Azolides in Organic Synthesis and Biochemistry. H. A. Staab, H. Bauer, K. M. Schneider

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Preface

Preparation, properties and the manifold synthetic applications of "azolides" in organic and bioorganic chemistry are the topics of this book. Azolides like the *N*-acyl, *N*-sulfonyl and *N*-phosphoryl derivatives of imidazoles, triazoles, tetrazoles, benzimidazoles and benzotriazoles represent an easily accessible class of activated acid derivatives, the distinct and gradually varied reactivity of which makes them especially useful for a wide variety of synthetic reactions. The systematic investigation and expansion of this group of compounds, as well as its introduction into synthetic chemistry, are based almost exclusively on syntheses, reactivity studies, and preparative developments introduced in our laboratory during the decade from the mid-50s to the mid-60s. Of special importance for the synthetic application of azolides was my synthesis in 1956 of *N,N'*-carbonyldiimidazole (CDI), followed by its analogues which as highly reactive reagents paved the way to a variety of new reactions. CDI still remains the most used compound in azolide syntheses.

A first review of our work in this field was published under the title "Syntheses Using Heterocyclic Amides (Azolides)" in *Angewandte Chemie* in 1962; an updated version co-authored by *W. Rohr* was included in Vol. V of the series *Newer Methods of Preparative Organic Chemistry* (Verlag Chemie, Weinheim 1967). Since then, however, azolide reactions, due to their versatility, ease of handling, and mild reaction conditions, have become widely used in very diverse fields of chemistry and biochemistry, as will be shown in this book.

After conceiving and working out most of the basic types of azolide reactions, our own group left this field completely more than 25 years ago to become engaged in quite different areas of organic chemistry. Nevertheless, we followed with interest the further growth of my first "scientific baby", and we note with satisfaction the wide scope within which azolide reactions are now being applied and continue to be introduced for new synthetic purposes. Under these circumstances we felt that a comprehensive account of azolide reactions with emphasis on their application in organic and bioorganic synthesis was overdue.

We soon found out that the material we had to deal with was much more extensive than we had anticipated. It was necessary to evaluate several thousands of papers dealing with azolide reactions in recent years. *Chemical Abstracts* lists more than 1500 references to CDI alone from 1967 to the present. Thus, what was originally planned as a progress review chapter in one of the existing series on organic reactions grew up into a real book, which we hope to be of value to organic chemists and biochemists interested in synthetic methods.

This book never would have been completed without the enthusiastic engagement of my co-authors Professor *Helmut Bauer* and Ms. *Karin M. Schneider*, whom I would like to thank for the great effort they devoted to this project, their careful collecting and evaluating of the extensive material, and their excellent achievement in preparing and drafting most of the manuscript. We also thank Ms. *Anke Friemel* for her outstanding word-processing and editing of chemical structures and equations.

Heinz A. Staab
Heidelberg, January 1998

Errata

Azolides in Organic Synthesis and Biochemistry

H. A. Staab, H. Bauer and K. M. Schneider

Some mistakes which occurred during typesetting failed to be corrected.
We apologize for the inconvenience.

p. xiii, 9th line from the bottom – the correct spelling of LDA reads:

LDA Lithium diisopropylamide

p. 1, line 6 – reads:

... reactions with nucleophiles at the carbonyl group ...

p. 1, line 19 – reads:

... nucleophilic reactions at the carbonyl group ...

p. 3, 5 and 7, the running head reads:

1.2 Reactivity of N-Acylazoles in Hydrolyses

p. 39, 4th line from the bottom – reads:

... if X=Li or Na, 60 °C and DMF ...

p. 72, headline of table 3-11 – add:

Carbohydrate
R, R^1, R^2, R^3 = H

p. 154, chapter 4.1.9, left formula – reads:

Asamycin analogue

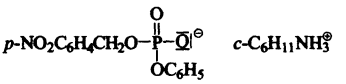
p. 209, line 13 – the correct spelling reads:

N-Protected amino acids ...

p. 209, line 15 – the correct hyphenation reads:

... dimethylform-
amide ...

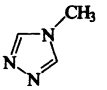
p. 306, section "Reaction with Phosphoric Diimidazolides", right formula in scheme a) – the correct position of the positive charge is:



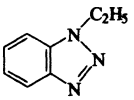
p. 387, formula at the bottom – the correct formula reads:

1. C_2H_5I, NaH, C_4H_9Li, THF

p. 444, table 19-1, right column, 2nd line from the bottom – the correct position of the double bonds is:



p. 444, table 19-1, right column, last line – the correct position of the double bond is:



List of Abbreviations

AIBN	Azoisobutyronitrile
ADP or ppA	Adenosine-5′-diphosphate
AMP	Adenosine-5′-monophosphate
AMP-Im or ImpA	Adenylic acid imidazolide
ara-A	Adenine arabinoside
ATP	Adenosine-5′-triphosphate
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bz	Benzoyl
CDI	*N,N′*-Carbonyldiimidazole
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMTr	4,4′-Dimethoxytrityl
HMPA or HMPT	Hexamethylphosphoric triamide
ImH	1*H*-imidazole
ITP	Inosine triphosphate
LDA	Lithium disopropylamide
MMTr	4-Monomethoxytrityl
npeoc	*p*-Nitrophenylethoxycarbonyl
OAc	Acetate
PEG	Polyethyleneglycol
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMTr	4,4′,4″–Trimethoxytrityl
Z	Benzyloxycarbonyl

Contents

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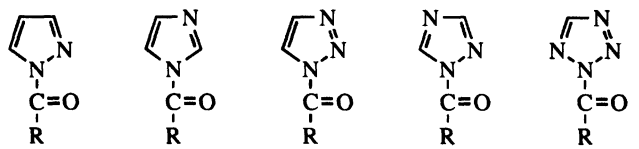
1 Reactivity of Azolides

1.1 General Introduction

The compounds referred to as "azolides" are heterocyclic amides in which the amide nitrogen is part of an azole ring, such as imidazole, pyrazole, triazole, tetrazole, benzimidazole, benzotriazole, and their substituted derivatives. In contrast to normal amides, most of which show particularly low reactivities in such nucleophilic reactions as hydrolysis, alcoholysis, aminolysis, etc., the azolides are characterized by high reactivities in reactions with nucleophiles within the carbonyl group placing these compounds at about the same reactivity level as the corresponding acid chlorides or anhydrides.[1]



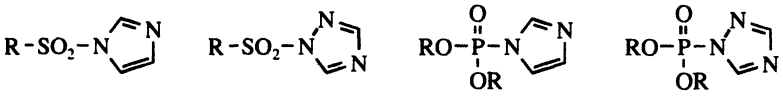
One of the unique advantages that the group of azolides offers to synthetic organic chemistry consists in the wide spectrum of reactivities displayed in nucleophilic reactions. This reactivity gradation depends on the number and location of the nitrogen atoms in the azole rings, which in turn determines the electron-withdrawing effect on the carbonyl group as well as the effectiveness of the azole units as leaving groups (for details of mechanisms see the following chapters). Whereas in such nucleophilic reactions on the carbonyl group as hydrolysis or alcoholysis *N*-acylpyrroles are nearly as inert as normal amides, the corresponding imidazolides react already under very mild conditions, and the triazolides and especially the tetrazolides are so activated that special care must be observed in storing and handling these reagents under strict exclusion of moisture. Benzoanellation like that in benzimidazolides and benzotriazolides reduces the reactivity toward nucleophilic reactions of the carbonyl group. In addition to this variability derived from the azole units themselves, further reactivity modifications can be achieved through substitutions on the azole rings (for problems associated with isomers of the azolides see Chapter 2).

The reactivity of the various azolides as well as the order of reactivities within this group can be explained on the basis of the quasi-aromatic character of the azole π-system: the lone electron pairs on the acyl-substituted nitrogens N(1) are part of the cyclic π-system of the azole units, leading to a partial positive charge on N(1) that interferes with the normal carboxamide resonance and exerts an electron-withdrawing effect on the

carbonyl groups, making these groups more susceptible to nucleophilic attack. Moreover, with increasing numbers of nitrogens the azole units become better leaving groups, especially in proton-donating solvents. Thus, the dramatic increase in reactivity in the series imidazolides/triazolides/tetrazolides, as shown for hydrolysis in Table 1 of Section 1.2, is a result of the increasing replacement of carbon atoms in the azole rings by the more electronegative nitrogen. For isomeric azolides with the same number of nitrogen atoms in the azole rings, those with the greater number of adjacent nitrogens show lower reactivity (e.g., pyrazolides < imidazolides; 1,2,3-triazolides < 1,2,4-triazolides). Obviously, neighboring nitrogens cannot accommodate the same electron density in the azole rings as nitrogens separated by a carbon atom.

Thus, the family of azolides represents a versatile system of reagents with graduated reactivity, as will be shown in the following section by a comparison of kinetic data. Subsequent chapters will then demonstrate that this reactivity gradation is found as well for alcoholysis to esters, aminolysis to amides and peptides, hydrazinolysis, and a great variety of other azolide reactions. The preparative value of azolides is not limited to these acyl-transfer reactions, however. For example, azolides offer new synthetic routes to aldehydes and ketones via carboxylic acid azolides. In all these reactions it is of special value that the transformation of carboxylic acids to their azolides is achieved very easily; in most cases the azolides need not even be isolated (Chapter 2).

The azolide concept can be extended further to other *N*-substituted azoles, such as *N*-sulfonyl- or *N*-phosphorylazoles, for which an analogous gradation of reactivity is observed depending on the choice of the specific azole system. The reactions of these compounds are dealt with in Chapters 10 and 12, respectively.



Not only this manifold and graduated reactivity of azolides, but also the facile preparation and generally very mild conditions for their reactions make this group of compounds a useful addition to the repertory of synthetic organic chemistry. Starting from the first synthetic applications described by our group in the late 50s and early 60s, azolides attracted increasing attention, and continues still to do so.

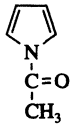
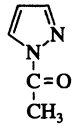
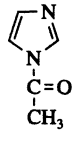
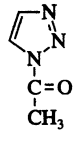
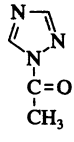
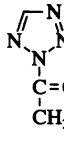
To our knowledge, only a very few references are to be found in the early literature on azolides, limited to specific imidazole derivatives. Thus, *Gerngross* described in 1913 *N*-benzoylimidazole and noted its easy hydrolysis to imidazolium benzoate.[2] On the basis of these findings *Bergmann* and *Zervas* observed the transfer of an acyl group from the imidazole unit of histidine to other amino acids, and discussed whether reactions of this type might play a role in the biosynthesis of peptides and proteins.[3] After earlier unsuccessful attempts, in 1952 *Boyer* prepared *N*-acetylimidazole from imidazole and isopropenyl acetate.[4] One year later, in 1953, *Wieland* and *Schneider* prepared the same compound using the method of *Gerngross*;[5] these authors were the first to carry out a few transacetylation experiments, and on the basis of these experiments

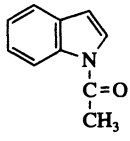
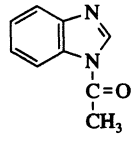
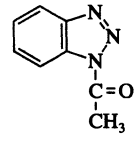
they classified this compound as an "energy-rich" acetyl derivative. At about the same time (1953–1955) the senior author of the present monograph, in his first independent research at the Max-Planck-Institute Heidelberg, became interested in this area from quite a different point of view while studying the in situ acetylation of choline to acetylcholine, using for detection the isolated guinea pig colon. In this context there was prepared the then unknown *N,N'*-diacetylhistamine, which indeed converted choline to acetylcholine by a transacetylation in which only the acetyl group on the imidazole ring of histamine participated.[6] This observation raised our interest in *N*-acylimidazoles and led eventually to the extended syntheses of azolides and their application in organic synthesis.[1],[7] A major breakthrough in this field was the synthesis in 1956 of *N,N'*-carbonyldiimidazole,[8] the first example of an *N,N'*-carbonylbisazole, which soon acquired practical significance in the preparation of azolides and their reactions, as well as for a variety of other synthetic applications. The reactivities of *N,N'*-carbonyldiimidazole and related *N,N'*-carbonylbisazoles as well as such analogues like *N,N'*-thiocarbonyl-, *N,N'*-sulfinyl- and *N,N'*-sulfonylbisazoles are dealt with in Section 1.3.

1.2 Reactivity of *N*-Acylazoles in Hydrolyses

Table 1–1 provides rate constants k' and half-lives $\tau_{1/2}$ for the hydrolysis of *N*-acetylazoles in pure water ("conductivity water," pH 7.0, 25 °C).[7],[9],[10] In all the cases

Table 1–1. Rate constants k' [10^5 sec^{-1}] and half-life times $\tau_{1/2}$ [min] for neutral hydrolysis of *N*-acylazoles ["conductivity water," pH 7.0, 25 °C] together with IR frequencies $\nu_{(C=O)}$ in CCl_4 and enthalpies.

						
$k' \cdot 10^5$ [sec^{-1}]	→ 0	1.27	28.2	43.5	180	> 2000
$\tau_{1/2}$ [min]	→ ∞	908	41	26.6	6.4	< 0.5
$\nu_{C=O}$ [cm^{-1}]	1732	1746	1747	1762	1765	1779
ΔH (kcal/mol)			−4.83		−7.29	−10.31

			
$k' \cdot 10^5$ [sec^{-1}]	→ 0	0.92	10.0
$\tau_{1/2}$ [min]	→ ∞	1260	115
$\nu_{C=O}$ [cm^{-1}]	1711	1729	1735

mentioned above, the rates of hydrolysis were determined by UV-spectroscopic measurements of the intensities of the typical longer-wavelength absorptions of azolides (c.f. *N*-acetylimidazole: λ_{max} 242 nm in THF) relative to corresponding hydrolyzed systems. The hydrolysis rates obtained spectroscopically were complemented in some cases by conductometric measurements[7] as well as by measurements of heats of hydrolysis.[11]

Whereas under the conditions specified above *N*-acetylpyrrole, like a typical acetamide, is not detectably hydrolyzed in neutral aqueous medium, the half-life of *N*-acetylpyrazole is 908 min, and that of *N*-acetylimidazole is reduced to 41 min; for 1-acetyl-1,2,4-triazole and for the isomeric 1-acetyl-1,2,3-triazole, half-lives of 6.4 and 26.6 min, respectively, were observed (for an explanation of the different reactivities of the two pairs of isomers see above). Hydrolysis of *N*-acetyltetrazole under the same conditions occurs too rapidly to be measured with conventional spectroscopic techniques. The reaction enthalpy ΔH was determined for *N*-acetylimidazole to be -4.83 kcal/mol; for the corresponding 1,2,4-triazolide the value was -7.29, and for the tetrazolide -10.31 kcal/mol.[11]

In the benzoanellated series *N*-acetylindol/*N*-acetylbenzimidazole/*N*-acetylbenzotriazole the rate of hydrolysis again increases with the number of nitrogen atoms in the five-membered rings. In each case, however, the hydrolysis rate is, as expected, lower than that for a monocyclic azolide with the same number and arrangement of ring nitrogens.[12] The half-lives under the same conditions as for the previously described series (pH 7.0, "conductivity water," 25 °C) are 1260 min for *N*-acetylbenzimidazole and 115 min for *N*-acetylbenzotriazole.

Substitution on the carbon atoms of the azole rings has the expected effect: electron-withdrawing substituents such as nitro or halogen increase the reactivity of the azolides, whereas alkyl substituents lead to a decrease in transacylation rates.[10]

The data in Table 1–1 reveal a strong increase in the infrared wave-number for carbonyl absorption with increasing hydrolysis rate. For the most reactive *N*-acetyltetrazole with $\nu(C{=}O) \approx 1780\ cm^{-1}$ (CCl_4) a carbonyl absorption is observed that is quite unusual for a carbonyl group of the carbonamide type,[7],[9] which demonstrates the strong influence the azole group exerts by its electron-attracting effect in competition with the amide resonance. In fact, the carbonyl frequencies $\nu(C{=}O)$ for substituted *N*-benzoylimidazoles and *N*-benzoyl-1,2,4-triazoles are so closely related to log k for neutral hydrolysis that the hydrolysis rates can be predicted, within the range of accuracy of the kinetic method, from the infrared spectra.[9]

The same order of reactivity observed for the hydrolysis of *N*-acetylazoles (Table 1–1) is also found for azolides with other *N*-acyl groups. Exceptional, however, are the *N*-formylazoles: *N*-formylimidazole in neutral water is hydrolyzed unmeasurably rapidly; even in a 1 : 1 mixture of water/tetrahydrofuran at 20.6 °C the half-life is in the order of only 3.7 min, approximately a factor of 100 faster than that for *N*-acetylimidazole under the same conditions.[13]

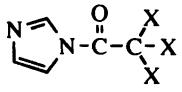
Although hydrolysis as well as other nucleophilic reactions of *N*-acylazoles (alcoholysis, aminolysis etc.) most likely follow the addition–elimination (AE) mechanism, there are indications that more complex mechanisms must be taken into account for hydrolysis under specific structural conditions. For example, for neutral hydrolysis of imidazolides with increasing steric shielding of the carbonyl group by one, two, and three

Table 1–2. Relative rates for aminolysis and neutral hydrolysis of *N*-acylimidazoles [$\sim 10^{-3}$ M solutions, 25 °C].[14]

	k′ (5% diethylamine in tetrahydrofuran)	k′ (conductivity water)
Im-CO-CH_3	1	1
Im-CO-CH_2CH_3	0.55	1.4
Im-CO-$CH(CH_3)_2$	0.22	4.2
Im-CO-$C(CH_3)_3$	0.16	11.2

methyl groups in the α-position of the *N*-acyl chain, no decrease in hydrolysis rate is observed. Instead, in the series *N*-acetylimidazole/*N*-propionylimidazole/*N*-isobutyrylimidazole/*N*-(trimethylacetyl)imidazole, despite the great increase in steric hindrance, the rates of neutral hydrolysis do not decrease but *increase* by more than a factor of ten [$8 \cdot 10^{-4}$ M solution in "conductivity water", 25 °C]. On the other hand, exactly the same series of compounds with increasing steric hindrance through α-branching methyl groups shows a strong rate *decrease* in reactions with stronger nucleophiles, as in aminolysis [5% diethylamine, dry tetrahydrofuran; 25 °C], obviously a consequence of a bimolecular mechanism of the AE type (Table 1–2[14],[15]).

N-(Trichloroacetyl)imidazole, although sterically comparable to *N*-(trimethylacetyl)-imidazole, reacts with water at room temperature almost instantaneously in a vigorous reaction, as does the corresponding trifluoroacetyl compound.[15] These highly reactive compounds can be used for the synthesis of symmetrical carboxylic acid anhydrides from carboxylic acids, as will be shown below.[16] Obviously, the high reactivity of *N*-(trichloroacetyl)imidazole/*N*-(trifluoroacetyl)imidazole, in contrast to the steric hindrance observed with *N*-isobutyrylimidazole/*N*-(trimethylacetyl)imidazole,[17] is due to strong inductive effects of the trihalogenated acetyl groups.



X = F, Cl, CH_3

Steric distortion by phenyl rings in the 4 and 5 positions of *N*-acylimidazoles further gave rise to enhanced rates of hydrolysis proceeding in a concerted manner.[17]

Kinetic data for the hydrolysis of an extended series of *m*- and *p*-substituted *N*-benzoylazoles[9] suggest an addition–elimination mechanism. Essentially the same results were confirmed later by other authors on a few of these substituted *N*-benzoylimidazoles.[18] All these hydrolysis reactions can be followed spectrophotometrically due to the characteristic intense absorption bands of azolides at wavelengths longer than those of the products obtained by hydrolysis. Fig. 1–1 shows as an example the change in the absorption spectrum of *N*-(4-methylbenzoyl)imidazole during neutral hydrolysis [21 °C, water/tetrahydrofuran 3 : 1]. The sharp isosbestic points observed in all these cases for both imidazolides and 1,2,4-triazolides of *meta*- and *para*-substituted benzoic acids prove the exclusion of any side-reactions.[9]

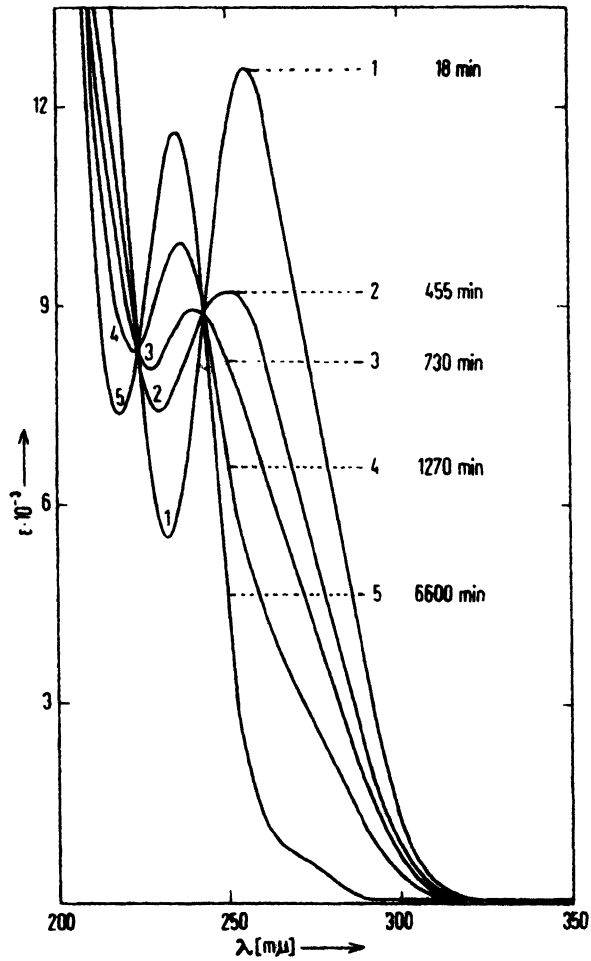


Fig. 1–1. Hydrolysis of *N*-(4-methylbenzoyl)imidazole in water/tetrahydrofuran (3 : 1) at 21 °C.[9]

Fig. 1–2 shows a Hammett diagram for 14 different imidazolides of benzoic acids with a wide range of substituents upon which the reactivity is strongly dependent; for example, the difference in rate constants between *N*-(4-nitrobenzoyl)imidazole and *N*-(4-dimethylaminobenzoyl)imidazole under the same reaction conditions amounts to a factor of about 3000. The Hammett reaction constant $\rho = +1.85$ for the series shown in Fig. 1–2 indicates clearly that the hydrolysis is following a nucleophilic addition–elimination reaction path.

Unexpectedly, the hydrolysis of *N*-(2,4-dinitrobenzoyl)imidazole at 25 °C was found to be slower by a factor of 25 in comparison to *N*-(4-nitrobenzoyl)imidazole. This lower reactivity of *N*-(2,4-dinitrobenzoyl)imidazole was explained by a combination of steric crowding at the reaction center and intramolecular stabilization of the reactant state.[19]

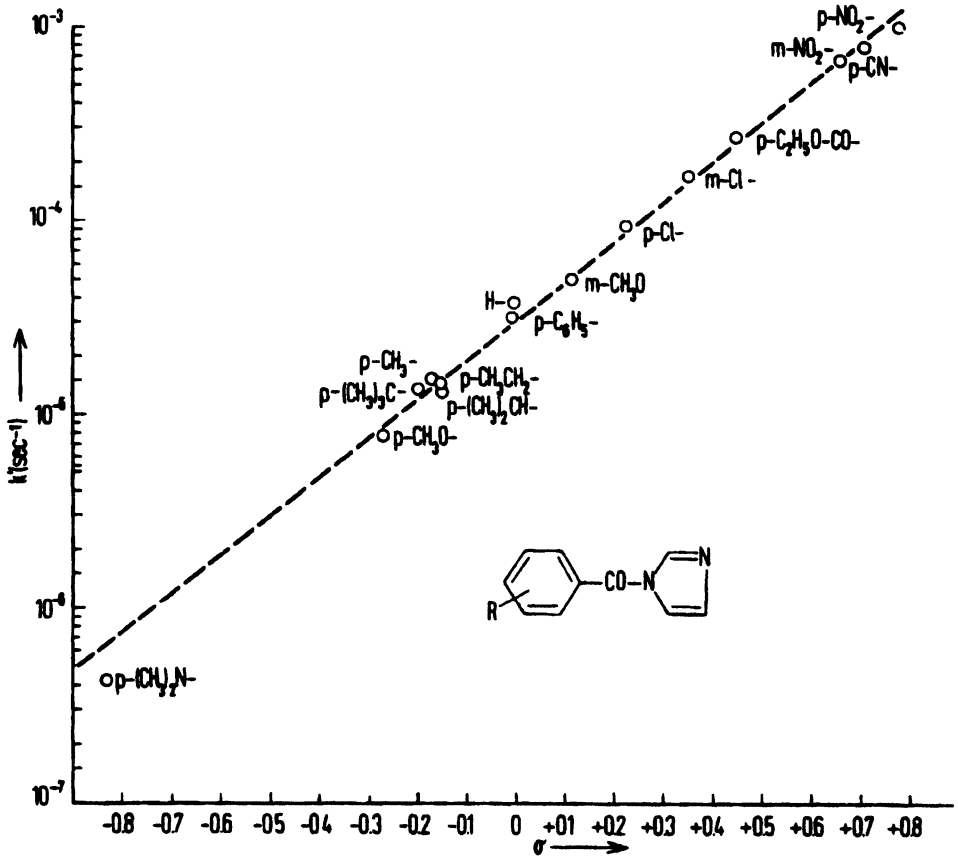


Fig. 1–2. Hammett diagram for the hydrolysis of imidazolides of aromatic carboxylic acids in water/tetrahydrofuran (3 : 1) at 21 °C.[9]

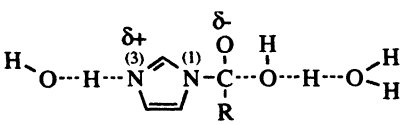
Results corresponding to those for the substituted *N*-benzoylimidazoles have been observed for a series of *meta*- and *para*-substituted *N*-benzoyl-1,2,4-triazoles which, under the same conditions and over the whole range of substituents, show reaction rates about ten times faster than those of the imidazolides.[9],[10]

Following the adoption of azolides as valuable and versatile reagents in synthetic organic chemistry,[1] and also in the context of their potential role in biochemistry, a great many kinetic, mechanistic, and theoretical papers appeared concerning this group of compounds and their properties. Some of these papers[18],[20] are very useful for a better understanding of the reactivity of azolides.

The present monograph deals primarily with synthetic applications of azolides, so kinetic and mechanistic problems cannot be treated in extensive detail. The chapters that

follow will therefore include only brief discussions on the mechanisms of acyl transfer of azolides to the extent that these are of interest in understanding the scope and limitations of the reactions themselves. As is true of most of the mechanistic studies in this area, we confine ourselves in this chapter to the hydrolysis of azolides.

Azolide hydrolysis proceeds, as noted previously, in neutral aqueous medium; it can be further catalyzed by acids and bases. Hydrolysis in neutral aqueous solution has been especially well studied for *N*-acylimidazoles because of the potential biochemical relevance of imidazolide systems. Formally, neutral hydrolysis of an *N*-acylimidazole is the cleavage of an amide bond by a water molecule acting as a nucleophile. In fact, however, it is generally agreed that more than one water molecule is involved.[21] Obviously, the water molecule acting as a nucleophile on the imidazolide carbonyl group is hydrogen-bonded to a second water, making the first one more nucleophilic. A further water molecule is expected to be attached by hydrogen bonding to N(3) of the imidazole. The imidazolyl group with respect to inductive substituent effects has been assigned a high "nucleofugicity" transmitted by σ-bonds; the corresponding estimated substituent constants for imidazolyl and chloro substituents with $+0.60$ and 0.58, respectively, are very similar.[22] Hydrogen bonding to N(3) of the imidazole as a stage preceding protonation should further increase the leaving-group capacity of the imidazolyl unit. This effect of hydrogen bonding may also play a role in the catalysis of *N*-acylimidazole hydrolysis by imidazole itself.[23]



In the acid-catalyzed hydrolysis of azolides,[23] protonation of the azole to afford an azolium unit leads to a stronger electron-withdrawing effect on the reaction center, which in turn favors addition of a nucleophile to the carbonyl group. Furthermore, protonation to the imidazolium group in the case of *N*-acylimidazoles has been shown to support the reaction by now permitting loss of neutral imidazole as the leaving group. In fact, by comparing *N*-acetylimidazole with 1-acetyl-3-methylimidazolium chloride it was found that the hydrolysis rate of *N*-acetylimidazole in dilute acid solution below pH 6 is very similar to that of 1-acetyl-3-methylimidazolium chloride. This result suggests that, in acid hydrolysis of azolides, protonation on the azole nitrogens plays an important role.

For the mechanism of azolide hydrolysis under specific conditions like, for example, in micelles,[24] in the presence of cycloamyloses,[25] or transition metals,[26] see the references noted and the literature cited therein. Thorough investigation of the hydrolysis of azolides is certainly important for studying the reactivity of those compounds in chemical and biochemical systems.[27] On the other hand, from the point of view of synthetic chemistry, interest is centred instead on the potential for chemical transformations; e.g., alcoholysis to esters, aminolysis to amides or peptides, acylation of carboxylic acids to anhydrides and of peroxides to peroxycarboxylic acids, as well as certain C-acylations and a variety of other preparative applications.

1.3 Reactivity of *N*,*N*′-Carbonylbisazoles and Analogous Compounds

Our discovery of the reactivity of azolides and its mechanistic interpretation, as described in the preceding section, led us rather soon to a new class of compounds that extended considerably the range of preparative applications of azolides. Given a knowledge of the way carbonyl groups in azolides could be activated by electron-attracting azole groups, it was an obvious challenge to try synthesizing *N*,*N*′-carbonylbisazoles in which this type of activation toward nucleophilic reactions should be increased by *two* azole units linked to the carbonyl group. Formally, such hitherto unknown *N*,*N*′-carbonylbisazoles can be regarded as *N*-substituted ureas. However, in contrast to the inertness of normal ureas with respect to nucleophilic attack at the carbonyl group, *N*,*N*′-carbonylbisazoles are reagents of very high reactivity toward nucleophiles. These compounds, which can also be considered as bisazolides of carbonic acid, show the same versatile gradation of reactivity as the azolides of carboxylic acids. Rate constants for hydrolysis and corresponding IR frequencies are given in Table 1–3.[8],[9],[28]

For preparative purposes, the most important *N*,*N*′-carbonylbisazole is *N*,*N*′-carbonyldiimidazole (abbreviated in the subsequent text as CDI), which as the first member of this family was synthesized in 1956 by the senior author.[29],[30] The unusual reactivity of this compound is demonstrated by its hydrolysis, which occurs instantaneously at room temperature with drops of water, causing effervescence of carbon dioxide.

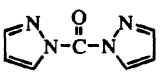
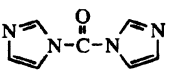
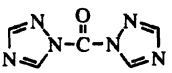
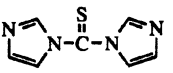
In addition to CDI, just as in the family of the carboxylic acid azolides (see the preceding Section), changes in the azole units have permitted preparation of a whole series of CDI analogues with graduated reactivities: *N*,*N*′-carbonyldipyrazole,[31] *N*,*N*′-carbonyldi-1,2,4-triazole,[32] as well as *N*,*N*′-carbonyldibenzimidazole and *N*,*N*′-carbonyldibenzotriazole.[33]

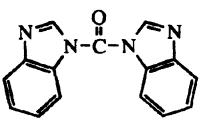
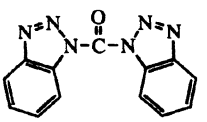
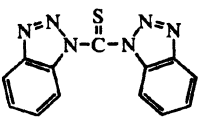
The increasing reactivity on going from CDI to *N*,*N*′-carbonyldi-1,2,4-triazole is also reflected in the corresponding dibenzo derivatives *N*,*N*′-carbonyldibenzimidazole and *N*,*N*′-carbonyldibenzotriazole.

CDI and the other *N*,*N*′-carbonylbisazoles of sufficiently high reactivity react with alcohols ROH to produce diesters of carbonic acid RO-CO-OR, and with amines R^1R^2NH to give diamides of carbonic acid (ureas) R^1R^2N-CO-NR^1R^2. By use of corresponding bifunctional partners, heterocyclic systems are accessible through insertion of the carbonyl group between two heteroatoms (see Chapter 7).

Much more important than these reactions, however, are the reactions of CDI and its analogues with carboxylic acids, leading to *N*-acylazoles, from which (by acyl transfer) esters, amides, peptides, hydrazides, hydroxamic acids, as well as anhydrides and various C-acylation products may be obtained. The potential of these and other reactions will be shown in the following chapters. In most of these reactions it is not necessary to isolate the intermediate *N*-acylazoles. Instead, in the normal procedure the appropriate nucleophile reactant (an alcohol in the ester synthesis, or an amino acid in the peptide synthesis) is added to a solution of an *N*-acylimidazole, formed by reaction of a carboxylic acid with CDI. Thus, CDI and its analogues offer an especially convenient vehicle for activation of

Table 1–3. Rate constants and half-life times $\tau_{1/2}$ [min] for hydrolysis of *N,N'*-carbonylbisazoles and their benzo and thio derivatives in THF/water (40 : 1; 27°C) and IR frequencies $\nu_{(C=O)}$ in $CHCl_3$.

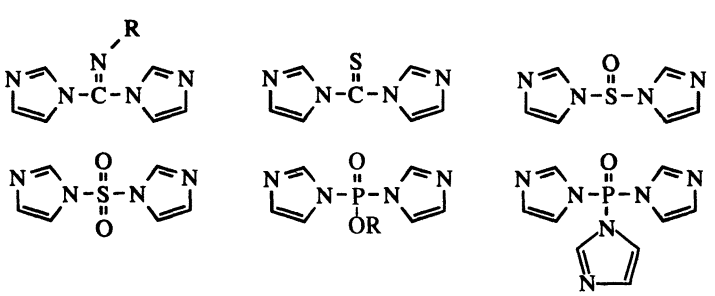
				
$k' \cdot 10^3$ [sec^{-1}]	—	6.43	12.9	0.042
$\tau_{1/2}$ [min]	—	1.8	0.9	275
$\nu_{C=O}$ [cm^{-1}]	1743, 1719 [34]	1762, 1732	1792, 1770	

			
$k' \cdot 10^3$ [sec^{-1}]	0.041	6.10	0.068
$\tau_{1/2}$ [min]	282	1.9	170
$\nu_{C=O}$ [cm^{-1}]	—	—	

carboxylic acids and subsequent reaction with nucleophiles. Both steps usually take place with excellent yields.

As will be shown below in subsequent chapters, CDI reacts in a corresponding way with sulfonic acids, which lead via the corresponding imidazolides to sulfonamides or sulfonic esters, and with phosphoric acid, which reacts with CDI to give the corresponding imidazolides of phosphoric acids that can in turn be used for phosphorylations.

The general concept applied to the group of *N,N'*-carbonylbisazoles has also been extended to the corresponding *N,N'*-iminocarbonyl analogues as well as to *N,N'*-thiocarbonyldiimidazole.[35] Of further interest are *N,N*-sulfinyldiimidazole and *N,N'*-sulfonyldiimidazole,[36] the reactivity of which will be discussed in Chapter 2. Preparation and synthetic applications of these CDI-analogues will be dealt with in detail in the appropriate chapters; they are mentioned briefly here only to show the wide scope of azolide chemistry. The corresponding activated phosphoryl imidazoles[37],[38] are also analogues of CDI, they will be dealt with in Section 2.2 and Chapter 12.



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2 Preparation and Properties of Azolides

2.1 Imidazolides of Carboxylic Acids

As shown by the kinetic studies reported in Chapter 1, the azolides of carboxylic acids constitute a series of versatile reagents with a broad range of gradually changing reactivities with respect to nucleophilic reactions at their carbonyl groups. It has already been pointed out on the basis of hydrolysis kinetics that this specific stepwise reacting capacity is a consequence of the gradual electron-withdrawing effect that the azole groups of azolides exert depending on the number and positions of nitrogen atoms in the azole rings (pyrazoles < imidazoles < 1,2,4-triazoles < 1,2,3-triazoles < tetrazoles). Benzoannelation of an azole group reduces its reactivity compared to the corresponding monocylic azolides; the reactivity dependence on number and position of the nitrogens follows, in general, the same tendencies observed with the monocyclic azolides.

Based on these reactivity studies on azolides, the imidazolides do not represent the most reactive members of the azolide family. In most cases, however, they are sufficiently reactive to undergo nucleophilic reactions leading to the desired products. Due to the easy and economical availability of imidazole, imidazolides are by far the most commonly used azolides for synthetic purposes. If, on the other hand, imidazolides are not sufficiently reactive in a specific case, one of the more active reagents from the arsenal of azolides might be used, as, for example, an azolide derived from a triazole or a tetrazole.

Preparation of Imidazolides by Acylation of Imidazole

Imidazolides may be obtained by the conventional acylation method: reacting imidazole with an acid chloride in a 2 : 1 molar ratio at room temperature in tetrahydrofuran or some other inert solvent in which imidazolium chloride is insoluble. After filtering off the imidazolium salt, imidazolides of good purity are in most cases obtained simply by removal of the solvents. Further purification may be effected by recrystallization from tetrahydrofuran, benzene, or similar solvents, or by vacuum sublimation. A great many imidazolides prepared in our group have been obtained in yields between 80 and 95% essentially independent of the structure of the acyl chain, which has ranged from straight to branched and from saturated to highly unsaturated acyl groups as well as to aromatic units with a wide variety of substituents.[1],[2] Imidazolides can be handled easily since in general only long exposure to moisture is likely to result in hydrolytic cleavage. Melting and – in the rare cases of non-crystalline compounds – boiling points are available today for well over a hundred imidazolides characterized by a wide choice of acyl groups. For the subsequent transacylation steps, however, it is usually not necessary to isolate the

imidazolides themselves since solutions of the compounds can be used directly in one-pot reactions.

The use of *N*-trimethylsilylimidazole has been suggested in the reaction with acid chlorides to form imidazolides.[3] In fact, the rate of conversion to imidazolides by reaction of *N*-trimethylsilylimidazole with acid chlorides is remarkably rapid even at rather low temperatures. On the other hand, the preparation of the *N*-trimethylsilylimidazole from imidazole requires the heating of imidazole with hexamethyldisilazane for several hours.

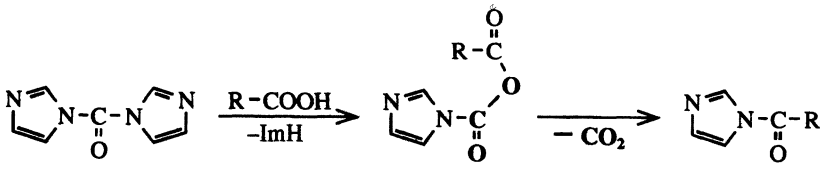
Direct acylation of imidazole can also be achieved with carboxylic acid anhydrides. For example, if imidazole is dissolved at room temperature in acetic anhydride, crystals of *N*-acetylimidazole begin to separate out; after removal of excess anhydride and the resulting acetic acid under vacuum at 60 °C, nearly pure *N*-acetylimidazole (m.p. 100–102 °C) is obtained in almost quantitative yield.[4]

The preparation of imidazolides by acylation of imidazole with acid chlorides is sometimes limited by the inaccessibility or instability of the required acid chlorides (e.g., formyl chloride, highly unsaturated acid chlorides, etc.) or by side-reactions in the case of multifunctional systems. For these reasons and due to the availability of an easy and convenient procedure involving very mild conditions, imidazolides today are usually prepared directly from the corresponding carboxylic acids with *N,N'*-carbonyldiimidazole (CDI) or one of its analoga (see page 16). Use of these reagents has become more and more the preferred method for activation of carboxylic acids to azolides and their further transacylation to esters, amides, peptides, etc. (see subsequent Chapters).

Preparation of Imidazolides from Carboxylic Acids Using *N,N'*-Carbonyldiimidazole (CDI)

N,N'-Carbonyldiimidazole (CDI) is prepared in a convenient and safe procedure from phosgene and imidazole as a non-toxic crystalline compound (m.p. 116–118 °C).[5],[6] It reacts almost quantitatively at room temperature or by short and moderate heating with an equimolar quantity of a carboxylic acid in tetrahydrofuran, chloroform, or similar inert solvents within a few minutes to give the corresponding carboxylic acid imidazolide, which is formed under release of carbon dioxide, together with one equivalent of readily separable and recyclable imidazole.[7],[8] Thus, this reaction leads under very mild conditions to the activation of a carboxylic acid appropriate for transacylation onto a nucleophile: with an alcohol to an ester, with an amino compound to an amide or peptide, etc.

A two-step mechanism must be assumed for this very valuable reaction of carboxylic acids with CDI.[9] Obviously the first step is a nucleophilic attack of the carboxylic acid or – depending on the acidity – the carboxylate ion on the carbonyl group of CDI, leading after elimination of imidazole to a mixed anhydride of imidazole-*N*-carboxylic acid and the attacking carboxylic acid. This intermediate must have a very short life-time since it has not been detected down to −50 °C. Rapid cleavage of CO_2 from this mixed anhydride involves exclusively the carbonyl group linked to the imidazole unit: If



[1-^{14}C]cinnamic acid is reacted with CDI, the radioactivity is completely preserved in the *N*-cinnamoylimidazole.[9] This result is fully in accordance with the observation that the CDI analogue *N,N'*-thiocarbonyldiimidazole reacts with carboxylic acids to form exclusively carbonoxysulfide COS and the imidazolide of a carboxylic acid, whereas formation of CO_2 and *N*-thioacylimidazoles is not observed. In the second step, reaction of the mixed anhydride to give acylimidazole, either an *inter-* or an *intra*molecular pathway is possible. The *inter*molecular pathway includes a transacylation reaction of the mixed anhydride with azole set free in the first step. Upon running the reaction with cinnamic acid and *N,N'*-carbonyldibenzimidazole instead of CDI in the presence of [2-^{14}C]benzimidazole, radioactivity was found exclusively in the *N*-cinnamoylbenzimidazole. This result provided strong evidence for the *inter*molecular pathway in the case of *N,N'*-carbonyldibenzimidazole, although exchange with [2-^{14}C] benzimidazole at the stage of *N,N'*-carbonyldibenzimidazole cannot be completely excluded.

The transformation of carboxylic acids with CDI into imidazolides has a wide range of applicability. CDI reacts with aliphatic, aromatic, and heterocyclic carboxylic acids under very mild conditions, and these reactions are not affected by the presence of functional groups unless the latter are strongly nucleophilic and themselves react with CDI; in such cases a reversible protection of the functional groups is necessary. The reaction of CDI also works in such specific cases as trifluoro- and trichloroacetic acids, leading to the very reactive *N*-trifluoro- and *N*-trichloroacetylimidazoles.[10],[11]

Dicarboxylic acids, including, for example, succinic acid, adipic acid, fumaric acid, and terephthalic acid, have been converted with CDI into the corresponding diimidazolides, which are generally obtained in very good yield[1],[12] and can be used due to their reactivity for further conversion to other bifunctional systems derived from two carboxyl groups. Difficulties were encountered, however, in an attempt to synthesize the diimidazolides of malonic acids; here, at the stage of the monoimidazolides, decarboxylation competes successfully with reaction of the second carboxyl group with CDI. In this case, the corresponding monocarboxylic acid imidazolides are obtained preferentially. For example, reaction of 2,2-dimethylmalonic acid with two equivalents of CDI resulted even at -5 °C in formation of the diimidazolide in only 15% yield, whereas the imidazolide of isobutyric acid was obtained in 70% yield.[12]

The reaction of carboxylic acids with CDI is surprisingly insensitive to steric hindrance. For example, from 2,4,6-tri-*tert*-butylbenzoic acid and CDI in refluxing tetrahydrofuran the sterically very crowded *N*-(2,4,6-tri-*tert*-butylbenzoyl)-imidazole was obtained in 80% yield.[13]

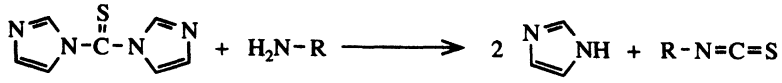
Azolides as acylating reagents are, of course, of special interest where the corresponding halides and anhydrides are not available due to their instability. Since neither

formyl chloride nor formic anhydride is stable at ordinary temperatures, the easy formation of *N*-formylimidazole as a formylating reagent was of considerable interest. In fact, CDI in dry tetrahydrofuran at room temperature reacts with the equivalent amount of formic acid to give *N*-formylimidazole in 85% yield (hygroscopic crystals, m.p. 53–55 °C, from tetrahydrofuran).[14] *N*-Formylimidazole is an extremely strong formylating reagent, reacting with alcohols to give formic esters and with amines to give formamides in exothermic reactions in excellent yields. For example, *tert*-butyl alcohol, which due to steric hindrance reacts rather slowly with other imidazolides even at higher temperatures, produces with *N*-formylimidazole the *tert*-butylester of formic acid in excellent yield even at room temperature. Aliphatic and aromatic amines react with *N*-formylimidazole in exothermic reactions to give formamides. One very unusual property among imidazolides is the fact that *N*-formylimidazole completely decomposes slightly above its melting point (at ca. 60 °C) into imidazole and carbon monoxide, 84% of which were detected by gas analysis.[14] Because of this instability of *N*-formylimidazole it is an important advantage to have available a series of azolides of formic acid that are much more stable than *N*-formylimidazole itself, but still sufficiently reactive for formylation reactions: *N*-formylbenzimidazole (m.p. 137–139 °C) and *N*-formylbenzotriazole (m.p. 94–96 °C), both prepared from the corresponding *N,N'*-carbonylbisazoles by reaction with formic acid.

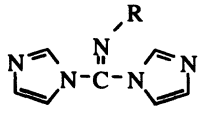
Preparation of Azolides from Carboxylic Acids Using CDI Analogues

In analogy to the reaction of CDI with carboxylic acids, the even more reactive *N,N'*-carbonyldi-1,2,4-triazole[5b] has been used instead of CDI in cases where specific structural effects require a higher reactivity of the azolide. On the other hand, the example of the last paragraph of the preceding section showed that *N,N'*-carbonyldibenzimidazole[15],[14] and *N,N'*-carbonyldibenzotriazole[15] have been useful for the syntheses of azolides with reduced reactivities when these are essential and sufficient for the specific reaction in question.

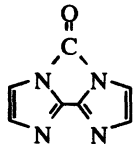
In addition to these *N,N'*-carbonylbisazoles there exist analogues of similar reactivity in which the carbonyl group is replaced by other groups that also react with nucleophiles to provide azolides. Closest to CDI is *N,N'*-thiocarbonyldiimidazole, which is easily prepared from thiophosgene and imidazole.[16] Replacement of the carbonyl oxygen by the less electronegative sulfur, in comparison to CDI, results in reduced reactivity in reactions with nucleophiles. Neutral hydrolysis with water leads at room temperature only slowly to imidazole and carbonoxysulfide COS (instead of CO_2 in the hydrolysis of CDI). With carboxylic acids, an imidazolide together with COS and imidazole is obtained after heating in chloroform or tetrahydrofuran for several hours. Primary aliphatic and aromatic amines react with *N,N'*-thiocarbonyldiimidazole in a 1 : 2 ratio to yield thioureas (see Chapter 4); in a 1 : 1 ratio, however, *N,N'*-thiocarbonyldiimidazole reacts with primary amines to give a mixture of an isothiocyanate and imidazole[17] (see Chapter 8).



In contrast to the *N,N'*-carbonylbisazoles and the corresponding thiocarbonyl compounds, certain analogues like the *N,N'*-carbiminodiimidazole with R = C_6H_5 (prepared from CDI and triphenylphosphine-*N*-phenylimide) are remarkably unreactive compared to CDI: this compound can be dissolved in aqueous 2 N hydrochloric acid and reprecipitated with ammonia.[18] The parent compound (R = H) was later prepared by reaction of two equivalents of imidazole with cyanogen bromide. Also this *N,N'*-carbiminodiimidazole (R = H) is less reactive than CDI. It was used as a condensing agent in both aqueous and anhydrous media for the formation of phosphordiester bond[18] (see Chapter 12.1).



R = H, C_6H_5



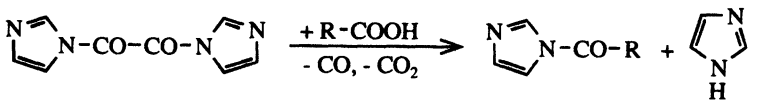
N,N'-Carbonyl-2,2'-biimidazole (*N,N'*-carbonyl-2,2'-biimidazyl) prepared from 2,2'-biimidazole and phosgene is relatively unreactive on hydrolysis, and shows reduced reactivity in reactions with carboxylic acids.[19],[2]

On the other hand, *N,N'*-sulfinyldiimidazole is an extremely reactive analogue of CDI prepared by reacting sulfinyl chloride in a 1 : 4 ratio with imidazole in tetrahydrofuran.[20] The product is extremely hygroscopic and sensitive to moisture. Therefore, *N,N'*-sulfinyldiimidazole is used immediately after separation of the precipitated imidazolium chloride in the tetrahydrofuran solution in which it is prepared. Analytically pure *N,N'*-sulfinyldiimidazole (m.p. 78–79 °C) was later obtained by reaction of sulfinyl chloride with *N*-trimethylsilylimidazole.[21] With alcohols and phenols *N,N'*-sulfinyldiimidazole reacts exothermally to give esters of sulfurous acid in excellent yields (see Chapter 10). With carboxylic acids it yields imidazolides nearly quantitatively at room temperature under development of SO_2, and it can thus be used like CDI for the synthesis of esters, amides, peptides, etc (see Chapters 3, 4 and 5). *N,N'*-sulfinyldiimidazole was already used very shortly after our synthesis by Wieland and Vogeler for peptide synthesis.[22]

The corresponding *N,N'*-sulfonyldiimidazole, prepared from sulfonyl chloride and imidazole, is of surprisingly low reactivity in every respect. It forms stable crystals of m.p. 141 °C which can be sublimed in vacuum and recrystallized from ethanol without alcoholysis. Even in dilute aqueous hydrochloric acid hydrolysis occurs only very slowly.

With carboxylic acids there was no activation to carboxylic acid imidazolides observed. Reaction with *p*-toluenesulfonic acid in boiling tetrahydrofuran did not yield the *p*-toluenesulfonic acid imidazolide, but rather the double *p*-toluene sulfonate, from which *N,N'*-sulfonyldiimidazole can be released again quantitatively with imidazole or aniline. Only from the melt of water-free *p*-toluenesulfonic acid and *N,N'*-sulfonyldiimidazole at 90 °C *p*-toluenesulfonic imidazolide (m.p. 75.5–77 °C; 87% yield) could be obtained[20] (see also Section 10.1.1).

Of great preparative potential with respect to the activation of carboxylic acids to imidazolides is *N,N'*-oxalyldiimidazole, which reacts with carboxylic acids or their sodium or lithium salts under release of CO and CO_2 to give imidazolides in excellent yield.[23]

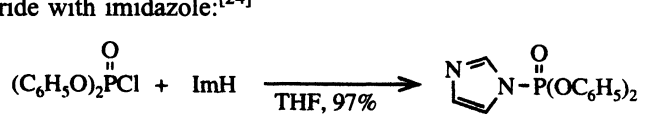


2.2 Azolides of Phosphoric and Phosphorous Acids

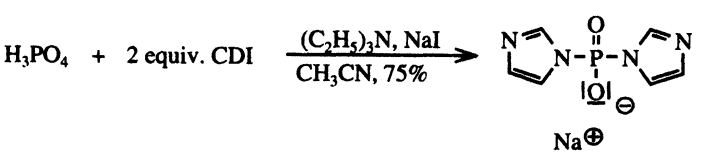
Azolides of Phosphoric Acid (Phosphoric Azolides)

The preparation of some frequently used mono-, bis-, and trisazolides of phosphoric and phosphorous acid is briefly described here and in the following section. Applications will be discussed in detail in Chapter 12.

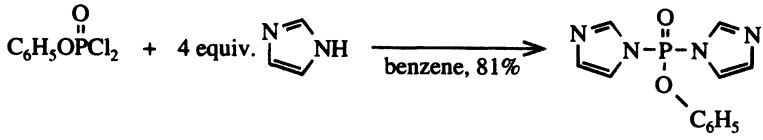
While monoimidazolides of orthophosphoric acid or its monoester are prepared from the corresponding phosphoric acid and CDI, the imidazolide of the diesterphosphate, because of its lower nucleophilicity, must be prepared by condensation of the corresponding chloride with imidazole:[24]



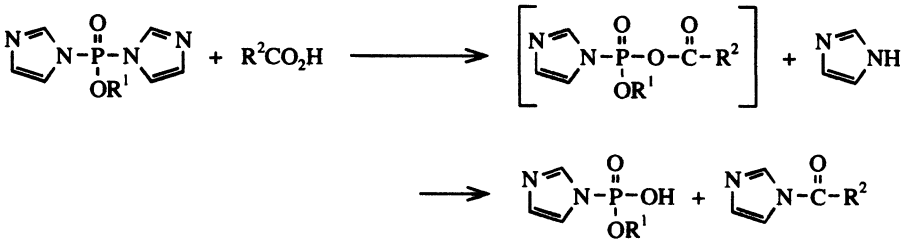
The diimidazolide of orthophosphoric acid can again be obtained by conversion of the acid with two equivalents of CDI in acetonitrile and triethylamine. Addition of sodium iodide permits its isolation as sodium salt.[24]



Other bisazolides of phosphoric acid include *O*-phenylphosphoric diimidazolide and -ditriazolide; *O*-phenylphosphoric diimidazolide, for instance, has been prepared from phenylphosphordichloridate and four equivalents of imidazole in benzene.

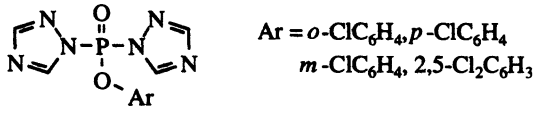


The diimidazolide is very hygroscopic.[24] In analogy to CDI it is also called "phenoxyphosphoryldiimidazole." Just like CDI, it reacts with carboxylic acids to give the corresponding *N*-acylimidazoles.



A mixed anhydride probably is formed as an intermediate which is cleaved intermolecularily by the imidazole set free in the first step. For example, reaction with the compound in which R^1 = thymyl and $R^2 = C_6H_5$ yielded quantitatively *O*-thymylphosphoric imidazolide and benzoylimidazole.[25] "Phosphoryldiimidazoles" are also used as condensing agents for the synthesis of amides and peptides, as well as for phosphorylations (see Chapters 4, 5 and 12).

Various chlorophenoxyphosphoryldiriazoles, prepared analogously to the phosphoryldiimidazoles from phosphordichloridate and triazole, are frequently used as reagents in the phosphorylation of nucleosides (see Chapter 12).



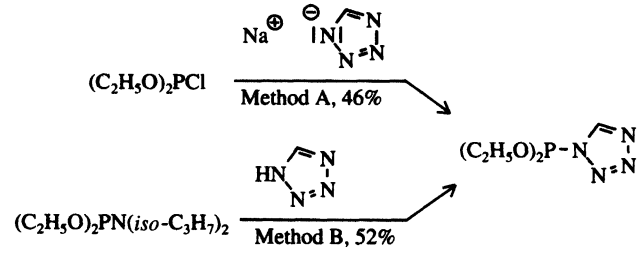
Ar = *o*-ClC_6H_4, *p*-ClC_6H_4
m-ClC_6H_4, 2,5-$Cl_2C_6H_3$

The condensation of phosphoryltrichloride with imidazole or *N*-trimethylsilylimidazole in THF provides (in 65 and 85% yields, respectively) the extremely hygroscopic phosphoric acid trisimidazolide[24], which reacts under effervescence with water or alcohols.

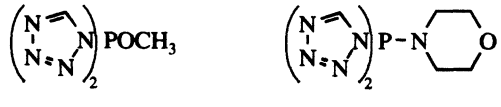
Analogously, the corresponding tristriazolide of phosphoric acid was prepared from $POCl_3$ and *N*-trimethylsilyl-1,2,4-triazole in 60% yield.[26] Both trisazolides are used for the phosphorylation of nucleosides.

Azolides of Phosphorous Acid

Tetrazolides of phosphorous acid esters or amides have been developed for the phosphitilation of nucleosides. For instance, the tetrazolide of the diester of phosphorous acid (*N*-tetrazolyldiethoxyphosphine) can be prepared either from diethylchlorophosphite and sodium tetrazolide (Method A) or from diethoxydiisopropylaminophosphine and two equivalents of tetrazole. The latter reaction (Method B) was undertaken to verify formation of a tetrazolide in the activation of phosphoramidites by tetrazole.[27]



The ditetrazolide of methylphosphite plays a role in the solid phase synthesis of polynucleotides. The ditetrazolide, which is stable for weeks when stored at −20 °C, is prepared in a simple condensation reaction between methylphosphordichloridite and two equivalents of tetrazole in anhydrous tetrahydrofuran in the presence of 2,4,6-trimethylpyridine.[28]

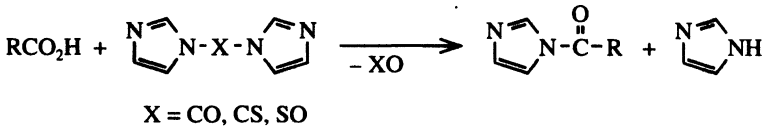


Another convenient phosphitylating reagent for use in an oligodeoxyribonucleotide synthesis based on the phosphoramidite approach is bis(tetrazolyl)morpholinophosphine. This is generally prepared in situ from morpholinophosphordichloridite containing diisopropylethylamine and two equivalents of tetrazole in dichloromethane/pyridine at 0 °C.[29],[30]

2.3 Examples of the Synthesis of Carboxylic Acid Imidazolides

In the preceding sections it has been shown – using the imidazolides as examples – that azolides can be prepared easily by a number of different reaction pathways. In view of the higher or lower reactivities of other members of the azolide family it becomes evident that this class of compounds contributes to a powerful arsenal in synthetic organic chemistry. The various reactions these azolides undergo are dealt with in detail in the chapters that follow. Since imidazolides are utilized for most of the azolide reactions, certain additional information is provided here for this particular group of the azolides.

In review articles[2] published about three decades ago, data were presented for about 100 imidazolides. In the meantime azolide reactions have developed to the point of becoming standard reactions, based mainly on imidazolides, so it seemed reasonable to underscore once again the structural diversity of the group of azolides. This is done mainly in the context of the following syntheses, most of which were essentially developed within our research group.



X = CO, CS, SO

Table 2–1. Various carboxylic acid imidazolides prepared by the use of *N,N'*-carbonyldiimidazole (CDI), *N,N'*-thiocarbonyldiimidazole (Im–CS–Im) and *N,N'*-sulfinyldiimidazole (Im–SO–Im).

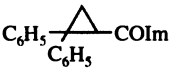
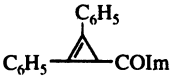
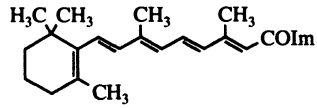
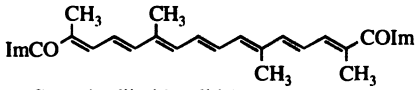
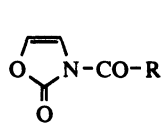
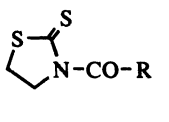
Imidazolides	M.P. (°C)	Yield (%)	Reagent	Ref.
H–COIm	53 - 55	85	CDI	[14]
CF_3–COIm	136 - 137	70	CDI	[11]
CCl_3–COIm	39 - 40	73	CDI	[11]
$C_{15}H_{31}$–COIm	81 - 82	83	ImCSIm	[10]
$CH_3OOC-(CH_2)_4$–COIm	63 - 64	75	CDI	[31]
	118 - 119	89	CDI	[32]
	163 - 164	97	CDI	[32]
4-$CH_3C_6H_4$–COIm	73 - 74	80	CDI	[12]
4-$[(CH_3)_3C]C_6H_4$–COIm	109 - 110	95	CDI	[12]
4-$[(CH_3)_3C]C_6H_4$–COIm	109 - 110	83	ImSOIm	[19]
4-$[(CH_3)_3C]C_6H_4$–COIm	109 - 110	84	ImCSIm	[10]
2,4,6-$[(CH_3)_3C]_3C_6H_2$–COIm	187 - 190	80	CDI	[13]
C_5H_4N–COIm (Isonicotinic acid)	95	70	CDI	[12]
4-$(CH_3)_2NC_6H_4N{=}NC_6H_4$–COIm	97 - 100	88	CDI	[12]
ImCO–$(CH_2)_2$–COIm	167	84	CDI	[12]
ImCO–$(CH_2)_4$–COIm	148 - 150	99	ImSOIm	[19]
ImCO–$(CH_2)_4$–COIm	146 - 147	75	ImCSIm	[15]
 (Vitamin A acid imidazolide)	112 - 113	80	CDI	[31]
 (Crocetin-diimidazolide)	201 - 203	92	CDI	[33]

Table 2–1 lists some examples of carboxylic acid imidazolides of various structures prepared by the use of *N,N'*-carbonyldiimidazole (CDI), *N,N'*-thiocarbonyldiimidazole (Im–CS–Im), and *N,N'*-sulfinyldiimidazole (Im–SO–Im). Independent of the specific method applied, the data in Table 2–1 show that reasonable yields of imidazolides and diimidazolides are quite general, irrespective of various substituents and of steric factors. The rather mild reaction conditions also permit the formation of imidazolides of highly unsaturated systems. As a further advantage, it should be mentioned that almost all imidazolides are crystalline compounds, which can be conveniently handled. Melting points are therefore included for the imidazolides listed in Table 2–1.

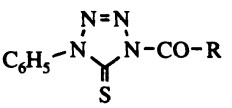
Following the development of azolide chemistry in the late 50s and mid-60s, a number of similar systems were described in which the azole rings are replaced by related heterocycles. These compounds share with azolides the characteristic of activation of the carbonyl groups toward nucleophilic reactions. Like the azolides, some of these compounds were introduced as coupling reagents for the synthesis of esters (a), amides (b), peptides (c), aldehydes (d), ketones (e), and glycosides (f). The letters in brackets below refer to specific reactions for which the compound have been used. The following formulas depict only a few examples of this group of "azolides in a wider sense."



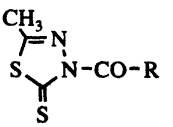
[a, b, c, d] [34]



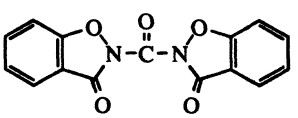
[a, b, c, d, e, f] [35]



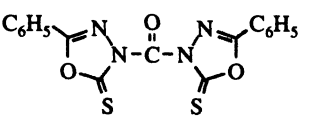
[a, b] [36]



[a] [37]



[a, b, c] [38]



[a, b] [39]

2.4 Physical Properties of Azolides

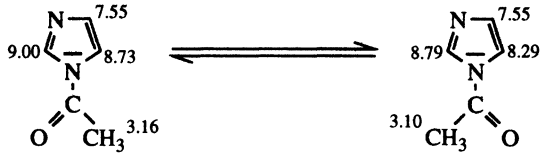
UV/VIS- and IR-Spectra

The UV-spectra of azolides have already been discussed in the context of hydrolysis kinetics in Chapter 1. Specific infrared absorptions of azolides were mentioned there as well: increased reactivity of azolides in nucleophilic reactions involving the carbonyl group is paralleled by a marked shift in the infrared absorption of the corresponding carbonyl bond toward shorter wavelength. For example, for the highly reactive *N*-acetyltetrazole this absorption is found in a frequency range (1780 cm^{-1}) that is very unusual for amides; obviously the effect is due to electron attraction by the heterocyclic system.[40] As mentioned previously in the context of hydrolysis kinetics of both imidazo-

lides and 1,2,4-triazolides of substituted benzoic acids, the observed carbonyl wave number $\nu_{C=O}$ is so closely proportional to $\log k$ for neutral hydrolysis that hydrolysis rates can be predicted from the infrared spectra within the accuracy range of the kinetic method.[40]

^{1}H-NMR- and ^{13}C-NMR

The NMR-spectra of azolides are in accordance with their structures and, in general, do not show distinctive features that could be correlated with reactivity.[41] In imidazole itself, rapid proton exchange between the two nitrogens leads to two absorptions for carbon-bound protons in a 2 : 1 ratio due to the apparent equivalence of H_4 and H_5; in *N*-substituted imidazoles there are, of course, three signals for carbon-bound protons (H_2, H_4, H_5). This is also the case for imidazolides, where a series of *N*-acyl- and *N*-benzoylimidazoles has been measured. Surprisingly, for *N*-benzoylimidazoles with a wide range of donor and acceptor substituents in the *para*-position the absorptions of the imidazole protons are remarkably constant.[41] A characteristic feature of ordinary amides is the partial double bond character associated with amide bonds, which may lead to *syn-anti* rotamers. In the case of imidazolides and other azolides, however, the barrier for this isomerisation is expected to be rather low due to the fact that the lone pair of N(1) is partially integrated into the cyclic quasi-aromatic π-system of the azoles. In fact, in earlier ^{1}H-NMR measurements of *N*-acetylimidazole and a series of *N*-benzoylimidazoles in $CDCl_3$ no splitting of ^{1}H-NMR signals was observed. This result indicates that in azolides the normal amide resonance is greatly reduced, leading to a very small π-bond order for the C···N-bond of the amide group of an azolide.



A in CD_3COCD_3 B

In later measurements at − 90 °C (100 Mhz, in acetone) for *N*-acetylimidazole, hindered rotation was found with about 75% of isomer A and 25% of isomer B;[42],[43] a rotation barrier ΔG^* of 10.5 kcal/mol (in $CHCl_2F$) was determined.[43],[44] This barrier is considerably lower than those found in normal carboxamides ($\Delta G^* =$ 14–18 kcal/mol); for formamides, where for steric reasons the planar arrangement is less hindered, higher values were measured (around 21 kcal/mol). On increasing steric hindrance (for example, with 2,4,6-tri-*tert*-butylbenzoylimidazole) a strong increase in the rotation barrier around the C-N bond in imidazolides was observed with ΔG^* of about 23 kcal/mol. For *N*-(2,4,6-tri-*tert*-butylbenzoyl)benzimidazoles the barrier was in the order of 28 kcal/mol, permitting preparative isolation of the isomers by thin-layer chromatography on silica at room temperature.[13] For ^{13}C-measurements of the rotational isomers see reference [43].

Dipole Moments

Dipole moments of azolides have been reviewed, with emphasis on the conformation of the acyl group.[44] Unfortunately, structural and conformational studies on azolides by X-ray structure analysis are almost totally lacking, although they would be of great interest with regard to the conformations and to the bond lengths and bond orders in these systems. Only an X-ray analysis of *N*-acetyl-4-bromopyrazole[45] has been reported.

Mass Spectrometry and Flash Vacuum Pyrolysis

The mass spectra of azolides are not very specific, since they depend to a large extent on the structures of the respective acyl groups. Flash vacuum pyrolyses of azolides has been studied for 1-acyl-1,2,4-triazoles and benzotriazolides by tandem mass spectrometry (MS/MS).[46] Rearrangements of triazolides resulted in the formation of oxazoles.[47]

Molecular Orbital (MO) Calculations

For calculations of electronic structures of azolides (CNDO, PCILO, EHMO, INDO and Molecular Mechanics Calculation) the interested reader should consult the relevant papers.[48]

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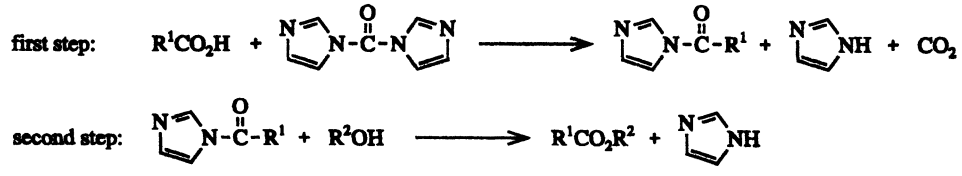
3 Syntheses of Carboxylic and Carbonic Esters

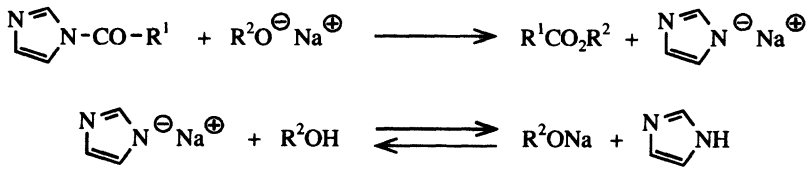
3.1 Syntheses of Carboxylic Esters

The reaction of a carboxylic acid with *N,N'*-carbonyldiimidazole[1]–[3] (abbreviated as CDI), forming an imidazolide as the first step followed by alcoholysis or phenolysis of the imidazolide (second step), constitutes a synthesis of esters that differs from most other methods by virtue of its particularly mild reaction conditions.[4],[5] It may be conducted in two separate steps with isolation of the carboxylic acid imidazolide, but more frequently the synthesis is carried out as a one-pot reaction without isolation of the intermediate. Equimolar amounts of carboxylic acid, alcohol, and CDI are allowed to react in anhydrous tetrahydrofuran, benzene, trichloromethane, dichloromethane, dimethylformamide, or nitromethane to give the ester in high yield. The solvents should be anhydrous because of the moisture sensitivity of CDI (see Chapter 2). Even such unusual solvent as supercritical carbon dioxide at a pressure of 3000 psi and a temperature of 36–68 °C has been used for esterification with azolides.[6]



3.1.1 Reactions of Imidazolides with Alcohols

The second step, nucleophilic attack of an alcohol or phenol on the activated carboxylic acid RCOIm (carboxylic acid imidazolide), is usually slow (several hours), but it can be accelerated by heating[7] or by adding a base[8],[9] such as NaH, $NaNH_2$, imidazole sodium (ImNa), NaOR, triethylamine, diazabicyclononene (DBN), diazabicycloundecene (DBU), or *p*-dimethylaminopyridine to the reaction mixture (see Tables 3–1 and 3–2). This causes the alcohol to become more nucleophilic. Sodium alcoholate applied in catalytic amounts accelerates the ester synthesis to such an extent that even at room temperature esterification is complete after a short time, usually within a few minutes.[7]–[9] This catalysis is a result of the fact that alcoholate reacts with the imidazolide very rapidly, forming the ester and imidazole sodium.



The resulting imidazole anion is in equilibrium with the alcoholate, because the acidity constants of alcohols and imidazole are of the same order of magnitude. Hence, alcoholate is constantly supplied as long as it is used up by its reaction with the imidazolide. In agreement with this explanation, imidazole sodium or other alkali metal compounds capable of converting alcohols to alcoholates (e.g. sodium amide) may be used to initiate the catalytic cycle. In the presence of these catalysts, CDI itself reacts with alcohols to give carbonic esters, so in an ester synthesis based on one-pot procedure the catalyst must be added only after the reaction of CDI with the carboxylic acid has proceeded to the imidazolide stage, as indicated by ceasing of CO_2 evolution. An approximately 0.05 mol-% solution of sodium alcoholate or imidazole sodium is usually used, easily prepared by dissolving sodium in alcohol or in a tetrahydrofuran solution of imidazole.

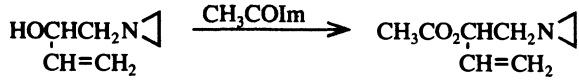
If in the ester synthesis CDI is introduced in excess and benzene is used as solvent without any base, treatment of the reaction mixture after the first step with Sephadex LH-20 is recommended in order to remove the abundant CDI and thereby eliminate possible reactive by-products such as imidazolecarboxylates (ImCOOR).[10]

The imidazolide method catalyzed by base permits even esters of polyenecarboxylic acids and polyene alcohols [e.g. the indicated esters of the vitamin A group (see Table 3–1)] to be obtained in excellent yields. The same is true for esters of sterically hindered carboxylic acids and sterically hindered alcohols (e.g., tertiary alcohols), in which case use of a basic catalyst is indispensible. For example, *tert*-butylbenzoate was obtained with base catalysis in 91% yield, but only in 5% yield without base even under reflux and longer reaction time. Under the latter conditions the reaction with primary and secondary alcohols provided benzoic esters in 75–85% yield.[9],[11] However, this imidazolide method with base catalysis cannot be used for esters of tertiary alcohols and carboxylic acids containing acidic hydrogen atoms on the α-C atom, since in this case the reaction leads to C–C condensation. Thus, *N*-acetylimidazole and *tert*-butanol, in contrast to primary or secondary alcohols, could not be converted into the corresponding ester with sodium *tert*-butanolate as catalyst. Instead, dehydroacetic acid was formed via hydrolysis of the intermediate sodium enolate of acetoacetic acid imidazolide. Also *N*-propionylimidazole and *tert*-butanol in the presence of sodium *tert*-butanolate underwent a C–C condensation to give the 2-propionylpropionic *tert*-butyl ester. Aliphatic imidazolides, however, for which the C–C condensation is rendered more difficult or impossible (e.g. imidazolides of isobutyric acid and pivalic acid), could be easily converted into the *tert*-butyl esters by the catalyzed method.[9]

Esterification of a dicarboxylic acid such as terephthalic acid via the diimidazolides with diols readily leads to the corresponding polyesters.[12]

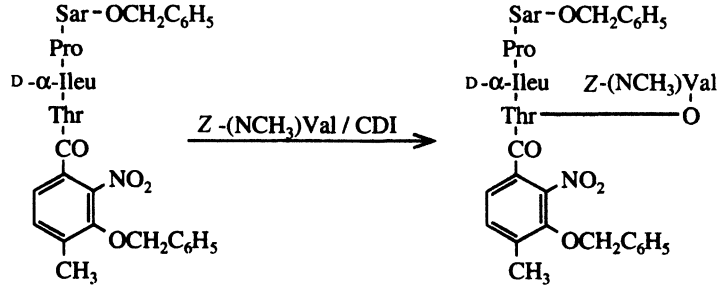
Cytostatically active esters of 1- or 2-ethyleneimino-2-hydroxy-3-butene, which are difficult to obtain by conventional methods because of the sensitivity of the unsaturated

alcohol component, have been synthesized in excellent yields by the imidazolide method with reaction times of only a few minutes at room temperature. In this case the superiority of the base-catalyzed ester synthesis with acetylimidazole is convincingly demonstrated:

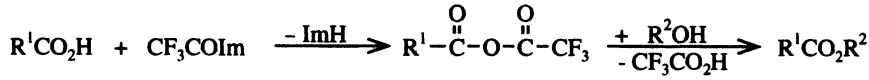


While in the uncatalyzed reaction of 1-ethyleneimino-2-hydroxy-3-butene in THF, refluxing for four hours was necessary to produce 70% of the ester, in the presence of $NaNH_2$ a 90% yield was achieved at room temperature after only five minutes.[13],[14]

An especially interesting example of the use of the imidazolide method for ester synthesis is illustrated by the total synthesis of actinomycin C_3.[15],[16] Working with *N*-protected L-*N*-methylvaline and CDI, esterification of the hydroxyl group on the threonine residue proved successful whereas this could not be accomplished by any of the conventional methods.



p-Nitrophenyl esters of amino acids, which are important for peptide syntheses, have been obtained in a one-pot reaction from *N*-protected amino acids, CDI, and *p*-nitrophenol at room temperature; however, better yields of these esters could be achieved by use of *N*-trifluoroacetylimidazole. In this reaction a mixed anhydride is presumably formed as an intermediate, which then acylates the alcohol component:[17]



By the way, *N*-trifluoroacetylimidazole and *N*-trichloroacetylimidazole are both such remarkably strong acylation agents that base catalysis is not necessary in their reactions with alcohols to the corresponding esters.[18],[19]

In general, phenolic hydroxyl groups in complex molecules, which could not be esterified by the usual methods, were smoothly acylated with imidazolides. For example, a cyclohexapeptide containing two tyrosine groups reacts with 3,5-dinitrobenzoylimidazole to give a 95% yield of the crude bis-3,5-dinitrobenzoate.[20]

Since the imidazolide method proceeds almost quantitatively, it has been used for the synthesis of isotopically labeled esters (see also Section 3.2), and it is always useful for the esterification of sensitive carboxylic acids, alcohols, and phenols under mild conditions. This advantage has been utilized in biochemistry for the study of transacylating enzymes. A number of enzymatic transacylations (e.g., those catalyzed by α-chymotrypsin) have been shown to proceed in two steps: an acyl group is first transferred from the substrate to the enzyme to form an acyl enzyme, which is then deacylated in a second step. In this context it has been shown[21] that α-chymotrypsin is rapidly and quantitatively acylated by *N-trans*-cinnamoylimidazole to give *trans*-cinnamoyl-α-chymotrypsin, which can be isolated in preparative quantities and retains its enzymatic activity (see also Chapter 6).

3.1.2 Typical Procedures for the Preparation of Carboxylic Esters

a) Using isolated imidazolide

tert-Butyl formate[22] A mixture of 9.8 g (102 mmol) of *N*-formylimidazole and 7.3 g (98.5 mmol) of anhydrous *tert*-butyl alcohol was stirred for two hours, in the course of which the imidazolide dissolved completely. After standing for 12 h, distillation directly from the reaction flask yielded 7.93 g (78%) of the ester, with b.p. 82–83 °C.

b) Using a one-pot reaction without base catalysis

Ethyl cinnamate[7] To 2.96 g (20.0 mmol) of cinnamic acid in 25 mL of anhydrous THF 3.24 g (20.0 mmol) of CDI was added. When CO_2 evolution had ceased, 5 mL of ethanol was added and the mixture was refluxed for 30 min. After concentration in a rotary evaporator the residue was taken up in 100 mL of diethylether and extracted three times each with 50 mL of water. After drying of the ethereal solution and concentration in vacuo the residue was distilled to give ethyl cinnamate (b.p. 145–147 °C/17 mm) in 80% yield.

c) Using a one-pot reaction with base catalysis

Methylretinoate[9] To a suspension of 2.37 g (7.9 mmol) of retinoic acid in 50 mL of benzene 1.34 g (8.3 mmol) of CDI was added under nitrogen. The mixture was stirred for four hours and then refluxed for a few minutes before concentrating in vacuo. The crystalline residue was dissolved in 45 mL of anhydrous methanol and treated under nitrogen with a solution of 0.15 g (8 mmol) of sodium in 15 mL of methanol. After standing for 12 h the excess methanol was removed in vacuo and the residue shaken with water. On cooling in the refrigerator 2.25 g (91%) of crude material (m.p. 51–55 °C) was obtained which after recrystallization from methanol/water (6 : 1) provided 1.66 g (70%) slightly yellow needles with m.p. 55.5–56.5 °C.

By this method numerous carboxylic esters have been prepared as is shown in Table 3–1. Diesters are compiled in Table 3–2.

Table 3–1. Monoesters prepared from carboxylic acids and alcohols or phenols using *N,N'*-carbonyldiimidazole (CDI), *N*-acylimidazole (RCOIm), or *N,N'*-sulfinyldiimidazole (ImSOIm).

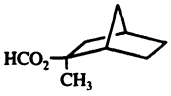
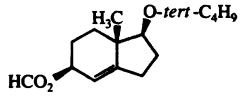
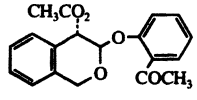
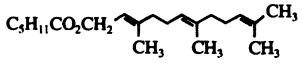
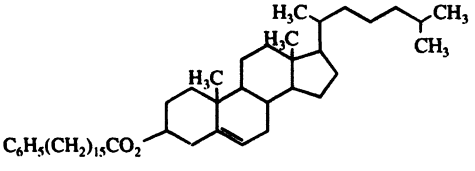
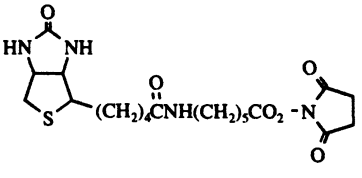
Ester	Coupling reagent	Yield (%)	Ref.
HCO_2CH_3	CDI	80	[22]
$HCO_2(CH_2)_2CH(CH_3)_2$	CDI	80	[22]
HCO_2-*tert*-C_4H_9	CDI	78	[22]
	HCOIm	71	[23]
	HCOIm	87	[24]
$HCO_2(CH_2)_{10}CH{=}CHC_4H_9$	CDI / ImNa	79	[25]
$CH_3CO_2C_4H_9$	CH_3COIm	57	[6] [1]
$CH_3CO_2CH_2CH(CH{=}CH_2)N$	CH_3COIm / $NaNH_2$	90	[13] [1] [8] [1]
$CH_3CO_2CH(CH{=}CH_2)CH_2N$	CH_3COIm / $NaNH_2$	72	[14] [1]
CH_3CO_2-retinyl	CH_3COIm / ImNa	66	[8],[9]
	CH_3COIm / NaH	80	[26]
$CH_3CO_2CH_2CH{=}CHC_6H_5$	CH_3COIm / NaIm	78	[9]
CF_3CO_2-*c*-C_6H_{11}	CF_3COIm	73	[19]
		67	[18]
$CCl_3CO_2(CH_2)_2CH(CH_3)_2$	CCl_3COIm	84	[19]
	CDI	87	[27]
$C_{15}H_{31}CO_2CH_2CH{=}CHC_6H_5$	$C_{15}H_{31}COIm$ / ImNa	80	[8],[9]
	CDI / alcoholate	68	[28][29] [1]
	CDI	61	[30]

Table 3–1. (*continued*)

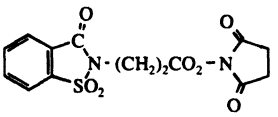
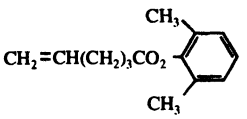
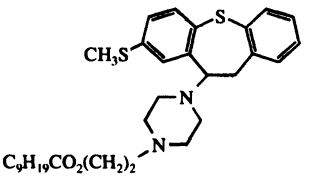
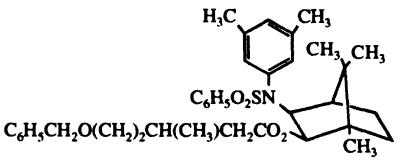
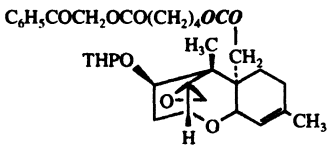
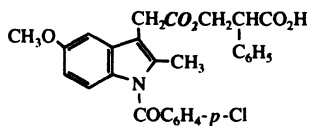
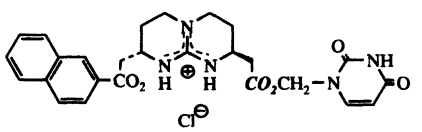
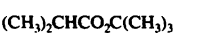
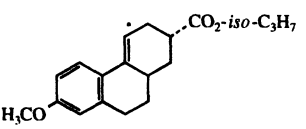
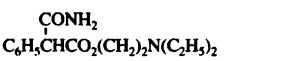
Ester	Coupling reagent	Yield (%)	Ref.
	CDI	70	[31]
	CDI	95	[32]
	CDI	63	[33]
	CDI / alcoholate	65	[34]
	CDI / DBN	52	[35] [1]
	CDI	81	[36] [1) 2)]
	CDI	85	[37][38]
	$(CH_3)_2CHCOIm$ / alcoholate	70	[8][9]
	CDI / alcoholate	98	[39]
	CDI / NaH	57	[40]

Table 3–1. (*continued*)

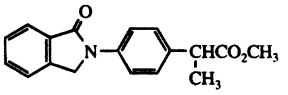
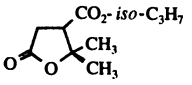
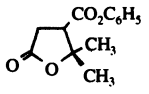
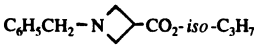
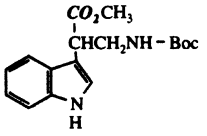
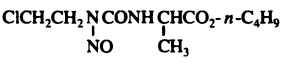
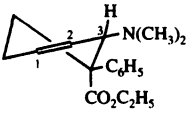
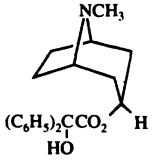
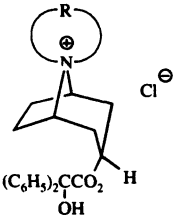
Ester	Coupling reagent	Yield (%)	Ref.
	CDI / $N(C_2H_5)_3$	quant.	[41] [1]
	CDI	80	[42]
	CDI	70	[42]
	CDI / alcoholate	86	[43] [1]
	CDI / *p*-dimethyl-aminopyridine	75	[44]
	CDI	68	[45]
$(C_6H_5)_2CHCO_2C_2H_5$	$(C_6H_5)_2CHCOIm$	71	[46]
$(CH_3)_3CCO_2C(CH_3)_3$	$(CH_3)_3CCOIm$ / alcoholate	64	[8][9]
	CDI / alcoholate	64	[47] [1]
	CDI	86	[48]
	CDI		[49] [1]
	R		
	$-(CH_2)_4-$	70	
	$-CH_2CH=CHCH_2-$	62	
		54	
	$-(CH_2)_2O(CH_2)_2-$	60	

Table 3–1. (*continued*)

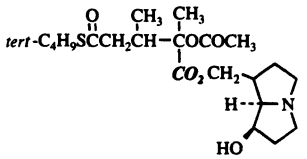
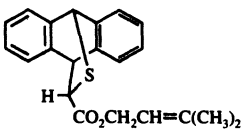
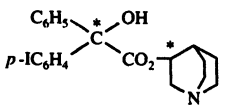
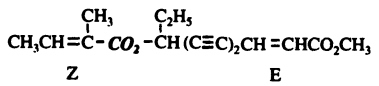
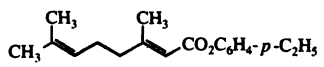
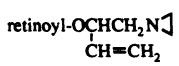
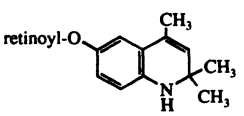
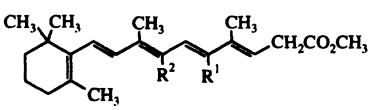
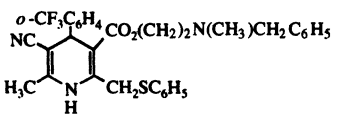
Ester		Coupling reagent	Yield (%)	Ref.
		CDI / NaH	62	[50]
		CDI / BuLi	85	[51] [1]
	*RR*	CDI	73	[52] [1]
	SR	CDI	75	
	RS	CDI	80	
	SS	CDI	70	
		CDI / ImNa	60	[53]
		CDI / NaH	31	[54]
retinoyl-OCH_3 (methyl retinoate)		CDI / alcoholate	70	[8][9] [1]
retinoyl-$O(CH_2CH_2O)_2CH_3$		CDI	47	[55]
		retinoyl-Im / $NaNH_2$	83	[13]
		retinoyl-Im / ImNa	75	[56]
		fluororetinoyl-Im / ImNa		[57] [1]
	$R^1 = H$, $R^2 = F$		40	
	$R^1 = F$, $R^2 = H$		30	
retinoyl-O-retinyl		retinoyl-Im / ImNa	73	[8][9]
		CDI	91	[58] [1]

Table 3–1. (*continued*)

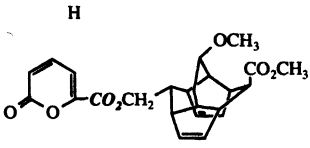
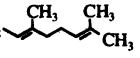
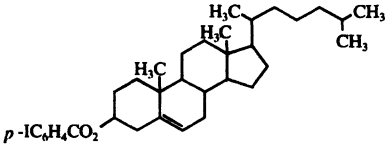
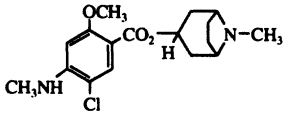
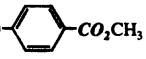
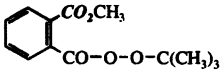
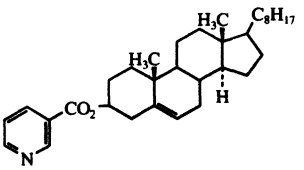
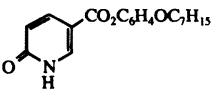
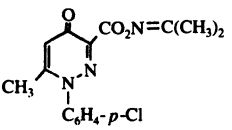
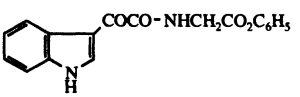
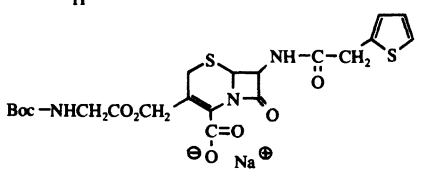
Ester	Coupling reagent	Yield (%)	Ref.
	CDI	83	[59] [1]
$C_6H_5CH{=}CHCO_2CH_3$	CDI / alcoholate	72	[8][9]
$C_6H_5CO_2C_2H_5$	CDI	75	[7]
$C_6H_5CO_2C_6H_5$	CDI	85	[7]
$C_6H_5CH{=}CHCO_2C_2H_5$	CDI	80	[7]
$C_6H_5CH{=}CHCO_2\underset{\underset{CH=CH_2}{|}}{C}HCH_2N\rangle$	$C_6H_5CH{=}CHCOIm$ / NaIm	79	[13]
$C_6H_5CO_2CH_2C_6H_5$	CDI / alcoholate	89	[8][9]
$C_6H_5CO_2CH_2CH{=}CHC_6H_5$	RCOIm / ImNa	85	[8][9] [1]
$C_6H_5CO_2\underset{\underset{CH=CH_2}{|}}{C}HCH_2N\rangle$	C_6H_5COIm / $NaNH_2$	87	[13] [1]
$C_6H_5CO_2$-*tert*-C_4H_9	CDI / alcoholate	91	[8][9]
$C_6H_5CO_2$-*tert*-C_4H_9	CDI / DBU	91	[60] [1]
p-$C_2H_5C_6H_4CO_2CH_2$ 	CDI	74	[54]
tert-$C_4H_9C_6H_4CO_2C(CH_3)_3$	*tert*-$C_4H_9C_6H_4COIm$ / alcoholate	75	[8][9]
	CDI / NaH	69	[61]
	CDI / Li tropanolate	89	[62] [1),3)]
$(CH_3)_3CO{-}O{-}CO{-}$ 	CDI	80	[63]
	CDI	80	[63]

Table 3–1. (*continued*)

Ester	Coupling reagent	Yield (%)	Ref.
	CDI	93	[64]
	CDI / alcoholate	52	[65][1)]
	CDI	67	[66]
$CF_3CONHCH_2CO_2CH_2CH{=}CH_2$	CDI	73	[67]
Boc-Ala-OCH_2COCH_3	CDI	80	[68]
	CDI	59	[69]
	CDI	59	[70]
Z-Ala-OCH_2CO_2H	Z-Ala-OC_6H_4-*p*-NO_2/ ImH	75	[71]
Z-Ala-OC_6H_4-*p*-NO_2	CDI	30	[17]
Z-Ala-OC_6H_4-*p*-NO_2	CF_3COIm	72	[17]
Z-Asp-OC_6H_4-*p*-NO_2	CF_3COIm	66	[17]
Z-Glu-OC_6H_4-*p*-NO_2	CF_3COIm	65	[17]
Z-Pro-OC_6H_4-*p*-NO_2	CF_3COIm	79	[17]
Z-(OCH_3)-Tyr-OC_6H_4-*p*-NO_2	CDI	40	[17]
Z_3-Arg-OC_6H_4-*p*-NO_2	CDI	52	[17]
Z_3-Arg-OC_6H_4-*p*-NO_2	CF_3COIm	80	[17]
Boc-Ala-Lac-$OCH_2C_6H_5$	CDI	68	[72]
Boc-Ala-Lac-Lac-$OCH_2C_6H_5$	CDI	65	[72]
Boc-Lys(Z)-O-CH($CH(CH_3)_2$)-$CO_2CH_2C_6H_5$ (D)	CDI	quant.	[73]

1) Ref. [65]

Table 3–1. (*continued*)

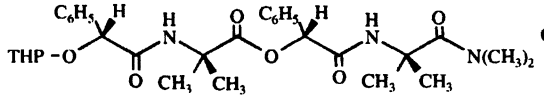
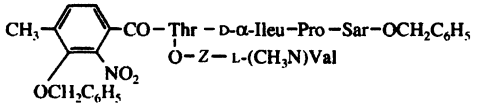
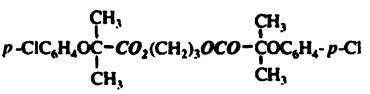
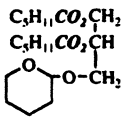
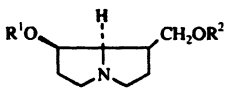
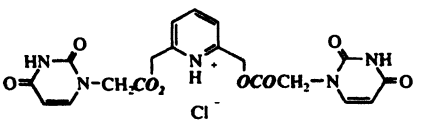
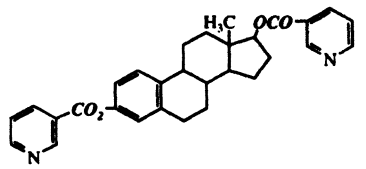
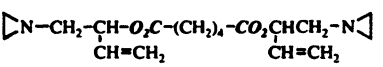
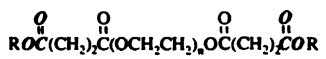
Ester		Coupling reagent	Yield (%)	Ref.
Boc–Lys–O–CH(CH(CH$_3$)$_2$)–CO$_2$CH$_2$C$_6$H$_5$ (D)		CDI	quant.	[73]
Boc–Val–O–CH(CH(CH$_3$)$_2$)–CO$_2$CH$_2$C$_6$H$_5$		CDI	quant.	[74]
Boc–Leu–O–CH(CH$_2$CH$_2$SCH$_3$)–CO$_2$CH$_2$C$_6$H$_5$		CDI	69	[75]
Boc–D-Val–O–L-Lac–OCH$_2$C$_6$H$_5$		CDI	97	[74]
		CDI	81	[76]
Z–Val–O–CH(C$_6$H$_5$)CO$_2$-*tert*-C$_4$H$_9$ (D)		CDI	68	[77]
Z–Gly–O–Ser(Z)–OH		CDI	78	[78][4]
C$_6$H$_5$CO–Phe–O–CH(CH$_2$C$_6$H$_5$)–CH$_2$–NHCOC$_6$H$_5$		CDI	65 (LL)	[79][80] [1]
Boc–D-Val–O–CH(CH(CH$_3$)$_2$)CO$_2$CH$_2$C$_6$H$_5$ (D)		CDI	90	[71]
Z–D-Val–O–CH(CH(CH$_3$)$_2$)CO$_2$NHNH–Boc (D)		CDI	65	[71]
Z–Val–O–CH((CH$_2$)$_8$CH$_3$)CH$_2$CO-*tert*-C$_4$H$_9$	L,D	CDI / ImNa	59	[81]
	L,L		69	
THP–O–CH(CH(CH$_3$)$_2$)–C(=O)–D-Val–O–CH(CH(CH$_3$)$_2$)–C(=O)–D-Val–OCH$_2$C$_6$H$_5$ (D) (D)		CDI	52	[71][4]
Boc–NH–CH(C$_6$H$_5$)–O–Tyr(Z)–OH		CDI / N(C$_2$H$_5$)$_3$	52	[82]
cyclo-(Gly-Tyr-Gly)$_2$bis-3,5-dinitrobenzoate		3,5-(NO$_2$)$_2$C$_6$H$_3$COIm	75	[20]
		CDI / ImNa	83	[83]-[85] [5]
		CDI	25	[86]

Table 3–2. Diesters prepared from carboxylic acids and alcohols using *N,N'*-carbonyldiimidazole (CDI).

Ester	Coupling reagent	Yield (%)	Ref.
	CDI	48	[87]
	CDI / CH_3SOCH_2Na	93	[65]
 $R^1 = R^2 = (E)CH_3CH{=}C(CH_3)CO$	CDI / ImNa	53	[88]
$R^1 = R^2 = (CH_3)_2C(OH)CO$	CDI	95	[88]
	CDI	94	[37] [1]
	CDI	87	[89]
$CH_3O_2C-(CH_2)_4-CO_2CH_3$	CDI / alcoholate	84	[8],[7]
	ImOC$(CH_2)_4$COIm / ImNa	43	[14]
p-$C_2H_5O_2CC_6H_4CO_2C_2H_5$	ImOCC_6H_4COIm	90	[12]
	ImH / DCC	quant.	[90] [6]
	$R = CH_3$	35%	
	$R = c\text{-}C_6H_{11}$		

[1] For further examples see the references cited
[2] Isolated as cyclohexylammonium salt from (+) ROH and (−) ROH, respectively
[3] Isolated as hydrogenmaleate
[4] After deprotection
[5] No racemization
[6] MW of diimidazolide ~2000

Remarks associated with Table 3–1: In ref. [43] the authors claim that one equivalent of alkoxide is necessary on a preparative scale instead of catalytic amounts. As an explanation they quote the difference between the pk_A of imidazole ($pk_A = 14.17$) and that of alcohols ($pk_A = 18$–19). This conclusion, however, seems to be erroneous, because of the higher nucleophilicity of the $RO^{\ominus}$ in comparison to imidazole anion must also be taken into account. In ref. [56] *d*-α-tocopherol was also converted into the retinoate in 96% yield. The imidazolide in ref. [47] is easily formed despite steric hindrance of the carboxyl group. With the diastereomeric carboxylic acid an epimerization was observed during formation of the imidazolide. The method in ref. [60] with diazabicycloundecane as base was not applicable to either pivalic acid (less than 10% yield even after prolonged heating at 80 °C) or *N*-acyl-α-amino acids (complex mixtures, probably by oxazolone formation and subsequent reactions). In reference [71] the imidazolide was generated in situ from the active *p*-nitrophenylester and imidazole. The yield of the ester in ref. [80] was only 15% if benzenesulfonyl chloride was used instead of CDI. A peptolide of *N*-protected methylvaline and an *N*-protected Ser-Ala-*tert*-OC_4H_9 prepared by CDI is described in reference [91]. With 2,2′-dimethyl-*N*,*N*′-carbonyldiimidazole as condensing agent the yields were lower than with CDI.

Appendix to Tables 3–1 and 3–2: Other esters, especially of natural products, synthesized by the CDI method but not mentioned in the tables include: steroidal esters of α-amino acids,[92] of alkanoic acids,[93] of a chiral alkanoic acid[94] and of iodobenzoic acids;[61],[95] mono esters from ursodeoxycholic acid and polyglycols;[96] di- and tetra-esters of succinic acid and steroidal alcohols, such as androgens and progestagens;[97],[98] depsides (aroylation of phenol derivatives);[99] mono- and diacylation of glycerylphosphatidylcholines with various carboxylic acids;[100]–[103] acylcarnitines;[104] 18-deoxyreserpic esters;[105] bilirubindiesters and glucuronides;[106] pyropheophorbide-glycol-ester;[107] high molecular peptolide.[108]

3.1.3 Reactions with *N*,*N*′-Oxalyldiimidazole

Similarly applicable for ester syntheses as CDI is *N*,*N*′-oxalyldiimidazole, which was first described in reference [109]. It has been used to convert not only carboxylic acids but also metal carboxylates into the corresponding imidazolides.[110] Typical reaction conditions for the reactions with oxalyldiimidazole are: for the first step 1–2 h, 25–45 °C, and for the second step 4 h, room temperature if X = H; if X = Li or Na, if 60 °C and DMF as solvent. In the latter case the resulting LiIm or NaIm function as catalysts in the conversion of alcohol into the alcoholate. Results are given in Table 3–3.[110]

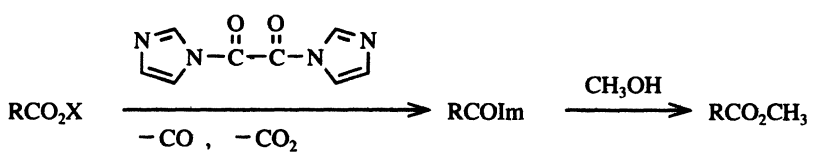


Table 3–3. Esters prepared with ImCOCOIm.

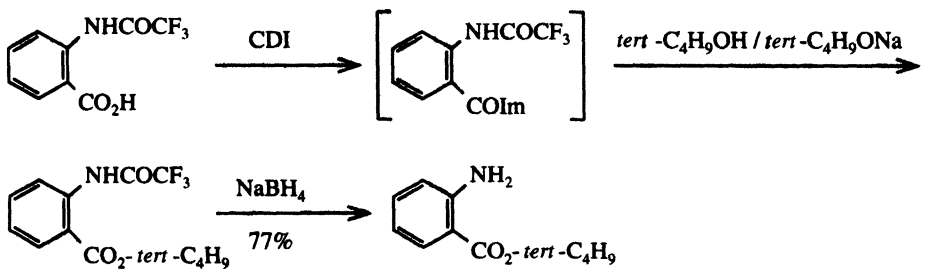
RCO_2X	RCO_2CH_3	Yield (%)
linoleic acid	methyl linoleate	79
lithium linoleate	methyl linoleate	72
sodium linoleate	methyl linoleate	85
linolenic acid	methyl linoleate	78
arachidonic acid	methyl arachidonate	72

Further examples are mentioned in the reference [110]

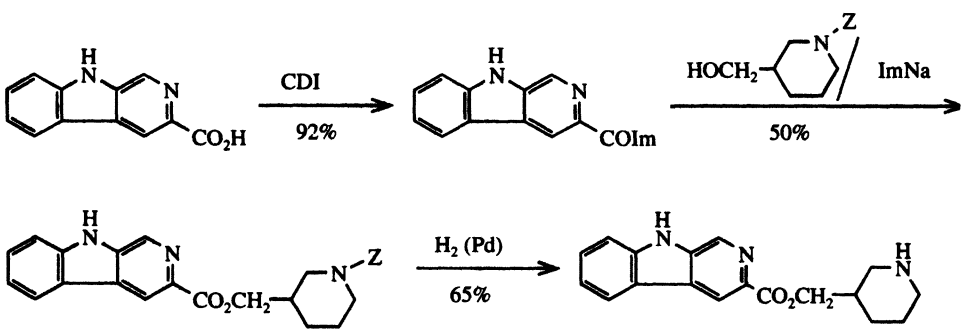
A base-catalyzed (*tert*-C_4H_9OK) reaction of *N,N'*-oxalyldiimidazole, prepared in situ from oxalyldichloride and imidazole, to give methyl linoleate (93%) is described in reference [111].

3.1.4 Selectivity of Reactions with Imidazolides

a) For the esterification of anthranilic acid and analogues it is necessary to protect the strongly nucleophilic amino group and reduce its nucleophilicity in the following way:[112]



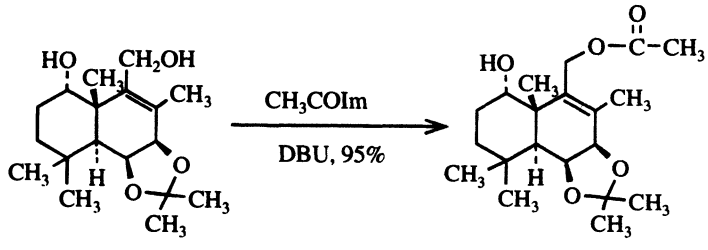
b) In the reaction of pyridinoindolecarboxylic acid with 3-hydroxymethylpiperidine the nucleophilic NH group of the alcohol component must be protected in order to obtain the corresponding ester.[113]



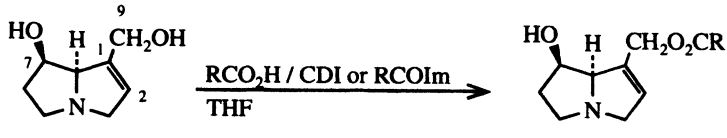
In the case of 2-(2-hydroxyethyl)piperidine it is not necessary to protect the NH group because of steric hindrance at this position. The imino function within the pyridinoindole is not nucleophilic enough to react with CDI.

For analogous syntheses of β-enamino esters or *o*-aminophenyl esters see references [114] and [115], respectively.

c) A selective acylation of a primary alcohol in the presence of a secondary alcohol group is shown in reference [116]:



A further example is given in reference [88]: Selective esterification of retronecine, the dialcoholic component of a pyrolizidine alkaloid, by the imidazolide method was found to be superior to the acid chloride/pyridine method. Acylation of the 9-position of retronecine with tiglic acid, pivalic acid, isobutyric acid, and propionic acid was investigated concerning the steric requirement of the carboxylic acid.



Retronecine

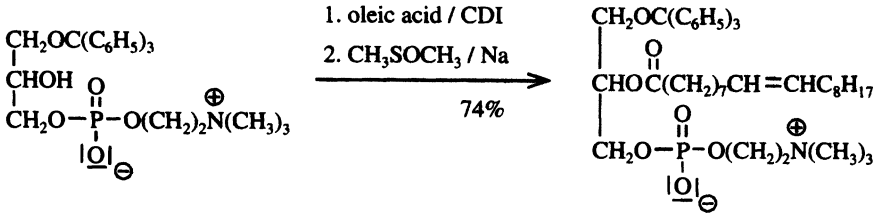
R	Yield of C9-monoester (%)	
(*E*)-$CH_3CH{=}C(CH_3)$	40;	50[1)]
tert-C_4H_9	75;	35[2)]
$(CH_3)_2CH$	60;	25[2)]
C_3H_7	40;	20[2)]

[1)] In $CHCl_3$

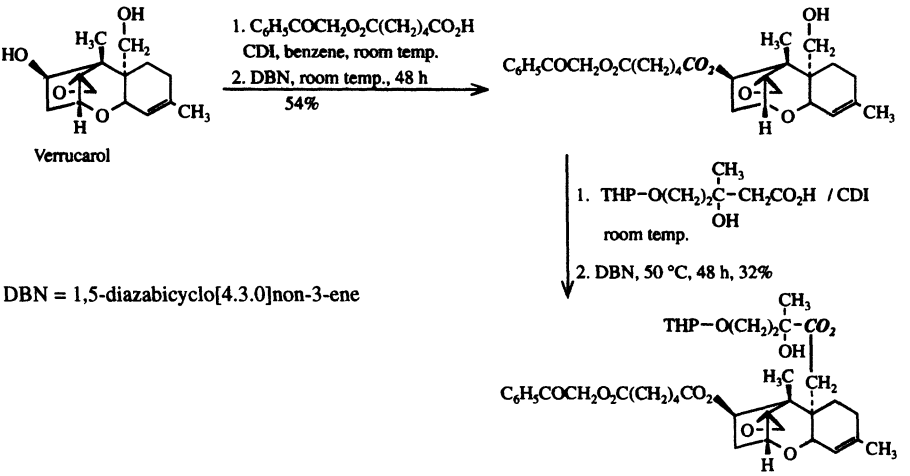
[2)] With acid chloride/pyridine

A similar example is found in reference [117].

d) Selective acylation of a secondary OH-group in the presence of a primary OH-group can be achieved as in the glycerylphosphatidyl choline by protecting the primary OH-group with the trityl group, which can be removed after acylation.[118]

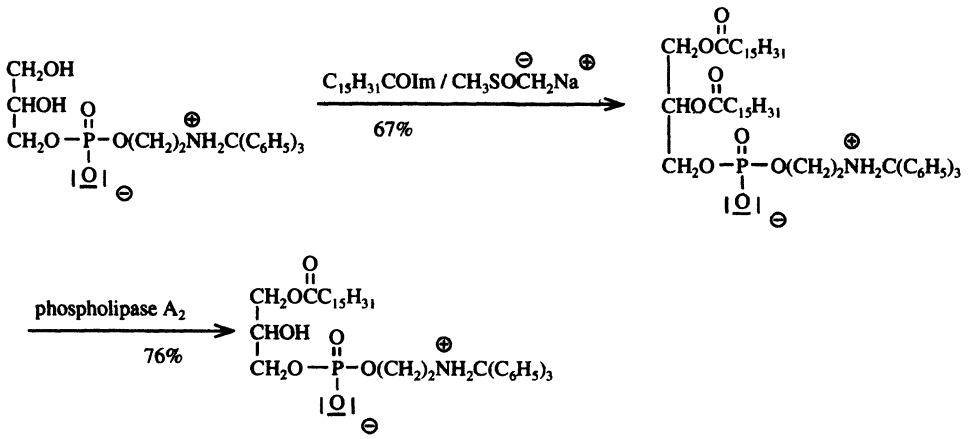


e) In the acylation of verrucarol the secondary OH-group reacts in preference to the crowded primary group, thus depending on the reaction conditions, the two OH-groups can be successively acylated by two different carboxylic acids.[35]



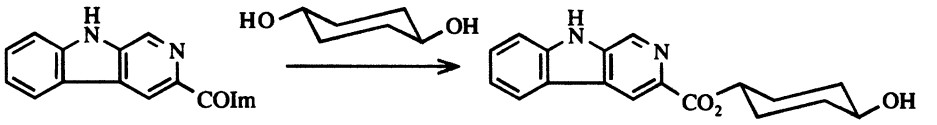
DBN = 1,5-diazabicyclo[4.3.0]non-3-ene

f) A selective synthesis of 1-palmitoylglycerylphosphatidyl-*N*-tritylaminoethanol from glyerol-3-phospho-*N*-tritylaminoethanol via the dipalmitoyl derivative is described in reference [119].

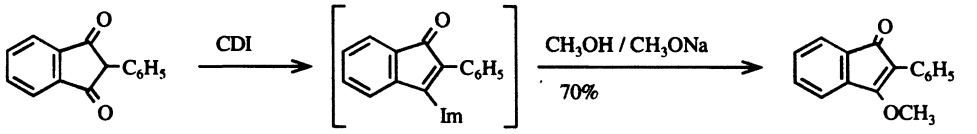


Examples for analogous reactions with polymer-bound bases such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene or 1,8-diazabicyclo[5.4.0]undec-7-ene [DBU] are given in reference [120].

g) Monoacylation of diols like cyclohexane-1,4-diols can be achieved in 50–80% yield if a high (~sevenfold) excess of the diol is utilized.[113]

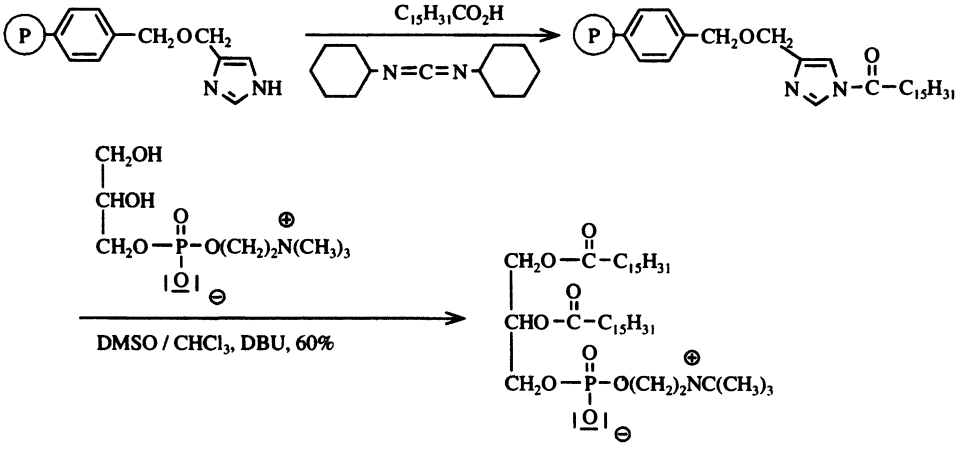


h) 2-Phenylindan-1,3-dione reacts with CDI in the form of a vinylogous acid to give with methanol the vinylogous ester:[121]



3.1.5 Preparation of Esters by Use of a Polymer-Supported Carboxylic Acid Imidazolide

An imidazolide-supported polymer was used for transacylation of phosphatidylcholine. The polymer Ⓟ was obtained from a chloromethylated polystyrene with two mol-% divinylbenzene. The imidazolide group was anchored by reaction with 3-hydroxymethyl-1-tritylimidazole, cleavage of the trityl group, and condensation with palmitic acid:[122]

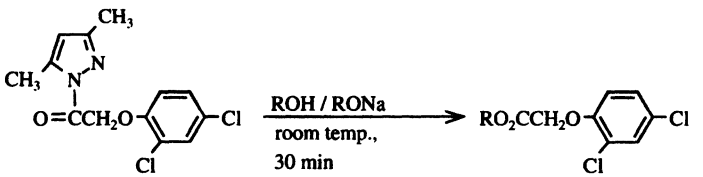


With nonsupported 1-palmitoylimidazole and DBU, however, a higher yield of the dipalmitoylphosphatidylcholine was obtained (91%).

3.1.6 Preparation of Esters Using Azolides Other than Imidazolides

Reactions with Pyrazolides

The pyrazolide indicated below was used for ester syntheses in the presence of an alcoholate.

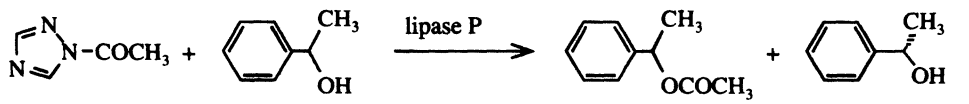


R	yield (%)
C_2H_5	74
$C_6H_5CH_2$	77
C_6H_5	88

Whereas in alcohols as solvents good yields of esters are obtained a self-condensation of the ester was observed in THF.[123]

Reactions with Triazolides and Benzotriazolides

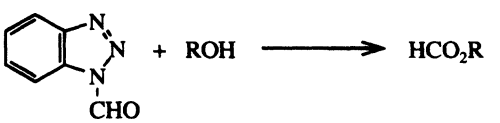
a) With *N*-acetyl-1,2,4-triazole and lipase as catalyst the following enantioselective acylation of 1-phenylethanol was achieved:[124]



RS 47% 51%

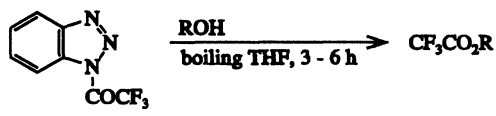
99% ee *(R)* 92% ee *(S)*

b) While *N*-formylimidazole, as used in formate syntheses, has the disadvantage of being extremely hygroscopic, *N*-formylbenzotriazole is stable and nonhygroscopic. It is accessible from *N,N'*-carbonyldibenzotriazole and formic acid[22] or from benzotriazole, formic acid, and dicyclohexylcarbodiimide,[125] and it conveniently formylates both alcohols and phenols (diethylether, 20 °C, 24 h or THF, 67 °C, 5 h).



R	yield (%)	[125]
C_4H_9	88	
2-naphthyl	75	

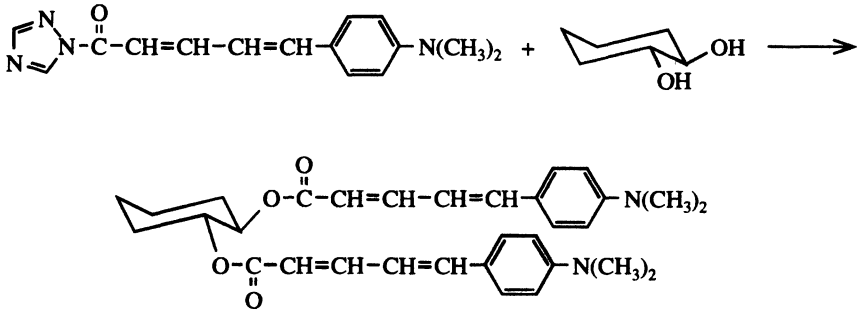
Trifluoroacetylbenzotriazole,[125a] which is easily prepared from benzotriazole and trifluoroacetic anhydride, is a very expedient trifluoroacetylating agent. Because of its stability the solid product can be stored in the covered bottle for several weeks without decomposition. By reaction with alcohols the trifluoroacetate esters were obtained in high yields:



R	Yield (%)
$C_6H_5CH_2$	95
$(CH_3)_3CCH_2$	79
$4\text{-}ClC_6H_4$	94

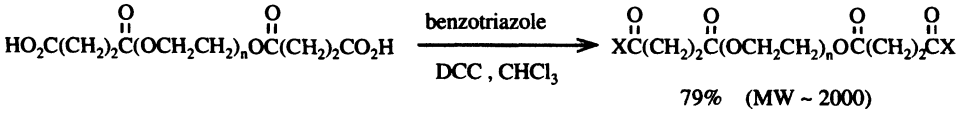
Further examples are described.

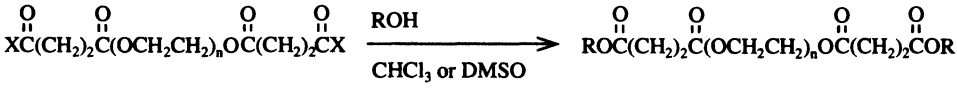
c) Diesters of 1(*R*),2(*R*)-*trans*-cyclohexanediol and various polyene carboxylic acids are synthesized via the corresponding carboxylic acid triazolides[126]:

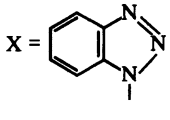


88%

d) A diester of a polymeric diacid was prepared via the bisbenzotriazolide. In this case the azolide was formed from the carboxylic acid, benzotriazole, and dicyclohexylcarbodiimide.[90]





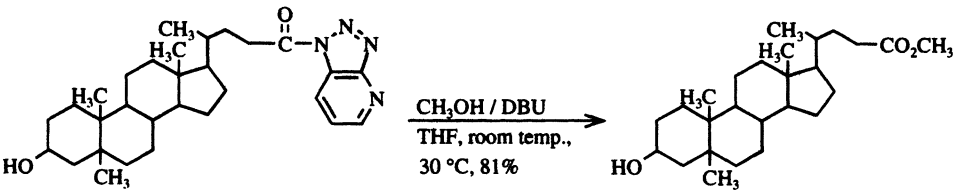


R	Yield (%)
CH_3	75
$p\text{-}HO_2CC_6H_4$	60

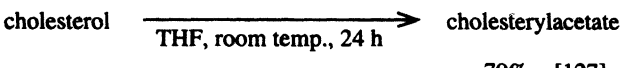
For esterification of the bisbenzotriazolide, the presence of triethylamine was recommended (methanol: 100% yield, cyclohexanol: 33%).

