Lecture 28

Organic Chemistry 1

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April 22, 2010
Today’s Lecture

Topics Covered:

1. **Aryl Halides** - Bonding, Physical Properties and Reactions

2. **Nucleophilic Aromatic Substitution** of Chlorobenzene

3. Nucleophilic Aromatic Substitution: **Addition-Elimination**

4. **Floxcin** - Application of Nucleophilic Aromatic Substitution

5. Nucleophilic Aromatic Substitution: **Elimination-Addition**
What’s the Difference Between Ar- and Ph-?

Phenyl refers specifically to this:

Aryl is a general term for all aromatic ring systems:
Chapter 23
Aryl Halides
23.1
Bonding in Aryl Halides
Aryl halides are halides in which the halogen is attached directly to an aromatic ring.

Carbon-halogen bonds in aryl halides are shorter and stronger than carbon-halogen bonds in alkyl halides.
## Dissociation Energies of Selected Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Bond Type</th>
<th>Bond Energy: kJ/mol (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CH$_2$X</td>
<td>$sp^3$</td>
<td>X = H: 410 (98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X = Cl: 339 (81)</td>
</tr>
<tr>
<td>H$_2$C≡CHX</td>
<td>$sp^2$</td>
<td>X = H: 452 (108)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X = Cl: 368 (88)</td>
</tr>
<tr>
<td><img src="image" alt="苯环" /></td>
<td>$sp^2$</td>
<td>X = H: 469 (112)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X = Cl: 406 (97)</td>
</tr>
</tbody>
</table>
C-X bonds in aryl halides have more double bond character than C-X bonds in alkyl halides
23.2
Sources of Aryl Halides
Preparation of Aryl Halides

Halogenation of arenes (Section 12.5)

\[
\text{苯} + \text{Br}_2 \xrightleftharpoons{\text{FeBr}_3} \text{苯} + \text{HBr}
\]

electrophilic aromatic substitution
Preparation of Aryl Halides

The Sandmeyer reaction (Section 22.17)

### Diazotization-Nucleophilic Aromatic Substitution

1. **Primary Arylamine**
2. **Aryl Diazonium Salt**
3. **Aryl Chloride**

- **Primary Arylamine**: $H_2NHC\text{Cl}$, HCl, H₂O
- **Aryl Diazonium Salt**: $HN=NNCl$, CuCl, heat
- **Aryl Chloride**: $HN=NNCl^{-}$
Preparation of Aryl Halides

The Schiemann reaction (Section 22.17)

1. NaNO₂, HCl, H₂O
2. HBF₄

Primary Arylamine → Aryl Diazonium Salt → Aryl Fluoride

Diazotization-nucleophilic aromatic substitution
Preparation of Aryl Halides

Reaction of aryl diazonium salts with iodide ion
(Section 22.18)

Diazotization-nucleophilic aromatic substitution
23.3
Physical Properties of Aryl Halides
Physical Properties of Aryl Halides

resemble alkyl halides
are essentially insoluble in water
less polar than alkyl halides

\[ \mu \text{ 2.2 D} \quad \mu \text{ 1.7 D} \]
23.4
Reactions of Aryl Halides:
A Review and a Preview
Reactions Involving Aryl Halides

Electrophilic aromatic substitution (Section 12.14)

Bromobenzene

Bromobenzene (hypobromous acid) → 35.7% 1.0% 64.3%

halide substituents are ortho-para directing & deactivating
Reactions Involving Aryl Halides

Electrophilic aromatic substitution (Section 12.14)

ADD DDT SYNTHESIS
Reactions Involving Aryl Halides

Formation of aryl Grignard reagents (Section 14.4)

Bromobenzene $\xrightarrow{\text{Mg, Et}_2\text{O}}$ Phenylmagnesium bromide
We have not yet seen any nucleophilic substitution reactions of aryl halides.

Nucleophilic substitution on chlorobenzene occurs so slowly that forcing conditions are required.
Nucleophilic Substitution of Chlorobenzene

This reaction does not proceed via SN2........
The $S_{N}2$ is not reasonable because the aromatic ring blocks back-side approach of the nucleophile. Inversion is not possible.
S<sub>N</sub>1 Also Unlikely:
Aryl Cations are Highly Unstable

S<sub>N</sub>1 not reasonable because:

1) C—Cl bond is strong; therefore, ionization to a carbocation is a high-energy process

2) aryl cations are highly unstable
SN1 Reaction is Possible with Very Powerful Leaving Groups such as Dinitrogen

This is a unique case: halides are not good enough leaving groups for this process to occur.
What is the Mechanism of This Reaction?

