

Electrophilic Substitution Reaction

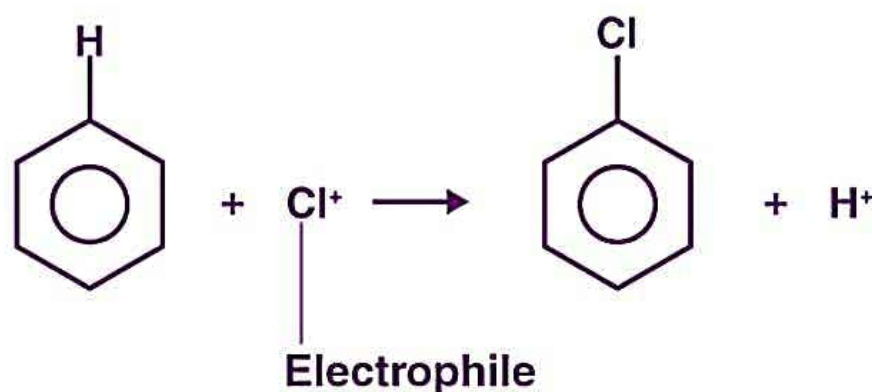
What is an Electrophilic Substitution Reaction?

An electrophilic substitution reaction is a chemical reaction in which the functional group attached to a compound is replaced by an electrophile. The displaced **functional group** is typically a hydrogen atom. Electrophilic substitution reactions generally proceed via a three-step mechanism that involves the following steps.

- The generation of an electrophile
- The formation of a carbocation (which is an intermediate)
- The removal of a proton from the intermediate

Types of Electrophilic Substitution Reactions

The two primary types of electrophilic substitution reactions undergone by organic compounds are **electrophilic aromatic substitution** reactions and electrophilic aliphatic substitution reactions. An illustration describing the electrophilic substitution of a hydrogen atom (belonging to a benzene molecule) with a chlorine atom is provided below.



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Here, the chlorine cation acts as an electrophile and replaces a hydrogen atom in the benzene ring. The products formed in this electrophilic substitution reaction include a proton and a chlorobenzene molecule.



Electrophilic Aromatic Substitution Reaction

In electrophilic aromatic substitution reactions, an atom attached to an aromatic ring is replaced with an electrophile. Examples of such reactions include aromatic nitrations, aromatic sulphonation, and Friedel-Crafts reactions.

It is important to note that the **aromaticity** of the aromatic compound is preserved in electrophilic aromatic substitutions. Therefore, these reactions can be used to obtain aryl halides from aromatic rings and iodine, bromine, or chlorine.

Electrophilic Aliphatic Substitution Reaction

In electrophilic aliphatic substitution reactions, an electrophile replaces the functional group (generally hydrogen) in an aliphatic compound. These reactions can be classified into the following five types.

- Halogenation of ketones
- Nitrosation
- Keto-Enol tautomerism
- Insertion of a carbene into a carbon-hydrogen bond
- Diazonium coupling (aliphatic)

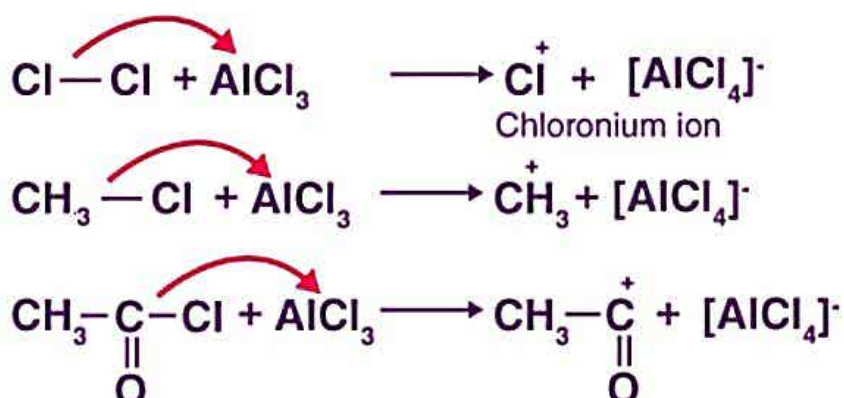
These electrophilic substitution reactions can result in an inversion of configuration if the electrophilic attack occurs at an angle of 180° to the leaving group (attack from the rear).

