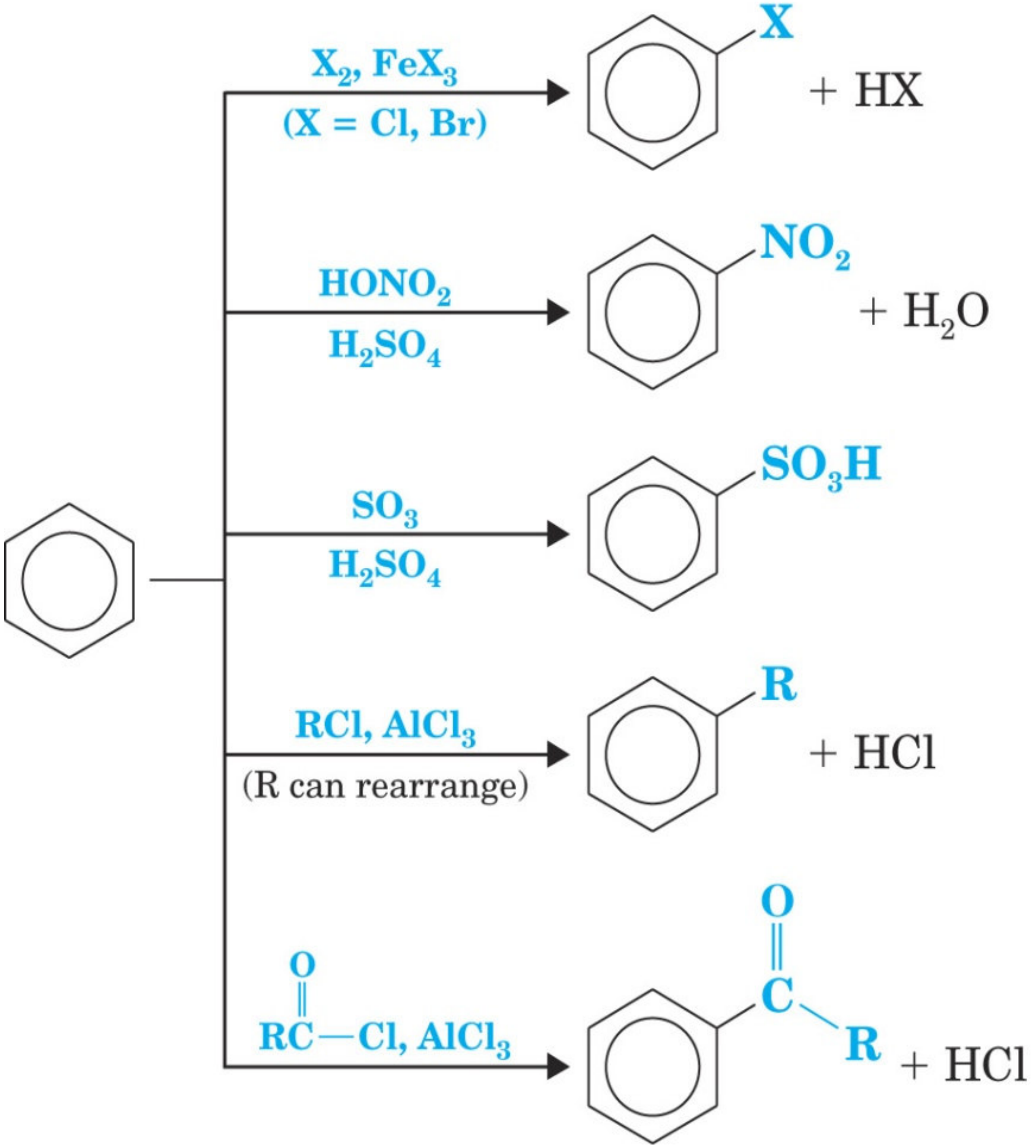
4.8 Electrophilic Aromatic Substitution

- Arene (Ar-H) is the generic term for an aromatic hydrocarbon
  - The aryl group (Ar) is derived by removal of a hydrogen atom from an arene
- Aromatic compounds undergo electrophilic aromatic substitution (EAS)
  - The electrophile has a full or partial positive charge



Halogenation
[redacted]

Nitration
[redacted]

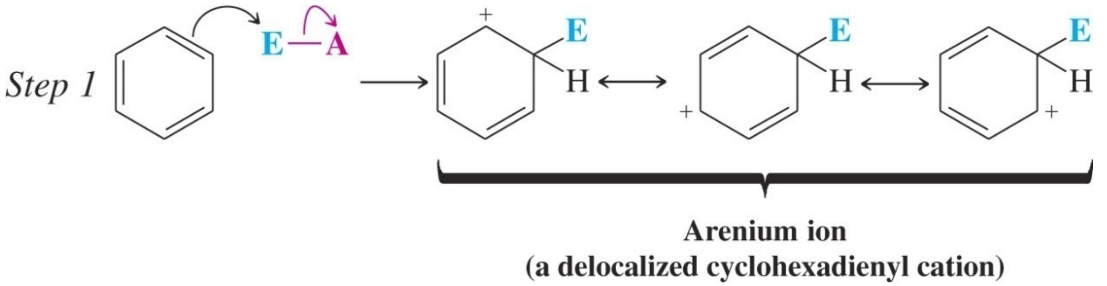
Sulfonation
[redacted]