1. NaOH, H₂O, 370°C
2. H⁺

(97%)
23.5
Nucleophilic Substitution in Nitro-Substituted Aryl Halides
Nucleophilic Aromatic Substitution (S_{N}Ar)?

Electrophilic Aromatic Substitution

Nucleophilic Aromatic Substitution?
Electron-Deficient Haloarenes Undergo Nucleophilic Aromatic Substitution

In contrast to chlorobenzene, nitro-substituted aryl halides undergo nucleophilic aromatic substitution at reasonable temperatures.

Cl\[\text{NO}_2\] + NaOCH\(_3\) \rightarrow \text{CH}_3\text{OH} \rightarrow 85^\circ\text{C} \rightarrow \text{OCH}_3\[\text{NO}_2\] (92%) + NaCl
The More Electron-Deficient the Haloarene, the Faster the Substitution

\[ \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \]

\[ \text{N}^+ \quad \text{N}^+ \quad \text{N}^+ \quad \text{N}^+ \]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

1.0 \quad 7 \times 10^{10} \quad 2.4 \times 10^{15} \quad \text{too fast to measure}
Direct Displacement Doesn’t Occur!
Kinetics of Nucleophilic Aromatic Substitution

follows second-order rate law:

\[
\text{rate} = k \text{[aryl halide]} \text{[nucleophile]}
\]

inference:

both the aryl halide and the nucleophile are involved in rate-determining step
Effect of Leaving Group Upon Rate of $\text{SN}_2$

During $\text{SN}_2$ reactions, the C-X bond breaks during the rate-determining step.

Reaction Rate Depends on $X$: $I > Br > Cl > F$

C-F (485 kJ/mol), C-Cl (327 kJ/mol)
C-Br (285 kJ/ml, C-I (213 kJ/mol)
Effect of Leaving Group in Nucleophilic Aromatic Substitution

*NaOCH₃, CH₃OH, 50°C

<table>
<thead>
<tr>
<th>X</th>
<th>Relative Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>312</td>
</tr>
<tr>
<td>Cl</td>
<td>1.0</td>
</tr>
<tr>
<td>Br</td>
<td>0.8</td>
</tr>
<tr>
<td>I</td>
<td>0.4</td>
</tr>
</tbody>
</table>

C-F (485 kJ/mol), C-Cl (327 kJ/mol)

C-Br (285 kJ/ml), C-I (213 kJ/mol)
General Features of Mechanism

1. bimolecular rate-determining step in which nucleophile attacks aryl halide

2. rate-determining step precedes carbon-halogen bond cleavage

3. rate-determining transition state is stabilized by electron-withdrawing groups (such as NO₂)
23.6
The Addition-Elimination Mechanism of
Nucleophilic Aromatic Substitution
Addition-Elimination Mechanism

Two step mechanism:

**Step 1**

nucleophile attacks aryl halide and bonds to the carbon that bears the halogen  
(slow: aromaticity of ring lost in this step)

**Step 2**

intermediate formed in first step loses halide  
(fast: aromaticity of ring restored in this step)
Addition-Elimination Mechanism

\[
\text{F} + \text{NO}_2^2 + \text{NaOCH}_3 \xrightarrow{\text{CH}_3\text{OH} \, 85^\circ\text{C}} \text{OCH}_3 + \text{NO}_2^2 (92\%) + \text{NaF}
\]
Addition-Elimination Mechanism

Step 1 - Addition

\[ \text{Rate} = k \ [\text{CH}_3\text{ONa}] \ [\text{arene}] \]

- Bimolecular, consistent with second-order kinetics;
- First order in aryl halide, first order in nucleophile.
Addition-Elimination Mechanism

Step 1 - Addition

\[
\text{CH}_3\text{O} : \text{O} : \text{O}^-
\]

\[
\begin{align*}
\text{F} & \quad \text{NO}_2 \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

\[
\text{Slow}
\]

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{F} \\
\text{H} & \quad \text{NO}_2 \\
\end{align*}
\]
intermediate is negatively charged

formed faster when ring bears electron-withdrawing groups such as NO$_2$ because negative charge is stabilized
Stabilization of Addition Product by Electron-Withdrawing Group
Rapid Collapse of Cyclohexadienyl Anion Intermediate

