Organic Chemistry III

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By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

22-4 PREPARATION OF PHENOLS: NUCLEOPHILIC AROMATIC SUBSTITUTION

Phenols are synthesized quite differently from the way in which ordinary substituted benzenes are made.

Direct *electrophilic* addition of OH to arenes is difficult because of the scarcity of reagents that generate an electrophilic hydroxy group, such as HO^+.

Instead, phenols are prepared by formal *nucleophilic* displacement of a leaving group from the arene ring by hydroxide, HO^-, but mechanistically quite different from the synthesis of alkanols from haloalkanes.

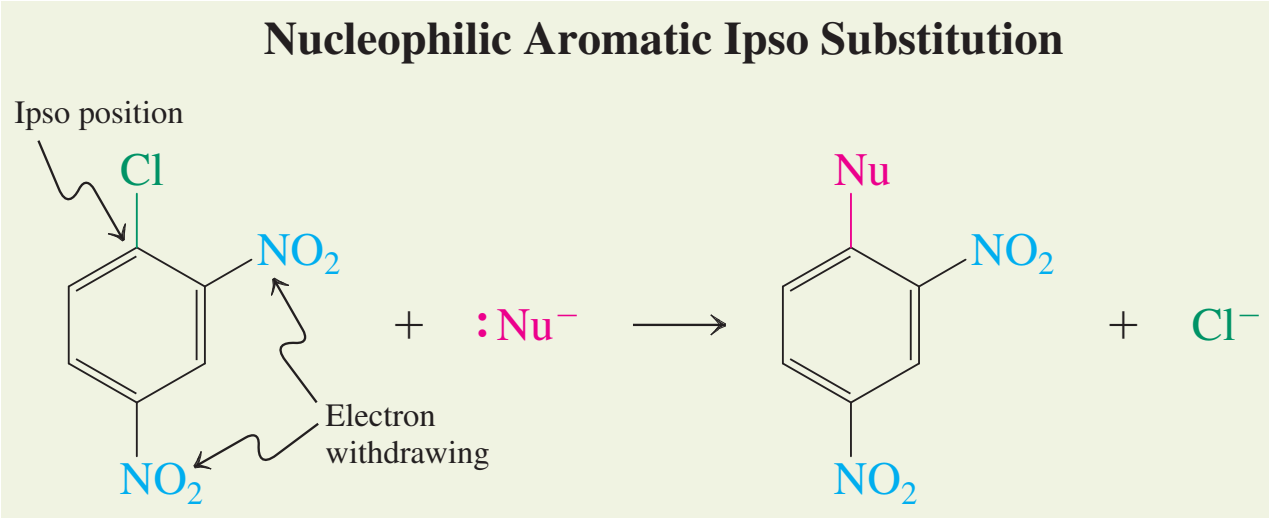
Nucleophilic aromatic substitution may follow an addition–elimination pathway

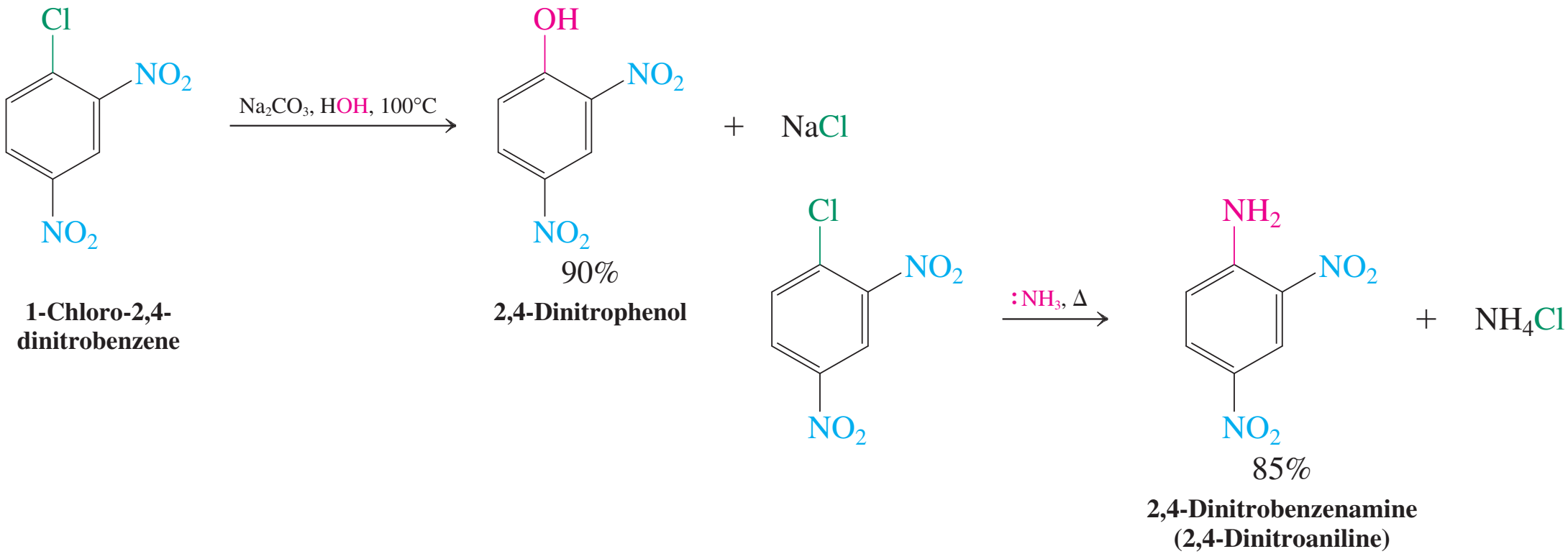
Treatment of 1-chloro-2,4-dinitrobenzene with hydroxide replaces the halogen with the nucleophile, furnishing the corresponding substituted phenol.

Other nucleophiles, such as alkoxides or ammonia, may be similarly employed, forming alkoxyarenes and arenamines, respectively.

Processes such as these, in which a group other than hydrogen is displaced from an aromatic ring, are called **ipso substitutions** (*ipso,* Latin, on itself).

The products of these reactions are intermediates in the manufacture of useful dyes.



