Organic Chemistry II / CHEM 252

Chapter 21 – Phenoles and Aryl Halides – Nucleophilic Aromatic Substitution

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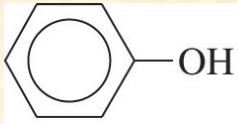
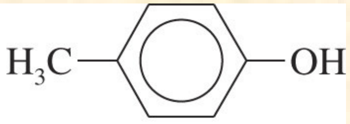
Nomenclature

Phenols have hydroxyl groups bonded directly to a benzene ring

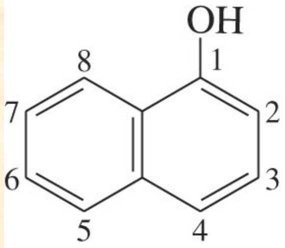
- Naphthols and phenanthrols have a hydroxyl group bonded to a polycyclic benzenoid ring



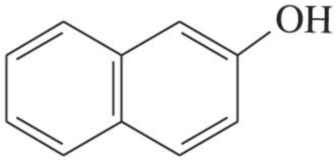
Phenol



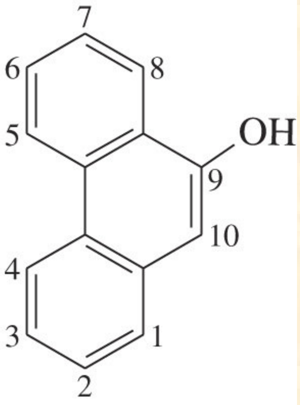
4-Methylphenol
(a phenol)



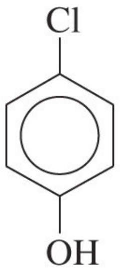
1-Naphthol
(*α*-naphthol)



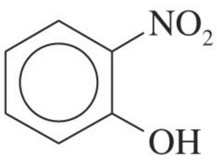
2-Naphthol
(*β*-naphthol)



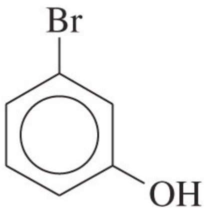
9-Phenanthrol



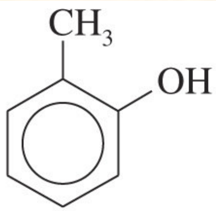
4-Chlorophenol
(*p*-chlorophenol)



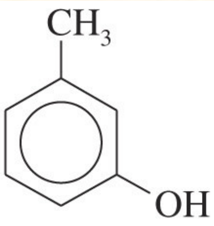
2-Nitrophenol
(*o*-nitrophenol)



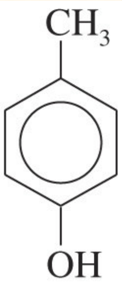
3-Bromophenol
(*m*-bromophenol)



2-Methylphenol
(*o*-cresol)



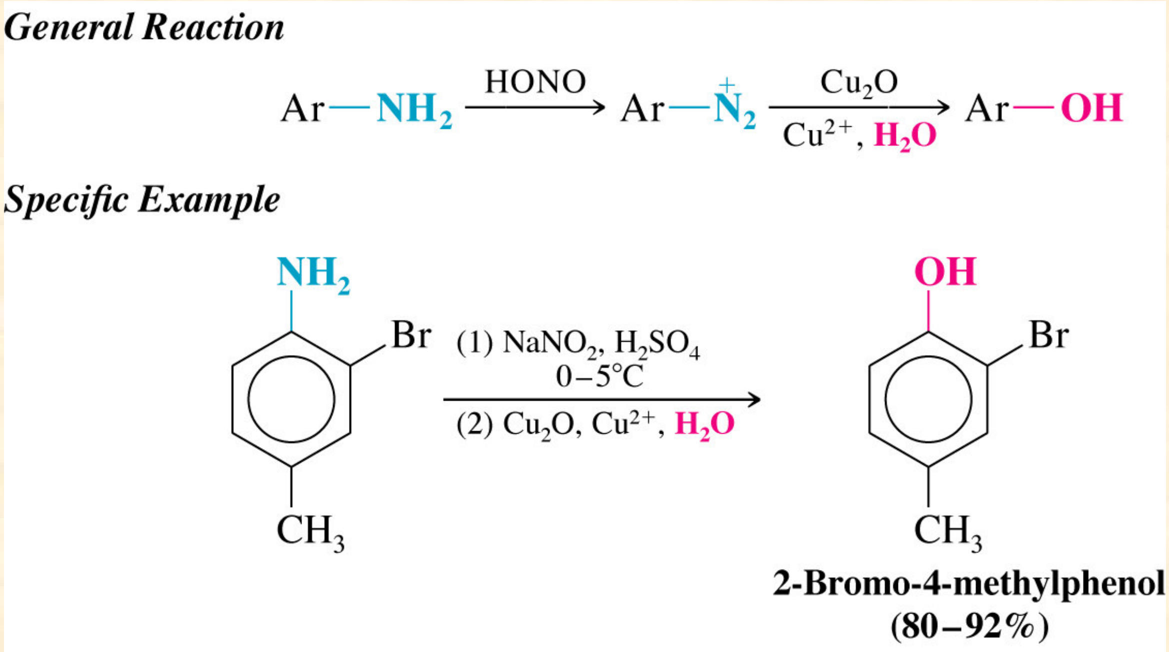
3-Methylphenol
(*m*-cresol)



4-Methylphenol
(*p*-cresol)

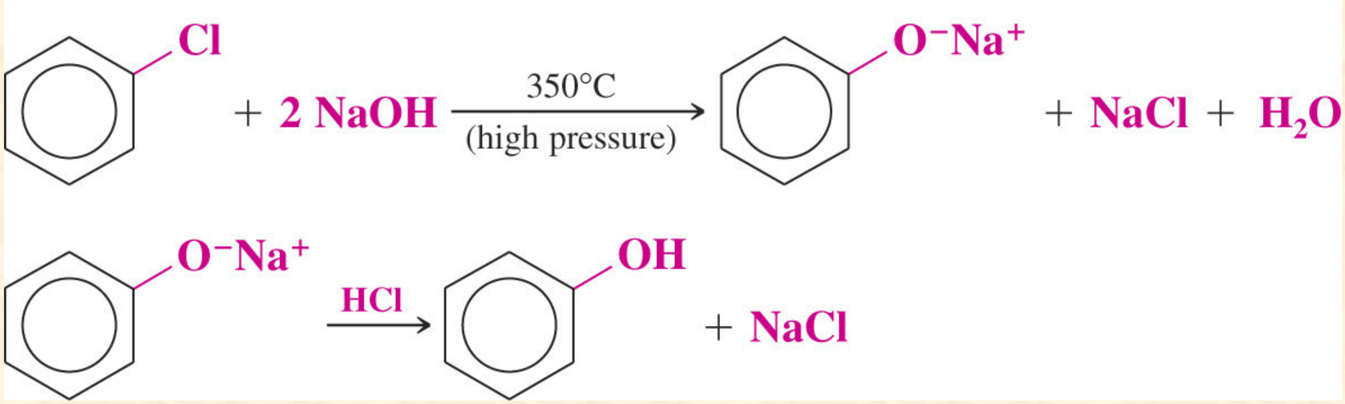
Synthesis of Phenols

- Laboratory Synthesis
  - Phenols can be made by hydrolysis of arenediazonium salts