Step 2 - Elimination

\[
\text{CH}_3\text{O} \quad \text{F} \quad \text{H} \quad \text{OCH}_3
\]

\[
\text{NO}_2 \quad + \quad \text{F}^\text{−}
\]

Fast
F > Cl > Br > I is unusual, but consistent with mechanism

carbon-halogen bond breaking does not occur until after the rate-determining step

electronegative F stabilizes negatively charged intermediate
The Role of Leaving Groups

Most Stabilized  Least Stabilized
23.7
Related Nucleophilic Aromatic Substitution Reactions
Six fluorine substituents stabilize negatively charged intermediate formed in rate-determining step and increase rate of nucleophilic aromatic substitution.
Substitution of 2-Chloropyridine

2-Chloropyridine reacts 230,000,000 times faster than chlorobenzene under these conditions.
Substitution of 2-Chloropyridine

Nitrogen is more electronegative than carbon, stabilizes the anionic intermediate, and increases the rate at which it is formed.

Anionic Intermediate
Compare 2-Chloropyridine with Chlorobenzene

2-Chloropyridine with NaOCH₃ in CH₃OH at 50°C yields a product.

Chlorobenzene with 1. NaOH, H₂O at 370°C followed by 2. H⁺ yields the final product.
Synthetic Application of Nucleophilic Aromatic Substitution
Ofloxacin (trade name Floxin) is a broad-spectrum quinolone antibiotic.

http://www.ofloxacin.com/
Synthesis of Ofloxacin, Part 1

1,4-Addition

Elimination
Synthesis of Ofloxacin, Part 2

Addition

Elimination

Nucleophilic Aromatic Substitution
Synthesis of Ofloxacin, Part 3

Addition

Elimination

Nucleophilic Aromatic Substitution
Synthesis of Ofloxacin, Part 4

Addition

Elimination

Nucleophilic Aromatic Substitution
Synthesis of Ofloxacin, Part 5

![Chemical structure of Ofloxacin](attachment:image.png)
Synthetic Application of Nucleophilic Aromatic Substitution
Ofloxacin (trade name Floxin) is a broad-spectrum quinolone antibiotic.

Prozac another good idea
23.8
Benzyne & the Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution
Aryl Halides Undergo Substitution When Treated With Very Strong Bases

\[
\text{Cl} \xrightarrow{\text{KNH}_2, \text{NH}_3} \text{NH}_2
\]

-33 °C

(52%)

Ammonia: pKa = 34; b.p. = -33 °C

Potassium Amide: strong base
new substituent becomes attached to either the carbon that bore the leaving group or the carbon adjacent to it

\[
\text{CH}_3 \text{Br} \xrightarrow{\text{NaNH}_2, \text{NH}_3} \text{CH}_3 \text{NH}_2
\]

-33 °C

Cine substitution product
Cine Substitution Defined

**cine-substitution**
A substitution reaction (generally aromatic) in which the entering group takes up a position adjacent to that occupied by the leaving group.
new substituent becomes attached to either the carbon that bore the leaving group or the carbon adjacent to it.

\[
\text{CH}_3\text{Br} \xrightarrow{\text{NaNH}_2, \text{NH}_3} \text{CH}_3\text{NH}_2 + \text{Cine substitution product}
\]
Regiochemistry

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br} & \quad \text{NaNH}_2, \text{NH}_3 & \quad -33 ^\circ \text{C} \\
& & & \\
\text{Cine substitution product} & & & \\
\text{Cine substitution product} & & & 
\end{align*}
\]
Further Proof of Cine Substitution via $^{14}$C Label

$$\text{Cl}^* \xrightarrow{\text{KNH}_2, \text{NH}_3} \text{NH}_2^* + \text{NH}_2^*$$

-33 °C

Cine substitution product

(48%) (52%)
compound formed in this step is called benzyne
Benzyne - A Reactive Molecule With an Abnormal $\pi$-Bond

Benzyne has a reactive triple bond.
It cannot be isolated in this reaction, but is formed as a reactive intermediate.
Benzyne - A Reactive Aromatic Molecule With An Abnormal, In-Plane $\pi$-Bond

'Normal' C-C Triple Bond

Benzyne C-C Triple Bond

overlapping $sp^2$ orbitals
poor overlap results in a weak, reactive bond
Arynes are Highly Reactive Electrophiles

Step 2 - Addition

Benzyne

Aryl Anion
Aryl Anions are Strongly Basic

Step 3 - Protonation

Benzyne

Substitution Product
$^{14}$C labeling indicates that the high-temperature reaction of chlorobenzene with NaOH proceeds via benzyne.

