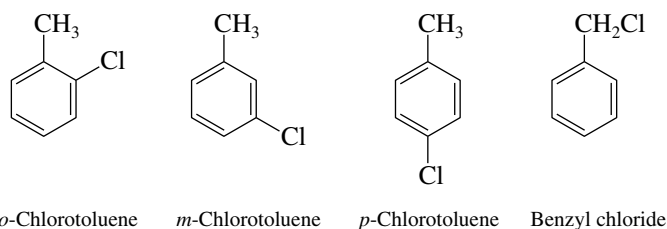


CHAPTER 23

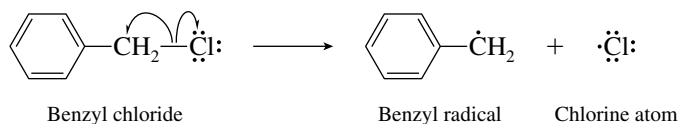
ARYL HALIDES

SOLUTIONS TO TEXT PROBLEMS

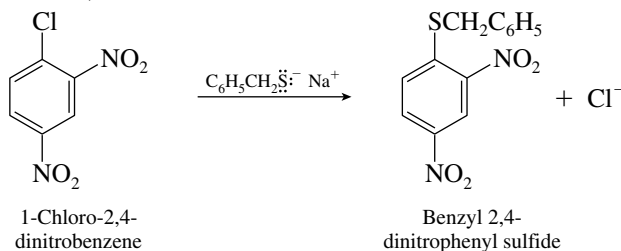
- 23.1 There are four isomers of C_7H_7Cl that contain a benzene ring, namely, *o*-, *m*-, and *p*-chlorotoluene and benzyl chloride.



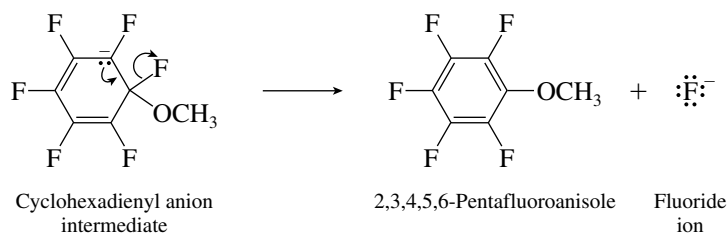
Of this group only benzyl chloride is not an aryl halide; its halogen is not attached to the aromatic ring but to an sp^3 -hybridized carbon. Benzyl chloride has the weakest carbon–halogen bond, its measured carbon–chlorine bond dissociation energy being only 293 kJ/mol (70 kcal/mol). Homolytic cleavage of this bond produces a resonance-stabilized benzyl radical.



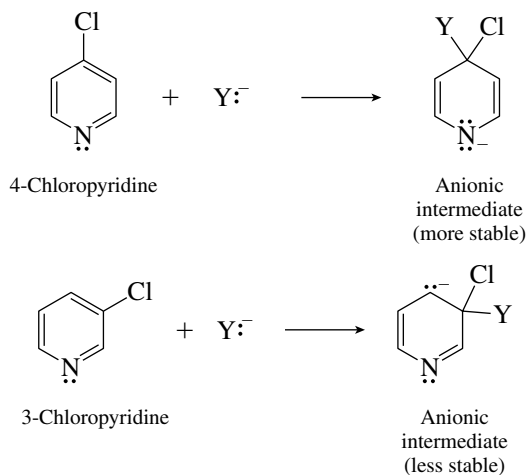
- 23.2 (b) The negatively charged sulfur in $C_6H_5CH_2S^-Na^+$ is a good nucleophile, which displaces chloride from 1-chloro-2,4-dinitrobenzene.



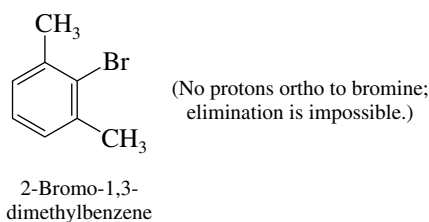
Elimination of fluoride ion from the cyclohexadienyl anion intermediate restores the aromaticity of the ring and completes the reaction.



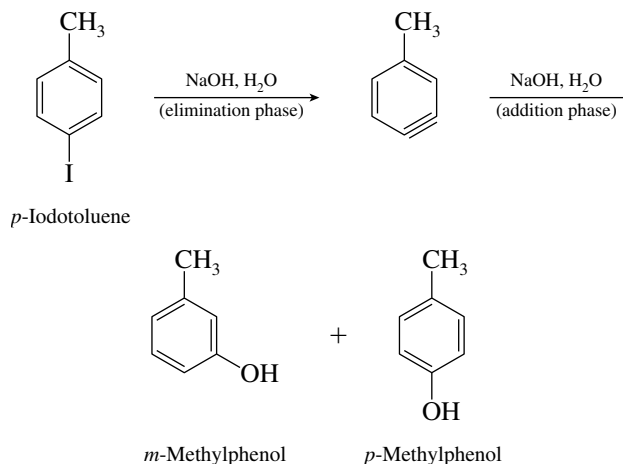
- 23.6** 4-Chloropyridine is more reactive toward nucleophiles than 3-chloropyridine because the anionic intermediate formed by reaction of 4-chloropyridine has its charge on nitrogen. Because nitrogen is more electronegative than carbon, the intermediate is more stable.



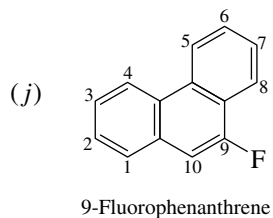
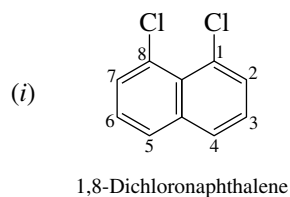
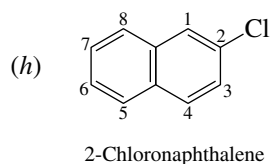
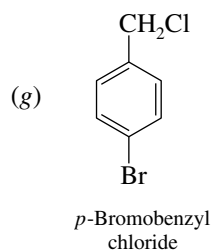
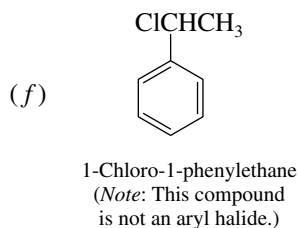
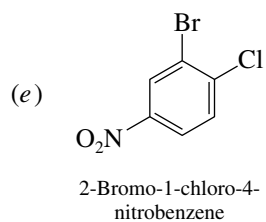
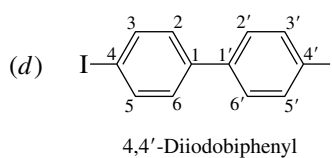
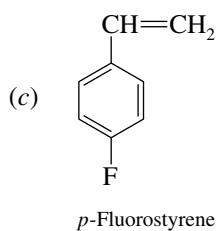
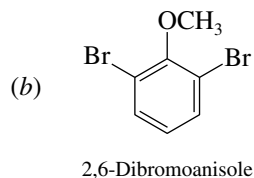
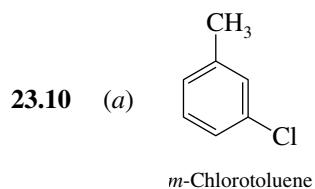
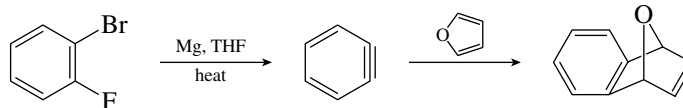
- 23.7** The aryl halide is incapable of elimination and so cannot form the benzyne intermediate necessary for substitution by the elimination–addition pathway.



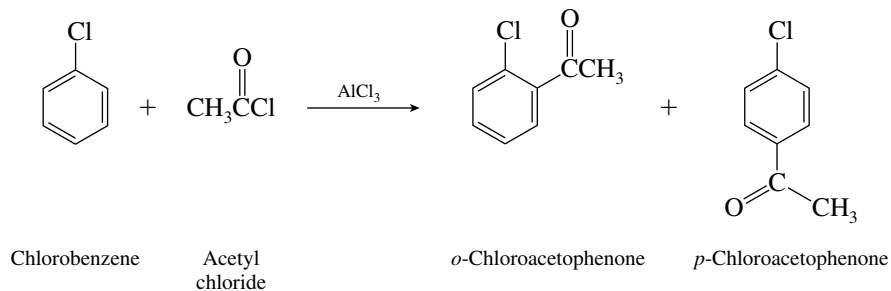
- 23.8** The aryne intermediate from *p*-iodotoluene can undergo addition of hydroxide ion at the position meta to the methyl group or para to it. The two isomeric phenols are *m*- and *p*-methylphenol.