Mechanism of Electrophilic Substitution Reaction

The electrophilic substitution reaction mechanism involves three steps.

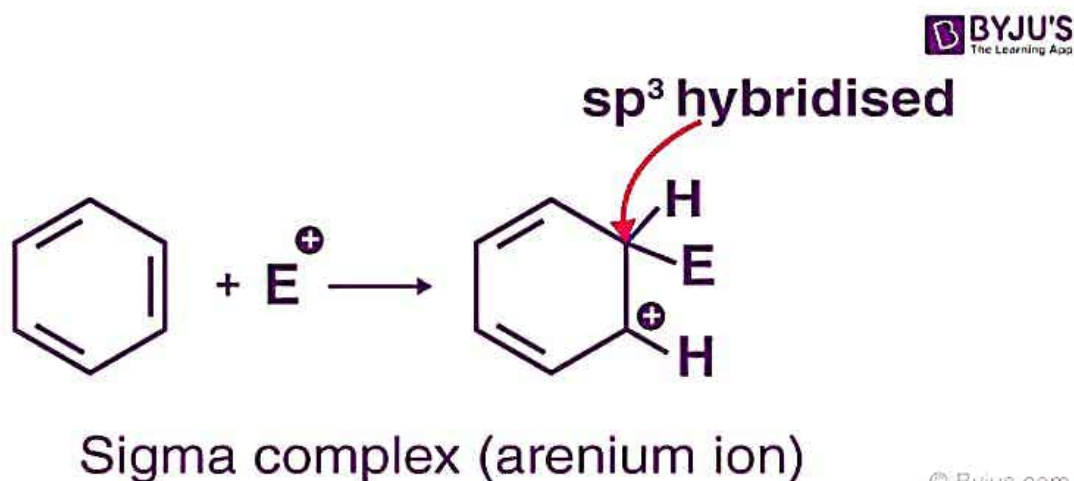
Step 1: Generation of Electrophile

Anhydrous aluminium chloride is a very useful Lewis acid in the generation of electrophile from the chlorination, alkylation, and acylation of an aromatic ring. The resulting electrophiles (from the combination of anhydrous aluminium chloride and the attacking reagent) are Cl^+ , R^+ , and RC^+O respectively as shown below:

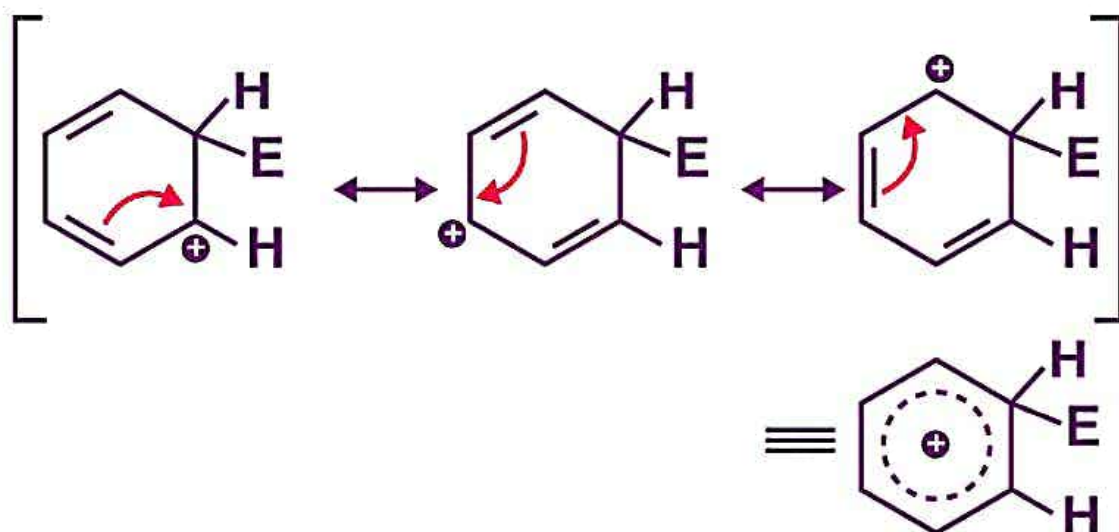


Step 2: Formation of Carbocation

The electrophile attacks the aromatic ring, forming a sigma complex or an arenium ion. One of the carbons in this arenium ion is sp^3 hybridized.



