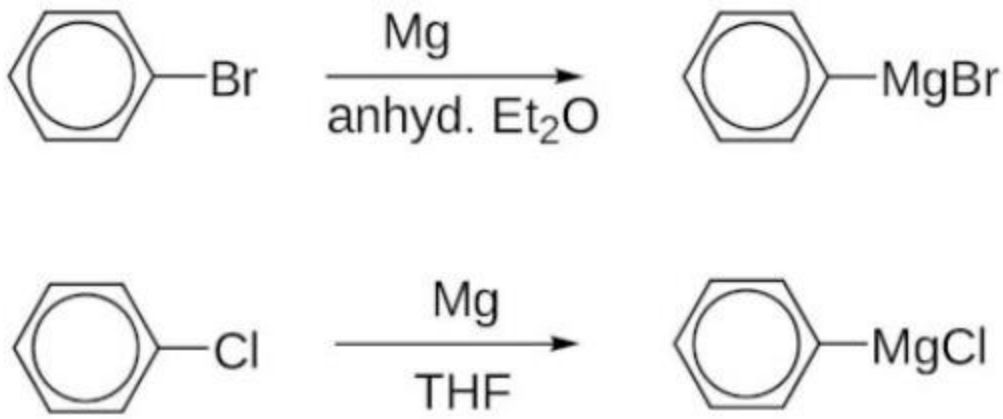
Aryl halides, reactions:

1. Formation of Grignard reagent
2. EAS (Electrophilic aromatic substitution)
3. Nucleophilic aromatic substitution (bimolecular displacement)

   (Ar must contain strongly electron withdrawing groups ortho and/or para to X)
4. Nucleophilic aromatic substitution (elimination-addition)

   (Ring not activated to bimolecular displacement)

1) Preparation of Grignard reagent

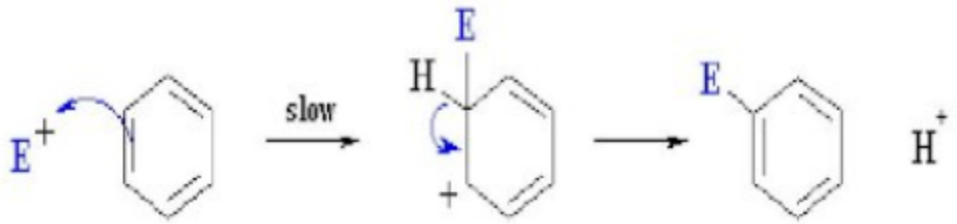


2) EAS

Overall an electrophilic aromatic susbtitution (EArS) can be represented as follows:

There are three fundamental components to an electrophilic aromatic substitution mechanism:

1.formation of the new σ bond from a **C=C** in the arene nucleophile
2.removal of the proton by breaking the **C-H** σ bond
3.reforming the **C=C** to restore the aromaticity

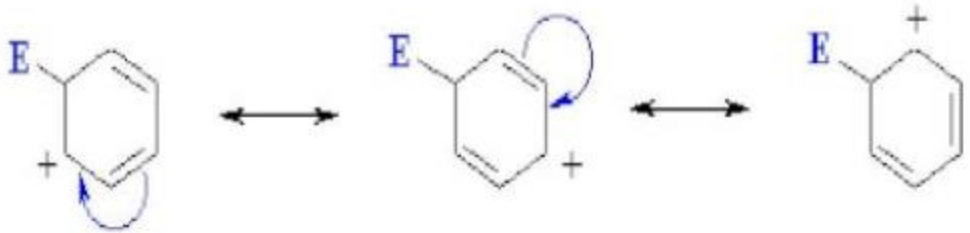


The mechanism is represented by the following series of events:

1.Formation of the reactive electrophile, **E**$^+$from the reagents.

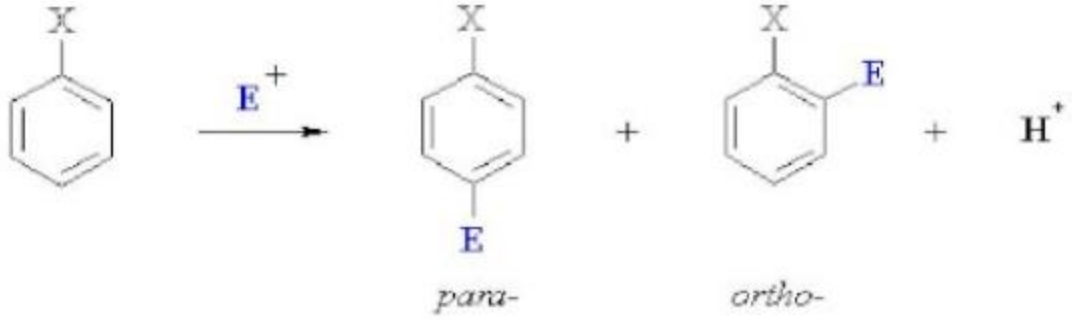
2.*Slow* reaction of the arene **C=C** with the **E**$^+$ to give a resonance stabilised carbocation.

3. Loss of **H**$^+$ from the carbocation to restore the **C=C** and the aromatic system

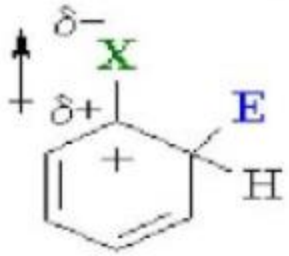


The reaction of the electrophile **E**$^+$ with the arene is the slow step since it results in the loss of aromaticity even though the resulting cation is still resonance stablised. This carbocation is also described as the **cyclohexdienyl cation** or **arenium ion** or as a **sigma-complex**.

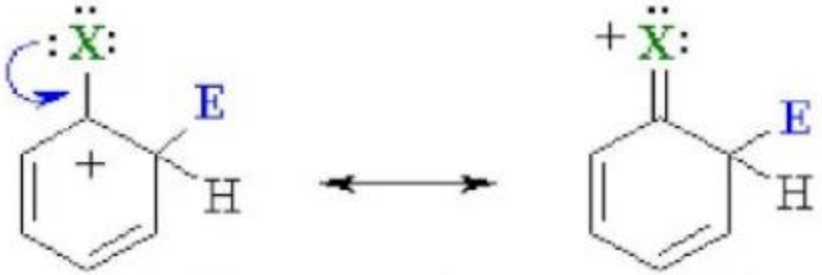
Electrophilic Aromatic Substitution of Aryl Halides



1. *Aryl halides* are themselves reactive towards EAS but they are less reactive than benzene.
2. This is because halides are weak deactivators
3. Halides direct subsequent reactions ortho, para.
4. This makes them a little unusual (activators are usually *ortho, para-directing*, deactivators *meta-directing*).
5. The weak deactivation is due to the electronegativity of the halogen making the intermediate cations less stable than those produced when benzene undergoes substitution:

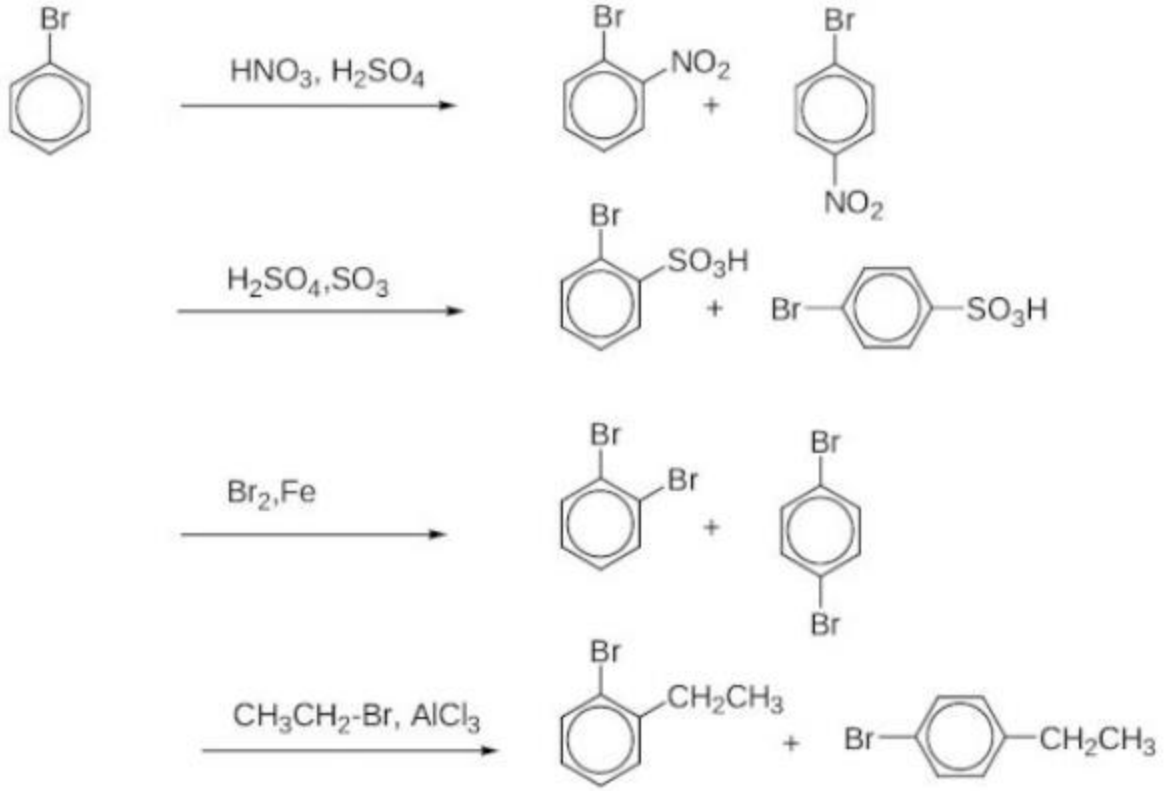


The directing effect is due to the resonance stabilisation of the cationic intermediates derived by *ortho* or *para* attack but not by *meta* attack. For example, the stabilisation during *ortho* attack is shown below :



However, aryl halides can undergo many of the same electrophilic aromatic substitution reactions that benzene can including nitration, sulfonation, further halogenation and Friedel-Crafts alkylation or acylation reactions.

The –X group is electron-withdrawing and deactivating in EAS, but is an *ortho/para* director.



3) Nucleophilic aromatic substitution (bimolecular displacement)

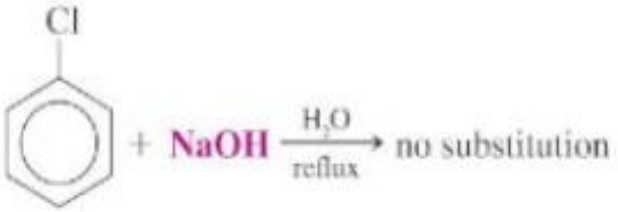
Aryl halides and vinylic halides are relatively unreactive toward nucleophilic substitution under conditions that give facile nucleophilic substitution with alkyl halides.

Reason:

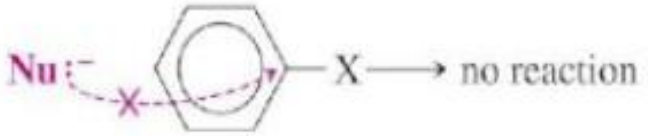
(1) Phenyl cations are very unstable.
(2) Halogen bonds of aryl (and vinylic) halides are shorter and stronger than those of alkyl, allylic, and benzylic halides because of the hybridized state and the resonance.

But aryl halides can be remarkably reactive toward nucleophiles if they bear certain substituents or when we allow them to react under the proper conditions.

- Aryl Halides and Nucleophilic Aromatic Substitution
  - Simple aryl and vinyl halides do not undergo nucleophilic substitution

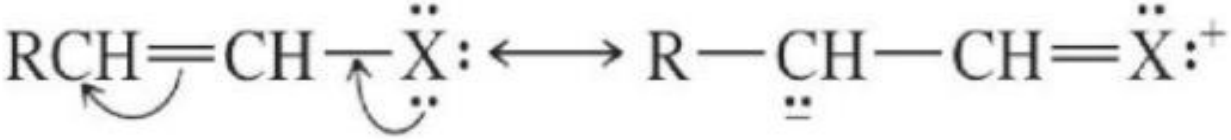


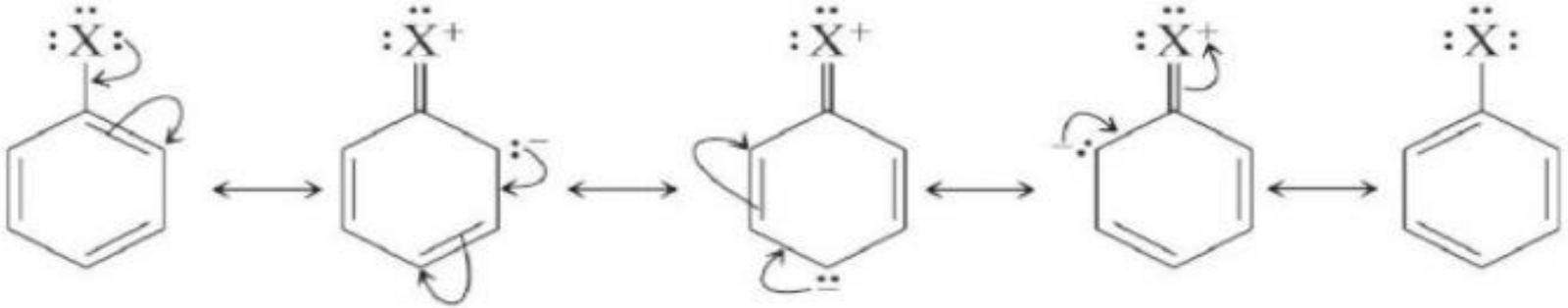
$$CH_2{=}CHCl + NaOH \xrightarrow[\text{reflux}]{H_2O} \text{no substitution}$$