\[
\begin{align*}
\text{Cl} & \hspace{2cm} \text{NaOH, H}_2\text{O} \\
\begin{array}{c}
\text{OH} \\
\end{array} & \hspace{2cm} 395 \degree \text{C} \\
\begin{array}{c}
\text{(54\%)} \\
\end{array} & \hspace{2cm} \begin{array}{c}
\text{OH} \\
\end{array} \hspace{2cm} \begin{array}{c}
\text{(43\%)} \\
\end{array}
\end{align*}
\]
Substitution of Chlorobenzene Proceeds via Benzyne

\[
\begin{align*}
\text{Cl} & \xrightarrow{\text{NaOH}} \text{H} \\
\text{H} & \xrightarrow{\text{NaOH}} \text{H} \\
\text{H} & \xrightarrow{\text{H}_2\text{O}} \text{H}
\end{align*}
\]

Cine substitution product
Why the Temperature Difference?

Sodium amide is a considerably stronger base than hydroxide and consequently better able to carry out the rate-determining step.
All is Revealed

CH₃Br + NaNH₂ → CH₃ + 1. NaNH₂
2. NH₃ → CH₃NH₂ + CH₃NH₂
All is Revealed

\[
\begin{align*}
\text{CH}_3 & \quad \text{NaNH}_2 \\
\text{Br} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad 1. \text{NaNH}_2 \\
\text{CH}_3 & \quad 2. \text{NH}_3 \\
\text{NH}_2 & \quad + \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]
All is Revealed

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{NaNH}_2} \quad \text{NaNH}_2 + \text{NaNH}_2 \\
& \quad 1. \text{NaNH}_2 \quad 2. \text{NH}_3
\end{align*}
\]
Other Methods for the Preparation of Benzyne

Benzyne can be prepared as a reactive intermediate by methods other than treatment of chlorobenzene with strong bases.

Another method involves loss of fluoride ion from the Grignard reagent of 1-bromo-2-fluorobenzene.
Other Methods for the Preparation of Benzyne

Aryl bromide faster with Mg than aryl fluoride

Benzylene
Preparation of Benzyne via Diazotization of Anthranilic Acid

See Question 23.23

Anthranilic Acid

\[
\begin{align*}
\text{Anthranilic Acid} & \quad \text{NaNO}_2 \\
& \quad \text{HCl, H}_2\text{O} \\
& \quad \text{Aryl Diazonium Salt} \\
& \quad \text{NaOH} \\
& \quad \text{Benzyne} \\
& \quad \text{N}_2 + \text{CO}_2
\end{align*}
\]
23.9
Cycloaddition Reactions of Benzyne
What is a Cycloaddition?

**Cycloaddition, n.**
a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic *adduct* in which there is a net reduction of the bond multiplicity.
The Diels-Alder Reaction Revisited

Section 10.12

Diene + Dienophile $\rightarrow$ Cycloadduct

Cycloaddition

Isoprene + Maleic anhydride $\rightarrow$ Cycloadduct

100°C
Electron-Deficient Alkynes Behave as Dienophiles

\[
\text{butadiene} \quad + \quad \text{CH}_3\text{C} = \text{C} = \text{CH}_2 \quad \text{but-3-yn-2-one} \quad \xrightarrow{120^\circ \text{C}} \quad \text{cycloadduct}
\]
Benzyne Behaves as a Dienophile

Benzyne is a fairly reactive dienophile, and gives Diels-Alder adducts when generated in the presence of conjugated dienes.
Benzyne Participates in Diels-Alder Reactions

\[
\begin{align*}
\text{Br} & \quad \text{F} & \quad \text{Diene} & \quad \text{Mg} \\
\text{Dienophilie} & \quad \text{Cycloadduct (46\%)}
\end{align*}
\]
In the Absence of Dienes (or other nucleophiles) Benzyne Undergoes Dimerization and Trimerization.
Today’s Lecture

Topics Covered:

1. Aryl Halides - Bonding, Physical Properties and Reactions
2. Nucleophilic Substitution of Chlorobenzene
3. Nucleophilic Aromatic Substitution: Addition-Elimination
4. Synthetic Application of Nucleophilic Aromatic Substitution
5. Nucleophilic Aromatic Substitution: Elimination-Addition
6. Benzyne: Generation, Bonding and Reactions
Information & Suggested Problems

Suggested Problems: 23.10-23.27