

St Peter's Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Pharmaceutical Organic Chemistry II

Subject Code: BP301T

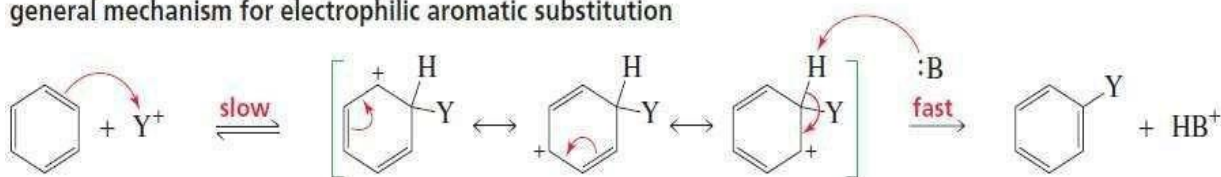
Reactions of Benzene:

Benzene readily undergoes a new set of reactions, all involving substitution i.e. Electrophilic Aromatic Substitution Reactions. It involves the reaction of an electrophile with an aromatic compound, where electrophile substitutes for a hydrogen of an aromatic compound.

General Mechanism for Electrophilic Aromatic Substitution Reactions:

- Similar to alkenes, benzene (aromatics) has a cloud of π electrons available to attack electrophiles (the aromatic ring is nucleophilic)
- The resulting carbocation is stabilized by resonance and is called: Sigma complex
- These reactions are greatly facilitated by addition of Lewis acid catalyst.
- Key bonds formed C-Y and key bonds broken C-H
- Electron donating substituents increase the rate of substitution reaction by activating the benzene ring to electrophilic attack.
- Electron withdrawing substituents decrease the rate of substitution reaction by deactivating the benzene ring to electrophilic attack.

general mechanism for electrophilic aromatic substitution



The general mechanism can be applied to the following reactions and the only difference will be the nature of the electrophile, and how it is formed.

1. **Halogenation:** A bromine (Br), a chlorine (Cl), or an iodine (I) substitutes for a hydrogen (Lewis acid: $AlCl_3/FeCl_3/AlBr_3/FeBr_3$, etc.)
2. **Nitration:** A nitro (NO_2) group substitutes for a hydrogen (acid: H_2SO_4).
3. **Sulfonation:** A sulfonic acid (SO_3H) group substitutes for a hydrogen (acid: H_2SO_4).
4. **Friedel-Crafts acylation:** An acyl ($RC=O$) group substitutes for a hydrogen (Lewis acid: $AlCl_3/FeCl_3$)

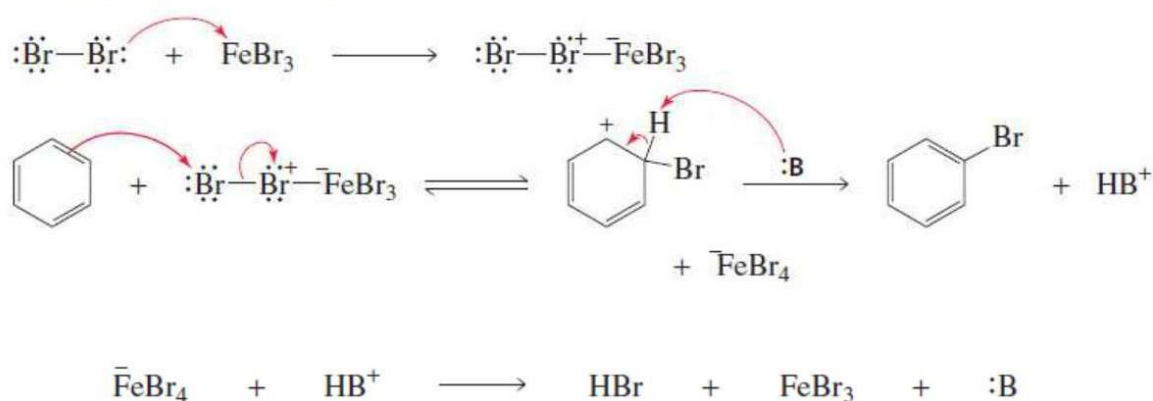
5. **Friedel–Crafts alkylation:** an alkyl (R) group substitutes for a hydrogen (Lewis acid: $\text{AlCl}_3/\text{FeCl}_3$)

Halogenation of Benzene: The bromination or chlorination of benzene requires a Lewis acid such as ferric bromide or ferric chloride. Recall that a Lewis acid is a compound that accepts a share in a pair of electrons.