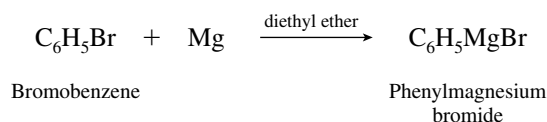
23.9 The “triple bond” of benzyne adds to the diene system of furan.



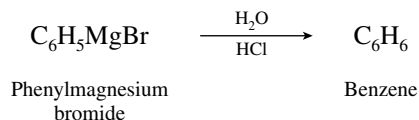
23.11 (a) Chlorine is a weakly deactivating, ortho, para-directing substituent.



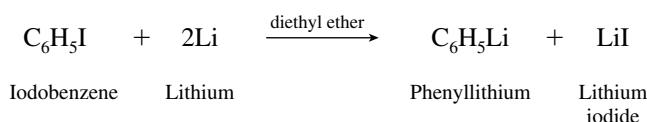
- (b) Bromobenzene reacts with magnesium to give a Grignard reagent.



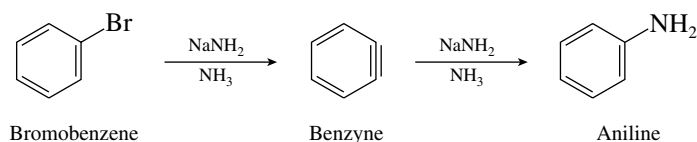
- (c) Protonation of the Grignard reagent in part (b) converts it to benzene.



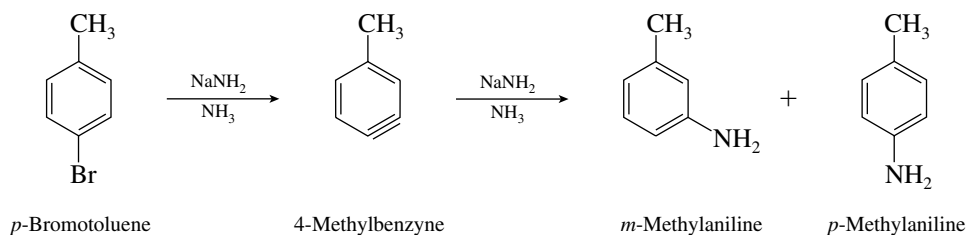
- (d) Aryl halides react with lithium in much the same way that alkyl halides do, to form organolithium reagents.



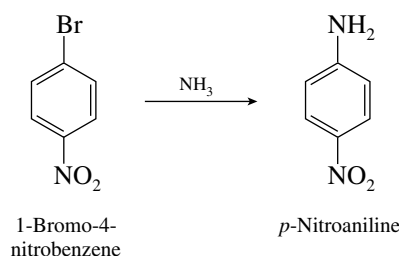
- (e) With a base as strong as sodium amide, nucleophilic aromatic substitution by the elimination–addition mechanism takes place.



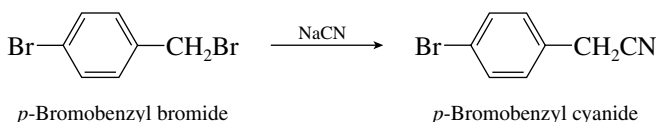
- (f) The benzyne intermediate from *p*-bromotoluene gives a mixture of *m*- and *p*-methylaniline.



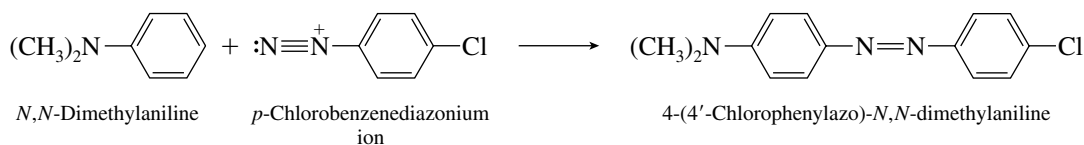
- (g) Nucleophilic aromatic substitution of bromide by ammonia occurs by the addition–elimination mechanism.



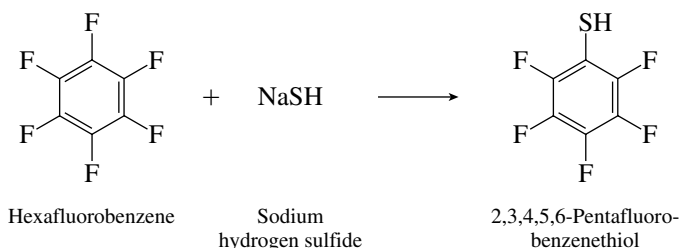
- (h) The bromine attached to the benzylic carbon is far more reactive than the one on the ring and is the one replaced by the nucleophile.



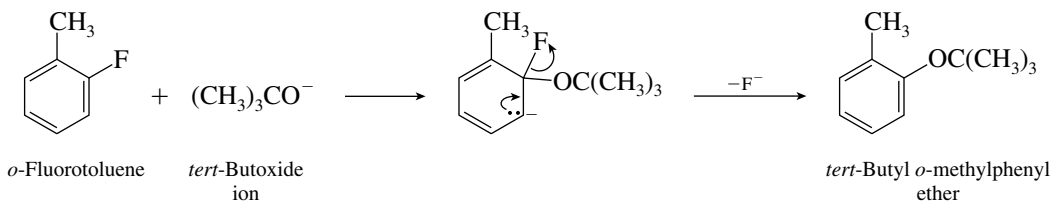
- (i) The aromatic ring of *N,N*-dimethylaniline is very reactive and is attacked by *p*-chlorobenzene-diazonium ion.



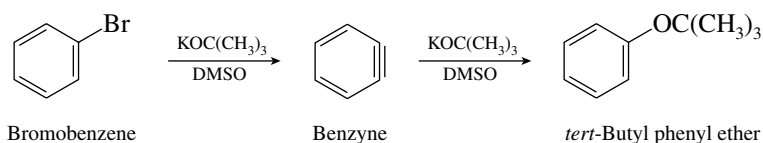
- (j) Hexafluorobenzene undergoes substitution of one of its fluorines on reaction with nucleophiles such as sodium hydrogen sulfide.



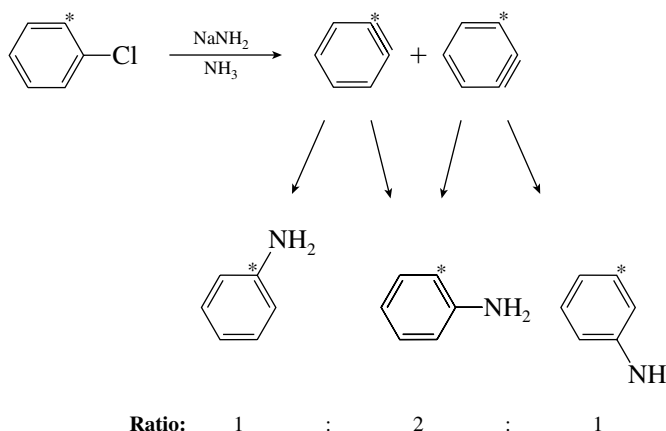
- 23.12 (a) Since the *tert*-butoxy group replaces fluoride at the position occupied by the leaving group, substitution likely occurs by the addition–elimination mechanism.



- (b) In nucleophilic aromatic substitution reactions that proceed by the addition–elimination mechanism, aryl fluorides react faster than aryl bromides. Because the aryl bromide is more reactive in this case, it must be reacting by a different mechanism, which is most likely elimination–addition.