  - Back-side attack required for S_N2 reaction is blocked in aryl halides

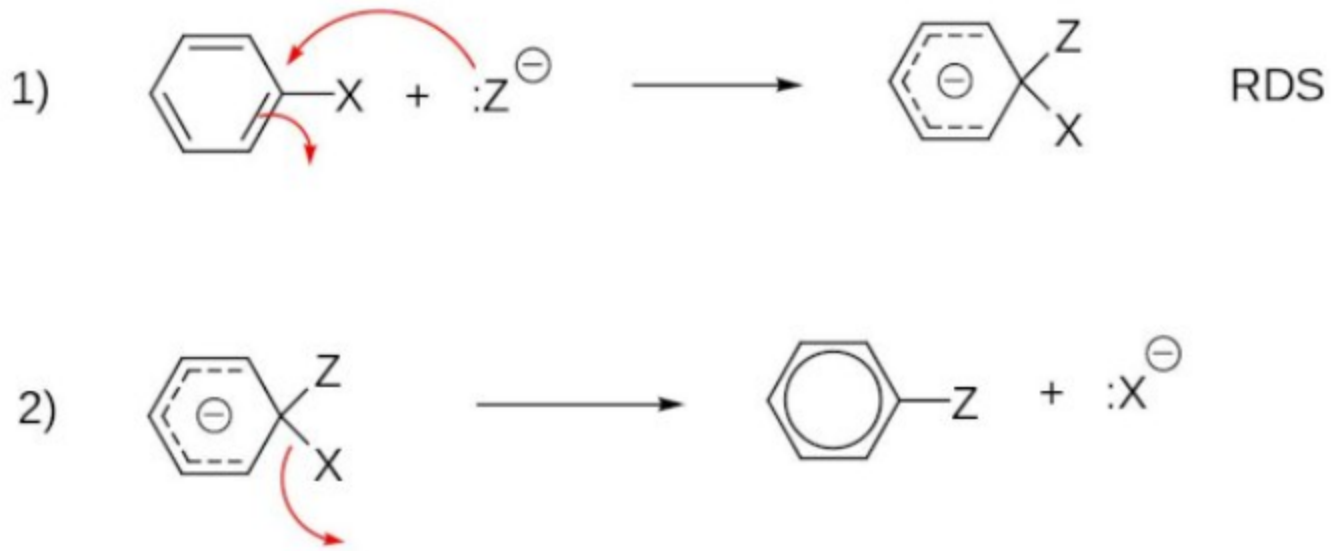
- S_N2 reaction also doesn't occur in aryl (and vinyl halides) because the carbon-halide bond is shorter and stronger than in alkyl halides
  - Bonds to sp^2-hybridized carbons are shorter, and therefore stronger, than to sp^3-hybridized carbons
  - Resonance gives the carbon-halogen bond some double bond character

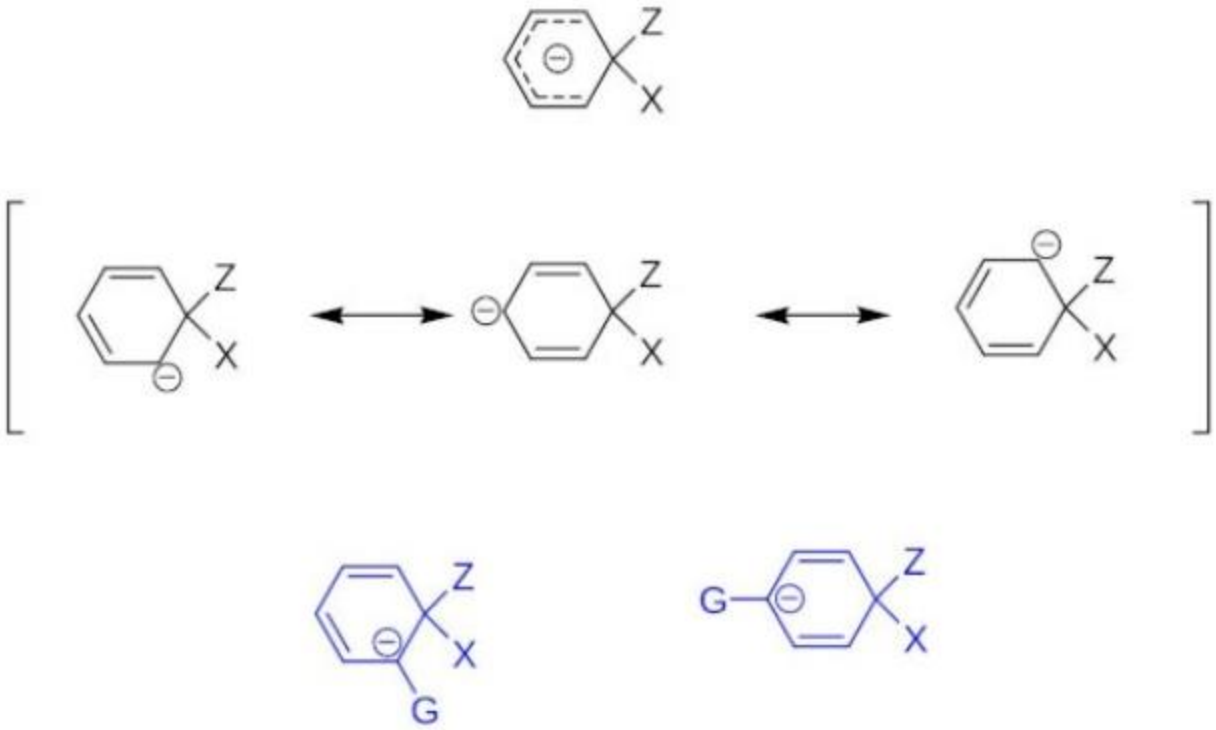




bimolecular displacement (nucleophilic aromatic substitution)

mechanism:

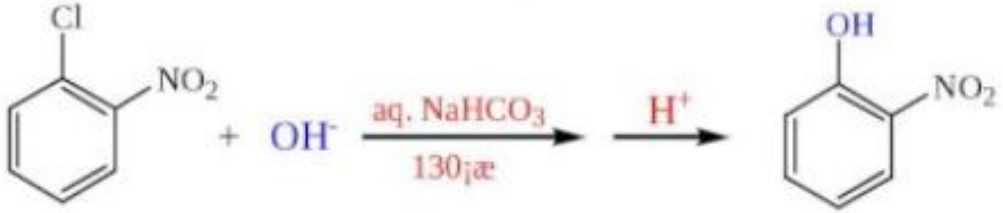


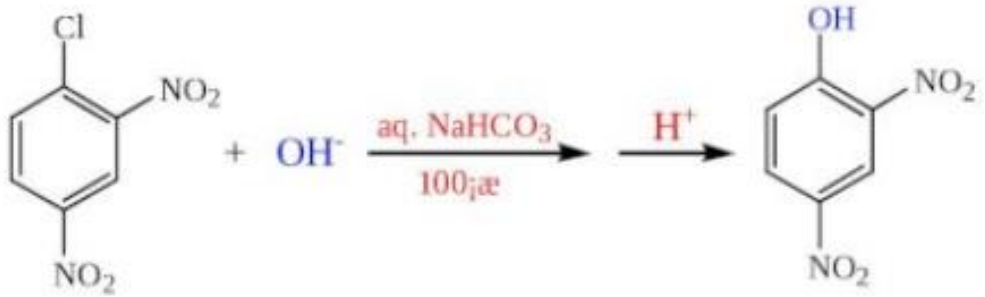


If G is an electron withdrawing group in the ortho and para positions, it will stabilize the intermediate anion.

