a nonpolar solvent.

This study was prompted by a report that phthalimidoacetic acid ($R = CH_2CO_2H$, see also Scheme 4.11, *vide supra)* could be synthesized by the reaction of phthalic anhydride with glycine in the absence of solvent, which involves the reaction between two solids [56]. However, in this study [45], it was established that the synthesis of phthalimides under solvent-free reactions requires at least one liquid reactant in order to occur. This was possible when reacting a liquid amine (e. g. $R = CH_2Ph$) or a solid with a sufficiently low melting point to melt rapidly under MW (e. g. $R = (CH_2)_6OH$, m.p. 56–58). In these cases, the reaction temperature was typically over 135 °C after 2 or 3 min of MW heating resulting in dissolution of phthalic anhydride in the molten



Scheme 4.20 Microwave-assisted synthesis of phthalimides.

amine, thus producing a homogeneous mixture. Evidence was found in some cases for a faster reaction under MW irradiation. For example the reaction of phthalic anhydride with 6-amino-1-hexanol (R = $(CH_2)_6OH$) in mesitylene (a nonpolar solvent) gave a 60% yield of the phthalimide on heating for 10 min at 160 °C using an oil bath. The yield increased to 97% when the same reaction was performed using monomode MW heating for 10 min at the same temperature. The same reaction also occurred faster in the absence of a solvent when MW heating was used.

If no liquid phase is present, that is, for reactions between two solids, the reaction will not take place and requires the use of a high-boiling solvent. Thus, contrary to the previous report [56], the reaction of phthalic anhydride and glycine [R = CH_2CO_2H, m.p. 240 °C] did not occur in the absence of a solvent, but when performed in either DMF or xylenes gave a good yield (90%) of the phthalimide after only 10 min of MW heating. Finally, in all cases, excellent yields of phthalimides (about 90%) were obtained in short reaction times (5–10 min) giving products of high purity.

Also, as mentioned earlier, Berlan et al. [28] had observed that the use of a nonpolar solvent resulted in a more significant rate enhancement in a Diels–Alder reaction (*vide supra,* Scheme 4.12), although later kinetic studies by Raner et al. [33] cast some doubt on this result.

4.4.5
Reactions in Homogeneous Media Showing no MW Rate Enhancement

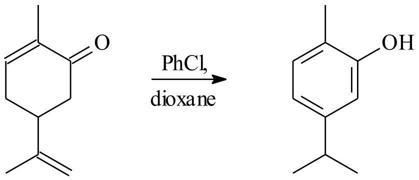
A number of other reactions in homogeneous media have been shown to occur at the same rate under MW heating and classical heating at the same temperature.

In our early studies [20] we compared the rate of the esterification of benzoic acid with propanol (*vide supra,* Scheme 4.1) using the two heating methods. Identical mixtures of benzoic acid, propanol and sulfuric acid were heated in an open vessel in a domestic MW oven and in an oil bath at 160 °C for 4 min. Although the temperature of the MW reaction could only be estimated roughly using an infrared sensor immediately after the reaction, the results showed that there was no significant MW rate enhancement, the yields of propyl benzoate using MW and oil bath heating being 25% and 29% respectively.

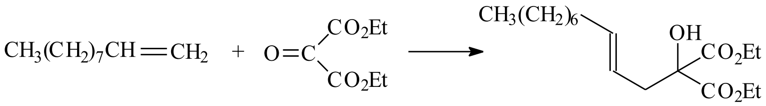
Later, in a more carefully controlled comparison, Pollington et al. [57] showed that the esterification of acetic acid with 1-propanol also occurred at the same rate under MW and conventional reflux.

Other reactions shown to occur at the same rate under the two heating methods include the acid-catalyzed isomerization of carvone **40** to carvacrol **41** [33], and ene reactions involving carbonyl enophiles (Scheme 4.21) [32]. The former reaction was performed in a mixture of chlorobenzene (slightly polar) and dioxane (nonpolar) and in the latter reaction a large excess of 1-decene was used and so the reaction was effectively performed in a solution of low polarity.

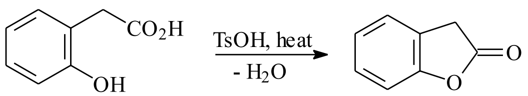
A recent study by Goncalo et al. [58] adds support to the hypothesis that observed rate increases of MW heated reactions compared with classical heating are due only to thermal effects. They studied the intramolecular cyclization of 2-hydroxyphenyla-



40 **41**



Scheme 4.21 Reactions occurring at the same rate under the action of microwave and classical heating.



42 **43**

Scheme 4.22 Cyclization of 2-hydroxyphenylacetic acid to coumaran-2-one

cetic acid **42** to.coumaran-2-one **43** in the presence of a trace of *p*-toluenesulfonic acid under MW irradiation and conventional heating (Scheme 4.22).

The reactions were performed in the absence of a solvent or a solid support at temperatures above the melting point of the acid **42**. The use of a monomode MW oven and an optical fluorescence thermometer allowed accurate measurement of temperature distribution in the reaction mixture and showed a large and unexpected temperature heterogeneity. Initially it was observed that a yield of 85% of **43** was obtained after 6 min of MW heating at 200 °C, whereas when oil bath heating at the same temperature was used the yield did not exceed 65%. When the temperature distribution in the reactor was taken into account (varying by 40 °C for a gap of 2–3 mm in the irradiated liquid), it was estimated that the average temperature was at least 245 °C, and the reaction was therefore performed at 245 °C using oil bath heating. Under these conditions, the same yield of 85% of **43** was obtained either by classical or MW heating. It was concluded that some previous studies, which have shown faster reactions using MW heating than classical heating at the same temperature, leading to postulations of nonthermal effects, may be flawed due to inaccuracies in temperature measurement. It was emphasized, however, that the use of monomode MW irradiation was an attractive and safe alternative to classical heating. The short reaction time of 6 min included the time required for the rise in temperature, whereas it took at least 30 min to heat the oil bath to the required temperature, when the bath became dangerously hot.

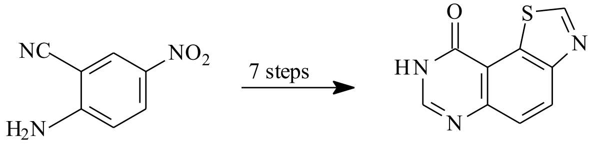
4.4.6
Reactions in Homogeneous Media Showing MW Rate Enhancement

As mentioned earlier, a number of reactions initially observed to show MW rate enhancements compared with conventionally heated reactions at the same temperature, have since, with more careful comparison, been shown to occur at the same rate under the two heating modes. Other reactions, such as Knoevenagel reactions in ethanol solution (*vide supra,* Schs. 15 and 16), have been shown to have modest rate enhancements, occurring typically 2 or 3 times faster under MW heating than under conventional heating at the same temperature. These rate increases are not surprising considering that solvents superheat by 10 °C or more on MW reflux, particularly as the reaction mixtures were not stirred.

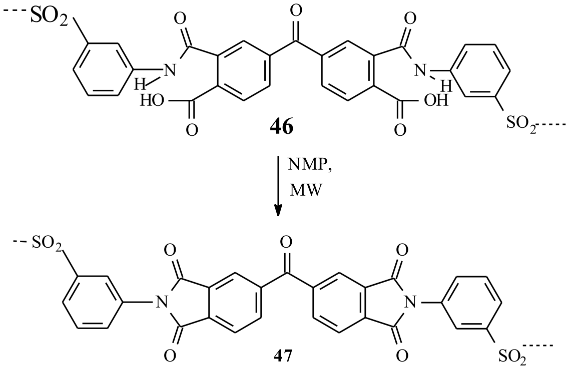
On the other hand, there have been a few reports of MW assisted reactions at atmospheric pressure which have been reported to show more substantial rate enhancements, and these will now be discussed.

Besson et al. have published a series of papers describing MW-assisted syntheses of polyheterocyclic compounds of potential pharmacological value, such as quinazolines [59–63]. These MW applications are of particular interest because of the substantial reductions in reaction time in multistep syntheses. The MW heated reactions were performed in a monomode MW oven with focused irradiation, mostly under reflux in homogeneous solution in polar solvents. For example, MW heating in homogeneous solution was used in four of the steps in the synthesis of the thiazoquinazoline **45** from 2-amino-5-nitrobenzonitrile **44** (Scheme 4.23) leading to a considerable overall time-saving in the seven-step synthesis. Based on the reaction times for MW and conventional heating, rate enhancements for the individual steps were in the range 6–8 times. The total time required for these four reactions was reduced from 14 h (conventional heating) to 2 h (MW) and the overall yield was increased. The reactions were also reported to be cleaner and the products more easily purified.

The rates of certain reactions of polymers have been reported to be enhanced by MW under homogeneous conditions at atmospheric pressure. Lewis et al. [64] performed kinetic studies on the imidization of the polymer BDTA–DDS polyamic acid **46** in *N*-methylpyrrolidone (NMP) giving the polymer **47** (Scheme 4.24) and showed that the apparent activation energy was reduced from 105 kJ mol^{-1} under conventional heating to 55 kJ mol^{-1} under MW heating. Rate enhancements ($k_{MW}/k_{thermal}$)



Scheme 4.23 Microwave-assisted synthesis of a thiazoquinazoline.



Scheme 4.24 Imidization of polymer BDTA–DDS polyamic acid.

at various temperatures, were in the range 20–30 times It was suggested, however, that these rate enhancements were due to nonuniform heating on a molecular scale rather than to nonthermal effects.

Wei et al. [65, 66] compared the MW and thermal cure of epoxy resins for stoichiometric mixtures of diglycidyl ether of bisphenol A (DGEBA) and a curing agent of high dipole moment, diaminodiphenylsulfone (DDS), and for DGEBA and a curing agent of low dipole moment, *m*-phenylenediamine (mPDA) at the same temperature. They found significant increases in reaction rates in the MW cured DGEBA/DDS samples but only slight rate increases for the MW cured DGEBA/mPDA samples. A possible explanation for the higher rate enhancements of the DGEBA/DDS system is that when polymers are irradiated with MW, the energy is directly coupled to the polar functional groups and it takes a finite time for the absorbed energy to distribute itself evenly with the rest of the system. If this distribution time is significantly longer than the reciprocal of the frequency of the MW irradiation, this will result in a localized higher molecular temperature in the case of the more polar DDS than in the less polar mPDA [66]. However it was also suggested that nonthermal effects could be involved since the MW cured samples showed a higher glass transition temperature, T_g than the thermally cured samples after gelation. It was argued that if the effects were purely thermal, the T_g should be the same for the MW and thermally cured samples at the same extent of cure [66].

Scola et al. [67] studied the kinetics of the MW cure of a phenylethyl-terminated imide polymer model compound and an oligomer using a variable frequency MW source and found that the activation energy of the MW cures were 68% and 51% of the thermal cure respectively. It should be noted that the reactions were performed in the liquid phase in the absence of solvent.

4.4.7
Possible Explanations of MW Acceleration

In summary, observations of increased rates of MW-assisted homogeneous reactions, compared with classically heated reactions at the same apparent temperature, may be explained by one or more of the following problems or effects:

- localized or general superheating of the solvent;
- inaccurate temperature measurement;
- nonhomogeneous distribution of temperature in the reaction mixture;
- evaporation of the solvent in open vessels, leading to higher temperatures and concentrations; and
- nonthermal effects.

Because observed rate enhancements are usually small, or zero, nonthermal effects do not seem to be important in MW heated reactions in homogeneous media, except possibly in some reactions of polymers and reactions in nonpolar solvents. Relatively few studies have been conducted on MW-assisted reactions of polar reactants in nonpolar solvents. Also, since there is some disagreement as to whether or not these reactions are accelerated significantly by MW, in comparison with conventionally heated reactions at the same temperature, more research on the effect of MW irradiation on the rates of these reactions is required. Nonthermal effects may, however, explain the more substantial MW rate enhancements in solvent-free reactions on solid supports [44] (see Chapt. 5) and solid state reactions [68, 69].

4.5
Selectivity in MW-assisted Reactions

Another interesting question is whether MW heating can result in changes in selectivity, leading to different product compositions than those obtained using conventional heating. The effect of MW irradiation on selectivity was discussed in a review by Langa et al. in 1997 [9] and more recently by Loupy et al. [44, 70]

In this regard Gedye et al. studied reactions of alkyl halides with bases in which the amounts of elimination and substitution were compared and a Diels–Alder reaction in which the ratio of *endo* to *exo* adducts was investigated [71]. In the first set of experiments, the ratios of elimination to substitution products for the reactions of 1- and 2-bromooctane with methoxide ion in methanol and with *tert*-butoxide ion in *tert*-butyl alcohol, obtained under MW heating in a sealed Teflon container, were compared with those found using normal reflux conditions (Scheme 4.25).

It was observed that there were only slight differences in composition between the products of the MW and conventionally heated reactions. The greatest change in composition was observed in the reaction of 1-bromooctane with *tert*-butoxide ion where the percent of the elimination product (the alkene) increased from 5%, under conventional reflux to 14% under MW heating. On the other hand there

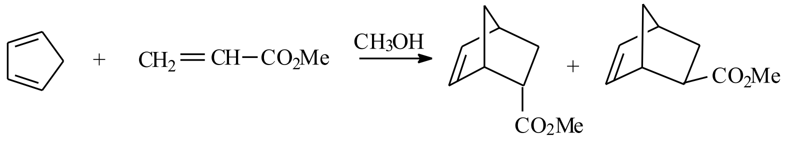
$$CH_3(CH_2)_6CH_2Br + OR^- \xrightarrow{ROH} CH_3(CH_2)_5CH{=}CH_2 + CH_3(CH_2)_6CH_2OR$$

$$CH_3(CH_2)_5CHBrCH_3 + OR^- \xrightarrow{ROH} CH_3(CH_2)_5CH{=}CH_2 + CH_3(CH_2)_4CH{=}CHCH_3$$

$$+ CH_3(CH_2)_5CHORCH_3$$

$$(R = CH_3 \text{ and } (CH_3)_3C)$$

Scheme 4.25 Substitution and elimination reactions of alkyl halides with base.



48 **49**

Scheme 4.26 Diels–Alder reaction of cyclopentadiene with methyl acrylate.

was no significant change in composition in the reactions of 2-bromooctane with base.

The Diels–Alder reaction of cyclopentadiene with methyl acrylate in methanol was studied by Berson et al. [72] under conventional conditions, and shown to give a mixture of the *endo* and *exo* isomers **48** and **49** (Scheme 4.26).

The *endo* isomer was the major product, but the proportion of the *endo* isomer decreased with temperature, from approximately 90% at 0 °C to 85% at 60 °C [69]. Gedye et al. [71] performed the reaction in methanol solution under MW heating in a closed Teflon container and found that the product contained 79% of the *endo* isomer at an estimated temperature of 110 °C. A plot of temperature versus percent *endo* isomer is effectively linear between 0 °C and 60 °C and assuming it remains linear to 110 °C, the product should contain 80% *endo* isomer at this temperature. Thus it was concluded that the change in product composition was due to the change in temperature rather than to some special effect of MW. At higher temperatures there is an increase in the proportion of the *exo* isomer, which is thermodynamically more stable than the *endo* isomer.

However, more significant modifications in selectivity, which have useful applications in synthesis, have been reported in a number of other reactions performed under the action of MW irradiation [9, 44, 70]. Many of these reactions were performed under heterogeneous and/or solvent-free conditions, and only those performed under homogeneous conditions will be discussed here.

Linders et al. [73] studied the Diels–Alder reaction of 6-demethoxy-β-dihydrothebaine with an excess of methyl vinyl ketone (used both as reactant and solvent), which gives a mixture of two isomeric adducts. When the reaction was performed using classical heating extensive polymerization occurred, whereas much less polymeric material was formed when the reaction was performed in a modified MW oven under reflux conditions, resulting in a 32% yield of the isomeric mixture of the mixture of adducts.

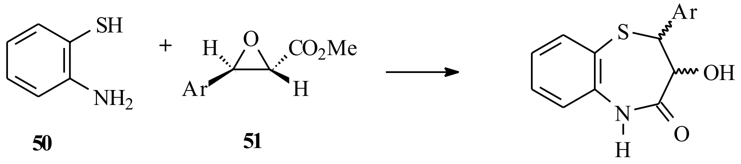
In some MW-assisted reactions, in which a mixture of products is formed, the ratio of products may be influenced by the heating rate or by the polarity of the solvent.

Stuerga et al. [74] showed that, in the sulfonation of naphthalene, the ratio of the products, naphthalene-1- and 2-sulfonic acids, depends on the MW power applied. Higher powers, which cause higher heating rates, increase the proportion of the thermodynamically more stable product, naphthalene 2-sulfonic acid, in the product mixture.

Alvarez-Builla et al. [75] have shown that the stereochemical outcome of the MW-assisted addition of 2-aminothiophenol **50** to the glycidic ester **51** (Scheme 4.27) is affected by the nature of the solvent and by the MW power output. When the nonpolar solvent toluene was used, the *cis* isomer of the product **52** predominated, whereas in the presence of acetic acid the *trans* isomer was the chief product. Increasing the power level caused an increase in the proportion of the *trans* isomer when toluene was used as the solvent. The reactions were performed in open vessels in a domestic MW oven.

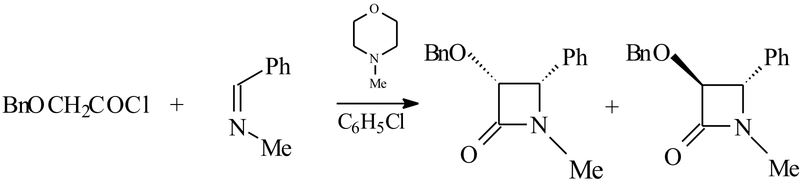
Also, Bose et al. [76] have shown that the steric course of β-lactam formation can be influenced by the MW heating rate. For example, in the reaction of the benzoyloxyacetyl chloride **53** with the Schiff base **54** (Scheme 4.28) the *cis* adduct **55** is the main product at low irradiation power whereas high power favors the formation of the *trans* adduct **56**. Lactams of this type can serve as intermediates for the side chain of taxol and its analogs.

Bose et al. [77] compared a similar reaction of the acid chloride of tetrachlorophthaloyl glycine **57** with a Schiff base under MW irradiation and conventional



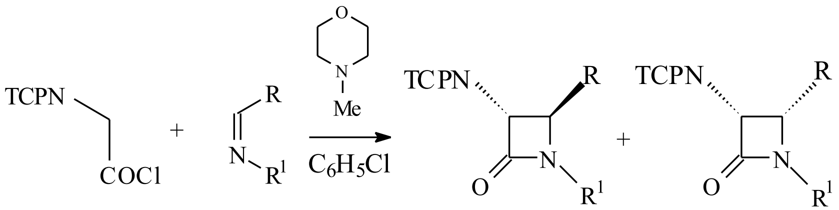
50 **51** **52**

Scheme 4.27 Addition of 2-aminophenol to a glycidic ester.



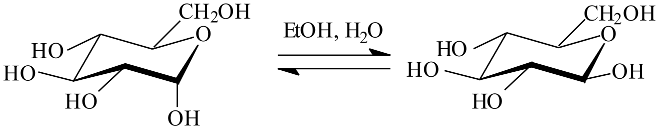
53 **54** **55** **56**

Scheme 4.28 Microwave-assisted β-lactam synthesis.



57 **58** **59**

Scheme 4.29 Reaction of the acid chloride of tetrachlorophthaloyl glycine with a Schiff base.



60 **61**

Scheme 4.30 Mutarotation of glucose.

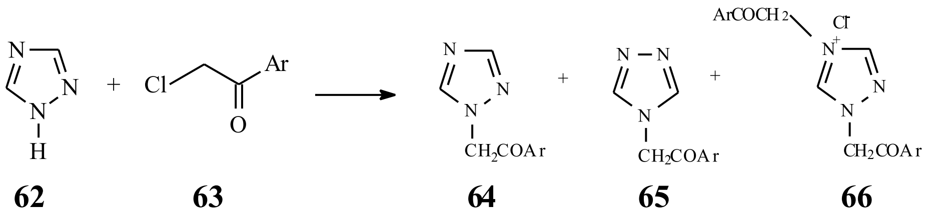
heating (Scheme 4.29). When MW heating was used, the *trans* isomer **58** was formed almost exclusively, whereas a mixture of *cis* and *trans* isomers **59** and **58** was obtained under conventional heating. It was noted that the temperature at which the acid chloride was added to the imine solution was crucial for *trans* selectivity. The imine solution was initially heated in the MW oven to about 100 °C and then the acid chloride added and the mixture heated at a low power level for 3 min.

Pagnotta et al. [78] reported that the mutarotation of α-D-glucose **60** to *β*-D-glucose **61** in aqueous ethanol (Scheme 4.30) not only occurred more rapidly under MW heating than conventional heating but also gave a different equilibrium composition, with a larger concentration of α-D-glucose being obtained using MW irradiation.

Because this change in selectivity is difficult to explain by a classical heating effect, Langa et al. [9] consider that it is one of the most convincing examples of a possible specific microwave effect.

Langa et al. [79] recently observed that the regioselectivity of the cycloaddition of *N*-methylazomethane to C_{70} fullerene could be modified by MW irradiation. The extent of the modification in selectivity, compared with conventional heating, was shown to be greater in the presence of the polar solvent, *o*-dichlorobenzene, than in the nonpolar solvent, toluene. It was suggested that the effect on selectivity in this reaction could be because of (1) the presence of hot-spots, (2) the greater heating rate induced by MW or (3) a selective interaction of the electromagnetic field with the transition state, which gives rise to the different isomers if they have different polarities.

Loupy et al. [70] have studied the effect of solvent on the selectivity of the alkylation of 1,2,4-triazole **62** by 2,2′,4′-trichloroacetophenone **63** (Scheme 4.31) under MW and conventional heating. The reactions were all performed at 140 °C.



Scheme 4.31 Alkylation of 1,2,4-triazole.

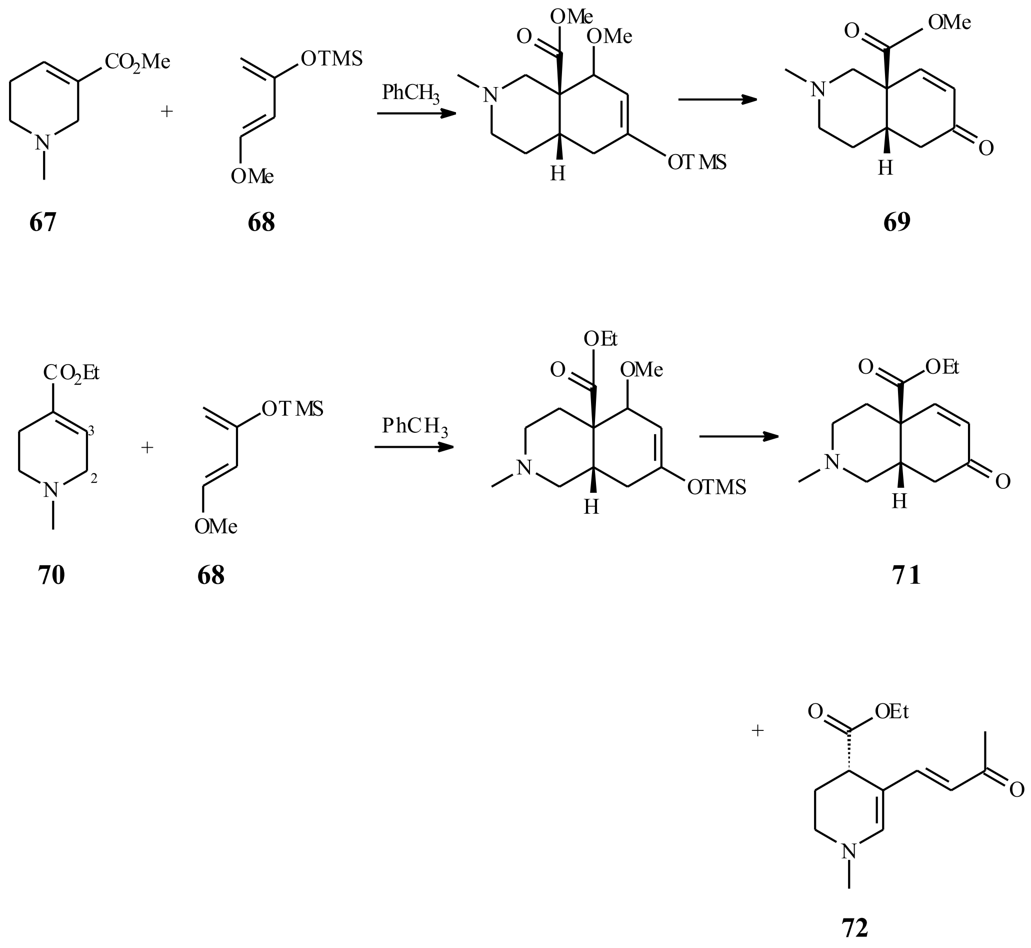
In contrast with the results of Langa et al. on the cycloaddition reaction to C_{70}, MW irradiation had no effect on the regioselectivity of the reactions in polar solvents, but a substantial effect was observed both in the nonpolar solvent, xylene and under solvent-free conditions. In polar solvents (pentanol and DMF) the ratio of products **64**, **65**, and **66** was 95 : 5 : 0 under both MW and conventional heating. In xylene and in the absence of solvent the ratio of isomers changed from 32 : 28 : 40 (xylene) and 36 : 27 : 27 (no solvent) under conventional heating to 100 : 0 : 0, i. e. totally regioselective, under MW activation.

The effect of solvent on regioselectivity was attributed to nonthermal effects, which are favored in nonpolar solvents and under solvent-free conditions, where products formed *via* more polar transition states would be expected to predominate.

Recently, Jankowski et al. [80] reported the application of MW to the Diels–Alder synthesis of *N*-methyloctahydroisoquinoline adducts, which are important intermediates in the synthesis of medicinally important compounds, such as HIV protease inhibitor isoquinoline carboxylate pharmaceuticals. The reaction of the arecoline **67** or its isomer **70** with Danishefsky's diene **68** in toluene (Scheme 4.32) was studied under both conventional and MW heating in sealed tubes, i. e. at elevated pressure.

The MW-assisted reaction was performed in a focused MW extraction system (Prolabo Soxwave-10) and occurred not only much more rapidly than the conventionally heated reaction, but also resulted in higher yields and purer products. Under conventional heating (160 °C for 5 days) the yields of the adducts **69** and **71** from **68** with **67** and **70** respectively, were 30% and 50%. In contrast, the MW method resulted in yields of 73% of **69** and 63% of **71** in only 5 min. The stereochemistry of the products was not affected by the heating mode. Under conventional reaction conditions a significant level of diene decomposition and polymerization as well as the formation of dienophile dimers was observed. Under MW activation, however, the reaction was cleaner and amount of dimerization was reduced. It is interesting to note that in the case of the MW reaction of **70** with **68** a new $\alpha\beta$-unsaturated pyridyl ketone **72** was also produced. It was suggested that this product was formed *via* the isomerization of the double bond of the dienophile **70** from the conjugated position 3 to position 2 (presumably due to the higher temperature of the MW reaction) which then reacts with the diene to afford compound **72**.

Most of the changes in selectivity due to MW heating in homogeneous media discussed here may be explained by higher reaction temperatures or greater heating rates in the MW-assisted reactions. However, the observations of Pagnotta et al. [78]



67 **68** **69**

70 **68** **71**

72

Scheme 4.32 Diels–Alder synthesis of isoquinoline carboxylates.

and Loupy et al. [70] suggest that nonthermal effects may be involved in some cases. More detailed comparisons between the selectivity of MW and conventionally heated reactions at the same temperatures and in solvents of different polarity need to be conducted before definite conclusions can be reached (see also Chapt. 5).

4.6
Comparison of Homogeneous and Heterogeneous Conditions

As discussed earlier, careful comparisons of the rates of MW irradiated reactions in homogeneous media, particularly in polar solvents, at atmospheric pressure show that these rates are the same or only slightly higher than similar reactions under conventional heating. Any small rate enhancements can be explained by hot-spots or general superheating of the solvent.

In fact, most reports of substantial rate enhancements by MW in open vessels are in reactions performed under dry-media conditions, in which the reactants are absorbed on inert solid supports [11–16]. Since one or more of the reactants is usually a liquid at the reaction temperature [44], these reactions are performed under heterogeneous conditions. Although it is difficult to perform kinetic studies on these reactions, there is little doubt that they generally occur considerably faster than similar conventionally heated reactions.

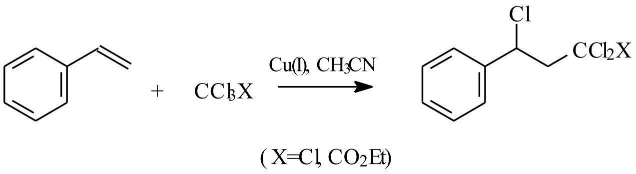
There have also been a number of reports of accelerations of reactions in the liquid and gaseous phase in the presence of a solid catalyst which absorbs MW irradiation [81].

Chemat et al. [82] compared the rates of esterification reactions under MW and classical heating using homogeneous and heterogeneous catalysis. They showed that rate enhancements of 1.5 to 2 times were observed with heterogeneous catalysts whereas no rate enhancements were observed under homogeneous conditions. For example, the rate constants for the esterification of acetic acid with propanol in the presence of sulfuric acid (homogeneous conditions) under classical and MW heating at 80 °C were almost identical, as previously observed by Pollington et al. [57]. On the other hand, when iron III sulfate with montmorillonite was used as the catalyst (heterogeneous conditions) the rate constant of the MW-heated reaction was twice that of the classically heated reaction.

These results suggest that selective heating of the catalyst to temperatures higher than that of the liquid phase is responsible for the modest increases in rate in the presence of a heterogeneous catalyst.

Adamek and Hajek [83] reported that the addition of CCl_4 and CCl_3CO_2Et to styrene in the presence of a homogeneous Cu(I)-amine catalyst in acetonitrile (Scheme 4.33) occurred more rapidly under MW heating than conventional heating.

Gedye and Wei repeated this reaction, comparing the rates under MW and conventional reflux [19]. When the catalyst solution, prepared by the reaction of CuCl with *n*-butylamine in acetonitrile, was carefully filtered before mixing with the reactants (homogeneous conditions), a MW rate enhancement of only 1.5 times was observed for the addition of CCl_3CO_2Et and no rate increase was observed for the addition of CCl_4. Higher rate enhancements were observed, however, when the catalyst solution was not filtered and some solid CuCl was present in the reaction mixture (heterogeneous conditions). The rate enhancements for the additions of CCl_3CO_2Et and CCl_4



Scheme 4.33 Addition of CCl_3X to styrene in the presence of a Cu-amine catalyst.

to styrene were then 11 and 3 times respectively. Again, the higher MW rate enhancements under heterogeneous conditions can be accounted for by the increased temperature of the solid catalyst. It has been reported that CuCl absorbs MW strongly and heats at a rate of $20\,^{\circ}\,s^{-1}$ in a 2.45 GHz MW cavity [84].

Recently, Hajek and Radoiu observed that MW not only increase the rate of heterogeneous catalytic reactions, but also affect the product selectivity [85]. The results were explained in terms of MW-induced polarization, involving the absorption of MW by highly polarized reagent molecules on the active site of the catalyst. On the other hand there is little, if any, activation of homogeneous catalytic reactions in polar solvents [86], presumably due to the high absorbent power of MW irradiation by the solvent.

4.7
Advantages and Limitations of MW Heating in Organic Synthesis

The most obvious advantage of MW heating over conventional heating is that it allows many reactions to be performed more rapidly. In addition there have been many reports of increased yields and fewer side-reactions when MW heating is used. Rate increases of two or three orders of magnitude are achievable by performing reactions in sealed containers and hence at increased pressures. Earlier applications of this technique were limited to small-scale reactions at pressures of up to about 700 Kpa to avoid the possibility of vessel rupture or explosions [1–3, 20]. Computerized MW systems with temperature and pressure control are now available allowing reactions to be performed safely and rapidly [8, 21, 23]. Hence there can be considerable time savings in a synthesis, which may have one or more steps requiring long reflux periods of conventional heating. Unfortunately, such systems are expensive at present, and are not, for example, usually available for routine use in university research laboratories. It can be expected, however, that this situation will change in the next few years as organic chemists become more aware of their potential to drastically reduce the time required for slow reactions as well as for obtaining products of greater purity.

MW-assisted reactions are often performed in comparatively inexpensive domestic MW ovens at ambient pressure. The ovens are sometimes modified to allow the reactions to be performed under reflux [7, 19], thus preventing rapid evaporation of the solvent which could otherwise present a fire hazard. Alternatively, the MORE technique [17] can be used, where the reactants are dissolved in a high-boiling solvent such as DMF or may be performed in the absence of a solvent. Although actual rate enhancements are small and sometimes nonexistent, reaction mixtures can be heated more rapidly than under classical heating leading to some time-saving. MW heating avoids the use of dangerously hot oil baths, which also require a considerably longer time to reach the required temperature [58].

The variability of domestic MW ovens, nonhomogeneity of the MW field, and difficulties in temperature measurement often make it difficult to obtain reproducible rates and yields [10], and this may partly explain why MW heating has not become more widely used by synthetic organic chemists. These problems also apply to solvent-free reactions on solid supports, when performed in domestic microwave ovens, but they can be avoided by using focused microwaves in monomode systems [43]. Again, the expense of these systems has so far limited their use to specialized research laboratories. However, with the impressive advances in technology for the design of MW systems for organic synthesis in the last few years, there is little doubt that these systems will soon become much more widely used by organic chemists. The MW technique offers considerable advantages over conventional heating for solvent-free reactions on solid supports because of rapid heating, substantial rate enhancements and cleaner reactions.

For these reasons, and because avoidance of solvents makes the technique more environmentally friendly, the majority of recent papers on MW-assisted organic synthesis have reported the use of solvent-free reactions.

MW heating will, of course, only be effective if the reaction mixture absorbs MW irradiation and so is limited to reactions of polar molecules, either in polar solvents or in the absence of a solvent. In some cases, reactions of polar compounds in nonpolar or slightly polar solvents can be heated with MW [19, 53], but the solutions must be must be sufficiently concentrated in order to heat effectively. Relatively high MW powers are also required. For this reason, some reactions requiring several hours of classical reflux in solvents of low polarity can be performed more rapidly in a MW oven by using a more polar solvent [17].

Although most applications have been in small-scale syntheses, recent technology has led to the design of continuous flow and batch systems [8, 23] making it feasible to synthesize products on the kilogram scale. Many noteworthy applications of MW-assisted synthesis have been reported including the synthesis of radiopharmaceuticals containing atoms with short half-lives [27], the synthesis of organometallic compounds [7] and the synthesis and cross-linking of polymers [64, 87, 88]. Recently, the great potential of rapid MW-assisted organic synthesis for combinatorial chemistry and drug discovery is receiving considerable interest and has been recognized in two reviews [89, 90].

Finally, there are a number of reports of modifications in selectivity and this aspect of MW synthesis [9, 44, 70] promises to receive much attention in the future.

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5

Microwave and Phase-transfer Catalysis

André Loupy, Alain Petit, and Dariusz Bogdal

5.1

Phase-transfer Catalysis

In the last three decades there have been many reports of organic reactions performed under phase-transfer catalytic conditions (PTC) [1–4]. PTC has found numerous applications in essentially all fields of organic syntheses, industrial chemistry, biotechnology, and material sciences. It can be encountered in the manufacture of advanced pharmaceuticals, fragrances, crop-protection chemicals, highly advanced engineering plastics, materials for semiconductors, and electro-optical and data storage devices [5]. It is worth remarking that in the 1990s sales of products made by use of phase-transfer catalysis exceeded 10 USD billion year^{-1}.

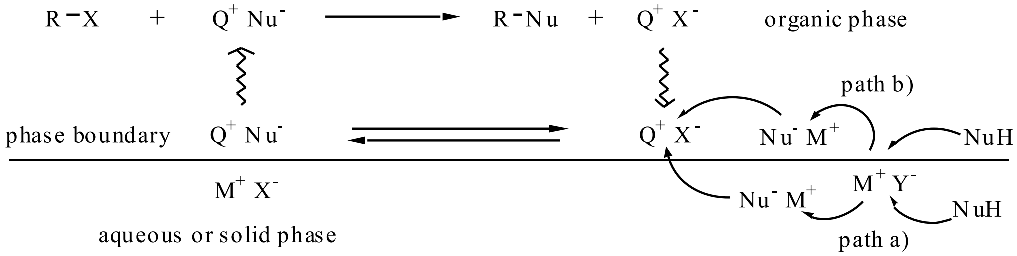
The concept of PTC was developed mainly because of the work of independent research groups led by Makosza [1] and, later, Starks [2], Brandstrom [3], and Dehmlow [4]. They introduced techniques in which the reactants were situated in two separate phases, e.g. liquid–liquid or solid–liquid. Because the phases were mutually insoluble, ionic reagents (i.e. salts, bases, or acids) were dissolved in the aqueous phase while the substrate remained in the organic phase (liquid–liquid PTC). In solid–liquid PTC, on the other hand, ionic reagents can be used in their solid state as a suspension in the organic medium. Transport of the anions from the aqueous or solid phase to the organic phase, where the reaction occurred, was ensured by use of catalytic amounts of lipophilic agents, usually quaternary onium salts or cation-complexing agents (e.g. crown ethers). Because the reactions proceeded very slowly, or not at all, in the absence of a catalyst, phase-transfer catalysts have been found to be of utmost importance in the extraction of reaction species between phases so that the reaction can proceed, thus increasing yields and rates of reactions substantially.

In general, under PTC conditions, three types of catalytic procedure can be considered (Scheme 5.1).

1. Liquid–liquid PTC in which the inorganic anions or anionic species generated from relatively strong organic acids are located in the aqueous phase and react with organic compounds in a liquid–liquid two-phase system by transfer into the

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9



Scheme 5.1

organic phase as loose lipophilic ion pairs, because of the intervention of the phase-transfer catalyst, which continuously transfers the anionic species from the aqueous phase to the organic phase, in which the reaction occurs (Scheme 5.1; path a);

2. Liquid–liquid PTC conditions in which weak organic acids (e. g. carboanions) react in the presence of concentrated aqueous sodium or potassium hydroxide which is in contact with the organic phase containing an anion precursor and organic reactants; the anions are created on the phase boundary and continuously introduced, with the cations of the catalyst, into the organic phase, in which further reactions occur (Scheme 5.1; path b).
3. Solid–liquid PTC conditions in which the nucleophilic salts (organic or mineral) are transferred from the solid state (as they are insoluble) to the organic phase by means of a phase-transfer agent. Most often the organic nucleophilic species can be formed by reaction of their conjugated acids with solid bases (sodium or potassium hydroxides, or potassium carbonate) (Scheme 5.1; path b). Another proposed mechanism suggests that interfacial reactions occur as a result of absorption of the liquid phase on the surface of the solid.

The organic phase can be a nonpolar organic solvent (e. g., benzene, toluene, hexane, dichloromethane, chloroform, etc.) or a neat liquid substrate, usually the electrophilic reagent, which acts both as a reactive substrate and the liquid phase.

In chemical syntheses under the action of microwave irradiation the most successful applications are necessarily found to be the use of solvent-free systems [6]. In these systems, microwaves interact directly with the reagents and can, therefore, drive chemical reactions more efficiently. The possible acceleration of such reactions might be optimum, because they are not moderated or impeded by solvents. Reactions on solid mineral supports and, in turn, the interaction of microwaves with the reagents on the solid phase boundary, which can substantially increase the rate of the reactions, are of particular interest [7].

PTC reactions are perfectly tailored for microwave activation, and combination of solid–liquid PTC and microwave irradiation gives the best results in this area [8]:

1. after ion-pair exchange with the catalyst, the nucleophilic ion pair [Q^+Nu^-] is a highly polar species especially prone to interaction with microwaves;

2. the extraction processes, during the reaction, in which a PTC mechanism is mainly involved, can be accelerated on the phase boundary, and an increase of reaction rate might be expected; and
3. reactions under solid–liquid PTC-like reactions on mineral supports under solventless conditions often suffer from difficulties with heat transfer through the reaction medium and homogenous heating under conventional conditions. Because microwave irradiation is a means of volumetric heating of materials, temperature is more uniform under microwave conditions. Improvement of temperature homogeneity and heating rates implies faster reactions and less degradation of the final products.

Similarly to classical PTC reaction conditions, under solid–liquid PTC conditions with use of microwaves the role of catalyst is very important. On several occasions it has been found that in the absence of a catalyst the reaction proceeds very slowly or not at all. The need to use a phase-transfer catalyst implies also the application of at least one liquid component (i.e. the electrophilic reagent or solvent). It has been shown [9] that ion-pair exchange between the catalyst and nucleophilic anions proceeds efficiently only in the presence of a liquid phase. During investigation of the formation of tetrabutylammonium benzoate from potassium benzoate and tetrabutylammonium bromide, and the thermal effects related to it under the action of microwave irradiation, it was shown that potassium benzoate did not absorb microwaves significantly (Fig. 5.1, curves a and b). Even in the presence of tetrabutylammonium bromide (TBAB) the temperature increase for solid potassium benzoate

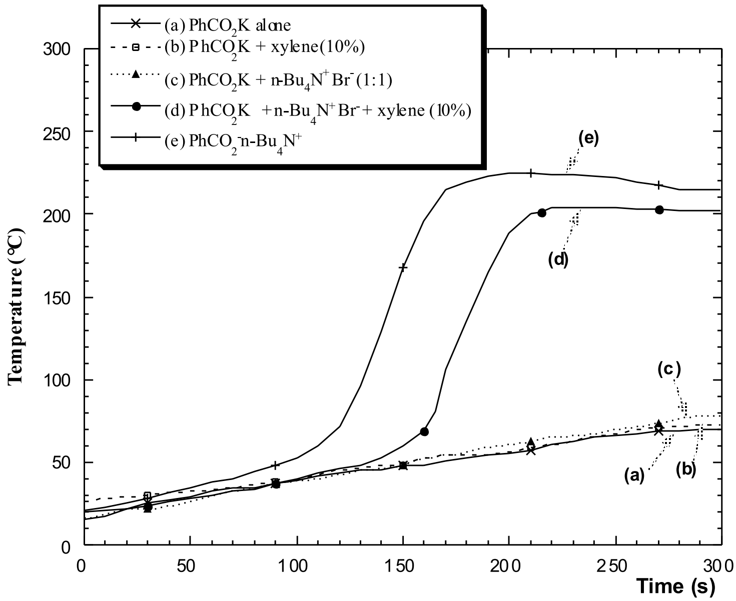


Fig. 5.1 Thermal behavior induced by microwave irradiation of $PhCO_2K$ under different conditions (monomode reactor, 180 W).

was very modest (Fig. 5.1, curve c). In the presence of small amounts of xylene (Fig. 5.1, curve d), a nonpolar solvent (i.e. inert to MW irradiation), a large temperature increase provides evidence of the formation of tetrabutylammonium benzoate in the liquid phase, from which the positive thermal effect results (Fig. 5.1, curve d).

It must be stressed that a liquid component can be substituted with an efficient absorber of microwave irradiation together with a low-melting component. The use of most typical PTC solvents (nonpolar aromatic or aliphatic hydrocarbons, or highly chlorinated hydrocarbons) is most interesting for microwave activation, because such solvents are transparent or absorb microwaves only weakly. They can, therefore, enable specific absorption of microwave irradiation by the reagents, and the results or product distributions might be different under microwave and conventional conditions [7].

Hence, by coupling microwave technology and solid–liquid phase-transfer conditions, we create a *clean, selective, and efficient methodology* for performing organic reactions, with substantial improvements in terms of conditions and simplicity in operating procedures; this is essentially useful for poorly reactive systems involving, for instance, hindered electrophiles or long-chain halides.

Numerous reactions in organic synthesis can be achieved under solid–liquid PTC and with microwave irradiation in the absence of solvent, generally under normal pressure in open vessels. Increased amounts of reactants can be used to ensure better compatibility between the in-depth penetrability of materials and the radiation wavelength.

Because microwave activation is rather a new technique, the number of examples might seem limited at the present time; it is, however, increasing rapidly.

5.2
Synthetic Applications of Phase-transfer Processes

5.2.1
O-Alkylations

In conventional methods, PTC has provided interesting procedures for O-alkylation, and coupling PTC conditions with microwave activation has proved to be quite fruitful for such reactions.

5.2.1.1 Ester Synthesis

Alkyl acetates

Potassium acetate can be readily alkylated in a domestic microwave oven by use of equivalent amounts of salt and alkylating agent in the presence of Aliquat 336 (10 mol%). Some important results, exemplified by Eq. (1), are given in Tab. 5.1 [10, 11].

$$CH_3COO^-K^+ \; + \; R{-}X \longrightarrow CH_3COOR \; + \; K^+X^- \qquad \text{Eq. (1)}$$

Tab. 5.1 Alkylation of $CH_3COO^-K^+$ under MW + PTC conditions (domestic oven, 600 W).

RX	*Time (min)*	*Final temperature (°C)*	*Yield (%)*
n-$C_8H_{17}Br$	1	187	98
n-$C_8H_{17}Cl$	1	162	98
n-$C_8H_{17}I$	2	165	92
n-$C_{16}H_{33}Br$	1	169	98

Yields are always almost quantitative within 1–2 min, irrespective of chain length and the nature of the halide leaving groups.

This procedure was scaled up from 50 mmol to the 2 mol scale (i.e. from 15.6 to 622.4 g total starting materials) in a larger batch reactor (Synthewave 1000) [12]. Yields were equivalent to those obtained under the original conditions (5 min, 160 °C) in the laboratory-scale experiment (Synthewave 402) (Tab. 5.2).

Tab. 5.2 Synthesis of n-octyl acetate under MW + PTC conditions (Synthewave, 5 min, 160 °C).

Reactor	*Amounts of materials [g (mol)]*			*Total amount (g)*	*Yield (%)*
	CH_3COOK	*n-OctBr*	*Aliquat*		
MW S402	4.9 (0.05)	9.7 (0.05)	1 (0.0025)	15.6	98
MW S1000	196 (2)	386 (2)	40.4 (0.1)	622.4	98

Xu et al. have obtained similar results with n-butyl bromide using TBAB (10 mol%) and alumina (4 : 1 *w/w*) as the catalyst [13]. Benzyl acetate was also conveniently prepared from sodium acetate and benzyl halide by use of microwave irradiation and PTC in synergy [14].

Long-chain esters

As a generalization of the above method, stearyl stearate was synthesized in 1 min in quantitative yield (Eq. 2) [11].

$$\mathrm{C_{17}H_{35}COO^{-}K^{+}} + n\text{-}\mathrm{C_{18}H_{37}Br} \xrightarrow[\text{MW (600 W) 1 min.}]{\text{Aliquat 10\%}} \underset{99\%}{\mathrm{C_{17}H_{35}COO}n\text{-}\mathrm{C_{18}H_{37}}} \qquad \text{Eq. (2)}$$

It has been shown that reaction of carboxylic acids with benzyl halides, which does not occur when heated conventionally, could be performed efficiently under the action of MW irradiation in the presence of a quaternary ammonium salt as a catalyst (Eq. 3) [15]. Typical results are given in Tab. 5.3.

$$\mathrm{Ar{-}CH_2X} + \mathrm{n\,C_5H_{11}COOH} \xrightarrow{\mathrm{Q^+X^-}} \mathrm{Ar{-}CH_2{-}O{-}CO{-}C_5H_{11}} + \mathrm{HBr} \qquad \text{Eq. (3)}$$

Tab. 5.3 Reaction of benzyl halides with hexanoic acid under MW + PTC conditions (10 min, 560 W, 10% $PhCH_2N^+Me_3Cl^-$).

$ArCH_2X$	*Yield (%)*
Benzyl bromide	72
Benzyl iodide	90
α-Bromo-*p*-xylene	76
α-Iodo-*p*-xylene	92
α-Bromomesitylene	81

Aromatic esters

It is possible to alkylate benzoic acids directly, without the need to prepare reactive potassium salts in a separate step, because they can be generated *in situ* by reacting the acid with a base (potassium carbonate or hydroxide) in the presence of a phase-transfer catalyst.

As an illustration of this principle, a volatile polar molecule is a byproduct, eliminated as a result of the microwave heating (Eq. 4), and the equilibrium is shifted to completion. The second effect of irradiation is activation of the alkylation step itself (Eq. 5). All the reagents can be used in the theoretical stoichiometry. Some indicative results are given in Tab. 5.4 [9].

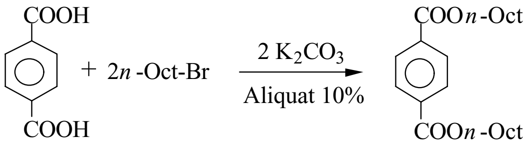
$$\mathrm{ArCOOH} + \mathrm{KOH} \overset{\text{Aliquat 10\%}}{\rightleftharpoons} \mathrm{ArCOO^-K^+} + \mathrm{H_2O}\nearrow \qquad \text{Eq. (4)}$$

$$\mathrm{ArCOO^-K^+} + \mathrm{R{-}X} \xrightarrow{\text{Aliquat 10\%}} \mathrm{ArCOOR} + \mathrm{K^+X^-} \qquad \text{Eq. (5)}$$

Tab. 5.4 Alkylation of potassium 4-Z-benzoate under MW + PTC conditions (domestic oven, 600 W, 10% Aliquat).

Z	*Time (min)*	*Yield (%)* *Performed salt*	*Salt in situ*
H	2.5	99	99
NMe_2	3	97	100
OMe	2	82	98
CN	3	80	95
NO_2	2	81	95

A striking example in this series is the alkylation of terephthalic acid (Eq. 6). The specific effect of the microwaves appears clearly in this example, because, other factors being equal, the yields are unambiguously much higher.



(Eq. (6))

MW (600 W)	7 min.	227°C	87%
Classical heating	7 min.	227°C	20%

5.2.1.2 **Ether Synthesis**

Aliphatic ethers

Yuan et al. studied two types of condition for this reaction – use of either the alcohols or the corresponding halides as starting materials [16, 17]. In the presence of quaternary ammonium salts the reaction shown in Eq. (7) is complete within a few minutes. Typical results are given in Tab. 5.5.

$$ROH + R'X \xrightarrow{PhCH_2N^+Me_3Cl^-} R\text{-}O\text{-}R' + HX$$

Eq. (7)

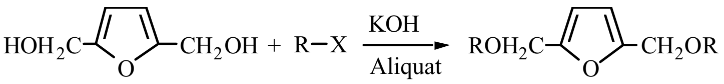
Tab. 5.5 Synthesis of ethers under MW + PTC conditions (domestic oven, 560 W).

R	*RX*	*Time (min)*	*Yield (%)*
Et	$PhCH_2Cl$	5	85
n-Bu	$PhCH_2Cl$	10	78
n-Oct	$PhCH_2Cl$	10	88
n-Oct	*n*-BuBr	10	78
$PhCH_2$	*n*-BuBr	10	92

More recently, this method has been extensively applied to a wide range of Williamson syntheses in dry media with K_2CO_3 and KOH as bases, TBAB as phase-transfer agent, and a variety of aliphatic alcohols (e. g. *n*-octanol and *n*-decanol, yields 75–92%) [18].

Furan diethers [19]

A new family of furan diethers has been obtained by alkylation of 2,5-furandimethanol (Eq. 8) under the action of microwaves under PTC solvent-free conditions.



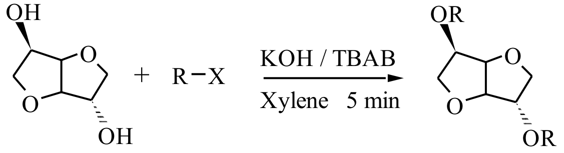
Eq. (8)

Microwaves Monomode Reactor (30 W)	5 min.	180°C	93%
Conventional heating (Oil Bath)	5 min.	180°C	41%

The diethers were synthesized in high yield within short reaction times. When compared with classical heating, under otherwise comparable conditions, reactions times were improved by microwave activation.

Diethers from dianhydrohexitols

A series of new ethers has been obtained by alkylation of dianhydrohexitols (i.e. isosorbide, isomannide, isoidide) under the action of microwave irradiation and PTC conditions. Yields exceeded 90%, a dramatically improvement compared with those from conventional heating, despite similar temperature profiles. The best yields, for example from isosorbide, were obtained in the presence of a small amount of xylene and TBAB as catalyst at 140 °C (Eq. 9 and Tab. 5.6) [20].



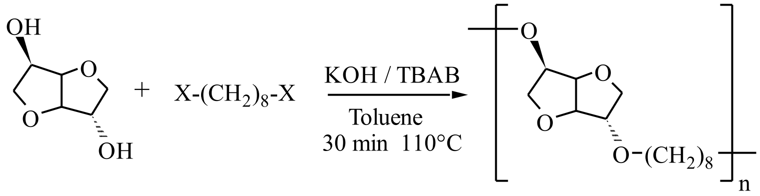
Eq. (9)

R = n-Oct, $ArCH_2$, $CH_3CH_2OCH_2CH_2$
X = Cl, Br

Tab. 5.6 Reaction of isosorbide with several alkylating agents in the presence of KOH and TBAB (relative amounts 1 : 3 : 3 : 0.1) under the action of microwave irradiation in a xylene solution.

R-X	*Time (min)*	*Temperature (°C)*	*Yield (%)*	
			MW	Δ
n-$C_8H_{17}Br$	5	140	96	10
$C_6H_5CH_2Cl$	5	125	98	13
3-Cl-$C_6H_4CH_2Cl$	5	125	95	15
4-Cl-$C_6H_4CH_2Cl$	5	125	96	14
3-F-$C_6H_4CH_2Cl$	5	125	95	15
$CH_3CH_2OCH_2CH_2Br$	30	100	78	45

Polyethers were next synthesized from isosorbide by means of a MW-assisted PTC method (Eq. 10). In addition to increasing the rate of the reaction, the MW affected the structure of the polymer (determined by MALDI/TOF mass spectrometry; Tab. 5.7). Polymers of higher molecular weights, with ethylenic groups as chain terminations, were obtained; conventional heating led to shorter hydroxylated compounds [21].



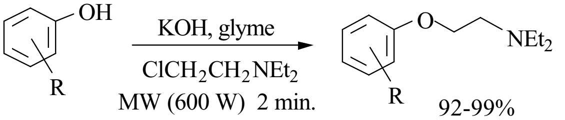
Eq. (10)

Tab. 5.7 Polyethers from isosorbide and 1,8-dibromo- or dimesyloctane; yield and distribution data for the microwave procedure (*Mn* and *Mw* are, respectively, the number average and weight average molecular weights, the ratio *Mw*/*Mn* being the polydispersity index).

X	*Yield (%)*	*Mn*	*Mw*	*Mw/Mn*
Br	68	3300	4300	1.30
OMs	76	3650	5100	1.39

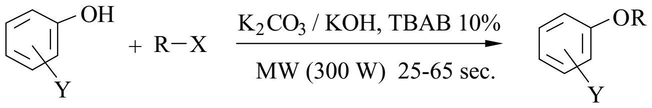
Phenolic ethers

Gram quantities of aryl-2-(*N,N*-diethylamino)ethyl ethers, compounds of biological interest, have been prepared in a household microwave oven, with potassium hydroxide and glyme as the transfer agent, according to Eq. (11) [22].



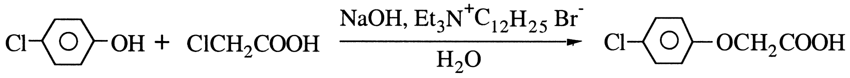
Eq. (11)

Under the action of microwave irradiation several phenol reacts remarkably fast in dry media with primary alkyl halides to give aromatic ethers (Eqs. 12 and 13) [23, 24].



Eq. (12)

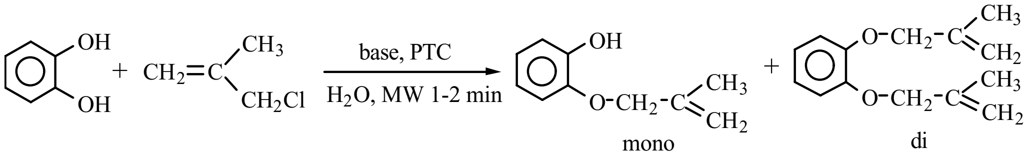
Ex : Y = H	R-X = $PhCH_2Cl$	50 sec.	78%
	Me_2SO_4	25 sec.	87%
Y = *p* NH_2	$PhCH_2Cl$	40 sec.	89%



MW	0.5 h	92%
Δ	5 h	96%

Eq. (13)

Catechol was reacted with *β*-methallyl chloride under the action of MW and PTC conditions; yields of 2-methallyloxyphenols varied from 59 to 68% under liquid–liquid conditions (Tab. 5.8), whereas no reaction was observed in a solid–liquid PTC procedure (Eq. 14) [25].

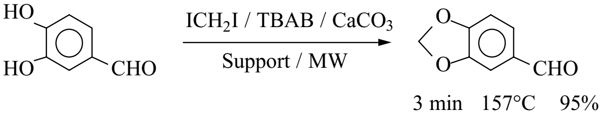


Eq. (14)

Tab. 5.8 Reaction of catechol with β-methallyl chloride (8 mmol) in the presence of base (2 mmol) and phase-transfer catalyst (0.2 mmol) under microwave irradiation.

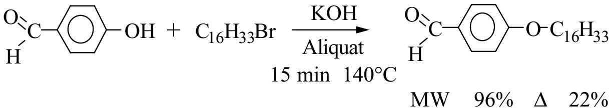
Base	***PTC***	***Yield (%)***	***Mono/di ratio***
NaOH	PEG-400	64	6.1
KOH	TBAB	59	5.1
K_2CO_3	TBAB	68	6.4

A similar reaction is the methylenation of 3,4-dihydroxybenzaldehyde in the presence of a phase-transfer catalyst on a benign calcium carbonate surface [26]. Presumably, bonding of the vicinal hydroxyl groups is low thereby enhancing the reaction with the alkylating agent under the action of solvent-free microwave irradiation (Eq. 15).

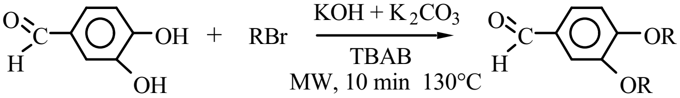


Eq. (15)

With the purpose of improvement and simplification of the synthesis of potential cosmetic compounds, alkylation of mono- and dihydroxybenzaldehydes with long-chain halides was efficiently realized under solvent-free MW + PTC conditions (Eqs. 16 and 17 and Tab. 5.9) [27, 28].



Eq. (16)

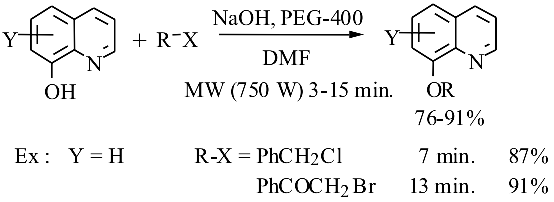


Eq. (17)

Tab. 5.9 Alkylation of 3,4-dihydroxybenzaldehyde with long chain alkyl bromides under the action of MW + PTC conditions.

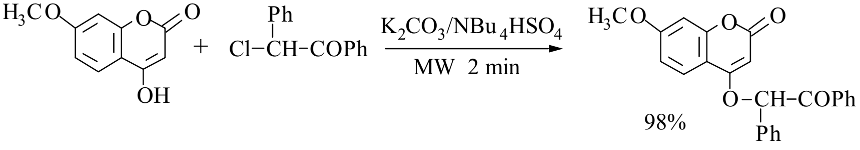
R	$C_{12}H_{25}$	$C_{14}H_{29}$	$C_{16}H_{33}$	$C_{18}H_{37}$
Yield (%)	86 (Δ 18)	80	81	80

The synthesis of 8-quinolinyl ethers from 8-hydroxyquinolines and organic halides has also recently been reported under PTC conditions with microwave irradiation (Eq. 18) [29].



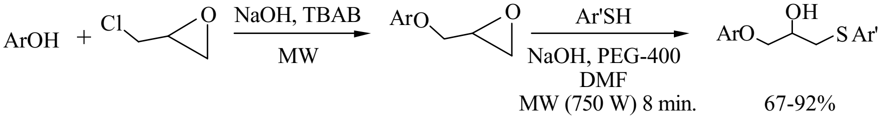
Eq. (18)

Desyl ethers are key intermediates in the synthesis of biologically active furanopyrones. MW-assisted synthesis of these has been performed in an open vessel under PTC solvent-free conditions (Eq. 19) by alkylation of 7-hydroxy-4-methyl coumarin with desyl chloride [30].

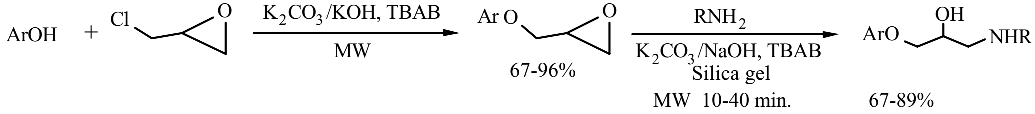


Eq. (19)

Alkylations of phenols with epichlorohydrin under PTC conditions and microwave irradiation were described twice in 1998. Subsequently, ring-opening reactions of the epoxide group were also performed using microwaves (Eqs. 20 and 21) [31, 32]. In the first catalytic synthesis of chiral glycerol sulfide ethers was described [31]; in the second biologically active amino ethers were prepared [32].

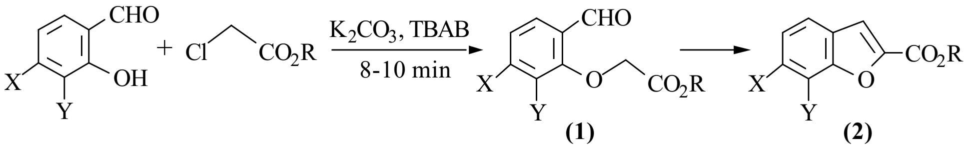


Eq. (20)



Eq. (21)

Condensation of salicylaldehyde and its derivatives with a variety of esters of chloroacetic acids in the presence of TBAB led to the synthesis of benzo[*b*]furans by means of a solid–liquid PTC reaction under the action of microwave irradiation [33]. This was a modification of one of the most popular routes to substituted benzo[*b*]furans, i. e. O-alkylation of *o*-hydroxylated aromatic carbonyl compounds with α-halogenated carbonyl compounds, then intramolecular condensation. The mixture of aldehydes and chloroacetic acid esters were absorbed on potassium carbonate, then irradiated in an open vessel in a domestic microwave oven for 8–10 min (Eq. 22).



Eq. (22)

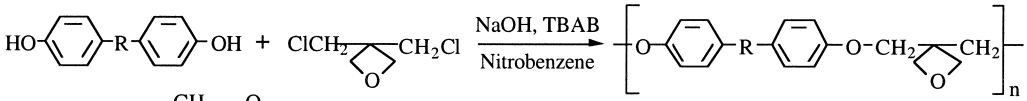
It was found that the first step was rate determining. When, moreover, the reaction was run with the same reaction-temperature profiles under both conventional (oil) and microwave (monomode cavity) conditions, different distributions of the intermediate (**1**) and final (**2**) products were obtained (Tab. 5.10). Indeed, the product distribution was strongly affected by microwaves when the reaction was run at 85 °C rather than 110 °C, and addition of a small amount of a polar or nonpolar solvent also affected the product distribution. In this work two solvents capable of extensive coupling (i. e. ethanol) and not coupling (i. e. cyclohexane) with microwaves were used. Addition of ethanol strongly shifted the product distribution towards the final product (**2**), whereas addition of cyclohexane resulted in much lower yield of **2** [34].

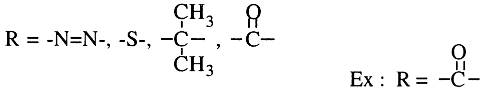
Tab. 5.10 Distribution of the intermediate (**1**) and final product (**2**) in the synthesis of benzo[*b*]furans under both conventional and microwave conditions.

Temperature (°C)	*Time (min)*	*Solvent (mL)*	*Yield (%)*	
			1	*2*
110	10/MW	–	12	66
110	20/MW	–	–	100
110	20/Δ	–	4	96
85	20/MW	–	15	85
85	20/Δ	–	90	10
85	30/MW	Cyclohexane/1.5	62	38
85	30/MW	EtOH(100%)/1.5	0	100
85	30/MW	EtOH(96%)/1.5	0	100
85	30/Δ	EtOH(100%)/1.5	47	53

Phenolic polyethers

Polycondensations of 3,3-bis(chloromethyl)oxetane and a variety of bisphenols were studied using the microwave-PTC technique (Eq. 23) [35]. The results obtained showed the advantages of microwaves in terms of the molecular weights for crystalline polymer, as reflected in higher values of the transition temperature (T_g) and melting point (T_m) but also in reduction of reaction times for all types of structure.





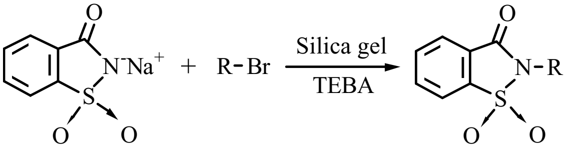
	Microwave	Conventional thermal
Yield	72%	50%
Tg	117°C	103°C
Tm	256°C	232°C

Eq. (23)

5.2.2
N-Alkylations

5.2.2.1 **Saccharin** [36]

Rapid N-alkylation of saccharin (Eq. 24) by a series of halides was performed on silica gel via its sodium salt in a microwave oven. TEBA was shown to have a useful co-catalytic effect (Tab. 5.11).



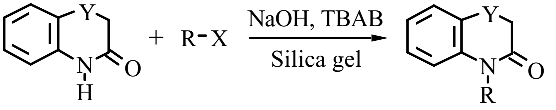
Eq. (24)

Tab. 5.11 N-Alkylation of saccharin with bromides under MW + PTC conditions (750 W).

R	*Catalyst*	*Time (min)*	*Yield (%)*
$PhCH_2$	None	4	8
	SiO_2	4	75
	SiO_2 + TEBA	4	92
n-$C_{16}H_{33}$	SiO_2	6	82
	SiO_2 + TEBA	6	97

5.2.2.2 **Benzoxazinones and Benzothiazinones**

Rapid N-alkylation of title products was performed under PTC with MW irradiation (Eq. 25) [37].



Y = O, S MW 8-10 min. 72-90%

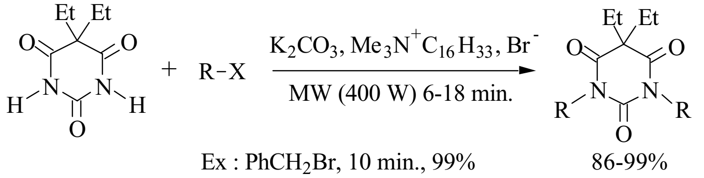
Eq. (25)

Y = O	RX = MeI	8 min.	90%
	$PhCH_2Br$	10 min.	84%
Y = S	RX = MeI	9 min.	86%
	$PhCH_2Br$	10 min.	80%

The Michael reaction of the same compounds with acrylonitrile and methyl acrylate was promoted under the same conditions within 9–10 min [38].

5.2.2.3 **Barbitone [39]**

Under solid–liquid PTC conditions 5,5-diethylbarbituric acid was N,N-dialkylated in a good yield in the presence of a lipophilic ammonium salts and potassium carbonate when reaction mixtures were irradiated in a household microwave oven (Eq. 26).

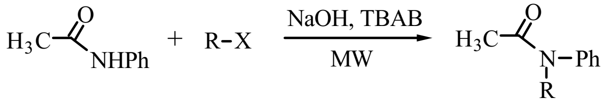


Ex : $PhCH_2Br$, 10 min., 99%   86-99%

Eq. (26)

5.2.2.4 **Amides and Lactams**

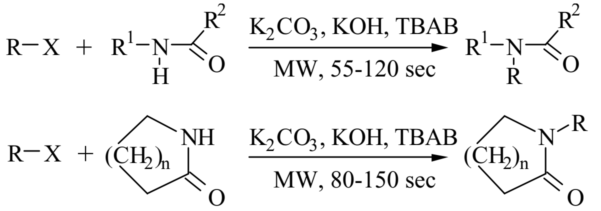
The N-alkylation of acetanilide under the action of microwave irradiation in the presence of a phase-transfer catalyst has also been reported (Eq. 27) [40].



Ex : R-X = *n*-BuI   80 sec.   88%

Eq. (27)

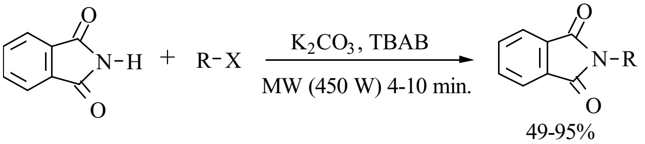
N-Substituted amides and lactams can be rapidly N-alkylated under solid–liquid PTC conditions by use of microwave irradiation. The reactions were performed simply by mixing an amide with 50% excess of an alkyl halide and a catalytic amount of TBAB. These mixtures were absorbed on a mixture of potassium carbonate and potassium hydroxide [41] and then irradiated in an open vessel in a domestic microwave oven for 55–150 s (Eq. 28).



Microwaves   55-120 sec   45-92%

Eq. (28)

The starting reagents in Gabriel amine synthesis, *N*-alkylphthalimides, were obtained under the action of microwave irradiation in a solid–liquid PTC system. The reactions were conducted with high yield (50–90%) simply by mixing phthalimide with 50% excess alkyl halide and catalytic TBAB, which were later absorbed on potassium carbonate. Irradiation of the reaction mixtures in a domestic oven led to the desired phthalimide derivatives (Eq. 29) in a short time (4–10 min) [42].



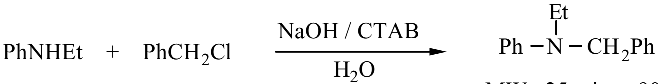
Eq. (29)

Ex : R-X =		
$PhCH_2Cl$	4 min.	93%
n-BuBr	4 min.	73%
n-$C_{12}H_{25}I$	10 min.	95%

The same reaction (R–X = *n*-OctBr) was studied using TBAB and several basic supports. Na_2SO_4 and $CaCO_3$ (yields 93 and 95%, respectively, within 3 min of MW irradiation) were shown to be more efficient than K_2CO_3 (71%) [43].

5.2.2.5 **Aromatic Amines**

N-Ethylaniline was alkylated by reaction with benzyl chloride under liquid–liquid PTC conditions in the presence of 30% sodium hydroxide solution and CTAB as a catalyst. Microwave irradiation (25 min) of the reaction mixture in a sealed vessel afforded *N*-benzyl-*N*-ethylaniline in 90% yield, compared with 16 h of conventional heating (oil bath) (Eq. 30) [24].



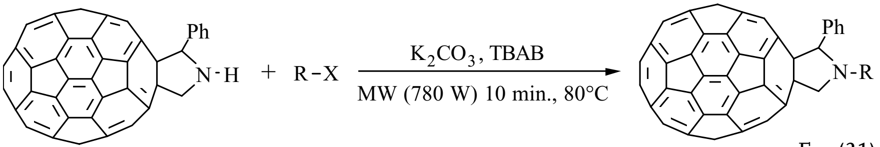
$$\text{PhNHEt} + \text{PhCH}_2\text{Cl} \xrightarrow[\text{H}_2\text{O}]{\text{NaOH / CTAB}} \text{Ph}-\overset{\text{Et}}{\overset{|}{\text{N}}}-\text{CH}_2\text{Ph}$$

Eq. (30)

MW	25 min	90%
Δ	16h	90%

5.2.2.6 **Phenylpyrrolidino[60]fullerene** [44]

A facile synthesis of a series of *N*-alkylpyrrolidino[60]fullerenes by solvent-free PTC under the action of microwaves has been described (Eq. 31).



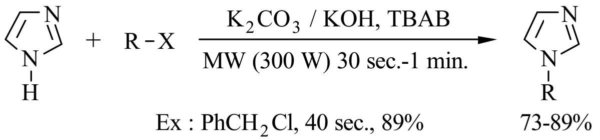
Eq. (31)

Ex : R-X =	
$PhCH_2Br$	70%
CH_2=CH_2-CH_2Br	39%
n-$C_8H_{17}Br$	31%

The synergy between the dry media and microwave irradiation was convincingly demonstrated in this work. For instance, with the allyl compound, the yield is only 16% after 24 h in toluene under reflux, and no reaction occurs after 10 min at 100 °C (classical heating), thus revealing an important specific microwave effect.

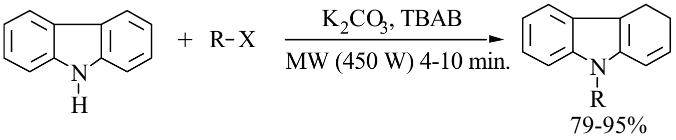
5.2.2.7 Five-membered Nitrogen Heterocycles

Under microwave irradiation several azaheterocycles (i.e. pyrrole, imidazole, indole and carbazole) can react remarkably fast with alkyl halides to give, exclusively, *N*-alkyl derivatives (Eqs. 32 and 33) [45, 46]. Such reactions have been performed simply by mixing an azaheterocycle compound with 50% excess alkyl halide and a catalytic amount of TBAB. The reactants were absorbed either on a mixture of potassium carbonate and potassium hydroxide or on potassium carbonate alone and then irradiated in a domestic microwave oven for 30 s–10 min.



Ex : $PhCH_2Cl$, 40 sec., 89% 73-89%

Eq. (32)

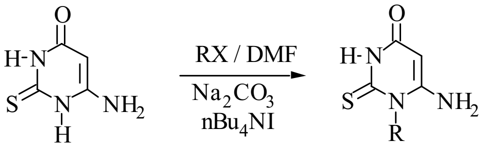


Eq. (33)

Ex : R-X =		
$PhCH_2Cl$	4 min.	70%
n-BuBr	4 min.	73%
n-$C_{10}H_{21}Cl$	10 min.	95%

5.2.2.8 Pyrimidine and Purine Derivatives [47]

Selective N-alkylation of 6-amino-2-thiouracil with different halides has been performed efficiently by use of MW-assisted methods in the presence of small amounts of DMF to improve energy transfer (Eq. 34 and Tab. 5.12). No reaction was observed under the same conditions in a thermoregulated oil bath.



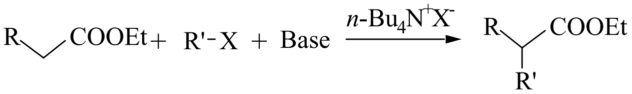
Eq. (34)

Tab. 5.12 Alkylation of 6-amino-2-thiouracil under PTC + MW conditions.

RX	*Time (min)*	*Temperature (°C)*	*Yield (%)*
p-$NO_2C_6H_4CH_2Cl$	6	70– 75	91
p-$BrC_6H_4COCH_2Br$	6	70– 75	95
Br-$(CH_2)_5$-Br	10	80– 85	87
n-$C_{16}H_{33}Br$	9	105–110	91

5.2.3
C-Alkylations of Active Methylenes [48–57]

Several monoalkylations of functionalized acetates (Eq. 35) have been described in a series of papers; the reactions were performed on potassium carbonate, either pure or mixed with potassium hydroxide. Some significant results are given in Tab. 5.13.



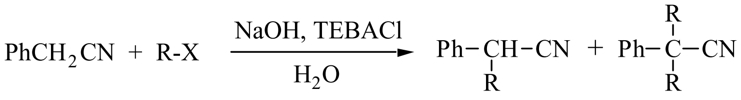
Eq. (35)

Tab. 5.13 Monoalkylation of functionalized acetates in a microwave oven (650 W).

R	*R′X*	*Time (min)*	*Yield (%)*	*Ref.*
$PhSO_2$	$PhCH_2Cl$	3	76	
	n-BuBr	3	83	49
	n-OctBr	3	79	
PhCH=N	$PhCH_2Cl$	1	63	50
	n-BuBr	2	55	
PhS	$PhCH_2Cl$	4.5	83	51, 52
	n-BuBr	4.5	59	
CH_3CO	$PhCH_2Cl$	3	81	53
	n-BuBr	4.5	61	
COOEt	$PhCH_2Cl$	2	72	
	n-BuBr	2	86	54
	AllylBr	2	75	
p-NO_2-C_6H_4	Ph-$(CH_2)_3$-I	3.5	55	55
	Ph-$(CH_2)_8$-I	7	79	
p-NO_2-C_6H_4	Ph-S-$(CH_2)_6$-Br	7	50	55
	Ph-S-$(CH_2)_8$-Br	7	59	

Rapid monoalkylations are achieved in good yield compared with classical methods. Of particular interest is the synthesis of α-amino acids by alkylation of aldimines with microwave activation. Subsequent acidic hydrolysis of the alkylated imine provides leucine, serine, or phenylalanine in preparatively useful yields within 1–5 min [50].

Alkylation of phenylacetonitrile was performed by solid–liquid PTC in 1–3 min under microwave irradiation (Eq. 36 and Tab. 5.14). The nitriles obtained can subsequently be quickly hydrolyzed in a microwave oven to yield the corresponding amides or acids [56].

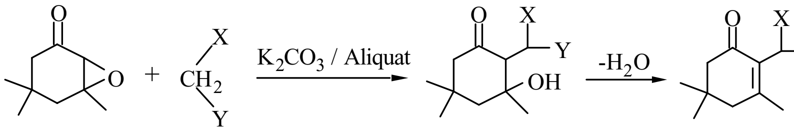


$$PhCH_2CN + R\text{-}X \xrightarrow[H_2O]{NaOH,\ TEBACl} Ph-\underset{R}{\underset{|}{C}}H-CN + Ph-\overset{R}{\overset{|}{\underset{R}{\underset{|}{C}}}}-CN \qquad \text{Eq. (36)}$$

Tab. 5.14 Alkylation of phenylacetonitrile under MW + PTC conditions (NaOH 6 equiv., TEBA 15%).

R	*$PhCH_2CN/RX$*	*Time (min)*	*Power (W)*	*Yield (%)*
$PhCH_2Br$	1.5	1	350	62/32
	1.5	3	160	58/35
n-HexBr	1.5	1	350	70/0
AllylBr	1.5	3	160	48/10
	0.5	2	160	96/2

Functional groups were selectively introduced at the C-2 position of isophorone by epoxide ring-opening by several nucleophiles with active methylene groups. Different behavior was observed depending on the reaction conditions and the nature of the nucleophilic agents [57]. The best experimental systems involved PTC or KF-alumina under solvent-free conditions and MW irradiation (Eq. 37 and Tab. 5.15).



Eq. (37)

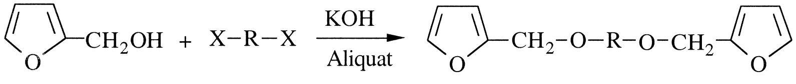
Tab. 5.15 Epoxyisophorone ring opening by reaction with several active methylene compounds under MW + PTC conditions.

X	*Y*	*Temperature (°C)*	*Time*	*Yield (%)*	
				MW	Δ
COOEt	COOEt	95	2 min	83	40
CN	Ph	70	40 s	91	51
CN	CN	58	20 s	94	64
COMe	COOEt	85	2 min	78	40
CN	$CONH_2$	90	1 min	91	54

5.2.4
Alkylations with Dihalogenoalkanes

5.2.4.1 **O-Alkylations**

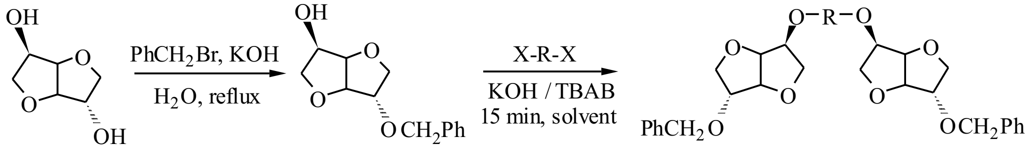
Ethers from alkylation of furfuryl alcohol with dihalides were obtained under solvent PTC + MW conditions with quasi-quantitative yields (Eq. 38) [19].



Ex : X-R-X = $Br(CH_2)_{12}Br$ MW (60 W) 10 min. 170°C 96%

Eq. (38)

In an analogous manner, the selectively obtained *exo* mono-benzylated isosorbide [58] was alkylated by reaction with alkyl dibromides to afford new ethers from dianhydrohexitols moieties separated by ether functions (Eq. 39 and Tab. 5.16) [59].



Eq. (39)

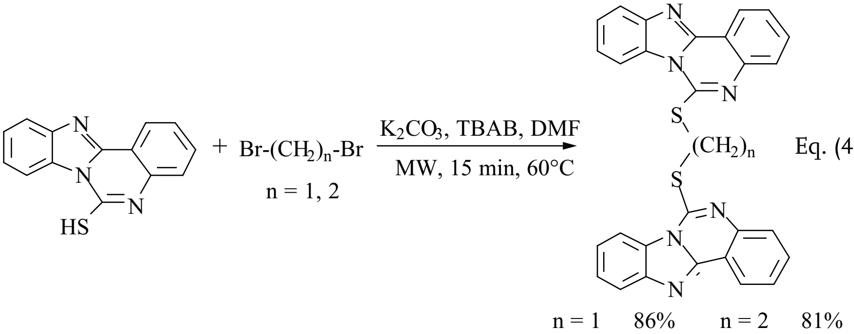
Tab. 5.16 Reaction of monobenzyloxy isosorbide with X–R–X under microwave irradiation.

X	*R*	*Solvent*	*Temperature (°C)*	*Yield (%)* *MW*	Δ
Br	$(CH_2)_8$	Toluene	110	63	
Br	$(CH_2)_6$	Toluene	110	68	
Br	$(CH_2)_4$	Toluene	110	60	
OTs	$(CH_2)_8$	Cyclohexane	80	96	39
OTs	$(CH_2)_6$	Cyclohexane	80	96	40
OTs	$(CH_2)_4$	Cyclohexane	80	96	45
OTs	$CH_2CH_2OCH_2CH_2$	Cyclohexane	80	91	36

Tosylate seemed to be a better leaving group for minimizing competitive *β*-elimination [60].

5.2.4.2 **S-Alkylations**

6-Mercaptobenzimidazo[1,2-*c*]quinazoline reacts with dibromo derivatives under PTC conditions (K_2CO_3/TBAB). Microwave irradiation enabled a striking reduction in reaction times (12 h compared with 15 min) with similar yields (86 and 81%) when compared with conventional heating (Eq. 40) [61].



Eq. (40)

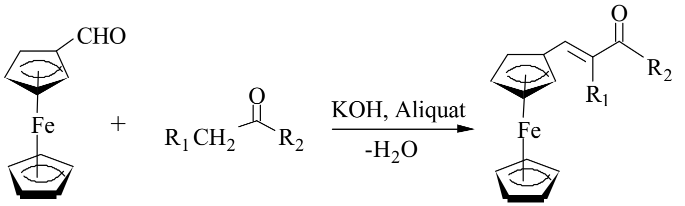
5.2.5
Nucleophilic Additions to Carbonyl Compounds

5.2.5.1 Aldol Condensation

Jasminaldehyde can be obtained classically from heptanal and benzaldehyde in 70% yield within 3 days at room temperature (Eq. 41). By use of a 600-W domestic microwave oven, however, an enhanced yield of 82% was achieved in only 1 min. The amount of side-products (self condensation of *n*-heptanal) decreased from 30 to 18% when this technique was used [62].

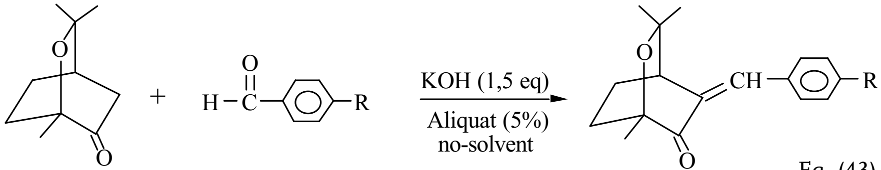
Eq. (41)

A second example of aldolization (Eq. 42) is the "dry" reaction of ferrocene carbaldehyde with carbonyl compounds in the presence of potassium hydroxide, and Aliquat as catalyst [63]. Reactions which are too slow at room temperature are efficiently accelerated by use of microwaves, giving good yields within a few minutes.



Eq. (42)

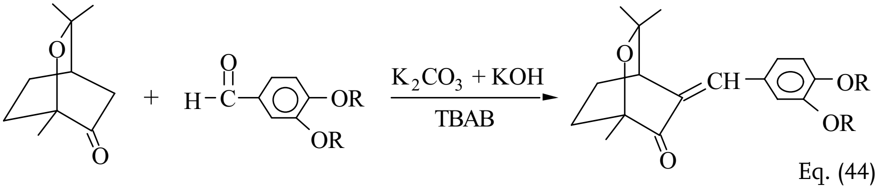
Microwave activation and solvent-free PTC have been shown to be of prime efficiency for the synthesis of new benzylidene cineole derivatives (UV sunscreens) by the Knoevenagel reaction. When performed classically by use of KOH in ethanol at room temperature for 12 h (Eqs. 43 and 44) the yield was 30%. This was improved to 90–94% within 2–6 min under PTC + MW conditions (Tabs 5.17 and 5.18) [27, 28].



Eq. (43)

Tab. 5.17 Benzylidene derivatives of 2-cineolylol from *p*-substituted benzaldehydes [27].

R	*Time (min)*	*Temperature (°C)*	*Yields (%)*	
			MW	Δ
CH_3	2	180	90	20
$N(CH_3)_2$	2	180	94	40
$OC_{16}H_{33}$	6	200	94	12


Eq. (44)

Tab. 5.18 Benzylidene derivatives of 2-cineolylol from 3,4-dialkoxybenzaldehydes [28].

R	*Time (min)*	*Temperature (°C)*	*Yields (%)*	
			MW	Δ
$C_{12}H_{25}$	60	140	80	13
$C_{14}H_{29}$	60	140	78	
$C_{16}H_{33}$	60	140	81	
$C_{18}H_{37}$	60	140	87	

5.2.5.2 **Ester Saponification**

Esters are easily saponified in a few minutes by use of powdered potassium hydroxide (2 mol equiv.) and Aliquat (10 mol%) in the absence of solvent (Eq. 45 and Tab. 5.19) [64].

$$R{-}COOR' \xrightarrow[\text{2. HCl}]{\text{1. KOH, Aliquat}} R{-}COOH \qquad \text{Eq. (45)}$$

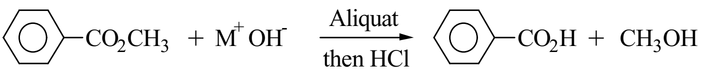
Tab. 5.19 Ester saponification under MW + PTC conditions.

R	*R′*	*Multimode oven (250 W)*		*Monomode reactor (90 W)*			*Classical heating*		
		Time (min)	*Yield (%)*	*Time (min)*	*T (°C)*	*Yield (%)*	*Time (min)*	*T (°C)*	*Yield (%)*
Ph	Me	0.5	87	1	205	96	1	205	90
Ph	*n*-Oct	1	83	2	210	94	2	210	72
2,4,6-$Me_3C_6H_2$	Me	2	75	2	140	84	2	140	38
2,4,6-$Me_3C_6H_2$	*n*-Oct	2	57	4	223	82	4	223	0

From the few examples summarized in Tab. 5.19, three important conclusions can be drawn:

- Rapid and easy reactions occur, even with the most hindered mesitoic esters, which are otherwise practically nonsaponifiable under classical conditions [65].
- The advantage of using a monomode reactor rather than a domestic oven is clearly apparent.
- More interesting fundamentally is the very strong specific nonthermal effect of microwaves, as evidenced by comparison with classical heating. This effect grows as ester reactivity falls.

In a more detailed study, it was shown that MW effects are strongly dependent on the temperature and the nature of the cation associated with hydroxide anion [66] (for example Eq. (46) and Tab. 5.20).



Eq. (46)

Tab. 5.20 Saponification of methyl benzoate under MW + PTC conditions.

M^+	*Base (eq)*	*Temperature (°C)*	*Time (min)*	*Yield (%)* *Without Aliquat*		*With Aliquat*	
				MW	Δ	*MW*	Δ
K^+	2	200	5	94	90	98	98
K^+	1	70	60	77	42	67	65
Na^+	2	200	5	92	77	90	73

5.2.5.3 **Base-catalyzed Transesterifications**

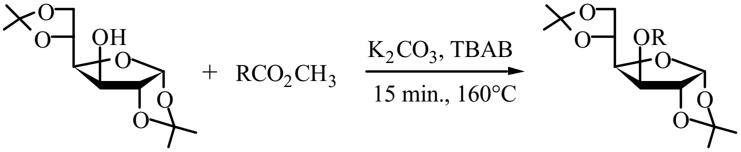
Transesterifications of methyl esters with high boiling alcohols, as shown in Eq. (47), occur readily in microwave ovens because of displacement of the evaporation of the polar volatile methanol (Tab. 5.21) [11].

$$\mathrm{ArCOOMe} + n\text{-}\mathrm{C_8H_{17}OH} \underset{\text{Aliquat}}{\overset{\text{Base}}{\rightleftharpoons}} \mathrm{ArCOO}n\text{-}\mathrm{C_8H_{17}} + \mathrm{MeOH} \qquad \text{Eq. (47)}$$

Tab. 5.21 Base-catalyzed transesterifications under MW + PTC conditions (600 W).

Ar	*Base*	*Time (min)*	*Yield (%)*
C_6H_5	KOH	3	40
	KO*t*-Bu	3	42
	K_2CO_3	2.5	90
2,4,6-$Me_3C_6H_2$	KOH	10	64
	KO*t*-Bu	10	68
	K_2CO_3	10	89

This study was next extended to the synthesis of benzoyl and dodecanoyl derivatives from protected carbohydrates [67]. Microwave-assisted PTC transesterifications with methyl benzoate or dodecanoate were studied for several carbohydrates. Small amounts of dimethylformamide (DMF) were shown to be necessary to provide good yields (76–96%) within 15 min. Rate enhancements when compared to conventional heating (Δ) and specific microwave activation were especially noticeable when less reactive fatty compounds were involved (Eq. 48).



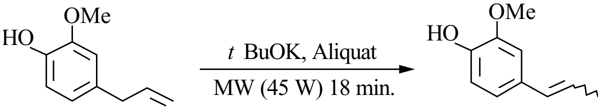
Eq. (48)

R = Ph		MW	44%	
	DMF	MW	96%	Δ 21%
R = $CH_3(CH_2)_{10}$	DMF	MW	88%	Δ 0% (id. 12h)

5.2.6
Deprotonations

5.2.6.1 Base-catalyzed Isomerization of Allylic Aromatic Compounds [68]

Eugenol is a natural product available from a variety of essential oils (cinnamon-tree or pimentos leaves). Its isomerization (Eq. 49) into isoeugenol, the starting material for synthetic vanillin, is rather difficult and proceeds in modest yields under relatively harsh conditions. It can, however, be very efficiently prepared by use of 2.2 molar equivalents of base and catalytic (5%) amounts of Aliquat in the absence of solvent.

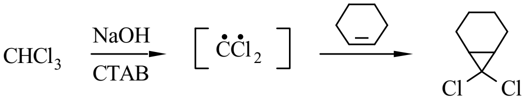


94%

Eq. (49)

5.2.6.2 Carbene Generation (α-Elimination) [69]

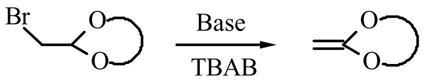
Dichlorocarbene has been generated under solid–liquid conditions by use of microwaves. Heating a mixture of $CHCl_3$, powdered NaOH, and trace amounts of CTAB under reflux in cyclohexene with microwave irradiation afforded 90% dichloronorcarane (Eq. 50) within 20 min, compared with 81% in 60 min without microwave exposure, or only 12% in 90 min without the catalyst.



Eq. (50)

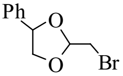
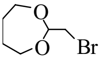
5.2.6.3 β-Elimination

Bromoacetals in basic media can be converted to cyclic ketene acetals (Eq. 51). These β-eliminations, previously performed under solid–liquid PTC without solvent and with sonication [70], were further improved by microwave irradiation (Tab. 5.22) [71].



Eq. (51)

Tab 5.22 *β*-Elimination from bromoacetals in a monomode reactor (75 W); comparison with sonochemical conditions and classical heating.

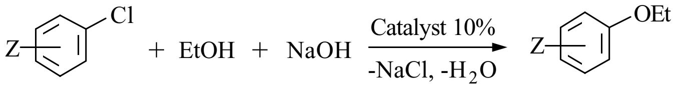
	Base	*Ultrasound conditions*			*Microwave conditions*			*Classical heating*		
		t (h)	*T (°C)*	*Yield (%)*	*t (min)*	*T (°C)*	*Yield (%)*	*t (min)*	*T (°C)*	*Yield (%)*
	KOH, TBAB	1	75	81	10	130	81			
	t-BuOK, TBAB	1	35	70	5	75	87	5	75	36
	KOH, TBAB	1	75	81	10		28			
	t-BuOK, TBAB	1	45	70	5	60	95	5	64	41

With potassium *t*-butoxide and TBAB, higher yields are obtained more rapidly than under sonication conditions or with conventional heating.

5.2.7
Miscellaneous Reactions

5.2.7.1 Aromatic Nucleophilic Substitution (S_NAr)

The irradiation of a mixture of *ortho*- or *para*-nitrochlorobenzene and ethanol in the presence of sodium hydroxide and a phase-transfer agent yields the corresponding ethoxy aromatic compounds within a few minutes (Eq. 52) [72]. The same procedure was subsequently applied to 2-chlorophenol [73]. In both reactions PEG 400 was shown to be the most efficient catalyst (Tab. 5.23).



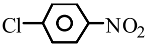
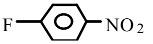
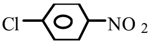
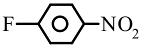
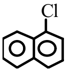
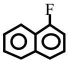
Eq. (52)

Tab. 5.23 Aromatic nucleophilic substitution under MW + PTC conditions (420–700 W).

Z	*Catalyst*	*Time (min)*	*Yield (%)*	*Ref.*
4-NO_2	None	2	14	
	$PhCH_2N^+Me_3Cl^-$	2	51	72
	PEG 400	2	99	
2-NO_2	PEG 400	2	99	72
2-OH	None	2	63	
	$PhCH_2N^+Me_3Cl^-$	2	70	73
	PEG 400	2	82	

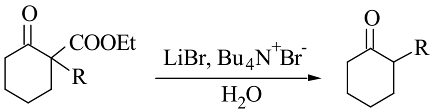
Solvent-free S_NAr reactions under solid–liquid PTC conditions were realized by using methoxide or phenoxide as nucleophiles. The main results, and comparison with those from classical heating, are indicated in Tab. 5.24 for activated (e.g. 4-nitrohalobenzenes) or nonactivated (e.g. α-naphthyl halides) substrates [74].

Tab. 5.24 Solvent-free PTC S_NAr reactions under MW + PTC conditions (potassium salts).

	Catalyst	*Time (min)*	*Temperature (°C)*	*Yield (%)* *MW*	 Δ
 $+ PhO^-$	18-crown-6	5	150	93	86
 $+ PhO^-$	–	30	150	98	73
 $+ CH_3O^-$	18-crown-6	20	170	90	37
 $+ CH_3O^-$	18-crown-6	3.5	80	100	81
 $+ CH_3O^-$	18-crown-6	60	100	71	27
 $+ CH_3O^-$	18-crown-6	60	80	94	57

5.2.7.2 Dealkoxycarbonylations of Activated Esters (Krapcho Reaction)

This type of reaction is usually best performed in DMSO solution. A simpler procedure has been proposed which uses anionic activation and microwave irradiation, with a metallic salt as the reagent and a PTC in the absence of solvent [75]. This procedure was applied to the striking example of cyclic β-ketoesters with considerable improvements (Eq. 53 and Tab. 5.25) which are readily apparent when the maximum yields obtained under classical Krapcho conditions (<20% when R–H) are considered [76].



Eq. (53)

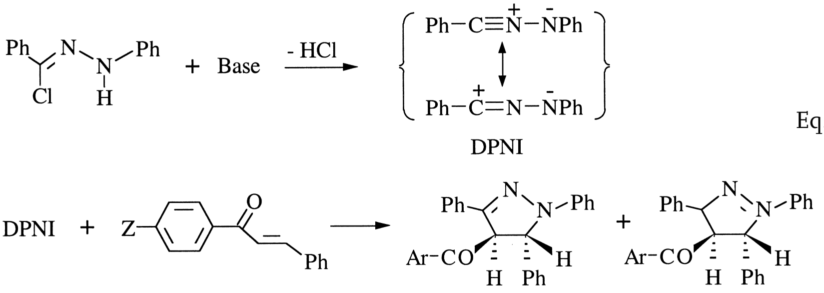
Tab. 5.25 Dealkoxycarbonylation of cyclic β-ketoesters in a monomode reactor.

R	*Microwave conditions* *Time (min)*	 *Power (W)*	*T (°C)*	*Yield (%)*
H	8	30	138	96
Et	15	30	160	94
n-Bu	20	45	167	89
n-Hex	20	90	186	87

To verify the specific effects of microwave irradiation, the second experiment (R = Et) was performed using conventional oil bath heating under the same conditions of time and temperature (15 min, 160 °C). No reaction was observed. Further heating for 3 h led to total conversion but the yield (60 %) was limited by product degradation. Clearly, when compared with conventional heating, microwave heating results in a large reduction in time, simplified experimental conditions, and the prevention of product degradation at high temperature.

5.2.7.3 **1,3-Dipolar Cycloaddition of Diphenylnitrilimine** [77]

Diphenylnitrilimine (DNPI) can be subjected to 1,3-dipolar cycloaddition with activated double bonds as dipolarophiles (Eq. 54). It can be generated *in situ* by reaction of hydrazonoyl chloride with a base.



Eq. (54)

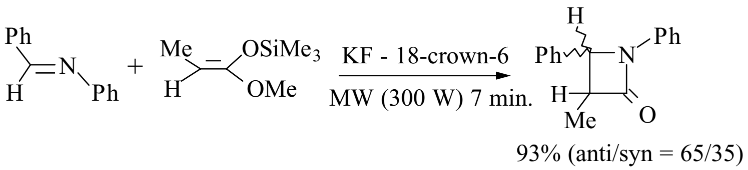
The cycloaddition can be performed almost quantitatively within 6 min under the action of microwaves, with KF as base, and Aliquat. For the sake of illustration, results for substituted chalcones are listed in Tab. 5.26. When the same reactions are performed all other factors being equal (time, temperature), no reaction occurs under classical thermal conditions. This behavior once more confirms a specific radiation effect.

Tab. 5.26 1,3-Dipolar cycloaddition of DNPI to chalcones in a monomode reactor (30 W).

Z	*Time (min)*	*T (°C)*	*Yield (%)*
H	6	170	90
Br	5	170	93
Cl	6	174	95
Me	6	168	87
OMe	6	175	89

5.2.7.4 **Synthesis of *β*-Lactams** [78]

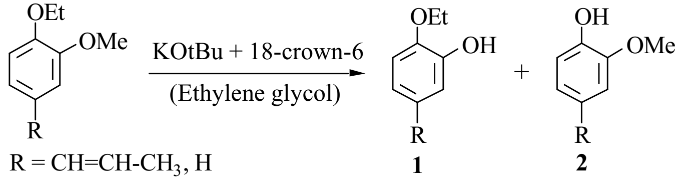
With KF in the presence of a phase-transfer agent (18-crown-6) silyl ketene acetals react with aldimines to give *β*-lactams within a few minutes under the action of microwave irradiation in closed Teflon vessels (Eq. 55).



Eq. (55)

5.2.7.5 **Selective Dealkylations of Aromatic Ethers**

Ethylisoeugenol and ethoxyanisole can be selectively demethylated or deethylated by use of potassium *t*-butoxide in the presence of 18-crown-6 (Eq. 56) [79].



Eq. (56)

Under solvent-free conditions only deethylation is observed whereas in the presence of ethylene glycol (EG), the selectivity is totally reversed and demethylation becomes the major process. In both, considerable increases in reaction rate were observed under the action of microwave irradiation when compared with classical heating (Δ) (Tab. 5.27).

Tab. 5.27 Selective dealkylations of 2-ethoxyanisole under MW + PTC conditions (R = H).

		Time (min)	*Temperature (°C)*	*Starting material (%)*	*1 (%)*	*2 (%)*
–	MW	20	120	7	–	90
–	Δ	20	120	48	–	50
EG	MW	75	180	–	72	23
EG	Δ	75	180	98	–	–

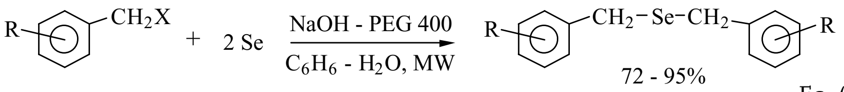
This procedure was extended to the hundred-gram scale with success because, under rather similar conditions, yields remained excellent (82%) requiring only a slight modification in temperature (140 instead of 120 °C) (Tab. 5.28) [12].

Tab. 5.28 Deethylation of 2-ethoxyanisole within 20 min under MW + PTC conditions (KO*t*Bu 2 equiv.; TDA-1 10%).

Reactor	*Temperature (°C)*	*Amounts of materials [g (mmol)]*			*Total amount (g)*	*Yield (%)*
		Ethoxyanisole	*KOtBu*	*TDA-1*		
MW S402	120	0.76 (5)	1.12 (10)	0.324 (1)	2.206	90
MW S1000	140	37.24 (245)	54.98 (490)	15.9 (49)	108.12	82

5.2.7.6 **Synthesis of Dibenzyl Diselenides**

A simple, rapid and efficient method has been reported for the synthesis of dibenzyl diselenides under the action of MW irradiation. Benzyl halides are reacted with selenium powder in the presence of a base and phase-transfer agent (Eq. 57 and Tab. 5.29) [80]. The reactions were performed either in THF or in C_6H_6–H_2O.



Eq. (57)

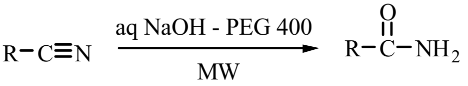
Tab. 5.29 Dibenzyl diselenides under MW + PTC conditions (15 min, 750 W; 15 equiv. NaOH; 5% PEG 400).

R	*X*	*Yield (%)*
H	Cl	75
H	Br	95
4-Br	Br	85
4-CH_3	Br	91
4-NO_2	Br	72

The same authors have more recently described the synthesis of dibenzoyl diselenides by reaction of selenium with sodium hydroxide under PTC and MW irradiation conditions to afford sodium diselenides which react further with benzoyl chloride at 0 °C [81].

