24.6
Sources of Phenols

Phenol is an important industrial chemical.

Major use is in phenolic resins for adhesives and plastics.

Annual U.S. production is about 4 billion pounds per year.
Industrial Preparations of Phenol

1. NaOH
2. Heat

Phenol

1. NaOH
2. H^+

1. Phenol

1. O_2
2. H_2O

H_2SO_4
Laboratory Synthesis of Phenols from arylamines via diazonium ions

1. NaNO₂, H₂SO₄, H₂O
2. H₂O, heat

(81-86%)
24.7
Naturally Occurring Phenols

Many phenols occur naturally
Thymol
(major constituent of oil of thyme)
Example: 2,5-Dichlorophenol

2,5-Dichlorophenol
(from defensive secretion of a species of grasshopper)
24.8
Reactions of Phenols:
Electrophilic Aromatic Substitution

*Hydroxyl group strongly activates the ring toward electrophilic aromatic substitution*
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
Halogenation

monohalogenation in nonpolar solvent
(1,2-dichloroethane)

\[
\text{OH} \quad + \quad \text{Br}_2 \quad \xrightarrow{\text{CICH}_2\text{CH}_2\text{Cl}} \quad 0^\circ \text{C} \quad \xrightarrow{\text{Br}} \quad \text{Br}
\]

(93%)
Halogenation

multiple halogenation in polar solvent (water)

$\text{OH} + 3\text{Br}_2 \rightarrow \text{H}_2\text{O}$

$25^\circ\text{C}$

(95%)
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
Nitration

OH group controls regiochemistry

(73-77%)
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
Nitrosation

only strongly activated rings undergo nitrosation when treated with nitrous acid

\[
\text{Nitrosation} \rightarrow \begin{array}{c}
\text{OH} & \xrightarrow{\text{NaNO}_2, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} & 0^\circ\text{C} \\
\text{NO} & \text{OH} \\
\end{array}
\]
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
**Sulfonation**

\[
\begin{align*}
\text{OH group controls regiochemistry} \\
(69\%)
\end{align*}
\]
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
Friedel-Crafts Alkylation

\[
\text{(CH}_3\text{)}_3\text{COH reacts with H}_3\text{PO}_4 \text{ to give (CH}_3\text{)}_3\text{C}^+ \text{ (63%)}
\]
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
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Acylation of Phenols

Acylation can take place either on the ring by electrophilic aromatic substitution or on oxygen by nucleophilic acyl substitution.
under Friedel-Crafts conditions, acylation of the ring occurs (C-acylation)

Friedel-Crafts Acylation

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{C} & \quad \text{CH}_3
\end{align*}
\]

(74%)

(16%)
in the absence of AlCl₃, acylation of the hydroxyl group occurs (O-acylation)
**O- versus C-Acylation**

O-Acylation is kinetically controlled process; C-acylation is thermodynamically controlled.

AlCl₃ catalyzes the conversion of the aryl ester to the aryl alkyl ketones; this is called the Fries rearrangement.

O-acylation formed faster, more stable.
24.10
Carboxylation of Phenols

Aspirin and the Kolbe-Schmitt Reaction
Aspirin is prepared from salicylic acid

\[
\text{Salicylic acid} + \text{Acetic anhydride} + \text{H}_2\text{SO}_4 \rightarrow \text{Aspirin}
\]
Preparation of Salicylic Acid

called the Kolbe-Schmitt reaction
acidification converts the sodium salt shown above to salicylic acid

$$\text{C}_6\text{H}_5\text{ONa} \xrightarrow{\text{CO}_2 \text{, } 125^\circ \text{C, } 100 \text{ atm}} \text{C}_6\text{H}_4\text{OHNa}_2\text{CO}_3$$
What Drives the Reaction?

acid-base considerations provide an explanation:
stronger base on left; weaker base on right

stronger base:
$pK_a$ of conjugate acid = 10

weaker base:
$pK_a$ of conjugate acid = 3
how does carbon-carbon bond form?
recall electron delocalization in phenoxide ion
negative charge shared by oxygen and by the ring carbons that are ortho and para to oxygen
Mechanism of ortho Carboxylation
Why ortho? Why not para?
Why ortho?
Why not para?

weaker base:
\[ pK_a \text{ of conjugate acid } = 3 \]

stronger base:
\[ pK_a \text{ of conjugate acid } = 4.5 \]
Hydrogen bonding between carboxylate and hydroxyl group stabilizes salicylate ion. Salicylate is less basic than para isomer and predominates under conditions of thermodynamic control.