Friedel–Crafts Alkylation
[redacted]

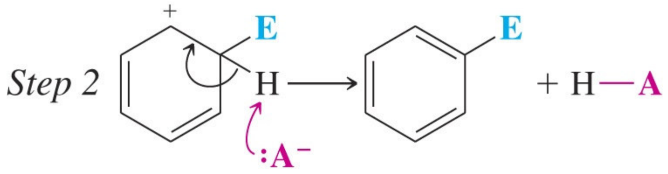
Friedel–Crafts Acylation
[redacted]

4.9 A General Mechanism for Electrophilic Aromatic Substitution: Arenium Ion Intermediates

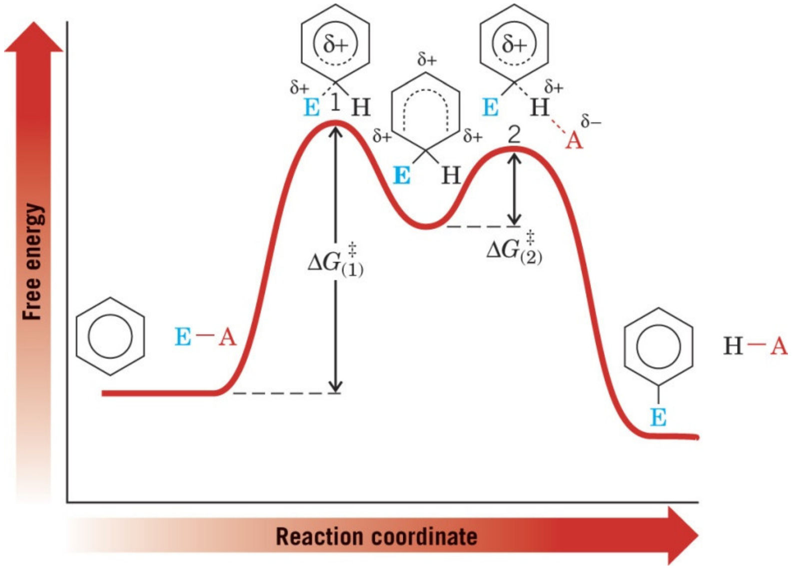
- Benzene reacts with an electrophile using two of its π electrons
  - This first step is like an addition to an ordinary double bond
- Unlike an addition reaction, the benzene ring reacts further so that it may regenerate the very stable aromatic system
- In step 1 of the mechanism, the electrophile reacts with two π electrons from the aromatic ring to form an arenium (benzenonium) ion
  - The arenium ion is stabilized by resonance which delocalizes the charge

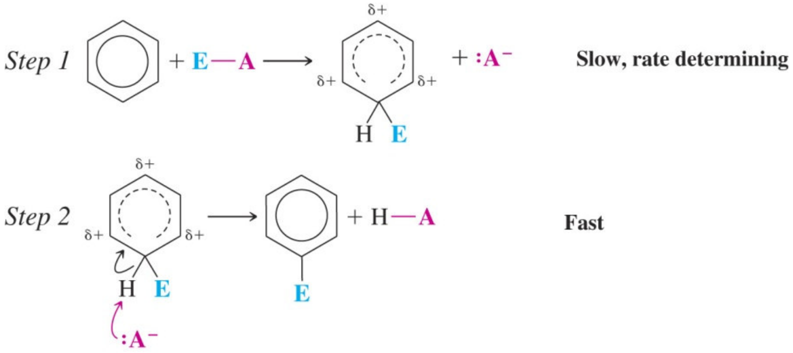


- In step 2, a proton is removed and the aromatic system is regenerated



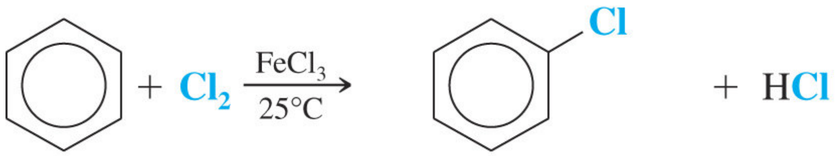
- The energy diagram of this reaction shows that the first step is highly endothermic and has a large $\Delta G^{\ddagger}_{(1)}$
  - The first step requires the loss of aromaticity of the very stable benzene ring, which is highly unfavorable
  - The first step is rate-determining
- The second step is highly exothermic and has a small $\Delta G^{\ddagger}_{(2)}$
  - The ring regains its aromatic stabilization, which is a highly favorable process