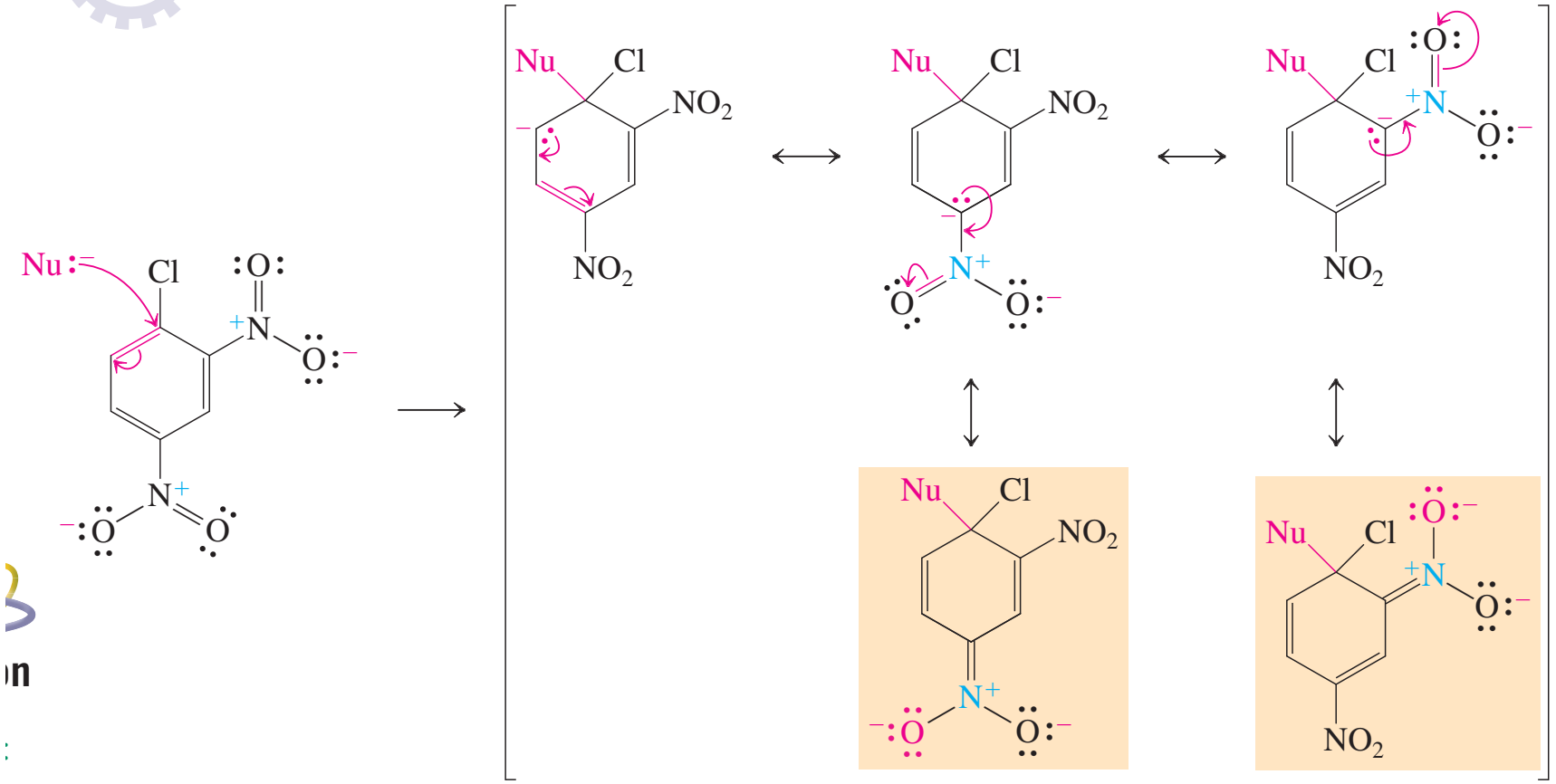


The transformation is called **nucleophilic aromatic substitution.** The key to its success is the presence of one or more strongly **electron-withdrawing groups** on the benzene ring located ***ortho*** or ***para*** to the leaving group. Such substituents stabilize an intermediate anion by resonance.

In contrast with the S_N2 reaction of haloalkanes, substitution in these reactions takes place by a *two-step mechanism,* an *addition–elimination sequence* similar to the mechanism of substitution of carboxylic acid derivatives.

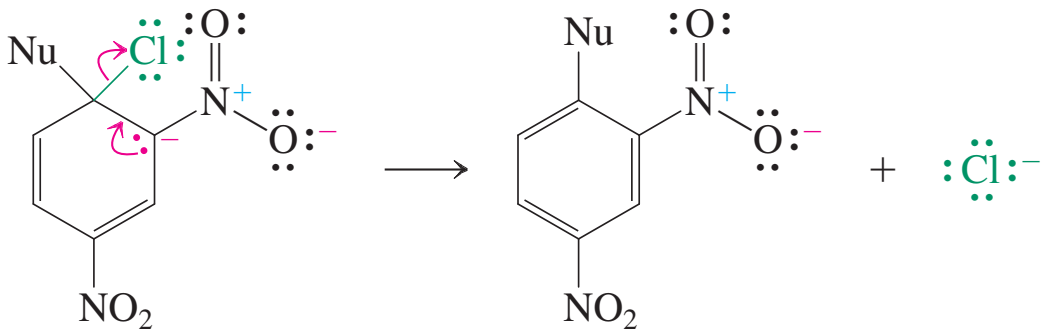
Mechanism

Step 1. Addition (facilitated by resonance stabilization)



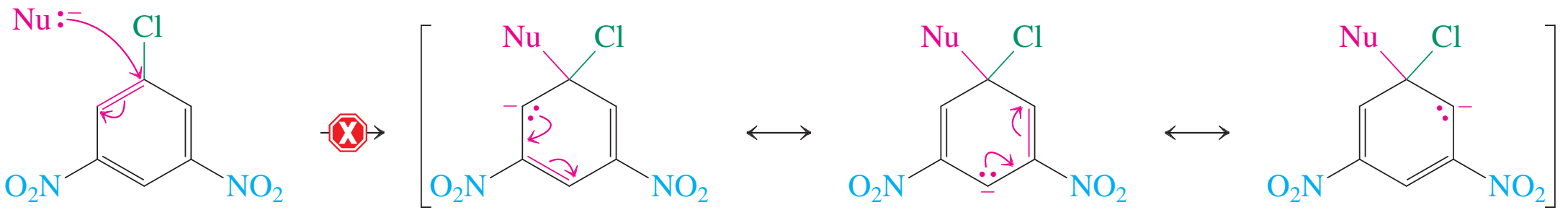
The negative charge is strongly stabilized by resonance involving the ortho- and para-NO_2 groups.

Step 2. Elimination (only one resonance structure is shown)



In the first and rate-determining step, ipso attack by the nucleophile produces an anion with a highly delocalized charge, for which several resonance structures.

In contrast, such delocalization is *not* possible in 1-chloro-3,5-dinitrobenzene, in which these groups are located ***meta***; so this compound does *not* undergo ipso substitution under the conditions employed.



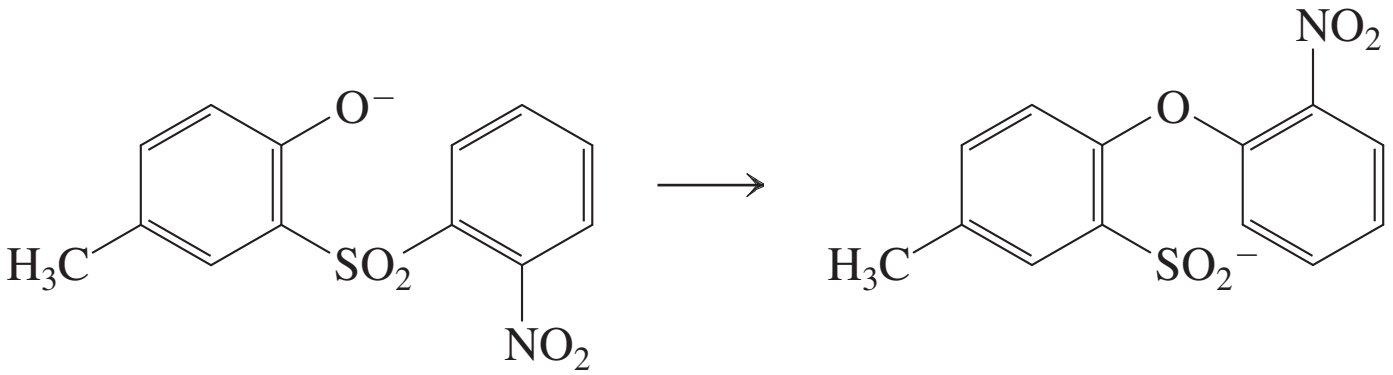
Meta-NO_2 groups do *not* provide resonance stabilization of the negative charge.

In the second step, the leaving group is expelled to regenerate the aromatic ring.

The reactivity of haloarenes in nucleophilic substitutions increases with the nucleophilicity of the reagent and the number of electron-withdrawing groups on the ring, particularly if they are in the ortho and para positions.

Exercise 22-10

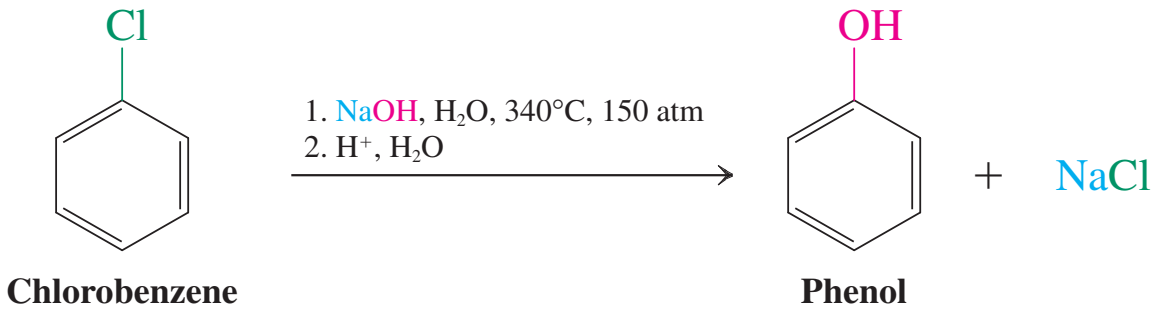
Propose a mechanism for the following conversion. Considering that the first step is rate determining, draw a potential-energy diagram depicting the progress of the reaction. (**Hint:** This is a nucleophilic aromatic substitution.)