5.2.7.7 **Selective Hydrolysis of Nitriles to Amides** [82]

As has already been mentioned (Sect. 5.3), nitriles can be hydrolyzed to amides or acids [56]. Nitriles can be efficiently converted into the corresponding amides in the presence of PEG-400 and aqueous sodium hydroxide system under the action of MW irradiation (Eq. 58 and Tab. 5.30).



$$R-C\equiv N \xrightarrow[\text{MW}]{\text{aq NaOH - PEG 400}} R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$$

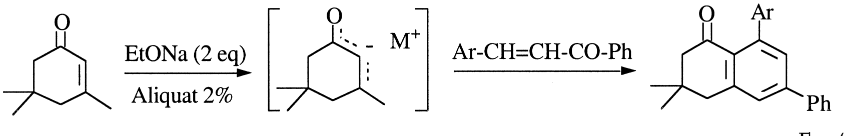
Eq. (58)

Tab. 5.30 MW-promoted hydrolysis of nitriles by use of the NaOH–PEG system.

R	*Time (s)*	*Yield (%)*
Ph_2CH	90	94
Ph	45	83
$PhCH_2$	90	71
$C_{17}H_{35}$	60	78
2-Pyridyl	40	52

5.2.7.8 **Synthesis of Diaryl-α-tetralones** [83]

One-pot syntheses of diaryl-α-tetralones by Michael condensation and subsequent Robinson annulation reactions of isophorone with chalcones were performed efficiently in a solvent-free PTC system under the action of MW irradiation. Compared with conventional heating substantial rate enhancements were observed, within very short reaction times, by use of microwaves (Eq. 59 and Tab. 5.31). They were far better than those achieved by the classical method (NaOEt in EtOH under reflux for 24 h; 40–56%).



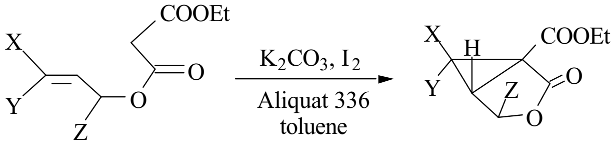
Eq. (59)

Tab. 5.31 Synthesis of diaryl-α-tetralones from isophorone and chalcone under MW + PTC conditions.

Ar	*Time (min)*	*Temperature (°C)*	*Yield (%)*	
			MW	Δ
C_6H_5	5	110	86	51
p-CH_3O-C_6H_4	5	108	86	51
p-CH_3-C_6H_4	6	120	89	52
o-Cl-C_6H_4	5	110	88	54
p-Cl-C_6H_4	6	110	86	56

5.2.7.9 **Intramolecular Cyclization**

Malonic acid allylic esters undergo intramolecular cyclization reaction under solid–liquid phase transfer catalytic conditions in the presence of Aliquat 336, potassium carbonate, and iodine (Eq. 60) [84]. Application of microwave irradiation to this procedure enabled 2–3-fold reduction in the reaction time compared with conventional conditions. It was found that use of microwaves affected the *exo*/*endo* diastereoisomers ratio – a linear correlation between microwave power and *exo* isomer concentration was observed [85].

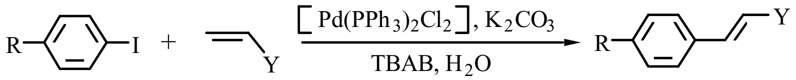


Eq. (60)

Microwave (boiling toluene)	10-16 min	65-67%
Conventional heating (boiling toluene)	25-30 min	65-94%
Room temperature (toluene)	6-13 h	65-94%

5.2.7.10 **Heck Cross-coupling Reaction**

Reaction of organic halides with alkenes catalyzed by palladium compounds (Heck-type reaction) is known to be a useful method for carbon–carbon bond formation at unsubstituted vinyl positions. The first report on the application of microwave methodology to this type of reaction was published by Hallberg et al. in 1996 [86]. Recently, the palladium catalyzed Heck coupling reaction induced by microwave irradiation was reported under solventless liquid–liquid phase-transfer catalytic conditions in the presence of potassium carbonate and a small amount of $[Pd(PPh_3)_2Cl_2]$-TBAB as a catalyst [87]. The arylation of alkenes with aryl iodides proceeded smoothly to afford exclusively *trans* product in high yields (86–93 %) (Eq. 61).

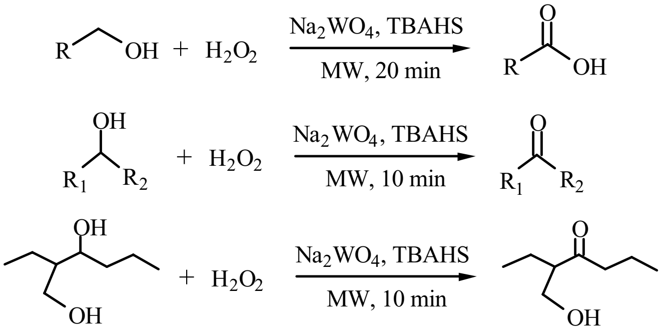


Eq. (61)

Microwaves	10 min	86-93%
Conventional heating	10 min	5-15%
	3-7 h	54-90%

5.2.7.11 **Oxidation Reactions**

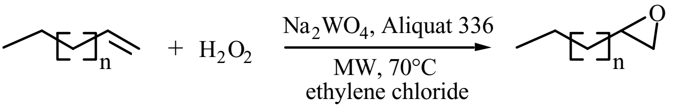
By a modification of Noyori's procedure of alcohol oxidation by hydrogen peroxide [88], primary and secondary alcohols have been oxidized to the equivalent carboxylic acids and ketones within 20–30 min under the action of microwave irradiation [89]. The reactions were performed under liquid–liquid phase-transfer catalytic conditions using 30 % aqueous H_2O_2 in the presence of sodium tungstate and tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst. The experimental procedure involves simple mixing of an alcohol, $Na_2WO_4.H_2O$, and TBAHS then addition of 30 % aqueous H_2O_2, in 25 : 1 : 1 : 125 molar ratios for primary alcohols and 25 : 1 : 1 : 40 molar ratios for secondary alcohols, in an open vessel. The best results were obtained when the temperatures of reaction mixtures were 90 °C and 100 °C for primary and secondary alcohols, respectively (Eq. 62)



Eq. (62)

Microwaves	10-20 min	60-97%
Conventional heating at 90°C	4 h	83-96%

Hydrogen peroxide has also been used with microwave irradiation for the epoxidation of simple or cyclic alkenes. The reactions were accomplished under liquid–liquid PTC conditions in ethylene chloride solution in the presence of Na_2WO_4 and Aliquat 336 as catalysts. The best results were obtained at 70 °C when the concentration of hydrogen peroxide was set to 8% and the pH of aqueous phase was kept below 2 (Eq. 63) [90].



Eq. (63)

Microwaves	100 min	91-98%
Conventional heating	100 min	54-65%

5.2.7.12 **S-Alkylation of *n*-Octyl Bromide** [43]

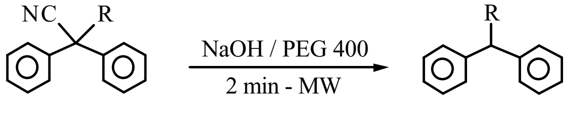
The synthesis of octylthiocyanate by reaction of *n*-octyl bromide with KSCN, and its subsequent isomerization to isothiocyanate, have been realized by use of TBAB under the action of MW irradiation. The effect of inorganic solid supports was studied (SiO_2, K10, graphite, NaCl) (Eq. 64).

$$\text{R-Br} \xrightarrow[\text{4 min - MW}]{\text{KSCN / TBAB}} \text{R-SCN} \longrightarrow \text{R-NCS} \qquad \text{Eq. (64)}$$

support	% R-SCN	% R-NCS	Σ Yield
SiO_2	92	8	36
K10	95	5	30
Graphite	71	29	68
NaCl	52	48	94

5.2.7.13 **Reductive Decyanation of Alkyldiphenylmethanes** [91]

The reaction was performed in aqueous NaOH and PEG-400 as phase-transfer agent (Eq. 65).



Eq. (65)

$R = H, (CH_2)_nCH_3, CH_2CH_2CH_2NR_2$ (R = H 94%)

5.3
Conclusion

The use of microwave irradiation to provide the activation energy for synthetic chemistry certainly leads to faster and cleaner reactions when compared to conventional heating. The coupling of microwave technology with solvent-free solid–liquid PTC conditions constitutes a new and particularly efficient, powerful and attractive method.

Significant improvements in yields or reaction conditions can be achieved, together with considerable simplification of operating procedures. The powerful synergistic combination of PTC and microwave techniques has certainly enabled an ever increasing number of reactions to be conducted under clean and mild conditions. The inherent simplicity of the method can, furthermore, be allied with all the advantages of solvent-free procedures in terms of reactivity, selectivity, economy, safety, and ease in manipulation.

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6

Organic Synthesis Using Microwaves and Supported Reagents

Rajender S. Varma

6.1

Introduction

In the electromagnetic radiation region, microwaves (0.3 GHz–300 GHz) lie between radiowave (Rf) and infrared (IR) frequencies with relatively large wavelengths (1 mm–1 m). Microwaves, nonionizing radiation incapable of breaking bonds, are a form of energy that manifest as heat through their interaction with the medium or materials wherein they can be reflected (metals), transmitted (good insulators that will not heat) or absorbed (decreasing the available microwave energy and rapidly heating the sample). This unconventional microwave (MW) energy source has been used for heating food materials for almost 50 years [1] and is now being utilized for a variety of chemical applications including organic synthesis [2–11] wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, nonpolar molecules being inert to the MW dielectric loss [12]. The initial experiments with microwave heating exploited the use of high dielectric solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) in a household kitchen MW oven. The rate enhancements in such reactions are now believed to be due to rapid superheating of the polar solvents and pressure effects [12]. However, in these solution-phase reactions, the development of high pressures, and the use of specialized sealed vessels are some of the limitations, although they have been circumvented by the introduction of commercial MW instruments with appropriate temperature and pressure controls.

Heterogeneous reactions facilitated by supported reagents on inorganic oxide surfaces have received attention in recent years, both in the laboratory as well as in industry. Although the first description of the surface-mediated chemical transformation dates back to 1924 [13], it was not until almost half a century later that the technique received extensive attention with the appearance of several reviews, books and account articles [14–22].

A related development that had profound impact on heterogeneous reactions is the use of microwave (MW) irradiation techniques for the acceleration of organic reactions. Since the appearance of initial reports on the application of microwaves for chemical synthesis in polar solvents [11], the approach has blossomed into a useful

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

technique for a variety of applications in organic synthesis and functional group transformations, as is testified by a large number of publications and review articles on this theme [2–10, 22–25]. Although reactions in conventional organic solvents [23], ionic liquids [26–28] and aqueous media [29] have grown in view of the availability of newer commercial MW systems, the focus has shifted to less cumbersome solvent-free methods wherein the neat reactants, often in the presence of mineral oxides or supported catalysts [2–6, 8, 10, 22, 25], undergo facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents. The application of microwave irradiation with the use of catalysts or mineral supported reagents, under solvent-free conditions, enables organic reactions to occur expeditiously at ambient pressure [2–6, 8, 10, 22], thus providing unique chemical processes with special attributes such as enhanced reaction rates, higher yields and the associated ease of manipulation. These reactions are effected by the reagents immobilized on the porous solid supports and have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier workup.

The ready availability of inexpensive household MW ovens that can be safely used for solvent-free reactions and an opportunity to work with open vessels, thus avoiding the risk of high pressure development, are the main reasons for the popularity of this approach worldwide. The bulk temperature attained in these solvent-free reactions is relatively low although higher localized temperatures may be reached during microwave irradiation. Unfortunately, in many of the reactions reported such accurate temperature measurements have not been made. Although there is relatively poor understanding of the reasons for dramatic rate acceleration and some researchers are skeptical in terms of reproducibility, this MW strategy, however, has been the most widely practiced approach in laboratories around the globe. The recyclability of some of these solid supports makes these processes into truly eco-friendly green procedures.

6.2
Microwave-accelerated Solvent-free Organic Reactions

The initial laboratory-scale feasibility of microwave promoted solvent-free procedure [24] has now been illustrated for a wide variety of useful chemical transformations such as protection/deprotection (cleavage), condensation, rearrangement reactions, oxidation, reduction, and in the synthesis of several heterocyclic compounds on mineral supports [4, 8, 22]. A range of industrially significant chemical entities and precursors such as, imines, enamines, enones, nitroalkenes, sulfur compounds and heterocycles have been synthesized in a relatively environmentally benign manner using MW approach [2–6, 8, 10, 22, 25]. A vast majority of these solventless reactions have been performed in open glass containers such as test tubes, beakers and round-bottomed flasks etc. using neat reactants in an unmodified household MW oven or a commercial MW equipment usually operating at 2450 MHz. The general procedure involves simple mixing of neat reactants with the catalyst, their adsorption on mineral or “doped” supports, and exposing the reaction mixture to irradiation in a microwave oven.

In many cases, the comparison of a reaction accelerated by microwave irradiation has been made with the same reaction in an oil bath at the same bulk temperature. Unfortunately, there have been quite a few reports in the chemical literature that have not been conducted with such proper control of conditions and consequently a fair comparison is not possible. Nevertheless, using this MW approach, the problems associated with waste disposal of solvents that are used several fold in chemical reactions, and excess usage of chemicals are avoided or minimized. The discussion pertaining to the preparation of supported reagents or catalysts has not been included in this chapter because numerous review articles are available on this theme [14–22].

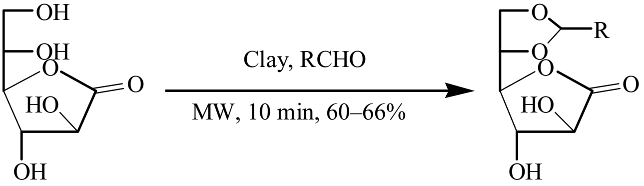
6.2.1
Protection–Deprotection Reactions

The protection–deprotection reaction sequences constitute an integral part of organic syntheses such as the preparation of monomers, fine chemicals, and reaction intermediates or precursors for pharmaceuticals. These reactions often involve the use of acidic, basic or hazardous reagents and toxic metal salts [30]. The solvent-free MW-accelerated protection/deprotection of functional groups, developed during the last decade, provides an attractive alternative to the conventional cleavage reactions.

6.2.1.1 Formation of Acetals and Dioxolanes

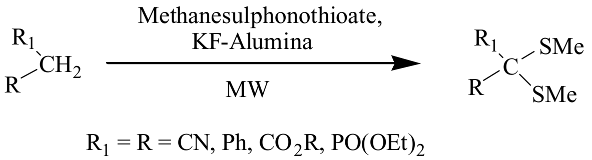
Loupy and colleagues have prepared acetals of 1-galactono-1,4-lactone in excellent yields [31] by adsorbing the lactone and the aldehyde on montmorillonite K 10 or KSF clay followed by exposing the reaction mixture to microwave irradiation (Scheme 6.1).

Aldehydes and ketones have been protected as acetals and dioxolanes using orthoformates, 1,2-ethanedithiol or 2,2-dimethyl-1,3-dioxolane by Hamelin and coworkers. This acid-catalyzed reaction proceeds in the presence of *p*-toluenesulfonic acid (*p*-TsOH) or KSF clay under solvent-free conditions (Scheme 6.2). The yields ob-



Scheme 6.1 Formation of acetal derivatives of 1-galactono-1,4-lactone.

Scheme 6.2 Formation of dioxolanes.



Scheme 6.3 Formation of thioacetals.

tained with the microwave method are better than those obtained using conventional heating in an oil bath [32].

Thioacetals have been prepared using essentially a similar technique [33]. The active methylene compounds are adsorbed on KF-alumina, admixed with methanesulfonothioate and are irradiated in microwave oven to produce thioacetals in good yields (Scheme 6.3).

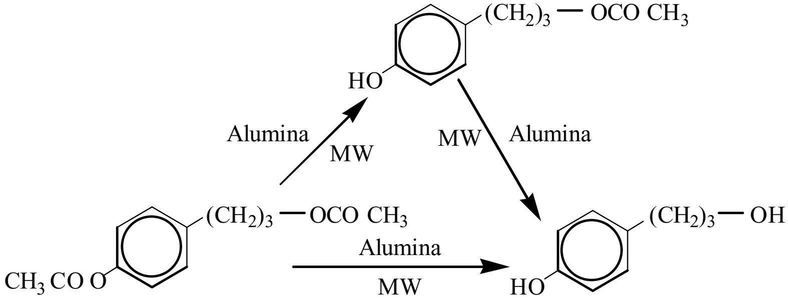
6.2.1.2 N-Alkylation Reactions

Several solvent-free N-alkylation reactions have been reported which involve the use of phase transfer agent, tetrabutylammonium bromide (TBAB), under microwave irradiation conditions, an approach that is described in Chapt. 5 [34].

6.2.1.3 Deacylation Reactions

The first report on the utility of recyclable alumina as a viable support surface for deacylation reaction is credited to Varma and his colleagues [35]. This high school science project demonstrated that the orthogonal deprotection of alcohols is possible under solvent-free conditions on neutral alumina surface using MW irradiation (Scheme 6.4). Interestingly, chemoselectivity between alcoholic and phenolic groups in the same molecule has been achieved simply by varying the reaction time; the phenolic acetates are deacetylated faster than alcoholic analogs [35].

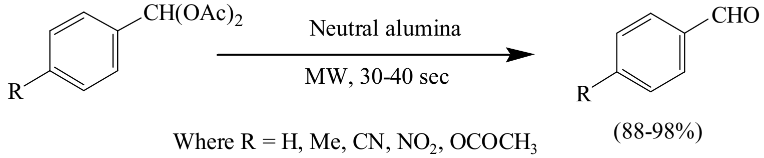
In an utmost simplistic approach, an unmodified household microwave oven has been used in this study with excellent results and the generation of higher temperatures is simply avoided by intermittent heating [35].



Scheme 6.4 Deacylation of alcohols and phenols on alumina.

6.2.1.4 **Cleavage of Aldehyde Diacetates**

A brief exposure of diacetate derivatives of aromatic aldehydes to MW irradiation on neutral alumina surface rapidly regenerates aldehydes (Scheme 6.5) [36]. The selectivity in these deprotection reactions is achievable by merely adjusting the time of irradiation. As an example, for molecules bearing acetoxy functionality (R = OAc), the aldehyde diacetate is selectively removed in 30 s, whereas an extended period of 2 min is required to cleave both the diacetate and ester groups. The yields obtained are better than those possible by conventional heating methods and the procedure is applicable to compounds bearing olefinic moieties such as cinnamaldehyde diacetate [36].

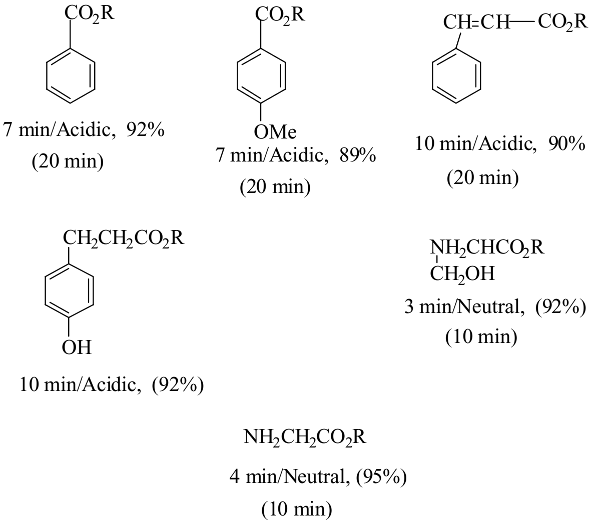


Scheme 6.5 Cleavage of aldehyde diacetates on alumina.

Interestingly, acylal formation has been accomplished with acetic anhydride [37] on K 10 clay (75–98%) as well as deacylation [38].

6.2.1.5 **Debenzylation of Carboxylic Esters**

An efficient procedure for the debenzylation of esters has been reported by Varma et al. under solvent-free conditions (Scheme 6.6) [39]. By altering the surface charac-



Where R= $CH_2C_6H_5$ and time in parentheses refer to deprotection in oil bath at the same temperature

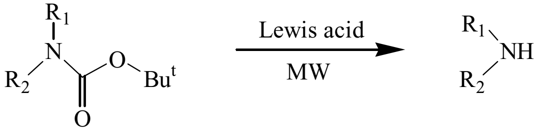
Scheme 6.6 Debenzylation of carboxylic esters on alumina.

teristics of the solid support, the cleavage of 9-fluorenylmethoxycarbonyl (Fmoc) group and related protected amines can be achieved in a similar fashion. The optimum conditions for cleavage of N-protected moieties require the use of basic alumina and irradiation time of 12–13 min at ~130–140 °C.

The hydrolysis of allyl esters has been achieved with K 10 clay [40].

6.2.1.6 Selective Cleavage of the *N-tert*-butoxycarbonyl Group

This approach may find application in peptide bond formation that would eliminate the use of irritating and corrosive chemicals such as trifluoroacetic acid and piperidine as has been demonstrated recently for the deprotection of N-boc groups (Scheme 6.7); a solvent-free deprotection of *N-tert*-butoxycarbonyl group occurs upon exposure to microwave irradiation in the presence of neutral alumina "doped" with aluminum chloride (Scheme 6.7) [41].



Scheme 6.7 Deprotection of *N-tert*-butoxycarbonyl group.

6.2.1.7 Desilylation Reactions

A variety of alcohols, protected as *t*-butyldimethylsilyl (TBDMS) ether derivatives, can be rapidly regenerated to the corresponding hydroxy compounds on alumina surface using MW irradiation (Scheme 6.8) [42]. This approach prevents the use of corrosive fluoride ions that are normally employed for cleaving the silyl protecting groups.

Deprotection of trimethyl silyl ether has also been accomplished (88–100 %) on K 10 clay [43] or oxidative cleavage (70–95 %) in presence of clay and iron(III) nitrate [44].

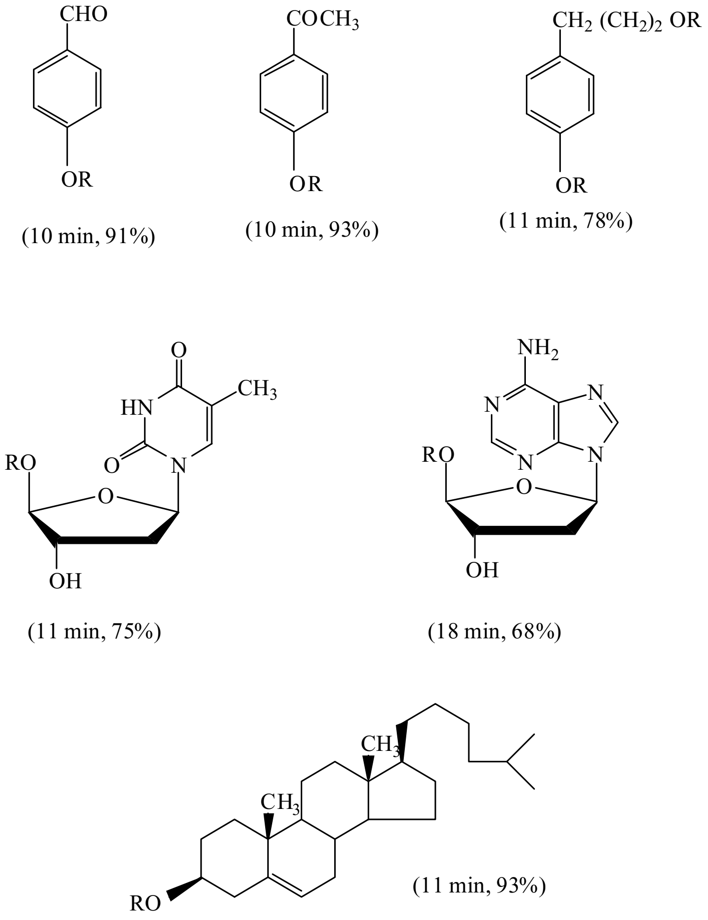
6.2.1.8 Dethioacetalization Reaction

Thio acetals and ketals are important protecting groups employed in organic manipulations. The regeneration of carbonyl compounds by cleavage of acid and base stable thioacetals and thioketals is a challenging task. Normally, the cleavage of thioacetals requires the use of toxic heavy metals such as Ti^{4+}, Cd^{2+}, Hg^{2+}, Ag^{2+}, Tl^{3+}, or uncommon reagents such as benzeneseleninic anhydride [45]. A high yielding solid-state dethioacetalization reaction has been reported by Varma et al. using clayfen (Scheme 6.9) [45]. The reaction is quite general and is devoid of any byproducts formation except for substrates bearing free phenolic groups where ring nitration may compete with dethioacetalization.

A report on the deprotection of thioacetals with clayan (80–89 %) soon followed [46].

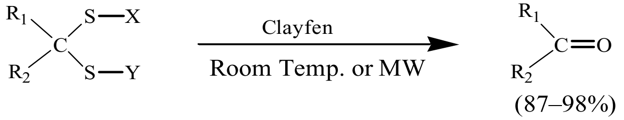
6.2.1.9 Deoximation Reactions

Oximes have been used as protecting groups for carbonyl compounds owing to their hydrolytic stability. Consequently, the development of newer deoximation reagents



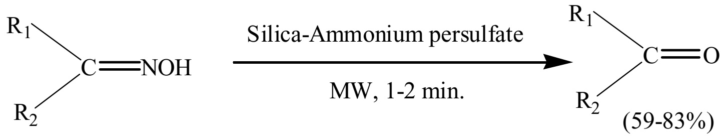
Where R = *tert*-Butyldimethylsilyl (TBDMS)

Scheme 6.8 Desilylation reaction on alumina.



Where R_1 = Ph, *p*-CH_3 C_6H_4, *p*-$NO_2C_6H_4$; R_2 = H ; X–Y = –$(CH_2)_2$–
$R_1 = R_2 = C_2H_5$; X–Y = –$(CH_2)_2$– ; $R_1 = R_2$ = Ph ; X = Y = C_2H_5
R_1 = Ph ; $R_2 = CH_3$; X–Y = –$(CH_2)_2$–
R_1–R_2 = isoflavanolyl , 2-Methylcyclohexyl; X–Y = –$(CH_2)_2$–

Scheme 6.9 Dethioacetalization reaction using clayfen.

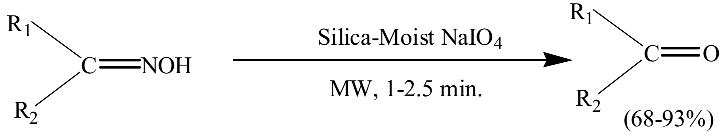


Where $R_1 = C_6H_5$, p-Cl C_6H_4, p-CH_3 C_6H_4, p-CH_3O C_6H_4; $R_2 = CH_3$
R_1 = 2-thienyl, 1 naphthyl, C_6H_5, p-NO_3 C_6H_5, m, p-$(CH_3O)_2$ C_6H_3; R_2 = H
and $R_1 = R_2$ = Cyclohexyl

Scheme 6.10 Deoximation of carbonyl compounds by silica-supported ammonium persulfate.

has continued with the availability of a wide range of such agents namely, Raney nickel, pyridinium chlorochromate, pyridinium chlorochromate–H_2O_2, triethylammonium chlorochromate, dinitrogen tetroxide, trimethylsilyl chlorochromate, Dowex-50, dimethyl dioxirane, H_2O_2 over titanium silicalite-1, zirconium sulfophenyl phosphonate, *N*-haloamides, and bismuth chloride [47, 48].

The quest for a solvent-free deprotection procedure has led to the use of relatively benign reagent, ammonium persulfate on silica, for regeneration of carbonyl compounds (Scheme 6.10) [48]. Neat oximes are simply mixed with solid supported reagent and the contents are irradiated in a MW oven to regenerate free aldehydes or ketones in a process that is applicable to both, aldoximes and ketoximes. The critical role of surface needs to be emphasized since the same reagent supported on clay surface delivers predominantly the Beckmann rearrangement products, the amides [49].



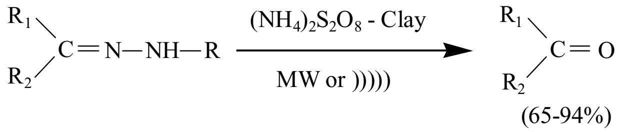
Where $R_1 = CH_3$; R_2 = Ph, p-Cl C_6H_4, p-Br C_6H_4, p-CH_3 C_6H_4, p-CH_3O C_6H_4; p-NH_2 C_6H_4,
$R_1 = R_2$ = Ph; $R_1 = R_2$ = Cyclohexyl, tetrahydronaphthyl,
and $R_1 = C_2H_5$, R_2 = n-Butyl

Scheme 6.11 Deoximation of ketoximes with silica-supported periodate.

A facile deoximation procedure with sodium periodate impregnated on moist silica (Scheme 6.11) has also been introduced that is applicable exclusively to ketoximes [50]. Aldehydes have been regenerated from the corresponding bisulfites (85–98%) on KSF clay surface [51].

6.2.1.10 Cleavage of Semicarbazones and Phenylhydrazones

Carbonyl compounds are also rapidly regenerated from the corresponding semicarbazone and phenylhydrazone derivatives using ammonium persulfate impregnated



Where $R_1 = C_4H_9$, Ph, p-Cl C_6H_4, p-CH_3 C_6H_4, p-OH C_6H_4;
$R_2 = CH_3$; C_2H_5
and R = $CONH_2$, Ph

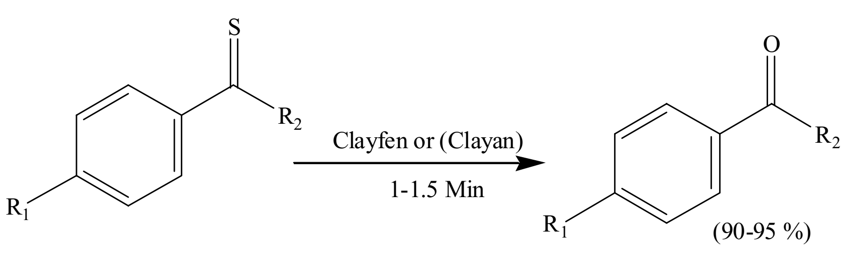
Scheme 6.12 Regeneration of carbonyls from semicarbazone and phenylhydrazone derivatives.

on montmorillonite K 10 clay (Scheme 6.12) [52]. Interestingly, the microwave or ultrasound irradiation techniques can be employed in these solventless procedures; microwave exposure achieves deprotection in minutes whereas ultrasound-promoted reactions require 1–3 h for the regeneration of carbonyl compounds [52].

Regeneration of carbonyl compounds from the hydrazones (75–98%) [53] and from semicarbazones (55–90%) [54] has also been achieved with bismuth trichloride.

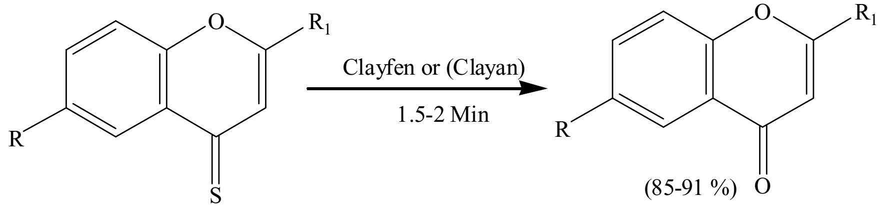
6.2.1.11 Dethiocarbonylation

Dethiocarbonylation, transformation of thiocarbonyls to carbonyls, has been accomplished with several reagents namely, trifluoroacetic anhydride, CuCl/MeOH/NaOH, tetrabutylammonium hydrogen sulfate/NaOH, clay/ferric nitrate, $NOBF_4$, bromate and iodide solutions, alkaline hydrogen peroxide, sodium peroxide, thiophosgene, trimethyloxonium fluoroborate, tellurium based oxidants, dimethyl selenoxide, benzeneseleninic anhydride, benzoyl peroxide and halogen-catalyzed alkoxides under phase transfer conditions [55]. However, these methods have certain limitations such as the use of the stoichiometric amounts of the oxidants that are often inherently toxic or require longer reaction time or involve tedious procedures. In a process that is accelerated by microwave irradiation, Varma et al. have demonstrated efficient dethiocarbonylation process under solvent-free conditions using clayfen or clayan (Schs. 6.13 and 6.14) [55].



Where R_1 = H, $R_2 = CH_3$; R_1 = H, Br, CH_3, R_2 = Ph

Scheme 6.13 Solvent-free dethiocarbonylation using clayfen or clayan.



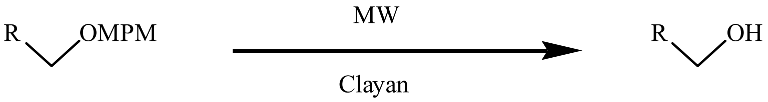
Where R = H; R_1 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$
R =OCH_3; R_2 = *p*-MeC_6H_4

Scheme 6.14 Transformation of thiocarbonyl derivatives of flavonoids with clayfen and clayan.

6.2.1.12 Cleavage of Methoxyphenyl Methyl (MPM) and Tetrahydropyranyl (THP) Ethers

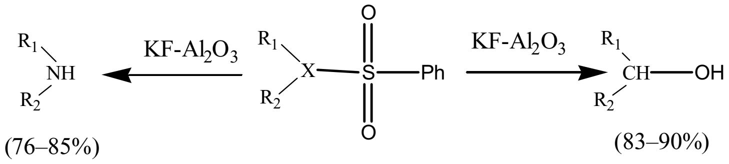
Using clay supported ammonium nitrate (clayan), selective deprotection of methoxyphenyl methyl (MPM) ether has been achieved recently using microwave irradiation in solvent-free conditions (Scheme 6.15) [56]. The same reagent has been used for the cleavage of tetrahydropyranyl (THP) ethers. A similar selective preparation and cleavage of THP ethers has been achieved under microwave irradiation catalyzed by iodine [57] or neat reaction in an ionic liquid [28].

Alcohols and amines have been regenerated by MW-promoted cleavage of sulfonates (83–90%) and sulfonamides (76–85%) respectively, on basic KF-alumina surface (Scheme 6.16) [58].



R = alkyl, alkenyl, alkynyl, aryl, acetate, ester, benzyl or silyl ether groups

Scheme 6.15 Cleavage of methoxyphenyl methyl (MPM) ethers using clayan.



Where X = N, CH-O-

Scheme 6.16 Cleavage of sulfonates and sulfonamides on a basic KF-alumina surface.

6.2.2
Condensation Reactions

A wide variety of MW-assisted aldol [59, 60] and Knoevenagel condensation reactions have been accomplished using relatively benign reagents such as ammonium acetate [61], including the Gabriel synthesis of phthalides with potassium acetate [62].

6.2.2.1 Wittig Olefination Reactions

Some difficult Wittig reactions of stable phosphorus ylides with ketones have been accelerated by microwave irradiation (Scheme 6.17) [63]. When compared to conventional method, an improved yield has been achieved within a shorter time using MW irradiation in the absence of solvent.

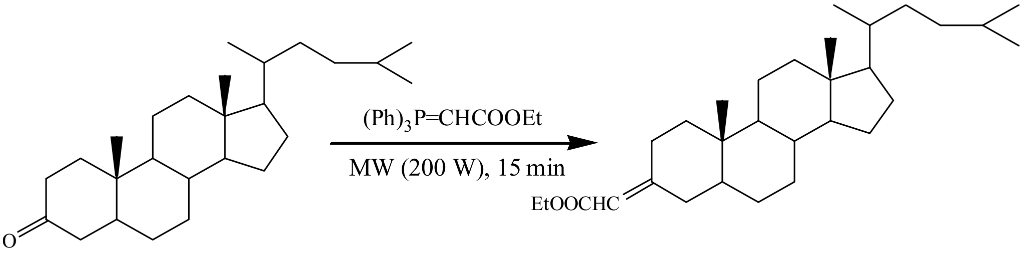
Additional reports on olefination reactions have appeared [64] including the preparation of several phosphonium salts using a domestic MW oven wherein the reaction of neat triphenylphosphine and organic halide shows remarkable rate enhancement in a pressure tube with a threaded Teflon cap [65].

6.2.2.2 Knoevenagel Condensation Reactions – Synthesis of Coumarins

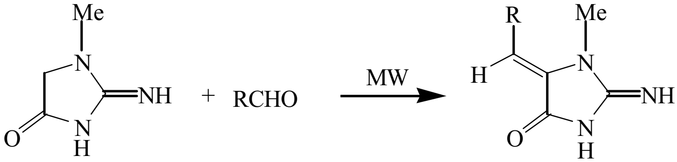
Knoevenagel condensation reaction of creatinine with aldehydes occurs rapidly under solvent-free reaction conditions at 160–170 °C using focused microwave irradiation (Scheme 6.18) [66].

5-Nitrofurfurylidines have been prepared by condensation of 5-nitrofurfuraldehyde with active methylene compounds under microwave irradiation using $ZnCl_2$ and K 10 as catalysts [67].

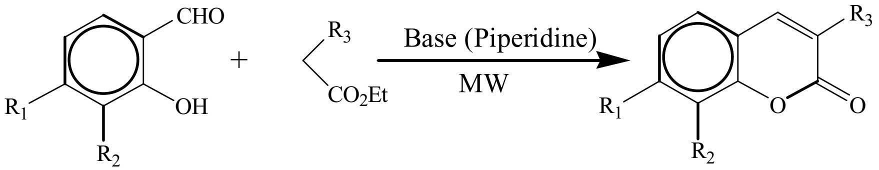
The classical Pechmann approach for the synthesis of coumarins via the microwave-promoted reaction [68] has been extended to solvent-free system wherein salicy-



Scheme 6.17 MW-assisted Wittig olefination reaction.



Scheme 6.18 Knoevenagel condensation reaction of creatinine with aldehydes.



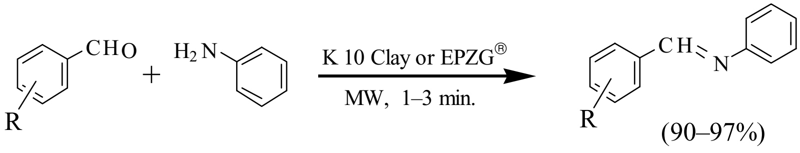
Scheme 6.19 MW-assisted synthesis of coumarins.

laldehydes undergo Knoevenagel condensation with a variety of ethyl acetate derivatives in the presence of piperidine to afford coumarins (Scheme 6.19) [69].

6.2.2.3 Synthesis of Imines, Enamines, Nitroalkenes and *N*-Sulfonylimines

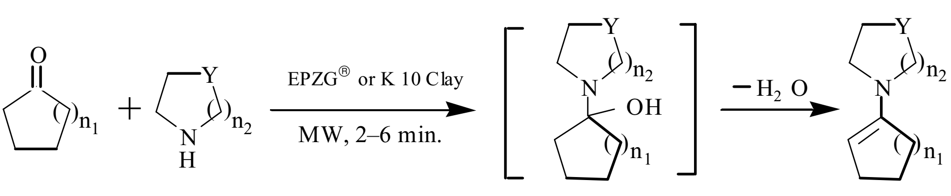
The preparation of imines, enamines, nitroalkenes and *N*-sulfonylimines proceeds via the azeotropic removal of water from the intermediate in reactions that are normally catalyzed by *p*-toluenesulfonic acid, titanium(IV) chloride, or montmorillonite K 10 clay. A Dean–Stark apparatus is traditionally used which requires a large excess of aromatic hydrocarbons such as benzene or toluene for azeotropic water elimination.

MW-expedited dehydration reactions using montmorillonite K 10 clay [70] (Schs. 6.20 and 6.21) or Envirocat reagent, EPZG [71] (Schs. 6.20 and 6.21) have been demonstrated in a facile preparation of imines and enamines via the reactions of primary and secondary amines with aldehydes and ketones, respectively. The generation of polar transition state intermediates in such reactions and their enhanced



Where R = H, *o*-OH, *p*-OH, *p*-Me, *p*-OMe, *p*-NMe_2

Scheme 6.20 Clay-catalyzed formation of imines under solvent-free conditions.



$n_1 = 1$; $n_2 = 2$; $Y = CH_2$; $n_1 = 1$; $n_2 = 2$; $Y = O$ (90–96%)
$n_1 = 2$; $n_2 = 1$; $Y = CH_2$; $n_1 = 2$; $n_2 = 2$; $Y = CH_2$
$n_1 = 2$; $n_2 = 2$; $Y = O$

Scheme 6.21 Clay-catalyzed formation of enamines under solvent-free conditions.

coupling to microwaves is possibly responsible for these rapid imine- or enamine-forming reactions. To prevent the loss of low boiling reactants, the use of microwave oven at lower power levels or intermittent heating has been used [70, 71].

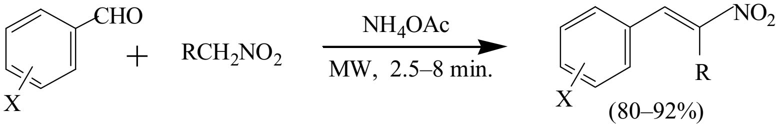
The condensation reaction of neat carbonyl compounds with nitroalkanes to afford nitroalkenes, Henry reaction, also proceeds rapidly via this MW approach in the presence of only catalytic amounts of ammonium acetate, thus avoiding the use of a large excess of polluting nitrohydrocarbons normally employed (Scheme 6.22) [72].

The cycloaddition, reduction and oxidation reactions emanating from α,β-unsaturated nitroalkenes provide easy access to a vast array of functionalities that include nitroalkanes, *N*-substituted hydroxylamines, amines, ketones, oximes, and α-substituted oximes and ketones [73–75]. Consequently, there are numerous possibilities of using these *in situ* generated nitroalkenes for the preparation of valuable building blocks and synthetic precursors.

Expeditious preparation of *N*-sulfonylimines has been optimized for one-pot solventless operation that involves microwave thermolysis of aldehydes and sulfonamides in presence of relatively benign reagents, calcium carbonate and montmorillonite K 10 clay (Scheme 6.23) [76].

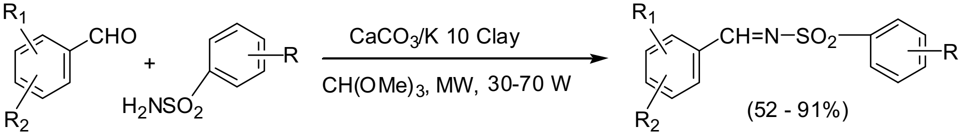
Bis(indolyl)nitroethanes are obtained readily in 7–10 min in high yields (70–86%) on fine TLC-grade silica gel (5–40 μm) by Michael reaction of 3-(2′-nitrovinyl) indole with indoles. The same reaction reported requires 8–14 h for completion at room temperature [77]. Several functionalized resins have been prepared from Merrifield resin via a MW-assisted procedure that utilized mixed solvent system to facilitate the swelling of resins and coupling with microwaves [78]. These resins can function as solid supports or polymeric scavengers in solid phase synthesis.

The formation of hydrazones from the corresponding carbonyl compounds has been accomplished initially in toluene [79]. The treatment of hydrazone with alkali (KOH) accomplishes Wolff–Kichner reduction that proceeds in good yield under



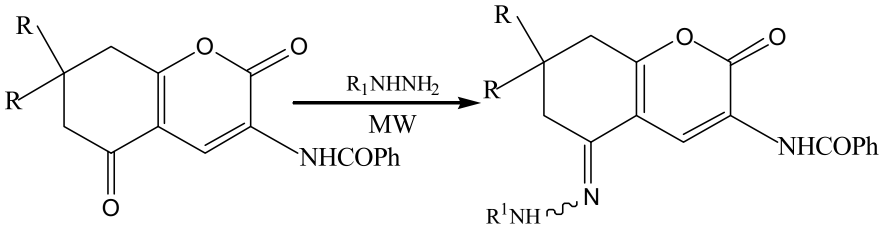
Where R = H, X = H, *p*-OH, *m,p*-$(OMe)_2$, *m*-OMe-*p*-OH, 1-naphthyl, 2-naphthyl
R = Me, X = H, *p*-OH, *p*-OMe, *m,p*-$(OMe)_2$, *m*-OMe-*p*-OH

Scheme 6.22 MW-assisted preparation of α,β-unsaturated nitroalkenes.



Where R = H, Me, COOMe, Cl; R_1 = H, OMe, OCOMe, Br; R_2 = H, OMe, OCOMe

Scheme 6.23 One-pot solventless preparation of *N*-sulfonylimines.



Where R = H or Me and R_1 = Aryl and substituted aryl groups

Scheme 6.24 Formation of hydrazones under solvent-free and catalyst-free conditions.

MW irradiation conditions [80]. More recently, however, Varma and Kocevar's group have shown that a solvent-free and catalyst-free reaction of hydrazines with carbonyl compounds is possible upon MW irradiation (Scheme 6.24) [81]. Interestingly, the general reaction proceeds smoothly even for solid reactants and is completed below the melting points of the two reactants possibly via the formation of a eutectic. The reactions have been conducted in household MW oven and the control experiments are conducted concurrently in separate open beakers; the reactions can be essentially followed by visual observation when a melt is obtained [82].

An interesting solid-state synthesis of amides has also been reported in a MW oven that uses potassium *tert*-butoxide and easily accessible reagents, nonenolizable esters and amines [83].

The kinetics of the acid-catalyzed esterification reaction of 2,4,6-trimethylbenzoic acid in *i*-PrOH under microwave irradiation have been investigated [84]. A simple and practical technique for MW-assisted synthesis of esters has been reported wherein the reactions are conducted either on solid mineral supports or by using a phase transfer catalyst (PTC) in the absence of organic solvents [85]. The esterification of enols with acetic anhydride and iodine has also been recorded [86].

The detailed account of condensation reactions as applied to heterocyclic chemistry is found in subsequent section (Sect. 6.2.6), Chapt. 8 [87] and for cycloaddition reactions in Chapt. 9 [88].

6.2.3
Isomerization and Rearrangement Reactions

Numerous rearrangement and isomerization reactions have been reported using MW irradiation. Some reactions are performed in solution phase while others on graphite or mineral support surface often "doped" with Lewis acids and sometimes even by heating the neat reactants. The notable examples are, Benzil–benzilic acid rearrangement [89], solventless Beckmann rearrangement on K 10 clay [49], Fries rearrangement on K 10 clay that affords mixture of *ortho* and *para* products [90], and thia-Fries rearrangement of arylsulfonates using aluminum and zinc chloride on silica gel [91].

6.2.3.1 **Eugenol–Isoeugenol Isomerization**

Eugenol undergoes MW-assisted isomerization to isoeugenol under solvent-free condition in the presence of potassium *tert*-butoxide, *t*-BuOK, and a catalytic amount of phase transfer reagent [34].

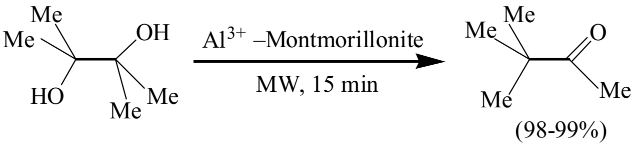
6.2.3.2 **Pinacol–Pinacolone Rearrangement**

A solvent-free pinacol–pinacolone rearrangement has been reported using microwave irradiation. The process involves the irradiation of the *gem* diols with Al^{3+}-montmorillonite K 10 clay for 15 min to afford the rearrangement product in excellent yields (Scheme 6.25) [24]. The comparative studies performed by conventional heating in an oil bath showed that the reaction times are too long (15 h).

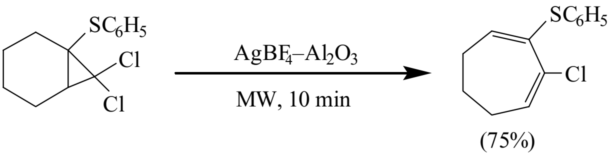
An efficient ring-expansion transformation has also been described under solvent-free conditions (Scheme 6.26) [92]. This microwave procedure is superior to the same reactions conducted in traditional methanolic solution.

6.2.3.3 **Beckmann Rearrangement**

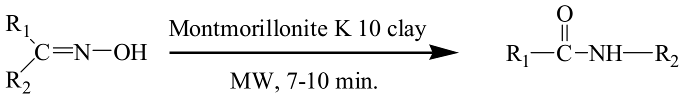
A simple montmorillonite K 10 clay surface is one among numerous acidic supports that have been explored for the Beckmann rearrangement of oximes (Scheme 6.27) [54]. However, the conditions are not adaptable for the aldoximes that are readily dehydrated to the corresponding nitriles under solventless conditions. Zinc chloride has been used in the above rearrangement for benzaldehyde and 2-hydroxyacetophenone, the later being adapted for the synthesis of benzoxazoles.



Scheme 6.25 Pinacol–pinacolone rearrangement on Al^{3+}-montmorillonite K 10 clay.



Scheme 6.26 MW-assisted ring expansion reaction on alumina.



Where $R_1 = CH_3$ or Ph and R_2 = Ph or substituted phenyl

Scheme 6.27 Beckmann rearrangement of oximes on clay.

Among numerous other studies, Ferrier rearrangement is notable since it proceeds well (72–83%) upon irradiation of neat reactants [93].

6.2.4
Oxidation Reactions – Oxidation of Alcohols and Sulfides

Metal-based reagents have been extensively used in organic synthesis. Peracids, peroxides, potassium permanganate ($KMnO_4$), manganese dioxide (MnO_2), chromium trioxide (CrO_3), potassium dichromate ($K_2Cr_2O_7$) and potassium chromate (K_2CrO_4) are some of the common oxidizing reagents employed for organic functional groups [94, 95].

The utility of such reagents in the oxidation processes is compromised due to their inherent toxicity, cumbersome preparation, potential danger in handling of metal complexes, difficulties encountered in product isolation and waste disposal problems. Immobilization of metallic reagents on solid supports has circumvented some of these drawbacks and provided an attractive alternative in organic synthesis because of the selectivity and associated ease of manipulation. Further, the localization of metals on the mineral oxide surfaces reduces the possibility of their leaching into the environment.

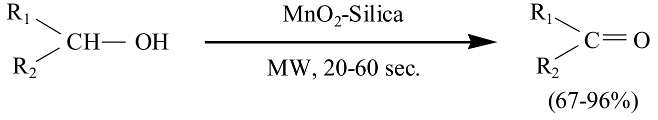
6.2.4.1 Activated Manganese Dioxide–Silica

Manganese dioxide (MnO_2) supported on silica provides an expeditious and high-yield route to carbonyl compounds. Benzyl alcohols are selectively oxidized to carbonyl compounds by use of 35% MnO_2 "doped" silica under MW irradiation conditions (Scheme 6.28) [96].

Manganese dioxide on bentonite clay has also been used for oxidation of phenols to quinones (30–100%) [97] and MnO_2 on silica effects the dehydrogenation of pyrrolidines (58–96%) [98].

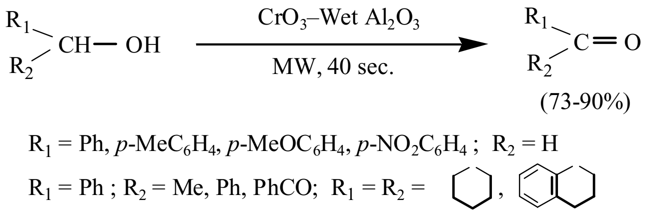
6.2.4.2 Chromium Trioxide–Wet Alumina

The deployment of chromium(VI) reagents in the oxidative transformation is compromised due to inherent toxicity, involved preparation of its various complex forms (with pyridine or acetic acid) and cumbersome workup procedures. Chromium trioxide (CrO_3) immobilized on premoistened alumina enables efficient oxidation of ben-



Where $R_1 = H$; $R_2 = Ph$, p-MeC_6H_4, p-$MeOC_6H_4$, PhCH=CH
R_1 = Et, Ph, PhCO; R_2 = Ph ; $R_1 = R_2$ = hydroquinone
R_1 = p-$MeOC_6H_4CO$; R_2 = p-$MeOC_6H_4$

Scheme 6.28 Oxidation of alcohols by silica-supported manganese dioxide.



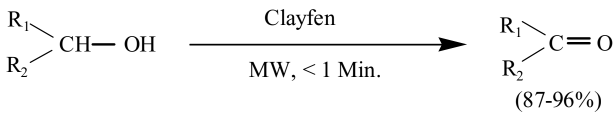
Scheme 6.29 Oxidation of alcohols by chromium trioxide supported on premoistened alumina.

zyl alcohols to carbonyl compounds by simple mixing with various substrates (Scheme 6.29). Interestingly, no overoxidation to carboxylic acids is observed and products are devoid of tar contaminants, a typical occurrence in many CrO_3 oxidations [99].

6.2.4.3 **Selective Solvent-free Oxidation with Clayfen**

A facile method for the oxidation of alcohols to carbonyl compounds has been reported by Varma et al. using montmorillonite K 10 clay-supported iron(III) nitrate (clayfen) under solvent-free conditions [100]. This MW-expedited reaction presumably proceeds via the intermediacy of nitrosonium ions. Interestingly, no carboxylic acids are formed in the oxidation of primary alcohols. The simple solvent-free experimental procedure involves mixing of neat substrates with clayfen and a brief exposure of the reaction mixture to irradiation in a MW oven for 15–60 s. This rapid, manipulatively simple, inexpensive and selective procedure avoids the use of excess solvents and toxic oxidants (Scheme 6.30) [100]. Solid state use of clayfen has afforded higher yields and the amounts used are half of that used by Laszlo et al. [17, 19].

A ground mixture of iron(III) nitrate and HZSM-5 zeolite, termed “zeofen”, has also been used both, in dichloromethane solution and in solid state under MW irradiation conditions [101]. It has been suggested that the zeolite aids the reproducibility of the reaction but any other aluminosilicate support would probably be equally effective. Recent studies point out attractive alternatives that do not employ any of the solid supports in such oxidations with nitrate salts [102].



Where R_1 = H; R_2 = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, 2-tetrahydrofuranyl
R_1 = Et, PhCO; R_2 = Ph ; R_1 - R_2 = cyclohexyl
R_1 = p-$MeOC_6H_4CO$; R_2 = p-$MeOC_6H_4$

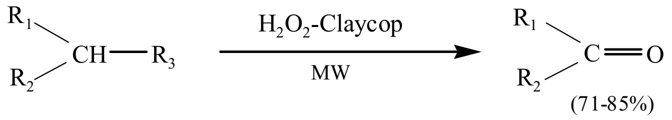
Scheme 6.30 Solvent-free selective oxidation of alcohols with clayfen.

6.2.4.4 Oxidations with Claycop–Hydrogen Peroxide

Metal ions play an important role in several of these oxidative reactions as well as in biological dioxygen metabolism. As an example, copper(II) acetate and hydrogen peroxide have been used to produce a stable oxidizing agent, hydroperoxy copper(II) compound. The same oxidation system is also obtained from copper(II) nitrate and hydrogen peroxide (Eq. 1) [103] but requires the neutralization of ensuing nitric acid by potassium bicarbonate to maintain a pH $\approx$ 5.

$$2\,Cu(NO_3)_2 + H_2O_2 + 2\,H_2O \longrightarrow 2\,Cu\,O_2H + 4\,HNO_3 \qquad \text{Eq. (1)}$$

Copper(II) nitrate immobilized on K 10 clay (claycop)–hydrogen peroxide system is an effective oxidant for a variety of substrates and provides excellent yields (Scheme 6.31) [104] wherein the maintenance of pH of the reaction mixture is not required.

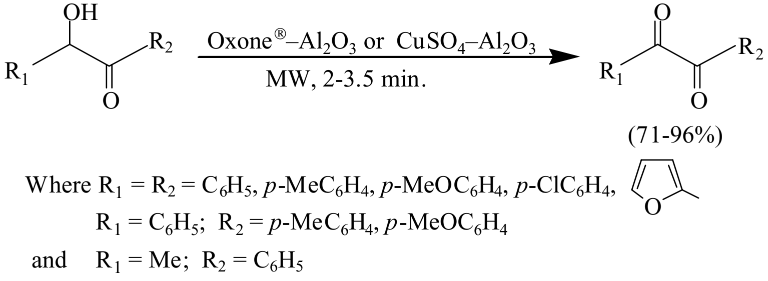


Where R_1 = Ph, p-$NO_2\,C_6H_4$; R_2 = H, Ph; R_3 = H, Br, CN, NH_2, COOH

Scheme 6.31 Oxidation reactions with claycop and hydrogen peroxide.

6.2.4.5 Other Metallic Oxidants – Copper Sulfate or Oxone–Alumina

Symmetrical and unsymmetrical benzoins have been rapidly oxidized to benzils in high yields using solid reagent systems, copper(II) sulfate–alumina [105] or Oxone–wet alumina [105, 106] under the influence of microwaves (Scheme 6.32). Conventionally, the oxidative transformation of α-hydroxyketones to 1,2-diketones is accomplished by reagents such as nitric acid, Fehling's solution, thallium(III) nitrate (TTN), ytterbium(III) nitrate, ammonium chlorochromate–alumina and clayfen. In addition to the extended reaction time, most of these processes suffer from drawbacks such as the use of corrosive acids and toxic metals that generate undesirable waste products.



Where $R_1 = R_2 = C_6H_5$, p-MeC_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4,
$R_1 = C_6H_5$; $R_2 = p$-MeC_6H_4, p-$MeOC_6H_4$
and R_1 = Me; $R_2 = C_6H_5$

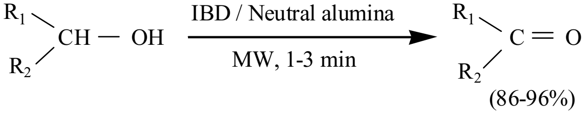
Scheme 6.32 Oxidation of α-hydroxyketones with alumina-supported copper sulfate or Oxone.

Under these solvent-free conditions, the oxidation of primary alcohols (e.g. benzyl alcohol) and secondary alcohols (e.g. 1-phenyl-1-propanol) is rather sluggish and poor and is of little practical utility. Consequently, the process is applicable only to α-hydroxyketones as exemplified by various examples including a mixed benzylic/aliphatic α-hydroxyketone, 2-hydroxypropiophenone that delivers the corresponding vicinal diketone [106, 107].

6.2.4.6 **Nonmetallic Oxidants: Iodobenzene Diacetate (IBD)-Impregnated Alumina**

Several organohypervalent iodine reagents have been used for the oxidation of alcohols and phenols such as iodoxybenzene, *o*-iodoxybenzoic acid (IBX), bis(trifluoroacetoxy)iodobenzene (BTI), and Dess–Martin periodinane etc. But the use of inexpensive iodobenzene diacetate (IBD) as an oxidant, however, has not been fully exploited. Most of these reactions are conducted in high boiling DMSO or toxic acetonitrile media that results in increased burden on the environment.

Varma and coworkers have explored the use of hypervalent iodine compounds on solid support for the first time and developed a facile oxidative procedure that rapidly converts alcohols to the corresponding carbonyl compounds using alumina-supported IBD under solvent-free conditions and MW irradiation in almost quantitative yields [108]. The use of alumina as a support improved the yields markedly as compared to neat IBD (Scheme 6.33). 1,2-Benzenedimethanol, under these conditions, undergoes cyclization to afford 1(^{3}H)-isobenzofuranone.

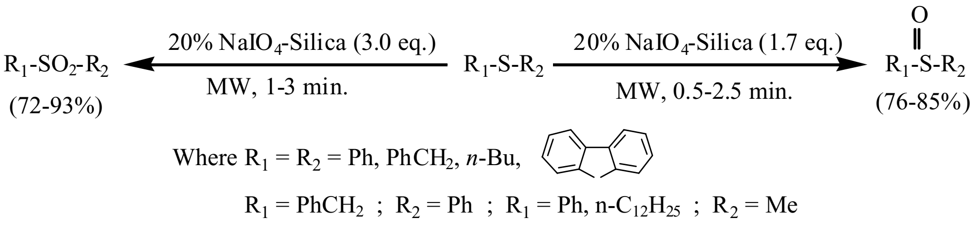


Where R_1 = Ph, substituted Ph and R_2 = H, C_2H_5, COC_6H_5

Scheme 6.33 Oxidation of alcohols using alumina-supported iodobenzene diacetate.

6.2.4.7 **Oxidation of Sulfides to Sulfoxides and Sulfones – Sodium Periodate–Silica**

The oxidation of sulfides to the corresponding sulfoxides and sulfones proceeds under rather strenuous conditions requiring strong oxidants such as nitric acid, hydrogen peroxide, chromic acid, peracids, and periodate. Using MW irradiation, this oxidation is achievable under solvent-free conditions and with desired selectivity to either sulfoxides or sulfones using 10% sodium periodate on silica (Scheme 6.34)



Where R_1 = R_2 = Ph, $PhCH_2$, *n*-Bu,

R_1 = $PhCH_2$; R_2 = Ph ; R_1 = Ph, n-$C_{12}H_{25}$; R_2 = Me

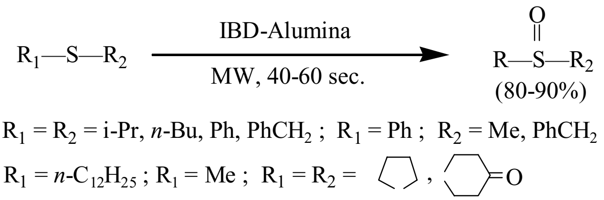
Scheme 6.34 Oxidation of sulfides to sulfoxides and sulfones by silica-supported sodium periodate.

[109]. A relatively reduced amount of the active oxidizing agent is employed which is safer and easier to handle.

Several refractory thiophenes, that are often not reductively removable by conventional refining processes, can be oxidized under these conditions, e.g. benzothiophenes are oxidized to the corresponding sulfoxides and sulfones using ultrasonic and microwave irradiation, respectively, in the presence of $NaIO_4$–silica [109]. A noteworthy feature of the procedure is its applicability to long chain fatty sulfides that are insoluble in most solvents and are consequently difficult to oxidize.

6.2.4.8 Oxidation of Sulfides to Sulfoxides – Iodobenzene Diacetate–Alumina

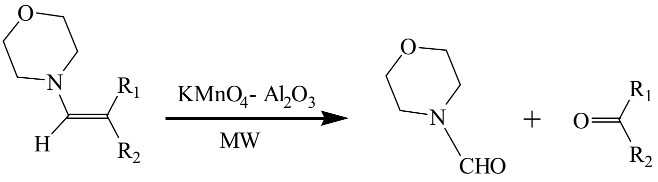
As described earlier (Sect. 6.2.4.6), the solid reagent system, IBD–alumina, is a useful oxidizing agent and its use is extendible to rapid, high yield and selective oxidation of alkyl, aryl and cyclic sulfides to the corresponding sulfoxides upon microwave activation (Scheme 6.35) [110].



Scheme 6.35 Oxidation of sulfides to sulfoxides by alumina-supported iodobenzene diacetate.

6.2.4.9 Oxidation of Arenes and Enamines – Potassium Permanganate ($KMnO_4$)–Alumina

$KMnO_4$ impregnated alumina oxidizes arenes to ketones within 10–30 min under solvent-free conditions using focused microwaves [111]. β,β-Disubstituted enamines have been successfully oxidized into carbonyl compounds with $KMnO_4$–Al_2O_3 in domestic (255 W, 82 °C) and in focused microwave ovens (330 W, 140 °C) under solvent-free conditions by Hamelin et al. [112]. The yields are better in the latter case. When the same reactions are conducted in an oil bath at 140 °C, no carbonyl compound formation is observed (Scheme 6.36).



Scheme 6.36 Oxidation of enamines with alumina-supported potassium permanganate.

6.2.4.10 Other Oxidation Reactions

A rapid self coupling reaction of β-naphthols occurs in presence of iron(III) chloride, $FeCl_3.6H_2O$, using a focused MW oven under solvent-free conditions and is superior to classical heating mode [113].

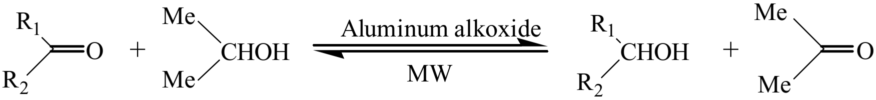
Additional examples of oxidative procedures with microwave irradiation include the oxidation of benzylic bromides to corresponding aldehydes with pyridine *N*-oxides (15–95%) [114]. The catalyst system, V_2O_5/TiO_2 and modified forms thereof by addition of an effective MW coupling dielectric such as MoO_3, WO_3, Nb_2O_5 or Ta_2O_5 have been explored in the selective oxidation of toluene to benzoic acid under MW irradiation. In the conventional heating process, the additives have no positive influence on catalyst's performance [115].

6.2.5
Reduction Reactions

In MW-assisted chemistry reduction reactions were the last to appear on the scene; the use of ammonium formate and catalytic transfer hydrogenation were initial examples [23 b].

6.2.5.1 Reduction of Carbonyl Compounds with Aluminum Alkoxides

The pioneering work of Posner, on the reduction of carbonyl compounds with isopropyl alcohol and alumina [116], has now been adapted to an expeditious solvent-free reduction procedure that utilizes aluminum alkoxides under microwave irradiation conditions (Scheme 6.37) [117].

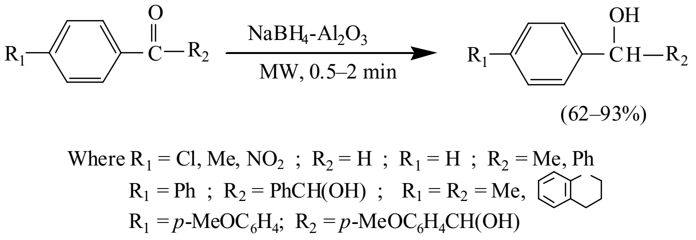


Scheme 6.37 Solvent-free reduction of carbonyls using aluminum alkoxides.

6.2.5.2 Reduction of Carbonyl Compounds to Alcohols – Sodium Borohydride–Alumina

Inexpensive and safe sodium borohydride ($NaBH_4$) has been extensively used as a reducing agent because of its compatibility with protic solvents. Solid-state reduction of carbonyl compounds has been achieved by admixing substrates with $NaBH_4$ and storing the reaction mixture in a dry box for five days. The disadvantage in the heterogeneous reduction reaction with $NaBH_4$ is that the solvent slows down the reaction rate while in the solid-state reactions, the required time (5 days) is too long for it to be of any practical utility [118].

Varma and coworkers reported, for the first time, a simple method for the expeditious reduction of aldehydes and ketones that uses alumina-supported $NaBH_4$ and proceeds in the solid state using microwaves [119]. The process, in its entirety, involves mixing of carbonyl compounds with (10%) $NaBH_4$–alumina and irradiation of the reaction mixture in a household MW oven for 0.5–2 min (Scheme 6.38).



Where R_1 = Cl, Me, NO_2 ; R_2 = H ; R_1 = H ; R_2 = Me, Ph
R_1 = Ph ; R_2 = PhCH(OH) ; R_1 = R_2 = Me,
R_1 = *p*-$MeOC_6H_4$; R_2 = *p*-$MeOC_6H_4CH(OH)$

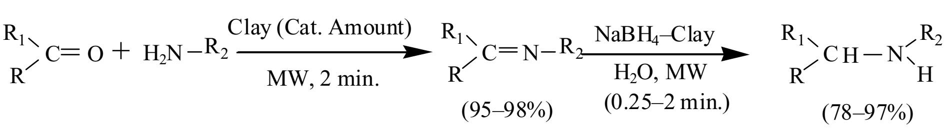
Scheme 6.38 Reduction of carbonyl compounds using alumina-supported sodium borohydride.

The useful chemoselective feature of the reaction is apparent from the reduction of *trans*-cinnamaldehyde (cinnamaldehyde/$NaBH_4$–alumina, 1:1 mol equivalent); olefinic moiety remains intact and only the aldehyde functionality is reduced in a facile reaction.

No side products are formed and the reaction does not proceed in the absence of alumina. Further, the reaction rate improves in the presence of moisture. The moisture is absorbed by alumina during the recovery of the product. The alumina support can be recycled and reused for subsequent reduction, repeatedly, by mixing with fresh borohydride without any loss in activity. In terms of safety, the air used for cooling the magnetron ventilates the microwave cavity, thus preventing any ensuing hydrogen from reaching explosive concentrations. The technique has been elegantly utilized for MW-enhanced solid-state deuteration using sodium borodeuteride impregnated alumina [120]. Further extension of this work in the specific labeling of molecules has been explored [121] and is discussed elsewhere in this book [122].

6.2.5.3 Reductive Amination of Carbonyls

Sodium cyanoborohydride [123], sodium triacetoxyborohydride [124] or $NaBH_4$ coupled with sulfuric acid [125] are common agents used for the reductive amination of carbonyl compounds. These reagents either generate waste or involve the use of corrosive acids. The environmentally friendlier procedures developed by Varma and coworkers have been extended to a solvent-free reductive amination protocol for carbonyl compounds using moist montmorillonite K 10 clay supported sodium borohydride that is facilitated by microwave irradiation (Scheme 6.39) [126].



R = i-Pr, Ph, *o*-HOC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$; R_1 = H ; R_2 = Ph
R & R_1 = $-(CH_2)_5-$; R_2 = Ph ; R & R_1 = $-(CH_2)_6-$; R_2 = n-Pr
R = *p*-ClC_6H_4 ; R_1 = H ; R_2 = *o*-HOC_6H_4 ; R = R_1 = Et ; R_2 = Ph
R = n-C_5H_{11} ; R_1 = Me ; R_2 = morpholine, piperidine ; R = i-Pr ; R_1 = H ; R_2 = n-$C_{10}H_{21}$

Scheme 6.39 Reductive amination of carbonyls using clay-supported sodium borohydride.

The practical applications of $NaBH_4$ reductions on mineral surfaces for *in situ* generated Schiff's bases have been successfully demonstrated. The solid-state reductive amination of carbonyl compounds on various inorganic solid supports such as alumina, clay, silica etc. and especially on K 10 clay surface rapidly afford secondary and tertiary amines [126]. Clay behaves as a Lewis acid and also provides water from its interlayers thus enhancing the reducing ability of $NaBH_4$ [22].

6.2.5.4 **Solid-state Cannizzaro Reaction**

The Cannizzaro reaction, the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt [127, 128], is restricted to aldehydes lacking the α-hydrogens that cannot undergo aldol condensation. This oxidation–reduction reaction is usually conducted under strongly basic conditions and suffers from the disadvantage of the lower yields of the desired products [129, 130]. The crossed Cannizzaro reaction [129], using a scavenger and inexpensive paraformaldehyde, however, has provided improved yields of alcohols prior to the introduction of hydride reducing agents. The popularity of Cannizzaro reaction in synthetic organic chemistry dwindled considerably after the discovery of lithium aluminum hydride, $LiAlH_4$, in 1946.

In numerous reactions involving arylaldehydes on a variety of mineral oxide surfaces, the formation of Cannizzaro-derived alcoholic contaminants has been consistently observed [131]. Interestingly, no meaningful product formation occurs under solventless MW-irradiation conditions on alumina surface with calcium hydroxide or in the presence of a strong base such as sodium hydroxide; the reaction remains incomplete with concomitant formation of several unidentified products reminiscent of earlier described observations on basic alumina surface [131]. Finally, Varma et al. discovered that the reaction proceeds rapidly on barium hydroxide, $Ba(OH)_2.8H_2O$ surface, which constitutes the first application of this reagent in a solvent-free crossed Cannizzaro reaction [132]. In a typical experimental procedure, a mixture of benzaldehyde (1 mmol) and paraformaldehyde (2 mmol) is mixed with barium hydroxide octahydrate (2 mmol) and irradiated in a MW oven (100–110 °C) or heated in an oil bath (100–110 °C) (Scheme 6.40). Arylaldehydes bearing an electron withdrawing substituent undergo reaction at a much faster rate than aldehydes with electron releasing groups appended [132]. Soon thereafter, additional groups started exploring the general utility of this reaction using microwaves [133, 134].

$$\mathrm{RCHO} + (\mathrm{CH_2O})_n \xrightarrow[\text{MW or oil bath}]{\mathrm{Ba(OH)_2 \cdot 8H_2O}} \underset{(80\text{-}99\%)}{\mathrm{RCH_2OH}} + \underset{(1\text{-}20\%)}{\mathrm{RCOOH}}$$

Scheme 6.40 Solvent-free crossed Cannizzaro reaction using paraformaldehyde.

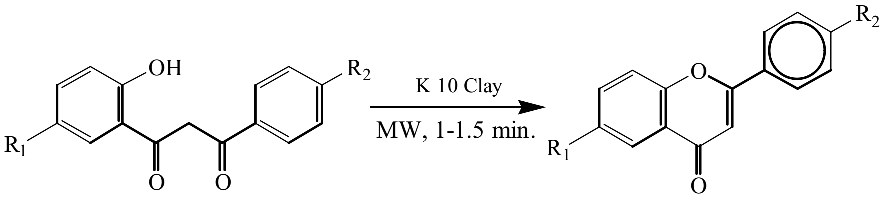
6.2.6
Synthesis of Heterocyclic Compounds

Heterocyclic chemistry has benefited substantially from MW-expedited processes developed over the last decade. An exhaustive overview is provided in adjoining chapters [87, 88] with limited solvent-free chemistry utilizing mineral supported reagents being covered in this section.

6.2.6.1 Flavones

Naturally occurring flavonoids are widely distributed oxygen heterocyclic compounds in plant kingdom, the most abundant being the flavones. Members of this class display a wide variety of biological activities and have been useful in the treatment of various diseases [135, 136]. Flavones have been prepared by a variety of methods such as Allan–Robinson synthesis, and synthesis from chalcones via an intramolecular Wittig strategy [137]. The commonly followed approach, however, involves the Baker–Venkataraman rearrangement, wherein *o*-hydroxyacetophenone is benzoylated to form the benzoyl ester followed by the treatment with base (KOH/pyridine) to effect acyl migration, forming a 1,3-diketone [138, 139]. The ensuing diketone is then cyclized under strongly acidic conditions with sulfuric acid and acetic acid to afford flavone.

A solvent-free synthesis of flavones has been achieved that simply involves the MW irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K 10 clay for 1–1.5 min. A rapid and exclusive formation of cyclized flavones occurs in good yields (Scheme 6.41) [140]. The intramolecular Michael addition of *o*-hydroxychalcones on silica gel surface has also been reported [141].

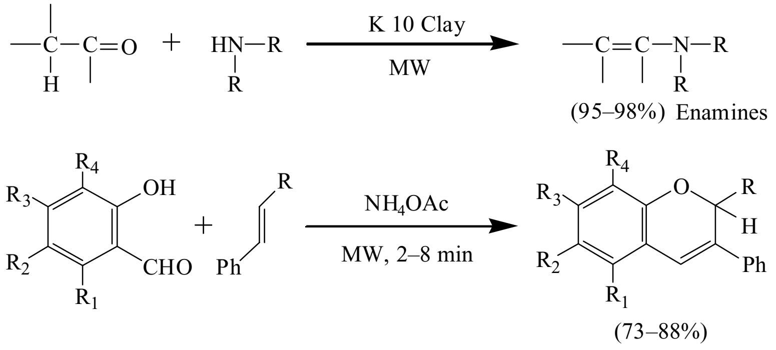


Where R_1 = H ; R_2 = H, Me, OMe, NO_2
R_1 = OMe ; R_2 = H, Me, OMe

Scheme 6.41 Formation of flavones by cyclization of *o*-hydroxydibenzoylmethanes on K 10 clay.

6.2.6.2 2-Amino-substituted Isoflav-3-enes

The estrogenic properties of isoflav-3-enes are well known and consequently, several derivatives of these chromene heterocycles have been the target of medicinal chemists. Varma and coworkers uncovered a useful enamine-mediated pathway to this class of compounds [142–144]. Now the group has discovered a facile and general method for the MW-expedited synthesis of isoflav-3-enes substituted with basic moieties at the 2-position (Scheme 6.42) [145]. These promising results are especially appealing in view of the convergent one-pot approach to 2-substituted isoflav-3-enes



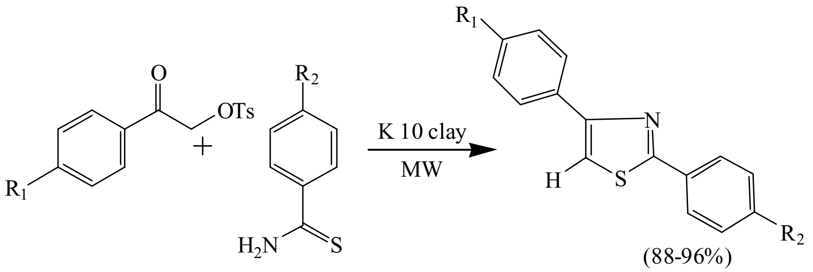
Where R = morpholinyl, piperidinyl or pyrrolidinyl
and $R_1 = R_3 = R_4 = H$; R_2 = H, Cl, NO_2

Scheme 6.42 One-pot synthesis of 2-substituted isoflav-3-enes from *in situ*- generated enamines.

wherein the *in situ* generated enamine derivatives have been subsequently reacted with *o*-hydroxyaldehydes in the same pot (Scheme 6.42) [145].

6.2.6.3 **Substituted Thiazoles**

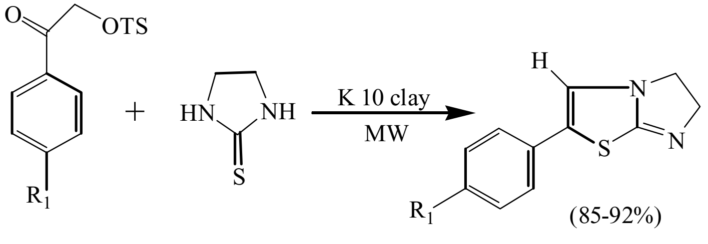
Thiazole and its derivatives are conventionally prepared from lachrymatory, α-haloketones and thioureas (or thioamides) by Hantzsch procedure [146]. In a marked improvement, Varma et al. have synthesized the title compounds by the simple reaction of *in situ*-generated α-tosyloxyketones, from arylmethyl ketones and [hydroxy(tosyloxy)iodo]benzene (HTIB), with thioamides in the presence of K 10 clay using microwave irradiation (Scheme 6.43); the process is solvent-free in both the steps [147].



Where R_1 = H, Me, OMe, Cl and R_2 = Cl, OMe

Scheme 6.43 Synthesis of substituted thiazoles from *in situ*-generated α-tosyloxyketones.

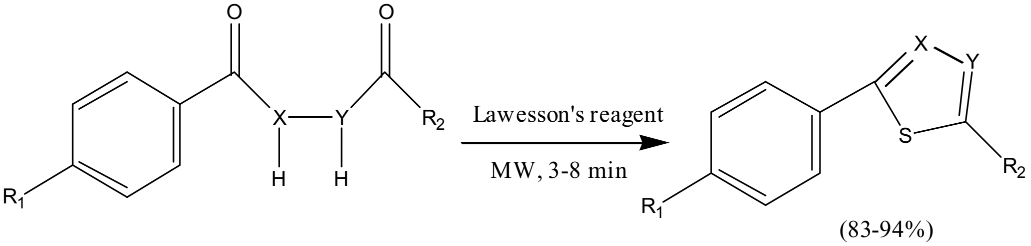
The corresponding bridgehead heterocycles are difficult to obtain by conventional heating methods since the reactions of α-tosyloxyketones with ethylenethioureas remain incomplete in an oil bath. The microwave-accelerated process, on the other hand, gets completed in a short time (Scheme 6.44) [147, 148].



Where R_1 = H, Me, OMe, Cl

Scheme 6.44 Synthesis of bridgehead thiazoles from α-tosyloxyketones.

Several 1,4-dicarbonyl compounds have been successfully subjected to microwave-mediated ring closure with Lawesson's reagent to afford useful *S*-heterocycle-containing liquid crystalline targets. The new ring-closure methodology has proven useful in improving the yield of an earlier synthesized liquid crystal entity and a number of newer reactions have been scaled up to several grams without compromising the yield (Scheme 6.45) [149].



Where R_1 = H, OMe, Br; R_2 = Ph, O-alkyl
and X = Y = CH or N

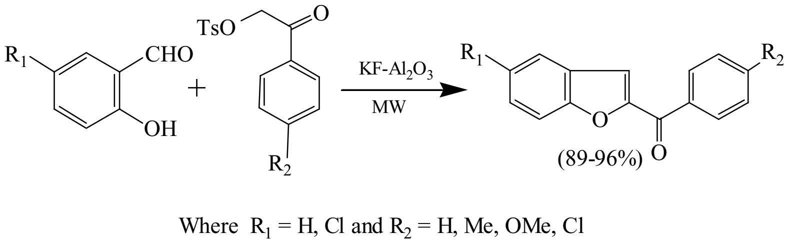
Scheme 6.45 MW-assisted synthesis of *S*-heterocycle-containing liquid crystalline compounds.

6.2.6.4 Synthesis of 2-Aroylbenzofurans

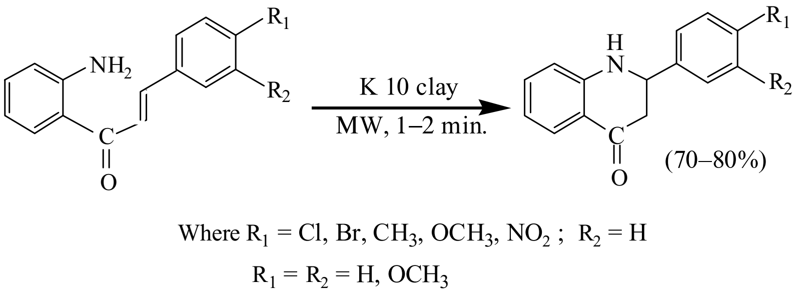
In an analogous manner, pharmacologically important natural 2-aroylbenzofurans are easily obtainable under basic solvent-free conditions from α-tosyloxyketones and salicylaldehydes in the presence of potassium fluoride doped alumina using microwave irradiation (Scheme 6.46) [147, 148].

6.2.6.5 Synthesis of Quinolones

The readily available 2′-aminochalcones provide easy access to 2-aryl-1,2,3,4-tetrahydro-4-quinolones in yet another solvent-free cyclization reaction using montmorillonite K 10 clay under microwave irradiation conditions [150]; the products are valuable precursors for the medicinally important quinolones (Scheme 6.47).



Scheme 6.46 Synthesis of 2-aroylbenzofurans on potassium fluoride doped alumina.

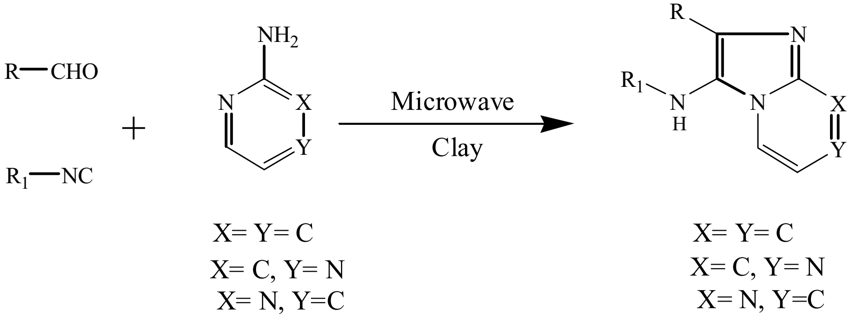


Scheme 6.47 Synthesis of 2-aryl-1,2,3,4-tetrahydro-4-quinolones via cyclization reaction on clay.

6.2.6.6 Multi-component Reactions (Imidazo[1,2-*a*]annulated *N*-heterocycles – Ugi reaction)

Multiple component condensation (MCC) approach is attracting attention since the diversity can be conveniently achieved in a single step simply by varying the reacting components. The generation of small-molecule libraries requires the development of efficient procedures with special emphasis on the ease of reaction manipulation. Varma and Kumar have succeeded in developing such a facile procedure which is amenable to the generation of a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines under solvent-free conditions using MW irradiation (Scheme 6.48) [151]. This is a marked improvement over the conventional two-component synthesis that requires lachrymatory α-haloketones and restricts the generation of a diverse library of these molecules.

Aldehydes and the corresponding 2-aminopyridine, pyrazine, or pyrimidine are admixed in presence of a catalytic amount of clay (50 mg) to generate iminium intermediate. Isocyanides are subsequently added to the same container and the reactants are further exposed to MW to afford the corresponding imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines (Scheme 6.48). The process is general for all the three components, e. g. aldehydes (aliphatic, aromatic and vinylic), isocyanides (aliphatic, aromatic and cyclic) and amines (2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine). A library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines can be readily obtained by varying the three components [151].



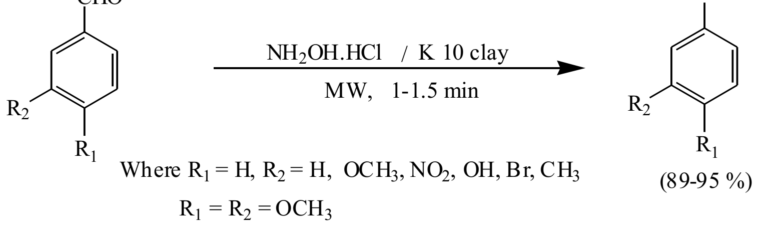
Scheme 6.48 Synthesis of imidazo[1,2-*a*]annulated *N*-heterocycles via the Ugi reaction.

A similar strategy has been used for the Biginelli condensation reaction to synthesize a set of pyrimidinones (65–95%) in a household MW oven [152]. This MW approach has been successfully applied to combinatorial synthesis [153]. Yet another example is the convenient synthesis of pyrroles (60–72%) on silica gel using readily available enones, amines and nitro compounds [154].

6.2.7
Miscellaneous Reactions

6.2.7.1 Transformation of Arylaldehydes to Nitriles

Arylaldehyde to nitrile conversion is an important chemical transformation [155]. Usually the reaction proceeds via an aldoxime intermediate that is subsequently dehydrated using a wide variety of reagents such as chloramine/base [156], *O,N-bis*-(trifluoroacetyl)hydroxylamine or trifluoroacetohydroximic acid [157], *p*-chlorophenyl chlorothionoformate/pyridine [158], triethylamine/dialkyl hydrogen phosphinates [159], $TiCl_4$/pyridine [160], triethylamine/phosphonitrilic chloride [161] and 1,1-dicarbonylbiimidazole [162]. The dehydration of aldoxime is a time consuming process even for one-pot reactions [163]. The application of hydroxylamine hydrochloride impregnated clay developed by Varma et al. reduces the entire operation to one-pot synthesis using microwaves wherein arylaldehydes are rapidly converted into nitriles in good yields (89–95%) in the absence of solvent [107, 164]. In this general reaction,



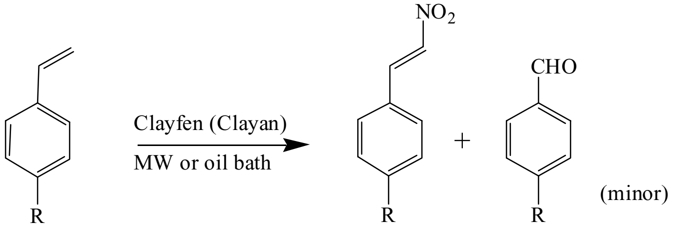
Scheme 6.49 Transformation of arylaldehydes to nitriles by hydroxylamine hydrochloride–clay.

a variety of aldehydes undergo this facile conversion to the corresponding nitriles in a short time (1–1.5 min) upon MW irradiation (Scheme 6.49). However, in the case of aliphatic aldehydes, only poor yields of nitriles (10–15 %) are obtained with concomitant formation of undesirable products.

Several variations of the aforementioned transformation soon followed using silica as surface [165–167]. The nitriles have been obtained from carboxylic acids (20–93 %) on alumina support [168] and from the corresponding amides (80–95 %) in toluene [169].

6.2.7.2 **Nitration of Styrenes – Preparation of *β*-Nitrostyrenes**

Solid-state synthesis of *β*-nitrostyrenes has been reported by Varma et al. in a process that uses readily available styrene and its substituted derivatives and inexpensive clay-supported nitrate salts, clayfen and clayan (Scheme 6.50) [170]. In a simple experiment, admixed styrene with clayfen or clayan is irradiated in a MW oven (~100–110 °C, 3 min) or heated in an oil bath (~100–110 °C, 15 min). For clayan intermittent heating is recommended with 30-s intervals to maintain the temperature below 60–70 °C. Remarkably, the reaction proceeds only in solid state and leads to the formation of polymeric products in organic solvent.

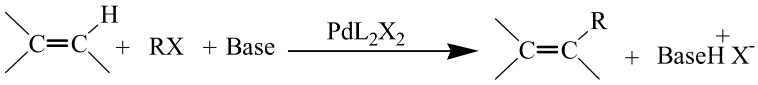


Where R = H, Cl, CH_3, OCH_3

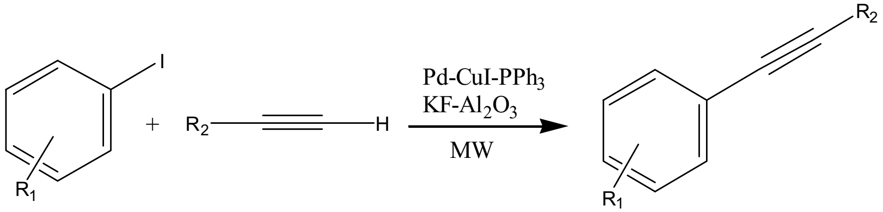
Scheme 6.50 Preparation *β*-nitrostyrenes using clay-supported nitrate salts.

6.2.7.3 **Organometallic Reactions (Carbon–Carbon Bond-forming Reactions)**

Palladium catalyzed reaction of aryl halides and olefins provide a useful synthetic method for C–C bond formation reaction [171, 172]. The commonly used catalyst is palladium acetate, although other palladium complexes have also been used. A solvent-free Heck reaction has been conducted in excellent yields using a household MW oven and palladium acetate as catalyst and triethylamine as base (Scheme 6.51) [173]. A comparative study revealed that the longer reaction times and deployment of high pressures, typical of classical heating method, are avoided using this MW procedure.



Scheme 6.51 Palladium-catalyzed carbon–carbon bond forming reactions using microwaves.



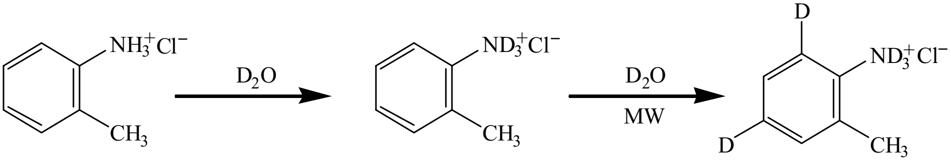
Scheme 6.52 MW-expedited Sonogashira coupling reaction on palladium-doped alumina.

A rapid MW-assisted palladium-catalyzed coupling of heteroaryl and aryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored on TentaGel has been achieved [174]. An environmentally friendly Suzuki cross-coupling reaction has been developed that uses polyethylene glycol (PEG) as the reaction medium and palladium chloride as a catalyst [175]. A solventless Suzuki coupling has also been reported on palladium-doped alumina in the presence of potassium fluoride as a base [176]. This approach has been extended to Sonogashira coupling reaction wherein terminal alkynes couple readily with aryl or alkenyl iodides on palladium-doped alumina in the presence of triphenylphosphine and cuprous iodide (Scheme 6.52) [177].

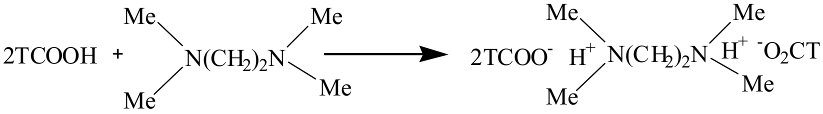
A fast and efficient molybdenum-catalyzed asymmetric allylic alkylation under noninert conditions has been reported using MW-accelerated reaction [178]. Intermolecular hydroacylation of 1-alkenes with aldehydes has been presented as a greener alternative to classical approach using a homogeneous catalyst in toluene.

6.2.7.4 **Synthesis of Radiolabeled Compounds – Exchange Reactions**

The earlier described MW-expedited borohydride reduction reaction [119] has been adapted for the efficient deuteration and tritiation procedures using MW irradiation and solid hydrogen/deuterium/tritium donors with minimal radioactive waste generation, a contrast from the classical tritiation efforts [179]. Jones and coworkers have circumvented the traditional disadvantages associated with tritium labeling techniques as demonstrated in the deuterated and tritiated borohydride reductions [120, 121], based on similar MW-expedited reduction executed on alumina surface [119]. The hydrogen exchange reactions that require prolonged reaction time (24 h) [180, 181] and elevated temperatures are the primary beneficiary of this microwave approach (Scheme 6.53) [120, 122]. The high purity of labeled materials, efficient insertion and excellent regioselectivity are some of the advantages of this emerging technology.



Scheme 6.53 Deuteration and tritiation reactions using MW irradiation.



Scheme 6.54 Hydrogenation reactions using formates.

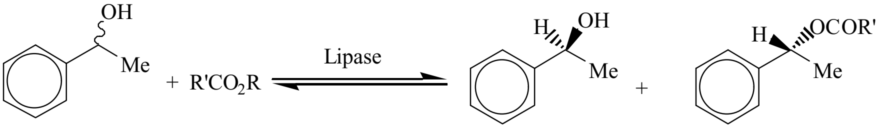
In a faster, selective and cleaner applications of the microwave-accelerated reactions, Stone-Elander et al. have synthesized a variety of radiolabeled (with ^3H, ^{11}C, and ^{19}F) organic compounds via the nucleophilic aromatic and aliphatic substitution reactions, esterifications, condensations, hydrolysis and complexation reactions using monomodal MW cavities on microscale [121]. A substantially reduced level of radioactive waste is generated in these procedures that are discussed, at length, in Chapt. 13 [122].

Hydrogenation reactions in which $H_2/D_2/T_2$ gases are replaced by various formates proceed very rapidly under MW irradiation conditions (Scheme 6.54) [182]. The pattern of labeling can be easily modified and the advantages are especially noteworthy in the case of tritium where high specific activity tritiated water is hazardous to use.

6.2.7.5 **Enzyme-catalyzed Reactions**

In conventional synthetic transformations, enzymes are normally used in aqueous or organic solvent at moderate temperatures to preserve the activity of enzymes. Consequently, some of these reactions require longer reaction times. In view of the newer developments wherein enzymes can be immobilized on solid supports [183], they are amenable to relatively higher temperature reaction with adequate pH control. The application of MW irradiation has been explored with two enzyme systems namely *Pseudomonas* lipase dispersed in Hyflo Super Cell and commercially available SP 435 Novozym (*Candida antarctica* lipase grafted on an acrylic resin).

The resolution of racemic 1-phenylethanol has been achieved under solvent-free microwave irradiation conditions by transesterification using above set of enzymes (Scheme 6.55) [184]. A comparison of the MW-assisted reaction with conventional heating revealed an enhanced enantioselectivity for the former presumably due to the efficient removal of low molecular weight alcohols or water upon exposure to microwaves or alternatively an entropic effect due to dipolar polarization that induces a previous organization of the system. Thermostable enzymes such as crude homogenate of *Sulfolobus solfataricus* and recombinant *β*-glucosidase from *Pyrococcus furiosus* have been successfully applied to transglycosylation reactions where recycling of the biocatalyst is feasible.

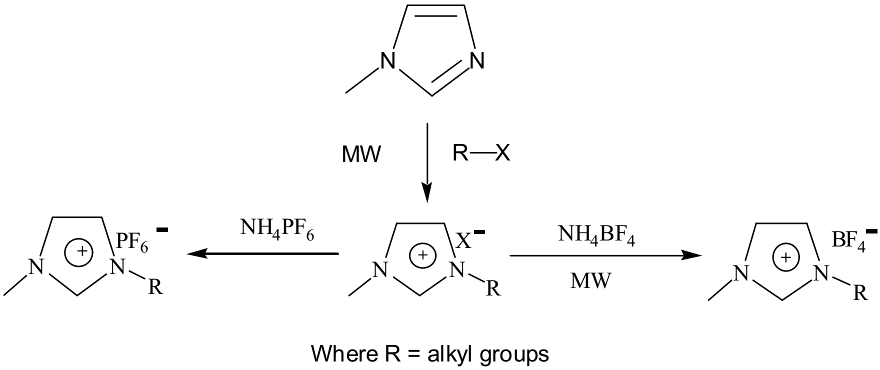


Scheme 6.55 MW-assisted resolution of racemic 1-phenylethanol via transesterification.

6.2.7.6 Solvent-free Synthesis of Ionic Liquids

Room temperature ionic liquids (RTIL) consisting of *N*-alkylimidazolium cations and a variety of anions [185], have received tremendous attention due to their potential in a variety of commercial applications especially as substitutes for traditional volatile organic solvents [186, 187]. They are polar in nature but consist of poorly coordinating ions and provide a polar alternative for biphasic systems. Other important attributes of these ionic liquids include negligible vapor pressure, potential for recycling, compatibility with various organic compounds and organometallic catalysts, and ease of separation of products from reactions [188]. Unfortunately, most of the conventional preparative procedures for the synthesis of ionic liquids involve several hours of heating in solvents under reflux and use a large excess of alkyl halides/organic solvents that diminish their true potential as "greener" solvents.

Ionic liquids, being polar and ionic in character, couple to the MW irradiation very efficiently and therefore are ideal microwave absorbing candidates for expediting chemical reactions. An efficient preparation of the 1,3-dialkylimidazolium halides via microwave heating has been described by Varma et al. that reduces the reaction time from several hours to minutes and avoids the use of a large excess of alkyl halides/organic solvents as the reaction medium (Scheme 6.56) [26–28].



Scheme 6.56 MW-assisted preparation of ionic liquids.

The approach precludes the usage of volatile organic solvents, is relatively much faster, efficient, and eco-friendly. Significant rate enhancements are reported in the 1,3-dipolar cycloaddition reactions including the use of covalently grafted dipolarophiles on the ionic liquids [189].

6.3
Conclusions

Microwave heating, being specific and instantaneous, is unique and has found a place in the expeditious chemical synthesis domain. Specifically, the solvent-free reactions are convenient to perform and have demonstrated clear advantage over the conventional heating procedures as summarized in this chapter. Numerous selective organic functional group transformations have been accomplished more efficiently and expeditiously using a variety of supported reagents on mineral oxides as catalysts. Although a large body of work has been performed around the world using an unmodified household microwave oven (multimode applicator), more recent work does point out the advantages of using commercial systems wherein not only the improved temperature/power control is possible but also the relatively large-scale reactions can be conducted [190, 191] with additional options for a continuous operation. The engineering and scale-up aspects for the chemical process development have also been discussed [192].

There are distinct advantages of these solvent-free procedures in instances where catalytic amounts of reagents or supported agents are used since they provide reduction or elimination of solvents, thus preventing pollution "at source". Although not delineated completely, the reaction rate enhancements achieved in these methods may be ascribable to nonthermal effects. The rationalization of microwave effects and mechanistic considerations are discussed in detail elsewhere in this book [25, 193]. A dramatic increase in the number of publications [23 c], patents [194–203], a growing interest from pharmaceutical industry, with special emphasis on combinatorial chemistry, and development of newer microwave systems bodes well for microwave-enhanced chemical syntheses.

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7

Microwave-assisted Reactions on Graphite

André Laporterie, Julien Marquié, and Jacques Dubac

7.1

Introduction

During the last 15 years numerous papers dealing with the use of microwave (MW) irradiation, rather than conventional heating, in organic and inorganic chemistry have reported dramatic reductions of reaction time and significant enhancement of yields and purity of the products. Despite the possibility of operating with pressurized reactors [1], however, MW irradiation of chemical reactions involving low boiling reagents and/or products can involve serious safety problems. Consequently, MW-assisted solvent-free reactions (“dry media”) have been widely investigated in organic synthesis [2]. Among the materials most often used as supports are alumina, silica, clays, and zeolites, which are sometimes also used as catalysts. When properly dried, however, these materials are weak MW absorbers and poor thermal conductors. For reactions which require high temperatures the idea of using a reaction support which takes advantage both of strong MW coupling and strong adsorption of organic molecules has stimulated great interest. Because most organic compounds do not interact appreciably with MW radiation, such a support could be an ideal “sensitizer”, able to absorb, convert, and transfer energy provided by a MW source to the chemical reagents.

Most forms of carbon, except diamond, which are renowned as supports for precious metal catalysts in certain applications [3], interact strongly with MW [4]. Amorphous carbon and graphite, in their powdered form, irradiated at 2.45 GHz, rapidly (within 1 min) reach very high temperatures (>1300 K). This property has been used to explain MW-assisted syntheses of inorganic solids [5]. In these syntheses carbon is either a “secondary susceptor” which assists the initial heating but does not react with other reactants, or is one of the reactants, e.g. in the synthesis of metal carbides. MW–carbon coupling has also been widely developed:

- by Wan et al. for gas-phase reactions; for example, in the synthesis of hydrogen cyanide from ammonia and carbon or methane [6], in the MW-induced catalytic reaction of water and carbon [7], and in the removal and/or destruction of acid gaseous pollutants such as SO_2 and NO_x [7, 8]; and

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

- for the processing of polymers and composites in which carbon black or graphite particles or fibers are included in the material [9].

The MW-promoted cracking of organic molecules in the presence of silica-supported graphite [10 a] or activated charcoal [10 b] has also been reported.

Graphite, the most stable of the three allotropic forms of carbon, has two structures, α (hexagonal form) and β (rhombohedral form), which interconvert easily [11]. In a graphite layer, each carbon atom is strongly bonded to three other carbon atoms in a planar configuration (sp^2 hybridization), and the remaining p electrons (one per carbon) are delocalized. The resulting carbon–carbon bonds are very strong (477 kJ mol^{-1}). The interlayer bonds, in contrast, are weak (17 kJ mol^{-1}), giving rise to the mechanical (lubricant) and chemical (intercalation) properties of graphite. Electronically, graphite is a semimetal of high electrical and thermal conductivity [11]. As for other semimetallic materials, the electronic current (σ) is the main factor in the graphite–MW interaction [5]. The rate of heating of a MW-irradiated material has been estimated to be $\Delta T/t = \sigma|E|^2/\rho C$, where E is the electric field, ρ is the density, and C is the specific heat capacity of the material [5]. Compared with other dielectric solids graphite has an unusually high thermal conductivity (a weak C, 0.63 kJ kg^{-1} K^{-1} at room temp.) [11]. This thermal conductivity, which decreases exponentially with increasing temperature, is a determining factor in the high rate of heating of graphite on MW irradiation, although other types of MW interaction, e. g. the excitation of weak interlayer bonds, and, especially in graphite powder, eddy currents or localized plasma effects, can also lead to very rapid dissipation of energy in graphite [5].

Because of its strong coupling with MW, its good adsorbent properties towards organic molecules [12], and its layer structure which enables it to form intercalated compounds [13], graphite has great potential in MW-assisted synthetic applications in organic chemistry, despite its weak fractal dimension ($D \approx 2$) [14].

Before the works of Laurent et al. [15, 16], which described several examples of MW-assisted organic syntheses in the presence of graphite (Sects. 7.2.1, 7.2.2, 7.2.4, 7.2.7, 7.3.2, and 7.3.3), Bond et al. [17] (Sect. 7.2.3), and Villemin et al. [18] (Sect. 7.2.4), no other studies were reported in this field. Literature results are, therefore, very recent. They are presented here in two parts. The first concerns reactions in which graphite behaves as an energy converter (or "sensitizer") capable of conveying the energy carried by MW radiation to the chemical reagents. The second includes results which reveal surprising catalytic activity of some metal inclusions of graphite.