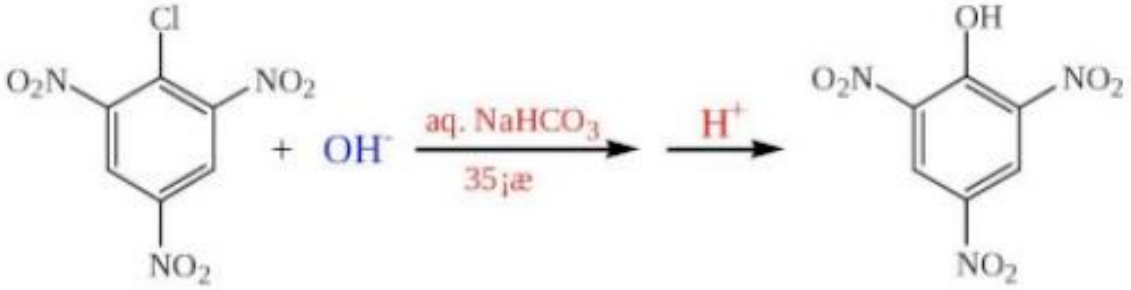
NUCLEOPHILIC AROMATIC SUBSTITUTION BY ADDITION – ELIMINATION: THE SNAr MECHANISM

Nucleophilic substitution can occur when strong electron-withdrawing groups are ortho or para to the halogen atom.





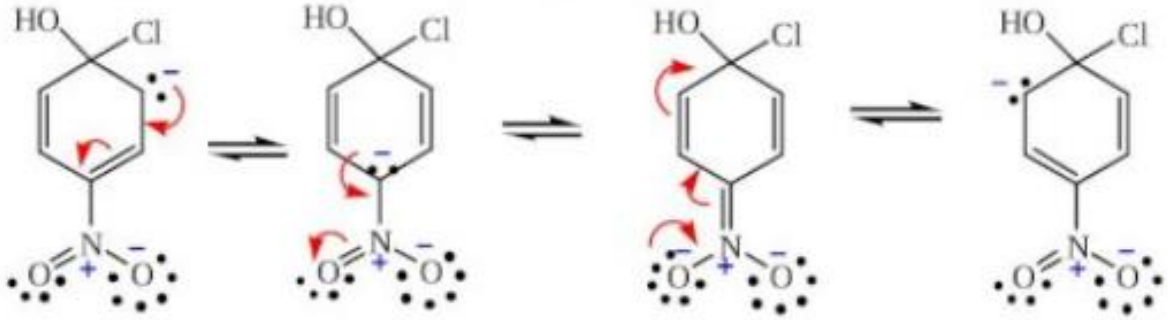
The temperature is related to the number of ortho or para nitro groups



But the meta-nitro group does not produce a similar activating effect.

Mechanism:

The delocalized carbanion is stabilized by electron-withdrawing groups in the positions ortho and para to the halogen atom.



Addition-Elimination Mechanism

Two step mechanism:

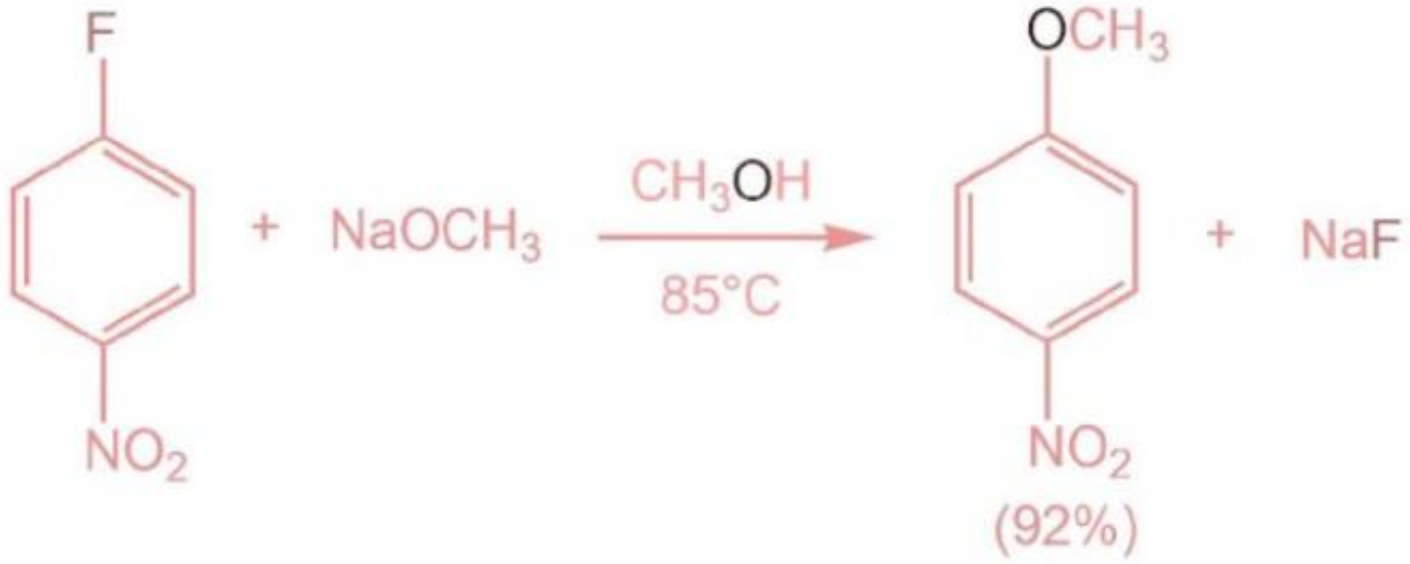
Step 1

nucleophile attacks aryl halide and bonds to the carbon that bears the halogen
(slow: aromaticity of ring lost in this step)

Step 2

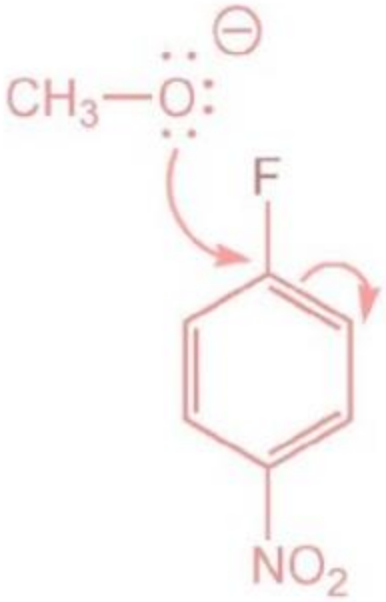
intermediate formed in first step loses halide
(fast: aromaticity of ring restored in this step)