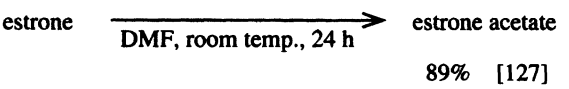
Reactions with Pyridinotriazolides

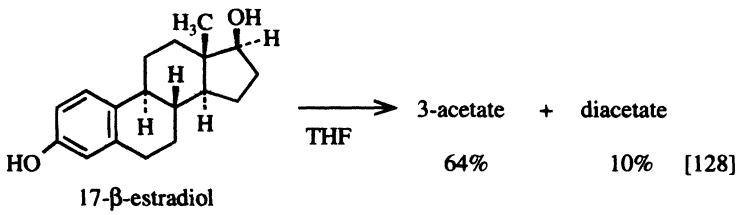
Pyridinotriazolides were used for esterification in the presence of DBU under mild conditions, and for the selective acylation of steroids.[127]

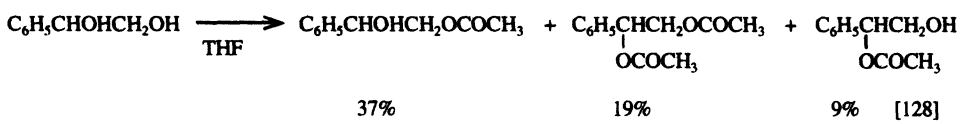


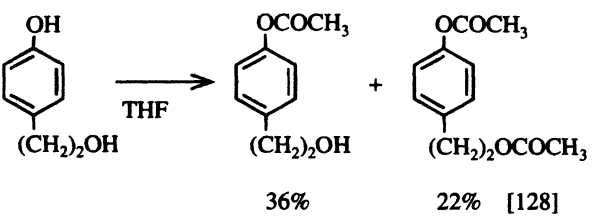
A series of acetates was prepared using 1-acetylpyridinotriazole and DBU:[127],[128]



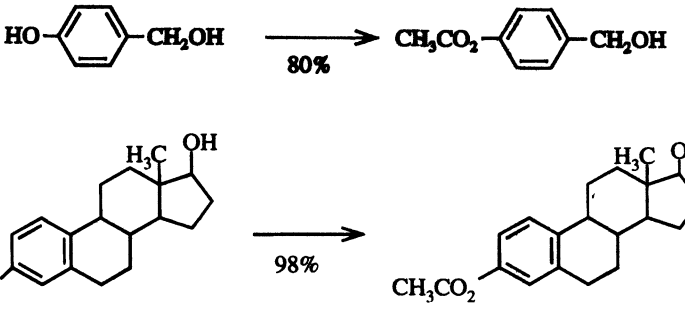








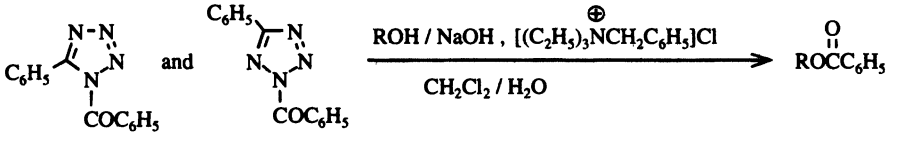
Selective acetylations of hydroxyalkyl phenols by 1-acetylpyridinotriazolide were carried out with excellent results in 1 N aqueous sodium hydroxide solution:[128]



Reactions with Tetrazolides

Even tetrazolides, which are among the most reactive azolides, have been applied in esterifications.

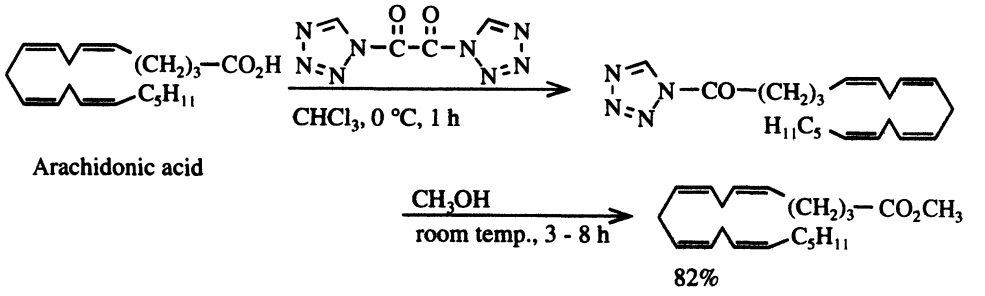
a) In a phase-transfer reaction[129] or in THF,[130] benzoic esters were prepared with the highly reactive 1-benzoylphenyltetrazole. This tetrazolide, made from 5-phenyltetrazole and benzoyl chloride, is supposed to be a mixture of the 1- and 2-benzoyl-5-phenyltetrazoles. The isomers were not separated because both lead to the same product.



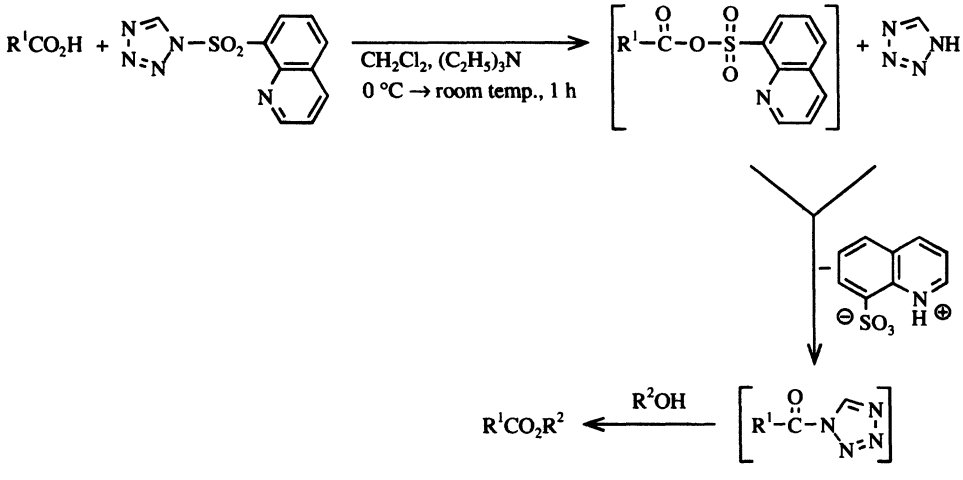
R:	C_2H_5	C_6H_5	4-$NO_2C_6H_4$	β-naphthyl [129]
%:	70	73	38	86

Methyl and other alkyl esters were prepared in THF, also in high yields.[130]

b) Arachidonic acid was converted via its tetrazolide with the aid of oxalyldi(1,2,3,4-tetrazole), prepared in situ, into the methyl ester.[111]



c) A special example in the series of tetrazolides applied for ester syntheses is the use of 8-quinolinesulfonyltetrazole.[131] In the first step a mixed anhydride is assumed to be formed, followed by an acylation of the resulting tetrazole to give the carboxylic acid tetrazolide, which then reacts in the normal way with added alcohol. The zwitterionic 8-quinolinium sulfonates separate as a precipitate from the reaction mixture. This procedure is very effective in the esterification of carboxylic acids with sterically hindered alcohols. When 8-quinoline sulfonylchloride is used instead of 8-quinoline sulfonyltetrazolide the carboxylic esters are obtained in lower yields along with acid anhydrides as by-products.

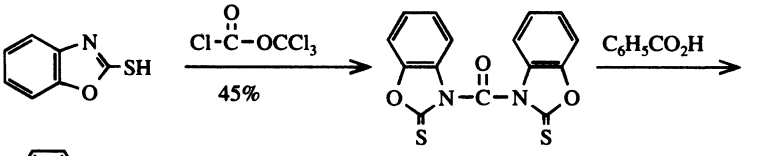


R^1	C_6H_5	$C_6H_5CH{=}CH$	$(CH_3)_2CH$	$(CH_3)_3C$	C_6H_5
R^2	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	$(CH_3)_3C$
%	89	87	84	79	82

Further examples are mentioned in reference [131]

Reactions with *N,N'*-Carbonylbis[2(3H)-benzoxazolethione]

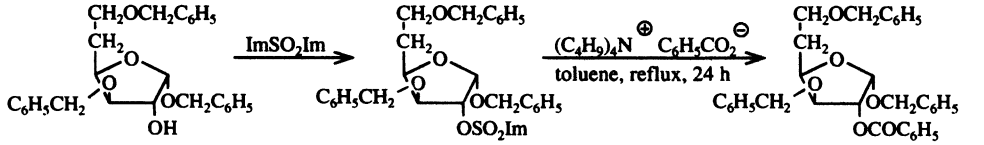
N,N'-Carbonylbis[2(3*H*)-benzoxazolethione], obtained from mercaptobenzoxazole and dimeric phosgene as the more thermodynamically stable *N*-acyl product, also represents a reactive heterocyclic diamide of carbonic acid, and is therefore used in the same way for ester syntheses as *N,N'*-carbonyldibenzimidazole.[132]



R	C_6H_5	$C_6H_5CH_2$	p-$NO_2C_6H_4$
%	90	80	98

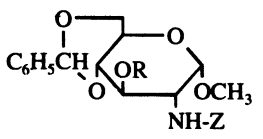
3.1.7 Preparation of Esters with Imidazolesulfonates

In this case the alcohol component is activated. By treating an imidazolesulfonate, prepared from an alcohol and sulfonyldiimidazole, with tetrabutylammonium benzoate, the corresponding benzoic ester is obtained:[133]

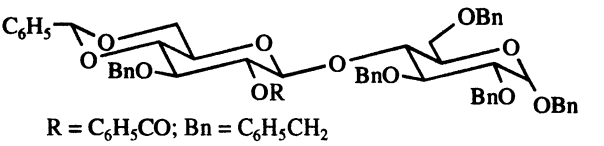


82% 53%

Further examples of the preparation of benzoic esters via imidazolesulfonates include:



85% [134]



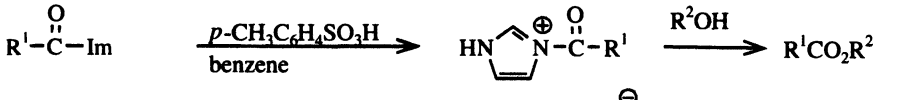
R = C_6H_5CO; Bn = $C_6H_5CH_2$

90% [135]

3.1.8 Preparation of Esters with Activated Azolides

Activation of Azolides by Protonation

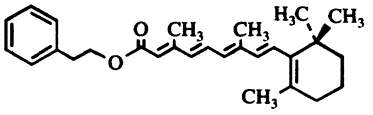
Protonation of an imidazolide increases the electron-withdrawing effect of the heterocycle and, in this way, enhances the reactivity of the *N*-carbonyl group toward nucleophilic attack. A number of retinoates have been synthesized by this method.[136]



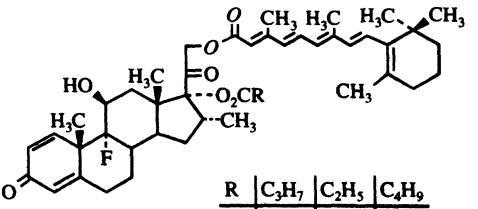
retinoyl imidazole

p-$CH_3C_6H_4SO_3^{\ominus}$

Examples:

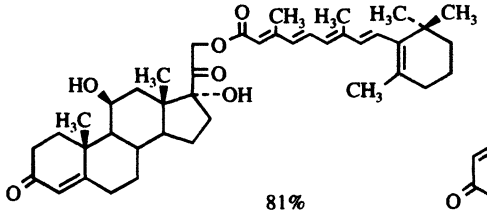


78%

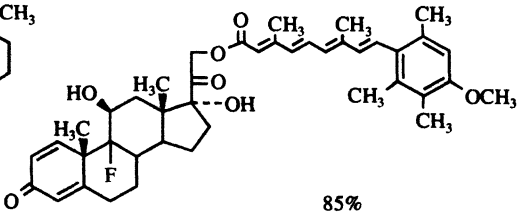


R	C_3H_7	C_2H_5	C_4H_9
%	89	76	83

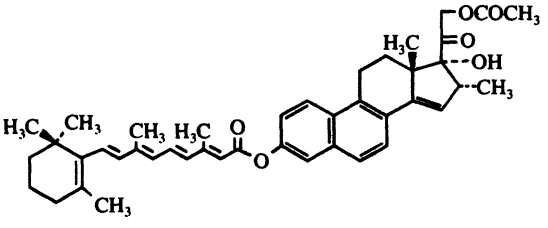
In the reaction with steroidal dialcohols, activated azolides attack the less hindered OH-group with a high degree of preference:[136]



81%

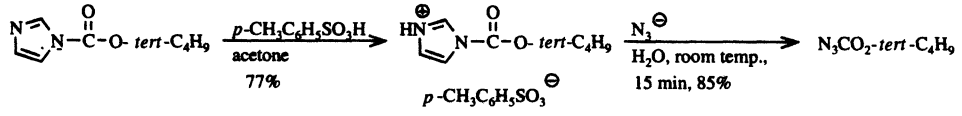


85%

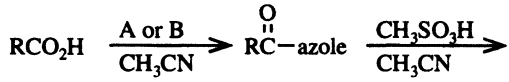


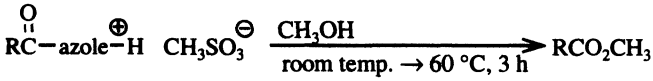
82%

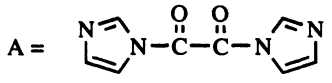
Substitution of a protonated imidazole group by an azide anion permits an azido-carboxylic ester to be obtained in good yield:[137]

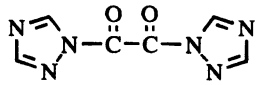


The following compilation shows the results of a reaction sequence consisting of the conversion of carboxylic acids by *N,N'*-oxalyldiimidazole (A) or *N,N'*-oxalyldi(1,2,4-triazole) (B) into the corresponding azolides followed by acid-catalyzed reaction with alcohols to give the appropriate esters.[138]





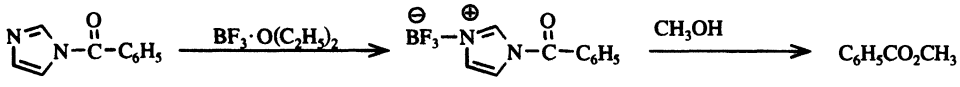




R	With Azolide A Yield (%)	Azolide B Yield (%)
$CH_3(CH_2)_5$	61	72
c-C_6H_{11}	65	60
C_6H_5	67	61
p-$NO_2C_6H_4$	83	76
	73	68

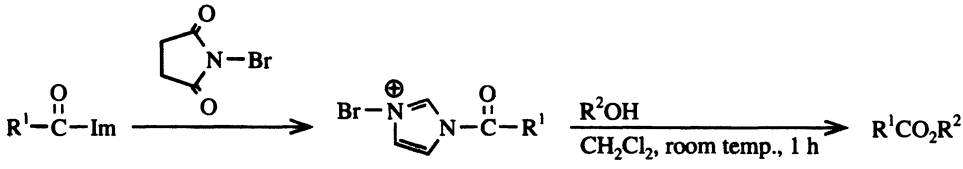
R	With Azolide A Yield (%)	Azolide B Yield (%)
	74	53
	76	68

Analogous to the activation of imidazolides by protonation, boron trifluoride also activates an imidazolide:



The effective half-time for this reaction at room temperature is 9 min in comparison with 79 min without BF_3·etherate.[139]

In a similar way, *N*-bromination on the imidazole group of an imidazolide by *N*-bromosuccinimide increases the compound's reactivity:[11],[140]



R^1	R^2	Yield (%)
tert-C_4H_9	C_2H_5	84
tert-C_4H_9	*tert*-C_4H_9	48
$CH_3(CH_2)_2CH(CH_3)$	*tert*-C_4H_9	95
2,3,6-$(CH_3)_3C_6H_2$	*tert*-C_4H_9	65

Further examples are mentioned in the references cited above

Activation of Imidazolides by *N*-Alkylation

a) *N*-Benzylation of imidazolides by benzyl chloride or bromide, which at room temperature in acetonitrile form the corresponding imidazolium salts in nearly quantitative yield, leads to highly reactive acylating agents.[141] Acylation is carried out with equimolar amounts of the imidazolium salts. Primary and secondary alcohols react especially well. If solvents other than chloroform are used (e.g., CH_2Cl_2, CH_3CN, THF, or CCl_4) the yields of the esters are considerably lower.

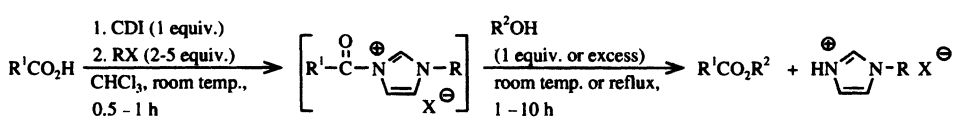
R^2OH	R^1	X	Yield (%) of $R^1CO_2R^2$
$C_6H_5CH_2OH$	CH_3	Br	97 [1]
$C_6H_5CH_2OH$	C_6H_5	Cl	84 [1]
$C_6H_5CH_2OH$	C_6H_5	Br	96 [1]
$C_6H_5CH_2CH_2OH$	CH_3	Br	94 [2]
$C_6H_5CH_2CH_2OH$	CH_3	Cl	81 [1]

R^2OH	R^1	X	Yield (%) of $R^1CO_2R^2$
$C_6H_5CH{=}CHCH_2OH$	CH_3	Br	96 [1]
$(CH_3)_2CHCH_2CH(CH_3)OH$	CH_3	Br	80 [1]
borneol	CH_3	Br	88 [1]
p-$CH_3C_6H_4OH$	CH_3	Br	99 [1]
2,6-dichlorophenol	CH_3	Br	94 [1]

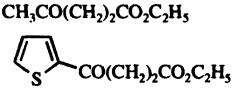
[1] yields spectroscopically determined
[2] isolated yields

b) A mechanistically analogous activation of imidazolides is achieved by *N*-allylation or *N*-methylation with allyl bromide or methyl iodide.[142] *N*-Substitution and transacylation are again one-pot reactions under neutral conditions giving high yields. Two methods have been described for the application of this principle in the ester synthesis. In method A, the respective carboxylic acids are converted by CDI (one equiv.) into imidazolides, which then are *N*-alkylated by RX (two to five equiv.). In method B, CDI is first mono- or dialkylated to the activated species, which is then treated with the appropriate carboxylic acid.[142]

Method A:



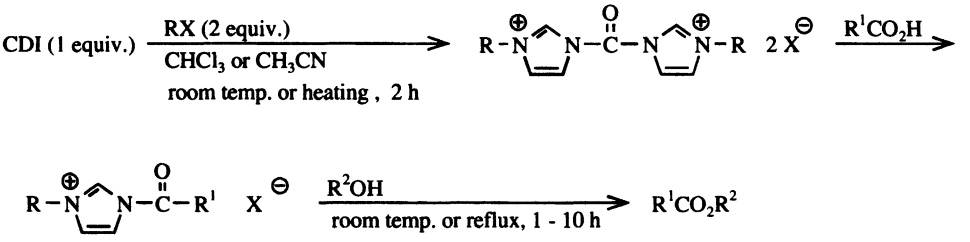
RX = $CH_2{=}CHCH_2Br$ or CH_3I

$R^1CO_2R^2$	Yield (%)
$HCO_2(CH_2)_2C_6H_5$	95
$C_6H_5(CH_2)_3CO_2$-*tert*-C_4H_9	95 (<5) [1]
$CH_3CO(CH_2)_2CO_2C_2H_5$	88
	95
tert-$C_4H_9CO_2$-*tert*-C_4H_9	90

$R^1CO_2R^2$	Yield (%)
Z-$NHCH(CH_3)CO_2C_2H_5$	95
$CH_3(CH{=}CH)_2CO_2CH_3$	95
p-$HOC_6H_4CO_2CH_3$	95
p-$CH_3OC_6H_4CO_2$-*tert*-C_4H_9	80 (<5) [1]
p-$HOC_6H_4CO_2C_2H_5$	79
p-$CH_3COC_6H_4CO_2C_2H_5$	95
p-$IC_6H_4CO_2C_2H_5$	93

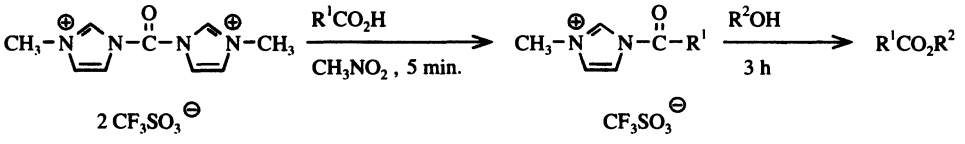
[1] Yield in the absence of the N-alkylating agent RX

Method B:



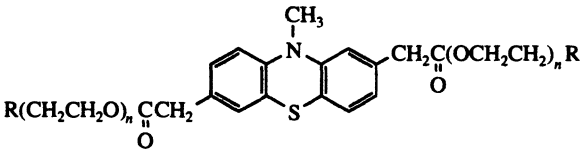
$R^1CO_2R^2$	Yield (%)
$C_6H_5(CH_2)_3CO_2C_2H_5$	86
	75

The activation of CDI by *N*-alkylation (method B) has been used for the reaction between carboxylic acids or *N*-protected amino acids and alcohols to give the esters in excellent yields.[143] Under the following conditions, which are free of any acids and stronger bases no racemization was observed.



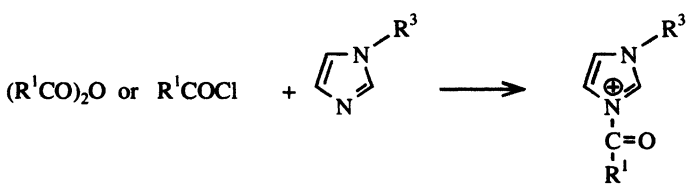
R^1CO_2H	R^2OH	Yield of $R^1CO_2R^2$ (%)
$C_6H_5CO_2H$	$C_6H_5CH_2OH$	quant.
Z-Phe	C_2H_5OH	95
Z-Phe	$C_{18}H_{37}OH$	95
Z-Phe	l-menthol	98
Z-Gly	± $CH_3CH(OH)CO_2C_2H_5$	95
Z-Ala	L-$C_6H_5CH_2CH(OH)CO_2CH_3$	94

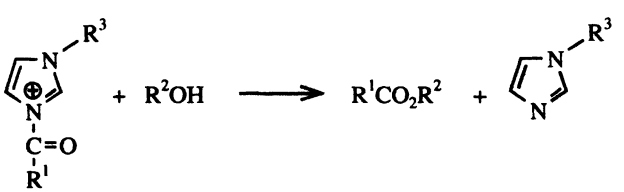
Analogously prepared are the diesters of *N*-methyl-phenothiazine diacetic acid and mono-*p*-toluenesulfonyl-, chloro- or iodooligoethylene glycols.[144]



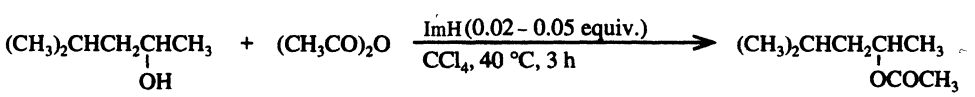
n	R	Yield (%)
5	p-$CH_3C_6H_4SO_3$	60
6	p-$CH_3C_6H_4SO_3$	54
1	Cl	66
2	Cl	60
3	Cl	44
2	I	87
4	I	45

The reactive 1-acyl-3-alkylimidazolium species also plays a role in acylation of alcohols with carboxylic anhydrides or carboxylic acid chlorides using 1-substituted imidazoles as catalysts.[145] In this case the reactive species is formed in situ:

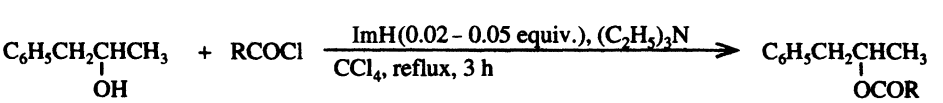




Acylation with acetic anhydride and imidazole catalyst:

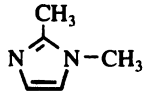


Acylation with an acid chloride and imidazole catalyst:



Illustrative yields for the two acylation methods catalyzed by *N*-substituted imidazoles are given in the following tables.

Table 3–4. Acylation of 4-methyl-2-pentanol with acetic anhydride to produce the acetate, with the indicated N-substituted imidazoles as catalysts.[145]

N-substituted imidazoles as catalyst	Yield (%)
$ImCH_3$	74
$Im(CH_2)_4CH_3$	75
$ImCH(CH_3)_2$	92
$ImC(CH_3)_3$	81
$ImC(C_6H_5)_3$	20
ImC_6H_5	28
	9

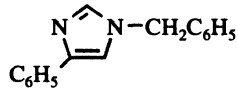
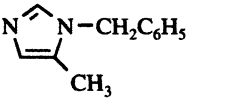
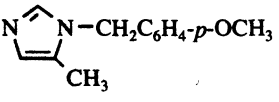
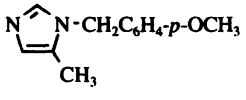
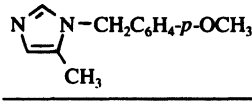
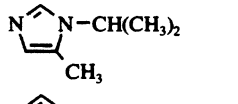
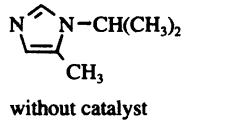
N-substituted imidazoles as catalyst	Yield (%)
	<5
	86
	96

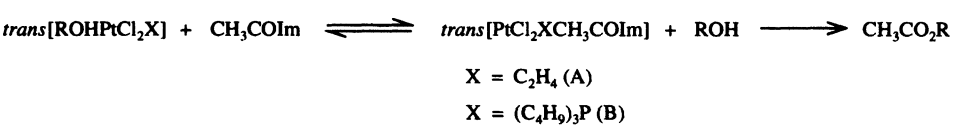
Table 3–5. Imidazole catalyzed acylation of 3-phenyl-2-propanol with acid chloride RCOCl.[145]

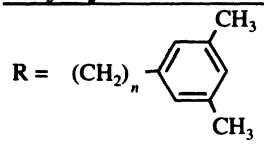
N-substituted imidazoles as catalyst	R	Yield (%)
$ImCH(CH_3)_2$	C_6H_5	quant.
$ImCH(CH_3)_2$	*tert*-C_4H_9	82
	C_6H_5	88
	*tert*-C_4H_9	88

N-substituted imidazoles as catalyst	R	Yield (%)
	C_6H_5	quant.
	*tert*-C_4H_9	quant.
without catalyst	C_6H_5	39

Activation of Imidazolides by Complexation

The reaction of interest occurs when either the imidazolide or the alcohol is initially bound in the form of a Pt(II) olefin or phosphine complex.[146]



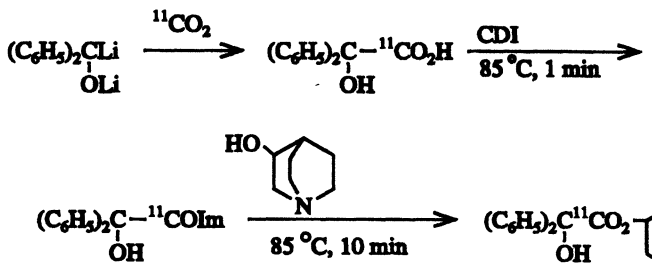
CH_3CO_2R	Method	Yield of ester (%)
R = 		
n= 1	A	62
n= 2	A	88
n= 2	B	74
n= 3	A	85
$(CH_2)_3C_6H_5$	A / collidine	80
	B / $(C_2H_5)_3N$	70

For the complex-catalyzed acetylation of 1-phenyl-3-propanol, an equimolar amount of a base such as collidine or triethylamine was necessary.

3.2 Syntheses of Isotopically Labeled, Spin-labeled, and Photoreactive Esters

Syntheses of Isotopically Labeled Esters

Due to excellent yields, mild reaction conditions, and a fast reaction rate, the azolide method is well suited to the synthesis of isotopically labeled esters, even ones with very short half-lives, just as it is always useful for the esterification of sensitive carboxylic acids, alcohols, and phenols under mild conditions. An example is provided by the synthesis of [^{11}C]-quinuclidinyl benzilate prepared from benzilic acid, CDI, and ^{11}C-labeled quinuclidinol.[147]

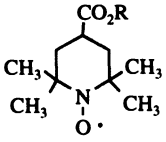
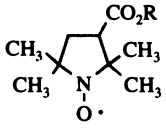
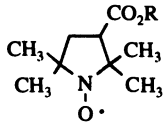
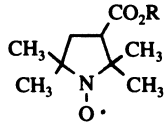
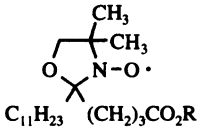
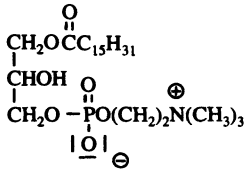
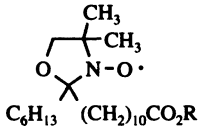
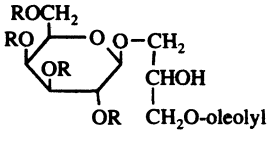
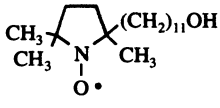
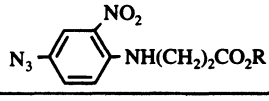


As an example for the synthesis of a ^{14}C-labeled depsipeptide from ^{14}C-glycine and serine by the imidazolide method, see reference [78].

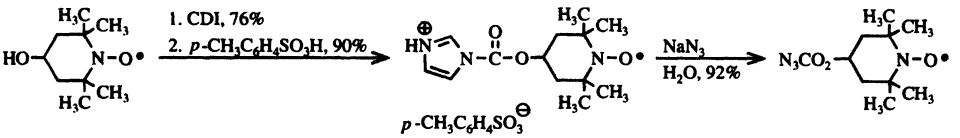
Syntheses of Spin-labeled and Photoreactive Esters

The spin label in question may as well be in the carboxylic acid fragment as in the alcohol moiety. Photoreactive esters bear azido groups in their carboxylic acid moieties. The esterification of nitroxide- or azide-bearing carboxylic acids with complex alcohols and CDI is illustrated in Table 3–6 by way of some examples.

TABLE 3–6. Spin-labeled and photoreactive esters prepared with imidazolides.

Ester	ROH	Coupling agent	Yield (%)	Ref.
	Pheophytine b-alcohol	CDI / ImNa	45	[148]
	Testosterone	CDI /*tert*-C_4H_9OK	19	[149]
	Cortisol (C(21)-OH)	ImSOIm	16	[150]
	ATP (2'- and / or 3'-OH)	CDI	32	[151]
		CDI	14	[152]
	 R = $CH_3CH(OC_2H_5)$ ·	CDI	68	[153]
Pyropheophorbide a ester		CDI / ImNa	67	[154]
	Amorphigenin	CDI / NaIm	25	[155][156]

The following reaction illustrates conversion of a nitroxide radical-bearing alcohol by CDI and azide ion to a spin-labeled ester of azido formic acid, which is used for the labeling of amino acids, giving carbamates:[137]



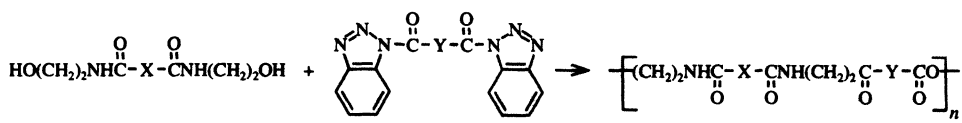
An analogous reaction was carried out with *tert*-butyl alcohol to give the imidazolium carboxylate in 77% yield and the azido formic ester in 85% yield.[137]

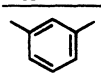
3.3 Azolide Esterification to and on Polymers

Polymeric esters by use of imidazolides or benzotriazolides have been obtained in different ways.

a) By reaction of a diol monomer with a bisazolide monomer.

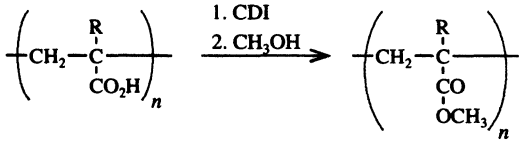
With 1,6-hexanediol a polyester was analogously prepared.[12] Further examples are shown below.



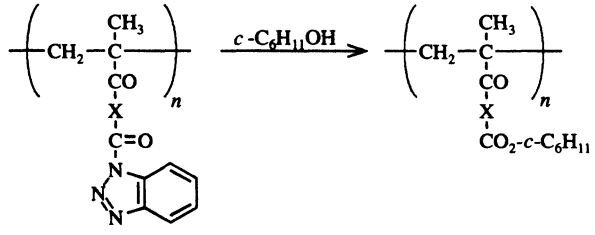
X	Y	Yield (%)	Ref.
		70	[157]
		97	[157]

X	Y	Yield (%)	Ref.
		82	[157]
		90	[157]

b) By treating a poly(carboxylic acid) imidazolide or benzotriazolide with an alcohol.

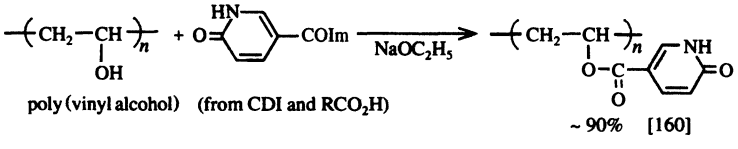


R = H, 79%; also with R = CH_3 and c-C_6H_{11} [158]



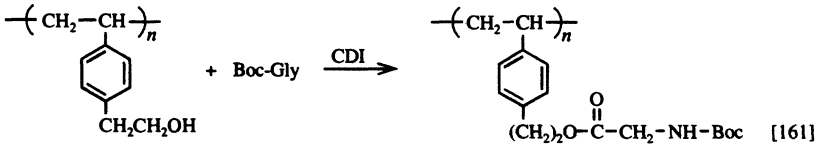
X = $-NH(CH_2)_5-$ or $-O-p-C_6H_4-$ [159]

c) By the reaction of a polyalcohol with an imidazolide formed from CDI and the appropriate carboxylic acid.[160]-[164] The polyalcohol could also be formed via the azolide method.

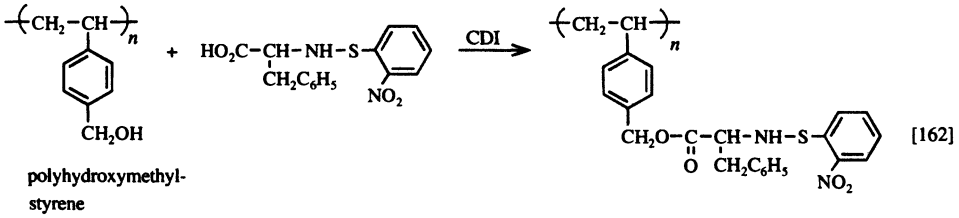


poly(vinyl alcohol) (from CDI and RCO_2H)

~ 90% [160]

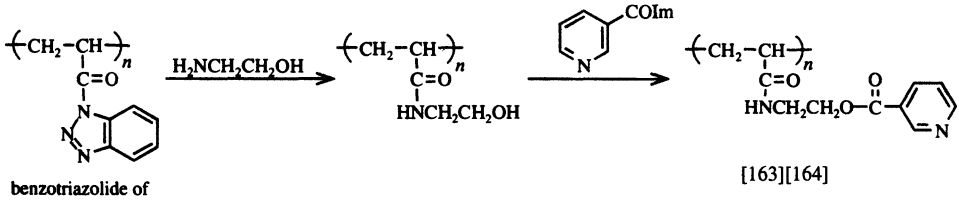


[161]



polyhydroxymethyl-styrene

[162]

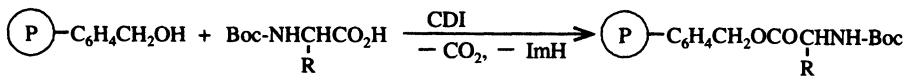


benzotriazolide of polyacrylic acid

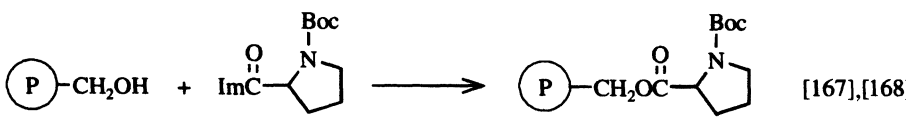
[163][164]

d) Attaching of an *N*-protected amino acid to a polyalcohol.

In the peptide synthesis for connection of the first protected amino acid with a hydroxymethyl polymer from styrene and divinyl benzene (Merrifield resin or other OH-containing resin) CDI is very suitable as coupling agent compared to *N,N'*-carbonyldi-1,2,4-triazole or dicyclohexylcarbodiimide (DCC). The yields obtained with this method are higher than those with the other two coupling agents, the conditions are mild, the reaction time is short, and the undesired formation of by-products is lessened.[165]–[169] The remaining hydroxymethyl groups were esterified with acetic acid, again by use of CDI[165] or acetic anhydride.[167]

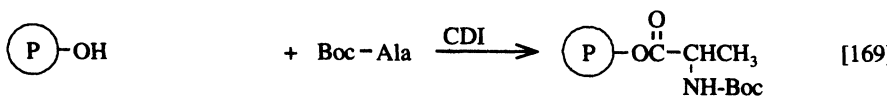


Boc–Gly–polymer, 78%;
Boc–Pro–polymer, 37%;
Boc–Arg(NO_2)–polymer, 40%; [165]



[167],[168]

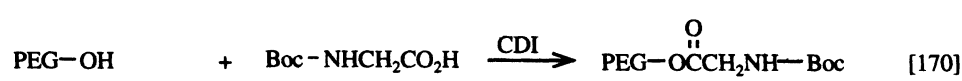
hydroxymethyl resin from Boc-Pro and CDI



[169]

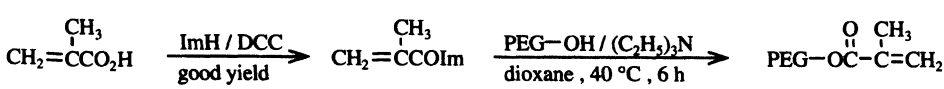
hydrolyzed copolymer
of 1-vinyl-2-pyrrolidone
and vinylacetate

e) Syntheses of high molecular weight esters of poly(ethylene glycol) with an amino acid[170] or methacrylic acid leading to an unsaturated end group[171] have also been carried out with CDI.



[170]

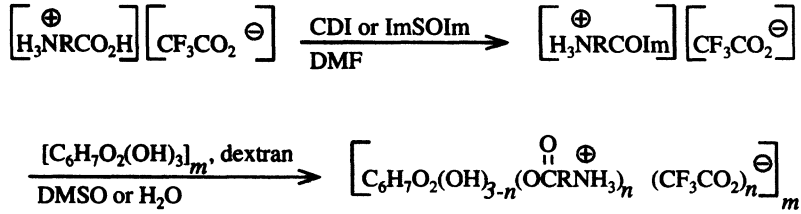
poly(ethylene glycol)



quant. [171]

For an analogous reaction of ferrocene carboxylic acid with poly(ethylene glycol) see reference [172].

f) Acylation of dextran with imidazolides of *N*-protonated amino acids or dipeptides in anhydrous or aqueous medium.[173]

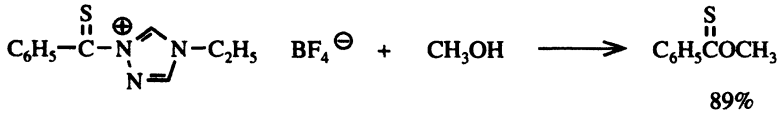


Amino acids used include Gly, Ala, Phe, Leu, His, ω-aminoheptanoic acid, and Ala-His dipeptide. It was found that not only single amino acids were added to the dextran, but also poly(amino acid) chains formed during the reaction.

A suitable degree of esterification of dextran with butyric or palmitic acid is achieved by CDI in formamide or DMSO. In the absence of carboxylic acids dextran can be converted by CDI into a crosslinked product with intrachain as well as interchain carbonate links. Such carbonate links permit drugs containing hydroxyl groups to be coupled to the dextran.[174]

3.4 Synthesis of Thionocarboxylic Esters

Analogously to carboxylic esters, thionocarboxylic esters can be synthesized by the azolide method. An example is the synthesis of thionobenzoic acid methyl ester via a 1-thioacyl-4-alkyl-1,2,4-triazolium tetrafluoroborate and methanol.[175]



3.5 Synthesis of Thiol- and Selenolesters

A series of thiol and selenolesters can be prepared from carboxylic acids and the coupling agents CDI, oxalyldiimidazole, or oxalylditriazole via the corresponding carboxylic acid azolides (Tables 3–7 and 3–9).

Generally the azolides RCOIm used for the thiolester synthesis are prepared in situ in benzene, THF, CH_3CN, or DMF. The reaction conditions range from refluxing benzene,

six hours,[176] to THF at room temp. for four hours.[177] In some cases the addition of a catalytic amount of base such as $NaOCH_3$ (refluxing benzene, three hours)[178] or $Mg(OC_2H_5)_2$ (DMF, room temp., 12 h)[179] was recommended to obtain high yields (Table 3–8). An amino acid thiolester could be obtained in base-free DMF without racemization.[180] Especially mild conditions ($CHCl_3$, room temp., 0.5–1 h) are described for the reaction of a benzyl-activated imidazolide with thiols.[141] A quantitative preparation of c-$C_6H_{11}COSC_6H_5$[180] is also described (CDI, cyclohexane, $NaOC_6H_5$ as catalyst) in reference [181].

1) Synthesis of thiolesters from carboxylic acids R^1CO_2H.

$$R^1CO_2H \xrightarrow{CDI} R^1COIm \xrightarrow[(base)]{R^2SH} R^1\overset{O}{\overset{\|}{C}}SR^2$$

Table 3–7. Carboxylic thiolesters R^1COSR^2 prepared by use of CDI.

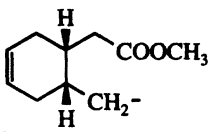
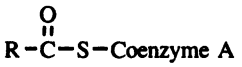
R^1	R^2	Yield (%)	Ref.
C_6H_5	C_6H_5	97	[180]
$(CH_3)_3C$	C_2H_5	93	[180]
c-C_6H_{11}	$(CH_3)_2CH$	92	[180]
$C_2H_5SCO(CH_2)_4$	C_2H_5	87	[180]
$CH_3(CH_2)_{16}$	$(CH_3)_2CH$	92	[180]
6,8-dimethylazulen-4-ylmethyl	C_6H_5	91	[180]
trans-8-heptadecenyl	C_6H_5	91	[180]
11-hydroxy-*trans*-8-heptadecenyl	C_2H_5	81	[180]
$CH_3SCH{=}C(SCH_3)$	1,5-dioxa-9-thia spiro[5.5]undec-8-yl	87	[180]
$C_6H_5CH_2CHNH$-*Z*	$(CH_3)_2CH$	92	[180]
	C_6H_5	77	[180a]

Table 3–8. R^1COSR^2 by use of CDI and $Mg(OC_2H_5)_2$.[179]

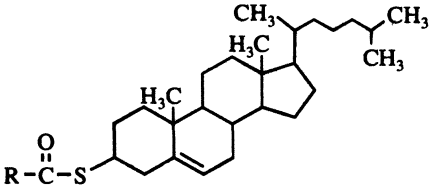
R^1	R^2	Yield (%)
C_6H_5	*tert*-C_4H_9	87
o- HOC_6H_4	C_2H_5	87
o-ClC_6H_4	*tert*-C_4H_9	quant.
β-pyridyl	*tert*-C_4H_9	quant.
tert-C_4H_9	*tert*-C_4H_9	87
Z-$NHCH_2CH(OH)CH_2$	C_2H_5	85

Acyl-coenzyme A compounds, which, because of their high acetyl group transfer potential represent carriers of activated acyl groups in biological systems, are prepared from the corresponding carboxylic acid, CDI, and coenzyme A.[4–6],[177],[182],[183]

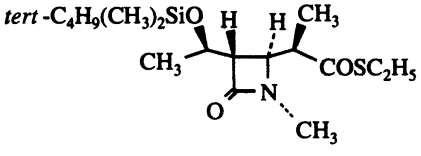


R	CH_3	CH_3 ($CH_3{}^{14}COS$-)	C_8H_{17}	3,4-dihydroxy-cinnamoyl	oleoyl	linoleoyl	linolenoyl
%	82	40	68	80	70	61	72
Ref.	[177]	[182]	[177]	[183]	[177]	[177]	[177]

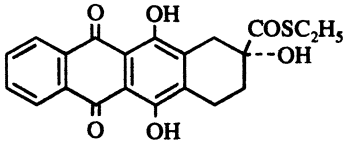
Further interesting S-acylations have been reported for the synthesis of a cholesteryl thiolester[176] (see also references [184] and [178]) or an azetidinoneacetic acid thiolester[184] by use of CDI, as well as of a thiolester with the deoxydaunomycinone structure by use of CDI and $Mg(OC_2H_5)_2$.[186]



R	H	CH_3	C_2H_5	$C_{20}H_{41}$	[176]
%	31	85	65	60	

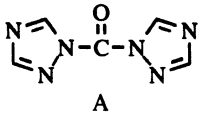


quant. [185]

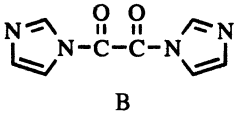


67% [186]

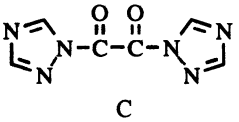
Thiolesters prepared with coupling agents other than CDI (A, B, and C below) are listed in Table 3–9.



A



B

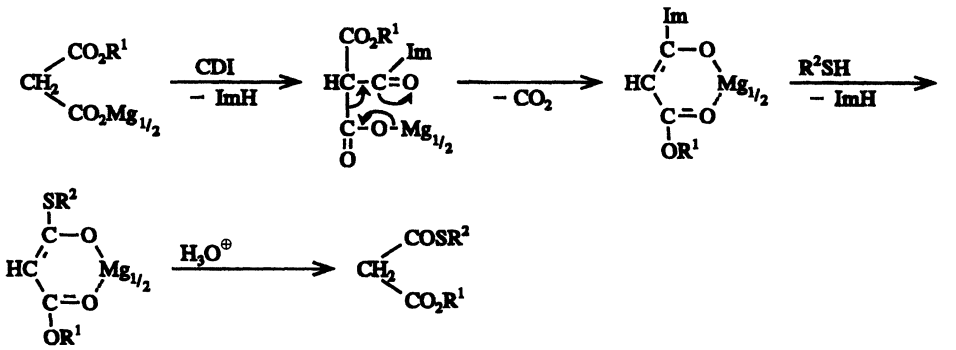


C

Table 3–9. Thiolesters prepared with the coupling agents A, B, and C.

R^1COSR^2		Coupling agent	Yield (%)	Ref.
R^1	R^2			
C_6H_5	α-pyridyl	A	86	[180]
C_6H_5	C_6H_5	B / CH_3SO_3H	78	[138]
C_6H_5	α-pyridyl	B / CH_3SO_3H	63	[138]
p-$NO_2C_6H_4$	C_6H_5	B / CH_3SO_3H	54	[138]
C_6H_5	C_6H_5	C / CH_3SO_3H	75	[138]
C_6H_5	α-pyridyl	C / CH_3SO_3H	70	[138]
p-$NO_2C_6H_4$	C_6H_5	C / CH_3SO_3H	66	[138]

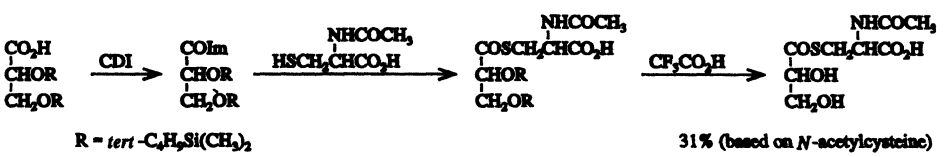
2) Malonic half thiolesters are prepared in good yields from magnesium monomethylmalonate with CDI under C-acylation and subsequent addition of a thiol.[179] Benzyl- and allylmalonic half thiolesters are prepared analogously.

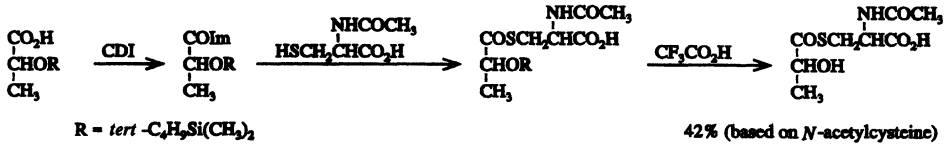


	Yield (%)
$CH_3OCCH_2COSC_6H_5$ (O)	quant.
tert-$C_4H_9OCCH_2COSC_6H_5$ (O)	86

	Yield (%)
C_2H_5OC(O)–$CH(CH_2C_6H_5)COS$-*tert*-C_4H_9	quant.
C_2H_5OC(O)–$CH(CH_2CH{=}CH_2)COSC_2H_5$	76

3) Selective thioesterification of glyceric acid and lactic acid.[187]



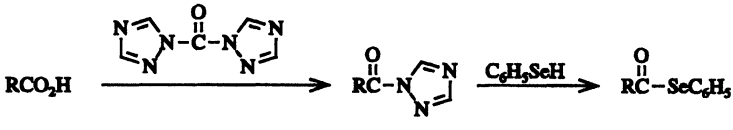


4) Preparation of a thiolester from an azolide activated by benzylation.[141]

R = C_6H_5, 99% (from NMR); 2-naphthyl, 94% (isolated)

5) Selenolesters

In analogy to the formation of thiolesters, some selenolesters have also been synthesized from carboxylic acid, phenylselenol, and *N,N'*-carbonyldi-1,2,4-triazole.[180]

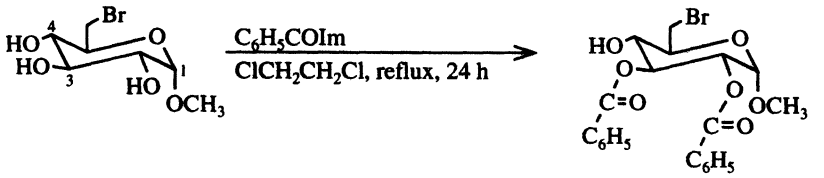


R	C_6H_5	$(CH_3)_3C$	*c*-C_6H_{11}	$C_{17}H_{35}$	6,8-dimethyl-azulen-4-ylmethyl	*trans*-8-hepta-decenyl	$C_6H_5CH_2CHNH$-Z
Yield (%)	92	90	94	94	94	88	89

3.6 Esters of Carbohydrates (Mono- and Disaccharides)

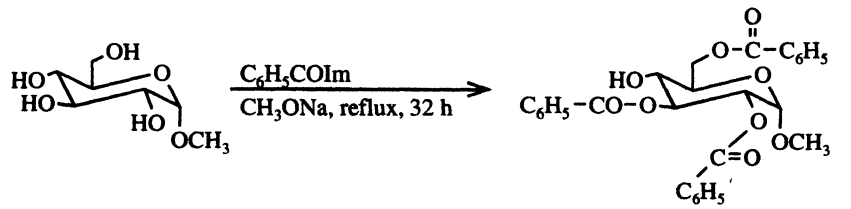
Selective acylations of many carbohydrates have been achieved by the azolide method. A short review on acylation of carbohydrates is given in reference [188]. Of special interest is the selectivity of acylation by azolides, as demonstrated by the following examples.

For reaction of methyl 6-bromo-6-deoxy-α-D-glucopyranoside with benzoylimidazole the yield of the 2,3-dibenzoyl product is 75%; further benzoylation at C-4 occurs only to the extent of 15%:[189]

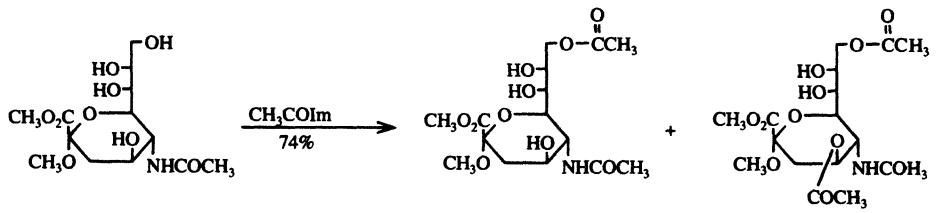


Similarly, methyl 6-deoxy-α-D-glucopyranoside yields predominantly 2,3-benzoylation (59%), whereas 2,4- and 3,4-dibenzoylations were observed only in minor yield (13 and 12%, respectively).

The selective benzoylation of methyl α-D-glucopyranosides[190] gives as major product the 2,3,6-tribenzoyl derivative (71% yield), whereas the 2,6-dibenzoyl-, the 2,4,6-tribenzoyl- and the completely benzoylated 2,3,4,6-tetrabenzoyl compounds are minor products (13, 3 and 11% yield, respectively).

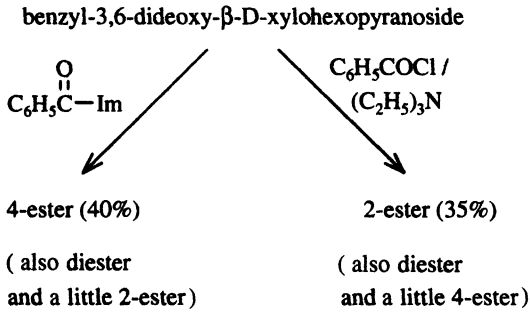


Selective acetylation of the methylester of *N*-acetyl-β-D-neuraminic acid methylglycoside produces, roughly in a one to one ratio and in 74% yield, the two acetylation products shown:[191]



4,6-Benzylidene-D-hexopyranoside and benzyl-3,6-dideoxy-β-D-xylohexopyranoside are benzoylated with *N*-benzoylimidazole yielding the product ratios indicated in Table 3–10.[192]

The product ratio obtained with *N*-benzoylimidazole has been compared with those obtained through the reaction with triethylamine/benzoyl chloride and also pyridine/benzoyl chloride. With triethylamine/benzoyl chloride the yields and selectivities are in most cases higher, but those with pyridine/benzoyl chloride are usually lower than with *N*-benzoylimidazole:

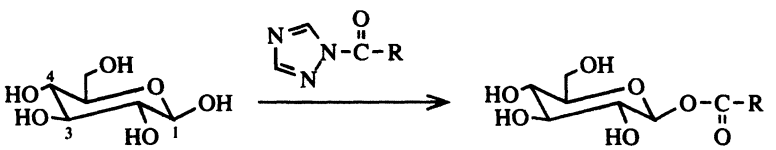


Thus the reactions of *N*-benzoylimidazole and benzoylchloride/triethylamine with benzyl-3,6-dideoxy-β-D-xylohexopyranoside are supplementary to each other.[192]

Table 3–10. Various benzoates of carbohydrates.

Starting carbohydrate	Yield of benzoates (%)		
Methyl 4,6-O-benzylidene-X-pyranoside	2-benzoate	3-benzoate	2,3-dibenzoate
X = α-D-gluco	44	33	11
β-D-gluco	26	42	9
α-D-allo	46	18	15
α-D-altro	53	2	22
α-D-manno	53		23

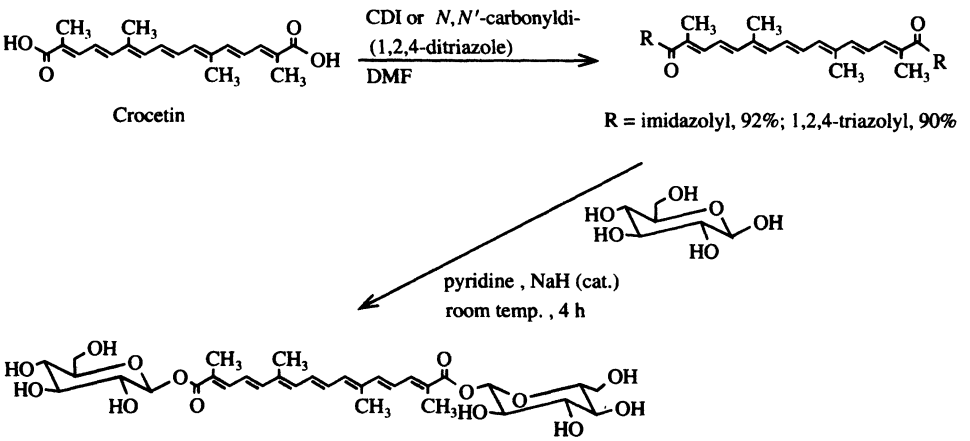
Acylation of β-D-glucose with azolides yields preferentially esterification in the 1-position of which for example, with R = C_6H_5 60% and with R = $C_{17}H_{35}$ 71% yield are obtained. Azolides of sterically crowded acids [R = $(C_6H_5)_2CH$ or $(CH_3)_3C$] give poorer yields (~28%).[193]



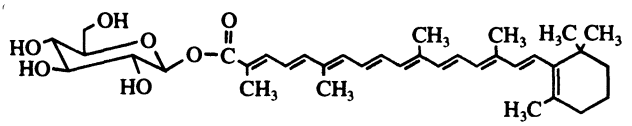
1-*O*-Stearoyl-β-D-glucopyranose is prepared analogously with 1-stearoylimidazole or 1-stearoyltetrazole, and 1-*O*-diphenylacetyl-β-D-glucopyranose with 1-diphenylacetyl-imidazole. The azolide method for synthesis of 1-*O*-acyl-β-D-glucopyranoses is both convenient and of potential general applicability, as well as being regio- and stereo-selective.[193]

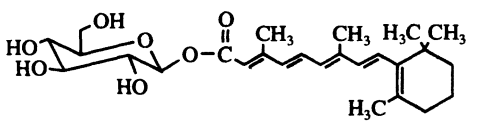
The reaction of crocetin bisazolide has also been achieved with unprotected (!) β-D-glucose in excellent yields (67% from the imidazolide; 70% from the 1,2,4-triazolide). Esterification takes place exclusively at the anomeric C-atom, and produces only the β-anomer. The higher acidity of the anomeric hydroxyl group compared with the other

hydroxyl groups of the carbohydrate was claimed to be responsible for this selectivity. The high degree of regioselectivity and stereoselectivity by this method is noteworthy.[194]



Analogously prepared are the β-D-glucosyl ester of 8'-apo-β-carotene-8'-oic acid (as imidazolide and triazolide, obtained in 81 and 66% yield, respectively) and vitamin A acid (as triazolide, obtained in 87% yield):[195]


80% from the imidazolide;
84% from the triazolide

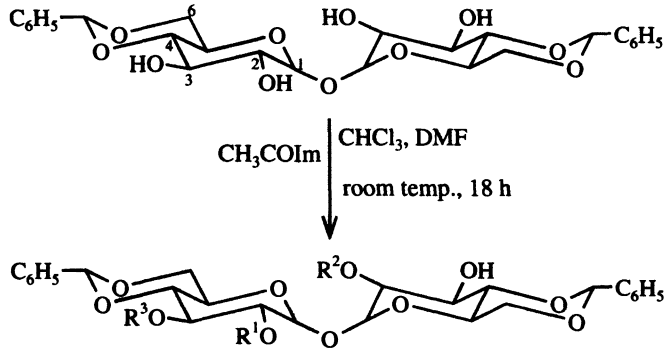

76% from the imidazolide; 92% from the triazolide

The esterification can also be carried out as a one-pot reaction without isolation of the azolide; for example, an 80% yield of crocetin bis(β-D-glucosyl ester) was obtained via the triazolide.[195] Reactions of 8'-apo-β-carotene-8'-oic acid with D-galactose or lactose were claimed to proceed also with a high degree of regioselectivity.[196]

The ratio of the α- to the β-anomeric D-glucosyl ester can be influenced by changing the reaction conditions. In DMF the α-anomer of the crocetin bis(D-glucosyl ester) was formed in about 70% yield.[196] Esterification of D-glucose with the imidazolides of benzoic acid or stearic acid in pyridine furnished a mixture of the α- and β-anomers of the C(1) glucosyl ester.[196]

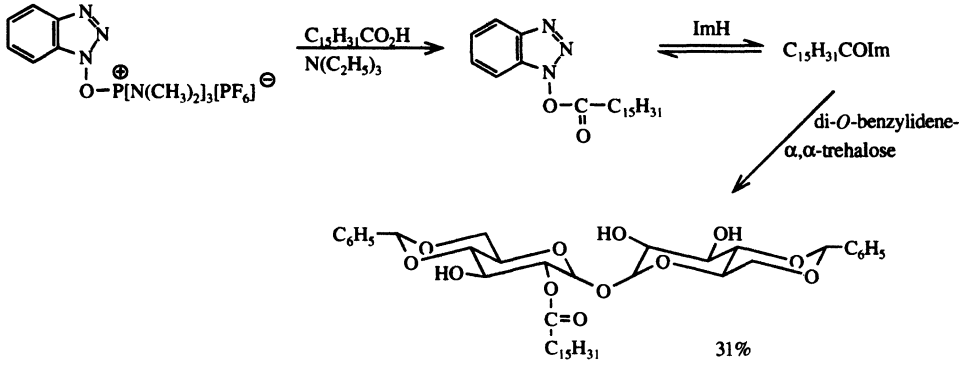
The acetylation of methyl-α-D-glucopyranoside with *N*-acetylimidazole (DMF, room temp., 48 h) affords no significant selectivity, and leads to partial substitution at all four hydroxyl groups (2-OAc : 3-OAc : 4-OAc : 6-OAc = 35 : 15 : 20 : 35).[197]

Acetylation of 4,6 : 4′,6′-di-*O*-benzylidene-α,α-trehalose with *N*-acetylimidazole ($CHCl_3$/DMF, 18 h, room temp.) yields 50% diacetylation at R^1 and R^2, 32% monoacetylation at R^1, as well as acetylation in all three positions R^1, R^2, and R^3 (altogether about 10%):[198]



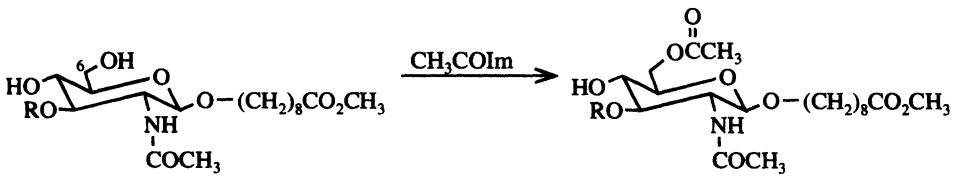
$R^1 = R^2 = CH_3CO$, $R^3 = H$ 50%
$R^1 = CH_3CO$, $R^2 = R^3 = H$ 32%
$R^1 = R^2 = R^3 = CH_3CO$ 10%

Improved selective acylation of 4,6 : 4′,6′-di-*O*-benzylidene-α,α-trehalose was achieved in acetone by the following method, in which a gentle liberation of *N*-acylimidazole occurs on the conversion of benzotriazolyl-*N*-oxytris(dimethylamino)phosphonium hexafluorophosphate with the carboxylic acid in the presence of triethylamine and addition of imidazole:[199]



If the acylation is carried out in CH_3CN, DMF, or HMPA, 2,2′-diester is formed along with the trehalose 2-ester.

A selective 6-acetylation of the following diglucoside in 71% yield by *N*-acetylimidazole has been reported:[200]



R = tetra-O-acetyl-β-D-galactopyranosyl

Further acylations/selective acylations of carbohydrates are compiled in Table 3–11. The acylations are carried out either by using imidazolides prepared in situ from the carboxylic acid and CDI (method A), or by using the isolated carboxylic acid imidazolides (method B).

By the azolide method a great number of carbohydrates has been acylated of which only a few examples can be mentioned here. Reactions have been reported with an oleandrose,[201] α-D-mannopyranoside,[202] α-D-glucopyranosides,[189],[203]–[207] β-D-glucopyranosides,[208] β-D-galactopyranosides,[209],[210] a 4,6-dideoxy-α-D-xylohexopyranoside,[211] a 2-acetamino-2-deoxy-β-D-glucopyranoside,[212] an α-D-altropyranoside,[213] a 2,6-dideoxy-α-D-lyxohexopyranoside,[214] a β-D-galactopyranoside,[215] an α-D-galactofuranoside,[216] a myoinositol,[217] an α-D-mannopyranosyl glyceride,[218] a rhamnal,[219] α,α-trehaloses,[220]–[222] and a (β-D-galactopyranosyl)-2-acetamino-2-deoxy-β-D-glucopyranoside.[223]

Table 3–11. Acylated carbohydrates.

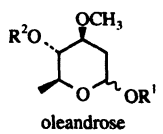
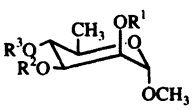
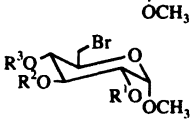
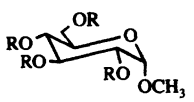
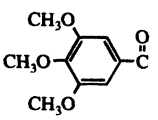
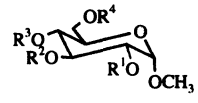
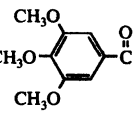
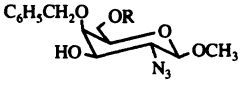
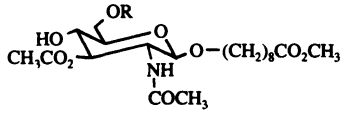
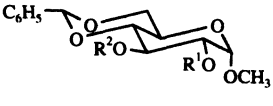
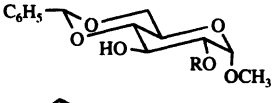
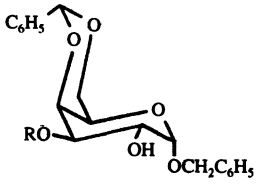
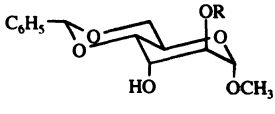
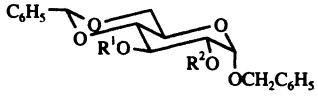
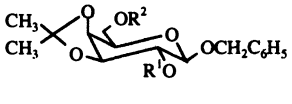
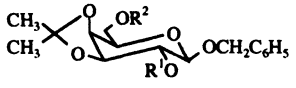
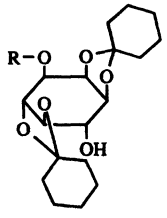
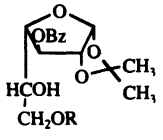
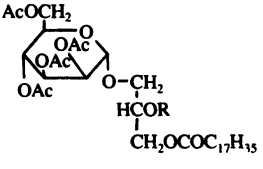
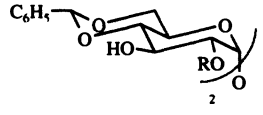
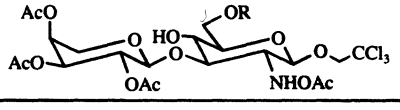
Carbohydrate R,R,^{1},R^2,R^3 = H	Acylated carbohydrate	Method	Yield	Ref.
 oleandrose	$R^1 = R^2 = CH_3CO$ $R^1 = CH_3CO$, $R^2 = H$	A (2 equiv. CDI, CH_2Cl_2)	40 53	[201]
	$R^1 = R^2 = C_6H_5CO$, $R^3 = H$ $R^1 = R^2 = R^3 = C_6H_5CO$	B (2.2 equiv. CDI, $ClCH_2CH_2Cl$)	43 22	[202]
	$R^1 = R^2 = C_6H_5CO$, $R^3 = H$ $R^1 = R^2 = R^3 = C_6H_5CO$	B (2.4 equiv. CDI, $ClCH_2CH_2Cl$)	75 15	[189]
	R = 	A (ImNa, DMF)	90	[203]

Table 3–11. (*continued*)

Carbohydrate R,R^1,R^2,R^3 = H	Acylated carbohydrate	Method	Yield (%)	Ref.
	$R^1 = R^2 = R^3 = H$, R^4 = 	A (1 equiv. CDI/ ImNa, dioxane)	63	[204]
	R = CH_3CO	B ($ClCH_2CH_2Cl$)	78	[224]
	R = CH_3CO	B (CH_2Cl_2)	88	[212]
	$R^1 = C_{11}H_{23}CO$, $R^2 = H$ $R^1 = H$, $R^2 = C_{11}H_{23}CO$	B ($CHCl_3$)	83 6	[205]
	R = C_6H_5CO	B ($CHCl_3$)	78 61	[206] [207]
	R = C_6H_5CO	B ($CHCl_3$)	89–93	[209]
	$R^1 = C_6H_5CO$, $R^2 = H$ $R^1 = H$, $R^2 = C_6H_5CO$ $R^1 = R^2 = C_6H_5CO$	B ($CHCl_3$)	30 45 6	[208]
	R = C_6H_5CO	B ($CHCl_3$)	48	[213]
	$R^1 = H$, $R^2 = C_6H_5CO$ $R^1 = C_6H_5CO$, $R^2 = H$	B	40 12	[210]
	$R^1 = H$, $R^2 = C_6H_5CO$ $R^1 = R^2 = C_6H_5CO$	B ($CHCl_3$)	81 3	[215]

(*continued*)

Table 3–11. (*continued*)

Carbohydrate R,R^1,R^2,R = H	Acylated carbohydrate	Method	Yield (%)	Ref.
	$R^1 = H, R^2 = C_6H_5CO$ $R^1 = R^2 = C_6H_5CO$	B ($CHCl_3$)	81 3	[215]
	$R = C_6H_5CO$	B (CsF, DMF)	65	[217] see also [225]
	$R = C_6H_5CO$	B ($CHCl_3$)	56	[216]
	$R = CO(CH_2)_5CO$-β-anthryl	A (CH_2Cl_2)	31	[218]
	$R = C_6H_5CO$	B ($CHCl_3$)	75	[220]
	$R = CH_3CO$	B ($CHCl_3$)	76	[223]

Remarks to Table 3–11: In ref. [203] the reaction time with base as catalyst was 3 h, without base 15 h. In ref. [204] the order of reactivity for the secondary OH groups in α-methyl-D-glucopyranoside was found to be 2-OH > 3-OH > 4-OH. The primary OH group (6-OH) was more reactive than the secondary one. The selective acylation is thought to be due to the formation of intramolecular hydrogen bonds. In ref. [206] the azolide method, in contrast to other benzoylation procedures, revealed a high degree of discrimination between the hydroxyl groups at C-2 and C-3, leading to exclusive for-

mation of the 2-benzoate. In ref. [209] the reaction with benzoyl chloride/pyridine was reported to give a mixture of 3-benzoate as the main product, with 2-benzoate, dibenzoate, and starting material. If in ref. [217] benzoyl chloride or benzoic anhydride is used for the benzoylation, a significant amount of the other isomeric monobenzoate is formed as well.

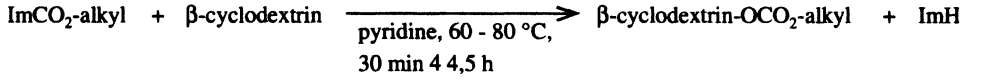
3.7 Carboxylic and Carbonic Esters of Polysaccharides

Ester formation from polysaccharides can be achieved in several ways: First by acylation of the OH groups with carboxylic or sulfonic acid azolides, second by converting the OH groups with imidazole carboxylates into carbonates, and third by reaction of an acid "leash" on the polysaccharide with an alcohol by means of CDI or analogous azolides. The acid leash might, for example, be a succinate attached to the polysaccharide.

Starch esters have been obtained by reactions of starch and carboxylic or sulfonic acid imidazolides in aqueous NaOH or nonaqueous solutions, as described in reference [226]. The esterification of dextran with butyric or palmitic acid using CDI in DMSO or formamide is discussed in reference [174].

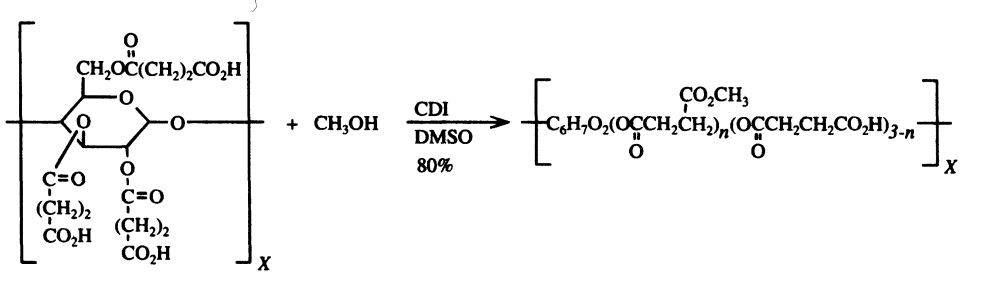
Carbonates of β-cyclodextrin are prepared with imidazole carboxylates:

Yields of carbonates are good ($\sim$80%, degree of substitution 4.2-5.7) with the



exception of the methoxycarbonyl derivative ($\sim$50%). It was not possible in this case to obtain complete substitution of the hydroxy groups of the β-cyclodextrin even by using a large excess of the alkoxy-carbonylating agent.[227]

The esterification of dextrantrisuccinate is illustrated by the following example.[228]



The required imidazolide in this reaction could also be prepared from imidazole and dicyclohexylcarbodiimide. The latter method was used for preparation of the fairly stable

benzotriazolides (97%), which are soluble in chloroform and therefore easier to deal with than the imidazolides in DMSO.

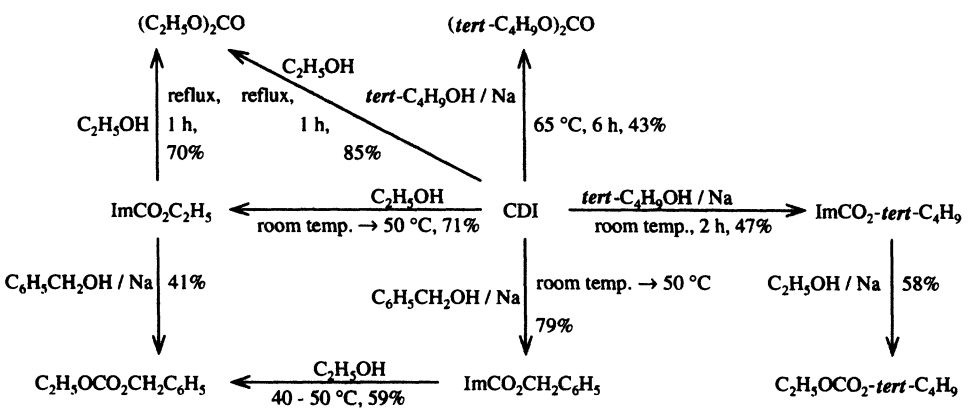
3.8 Syntheses of Carbonic Esters (Carbonates)

The reaction of CDI with a single mole of alcohol yields imidazole-*N*-carboxylates,[229]–[231] which by reaction with a second mole of alcohol lead to carbonic esters. With bifunctional alcohols CDI yields polycarbonic esters.[1],[232]

3.8.1 Acyclic Carbonic Esters

CDI reacts with alcohols and phenols via the imidazole-*N*-carboxylates to give the diesters of carbonic acid (carbonates).

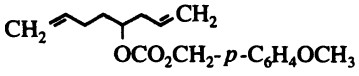
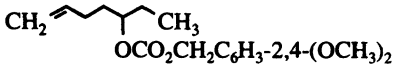
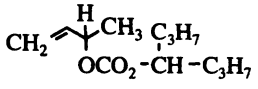
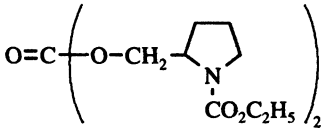
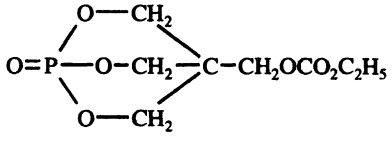
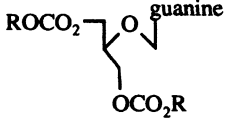
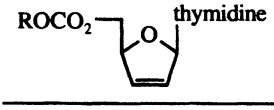
By adding one equivalent of alcohol to CDI at room temperature with or without base it is possible to isolate the imidazole-*N*-carboxylate, which then reacts with a second mole of ROH to yield the carbonate. As in the case of alcoholysis of imidazolides, the reaction can be accelerated so effectively with catalytic amounts of $NaOC_2H_5$ or ImNa that it takes place in most cases exothermically, even at room temperature. However, *tert*-butyl alcohol, even when in excess, affords with CDI and base catalysis at room temperature only the imidazole-*N*-*tert*-butylcarboxylate, obviously for steric reasons. At higher temperature the carbonic ester is formed. Mixed carbonates such as ethyl benzyl carbonate or ethyl *tert*-butyl carbonate can be prepared with two different alcohols added sequentially.[9],[229]



Imidazole-*N*-carboxylates can also be prepared from imidazole and chloroformate.[229]

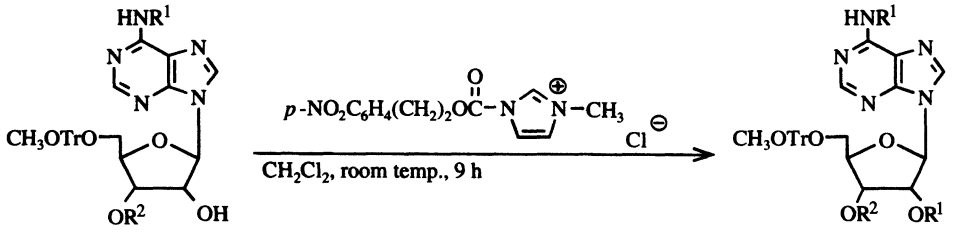
The solvents used for preparing carbonates from alcohols and CDI are THF, DMF, benzene, toluene, chloroform, 2-butanone, and pyridine. It is also possible to carry out the reaction without solvent. A collection of acyclic carbonates is given in Table 3–12.

Table 3-12. Acyclic carbonates.

		Yield (%)	Ref.
		33	[233]
		50	[233]
		76	[234]
		72	[235]
		25	[236]
	R = CH_3	72	[237]
		34	[237]
	C_4H_9	30	[237]
	$CH_3(CH_2)_7$	54	[237]
	R = CH_3	46	[238]
	R = *c*-C_6H_{11}	79	[238]

Further examples referred to unsymmetrical carbonic esters of interest are treated below.

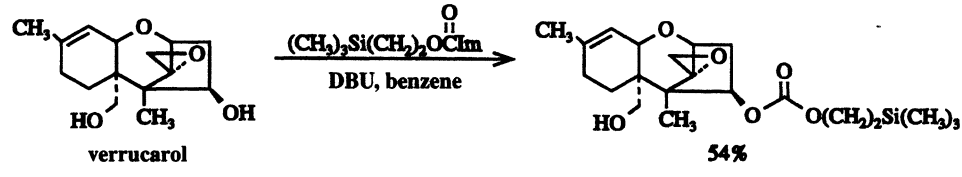
An interesting synthesis of a nucleoside carbonic ester was conducted in excellent yield by reaction with 1-methyl-3-[2-(*p*-nitrophenyl)ethoxycarbonyl]-imidazolium chloride (for an analogous introduction of the npeoc-protecting group, see also Section 3.10.1);[239] as mentioned in Section 3.1.8, methylation of the imidazole unit increases significantly the reaction rate.



$R^1 = p\text{-}NO_2C_6H_4(CH_2)_2OC(=O)$

$R^2 = CH_3CO(CH_2)_2CO_2(CH_2)_{11}$

In a one-to-one ratio the reaction of CDI with $(CH_3)_3Si(CH_2)_2OH$ gave the corresponding imidazole carboxylate (97% yield), which was used in a selective protection of verrucarol, the parent compound of mycotoxines, as follows:[240]



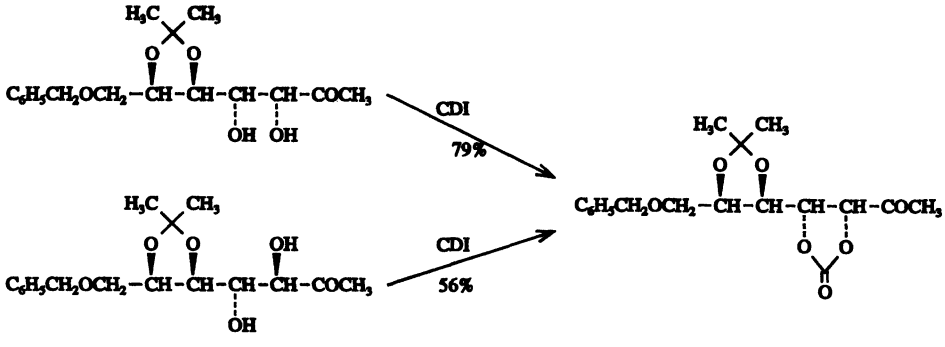
In a reaction of CDI with 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-desmethyl-6-*O*-methylerythromycin A the corresponding imidazolecarboxylate (K_2CO_3, THF, 36% yield) was formed, which yielded in a further reaction with $C_6H_5CH_2OH$ the 4′-benzyloxycarbonic ester of this erythromycin A analogue in 40% yield.[241]

3.8.2 Cyclic Carbonic Esters

Cyclic carbonic esters can be readily obtained from 1,2-diols and CDI.[242]–[254] Apart from the observed high yields, the procedure is so straightforward that it undoubtedly constitutes the method of choice for compounds of this type. The procedure offers the advantages of mildness, simplicity, and absence of by-products other than imidazole,

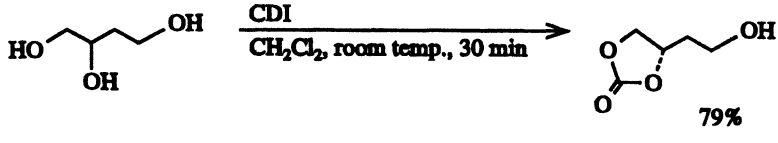
which is water soluble and easily removable from the desired product.[245] It also provides high yields in cases where no cyclic carbonic esters could be obtained with ethyl chloroformate even under vigorous conditions.[245] Cyclic carbonates are widely used as protecting agents for vicinal hydroxyl groups, especially in the field of carbohydrate chemistry. They are base labile, but relatively stable under acidic conditions.[248] The reaction occurs most readily with *cis*-1,2-diols whereas, for example, *trans*-acenaphthenediol provided a cyclic carbonic ester only in low yield.[245]

Preferred formation of the *cis*-carbonic ester is demonstrated by the following example:[248]



The best procedure for obtaining a cyclic carbonic ester requires that CDI (4 equiv.) be added gradually over a period of ca. eight hours during refluxing of the reaction mixture. However, it was found in the case of *cis*-cyclohexane diol that if the diol and CDI are dissolved together in benzene and the solution heated under reflux, the bis(imidazole-*N*-carboxylate) is obtained instead of the cyclic carbonic ester.[245]

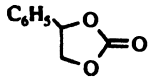
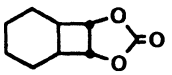
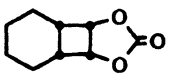
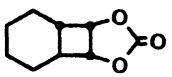
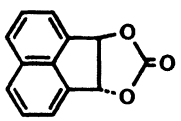
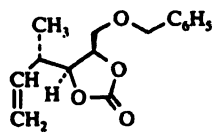
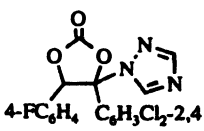
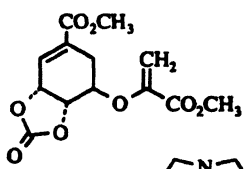
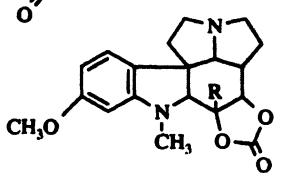
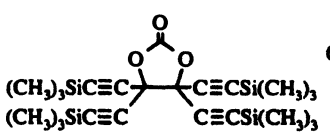
A cyclic carbonate was utilized as a protecting group for the *cis*-diol system in butane-1,2,4-triol:

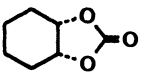
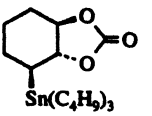
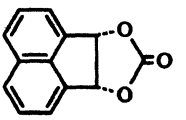
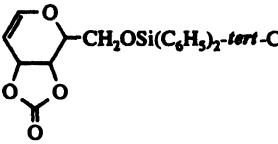
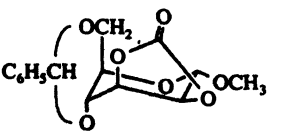
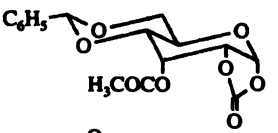
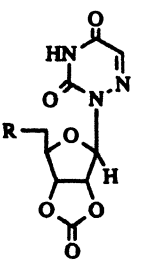
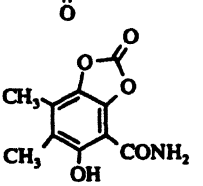


The five-membered 1,2-cyclic carbonate was isolated as the only product (regio-selective protection of the vicinal diol system).[255] Analogous formation of a cyclic carbonate containing a secondary hydroxy group is described in reference [256].

Further examples of cyclic carbonates are collected in Table 3–13.

Table 3–13. Cyclic carbonic esters obtained by the reaction of 1,2-diols with CDI.

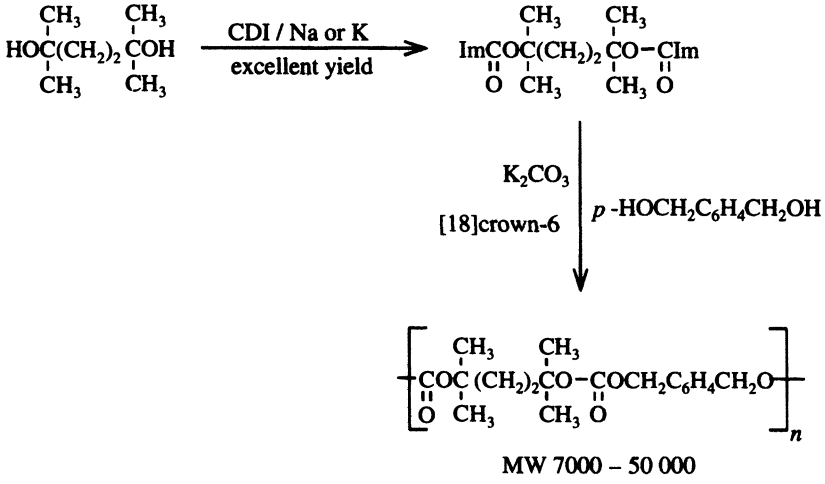
Product	Yield (%)	Ref.
	64	[242]
	85	[243]
	97	[243]
	84	[243]
	20	[245]
	76	[246]
	79	[250]
	95	[244]
	92	[245]
	68	[251a]

Product	Yield (%)	Ref.
	94	[245]
	96	[247]
	95	[245]
	74	[254]
	80	[245]
	90	[249]
	R = $(C_6H_5)_3CO$ 89 R = H 81 R = CH_3SO_2O 60	[252] [253] [253]
	80	[251]

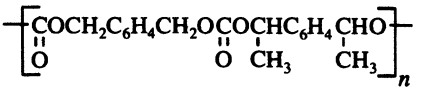
Cyclic carbonic esters were also prepared, for example, from the cardiac glycoside proscillaridine[257] (where besides CDI the benzyloxycarbonylimidazole was successfully used), ingenol,[258] the macrolide antibiotic tylosine,[259] and an erythromycin A derivative.[260]

3.8.3 Polycarbonates

With bifunctional alcohols CDI yields polycarbonates.[5] Syntheses of polycarbonates based on the CDI-method in a solid/liquid phase-transfer catalyzed reaction are described in references [261]–[263].



Analogously prepared:



The synthesis of copolycarbonates from 2,5-dimethyl-2,5-hexanediol and bis(hydroxymethyl)benzene was also achieved by this method.[264]

If in the synthesis of carbonic esters with CDI one alcohol component is replaced by a hydroperoxide, peroxycarbonates are formed.[265] More details on this reaction are given in Section 3.11.

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4 Syntheses of Amides and Analogous Compounds with CO–NR Functions

4.1 Amides and Imides

4.1.1 Amides from Imidazolides and Amines

Amides are conveniently prepared by the azolide method, usually in two steps: first by reaction of the free carboxylic acid at room temperature with CDI in a 1 : 1 molar ratio under elimination of CO_2 the carboxylic acid imidazolide is formed; after CO_2 evolution has ceased an equimolar amount of amine is then added.[1]

$$RCO_2H + ImCOIm \longrightarrow RCOIm + ImH + CO_2$$

$$RCOIm + HNR^1R^2 \longrightarrow RCONR^1R^2 + ImH$$

The reaction is complete after one to two hours at room temperature. Amides are usually obtained in very good yields. A wide range of solvents can be used, including tetrahydrofuran, chloroform, acetonitrile, dimethylformamide, and benzene.[2] The reaction can also be carried out in the melt. Examples have been collected in the following pages. In some cases the intermediate imidazolides were isolated, but the reactions are preferably carried out as "one-pot reactions".

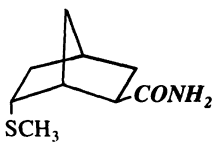
Instead of CDI, analogues like *N,N'*-thiocarbonyldiimidazole (ImCSIm), *N,N'*-sulfinyldiimidazole (ImSOIm), or *N,N'*-oxalyldiimidazole (ImCOCOIm) have been used for forming the azolides.

For the aminolysis of *N*-acylimidazoles in dry tetrahydrofuran a bimolecular reaction is suggested. The rate constant for conversion of *N*-acetylimidazole with an ammonia-saturated solution in tetrahydrofuran at 25 °C was found to be $0.01\ min^{-1}$, with $\tau_{1/2} = 69.3$ min.[3]

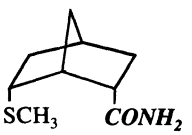
The reaction with *N*-acetyltriazole is about a hundred times faster; for example the rate constant of its reaction with dry ammonia saturated in tetrahydrofuran is $k = 0.95\ min^{-1}$, with $\tau_{1/2} \sim 0.73 \pm 0.015$ min.[3] (For other reactions with triazolides see Section 4.1.2.)

1.) Amides prepared from carboxylic acids and ammonia using CDI. Yields refer to reaction of the azolides with ammonia.

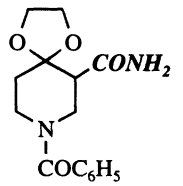
Examples:



73% [4]

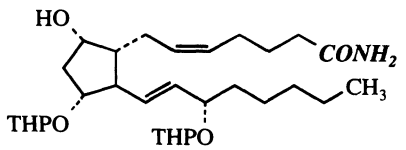


75% [4]

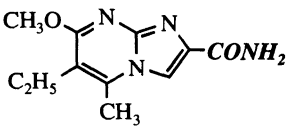


quant. [5]

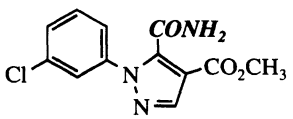
32% [6]



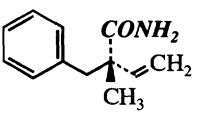
69% [7]



90% [8]

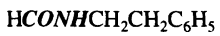


61% [9]



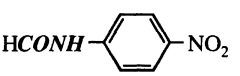
95% [10]

2.) Amides prepared from carboxylic acids and primary amines using CDI.
Examples:

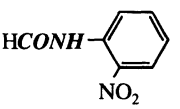


81% [11]

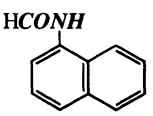
67% [11]



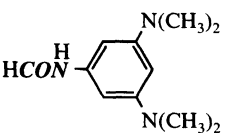
70% [11]



84% [11]



82% [11]



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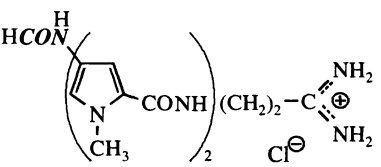
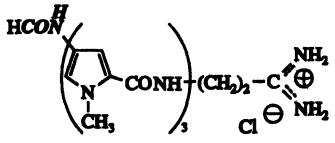
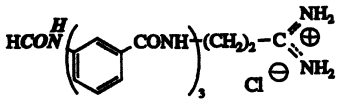


70% [13]



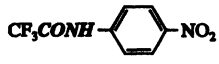
71% [13]



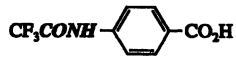
51% [14]

83% [3]

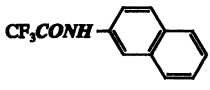
83% [15]



84% [15]

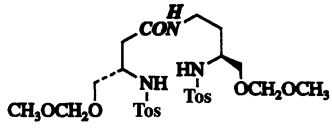


78% [15]

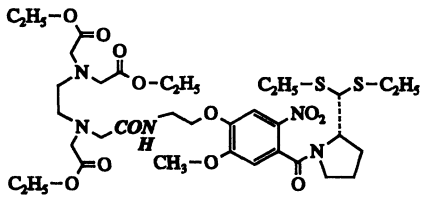


83% [15]

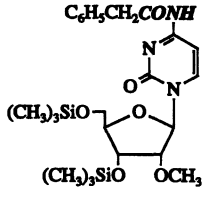
90% [15]



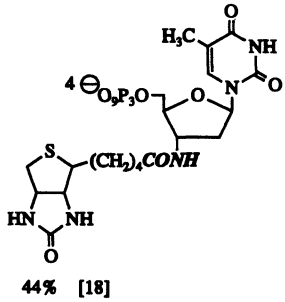
70% [16]



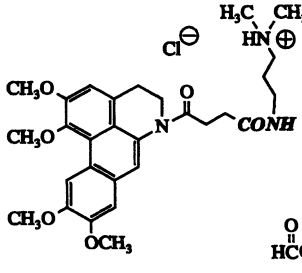
84% [16a]



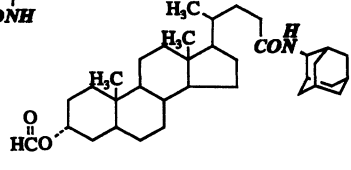
90% [17]
(after desilylation)



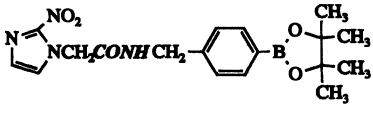
44% [18]



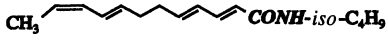
84% [19]



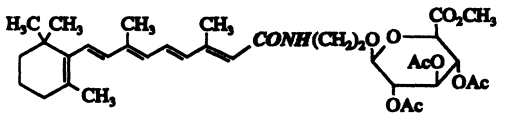
78% [20]



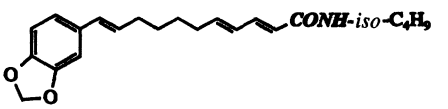
21% [21]



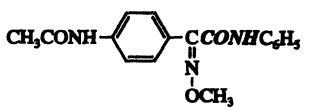
52% [22]



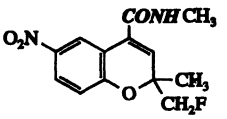
29% [23]



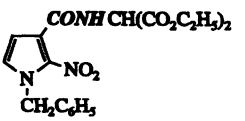
89% [24]



quant. [25]

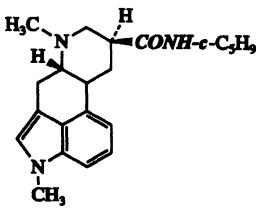


86% [26]



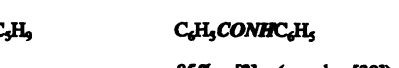
96% [27]

71% [28]

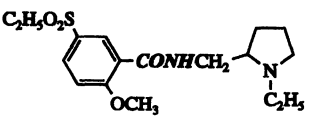


N^1-methyl-D-dihydrolysergic acid amide

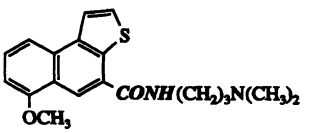
85% [29]



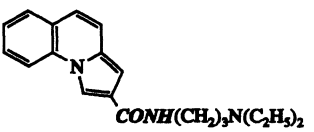
85% [2] (see also [30])



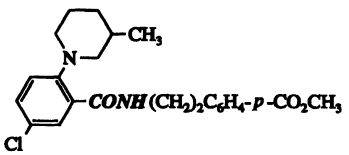
72% [31]



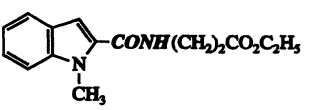
41% [32]



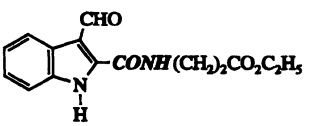
92% [33]



51% [34]

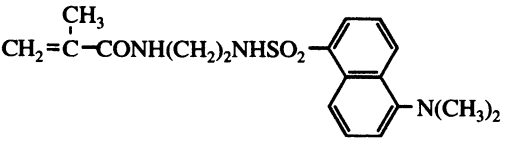


70% [35]

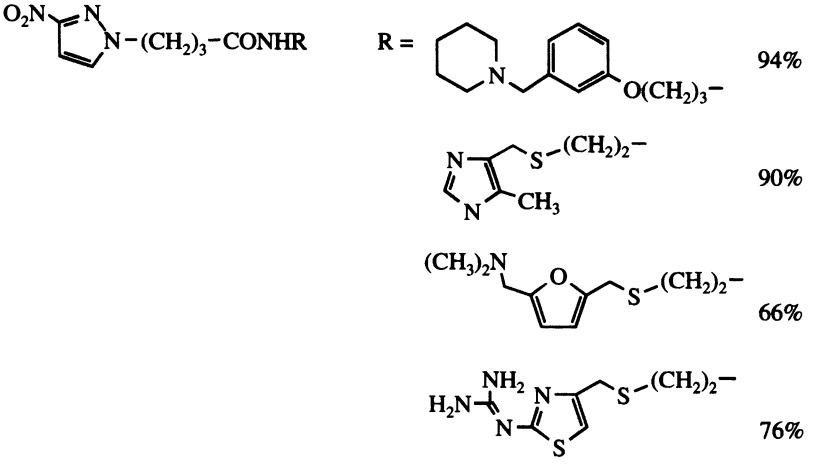


42% [35]

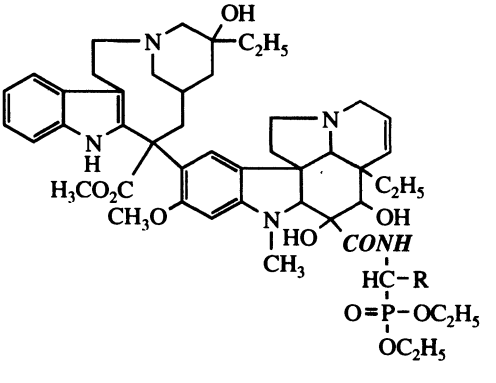
In the condensation of methacrylic acid and *N*-dansylethylenediamine to give the corresponding methacrylamide in 19% yield (part of the monomer polymerized during the purification process), the methacryloylimidazole prepared from the acid with CDI proved to be more efficient than methacryloyl chloride:[36]



The following amides prepared from 4-(3-nitro-1-pyrazolyl)butanoic acid, CDI, and primary amines represent partial structures of the histamine H_2-receptor antagonists roxatidine, cimetidine, ranitidine, and famotidine:[37]



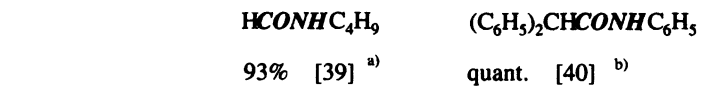
Other amides with very complicated structures, including the following amides of the alkaloid vinblastoic acid, could also be synthesized with CDI:[38]



R	Yield (%)
H	50
iso-C_3H_7	35

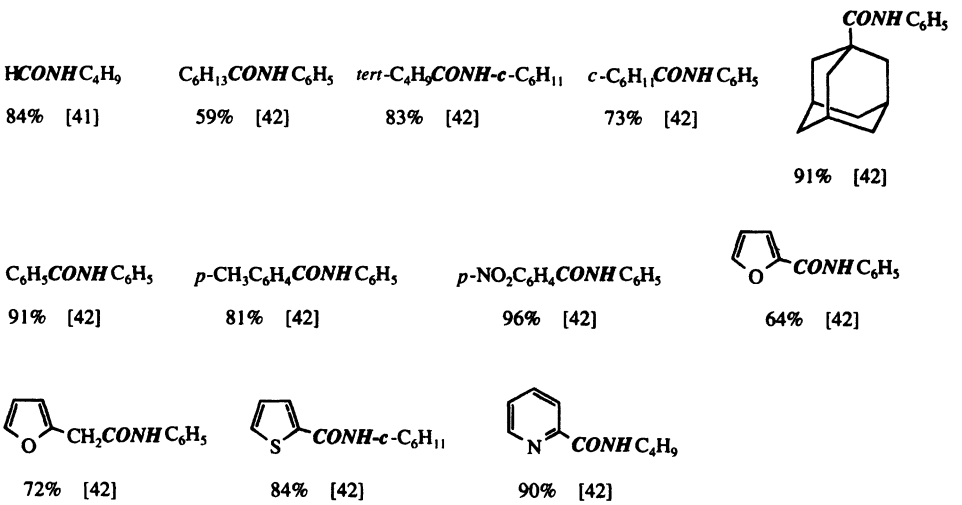
3.) Amides prepared from carboxylic acids and primary amines using azolides obtained from acid chloride/imidazole[a] or ketene/imidazole systems.[b]

Examples:



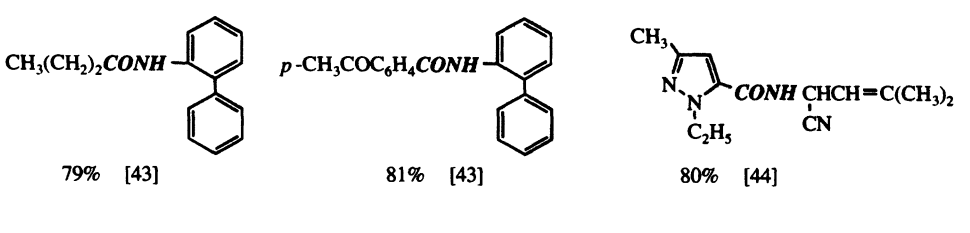
4.) Amides prepared from carboxylic acids and primary amines using *N,N'*-oxalyldiimidazole (ImCOCOIm).

Examples:



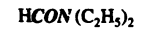
5.) Amides prepared from carboxylic acids and primary amines using *N,N'*-sulfinyldiimidazole (ImSOIm) or phenoxyphosphoryldiimidazole ($Im_2P(O)(OC_6H_5)$)*.

Examples:

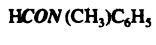


6.) Amides prepared from carboxylic acids and secondary amines using CDI.

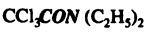
Examples:



72% [11]

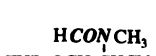


64% [11]



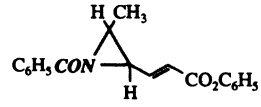
82% [15]

87% [15]

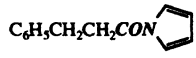


84% [46]

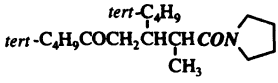
quant. [47]*



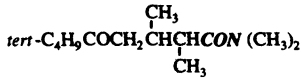
57% (mixture) [48]



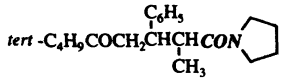
72% [48a]



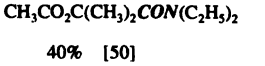
80% [49]



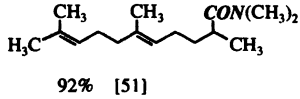
65% [49]



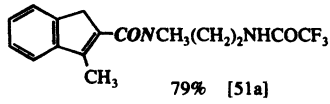
quant. [49]



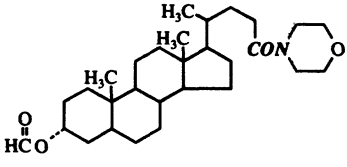
40% [50]



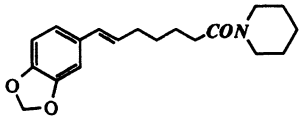
92% [51]



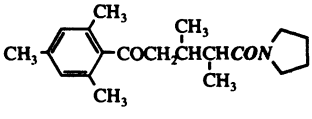
79% [51a]



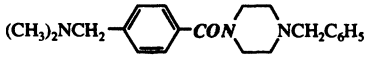
65% [52]



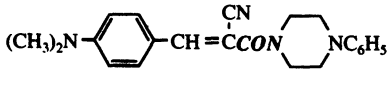
90% [24]



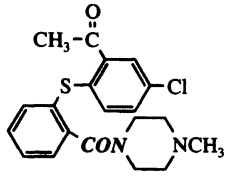
82% [53]



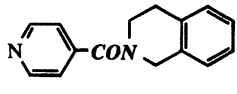
43% [54]



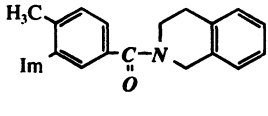
83% [55]



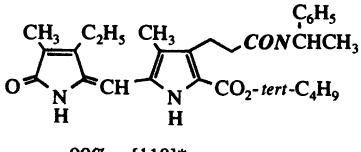
75% [56]



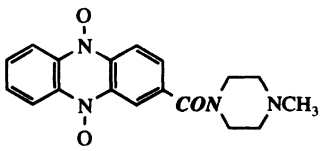
90% [57]



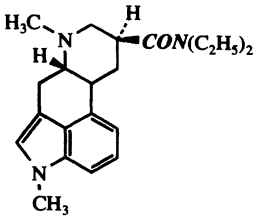
96% [58]



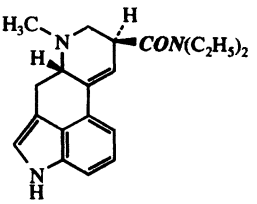
90% [118]*



72% [59]



N^1-methyl-D-dihydrolysergic acid amide
99% [29]



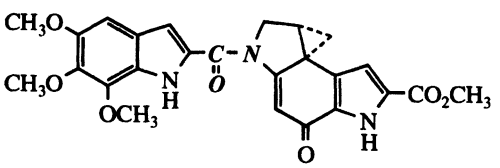
D-lysergic acid amide
81% [29]
mixture of lysergic and isolysergic acid amides

* Further examples are given in the references cited.

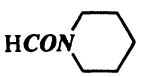
In the preparation of the oxocarboxylic acid imidazolides in ref. [49] and [53], as well as in their aminolysis, the stereochemical integrity was maintained.

Because of the easy conversion of *N*-acylaziridines[47] into oxazolines, this method is also useful for protecting carboxylic acids; furthermore, it is a means for resolving chiral carboxylic acids.

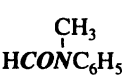
The last step of the total synthesis of natural (+)-duocarmycin SA, a potent antitumor antibiotic, was accomplished by forming the amide bond with CDI in 74% yield:[60]



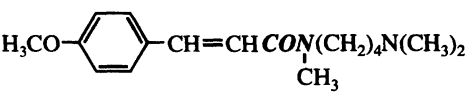
7.) Amides prepared from secondary amines and acylchloride/imidazole,[39] carboxylic acid/oxalyldiimidazole,[41] carboxylic acid/sulfinyldiimidazole[61] or isolated imidazolide.[62]



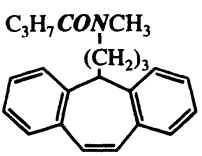
83% [39]
98% [41]



92% [41]



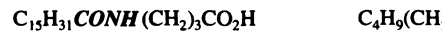
30% [61]



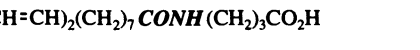
86% [62]

8.) Amides prepared from carboxylic acids and amines containing other reactive groups (OH, CO_2H) by using CDI.

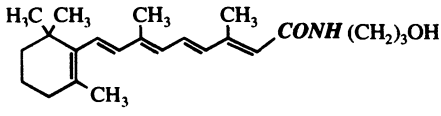
Examples:



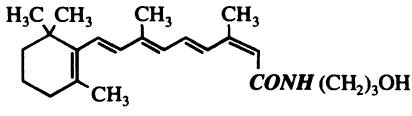
78% [68]



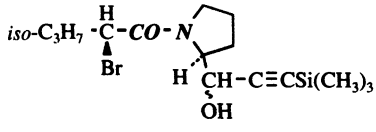
61% [69]



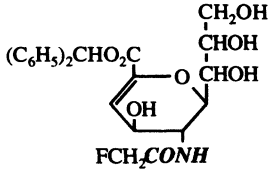
65% [63]



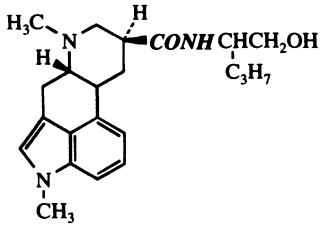
66% [63]



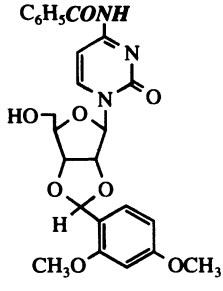
56% [64]



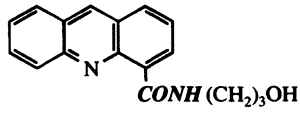
79% [65]



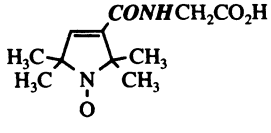
N^{1}-methyl-D-dihydrolysergic acid amide 94% [29]



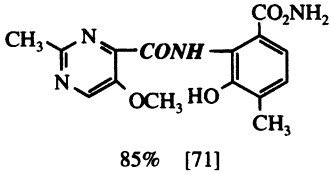
69% [66]



98% [67]



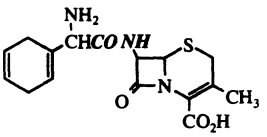
40% [70]



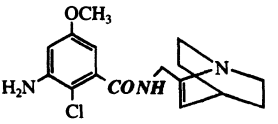
85% [71]

9.) Amides prepared from OH- or NH-containing carboxylic acids and amines by using CDI.

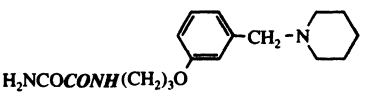
Examples:



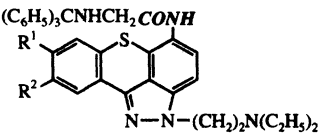
92% [72]



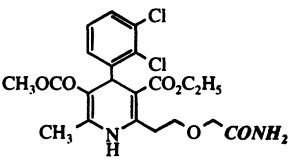
47% [73]



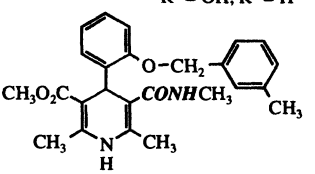
72% [74]



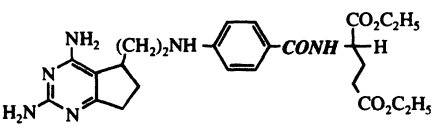
$R^1 = H, R^2 = OH$ 73% [74a]
$R^1 = R^2 = H$ 77% [74a]
$R^1 = OH, R^2 = H$ 81% [74a]



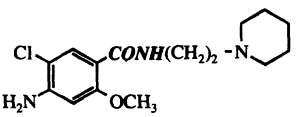
87% [75]



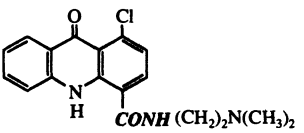
40% [76]



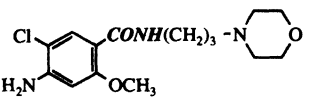
31% [77]



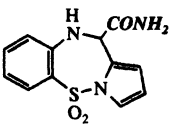
32% [78]



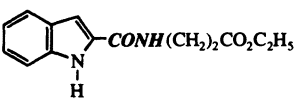
87% [79]



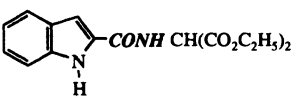
58% [80]



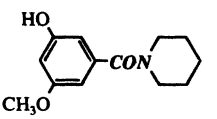
50% [81]



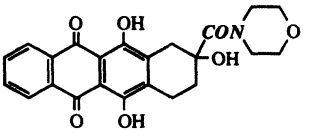
88% [35]



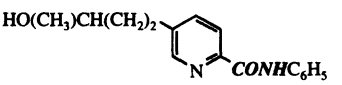
88% [35]



85% [82]



56% [83]



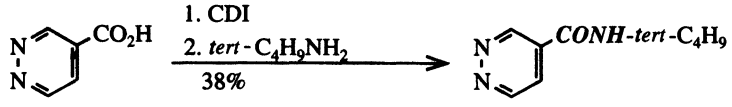
46% [84]

90% [85]

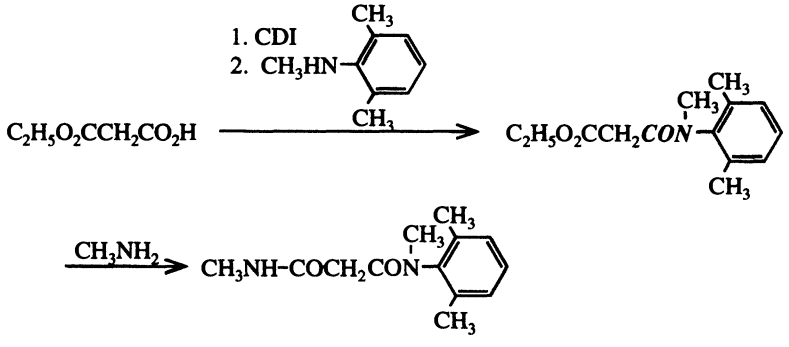
In addition to the amides described in ref. [72], further examples prepared by means of CDI from amino compounds of the cephalosporin or penicillin type, and various heterocyclic carboxylic acids, are reported in ref. [86] and [87] and ref. [88] and [89], respectively.

Sterically Crowded Amides

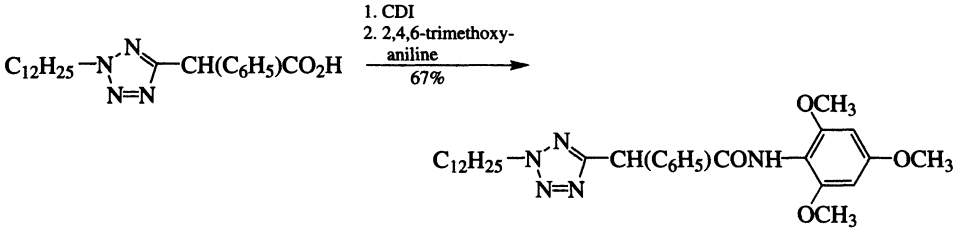
Condensation of 4-pyridazinecarboxylic acid with *tert*-butylamine and CDI opens the way to the corresponding sterically hindered *N-tert*-butylcarboxamide:[28]



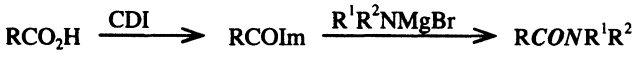
Still more crowded amides were prepared with *N*-methyl-2,6-xylidine as the amino component[28a] or with 2,4,6-trimethoxyaniline:[28b]



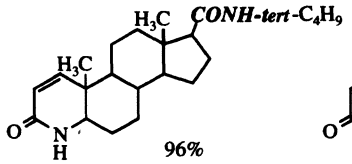
40% overall yield



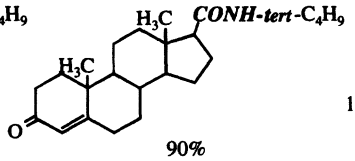
For the preparation of sterically crowded amides amino magnesium salts have been recommended for the reaction with imidazolides in order to increase the nucleophilicity of the amine moiety. Amino magnesium salts are prepared from the appropriate amines and ethyl magnesium bromide in tetrahydrofuran:[90]



The following are further examples of amides prepared from carboxylic acids/CDI and primary amines activated by magnesium salts (additional examples are reported in ref. [90]):



96%



90%

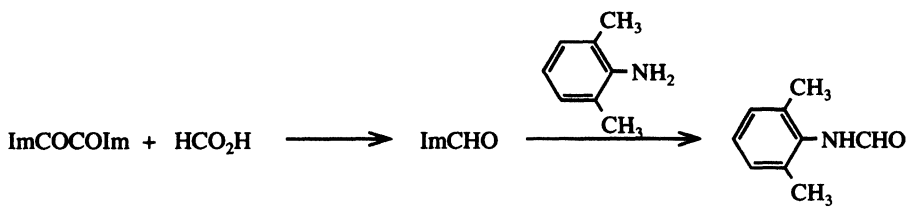
88%

82%

92%

This method also provides the amide from the reaction of diethylamine with the Δ^1-4-aza-5α-androsten-3-keto-17-carboxylic acid in 92% yield.[90]

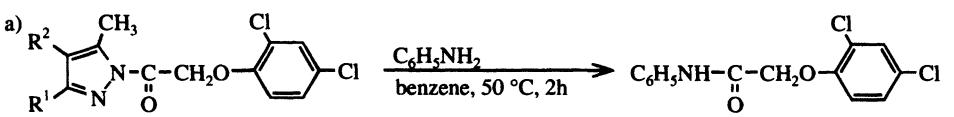
Sterically hindered amines like 2,6-dimethylaniline can be formylated with *N*-formylimidazole in excellent yield starting from formic acid and *N,N'*-oxalyldiimidazole:[41]



93%

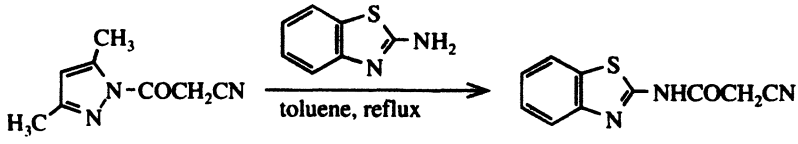
4.1.2 Syntheses of Amides with Other Azolides

1. *Pyrazolides* with various substituents are sufficiently reactive to yield amides in very good yields:



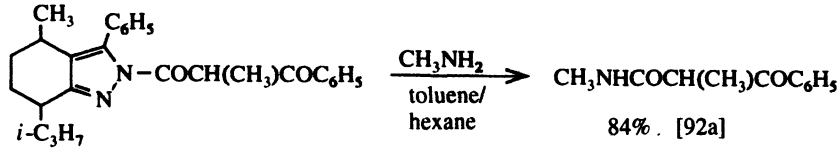
R^1	R^2	Yield (%)	Ref.
CH_3	H	74	[91]
CH_3	NO_2	87	[91]
C_6H_5	H	94	[91]
C_2H_5O	H	89	[91]

b)



91% [92]

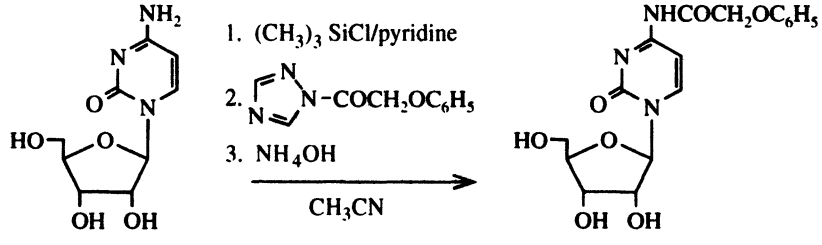
c)



84%. [92a]

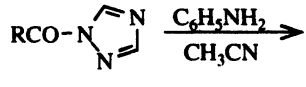
2. Examples of amide syntheses based on the more reactive *triazolides* are presented below:

a) An efficient synthesis of *N*-protected ribonucleosides like cytidine or adenosine was performed by use of 1-phenoxyacetyl-1,2,4-triazole under additional application of the transient protection of the sugar OH-groups by silylation.[93]



88%

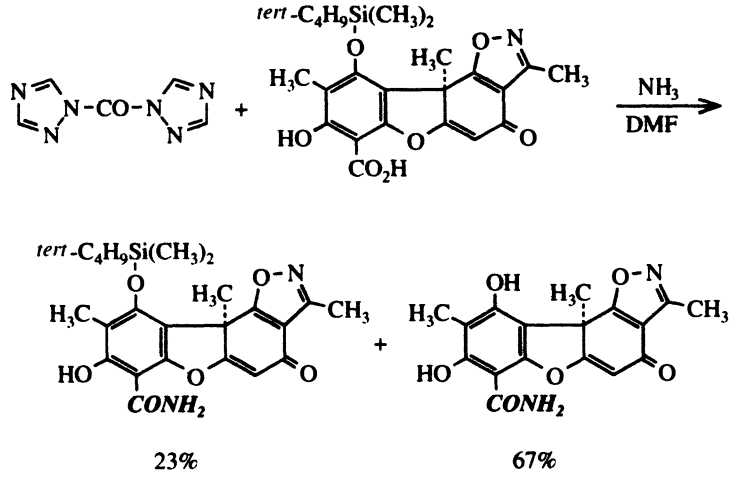
b)



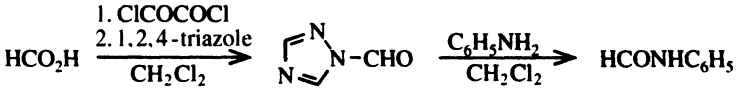
from RCO_2H and oxalydi(1,2,4-triazole)

R	Yield (%) [42]
C_6H_{13}	88
tert-C_4H_9	80
c-C_6H_{11}	67
C_6H_5	83

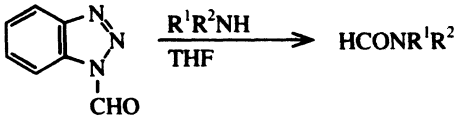
c) In the synthesis of 8-methylcercosporamide, an amidation was achieved using *N,N'*-carbonyldi-1,2,4-triazole and NH_3, the tert-butyldimethylsilyl group predominantly is split off in this reaction.[94]



d) Formylation of amines is feasible in a one-pot reaction via N^1-formyltriazole, prepared from formic acid, oxalyldichloride and 1,2,4-triazole (overall yield 82%).[39] However, the combination of imidazole/triethylamine instead of the triazole gave a higher yield (95%).