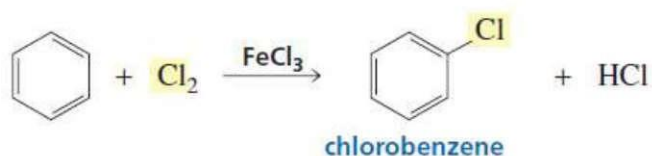
Bromination: Electrophile Br^+



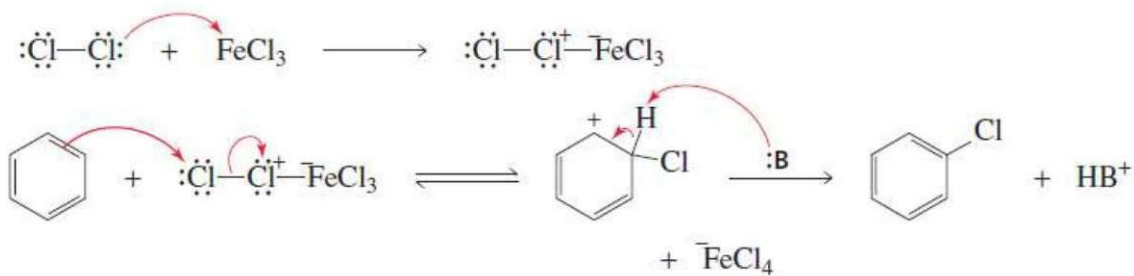
mechanism for bromination



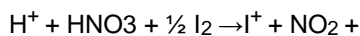
Chlorination: Electrophile Cl^+



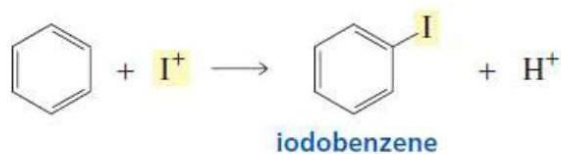
mechanism for chlorination



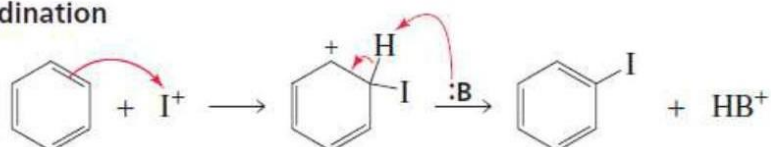
Iodination: For iodination, iodine is simply oxidized with nitric acid (HNO₃) to liberate the I⁺, which is then used as the electrophile.



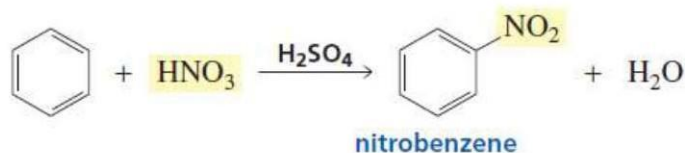
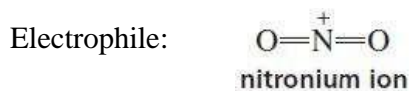
H₂O OR



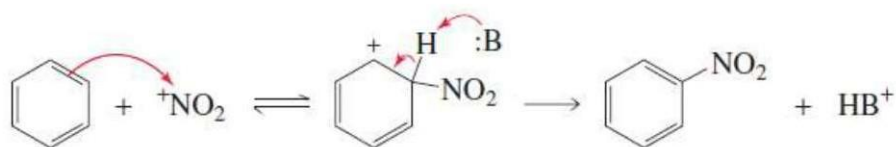
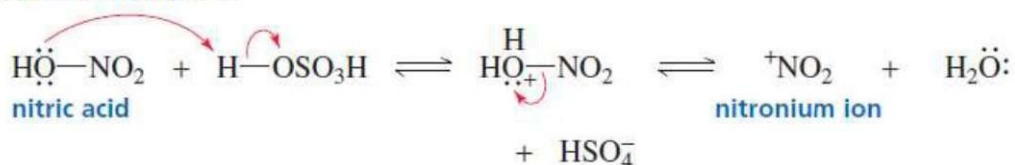
mechanism for iodination



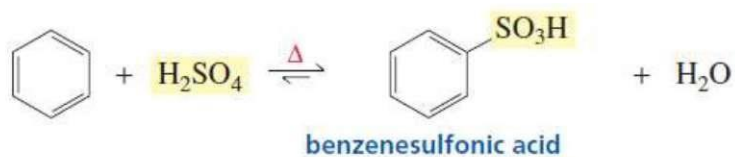
Nitration of Benzene: Nitration of benzene with nitric acid requires sulfuric acid as a catalyst.