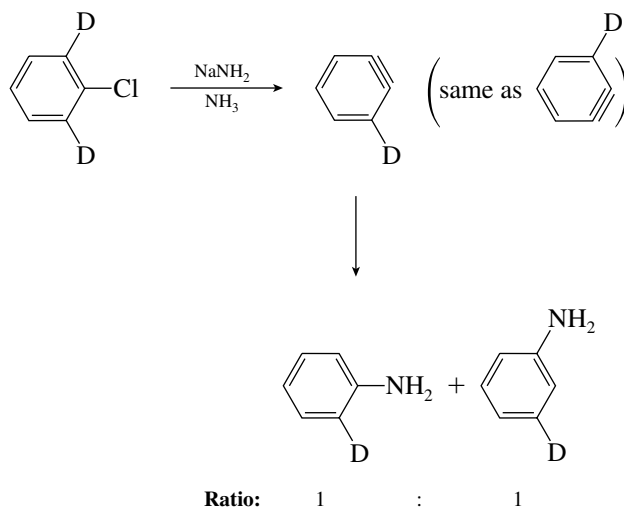


- 23.13 (a) Two benzyne intermediates are equally likely to be formed. Reaction with amide ion can occur in two different directions with each benzyne, giving three possible products. They are formed in a 1:2:1 ratio.



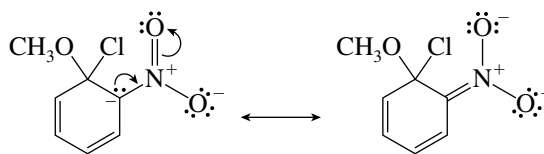
Asterisk (*) refers to ^{14}C .

- (b) Only one benzyne intermediate is possible, leading to two products in a 1:1 ratio.



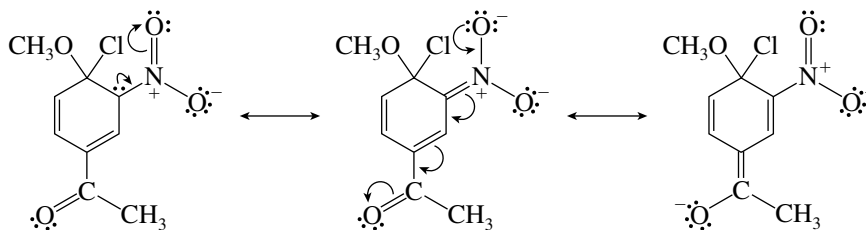
D refers to ^2H (deuterium).

- 23.14 (a) *o*-Chloronitrobenzene is more reactive than chlorobenzene, because the cyclohexadienyl anion intermediate is stabilized by the nitro group.

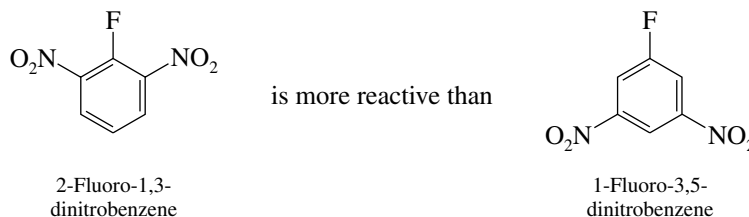


Comparing the rate constants for the two aryl halides in this reaction reveals that *o*-chloronitrobenzene is more than 20 billion times more reactive at 50°C.

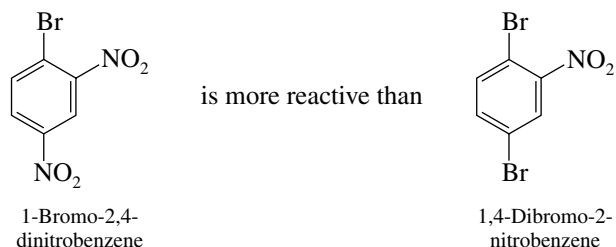
- (b) The cyclohexadienyl anion intermediate is more stable, and is formed faster, when the electron-withdrawing nitro group is ortho to chlorine. *o*-Chloronitrobenzene reacts faster than *m*-chloronitrobenzene. The measured difference is a factor of approximately 40,000 at 50°C.
- (c) 4-Chloro-3-nitroacetophenone is more reactive, because the ring bears two powerful electron-withdrawing groups in positions where they can stabilize the cyclohexadienyl anion intermediate.



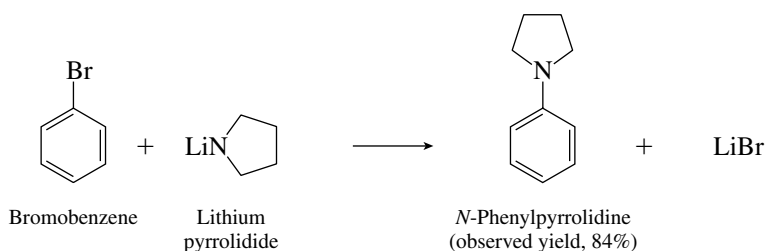
- (d) Nitro groups activate aryl halides toward nucleophilic aromatic substitution best when they are ortho or para to the leaving group.



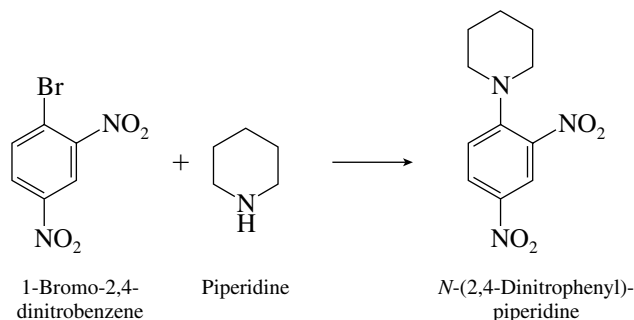
- (e) The aryl halide with nitro groups ortho and para to the bromide leaving group is more reactive than the aryl halide with only one nitro group.



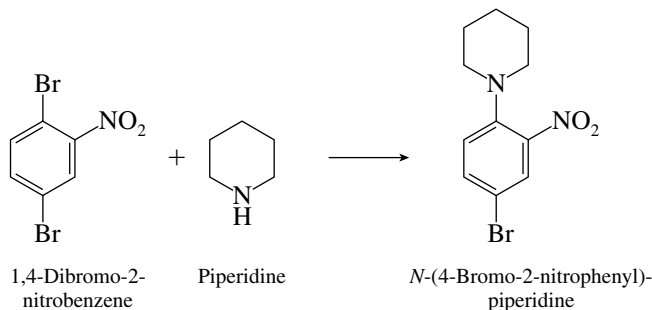
- 23.15 (a) The nucleophile is the lithium salt of pyrrolidine, which reacts with bromobenzene by an elimination–addition mechanism.



- (b) The nucleophile in this case is piperidine. The substrate, 1-bromo-2,4-dinitrobenzene, is very reactive in nucleophilic aromatic substitution by the addition–elimination mechanism.

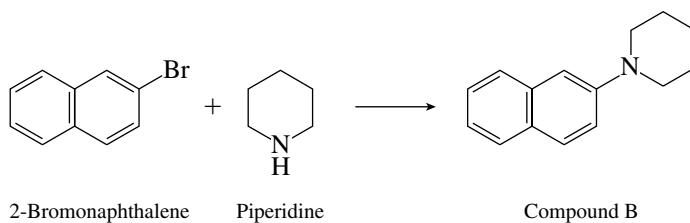
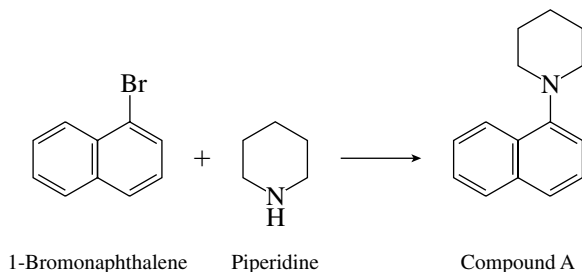


- (c) Of the two bromine atoms, one is ortho and the other meta to the nitro group. Nitro groups activate positions ortho and para to themselves toward nucleophilic aromatic substitution, and so it will be the bromine ortho to the nitro group that is displaced.