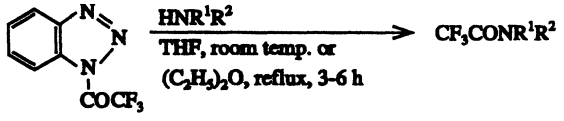


e) N^1-Formylbenzotriazole was demonstrated in a series of reactions to be a convenient *N*-formylating agent.[95]



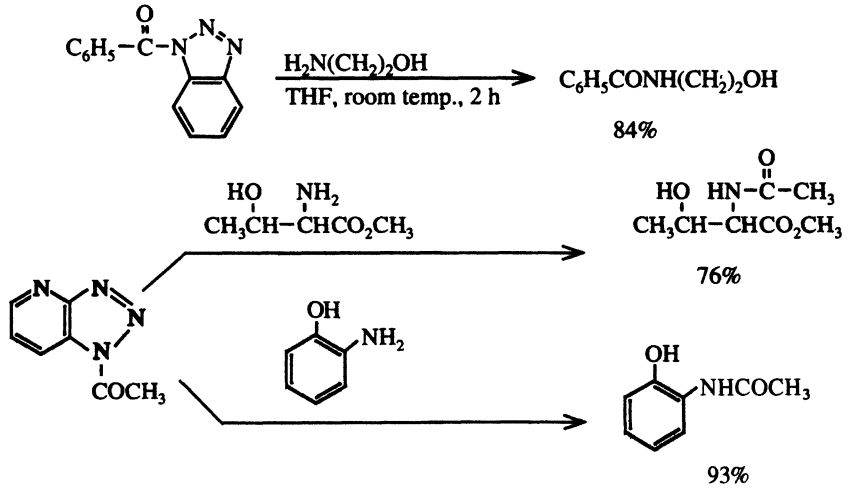
R^1	R^2	Yield (%)
C_2H_5	C_2H_5	78
$C_6H_5CH_2$	H	84
C_6H_5	H	59
2-thiazolyl	H	78

As for the reaction with alcohols N^1-trifluoroacetylbenzotriazole is conveniently used for trifluoroacetylation of primary or secondary alkyl or aryl amines to give excellent yields of trifluoroacetamides:[95a]

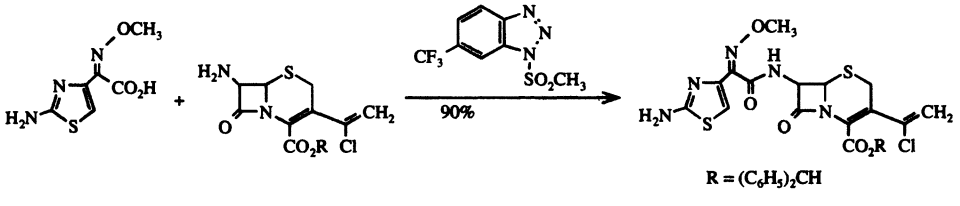


R^1	R^2	Yield (%)
$C_6H_5CH_2CH_2$	H	100
$(CH_3)_3C$	H	95
4-$NO_2C_6H_4$	H	90
C_6H_5	C_2H_5	85

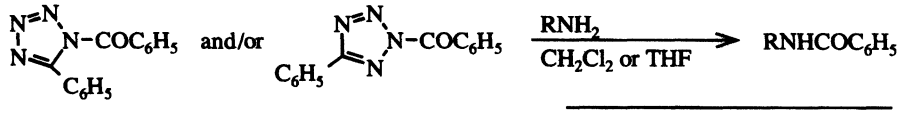
f) 2-Aminoethanol, derivatives thereof, other aminoalcohols or aminophenols are selectively acylated at the nitrogen with N^1-benzoyl- or trifluoroacetyl-benzotriazole[96][95a] and N^1-acetylpyridinotriazole.[97]



g) In the amide synthesis by means of a N^1-methylsulfonylbenzotriazole as condensing agent a mixed anhydride is presumably formed as the intermediate acylating agent.[98]



3. A wide array of aliphatic and aromatic amines has been converted to amides in very high yields by the particularly reactive *tetrazolides*. The reaction temperature was 10 °C to 20 °C. Higher temperatures (refluxing THF) should be avoided because of instability of the tetrazolide, which in this case was prepared from benzoyl chloride and phenyltetrazole in 68% yield.[99],[100]



R	Yield (%)	Ref.
C_6H_5	99	[99]
p-$NO_2C_6H_4$	34	[100]
2-$C_{10}H_7$	67	[100]
C_4H_9	99	[99]

4.1.3 Amides of Amino Acids

Amides of Amino Acids Involving the Carboxyl Group

Examples are given in Table 4–1 for the synthesis of amides of *N*-protected amino acids by means of imidazolides and triazolides (where *Z* and Boc represent the protecting groups benzyloxycarbonyl and *tert*-butoxycarbonyl):

TABLE 4–1. Amides of *N*-protected amino acids.

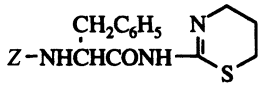
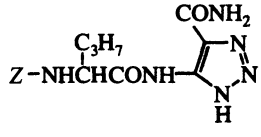
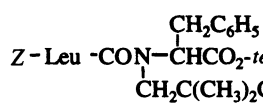
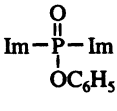
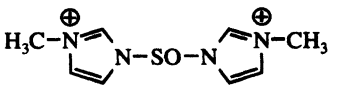
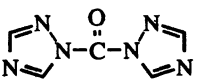
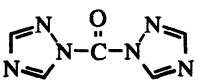
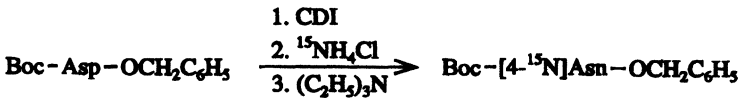
Amide	Coupling agent	Yield (%)	Ref.
	CDI	84	[101]
	CDI	72	[101]
	CDI	51	[101a]
Z-NHCH$_2$CONHC$_6$H$_4$-p-CO$_2$C$_2$H$_5$	CDI	95	[102]*
Boc-NH(CH$_2$)$_3$N(Z)(CH$_2$)$_2$CONH-c-C$_6$H$_{11}$	CDI	87	[103]
	CDI	26	[104]
		92	[45]

Table 4–1. (*Continued*)

Amide	Coupling agent	Yield (%)	Ref.
$Z\text{-NHCHCONH-}c\text{-}C_6H_{11}$ (CH$_2$C$_6$H$_5$)		72	[105]
$Z\text{-Gly-NHC}_6H_5$		85	[106]
$Z\text{-Gly-NH-}c\text{-}C_6H_{11}$		81	[106]

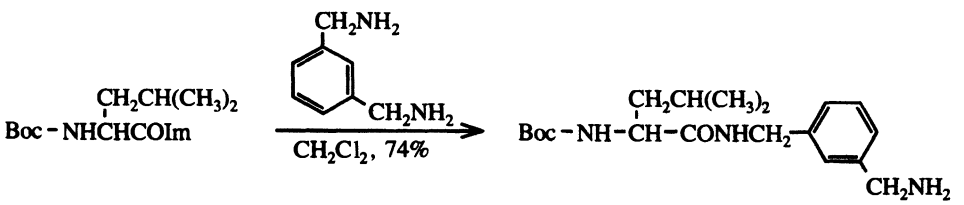
* Further examples are described in the references cited

^{15}N-labelling of amino acids was achieved via the amino acid imidazolides:[107]

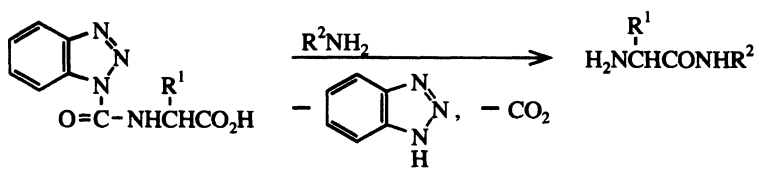


The same method was used to prepare Boc-[5-^{15}N]Gln-$OCH_2C_6H_5$ in 54% yield[107] and Boc-$NHCH_2CO^{15}NH_2$ in 77% yield.[108]

The reaction of an amino acid imidazolide with a diamino compound could be directed so that a mono amide was obtained in good yield,[109] as shown by the following example:



Another method for the synthesis of amino-acid amides entails the conversion of *N*-(1-benzotriazolylcarbonyl) amino acids with amines in anhydrous or aqueous systems:[110]



R^1	R^2	Yield of amide (%)
C_6H_5	$C_6H_5CH_2$	78
$C_6H_5CH_2$	$CH_3S(CH_2)_2CH(CH_2OH)-$	63
CH_3	*c*-C_6H_{11}	93

The reaction mechanism was not discussed by the authors.

Amides of Amino Acids Involving the Amino Group (*N*-Acylamino Acids)

Examples of amides of this type synthesized via azolides are presented in Table 4–2.

Table 4–2. *N*-Acylamino acid esters.

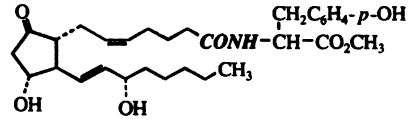
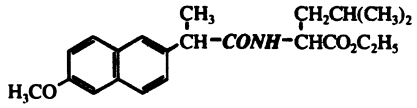
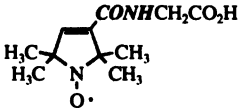
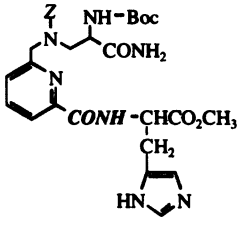
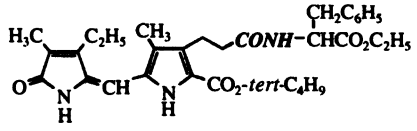
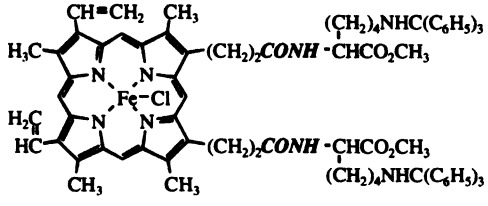
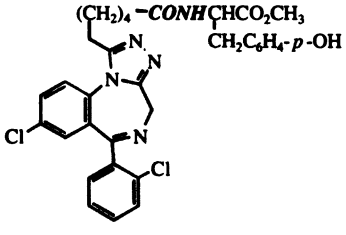
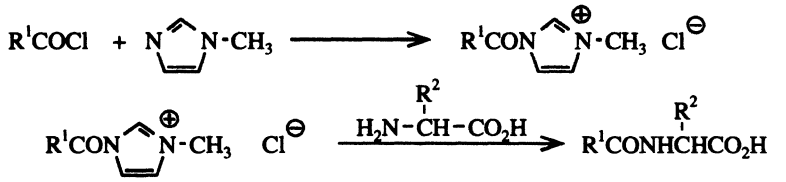
Amide	Coupling agent	Yield (%)	Ref.
$CF_3CONHCH_2CO_2C_2H_5$	CDI	51	[15]
p-$CH_3C_6H_4SO_2OCH_2CH(CH_3CONH)CO_2CH_3$	CH_3COCl/ImH	40	[111]
Boc-$NH(CH_2)_3N(Boc)(CH_2)_2CONHCH(CH_3)CONHC_3H_7$	CDI	77	[103]
$CH_3CONH-C(CH_3)(\triangledown)-CONH-CH(CH_2C_6H_5)CON(CH_3)_2$	CDI	87	[7]
$C_2H_5-CH(CH_3)(CH_2)_4CONH-CH((CH_2)_2-NH-Z)-CONH-CH(CHOH(CH_3))-CO_2CH_3$	CDI	71	[112]
$O(-CH_2CONH-CH(CH_2C_6H_5)CO_2C_2H_5)_2$	ImSOIm	70	[113]* see also [114]
$O(-CH_2CONH-CH(tert\text{-}C_4H_9)CONH-CH(CH_2CH(CH_3)_2)CO_2C_2H_5)_2$	CDI	quant.	[114]*
	CDI	> 40	[115]

Table 4–2. (*Continued*)

Amide	Coupling agent	Yield (%)	Ref.
	ImSOIm	85	[116]
	CDI	40	[70]
	CDI	83	[117]
	CDI	85	[118]*
	ImCSIm	53	[119]
	CDI	57	[120]

* Amides derived from other amino acids are described in the references cited

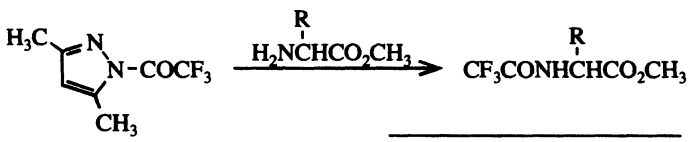
In the following examples, acylations of amino acids were accomplished with the more reactive *N*-acylimidazolium compounds in aqueous systems:[105]



R^1	Amino acid	R^2	Yield of amide (%) *
C_7H_{15}	glycine	H	quant.
C_6H_5	glycine	H	85
C_6H_5	serine	CH_2OH	35
CH_3	leucine	$CH_2CH(CH_3)_2$	88

* Additional examples are described in the references.

N-Trifluoroacetylations of amino acid esters by a pyrazolide are described in reference [121].



R	Yield (%)
H	67
CH_3	54
$CH_2CH(CH_3)_2$	65

4.1.4 Amides by Reaction with Polymer-Supported Azolides

Azolides can also be used in amide syntheses with very good results when incorporated into copolymers. For example, reactions with 1-acyl-4-vinylimidazole/divinylbenzene (96 : 4) copolymer in solvents like 1,4-dioxane or acetonitrile provide amides in good yields within 1–4 h:[122]

Table 4–3. Amides from 1-acyl-4-vinyl imidazole/divinylbenzene copolymer.

Acyl group at the polymer	Amine	Yield (%)
acetyl	$HOCH_2CH_2NH_2$	86
acetyl	*c*-$C_6H_{11}NH_2$	97
acetyl	piperidine	71
propionyl	$C_6H_5CH_2NH_2$	98
benzoyl	$C_6H_5CH_2NH_2$	84
benzoyl	piperidine	92

It is interesting that one observes exclusive *N*-acylation of ethanolamine even when the molar ratio of polymer-bound acylimidazole to amine is 1 : 2.

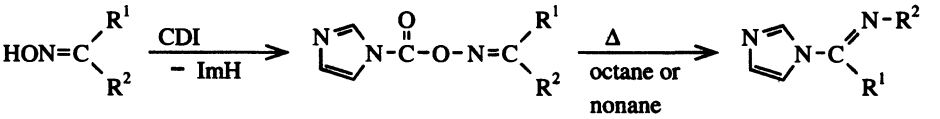
Other acylations using the copolymer 1-acyl-4-vinylimidazole/divinylbenzene/styrene (48 : 4 : 48) in solvents like 1,4-dioxane, benzene, diethylether, or acetone produce within reaction times of three hours the amide yields listed in Table 4–4.[122]

TableE 4–4. Amides from 1-acyl-4-vinylimidazole/divinylbenzene/styrene copolymer.

Acyl group in the polymer	Amine	Yield (%)
acetyl	$C_6H_5CH_2NH_2$	92
acetyl	$C_6H_5NH_2$	97
acetyl	*tert*-$C_4H_9NH_2$	63
propionyl	$C_6H_5CH_2NH_2$	98
benzoyl	$C_6H_5CH_2NH_2$	84
benzoyl	*c*-$C_6H_{11}NH_2$	45
benzoyl	piperidine	67

4.1.5 Amides via Oximinoimidazolides

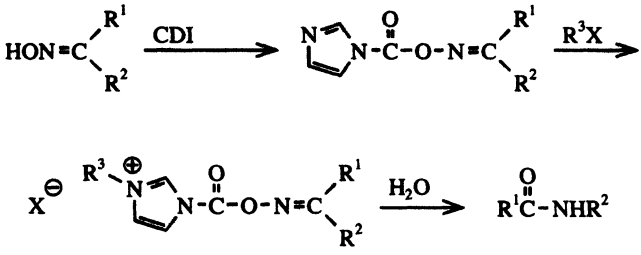
Oximinoimidazolides can be obtained from oximes and CDI with retention of stereochemistry; heating in octane or nonane under anhydrous conditions leads to their conversion to imidazolylimidates:[123]



R^1	R^2	Yield (%)
CH_3	C_6H_5	77
C_6H_5	C_6H_5	95

Hydrolysis then provides the amides in good to excellent yields ($R^1 = CH_3$, $R^2 = C_6H_5$, quant.; $R^1 = R^2 = C_6H_5$, quant.; R^1, $R^2 = (CH_2)_5$, 55%).

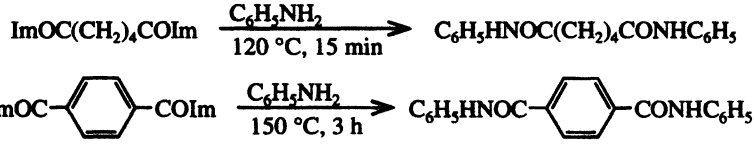
A modification of this method, related to the Beckmann rearrangement, entails treatment of a ketoxime with one equivalent of CDI, then four to five equivalents of a reactive halide such as allyl bromide or methyl iodide (R^3X) under reflux in acetonitrile for 0.5–1.5 h. Quaternization of the imidazole ring effectively promotes the reaction by increasing the electron-withdrawing effect. The target amides then are obtained by hydrolysis. High yields, neutral conditions, and a very simple procedure make this modification of the synthesis of amides by azolides a very useful alternative.[124]



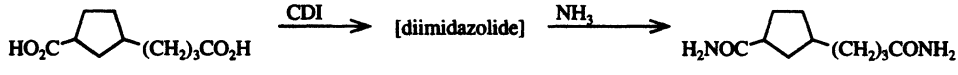
R^1	R^2	R^3X	Yield (%)
CH_3	*p*-$CH_3C_6H_4$	CH_2=$CHCH_2Br$	93
C_6H_5	C_6H_5	CH_2=$CHCH_2Br$	80
$C_6H_5CH_2$	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	93
C_6H_5	C_6H_5	CH_2=$CHCH_2Br$	80
$C_6H_5CH_2$	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	93
$-(CH_2)_5-$		CH_2=$CHCH_2Br$	93
C_2H_5	C_6H_5	CH_3I	98

4.1.6 Diamides of Dicarboxylic Acids

The following diimidazolides, prepared from the dicarboxylic acid, are quantitatively converted with amines into the corresponding diamides:[125]

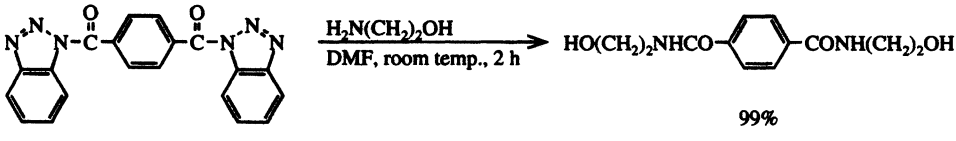


Diamides can also be prepared in a one-pot reaction using CDI or ImCSIm, dicarboxylic acids, and amines:[126]

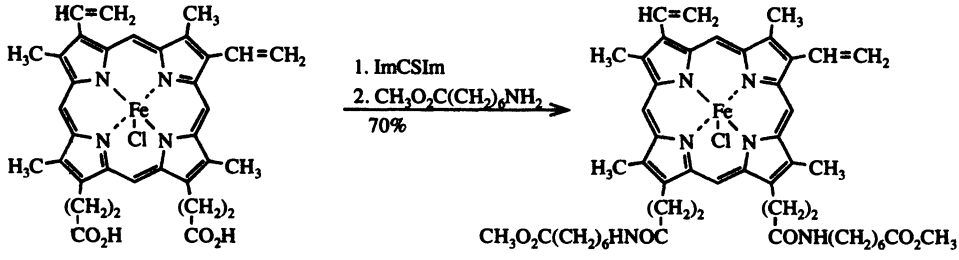


From the *cis*-compound, the *cis*-diamide was obtained exclusively (80% yield); analogously, the *trans*-compound is obtained from the corresponding *trans* starting material.

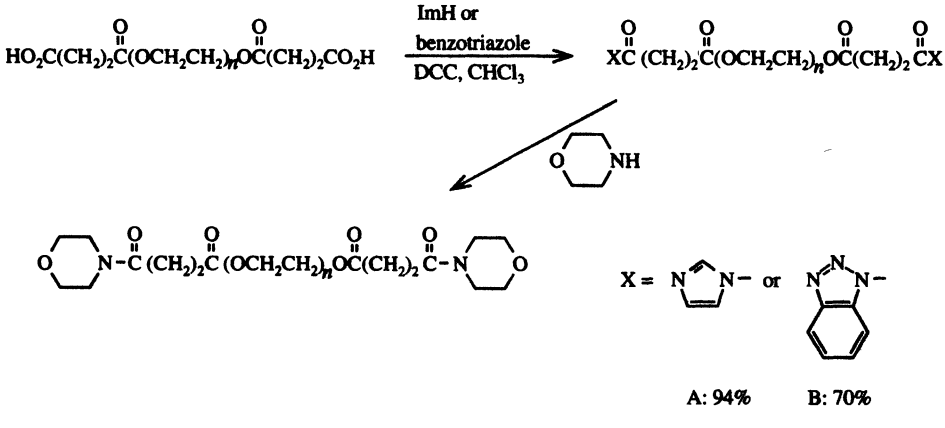
The bisbenzotriazolides of terephthalic acid or isophthalic acid react with 2-aminoethanol to give bisamides selectively in high yield:[96]



The carboxylic groups of hemin are successfully converted into a bisamide by means of ImCSIm without affecting other functional groups of the hemin[127] (see also Table 4–2 in Section 4.1.3):

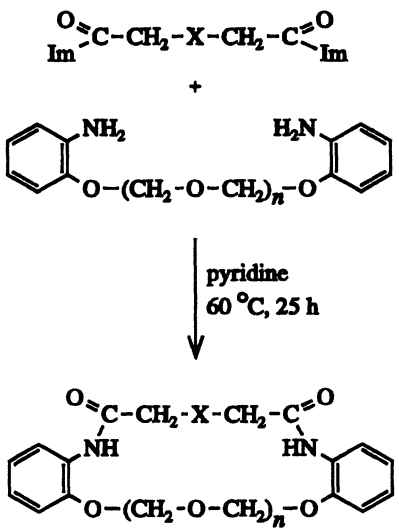


A further example of bisazolidization is the formation of a diamide from a succinic half-ester of poly(ethylene glycol) (MW ~2000) via a bisimidazolide (A) or a bisbenzotriazolide (B):[128]



4.1.7 Lactams

Macrocyclic lactams making use of the double reaction of bisimidazolides – in this case, prepared from the corresponding dicarboxylic acids by in-situ reaction with $C_6H_5POIm_2$ – were obtained in acceptable yield considering the unfavorable ring sizes of the products:[129]

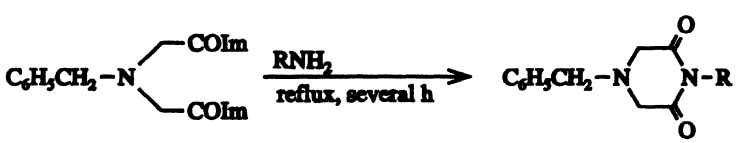


X	*n*	Yield (%)
O	1	41
O	2	14
S	1	18
S	2	16
NCH_3	1	10

A similar reaction of a bispyrazolide to a macrocyclic dilactam was also successful:[130]

4.1.8 Imides

Dicarboxylic acids were converted in a "one-pot procedure" with CDI (boiling THF, 15 min) into the bisimidazolides, and then by subsequent treatment with aliphatic, aromatic, or heteroaromatic primary amines into imides (piperazine-2,6-diones) in excellent yields:[131]

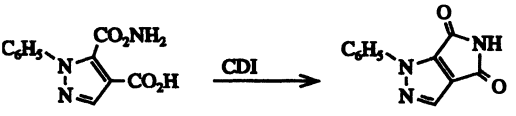


R	Yield (%)
phenyl	88
4-methoxyphenyl	98
4-nitrophenyl	94
2,6-dimethylphenyl	79
2,6-dichlorophenyl	90
1-adamantyl	65

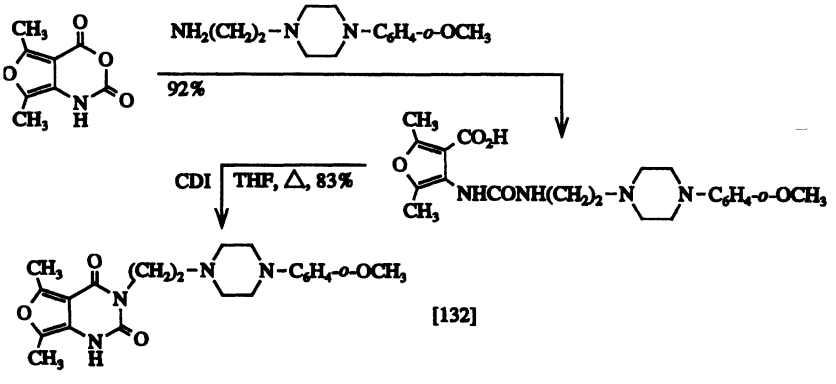
For the reaction with sterically highly demanding amines the higher boiling solvent dioxane is used in order to obtain good yields. With ethylenediamine as amine component, an ethylenedipiperazine derivative is obtained from (benzylimino)diacetic acid in good yield.[131]

The following examples illustrate the intramolecular cyclization of suitably substituted systems by the intermediate formation of azolides:

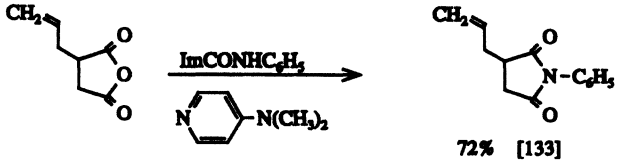
83% [131]



67% [9]

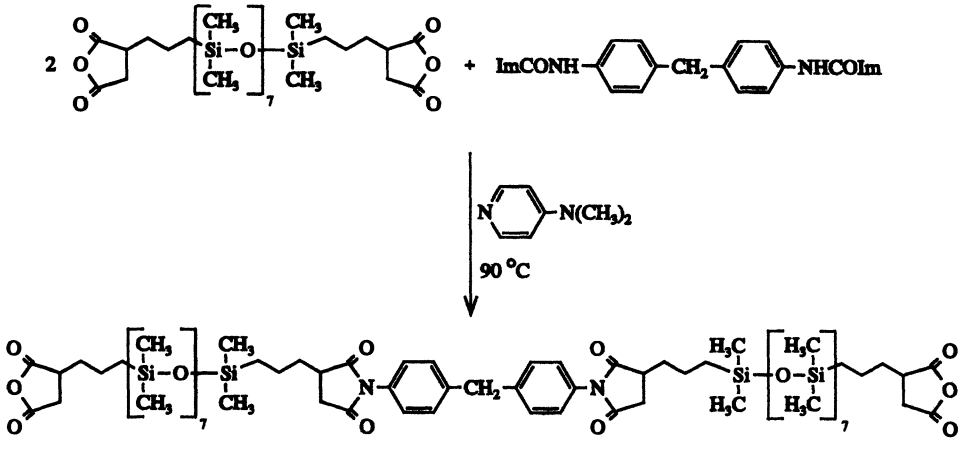


[132]



72% [133]

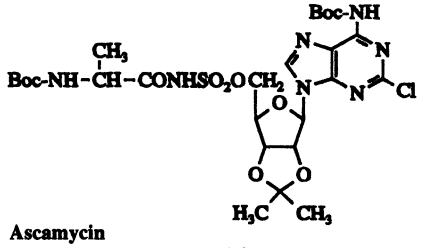
This type of conversion of a cyclic anhydride into an imide was also applied in the following double reaction to give a bisimide in surprisingly good yield:[133]



4.1.9 Some Special Azolide Reactions Related to Amides

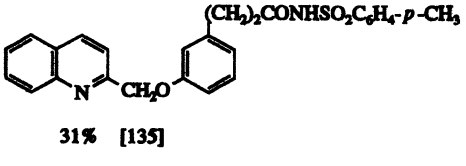
Acylsulfamoyl Compounds

The reaction of imidazolides of carboxylic acids with sulfamoyl compounds affords the corresponding acylsulfamoyl derivatives.



Ascamycin amalogue

86% [134]

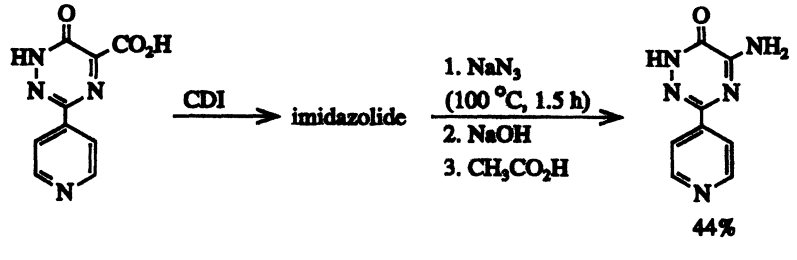


31% [135]

Leukotriene D_4 antagonist

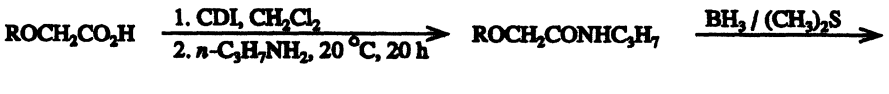
Primary Amines from Carboxylic Acids

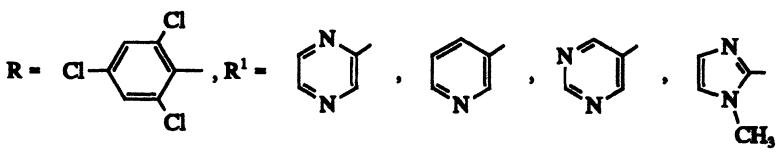
The carboxylic acid group is converted by CDI and sodium azide into an acid azide, which via a Curtius rearrangement gives the corresponding amine.[135a]



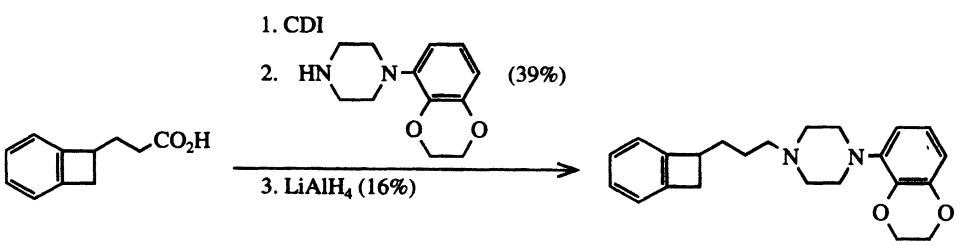
Secondary and Tertiary Amines via Amides

Tertiary amines have been prepared in good yield by a repetitive generation of imidazolides and subsequent reduction with borane/dimethylsulfide,[136] as the following examples show:



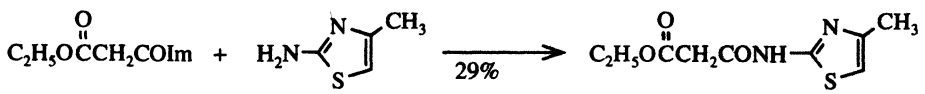


$LiAlH_4$ has also been applied as reducing agent of the resulting amide group.[137]



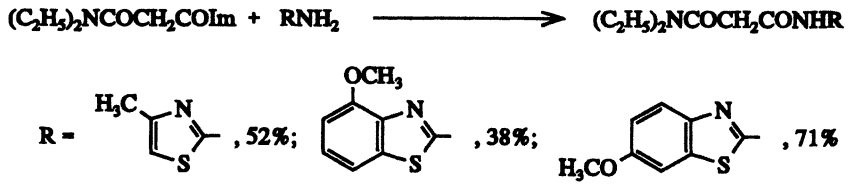
Amides from Heterocyclic Amino Compounds

Heterocyclic amino compounds including, for instance, 2-aminothiazoles or 2-aminobenzothiazoles, which contain a nitrogen in the ring capable of forming tautomeric structures, yielded the corresponding amides, although in general in lower than usual yield:[138]

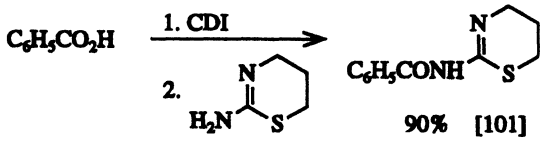


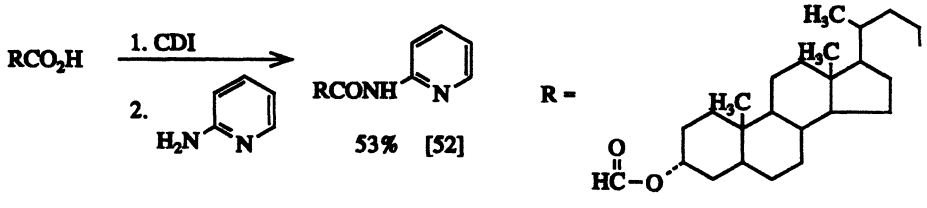
Other heterocyclic amines used for the synthesis of amides include, among others, 4-amino-1,2,3-trimethylpyrazolone (27%) and 6-aminoindazole (15%).

The yields of malondiamides starting from various malonamic acids are, however, higher:[138]

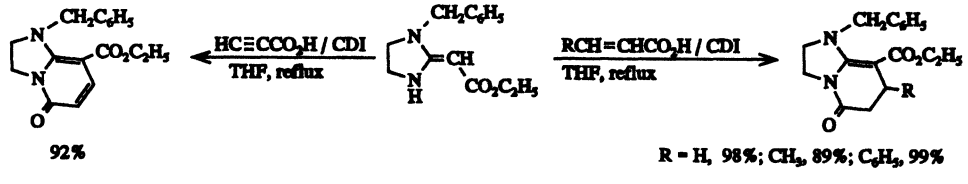


For similar cases of tautomeric heterocyclic amines, fairly good yields have been reported:[101],[52]



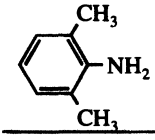


Some heterocyclic amides, in principle similar to those described above, were shown to cyclize in a Michael type reaction to give anellated pyridones in excellent yield:[139]

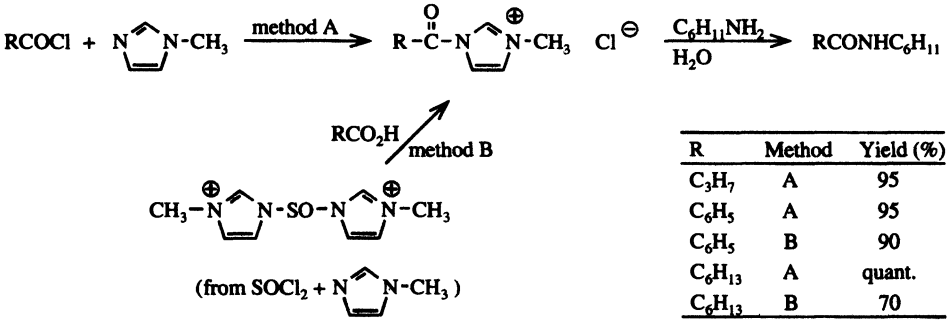


Amides by Reaction with Acylimidazolium Salts

While with *N*-acetylimidazole (A) only primary amines are generally converted to amides in high yields, and secondary amines are formed in moderate or low yields, both primary and secondary amines can be acetylated in high yield using 1-acetyl-3-benzylimidazolium bromide (B) at room temperature:[140]

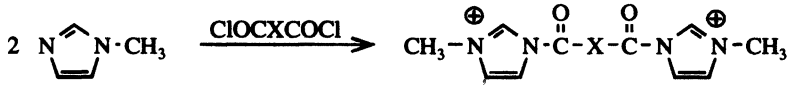
Amine	Acylating agent	Yield (%)
$(n\text{-}C_5H_{11})_2NH$	A	5
$(n\text{-}C_5H_{11})_2NH$	B	94
piperidine	B	93
$C_6H_5CH_2NHCH_3$	B	91
	B	80

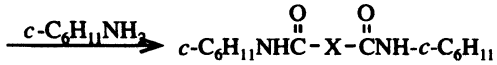
A similar principle of increasing the reactivity of imidazolides was used for the acylation of cyclohexyl amine and amino acids in an aqueous system:[105]



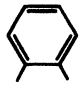
R	Method	Yield (%)
C_3H_7	A	95
C_6H_5	A	95
C_6H_5	B	90
C_6H_{13}	A	quant.
C_6H_{13}	B	70

Dicarboxylic acids are analogously converted to diamides:[105]



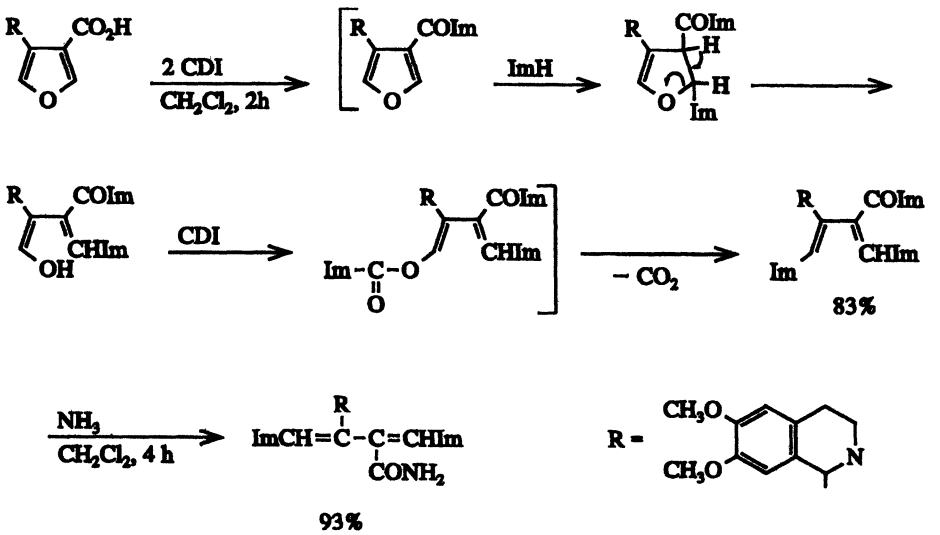


X = $-CH_2-CH_2-$ 80%

X =  70%

Amides by Ring Cleavage of a Furan Compound

A special case of amide formation was observed in the reaction of a furan-2-carboxylic acid with two moles of CDI and subsequent conversion with amines. In this reaction, besides formation of the imidazolide, addition of imidazole also takes places.[141]



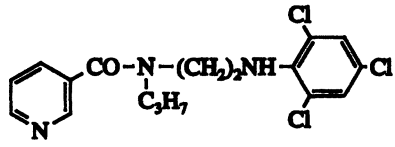
Analogous products are obtained if 2-furylmethylamine, di-*n*-propylamine, or *N*-(1,5-dimethyl)hexylamine are used instead of NH_3, with yields of 67, 88 and 84%, respectively.

4.2 Acylation of Diamino and Triamino Compounds by Azolides

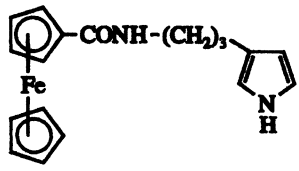
4.2.1 Reactions of Azolides with Diamino Compounds

Diamines react with azolides to produce diamides in cases where the nucleophilicity, the steric situation, etc. for the two amino groups are similar. If this is not the case, azolides may react selectively to give monoamides, as the examples below illustrate.

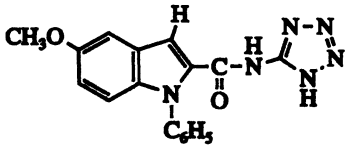
Examples of monoamides from diamino compounds using CDI:



30% [142]

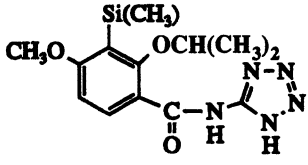


24% [143]

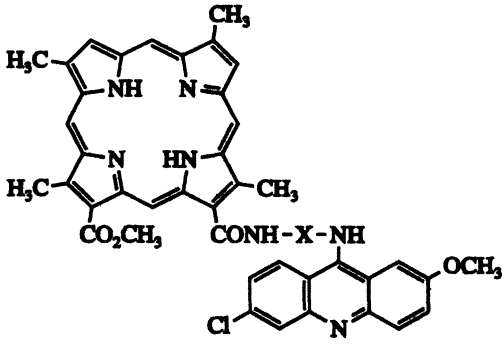


84% [144]

92% [145]

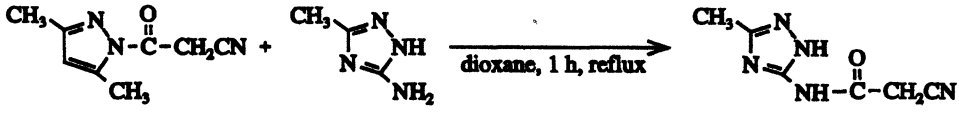


79% [145]



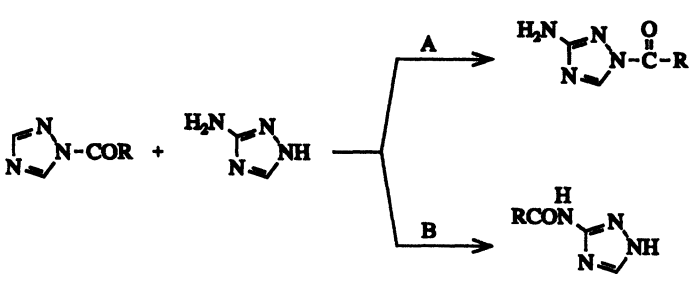
X = $(CH_2)_n$, n = 2,3,4 50 - 60% [146]

An example of the aminoacylation of a 5-aminotriazole with a pyrazolide is presented in reference [147]:



88%

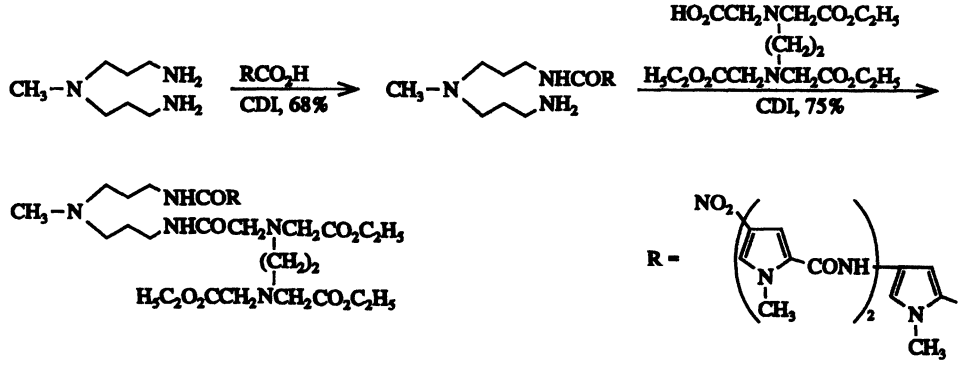
Treatment of 3-amino-1,2,4-triazole with 1-acyl-1,2,4-triazole containing acetyl, benzoyl, or ethoxycarbonyl groups leads to an acylation of the ring nitrogen (method A), whereas with 1-acyl-1,2,4-triazoles containing electron-withdrawing groups in the acyl function acylation at the exocylic amino group is achieved (method B):[148]



R	Yield (%)
CH_3	93
C_6H_5	93
C_2H_5O	94

R	Yield (%)
CH_2Cl	95
CHF_2	88
$(CF_2)_2CF_3$	91

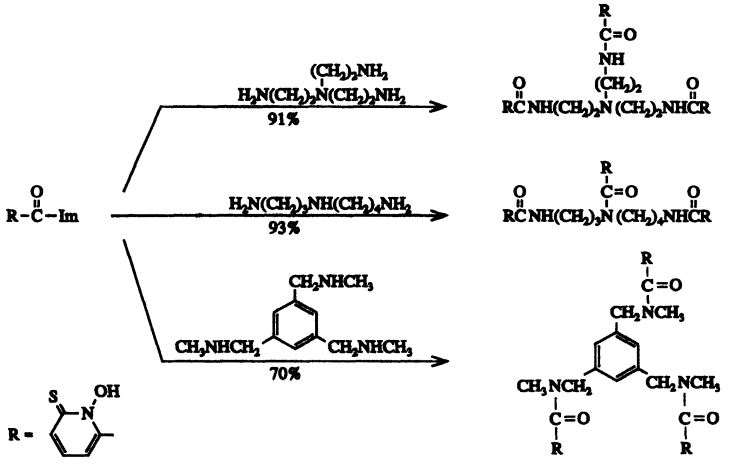
A sequence of imidazolide reactions was used in the following synthesis:[149]



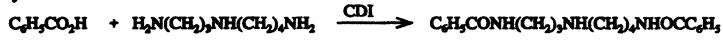
Eventually, the nitro group in the product was catalytically reduced (Pd/C, H_2) to an amino group, which was acetylated with acetic acid and CDI in 54% overall yield.

4.2.2 Reactions of Azolides with Triamino Compounds

Syntheses of Triamides:[150]



Selective Acylations to Diamides:



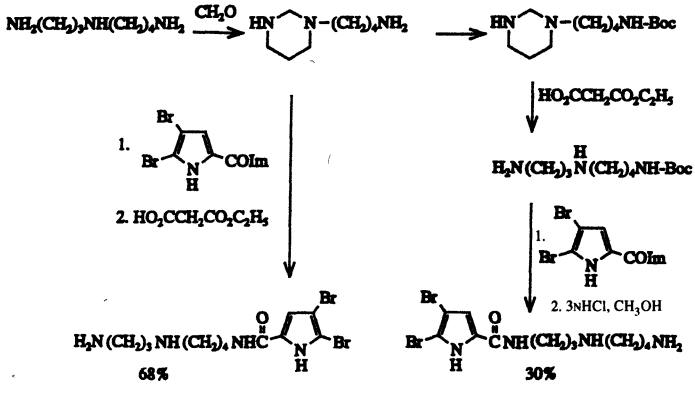
A similar diacylation of spermidine is also described with the imidazolide of dibromopyrrolcarboxylic acid.[151a]

Analogous diamides are prepared by using other carboxylic acids and triamines.[151]

$RCONH(CH_2)_n NH(CH_2)_n NHCOR$

R	n	Yield (%)
C_6H_5	2	70
$C_6H_5CH_2$	2	75
$2,3\text{-}(CH_3O)_2C_6H_3$	2	77
$2,3\text{-}(C_6H_5CH_2O)_2C_6H_3$	2	72
$C_6H_5CH_2$	3	82

The two primary amino groups of spermidine can be selectively acylated by the following two routes:[151a]

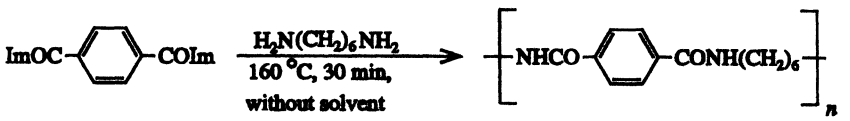


4.3 Synthesis of Polyamides and Polyimides

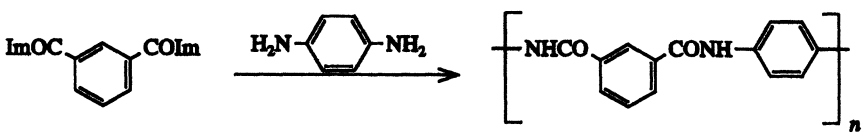
The azolide method has also been used for the synthesis of polyamides and polyimides. These can be obtained by several routes: First by condensation of two dihomofunctional components (dicarboxylic acid diimidazolides and diamines), secondly by condensation of a heterodifunctional compound (amino carboxylic acid and CDI), or through reaction on a polymer (for example, polymeric carboxylic acid imidazolides and amines).

Polyamides from Monomers

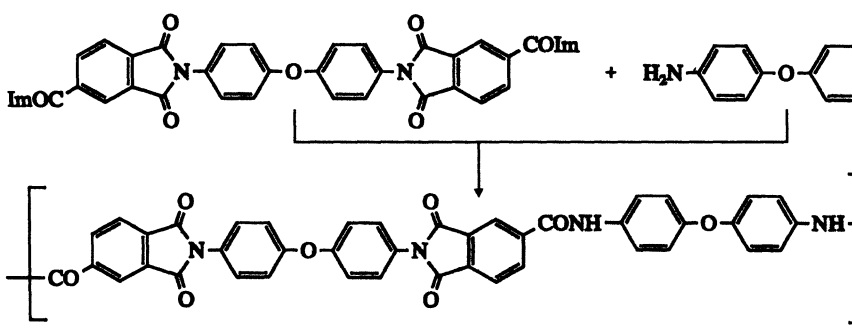
Examples:



[125]

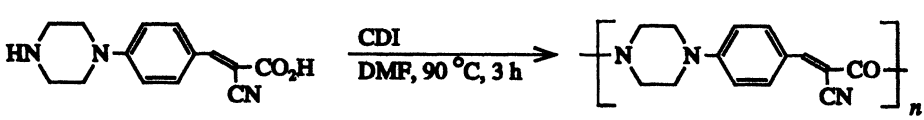


[152]



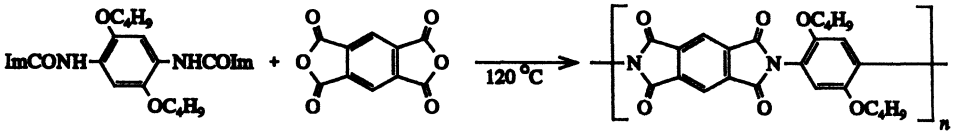
[153]

For preparation of dipolar polymers with dielectric properties and nonlinear optical applications, a piperidino-substituted α-cyanocinnamic acid was polycondensed with CDI.[55],[154]



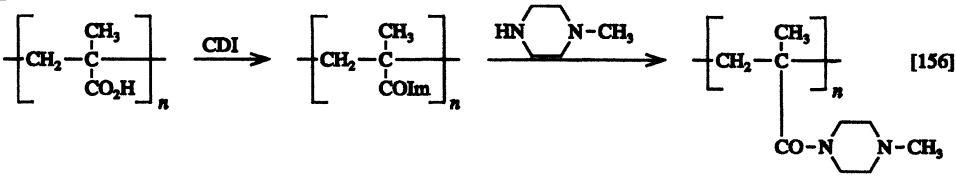
Polyimides from Monomers

The following preparation of a polyimide from a diimidazolide and pyromellitic anhydride took advantage of the fact that imidazole is an excellent blocking agent for isocyanates:[155]



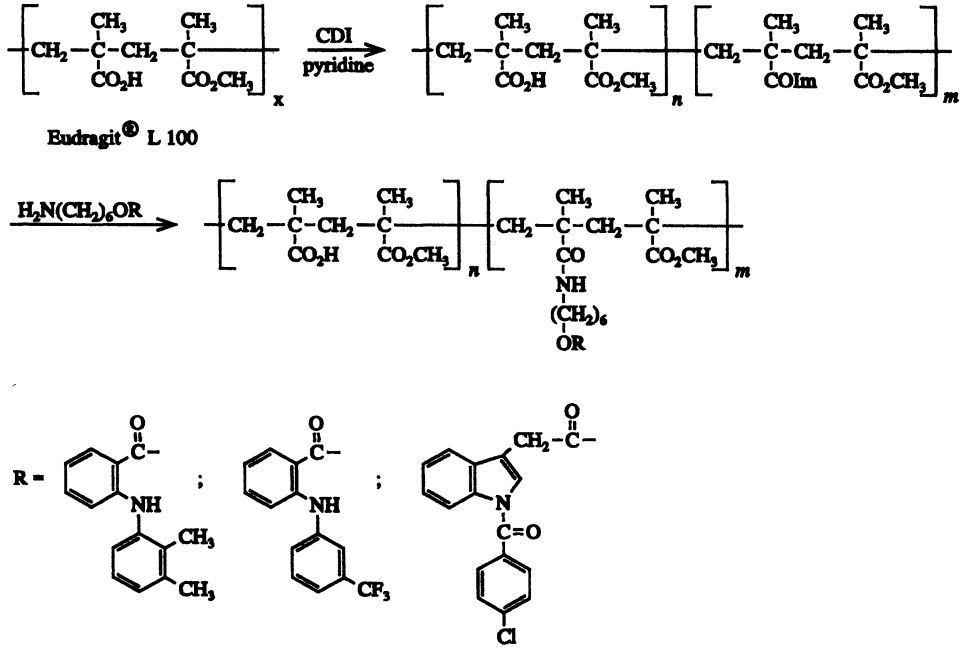
Polyamides and Polyimides by Reaction on Polymers

For the preparation of poly(methacrylamide), the poly(methacrylic acid) is converted with CDI into a polymer imidazolide, which reacts with an amine to give the corresponding polyamide:[156],[157]

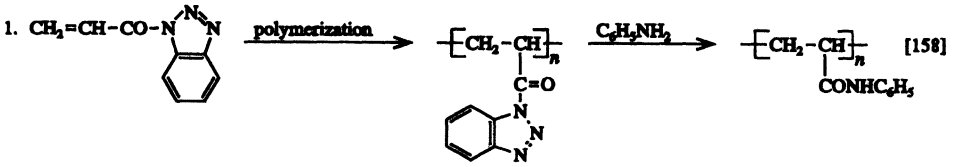


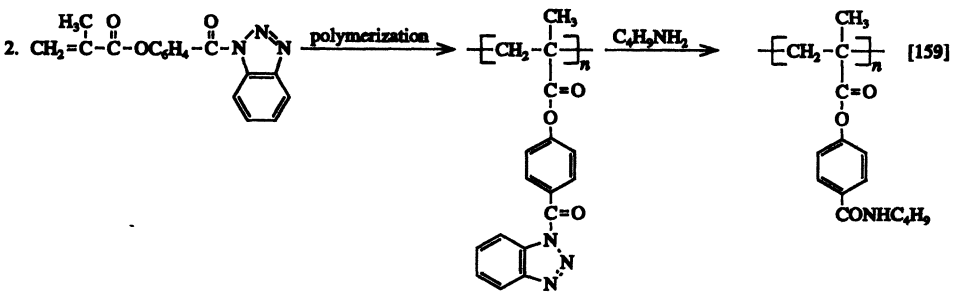
[156]

In the context of the synthesis of polymer-bound antiphlogistic drugs, a polymeric carboxylic acid was converted into the polyimidazolide, to which pharmaceutical agents were attached in the form of their amino esters:[157]



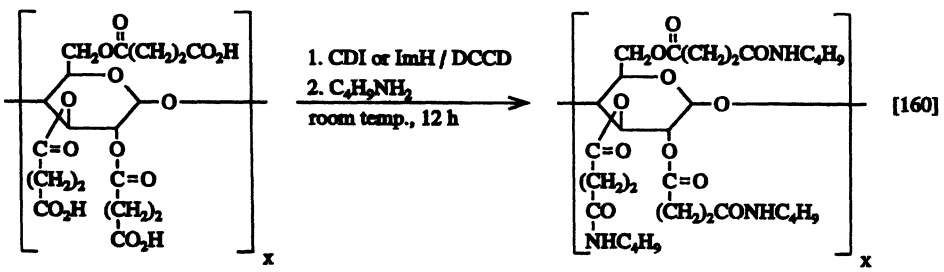
Another way to prepare a poly(acrylamide) illustrates the polymerization of the benzotriazolide of acrylic acid and reaction of the resulting polyazolide with an amine:[158],[159]



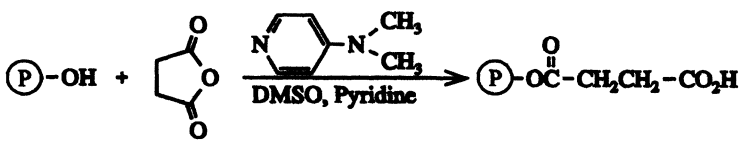


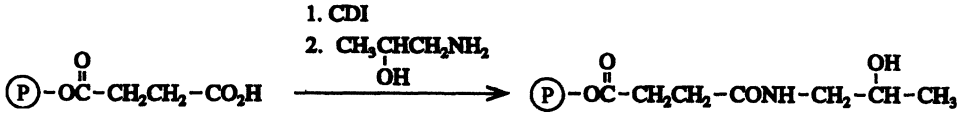
Further examples of this type are reported in the references cited.

In the context of synthesis and exchange reactions of biodegradable drug-binding matrices, starch trisuccinic acid was loaded via imidazolides with amines such as *n*-butylamine, morpholine, 4-aminobenzoic acid, or 3,4-dihydroxyphenylalanine to prepare the respective amides in high yields;[160] an example is presented below.



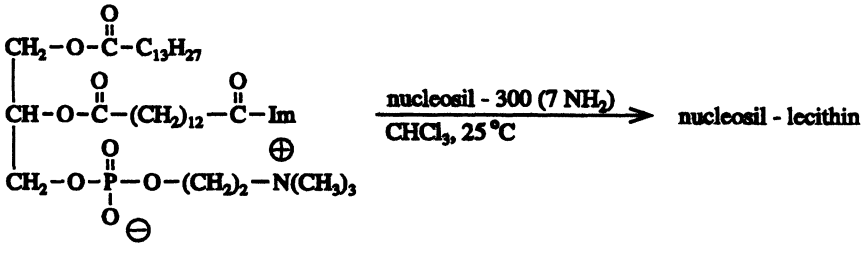
With respect to macromolecular drug-carrier approaches, the linear polysaccharide poly α-1,6-maltotriose (pullulan Ⓟ-OH) was combined with 1-aminopropan-2-ol via the succinate ester in the following way:[161]





A benzotriazolide was also used instead of the imidazolide.

Polyamides can also be prepared by the reaction of polyamines with azolides, as shown by the following reaction of nucleosil–300 (7 NH_2), a spherical silica derivatized with propyl amine, with lecithin imidazolide:[162]

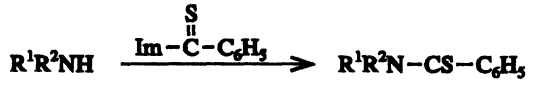


A polyimide film was made by heating a polyamide carboxylic acid at 300 °C for 30 min with azolides such as *N*-acetylimidazole, *N*-trifluoroacetylimidazole, or *N*-benzoylimidazole.[163]

4.4 Thioamides

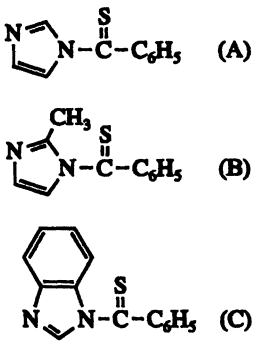
Thioamides can be synthesized by reacting thioazolides with primary or secondary amines in cyclohexane, THF, or CH_2Cl_2, or without solvent at 20–50 °C.[164],[165]

For example:



Thiobenzamides synthesized via the thioazolides *N*-thiobenzoylimidazole (A), *N*-thiobenzoyl-2-methylimidazole (B) and *N*-thiobenzoylbenzimidazole (C) are listed in Table 4–5.

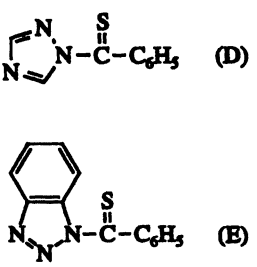
Table 4–5. Thiobenzamides from imidazolides.



$R^1R^2NCSC_6H_5$	Yield (%) from A	from B	from C
$R^1 = R^2 = H$	63	33	71
$R^1 = CH_3$, $R^2 = H$	49	35	31
$R^1 = C_6H_5$, $R^2 = H$	71	78	73
$R^1 = CH_3C_6H_4$, $R^2 = H$	65	70	—
$R^1 = R^2 = C_2H_5$	49	9	33
$R^1–R^1 = -(CH_2)_5-$	54	48	52
$R^1–R^1 = -(CH_2)_2O(CH_2)_2-$	60	58	69
$R^1 = CH_3$, $R^2 = C_6H_5$	—	42	—

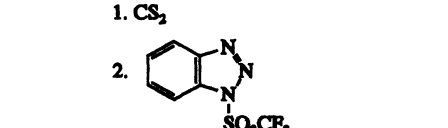
Thiobenzamides can also be obtained by reaction of *N*-thiobenzoyl-1,2,4-triazole (D) or *N*-thiobenzoylbenzotriazole (E) and amines (in cyclohexane, $CHCl_3$, or acetone as solvents, at temperatures between 10 and 50 °C),[166] as indicated in Table 4–6.

Table 4–6. Thiobenzamides from triazolides.



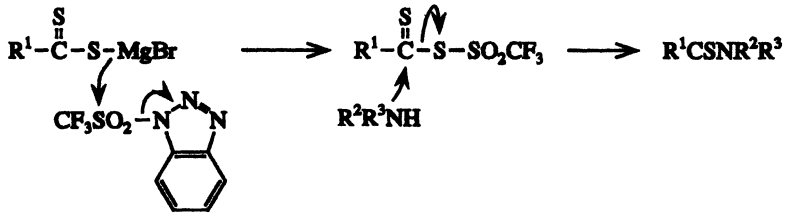
$R^1R^2NCSC_6H_5$	Yield (%) from D	from E
$R^1 = R^2 = H$	32	47
$R^1 = CH_3$, $R^2 = H$	24	0
$R^1 = C_6H_5$, $R^2 = H$	63	53
$R^1 = o\text{-}CH_3C_6H_4$, $R^2 = H$	26	72
$R^1 = R^2 = C_2H_5$	88	44
$R^1–R^1 = -(CH_2)_5-$	56	58
$R^1–R^1 = -(CH_2)_2O(CH_2)_2-$	60	39
$R^1 = CH_3$, $R^2 = C_6H_5$	43	0

A novel and convenient one-pot synthesis of *N*-mono-and *N,N'*-disubstituted thioamides mediated by *N*-trifluoromethylsulfonylbenzotriazole is described in reference [167].

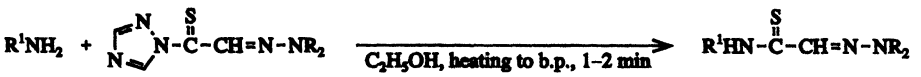


R^1	R^2	R^3	Yield (%)
C_6H_5	H	C_4H_9	63
$C_6H_5CH_2$	H	$C_6H_5(CH_2)_2$	79
C_4H_9	$CH_2CH_2OCH_2CH_2$		64
C_7H_{15}	H	α-pyridyl	45

For this reaction the following mechanism is proposed:

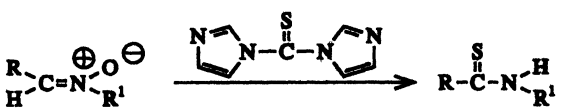


Hydrazono derivatives of a thiocarbonyl-1,2,4-triazole have been converted with primary amines into the corresponding thioamides:[168]



R^1	R	Yield (%)
H	*iso*-C_3H_7	89
H	$C_6H_5CH_2$	90
$C_6H_5CH_2$	CH_3	81
C_6H_5	CH_3	48

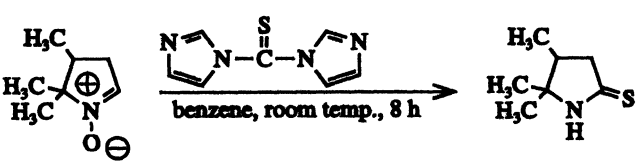
Another way of preparing thioamides is by treating aldonitrones with *N,N'*-thiocarbonyldiimidazole (ImCSIm) in refluxing benzene:[169],[170]



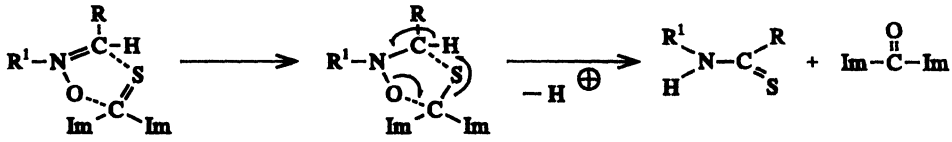
R	R^1	Yield (%)
C_6H_5	CH_3	75
α-furanyl	CH_3	68
C_6H_5	$C_6H_5CH_2$	70

Similar results are obtained by using *N,N'*-thiocarbonyldi-1,2,4-triazole instead of ImCSIm.

Analogously, reaction of the cyclic aldonitrone 3,4-dihydro-2,2,3-trimethyl-2*H*-pyrrole-1-oxide with ImCSIm yields 2,2,3-trimethyl-γ-butyrothiolactam in 84% yield:[170]

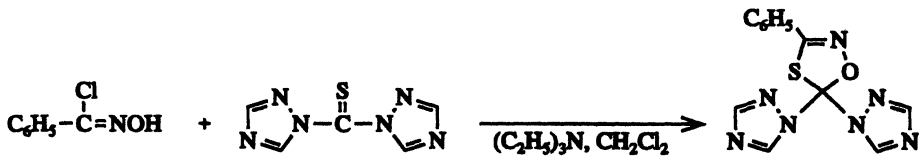


For the reaction mechanism of this way a 1,3-dipolar cycloaddition has been proposed:



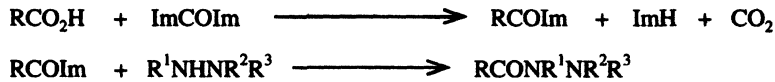
With base (e.g., pyridine) the reaction rate is enhanced. No thioamides could be obtained starting with ketonitrones. If *C*-phenyl-*N*-methylnitrone is treated with thiophosgene instead of a thioazolide, only *N*-methylbenzamide (73%) is formed, but no thioamide.[170]

In the reaction of benzonitrile oxide (1,3-dipolar addition) with *N,N'*-thiocarbonyldi-1,2,4-triazole the cyclic addition product has been isolated in 87% yield:[170]



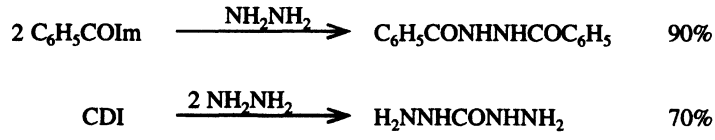
4.5 Hydrazides and Thiohydrazides

Hydrazides of carboxylic acids can be prepared by the imidazolide method in a similar manner as amides.[2] These syntheses are also conveniently carried out as one-pot reactions (room temperature, 12 h):

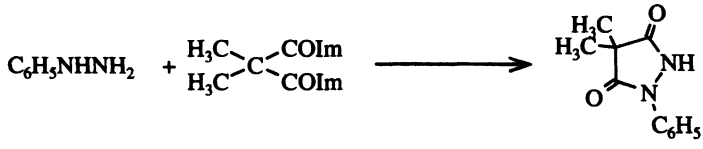


R	R^1	R^2	R^3	Yield (%)
γ-pyridyl	H	H	H	80
$(C_6H_5)_2CH$	H	C_6H_5	C_6H_5	83

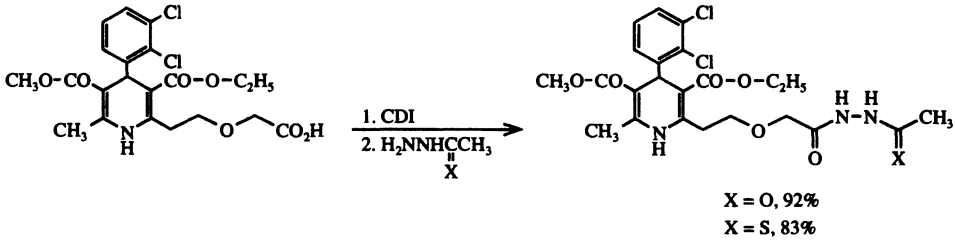
N,N'-Dibenzoylhydrazine is obtained with an imidazolide/hydrazine ratio of 2 : 1. For preparation of the carbonic acid bishydrazide the ratio CDI : hydrazine was 1 : 2:[2]

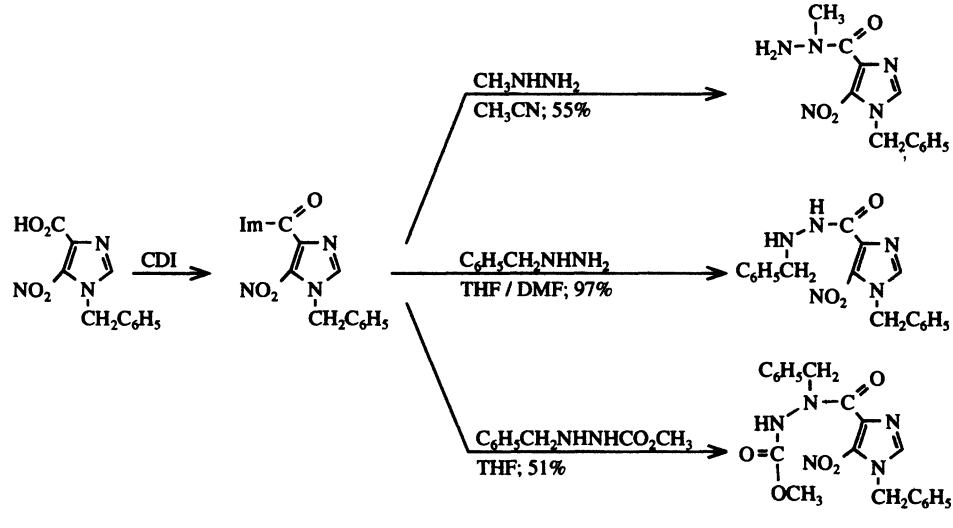


Diimidazolides of dicarboxylic acids react with hydrazines in a 1 : 1 molar ratio to form cyclic hydrazides; e.g., the diimidazolide of 2,2-dimethylmalonic acid and phenylhydrazine affords 1-phenyl-4,4-dimethyl-3,5-dioxopyrazolidine in 67% yield:[2]

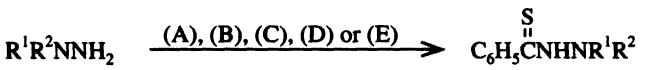


Examples of the synthesis of other hydrazides from carboxylic acids and acyl- or alkylhydrazines are provided below:[75],[171]

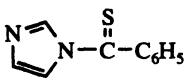




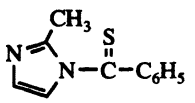
Thiohydrazides can be prepared from alkyl- and aryl-substituted hydrazines and various *N*-thiobenzoylazoles,[165] as the following examples illustrate:[165],[166]



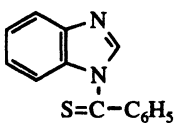
(A):



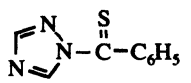
(B):



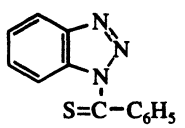
(C):



(D):

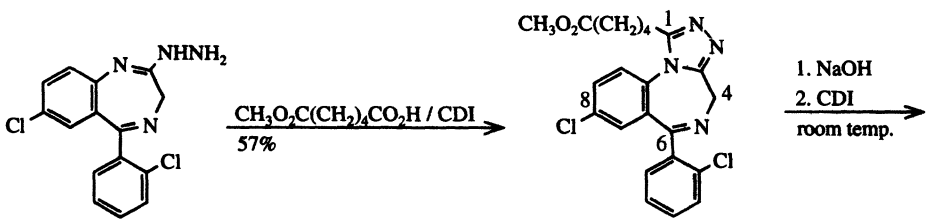


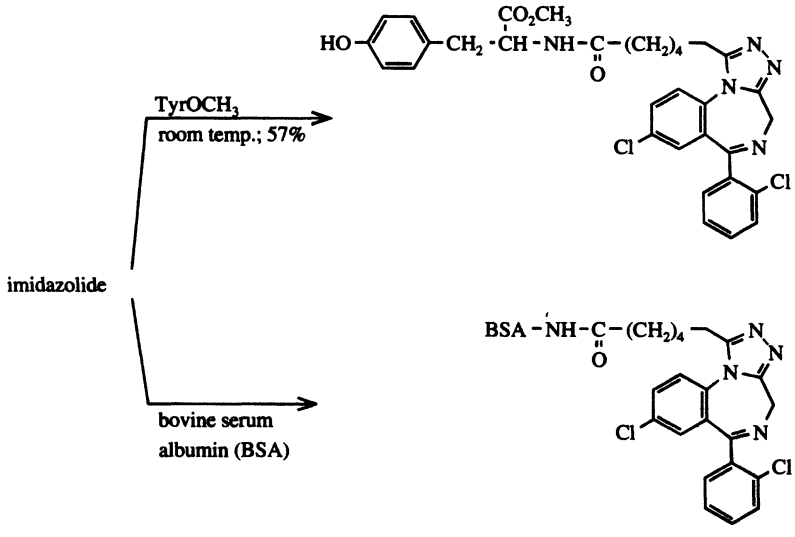
(E):



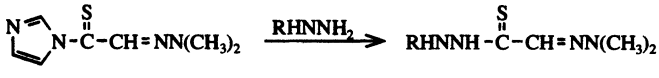
R^1	R^2	Yield (%), (azolide used)
CH_3	CH_3	71 (A), 29 (B), 28 (C), 30 (D), 39 (E)
CH_3	C_6H_5	68 (A), 56 (B)
C_6H_5	C_6H_5	10 (A), 45 (D), 27(E)

For testing sedative hypnotic drugs of the triazolam type the preparation was undertaken of 8-chloro-6-(*o*-chlorophenyl)-4*H*-*s*-triazolo[4,3-a][1,4]benzodiazepin-1-valeric acid methyl ester as an intermediate, with subsequent cyclization and amidation:[120]





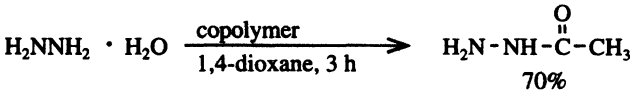
The synthesis of hydrazono derivatives of thiohydrazides is described in reference [168].



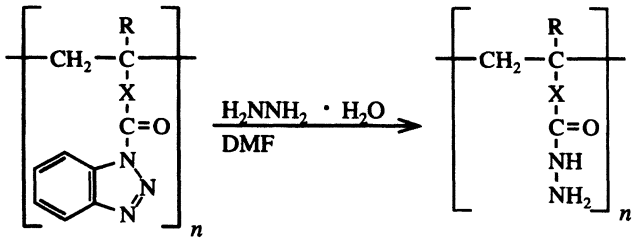
R	Yield (%)
H	72
p-$CH_3C_6H_4SO_2$	48
C_2H_5NHCS	47
C_6H_5CO	98

Hydrazides from Polymer-Supported Azolides

As mentioned before for other azolide reactions, acylations can be carried out with polymer-supported azolides as acylating reagents. For example, acetic acid hydrazide can be prepared with a polymer of 1-acetyl-4-vinyl-imidazole/divinylbenzene (96 : 4) and hydrazine (no diacylation occurs when this method is used):[122]

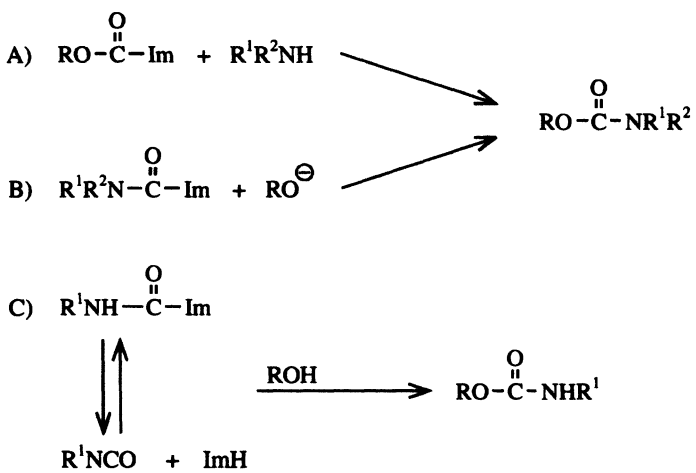


Polymeric hydrazides are obtained in quantitative yield by the reaction of hydrazine with polymer-supported benzotriazolides.[172] (R may be H or CH_3, X preferably $CONH(CH_2)_5$ or COC_6H_4):



4.6 Monoamides and Monothioamides of Carbonic Acid: Carbamates and Related Compounds

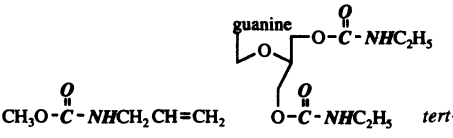
Carbamates can be synthesized from imidazolides or other azolides according to the following three routes, which usually give excellent yields. As solvents, THF, $CHCl_3$, and benzene are generally used. The reaction of imidazole-*N*-carboxylates with amines works satisfactorily only by heating (A). Whereas the imidazole-*N*-carboxamides of secondary amines react with alkoxides also if the solution is heated (B), imidazole-*N*-carboxamides of primary amines react with alcohols even at room temperature (C).[1] Nevertheless the reaction mixture is usually heated since in the latter case a dissociation occurs forming the corresponding isocyanate, which reacts rapidly with alcohol to give a carbamate. For the dissociation of imidazole-*N*-carboxamides into imidazole and isocyanates see references [217],[218] and [173],[174].



Because of the higher reaction rate, *N*(3)-alkylimidazolium-*N*(1)-carboxylates or thiocarboxylates have often been used for the synthesis of carbamates and thiocarbamates by the azolide method instead of imidazole-*N*-carboxylates.

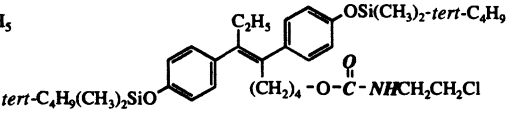
4.6.1 Carbamates by Reaction of Imidazole- or Imidazolium-*N*-carboxylates. Introduction of Amino Protecting Groups

a) Carbamates from imidazole-*N*-carboxylates

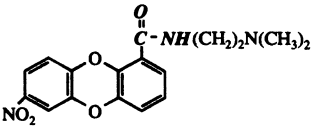


59% [176],[177]

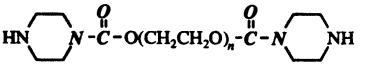
42% [178]



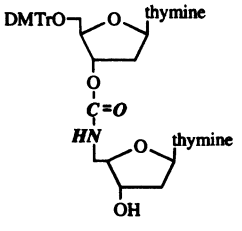
quant. [179]



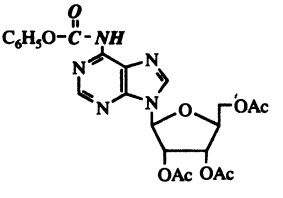
92% [180]



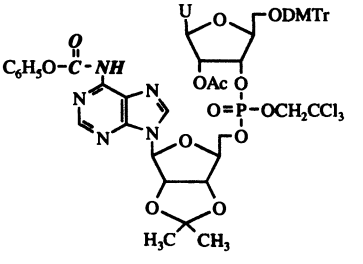
n = 181, PEG 8000 83% [181]
45, PEG 2000 84% [181]
22, PEG 1000 86% [181]



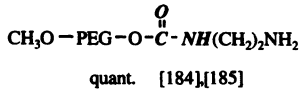
87% [182]
DMTr = dimethoxytrityl



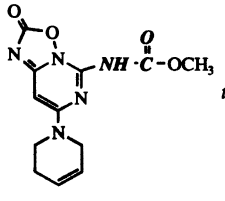
90% [183]



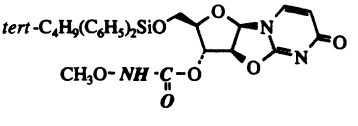
88% [183]



quant. [184],[185]
PEG = polyethylene glycol

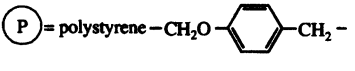


91% [186]



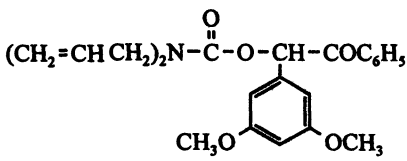
93% [186b]

[186a]

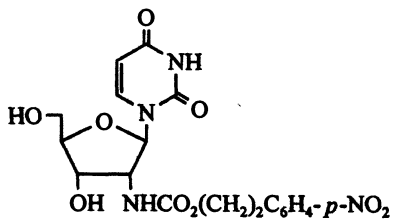


b) Carbamates from imidazolium-*N*-carboxylates

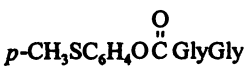
This method is used, for example, for the mild introduction of protecting groups like benzyloxycarbonyl (Z), *tert*-butoxycarbonyl (Boc) and *p*-nitrophenylethoxycarbonyl (npeoc).



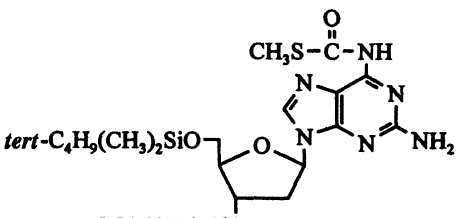
90% [187]



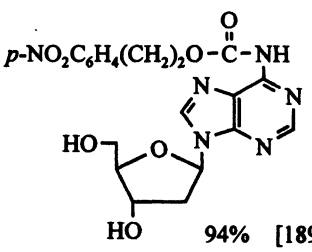
75% [187a]



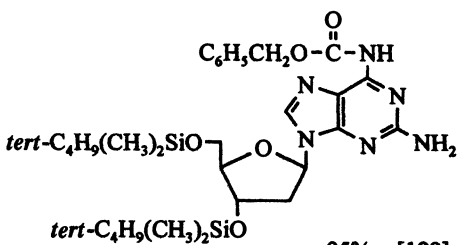
85% [188]



60% [189]



94% [189a]

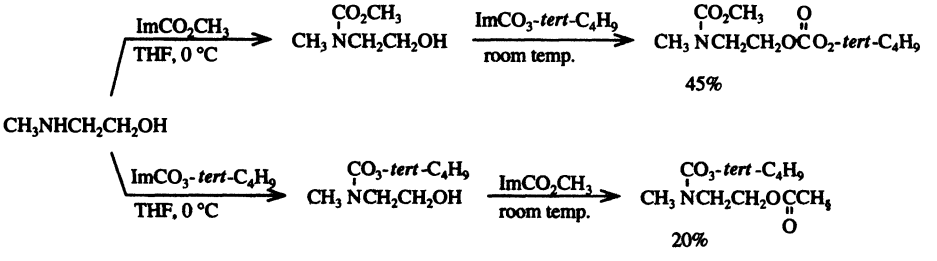


95% [189]

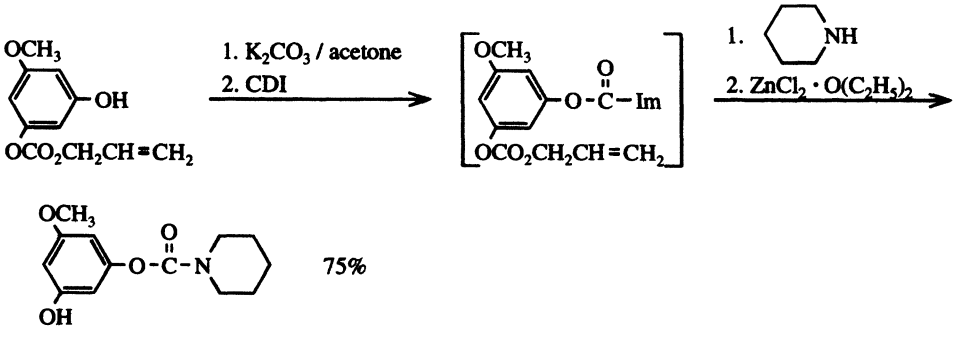
The water soluble 1-methyl-3-(methylthiophenyloxycarbonyl)imidazolium chloride is used for introduction of the methylthiophenyloxycarbonyl protecting group at the amino nitrogen of peptides. Higher yields are achieved with this compound than with the corresponding chloroformate.

It should be emphasized that benzyloxycarbonylimidazolium salts are effective agents for the direct mono-*N*-protection of deoxynucleosides as their benzyloxycarbonyl derivatives. No over-acylation occurs. However, bis(*tert*-butyldimethylsilyl)-deoxyguanosine failed to react with this reagent.[189]

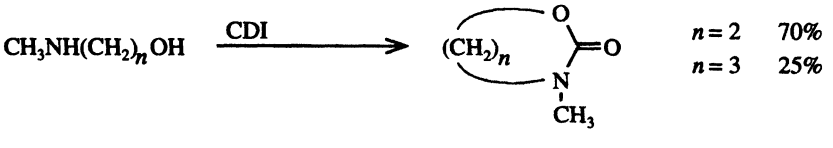
In the reaction of an aminoalcohol with a methyl imidazole-*N*-carboxylate or *tert*-butyl imidazole-*N*-peroxycarboxylate, selective acylation of the amino function can be achieved[190] to give the carbamate and peroxycarbamate, respectively, the hydroxy groups of which can be further acylated:



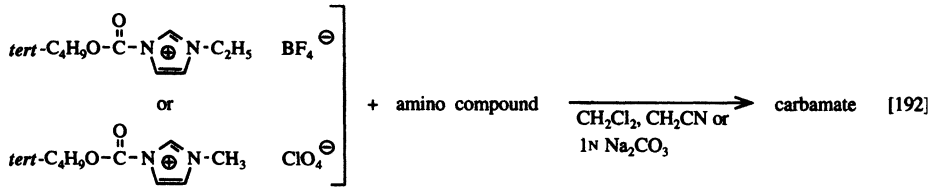
The reaction below illustrates the synthesis of a hydroxyphenylcarbamate:[191]



A cyclic carbamate (see also Chapter 7) is obtained in the reaction of an aminoalcohol with CDI:[190]



The Boc-protecting group is easily transferred onto amino compounds (for example, amino acids) with the aid of *tert*-butoxycarbonylimidazolium compounds.[192] As solvent CH_2Cl_2, CH_3CN, or an aqueous 1 N Na_2CO_3 solution can be employed. The reaction is rapid (five minutes) at room temperature, in comparison to that with the *tert*-butoxycarbonylimidazole, which requires prolonged heating at 110 °C.[193]

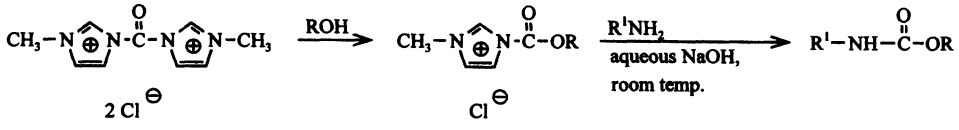


[192]

Amino compound	Carbamate	Yield (%)
c-$C_6H_{11}NH_2$	Boc-NH-*c*-C_6H_{11}	95
Gly-OC_2H_5	Boc-Gly-OC_2H_5	75
Gly	Boc-Gly	80
L-Pro	Boc-L-Pro	95
Z-Lys	Boc-Z-Lys	75
L-Phe	Boc-L-Phe	74
L-Ala	Boc-L-Ala	95

Boc = *tert* - butyloxycarbonyl

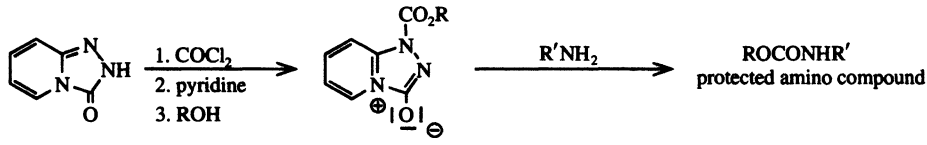
A variant of this method for the introduction of amino protecting groups into amino acids via the alkoxycarbonylimidazolium salts starts from the more reactive carbonyl-bis(methylimidazolium) salts:[105]



R	Amino acid, R^1NH_2	Yield (%) of alkoxycarbonyl-amino acids
C_2H_5	glycine ethyl ester · HCl	50
i-C_3H_7	glycine	65
$C_6H_5CH_2$	L-lysine (ε-NH_2)	60
$C_6H_5CH_2$	L-histidine (N_1-imidazole)	quant.
$C_6H_5CH_2$	L-serine (α-NH_2)	quant.

Some examples for the introduction of amino protecting groups such as 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) or benzyloxycarbonyl (*Z*) were already given in the compilation of carbamates produced with imidazolium carboxylates in Section 4.6.1.

Analogously to these reactions of imidazolium carboxylates, the introduction of urethane-type amino-protecting groups can be accomplished with the following mesoionic azolides:[194]



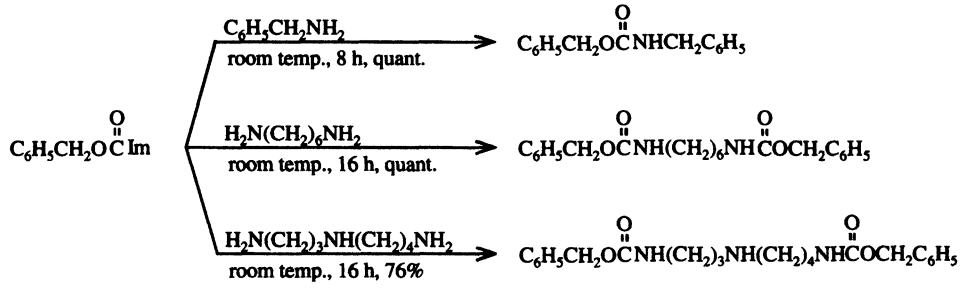
R	Yield (%)
tert-C_4H_9	87
$C_6H_5CH_2$	90
p-$CH_3OC_6H_4CH_2$	82
p-$NO_2C_6H_4CH_2$	92
$(C_6H_5)_2CH$	95
Cl_3CCH_2	88

	Yield (%)
Boc-L-Trp-OH	90
Boc-L-Glu-OH	82
p-$CH_3OC_6H_4CH_2OCO$-(D)-Phg-OH	82
Z-Gly-OH	86
Cl_3CCH_2OCO-(D)-Phg-OH	93
$(C_6H_5)_2CHOCONHCH_2CH_2OH$	96
p-$NO_2C_6H_4CH_2OCONHCH_2CH_2SH$	81

Phg = phenylglycine

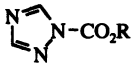
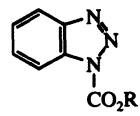
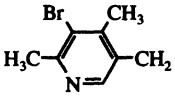
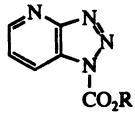
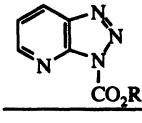
The mesoionic azolides are reported to be relatively stable toward hydrolytic decomposition, but more reactive against amines than the corresponding imidazolides.[194] *N*-Protection of the amino compounds (for example by the Boc group) takes place smoothly at room temperature in about one to five hours and with high yield. The amino acids are introduced as sodium salts in aqueous acetone.

The benzyloxycarbonyl protecting group for amines is introduced in high yield using benzyl imidazole-carboxylate with a catalytic amount (5%) of dimethylaminopyridine.[195]

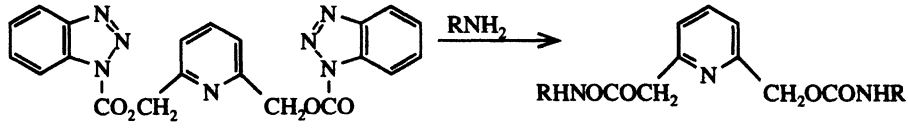


The alkoxycarbonyl protecting groups can also be introduced into amines by triazolides (Table 4–7). With *N*-*tert*-butoxycarbonyl-1,2,4-triazole the *tert*-butoxycarbonyl protecting group (Boc) is transferred readily onto amino functions of primary amines, trimethylbenzyl ammonium salts of amino acids, or peptides.[196] Alternatively, the Boc group can be transferred with *tert*-butylphenylcarbonate in the presence of 1,2,4-triazole. In this latter approach the triazolide is presumably formed as an intermediate.[196]

Table 4–7. Carbamates synthesized from triazolides.

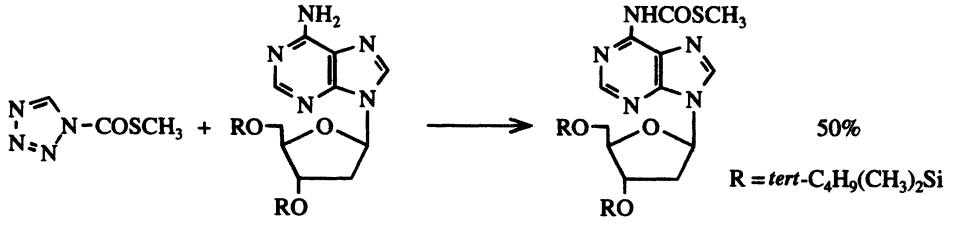
Azolide	R	Amine	Carbamate	Yield (%)	Ref.
	*tert*-C_4H_9	*c*-$C_6H_{11}NH_2$	ROCONH-*c*-C_6H_{11}	88	[196]
	tert-C_4H_9	Gly-OC_2H_5	$ROCONHCH_2CO_2C_2H_5$	82	[196]
	tert-C_4H_9	Phe	$ROCONHCHCO_2H$ ($CH_2C_6H_5$)	84	[196]
	C_2H_5	$C_{18}H_{37}NH_2$	$ROCONHC_{18}H_{37}$	85	[197]
	$C_6H_5CH_2$	$C_3H_7NH_2$	$ROCONHC_3H_7$	90	[197]
	$C_6H_5CH_2$	$NaO_2SCH_2NH_2$	$ROCONHCH_2SO_2Na$	50	[197a]
	C_6H_5	*c*-$C_6H_{11}NH_2$	ROCONH-*c*-C_6H_{11}	95	[197]
	C_2H_5	$H_2N(CH_2)_2NH_2$	$ROCONH(CH_2)_2NHCO_2C_2H_5$	76	[197]
	p-$NO_2C_6H_4(CH_2)_2$	Cytidine	N^4-npeoc-cytidine	90	[197b]
		*c*-$C_6H_{11}NH_2$	ROCONH-*c*-C_6H_{11}	83	[198]
	*tert*-C_4H_9	$C_6H_5CH_2NH_2$	$ROCONHCH_2C_6H_5$	80	[97]
	$C_6H_5CH_2$	Ser	$ROCONHCHCO_2CH_3$ (CH_2OH)	92	[97]
	*tert*-C_4H_9	$C_6H_5CH_2NH_2$	$ROCONHCH_2C_6H_5$	82	[97]
	$C_6H_5CH_2$	$C_6H_5CH_2NH_2$	$ROCONHCH_2C_6H_5$	quant.	[97]

Analogously, bisbenzotriazole-*N*-carboxylates react with amines to give biscarbamates.[197],[198] For example:



R	Yield (%)
CH_3	96
iso-C_3H_7	76
$C_{18}H_{37}$	89

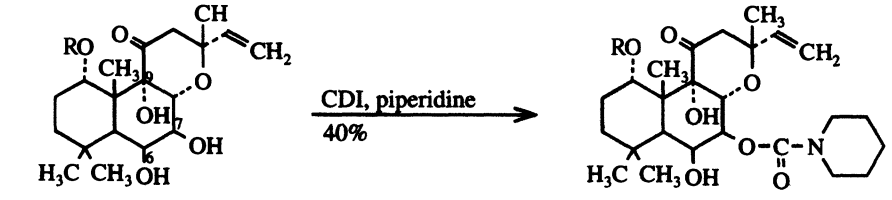
With tetrazole-*N*-thiocarboxylate the amino group of an OH-protected deoxyadenosine is converted into a thiocarbamate:[189]



Conversion of Natural Compounds into Carbamates

The hydroxy groups in natural products like, for example, the macrolide antibiotics erythromycin,[199] and desmycosin,[200],[201] as well as the 3-(hydroxymethyl)-2- or 3-cephems[202] and derivatives of the amino sugar garamin[203] have been converted into the carbamate function with CDI and amines. In the case of aminoglycoside antibiotics of the sisomicin series, thiocarbamates or dithiocarbamates have been prepared from alcohols or thiols using ImCSIm and amines.[204]

The synthesis of a monocarbamate (monothiocarbamate) from trihydroxy-abdenone, CDI, and piperidine is described in conjunction with tests of drugs for treatment of glaucoma:[205]



R = *tert* - $C_4H_9(CH_3)_2Si$–

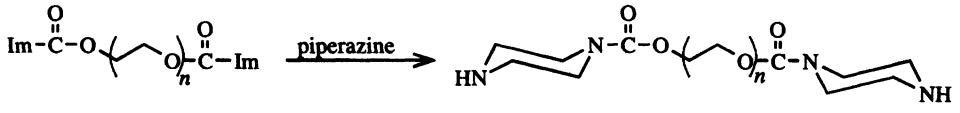
The synthesis was carried out as a one-pot reaction in ethyl acetate. The result is actually surprising, since there are three hydroxy groups in the educt, any of which might in principle react with the imidazolide. Probably the 6β-OH- and the 9α-OH groups are more sterically hindered than the 7β-OH group. With ImCSIm in the presence of methylamine the corresponding thiocarbamate was obtained in 15% yield.

Carbamates of High Molecular Weight Alcohols

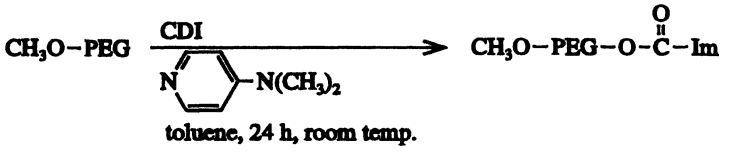
The activation of the 5′-hydroxy group of synthetic deoxyoligonucleotides on a controlled porous glass support was achieved with CDI to give a 5′-imidazolide, which was subsequently converted with hexamethylenediamine to yield as the carbamate a 5′-aminoalkylated supported deoxynucleotide.[206]

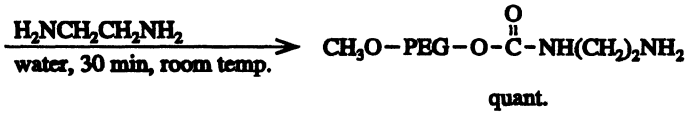
Imidazole carboxylates of polyethylene glycols prepared with CDI react with amines to give polyethylene glycols (PEG) with carbamate end groups.[207] For example, PEG-

piperazinecarbamates from PEG 8000, PEG 2000, and PEG 1000 have been prepared in this way:[181]

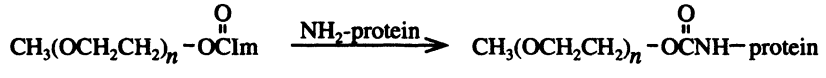


The following reaction of imidazole carboxylate of PEG was chosen for the purpose of introducing amino functions onto methoxypoly(ethylene glycol) chains (CH_3O-PEG):[184]

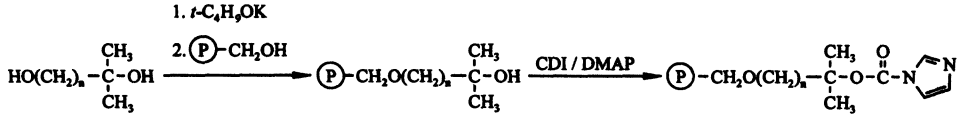


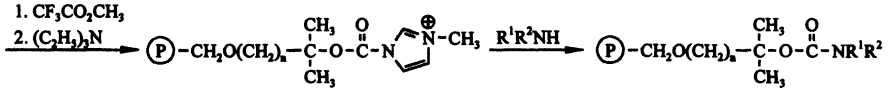


In a similar fashion, polyethylene glycol can be activated with CDI for connection to a protein, as has been shown for superoxide dismutase, α_2-macroglobulin, α_2-macroglobulin-trypsin, lactoferrin, and tissue plasminogen activator:[208],[209]



The formation of resin-bound tert.-alkyl carbamates for anchoring of amines was recently described: [209a]

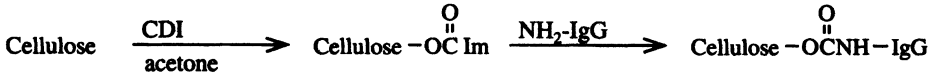




n = 2-4, P-CH_2OH = Merrifield resin
DMAP = 4-dimethylaminopyridine

R^1R^2NH = p-Cl-$C_6H_4CH_2NH_2$
c-$C_6H_{11}NHC_2H_5$
Trp-OCH_3
and others

Cellulose can be activated by CDI and coupled with the amino groups of peptides or immunoglobulins in aqueous alkaline solution to give immobilized peptides or antibodies such as the immunoglobulin IgG [210] (see also Section 6.2):



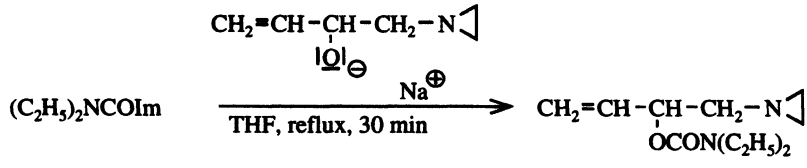
This method was used, for example, for the solid-phase immunoassay of thyroxine (affinity chromatography). Various activation methods (CDI, periodate, and cyanogen bromide procedures) were compared with each other for coupling antibodies to magnetizable cellulose/iron oxide solid-phase particles.[211]

Other hydroxylic solid-phase supports such as cross-linked agarose are similarly activated with CDI or *N,N'*-carbonyldi-1,2,4-triazole. The activated matrices can then be smoothly coupled with *N*-nucleophiles such as glycine, 6-aminohexanoic acid, diamines, or proteins.[212]

The antibody of human epidermal growth factor (EGF) was coupled to diol silica (prepared from silica and 3-glycidoxypropyltrimethoxysilane via an epoxy silica) by means of CDI. This supported antibody was utilized for immunoaffinity HPLC analysis of human epidermal growth factor.[213]

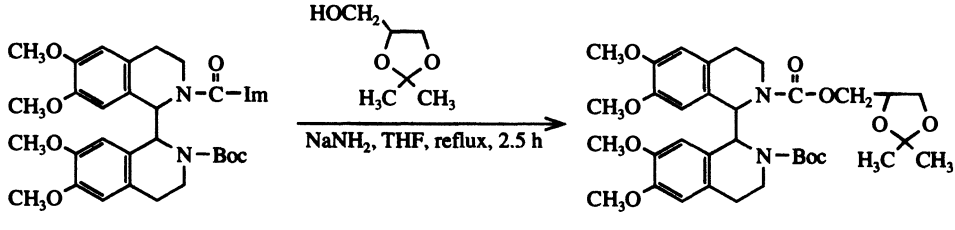
4.6.2 Carbamates by Reaction with Carbamoylazoles (Azole-*N*-Carboxamides) of Secondary Amines

In the course of an investigation of cytostatically active derivatives of 1-ethylenimino-2-hydroxybuten-(3), also called Tetramine, the following carbamate was prepared:[214]



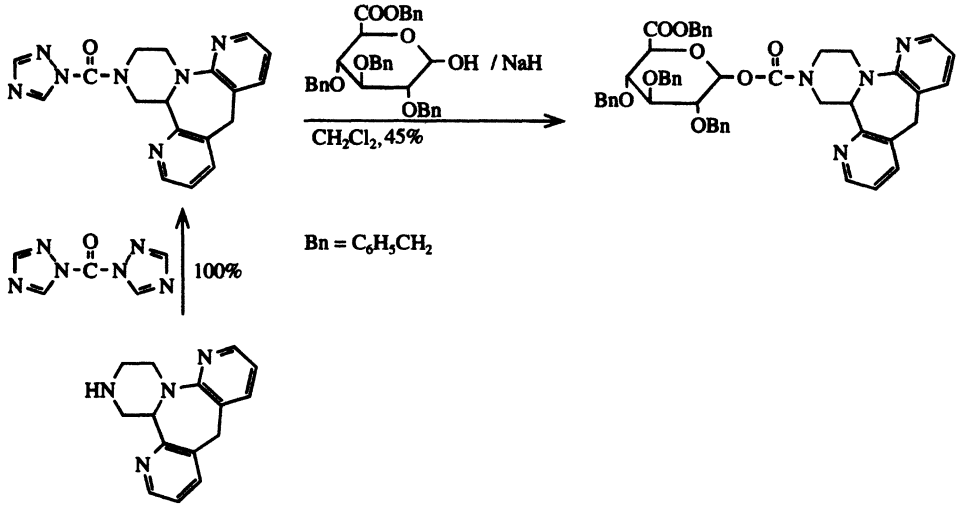
60%

The corresponding *N,N'*-diphenylcarbamate was prepared in 64% yield.
In an analogous reaction the following carbamate was synthesized:[214a]

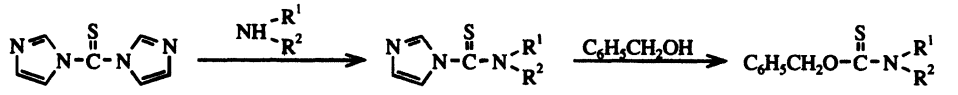


39%

Carbamates can also be obtained from the carbamoyltriazole of a secondary amine by reaction with an alkoxide, as the following example shows:[215]



Analogous to this reaction, thiocarbamates have been prepared using ImCSIm, which is generated in situ from two equivalents of imidazole, CS_2, sodium hydride, and one equivalent of a thiazolium salt[216]:

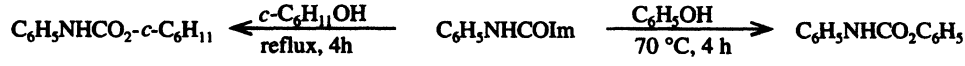


$R^1 = C_6H_5CH_2$, $R^2 = CH_3$, 64%; $R^1 = C_6H_5$, $R^2 = CH_3$, 47%

$R^1 = C_6H_5CH_2$, $R^2 = CH_3$, 73%; $R^1 = C_6H_5$, $R^2 = CH_3$, 90%

4.6.3 Carbamates by Reaction with Carbamoylazoles (Azole-*N*-Carboxamides) of Primary Amines

The great reactivity of carbamoylimidazole and carbamoylbenzimidazole is explained by the easy dissociation of these compounds into the corresponding azole and isocyanate.

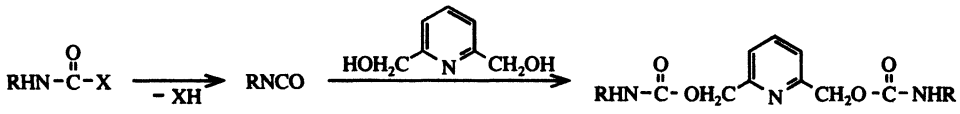


$C_6H_5NHCO_2$-*c*-C_6H_{11} 68% [217]

$C_6H_5NHCO_2C_6H_5$ 86% [218]

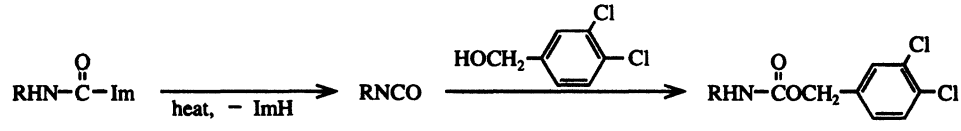
Carbamoylazoles of pyrazole and triazoles dissociate only at 130 °C and 145 °C, respectively. An activating influence of imidazole (significant shortening of reaction time

and slight enhancement of yield) was observed on the reaction of carbamoylbenzotriazoles with a diol.[219]

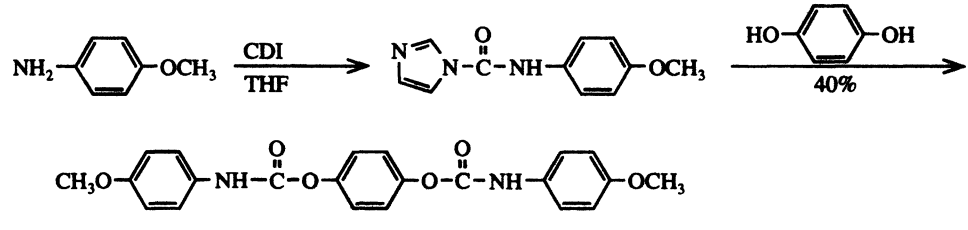


X	R	Reaction temp. / °C	Reaction time / h	Yield (%)
1-imidazolyl	CH_3	95	2.0	96
1-imidazolyl	CH_3	95	0.5	95
1-benzimidazolyl	CH_3	130	0.5	84
1-pyrazolyl	CH_3	145	14.0	72
1-triazolyl	CH_3	145	10.0	64
1-benzotriazolyl	CH_3	145	14.0	55
1-benzotriazolyl	*iso*-C_3H_7	145	24.0	36
1-benzotriazolyl	*c*-C_6H_{11}	145	14.0	73

The following carbamoylimidazole, which was prepared from ^{14}C-labeled methylammonium chloride and CDI, was not isolated. It was instead fragmented by heating in vacuo into the isocyanate, which was then reacted with an alcohol to give the labeled carbamate:[220]

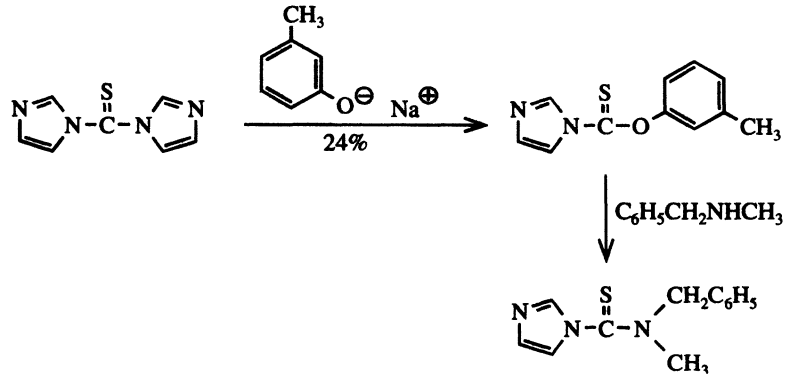


A biscarbamate was obtained from *p*-anisidine, CDI, and hydroquinone in a one-pot reaction:[221]

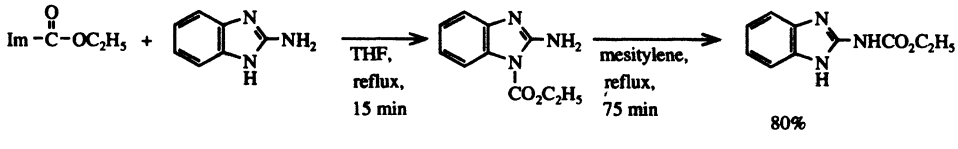


4.6.4 Special Cases of Carbamate Syntheses with Azolides

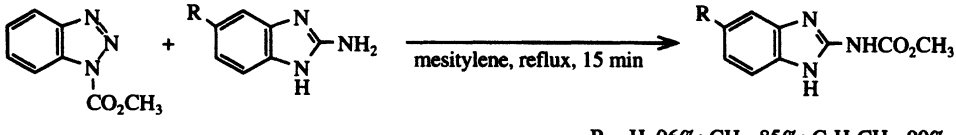
As compared to the carbamate synthesis above, an abnormal reaction course was observed in the reaction of *m*-tolyloxythiocarbonylimidazole with benzylmethylamine; here the phenolate is exchanged instead of the imidazole, obviously because the substituent with the lower pK is eliminated:[216]



In the reaction of 1-alkoxycarbonylimidazoles with 2-aminobenzimidazole at low temperature and short reaction time an acylation at the ring nitrogen was encountered. At higher temperature (refluxing mesitylene) and longer reaction time, however, the 2-amino group is acylated:[222]



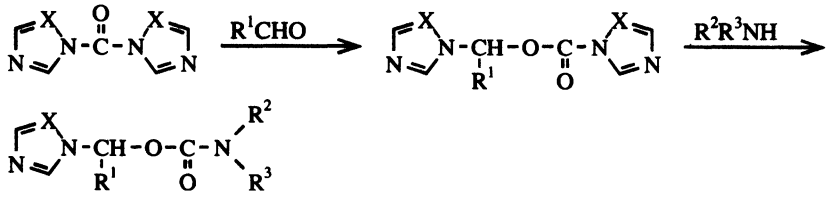
Similar findings applied to other azolides as, for example, benzotriazole systems:[222]



R = H, 96%; CH_3, 85%; $C_6H_5CH_2$, 90%

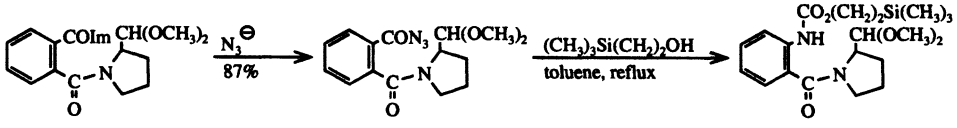
1-Methoxycarbonyl-3,5-dimethylpyrazole and 1-methoxycarbonyl-5-*p*-tolyloxytetrazole are also used as acylating reagents in this reaction.[222]

A special carbamate still containing an azole moiety is formed if an aldehyde is inserted into a carbonylbisazole and subsequently treated with an amine:[223]



$X = CH, R^1 = C_3H_7(CH_3)_2C, R^2\text{-}R^3 = CH_2CH(CH_3)OCH(CH_3)CH_2$ 69%
$X = N, R^1 = C_3H_7(CH_3)_2C, R^2 = H, R^3 = p\text{-}ClC_6H_4$ 67%

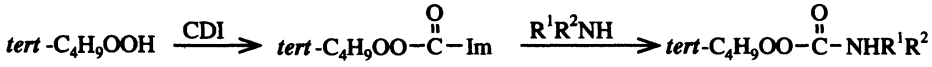
Another way to obtain a carbamate via an isocyanate intermediate is the conversion of an imidazolide RCOIm into the azide $RCON_3$, followed by the Curtius–Schmidt rearrangement and treatment with an alcohol:[224]



50% overall yield

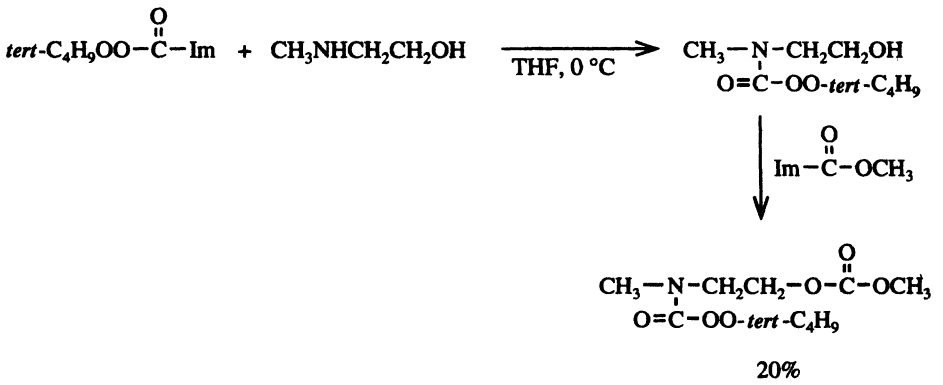
4.6.5 Peroxycarbamates

The syntheses of *tert*-butylperoxycarbamates begins with *tert*-butylperoxide and CDI, forming in 92% yield the surprisingly stable (at room temperature) *tert*-butylperoxycarbonylimidazole, which is then converted with an amine. This synthesis might also be carried out as a one-pot procedure:[176],[225]



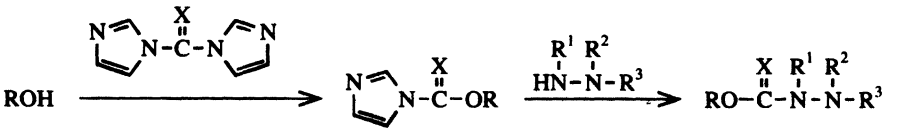
R^1	R^2	Yield (%)	Ref.
H	$CH_2{=}CHCH_2$	62	[176]
H	C_2H_5	60	[225]
C_2H_5	C_2H_5	55	[225]

In the reaction of an aminoalcohol with *tert*-butylperoxycarbonylimidazole, selective acylations on N and O can be achieved:[190]

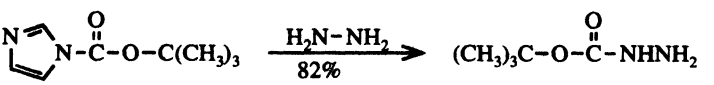


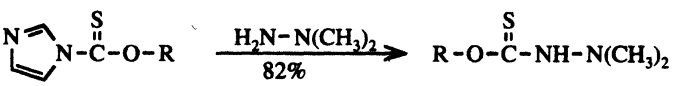
4.7 Monohydrazides and Thiohydrazides of Carbonic Acid

Alkoxycarbonylimidazoles or alkoxythiocarbonylimidazoles, easily prepared from alcohols and CDI or ImCSIm, are treated with hydrazines to give alkoxycarbonic acid hydrazides and thiohydrazides, respectively:[226],[227]

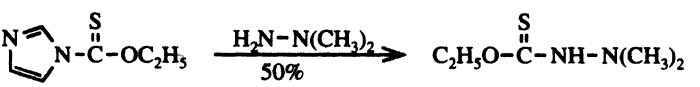


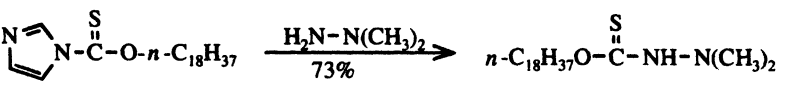
A few hydrazides and thiohydrazides prepared with the aid of alkoxycarbonylimidazoles or thiocarbonylimidazoles are shown below:[226],[227]





R = 5α-cholestan-3β-yl





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5 Synthesis of Peptides

5.1 Syntheses of Peptides via *Carboxyl*-Activation of Amino Acids

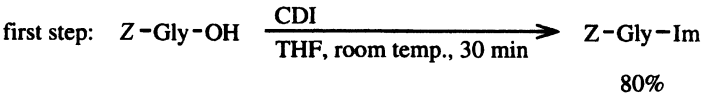
Short Historical Introduction

The first peptide synthesis according to the "imidazolide method" was observed in 1928 when *N*-benzoyl-L-histidine methyl ester, substituted at the imidazole nitrogen, was converted at room temperature with glycine to *N*-benzoylglycylglycine.[1] Later, in analogy to the first experiments, it was demonstrated by the example of the synthesis of *Z*-glycylalanine methyl ester that under very mild conditions an aminoacyl residue on the imidazole ring of histidine can indeed be transferred to the amino group of an amino acid, thus forming a peptide.[2] However, due to the difficult synthesis and the poor yields of the reactions, no preparative value was attributed to this synthesis of peptides. The wide scope of the use of azolides for peptide syntheses was, however, initiated by the discovery of CDI and its analogues in 1956 and of the acyl transfer to amides and esters by azolides in the same year.[3],[4]

CDI as Coupling Agent

The broad use of *N,N'*-carbonyldiimidazole (CDI) for the synthesis of amide and peptide linkages became a routine method only in the early sixties.[5] *N*-Protected amino acids were treated at room temperature with an equimolar amount of CDI to give imidazolides. Anhydrous tetrahydrofuran, dimethoxyethane, dichloromethane, pyridine, dimethylformamide, and diethyl phosphite were utilized as solvents. In the second step the esters of amino acids, their hydrochlorides, or sodium salts were added to yield the peptide after several minutes or hours of reaction time.

