WELCOME

TO

FDSPharmacy
Learn and Educate

This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site http://www.fdspharmacy.in/

You tube https://www.youtube.com/c/FDSpharmacy

Telegram https://t.me/Fdspharmacy

App https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy

E-mail fdspharmacyinfo@gmail.com

Bachelor of Pharmacy

Physical Pharmaceutics I

NOTES

- ✓ Unit 1
- ✓ Unit 2
- ✓ Unit 3
- ✓ Unit 4
- ✓ Unit 5

All Unit in One PDF

Visit our Website
WWW.fdspharmacy.in

Bachelor of Pharmacy

Pharmaceutical Engineering

NOTES

- ✓ Unit 1
- ✓ Unit 2
- ✓ Unit 3
- ✓ Unit 4
- ✓ Unit 5

All Unit in One PDF

Visit our Website
WWW.fdspharmacy.in

Bachelor of Pharmacy

Pharmaceutical Organic Chemistry II

NOTES

- ✓ Unit 1
- ✓ Unit 2
- ✓ Unit 3
- ✓ Unit 4
- ✓ Unit 5

All Unit in One PDF

Visit our Website
WWW.fdspharmacy.in

Bachelor of Pharmacy

Pharmaceutical Microbiology

NOTES

- ✓ Unit 1
- ✓ Unit 2
- ✓ Unit 3
- ✓ Unit 4
- ✓ Unit 5

All Unit in One PDF

Visit our Website
WWW.fdspharmacy.in

Pharmacy
Learn and Educate

FDPharmacy

D.Pharma
B.Pharma

- PDF Notes
- Practical Manual
- Important Questions
- Assignment etc

Download Now

ANDROID APP ON Google play

www.fdpharmacy.in

PHARMACEUTICAL ORGANIC CHEMISTRY - II

UNIT 1

TOPIC :

- Reactions of benzene- nitration, sulphonation, halogenation reactivity, Friedelcrafts alkylation reactivity, limitations, Friedelcrafts acylation.

FDSPharmacy
Learn and Educate

CHEMICAL REACTIONS OF BENZENE

- Benzene mainly undergoes electrophilic aromatic substitution (EAS) reactions.
- In these reactions, one hydrogen atom of the benzene ring is replaced by an electrophile.

Types of Electrophilic Aromatic Substitution Reactions

Benzene undergoes the following five major types of electrophilic substitution reactions:

1. Nitration
2. Sulfonation
3. Halogenation
4. Friedel-Crafts Alkylation
5. Friedel-Crafts Acylation

Nitration of Benzene

- In nitration, benzene reacts with concentrated nitric acid (HNO_3) in the presence of concentrated sulfuric acid (H_2SO_4) to form nitrobenzene.

Reaction:

$$C_6H_6 + HNO_3 \rightarrow C_6H_5NO_2 + H_2O$$

(H_2SO_4 acts as a catalyst)

Mechanism:

STEP I – Formation of the Electrophile (Nitronium Ion, NO_2^+):

Concentrated H_2SO_4 protonates nitric acid:

$HNO_3 + H^+ \rightarrow H_2NO_3^+$
$H_2NO_3^+ \rightarrow NO_2^+ + H_2O$

Thus, the electrophile formed is the nitronium ion (NO_2^+).

STEP II – Attack of Electrophile on Benzene Ring:

Benzene donates π electrons to NO_2^+ forming a carbocation intermediate (arenium ion).

$C_6H_6 + NO_2^+ \rightarrow [C_6H_6NO_2]^+$ (resonance-stabilized carbocation)

STEP III – Loss of Proton:

The intermediate loses a proton (H^+), restoring aromaticity:

$[C_6H_6NO_2]^+ \rightarrow C_6H_5NO_2$ (Nitrobenzene) + H^+

The H^+ combines with HSO_4^- to regenerate H_2SO_4.

Sulfonation of Benzene

- In sulfonation, benzene reacts with concentrated or fuming sulfuric acid to form benzene sulfonic acid.

Reaction:

$C_6H_6 + H_2SO_4 \rightleftharpoons C_6H_5SO_3H + H_2O$
(Reversible reaction, favored by heat)

Mechanism:

STEP I – Formation of Electrophile (SO_3 or HSO_3^+):

In fuming H_2SO_4 (contains SO_3), the electrophile is either SO_3 **or** protonated SO_3 (HSO_3^+).

$H_2SO_4 \rightleftharpoons H_2O + SO_3$
$SO_3 + H^+ \rightarrow HSO_3^+$

STEP II – Attack of Electrophile on Benzene Ring:

Benzene reacts with the electrophile (SO_3 or HSO_3^+), forming a carbocation intermediate.