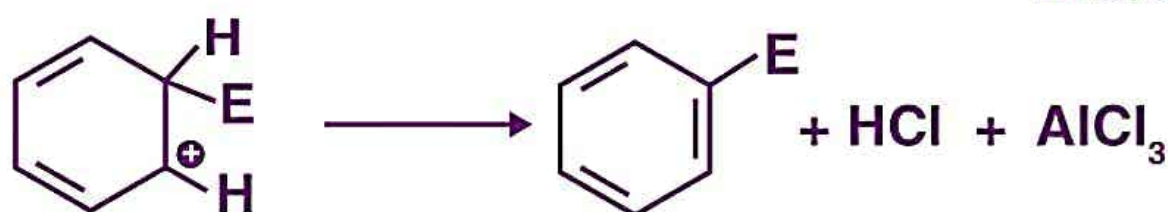
This arenium ion finds stability in a resonance structure. Since the delocalization of electrons stops at the sp^3 hybridized carbon, the sigma complex or the arenium ion loses its aromatic character.



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Step 3: Removal of Proton

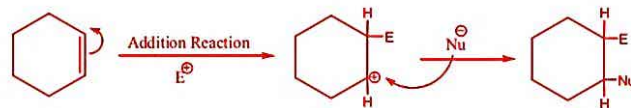
In order to restore the aromatic character, the sigma complex releases a proton from the sp^3 hybridized carbon when it is attacked by the $[AlCl_4]^-$. The reaction describing the removal of a proton from the sigma complex is given below:



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ELECTROPHILIC ADDITION IN ALKENE



WHY ELECTROPHILIC ATTACK IN BENZENE?

Theory The high electron density of the ring makes it open to attack by electrophiles

HOWEVER...

Because the mechanism involves an initial disruption to the ring, electrophiles will have to be more powerful than those which react with alkenes.

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A fully delocalised ring is stable so will resist ELECTROPHILIC ADDITION.



STABLE DELOCALISED SYSTEM

DOES NOT FORM THIS PRODUCT SINCE LESS STABLE THAN STARTING MATERIAL DUE TO LOSS OF AROMATICITY

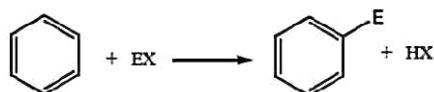
ELECTRONS ARE NOT DELOCALISED AROUND THE WHOLE RING - LESS STABLE

THEREFORE, BENZENE UNDERGOES SUBSTITUTION REACTION RATHER THAN ADDITION REACTION

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ARENEM ION, ITS MECHANISM, S_E2 REACTION

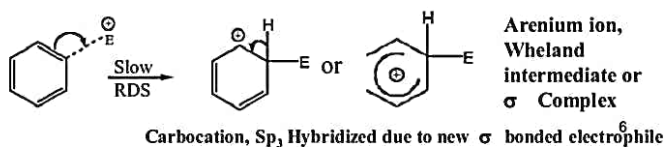
The general equation for this reaction is:



Generation of E^{\oplus}



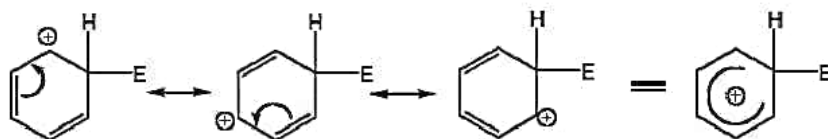
STEP I



Arenium ion, Wheland intermediate or σ Complex

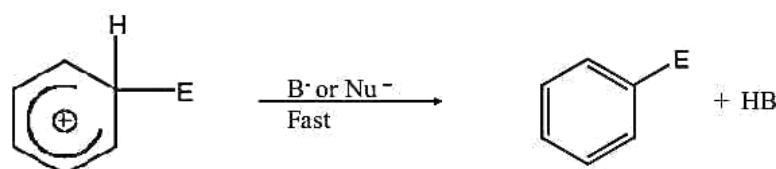
Carbocation, sp_3 Hybridized due to new σ bonded electrophile

