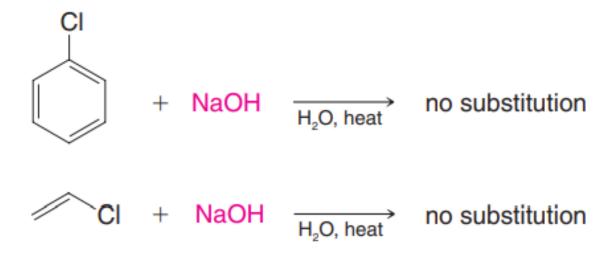
# PHA284 Organic Chemistry II

Ankara University
Faculty of Pharmacy
Department of Pharmaceutical Chemistry

# Aryl Halides and Nucleophilic Aromatic Substitution

# Aryl Halides and Nucleophilic Aromatic Substitution



Aryl halides can be remarkably reactive toward nucleophiles if they bear certain substituents or when we allow them to react under the proper conditions.

- A- Nucleophilic Aromatic Substitution by Addition–Elimination: The S<sub>N</sub>Ar Mechanism:
- B- Nucleophilic Aromatic Substitution through an Elimination—Addition Mechanism: Benzyne
- C- Phenylation

Nucleophilic substitution reactions of aryl halides *do* occur readily when an electronic factor makes the aryl carbon bonded to the halogen susceptible to nucleophilic attack.

# A- Nucleophilic Aromatic Substitution by Addition–Elimination: The S<sub>N</sub>Ar Mechanism:

$$\begin{array}{c} \text{CI} \\ \text{NO}_2 \\ \text{HO}^- \end{array} \begin{array}{c} \frac{\text{aq. NaHCO}_3}{130 \, ^{\circ}\text{C}} \xrightarrow{\text{H}_3\text{O}^+} \\ \text{NO}_2 \\ \text{NO}_2 \\ \text{HO}^- \end{array} \begin{array}{c} \frac{\text{aq. NaHCO}_3}{100 \, ^{\circ}\text{C}} \xrightarrow{\text{H}_3\text{O}^+} \\ \text{NO}_2 \\ \text{NO}_2 \\ \text{NO}_2 \\ \text{HO}^- \end{array} \begin{array}{c} \frac{\text{aq. NaHCO}_3}{35 \, ^{\circ}\text{C}} \xrightarrow{\text{H}_3\text{O}^+} \\ \text{NO}_2 \\ \text{NO}_2 \\ \text{NO}_2 \\ \text{NO}_2 \\ \end{array}$$

 B-Nucleophilic Aromatic Substitution through an Elimination—Addition Mechanism: Benzyne

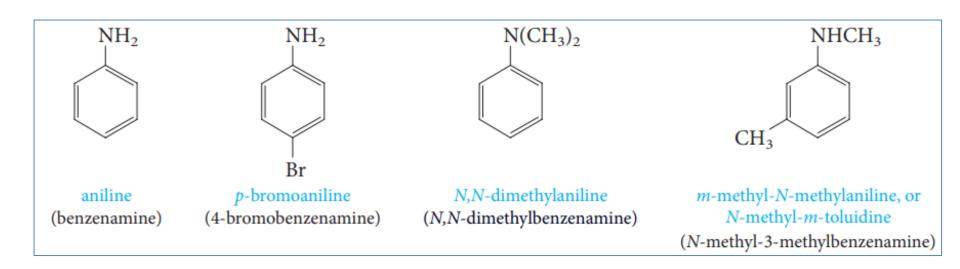
$$\frac{\ddot{K} : \ddot{N}H_{2}}{-33 \, ^{\circ}C} + KBr$$
Aniline

#### **C- Phenylation**

 Reactions involving benzyne can be useful for formation of a carbon– carbon bond to a phenyl group (a process called phenylation).

# **Aromatic amines**

# **Aromatic amines**



# **Basicity of Aromatic amines**

$$\begin{array}{c|cccc}
& \vdots \\
& NH_2 \\
& NH_2 \\
& \text{or ammonium ion} \\
& 4.62 \\
& 9.8 \\
\end{array}$$

# **Preparation of Aromatic amines**

$$CH_{3} \xrightarrow{NO_{2}} \frac{3 \text{ H}_{2}, \text{ Ni catalyst}}{\text{or}} CH_{3} \xrightarrow{NH_{2} + 2 \text{ H}_{2}O} NH_{2} + 2 \text{ H}_{2}O$$

$$p\text{-nitrotoluene} \qquad 2. \text{ NaOH,H}_{2}O \qquad p\text{-toluidine}$$