Example:



second step: $Z\text{-Gly-Im} \xrightarrow{\text{Tyr-OC}_2\text{H}_5} Z\text{-Gly-Tyr-OC}_2\text{H}_5$ 83%

Although the yields are lower, it is possible to use even aqueous solutions of salts of amino acids in the second step. The first step, however, must be carried out under anhydrous conditions. Usually the reaction is carried out as a one-pot procedure.

Example:

$$Z\text{-Gly-OH} + \text{Tyr-OC}_2\text{H}_5 \xrightarrow{\text{CDI}} Z\text{-Gly-Tyr-OC}_2\text{H}_5 \quad 95\%$$

An excess of CDI must be avoided because this would react with the amine component to give a urea derivative.[5] Further examples are compiled in Table 5–1.

Table 5–1. Di-and tripeptides prepared with CDI.

	Yield (%)	Ref.
Boc-Phe-Gly-OC_2H_5	78	[5]
Z-Gly-Leu	68	[5][1)]
Z-Gly-Phe	40	[5][2)]
Z-Ala-Gly-OC_2H_5	65	[5]
Z-Gly-Phe-OC_2H_5 (DL)	82	[5][3)]
Z-Phe-Tyr-OC_2H_5	57	[5]
CF_3CO-Gly-Pro-O-*tert*-C_4H_9	51	[5]
Z-Glu-His-OCH_3	88	[6]
Boc-Ser($OCH_2C_6H_5$)-Ser($OCH_2C_6H_5$)-OC_2H_5	84	[7]
Boc-DL-Val-DL-Val-OCH_3	40–45	[8]
Boc-Met-Glu-His-OCH_3	53	[9]

[1)] via Leu-OC_2H_5·HCl and saponification
[2)] via Phe-ONa
[3)] via Phe-OC_2H_5·HBr

Racemization studies in the synthesis of the tripeptide *Z*-Gly-Phe-Gly from *Z*-Gly-Phe and Gly-OC_2H_5 revealed that in THF at room temperature such racemization occurred to the extent of about 5%, in DMF at −10 °C, however, less than 0.5%.[5],[10]

In the synthesis of Boc-Val-Tyr-OC_2H_5 (50%) from Boc-Val and Tyr-OC_2H_5 with CDI, a small amount of *O*-acylation of tyrosine (4%) also occurred in the dipeptide.[11]

N,N'-Carbonyldibenzimidazole was found inferior to CDI in the synthesis of peptides because of poorer yields and more rigorous reaction conditions needed.[5]

The synthesis of the octapeptide isoleucine-5-angiotensin *Z*-Asp(NH_2)-Arg(NO_2)-Val-Tyr-Ile-His-Pro-Phe-OCH_3 using CDI as condensing agent was achieved by preparing the four required dipeptides (1–2), (3–4), (5–6), (7–8), two tetrapeptides (1–4) and (5–8), and finally the octapeptide itself.[12]

The CDI method was also used in a block condensation to give a hexapeptide from a tetrapeptide and a dipeptide,[13] as well as an undecapeptide from a pentapeptide and a hexapeptide.[13] Further syntheses of peptides with the CDI method are described in references [14]–[16].

The reactivity of an amino acid imidazolide is examined in reference [17]. Thus, the reactivity of *Z*-glycine imidazolide ($k = 2.6 \pm 0.2 \times 10^{-2}$ [$l \cdot mol^{-1} \cdot s^{-1}$]) toward *N*-methylbenzylamine is between that of *Z*-glycine 2,4,5-trichlorophenyl ester ($k = 5.2 \pm 0.2 \times 10^{-2}$) and *Z*-glycine 4-nitrophenyl ester ($k = 0.98 \pm 0.09 \times 10^{-2}$). Based on this range of reactivity, the glycine-imidazolide was prepared from *Z*-glycine-trichlorophenyl ester and *N*-trimethylsilylimidazole in 79% yield. With respect to the conversion of various activated glycine compounds with *N*-methylbenzylamine (in ethyl acetate, 25 °C, 12 h), the yield of the amide with *Z*-glycine imidazolide was highest.

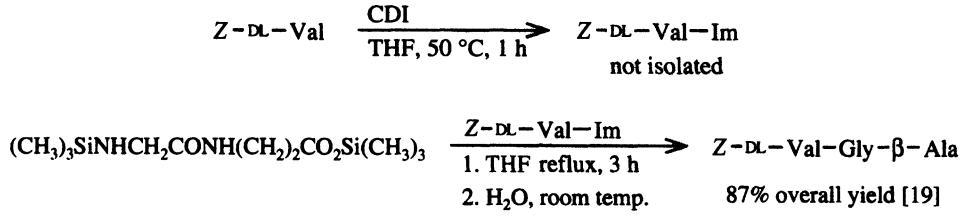
Syntheses of Peptides from Silylated Amino Acids and CDI

Application of amino acid silyl esters or *N*-silyl amino acid silyl esters as amino components is very convenient in peptide synthesis with CDI, because the resulting peptide silyl esters are easily hydrolyzed to dipeptides during the usual work up. They need not be saponified in a separate step, as would be the case with the corresponding alkyl esters. Furthermore, no racemization occurs with this method.[18],[19]

Example 1:

Analogously prepared was phthalyl-Gly-β-Ala in 85% yield.

Example 2:



Additional di-, tri-, and tetrapeptides have been prepared[20] according to this method, as indicated in Table 5–2.

N,N'-Sulfinyldiimidazole has also been recommended as a condensing agent for peptide syntheses.[22] In a one-pot reaction the *N*-protected amino acid, sulfinyldiimidazole, amino acid ester hydrochloride, and triethylamine combine to form the peptide in good yield. Thus, the peptide *Z*-Asp($OCH_2C_6H_5$)-Phe-OCH_3 was obtained in 89% yield.[23]

Table 5–2. Polypeptides from silylated amino acids and CDI.

Dipeptides	Yield (%)	Ref.
Z-Gly-DL-Ala	85	[20]
Z-Gly-DL-Val	70	[20]
Z-Gly-DL-Ser	80	[20]
Z-Gly-L-Cys	40	[20]
phthalyl-Gly-β-Ala	83	[18]

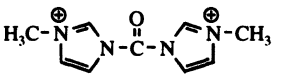
Tri-and tetrapeptides	Yield (%)	Ref.
Z-Gly-DL-**Ala**-DL-**Val**	60	[20]
Z-Gly-DL-**Val**-DL-**Ala**	80	[20]
Z-Gly-DL-**Val**-DL-**Val**	65	[20]
Z-Gly-DL-**Leu**-DL-**Ala**	90	[20]
Z-**Gly**-**Gly**-Gly-β-Ala	80	[21]

Syntheses of Peptides with *N,N'*-Carbonylbis(3-methylimidazolium) Triflate

N,N'-Carbonylbis(3-methylimidazolium) triflate was introduced into peptide synthesis because of its greater reactivity in comparison to CDI.[24] Recently, *N,N'*-carbonylbis(3-methylimidazolium) triflate has been applied in combination with anhydrous $CuCl_2$ and $Cu(OSO_2CF_3)_2$.[25] Activation of the carboxy terminus of a peptide with this reagent followed by reaction with an unhindered amino acid ester in the presence of $CuCl_2$ or $Cu(CF_3SO_3)_2$ gave peptide segment coupling with sometimes less than 0.1% racemization,[25] as shown in Table 5–3.

TABLE 5–3. Peptides prepared with *N,N'*-carbonylbis(3-methylimidazolium) triflate.

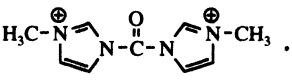
Peptides prepared with



$2\ CF_3SO_3^{\ominus}$ [24]*

	Yield (%)
Z-Gly-Leu-OCH_3	90
Z-Phe-Leu-OCH_3	94
Z-Phe-Val-OCH_3	90
Z-Ala-Val-OCH_3	80
Z-Ala-Ser-OCH_3	92

Peptides prepared with



$\cdot\ CuCl_2 \cdot Cu(CF_3SO_3)_2$ [25]

$2\ CF_3SO_3^{\ominus}$

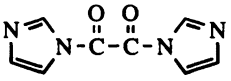
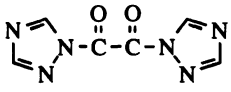
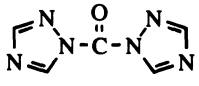
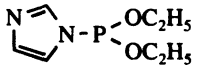
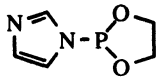
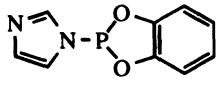
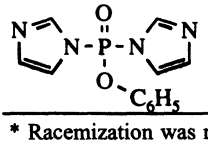
	Yield (%)	Racemization at Phe in %
Z-Ala-**Phe**-**Gly**-$OCH_2C_6H_5$	81	< 0.1
Z-Ala-D-**Phe**-**Ala**-OCH_3	79	< 0.1
Z-Ala-D-**Phe**-**Phe**-$OCH_2C_6H_5$	84	< 0.1
Z-Ala-**Phe**-**Val**-OCH_3	73	0.2 - 0.3
Z-Ala-**Phe**-**Phe**-Phe-OCH_3	76	0.2 - 0.5

* More examples are described in the references cited

Syntheses of Peptides with Other Imidazolides and Triazolides

Besides CDI, other azolides such as *N,N'*-oxalyldiimidazole, *N,N'*-carbonyldi-1,2,4-triazole, *N,N'*-oxalyldi-1,2,4-triazole, and phosphorous and phosphoric imidazolides have been used in the synthesis of peptide bonds, as displayed in Table 5–4.

TABLE 5–4. Peptides prepared with other imidazolides and triazolides.

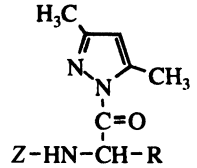
Azolides as coupling agents	Peptides	Yield (%)	Ref.
 resp. 	Z-Ala-Gly-OC_2H_5 *	84, resp. 84	[26]
	Z-Ala-Phe-OCH_3 *	79 83	[26]
	Z-Phe-Gly-OC_2H_5 *	92 97	[26]
	Z-Phe-Leu-OCH_3 *	71 90	[26]
	Boc-Phe-Val-OCH_3 *	85 95	[26]
	Z-Gly-Tyr-OC_2H_5 *	70	[27]
	Z-Gly-Ser-OCH_3 *	69	[27]
	Z-Gly-Phe-OCH_3 *	97	[27]
	Z-Phe-Gly-OC_2H_5 *	71	[27]
	Boc-DL-Val-DL-Val-OCH_3	45 - 50	[8]
	Z-Ala-Ala-OC_2H_5	76	[28]
	Z-Ala-Ala-OC_2H_5	79	[28]
	Z-Ala-Ala-OC_2H_5	73	[28]
	Z-Ala-Ala	85	[29]

* Racemization was not detectable[26],[27]

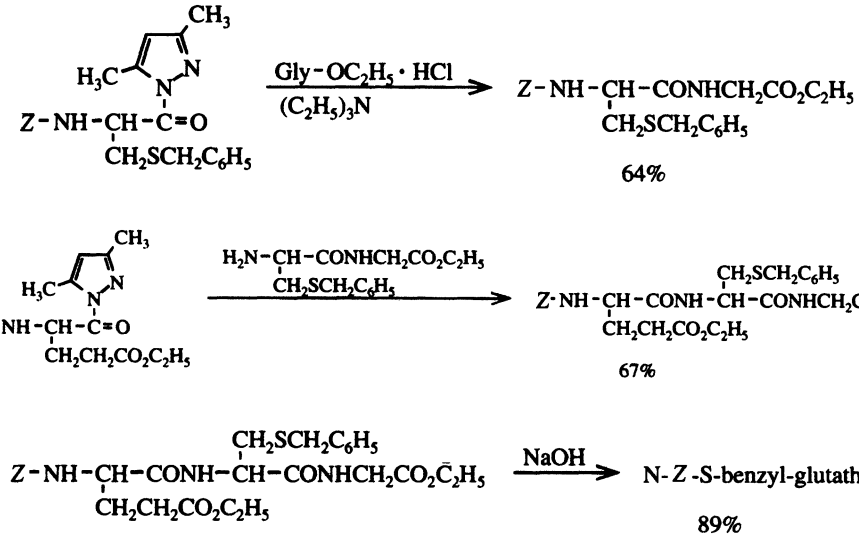
Syntheses of Peptides by Means of Pyrazolides

Peptides can be formed by aminolysis of *N*-aminoacyl-3,5-dimethylpyrazole with free amino acid esters[30] as shown in Table 5–5.

TABLE 5–5. Peptides prepared from pyrazolides.

Pyrazolide	Amino acid ester	Peptide	Yield (%)
	Gly-OC_2H_5	Z-Gly-Gly-OC_2H_5	75
		Z-DL-Ala-Gly-OC_2H_5	78
		Z-Leu-Gly-OC_2H_5	73
		Z-Tyr-Gly-OC_2H_5	88
		Z-DL-Trp-Gly-OC_2H_5	81

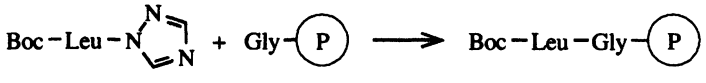
β-Aminoacid peptides (c.f. *Z*-β-Ala-β-Ala-OC_2H_5, 75% yield) have also been prepared by this pyrazolide method.[31] A glutathione synthesis was accomplished by the pyrazolide method in the following way:[32]



O-Ethylphosphoric acid dipyrazolide was used to synthesize *Z*-Phe-Gly-OC_2H_5 in 85% yield.[33]

Solid-Phase Synthesis of Peptides with Triazolides and Imidazolides

The amino acid attached to a polymer is treated with an *N*-protected, carboxyl-activated amino acid to give the supported peptide. In the following reaction the triazolide was formed in situ from the *p*-nitrophenyl ester and 1,2,4-triazole:[34]

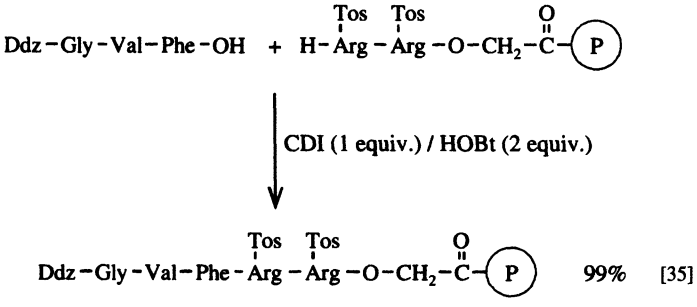


P = polymer from chloromethylated polystyrene / 1,4-divinylbenzene

For the coupling of a supported peptide fragment with an *N*-protected amino acid (or a peptide), CDI and 1-hydroxybenzotriazole (HOBt) were used.[35]

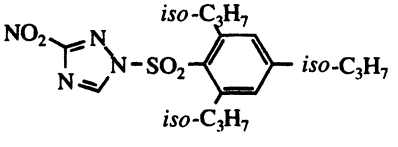
Another solid phase fragment condensation with CDI and 1-hydroxybenzotriazole in the synthesis of the human insulin B-chain afforded the oligopeptide in 75% yield. The reaction time with the coupling pair CDI/HOBt was shorter than in the case of the DCC/HOBt system.[36] The CDI/HOBt activation method was also applied to the synthesis of a

thymosin-α_1 analogue and a proalbumin prosequence. Racemization by that method was insignificant.[37] A further advantage of coupling with CDI/HOBt was the high-yield recovery of excess fragments.[35],[36]

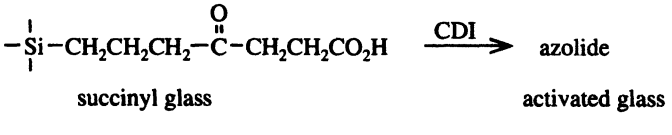


Ddz = α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl
Tos = 4-toluenesulfonyl
(P) = polymer from cross-linked polystyrene with 2-oxoethylbromide anchor functions
HOBt = 1-hydroxybenzotriazole

1-(2,4,6-Triisopropylbenzenesulfonyl)-3-nitro-1,2,4-triazole in the presence of 4-morpholine pyridine-1-oxide was used with advantage as a coupling reagent for a solid-phase (*p*-alkoxybenzyl ester type resin) synthesis of peptides such as Leu-Ala-Gly-Val-OH or Leu-enkephalinamide (Tyr-Gly-Gly-Phe-Leu-NH_2). The overall yield in the latter case was 70%, the purity of the peptide was 85–90%, and racemization was virtually zero.[38]



An application of CDI for the attachment of peptides to porous glass is described in reference [39]. Succinyl glass was treated with CDI to give the activated glass, which was stable at -20 °C under exclusion of moisture. The peptide glass was obtained by covalent attachment of a peptide (e.g., Gly-Leu > 95%, Gly-Leu-Ala > 95%, Gly-Leu-Tyr 93%) as its triethylammonium salt to the activated glass. This method permitted investigation of stepwise degradation of peptides from the CO_2-terminus.



Azolides as Terminating Agents

N-Acetylimidazole was found to be a very efficient terminating (capping) agent in the solid-phase synthesis of peptides.[40],[41] A terminating agent is used to block any *N*-terminal amino groups that have not reacted in the coupling steps.[40]

5.2 Syntheses of Peptides via *Amino*-Activation of Amino Acids

Activation by Imidazolide, Triazolide, and Pyrazolide Groups

The imidazolide group at the amino end of an amino acid is as reactive toward nucleophiles as the imidazolide group at the carboxylic end of an amino acid. If an *N*-protected amino acid is selected as nucleophile, this method can also be used for peptide synthesis. The amino-activated amino acids, for example *N*-(1-imidazolylcarbonyl)-amino acid esters, are prepared from α-isocyanatocarboxylic acids and imidazole.

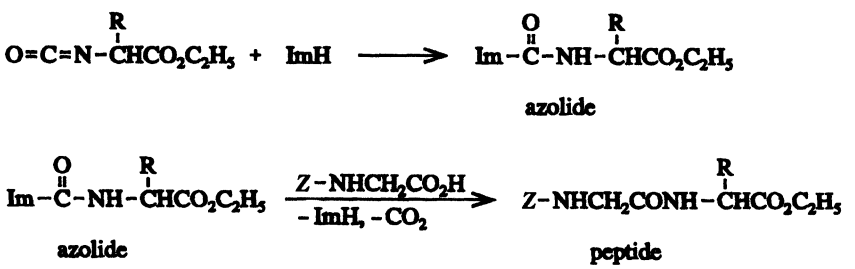


TABLE 5–6. Peptides from *N*-(1-imidazolyl or 1,2,4-triazolyl carbonyl)amino acid ester and *Z*-glycine.

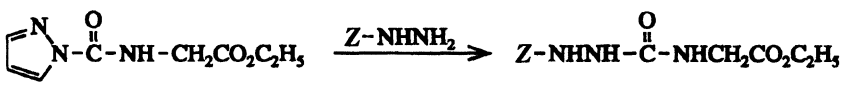
R	Azolide	Yield (%)	Yield of peptide (%)	Ref.
H	imidazolide	84	80	[42]
CH_3 (DL)	imidazolide	92	63	[42]
$C_6H_5CH_2$	imidazolide	89	70	[42]
$C_6H_5CH_2SCH_2$ (L)	imidazolide	79	61	[42]
H	triazolide	84	72	[43]
CH_3 (DL)	triazolide	79	59	[43]
$C_6H_5CH_2$ (L)	triazolide	95	87	[43]
$(CH_3)_2CHCH_2$	triazolide	75	76	[43]

The reaction conditions for this peptide synthesis are equimolar amounts of the reagents, five to eight hours, and 75–85 °C.[44] Use of α-isothiocyanatocarboxylic acids caused the yields of peptides to be lower. Instead of *N*-(1-imidazolylcarbonyl)amino acid esters, the corresponding triazolides were also utilized in the peptide synthesis.

If the reactions are carried out with hydrazides like *Z*-$NHNH_2$ or *Z*-Gly-$NHNH_2$ instead of *N*-protected amino acids, the reaction products are called azapeptides:[43]

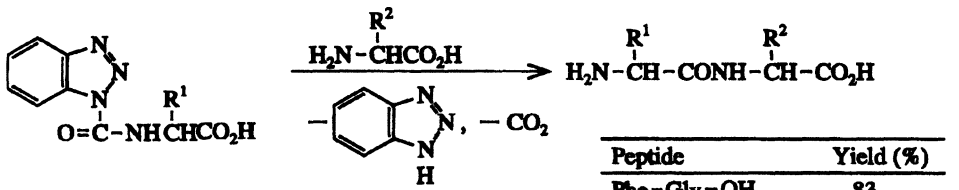
Example:

An azapeptide was also synthesized from a pyrazolide of an *N*-activated glycine ester:[42]



Activation by a Benzotriazolide Group

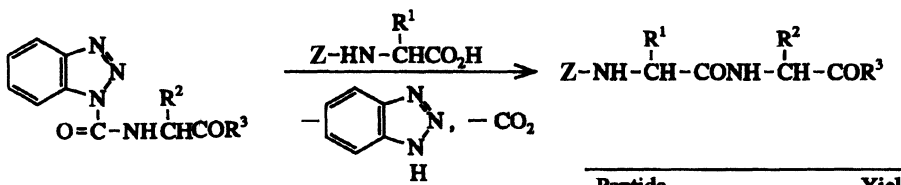
Amino acids activated at the amino group by a benzotriazolide moiety react with amino acids under elimination of benzotriazole and CO_2 to give peptides. Reaction is achieved by warming up equimolar amounts of the components in anhydrous acetonitrile or aqueous acetone.[45] The benzotriazolylcarbonylamino acids are prepared from benzotriazolyl-1-carboxylic acid chloride and amino acids.[46]



Peptide	Yield (%)
Phe-Gly-OH	83
Phe-Leu-OH	87
Gly-Phe-Leu-OH	81

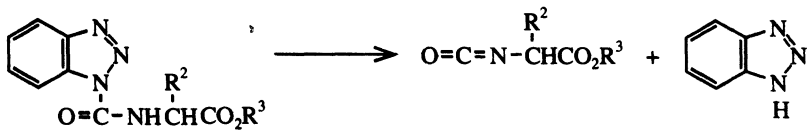
The mechanism of this reaction is not fully understood.[45]

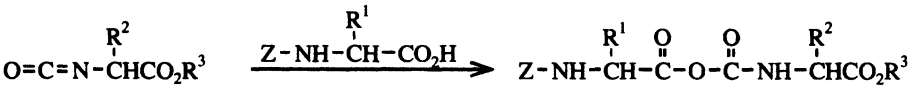
An analogous synthesis of *Z*-protected peptide esters is described in reference [47]. The reaction conditions were heating for several hours in anhydrous xylene at 140 °C.

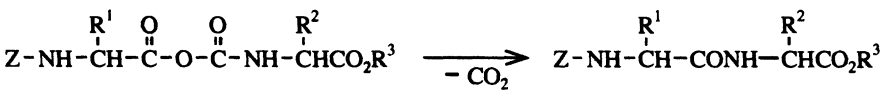


Peptide	Yield (%)
Z-Gly-Gly-OCH_3	60
Z-Gly-Gly-$OCH_2C_6H_5$	55
Z-Phe-Gly-$OCH_2C_6H_5$	75
Z-Phe-Met-OCH_3	51
Z-Gly-Phe-$OCH_2C_6H_5$	68
Z-Phe-Phe-$OCH_2C_6H_5$	75

Tripeptide esters can also be synthesized by this method. Dissociation of the benzotriazolide into benzotriazole and isocyanate has been suggested for the reaction mechanism.[47]

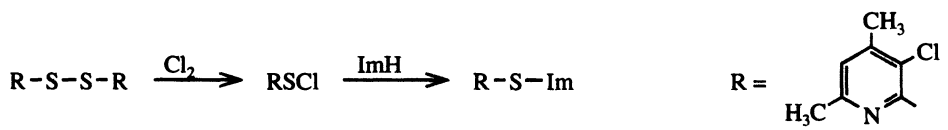


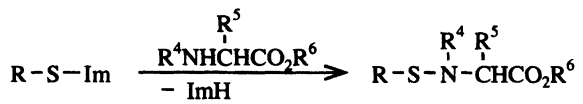




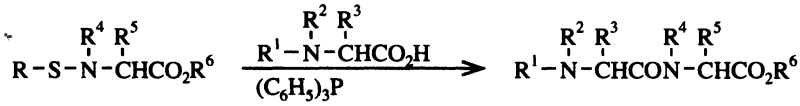
Activation by a Sulfenamide Group

Another *N*-activation of amino acids for peptide synthesis is achieved by preparing sulfenamides from sulfenylimidazoles. A sulfenylimidazole is formed in situ from the sulfenyl chloride (prepared from the disulfide and chlorine) and imidazole, which reacts further with an amino acid ester to give a sulfenamide in high yield. Conversion of such sulfenamides with *N*-acyl amino acids by means of triphenylphosphine affords dipeptides with racemization of less than 0.5%.[48]





R^4	R^5	R^6	Yield (%)
H	*iso*-C_3H_7	CH_3	81
CH_3	*iso*-C_4H_9	$C_6H_5CH_2$	96

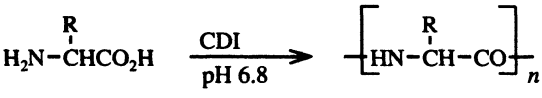


R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
Z	H	*iso*-C_3H_7	H	*iso*-C_3H_7	CH_3	78
Boc	CH_3	*iso*-C_4H_9	CH_3	*iso*-C_3H_7	$C_6H_5CH_2$	80

5.3 Polypeptides

Condensation by CDI

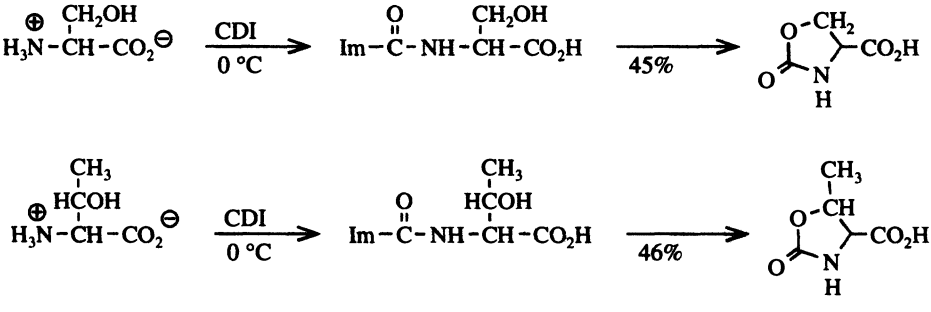
Amino acids such as glycine, alanine, or phenylalanine have been reacted to polypeptides by means of CDI in aqueous imidazole buffer.[49]



The reaction rate of glycine in the presence of CDI is about 700 times greater than without CDI.

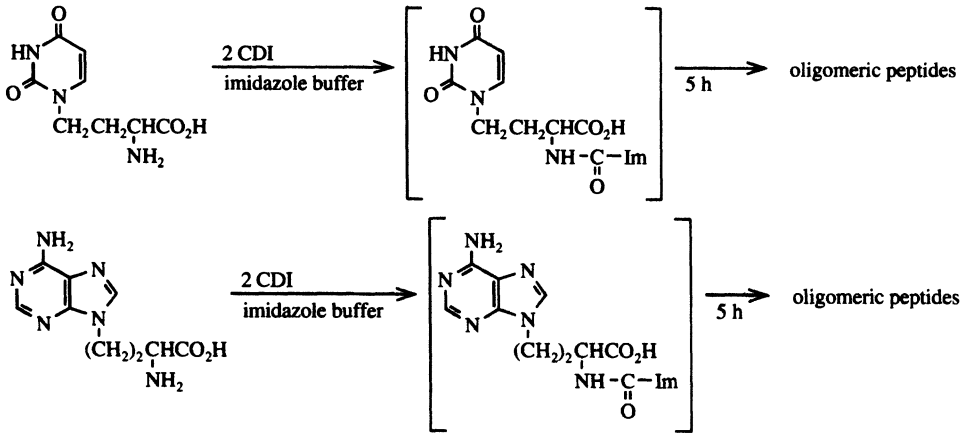
Amino acids containing nucleobases like uracil and adenine, as well as imidazole, such as β-(uracil-1-yl)-α-alanine, β-(adenin-9-yl)-α-alanine, and β-(imidazol-1-yl)-α-alanine, can also be polycondensed by CDI in aqueous imidazole buffer solution at pH 6.8 at 0 °C. The polycondensation leads to low conversion (yields of polymer ~ 1% after four days), but pure polypeptides resulted from the reaction. Thus, compared to other alternative procedures for polycondensation, that using CDI proved to be the most effective.[50]

Test results for a series of reactions of polyfunctional amino acids with CDI in aqueous solution are reported in reference [51]. Serine and threonine did not polycondense. Instead, via the *N*-imidazolyl-carbonyl amino acids, L-2-oxooxazolidine-4-carboxylic acid or L-(+)-*trans*-5-methyl-2-oxooxazolidine-4-carboxylic acid were obtained.



In the reaction of histidine with CDI, however, polycondensation was achieved at 30 °C with excellent yields of oligohistidines via a variety of histidine-containing intermediates.[51]

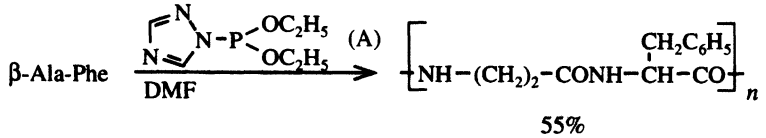
Amino acids containing nucleobases were polycondensed by means of CDI as indicated in the following examples:[52]



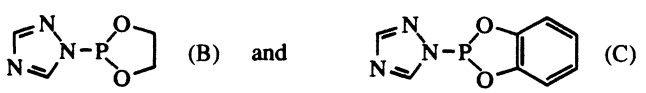
Among the polymeric peptides up to decamers are formed in varying yields.[52]

Condensation by Triazolides

Polycondensation of amino acids with phosphorous diester triazolide are described in references [28] and [53]. Below 80 °C, no racemization was found.

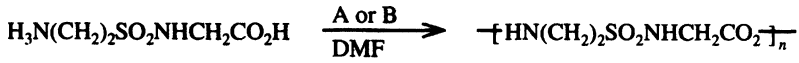


The following phosphorous triazolides, can also be used for this polycondensation. The most suitable triazolide, however, is the phosphorous acid diethyl ester triazolide because of an easy work-up of the reaction mixture.[28]



Other polypeptides obtained by polycondensation with phosphorous diester triazolides are: N^{ε}-*Z*-polylysine,[28] N^{α}-*Z*-isopolylysine,[28] and the sequence polypeptides from β-Ala-β-Ala-Gly.[53]

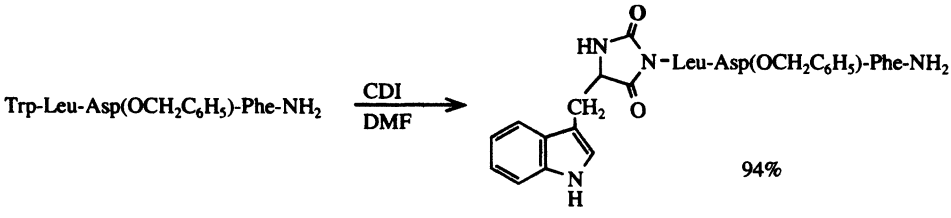
Sequence polypeptides were obtained by polycondensation of tauryl peptides and 3-aminopropansulfonylpeptides with the two phosphorous acid diester triazolides A and B:[54]

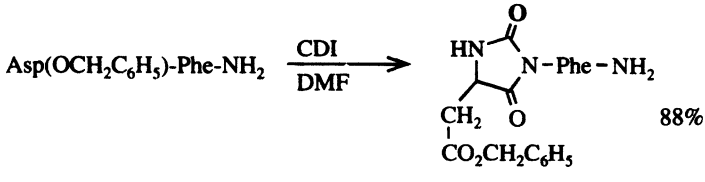


5.4 Determination of Amino Acids in Polypeptides

N-Terminal Cyclization of Peptides

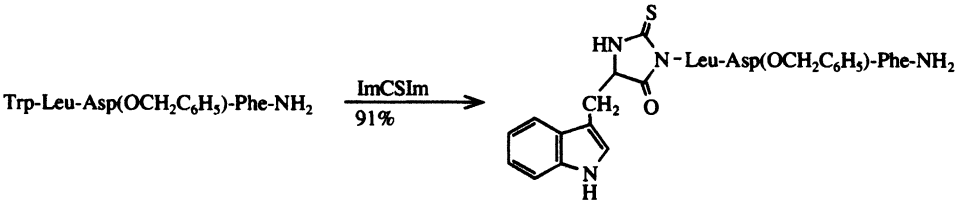
N-Terminal cyclization of peptides by heating to give hydantoins was achieved with CDI or *N,N'*-thiocarbonyldiimidazole (ImCSIm) under very mild conditions (room temp.) and without racemization.[55] This method is suitable for determination of the first two amino acids in the sequence of an unknown oligopeptide, as shown in the following two examples:



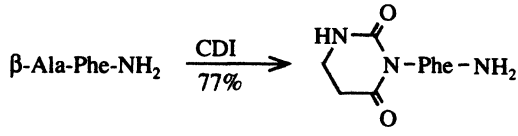


The cyclization reaction can also be carried out with oligopeptides in the solid phase.

Thiohydantoins are obtained analogously by conversion of oligopeptides with ImCSIm:[55]

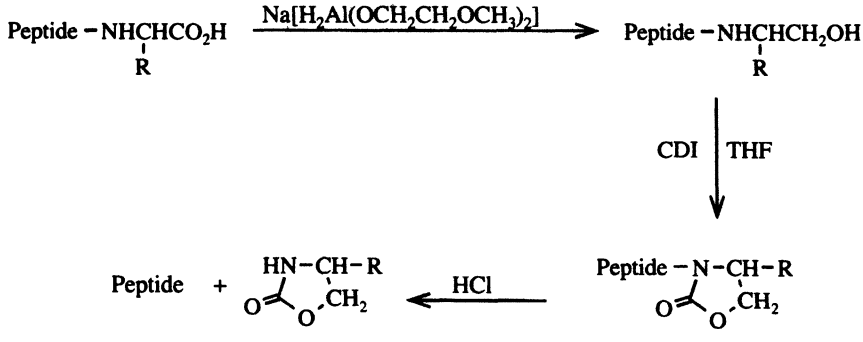


Peptides with *N*-terminal β-amino acids are cyclized by CDI to give 2,4-pyrimidinediones:[55]



Carboxyl Terminal Determination of Peptides

For carboxyl terminal determination of peptides by means of CDI the terminal carboxylic acid group of the peptide is selectively reduced with sodium dihydrobis(2-methoxyethoxy)aluminate to an alcohol. Subsequent conversion of the amino alcohol moiety with CDI yields an *N*-acyl-2-oxazolidone derivative, from which the oxazolidone unit can be easily removed and characterized.[56]



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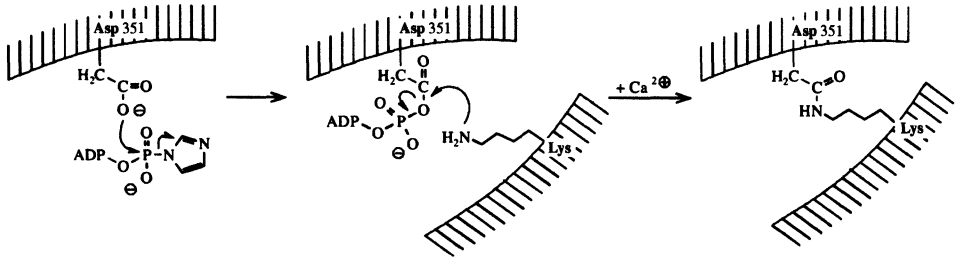
6 Modification and Immobilization of Proteins (Enzymes)

6.1 Modifications of Proteins (Enzymes) with Azolides

Chemical modifications of proteins (enzymes) by reacting them with *N*-acylimidazoles are a way of studying active sites. By this means the amino acid residues (e.g., tyrosine, lysine, histidine) essential for catalytic activity are established on the basis of acylation with the azolides and deacylation with other appropriate reagents (e.g., hydroxylamine).

Example of the modification of an enzyme by an azolide:

The inhibition of Ca^{2+}-ATPase at the active site by ATP-Im or ADP-Im with the participation of Ca^{2+} is illustrated by the following model. In the reaction of ATP-imidazolide with the carboxylate of Asp 351, a mixed anhydride is formed with the aspartate residue, followed by presumably nucleophilic attack of a lysine side chain, thereby displacing the nucleotide and leading to an intramolecular crosslink.[1]



Proteins/enzymes that have been modified with *N*-acetylimidazole include:

Acyl carrier protein[2]
Adenosine triphosphate sulfurylase (Penicillium chrysogenum)[3]
Aldolase (muscle and liver)[4]
Aminopeptidase[5]
α-Amylase (Bacillus subtilis)[6]
Apyrase (isoenzyme of high ATPase/ADPase ratio, potato)[7]
S-Aryltransferase (sheep liver glutathione)[8]
L-Asparaginase[9]
Aspartokinase-homoserine dehydrogenase (Escherichia coli)[10]
ATPase (H^+)[11]
ATPase (human erythrocyte)[12]
ATPase (renal Na, K-ATPase)[13]
Demineralized compact bone matrix[14]
Carboxypeptidase A (goat pancreas)[15]
Carboxypeptidase B (goat pancreas)[16]
Catalase (bovine liver)[17]
α-Chymotrypsin[18]
Colipase (pancreatic)[19]
Collagenase[20]
Complement (protein in the blood /Lymph from guinea pig)[21]
Concanavalin A[22]

Cytochrome C[23]
Cytochrome C (horse heart)[24]
Cytochrome P-450 (liver microsomal)[25]

Diamine oxidase (pig kidney, human pregnancy plasma, pea seedlings)[26]
Dihydrolipoyl transacetylase (Escherichia coli)[27]
Dipeptidyl carboxypeptidase[28]
DNA polymerase-α (human)[29]
DNA polymerase-α (human placenta)[30]

ε-Toxin (Clostridium perfringens)[31],[32]

Fructose 1,6-diphosphatase (rabbit liver)[33]
Fructose diphosphatase (liver)[34]
β-Fucosidase (Achatina balteata)[35]

β-Glucosidase and β-galactosidase (sweet almond emulsin)[36]
Glutamine synthetase (native octameric brain)[37]
Glycogen phosphorylase A[38]
Glycogen phosphorylase B (rabbit muscle)[39]
Glyoxalase I (yeast and human erythrocytes)[40]
Gonadotropin (human chorionic)[41]
Growth hormone (human)[42]

Haptoglobin (type 2-1 human)[43]
Hirudin thrombin complex[44]
D-β-Hydroxybutyrate dehydrogenase (rat liver mitochondrial)[45]

Lactate dehydrogenase (pig heart)[46]
Lectin (seeds of lentil)[47]
Lysozyme[48]

Malic enzyme (pigeon liver)[49]
Mitochondrial L-malate dehydrogenase (bovine heart muscle)[50]

Mutarotase (bovine kidney cortex)[51]

Nuclease (Staphylococcal)[52]

Ornithine transcarbamylase (Streptococcus faecalis and bovine liver)[53]

Pepsin[54]
Phosphorylase B[55]
Phosphorylase B (rabbit muscle)[56]
Prolactin[57]
Prostaglandin endoperoxide synthase[58],[59]
Proteinase (Bowman–Birk soybean)[60]
Proteinase (lima bean)[60]
Renin (mouse submaxillary gland)[61]
Ricin D[62]

Serotonin transporter (human placental)[63]
Sodium/glucose cotransporter (rabbit intestinal brush borders)[64]
Stearylcoenzyme A desaturase (rat liver microsomal)[65]
Subtilopeptidase amylosacchariticus[66]
Succinate dehydrogenase (mitochondrial)[67]

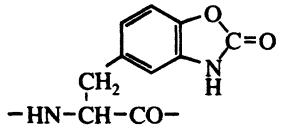
Thrombin (bovine)[68]
Thyroglobin (porcine)[69]
Trypsin (bovine)[70]
Trypsin (lima bean)[71]
Trypsin[72]

UDP–galactose–glucose galactosyltransferase[73]

In ref. [74] it is emphasized that *N*-acetylimidazole reacts with all tyrosyl residues in copolymers and denatured proteins but only with free tyrosyl residues in native proteins. In ref. [75] it is noted that *N*-acetylimidazole reacts extensively with both lysine and tyrosine chains.

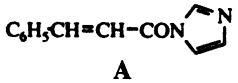
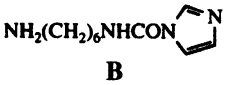
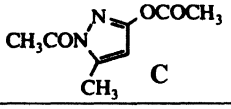
In a few cases when enzymes are treated with CDI the result is crosslinking. The enzyme is often stabilized in the process, thereby retaining its activity.

Enzymes modified with *N,N'*-carbonyldiimidazole (CDI) include: horseradish peroxidase,[76] β-lactamase after nitration and reduction,[77] lysozyme, and urease.[78] Ref. [77] describes how the tyrosine side chain of a protein was nitrated, reduced with dithionite to an amino group, and then treated with CDI or *N*-(2,2,2-trifluoroethoxycarbonyl)imidazole to give the benzoxazolinonyl alanine moiety:

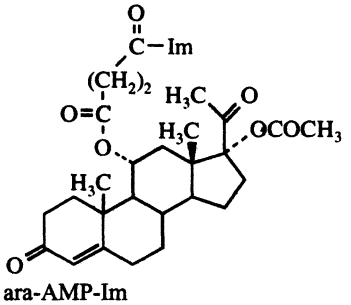


No significant loss of β-lactamase activity was associated with this modification.

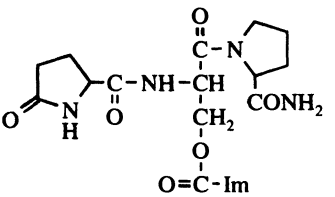
Several proteins have been modified with *N*-cinnamoylimidazole (A), 1-(*N*-6-aminohexyl)-carbamoylimidazole (B) or 1-acetyl-3-acetoxy-5-methylpyrazole (C):

 A	 B	 C
Acetylcholinesterase [79]	Kidney-cell plasminogen activator [92]	Bovine serum albumin [93]
α-Chymotrypsin [79]–[88]	Plasmin [92]	α-Chymotrypsin [93]
β-Chymotrypsin [89]	β-Trypsin [92]	β-Chymotrypsin [93]
Elastase [79]	Urokinase [92]	Insulin [93]
Papain [79], [90], [91]		Lysozyme [93]
Subtilisin [79], [89]		Ovalbumin [93]
Trypsin [79]		RNase [93]
		Trypsin [93]

Proteins modified with other azolides:

Proteins	Azolides	Ref.
Acyl carrier protein	$C_nH_{2n+1}CO$-Im ($n=3$, 13, 15; Δ^3-decenoyl-Im)	[1]
Bovine serum albumin		[94]
Lactosaminated human serum albumin (L-HSA)	ara-AMP-Im	[95]
Ca-ATPase	ATP-Im	[96]
α-Chymotrypsin	a) furylacryloyl-Im	[82], [97]
	b) indoleacryloyl-Im	[82]
	c) thienylacryloyl-Im	[97]
	d) $C_6H_5C\equiv C$-COIm	[98]

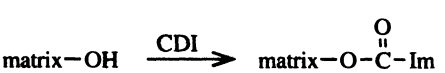
(*continued*)

Proteins	Azolides	Ref.
β-Chymotrypsin	indoleacryloyl-Im	[89]
δ-Chymotrypsin	*N*-acetylbenzotriazole	[99]
Creatine kinase	AMP-Im, ADP-Im, ATP-Im	[100]
DNA-polymerase	ATP-Im	[101]
Factor serum thymic	*N*-acetylbenzotriazole	[102]
Horseradish peroxidase	$C_8F_{17}(CH_2)_2COIm$	[103]
Phospholipase A_2 (bee venom)	oleoyl-Im	[104]
Subtilisin	a) indoleacryloyl-Im	[89]
	b) furylacryloyl-Im	[105]
Thyrotropin-releasing hormone (THR)	 Pyroglutamyl-*O*-(1-imidazolyl-carbonylseryl)-prolinamide	[106]
Urease	$C_8F_{17}(CH_2)_2COIm$	[107]

6.2 Immobilization of Proteins (Enzymes) and Affinity Ligands Mediated by CDI

A review covering CDI-mediated immobilization of enzymes and affinity ligands with preparations of activated matrices, ligand coupling to CDI-activated supports, and applications of CDI-derived biospecific affinity supports in the purification of enzymes is available in reference [108]. This method has been used in biospecific interaction chromatography (affinity chromatography for the purification of biologically active molecules such as enzymes[108] or antibodies[109]). Polymeric supports (gel matrices) containing hydroxy groups are activated by CDI to give intermediate imidazolylcarbamates that readily react with *N*-nucleophiles such as the free amino groups of the ligands (proteins), yielding non-basic, uncharged *N*-alkyl carbamates.[108],[110]

Activation of gel matrices by CDI (anhydrous milieu):



Coupling of a protein to the support (aqueous milieu):

$$\text{matrix}-O-\overset{\overset{O}{\|}}{C}-\text{Im} \xrightarrow[\text{pH 5 - 10}]{RNH_2} \text{matrix}-O-\overset{\overset{O}{\|}}{C}-NHR$$

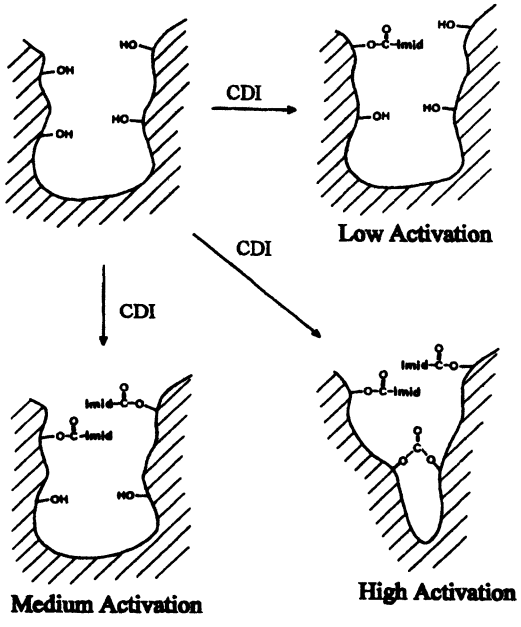
RNH_2 = protein or $HO_2C(CH_2)_5NH_2$ or $NH_2(CH_2)_6NH_2$

This method is considered to be superior to the standard cyanogen bromide procedure.[108],[110]

The activation reaction is usually carried out in acetone, dioxane, or dimethylformamide. The activated matrices have sufficient stability to aqueous conditions to allow isolation of the washed products.[111] In addition to CDI, *N,N'*-carbonyldi-1,2,4-triazole or *N,N'*-carbonyldi-1,2,3-benzotriazole have also been tested as activating agents.[108],[111],[112] Among them, however, CDI is most convenient for preparation of the activated matrices used in affinity chromatographic experiments. The carbonyldi-1,2,4-triazole-activated matrix is more reactive than the CDI-activated matrix, and therefore useful for the coupling of unstable protein ligands over short coupling times. Carbonyldibenzotriazole reacts with the matrix only slowly and inefficiently.[111] Proteins are attached to the supports either directly or via spacer molecules (leashes) such as 6-aminohexanoic acid,[108] 1,6-diaminohexane,[110] or 3-aminophenylboronic acid.[113] In the latter cases coupling of the leash to the matrix is achieved by CDI, while coupling of the protein to the leash is usually carried out with other mediators (for instance, with a carbodiimide, as described in references [111] and [112]). The matrices can be polysaccharides or similar soft polymeric gels such as agarose (e.g. sepharose CL-6B), cellulose, cross-linked dextrans, cross-linked allyl dextrans, agarose polyacrylamide copolymers, poly(ethylene glycols), hydroxylic vinyl-, acryl- or allyl copolymers, and silica-based supports such as quartz surfaces with spacer chains, glyceryl propyl bonded porous diol silica,[108] or primary hydroxyl silica.[109],[114],[115] In the activation of hydroxylic solid phase supports with CDI, high levels of activation can be achieved. For example, with cross-linked agarose in dioxane the yield of active groups was found to be 1.73 mmol/3 g of moist cake, or 65%. This CDI-activated agarose had a half life of greater than fourteen weeks when stored in dioxane, with good stability over a wide pH range.[116] Activation of various other insoluble polysaccharides with CDI and the properties of the activated matrices are discussed in reference [116].

The diverse activation levels of polyhydroxylic matrices generated by conversion with CDI is illustrated in reference [117].

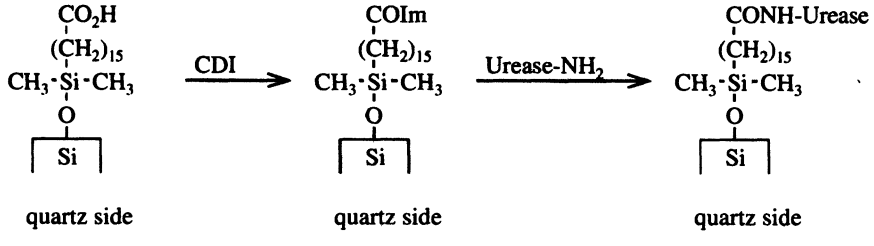
The scheme below shows reaction possibilities for carbonyldiimidazole activation of polyhydroxylic matrices. The formation of these activated sites depends on[117] 1. the partial disposition of hydroxyl groups accessible to the solvent, 2. the initial concentration of CDI, and 3. the chemical nature of the gel matrix.



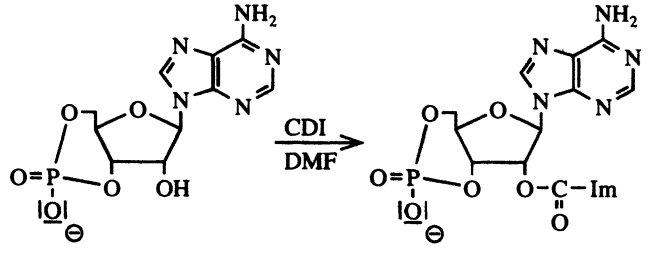
Optimization of the CDI method for the development of affinity membranes of the cellulosic or polyamide type is described in reference [118].

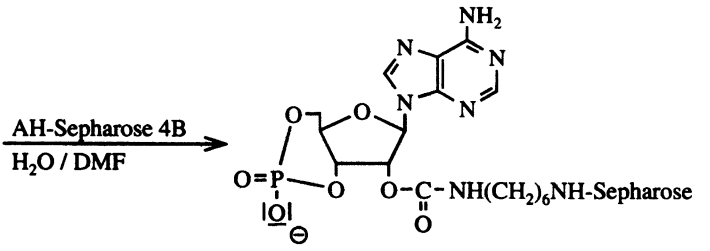
Different types of protein or ligand linkages to hydroxylic matrices via spacers are shown in the following three examples:

Example 1: Attachment of an enzyme to a quartz surface is usually effected via a spacer chain.[119]

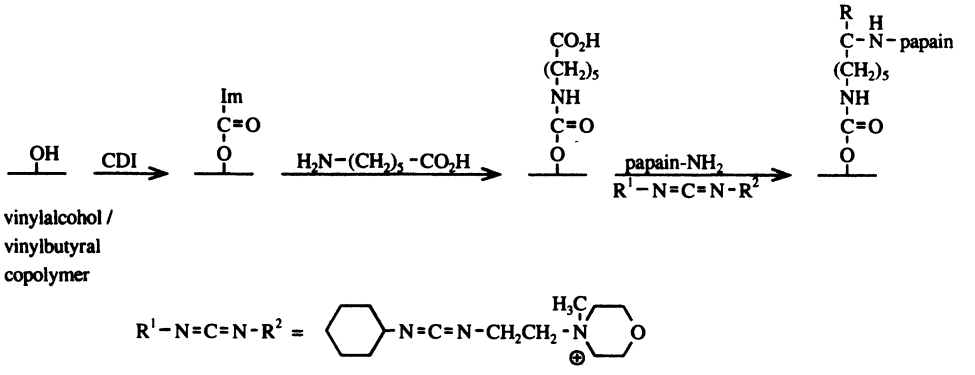


Example 2: Linkage of *c*-AMP to aminohexyl(AH)-Sepharose 4B.[120]



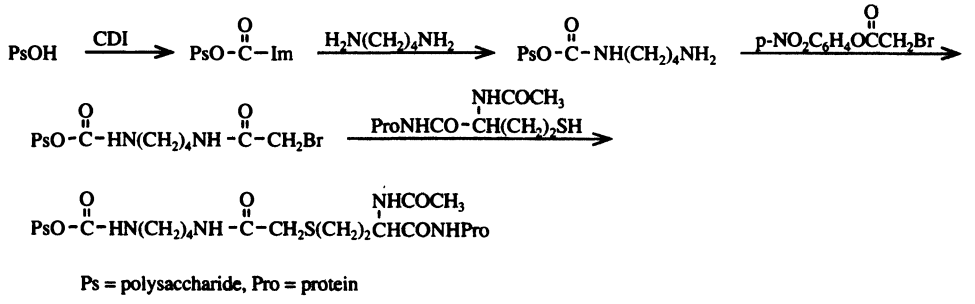


Example 3: Coupling of a protein to a copolymer via a spacer.[121]



Enzymes or affinity ligands attached by the aid of CDI to various matrices are listed in Tables 6–1, 6–2 and 6–3.

Bacterial polysaccharides were activated with CDI and then coupled via spacers to immunogenic membrane proteins.[133],[134]



Ps = polysaccharide, Pro = protein

Cellulose acetate-bonded photosensitizers are prepared by coupling a carboxyl-containing photosensitizer (such as bengale rosa, rhodamine B, or acridine orange modified with chloromethylbenzoic acid) to the hydroxyl containing cellulose acetate by means of CDI. Photosensitizers immobilized in this way by an ester linkage are used for the production of singlet oxygen.[135]

Table 6–1. Immobilization of enzymes and affinity ligands on polysaccharide matrices with CDI.

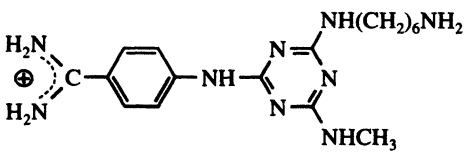
Matrix	Attached protein or affinity ligand, or spacer and affinity ligand	Ref.
Agarose	a) *m*-Aminophenylboronic acid	[113], [122]
	b) Insulin	[123]
Bead cellulose	6-Aminocaproyl-*p*-aminobenzamidine	[124]
Phosphocellulose	RNA	[125], [126]
Sepharose CL-4B	a) 	[127]
	b) Goat antiapolipoprotein B polyclonal antibody	[128]
AH Sepharose 4B	*c*-AMP	[120]
Sepharose CL-6B	a) 6-Aminocaproyl-*p*-aminobenzamidine	[108], [112], [124]
	b) 1,6-Diaminohexane/iminobiotin	[108], [129]
	c) 6-Aminohexanoic acid/trypsin inhibitor	[130], [131]
	d) Thyroglobulin	[132]
	e) Immunoglobulin (IgG)	[132]
	f) 6-Aminohexanoic acid/*p*-aminobenzamide	[112]
	g) Trypsin inhibitor	[110], [112]
	h) Lactate dehydrogenase	[108]

Table 6–2. Immobilization of enzymes and affinity ligands on silica gel matrices with CDI.

Matrix	Attached protein or affinity ligand or spacer/affinity ligand	Ref.
Diol bonded silica	Glucosamine, bovine serum albumin, immunoglobulin, acetylcholine esterase, horse liver alcohol dehydrogenase	[136]
Diol silica	Concanavalin	[137]
LiChrospher Si 500	Protein A	[108]
Porous glass	*p*-Aminophenylboronic acid	[138]
Primary hydroxy silica	a) Trypsin inhibitor	[109], [114]
	b) Trypsin	[115]
Silica gel coated with dextran or agarose	Protein A, concanavaline A	[139]
Nickel/silica composite	Invertase	[140]
Quartz surfaces	16-Carbon spacer chain, urease	[119]

TABLE 6–3. Immobilization of enzymes and affinity ligands on matrices from polyamides, proteins, or other polymers/copolymers with CDI.

Matrix	Attached protein or affinity ligand or spacer/affinity ligand	Ref.
Acid hydrolyzed nylon 6/6	Antibodies	[142]
Bovine serum albumin	7-Imidazolylcarbonyltaxol	[143]
Histone	*m*-Aminophenylboronic acid	[144]
Styrene/4-vinylbenzoic acid copolymer	Lysozyme	[145]
Fractogel HW 65 F	Antilysozyme	[146]
Poly(ethylene glycols)	Trypsin-radiolabeled a_2-macroglobulin complex	[108]
Ethylene glycol dimethacrylate/ hydroxyethyl methacrylate/ methyl methacrylate copolymer	Antibodies	[147], [148]*
Rayon polyester	Bovine serum albumin	[150]
Trisacryl GF 2000	a) Antilysozyme	[146]
	b) Protein A	[108]
	c) Pepsin	[108]
Vinylalcohol/vinylbutyral copolymer membrane	a) Papain	[121]
	b) 6-Aminocaproic acid/Papain	[121]

* Further examples are given in references [147]–[149]

The formation of a nucleosil bonded lecithin by means of an imidazolide is described in reference [141]. See also Chapter 4, page 165.

Antibodies were attached to liposomes by the CDI activation method via the glycolipid tetradecylmelibionamide.[151]

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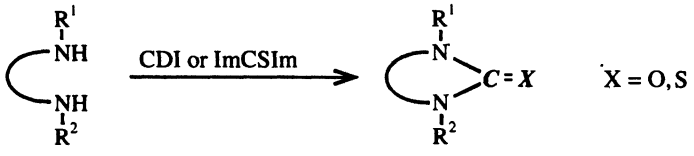
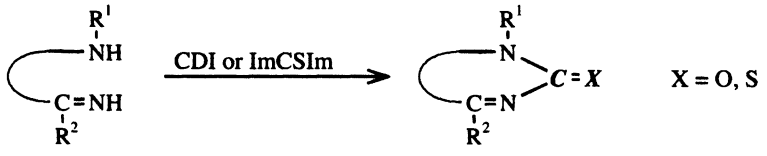
7 Syntheses of Heterocycles

7.1 Heterocycles Based on C=O, C=S, or S=O Insertion Using *N,N'*-Carbonyldiimidazole (CDI), *N,N'*-Thiocarbonyldiimidazole (ImCSIm), and *N,N'*-Sulfinyldiimidazole (ImSOIm)

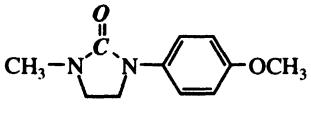
7.1.1 Five-Membered Rings with N–CO–N or N–CS–N Units

The insertion of a C=O or C=S group between two amino functions or one amino and one imino function of 1,2-diamino or amino/imino compounds leads to five-membered heterocyclic rings.

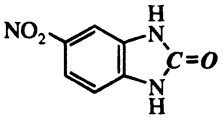




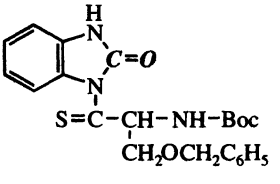
Various five-membered rings and their cyclization yields are shown below, with the inserted groups in italics:



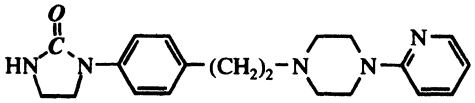
88% [1]



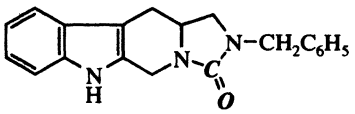
75% [2]



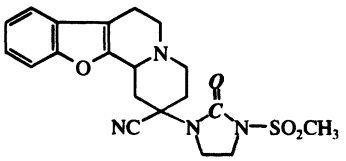
(prepared with carbonylditriazole)
91% [3]



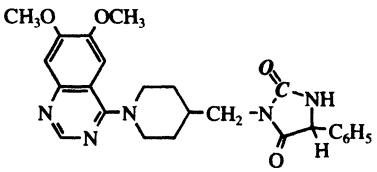
47% [4]



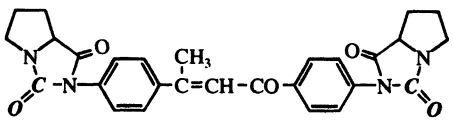
72% [5]



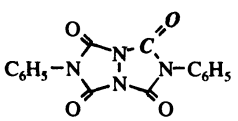
91% [6]



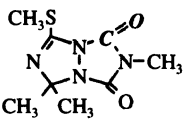
53% [7]



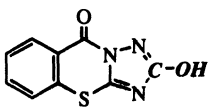
45% [8]



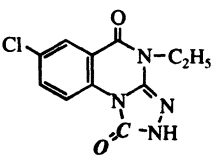
80% [9]



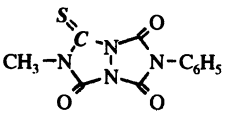
86% [10]



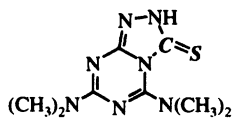
85% [11]



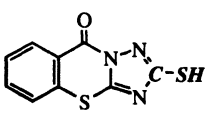
36% [12]



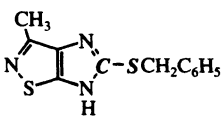
51% [13]



65% [14]



85% [11],[15]

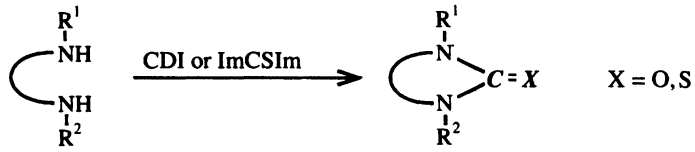


61% (after benzylation) [16]

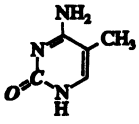
Further examples of this type are described in references [17]–[21].

7.1.2 Six-Membered Rings with N–CO–N or N–CS–N Units

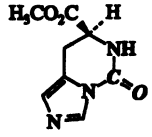
Insertion of a C=O or C=S group between the two amino functions of a 1,3-diamino compound proceeds correspondingly to give six-membered heterocycles.



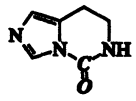
Examples:



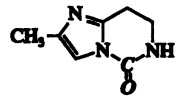
> 90% [22]



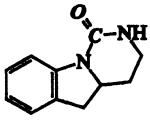
96% [23]



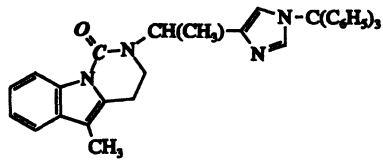
60% [24]



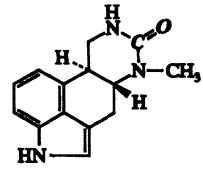
62% [25]



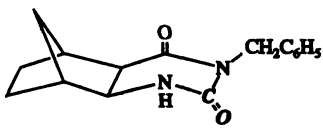
41% [26]



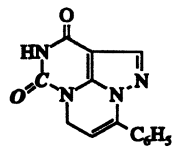
82% [26]



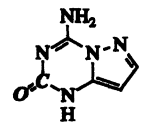
80% [27]



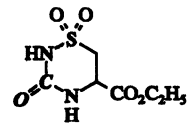
85% [28]



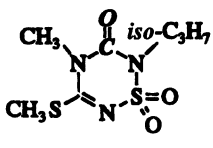
72% [29]



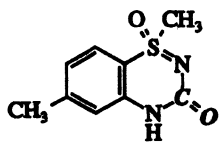
89% [30]



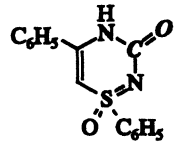
86% [31]



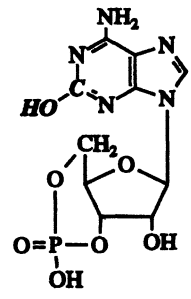
91% [32]



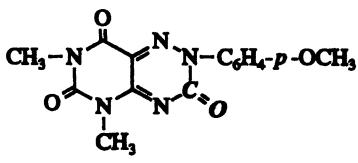
82% [33]



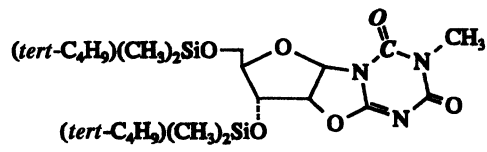
87% [34]



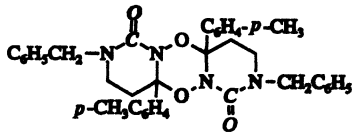
33% [35]



95% [36]



85% [36a]



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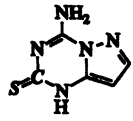
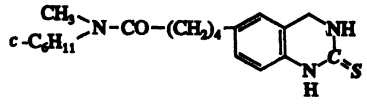


43% [30]



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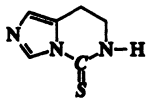
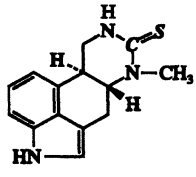
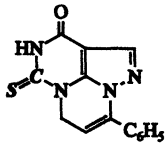


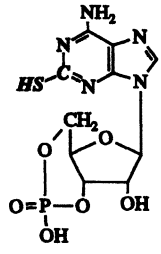
60% [39]



81% [27]



85% [29]

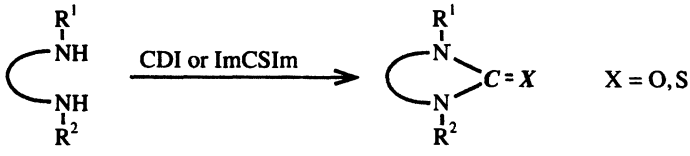


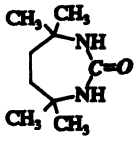
48% [35]

Further examples of this type are found in references [40]–[43].

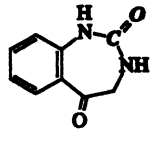
7.1.3 Seven-Membered Rings with N–CO–N or N–CS–N Units

The insertion of a C=O or C=S group between the two amino functions of a 1,4-diamino compound to give a seven-membered heterocycle usually occurs in very good yield. The yields of heterocycles are, in most cases,[44] considerably higher than in the corresponding reactions with phosgene or thiophosgene. For instance, the 1,3,5-triazepin-2-thione derivative in ref. [45] could not be obtained with thiophosgene at all.

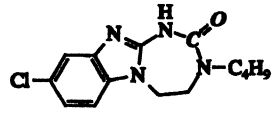




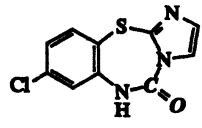
40% [46]
see also [46a],[46b]



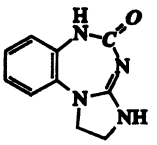
88% [47]



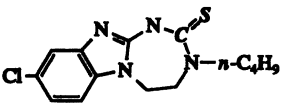
53% [45]



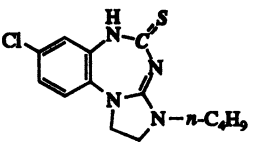
85% [48]



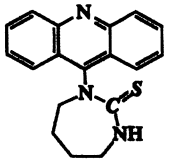
82–90% [44]



46% [45]



82% [44]

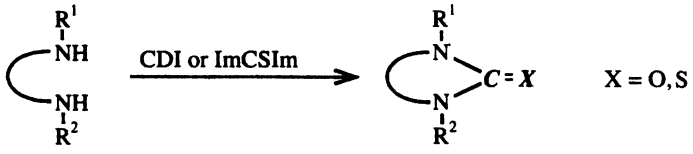


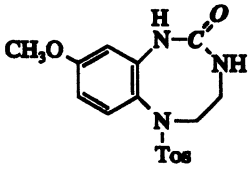
39% (with thiocarbonyl-ditriazole) [49]

For further examples of this type see reference [50].

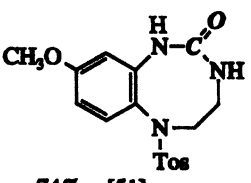
7.1.4 Eight- and Higher-Membered Rings with N–CO–N or N–CS–N Units

Insertion of a C=O or C=S group between the two amino functions of a 1,5-diamino compound can be used to produce eight-membered heterocycles. Higher membered heterocylces are also obtained on this way:

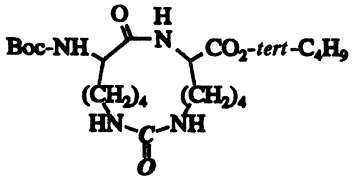




66% [51]



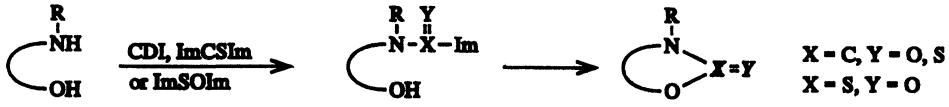
74% [51]



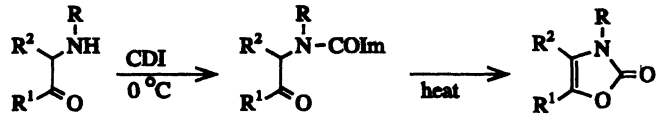
99% [52]

7.1.5 Five-Membered Rings with N–CO–O, N–CS–O, or N–SO–O Units

Insertion of a C=O, C=S or S=O group between an amino and a hydroxy function of a 1,2-aminoalcohol produces a five-membered heterocycle with O and N as ring hetero-atoms linked by –CO–, –CS– and –SO–groups. Although the reaction proceeds in two steps, it can often be carried out as a one-pot process.

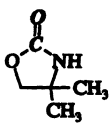


If R = H an isocyanate is formed as a further intermediate. The required OH group can also originate from a keto–enol equilibrium as below.[53]

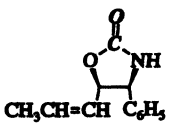


R^1	R^2	R	Imidazole-*N*-carboxamide	Oxazolone
C_6H_5	H	H	91%	40%
C_6H_5	CH_3	H	99%	98%
C_6H_5	H	CH_3	57%	34%

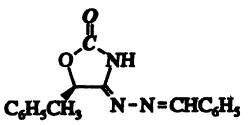
Further examples of heterocycles prepared accordingly:



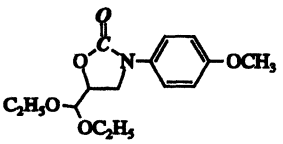
94% [54]



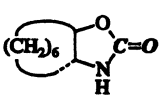
88% [54a]



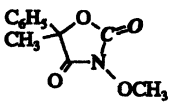
78% [55]



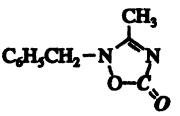
93% [56]



52% [57]



85% [58]



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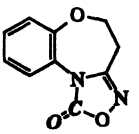

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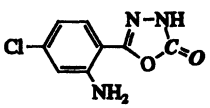
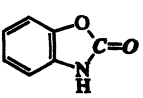
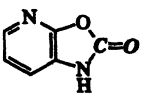


87% [61]



97% [62]



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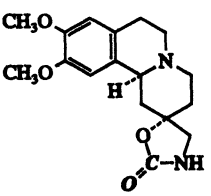

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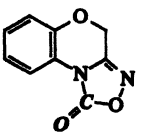

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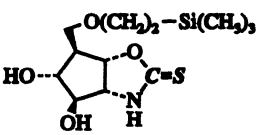

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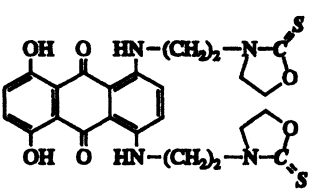
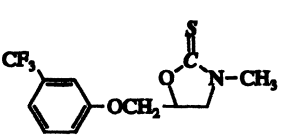
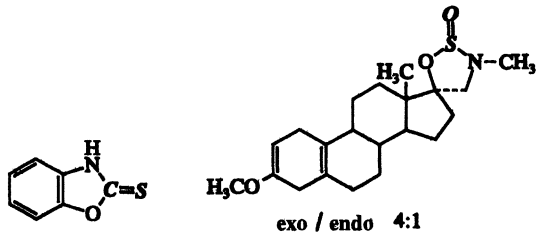


88% [67]

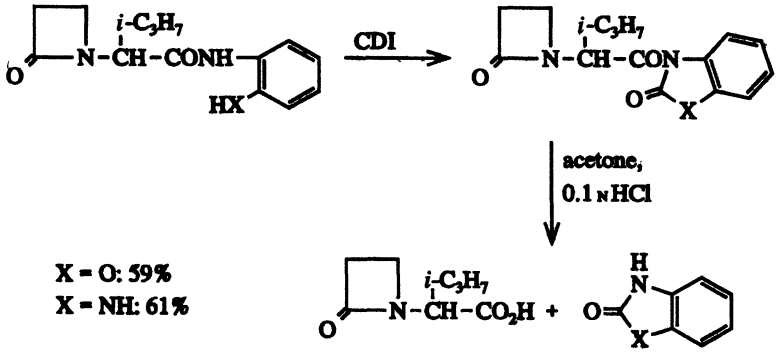


87% [68]



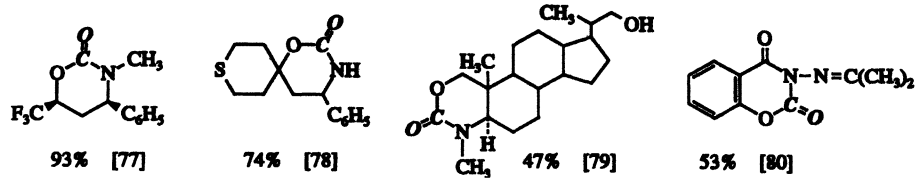
Other examples are described in references [1], [64], [71]–[75].

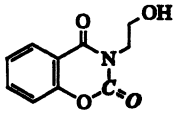
The CO-transfer reaction onto *o*-aminophenol or *o*-phenylenediamine by CDI has been used as a method for converting β-lactam carbanilides, obtained by a 4-component condensation, into the corresponding carboxylic acids without damaging the sensitive β-lactam moiety. The method has its basis in the production of easily cleavable compounds from *o*-hydroxy- and *o*-aminoanilides and CDI:[76]



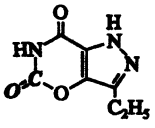
7.1.6 Six-Membered Rings with N–CO–O or N–CS–O Units

In analogy to the preceding Section 7.1.5 the insertion of a C=O or C=S group between an amino and a hydroxy function of 1,3-aminoalcohols using CDI or ImCSIm yields six-membered heterocycles with a carbamate or thiocarbamate structure.





83% [81]



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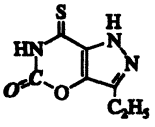
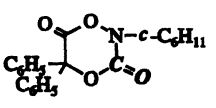
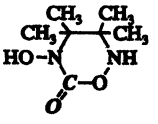


61% [82]



65% [83]



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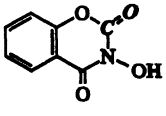

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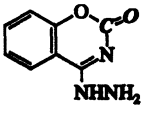
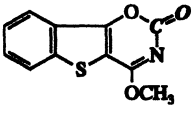
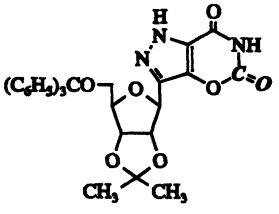


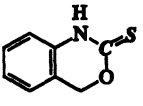
79% [86]



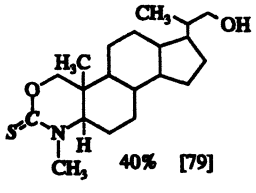
54% [86]



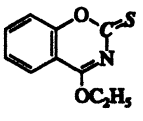
56% [87]



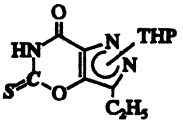
74% [69]



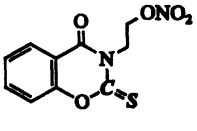
40% [79]



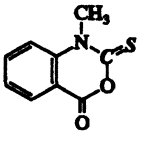
56% [86]



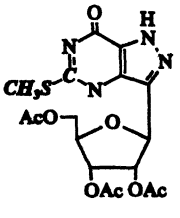
34% [82]



57% [81]



77% [69]

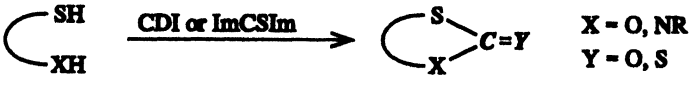


93% (after methylation with CH_3I) [88]

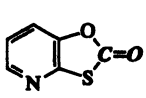
Further examples in references [89]–[91].

7.1.7 Five- and Six-Membered Rings with O–CO–S, N–CO–S, or N–CS–S Units

Insertion of a C=O or C=S group between hydroxy or amino groups and a thiol function in 1,2- or 1,3-positions leads to a five- or six-membered heterocycle:

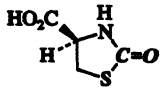


Examples:

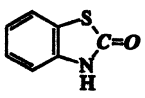


90% [92]

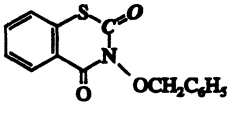
68% [93]



71% [94]

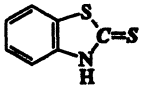


72% [95]

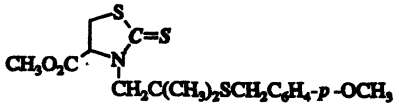


71% [96]

62% [97]



92% [69]

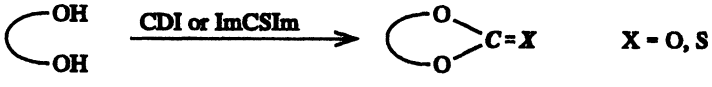


91% [98]

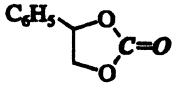
Further examples are described in reference [99].

7.1.8 Five- and Six-Membered Rings with O–CO–O or O–CS–O Units

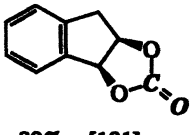
Insertion of a C=O or C=S group between the two hydroxy functions of 1,2- and 1,3-diols results in a five- or six-membered ring (see also Section 3.8).



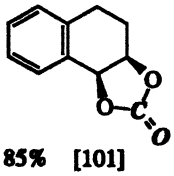
Examples:



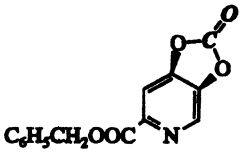
40 - 60% [100]



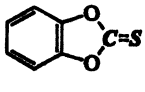
80% [101]



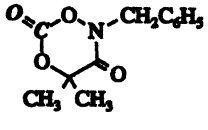
85% [101]



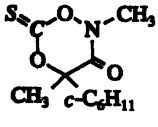
76% [102]



82% [69]



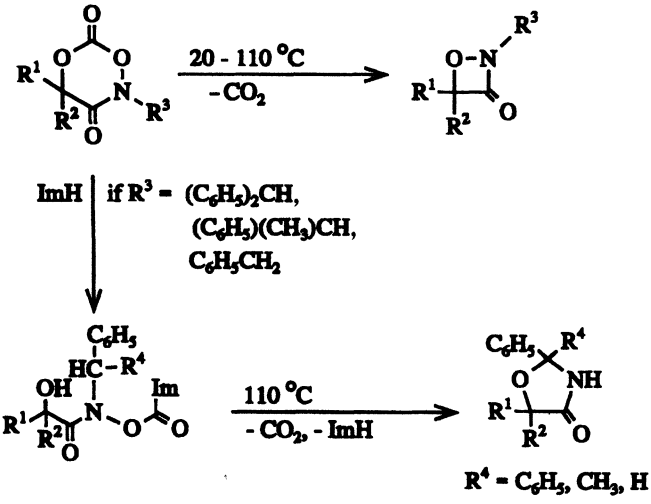
85% [103]



78% [104]

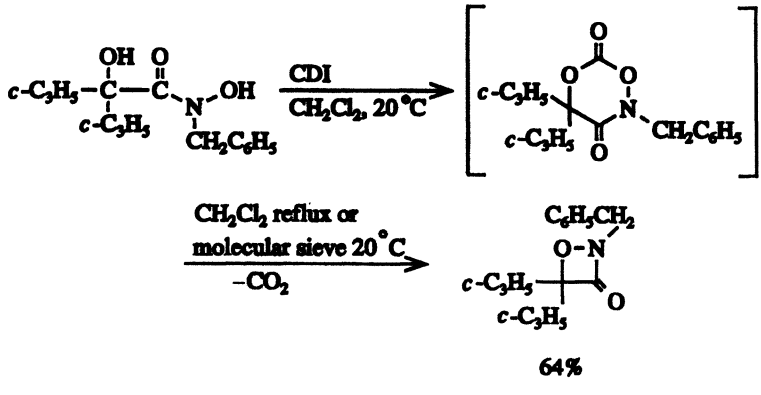
Further examples of the 1,5,2-dioxazinane-3,6-dione type obtained from glycolohydroxamic acids and CDI are described in references [105] and [106].

These compounds can be converted either to 1,2-oxazetidin-3-ones[105],[107]–[109] under elimination of CO_2 or to 4-oxazolidinones[107] by treatment with imidazole:



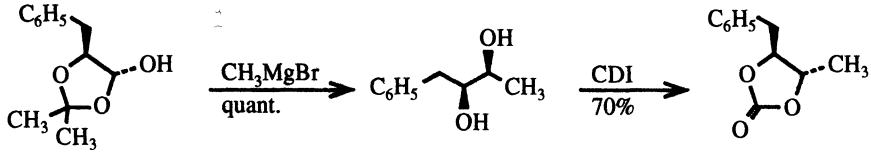
Other follow-up reactions from the 1,5,2-dioxazinane-3,6-diones are described in reference [106].

Reference [110] describes the synthesis of 1,2-oxazetidin-3-ones from *N*-substituted glycolohydroxamic acids and CDI without isolation or purification of the intermediate 1,5,2-dioxazinane-3,6-diones:



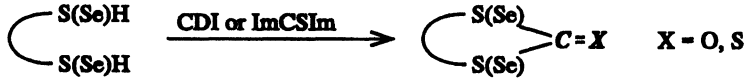
The conversion of 4-hydroxy-1,3-dioxolanes into 2-oxodioxolanes with CDI via a diol is described in reference [110a]:

Example:

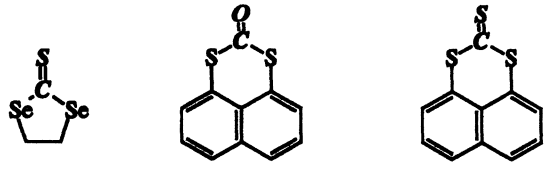


7.1.9 Five- and Six-Membered Rings with S–CO–S, S–CS–S, or Se–CS–Se Units

Insertion of a C=O or C=S group between two thiol or two selenol functions of a 1,2- or 1,3-dithiol or diselenol results in formation of the corresponding five- or six-membered heterocycles.



Examples:

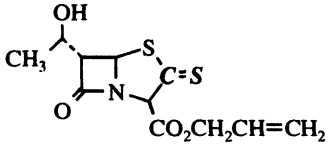


30% [111] 94% [112] 97% [112]

7.1.10 Five- and Six-Membered Rings with S–CS–C or N–CO–C Units

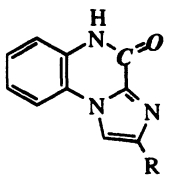
Insertion of a C=S group between a thiol and a CH function of a corresponding thiol (a) or of a C=O group between an amine and a CH function of a corresponding amino compound (b) may be achieved in the following ways:

Examples:

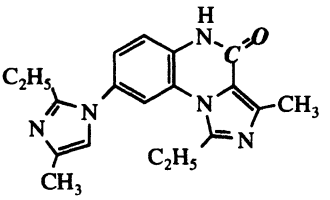


70% [113], see also [114]

Examples:



R = H, CH_3; 85 - 96% [115]

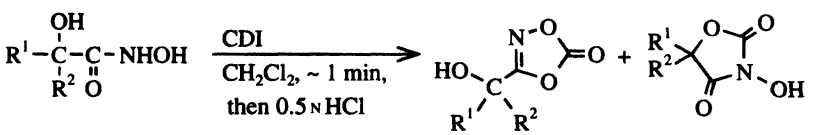


98% [115]

For further examples see reference [116].

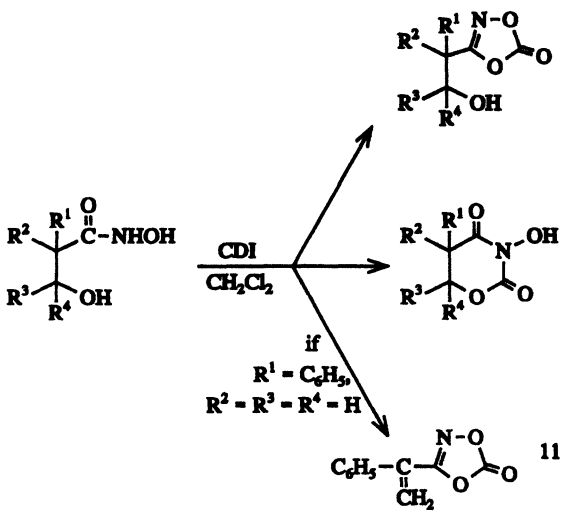
7.1.11 Special Cases of Syntheses of Five- and Six-Membered Rings by Use of CDI and *N,N'*-Sulfinyldiimidazole (ImSOIm)

Heterocycles like 1,4,2-dioxazole-5-ones and 3-hydroxy-1,3-oxazolidine-2,4-diones are formed from a 2-hydroxycarbohydroxamic acid and CDI in the following reactions:[117]



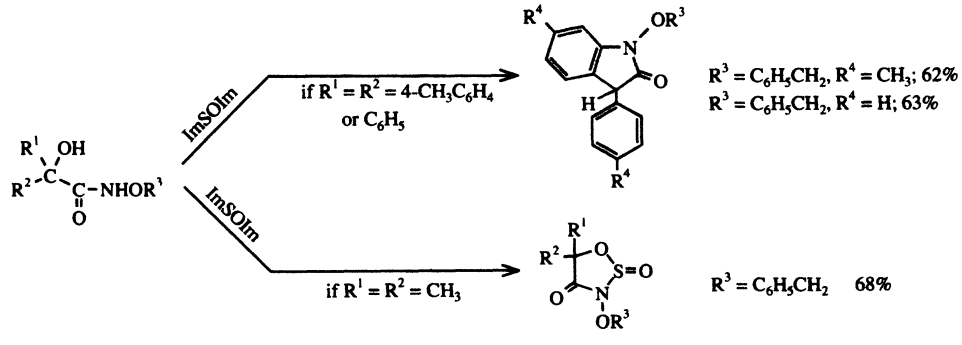
R^1	R^2		
C_6H_5	C_6H_5	91%	–
C_6H_5	*c*-C_6H_{11}	90%	–
C_6H_5	CH_3	93%	–
$-(CH_2)_6-$		89%	–
$C_6H_5CH_2$	H	25%	38%
C_6H_5	H	–	63%

Depending on the substitution of the 3-hydroxycarbohydroxamic acids, 1,4,2-dioxazole-5-ones, 1,3-oxazine-2,4-diones, or 3-ethenyl-1,4,2-dioxazole-5-ones are formed with CDI.[118]

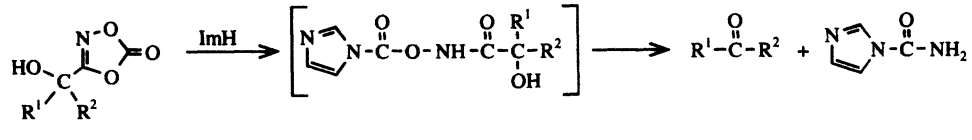


R^1	R^2	R^3	R^4	yield (%)
H	H	$-(CH_2)_5-$		91
C_6H_5	H	$-(CH_2)_5-$		90
$-(CH_2)_5-$		H	H	45
CH_3	C_6H_5	H	H	23
$-(CH_2)_5-$		H	H	35
CH_3	C_6H_5	H	H	42
C_6H_5	C_6H_5	H	H	88
C_6H_5	H	H	H	37

Starting with 2-hydroxycarbohydroxamic acids and ImSOIm, 3-alkoxy-1,2,3-oxathiazolidine-4-one 2-oxides or 1-alkoxy-3-arylindoline-2-ones can be obtained depending on the substituents at C-2 of the hydroxamic acid:[119]

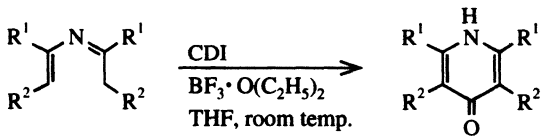


The 3-(1-hydroxyalkyl)-1,4,2-dioxazole-5-ones slowly fragment under imidazole assistence:[117]



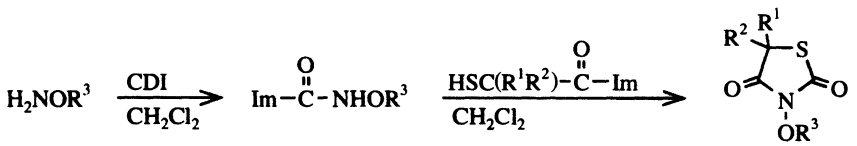
$R^1 = R^2 = C_6H_5$

Carbonylation by CDI of 2-aza-1,3-dienes yields 4-(1*H*)-pyridones[120] (see also Chapter 14):



R^1	R^2	Yield (%)
C_6H_5	C_2H_5	90
C_6H_5	n-C_3H_7	85
c-C_6H_{11}	CH_3	75

3-Alkoxy(hydroxy)thiazolidine-2,4-diones have been prepared by the reaction between two imidazolides:[121]



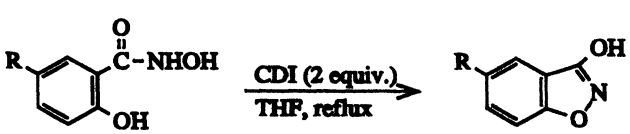
R^1	R^2	R^3	Yield (%)
H	H	$C_6H_5CH_2$	90
H	C_6H_5	CH_3	65
CH_3	CH_3	$C_6H_5CH_2$	68

7.2 Heterocycles by Intramolecular Dehydration or H_2S-Elimination

For further dehydration, for example, of aldoximes and amides to nitriles, of alcohols to olefines, as well as the synthesis of heterocycles like oxiranes and aziridines see Section 18.5.

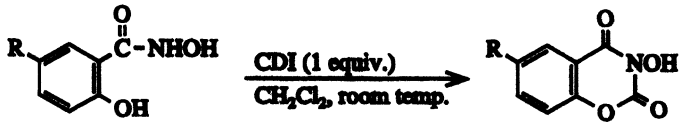
7.2.1 Benzisoxazoles

2-Hydroxybenzohydroxamic acids and CDI have been used[122] to produce 3-hydroxy-1,2-benzisoxazoles:



R	Yield (%)
CH_3CO	89
Cl	68
CH_3O	42

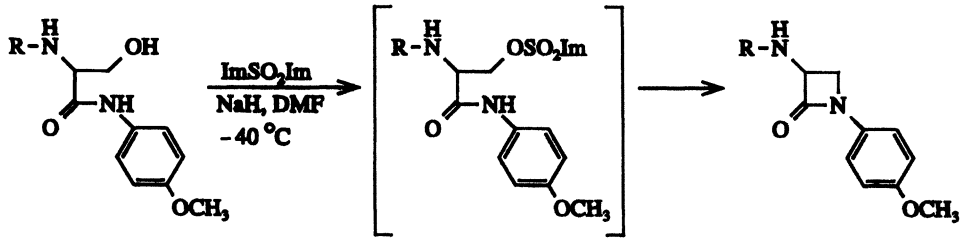
Under different reaction conditions, however, a 3-hydroxy-1,3-benzoxazin-2,4-dione is formed[122] (see also six-membered heterocycles containing an N–CO–O unit, Section 7.1.6):



R = H, 90%; Cl, 72%

7.2.2 β-Lactams

An interesting application of *N,N'*-sulfonyldiimidazole is illustrated by the synthesis of β-lactams from substituted L-serine amides.[123]

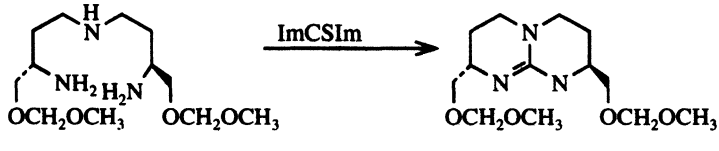


R = Z, 75%; Boc, 85%

In this reaction no epimerization was observed at the 3-position. Ring closure occurs in spite of the low nucleophilicity of the NH group of the amide.[123] Another β-lactam synthesis involving condensation of arylaldimines with 2-*p*-tolylsulfinylacetimidazolide is described in reference [124].

7.2.3 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

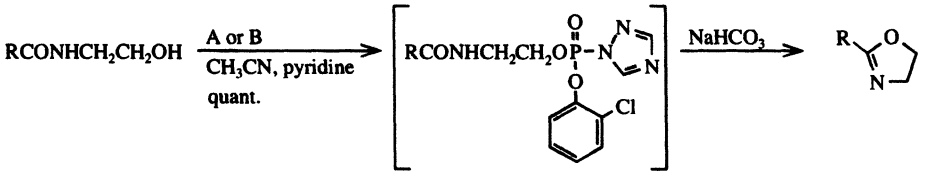
A 1,5,7-triazabicyclo[4.4.0]dec-5-ene containing a bicyclic guanidine system was obtained from a 4,4'-iminobis(butan-2-ylamine) and *N,N'*-thiocarbonyldiimidazole:[125]

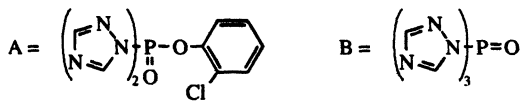


58%

7.2.4 2-Oxazolines (4,5-Dihydrooxazoles)

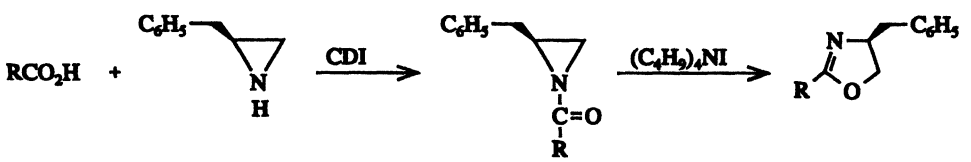
Reaction of *N*-acyl-*β*-amino alcohols with *o*-chlorophenoxyphosphoryldi-1,2,4-triazole (A) or phosphoryltris-1,2,4-triazole (B) leads to a variety of 2-substituted 2-oxazolines.[126]





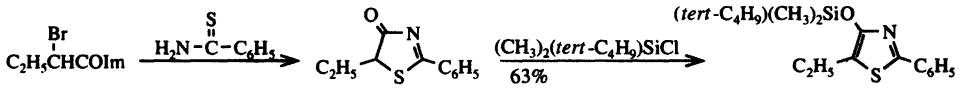
Reagent	R	Yield (%)
A	3-ClC_6H_4	74
A	4-$CH_3OC_6H_4$	86
B	4-$NO_2C_6H_4$	63
B	4-$NH_2C_6H_4$	84
B	4-*tert*-$C_4H_9C_6H_4$	85

2-Oxazolines have also been obtained from aziridines and carboxylic imidazolides via *N*-acylaziridines.[127] Isomerization of the *N*-acylaziridines can be achieved by heating with a catalytic amount of tetrabutylammonium iodide or bromide. The transformation can be carried out as a one-pot reaction in quantitative yield (solvents: THF, $CHCl_3$, benzene) with a wide spectrum of substituents R (R = H, alkyl, *c*-C_6H_{11}, C_6H_5, 3-pyridyl).



7.2.5 Thiazoles

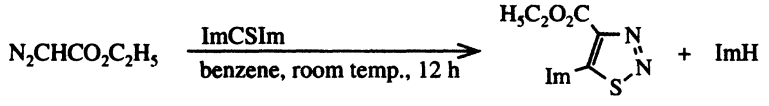
Thiazoles may be obtained starting from the imidazolides of α-bromocarboxylic acids and thiobenzamide, as shown by the following example:[128]



7.3 Various Other Syntheses of Heterocycles Using Azolides

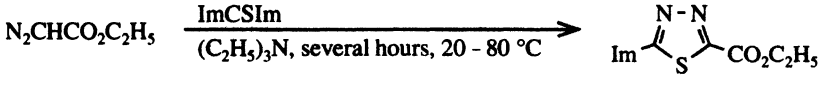
7.3.1 Thiadi(tri)azoles and Oxathiols

Ethyl diazoacetate and ImCSIm can be cyclized by a dipolar addition to give the corresponding ethyl 5-imidazolyl-1,2,3-thiadiazole-4-carboxylate:



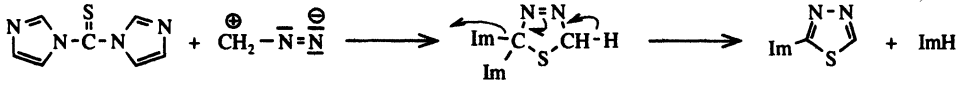
94%

With *N,N'*-thiocarbonyldi-1,2,4-triazole the corresponding ethyl-5-(1,2,4-triazol-1-yl)-1,2,3-thiadiazole-4-carboxylate was obtained in 90% yield.[129] However, analogous 1,3-dipolar reactions in the presence of $(C_2H_5)_3N$ are reported to yield the isomeric 2-(1-imidazolyl)-1,3,4-thiadiazoles:[130],[131]



74%

For corresponding reactions with 2-furyl- and 2-thienyldiazomethylketone see reference [131]. An obvious mechanism for the reaction of *N,N'*-thiocarbonyldiimidazole with diazomethane is a 1,3-dipolar addition:[130]

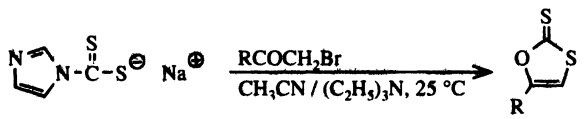


With hydrazoic acid or (better) trimethylsilyl azide and ImCSIm, 5-(1-imidazolyl)-1,2,3,4-thiatriazole is obtained:[130],[132]

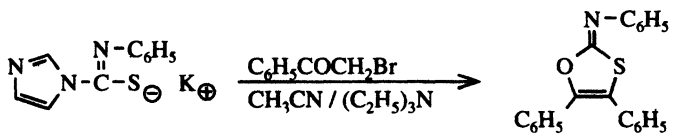
55%

Addition of thiophosgene to the reaction mixture of ImCSIm and trimethylsilylazide causes the yield to become quantitative.[130],[132] In the conversion with trimethylsilyl azide the required ImCSIm could also be made in situ from trimethylsilylimidazole and thiophosgene, giving the thiatriazoles in 70–80% yield.[132]

Oxathioles are prepared by the reaction of 1-imidazole-*N*-carbodithioate or 1-imidazolephenyliminothioate with α-haloketones, as shown below:[133]



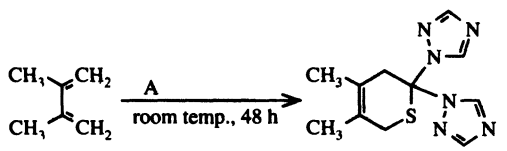
R	Yield (%)
C_6H_5	90 (66, without base)
4-$CH_3C_6H_4$	63
4-$CH_3OC_6H_4$	80
4-BrC_6H_4	70



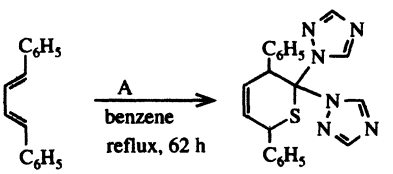
90%

7.3.2 Thiacyclohexenes by Diels–Alder Additions

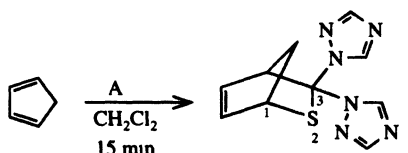
Diels–Alder reactions of thiocarbonyldi-1,2,4-triazole (A) or thiocarbonyldibenzotriazole (B) with 1,3-dienes lead in excellent yield to the expected addition products.[134]



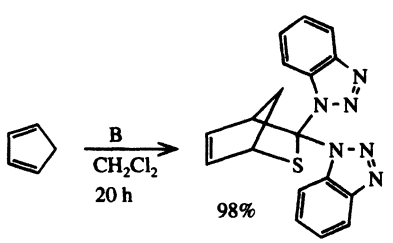
99%



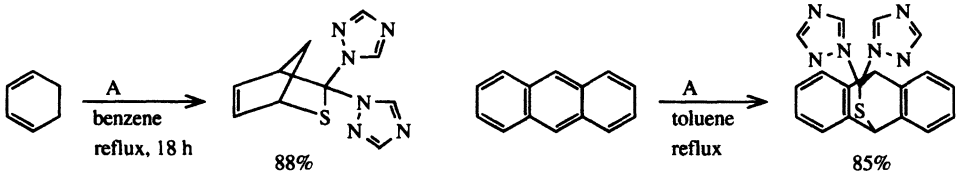
67%



99%

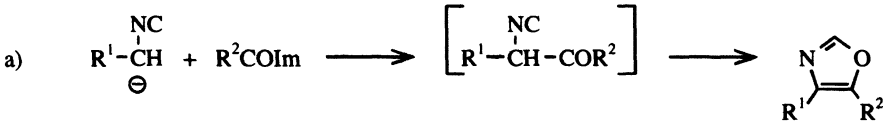


98%

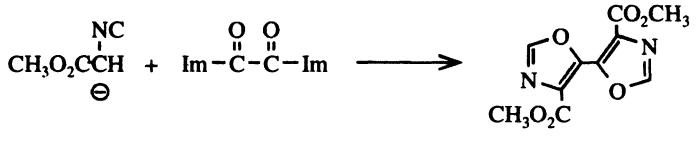


7.3.3 Oxazoles and Isoxazoles

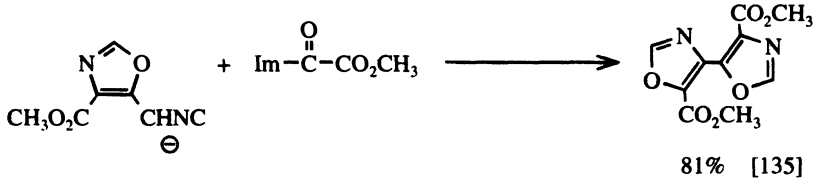
Oxazoles can be prepared from alkylisocyanide carbanions (base: $(C_2H_5)_3N$ or *tert*-C_4H_9OK) and azolides,[135],[136] as the following examples show:

a) 

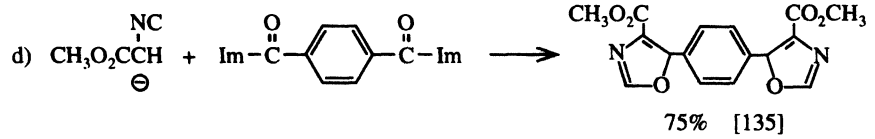
R^1	R^2	Yield (%)	[135]
CO_2CH_3	CO_2CH_3	89	
$CO_2C_2H_5$	H	74	
CO_2CH_3	*iso*-C_3H_7	75	
CO_2CH_3	*p*-$NO_2C_6H_4$	92	

b) 

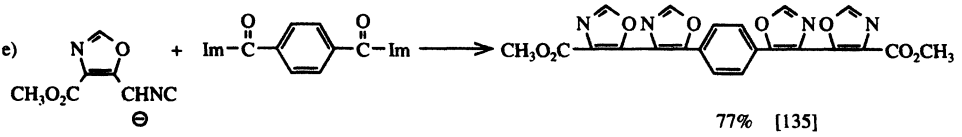
81% [135]

c) 

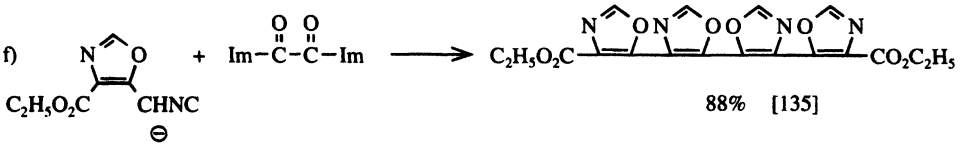
81% [135]

d) 

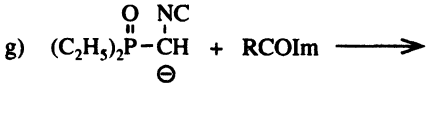
75% [135]

e) 

77% [135]

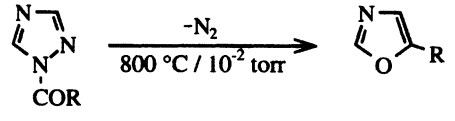
f) 

88% [135]

g) 

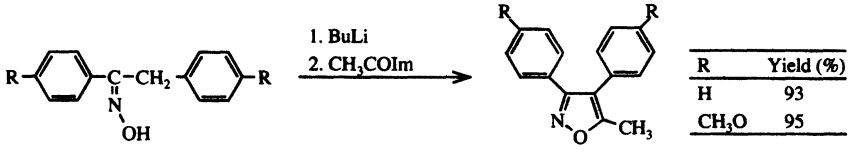
R	Yield (%)	[136]
CH_3	68	
C_6H_5	82	

A different synthesis of oxazoles based on azolides is the flash-vacuum pyrolysis of 1,2,4-triazolides, which includes a shift of the acyl group and elimination of nitrogen:[137]



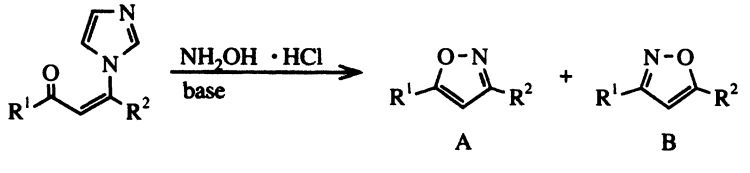
R	Yield (%)
CH_3	25
CH_2=CH	25
C_6H_5	90
CH_3OCO	60

The synthesis of isoxazoles by use of azolides is illustrated by the following example of 3,4-diphenyl-5-methylisoxazoles, prepared by conversion of the deoxybenzoin oximes with *N*-acetylimidazole with the aid of butyllithium:[138]



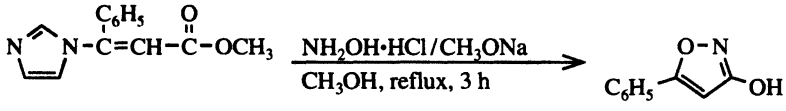
R	Yield (%)
H	93
CH_3O	95

Isomeric 3,5-disubstituted isoxazoles can be prepared from vinylogous azolides and hydroxylamine hydrochloride.[139] In this reaction the ratio of the two isomers A and B formed can be controlled by the nature of the base:



R^1	R^2	Base	Yield (%)	Ratio A / B
C_3H_7	CH_3	none	98	14 : 86
		K_2CO_3	87	77 : 23
		$(C_2H_5)_3N$	85	75 : 25
		2 $NaOCH_3$	92	14 : 86
CH_3	C_3H_7	none	50	20 : 80
		K_2CO_3	70	58 : 42
		$(C_2H_5)_3N$	50	78 : 22
		2 $NaOCH_3$	98	7 : 93
C_6H_5	CH_3	none	55	52 : 48
		K_2CO_3	63	82 : 18
		$(C_2H_5)_3N$	65	91 : 9
		2 $NaOCH_3$	57	23 : 77

3-Hydroxyisoxazoles were prepared by reaction of a vinylogous imidazole carboxylate with hydroxylamine hydrochloride and sodium methoxide:[140]



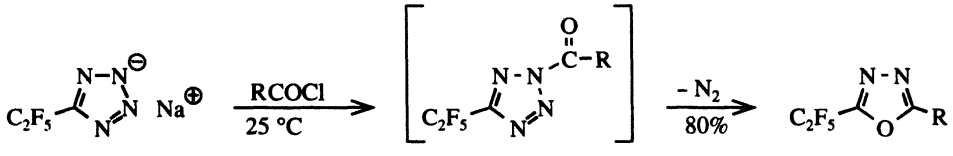
60%

7.3.4 Oxadiazoles

1,3,4-Oxadiazoles

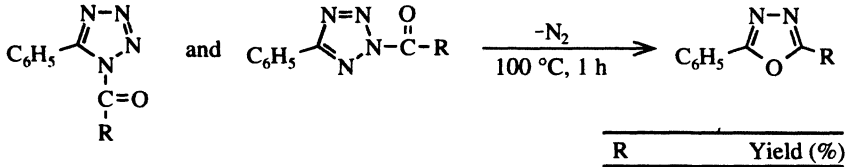
Tetrazolides are excellent starting materials for the synthesis of 1,3,4-oxadiazoles, as the following examples demonstrate.

Reaction of a perfluoroalkyltetrazole and a perfluoroacyl chloride yields, via a tetrazolide and under elimination of nitrogen, the corresponding substituted oxadiazole:[141]

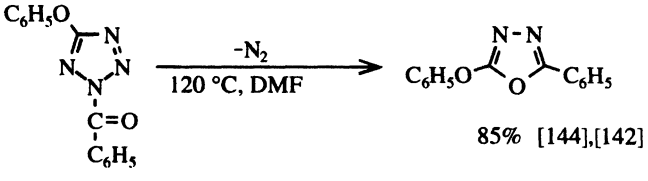


R = CF_3, C_2F_5

A more versatile approach is the thermolysis of tetrazolides, which leads to oxadiazoles in excellent yield:[142],[143]



R	Yield (%)
C_6H_5	95
p-$CH_3C_6H_4$	98
p-$NO_2C_6H_4$	91
p-BrC_6H_4	95 - 99
o-BrC_6H_4	95
o-ClC_6H_4	95

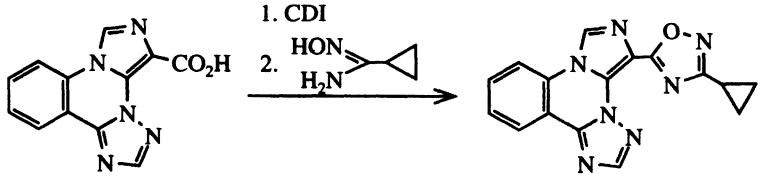


85% [144],[142]

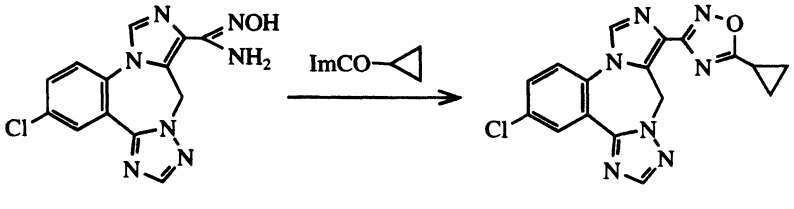
Semiempirical calculations have been carried out for the transformation of *N*-acyltetrazoles into 1,3,4-oxadiazoles.[144a]

1,2,4-Oxadiazoles

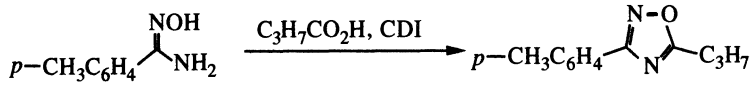
1,2,4-Oxadiazoles are synthesized by the reaction of an amidoxime with the imidazolide of a carboxylic acid.



84% [145]



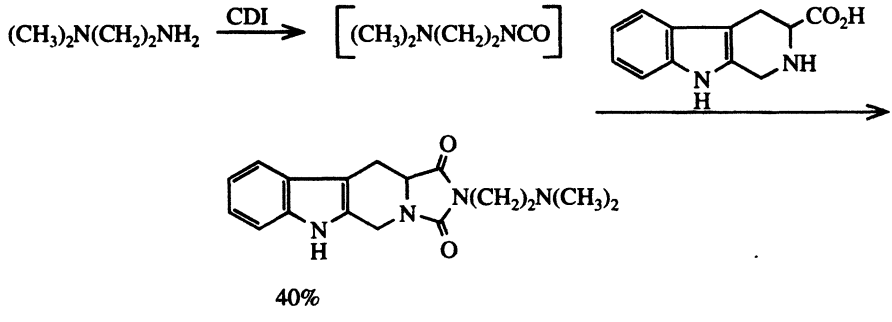
80% [145]



57% [145a]

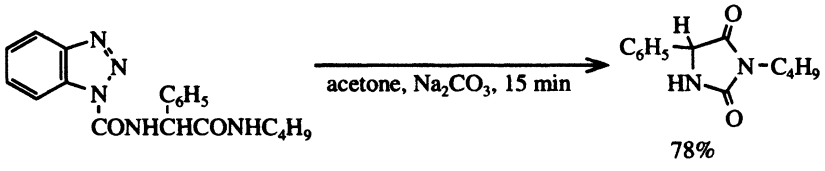
7.3.5 Hydantoins

A hydantoin structure can be built by the reaction of a primary amine with CDI to an isocyanate (Section 8.1), followed by conversion with an amino acid:[146]



40%

Another method for the synthesis of hydantoins is the cyclization of *N*-(1-benzotriazolylcarbonyl)phenylalanine butylamide.[147]

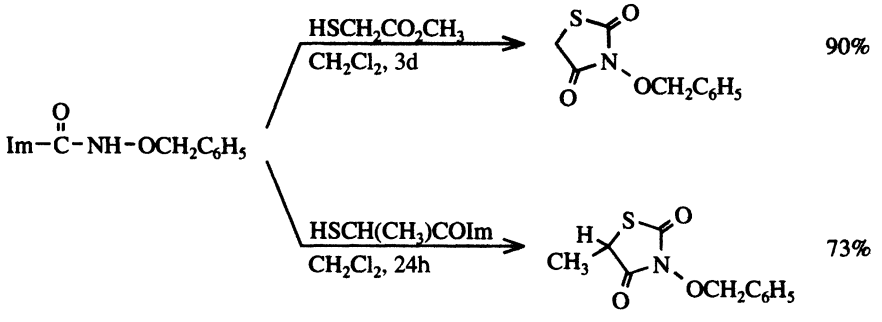


78%

The reaction can also be accomplished by heating the substituted benzotriazolide in xylene.[148]

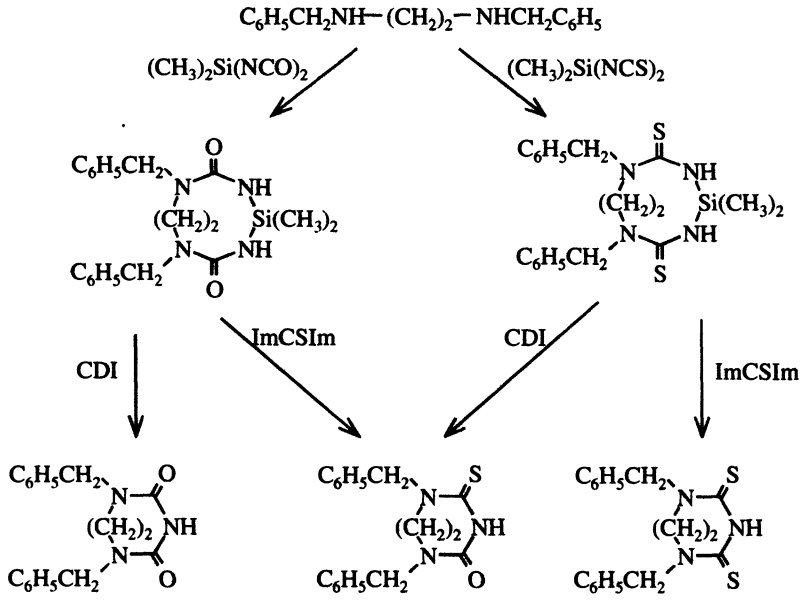
7.3.6 Thiazolidindiones

Using azolides, thiazolidindiones can be prepared by condensation of alkoxycarbamoylimidazoles obtained in situ from *O*-alkylhydroxylamines and CDI with thioglycolic acid methyl ester or the imidazolide of thiolactic acid obtained in situ from thiolactic acid and CDI:[121]



7.3.7 Triazepines

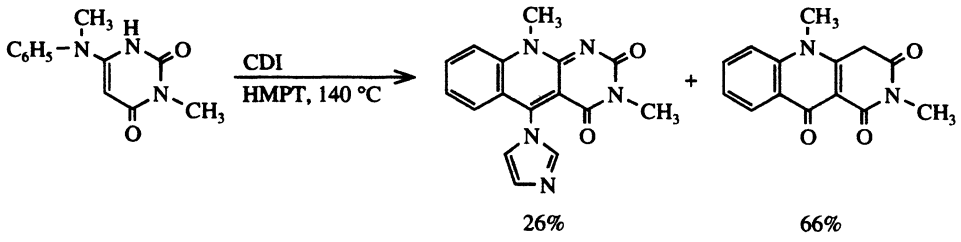
Interesting triazepine derivatives have been prepared from silaheterocycles with CDI or ImCSIm. For the conversions via the various routes with about 70% yields were reported.[149]



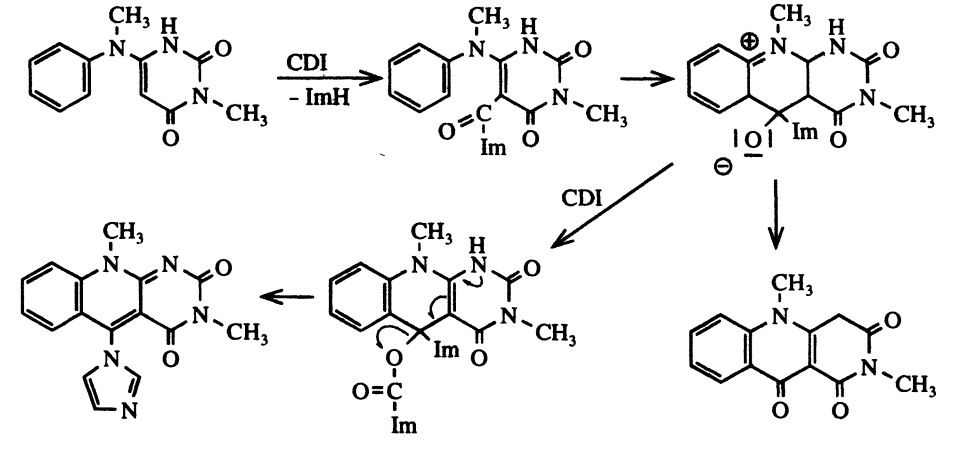
Analogous reactions are reported for the synthesis of urazoles (1,2,4-triazacyclopentandione-3,5), monothiouracoles, and dithiouracoles.[149]

7.3.8 Deazaflavines

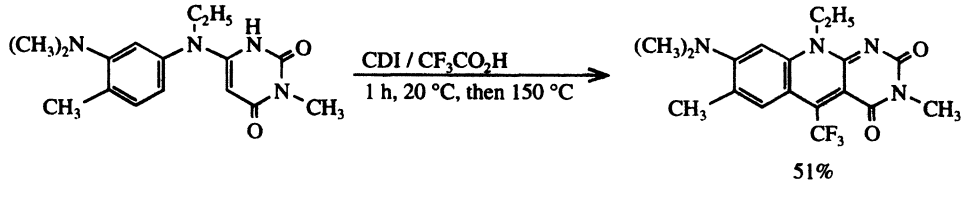
Reactions of anilinouracils and CDI lead to 5-deazaflavins, as shown in the following scheme:[150]



With a threefold excess of CDI the yield of the 5-imidazolyldeazaflavin can be enhanced to 80%. The following mechanism has been suggested for these reactions:[150]

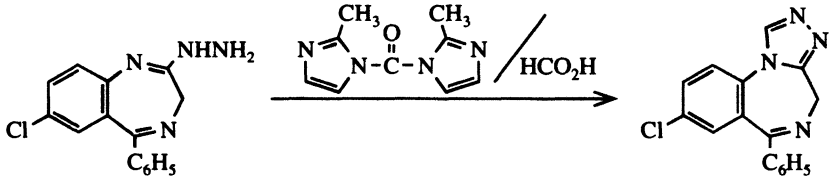


In analogy to this reaction, a substituted anilinouracil with CDI in trifluoroacetic acid was shown to yield the 5-deazaflavin with a trifluoromethyl group in the 5-position:[151]



7.3.9 *s*-Triazolo[4,3-*a*][1,4]benzodiazepine

2-Hydrazino-1,4-benzodiazepine and formic acid 2-methylimidazolide, prepared from *N,N'*-carbonylbis(2-methylimidazole), yield an interesting triazolobenzodiazepine in excellent yield.[152]

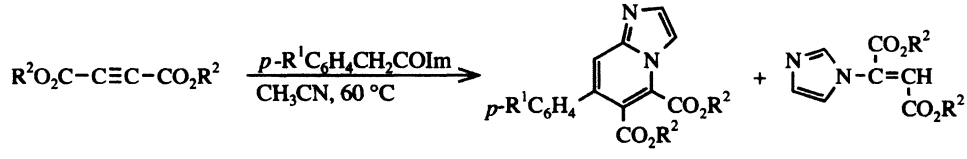


77%

This reaction was also carried out with ^{14}C-labeled formic acid, leading to the radiochemically labeled *s*-triazolo[4,3-*a*][1,4]benzodiazepine (58% yield).[153]

7.3.10 Imidazo[1,2-*a*]pyridines and Pyrido[1,2-*a*]benzimidazoles

Imidazo[1,2-*a*]pyridines are formed by condensation of *N*-arylacetylimidazoles with dimethyl acetylenedicarboxylate:[154]–[156]

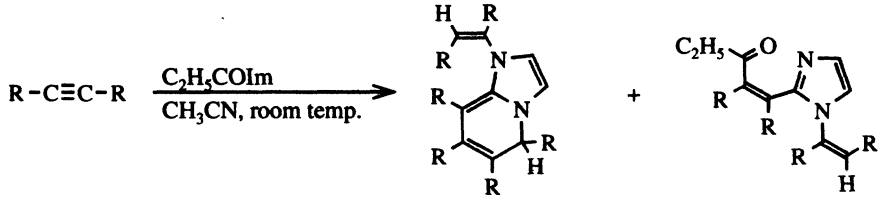


by-product

R^1	R^2	Yield (%)
H	CH_3	64
H	*tert*-C_4H_9	61
OCH_3	CH_3	89
NO_2	CH_3	11

The crystal structure of the compound with $R^1 = H$, $R^2 = CH_3$[155] was determined by X-ray crystallography. A mechanism for this reaction has been proposed.[155]

Products from the reaction of *N*-propionylimidazole with di-*tert*-butyl acetylenedicarboxylate at room temperature have a somewhat different structure:[157]

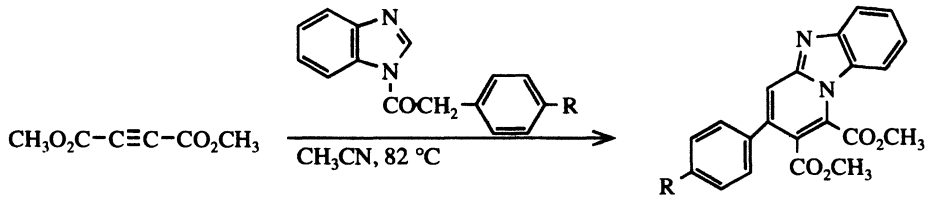


14% 10%

R = *tert*-C_4H_9OCO

For the mechanism of this reaction see reference [157].