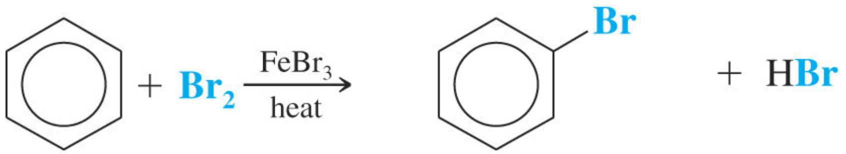


4.9.a Halogenation of Benzene

- Halogenation of benzene requires the presence of a Lewis acid

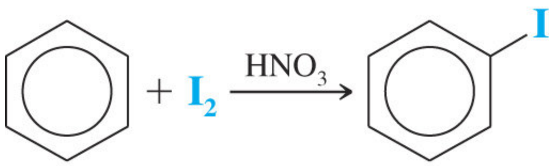


Chlorobenzene (90%)



Bromobenzene (75%)

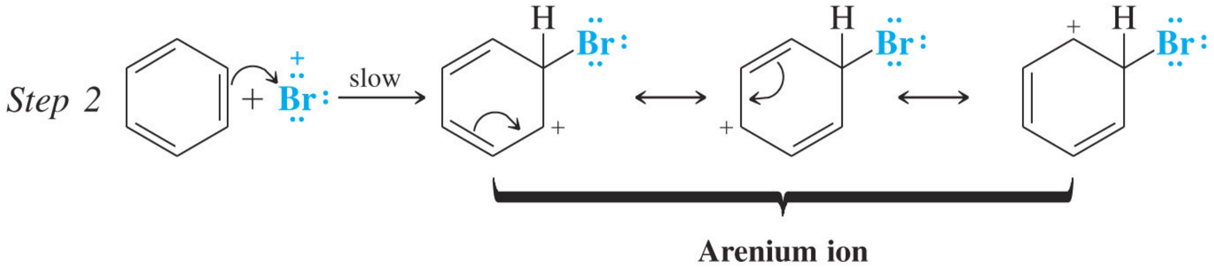
- Fluorination occurs so rapidly it is hard to stop at monofluorination of the ring
  - A special apparatus is used to perform this reaction
- Iodine is so unreactive that an alternative method must be used



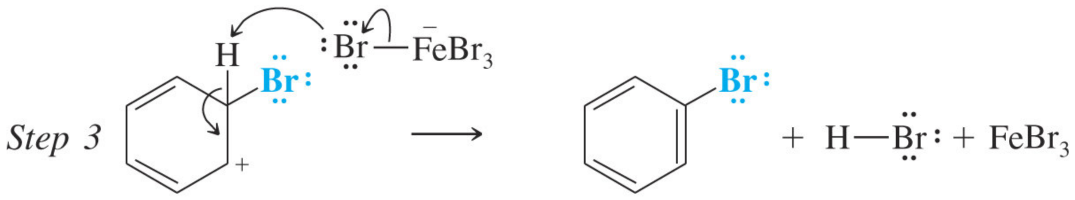
(86%)

- In the step 1 of the mechanism, bromine reacts with ferric bromide to generate an electrophilic bromine species
- In step 2, the highly electrophilic bromine reacts with π electrons of the benzene ring, forming an arenium ion
- In step 3, a proton is removed from the arenium ion and aromaticity is regenerated
  - The $FeBr_3$ catalyst is regenerated

Bromine combines with $FeBr_3$ to form a complex that dissociates to form a positive bromine ion and $FeBr_4^-$.