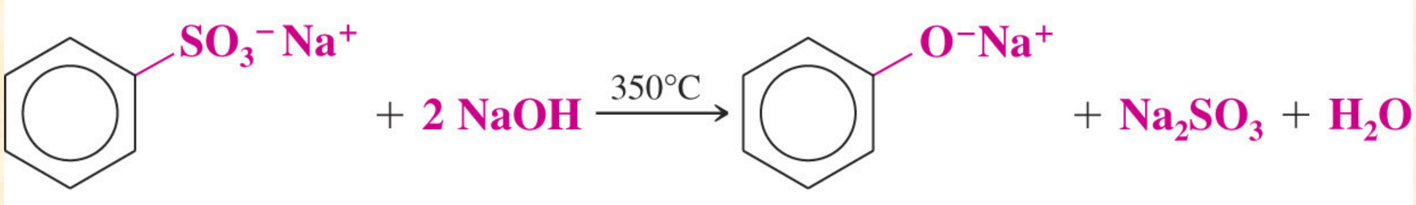


Synthesis of Phenols

- Industrial Syntheses
  - 1. Hydrolysis of Chlorobenzene (Dow Process)
    - Chlorobenzene is heated with sodium hydroxide under high pressure
    - The reaction probably proceeds through a benzyne intermediate



  - 2. Alkali Fusion of Sodium Benzenesulfonate
    - Sodium benzenesulfonate is melted with sodium hydroxide

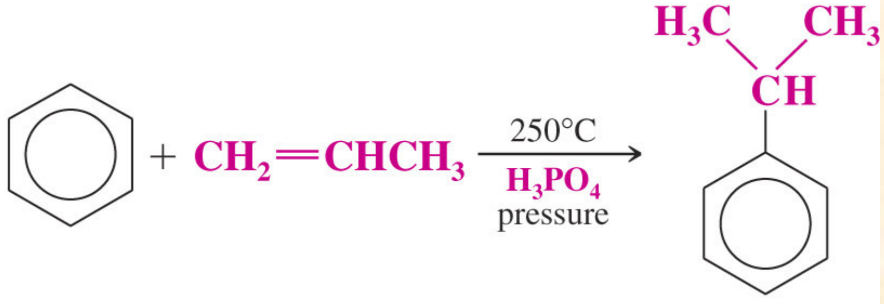


Sodium benzenesulfonate

Synthesis of Phenols

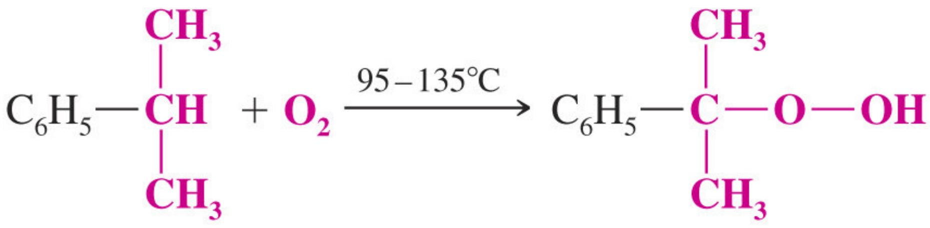
- 3. From Cumene Hydroperoxide
  - Benzene and propene are the starting materials for a three-step sequence that produces phenol and acetone

Reaction 1



Cumene

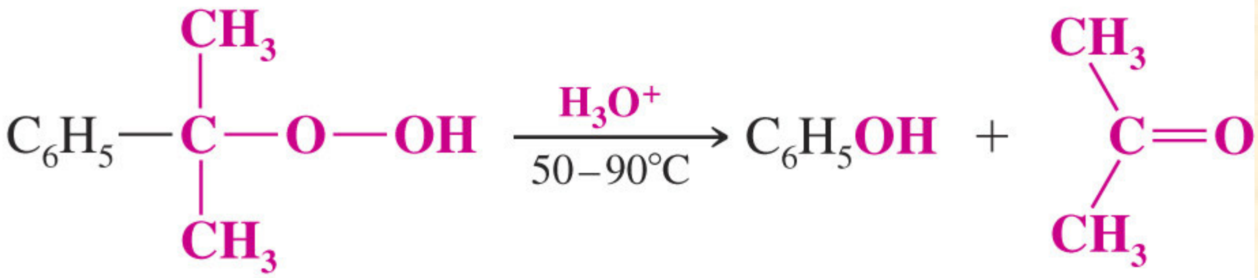
Reaction 2



$$C_6H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{CH}} + O_2 \xrightarrow{95-135^\circ C} C_6H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-O-OH$$

Cumene hydroperoxide

Reaction 3



$$C_6H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-O-OH \xrightarrow[50-90^\circ C]{H_3O^+} C_6H_5OH + \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{=}O$$

Phenol **Acetone**

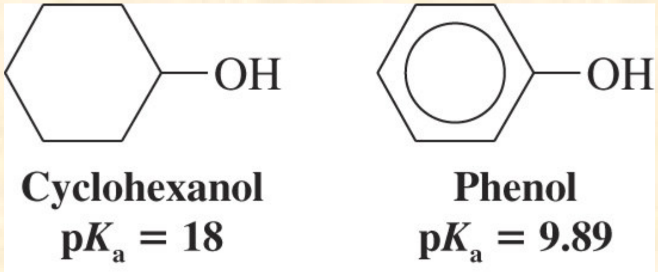
Reactions of Phenols as Acids

- Acid Strength of Phenols
  - Phenols are much stronger acids than alcohols

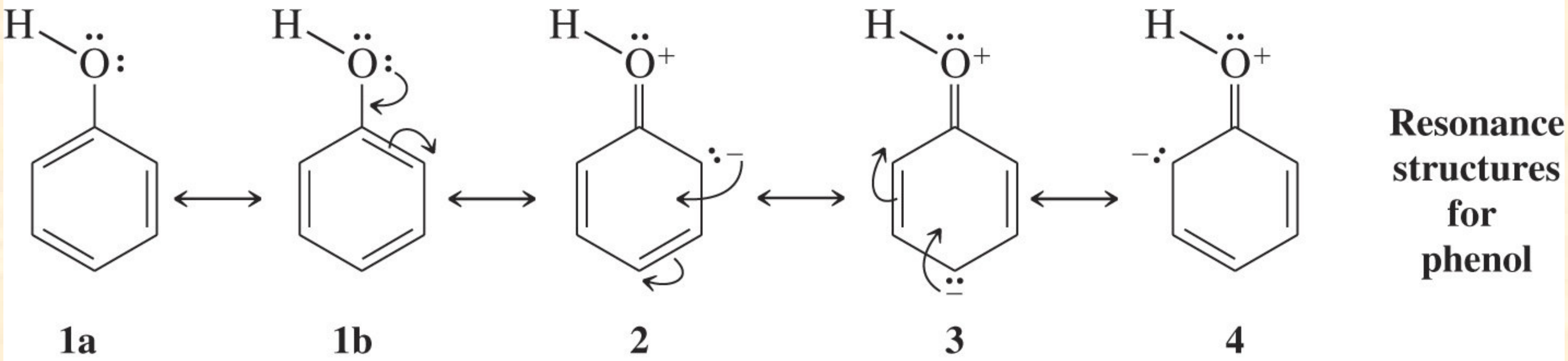
Name	**pK_a (in H_2O at 25°C)**
Phenol	9.89
2-Methylphenol	10.20
3-Methylphenol	10.01
4-Methylphenol	10.17
2-Chlorophenol	8.11
3-Chlorophenol	8.80
4-Chlorophenol	9.20
2-Nitrophenol	7.17
3-Nitrophenol	8.28
4-Nitrophenol	7.15
2,4-Dinitrophenol	3.96
2,4,6-Trinitrophenol (picric acid)	0.38
1-Naphthol	9.31
2-Naphthol	9.55