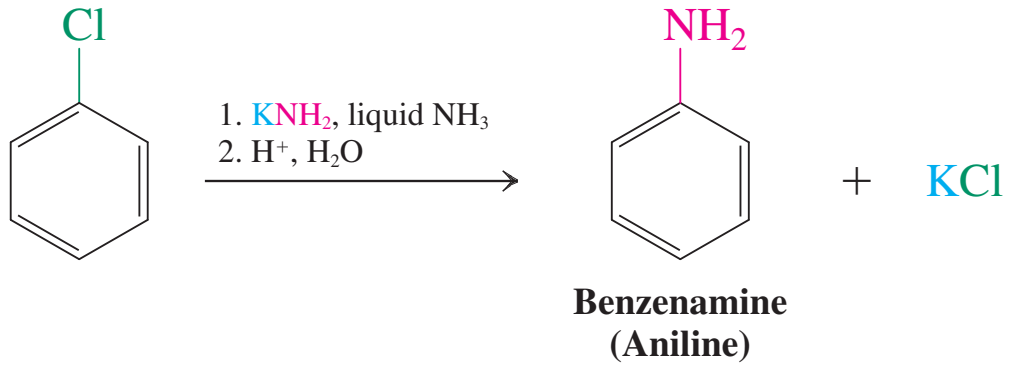
Haloarenes undergo substitution through benzyne intermediates

Haloarenes devoid of electron-withdrawing substituents do not undergo simple ipso substitution.

Nevertheless, when haloarenes are treated with nucleophiles that are also strong bases, if necessary at highly elevated temperatures, they convert to products in which the halide has been replaced by the nucleophile.

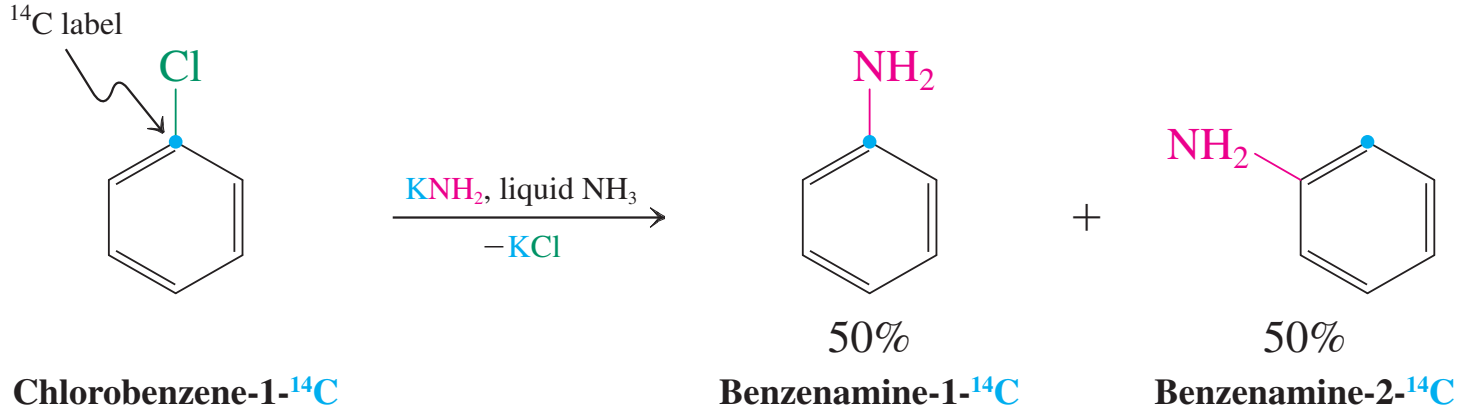


Treatment with potassium amide results in benzenamine (aniline).



It is tempting to assume that these substitutions follow a mechanism similar to that formulated for nucleophilic aromatic ipso substitution earlier.

However, when the last reaction is performed with radioactively labeled chlorobenzene (^{14}C at C1), a very curious result is obtained: Only half of the product is substituted at the labeled carbon; in the other half, the nitrogen is at the *neighboring* position.



Direct substitution does not seem to be the mechanism of these reactions.

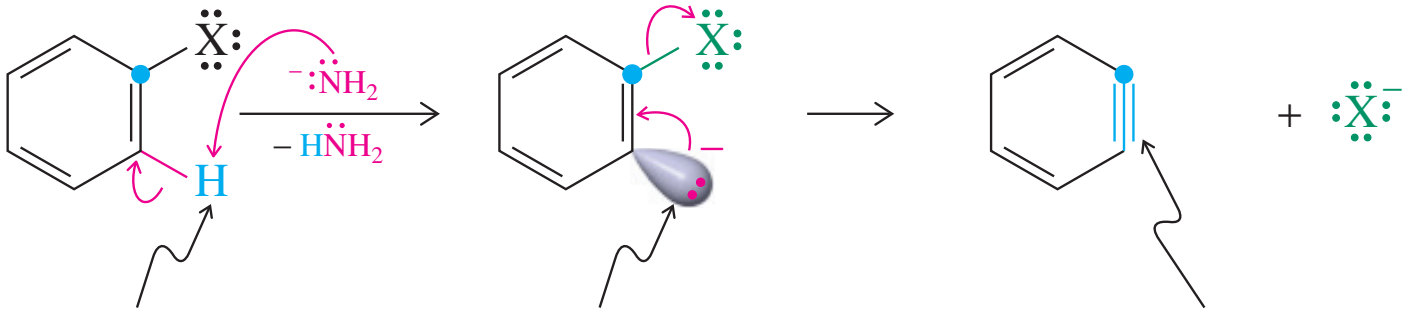
In the present case, elimination is not a concerted process, but rather takes place in a sequential manner, deprotonation preceding the departure of the leaving group (step 1 of the mechanism).

Both stages in step 1 are difficult, with the second being worse than the first. Why is that? With respect to the initial anion formation, the acidity of Csp^2–H is very low (pK_a = 44), and the presence of the adjacent **π** system of benzene does not help, because the negative charge in the phenyl anion resides in an sp^2 orbital that is *perpendicular* to the **π** frame and is therefore incapable of resonance with the double bonds in the six-membered ring. Thus, deprotonation of the haloarene requires a strong base. It takes place ortho to the halogen, because the halogen's inductive electron-withdrawing effect acidifies this position relative to the others.

Although deprotonation is not easy, the second stage of step 1, subsequent elimination of X^-, is even more difficult because of the highly strained structure of the resulting reactive species, called **1,2-dehydrobenzene** or **benzyne.**

Mechanism of Nucleophilic Substitution of Simple Haloarenes

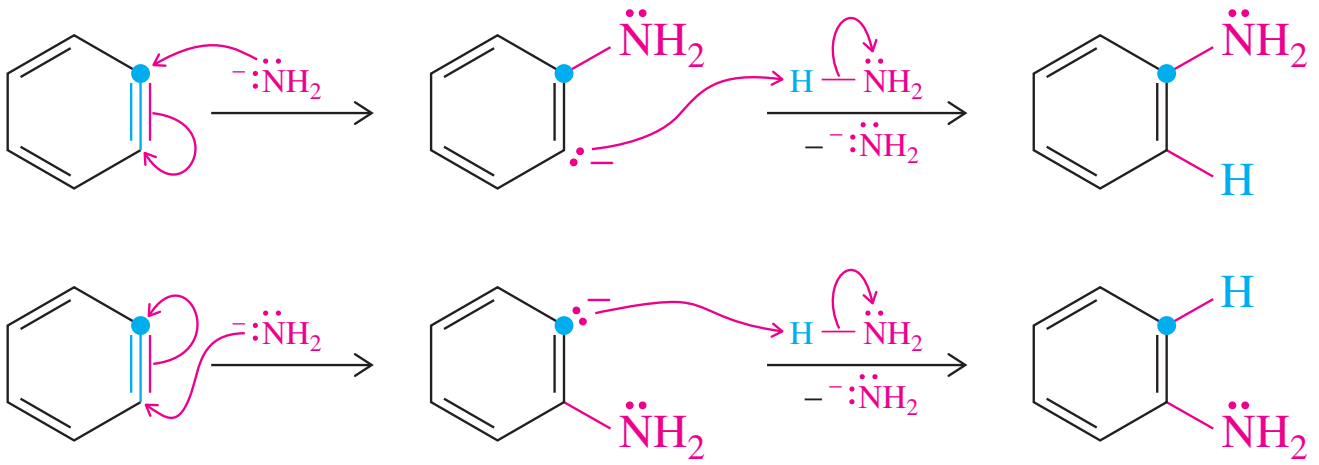
Step 1. Elimination occurs stepwise



Phenyl anion
(Intermediate)

Benzyne
(Reactive intermediate; not isolated)

Step 2. Addition occurs to both strained carbons

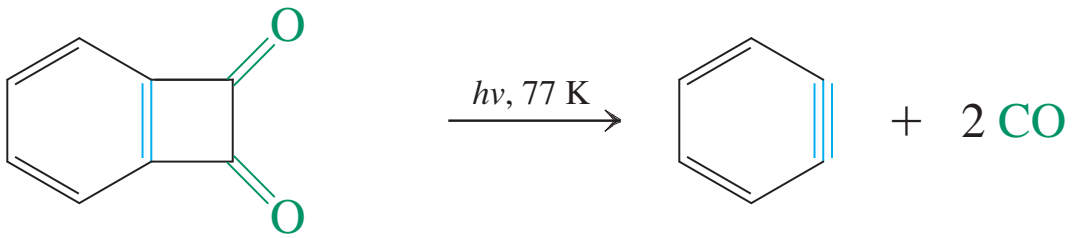


Why is benzyne so strained?