A similar reaction of 1-arylacetylbenzimidazoles with dimethyl acetylenedicarboxylate leads to pyrido[1,2-*a*]benzimidazoles:

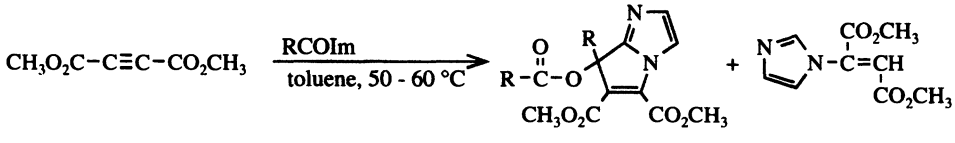


R = H, 8%; OCH_3, 6%

Although the yields are only moderate, this method provides easy access to the pyrido[1,2-*a*]benzimidazole framework in a one-pot reaction.[155]

7.3.11 7*H*-Pyrrolo[1,2-*a*]imidazoles and Imidazo[1′,2′ : 1,2]pyrrolo[2,3-*b*]furans

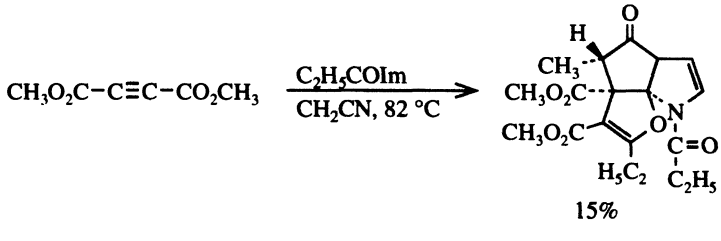
By condensation of 1-acetylimidazole or 1-(1-pentin-4-oyl)imidazole with dimethylacetyl-enedicarboxylate at higher temperature, 7*H*-pyrrolo[1,2-*a*]imidazoles are formed along with dimethyl(imidazol-1-yl)fumarate:[158],[157]



R = CH_3, 19%; $HC{\equiv}C(CH_2)_2$, 32%

by-product

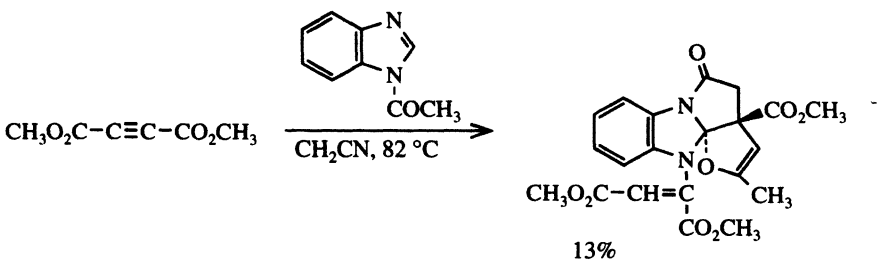
A crystal structure is available for the compound with R = $HC{\equiv}C(CH_2)_2$, and a mechanism was also proposed. On changing the reaction conditions (CH_3CN, 82°C) and using *N*-propionylimidazole, a tricyclic imidazo[1′,2′ : 1,2]pyrrolo[2,3-*b*]furan was obtained in a diastereoselective spirocyclization reaction:[159],[157]



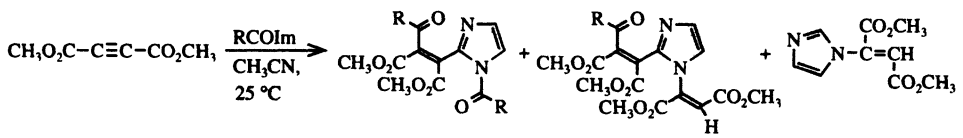
15%

Here, too, a crystal structure was solved, and a mechanism for the reaction has been proposed.

A similar spirobicyclization was observed in the reaction of *N*-acylbenzimidazoles with dimethyl acetylenedicarboxylate:[159]



The reaction of *N*-acylimidazole with dimethyl acetylenedicarboxylate in acetonitrile at 25 °C provided (2-imidazolyl)maleates and, as by-product, dimethyl(imidazol-1-yl)-fumarate:[157]



R = C_2H_5	13%	16%	by-product
R = *iso*-C_4H_9	34%	25%	

A mechanism for the reaction was proposed.[157]

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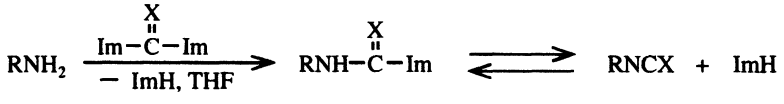
8 Synthesis of Isocyanates, Isothiocyanates, Aminoisocyanates, Aminoisothiocyanates, and *N*-Sulfinylamines

8.1 Isocyanates and Isothiocyanates

When *N,N'*-carbonyldiimidazole (CDI) is reacted with a primary amine in a 1 : 1 molar ratio, the product is an imidazole-*N*-carboxamide. However, these compounds dissociate in solution into isocyanates and imidazole even at room temperature,[1] forming a rapidly equilibrating system. Because of this equilibrium, primary imidazole-*N*-carboxamides can also be prepared from isocyanates and imidazole.

Analogous to the synthesis of isocyanates, isothiocyanates are obtained in good yield by reacting *N,N'*-thiocarbonyldiimidazole (ImCSIm) with primary aliphatic or aromatic amines in equimolar amount. In chloroform at room temperature the dissociation equilibrium of imidazole-*N*-thiocarboxamides is shifted completely to isocyanates.[2]



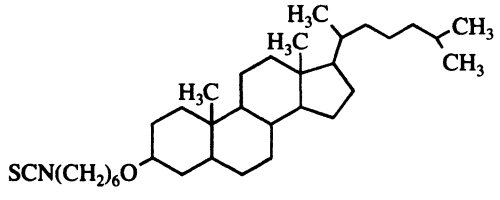
Im–C(=X)–Im	Primary amine	RNCX	Yield (%)	Ref.
CDI	$C_4H_9NH_2$	C_4H_9NCO	57	[1]
ImCSIm	$C_4H_9NH_2$	C_4H_9NCS	77	[2]
CDI	*c*-$C_6H_{11}NH_2$	*c*-$C_6H_{11}NCO$	83	[1],[3]
ImCSIm	*c*-$C_6H_{11}NH_2$	*c*-$C_6H_{11}NCS$	72	[2]
CDI	$C_6H_5NH_2$	C_6H_5NCO	63	[1]
ImCSIm	$C_6H_5NH_2$	C_6H_5NCS	78	[2]
ImCSIm	2,4-$(CH_3O)_2C_6H_3CH_2NH_2$	2,4-$(CH_3O)_2C_6H_3CH_2NCS$	60	[4]
ImCSIm	$H_5C_2O_2C-(CH_2)_3-NH_2$	$H_5C_2O_2C-(CH_2)_3-NCS$	98	[5]
ImCSIm	$CH_2=CH-CH_2NH_2$	$CH_2=CH-CH_2NCS$	43	[6]

From the intensity of the very characteristic IR-band at 2250 cm^{-1} for the N=C=O group it was found that the imidazole-*N*-carboxanilide in chloroform is dissociated to the

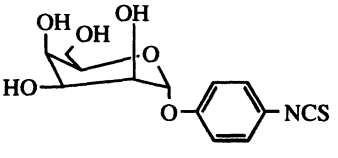
extent of 16.1% at 20 °C and 36.7% at 45 °C.[7] The corresponding reaction enthalpy ΔH was determined to be 14.5 ± 0.5 kcal/mol. A similar equilibrium exists for benzimidazole-*N*-carboxanilide in chloroform, with a dissociation of 14.0% at 20 °C and 36.8% at 50 °C, ΔH being 13.5 ± 0.5 kcal/mol. This dissociation forms the basis for a simple method of preparing isocyanates from aliphatic, alicyclic, and aromatic amines. One mole of amine is added dropwise at room temperature to a solution of one mole of CDI in THF or CH_2Cl_2. Distillation of the mixture then produces the pure isocyanate in good yield.[1] Because of their great tendency to dissociate, imidazole-*N*-carboxamides represent a type of masked isocyanate. Solutions thereof behave almost like isocyanates, even at room temperature. In the solid state, however, imidazole-*N*-carboxamides are crystalline, stable compounds that are easy to handle (see also Chapter 4.6).

If *N,N'*-carbonyldi-1,2,4-triazole or *N,N'*-carbonyldibenzimidazole is used for the synthesis of isocyanates instead of CDI, the yields are lower.[1],[3] For the synthesis of isocyanates and isothiocyanates according to this method see also references [8] and [9].

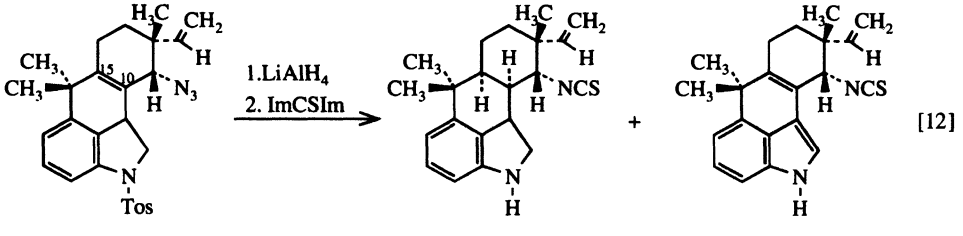
The ImCSIm-method has been used, for instance, in the synthesis of isothiocyanates containing steroid, sugar, and alkaloid components:



50% [10]



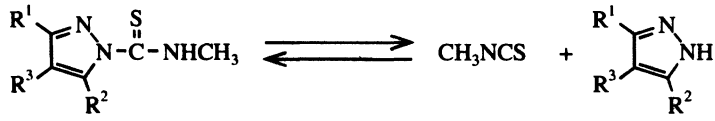
83% [11]



35% 9%

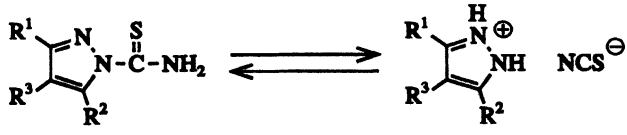
[12]

In analogy to imidazole-*N*-thiocarboxamides, the corresponding pyrazolides have also been introduced for the synthesis of isothiocyanates.[13] *N*-methylthiocarbamoylpyrazoles, see next page, are obtained from *N*-methylisothiocyanate and pyrazoles by gentle heating. If the two hydrogens of the thiocarbamoyl group in thiocarbamoylpyrazoles are substituted, no elimination of a thiocyanate is possible. These compounds are then thermostable.



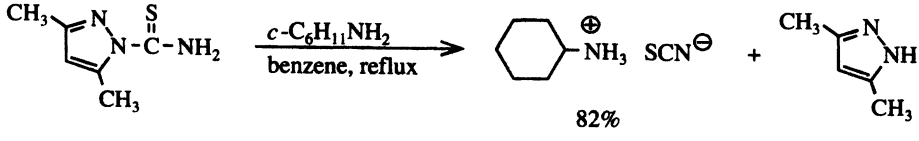
T (°C)	R^1	R^2	R^3
135 - 140	CH_3	CH_3	$(CH_2)_2-C(=N-NHCSNHCH_3)-CH_3$
135 - 140	CH_3	CH_3	$(CH_2)_2COCH_3$
185 - 190	CH_3	H	H
185 - 190	H	H	H

On short heating thiocarbamoylpyrazoles yield quantitatively the corresponding thiocyanate salts. Highly substituted thiocarbamoylpyrazoles such as 3,5-dimethyl-1-thiocarbamoylpyrazole undergo this transformation in solution even at room temperature.[13]



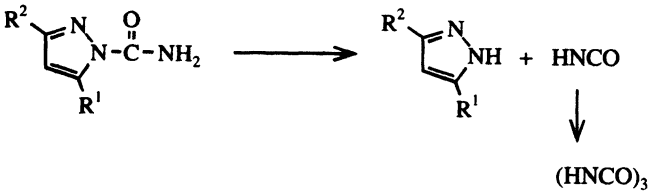
T (°C)	R^1	R^2	R^3
95 - 100°	CH_3	CH_3	$(CH_2)_2-C(=N-NHCSNHCH_3)-CH_3$
85 - 100°	CH_3	CH_3	H
100°	CH_3	CH_3	$(CH_2)_2COCH_3$
155 - 160°	H	H	H

With a stronger base such as cyclohexylamine the pyrazolethiocyanate salts are converted into cyclohexylammonium salts:[13]



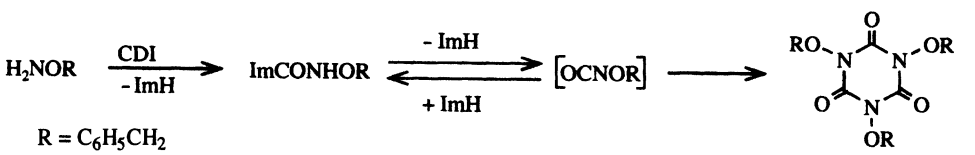
82%

1-Carbamoylpyrazoles are significantly more thermostable than their sulfur analogues. They decompose quantitatively only at high temperatures and long reaction times into a pyrazole and cyanic acid, which trimerizes into cyanuric acid:[13]



T (°C)	R^1	R^2
185 - 190	H	CH_3
185 - 190	CH_3	CH_3
195 - 200	H	H

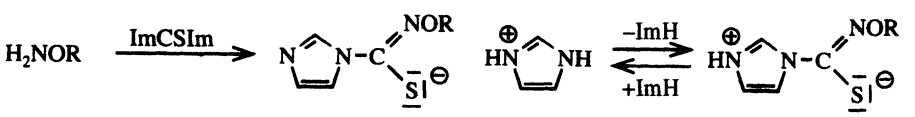
Prompted by the dissociation of imidazole-*N*-carboxamides into isocyanates, the preparation of alkoxyisocyanates (i.e. representatives of the hitherto unknown monoximes of carbon dioxide) was attempted.[14],[15] However, when *N*-benzyloxycarbamoylimidazole ($ImCONHOCH_2C_6H_5$) was heated, the corresponding trialkoxyisocyanuric acid was formed by trimerization of OCNOR.[14]



$R = C_6H_5CH_2$

It is very probable that aminolysis of $ImCONHOCH_2C_6H_5$, which, for example, gave a *N*-benzyloxyurea with cyclohexylamine in a few minutes at room temperature, proceded through the stage of OCNOR. These results suggest that compounds of the type OCNOR can in fact be formed, but their tendency to trimerize is apparently too great that direct detection is possible.

Conversion of *N*-alkoxy amines with ImCSIm at room temperature in ether produced, instead of *N*-alkoxythiocarbamoylimidazoles, the corresponding zwitterionic compounds:[2],[16]

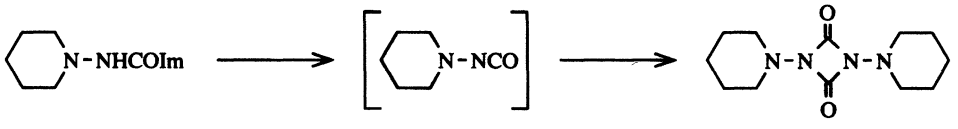


R	Yield (%)	Ref.
$C_6H_5CH_2$	73	[2]
CH_3	quant.	[16]
C_4H_9	85	[16]
C_2H_5	60 - 70	[16]

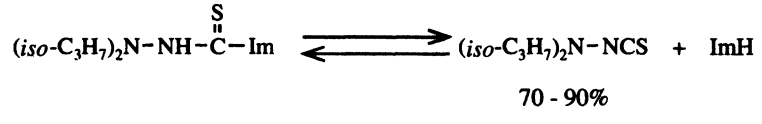
Dissociation of the product with $R = C_6H_5CH_2$ into the corresponding isothiocyanate could not be achieved. Upon treatment with cyclohexylamine instead of a thiourea, the cyclohexylammonium salt was obtained.[2]

8.2 Aminoisocyanates and Aminoisothiocyanates

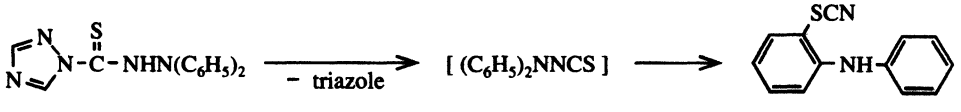
Attempts have been made to prepare aminoisocyanates from suitable hydrazidocarbonylimidazoles. However, because of the high reactivity of the expected product, a dimerization occurred instead, as illustrated by the thermolysis of imidazole-*N*-carboxylic acid (1,1-pentamethylene)hydrazide.[17]



However, *N*-isothiocyanatoamines could be prepared as a result of thermolysis of thiocarbazoylimidazoles under high vacuum.[18]–[20] The reaction was found to be reversible in solution.[20]



Thermolysis of *N,N*-diphenylthiocarbazoyl-1,2,4-triazole in vacuo led only to the rearranged product *N*-isothiocyanatodiphenylamine.[21]



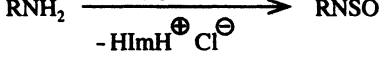
8.3 *N*-Sulfinylamines

N-Sulfinylamines have been prepared from imidazolides by two methods.[22]

Method A: Reaction of amines with *N,N'*-sulfinyldiimidazole.

R	Yield (%)
C_6H_5	73
p-$CH_3C_6H_4$	72
p-ClC_6H_4	69

Method B: Reaction of an amine with *N*-chlorosulfinylimidazole, which is formed from *N,N'*-sulfinyldiimidazole and $SOCl_2$. Using this method, *N*-sulfinylamines are obtained in good yield at 20 °C.[22]



R	Yield (%)
C_6H_5	89
p-$CH_3OC_6H_4$	86
p-$NO_2C_6H_4$	80
c-C_6H_{11}	77
tert-C_4H_9	63
p-$CH_3C_6H_4SO_2$	86

Generally, method B is superior to method A, because the imidazolium chloride formed in the reaction can easily be removed by filtration, in contrast to the imidazole formed in method A.

If *N*-sulfinyl-*p*-toluenesulfonamide is prepared from *p*-toluenesulfonamide by using $SOCl_2$ only, the yield turns out to be low even after heating the reaction mixture (refluxing benzene) for five days. By method B, however, the yield is high after only one hour at 20 °C in dichloromethane.

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Azolides in Organic Synthesis and Biochemistry. H. A. Staab, H. Bauer, K. M. Schneider

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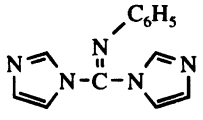
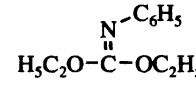
9 Reactions of Imino Analogues of Azolides

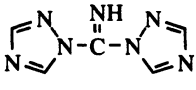
The preparation of the imino analogues of *N,N'*-carbonyldiimidazole has been dealt with above (see Chapter 2). Here we consider certain reactions of such carbiminobisazoles (iminocarbonylbisazoles) and also of other carbiminoazoles (iminocarbonylazoles) leading to *iminoesters*, *cyanamides*, *amidines*, *aldimines*, *enamines*, and *guanidines*. The results are very similar to those experienced with the corresponding carbonyl compounds, thus widening further the scope of azolide reactions as the following examples show:



$\xrightarrow[C_2H_5OH]{NaOC_2H_5}$



81% [1]

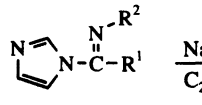


$\xrightarrow[ROH,\ THF]{2\ RO^{\ominus}}$ $RO-C(=NH)-OR$

R	Yield (%)	[2]
C_2H_5	73	
n-C_3H_7	81	

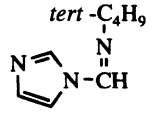
$\xrightarrow[THF]{R_2NH}$ $R_2N-C\equiv N$

R	Yield (%)	[2]
C_2H_5	70	
$CH_2=CHCH_2$	79	

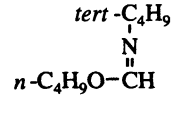


$\xrightarrow[C_2H_5OH]{NaOC_2H_5}$ $C_2H_5O-C(=N-R^2)-R^1$

R^1	R^2	Yield (%)	[1]
C_6H_5	CH_3	53	
C_6H_5	C_6H_5	83	
CH_3	C_6H_5	83	
$C_6H_5CH=CH$	C_6H_5	80	

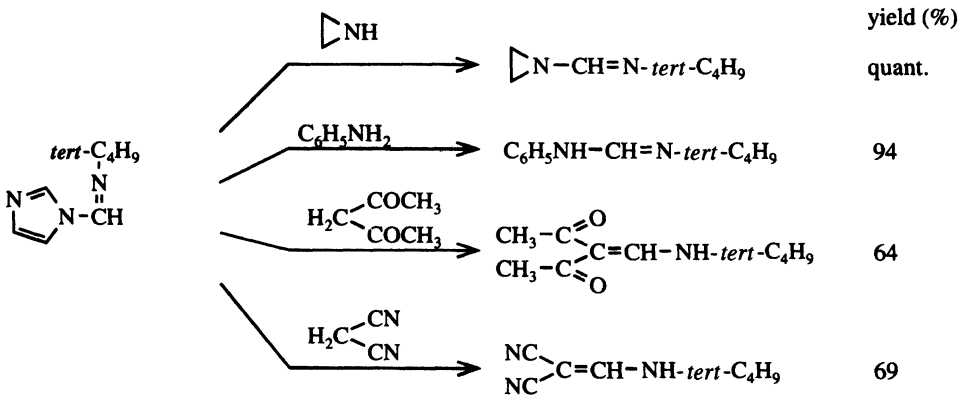


$\xrightarrow[100\ °C,\ 14\ h]{n\text{-}C_4H_9OH}$

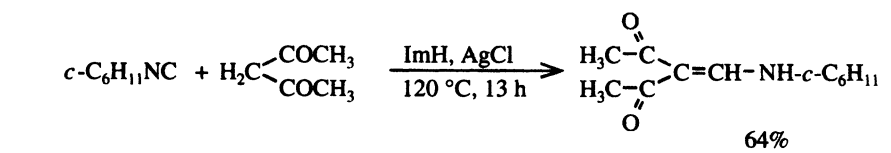


quant. [3]

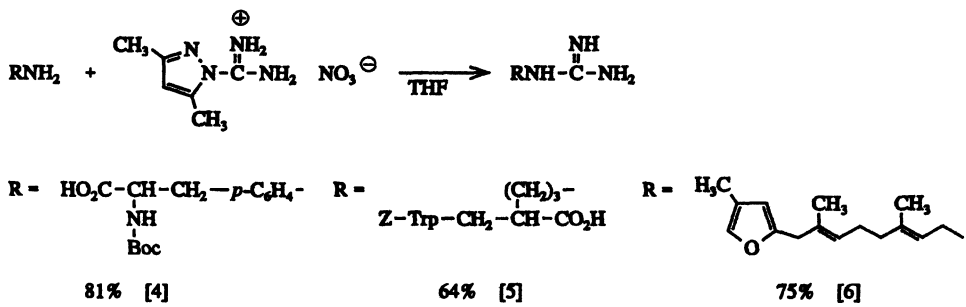
The formimidoyl group can be transferred onto either amines, alcohols or CH-active compounds without use of a catalyst, providing amidines or aldimines and enamines, respectively:[3]



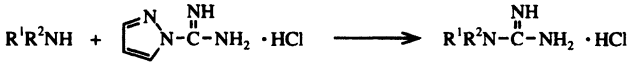
Compounds of the latter type can also be prepared from corresponding isocyanides and active methylene compounds in the presence of catalytic amounts of imidazole and AgCl. A 1-(*N*-alkyliminoformyl)imidazole (Im-CH=NR) is formed in this case as intermediate:[3]



Primary amines with various complex groups R can be transformed (amidinylation) into guanidine derivatives by reaction with 3,5-dimethylpyrazole-1-carboxamidinium nitrate in the presence of a tertiary amine such as diisopropylethyl- or triethylamine in THF or DMF;[4]–[6] see also reference [7].



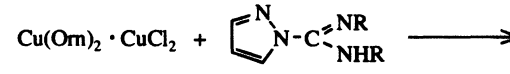
Very similar reactions have been described using unsubstituted pyrazole-1-carboxamidinium chloride.[8]



R^1R^2NH	Yield (%)
cyclohexylamine	84
piperidine	71
2-ethanolamine	88
glycine	77
4-methoxyaniline	60

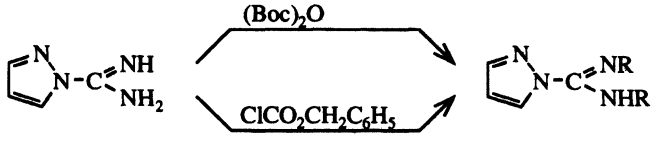
Pyrazole-1-carboxamidine has been used successfully in the solid-phase peptide synthesis for converting ornithine-containing peptides into the corresponding arginine peptides.[8]

Also *N,N'*-bisprotected pyrazole-1-carboxamidines are applied for preparation of guanidines.[9],[9a] A variation of this reaction permitted the copper salt of ornithine to be converted to the copper salt of arginine:[10]



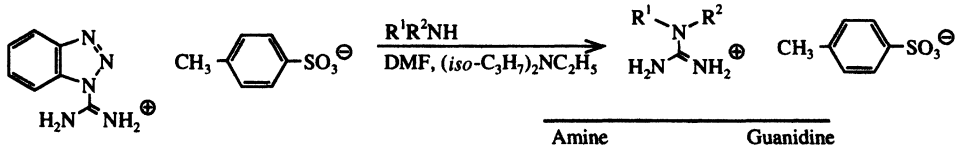
R	Yield (%)
Boc	91
Z	89

The bisprotected pyrazole-1-carboxamidines referred to above were obtained in the following way:[9]



R	Yield (%)
Boc	76
Z	77

The recently prepared benzotriazole-1-carboxamidinium tosylate represents a convenient reagent for conversion of amines to guanidines in moderate to good yields. The presence of the benzotriazole moiety causes the compound to be more reactive than pyrazole-1-carboxamidinium hydrochloride:[11]



Amine	Guanidine yield (%)
dimethylamine	69
piperidine	84
pyrrolidine	71
morpholine	86
hexylamine	67
p-methoxyaniline	68

The reaction could also be carried out in CH_3CN or in the absence of solvent.

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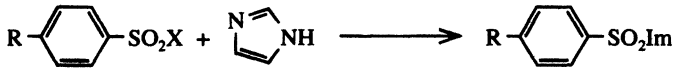
10 Syntheses of Sulfonates, Sulfinates, Sulfonamides, Sulfoxylates, Sulfones, Sulfoxides, Sulfites, Sulfates, and Sulfanes

10.1 Sulfonates and Sulfinates

Sulfonic Esters (Sulfonates)

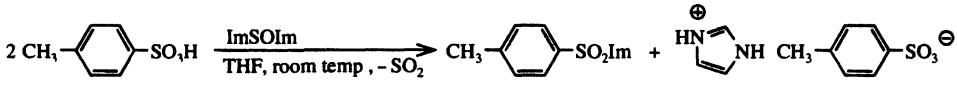
The imidazolides of aromatic sulfonic acids can be obtained in the following ways

1 By reaction of the appropriate aromatic sulfonic acid halide or anhydride with imidazole [1] Toluenesulfonic imidazolide was obtained from toluenesulfonic anhydride in very good yield [2]

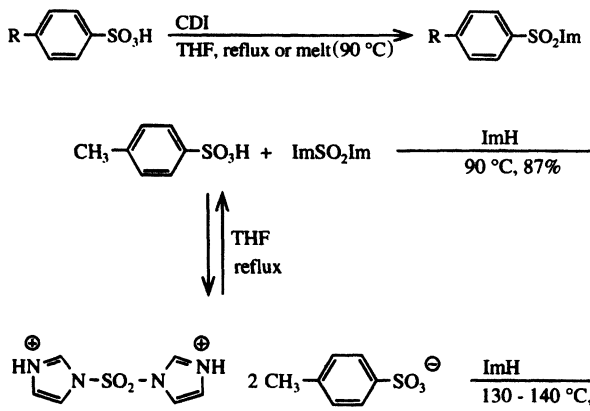


R	X	Yield (%)	Ref
CH_3	Cl	99	[1]
H	Cl	97	[1]
$C_6H_5N{=}N-$	Cl	98	[1]
NH_2	F	69	[2]

2 From an aromatic sulfonic acid and *N,N'*-carbonyldiimidazole (CDI), *N,N'*-sulfinyldiimidazole (ImSOIm), or *N,N'*-sulfonyldiimidazole ($ImSO_2Im$) While heating is necessary in the reaction with CDI or $ImSO_2Im$, room temperature is sufficient in the reaction with the more reactive ImSOIm

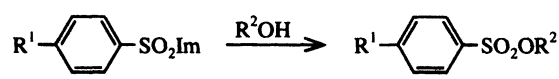


61% [3]



R	Yield (%)	[1]
CH_3	51 , 77 (melt)	
H	65	

Imidazolides of aromatic sulfonic acids react much more slowly in alcoholysis reactions than the carboxylic acid imidazolides. Although the reaction with phenols is quantitative when a melt is heated to 100 °C for several hours, with alcohols under these conditions only very slight alcoholysis is observed. In the presence of 0.05 equivalents (catalytic amount) of sodium ethoxide, imidazole sodium, or $NaNH_2$, however, imidazolides of sulfonic acids react with alcohols almost quantitatively and exothermically at room temperature in a very short time to form sulfonic acid esters (sulfonates). (If the ratio of sulfonic acid imidazolide to alcoholate is 1 : 2, ethers are formed; see Chapter 17). The mechanism of catalysis by base corresponds to that operative in the synthesis of carboxylic esters by the imidazolide method. Because of the more pronounced nucleophilic character of alkoxide ions, sulfonates can also be prepared in good yield by alcoholysis of their imidazolides in the presence of hydroxide ions; i.e., with alcoholic sodium hydroxide.[4] Examples of syntheses of sulfonates are presented below.



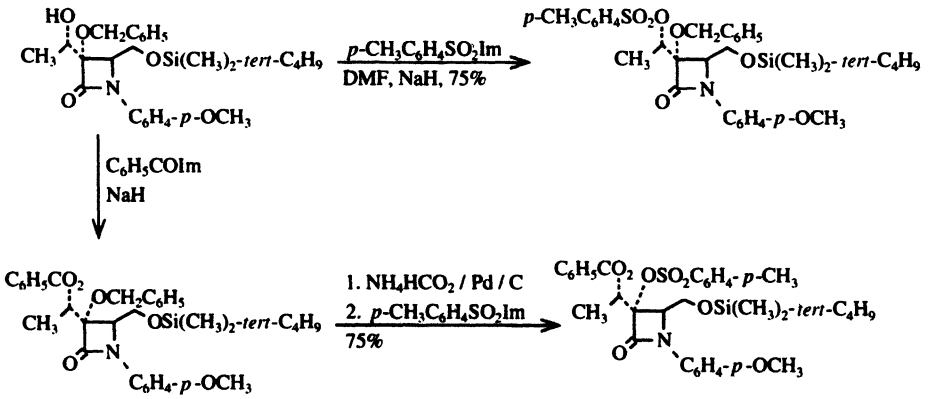
Reaction in the melt, 100 °C (without catalyst).

R^1	R^2	Yield (%)	Ref.
H	C_6H_5	90	[1]
CH_3	C_6H_5	97	[1]
CH_3	p-$NO_2C_6H_4$	78	[1]

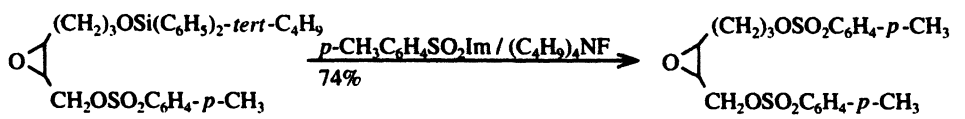
Reaction with basic catalyst at room temperature

R^1	R^2	Catalyst	Yield (%)	Ref.
CH_3	CH_3	CH_3ONa	70	[1]
CH_3	C_2H_5	C_2H_5ONa	84	[1]
CH_3	C_2H_5	ImNa	74	[1]
CH_3	C_2H_5	1 N NaOH	82	[1]
p-$C_6H_5N{=}N$-	C_2H_5	C_2H_5OH	91	[1]
CH_3	c-C_6H_{11}	$NaNH_2$	72	[2]
NH_2	C_2H_5	C_2H_5ONa	76	[1]
H	C_6H_5	C_6H_5ONa	93	[1]
CH_3	C_6H_5	C_6H_5ONa	97	[1]

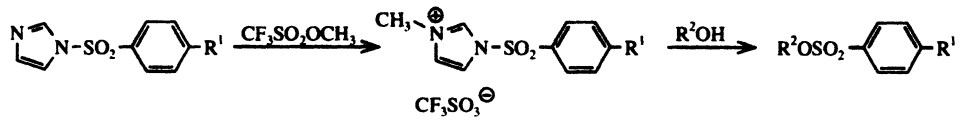
The mild conditions of the base-catalyzed sulfonate synthesis are particularly apparent in the case of two reactions in which the reacting OH groups are present in an azetidinone system:[5]



A silyl-protected alcohol can be converted into the corresponding sulfonate by treating with *p*-toluenesulfonylimidazole and tetrabutylammonium fluoride:[6]



For conversion of the more reactive 1-arylsulfonyl-3-methylimidazolium triflate (trifluoromethane sulfonate) with alcohols or phenols, no base is required:[7]



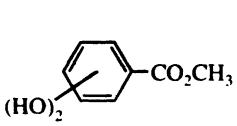
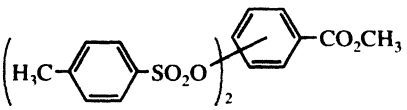
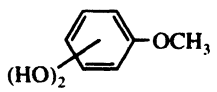
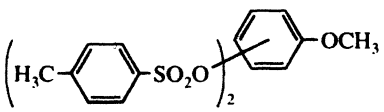
In this reaction the 1-arylsulfonyl-3-methylimidazolium triflate was prepared in situ. Table 10–1 reveals the broad scope of this reaction.

Table 10–1. Arylsulfonates from 1-arylsulfonyl-3-methylimidazolium triflate.

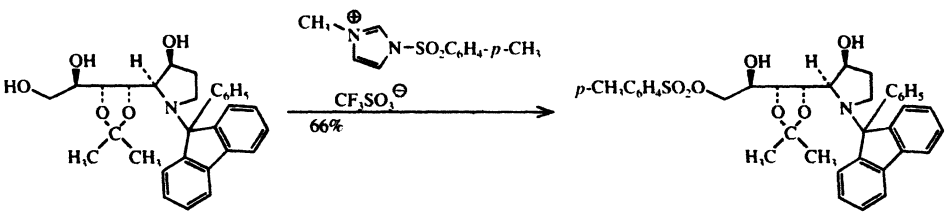
Alcohol/phenol (R_2OH)	Arylsulfonate (R^2OSO_2-C_6H_4-R^1)	Yield (%)	Ref.
(–) menthol	(–) menthyl-benzenesulfonate	95	[7]
methyl α-D-glucoside	methyl *O*-tetrakis(benzene sulfonyl)- α-D-glucoside	quant.	[7]
2,6-dimethylphenol	benzenesulfonyloxy-2,6-dimethyl-benzene	76	[7]
catechol	1,2-bis(benzenesulfonyl)benzene	quant.	[7]
1,3,5-trihydroxybenzene	1,3,5-tris(*p*-toluene-sulfonyloxy)benzene	quant.	[7]

(*continued*)

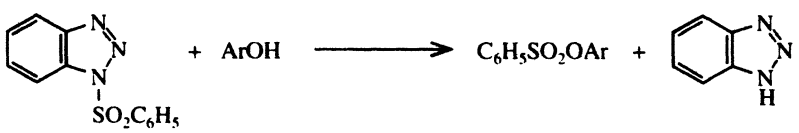
Table 10–1. (*continued*)

			
	2,3	97	[8]
	2,4	96	[8]
	2,5	83	[8]
	3,4	95	[8]
			
	2,3	82	[8]
	2,4	75	[8]
	2,5	72	[8]
	3,4	76	[8]

Application of this reaction to the sulfonic ester of a polyfunctional alcohol is demonstrated by the following example:[9]



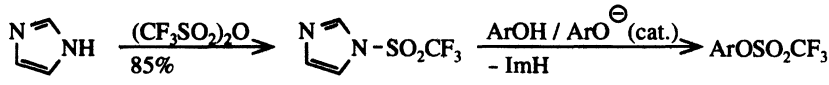
As in the synthesis of carboxylic esters, benzotriazolides may also be used in the preparation of aromatic sulfonic esters:[10]



Ar	Yield (%)
4-ClC_6H_4	88
3-$CH_3OC_6H_4$	91
4-$CH_3OC_6H_4$	99
2,6-$(CH_3)_2C_6H_3$	62
3,4-$(CH_3)_2C_6H_3$	96
1-naphthyl	51

Di- and trihydroxybenzenes could be completely benzosulfonylated in this way as well.[10]

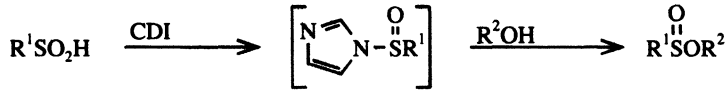
As an example of esters of aliphatic sulfonic acids trifluoromethylsulfonic imidazolide has been treated with various phenols to give phenyl sulfonic esters:[11]

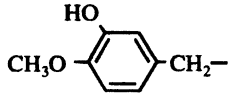
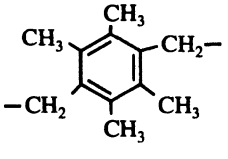


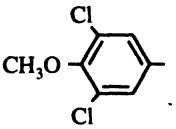
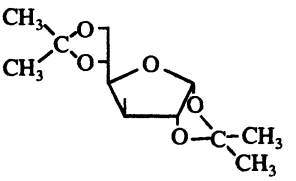
Ar	Yield (%)
C_6H_5	68
p-$CH_3C_6H_4$	76
p-ClC_6H_4	71
p-$NO_2C_6H_4$	73
β-naphthyl	70

Sulfinic Esters (Sulfinates)

In a way analogous to sulfonic esters, sulfinic esters are available quite readily and in very good yield. As usually the first step is the activation of sulfinic acid by CDI to the corresponding imidazolide which then reacts with alcohols:[12]–[14]

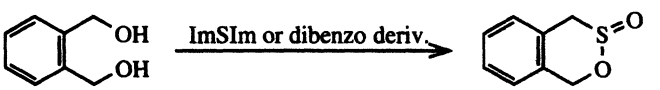


R^1	R^2	Yield (%)	Ref.
p-$CH_3C_6H_4$	1-adamantyl	78	[12]
p-$CH_3C_6H_4$	1-adamantylmethyl	92	[12]
p-$CH_3C_6H_4$	p-$NO_2C_6H_4$	57	[12]
p-$CH_3C_6H_4$	p-BrC_6H_4	69	[12]
p-$CH_3C_6H_4$		69	[12]
p-$CH_3C_6H_4$		53	[12]

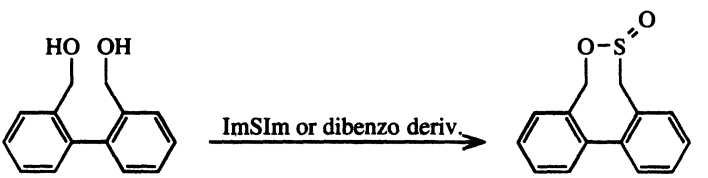
R^1	R^2	Yield (%)	Ref.
p-$CH_3C_6H_4$	9-fluorenylmethyl	78	[12]
p-$CH_3C_6H_4$	cholesteryl	56	[12]
	2-adamantyl	68	[13]
p-$CH_3C_6H_4$		94	[14]

Sulfinates from Bisazolylsulfides (*N,N'*-Thiobisazoles)

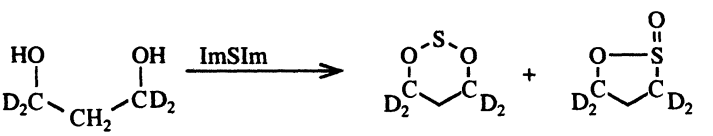
With *N,N'*-thiodiimidazole (ImSIm)[37] or *N,N'*-thiodibenzimidazole, (obtained from the *N*-trimethylsilylazoles and SCl_2), the following sulfinates can be formed. The sulfinates arise by rearrangement of the first formed sulfoxylates (see also Section 10.3).



quant. [15],[16]



95% [15],[16]



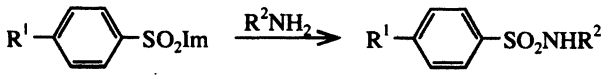
17 : 83

6% 31% [17]

10.2 Sulfonamides

Aminolyses of the imidazolides of aromatic sulfonic acids require prolonged heating with a primary amine at temperatures above 100 °C in a sealed tube to generate sulfonamides in good yield.

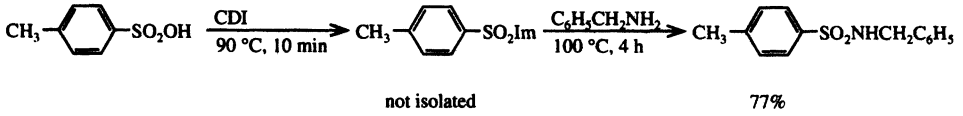
Examples:



R^1	R^2	Yield (%)
CH_3	$C_6H_5CH_2$	89
H	$C_6H_5CH_2$	88
CH_3	C_6H_5	88
NH_2	C_6H_5	86

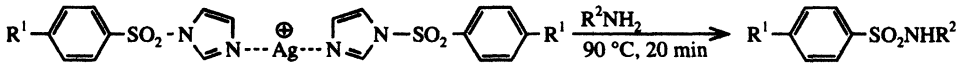
The imidazolides required for these reactions can be prepared from sulfonyl chlorides[1] or sulfonic anhydrides[2] and imidazole, or by treatment of the corresponding sulfonic acid with CDI,[1] ImSOIm,[3] or $ImSO_2Im$[3] (see Section 10.1.1). However, for the synthesis of sulfonamides it is more convenient to employ a one-pot reaction starting from the free sulfonic acid, CDI or ImSOIm, and the appropriate amine:[1]

For example:



not isolated 77%

Imidazolides of aromatic sulfonic acids form very sparingly soluble 2 : 1 complexes with $AgNO_3$, which undergo aminolysis to give sulfonamides much more rapidly than the imidazolides of sulfonic acids themselves.[2] As in the protonation of *N*-acylimidazoles in acid solution, binding of the lone electron pair on nitrogen by complex formation results in increased reactivity, attributable to the increased electronegativity of the relevant ring nitrogens.

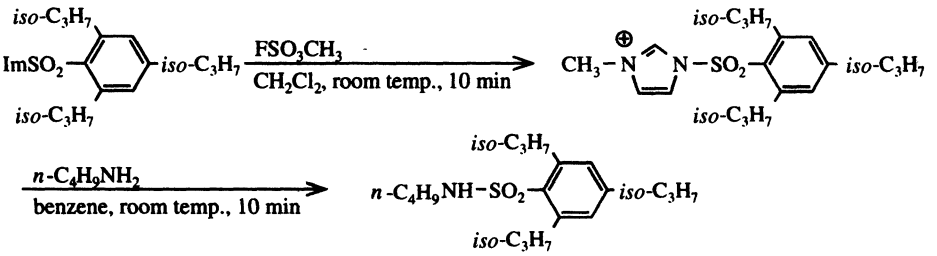


R^1	R^2	Yield (%)
CH_3	$C_6H_5CH_2$	75 *
CH_3	C_6H_5	85
H	C_6H_5	80
H	$C_6H_5CH_2$	88

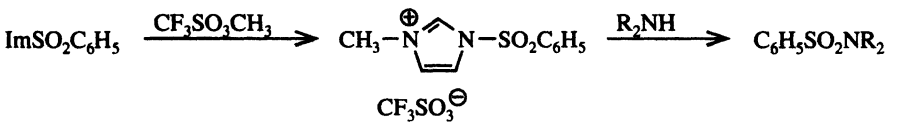
* without $AgNO_3$ 2.7%

[2]

A similar effect is achieved by *N*-methylation of the imidazolide with fluorosulfonic acid methyl ester[18] or methyl trifluoromethylsulfonate[7] as catalyst:

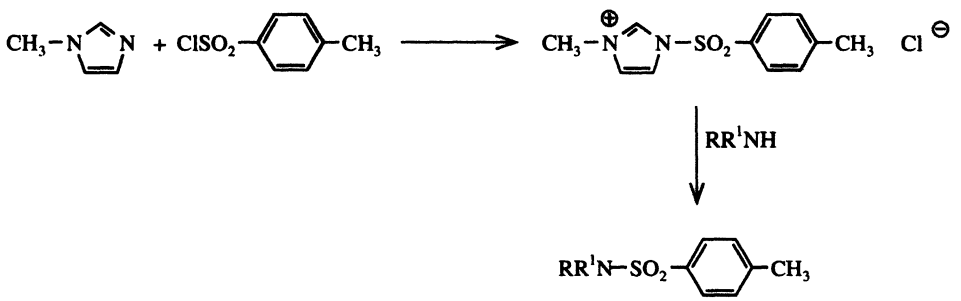


95%



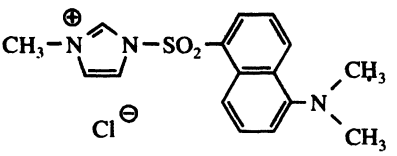
with (*iso*-C_3H_7)$_2$NH,71%; with prolin, 80%

The "imidazolium effect" is also used on the following route, where *N*-arylsulfonyl-*N'*-methylimidazolium salts as intermediates are aminolyzed easily in aqueous solution because hydrolysis is much slower:[19]



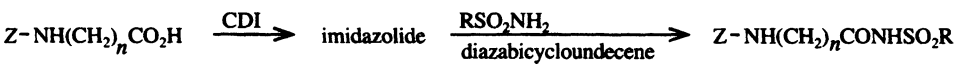
RR^1NH	Yield (%)
benzylamine	68
c-hexylamine	66
pyrrolidine	81
Gly	43
Gly–OC_2H_5	46

For the sulfonation step, amino acids were added as their sodium salts. The reactions were carried out in cold aqueous solution, in which the sulfonamides were immediately precipitated. By the same method "dansylations" of amino acids could be accomplished with *N*-(1-dimethylaminonaphthalene-5-sulfonyl)-*N'*-methylimidazolium chloride:

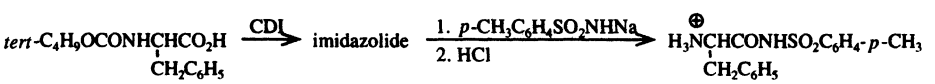


The *N*-dansylated amino acid (e.g., glycine, leucine, proline) exhibits a yellow fluorescence. The sensitivity of detection for amino acids by this method is about 10^{-9} mol of amino acid. The advantage of this prodecure in comparison with that using dansyl chloride is the fact that it can be carried out in homogenous aqueous solution without addition of a cosolvent.[19]

N-Acylsulfonamides are synthesized from carboxylic acid imidazolides and sulfonamides. Two typical procedures are worth noting here:[20],[21]

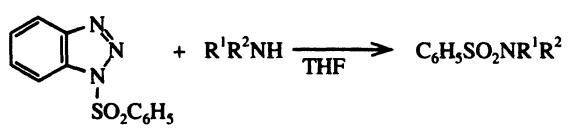


$Z = C_6H_5CH_2OCO$, $R = C_8H_{17}$; n:2, 77%; n:3, 33% [20]



52% [21]

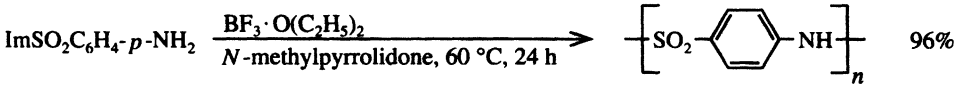
Sulfonamides can also be obtained by sulfonation of amines with *N*-sulfonylbenzotriazole in THF:[10]



R^1	R^2	Yield (%)
$C_6H_5CH_2CH_2$	H	93
$-(CH_2)_5-$		99
C_6H_5	H	87
C_6H_5	C_2H_5	78

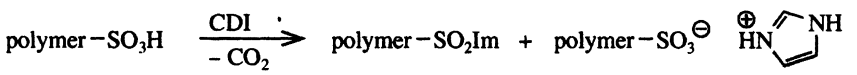
Primary aliphatic amines and piperidine react even at room temperature, whereas secondary aliphatic amines require reflux temperature. Primary and secondary aromatic amines also require reflux temperature and *N*-methylimidazole as catalyst.

A polysulfonamide was prepared in the following way:[22]

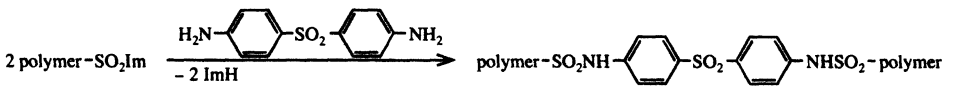


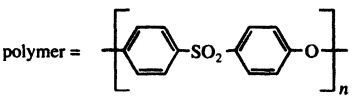
The crosslinking of a sulfonylated polyarylene ether sulfone was accomplished by addition of CDI and bis-4-aminophenylsulfone as crosslinking agents:[23]

a) Activation of the sulfonic acid group



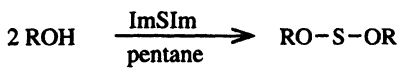
b) Crosslinking





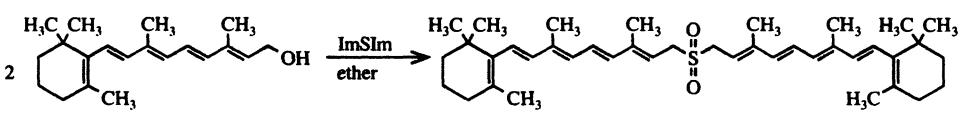
10.3 Sulfoxylates and Sulfones

Sulfoxylates have been obtained by the treatment of alcohols with the reactive *N,N'*-thiodiimidazole (ImSIm, see Section 10.1, page 290).



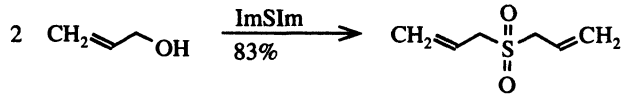
R	Yield (%)	Ref.
CH_3	34	[24]
C_2H_5	76	[25]
iso-C_3H_7	72	[25]
C_4H_9	78	[25]
s-C_4H_9	83	[25]
tert-C_4H_9	71	[25]

Sulfones are prepared by rearrangement of the first formed sulfoxylates. For example, treatment of vitamin A alcohol with ImSIm yields the corresponding sulfone, which can be converted to β-carotene:[26]



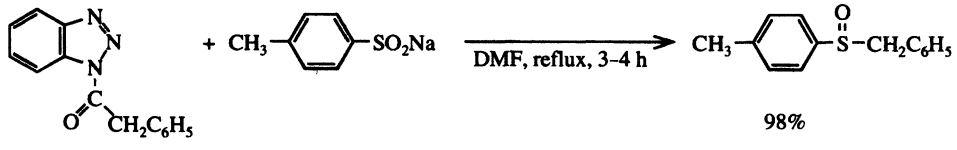
46%

Allyl alcohol reacts analogously with ImSIm, which in this case was made in situ from four moles of imidazole and SCl_2.[27]

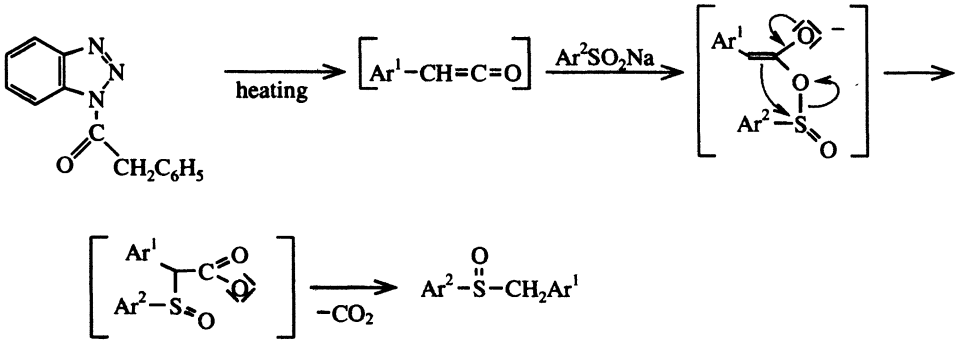


10.4 Sulfoxides

A recently discovered novel synthesis of toluenebenzylsulfoxides is based on the reaction of *N*-phenylacetylbenzotriazoles with sodium toluenesulfinates:[27a]



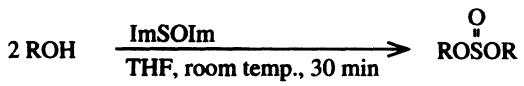
In the mechanism proposed, arylketene (which is thought to be an intermediate in this reaction), is attacked by the sulfinate anion acting as a nucleophile.

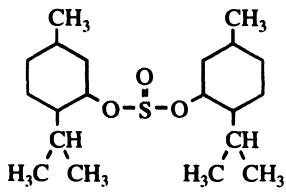


10.5 Sulfites and Sulfates

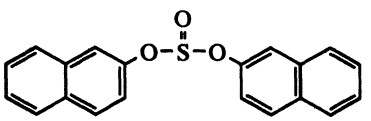
Esters of sulfurous acid (sulfites) or sulfuric acid (sulfates) can be synthesized by reaction of alcohols with *N,N'*-sulfinyldiimidazole (ImSOIm) and *N,N'*-sulfonyldiimidazole ($ImSO_2Im$), respectively.

Linear sulfites were prepared as follows[3],[28]



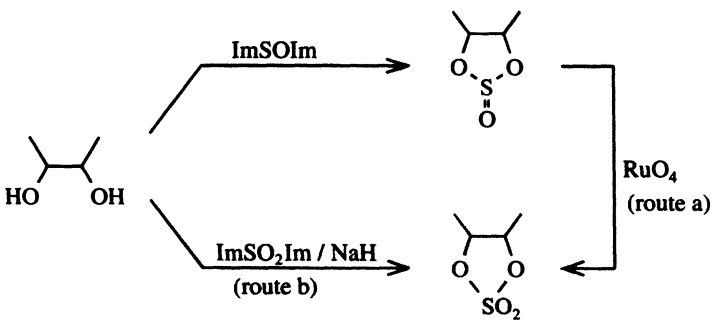


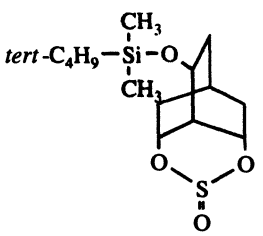
94%



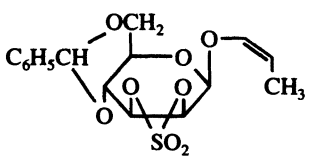
75%

Cyclic sulfites and sulfates are obtainable by the following reactions:[29]–[31]



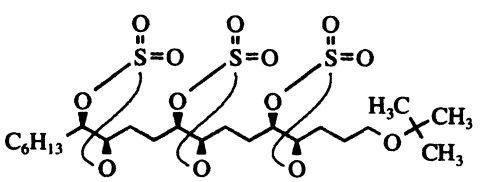


94% [29]



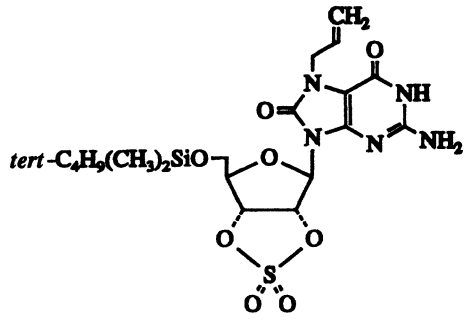
78% [30]

The bicyclooctane sulfite illustrated can be oxidized with RuO_4 to the sulfate in 72% yield.[29] The mannopyranoside sulfate was obtained by means of *N,N'*-sulfonyldiimidazole ($ImSO_2Im$).[30] A trifold cyclic sulfate was synthesized according to route b.[31]

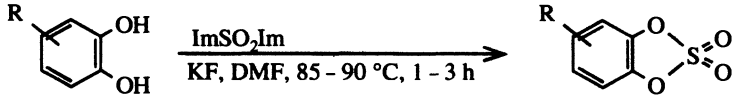


82% [31]

The following ribofuranosyl sulfate was obtained with $ImSO_2Im/LiH$ in 42% yield:[32]



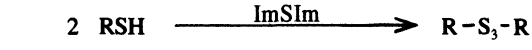
Catechol sulfates are efficiently synthesized by reacting the appropriate catechol with *N,N'*-sulfonyldiimidazole in the presence of potassium fluoride:[33]



R	Yield (%)
H	85
4-*tert*-C_4H_9	79
3-CH_3O	81
4-Z-$NHCH_2CH_2$	80

10.6 Sulfanes (Polysulfides)

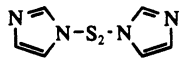
Sulfur insertion into thiols RSH to give symmetrical trisulfides in high purity is easily accomplished by diimidazolylsulfide (reaction conditions: hexane, 0–25 °C, 0.5–2 h).[34]

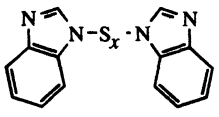


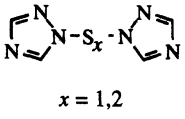
R	Yield (%) [34]
CH_2=$CHCH_2$	80
C_3H_7	80
iso-C_3H_7	80
tert-C_4H_9	90
C_6H_5	80

Diimidazolyldisulfide, dibenzimidazolylsulfide and -disulfide, ditriazolylsulfide and ditriazolyldisulfide as well as the corresponding dibenzo derivatives have also been used for sulfur insertions.[15]

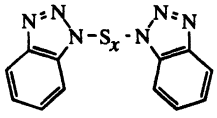
The bisazolylsulfides shown below are much better sulfur transfer reagents than S_xCl_2 ($x = 1, 2$). Moreover they are reactive toward alcohols and primary and secondary amines.



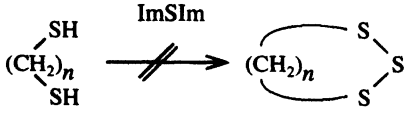




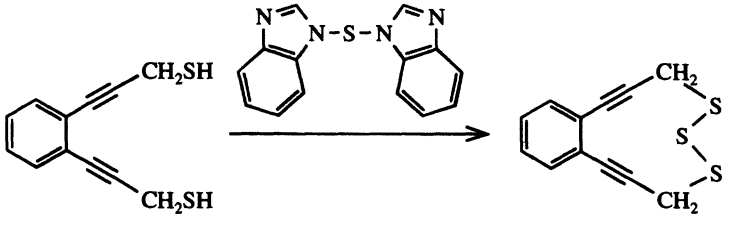
$x = 1,2$



Syntheses of small cyclic trisulfides were not successful, but a larger ring was achieved:

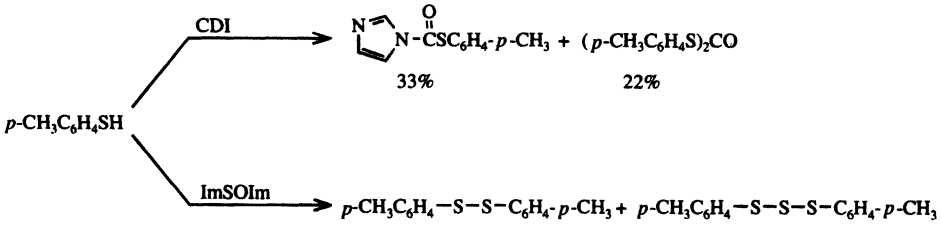


$n = 2, 3, 4$ [34]



30% [35]

Whereas CDI reacts with thiols to give thiocarboxylic imidazolide and the corresponding dithiocarbonate. The reaction with *N,N'*-sulfinyldiimidazole afforded, surprisingly, a mixture of dithio and trithio compounds in good yield:[36]

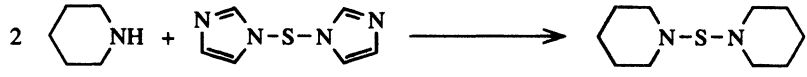


The ratio disulfide/trisulfide varies from 1:1 to 3.9:1 depending on the diol used in this reaction ($C_6H_5CH_2SH$, *o*-$CH_3OC_6H_4SH$). With *p*-$NO_2C_6H_4SH$, only the disulfide was obtained in 70% yield.

The formation of disulfides and trisulfides has also been accomplished with *N,N'*-sulfinyldibenzimidazole,[36] although such a reaction was not observed in reference [16].

10.7 Diaminosulfanes

These compounds are prepared from bisimidazolyl sulfide (*N,N'*-thiodiimidazole) and secondary amines such as piperidine.[37]

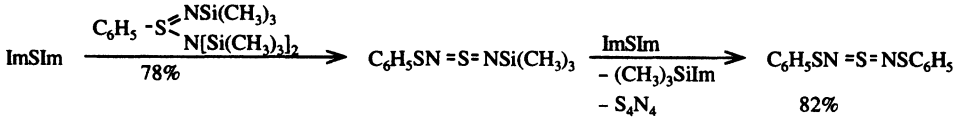


quant. [14]

Reactions with aziridine were also described.[38]

Moreover, *N,N'*-thiodiimidazole has been used for the preparation of dithiosulfurdiimides.[39]

Example:



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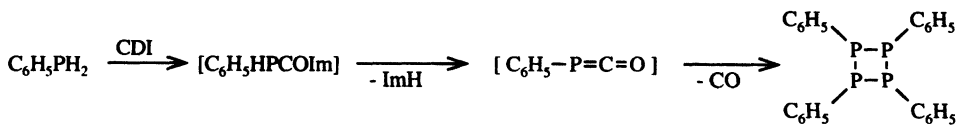
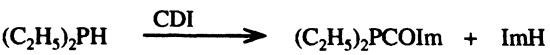
11 Reaction of Phosphines with *N,N'*-Carbonyldiimidazole (CDI)

The reaction of CDI with primary phosphines was expected to lead first to an azolide ImCOPHR, analogous to imidazole-*N*-carboxamide as the reaction product of primary amines and CDI. In fact, reaction of phenylphosphine with CDI leads directly to imidazole, carbonmonoxide, and tetraphenylcyclotetraphosphine (THF, reflux, 5h). In analogy to the dissociation of imidazole-*N*-carboxamide into isocyanates and imidazole, this can be explained by the assumption that the first-formed $ImCOPHC_6H_5$ dissociates into an isocyanate analogue, $C_6H_5P{=}C{=}O$, which is unstable and decomposes into carbon monoxide and phenylphosphene (C_6H_5P) which tetramerizes. However, the intermediate formation of phenylphosphene has not yet been definitely proved.[1]

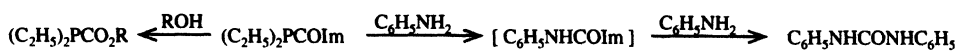


74%

With secondary phosphines the reaction with CDI is similar to the reaction of the corresponding amines, but more vigorous conditions are required (reflux in dioxane for several hours). Thus, diethylphosphine gives diethylphosphinocarbonylimidazole, in which, however, the imidazole groups cannot be replaced even by prolonged heating with an excess of diethylphosphine in contrast to the corresponding diethylaminocarbonylimidazole:[1]



Reactions of diethylphosphinocarbonylimidazole with alcohols such as ethanol or benzyl alcohol are strongly exothermic, and lead to diethylphosphinocarboxylates. For the reaction with aniline, leading to diphenylurea, another mechanism seems to apply.



R = C_2H_5, 86%;
$C_6H_5CH_2$, 62%

Reference

[1] D. W. Müller, Ph. D. Thesis, University of Heidelberg, **1963**; see also H. A. Staab, W. Rohr, *Newer Meth. Prep. Org. Chem.* **1968**, Vol. V, p. 61–108.

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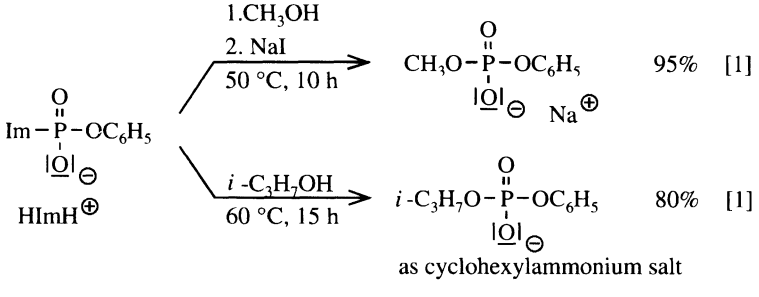
12 Phosphorylation and Nucleotide-Syntheses

The following sections deal with a variety of rather complex syntheses using different versions of phosphorylations by azolides. The syntheses described here are selected primarily not for their specific practical applications but to show the versatility of the azolide method in synthesizing very complicated phosphorus-containing structures.

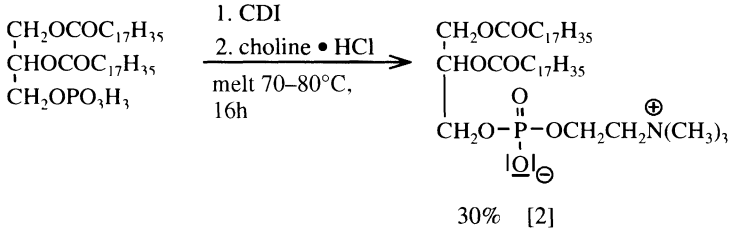
12.1 Phosphorylation, Phosphonylation and Phosphinylation of Alcohols

Reactions with Phosphoric and Phosphinic Monoimidazolides

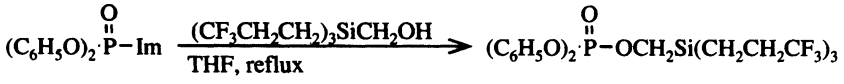
Alcohols can be phosphorylated to phosphoric diesters by ionic phosphoric monoimidazolides in acetone at temperatures of about 50–60 °C over the course of several hours. These imidazolides are generally prepared by reaction of the appropriate phosphate with CDI (see Section 2.2). Reactions with ethyl, *n*-butyl, *n*-pentyl, *n*-octyl benzyl alcohol and various other alcohols have also been described.[1]



In 1,2-diacylglycerol-3-phosphate the phosphate group was esterified with choline by means of CDI to give the phosphatidyl choline:

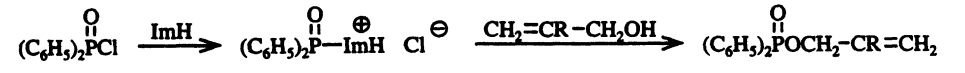


The reaction of phosphoric diphenylester imidazolide (for preparation see Section 2.2) with tris(1,1,1-trifluoropropyl-3)silylmethanol yields a phosphoric triester.[3]



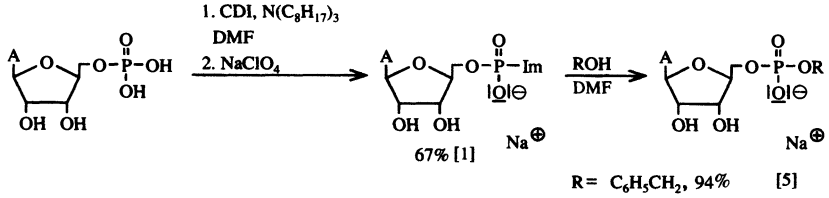
62% [3]

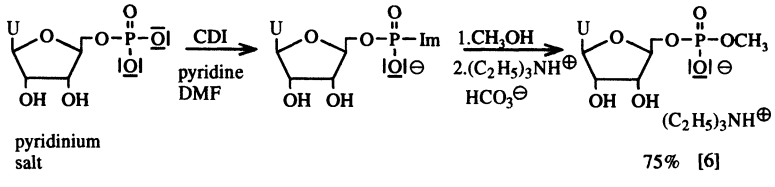
Analogously to the phosphorylation of alcohols with phosphoric azolides the phosphinylation is carried out by means of phosphinic azolides ($CH_2Cl_2/C_2H_5OC_2H_5$). In the following case a $I_2/C_2H_5OC_2H_5$) protonated diphenylphosphinic imidazolide is used to give the allylic diphenylphosphinic esters in good yields:[4]



R = H, 81%; CH_3, 87%

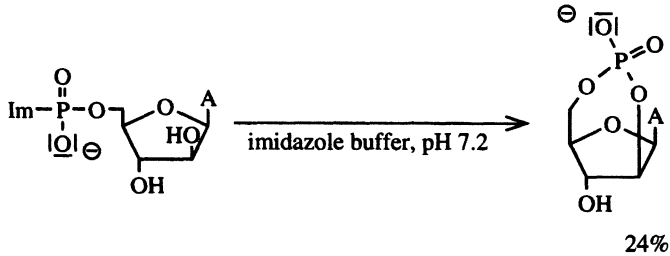
Adenosine and uridine monosphophate (AMP and UMP, resp.) react via their imidazolides with alcohols to give the phosphoric diesters:





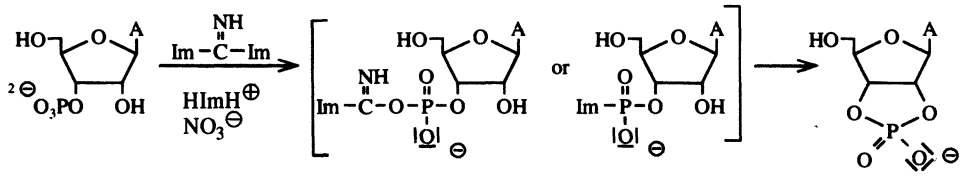
The formation of a 2′,3′-cyclic carbonate during the reaction of AMP with CDI is discussed in reference [7] (see also Section 3.8.2).

In the case of arabinosyladenine-5′-phosphoric imidazolide, a reaction with the 2′-OH of the sugar moiety was observed:[8]

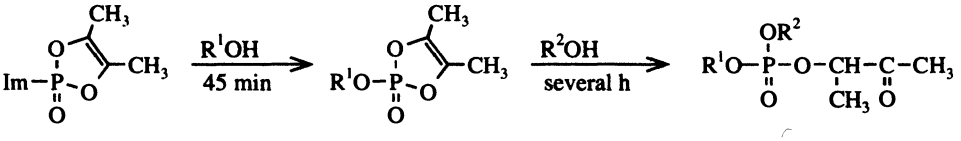


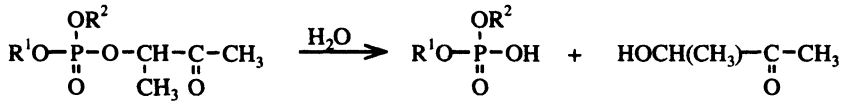
24%

Another cyclization of 3′-adenylic acid (3′-AMP) to 2′,3′-cyclic adenylic acid (2′,3′-cAMP) took place by condensation with carbiminodiimidazole (or *N*-cyanoimidazole) in aqueous or anhydrous medium. It is supposed that the reaction of 3′-AMP probably proceeds via a phosphoric imidazolide:[9]



With neutral phosphoric monoimidazolides, which are more reactive than the ionic species, the reaction time for phosphorylation of an alcohol is reduced. A one-flask synthesis of unsymmetrical phosphoric diesters from *N*-(1,2-dimethylethylenedioxyphosphoryl)imidazole, prepared from di(1,2-dimethylethylene)pyrophosphate and imidazole, is presented below:[10],[11]

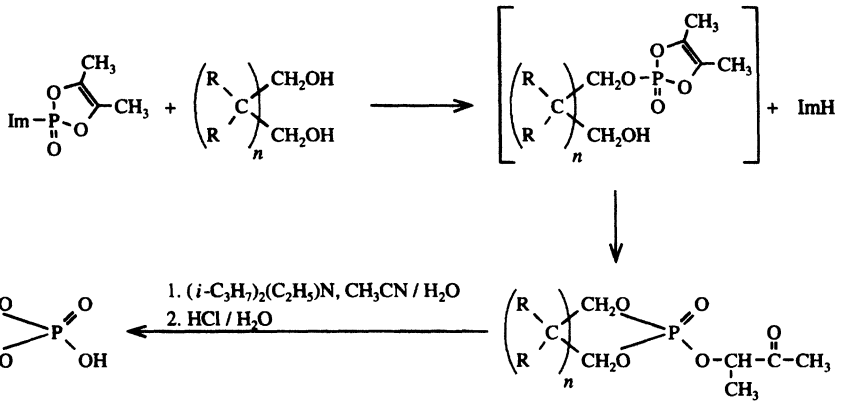




R^1	R^2	Yield (%) as dicyclohexylammonium salt
$(CH_3)_3CCH_2$	$(CH_3)_2CHCH_2$	74
c-C_5H_9	$C_6H_5CH_2$	80
$(C_2H_5)_2CH$	$C_6H_5CH_2$	74

The dialkyl(1-methylacetonyl)phosphates, which were easily hydrolyzed, are obtained in higher than 90% yields. Such reactions can also be carried out by making the phosphoric imidazolide in situ from the di(1,2-dimethylethylene)pyrophosphate and imidazole.[10]

If 1,3-, 1,4-, and 1,5-alkanediols are introduced in this phosphorylation reaction, 6-, 7-, and 8-membered cyclic phosphordiesters are obtained:[12]

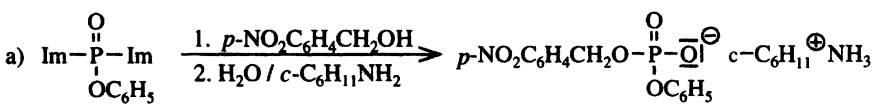


R	n	Yield (%)
H	1	77
CH_3	1	80
H	2	86
H	3	82

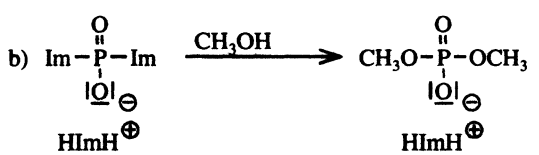
R	n	Yield (%)
H	1	70
CH_3	1	90
H	2	82
H	3	43

Reactions with Phosphoric Diimidazolides

In the reaction of a phosphoric ester diimidazolide (for preparation see Section 2.2) with an alcohol it is possible to substitute either one or two of the imidazole groups.



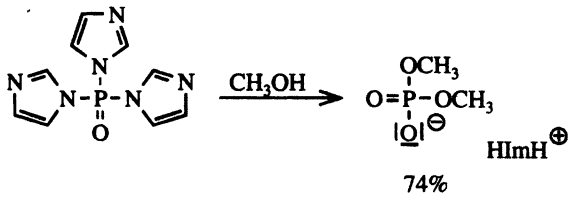
91% [13]



98% [1]

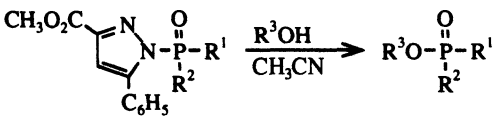
Reactions with Phosphoric Triimidazolide

In the reaction of the very reactive phosphoric triimidazolide[1] (for preparation see Section 2.2), which is also called phosphoryltriimidazole in analogy to the carbonyldiimidazole CDI, with an excess of methanol, as products trimethylphosphate, dimethylphosphate, and *O*-methylphosphoric imidazolide were detected after one hour, and after two days the imidazolium salt of dimethylphos-phate was obtained in high yield:[13]



Reactions with Phosphoric Pyrazolides

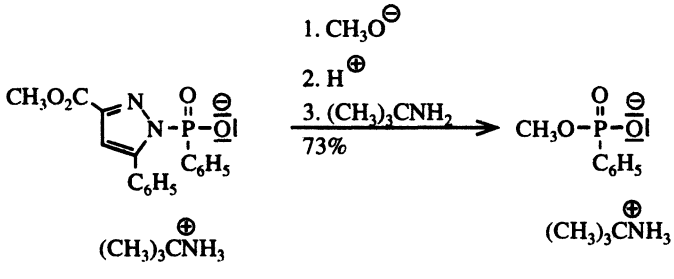
Phosphoric, phosphonic and phosphinic pyrazolides have been used for phosphorylation, phosphonylation, or phosphinylation of primary and secondary alcohols:[14]



R^1	R^2	R^3	Yield (%)
OCH_3	OCH_3	i-C_3H_7	77
OCH_3	C_6H_5	C_2H_5	83
C_6H_5	C_6H_5	i-C_3H_7	83

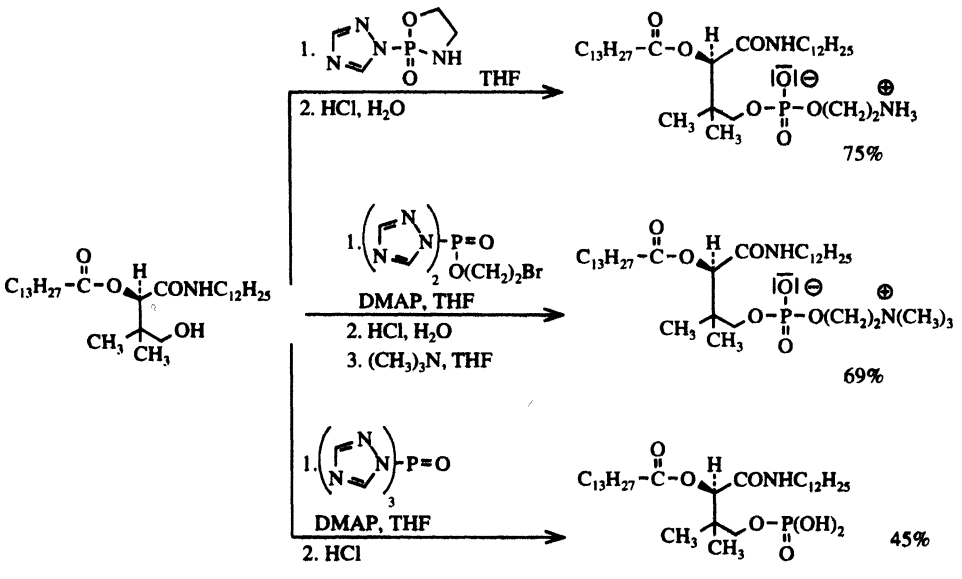
β-Oxenols[14] and oximes[15] can also be phosphonylated successfully in this way. In the reaction with diols, selective monophosphonylation has been achieved.[14]

The synthesis of phosphonates with anionic phosphonic pyrazolides is described in reference [16]:



Reactions with Phosphoric Triazolides

Analogues of phosphatidyl ethanolamine, phosphatidyl choline, and phosphatidic acid with pantoic acid skeleton were prepared by phosphorylation with the respective phosphoric mono-, bis-, and tristriazolide:[17]

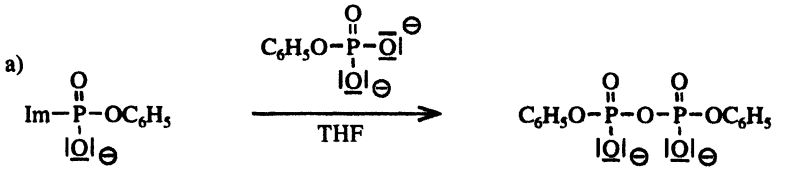


DMAP = *p*-dimethylaminopyridine

12.2 Diphosphates and Triphosphates

Access to diphosphates (pyrophosphates) and triphosphates is provided through the reaction of phosphoric mono- or diimidazolides with a monoester phosphate.

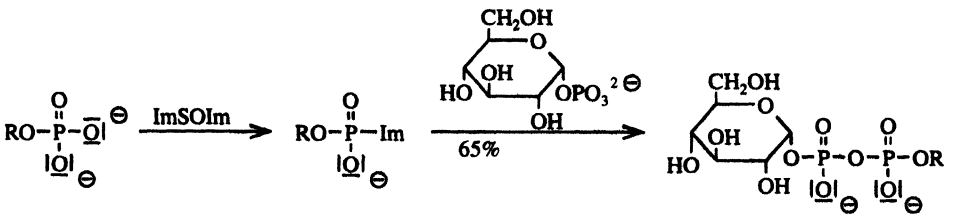
a)

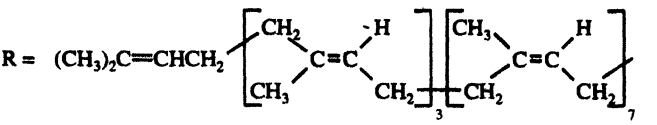


in situ by CDI

imidazolium salt, 97% [1]

b) Polyprenylpyrophosphate sugars, which are intermediates in the biosynthesis of Salmonella *O*-specific polysaccharides, were prepared from polyprenylphosphoric-imidazolide and glycosylphosphates, for example, α-D-glucopyranosylphosphate:[18]–[20]

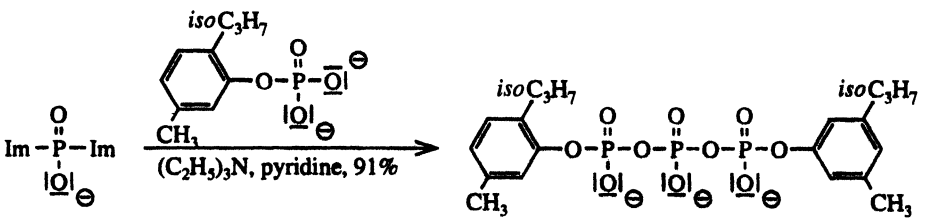




Polyprenyl

The reaction was also carried out with other glycosylphosphates.[21]–[23]

c) In the reaction of phosphoric diimidazolide (for preparation see Section 2.2) with thymylphosphate, a triphosphate was formed:[1]

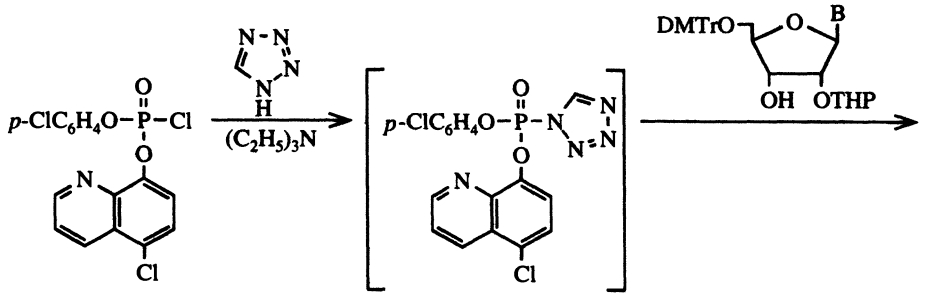


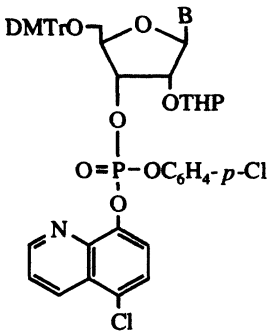
cyclohexylammonium salt

12.3 Phosphorylation of Nucleosides

Reactions with Phosphoric Monoazolides

By using a phosphoric diester monotetrazolide, made in situ from the corresponding phosphoric chloride and tetrazole in the presence of triethylamine, the 3′-OH of a suitably protected nucleoside could be phosphorylated to give a fully protected nucleotide:[24]



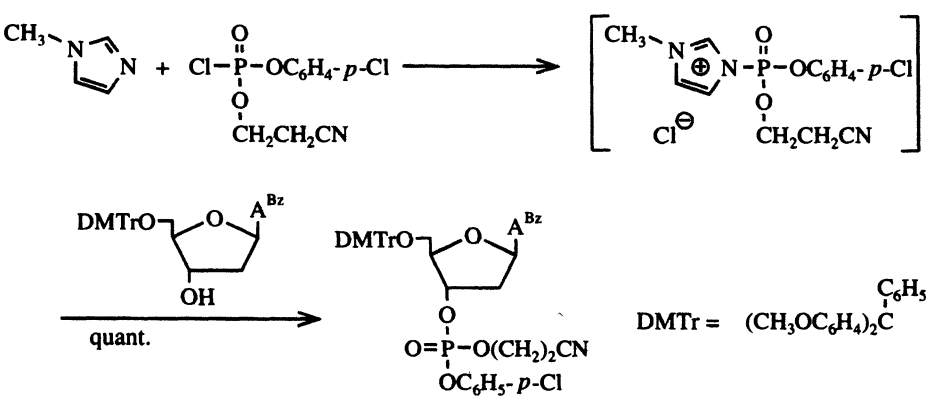


B	Yield (%)
A^{Bz}	91
C^{Bz}	92
U	96
G^{Bz}	82

A^{Bz} = *N*-benzoyladenine

DMTr = $(CH_3OC_6H_4)_2C(C_6H_5)$

Fully protected nucleotides could also be prepared with a phosphoric diester chloride/ *N*-methylimidazole combination, probably via a phosphoric imidazolium intermediate:[25]

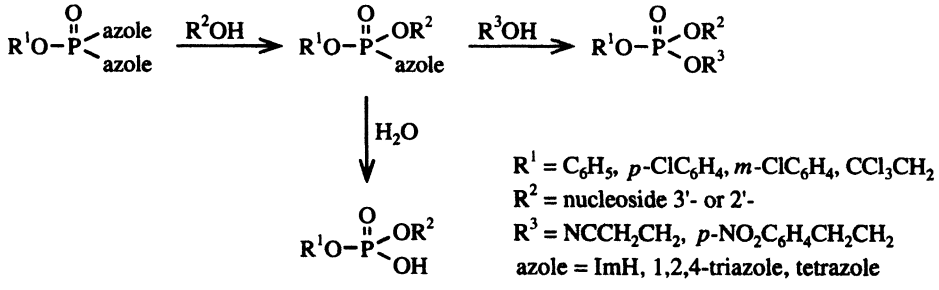


DMTr = $(CH_3OC_6H_4)_2C(C_6H_5)$

Reactions With Phosphoric Bisazolides

More important than the phosphoric monoazolides are the phosphoric bisazolides in the generation of nucleoside 3′- and 2′-phosphates or 3′,5′-dinucleotides. The phosphoryla-

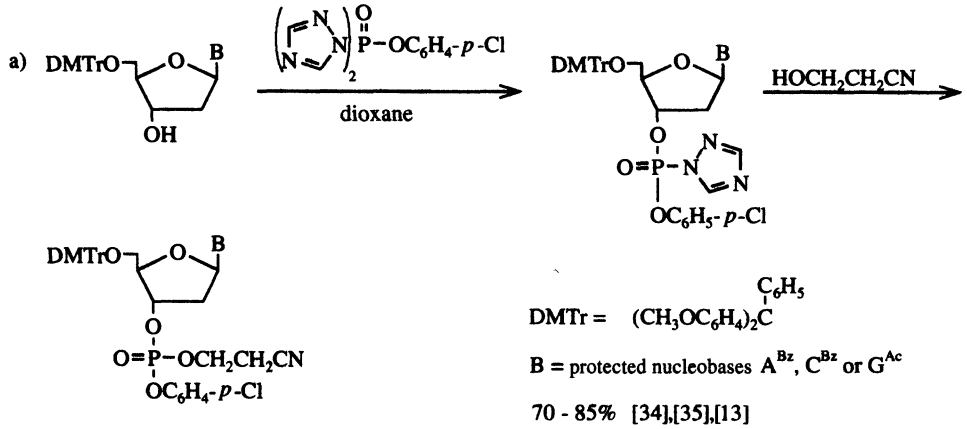
tion of nucleosides has been conveniently achieved with phosphoric bisazolides, frequently prepared in situ from phosphoric dichloride and azoles. The first azole group is generally substituted by a nucleoside 3′-OH, the second by an alcoholic or phenolic protecting group to give the fully protected nucleotide triester. Hydrolysis of the second azole affords the nucleoside phosphordiester.



The phosphoric bisazolide reacted only with one nucleoside 3′-OH to give a diesterified product (cf.[26]–[32]); however, with a nucleoside 5′-OH component, one or two triazole groups could be substituted, depending on the ratio of the reaction partners.[33]

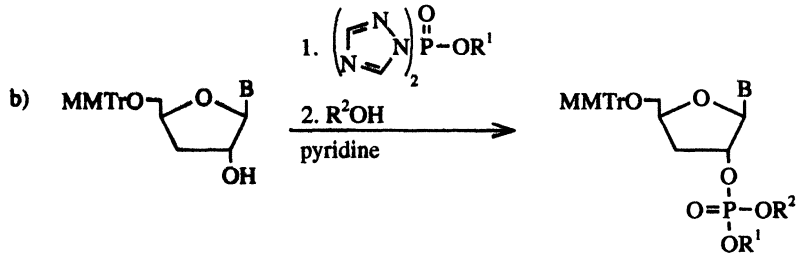
The 3′- or 2′-phosphordiester and -triester were generally obtained in good yield.

Examples:



The 5′-dimethoxytrityl or β-cyanoethyl group of the fully protected mononucleotide could then be selectively cleaved.

b)

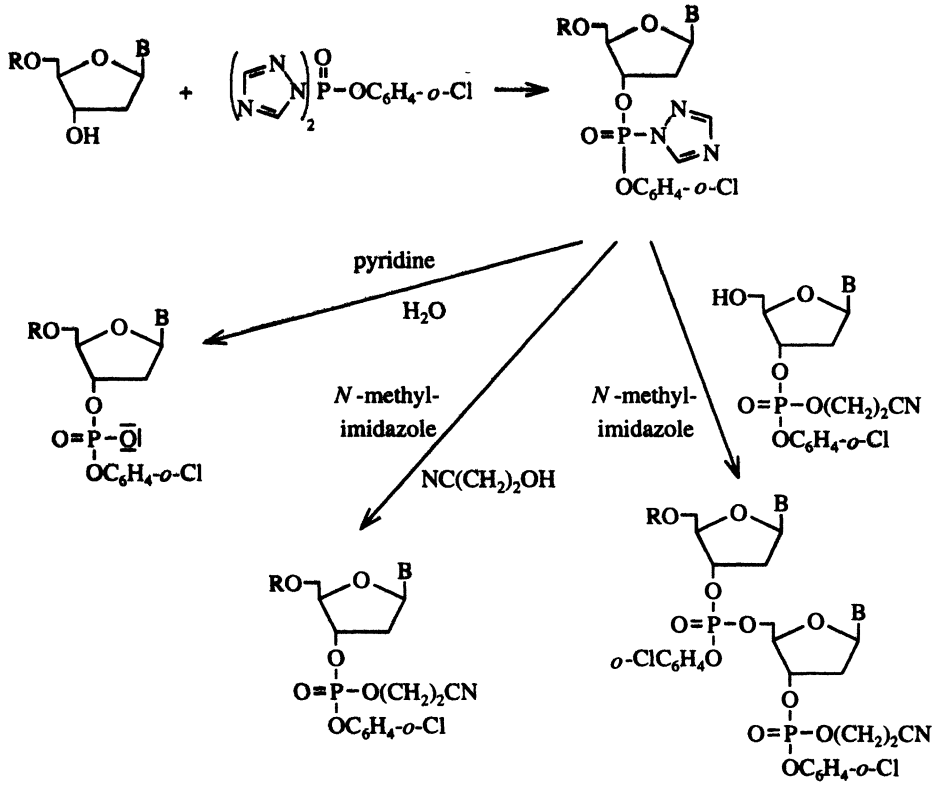


B	R^1	R^2	Yield (%)
A^{Bz}	*o*-ClC_6H_4	$NCCH_2CH_2$	79
A^{Bz}	1,4-$Cl_2C_6H_3$	*p*-$NO_2C_6H_4(CH_2)_2$	88
A^{npeoc}	1,4-$Cl_2C_6H_3$	*p*-$NO_2C_6H_4(CH_2)_2$	81

[36]

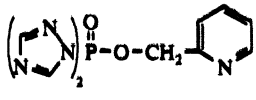
MMTr = 4-monomethoxytrityl
A^{Bz} = *N*-benzoyladenine
A^{npeoc} = *N*-2-(*p*-nitrophenyl)ethoxycarbonyladenine

c) Synthesis of di-, tri- and tetradeoxyribonucleotides, utilizing an *O*-arylphosphoric ditriazolide with *N*-methylimidazole as catalyst:[37]

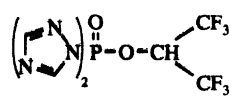


Trinucleotides are formed by 5′-deprotection of the dinucleotide and subsequent conversion with the monotriazolide in the presence of *N*-methylimidazole. The fully protected di- and trideoxyribonucleotides of the following nucleotide sequences have been obtained in high yield: T–T (82%), C–T (88%), C–C (84%), G–G (81%), G–T (83%), A–G–T (65%), C–G–T (61%). The yields are similar to those obtained in a reaction involving 1-(triisopropylbenzenesulfonyl)tetrazole as coupling agent [37]–[39] (see also Section 12.7).

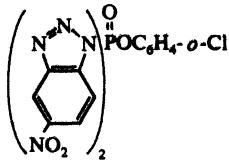
Other phosphoric bisazolides employed for the synthesis of 3′,5′-nucleotides are:



(α-pyridyl)methyl phosphoric ditriazolide [40]

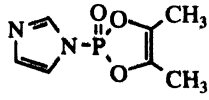


hexafluoro-2-propylphosphoric ditriazolide [41]



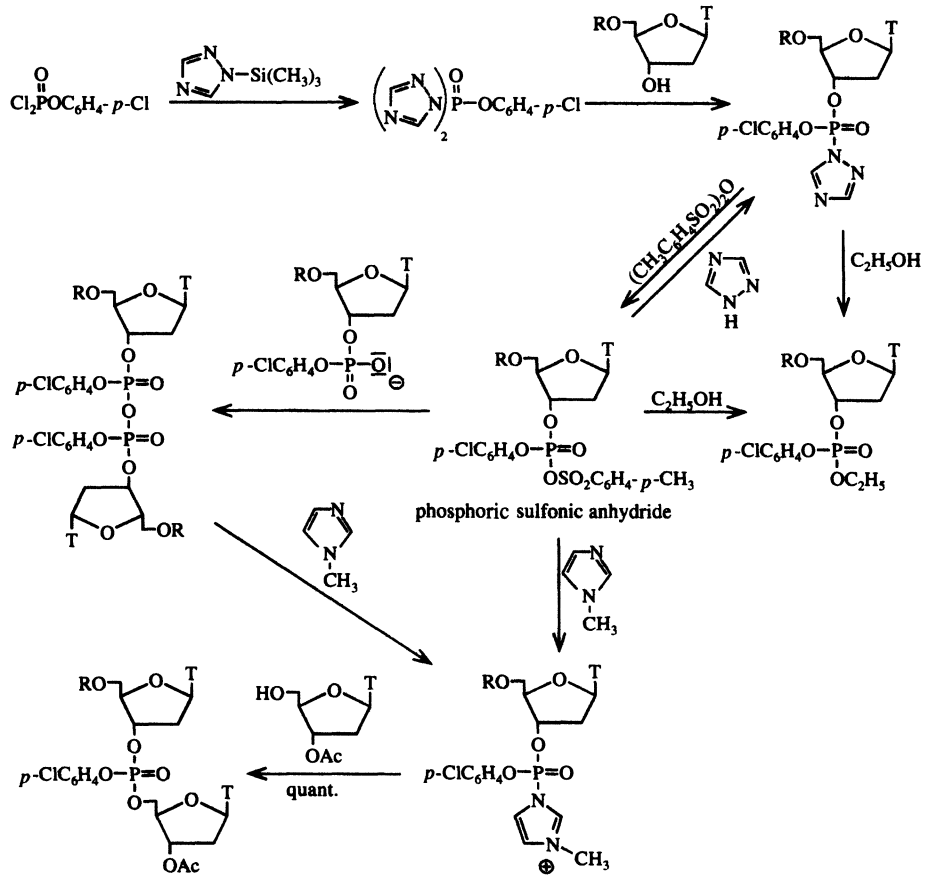
o-chlorophenyl phosphoric bis(nitrobenzotriazolide) [42]

A cyclic enediolphosphoric imidazolide, although a monoimidazolide, works in the same manner as a bisazolide:



[43]

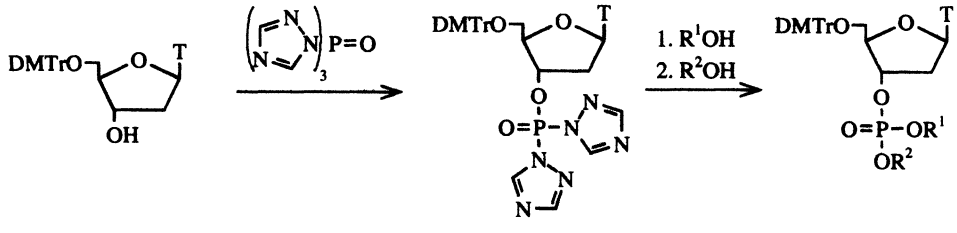
Another synthesis of nucleotides by means of phosphoric bisazolides proceeds via phosphoric-sulfonic anhydrides or pyrophosphates. The arylsubstituted phosphoric sulfonic anhydrides are prepared from a phosphoric imidazolide or phosphoric triazolide and a sulfonic anhydride. It reacts with nucleophiles like alcohols to give phosphortriesters, with triazole to give back the triazolide, and with a nucleoside phosphordiester to give a pyrophosphate derivative. However, it does not react with the 5′-hydroxyl of a nucleoside such as 3′-*O*-acetylthymidine to give the phosphortriester except in the presence of *N*-methylimidazole. The highly reactive intermediate produced upon addition of *N*-methylimidazole to the phosphoric sulfonic anhydride was observed using ^{31}P-NMR-spectroscopy. Formation of the dinucleoside phosphortriester could also be achieved from the symmetrical tetrasubstituted pyrophosphate in the presence of *N*-methylimidazole:[44]



Reactions with Phosphoric Trisazolides (Phosphoryltrisazoles)

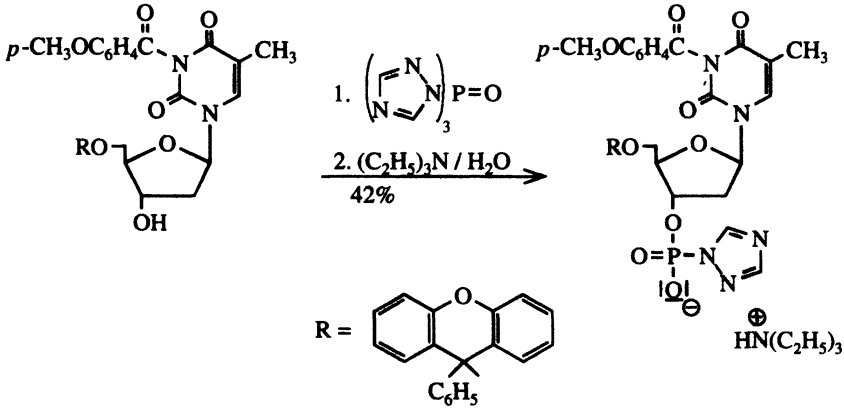
The 3′-OH of a nucleoside can be phosphorylated with phosphoryltristriazole or phosphoryltrisimidazole.

a) Phosphoryltristriazole is considered very useful for the preparation of nucleoside 3′-phosphortriesters bearing various phosphate protecting groups. It is generally obtained from $POCl_3$ and 1,2,4-triazole. As a stock solution in dioxane it is stable for at least 10 days:[45]



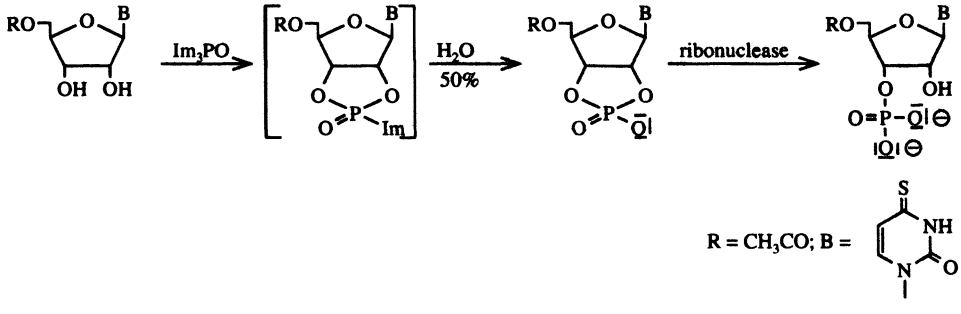
R^1	R^2	Yield (%)
$NCCH_2CH_2$	C_2H_5	60
$NCCH_2CH_2$	$C_6H_5OCOCH_2$	61
$NCCH_2CH_2$	$BrCH_2CH(Br)CH_2$	63
$NCCH_2CH_2$	Cl_3CCH_2	75

If the nucleoside is treated with a threefold excess of phosphoryltristriazole and subsequently with a mixture of triethylamine and water, the ionic nucleotide phosphoric triazolide can be obtained:[46]

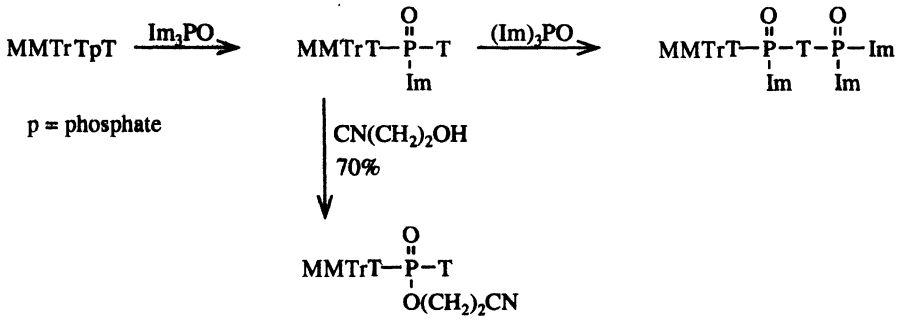


With thiophosphoryltristriazole the corresponding thiophosphoric triazolide was formed in 80% yield.[46]

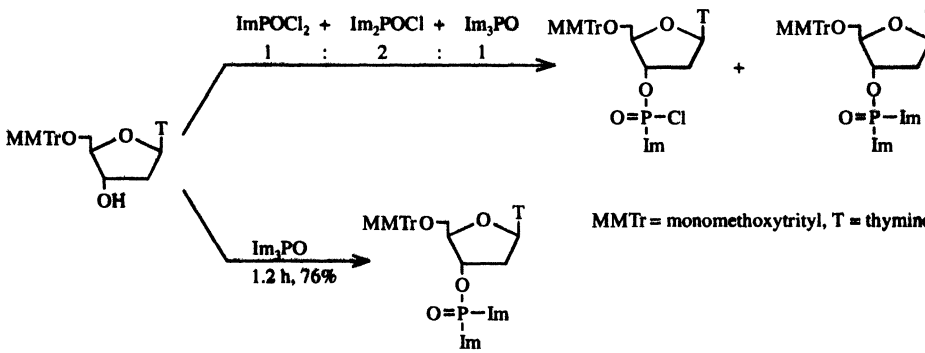
b) The reaction of phosphoryltriimidazole with a 5′-protected ribonucleoside gives the 2′,3′-cyclic phosphate, which is cleaved by ribonuclease to afford a nucleoside 3′-phosphate:[47]



c) In the phosphorylation of a 5′-protected dideoxynucleoside phosphate with phosphoryltriimidazole, the phosphordiester group is converted in the first step of the reaction into a phosphoric diester imidazolide, which in the second step is phosphorylated at the free 3′-OH group. Hydrolysis of the imidazolide groups gives the dinucleotide. If the monoimidazolide is treated with β-cyanoethanol the corresponding phosphortriester is formed. Further examples are presented in ref. [48].

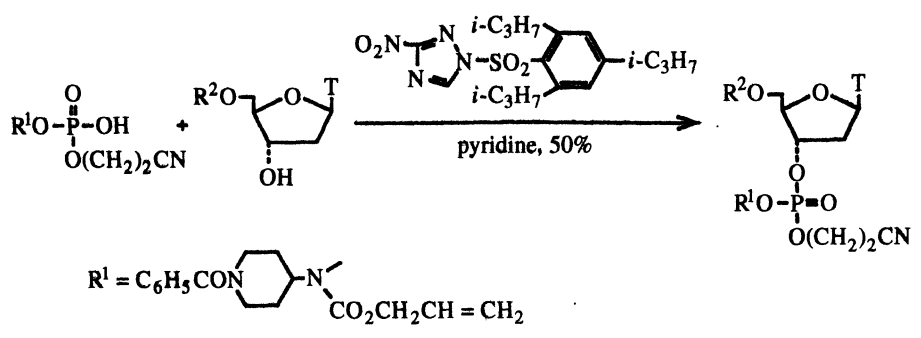


d) Deoxyribonucleosides are instantaneously and quantitatively phosphorylated in pyridine with a mixture of imidazolides obtained when $POCl_3$ and imidazole are mixed in a 1 : 2 ratio. The nucleoside is also phosphorylated with Im_3PO alone, albeit more slowly:[49]



Reactions with Arylsulfonylazoles

The phosphorylation of the 3′-OH of a 5′-substituted thymidine was achieved with 2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole: [49a]

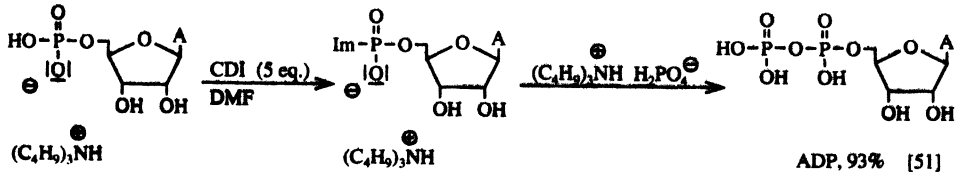


12.4 Nucleoside Oligophosphates

Nucleoside Diphosphates

Nucleoside diphosphates can be synthesized by either of two azolide methods. The first method consists of the reaction of a nucleoside phosphate with CDI, followed by treatment of the resulting imidazolide with trisbutylammonium phosphate to give the diphosphate. The second method takes advantage of the reaction of phosphoric bisazolides with a nucleoside phosphate. 5′-Phosphates such as AMP, UMP, GMP, CMP, and IMP (but also 3′-phosphates[50]) are in this way converted into the corresponding diphosphates ADP, UDP, etc.[51],[5],[1],[52]–[54]

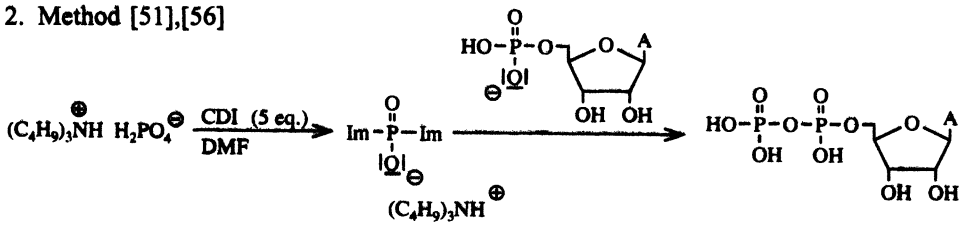
1. Method [51],[55]



ADP, 93% [51]

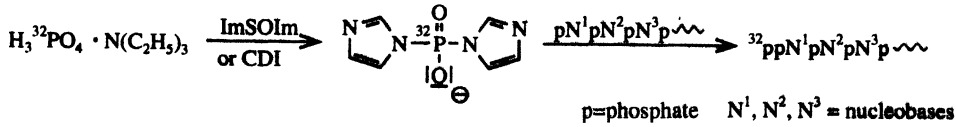
Instead of CDI, carbonyl-, thiocarbonyl- or sulfinyldibenzotriazole have also been used for formation of the nucleoside phosphoric azolide.[55]

2. Method [51],[56]



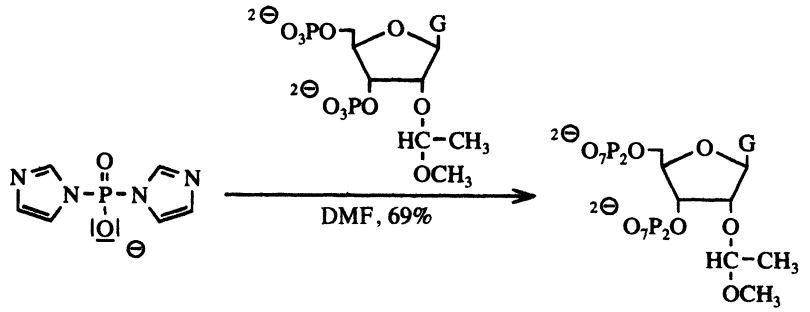
ADP, 91% [51]

With [^{32}P]phosphoric diimidazolide, prepared from sulfinyldiimidazole or CDI and $H_3{}^{32}PO_4$, the 5′-terminal monoester phosphate groups in various RNAs could be selectively phosphorylated (radioactive labeling method):[57],[58]



p=phosphate N^1, N^2, N^3 = nucleobases

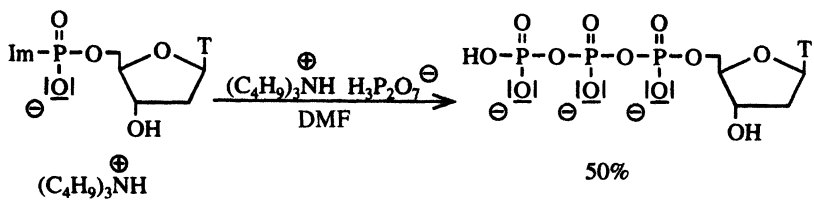
A guanosine tetraphosphate with pyrophosphate groups in the 3′- and 5′-positions was synthesized by double phosphorylation of the corresponding guanosine 3′,5′-diphosphate.[50]



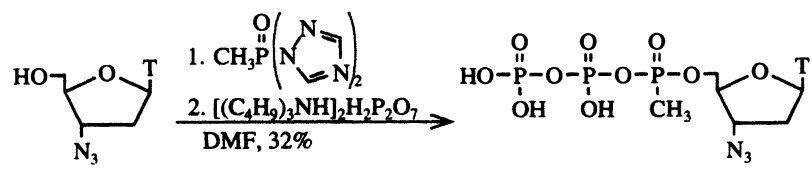
Nucleoside Triphosphates

Nucleoside triphosphates are prepared analogously to the diphosphates by the methods a, b, c, and d, representing conversion of a nucleoside phosphoric azolide with inorganic pyrophosphate (Method a), of a nucleoside diphosphoric azolide with inorganic phosphate (Method b), of a phosphoric bisazolide with a nucleoside diphosphate (Method c), and of a diphosphoric bisazolide (bisazolide of pyrophosphoric acid) with a nucleoside phosphate (Method d).

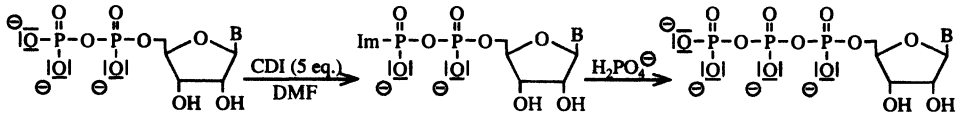
Method a [59] (see also [60]–[65],[65a],[53],[54]).
By this method, for instance, thymidine triphosphate (p_3T) has been synthesized.[59]



Whereas imidazolides of nucleotides react only in organic solvents with phosphates or pyrophosphates to give the corresponding anhydride derivatives in high yield, ATP can also be formed enzymatically in aqueous solution from AMP-Im with inorganic pyrophosphate in the presence of valyl-*t*-RNA synthetase.[66] A variant of this method is the one-pot reaction of a nucleoside with phosphoryltristriazole and tributylammonium pyrophosphate.[67] An α-methylphosphonyl-β,γ-diphosphate of a thymidine derivative has been synthesized in a similar way:[68]

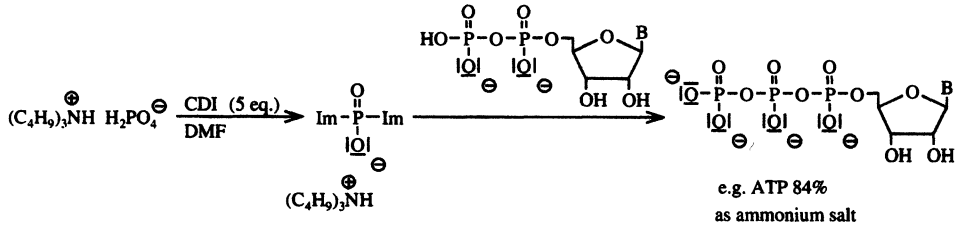


Method b [51],[69]

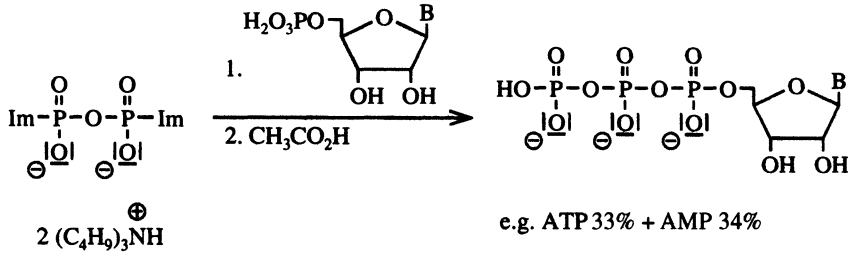


By this method adenosine triphosphate (ATP) and inosine triphosphate (ITP) were prepared in 89% and 93% yield, respectively.[51]

Method c [51],[70]



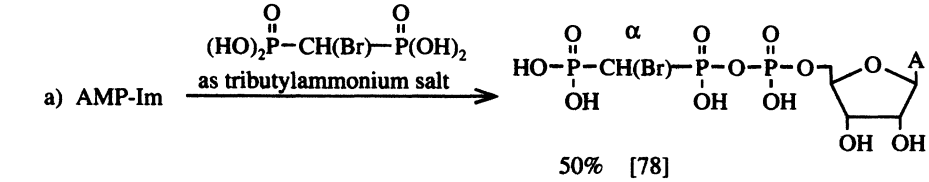
Method d [7]

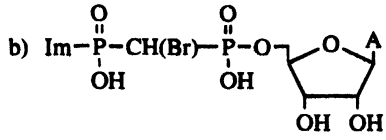


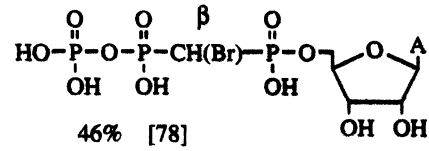
Method a has been used to synthesize ATPs modified in the ribose portion and/or in the nucleobase[71]–[73] as well as 5′-triphosphates of 2′,5′-oligoadenylates [for example pppA(p5′A2′)$_n$ with $n = 1$ and 2].[74],[75]

Use of the bisimidazolide of peroxydiphosphate permitted adenosine 5′-(β,γ-peroxytriphosphate) to be prepared.[76] An adenosine 5′-[$\beta^{18}O_2$]triphosphate was obtained in 54% yield.[77]

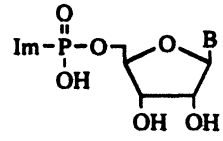
Other nucleoside triphosphates modified in the α- or β-positions were obtained according to the following routes:

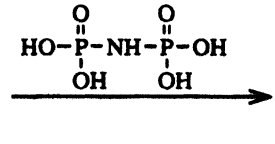


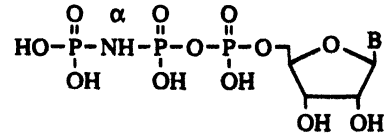
b) 



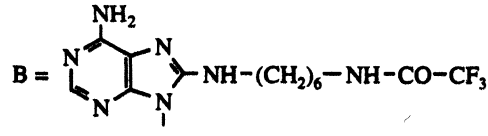
46% [78]

c) 



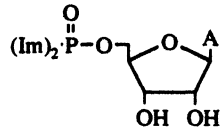


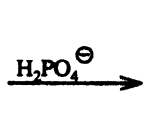
20 - 30% [53]

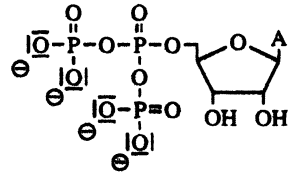


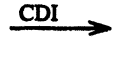
Synthesis of pseudo ATP (ψ-ATP):

Adenosine 5′-α,β,β'-triphosphate (pseudo ATP = Ψ-ATP) was obtained by treatment of the phosphoric diimidazolide of adenosine 5′-monophosphate with tributylammonium phosphate. It rearranges with CDI into ATP.[51]









ATP [51]

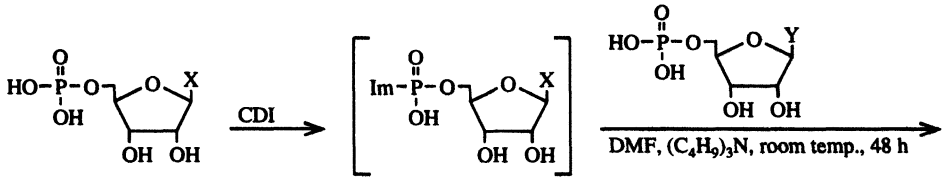
A mixture of adenosine 5′-di (ppA), tri (pppA), and tetra (p4A) phosphates is formed if adenosine 5′-phosphate (pA) is reacted with phosphoryltriimidazole in aqueous solution (*N*-ethylmorpholine buffer, pH 7) in the presence of Mg^{II} ions.[79]

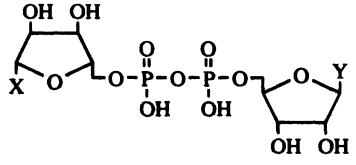
12.5 Analogues of Dinucleoside Di(Tri)phosphates and Oligonucleotides with a Di(Tri)phosphate Bridge

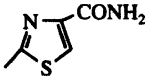
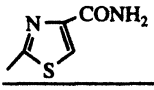
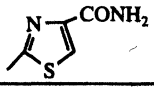
Analogues of Dinucleoside Di(Tri)phosphates

The following diphosphates and triphosphates can be prepared by reaction of nucleotide azolides with nucleotides, sugar phosphates, phosphopeptides, or aminohexyl phosphates.