Reactions of Phenols as Acids

- Phenol is much more acidic than cyclohexanol



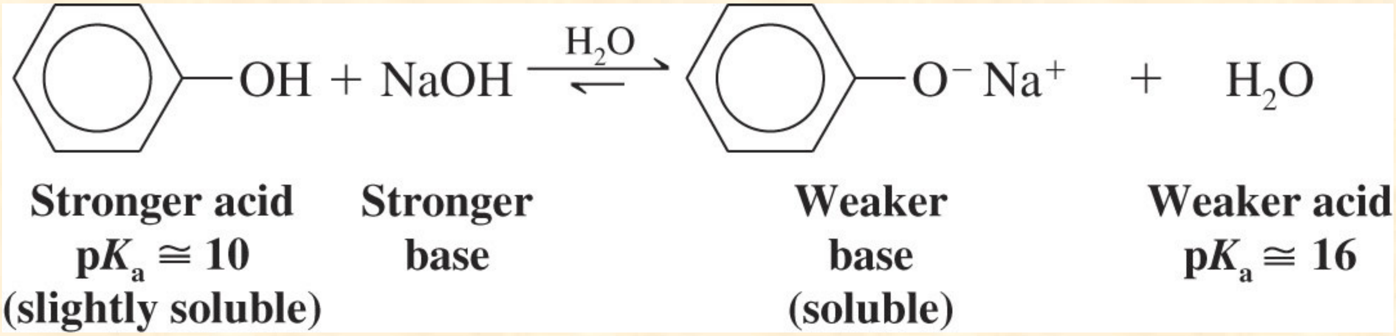
- Experimental results show that the oxygen of a phenol is more positive and this makes the attached hydrogen more acidic
  - The oxygen of phenol is more positive because it is attached to an electronegative sp^2 carbon of the benzene ring
  - Resonance contributors



Reactions of Phenols as Acids

– Separating Phenols from Alcohols and Carboxylic Acids

- Phenols are soluble in aqueous sodium hydroxide because of their relatively high acidity - most alcohols are not



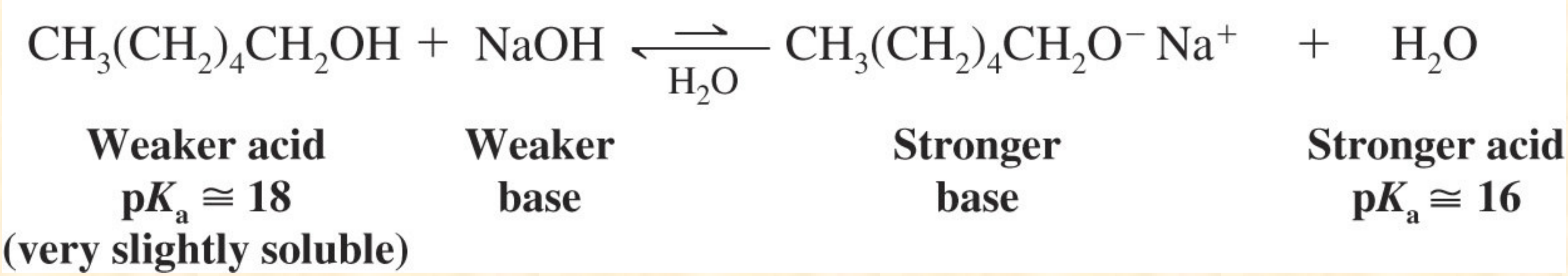
$$C_6H_5OH + NaOH \overset{H_2O}{\rightleftharpoons} C_6H_5O^- Na^+ + H_2O$$

Stronger acid $pK_a \cong 10$ (slightly soluble)

Stronger base

Weaker base (soluble)

Weaker acid $pK_a \cong 16$



$$CH_3(CH_2)_4CH_2OH + NaOH \underset{H_2O}{\rightleftharpoons} CH_3(CH_2)_4CH_2O^- Na^+ + H_2O$$

Weaker acid $pK_a \cong 18$ (very slightly soluble)

Weaker base

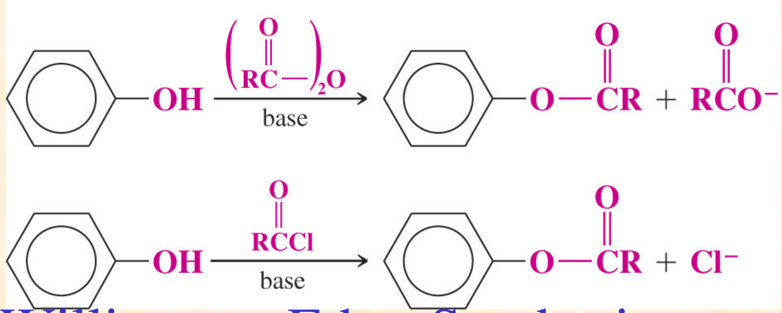
Stronger base

Stronger acid $pK_a \cong 16$

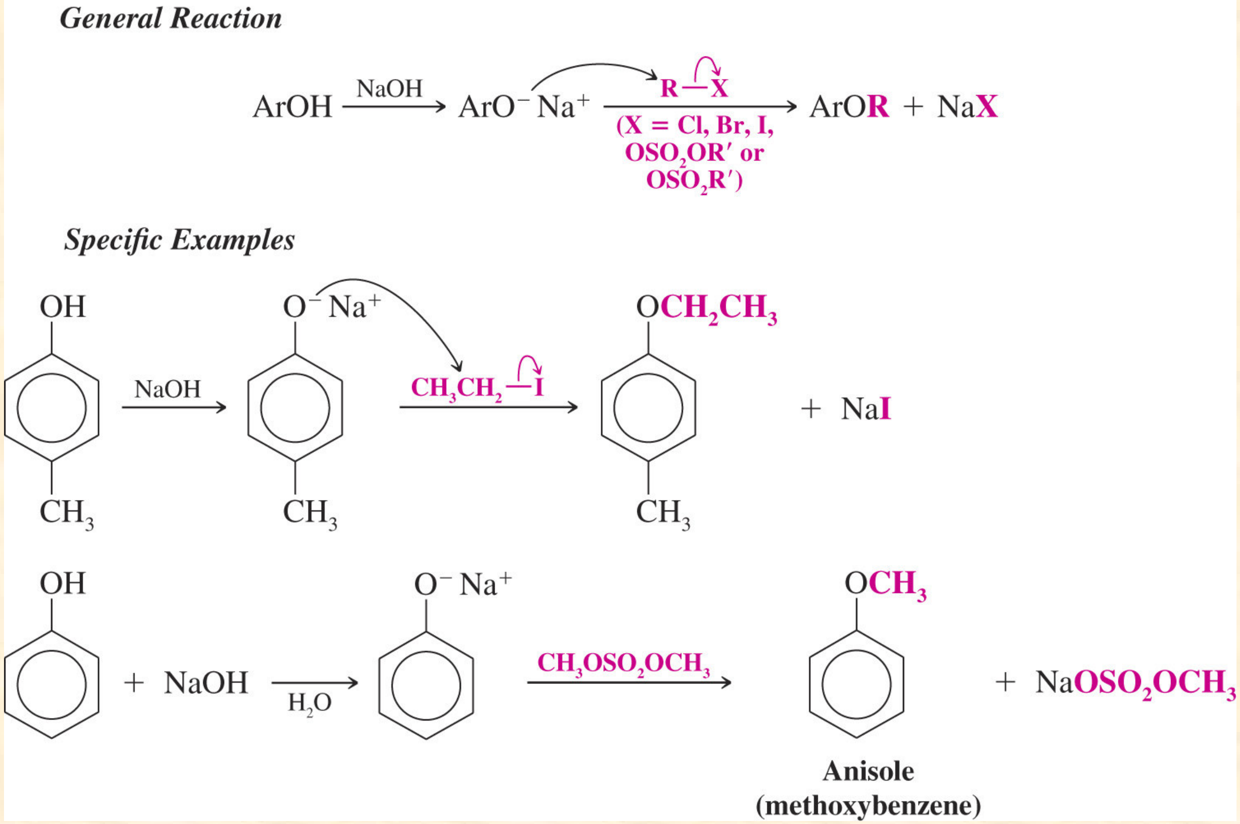
- Phenols are not acidic enough to be soluble in aqueous sodium bicarbonate ($NaHCO_3$)
  – Carboxylic acids are soluble in aqueous sodium bicarbonate