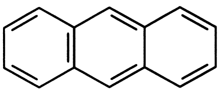
7.2
Graphite as a Sensitizer

This section covers reactions in which graphite is a sensitizer, without participation of its metal inclusions as possible catalysts, although a catalyst can be added to the graphite. The amount of graphite can be varied. It is generally at least equal to and most often greater than that of the reagents, resulting in a graphite-supported/microwave (GS/MW) process.

7.2.1
Diels–Alder Reactions

Many Diels–Alder (DA) cycloadditions have been studied under MW irradiation [19]. The use of a "dry process", as in GS/MW coupling, is of great interest for difficult reactions which need high temperatures, particularly for those involving poor MW-absorbing reagents. Some reactions which normally require use of an autoclave can, moreover, occur in an open reactor, owing to retention of a possibly volatile reagent by the graphite.

Among the dienes known as weakly reactive are anthracene (**1**), metacrolein dimethylhydrazone (**2**) and 3,6-diphenyl-1,2,4,5-tetrazine (**3**). DA cycloadditions with these dienes require long reaction times under classical heating conditions (Tab. 7.1).



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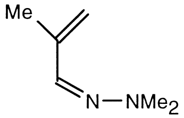

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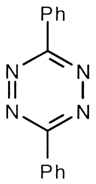

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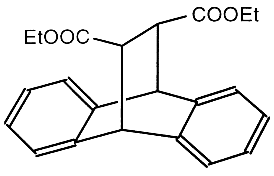

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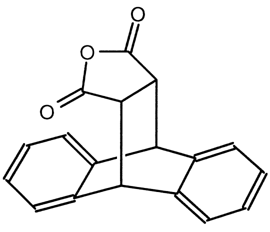

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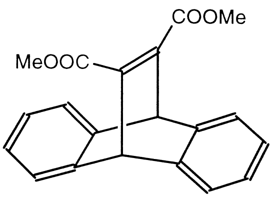

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Three reactions of **1** successively with diethyl fumarate, maleic anhydride, and dimethyl acetylenedicarboxylate (DMAD) are highly representative of the variety of experimental conditions used in the GS/MW process [26, 27]. Continuous MW irradiation (CMWI) with an incident power of 120 W for 1 min led to a high increase in temperature ($T_{\max} > 300\,^\circ\mathrm{C}$). Adduct **4** was obtained almost quantitatively (Tab. 7.1, entry 1), whereas only traces of adducts **5** and **6** were detected. When the incident power was reduced (30 W) and sequential MW irradiation (SMWI) was used, adducts **5** and **6** were obtained in good yield (Tab. 7.1, entries 3 and 4). This controlled irradiation enabled the temperature to be limited ($T_{\max} < 200\,^\circ\mathrm{C}$) and avoided the retro-DA reaction. In the reaction between **1** and diethyl fumarate similar SMWI conditions also gave the adduct **4** in high yield (Tab. 7.1, entry 2).

Other DA reactions of **1** (and some of its derivatives) in SMWI processes have been reported [28]. Under powerful irradiation ($T_{\max} > 300\,^\circ\mathrm{C}$), all products decomposed by the retro-DA reaction.

Tab. 7.1 Diels–Alder reactions of dienes **1–3** using the GS/MW process [15, 16].

Entry	*Adduct*	*SG/MW irradiation Conditions*[a] *(T_{max})*	*Yield (%)*[b]	*Conventional heating Conditions*	*Yield (%)*
1	**4**	120 W; 1 min[c], (370 °C)	92	Dioxane, reflux, 60 h [20]	90
2	**4**	30 W; 1 min × 3[d], (147 °C)	92		
3	**5**	30 W; 1 min × 3[d], (155 °C)	75	*p*-Xylene, reflux, 10 min [21]	90
4	**6**	30 W; 1 min × 3[d], (130 °C)	97	–[e] [20]	Quant.
5	**7**	30 W; 1 min × 10[d], (171 °C)	50	No reaction [21, 22]	
6	**8**	30 W; 1 min × 10[d], (157 °C)	62	$CHCl_3$, reflux, 120 h[f]	70
7	**9**	30 W; 1 min × 5[d], (168 °C)	72	CCl_4, 60 °C, 3 h [23]	–[e]
8	**10b**	30 W; 1 min × 5[d], (154 °C)	93	75 °C, 30 min [24]	–[e]
9	**11**	30 W; 1 min × 20[d], (160 °C)	60	Toluene, reflux, 50 h [25]	94

[a] See typical procedure; reagents used in equimolar amounts (entries 1–5) or in excess dienophile, 5/1 (entries 6, 7, 9), 2/1 (entry 8)

[b] Yield of isolated product relative to the minor reagent

[c] Continuous MW irradiation (CMWI); applied incident power; irradiation time; maximum temperature indicated by IR pyrometer

[d] Sequential MW irradiation (SMWI); applied incident power; time and number of irradiations; interval between two irradiations: 2 min (entries 2–5), 1 min (entries 6–9)

[e] Not given

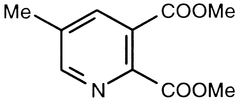
[f] This work

The hetero-DA reaction with azadienes, a well known synthetic method for obtaining nitrogen heterocycles, suffers from some difficulties, because of the low reactivity of the diene. For example, azadiene **2** did not react with DMAD under the action of conventional heating [22]. Sequential exposure to MW irradiation (30 W) for 10 min on a graphite support ($T_{max} = 171\ ^\circ C$) led to the adduct **7** with 60% conversion (50% in isolated product) [26, 27]. An equivalent yield was obtained by ultrasonic irradiation of the neat reaction mixture at 50 °C for 50 h [29].

The DA reaction of tetrazines such as **3** was also studied by use of the GS/MW process [26, 27]. The expected adduct, however, decomposed by nitrogen elimination followed by dehydrogenation, giving a pyridazine or a dihydropyridazine [23–25]. With 2,3-dimethylbutadiene and cyclopentadiene as dienophiles, SMWI gave dihydropyridazines **8** and **9**, as with classical heating [23] (Tab. 7.1, entries 6 and 7).

Under classical conditions, the reaction between **3** and styrene required 50 h of heating at 110 °C, and gave the dihydropyridazine adduct **10a** [24]. After SMWI with 30 W incident power for 5 min ($T_{max} = 154\ ^\circ C$), the adduct **10a** was not detected whereas the totally dehydrogenated product, pyridazine **10b**, was isolated in almost quantitative yield (Tab. 7.1, entry 8). Ethyl vinyl ether and **3** gave the same product, pyridazine **11**, under both classical heating [25] and MW irradiation conditions (Tab. 7.1, entry 9). In this instance the DA adduct lost nitrogen and ethanol.

The synthesis of these adducts was realized in very short times compared with the same reactions under the action of classical heating. The efficiency of the MW pro-



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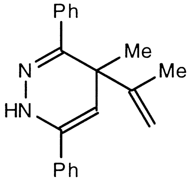

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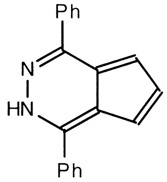

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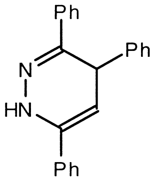

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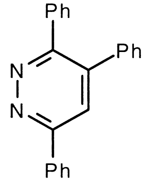

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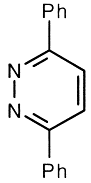

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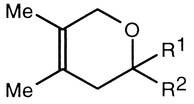
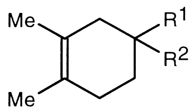
cess is all the more noteworthy because the three dienophiles dimethylbutadiene, cyclopentadiene and ethyl vinyl ether are volatile. Although an excess of these reagents with respect to **3** was used, the adsorption power of graphite was responsible of their retention, because the temperature of the reaction mixture exceeded their boiling points of approximately 120–130 °C.

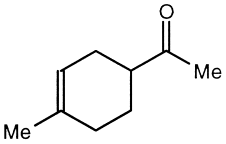
This retention of reagents by the graphite support has been shown in a series of experiments involving volatile dienes such as 2,3-dimethylbutadiene (**12**) and isoprene (**13**) (Tab. 7.2) [30, 31]. The reaction of **12** with diethyl mesoxalate gave **14** in 75% yield after SMW irradiation at low power (30 W) for 20 × 1 min only (Tab. 7.2, entry 1). When conventional heating was used a satisfactory yield was obtained after 4 h at 135 °C in a sealed tube [32]. Ethyl glyoxylate is a weaker carbonyl dienophile



$R^1 = R^2 = COOEt$ (**14**)
$R^1 = H$, $R^2 = COOEt$ (**15**)
$R^1 = H$, $R^2 = COOH$ (**16**)



$R^1 = H$, $R^2 = COMe$ (**17**)
$R^1 = Me$, $R^2 = CHO$ (**18**)



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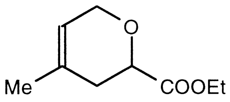

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Tab. 7.2 Diels–Alder reactions with 2,3-dimethylbutadiene (**12**) and isoprene (**13**) by use of the GS/MW process [27, 30, 31].

Entry	*Adduct*	*GS/MW irradiation Conditions*[a] *(T_{max})*	*Yield (%)*[b]	*Conventional heating Conditions*	*Yield (%)*
1	**14**	30 W; 1 min × 20[c], (165 °C)	75	MeCN, 135 °C[d], 4 h [32]	86
2	**15**	30 W; 1 min × 10[c,e], (165 °C)	87	140 °C, 6 h [33]	65
3	**16**	30 W; 1 min × 10[c], (249 °C)	54		
4	**17**	30 W; 1 min × 10[c], (126 °C)	89	Xylene, 95 °C, 80 h [35]	–[f]
5	**18**	30 W; 1 min × 10[c], (133 °C)	77	Benzene, 150 °C[d] [36]	65
6	**19**	30 W; 1 min × 2[c,e], (89 °C)	54	$CH_2Cl_2(AlCl_3)$, 20 °C, 24 h [37]	26
7	**20**	30 W; 1 min × 10[c,e], (146 °C)	73	CH_2Cl_2 ($SnCl_4$), 20 °C, 18 h [34]	10

[a] Reagents used in equimolar amounts (entries 4–6) or in excess of diene, 5/1 (entries 2, 3), 3/1 (entry 7), 2/1 (entry 1)

[b] Yield of isolated product relative to the minor reagent.

[c] Sequential MW irradiation (SMWI); applied incident power; time and number of irradiations; interval between two irradiations: 1 min (entries 1–3), 3 min (entries 4–7)

[d] Reaction in sealed tube

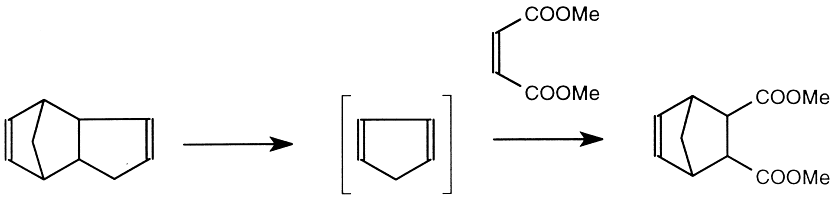
[e] Reaction performed in the presence of a catalyst: $ZnCl_2$ (entries 2, 7), $AlCl_3$ (entry 6)

[f] Not given.

than diethyl mesoxalate, and a catalyst ($ZnCl_2$) was added to afford the expected DA adducts with dienes **12** and **13** in good yields (Tab. 7.2, entries 2 and 7). For reaction with **13** the catalyst $SnCl_4$ [34] was substituted by $ZnCl_2$ to prevent the formation of the ene reaction product (Tab. 7.2, entry 7). Although adduct **16** was previously prepared from **15** [32], its direct DA synthesis from **12** and glyoxylic acid could be performed under the action of MW and without a catalyst (Tab. 7.2, entry 3).

Reactions performed with methyl vinyl ketone and metacrolein as ethylenic dienophiles also showed the clear advantage of SMWI conditions over conventional heating (Tab. 7.2, entries 4–6) [31]. In the reaction of isoprene with methyl vinyl ketone (Tab. 7.2, entry 6) selectivity for the *para* adduct (54%) was much better than when conventional heating was used (26%), probably owing to the shortening of reaction time.

Another example of the retention of volatile DA reagents is that of cyclopentadiene in a tandem retro-DA/DA "prime" reaction [15, 16, 38]. This reaction type is the thermal decomposition of a DA adduct (A) and the generation of a diene (generally the initial diene) which is trapped *in situ* by a dienophile leading to a new adduct (B) [39]. Cyclopentadiene (**22**) (b.p. 42 °C) is generated by thermolysis of its dimer at approximately 160 °C [40]. An equimolar mixture of commercial crude dicyclopentadiene (**21**) and dimethyl maleate was irradiated in accordance with the GS/MW process, in an open reactor, under 60 W incident power, for 4 min (8 × 30 s). The expected adduct **23** was isolated in 40% yield (Scheme 7.1). The isomeric composition of **23** (*endo–endo*/*exo–exo* = 65/35) was identical with that obtained under classical conditions from **22** and methyl maleate [41]. The overall yield of this tandem reaction can be increased from pure dimer **21** (61%) and the same tandem reaction has also been reported using ethyl maleate as dienophile [31].



21 22 23

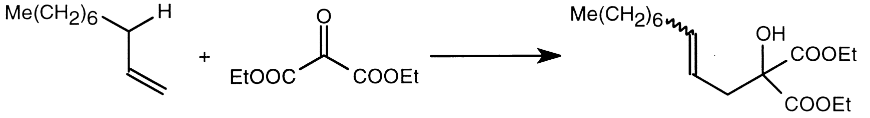
Scheme 7.1

The main advantages of the GS/MW process are the rapid increase of temperature, the retention of organic molecules, and the possibility of performing some reactions under one-pot conditions.

7.2.2
Ene Reactions

The ene reaction (or Alder reaction) is a cycloaddition which requires an activation energy higher than that of the Diels–Alder reaction [41]. Without a catalyst it usually occurs under pressure and/or at high temperature. The reaction with an alkene (ene) is much easier if the latter is more substituted (high HOMO) and the enophile is more electron-poor (low LUMO).

The alkene 1-decene (**24**) was poorly reactive in the carbonyl–ene reaction with ethyl mesoxalate and required a temperature up to 170 °C for a very long time (5 h) [42]. When performed in a homogeneous liquid medium at the same temperature but under the action of MW irradiation the reaction gave a similar result. Reaction time was appreciably shortened by use of GS/MW coupling [30]. Thus, irradiation at 60 W for only 10 min led to the ene adduct **25** in 50% yield (Scheme 7.2). Under these conditions a maximum temperature of 230 °C was measured. To obtain the same yield with conventional heating at 170 °C reaction for 1 h is required. The stereoselectivity of the reaction was not related to the mode of heating. A higher con-



24 25

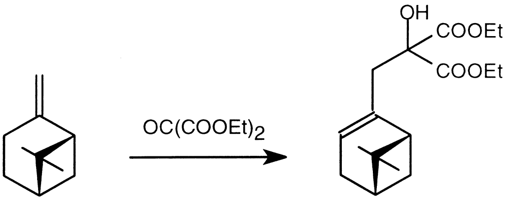
Thermal heating: 170°C, 1 h	50%
5 h	quant. (c/t = 26/74) [42]
GS/MW: 60 W, 1 min x 10	50% (c/t = 30/70) [30]

Scheme 7.2

version of **24** was obtained by increasing the irradiation (incident power >60 W), but the occurrence of side products made the isolation of **25** more difficult.

(–)-*β*-Pinene (**26**), a more reactive ene than **24**, reacted with ethyl mesoxalate under CCl_4 reflux in 90% yield after 5 h conventional or MW heating [42]. The reaction supported on graphite occurred in only 2 × 1 min of MW irradiation with an incident power of 60 W. The adduct **27** was obtained in 67% isolated yield (Scheme 7.3) [30]. This yield was obtained after 2 h of reaction under CCl_4 reflux.

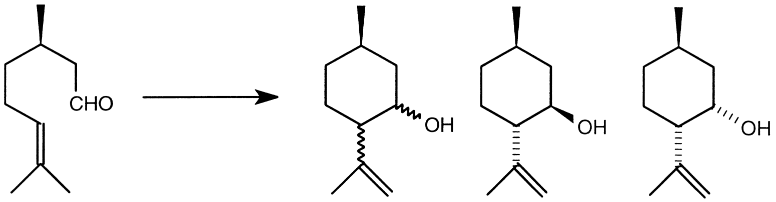
The intramolecular cyclization of (+)-citronellal (**28**) leads to a mixture of isomeric pulegols (**29**) and, particularly, to the (–)-isopulegol (**29a**) which is an intermediate in the synthesis of (–)-menthol [43]. The reaction can be performed by heating in the absence [44] or presence [43, 45] of a catalyst, including zeolite [46] and montmorillonite [42] under the action of MW. The cyclization of **28**, when performed by the GS/MW process – 4 min (8 × 30 s) of irradiation at 30 W incident power – resulted in 88% conversion (80% isolated yield) to the pulegols (**29**) (Scheme 7.4).



26 27

Therrmal heating: CCl_4 reflux, 2 h	65%
5 h	92% [42]
GS/MW: 60 W, 1 min x 2	67% [30]

Scheme 7.3



28 29 29a 29b

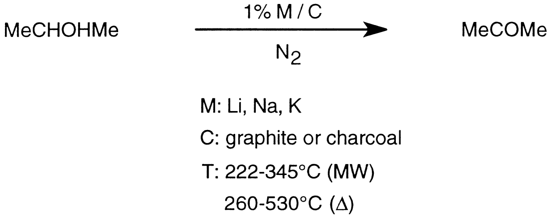
Thermal heating: 180°C, 30 h	90% (**29a**/**29b**/other = 71/16/13) [44]
GS/MW: 30 W, 30 s x 8	80% (**29a**/**29b**/other = 68/30/2) [30]

Scheme 7.4

The same reaction with conventional or MW heating at a constant temperature of 180 °C yielded only 50% conversion after 4 h [42]. Considering that the maximum temperature measured during GS/MW irradiation was only 210 °C, and that the reaction was not catalyzed, the acceleration was clearly very strong. It has been observed that, in contrast with clays such as montmorillonite, graphite in catalytic amounts does not accelerate the cyclization of **28** from room temperature to 180 °C [42]. We believe that under the heterogeneous conditions of the GS/MW process the temperature shown by the IR pyrometer is too low and gives no indication of probable "hot spots" produced at the surface of graphite grains (Sect. 7.4.2). The stereoselectivity was, moreover, somewhat different from that obtained by classical heating – although the amount of (+)-neoisopulegol (**29b**) was increased (–)-isopulegol (**29a**) remained the main diastereoisomer (68%).

7.2.3
Oxidation of Propan-2-ol

Reaction of an alcohol over basic catalysts favors dehydrogenation to give the corresponding carbonylated derivative. This reaction has been studied for propan-2-ol over a series of alkaline carbon catalysts, under the action of conventional heating and MW irradiation (Scheme 7.5) [17].



$$\mathrm{MeCHOHMe} \xrightarrow[\mathrm{N_2}]{1\%\ \mathrm{M/C}} \mathrm{MeCOMe}$$

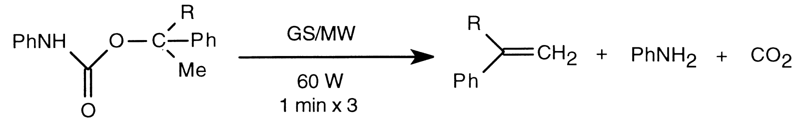
M: Li, Na, K
C: graphite or charcoal
T: 222-345°C (MW)
260-530°C (Δ)

Scheme 7.5

The main effect of MW irradiation on the graphite- and charcoal-supported catalysts is to reduce the average temperature required for the reaction to occur. The authors believe this is the result of "hot spots" formed within the catalyst bed (Sect. 7.4.2). Graphite-supported catalysts, moreover, seem to be more selective than the equivalent charcoal-supported catalysts, especially under the action of MW irradiation – 83.6–97.7% compared with 68.4–86.3%. This might be because of the hydrophobic nature of the graphite which directs the reaction away from the production of water by dehydration of the alcohol.

7.2.4
Thermolysis of Esters

The thermolysis of esters is a much used reaction in organic [47] and organometallic [48] syntheses, generally for the creation of a carbon–carbon double bond. The me-



R = Me **30** **32**

R = H **31** **33**

Scheme 7.6

chanism is often like that of the retro-ene reaction, requiring high temperatures. Among the esters, those of carbamic acid are more easily decomposed than those of carboxylic acids.

The high temperatures reached in the GS/MW process have been used to achieve the thermal decomposition of *O*-alkylcarbamates (Scheme 7.6) [15, 16]. The latter are prepared from corresponding alcohols and phenyl isocyanate in the presence of stannous octanoate [49].

With 1,1-dimethylbenzyl phenylcarbamate (**30**), a tertiary carbamate:

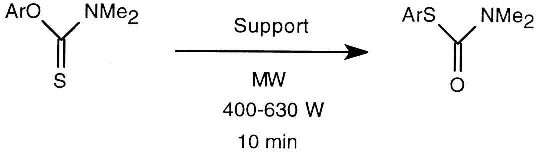
- heating in *p*-xylene under reflux for 10 h led to no decomposition;
- MW irradiation (150 W) of pure crystalline **30** led to 45% 2-methylstyrene (**32**) after 60 min (6 × 10 min); and
- MW irradiation of graphite powder impregnated with **30** gave 90% **32** after 3 min (3 × 1 min) under 60 W incident power (T_{max} = 320 °C).

This example shows that the GS/MW process can be used to accomplish thermal decomposition which cannot be performed efficiently by use of MW irradiation alone, because of weak MW absorption by the starting compound (**30**) of probable low dielectric loss.

The decomposition of a secondary carbamate, 1-methylbenzyl phenylcarbamate (**31**), was more difficult, and only 60% of styrene (**33**) was obtained under the same conditions (T_{max} = 340 °C). Attempts to decompose a primary carbamate, 1-octyl phenylcarbamate, failed because its sublimation preceded its decomposition [15, 16]. All these reactions have been performed in an open reactor by the above procedure (Sect. 7.2.1).

Some esters not having an aliphatic hydrocarbon chain are liable to thermal rearrangement. This is observed for *O*-arylthiocarbamates, for which rearrangement into *S*-arylthiocarbamates has been studied by Villemin et al. on different supports and under the action of MW irradiation (Scheme 7.7) [18].

No rearrangement was observed for the pure compound **34a**, adsorbed or not on KF-Al_2O_3, probably owing to its low dielectric loss. By using supports known to convert MW energy into thermal energy, the authors observed a conversion rate of 15 to 90% for **34**. The best yields (30 (**35e**) to 90% (**35c**)) were obtained on graphite powder.



34 **35**

Ar	Support	Conversion (%)
Ph (**a**)	alumina[a]	15
Ph (**a**)	silica[a]	20
Ph (**a**)	vermiculite[a]	30
Ph (**a**)	silicon carbide[a]	40
Ph (**a**)	graphite[b]	70
4-methylphenyl (**b**)	graphite[b]	45
4-nitrophenyl (**c**)	graphite[b]	90
4-carboxymethylphenyl (**d**)	graphite[b]	70
2-naphthyl (**e**)	graphite[b]	30

[a] MW irradiation: 630 W, 10 min; [b] MW irradiation: 400 W, 10 min; T_{end}=240-270°C.

Scheme 7.7

7.2.5
Thermal Reactions in Heterocyclic Syntheses

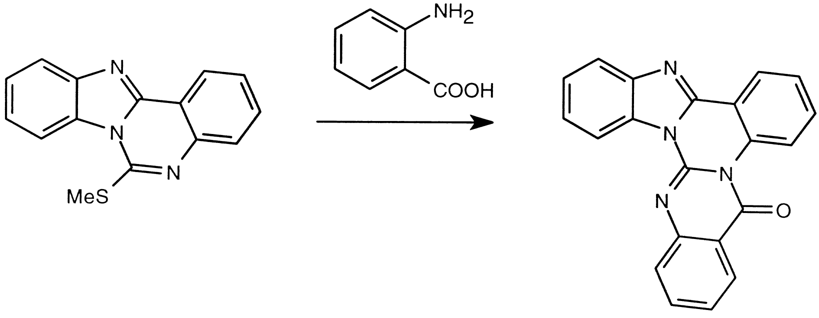
Many reactions in heterocyclic multistep syntheses involve thermal condensations.

Thermal heating of benzimidazoquinazoline **36** and anthranilic acid gave the cyclized tetraazaanthracenone **37** (Scheme 7.8).

As Besson et al. have shown, the yield of this reaction depends on the mode of heating [50]. Thus, thermal heating of the two starting compounds, neat at 120 °C or in butanol under reflux for 48 h, did not give more than 50% of product **37**. MW heating enabled reduction of the reaction time but not improvement in the yield. A longer heating period resulted in degradation products.

MW irradiation of a mixture of **36** and anthranilic acid adsorbed on graphite powder led to the product **37** in high yield (95%) and in a short time (1.5 h) [50]. When this GS/MW process was extended to the reaction between **36** and 5-methylanthranilic acid it gave the corresponding cyclized product in 75% yield.

Among polyheterocyclic systems, coumarins are synthesized by many routes, including the Pechmann reaction, which involves condensation of phenols with β-ketoesters [51]. This reaction, which has been the most widely applied method, has re-



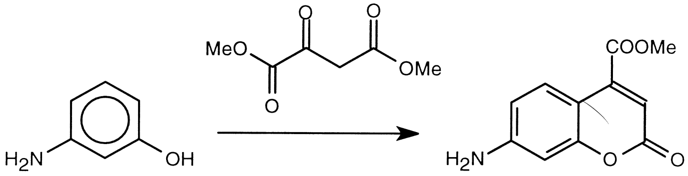
36

37

Thermal heating: neat, 120°C, 48 h	50%
butanol reflux, 48 h	50%
MW irradiation, 6 h	50%
GS/MW, 1.5 h	95%

Scheme 7.8

cently been studied under the action of MW irradiation by several authors [52], including the GS/MW process for 4-substituted 7-aminocoumarins [53]. Synthesis of aminocoumarin **38** by the Pechmann reaction involves heating a mixture of *m*-aminophenol and dimethyloxalacetate at 130 °C (Scheme 7.9). Under such conditions, however, the yield of the reaction is variable, and usually low (36%). Use of graphite as a support led to **38** in slightly better yield (44%).

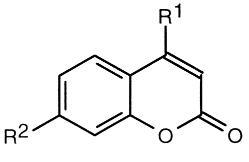


38

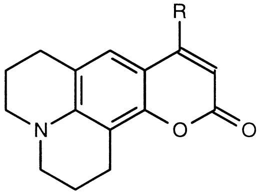
Thermal heating, 130°C, 2 h	36%
MW irradiation, 130°C, 85 min	39%
GS/Δ, 130°C, 2 h	44%
GS/MW, 130°C, 50 min	44%
GS,K10/Δ, 130°C, 66 min	64%
GS,K10/MW, 130°C, 30 min	66%

Scheme 7.9

Addition of a solid acid catalyst such as Montmorillonite K10 increased the yield significantly under the action of either thermal heating (64%) or MW irradiation (66%) [52c]. Under the latter conditions the reaction time was reduced. Comparable results were obtained for the synthesis of aminocoumarins **39–42** (Tab. 7.3) [53].



R^1 = COOMe, R^2 = NMe_2 (**39**)
R^1 = Me, R^2 = NH_2 (**40**)



R = COOMe (**41**)
R = Me (**42**)

Tab. 7.3 Preparation of 7-aminocoumarin derivatives **38–42** using GS,K10/Δ and GS,K10/MW processes [53].

Entry	*Product*	*MW irradiation*[a]		*Conventional heating*[b]	
		Reaction time (min)	*Yield (%)*	*Reaction time (min)*	*Yield (%)*
1	**38**	30	66	66	64
2	**39**	8	61	45	54
3	**40**	5	65	30	66
4	**41**	8	75	56	68
5	**42**	12	62	390	62

[a] The irradiation was programmed to furnish a constant temperature of 130 °C
[b] Reactions were performed at 130 °C (oil bath)

We believe that shortening of the reaction times for all GS,K10/MW experiments, compared with those using GS,K10/Δ, are the result of "hot spots" in the graphite powder (Sect. 7.4.2).

7.2.6
Decomplexation of Metal Complexes

Decomplexation of some metal complexes calls for drastic conditions. This is true for (η-arene)(η-cyclopentadienyl)iron(II) hexafluorophosphates, [FeAr(Cp)][PF_6] [54, 55]. Although their chemical decomplexation is known [55a], the most widely used method is pyrolytic sublimation at high temperatures (>200 °C) [55b]. To evaluate MW irradiation as the method of decomplexation of such iron complexes, Roberts et al. performed the reaction in the presence of graphite [54]. They discovered that the yield of the free ligand from the [Fe(η-*N*-phenylcarbazole)(η-Cp)][PF_6] complex (**43**) depended on the kind (flakes or powder) and amount of graphite, and on the irradiation time. In an optimized experiment 96% *N*-phenylcarbazole was obtained from **43** (1 g) by use of 1 g graphite flakes and 2 min MW irradiation. Experiments were performed using a conventional MW domestic oven; the temperature of the reaction mixture at the end of the irradiation was not given.

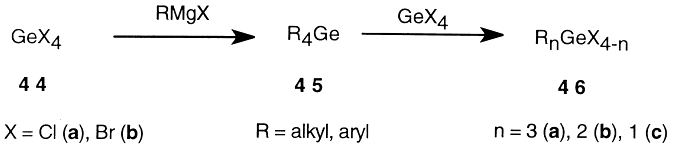
Pentamethylbenzene, *N*-phenylpyrrole, and 1,2-diphenylindole have been decomplexed from corresponding iron(II) complexes by use of the same GS/MW process; yields were 94%, 62%, and 71%, respectively. The results showed this to be a rapid and efficient method of decomplexation.

7.2.7

Redistribution Reactions between Tetraalkyl- or Tetraarylgermanes and Germanium Tetrahalides

Synthesis of alkyl (or aryl) halogermanes (**46**) from a germanium tetrahalide (**44**) occurs in two steps (Scheme 7.10) [56]. The most difficult to realize, and the least selective, is the second, i. e. the redistribution between alkyl (or aryl) and halide substituents of R_4Ge and GeX_4 compounds. Depending on the ratio of these two compounds the reaction gives alkyl (or aryl) halogermanes, **46a**, **46b**, or **46c**. It requires a catalyst, the most frequently used being the corresponding aluminum halide, and its amount must be relatively high (approx. 20 mol %) [56]. The experimental conditions are, moreover, rather drastic – heating in a sealed tube between 120 °C (arylated series) and 200 °C (alkylated series) for several hours.

These redistribution reactions are possible at atmospheric pressure under the action of MW; irradiation is performed for a few minutes in the presence of the same catalysts [57]. These reactions with the less volatile germanium tetrabromide (**44b**) (b.p. 184 °C) have also been performed by use of the GS/MW process, without added catalyst (Tab. 7.4, entries 1 and 3) [15, 16]. In this instance, despite the use of weaker incident power, the temperature reached 420 °C, very much higher than that obtained under the action of MW irradiation of a reaction mixture containing $AlBr_3$ (200 °C to 250 °C) (Tab. 7.4, entries 2 and 4). The presence of this catalyst considerably favors redistribution towards the dibrominated products (**46b**) (84% for $R = {}^{n}Bu$, 85% for R = Ph) relative to the monobrominated compounds (**46a**), which are the major products of the GS/MW process (78% and 43% respectively). The tribrominated products (**46c**), the most difficult to prepare, have been obtained with a rather high selectivity (73 to 80%) by use of the catalytic process under the action of MW [57]. In this reaction, therefore, the GS/MW process seems less effective than the MW-assisted and AlX_3-catalyzed process.



Scheme 7.10

Tab. 7.4 Redistribution reactions between germanium tetrabromide (**44b**) and tetrabutyl- or tetraphenylgermanes (**45**) under the action of MW irradiation [15, 16].

Entry	*R*	*Initial mixture (mmol)*			*Exp. conditions*	*Products (%)*[c]		
		GeBr$_4$	*R$_4$Ge*	*AlBr$_3$*		*R$_4$Ge*	*46 (a/b/c)*	*Yield*[d]
1[a]	^{n}Bu	5.20	5.75		90 W, 3 min[e]	17	83 (78/3/19)	80
2[b]	^{n}Bu	5.20	6.10	1.0	300 W, 8 min[f]		100 (8/84/8)	87
3[a]	Ph	5.75	5.20		90 W, 3 min[e]	9	91 (43/32/25)	85
4[b]	Ph	5.70	5.20	1.0	210 W, 8 min[f]	3	97 (9/85/6)	96

[a] Reaction performed by the GS/MW process with 6 g graphite as support

[b] Ref. [57]

[c] Products were analyzed by GC and ^{1}H NMR after alkylation [57]

[d] Recovered Ge products

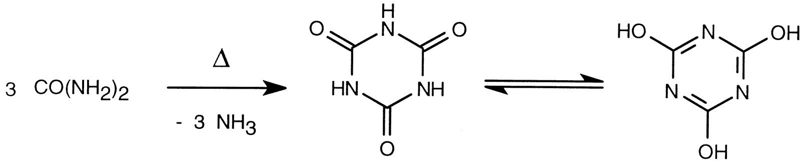
[e] Continuous irradiation

[f] Sequential irradiation, 2 min × 4

7.2.8
Pyrolysis of Urea

The reaction usually used to produce cyanuric acid (**48**) is the thermolysis of urea (**47**) between 180 °C and 300 °C (Scheme 7.11) [58]. The reaction occurs with formation of ammonia, which itself can react with **48** to give secondary products. It is, therefore, necessary to eliminate NH$_3$ and to operate with an open reactor.

This reaction has been studied with classical and MW heating under homogeneous and heterogeneous conditions [59]. Tab. 7.5 summarizes the results. When the reaction was conducted in the homogeneous phase at 200 °C (Tab. 7.5, entries 1–4), identical reaction rates and similar yields and selectivities were obtained for both heating modes. Kinetic data for the first-order equation were similar: $Ea\ (\mathrm{MW}) = 159 \pm 3\ \mathrm{kJ\ mol^{-1}}$, $Ea\ (\Delta) = 160 \pm 3\ \mathrm{kJ\ mol^{-1}}$; $\ln A\ (\mathrm{MW}) = 35 \pm 1$, $\ln A\ (\Delta) = 34 \pm 1$. In contrast, in the presence of graphite (**47**/graphite = 4/1, *w*/*w*), improved yield and selectivity were obtained under the action of MW irradiation compared with conventional heating (Tab. 7.5, entries 5–8) at the same bulk temperature. The authors ascribed this phenomenon to localized superheating ("hot spots") on the graphite surface (Sect. 7.4.2).



47 **48**

Scheme 7.11

Tab. 7.5 MW-assisted thermolysis of urea (**47**) under solvent-free conditions (Scheme 7.11) [59].

Entry	Conditions[a,b]	T_{max} (°C)	Time (min)	Yield (%)	Selectivity (%)	Reaction rate (10^3 s^{-1})
Homogeneous phase[c]						
1	MW	200	1	5.2	20.2	8.8
2	Δ	200	1	4.5	30.3	8.7
3	MW	200	30	68.4	73.6	8.8
4	Δ	200	30	67.9	72.2	8.7
Heterogeneous phase[d]						
5	MW	200	1	9.9	56.3	21.9
6	Δ	200	1	4.6	33.6	8.7
7	MW	300	3	61.2	93.5	12 028
8	Δ	300	3	15.2	45.6	7156

[a] Microwave (MW) or conventional (Δ) heating

[b] The incident MW power was adjusted to furnish the maximum temperature (T_{max})

[c] From 20 g urea (mp 133–135 °C)

[d] From 20 g urea + 5 g graphite.

7.2.9
Esterification of Stearic Acid by *n*-Butanol

Esterification of stearic acid (**49**) by butanols has been studied under homogeneous and heterogeneous conditions [60]. The yield of butyl stearates [$Me(CH_2)_{14}COOR$ (**50**), R = ^{n}Bu (**a**), ^{s}Bu (**b**), ^{t}Bu (**c**)] depended on the catalysts, on the isomeric form of the butanol, and on the mode of heating (conventional heating and MW irradiation). The esterification yield was similar under homogeneous conditions, irrespective of the mode of heating. In contrast, under heterogeneous conditions (e. g. with iron(III) sulfate or potassium fluoride as catalyst), after 2 h at the same bulk temperature (140 °C), the MW-irradiated reaction resulted in a higher (1.2 to 1.4-fold) yield of **50a** than did conventionally heating. This difference was more evident when graphite was added to the reaction mixture – similar yields (75–95 % **50a**) were obtained after only 5 min MW irradiation. Despite the small amount of added graphite (about 1/10, *w*/*w*, relative to the reagents), the reaction mixture rapidly reached a much higher temperature (250 to 300 °C) than in the absence of graphite.

7.3
Graphite as Sensitizer and Catalyst

As a support for chemical reactions graphite has often been "modified" by addition of a variety of substances which can be intercalated between the carbon layers (GIC – graphite intercalation compounds) or dispersed on the graphite surface, depending on the preparation conditions [13]. The resulting compounds, especially the GIC, have been used as reagents and as catalysts in numerous reactions, particularly in organic transformations [13, 61]. Depending on the intercalating guest the carbon lattice can behave as an electron acceptor (e. g. with metals – C_8K) or as an electron donor (e. g. with halogens – C_8Br). The electron power does not, however, seem to give Lewis-type catalytic activity to the graphite itself. As long ago as 1994 [15, 16] we reported that reactions known to require a Lewis acid catalyst can be conducted in the presence of unmodified graphite; this has been confirmed more recently by other authors [62–65]. We showed that the catalytic ability of graphite is a result of metal impurities, not the carbon lattice [66]. Most reported graphite-catalyzed reactions have been performed under the action of conventional heating, in the presence of a solvent and a small amount of graphite [62–64].

Use of graphite-supported methodology has been reported for three types of reaction – the Friedel–Crafts acylation [15, 16, 27, 66], the acylative cleavage of ethers [15, 16], and the ketodecarboxylation of carboxylic diacids [67, 68], either with conventional heating (GS/Δ) or MW irradiation (GS/MW coupling); these are discussed below. First, however, we describe the analysis of two commercial graphites of different purity which are used for these experiments.

7.3.1
Analysis of Two Synthetic Commercial Graphites

The two synthetic, unmodified graphites used in the experiments were:

- graphite **A**, Aldrich 28,286–3; purity 99.1%; particle size 1–2 μm; and
- graphite **B**, Fluka 50870; purity 99.9%; similar granulometry.

Elemental analysis of graphites **A** and **B** by X-ray fluorescence and optical emission (ICP–MS) spectrometry showed the presence of approximately a dozen elements. Graphite **A** contained more iron and aluminum than graphite **B** – **A**: Fe 0.41%, Al 0.02%; **B**: Fe 0.007%, Al 0.002% (by weight). Other elements (Ca, K, Si, Ti, V, Mn) were also present at lower concentrations. A careful study by transmission electron microscopy (TEM) of graphite **A** revealed small crystallites; the EDX spectrum of these showed that iron and oxygen were the main elements (Fig. 7.1). From these crystallites it was possible to obtain X-ray diffraction patterns in which, in addition to ring-shaped spots from graphite, heavy spots corresponding to magnetite (Fe_3O_4) were observed [66]. In a sample of graphite **B**, these particles were not noticeable owing to their small density.

We were therefore using two graphites of sharply different purity. The high iron content (0.41%) of graphite **A** leads one to expect catalytic action, either directly by the oxide (Fe_3O_4) or after a possible transformation on contact with MW radiation or a chemical reagent.

7.3.2
Acylation of Aromatic Compounds

Acylation of aromatic compounds (Friedel–Crafts (FC) acylation), of great industrial interest, suffers from an important catalysis problem [69]. Most of the Lewis acids used as catalysts (traditionally metal chlorides such as $AlCl_3$) complex preferentially

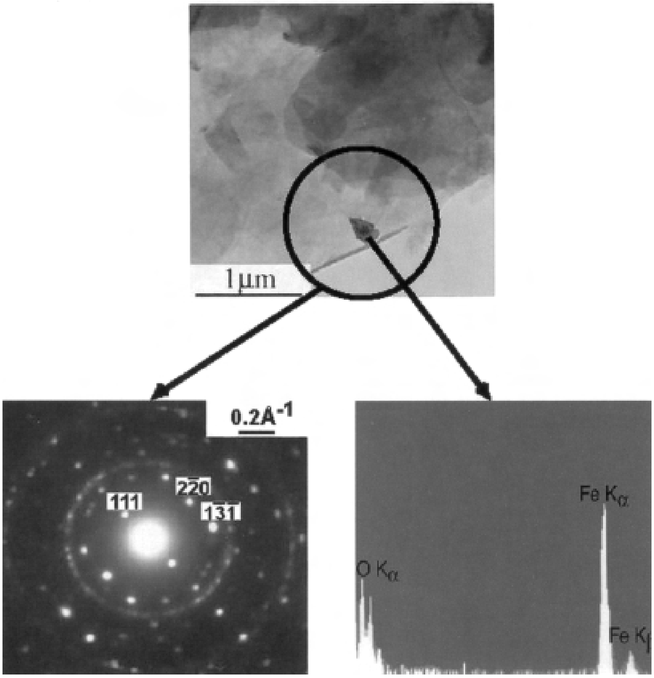
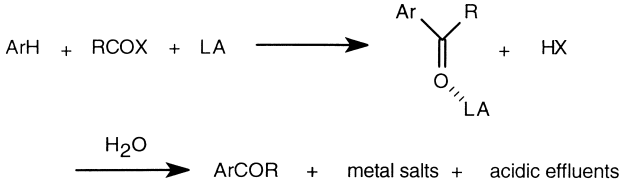


Fig. 7.1 Three results from transmission electron microscopy (TEM) with a Philips CM20 instrument operating at 200 kV. The first image shows a bright field of carbon deposited on a thin amorphous carbon layer supported by a copper grid. A small crystallite (dark contrast) is clearly apparent; this is also evident in other regions of the sample. The X-ray diffraction pattern (second figure) was obtained by examining the circled area of the bright-field image. The indexation is in good agreement with the magnetite (Fe_3O_4) cubic structure with a cell dimension of 8.39 Å, known as magnetite in the PDF database. The final figure corresponds to the EDXS analysis obtained with the electron beam focused on the small crystallite. The X-ray signal was captured by an Si(Li) detector. This clearly shows the presence of iron and oxygen inside the crystallite.

with the ketone produced instead of with the acylating agent [70] (Scheme 7.12). Rarely does a metal chloride complex preferentially with the acylating agent, except bismuth(III) chloride with acid chlorides [71, 72].

A stoichiometric amount of promoter, at least, is required for the reaction to proceed, leading to an environmentally hostile process with gaseous effluents and mineral wastes. With some metal salts, however, an increase in reaction temperature sets them free from their complex with the ketone, and a true catalytic reaction becomes possible [73]; this is observed for iron(III) chloride [74] and some metal triflates [72, 75], including their use under the action of MW heating [76].

In 1994 our preliminary results revealed, surprisingly, that FC acylation could be realized in the presence of graphite **A**, under solvent-free conditions, under the ac-



(X = Cl, OC(O)R, ...; LA : Lewis acid)

Scheme 7.12

tion of either classical heating or MW irradiation [15, 16]. More recently the same reaction has been reported in the presence of a small amount of the same graphite and using a solvent [62]. We have explained this "catalytic effect" of graphite [66].

The procedure entailed MW irradiation, at atmospheric pressure, of graphite powder **A** impregnated with reagents. The first experiments were performed with an activated aromatic, anisole (**51**), using a variety of acylating reagents (Tab. 7.6). With volatile acid chlorides such as acetyl or isobutyryl the reaction occurred in convenient yields (entries 1 and 2), and boiling was delayed as a result of graphite adsorption. With nonvolatile benzoyl chloride, the conversion became quantitative (entry 4). Good yields were also obtained for a long-chain derivative, which is more difficult to desorb from graphite, and for a furan derivative, known to resinify in the presence of a Lewis acid (entries 3 and 5).

Tab. 7.6. Graphite-supported acylation of anisole (**51**) by use of a variety of acylating reagents (RCOX) under the action of MW irradiation[a] [27, 66].

Entry	*RCOX*[b]	*Conditions*[c], *(T_{max})*	*Product*[d]	*Conversion and yield (%)*[e]
1	MeCOCl	45 W; 1 min × 8, (230 °C)	**58**[g]	62 (54)
2	^{i}PrCOCl	60 W; 1 min × 8, (260 °C)	**59**[g]	80 (74)
3	UndCOCl[f]	90 W; 2 min × 4, (410 °C)	**60**[g]	82 (74)
4	PhCOCl	150 W; 20 s × 15, (330 °C)	**61**[g]	100 (91)
5	FuCOCl[f]	90 W; 2 min × 5, (430 °C)	**62**[h]	60 (50)
6	$(MeCO)_2O$	+ $FeCl_3$[i], 60 W; 2 min × 6, (310 °C)	**58**[g]	65 (56)
7	$(^{i}PrCO)_2O$	+ $FeCl_3$[i], 90–30 W; 10 min[j], (260 °C)	**59**[g]	69 (63)

[a] Graphite **A**, 5 g; **51**, 10 to 20 mmol

[b] **51**/RCOX (mol) = 2/1 (entries 1, 2), 4/1 (entries 3–7)

[c] Applied incident power; sequential irradiation time; period between two irradiations 2 min, except entry 4, 1 min 40 s

[d] Products: $MeO(C_6H_4)COR$, R = Me(**58**), ^{i}Pr(**59**), Und(**60**), Ph(**61**), Fu(**62**)

[e] Conversion determined by GC; yield of isolated product (in brackets) relative to the minor reagent

[f] Und = undecyl; Fu = 2-furyl

[g] $p/o \geq 95/5$

[h] $p/o = 82/18$

[i] $FeCl_3/(RCO)_2O = 1/10$ (mol)

[j] Continuous MW irradiation with degressive power

The method was also applied to the benzoylation of other aromatic compounds (Tab. 7.7). The benzoylation of benzene itself, volatile and less reactive, seemed more difficult to perform (Tab. 7.7, entry 4). Silyl-substituted aromatics reacted by *ipso* Si-substitution [77], and were less volatile. With trimethylsilylbenzene, benzoylation occurred with an overall yield higher than for benzene, but the competitive H-substitution was also observed (entry 5).

Tab. 7.7 Graphite-supported benzoylation of aromatics under MW irradiation[a] [27, 66].

Entry	*ArH*[b]	*Conditions,*[c] *(T_{max})*	*Product*[d]	**Conversion and yield (%)**[e]
1	**52**	90 W; 2 min × 5, (390 °C)	**63**	73 (64)
2	**53**	60 W; 2 min × 7, (350 °C)	**64**[f]	54 (45)
3	**54**	90 W; 2 min × 6, (450 °C)	**65**[g]	85 (76)
4	**55**	60 W; 2 min × 7, (370 °C)	**66**	23 (15)
5	**56**	150 W; 20 s × 15, (328 °C)	**66**	42 (25)
			67	(8)
6	**57**	90 W; 2 min × 4, (380 °C)	**61**[h]	60 (50)

[a] Graphite **A**, 5 g; **51**, 10 to 20 mmol

[b] ArH: veratrole (**52**), toluene (**53**), naphthalene (**54**), benzene (**55**), Me_3SiPh (**56**), *p*-$Me_3Si(C_6H_4)OMe$ (**57**); ArH/PhCOCl (mol) = 4/1 (entries 1–5), 1/1.2 (entry 6)

[c] Applied incident power; sequential irradiation time; interval between two irradiations: 2 min, except entry 5, 1 min 40 s

[d] Products: 2,4-$MeO(C_6H_3)COPh$ (**63**), $Me(C_6H_4)COPh$ (**64**), $C_{10}H_8COPh$ (**65**), PhCOPh (**66**), *p*-$Me_3Si(C_6H_4)COPh$ (**67**)

[e] Conversion determined by GC; yield of isolated product (in brackets) relative to the minor reagent

[f] $p/o = 85/15$

[g] $\alpha/\beta = 55/45$

[h] $p/o = 95/5$

If graphite **A** has catalytic activity in these reactions, the amount of graphite could be reduced, and 0.5 g (instead of 5 g) of graphite **A** was, indeed, sufficient to promote these reactions (Tab. 7.8) [66]. In the process in which a small amount of graphite was used:

- the temperature gradient was lower than for the GS/MW process; and
- vaporization of the reactants was not delayed.

Consequently:

- sequential MW irradiation was preferable to continuous (compare Tab. 7.8, entries 3 and 5); and
- the MW power must be reduced and the reaction time increased (compare Tab. 7.6, entry 4, and Tab. 7.8, entry 5).

Comparative attempts at graphite-supported acylation of anisole, toluene, and naphthalene using classical heating afforded interesting results [66]. With nonvolatile reactants the yields were almost identical with those obtained under the action of MW. In contrast, if at least one reactant was volatile (MeCOCl, ^{i}PrCOCl) or sublim-

Tab. 7.8 Acylation of aromatic compounds in the presence of a small amount of graphite and under the action of MW irradiation [27, 66].

Entry	*ArH*[a]	*RCOX*[b]	*Graphite*[c]	*Conditions*[d], *(T_{max})*	*Product*[a]	*Conversion and yield (%)*[e]
1	**51**	MeCOCl	A	45 W; 1 min × 8, (120 °C)	**58**[f]	27 (20)
2	**51**	^{i}PrCOCl	A	60 W; 1 min × 8, (120 °C)	**59**[f]	90 (80)
3	**51**	PhCOCl	A	300 W; 1 min, (165 °C)	**61**[f]	85 (76)
4	**51**	PhCOCl	C	300 W; 1 min, (159 °C)	**61**[f]	95 (85)
5	**51**	PhCOCl	A	60 W; 2 min × 7, (178 °C)	**61**[f]	100 (98)
6	**53**	PhCOCl	A	150 W; 20 s × 60, (120 °C)	**64**[g]	36 (29)
7	**54**	PhCOCl	A	300 W; 1 min, (160 °C)	**65**[h]	40 (35)

[a] ArH: anisole (**51**), toluene (**53**), naphthalene (**54**)

[b] ArH/RCOX (mol) = 4/1 (entries 3–6), 2/1 (entries 1, 2, 7)

[c] Graphite **C**: iron-graphimet (Alfa 89 654)

[d] Continuous (entries 3, 4, 7) or sequential (entries 1, 2, 5, 6) MW irradiation; interval between two irradiations: 1 min (entry 5), 2 min (entries 1, 2), 40 s (entry 6)

[e] Conversion determined by GC; yield of isolated product (in brackets) relative to the minor reagent

[f] $p/o \geq 93/7$

[g] $p/m/o = 82/2/16$

[h] $\alpha/\beta = 70/30$

able (naphthalene), the yield obtained under the action of MW was higher. SMWI enables control and limitation of these phenomena.

With regard to a mechanistic hypothesis, the catalytic effect of graphite itself behaving as a Lewis acid was excluded – the use of graphite **B** instead of graphite **A** resulted in no reaction, or sometimes only a trace of the acylation product [27, 66]. The presence of relatively large amounts of Fe_3O_4 in graphite **A** (Sect. 7.3.1) led us to believe this impurity was responsible for the catalytic activity observed. Several further experiments supported this.

Graphites combined with a variety of metals ("Graphimets") are known for their catalytic properties [13]. The iron–graphite compound in which the presence of Fe_3O_4 crystallites has been shown [78] proved very efficient for the acylation of anisole (Tab. 7.8, entry 4). Because the iron content (5%) was much higher than that of graphite **A**, this graphimet could be a convenient material for GS/MW experiments, but its cost, especially relative to that of graphite **A**, limits its use.

For the benzoylation of anisole (Tab. 7.6, entry 4), graphite **A** was replaced by graphite **B** doped with Fe_3O_4 (28 mg for 5 g graphite, the same iron content as in graphite **A**). Although unachievable with graphite **B** alone, benzoylation of anisole was now possible, but with lower yield than for use of graphite **A** (50% instead of 100%). This showed the activity of Fe_3O_4 became much stronger when subjected to the high graphitization temperature.

The catalytic effect of graphite **A** thus depends on iron impurities, e.g. Fe_3O_4, and probably also on iron sulfides or sulfates, because sulfur is also present in this graphite, and all these iron compounds are known catalysts of FC acylation [69, 73, 74]. In this respect, it seems that $FeCl_3$ could be the true catalyst generated *in situ* by the reaction of the different iron compounds with acid chloride and hydrogen chloride. In the absence of a chlorinating agent, for example using an acid anhydride as the reagent and an iron oxide (Fe_2O_3 or Fe_3O_4) as the catalyst, acylation does not occur. We have effectively shown that the GS/MW process using acid anhydrides as reagents is efficient only after addition of a catalytic amount of $FeCl_3$ (Tab. 7.6, entries 6 and 7).

Finally, a sample of graphite **A** was analyzed after acylation using an acid chloride as reagent. No Fe_3O_4 crystallites were observed and an EDX spectrum revealed small deposits containing iron, chlorine, and oxygen. Thus formation of $FeCl_3$ from Fe_3O_4 crystallites is highly probable. Loupy et al. have shown that α-Fe_2O_3 can be generated from Fe_3O_4 under the action of MW at high temperature [79]; the formation of $FeCl_3$ would be a result of chlorination of Fe_3O_4 and/or Fe_2O_3. Because Fe_3O_4 interacts strongly with MW [4], the presence of hot spots in the region of Fe_3O_4 crystallites could also lead to increased catalytic activity.

Comparison with previous FC acylations, the above processes are clean, without aqueous workup, and therefore without effluents ("green chemistry"). The graphite is, moreover, inexpensive and can be safety stored or discarded. Its activity is, however, limited to activated aromatic compounds.

The process which seems to have the most possibilities for a scale-up development is that using a low amount of graphite, for which the desorption treatment can be totally suppressed in a continuous flow system. We recently proposed the use of such a process to perform FC acylations under the action of MW with $FeCl_3$ as catalyst [76d]. The replacement of $FeCl_3$ by a graphite bed is quite conceivable in the same continuous flow apparatus.

7.3.3
Acylative Cleavage of Ethers

The preparation of esters using an acid chloride as reagent is usually performed from alcohols and rarely from ethers [80]. However, the protection of the hydroxyl group as ether derivatives constitutes a widely used method in organic synthesis [81]. The acylative cleavage of ethers is one of possible deprotection processes. It occurs with an acid halide or anhydride in the presence of a catalyst, usually a Lewis acid. In 1998, Kodomari et al. reported a cleavage of some ethers (benzylic, allylic, *tert*-butylic, and cyclic) with acid halides in the presence of graphite **A** [63]. The reaction was performed under reflux in dichloroethane. Under these conditions, however, cleavage of primary or secondary alkyl ethers did not occur.

According to the solvent-free GS/MW process, which enables reaction at high temperatures, the cleavage of these alkyl ethers became possible (Scheme 7.13) [15, 16].

An equimolar (10 mmol) mixture of benzoyl chloride and *n*-butyl oxide adsorbed on 5 g graphite **A** was sequentially irradiated with 90 W incident power. The conversion reached 80% (Yield of isolated *n*-butyl benzoate (**69**): 62%). With ethyl oxide, the yield of ethyl benzoate (**68**) was lower, but noteworthy considering the volatility of this oxide, and the significant retentive power of graphite towards organic compounds. These preliminary results have not yet been expanded, but it is certain that more reactive ethers, like those substituted with *sec*- or *tert*-alkyl, benzylic or allylic groups, are cleavable in the same way.

$$\text{PhCOCl} + \text{R}_2\text{O} \xrightarrow{\text{Graphite } \mathbf{A}} \text{RCl} + \text{PhCOOR}$$

R = Et	60 W; 2 min x 7 (Tmax = 350°C)	**68** (50%)*
R = ^{n}Bu	90 W; 2 min x 4 (Tmax = 450°C)	**69** (62%)*

(*) Not maximized yields

Scheme 7.13

Concerning the mechanism of such a reaction and the nature of the catalyst, we do not think that the graphite itself is the catalyst. In fact, diethyl- and di-*n*-butyl ethers are inert towards benzoyl chloride in the presence of graphite **B**. Moreover, it is known that metal chlorides, especially $FeCl_3$ [82], are catalysts for this reaction. After the careful mechanistic study realized in the case of FC acylations (Sects. 7.3.1 and 7.3.2), we propose that the catalyst of the graphite-assisted acylative cleavage of ethers is $FeCl_3$ generated *in situ* from Fe_3O_4 (and/or Fe_2O_3) and the acid chloride. Then, the C–O bond cleavage would involve the O-acylation of ether ($[R_2O\text{–}COR']^+$) followed by the nucleophilic displacement (S_N1 or S_N2) of one of the two hydrocarbon groups (R) of ether by the anionic part of the reagent (Cl^-), as with the $FeCl_3$–Ac_2O system [82]. It is interesting to note here that phenolic ethers, such as anisole or veratrole, preferentially give the acylation of aromatic nuclei towards the cleavage of the ether group (Sect. 7.3.2).

7.3.4
Ketodecarboxylation of Carboxylic Diacids

Thermal decomposition of carboxylates gave ketones by a decarboxylation mechanism [83]. The same ketones were obtained directly from the corresponding carboxylic acids by a decarboxylation–dehydration process in the presence of several catalysts, such as thorium [84] or manganous [85] oxides. This catalytic way allows a lowering of the reaction temperature, which still remains high (250–350 °C). Even though the method is of little use in the synthesis of aliphatic ketones, it is an important route for preparing cyclic ketones from carboxylic diacids [83, 86]. Among these ketones, the cyclopentanone is an important industrial compound [87]. For its synthesis from adipic acid, typical procedures using various catalysts (barium hydroxide [88 a], metal oxides [83], carbonates [88 b], potassium fluoride [88 c]) have been described. However, the search for an efficient and eco-friendly industrial process is still the subject of current interest [89, 90]. In this respect, with a view to reducing energy and raw material consumption, a new approach has been undertaken using graphite-supported chemistry [67, 68].

The catalytic cyclization of a diacid requires two contradictory thermal conditions: a temperature high enough to have a convenient reaction rate, but low enough to avoid vaporization of the diacid. For adipic acid, the limiting temperature is about 290–295 °C [83, 86, 88]. Thanks to its properties of rapid conversion of MW energy and retention of organic molecules, graphite could allow a high reaction temperature to be reached rapidly, although it delays the vaporization of the diacid. Moreover, since magnetite (Fe_3O_4) is a catalyst for the decarboxylation of acids [91], no added catalyst would be necessary.

To determine approximately the optimum temperature of a graphite-supported cyclization of adipic acid, a series of experiments was performed with classical heating. Using the two graphites **A** and **B** (Sect. 7.3.1), no significant vaporization of adipic acid (**70**) was observed up to 450 °C at atmospheric pressure. Graphite **A** proved to be the more efficient, giving 90% yield of cyclopentanone (**74**) after 30 min of heating (Tab. 7.9, entry 1). Graphite **B** gave a lower yield under the same conditions (entry 2).

Tab. 7.9 Graphite-supported thermal ketodecarboxylation of diacids **70–73**[a,b] [67, 68].

Entry	*Diacid*	*Graphite*	*Ketone yield (%)*[c]
1	**70**	A	**74**, 90 (85)
2	**70**	**B**	**74**, 22
3	**71**	A	**75**, 60
4	**71**	A	**75**, 80 (74)
5	**72**	A	**76**, 80 (72)
6	**73**	A	**77**, 17

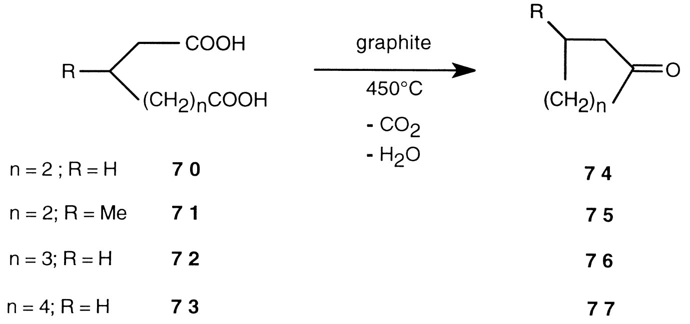
[a] Temperature of the electrical oven: 450 °C; reaction time: 30 min (entries 1–4), 60 min (entries 5, 6); pressure: atm. p. (entries 1–3), 300 mm Hg (entries 4–6)

[b] Optimized diacid/graphite ratio: 15 mmol/5 g

[c] Conversion determined by GC and isolated yield (in brackets) from four experiments

The retentive power of graphite towards adipic acid and the catalytic effect of the magnetite, especially present in **A**, are obvious. TEM examinations of a graphite **A** sample before and after reaction showed that crystallites of Fe_3O_4 appeared to be smaller after the reaction. However, the same graphite sample was reused for three successive reactions without significant loss in yield. When applied to the synthesis of other cyclic ketones (Scheme 7.14), less volatile than **74**, it was observed that pressure had an effect on the recovery of product (Tab. 7.9, entries 3 and 4). A slightly reduced pressure (300 mm Hg) was necessary to obtain 3-methylcyclopentanone (**75**) or cyclohexanone (**76**) in convenient yield (Tab. 7.9, entries 4 and 5). For the cyclization of suberic acid (**73**), a less favorable structure, the yield in cycloheptanone (**77**) remained low (Tab. 7.9, entry 6).

Some MW-promoted decarboxylations have been reported in the literature [92], even the decarboxylation of magnesium, calcium and barium salts of alkanoic acids [92 a]. We have shown for FC acylations and acylative cleavage of ethers (Sects. 7.3.2 and 7.3.3) that the graphite-supported process takes advantage of MW, since graphite and magnetite are among the solids having the most efficient MW absorbing power [4], and then providing elevated temperature in core. Consequently, the cyclization of **70** was realized under GS/MW conditions. A SMWI mode was optimized and



Scheme 7.14

coupled with a limitation of the reaction temperature to 450 °C, using the two graphites **A** and **B** (Tab. 7.10, entries 1–4). Graphite **A** showed again its superiority, giving under these optimized conditions (entry 2) a 90% yield in cyclopentanone (**74**) after only 6 × 2 min of irradiation. Under the same conditions, graphite **B** gave only a 33% yield (entry 4).

Tab. 7.10 Graphite-supported ketodecarboxylation of adipic acid (**70**) under MW irradiation[a] [67, 68]

Entry	*Graphite and added catalyst*	*MW conditions*[b,c]	*Yield (%)*[d]
1	**A**; none	90 W; 2 min × 2	60
2	**A**; none	90 W; 2 min × 2 + 75 W; 2 min × 4	90
3	**B**; none	90 W; 2 min × 2	19
4	**B**; none	90 W; 2 min × 2 + 75 W; 2 min × 4	33
5	**B**; Fe_3O_4 (28 mg)	90 W; 2 min × 2	51
6	**B**; Fe_2O_3 (29 mg)	90 W; 2 min × 2	51
7	**B**; FeO (26 mg)	90 W; 2 min × 2	35
8	**B**; Al_2O_3 (28 mg)	90 W; 2 min × 2	15
9	**B**; Bi_2O_3 (28 mg)	90 W; 2 min × 2	16
10	**B**; KF (21 mg)	90 W; 2 min × 2	14
11	**B**; Na_2CO_3 (80 mg)	90 W; 2 min × 2	29
12	**B**; Cs_2CO_3 (244 mg)	90 W; 2 min × 2	26
13	Fe_3O_4 (3.47 g) without graphite	90 W; 2 min × 2	10

[a] Mass of **70**: 2.19 g (15 mmol); mass of graphite: 5 g
[b] Sequential MW irradiation controlled to a maximum temperature of 450 °C
[c] Applied incident power and irradiation time; interval between two irradiations: 2 min
[d] Yield of cyclopentanone (**74**) from GC analysis

To compare their activities further, various catalysts were added to graphite **B**, and the results were analyzed with respect to the reference experiment (Tab. 7.10, entry 3) which gave a low yield (19%). When doped with Fe_3O_4, graphite **B** gave a 51% conversion of **70** (entry 5), almost as much as graphite **A** alone (entry 1). The two other iron oxides, Fe_2O_3 and FeO, seemed to be active but other catalysts, Al_2O_3, Bi_2O_3 and KF were inactive.

Because Fe_3O_4 itself is strongly absorbent of MW [4] and is a good catalyst for decarboxylations [91], is the graphite necessary? When Fe_3O_4 was used in the absence of graphite, the yield in ketone **74** decreased dramatically (10%) (Tab. 7.10, entry 13). Adipic acid was recovered almost completely on the walls of the reactor and on the cold finger. Consequently, the presence of graphite as a support, able to adsorb and retain the adipic acid, and then allow the cyclization before its vaporization, is essential.

Comparison of reaction times revealed a shortening under MW irradiation (Tab. 7.10, entry 2: overall reaction time = 22 min) with respect to conventional heating (Tab. 7.9, entry 1, 30 min), for the same maximum temperature. This can be explained by a higher temperature gradient and the presence of "hot spots" at the graphite surface under MW.

A reaction mechanism with Fe_3O_4 as catalyst has been proposed [68], in agreement with previous work concerning decarboxylation of acids in the presence of a metal oxide [83]. After the transient formation of iron(II) and iron(III) carboxylates from the diacid and Fe_3O_4 (with elimination of water), the thermal decarboxylation of these salts should give the cyclic ketone and regeneration of the catalyst.

This "dry", solvent-free GS/MW process, which allows high temperatures rapidly, is very useful for the ketodecarboxylation of diacids. This has several advantages such as:

- medium grade commercial graphite, of low cost, can be used;
- the diacid is confined to the graphite which prevents its vaporization; and
- the volatile ketone produced is recovered by distillation as the only organic compound.

A large-scale process could be devised by using a continuous supply of diacid (as a solid or in the molten state) in a graphite bed.

7.4
Notes

7.4.1
MW Apparatus, Typical Procedures, and Safety Measures

Graphite reflects MW like a metal and its heating depends strongly on particle size. With large particles (flakes), electric discharges were observed under MW irradiation, whereas with fine ones (powder) a rapid increase of temperature was obtained. The temperature of the reaction mixture must be controlled to avoid melting point of the reactor, if it is Pyrex glass. The use of a quartz reactor is highly preferable.

A MW applicator, such as the Synthewave 402 from Prolabo or nowadays Discover from CEM, equipped with:

- a monomode cavity;
- open vessels allowing reactions at normal or reduced pressure;
- a rotating reactor;
- a MW power modulator;
- an IR pyrometer allowing a continuous record of reaction mixture temperature;
- a computer to monitor the different irradiation modes and the main experimental parameters (incident MW power, temperature and time),

is a convenient apparatus to perform graphite-supported reactions [2a–c, 93]. The reactor equipment was completed by a dry-ice condenser allowing an easy rotation of the whole set.

Typical procedures for the GS/MW process have been described in the literature cited above. The deposition of nonvolatile reactants on graphite was performed using a volatile solvent (generally Et_2O), removed under reduced pressure before MW irradiation. When one of reactants was volatile, it was added neat to the graphite powder previously prepared with the nonvolatile reactant as above. The ether used for impregnation of graphite must be totally evaporated before MW irradiation; if not, in some cases, owing to high reaction temperatures reached, Et_2O can react with one of reactants. For example, the formation of the ester RCOOEt resulting from an acylative cleavage of Et_2O by RCOCl (Sect. 7.3.3) has been observed in FC acylations [15, 27]. In such cases, the impregnation can be performed by use of another volatile and inert solvent, such as dichloromethane. The desorption of the reaction product(s) was performed by washing of graphite with a proper solvent. The use of an ultrasonic bath can be advantageous.

7.4.2
Temperature Measurement

A knowledge of the temperature of the reaction media is fundamental. Under MW irradiation, this measurement poses some conditions [94]. In stirred homogeneous media, the measurement with an IR pyrometer is significant enough. However, an optical fiber thermometer is preferable, but limited in high temperature levels. Consequently, for the temperature measurement of graphite-supported reactions under MW irradiation, the IR pyrometer was used which allows to measure the temperature of the lower reactor walls, and not inside of the reaction mixture. Stuerga and Gaillard showed that the temperature of a MW-irradiated heterogeneous (especially solid) medium was not uniform, but there were “hot spots” [95]. We had ourselves observed, using a thermocouple at the end of a reaction, that the temperature inside the graphite powder was 20 °C to 50 °C higher than that indicated by the IR pyrometer. At the time of the MW irradiation of C-supported catalysts in the absence of nitrogen carrier, Bond et al. [17] observed very small bright spots within the catalyst bed. They proposed that these bright emissions, of continually fluctuating positions, would be due to the generation of plasmas.

Moreover, some MW absorbing impurities on the graphite surface, such as the Fe_3O_4 crystallites, could induce other local superheating.

7.4.3
The Retention Mechanism of Reactants on Graphite

The adsorption phenomenon of organic molecules by graphite is well known, molecular arrangements on surfaces have been recorded and thermodynamic data have been determined [12]. The specific surface of graphite **A** is 13 $m^2\ g^{-1}$ [15]. Therefore, adsorption of 2 mL of an organic compound by 5 g of graphite would give a layer of thickness 300 Å. Van der Waals interactions, responsible for the adsorption, is not effective on such a large thickness. Other dynamic phenomena must be considered, such as intercalation and diffusion between carbon layers. Molecules of appreciable size, such as aromatic hydrocarbons and C_{60} fullerene, have been intercalated [96]. In view of the high temperatures in the GS/MW process, operation of these different phenomena (adsorption, diffusion, intercalation) seems likely. The interlayer spaces could behave as microreactors (or micro-"pressure cookers") in which reactants, or at least a part of them, should be confined. However, after a reaction, we have not observed (by XRD) any change in the interlayer distance of graphite. Consequently, at the end of the reaction, and at room temperature, the interlayer distance should revert to its basic value (3.354 Å) [11], after ejecting the reaction product to the surface. It must be noted here that the intercalation of organic compounds (pyridine derivatives) into a layered mineral oxide (α-$VO(PO_4).2H_2O$) occurs more rapidly using MW than with conventional thermal methods [97]. Moreover, as the graphite used is of low granular size (1–2 μm), intergrain confinement due to capillary action is also possible.

7.4.4
Graphite or Amorphous Carbon for C/MW Coupling?

Because amorphous carbon as graphite heats up strongly under MW irradiation [4], its use as a sensitizer has been widely reported [5–10] (Sect. 7.1). Recently, MW-assisted esterification of carboxylic acids with alcohols was performed on activated carbon in good yields (71–96%) [98]. For our part, when charcoal powder was used as a support, we had difficulty in desorbing the reaction products [15]. Even with a continuous extractor, the desorption was never quantitative. The desorption of reaction products from graphite powder is much easier than from amorphous carbon powder.

Charcoals and various carbon blacks show great variability of their structure and properties as a function of the carbonaceous starting material and the preparation conditions [3, 11]. The graphitization of carbon, which is required to achieve a high corrosion resistance, lead to materials of more homogeneous structures and properties, allowing a good reproducibility of reactions.

Therefore, graphite is preferable in a supported reaction, although the use of intercalated reagents remains possible.

7.5
Conclusion

Owing to a particularly strong interaction with MW radiation and a high thermal conductivity, graphite is an efficient sensitizer. It is capable of converting radiation energy to thermal, which is then transmitted instantaneously to supported chemical compounds. High temperatures, which must be controlled, are rapidly reached, and reaction times are most often shortened with respect to the same reactions effected by classical heating. Two reaction types take advantage of this graphite/MW coupling:

1. reactions which require a high temperature
2. reactions involving chemical compounds which, as in the case of organic ones, have low dielectric loss and do not heat up sufficiently under MW irradiation.

Its inert behavior towards numerous chemical compounds and its adsorbent properties (responsible for the retention of volatile or sublimable organic compounds), make graphite the choice support for thermal reactions. Among its impurities, magnetite was revealed to be an active catalyst, and some reactions can be performed without any added catalyst. Two processes are then possible, the graphite-supported reaction ("dry" process), and the reaction in the presence of a small amount of graphite (solid–liquid medium).

In a broad perspective, large scale development seems possible for some reactions, either by a continuous-flow process through a MW-irradiated graphite plate (solid–liquid (or gas) reactions), or by a continuous supply of solid starting compound on a graphite bed ("dry" reactions). In this respect, continuous processes have recently given excellent results in large scale development of MW-assisted reactions in homogeneous and heterogeneous media [76d, 99].

Acknowledgments

We thank Professor M. Onyszchuk (McGill University, Montreal), for his assistance in the preparation of the manuscript, and Drs M. Audhuy-Peaudecerf, M. Poux (Institut National Polytechnique, Toulouse), P. Baulès (Center d'Elaboration de Matériaux et d'Etudes Structurales, C.N.R.S., Toulouse), J.-R. Desmurs, N. Roques (Rhodia Organique Fine, France), our co-workers B. Garrigues, R. Laurent, and C. Laporte for their effective and friendly collaboration.

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8

Microwaves in Heterocyclic Chemistry

Jack Hamelin, Jean-Pierre Bazureau and Françoise Texier-Boullet

8.1

Introduction

This chapter will deal with applications of microwave irradiation in the synthesis of heterocycles by a variety of means, excluding cycloadditions, which will be described in the next chapter. We have chosen to report first reactions in solution in organic solvents, then heterogeneous reactions without solvent under a variety of conditions, and finally to deal with emerging techniques which employ ionic liquids.

8.2

Microwave-assisted Reactions in Organic Solvents

In this section we will examine examples of organic transformations performed by using microwave energy to heat organic mixtures. In all the examples included in this section, the chemical reagents are dissolved in a solvent that couples effectively with microwaves and generates the heat energy required to promote the transformations.

8.2.1

Heck, Suzuki, and Stille reactions

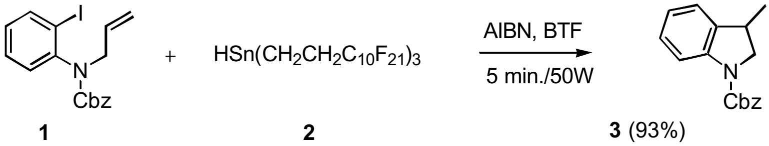
The palladium-catalyzed Heck [1], Suzuki [2] and Stille [3] reactions are robust and general methods for C–C bond-formation and have therefore emerged as important reactions in the synthesis of natural heterocyclic compounds.

Hallberg and coworkers [4a] have used a single-mode microwave oven [4b] at 50 W to improve radical-mediated reduction and cyclization of the heterohalide **1** with $HSn(CH_2CH_2C_{10}F_{21})_3$ **2** in benzotrifluoride (BTF). The authors claim the preparation of **3** in high yield (93%) after 5 min, as illustrated in Scheme 8.1.

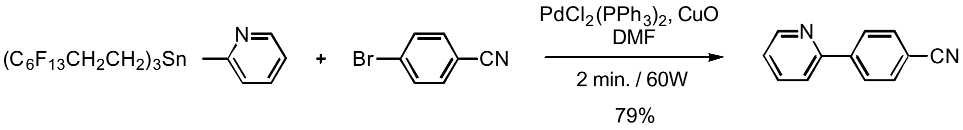
The efficiency of fluorous Stille coupling reactions [5a] is enhanced by use of microwave irradiation (Scheme 8.2). The reaction proceeds in 79% yield after 2 min with DMF as the microwave-active solvent.

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9



Scheme 8.1

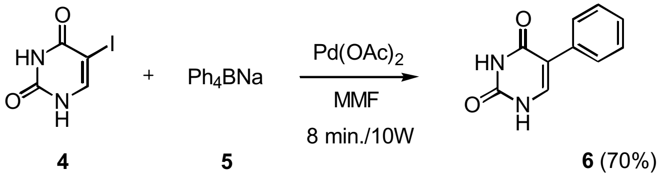


Scheme 8.2

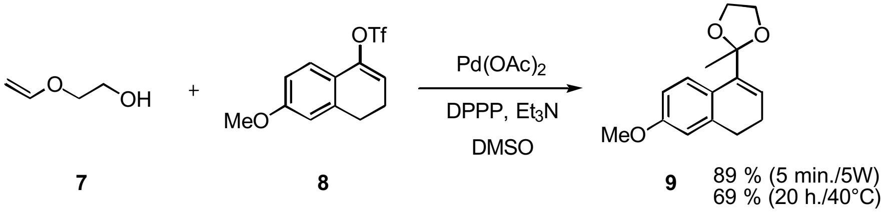
The same authors performed a microwave assisted Stille reaction on the Rink amide (RAM) Tentagel polymer-tethered 4-iodobenzoic acid [5 b]. Successful palladium-catalyzed coupling of heteroaryl boronic acid with anchored 4-iodobenzoic acid enabled both >99% conversion of the starting material within 3.8 min (45 W) and a minimal decomposition of the solid support. The coupling reactions were realized in a mixture of polar solvents (H_2O–EtOH–DME, 2.5 : 1.5 : 6).

A recent report [6] has discussed the effect of monomode microwave irradiation in the palladium-catalyzed phenylation of 5-iodouracil **4** with the nontoxic sodium tetraphenylborate **5** as phenyl reagent (Scheme 8.3). The authors showed that the use of monomethylformamide (MMF) as solvent increases the yield of **6** (70%), because MMF has a high boiling point (180 °C) and is more polar ($\varepsilon = 182.5$) than other amides used in microwave-activated reactions.

A regiocontrolled Heck vinylation [7] of commercially available 2-hydroxyethyl vinyl ether **7** in dry DMSO has been reported (Scheme 8.4). Flash heating by micro-



Scheme 8.3

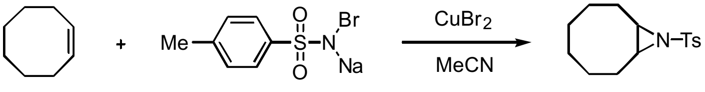


Scheme 8.4

wave irradiation (5 min, 5 W), as a complement to the standard thermal heating (20 h, 40 °C), was used to reduce reaction times drastically, with better yields of isolated product **9**.

8.2.2
Aziridine Synthesis

Aziridines, the smallest heterocycles, are an important class of compounds in organic chemistry. Interesting access [8] to aziridines by using Bromamine-T as a source of nitrogen in the copper (II)-catalyzed aziridination of olefins in MeCN was recently reported. Application of microwaves has resulted in enhanced yields for aziridines [9] with short reaction times (Scheme 8.5).

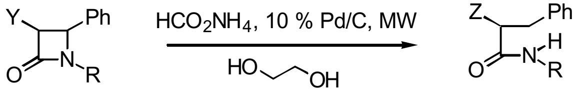


81 % (MW, 12 min.)

Scheme 8.5

8.2.3
β-Lactam Chemistry

Bose and coworkers [10] have described hydrogenation using ammonium formate as hydrogen donor and Pd/C as catalyst for selective transformations (Tab. 8.1) of *β*-lactams **10**, as shown in Scheme 8.6.

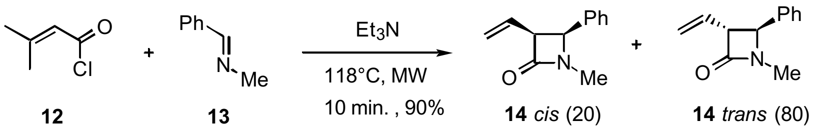


Scheme 8.6 **10** **11** (80-90 %)

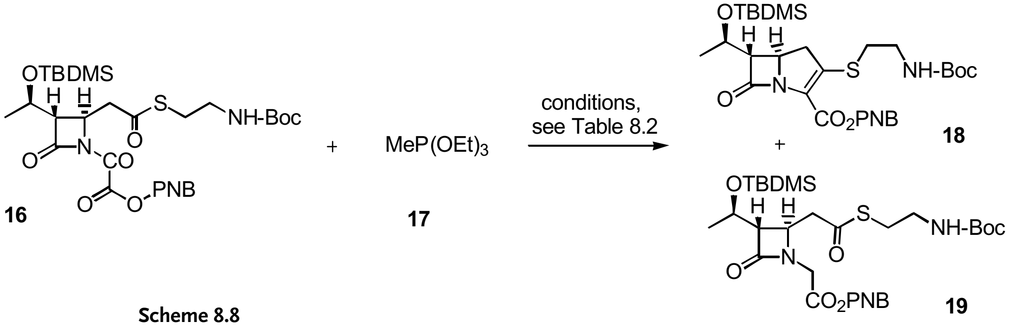
Tab. 8.1 Transformations of *β*-lactams **10** by hydrogenation under the action of microwaves.

Product 10	*Y*	*R*	*Product 11*	*Z*	*Yield of 11 (%)*
10a	CH_2=CH	An	**11a**	CH_3–CH_2	83
10b	MeC(=CH_2)	An	**11b**	MeCH(Me)	80
10c	CH_2=CH	Ph	**11c**	CH_3–CH_2	90
10d	CH_2=CH–CHO	An	**11d**	$CH_3CH_2CH_2O$	87
10e	OBn	An	**11e**	OH	80
10f	OPh	An	**11f**	OPh	84
10g	CH_2=CH	Bn	**11g**	CH_3–CH_2	85
10h	OBn	Bn	**11h**	OH	83

Ph = C_6H_5, An = C_6H_4OMe-4, Bn = $CH_2C_6H_5$



Scheme 8.7



Scheme 8.8

The authors report reaction times similar to those achieved with a preheated oil bath at 130 °C on a small scale; on a larger scale, however, microwave-assisted reactions seem to proceed more rapidly.

The same authors also studied recently the preparation of substituted vinyl *β*-lactams **14**, with efficient stereocontrol [11], by use of limited amounts of solvent (chlorobenzene) (Scheme 8.7). Microwave oven-induced reaction enhancement (MORE) chemistry techniques have been used to reduce pollution at the source and to increase atom economy.

A comparative study [12] of the reactivity of the oxalimide **16** in a variety of solvents (xylene, chlorobenzene, toluene) and of methylphosphinite **17** was performed with the focused microwave Synthewave 402 reactor (Merck Eurolab, div. Prolabo, France), using different conditions of power and exposure time (Scheme 8.8). In all experiments yields were better than those of previous procedures with classical heating (Tab. 8.2), and the authors wrote "it is clear that microwave technique is applicable to highly functionalized compounds containing stereogenic centers without appreciable modification of these centers".

Tab. 8.2 Cyclization of **16** under the action of microwave irradiation.

Solvent	*Time (min)*	*Power (W)*	*Final temp. (°C)*	*Yield of 18 (%)*
Xylene	10	300	140	50
Chlorobenzene	2	300	150	35
Neat	10	300	80	0

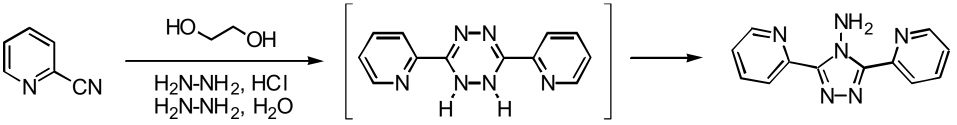
8.2.4
1,2,4-Triazole, Pyrazole Synthesis

Barbry and coworkers conducted extensive investigations leading to the development of a range of microwave-assisted synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles [13 a] as potentially good corrosion inhibitors. The group found, for example, that the 4-amino-1,2,4-triazole **22** is quickly prepared (5 min) by reaction of the 2-cyanopyridine **20** on hydrazine dihydrochloride in the presence of excess hydrazine hydrate in ethylene glycol under the action of microwave irradiation (95% yield). The analogous reaction performed with conventional heating proceeds in 85% yield and requires a longer reaction time (ca. 45 min) (Scheme 8.9 a).

Interestingly, the same authors [13 b] have isolated the 1,2-dihydro-1,2,4,5-tetrazine intermediate **21** by condensation of 2-cyanopyridine **20** with hydrazine hydrate in presence of flower of sulfur (Scheme 8.9 b). The reaction time is reduced under the action of microwave irradiation (125 W); protic solvents also promote the transformation.

Kidwai et al. have demonstrated that formic acid can be used to catalyze and accelerate cyclocondensation of hydrazones to give new fungicidal pyrazoles [14], as shown in Scheme 8.10.

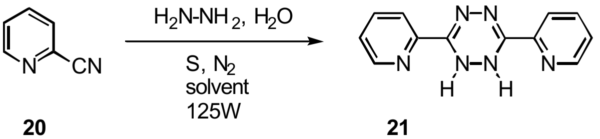
The significance of their work using microwave heating is that the classical approach to cyclocondensation of hydrazones requires 30–35 h with constant heating



20 **21** **22**

MW	oil bath
95% in 5 min.	85% in 45 min.

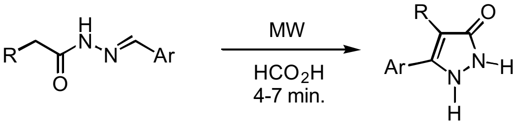
Scheme 8.9 a



20 **21**

68%, 10 min. in DMF
77%, 10 min. in EtOH

Scheme 8.9 b



75-86%

R = phenoxy, octyl
Ar = 2-hydroxyphenyl, 2-hydroxynaphthyl
3-nitrophenyl, phenyl, 4-chlorophenyl
4-methoxyphenyl

Scheme 8.10

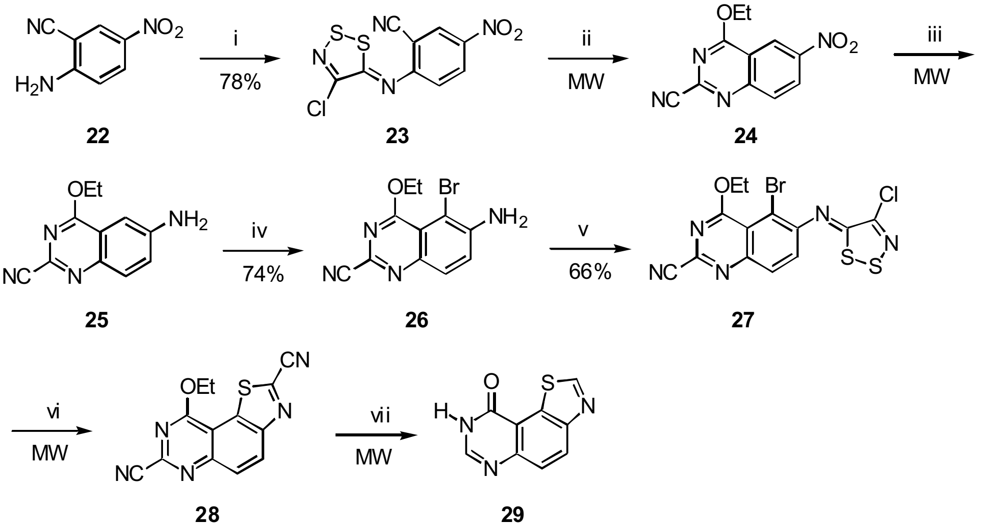
at 100–120 °C whereas the same reaction is complete in 4–7 min with improved yield when performed under the action of microwave irradiation.

8.2.5
Multistep Synthesis of Polyheterocyclic Systems

The purpose of this section is to highlight the applications of microwave irradiation to multistep synthesis of polyheterocyclic systems with potent pharmaceutical value. When conventional thermal procedures (metal or oil bath) fail, and irrespective of the conditions needed in the homogeneous phase, microwave irradiation can be used as an alternative to classical methods enabling development of easy and rapid access to new heterocycles.

Besson and coworkers reported an original approach for the synthesis of the rare thiazolo-[5,4-*f*]-quinazoline **29** in six steps [15] from commercially available 2-amino-5-nitrobenzonitrile **22** (Scheme 8.11). The authors studied the transposition of four steps (ii, iii, vi, and vii) of the synthesis of thiazoloquinazoline **29** to microwave irradiation of solutions, with the same concentration of starting material and volume of solvent, and found that yields of the desired compounds were better than those obtained by conventional heating (Tab. 8.3). The overall time for the synthesis of **29** was considerably reduced and the overall yield was enhanced.

A new means of access to 5*a*,10,14*b*,15-tetraazabenzo[*a*]indeno-[1,2-*c*]-anthracen-5-one **33** and to benzimidazo-[1,2-*c*]-quinazoline **31** was reported recently [16] (Scheme 8.12). The preparation of 6-mercaptobenzimidazo-[1,2-*c*]-quinazoline **31**



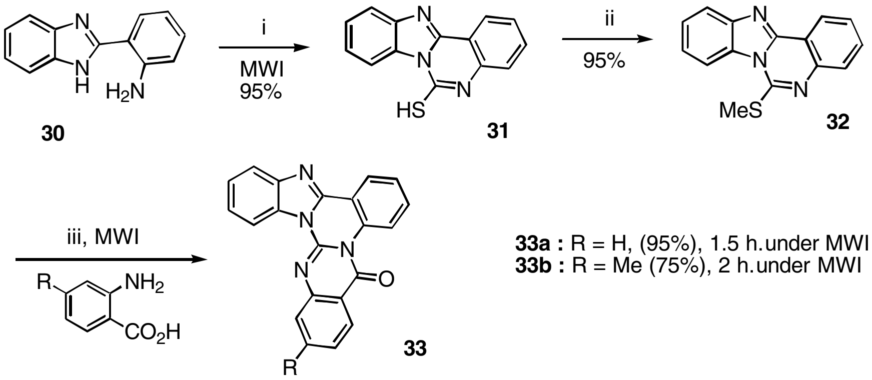
Scheme 8.11 Reagents and conditions (for time and yields of steps ii, iii, vi, and vii see Tab. 8.3). (i) 4,5-dichloro-1,2,3-dithiazolium chloride, pyridine, rt, 10 h; (ii) NaH, EtOH, reflux; (iii) $SnCl_2.2H_20$, EtOH, 70 °C; (iv) Br_2, AcOH, rt, 24 h; (v) 4,5-dichloro-1,2,3-dithiazolium chloride, rt, 4 h; (vi) CuCN, pyridine, reflux; (vii) HCl, reflux.

Tab. 8.3 Comparison of conventional heating and microwave irradiation for steps (ii), (iii), (vi), and (vii) of Scheme 8.11.

Step	*Starting material*	*Product*	*Conventional heating*		*Microwave irradiation*	
			Reaction time (min)	*Yield (%)*	*Reaction time (min)*	*Yield (%)*
ii	**23**	**24**	640	37	80	61
iii	**24**	**25**	60	72	10	94
vi	**27**	**28**	90	50	20	53
vii	**28**	**29**	60	49	10	50

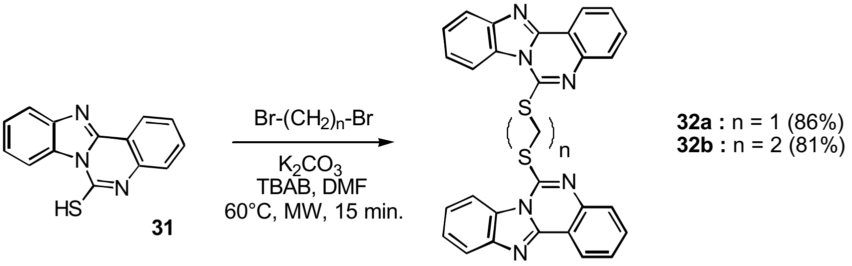
was easily accomplished at 60 °C (in 55 min), under the action of focused microwave irradiation, by reaction of the starting 2-(2-aminophenyl)benzimidazole **30** with CS_2 in the presence of KOH and a protic solvent (MeOH). Under the same conditions conventional heating led to the same yield but with a reaction time of 24 h.

Alkylation of **31** with dibromomethane and 1,2-dibromoethane was performed under solvent-PTC conditions with good yields and short irradiation times (15 min) [16]. The synthesis of original benzimidazo-[1,2-*c*]-quinazoline dimers **32(a,b)** was successfully achieved by use of potassium carbonate in the microwave active DMF solvent (Scheme 8.13).



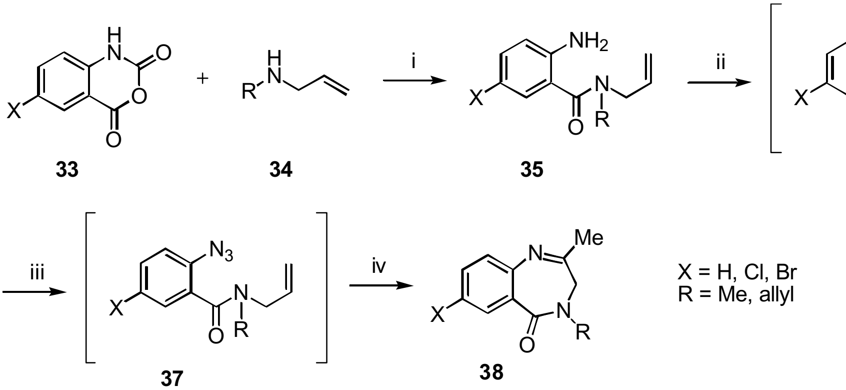
33a : R = H, (95%), 1.5 h.under MWI
33b : R = Me (75%), 2 h.under MWI

Scheme 8.12 Reagents and conditions: (i) CS_2, MeOH, reflux, MW, 55 min; (ii) MeI, NaH, DMF, 25 °C, 5 min; (iii) graphite, MW.



32a : n = 1 (86%)
32b : n = 2 (81%)

Scheme 8.13



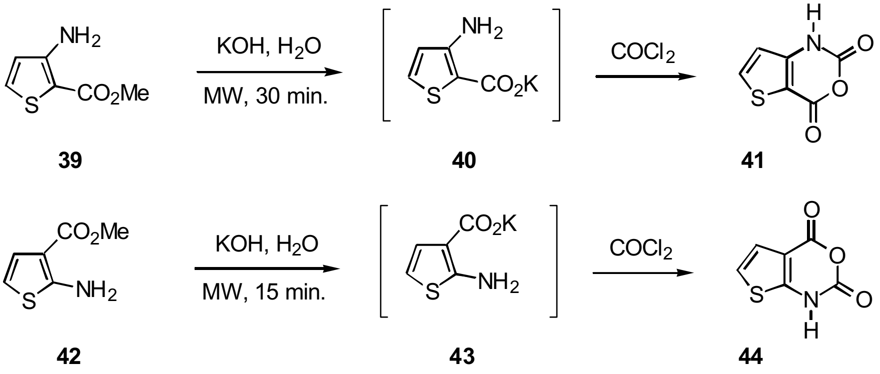
Scheme 8.14 Reagents and conditions: (i) DMF, reflux, 1 h, MW. (ii) HCl N, $NaNO_2$, AcOH, 30 min (iii) NaN_3, Et_2O, 40 min (iv) DMF, MW.

The benzodiazepine nucleus is a well studied traditional pharmacophoric scaffold that has emerged as a core structural unit of a variety of sedative–hypnotic, muscle relaxant, anxiolytic, antihistaminic, and anticonvulsant agents. The literature on this subject, although very copious, is mainly patents. Among many of these reports, an original investigation [17] was described by the group of Santagada for the preparation of 1,5-benzodiazepin-5-ones **38** (Scheme 8.14).

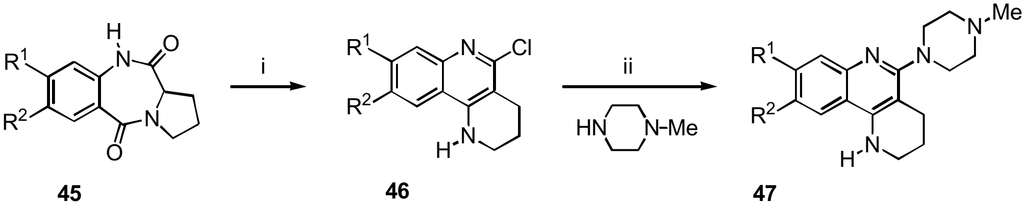
Noticeable improvements were achieved for steps (i) and (iv) when the experimental conditions were realized under the action of microwave irradiation with the same concentration of starting material and volume of dimethylformamide. Product **35a** (R = Me, X = H) was obtained in 91% yield after 5 min under the action of microwave irradiation at 150 W; conventional heating in oil bath resulted in only 65% yield of **35a** after 180 min (DMF, reflux). For step (iv), transposition of the conventional heating conditions for reaction of **38a** (40% yield, 60 min, reflux) to microwave irradiation of solutions gave the desired compound **38a** in better yield (60%) and reduced reaction time (5 min, 80 °C, 150 W).

Thiaisatoic acid is a starting material of great interest in the field of heterocyclic chemistry, as a potential new pharmacological scaffold. Rault and coworkers [18], in the synthesis of 2-thiaisatoic anhydride **41** and 3-thiaisatoic anhydride **44** performed the alkaline hydrolysis of *ortho* aminoesters **39** and **42** as a key step in the preparation of these anhydrides (Scheme 8.15).

The authors showed that it was possible to perform this reaction in a multimode microwave oven [19] in a few minutes on a large scale in water containing a slight excess of potassium hydroxide but without cosolvent. Under the action of classical heating the major problem with these syntheses is the instability of the thiophene *o*-amino acids, which readily decarboxylate at room temperature to give aminothiophenes which are themselves unstable [20a] and have to be used as soon as they are prepared. With large quantities of reactants, moreover, the hydrolysis step is not easy to perform because of the low reactivity of thiophene carboxylates **39** and **42** [20b].



Scheme 8.15



Scheme 8.16 Reagents and reaction conditions: (i) $POCl_3$, pyridine, reflux, MW (700 W), 1 h 45 min; (ii) DMF, 240 °C, 6 bar; MW, 1 h.

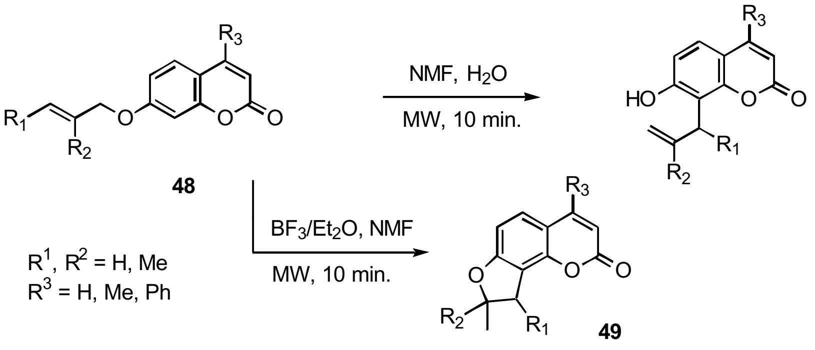
After microwave heating, the potassium carboxylates **40** and **43** could be treated directly by bubbling phosgene in the aqueous solution to yield the anhydrides **41** and **44** in 85 and 67% yields, respectively, with purity >90%.

Under conventional heating the rearrangement [21] of pyrrolo-[2,1-*c*]-benzodiazepine, **45**, in boiling phosphorus oxychloride, into benzo-[*h*][1,6]-naphthyridine **46** required a long reaction time (5 h) (Scheme 8.16).

Under microwave heating conditions compound **46** is obtained with reduced reaction time (1.5 h) and better purity. A dramatic improvement was achieved when **46** was treated with *N*-methyl piperazine in DMF in a sealed glass vessel. After 1 h under microwave irradiation, the *N*-methyl piperazino derivative **47** was obtained in 68% yield.

8.2.6
Claisen Rearrangement

For preparation of allyl coumarins and dihydrofuranocoumarins by tandem Claisen rearrangement–cyclization the usual procedures required vigorous reaction conditions, workup procedures were tedious, and long reaction times led to low yields. The rearrangement of allyloxycoumarins **48** to dihydrofuranocoumarins **49** has been optimized in good yields in a sealed Teflon containers with BF_3–ether in *N*-methyl-



Scheme 8.17

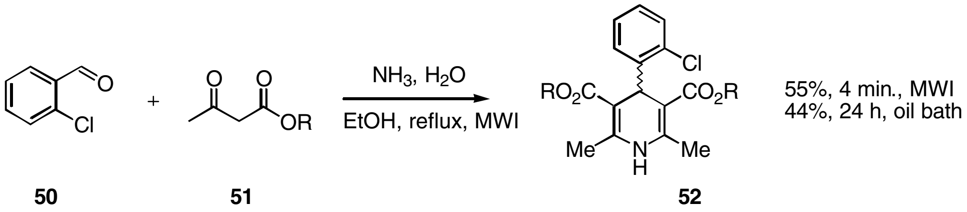
formamide (NMF) [22]; the short reaction time (10 min) associated with the microwave-assisted procedure is the best means of preparation of these compounds, as shown in Scheme 8.17.

8.2.7
Hantzsch Cyclocondensations

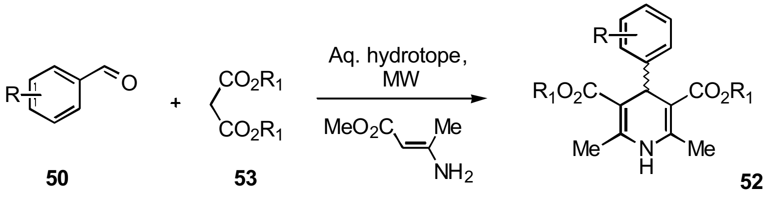
Alvarez-Builla and coworkers have used microwave irradiation to improve Hantzsch-1,4-dihydropyridine synthesis [23] (Scheme 8.18). Reduced reaction times and improved yields are generally associated with this procedure as exemplified by the preparation of **52** from 2-chlorobenzaldehyde **50**.

Khadilkar and Madyar [24] have developed a large scale and continuous Hantzsch-1,4-dihydropyridine-3,5-dicarboxylate synthesis in aqueous hydrotope solution [25], using a modified domestic microwave oven. The authors used novel reusable aqueous hydrotope solution [26] as a safe alternative to inflammable organic solutions, in a microwave cavity, for synthesis of commercially important calcium blockers such as nifedipine, nitrendipine, and a variety of other 1,4-dihydropyridines (DHP) (Scheme 8.19).

Nitrendipine (R = 3-NO_2, R^1, R^2 = Me) has been obtained in 94% yield (50 g) after 24 min by microwave irradiation of the reaction mixture (final temperature: 86 °C) at a flow rate of 100 mL · min^{-1}. The reaction mixture was circulated through the



Scheme 8.18



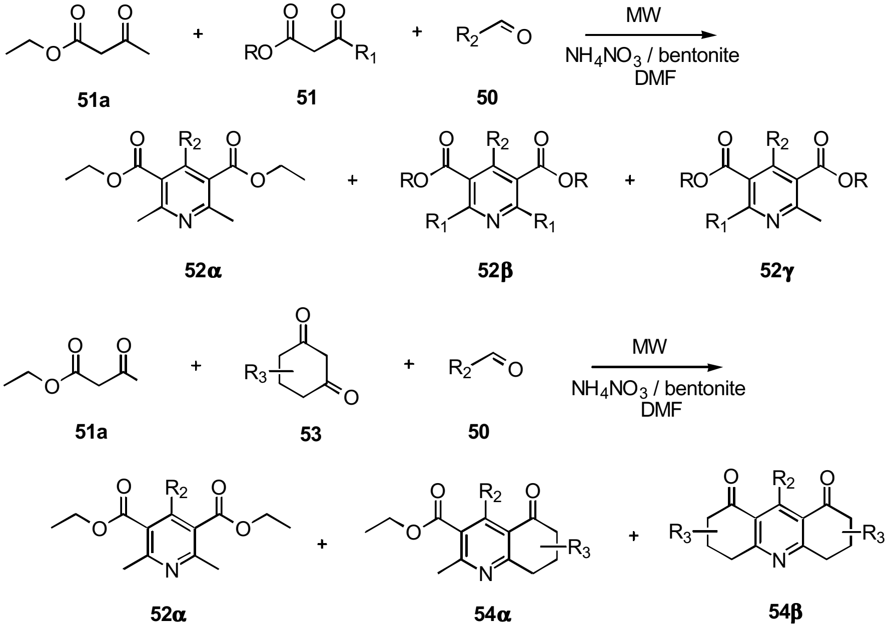
Scheme 8.19

microwave cavity in four cycles of 6 min each; a 2-min gap between each cycle was imposed to avoid excessive heating.