Alkynes normally adopt a linear structure, a consequence of the *sp* hybridization of the carbons making up the triple bond. Because of benzyne's cyclic structure, its triple bond is forced to be bent, rendering it unusually reactive. Thus, benzyne exists only as a reactive intermediate under these conditions, being rapidly attacked by any nucleophile present.

Benzyne is too reactive to be isolated and stored in a bottle, but it can be observed spectroscopically under special conditions. Irradiation of benzocyclobutenedione at 77 K (-196 °C) in frozen argon (m.p. = -189 °C) produces a species whose IR and UV spectra are assignable to benzyne, formed by loss of two molecules of CO.

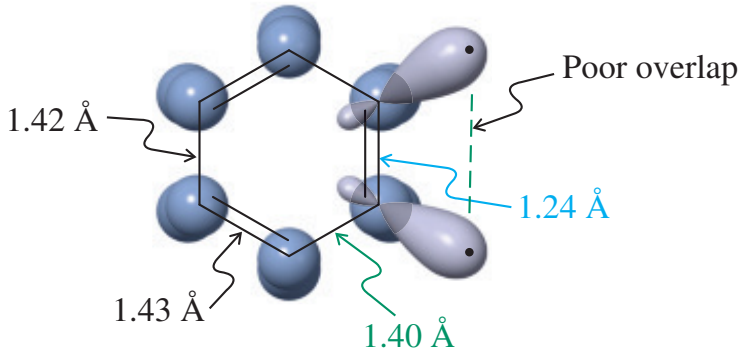
Generation of Benzyne, a Reactive Intermediate

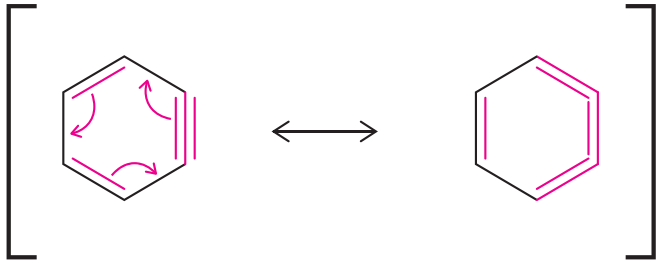


Benzocyclobutene-1,2-dione

Although benzyne is usually represented as a cycloalkyne, its triple bond exhibits an IR stretching frequency of 1846 cm^{-1}, intermediate between the values for normal double (cyclohexene, 1652 cm^{-1}) and triple (3-hexyne, 2207 cm^{-1}) bonds.

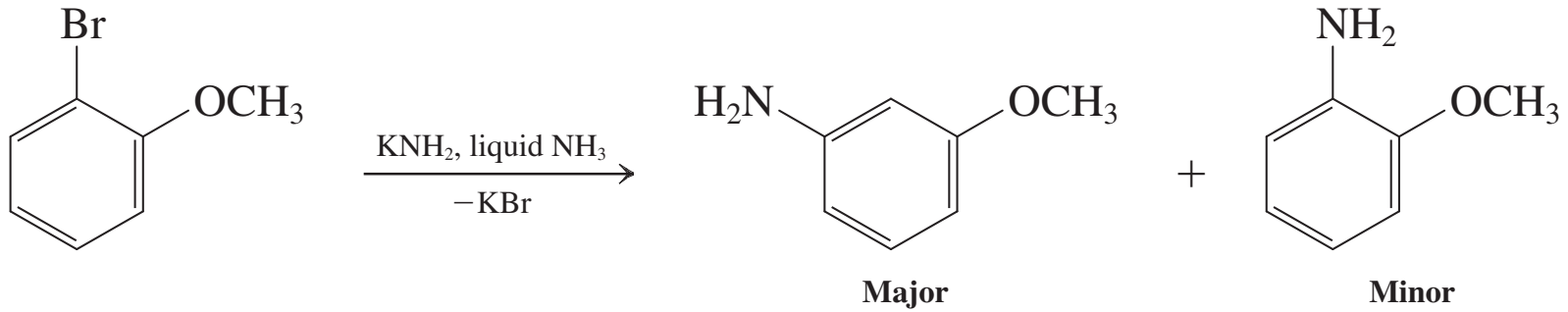
The ^{13}C NMR values for these carbons (δ = 182.7 ppm) are also atypical of pure triple bonds, indicating a considerable contribution of the cumulated triene resonance form. The bond is weakened substantially by poor *p* orbital overlap in the plane of the ring.





Exercise 22-12

Explain the regioselectivity observed in the following reaction. (**Hint:** Consider the effect of the methoxy group on the selectivity of attack by amide ion on the intermediate benzyne.)



Major **Minor**

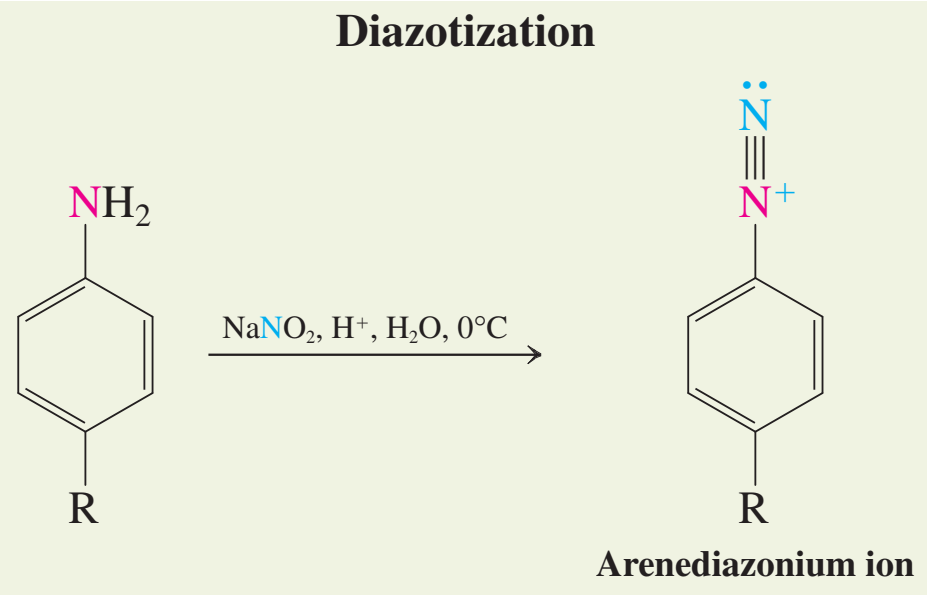
Phenols are produced from arenediazonium salts

The most general traditional laboratory procedure for making phenols is from arenamines through their **arenediazonium salts,** $ArN_2^+X^-$.

The primary alkanamines can be *N*-nitrosated but that the resulting species rearrange to diazonium ions, which are unstable— they lose nitrogen to give carbocations.

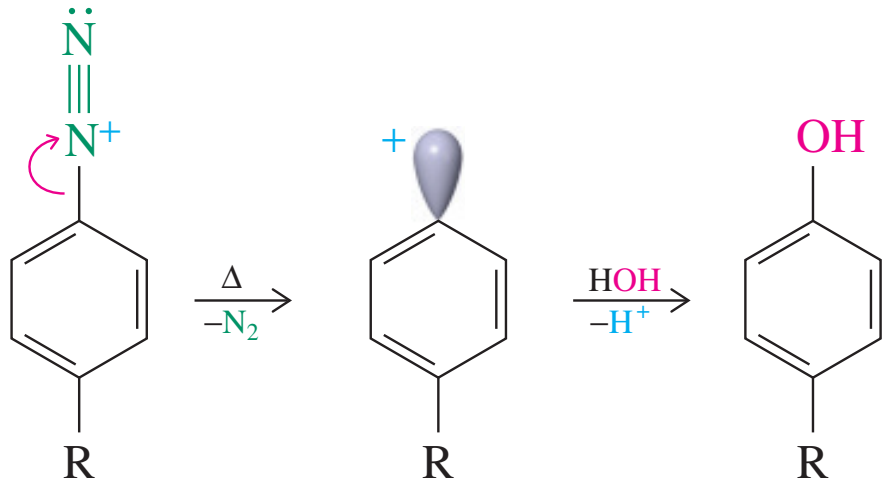
In contrast, primary benzenamines (anilines) are attacked by cold nitrous acid, in a reaction called **diazotization,** to give relatively stable, isolable, although still reactive arenediazonium salts.