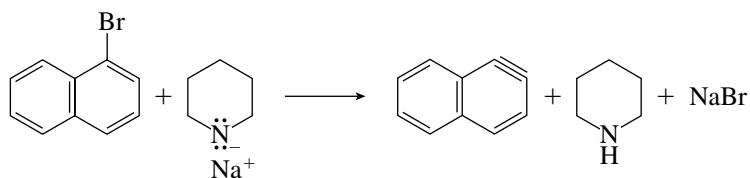


- 23.16 Because isomeric products are formed by reaction of 1- and 2-bromonaphthalene with piperidine at elevated temperatures, it is reasonable to conclude that these reactions do not involve a common

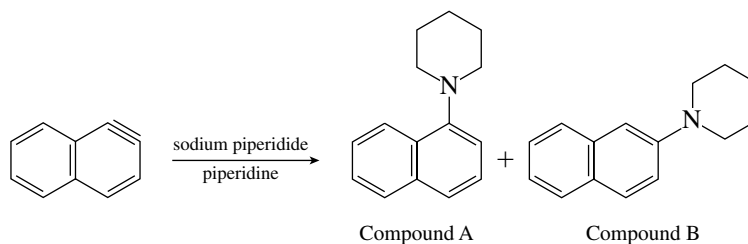
intermediate and hence follow an addition–elimination pathway. Piperidine acts as a nucleophile and substitutes for bromine on the same carbon atom from which bromine is lost.



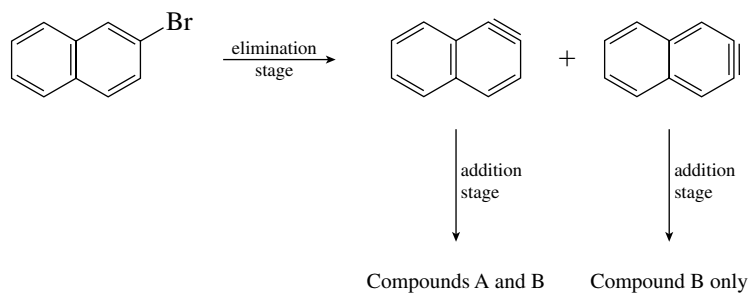
When the strong base sodium piperidide is used, reaction occurs by the elimination–addition pathway via a “naphthalene” intermediate. Only one mode of elimination is possible from 1-bromonaphthalene.



This intermediate can yield both A and B in the addition stage.

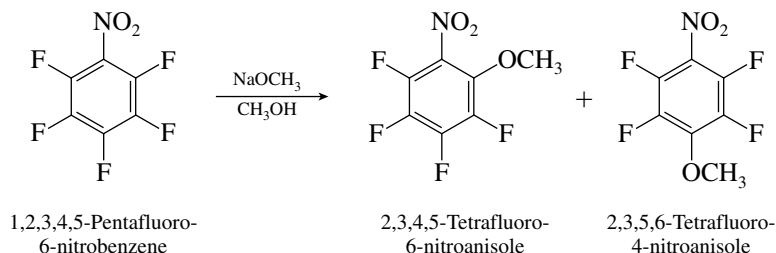


Two modes of elimination are possible from 2-bromonaphthalene:

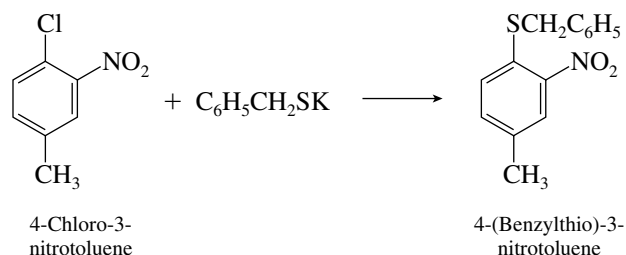


Both naphthalene intermediates are probably formed from 2-bromonaphthalene because there is no reason to expect elimination to occur only in one direction.

- 23.17 Reaction of a nitro-substituted aryl halide with a good nucleophile leads to nucleophilic aromatic substitution. Methoxide will displace fluoride from the ring, preferentially at the positions ortho and para to the nitro group.

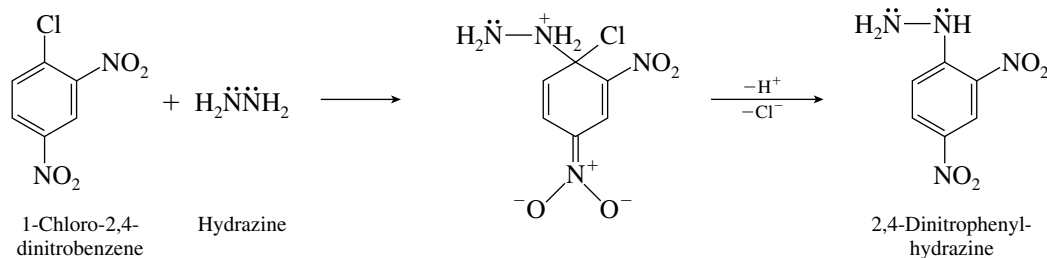


- 23.18 (a) This reaction is nucleophilic aromatic substitution by the addition–elimination mechanism.



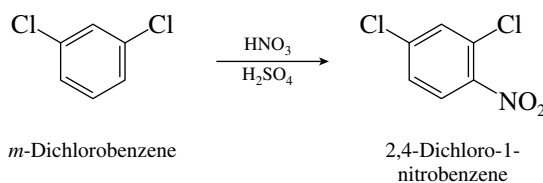
The nucleophile, $\text{C}_6\text{H}_5\text{CH}_2\ddot{\text{S}}^-$, displaces chloride directly from the aromatic ring. The product in this case was isolated in 57% yield.

- (b) The nucleophile, hydrazine, will react with 1-chloro-2,4-dinitrobenzene by an addition–elimination mechanism as shown.



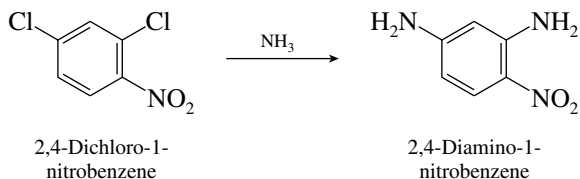
The nitrogen atoms of hydrazine each has an unshared electron pair and hydrazine is fairly nucleophilic. The product, 2,4-dinitrophenylhydrazine, is formed in quantitative yield.

- (c) The problem requires you to track the starting material through two transformations. The first of these is nitration of *m*-dichlorobenzene, an electrophilic aromatic substitution reaction.

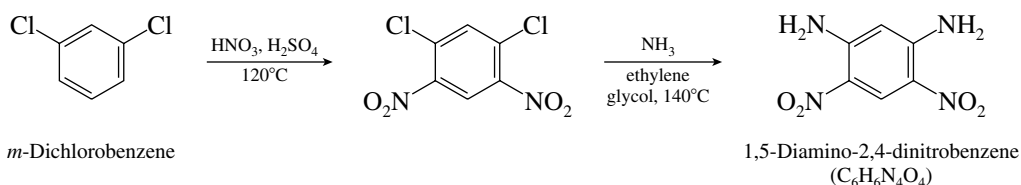


Because the final product of the sequence has four nitrogen atoms ($\text{C}_6\text{H}_6\text{N}_4\text{O}_4$), 2,4-dichloro-1-nitrobenzene is an unlikely starting material for the second transformation. Stepwise

nucleophilic aromatic substitution of both chlorines is possible but leads to a compound with the wrong molecular formula ($C_6H_7N_3O_2$).

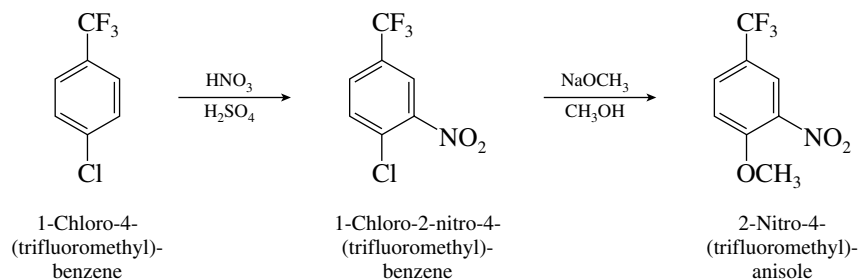


To obtain a final product with the correct molecular formula, the original nitration reaction must lead not to a mononitro but to a dinitro derivative. This is reasonable in view of the fact that this reaction is carried out at elevated temperature ($120^\circ C$).