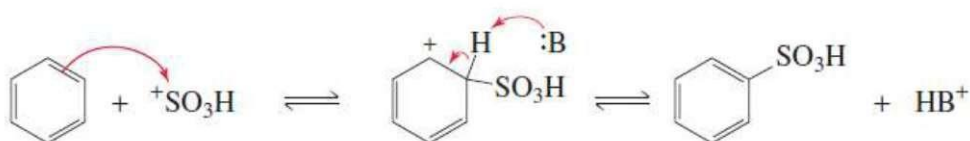
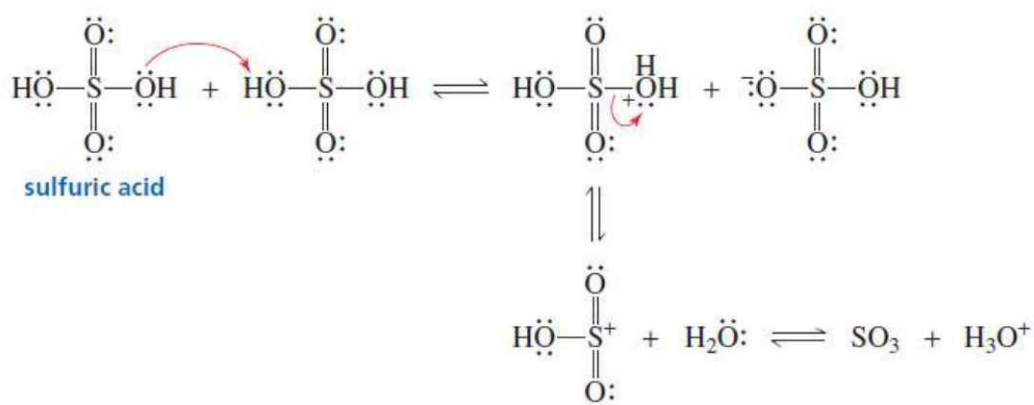
mechanism for nitration



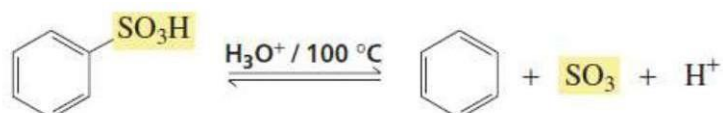
Sulfonation of Benzene: Fuming sulfuric acid (a solution of in sulfuric acid) or concentrated sulfuric acid is used to sulfonate aromatic rings. Electrophile: HSO_3^+



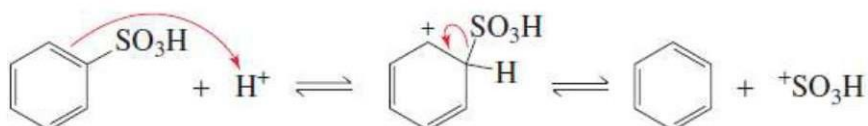
mechanism for sulfonation



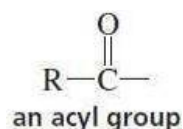
Sulfonation of benzene is a reversible reaction. If benzenesulfonic acid is heated in dilute acid, the reaction proceeds in the reverse direction.