It should be noted that the Hantzsch-1,4-DHP synthesis can be conducted with a soluble polymer. Successful derivatization of poly(styrene–co-allyl alcohol) under the action of microwave irradiation with a variety of ethyl oxopropanoates and ethyl 3-aminobut-2-enoates were reported by Vanden Eynde's group [27].

Khmelnitsky and coworkers have also examined microwave-assisted parallel Hantzsch pyridine synthesis [28]. They have demonstrated the benefits of microwave irradiation in a 96-well plate reactor for high throughput, automated production of a pyridine combinatorial library (Scheme 8.20).

In each reaction ethyl acetoacetate **51 a** was used as one of the components of the Hantzsch synthesis, whereas the second 1,3-dicarbonyl compound **51** (or **53**) and the aldehydes **50** were used in all possible combinations (one unique combination per

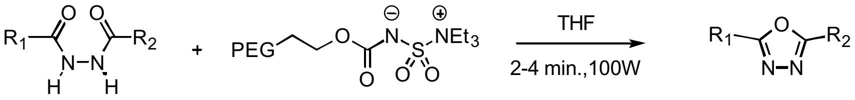


Scheme 8.20

well). Each well plate containing ammonium nitrate (on bentonite) was impregnated with *N*,*N*-dimethylformamide as energy-transfer medium. The 96-well reactor placed in a microwave oven (1300 W) was irradiated for 5 min at 70 % power level.

8.2.8
1,3,4-Oxadiazole Synthesis

In the preparation of novel 1,3,4-oxadiazoles **56** from 1,2-diacylhydrazines **55**, Brain and coworkers [29] used a highly efficient cyclodehydration assisted by use of microwaves, in THF as solvent, using polymer-supported Burgess reagent (Scheme 8.21).



55

R^1 = furyl, 3-pyridyl, 4-pyridyl, $PhSO_2CH_2$
R^2 = Ph, Me, NHPh

56 (75-98%)

Scheme 8.21

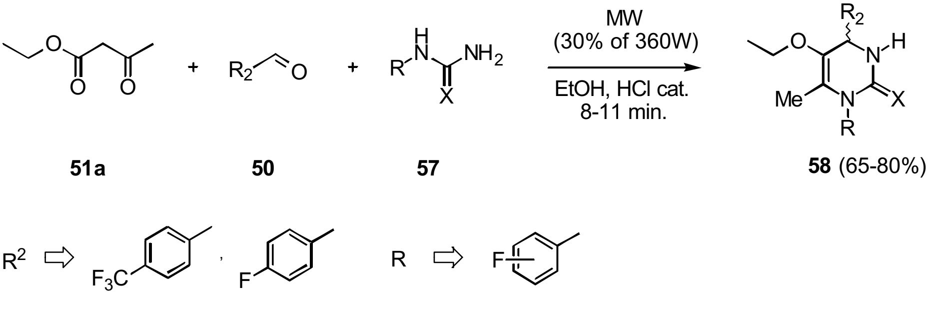
Microwave irradiation coupled with poly(ethylene glycol)-supported Burgess reagent reduced the reaction time to 2–4 min and led to improved yields. Use of harsh reagents, e. g. $SOCl_2$, $POCl_3$, and polyphosphoric acid, for the cyclodehydration were avoided.

8.2.9
Biginelli Cyclocondensation

In recent decades, the Biginelli-type dihydropyrimidinones (DHPM) have received considerable attention, because of the interesting pharmacological properties of this heterocyclic scaffold [30]. It was soon established that DHPM has a similar pharmacological profile to the well-known dihydropyridine (DHP) calcium-channel modulations of the Hantzsch type [31].

The introduction of a fluorine atom or CF_3 group into an organic molecule frequently provides compounds of pharmacological interest, compared with their non-fluorinated analogs. Microwaves have been found to greatly accelerate the Biginelli synthesis of fluorine-containing ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one/thione-5-carboxylates [32] **58** in unsealed vessels with ethanol as energy-transfer medium and a small amount of concentrated HCl as catalyst (Scheme 8.22). Short reaction times, enhanced yields, and easy workup are the main advantages observed by Dandia and coworkers. This Biginelli reaction has also been studied recently [33].

Varma and Kappe have developed a method that enables the rapid and parallel synthesis of DHPM **58** (Scheme 8.22) but does not rely on polymer-supported building blocks and therefore does not require the development of solid-phase linking–cleaving chemistry. They showed that polyphosphate ester (PPE) serves as an excel-



Scheme 8.22

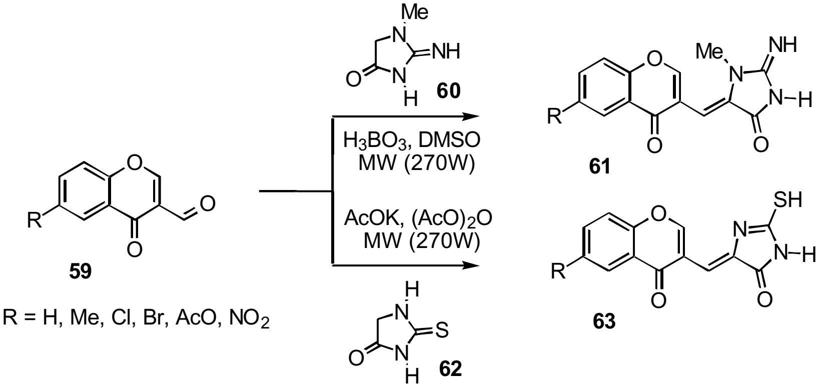
lent reaction mediator in the microwave-assisted three-component Biginelli reaction [34]. The DHPM **58** obtained by use of the microwave/PPE-mediated Biginelli procedure was usually at least 95% pure. In most experiments a very significant increase (20–50%) in yield can be achieved by use of the MW-induced procedure (a 800-W microwave oven was used at 50% power level).

Simultaneously the reaction time is reduced from typically 4–8 h under reflux (traditional heating) to a few minutes (MW irradiation).

8.2.10
Condensation Reactions with Creatinine and Thiohydantoin

Microwave-mediated condensation can be used to prepare heterobicycles [35] as illustrated in Scheme 8.23.

Imino derivatives **61** were obtained directly from 3-formylchromone [36] **59** and creatinine [37] **60**, with DMSO as solvent and boric acid as catalyst, and with microwave irradiation and classical heating (Tab. 8.4). The authors have also investigated the preparation of the 2-thioxo-5-imidazolidin-4-ones **63** from thiohydantoin **62** in



Scheme 8.23

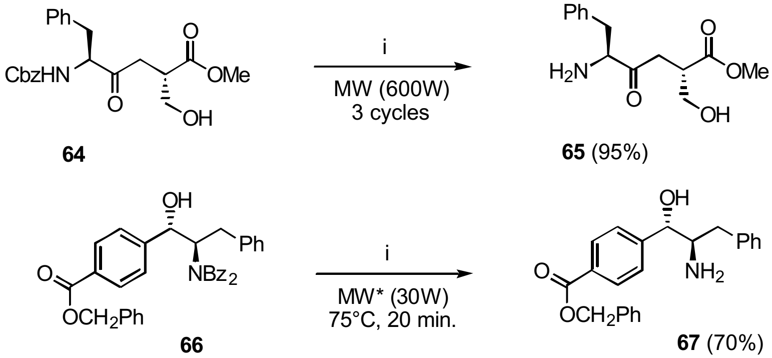
the presence of potassium acetate and acetic anhydride as solvent, using both methods. Here, the effect of microwave irradiation was shortening of the reaction times and a small increase in the yields.

Tab. 8.4 Condensation of 3-formyl chromone **59** with creatinine **60** and thiohydantoin **62**.

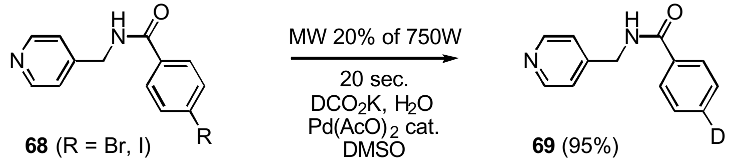
Product	*R*	*Conventional heating*		*Microwave irradiation*	
		Reaction time (min)	*Yield (%)*	*Reaction time (min)*	*Yield (%)*
61a	H	60	71	3	75
61b	Cl	60	72	2	76
63a	H	60	72	8	79
63b	Br	60	88	9	96

8.2.11
Deprotection of N-Cbz and N-Bn derivatives; Deuterium-labeled Aromatic Dehalogenation

Microwave irradiation has been shown to be of particular utility [38] in functional group protection and deprotection strategies. The benzyl carbamate (Cbz) and the benzyl (Bn) groups are very popular for protection of amines. Following Bose's report [10] on the effect of microwaves on the catalytic hydrogenation of double bonds [39], Daga and coworkers [40] found that amino groups protected by Cbz and Bz can be deprotected in few minutes by microwave-assisted transfer hydrogenation with Pd/C 10% in *i*-PrOH as the solvent and HCO_2NH_4 as the hydrogen donor. For dipeptide **64**, deprotection was complete (95% yield of the free amine) after three cycles of irradiation (1 min at 600 W then at least 1 min of rest were applied until no trace of the starting material was detected by TLC analysis). No racemization was observed (Scheme 8.24).



Scheme 8.24 Reagents and conditions: (i) HCO_2NH_4 (4 equiv.), Pd/C 10%, *i*-PrOH. *Synthewave 402 oven, Prolabo, Fr.



Scheme 8.25

This procedure was also compatible with the benzyl ester, as demonstrated in Scheme 8.24 by selective deprotection of compound **66** (**67** was isolated in 70% yield by chromatography after 20 min irradiation at 75 °C (30 W) in the Synthewave 402 reactor).

It is interesting to remark that classical hydrogenation is a method used to prepare deuterium-labeled compounds by aromatic dehalogenation, but the usual reaction conditions suffer from several limitations. A microwave-enhanced catalytic dehalogenation procedure for rapid and specific deuterium labeling of *N*-4-picolyl-4-halogenobenzamide **68**, by use of deuterated formate, [41] was recently reported (Scheme 8.25).

8.3
Solvent-free Synthesis

Although the initial reason for the development of solvent-free conditions for microwave irradiation was safety, it soon became apparent that use of these conditions had many other benefits – simplicity, efficiency, easy work-up, very often higher yields, and enhanced reaction rates. The absence of solvent is, furthermore, time- and moneysaving and often enables elimination of waste treatment.

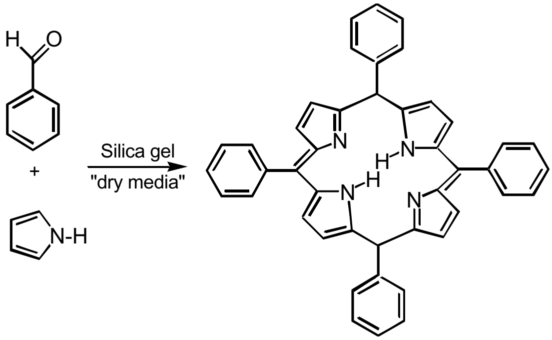
Solvent-free synthesis can be realized under a variety of conditions; for each we give selected results and, when available, results from comparison with the same solvent-free conditions but with classical heating.

8.3.1
Solvent-free Synthesis under Acidic Conditions

This section covers synthesis catalyzed either by organic acids or by inorganic acidic supports.

8.3.1.1 **Tetraphenyl Porphyrin Synthesis** [42]
A simple and rapid synthesis of tetrapyrrolic macrocycle has been achieved under dry media conditions with microwave activation. Pyrrole and benzaldehyde adsorbed on silica gel afford tetraphenylporphyrin within 10 min (Scheme 8.26), whereas with conventional methods (e. g. acetic acid in the presence of pyridine) 24 h were necessary.

In the monomode Prolabo Synthewave 402 reactor (at 135 W) a yield of 9.5% was obtained compared with 4% in a multimode domestic oven. The advantages of the



Scheme 8.26

method are its rapidity and more straightforward workup; yields suffer from the same limitations as under classical conditions. It has been shown later that the yield increases to 31% when the irradiation was performed in the presence of toluene [43].

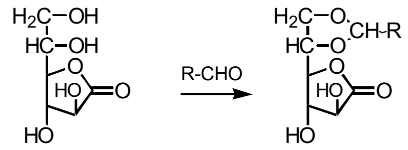
8.3.1.2 **Acetalization of L-galactono-1,4-lactone** [44]

Acetals of L-galactono-1,4-lactone (an abundant byproduct of the sugar beet industry) have thermotropic liquid crystalline properties. Acetalization in DMF containing H_2SO_4 in the presence of anhydrous $CuSO_4$ gave (after 12 to 24 h at 40 °C) yields of 20–35% (Scheme 8.27).

Use of montmorillonites KSF or K10 as acidic supports and irradiation at 60 W (monomode oven, final temperature 155 °C) led to yields threefold higher in 10 min.

8.3.1.3 **Aziridine Synthesis**

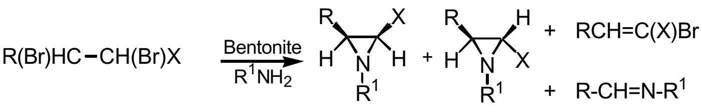
A dry-media technique with microwave irradiation for synthesis of aziridines has recently appeared in the literature [45] (Scheme 8.28).



Example : R = CH_3-$(CH_2)_{11}$

DMF, H_2SO_4, $CuSO_4$	24 h	40°C	25%
KSF "dry media"	10 min.	60W	66%
K10 "dry media"	10 min.	60W	89%

Scheme 8.27



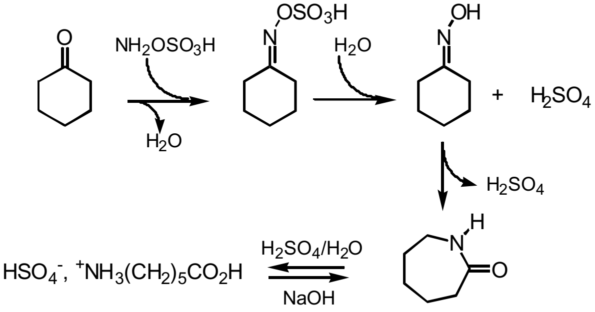
X = electron withdrawing group

Scheme 8.28

The reaction was studied under the action of focused microwaves and conventional heating and it is noteworthy that elimination is more efficient than Michael addition (leading to aziridines) under irradiation, the conditions being the same.

8.3.1.4 **Lactam Synthesis** [46]

In 1979, Olah [47] reported a one step conversion of alicyclic ketones into lactams by means of hydroxylamine *O*-sulfonic acid and formic acid under reflux for a few hours. More recently this reaction has been realized under solvent-free conditions with SiO_2 as inorganic support and focused irradiation, as exemplified in Scheme 8.29 for caprolactam synthesis.



Scheme 8.29

Ketone	*Lactam*	*Time*[a] *(min)*	*Yield (%)*
Cyclopentanone	Valerolactam	15	60
Cyclohexanone	Caprolactam	10	86
Cycloheptanone	2-Azacyclooctanone	20	72
Cyclooctanone	2-Azacyclononanone	15	65
Cycloundecanone	2-Azacyclododecanone	15	72
Cyclododecanone	2-Azacyclotridecanone	20	82

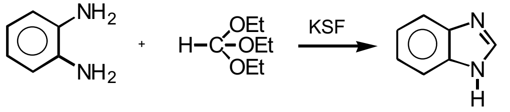
[a] Irradiation at 30 W, the temperatures reached by the reaction mixture are in the range 100–120 °C, depending on the nature of the ketone.

In a multimode oven the power is too high and cannot be modulated, so only decomposition products are obtained.

8.3.1.5 **Arylimidazole Synthesis**

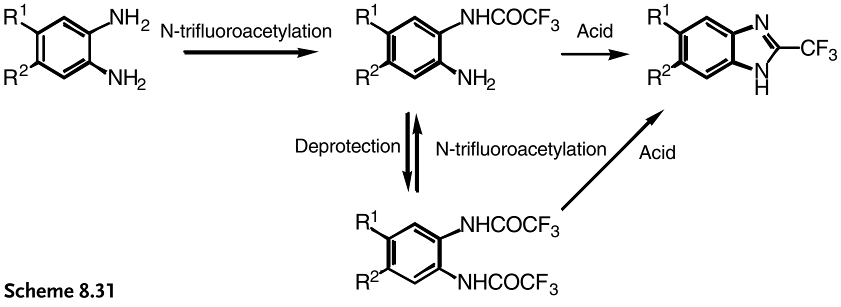
In 1996, the condensation of orthoesters with *ortho*-phenylenediamines leading to benzimidazoles [48] was achieved either in toluene under reflux or without solvent by use of focused microwaves (Scheme 8.30).

A more striking example was reported more recently by Soufiaoui et al. [49a] who studied the cyclocondensation of *N*-(carbotrifluoromethyl)-*ortho*-arylenediamines on clay K_{10} in dry media under the action of irradiation for 2 min in a domestic oven (Scheme 8.31). It is worth noting that with classical heating under the same condi-



Monomode MW, dry media	**60W**	**5 min.**	**74%**
Δ, toluene	110°C	12 h	79%

Scheme 8.30



Scheme 8.31

tions only traces of heterocycles are observed. The difference is discussed in terms of the polarity of the transition state compared with that of the initial state (cf. Chapt. 3 and Ref. [49b]).

8.3.1.6 Pyridine, Pyrazine, and Pyridine Derivatives

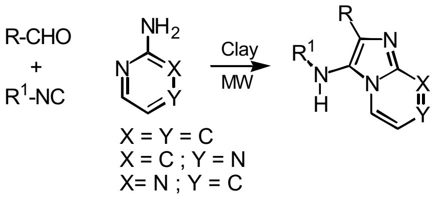
A rapid one-pot synthesis of imidazo-[1,2-*a*]-pyridines, pyrazines and pyrimidines was described in 1999 by Varma et al. [50], who used recyclable montmorillonite clay K_{10} under solvent-free conditions and microwave irradiation (Scheme 8.32).

The whole process, formation of the iminium ion by condensation of the aldehyde with an amine (1 min at 900 W in a domestic oven) then nucleophilic attack of the isocyanide (1 min at 450 W and 1 min cooling) takes 3 min to give yields ranging from 56 to 88% of the pure product.

Also of interest is a new easy means of preparing (*S*)-3-substituted 2,3,6,7,12,12*a*-hexahydropyrazino-[1,2:1,6]-pyrido-[3,4-*b*]-indole-1,4-diones [51] (Scheme 8.33).

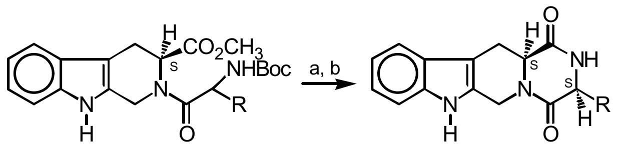
This process is much more efficient than the classical procedure with TFA in CH_2Cl_2 for 2 h at 30 °C which leads to 60% yield instead of 95% after 5 min under irradiation.

A one-pot synthesis of N-substituted 4-aryl-1,4-dihydropyridines (Scheme 8.34) was recently [52] mentioned at the Fifth International Electronic Conference on Syn-

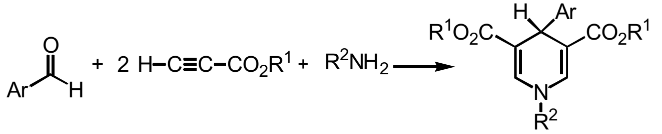


Scheme 8.32

Scheme 8.33



a) adsorption on flash column silica gel (250-400 mesh)
b) irradiation 5 minutes at 500 W



Scheme 8.34

thetic Organic Chemistry (ECSOC-5), a special session of which was devoted to microwave-assisted synthesis.

Among various solid supports (K10, acidic alumina, zeolite HY, silica gel) silica gel proved to be the best; after irradiation for 4 min the reactions led to yields ranging from 62 to 94%.

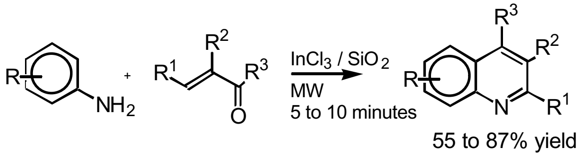
8.3.1.7 **Quinolines and Quinoxalines**

It is of primary interest to avoid corrosive mineral acids in synthetic processes. This can easily be achieved by use of acidic solid supports coupled with microwave irradiation. This has been applied to the preparation of quinolines [53] (Scheme 8.35).

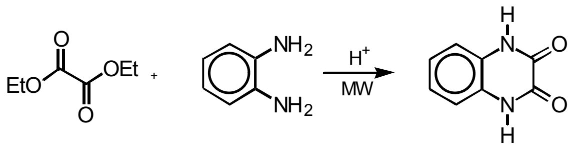
This procedure is a safe, green alternative to the use of H_2SO_4 at more than 150 °C.

In the same way, quinoxaline-2,3-diones were prepared [54] by use of single-mode irradiation. Previous attempts in solution led to explosions, but the authors successfully used solvent-free conditions with acidic supports or catalysts (the best being *p*-toluenesulfonic acid) and irradiation times of 3 min (Scheme 8.36).

p-Toluenesulfonic acid proved to be the best catalyst for the formation of pyrazolo-[3,4-*b*]-quinolines from 2-chloro-3-formylquinolines and hydrazine hydrate–phenyl hydrazine under irradiation [55].



Scheme 8.35



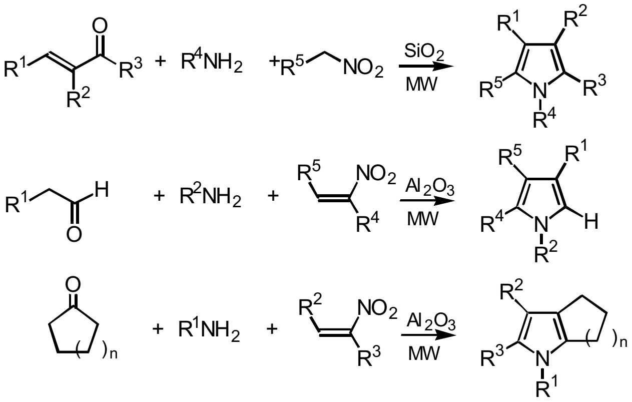
Scheme 8.36

8.3.1.8 **Pyrroles, Indoles and Related Compounds; Imidazoles**

Efficient synthesis of highly substituted alkylpyrroles and fused pyrroles has been achieved by three-component coupling of:

- an α,β-unsaturated aldehyde or ketone, an amine, and a nitroalkene on the surface of silica gel;
- an α,β-unsaturated nitroalkene, an aldehyde or ketone, and an amine on the surface of alumina without solvent under microwave irradiation.

The various routes are as shown in Scheme 8.37 [56].



Scheme 8.37

A wide range of starting compounds was used and yields of isolated products ranged from 60 to 86% for irradiation times of 5 to 15 min. This green procedure avoiding solvents is a better and more practical alternative to existing methods. Different heterocycles [57a], e.g. furan, pyrrole, *N*-benzylpyrrole, indole, and pyrazole react with methyl α-acetamidoacrylate to give α-amino acid precursors under irradiation with silica-supported Lewis acids as catalysts. In homogeneous catalysis, long reaction times were required. The reaction of vinylpyrazoles with imines has also been realized [57b].

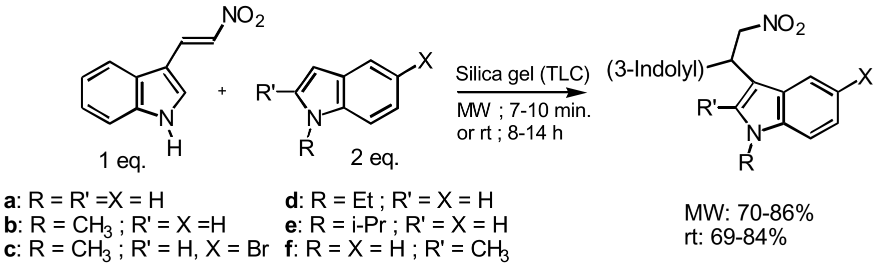
A variety of bisindolylnitroethanes [58] has been obtained in high yields (70–86%) by reacting 3-(2-nitrovinyl)indole with indole and 1- or 2-alkylindoles on silica gel (TLC-grade) under irradiation (Scheme 8.38).

Silica gel or zeolite HY have also been used successfully for the synthesis of imidazoles, isoxazoles, and pyrazoles [59], under irradiation, without solvent (Scheme 8.39).

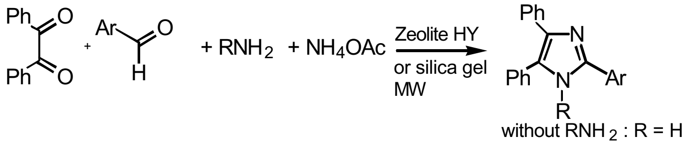
8.3.1.9 **Preparations of Coumarins**

Coumarins are important compounds with applications as pharmaceuticals and agrochemicals.

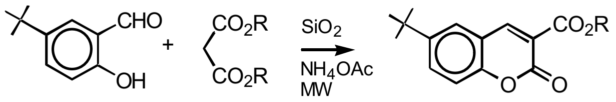
An easy means of access has recently [59] been reported by NH_4OAc on silica gel as catalyst for the condensation of salicylaldehyde (and 2-hydroxy-1-naphthylalde-



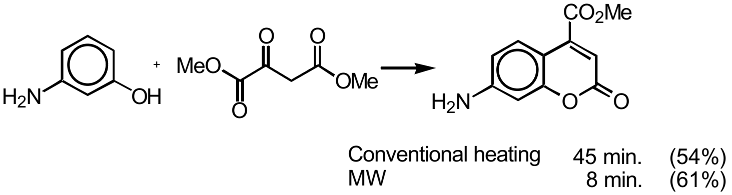
Scheme 8.38



Scheme 8.39



Scheme 8.40



Scheme 8.41

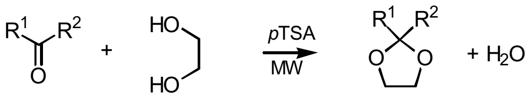
hyde) with ethyl and methyl malonate under solvent-free conditions and with MW irradiation (Scheme 8.40).

Irradiation for 2–15 min, rather than many hours under reflux in a variety of solvents in the presence of base (pyridine or piperidine), gives high yields.

Some 7-aminocoumarins-4-carboxylates [60a] were synthesized by the Pechmann reaction, by microwave irradiation of the reactants on solid supports (graphite–K_{10}) (Scheme 8.41). Synthesis of unsubstituted coumarins (C-4 position) has been also reported [60b].

8.3.1.10 Dioxolane Synthesis

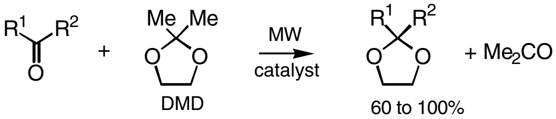
A mixture of an aldehyde or a ketone with ethylene glycol (EG) and *p*-toluenesulfonic acid (pTSA) leads to the corresponding dioxolane, after irradiation [61] (Scheme 8.42).



Scheme 8.42

Example: R^1 = Ph; R^2 = H			
Focused microwave oven, EG 1.5 equiv.	15 min	80 °C	80% [61]
Domestic oven, EG: 10 to 15 equiv.	2 min	650 W	81% [62]
Example: R^1 = Ph; R^2 = CH_3			
Focused microwave oven, EG 3 equiv.	30 min	120 °C	90% [61]
Domestic oven, EG: 10 to 15 equiv.	2 min	650 W	71% [62]

Unfortunately, the comparison is not reliable because the temperature was not measured in the domestic oven. Dioxolane formation by acid-catalyzed exchange between 2,2-dimethyl-1,3-dioxolane (DMD) and a ketone in a inert solvent, or simply in excess DMD, requires 4 to 7 h under classical conditions [63]. This reaction is readily achieved under microwave irradiation in high yields in 4 to 30 min (Scheme 8.43).



Scheme 8.43

R^1	R^2	DMD	Catalyst	Power (W)	Time (min)	Tmax (°C)	Yield (%)
Ph	H	1.5	KSF	300	4	80	90
Ph	Me	3	*p*TSA	150	30	110	95
Ph	Ph	3	*p*TSA	150	30	120	60
$-(CH_2)_5-$	$-(CH_2)_5-$	3	*p*TSA	150	30	120	100
Me	CH_2COMe	3	*p*TSA	150	30	110	100
Me	CH_2COMe	3	*p*TSA	150	30	120	95

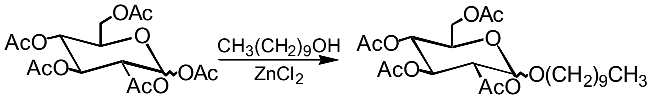
It has been shown [61] that yields are higher under the action of irradiation. This dioxolane exchange was subsequently scaled up to 250 g in the Synthewave 1000 with the same yields [64] and this type of carbonyl protection was extended to dithiolanes and oxathiolanes [65].

8.3.1.11 Carbohydrate Glycosylations

Peracetylated D-glucopyranose were glycosylated with decanal (1.5 eq.) without solvent under irradiation in the presence of $ZnCl_2$ [66] (1 eq.) (Scheme 8.44).

The reaction was performed in a Synthewave 402 apparatus under controlled temperature conditions to avoid decomposition of alkyl glycosides. Comparison with classical heating under strictly the same conditions revealed that yields dropped dramatically.

Scheme 8.44



Monomode MW	**60W-20W 3 min.**	**113°C**	**74%**
Δ (oil bath)	3 min.	113°C	0%
Δ (oil bath)	5 h	113°C	25%

8.3.2
Reactions under Basic Conditions

Some examples of the *in situ* generation of 1,3-dipoles in basic media followed by 1,3-dipolar cycloaddition are reported in Chapt. 9.

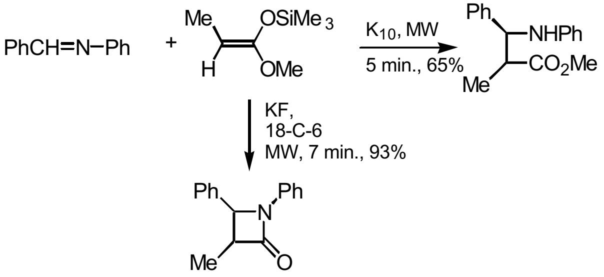
8.3.2.1 Lactam Synthesis

The reaction of silyl ketone acetals with imines under irradiation has been explored. The versatility of the microwave approach is illustrated in Scheme 8.45.

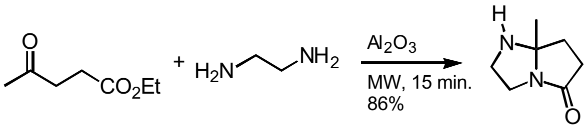
When the reactions are performed by adsorption of the reagents on to K_{10} montmorillonite clay the aminoester is formed but when the reaction is performed by mixing the neat reagents with KF and 18-crown-6 and irradiation in a closed vessel *β*-lactams were isolated in moderate to good yields [67].

The same group reported the formation of heterobicyclic lactams as illustrated below [68] (Scheme 8.46).

The reaction was performed by supporting the reagents on alumina and irradiation in an open vessel.



Scheme 8.45

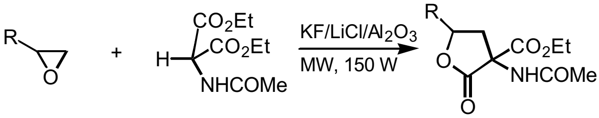


Scheme 8.46

8.3.2.2 Lactone Preparation

An interesting ring opening of a fatty oxirane has been reported by Loupy [69]. Diethyl acetamidomalonate opens the oxirane ring according to Scheme 8.47.

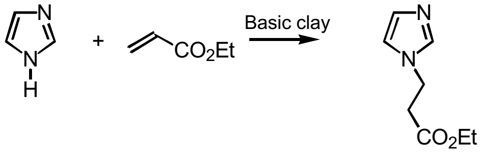
Addition of lithium chloride is necessary for the reaction to proceed. Whereas no reaction was observed under salt-free conditions, the lactone is obtained in 90% yield within 5 min in the presence of LiCl impregnated with KF on alumina (KF–LiCl–Al_2O_3 = 1 : 1 : 4 by weight) under the action of focused microwave irradiation at 150 W. With conventional heating no reaction occurred.



Scheme 8.47

8.3.2.3 N-substituted Imidazoles and Imidazolines

Imidazole has been condensed with ethyl acrylate by using two basic clays (Li^+ and Cs^+ montmorillonites) as catalysts in a microwave oven [70]. The role of alkali promoters (Li^+ and Cs^+) was studied and it was found that the greater the basicity and the irradiation time and power, the higher were the conversions. The yield of N-substituted imidazole is maximum for 0.1 g Cs^+ montmorillonite at 850 W after irradiation for 5 min (Scheme 8.48).



Scheme 8.48

The reaction proceeds with high yields and selectivity under the action of irradiation and is more efficient than with conventional heating.

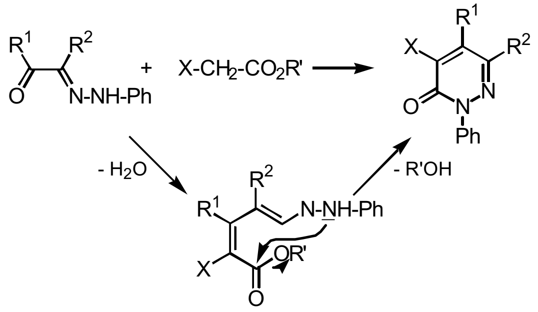
Quite recently [71] an expeditious solvent-free synthesis of imidazoline derivatives, using basic or neutral alumina under microwave irradiation, was reported. The reaction time was reduced from hours to minutes with improved yield compared with conventional heating.

8.3.2.4 Base-catalyzed Reactions of Glyoxal Monohydrazones with Active Methylene Compounds

Several 3-(*2H*)pyridazinones have been prepared from monophenyl hydrazones of 1,2-dicarbonyl compounds and a variety of active methylene compounds within 1–20 min without solvent under focused irradiation in the presence of carefully adjusted amounts of piperidine or solid potassium *tert*-butoxide (isolated yields 50–89%), in accordance with Scheme 8.49 [72, 73].

In the synthesis of the pyridazinone (X = CN, R^1 = Me, R^1 = R^2 = H) microwave irradiation has no specific effect, because the result (72%) was identical with that ob-

Scheme 8.49



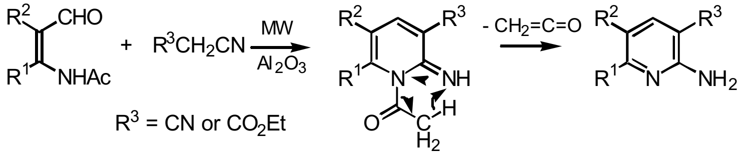
tained by use of classical heating under the same conditions. With the dry media procedure it was possible to isolate the intermediate alkene, which was not obtained in the previously reported procedure. When the active methylene compound is a keto ester the reaction follows a different pathway [73].

8.3.2.5 Annelated Pyridines and Dihydropyridines

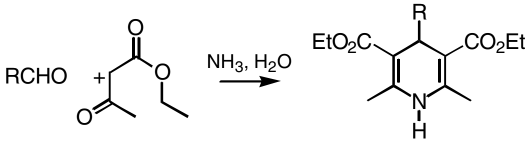
The condensation of β-formyl enamides with cyanomethylenes under irradiation is catalyzed by basic alumina to afford fused pyridines in excellent yields in very short times [74] (Scheme 8.50). This procedure avoids harsh conditions.

The Hantzsch dihydropyridine synthesis has been performed [75] in a single-mode microwave cavity. In comparison with both conventional methods and microwave-assisted reactions performed in a domestic oven, reaction times were shorter and yields were higher (Scheme 8.51).

The improved yields under microwave conditions enable the synthesis of a small library.



Scheme 8.50

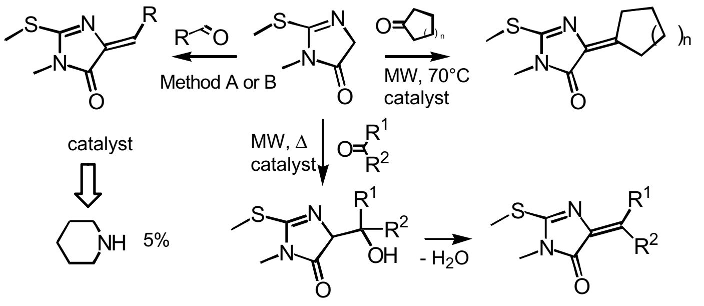


R = XPh, iPr, n-heptyl, cyclohexyl
yields from 51 to 92% in 10 minutes

Scheme 8.51

8.3.2.6 Stereoselective Route to 3,5-Dihydroimidazol-4-one Derivatives

An efficient solventless synthesis of imidazolones via the Knoevenagel reaction using microwave irradiation has appeared recently in Green Chemistry [76] (Scheme 8.52).

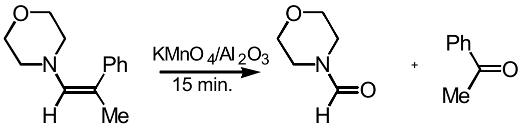


Scheme 8.52

In method A the reaction is performed under reflux in CH_2Cl_2. Method B is without solvent under irradiation. It has been shown that yields are higher and reaction times much lower for method B. This methodology was applied to the synthesis of the precursor of leucettamine B (mediator of inflammation).

8.3.2.7 **Oxidation using $KMnO_4$–Al_2O_3**

Oxidation of *β*,*β*-disubstituted enamines have been performed over $KMnO_4$–Al_2O_3 and the results compared with those obtained by use of a domestic oven, a focused oven, and classical heating (Scheme 8.53) [77].



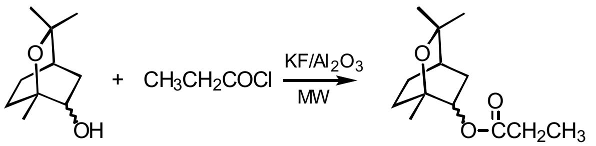
Domestic oven	255 W		73%
Monomode reactor	300 W	140°C	83%
Classical heating		140°C	<2%

Scheme 8.53

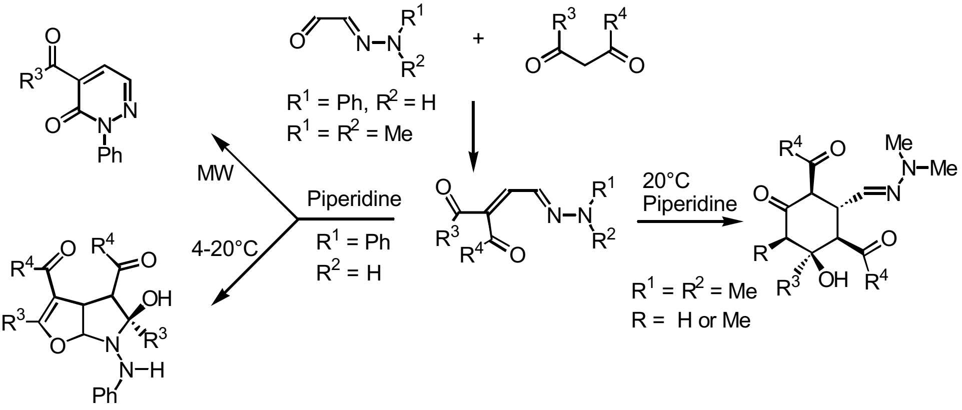
8.3.2.8 **Synthesis of 1,8-Cineole Derivatives** [78]

1,8-Cineole derivatives, of interest as potential cosmetic products, were obtained under a “green chemistry procedure”, i. e. one without solvent, with microwave activation according to Scheme 8.54.

The yields are significantly better than for a previously reported procedure (90–98 % instead of 50–70 %) and the reaction times are considerably reduced. These improvements are connected “to the intervention of highly polar reactants and then consequently prove to develop strong interactions with microwaves”.



Scheme 8.54



Scheme 8.55

8.3.2.9 1-Aminopyroles and Related Compounds

Starting from glyoxal monohydrazones and active methylene compounds, *N*-anilinopyrroles were prepared under solvent-free conditions by use of piperidine as catalyst [79] (Scheme 8.55).

Further microwave irradiation isomerizes the anilinopyrroles.

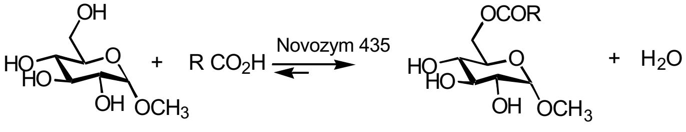
8.3.3
Enzymatic Catalysis in "Dry Media"

Enzymes are usually used in aqueous or organic media and the temperature is limited to 40 °C to preserve enzyme activity; as a consequence the reactions need very long times. With enzymes immobilized on solid supports [80] it is possible to operate at higher temperatures.

Systems such as *Pseudomonas* lipase dispersed inside Hyflo Supercell (a diatomaceous silica of pH 8.5–9) and SP 435 Novozym (*Candida antarctica* lipase grafted on an acrylic resin) are thermally stable and have optimum activity in the range 80–100 °C. They can therefore be used with conventional or microwave heating if the temperature is strictly controlled.

8.3.3.1 Regioselective Esterification of Glycopyranosides

The regioselective esterification at position 6 of α-D-glucose and α-D-glucopyranosides with fatty acids [81] is readily achieved by use of Novozym 435, in accordance with Scheme 8.56.

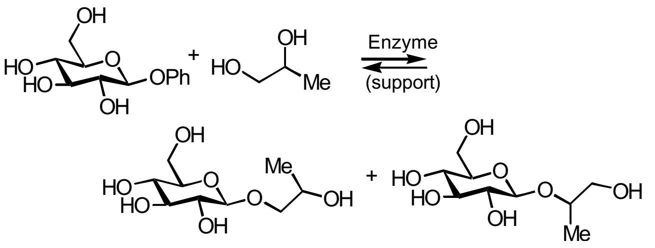


Scheme 8.56

Reaction conditions and yield of the esterified product ($R = CH_3(CH_2)_{11}$) are: (i) classical method, solvent-free, reduced pressure, 24 h, 70 °C, 53%; (ii) microwave, single-mode reactor, 12–40 W, 5 h, 95 °C, 95%; (iii) 120–60 W, 2 h, 110 °C, 97%; (iv) conventional heating (oil bath), 5 h, 95 °C, 55%.

8.3.3.2 **Transglycosylations**

The transesterification of phenyl-β-D-glucoside catalyzed by *Sulfolobus solfataricus* [81 b] was quantitative within 2 h at 110 °C under the action of irradiation whereas the yield was only 60% after 40 h under classical conditions (Scheme 8.57).



Scheme 8.57

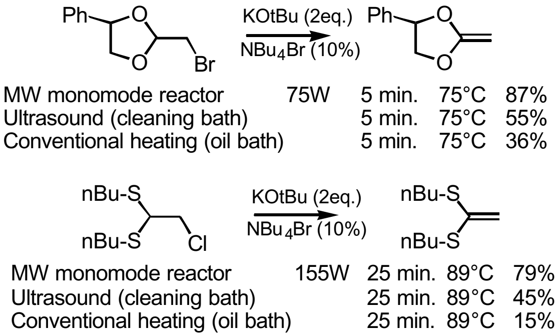
8.3.4
Solvent-free Solid–Liquid Phase-transfer Catalysis (PTC)

This method is described in Chapt. 5; it is specific for anionic reactions because it involves "anionic activation".

8.3.4.1 **β-Eliminations of Halogenated Acetals**

Ketene acetals and dithioacetals have been prepared in a solvent-free procedure by base catalyzed β-elimination under PTC conditions. The yields obtained by use of irradiation are much higher than those obtained by use of ultrasound or conventional heating under the same conditions [82] (Scheme 8.58).

These results are obviously indicative of a specific effect of irradiation.



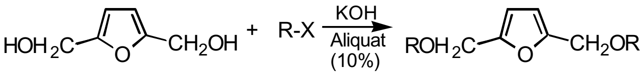
MW monomode reactor	75W	5 min.	75°C	87%
Ultrasound (cleaning bath)		5 min.	75°C	55%
Conventional heating (oil bath)		5 min.	75°C	36%

MW monomode reactor	155W	25 min.	89°C	79%
Ultrasound (cleaning bath)		25 min.	89°C	45%
Conventional heating (oil bath)		25 min.	89°C	15%

Scheme 8.58

8.3.4.2 Synthesis of Furanic Diethers

Among the various derivatives of biomass, furanic compounds obtained from furfural are important (200,000 t year^{-1}). A new family of furanic diethers has been obtained by alkylation of 2,5-furandimethanol or furfuryl alcohol under microwave irradiation with PTC solvent-free conditions [83] (Scheme 8.59).



Reaction conditions and yields for example: RX = $C_{12}H_{25}Br$
1. Microwave monomode reactor 30 W: 5 min/180°C, 93%.
2. Conventional heating (oil bath): 5 min/180°C, 41%.
3. Conventional heating (oil bath): 30 min/180°C, 89%.

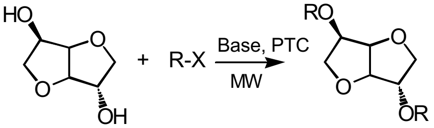
Scheme 8.59

Reaction times were improved by microwave irradiation, and the same conditions were extrapolated to the synthesis of a series of new furanic diethers by alkylation of furfuryl alcohol by dihalides [83].

8.3.4.3 Synthesis of Diethers and New Diols Derived from Dianhydrohexitols

Loupy et al. [84] have synthesized new diethers by alkylation of dianhydrohexitol under the action of irradiation with PTC conditions. The yields were very good (>90%) within a few minutes. Even when similar temperature profiles were used the yields were much lower under the action of conventional heating (Scheme 8.60).

In the same way, new diols have been obtained from dianhydrohexitol ethers [85].



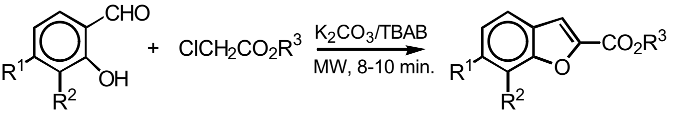
Scheme 8.60

Yields > 90%

8.3.4.4 Preparation of Benzo[*b*]furans

Benzo[*b*]furans have been formed by condensation of salicylaldehydes with a variety of esters of chloroacetic acids, in the presence of tetrabutyl ammonium bromide (TBAB), under the action of irradiation without solvent [86] (Scheme 8.61).

Potassium carbonate (20 mmol), TBAB (0.5 mmol) and salicylaldehyde derivative (5.0 mmol) were mixed and a chloracetic ester (10 mmol) was then added dropwise.



R^1 = H, Et_3N R^3 = Et, allyl, cyclohexyl Yields : 65 to 96%
R^2 = H, OMe

Scheme 8.61

The mixture was stirred and then irradiated for 8 to 10 min. After extraction with CH_2Cl_2 and evaporation, the products were purified by column chromatography. In an oil bath, the full conversion of an aldehyde needs usually 3 h.

8.3.4.5 Cineole Derivatives

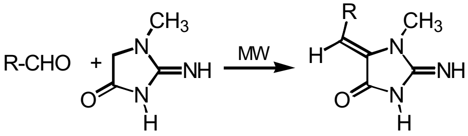
The PTC process was also used for the synthesis of cineole derivatives already covered in Sect. 8.3.2.8, and more recently in Green Chemistry [87].

8.3.5
Solvent-free Reactions without Support or Catalyst

In heterocycle synthesis these conditions have been particularly used in 1,3-dipolar cycloadditions and Diels–Alder reactions (Chapt. 9). These conditions are, in fact, ideal for “green chemistry”.

8.3.5.1 Condensation of Creatinine with Aldehydes

Knoevenagel condensation under the action of microwave irradiation has been widely studied; it has also been used for synthesis of heterocycles in accordance with Scheme 8.62 [88].



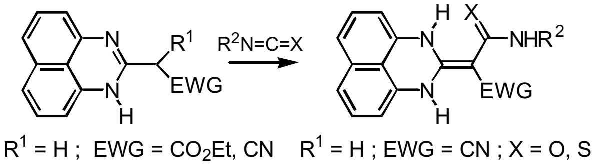
Scheme 8.62

At 160–170 °C under the action of focused irradiation (40–60 W), condensation occurs within 45 s to 4 min, without solvent, without base, and without catalyst. Unfortunately, no comparisons were made with conventional heating and classical methods.

8.3.5.2 Addition of Isocyanates to 2-substituted 1*H*-Perimidine

New heterocyclic ketene aminals have been obtained in yields ranging from 60 to 94% [89] starting from ethyl 1*H*-perimidine-2-acetate or acetonitrile and isocyanates (Scheme 8.63).

The reaction was studied at room temperature, under the action of irradiation and with conventional heating. No specific effect of microwaves was evidenced.

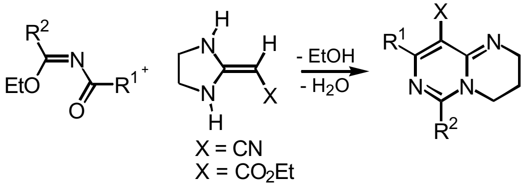


Scheme 8.63

8.3.5.3 **Pyridine Derivatives**

Synthesis of 2,3-dihydroimidazo-[1,2-*c*]-pyrimidines

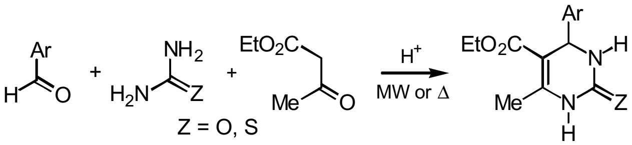
Focused irradiation of *N*-acylimidates mixed with imidazolidine ketene aminals provides a new means of access to 2,3-dihydroimidazo-[1,2-*c*]-pyrimidines [90] (Scheme 8.64).



Scheme 8.64

Microwave-mediated Biginelli reactions

Quite recently this reaction was revisited by Kappe [91] et al. who reinvestigated the Biginelli synthesis under the action of microwave irradiation under a variety of different conditions. At atmospheric pressure in ethanol solution there is no difference from conventional heating. Under pressure the yield is reduced and byproducts are formed. In an "open system" rate and yield enhancements are significant and this is rationalized by the rapid evaporation of the solvent which means that this is in fact a solvent-free reaction. This was confirmed by running the reaction without solvent under the action of microwaves and with thermal heating. (Scheme 8.65)

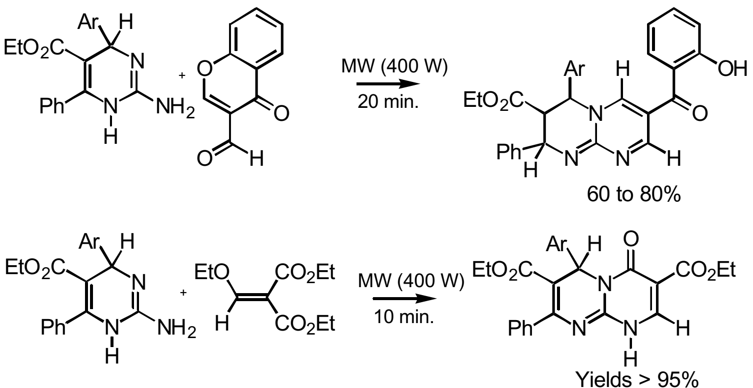


Scheme 8.65

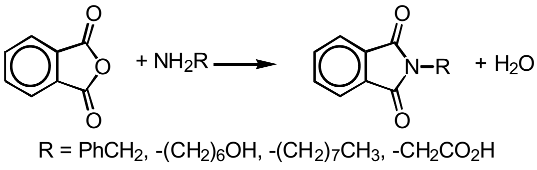
This was later extended to the synthesis of novel pyrimido-[1,3-*a*]-pyrimidines under solvent-free conditions; ethyl-2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylates react regioselectively with 3-formyl chromone or diethyl (ethoxymethylene) malonate, without solvent, to afford pyrimido-[1,3-*a*]-pyrimidines [92] (Scheme 8.66).

8.3.5.4 **Phthalimide Synthesis**

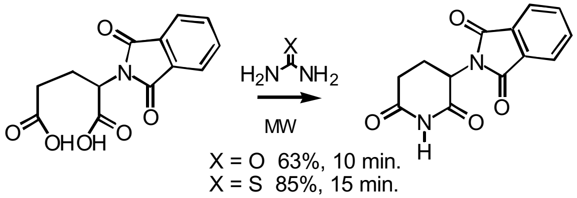
Solvent-free microwave reactions between phthalic anhydride and amino compounds were carefully re-examined by Gedye et al. [93], who showed that the reaction needs at least one liquid phase. The reaction occurs after melting of the phthalic anhydride and subsequent solubilization in the amine. It was concluded that reactions between two solids might not occur and that a high-boiling joint solvent might be necessary. Excellent yields (>90%) were always obtained within short reaction times (5–10 min) (Scheme 8.67).



Scheme 8.66



Scheme 8.67



Scheme 8.68

More recently this procedure has been used for a new synthesis of thalidomide, now a "rehabilitated drug [94]" (Scheme 8.68).

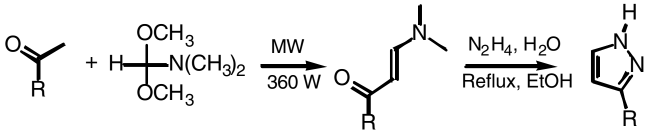
8.3.5.5 **Pyrazoles and Triazoles**

Pyrazoles

Condensation of aromatic acyl compounds with *N*,*N*-dimethylformamide diethyl acetal in a pressure tube under the action of microwave irradiation affords easy access to 1-aryl-3-dimethylaminoprop-2-enones in almost quantitative yield after 6 min. These intermediates can then be reacted with hydrazine hydrate under conventional reflux in ethanol to form the corresponding 3-substituted pyrazoles [95] (Scheme 8.69).

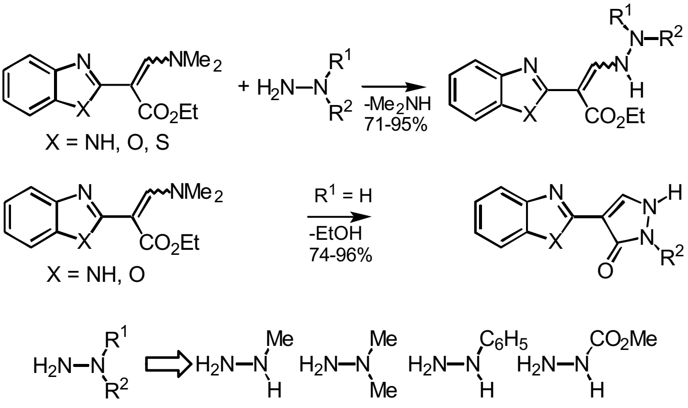
β-Hydrazinoacrylates derived from benzimidazole, benzoxazole and benzothiazole are readily prepared in good yields by transamination of the corresponding 3-dimethylamino acrylates with a variety of hydrazines [96] (Scheme 8.70).

Scheme 8.69



$R = C_6H_5, C_5H_4N, C_6H_4OH$, naphthyl

Scheme 8.70



These hydrazino acrylates can then be cyclized to the corresponding 1,2-dihydropyrazol-3-ones either under the action of irradiation or by heating conventionally. These last compounds have also been prepared directly from the starting acrylates.

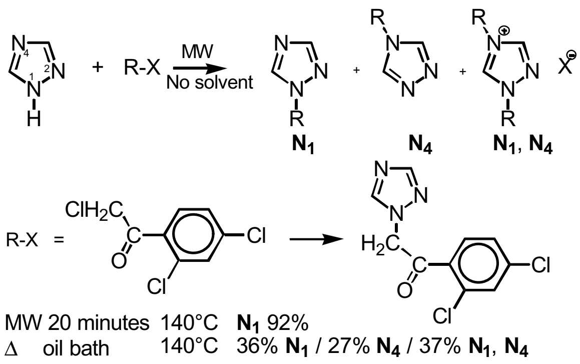
Phenacylation of 1,2,4-Triazole [97]

Selective alkylation of 1,2,4-triazole in position 1 is of primary interest for the synthesis of biologically active molecules such as fungicides (fluconazole, flutriafole ...). Direct alkylation with classical heating gave a mixture of 1- and 4-alkylated triazole together with quaternary salts resulting from alkylations at both the 1 and 4 positions. Interestingly, it has been shown [97a] that benzylation and phenacylation occurred selectively at position 1 without any base under the action of irradiation and solvent-free conditions (Scheme 8.71). The reaction with (2,4-dichloro)phenacyl chloride was studied in particular depth. Benzylation of 1,2,4-triazole and benzotriazole has been achieved by de la Hoz and coworkers [97b].

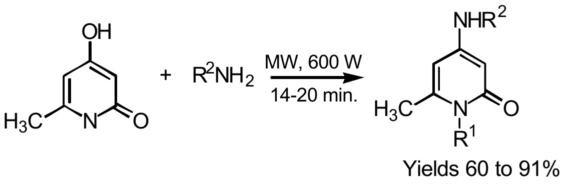
This reaction has been scaled-up to more than one hundred grams by use of a Synthewave 1000 oven.

8.3.5.6 Pyridines and Pyridones

A survey of microwave activation in the chemistry of Hantzsch 1,4-dihydropyridines (1,4-DHP) has recently been reported [98]. The experimental method proposed more than a century ago remains the most widely used to synthesize these heterocycles. Since 1992 this process has been adapted to microwave irradiation under a variety of conditions to reduce the reaction time and enhance the yield. Among these experiments, Zhang [99] reported a solvent-free process starting from 3-aminocrotonate



Scheme 8.71



Scheme 8.72

(20 mmol) methylacetoacetate (20 mmol) and arylaldehydes (20 mmol) in a domestic oven. Yields from 59 to 77% are reported for 10 min reaction.

A variety of conditions (solution, dry media, solvent-free) has been used for microwave-assisted synthesis of Hantzsch 1,4-DHP; only procedures involving solvent-free conditions under the action of irradiation led to the aromatized pyridine derivatives.

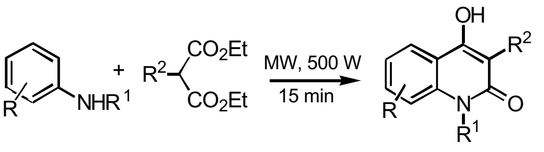
2-Pyridones were studied for N- and C-alkylation reactions by de la Hoz et al. [100]; as already mentioned for 1,2,4 triazoles, the selectivity of the alkylation is highly dependent on the activation technique (microwave or conventional heating).

The microwave-assisted nucleophilic substitution of 4-hydroxy-6-methyl-2(1*H*)-pyridones [101] has also been studied (Scheme 8.72).

It is noteworthy that the reaction works with araliphatic amino compounds. This is, nevertheless, an improvement on classical methods.

8.3.5.7 Synthesis of 3-Aryl-4-hydroxyquinolin-2(1*H*)ones

The title compounds, which are of pharmaceutical interest, are easily obtained in a one-pot procedure as a result of the formal amidation of malonic ester derivatives with an aniline followed by the cyclization of the intermediate malondianilides [102] (Scheme 8.73).



Scheme 8.73

The synthesis of Merck's glycine NMDA receptor or antagonist L-701,324 is illustrative, it can be prepared in one step by use of this procedure; the reported synthetic procedure comprises several reaction steps.

8.4
Room-temperature Ionic Liquids (RTIL) – Synthesis and Applications in Organic Synthesis under the Action of Microwaves

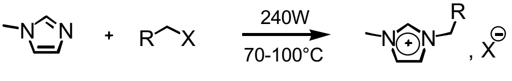
RTIL are a new class of solvents composed entirely of ions, most often alkylpyridinium or dialkylimidazolium salts and a Lewis acid [103]. These solvents have a number of interesting properties, especially their lack of vapor pressure, a wide accessible temperature range, lack of flammability, and ease of reuse [104]. RTIL have emerged as a set of new green solvents [105], mainly as a replacement for conventional volatile organic solvents. The use of a large excess of conventional volatile solvents to perform a chemical reaction is of ecological and economic concern. Much attention has been focused on organic reactions catalyzed by RTIL, and several organic reactions of high importance catalyzed by ionic liquids have been reported.

8.4.1
Synthesis of 1,3-Dialkylimidazoliums as RTIL

The preparation of 1,3-dialkylimidazolium halides by conventional heating in solvent under reflux requires several hours to afford reasonable yields and also uses a large excess of alkyl halides and/or organic solvents as the reaction medium. To circumvent these problems Varma and coworkers [106] investigated the preparation of a series of ionic liquids **72** (Scheme 8.74), using microwave irradiation as the energy source, by simple exposure of neat reactants, in open containers, to microwaves by use of an unmodified household MW oven (240 W).

It is interesting to point out that under the action of microwave irradiation the formation of ionic liquid **72** could be monitored visibly in the reaction – when it turns from a clear solution to opaque and finally clear. After the first irradiation for 30 s at 240 W (bulk temperature ~70–100 °C) the homogeneity of the reaction mixture changes because of the formation of a small amount of ionic liquid **72**. Additional irradiation was then repeated for 15 s until the formation of a clear, single-phase ionic liquid product. A series of ionic liquids **72** was prepared by microwave heating and the procedure was then compared with conventional heating (oil bath at 80 °C) using the same preparation (Tab. 8.5).

The purity of ionic salts obtained by use of microwave heating was found to be superior to that of those prepared by use of conventional heating methods. This eco-



Scheme 8.74 **70** **71** (X = Cl, Br, I) **72**

Tab. 8.5 Comparison of conventional and microwave heating for preparation of ionic liquids.

Alkyl halide **71**	*MW time (s)*	*RTIL* **72**	*Yield (%)*[a]	*Yield (%)*[b]
1-Chlorobutane	30 + 15 + 15 + 15 + 15	**72a**	76	50
1-Bromobutane	30 + 15 + 15 + 15	**72b**	86	76
1-Bromohexane	30 + 15 + 15 + 15	**72c**	89	78

[a] Use of MW, power 240 W
[b] Oil bath at 80 °C

friendly method uses only stoichiometric amounts of reactants and yields were enhanced.

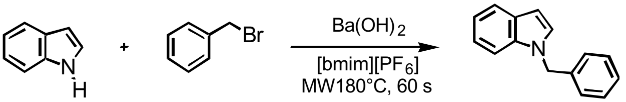
This method has some major drawbacks, however:

- the hygroscopic nature of salts might not enable large-scale preparation by the previous method, because the reaction is performed in an open vessel;
- heating irritant volatile alkyl halides in an open container in a microwave oven can be hazardous;
- the waste contains corrosive and hygroscopic methyl imidazole.

Khadilkar and Rebeiro have investigated a new method [107] that overcomes all these problems and is far safer. The authors used closed pressure reactor [108], with no apparent loss of yield. The microwave reactor used for these reactions has a possibility for recording temperature and pressure during irradiation. For example, 1-butyl-3-methylimidazolium chloride was isolated in 91% yield in 24 min [109] at 150 °C and 57 psig was the maximum pressure reached.

8.4.2
N-alkylation in RTIL

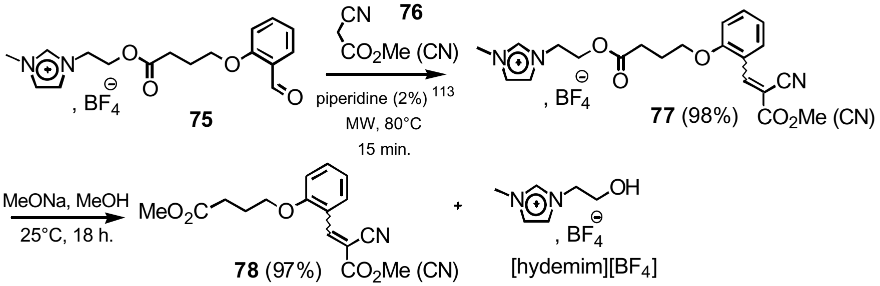
Indole **73** can be selectively alkylated [110] (Scheme 8.75) by benzyl bromide to give **74** in high yield (>90%) when the reactants were mixed with 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) as polar solvent and the reaction was performed with brief (1 min) microwave irradiation at 180 °C. Product **74** was fully extracted with diethyl ether and [bmim][PF_6] was reused in another cycle of synthesis.



Scheme 8.75

8.4.3
Knoevenagel Reactions on a Grafted Ionic Liquid Phase

Previous work [111] by our group has demonstrated that RTIL-catalyzed 1,3-dipolar cycloaddition under the action of microwave irradiation leads to dramatically shorter reaction times with better yields of isolated products. We have recently investigated the reactivity of the formyl group covalently grafted on the ionic liquid phase **75** in the Knoevenagel reaction with malonic derivatives **76** [112], as shown in Scheme 8.76.



Scheme 8.76

The bound products **77** prepared in high yields (98%) with reduced reaction times (15 min) were subjected to a very efficient cleavage from the IL-phase. The expected products **78** were extracted with dichloromethane in 97% yield and the insoluble [hydemim][BF_4] was reused in another cycle of synthesis.

8.5
Conclusion

These examples of the use of microwave irradiation in the synthesis of heterocyclic compounds show the great versatility of this technique, which can be used under a variety of experimental conditions. Even when there is no improvement of yields, or rates, or specificity, the technique is worthwhile owing to its simplicity. It can be foreseen that microwave ovens are going to be among the basic equipment of research laboratories in the near future. Combinatorial and parallel synthesis under the action of microwave irradiation is becoming a powerful tool for discovery of new molecules and should develop very rapidly.

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9

Microwaves in Cycloadditions

ANTONIO DE LA HOZ, ANGEL DÍAZ-ORTIZ, and FERNANDO LANGA

9.1

Introduction

Cycloaddition reactions, which increase molecular complexity by formation of a cyclic compound and, simultaneously, two C–C or C–X bonds [1], are among the most widely used reactions in organic synthesis. The reactions are also regio- and stereoselective. For these reasons, such processes are usually the key step in the multistep synthesis of natural products.

The successful application of microwave irradiation in chemistry dates from 1975 [2]. Several examples have been described in analytical [3], environmental [3a, 4], and materials and inorganic chemistry [5], radiochemistry [6], and organometallic [7] and organic chemistry [8].

Cycloaddition reactions often require the use of harsh conditions such as high temperatures and long reaction times. These conditions are not compatible with sensitive reagents or products such as natural products. The applicability of Diels–Alder cycloadditions is, moreover, limited by the reversibility of the reaction when a long reaction time is required. The short reaction times associated with microwave activation avoid the decomposition of reagents and products and this prevents polymerization of the diene or dienophile. All these problems have been conveniently solved by the rapid heating induced by microwave irradiation, a situation not accessible in most classical methods. With the aid of microwave irradiation, cycloaddition reactions have been performed with great success [9, 10].

In this paper we review the techniques and applications of microwave irradiation in cycloaddition reactions. This mode of heating requires not only appropriate microwave equipment and glassware, but also a new experimental outlook. A special section will focus on modifications of chemo-, regio- and stereoselectivity which result from use of microwaves, and possible explanations of this behavior will be given.

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

9.2
Reactions in Solution

9.2.1
Reactions under Pressure

The first examples of microwave-induced reactions were cycloadditions and pericyclic reactions performed under pressure, because of the use of domestic ovens, to avoid the risk of igniting flammable solvents (Scheme 9.1) [11, 12].

Reactions were performed in sealed thick-walled glass tubes or in Teflon acid-digestion vessels, in domestic microwave ovens [13]. Teflon vessels can be used at pressures up to 14 atm, at temperatures below 250 °C, and are resistant to most commonly used chemicals, although they deform at temperatures >250 °C.

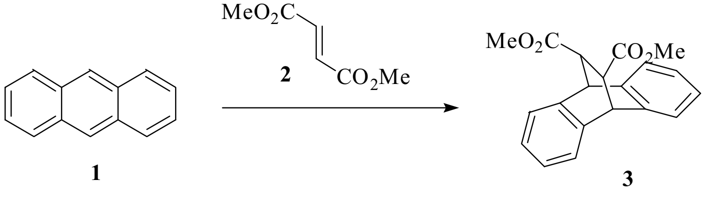
The lack of temperature and pressure control in these systems could lead to safety problems, because of overpressure resulting from the heating rate caused by microwaves. These problems can be reduced by using solvent-free methodology, which also enables the use of larger quantities of reagents. Yields have been greatly improved, and reaction times reduced, in comparison with conventional procedures in solvents under reflux.

These reactions were next revisited by Strauss and it was shown that, under identical conditions in xylene, the reaction rates were strictly identical within experimental error [14].

9.2.2
Reactions under Reflux

Reactions involving a solvent under reflux require the use of modified commercial microwave ovens. In these modified systems the oven is perforated on the top to accommodate a reflux condenser and a 10 cm pipe is used to avoid microwave leakage; the turnable dish is replaced by a magnetic stirrer or by monomode reactors especially designed for chemical synthesis [15].

The advantage of reactions involving solvent is that the reaction temperature is controlled by the reflux temperature of the solvent [16]. It should, however, be re-



MICROWAVE	CONTROL
10 min	4 h
p-xylene, 87%	*p*-xylene, 67%
325°<361 °C	138 °C

Scheme 9.1

membered that overheating by between 13 and 26 °C above the normal boiling point of polar solvents can occur as a result of the “inverted heat transfer” effect, because boiling nuclei are formed at the surface of the liquid [17]. This superheating effect was shown to disappear when the experiments were performed with efficient stirring and use of low microwave power [18].

For instance, cycloadditions of [60]fullerene (**4**) under the action of microwave irradiation usually require the use of this technique, because reactions are performed on a very small scale and C_{60}, in common with many dienophiles, does not absorb microwaves efficiently [19].

9.2.3
Microwave Organic Reaction Enhancement (MORE)

Microwave organic reaction enhancement (MORE) chemistry was described by Bose as a safe and convenient alternative to pressure reactions and modified microwave ovens [20].

In MORE chemistry the solvent of choice absorbs microwaves in an energy-efficient manner and is, therefore, heated rapidly under microwave irradiation. The solvent should also have a boiling point at least 20–30 degrees higher than the desired reaction temperature [17].

High-boiling polar solvents such as dimethylformamide (b.p. 160 °C), chlorobenzene (b.p. 132 °C), 1,2-dichlorobenzene (b.p. 180 °C), and 1,2,4-trichlorobenzene (b.p. 214 °C) have been used. It is not necessary to employ a large volume of the reaction medium and, often, a slurry at room temperature was found to give a clear solution during the rapid rise in temperature resulting from microwave heating. This type of methodology is particularly valuable for medium-scale operations. Tall, loosely covered beakers with a capacity much greater than that of the reaction mixture were employed and the use of closed vessels and overpressure were avoided, thus reducing the possibility of explosions [21]. Subsequent removal of the high-boiling solvent is, however, always the main drawback of this methodology.

Several reactions have been performed by use of this methodology, including [4+2] and [2+2] cycloadditions; reaction time was significantly reduced and yields improved.

9.3
Solvent-free Conditions

Solvent-free conditions are especially suitable for microwave activation. Several advantages of this approach are evident [22]:

- in the absence of solvent the radiation is absorbed directly by the reagents, so the effect of microwaves is more marked.
- solid supports can be used efficiently; many mineral oxides are poor conductors of heat yet absorb microwave radiation very efficiently [23].

- this methodology can be used in conjunction with other synthetic methods, e.g. phase-transfer catalysis in the absence of solvent [24].

Particular advantages of solvent-free methods are enhancement of reactivity, because of the increased concentration, and specific selectivity, because of the restricted mobility.

The use of solvent-free methods is particularly interesting because environmentally benign syntheses can be easily designed:

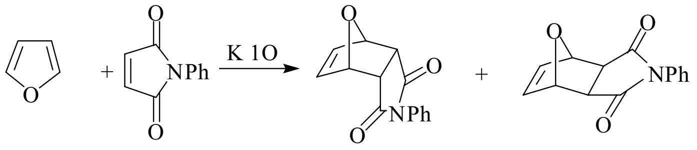
- the use of large volumes of solvent can be avoided, thus reducing solvent emissions and precluding the need for redistillation;
- work-up procedures are considerably simplified, because the pure product can often be obtained directly from the crude reaction mixture by simple extraction, distillation, or sublimation;
- recyclable solid supports can be used efficiently in place of mineral acids and oxidants;
- scale-up is facilitated by the absence of solvent; and
- under these conditions, reaction times are very short, which leads to savings in time, money, and energy.

These solvent-free conditions are included in the twelve principles of Green Chemistry [25], and facilitate the design of sustainable processes for the chemical industry.

9.3.1
Reactions using Mineral Supports

Alumina, silica, clays, and zeolites are increasingly used as acidic or basic supports [26]. Cycloaddition reactions often require Lewis-acid catalysts if good yields are to be obtained. Clay and doped silica gel catalysts have emerged as useful alternatives to the use of Lewis acids. Cycloaddition of furan (**5**) under solvent-free conditions, catalyzed by K10 montmorillonite, results in a decrease in the reaction time; the *endo–exo* relationship is no different that obtained by use of classical heating (Scheme 9.2) [27].

The use of silica-supported Lewis acids as catalysts for the Diels–Alder reactions of 2,5-dimethylfuran leads to fairly good yields of adducts [28]. Solid supports such as



5 **6** **7** **8**

Conventional heating	1.3	1
Microwave irradiation	1.5	1

Scheme 9.2

silica gel [29] and alumina [30] have also been used to generate 1,3-dipoles and, in this way, heterocyclic compounds can be obtained in a one-pot procedure. In these reactions changes in the regioselectivity of the reaction have not been observed under the action of microwave irradiation.

9.3.2
Reactions without Support

An alternative to the use of supported reagents is the use of uncatalyzed "neat reactions". Under these conditions the radiation is absorbed directly by the reagents and this results in spectacular acceleration, higher yields and purity of the reaction products, a simple workup procedure, and sometimes changes in the selectivity of the cycloaddition.

Diels–Alder reactions [31] and 1,3-dipolar cycloadditions [32, 33] have been performed by use of this methodology. For example, Díaz-Ortiz described the hetero-Diels–Alder and 1,3-dipolar cycloaddition reactions of ketene acetals. The reactions were improved and products were isolated directly from the crude reaction mixture without polymerization of the ketene acetals [34].

When the enantiomerically pure ketene acetal **16** was used, cycloaddition with *N*,α-diphenylnitrone (**11**) or chalcone (**12**) was achieved within 3 min in 98 and 96% yield, respectively. Under the same reaction conditions the use of classical heating in the absence of solvent at 120–124 °C for 3 min caused the yields to decrease to 3–4%. These results suggest that the excellent yields achieved by use of microwave irradiation are perhaps not entirely a result of the rapid heating of the reaction mass (Scheme 9.3).

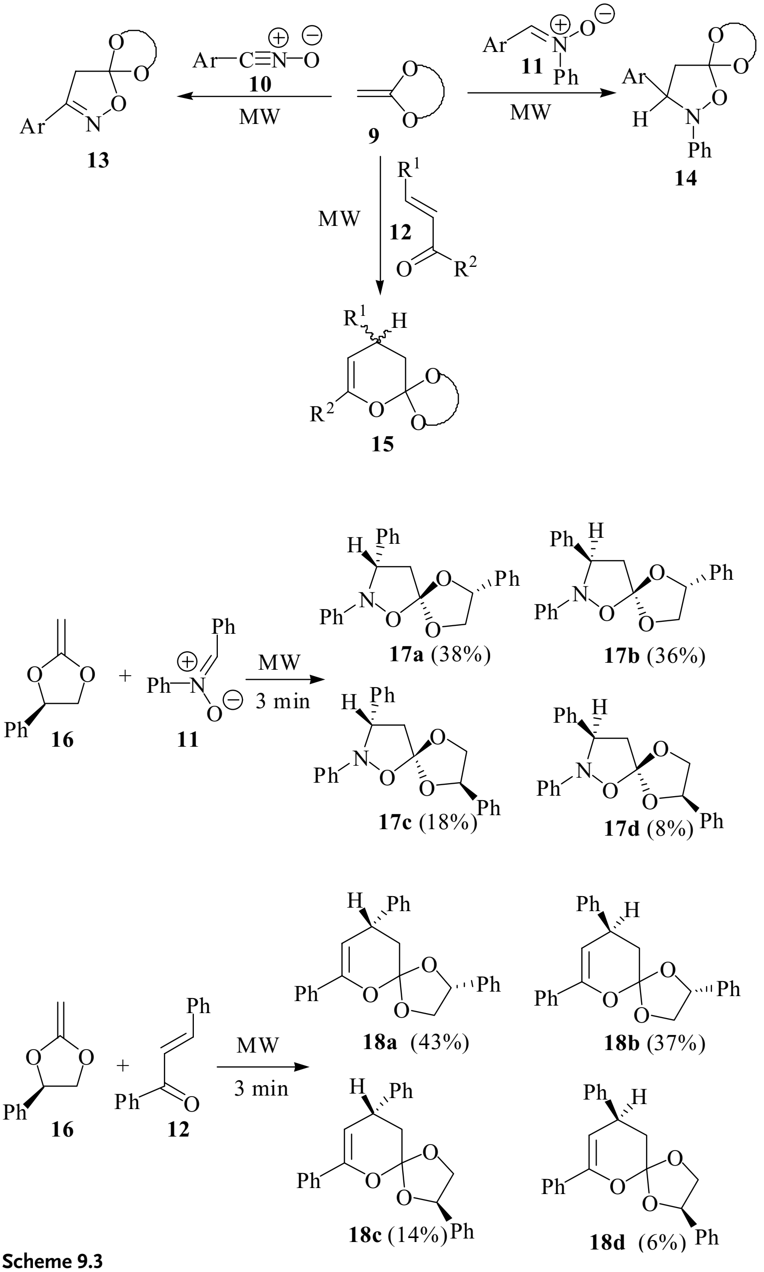
9.3.3
Reactions with a Heat Captor

Garrigues described the use of graphite as a heat captor under the action of microwave irradiation. Graphite is a chemically inert support that couples strongly with microwaves by a conduction process and is able to transmit intense thermal energy to the supported reagents [35].

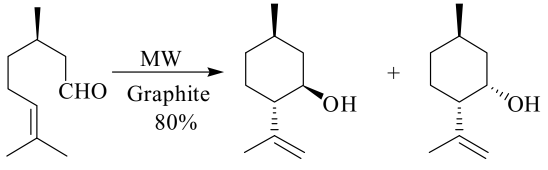
Methods have been described that involve microwave-assisted graphite-supported dry media for the cycloaddition of anthracene, 1-azadienes and 1,2,4,5-tetrazines with several C–C dienophiles and carbonyl compounds in hetero-Diels–Alder reactions [35]. This technique leads to a shortening of reaction times, a situation that enables work to be undertaken at ambient pressure in an open reactor to avoid the formation of unwanted compounds by thermal decomposition of reagents or products.

Similarly, the use of a higher input power in retro-Diels–Alder reactions of anthracene derivatives has been reported to afford complete reaction in 3–5 min [36]. This method is an alternative to the use of flash thermolysis. The use of graphite is a prerequisite for obtaining high temperatures in a short time.

This methodology has been extended by the same author to include carbonyl-ene reactions [37]. The cyclization of (+)-citronellal (**19**) to pulegols **20** and **21** is faster


10
MW
9
11
MW
13
14
MW
12
15
16
11
MW
3 min
17a (38%)
17b (36%)
17c (18%)
17d (8%)
16
12
MW
3 min
18a (43%)
18b (37%)
18c (14%)
18d (6%)

Scheme 9.3



Scheme 9.4 19 20 21

when performed under the action of microwave irradiation with a graphite support and the stereoselectivity was different from that obtained by use of classical heating, with the amount of (+)-neoisopulegol (**21**) being greater in the former (Scheme 9.4).

9.4
Specific Effects in Cycloaddition Reactions

The existence of results that cannot be explained solely by the effect of rapid heating has led authors to postulate the existence of a so-called "microwave effect". Hence, acceleration or changes in reactivity and selectivity could be explained by a specific radiation effect and not merely by a thermal effect. Several reviews have collected synthetic results that have been attributed to the microwave effect [5 b, 38, 39].

Several authors have proposed that changes in thermodynamic behavior under the action of microwave irradiation are the cause of the "microwave effect". When a compound absorbs microwaves, however, dielectric heating causes an increase in the temperature of the system. When the internal energy of the system is raised it is distributed among translational, rotational, or vibrational energies, irrespective of the mode of heating. Consequently, it was concluded there should be no kinetic differences between reactions heated by microwaves or by classical heating if the temperature is known and the solution is thermally homogenous [8 c, 40].

The existence of the so-called "microwave effect" has not been proved. It does, however, seem to have been demonstrated that overheating of polar liquids [17] occurs and that "hot spots" are present in heterogeneous systems, especially at the interface [38]. Similarly, microwave irradiation results in an increase in the molecular mobility in solids [5 b].

The utility of microwaves in improving numerous processes or in modifying chemo, regio-, or stereoselectivity is evident. These changes often seem to arise from the rate of heating which results from use of microwaves, a situation that is not possible with classical heating. Suard considered two important differences between conventional heating and microwave radiation [41 a]. First, under the action of microwave irradiation the initial slope of the sample temperature is different from zero and, second, in contrast with the situation observed with conventional heating, conduction flow is the major flow of the system. As a consequence, a rapid heating rate must be responsible for the observed effects [41 b].

In cycloaddition reactions few examples have been described in which changes in selectivity have been observed on use of microwave irradiation. In concerted processes the regio- and stereoselectivity of the reaction is governed by frontier orbital interactions, and changes in selectivity are not expected unless a change in the reaction mechanism occurs.

These effects have been justified in competitive reactions by two compatible hypotheses:

1. by considering that under the action of microwave irradiation the more polar route will be favored [42]; and
2. by considering that the relative ratio of isomers is related to the hardness and, under the action of microwave irradiation, formation of the intermediate of greatest hardness should be favored [43].

Some examples of this behavior will be described in the following sections.

9.5
[4+2] Cycloadditions

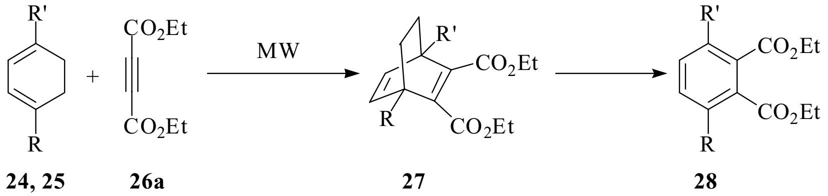
9.5.1
Diels–Alder Reactions

The usefulness of the Diels–Alder reaction in organic synthesis comes from its versatility and its high regio- and stereoselectivity. A wide variety of dienes and dienophiles can be used with a varied range of substitution patterns. Numerous types of ring structure can be designed by use of this approach. Not all the atoms of the diene or dienophile need be carbon atoms, meaning that both carbocyclic and heterocyclic rings can be constructed.

The Diels–Alder reaction is important because it is frequently used at an early stage of a synthesis to establish a structural core which can then be elaborated to give the more complex target structure. Classical Diels–Alder reactions have been greatly improved by the use of microwaves – yields have been increased and reaction times reduced. For instance, dramatic improvements have been seen in reactions involving *trans,trans*-1,4-diphenylbutadiene (**22**) [12, 31], and in the reaction of cyclopentadiene (**23**) under pressure and solvent-free conditions [44] or, in the latter circumstances, by using graphite [45] as a support for the tandem retro Diels–Alder/Diels–Alder reaction starting from dicyclopentadiene. Similarly, anthracene (**1**) has been reacted under pressure under both solvent-free conditions [12, 31] and in solution in 1,2-xylene [14]. Finally, cyclohexadiene (**24**) and α-terpinene (**25**) have been reacted with diethyl acetylenedicarboxylate (**26a**) [46]. Some Diels–Alder adducts undergo a retro Diels–Alder reaction to provide, by loss of ethylene and aromatization, substituted benzenes (Scheme 9.5).

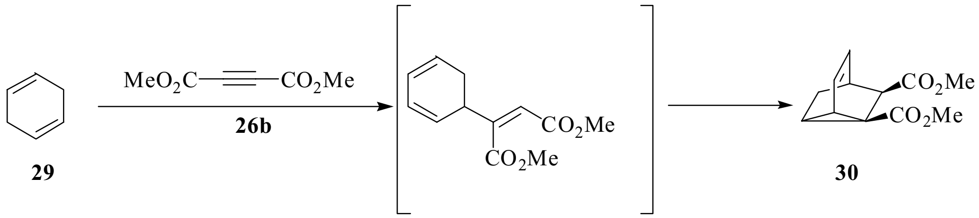
Giguere performed tandem ene-intramolecular Diels–Alder reactions between 1,4-cyclohexadiene (**29**) and dimethyl acetylenedicarboxylate (**26b**) in sealed tubes in a commercial microwave oven (Scheme 9.6) [47].

Berlan found that cycloaddition reactions performed under reflux in xylene or dibutyl ether (Scheme 9.7) were always faster under microwave conditions than when



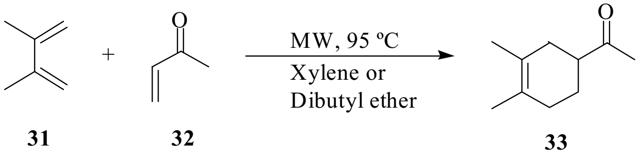
24 R = R' = H; **25** R = CH_3, R' = iPr

Scheme 9.5



Scheme 9.6

Conventional heating: DMF, reflux, 40 h, 14%
Microwaves: DMF, 179-184 °C (90 psi), 20 min, 49%

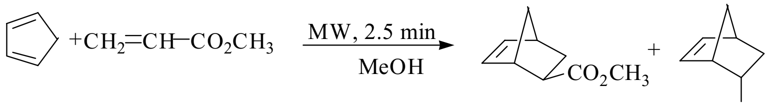


Scheme 9.7

using classical heating methods [48]. The observed acceleration is more significant in apolar solvents, for which dielectric losses are weak. On this basis the authors propose that $G^{\ddagger}$ is changed, possibly as a result of a change in the entropy of the system. Subsequently, Strauss indicated that the kinetics of these and other reactions are similar under the action of microwave irradiation and classical heating – hence there is no specific effect [14].

Similarly, in the cycloaddition of cyclopentadiene (**23**) with methyl acrylate (**34**), described by Gedye, microwave radiation does not alter the *endo*/*exo* selectivity and the observed changes can be explained on the basis of the reactions under microwave conditions occurring at higher temperatures than those occurring under reflux and under pressure (Scheme 9.8) [49].

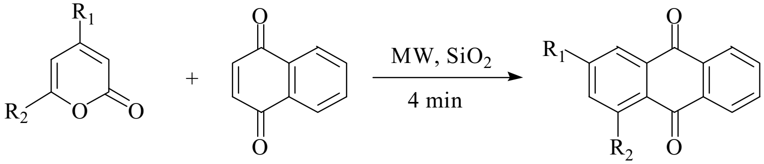
Reaction of pyrones under classical conditions requires the use of high temperatures to obtain low to moderate yields. The Diels–Alder reaction of pyrones has been performed in a commercial microwave oven under solvent-free conditions on solid supports such as silica gel, montmorillonite, fitrol clay and alumina. The reaction time was dramatically reduced – from 4 h to 4 min (Scheme 9.9) [50].



23 **34** **35a** **35b**

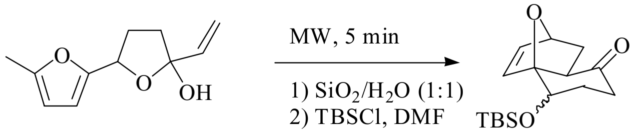
Classical heating, 56 °C, 85% *endo*
Microwaves, 110 °C, 79% *endo*

Scheme 9.8



36 **37** **38** (73%)

Scheme 9.9



40 **41** (64 %)

Scheme 9.10

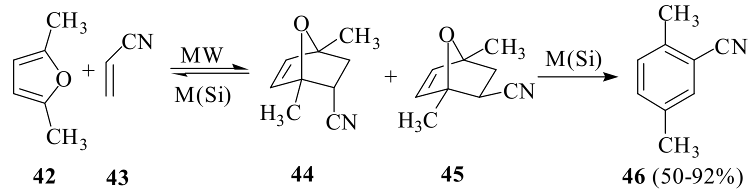
Cycloaddition of furan (**5**) has again been performed successfully under pressure and solvent-free conditions [12, 44]. Usually, however, the cycloaddition of furan and heterocyclic compounds requires a Lewis-acid catalyst to give good yields.

Reactions of furan (**5**) under solvent-free conditions, catalyzed by Montmorillonite K10, have been described by Cintas [27]. The reaction with methyl vinyl ketone (**32**) produced Michael addition in positions 2 and 5, whereas reaction with symmetrically substituted cyclic dienophiles produced a mixture of the *endo* and *exo* adducts with the kinetically favored *endo* adduct predominating, except when maleic anhydride (**39**) was used as the dienophile (Scheme 9.2).

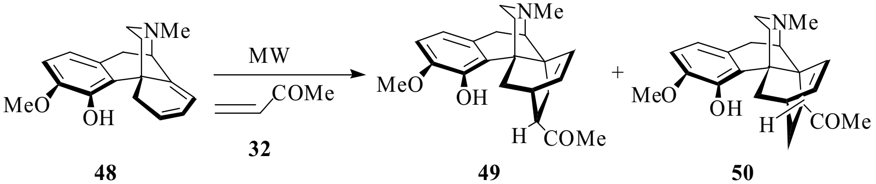
Although the intramolecular Diels–Alder reaction of furan **40** does not occur with classical heating (Scheme 9.10) [51], the reaction has been performed successfully in 64% yield by using microwaves and absorbing the product on to silica gel–water.

Moreno described the cycloaddition of 2,5-dimethylfuran (**42**) catalyzed by silica-supported Lewis acids under solvent-free conditions in closed Teflon vessels using a commercial microwave oven (Scheme 9.11) [28, 52]. Under these conditions coordination of the silica-supported catalyst with the oxygen bridge favors ring opening, thus leading to the aromatic compounds in one step. The use of Si(Ti) gave the best results for aromatic compounds.

Most of these compounds gave very low yields when the reactions were performed using classical heating in an oil bath under comparable reaction conditions and, in



Scheme 9.11



Scheme 9.12

Microwaves, 32%, 3 : 2 ratio

fact, mixtures of the cycloadducts and aromatic compounds were often obtained. When the same reactions were performed in a monomode reactor the cycloadducts could be isolated relatively easily.

Computational results showed that activation barriers for the aromatization process are always lower for aluminum-catalyzed reactions and, similarly, lower for titanium-catalyzed than for zinc-catalyzed reactions [52].

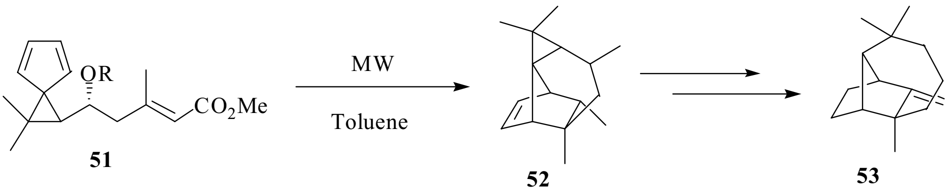
Surprisingly, the aromatic product is not obtained in the reaction with fumaronitrile (**47**) – the Diels–Alder cycloadduct is the only product. The activation barriers calculated for this aromatization were the highest reported in this work [52].

In an attempt to prepare new diprenorphine analogs, Linders, in one of the first examples of microwave-induced organic reactions, reported the reaction between methyl vinyl ketone and 6-demethoxy-β-dihydrothebaine (**48**) [53]. The Diels–Alder reaction, when performed under classical conditions, led to extensive polymerization of the dienophile. A dramatic improvement was achieved when the cycloaddition was conducted in a modified microwave oven at the reflux temperature of methyl vinyl ketone. By use of these conditions adducts **49** and **50** were obtained in a 3 : 2 ratio, according to HPLC (Scheme 9.12).

The same authors showed that in the cycloaddition of northebaine derivatives the reaction time with microwave heating was considerably shorter than when conventional heating was used [54]. When, however, cycloadditions were performed in benzene, a poor absorber of microwave irradiation, microwave heating did not result in a significant increase in the rate of the reaction.

Fallis, in the synthesis of longifolene (**53**), a bridged sesquiterpene, performed the intramolecular cycloaddition of compound **51** as a key reaction in the construction of the bridged system (Scheme 9.13) [55].

The cycloaddition afforded 10% of cycloadduct **52** after 24 h under reflux in toluene in a modified household oven, whereas decomposition predominated at higher temperatures. When the triene was heated in a sealed glass vessel in a modified microwave oven the adduct was obtained in 92% yield.

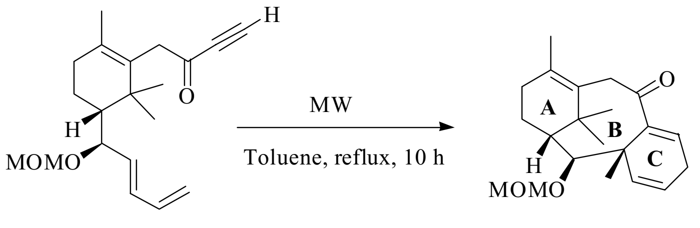


51 **52** **53**

R = SiMe$_2{}^t$Bu

52 Conventional heating, 10%
Microwave irradiation, 92%

Scheme 9.13



54 **55** (40%)

Scheme 9.14

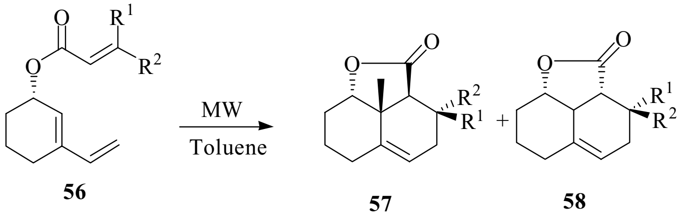
The same author used this strategy to synthesize tricyclic taxoid skeletons **55**, an intramolecular Diels–Alder approach that proceeds in the direction from left to right (ring A to BC) (Scheme 9.14) [56]. Once again, microwave irradiation was necessary to perform the required cycloaddition in good yield.

The cycloaddition of ketone **54** could be effected in a sealed glass tube in a modified microwave oven to afford the tricyclic system stereoselectively. This major adduct arose via the preferred transition state, in which the nonbonded interactions were minimized, because of the alignment of the dienophile beneath the triene unit furthest from the MOM substituent. This pattern of π-facial selectivity implies that, with the "natural" C2 stereoselectivity, the preferred geometry should provide the relative stereochemistry required for taxol itself.

The synthesis of the decalin unit of compactin (**59**), a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which acts as an effective hypocholesterolemic agent, was planned to incorporate an intramolecular Diels–Alder reaction (Scheme 9.15) [57].

The reaction was performed by heating the reagents at 150 °C for 10 h in *o*-xylene. The desired *exo* adduct was obtained with high stereoselectivity and subsequent formation of the diastereoisomer **58** was considered to occur by isomerization of the *exo* adduct. The reaction was dramatically accelerated by use of microwave irradiation in a domestic microwave oven, and the carboxylic acid was obtained after 45 min with a small increase in stereoselectivity (Scheme 9.15) [57].

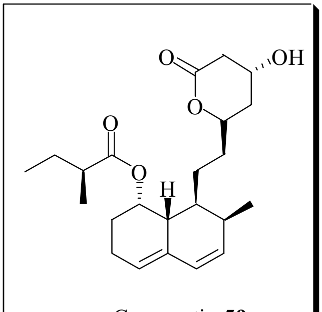
The Diels–Alder reaction between azonianthracene (**61**) and bis-substituted olefins to give 6,11-ethanobenzo-[*b*]-quinolizinium salts **62** was greatly accelerated by the action of microwave irradiation and, consequently, the reaction might be applicable to



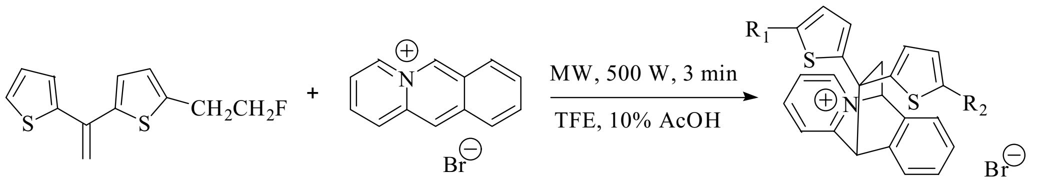
56 **57** **58**

57 $R_1 = CO_2Et$, $R_2 = H$; Conventional heating: *exo/endo*: 91/9
Microwave irradiation: *exo/endo*: 94/6
58 $R_1 = CO_2H$, $R_2 = H$; Conventional heating: *exo/endo*: 82/18
Microwave irradiation: *exo/endo*: 85/15

Scheme 9.15



Compactin **59**



60 **61** **62**

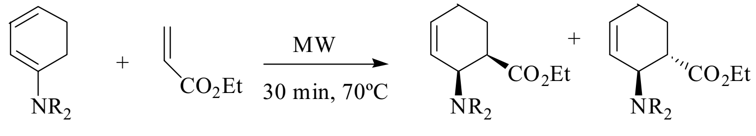
a $R_1 = H$; $R_2 = CH_2CH_2F$
b $R_1 = CH_2CH_2F$; $R_2 = H$

Scheme 9.16

labeling with ^{18}F, which has a short half-life (Scheme 9.16) [58]. The most efficient reaction occurred in 10% AcOH in TFE in a commercial microwave oven and the reaction was approximately 200 times faster than that in CH_3CN. In the synthesis of **62a**, the radiochemical yield was 20% in a 1:1 ratio after a synthesis time of 77 min, including HPLC purification.

Deshayes described the cycloaddition of 1-amino-1,3-butadienes **63** with ethyl acrylate (**34**) under the action of microwave irradiation in a monomode reactor with temperature control [59]. Irradiation for 30 min at 70 °C in the absence of solvent afforded a 60:40 ratio of an inseparable mixture of the *endo* and *exo* isomers in 90% yield. Classical heating under the same conditions did not affect the selectivity but the yield was lower (Scheme 9.17).

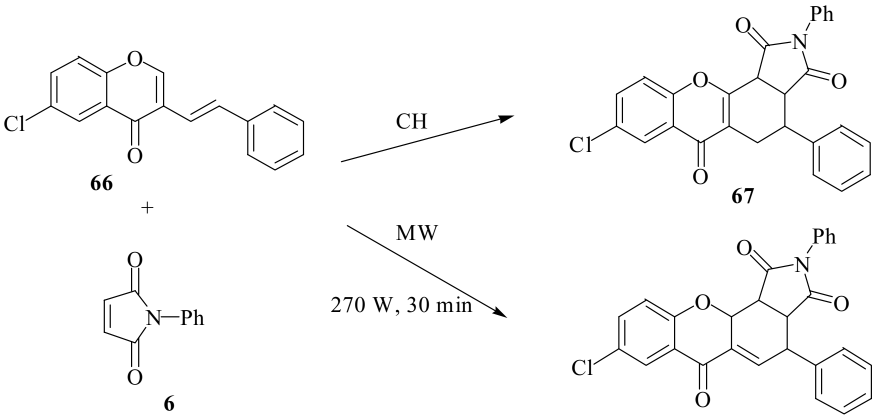
Lacova described the cycloaddition of vinylchromones with a variety of dienophiles, by use of both classical heating and microwave irradiation. Only reaction with maleic



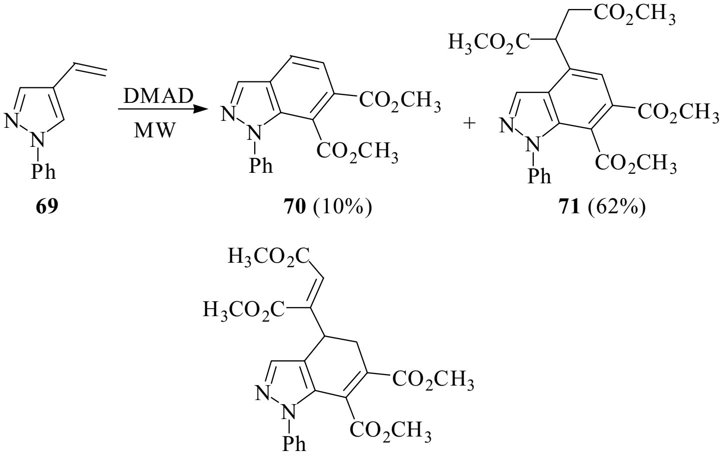
Scheme 9.17 **63** **34** **64** (60%) **65** (40%)

anhydride (**39**) was successful under classical conditions [60]. The use of microwave irradiation for the Diels–Alder experiments was unsuccessful in this instance. Silva and de la Hoz have, however, performed the cycloaddition of styrylchromones **66** with *N*-methyl- and *N*-phenylmaleimide (**39**) and (**6**), respectively. The reaction performed with conventional heating resulted in cycloaddition then aromatization, whereas the same reaction under the action of microwaves gave the cycloadduct **68**, which could be isolated without migration of the double bond (Scheme 9.18) [61].