Compared to their alkanediazonium counterparts, these species enjoy resonance stabilization and are prevented from undergoing immediate N_2 loss by the high energy of the resulting **aryl cations**.



When arenediazonium ions are gently heated in water, nitrogen is evolved and the resulting aryl cations are trapped extremely rapidly by the solvent to give phenols.

Decomposition of Arenediazonium Salts in Water to Give Phenols

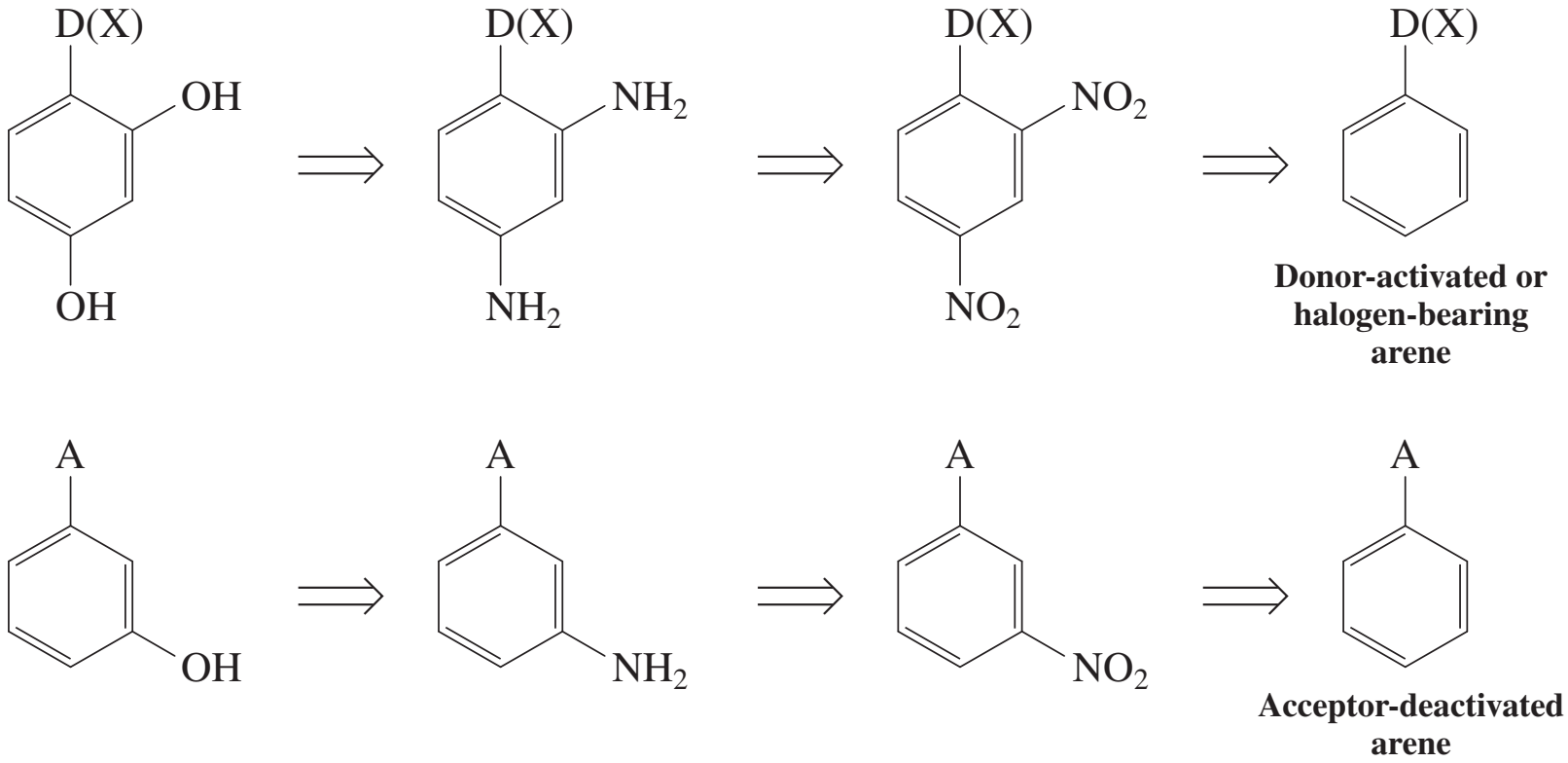


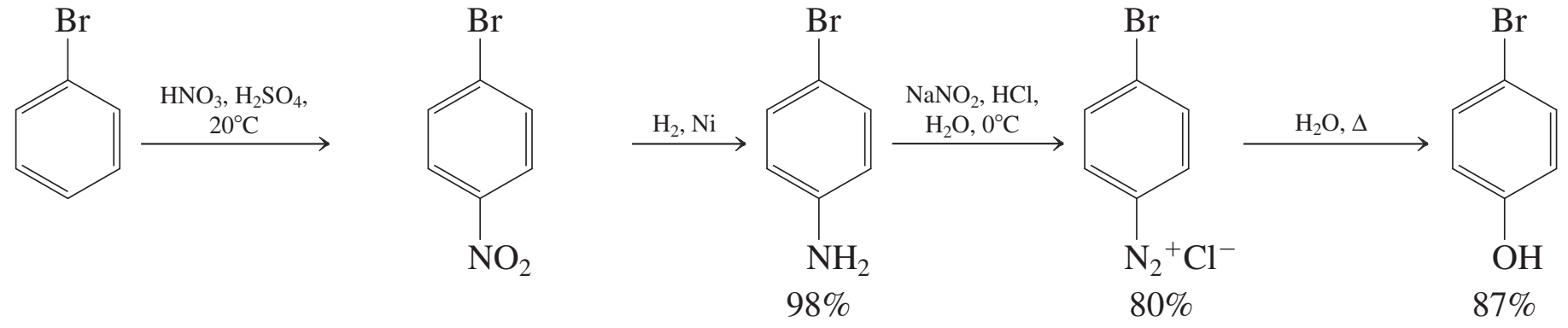
In these reactions, the “super” leaving group N_2 accomplishes what halides are only able to do when attached to a highly electron-deficient benzene nucleus (nucleophilic aromatic substitution) or under extreme conditions (through benzyne intermediates), namely, replacement by hydroxide.

The three mechanisms are completely different. In nucleophilic aromatic substitution, the nucleophile attacks prior to departure of the leaving group. In the benzyne mechanism, the nucleophile acts initially as a base, followed by extrusion of the leaving group and subsequent nucleophilic attack on the strained triple bond. In the arenediazonium-ion decomposition, the leaving group exits first, followed by trapping by water.

The utility of this phenol synthesis is apparent when you recall that arenamines are derived from nitroarenes by reduction, and nitroarenes are made from other arenes by electrophilic aromatic substitution. Therefore, retrosynthetically, we can picture the hydroxy group in any position of a benzene ring that is subject to electrophilic nitration.

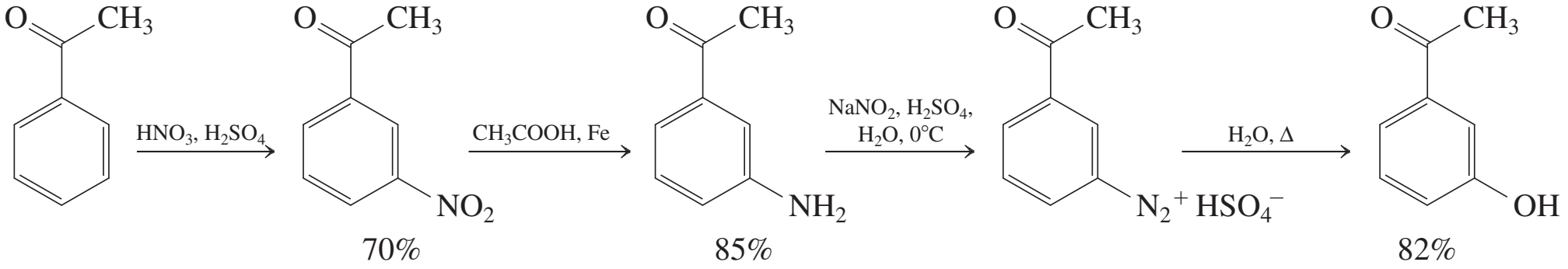
Retrosynthetic Connection of Phenols to Arenes