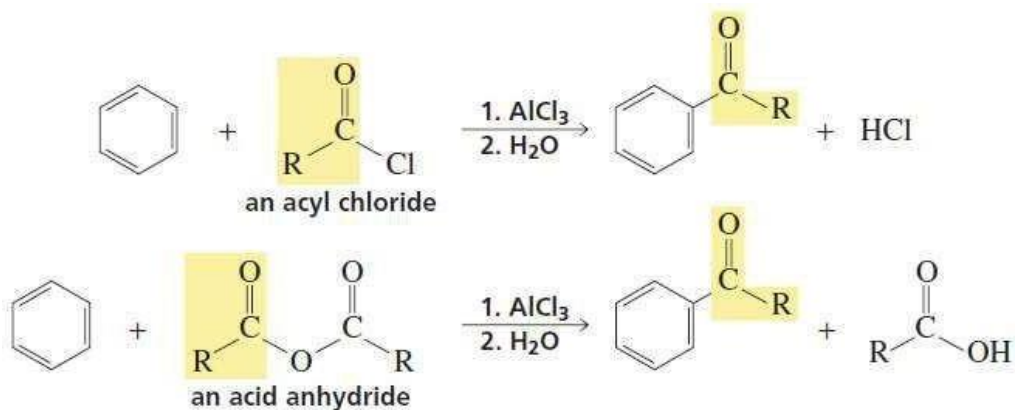
mechanism for desulfonation



Friedel–Crafts Acylation: Friedel–Crafts acylation places an acyl group on a benzene ring.

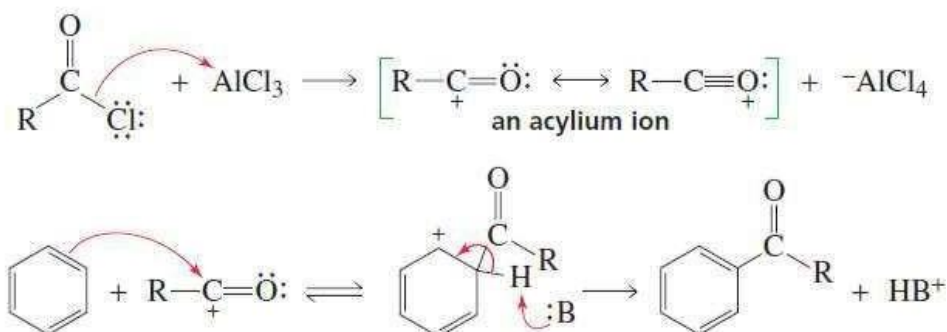


Either an acyl halide or an acid anhydride can be used for Friedel–Crafts acylation.



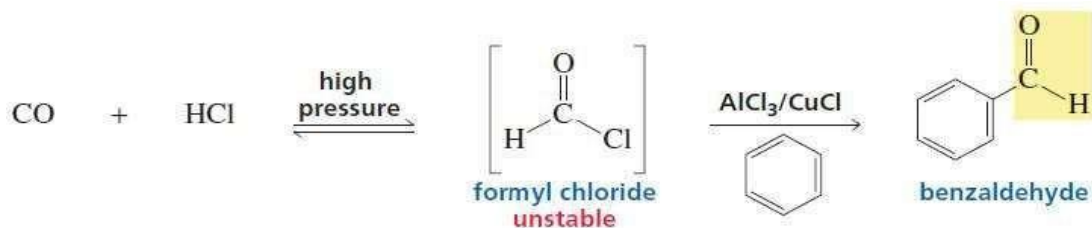
An acylium ion is the electrophile required for a Friedel–Crafts acylation reaction. This ion is formed by the reaction of an acyl chloride or an acid anhydride with AlCl_3 a Lewis acid.

mechanism for Friedel–Crafts acylation

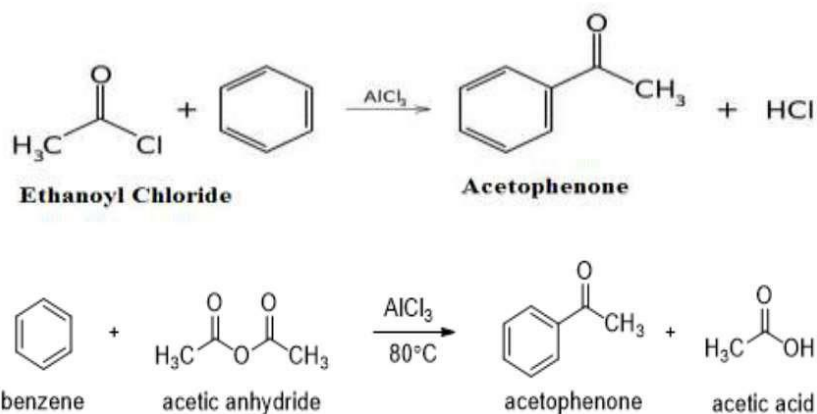


Example:

The synthesis of benzaldehyde from benzene and formyl chloride (the acyl halide required for the reaction), which is unstable and obtained by means of the Gatterman–Koch formylation reaction. This reaction uses a high-pressure mixture of carbon monoxide and HCl to generate formyl chloride, along with an aluminum chloride–cuprous chloride catalyst to carry out the acylation reaction.