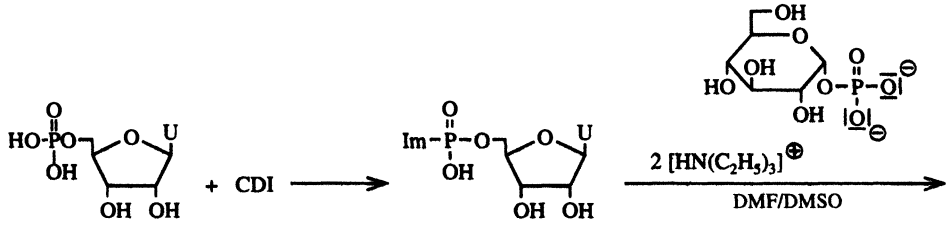
a) NAD-analogues and P^1, P^2-dinucleoside-5′-diphosphates:[80]

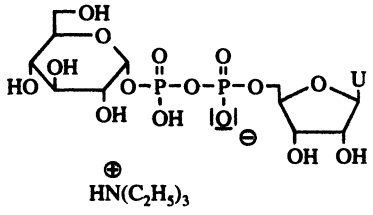




X	Y	Yield(%)	Ref.
A	G	73	[81],[82]
A	A	98	[81]
G	G	62	[81]
	A	61	[80]
		78	[80]

b) Condensation of a nucleotide imidazolide with a sugar phosphate:





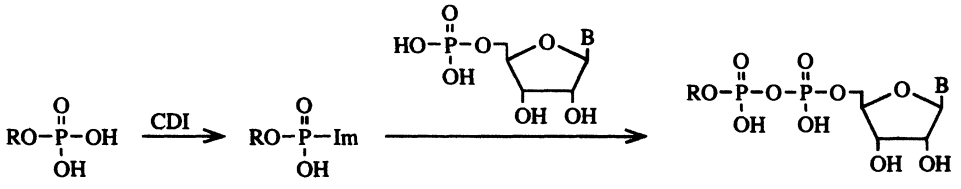
95% [83]; see also [65]

Nucleotides containing the nucleobases T, G, and C are also subject to conversion in an analogous way. In place of CDI, carbonyldibenzimidazole, carbonyldi-1,2,4-triazole, and carbonyldibenzotriazole were utilized in these reactions.

Nucleoside 5′-phosphoric azolides are generally obtained in high yield, although yields from the reactions with carbonyldibenzimidazole and carbonyldibenzotriazole are slightly lower (~ 70%) in comparison with those achieved with carbonyldiimidazole and carbonylditriazole (~ 90%). With phosphoric imidazolides or triazolides the synthesis of diphosphates was accomplished in high yield. Although yields with the phosphoric

benzimidazolide and phosphoric benzotriazolide were slightly lower, they could be increased by adding *N*-methylimidazole to the reaction mixture, probably forming the zwitterionic phosphoric-*N*-methylimidazolide as a highly reactive intermediate.

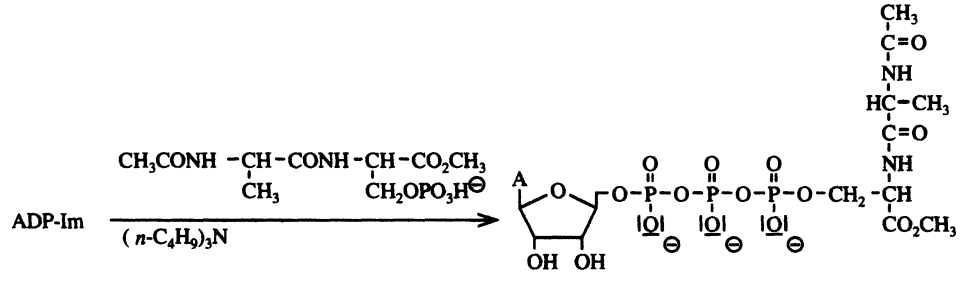
Another route to such nucleoside diphosphates starts from imidazolides of phosphoric acid monoester and nucleoside phosphates:



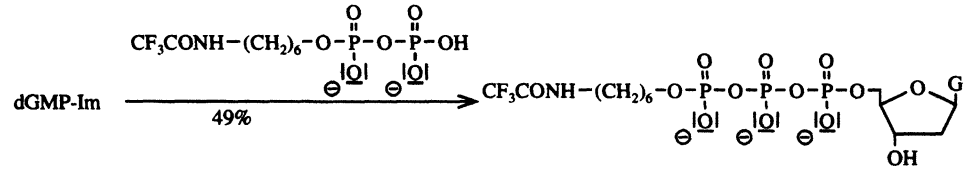
R	B	Ref.
CF_3-C(=O)-NH-$(CH_2)_6$	A	[53]
CF_3-C(=O)-NH-$(CH_2)_6$	U	[54]
DMTr-N(H)-$(CH_2)_2$	G	[84]
Cortison-21-yl	A	[85]

c) Flavin adenine dinucleotide (FAD) was synthesized from flavin mononucleotide (FMN), adenosine monophosphate, and CDI in 92% yield.[5],[86]–[88]

d) The synthesis of a γ-dipeptidyl ester of ATP by coupling of a phosphopeptide to ADP in the presence of CDI has been reported:[89]



e) Synthesis of triphosphate P^3-(6-trifluoroacetylaminohex-1-yl)-dGTP.[90]



Oligonucleotides with Di- and Triphosphate Bridges

Similarly to the foregoing reactions, di(pp) and triphosphate (ppp) bridges could be constructed in oligonucleotides:[91]

$$\text{AMP} + \text{Im(p5'A2')}_3 \longrightarrow \text{A5'pp5'A2'p5'A2'p5'A} \quad 50\%$$

$$\text{ADP} + \text{Im(p5'A2')}_3 \longrightarrow \text{A5'ppp5'A2'p5'A2'p5'A} \quad 27\%$$

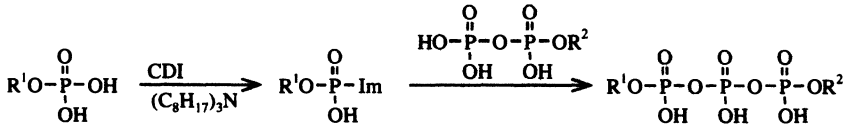
The phosphoric imidazolide was prepared either from the corresponding oligonucleotide and CDI or from the oligonucleotide, imidazole, dipyridyldisulfide, and triphenylphosphine. Both procedures led to yields greater than 90%.[91]

$$\text{GDP} + \text{ImpA} \longrightarrow \text{Gp}_3\text{A} \quad 23\% \ [92]$$

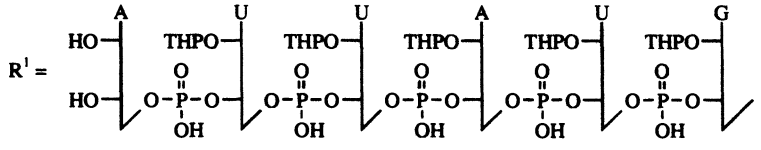
$$\text{GDP} + \text{Im(pA)}_2 \longrightarrow \text{Gp}_3\text{A3'pA} \quad 16\% \ [93]$$

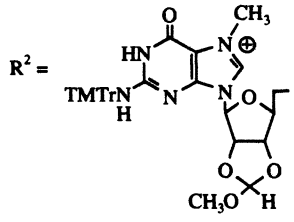
Analogously prepared were dGp_3A, Ip_3A,[92] $Gp_3A2'pA$, and a $Gp_3A3'A$ derivative.[93]

Another triphosphate synthesis is described in reference [94], where a partially protected hexaribonucleotide derivative is converted by CDI into the imidazolide and subsequently condensed with a protected 7-methyl guanosine diphosphate to give the triphosphate.



16% overall yield





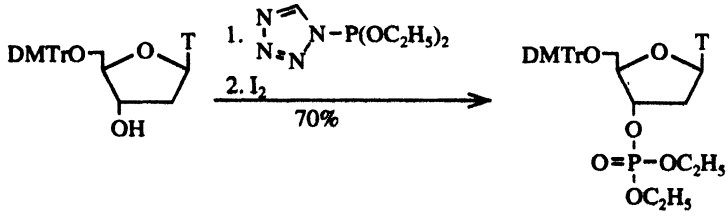
THP = tetrahydropyranyl
TMTr = trimethoxytrityl

The capped leader sequence of the brome mosaic virus mRNA, an oligonucleotide 5′-triphosphate, has been synthesized analogously by reaction of an oligoribonucleotide 5′-phosphoric imidazolide.[95]

12.6 Phosphitylation with Azolides of Phosphorous Acid: Synthesis of Oligonucleotides

Reactions of Phosphorous Acid Mono- and Bisazolides

Reaction of the tetrazolide of phosphorous acid diester with a 5′-protected thymidine and subsequent oxidation with iodine yields the corresponding thymidine phosphortriester:[96]

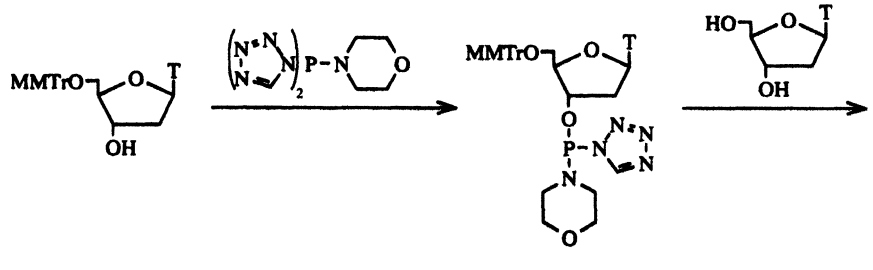


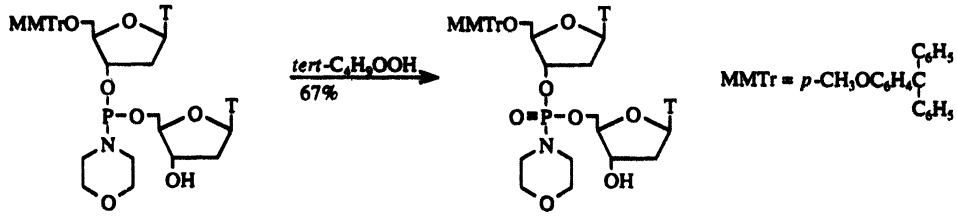
For an analogous synthesis of a phosphortriester see also reference [97].

The phosphitylation agent *N*-tetrazolyldiethoxyphosphine (phosphorous diester tetrazolide) can be made in situ from diethoxydiisopropylaminophosphine and two moles of tetrazole (tetrazole activation of phosphoramidites).[96]

In the phosphite triester approach to the synthesis of nucleotides, morpholinophosphorous ditetrazolide is used as the phosphitylating agent. The procedure generally consists of three steps:

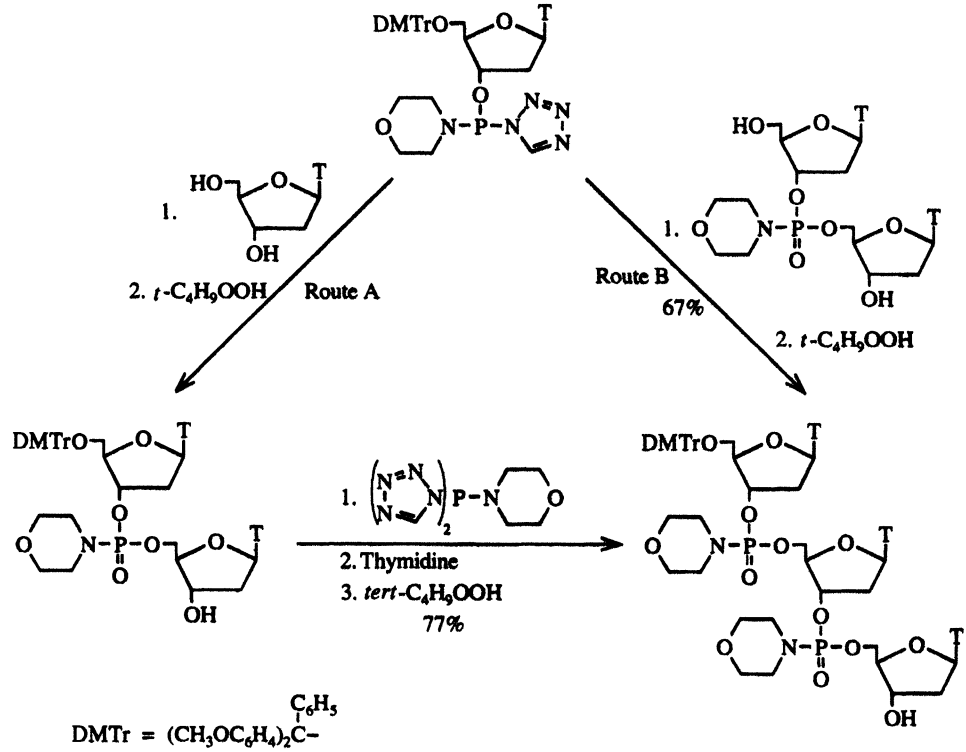
1. Reaction of a 5′-*O*-protected nucleoside with morpholinophosphorous ditetrazolide (phosphitylation),
2. Reaction of the resulting mononucleoside phosphoramidite with a second nucleoside (condensation), and
3. Non-aqueous oxidation with *tert*-BuOOH (oxidation).[98],[99]





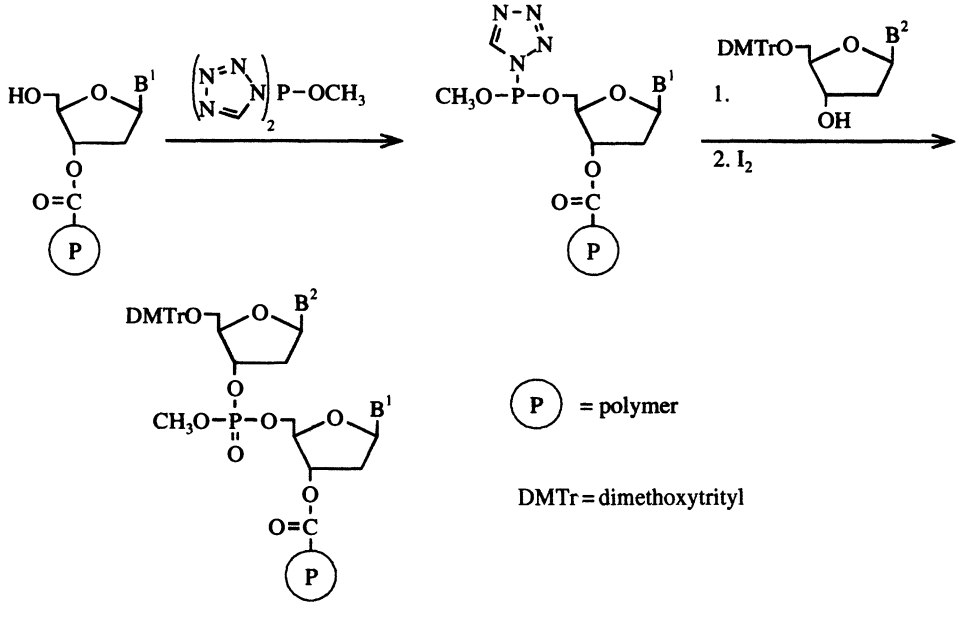
In the approach using bis(tetrazolyl)morpholinophosphine for synthesizing bis-(deoxyribonucleoside) phosphates it is not necessary to protect the 3′-hydroxyl group of the second deoxyribonucleoside (selective attack on the 5′-OH).[98],[100] In this reaction bis(tetrazolyl)morpholinophosphine is superior to other bis(azolyl)morpholinophosphines or azolylchloromorpholinophosphines.[100]

Dinucleotides with A^{Bz}, C^{Bz}, or G^{iB} (N^2-isobutyrylguanosine) as protected nucleobase can also be prepared in good yield according to this method, whereby the bistetrazolide is formed in situ from two moles of tetrazole and one mole of dichloromorpholinophosphine. Consecutive treatment of a dinucleotide prepared in this way with a ditetrazolide, unprotected thymidine, and tertiary butylperoxide, provides a trinucleotide in 77% yield (route A). A second and also convenient route (B) to the trinucleotide involves coupling of the 5′-protected deoxy-ribonucleoside with a dinucleotide derivative containing free 3′- and 5′-OH groups.[100]



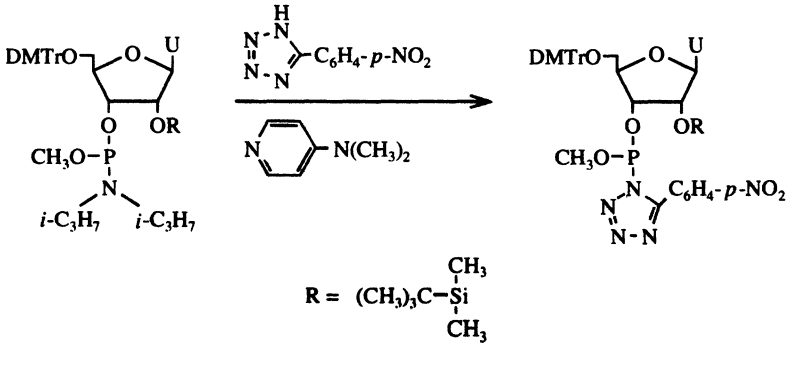
Similar phosphitylation and subsequent conversion to a dinucleotide has been carried out using the methyl- or *m*-chlorophenyl esters of a phosphorous acid bisazolide.[101]–[103]

Tetrazolide-activated nucleotide phosphites have been employed in the synthesis of polynucleotides on a polymer support using methoxybistetrazolylphosphine as phosphitylating agent:[104]

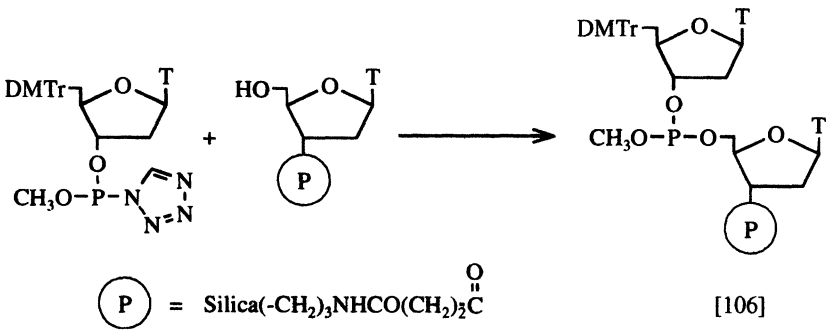


The condensations (B^1, B^2 = protected dA, dC, dG or T) afford yields greater than 98%.

Tetrazolides can also be formed from phosphoramidites (phosphorous amides) by reaction of tetrazoles in the presence of *p*-dimethylaminopyridine:[105]



Such compounds have been used in the solid-phase synthesis of oligoribonucleotides. In the synthesis of $(Up)_8U$, for example, the coupling reaction gave a yield of 96%.[105]

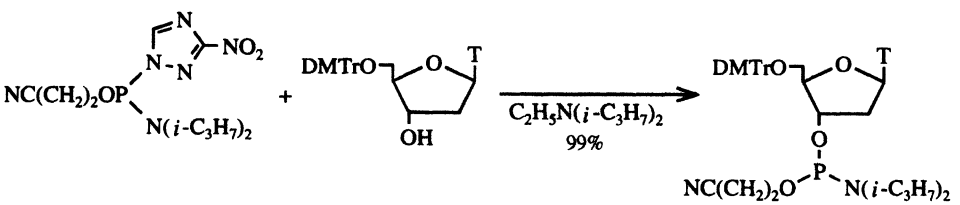


[106]

Unreacted support-bound nucleoside hydroxy groups can be blocked with diethoxytriazolylphosphine. Oxidation of the phosphite triester to phosphate triester was achieved by I_2. Yields in the condensation exceeded 95%. Tetrazolide as phosphitylating reagent is superior to a 4-nitroimidazolide, a triazolide, or even a chloride.[106]

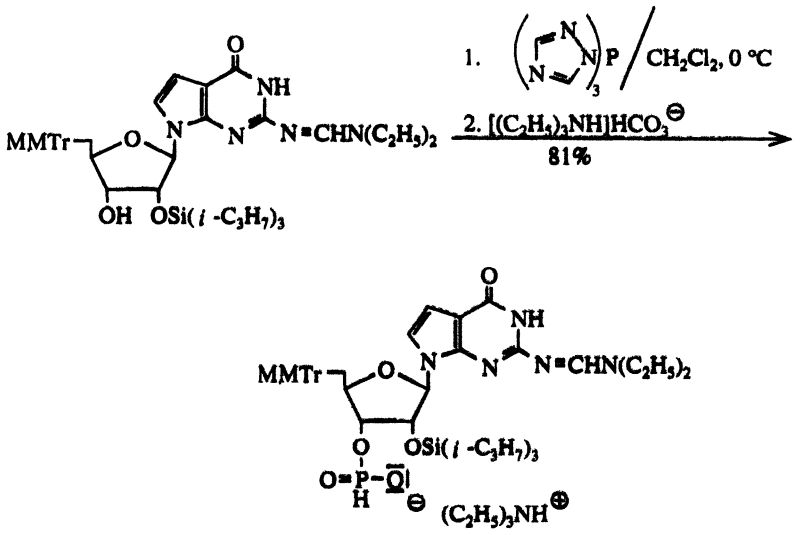
Trifluoromethylphosphonous bistriazolide (trifluoromethylbistriazolylphosphine) has been employed in the synthesis of trifluoromethylphosphonate analogues of nucleotides.[107]

Another effective synthesis of a nucleosidephosphoramidite takes advantage of condensation of the phosphitylating reagent 2′-cyanoethoxy(*N,N*-diisopropyl)amino-3-nitro-1,2,4-triazolylphosphine with 5′-dimethoxytritylthymidine.[108]

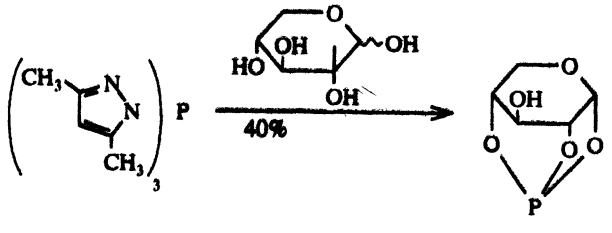


Reactions with Phosphorous Acid Trisazolides (Triazolylphosphines)

a) Phosphorous acid tris(1,2,4-triazolide), generated in situ from PCl_3 and three moles of 1,2,4-triazole, reacts under mild conditions with a 7-deazaguanosine derivative to give, after hydrolysis, a nucleoside phosphonate:[109]



b) Reaction of phosphorous tris(2,5-dimethylpyrazolide) with D-xylopyranose[110] yields a bicyclophosphite, which after protection of the free hydroxy group by acetylation (acetic anhydride) or benzoylation (benzoyl chloride) can be oxidized with ozone to give the triesterphosphate in quantitative yield; alternatively treatment with sulfur or selenium gives the bicyclothionophosphate (60% yield) or selenophosphate (69%), respectively.



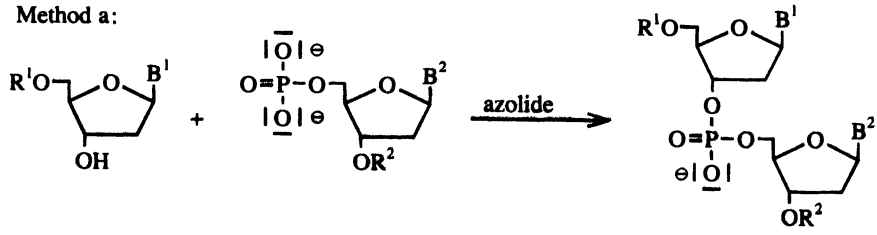
12.7 Oligonucleotides with Arylsulfonic Azolides (Arylsulfonylazoles) as Condensing Agents

3′,5′-Oligodeoxyribonucleotides

Imidazolides, 1,2,4-triazolides, or tetrazolides of arylsulfonic acids have been used as condensing agents in expedient syntheses of oligodeoxynucleotides.

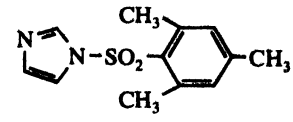
The 3′,5′ internucleotide linkage is formed either by condensing the 3′-hydroxy group of an appropriately protected deoxyribonucleotide or -nucleoside with the 5′-phosphate of a deoxyribonucleotide (method a), or by condensing a 3′-phosphordiester with the 5′-hydroxy group of a nucleoside in a modified phosphortriester approach (method b).

Method a:

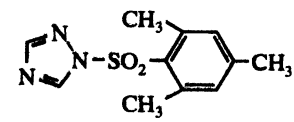


[111,112]

Azolides:



(I) ,



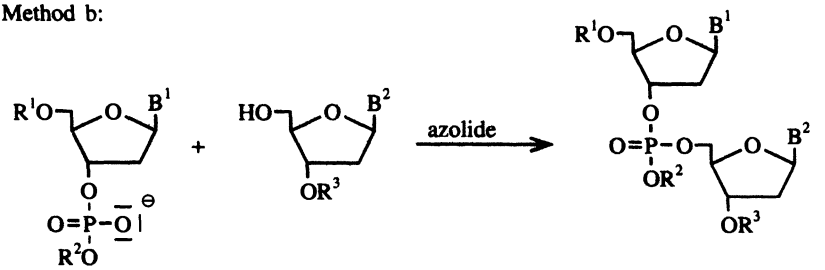
(II)

R^1	B^1	R^2	B^2	Azolide	Oligonucleotide Yield (%)	Ref.
$NC(CH_2)_2O\overset{O}{\overset{\|}{P}}-$ $\underline{O}\ominus$	T	CH_3CO	T	I	82	[111],[112]
$p\text{-}CH_3OC_6H_4\overset{C_6H_5}{\overset{\|}{C}}-$ C_6H_5	T	CH_3CO	T	II	60	[111],[112]
$NC(CH_2)_2O\overset{O}{\overset{\|}{P}}-$ $\underline{O}\ominus$	G^{iB}-T-	$i\text{-}C_3H_7CO$	G^{iB}	I	63	[111],[112]

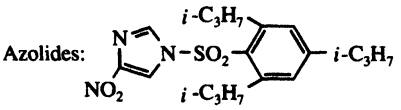
Using method a, oligodeoxyribonucleotides were synthesized from di- to decadeoxyribonucleotides by means of mesitylenesulfonylimidazole and mesitylenesulfonyl-1,2,4-triazole. With triisoproylbenzenesulfonylimidazole the condensation took place more slowly.[112] Compared with the corresponding arylsulfonyl chlorides, imidazolides induced internucleotide condensation much more slowly, but caused no darkening of the reaction mixture, did not affect acid-sensitive bonds in trityl protected nucleotides, and did not sulfonate the 3′-hydroxy groups.[111] The reaction conditions were room temperature, 5–6 days, and pyridine as solvent.[111]

The phosphortriester approach was reported to be still the most versatile method by far for oligodeoxyribo- and oligoribonucleotide synthesis, with a number of really significant advantages over other methods (e.g., phosphoramidite approach) that have been developed for the same purpose. The main advantage lies in large-scale synthesis in solution "when economy of building blocks and coupling efficiency rather than coupling rates are likely to be of paramount importance."[113]

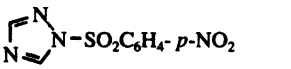
Method b:



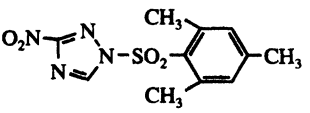
Azolides:



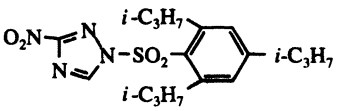
(III)



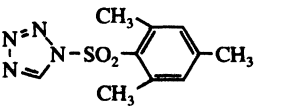
(IV)



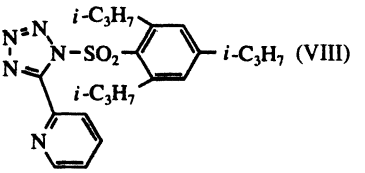
(V)



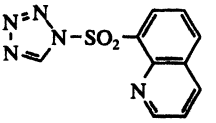
(VI)



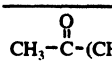
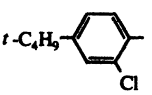
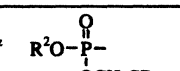
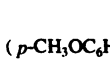
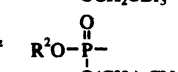
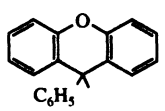
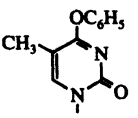
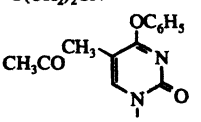
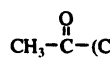
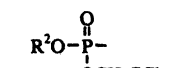
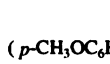
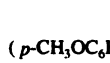
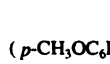
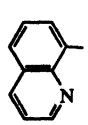
(VII)



(VIII)



(IX)

R^1	R^2	B^1	R^3	B^2	Azolide	Oligonucleotide Yield (%)	Ref.
		A^{Bz}		A^{Bz}	III	80	[114]
	p-C_6H_4	C^{Bz}		T	IV	82	[34] see also [115,116]
					V	91	[113]
	m-ClC_6H_4	T		T	VI	88	[117] see also [118-120]
	p-C_6H_4	T	C_6H_5CO	T	VII	82	[121] see also [122]
	p-C_6H_4	A^{Bz}	C_6H_5CO	A^{Bz}	VIII	quant.	[123] see also [124]
		T	CH_3CO	T	IX	95	[125]

With mesitylenesulfonyl-1,2,4-triazole (II) as condensing agent (room temperature, 24 h, pyridine) fully protected trideoxyribonucleotides such as d-GAG (48%), d-AAT (74%), d-TGT (62%), and d-CGG (50%), as well as such hexadeoxyribonucleotides as d-AATTGT (45%) and d-GAGCGG (38%), were also synthesized.[115] In the triester synthesis of oligodeoxynucleotides with mesitylenesulfonyl-1,2,4-triazole (II), 4-dimethylaminopyridine was found to possess a particularly high catalytic activity.[38] The reaction rate with mesitylenesulfonyl-1,2,4-triazole (II) was slightly slower than in the case of arylsulfonyl chlorides, but the yield was considerably higher. Reaction with *p*-toluenesulfonylimidazole was very slow.[34] Compared to arylsulfonic acid imidazolides, the corresponding triazolides react three times as rapidly.[115]

Among the 1,2,4-triazolides benzenesulfonyl-, *p*-toluenesulfonyl-, mesitylenesulfonyl-, triisopropylsulfonyl-, and *p*-nitrobenzenesulfonyltriazole (IV), the latter is the most reactive one (room temperature, 24 h, pyridine).[115],[34],[126] It was therefore also used for large-scale synthesis of fully protected di-, tri-, and hexadeoxyribonucleotides of defined sequence.[34],[116]

The preparation of oligo(tri- up to heptadeca-)deoxyribonucleotides could also be accomplished using 1-(2,4,6-triisopropylbenzenesulfonyl)-3-nitro-1,2,4-triazole (VI) as activating agent for the high-yield formation of phosphortriester linkages.[117] This 3-nitrotriazolide proved superior to 1-(2,4,6-triisopropylbenzenesulfonyl)-4-nitroimidazole (III), which promoted block condensations between small and large oligonucleotides to a greater extent than triisopropylbenzenesulfonyl chloride, but was shown to be rather ineffective for coupling together large oligonucleotides.

In ref. [127] an investigation was made on the rate of phosphortriester formation and the percentage of sulfonated products in the cases of mesitylenesulfonyl-3-nitro-1,2,4-triazole (V), 2,4,6-triisopropylbenzenesulfonyltetrazole, and 2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (VI) as condensing agents.

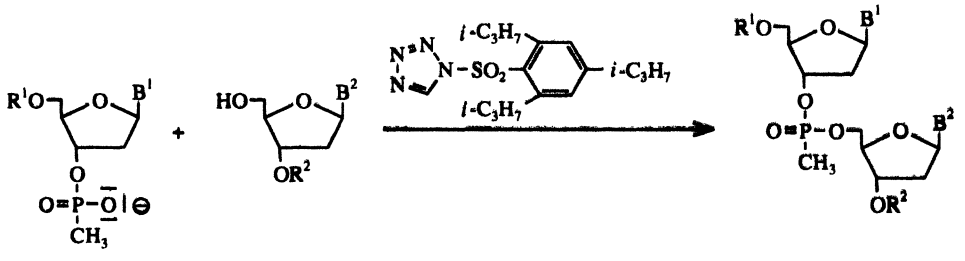
Also benzenesulfonyltetrazole is used as condensing agent in the synthesis of oligodeoxyribonucleotides.[31] It was found that this compound reacts faster than mesitylene- or triisopropylbenzenesulfonyltetrazole. All the tetrazolides reacted faster than the triazolides, or even triisopropylbenzenesulfonyl chloride. However, they do decompose during storage in a desiccator,[121],[128] and therefore must be freshly prepared before use.[117] Coupling reactions to give di- and oligodeoxyribonucleotides in good yield using 1-mesitylenesulfonyltetrazole are described in reference [25]. 2,4,6-Triisopropylbenzenesulfonyltetrazole is a powerful condensing agent for nucleoside aryl phosphates, but not for nucleoside alkyl phosphates, which also undergo sulfonation reactions.[122] Nonetheless, it has been used as a condensing agent in a solid-phase synthesis of tri- and pentadeoxyribonucleotides by the block coupling phosphortriester method.[129]

Other condensations by means of triisopropylbenzenesulfonyltetrazole to give di- and trideoxynucleotides as well as hexa- and pentadecamers are described in references [130] and [131], respectively.

In ref. [123], 1-triisopropylbenzenesulfonyl- or mesitylenesulfonyl-5-(pyridine-2-yl)-tetrazole (VIII) was successfully used as a coupling agent for the synthesis of protected di- and trinucleotides. In comparison with the sulfonic acid tetrazolides these are able to achieve a stereoselective synthesis of dinucleoside monophosphate aryl esters.[31],[124]

Compared to 8-quinolinesulfonyltetrazole (IX) as a coupling agent (yield 95%), 8-quinolinesulfonyl-1,2,4-triazole or 8-quinolinesulfonyl chloride gave only 21% and 15%, respectively, of the corresponding dinucleotides.[125] (See table on page 330).

Dideoxyribonucleoside methylphosphonates were synthesized utilizing triisopropylbenzenesulfonyltetrazole according to method b:[132]



R^1	B^1	R^2	B^2	Yield (%)
MMTr	T	$CH_3-\overset{O}{\overset{\|}{P}}-OCH_2CH_2CN$	T	55
DMTr	A^{Bz}	$CH_3-\overset{O}{\overset{\|}{P}}-OCH_2CH_2CN$	A^{Bz}	46

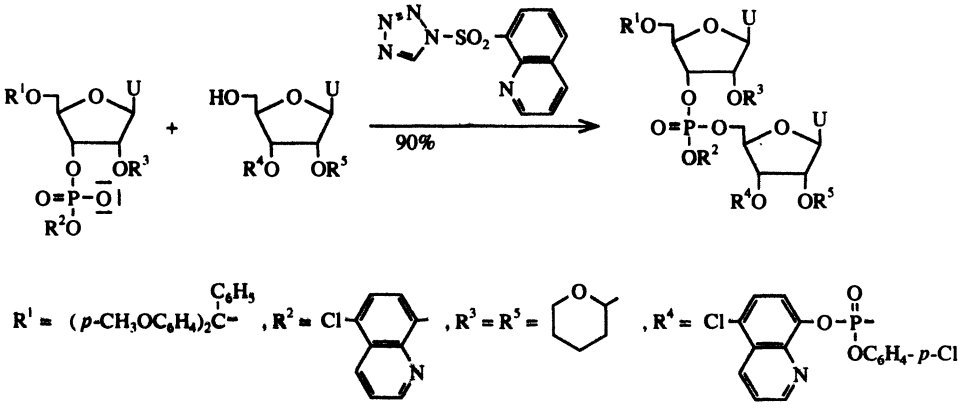
Instead of the isolated arylsulfonic acid azolides, mixtures of arylsulfonic acid chlorides and azoles have also been used for phosphorylation on a nucleoside 5′-OH or as coupling agents in the synthesis of oligodeoxyribonucleotides.[94],[133]–[137]

Short reviews of the synthesis of oligodeoxynucleotides with mesitylenesulfonyl- or triisopropylbenzenesulfonyltetrazoles as coupling agents are provided in references [26] and [27].

3′,5′-Oligoribonucleotides

3′,5′-Oligoribonucleotides have been synthesized analogously to deoxyribonucleotides according to method b by means of 1-arylsulfonyl-4-nitroimidazoles,[138]–[140] 1-arylsulfonyltriazoles,[75],[139],[141] and 1-arylsulfonyl-3-nitrotriazoles,[29],[142] as well as arylsulfonyltetrazoles.[24],[32],[139],[143]–[146]

Example:

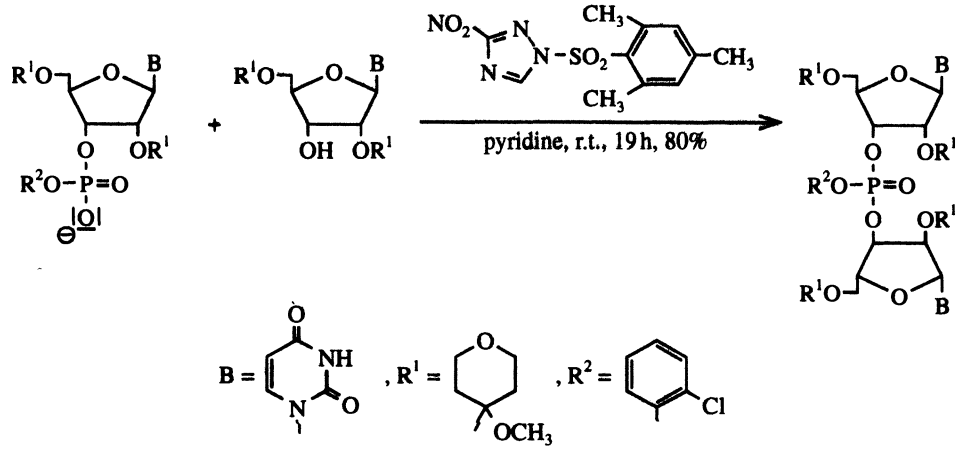


In these cases, arylsulfonyl chloride/azole mixtures were also used as coupling agents.[147],[133]

Diribonucleoside 3′,3′-phosphates and 2′,5′-Oligoribonucleotides

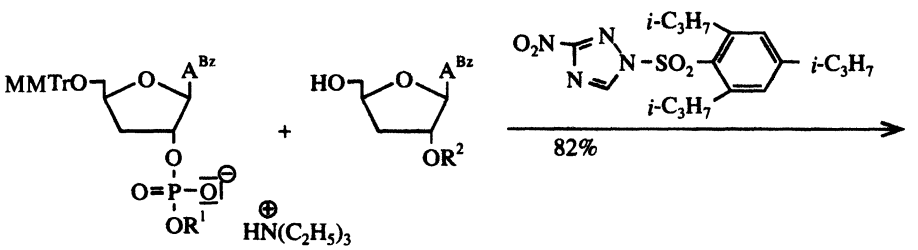
Arylsulfonylazoles such as mesitylenesulfonyl-3-nitrotriazole, triisopropylbenzenesulfonyl-3-nitrotriazole or 8-quinolinesulfonyl-3-nitrotriazole have furthermore been used for the synthesis of a diribonucleoside 3′,3′-phosphate[148] and a 2′,5′-oligoribonucleotide.[75],[36],[142]

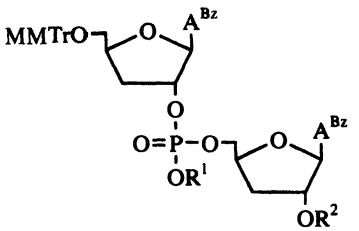
Example for a diribonucleoside 3′,3′-phosphate:[148]



Examples for 2′,5′-oligonucleotides:

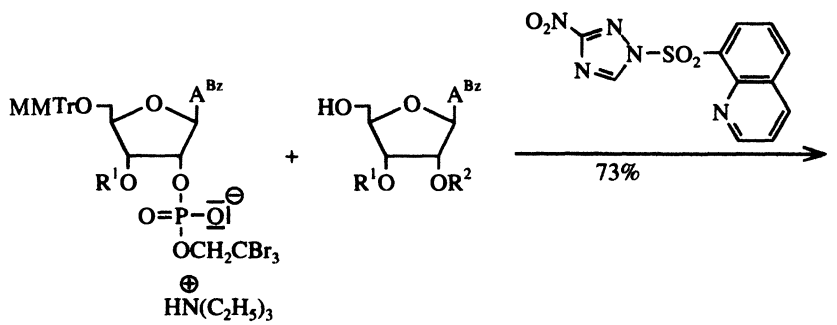
a)

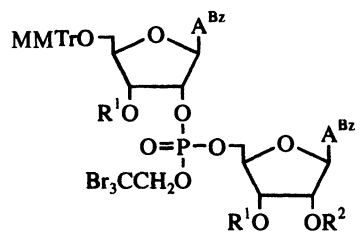




R^1 = *p*-$NO_2C_6H_4CH_2CH_2$-
R^2 = *t*-$C_4H_9(CH_3)_2Si$- [36]

b)





R^1 = C_6H_5CO

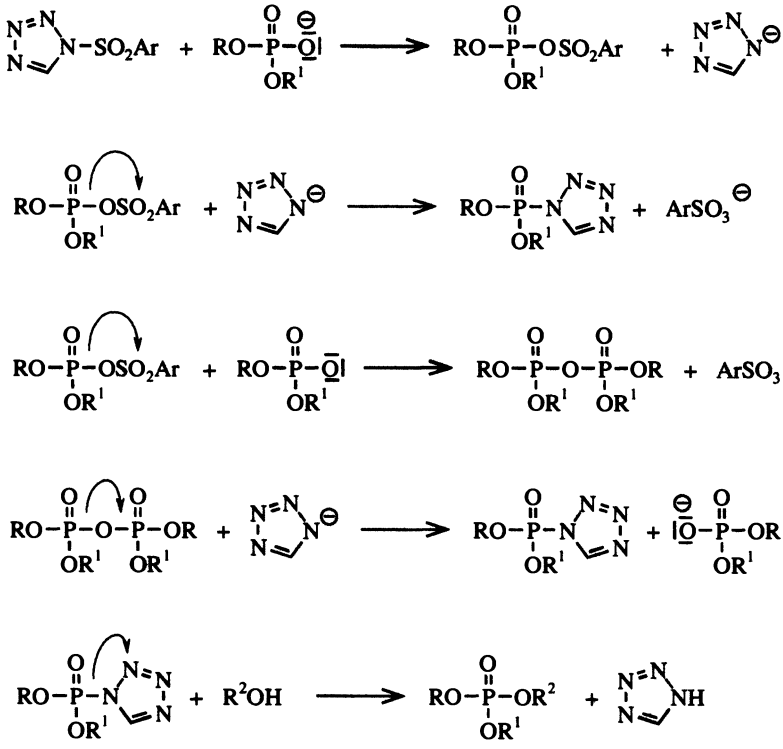
R^2 = $Br_3CCH_2-O-P(O)(NCCH_2CH_2O)-$ [142]

A^{Bz} = *N*-benzoyladenine

MMTr = monomethoxytrityl

Comparing reaction times and yields for the condensing agents 1-triisopropylbenzenesulfonyl-4-nitroimidazole, mesitylenesulfonyl-3-nitro-1,2,4-triazole, 1-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole, and 8-quinolinesulfonyl-3-nitro-1,2,4-triazole, the latter showed the highest yield and shortest reaction time. A fully protected 2′,5′-trinucleotide diphosphate was also successfully synthesized by means of a mixture of 8-quinolinesulfonyl chloride and 3-nitro-1,2,4-triazole.[142]

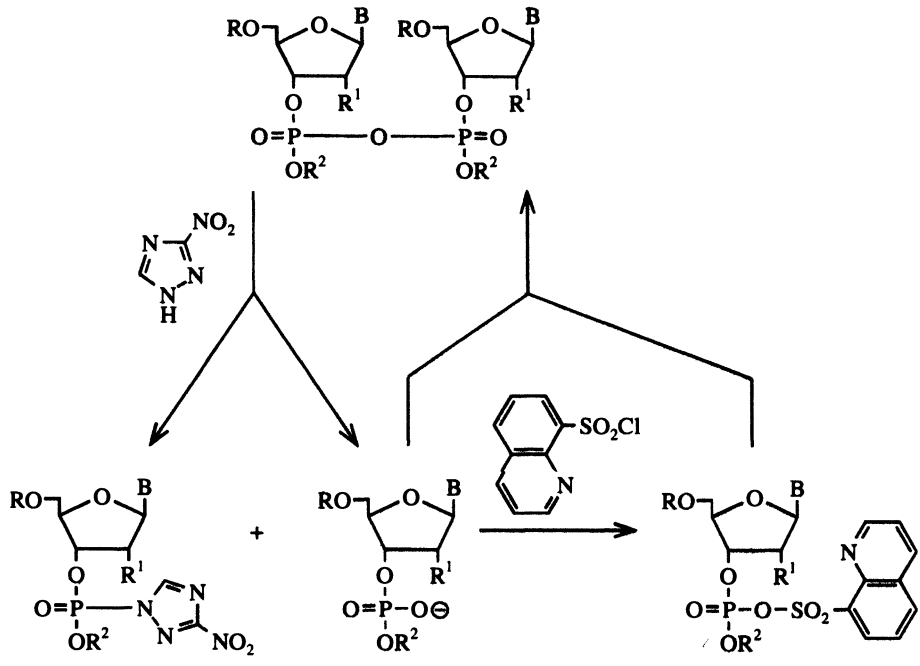
As reaction mechanism for the modified triester approach with sulfonic acid azolides as coupling agents,[149] the following reactions have been suggested[149],[147],[150],[44],[151] in the case of a sulfonyltetrazole:



The condensation reactions are preferentially carried out in pyridine. As reactive species for phosphorylation of the nucleoside R′OH (synthesis of a phosphortriester), the phosphoric acid azolide has been assumed. The mixed phosphoric sulfonic anhydride and a pyrophosphate tetraester have been suggested as intermediates leading to the phosphoric acid azolide.

Ref. [152] discusses the transformation of a dinucleoside pyrophosphate into a reactive azolide with an azole (e.g., 3-nitro-1,2,4-triazole or tetrazole). With quinoline-8-sulfonyl chloride the concomitantly formed phosphordiester can be converted back to the dinucleoside pyrophosphate (see scheme on the next page).

In the reaction of di-(5′-*O*-monomethoxytrityluridine-3′-*p*-nitrophenylethyl)-pyrophosphate with a 5′-OH nucleoside component, simultaneous addition of quinoline-8-sulfochloride and 3-nitro-1,2,4-triazole is recommended to obtain a high yield of the fully protected dimer.[152]



12.8 Oligonucleotides by Polycondensations

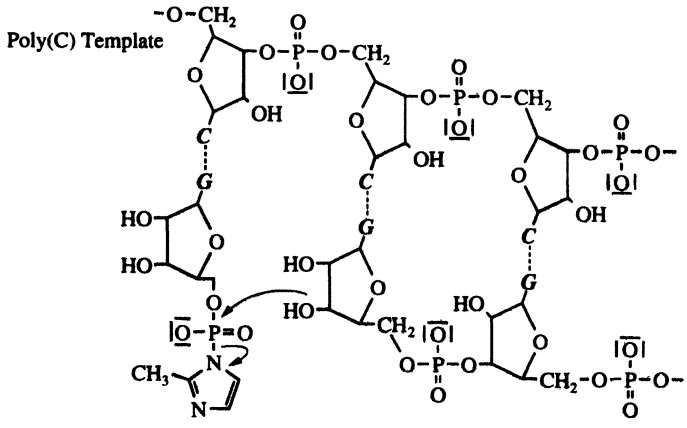
Template-Directed Polycondensations of Nucleotide Azolides

An early review on the template-directed synthesis of oligonucleotides using imidazolides of nucleoside 5′-phosphate is included in reference [153].

Polycytidylate-directed oligomerizations of guanosine 5′-phosphoric imidazolides with various substituents in the imidazole portion are described in reference [154]. It was found that guanosine 5′-phosphoric 2-methylimidazolide in pH 7 buffer at 0 °C for 14 d yielded predominantly 3′,5′-linked oligomers with a mean chain length of 14. At pH-values above 7.6, however, the template-directed oligomerization achieved oligoguanylates $(pG)_n$ up to the 50-mer level in greater than 80% yield[155] (see also ref. [156]). This chemical system represents an efficient non-enzymatic RNA-type semi-replication model.

The poly(C)-directed oligoguanylate synthesis from guanosine 5′-phosphoric 2-methylimidazolide has been studied kinetically.[157] An intermediate elongation process on polycytidylate acting as template is illustrated schematically below.

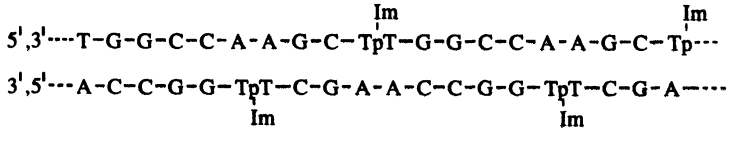
The reaction of adenosine 5′-phosphoric imidazolide with adenosine analogues on a polyuridylic acid template is discussed in reference [158]. Another polymerization of oligoadenylates $(pA)_4$ and $(pA)_6$ on a polyuridylic acid template in an aqueous system



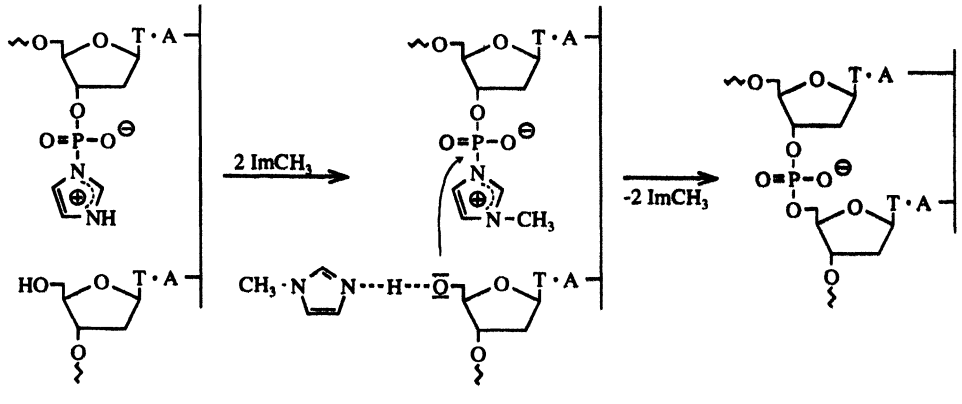
was accomplished with *N,N'*-carbiminodiimidazole or *N*-cyanoimidazole in the presence of transition metals.[159]

Oligomerization of 2-MeImpG and 2-MeImpA by means of poly(C,U) random copolymer templates produced a variety of oligo(G,A)s.[160]

An efficient template-guided polycondensation of a decadeoxynucleotide into long-chain double-stranded polydeoxynucleotides was achieved with the thymidine 3'-phosphoric imidazolides:[161]



The production of oligomers with 3',5'-linkages to an extent exceeding 80% proceeded only in buffers containing *N*-methylimidazole for improved activation of the 3'-phosphate. The formation of a stable duplex was suggested:[161]



Additional template-guided polycondensations of nucleotide azolides are described in references [161]–[165].

Metal Ion- and Montmorillonite-Catalyzed Polycondensation of Nucleotide Azolides

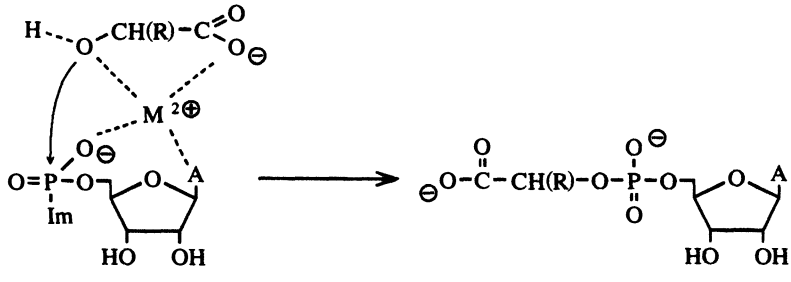
A review on the polycondensation of nucleotide imidazolides by means of metal ions or templates to provide oligonucleotides is available in reference [166].

Imidazolides of adenylic acid (ImpA) or uridylic acid (ImpU) are polycondensed to oligonucleotides by means of Zn^{2+} ions.[167] The resulting phosphordiester bond was found to be of the 2′,5′ type. In the reaction of nucleoside 5′-phosphoric acid methyl ester with ImpA in the presence of $MgCl_2$, 2′,5′-dinucleotides are formed six to nine times more frequently than the corresponding 3′,5′ compounds.[6] Polycondensations of ImpA in aqueous solution in the presence of various divalent metal ions lead to short oligoadenylic acids $(pA)_n$ ($n = 1$–5) mainly with 2′,5′-internucleotide linkages. With Pb^{2+}, for example, the total yield of oligomers was as high as 57%.[168],[169]

Azole-activated nucleotides are also polycondensed in aqueous medium with uranyl ion as catalyst. Azoles employed as activating groups for adenylic acid include imidazole, 2-methylimidazole, 4-methylimidazole, triazole, nitrotriazole, tetrazole, and 2-methylbenzimidazole. For instance, adenylic acid 2-methylbenzimidazolide is polycondensed in 4 h at 50 °C by this method, giving 2′,5′-linked oligoadenylates from dimers to heptamers in greater than 55% total yield.[170] In the polycondensation of adenylic acid imidazolide, up to 95% of the introduced imidazolide is converted primarily to 2′,5′-linked oligoadenylates from dimers to hexadecamers.[171]

Condensation of the 5′-phosphoric imidazolide of adenosine (ImpA) with itself and *P′,P′*-diadenosine 5′,5′-phyrophosphate (AppA) in water in the presence of Na^+-montmorillonite clay leads mainly to 3′,5′-linked oligomers. These results are discussed in the context of the potential importance of mineral catalysts to the formation of RNA on the primitive earth.[172]–[174]

Condensations of adenosine 5′-phosphoric imidazolide with glycolic or lactic acid in aqueous solution with divalent metal ions as catalysts to give glycolyl adenylate or lactyl adenylate are described in reference [175].

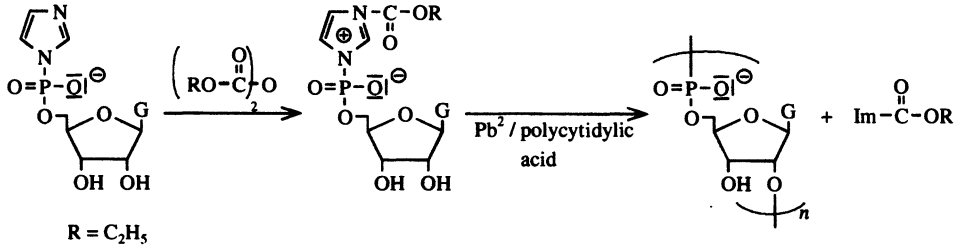


$M^{2\oplus} = Pb^{2\oplus}$, R = H, 75%; CH_3, 37%

With 3-hydroxypropionic or 4-hydroxybutyric acid very little or no phosphor diester bond formation occurred.[175]

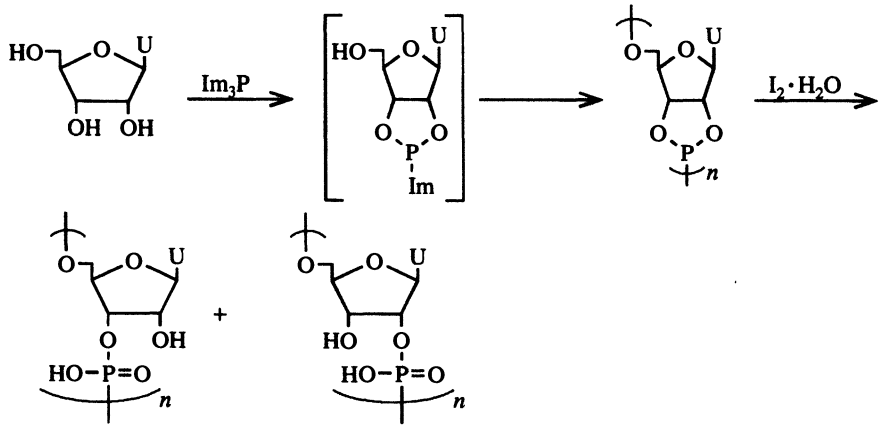
Acceleration of the Template- and Metal-Directed Polycondensation of Nucleoside-5′-phosphoric Imidazolides by Acylation

The reactions in question were complete within about one hour, whereas in the absence of an acylating agent such a reaction takes several hours. Long 2′,5′-linked oligomers are formed in the case of $R = C_2H_5$.[175],[155]



Polycondensation of Azolides from Ribonucleosides and Tri(azolyl)phosphine, Followed by Oxidation

In the reaction of unprotected uridine with tri(imidazolyl-1)phosphine (ratio 1 : 1.5) under mild conditions (THF, − 78° to 0 °C, 10 min) and subsequent oxidation with iodide, two types of polymers [$(Up)_n$ ($n = 2$–6) and $(Up)_nU$ ($n = 2$–5)] are formed. Additives such as metal cations or polynucleotides (poly U and poly A) acting as templates in the oxidation process showed a significant effect on the ratio of the 3′,5′-linked to 2′,5′-linked oligomers.[176],[177]



The internucleotide phosphordiester bonds are composed of both 3′,5′- and 2′,5′-linkages. It was noted that tri(imidazolyl-1)phosphine does not attack the 5′-OH of unprotected uridine.

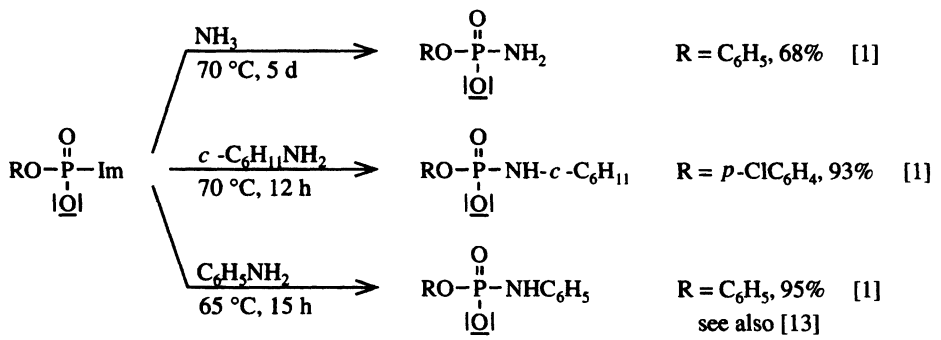
In ref. [178] other tri(azolyl)phosphines are used for the synthesis of uridine-, adenosine-, and cytidine-oligoribonucleotides according to this method, with azolyl groups

such as 2-methylimidazolyl, 2-ethyl-4-methyl-imidazolyl, benzotriazolyl, benzimidazolyl, pyrazolyl, 1,2,4-triazolyl, and tetrazolyl. Among the tri(azolyl)phosphines, those containing imidazole, 2-methylimidazole, and 2-ethyl-4-methylimidazole were found to be most effective.

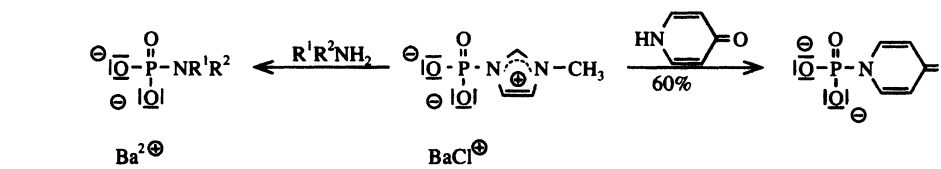
12.9 Phosphoric Acid Amides

Via Phosphoric Acid Imidazolides

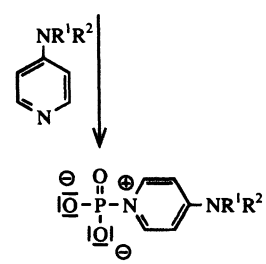
a) The nucleophilic reaction of amines with ionic phosphoric imidazolides requires a relatively long reaction time (several hours or days) to achieve moderate to good yields. It is usually carried out in aqueous phase:



b) Among the reactions described involving the barium salt of phosphoric acid *N*-methylimidazolide, (with ammonia, primary and secondary amines), those with amino-alcohols, 4-aminopyridines and 4-pyridone are illustrated below:[179],[180]



R^1R^2NH	Yield (%)
$HOCH_2CH_2NH_2$	95
$HOCH_2-C(NH_2)(CH_3)-CH_2OH$	45
$HOCH_2-CH(OH)-CH_2NH_2$	47

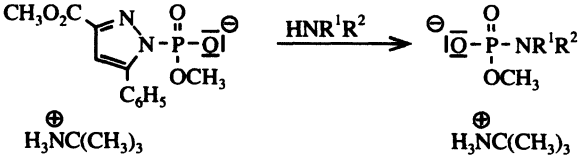


R^1	R^2	Yield (%)
H	H	60
CH_3	CH_3	40
H	*i*-C_3H_7	90

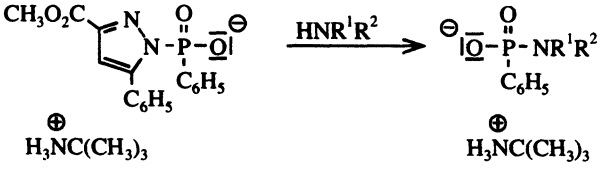
Via Phosphoric Acid Pyrazolides

A series of amides, hydrazides, and azides of phosphoric, phosphonic, and phosphinic acids were synthesized via the corresponding pyrazolides.

a) By transfer of an anionic phosphate or phosphonate group onto a primary or secondary amine:[16]

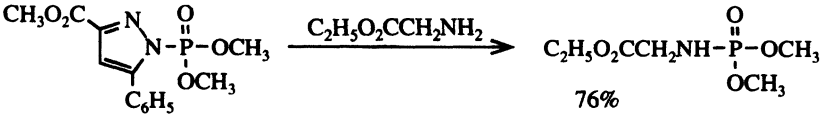


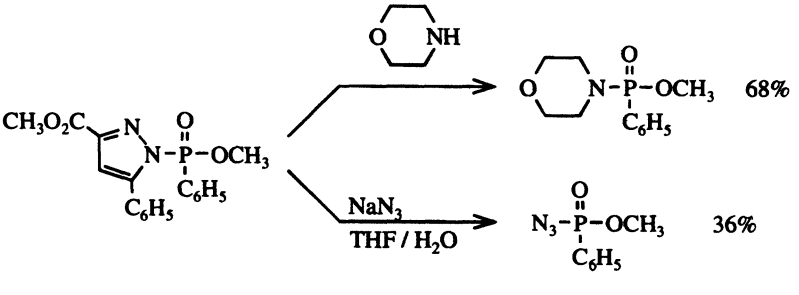
R^1	R^2	Yield (%)
H	i-C_3H_7	83
CH_3	CH_3	65

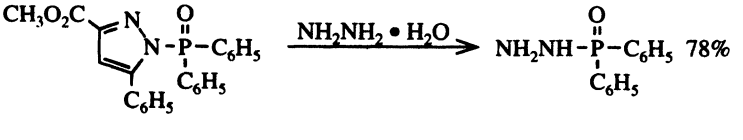


R^1	R^2	Yield (%)
H	i-C_3H_7	40
CH_3	CH_3	27

b) By transfer of a neutral phosphate, phosphonate, or phosphinate group onto an amine, azide or hydrazine.[181],[15]



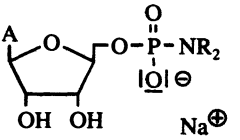




Amides of Nucleotides

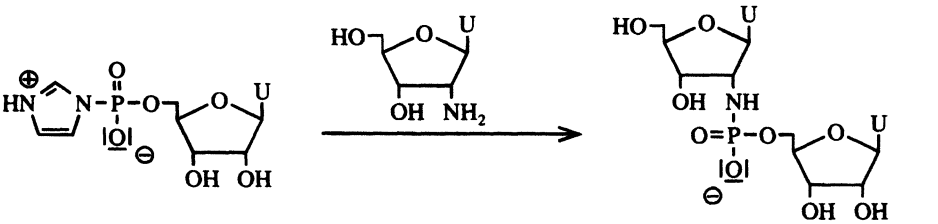
Nucleotide imidazolides react with amino components to produce the corresponding nucleotide amides:

a) AMP-Im (sodium salt) $\xrightarrow{HNR_2}$



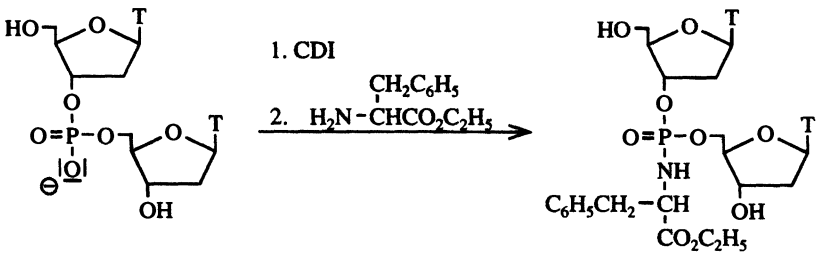
R = H, 86% [182]
R = *c*-C_6H_{11}, 95% [1]; see also [5]

b)



76% [183]; see also [184]

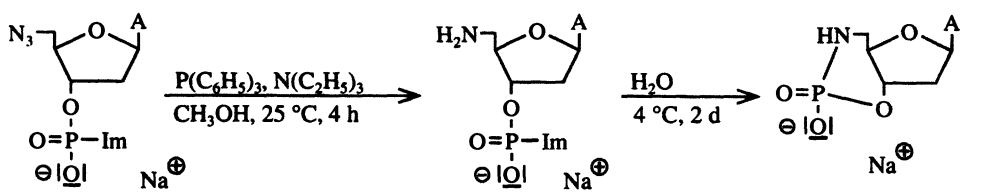
c)



80% [185]

In the last reaction CDI was found to be superior to both $(C_6H_5O)_2P(O)Cl$ (50% yield) and triisopropylbenzenesulfonyl chloride (33% yield).

d) A cyclic nucleotide amide was synthesized via a 3′-phosphoric imidazolide and a 5′-amino group of the adenosine moiety.[186] The amino group in this case was formed from an azide by a Mukaiyama redox condensation reaction:

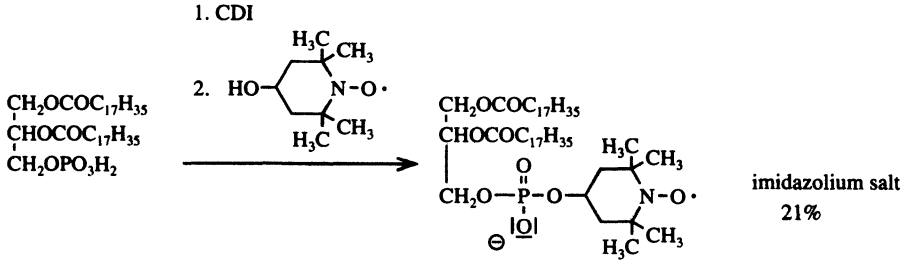


94% 89%

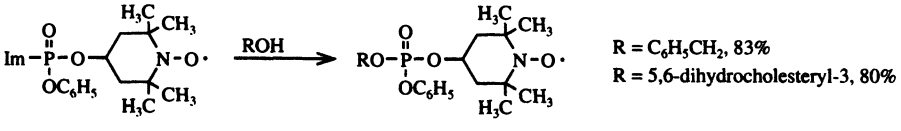
12.10 Spin-labeled Esters and Amides of Phosphoric Acid

Syntheses with Phosphoric Monoimidazolides

In this procedure a diacylglyceryl phosphate is first converted with CDI into a reactive phosphoric imidazolide, which is then treated with a labeled alcohol to give a labeled phosphoric acid diester:[2]

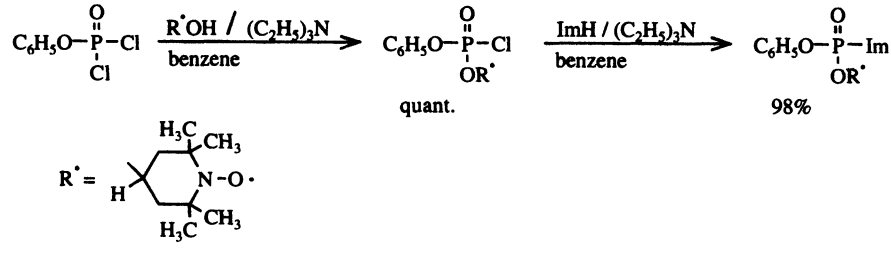


A labeled phosphoric acid triester is formed by phosphorylation of an alcohol with a labeled phosphoric diester imidazolide:[187],[188]

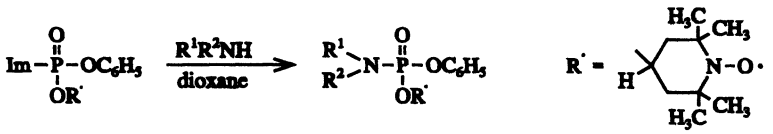


The reaction is carried out under mild neutral conditions (dioxane, room temperature, 20 h) without the need for a base such as triethylamine, as would be required if the chloridate were used instead of the imidazolide. Furthermore, yields of phosphates are higher by using the phosphoric imidazolide.[187]

The labeled imidazolide itself is prepared by a stepwise reaction of phenyl phosphordichloridate (phosphoric phenylester dichloride):[188]

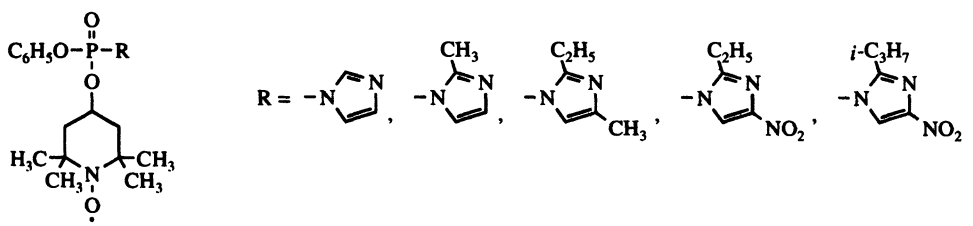


Spin-labeled phosphoramidates are synthesized analogously by the reaction of phosphoric imidazolides with primary or secondary amines[189] or amino acid esters.[188]



R^1	R^2	Yield (%)	Ref.
iso-C_3H_7	H	75	[189]
n-C_4H_9	*n*-C_4H_9	51	[189]
$-CH_2CH_2OCH_2CH_2-$		85	[189]
$CH(CH_3)CO_2CH_3$	H	72	[188]
$CH_2CO_2C_2H_5$	H	89	[188]

The inductive effect of the imidazole substituents on the transphosphorylation of alcohols and amines with the following spin-labeled phosphoric imidazolides is discussed in reference [190].

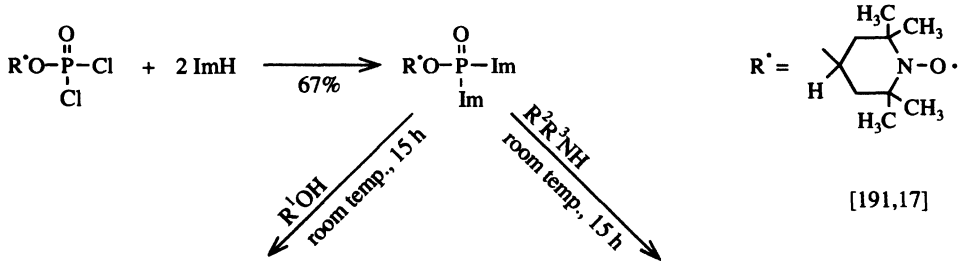


The methylimidazolide reacts more slowly with an alcohol (cf. *c*-$C_6H_{11}OH$) but not with respect to an amine (cf. *c*-$C_6H_{11}NH_2$) in comparison with the unsubstituted imidazolide. Introduction of an additional alkyl group into the imidazole ring further retards the transphosphorylation. Thus, the 2-ethyl-4-methylimidazolide did not react with cyclohexanol within 70 h at room temperature, while with cyclohexylamine an amide was produced, albeit with a reduction in yield.[190] Hence, a certain degree of selectivity towards amines was achieved with the 2-ethyl-4-methylimidazolide. Selectivity toward amines and alcohols was also observed with the 2-ethyl- or isopropyl-4-nitroimidazolide.

The effect upon the transphosphorylation reaction with alcohols and amines of electron-releasing (CH_3) and electron-withdrawing (Cl, NO_2) groups in the benzene ring of phosphoric imidazolides has been studied as well.[191]

Syntheses with Phosphoric Bisazolides

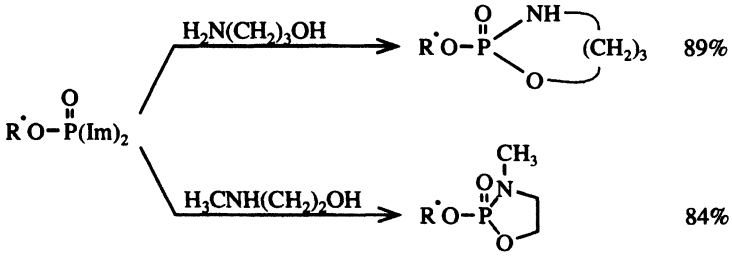
Labeled phosphoric acid triesters and diamides have been synthesized from phosphoric diimidazolide.[192],[193] This method was found to be superior to that involving the dichloridate (phosphoric dichlorides).



R^1	Yield (%)
n-C_4H_9	53
i-C_4H_9	69
C_6H_5	82
$C_6H_5CH_2$	85

R^2	R^3	Yield (%)
H	n-C_4H_9	60
H	s-C_4H_9	83
H	$C_6H_5CH_2$	79
$-CH_2CH_2OCH_2CH_2-$		89

Cyclic phosphoramidates (phosphoric amides) were obtained by the reaction of amino alcohols with a phosphoric diimidazolide.[193],[2]



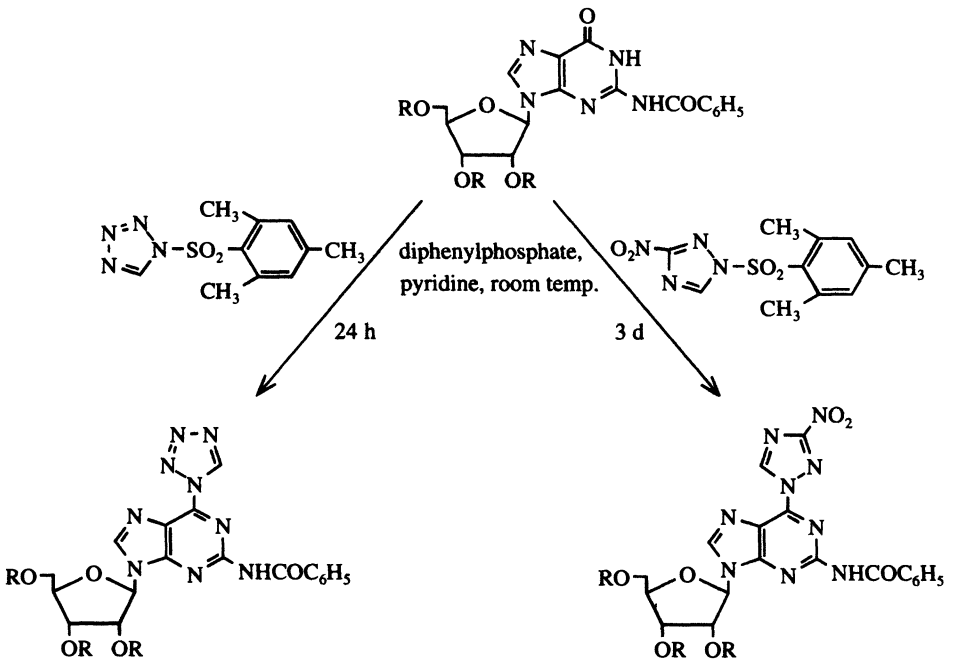
If one methyl group was introduced at C-2 in the imidazole moiety of the phosphoric diimidazolide the reaction rate of transphosphorylation was retarded.[2] Introduction of a further alkyl group at C-4 in the imidazole unit diminished the reactivity of the diimidazolide to such an extent that the second imidazole moiety could not be replaced.[193]

12.11 Modification of Nucleobases

Modification of Nucleobases with Arylsulfonylazoles

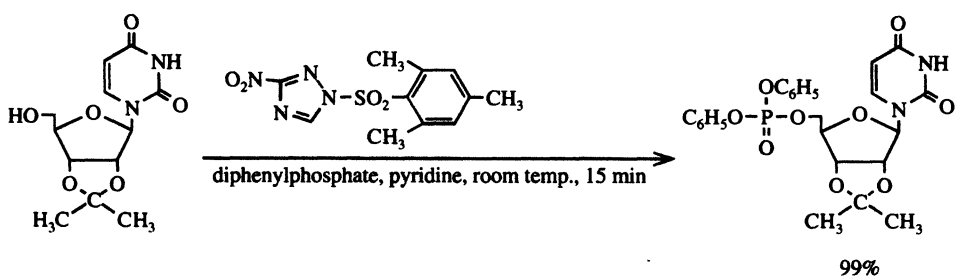
These reactions are interesting because the modified nucleobases are formed as by-products during the synthesis of oligonucleotides according to the phosphotriester

approach if excess arenesulfonyltriazoles or -tetrazoles are used as condensing agents over the course of a longer reaction time.[194],[195] An example with 2-*N*-acyl-2′,3′,5′-tri-*O*-acyl guanosine is given.



An analogous reaction with 2′,3′,5′-triacetyluridine and mesitylenesulfonyl-3-nitrotriazole or triisopropylbenzenesulfonyl-3-nitrotriazole proceeds with the same high yield. Treatment of the nitrotriazolyl nucleoside with ammonia leads to 2′,3′,5′-triacetylcytidine.[194]

If the 5′-OH of uridine is unprotected, however, a 5′-phosphate is obtained:

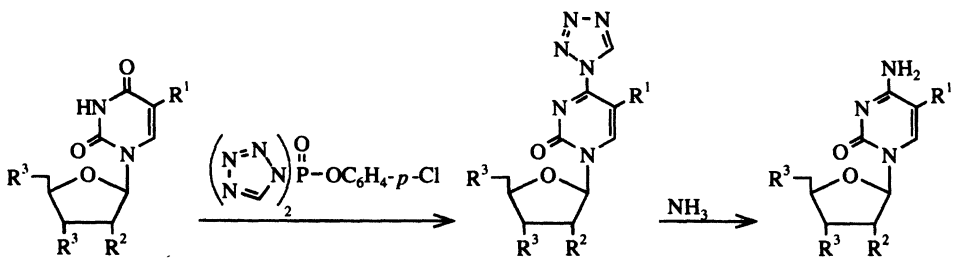


This shows that the combination of diphenylphosphate and arylsulfonyl-3-nitrotriazole is a powerful phosphorylating agent in pyridine solution.

Modification of Nucleobases with Phosphoric Azolides

Phosphoric bis- or trisazolides can also be used for the modification of nucleobases. As mentioned before with ammonia the azolyl group is easily exchanged against the amino group.

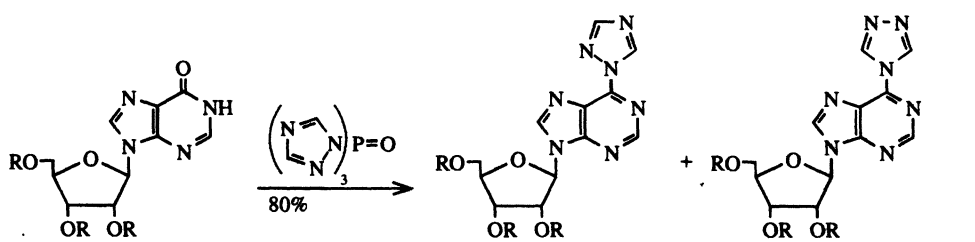
a) Reaction with phenoxyphosphoryldditetrazole[33]



R^1	R^2	R^3		
F	OAc	OAc	85 %	70 %
H	F	$C_6H_5-\overset{\overset{O}{\|}}{C}-O$	73 %	56 %

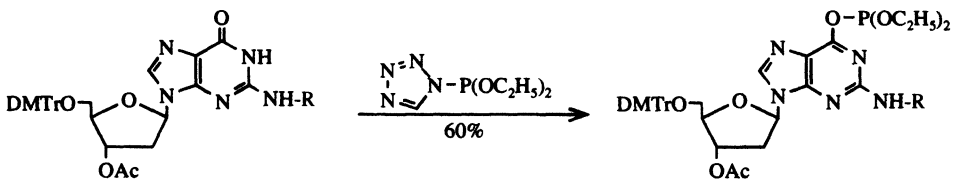
The amination of thymidine derivatives can also be carried out as a one-pot reaction, in which the ditetrazolide is prepared in situ from the corresponding dichloride and tetrazole.[196] Similar reactions are described in references [197], [198] and [33a].

b) Reaction with phophoryltristriazole



R = $(CH_3)_2CHCH_2CO$ 6 : 1 [199]

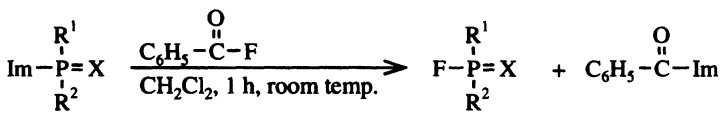
A phosphitylation instead of an azole transfer occurred in the reaction of a guanosine derivative with phosphorous diester tetrazolide (diethoxytetrazolylphosphine):[200],[201]



R=$(CH_3)_2CHCH_2CO$

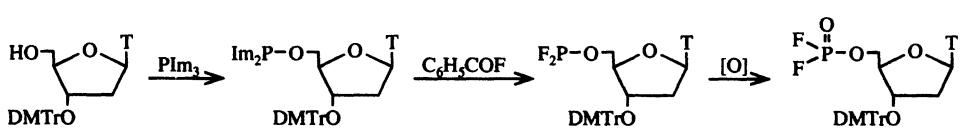
Fluorophosphates from Phosphoric Azolides

Fluorophosphates (phosphorfluoridates), which are important for backbone modified oligonucleotides in molecular biology, are generally synthesized from phosphoric imidazolides or triazolides and acylfluorides. In these reactions, for example, the azole group (of the phosphoric or phosphinic imidazolide) is substituted by a fluorine atom, forming an acylazole compound as by-product.[202],[203]



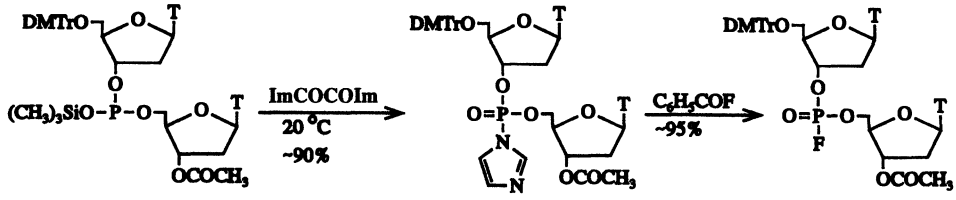
R^1	R^2	X	Yield (%)
C_2H_5O	C_2H_5O	O	98
tert-C_4H_9	C_6H_5	O	98
C_2H_5O	C_2H_5O	S	95

A difluorophosphate can be obtained from a phosphorous diimidazolide as demonstrated by the synthesis of a thymidine 5′-difluorophosphate. The diimidazolide was constructed from 3′-dimethoxytritylthymidine and triimidazolylphosphine.[202],[203]



The reaction can also be accomplished with phosphoryltriimidazol $Im_3P=O$.[202],[203]

Recently a very mild method was discovered for the synthesis of dinucleoside fluorophosphates in the conversion of a dinucleoside phosphite with *N,N′*-oxalyldiimidazole into the corresponding phosphoric imidazolide, which is then treated with acyl fluoride:[204], [202]



By this method, fluorine can be incorporated through a mild procedure into the internucleotide bond of oligonucleotides.

12.12 Mixed Anhydrides of Phosphoric, Phosphonic, and Phosphinic Acids with Sulfonic Acids

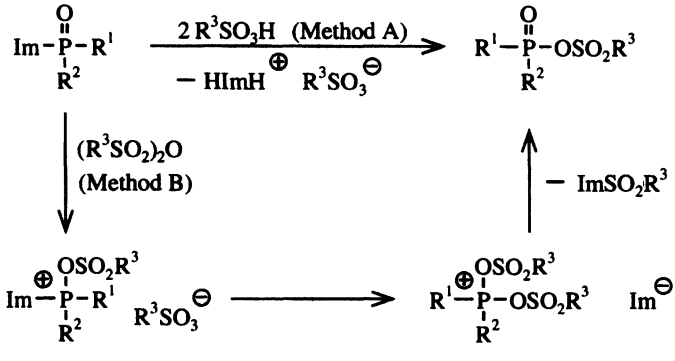
Mixed Anhydrides via Phosphoric Imidazolides

Mixed anhydrides between phosphoric, phosphonic, and phosphinic acids on one side and sulfonic or carboxylic acids on the other are conveniently prepared via phosphorazolides.[150]

There are two methods for the synthesis of mixed anhydrides. In method A the acids, and in method B the corresponding anhydrides, are introduced for reaction with phosphorimidazolides. Both methods afford the anhydrides nearly quantitatively.

The required phosphorimidazolides are prepared from acid chlorides and imidazole or *N*-trimethylsilylimidazole.

Mixed anhydrides prepared according to these methods include:



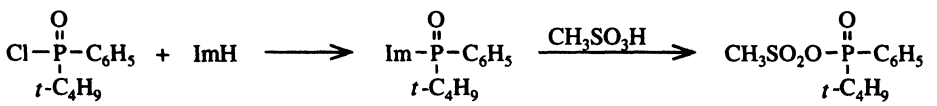
Method A

R^1	R^2	R^3	Yield (%)	Ref.
t-C_4H_9	C_6H_5	CH_3	92	[205]
C_2H_5O	C_2H_5O	CH_3	quant.	[205]
t-C_4H_9	C_6H_5	CF_3	quant.	[150]
t-C_4H_9	OCH_3	CF_3	quant.	[150]
OC_2H_5	OC_2H_5	CF_3	quant.	[150]

Method B

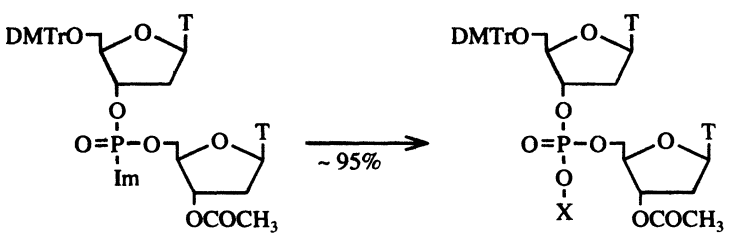
R^1	R^2	R^3	Yield (%)	Ref.
t-C_4H_9	C_6H_5	CH_3	58	[205]
i-C_3H_7O	i-C_3H_7O	CH_3	quant.	[205]
C_2H_5O	C_2H_5O	CH_3	quant.	[205]
C_2H_5O	C_2H_5O	p-$CH_3C_6H_4$	quant.	[150]

Method A permitted the synthesis of an optically active phosphinic-sulfonic anhydride via the optically active imidazolide:[205]



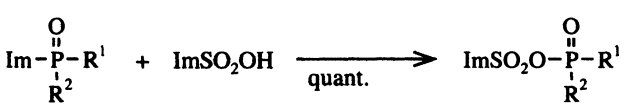
$[\alpha]_D^{20} = +27.4°$ (benzene) $[\alpha]_D^{20} = -1.5°$ (benzene) $[\alpha]_D^{20} = +2.6°$ ($CHCl_3$)

Utilizing method B, mixed anhydrides of a dinucleoside phosphate and methylsulfonic or trifluoroacetic acid could be prepared:[204]



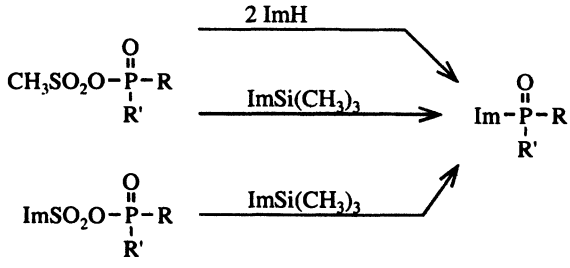
X = CH_3SO_2 or CF_3CO

1-Imidazolesulfonic acid reacts with phosphinic and phosphoric imidazolides to give mixed anhydrides of the following type:[150]



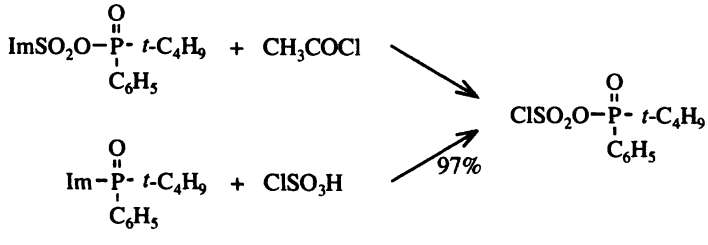
R^1 = *tert*-C_4H_9, $R^2 = C_6H_5$; $R^1 = R^2 = C_2H_5O$

Mixed anhydrides can be converted back to imidazolides in yields exceeding 90% by treatment either with two moles of imidazole or one mole of *N*-trimethylsilylimidazole:[150]



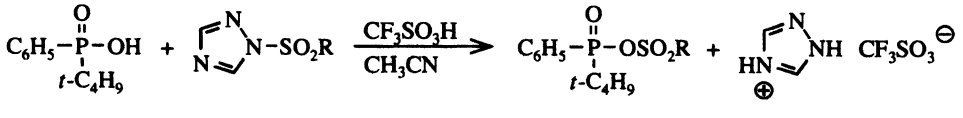
Phosphoric-sulfonic anhydrides are of special interest because they are presumed to be intermediates in oligonucleotide coupling reactions involving phosphordiester activation by arenesulfonyl derivatives (see Section 12.7).

The mixed anhydride of a phosphinic acid and chlorosulfonic acid has been formed in two ways:[44]



Mixed Anhydrides via Triazolides of Sulfonic Acids

A further method for the synthesis of a mixed anhydride between a phosphinic acid and a sulfonic acid employs a sulfonic triazolide:



R = *p*-$CH_3C_6H_4$, 68%; CH_3, 58%

However, this method is not suitable for the preparation of phosphonic- or phosphoric-sulfonic anhydrides.[150]

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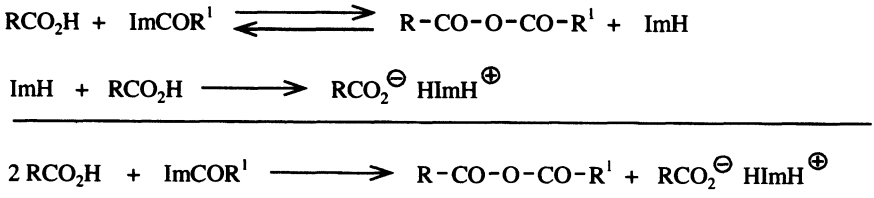
13 Syntheses of Acid Anhydrides and Acyl Chlorides

13.1 Acid Anhydrides

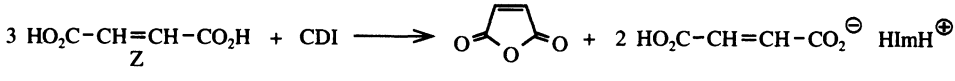
Three methods are known for the synthesis of acid anhydrides from carboxylic acids by means of azolides:

1. Reaction of imidazolide with carboxylic acid in a 1 : 2 ratio at room temperature leads to carboxylic acid antydride and imidazolium carboxylate.



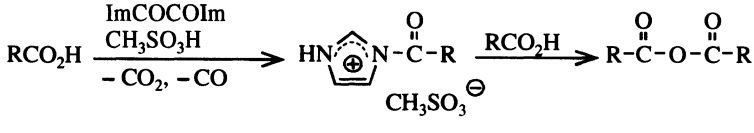
The equilibrium in this first step favors the shift to anhydride formation if the second mole of carboxylic acid in the second step with forms imidazole to form a salt that is insoluble in the solvent used (ether, tetrahydrofuran, benzene).

This method permits, for example, trifluoroacetic anhydride to be obtained in 60% yield ($R = R' = CF_3$).[1] Similarly, maleic and phthalic anhydrides are synthesized by treating the dicarboxylic acid with CDI in THF in a 3 : 1 ratio at room temperature, forming the antydrides and two moles of the insoluble monoimidazolium salt of the dicarboxylic acid:[1]

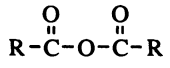


80%

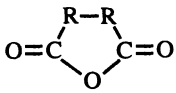
2. Antydrides are also abtained by the reaction of carboxylic acids with *N*,*N*′-oxalyldiimidazole in the presence of methanesulfonic acid.[2]

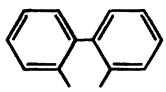


Reaction conditions: acetonitrile as solvent; for the first step 40 °C, for 1–2 h, the second step refluxing acetonitrile, 2–3 h. In this way the following anhydrides have been prepared from mono- and dicarboxylic acids:[2]

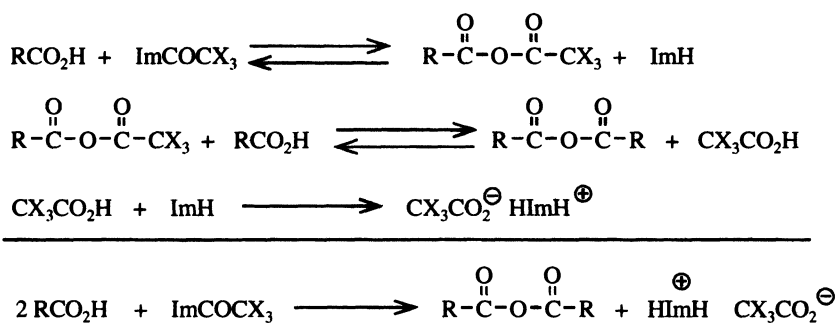


R	Yield (%)
$CH_3(CH_2)_{14}$–	94
C_6H_5	98
p-$NO_2C_6H_4$	56
	66
	71



R-R	Yield (%)
$-CH_2CH_2-$	39
$-CH_2CH_2CH_2-$	30
	84
	42

3. By use of *N*-(trifluoroacetyl)- or *N*-(trichloroacetyl)-imidazoleare obtained symmetric aliphatic and aromatic anhydrides even from carboxylic acids that do not form insoluble salts in benzene, ether, or THF (Table 13–1). In this case the acid is treated with the imidazolide in a 2 : 1 molar ratio, and an insoluble imidazolium trifluoro- or trichloroacetate is formed.



X = F or Cl

Intermediate anhydride formation by means of *N*-trifluoroacetylimidazole has been employed in the preparation of *p*-nitrophenylesters of *N*-protected amino acids, which are important in peptide synthesis.[3]

For mixed anhydrides of phosphoric acid see Chapter 12.

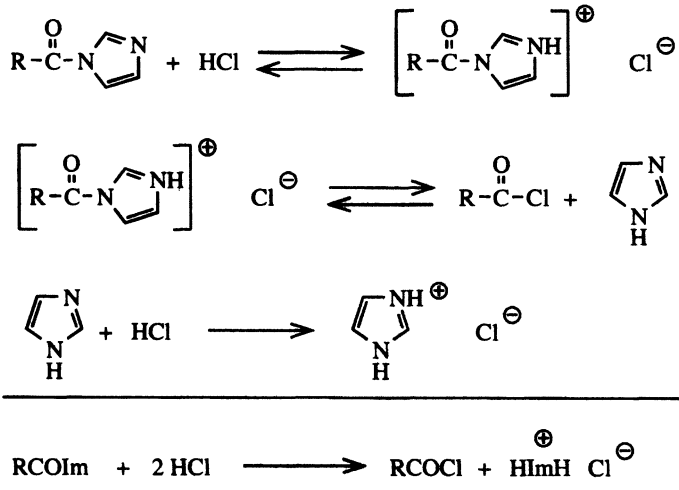
Table 13–1. Anhydrides synthesized by method 3.

Azolide	Anhydride	Yield (%]
$ImCOCF_3$	benzoic anhydride	78
$ImCOCCl_3$	benzoic anhydride	81
$ImCOCF_3$	phthalic anhydride	89
$ImCOCCl_3$	phthalic anhydride	89

Azolide	Anhydride	Yield (%)
$ImCOCF_3$	maleic anhydride	79
$ImCOCCl_3$	maleic anhydride	80
$ImCOCF_3$	palmitic anhydride	54
$ImCOCCl_3$	palmitic anhydride	50

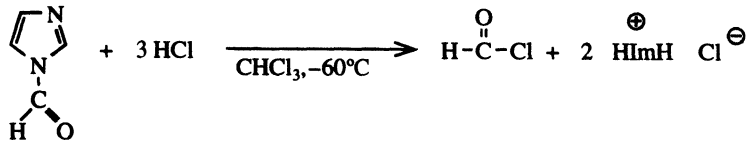
13.2 Acyl Chlorides

Acyl chlorides can be prepared by direct acylation of hydrogen chloride with imidazolides. If two moles of hydrogen chloride are passed into a solution containing one mole of an imidazolide in a solvent in which the imidazolium chloride is insoluble (e.g., chloroform, dichloroethane), the imidazolium chloride precipitates and the acyl chloride is formed in excellent yield and a high degree of purity. Examples are provided in Table 13–2.[4]



While the first two reactions are reversible in chloroform, the third is irreversible, shifting the equilibrium to the side of the acid chloride..

The acylation of hydrogen chloride by imidazolides is especially of interest for the preparation of acyl chlorides that cannot be prepared, or can only be prepared with difficulty, due to their instability. A distinguished example is the preparation of formyl chloride by this route:[5]

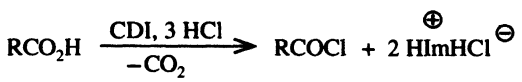


The resulting formyl chloride is stable in chloroform at − 60 °C for several hours.

Table 13–2. Acyl chlorides obtained by acylation of hydrogen chloride with imidazolides.

Acyl chloride	Yield (%)	Acyl chloride	Yield (%)
benzoyl chloride	81	caproyl chloride	73
p-methoxybenzoyl chloride	91	palmitoyl chloride	68
p-nitrobenzoyl chloride	94	2,2-diphenylcyclopropanecarboxyl chloride	93

For the preparation of acid chlorides from the corresponding imidazolides it is not necessary that the imidazolide be isolated. Instead it can be formed in situ by conversion of the appropriate carboxylic acid with CDI.



However, because CDI reacts with HCl to give phosgene ($COCl_2$), reaction of the carboxylic acid with CDI must be complete before treatment with hydrochloric acid is undertaken. The yield of an acid chloride prepared by this one-pot reaction is comparable to those reported in Table 13–2. In general, acid chlorides are formed at room temperature within a few minutes.

p-Nitrobenzoylimidazole, however, forms with HCl a sparingly soluble salt that reacts at room temperature only slowly. At higher temperature *p*-nitrobenzoyl chloride can be readily obtained (refluxing 1,2-dichloroethane). Analogous preparations are those of *N*-palmitoyl chloride and caproyl chloride (chloroform, 55–60 °C).

2,6-Dimethoxybenzoylimidazolium chloride also reacts rather slowly because of steric hindrance and electronic deactivation of the carbonyl group by the two methoxy groups. The synthesis of 2,6-dimethoxybenzoyl chloride was carried out in chloroform at 90 °C in a bomb tube to give a yield of 60% after 3 h.[4]

References

[1] H. A. Staab, G. Walther, W. Rohr, *Chem. Ber.* **1962**, *95*, 2073–2075.
[2] T. Kitagawa, H. Kuroda, H. Sasaki, *Chem. Pharm. Bull.* **1987**, *35*, 1262–1265.
[3] H. D. Law, *J. Chem. Soc. (London)* **1965**, 3897–3900.
[4] H. A. Staab, K. Wendel, A. P. Datta, *Liebigs Ann. Chem.* **1966**, *694*, 78–85.
[5] H. A. Staab, A. P. Datta, *Angew. Chem.* **1963**, *75*, 1203; *Angew. Chem. Int. Ed. Engl.* **1969**, *3*, 132.

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14 C-Acylations by Azolides

14.1 (Acylalkylidene)triphenylphosphoranes

C-Acylations of Alkylidenetriphenylphosphoranes by *N*-Acylimidazoles

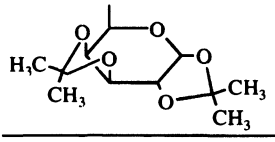
Alkylidenetriphenylphosphoranes can be C-acylated in good yield by reacting them with imidazolides of carboxylic acids in a molar ratio of 2 : 1 at room temperature in benzene, benzene/ether, or benzene/THF. The second mole of alkylidenetriphenylphosphorane acts as a proton acceptor in the subsequent "transylidation".[1]

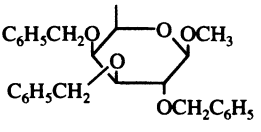
$$RCOIm + CH_2{=}P(C_6H_5)_3 \longrightarrow RCOCH_2{-}\overset{\oplus}{P}(C_6H_5)_3 + \overset{\ominus}{Im}$$

$$RCOCH_2{-}\overset{\oplus}{P}(C_6H_5)_3 + CH_2{=}P(C_6H_5)_3 \longrightarrow RCOCH{=}P(C_6H_5)_3 + CH_3{-}\overset{\oplus}{P}(C_6H_5)_3$$

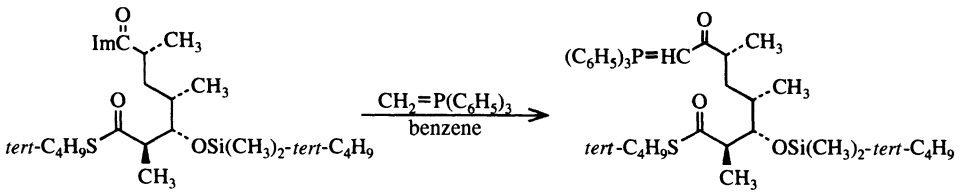
A particularly interesting reaction is the C-formylation[2] of alkylidenephosphoranes by *N*-formylimidazole to give α-formyl derivatives $(C_6H_5)_3P{=}C(R)CHO$ which can be further transformed into α,β-unsaturated aldehydes by Wittig reaction, or hydrolyzed to produce aldehydes RCH_2-CHO.

Table 14–1. (Acylmethylidene)triphenylphosphoranes $RCOCH{=}P(C_6H_5)_3$.

R	Yield (%)	Ref.
H	81	[2]
C_6H_5	99	[1]
C_7H_{15}	52	[3]
$C_4H_9C(CH_3)H$	55	[3]
$c\text{-}C_6H_{11}(CH_2)_2$	56	[3]
$CH_3O(CH_2)_3$	31	[3]
$HC{\equiv}C(CH_2)_2$	82	[4]
	73	[5]

R	Yield (%)	Ref.
	60	[6]
	45	[3]

If the acyl moiety is sensitive to acid and base the imidazolide method for synthesis of (acylmethylidene)phosphoranes is the method of choice, as shown by the following example, which represents a step on the way to the antibiotic methynolide:[7]

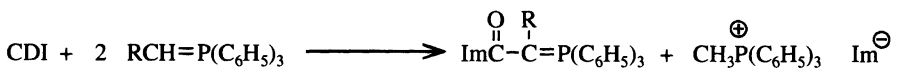


from the carboxylic acid and CDI

95% based on the carboxylic acid

Because in this case an elimination reaction could occur to form an α,β-unsaturated ester, use of two equivalents of the phosphorane should be avoided.[7] The (α-acylalkylidene)triphenylphosphorane can be subjected to a subsequent Wittig reaction with an aldehyde.[4],[5],[8]

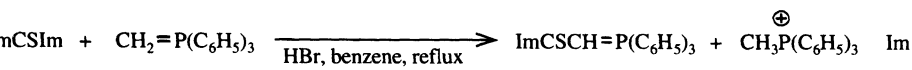
Alkylidenetriphenylphosphoranes react also with CDI to give imidazolides of alkylidine-α-carboxylic acid triphenylphosphoranes in good yield.[2]



R	Yield (%)
H	81
CH_3	60

These compounds can be converted by hydrolysis into the corresponding carboxylic acids RCH_2CO_2H, or they can undergo a Wittig reaction, albeit only in moderate yield, to produce α,β-unsaturated carboxylic acids.

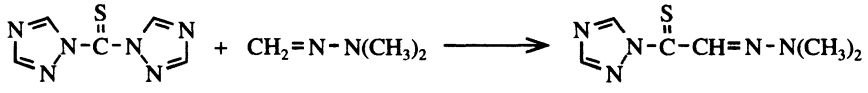
The reaction of *N,N'*-Thiocarbonyldiimidazole (ImCSIm) with (methylidene)-triphenylphosphorane is carried out in analogy to that of CDI.[9]



31%

14.2 *N*-Azolylthiocarbonylhydrazones

Formaldehyde hydrazones react with *N,N'*-thiocarbonyldi-1,2,4-triazole to give hydrazones of thioglyoxalyl-1,2,4-triazoles, which react readily under displacement of 1,2,4-triazole with nucleophilic reagents such as amines and hydrazines but also with less nucleophilic compounds, including hydrazones, sulfonylhydrazides, thiosemicarbazides, and hydrazides.[10]



No corresponding reactions have been reported with ImCSIm. Attempts to extend the reaction to other aldehyde hydrazones (e.g., acetaldehyde-*N,N*-dimethylhydrazone) failed.[10]

14.3 Acylnitroalkanes

Nitroalkanes can be acylated by imidazolides via their sodium, potassium, lithium, or ammonium salts in refluxing THF or in DMSO. Acylation in this case takes place exclusively at the α-carbon of the nitro compound.

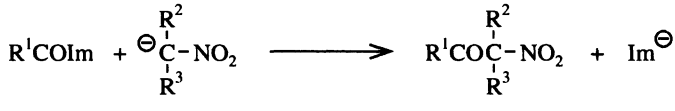
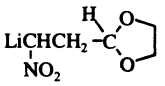
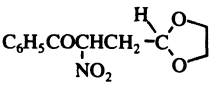
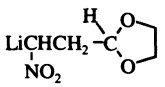
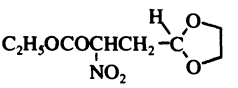
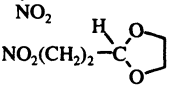
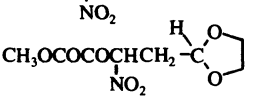
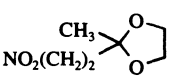
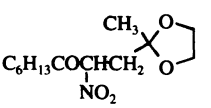


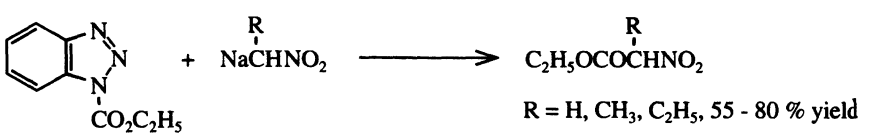
Table 14–2. Acylnitroalkanes.

R^1 of R^1COIm	Nitroalkane / base	Acylnitroalkane	Yield (%)	Ref.
CH_3	$NaCH_2NO_2$	$CH_3COCH_2NO_2$	80	[11]
CH_3	CH_3NO_2 / KO-*tert*-C_4H_9	$CH_3COCH_2NO_2$	56	[12]
3-ClC_6H_4	CH_3NO_2 / KO-*tert*-C_4H_9	3-$ClC_6H_4COCH_2NO_2$	72	[12]
3-$NO_2C_6H_4$	CH_3NO_2 / NaH	3-$NO_2C_6H_4COCH_2NO_2$	77	[12]
3,5-$(CH_3O)_2C_6H_3$	CH_3NO_2 / NaH	3,5-$(CH_3O)_2C_6H_3COCH_2NO_2$	88	[12]
p-$ImCOC_6H_4$	CH_3NO_2 / NaH	$NO_2CH_2COC_6H_4COCH_2NO_2$	75	[13]

Table 14–2. (*continued*)

R^1 of R^1COIm	Nitroalkane / base	Acylnitroalkane	Yield (%)	Ref.
C_6H_5			95	[14]
C_2H_5O			91	[14]
C_6H_5	$LiCHCH_3$ NO_2	$C_6H_5COCHCH_3$ NO_2	92	[14]
CH_3O	$LiCHCH_3$ NO_2	$CH_3OCOCHCH_3$ NO_2	91	[14]
C_6H_5	$LiC(CH_3)_2$ NO_2	$C_6H_5COC(CH_3)_2$ NO_2	30	[14]
CH_3OCO	 /NaH		24	[14]
C_6H_{13}	$NO_2CH_2C_2H_5$ / KO-*tert*-C_4H_9	$C_6H_{13}COCHC_2H_5$ NO_2	73	[15]
CH_3	$NO_2CH_2CH_2C_6H_5$ / KO-*tert*-C_4H_9	$CH_3COCHCH_2C_6H_5$ NO_2	87	[15]
C_6H_{13}	$NO_2(CH_2)_3COCH_3$ / KO-*tert*-C_4H_9	$C_6H_{13}COCH(CH_2)_2COCH_3$ NO_2	62	[15]
CH_3	$NO_2(CH_2)_5CO_2CH_3$ / KO-*tert*-C_4H_9	$CH_3COCH(CH_2)_4CO_2CH_3$ NO_2	65	[15]
C_6H_{13}	 /KO-*t*-C_4H_9		88	[15]
CH_3	$NO_2(CH_2)_3CHCH_3$ / DBU $O-Si(CH_3)_2$-*tert*-C_4H_9	$CH_3COCH(CH_2)_2CHCH_3$ NO_2 $O-Si(CH_3)_2$-*tert*-C_4H_9	62	[16]

Instead of an imidazolide, a benzotriazolide was used for alkoxycarbonylation of nitroalkanes:[17]



14.4 Reactions of Imidazolides with CH-Activated Compounds

The CH groups of those compounds are activated by CN, CO_2R, Benzimidazolium, or Pyridazine

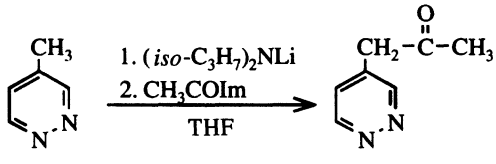
Intermolecular Reactions:

a) $R^1CH(CH_2C_6H_5)COIm + R^2CH_2R^3 \xrightarrow[THF]{NaH} R^1CH(CH_2C_6H_5)-C(OH)=CR^2R^3$ [18]

R^1	R^2	R^3	Yield (%)
Boc	CN	CN	97
Boc	CN	CO_2CH_3	93
Boc	CN	*p*-$NO_2C_6H_4$	81
N-Ac-Leu	CN	*p*-$NO_2C_6H_4$	63
N-Ac-Leu	CN	$P(O)(OC_2H_5)_2$	47

R^1	R^2	R^3	Yield (%)
N-Ac-Leu	CN	CN	96
N-Ac-Leu	CN	CO_2CH_3	55
N-Ac-Leu	CN	2-pyridyl	59
N-Ac-Leu	CO_2CH_3	$SO_2C_6H_5$	72
N-Ac-Leu	CO_2CH_3	$P(O)(OCH_3)_2$	66

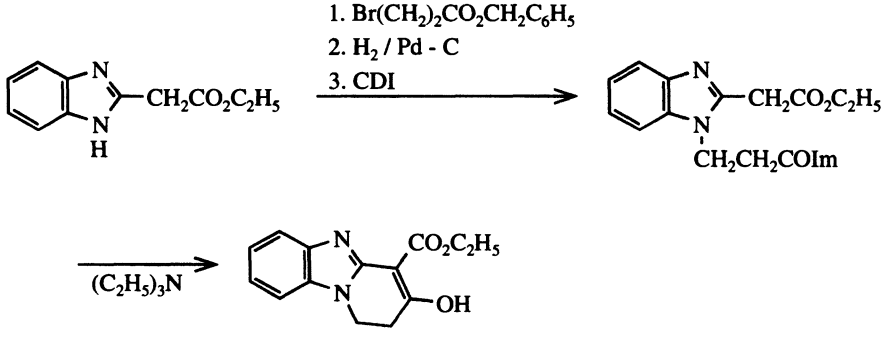
b)



40% [19]

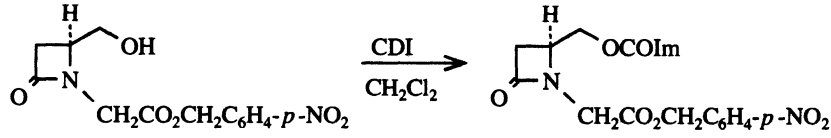
Intramolecular Reactions:

a)

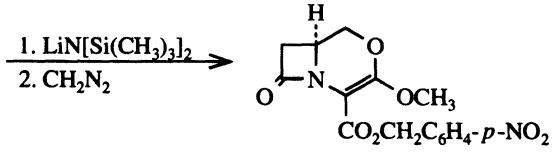


43% overall yield [20]

b)

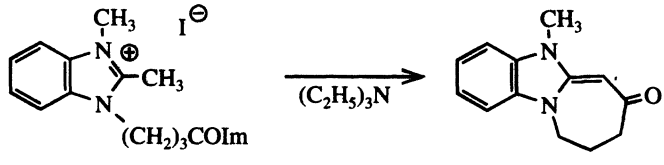


87%



64% [21]

c)

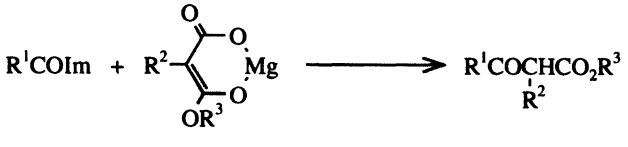


60% [22]

14.5 β-Ketoesters

β-Ketoesters from Imidazolides and Magnesium Enolates

Reactions of imidazolides with the magnesium enolates of malonates (Mg^{2+}/malonate, ratio 1 : 1) are used for the elongation of carboxylic acids by two carbon atoms to give β-ketoesters (Tables 14–3 and 14–4).



The magnesium enolates are prepared by treatment of malonic acid half ester either with magnesium ethylate[24],[32] or with isopropylmagnesium bromide[24] or chloride.[26] Ref. [23] describes the synthesis of a ^{13}C-labelled ethyl acetoacetate. Concerning the synthesis of porphyrin β-ketoesters,[37] it was noticed that the method via imidazolides is more efficient than the other approach via acid chlorides and sodiomalonic esters.

Table 14–3. $R^1COCHR^2CO_2C_2H_5$

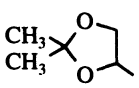
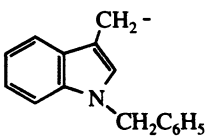
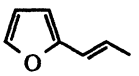
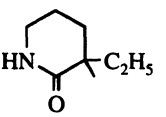
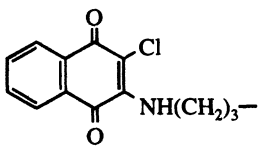
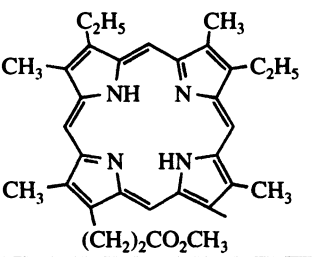
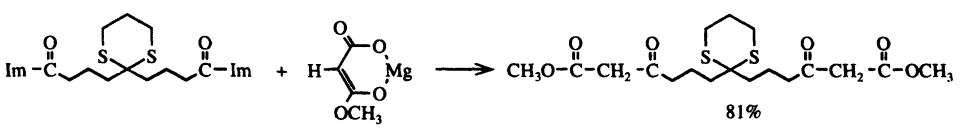
R^1	R^2	Yield (%)	Ref.
CH_3	H	63	[23]
C_3H_7	H	74	[24]
C_6H_5	H	65	[24]
$C_6H_5CH_2$	H	79	[24]
$CH_3C\equiv C$	CH_3	60	[25]
iso-$C_3H_7CH_2CHN(CH_2C_6H_5)_2$	H	74	[26]
Boc-NHCH($CH_2C_6H_5$)	H	88	[27]
Boc-NHCH(CH_2CO_2-*tert*-C_4H_9)CH_2-	H	86	[28]
Boc-NHCHCH$_2C_6H_{11}$	H	62	[29]
(4S)- CH_3CHCH_2CH(NH-Boc)CH_3	H	37	[30]
	CH_3	82	[31]
	H	76	[32]

Table 14–4. $R^1COCHR^2CO_2CH_3$

R^1	R^2	Yield (%)	Ref.
Boc-NHCHCH$_2C_6H_5$	H	60	[33]
	H	83	[34]
	H	60	[35]
	H	75	[36]
	H	80	[37]

By the same method, dicarboxylic acids can be elongated by four carbon atoms.[38]



β-Ketoesters from Imidazolides and Magnesium Bis(alkyl malonates) or Bis(alkyl thiomalonates)

$$R^1COIm + (R^3XCOCHR^2CO_2)_2Mg \rightarrow R^1COCHR^2COXR^3$$

In these cases the molar ratio of magnesium/carboxylic acid is 1 : 2.[39]–[53]

It is advantageous to utilize neutral magnesium salts in the cases cited in Table 14–5 instead of basic magnesium enolates, because with the latter reagents the yields are much

lower. In ref. [50] the starting imidazolide was prepared by treatment of the sodium salt of the carboxylic acid with CDI in THF (room temperature, 30 min). Analogous chain elongations of silylated azetidinone carboxylic acids with CDI and *p*-nitrobenzylhemimalonates are described in reference [54].