Diels–Alder cycloadditions of vinylpyrazoles under classical conditions require highly reactive dienophiles and extreme conditions, i. e. high pressures and temperatures (8–10 atm and 120–140 °C) for long reaction times (several days), and usually afford moderate yields only [62]. The main obstacle to these reactions is extensive polymerization of the reagents. 1-Phenyl-4-vinylpyrazole (**69**) reacted with dimethyl acetylenedicarboxylate (**26b**) within 6 min under the action of microwave irradiation to afford the adducts **70** and **71** in 72% overall yield (Scheme 9.19) [63]. The cycload-



Scheme 9.18



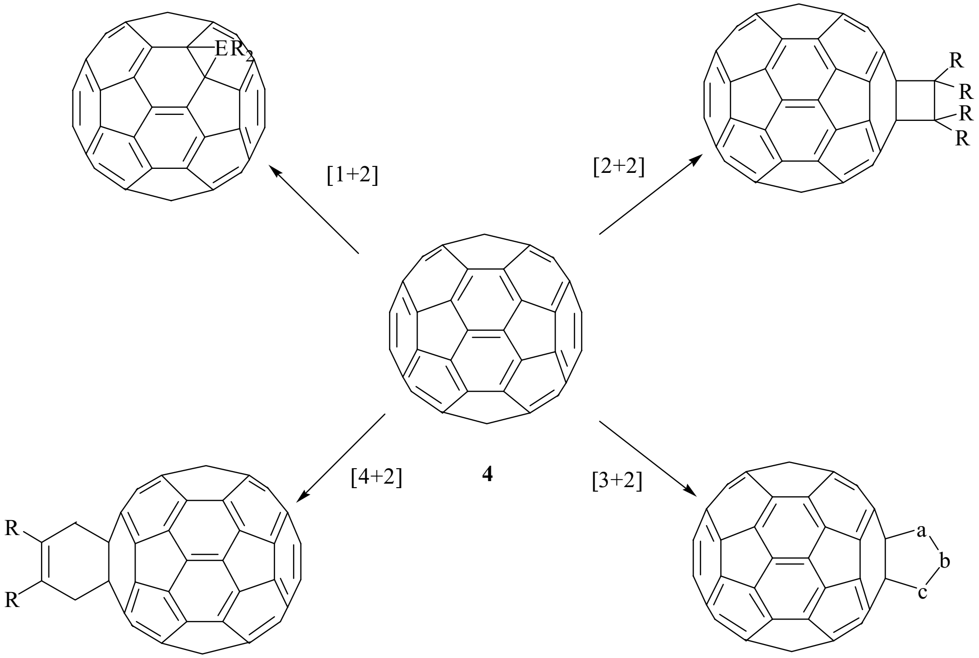
Scheme 9.19

dition was performed in a Teflon vessel in a domestic oven. The clean nature of the reaction enabled characterization of intermediate **72**, although this compound is not detected when classical heating is used, because it rearranges spontaneously in a few minutes at the reaction temperature to give the aromatic compound.

The reaction proceeds even with a very poor dienophile such as ethyl phenylpropiolate (**73**), which does not react under classical conditions.

C_{60} (**4**) reacts as an electron-deficient polyolefin and, consequently, one of the main ways of functionalizing fullerenes involves cycloaddition reactions [64] in which C_{60} (**4**) is a reactive 2 component. In this context, [1+2], [2+2], [3+2], and [4+2] cycloadditions have been performed (Scheme 9.20) and the conditions for cycloadduct formation found to depend strongly on the gap between the controlling orbitals. For this reason it is frequently necessary to use conditions involving several hours (or days) under reflux in high boiling solvents. It thus seemed interesting to investigate the potential of microwave irradiation in the preparation of fullerene derivatives when this type of reaction is involved. The characteristics of [60]fullerene (**4**), i.e. the absence of a dipole moment and the need to work on a very small scale, imply the use of a solvent in these reactions.

[4+2] Cycloadditions selectively afford the adducts on the 6,6-ring junctions [65], and the products occasionally undergo a facile retro-Diels–Alder reaction as a consequence of the low thermodynamic stability of the adduct. Very stable Diels–Alder cycloadducts have, however, been prepared by use of different substituted *o*-quinodimethanes, probably because of stabilization by aromatization of the resulting adducts [66].



Scheme 9.20

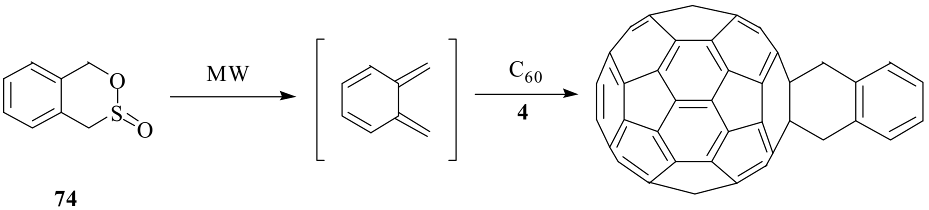
Langa et al. [67] described the microwave-induced Diels–Alder reaction of *o*-quinodimethane, generated *in situ* from 4,5-benzo-3,6-dihydro-1,2-oxathiin-2-oxide (**74**) (sultine), [68, 69] leading to cycloadduct **75** (Scheme 9.21). This reaction was the first application of microwave irradiation to the preparation of a functionalized C_{60} [67].

To avoid explosion hazards [70], a modified domestic microwave oven was used. Higher yields were obtained in shorter periods of time on use of microwave irradiation (39% yield after 20 min irradiation) in comparison with thermal conditions. Longer irradiation times led to a decrease in the yield of **75**, because of increased bis adduct formation.

The scope of the microwave technique in the preparation of fullerene derivatives was determined in the well known Diels–Alder reaction of C_{60} with anthracene (**1**) [71], which has been reported to occur under thermal conditions (13% [71 a], reflux, toluene, three days; 25% [71 b], reflux, benzene, 12 h) (Scheme 9.22). In addition to **76**, multiply-substituted adducts that undergo cycloreversion to the starting materials were formed.

Under the action of microwave irradiation, with toluene as a solvent, cycloadduct **76** was formed in 35% yield after 15 min at 800 W [72]; this is an improvement on the yields obtained by conventional heating and probably occurs because of a decrease in the reversion of the cycloaddition in the shorter period of time needed for the irradiated reaction. It is remarkable that under microwave conditions the formation of bis adducts was not observed in these reactions.

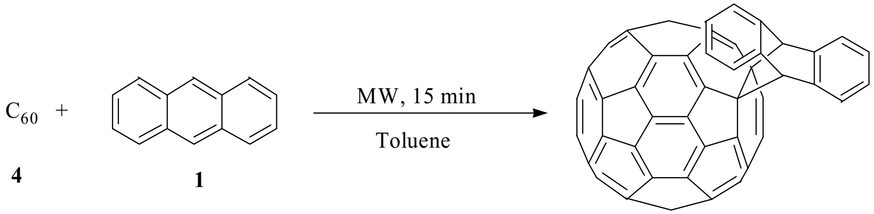
Novel pyrazine-containing cycloadducts **80a–c** were synthesized by Diels–Alder reaction of [60]fullerene with the corresponding 2,3-bis(bromomethyl)pyrazine derivatives **79a–c** (Scheme 9.23) [73]; the 2,3-pyrazinoquinodimethanes were trapped as the Diels–Alder adducts by reaction with [60]fullerene under reflux in *o*-dichlorobenzene (ODCB) as solvent with classical heating and under the action of microwave ir-



74

Scheme 9.21

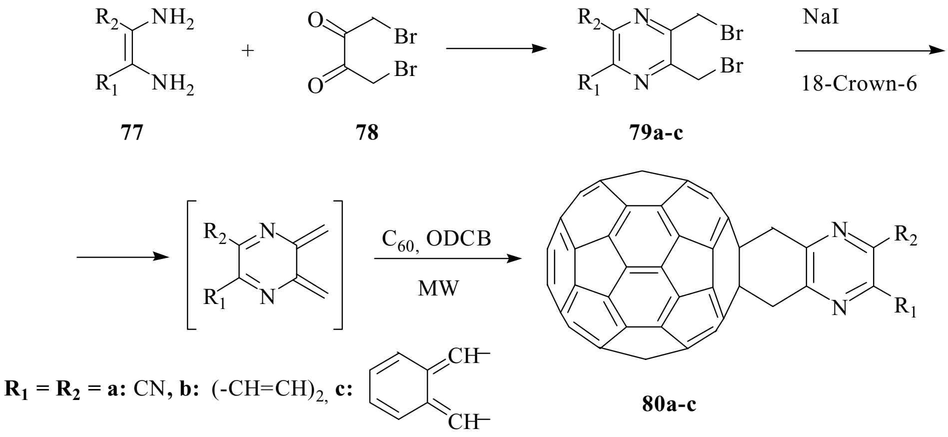
75 (39%)



4 **1**

Scheme 9.22

76 (35%)



77 **78** **79a-c** **80a-c**

$R_1 = R_2 =$ **a**: CN, **b**: $(\text{-CH=CH})_2$, **c**:

Scheme 9.23

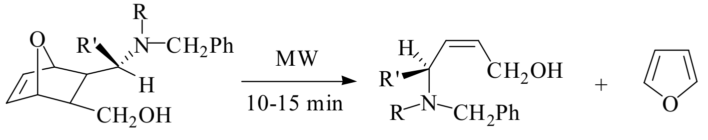
radiation in a focused microwave reactor. Once again, the use of microwave irradiation led to higher yields than classical heating for **80a** and **80b** (up to 4.5-fold) and reaction times were significantly reduced – from 24 h to 0.5 h. For **80c**, large amounts of polyadducts were detected when microwave irradiation was used; this reduced the yield.

Interestingly, in syntheses of thiophene cycloadducts **81** use of microwave irradiation led to lower yields [73] than conventional heating (23% compared with 43%), although reaction times were significantly reduced [74].

9.5.2
Retro Diels–Alder Reactions

Retro Diels–Alder reactions often require severe conditions, high temperatures, and, sometimes, flash vacuum thermolysis. Microwave irradiation has been used as an alternative to these harsh conditions [12], even using graphite as a support [45]. Similarly, the use of higher input power has enabled retro-Diels–Alder reactions of anthracene derivatives to occur in 3–5 min [41]. This method is an alternative to the use of flash thermolysis. The use of graphite is a prerequisite for obtaining high temperatures in a short time.

Bortolussi described the synthesis of unsaturated amino alcohols **83** by thermolysis of furan adducts **82**; use of microwaves resulted in a significant reduction in reaction time (Scheme 9.24) [75].



Scheme 9.24 **82** **83** (98%) **5**

9.5.3
Hetero Diels–Alder Reactions

The hetero-Diels–Alder reaction is one of the most important methods of synthesis of heterocycles, yet as a potentially powerful synthetic tool it has found relatively little general use. Microwave irradiation has been used to improve reactions involving heterodienophiles and heterodienes of low reactivity.

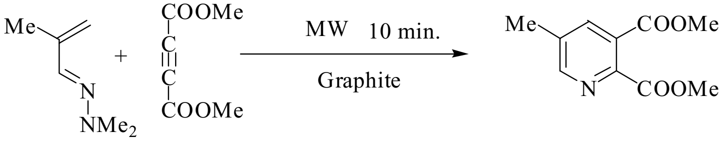
9.5.3.1 Heterodienes

The introduction of a nitrogen atom into a conjugated system will confer electrophilic character on the system. This has led to the development of the inverse-electron-demand Diels–Alder reaction [1b, 10]. Substitution of the azadiene with electron-withdrawing groups accentuates the electron-deficient nature of the azadiene and enables the use of electron-rich dienophiles. The magnitude of the $\mathrm{LUMO_{diene}}$–$\mathrm{HOMO_{dienophile}}$ energy separation has been related to the rate of inverse-demand cycloadditions. Alternatively, addition of a strong electron-donating substituent to the azadiene enables the use of conventional electron-deficient dienophiles in a normal demand Diels–Alder reaction.

The Diels–Alder reaction of 1-azadienes suffers from low conversion, because of the low reactivity of these systems. In an attempt to overcome this problem, considerable effort has been focused on both inter- and intramolecular versions of the reaction.

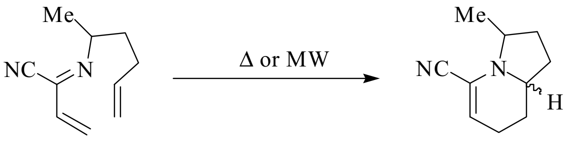
Garrigues described the reaction of the 1-azadiene **84** with dimethyl acetylenedicarboxylate (**26b**) on a graphite support [35]. After sequential microwave irradiation for 10 min in a monomode reactor pyridine **85** was obtained in 60% yield. This azadiene does not react when conventional heating is used (Scheme 9.25).

Similarly, Motorina described the intramolecular hetero-Diels–Alder reaction of *N*-alkyl-2-cyano-1-azadienes **86** (Scheme 9.26) [76]; although the reaction had already been performed by heating the reactants in benzene overnight in a sealed tube at 110 °C, it was found that reaction time could be reduced to 14 min in a microwave oven at 650 W.



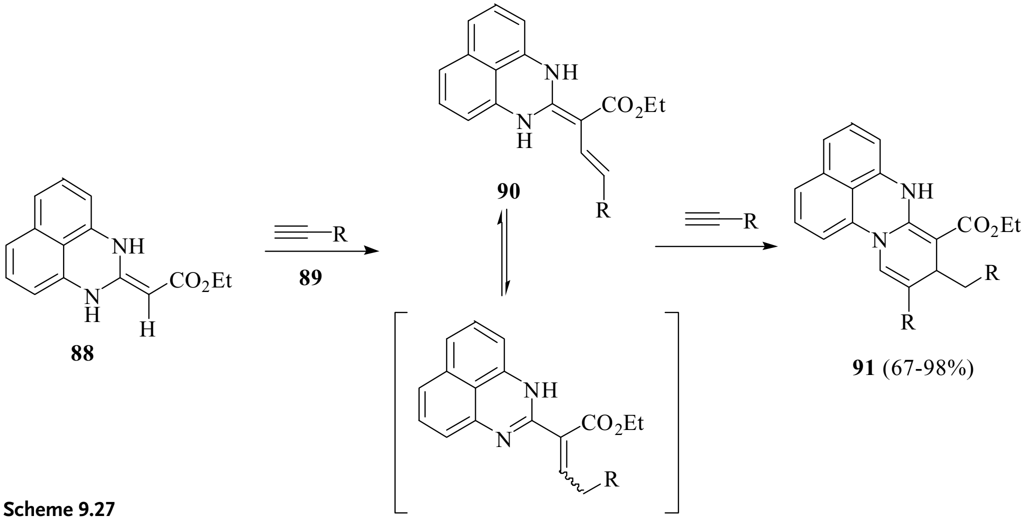
84 **26b** **85** (60%)

Scheme 9.25



86 **87**

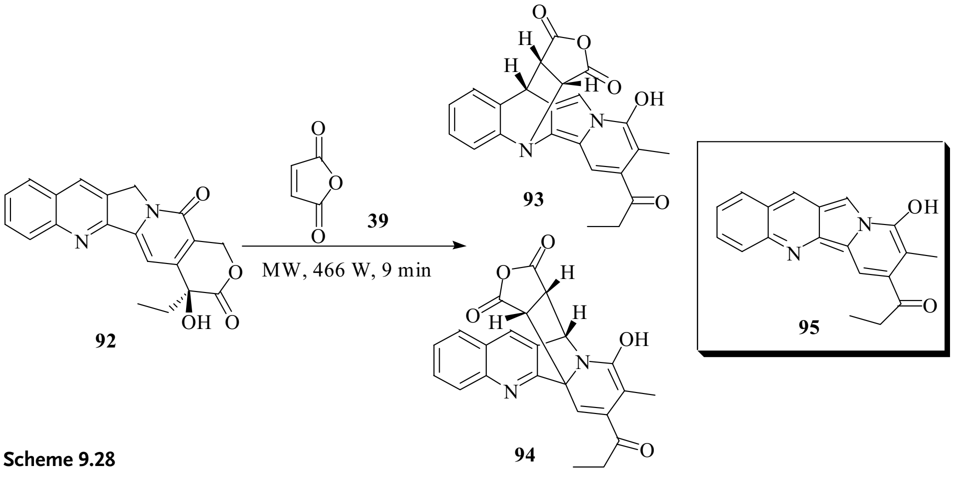
Scheme 9.26



Scheme 9.27

Bazureau described a tandem conjugate addition–intermolecular hetero-Diels–Alder reaction of perimidine derivatives under solvent-free conditions with focused microwave irradiation [77]. The main feature of this reaction was attainment of complete addition in less than 8 min. When the reaction mixture was heated in an oil bath set at the same temperature for the same time the results were analogous (Scheme 9.27).

Das has described the cycloaddition of camptothecin (**92**), an alkaloid with potent antitumor activity, with maleic anhydride under the action of microwave irradiation in a commercial microwave oven for 9 min [78]. Two unprecedented adducts, **93** and **94**, were produced. The first was formed by involvement of the B-ring in a hetero Diels–Alder reaction whereas the second was formed by involvement of the C-ring, probably through Diels–Alder reaction of intermediate **95** (Scheme 9.28).



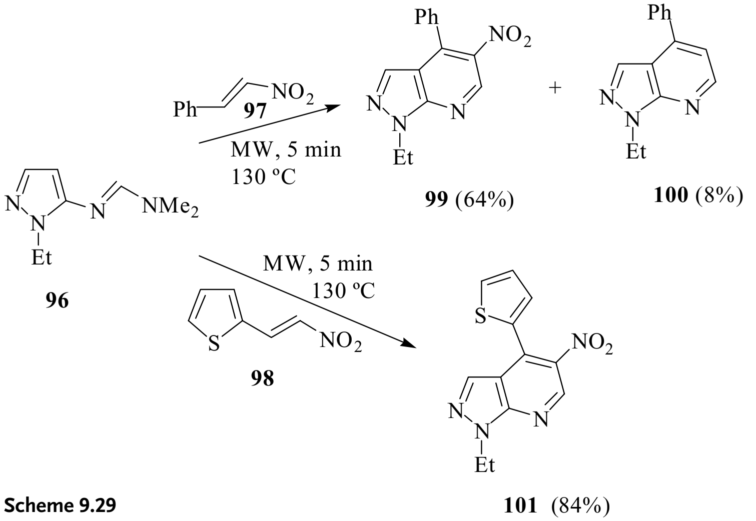
Scheme 9.28

Pyrazole derivatives are very reluctant to participate as dienes in Diels–Alder cycloadditions that involve the pyrazole ring, because of the loss of aromatic character during the process [79]. Microwave irradiation under solvent-free conditions, however, induces pyrazolyl 2-azadienes **96** to undergo Diels–Alder cycloadditions with nitroalkenes **97** and **98** in 5–10 min to give good yields of pyrazolo-[3,4-*b*]-pyridines (Scheme 9.29) [80]. Under the action of classical heating only traces of the corresponding cycloadducts were detected.

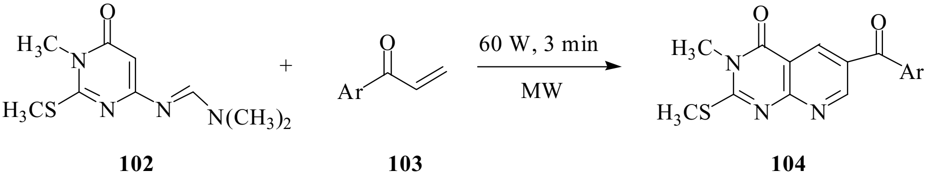
This is the first example of a [4+2] cycloaddition involving a pyrazole ring; it is a new, interesting, and versatile approach to the preparation of pyrazolo-[3,4-*b*]-pyridines.

Later, Quiroga described a similar reaction – the cycloaddition of 2-azadienes derived from pyrazoles and pyrimidones with arylvinylketones **103** as dienophiles (Scheme 9.30) [81].

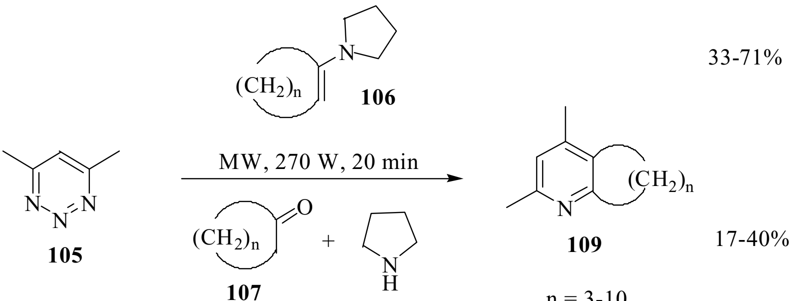
Díaz-Ortiz described the cycloaddition of 4,6-dimethyl-1,2,3-triazine (**105**) with enamines to give condensed pyridine systems [82]. These reactions were performed in a monomode reactor at a power of 270 W for 20 min at 15 °C. The reactions can also be performed with pyrrolidine, with cyclic ketones used as precursors of the enam-



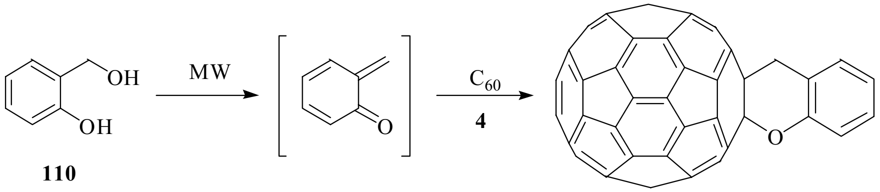
Scheme 9.29



Scheme 9.30



Scheme 9.31



Scheme 9.32

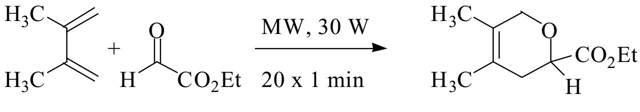
ines. This methodology is a dramatic improvement on the classical method and enables such heterocyclic derivatives to be obtained in good yield (Scheme 9.31).

The reaction of C_{60} with *o*-quinonemethide, prepared from *o*-hydroxybenzyl alcohol (**110**) (Scheme 9.32), was performed in a modified domestic oven at 800 W and gave **111** in 27% yield after only 4 min [72]. Although Eguchi et al. [83] reported the same reaction with a slightly better yield (31%) by thermolysis in a sealed vessel, the microwave approach to this adduct has the advantage of simplicity, and avoids the risks associated with high-pressure conditions.

9.5.3.2 **Heterodienophiles**

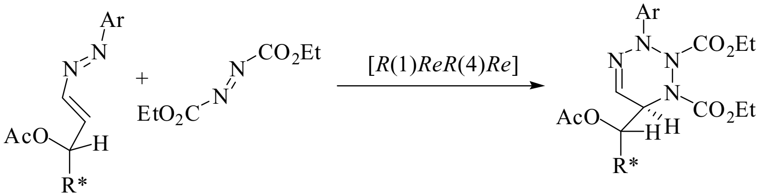
Examples of the use of heterodienophiles under the action of microwave irradiation are not common. Soufiaoui [84] and Garrigues [37] used carbonyl compounds as dienophiles. The first example employed solvent-free conditions; the second is an example of the use of graphite as a susceptor. Cycloaddition of a carbonyl compound provided a 5,6-dihydro-2*H*-pyran derivative. These types of reaction proceed poorly with aliphatic and aromatic aldehydes and ketones unless highly reactive dienes and/or Lewis acid catalysts are used. Reaction of 2,3-dimethyl-1,3-butadiene (**31**) with ethyl glyoxylate (**112**) occurred in 75% yield in 20 min under the action of microwave irradiation. When conventional heating is used it is necessary to heat the mixture at 150 °C for 4 h in a sealed tube to obtain a satisfactory yield (Scheme 9.33).

Jiménez et al. studied the asymmetric Diels–Alder reactions of 1-aryl-1,2-diaza-1,3-butadienes **114**, heterodienes derived from sugars, with diethyl azodicarboxylate (**115**), a heterodienophile [85]. The reactions were performed without solvent in a focused microwave reactor for periods of a few hours. The reaction is stereoselective



31 **112** **113**

Scheme 9.33



114 **115** **116**

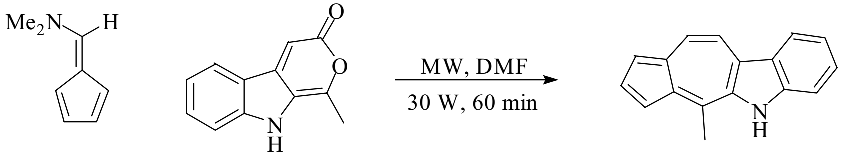
Scheme 9.34

and the major diastereoisomers have the (6*R*)-configuration if the chiral descriptor of the heterodiene at C-1 is *R*. The relative induction arises from the preferential reaction of DEAD with the *Re* face of the azoalkane (Scheme 9.34). This results in a like (*lk*) combination and the stereochemical course can be designated self-consistently as [*R*(1)*ReR*(4)*Re*].

9.5.4
Miscellaneous

Hong described the [6+4] cycloaddition of fulvenes **117** with α-pyrones **118** to give azulene-indoles **119**, which have potential antineoplastic activity [86a]. Reactions were performed in DMF solution by use of a monomode reactor (30 W for 60 min). It is worthy of note that reactions performed using conventional heating require long reaction times (5 days) and give low yields of the final product, along with recovered starting materials and decomposition products (Scheme 9.35).

The same authors showed that microwave irradiation can alter the reaction pathway. Occasionally with conventional heating the Diels–Alder adducts are favored whereas the tandem [6+4]–[4+2] cycloaddition products were obtained exclusively under the action of microwaves [86b].



117 **118** **119** (65%)

Scheme 9.35

9.6
1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions are one of the best and most widely used procedures to prepare five-membered heterocycles. The process involves a concerted reaction between a 1,3-dipole and a multiple-bonded compound.

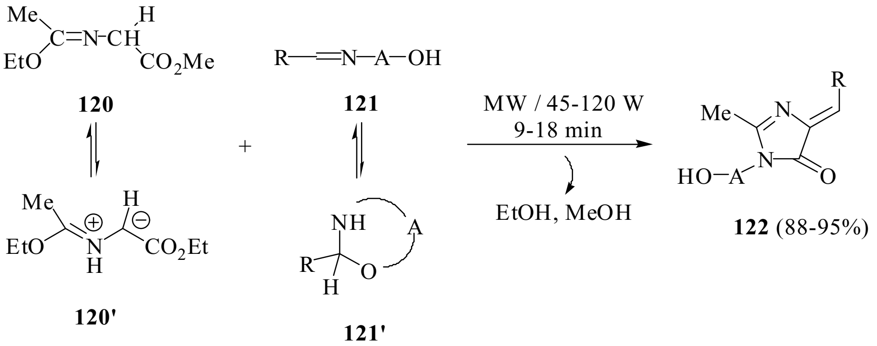
The 1,3-dipole is often very unstable, its formation requires high temperatures and the subsequent cycloadditions require often long reaction times. Both of these conditions result in a decrease in yields and purity of products. The rapid heating induced by microwave irradiation avoids the harsh reaction conditions associated with classical heating and facilitates 1,3-dipolar cycloadditions that are very difficult (or impossible) to achieve with classical energy sources.

In the nineteen-nineties, numerous examples of 1,3-dipolar cycloadditions under microwave heating were reported with a wide variety of dipoles. In many cases the product yields and/or reaction times were improved and the method was used to prepare valuable compounds that could not be obtained by classical heating and, in some instances, the regioselectivity of the reaction was modified. Most of these processes were performed in the absence of solvent.

In the following section the main 1,3-dipolar cycloadditions under microwaves will be reviewed according to the nature of the dipole.

9.6.1
Azomethine Ylides

Microwave-induced 1,3-dipolar cycloadditions involving azomethine ylides have been widely reported in the literature. Bazureau showed that imidates derived from α-amino esters **120**, as potential azomethine ylides, undergo 1,3-dipolar cycloadditions with imino-alcohols **121** in the absence of solvent under microwave irradiation. This reaction leads to polyfunctionalized 4-yliden-2-imidazolin-5-ones **122** (Scheme 9.36) [87].



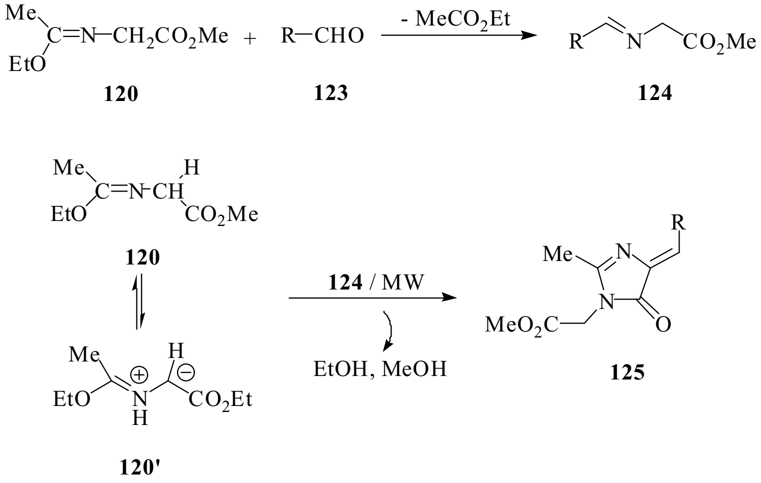
A = Alkyl chain

Scheme 9.36

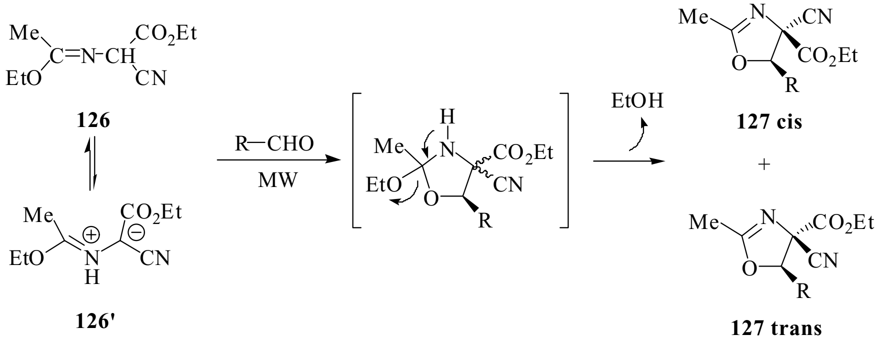
Comparison of this reaction with that performed using classical heating shows an acceleration of the 1,3-dipolar cycloaddition upon irradiation and yield enhancements for the synthesis of imidazolones **122**. These advantages occur by virtue of diminished formation of the byproduct **125** (see Scheme 9.37).

The same authors also investigated the reaction of the imidate **120** and aldehydes **123** with dry acetic acid as a catalyst in the absence of solvent. The mixture was immediately submitted to focused microwave irradiation to afford compounds **125** together with alcohols, ethyl acetate and a small amount of imine **124** (Scheme 9.37) [88].

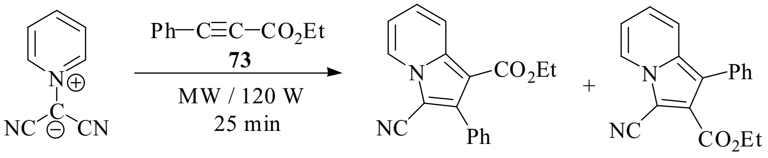
Likewise, imidate **126** undergoes highly regioselective cycloadditions with a wide range of aldehydes – as dipolarophiles – in short reaction times to afford ethyl 4-cyano-2-oxazoline-4-carboxylates **127** in good yields (81–98%) and moderate diastereomeric ratios (Scheme 9.38). The use of microwave radiation gave higher yields than classical heating but the moderate diastereomeric composition was the same [89]. In a similar way, addition of imidate **126** to the dipolarophile *N*-benzylidenemethyl-



Scheme 9.37



Scheme 9.38



130 **131** **132**

	131	132
celite	88	12
bentonite	98	2

Scheme 9.39

amine (**128**) under focused microwaves gave the expected product ethyl 4-cyano-2-methyl-5-phenyl-2-imidazoline-4-carboxylate (**129**) in good yield.

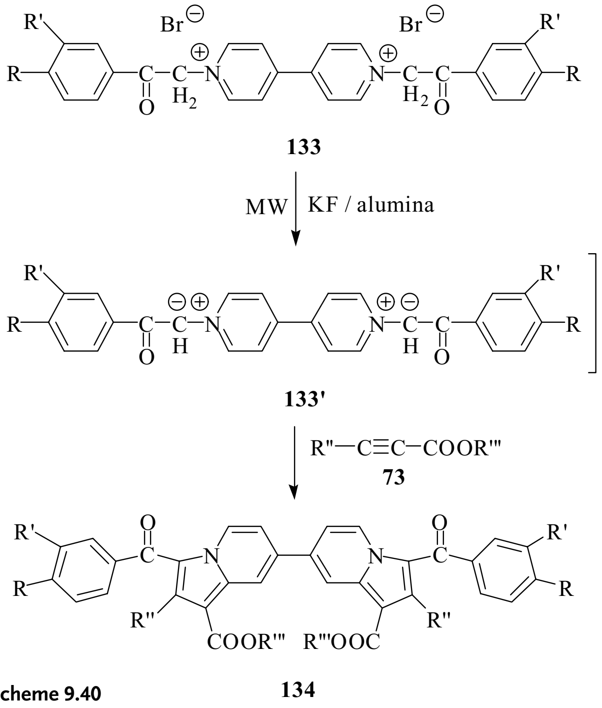
Solid supports such as silica gel and alumina have also been used in the generation of 1,3-dipoles to obtain heterocyclic compounds. However, changes in regioselectivity were not observed under microwave irradiation conditions. The regioselectivity can be modified by changing the polarity of the solid support [90]. De la Hoz reported the reaction of pyridinium dicyanomethylidene ylide (**130**) with ethyl phenylpropiolate (**73**), and found that the selectivity changes from 88:12 to 98:2 when the support is changed from celite, to neutral bentonite (Scheme 9.39).

4,4-Bipyridinium ylides **133**, generated *in situ* from 4,4-bipyridinium diquaternary salts **133**, undergo 1,3-dipolar cycloaddition with activated alkynes under microwaves, on KF–alumina in the absence of solvent, to give 7,7-bis-indolizines **134** in 81–93% yield (Scheme 9.40) [91]. The same reactions, when performed using benzene as a solvent under classical heating, yielded 7,7-bis-indolizine derivatives in yields of only 50–60% [92].

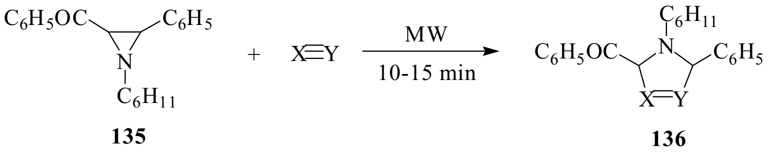
Microwave irradiation in solvent-free conditions induces the cleavage of the 2,3-bond of 2-aroyl-aziridines **135** to give an azomethine ylide intermediate, which subsequently undergoes cycloadditions to a multiple bond and leads to oxazolidine, imidazoline, naphthooxazole and pyrroline derivatives **136** in good yields (Scheme 9.41) [32b]. Reactions were performed at atmospheric pressure in an Erlenmeyer flask placed in a commercial domestic oven. The reactions were complete in 10–15 min while the conventional method requires 18–20 h.

Highly stereoselective intramolecular cycloadditions of unsaturated *N*-substituted azomethine ylides have been conducted under microwave irradiation. Oritani reported that a mixture of the aldehyde **137** and *N*-methyl- or *N*-benzylglycine ethyl ester (**138**) on the surface of silica gel, irradiated under microwaves for 15 min, generated azomethine ylides **139** that subsequently underwent *in situ* intramolecular cycloadditions to afford the corresponding tricyclic compounds **140** in 79 and 81% yield, respectively (Scheme 9.42) [93].

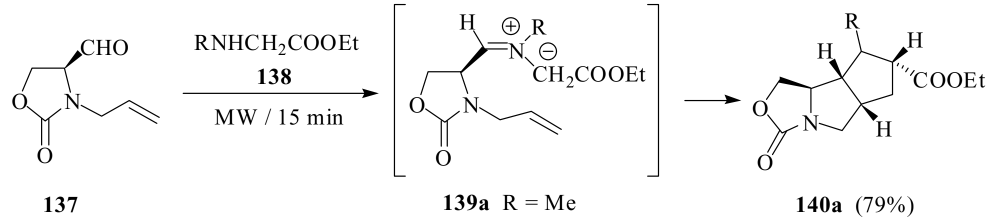
A general method for the functionalization of C_{60} (**4**) is the 1,3-dipolar cycloaddition of azomethine ylides. This process was first described by Prato [94] and leads to fulleropyrrolidines. Several fulleropyrrolidines (**143a–c**) have been prepared under microwave irradiation by Langa et al. [72]. These authors observed that microwave irradiation again competes favorably with thermal heating and, in this way, **143a** was



Scheme 9.40



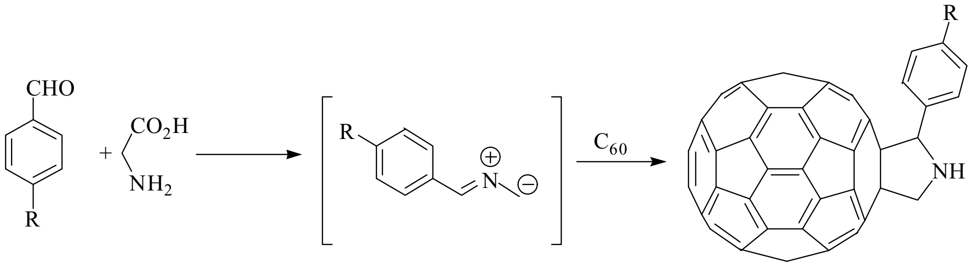
Scheme 9.41



Scheme 9.42

prepared in 37% using a focused microwave reactor. In addition, **143b** and **143c**, which had not been previously been reported, were prepared in 30% and 15% yield, respectively (Scheme 9.43).

Langa also described the cycloaddition of *N*-methylazomethine ylides to C_{70} (**144**) to give three regioisomers (**145a–c**) by attack at the 1–2, 5–6, and 7–21 bonds, respec-



123 **141** **142**

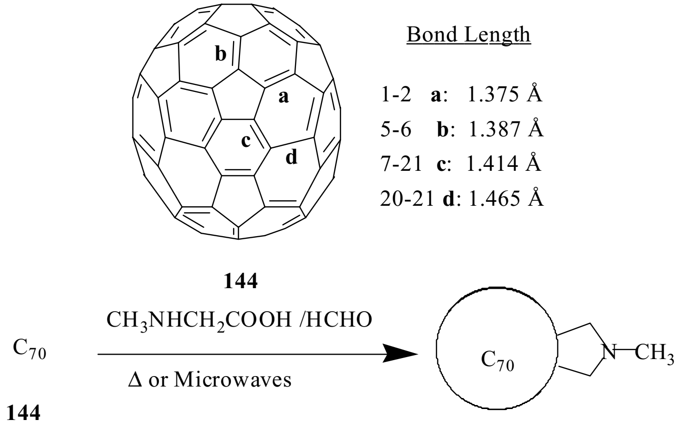
a, R=H; b, R= OMe; c, R= NO_2

143a-c

Scheme 9.43

tively (Scheme 9.44) [43]. Under conventional heating the 7–21 isomer (**145c**) was formed in only a low proportion and the 1–2 isomer (**145a**) was found to predominate. Under microwave irradiation, and on using *o*-dichlorobenzene (ODCB), a polar a solvent that absorbs microwaves efficiently, significant changes were observed. In contrast to classical conditions, **145c** was not formed under microwave irradiation regardless of the irradiation power, and isomer **145b** was found to be predominant at higher power (Scheme 9.44 and Fig. 9.1).

A computational study on the mode of cycloaddition showed that the reaction is stepwise, the first step consisting of a nucleophilic attack on the azomethine ylide. The most negative charge of the fullerene moiety in the transition states leading to **145a** and **145b** are located at the carbon adjacent to the carbon–carbon bond being formed. In the transition state that affords **145c**, however, the negative charge is delocalized all around the C_{70} subunit. The relative ratio of isomers **145a–c** is related to the greatest hardness, and the formation of the product along the harder transition state should be favored under microwave irradiation. It is noteworthy that purely



Bond Length

1-2 **a**: 1.375 Å
5-6 **b**: 1.387 Å
7-21 **c**: 1.414 Å
20-21 **d**: 1.465 Å

144

144

Scheme 9.44

145a, b, c

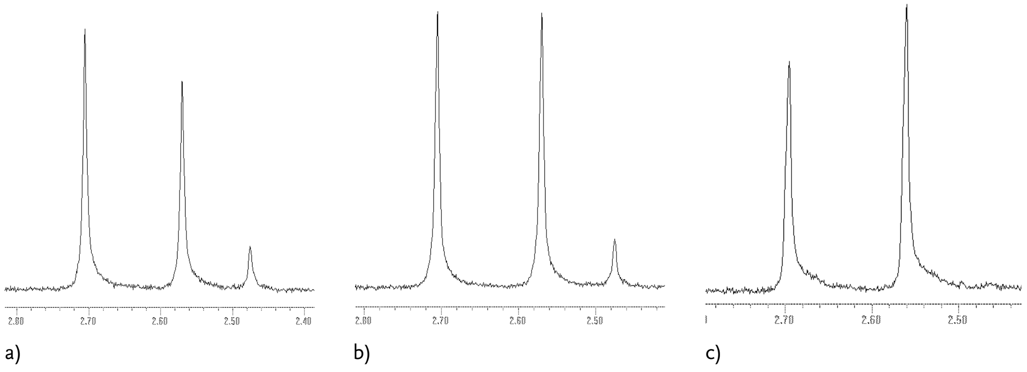


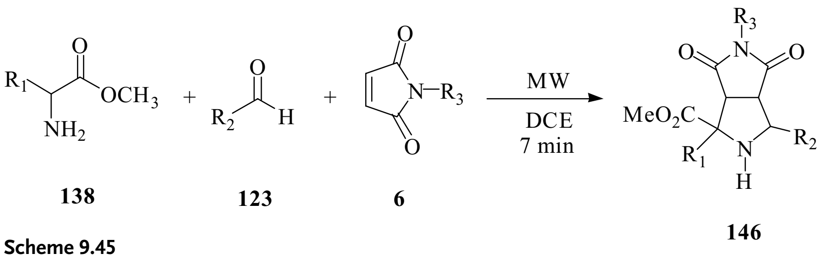
Fig. 9.1 ^{1}H NMR spectra (methyl groups) of the adducts **145a**, **145b**, and **145c** from left to right. (a) classical heating in toluene; (b) classical heating in ODCB; (c) microwave irradiation at 180 W in ODCB.

thermal arguments predict the predominance of **145c** under microwave irradiation, which is opposite to the result found experimentally.

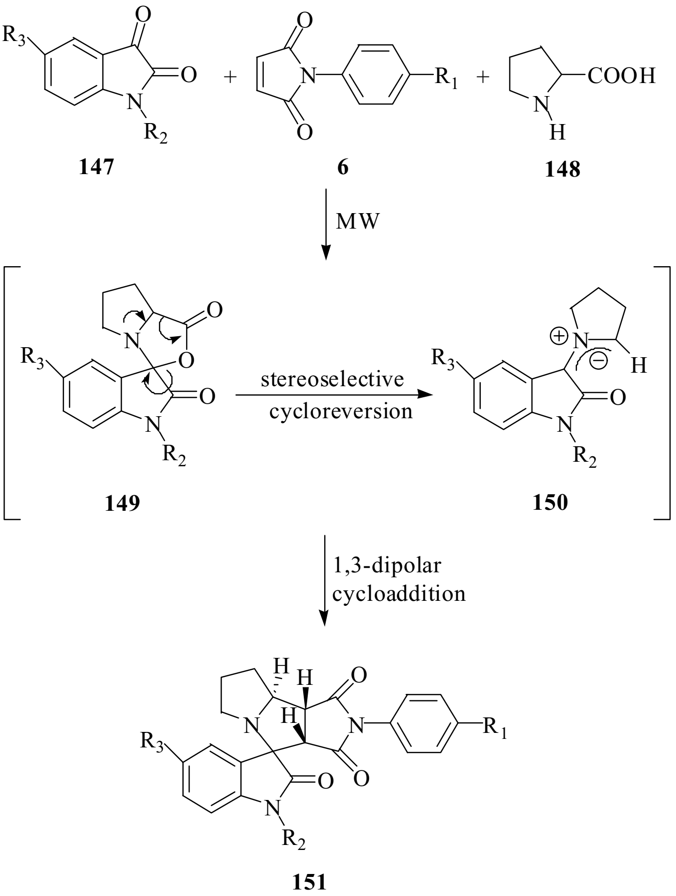
Recently, a novel method for the synthesis of a library of substituted prolines with microwave technology [95] has been described. In the first step, 1 equivalent of an amine is added to 1.1 equivalents of an aldehyde in 1,2-dichloroethane (DCE), with subsequent irradiation at 180 °C for 2 min. In the second step, 0.85 equivalents of the maleimide are added and the resulting solution is heated at 180 °C for an additional 5 min. This methodology allowed the production of a solution-phase library of 800 compounds with a crude purity between 65 and 82% (Scheme 9.45). The compounds were purified by solid-supported reagent scavenging to afford the final products with a purity between 90 and 98% and in 79–85% yield [96].

Also in 2001, Azizian described a one-pot diastereoselective synthesis of 2-substituted 1,1,2,3,3aα,3bβ,4,5,6,8,8aα-decahydro-8-(spiro-3-indolino-2-one)pyrrolo[3,4-*b*] pyrrolizine-1,3-dione (**151**) in good yield and diastereomeric excess using microwave irradiation (Scheme 9.46).

Isatin derivatives and proline react to give stereospecific formation of an azomethine ylide intermediate via the decarboxylation route. The resulting 1,3-dipole undergoes a cycloaddition reaction with *N*-substituted maleimide (**6**), as a dipolaro-



Scheme 9.45



Scheme 9.46

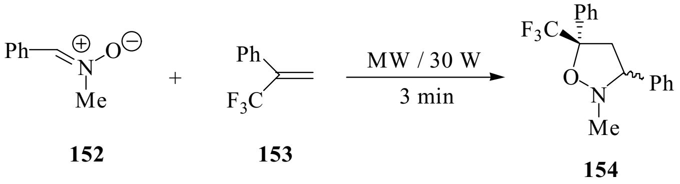
phile, to produce the adduct stereoselectively [97]. It is noteworthy that the adduct has five chiral centers, but the synthesis affords only one diastereoisomer owing to the dipole configuration and *exo*-transition state structure.

9.6.2
Nitrones

Inter- and intramolecular 1,3-dipolar cycloadditions of nitrones under microwave irradiation have been reported to give heterocyclic derivatives.

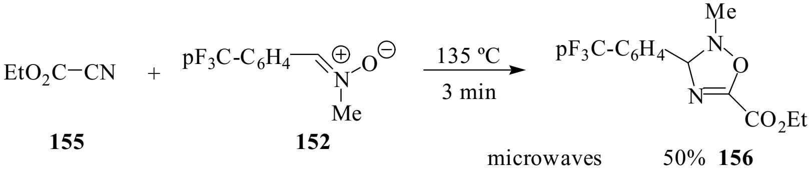
Sandhu reported that conjugated nitrones react with unactivated alkenes under microwave activation more rapidly (6–15 min) than in the corresponding thermolytic or sonochemical reactions [32a].

Likewise, Loupy showed the utility of focused microwaves as an energy source in the 1,3-dipolar cycloaddition of *N*-methyl-α-phenylnitrone (**152**) with fluorinated dipolarophiles in solvent-free conditions (Scheme 9.47) [98].



152 **153** **154**

Scheme 9.47



155 **152**

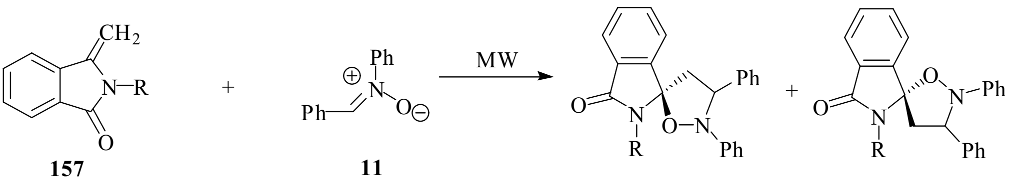
microwaves 50% **156**
classical heating 17%

Scheme 9.48

Microwave irradiation induces 1,3-dipolar cycloadditions of nitrones, such as **152**, with aliphatic and aromatic nitriles in the absence of solvent. The products of these reactions are the corresponding 2,3-dihydro-1,2,4-oxadiazoles **156** (Scheme 9.48). The use of microwaves led to yields that were always higher than those obtained with classical heating, with the differences being more significant with the less reactive nitriles [99].

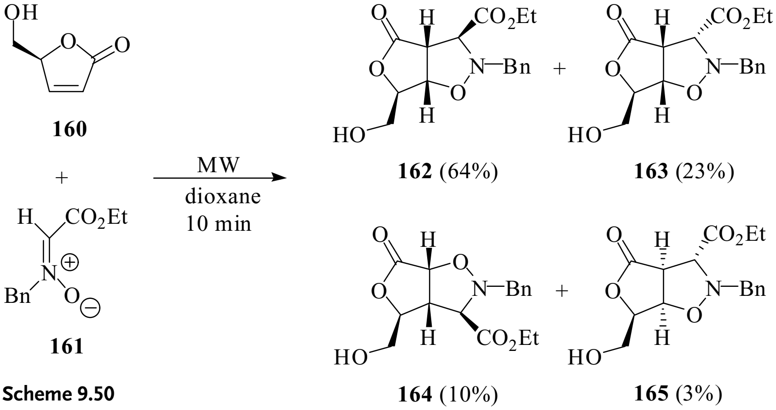
3-Methylene-*N*-substituted isoindolones **157** react with *N*-arylnitrones, such as **11**, to give the diastereomeric spiro[1*H*-isoindol-1,5(4*H*)-isoxazol] -7(6*H*)-ones **158** and **159** (Scheme 9.49). These cycloadditions can be performed using classical heating, although both starting materials and spiro adducts are particularly sensitive to overheating. This situation explains the fact that the kinetics and yields improve when a mixture of **157** and **11** were subjected to microwave irradiation [100].

Cycloaddition of the nitrone **161** to the lactone **160** in boiling benzene for 6 h gave a 53 : 37 : 10 mixture of the three optically active adducts **162–164** in 66% combined yield (Scheme 9.50). Formation of the diastereoisomers **162–164** can be rationalized in terms of a highly preferred *anti* approach of the nitrone to the hydroxymethyl group in the transition state. The isomer ratio in the adducts was found to be dependent upon the solvent used in the reaction. Optimization of the reaction or the diastereoselectivity by Lewis acid catalysis failed. However, attempts to accelerate the cycloadditions by microwave irradiation, using 1,4-dioxane as the solvent, were successful and the reaction time decreased from hours to less than 10 min with only a



157 **11** **158** **159**

Scheme 9.49

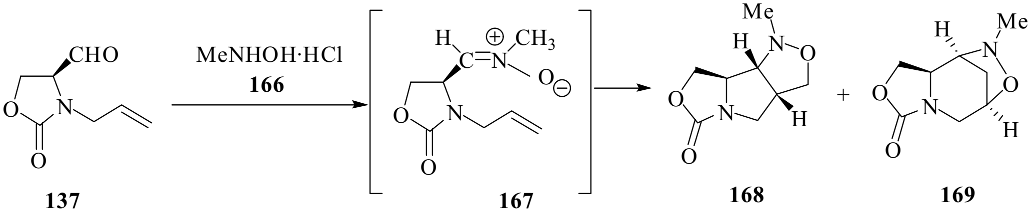


Scheme 9.50

small change in the stereoselectivity (in favor of the *exo*-**162** isomer). Moreover, the use of microwaves also led to the formation of a small amount of the unexpected *syn* adduct **165** [101].

When the aldehyde **137** and *N*-methylhydroxylamine (**166**) were mixed with silica gel and irradiated with microwaves for 15 min the adduct obtained was **168** (82% yield). A mixture of **137** and *N*-methylhydroxylamine (**166**) in alcohol, heated at 120 °C in a sealed tube, afforded the products **168** and **169** in an 8 : 1 ratio (Scheme 9.51) [93]. The authors proposed that the selectivity observed in the microwave-induced reaction results from a faster transformation leading to the kinetically controlled product.

In a recent study, classical heating, microwave radiation and gamma radiation have been compared as energy sources to perform 1,3-dipolar reactions between unsaturated oximes and conventional dipolarophiles. On using gamma radiation the reactions were clean and yields obtained were similar to those for the thermal reactions. However, microwave radiation reactions were extremely clean, occurred more rapidly and gave higher yields [102].



	168	169
Microwaves / silica gel - 15 min	100	0
$NaHCO_3$ / EtOH 90% reflux	88.9	11.1

Scheme 9.51

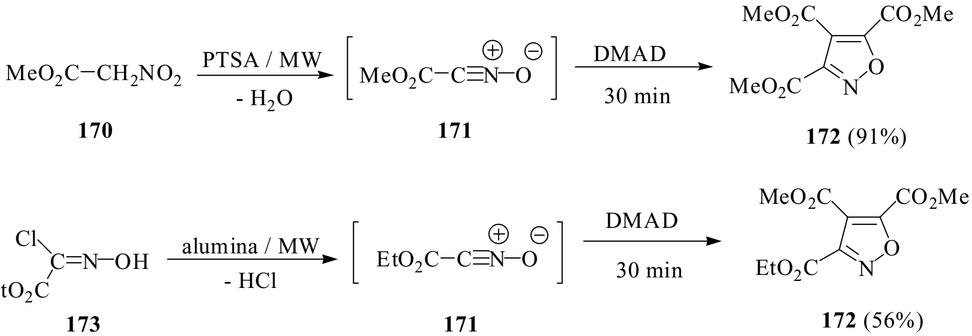
9.6.3
Nitrile Oxides

Microwave irradiation has been extensively employed to generate nitrile oxides and to promote 1,3-dipolar cycloadditions of the previously prepared dipole.

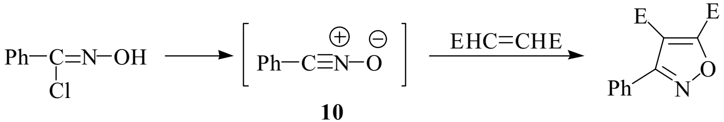
The first application of microwave irradiation in conjunction with dry media in the generation of nitrile oxide intermediates was reported by Hamelin [29]. In this example, methyl nitroacetate (**170**) was mixed with a dipolarophile in the presence of catalytic amounts of toluene-*p*-sulfonic acid (PTSA) (10% weight). Subsequent microwave irradiation led to the formation of the corresponding heterocyclic adducts (Scheme 9.52). Reactions were performed in an open vessel from which water was continuously removed [103]. Likewise, irradiation in a domestic oven of a mixture of ethyl chloro(hydroxyimino)acetate (**173**) and a dipolarophile over alumina led to the same results in only a few minutes (Scheme 9.52) [103].

In 1999 Hamelin and Benhaoua reported a comparative study between dry media conditions and the procedure in homogeneous solution under microwaves and classical heating [104]. Reactions undertaken with aromatic oxime chlorides **174** over alumina, without solvent and under microwaves, showed that alkynes and disubstituted alkenes give moderate yields of cycloadducts (40–60%). The corresponding procedure with trisubstituted alkenes did not give any products. These reactions were also performed in the presence of *N*-methylmorpholine (NMM) in xylene at 130 °C during 30 min under focused microwaves. The same products were obtained in these cases and the yields were better than for the reactions in dry media. The use of classical heating resulted in worse yields in all cases (Scheme 9.53).

Soufiaoui reported that arylnitrile oxides **10** can be generated under microwaves not only from aromatic oxime chlorides, such as **174**, by the action of alumina (Method A) but also from aryloximes, such as **176**, by the addition of a chlorination agent, *N*-chlorosuccinimide (NCS), supported on alumina (Method B) (Scheme 9.54) [29 a]. Both methods afforded identical cycloadducts in similar yields – when indene was used as the dipolarophile the yield was 86%. In the absence of alumina, method B fails (reagents are less reactive and decompose) and method A does not yield any cycloadduct but a dimer of the dipole.



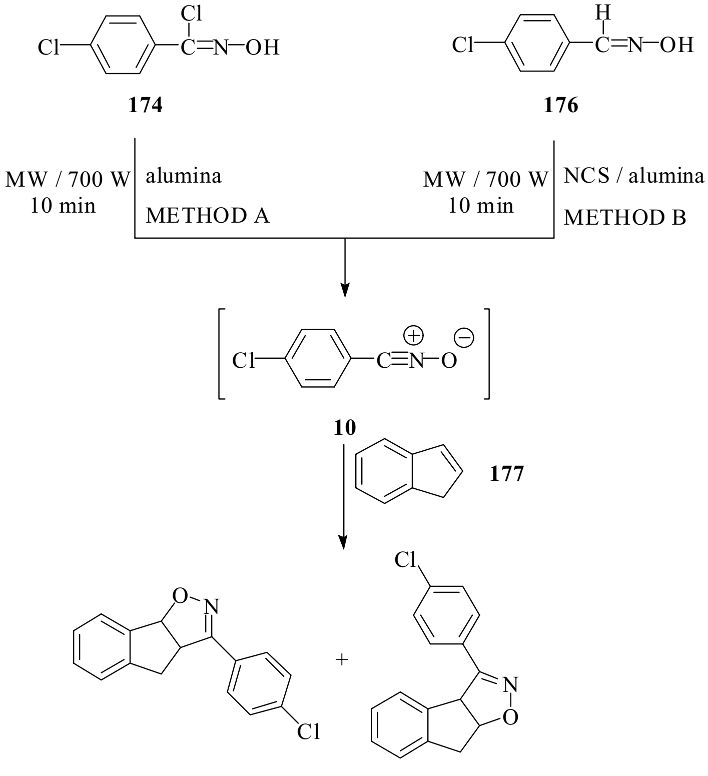
Scheme 9.52



174 **10** **175**

alumina / neat / MW / 30 min	60%
NMM / xylene / MW / 130 °C, 30 min	65%
classical heating	30%

Scheme 9.53

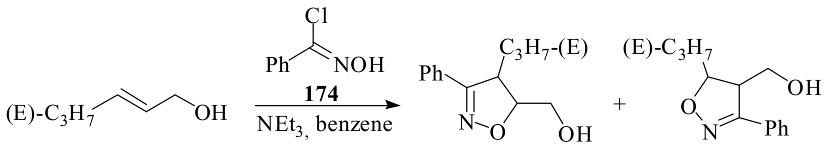


174 **176** **10** **177**

Scheme 9.54 **178** **179**

The application of microwaves to the cycloaddition reactions of allyl alcohols **180** with nitrile oxides not only achieved a substantial reduction of the reaction time and an improvement of the adduct yields, but also altered the regioselectivity of the cycloaddition in favor of the nonhydrogen bond-directed cycloadduct **182** (Scheme 9.55) [105].

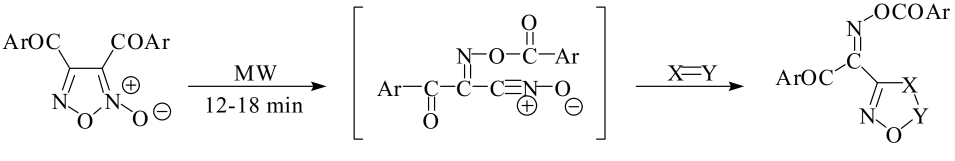
Aroylnitrile oxides can also be generated from diaroyl furoxans **183** under microwave irradiation [33]. Formation of the nitrile oxide intermediate **184** and its cycloaddition with dipolarophiles proceeds at atmospheric pressure within minutes in the absence of solvent and in good yields (Scheme 9.56). The reaction occurs by the rear-



180 **181** **182**

classical method:
50 h, r. t. (54% yield) 57 : 43
microwave irradiation:
400 W, 2 min (53% yield) 46 : 54

Scheme 9.55



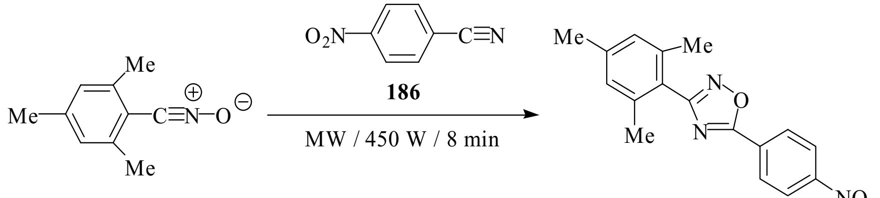
183 **184** **185** (55-65%)

Scheme 9.56

rangement of dibenzoylfuroxan **183** and intramolecular transfer of the benzoyl group to afford the nitrile oxide intermediate **184**. The presence of the polar $N^+–O^-$ functionality in the furoxans and nitrile oxides increases the efficiency of the microwaves.

Díaz-Ortiz described the microwave-induced 1,3-dipolar cycloadditions of the mesitonitrile oxide **10** with aliphatic and aromatic nitriles in solvent-free conditions [99]. The procedure allowed the corresponding heterocyclic adducts, the 1,2,4-oxadiazoles **187**, to be obtained in a domestic oven. The reaction times were shorter and the yields better than those seen with the classical homogeneous reactions (Scheme 9.57).

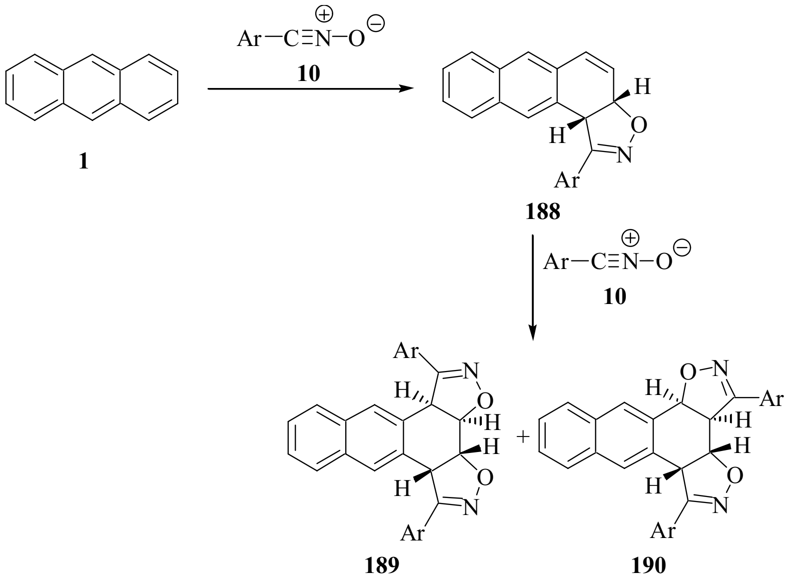
Corsaro reported the cycloaddition of previously prepared nitrile oxides **10** with aromatic polycyclic compounds as dipolarophiles under microwaves and in the absence of solvent (Scheme 9.58) [106]. The same cycloadducts were obtained as in the



10

187 (68%)
classical heating, 48% yield

Scheme 9.57



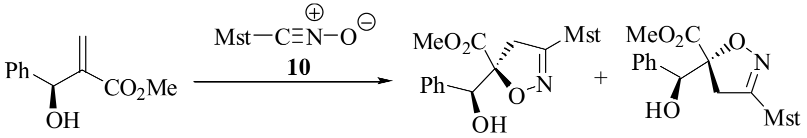
	Products (yield, %)
Classical heating with solvent 24 h in refluxing toluene	**188** (15.7) + **189** (traces) + **190** (4.6)
Microwave irradiation 650 W, 6 min	**188** (11) + **189** (10.2) + **190** (32.7)

Scheme 9.58

case with classical heating and, moreover, the symmetrical bis-cycloadduct **189** was also isolated. Reaction times were shortened from 24 h to 3–10 min and yields of cycloadducts increased by a factor of 3–7 on changing from heating at reflux to microwave irradiation. The highest yields of bis-cycloadducts suggested that these could be because of the effect of the lowest temperature used in classical heating. An attempt to perform the reaction under reflux in decalin failed, however, because the 1,3-dipole underwent degradation rather than cycloaddition.

Methylmagnesium bromide (**191**) exerts a great influence on the stereoselectivity of the reactions between mesitonitrile oxide **10** and the Baylis–Hillman adducts **192**. In the absence of a Grignard reagent, a mixture of isomers is formed in which compounds **194** are the main products. The presence of a Grignard reagent reverses the stereoselectivity (Scheme 9.59). When Fišera [107] performed these reactions under microwave irradiation, the reaction times decreased from days to less than 5 min without any loss of stereoselectivity for noncatalyzed cycloadditions, but with a small change in the stereoselectivity in the chelated reactions.

Nitrile oxides have been used in conjunction with microwaves in the field of fullerene chemistry. For example, 3-(*N*-phenylpyrazolyl)isoxazolo[60]fullerene dyads **198**



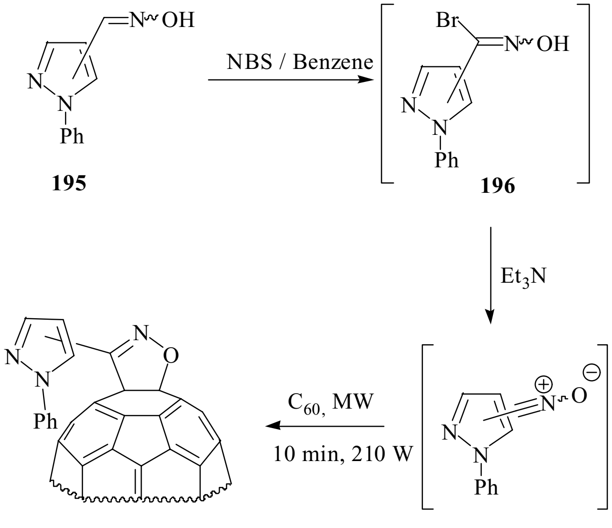
192 **193** **194**

Entry	Solvent	Lewis acid	Reaction time	Reaction temp.	Yield (%)	Ratio 193 : 194
1	toluene	---	4 h	80 °C	92	42 : 58
2	chlorobenzene	---	1.5 min	MW	99	43 : 57
3	dichloromethane	MeMgBr	24 h	r. t.	57	61 : 39
4	chlorobenzene	MeMgBr	4 min	MW	40	70 : 30

Scheme 9.59

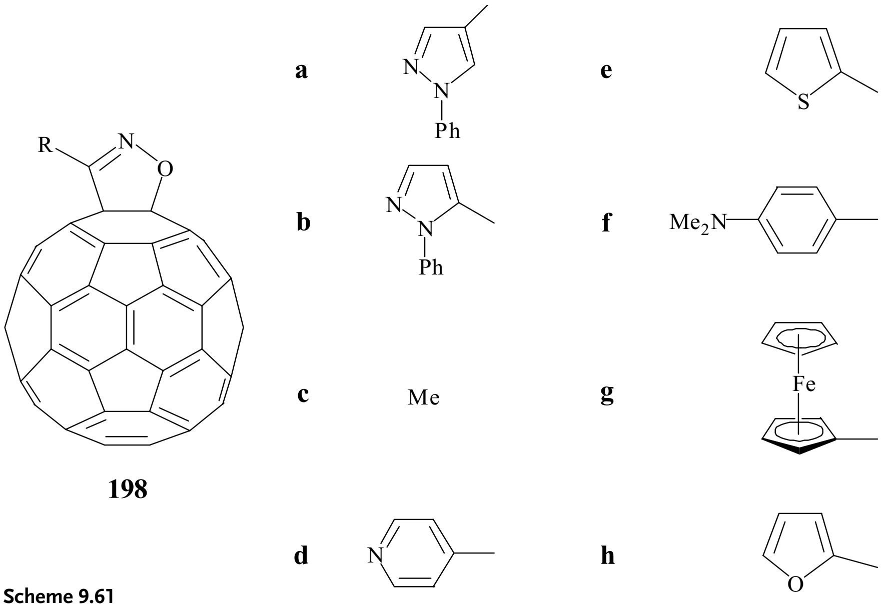
have been prepared in 22% yield from the corresponding nitrile oxides (Scheme 9.60) [108]. Longer reaction times afforded larger amounts of bis adducts. The same reactions under thermal conditions produced markedly lower yields (14–17%). A significant accelerating effect (10 min compared with 24 h) is observed on using microwave irradiation.

The scope of the reaction has been demonstrated by the preparation of a series of isoxazolo[60]fullerenes **198** (Scheme 9.61) [109]. The nitrile oxides were prepared from the corresponding oximes by reaction with NBS or NCS and subsequent treatment of the mixture with triethylamine under microwave irradiation.



195 **196** **197** **198** (22%)

Scheme 9.60



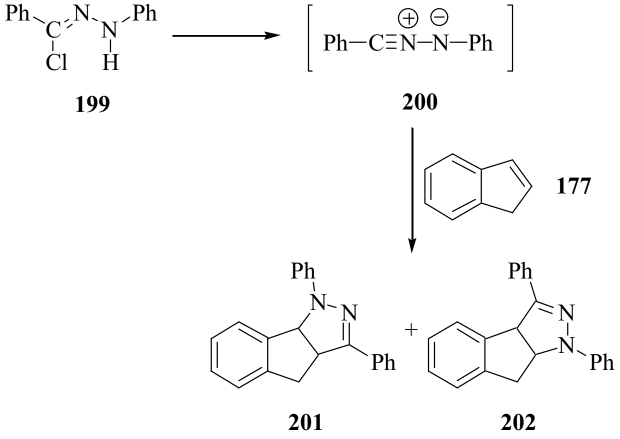
Scheme 9.61

9.6.4
Nitrile Imines

Loupy and Soufiaoui described a comparative study of the reactivity of diphenylnitrilimine **200** with several dipolarophiles under microwave irradiation in the absence of solvent using a solid mineral support or phase-transfer catalysis (PTC) conditions (Scheme 9.62) [30b]. The results showed that the best yields of adducts were achieved upon impregnating KF–alumina with a mixture of the hydrazynoyl chloride **199** and the dipolarophile followed by irradiation of the mixture in a focused oven. Reaction of this mixture under solid–liquid PTC conditions with KF-Aliquat under microwaves afforded lower yields of cycloadducts, perhaps owing to the partial decomposition of Aliquat at the reaction temperature (140 °C). In all cases, worse yields were obtained by classical heating under comparable reaction conditions (time and temperature).

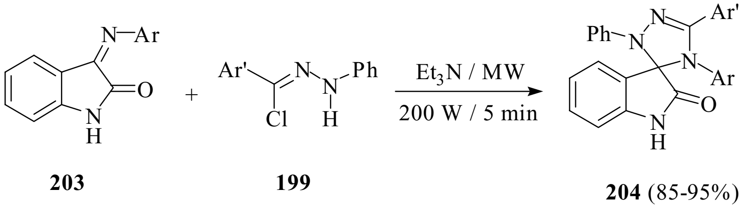
Spiro[3*H*-indole-3,5(4*H*)-(1,2,4)triazoline]-2-one derivatives **204** have been obtained using microwave irradiation in the reaction between imines of isatin **203** and nitrile imines generated *in situ* from the corresponding hydrazonyl chlorides **199** (Scheme 9.63). The yields are in the range 85–95% and the reaction is complete within 5 min [110]. Similar reactions performed under thermal conditions were complete in 6–10 h and yields decreased to 20–30%. However, when the reaction was performed at ambient temperature, the products were obtained in excellent yields but only after a prolonged reaction time (30 h).

As mentioned in Sect. 9.6.3., a comparative study between dry media conditions and reactions in homogeneous solution under microwave irradiation has shown that



Entry	Reaction time (min)	Technique	Yield (%)	Ratio 201 : 202
1	20	MW (domestic oven)	96	93 : 7
2	5	MW (focused oven)	98	94 : 6
3	3	PTC solid-liquid	68	93 : 7
4	5	classical heating, 165 °C	traces	---

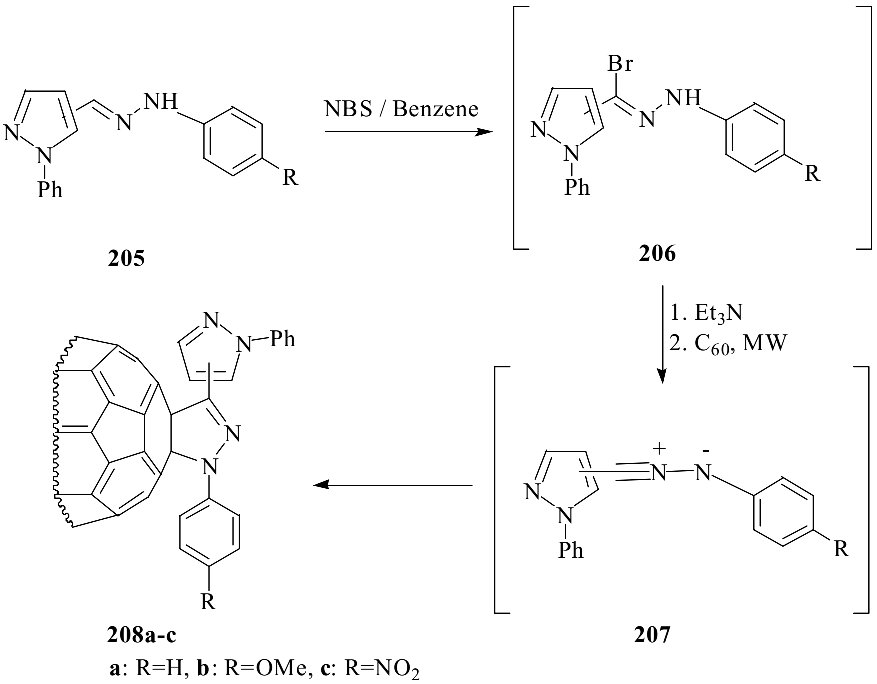
Scheme 9.62



Scheme 9.63

nitrile imines are generated and react with several dipolarophiles. These reactions appear better in homogeneous solution in xylene in the presence of *N*-methylmorpholine (NMM) under focused microwaves than in dry media [104]. In any case, both methods afford better yields of cycloadducts than the corresponding reactions under classical heating.

The formation of several pyrazolylpyrazolino[60]fullerene adducts (**208a–c**) from nitrile imines have been described (Scheme 9.64) [111]. The nitrile imines are generated *in situ* from the corresponding hydrazone **205** and NBS in the presence of Et_3N



Scheme 9.64

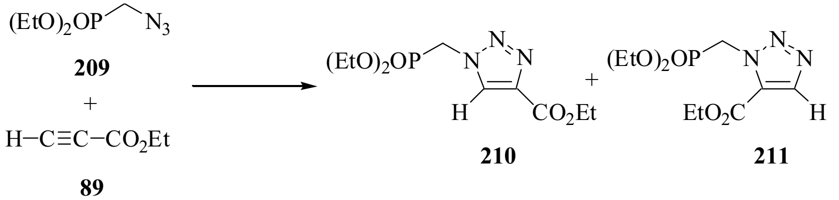
and reacted with C_{60} (4) under microwave irradiation. This approach has also been used to obtain a 2-pyrazoline ring fused to C_{60} in a one-pot process from the hydrazone. The route is simpler than the previously described method, which involved cycloaddition of C_{60} to nitrile imines prepared from the corresponding *N*-chlorobenzylidene derivatives [112].

This route has been used to prepare fullerodendrimers in 31–34% yield [113].

9.6.5
Azides and Azomethine Imines

Other 1,3-dipoles, such are azides and azomethine imines, have also been employed in microwave-induced cycloadditions. The main results reported are reviewed in this section.

1,2,3-Triazole derivatives are very interesting compounds that can be prepared by 1,3-dipolar cycloadditions between azides and alkynes. Loupy and Palacios reported that electron-deficient acetylenes react with azidoethylphosphonate **209** to form the regioisomeric substituted 1,2,3-triazoles **210** and **211** under microwaves in solvent-free conditions (Scheme 9.65) [114]. This procedure avoids the harsh reaction conditions associated with thermal cycloadditions (toluene under reflux) and the very long reaction times.

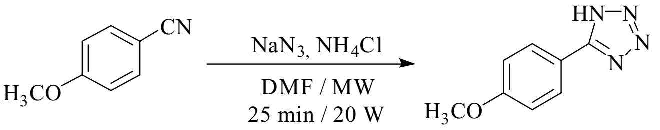


Entry	Reaction temp. (°C)	Reaction time	Solvent	Technique	Yield (%)	Ratio 210 :211
1	110	30 h	toluene	classical heating	86	75 : 25
2	100	48 h	---	classical heating	98	88 : 12
3	100	5 min	---	classical heating	70	75 : 25
4	100	5 min	---	MW	92	66 : 34

Scheme 9.65

Aryl and vinyl nitriles have been prepared very efficiently from the corresponding bromides by palladium-catalyzed reactions under microwaves. This energy source has been employed for the conversion of these nitriles into aryl and vinyl tetrazoles by cycloaddition reactions with sodium azide (Scheme 9.66). The direct transformation of aryl halides to the aryl tetrazoles in a one pot procedure could be accomplished both in solution and on a solid support [115]. The reactions were complete in a few minutes, a reaction time considerably shorter than those previously reported for the thermal reactions. The cycloadditions were performed with sodium azide and ammonium chloride in DMF and, although no explosion occurred in the development of this work, the authors point out the necessity of taking adequate precautions against this eventuality.

The thermal hydrazone–azomethine imine isomerization can be easily performed under microwave irradiation in the absence of solvent. The subsequent 1,3-dipolar cycloadditions with electron-deficient dipolarophiles occur in only a few minutes to afford the corresponding cycloadducts. The use of pyrazolyl hydrazones **205** leads to valuable compounds, such as bipyrazoles **213**, in good yields and this provides a new approach to the preparation of these heterocyclic derivatives [116] (Scheme 9.67). Reactions undertaken with classical heating under comparable reaction conditions (time and temperature) lead to cycloadduct yields that are considerably lower and, indeed, several dipolarophiles do not react at all.

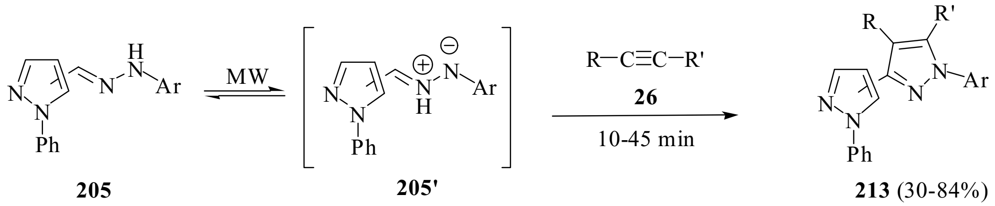


186

212 (96%)

Scheme 9.66

thermal heating, 24 h, 68% yield



Scheme 9.67

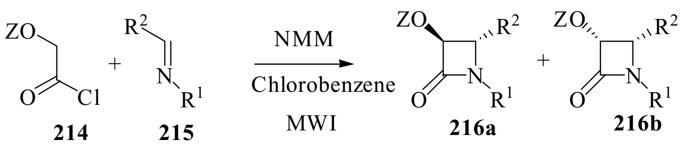
9.7
[2+2] Cycloadditions

[2+2] Cycloadditions give rise to four-membered rings. Thermal concerted [2+2] cycloadditions have to be antarafacial on one component and the geometrical and orbital constraints thus imposed ensure that this process is encountered only in special circumstances. Most thermal [2+2] cycloadditions of alkenes take place by a stepwise pathway involving diradical or zwitterionic intermediates [1a]. Considerably fewer studies have been performed regarding the application of microwave irradiation in [2+2] cycloadditions than for other kinds of cycloaddition (*vide supra*). Such reactions have been commonly used to obtain β-lactam derivatives by cycloaddition of ketenes with imines [18–20, 117, 118].

In 1991 Bose described the synthesis of α-vinyl β-lactams by reaction of α,β-unsaturated acyl chlorides with a Schiff base in chlorobenzene under microwave irradiation (an example of the "eco-friendly" MORE chemistry, in which only a limited amount of solvent is used) [20b]. Under these conditions, α-vinyl β-lactam formation can be achieved in 65–70% in approximately 5 min (classical conditions require several hours and lead only to modest yields).

This methodology has also been used by Bose, who described the synthesis of the thienamycin side chain [119], the first step of which was a [2+2] cycloaddition under microwave irradiation. Likewise, Khajavi described the reaction of trichloroacetic anhydride with imines [120]; with classical heating the reaction requires the use of $Fe_2(CO)_9$ as a catalyst, whereas under microwave irradiation a catalyst is not required.

Bose has described reactions between acid chlorides **214** and Schiff bases **215** where the stereoselectivity depends on the order of addition of the reagents (Scheme 9.68) [117]. When the condensation was conducted by a "normal addition" sequence (i.e. acid chloride last), only the *cis* β-lactam (**216b**) was formed. However,



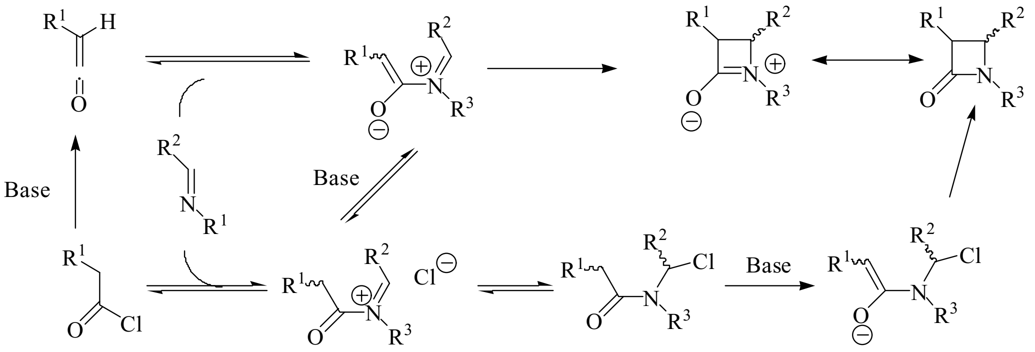
Scheme 9.68 Z = $COCH_3$, Ph, $R_1 = CH_2Ar$, R_2 = Ar NMM: N-methylmorpholine

if the “inverse addition” technique (triethylamine last) was used, 30% *cis* and 70% *trans* β-lactams were obtained under the same conditions. When the reaction was conducted in a microwave oven using chlorobenzene, the ratio of *trans* and *cis* β-lactams was 90 : 10 irrespective of the order of addition. Moreover, there was no isomerization to the thermodynamically more stable *trans* β-lactam (**216a**). These data can be rationalized by assuming that at higher reaction temperatures the rate of formation of the *trans* β-lactam is faster than that of the *cis* β-lactam [20].

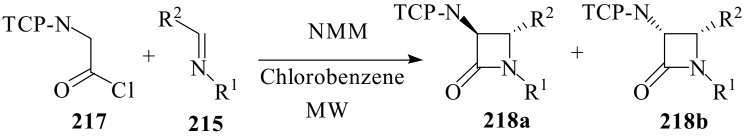
This effect has recently been explained by considering that under microwave irradiation the route involving direct reaction between the acyl chloride and the imine competes efficiently with the ketene–imine reaction pathway, a situation highlighted by theoretical calculations (Scheme 9.69) [42 a].

A rapid approach to α-amino β-lactams has been developed by Bose and uses the tetrachlorophthalimido group as a masked amino substituent (Scheme 9.70) [118]. The *trans* β-lactam **218a** could be obtained almost exclusively in 98% yield after 3–5 min under strong microwave irradiation. Under classical conditions the *cis* isomer (**218a** : **218b** = 10 : 90) is obtained in 52% yield.

N-(4-hydroxycyclohexyl)-3-mercapto-3-cyano-4-arylazetidine-2-ones were synthesized from *N*-(4-hydroxycyclohexyl)aryldiimine by reaction with ethyl α-mercapto-α-cyanoacetate on basic alumina under microwaves. The reaction time was reduced from hours to minutes in comparison to conventional heating and, moreover, the yield was improved [121].



Scheme 9.69



$R_1 = R_2 =$ *p*-methoxyphenyl

NMM: N-methylmorpholine, TCP: Tetrachlorophthaloyl

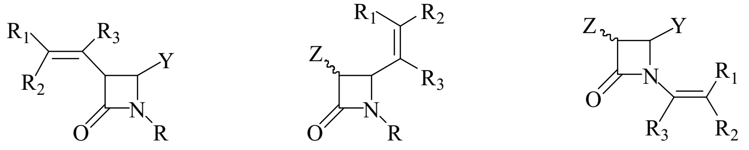
Scheme 9.70

Several eco-friendly approaches to vinyl-β-lactams (**219–221**) bearing a vinyl substituent at various positions on the ring (Scheme 9.71) have recently been described by Manhas [122]. Vinyl-β-lactams are efficient synthons for a variety of compounds of biomedical interest, e.g. isocephalosporins, carbapenem intermediates and pyrrolidine alkaloids. MORE chemistry techniques allow highly accelerated syntheses using limited amounts of solvent and with efficient stereocontrol, thus achieving high "atom economy".

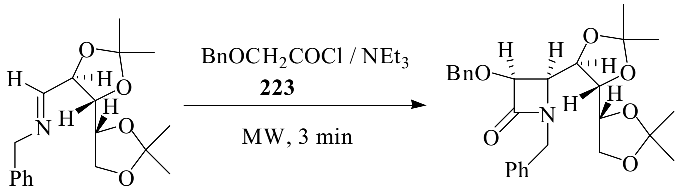
The same group has developed the enantiospecific synthesis of α-hydroxy β-lactams **224** from readily available carbohydrates (Scheme 9.72) [123]. Microwave-assisted chemical reactions have been utilized for the preparation of these 3-hydroxy-2-azetidinones **224** and their subsequent conversion to enantiomeric forms of intermediates for natural products.

The one-pot synthesis of β-lactams containing the ferrocene moiety **226** (Scheme 9.73) was described by Bonini [124]. The reactions were performed under classical heating (3.5–24 h) and/or by using a focused microwave reactor (4–6 min). In this case, the stereochemical outcome of the reaction is the same with both procedures and microwave irradiation does not necessarily improve on the yields obtained by classical heating.

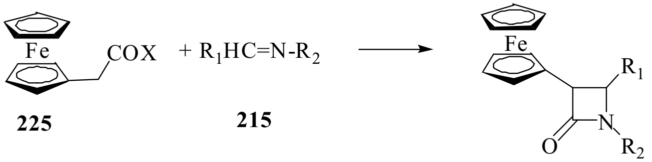
Finally, Podlech has recently reported [125] the transformation of diazoketones **227**, derived from α-amino acids, to ketenes that can react further with imines to afford β-lactams **228** (Scheme 9.74). It was found that this route proceeds not only by



Scheme 9.71 **219** **220** **221**

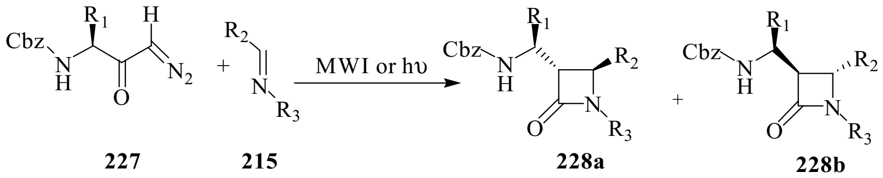


Scheme 9.72 **222** **224** (72%)



225 **215** **226**

Scheme 9.73 X= OH, Cl



Scheme 9.74

utilizing photochemical reaction conditions but also under the action of microwave irradiation. *β*-Lactams with a *trans*-substitution pattern on the ring were obtained exclusively in 40–85 % yield.

9.8
Conclusions

We have shown that microwave irradiation is an efficient methodology in cycloaddition reactions. The special characteristics of the radiation (i. e. dielectric properties, energy transfer, penetration depth, etc.) are completely different from conventional heating and have led to the development of new laboratory techniques, equipment, glassware and a different outlook on chemical reactions. Numerous procedures have been designed to work in solution or solvent-free conditions and the choice of method depends on the nature of the reagents and the reaction, although solvent-free conditions using solid supports are especially suited to microwave conditions.

The application of microwave irradiation to organic synthesis shows that the effect of microwaves on the yield is particularly important in compounds with low reactivity and reagents and products with high sensitivity. The particular suitability of microwave radiation for such reactions stems from the fact that mild reaction conditions, shorter times and/or lower temperatures can be used.

In some cases, modifications in the selectivity, in relation to classical heating, have been observed. These modifications have been ascribed to changes in the reaction path; under microwave irradiation the more polar path will be favored. Computational studies have shown that the harder transition state must be favored under microwave irradiation. This result opens new possibilities for the application of microwave irradiation to organic and inorganic synthesis as dramatic modifications in the selectivity of competitive reactions can be expected if the transition states are of different hardness.

Acknowledgments

Financial support from Spanish DGI (projects BQU2001–1095 and BQU2001–1512) is gratefully acknowledged.

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10

Microwave Catalysis in Organic Synthesis

Milan Hájek

10.1

Introduction

The aim of this chapter is to draw the attention of experimental organic and catalytic chemists to a new field of catalysis, especially to catalytic methods which use microwave irradiation as a new means of activation of chemical reactions, called “microwave catalysis”. It is intended to advise synthetic organic chemists about the choice of catalytic steps which might be more efficient than conventional synthetic methods.

This chapter focuses exclusively on *microwave heterogeneous catalysis*. Microwave homogeneous catalysis by transition metal complexes is treated in Chapt. 11, phase transfer catalysis in Chapt. 5, catalytic reactions on graphite in Chapt. 7, photocatalytic reactions in Chapt. 14, and catalytic synthesis of labeled compounds in Chapt. 13.

The development of microwave heterogeneous catalysis is, however, impeded because most synthetic chemists are not well acquainted with factors affecting both heterogeneous catalysis and microwaves. Although attempts have been made to accelerate reaction rate or to improve yield and selectivity, they have been based on the rule “let’s try microwaves and see what happens”.

This chapter is written to help the synthetic chemist to understand the effect of microwaves on heterogeneously catalyzed reactions. Not only are metal catalysts discussed, but also metal oxides, zeolites, clays, and similar materials that act either as catalysts or as potential supports for the catalytically active species. The factors involved in the preparation of catalysts under microwave conditions are summarized and discussed in terms of their effect on catalyst activity and selectivity. Basic mechanistic understanding can frequently be used to modify reaction conditions to achieve product formation in high yield. Such an approach cannot be readily applied to heterogeneously catalyzed processes, because the mechanistic understanding needed by the synthetic chemist is not yet commonly available for this type of reaction. This chapter is intended to call the attention of synthetic chemists to microwave catalysis, because it has some advantages over conventional heterogeneous catalysis (there are also some problems). Hopefully, this may encourage synthetic and catalytic chemists to use the process more frequently and thus extend the application of microwaves to the preparation of a variety of materials.

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

10.1.1
Definitions

A catalyst is a substance that increases rate of a chemical reaction without being changed in the process. During the reaction it can become a different entity, but after the catalytic cycle is closed the catalyst is the same as at the start. The function of the catalyst is to reduce the energy of the reaction pathway. Catalysts can, in general, be heterogeneous, homogeneous, or biological. Typical types of heterogeneous catalyst are bulk metals, supported inorganic metallic compounds, and supported organometallic complexes. Catalyst interaction with reactants can occur homogeneously, i. e. with the reactants and the catalyst in the same phase (usually liquid), or heterogeneously at the interface between two phases. The latter type of catalyzed reaction utilizes a solid catalyst, and the interaction occurs at either the liquid/solid or gas/solid interface.

Microwave catalysis is a catalytic process performed in the presence of a microwave (electromagnetic) field in which the catalyst acts as an energy "convertor". It uses microwave irradiation to stimulate catalytic reactions. It is necessary to stress that any sort of electromagnetic or microwave radiation is not itself a catalyst, as has sometimes erroneously stated [1]. Similarly, it is not correct to say that microwave irradiation catalyzes chemical reactions [1]. The principles of microwave catalysis will be described in the following sections.

A catalytic reaction is one in which more than one turnover or event occurs per reaction center or catalytically active site. If, however, less than one turnover occurs per active site, it cannot be a true catalytic reaction. This occurs for reactions on supported reagents in the absence of solvent, when support or catalyst is used in excess (called also solvent-free, solvent-less, dry media etc.; Chapts. 3 and 6). Catalytic reactors usually contain a small amount of solid catalyst compared with the amounts of reactants that pass over the catalyst as liquids or gases. For microwave heating to be successfully applied in catalytic systems the catalyst itself must absorb microwave energy. Many supported catalysts (metal, metal oxides, etc.) are known to absorb microwave energy readily to different extents, whereas the support (silica, alumina) does not. Thus, after conversion, a liquid or gas stream passing over the catalyst reaches the cooler part of the reactor more quickly, thus preserving the reactive products otherwise destroyed in a conventional system. Microwave catalyzed reactions thus occur at lower temperatures with substantial energy savings and often with higher yields of the desired products.

Heterogeneously catalyzed reactions are rather complex processes. In a two-phase system, either liquid/solid or gas/solid, several steps are needed to complete the catalytic cycle:

- transport of the reactants to the catalyst;
- interaction of the reactants with the catalyst (adsorption);
- reaction of adsorbed species to give the products (surface reaction);
- desorption of the products; and
- transport of the products away from the catalyst.

Microwave radiation can be used to prepare new catalysts, enhance the rates of chemical reactions, by microwave activation, and improve their selectivity, by selective heating. The heating of the catalytic material generally depends on several factors including the size and shape of the material and the exact location of the material in the microwave field. Its location depends on the type of the microwave cavity used [2].

The aim of this chapter is to describe some advances in catalysis achieved by use of microwave heating. The aspects of microwave catalytic reactions which differ from traditional thermal methods are emphasized. The input of microwave energy into a reaction mixture is quite different from conventional (thermal) heating and it is the task of synthetic chemists to exploit this special situation as fully as possible.

10.2
Preparation of Heterogeneous Catalysts

The interaction of microwaves with solid materials has proven attractive for the preparation and activation of heterogeneous catalysts. It has been suggested that microwave irradiation modifies the catalytic properties of solid catalysts, resulting in increasing rates of chemical reactions. It is evident that microwave irradiation creates catalysts with different structures, activity, and/or selectivity. Current studies document a growing interest in the preparation of microwave-assisted catalysts and in the favorable influence of microwaves on catalytic reactions.

The preparation of catalysts usually involves the impregnation of a support with a solution of active metal salts. The impregnated support is then dried, calcined to decompose the metal salt and then reduced (activated) to produce the catalyst in its active form. Microwaves have been employed at all stages of catalyst preparation. Beneficial effects of microwave heating, compared with conventional methods, have been observed especially in the *drying*, *calcination*, and *activation* steps.

10.2.1
Drying and Calcination

It is well known that microwave drying of many solid materials is a very efficient and widely used process even on an industrial scale [3]; it is also an attractive means of drying of heterogeneous catalysts. Microwave drying of catalysts and supported sorbents has several advantages:

- reduction of drying time;
- higher surface area and catalytic activity;
- thermal dispersion of active species facilitated by microwave energy, providing more uniform metal distribution; and
- higher mechanical strength of catalyst pellets.

Microwave heating has been reported to produce materials with particular physical and chemical properties [4]. Stable solid structures are formed at low reaction temperatures with unusually high surface areas, making them very useful as catalysts or catalyst supports. Calcination of solid precursors in a microwave field has significant advantages over conventional heating. The effective synthesis of the catalysts and supporting adsorbents has been reported for the examples below.

Microwave drying of an alumina-supported nickel catalyst reduced the drying time by a factor of 2–3 [4]. The results indicated that better dispersion of nickel was achieved by microwave drying, presumably because of minimization of moisture gradients during drying. Analysis of the results confirmed, moreover, that the microwave-dried samples were significantly stronger than those dried conventionally. As a consequence of minimal moisture gradients, the metal ions are not redistributed to the same extent during the microwave-drying process as they are when the samples are dried conventionally, because of the moisture leveling [2, 3] process. As a consequence of minimal moisture gradients, metal ions are not distributed to the same extent during MW drying process as under conventional drying. This causes the resulting dry pellets to be stronger, as shown by analysis of crushing strengths [4]. Because the heating effect is approximately proportional to the moisture content, microwaves are ideal for equalizing moisture within the product in which the moisture distribution is initially nonuniform. Microwave drying also proceeds at relatively low temperatures, and no part of the product needs be hotter than the evaporating temperature.

The microwave technique has also been found to be a potential method for the preparation of the catalysts containing highly dispersed metal compounds on high-porosity materials. The process is based on thermal dispersion of active species, facilitated by microwave energy, into the internal pore surface of a microporous support. Dealuminated Y zeolite-supported CuO and CuCl sorbents were prepared by this method and used for SO_2 removal and industrial gas separation, respectively [5]. The results demonstrated the effective preparation of supported sorbents by microwave heating. The method was simple, fast, and energy-efficient, because the synthesis of both sorbents required a much lower temperature and much less time compared with conventional thermal dispersion.

The V_2O_5/SiO_2 catalyst for *o*-xylene oxidation prepared by wet impregnation under microwave irradiation had several advantages [6] compared with that prepared by the conventional thermal method:

- dispersion of V_2O_5 on the surface of SiO_2 was more homogeneous;
- the nonisothermal process was minimized;
- dispersion of active phase (V_2O_5) was highly uniform; and
- in the catalytic microwave process the optimum reaction temperature of *o*-xylene oxidation was reduced by 100 K (from 653 to 553 K).

The more active cobalt catalyst for pyrolytic reactions was prepared by microwave calcination of cobalt nitrate which was converted to cobalt oxide by rapid microwave heating [7].

The high dispersion of inorganic salts ($CuCl_2$, $NiCl_2$, $AuCl_3$, $RuCl_3$, etc.) on the surface of zeolites (NaZSM-5, NaY, NaBeta) and alumina with high loading of the active components has recently been achieved by microwave techniques [8–10]. The catalysts were very active in NO_x decomposition, even at room temperature, CO and NO were partially converted to CO_2 and N_2. It was concluded that microwave treatment is a new route for dispersing a high loading of inorganic compounds onto the surface of supports to form highly active catalysts.

The microwave technique has been also found to be the best method for preparing strongly basic zeolites (ZSM-5, L, Beta, etc.) by direct dispersion of MgO and KF. This novel procedure enabled the preparation of shape-selective, solid, strongly base catalysts by a simple, cost-effective, and environmentally friendly process [11, 12]. New solid bases formed were efficient catalysts for dehydrogenation of 2-propanol and isomerization of *cis*-2-butene.

In the microwave synthesis of zeolites, a mixture of a precursor and a zeolite support is heated in a microwave oven. The sample is then tested for its catalytic activity and the results compared with the sample obtained by the conventional method. Microwave irradiation at the calcination stage led to samples with a more uniform particle-size distribution and microstructure and to a bimetallic catalyst with different morphology. Microwave calcination of magnesia-, alumina-, and silica- supported Pd and Pd–Fe catalysts resulted in their having enhanced catalytic activity in test reactions – hydrogenation of benzene and hydrodechlorination of chlorobenzene – compared with conventionally prepared catalysts [13–15]. The higher catalytic activity was attributed to the prevention of formation of a Pd–Fe alloy of low activity, which occurs at the high reduction temperature used in conventional heating.

The microwave technique for drying then calcination is an excellent way of obtaining highly porous silica gel with a high surface area (as high as 635 $m^2\ g^{-1}$) for use as a catalyst and as a catalyst support [16].

The dispersion and solid-state ion exchange of $ZnCl_2$ on to the surface of NaY zeolite by use of microwave irradiation [17] and modification of the surface of active carbon as catalyst support by means of microwave induced treatment have also been reported [18]. The ion-exchange reactions of both cationic (montmorillonites) and anionic clays (layered double hydroxides) were greatly accelerated under conditions of microwave heating compared with other techniques currently available [19.]

Microwave irradiation has also been applied to the preparation of Fe_2O_3/SO_4^{2-} superacid [20, 21] and high-surface aluminum pillared montmorillonites [20].

The most successful application of microwave energy in the preparation of heterogeneous solid catalysts has been the microwave synthesis and modification of zeolites [21, 22]. For example, cracking catalysts in the form of uniformly sized Y zeolite crystallites were prepared by microwave irradiation in 10 min, whereas 10–50 h were required by conventional heating techniques. Similarly, ZSM-5 was synthesized in 30 min by use of this technique. The rapid internal heating induced by microwaves not only led to a shorter synthesis time, and high crystallinity, but also enhanced substitution and ion exchange [22].

Microwave processing of zeolites and their application in the catalysis of synthetic organic reactions has recently been excellently reviewed by Cundy [23] and other authors [24]. The microwave synthesis of zeolites and mesoporous materials was surveyed, with emphasis on those aspects which differ from conventional thermal methods. The observed rate enhancement of microwave-mediated organic synthesis achieved by use of these catalysts was caused by a variety of thermal effects, including very high rates of temperature increase, bulk superheating, and differential heating. Examples of microwave activation of chemical reactions catalyzed by zeolites will be presented in Sect. 10.3.

An efficient oxidation catalyst, OMS-1 (octahedral mol. sieve), was prepared by microwave heating of a family of layered and tunnel-structured manganese oxide materials. These materials are known to interact strongly with microwave radiation, and thus pronounced effects on the microstructure were expected. Their catalytic activity was tested in the oxidative dehydrogenation of ethylbenzene to styrene [25].

In the preparation of microporous manganese oxide materials different chemical properties were observed for the microwave and thermal preparations. In the conversion of ethylbenzene to styrene the activity and selectivity of the materials was different [26].

An alternative approach for the preparation of supported metal catalysts is based on the use of a microwave-generated plasma [27]. Several new materials prepared by this method are unlikely to be obtained by other methods. It is accepted that use of a microwave plasma results in a unique mechanism, because of the generation of a nonthermodynamic equilibrium in discharges during catalytic reactions. This can lead to significant changes in the activity and selectivity of the catalyst.

10.2.2
Catalyst Activation and Reactivation (Regeneration)

Microwave irradiation of catalysts before their use in chemical reactions has been found to be a new promising tool for catalyst activation. Microwave irradiation has been found to modify not only the size and distribution of metal particles but probably also their shape and, consequently, the nature of their active sites. These phenomena might have a significant effect on the activity and selectivity of catalysts, as found in the isomerization of 2-methylpentene on a Pt catalyst [2].

As an example, the microwave activation of the platinum catalyst under conditions when it was highly sensitive to thermal treatment resulted in an increase of its catalytic activity and selectivity (from 40 to 80%) [28].

Durable changes of the catalytic properties of supported platinum induced by microwave irradiation have been also recorded [29]. A drastic reduction of the time of activation (from 9 h to 10 min) was observed in the activation of NaY zeolite catalyst by microwave dehydration in comparison with conventional thermal activation [30]. The very efficient activation and regeneration of zeolites by microwave heating can be explained by the direct desorption of water molecules from zeolite by the electromagnetic field; this process is independent of the temperature of the solid [31]. Interaction between the adsorbed molecules and the microwave field does not result simply in heating of the system. Desorption is much faster than in the conventional thermal process, because transport of water molecules from the inside of the zeolite pores is much faster than the usual diffusion process.

Very little is known about the reactivation (regeneration) of used catalysts by microwave irradiation. Catalyst activity has been shown to decay with increasing carbon deposition, and several patents disclose the decarbonization of cracking zeolite catalysts by microwaves [32]. Because carbon is a very lossy material (it absorb microwaves very efficiently), any carbon deposited on the surface of the catalyst is strongly heated. In the presence of air or hydrogen the carbon is removed in the form of carbon dioxide or methane, respectively. When carbon deposition reaches a certain level it starts to absorb microwave energy strongly and is, therefore, subsequently removed, leading to an increase in the activity of the catalyst.

Alumina spheres polluted by carbon residues have been also reactivated by use of microwaves [33]. Their regeneration has been performed in a stream of air and in the presence of silicon carbide as an auxiliary microwave absorber. Microwave heat treatment led to full recovery of the catalyst in times varying from a half to a quarter of the conventional treatments. Regeneration of a commercial Ni catalyst (Ni/Al_2O_3) deactivated, presumably, by coke formation, by means of a flow of hydrogen or oxygen and water vapor under the action of microwave irradiation was, however, unsuccessful [34].