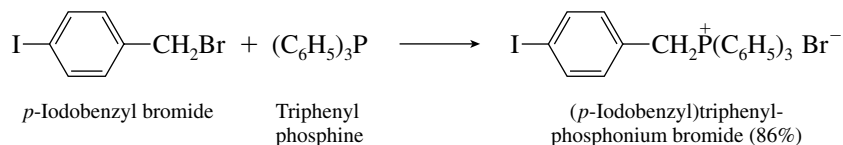


This two-step sequence has been carried out with product yields of 70–71% in the first step and 88–95% in the second step.

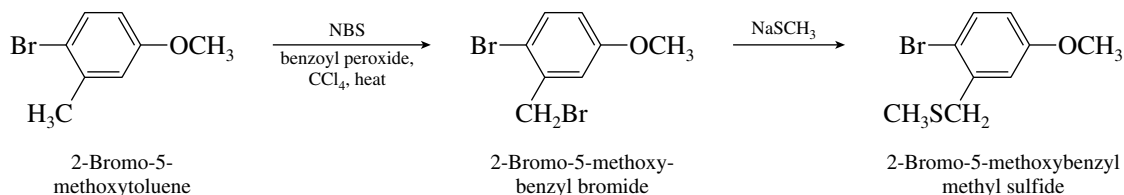
- (d) This problem also involves two transformations, nitration and nucleophilic aromatic substitution. Nitration will take place ortho to chlorine (meta to trifluoromethyl).



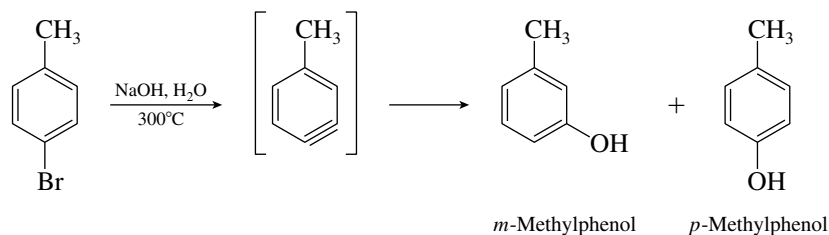
- (e) The primary alkyl halide is more reactive toward nucleophilic substitution than the aryl halide. A phosphonium salt forms by an S_N2 process.



- (f) *N*-Bromosuccinimide (NBS) is a reagent used to substitute benzylic and allylic hydrogens with bromine. The benzylic bromide undergoes S_N2 substitution with the nucleophile, methanethiolate. As in part (e), the alkyl halide is more reactive toward substitution than the aryl halide.

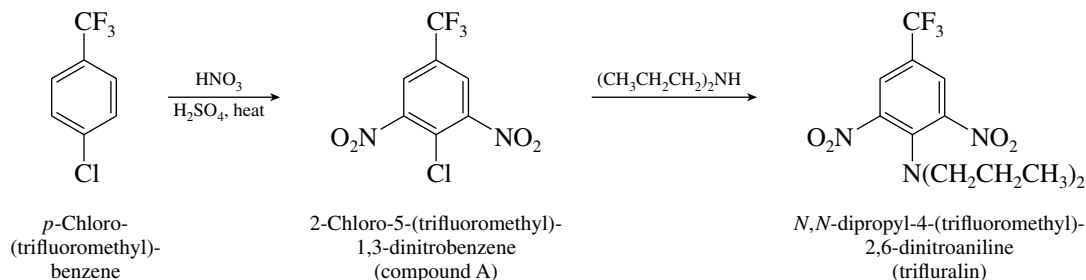


- 23.19 The reaction of *p*-bromotoluene with aqueous sodium hydroxide at elevated temperature proceeds by way of a benzyne intermediate.

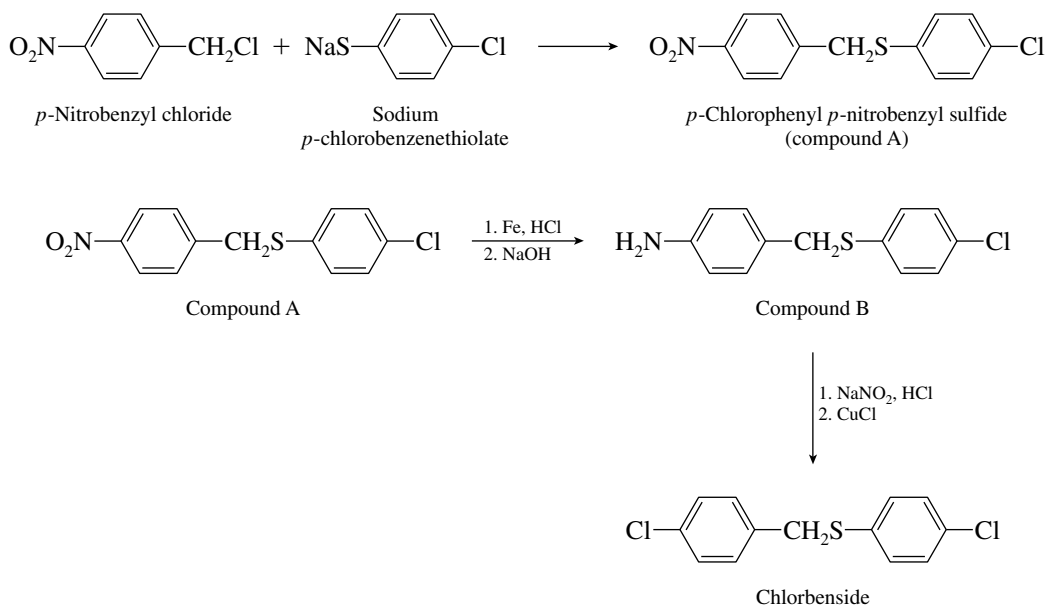


The same benzyne intermediate is formed when *p*-chlorotoluene is the reactant, and so the product ratio must be identical regardless of whether the leaving group is bromide or chloride.

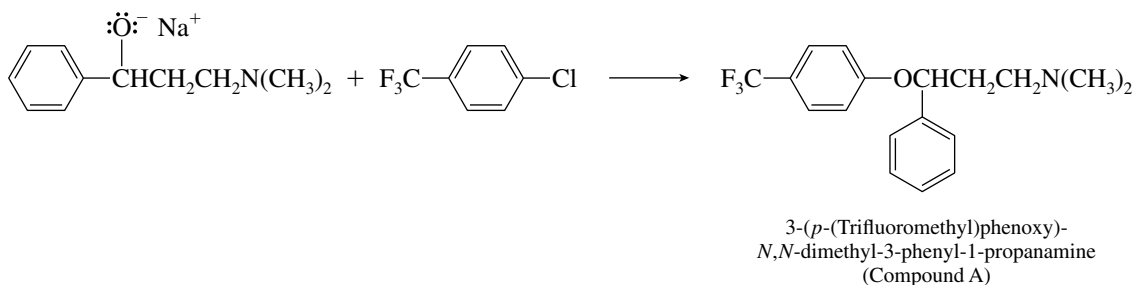
- 23.20 Dinitration of *p*-chloro(trifluoromethyl)benzene will take place at the ring positions ortho to the chlorine. Compound A is 2-chloro-5-(trifluoromethyl)-1,3-dinitrobenzene. Trifluralin is formed by nucleophilic aromatic substitution of chlorine by dipropylamine. Trifluralin is *N,N*-dipropyl-4-(trifluoromethyl)-2,6-dinitroaniline.



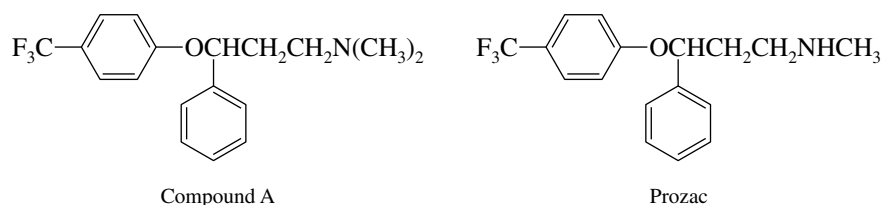
- 23.21 *p*-Chlorobenzenethiolate reacts with *p*-nitrobenzyl chloride by an $\text{S}_{\text{N}}2$ process to give compound A. Reduction of the nitro group yields the aniline derivative, compound B. Chlorbenside is then formed by a Sandmeyer reaction in which the diazonium ion is replaced by chlorine.