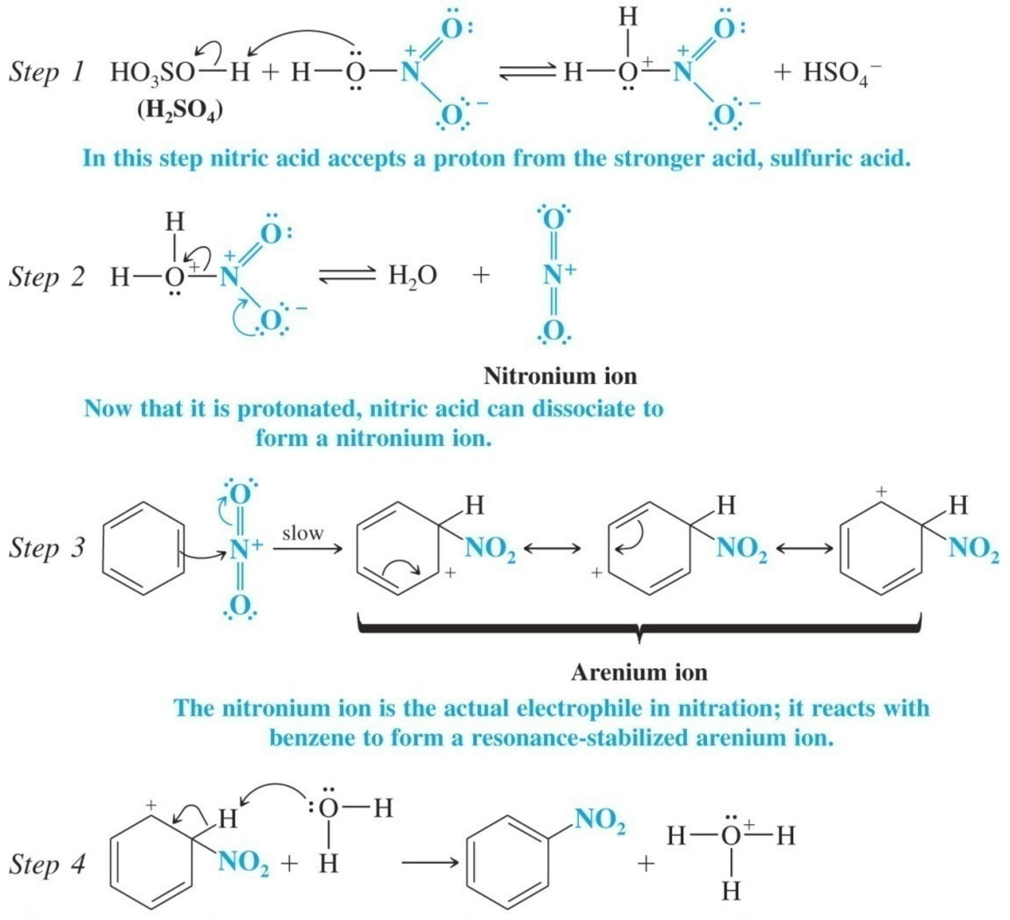
The positive bromine ion attacks benzene to form an arenium ion.



A proton is removed from the arenium ion to become bromobenzene.

4.9.b Nitration of Benzene

- Nitration of benzene occurs with a mixture of concentrated nitric and sulfuric acids
  - The electrophile for the reaction is the nitronium ion (NO_2^+)



In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.

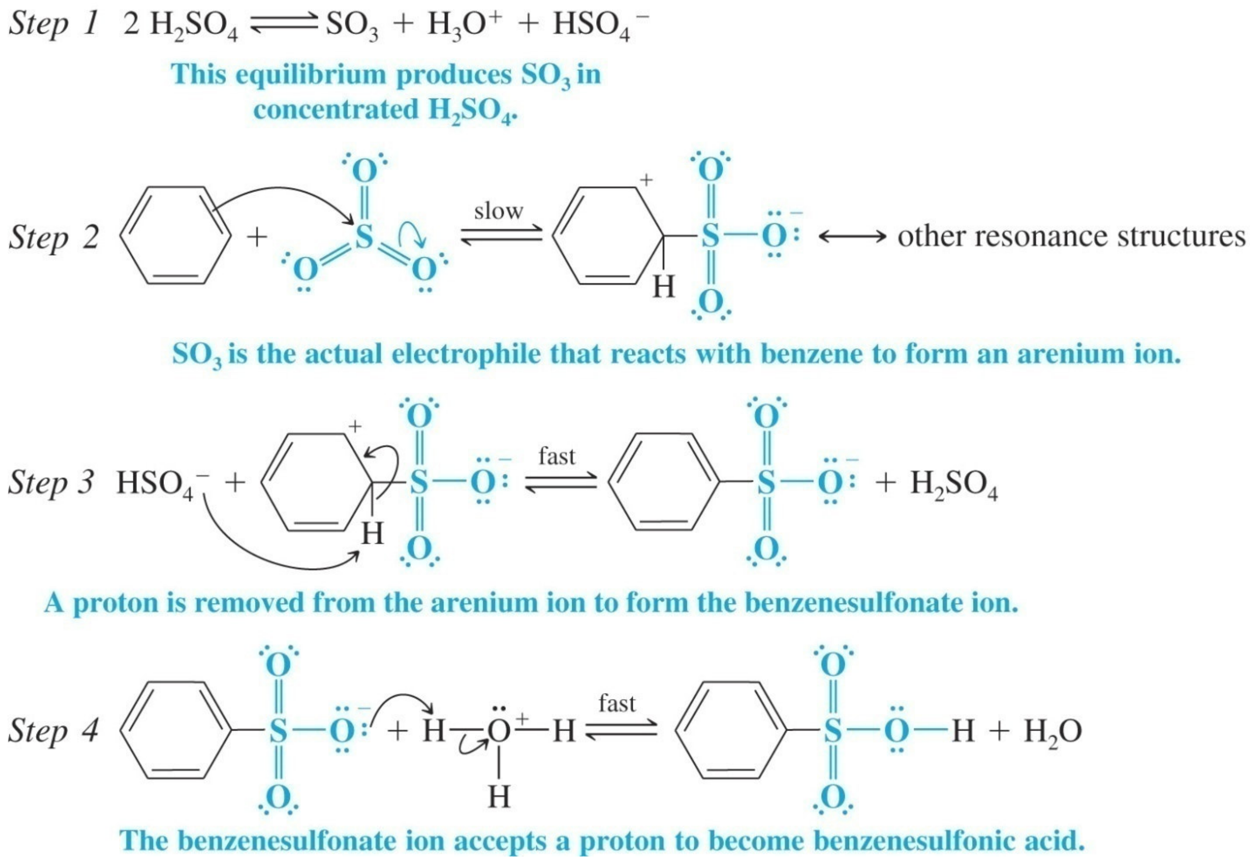
Now that it is protonated, nitric acid can dissociate to form a nitronium ion.