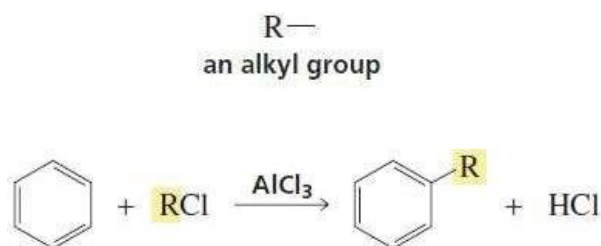
Example: Preparation of Acetophenone from alkyl halide and acid anhydride.



LIMITATIONS of Friedel-Crafts acylation:

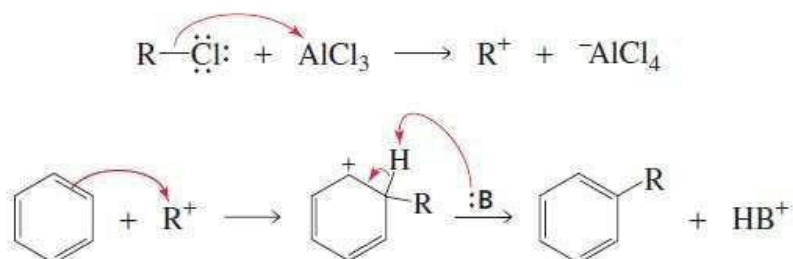
1. Acylation can only be used to give ketones. This is because HCOCl decomposes to CO and HCl under the reaction conditions.
2. Deactivated benzenes are not reactive to Friedel-Crafts conditions, the benzene needs to be as or more reactive than a mono-halobenzene.
3. The Lewis acid catalyst AlCl₃ often complexes to aryl amines making them very unreactive.
4. Amines and alcohols can give competing N or O acylations rather than the require ring acylation

Friedel-Crafts alkylation: Friedel-Crafts alkylation places an alkyl group on a benzene ring.



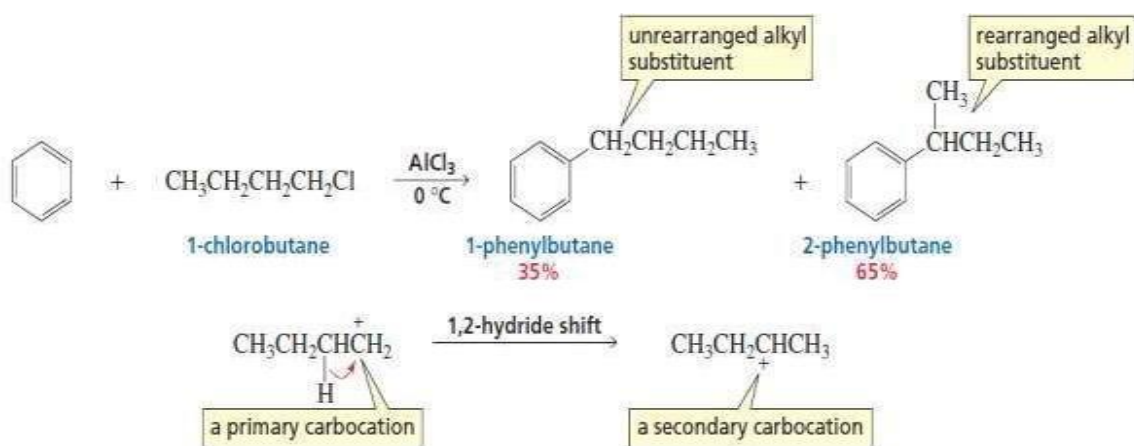
- A carbocation is formed from the reaction of an alkyl halide with AlCl_3 . Alkyl fluorides, alkyl chlorides, alkyl bromides, and alkyl iodides can all be used. Vinyl halides and aryl halides cannot be used because their carbocations are too unstable to be formed.