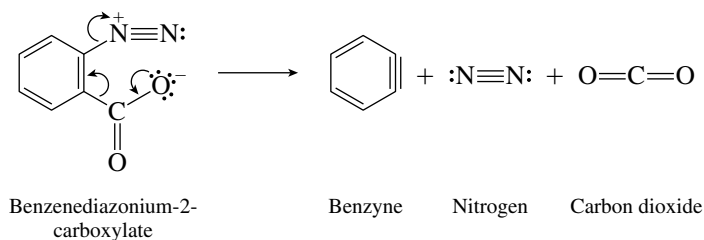
- 23.22 *p*-Chloro(trifluoromethyl)benzene undergoes nucleophilic substitution by the alkoxide anion to give compound A.



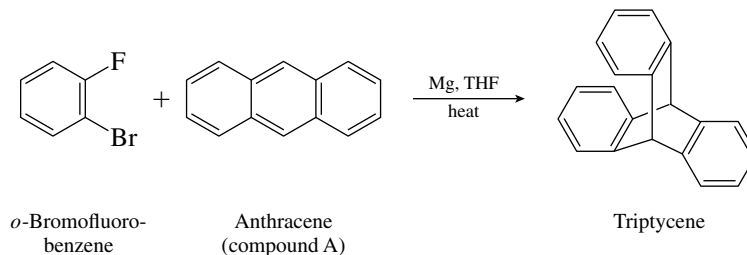
Prozac (Fluoxetine hydrochloride) differs from compound A in having an —NHCH_3 group in place of $\text{—N(CH}_3)_2$.



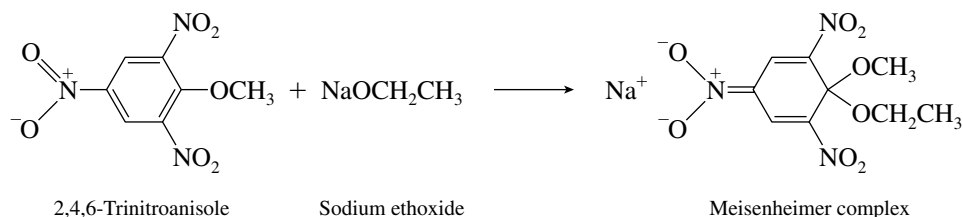
- 23.23 Benzyne is formed by loss of nitrogen and carbon dioxide.



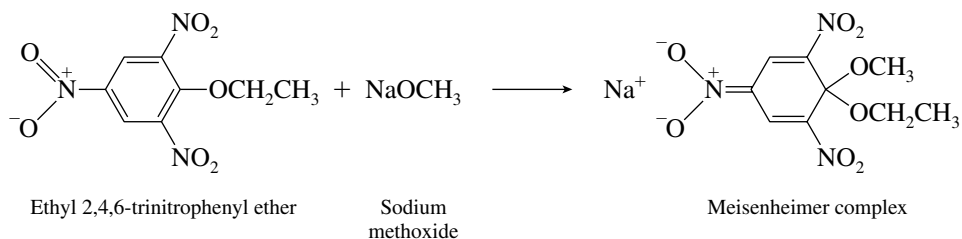
- 23.24 *o*-Bromofluorobenzene yields benzyne on reaction with magnesium (see text Section 23.9). Triptycene is the Diels–Alder cycloaddition product from the reaction of benzyne with anthracene (compound A). Although anthracene is aromatic, it is able to undergo cycloaddition at the center ring with a dienophile because the adduct retains the stabilization energy of two benzene rings.



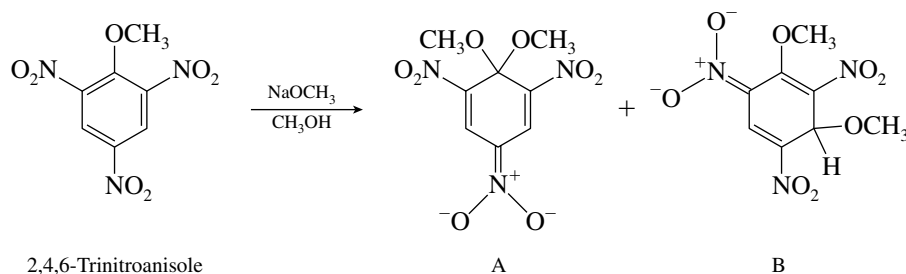
- 23.25 (a) Ethoxide ion adds to the aromatic ring to give a cyclohexadienyl anion.



- (b) The same Meisenheimer complex results when ethyl 2,4,6-trinitrophenyl ether reacts with sodium methoxide.

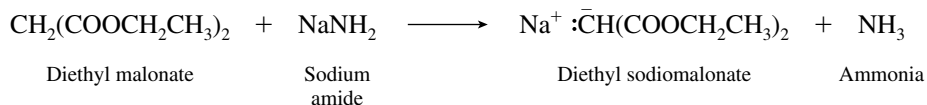


- 23.26** Methoxide ion may add to 2,4,6-trinitroanisole either at the ring carbon that bears the methoxyl group or at an unsubstituted ring carbon.

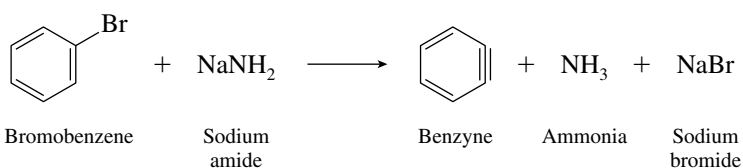


The two Meisenheimer complexes are the sodium salts of the anions shown. It was observed that compound A was the more stable of the two. Compound B was present immediately after adding sodium methoxide to 2,4,6-trinitroanisole but underwent relatively rapid isomerization to compound A.

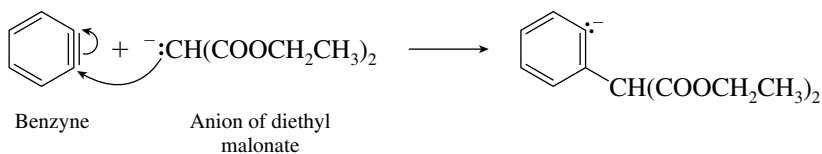
- 23.27** (a) The first reaction that occurs is an acid–base reaction between diethyl malonate and sodium amide.



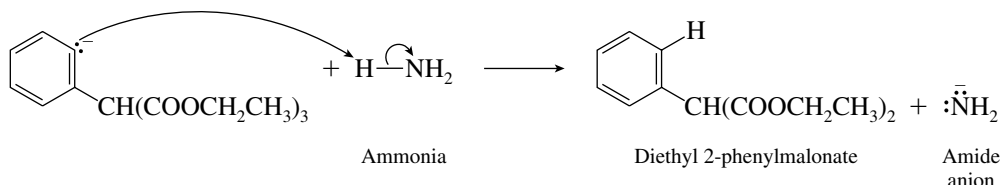
A second equivalent of sodium amide converts bromobenzene to benzyne.



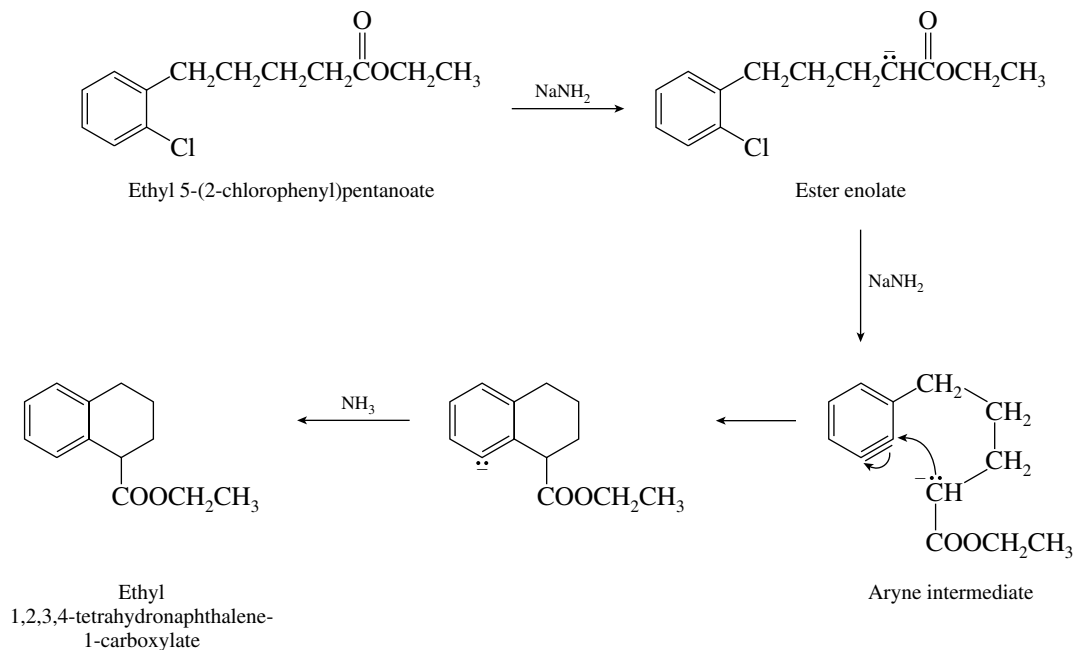
The anion of diethyl malonate adds to benzyne.