70% (separated from the ortho isomer by crystallization)

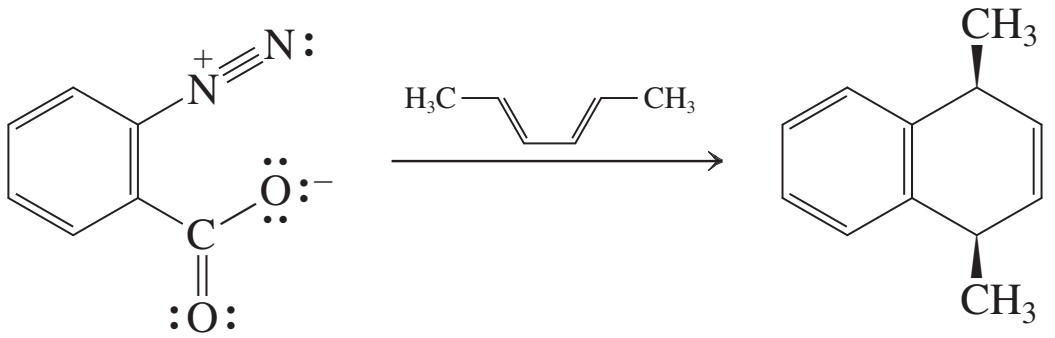
4-Bromophenol (*p*-Bromophenol)



1-(3-Hydroxyphenyl)ethanone (*m*-Hydoxyacetophenone)

Exercise 22-13

ortho-Benzenediazoniumcarboxylate A (made by diazotization of 2-aminobenzoic acid, Problem 59 of Chapter 20) is explosive. When warmed in solution with *trans*,*trans*-2,4-hexadiene, it forms compound B. Explain by a mechanism. (**Hint:** Two other products are formed, both of which are gases.)

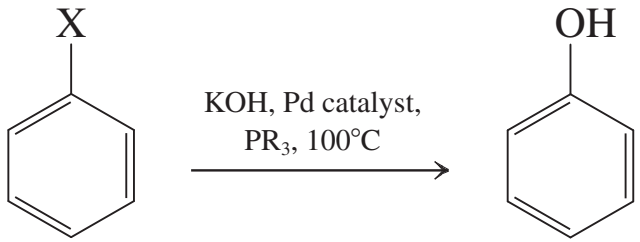


A **B**

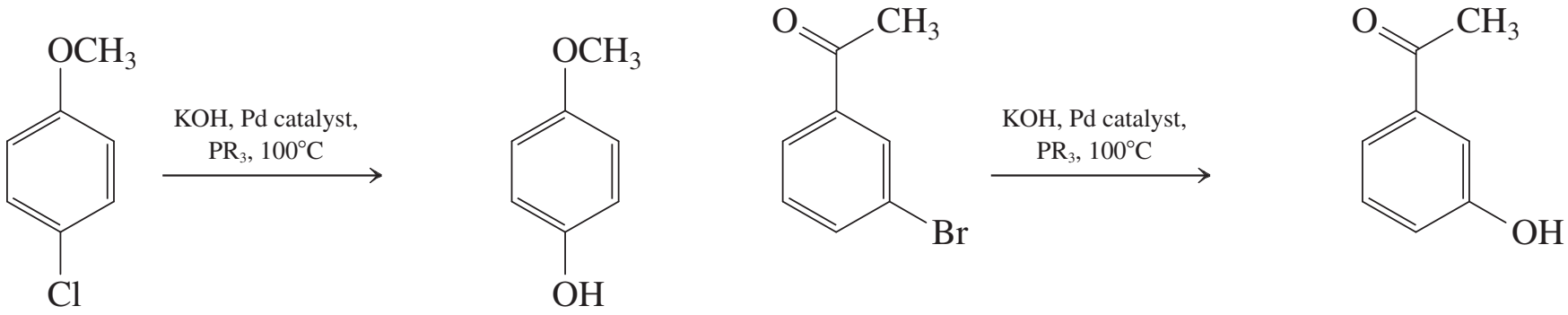
Phenols can be made from haloarenes by Pd catalysis

Ordinary halobenzenes are resilient to reaction with hydroxide, they undergo such nucleophilic displacements in the presence of Pd salts and added phosphine ligands PR_3.

Pd-Catalyzed Phenol Synthesis from Haloarenes



The reaction is general for substituted benzenes, providing a complement to the diazonium method.



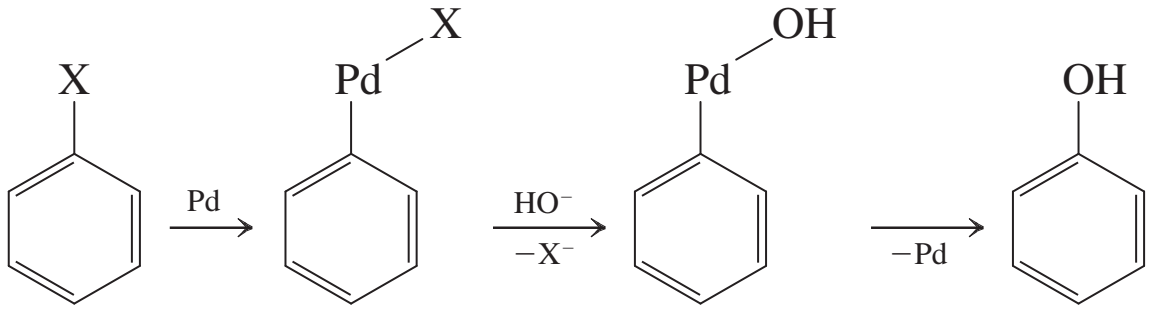
90%

4-Methoxyphenol
(*p*-Methoxyphenol)

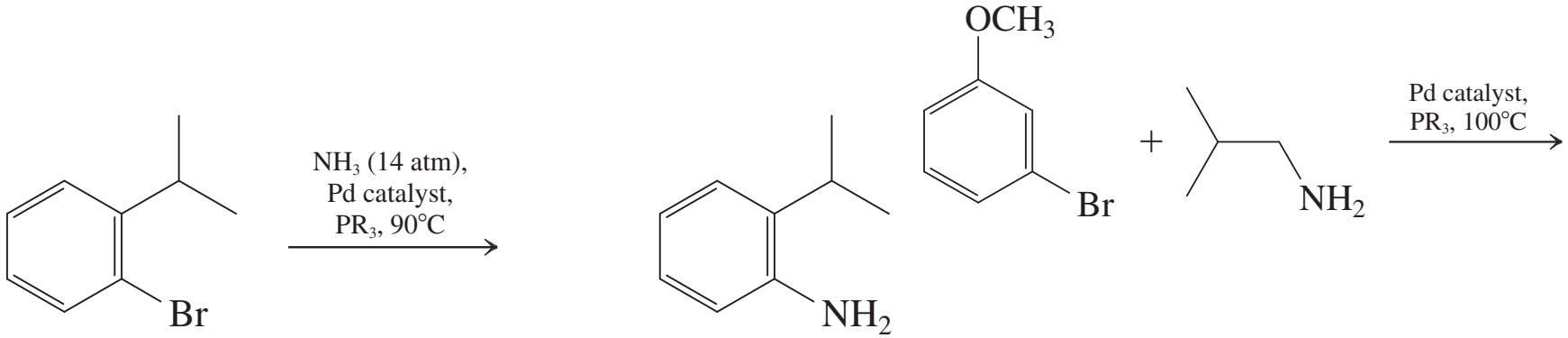
98%

1-(3-Hydroxyphenyl)ethanone
(*m*-Hydroxyacetophenone)

The mechanism is related to that of the Heck and other Pd-catalyzed reaction. It begins by insertion of the metal into the aryl halide bond, exchange of the halide for hydroxide, and extrusion of the final product with regeneration of the catalyst.



Similar substitutions can be carried out with alkoxides to give phenol ethers, and with amines, including ammonia, to furnish benzenamines.