Addition-Elimination Mechanism



Addition-Elimination Mechanism

Step 1 - Addition



bimolecular

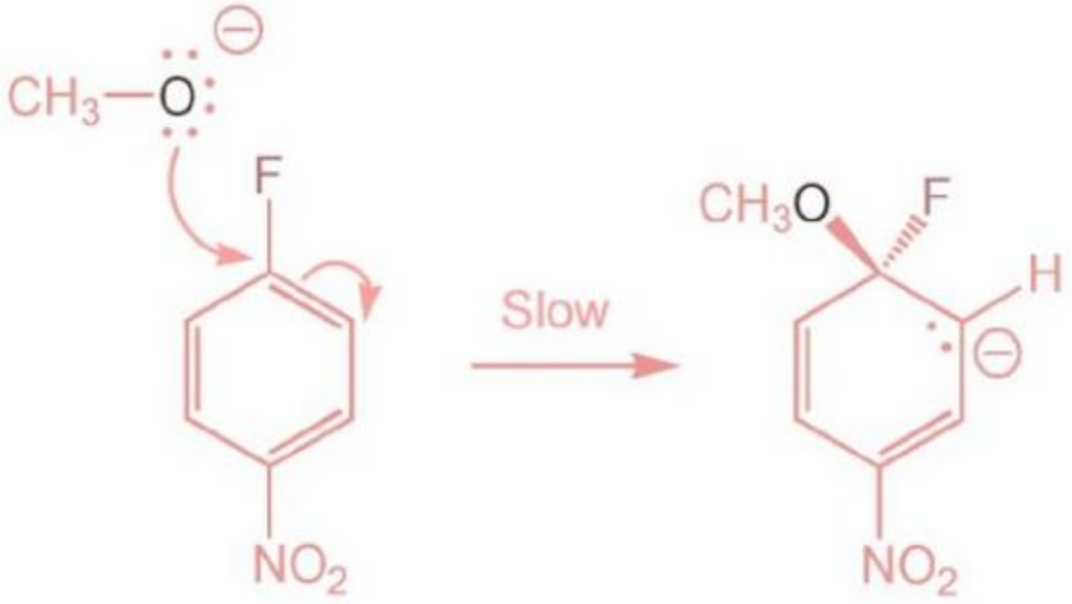
consistent with second-order kinetics;

first order in aryl halide,
first order in nucleophile

Rate = k [CH_3ONa] [arene]

Addition-Elimination Mechanism

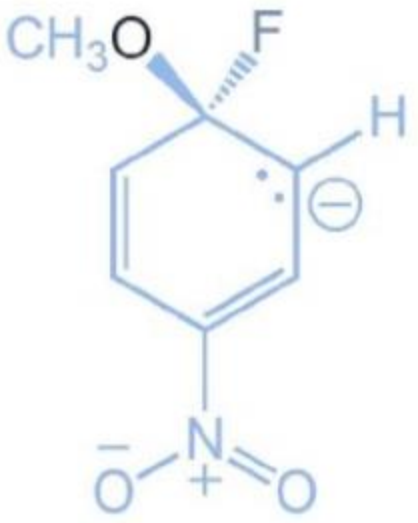
Step 1 - Addition



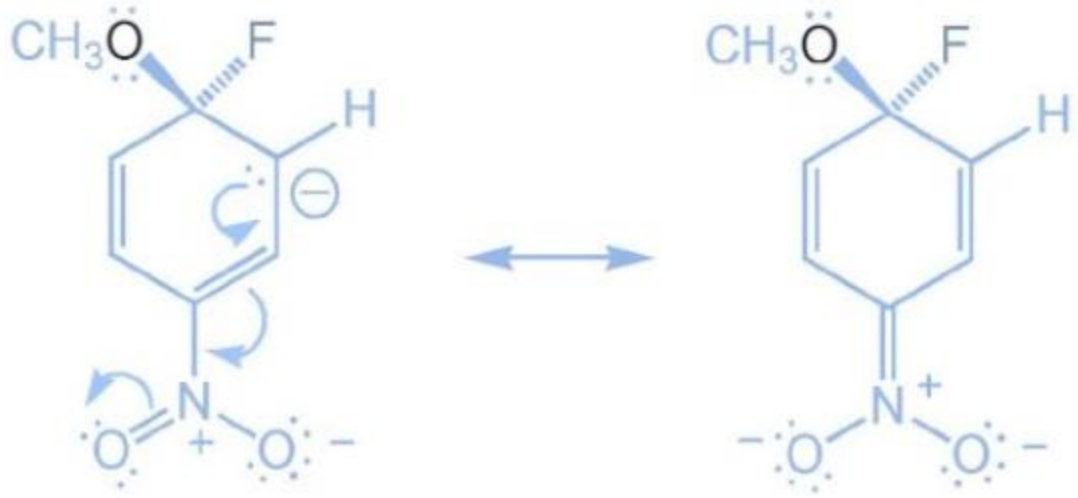
Reaction Involves an Anionic Intermediate

intermediate is negatively charged

formed faster when ring bears electron-withdrawing groups such as NO_2 because negative charge is stabilized……..