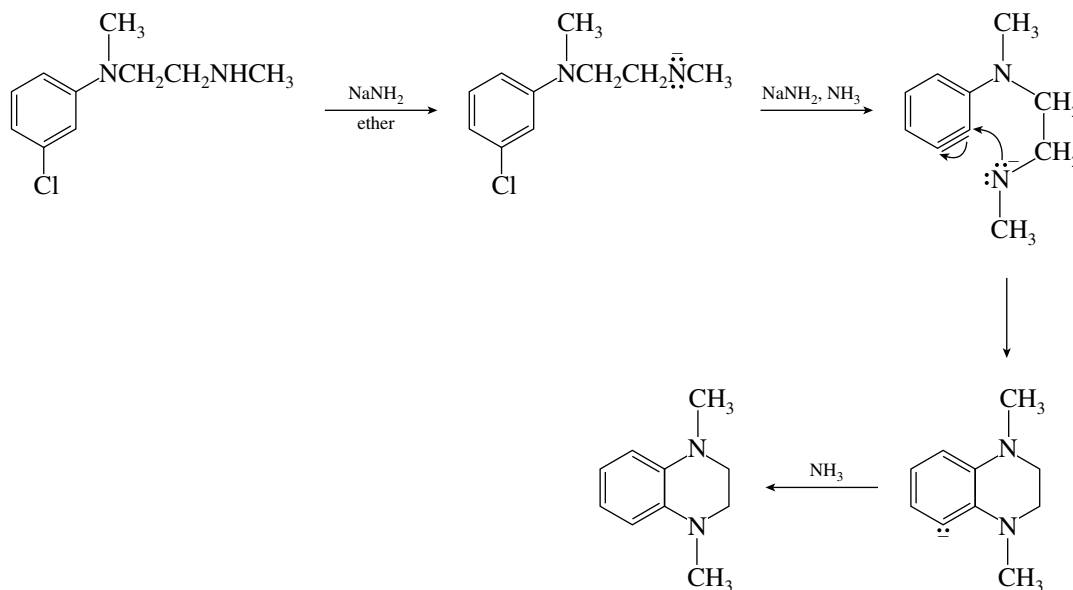
This anion then abstracts a proton from ammonia to give the observed product.



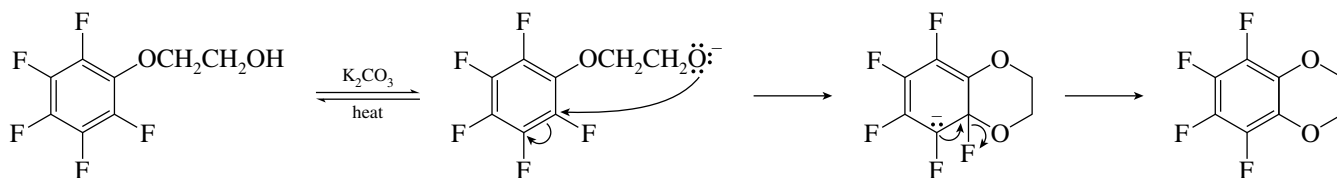
- (b) The ester is deprotonated by the strong base sodium amide, after which the ester enolate undergoes an elimination reaction to form a benzyne intermediate. Cyclization to the final product occurs by intramolecular attack of the ester enolate on the reactive triple bond of the aryne.



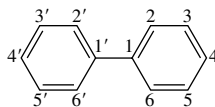
- (c) In the presence of very strong bases, aryl halides undergo nucleophilic aromatic substitution by an elimination–addition mechanism. The structure of the product indicates that a nitrogen of the side chain acts as a nucleophile in the addition step.



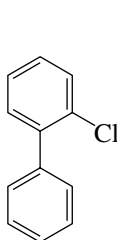
- (d) On treatment with base, intramolecular nucleophilic aromatic substitution leads to the observed product.



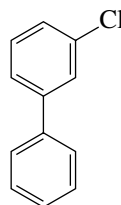
23.28 Polychlorinated biphenyls (PCBs) are derived from biphenyl as the base structure. It is numbered as shown.



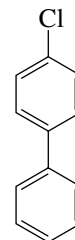
(a) There are three monochloro derivatives of biphenyl:



2-Chlorobiphenyl
(*o*-chlorobiphenyl)

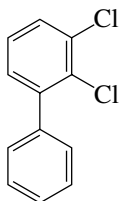


3-Chlorobiphenyl
(*m*-chlorobiphenyl)

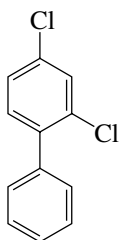


4-Chlorobiphenyl
(*p*-chlorobiphenyl)

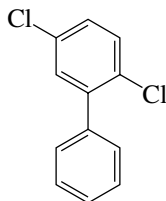
(b) The two chlorine substituents may be in the same ring (six isomers):



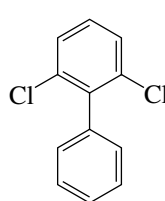
2,3-Dichlorobiphenyl



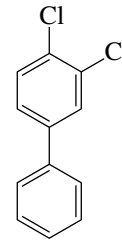
2,4-Dichlorobiphenyl



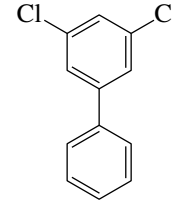
2,5-Dichlorobiphenyl



2,6-Dichlorobiphenyl

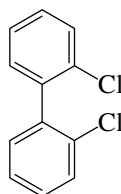


3,4-Dichlorobiphenyl

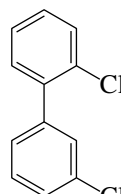


3,5-Dichlorobiphenyl

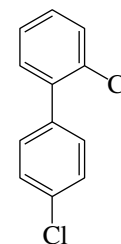
The two chlorine substituents may be in different rings (six isomers):



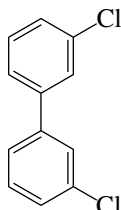
2,2'-Dichlorobiphenyl



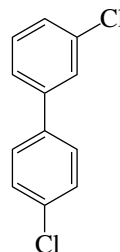
2,3'-Dichlorobiphenyl



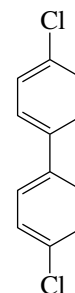
2,4'-Dichlorobiphenyl



3,3'-Dichlorobiphenyl



3,4'-Dichlorobiphenyl



4,4'-Dichlorobiphenyl

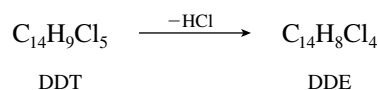
There are therefore a total of 12 isomeric dichlorobiphenyls.

- (c) The number of octachlorobiphenyls will be equal to the number of dichlorobiphenyls (12). In both cases we are dealing with a situation in which eight of the ten substituents of the biphenyl system are the same and considering how the remaining two may be arranged. In the dichlorobiphenyls described in part (b), eight substituents are hydrogen and two are chlorine; in the octachlorobiphenyls, eight substituents are chlorine and two are hydrogen.
- (d) The number of nonachloro isomers (nine chlorines, one hydrogen) must equal the number of monochloro isomers (one chlorine, nine hydrogens). There are therefore three nonachloro derivatives of biphenyl.