Other Reactions

- Phenols can be acylated with acid chlorides and anhydrides

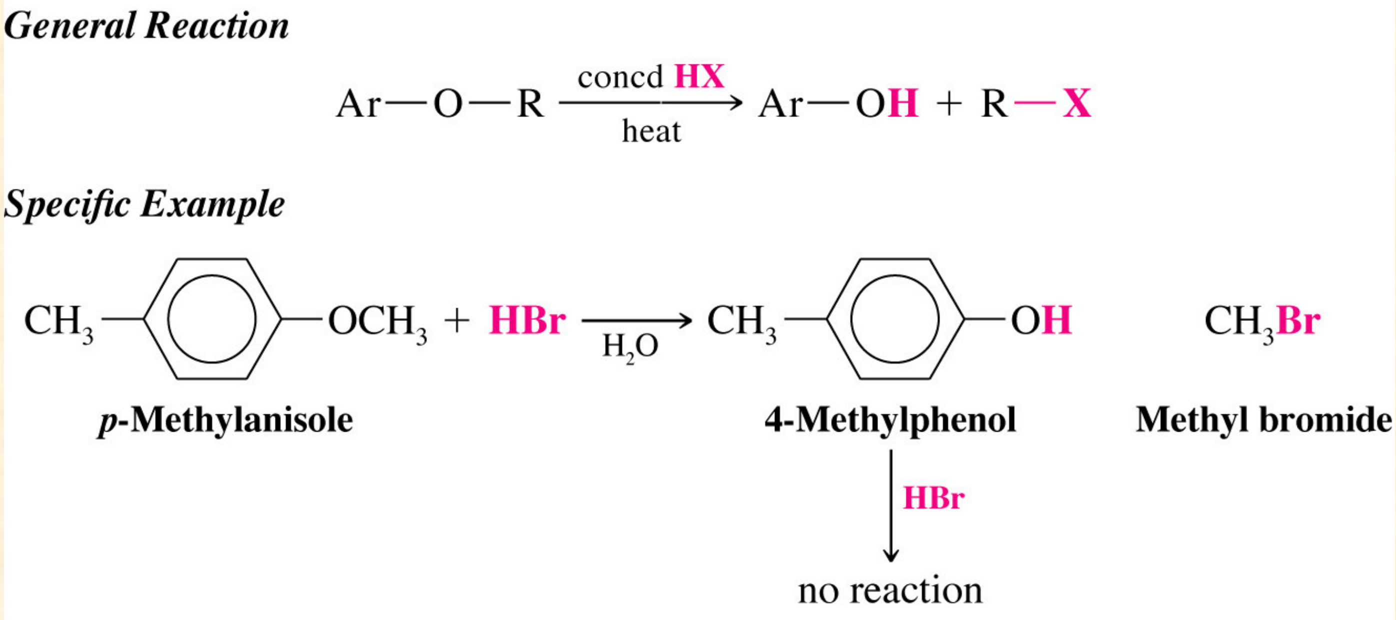


- Phenols in the Williamson Ether Synthesis
  - Phenoxides (phenol anions) react with primary alkyl halides to form ethers by an S_N2 mechanism



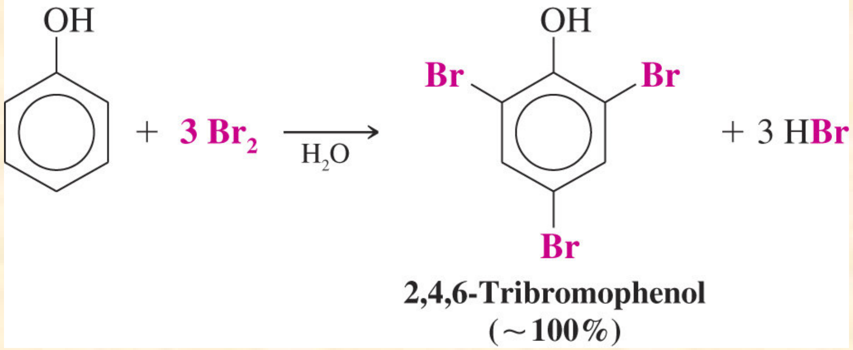
Other Reactions

- Cleavage of Alkyl Aryl Ethers
  - Reaction of alkyl aryl ethers leads to an alkyl halide and a phenol
    - Recall that when a dialkyl ether is reacted, two alkyl halides are produced

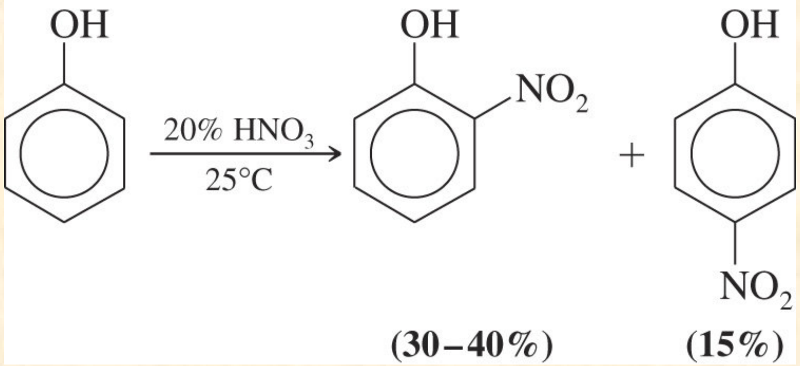


Other Reactions

- Reaction of the Benzene Ring of Phenols
  - Bromination - usually the tribromide is obtained; monobromination - in the presence of carbon disulfide at low temperature