The nitronium ion is the actual electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.

The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

4.9.c Sulfonation of Benzene

- Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3)
  - The reaction also occurs in conc. sulfuric acid, which generates small quantities of SO_3, as shown in step 1 below



Step 1 $2\,H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$

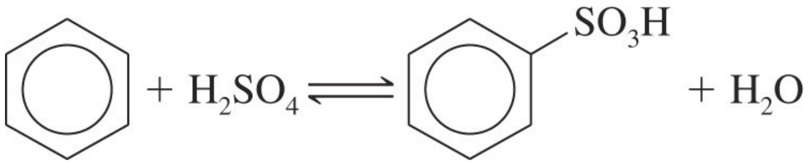
This equilibrium produces SO_3 in concentrated H_2SO_4.

SO_3 is the actual electrophile that reacts with benzene to form an arenium ion.

A proton is removed from the arenium ion to form the benzenesulfonate ion.

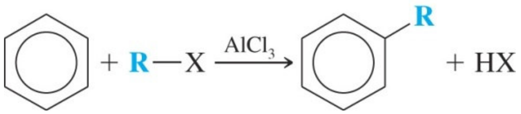
The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

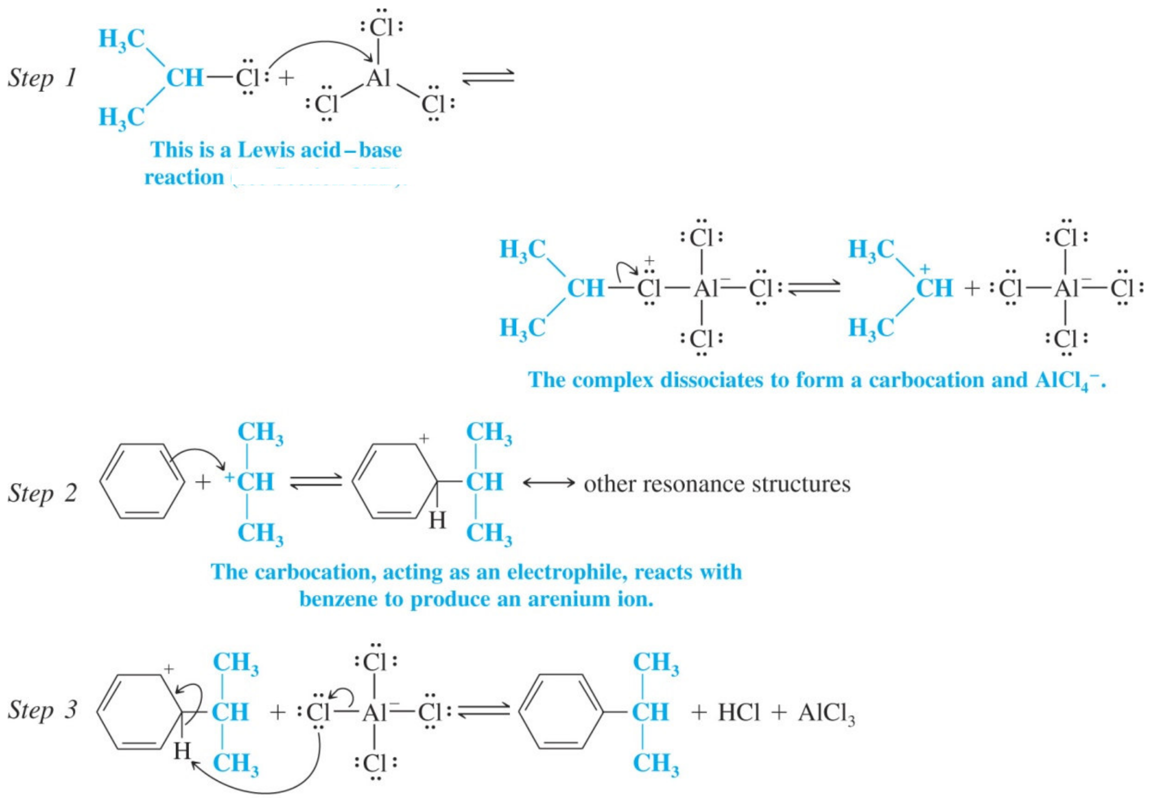
- Sulfonation is an equilibrium reaction; all steps involved are equilibria
  - The sulfonation product is favored by use of concentrated or fuming sulfuric acid
  - Desulfonation can be accomplished using dilute sulfuric acid (*i.e*. with a high concentration of water), or by passing steam through the reaction and collecting the volatile desulfonated compound as it distils with the steam