Microwaves are frequently used in the laboratory by synthetic organic chemists for regeneration and activation of solids such as molecular sieves, silica gel or alumina when fast and complete drying is required.

10.3
Microwave Activation of Catalytic Reactions

Heterogeneous catalysts have been employed in a number of organic reactions in which microwave heating was used. There is, unfortunately, a limited number of control data, which makes comparison with conventional heating difficult. Nevertheless, from the data so far reported it can be concluded that use of microwave radiation has yielded some remarkable results relating to rate enhancement and selectivity improvement. Activation can be achieved by superheating of the catalyst or by selective heating of active sites (Sect. 10.3.3) which cannot be achieved by conventional heating. The numerous reactions performed using heterogeneous catalysts can be divided into two groups – liquid-phase reactions and gas-phase reactions

10.3.1
Reactions in the Liquid Phase

There has been a limited number of reports of heterogeneously catalyzed reactions in the liquid phase under the action of microwave irradiation.

10.3.1.1 Esterification, Transesterification

Chemat et al. [35] examined rates of esterification of stearic acid by butanols as a model reaction to compare differences between homogeneously and heterogeneously catalyzed reactions, Scheme 10.1. Particular attention was paid to whether the effect of microwaves can be advantageously used to improve yields and to accelerate the rate of esterification.

$$CH_3(CH_2)_{14}COOH + CH_3(CH_2)_2CH_2OH \overset{\text{Cat.}}{\rightleftharpoons} CH_3(CH_2)_{14}COOCH_2(CH_2)_2CH_3 + H_2O$$

Scheme 10.1 Esterification of stearic acid with 1-butanol.

It was found that the reaction under microwave conditions was faster than that heated conventionally. Yields were greatly improved – from 50–82% for conventional heating to 71–95% for microwave heating when heterogeneous catalysts were used. The catalysts $Fe_2(SO_4)_3$, $TiBu_4$, KF, KSF, and PTSA were used in a continuous-flow reactor. The results were further improved by use of a heat captor (graphite) and simultaneous use of ultrasound. Better results (yield and rate) under microwave conditions were also achieved in other esterification reactions of stearic and acetic acid in the presence of a heterogeneous catalyst ($Fe_2(SO_4)_3$) adsorbed on montmorillonite clay pellets 4–5 mm in diameter [36, 37]. The reaction rate increased by 50–150% compared with conventional heating. This increase was most probably because of superheating of voluminous pellets (5 mm), the temperature of which was calculated to be 9–18 K above the bulk temperature. When the esterification was homogeneously catalyzed by sulfuric acid using the two modes of heating no differences between yield and reaction rates were observed.

The effect of the mode of heating was also studied in heterogeneously catalyzed esterification of acetic acid by isopentyl alcohol in the presence of Amberlyst-15 cation exchange resin catalyst [38], Scheme 10.2.

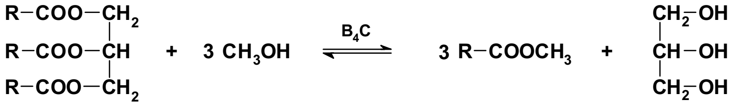
$$CH_3COOH + (CH_3)_2CHCH_2CH_2OH \overset{\text{Amberlyst}}{\rightleftharpoons} CH_3COOCH_2CH_2CH(CH_3)_2 + H_2O$$

Scheme 10.2 Esterification of acetic acid with isopentyl alcohol.

Because the reaction is driven by protonation of the carbonyl functionality, reacting species were expected to be localized on the bed of the acid catalyst subjected to microwave irradiation. Hexane was used as a nonpolar solvent to minimize solvent absorption and superheating. Elimination of catalyst superheating in a continuous-flow reactor was most probably the reason why no significant differences were observed between the reaction rates under the action of microwave and conventional heating.

Similar results were obtained in the esterification of acetic acid with 1-propanol performed in the presence of a heterogeneous silica catalyst [39]. The results showed that for this reaction microwave irradiation and conventional heating had similar effects on the reaction rate.

The rates of transesterification of triglycerides to methyl esters, efficiently catalyzed by boron carbide (B_4C), were, on the other hand, faster under microwave conditions, probably because of superheating of the boron carbide catalyst, which is known to be a very strong absorber of microwaves [40], Scheme 10.3. Yields of methyl ester of up to 98% were achieved.



Scheme 10.3 Transesterification of triglycerides with methanol.

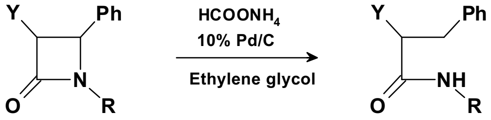
10.3.1.2 **Hydrogenation, Hydrogenolysis**

Another attractive heterogeneous catalytic reaction of great interest in organic synthesis is hydrogenation. Catalytic transfer hydrogenation of soybean oil in the presence of palladium catalyst (10% Pd/C) was investigated using microwave and conventional heating [41]. Sodium formate was used as hydrogen donor. Kinetic results revealed the reaction rate increased significantly when microwave heating was used. The rate enhancement was attributed to microwave heating assistance of transport processes at the catalyst and oil–water interface.

Microwave-assisted catalytic hydrogenation of steroid compounds, e.g. cholesterol, campesterol, sitosterol, etc., in the presence of Pd/C catalyst and ammonium formate in glycol solvent was fast and afforded the corresponding products in high yield (80–95%) and purity [42].

A simplified and rapid hydrogenation of *β*-lactams under the action of microwave irradiation has been described by Bose et al. [43, 44], Scheme 10.4. Pd/C and Raney nickel were used as catalysts and a high-boiling solvent such as ethylene glycol was used as the microwave energy transfer agent in the presence of ammonium formate as the hydrogen donor. The yields of the corresponding amides were 80–90%.

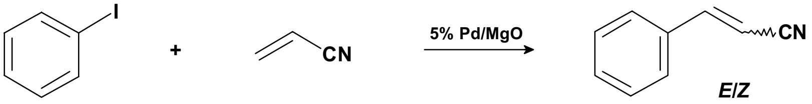
Scheme 10.4 Selective transformation of *β*-lactams.



Hydrogenation of C–C double bonds and hydrogenolysis of several functional groups have been described as a safe, rapid, and efficient method resulting in high yields (80–90%) of products. The technique described was recommended as suitable for research and for undergraduate and high school exercises [43, 44]. Hydrogenolysis and dehalogenation of aromatic compounds with the same catalytic system was also successful. Thus, several *β*-lactams and isoquinoline derivatives were smoothly dehalogenated in a few minutes [44].

10.3.1.3 **Miscellaneous Reactions**

A heterogeneous Pd catalyst dispersed on supports such as $\tilde{\alpha}$-Al_2O_3, C, MgO and $CaCO_3$ was found to be an recyclable and selective catalyst for heterogeneous Heck arylation (an important method of C–C bond formation – Chapt. 11) of several olefins (styrene, α-methylstyrene, 1-decene, acrylonitrile, etc.) with iodobenzene [45], Scheme 10.5.



Scheme 10.5 Arylation of acrylonitrile with iodobenzene.

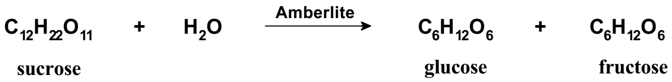
The *E*/*Z* ratio of the isomers formed over a supported Pd catalyst differed from that obtained with the homogeneous counterpart. The activity of the catalyst under the action of microwave and conventional conditions was comparable, but microwave irradiation improved yields and reduced reaction times.

Heck C–C coupling reactions were also facilitated by the presence of a palladium catalyst when Pd was deposited on a tubular membrane of porous glass. Thus, the coupling of iodobenzene with allyl alcohol affording 3-phenylpropionaldehyde in the presence of this Pd catalyst had several advantages – the ease of catalyst manufacture, mechanical strength, thermal stability, and resistance to organic solvents [46].

The hydrolysis of sucrose catalyzed by the strongly acidic cation-exchange resin Amberlite 200C in RH form was chosen as a model reaction to compare the use of stirred tank and continuous-flow reactors [47–49], Scheme 10.6.

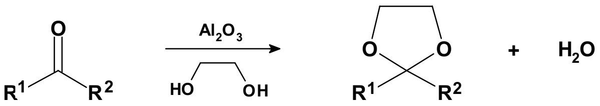
No rate enhancement was observed when the reaction was performed under microwave irradiation at the same temperature as in conventional heating [47]. Similar reaction kinetics were found in both experiments, presumably because mass and heat effects were eliminated by intense stirring [47]. The model developed enabled accurate description of microwave heating in the continuous-flow reactor equipped with specific regulation of microwave power [47, 48]. Calculated conversions and yields of sucrose based on predicted temperature profiles agreed with experimental data.

Several other miscellaneous heterogeneously catalyzed reactions have been performed in the liquid phase. Hexane was successfully oxyfunctionalized with aqueous hydrogen peroxide by use of the zeolite TS-1 catalyst [50] and microwave-promoted acetalization of a number of aldehydes and ketones with ethylene glycol proceeded readily (2 min) in the presence both of heterogeneous (acidic alumina) and homogeneous (PTSA, Lewis acids) catalysts [51], Scheme 10.7.

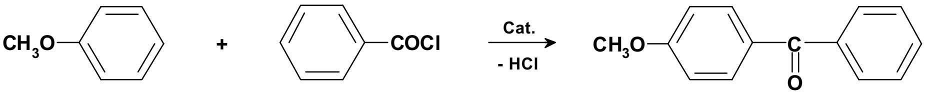


$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{\text{Amberlite}} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

Scheme 10.6 Hydrolysis of sucrose.



Scheme 10.7 Acetalization of ketones with ethylene glycol.



Scheme 10.8 Benzoylation of anisole.

Yields were high (up to 97%) and comparable with those of homogeneously catalyzed reactions. A much higher catalyst-to-substrate ratio had to be used with heterogeneous alumina (10–15) than with the homogeneous catalysts (0.015–0.050), however. It was concluded that the microwave method led to considerable improvement of acetalization reactions, compared with conventional methods.

Friedel–Crafts acylation of aromatic ethers has been performed in the presence of a variety of metal chlorides and oxides ($FeCl_3$, $ZnCl_2$, $AlCl_3$, Fe_2O_3, Fe_3O_4, etc.) but without temperature control [52], Scheme 10.8.

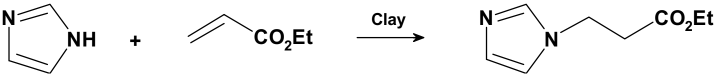
The short reaction time (1 min, 160 °C) in the benzoylation of anisole was probably a result of large temperature gradients rather than a nonthermal microwave effect.

Some reactions have been found to proceed with better results in the absence of solvent, probably because of the creation of temperature gradients which are eliminated in the presence of a stirred solvent. This was observed for the Diels–Alder reaction of α-amino acid precursors with cyclopentadiene catalyzed by heterogeneous catalysts (SiO_2–Al, SiO_2–Ti), when the reaction was performed in toluene or in the absence of solvent [53]. Microwave activation increased the rate of reaction without reducing the selectivity of the reaction.

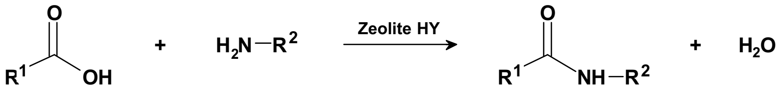
The microwave activation of Michael additions in the preparation of N-substituted imidazoles afforded excellent yields in very short reaction times under mild reaction conditions, Scheme 10.9. Basic clays (Li^+, Cs^+) exchanged montmorillonites were found to be very active and selective catalysts for the Michael addition of imidazole and ethyl acrylate [54].

A total of 75% conversion with 100% selectivity was obtained in only 5 min in the absence of solvents.

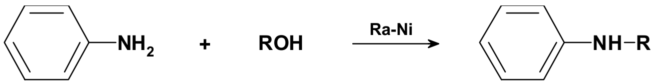
An efficient method for conversion of a variety of acids into their corresponding amides in the presence of zeolite–HY under the action of microwave irradiation has recently been described [55], Scheme 10.10.



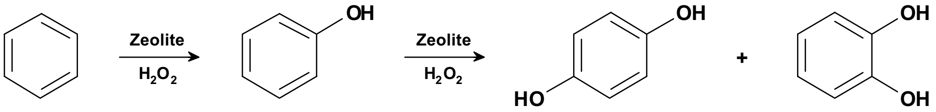
Scheme 10.9 Michael addition of imidazole with ethyl acrylate.



Scheme 10.10 Preparation of amides.



Scheme 10.11 Alkylation of aniline with alcohols.



Scheme 10.12 Oxidation of benzene with hydrogen peroxide.

The reactions proceeded at atmospheric pressure with high yields (80–97%) in the absence of solvent.

Facile N-alkylation of anilines with alcohols in the presence of Raney nickel proved the high efficiency of the catalyst, which is a highly absorptive material for microwaves [56], Scheme 10.11.

A 6- to 48-fold rate enhancement was observed for this reaction. The authors suggested that a nonthermal effect might account for this enhancement [56].

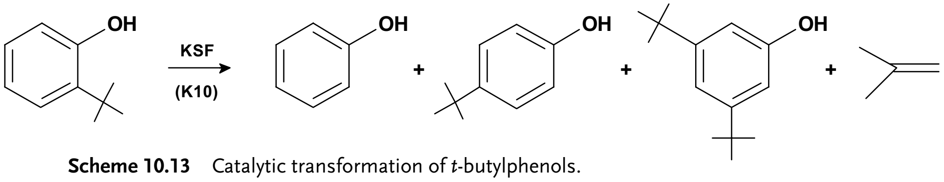
Hydroxylation of benzene with hydrogen peroxide in the presence of solid zeolite catalyst (titan–silicate–zeolite) was chosen by Radoiu et al. [57] as a model heterogeneous liquid-phase reaction for study of microwave effects, Scheme 10.12.

Titanium-containing zeolite was an efficient catalyst for oxidation of benzene with hydrogen peroxide in a microwave field, affording phenol with high selectivity. It was reported that microwaves had a strong effect on the selectivity of the reaction.

A detailed study of microwave activation of catalytic reactions in the liquid phase has recently been performed by Hájek et al. [58–60], Scheme 10.13.

It was found that in the catalytic transformation of 2- and 4-*t*-butylphenol in the liquid phase on heterogeneous KSF and K10 montmorillonite catalysts under microwave and conventional conditions the microwaves affected both the rate and the selectivity of the reaction.

The rate was enhanced up to 2.6-fold for reaction of the 2-isomer and up to 14-fold for the 4-isomer. The product distribution in the final reaction mixtures was always somewhat different when microwave heating was used. The results were explained in terms of efficient interaction of microwaves with a highly polarized reagent molecule adsorbed on the acidic active site. Possible superheating of the active sites was difficult to detect (Sect. 10.3.3).



Scheme 10.13 Catalytic transformation of *t*-butylphenols.

To elucidate the cause of the microwave-induced enhancement of the rate of this reaction in more detail the transformation of 2-*t*-butylphenol was performed at low temperatures (up to –176 °C). At temperatures below zero the reaction did not proceed under conventional conditions. When the reaction was performed under microwave conditions in this low temperature region, however, product formation was always detected (conversion ranged from 0.5 to 31.4%). It was assumed that the catalyst was superheated or selectively heated by microwaves to a temperature calculated to be more than 105–115 °C above the low bulk temperature. Limited heat transfer in the solidified reaction mixture caused superheating of the catalyst particles and this was responsible for initiation of the reaction even at very low temperatures. If superheating of the catalyst was eliminated by the use of a nonpolar solvent, no reaction products were detected at temperatures below zero (see also Sect. 10.3.3).

10.3.2
Reactions in the Gas Phase

Heterogeneous catalytic gas-phase reactions are most important in industrial processes, especially in petrochemistry and related fields, in which most petrochemical and chemical products are manufactured by this method. These reactions are currently being studied in many laboratories, and the results of this research can be also used for synthetic purposes. The reactions are usually performed [61] in a continuous system on a fixed catalyst bed (exceptionally a fluidized bed).

In catalytic reactions sufficient heat is usually required to overcome the activation energy barrier. In kinetic terms, the activation energy is the minimum energy required to form an activated complex undergoing transformation to the reaction products. Microwaves can be used as the source of thermal energy to induce catalytic reactions. The advantage of microwaves is that they can heat microwave-absorptive catalysts selectively to a temperature well above the bulk temperature of the reactants. The ability to heat the catalyst in microwave field enables heating of the bed from the interior and not from a hot exterior, as by conventional thermal means. Thus, the gas stream passing over the catalyst enters the cooler part of the reactor more quickly, so preserving the reactive products which would otherwise be destroyed in a conventional system. During microwave irradiation the catalyst active sites are, ideally, heated to the required temperature well before the adsorbed reactants have time to desorb. In general, because the bond breaking step occurs on the catalyst surface (the surface reaction is the rate-determining step) it is understandable that the reaction is enhanced. Because the temperature of the bulk reactants (and nonabsorptive support) is lower, the back, side or consecutive reactions can occur to a lesser extent, i.e. the selectivity of the reaction can be significantly improved. For example, in the formation of ethane and ethylene from methane in the presence of doped catalysts, oxygen, and microwave irradiation, the undesirable reactions producing gaseous carbon dioxide and carbon monoxide were slower by one to three orders of magnitude, because the temperature of the bulk gas was lower than when conventional heating was used [62].

10.3.2.1 Reactions of Methane

The most studied catalytic gas-phase reaction has been the transformation of methane to the higher hydrocarbons or oxygenated products. This reflects the large effort being made by catalytic chemists to find a simple process by which world's large resources of natural gas can be utilized.

The existence of vast worldwide reserves of the natural gas, of which methane is the main component, has focused attention on the possibility of converting it directly to more valuable chemicals. A single-step conversion of methane to more valuable products is of immense industrial significance and economic importance.

The activation of methane by microwaves has long been a goal of scientists in attempts to convert this natural gas component into higher hydrocarbons valuable in petrochemistry and the chemical industry. Two pathways are being extensively investigated by research groups all over the world:

- oxidative coupling of methane to yield C_2 and higher hydrocarbons; and
- direct partial oxidation of methane to produce methanol and other oxygenates.

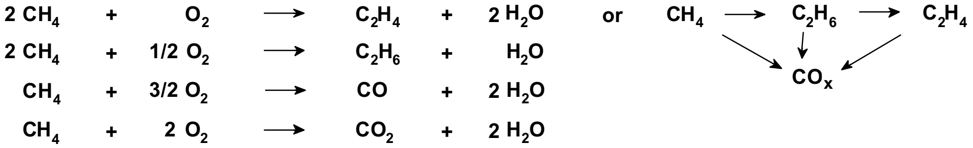
Oxidative coupling of methane to yield C_2 and higher hydrocarbons

The oxidative coupling of methane has been studied by several authors. The most elusive transformation has been the oxidative coupling of methane into C_2 hydrocarbons (ethene, ethane), because the reaction is more endothermic than other transformations [2]. The application of fast and efficient microwave heating to endothermic reactions is particular interest.

Many attempts had been made to solve this problem. One is partial oxidation of methane over a special catalyst capable of inhibiting further oxidation into CO and CO_2 during the transformation. The reactions in question are shown in Scheme 10.14.

The most efficient catalysts for the desired transformation are metal oxides such as MgO, CaO, La_2O_3, Sm_2O_3, and LiO_2. The problem is, however, far from being solved. The best C_2 selectivity so far obtained is only 60 % [2].

In conventional experiments the gas and catalyst are maintained at the same temperature. In microwave experiments the power is deposited within the catalyst, which is cooled by the gas flow and thermal conduction to the surroundings. If the catalyst bed is not thick, the gas is always at a lower temperature than the solid catalyst. The increased loss factor of the catalyst favors the formation of CH_3 radicals because they are produced at active "O_2" sites and these *specific sites* are preferentially excited by the microwave field. Hence the observed enhancement of C_2 selectivity is,



Scheme 10.14 Oxidative coupling of methane.

in fact, a “thermal” phenomenon in that it can be completely explained by temperature gradients within catalyst particles, i. e. by locally excited catalytic sites. This observed effect can be explained by assuming that under microwave irradiation the temperature of the reaction sites is higher than the mean temperature of the catalyst bed (see also Sect. 10.3.3).

Similarly, Bond et al. [4] confirmed that the microwave stimulation of methane transformation reactions in the presence of a number of rare earth basic oxides to form C_2 hydrocarbons (ethene, ethane) was achieved at a lower temperature and with the increased selectivity. Microwave irradiation resulted in an increase of the ethene/ethane ratio, which was desirable. The results obtained were explained by the formation of hot spots (Sect. 10.3.3) of higher temperature than the bulk catalyst. This means that methane is activated at these hot spots.

Microwave-induced, catalytic gas-phase reactions have primary been pursued by Wan [63, 64]. Wan et al. [65] have used pulsed-microwave radiation (millisecond high-energy pulses) to study the reaction of methane in the absence of oxygen. The reaction was performed by use of a series of nickel catalysts. The structure of the products seemed to be function of both the catalyst and the power and frequency of microwave pulses. A Ni/SiO_2 catalyst has been reported to produce 93% ethyne, whereas under the same irradiation conditions a Ni powder catalyst produced 83% ethene and 8.5% ethane, but no ethyne.

Wan et al. [61] also reported the highly effective conversion of methane to aromatic hydrocarbons over Cu, Ni, Fe, and Al catalysts. The effects of the type of catalyst, its configuration, and the microwave irradiation conditions on reaction path and product selectivity were examined under both batch and continuous-flow conditions.

Catalytic microwave heating has been used to oligomerize methane to higher hydrocarbons in the presence of Ni and Fe powder and activated carbon as the most active and efficient catalysts [66]. Oligomers ranging from C_2 to C_6 hydrocarbons, including benzene, have been prepared with good selectivity, depending on the nature of the diluent (helium) which favors the oligomerization of methane by microwave heating.

Mechanistic details of the microwave-induced oligomerization of methane on a microporous MnO_2 catalyst were studied by Suib et al. [67], with emphasis on fundamental aspects such as reactor configuration, additives (chain propagators, dielectrics), temperature measurements, magnetic field effect, and reaction conditions.

Oxidative coupling of methane has also been examined by other authors [2, 68–70], who have used different catalysts.

Pyrolysis of methane under the action of pulsed microwave radiation in the presence of solid catalysts has been reported by Russian authors [71, 72]. The application of pulse microwave power was shown to be a promising means of production of hydrogen syngas, ethyne, and filament carbon.

Partial oxidation of methane to syngas over Ni and Co catalysts was effected by use of microwave irradiation, and compared with conventional heating [73]. Although the same conversion levels and H_2/CO ratio (2.0 ± 0.2) were observed, the temperature of the catalyst bed was much lower (200 K) when microwave irradiation was used than with conventional heating. Under both activation modes the Ni-based catalyst (Ni/ZrO_2, Ni/La_2O_3) had higher activity and selectivity than the Co catalyst (Co/ZrO_2, Co/La_2O_3). It was proposed that nonuniform distribution of the microwave energy on the catalyst surface created "hot spots" (Sect. 10.3.3) as active centers for the catalytic reaction.

Microwaves have been used to generate plasma in methane at 5–50 Torr. The radicals produced in such a system were then allowed to react over a nickel catalyst, affording a mixture of ethane, ethene, and ethyne [74].

Methane has also been used as the reducing agent in the catalytic conversion of NO to N_2 over Co-ZSM-5 zeolites [75] in the presence of oxygen. The high NO conversions (>70 %) were achieved by microwave irradiation at 250–400 °C, whereas under similar conditions thermal runs failed to convert either NO or methane in significant amounts. The high activity and selectivity of the reduction of NO by methane achieved with microwave irradiation was probably because of the activation of methane to form methyl radicals at relatively low reaction temperatures.

Direct partial oxidation of methane to produce methanol and other oxygenates

The formation of oxygenates by reaction of methane with oxygen and vapor under the action of conventional heating has received considerably less attention than the methane coupling reaction. The problem was poor selectivity and the formation of large amounts of CO_x. The use of microwave radiation for formation of the oxygenates from methane has, nevertheless, yielded some encouraging results. Wan et al. [76] used the vapor as the oxidant in preference to oxygen. The authors showed that acetone, 2-propanol, methanol, and dimethyl ether can be produced by this method.

Suib et al. [77] used microwaves to generate plasma in an atmosphere containing methane and oxygen. The plasma passing over a metal or metal oxide catalyst led to formation of C_2 hydrocarbons and some oxygenates.

Wan and Koch [78] also developed a method for producing HCN on a small scale by reaction of methane with ammonia, Scheme 10.15.

$$CH_4 + NH_3 \xrightarrow{M / Al_2O_3} HCN + 3\,H_2$$

Scheme 10.15 Synthesis of hydrogen cyanide.

The reaction was performed over a series of Pt/Al_2O_3, Ru/Al_2O_3, and carbon-supported catalysts under the action of pulsed microwave radiation; conversions exceeded 90 % and acetonitrile was formed as the byproduct.

10.3.2.2 Reactions of Higher Hydrocarbons

Microwave activation of alkane transformations was studied in detail by Roussy et al., who summarized their results in several papers [2, 28, 29, 79]. Isomerization of hexane, 2-methylpentane, 2-methyl-2-pentene, and hydrogenolysis of methylcyclopentane have been investigated, and the diversity of possible effects has been specified [2]. The course of 2-methylpentane isomerization on a 0.3 % Pt/Al_2O_3 catalyst depended on the mode of heating – the distribution of hexane products was different under the action of conventional and microwave heating [28, 79]. The isomer selectivity of transformation of 2-methylpentane to 3-methylpentane, methylcyclopentane, and hexane on this catalyst increased from 40 to 80% when the catalyst was pretreated with microwave energy [79]. The beneficial change in selectivity was found to be permanent. Microwave irradiation has been found to be a new, original means of activation of supported metal catalysts, in particular reforming catalysts [28, 29]. Hydrogenolysis of methylcyclopentane was studied mechanistically, because methylcyclopentane is one of the four molecules in equilibrium with the intermediate cyclopentane in the cyclic mechanism [2]. Four possible effects of the electromagnetic field on catalytic reactions were identified.

1. Microwave treatment can permanently modify the catalyst.
2. Heterogeneous phases (solid and gas) may give rise to inter-phase temperature gradients.
3. The electromagnetic field can act directly on the reaction sites to activate adsorbed organic molecules.
4. The electromagnetic field can act on polar intermediate species, e. g. carbenium ions.

Hydrogenolysis of 2-methylpentane, hexane, and methylcyclopentane has been also studied on tungsten carbide, WC, a highly absorptive catalyst, at 150–350 °C in a flow reactor [80]. These reforming reactions were mainly cracking reactions leading to lower molar mass hydrocarbons. At the highest temperature (350 °C) all the carbon–carbon bonds were broken, and only methane was formed. At lower temperatures (150–200 °C) product molecules contained several carbon atoms.

The effect of microwave irradiation on the catalytic hydrogenation, dehydrogenation, and hydrogenolysis of cyclohexene was studied by Wolf et al. [81]. Optimum conditions for benzene formation were a hydrogen flow, N–$CaNi_5$ catalyst, atmospheric pressure, and 70 s irradiation time. Cyclohexane was the main product when the irradiation time was 20 s, or in a batch/static system.

The oxidation of toluene to benzaldehyde and benzoic acid over V_2O_5/TiO_2 assisted by microwaves was studied by Liu et al. [82]. The authors concluded that microwave energy can greatly improve the process of selective toluene oxidation. The highest yields of benzoic acid were, however, only 38–41% and the highest selectivity was 51% at 80% conversion to benzoic acid.

In the cracking of benzene to acetylene over alumina- and silica-supported nickel catalysts it was observed that the selectivity of the reaction, expressed as the ethyne/ethene ratio, was dramatically affected (from 1 : 9 to 9 : 1) by controlling the microwave energy input (i. e. 90% selectivity) [83].

Other catalytic hydrocarbon reactions include decomposition of olefins over a powdered nickel catalyst [84], hydrogenation of alkenes, hydrocracking of cycloalkenes, and water-gas shift reactions [64].

10.3.2.3 **Miscellaneous Reactions**

Several reactions have already been mentioned in Sect. 10.2 – NO_x decomposition over modified zeolites [8–10], dehydrogenation of 2-propanol, isomerization of *cis*-butene over basic zeolites [11, 12], hydrogenation of benzene and hydrodechlorination of chlorobenzene [13–15], and oxidative dehydrogenation of ethylbenzene to styrene [26, 27]. Microwave-assisted decomposition of NO_x or its mixture with SO_2 was reported by Tse [76] and other authors [75, 85–87]. Oxygen, nitrogen, and solid sulfur were the major products of the decomposition performed over a range of nickel and copper catalysts [76]. The reaction of nitrogen oxides under an oxidative atmosphere is a very extensively studied reaction, but the true reaction pathways are still very difficult to understand. The high activity and selectivity of Co-ZSM-5 zeolite catalysts for reduction of NO by methane is probably because of activation of methane to form methyl radicals at relatively low temperatures [75], as already mentioned. Wan et al. [88] have also shown that carbon dioxide can be reacted over a supported metal catalyst in the presence of water vapor to yield alcohols and other oxygenates if the catalyst is irradiated with microwaves. The reaction proceeded at relatively low temperatures (220–350 °C). It seems likely that the surface temperature of the metal is several hundred degrees higher than the bulk temperature of the catalyst. Decomposition of chloromethane over a metal catalyst irradiated by pulsed-microwave radiation afforded methane, although the metal catalyst was inhibited by partial formation of the metal chloride by reaction with hydrogen chloride [89].

The reaction of 2-propanol to propanone and propene over a series of alkali-metal-doped catalysts with use of microwave irradiation has been studied by Bond et al. [90]. The nature of the carbon support was shown to affect the selectivity of the catalyst. Under microwave irradiation the threshold reaction temperature (i. e. the lowest temperature at which the reaction proceeded) was substantially reduced; this was explained in terms of “hot spots” (Sect. 10.3.3) formed within the catalyst bed.

The effect of microwave irradiation on the catalytic properties of a silver catalyst (Ag/Al_2O_3) in ethane epoxidation was studied by Klimov et al. [91]. It was found that on catalyst previously reduced with hydrogen the rates of both epoxidation and carbon dioxide formation increased considerably on exposure to a microwave field. This effect gradually decreased or even disappeared as the catalyst attained the steady state. It was suggested that this was very likely because of modification of electronic properties of the catalyst exposed to microwave irradiation.

10.3.3
Mechanistic Aspects

Although microwave activation of catalytic reactions has been the subject of many studies (Sects. 10.3.1 and 10.3.2), the mechanism of these reactions is not yet fully understood. In heterogeneous catalytic liquid/solid and gas/solid systems many results have revealed significant differences between the rates of conventionally and microwave heated reactions. As a rule, at the same temperature microwave heated reactions were faster than conventional and their rate enhancement was over one order of magnitude. Such rate differences have not been reported for other catalytic reactions, so how should they be interpreted? The reactions can be divided into two categories according to the rate enhancement effect observed under microwave conditions compared to conventional heating – those accelerated by application of microwaves and those which are not.

Reactions accelerated by microwaves

1. Esterification of stearic acid and acetic acid with propanol and butanol in the presence of $Fe_2(SO_4)_3$/KSF montmorillonite [37]. The rate enhancement observed (1.5–2.5 times) was ascribed to the higher temperature of the catalyst bed (calculated to be 9–18 K above the bulk temperature). Reaction conditions: batch (no stirring) and a stirred single-mode tank reactor, catalyst particle size 5 mm, 10-fold excess of alcohol.
2. Transesterification of triglycerides in the presence of B_4C [40]. The rate enhancement was not assessed quantitatively. Reaction conditions: a stirred multi-mode tank reactor, no solvent.
3. Acylation of aromatic ethers in the presence of a variety of metal chlorides and oxides [52]. The rate enhancement was probably caused by large temperature gradients but was not evaluated quantitatively. Reaction conditions: a single-mode stirred tank reactor, fourfold excess of anisole, no solvent.
4. Transformation of 2- and 4-*t*-butylphenols in the presence of KSF catalyst [58]. Rate enhancement up to 21.6 was recorded. Reaction conditions: a stirred multi-mode tank reactor, no solvent or polar and nonpolar solvents.
5. Diels–Alder reaction of methyl 2-acetamidoacrylate with cyclopentadiene in the presence of SiO_2–Al and SiO_2–Ti catalysts [53]. Rate enhancement was not expressed quantitatively. Reaction conditions: a stirred multi-mode tank microreactor, no solvent.
6. Oxidation of *o*-xylene over V_2O_5/SiO_2 [6]. The rate enhancement was because of a temperature gradient of approx. 100 K in the catalyst bed. Reaction conditions: a flow fixed-bed multi-mode reactor.
7. Decomposition of H_2S over MoS_2 [92]. The rate enhancement, quantitatively unspecified, was attributed to the creation of "hot spots" with temperatures 100–200 K above that of the bulk. Reaction conditions: a flow fixed-bed single-mode reactor.

Reactions not accelerated by microwaves

8. Esterification of acetic acid by isopentanol in the presence of Amberlyst-15 [38]. Reaction conditions: hexane solvent, continuous-flow reactor.
9. Esterification of acetic acid with 1-propanol in the presence of SiO_2 [39]. Reaction conditions: reflux, tenfold molar excess of 1-propanol, batch reactor.
10. Arylation of alkenes with iodobenzene in the presence of supported Pd catalyst [45]. Reaction conditions: acetonitrile as solvent, pressure CEM reactor.
11. Hydrolysis of sucrose in the presence of Amberlite 200C [47–49]. Reaction conditions: 9% aqueous solution of sucrose, a stirred tank [47] or continuous-flow fixed-bed reactor [48, 49].

12. Cyclization of citronellal in the presence of KSF catalyst [93]. Reaction conditions: reflux, CCl_4 as solvent, single-mode reactor„
13. CO oxidation over Pd/γ-Al_2O_3 and Pt/γ-Al_2O_3 [94, 95]. Reaction conditions: single-mode packed bed microwave reactor operated on continuous basis at 915 MHz.

Several reasons have been proposed to account for the effect of microwave heating on chemical reactions and catalytic systems. The results summarized in 1 to 7, above, show that under specific conditions microwave irradiation favorably affects reaction rates of both the liquid- and gas-phase processes. This phenomenon has been explained in terms of *microwave effects*, i. e. effects which cannot be achieved by conventional heating. These include *superheating, selective heating*, and formation of *hot spots* (and possibly *nonthermal effects*).

- *Superheating* can occur as superheating of a liquid reaction mixture in liquid/solid reactions or as localized superheating in gas/solid reactions.
- *Selective heating* can occur as selective heating of catalyst particles or in the extreme case as selective heating of active sites.
- *Hot spots* are either macroscopic hot spots (measurable) or microscopic hot spots (on a molecular level, immeasurable and similar to those in sonochemistry).

These microwave effects can be regarded as *thermal*. The proposal of some authors on the operation of *nonthermal effects* is still controversial (see Chapt. 3).

In the literature, thermal microwave effects are still the subject of some misunderstandings. For that reason, let us discuss the matter in more detail.

Superheating of liquid reaction mixture

Superheating of liquid reaction mixture above the boiling point [96, 97] and localized superheating of solid samples generating temperature gradients [98] is very often responsible for enhancement of reaction rates in both homogeneous and heterogeneous reactions. It is generally known that the irradiation of a heterogeneous system (e. g. suspension) by means of a electromagnetic field leads to nonuniform temperature distribution. If the reaction is performed under reflux, the reaction temperature can be significantly higher under the action of microwaves than under conventional conditions, because of the superheating effect of microwaves on the polar reaction mixture. Superheating occurs because the sample is heated so quickly that convection to the surface of the liquid and vaporization cannot adequately dissipate the excess energy. Organic chemists can use the superheating effect to accelerate both heterogeneous and homogeneous liquid-phase reactions. Under these conditions the reactions proceed at temperatures higher than the boiling point of the liquid mixture, without the need to work under pressure. The superheating of liquids can be reduced or suppressed by addition of a boiling stone or by efficient stirring. Localized superheating accompanied by the creation of hot zones is more significant for solids than for liquids.

Localized superheating in the solid phase

In gas/solid phase reactions enhancement of the rate by microwaves can be caused by the localized superheating of a solid catalyst bed to a much larger extent than in the liquid phase. Both differential coupling abilities of materials and distribution of electromagnetic fields can result in localized temperature distribution in the catalytic bed, but the contribution of these effects is difficult to quantify. Localized superheating creates hot zones, and consequently, leads to temperature gradients in solid materials. It also increases the frequency of collision of reactants. The preferential alignment of dipolar or ionic functional group, because of the microwave field can create a favorable situation for collisions to occur at the active sites of catalyst, thus increasing the collision efficiency. The large difference between temperature profiles of the catalyst bed under microwave and conventional heating can result in a different product distribution for catalytic reactions. Stuerga et al. [98] have suggested that localized rate enhancement might be responsible for nonisothermal and heterogeneous kinetic phenomena.

Measurement and estimation of temperature distributions induced by microwave heating in solid materials is, however, very difficult. Consequently, most local temperature fluctuations are greater than those measured. Under stronger microwave irradiation it is, therefore, very easy to obtain local temperature gradients. Temperature measurements usually yield an average temperature, because temperature gradients induce convective motions. Despite these difficulties, some methods, e.g. IR thermography, can reveal the surface temperature distribution without any contact with the sample studied. By this method the temperature gradients between 7 and $70\,^\circ\,\mathrm{cm}^{-1}$ were detected in an alumina layer [98] and $50\,^\circ\,\mathrm{mm}^{-1}$ in a magnetite sample [99]. Similar temperature gradients – $30–50\,^\circ\,\mathrm{cm}^{-1}$ – have also been found by Hajek et al. [100] for a cylindrical sample of alumina.

A systematic theoretical study of temperature profiles in microwave-heated solids has been performed by Dolande et al. [101]. According to these results, differences between reaction rates and/or yields observed for conventional and microwave heating can be explained in terms of localized superheating. The main interest in the use of microwave heating is its ability to produce very steep thermal gradients and very fast heating rates. One can also induce localized superheating, which leads to localized rate enhancement [98–100]. Localized superheating can be advantageously used by synthetic chemists, especially for reactions performed on inorganic supports under solvent-free conditions (Chapt. 6). In conclusion, it should be stressed that localized superheating can have a beneficial effect on heterogeneous catalytic reactions because of both rate enhancement and selectivity improvement.

Selective heating

Selective heating generally means that in a sample containing more than one component, only that component which couples with microwaves is selectively heated. The nonabsorbing components are not thus heated directly but only by heat transfer from the heated component. For example:

- liquid–liquid – polar reactants in nonpolar solvents (e.g. mixture of H_2O with CCl_4).

- solid–liquid – solid reactants or solid catalysts in nonpolar reaction mixtures (e.g. KSF in CCl_4).
- solid–solid – mixtures of strong microwave absorbers (e.g. C, SiC, CuO, etc.) with transparent materials (e.g. SiO_2, MgO etc.) or supported catalysts (e.g. Pt/SiO_2, Pd/Al_2O_3 etc.).

The selective heating is more enhanced when the catalyst contains a low microwave absorbing support (e.g. α-Al_2O_3 rather than γ-Al_2O_3). Metal or metal oxides supported on transparent support may be therefore selectively heated. Thus for example, Pt sites in Pt/SiO_2 catalyst can be selectively heated, in contrast to the transparent, unheated SiO_2 support. Hence, selective heating of the active sites to the temperature higher than that of the support may occur if heat loss from the metal particles is not too fast. Microwave field does not couple with transparent ceramic support, but it may strongly couple with metal particles because of their high electrical conductivity. Unfortunately, to get a direct experimental proof of this concept seems very unlikely, since to measure the temperature of individual active sites is beyond current experimental possibilities. Until now, the possibility to heat selectively the active sites without rising the temperature of the catalyst bed has been only modeled [102] and found to be strongly dependent on the size of catalyst particles and microwave frequency [103]. A number of experimental studies on catalytic reactions under microwave conditions were concerned with kinetic aspects and showed that the reaction rates and product distribution correspond to a higher reaction temperature than was that measured for the bulk of catalyst bed. Both reaction characteristics were often explained in terms of the higher local temperature of certain active centers within the catalyst bulk. It is worth mentioning that the results of theoretical calculation reported by Thomas [102] did not substantiate the possibility of achieving selective heating of supported metal catalysts by microwaves. However, a recent detailed modeling of small-scale, microwave-heated, packed bed and fluidized bed catalytic reactors indicated that under specific conditions, the active sites may be selectively heated in both types of catalyst bed [103, 104].

Hot spots

Hot spots are created by a nonlinear dependence of thermal and electromagnetic properties of the material being heated on temperature. If the rate at which microwave energy is absorbed by the material increases faster than linearly with temperature, then heating does not take place uniformly, and the regions of very high temperature can create hot spots. Nonhomogenity of electromagnetic field contributes to the creation of hot zones significantly. Generally, hot spots can be created by localized superheating, selective heating as well as by nonhomogenity of electromagnetic field.

In a microwave-heated packed catalyst bed, two different forms of hot spots can be created.

1. Hot spots as large scale nonisothermalities, which can be detected and measured by optical pyrometers, fiber optic or IR pyrometers, i.e. these are macro scale hot zones.

2. Hot spots as a temperature gradient between the metal particles and the support, which cannot be detected and measured because they are close to micro scale, i. e. they possess molecular dimensions, they are closed to selective heating of active sites.

Unfortunately, the microwave radiation effects on molecular level are not well understood.

Zhang et al. [92] presented a certain evidence for the formation of hot spots in the microwave experiments and demonstrated that these hot spots need not be exclusively localized on the active sites but may also involve the support material (γ-Al_2O_3). They also estimated the dimensions of these hot spots to be in the region of 90–1000 µm. Development of hot spots in the catalyst bed in the course of the gas phase decomposition of H_2S catalyzed by MoS_2/Al_2O_3 was probably the reason for a significant apparent shift in the equilibrium constant. The temperature of these hot spots was probably by 100–200 K above the bulk temperature. The formation of hot spots in the support could be due to the absorptive properties of γ-Al_2O_3 (compared to low absorptive α-Al_2O_3). It was concluded that these hot spots also induce a considerable reorganization of the catalyst under microwave conditions. Such selective or localized superheating to create hot spots as effected with microwave heating cannot be achieved by conventional heating methods.

If microwave heating leads to enhanced reactions rates, it is plausible to assume that the active sites on the surface of the catalyst (micro hot spots) are exposed to selective heating which causes some pathways to predominate. In the case of metal supported catalysts, the metal can be heated without heating of the support due to different dielectric properties of both catalyst components. The nonisothermal nature of the microwave-heated catalyst and the lower reaction temperature affects favorably not only reaction rate but also selectivity of such reactions.

Chen et al. [70] suggested that temperature gradients may have been responsible for the more than 90% selectivity of the formation of acetylene from methane in a microwave heated activated carbon bed. The authors believed that the highly nonisothermal nature of the packed bed might allow reaction intermediates formed on the surface to desorb into a relatively cool gas stream where they are transformed via a different reaction pathway than in a conventional isothermal reactor. The results indicated that temperature gradients were approximately 20 K. The nonisothermal nature of this packed bed resulted in an apparent rate enhancement and altered the activation energy and pre-exponential factor [94]. Formation of hot spots was modeled by calculation and, in the case of solid materials, studied by several authors [105–108].

It is obvious that nonisothermal conditions induced by microwave heating lead to very different results from those obtained under conventional heating conditions. In summary microwave effects like superheating, selective heating and hot spots, can all be characterized by temperature gradients ranging from macroscopic to molecular scale dimensions.

Let us now return to the question “How to interpret or explain the fact that some reactions are affected by microwaves and some reactions do not”, as documented by examples 1–7 and 8–13, above. A detailed study of this subject has been performed by Hájek et al. [58–60] for heterogeneous catalytic liquid phase reactions. Transformation of 2-*t*-butylphenol into phenol, 4-*t*-butylphenol, 2,4-di-*t*-butylphenol and isobutene on montmorillonites as catalysts (KSF, K10) was chosen as a model reaction. Both the reactant and the catalysts coupled very well with microwaves. KSF and K10 catalysts in the form of a fine powder (10–15 μm) were used to avoid creation of hot spots (as in the presence of voluminous catalyst pellets, e.g. 5 mm [36, 37]). The results can be summarized as follows.

Effect of microwaves on selectivity

The product distribution determined for the reactions performed over a broad temperature range (from –176 to 199 °C) under microwave heating was always more or less different from that obtained by conventional method. Thus, a vigorous formation of isobutene under reflux using microwave heating indicates superheating of the catalyst to a higher temperature. This facilitates the dealkylation reaction, which is promoted by elevated temperature.

Effect of microwaves on rate enhancement

Temperature and solvent effects were examined with the following results. When the reaction temperature was gradually decreased from the reflux temperature (199 °C), the rate enhancement factor increased from 1.0 at 199 °C to 1.4 at 105 °C, and to 2.6 at 75 °C. These results may indicate that the superheating of the catalyst is more pronounced at lower temperatures. In the presence of nonpolar solvents like hexane and heptane, the more efficient heat transfer from the superheated catalyst particles can explain the lower value of the rate enhancement 1.2 at 105 °C (heptane) and 1.6 at 75 °C (hexane). In order to suppress the reaction under conventional heating, the reaction was performed at very low temperatures ranging from –176 to 0 °C, i.e. in the temperature region in which conventional conditions [60] do not lead to any reaction. The efficient cooling of the reaction mixture by liquid nitrogen or dry ice was used to perform the reaction at the above mentioned low temperatures. The reaction was taking place in the solid state because 2-*t*-butylphenol solidified at these temperatures (m.p. is –7 °C). It seems likely that under these conditions the heat transfer from the superheated catalyst particles in the solid reaction mixture at –176 to 0 °C was not so efficient, and rather significant conversions (0.5–31.4%) were recorded. The superheating of catalyst particles (or acidic active sites?) was calculated to be 105–115 °C over the bulk. When the reaction mixture was diluted by a nonpolar solvent (hexane + tetrachloromethane) under efficient stirring, no reaction was observed to take place, similarly as under conventional conditions [60]. This finding can be accounted for an efficient heat transfer from the catalyst particles due to efficient stirring of the liquid reaction mixture. The question is the extent of catalyst superheating. Are catalyst particles of 10–15 μm or polar acidic sites superheated, participating in the interaction of microwave energy with highly polarized reagent molecules via adsorption of these molecules on their active sites? The above finding related to selective heating of active acidic sites was not excluded but also no direct evidence has been found for this assertion.

When the results obtained in the liquid phase are applied to the reactions 1–7 and 8–13, above, both for the liquid and gas phase, one can conclude that if reactions are performed under conditions where temperature gradients can be completely eliminated, e.g. on using efficient stirring, nonpolar solvents, a high flow of reactants in continuous flow system, fluidized bed and then any differences between microwave and conventional heating conditions may disappear. However, from the synthetic point of view it is more attractive to perform synthetic reactions using microwaves under conditions favorable to the production of temperature gradients, because higher reaction rate and improved selectivities can be obtained more easily compared to conventional heating methods.

10.3.4
Microwave Catalytic Reactors

10.3.4.1 Batch Reactors

The instrumentation which has been used for microwave catalytic reactions varied from domestic multi-mode ovens to continuous-flow single-mode reactors. In domestic microwave ovens the microwave output is changed by varying the patterns of on–off cycles. Thus, for example, a half microwave output does not mean real half output power but only that the full power is switched on and off for a certain period (e.g. half power corresponds to 10 s full power and 10 s of no power). In this case the catalyst and/or reaction mixture suffer thermal shocks, which is not desirable. Moreover, in domestic microwave ovens the microwaves are randomly distributed in oven space, thereby yielding ill-defined regions of the high and low intensities inside the oven. The second disadvantage of domestic ovens is the problem of temperature measurement, because in the absence of correct temperature profile in the reaction mixture, the reaction is not comparable with conventional heating and may not be reproducible when performed in two different microwave systems.

The problem of switch on–off system of the most domestic ovens has been overcome by an inverter circuit that allows power levels to be adjusted in increments (e.g. 10% of output) [109]. The desired power is continuous at different levels, as compared to the long pulsed operations of the magnetrons in most domestic ovens. The advantage of this system for laboratory applications, where small loads are normally used, is that lower power levels can be applied, which minimizes the amount of the reflected power reaching the magnetrons. Therefore, a simple unmodified microwave domestic oven operating on multi-mode system cannot be recommended for catalytic reactions (and generally for organic synthesis) induced by microwaves. Disadvantages are quite evident:

- no possibility of temperature measurement and no temperature control.
- reaction mixtures subjected to thermal shocks by switch on–off cycles.
- nonhomogenity of microwave field.

However, an inexpensive and safe modification of domestic ovens can be made, which almost eliminates these disadvantages and allows independent temperature

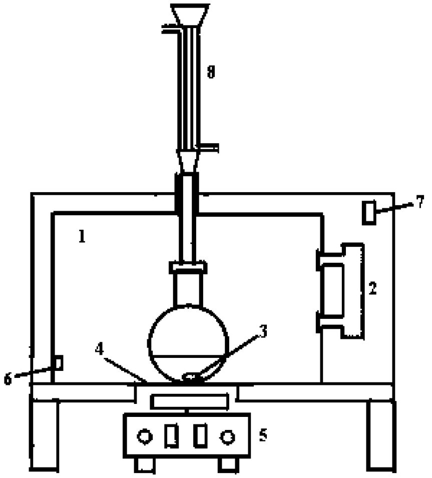


Fig. 10.1 Microwave batch reactor: 1. microwave cavity, 2. magnetron, 3. stirring bar, 4. aluminum plate, 5. magnetic stirrer, 6. IR pyrometer, 7. switch on/off, 8. water cooler.

measurement as well as reasonable temperature control. For temperature measurement IR thermometer or better fiber optic thermometer [58–60] have been recommended. Such a batch microwave reactor made by modification of microwave domestic oven is represented in Fig. 10.1 and was described in some papers [40, 58–60, 109–112] and references cited therein.

A complementary, more advanced, laboratory-scale microwave batch reactor for synthesis and kinetics studies was developed by Strauss et al. [113] (Fig. 10.2).

The reactor is equipped with magnetic stirrer, microwave power and temperature control by computer and can operate under pressure. Even though it was developed for homogeneous organic synthetic reactions, it can be used also for heterogeneous catalytic reactions in the liquid phase.

The first continuous-flow reactor was developed by Strauss [113, 115, 116] and has recently been commercialized.

The reactor (Fig. 10.3) consists of microwave cavity fitted with a tubular coil (3 × 3 mm) of microwave-transparent, inert material. The coin is attached to a meter-

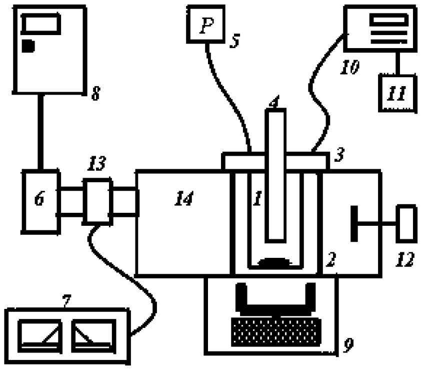


Fig. 10.2 Schematic diagram of the microwave batch reactor: 1. reaction vessel, 2. retaining cylinder, 3. top flange, 4. cold finger, 5. pressure meter, 6. magnetron, 7. power meters, 8. power supply, 9. stirrer, 10. fiber optic thermometer, 11. computer, 12. load-matching device, 13. waveguide, 14. microwave cavity. Reproduced from Ref. [114] by permission of CSIRO Publishing.

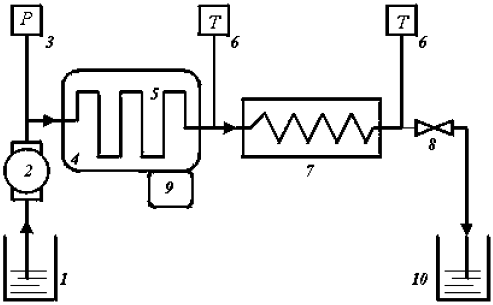


Fig. 10.3 Schematic diagram of the continuous-flow microwave reactor: 1. reactants for processing, 2. metering pump, 3. pressure transducer, 4. microwave cavity, 5. reaction coil, 6. temperature sensor, 7. heat exchanger, 8. pressure regulator, 9. microprocessor regulator, 10. product vessel. Reproduced from Ref. [114] by permission of CSIRO Publishing.

ing pump and pressure gauge at the inlet end and to a heat exchanger and pressure-regulating valve at the effluent end. Temperature is monitored outside the cavity at the inlet and the outlet.

The reactor has facilitated a diverse range of synthetic reactions at temperatures up to 200 °C and 1.4 Pa. The temperature measurements taken at the microwave zone exit indicate that the maximum temperature is attained, but they give insufficient information about thermal gradients within the coil. Accurate kinetic data for studied reactions are thus difficult to obtain. This problem has recently been avoided by using fiber optic thermometer. The advantage of continuous-flow reactor is the possibility to process large amounts of starting material in a small volume reactor (50 mL, flow rate 1 L h^{-1}). A similar reactor, but of smaller volume (10 mL), has been described by Chen et al. [117].

It was noted that hydrolysis of sucrose using a strong acidic cation-exchange resin as heterogeneous catalyst gives better results than with soluble mineral acids [118]. The hydrolysis of sucrose catalyzed by the strong acidic cation-exchange resin Amberlite 200C was used by Plazl et al. [48, 49] to test successfully a continuous-flow catalytic reactor with packed catalyst bed made by a modification of a commercial microwave oven (Panasonic NE-1780). The continuous-flow catalytic reactor was built by modification of domestic ovens (Panasonic, General Electric) also by other authors [38, 40]. The continuous-flow microwave reactor based on single-mode system was described by Chemat [37] and Marquié [118]. Better isothermal conditions, the possibility of selective heating of catalyst bed and scaling-up are the main advantages of single-mode continuous-flow reactors compared to multi-mode systems for catalytic reactions in the liquid phase.

For gas phase heterogeneous catalytic reactions, the continuous-flow integral catalytic reactors with packed catalyst bed have been exclusively used [61–91]. Continuous or short pulsed-radiation (milliseconds) was applied in catalytic studies (see Sect. 10.3.2). To avoid the creation of temperature gradients in the catalyst bed, a single-mode radiation system can be recommended. A typical example of the most advanced laboratory-scale microwave, continuous single-mode catalytic reactor has been described by Roussy et al. [79] and is shown in Figs. 10.4 and 10.5.

The principle aspects of this microwave irradiation system are, briefly:

- continuously variable microwave power from 20 to 200 W;
- temperature of the catalyst bed is measured by use of two thermocouples; and
- homogeneous distribution of electromagnetic field.

In addition to packed catalyst bed, a *fluidized* bed irradiated by single and multimode microwave field, respectively, was also modeled by Roussy et al. [120]. It was proved that the equality of solid and gas temperatures could be accepted in the stationary state and during cooling in a single-mode system. The single-mode cavity eliminates the influence of particle movements on the electric field distribution. When the bed was irradiated in the multimode cavity, the model has failed. Never-

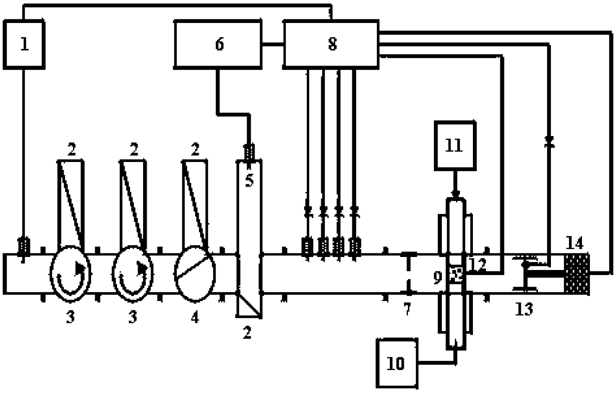


Fig. 10.4 Schematic diagram of the microwave system for catalytic study: 1. generator, 2. water load, 3. circulator, 4. switch, 5. input power, 6. power meter, 7. coupling iris, 8. microcomputer, 9. catalyst, 10. chromatograph, 11. gas production setup, 12. thermocouple, 13. short-circuit, 14. stepping motor. Reprinted from Ref. [119] with permission from Elsevier Science.

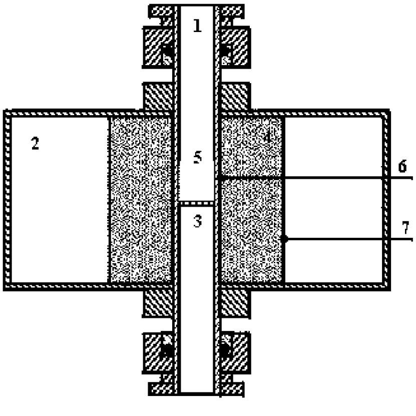


Fig. 10.5 Schematic diagram of the microwave applicator: 1. reactor, 2. wave guide, 3. fritted silica disc, 4. thermal insulation, 5. catalyst, 6, 7. thermocouples. Reprinted from Ref. [119] with permission from Elsevier Science.

theless, the combination of the fluidization technique with microwave heating provides significant benefits such as reduced energy costs, appreciable reduction in processing time, and higher product quality. A fluidized bed reactor has been successfully applied in the destruction of hazardous/toxic organic compounds as trichloroethylene, *p*-xylene, naphthalene, and some gasoline-like hydrocarbon materials [121]. Granulated activation charcoal was used as the catalyst. All these organic compounds could be completely decomposed by the combination of these two technologies.

10.4
Industrial Applications

Since the early 1980s there has been a great deal of interest in the development of industrial applications of microwave irradiation in catalytic processes. This interest has been driven by the unique attributes of the selective interactions of microwave radiation with different materials as the basis for the initiation and control of catalytic chemical reactions. The microwave mode of energy conversion has many attractive features for the chemist because some liquids and solids can absorb in situ and transform electromagnetic energy into heat very effectively [2]. However, microwave technology has so far only rarely attracted industrial attention. A number of potential chemical processes using this technique have been established in research laboratories, but the large scale-up to commercial practice remains elusive. Microwave technology is not new to physicists and electrical engineers, but the concept of using microwaves as an energy source for chemical reactions has only recently been appreciated by chemists. In the subsequent stage of the scale-up of the process, some of potential advantages of the microwave induced catalysis proved in laboratory experiments might not be easy to realize in a commercial scale production. This is because of the necessity to identify many difficulties and modifications, technical and economical, before the final choice of a proper system can be designed and installed [122].

Wan et al. [122] demonstrated problems of the scaling-up in the case of the catalytic conversion ethane into ethyne by finding that the optimization of the process for the large-scale reaction system was quite different from the laboratory experiment. It is not practical to construct a huge quartz reactor enclosed by a huge microwave oven. Rather, the microwave radiation can be introduced into a stainless steel reactor. There are obviously many other engineering problems to be encountered, such as penetration depth, uniformity of temperature profile of catalyst bed and the like, which are specific to a microwave reactor. In large scale processes the spatial uniformity may be often critical. Engineering and scale-up aspects of microwave induced catalytic reactions were summarized by Mehdisadeh [123] of DuPont de Memours Co. It was recommended that the choice of the catalyst should be made not only for its chemical merits, but also for its microwave properties. For example, a catalyst with too low a dielectric loss would be inefficient, and could cause control difficulties. On the other hand, a catalyst with too high a dielectric loss can cause low penetration and uniformity problems.

Despite the scaling-up problems, the following industrial processes have been proposed, and disclosed mainly in the patent literature:

- microwave induced catalytic conversion of methane to ethene and hydrogen [63];
- microwave induced catalytic conversion of methane to C_3 oxygenates [124];
- oxidative coupling of methane to C_2–C_4 oxygenates [125];
- oxidative coupling of methane to ethane and ethene [126];
- cracking of heavy hydrocarbon feeds [127];
- reforming of hydrocarbons [128];
- production of terminal alkenes from long chain alkanes [129–131];
- formation of shorter-chain hydrocarbons from higher hydrocarbons [132];
- preparation of vinyl acetate [133]; and
- production of organic nitrogen compounds by direct conversion of elemental nitrogen [134].

In conclusion, one can ask the question "Which microwave catalytic process is operated on industrial scale"? The answer has been frequently looked for at AMPERE meetings, in particular at conferences in Prague (1998), Valencia (1999), or Antibes (2000) and Bayreuth (2001). It was stated that relevant information concerning this matter was missing, because an industrial microwave catalytic process put in operation had not been disclosed. The reason could be either that such a process has not yet been successfully realized or that the disclosure of new technology has been strictly protected by industry. Nevertheless, the potential of the microwave catalysis for industrial application is quite great, both for gas phase processes and continuous-flow liquid phase reactors where even a small equipment can produce significant amounts of products. Moreover, another potential application exists in environmental catalysis, since recent legislative measures have stimulated the development of new technologies to reduce toxic emissions or to remove and dispose of hazardous wastes.

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11

Transition Metal Catalysis and Microwave Flash Heating in Organic Chemistry

Kristofer Olofsson, Anders Hallberg, and Mats Larhed

11.1

Introduction

The combination of homogeneous catalysis and microwave heating is not only a hot topic but also a research area that is likely to have an impact on several fields of modern chemistry [1–11]. Transition metal-catalyzed reactions that typically needed hours or days to reach completion with standard, thermal heating can now with high reproducibility be brought to full conversion in only seconds or minutes, consuming only a fraction of the energy normally needed for a standard, oil-bath-heated reaction. What is more, the application of microwave heating is in many cases associated with advantages not easily achieved by the use of traditional heating. Indeed, transition metal-catalyzed chemistry has on several occasions been proven to be even more efficient under the action of microwaves than with standard heating [9]. In addition, the preparative value of this heating method has increased with the attentive development of catalytic systems that can withstand the sometimes extreme temperatures that are induced under irradiation [12]. This chapter will discuss some of the factors which make the combination of organometallic chemistry and microwave heating one of the most promising research areas in the field of modern synthetic chemistry.

We review herein progress in microwave-assisted homogeneous metal catalysis in the liquid phase. Most of the work published in this field is, as the reader will see, associated with palladium chemistry, and this will, by necessity, also be reflected in the text.

11.2

Safety

The use of microwave techniques introduces unique challenges in safety considerations. Guidelines for the use of microwave systems in the analytical laboratory have been published and most of these also apply to microwave-assisted organic chemistry [13]. The health hazards of microwave radiation are also still under investigation, and it is not yet known whether or not low level exposure is detrimental. Recom-

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

mended safety levels tend to move in the direction of lower doses of radiation, so great care should be taken to minimize microwave leakage.

Although microwave-heated organic reactions can be smoothly conducted in open vessels, it is often of interest to work with closed systems, especially if superheating and high-pressure conditions are desired. When working under pressure it is strongly recommended to use reactors equipped with efficient temperature feedback coupled to the power control and/or to use pressure-relief devices in the reaction vessels to avoid vessel rupture. Another potential hazard is the formation of electric arcs in the cavity [2]. Closed vessels can be sealed under an inert gas atmosphere to reduce the risk of explosions.

11.3
Metal-catalyzed Reactions

The first examples of the use of palladium as a catalyst for carbon–carbon coupling reactions were reported almost thirty years ago [14], and over recent decades a massive effort has been devoted to the extension of the scope of palladium-catalyzed reactions. Organic and organometallic chemists have received extensive input from palladium-coordination chemistry in the task of understanding the mechanisms behind these efficient synthetic procedures [14].

Palladium(0)-catalyzed coupling reactions – i.e. the Heck and Sonogashira reactions, the carbonylative coupling reactions, the Suzuki and Stille cross-coupling reactions, and allylic substitutions (Fig. 11.1) – have enabled the formation of many kinds of carbon–carbon attachments that were previously very difficult to make. These reactions are usually robust and occur in the presence of a wide variety of functional groups. The reactions are, furthermore, autocatalytic (i.e. the substrate regenerates the required oxidation state of the palladium) and a vast number of different ligands can be used to fine-tune the reactivity and selectivity of the reactions.

The long reaction times (ranging from hours to days) frequently required for full conversions have, however, limited the exploitation of homogeneous catalysis in

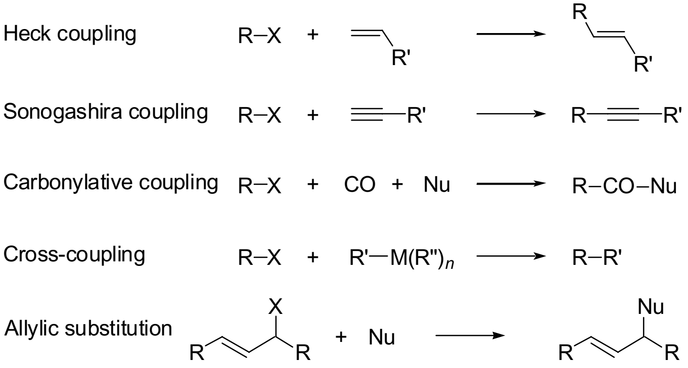


Fig. 11.1 Examples of important palladium(0)-catalyzed transformations.

high-throughput synthesis. Rapid and reliable microwave applications are therefore desired not only for the fast production of new chemical entities but also for homogeneous catalysis in general. In addition, if flash-heated metal-catalyzed reactions can be combined with modern high-speed purification techniques the large repertoire of smooth transformations available will make this methodology highly attractive for the rapid creation of compound libraries [9].

11.3.1
Heck Reactions

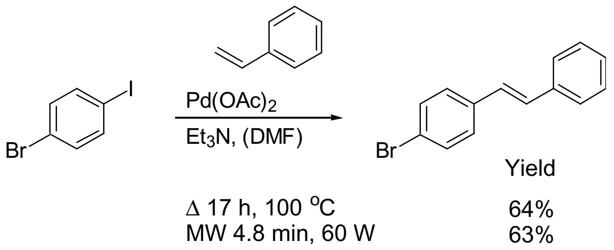
The Heck reaction, a palladium-catalyzed vinylic substitution, is conducted with olefins and organohalides or pseudohalides are frequently used as reactants [15, 16]. One of the strengths of the method is that it enables the direct monofunctionalization of a vinylic carbon, which is difficult to achieve by other means. Numerous elegant transformations based on Heck chemistry have been developed in natural and non-natural product synthesis. Intermolecular reactions with cyclic and acyclic alkenes, and intramolecular cyclization procedures, have led to the assembly of a variety of complex and sterically congested molecules.

Reaction temperatures of 60–120 °C are routinely used with standard catalysts and conventional heating sources [16]. Attempts to reduce reaction times by the use of higher temperatures are seldom effective, because the catalytic systems are often sensitive to heat [17]. As a consequence, access to new methods that enable fast coupling reactions has been highly desirable.

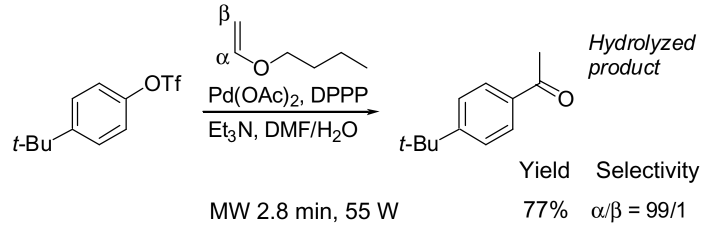
The Heck arylations in Eqs. (11.1)–(11.4), were reported in 1996 and constitute the first examples of microwave-promoted, palladium-catalyzed C–C bond formations [17]. The power of the flash-heating methodology is amply illustrated by the short reaction times and high yields of these couplings. The reactions were conducted in a single-mode cavity in septum-sealed Pyrex vessels without temperature control. The Heck reaction in Eq. (11.1) (and in four additional Heck coupling examples) was originally performed in the absence of solvent. To enhance yields and reduce reaction times 0.5 mL DMF was added to increase the polarity and the dielectric loss tangent of the reaction mixture. This small modification of the original reaction conditions enabled isolation of the products in high purity after very short reaction times (2.8–4.8 min). The same high chemo- and regioselectivity experienced in classical, oil-bath heating was found to apply to these microwave promoted reactions. 4-Bromostilbene was conveniently synthesized within 4.8 min with high chemoselectivity in complete agreement with the literature procedure if a relatively low microwave power was employed (Eq. 11.1).

Microwave promoted, palladium-catalyzed, DPPP-controlled arylation of butyl vinyl ether with 4-*tert*-butylphenyl triflate afforded the branched arylation product and the corresponding methyl ketone, indicating the occurrence of selective internal α-arylation. Addition of water to the reaction mixture and microwave-heating for 2.8 min at 55 W smoothly produced the hydrolyzed product, 4-*tert*-butylacetophenone, with an isolated yield of 77% (Eq. 11.2) [17].

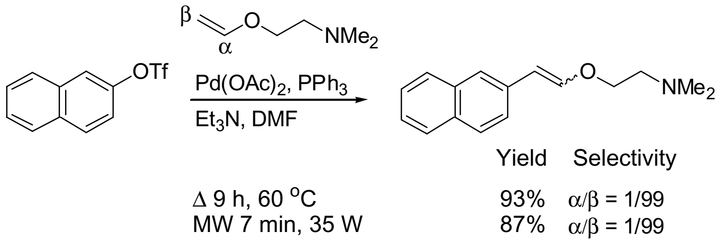
Equally high terminal selectivity was achieved by application of low-power microwave dielectric heating in Eq. (11.3); 87% of the β-product was isolated. This high re-



Equation 11.1 Heck-coupling of 4-bromoiodobenzene and styrene.



Equation 11.2 Heck-coupling of 4-*tert*-butylphenyl triflate and butyl vinyl ether in the presence of water (DPPP = 1,3-bis(diphenylphosphino)propane).

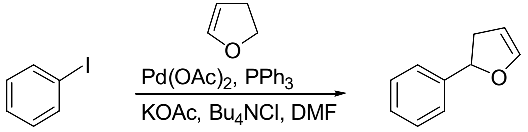


Equation 11.3 Chelation-controlled Heck coupling of 2-naphthyl triflate.

gioselectivity corroborates the applicability of chelation-controlled Heck reactions under microwave heating conditions [17].

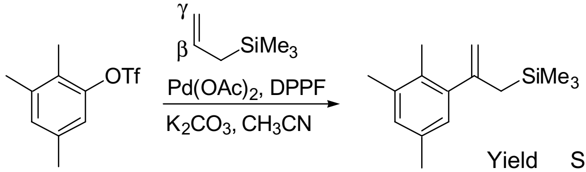
One exception to the preservation of selectivity in microwave reactions was the C2 arylation of 2,3-dihydrofuran, which yielded an isomeric byproduct under the action of microwaves (2-phenyl-2,3-dihydrofuran/byproduct = 71/29), in contrast with the reported procedure using conventional heating (Eq. 11.4). The desired product could be isolated in 58% yield. Attempts to reduce the reaction time by using oil baths (125 °C or 150 °C) did not result in similar yields, but instead furnished complicated reaction mixtures, in definite contrast with the microwave procedure [17].

Regioselectivities that are usually high to excellent have been reported in novel palladium-catalyzed Heck arylation reactions with a variety of allylic substrates. The *β*-stabilizing effect of silicon enhanced regiocontrol in the internal arylation of allyltrimethylsilane (Eq. 11.5) [18], and coordination between palladium and nitrogen



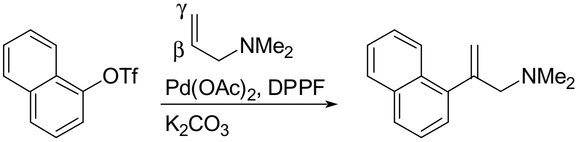
	Yield
Δ 24 h, 80 °C	76%
MW 6 min, 30 W	58%

Equation 11.4 Heck-coupling of iodobenzene and 2,3-dihydrofuran.



		Yield	Selectivity
Δ 20 h, 80 °C		60%	β/γ = 100/0
MW 5 min, 50 W	(GC-MS Yield)	66%	β/γ = 93/7

Equation 11.5 Internal arylation of allyltrimethylsilane (DPPF = 1,1-bis(diphenylphosphino)ferrocene).

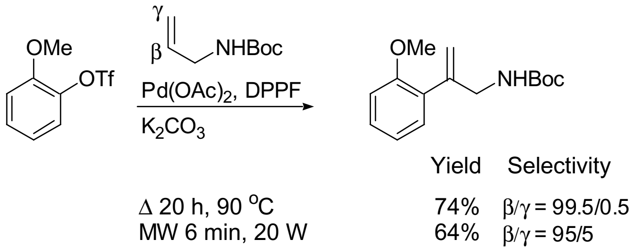


	Yield	Selectivity
Δ 20 h, 80 °C	71%	β/γ = 99.5/0.5
MW 5 min, 15 W	42%	β/γ = 99.5/0.5

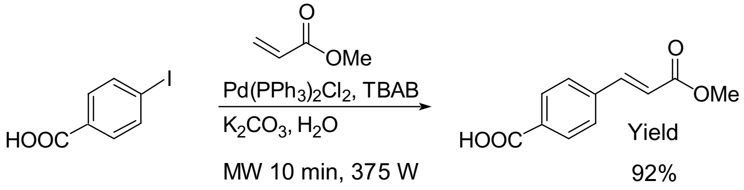
Equation 11.6 Internal arylation of *N,N*-dimethylallylamine.

resulted in very high regioselectivity in the arylation of *N,N*-dialkylallylamines (Eq. 11.6) [19] and the Boc-protected allylamine, producing *β*-arylated arylethylamines (Eq. 11.7) [20]. These internal arylations can be completed in less than 10 min under the action of single-mode microwave irradiation, compared with overnight reactions with conventional heating. Slightly lower selectivity and yields were, however, often obtained in the high-temperature microwave-mediated couplings compared with the corresponding thermal reactions.

In the Heck reactions discussed above it was essential to use polar aprotic solvents such as acetonitrile or DMF if high regioselectivity was to be achieved. In other Heck couplings the use of water as a solvent has recently gained attention. The advantages of water compared with standard organic solvents are many – it is, for example, cheap and nontoxic – but its usefulness extends only over a number of well-defined applications, partly because of problems with the solubility of the reactants and catalysts. The development of aqueous catalytic systems is, consequently, an important field [21].



Equation 11.7 Internal arylation of the Boc-protected allylamine.

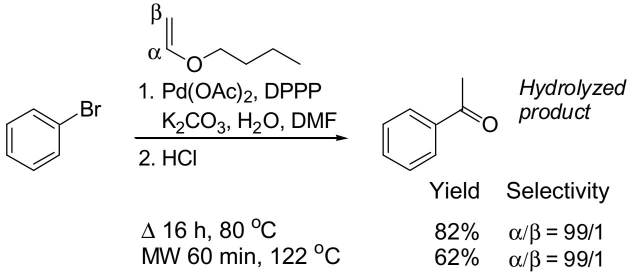


Equation 11.8 Arylation of methyl acrylate under phase-transfer conditions. (TBAB = tetrabutyl ammonium bromide)

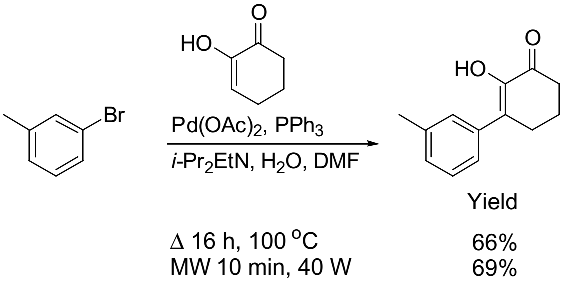
In a recent report by Wang, microwave-mediated Heck couplings were rapidly performed in water under phase-transfer conditions (Eq. 11.8) [22]. Villemin has also reported the use of water and acetonitrile in the context of using water-soluble ligands in microwave-assisted Heck couplings [23].

Even though the excellent internal regioselectivity reported in Eqs. (11.5)–(11.7) is restricted to the use of aryl triflates as aryl precursors, many similar reactions can use aryl bromides in combination with thallium salts. These salts are thought to act as halide scavengers and can thus mimic the leaving group properties of the triflate group by promoting abstraction of the halide [16]. Preparatively, this modification of the Heck coupling is somewhat perilous as the thallium salts are known for their toxicity. With this in mind, the discovery that thallium derivatives could be replaced by the simple addition of water as a cosolvent was conceptually stimulating. Internal arylations of butyl vinyl ether followed by acid workup, resulted in a good yield of acetophenone after 60 min of microwave-heating at the optimized temperature of 122 °C, compared with a reaction time of 16 h with classical heating (Eq. 11.9) [24].

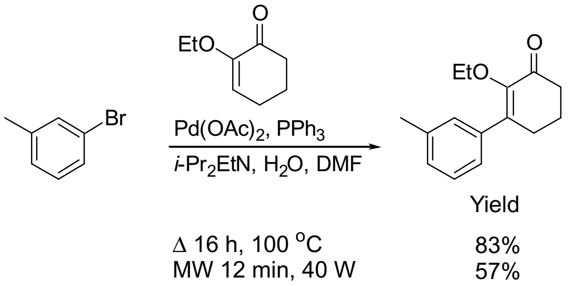
A perhaps more exotic substrate for the Heck reaction is 1,2-cyclohexanedione [25]. The reactivity of this molecule under Heck coupling conditions can probably be attributed to its resonance enol form. This reaction is attractive, because the literature contains relatively few examples of the preparation of 3-aryl-1,2-cyclohexanediones. Yields varied from good to modest when classic heating and electron-rich aryl bromides were used, and reaction times typically ranged from 16 to 48 h. Similar yields were obtained under continuous microwave irradiation with a single-mode microwave reactor for 10 min at 40–50 W (Eq. 11.10) [25].



Equation 11.9 Internal arylation of butyl vinyl ether with bromobenzene.



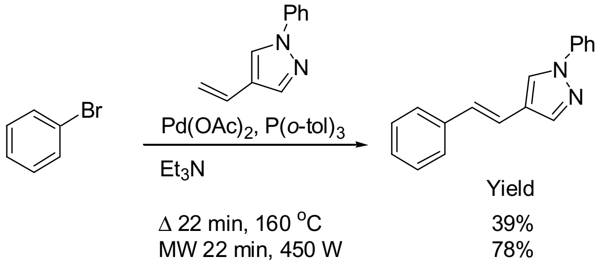
Equation 11.10 Arylation of the enol form of 1,2-cyclohexanedione.



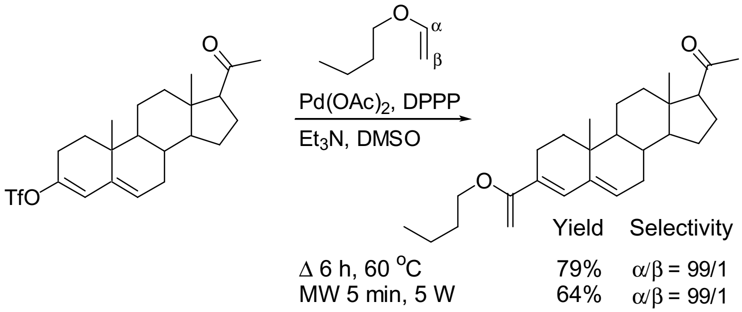
Equation 11.11 Arylation of the ethyl vinyl ether of 1,2-cyclohexanedione.

Traditional Heck arylation of the corresponding ethyl vinyl ether afforded high yields with most of the aryl bromides investigated (Eq. 11.11). Under continuous single-mode microwave treatment the transformations were complete within 10–12 min [25].

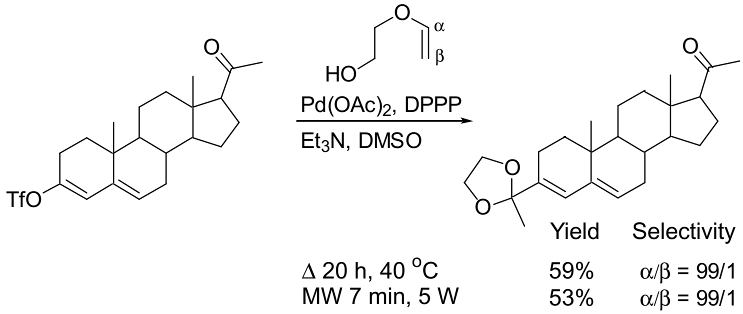
Heck reactions without solvent in a domestic microwave oven have been examined by Díaz-Ortiz [26]. The reactions were conducted in closed vessels with reported temperatures of 150 °C. A study was performed in which reactions performed with microwave irradiation were compared with oil-bath-heated reactions with identical reaction times and temperatures. The isolated yields tended to substantially favor the microwave-heated reactions (Eq. 11.12).



Equation 11.12 Heck reaction with phenyl bromide.



Equation 11.13 Internal vinylation of butyl vinyl ether with a vinyl triflate.



Equation 11.14 Internal vinylation of 2-hydroxyethyl vinyl ether with a vinyl triflate.

A challenge of a different kind was encountered in the internal vinylation of various vinyl triflates and bromides as depicted in Eq. (11.13) [27]. The electron-rich structures obtained from the reactions were of interest for further use in Diels–Alder reactions, but the risk of degrading the products in the hot reaction medium posed a problem and a prudent choice of energy input was imperative. It turned out that single-mode microwave heating for 5 min at the very low power of 5 W was sufficient to yield 64% of the product with excellent regioselectivity. Measurements with a fluoroptic probe revealed an unexpectedly high temperature of 76 °C [27].

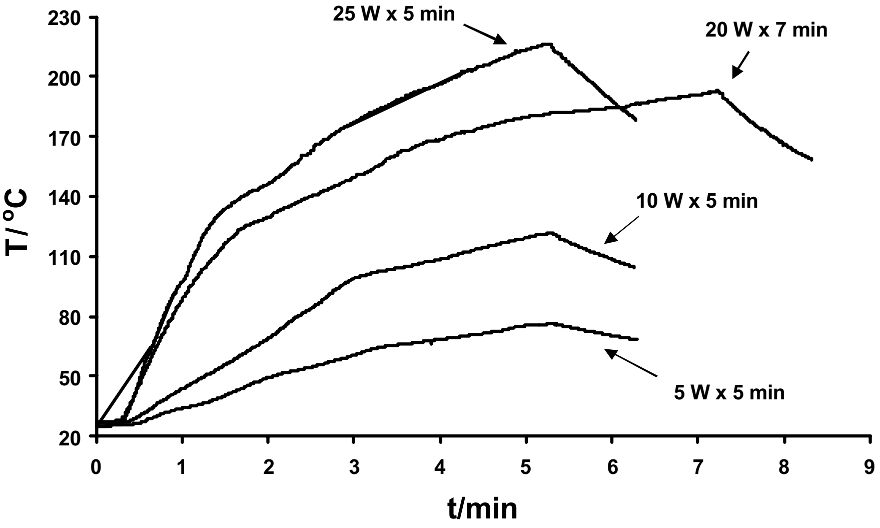


Fig. 11.2 Selected temperature profiles for the single-mode heating of internal vinylations in DMSO at different power inputs (fluoroptic thermometer, Smith prototype).

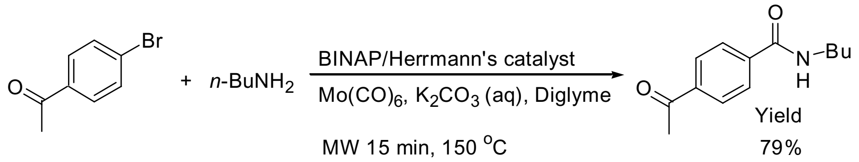
Exchange of the butyl vinyl ether for 2-hydroxyethyl vinyl ether enabled the facile transformation of vinyl triflates or bromides into protected α,β-unsaturated methyl ketones (Eq. 11.14) [27]. One interesting aspect of this reaction is that a masked methyl ketone can easily be introduced into a structure even in the presence of other free ketone groups.

Selected temperature profiles for the reactions represented in Eqs (11.13) and (11.14) are shown in Fig. 11.2. Note that the high tan δ value of DMSO (0.825) [5] results in extensive heating even at a relatively modest power input of single-mode irradiation.

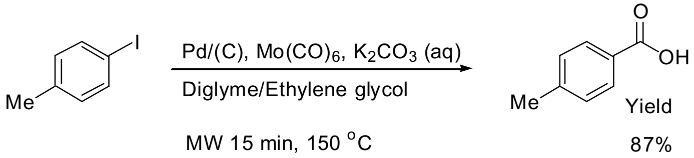
11.3.2
Carbonylative Couplings

The palladium-catalyzed Heck carbonylation reaction is a powerful means of generating amides, esters, and carboxylic acids from aryl halides or pseudohalides [28]. The development of rapid, reliable, and convenient procedures for the introduction of carbonyl groups is important for the development of high throughput chemistry in general and high-speed microwave-mediated chemistry in particular. Unfortunately, the traditional method of introducing carbon monoxide into a reaction mixture via a balloon or gas tube is not practical because of the special requirements of microwave synthesis.

The molybdenum hexacarbonyl complex was recently introduced as a condensed source of carbon monoxide for Heck carbonylations [29]. This easily handled and inexpensive solid delivers a fixed amount of carbon monoxide when heated to approxi-



Equation 11.15 Carbonylative coupling with molybdenum hexacarbonyl.



Equation 11.16 Carbonylative synthesis of benzoic acid in the presence of ethylene glycol.

mately 150 °C. This enables the *in situ* generation of carbon monoxide directly in the reaction mixture, without the need for external devices.

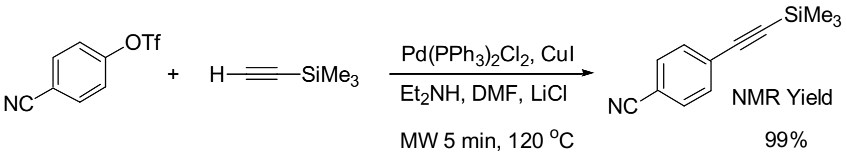
A variety of amides has been formed in moderate to high yields with aryl bromides or iodides as aryl precursors and single-mode microwave heating for 15 min at 150 °C (Eq. 11.15) [29]. Under these conditions, aliphatic, unhindered primary, and secondary amines reacted readily, whereas sterically hindered amines or amines of low nucleophilicity, e. g. anilines, afforded low yields and incomplete conversions. Among the homogeneous catalytic systems tested the most suitable for the use with aryl bromides was a 2 : 1 mixture of BINAP and Herrmann's palladacycle.

Addition of ethylene glycol as cosolvent, as in Eq. (11.16), resulted in efficient formation of the corresponding benzoic acid, instead of the amide [29].

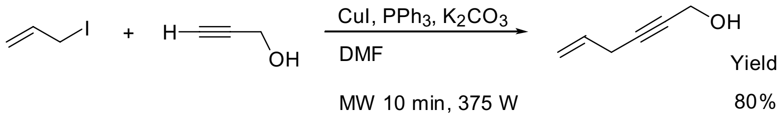
11.3.3
Sonogashira Coupling Reactions

The palladium-catalyzed Sonogashira coupling enjoys considerable popularity as a reliable and general method for the preparation of unsymmetrical acetylenes [30]. Erdélyi and Gogoll recently highlighted the potential of controlled microwave heating to promote homogeneous Sonogashira couplings under single-mode reaction conditions [31]. Problems with thermal runaway effects had been reported after previous attempts to execute similar reactions with microwaves, a difficulty that seemingly could be dealt with more easily with a single-mode apparatus with temperature control. An illustration is shown in Eq. (11.17), where 4-cyanophenyl triflate was completely consumed after only 5 min of irradiation. Several different examples of reactions with aryl halides were also reported.

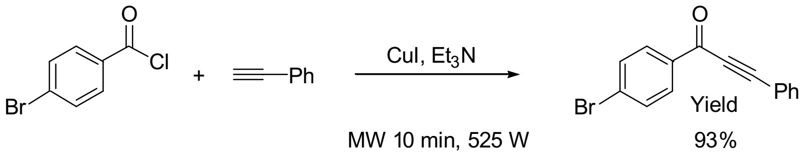
Wang also reported efficient Sonogashira-type reactions in DMF (Eq. 11.18) [32]. Interestingly, the generally most efficient palladium catalysts did not have to be



Equation 11.17 Sonogashira coupling of 4-cyanophenyl triflate.



Equation 11.18 Sonogashira coupling of allyl iodide.



Equation 11.19 Synthesis of conjugated acetylenic ketones with CuI-catalysis.

used, because the cheaper CuI could be employed with reasonable yields. The copper-catalyzed aroylation reactions were performed in triethylamine and in the absence of any added solvent (Eq. 11.19) [33]

11.3.4
Cross-coupling Reactions

A cross-coupling can be described as a transition metal-catalyzed reaction of a nucleophilic organometallic reagent with an organic halide or pseudohalide, leading to a new carbon–carbon σ-bond and a metal halide. The most preparatively useful reagents include organoboron, organotin, and organozinc compounds. An attractive feature of many cross-coupling reactions is that the most commonly used functional groups, in either or both of the coupling partners, are unreactive under the reaction conditions used, which means that the use of protection groups is often unnecessary. Organoboron and organotin reactants have the benefit of being comparatively stable to air and moisture and organoboron compounds have the added advantage of low toxicity.

11.3.4.1 Suzuki Couplings

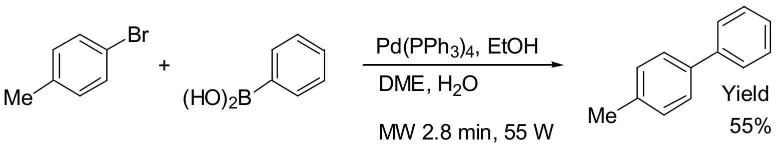
Organoboron compounds were first thought to be poor coupling partners in cross-coupling reactions, because the organic groups on boron are only weakly nucleophilic. Suzuki, however, discovered that coupling reactions of organoboron compounds proceeded in the presence of ordinary bases such as hydroxide or alkoxide ions [34].

This modification proved generally applicable and the Suzuki reaction is arguably the most versatile of modern cross-coupling reactions. The reaction has, for example, attracted the interest of groups involved in high-throughput chemistry, because a large variety of boronic acids are commercially available.

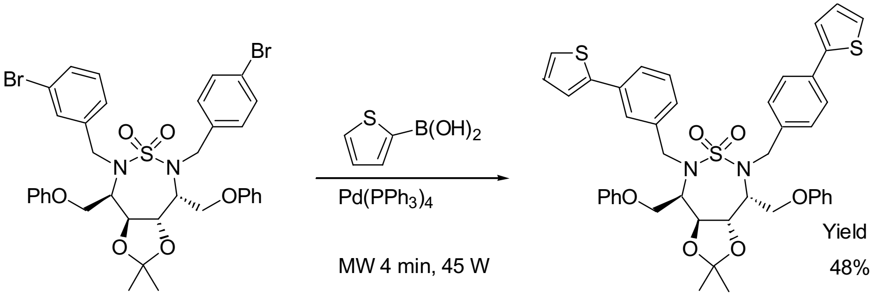
The first microwave-promoted Suzuki couplings were reported in 1996 (Eq. 11.20) [17]. Phenyl boronic acid was coupled with 4-bromotoluene to give a fair yield of product after a reaction time of less than 3 min under single-mode irradiation. The same reaction had previously been conducted with a reported reaction time of 4 h.

Equation (11.21) is an example of a single-mode microwave-promoted Suzuki coupling, delivering a cyclic HIV-protease inhibitor after a subsequent hydrolysis of the ketal group [35]. Half a dozen compounds were synthesized with the help of microwaves and some of the compounds had K_i values in the nanomolar range.

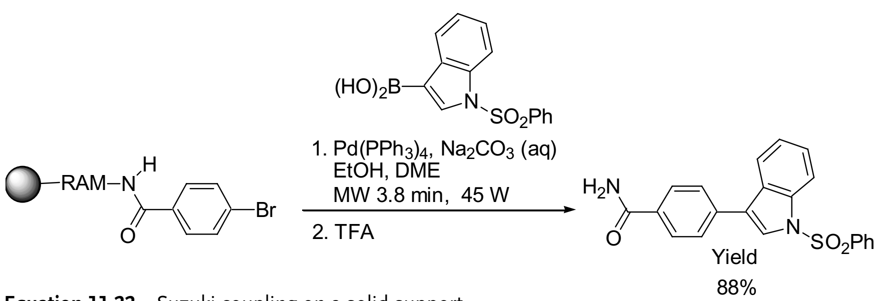
Interestingly, the Suzuki reaction worked smoothly on solid supports and high yields of a variety of products were reported under these reaction conditions (Eq. 11.22) [36]. 4-Bromo- and 4-iodobenzoic acid linked to Rink-amide TentaGel re-



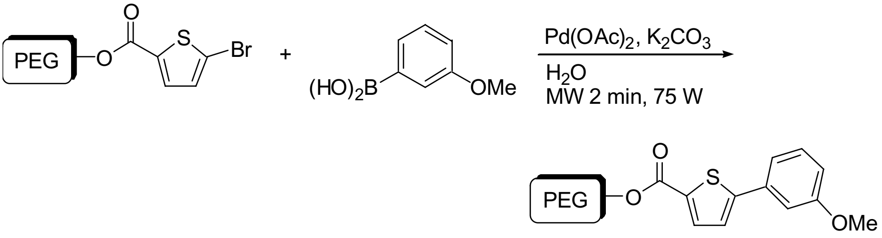
Equation 11.20 Suzuki coupling of phenyl boronic acid with 4-bromotoluene.



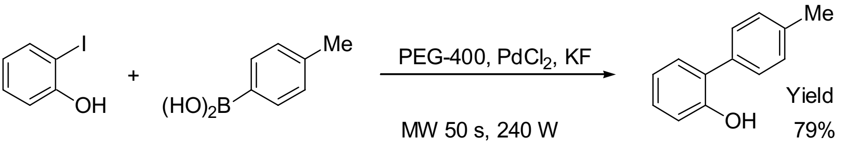
Equation 11.21 Double Suzuki coupling generating a precursor to an HIV-protease inhibitor.



Equation 11.22 Suzuki coupling on a solid support.



Equation 11.23 PEG-supported, aqueous Suzuki coupling.



Equation 11.24 Suzuki coupling in PEG as a nontoxic reaction medium.

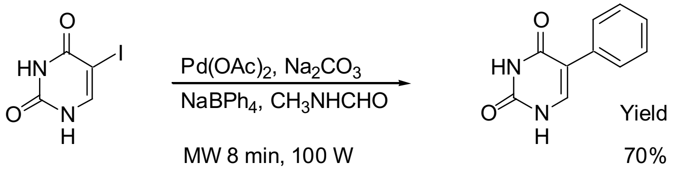
sulted in more than 99% conversion of the starting material, and the whole reaction was brought to completion within 4 min. The high yields suggest the high potential of the use of microwave-assisted reactions on polymer supports [37].

Another interesting report by König deals with rapid parallel Suzuki reactions in water with phase-transfer catalysts [38]. The polymeric support used in these reactions was PEG and a variety of aryl-palladium precursors was evaluated (halides, triflates, and nonaflates, Eq. 11.23). The soluble polymer-supported liquid phase strategy with PEG is appealing because, apart from facilitating the purification procedure, PEG also helps solubilize the reagents and it has been suggested that PEG stabilizes the palladium catalyst in the absence of phosphine ligands. The reactions typically reached full conversion in only 2 min of 75 W heating in a multimode oven, whereas the parallel reactions needed 4 min to reach completion. The standard heating techniques required 2 h for the same reactions. The polymers and the esters were both reported to withstand 10 min of 900 W microwave heating whereas conventional thermal conditions induced substantial (up to 45%) ester cleavage [38].

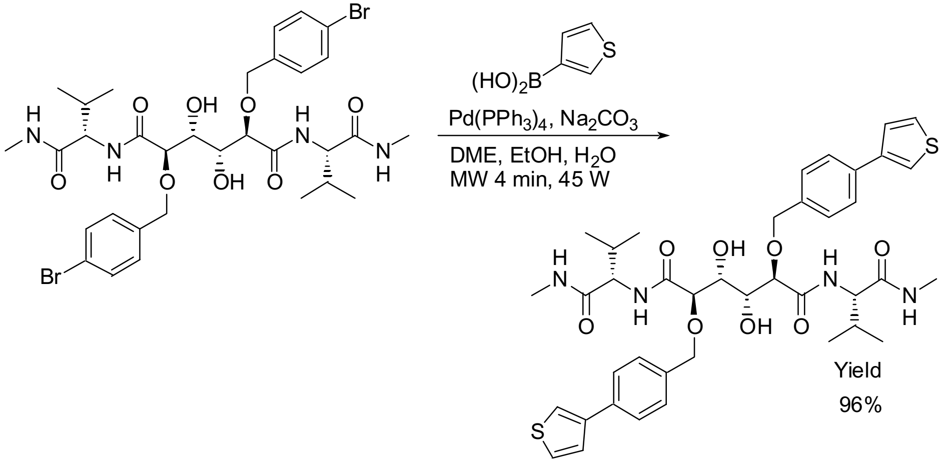
Similar Suzuki couplings performed with PEG as a nontoxic reaction medium have been reported by Varma (Eq. 11.24) [39]. A domestic microwave oven with inverter technology was used for these experiments and it was suggested that this technology enabled more realistic control of the microwave power input.

Villemin has reported the use of sodium tetraphenylborate as a stable reactant for Suzuki couplings performed in water or *N*-methylformamide (NMF) as solvents (Eq. 11.25) [40].

A series of potent, linear C2-symmetric HIV-1 protease inhibitors with K_i values in the nanomolar range was prepared from a diaryl bromide precursor emanating from a carbohydrate scaffold, by application of Heck, Suzuki, Stille, and cyanation reactions. Included in this series was the first reported microwave-promoted Suzuki coupling with an alkyl borane [41]. A very high-yielding Suzuki coupling is presented



Equation 11.25 Suzuki coupling with sodium tetraphenylborate.



Equation 11.26 Synthesis of a linear HIV-protease inhibitor by a double Suzuki coupling.

in Eq. (11.26) and demonstrates that even relatively complex structures, such as these peptidomimetics, do not decompose or are in any other way unsuitable for applications with flash heating chemistry. These syntheses of HIV-protease inhibitors were reported to be the first examples in medicinal chemistry of the application of homogeneous palladium-catalyzed reactions conducted with flash heating [41].

11.3.4.2 **Stille Couplings**

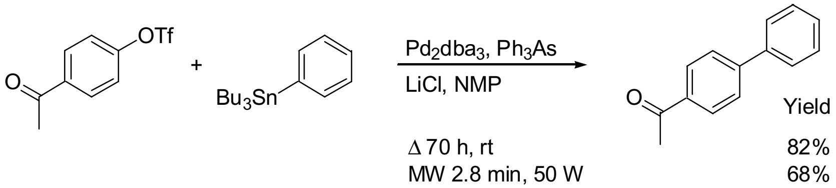
The defining feature of the Stille cross-coupling reaction (or the Migita–Kosugi–Stille coupling) is the use of an organotin moiety in combination with palladium catalysts [42]. This reaction is, in the same way as the Suzuki reaction, very reliable, high yielding, and tolerant of many functionalities. The main drawback is the modest reactivity of the organotin reactants, but this limitation can often be overcome by judicious choice of experimental conditions. The nonreacting ligands are usually methyl or butyl, although newer dummy ligands have been proposed. Typically, the transferable fourth ligand on tin is an unsaturated moiety. The group transfer order is believed to be alkynyl > vinyl > aryl > alkyl.

The Stille reaction was one of the earliest transition-metal-catalyzed reactions to be reported with microwave-heating, and single-mode irradiation with very short reaction times was easily applied to Stille reactions in solution (Eq. 11.27) [17] and on polymer supports (Eq. 11.28) [36].

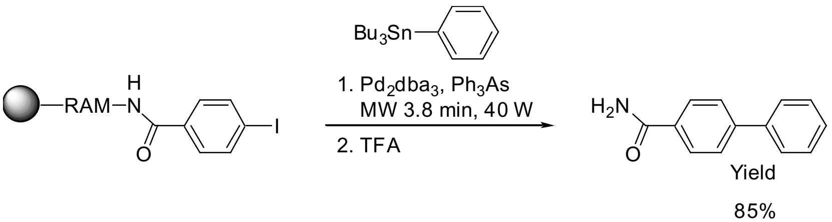
We [43] and, more recently, Maleczka [44] have reported one-pot microwave-assisted hydrostannylations and Stille coupling sequences. Eq. (11.29) depicts one of Maleczka's reactions (see also Eq. 11.32).

Some of the disadvantages of the Stille reaction, e. g. the low reactivity of some substrates, separation difficulties in chromatography, and the toxicity of tin compounds, have been ameliorated by recent efforts to improve the procedure. Curran has, in a series of papers, reported the development of the concept of fluorous chemistry, in which the special solubility properties of perfluorinated or partly fluorinated reagents and solvents are put to good use [45]. In short, fluorinated solvents are well known for their insolubility in standard organic solvents or water. If a compound contains a sufficient number of fluorine atoms it will partition to the fluorous phase, if such a phase is present. An extraction procedure would thus give rise to a three-phase solution enabling ready separation of fluorinated from nonfluorinated compounds.

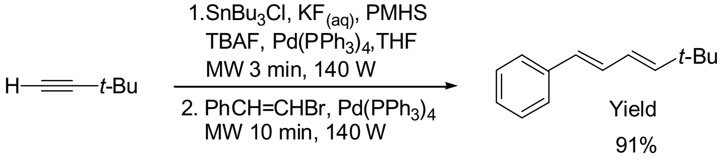
Among the many applications of fluorous chemistry is the Stille coupling of tin reagents with fluorinated tags in which the products and excess of the tin-containing reagents can be conveniently removed from the reaction mixture, and recycled. Un-



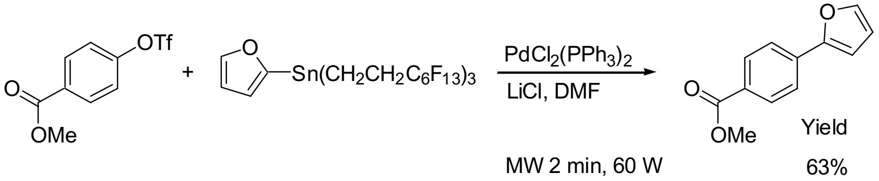
Equation 11.27 Stille coupling in solution with 4-acetylphenyl triflate.



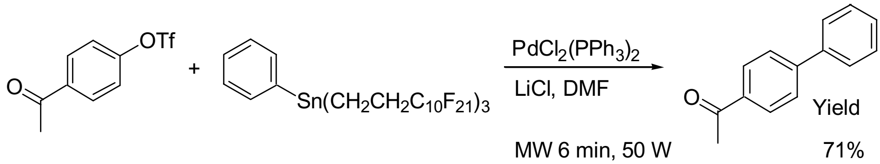
Equation 11.28 Stille coupling utilizing a RAM-linker on a polymer support.



Equation 11.29 One-pot hydrostannylation and Stille coupling (PMHS = polymethylhydrosiloxane).



Equation 11.30 Stille reaction with the F-13-tagged furyltin reagent.



Equation 11.31 Stille reaction with the F-21-tagged phenyltin reagent.