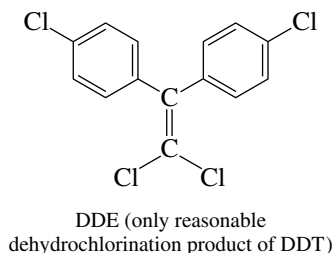
23.29 The principal isotopes of chlorine are ^{35}Cl and ^{37}Cl . A cluster of five peaks indicates that dichlorodiphenyldichloroethane (DDE) contains *four* chlorines.

m/z for $\text{C}_{14}\text{H}_8\text{Cl}_4$				
316	^{35}Cl	^{35}Cl	^{35}Cl	^{35}Cl
318	^{35}Cl	^{35}Cl	^{35}Cl	^{37}Cl
320	^{35}Cl	^{35}Cl	^{37}Cl	^{37}Cl
322	^{35}Cl	^{37}Cl	^{37}Cl	^{37}Cl
324	^{37}Cl	^{37}Cl	^{37}Cl	^{37}Cl

The peak at m/z 316 therefore corresponds to a compound $\text{C}_{14}\text{H}_8\text{Cl}_4$ in which all four chlorines are ^{35}Cl . The respective molecular formulas indicate that DDE is the dehydrochlorination product of dichlorodiphenyltrichloroethane (DDT).



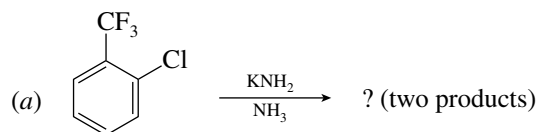
The structure of DDT was given in the statement of the problem. This permits the structure of DDE to be assigned.

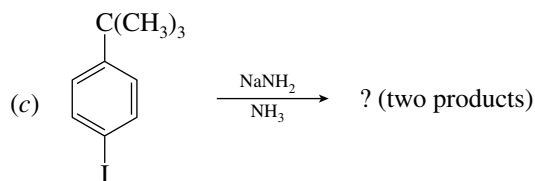
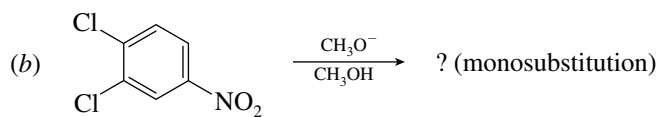


SELF-TEST

PART A

A-1. Give the product(s) obtained from each of the following reactions:





A-2. Draw the structure of the intermediate formed in each reaction of problem A-1.

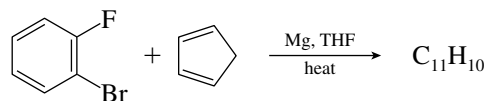
A-3. Suggest synthetic schemes by which chlorobenzene may be converted into

(a) 2,4-Dinitroanisole (1-methoxy-2,4-dinitrobenzene)

(b) *p*-Isopropylaniline

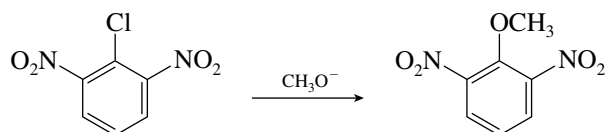
A-4. Write a mechanism using resonance structures to show how a nitro group directs ortho, para in nucleophilic aromatic substitution.

A-5. What is the cycloaddition product of the following reaction? What is the structure of the short-lived intermediate formed in this reaction?



PART B

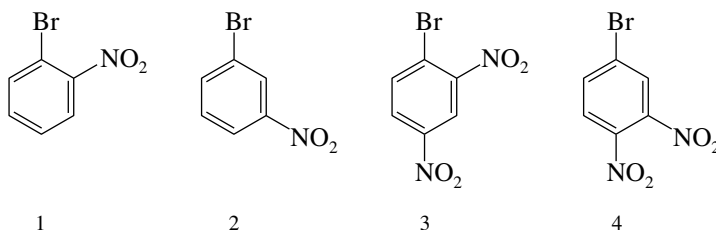
B-1. The reaction



most likely occurs by which of the following mechanisms?

- (a) Addition–elimination
 (b) Elimination–addition
 (c) Both (a) and (b)
 (d) Neither of these

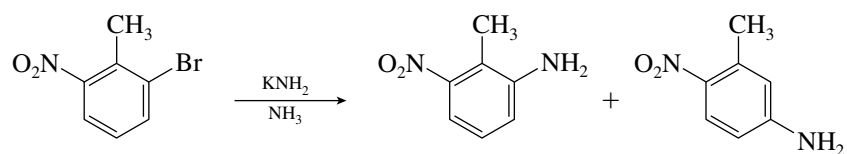
B-2. Rank the following in order of decreasing rate of reaction with ethoxide ion ($\text{CH}_3\text{CH}_2\text{O}^-$) in a nucleophilic aromatic substitution reaction:



- (a) $3 > 4 > 1 > 2$
 (b) $2 > 1 > 4 > 3$

- (c) $3 > 4 > 2 > 1$
 (d) $4 > 3 > 2 > 1$

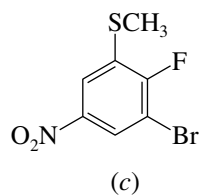
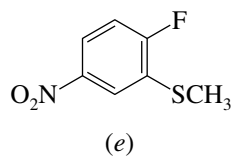
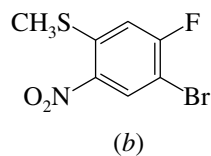
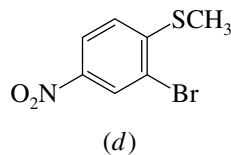
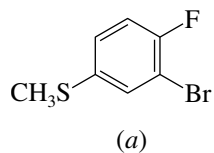
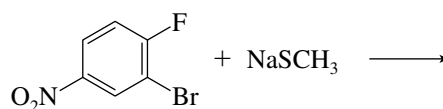
B-3. The reaction



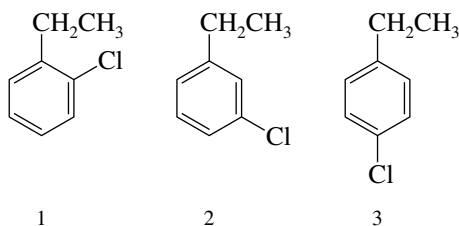
most likely involves which of the following aromatic substitution mechanisms?

- (a) Addition–elimination
- (b) Electrophilic substitution
- (c) Elimination–addition
- (d) Both (a) and (c)

B-4. Identify the principal organic product of the following reaction:

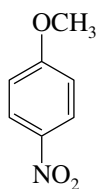


B-5. Which of the following compounds gives a single benzyne intermediate on reaction with sodium amide?

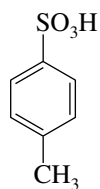


- (a) 1 only
- (b) 1 and 3
- (c) 3 only
- (d) 1 and 2

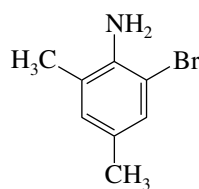
B-6. Which one of the following compounds can be efficiently prepared by a procedure in which nucleophilic aromatic substitution is the last step?



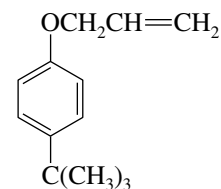
(a)



(b)

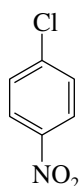


(c)

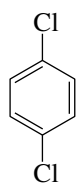


(d)

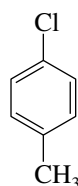
B-7. Which one of the following undergoes nucleophilic aromatic substitution at the fastest rate?



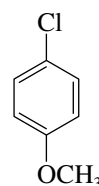
(a)



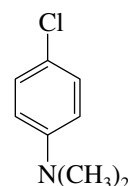
(b)



(c)

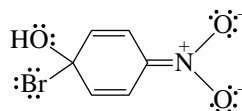


(d)



(e)

B-8. What combination of reactants will give the species shown as a reactive intermediate?



- (a) 1-Bromo-4-nitrobenzene and NaOH
- (b) 4-Nitrophenol and HBr
- (c) 4-Nitrophenol, Br₂, and FeBr₃
- (d) Bromobenzene and HONO₂
- (e) Nitrobenzene, Br₂, and water