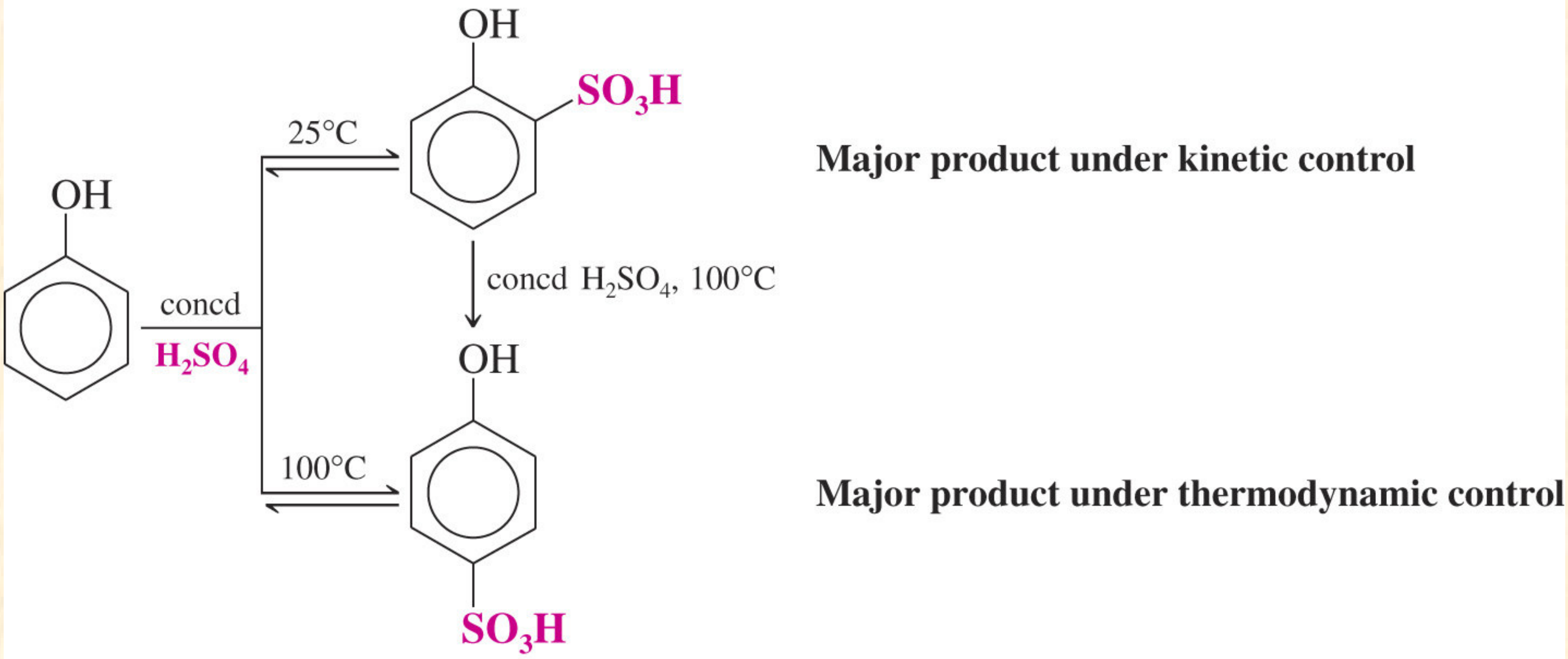


  - Nitration - produces *o*- and *p*-nitrophenol (Low yields)



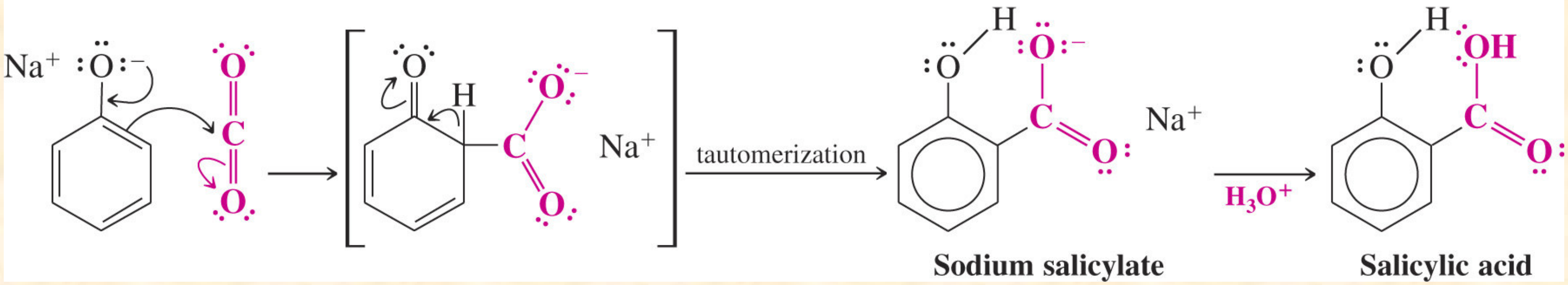
Other Reactions

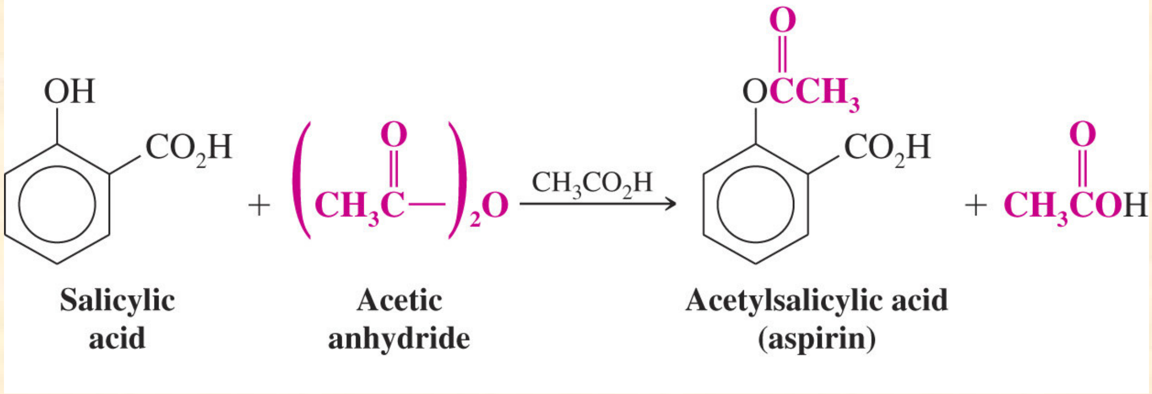
- Sulfonation
  - Sulfonation gives mainly the ortho (kinetic) product at low temperature and the para (thermodynamic) product at high temperature



Other Reactions

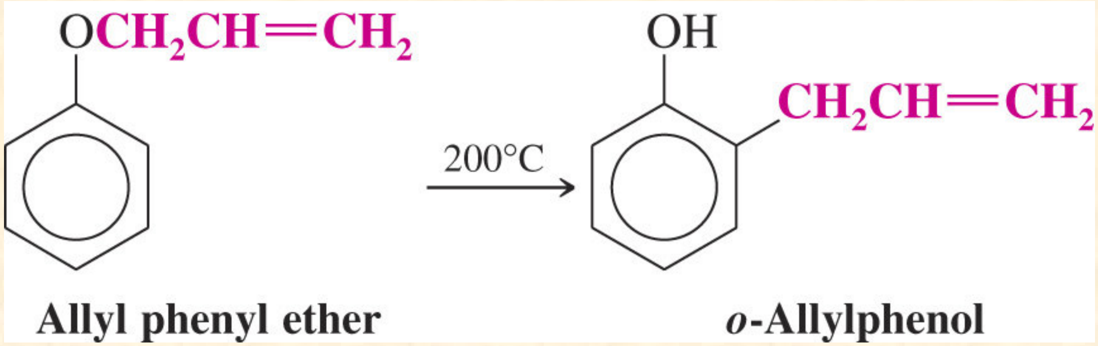
- The Kolbe Reaction
  - Carbon dioxide is the electrophile for an electrophilic aromatic substitution with phenoxide anion
    - The phenoxide anion reacts as an enolate
    - The initial keto intermediate undergoes tautomerization to the phenol
    - Kolbe reaction of sodium phenoxide results in salicyclic acid, a synthetic precursor to acetylsalicylic acid (aspirin)