mechanism for Friedel–Crafts alkylation

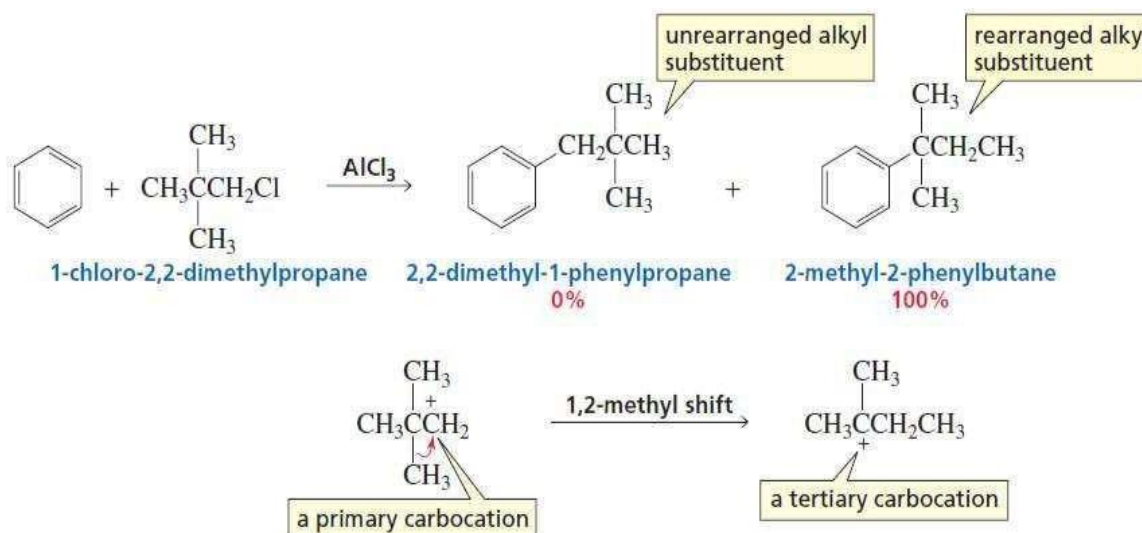


- An alkyl-substituted benzene is more reactive than benzene. Therefore, to prevent further alkylation of the alkyl-substituted benzene, a large excess of benzene is used in Friedel–Crafts alkylation reactions.
- A carbocation will rearrange if rearrangement leads to a more stable carbocation.
- When the carbocation can rearrange in a Friedel–Crafts alkylation reaction, the major product will be the product with the rearranged alkyl group on the benzene ring.

Example: less stable primary carbocation to stable secondary carbocation

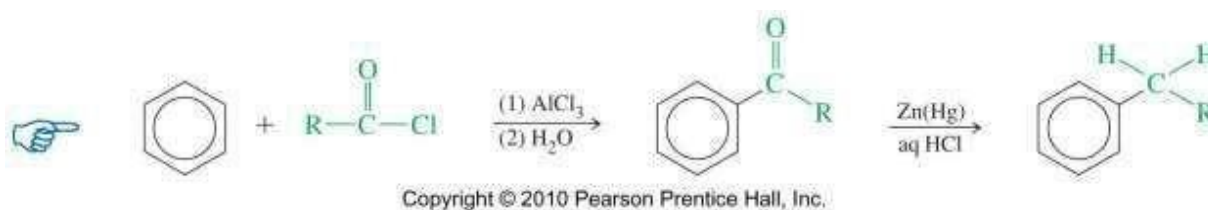


Example: less stable primary carbocation to stable tertiary carbocation

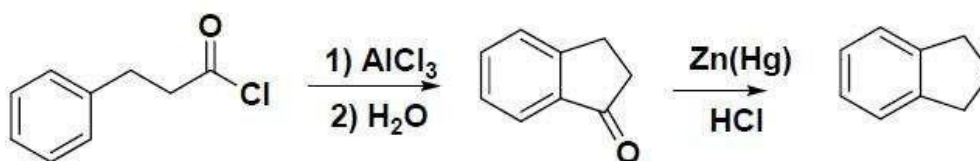


- We have just seen that Friedel-Crafts alkylation rarely provides a straight chain alkyl function on the aromatic (due to rearrangement)
- To avoid this problem, one can use either of the Clemmensen reduction of acyl benzene to form the desired alkylated aromatic.
- The Clemmensen reduction is a series of 2 reaction, (1) Friedel-Crafts Acylation, (2) decarbonylation of the resulting ketone.