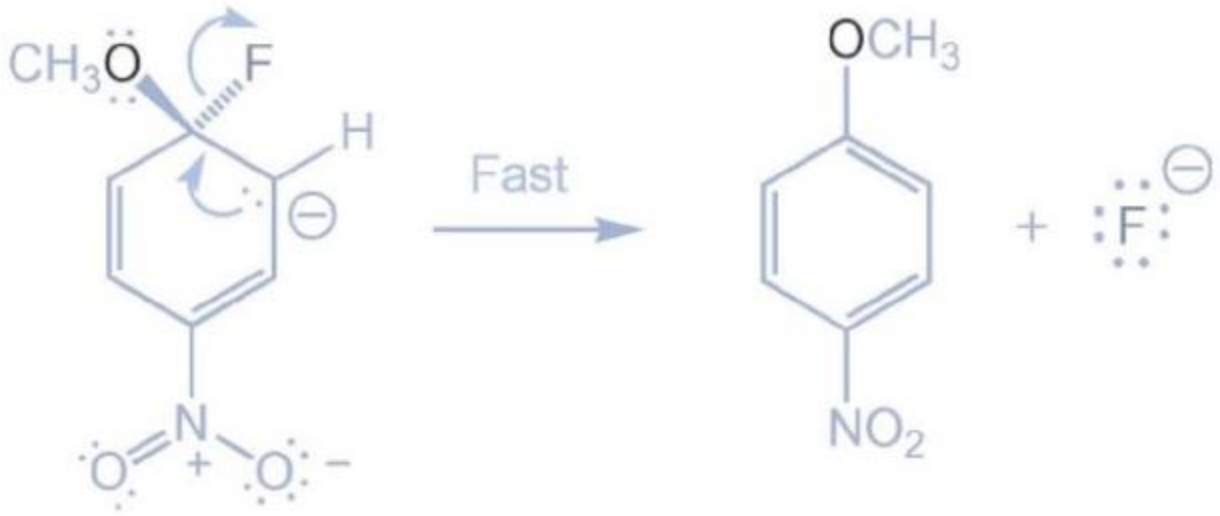


Stabilization of Addition Product by Electron-Withdrawing Group



Rapid Collapse of Cyclohexadienyl Anion Intermediate

Step 2 - Elimination

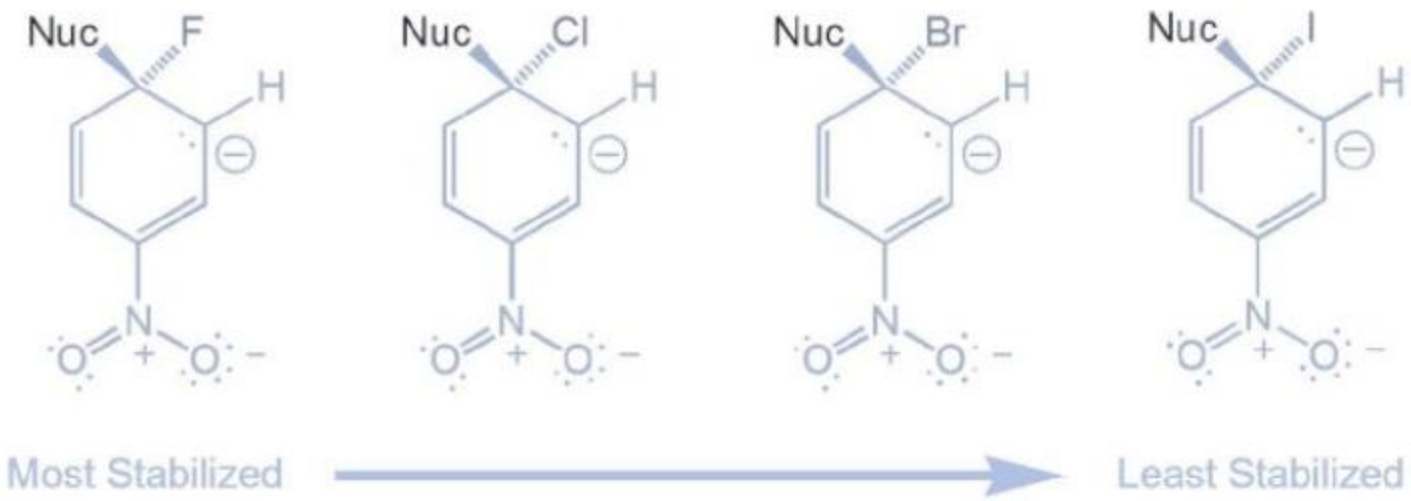


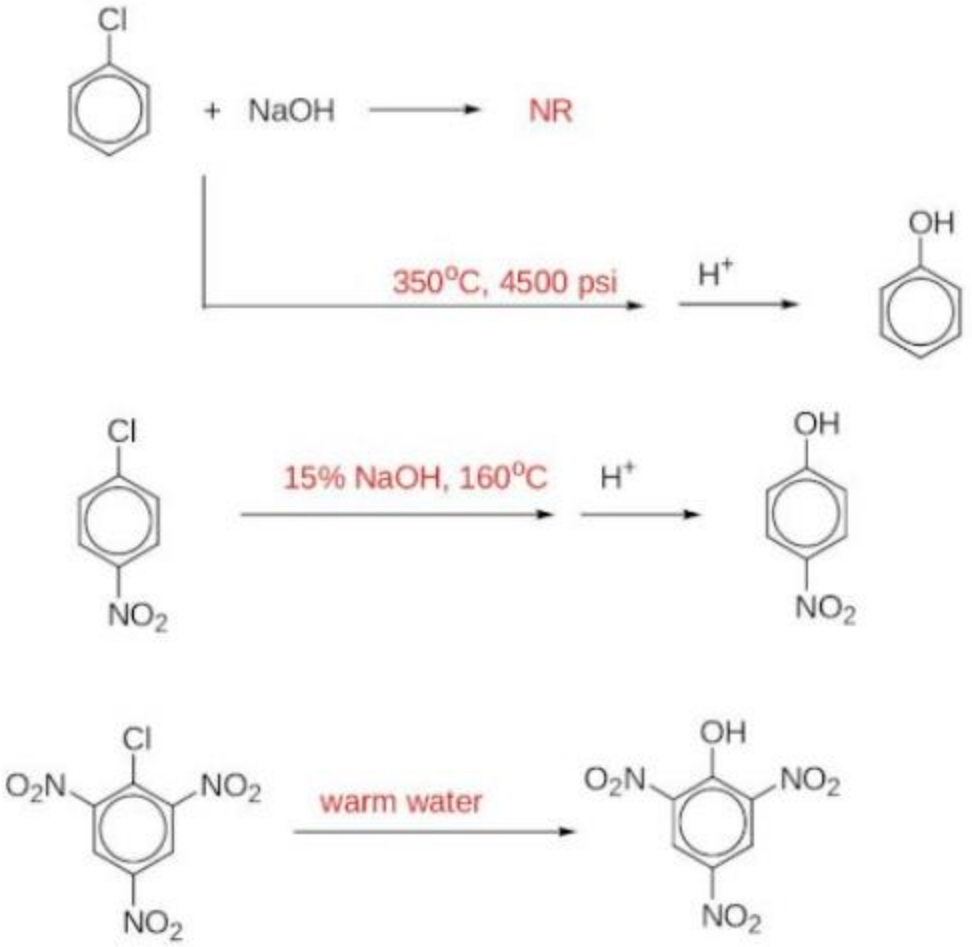
The Role of Leaving Groups

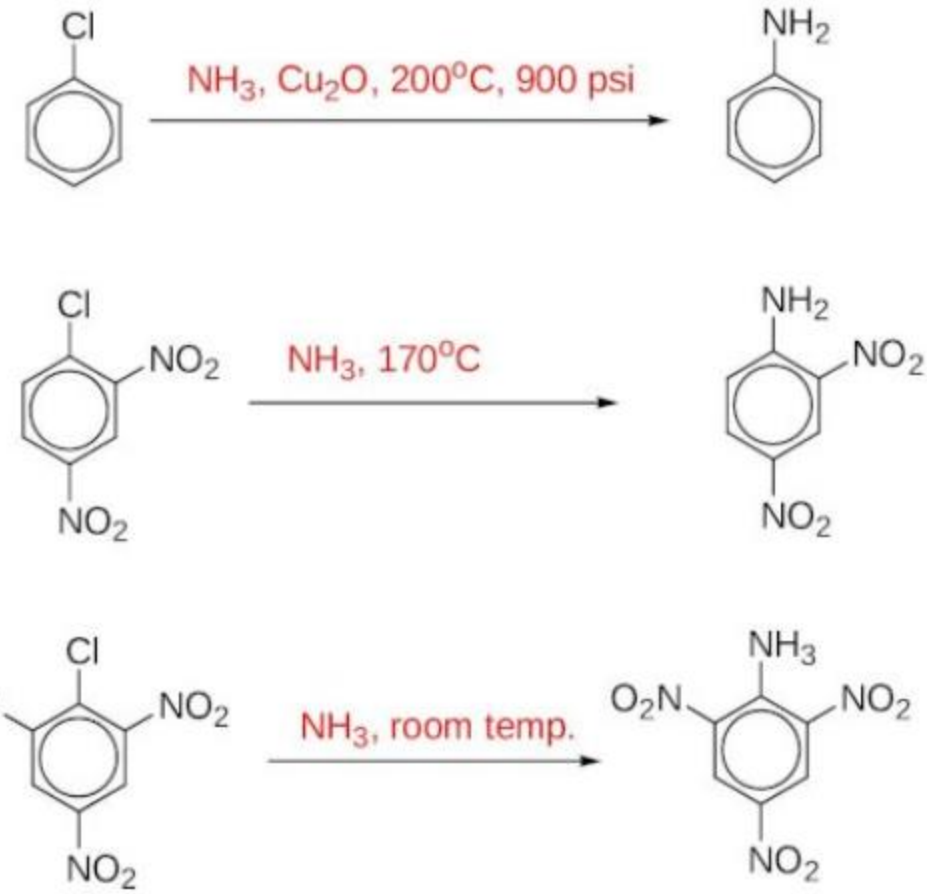
F > Cl > Br > I is unusual, but consistent with mechanism

- carbon-halogen bond breaking does not occur until after the rate-determining step
- electronegative F stabilizes negatively charged intermediate

The Role of Leaving Groups