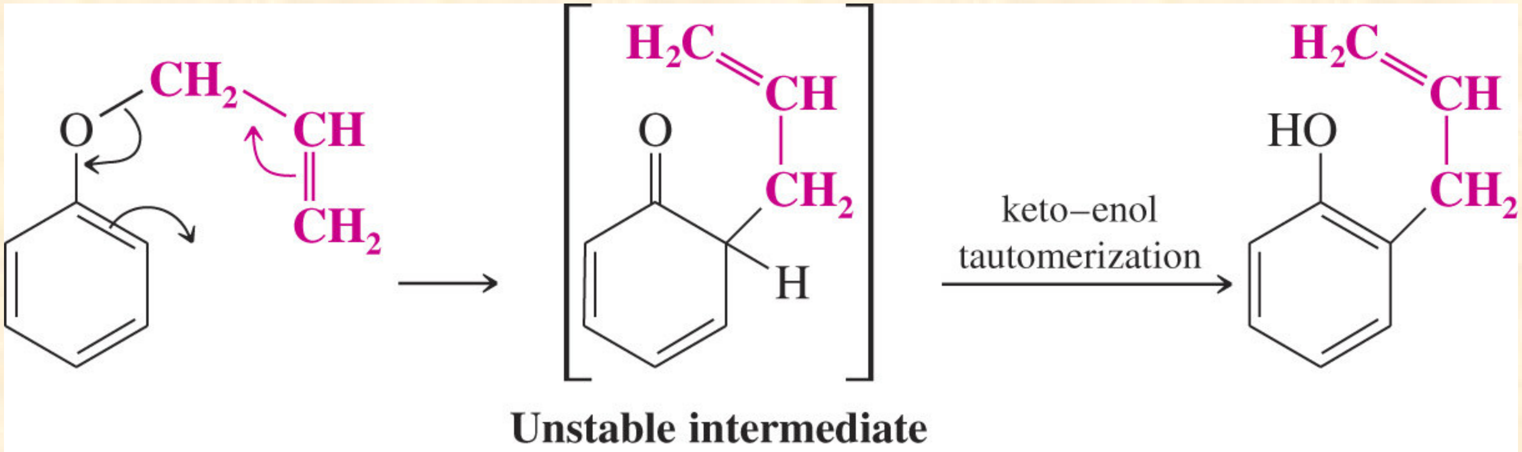




Other Reactions

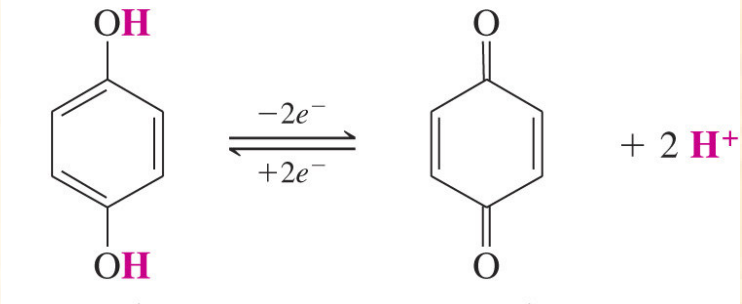
- The Claisen Rearrangement
  - Allyl phenyl ethers undergo a rearrangement to an allyl phenol
  - intramolecular; the allyl group migrates to the aromatic ring
    - The unstable keto intermediate undergoes keto-enol tautomerization to give the phenol group
  - The reaction is concerted.





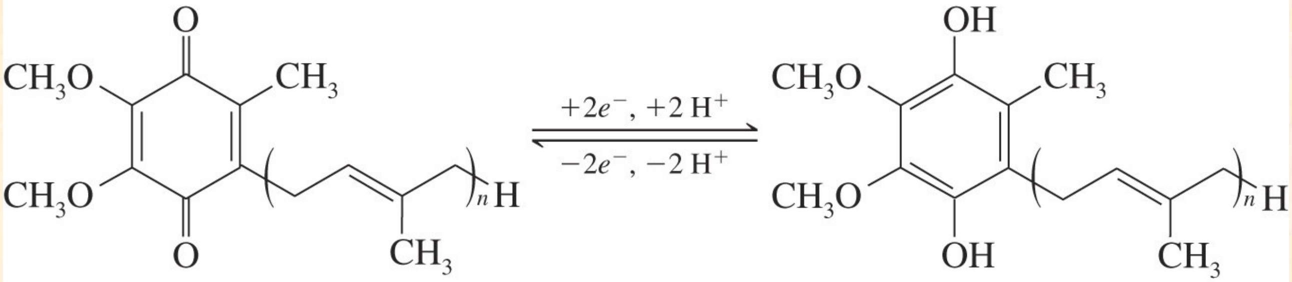
Other Reactions

- Quinones
  - Hydroquinone is oxidized to *p*-benzoquinone by mild oxidizing agents
    - Formally this results in removal of a pair of electrons and two protons from hydroquinone - This reaction is reversible



Hydroquinone **p-Benzoquinone**

  - Every living cell has ubiquinones (Coenzymes Q) in the inner mitochondrial membrane
    - These compounds serve to transport electrons between substrates in enzyme-catalyzed oxidation-reduction reactions

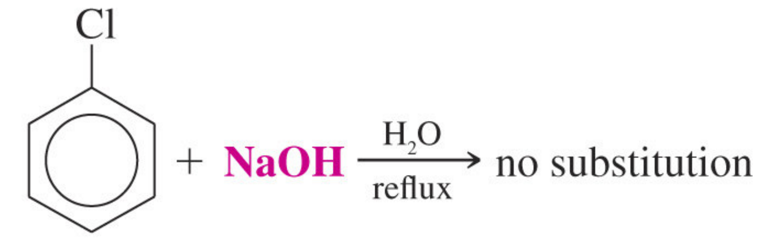


Ubiquinones ($n = 6-10$)
(coenzymes Q)

Ubiquinol (hydroquinone form)

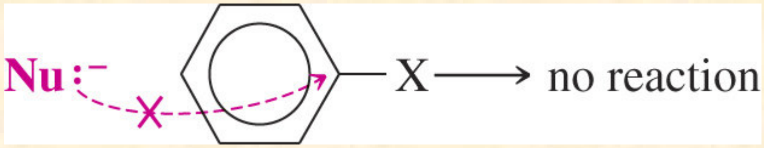
Aryl Halides

- Nucleophilic Aromatic Substitution
  - Simple aryl and vinyl halides do not undergo nucleophilic substitution

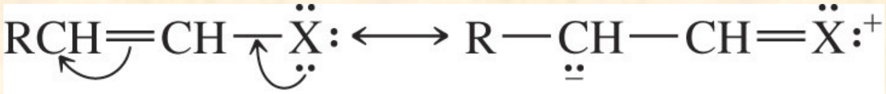


$$+ \text{NaOH} \xrightarrow[\text{reflux}]{H_2O} \text{no substitution}$$

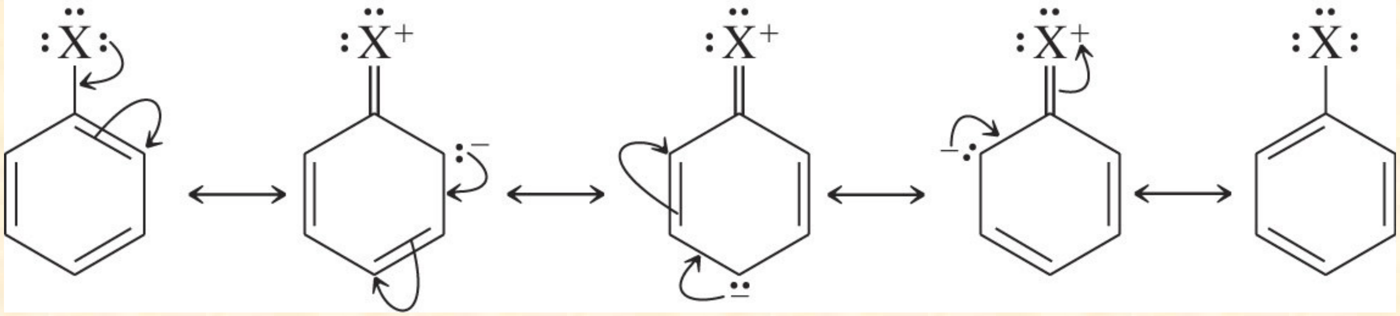
$$CH_2{=}CHCl + \text{NaOH} \xrightarrow[\text{reflux}]{H_2O} \text{no substitution}$$



- S_N2 reaction also doesn't occur because the carbon-halide bond is shorter and stronger than in alkyl halides