4.9.d Friedel-Crafts Alkylation

- An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid
  - The Lewis acid serves to generate a carbocation electrophile





This is a Lewis acid–base reaction

The complex dissociates to form a carbocation and $AlCl_4^-$.

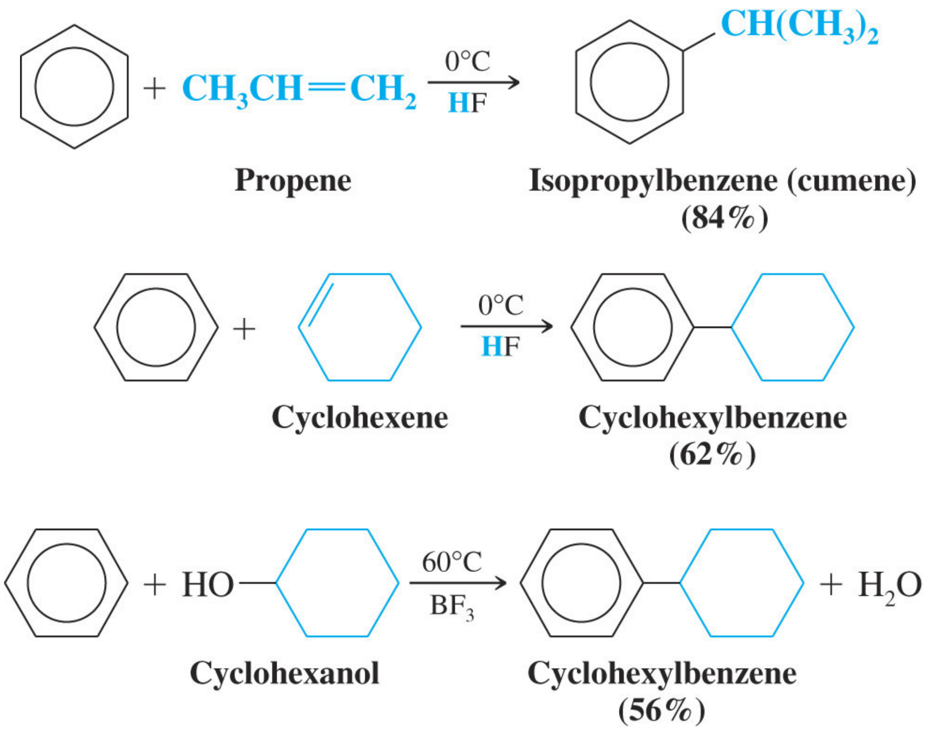
The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.

A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

- Primary alkyl halides probably do not form discreet carbocations but the primary carbon in the complex develops considerable positive charge

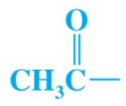
$$\mathrm{R}\overset{\delta+}{\mathrm{C}}\mathrm{H_2}\ \text{----}\ \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}}:\overset{\delta-}{\mathrm{A}}\mathrm{lCl_3}$$

- Any compound that can form a carbocation can be used to alkylate an aromatic ring

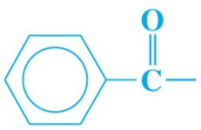


Friedel-Crafts Acylation

- An acyl group has a carbonyl attached to some R group

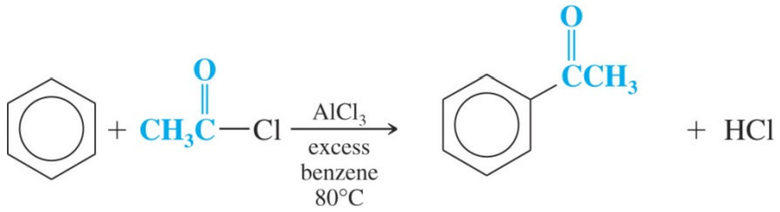


Acetyl group (ethanoyl group)