$C_6H_6 + SO_3 \rightarrow [C_6H_6SO_3]^+$

STEP III – Loss of Proton:

The intermediate loses a proton to give benzene sulfonic acid:

$[C_6H_6SO_3]^+ \rightarrow C_6H_5SO_3H$

Halogenation of Benzene

In halogenation, benzene reacts with halogens (Cl_2, Br_2, I_2) in the presence of a Lewis acid catalyst ($AlCl_3$, $FeCl_3$, $FeBr_3$) to form halogen-substituted benzene such as:

- Chlorobenzene (with Cl_2)
- Bromobenzene (with Br_2)
- Iodobenzene (with I_2 – requires oxidizing agents like HNO_3)

General Reaction:

$C_6H_6 + Cl_2 \rightarrow C_6H_5Cl + HCl$
(In presence of $AlCl_3$)

Mechanism of Chlorination:

STEP I – Formation of Electrophile (Chloronium Ion, Cl^+):

The Lewis acid $AlCl_3$ polarizes the Cl–Cl bond and facilitates the generation of a chloronium ion (Cl^+):

$Cl_2 + AlCl_3 \rightarrow Cl^+ + AlCl_4^-$
(Cl^+ is the electrophile)

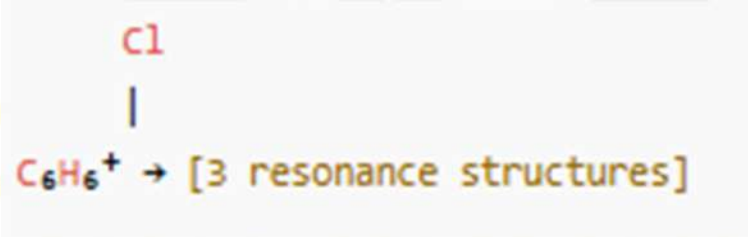
STEP II – Attack of Electrophile on Benzene Ring:

The π electrons of benzene attack the **Cl^+**, forming a resonance-stabilized carbocation (arenium ion)**:**

$C_6H_6 + Cl^+ \rightarrow [C_6H_6Cl]^+$
(Carbonium ion intermediate)

Resonance Stabilization of Carbocation:

The intermediate exists as a resonance hybrid where the positive charge is delocalized across the ring:



STEP III – Loss of Proton and Formation of Chlorobenzene:

The intermediate loses a proton (H^+) which combines with $AlCl_4^-$, forming HCl and regenerating $AlCl_3$**:**

$[C_6H_6Cl]^+ \rightarrow C_6H_5Cl$ (Chlorobenzene) + H^+
$H^+ + AlCl_4^- \rightarrow HCl + AlCl_3$

Final Products:

- Chlorobenzene
- Hydrogen chloride (HCl)

Friedel-Crafts Alkylation

- In Friedel-Crafts Alkylation, benzene reacts with an alkyl halide (R–Cl) in the presence of a Lewis acid catalyst such as $AlCl_3$ to form alkyl benzene.
- This reaction was discovered by Charles Friedel (France) and James Crafts (USA).

General Reaction:

$C_6H_6 + CH_3Cl \rightarrow C_6H_5CH_3 + HCl$
(In presence of $AlCl_3$)

Product: Methylbenzene (Toluene)

Mechanism

STEP I – Formation of Electrophile (Carbocation or Alkyl Cation):

The alkyl halide reacts with $AlCl_3$ to generate the alkyl carbocation (electrophile):

$CH_3Cl + AlCl_3 \rightarrow CH_3^+ + AlCl_4^-$
(Here, $\mathbf{CH_3^+}$ is the electrophile)

STEP II – Attack of Electrophile on Benzene Ring:

The π electrons of benzene attack the methyl cation, forming a carbocation intermediate (also called arenium ion):

$C_6H_6 + CH_3^+ \rightarrow [C_6H_6CH_3]^+$
(Carbocation intermediate)

STEP III – Loss of Proton and Regeneration of Aromaticity:

The intermediate loses a proton (H^+), and the aromatic nature of the ring is restored:

$[C_6H_6CH_3]^+ \rightarrow C_6H_5CH_3$ (Methylbenzene) + H^+

$H^+ + AlCl_4^- \rightarrow HCl + AlCl_3$

Final Products:

- Alkyl benzene (e.g., methylbenzene)
- Hydrogen chloride (HCl)

FDSPharmacy
Learn and Educate

FRIEDEL-CRAFTS ACYLATION

- In Friedel-Crafts Acylation, benzene reacts with an acyl halide (RCOCl) in the presence of a Lewis acid catalyst ($AlCl_3$) to form an aromatic ketone (also called aryl ketone).
- This is another important reaction discovered by Friedel and Crafts.

General Reaction:

$C_6H_6 + CH_3COCl \rightarrow C_6H_5COCH_3 + HCl$
(In presence of $AlCl_3$)

Product: Acetophenone (Aromatic Ketone)

Mechanism

STEP I – Formation of Electrophile (Acylium Ion):

The acyl halide reacts with $AlCl_3$ to generate a resonance-stabilized acylium ion (RCO^+):

$CH_3COCl + AlCl_3 \rightarrow CH_3C^+{\equiv}O$ (acylium ion) + $AlCl_4^-$

Acylium ion ($R–C^+{\equiv}O$) is a strong electrophile.

STEP II – Attack of Electrophile on Benzene Ring:

The π electrons of benzene attack the acylium ion, forming a carbocation intermediate (arenium ion):

$C_6H_6 + CH_3C^+{=}O \rightarrow [C_6H_6COCH_3]^+$

STEP III – Loss of Proton and Aromaticity Restoration:

The intermediate loses a proton, restoring aromaticity and forming acetophenone:

$$[C_6H_6COCH_3]^+ \rightarrow C_6H_5COCH_3 \text{ (Acetophenone)} + H^+$$

$$H^+ + AlCl_4^- \rightarrow HCl + AlCl_3$$

Final Products:

- Aromatic ketone (e.g., Acetophenone)
- Hydrogen chloride (HCl)

FDSPharmacy
Learn and Educate