89%

2-(1-Methylethyl)benzenamine
(*o*-Isopropylaniline)

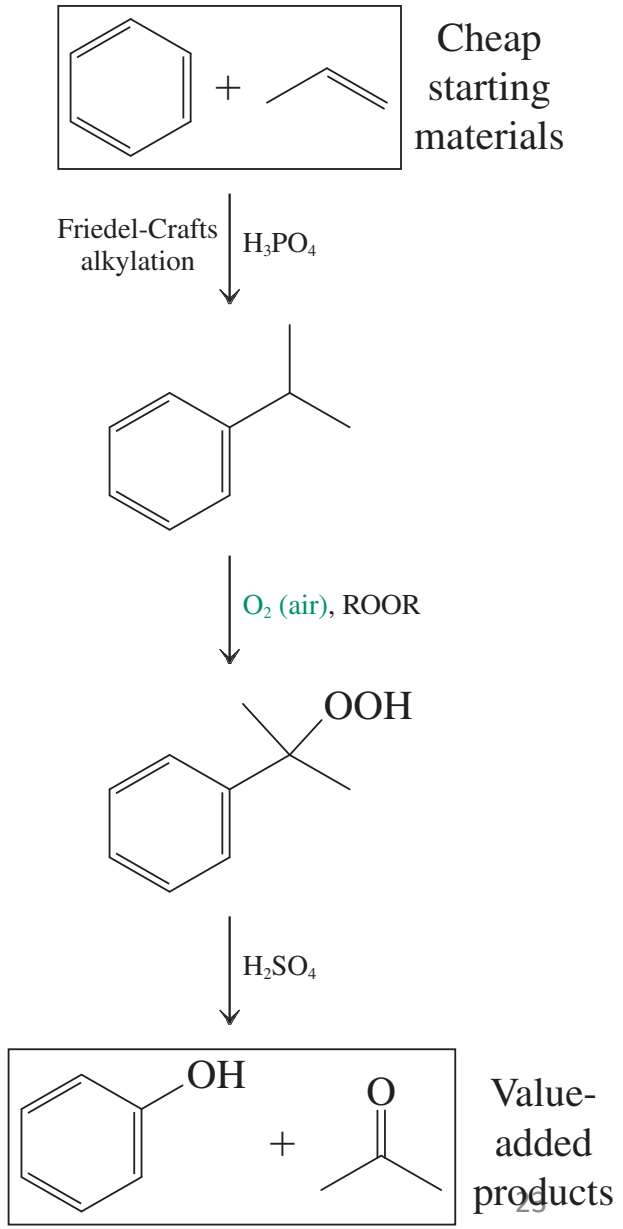
98%

3-Methoxy-*N*-(2-methylpropyl)benzenamine
3-Methoxy-*N*-(2-methylpropyl)aniline

A "Green" Industrial Phenol Synthesis

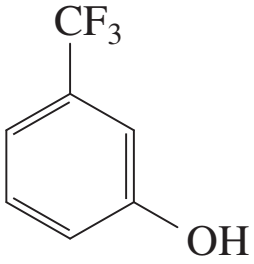
Although the preceding methods are valuable in the preparation of specifically substituted phenols, the parent compound is made industrially by the air oxidation of (1-methylethyl)benzene (isopropylbenzene or cumene) to the benzylic hydroperoxide and its subsequent decomposition with acid.

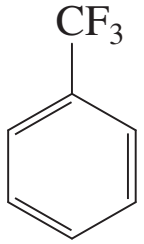
The "by-product" acetone is valuable in its own right and makes this process highly cost effective, quite apart from the environmentally benign use of air as an oxidant.

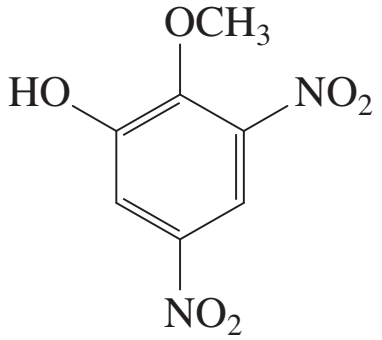


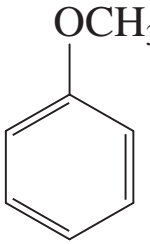
Exercise 22-15

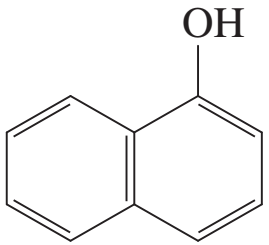
How would you make the following phenols from the given starting materials? **(Hint:** Consult Chapters 15 and 16.)

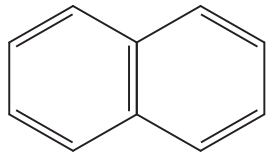
(a) 

from 

(b) 

from 

(c) 

from 

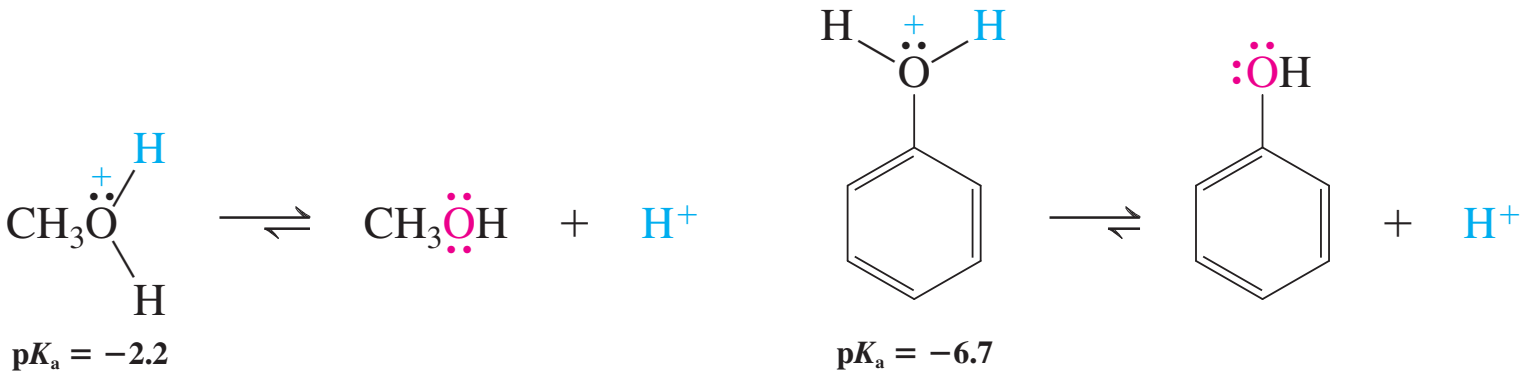
22-5 ALCOHOL CHEMISTRY OF PHENOLS

The phenol hydroxy group undergoes several of the reactions of alcohols, such as protonation, Williamson ether synthesis, and esterification.

The oxygen in phenols is only weakly basic

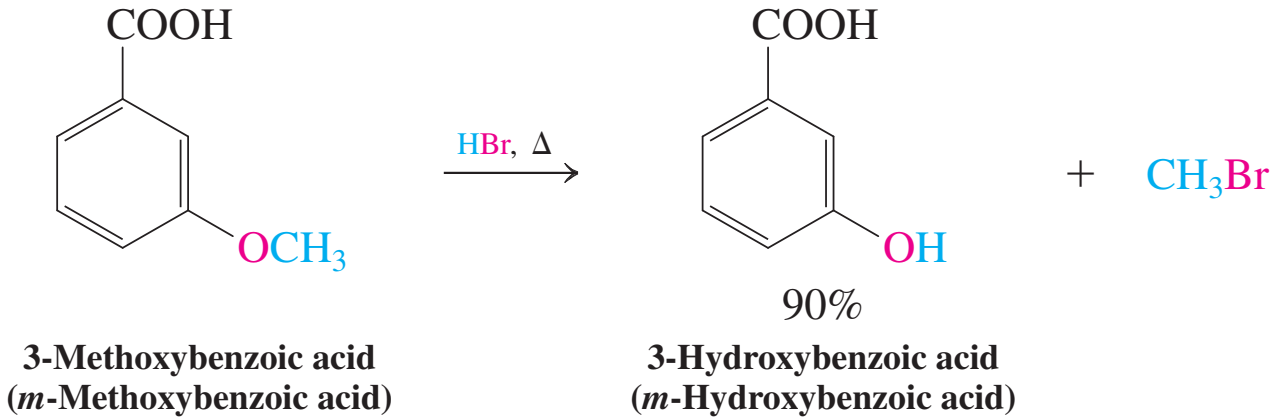
Phenols are not only acidic but also weakly basic. They (and their ethers) can be protonated by strong acids to give the corresponding **phenyloxonium ions.** Thus, as with the alkanols, the hydroxy group imparts amphoteric character.

However, the basicity of phenol is even less than that of the alkanols, because the lone electron pairs on the oxygen are delocalized into the benzene ring. The pK_a values for phenyloxonium ions are, therefore, lower than those of alkyloxonium ions.



Unlike secondary and tertiary alkyloxonium ions derived from alcohols, phenyloxonium derivatives do not dissociate to form phenyl cations, because such ions have too high an energy content.