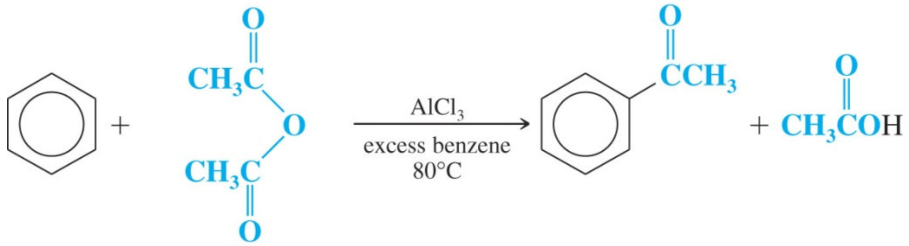
Benzoyl group

- Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminium chloride



Acetyl chloride

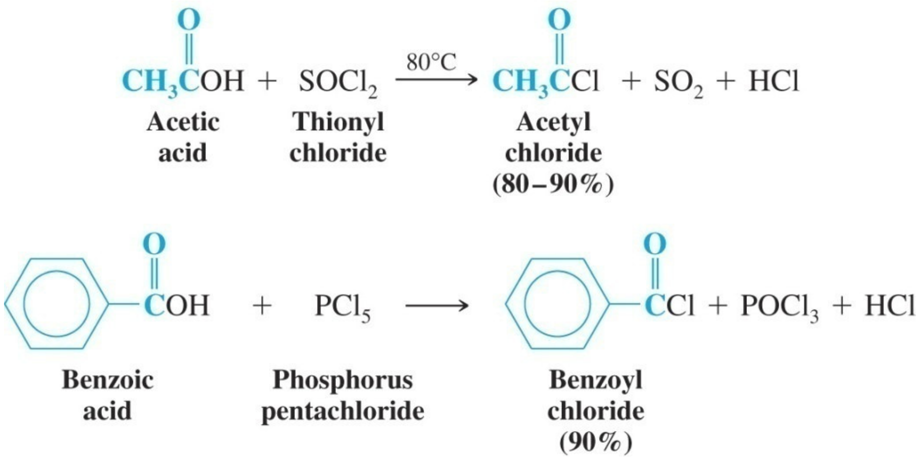
Acetophenone (methyl phenyl ketone) (97%)



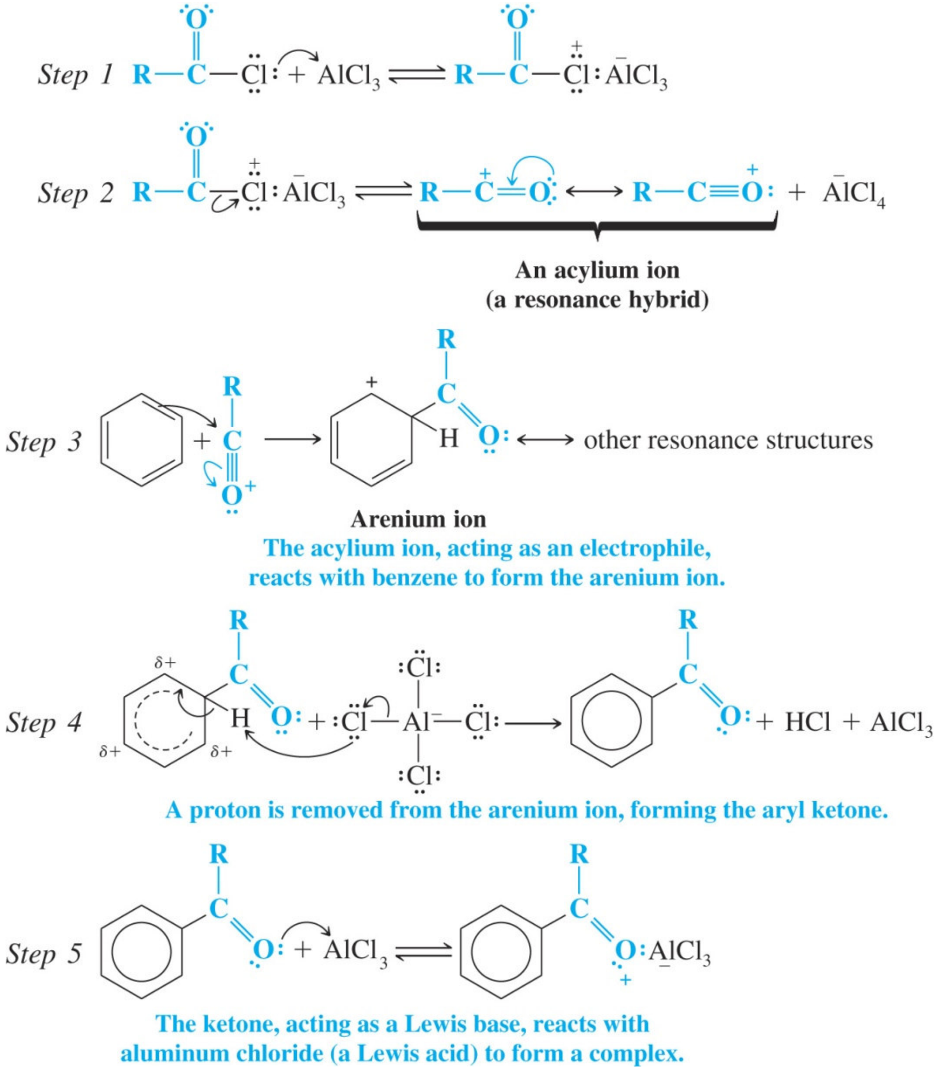
Acetic anhydride (a carboxylic acid anhydride)