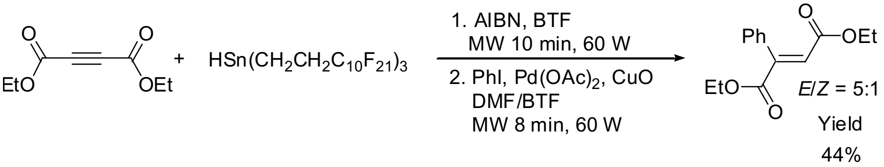
fortunately, fluorous Stille reactions require long reaction times, typically one day at 80 °C and the solubilities of fluorous compounds in most of the common solvents used in synthesis are low, which limits the scope of the procedure.

The long reaction times under the action of classic heating were reduced to only a few minutes with single-mode heating at a power of 50–70 W. One example of the use of $CH_2CH_2C_6F_{13}$ (denoted F-13) -tagged organostannanes is presented in Eq. (11.30) [46].

Occasionally it was apparent that the fluoricity provided with the F-13 tags was not sufficient to enable full partitioning of the products to the fluorous phase. The use of more heavily fluorinated tags, e.g. the $-CH_2CH_2C_{10}F_{21}$ (F-21) tag, was investigated, but proved to be preparatively elusive, because the solubility of these compounds was very poor. Heating the reactions to 80 °C in fluorinated solvents resulted in very sluggish and irreproducible reactions. The use of single-mode heating enabled rapid and efficient reactions (Eq. 11.31) [43]. Superheating of the solvent made solution of the reactants possible and a one-phase system was generated by the heating procedure. On cooling, the fluorous reagents and products separated from the mixture again and separation of fluorous from nonfluorous compounds ensued without complications. The use of highly fluorinated tags could be said to combine the attractive features of both solid- and liquid phase chemistry, because the ease of separation is reminiscent of the former and the versatility and reactivity of the soluble reagents is typical of the latter.

The fluorous Stille procedure has also been applied to a one-pot hydrostannylation of an acetylenic compound in the hybrid fluorous/organic solvent benzotrifluoride (BTF). Subsequent Stille coupling of the product in BTF/DMF, as shown in Eq. (11.32), was easily achieved in 8 min with 60 W single-mode microwave irradiation [43].

To take advantage of the fluorous extraction procedure, or the use of the preparatively simple filtration, the use of highly fluorous reagents is crucial. The usefulness of the microwave heating technique is obvious in these examples.



Equation 11.32 One-pot hydrostannylation and Stille reaction with F-21-tagged reagents.

The first examples of microwave-assisted cross-couplings with organozinc compounds were recently reported [47]. In addition, the first high-speed synthesis of aryl boronates (Suzuki coupling reactants) has been performed under the action of single-mode irradiation with an *in-situ*-generated palladium carbene catalyst [48].

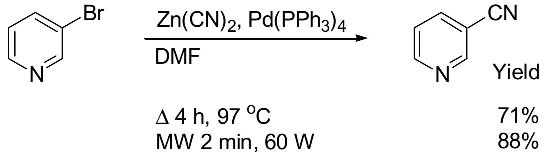
11.3.5
Other Palladium-catalyzed Reactions

The synthesis of nitriles from halides is valuable in medicinal chemistry because nitriles are flexible building blocks readily converted into carboxylic acids, amides, amines, or a variety of heterocycles, e. g. thiazoles, oxazolidones, triazoles, and tetrazoles. The importance of the tetrazole group in medicinal chemistry is easily understood if we consider that it is the most commonly used bioisostere of the carboxyl group.

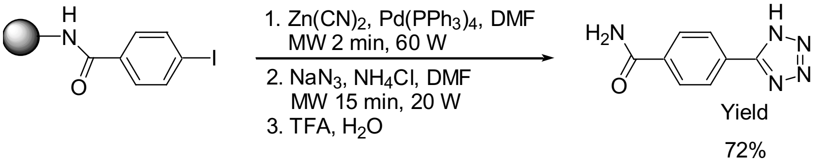
An improvement of the palladium-catalyzed cyanation of aryl bromides, in which zinc cyanide was used as the cyanide source, was reported in the middle of the nineties [49]. Typically, the conversion from halide to nitrile takes at least 5 h by this route and the subsequent cycloaddition to the tetrazole is known to require even longer reaction times.

A single-mode microwave procedure has been reported for the palladium-catalyzed preparation of both aryl and vinyl nitriles from the corresponding bromides. The reaction times were short and full conversions were achieved in just a few minutes (Eq. 11.33) [50]. The cycloadditions to yield the tetrazoles needed slightly longer reaction times, from 10 to 25 min, but only 20 W of power was required as a temperature of 220 °C was reached after 10 min heating. The yields in this step ranged from 36% to 96%. This method for transforming halides into tetrazoles has been used for the synthesis of a novel HIV-protease inhibitor [50].

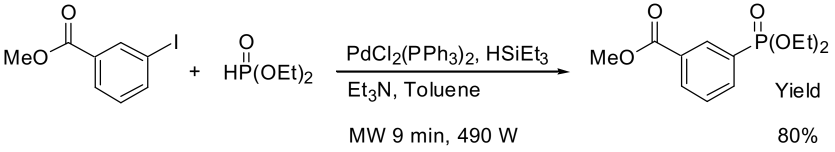
The coupling and cycloaddition could also be achieved as a one-pot procedure on a polymer support, as shown in Eq. (11.34), in which a Rink linker on TentaGel was used. Negligible decomposition of the solid support was reported [50].



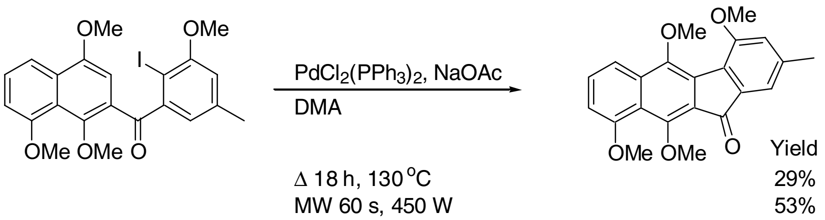
Equation 11.33 Palladium-catalyzed conversion of aryl bromides into aryl nitriles.



Equation 11.34 One-pot procedure for tetrazole synthesis on a polymer support.



Equation 11.35 Conversion of aryl iodides into aryl phosphonates.



Equation 11.36 Intramolecular ring-closure to kinafluorenones.

The conversion of aryl iodides into aryl phosphonates, a useful precursor to aryl phosphonic acids, was performed in a Teflon autoclave by Villemin [51]. A domestic microwave oven was used for these experiments and the reaction times for classic heating were effectively reduced from 10 h to 4–22 min. The reactivity of iodides was good whereas the use of bromides resulted in lower yields and reactions with triflates were very slow (Eq. 11.35). It is notable that the reactions were brought to completion with short reaction times in a non-polar solvent.

The synthesis of kinafluorenones, which are of interest for the synthesis of *Streptomyces*-related antibiotics, has been investigated by Jones [52]. The palladium-mediated ring closure depicted in Eq. (11.36) resulted in poor yields under conventional heating but irradiation with a domestic microwave oven for 60 s improved the yield substantially.

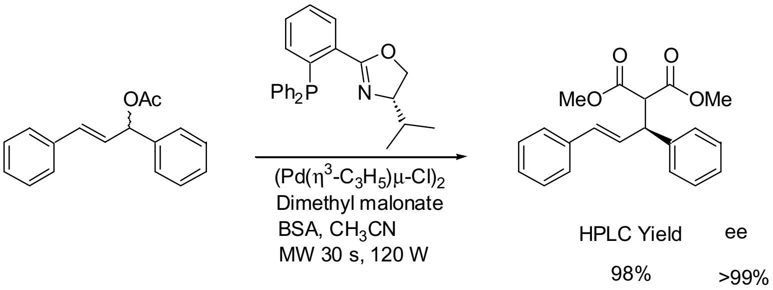
11.3.6
Asymmetric Catalysis

Palladium-catalyzed allylic substitution reactions are popular in the chemical community and the number of applications of the reaction, perhaps in particular for asymmetric procedures, continues to grow [53]. The efficiency of asymmetric chemistry is best described in terms of the enantiomeric excess (ee) of the reaction, and it has been shown that microwave heating can dramatically reduce the reaction times in asymmetric catalysis without significantly affecting ee values [54].

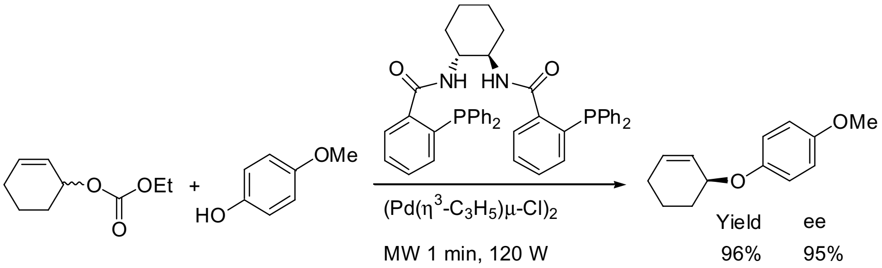
This particular field of palladium chemistry has been responsible for attempts to develop temperature-stable catalyst systems, sometimes with very fascinating results. The high temperatures of microwave synthesis can be a double-edged sword – the high temperatures result in high reaction rates but also increase the risk of catalyst breakdown. It is often the metal ligands that are temperature sensitive, and because these ligands induce the asymmetry in the reactions, catalyst breakdown is associated with loss of ee. The development of temperature-stable ligands for asymmetric reactions has thus been of great importance.

A highly thermostable palladium–phosphine oxazoline catalytic system, shown in Eq. (11.37), has recently been reported to yield high ee under single-mode microwave irradiation [54, 55]. The use of this P,N-ligand catalytic system resulted in even higher ee than the P,P-ligand BINAP [56]. The reactions were performed in acetonitrile (b.p. 81–82 °C) and superheating increased the temperatures up to 145 °C, as measured by means of a fluoroptic probe.

The palladium-catalyzed substitution of the less reactive racemic ethyl 3-cyclohexenyl carbonate could, in a similar fashion, be completed with dimethyl malonate, *p*-methoxyphenol, or phthalimide as nucleophiles, with satisfactory ee (Eq. 11.38) [55]. These reactions, when irradiated for 1 min with temperatures up to 100 °C, delivered yields (91–96%) and ee values (94–95%) identical with those performed in



Equation 11.37 Asymmetric palladium-catalyzed allylic alkylation (BSA = *N*,*O*-bis(trimethylsilyl)acetamide).

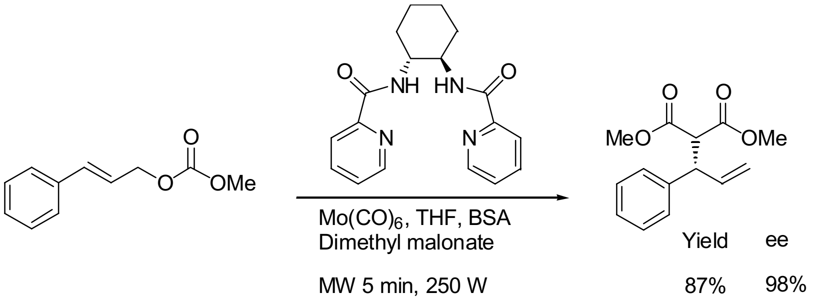


Equation 11.38 Asymmetric substitution of racemic ethyl-3-cyclohexenyl carbonate.

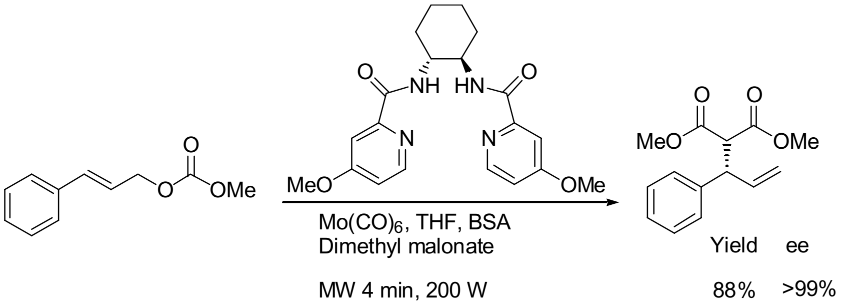
closed vessels in an oil bath at 100 °C for 5 min. A related experiment, conducted in acetonitrile with phthalimide as nucleophile in which the temperature was increased to 140 °C, resulted in much higher yields when microwave heating was used, although the enantiomeric excesses remained the same (95–96%) [55].

The molybdenum-catalyzed asymmetric reaction differs from the palladium-catalyzed reaction in several ways, the most important of which is the different regioselectivity achieved. Molybdenum-catalyzed reactions favor the most sterically hindered position (Eq. 11.39), in contrast with palladium catalysis. The molybdenum-catalyzed allylations also suffer from significantly lower reactivity.

It was found by Trost that the low reactivity could be circumvented by the employment of labile ligands, such as the propionitrile in the $Mo(CO)_3(EtCN)_3$ precatalyst [57]. Instead of directly transferring this procedure to microwave heating applications, a useful and easily handled microwave procedure was developed for rapid and selective molybdenum-catalyzed allylic alkylations under noninert conditions (Eq. 11.39) [12]. The former, more sensitive, two-step reaction was fine-tuned into a robust one-step procedure employing the inexpensive and stable precatalyst $Mo(CO)_6$, used in low concentrations. The alkylations were conducted in air and resulted in complete conversions, high yields, and an impressive enantiomeric excess (98%) in only 5–6 min. Despite the daunting temperatures, up to 250 °C with THF



Equation 11.39 Asymmetric molybdenum-catalyzed allylic alkylation.



Equation 11.40 Asymmetric molybdenum-catalyzed allylic alkylation with an optimized ligand.

as solvent (b.p. 65–67 °C), the high enantiomeric purity remained constant, which suggests that the coordination of the ligand to the metal is not broken, despite of these stressing reaction conditions [12].

After preparation of several different chiral *trans*-1,2-bis-(2-carboxyamidopyridine) cyclohexane ligands, a 4-methoxypyridine derivative (Eq. 11.40) was discovered to have superior qualities and to deliver a high yield (88%) of the branched product with >99% ee and a regioisomer ratio of 41 : 1 (alkylation at the most, rather than least, substituted position) [58]. Single-mode microwave irradiation was applied at the very high power of 200 W for 4 min and superheating caused THF to reach temperatures of 150–180 °C.

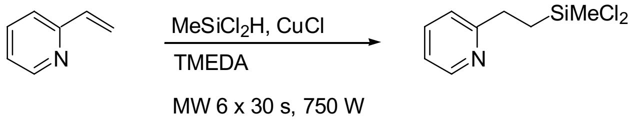
11.3.7
Other Metal-catalyzed Reactions

The copper-catalyzed hydrosilylation of 2-vinylpyridine is reported to be a very dirty reaction associated with low yields and a tedious workup procedure. As early as 1991 Abramovitch used well-defined heating cycles of microwave irradiation to improve this reaction and reported a 360-fold decrease in reaction time and a considerable improvement in yield (Eq. 11.41) [59].

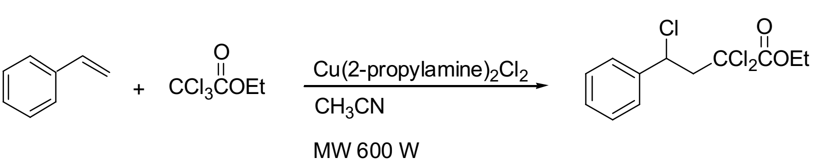
Shortly thereafter Hájek investigated the related CuCl/2-propylamine-catalyzed addition of tetrachloromethane or ethyltrichloroacetate to styrene (Eq. 11.42) and reported a more modest increase in the reaction rate [60]. The reactions were performed under both microwave and classic heating conditions, and the temperatures in the samples were measured by a quick-response digital thermometer.

Gordon used a household microwave oven for the transfer hydrogenation of benzaldehyde with (carbonyl)-chlorohydridotris-(triphenylphosphine)ruthenium(II) as catalyst and formic acid as hydrogen donor (Eq. 11.43) [61]. An improvement in the average catalytic activity from 280 to 6700 turnovers h^{-1} was achieved when the traditional reflux conditions were replaced by microwave heating.

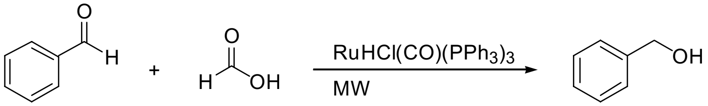
More recently a Ru-catalyzed hydrogen transfer of acetophenone under microwave conditions with monotosylated (*S,S*)-diphenylethylenamine as a chiral source, has



Equation 11.41 Hydrosilylation of 2-vinylpyridine.



Equation 11.42 Addition of ethyltrichloroacetate to styrene.

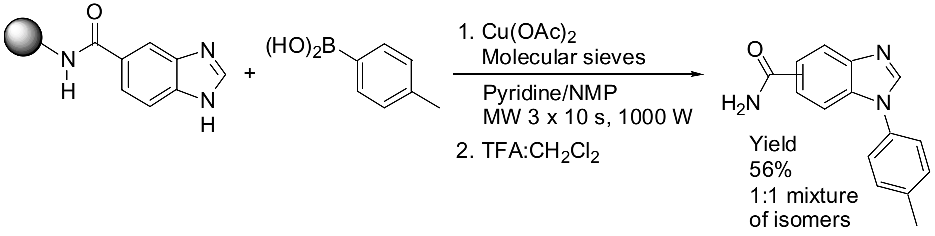


Equation 11.43 Transfer hydrogenation of benzaldehyde with ruthenium catalysis.

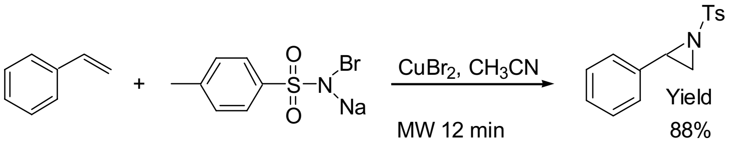
afforded (*R*)-1-phenylethanol in over 90% yield and 82% ee within 9 min [62]. *t*-Butyl phenyl ketone was reduced in almost quantitative yield, although with low ee. Microwave-assisted hydrogenation of electron-deficient alkenes with Wilkinson's catalyst and a polymer-supported hydrogen donor has also been described [63].

Combs recently reported the first examples of a microwave induced copper-catalyzed aryl-heteroaryl C–N coupling reaction in which libraries of *N*-arylated heterocycles were produced for biological screening [64]. An aryl boronic acid was used as a coupling partner and the heterocyclic carboxylic acids were coupled to a PS–PEG resin via a PAL-linker. The yields of the reactions were poor at 80 °C for 48 h with conventional heating. The heating time was reduced to 5 min with a domestic, 1000-W oven at full power after five cycles of 3 × 10 s of irradiation, with manual agitation and addition of fresh reagents between each interval (Eq. 11.44). The reactions worked equally well with a polystyrene resin.

Aziridines comprise a useful group of organic compounds. Chanda and Bedekar reported the microwave-assisted synthesis of aziridines from a variety of olefins with the reagent Bromamine-T (TsN–NaBr). The reaction was catalyzed by metal halides and $CuCl_2$ and $CuBr_2$ were found to give the best yields among the compounds tested (Eq. 11.45) [65]. Microwave heating was reported to increase the reactivity of compounds not reactive under classic heating conditions, although the reported yields were modest.



Equation 11.44 Solid support aryl/heteroaryl C–N coupling reactions.



Equation 11.45 Transition metal-catalyzed aziridation of olefins.

11.4
Summary

The development in microwave chemistry has been remarkable during the last few years; from the first reports in which, typically, domestic ovens were used to modern applications with state-of-the-art single-mode cavities. We believe that it is today possible today to develop robust microwave-assisted methods for nearly any reaction that needs an external heat source and we have proved it is possible to perform transition-metal catalyzed reactions very cleanly and selectively.

Heating by means of single-mode microwave irradiation enables readily adjustable and controlled bulk heating which can be performed safely and with very low energy consumption. The synthetic chemist of today can take advantage of the unique carbon–carbon bond formation reactions afforded by organometallic chemistry and make the reaction happen in seconds or minutes, an important feat, because many transition-metal-catalyzed reactions are time-consuming.

The examples presented indicate that the combined approach of microwave heating and homogeneous catalysis can be an almost synergistic strategy, in the sense that the combination in itself has more potential than its two separate parts in isolation. There are, furthermore, still many other catalytic reactions with great potential for microwave heating [66]. It might, for example, be expected that increasing numbers of aqueous biocatalytic reactions might respond well to microwave heating. It is already clear that modern automatic microwave synthesizers have much to offer in the high-speed generation of combinatorial libraries.

Acknowledgment

We thank the Swedish Natural Science Research Council, the Swedish Foundation for Strategic Research, Knut and Alice Wallenberg's Foundation, PersonalChemistry AB, Medivir AB and Gunnar Wikman.

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12

Microwave-Assisted Combinatorial Chemistry

C. Oliver Kappe and Alexander Stadler

12.1

Introduction

Combinatorial chemistry, the art and science of synthesizing and testing compounds for bioactivity *en masse*, has emerged as one of the most promising approaches to drug discovery [1–5]. Because of the enormous progress made in genomic sciences, molecular biology, and biochemistry, a large number of biologically important target proteins has now become available for screening purposes. This has led to an ever-growing demand for large libraries of novel compounds that are being evaluated for their biological properties by use of appropriate screening procedures. The discovery of novel biological targets was paralleled by the development of novel assays and high-throughput screening (HTS) technologies including miniaturized formats, enabling the testing of thousands of individual compounds per day. Traditional methods of organic synthesis are orders of magnitude too slow to satisfy the increasing demand for these compounds.

Combinatorial chemistry officially dates back to the mid-1980s and since then has experienced enormous growth and has steadily attracted the interest of researchers from a variety of different fields. The essence of combinatorial synthesis is the ability to generate large numbers of chemical compounds very quickly [1–5]. Chemistry in the past has been characterized by slow, steady, and painstaking work; combinatorial chemistry has broken many of the preconceptions and resulted in a level of chemical productivity thought impossible a few years ago. In the past chemists made one compound at a time, in one reaction at a time. For example, compound A would have been reacted with compound B to give product AB, which would have been isolated after reaction, workup, and purification by chromatography. In contrast with this approach combinatorial chemistry offers the potential to make every combination of compound A_1 to A_n with compound B_1 to B_n (Fig. 12.1). The range of combinatorial techniques is highly diverse and the products could be made individually in a parallel fashion or in mixtures, by use of either solution or solid-phase techniques [1–6].

Parallel to these developments in combinatorial chemistry, microwave-enhanced organic synthesis has attracted a substantial amount of attention in recent years. As evidenced from the other chapters in this book and the large number of review articles available on this subject [7–14], high-speed microwave-assisted synthesis has

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

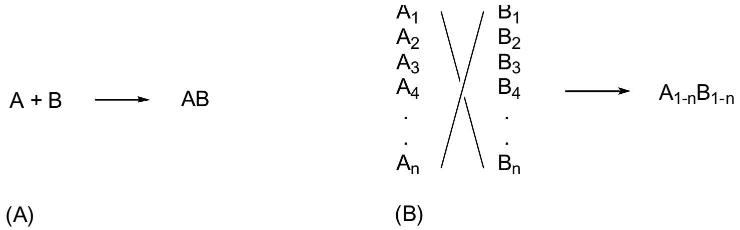


Fig. 12.1 (A) In a conventional synthesis, one starting material A reacts with one reagent B resulting in one product AB. (B). In a combinatorial synthesis, different building blocks of type A_1–A_n are treated with different building blocks of type B_{1-n} according to combinatorial principles.

been applied successfully in many fields of synthetic organic chemistry. It is, in fact, becoming evident that microwave approaches can probably be developed for most chemical transformations requiring heat, and/or for processes in which small polar molecules are removed from a chemical equilibrium. Although different hypotheses have been proposed to account for the rate-enhancements observed under microwave irradiation, a generally accepted rationalization remains elusive (Chapt. 3) [13, 14]. Irrespective of the origin and/or existence of a special microwave effect, rapid microwave dielectric heating (microwave flash heating) is extremely efficient and applicable to a broad range of practical synthesis [7–12].

The main benefits of performing reactions under microwave irradiation conditions are the significant rate-enhancements and the higher product yields that can frequently be observed. Not surprisingly, these features have recently also attracted interest from the combinatorial and/or medicinal chemistry community, for whom reaction speed is of great importance [15–18]. Combination of microwave heating technology and combinatorial chemistry applications is, therefore, a logical consequence of the increased speed and effectiveness afforded by microwave heating. In that respect, all chemical transformations that can be speeded up by microwave irradiation should, by definition, be of interest to practitioners in the field of combinatorial and medicinal chemistry [15–18].

This attractive linking of combinatorial processing with microwave heating was recognized in a 1995 summary of microwave-assisted organic reactions [8]. This review is limited to microwave-assisted processes and techniques that are of direct relevance to combinatorial chemistry applications, including solid-phase organic synthesis, the use of polymer-bound scavengers or reagents, synthesis on soluble polymer supports, fluorous phase techniques, parallel synthesis, and the construction of libraries in automated format by use of microwave technology. Because some of these applications require specialized equipment, a section will be devoted to microwave reactor technology for high-throughput synthesis. In many of the examples of microwave chemistry presented in this review we mention reported “rate-enhancements” in the microwave-heated reactions compared with conventional heating. The reader should be aware that such comparisons are inherently troublesome (Chapt. 3) [13, 14] and do not *a priori* imply the existence of nonthermal or specific microwave effects.

12.2
Solid-Phase Organic Synthesis

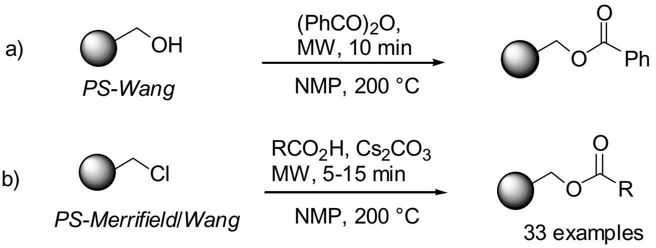
One of the cornerstones of combinatorial synthesis has been the development of solid-phase organic synthesis (SPOS) based on the original Merrifield method for peptide preparation [19]. Because transformations on insoluble polymer supports should enable chemical reactions to be driven to completion and enable simple product purification by filtration, combinatorial chemistry has been primarily performed by SPOS [19–23]. Nonetheless, solid-phase synthesis has several shortcomings, because of the nature of heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reaction, solvation problems, and degradation of the polymer support, because of the long reactions, are some of the problems typically experienced in SPOS. It is, therefore, not surprising that the first applications of microwave-assisted solid-phase synthesis were reported as early 1992 [24].

The earliest published example of microwave-assisted SPOS involved diisopropylcarbodiimide (DIC)-mediated solid-phase peptide couplings [24]. Numerous Fmoc-protected amino acids and peptide fragments were coupled with glycine-preloaded polystyrene Wang resin (PS-Wang) in DMF, using either the symmetric anhydride or preformed *N*-hydroxybenzotriazole active esters (HOBt) as precursors (Scheme 12.1).

Reactions were performed in an unmodified domestic microwave oven employing a custom-made solid-phase reaction vessel under atmospheric pressure. Efficiencies were significantly improved by use of microwave irradiation for all the peptide couplings tested, the rate enhancement being at least 2–3-fold compared with conventional couplings at room temperature. In general, peptide bond formations were completed within 2–6 min, compared to 30 min for reactions without microwave irradiation at room temperature. As with so many of the early publications in microwave-assisted chemistry, the exact reaction temperature during the irradiation period was not determined, presumably because of lack of suitable instrumentation (although the temperature at the end of the reaction could have been measured). The reasons for the observed rate-enhancements, and the possible involvement of so-called nonthermal microwave effects (Chapt. 3) [13, 14] therefore remain unclear.

In a more recent study using dedicated multimode microwave reactors for chemical synthesis, which enable temperature and power control, it was demonstrated that microwave irradiation could be effectively employed to couple aromatic carboxylic acids to polystyrene Wang resin [25], if the symmetrical anhydride procedure was used, and not the three-component *O*-acylisourea activation method [19]. Almost quantitative loading was achieved in 1-methyl-2-pyrrolidone (NMP) at 200 °C within 10 min under

Scheme 12.1 Peptide couplings on solid support.



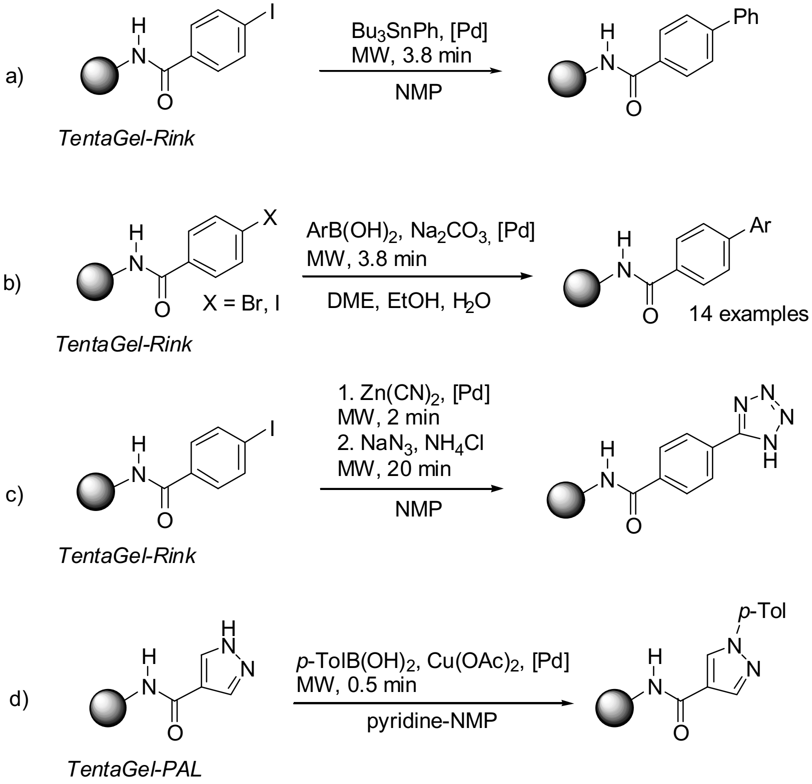
Scheme 12.2 Attachment of carboxylic acids to Wang and Merrifield resins.

atmospheric pressure, as opposed to 2–3 days by use of conventional coupling procedures at room temperature (Scheme 12.2 a). In a related study, the attachment of carboxylic acids to chloromethylated polystyrene resins (Merrifield or Wang linker) via the cesium carbonate method was also investigated (Scheme 12.2 b) [26].

Significant rate-accelerations and higher loadings were observed when the microwave-assisted procedure was compared with the conventional thermal method. Reaction times were reduced from 12–48 h with conventional heating at 80 °C to 5–15 min with microwave flash heating at temperatures up to 200 °C. Detailed kinetic comparison studies using fluoroptic temperature measurements have, however, shown that the rate enhancements observed were because of rapid direct heating of the solvent by microwaves rather than a specific nonthermal microwave effect [26]. Importantly, no degradation of the polystyrene resins was observed, even under prolonged exposure to microwave irradiation at 200 °C.

Transition-metal catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions are processes in which microwave irradiation has often been demonstrated to reduce reaction times from many hours to only a few minutes (Chapt. 11). Several of those important microwave-induced coupling procedures have also been successfully adapted to work on polymeric supports. These include, for example, the palladium-catalyzed Stille and Suzuki couplings shown in Scheme 12.3 (reactions a and b) [27]. A TentaGel resin (poly(ethylene glycol)-grafted polystyrene) was used as the polymeric support, and incorporated the acid labile Rink linker. Microwave irradiation of the reaction mixtures in sealed Pyrex tubes using dedicated monomode reactors (without temperature monitoring) provided the coupled products after only 4 min reaction. Standard acidic cleavage with trifluoroacetic acid (TFA) furnished the corresponding biaryls in good to excellent yield. In both reactions minimal decomposition of the polymeric support was observed, resulting in the isolation of minor amounts of free polyethylene glycol. In a related example using the same type of resin/linker system and identical microwave equipment an aryl nitrile was prepared by microwave-assisted palladium-catalyzed cyanation of the corresponding polymer-bound aryl iodide. Subsequent conversion of the nitrile into the tetrazole was again performed by microwave irradiation, in a one-pot reaction (Scheme 12.3 c) [28].

N-Arylated heterocycles are an important class of compounds often associated with biological activity. It has been shown that yields and reaction rates in copper(II)-mediated C–N cross coupling reactions on a solid support could be dramatically im-

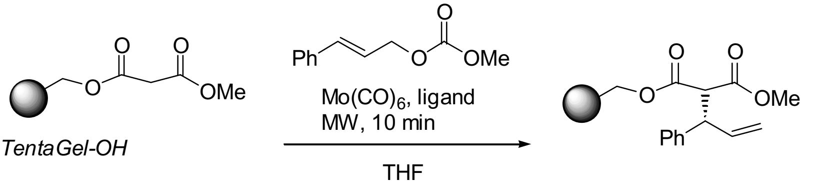


Scheme 12.3 Palladium-catalyzed solid-phase organic synthesis.

proved by use of microwave irradiation (e.g. Scheme 12.3 d) [29]. These experiments were performed with a domestic microwave oven and use of several intermittent irradiation cycles and multiple additions of excess reagent. Compared with the conventional thermal procedure (80 °C) the reaction time was effectively reduced from 48 h (overall) to less than 5 min and afforded a variety of *N*-arylated heterocycles in high yield and purity after cleavage from the solid support.

Another metal-catalyzed microwave-assisted transformation performed on a polymer support involves the asymmetric allylic malonate alkylation reaction shown in Scheme 12.4. The rapid molybdenum(0)-catalyzed process involving thermostable chiral ligands proceeded with 99% ee on a solid support. When TentaGel was used as as support, however, the yields after cleavage were low (8–34%) compared with the corresponding solution phase microwave-assisted process (monomode cavity) which generally proceeded in high yields (>85%) [30].

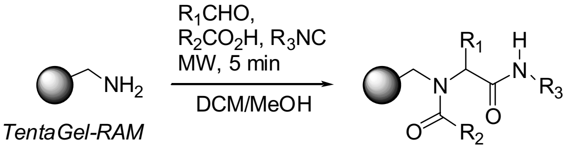
Multicomponent reactions (MCR), in which three or more reactions combine to give a single product, have lately received much attention. The Ugi four-component condensation in which an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide combine to yield an α-acylamino amide, is particularly interesting, because



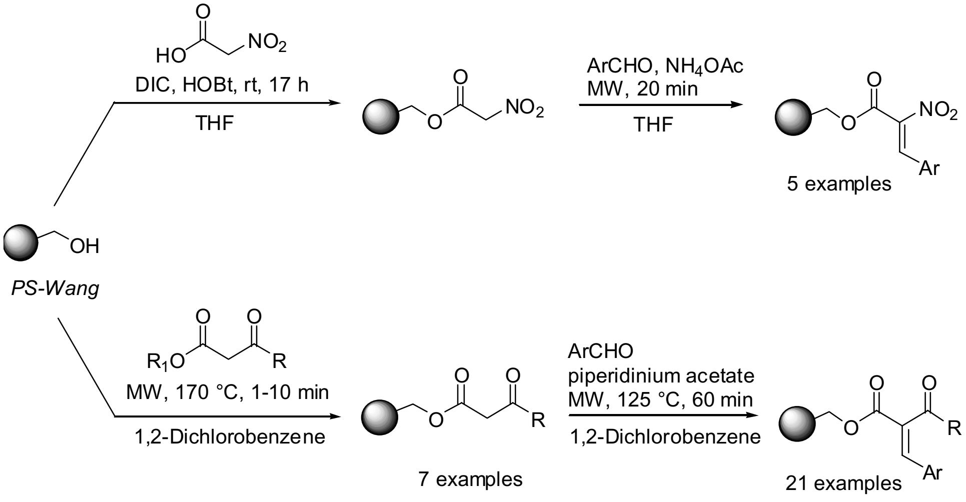
Scheme 12.4 Solid-phase molybdenum(0)-catalyzed allylic alkylation.

of the wide range of products obtainable by variation of the starting materials [31]. Although conventional solid-phase Ugi reactions require several days for completion, it has been demonstrated that by use of microwave irradiation (monomode instrument, sealed Pyrex vessel), products of high purity were obtained in moderate to excellent yields (24–96% yield) within 5 min irradiation time (Scheme 12.5) [32]. A polymer-bound amino component was used and a mixture of dichloromethane and methanol (DCM–MeOH 2 : 1) as solvent which both absorbed microwave energy and solvated the resin. A library comprising 18 members was obtained after cleavage of the resin-bound material from the support with TFA : DCM 19 : 1.

Another condensation process that has been performed by microwave heating is the Knoevenagel reaction (Scheme 12.6). Resin-bound nitroalkenes, for example,



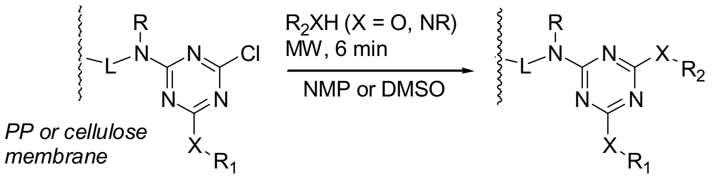
Scheme 12.5 Ugi 4-component reactions on a solid support.



Scheme 12.6 Knoevenagel condensations on solid support.

were prepared by microwave-assisted Knoevenagel condensation of resin-bound nitroacetic acid with a variety of aldehydes. The formation of the resin-bound enones was realized by microwave-assisted condensation of the aldehyde to the resin within 20 min, by use of a domestic microwave oven. The resin-bound nitroalkenes were subsequently used in high pressure Diels–Alder and three-component tandem [4+2]/[3+2] cycloaddition reactions [33]. In a related example, synthesis of Knoevenagel products involving resin-bound β-ketoesters has been reported. Here, the required resin-bound 1,3-dicarbonyl compounds were generated by rapid, microwave-mediated acetoacetylation of Wang resin with a variety of β-ketoesters. By use of microwave flash heating at 170 °C complete conversions were achieved within 1–10 min, a significant improvement over the conventional thermal method, which required several hours for completion [34]. Significant rate enhancements were also observed for the subsequent microwave-heated Knoevenagel condensations with a set of different aldehydes. Reaction times were reduced to 30–60 min at 125 °C, the optimized reaction temperature in the microwave procedure, compared with 1–2 days using the literature procedures. Kinetic comparison studies indicated that the observed rate-enhancements could be attributed to the rapid direct heating of the solvent (1,2-dichlorobenzene) by microwaves rather than to any specific microwave effect [34]. Both reaction steps were performed in dedicated multimode microwave reactors in open Teflon vessels with on-line temperature measurement. A library of 21 polymer-bound enones was obtained in a single microwave irradiation experiment by use of parallel synthesis techniques (Sect. 12.7).

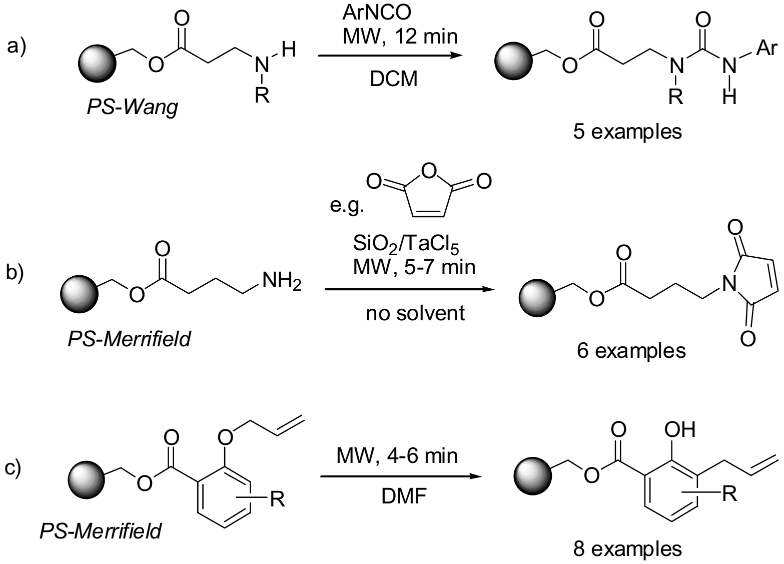
An 8000-member library of trisamino- and aminooxy-1,3,5-triazines has been prepared by use of highly effective, microwave-assisted nucleophilic substitution of polypropylene (PP) or cellulose membrane-bound monochlorotriazines. The key step relied on the microwave-promoted substitution of the chlorine atom in monochlorotriazines (Scheme 12.7) [35]. Whereas the conventional procedure required relatively harsh conditions such as 80 °C for 5 h or very long reaction times (4 days), all substitution reactions were found to proceed within 6 min, with both amines and solutions of cesium salts of phenols, and use of microwave irradiation in a domestic oven under atmospheric reaction conditions. The reactions were conducted by applying a SPOT-synthesis technique [36] on 18 × 26 cm cellulose membranes leading to a spatially addressed parallel assembly of the desired triazines after cleavage with TFA vapor. This concept was later also extended to other halogenated heterocycles, such as 2,4,6-trichloropyrimidine, 4,6-dichloro-5-nitropyrimidine, and 2,6,8-trichloro-7-methylpurine, and applied to the synthesis of macrocyclic peptidomimetics [37].



Scheme 12.7 High-speed nucleophilic substitution reactions on polypropylene or cellulose membranes.

Other microwave-assisted SPOS processes reported in the literature are summarized in Scheme 12.8. The addition of isocyanates to amines bound to Wang resin, for example, was studied both under conventional conditions at room temperature and under the action of microwave irradiation in open vessels by use of a monomode instrument. By monitoring the progress of the addition by on-bead FTIR it was demonstrated that the microwave procedure proceeded significantly faster than the reaction at room temperature (12 compared with 210 min) [38]. The temperature during the microwave irradiation experiment was not determined, however, so it is unclear if any nonthermal microwave effects were responsible for the observed rate-enhancements (Scheme 12.8 a) [38].

A very unusual microwave-assisted procedure involving the preparation of *N*-alkyl imides from anhydrides and polymer-bound γ-aminobutyric acid has been described (Scheme 12.8 b) [39]. This transformation is reported to proceed in the absence of solvent, and involves $TaCl_5$-doped silica gel as reaction medium. After cleavage with TFA, the corresponding carboxylic acids were obtained in 58–72% yield. These results, involving dry, unswollen resin, are somewhat unexpected and deserve further in-depth investigation [40]. Very rapid Claisen rearrangements on the solid-phase have also been described; they involve microwave heating of the resin in DMF (Scheme 12.8 c). Compared with classical heating in an oil bath at 140 °C the reaction times were reduced from 10–16 h to 4–6 min and led to similar or higher yields of products after TFA cleavage [41]. Unfortunately, no temperature measurements were documented. In another application of microwave heating for SPOS, several functionalized resins (Wang resin, piperazinomethyl resin) were prepared from standard PS-Merrifield resin by rapid nucleophilic substitution of the chloride [42].

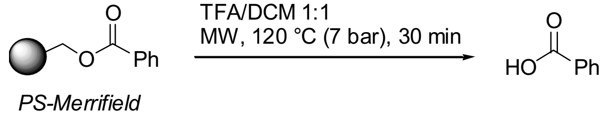


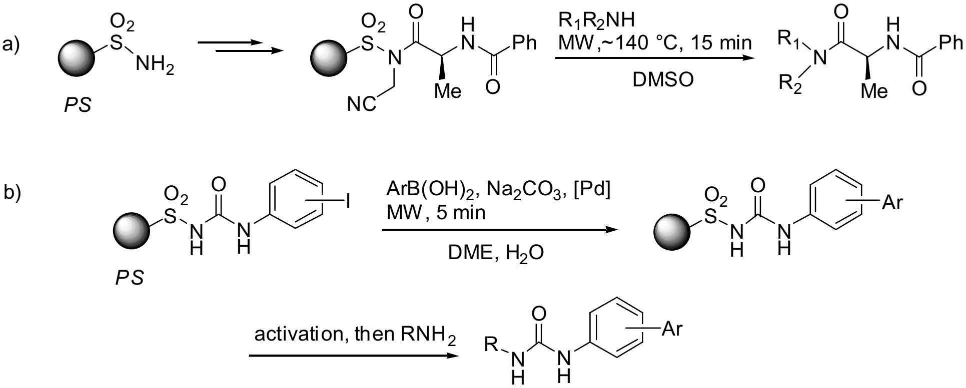
Scheme 12.8 Miscellaneous solid-phase reactions performed under the action of microwave irradiation.

In addition to the aforementioned microwave-assisted reactions on solid supports, several publications also describe microwave-assisted resin cleavage. In this context it has been demonstrated that carboxylic acids could be cleaved from conventional Merrifield resin, using the standard TFA–DCM 1:1 mixture, by exposure of the polymer-bound ester and the cleavage reagent to microwave irradiation in a dedicated Teflon autoclave (multimode instrument). After 30 min at 120 °C, complete recovery of the carboxylic acid was achieved (Scheme 12.9) [26]. At room temperature, however, virtually no cleavage was detected after 2 h in 1:1 TFA–DCM.

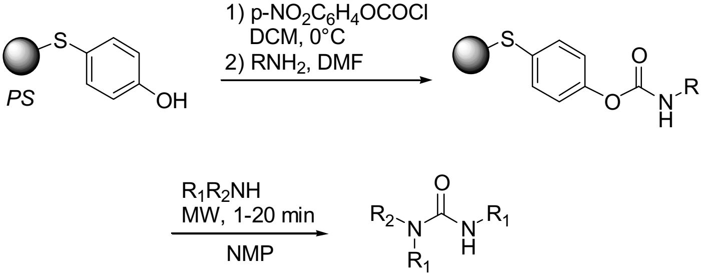
In another application of microwave-assisted resin cleavage, *N*-benzoylated alanine attached to 4-sulfamylbutyryl resin was cleaved (after activation of the linker to bromoacetonitrile by use of Kenner's safety-catch principle) with a variety of amines (Scheme 12.10a) [43, 44]. Cleavage rates in DMSO were investigated for diisopropylamine and aniline under different reaction conditions using both microwave (domestic oven) and traditional oil-bath heating. It was determined that microwave heating did not accelerate reaction rates compared with traditional heating when experiments were run at the same temperature (ca. 80 °C). When microwaves were used, however, even cleavage with normally unreactive aniline could be accomplished within 15 min at ca. 140 °C. This principle was extended to the parallel synthesis (Sect. 12.7) of an 880-member library by utilizing 96 well plates, employing 10 different amino acids each bearing a different acyl group, and using 88 different amines for cleavage. In closely related work, similar SPOS chemistry was employed by the same research group to prepare biaryl urea libraries, via microwave-assisted Suzuki couplings, followed by cleavage with amines (Scheme 12.10b) [44].

Scheme 12.9 Microwave-assisted cleavage of benzoic acid from Merrifield resin.





Scheme 12.10 Microwave-assisted aminolysis (Kenner safety-catch linker).



Scheme 12.11 Microwave-assisted aminolysis (Marshall linker).

In a related approach ureas were generated by microwave-assisted aminolysis of resin-bound carbamates (Scheme 12.11) [45]. The carbamates were formed by treatment of thiophenoxy resin (Marshall linker) with *p*-nitrophenylchloroformate, followed by reaction with a primary amine in DMF. A variety of conditions were tested for subsequent cleavage with amines. Significantly improved reaction times and product purity, compared with those obtained by use of the standard thermal procedure, were achieved by use of NMP or excess amine as the solvent and irradiating the mixture (multimode oven) for 1–20 min. A single example of a microwave-assisted cyclative cleavage procedure leading to hydantoins has also been reported [46].

In all the examples of microwave-assisted SPOS summarized above, the choice of solvent deserves special attention [47]. Ideally, the solvent should have:

- good swelling properties for the resin involved;
- a high boiling point if reactions are to be performed at atmospheric pressure;
- a high loss tangent (tan δ) for good interaction with the microwaves [48]; and
- high chemical stability and inertness, to minimize side reactions.

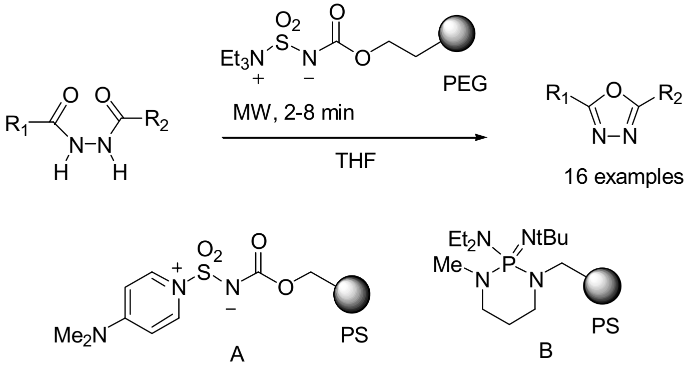
Solvents such as NMP, DMF, DMSO, or 1,2-dichlorobenzene have therefore been used frequently. As far as the polymer supports are concerned, the use of cross-linked polystyrene resin has been most prevalent. These resins have been shown to withstand microwave irradiation for prolonged periods of time, even at 200 °C [26]. TentaGel resins [27–30, 32] and cellulose membranes [35, 37] have also been used successfully in microwave-assisted SPOS, although some degradation of TentaGel resins has been observed during irradiation [27]. In most reported studies involving SPOS, temperature was not, unfortunately, measured during the microwave irradiation period. Consequently, the reasons for the observed rate enhancements in these transformations, which are potentially highly useful in the field of combinatorial chemistry, remain unclear. When kinetic comparison studies of differences between conventional and microwave heating experiments were conducted [26, 27, 34, 43, 44], so-called non-thermal or specific microwave effects (Chapt. 3) [13, 14] were not observed.

12.3
Polymer-supported Reagents, Scavengers, and Catalysts

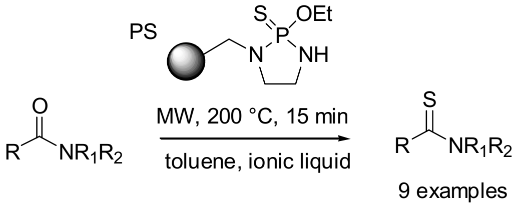
Apart from traditional solid-phase organic synthesis (SPOS), the use of polymer-supported reagents (PSR) has gained increasing attention from practitioners in the field of combinatorial chemistry [49–52]. The use of PSR combines the benefits of SPOS with the advantages of solution-phase synthesis. The most important advantages of these reagents are simplification of reaction workup and product isolation, the workup being reduced to simple filtration. PSR can also be used in excess without affecting the purification step. By using this technique, reactions can be driven to completion more easily than in conventional solution-phase chemistry. So far only a few applications of microwave-assisted PSR strategies have been reported in the literature.

One recent process involves the use of a polymer-supported Burgess reagent for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines (Scheme 12.12). Irradiation of a variety of 1,2-diacylhydrazines with a polyethylene glycol (PEG 750)-supported Burgess reagent in THF provided the corresponding 1,3,4-oxadiazoles in 75–96% yield and high purity after only 2–8 min irradiation [53]. Under conventional reflux conditions a 40% conversion was obtained after 3 h. Apart from filtration through silica gel to remove the soluble polymer-supported reagent, and evaporation of the solvent, no purification was necessary. Reactions were performed in dedicated monomode instruments under sealed vessel conditions (no temperatures given). In a variation of this procedure the same authors also described the cyclodehydration of diacylhydrazines to oxadiazoles by use of the insoluble polystyrene-supported reagents A and B (Scheme 12.12) [54]. Similar reduced reaction times as with the soluble polymer support (5–10 min) were also achieved by use of either of the two polystyrene-supported reagents in THF with microwave irradiation in sealed vessels.

Another example of microwave-assisted PSR chemistry involves the rapid conversion of amides to thioamides by use of a polystyrene-supported Lawesson-type thionating reagent. By use of microwave irradiation at 200 °C in sealed vessels (monomode reactor), a range of secondary and tertiary amides was converted within



Scheme 12.12 Synthesis of 1,3,4-oxadiazoles by use of polymer-supported reagents.

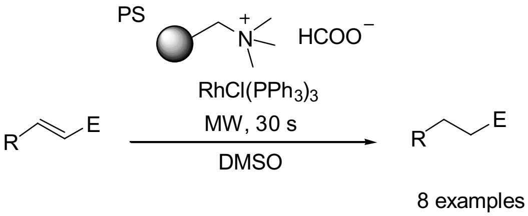


Scheme 12.13 Microwave-mediated thionation of amides.

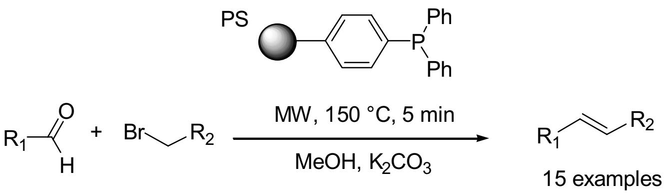
15 min to the corresponding thioamides, in high yield and purity (Scheme 12.13) [55]. Compared with classical reflux conditions, these thionation reactions were much faster and reaction times were reduced from 30 h to 10–15 min. Interestingly, even heating at these elevated temperatures caused no damage to the polymeric support. Because toluene is not an optimum solvent for absorption and dissipation of microwave energy [48], a small amount of ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate) was added to the reaction mixture to ensure even and efficient distribution of heat.

In a related example, the catalytic transfer hydrogenation of olefinic substrates using a polymer-supported hydrogen donor has been reported. By use of microwave irradiation (monomode reactor) high yields of products (80–95 %) could be obtained by irradiation of a mixture of an Amberlite-derived supported formate, Wilkinson's catalyst ($RhCl(PPh_3)_3$), and the olefinic substrate in the minimum quantity of DMSO (Scheme 12.14) [56]. After separation of the Amberlite at the end of the reaction the polymer-supported formate salt could easily be regenerated and used in further hydrogenation reactions. In total, five reaction–regeneration cycles were possible before an appreciable decrease in the reaction yield was noted.

Very recently a novel one-pot three-step Wittig reaction using microwave irradiation and polymer-supported triphenylphosphine has been reported [57]. By use of



Scheme 12.14 Microwave-mediated hydrogenation using a polymer-supported hydrogen donor.



Scheme 12.15 Microwave-mediated one-pot, three-component Wittig olefinations utilizing polymer-supported triphenylphosphine.

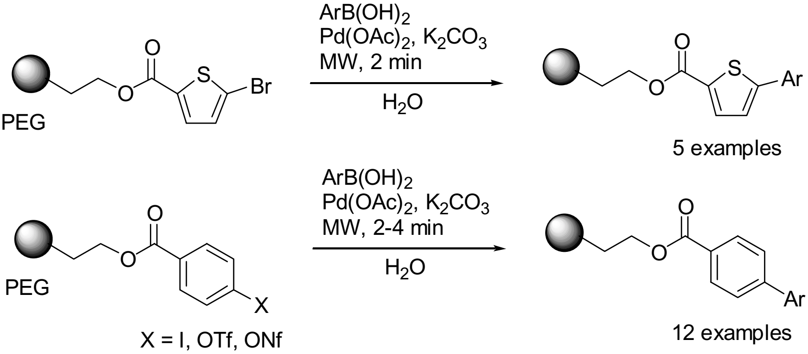
monomode irradiation in closed vessels olefins could be formed efficiently in just a few minutes, by use of a three-component coupling process (Scheme 12.15). Yields of the olefinic products were moderate to good (11–95 %, 15 examples), and the purity of olefins after automated chromatographic purification was always high.

One of the disadvantages of using polymer-supported scavengers to remove excess reagents is the long reaction times frequently encountered. It has been shown that excess primary amine can be successfully scavenged from a reaction mixture by use of PS aldehyde Wang resin under microwave conditions. Compared with 24–36 h at room temperature, the amine was completely scavenged by 3.5 equivalents of the aldehyde resin within 20–40 min by use of microwave irradiation and dioxane as solvent [58].

12.4
Soluble Polymer-supported Synthesis

Besides solid-phase organic synthesis (SPOS) involving insoluble cross-linked polymer supports, chemistry on soluble polymer-matrixes, sometimes called liquid-phase organic synthesis, has recently emerged as a viable alternative [59–62]. Problems associated with the heterogeneous nature of the ensuing chemistry and on-bead spectroscopic characterization in SPOS have led to the development of soluble polymers as alternative matrixes for combinatorial library production. Synthetic approaches that utilize soluble polymers couple the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis) with those of solid-phase methods (use of excess reagents and easy isolation and purification of products). Separation of the functionalized matrix was achieved by solvent or heat precipitation, membrane filtration, or size-exclusion chromatography [59–62].

Several microwave-assisted procedures have been described for soluble polymer-supported syntheses. Poly(ethylene glycol) (PEG)-supported aryl bromides have been shown to undergo rapid palladium(0)-catalyzed Suzuki couplings with aryl boronic acids in water (Scheme 12.16) [63]. The reaction proceeded without organic cosolvent



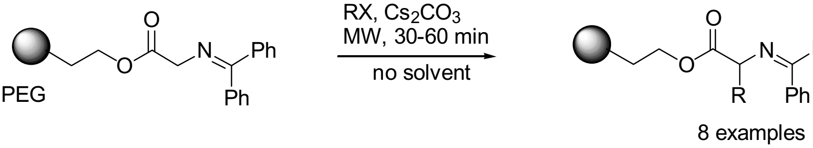
Scheme 12.16 Microwave-assisted aqueous Suzuki couplings with PEG-bound aryl halides or sulfonates.

under thermal conditions or microwave conditions. Compared with classical heating (70 °C), microwave irradiation shortened the reaction times with representative boronic acids from 2 h to 2–4 min, with conversions typically >95%. Even at high irradiation energy levels (domestic oven, septum-sealed vessels), the polymer support and the ester remained stable. Whereas the use of conventional thermal conditions induced ester cleavage, this side reaction was apparently suppressed under microwave conditions. The reaction proceeded well also for PEG-bound aryl iodides, triflates (OTf), and nonaflates (ONf) and could be performed in a parallel format [63].

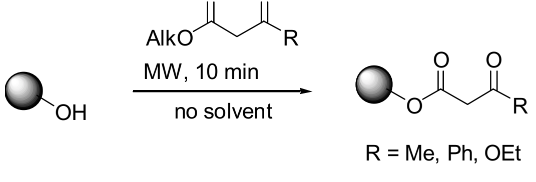
In a related example, the microwave-promoted alkylation of Schiff base-protected PEG-bound glycine was investigated (Scheme 12.17) [64]. Here PEG (molecular weight 3400) was used simultaneously as polymeric support, solvent, and phase-transfer catalyst. The best results were obtained when alkylations with alkyl bromides or iodides (RX) were performed neat in the presence of a base such as Cs_2CO_3 or K_2CO_3 in a domestic microwave oven in open glass vessels. Comparison experiments involving thermal heating (85 °C) revealed little evidence of any non-thermal or specific microwave effects (Chapt. 3); the microwave technique was found to be more practical than conventional heating, especially for performing reactions in a parallel format.

Microwave-mediated transesterification of commercially available neat poly(styrene–co-allyl alcohol) with ethyl 3-oxobutanoate, ethyl 3-phenyl-3-oxopropanoate, and diethyl malonate provided the desired polymer-supported β-dicarbonyl compounds (Scheme 12.18) [65]. Multigram quantities of these interesting building blocks for heterocycle synthesis were obtained simply by exposing the neat mixture of reagents to microwave irradiation in a domestic microwave oven for 10 min.

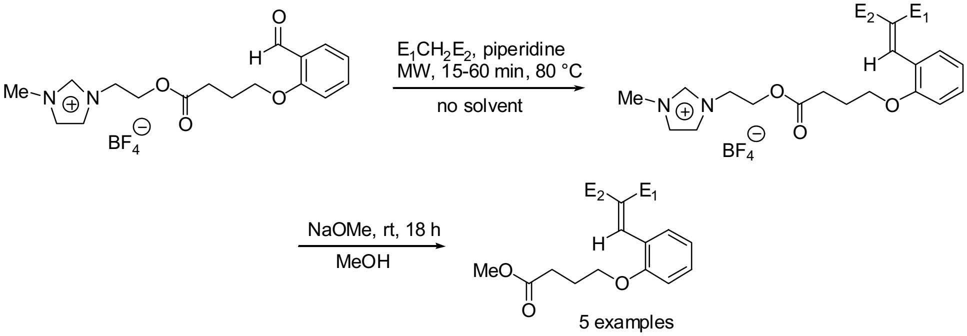
The first use of room temperature ionic liquids as potential novel soluble phases for combinatorial synthesis has recently been described. As model reaction the Knoevenagel condensation of salicyl aldehyde grafted on to an imidazolium-derived ionic liquid was studied under the action of microwave irradiation (Scheme 12.19) [66]. Reactions were performed without additional solvent in the presence of a basic catalyst, utilizing microwave irradiation in a designated monomode microwave reac-



Scheme 12.17 Microwave-assisted alkylations on PEG support.



Scheme 12.18 Derivatization of poly(styrene-co-allyl alcohol) with β-dicarbonyl compounds.



Scheme 12.19 Ionic liquid-phase supported synthesis performed with microwave irradiation.

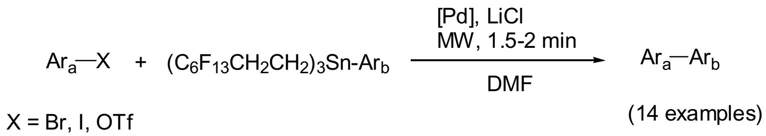
tor at 80 °C. Knoevenagel condensations proceeded quantitatively within 15–60 min and furnished, after cleavage from the ionic liquid (reusable), the desired products in high yield without the need for further purification [66]. In a second example of this unconventional methodology imines were successfully prepared from the grafted formyl functionality by reaction with a variety of amines, again using microwave irradiation (80 °C, 20 min) [66].

12.5
Fluorous-phase Synthesis

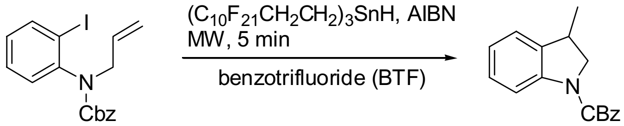
In so-called fluorous-phase synthesis, an organic molecule is rendered soluble in fluorocarbon solvents by attachment of a suitable fluorocarbon group ("fluorous tag"). Fluorocarbon solvents are usually immiscible with organic solutions and water at room temperature, and fluorous molecules partition out of an organic phase and into a fluorous phase by standard liquid–liquid extraction. At the desired stage of the synthesis, the fluorous label is cleaved and the product is rendered "organic" again [67]. Fluorous techniques (in particular fluorous chromatography) are rapidly becoming a means of integrating synthesis and purification strategies in combinatorial chemistry [68].

One example of microwave-assisted fluorous synthesis involves palladium-catalyzed Stille couplings of fluorous tin reagents with aryl halides or triflates (Scheme 12.20) [69]. While the comparable thermal process required one day for completion, the microwave-heated reactions (sealed vessels in monomode reactors) were completed within 2 min, with the additional benefit of reduced homocoupling of the tin reagent leading to Ar_a–Ar_b. The desired biaryl products were isolated in good yields and purities after three-phase extraction. Similar results were also achieved by utilizing so-called F-21 fluorous tags ($CH_2CH_2C_{10}F_{21}$) on the tin reagent [70].

In an additional application of fluorous chemistry, radical-mediated cyclizations were performed in benzotrifluoride using microwave irradiation [70]. In the pre-



Scheme 12.20 Fluorous Stille couplings under the action of microwave irradiation.



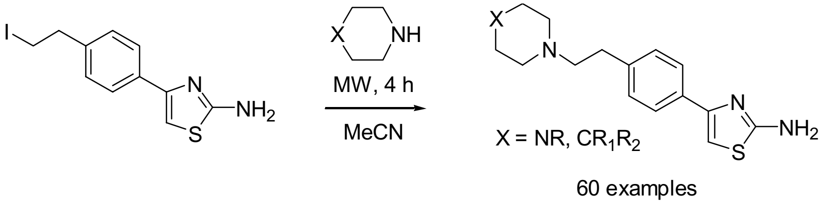
Scheme 12.21 Microwave-mediated radical cyclizations.

sence of 2,2-azobizisobutyronitrile (AIBN) as radical initiator, the aryl iodide shown in Scheme 12.21 for example smoothly underwent microwave-mediated cyclization to the corresponding indole derivative in 93% isolated yield. The reaction time using sealed Pyrex vessels (monomode reactor) was 5 min. The ability to promote highly fluorous reactions with microwave heating deserves special attention. With these highly fluorous tin reagents, microwave irradiation is more than an expedient to reduce reaction times. Reactions conducted under traditional heating either did not work at all or did not work nearly as well. The advantage of microwave heating may be the rapid coalescence of the organic and fluorous phase to form a homogeneous solution [70].

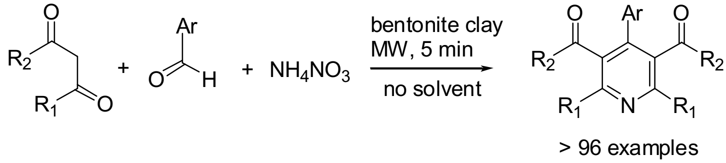
12.6.
Parallel Synthesis

Parallel processing of synthetic operations has been one of the cornerstones in combinatorial chemistry for years [1–6]. In the parallel synthesis of combinatorial libraries, compounds are synthesized using ordered arrays of spatially separated reaction vessels adhering to the traditional "one vessel-one compound" philosophy. The defined location of the compound in the array provides the structure of the compound. A commonly used format for parallel synthesis is the 96-well microtiter plate, and today combinatorial libraries comprising hundreds to thousands of compounds can be synthesized by parallel synthesis, often in an automated fashion [6].

As demonstrated in the previous sections of this review, microwave-assisted reactions allow rapid product generation in high yield under uniform conditions. Therefore, they should be ideally suited for parallel synthesis and/or combinatorial chemistry applications. The first example of parallel reactions performed under microwave irradiation conditions involved the nucleophilic substitution of an alkyl iodide with 60 diverse piperidine or piperazine derivatives (Scheme 12.22) [71]. Reactions were performed in a multimode microwave reactor in individual sealed polypropy-



Scheme 12.22 Nucleophilic substitution reactions performed in parallel.

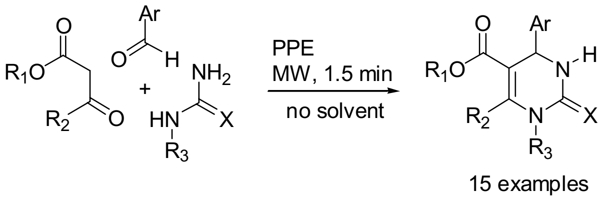


Scheme 12.23 Microwave-assisted Hantzsch pyridine synthesis.

lene vials using acetonitrile as solvent (no further details given). Screening of the resulting 2-aminothiazole library in a herpes simplex virus-1 (HSV-1) assay led to three confirmed hits, demonstrating the potential of this method for rapid lead optimization.

In a key 1998 publication, the concept of microwave-assisted combinatorial chemistry was introduced for the first time. Using the three-component Hantzsch pyridine synthesis as a model reaction, libraries of substituted pyridines were prepared in a high-throughput parallel fashion. In this variation of the Hantzsch multicomponent reaction, ammonium nitrate was used as the ammonium source as well as oxidizing agent, employing bentonite clay as inorganic support (Scheme 12.23) [72]. Microwave irradiation was performed in 96-well filter-bottom polypropylene plates, in which the corresponding eight 1,3-dicarbonyl compounds and twelve aldehyde building blocks were dispensed using a robotic liquid handler. Microwave irradiation of the 96-well plate containing aldehydes, 1,3-dicarbonyl compounds, and ammonium nitrate–clay in a domestic microwave oven for 5 min produced the expected pyridine library directly, after the desired products were extracted from the solid support by organic solvent and collected in a receiving plate. HPLC–MS analysis showed that the reactions were uniformly successful across the 96-well reactor plate, without any starting material being present. The diversity of this method was further extended when mixtures of two different 1,3-dicarbonyl compounds were used in the same Hantzsch synthesis, potentially leading to three distinct pyridine derivatives (not shown).

Using a similar format, dihydropyrimidines were obtained in a microwave-expedited version of the classical Biginelli three-component condensation (Scheme 12.24) [73]. Neat mixtures of β-ketoesters, aryl aldehydes and (thio)ureas with polyphosphate ester (PPE) as reaction mediator were irradiated in a domestic microwave oven for 1.5 min. The desired dihydropyrimidines were obtained in 61–95% yield after aqu-

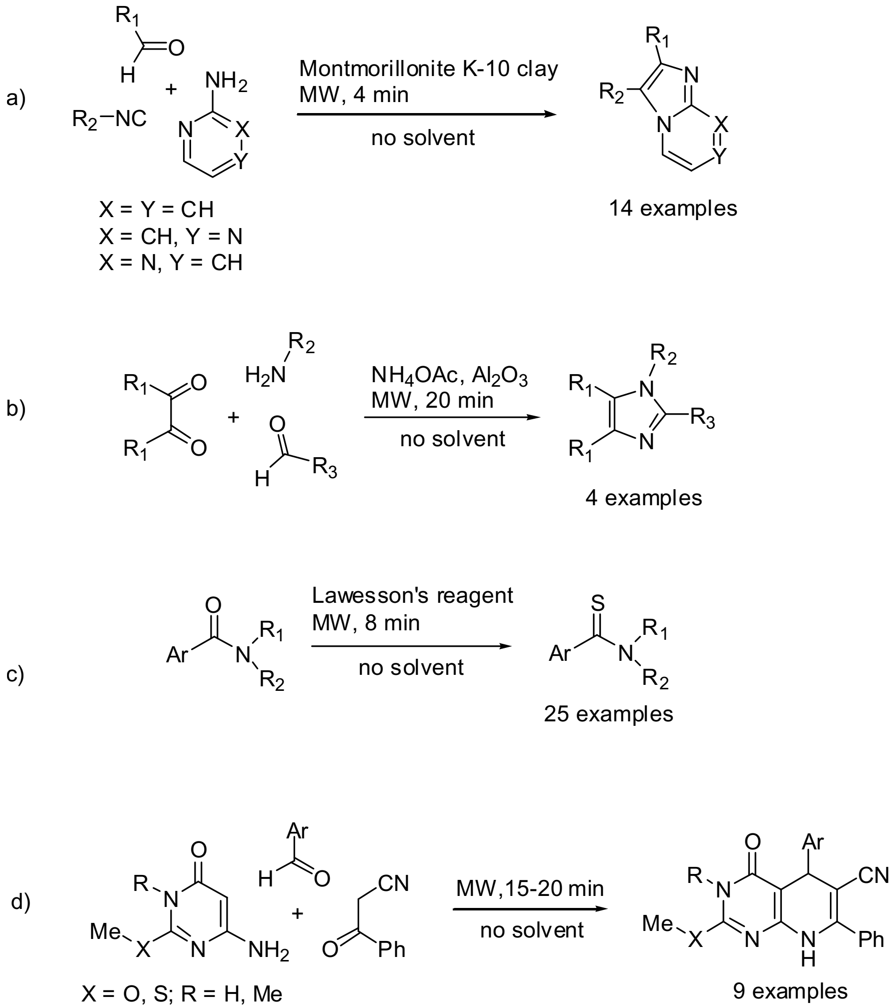


Scheme 12.24 Microwave-assisted Biginelli dihydropyrimidine synthesis.

eous workup. Furthermore, it was shown that, for example, 10 dihydropyrimidine analogs could be prepared in parallel fashion in a single microwave irradiation experiment when 10 Pyrex beakers containing the individual building blocks–reagent mixtures were immersed in an alumina bath (acting as a heat sink) and subsequently irradiated. This strategy is therefore clearly applicable for the parallel synthesis of single compound libraries. In a related approach hydantoins were obtained by parallel microwave-assisted condensation of arylglyoxals and phenylurea using PPE as reaction mediator [74].

Related applications of solvent-free microwave-enhanced parallel processes are summarized in Scheme 12.25. Imidazo-annulated pyridines, pyrazines, and pyrimidines were rapidly prepared in high yield by an Ugi-type multicomponent reaction using montmorillonite K-10 clay as inorganic support (reaction a) [75]. A diverse set of 1,2,4,5-substituted imidazoles was similarly synthesized by condensation of 1,2-dicarbonyl compounds with aldehydes, amines, and ammonium acetate on acidic alumina as support (reaction b) [76]. After chromatographic workup, the imidazoles were obtained in 68–80% yield. Related 2,4,5-substituted imidazoles were synthesized analogously from 1,2-dicarbonyl compounds and aldehydes using ammonium acetate as ammonium source (4 examples, 67–82% yield). A 25-member thioamide library containing additional basic amine functionalities (R_1R_2) was prepared by oxygen–sulfur exchange utilizing Lawesson's reagent. Microwave irradiation of the thoroughly mixed amide–thionation reagent mixture for 8 min produced the corresponding thioamides in good yields and high purities after solid-phase extraction (reaction c) [77]. In another example, the regiospecific three-component cyclocondensation of equimolar amounts of aminopyrimidin-4-ones, benzoylacetonitrile, and arylaldehydes furnished the densely functionalized pyrido[2,3-*d*]pyrimidinones in 70–75% yield (Scheme 12.25 d) [78]. The process was conducted in a domestic microwave oven using Pyrex glass vials in the absence of any solvent or support.

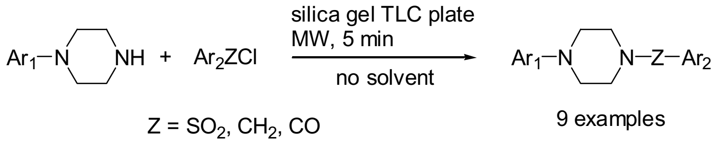
Most of the parallel reactions described in Schs. 12.23–12.25 were performed as dry-media reactions, in the absence of any solvent. In many cases, the starting materials and/or reagents were supported on an inorganic solid support, such as silica gel, alumina, or clay that absorbs microwave energy or acts as a catalyst for the reaction (see also Chapt. 6) [10, 11]. In this context, an interesting method for optimization of silica supported reactions has been described [79]. The reagents were cospotted neat or in solution on to a thin-layer chromatographic (TLC) plate. The glass plate was exposed to microwave irradiation, eluted and viewed by standard TLC vi-



Scheme 12.25 Rapid dry-media reactions under microwave conditions.

sualization procedures for the results of the reaction. In this particular example, the synthesis of an arylpiperazine library (Scheme 12.26) was described, but the simplicity and general utility of the approach for the rapid screening of solvent-free microwave reactions may make this a powerful screening and reaction optimization tool.

Other microwave-assisted parallel processes, for example, involving solid-phase organic synthesis (SPOS) have already been discussed in Sect. 12.2. (Schs. 12.6, 12.7, and 12.10). In the majority of cases described so far, however, domestic multimode microwave ovens have been used as heating devices, without utilizing specialized reactor equipment. Since reactions in household multimode ovens are notoriously difficult to reproduce due to the lack of temperature and pressure control, pulsed irra-



Scheme 12.26 Microwave chemistry on a TLC plate.

diation, uneven electromagnetic field distribution, and the unpredictable formation of hotspots [10, 43], a recent trend has been to use dedicated, commercially available reactor systems that make microwave-assisted chemistry more reproducible (Sect. 12.7).

12.7
Equipment for High-throughput Microwave-assisted Synthesis

Although the examples of microwave-assisted reactions presented in this and other chapters demonstrate that rapid synthetic transformations can in many cases be achieved using microwave irradiation, the possibility of high-speed synthesis does not necessarily mean that these processes can also be adapted to a truly high-throughput format. As of the year 2000, virtually all commercial suppliers of microwave instrumentation for organic synthesis [80–82] have moved toward combinatorial and/or high-throughput platforms. In this section, specialized equipment for either parallel or rapid sequential microwave-assisted chemistry is presented. However, due to space restrictions no attempt can be made to discuss basic microwave reactor design and technology (see Chapts. 1 and 2).

Several articles in the area of microwave-assisted parallel synthesis have described irradiation of 96-well filter-bottom polypropylene plates in conventional household microwave ovens for high-throughput synthesis [29, 43, 44, 72]. While some authors did not report any difficulties associated with use of such equipment (see Scheme 12.23) [72], others have experienced problems in connection with the thermal instability of the polypropylene material itself [43], and with respect to temperature gradients developing between individual wells upon microwave heating [43, 44]. Fig. 12.2 shows the temperature gradients after 1 min irradiation of a conventional 96-well plate in a domestic microwave oven. For the particular chemistry involved (Scheme 12.10), the 20 °C difference between inner and outer wells was, however, not critical.

Apart from domestic household microwave ovens, a number of commercial microwave synthesis systems have been available for a number of years that can be adapted to high-throughput format [80–82]. Currently, two different cavity designs are being used. In so-called multimode cavities (conceptually similar to a domestic oven), the microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. A mode stirrer ensures that the field distribution is as homogeneous as possible. In the much smaller mono- or single-mode cavities,

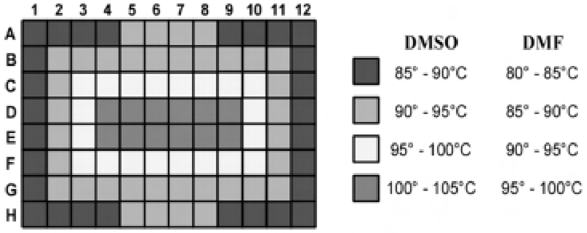


Fig. 12.2 Temperature gradients within a microwave-heated microtiter plate. 1 mL per well heated continuously for 1 min at full power in a conventional microwave oven (adapted from Ref. [44]).

only one mode is present and the electromagnetic irradiation is focused directly through an accurately designed wave guide on to the reaction vessel mounted in a fixed distance from the radiation source. For combinatorial chemistry applications, the key difference between the two types of reactor systems is that in multimode cavities several reaction vessels can be irradiated simultaneously, whereas in monomode systems, only one vessel can be irradiated at a time. One instrument designed for high-throughput organic synthesis is the Ethos SYNTH microwave labstation (Milestone Inc.) [80, 83]. This multimode instrument features a built-in magnetic stirrer, direct temperature control of the reaction mixture with the aid of fiber-optic probes and software that enables online temperature and/or pressure control by regulation of microwave power output (1000 W maximum). The flexible modular platform allows the use of standard glassware for reactions performed at atmospheric pressure, sealed reaction vessels for performing synthetic transformations at elevated temperature and pressure, and the application of various parallel reactors [80, 83]. For all configurations, the operator has full on-line access to all control parameters such as temperature, pressure, microwave power, and irradiation time. For this reactor so-called multiPREP rotors have been developed that house 36, 50, or 80 reaction vessels that fit into the large multimode cavity. These continuously moving rotors operate at atmospheric pressure with ca. 20 mL glass, TFM, or PFA vessels. For applications requiring sealed vessel conditions a rotor system with 36 glass vessels (Ethos multiPREP-36/P, Fig. 12.3) with a maximum operating temperature and pressure of 200 °C and 15 bar, respectively, has also been developed. In general, the temperature in a parallel reaction is measured in one reference vessel either by fiber-optic sensor or with the aid of a shielded thermocouple. During the reaction the temperature can additionally be controlled by an external IR sensor in the wall of the instrument, monitoring the surface temperature of the individual vessels as they move by the sensor. Magnetic stirring of each vessel ensures homogeneous mixing of the sample and even temperature distribution. Published applications of the multiPREP 50-rotor system (open vessels) have included the generation of a 21-member library by parallel solid-phase Knoevenagel condensations (Scheme 12.6) [34]. Here the temperature was monitored with the aid of a shielded thermocouple inserted into one of the reaction containers. It has been confirmed by standard temperature measurements performed immediately after the irradiation period that the resulting end temperature in each vessel was the same within ±2 °C [34]. In a different study involving the multiPREP 36/P rotor (Fig. 12.3) utilizing sealed glass vessels, the uniformity of the reaction conditions in such a parallel set-up was investigated. For that

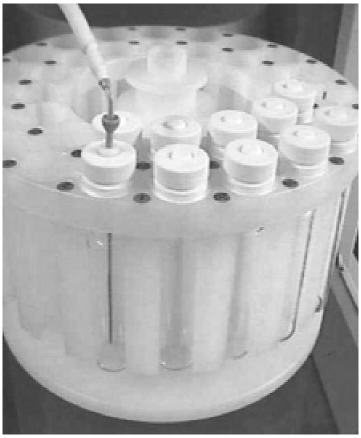


Fig. 12.3 MultiPREP 36/P rotor used in an ETHOS multimode microwave reactor. Temperature measurement with a shielded thermocouple in one reference vessel (Milestone, Inc.) [80].

purpose, 36 identical Biginelli condensations using benzaldehyde, ethyl acetoacetate, and ureas as building blocks (see Scheme 12.24) were run employing ethanol as solvent and HCl as catalyst [84]. All 36 individual vessels provided identical yields of dihydropyrimidine product (65–70%) within experimental error (no reaction details provided). In a subsequent experiment, six different aldehyde components (Fig. 12.4) were used to construct a small library of dihydropyrimidine analogs. Again, the yields of isolated products did not vary significantly depending on the position in the rotor, although slightly increased yields were obtained for mixtures that were placed in the inner circle, which would indicate a somewhat higher temperature in those reaction vessels (Fig. 12.4) [84].

An even higher throughput can be achieved using, for example, specifically designed 96 deep-well format plates (1 mL volume/vial) (Fig. 12.5) that can be mounted

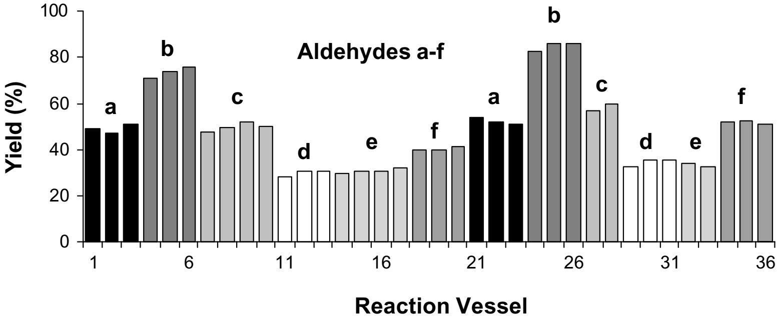


Fig. 12.4 Isolated yields of Biginelli dihydropyrimidine products (Scheme 12.24) in different reaction vessels of the MultiPREP 36/P rotor (Fig. 12.3). Outer ring, vessels 1–20; inner ring, vessels 21–36). Aldehydes: a, benzaldehyde; b, 2-hydroxybenzaldehyde; c, 3,4-dimethoxybenzaldehyde; d, 3-nitrobenzaldehyde; e, 2-chlorobenzaldehyde; f, 4-(*N*,*N*-dimethylamino)benzaldehyde. Adapted from Ref. [84].

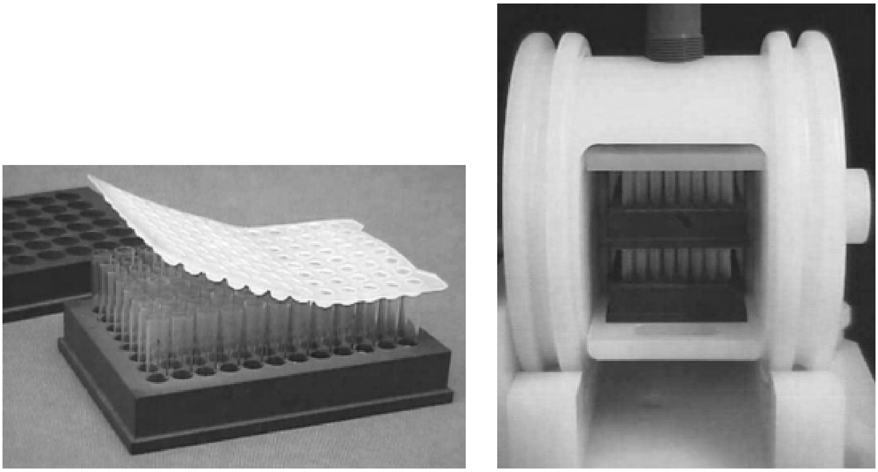


Fig. 12.5 Ethos combCHEM system (Milestone, Inc.); left: 96 deep-well plates; right: overhead rotor with two plates [80, 84, 85].

in an overhead rotor system in the large multimode microwave cavity (ETHOS combCHEM system, Fig. 12.5). Since several of such devices can be mounted on top of each other, several hundred reactions may potentially be performed in one irradiation cycle [85]. It is important to note that with this system, the material used for the preparation of the plates (Weflon) absorbs microwave energy which means that the sealed glass vials will be heated by microwave irradiation regardless of the dielectric properties [47] of the reactants and/or solvents (Chapt. 1). The system is designed to interface with conventional liquid handler and/or dispensers to achieve a high degree of automation in the whole process. At the time of writing this review no published material on the performance of this setup in combinatorial synthesis was available [85].

Similar parallel reactors as described above for the ETHOS multimode microwave reactor (Milestone, Inc.) are also available for the MARS-S multimode reactor from CEM Corp. [81]. Recently the construction of a parallel reactor with expandable reaction vessels that accommodate the pressure build-up during a microwave irradiation experiment has been reported [87]. The system was used for the parallel synthesis of a 24-membered library of substituted 4-sulfanyl-1*H*-imidazoles [87].

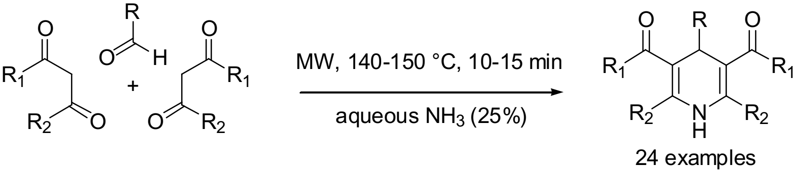
A different strategy to achieve high throughput in microwave-assisted reactions has been realized for monomode instruments such as the Emrys Synthesizer (PersonalChemistry AB, Fig. 12.6) [82, 86]. Since it is not feasible to have more than one reaction vessel in a monomode microwave cavity, a robotic system has been integrated into the platform that moves individual reaction vessels in and out of a specifically designed cavity that operates with continuous microwave irradiation and a maximum power of 300 W. A liquid handler allows dispensing of reagents into the Teflon-sealed reaction vials, while the gripper moves each sealed vial in and out of the microwave cavity after irradiation. The temperature is monitored by an IR sensor on

Fig. 12.6 Monomode microwave reactor with integrated robotics interface for automated use (left). Details of the cavity/gripper (top right) and reaction vials (bottom right) are also displayed (Emrys Synthesizer, Personal Chemistry AB) [86].

the outside of the reaction vessel. The instrument processes up to 120 reactions per run with a typical throughput of 12–15 reactions h^{-1}. Magnetic stirring of each individual process vial (250 °C, 20 bar maximum temperature and pressure, respectively) and unattended operation are some of the features of this microwave reactor. In contrast to the parallel synthesis application in multimode cavities this, approach allows the user to perform a series of optimization reactions with each reaction separately programmed.

The use of this setup for automated sequential microwave-assisted library synthesis was first reported in the context of preparing a series of dihydropyrimidines by the Biginelli reaction (see Scheme 12.24). A diverse set of 17 CH-acidic carbonyl compounds, 25 aldehydes, and 8 urea and/or thioureas was used in the preparation of a dihydropyrimidine library [88]. Of the 3400 theoretically possible dihydropyrimidine derivatives, a representative subset of 48 analogs was prepared using automated addition of building blocks and subsequent sequential microwave irradiation of each process vial. For most building block combinations, 10 min of microwave flash heating at 120 °C using AcOH–EtOH, 3 : 1, and 10 mol % $Yb(OTf)_3$ as solvent–catalyst system proved to be successful, leading to an average isolated yield of 52% of DHPM with >90% purity. For some building block combinations the general conditions were modified, by changing the solvent, catalyst, reaction temperature, or irradiation time. The unattended automation capabilities of the microwave synthesizer enables a library of this size to be prepared within 12 h.

In a related example involving the use of the same instrument (Fig. 12.6) in the Hantzsch multicomponent condensation, the serial synthesis of 24 dihydropyridine



Scheme 12.27 Generation of a dihydropyridine library using automated sequential microwave processing.

derivatives was reported, involving the microwave assisted reaction of 6 different aldehydes with 4 different β-ketoesters or 1,3-dicarbonyl compounds and aqueous ammonia (Scheme 12.27) [89]. Reactions were run in sealed vessels (see above) at 140–150 °C for 10–15 min, providing the desired products in 39–89% yield and low to excellent purities (53–99%).

Additional applications of this technology for rapid lead discovery and lead optimization have been reported [87, 90–93]. It should also be noted that a variety of chemical transformations, in particular in the area of transition-metal catalyzed reactions, have been performed with this or related equipment (Chapt. 11) [25]. Other monomode microwave reactors using related concepts to introduce high-throughput were recently introduced by CEM Corp. (Discover or Explorer line of products, Fig. 12.7.) [81]. At the time of writing this review no published synthetic applications using this microwave reactor were available.

The issue of parallel versus sequential synthesis using multimode or monomode cavities, respectively deserves special comment. While the parallel setup allows for considerable throughput that can be achieved in the relatively short timeframe of a microwave-enhanced chemical reaction, the individual control over each reaction vessel in terms of reaction temperature and/or pressure is limited. In the parallel

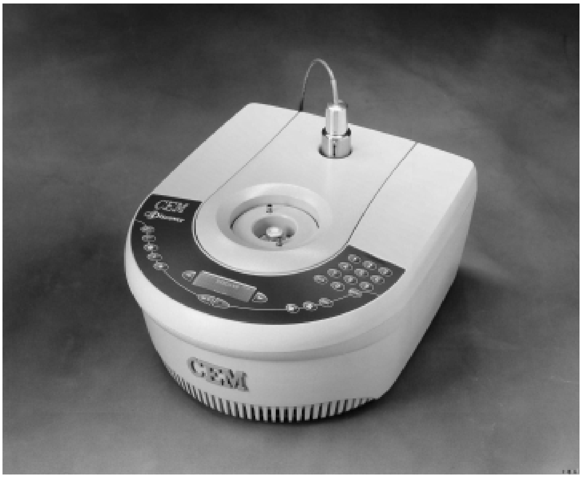


Figure 12.7 Monomode microwave reactor Discover (without automation) for use with open or sealed vessels of different volumes (CEM Corp.) [81]. A related instrument with automation (Explorer) has recently been introduced.

mode, all reaction vessels are exposed to the same irradiation conditions. In order to ensure similar temperatures in each vessel, the same amount of the identical solvent should be used in each reaction vessel because of the dielectric properties involved [48]. An alternative to parallel processing the automated sequential synthesis of libraries can be a viable strategy. Irradiating each individual reaction vessel separately gives better control over the reaction parameters, and allows for the rapid optimization of reaction conditions. For the preparation of relatively small libraries, where delicate chemistries are to be performed, the sequential format may be preferable.

12.8
Conclusion

The combination of modern microwave reactor technology and combinatorial chemistry applications is a logical consequence of the increased speed and effectiveness offered by microwave dielectric heating. While this technology is heavily used in pharmaceutical and agrochemical research laboratories already, a further increase in the use of microwave-assisted combinatorial chemistry applications both in industry and in academic laboratories can be expected. This will depend also on the availability of modern instrumentation, either for parallel or for sequential processing mode [94, 95]. Unfortunately, the number of publications reporting combinatorial chemistry applications involving microwave heating technology is still comparatively small. One has to realize that most of the examples so far have been conducted in industrial laboratories where only a very small fraction of work is getting published. Despite this fact, it is clear that microwave-assisted combinatorial chemistry has a great potential and will likely become a standard tool in most combinatorial chemistry laboratories in a few years [96–98].

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13
Microwave-Enhanced Radiochemistry

John R. Jones and Shui-Yu Lu

13.1
Introduction

The synthesis, analysis and applications of labeled compounds is an area in which basic and applied research go hand-in-hand. Over the last quarter of a century the field has seen considerable expansion as reflected in the emergence of a specific journal (*Journal of Labeled Compounds and Radiopharmaceuticals*) and the publication of the proceedings of international conferences held at three-yearly intervals. The formation of the International Isotope Society is also an indication of the increasing importance of isotopes and isotopically labeled compounds.

Within the pharmaceutical industry labeled compounds are used for a variety of purposes e. g. screening new targets, for binding experiments, for identification of metabolites, in absorption, distribution and excretion studies and for quantifying concentrations in target organs [1]. Understanding reaction mechanisms are greatly assisted by the availability of suitably labeled compounds.

As most of the compounds used in the above areas are organic it follows that most of the isotopes used are those of hydrogen and carbon with oxygen, nitrogen and the halogens being used in a minority of cases [2, 3]. Whilst radioisotopes are preferred in terms of sensitivity the problems associated with the use of radioactivity (separate laboratory facilities required as well as trained personnel) and the production of radioactive waste (costs of storage and disposal) means that increasing use is being made of compounds labeled with stable isotopes, especially as some of the analytical methods, notably nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry are becoming more sensitive and versatile [4–7]. Indeed more and more pharmaceutical companies are developing policies which require drug candidates to be labeled (separately) with both stable and radioactive isotopes. Consequently there is the added benefit to those interested in the preparation of radiolabeled compounds that the information obtained can be used for preparing the corresponding compounds labeled with a stable isotope. Indeed for those in academic centers it is customary practice to label the target compound, first with a stable isotope, and then with the radioactive isotope.

In labeling a compound with a stable isotope and with a radioactive isotope there are several differences. The former tends to be done on the mg g^{-1} scale whereas the

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

radiolabeled compound is usually prepared on the µg to mg scale. Purification of the former can be achieved by recrystallization or distillation as well as by one or more chromatographic methods whereas radiolabeled compounds are invariably purified by radiochromatographic methods.

Within the pharmaceutical industry there is pressure to produce more drug candidates in a shorter time (greater efficiency). This trend makes it necessary to devise new and more efficient methods for preparing labeled compounds. There is also a growing need for a drug candidate to be labeled with several isotopes i. e. multideuterated or multitritiated rather than monodeuterated or monotritiated. Finally, and as mentioned already, there is a need at the end of a particular study, to convert the radioactive waste to a form which can then be reused, even though the specific activity may not be as high as in the original study. The movement towards a more environmentally friendly chemical industry, with faster, more selective and efficient synthesis, with greatly reduced levels of waste, both radioactive and otherwise, is gathering momentum and it is one in which microwaves are destined to play an important role. Whilst the work that we focus on in this chapter concerns the preparation of tritium and inevitably deuterium labeled compounds examples are given where the benefits can also be applied to the carbon (^{11}C, ^{13}C and ^{14}C)-labeled area [8]. Finally we refer to the use of microwaves in the synthesis of ^{18}F-labeled radiopharmaceuticals. The latter area has been the subject of a recent review [9].

13.1.1
Methods for Incorporating Tritium into Organic Compounds

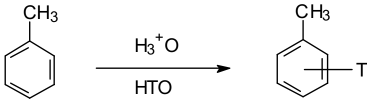
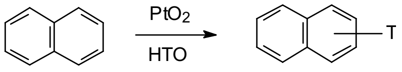
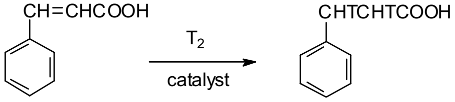
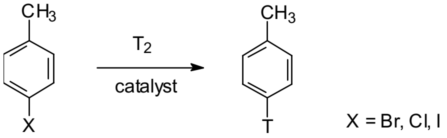
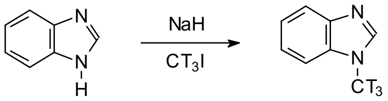
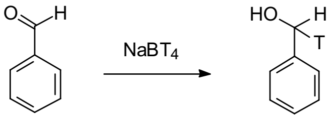
The standard work of Evans [2] as well as a survey of the papers produced in the *Journal of Labeled Compounds and Radiopharmaceuticals* over the last 20 years shows that the main tritiation routes are as given in Tab. 13.1. One can immediately see that unlike most ^{14}C-labeling routes they consist of one step and frequently involve a catalyst, which can be either homogeneous or heterogeneous. One should therefore be able to exploit the tremendous developments that have been made in catalysis in recent years to benefit tritiation procedures. Chirally catalyzed hydrogenation reactions (Knowles and Noyori were recently awarded the Nobel prize for chemistry for their work in this area, sharing it with Sharpless for his work on the equivalent oxidation reactions) immediately come to mind. Already optically active compounds such as tritiated l-alanine, l-tyrosine, l-dopa, etc. have been prepared in this way.

The development of phase transfer catalysis, of supercritical fluids, of ionic liquids and of course, new reagents, should also have considerable potential in the labeling area. Furthermore there is the possibility of combining these approaches with energy-enhanced conditions – in this way marked improvements can be expected.

13.1.2
Problems and Possible Solutions

The tritiation procedures given in Tab. 13.1 all have serious limitations/disadvantages. Thus for all three hydrogen isotope exchange reactions HTO is used as the do-

Tab. 13.1 Main tritiation procedures.

Reaction	*Example*
1 Hydrogen isotope exchange	
(a) Base-catalyzed	$C_6H_5COCH_3 + OH^- \xrightarrow{HTO} C_6H_5COCH_2T$
(b) Acid-catalyzed	
(c) Metal-catalyzed	
2 Hydrogenation (a) Homogeneous (b) Heterogeneous	
3 Aromatic dehalogenation	
4 Methylation	
5 Borohydride reduction	

nor. For health and safety reasons 50 Ci mL^{-1} (1 Ci = 37 GBq), corresponding to close on 2% isotopic abundance, is the highest specific activity that we have used and this inevitably limits the maximum specific activity of the products that can be obtained by these routes.

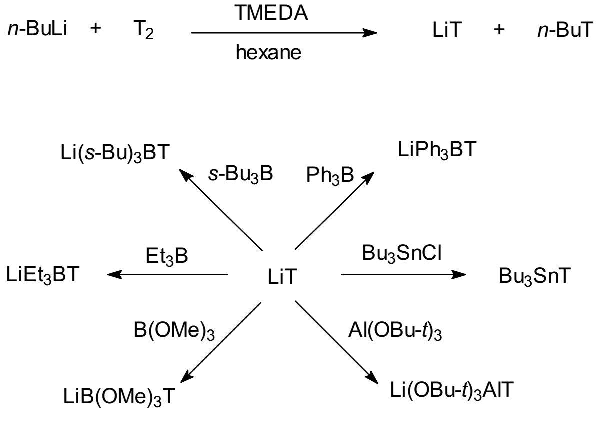
The success of the base-catalyzed hydrogen isotope exchange reaction very much depends on the acidity of the carbon acid – the weaker it is (higher pK_a) the stronger the base required to abstract the proton to form the reactive carbanion [10]. Within the pharmaceutical industry there is a reluctance to use tritium labeled compounds produced by this route – this is because of the dangers of "back exchange". If the compound to be labeled contains several acidic sites then the label will no longer be incorporated at one site. This may or may not be a disadvantage depending on what use is to be made of the labeled compound.

Although many pharmaceutical compounds are unable to withstand harsh acidic conditions a surprisingly large number of compounds have been labeled by this route. Werstiuk [11], for example, has reduced the acid concentration but increased the temperature, one effect more than compensating for the other – however, the time required is frequently very long, extending into days. Ion exchange resins, both acid and base forms, can be used to overcome separation problems [12, 13].

Since the pioneering work of Garnett and Long [14, 15] much progress has been made in increasing the selectivity of one-step metal-catalyzed hydrogen isotope exchange reactions. $RhCl_3$, and iridium(I) catalysts of the type $[Ir(COD)(L)_2]PF_6$ (COD: *cis,cis*-1,5-cyclooctadiene) have been successfully used by, amongst others, Heys, Hesk, Lockley, Salter and their coworkers [16–19]. In some of these studies HTO has been replaced by T_2 as donor so that compounds of very high specific activity can be obtained. Myasoedov and colleagues [20, 21] have also made extensive use of high temperature solid state catalytic isotope exchange (HSCIE) for the tritiation of a wide range of organic compounds at high specific activity.

Until recently hydrogenation reactions with T_2 were performed on glass gas lines but this is now frowned upon by the environmental and health and safety inspectorate. Fortunately there are two commercial instruments available, one manufactured in Switzerland and the other in the USA, which are entirely metallic and use an uranium "getter" for storing T_2 gas; gentle heating allows a predetermined volume of gas to be transferred to the reaction vessel and on completion of the reaction any excess can be returned to a secondary bed for storage and reuse. T_2 gas is relatively inexpensive and available at 100% isotopic incorporation (specific activity of 56 Ci $mmol^{-1}$). The main disadvantage now is that it is sparingly soluble in many organic solvents with the result that the catalyzed reactions, under both homogeneous and heterogeneous conditions, are frequently very slow.

Aromatic dehalogenation suffers from the disadvantage that only 50% of the tritium is incorporated, the rest appearing as waste. This situation is even more marked for borotritide reductions but the problem can be overcome by using some of the new tritide reagents that have recently become available as a result of the synthesis of carrier-free lithium tritide (Scheme 13.1) [22]. Their reactivity can be fine-tuned through the elements (e. g. B, Al, Sn) to which the tritium is attached and by the electronic and steric nature of the substituents at the central atom.



Scheme 13.1 Preparation of tritide reagents from LiT.

Tritiated methyl iodide has the advantage that three tritiums can be incorporated in one step so that compounds with a specific activity close to 80 Ci $mmol^{-1}$ can be prepared. CT_3I is available from commercial sources and being a low boiling liquid needs very careful handling. It is stable for short periods, consequently there is a need for new methylating agents that offer greater flexibility.

13.1.3
The Use of Microwaves

The possibility of accelerating chemical reactions through the application of a source of energy, be it in the form of external radiation or an electric or magnetic field, has a long history. The first radiation induced method of labeling was reported by Wilzbach [23] in 1957 and was subsequently described as the Wilzbach gas exposure method. Typically 0.5–4.0 g substrate was exposed to 7–14 Ci of T_2 gas for between 3 and 10 days, leading to 20–600 mCi incorporation with specific activities of the product being in the 1–100 mCi g^{-1} region. This work was done long before the development of ^3H NMR spectroscopy [24] so that the pattern of labeling could not be ascertained. Furthermore purification of the products by techniques such as high performance liquid chromatography (HPLC) was not possible. The hopes of the author that "the availability of T_2 gas at low cost and the high levels of radioactivity attainable, even in materials of complex structure, combine to make exposure to tritium gas an attractive method for the preparation of tritium labeled compounds" were not therefore fully realized and, in the course of time, more attractive tritiation methods were developed. Nevertheless the work stimulated a great deal of interest with the objective of minimizing radiation damage and increasing the specific activity of the labeled substrate. Many improved versions of the Wilzbach method were reported, of which the following are best known:

- recoil labeling
- electrical discharge method
- low pressure method
- ion beam method
- microwave discharge activation (MDA) method
- adsorbed tritium method

The recoil method does in fact predate the Wilzbach method.