Example 1:



Example 2:

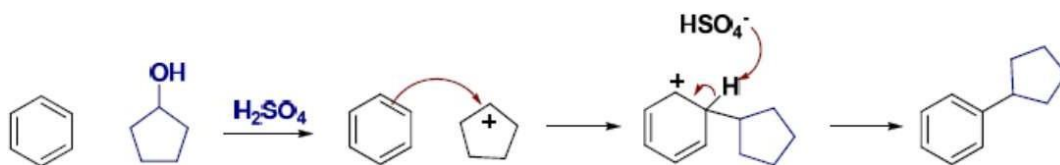
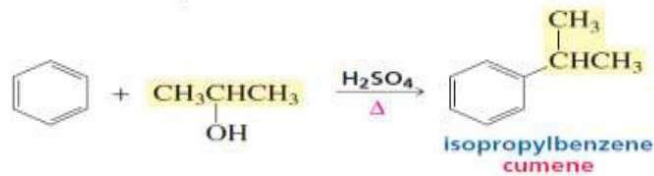


Any other carbocation source can be used in the presence of an aromatic ring to give Friedel Crafts substitution products.

alkylation of benzene by an alkene

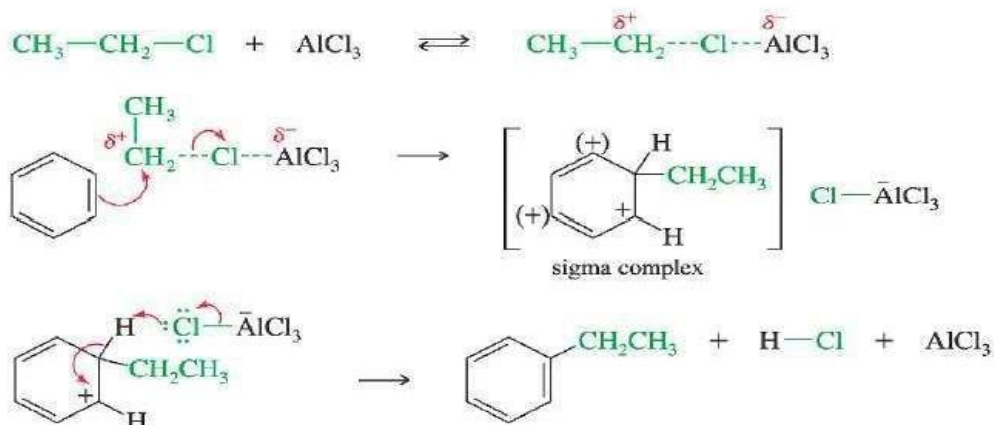


alkylation of benzene by an alcohol

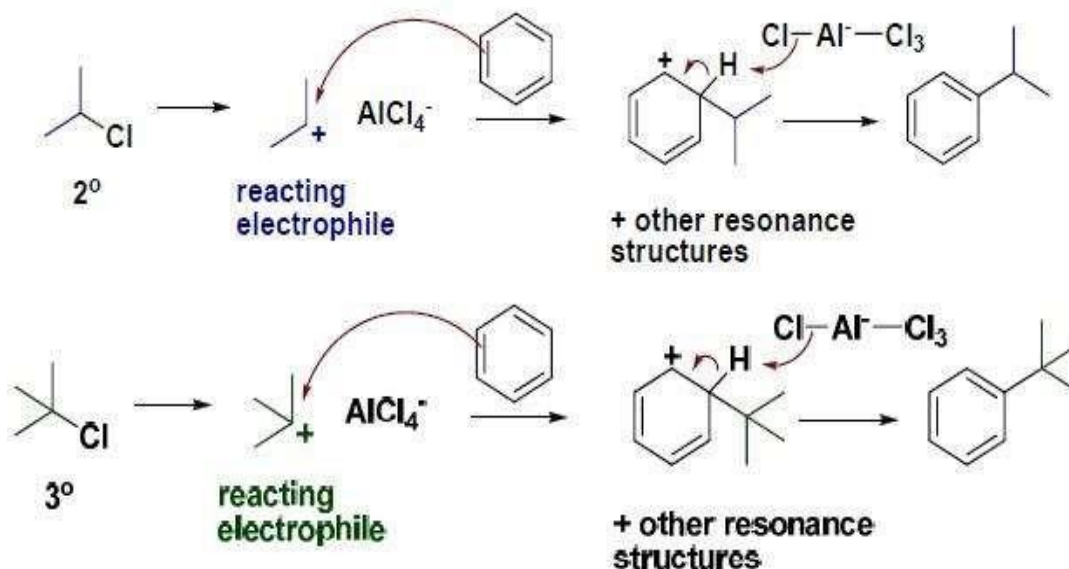


Example: Friedel-Crafts alkylation

Mechanism of Friedel-Crafts Alkylation (1° halides)

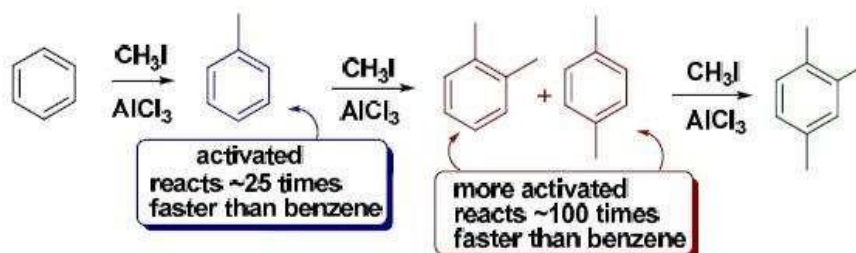


Example: When secondary and tertiary alkyl halides are used, the electrophile is the corresponding carbocations.



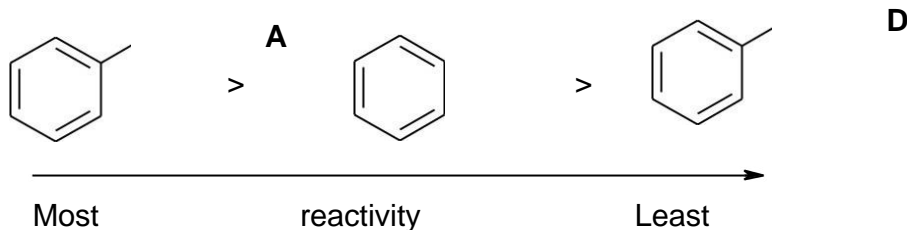
There are 3 important LIMITATIONS to the Friedel-Crafts Alkylation:

1. Works only with benzene and activated derivatives (no reaction when deactivators are present).
2. Rearrangements of carbocations or carbocation like species is common.
3. Vinyl or aryl halides do not react (their intermediate carbocations are too unstable).
4. The Lewis acid catalyst AlCl₃ often complexes to aryl amines making them very unreactive.
5. Poly-alkylation is often the result since the alkylation product is more reactive than the original compound (Note: This can usually be controlled with an excess of the benzene). For example:



Effect of Substituents on Reactivity and Orientation of Mono Substituted Benzene Compounds towards Electrophilic Substitution Reaction

- The reactions of substituted benzenes are similar to those of benzene, but can take place faster or slower than benzene depending on the substitution pattern.
- The substituent can either increase or decrease the rate of the reaction depending on its nature.



- Activating (**A**) if the benzene ring it is attached to is more reactive than benzene i.e. one that provides more electrons (electron donating groups) to the aromatic system
- Deactivating (**D**) if the ring it is attached to is less reactive than benzene i.e. one that pulls electrons away from the aromatic system.
- Substituent(s) direct the incoming electrophile to a specific location.
- As shown in **Table 1**, nearly all groups fall into one of two classes: activating and ortho, para directing, or deactivating and meta-directing. The halogens are in a class by themselves, being deactivating but ortho, para-directing.

References:

- Organic Chemistry by Morrison and Boyd
- Organic Chemistry by I.L. Finar, Volume-I
- Textbook of Organic Chemistry by B.S. Bahl & Arun Bahl.
- Organic Chemistry by P.L.Soni
- Practical Organic Chemistry by Mann and Saunders.
- Vogel's text book of Practical Organic Chemistry
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- Introduction to Organic Laboratory techniques by Pavia, Lampman and Kriz.
- Reaction and reaction mechanism by Ahluwalia/Chatwal.