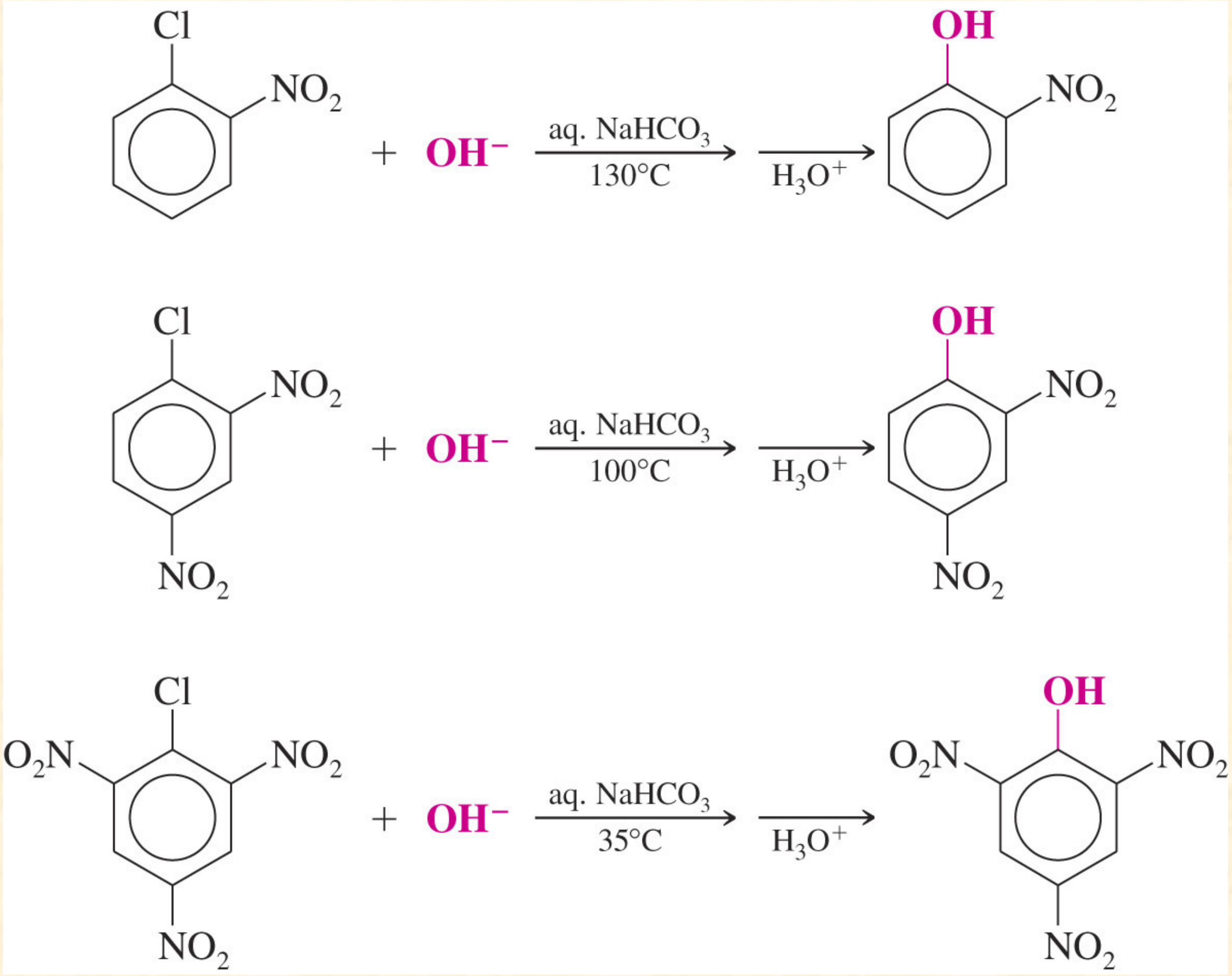


$$RCH{=}CH{-}\ddot{\underset{\cdot\cdot}{X}}\!: \longleftrightarrow R{-}\underset{\cdot\cdot}{C}H{-}CH{=}\ddot{X}\!:^{+}$$



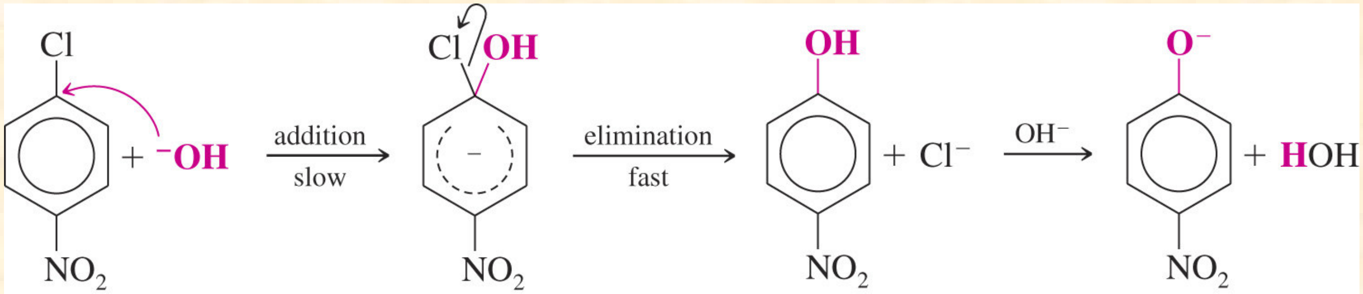
Aryl Halides

- Nucleophilic Aromatic Substitution by Addition-Elimination: The S_NAr Mechanism
  - Nucleophilic substitution can occur on benzene rings when strong electron-withdrawing groups are ortho or para to the halogen atom



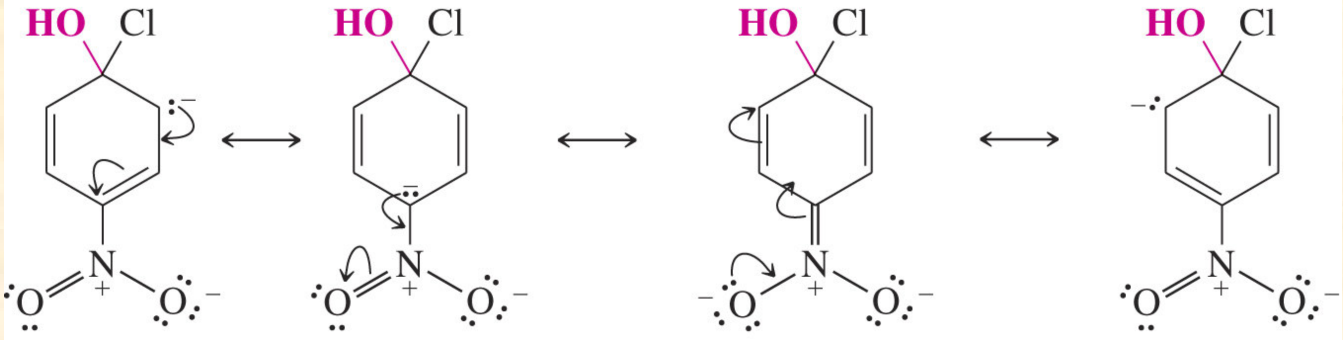
Aryl Halides

- The reaction occurs through an addition-elimination mechanism
  - A Meisenheimer complex, which is a delocalized carbanion, is an intermediate – it is called nucleophilic aromatic substitution (S_NAr)



Carbanion
(Meisenheimer complex)
Structures of the contributing resonance forms are shown below.