Table 14–5. *β*-Ketoesters ($R^1COCHR^2COXR^3$) from imidazolides (R^1COIm) and magnesium salts ($(R^3XCOCHR^2CO_2)_2Mg$ mainly in THF.

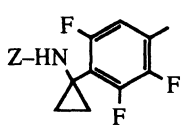
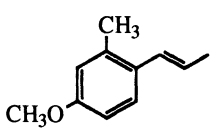
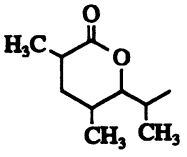
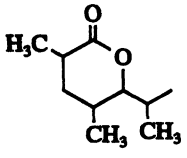
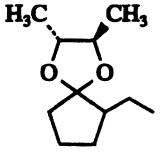
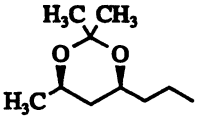
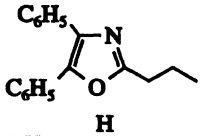
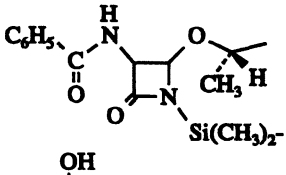
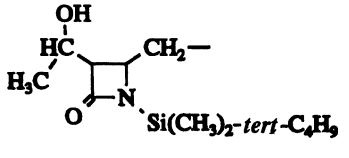
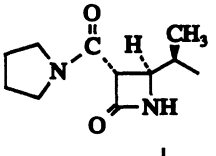
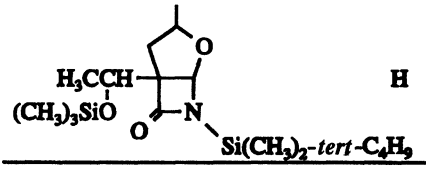
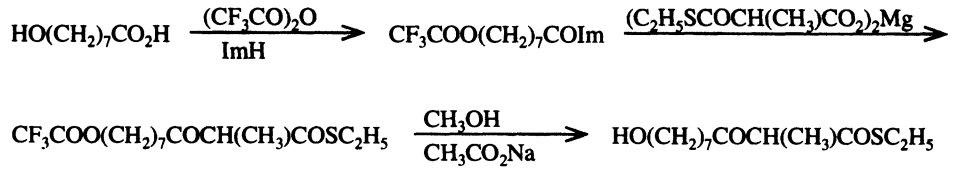
R^1	R^2	X	R^3	Yield (%)	Ref.
n-C_4H_9	H	O	CH_3	quant.	[39]
C_8H_{17}	H	O	C_2H_5	95	[40]
$CH_3CO(CH_2)_2$	CH_3	S	C_2H_5	85	[41]
$C_6H_5(CH_2)_2$	H	O	CH_3	quant.	[41]
$C_6H_5(CH_2)_2$	CH_3	O	CH_3	95	[41]
$C_6H_5(CH_2)_2$	CH_3	S	C_2H_5	quant.	[41]
$(CH_3)_3C$	H	S	C_2H_5	quant.	[41]
c-C_6H_{11}	H	O	CH_3	quant. / 85	[39,41]
c-C_6H_{11}	H	S	C_2H_5	quant.	[41]
c-C_6H_{11}	CH_3	S	C_2H_5	90	[41]
t,t-$CH_3(CH{=}CH)_2$	CH_3	S	*tert*-C_4H_9	95	[41]
$CH_3(CH_2)_5CHOH(CH_2)_{10}$	H	O	CH_3	95	[41]
$CH_3(CH_2)_5CHOH(CH_2)_{10}$	CH_3	S	*tert*-C_4H_9	95	[41]
$CH_3O_2CCH_2CH_2$	H	O	*tert*-C_4H_9	75	[41a]
tert-$C_4H_9O_2CCH_2CH(CH_2)_2$ – $OSi(CH_3)_2$-*tert*-C_4H_9	H	O	CH_3	70	[41a]
$CH_3O(CH_2)_2CH$– $OSi(CH_3)_2$-*tert*-C_4H_9	H	O	CH_3	48	[42]
$CH_3CO_2CCH_2CHCH_2$ $OSi(C_6H_5)_2$-*tert*-C_4H_9	H	S	*tert*-C_4H_9	90	[43]
$CH_3CO_2CCH_2CHCH_2$ O $(C_6H_5)_2Si$–*tert*-C_4H_9	H	O	$C_6H_5CH_2$	86	[44]
(R)-Boc-NHCH(CH_3)	H	O	CH_3	57	[45]
C_6H_5	CH_3	S	*tert*-C_4H_9	85	[41]
	H	O	C_2H_5	90	[46]
	H	O	CH_3	78	[46a]

Table 14–5. (*continued*)

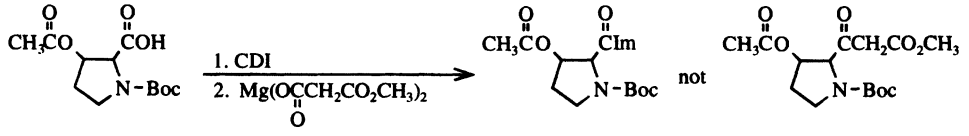
R^1	R^2	X	R^3	Yield (%)	Ref.
	H	S	C_2H_5	88	[41]
	CH_3	S	*tert*-C_4H_9	75	[41]
	H	O	CH_3	88	[47]
	CH_3	O	C_2H_5	88	[48]
	H	O	C_2H_5	90	[49]
	H	O	$(C_6H_5)_2CH$	40	[50]
	H	O	*p*-$NO_2C_6H_4CH_2$	86	[51]
	H	O	CH_2=$CHCH_2$	72	[52]
	H	O	*p*-$NO_2C_6H_4CH_2$	84	[53]

Because primary hydroxy groups are somewhat more reactive toward CDI than a carboxy group, the method was modified for chain elongations of ω-hydroxycarboxylic acids with protection of the OH-group:[41]



90%

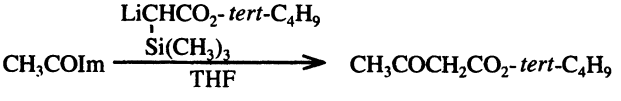
Crowded imidazolides do not react with magnesium bis (methyl malonate) because of steric hindrance.[55]



53%

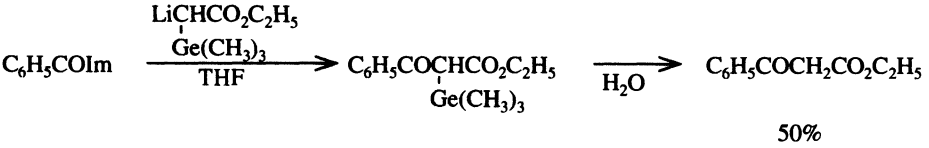
β-Ketoesters and β-Ketoamides from α-Lithiated Carboxylic Acid Derivatives

a) Reaction of *N*-acylimidazole with lithio *tert*-butyl trimethylsilylacetate:[56]



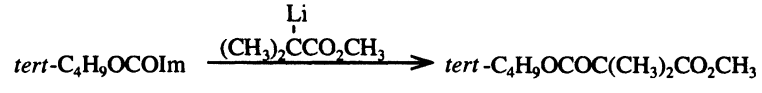
94%

b) Reaction of *N*-acylimidazole with lithio ethyl trimethylgermylacetate:[57]



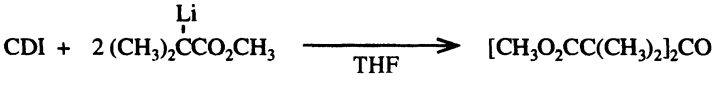
50%

c) Reaction of imidazole-*N*-*tert*-butylcarboxylate with lithio methyl isobutyrate:[58]



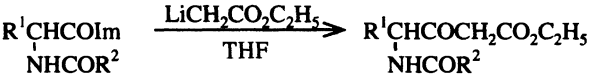
65%

β-Ketodicarboxylic esters can be synthesized in a similar way using CDI and an α-lithiated carboxylic ester:[58]



60%

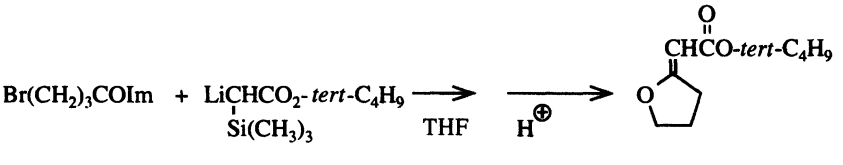
d) Reaction of an *N*-acyl-amino acid imidazolide with α-lithio ethyl acetate:



R^1	R^2	Yield (%)	Ref.
$CH_3CH(CH_3)CH_2$	*tert*-C_4H_9O	82	[59]
CH_3	2-naphthyl	69	[60]
iso-C_3H_7	C_6H_5	75	[60]
H	$C_6H_5CH_2$	74	[60]

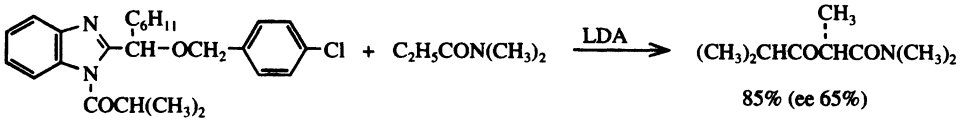
For an analogous reaction see also reference [61].

e) The reaction of an ω-bromo-n-butyric acid imidazolide with an α-lithio α-trimethylsilylacetic acid *tert*-butylester leads to a cyclized product:[56]



75%

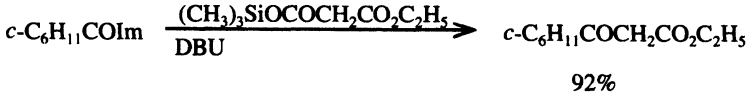
f) The asymmetric acylation of propionamides has been studied using an optically active *N*-acylbenzimidazole. The highest yields of β-ketoamides were obtained in THF as solvent:[62]



β-Ketoesters from Imidazolides and *O*-(Trimethylsilyl)malonates

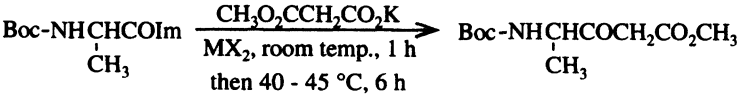
The synthesis of β-ketoesters using trimethylsilylmalonates generated in situ is described in reference [63].

Example:



β-Keto-γ-aminocarboxylates

The reaction of amino acid imidazolides with the potassium salt of monomethyl malonate in the presence of one equivalent of $MgCl_2$, $CoCl_2$, or $MnCl_2$ results in the formation of β-keto-γ-aminocarboxylates.[64]

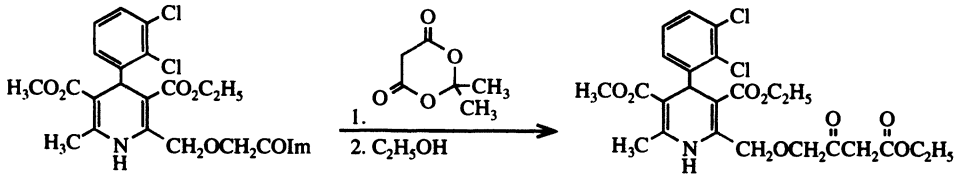


The use of $MgCl_2$, $CoCl_2$, and $MnCl_2$ give comparable yields. In the absence of these catalysts no carbon acylation has been observed.[64]

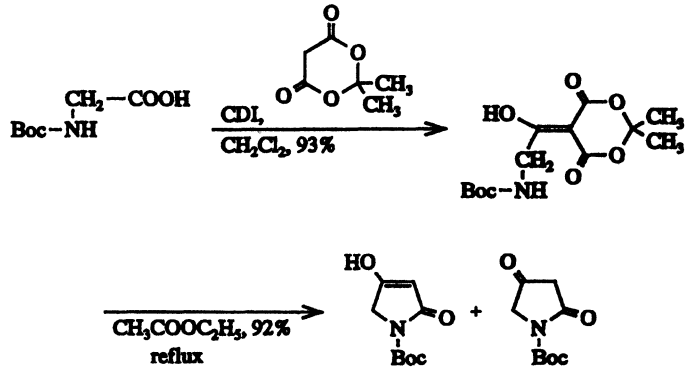
Another synthesis of β-keto-γ-aminocarboxylates starts from *N*-protected amino-acid imidazolides and magnesium *p*-nitrobenzyl malonate (50–60 °C, about 6 h).[65]

β-Ketoesters from Reactions of Imidazolides with CH Acidic Compounds in the Absence of Base

a) A β-ketoester was obtained in the reaction of an imidazolide with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid).[66]



b) *N*-Protected tetramic acid could be obtained by aminoacylation of Meldrum's acid via a β-ketoester:[66a]

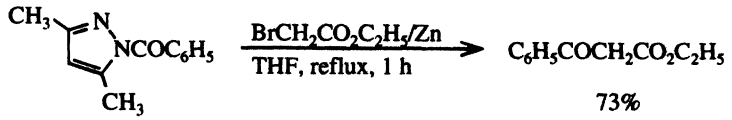


c) The imidazolide of monomethyl malonate reacted in a type of Claisen condensation to give dimethyl β-ketoglutarate.[39]

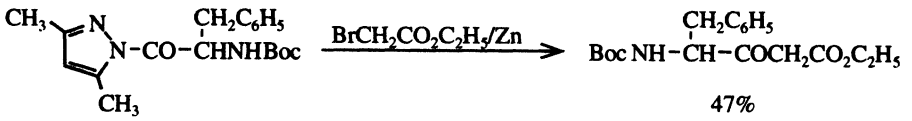
2-Methyl monoethyl malonate and 2-methylacetoacetic acid, however, did not give definite condensation products.

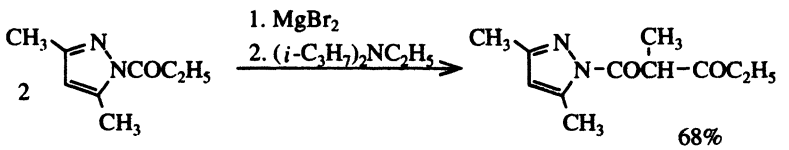
β-Ketoesters from Pyrazolides

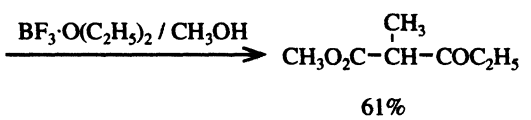
Two further methods for the preparation of β-ketoesters consist of the Reformatsky reaction of pyrazolides[67] (a) and the magnesium bromide-induced Claisen condensation of pyrazolides[68] (b).

a) 

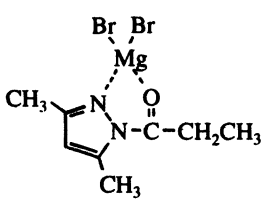
The pyrazolides were in turn synthesized from *N*-protected amino acids, pyrazole, and thionyl chloride/triethylamine. Using *N*-protected aminoacylpyrazoles, 4-amino-3-oxoalkanoic acid derivatives were thus conveniently prepared.[67]



b) 



It is suggested that this reaction proceeds via a 5-membered C=O-Mg-N(2) chelate complex

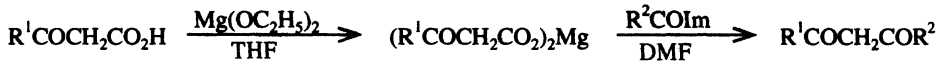


affording then the Claisen condensation product by action of a tertiary amine through the corresponding enolate. With pyrrolidine instead of methanol the related β-ketoamide is obtained in 87% yield.[68]

14.6 β-Diketones

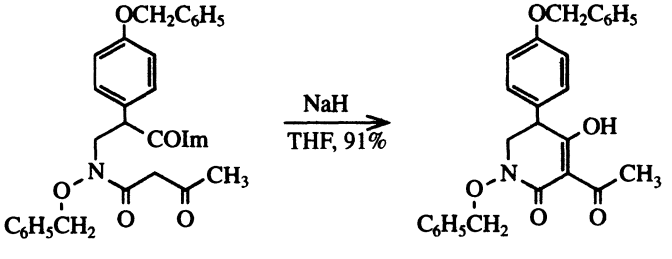
β-Diketones from Reactions of an Imidazolide with a β-Keto Acid Derivative

a) The β-ketoesters obtained by reaction of imidazolides with neutral magnesium salts of alkyl malonates can, after hydrolysis and further treatment with the corresponding magnesium salt, be acylated once again by imidazolides to give β-diketones.[39]

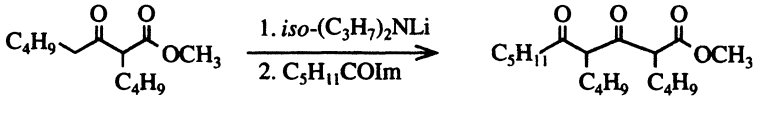


R^1	R^2	Yield (%)
C_6H_5	CH_3	85
C_6H_5	*tert*-C_4H_9	62
c-C_6H_{11}	*n*-C_4H_9	76
CH_3	3-pyridyl	87

b) An intramolecular acylation of a β-ketoamide is illustrated by the following example:[69]



c) The intermolecular acylation of a 2-butyl-3-oxo-methyloctanoate furnished 2,4-dibutyl-3,5-dioxo-methyldecanoate.[70]



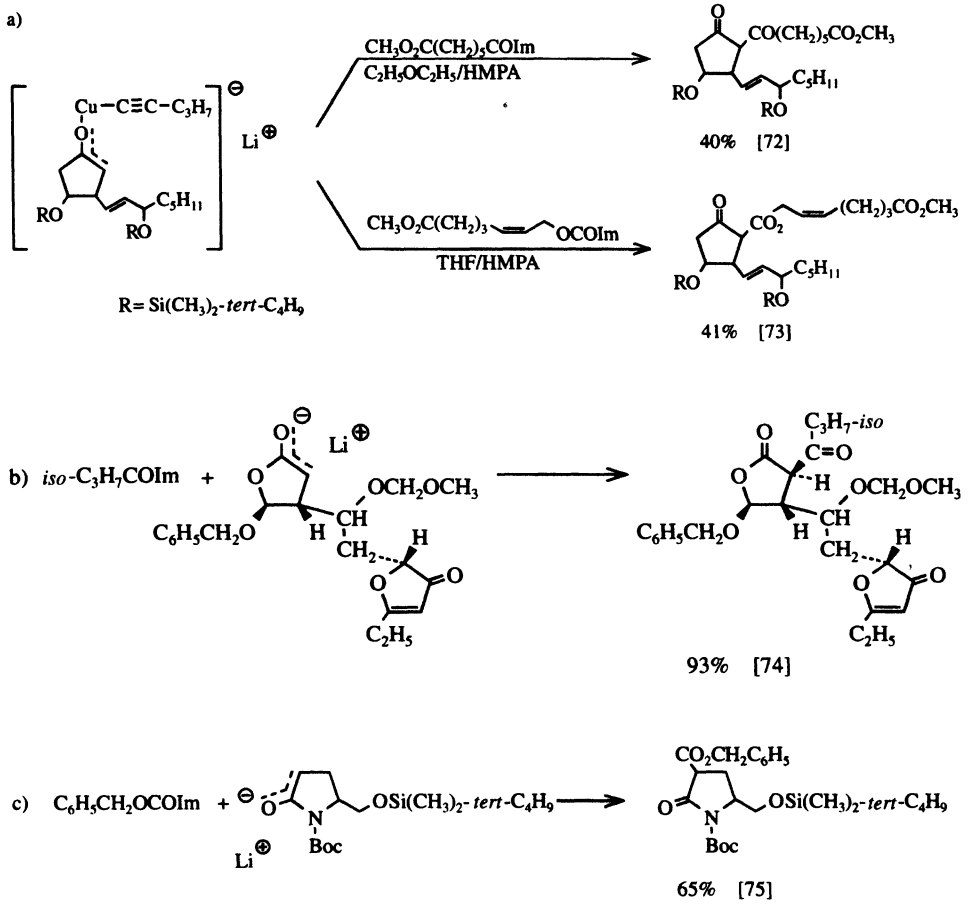
60%

Probably because of steric hindrance at the α-carbon, acylation here takes place at the γ-carbon.

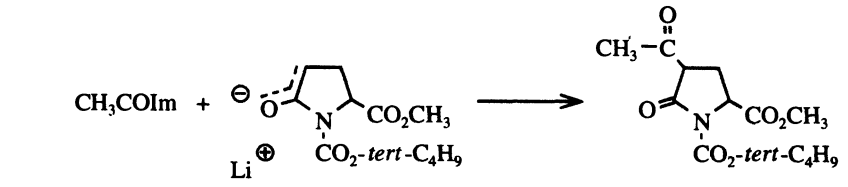
The imidazolide of 2-methylthiobenzoic acid was transformed with the thallium salt of ethyl acetoacetate into ethyl acetyl(2-methylthiobenzoyl)acetate.[71]

β-Diketones and β-Ketoesters from Reactions of Imidazolides with Lithium Enolates

Organo copper and lithium enolates of cyclic ketones, lactones, and lactams or acyclic ketones are converted with acylimidazoles or imidazole-N-carboxylates into the corresponding β-diketones or β-ketoesters:

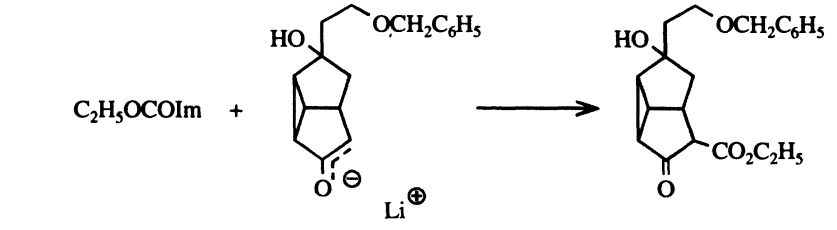


With an acid chloride instead of the imidazolide, the yield was only 25%.

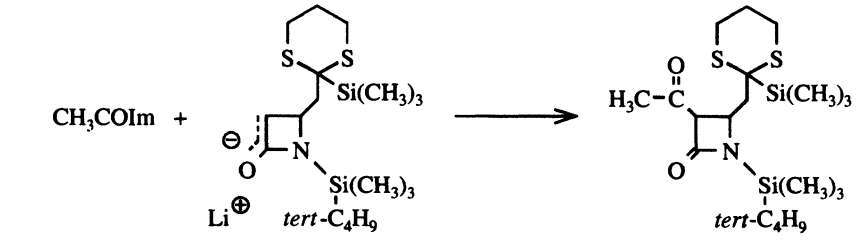
d) 

72% [76]

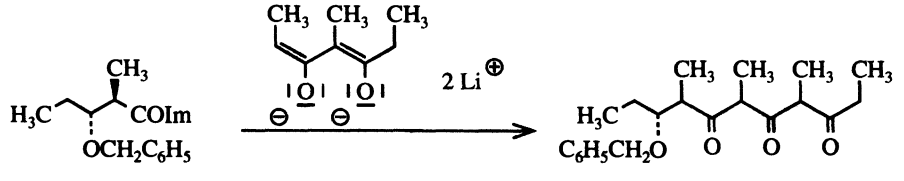
Further examples of this type are described in references [77]–[80].

e) 

84% [81]

f) 

82% [51]

g) 

46% [82]

14.7 α-Diketones and α-Ketoesters

α-Diketones and α-ketoesters can be prepared in good yield from *N,N'*-oxalyldiimidazole (a) or oxalic acid monoester imidazolide (b) and Grignard reagents.

a) $Im-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Im + 2\,RMgBr \xrightarrow[THF]{} R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R$

R	Yield (%)	[83]
o-$CH_3C_6H_4$	80	
2,6-dimethylphenyl	70	
3-pyridyl	60	

b) $R^1O-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Im + R^2MgBr \xrightarrow[THF]{} R^1O-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R^2$

R^1	R^2	Yield (%)	[84]
C_2H_5	C_6H_5	72	
C_2H_5	*p*-ClC_6H_4	72	
tert-C_4H_9	C_6H_5	77	

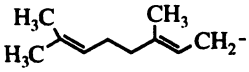
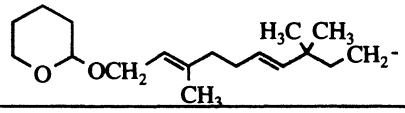
14.8 Ketone and Ester Syntheses

Reaction of Imidazolides with Grignard Reagents, Organolithium, and Organoaluminum Compounds

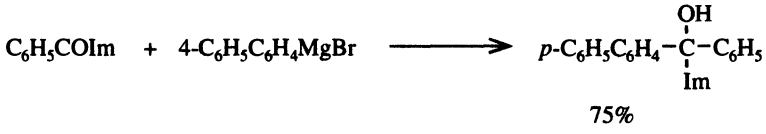
The preparation of ketones proceeds conveniently by reaction of imidazolides with organomagnesium reagents, as shown in Table 14–6 for several examples of purely aromatic, aromatic–aliphatic, and purely aliphatic ketones. The yields are very satisfactory even for purely aliphatic ketones, since in this case, too, alcohol formation is completely suppressed.[85],[86]

$$R^1COIm + R^2MgBr \xrightarrow[THF]{} R^1COR^2$$

Table 14–6. Ketones from imidazolides and Grignard reagents.

R^1	R^2	Yield (%)	Ref.
C_6H_5	C_6H_5	72	[85]
3-ClC_6H_4	C_6H_5	94	[85]
$CH_3(CH_2)_4$	C_6H_5	69	[85]
$CH_3(CH_2)_4$	CH_3	74	[85]
		43	[86]

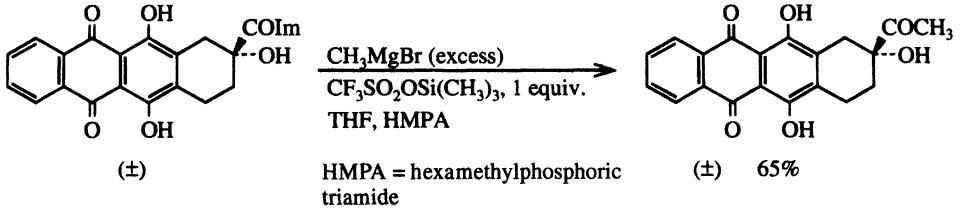
The intermediate addition product from the reaction of an imidazolide and a Grignard reagent could be isolated:[87]



$C_6H_5COIm + 4\text{-}C_6H_5C_6H_4MgBr \longrightarrow p\text{-}C_6H_5C_6H_4\text{-}C(OH)(Im)\text{-}C_6H_5$ (75%)

Other reactions described are those of imidazolides with Grignard reagents, which are carried out in the presence of the catalysts trimethylsilyl triflate, iron trichloride, or iron trisacetylacetonate:

a) Reaction in the presence of trimethylsilyl triflate.[88],[89]

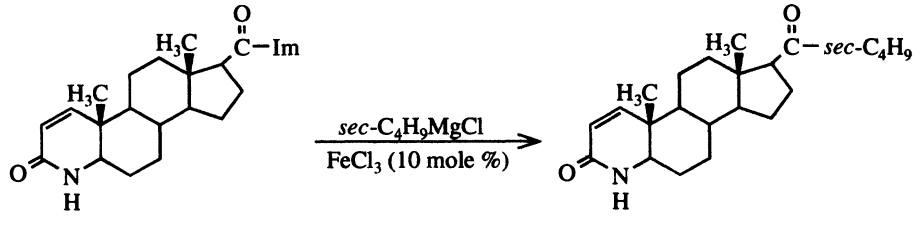


(±) — CH_3MgBr (excess), $CF_3SO_2OSi(CH_3)_3$, 1 equiv., THF, HMPA — (±) 65%

HMPA = hexamethylphosphoric triamide

With boron trifluoride etherate instead of trimethylsilyl triflate the yield was 51%, without catalyst 40% and without catalyst and HMPA 25%.[88],[89] With CH_3MgI instead of CH_3MgBr the ketone is further transformed into a tertiary alcohol.[89]

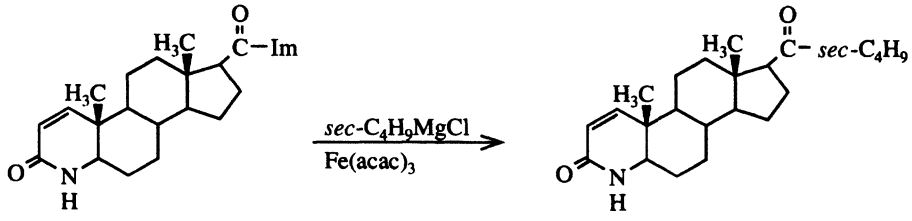
b) Reaction in the presence of $FeCl_3$.[90]



sec-C_4H_9MgCl, $FeCl_3$ (10 mole %) — 80%

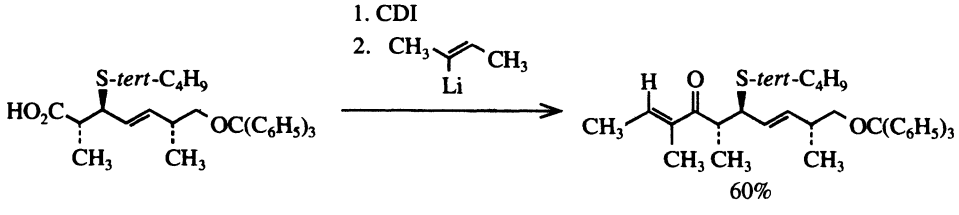
Sterically congested ketones have been prepared in good yield in this way without significant formation of alcohols.

c) Reaction in the presence of iron trisacetoacetate $Fe(acac)_3$.[91]



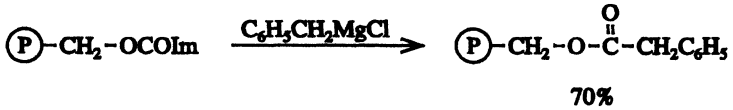
58%

Organolithium compounds such as 2-lithio-2-butene have been acylated by an imidazolide to give a ketone:[92]



60%

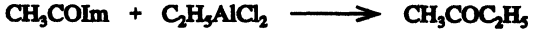
The reaction of a polymer-bound imidazole-*N*-carboxylate with a Grignard reagent leads to an ester:[93]



70%

Another method for the preparation of ketones is the reaction of imidazolides, benzimidazolides, or benzotriazolides with organoaluminum compounds:[94]

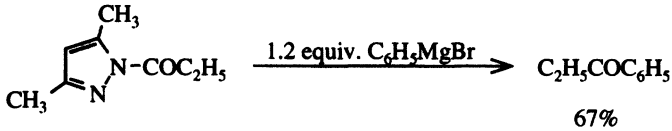
Example:



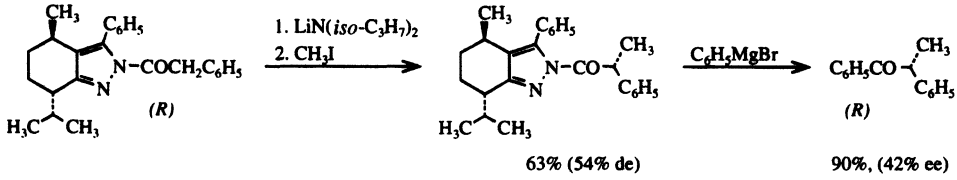
72%

Ketones from Reaction with Pyrazolides

Ketones can also be synthesized from pyrazolides and small excess amounts of Grignard reagents:[95]

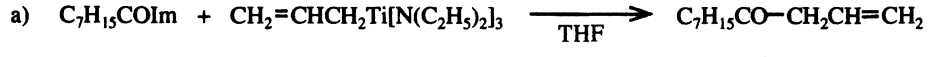


Using optically active pyrazolides as auxiliary compounds, optical asymmetry in the ketones was retained to a comparable degree:[95]



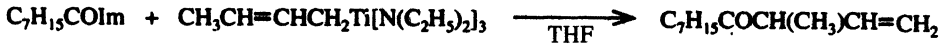
Allyl Ketones from Imidazolides and Allyl Titanium(IV) Compounds

Imidazolides are useful for the conversion of allyl titanium compounds into allyl ketones:[96]



In contrast to allyl magnesium chloride and allyl titanous triisopropoxide, allyl titanous trisdiethylamide reacts cleanly with imidazolides to give β,γ-unsaturated ketones practically free of concomitant carbinols. Furthermore, the products can be obtained free of isomers (α,β-unsaturated ketones) if they are purified by distillation rather than chromatography.

b) *trans*-2-Butenyl titanous trisdiethylamide reacts regioselectively with imidazolides to ketones under a double-bond shift in the allyl part (allyl inversion).[96]

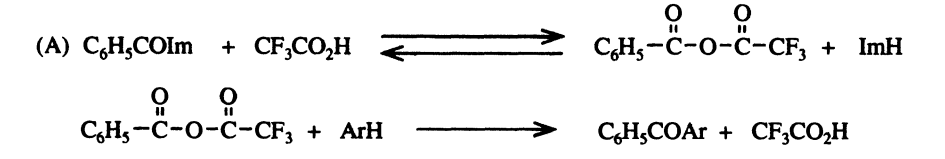


Because in the case of a sterically crowded imidazolide the formation of a carbinol is more difficult, reaction with the titanium reagent or the corresponding Grignard compound produces the allyl ketone in about the same yield:[96]

For further syntheses of β,γ-unsaturated ketones via imidazolides and pyrazolides see reference [96a].

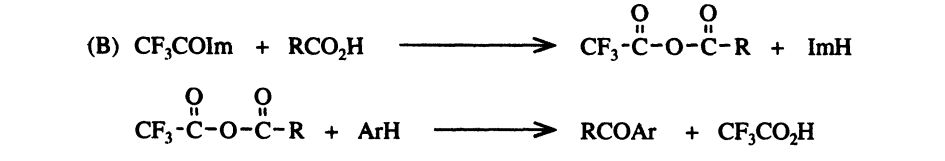
Acylation of Aromatic Compounds

Electron-rich aromatic compounds such as durene, *p*-dimethoxybenzene, mesitylene, anisole, thiophene, and fluorene can be benzoylated or acetylated by the corresponding *N*-acylimidazole in trifluoroacetic acid to give the corresponding benzophenone or acetophenone derivative in good yield (Method A). As the actual acylating agent, a mixed anhydride of trifluoroacetic acid and benzoic acid has been proposed:[97]



Reaction conditions: reflux of a mixture of the aromatic compound, *N*-benzoylimidazole, and trifluoroacetic acid in a molar ratio of 1 : 1.2 : 10. This method for acylating aromatic hydrocarbons works without the use of classical Friedel–Crafts catalysts.

In method B, *N*-trifluoroacetylimidazole and carboxylic acids are the acylating reagents. This method is also thought to proceed via a carboxylic trifluoroacetic anhydride. This second system is a very convenient reagent for obtaining aromatic ketones because of the use of free carboxylic acids:[97]



Reaction conditions: reflux of a mixture of aromatic substrate, carboxylic acid, and *N*-trifluoroacetic imidazolide in a molar ratio of 1 : 1.2 : 1.2 in trifluoroacetic acid. A comparison of methods A and B (see above) is presented in Table 14.7.

Table 14–7. Syntheses of aromatic ketones by acylation[97]

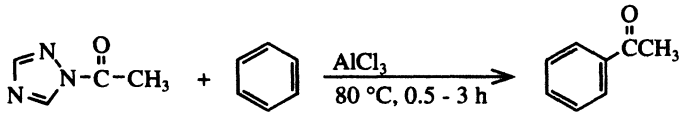
Aromatic hydrocarbon	Ketone	Yield (%)	
		method A	method B
durene	3-C_6H_5CO-durene	77	99
p-dimethoxybenzene	2-C_6H_5CO-p-dimethoxybenzene	73	95
mesitylene	2-C_6H_5CO-mesitylene	78	98
thiophene	2-C_6H_5CO-thiophene	80	quant.
anisole	4-C_6H_5CO-anisole	86	98
anthracene	9-C_6H_5CO-anthracene	–	82
m-xylene	4-C_6H_5CO-m-xylene	–	66
p-xylene	2-C_6H_5CO-p-xylene	–	8
toluene	4-C_6H_5CO-toluene	–	5
benzene	——	0	–
fluorene	2-C_6H_5CO-fluorene	80	91
fluorene	2-CH_3CO-fluorene	89	82
fluorene	2-*p*-$CH_3OC_6H_4CO$-fluorene	93	95
fluorene	2-*p*-ClC_6H_4CO-fluorene	76	79
fluorene	2-*p*-$NO_2C_6H_4CO$-fluorene	16	15

method A : C_6H_5COIm / CF_3CO_2H, reflux, 5h

method B : CF_3COIm / $C_6H_5CO_2H$ / CF_3CO_2H, reflux, 10h

While benzene could not be acylated according to method A, such an acylation did succeed with triazolides in a Friedel–Crafts-type reaction:[98]

Example:

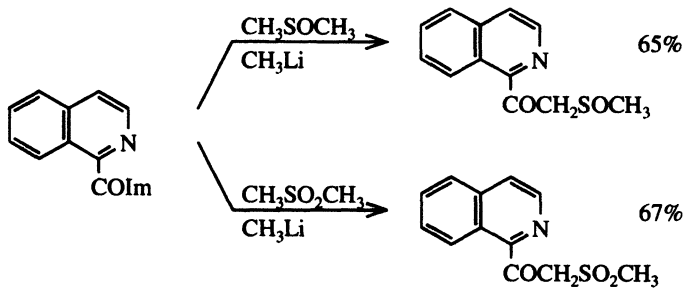


76%

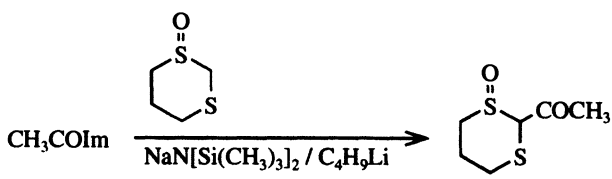
1-Acylimidazoles and 1-acyl-3,5-dimethylpyrazoles reacted with phenols and phenol ethers in the presence of $AlCl_3$ and at higher temperatures (110–120 °C) to give ketones in moderate yield.[99]

14.9 Syntheses of β-Ketosulfoxides, β-Ketosulfones, and Diarylsulfoxides

Sulfoxides and sulfones are acylated in the α-position by aroyl- or acylimidazoles in the presence of methyllithium as base:[100]



In the reaction of 1,3-dithiane oxide anions with *N*-acylimidazoles the optimum procedure involved a sodium hexamethyldisilazide/butyllithium mixture as base:[101]

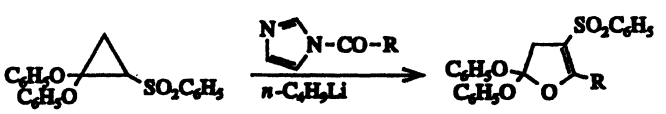


85%

Treatment of arylmagnesium bromides with *N,N'*-sulfinyldiimidazole yields diarylsulfoxides:[102],[103]

60%

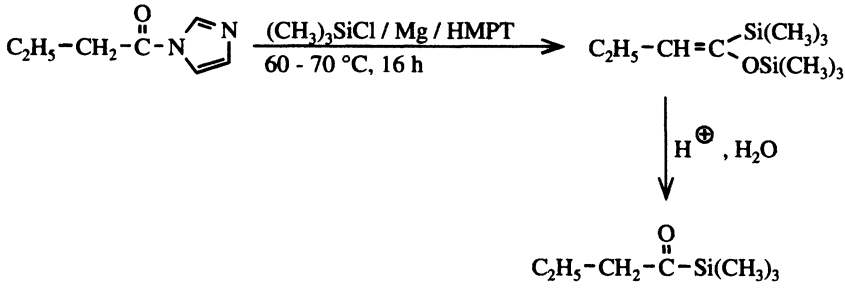
Acylation with imidazolides of a cyclopropane-CH activated by a phenylsulfonyl group proceeded under ring-enlargement to give a dihydrofuran system:[103a]



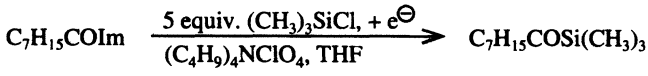
R = C_6H_5, 90%
R = *tert*-C_4H_9, 67%

14.10 Acylsilanes and Electroreductive Acylations

a) Enoxysilanes can be prepared in moderate yield (30–35%) from azolides, trimethylsilylchloride and magnesium to give, after acid hydrolysis, the corresponding acylsilanes.[104]



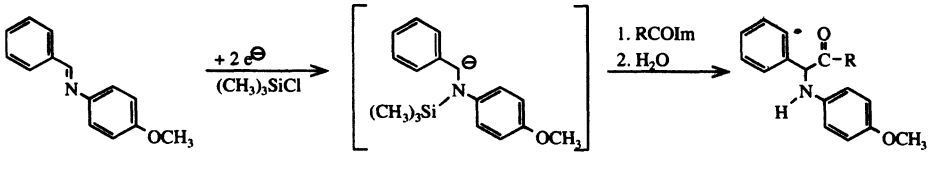
b) A similar synthesis of acylsilanes is achieved by employing electrochemistry instead of a metal:[105]



For the reaction mechanism see reference [105].

If cinnamic acid imidazolide is introduced into this reaction, the double bond of the corresponding acylsilane is reduced as well.[105]

c) The electroreductive acylation of aromatic imines by means of imidazolides leads to α-aminoketones or α-aminoesters. The reaction proceeds inter- and intramolecularly in the presence of trimethylchlorosilane as trapping agent.[106]



R	Yield (%)
iso-C_3H_7	60
OCH_3	62

14.11 Formylation of Metal Carbonyl Complexes

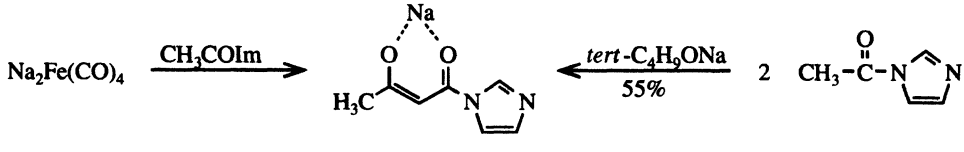
Azolides are also capable to acylate anionic metal carbonyl compounds. For instance, disodium tetracarbonylferrate as well as the corresponding ruthenium and osmium compounds can be formylated with formylimidazole in the presence of boric acid methyl ester:

$$Na_2Fe(CO)_4 \xrightarrow[HMPA]{HCOIm\,/\,(CH_3O)_3B\ (1:2)} NaFe(CHO)(CO)_4$$

80%

The imidazolide and the catalyst are combined in a molar ratio of 1 : 2. Without catalyst the formylation of $Na_2Fe(CO)_4$ yielded only $NaFeH(CO)_4$ and carbon monoxide quantitatively.[107]

A Lewis acid is also necessary for the acetylation of tetracarbonylferrate using *N*-acetylimidazole. In the absence of a Lewis acid, a Claisen-type condensation product was formed, which has been synthesized independently from 2 moles of *N*-acetylimidazole with sodium *tert*-butanolate in *tert*-butyl alcohol (55% yield) or with imidazole sodium in THF (95% yield):

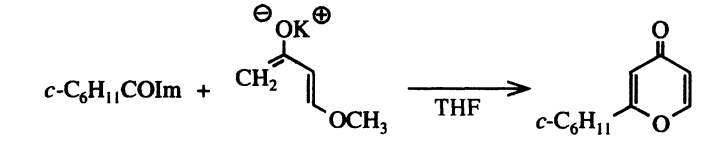


N-Pivaloyl- and *N*-benzoylimidazole, however, acylate $Na_2Fe_3(CO)_4$ both in the presence and in the absence of a Lewis acid, but the reaction takes place at a higher rate in the presence of the Lewis acid, which increases the susceptibility of *N*-acylimidazole to nucleophilic attack.[107]

14.12 Synthesis of γ-Pyrones, Lactones, 3(2*H*)-Furanones, and γ-Pyridones

γ-Pyrones, lactones, 3(2*H*)-furanones, and γ-pyridones can be synthesized by C-acylation of enolates with acylimidazoles, CDI, and oxalyldiimidazole, respectively, and subsequent cyclization; α-pyrones and isoflavones are formed by acylation of an activated CH_2-group without use of a base, followed by cyclization.

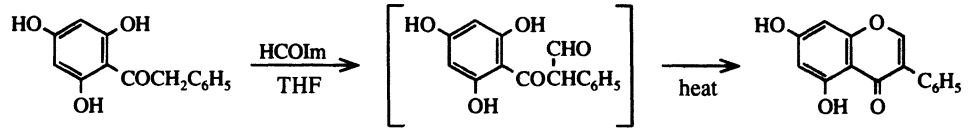
Synthesis of γ-Pyrones

a) 

60% [108]

If c-$C_6H_{11}COCl$ is used instead of the imidazolide, the yield of the γ-pyrone is only 23%.[108] For an analogous reaction see also reference [109].

b) In the formylation of benzyl 2,4,6-trihydroxyphenyl ketone to give an isoflavone, a β-ketoaldehyde has been proposed as an intermediate.[110]



76%

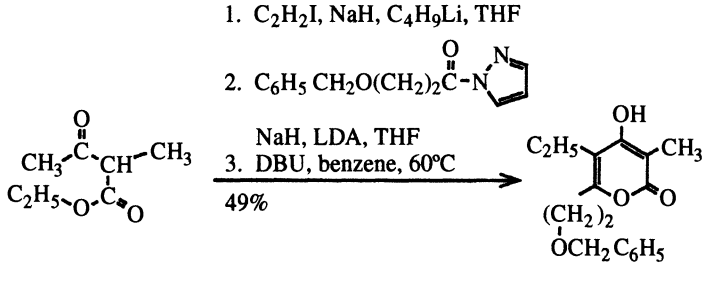
This reaction did not require protection of hydroxyl groups.

Synthesis of α-Pyrones, 5(2*H*)-Furanones and Other Lactones

A kind of Claisen condensation via the imidazolide of a monoester of acetone dicarboxylic acid with subsequent lactonization to give an α-pyrone is described in reference [39]. Only with the *tert*-butyl ester the yield of α-pyrone was high.

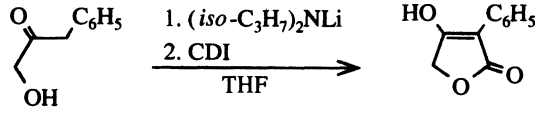
R = *tert*-C_4H_9, 92%; CH_3, 16%

Another synthesis of an α-pyrone is achieved by reaction of an acetoacetate with a pyrazolide:[110a]



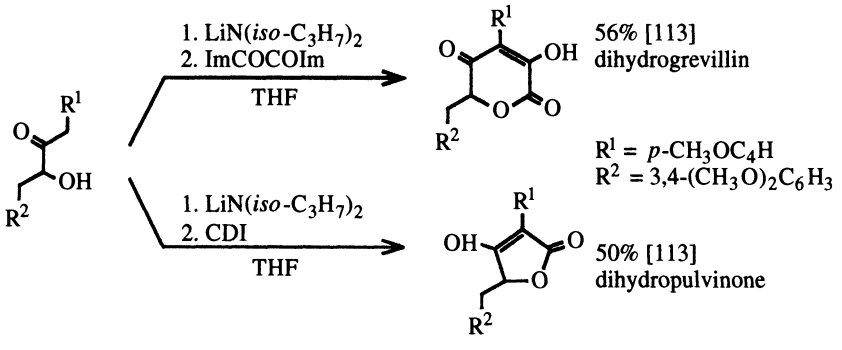
In the following reactions involving CDI and a base like lithium diisopropylamide, a C=O group is formally inserted between a hydroxy- and a CH-function of an α-hydroxyketone leading to 5(2*H*) furanones and other lactones; using *N,N'*-oxalyldiimidazole the oxalyl group –CO–CO– is inserted. Keying synthetic operations of this manner provides easy access to tetronic acids (a), to fungus pigments grevillin and pulvinone (b), to an enollactone intermediate in the total synthesis of the antibiotic (+)-actinobilin (c) and to the antibacterial 3-methoxy-2-isooxacephem (d).

a)

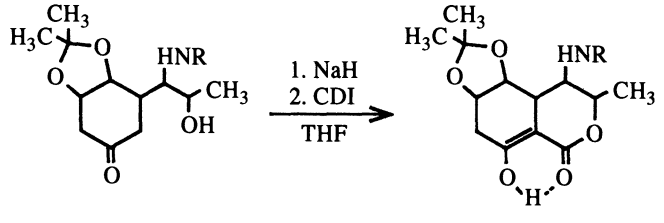


57% [111]

b)



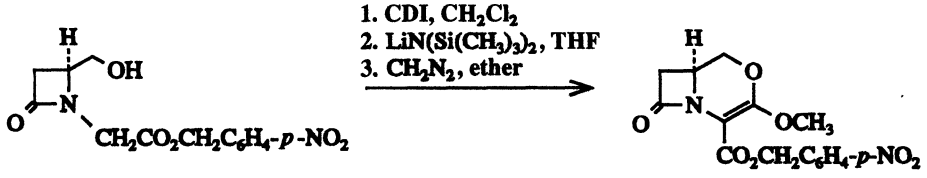
c)



R = p-$CH_3C_6H_4CH_2SO_2$

80% [112]

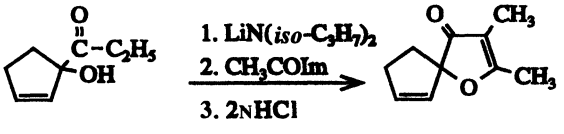
d)



64% [21]

Synthesis of 3(2*H*)-Furanones

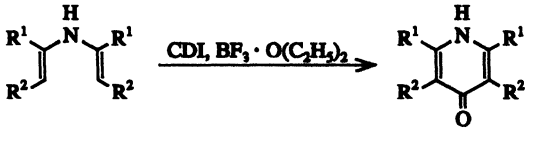
A key step in the approach to 3(2*H*)-furanone ring systems via the acid-catalyzed cyclization-dehydration of appropriately substituted α'-hydroxy-1,3-diketones involves the acylation of α-hydroxy-ketone dianions:[114]



76% [114]

Synthesis of γ-Pyridones

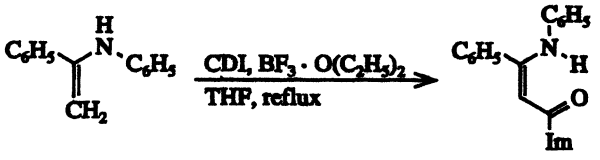
γ-Pyridones can be synthesized by reaction of 2-dieneamines with CDI, thereby inserting the CO group between two carbon atoms. The reaction takes place in the presence of $BF_3O(C_2H_5)_2$.[115]



R^1	R^2	Yield (%)
C_6H_5	CH_3	80
$c\text{-}C_6H_{11}$	CH_3	75
C_6H_5	$CH_2{=}CH(CH_2)_2$	87

With ImCSIm a corresponding reaction did not proceed.[115]

In the reaction of an enamine with CDI, β-enaminocarbonylimidazoles are obtained:[115a]

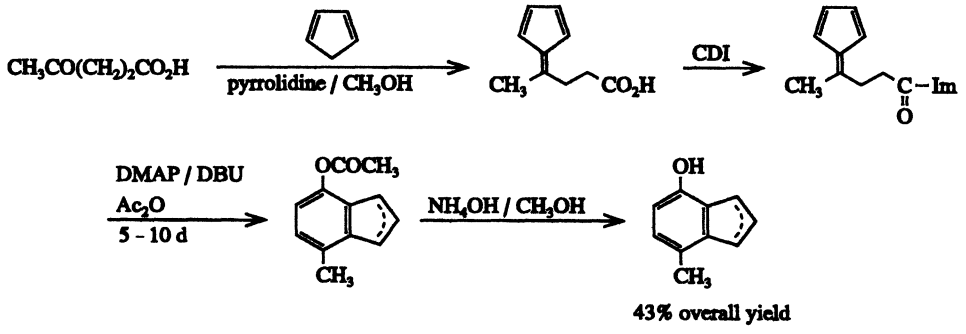


84%

14.13 Syntheses of Isocyclic Compounds

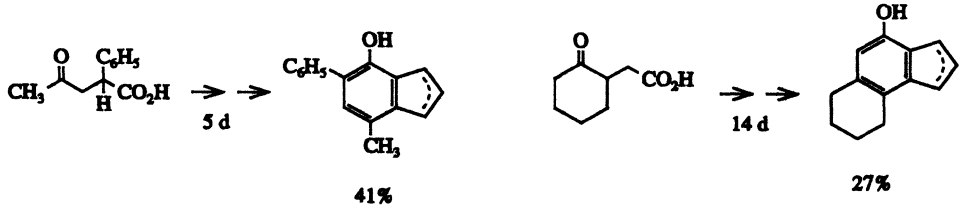
Indenes

The key step in the following synthesis of indenes by the azolide method is an intramolecular C-acylation of a fulvene intermediate. The added dimethylaminopyridine (DMAP) was thought to act as an acyltransfer agent, and diazabicycloundecene (DBU) as cyclization initiator via fulvene deprotonation:[116]



43% overall yield

This cyclocondensation reaction has also been examined with substituted levulinic acids:



41%

27%

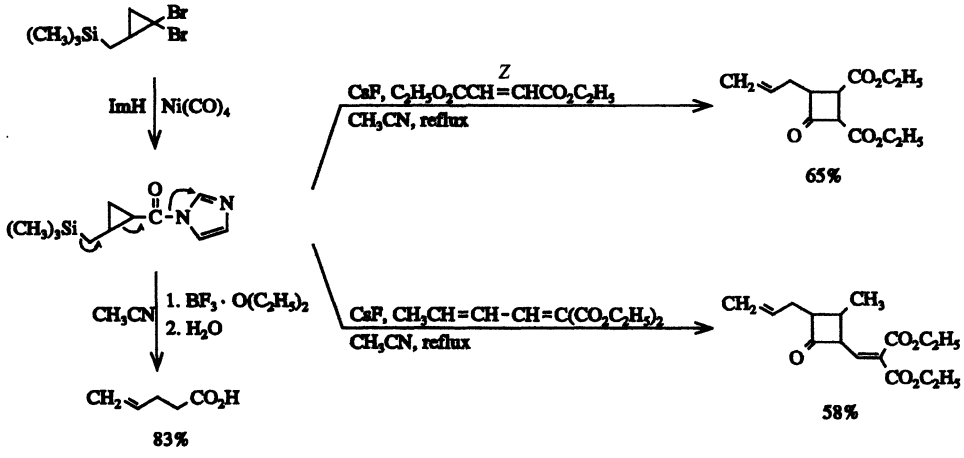
The ease of the synthesis makes this a valuable general method for the preparation of a variety of indenes despite moderate yields and prolonged reaction times.[116]

Cyclobutane and Benzene Rings

Substituted cyclobutanes or benzene rings are formed by the reaction of imidazolides with suitable double-bond systems.

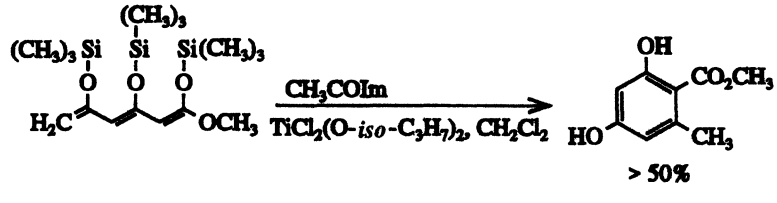
a) Synthesis of cyclobutanone rings

As starting material for the formation of a cyclobutanone ring, a silylated cyclopropylcarboxylic acid imidazolide was prepared in high yield by a $Ni(CO)_4$-induced reductive carbonylation of 1,1-dibromocyclopropane with imidazole. The success of this selective transformation into a cyclobutanone ring depends on the presence of the imidazolide moiety, the trimethylsilyl group, fluoride-containing reagents, and the solvent acetonitrile. A ketene is presumably formed as an intermediate after fragmentation of the cyclopropyl carboxylic imidazolide, because subsequent hydrolysis yields the corresponding carboxylic acid.[117]

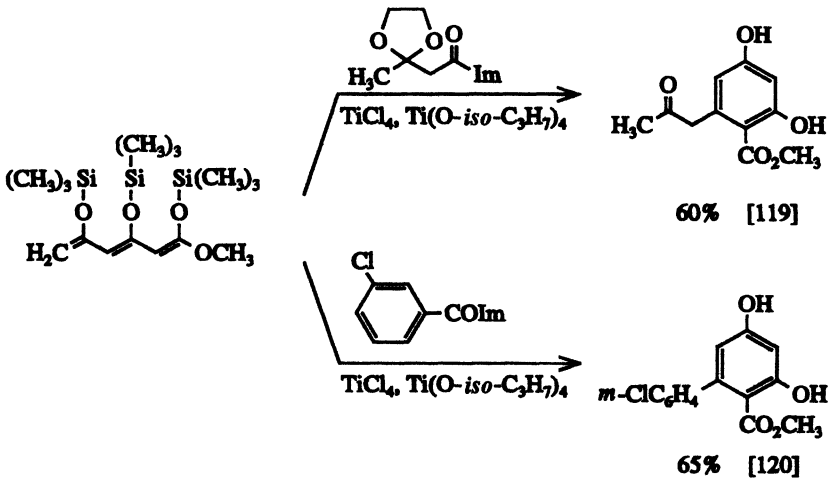


b) Synthesis of benzene rings

Tris(trimethylsiloxy)-methoxy hexatriene undergoes with aliphatic imidazolides in the presence of a Lewis acid a 5C + 1C cyclocondensation reaction leading to aromatic products:[118]



If CDI is employed as imidazolide, methyl 2,4,6-trihydroxybenzoate is obtained in 47% yield. Propionyl-1,2,4-triazole behaves in the same way as the imidazolides, giving similar yields (50%), but the benzotriazolides and benzimidazolides were not as effective. The *o*-nitrophenyl and *p*-chlorophenyl esters of propionic acid did not lead to any aromatic products.[118] Similar 5C + 1C condensation reactions are described in references [119] and [120].



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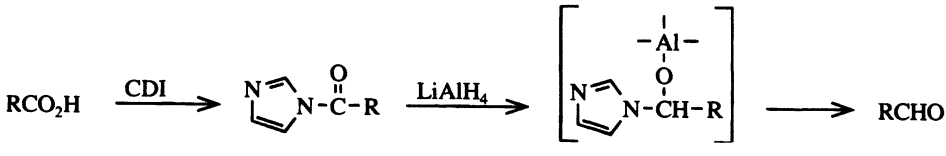
15 Reduction of Azolides to Aldehydes and Alcohols

Aldehydes from Carboxylic Acids via Imidazolides

N-Acylimidazoles are easily reduced to the corresponding aldehydes with $LiAlH_4$ in THF or ether as solvent.[1] Thus, aliphatic, conjugated aliphatic, aromatic, conjugated aromatic, and heteroaromatic aldehydes can all be obtained in this way in moderate to high yields.



Reductions are usually carried out with from 0.25 mole to more than 1 mole of $LiAlH_4$ per mole of imidazolide, and from $-20\,^{\circ}C$ up to room temperature for 30 to 60 min (Method a). The reaction from carboxylic acid to an aldehyde can also be conducted as a one-pot procedure (Method b).[1] However, in this case an additional 0.25 mole of $LiAlH_4$ is required, because the imidazolide solution resulting from the *N*,*N*′-carbonyldiimidazole (CDI) reaction with the carboxylic acid, contains 1 mole of active-hydrogen-containing imidazole per mole of imidazolide. Diimidazolides of dicarboxylic acids give dialdehydes. Imidazolides of mono esters of dicarboxylic acids yield mono ester aldehydes.[1] *N*-acylamino acid imidazolides can be converted into *N*-acylamino aldehydes in good yield and with high optical purity.[2] From *N*-protected (Boc or *Z* group) amino-acid imidazolides the corresponding amino aldehydes are obtained without attack on the protecting group. The reduction can also be carried out in the presence of an α,β-carbonyl, ester, or lactone group. Thus, the high reactivity of the imidazolide group permits it to be reduced selectively with $LiAlH_4$. Hydroxycarboxylic acids with unprotected hydroxyl groups have also been reduced to hydroxyaldehydes by this one-pot procedure, although in only moderate yields. For example, mandelic acid gave mandelaldehyde in 33.5% yield.[1] Instead of $LiAlH_4$, $Li[(tert\text{-}C_4H_9O)_3AlH]$ and $(iso\text{-}C_4H_9)_2AlH$ were also used as reducing agents. The preparation of aldehydes with isotopes in the formyl group (e.g., $-^{13}CHO$ or –CDO) via imidazolides is described in ref. [3] and [4], respectively.

Sometimes, along with the aldehyde, the corresponding alcohol has been obtained as a by-product.[2],[5],[6] In Ref. [5] an alcohol of this type was oxidized back to the aldehyde, thus enhancing the aldehyde yield.

Table 15–1. Aldehydes from carboxylic acids via imidazolides (method a: from isolated imidazolides; method b: via imidazolides prepared in situ).

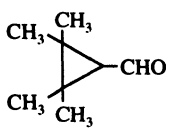
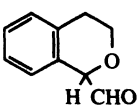
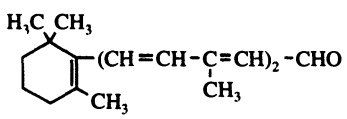
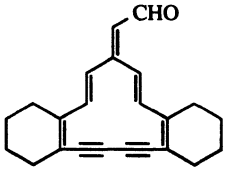
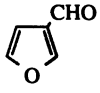
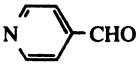
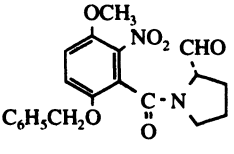
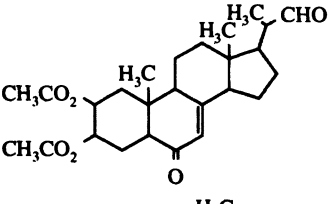
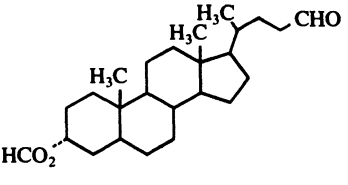
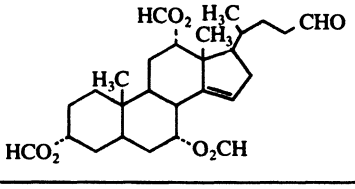
Aldehyde	Complex hydride	Method a/b	Yield (%)	Ref.
$CH_3(CH_2)_2CHO$	$LiAlH_4$	a	60	[1]
$CH_3(CH_2)_{14}CHO$	$LiAlH_4$	a	84	[1]
$(CH_3)_2CHCDO$	$LiAlD_4$	a	50	[4]
$CH_3O_2C(CH_2)_4CHO$	$LiAlH_4$	a	71	[1]
	$LiAlH_4$	b	59	[1]
$CH_2=CHCH(C_2H_5)CH_2CHO$	$LiAlH_4$	a	96	[7]
$Cl(CH_2)_2C(CH_3)_2CHO$	$LiAlH_4$	a	51	[8]
$C_6H_5CH_2CHO$	(*iso*-$C_4H_9)_2AlH$	b	83	[2]
$C_2H_5CH(C_6H_5)CHO$	$LiAlH_4$	a	50	[9]
$C_6H_5CH(OH)CHO$	$LiAlH_4$	b	34	[1]
$OHC(CH_2)_4CHO$	$LiAlH_4$	a	65	[1]
	$LiAlH_4$	b	39	[9a]
	(*iso*-$C_4H_9)_2AlH$	b	72	[10]
(S)-*iso*-$C_4H_9CH(NH\text{-Boc})CHO$	$LiAlH_4$	b	82	[11]
$C_6H_5CH_2CH(NH\text{-Z})CHO$	(*iso*-$C_4H_9)_2AlH$	b	70	[2]
$NO_2NHC(=NH)NH(CH_2)_3CH(NH\text{-Z})CHO$	$LiAlH_4$	b	70	[12]
	$LiAlH_4$	a	68	[1]
	$LiAlH_4$	b	56	[1]
C_6H_5CHO	$LiAlH_4$	a	78	[1]
	$LiAlH_4$	b	83	[1]
$C_6H_5{}^{13}CHO$	$LiAlH_4$	a / b	—	[3]
p-$CH_3C_6H_4CHO$	$LiAlH_4$	a	79	[1]
p-(*tert*-$C_4H_9)C_6H_4CHO$	$LiAlH_4$	a	76	[1]
	$LiAlH_4$	b	67	[1]
p-$CH_3OC_6H_4CHO$	$LiAlH_4$	a	79	[1]
p-$NO_2C_6H_4CHO$	$LiAlH_4$	a	88	[1]

Table 15–1. (*continued*)

Aldehyde	Complex	Method a/b	Yield (%)	Ref.
p-$CH_3CO_2C_6H_4CHO$	$LiAlH_4$	a	71	[1]
$C_6H_5CH{=}CHCHO$	$LiAlH_4$	a	70	[1]
	(*iso*-$C_4H_9)_2AlH$	b	60	[2]
	Li[(*tert*-$C_4H_9O)_3AlH$]	a	61	[5]
	$LiAlH_4$	b	38	[13]
	$LiAlH_4$	a	82	[1]
	$LiAlH_4$	b	92	[14]
	Li[(*tert*-$C_4H_9O)_3AlH$]	a	50	[15]
	Li[(*tert*-$C_4H_9O)_3AlH$]	a	72	[6]
	Li[(*tert*-$C_4H_9O)_3AlH$]	a	46	[16]

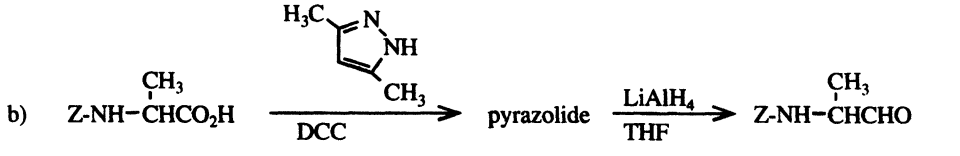
Furher syntheses of aldehydes via imidazolides are described in references [17]–[27].

Aldehydes from Triazolides and Pyrazolides, and Subsequent Reactions

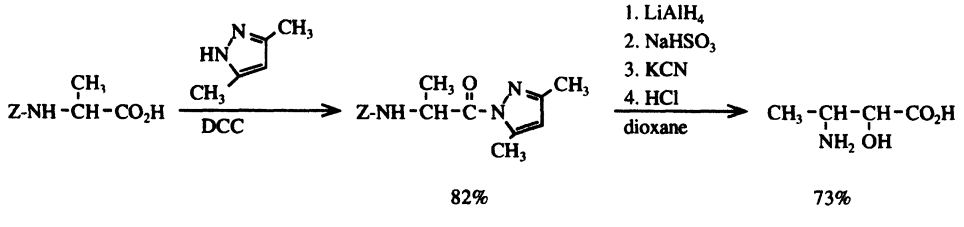
In analogy to imidazolides, both triazolides and pyrazolides have been converted into aldehydes by reduction with $LiAlH_4$:

c) The following example illustrates a cascade reaction of an *N*-protected amino acid

a) 

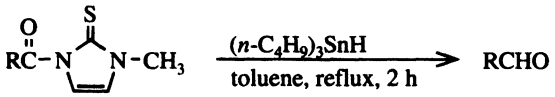
b) 

(via its pyrazolide as aldehyde precursor) into a 3-amino-2-hydroxybutanoic acid.[31]



Aldehydes from 1-Acyl-3-methylimidazole-2-thiones

A related convenient and mild method for the preparation of aliphatic and aromatic aldehydes in high yield from carboxylic acids is the reductive cleavage of 1-acyl-3-methylimidazole-2-thiones by tributylstannane.



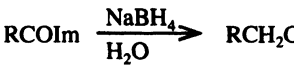
R	Yield (%)
$C_{17}H_{35}$	82
c-C_6H_{11}	94
C_6H_5	99
p-$NO_2C_6H_4$	80

The 1-acyl-3-methylimidazole-2-thiones are easily obtained either from bis-1-methyl-2-imidazole disulfide, a carboxylic acid, and triphenylphosphine, or from 2-mercapto-1-methylimidazole and a carboxylic acid chloride in the presence of triethylamine.[32]

Reduction of Azolides to Alcohols

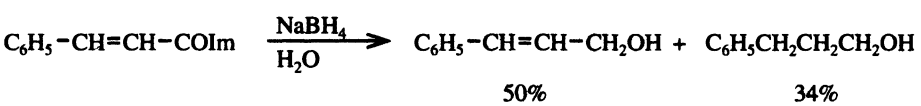
A selective, mild, and facile reduction of aromatic and aliphatic carboxylic acid imidazolides to primary alcohols is described in reference [33]. The reaction proceeds in water, water/dioxane or water/tetrahydrofuran solution at room temperature with 2–5 molar equivalents of $NaBH_4$ in about 1 h.

A variety of other functional groups such as halogen, nitro, cyano, ester, amide, and isolated double bonds are not attacked under these conditions:

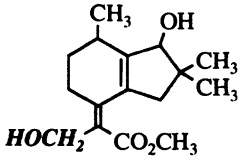


R	Yield (%)
C_6H_5	85
p-$NO_2C_6H_4$	81
m-CNC_6H_4	80
$C_8H_{17}CH{=}CH(CH_2)_7$	71
$C_{13}H_{17}$	93

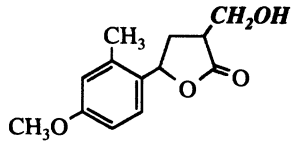
However, conjugated double bonds may also be reduced to some extent:



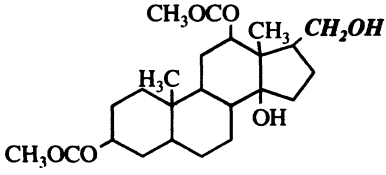
The presence of water is essential for the success of these reductions. In anhydrous THF, for example, treatment of *N*-benzoylimidazole with $NaBH_4$ leads to benzyl benzoate as the main product (73%), along with 19% benzyl alcohol.[33] Other reports, however, describe the conversion of carboxylic acid imidazolides to the corresponding alcohols by complex hydrides in organic solvents. Further alcohols have been synthesized via imidazolides:



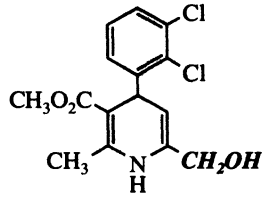
55%, with $LiBH_4$ in THF [34]



> 45%, with $Zn(BH_4)_2$ in dimethoxyethane [35]



96%, with $NaBH_4$ in THF [36]



61%, with $LiAlH_4$ then $NaBH_4$ / CH_3OH [37]

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16 Deoxygenation of Alcohols and C–C Coupling Reactions

16.1 Deoxygenation of Alcohols

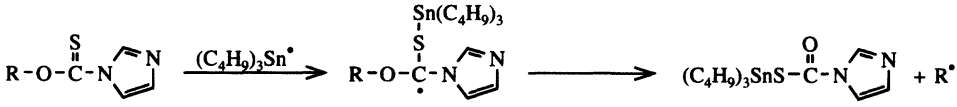
Imidazole-*N*-thionocarboxylates (also called "thiocarbonylimidazolides") are intermediates in a convenient radical-induced deoxygenation of primary and secondary alcohols with tributylstannane (Barton reaction).[1],[2]

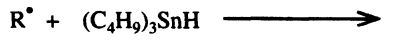
$$ROH \xrightarrow[THF]{ImCSIm} RO{-}\overset{\overset{S}{\|}}{C}{-}Im \xrightarrow[toluene,\ reflux]{(C_4H_9)_3SnH} RH$$

The imidazole-N-thionocarboxylates are easily prepared in high yield from alcohols and *N,N'*-thiocarbonyldiimidazole (ImCSIm) (in THF, CH_2Cl_2, 1,2-dichloroethane, or DMF as solvent, or without solvent simply by grinding[2a]).Treatment with tributyl or triphenyl stannane in refluxing toluene or xylene leads to the reduced product. Improved yields are generally obtained by use of $(C_4H_9)_3SnH$ instead of $(C_6H_5)_3SnH$. In most cases catalytic amounts of 2,2'-azoisobutyric nitrile (AIBN) are added in the second step. Yields by this azolide method are often better than those by the xanthate ester (dithiocarbonic ester) method.[2]

Typical examples of deoxygenation are collected in Table 16–1.

Reaction mechanism:[2]





Selectivity could be accomplished by this method in deoxygenation of primary and secondary alcohol groups,[2] as well as effective deoxygenation of hindered secondary hydroxyl groups, especially in the carbohydrate series.[3]

Analogous deoxygenations were carried out with antibiotics such as nargenicin,[42] fortimicin,[43] seldomycin,[44] erythromycin,[45]–[47] with baccatin (taxol group),[48] the triquinane hirsuten,[49] the tuberculosis inhibitor α-C-mannobioside,[49a] and the steroids alisol,[50] and progesterone.[51]

Table 16–1. Reduction of alcohols with tri-*n*-butyl stannane via imidazole-*N*-thionocarboxylates to the corresponding deoxygenated products.

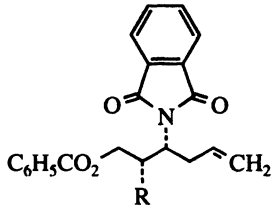
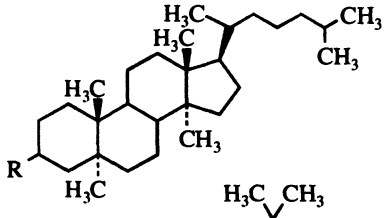
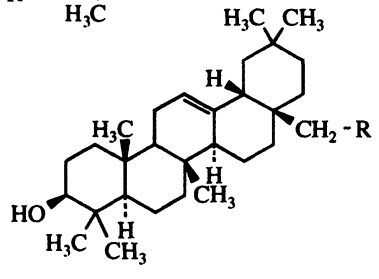
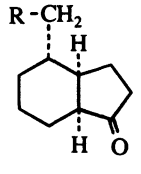
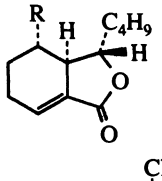
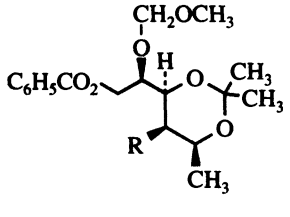
Alcohol, R=OH	Yield (%) imidazole-*N*-thiono-carboxylate, R=OCSIm	Yield (%) deoxygenated product, R=H	Ref.
	92	82	[4]
	90	79	[1]
	79	40	[2]
	95	79	[4a]
	–	68	[5]
	–	55	[6]

Table 16–1 (*continued*).

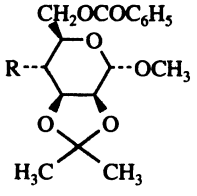
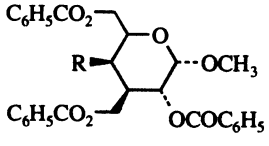
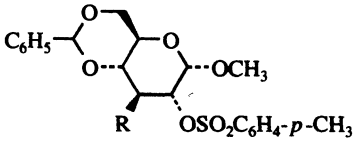
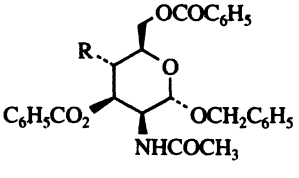
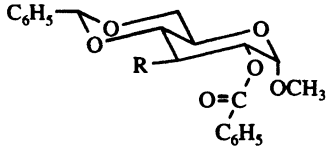
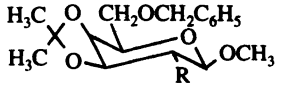
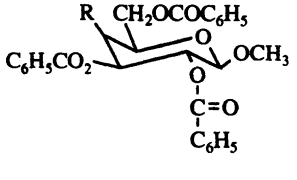
Alcohol, R=OH	Yield (%) imidazole-*N*-thiono-carboxylate, R=OCSIm	Yield (%) deoxygenated product, R=H	Ref.
	92	87	[7]
	94	92	[3]
	86	68	[3]
	85	80	[8]
	88	94	[9] see also [10]
	86	73	[11] see also [12]
	75	quant.	[11] see also [13]

Table 16–1 (*continued*).

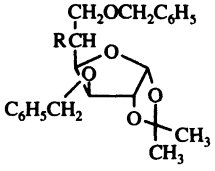
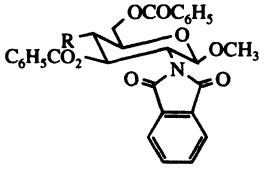
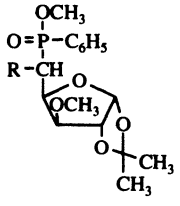
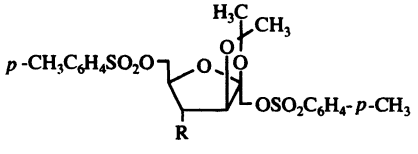
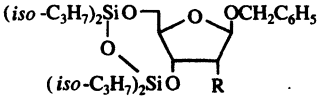
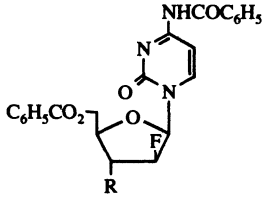
Alcohol, R=OH	Yield (%) imidazole-*N*-thiono-carboxylate, R=OCSIm	Yield (%) deoxygenated product, R=H	Ref.
	85	54	[14]
	quant.	87	[15]
	89	99	[16]
	98	85	[3]
	62	79	[17]
	78	87	[18]

Table 16–1 (*continued*).

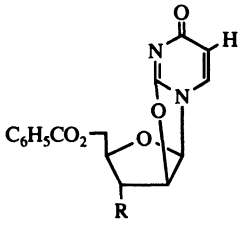
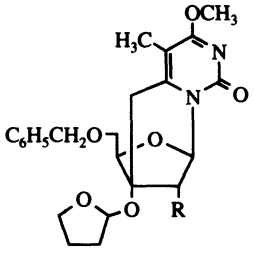
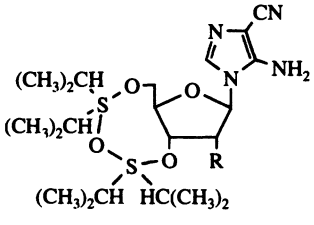
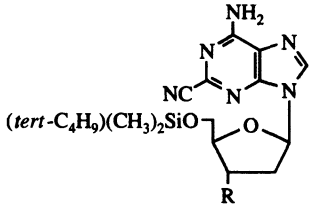
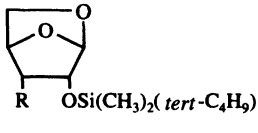
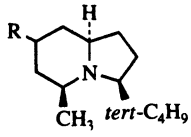
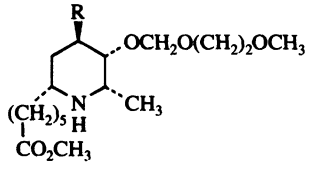
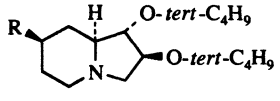
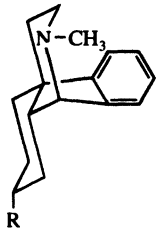
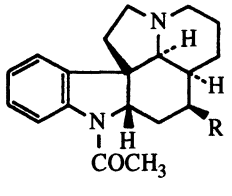
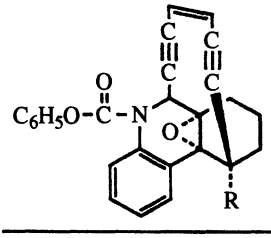
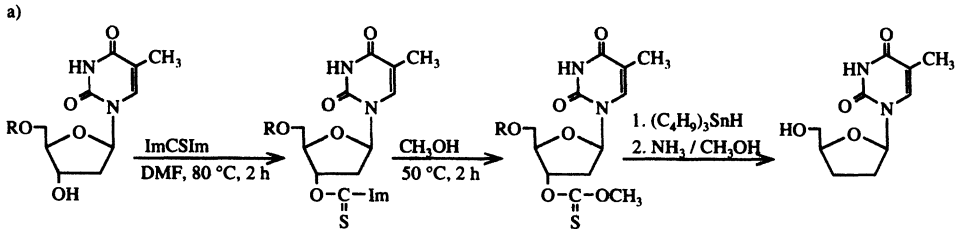
Alcohol, R=OH	Yield (%) imidazole-*N*-thiono-carboxylate, R=OCSIm	Yield (%) deoxygenated product, R=H	Ref.
	76	73	[19] see also [20]
	81	65	[21] see also [22]
	72	99	[23] see also [24]–[26]
	63	70	[27] see also [28]-[36]
	–	42	[37]

Table 16–1 (*continued*).

Alcohol, R=OH	Yield (%) imadazole-*N*-thiono-carboxylate, R=OCSIm	Yield (%) deoxygenated product, R=H	Ref.
	90	70	[38]
	–	93	[38a]
	99	68	[38b]
	81	63	[39]
	62	93	[40]
	95	86	[41]

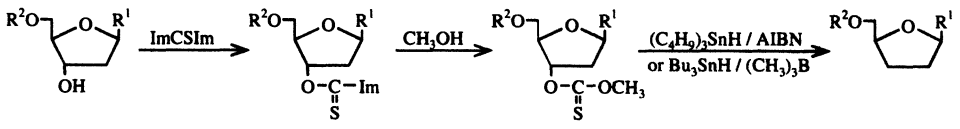
A modification of the azolide method for deoxygenation of alcohols is the conversion of the thiocarbonylimidazolide with methanol into the thionocarbonate, which is then treated with tri-*n*-butyl stannane/AIBN. Thus, 2,3-dideoxynucleosides (a), (b), and a secodeoxynucleoside (c) have been prepared as follows:[52]–[56]

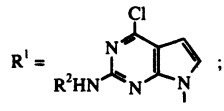
a)



R = CH_3CO 77% 90% [52]

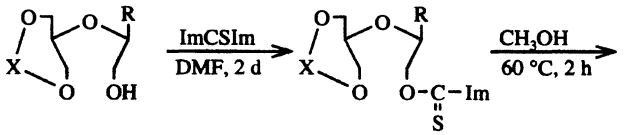
b)

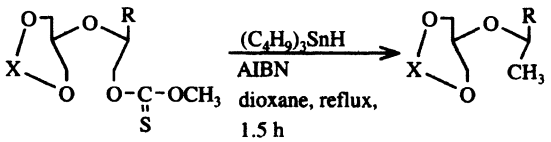




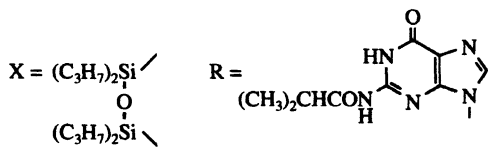
R^2 = *p*-$CH_3C_6H_4SO_2$ 75% 93% [53]
see also [54,55]

c)



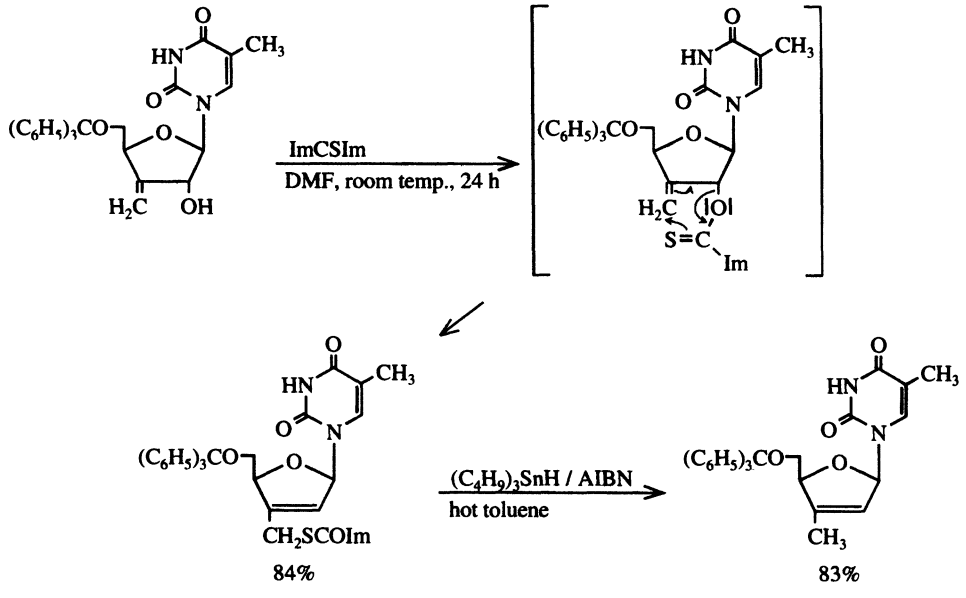


75% 57% [56]

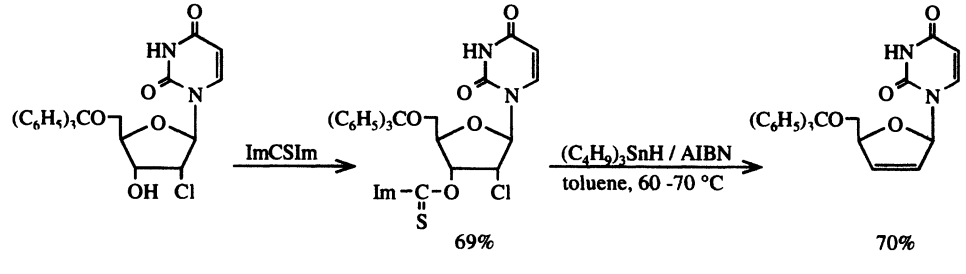


16.2 Deoxygenation of Alcohols with Concomitant Elimination or Rearrangement

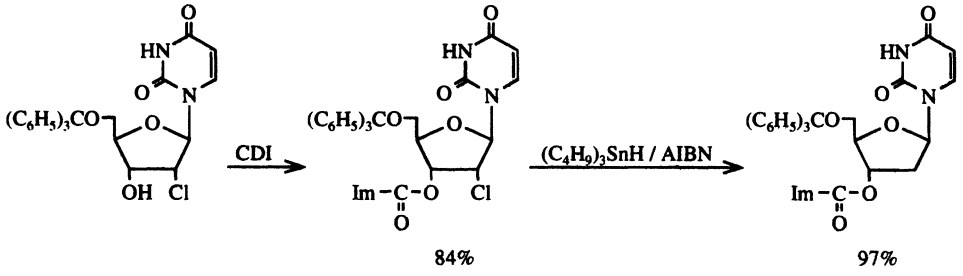
a) In the radical deoxygenation of an allyl alcohol system a rearrangement of the intermediate thiocarbonylimidazolide was observed, with successive migration of the double bond:[57]



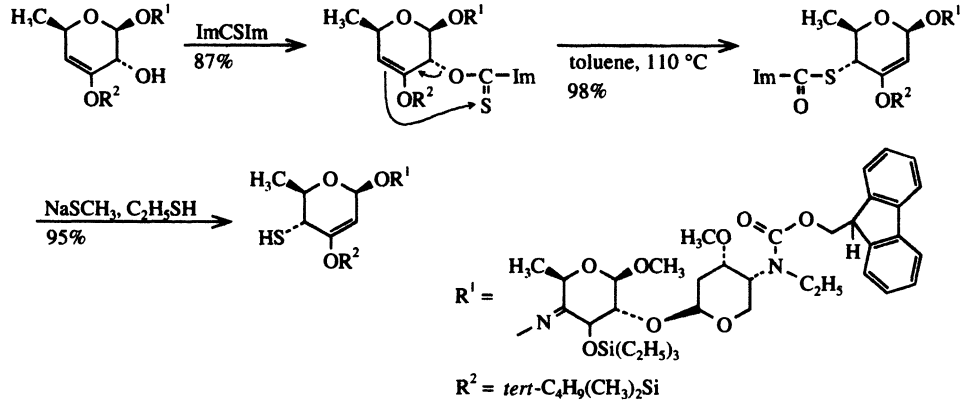
b) A deoxygenation with subsequent HCl elimination[58] occurred during radical deoxygenation with ImCSIm and tributyl stannane when a chlorine atom was vicinal to the hydroxy group.



With CDI instead of ImCSIm there was a dehalogenation, but no deoxygenation:

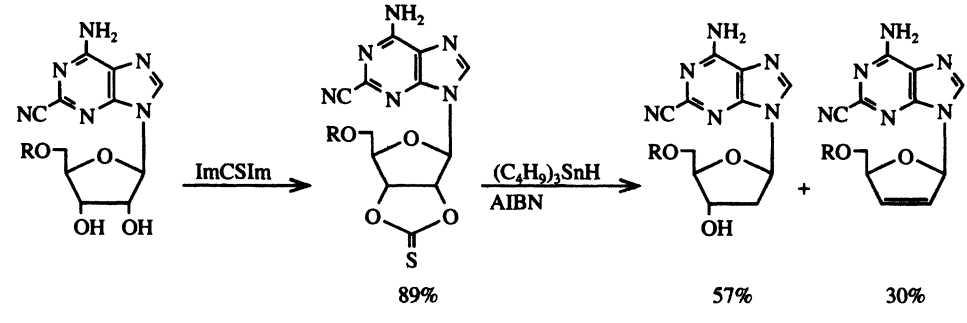


c) An example of a deoxygenation with simultaneous thiolation through a [3.3]-sigmatropic rearrangement of the thioimidazolide moiety is illustrated below;[59] see also reference [60].



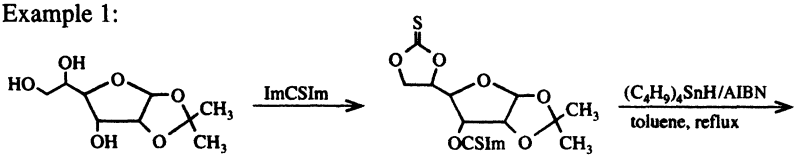
16.3 Deoxygenation of Di- and Trihydroxy Compounds

a) Deoxygenation of a cyclic thionocarbonate with tributyl stannane yields a mixture of a monohydroxy compound and an olefin.[28]

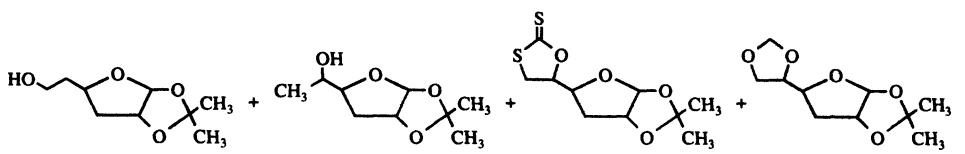


b) Deoxygenation of compounds containing three free hydroxy groups based on the ImCSIm/$(C_4H_9)_3SnH$ system are illustrated below.

Example 1:

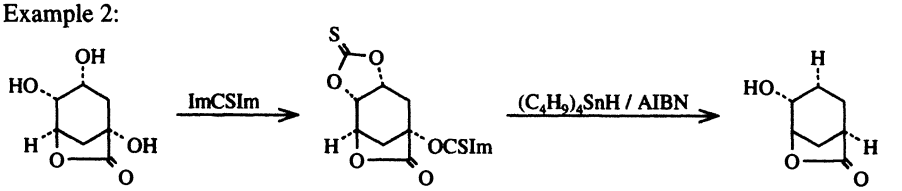


75%



41% 18% 9% 14% [61]

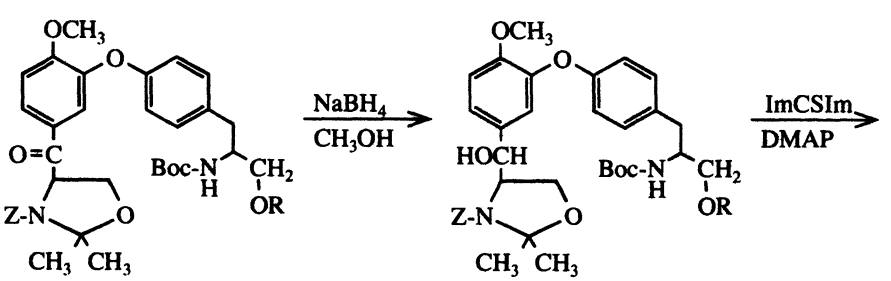
Example 2:



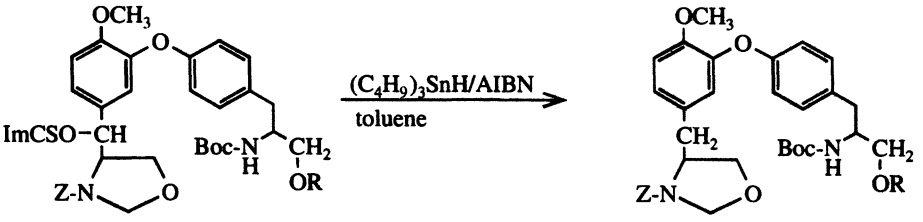
74% 43% [62]

For the conversion of a vicinal diol into an olefinic compound via a bisimidazolylsulfonate or a bisiodide see Chapter 21.

c) In the synthesis of differentially protected isodityrosinol, the transformation of a carbonyl group into a CH_2 group was accomplished by means of the azolide method according to the following route:[63]



93%



63% 96%

R = $Si(CH_3)_2$ *tert*-C_4H_9

16.4 Deoxygenation of α,β-Epoxy Alcohols with Concomitant Fragmentations

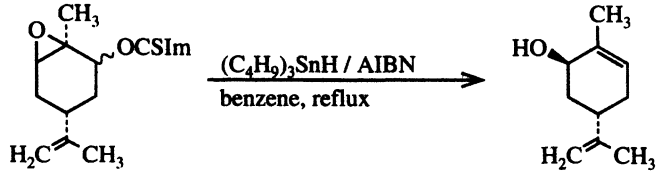
In these reactions, epoxide ring opening is achieved by an adjuvant carbon-centered radical generated during the conversion of a thioimidazolide moiety by a stannane. Carbon–oxygen bond cleavage leads to an alkoxy radical, which then undergoes hydrogen transfer and further rearrangement by cyclization or β-scission.[64]

Synthesis of Allyl Alcohols

α,β-Epoxyalcohols can be converted to allyl alcohols via thiocarbonylimidazolides and successive treatment with tri-*n*-butyl stannane. In this reaction the oxirane ring is opened, forming an allylic alkoxy radical, which is quenched by hydrogen transfer from the stannane.[65]

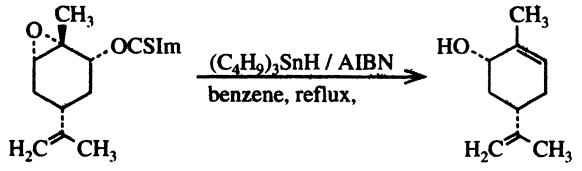
Examples:

a)



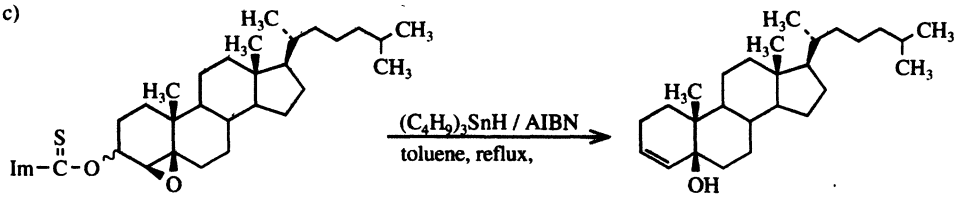
optically pure (+) - *trans* -carveol
isolated as 3,5-dinitrobenzoate ester
65%

b)



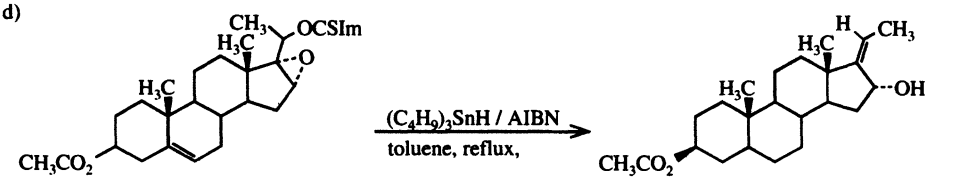
(+) -*cis*-carveol
isolated as 3,5-dinitrobenzoate ester
47%

c)



coprost-3-en-5β-ol
58%

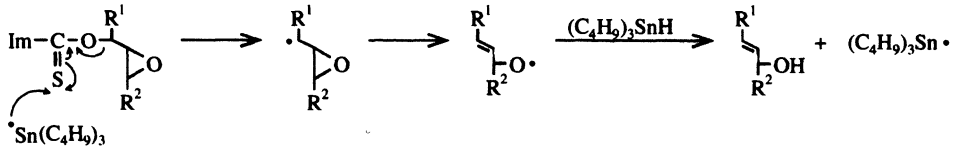
d)



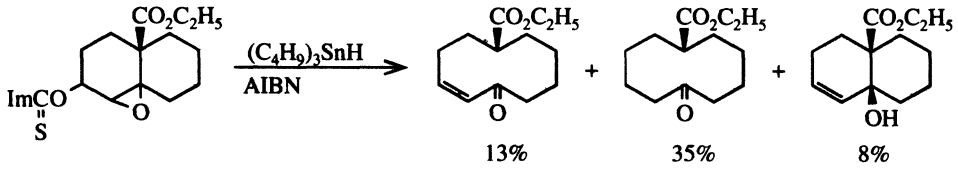
3β-acetoxypregna-15,17-diene-16α-ol
60%

In cases b)–d) it was necessary to add the imidazole-*N*-thionocarboxylate to the stannane (inverse addition).

For these reactions the following mechanism was assumed:

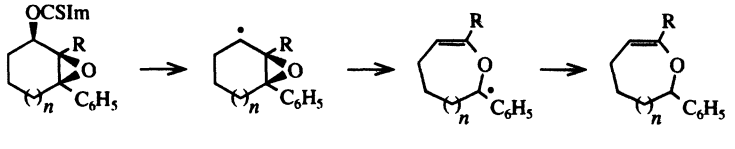


e) Ten-membered carbocycles, among other products, were obtained from epoxydecalin thiocarbonylimidazolides;[66] see also reference [64].



Synthesis of Cyclic Enol Ethers

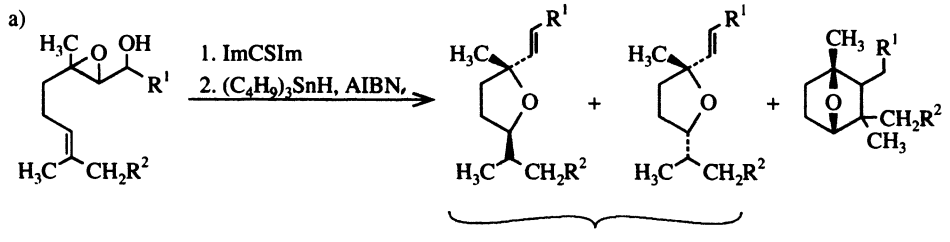
Seven- and eight-membered oxygen heterocycles can be obtained starting from epoxycyclohexane thiocarbonylimidazolides and $(C_4H_9)_3SnH$/AIBN.[66],[64]



R	n	Yield (%)
H	1	72
H	2	66
CH_3	1	58

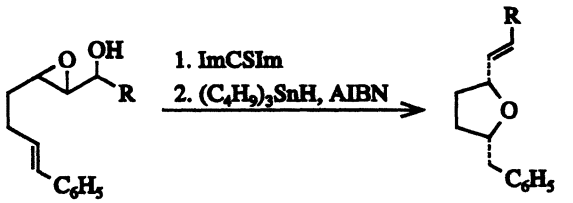
Synthesis of Vinylfurans

Vinylfurans can be formed from 2,3-epoxy-6-octenols via a C–O coupling reaction leading sometimes also to bicyclic ethers as by-product:[67]



$R^1 = H$	$R^2 = H$	14%	—
$R^1 = CH_3$	$R^2 = H$	59%	14%
$R^1 = C_4H_9$	$R^2 = H$	63%	22%
$R^1 = H$	$R^2 =$ *tert*-$C_4H_9(CH_3)_2SiO$	45%	—

b)

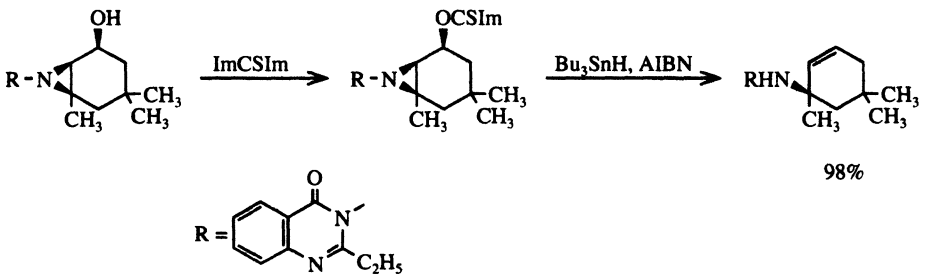


R = H, 65%; CH_3, 55%; C_4H_9, 82%

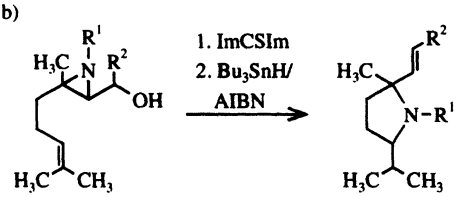
16.5 Deoxygenation of α,β-Aziridino Alcohols

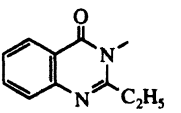
The radical-induced cleavage of α,β-aziridino alcohols proceeds in analogy to that of α,β-epoxyalcohols, leading regiospecifically to allyl amines (a). By successive reactions with double bond systems, pyrrolidines are formed (b):[68]

a)



b)



R^1	R^2	Yield (%)
	H	21 (70 *)
	C_4H_9	26 (83 *)

* in the presence of $MgBr_2 \cdot O(C_2H_5)_2$

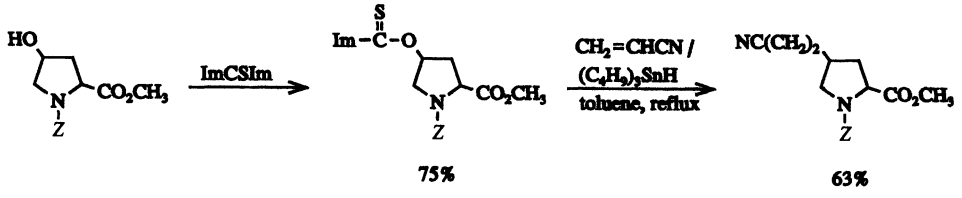
In the presence of magnesium bromide etherate, yields of the α-allylpyrrolidines could be considerably improved. If instead of the quinazolinone aziridine the phthalimido aziridine was selected, the reaction proceeded better in the absence of magnesium bromide.

Because the aziridine part of such a molecule can be obtained easily from a double bond system, these reactions constitute a method for converting allyl alcohols into allyl amines via aziridination.

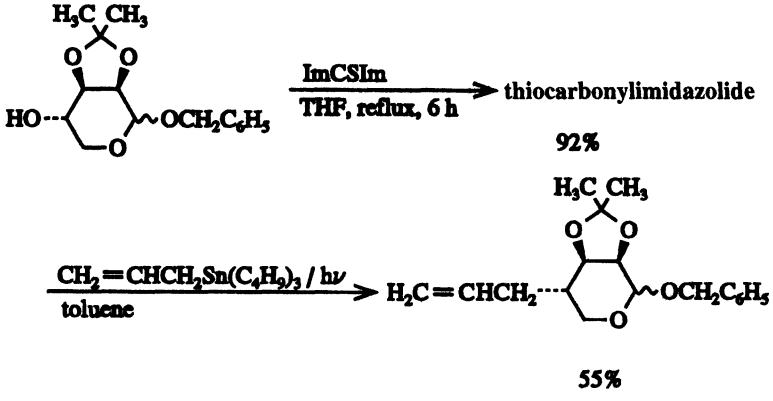
16.6 Deoxygenation Combined with C–C Coupling Reactions

Intermolecular C–C Coupling Reactions

a) This radical-induced reaction permits proline to be coupled with acrylonitrile taking 4-hydroxyproline as starting material.[69]



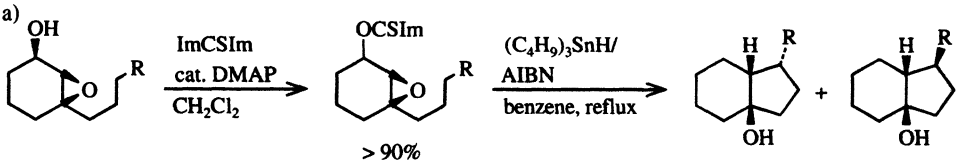
b) Photochemical treatment ($h\nu > 300$ nm) of an alkoxythiocarbonylimidazole (thiocarbonylimidazolide) derivative together with an allyl stannane resulted in substitution of the hydroxy group by an allyl group:[70]



Intramolecular C–C Coupling Reactions

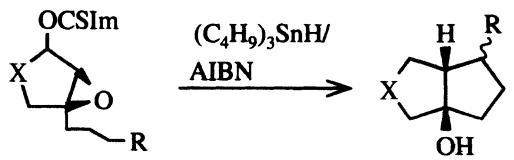
1. The following syntheses of five-membered carbocyclic systems involve radical-induced epoxide fragmentation with radical translocation and cyclization. The resulting bicyclic alcohols are formed as a mixture of two epimeric esters with *cis*-fused rings.[71]

a)



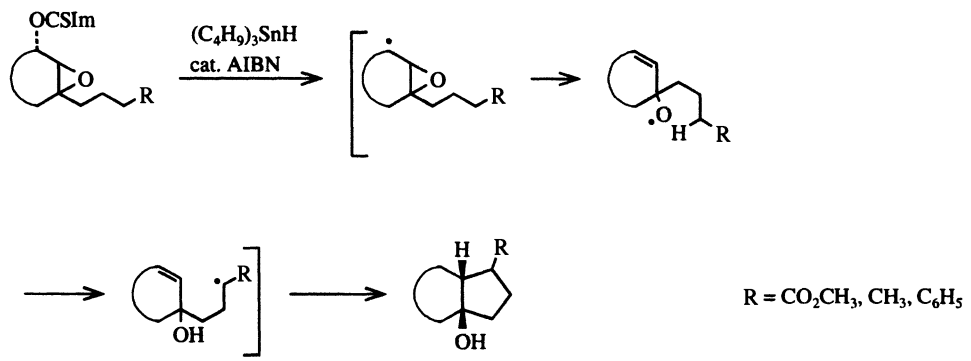
R	Yield (%)	Ratio
CO_2CH_3	69	1 : 2.7
CH_3	68	1 : 2.7
C_6H_5	47	1 : 2.7

b)



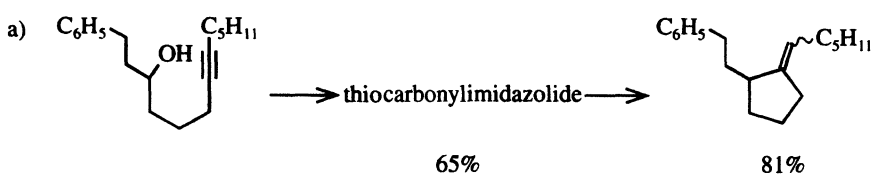
X	R	Yield (%)
CH_2	CH_3	52
$(CH_2)_3$	C_6H_5	58

A mechanism for these rearrangements has been suggested:[71]

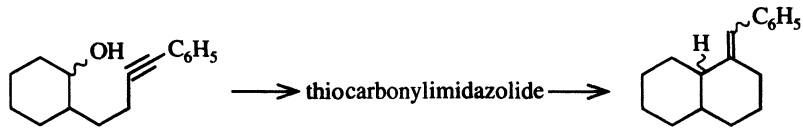


2. Intramolecular deoxygenation of alcohols containing double and triple bonds (such as hydroxyalkynes or hydroxynitriles) with ImCSIm leads via the corresponding thiocarbonylimidazolides to five- and six-membered cyclized systems with exocyclic double bonds.[72]

a)

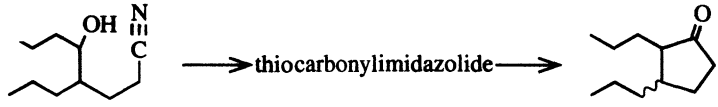


b)



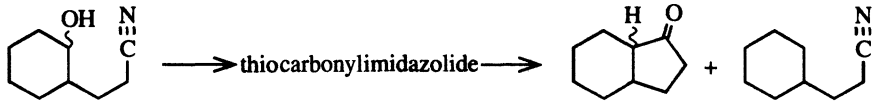
97% 79%

c)



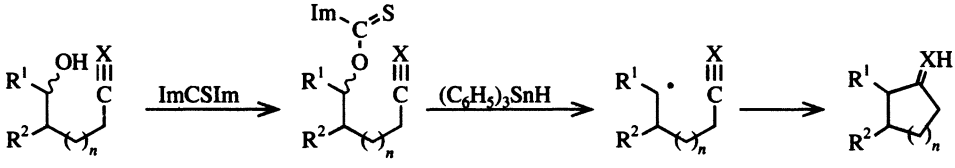
90% 73%

d)



99% 67% 11%

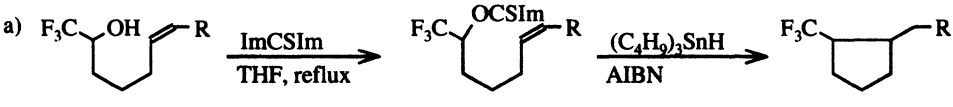
For these reactions the following mechanism is postulated:



X = CR^1 or N

3. Cycloalkanes can be synthesized from alcohols containing double-bond systems.

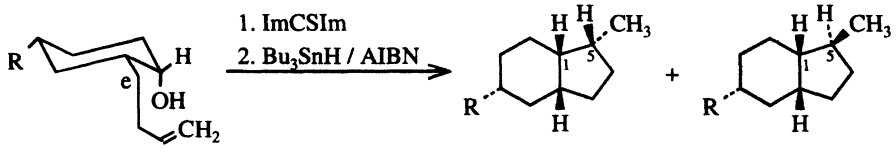
a)



quant.

R	Yield (%)	Ref.
C_9H_{19}	83	[73]
$C_6H_5OCCH_2$ (O)	81	[73]
C_6H_5	69	[73]

b)

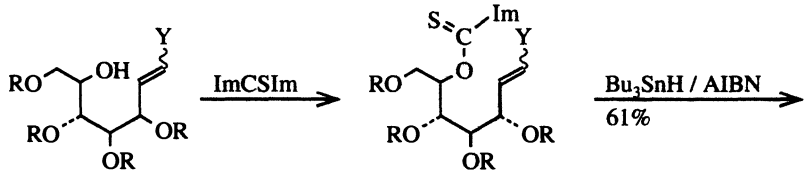


e = equatorial

R	Yield of cyclized compound (%)	Ratio of 1,5-*cis* to 1,5-*trans* product	Ref.
t-C_4H_9	29	8.2 : 1.1	[74]
C_6H_5	37	8.0 : 1.3	[74]

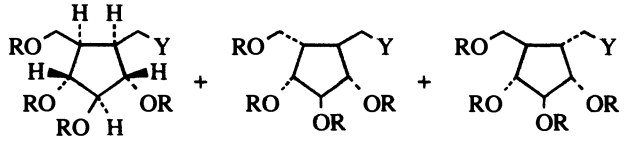
The reaction with 1-but-3-enyl in the axial position has been investigated as well.

c)



99%

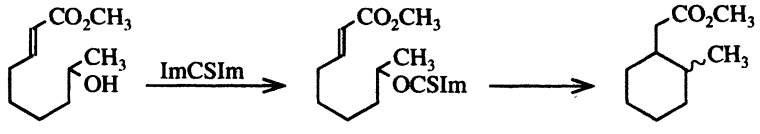
(Y = H, R = $C_6H_5CH_2$)



7.4 : 1.4 : 1.2

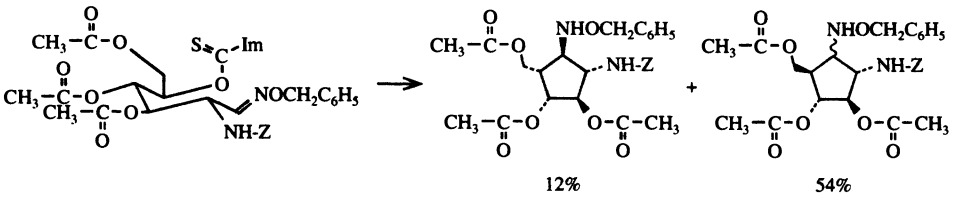
Moreover, the reaction with Y = OCH_3 and the stereochemical control of analogous hex-5-enyl radical cyclizations has also been studied. This method constitutes part of a synthetic route from carbohydrates to optically active carbocycles.[74],[75]

d)

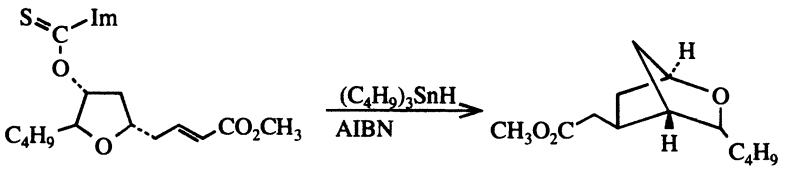


77% 65% [76]

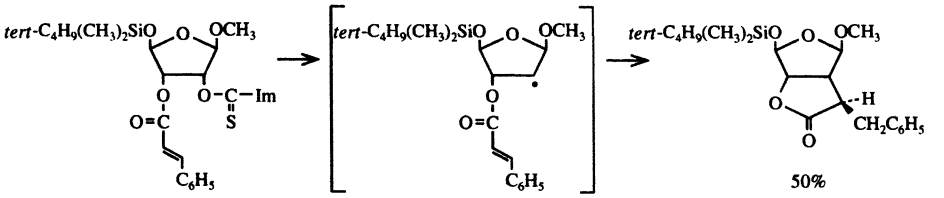
e) In the following reaction a mixture of diastereomeric five-membered diamino compounds from sugar precursors is obtained:[77]



f) A synthesis of 2-oxabicyclo[2.2.1]heptanes can be approached by this method starting from 3-hydroxyfurans:[78]



g) Another possibility is the synthesis of fused γ-butyrolactones of carbohydrates.[79]

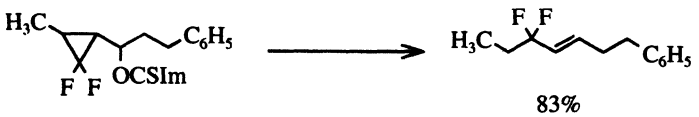


Analogous conversions of the corresponding uridine compound affords the γ-lactone in 35% yield.

16.7 Deoxygenation with Concomitant Opening of a Cyclopropane Ring

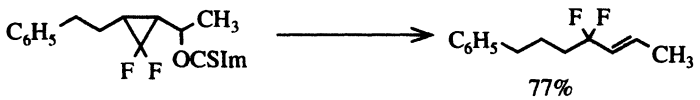
The thiocarbonylimidazolides shown on next page have been prepared in good yield from the corresponding alcohols and ImCSIm.[80] Ring opening occurs upon treating the azolides with tributyl stannane/AIBN in refluxing benzene, leading to (*E*)-difluoroallylic systems:

a)



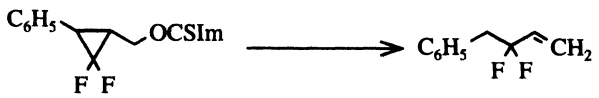
83%

b)



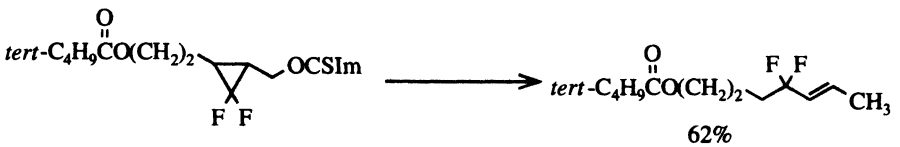
77%

c)



45%

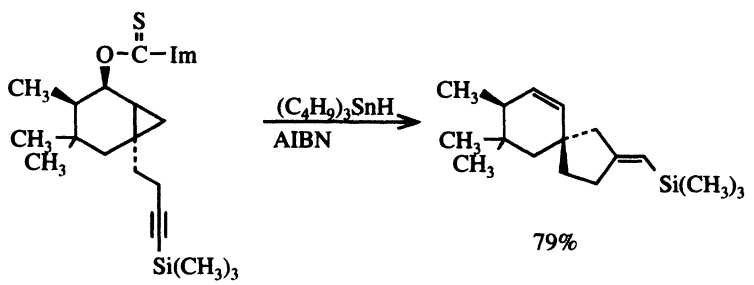
b)



62%

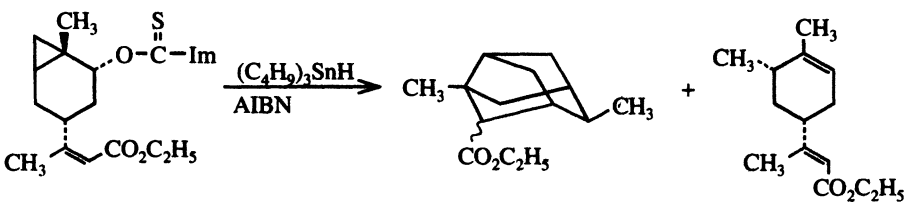
Synthesis of spiro bicyclic and tricyclic systems:[81]

a)



79%

b)



48%

23%

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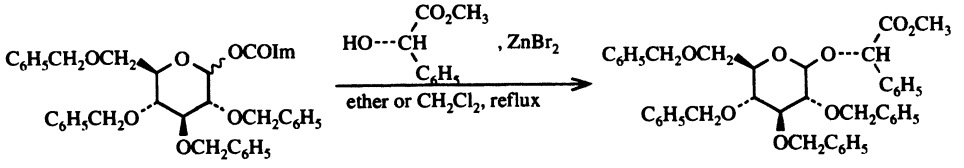
17 Synthesis of Glycosides and Ethers

Glycosides

A simple, one-pot glycosidation procedure via (1-imidazolylcarbonyl)glycosides with zinc bromide has been described.[1]

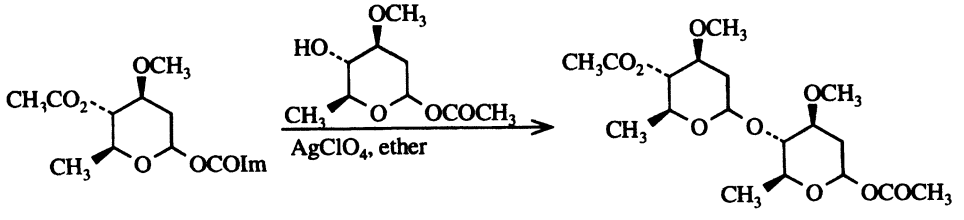
For example:



88% (α:β= 10 : 1)

This reaction is probably facilitated by the chelation of zinc bromide to N-3 of the imidazolyl group.[1]

Glycosides can also be prepared by means of 1-imidazolylcarbonyl glycosides in the presence of silver perchlorate, as shown by the synthesis of (1-*O*-acetyl-L-oleandrosyl)-(4-*O*-acetyl-L-oleandroside):[2]



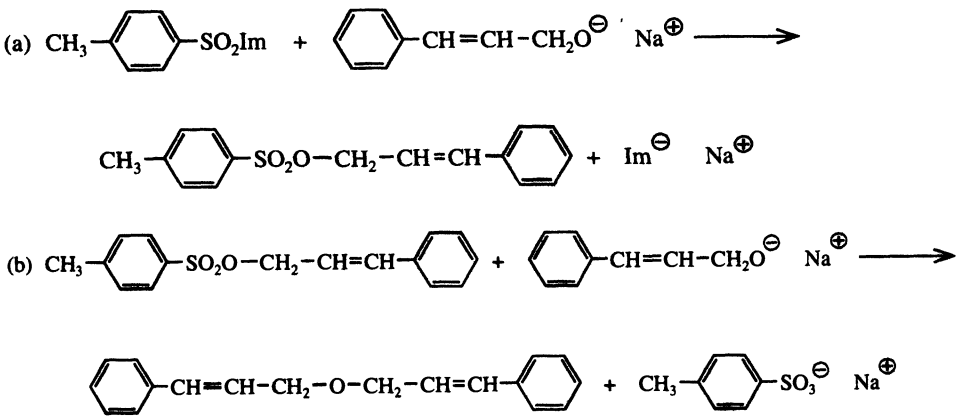
62%

In addition to 62% of the C-1′-α disaccharide diacetate, 11% of the C-1′-β anomer was still obtained.

