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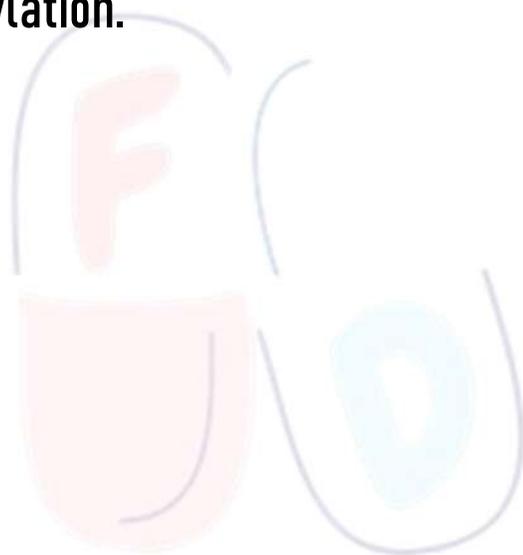
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PHARMACEUTICAL ORGANIC CHEMISTRY - II

UNIT 1

TOPIC :

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



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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

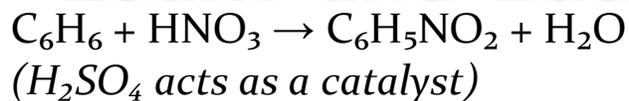
Benzene undergoes the following five major types of electrophilic substitution reactions:

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.

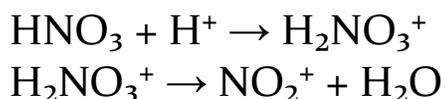
Reaction:



Mechanism:

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

Concentrated H_2SO_4 protonates nitric acid:



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).



STEP III – Loss of Proton:

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

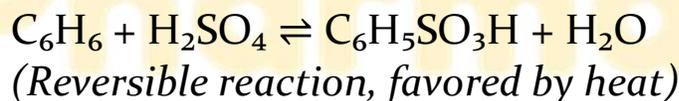


The H^+ combines with HSO_4^- to regenerate H_2SO_4 .

Sulfonation of Benzene

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

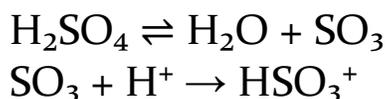
Reaction:



Mechanism:

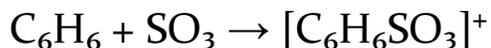
STEP I – Formation of Electrophile (SO_3 or HSO_3^+):

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

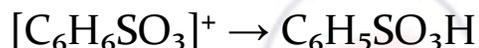


STEP II – Attack of Electrophile on Benzene Ring:

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

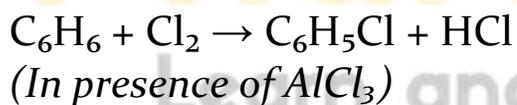
**STEP III – Loss of Proton:**

The intermediate loses a proton to give benzene sulfonic acid:

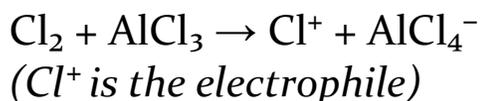
**Halogenation of Benzene**

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)

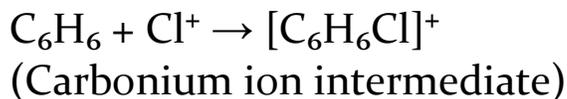
General Reaction:**Mechanism of Chlorination:****STEP I – Formation of Electrophile (Chloronium Ion, Cl^+):**

The Lewis acid AlCl_3 polarizes the $\text{Cl}-\text{Cl}$ bond and facilitates the generation of a chloronium ion (Cl^+):



STEP II – Attack of Electrophile on Benzene Ring:

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

**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 :

**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:

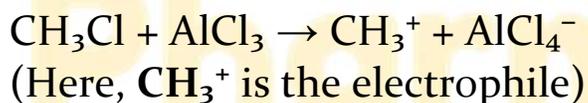


Product: Methylbenzene (Toluene)

Mechanism

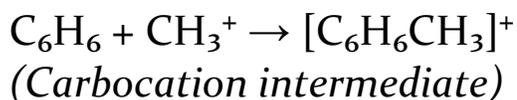
STEP I – Formation of Electrophile (Carbocation or Alkyl Cation):

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



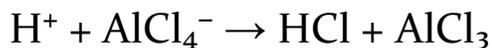
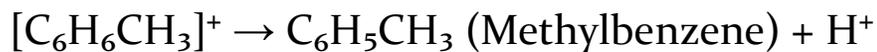
STEP II – Attack of Electrophile on Benzene Ring:

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



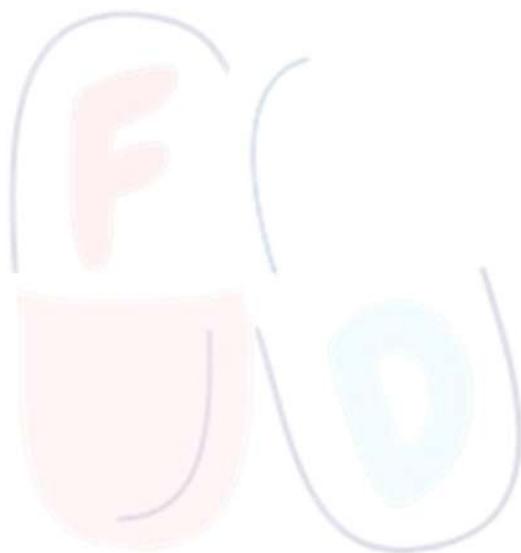
STEP III – Loss of Proton and Regeneration of Aromaticity:

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



Final Products:

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

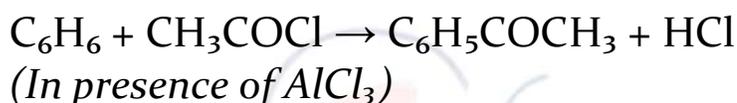


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FRIEDEL-CRAFTS ACYLATION

- In Friedel-Crafts Acylation, benzene reacts with an acyl halide (RCOCl) in the presence of a Lewis acid catalyst (AlCl₃) to form an aromatic ketone (also called aryl ketone).
- This is another important reaction discovered by Friedel and Crafts.

General Reaction:

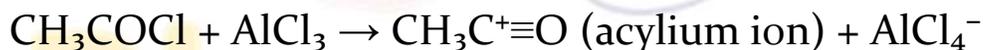


Product: Acetophenone (Aromatic Ketone)

Mechanism

STEP I – Formation of Electrophile (Acylium Ion):

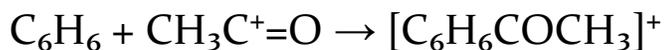
The acyl halide reacts with AlCl₃ to generate a resonance-stabilized acylium ion (RCO⁺):



Acylium ion (R-C⁺≡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):



STEP III – Loss of Proton and Aromaticity Restoration:

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





Final Products:

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



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