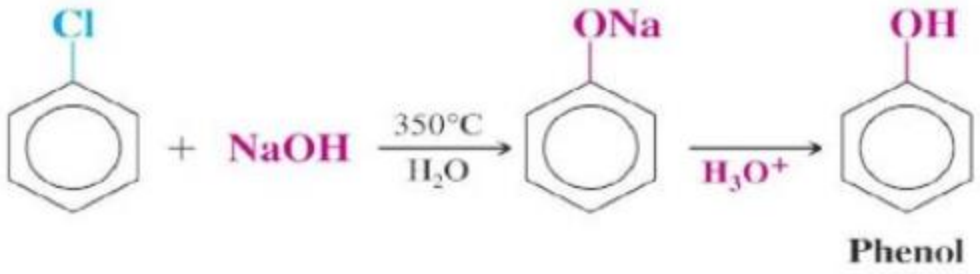


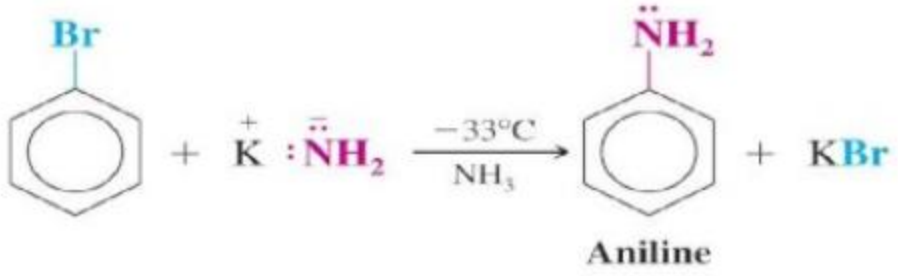

Cl
+ NaOH
NR
350°C, 4500 psi
H+
OH
Cl
15% NaOH, 160°C
H+
OH
NO2
NO2
Cl
O2N
NO2
NO2
warm water
OH
O2N
NO2
NO2


Cl
NH3, Cu2O, 200°C, 900 psi
NH2
Cl
NO2
NO2
NH3, 170°C
NH2
NO2
NO2
Cl
O2N
NO2
NO2
NH3, room temp.
NH3
O2N
NO2
NO2

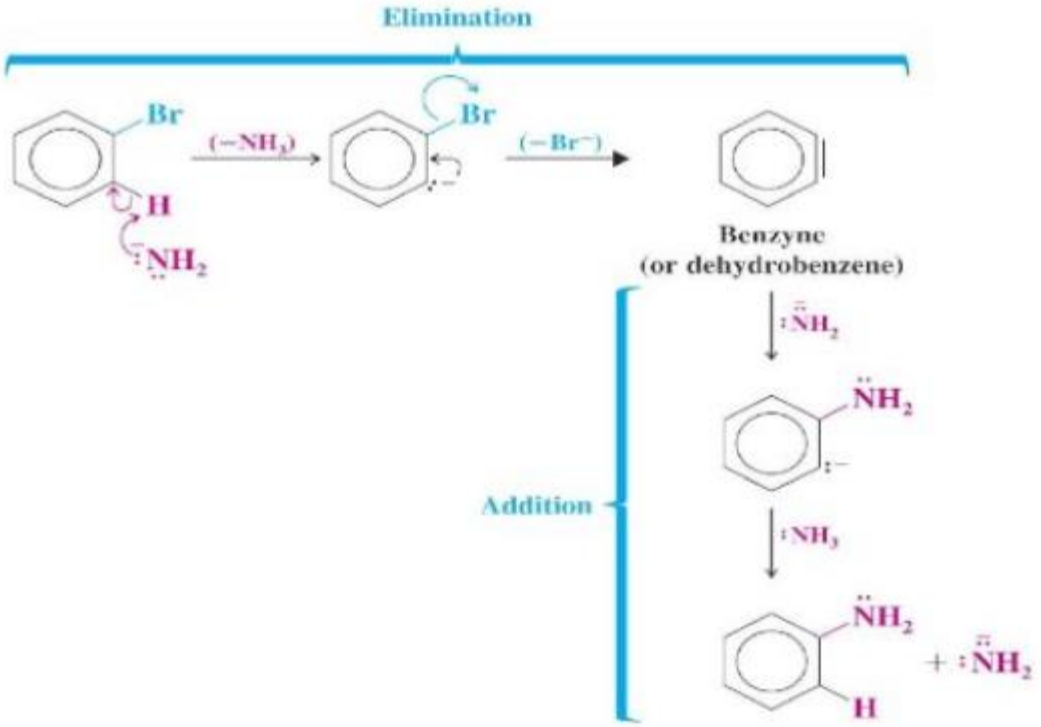
– Nucleophilic Aromatic Substitution through an Elimination-Addition Mechanism: Benzyne

- Under forcing conditions, chlorobenzene can undergo an apparent nucleophilic substitution with hydroxide
  - Bromobenzene can react with the powerful base amide