Although the Wheland intermediate is stabilized by resonance



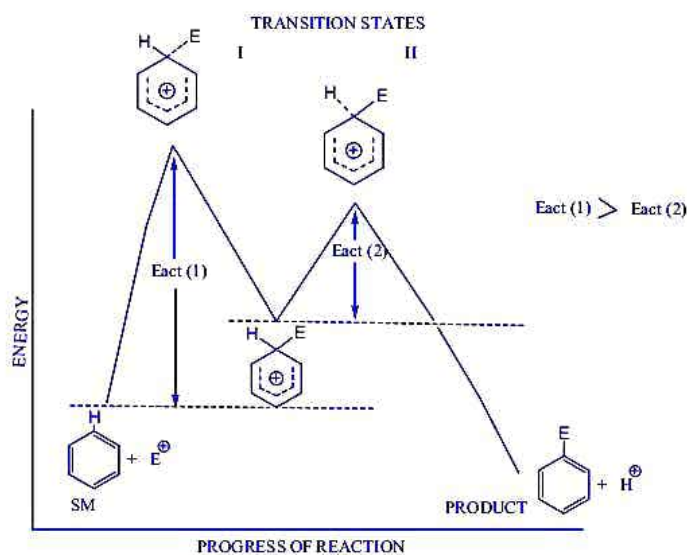
- we have clearly lost the aromatic stabilization of the starting material and hence the addition of the electrophile is going to be the slow step (rds = rate determining step).
- The second step will be fast since we regenerate the aromatic system by loss of the proton.

STEP II



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ENERGY PROFILE DIAGRAM OF ARENIUM ION



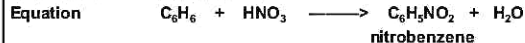
SUBSTITUTION ELECTROPHILIC BIMOLECULAR (S_E2)

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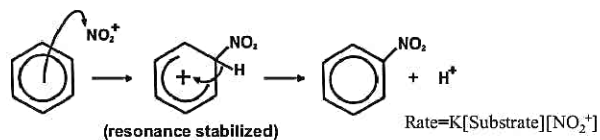
ELECTROPHILIC SUBSTITUTION REACTIONS - NITRATION

Reagents conc. nitric acid and conc. sulphuric acid (catalyst)

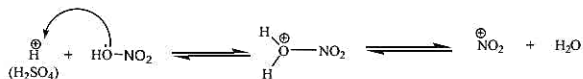
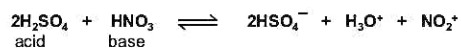
Conditions reflux at 55°C



Mechanism



Electrophile NO_2^+ , nitronium ion or nityl cation; it is generated in an acid-base reaction...

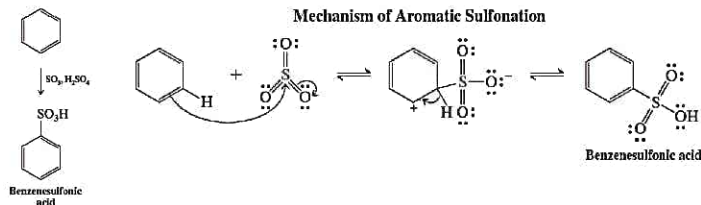


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Sulfonation (a reversible reaction).

Fuming sulfuric acid (8% SO_3 in concentrated H_2SO_4) reacts with benzene to form benzenesulfonic acid.

Sulfonation of Benzene

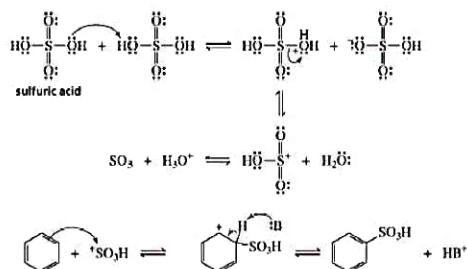


Because the reaction of SO_3 with water is so exothermic, the sulfonation of benzene can be reversed by heating benzenesulfonic acid in dilute aqueous acid.

Because sulfonation is reversible, it can be used as a blocking group to control further aromatic substitution and then later removed.