Acetophenone (82–85%)

- Acid chlorides are made from carboxylic acids



- The electrophile in Friedel-Crafts acylation is an acylium ion
  - The acylium ion is stabilized by resonance



An acylium ion
(a resonance hybrid)

Arenium ion

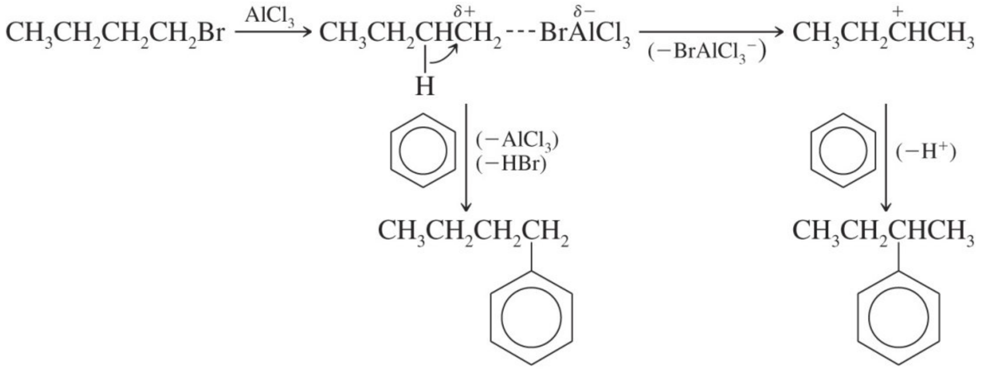
The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

A proton is removed from the arenium ion, forming the aryl ketone.

The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

Limitations of Friedel-Crafts Reactions

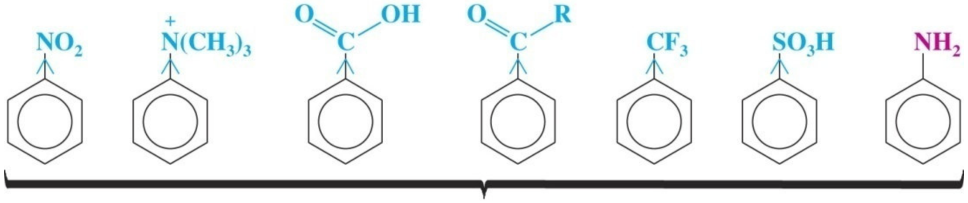
- In Friedel-Crafts alkylation, the alkyl carbocation intermediate may rearrange to a more stable carbocation prior to alkylation
  - The reaction of n-butyl bromide leads to a mixture of products derived from primary and secondary carbocations



Butylbenzene
(32–36% of mixture)

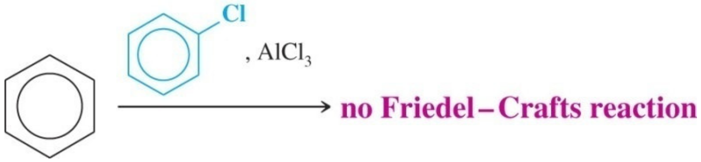
***sec*-Butylbenzene**
(64–68% of mixture)

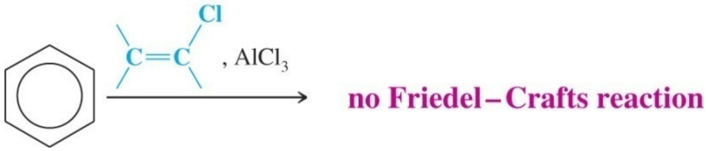
- Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation
  - Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst



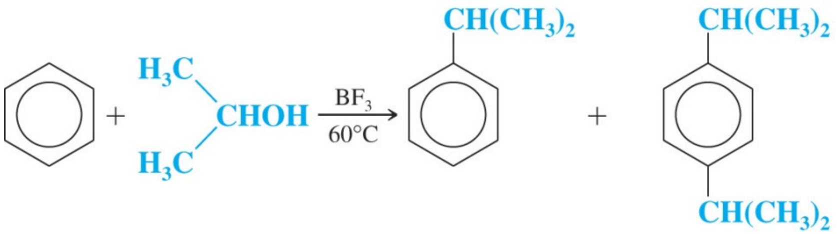
These usually give poor yields in Friedel–Crafts reactions.

- Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they do not form carbocations readily





- Polyalkylation occurs frequently with Friedel-Crafts alkylation because the first alkyl group introduced activates the ring toward further substitution
  - Polyacylation does not occur because the acyl group deactivates the aromatic ring to further substitution



Isopropylbenzene
(24%)

***p*-Diisopropylbenzene**
(14%)