The phenyl–oxygen bond in phenols is very difficult to break. However, after protonation of alkoxybenzenes, the bond between the *alkyl* group and oxygen is readily cleaved in the presence of nucleophiles such as Br^- or I^- (e.g., from HBr or HI) to give phenol and the corresponding haloalkane.

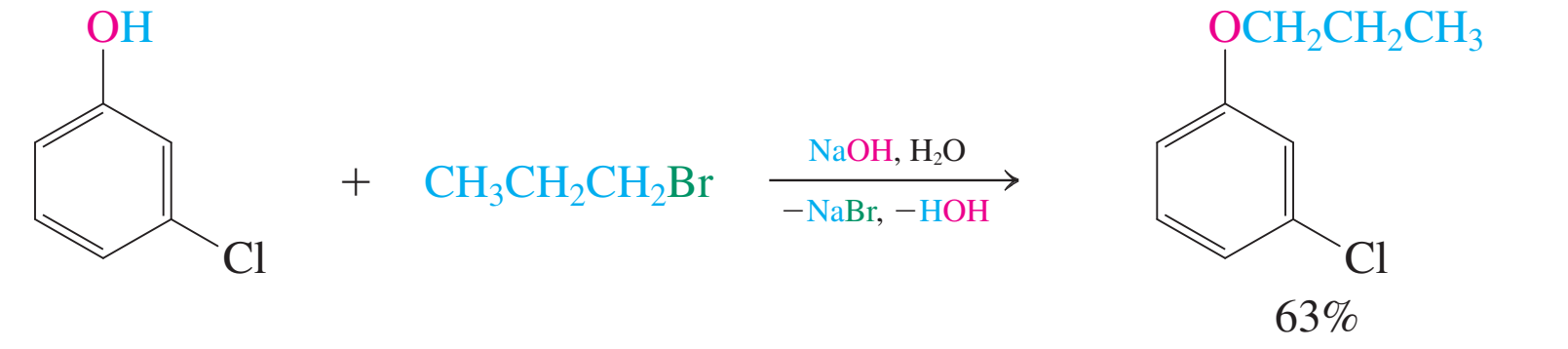


3-Methoxybenzoic acid (*m*-Methoxybenzoic acid)

3-Hydroxybenzoic acid (*m*-Hydroxybenzoic acid)

Alkoxybenzenes are prepared by Williamson ether synthesis

The Williamson ether synthesis permits easy preparation of many alkoxy-benzenes. The phenoxide ions obtained by deprotonation of phenols are good nucleophiles. They can displace the leaving groups from haloalkanes and alkyl sulfonates.

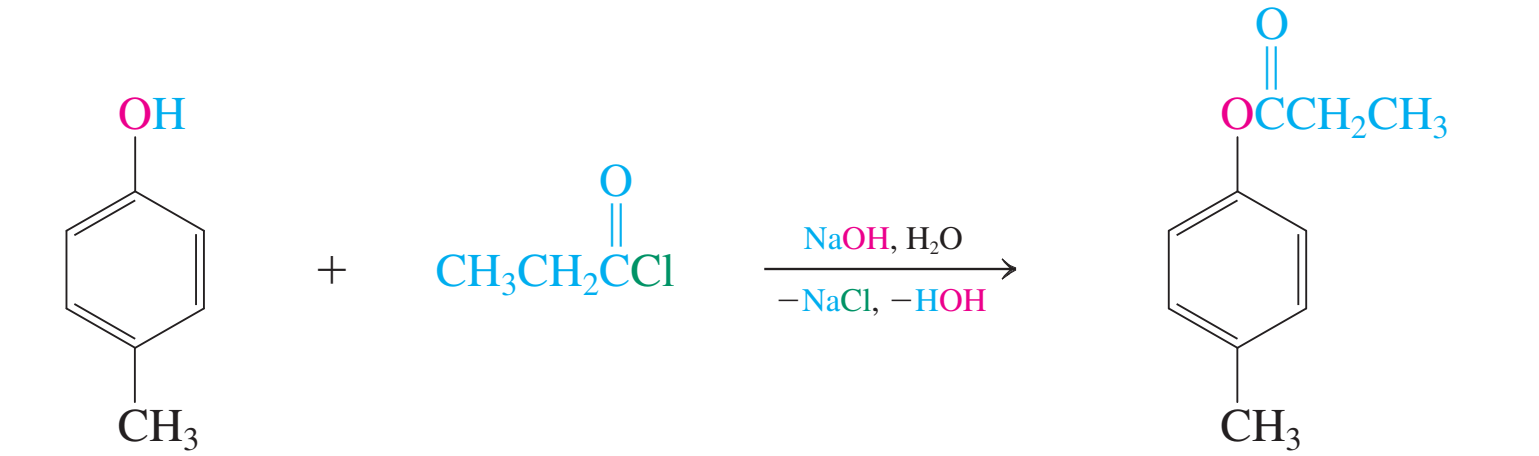


3-Chlorophenol
(*m*-Chlorophenol)

1-Chloro-3-propoxybenzene
(*m*-Chlorophenyl propyl ether)

Esterification leads to phenyl alkanoates

The reaction of a carboxylic acid with a phenol to form a phenyl ester is endothermic. Therefore, esterification requires an activated carboxylic acid derivative, such as an acyl halide or a carboxylic anhydride.

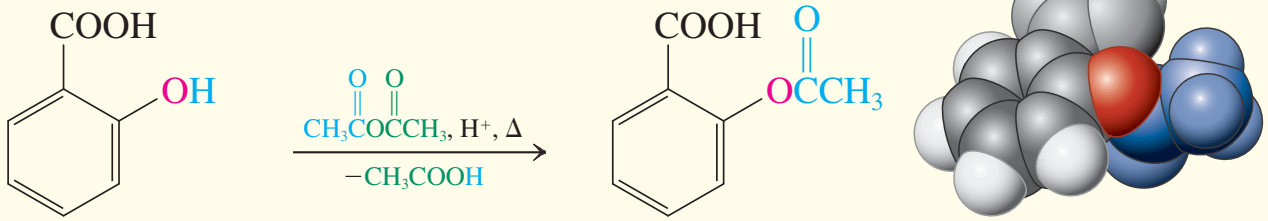


4-Methylphenol (*p*-Cresol) **Propanoyl chloride** **4-Methylphenyl propanoate (*p*-Methylphenyl propanoate)**

Exercise 22-17

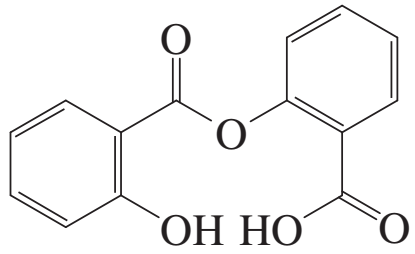
(a) Explain why, in the preparation of acetaminophen, the amide is formed rather than the ester.

(**b**) Salsalate (short for salicyl salicylate), an ester of two salicylic acid molecules, is prescribed to reduce pain and inflammation in rheumatoid arthritis patients as an alternative to naproxen or ibuprofen, because it avoids stomach upset. Formulate a synthesis from 2-hydroxybenzoic acid (salicylic acid). (**Hint:** You will need to develop a protecting-group strategy.)

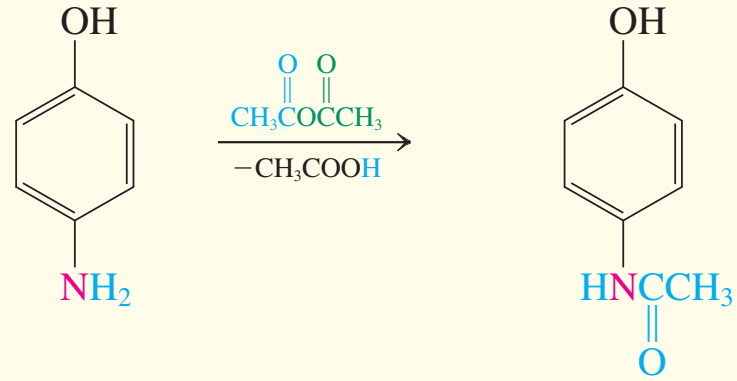


2-Hydroxybenzoic acid (*o*-Hydroxybenzoic acid, salicylic acid)

2-Acetyloxybenzoic acid (*o*-Acetoxybenzoic acid, acetylsalicylic acid, aspirin)



Salsalate



4-Aminophenol (*p*-Aminophenol)

***N*-(4-Hydroxyphenyl)acetamide [*N*-(*p*-Hydroxyphenyl)acetamide, acetaminophen, Tylenol]**