First H_2SO_4 donates a proton to SO_3 to produce HSO_3^+ (the reactive species)

• Mechanism for sulfonation

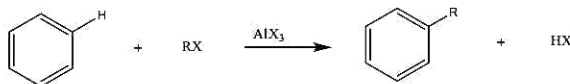


Friedel-Crafts Alkylation

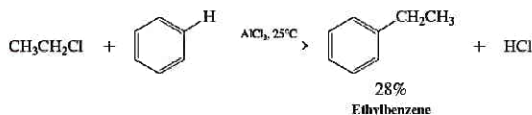
Carbon-carbon bonds to benzene can be created using a sufficiently electrophilic carbon based electrophile.

To create the necessary electrophilic carbon atom, a Lewis acid such as AlCl_3 is employed.

A alkyl halide reacts with benzene in the presence of an aluminum halide to form an alkylbenzene and a hydrogen halide.

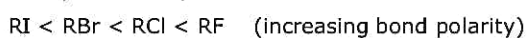


Friedel-Crafts Alkylation of Benzene with Chloroethane

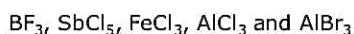


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Reactivity of the alkyl halides increases in the order:



Typical Lewis acids are:



A catalyst is used to increase the positive nature of the electrophile and make it better at attacking benzene rings. AlCl_3 acts as a Lewis Acid and helps break the C—Cl bond.

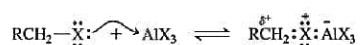
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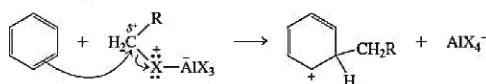
The mechanism of the Friedel-Crafts alkylation with primary haloalkanes (alkyl halides) involves coordination of the Lewis acid to the halogen atom:

Mechanism of Friedel-Crafts Alkylation with Primary Haloalkanes

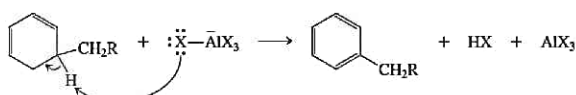
STEP 1. Haloalkane activation



STEP 2. Electrophilic attack



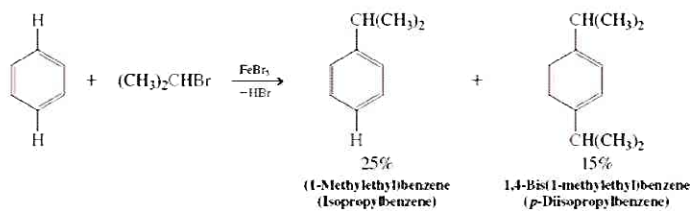
STEP 3. Proton loss



With secondary and tertiary alkyl halides, free carbocations are usually formed, which attack the benzene ring in the same way as the cation NO_2^+ .

Limitations of Friedel-Crafts Alkylations

Polyalkylation and carbocation rearrangement may cause the yield of desired products to diminish and lead to mixtures that may be difficult to separate:

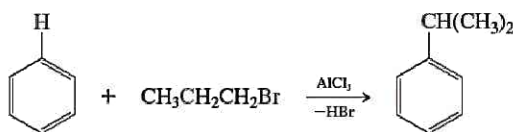


Polyalkylation occurs because the alkylbenzene first formed is electron-rich and activates the ring towards further substitution. This is in contrast to bromination, nitration and sulfonation, as they deactivate the ring towards further substitution (electron withdrawing substituents).

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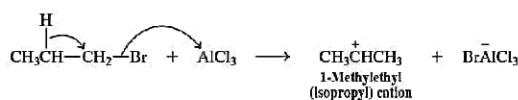
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Skeletal rearrangement of the carbocation is the second unwanted side-reaction in aromatic alkylation. The desired 1-propylbenzene is not obtained when benzene is alkylated using 1-bromopropane:



In the presence of the Lewis acid, the starting haloalkane rearranges to the secondary carbocation by a hydride shift:

Rearrangement of 1-Bromopropane to 1-Methylethyl (Isopropyl) Cation



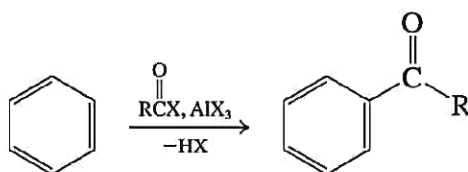
Because of polysubstitution and rearrangement reactions, Friedel-Crafts alkylations are rarely used in synthesis.

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Friedel-Crafts Acylation (Alkanoylation)

An alternate route to C-C bond formation to the aromatic nucleus that does not have the problems encountered with alkylations is the Friedel-Crafts **acylation** or **alkanoylation**.