Although chemists very frequently refer to two papers [25, 26] published in 1986 as the start of the "microwave-enhanced era" as an efficient new procedure for organic synthesis, it was Westermark et al. [27], way back in 1960, who first suggested that input of microwave power into a system containing tritium could accelerate the tritiation kinetics. A number of antibiotics, local anesthetics and amino acids were amongst the early compounds labeled. Wolf et al. [28–30] improved the technique by circulating the tritium gas within the labeling system and successfully tritiated a number of tripeptides, amongst other compounds. Essentially the same system was used by Peng et al. [31, 32] to tritiate a number of steroids. The apparatus was relatively simple to construct and the MDA method was seen to be superior to the other radiation-induced methods of labeling, requiring a short reaction time and using a small amount of tritium gas. However, the chemistry within this kind of microwave plasma is complex with various tritium species being formed e.g. T^+, T_3^+, T and T^-. Consequently there are several reaction mechanisms taking place concurrently so that the overall tritiation is characterized by low selectivity; extensive purification is also necessary. Being a radiation-induced method the work can not be applied to deuteration studies, in sharp contrast to the more recently developed microwave-enhanced methods. An excellent account of radiation-induced methods of labeling has been given by Peng [33].

The exponential growth in microwave-enhanced synthetic organic chemistry (see Fig. 1 in Refs. [8] and [34]) which Gedye and Giguere and their colleagues initiated in 1986 may come to represent one of the most significant events in the development of chemistry over the last half-century. Whilst microwave dielectric heating has been widely used in the food processing area for many years chemists have been slow in recognizing the potential, partly because the necessary theory is usually taught as part of a physics degree course and partly because of the lack of suitable instrumentation for making quantitative, as distinct from qualitative, measurements. This second problem will soon not exist as several powerful computer-controlled instruments have come to market within the last year.

A detailed account of the theory behind the interaction of microwaves with matter is beyond the scope of this chapter but there are several excellent and recent reviews available [35–37 and Chapt. 1], especially by Mingos and coworkers. Whilst microwaves are known to be electromagnetic waves in the frequency region 0.3 to 300 GHz current instrumentation tends to operate at a fixed frequency of 2450 MHz, corresponding to a wavelength of 12.2 cm, as the major part of the microwave region is assigned to radar and telecommunications. In the absence of free electric charges the interaction between the microwave field and a molecule can be expressed in terms of an interaction between an electric field and an electric dipole. The polarization, P, represents the response:

$$P = \varepsilon_0 \chi_e E$$

where E is the electric field, χ_e the electrical susceptibility and ε_0 the electrical permittivity in vacuum. The applied field creates a current which is the vector sum of the polarization current and the conduction current. At high frequencies the molecular inertia causes the polarization vector $\mathbf{P}$ to lag behind the applied field E and this is the origin of the term "dielectric loss", expressed as $\tan\delta$. Microwave energy is not therefore transferred by convection or conduction but by dielectric loss – a high value for $\tan\delta$ indicates a high susceptibility to microwave energy. Polar solvents and solids have high $\tan\delta$ values and are therefore favored for microwave-enhanced reactions. Increasing the ionic strength of the reaction medium can also provide benefits. In the case of nonpolar solvents, or under solvent-free conditions, it is claimed [34] that when polar mechanisms are involved that nonthermal and specific microwave effects may arise.

Microwave irradiation, in contrast to thermal heating, produces very efficient heat transfer resulting in even heating throughout the sample. The process can be optimized by giving careful thought to the dimensions of the reaction vessel and volume of reactants [9]; it is fortunate that radiochemical syntheses are usually performed on a very small scale ($< 5\ \text{cm}^3$) where a high and stable *E*-field intensity is easier to maintain, especially if a monomodal cavity, rather than a multimodal mode, is adopted.

13.1.4
Instrumentation

The instruments used for microwave-enhanced chemistry fall into two categories: the multimode type that we commonly use in the kitchen and the mono-mode (or single-mode) type that is specially designed for chemistry laboratories. The main difference between them comes down to how the microwave power is delivered and controlled. In the multimode oven a time pulse at a fixed power level is used and the waves within the cavity are not directed in any particular direction. The ovens do not possess well defined electric fields and consequently the heating pattern within the areas of the cavity is not homogeneous. In contrast, the mono-mode instrument has a waveguide which focuses the microwave field on the sample. The power control enables more precise energy to be delivered and this can be varied according to the needs of the reaction. It also has a temperature sensor, and some are equipped with a pressure sensor, which allow chemists to monitor or to control the heating process. These devices give better reproducibility, shorter reaction time and sometimes better chemical yields because the interaction between the microwave field and the sample can be optimized.

Most of the early work was carried out using the multimode oven or commercial domestic microwave oven. At Surrey we first used a Matsui M169BTunit (750 W), later on a Prolabo Synthewave S402 focused microwave reactor (300 W) was acquired. In our earlier studies, the reagents were contained in a thick walled glass tube sealed at the top but experience showed that a small conical flask ($20\ \text{cm}^3$) fitted with a septum stopper was well suited for most of the reactions. It was placed in a beaker containing vermiculite and slowly rotated during the course of the irradiation. To avoid undue pressure buildup the vessel can also be left unstoppered. For parallel reactions, the Radley's RDT 24 place PTFE carousel reaction station together with Pyrex glass tubes ($25\ \text{cm}^3$, o.d. = 15 mm) was placed on the turntable of the microwave oven. The reaction vessels for the Synthelabo S402 are quartz tubes of different sizes. For smaller scale reaction specially designed Pyrex tubes (o.d. = 9 mm) can be inserted inside the standard quartz tube (o.d. = 25 mm).

More and more researchers are using the mono-mode instruments and the manufacturers are bringing the second generation of microwave reactors (e.g. The SmithSynthesizer or the SmithCreator by Personal Chemistry, the Discover focused microwave synthesis system by CEM, and the Ethos Synth microwave labstations by Milestone) to the market; these are more effective and user friendly. New standard glassware, capable of withstanding high temperature and pressure is also being developed and marketed.

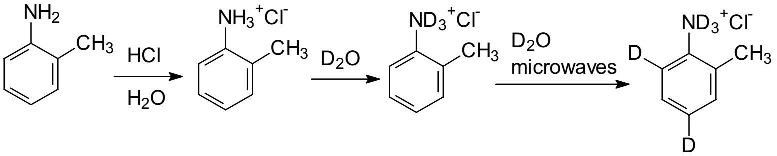
13.2
Microwave-enhanced Tritiation Reactions

13.2.1
Hydrogen Isotope Exchange

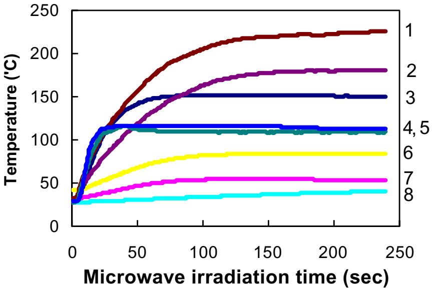
This is one of the most versatile reactions known as it can be catalyzed by acids, bases and metals as well as induced by photochemical and other means. It is also amongst the simplest of organic reactions so that studies in this area have greatly improved our understanding of reaction mechanisms. It is also one of the best methods for introducing deuterium/tritium into organic compounds. The knowledge gained from basic research studies can therefore be put to good use within a fairly short time interval.

Koves [38–40] was the first to show that acid-catalyzed aromatic hydrogen isotope exchange could benefit from the use of microwaves and shortly afterwards we showed that both heterogeneous and homogeneous metal-catalyzed reactions could also be greatly accelerated [41, 42]. It was during these studies that we recognized that further benefits could accrue by converting the organic compound (usually neutral) to an ionic form e.g. by protonating the $-NH_2$ group. These preliminary studies were then extended to take in a large number of nitrogen-containing heterocyclic compounds – here protonation on an NH_2 group or the ring-based nitrogen was possible. This work was prompted by the earlier findings of Werstiuk employing a high temperature, dilute acid, approach to the deuteration of many organic compounds. Extensive labeling could be obtained provided the heating times were long (typically 12–50 h). Rarely can compounds of pharmaceutical interest withstand such demanding conditions. Furthermore, the development of new, combinatorial chemistry, requires that labeling reactions should be rapid so that high sample throughput can be achieved.

The results for mono-, di- and fused ring substituted pyridines showed, as for the earlier study on the microwave-enhanced deuteration of *o*-toluidine, that by first forming the hydrochloride salt extensive labeling could be achieved within 20 min. Furthermore the reaction products were easily isolated and of high purity, a frequently noticed feature of these reactions. The reaction mechanism is represented in Scheme 13.2, the deuterium being inserted in the *ortho* and *para* positions. The time taken to reach a predetermined temperature depends greatly on the polarity of the solvent used and as the results in Fig. 13.1 show this can be altered either by changing the solvent or adding a cosolvent. For labeling purposes a D_2O (or HTO)–



Scheme 13.2 Deuteration of *o*-toluidine hydrochloride under microwave conditions.



Solvent	b.p (°C)	ε_s	Tanδ
1 DMSO	189	47	0.825
2 DMF	153	36.7	0.161
3 BuOH	118	n/a	n/a
4 H_2O	100	80.4	0.123
5 EtOH	78	24.6	0.941
6 $CHCl_3$	61	4.8	0.091
7 CH_2Cl_2	40	9.1	0.042
8 1,4-dioxane	101	n/a	n/a

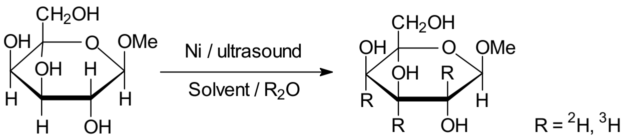
Fig. 13.1 Microwave heating profile of organic solvents using a Prolabo Synthewave S402 microwave instrument (5 cm^3 at 300 W)

DMSO mixture has great attraction as the heating time can now be reduced to a matter of 1–2 min.

The choice of solvent can also be beneficial in another respect. This possibility was highlighted by the findings of Cioffi on the Raney Nickel catalyzed hydrogen–deuterium exchange of a model carbohydrate [1-*O*-methyl-*β*-D-galactopyranoside] but under ultrasonic irradiation (Tab. 13.2) [43]. Extensive deuteration at C-4 position occurred for a series of ethereal solvents, the C-3 position was deuterated by seven solvent systems and the C-2 position deuterated less extensively, also by seven solvent systems. For 1,4-dioxane-D_2O no labeling at the C-2 position occurred and for 1,2-dimethoxyethane-D_2O no C-3 labeling was observed.

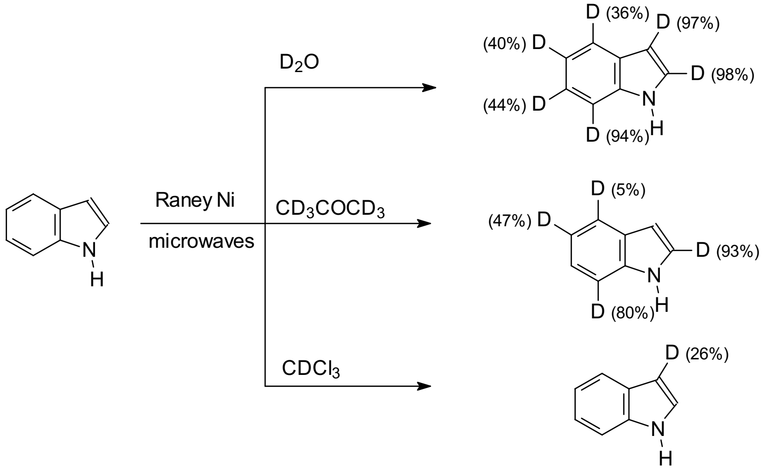
We chose the microwave-enhanced Raney Nickel catalyzed hydrogen isotope exchange of indole and *N*-methylindole as our substrates and D_2O, CD_3COCD_3, CD_3OD and $CDCl_3$ as the solvents. The thermal reaction had already been the subject of a recent study [44]. The microwave-enhanced method was some 500-fold faster than the corresponding thermal reaction (at 40 °C). Furthermore the pattern of labeling (Scheme 13.3) varied with the choice of solvent. Thus in the case of indole it-

Tab. 13.2 Pattern of labeling for a model carbohydrate under ultrasonic irradiation.



Position	*THF*	*DMTHF*	*THP*	*1,3-Dioxane*	*1,4-Dioxane*	*DME*
C_2	27	28	20	25	<1	15
C_3	73	84	59	60	62	<1
C_4	89	93	59	76	75	29

THF = tetrahydrofuran, DMTHF = 2,5-dimethyltetrahydrofuran, THP = tetrahydropyran, DME = 1,2-dimethoxyethane



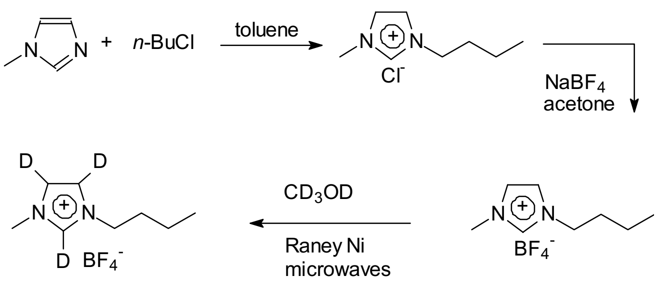
Scheme 13.3 Pattern of deuteration at different sites for indole using various solvents and microwave irradiation.

self the more polar solvents such as D_2O and CD_3OD give rise to general labeling whilst $CDCl_3$, for example, gave very regiospecific labeling. There is at this stage no indication that the pattern of labeling in the microwave-enhanced reactions is different in any way from that observed for the thermal reactions. However inherent in both sets of results are mechanistic features worthy of more detailed investigation.

The benefits of using ionic compounds in microwave-enhanced reactions led us to explore the possibility of using ionic solvents i.e. ionic liquids, as donors for both deuterium and tritium. Whilst D_2O is now relatively inexpensive and available at high isotopic enrichment, tritiated water is usually employed, for safety reasons, at low isotopic incorporation (we typically use HTO at 5 or 50 Ci mL^{-1} specific activity corresponding to 0.2–2% isotopic incorporation). This is a serious limitation when there is a need to provide compounds at high specific activity.

Ionic liquids [45–47] are liquids containing only ions, and are fluid at or close to, room temperature; those with higher melting points are called molten (or fused) salts. They are nonvolatile and many are both air- and moisture-stable as well as being good solvents for a wide range of both inorganic and organic molecules; they frequently permit unusual combinations of reagents to be brought into the same phase.

Many ionic liquids are based on *N,N*-dialkylimidazolium cations (BMI) which form salts that exist as liquids at, or below, room temperature. Their properties are also influenced by the nature of the anion e.g. BF_4^-, PF_6^-. The C-2(H) in imidazole is fairly labile but the C-4(H) and the C-5(H) are less so. Under microwave-enhanced conditions it is therefore possible to introduce three deuterium atoms (Scheme 13.4). As hydrogen isotope exchange is a reversible reaction this means that the three deuterium atoms can be readily exchanged under microwave irradiation. For storage purpose it might be best to back-exchange the C-2(D) so that the 4,5-[$^2H_2$] isotopomer can be safely stored as the solid without any dangers of deuterium loss. The recently



Scheme 13.4 Preparation of 2,4,5-[$^2H_3$]-BMI-BF_4 ionic liquid.

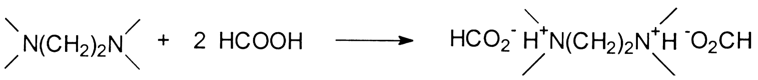
reported microwave-assisted preparation of a series of ambient temperature ionic liquids may well accelerate their use in this area [48]. We have already carried out some deuteration studies with the 2,4,5-[$^2H_3$]-BMI-BF_4 ionic liquid and found that for reasonably volatile organic compounds these can be separated off by simple evaporation leaving the deuterated ionic liquid available for repeated use i. e. until all the deuterium has been replaced by hydrogen [49]. Extension of the investigations to the tritium area will require the analog to be prepared using Raney Nickel and T_2 gas under thermal conditions.

Ease of separation of tritiated products from a reaction medium is an important feature in the choice of labeling procedure. Sometime ago we used polymer-supported acid and base catalysts [12, 13] to good effect and with the current interest in Green Chemistry one can expect to see more studies where the rate accelerations observed under microwave-enhanced conditions are combined with the use of solid catalysts such as Nafion, or zeolites.

13.2.2
Hydrogenation

Neither tritium or deuterium gas, with zero dipole moments, can be expected to interact positively with microwave radiation. Their low solubilities are seen as a further disadvantage. Our thoughts therefore turned towards an alternative procedure, of using solid tritium donors and the one that has found most favor with us is formate, usually as the potassium, sodium or ammonium salt. Catalytic hydrogen transfer of this kind is remarkably efficient as the results for α-methylcinnamic acid show [50]. The thermal reaction, when performed at a temperature of 50 °C, takes over 2 h to come to equilibrium whereas the microwave-enhanced reaction is complete within 5 min. A further advantage is that more sterically hindered alkenes such as α-phenylcinnamic acid which are reduced with extreme difficulty when using H_2 gas and Wilkinson's catalyst are easily reduced under microwave-enhanced conditions.

Formate can only donate one hydrogen, the other presumably coming from traces of water present in the solvent or on the surface of the reaction vessel. With the need to increase the specific activity of the product our thoughts turned to the preparation of a diformate salt and as a first example we synthesized the diformic acid salt of tetramethylethylenediamine (TMEDA).



$$Me_2N(CH_2)_2NMe_2 + 2\ HCOOH \longrightarrow HCO_2^-\ H^+NMe_2(CH_2)_2NMe_2H^+\ ^-O_2CH$$

The tritiated version could be prepared from tritiated formic acid which we had prepared at high specific activity (2.5 Ci mmol^{-1}) by a metal-catalyzed hydrogen–tritium exchange procedure using T_2 gas. The material can be stored either as a solid or as a solution; if the latter any release of tritium by back exchange can be easily monitored by ^3H NMR spectroscopy. In our experience very little exchange occurs over several weeks of storage [51].

The use of tritiated formates have further benefits. Firstly the exact amount necessary for 100% hydrogenation can be added so the problems associated with the use of excess T_2 gas are avoided and virtually no radioactive waste is produced. Secondly, the pattern of labeling can be easily varied, as illustrated for the case of cinnamic acid (using deuterium rather than tritium). When formate is used in D_2O there are three possible combinations: $H_2O + DCO_2^-$, $D_2O + HCO_2^-$ and $D_2O + DCO_2^-$ (or the DCO_2D salt of TMEDA on its own). The ^2H NMR spectra show that three isotopomers can be prepared – $C_6H_5CHDCH_2COOH$, $C_6H_5CH_2CHDCOOH$, and $C_6H_5CHDCHDCOOH$.

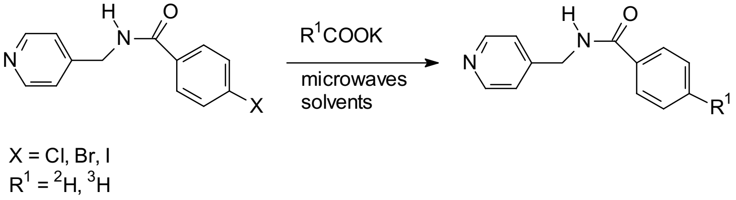
As of now no details of the synthesis of optically active tritiated compounds produced under microwave-enhanced conditions have been published. Another area of considerable interest would be the study of solvent effects on the hydrogenation of aromatic compounds using noble-metal catalysts as considerable data on the thermal reactions is available [52]. Comparison between the microwave and thermal results could then provide useful information on the role of the solvent, not readily available by other means.

13.2.3
Aromatic Dehalogenation

As far as preparing tritiated (and deuterated) compounds are concerned aromatic dehalogenation is second only to hydrogenation in importance. Furthermore it suffers from the same disadvantages e. g. slow rates which are caused in part by the poor solubility of the T_2 gas in many organic solvents. The situation is however worse as only 50% of the tritium is introduced into the desired product. Once again we modified the classical dehalogenation by replacing D_2/T_2 gas with labeled formates [53]. There were some previous examples [54–56] of the use of formates in dehalogenation reactions but none of these describe the utility of these agents for labeling organic compounds under the influence of microwave irradiation.

The *N*-4-picolyl-4-halogenobenzamide system (Scheme 13.5) was chosen as the basic substrate structure because:

- the Cl, Br and I derivatives were all easily synthesized;
- satisfactory purification procedures were to hand;



Scheme 13.5 Dehalogenation of *N*-4-picolyl-4-halobenzamide compounds.

- they yield strong pseudomolecular ions in both positive and negative ion HPLC/MS; and
- they have simple NMR spectra.

Under the experimental conditions dehalogenation proved to be extremely rapid and was complete within 1 min. This contrasts with the 90–270 min at 100 °C required for thermal debromination of 2-bromonapthalene. No dehalogenation takes place in the absence of the formate donor and when the deuterium is located in the cosolvent rather than the donor (i.e. HCOOK + D_2O) hardly any deuterium incorporation takes place. Another interesting observation was that the amount (%) deuterium incorporation was always lower when protic solvents such as alcohols were used than aprotic solvents such as dimethyl sulfoxide (DMSO). These are both interesting and useful findings which are valuable for proposed tritiation studies.

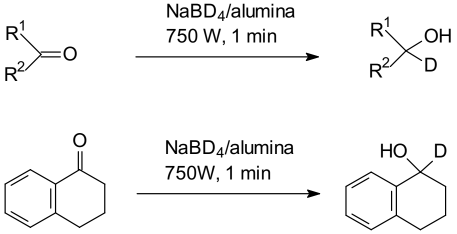
13.2.4
Borohydride Reductions

One of the most attractive features of borohydride reductions is that under microwave-enhanced conditions they can be performed in the solid state, and rapidly. We were attracted by the work of Loupy [57], and in particular Varma [58, 59] who has shown that irradiation of a number of aldehydes and ketones in a microwave oven in the presence of alumina doped $NaBH_4$ for short periods of time led to rapid reduction (0.5–2 min) in good yields (62–93%). In our study [60] seven aldehydes and four ketones were reduced (Tab. 13.3). Again reduction was complete within 1 min, the products were of high purity (>95%), of high isotopic incorporation (95%, same as the $NaBD_4$) and the reactions completely selective.

So far this remains the only microwave-enhanced borohydride deuteration study. Corresponding tritiation studies can be anticipated in due course, especially with the wider range of tritiated reducing agents, referred to previously, becoming available. Significant reductions in radioactive waste can be anticipated.

Many borohydrides are highly unstable and have to be used as freshly prepared ethereal solutions. However there are instances where the polymer-supported versions are more stable e.g. an Amberlyst anion exchange resin supported borohydride and cyanoborohydride [61], polyvinylpyridine supported zinc borohydride [62] and the corresponding zirconium borohydride [63]. Such compounds, in their labeled forms, should turn out to be very useful.

Tab. 13.3 Borodeuteride reduction of carbonyl compounds under microwave conditions (750W, 1 min).



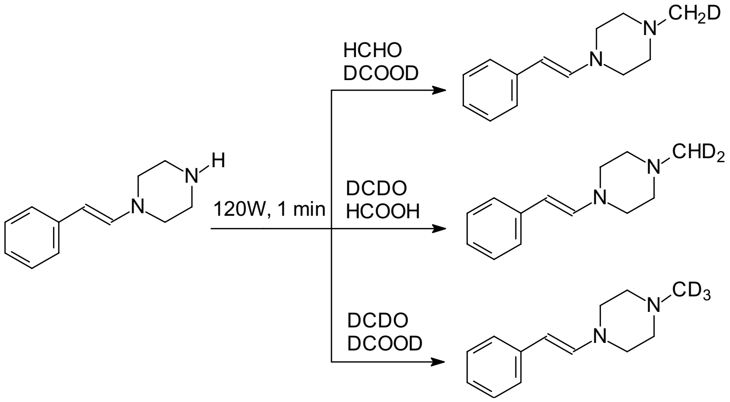
Aldehydes, R^2 = H							
R^1	Ph	$4\text{-}NO_2C_6H_4$	*trans*-PhCH=CH	$2,4,6\text{-}(OMe)_3C_6H_2$	1-Naphthyl	2-Naphthyl	$PhCH_2$
Yield (%)	37	37	77	83	85	89	68
Ketones							
R^1	Ph	$4\text{-}NO_2C_6H_4$	$3\text{-}ClC_6H_4$	5-methyltetralone			
R^2	Me	Me	Me	–			
Yield (%)	82	68	86	87			

13.2.5
Methylation Reactions

Methyl iodide is the most widely used methylating agent and is the favored route to CT_3- and CD_3- containing compounds. As it can be rapidly synthesized (from CH_4) the [^{11}C]-isotopomer also finds wide application (Sect. 13.4) in the rapidly expanding positron emission tomography (PET) area [64]. Nevertheless it is generally agreed that [^{11}C]-methyl triflate is a better methylating agent – it is more reactive and less volatile so that one does not require cooling for trapping or heating for reaction to take place.

We realized that using a low boiling liquid in a microwave environment, even on a small scale, did not constitute “best practice” and as for hydrogenations our thoughts turned to using formates in a modified Eshweiler–Clarke reaction [65–67] and successfully methylated a number of primary and secondary amines under microwave conditions (Scheme 13.6) [68].

The methylation of secondary amines works better than for primary amines because there is no competition between the formation of mono- or dimethylated products. The best results for the microwave-enhanced conditions were obtained when the molar ratios of substrate/formaldehyde/formic acid were 1 : 1 : 1, so that the amount of radioactive waste produced is minimal. The reaction can be carried out in neat form if the substrate is reasonably miscible with formic acid/aldehyde or in DMSO solution if not. Again the reaction is rapid – it is complete within 2 min at 120 W microwave irradiation compared to longer than 4 h under reflux. The reaction mechanism and source of label is ascertained by alternatively labeling the formaldehyde and formic acid with deuterium. The results indicate that formaldehyde contri-



Scheme 13.6 Microwave-enhanced methylation using Eshweiler–Clarke reaction.

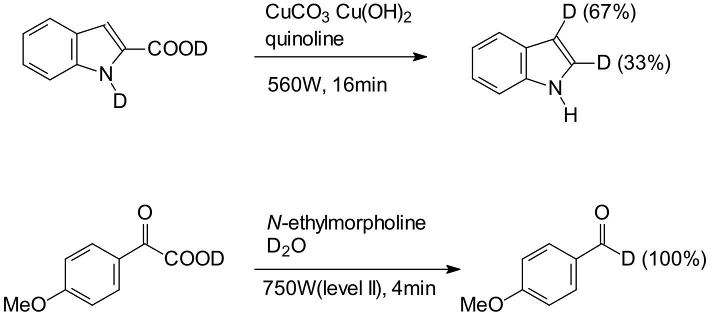
butes two deuterium atoms and the carbon whilst formic acid contributes one deuterium atom; there is no exchange between the formaldehyde and formic acid.

13.2.6
Aromatic Decarboxylation

As previous examples have shown the development of microwave-enhanced labeling technology means more than accelerating reactions – it provides alternative opportunities. It follows therefore that some previously used methods now become much more attractive and this is the case for certain aromatic decarboxylations which can now be used for tritiations as well as in the treatment of tritiated waste. In previous studies [69] of the reaction the overriding feature was the harsh experimental conditions required.

2-Unsubstituted indoles, widely used intermediates in organic chemistry, are commonly synthesized through decarboxylation of the parent acid [70]. This is achieved by prolonged heating in the presence of Cu (metal/salt) as catalyst and a basic solvent such as quinoline. In our studies [71] prior washing of the acid with CH_3OD to exchange the carboxyl proton with deuterium, followed by brief microwave activation, is sufficient to achieve decarboxylation/deuteration in ~100% yield. Other studies employing a commercial reactor and thick wall glass tubes capable of withstanding high pressure show that the decarboxylation proceeds in the absence of the environmentally undesirable copper catalysts and that quinoline can be replaced with water (Scheme 13.7) [72–74].

For a number of benzylformic acids we used *N*-ethylmorpholine as catalyst and D_2O as solvent/donor. Once again decarboxylation/deuteration occurs very rapidly and is complete within 4 min. The range of compounds that can be labeled in this manner has been further widened by the recent observation [75–77] that tributylphosphine and other trivalent phosphorus compounds (R_3P, $R = Bu$, Ph, Me_2N, OEt) catalyze the decarboxylation of α-iminoacids. By using deuterated/tritiated acetic



Scheme 13.7 Examples of microwave-enhanced decarboxylation.

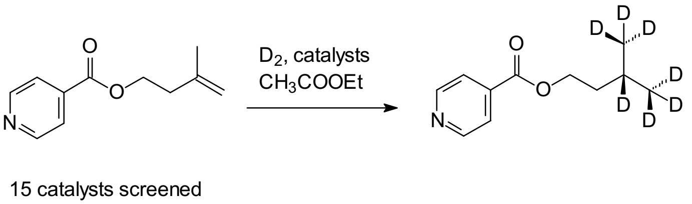
acid as a D^+/T^+ donor several labeled imines have been prepared. Under microwave-enhanced conditions the reactions would be expected to be much faster which again would be very useful as tritiated imines are frequently used to label β-lactams and other biologically interesting compounds such as α-aminophosphate [78]. It is also worth mentioning that the corresponding phosphites ($R_2HP{=}O$, R = OEt, OMe) are cheap, nontoxic hydrogen-atom donors and attractive alternatives to organic tin hydrides [79] and have been identified as effective radical reducing agents for organic halides, thioesters and isocyanides. The tritiated version of these reagents thus provide new opportunities, especially when coupled to microwave irradiation.

The potential of the microwave-enhanced decarboxylation route in the radioactive waste area is immediately apparent – washing the tritium waste with a protic solvent leads to exchange of the labile tritium. The solvent can then be used with one of the carboxylic acids mentioned above and after the microwave-enhanced decarboxylation the waste is now in the form of a solid (greatly reduced volume) which may have some further use.

13.2.7
The Development of Parallel Procedures

Chemistry as a subject has developed through the synthesis of individual compounds in a number of distinct steps. Recently it has benefited from the introduction of combinatorial/parallel chemistry techniques as well as microwave-enhanced technology but so far these studies have not been combined [80]. Lockley and coworkers [81–83] have shown very nicely how parallel chemistry techniques can be used for the rapid screening and ranking of catalysts using the hydrogenation of 3-methyl-3-butenylisonicotinate as the model reaction (Scheme 13.8).

The authors constructed an 80-well hydrogenator. Fifteen catalysts were screened and the isotopic incorporation assessed by LC/MS. The regiospecificity was determined by VAST Direct Injection NMR [82] in conjunction with SPADEZ [83], a multispectrum analysis tool – this is capable of displaying and quantifying up to 96 spectra. So far it has not been possible to vary the solvents as, under the experimental conditions, the more volatile distil over into the less volatile solvents.



Scheme 13.8 Parallel screening and ranking of catalysts for the reduction of isobutenyl groups.

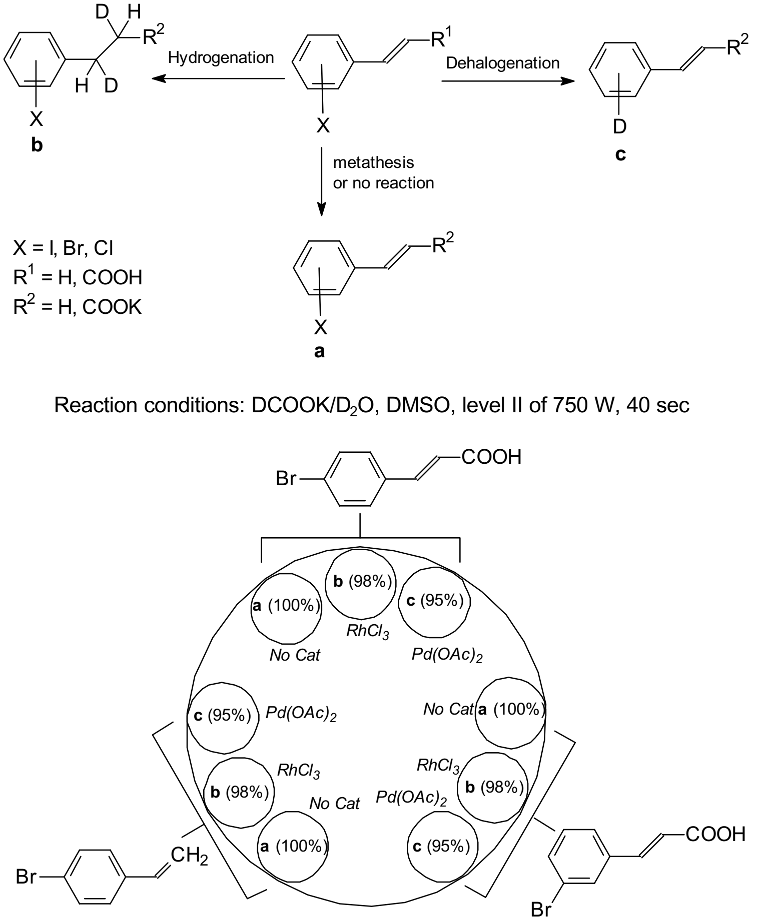
A similar study [84, 85] was performed for *ortho*-directing hydrogen isotope exchange reactions of substituted aromatics. The initial screening showed catalytic activity to reside exclusively with the Group VIII metals, especially the salts and complexes of Ru, Rh and Ir. Iridium based catalysts are superior to those previously used – they are more active, operate at lower temperatures and are applicable to a wider range of substrates. Eventually CODIrAcac (acac = acetylacetone or 2,4-pentanedione) was identified as the catalyst displaying the best activity; further optimization of activity was achieved by varying the ligand structure.

In our own preliminary studies [86] on parallel procedures under microwave-enhanced conditions, we have used the Radley's RDT 24 place PTFE carousel reaction station on the turntable of the Matsui M 169BT microwave oven. In this way, we have studied the catalytic activity of $RhCl_3$ and $Pd(OAc)_2$ towards the reduction or dehalogenation of 4-bromocinnamic acid and structurally similar compounds. A nine-reaction matrix was used under microwave-enhanced conditions as illustrated in Scheme 13.9 – greatly reduced reaction times and easy optimization of reaction conditions are immediate benefits. As robotics come to play an increasingly important role in chemistry, one can immediately see more sophisticated labeling experiments being undertaken.

13.2.8
Combined Methodology

In the search for labeled compounds at higher specific activity/isotope incorporation, we were aware of the fact that the most widely used methods (Tab. 13.1) are invariably performed separately. Consequently we embarked on a study to see whether, by choosing an appropriate compound, we could not combine e.g. hydrogenation and dehalogenation, or methylation and dehalogenation, or isotope exchange/hydrogenation/dehalogenation. Whilst the investigations are at an early stage, there are sufficient successful examples to indicate that in future more attention will be paid to using combined methodologies to improve isotopic incorporation.

As an example, *p*-bromocinnamic acid undergoes debromination in the presence of $HCOOK/H_2O/DMSO$ using $Pd(OAc)_2$ as catalyst. The reaction is complete in 60–90 s. On the other hand, the same compound undergoes hydrogenation under the same conditions using $RhCl_3$ as catalyst; again reaction is complete within 60 s. The combined debromination/hydrogenation of 4-bromocinnamic acid was complete

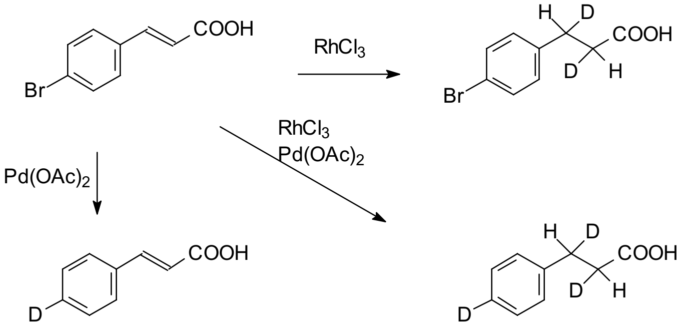


Reaction conditions: DCOOK/D_2O, DMSO, level II of 750 W, 40 sec

Scheme 13.9 A 9-reaction parallel matrix under microwave-enhanced conditions and schematic representation of carousel arrangement.

within 1 min when the reaction was performed under microwave-enhanced conditions (Scheme 13.10) [87]. Therefore one-pot M+3 deuterium labeling in a multifunctional molecule is achieved using a microwave-enhanced combined hydrogenation/aromatic dehalogenation procedure. Isotopic purity in all three positions was >95%.

The screening of the catalytic activity in these reactions is made possible by the readily available library of various heterogeneous and homogeneous transition metal catalysts. The use of microwaves ensures that two reactions, each requiring different times to reach equilibrium under thermal conditions, can now be completed within a very short interval.



Conditions for all reactions: catalysts, DCOOK/D_2O, DMSO, level II of 750W, 60sec.

Scheme 13.10 Example of multiple deuterium labeling using combined methodology.

13.3
Microwave-enhanced Detritiation Reactions

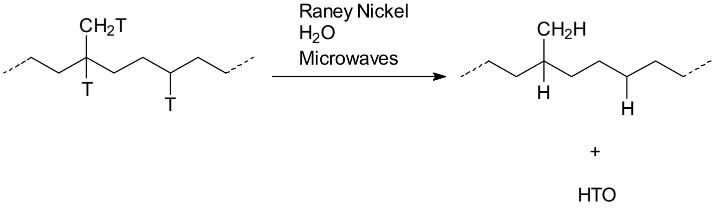
In the preparation of tritium-labeled compounds there are four stages:

- purchase of the tritiated reagent
- radiochemical synthesis
- storage of reagent/product followed by
- removal of radioactive waste

The first of these can be expensive as also can the last, consequently there is increasing interest in developing procedures which are more efficient than hitherto so that less radioactive waste is produced in the first place. Some radioactive waste can be disposed of via the drains but less so to the atmosphere, consequently there is also increasing interest in the possibility of converting the waste to a suitable reagent which can then be used in subsequent syntheses even though it is likely that the specific activity will be somewhat reduced. This philosophy can clearly be seen in the operation of both the Trisorber and Tritech tritium gas units which have replaced the old glass gas lines. In both instruments, the tritium gas is stored on an uranium "getter" which on warming, releases a predetermined amount of T_2 into the reaction vessel. On completion of the reaction, any surplus gas is returned to a secondary bed where it can be stored before use in a subsequent reaction.

Of all the methods used to tritiate organic compounds hydrogen isotope exchange stands on its own by virtue of the fact that it is the only truly reversible reaction. Consequently the benefits that have emerged from the study of microwave-enhanced hydrogen–tritium exchange should be immediately transferable to tritium–hydrogen exchange. By performing the reaction in a good microwave solvent such as water, a tritiated compound or mixture of compounds could be "decontaminated" and the HTO formed used in further tritiation studies, albeit at a lower level of specific activ-

Tab. 13.4 Microwave-enhanced and thermal detritiation of [^{3}H]-oils.



[^{3}H]-Oil	*Original activity (kBq mg^{-1})*	*Thermal detritiation*		*Microwave detritiation*[a]	
		% detritiation	*Time (h)*	*% Detritiation*	*Time (min)*
1	140	62[b]	48	60	5 × 2
2	1128	89[c]	48	87	5 × 2
3	2.1	60[c]	66	43	5 × 2
4	2.2	70[c]	66	71	5 × 2

[a] Microwave power set at level I (25%) of 750 W
[b] at 120 °C
[c] at 180 °C

ity. If the specific activity requirements are not too demanding the whole tritiation/detritiation cycle could be repeated several times, thereby making much better use of the tritiated water.

The first example [88] that we encountered was of an oil that had been exposed to a harsh tritium rich environment for a considerable time and had a level of radioactivity in the 2.1–2.2 kBq mg^{-1} range. An inactive oil, as represented by its ^{1}H NMR spectrum, had an identical composition and was used as a model compound. Based on previous work on shale oils [89] and engine basestocks [90] we knew that Raney Nickel could catalyze the hydrogen–tritium exchange reactions although the thermal reactions required high temperature (>180 °C) and long reaction times (48–66 h). However under microwave-enhanced conditions 5 × 2 min pulses was sufficient to exchange 60–90% of the tritium in the oils; repeating the procedure led to further detritiation (Tab. 13.4). Although these studies were performed on a small scale there is no reason why, as for other microwave-enhanced reactions, the scale of the operation can not be increased, or, alternatively a flow system designed.

13.4
Microwave-enhanced PET Radiochemistry

Positron emission tomography (PET) employs radiotracers and radioligands containing positron emitters e. g. ^{11}C, ^{13}N and ^{18}F in organic molecules, to study physiological, biochemical and pharmacological functions in humans at the molecular level [64, 91]. All of the three above-mentioned radionuclides have very short half-lives – ^{11}C (20.4 min), ^{13}N (10 min) and ^{18}F (110 min); consequently in order to achieve high radiochemical yields and specific activities the labeling procedures need to be rapid, simple to perform and the products easy to purify. Automation provides further benefits whilst the need to use reactants on a micro scale requires a good appreciation of both the reaction stoichiometry and the factors that influence the rates of chemical reactions.

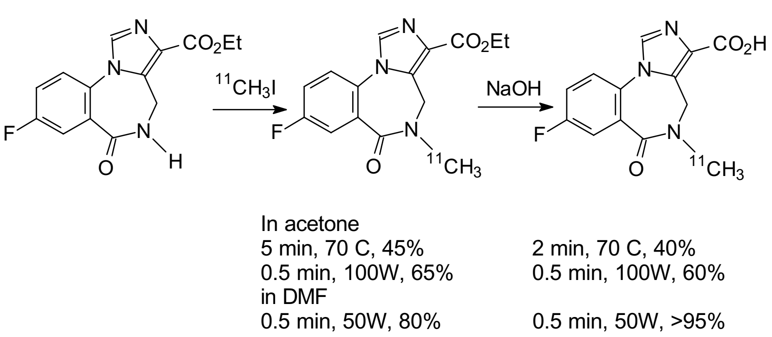
Because of these requirements, and in particular, the need to perform the reactions rapidly, it is not surprising that microwaves were used in the PET synthesis area at a very early stage [92]. However, the subsequent increase has not been as dramatic as one might have anticipated. Two recent reviews [8, 9] give an up-to-date picture whilst here we present some noteworthy examples.

13.4.1
^{11}C-Labeled Compounds

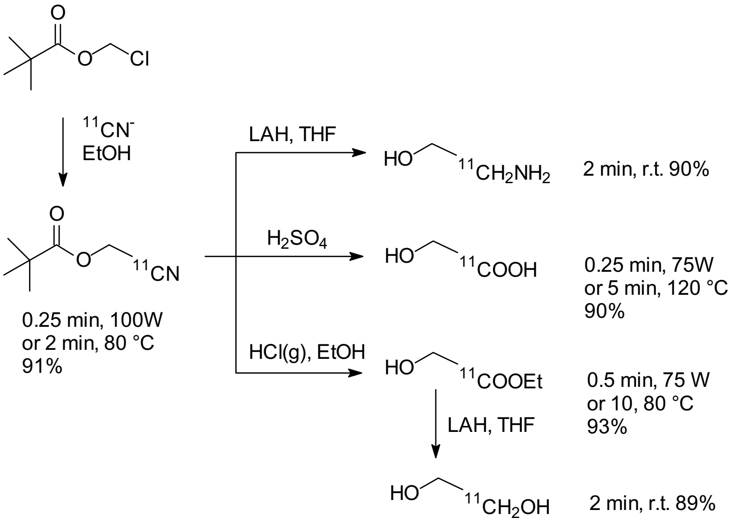
The most widely used synthetic routes follow on closely from those adopted for ^{14}C syntheses – a small number of key precursors such as $^{11}CO_2$, $^{11}CN^-$, $^{11}CH_3I$ and $H^{11}CHO$ are sufficient to label a wide range of compounds. *O*-, *N*- and *S*-alkylation can be achieved using $^{11}CH_3X$ (X = I, OTf) [93, 94]. Through the use of microwaves the time required to synthesize [*N*-methyl-^{11}C]Flumazenil can be reduced from 5 to 0.5 min, accompanied by a 20% improvement in yield. Further improvements can be achieved by changing the solvent, in this case from acetone to dimethylformamide (Scheme 13.11) [93].

[^{11}C]-Cyanide is a secondary precursor, produced from $^{11}CO_2$, but nevertheless as a result of microwave-enhanced accelerations can be used to label a wide range of amines, acids, esters and alcohols. Such an example is illustrated in Scheme 13.12 [95–98]. Reactions with less reactive substrates can be achieved by increasing the polarity of the reaction medium through the addition of various salts.

[^{11}C]-formaldehyde has been widely used for reductive methylation reaction but because of the marked fluctuation in the reported yields as well as impurities formed in its preparation from $^{11}CO_2$ the tendency has been to use $^{11}CH_3I$ for direct methylation. However, the recent development [99, 100] of a low temperature no-carrier-added method for preparing $H^{11}CHO$, coupled to the microwave-enhanced Eschweiler–Clarke reaction [65–68] has led to a resurgence of interest in the use of $H^{11}CHO$.



Scheme 13.11 Synthesis of [*N*-methyl-^{11}C]flumazenil acid.



Scheme 13.12 Synthesis of various ^{11}C-labeled amines, acids, esters and alcohols.

In their study Roeda and Crouzel shower that the LAH reduction of $^{11}CO_2$ produced 34% $H^{11}CHO$ plus 59% $H^{11}COOH$. Our experience in using a mixture of DCHO and DCOOH for the *N*-methylation of both primary and secondary amines suggests that the corresponding [^{11}C]-mixture would be ideal for the ^{11}C-labeling of amines under microwave-enhanced conditions.

13.4.2

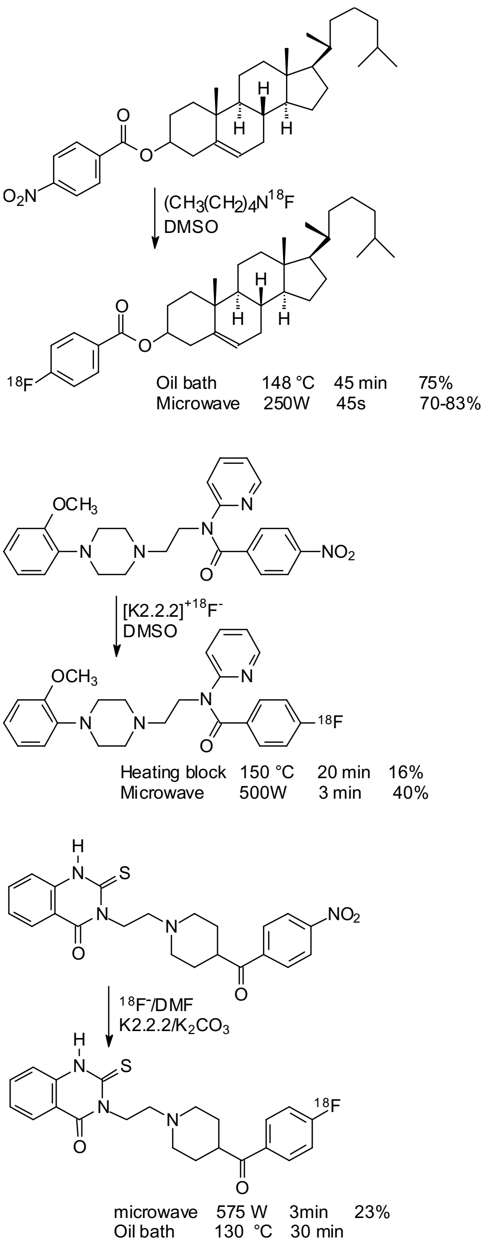
^{18}F-labeled Compounds

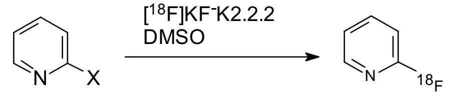
Substitution of fluorine for hydrogen in an organic compound causes little or no steric perturbation. However, as a result of its greater electronegativity and high C–F bond energy, the chemical and biological properties will be different. The much longer half-life, relative to ^{11}C, provides much greater scope for microwave-enhanced reactions, of which nucleophilic substitution, either aromatic or aliphatic, is the most widely used. Three examples of the former are given in Scheme 13.13 [101–103].

In a series of comparative studies Dolle et al. examined the nucleophilic aromatic substitution of a number of nitropyridine derivatives [104–106]. The results, as summarized in Scheme 13.14, show that under microwave-enhanced conditions the 2-NO_2 and 2-$^+NMe_3$ groups led to excellent fluorine incorporation whilst the 2-iodo compound was virtually unreactive. Under thermal conditions no fluorination was observed for the 2-chloro and 2-bromo compounds. In a separate study Banks et al. [107] again observed the beneficial effects of nitro and trimethylamino substitution (Scheme 13.15). The authors also developed a novel microwave-enhanced method of producing [^{18}F]-fluoromethane [108].

The use of microwaves, together with the involvement of a suitable protection group, can also be beneficial in reducing isotopic dilution as shown in Scheme 13.16

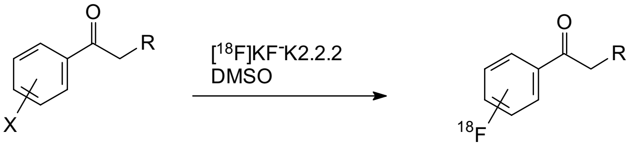
Scheme 13.13 Examples of aromatic nucleophilic substitutions used in the synthesis of ^{18}F-labeled radiopharmaceuticals.





X =	Cl	Br	I	NO_2	$N^+(CH_3)_3$
50W, 4 min	26%	68%	8%	76%	96%
100W, 2 min	22%	71%	14%	88%	90%

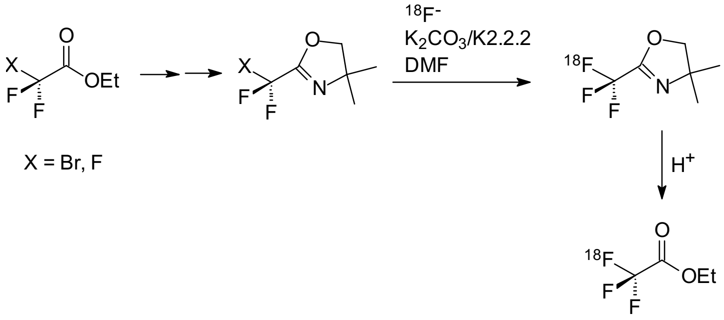
Scheme 13.14 Substituent effects in the microwave-enhanced nucleophilic fluorination of a number of pyridine derivatives.



700W, 2.5 min

X =	4-NO_2	2-NO_2	4-$N^+(CH_3)_3TfO^-$	2-$N^+(CH_3)_3TfO^-$	4-I	4-$N^+(CH_3)_3TfO^-$
R =	H	H	H	H	H	CH_3
	63%		77%		3%	

Scheme 13.15 Substituent effects in the microwave-enhanced nucleophilic fluorination of bifunctional radiopharmaceutical intermediates.



Heating block	20 min	110 °C
Microwave	15-30s	50W

Scheme 13.16. Protection–deprotection strategy in microwave-enhanced fluoro-debromination reaction.

[109]. Formation of the oxazoline reduced undesirable ^{18}F–^{19}F exchange and the desired product was rapidly (15s) isolated in good yield (45–55%) with a specific activity (1.1 GBq μmol^{-1}) that was 20 times higher than that obtained when using direct debromination route. In another example, the synthesis of 2-deoxy-2-^{18}F-fluoro-D-glucose [110] the high purity of the product and the improved specific activity is attributed to the short reaction times that are made possible via the use of microwaves.

13.5
Conclusion

From an early stage in the development of modern chemistry, it has been customary practice to simplify complex problems by the selective use of isotopes. For example, in the area of catalysis, relatively simple reactions such as hydrogen isotope exchange or hydrogenation reactions, have been investigated in order to delineate some of the finer details of reaction mechanisms. This information has then been applied so as to optimize the procedures that have been developed for labeling organic compounds. The last fifty years has seen the emergence of several, now large companies, specializing in these areas, as well as many smaller versions.

Now, with the emergence of new, microwave-enhanced technology, the process is destined to be repeated. In this case, faster, more selective and efficient procedures will emerge, where levels of radioactive waste will be greatly reduced and a more favorable, environmentally friendlier image of the chemical industry achieved. The products so produced can then go on to be used, in the words of Gordon Dean, sometime Chairman of the US Atomic Energy Commission, "to treat the sick, to learn more about disease, to improve manufacturing processes, to increase the productivity of crops and livestock, and to help man to understand the basic processes of his body, the living things about him, and the physical world in which he exists."

Acknowledgments

The tritium work at Surrey has been generously funded over many years by EPSRC (previously SERC and at the beginning, SRC), the EU, NATO and the chemical industry. The task of writing the current chapter was undertaken as part of the EU sponsored D10 COST Program (Innovative Methods and Techniques for Chemical Transformations). We are also grateful to Dr Norman De'ath (Radleys Discovery Technologies) for the loan of the RDT 24 place PTFE carousel reaction station.

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14

Microwave Photochemistry

PETR KLÁN and VLADIMÍR CÍRKVA

14.1

Introduction

Chemistry under extreme or nonclassical conditions is currently a dynamically developing issue in applied research and industry. Alternatives to conventional synthetic or waste-treatment procedures might increase production efficiency or save the environment by reducing the use or generation of hazardous substances in chemical production.

Microwave energy is a nonclassical energy source, with ultrasound, high pressure, mechanical activation, or plasma discharge [1]. Since first reports of the use of MW heating to accelerate organic chemical transformations [2, 3] over 1000 articles have been published on the subject of microwave-assisted synthesis and related topics – microwave chemistry has certainly become an important field of modern organic chemistry [4–13]. Microwave activation increases the efficiency of many chemical processes and can simultaneously reduce formation of the byproducts obtained from conventionally heated reactions. Chemical processes performed under the action of microwave radiation are believed to be affected in part by superheating, formation of hot-spots, polarization, and spin alignment [7, 8, 13]. The existence of a "specific microwave effect", i. e. a nonthermal effect, in homogeneous reactions has been a matter of controversy during the past decade [11, 14–17].

Microwave heating has already been used in combination with some other (un)-conventional activation processes. Such a combination might have a synergic effect on reaction efficiencies or, at least, enhance them by combining their individual effects. Application of MW radiation to ultrasound-assisted chemical processes has been recently described by some authors [18, 19]. Mechanical activation has also been successfully combined with MW heating to increase chemical yields of several reactions [1].

There have also been attempts to affect *photochemical* reactions by use of other sources of nonclassical activation, for example ultrasound [20, 21]. Combined chemical activation by use of two different types of electromagnetic radiation, microwave (MW) and ultraviolet (UV)/visible (VIS), is covered by the field broadly called *microwave photochemistry*. The energy of MW radiation is considerably lower than that of

Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9

UV radiation, certainly not sufficient to disrupt the bonds of common organic molecules. We therefore assume that, essentially, photoinitiation is responsible for a chemical change and MW radiation subsequently affects the course of the reaction. The objective of microwave photochemistry is frequently, but not necessarily, connected to the electrodeless discharge lamp (EDL) which generates UV radiation when placed in the MW field.

This chapter presents a complete picture of current knowledge about microwave photochemistry. It provides the necessary theoretical background and some details about synthetic and other applications, the technique itself, and safety precautions. Although microwave photochemistry is a newly developing discipline of chemistry, recent advances suggest it has a promising future.

14.2
Ultraviolet Discharge in Electrodeless Lamps

The electrodeless discharge lamp (EDL) [22] consists of a glass tube ("envelope") filled with an inert gas and an excitable substance and sealed under a lower pressure of a noble gas. A high-frequency electromagnetic field (radiofrequency or MW: 300–3000 MHz) can trigger gas discharge causing the emission of electromagnetic radiation. This phenomenon has been studied for many years [23] and was already well understood in the nineteen-sixties [24]. The term "electrodeless" means that the lamps lack the electrodes within the envelope. Meggers [24] developed the first EDL using the mercury isotope ^{198}Hg in 1942 (Fig. 14.1) and its earliest application was in absorption spectroscopy [25]. EDL is usually characterized by a higher emission intensity than that of hollow cathode lamps, lower contamination, because of the absence of the electrodes [26], and a longer lifetime [27].

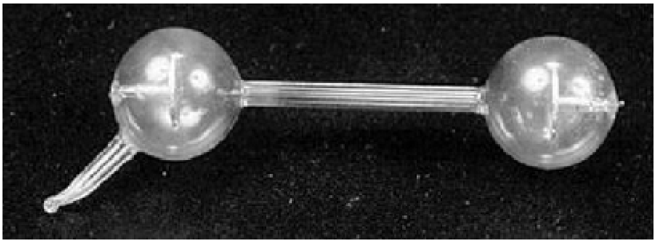


Fig. 14.1 The electrodeless mercury lamp made by William F. Meggers. With permission from the National Institute of Standards and Technology, Technology Administration, US Department of Commerce.

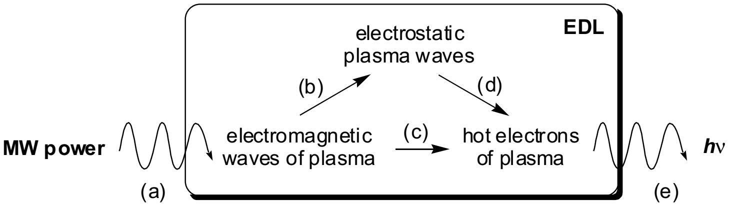


Fig. 14.2 Block diagram illustrating the operation of EDL: (a) energy flows from a MW source into the plasma chamber; (b) collisional or collisionless transformation; (c) normal or nonlinear wave absorption; (d) collisional or collisionless dumping; (e) collisional excitation of atoms and ions followed by emission. Adapted from Ref. [28].

14.2.1
Theoretical Aspects of the Discharge in EDL

The theory of EDL operation, as it is currently understood, is shown in the block diagram in Fig. 14.2 [28]. Free electrons in the fill (i. e. electrons that have become separated from the environment because of the ambient energy) accelerate as a result of the electromagnetic (EM) field energy. They collide with the gas atoms and ionize them to release more electrons. The repetitive effect causes the number of electrons to increase significantly over a short period of time, an effect known as an “avalanche”. The electrons are generated by processes including *collisional* or *collisionless* transformation of EM waves, and *normal* or *nonlinear wave absorption* [26]. The energetic electrons collide with the heavy-atom particles present in the plasma, exciting them from a ground state to higher energy levels. The excitation energy is then released as EM radiation with spectral characteristics which depend on the composition of the envelope. The excited molecular or atomic species in the plasma can emit photons over very broad region of the EM spectrum, ranging from X-rays to the IR [29].

14.2.2
The Fundamentals of EDL Construction and Performance

The EDL system is modular and consists of two basic parts, a gas filled bulb and a power supply with waveguides or external electrodes. A typical EDL consists of a scaled (usually quartz) tube envelope, which contains an inert gas (such as a noble gas) and an excitable substance (e. g. Hg, Cd, Na, Ga, In, Tl, Sc, S, Se, or Te) [30]. The envelope material must be impermeable to gases, an electrical insulator, and chemically resistant to the filling compounds at the temperature of operation.

Historically four basic methods have been used to excite discharges without electrodes [31–35]. In the first method, referred as the *capacitive coupling*, the electric field lines of the applied EM signal (usually 915 MHz) originate from one external electrode, pass through the gas-filled bulb containing the discharge, and terminate at a second external (coaxial) electrode. This discharge is similar to arc discharge in an electrode lamp, but needs a higher current. The second method of exciting EDL with MW power (typically 2450 MHz) is to place the bulb in the path of radiation from a directional antenna. The *microwave discharge* is excited by both electric and magnetic components of the EM field. Because free propagation of the MW power occurs, however, emission is often inherently inefficient. This method is used for excitation of EDL inside a MW oven. The third method is called the *traveling wave discharge* – a gap between the external electrodes provides the electric field that launches a surface wave discharge. The fourth method uses the *inductive coupling* of EDL and the system can be compared with an electrical transformer. An alternating current in the coil generates a changing magnetic field inducing the electric field that drives a current into the plasma. The operating frequency is limited to approximately 50 kHz [36].

The operating conditions affecting electrodeless lamp performance are a combination of many factors [30]:

- *The inert gas*. The arc chamber contains a buffer noble gas (usually Kr, Xe, or Ar) which is inert to the extent that it does not adversely affect the lamp operation. Helium has a higher thermal conductivity than other noble gases and, therefore, higher thermal conduction loss is observed [37]. The inert gas easily ionizes at low pressure but its transition to the thermal arc is slower and the lamp requires a longer warm-up time. Ionization is more difficult at higher pressures and it requires a higher input power to establish the discharge. The pressure in the EDL at the operating temperature is usually much higher (5–20 atm) than that of a conventional electrode lamp.
- *The choice of the fill material* initiating the discharge is very important. Together with a standard mercury fill it is often desirable to incorporate an additive in the fill material that has a low ionization potential [38, 39]. One category of low-ionization-potential materials is the group of alkali metals or their halides (LiI, NaI) but some other elements, such as Al, Ga, In, Tl [40, 41], Be, Mg, Ca, Sr, La, Pr, or Nd [23, 37, 42], can be used.
- *The dimensions and properties of the lamp envelope* are based on the discovery that the volume of Hg is critical for the effective UV operation [43]. Higher Hg pressures result in the need to use higher MW power levels. To focus the MW field efficiently into the EDL a special Cd low-pressure lamp with a metal antenna (a molybdenum foil) was developed by Florian and Knapp [44].
- *The nature and characteristics of the EM energy-coupling device* are discussed in Sect. 14.2.3.
- *The frequency and intensity* of EM energy is determined by the type of a device. A standard MW power source operates around 915 or 2450 MHz.

14.2.3
Spectral Characteristics of EDL

The spectral characteristics of EDL are of a general interest in microwave photochemistry. The right choice of filling material can provide a desirable ultraviolet radiation. Atomic fills usually furnish line emission spectra (e.g. that of an Hg-EDL is

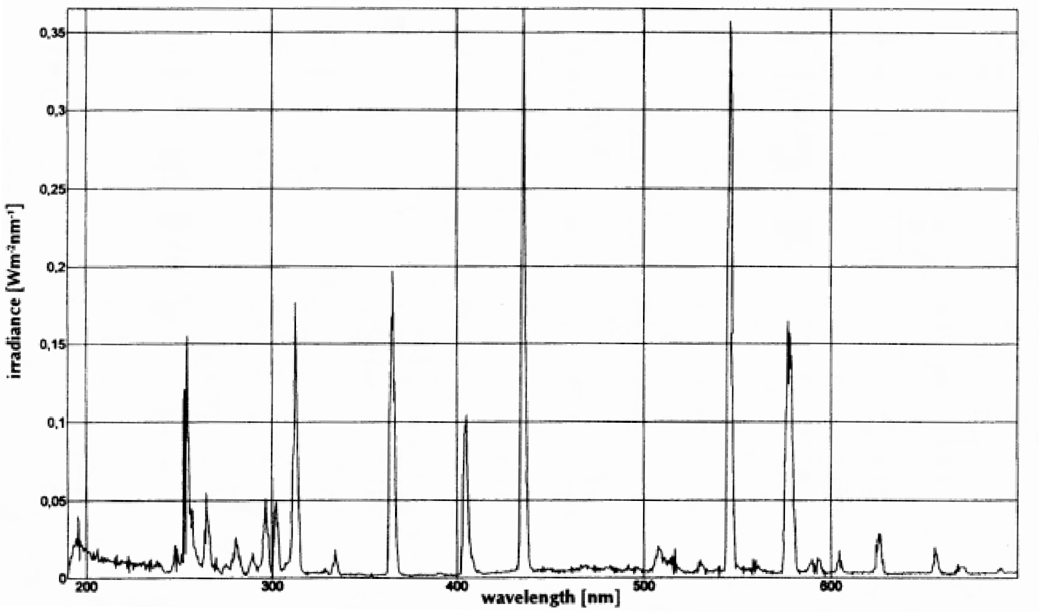


Fig. 14.3 Emission spectrum of MW-powered Hg-EDL [44]. With permission from the American Chemical Society.

shown in Fig. 14.3) and molecular fills give continuous spectra [45]. The total emission output of Hg-EDL in the region of 200–600 nm is approximately the same as that of the electrode lamp with the same power input [46]. The distribution of radiation is, however, markedly different, as a result of much higher Hg pressure and the greater number of atoms that can participate in the plasma. EDL emit over three times as much UV and less than a half as much IR as a conventional lamp [47]. It has been noted that EDL and electrode lamps furnish different spectra when the fill includes a rare-earth material but similar spectra when a nonrare-earth fills are used [48]. Addition of some elements (Sn, Pb, Ga) has a very significant effect on the spectral distributions of the EDL [46]. Most lamps emit less efficiently below 280 nm than a standard Hg lamp (Tab. 14.1). The advantages of EDL for microwave photochemical applications are discussed in the Sect. 14.3.

14.3
Microwave Photochemical Reactor

The microwave photochemical reactor is an essential tool for experimental work in this field. Such equipment enables simultaneous irradiation of the sample with both MW and UV/VIS radiation. The idea of using an electrodeless lamp (EDL), in which the discharge is powered by the MW field, for photochemistry was born half a century ago [46, 68]. The lamp was originally proposed as a source of UV radiation only,

Tab. 14.1 Filling compounds and the wavelength of EDL emission.

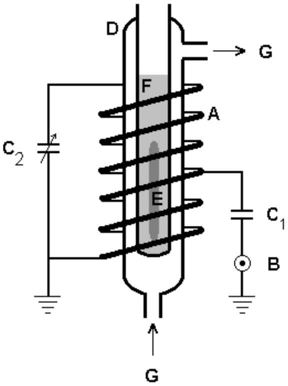
Filling material (filling gas)	*Excited species*	*Main emission bands, λ (nm)*	*References*
Hg (Ar)	Hg	185, 254, 365, 405, 436, 546	30, 31, 43, 44, 48–50
Cd (Ar)	Cd	229, 326	30, 44, 51
SnI_2 (Ar)	SnI_2	400–850, 610	52
$FeCl_2$ (Ar)	Fe	248	30
Zn (Ar)	Zn	214	30, 44, 53
CuCl (Ar)	Cu	325	30
NaI (Xe, Kr)	Na	589	54, 55
Mg, H_2 (Ar)	MgH	518, 521, 480–560	56
$AlBr_3$ (Ne)	AlBr	278	57
$AlCl_3$ (Ne)	AlCl	261	58, 59
Ga, GaI_3 (Ar)	Ga	403, 417, 380–450	49, 53
InI_3 (Ar)	In	410, 451	53
TlI (Ar)	Tl	277, 535	30, 53
PCl_4 (Kr)	P_2	380	60
S (Ar)	S	350–850, 525	40, 61, 62
Se (Ar, Xe)	Se	370–850, 545	62–64
Te (Xe)	Te	390–850, 565	62, 64
Ar (Ar)	Ar_2	126, 107–165	29, 65
Ar, Cl_2 (Ar)	ArCl	175	29, 65
Xe, Cl_2 (Xe)	XeCl	308	29, 65
B_2O_3, S (Kr)	B_2S_3	812	66
I_2, HgI_2 (Ar)	I	206	67

without considering the effects of microwaves on photochemical reactions. The first applications of EDL were connected with the construction of a high-intensity source of UV radiation for atomic fluorescence flame spectrometry [69–71].

Gunning, Pertel and their coworkers reported the photochemical separation of mercury isotopes [72–75] in a flow reactor which consisted of a microwave-operated discharge lamp [76, 77] cooled by a flowing film of water. A filter cell and a circulation system, preventing the filter solution and the cell from being heated, were placed concentrically and coaxially with the lamp. A similar reactor, for small-scale laboratory photolysis of organic compounds in the solution or gas phase, has been proposed by Den Besten and Tracy [78]. In this arrangement, EDL was placed in a reaction solution and was operated by means of an external microwave field from a radio- or microwave-frequency transmitter (Fig. 14.4). The lamp quantum output was controlled by changing the output of the transmitter or by using a dilute ionic solution circulating through the cooling jacket. For maximum lamp output a weakly conducting solution has been proposed. Placing the EDL into the solution was quite advantageous, because the full quantum output was utilized. The authors recommended keeping the sample temperature low, because EDL produce a substantial amount of heat.

Use of a domestic microwave oven has appeared in a patent [79], according to which gaseous reactants were irradiated with microwave and UV/VIS radiation to

Fig. 14.4 Apparatus for electrodeless photochemical irradiation. A. antenna, B. transmitter, C_1. capacitor, C_2. variable capacitor, D. jacketed flask, E. EDL, F. reaction mixture, G. circulating coolant. Adapted from Ref. [78].



produce desired photoproducts (the EDL was positioned inside the MW cavity, although outside the reaction vessel). Several similar reactors have been proposed for UV sterilization [80–82] or for treatment of waste water containing organic pollutants [83–85].

Církva and Hájek have proposed a simple application of a domestic microwave oven for microwave photochemistry experiments [86]. In this arrangement, the EDL (the MW-powered lamp for this application was specified as a microwave lamp or MWL) was placed in a reaction vessel located in the cavity of an oven. The MW field generated a UV discharge inside the lamp that resulted in simultaneous UV and MW irradiation of the sample. This arrangement provided the unique possibility of studying photochemical reactions under extreme thermal conditions (e. g. Ref. [87]).

Klán et al. published a series of papers that described the scope and limitations of this reactor [88–91]. In a typical design (Figs. 14.5 and 14.6) four holes were drilled

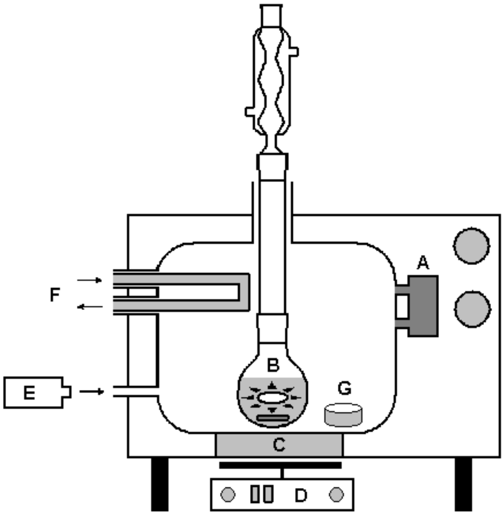


Fig. 14.5 A modified MW oven for microwave photochemistry experiments. A. magnetron, B. reaction mixture with the EDL and a magnetic stir bar, C. aluminum plate, D. magnetic stirrer, E. infrared pyrometer, F. circulating water in a glass tube, G. dummy load inside the oven cavity [88]. With permission from Elsevier Science.

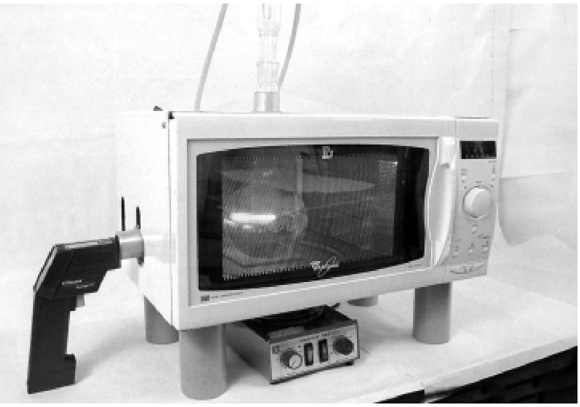


Fig. 14.6 Photochemistry in a microwave oven (the EDL floats on the liquid surface).

into the walls of a domestic oven – one for a condenser tube in the oven top, another in the side for an IR pyrometer, and two ports for a glass tube with circulating water. Part of the oven bottom was replaced with an aluminum plate to enable magnetic stirring. The opening for the IR pyrometer could also serve for an external (additional) source of UV radiation. The vessel was connected to a very efficient water-cooled condenser by means of a long glass tube. The circulating cool water or a MW-absorbing solid material (dummy load – basic Al_2O_3, molecular sieve, etc.) were used when a small quantity of a non- or poorly absorbing sample was used for microwave photochemical experiments. The material removed excess microwave power and prevented the magnetron from being destroyed by overheating.

The EDL had always to be placed in a position, in which the solvent cooled it efficiently, because lamp overheating might cause failure of lamp emission. Intense IR output from the lamp triggered immediate boiling of all solvents including nonpolar (MW-transparent) liquids [89, 90]. Polar solvents, on the other hand, absorbed most of MW radiation, resulting in reduction of UV output efficiency. Tab. 14.2 depicts the most important advantages and disadvantages of EDL applications.

Chemat and his coworkers [92] have proposed an innovative MW–UV combined reactor (Fig. 14.7) based on the construction of a commercially available MW reactor, the Synthewave 402 (Prolabo) [9]. It is a monomode microwave oven cavity operating at 2.45 GHz designed for both solvent and dry media reactions. A sample in the quartz reaction vessel could be magnetically stirred and its temperature was monitored by means of an IR pyrometer. The reaction systems were irradiated from an external source of UV radiation (a 240-W medium-pressure mercury lamp). Similar photochemical applications in a Synthewave reactor using either an external or internal UV source have been reported by Louerat and Loupy [93].

A microwave-assisted, high-temperature, and high-pressure UV digestion reactor has been developed by Florian and Knapp [44] for analytical purposes. The apparatus consists of the immersed electrodeless discharge lamp operating as a result of the MW field in the oven cavity (Fig. 14.8). An antenna fixed to the top of EDL enhanced the EDL excitation efficiency. Another interesting MW–UV reactor has

Tab. 14.2 Advantages and disadvantages of EDL applications in photochemistry. Adapted from Ref. [90].

Advantages
Simultaneous UV and MW irradiation of the sample
Possibility of performing photochemistry at high temperature
Good photochemical efficiency – the EDL is "inside" the sample
Simplicity of the experiment and the low cost of the EDL
Use of a commercially available microwave oven
"Wireless" EDL operation
Choice of the EDL material might modify its spectral output
Disadvantages
Technical difficulties of performing experiments at temperatures below the solvent b.p.
Greater safety precautions
EDL overheating causes lamp emission failure
Polar solvents absorb MW radiation, thus reducing the UV output efficiency of the EDL

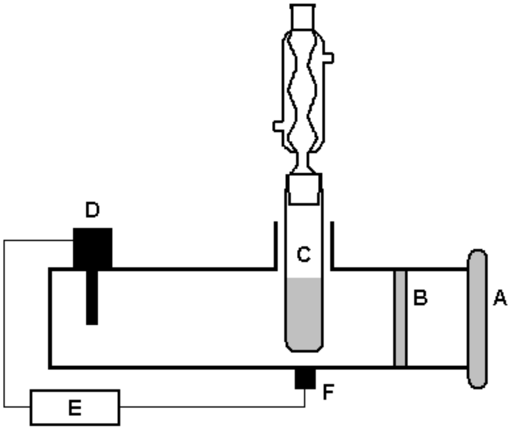


Fig. 14.7 A reactor for microwave photochemistry derived from the Synthewave 402 (Prolabo). A. medium-pressure Hg lamp, B. window hermetic to MW radiation, C. reaction mixture, D. magnetron, E. regulator, F. IR sensor. Adapted from Ref. [92].

been designed by Howard and his coworkers [94]. A beaker-shaped electrodeless discharge lamp, placed in a modified domestic MW oven has been used for mineralization of organophosphate compounds. The samples in quartz tubes were positioned in a carousel inside an open UV beaker; they were thus efficiently photolyzed from the whole surface of the beaker.

Microwave-enhanced chemistry introduces unique *safety considerations* that are not encountered by the chemist in other fields of chemistry [95]. Careful planning of all experiments is strongly advised, especially when the results are uncertain, because control of reaction temperature might be complicated by rapid heat-transfer mechanisms. It is, furthermore, well known that electronically excited singlet oxygen, capable of causing serious physiological damage, is generated by microwave dis-

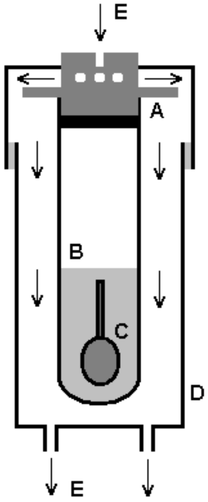


Fig. 14.8 Simplified schematic diagram of a high-pressure digestion vessel with an EDL. A. plug and seal, B. quartz pressure reaction vessel with a sample solution, C. EDL with an antenna, D. vessel jacket with a screw cap, E. air flow. Adapted from Ref. [44].

charge through an oxygen stream [96]. The combined effect of MW and UV irradiation could increase the singlet oxygen concentration in the MW cavity, particularly in the presence of a photosensitizer.

14.4
Microwave Photochemistry

14.4.1
Interactions of Ultraviolet and Microwave Radiation with Matter

Although microwave chemistry has already received widespread attention from the chemical community, considerably less information is available about the effect of microwave radiation on photochemical reactions. Photochemistry is the study of the interaction of ultraviolet or visible radiation ($E = 600–170$ kJ mol^{-1} at $\lambda = 200–700$ nm) with matter. The excess energy of electronically excited states significantly alters species reactivity – it corresponds, approximately, to typical reaction activation energies helping the molecules overcome activation barriers. The microwave region of the electromagnetic spectrum, on the other hand, lies between infrared radiation and radio frequencies. Its energy ($E = 1–100$ J mol^{-1} at $\nu = 1–100$ GHz) is approximately 3–6 orders of magnitude lower than that of UV radiation (a typical MW kitchen oven operates at 2.45 GHz). Microwave heating is not identical with classical external heating, at least at the molecular level. Molecules with a permanent (or induced) dipole respond to an electromagnetic field by rotating, which results in friction with neighboring molecules (thus generating heat). Additional (secondary) effects of microwaves include ionic conduction (ionic migration in the presence of an electric field) and spin alignment.

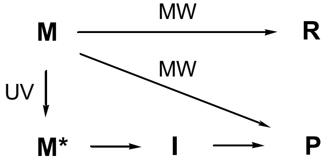


Fig. 14.9 Simplified model of nonsynergic effects of UV and MW radiation on a chemical reaction.

Simultaneous UV/VIS and MW irradiation of molecules, which does not necessarily cause any chemical change, might affect the course of a reaction by a variety of mechanisms at *each* stage of the transformation. From many possibilities, let us present a simplified model describing two main distinct pathways (Fig. 14.9). The first route, more probable, is a photochemical reaction starting with a ground state molecule, **M**, which is excited electronically to **M***, transformed into an intermediate (or a transition state) **I**, and, finally, a product, **P**. Virtually each step may be complicated by a parallel microwave-assisted reaction enabling a different chemical history. There is a theoretical possibility that MW radiation affects the electronically excited molecule **M*** or a short-lived transition state. In such circumstances the lifetime of the species should be long enough to provide a sufficient time for interaction with this low-frequency radiation. The second pathway becomes important when MW initiate a "dark" chemical reaction (essentially through polar mechanisms), competitive or exclusive to a photochemical pathway, yielding a different (**R**) or the same (**P**) product. Fig. 14.9 depicts a model in which MW and UV effects are easily distinguishable – it is assumed there is no synergic effect during a single step of the transformation.

Let us, on the other hand, assume that the efficiency of a photoreaction is altered by microwave induction. In an example shown in Fig. 14.10, microwave *heating* affects the excitation energy of the starting ground state molecule. The individual effects of both types of electromagnetic radiation simultaneously influence a single chemical step in which the ground state molecules **M** and $\mathbf{M}^{\Delta}$ (a MW-heated molecule) are being excited. If, furthermore, the intermediates **I** and $\mathbf{I}^{\Delta}$ react with different rate constants, the total observed rate constant k_{obs} of the reaction is proportional to the sum $(\chi k_{\mathrm{r}} + \chi^{\Delta} k_{\mathrm{r}}^{\Delta})$, where χ and χ^{Δ} represent the populations of **I** and $\mathbf{I}^{\Delta}$.

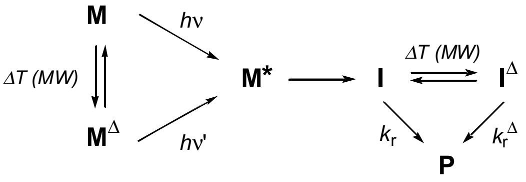


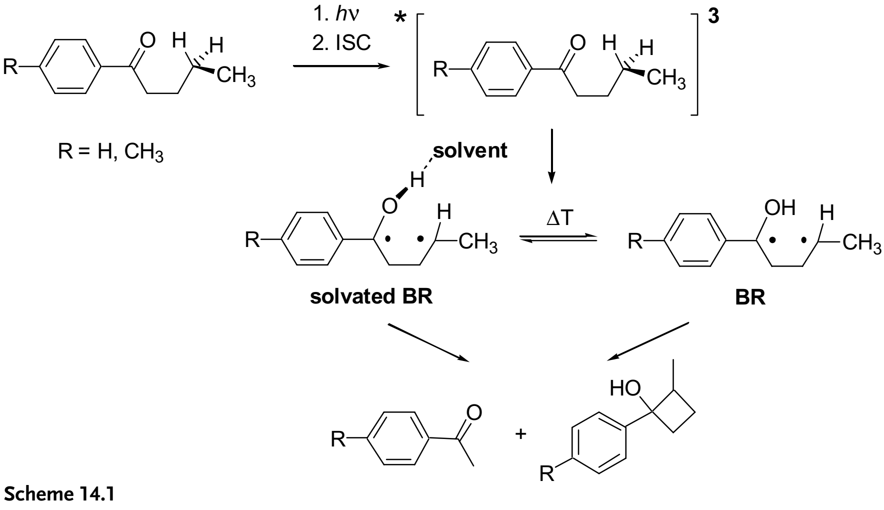
Fig. 14.10 A simplified model of the synergic effect of UV and MW radiation on a chemical reaction, where depicts "hot" molecules, and k_r and k_r are the rate constants of the pro-

14.4.2

Photochemical Reactions in the Microwave Field – Thermal Effects

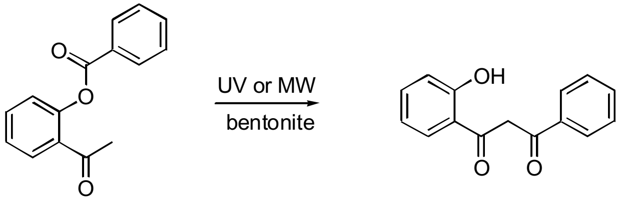
Baghurst and Mingos have hypothesized that superheating of polar solvents at atmospheric pressure, so that their average temperatures are higher than the corresponding boiling points, occurs as a consequence of dissipation of the microwaves throughout the whole volume of a liquid [97]. With the absence of nucleation points necessary for boiling heat loss occurs at the liquid/reactor wall or at liquid/air interfaces. Many reaction efficiency enhancements reported in the literature have been explained as the effect of superheating when the reactions were essentially performed in sealed vessels without stirring [98–102]; this effect is also expected in microwave photochemistry experiments in condensed media. Gedye and Wei [15], for example, have observed enhancement of the rate of several different thermal reactions by factors of 1.05–1.44 in experiments accomplished in a domestic-type MW oven but not in a variable-frequency microwave reactor. The enhancement was interpreted as a consequence of solvent superheating or hot-spot formation rather than nonthermal effects. Stadler and Kappe reported similar results in an interesting study of the MW-mediated Biginelli reaction [14].

Klán et al. [91] successfully evaluated MW superheating effects in polar solvents by use of a temperature dependent photochemical reaction. It is known that quantum efficiencies of the Norrish type II reaction [103] for a mixture of some *p*-substituted valerophenones depend on the presence of a weak base, because of specific hydrogen-bonding to the biradical OH group (**BR**; Sch. 14.1) [88, 91]. This reaction provided linear temperature dependence of the efficiency over a broad temperature region and the system served as a photochemical thermometer at the molecular level, even for the MW-heated mixtures. The magnitude of the photochemical change in the MW field suggested the existence of superheating effect (4–11 °C) for three ali-



Scheme 14.1

Scheme 14.2



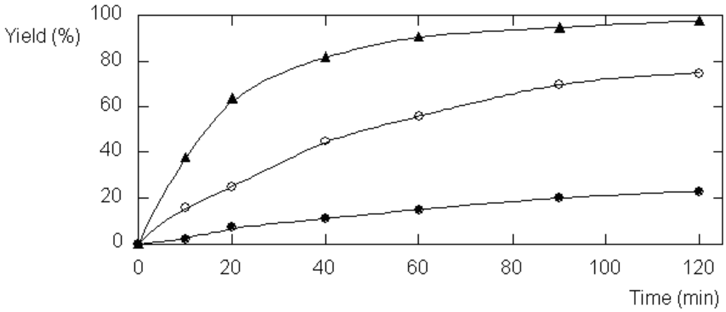
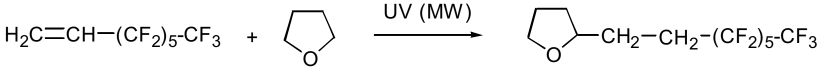


Fig. 14.11 Reaction yields in the rearrangement of 2-benzoyloxyacetophenone induced by microwave heating (●), ultraviolet irradiation (○), or simultaneous UV and MW irradiation (▲). Adapted from Ref. [92].

phatic alcohols and acetonitrile. The results were in a perfect agreement with measurements by use of a fiber-optic thermometer.

Chemat and his collaborators [92] reported the UV- and MW-induced rearrangement of 2-benzoyloxyacetophenone, in the presence of bentonite, into 1-(*o*-hydroxyphenyl)-3-phenylpropane-1,3-dione in methanol at atmospheric pressure (Sch. 14.2). The reaction, performed in the reactor shown in Fig. 14.7, was subject to a significant activation effect under simultaneous UV and MW irradiation; this corresponded at least to the sum of the individual effects (Fig. 14.11). The rearrangement, however, was not studied in further detail. Such competitive processes can be described by the diagram in Fig. 14.9, because the product obtained from both types of activation was the same.

Církva and Hájek [86] studied a photochemically or microwave-induced addition of tetrahydrofuran to perfluorohexylethene (Sch. 14.3). Whereas the thermal reaction was too slow, photochemical activation was very efficient, with no apparent thermal effects of MW radiation. Combined UV and MW radiation has principally been used to initiate EDL operation in the reaction mixture (Fig. 14.5). Another illustration of the MW–UV-assisted reaction has been demonstrated by Nüchter et al. [1] on dehydrodimerization reactions of some hydrocarbons. Zheng et al. [104, 105] reported microwave-assisted heterogeneous photocatalytic oxidation of ethylene using porous TiO_2 and SO_4^{2-}/TiO_2 catalysts. Significant enhancement of the photocatalytic activity was attributed to the polarization effect of the highly defected catalysts in the MW field. Louerat and Loupy studied some photochemical reactions (e.g. stilbene isomerization) in homogenous solutions and on solid supports such as alumina [93].



Scheme 14.3

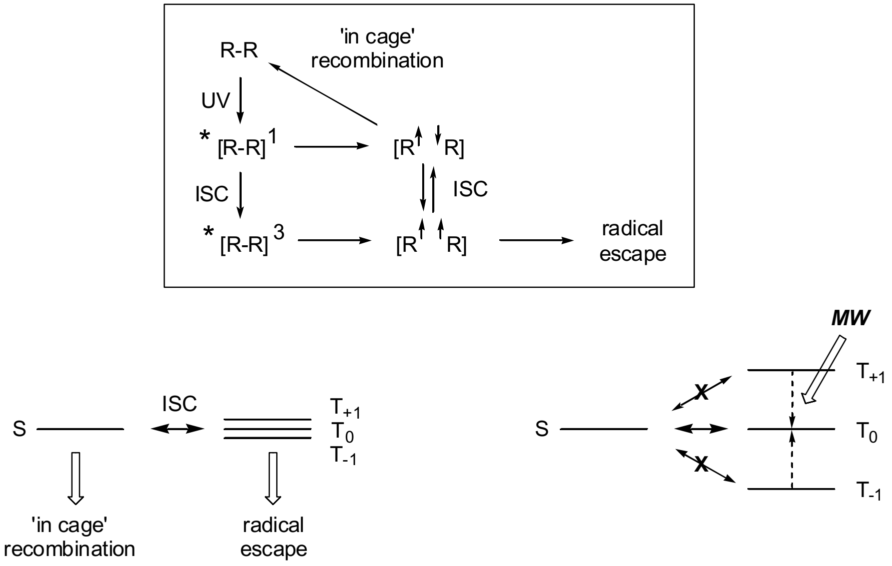
Product distributions and reaction conversions of several different photochemical systems, irradiated by conventional UV source and by EDL in a MW–UV reactor (Fig. 14.5), were compared to elucidate the advantages and disadvantages of a microwave photochemical reactor [90]. Some reactions, e. g. photolysis of phenacyl benzoate in the presence of triethylamine or photoreduction of acetophenone by 2-propanol, were moderately enhanced by MW heating. The efficiency of chlorobenzene photosubstitution in methanol, on the other hand, increased dramatically with increasing reaction temperature.

14.4.3

Nonthermal Microwave Effects – Intersystem Crossing in Radical-recombination Reactions

Radical pairs and biradicals are extremely common intermediates in many organic photochemical (and some thermal) reactions. A singlet state intermediate is formed from the singlet excited state in reactions that conserve spin angular momentum whereas the triplet intermediate is obtained via the triplet excited state. Radical pairs in solution coherently fluctuate between singlet and triplet electronic states [106, 107] and the recombination reactions are often controlled by electron–nuclear hyperfine interactions (HFI) on a nanosecond time scale [108, 109]. Only a pair of the neutral radicals with singlet multiplicity recombines. A triplet pair intersystem crosses into the singlet pair or the radicals escape the solvent cage and react independently at a later stage (Fig. 14.12) [110]. The increasing efficiency of triplet-to-singlet interconversion ('mixing' of states) leads to a more rapid recombination reaction and *vice versa*. It is now well established that a *static* magnetic field can effect intersystem crossing in biradicals (magnetic field effect, MFE) and the effect has been successfully interpreted in terms of the radical pair mechanism [111, 112]. This concept enabled explanation of nuclear and electronic spin polarization phenomena during chemical reactions, e. g. chemically induced dynamic nuclear polarization (CIDNP) or reaction yield-detected magnetic resonance (RYDMAR).

An external magnetic field that is stronger than the hyperfine couplings inhibits (because of Zeeman splitting) singlet–triplet interconversions by isolating the triplets T_{+1} and T_{-1} from the singlet (S), which can, therefore, mix only with T_0 (Fig. 14.12 a, b). For the *triplet-born pair*, the magnetic field reduces the probability of radical recombination. The microwave field, which is in resonance with the energy gaps between the triplet levels (T_{+1} or T_{-1}) and T_0, transfers the excess population from the T_{+1} or T_{-1} states back to a mixed state. Application of a strong magnetic field to the *singlet-born radical* pair leads to an increase in the probability of recombination that can, however, be also controlled by microwave irradiation [112].



(a) zero external magnetic field (b) applied external magnetic field

Fig. 14.12 Schematic illustration of magnetic field and microwave effects in radical-pair chemistry.

These microwave-induced spin dynamics can be considered as an archetype of a *nonthermal* MW effect. Because the radical pair (biradical) is usually created by a photochemical pathway, the topic certainly deserves to be included in the field of microwave photochemistry. The literature offers many examples that span photobiology, photochemistry, and photophysics. Wasielewski et al. [113], for instance, showed that the duration of photosynthetic charge separation could be controlled with microwave radiation. It was, moreover, possible to observe the dynamics of radical pair processes that involve primary bacterial photochemistry [114]. Okazaki and his collaborators [115] reported the possibility of controlling chemical reactions by inducing the ESR transition of the intermediate radical pair in the photoreduction of anthraquinone micellar solution under the action of an external magnetic field and simultaneous MW irradiation. A similar study with a bifunctional molecule was reported by Mukai et al. [116]. Research in this field is very well covered by several reviews and books [111, 112, 117, 118]. Weak static magnetic fields, smaller than an average hyperfine coupling, also affect radical pair recombination yields [119, 120]. This effect is opposite to that of a strong field [121, 122].

Little attention has been devoted to the effects of *time-dependent* magnetic fields (created by electromagnetic waves) in the absence of a strong magnetic field. Hore and his coworkers [123–125] recently described this effect as the *oscillating magnetic field effect* (OMFE) on the fluorescence of an exciplex formed in the photochemical reaction of anthracene with 1,3-dicyanobenzene over the frequency range 1–80 MHz.

Another study of the electron-hole recombination of radical ion pairs (pyrene anion and dimethylaniline cation) in solution has appeared recently [126]. Triplet–singlet interconversions as a result of HFI are relatively efficient in a zero magnetic field (to be more precise, in the Earth's field of ~50 μT). All the states are almost degenerate, assuming separation of the radicals is such that their electronic exchange interaction is negligible [111]. Jackson and his coworkers [127] suggested that the resonance energy of the oscillating field should be tuned to the HFI in one of the radicals. With a typical value of HFI in the radicals of 0.1–3.0 mT, the oscillating magnetic field effect, enhancing the conversion of the singlet state to the triplet (as was observed for weak static fields) is expected in the *radiofrequency* region (3–80 MHz) [124]. Canfield et al. [128–130] calculated the effects and proved them experimentally for the radical pairs involved in coenzyme B_{12}-dependent enzyme systems. Other theoretical studies have appeared in the past 5 years [126, 131, 132]. Whether electromagnetic fields influence animal and human physiology is still an open question. It has, for example, been suggested that radiofrequency fields might disorient birds [133]. Detailed experimental studies of OMFE in the microwave region have not yet been performed. Hoff and Cornelissen [134] reasoned in their paper that triplet state kinetics could be affected rather by a pulse of resonant microwaves than by equilibrium methods in the zero static field.

According to the OMFE model a weak oscillating magnetic field (the magnetic interactions are much smaller than the thermal energy of the molecule [131]) has no impact on equilibrium constants or activation energies; it can, however, have immense *kinetic* control over the reaction of the radicals [131]. The simplified kinetic scheme in Fig. 14.13 shows the excitation of a starting material R–R′ into the singlet state, which intersystem crosses to the triplet (k_{isc}) and is followed by cleavage (k_{cl}) to the triplet radical pair. The oscillating magnetic field influences the state of mixing of the radical pair (k_{TS} and k_{ST}). The probability that the triplet radical pair will form the products is given by the efficiency of radical escape from the solvent cage (k_{esc}) and of triplet-to-singlet intersystem crossing (k_{TS}). The recombination reaction is very fast when the tight radical pair reaches the singlet state.

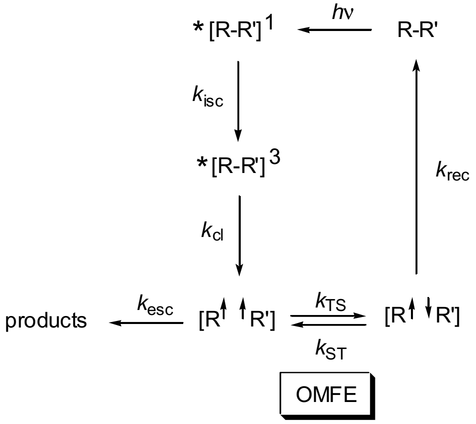


Fig. 14.13 The oscillating magnetic field effect (OMFE) in the triplet state radical pair reaction.

14.4.4
Analytical and Environmental Applications of Microwave Photochemistry

In addition to analytical applications in which microwaves serve as a power source for electrodeless discharge lamps, the first successful use of combined MW/UV irradiation for efficient degradation of a variety of samples before application of an analytical method has been reported. Florian and Knapp [44] proposed a novel MW–UV, high-temperature–high-pressure, digestion procedure for the decomposition of interfering dissolved organic carbon as a part of the trace element analysis of industrial and municipal wastewater or other liquid samples. Very efficient and fast mineralization was achieved in an original reactor (Fig. 14.8), because of the very high temperature (250–280 °C). The high temperature also enabled dissolution of solid organic matrixes by use of diluted mineral acids. A Cd low-pressure electrodeless discharge microwave lamp, strongly emitting at $\lambda = 228$ nm, guaranteed even more efficient degradation than standard mercury UV lamps. The pressurized sealed vessel did not require a separate cooling device to prevent sample evaporation. Efficient decomposition of organophosphate compounds, with the aim of colorimetric phosphate determination, has been achieved by Howard et al. in a novel beaker-shaped electrodeless MW–UV lamp [94]. Although no details of the organophosphate decomposition mechanism were presented, the authors suggested two possible pathways. In addition to direct photodegradation, much of the decomposition resulted from the photochemical generation of hydroxyl and oxygen radicals generated from dissolved O_2 in the samples. The concentration of OH radicals could be enhanced by addition of hydrogen peroxide.

Photodegradation [135] and microwave thermolysis [136] of pollutants and toxic agents in waste water, often in combination with a solid catalyst (e. g. TiO_2), are two important methods for their removal. It is, therefore, expected that combined MW–UV will be even more efficient. Results from the first environmentally relevant studies have already appeared in the scientific literature and the topic is also covered by several patents [79, 83–85]. Campanella et al. [137] reported minor but positive enhancement of the efficiency of photodegradation of *o*- and *p*-chlorophenol by microwave heating. The success of these model chemical systems suggests extension to other environmentally interesting compounds, e. g. sodium dodecylbenzenesulfonate or organophosphate pesticides. It has been suggested that microwave-assisted photodegradation of pollutants might be of great interest in the future. Heterogeneous catalytic degradation of humic acid in aqueous titanium dioxide suspension under MW–UV conditions was studied by Chemat et al. [92]. Enhancement in this application was reported as substantial – i. e. greater than simple addition of both effects. Zheng and his collaborators [105] investigated the microwave-assisted photocatalytic oxidation of ethylene and trichloroethylene in the presence of water. The reactions also served as a model study for photodegradation of organic pollutants in the microwave field.

14.5
Industrial Applications

Simultaneous application of UV and MW irradiation has found widespread use in industry. The techniques are based on the conventional UV lamps and MW-powered electrodeless lamps and MW devices [28]. The following paragraphs discuss several patents and papers that describe industrial microwave photochemistry, such as treatment of waste water, sterilization, or industrial photoinduced organic synthesis.

Photolithography is a technique for manufacturing semiconductor devices (i. e. transistors or integrated circuits). In the process the pattern of an optical mask is imaged with UV radiation on to a semiconductor wafer coated with a UV-sensitive photoresist. The main goal is to reduce the size of the components and to increase their densities. Application of shorter wavelengths (190–260 nm) results in a greater depth of the focus, i. e. sharper printing. The first EDL applied were made from a material known as commercial water-containing natural quartz [138]. It was found that the transmission of the envelope at vacuum UV wavelengths falls off sharply with time. The lamps developed later from water-free quartz [50] were much more transparent. Excimer lamps used for photoetching and microstructuring of the polymer surface have been developed for applications in standard MW ovens [65].

A *photochemical* apparatus for generating superoxide radicals (O_2^{-}) in an oxygen-saturated aqueous sodium formate solution by means of EDL has been described [139]. An interesting method of initiating and promoting chemical processes by irradiation of starting gaseous materials in the EM field under a lower pressure has been proposed by Lautenschläger [79]. EDL (containing GaI_3, InI_3, or AlI_3) with a "blue" output are now often used for dental purposes or curing polymers. The very small size of the lamps makes them particularly useful for supplying light to an optical fiber or a light pipe [140]. Another example of microwave photochemical treatment of solutions at different wavelengths has been described by Moruzzi [141]. Photooxidation of humic acids caused changes in their absorption and luminescence properties that might be of a great importance for environmental photophysics and photochemistry [142]. Aqueous aerated alkaline solutions of the acids were irradiated with an Hg-EDL in a flow system and analyzed by means of fluorescence, absorption, and chemiluminescence techniques.

Microwave photochemistry is generally quite advantageous for removal of a toxic material or pathogens from *wastewater*. Photochemical oxidation is a process in which a strong oxidizing reagent (ozone or hydrogen peroxide) is added to water in a UV-ionizing reactor, resulting in the generation of highly reactive hydroxyl radicals (OH). The first-generation techniques used commercial EDL (high pressure Hg–Xe lamps) immersed in the water tanks. The lamps rapidly deteriorated, however, leading to poor production of hydroxyl radicals. The second generation technique incorporated manual cleaning mechanisms and use of a polymer coating (PTFE) on the quartz sleeve, additional oxidizers (ozone), and catalyzing additives (TiO_2) to enhance the rate of the OH radical production [143]. A novel UV–oxidation system used a highly efficient EDL combined with a simple coaxial flow-through reactor design [85]. In this reactor, a liquid containing contaminants (MTBE, 2-propanol, or phenol) was pumped from the bottom and flowed vertically upward through the reactor vessel against gravity. The mercury UV source was mounted above the reactor vessel and the radiation was directed downward through the reactor vessel. An H_2O_2 solution was injected into the liquid being treated and thoroughly mixed by means of an in-line mixer just before the mixture entered the reactor vessel.

Sterilization techniques for intermittent or continuous destruction of pathogens in solid films or in organic and biological fluids, without significantly affecting the properties or physiological characteristics of the medium, have been based on the biocidal synergism of UV and MW irradiation. UV radiation induces a chemical modification of DNA in bacteria (usually because of thymine dimerization). The first apparatus involved a commercial UV-emitting lamp with a separate power source inside the chamber of a MW oven and was used for simple sterilization of biological fluids [144]. An apparatus using an Hg-EDL for surface sterilization or disinfection of objects such as bottles, nipples, contact lenses, or food, has been proposed by LeVay [81]. A continuous sterilizing apparatus has also been described [145, 146]. In addition, ozone treatment can be used in combination with UV exposure to sanitize or disinfect a variety of substances [80, 82, 147–149]. Another application of EDL (containing Hg, Cd/Ar or Kr) for disinfecting aqueous solutions has been recently reported by Michael [150].

14.6
Concluding Remarks

Understanding, on the molecular scale, of processes relevant to microwave photochemistry has not yet reached the degree of maturity of other topics in chemistry. Such a challenge is somewhat ambitious because of several difficulties. Although some obstacles have been overcome, study of the effects of microwaves on a photochemical reaction requires a special approach. Microwave photochemistry involves highly reactive, electronically excited molecules which are exposed to a different kind of reactivity-enhancing stimulation. Microwave heating strongly interferes with possible nonthermal effects that cannot be easily separated in the mechanistic studies. One solution seems to be investigation of the spin dynamics of photochemically generated biradicals. Many photochemical reactions might be accelerated by MW treatment if they pass through polar transition states and intermediates, e.g. ions or ion-radicals. Application of an EDL simplifies the technical procedure, especially in the field of organic synthesis, environmental chemistry, or analysis. Because of the lower reproducibility of the experimental results, however, an external UV source would serve better in kinetic studies.

In this review we have discussed how the concept of microwave photochemistry has already become an important issue in chemistry. Although still in the beginning, detailed analysis of past and present literature confirms explicitly the usefulness of this method of chemical activation. The field has been already established in industry and we hope it will also find its way into conventional chemical laboratories.

Acknowledgments

We would like to thank Milan Hájek and Jaromír Literák for their participation in our research projects, and André Loupy for fruitful discussions. We also acknowledge the Grant Agency of the Czech Republic (203/02/0879) for financial support.

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Microwaves in Organic Synthesis. Edited by André Loupy

ISBN: 3-527-30514-9