# **Preparation of Aromatic amines**

$$NH_3$$
 $200 \, ^{\circ}C$ 
 $NH_2$ 

#### **Reactions of Aromatic amines**

#### Alkylation:

#### **Reactions of Aromatic amines**

#### Amidification:

#### **Reactions of Aromatic amines**

$$NH_2$$
 + HCI  $\rightarrow$   $NH_3$ 

$$\begin{array}{c|c} & & & \\ &$$

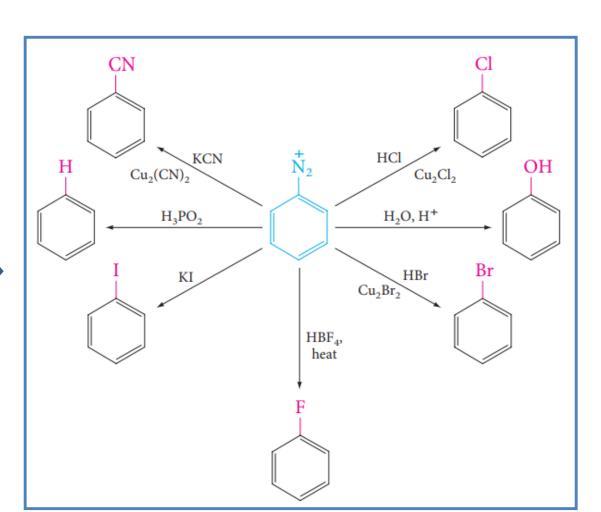
#### **Aromatic amines**

# **Aromatic Diazonium Compounds**

$$NH_2 + HONO + H^+Cl^- \xrightarrow{0-5^{\circ}C} N_2^+Cl^- + 2 H_2O$$
aniline
nitrous
acid
benzenediazonium
chloride

# **Aromatic Diazonium Compounds**

The nucleophile always takes the position on the benzene ring that was occupied by the diazonio group.



# Replacement of the Diazonium Group by -Cl, -Br, or -CN:

$$\begin{array}{c} \text{CH}_{3} \\ \text{NH}_{2} \\ \text{o-Toluidine} \end{array} \begin{array}{c} \text{HCI, NaNO}_{2} \\ \text{H}_{2}O \\ (0-5\,^{\circ}\text{C}) \end{array} \begin{array}{c} \text{CH}_{3} \\ \text{N}_{2}\text{CI} \\ \text{15-60\,^{\circ}\text{C}} \end{array} \begin{array}{c} \text{CH}_{3} \\ \text{O-Chlorotoluene} \\ \text{(74-79\% overall)} \end{array} + \text{N}_{2} \\ \text{HBr, NaNO}_{2} \\ \text{H}_{2}O \\ (0-10\,^{\circ}\text{C}) \end{array} \begin{array}{c} \text{CuBr} \\ \text{I00\,^{\circ}\text{C}} \end{array} \begin{array}{c} \text{CuBr} \\ \text{T00\,^{\circ}\text{C}} \end{array} \begin{array}{c} \text{HBr, NaNO}_{2} \\ \text{HBr, NaNO}_{2} \\ \text{H}_{2}O \end{array} \begin{array}{c} \text{CI} \\ \text{CI} \end{array} \begin{array}{c} \text{CuBr} \\ \text{T00\,^{\circ}\text{C}} \end{array} \begin{array}{c} \text{CI} \\ \text{CI} \end{array} \begin{array}{c} \text{NO}_{2} \\ \text{O-Nitrobenzonitrile} \end{array} \begin{array}{c} \text{NO}_{2} \\ \text{O-Nitrobenzonitrile} \end{array} \begin{array}{c} \text{NO}_{2} \\ \text{O-Nitrobenzonitrile} \end{array} \begin{array}{c} \text{O-Nitrobenzonitrile} \\ \text{(65\% overall)} \end{array}$$

### Replacement of the Diazonium Group by -F:

#### Replacement of the Diazonium Group by -I:

$$NO_2$$
 $H_2SO_4$ ,  $NaNO_2$ 
 $H_2O_{0-5 °C}$ 
 $P$ -Nitroaniline

 $P$ -Iodonitrobenzene
(81% overall)

### Replacement by -OH:

$$H_3C$$
  $\longrightarrow$   $N_2^+$   $HSO_4^ \xrightarrow{Cu_2O}$   $Cu^{2+}$ ,  $H_2O$   $\longrightarrow$   $P$ -Cresol hydrogen sulfate  $p$ -Cresol (93%)

## **Aromatic Diazonium Compounds**

# Diazo coupling

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## **Aromatic Diazonium Compounds**

# Diazo coupling

4-(phenyldiazenyl)aniline *p*-Aminoazobenzene 4-phenylazoaniline

#### • Diazo coupling

$$\bigcap_{N=N}^{\oplus} \bigcap_{N=N}^{OH} \longrightarrow \bigcap_{N=N}^{OH}$$

$$(CH_3)_2N$$
 —  $N=N$  —  $SO_3$  —  $M=N$  —  $M=N$ 

## References

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