These reactions proceed through an acylium cation intermediate ($RC=O^+$).

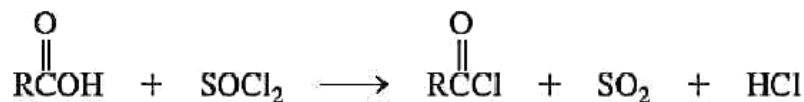


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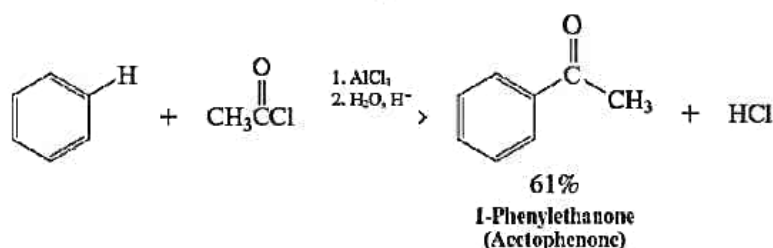
Friedel-Crafts acylation employs acyl chlorides

Benzene reacts with alkanoyl halides in the presence of aluminum halide to give 1-phenylalkanones (phenyl ketones).

Preparation of an Alkanoyl (Acyl) Chloride



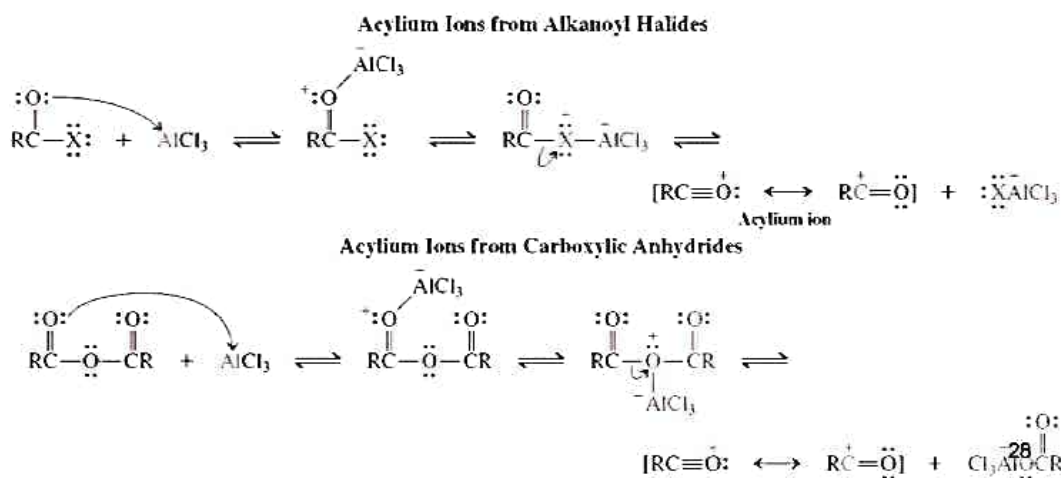
Friedel-Crafts Alkanoylation of Benzene with Acetyl Chloride



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Acyl halides react with Lewis acids to produce acylium ions.

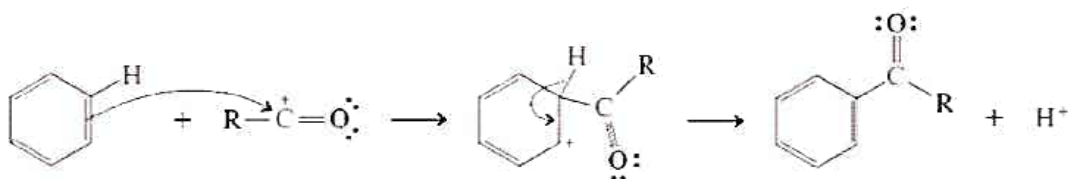
The acylium cation can be formed from either an acyl halide or a carboxylic anhydride:



Acylium ions undergo electrophilic aromatic substitution.

An acylium ion is capable of attacking benzene by the usual aromatic substitution mechanism:

Electrophilic Alkanoylation



The acyl substituent is electron withdrawing which deactivates the ring and protects it from further substitution.