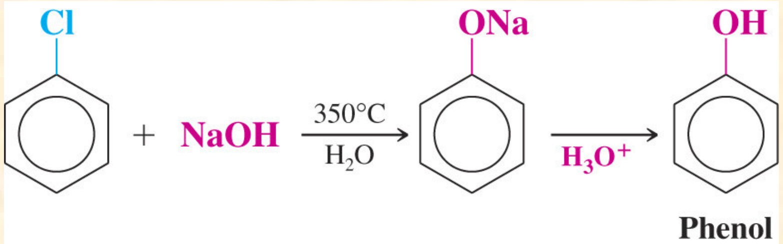
- The carbanion is stabilized by electron-withdrawing groups in the ortho and para positions

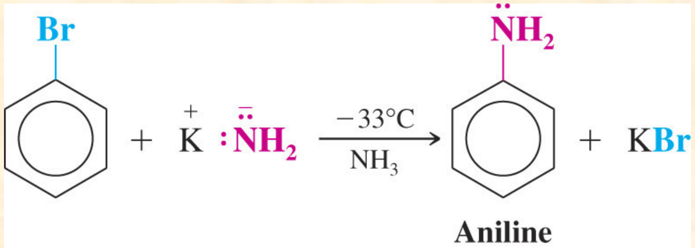


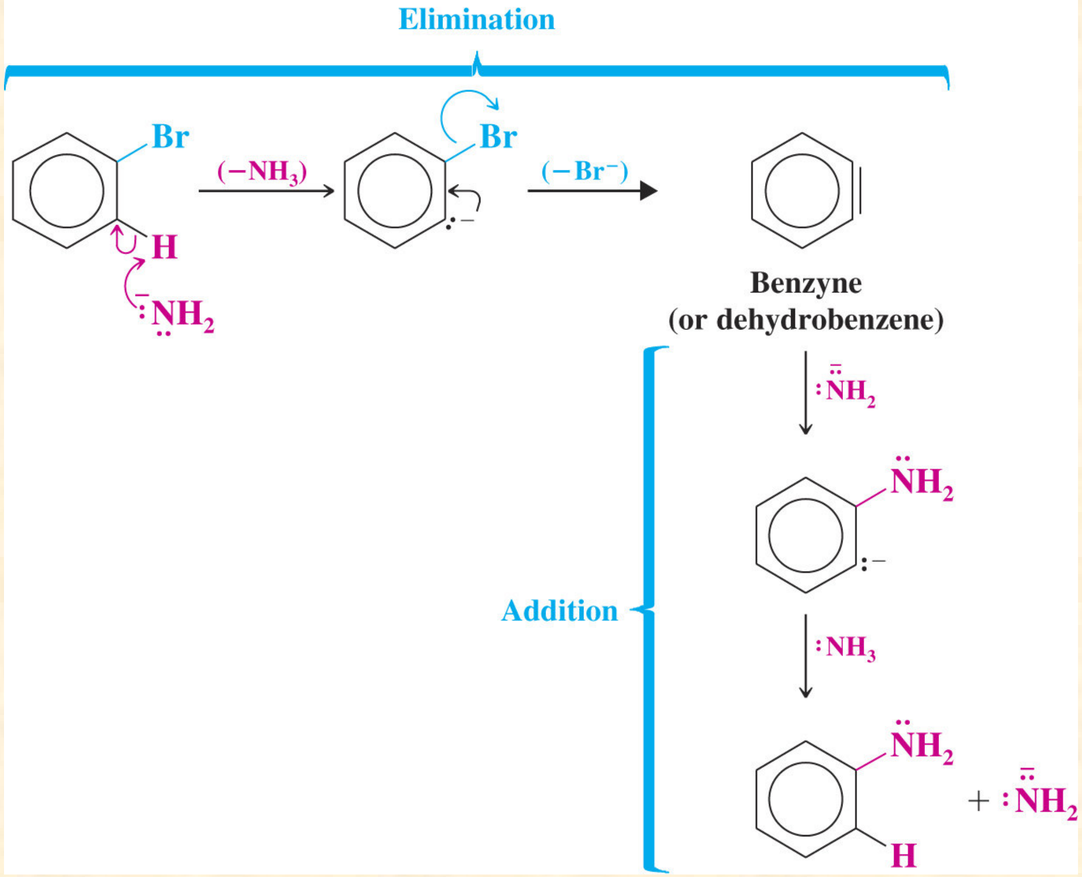
Especially stable
(Negative charges are both on oxygen atoms.)

Aryl Halides

- Nucleophilic Aromatic Substitution through an Elimination-Addition Mechanism: Benzyne – severe conditions

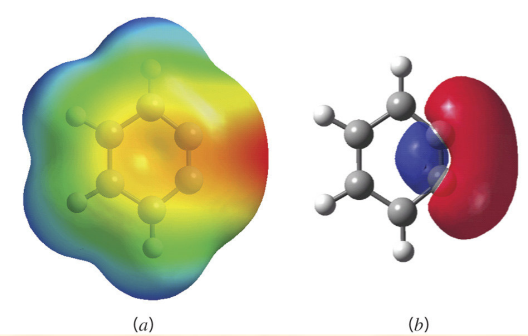




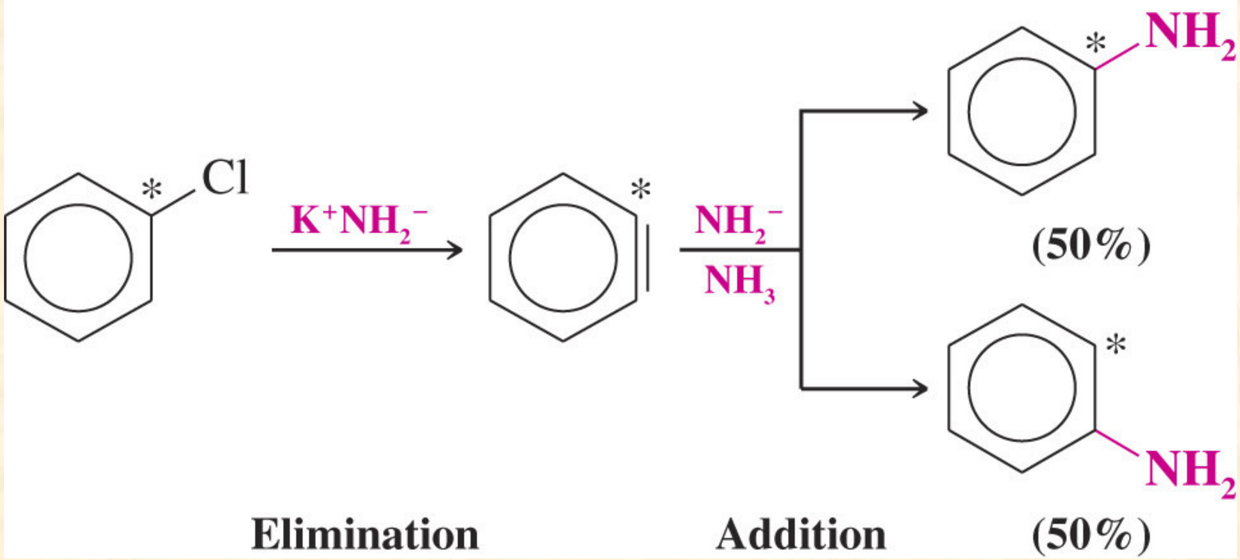


Alkyl Halides

- A calculated electrostatic potential map of benzyne shows added electron density at the site of the benzyne π bond
  - The extra π bond of benzyne is in the same plane as the ring



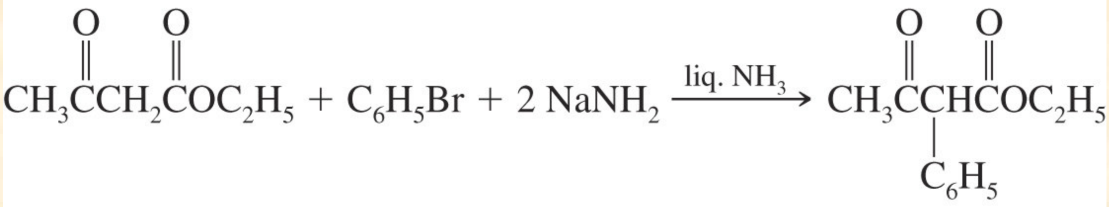
- A labeling study is a strong evidence for an elimination-addition mechanism and against a straightforward S_N2 mechanism



Aryl Halides

- Phenylation

  Acetoacetic esters and malonic esters can be phenylated by benzyne generated *in situ* from bromobenzene



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OC_2H_5 + C_6H_5Br + 2\,NaNH_2 \xrightarrow{\text{liq. } NH_3} CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{C_6H_5}{|}}{C}H\overset{\overset{O}{\|}}{C}OC_2H_5$$