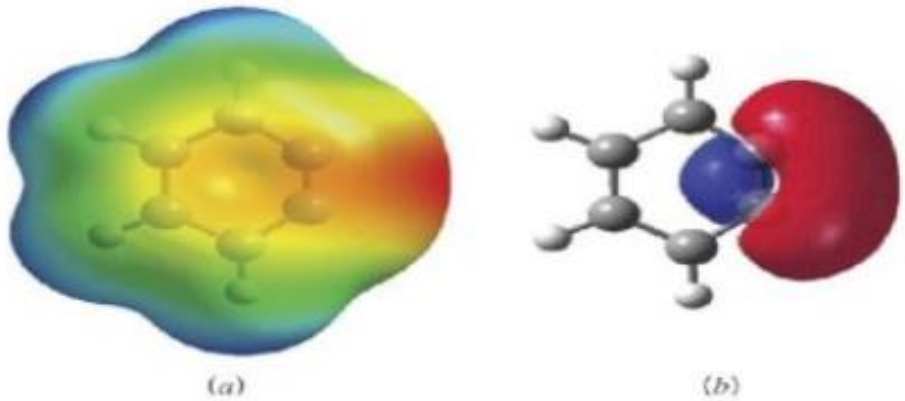


- The reaction proceeds by an elimination-addition mechanism through the intermediacy of a benzyne (benzene containing a triple bond)



A calculated electrostatic potential map of benzyne shows added electron density at the site of the benzyne π bond

- The additional π bond of benzyne is in the same plane as the ring

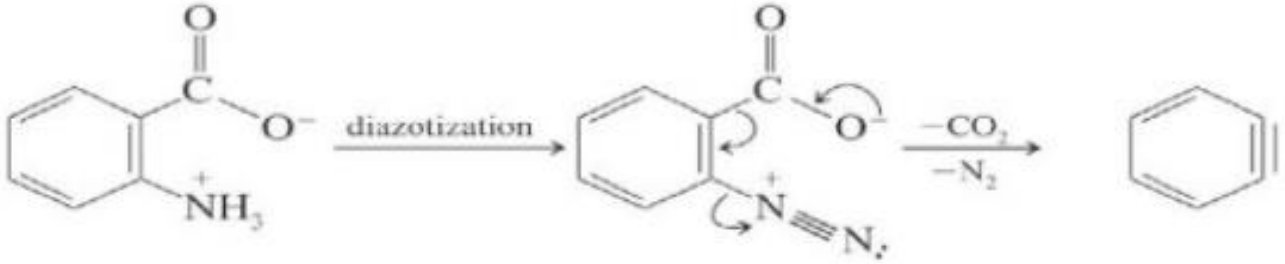


(a) (b)

- When chlorobenzene labeled at the carbon bearing chlorine reacts with potassium amide, the label is divided equally between the C-1 and C-2 positions of the product
  - This is strong evidence for an elimination-addition mechanism and against a straightforward S_N2 mechanism

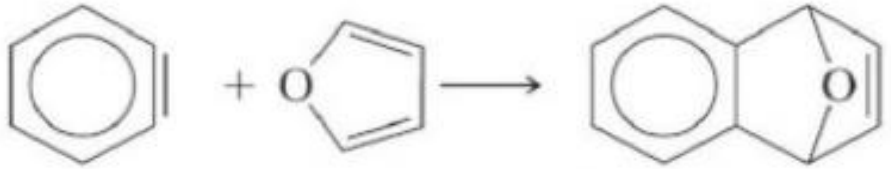
Benzyne can be generated from anthranilic acid by diazotization

- The resulting compound spontaneously loses CO_2 and N_2 to yield benzyne
- The benzyne can then be trapped *in situ* using a Diels-Alder reaction



Anthranilic acid

Benzene (trapped *in situ*)



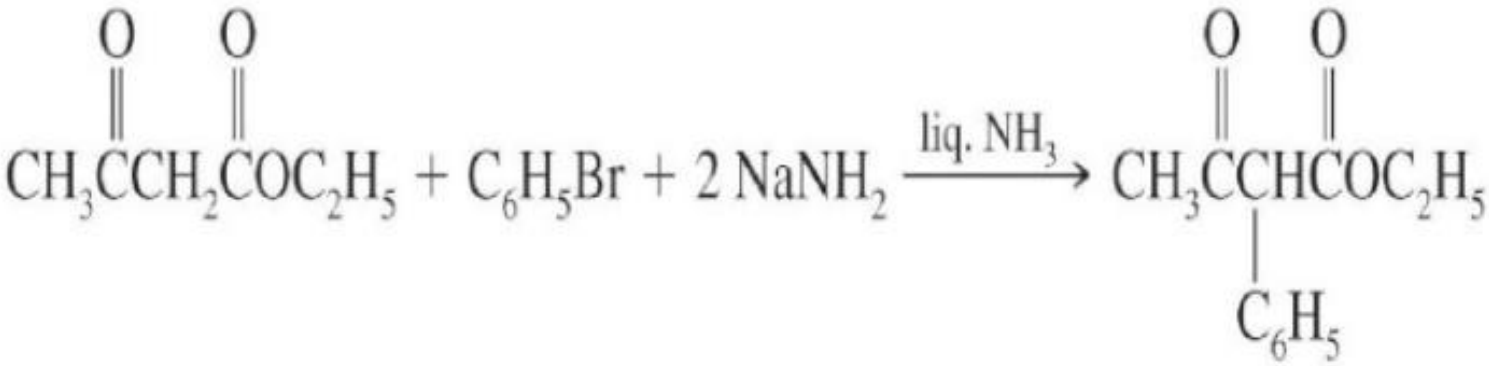
Benzyne (generated by an elimination reaction)

Furan

Diels–Alder adduct

Phenylation

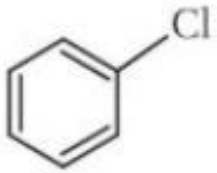
Acetoacetic esters and malonic esters can be phenylated by benzyne generated *in situ* from bromobenzene



1. Preparation of vinyl halides

Example of a vinyl halide:

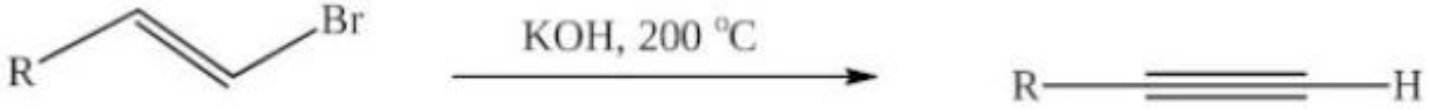
Example of an aryl halide:



a. Halogenation of alkynes
b. Hydrohalogenation of alkynes
c. Elimination in dihaloalkanes
d. S_EAr - halogenation

2. Elimination in aryl and vinyl halides

These reactions never proceed by E1 because of low stability of aryl and vinyl carbocatio
Vinyl halides are much less reactive in E2, than alkyl halides because of a stronger $C(sp^2)$-Cl bond .



3. Substitution in vinyl halides

This reaction proceeds through addition, followed by elimination. It never goes via S_N2, because of the lack of stabilization of the transition state.
(Same reason, why vinyl cations are less stable, than alkyl cations.)