Ethers

The following example illustrates an etherification[3],[4] of an alcohol using the imidazolide of a sulfonic acid.

Addition of *p*-toluenesulfonic imidazolide in benzene to a suspension in benzene of sodium cinnamoxide in a 1 : 2 molar ratio affords the dicinnamyl ether in 71% yield. Apparently, a highly reactive, so far not isolated sulfonate of cinnamyl alcohol is formed first (a), which then reacts further with a second mole of alkoxide to form the ether according to (b):



With the sodium derivative of benzyl alcohol, dibenzyl ether was obtained in 63% yield, accompanied by 24% of *N*-benzylimidazole. Formation of the latter compound results from the reaction of the benzyl sulfonate with imidazol sodium in competition with the second step of the ether synthesis (b).

For the synthesis of a cyclic ether see Section 18.5.

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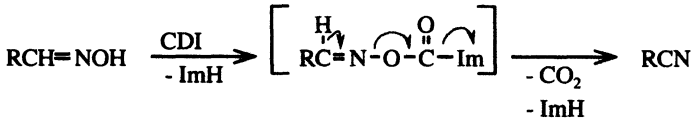
18 Dehydration Reactions

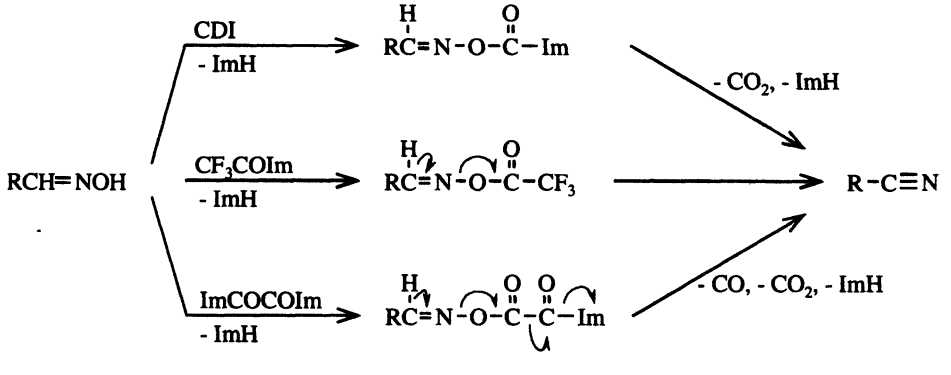
18.1 Synthesis of Nitriles from Aldoximes

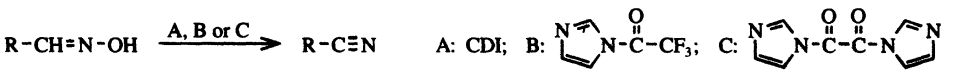
With Imidazolides

Aldoximes are readily dehydrated with *N,N'*-carbonyldiimidazole (CDI). An intermediate azolide is formed in the process under elimination of one mole of imidazole, which fragments into a nitrile through elimination of CO_2 and a second mole of imidazole.[1],[2]

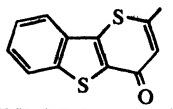


The reaction may be carried out either with or without solvent. In the latter case the process can be very vigorous.[1] Other dehydrating azolide reagents for preparing nitriles from aldoximes include *N*-trifluoroacetylimidazole[3] (refluxing ether or THF, 2–3.5 h, easy work up) and *N,N'*-oxalyldiimidazole[4] (benzene, CH_3CN, $CHCl_3$, or THF at 65–70 °C, a few minutes). These reactions also produce nitriles in good yield. With oxalyldiimidazole the intermediate formation of *O*-[2-(1-imidazolyl)oxalyl]oxime is assumed, with subsequent fragmentation into CO_2, CO, imidazole, and the nitrile:

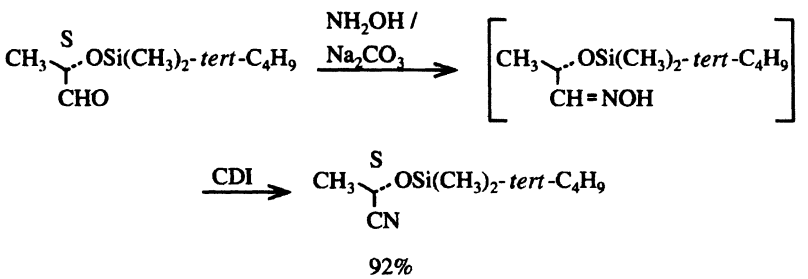




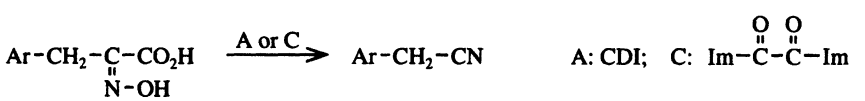
R	Reagent	Yield (%)	Ref.
n-C_5H_{11}	B	90	[3]
tert-$C_4H_9CH_2$	A	95	[1]
n-C_6H_{13}	B	96	[3]
n-C_6H_{13}	C	80	[4]
1-ethylpentyl	B	95	[3]
n-C_6H_{11}	C	81	[4]
1-propenyl	B	77	[3]
C_6H_5			
$CH_3N(CH=CH)_2$	A	51	[2]
C_6H_5	B	92	[3]
p-$CH_3C_6H_4$	B	81	[3]
p-$CH_3C_6H_4$	C	78	[4]
p-$CH_3OC_6H_4$	A	75	[1]
p-$CH_3OC_6H_4$	C	83	[4]

R	reagent	yield (%)	Ref.
p-ClC_6H_4	A	98	[1]
p-ClC_6H_4	B	94	[3]
p-ClC_6H_4	C	83	[4]
o-ClC_6H_4	B	97	[3]
p-$NO_2C_6H_4$	A	99	[1]
p-$NO_2C_6H_4$	C	79	[4]
m-$NO_2C_6H_4$	B	91	[3]
C_6H_5-CH=CH	B	95	[3]
	B	81	[3]
	C	73	[4]
	B	64	[5]

The azolide method has been used successfully in the conversion of an optically active aldehyde into the corresponding nitrile, with an optical purity of 100%:[6]



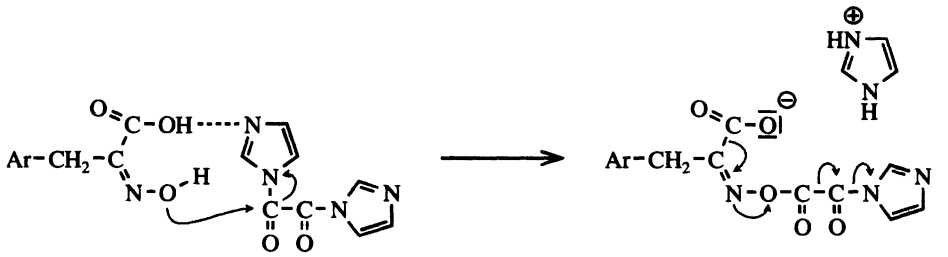
If α-carboxylated oximes are treated with CDI[7] (A) or *N,N'*-oxalyldiimidazole[8] (C) the dehydration proceeds with decarboxylation of the carboxy group.



Ar-CH_2CN	Yield (%)	
	with A	with C
C_6H_5	91	85
p-$CH_3C_6H_4$	95	95
p-$CH_3OC_6H_4$	93	90
p-ClC_6H_4	94	93
3-CH_3O,4-OHC_6H_3	83	82

Ar-CH_2CN	Yield (%)	
	with A	with C
3,4,5-$(CH_3O)_3C_6H_2$	85	88
α-naphthyl	97	90
α-furyl	75	83
thienyl	88	89
β-indolyl	—	84

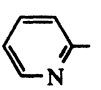
A likely mechanism for the reaction with *N,N'*-oxalyldiimidazole is as follows:



With the phosphoric imidazolides D, E, and F, dehydration of the aldoximes can also be achieved (dioxane, room temperature, several hours). With diphenylimidazole-1-phosphonate (D) and phenyldiimidazole-1,1'-phosphinate (E) the yields of nitriles are always higher than with $(C_6H_5O)_2P(O)Cl$ and $C_6H_5OP(O)Cl_2$; however, with phosphoryl triimidazole (F) the yields are a little lower than with $POCl_3$.[9] Spin-labeled phosphoric imidazolides of this type are also used for the dehydration of aldoximes.[10]

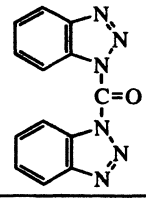
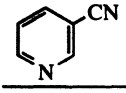
D: $R^1 = R^2 = C_6H_5O$
E: R^1 = Im; $R^2 = C_6H_5O$
F: $R^1 = R^2$ = Im

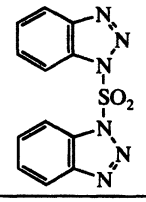
R	Reagent	Yield (%) [9]
$CH_3(CH_2)_5$	D	97
	E	93
	F	65
$(C_2H_5)_2CH$	D	89
	E	86
c-C_6H_{11}	D	81
	E	92
	F	50
p-$CH_3C_6H_4$	D	96
	F	59

R	Reagent	Yield (%) [9]
p-$CH_3OC_6H_4$	E	83
	F	60
2,4-$Cl_2C_6H_3$	D	95
	E	87
	F	64
$C_6H_5-CH=CH$	D	93
	E	95
	D	89
	E	52
	F	30

With Triazolides

Other effective azolide reagents for the dehydration of aromatic aldoximes to nitriles under mild conditions (refluxing THF) include the two triazolides *N,N'*-carbonyldibenzotriazole (G) and *N,N'*-sulfonyldibenzotriazole (H):[11]

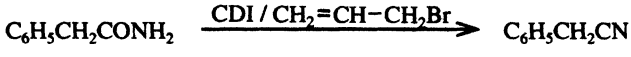
Nitrile	Reagent G	Yield (%)
C_6H_5CN		64
p-ClC_6H_4CN		84
p-$CH_3OC_6H_4CN$		75
		71

Nitrile	Reagent H	Yield (%)
p-ClC_6H_4CN		71

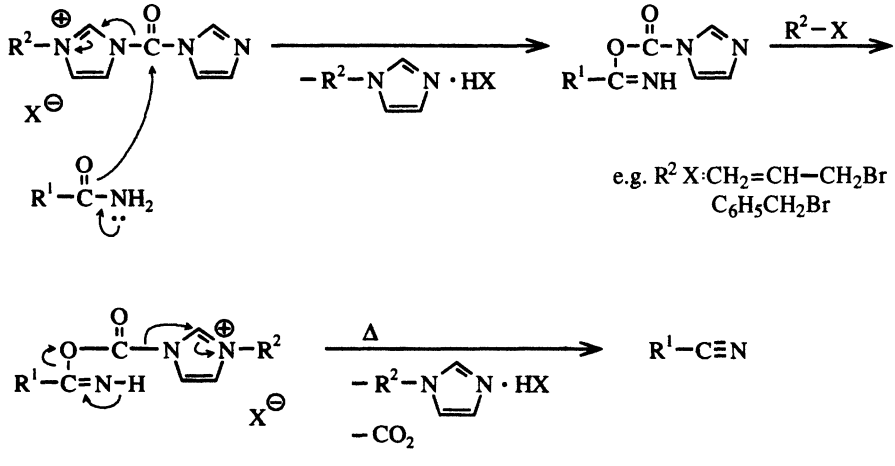
18.2 Synthesis of Nitriles from Amides

With Imidazolides

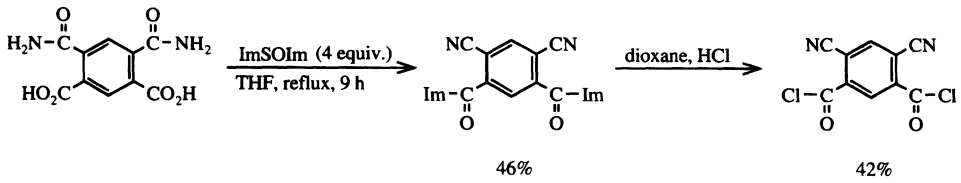
In the dehydration of primary aliphatic or aromatic amides to nitriles with CDI, the CDI is activated by an excess of a reactive halide, such as allyl bromide or benzyl bromide (2 equiv. of CDI, 8 equiv. of reactive halide, refluxing CH_3CN, 2–5 h):[12]



Proposed reaction mechanism:

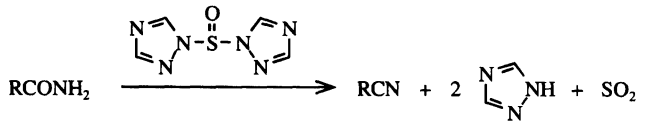


For the dehydration of pyromellitic acid diamide, *N,N'*-sulfinyldiimidazole was used as the dehydrating agent to give a moderate yield of dicyanoisophthalic diimidazolide, which was further transformed with hydrochloric acid into the corresponding dichloride:[13]



With Triazolides

Carboxamides can be converted into nitriles with *N,N'*-sulfinyldi-1,2,4-triazole under mild conditions (CH_2Cl_2, room temperature, 10–20 min.).[14]



R	Yield (%)
C_2H_5	89
$C_6H_5CH=CH$	90
C_6H_5	82
p-$CH_3OC_6H_4$	99
p-$NO_2C_6H_4$	0

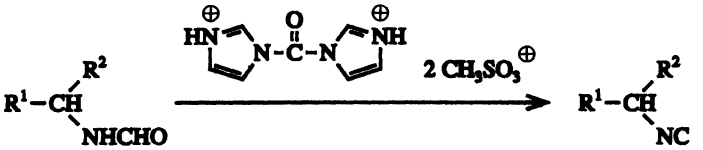
Aliphatic and aromatic carboxamides, with the exception of *p*-nitrobenzamide, are dehydrated in this way in high yield. Acid-labile protective groups such as tetrahydropyranyl and *tert*-butyldimethylsilyl ether and base-sensitive compounds are not attacked. *N,N'*-Sulfinyldi-1,2,4-triazole, easily prepared from thionylchloride and triazole [THF, $(C_2H_5)_3N$, 0 °C, 1 h] in 85–95% yield, was used without further purification.

N,N'-Sulfinyldiimidazole is not as effective as a dehydrating agent; when reacted with octanoic amide under the same conditions it produced only 25% octanenitrile together with 25% starting material, a large amount of black solid, and 9% octanoylimidazole.[14]

18.3 Synthesis of Isocyanides from *N*-Formylamino Compounds

For the dehydration of *N*-formylamino compounds to give isocyanides the CDI is activated by protonation into its bisimidazolium form (CH_3CN, room temperature, 4 h). Thus, chiral α-isocyano esters and other base-sensitive isocyanides are obtained in high yield. CDI itself did not produce this dehydration.

No isocyanide was obtained when 2-nitro-5-methoxyformanilide was treated with the carbonyldiimidazolium reagent.[15],[16]



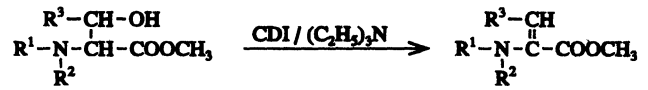
R^1	R^2	Yield (%)	Ref.
s-C_3H_7	$COOCH_3$	90	[15]
tert-C_4H_9	H	85	[15]
$C_6H_5CH_2$	$COOCH_3$	80	[15]
$C_6H_5CH_2$	$CONH-CH(CO_2CH_3)-CH_2C_6H_5$	75	[15]
6-CH_3O-naphthyl-2	CH_3	70	[16]

18.4 Synthesis of Olefins from Alcohols

Formation of a Conjugated Double Bond

Several examples of the dehydration of acyclic and cyclic hydroxy compounds with CDI, *N,N'*-thiocarbonyldiimidazole, and *N,N'*-sulfinyldiimidazole, are shown below.

a) Derivatives of dehydroalanine and dehydroalanine peptides can be prepared in good yield from the corresponding β-hydroxy compounds using equimolar amounts of CDI and $(C_2H_5)_3N$ (toluene, room temperature, 4–6 h,[17] or ether or THF, room temperature[18]):



R^1	R^2	R^3	Yield (%)	Ref.
Z	H	H	85	[17]
Z	H	CH_3	76	[17]
Z-Gly	H	H	68	[17]
Z-Ser	H	H	65	[17]
Z-Val	H	H	71	[17]

R^1	R^2	R^3	Yield (%)	Ref.
Boc	H	H	83	[17]
Boc	H	CH_3	71	[17]
4-$(C_6H_5)C_6H_4CH=$	H		62	[18]
$C_6H_5CH=$	H		90	[18],[19]

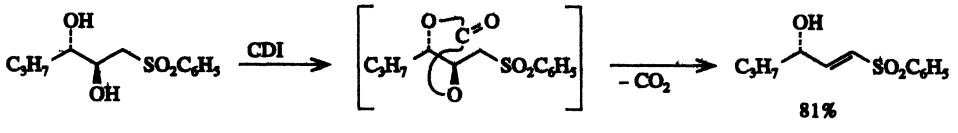
N-Benzylidene dehydroalanine, however, could not be isolated by this method because the compound decomposed during work up at room temperature.[18] CDI was inert toward a series of dipeptides containing a serine residue in the *N*-terminal position

(e.g. Z-Ser-Gly-OCH_3, Z-Ser-Ala-OCH_3, Z-Ser-Phe-OCH_3) or serine amides like Z-Ser-NH_2 and Z-Ser-NHC_3H_7.[17]

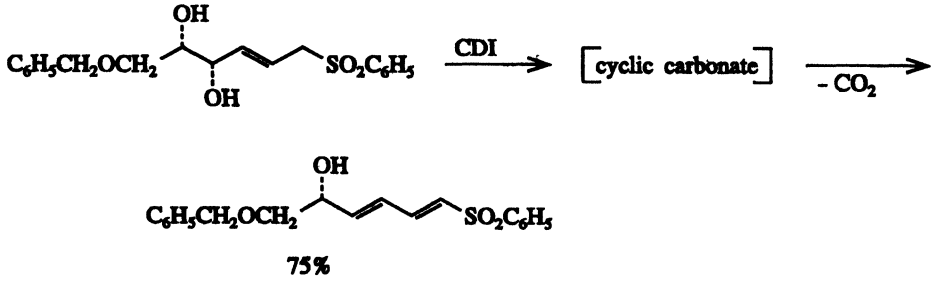
Formation of the very unstable dehydroalanine derivatives *N-p*-dimethylaminophenyl- and *N-p*-nitrophenylmethylenedehydroalanine methyl ester could only be verified by ^{1}H-NMR. Because of Michael-type reactions with cuprates, the *N*-arylmethylenedehydroalanine methyl esters have been applied as building blocks in the synthesis of amino acids.[18]

b) CDI has been shown to be a very suitable reagent for the dehydration of 2-hydroxyalkylsulfoximines (toluene, room temperature, 12 h). The *S*-phenyl-*S*-(1-propenyl)-sulfoximine is obtained as the *E*-isomer only.[20]

c) β,γ-Dihydroxysulfones react with CDI (2 equiv.) via cyclic carbonates with subsequent silica gel treatment (dichloromethane, room temperature, 6 h) to give γ-hydroxy-α,β-unsaturated sulfones. Isolation of the cyclic carbonate is not necessary in this procedure. When a dihydroxysulfone is treated with CDI for 12 h, the product is obtained directly in rather good yield after column chromatography on SiO_2:[21]

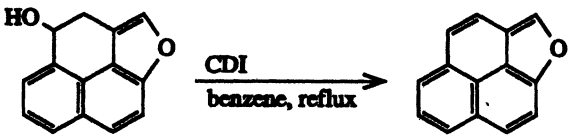


ε-Hydroxy-(*E,E*)-α,γ-dienylsulfones are prepared by an analogous one-pot dehydration procedure via an elimination reaction of the corresponding cyclic carbonate:[21]



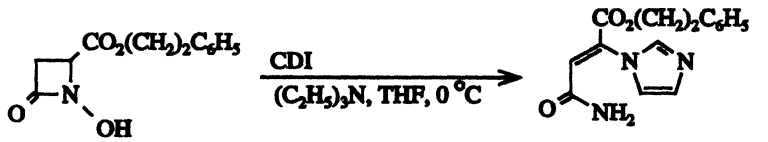
An analogous dehydration in the synthesis of lactone substituted derivatives of digitoxigenin is reported in reference [21a].

d) A phenalenofuran has been synthesized from the hydroxy precursor by means of CDI:[22]



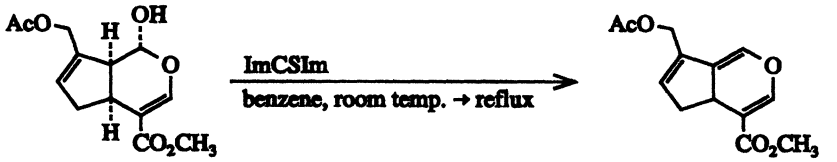
80%

e) A dehydration with concomitant addition of imidazole and opening of the four-membered azetidinone ring is described in reference [23].



85%

f) A dehydration of genipin acetate has been carried out with *N,N'*-thiocarbonyldiimidazole.[24]



55%

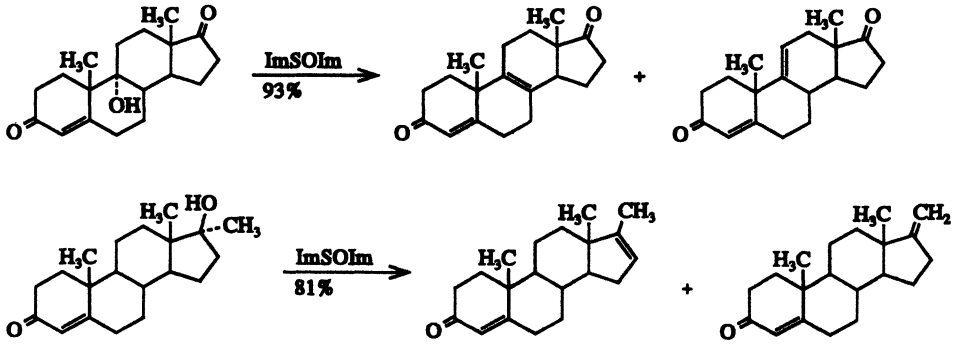
g) 1,1,2-Triphenyl-2-alkyl-1-alkanols are readily dehydrated with *N,N'*-sulfinyldiimidazole to give *E/Z* isomer mixtures of the double bond introduced (THF, 30–40 °C, 1–5 h).[25]

R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
F	CH_3	87	Cl	C_2H_5	73
F	C_2H_5	86	Br	C_2H_5	84
F	C_4H_9	72	OCH_3	C_2H_5	88

Formation of Non-Conjugated Double Bonds in Steriods

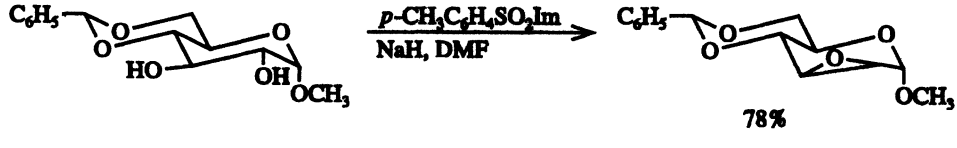
Non-conjugated double bonds have been successfully generated in steroid alcohols with *N*,*N*′-sulfinyldiimidazole.[26]

Examples:



18.5 Synthesis of Cyclic Ethers and Amines

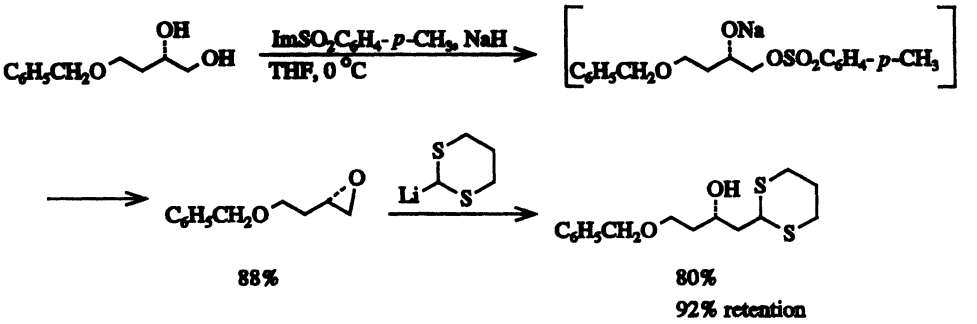
a) An epoxide ring is formed by reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with *p*-toluenesulfonylimidazole.[27]



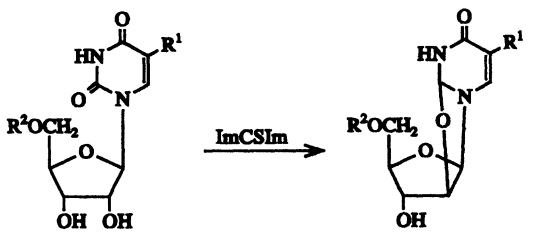
b) Synthesis of epoxides and their nucleophilic opening.[28]

A facile one-pot stereoselective epoxidation of vicinal diols has been accomplished using *N*-(*p*-toluenesulfonyl)imidazole or *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole and NaH. These reactions involve selective monoarylsulfonation of primary OH-group followed by displacement of arylsulfonate by the adjuvant secondary or tertiary alkoxide. The epoxides were further transformed with organometallic compounds into secondary or tertiary alcohols.

The following is an example for a sequential one-pot epoxide formation/nucleophilic opening process using (*S*)-4-(benzyloxy)-1,2-butanediol, *N*-(*p*-toluenesulfonyl)-imidazole, and 2-lithio-1,3-dithiane:



c) Reaction of 5′-trityl derivatives of uridines with *N*,*N*′-thiocarbonyldiimidazole gave directly in high yields crystalline 2,2′-anhydro-1-(5-trityl-β-D-arabinofuranosyl) uracils, which can be easily converted into 1-β-D-arabinofuranosyluracils (refluxing toluene, 1 h).[29],[30]

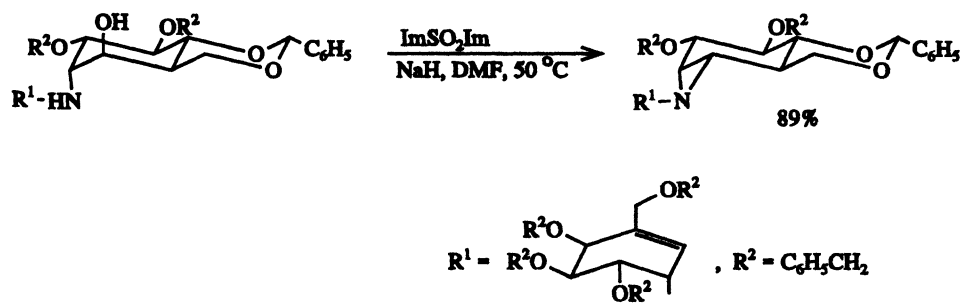


R^1	R^2	Yield (%)	Ref.
H	$(C_6H_5)_3C$	85	[29]
H	H	36	[29]
F	$(C_6H_5)_3C$	91	[29]
CH_3	MMTr	87	[30]

MMTr = 4-monomethoxytrityl

It is claimed that this reaction proceeds via a 2′,3′-thionocarbonate or a thiocarbamate derivative. If the 5′-OH group of uridine was not protected, the yield of the 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil was low.

d) Reaction of vicinal amino/hydroxy groups in a validoxylamine B derivative with sulfonyldiimidazole produces an aziridine ring, as was discovered in the course of synthetic studies on antibiotic validamycins.[31]



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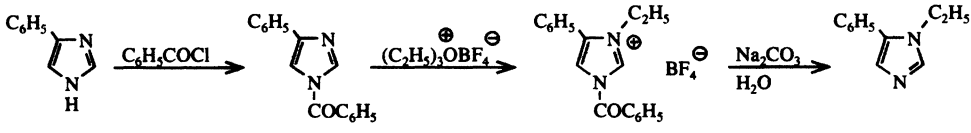
19 Substitution Reactions on Azoles

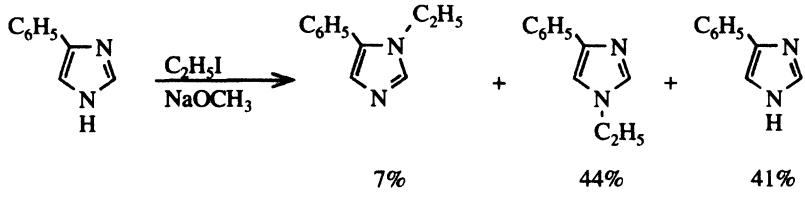
19.1 Syntheses of *N*-Alkylated Azoles

In the reactions considered here the *N*-acyl group functions as a readily cleavable protecting group in facilitating exclusive alkylation at normally unfavored positions in the azole moiety.[1]

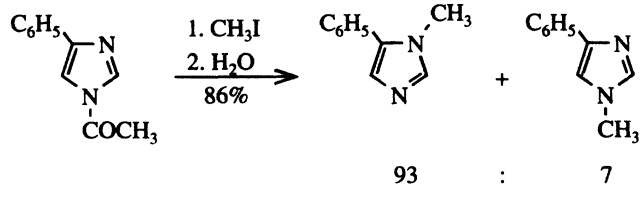
Example: Synthesis of 1-ethyl-5-phenylimidazole



In the direct alkylation of 4-phenylimidazole the desired 1-ethyl-5-phenylimidazole is obtained only as a minor product:[1]

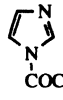
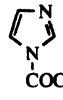
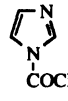
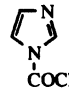
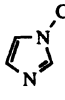
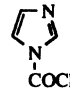
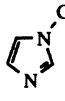
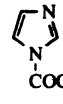
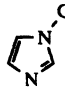
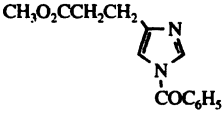
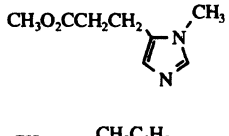
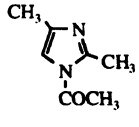
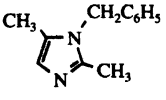
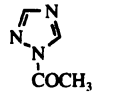
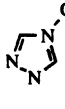
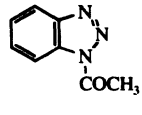
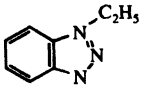


For this reason the regioselective methylation of various 4-substituted 1-acetylimidazoles was studied.[2] While reaction with 1-acetyl-4-phenylimidazole furnished the isomers 1-methyl-5-phenylimidazole and 1-methyl-4-phenylimidazole in a ratio of 93 : 7, reaction with 1-acetyl-4-methylimidazole produced an isomer ratio of 86 : 14.

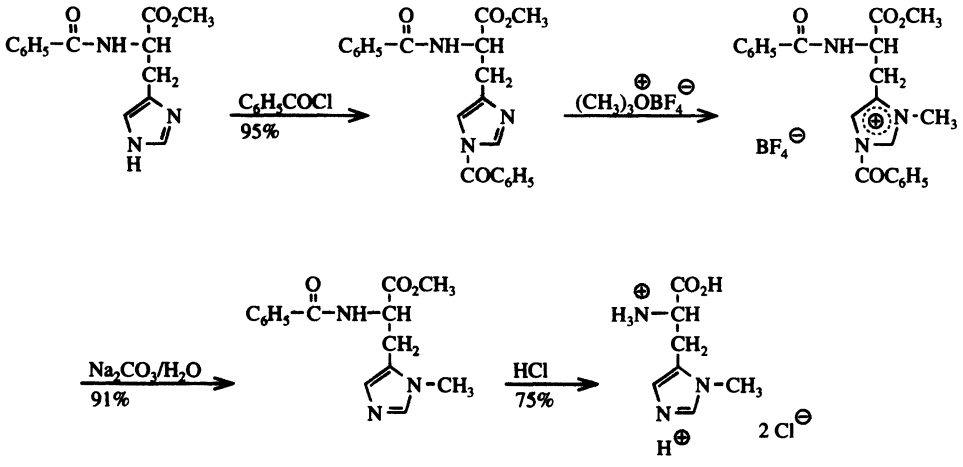


The *N*-alkylazoles in Table 19–1 can be prepared readily by the alkylation of azolides and subsequent cleavage of the acyl group.

Table 19–1. *N*-Alkylazoles from imidazolides and triazolides.

Azolide	Alkylating agent	*N*-Alkylazole	Yield (%)	Ref.
	$C_6H_{13}Br$/NaI		80	[3]
	$Br(CH_2)_3CO_2C_2H_5$/NaI		80	[4]
	$NC(CH_2)_3Br$/NaI		74	[3]
	$C_6H_5COCH_2Br$		91	[3]
	$CH_2CH{=}CH_2Br$		82	[3]
	$C_6H_5CH_2Br$		99	[3]
	*p*-$CH_3C_6H_4CH_2Cl$/NaI		92	[4]
	$(CH_3)_3OBF_4$		97	[5]
	$C_6H_5CH_2Br$		55	[6]
	$(CH_3)_3OBF_4$		88	[1]
	$(C_2H_5)_3OBF_4$		94	[1]

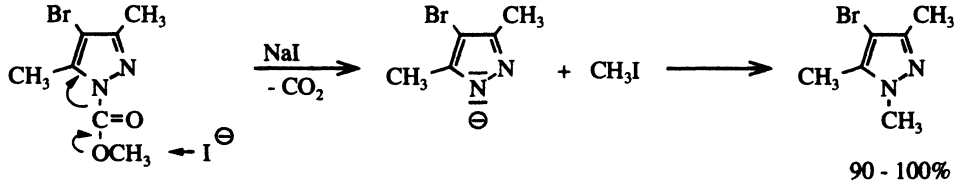
L-1-Alkylhistidines are conveniently obtained by the following route:[7]



The 2-adamantyloxycarbonyl group has been found suitable for protection of the imidazole function in histidine during peptide synthesis.[7a]

Alkylative decarboxylation of *N*-alkoxycarbonylpyrazoles yields *N*-alkylpyrazoles:[8]

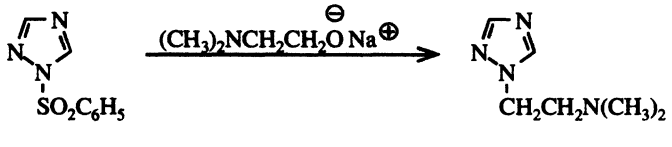
Example:



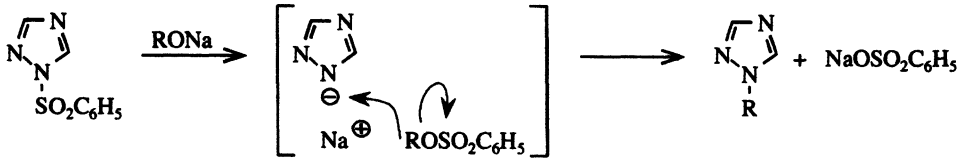
A similar alkylative decarboxylation takes place during the thermolysis of 1-alkoxycarbonylbenzotriazoles.[8a]

Syntheses of *N*-alkyl-1,2,4-triazoles and *N*-alkylbenzotriazoles have been carried out with the aid of the *N*-phenylsulfonyl protecting group:[9]

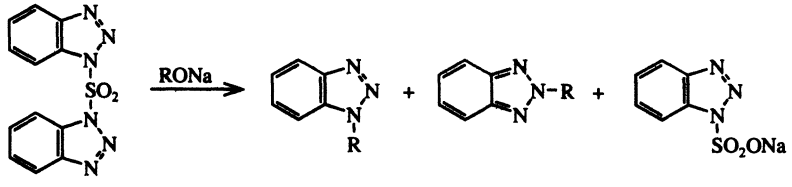
a) Alcoholates react with 1-phenylsulfonyl-1,2,4-triazole via a triazole anion and a sulfonic acid ester to give the N^1-alkylated triazole.



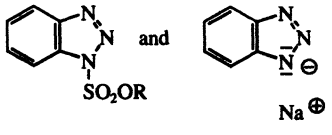
The following mechanism has been suggested:

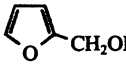


b) By an analogous reaction of alcoholates with *N,N'*-sulfonyldibenzotriazole a mixture of 1- and 2-substituted benzotriazoles was obtained:

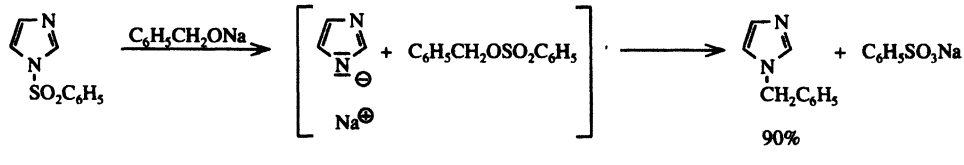


intermediates:



ROH	Yield (%) of 1- + 2-alkylbenzotriazoles
$(CH_3)_2NCH_2CH_2OH$	74
	73
sec-C_4H_9	46

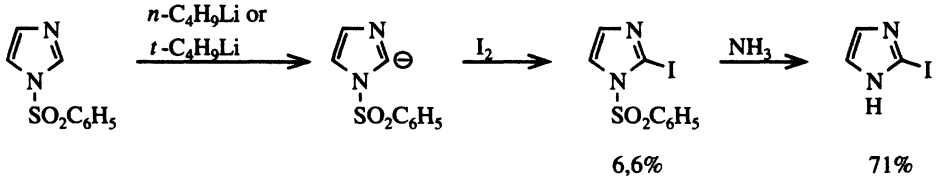
These reactions correspond to the transformation of sodium benzylalcoholate with benzenesulfonic acid imidazolide, leading to *N*-benzylimidazole[10] (see also references [11] and [12]):



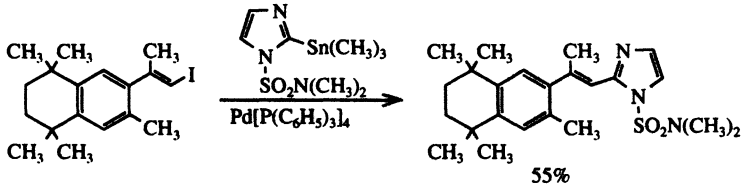
19.2 Syntheses of *C*-Substituted Azoles

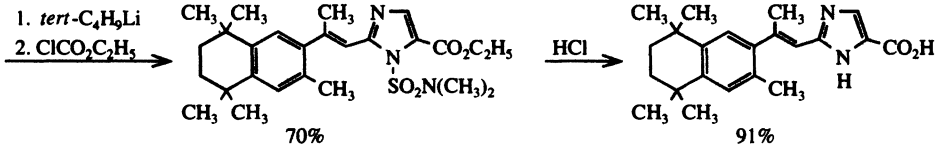
2-Substituted Imidazoles

a) Lithiation of sulfonylimidazoles and subsequent reaction with an electrophile leads cleanly to the 2-substituted imidazole.[13]



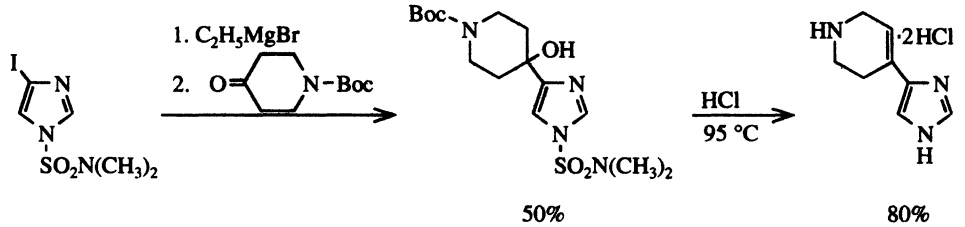
b) Reaction of an imidazole at C-2 with an alkenyl iodide is achieved via the azolide 1-dimethylsulfamoyl-2-trimethylstannylimidazole:[14]





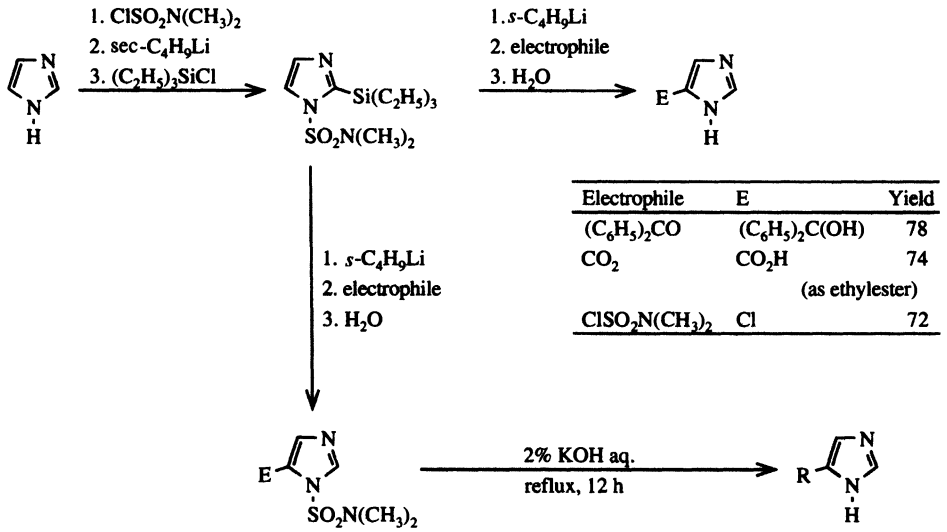
4(5)-Substituted Imidazoles and Pyrazoles

An *N*-dimethylsulfamoyl-protected 4-iodoimidazole is joined with *N-tert*-butoxycarbonyl-4-piperidone via a Grignard reaction to give, in good yield after dehydration and elimination of the two protecting groups with concentrated HCl, 4(5)-(1,2,5,6-tetrahydropyridin-4-yl)imidazole as dihydrochloride:[15]



Further examples for the preparation of 4(5)-substituted imidazoles with *N*-sulfamoylimidazoles are given below. In these cases both the sulfamoyl and the silyl groups are used as protecting functions (bisprotection of the imidazole moiety).[16]

a)

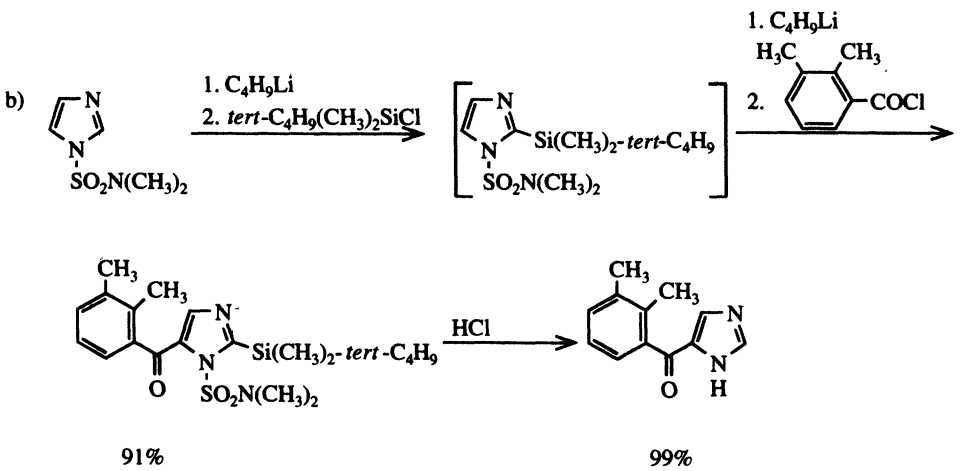


Electrophile	E	Yield
$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	78
CO_2	CO_2H	74 (as ethylester)
$ClSO_2N(CH_3)_2$	Cl	72

Electrophile	E	Yield (%)
$(CH_3)_2S_2$	CH_3S	92
CH_3I	CH_3	96
$C_6H_5CH_2Br$	$C_6H_5CH_2$	64
CH_3OD	D	89
$(CH_3)_3SiCl$	$(CH_3)_3Si$	88

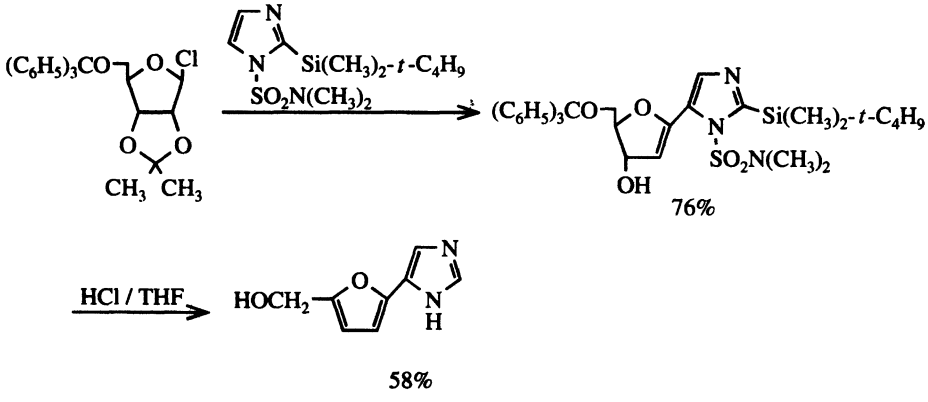
R	Yield (%)
CH_3S	90
CH_3	92
$C_6H_5CH_2$	64
H	92
H	89

b)

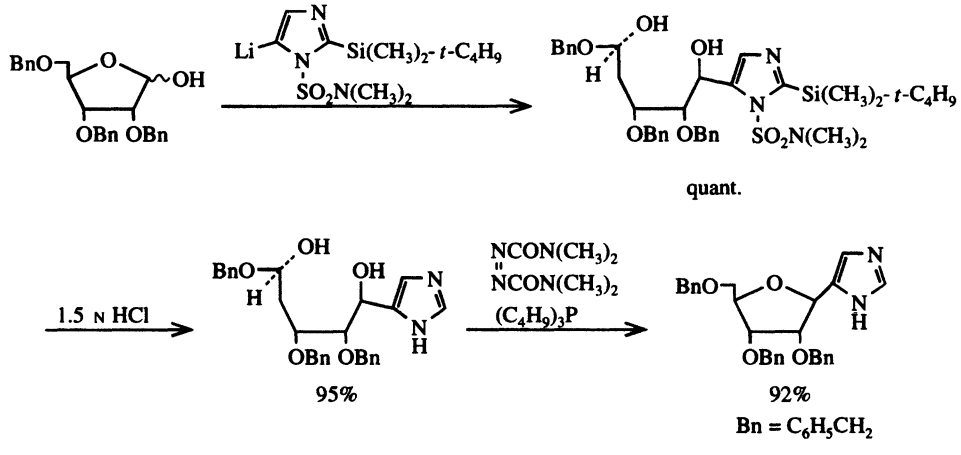


91% 99%

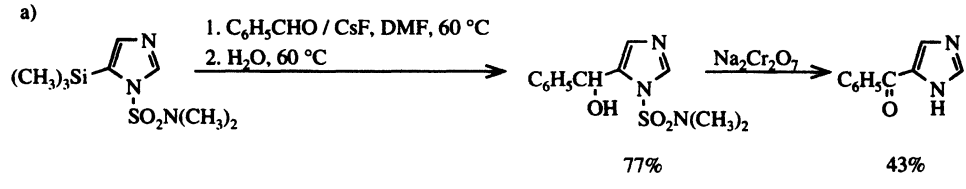
c) In reference [17] the reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride with 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilylimidazole leading finally to 5-(5-hydroxymethylfuran-2-yl)imidazole is described:



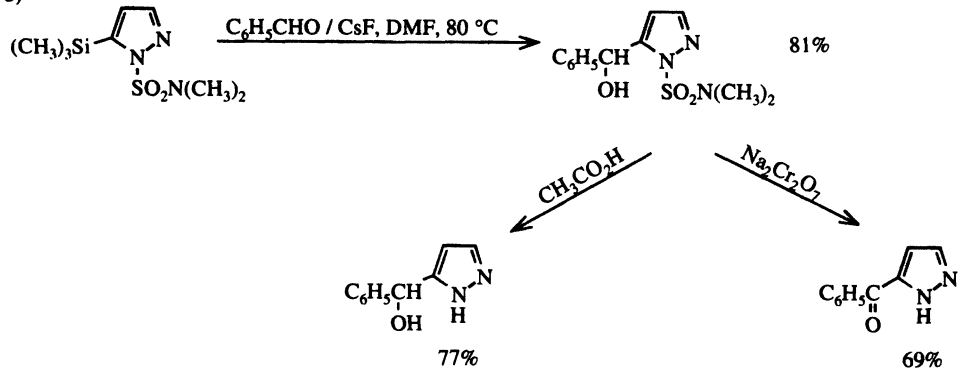
d) The stereoselective synthesis of 5-(β-D-ribofuranosyl)-imidazoles can be accomplished by conversion of the lithium salt of a 2-silylated *N*-(dimethylsulfamoyl)-imidazole with a ribose derivative followed by a Mitsunobu cyclization.[14a]



From silylated *N*-sulfamoyl-protected imidazoles or pyrazoles, imidazolyl or pyrazolyl anions can be generated with the strong base CsF (carbodesilylation) and subsequently treated with electrophiles. In this way 5-substituted imidazoles or pyrazoles can be prepared after the deprotection of N(1):[18]



b)



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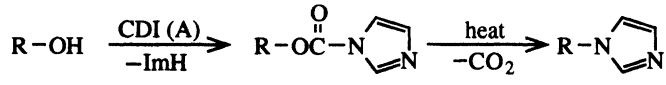
20 Azole-Transfer Reactions to Carbon Atoms

Imidazole- and Triazole-Transfer Reactions to Tertiary Alcohols, Halides, and Acetates

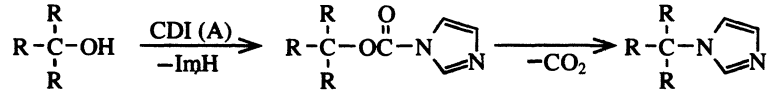
The first imidazole-transfer reactions to alcohols[1], i.e. substitution of an OH group by a 1-imidazole moiety, were accomplished in moderate to good yield by means of CDI via the imidazole-*N*-carboxylates at high temperature if a primary or a secondary alcohol is converted (250–260°C, if R = C_2H_5,[1],[2] and 110°C, if R = $C_6H_5CH_2$ or $(C_6H_5)_2CH$[1]).



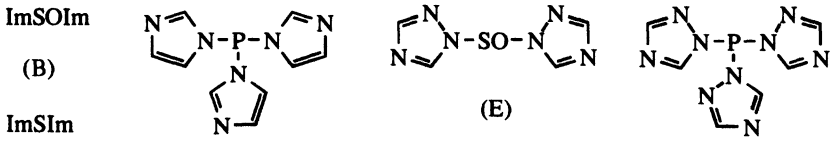
The reaction of imidazole-*N*-carboxylates with a second mole of alcohol to give the carbonic diester are dealt with in Chapter 3.8.

Tert-butyl imidazole-*N*-carboxylate fragments on heating (160–170°C) into isobutene, imidazole and CO_2.[1]

The corresponding reaction of CDI (A) with tertiary alcohols, the carbonium ions of which are relatively stable like, for example, triarylmethanols, are carried out at much lower temperature (often room temperature, CH_3CN, CH_2Cl_2, or $CHCl_3$, several hours) and are therefore of general preparative value.



Other applicable imidazole-transfer reagents include *N,N'*-sulfinyldiimidazole (B), diimidazolylsulfide (C) and tris(imidazolyl)phosphine (D). The 1,2,4-triazolyl group is transferred by *N,N'*-sulfinyldi-1,2,4-triazole (E) or tris(1,2,4-triazolyl)phosphine (F).



Some examples which found applications as antimycotics, fungicides and plant growth regulators are collected in Table 20–1.

Table 20–1. N-Substituted imidazoles and triazoles prepared by transfer reactions of azolides A–F with tertiary alcohols of the triphenylmethanol type and analogues.

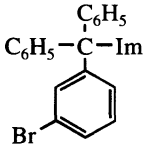
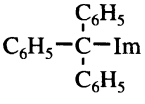
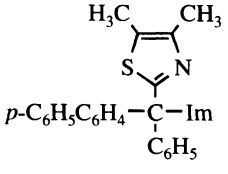
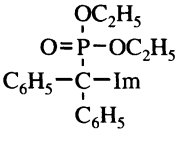
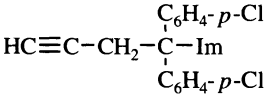
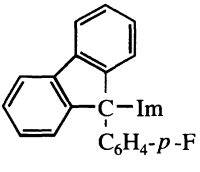
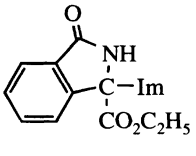
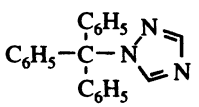
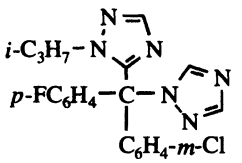
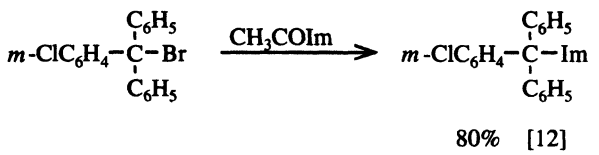
Azolide reagent	Azole product	Yield (%)	Ref.
A		47	[3]
C		50	[4]
A		49	[5]
B		50	[6]
B		23	[7]
D		66	[8]
B		89	[9]

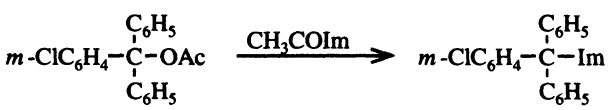
Table 20–1 (*Continued*)

Azolide reagent	Azole product	Yield (%)	Ref.
F		90	[10]
E		67	[11]

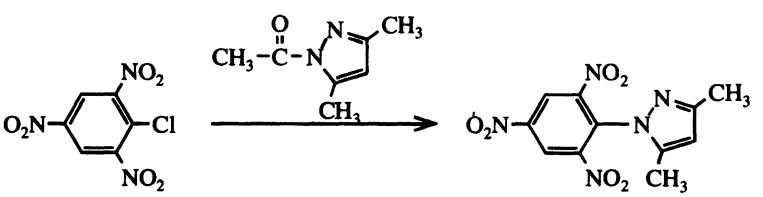
Triarylmethylazoles can also be synthesized by azole-transfer reactions of triarylmethyl halides or acetates with azolides. In a similar manner 2,4,6-trinitrophenylazoles are obtained from 2,4,6-trinitrophenyl chloride:



80% [12]



59% [13]

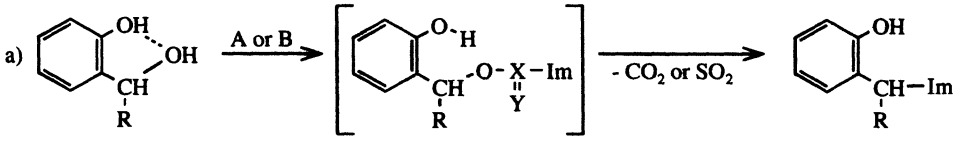


93% [14]

For imidazole-transfer reactions leading to imidoylimidazoles by conversion of secondary amides or thioamides with sulfinyldiimidazole, see reference [14a]. For imidazole-transfer reactions with nucleobases see Section 12.11.

Azole-Transfer Reactions with Benzylalcohols and Secondary Alcohols

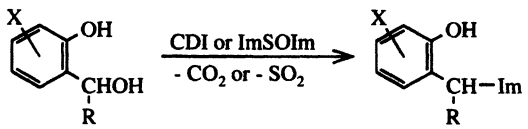
Internal hydrogen bonding promotes imidazole transfer in the reaction of primary and secondary benzyl alcohols with CDI (A) or ImSOIm (B):[15],[16]

a) 

X=Y: C=O or S=O

R	Azolide reagent	Yield (%)
H	A	44
H	B	33
CH_3	A	42

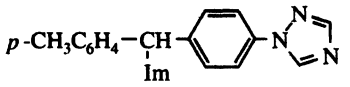
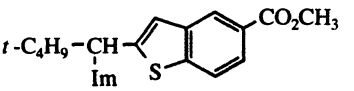
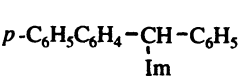
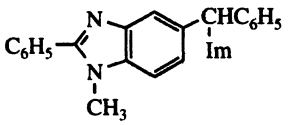
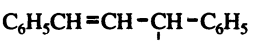
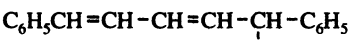
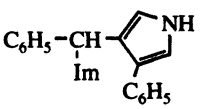
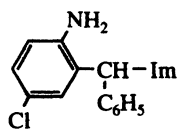
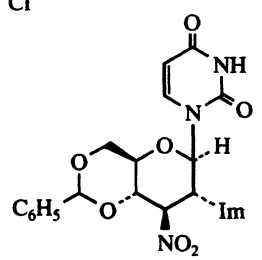
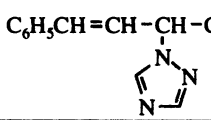
Imidazole-transfer reactions with variously substituted 2-hydroxybenzyl alcohols include, for example, the following reaction:[15],[16]



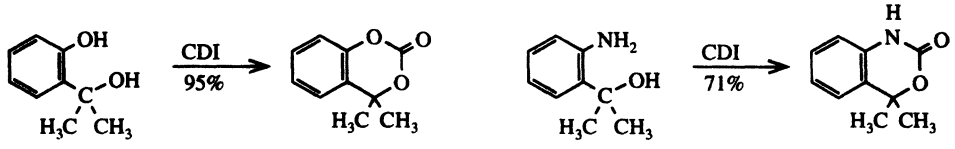
X	R	Azolide reagent	Yield (%)
5-NO_2	H	A	31
5-NO_2	H	B	61
5-Cl	C_6H_5	A	27
5-Cl	C_6H_5	B	23

b) Secondary alcohols mainly of the diphenylmethanol type lead to imidazole compounds in moderate to good yield with ImSOIm (B), CDI (A), or sulfinyldi-1,2,4-triazole (E), as shown in Table 20–2.

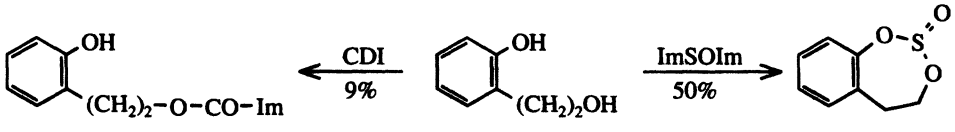
Table 20–2. Imidazoles and triazoles prepared through transfer reactions of azolides to secondary and tertiary alcohols.

Azole product	Azolide reagent	Yield (%)	Ref.
	B	53	[17]
	B	78	[18]
	B	56	[19]
	A	43	[20]
	A	81	[21]
	A	35	[21]
	B	94	[22]
	A B	29 45	[15],[16] [15],[16]
	A	86	[22a]
	E	57	[21]

c) With *o*-hydroxy-α,α-dimethylbenzyl alcohol or *o*-amino-α,α-dimethylbenzyl alcohol no imidazole transfer occurs; instead, a CO insertion reaction is observed:[15]



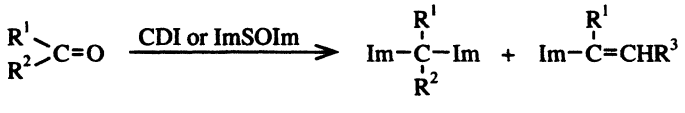
Also, in the reaction of *o*-hydroxyphenethyl alcohol with CDI or ImSOIm no imidazole is transferred, but the imidazole-1-carboxylate and the 1,3,2-benzodioxathiepin, respectively, are formed:[15][16]



On the compounds in references [15] and [16] no experimental details are given.

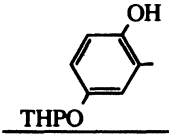
Imidazole- and Pyrazole-Transfer Reactions with Ketones, Aldehydes, and Carboxylic Acids

Ketones and aromatic aldehydes undergo facile addition reactions with CDI (A) or better with *N,N'*-sulfinyldiimidazole (B) to give diimidazolylmethanes and *N*-alkyleneimidazoles, depending on the presence of hydrogen atoms α to the carbonyl group:

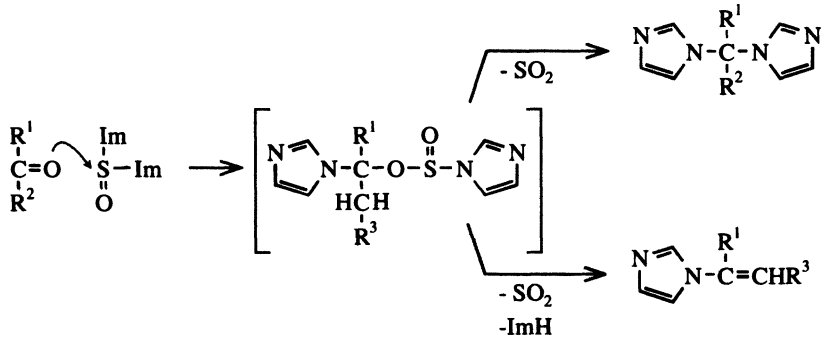


R^1	R^2	Azolide reagent	Diimidazolyl-methanes yield (%)	*N*-Alkylene-imidazole R^3, yield (%)		Ref.
C_6H_5	CH_3	B	37	H	12	[23]
C_6H_5	H	B	30		—	[23]
p-$CH_3OC_6H_4$	CH_3	B	49	H	2	[23]
p-$NO_2C_6H_4$	CH_3	B	26	H	33	[23]

(*continued*)

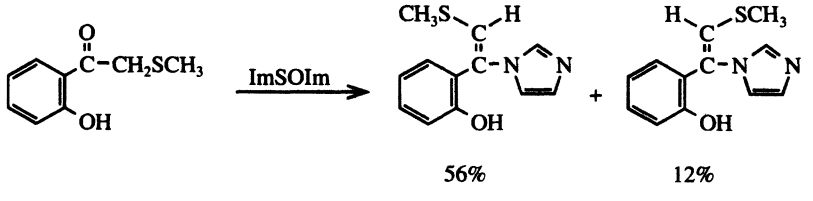
R^1	R^2	Azolide reagent	Diimidazolyl-methanes yield (%)	*N*-Alkylene-imidazole R^3, yield (%)		Ref.
p-$CH_3C_6H_4$	CH_3	B	32	H	7	[23]
α-pyridyl	C_6H_5	B	57		—	[23]
α-pyridyl	H	B	57		—	[23]
CH_3	CH_3	B	26	H	4	[23]
o-HOC_6H_4	C_6H_5	B	82		—	[23]
		A	37		—	[23]
o-HOC_6H_4	CH_3	B	—	H	94	[23],[24]
		A	—	H	31	[23]
o-HOC_6H_4	C_2H_5	B	—	H	75	[25]
	CH_3	B	—	H	70	[26]

Transfer reactions can also be carried out with *N,N'*-sulfinyldibenzimidazole.[26a] For these reactions the following mechanism has been suggested:

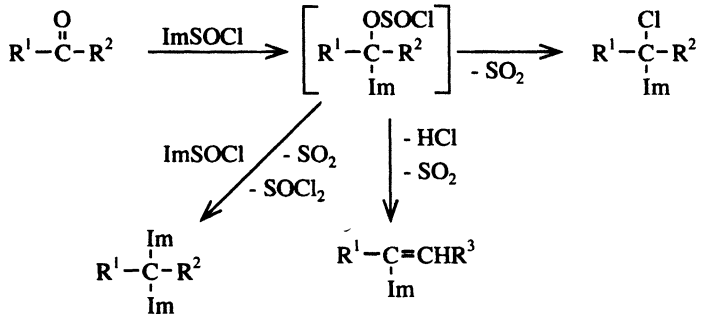


Benzophenone, *p*-methoxybenzophenone, and aliphatic aldehydes do not react with ImSOIm.[23]

Reactions with ω-substituted acetophenones yield mixtures of the two stereoisomeric *N*-alkylene-imidazoles:[27]

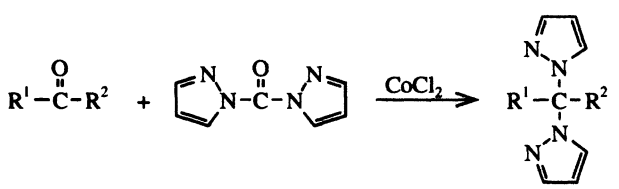


In the reaction with ketones, *N*-chlorosulfinylimidazole (ImSOCl) shows greater reactivity than sulfinyldiimidazole:[28]



$R^1-\overset{O}{\overset{\|}{C}}-R^2$		Azolide reagent	α-Chloro-α imidazolyl product (%)	*N*-Alkylene imidazole product (%)	Diimidazolyl methane (%)
R^1	R^2				
C_6H_5	C_2H_5OCO	ImSOCl	62	—	—
C_6H_5	C_2H_5OCO	ImSOIm	8	—	25
C_6H_5	C_6H_5CO	ImSOIm	1	—	32
C_6H_5	CH_3	ImSOCl	—	14	19
CH_3	CH_3	ImSOCl	—	2	2

N,N'-Carbonyldipyrazole reacts with ketones such as acetone, methyl ethyl ketone, and cyclic ketones, as well as such aldehydes as acetaldehyde and benzaldehyde to give dipyrazolylalkanes, also in the presence of catalyst, for example cobalt chloride.[29],[30]

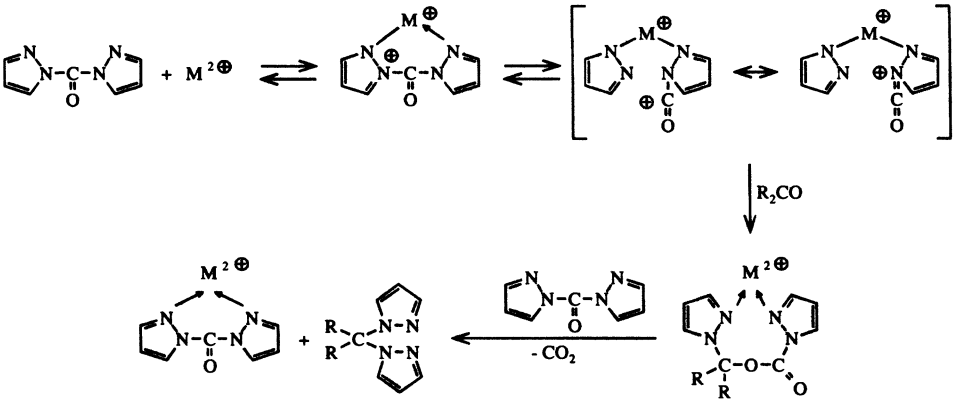


R^1	R^2	Yield (%)
CH_3	C_2H_5	84
$-(CH_2)_3-$		82
CH_3	H	75
C_6H_5	H	48

The dipyrazolylalkanes form complexes with $CoCl_2$, from which the ligand can be easily separated. 2-Methylcyclohexanone, acetophenone, and benzophenone did not

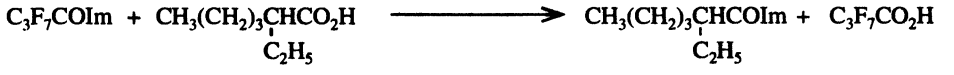
undergo this reaction with *N,N'*-carbonyldipyrazole. The synthesis of bis(pyrazol-1-yl)(pyridine-2-yl)methane from *N,N'*-carbonyldipyrazole and pyridine-2-aldehyde, as well as the analogous synthesis of bis(pyrazol-1-yl)(*N*-methylimidazole-2-yl)methane, were accomplished without addition of the $CoCl_2$ catalyst.[31]

Analogoues reactions with variously substituted bispyrazolides and triiron dodecacarbonyl as catalyst are reported.[32],[33] For these transformations the following mechanism has been suggested:



If competitive aldehydes or ketones are used, preferred or exclusive formation of the sterically least hindered alkylidene dipyrazole is observed.[32] If *N,N'*-carbonyldipyrazole is heated at 190 °C a pyrazole-transfer reaction also occurs to give tetrapyrazole-1-yl-methane in 50% yield.[33]

In the reaction of heptafluorobutyrylimidazole with a carboxylic acid such as 2-ethylhexanoic acid, the imidazole group is exchanged quantitatively.

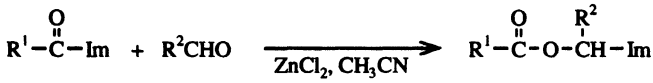


This azole transfer has been used for expedient gas chromatographic determination of 2-ethylhexanoic acid.[34]

Addition of Azolides

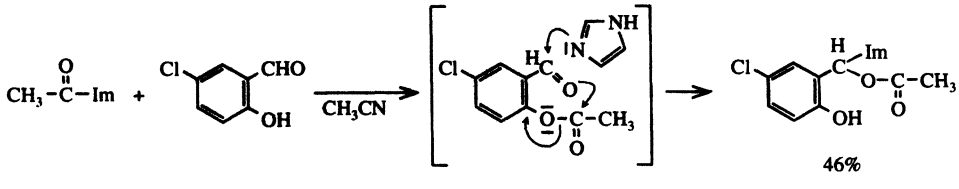
In contrast to the reactions presented above, the reactions described below yielded isolable addition products.

a) In the reaction of carboxylic acid imidazolides with aldehydes in the presence of zinc chloride as catalyst, 1-imidazolylmethyl esters are obtained:[35] The yield was low in the case of unsaturated aldehydes.

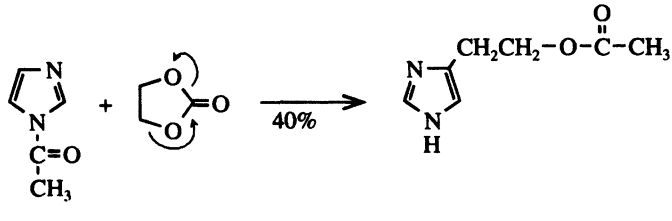


R^1	R^2	Yield (%)
CH_3	H	72
C_2H_5	CH_3	53
p-$CH_3C_6H_4$	H	79
p-$CH_3C_6H_4$	CH_3	54

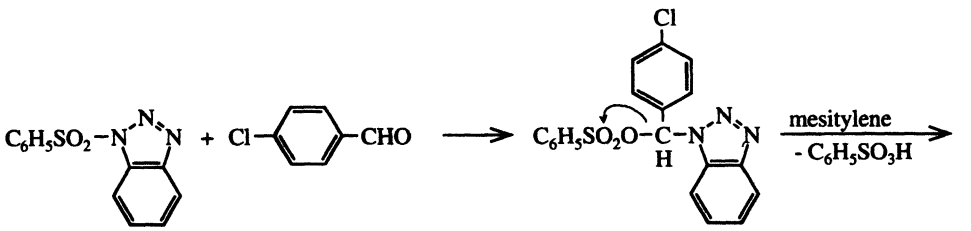
An analogous reaction with an *o*-hydroxybenzaldehyde proceeded with migration of the acetyl group:[36]

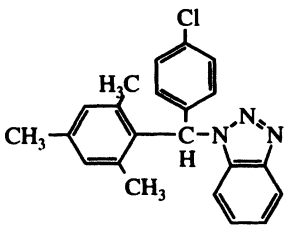


b) *N*-acetylimidazole reacts with ethylene carbonate under elimination of CO_2:[37]



c) In the reaction of 1-phenylsulfonylbenzotriazole with aromatic aldehydes an arylbenzotriazolylmethyl phenylsulfonate is formed (benzyl-stabilized carbocation), which can be used further in a Friedel–Crafts type reaction with aromatic compounds to afford benzotriazolyldiphenylmethanes.[38]





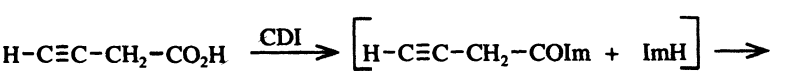
56%

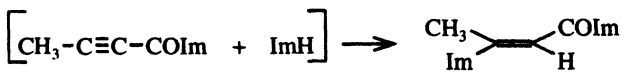
In addition to mesitylene, 2-methoxynaphthalene, 1,3,5-trimethoxybenzene, xylene, and anisole have also been benzotriazolylalkylated in this way (the latter two in lower yield).

d) Reaction of CDI with propynoic acid or 3-butynoic acid leads, along with the expected reaction of the carboxy group, to addition of the resulting imidazole to the triple bond, giving stereoselectively 1-[(*E*)-3-(1-imidazolyl)-2-alkenoyl]imidazoles[39] (see also the reaction of CDI with unsaturated carboxylic acids in Chapter 3):

58%

Suggested mechanism for the reaction of butynoic acid and CDI;





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Azolides in Organic Synthesis and Biochemistry. H. A. Staab, H. Bauer, K. M. Schneider

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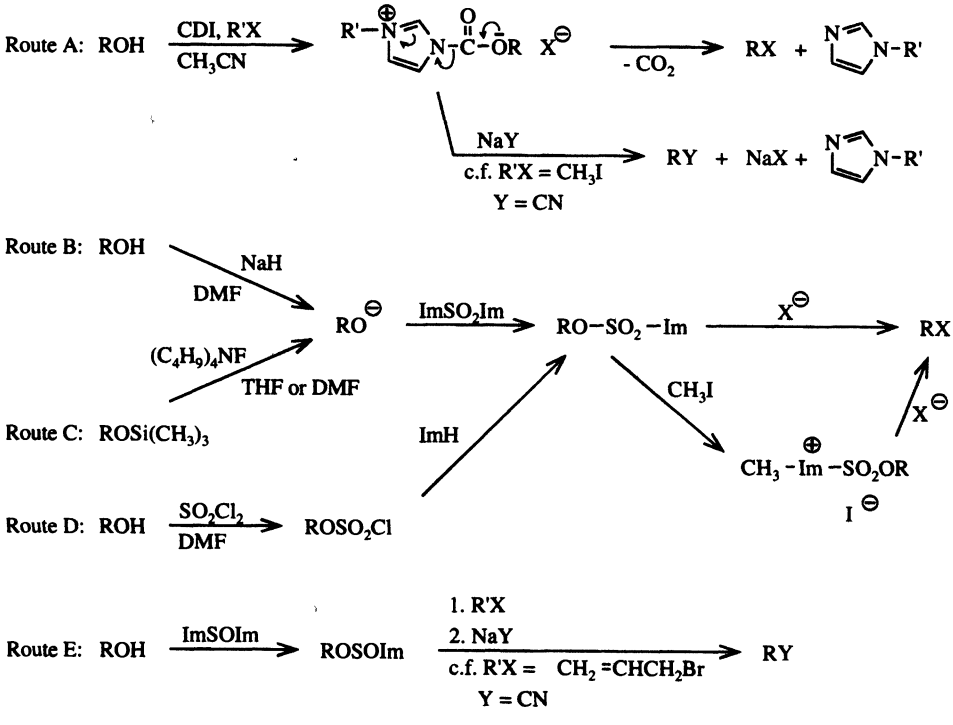
21 Syntheses of Organic Halides/ Pseudohalides and Aromatic Amines

Organic Halides/Pseudohalides from Alcohols

The conversion of primary and secondary alcohols into alkyl halides via imidazolides can be achieved by five different routes:



Route A[1] is very convenient for the substitution of OH groups by bromide or iodide. The reaction conditions are relatively mild (acetonitrile, room temperature, and reflux for 1–3 h, neutral medium). The activating halide (methyl iodide, allyl or benzyl bromide) is added in excess (5 equivalents) or in large excess (10 equivalents) when the resultant halide is nearly as reactive as the activating halide. The imidazolium-*N*-carboxylates are the important intermediates, which undergo a displacement reaction to give the halides,

under elimination of CO_2, in high yield. The reaction is usually carried out as a one-pot procedure. Racemization occurs in reactions with optically active alcohols. The method is not expedient for preparing alkyl chlorides or fluorides.[1]

Routes B, C, and D permit the hydroxy groups of carbohydrates to be converted via the alkoxide into imidazolesulfonates, which readily undergo nucleophilic substitution with F^-, Cl^-, I^- and N_3^- at room temperature or in refluxing THF or toluene to give the corresponding halide in high yield.[2] Benzoates can also be obtained by this displacement reaction (see Section 3.1.7). In route B the alkoxide is generated by sodium hydride, in route C by treatment of the trimethylsilylether with tetrabutylammonium fluoride. The resulting alkoxide reacts further with *N,N'*-sulfonyldiimidazole to give the imidazolesulfonate as a stable crystalline solid or a syrup. Route D proceeds through initial formation of a chlorosulfate ester.[2] Imidazolesulfonate anion or especially imidazoliumsulfonate constitute very good leaving groups. Route E corresponds to route A replacing CDI by *N,N'*-sulfinyldiimidazole.

Table 21–1. Halides prepared from alcohols via imidazole-*N*-carboxylates, -sulfonates and -sulfinates.

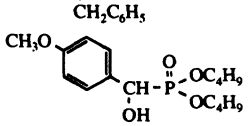
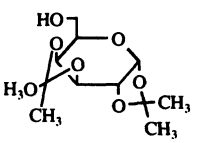
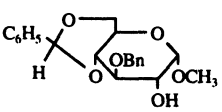
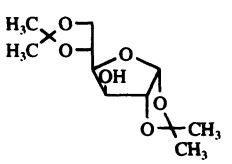
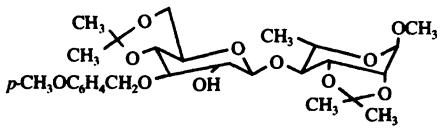
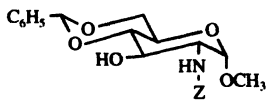
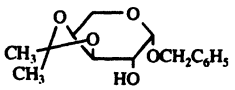
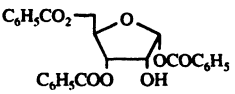
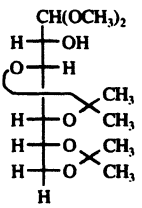
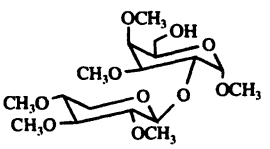
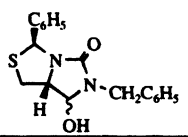
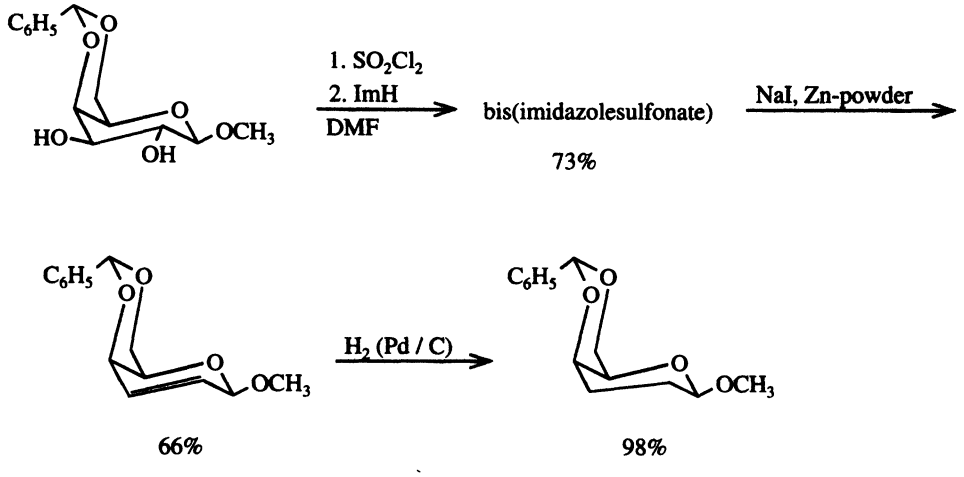
Alcohol ROH	Route	Intermediate imidazolide yield (%)	R'X/$X^{\ominus}$ and $Y^{\ominus}$, resp.	Product RX and RY, resp.	Yield (%)	Ref.
$C_6H_5(CH_2)_3OH$	A	not isolated	$CH_2=CHCH_2Br$	RBr	97	[1]
$C_6H_5(CH_2)_3OH$	A	not isolated	CH_3I	RI	96	[1]
$C_6H_5(CH_2)_4OH$	A	not isolated	$CH_2=CHCH_2Br$	RBr	98	[1]
$C_6H_5CH_2CHOH$ CH_3	A	not isolated	CH_3I	RI	80	[1]
$C_6H_5(CH_2)_2CHOH$ CH_3	A	not isolated	$CH_2=CHCH_2Br$	RBr	94	[1]
$C_6H_5CH_2CHOH$ $CH_2C_6H_5$	A	not isolated	$C_6H_5CH_2Br$	RBr	95	[1]
	A	not isolated	$CH_2=CHCH_2Br$	RBr	quant.	[1a]
			NaI	RI	81	[2]
	D	81	CH_3I / ImH	RI	78	[2]
			$[CH_3(CH_2)_3]_4NF$	RF	75	[2]
			NaN_3	RN_3	81	[2]
	B	87	$[CH_3(CH_2)_3]_4NCl$	RCl (inversion)	78	[2]
	D	96	$[CH_3(CH_2)_3]_4NI$	RI (inversion)	82	[2]
Bn = $C_6H_5CH_2$			$[CH_3(CH_2)_3]_4NCl$ / NaN_3	RN_3 (inversion)	89	[2]
	C	91	$[CH_3(CH_2)_3]_4NI$	RI (inversion)	71	[2] see also [2a]
	D	91	$[CH_3(CH_2)_3]_4NCl$ / NaN_3	RN_3 (inversion)	61	[2]

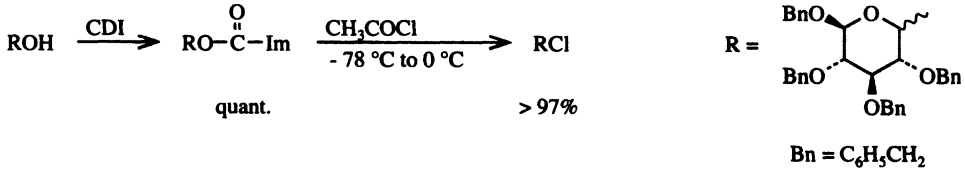
Table 21–1. (*continued*)

Alcohol ROH	Route	Intermediate imidazolide yield (%)	$R'X/X^{\ominus}$ and $Y^{\ominus}$, resp.	Product RX and RY, resp.	Yield (%)	Ref.
 glucopyranosyl-α - L-α-L-rhamnopyranoside	B	94	NaN_3	RN_3	83	[3]
	D	87	$[CH_3(CH_2)_3]_4NI$	R-α- or β-I	85	[4]
	D	68	$[CH_3(CH_2)_3]_4NCl$ / NaN_3	RN_3 (inversion)	80	[5]
	D	85	KHF_2 / HF	RF (inversion)	63	[6]
	B	quant.	NaN_3	RN_3 (inversion)	64	[7]
	B	95	$[CH_3(CH_2)_3]_4NI$	RI	81	[8]
	C E	95 59	CH_3I / KCN $CH_2{=}CHCH_2Br$/ NaCN	RCN RCN	89 50	[9] [10]

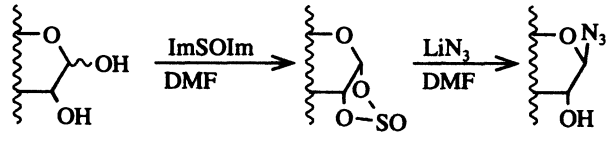
The displacement reaction of a vicinal bis(imidazolesulfonate) via the bisiodide has been used for double deoxygenation of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside:[11]



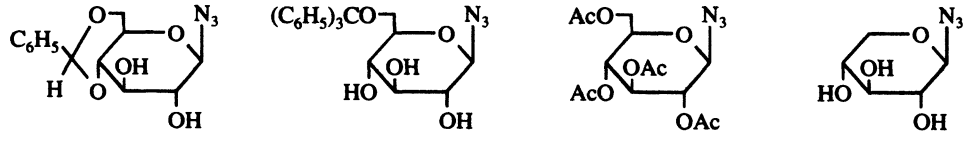
N-Alkoxycarbonylimidazoles can also be converted to chlorides by treatment with acetyl chloride. Anomeric chlorides are thereby produced, with inversion of the initial stereochemistry.[12]



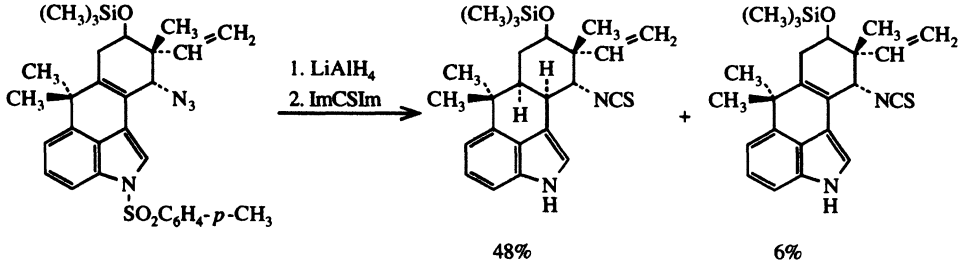
The activation of an anomeric hydroxyl group from partially protected or unprotected monosaccharides can be achieved via 1,2-cyclic sulfite formation. A subsequent *trans*-ring opening with azide N_3^- affords one anomeric derivative exclusively:[13]



By this stereoselective one-pot synthesis the following 1,2-*trans*-glycosylazides have been obtained:

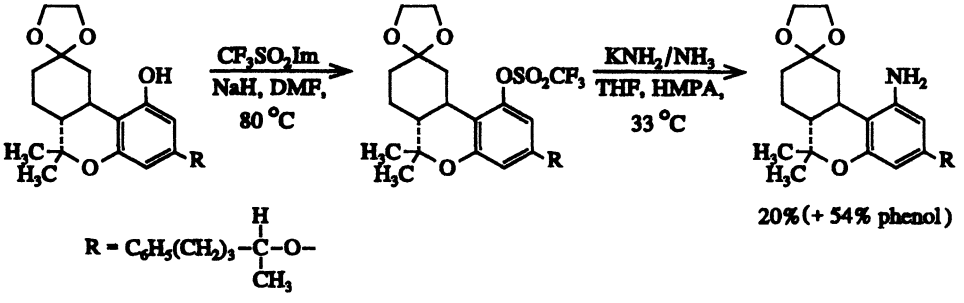


An azide group can be transformed into a thiocyanate group by reduction with $LiAlH_4$ followed by treatment with *N,N'*-thiocarbonyldiimidazole.[14]



Aromatic Amines from Phenols

Phenols can be converted with trifluoromethylsulfonic imidazolide in the presence of sodium hydride into the corresponding trifluoromethylsulfonates, which react with potassium amide/ammonia to give aromatic amines.[15]



This method is superior to that involving the phosphoric ester (treatment first with $(C_2H_5O)_2POCl$ and then with KNH_2).

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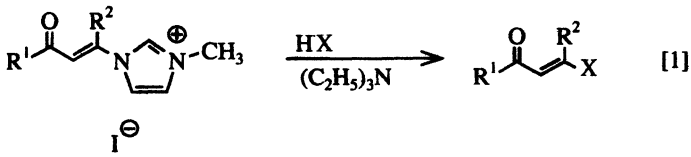
22 Reactions of Vinylogous Azolides

3-Heterosubstituted 2-Alkene-1-ones

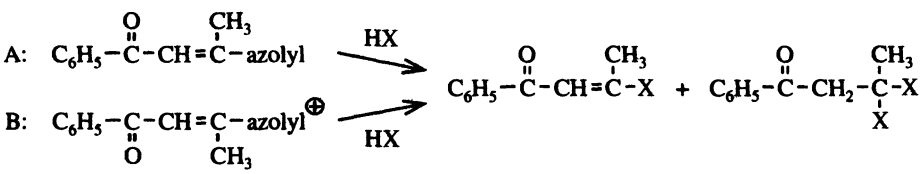
3-(1-Imidazolyl)-2-alkene-1-ones, which are vinylogous azolides, react like azolides with nucleophiles HX such as alcohols, phenols, mercaptans, and amines to give vinylogous esters and amides, respectively. For the reaction with phenols it is expedient to introduce the methiodide of 3-(1-imidazolyl)-2-alkene-1-one because of its greater reactivity.[1] The reactivity of the quaternary salt was found to be nearly equal to that of a 3-chloro-2-alkene-1-one.[2]



[1]

R^1	R^2	HX	vinylogous ester yield (%)
CH_3	CH_3	*p*-$CH_3C_6H_4OH$	63
C_6H_5	CH_3	*p*-ClC_6H_4OH	71
CH_3	C_6H_5	*p*-$CH_3C_6H_4OH$	50 (E/Z = 2:1)
C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4OH$	83 (E + Z)

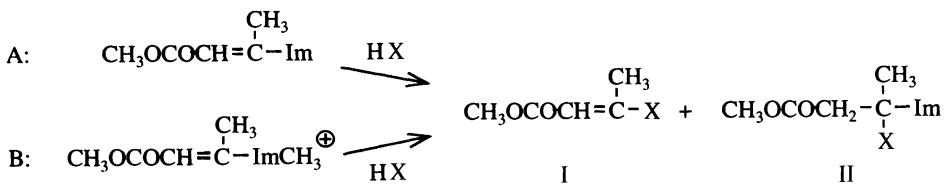
Analogously to vinylogous imidazolides, vinylogous benzimidazolides, triazolides, and pyrazolides also react with nucleophiles to give the corresponding 3-heterosubstituted 2-alkene-1-ones in fairly good yield. Whereas an alcohol is conveniently introduced as its sodium salt for the reaction with a vinylogous azolide, thiols and amines are nucleophilic enough for these reactions to occur directly. In some cases, addition of the nucleophile to the double bond of the alkenone system occurs:[3]



Nucleophile HX	Route	Azolyl	Yield (%)
CH_3OH*	A	1-imidazolyl	14
CH_3OH*	B	1-imidazolyl	41
C_2H_5SH	A	1-imidazolyl	73
C_6H_5SH	A	1-imidazolyl	22
C_6H_5SH	B	1-imidazolyl	96
pyrrolidine	A	1-imidazolyl	26
pyrrolidine	B	1-imidazolyl	44
CH_3OH*	A	1-benzimidazolyl	46
C_6H_5SH	A	1-benzimidazole	70
CH_3OH*	A	1,2,4-triazolyl	46
C_6H_5SH	A	1,2,4-triazolyl	82
pyrrolidine	A	1,2,4-triazolyl	78

* as sodium methylate

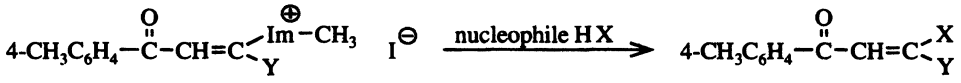
If vinylogous imidazole-*N*-carboxylates (route A) are treated with nucleophiles such as alkoxides or amines, the corresponding vinylogous carbonic esters or amides are obtained. While reaction of the vinylogous imidazole-*N*-carboxylate with a thiol (route A) yields the addition product only, that of the corresponding imidazolium compound (route B) leads to the carbonic thioester in a substitution reaction:[3]



Route	Nucleophile HX	Yield (%) I	Yield (%) II
A	CH_3OH*	71	—
A	C_2H_5SH	—	65
A	C_6H_5SH	—	80
A	pyrrolidine	42	—
B	C_2H_5SH	79	—
B	C_6H_5SH	42	—
B	pyrrolidine	27	—

* as sodium methylate

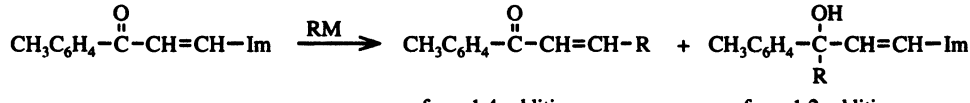
The 3-methylimidazolium-3-amino-2-propen-1-one compounds can also be considered as vinylogous azolides, as the following reactions with nucleophiles demonstrate:[4]



Y	HX	Yield (%)
pyrrolidinyl	C_6H_5SH	31
NH_2	CH_3OH	45
CH_3NH	CH_3OH	49
pyrrolidinyl	$NaBH_4$	47 (Y = H)
pyrrolidinyl	CH_3MgI	39 (Y = CH_3)

2-Alkene-1-ones

In the reaction of 3-(1-imidazolyl)-2-alkene-1-ones with organometallic compounds or sodium borohydride ($NaBH_4$), only the route leading to a 2-alkene-1-one via a 1,4-addition reflects azolide chemistry.[5]



RM	Total yield (%)			
CH_3MgI	60	50	:	50
C_4H_9MgI	47	70	:	30
CH_3Li	44	30	:	70
C_4H_9Li	50	65	:	35
$NaBH_4$	60	35	:	65

With 3-(1-imidazolyl)-2-alkene-1-ones bearing a substituent at C-3, regioselective 1,2-addition occurs because of steric hindrance.[6]

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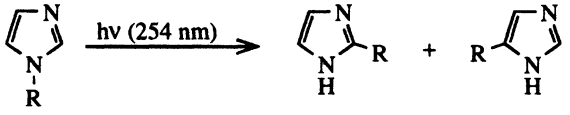
23 Photochemical Reactions

Photochemical 1,2-Shift of the Acyl Group in Imidazolides

Photochemical treatment of an *N*-acylimidazole results in a 1,2-shift (N-C migration) of the acyl group to give a mixture of 2- and 5-acylimidazoles (photo-Fries products):[1],[2]



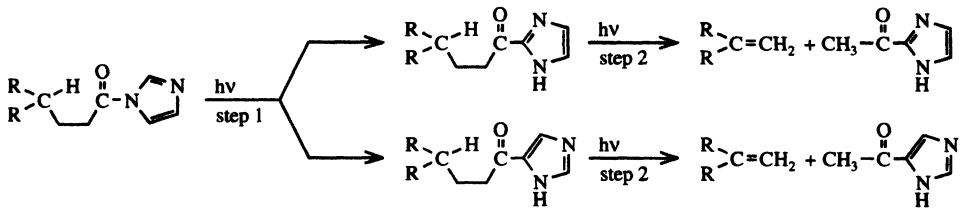
R	Yield (%)	Yield (%)
CH_3CO	26	30
c-$C_6H_{11}CO$	39	29
$(CH_3)_3CCO$	28	30
C_6H_5CO	13	23
$(CH_3)_2C{=}CHCO$	16	31
CH_3OCO	16	10
$(C_2H_5)_2NCO$	8	10

Deuteration experiments suggested an intra- as well as an intermolecular migration of the acyl group. *p*-Methoxybenzoyl- and *p*-nitrobenzoylimidazole did not undergo acyl migration upon irradiation. *N*-Crotyl- and *N*-geranylimidazoles are stable to irradiation.[2]

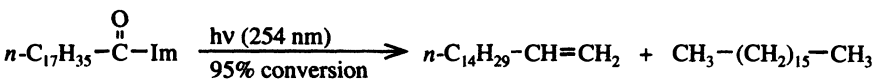
Migration of the imidazolylcarbonyl group in addition to N–C migration of the acyl moiety was observed upon irradiation of 1-(dehydroabietoyl)imidazole and 1-(13′-de-isopropyl-10′-*epi*-dehydroabietoyl)imidazole.[3]

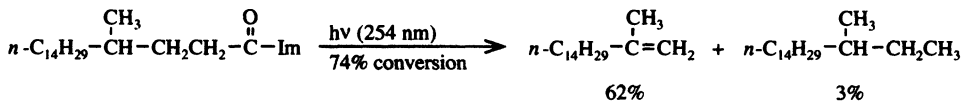
1,2-Shift and Fragmentation

If there are hydrogen atoms in the γ-position relative to the acyl group, irradiation of an imidazolide leads to a 1,2-shift of the acyl group (step one) followed by a Norrish type II or type I fragmentation (step two):[4],[5]

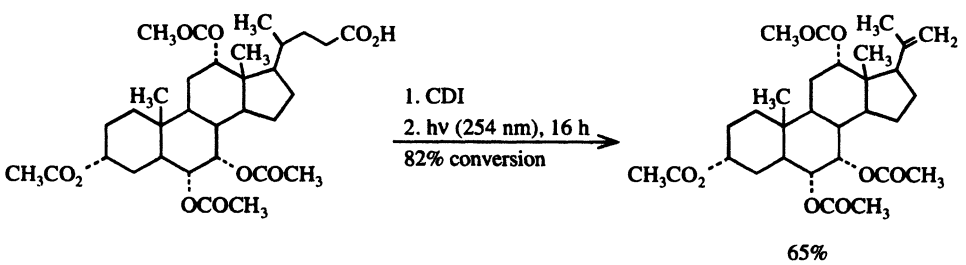


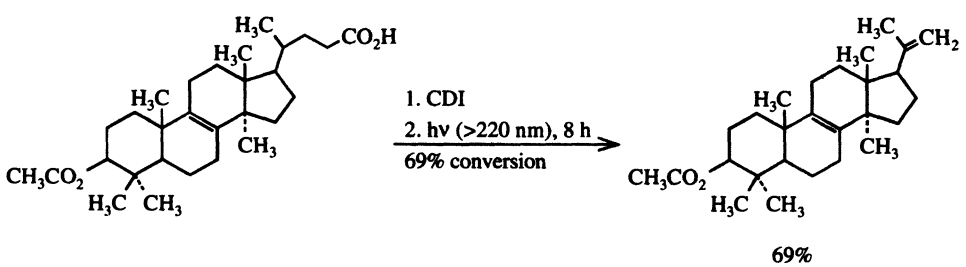
Examples:





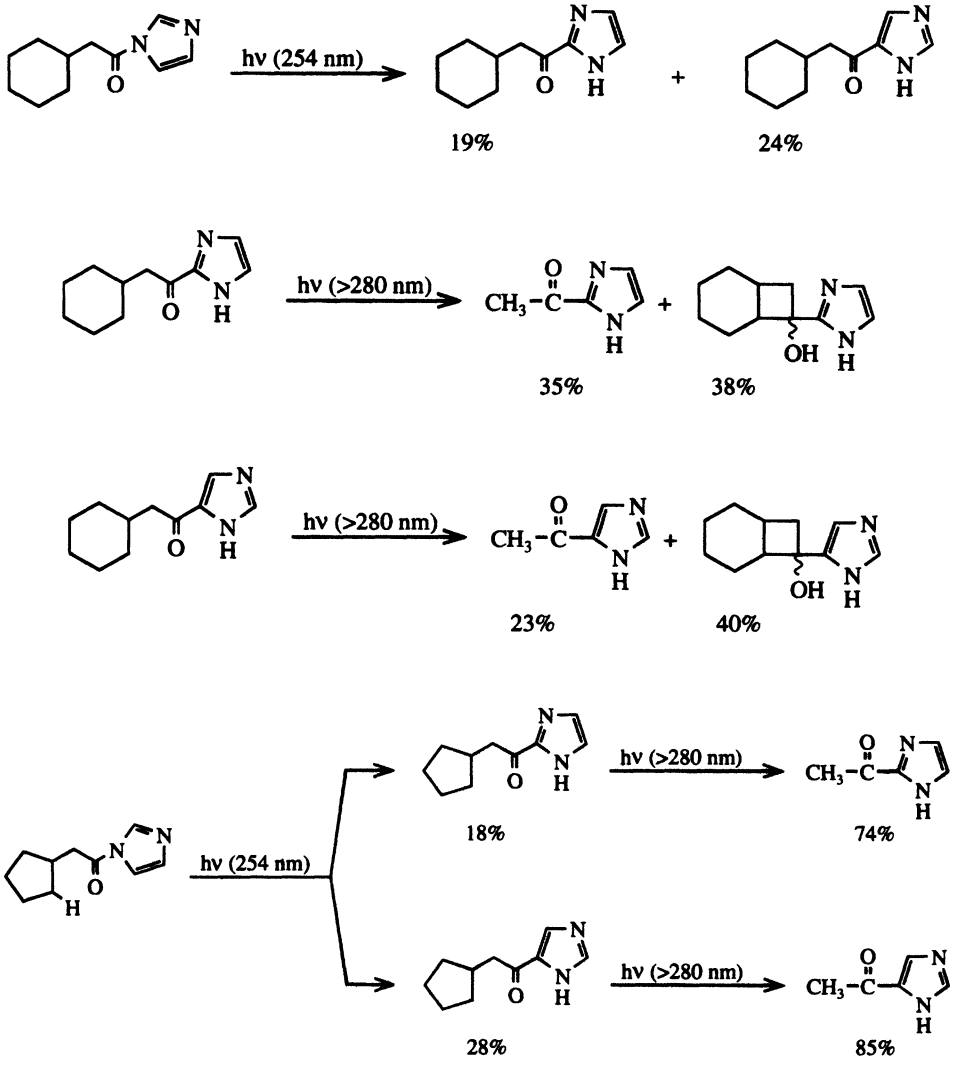
This reaction has been utilized for side-chain degradation of substituted cholic acids and lanostenoic acid:[4],[6]





Conformational factors in the photolysis of *N*-acylimidazoles leading to Norrish type II products or cyclobutanols have been discussed in reference [7]. *N*-Acylimidazoles have been irradiated in tetrahydrofuran using a low-pressure mercury lamp (quartz well,

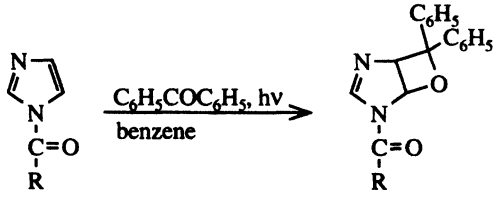
254 nm) to give photorearranged C-substituted products, which were irradiated further in methanol without or in the presence of acid using a medium-pressure mercury lamp (pyrex well, 280 nm). These procedures resulted in comparable yields of cyclobutanols and fragmentation products from 1-(cyclohexylacetyl)imidazole, while in the case of 1-(cyclopentylacetyl)imidazole only elimination products are formed:[7]



The photolysis of *cis*- and *trans*-decalin-9-carboxylic acid imidazolide has also been investigated.[7]

Addition onto Imidazolides

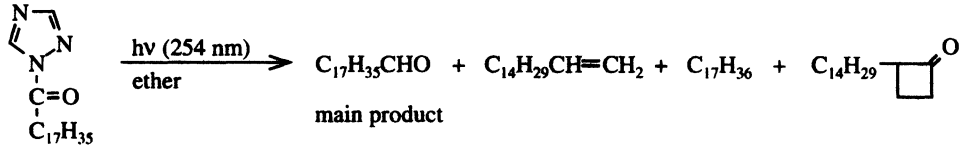
1-Acylimidazoles in the presence of benzophenone lead to oxetanes on irradiation with a medium-pressure mercury lamp:[8]



R	yield (%)
CH_3	50
C_6H_5	34
Im	51

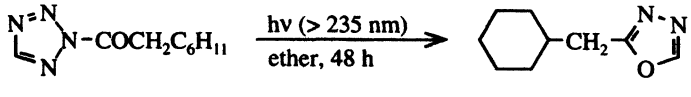
N-Acyl Fission in the Photolysis of Triazolides and Tetrazolides

Irradiation of 1-acyl-1,2,4-triazoles, contrary to *N*-acylimidazoles affords no photo-Fries products, but instead forms aldehydes and other products via the corresponding acyl radicals.[9]



Investigation of the photolysis of some *N*-acylbenzotriazoles is discussed in reference [10].

2-Acyltetrazoles did not give Fries products but rather 2-alkyl-1,3,4-oxadiazoles as the main products, among others.[9]



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Azolides in Organic Synthesis and Biochemistry. H. A. Staab, H. Bauer, K. M. Schneider

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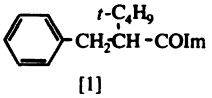
24 Azolides in Medicinal and Industrial Fields and in Analytical Methods

24.1 Applications in Various Medicinal and Industrial Fields

Some azolides are distinguished by their practical applications, extending from their potential as fungicides, herbicides, and insecticides to their utility as textile auxiliaries, antiflammatory agents, or phase-transfer catalysts. The various azolides of these properties have been compiled below in five groups.

1. Azolides used as pesticides, fungicides, herbicides, insecticides, acaricides, agricultural antibacterials, and plant-growth regulators: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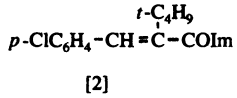
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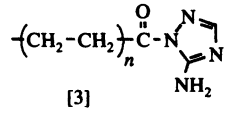
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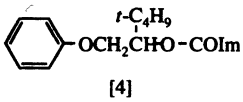
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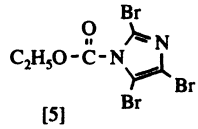
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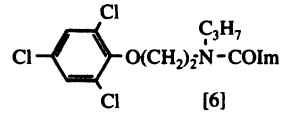
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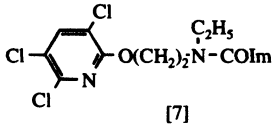
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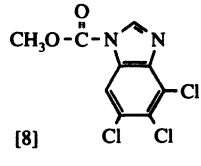
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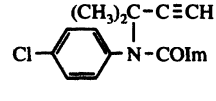
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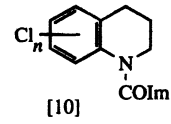
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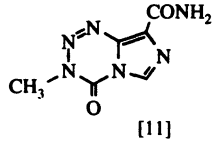
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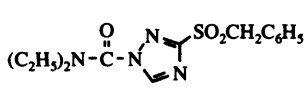
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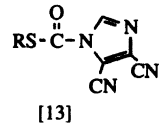
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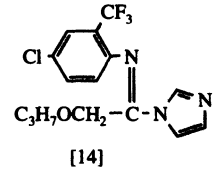
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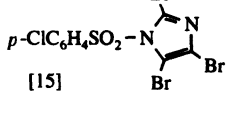
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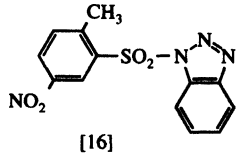
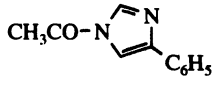

[16]

2. Azolides used as inhibitors for monoamine oxidase[17] or human leucocyte elastase,[18] as inductors of recessive lethal genes in Drosophila,[19] as histamine H_2-receptor antagonists,[20] as anti-ulcer agents,[21] or as pharmacophores for anthelmintic, analgesic, and antimicrobial activity:[22]



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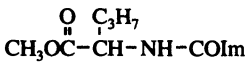

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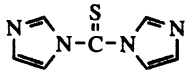

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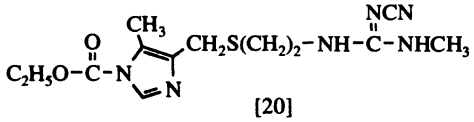

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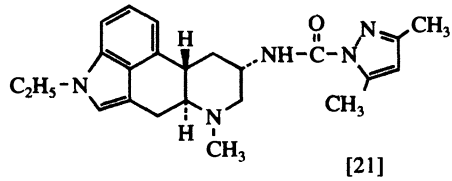

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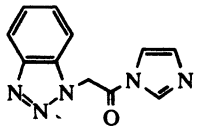

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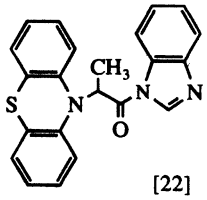

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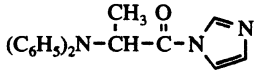
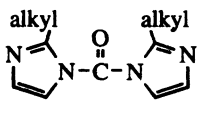
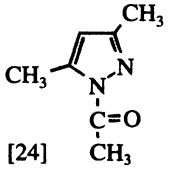


[22]

3. Azolides used as promotors in the anionic polymerization of lactams,[23],[24] and as plasticizers for PVC:[25]



[23,24]



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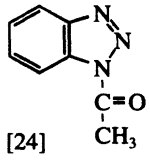

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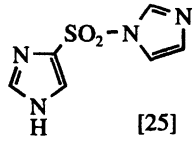
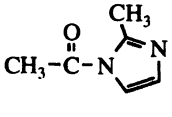
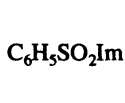


[25]

4. Azolides used as activators for sodium percarbonate/perborate in laundry bleaching,[26]–[29] for decreasing the affinity of polyamide textile materials for acid dyes,[30] and as antiflammatory agents:[31]



[26,30]



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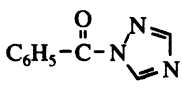
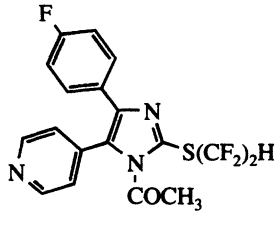
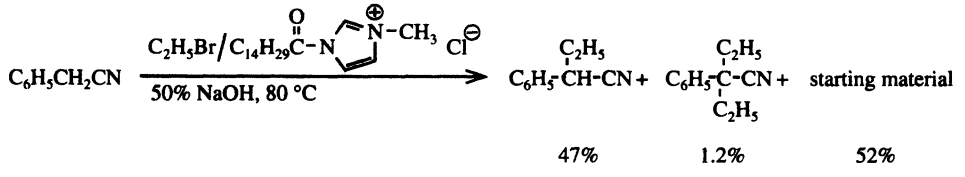


[27,29]



[31]

5. 1-Tetradecanoyl-3-methyl imidazolium chloride, which has been applied as a phase-transfer catalyst in the alkylation of benzyl cyanide at elevated temperature:[32]



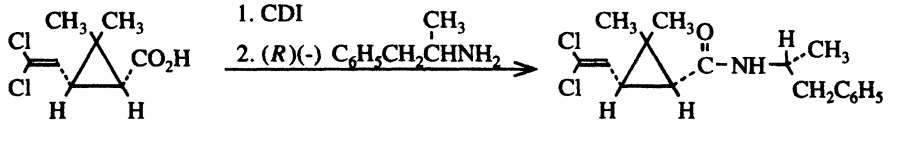
24.2 Applications in Analytical Methods

Chromatographic Determinations

A gas liquid chromatographic assay for determining the quantity and composition of fatty acids is based on conversion of the acids by means of CDI with methanol, ethanol, trifluoroethanol, pentafluoropropanol, or heptafluorobutanol into the corresponding esters. The alcohols in question were chosen because of the short retention times of their esters.[33]

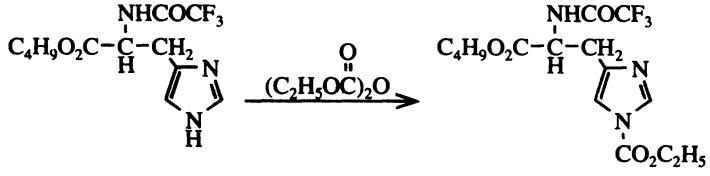
Gas liquid chromatographic determination of amphetamine, tryptamine, ephedrine, isopropanolamine, codeine, and morphine has been achieved by transforming these compounds on the column with *N*-trifluoroacetylimidazole or *N*-(heptafluorobutyryl)imidazole into *N,N*-bisacylamphetamine,[34] *N,N*-bisacyltryptamine,[35] *N,O*-bisacylephedrine,[34] *N,O*-bisacylisopropanolamine,[36] *O*-acylcodeine,[34],[37] and *O,O*-bisacylmorphine.[34],[37] In the same way, hydroquinone,[38] catechol,[38] 2-ethylhexanol,[39] and melatonin[40] were derivatized with *N*-(heptafluorobutyryl)imidazole and assayed chromatographically. The derivatization of 2-ethylhexanoic acid with *N*-heptafluorobutyrylimidazole leads to *N*-2-ethylhexanoylimidazole, which has good chromatographic properties.[39]

Mixtures of stereoisomeric 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acids (the acid moieties of permethrin insecticide), CDI, and chiral amines have been investigated by capillary gas chromatography. The diastereomeric amides could be identified by GC/MS-spectrometry:[41]

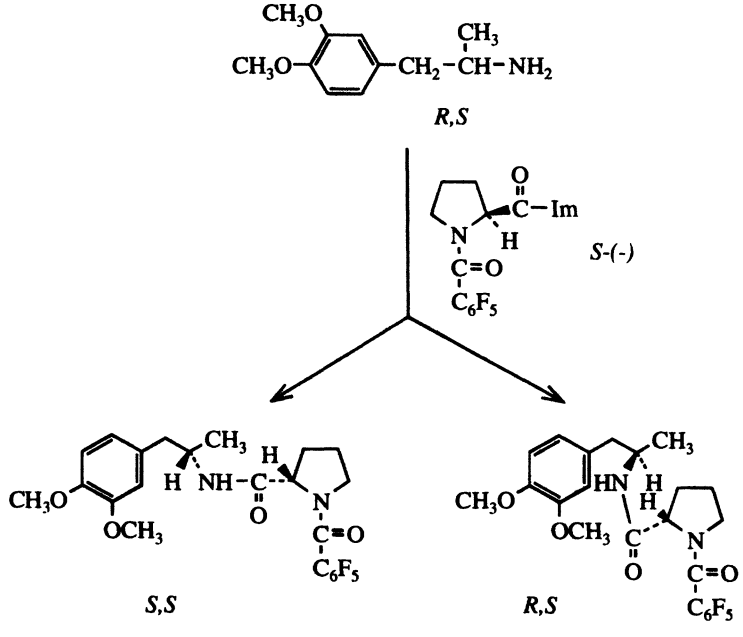


(1*R*,3*S*)-*cis* *R S R* diastereomer

N-Trifluoroacetylhistidine butylester is determined gaschromatographically by its conversion into an imidazole-*N*-ethylcarboxylate:[42]



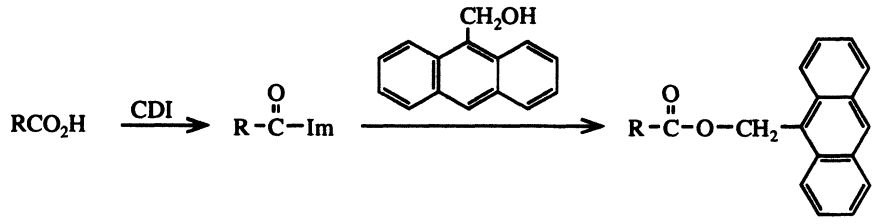
Based on gasliquidchromatography (GLPC) amides, formed from various enantiomeric amines and the chiral-derivatizing reagent (*S*)-(−)-*N*-pentafluorobenzoylprolyl-1-imidazole, could be detected at nanogram levels:[43],[44]



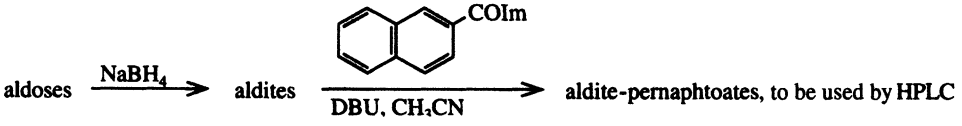
The two diastereomeric amides exhibit different retention times. Other 1-aryl-2-aminopropanes substituted in the phenyl ring as well as α-methylbenzylamine have also been investigated by this method.[44]

Determinations by Fluorescence and Chemiluminescence

Carboxylic acids can be detected fluorimetrically by attaching them to an anthracene moiety:[45]

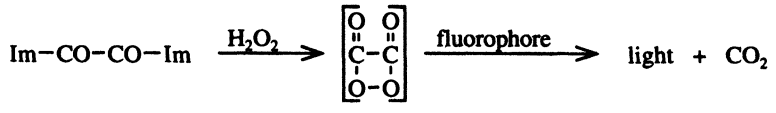


Aldoses, for example mannose, fucose, arabinose, and others, have been detected at the subpicomole level by their reduction to aldites, which are then transformed into pernaphthoates by means of naphthoylimidazole. These pernaphthoates show strong fluorescence at 374 nm, and can be easily separated by HPLC.[46]



For determination of low hydrogen peroxide concentrations, a chemiluminescent reagent system was developed consisting of oxalyldiimidazole and an immobilized fluorophore (3-aminofluoranthene) on an acrylate polymer.[47]

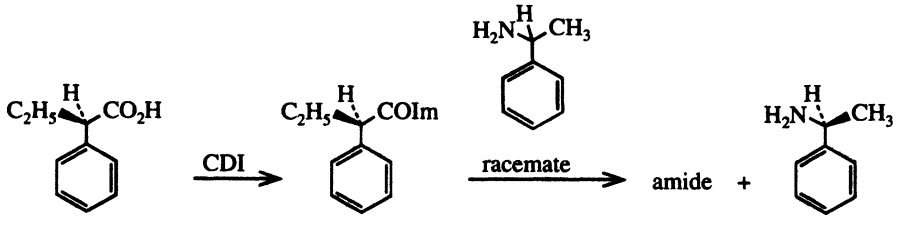
The resulting chemiluminescent intensity was about 10 times more sensitive compared with that from the usual reaction between trichlorophenyl oxalate and H_2O_2.[47]



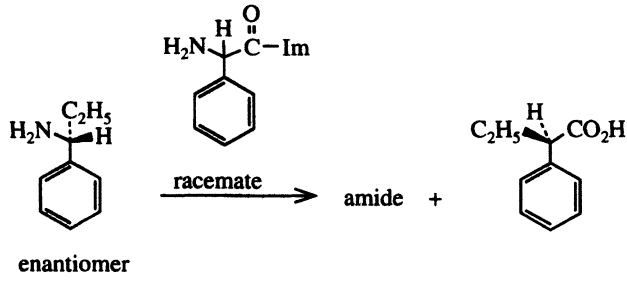
Determination of Chirality

The chirality of carboxylic acids, amines, or alcohols has been determined via azolides in the following ways:

If, according to a modified Horeau method (partial kinetic resolution of a racemate), an optically active carboxylic acid is treated with an excess of racemic amine or alcohol, the configuration of the carboxylic acid can be inferred from the optical rotation of the residual amine or alcohol:[48]



Analogously, the chirality of optically active amines or alcohols can also be determined:[49]



By this method, for example, the absolute configurations of the following compounds were established: (−)-2-phenylbutyric acid,[48] (−)-hydratropic acid,[48] (+)-*O*-acetylmandelic acid,[48] (−)-2-(*N*-carbazolyl)propionic acid,[48] (+)-1-phenylethanol,[48] (−)-menthol,[48] (+)-1-phenylethylamine,[48] and 1-alanine ethylester.[48] The determination of the absolute configuration of bacteriochlorophylles c, d and e was made possible by the esterification of the phaeophorbides by CDI to imidazolides.[49]

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