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AROMATIC
NUCLEOPHILIC
SUBSTITUTION-PART
-2

Electrophilic substitution

- The aromatic ring acts as a nucleophile, and attacks an added electrophile E^+
- An electron-deficient carbocation intermediate is formed (the rate-determining step) which is then deprotonated to restore aromaticity
- electron-donating groups on the aromatic ring (such as $-OH$, $-OCH_3$, and alkyl) make the reaction faster, since they help to stabilize the electron-poor carbocation intermediate
- Lewis acids can make electrophiles even more electron-poor (reactive), increasing the reaction rate. For example $FeBr_3 / Br_2$ allows bromination to occur at a useful rate on benzene, whereas Br_2 by itself is slow).

Summary: Nucleophilic Aromatic Substitution

In this reaction, a nucleophile (Nu^-) attacks an electron-poor aromatic molecule, resulting in the substitution of a leaving group:

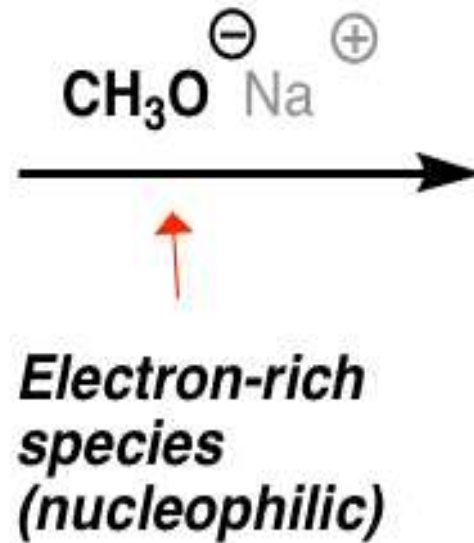
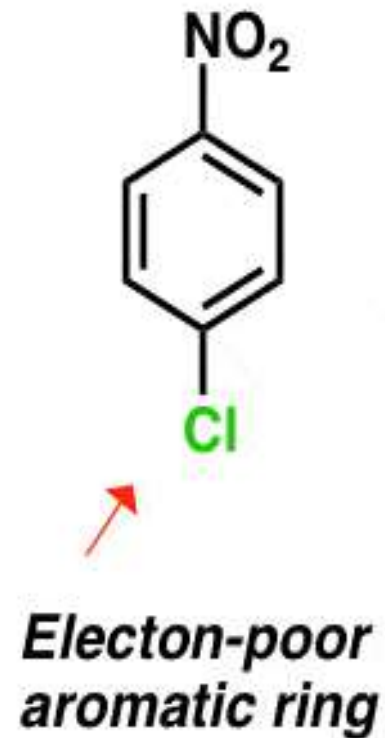


The rate-determining step is attack of the aromatic ring by the nucleophile, which disrupts aromaticity.

Electron-withdrawing groups on the aromatic ring help to stabilize the negative charge of the intermediate.

Because loss of the leaving group is not the rate-determining step, fluorine is often used as a leaving group due to its high electronegativity

How likely is this "electrophilic aromatic substitution" reaction?



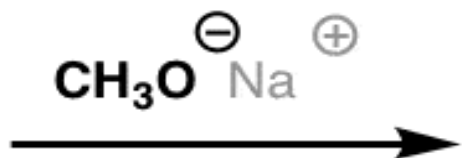
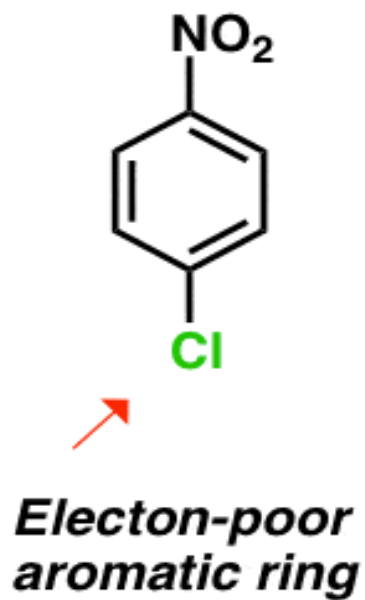
?

anything?

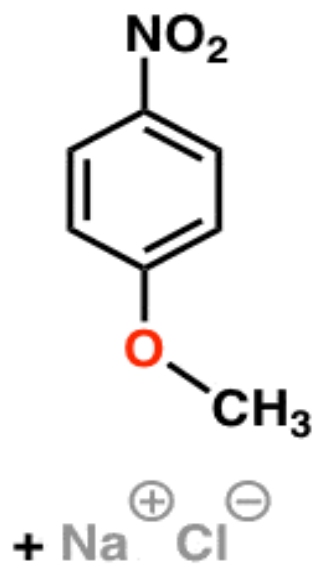
In fact, a substitution reaction does occur! (But, as you may suspect, this isn't an electrophilic aromatic substitution reaction.)

In this substitution reaction the C-Cl bond breaks, and a C-O bond forms on the same carbon.

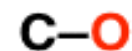
Would you believe..



Electron-rich species (nucleophile)



Bonds formed



Bonds broken



a substitution reaction...

by a nucleophile !?

**The species that attacks the ring is a nucleophile, not an electrophile
The aromatic ring is electron-poor (electrophilic), not electron rich (nucleophilic)**

The “leaving group” is chlorine, not H⁺

**The position where the nucleophile attacks is determined by where the leaving group is, not by electronic and steric factors (i.e. no mix of ortho- and para- products as with electrophilic aromatic substitution).
In short, the roles of the aromatic ring and attacking species are reversed!**

The attacking species (CH₃O⁻) is the nucleophile, and the ring is the electrophile.

Since the nucleophile is the attacking species, this type of reaction has come to be known as nucleophilic aromatic substitution.

In nucleophilic aromatic substitution (NAS), all the trends you learned in electrophilic aromatic substitution operate, but in reverse.

The first trend to understand is that electron withdrawing groups (EWG's) dramatically increase the rate of reaction, not decrease it.

From this, it follows that the more EWG's there are, the faster the reaction.

For example, the rate of NAS for 2,4-dinitrophenyl chloride is about 10⁵ times faster than for p-nitrophenyl chloride. [note]

(I don't have a rate constant for 2,4,6-trinitrophenyl chloride readily available, but it is orders of magnitude faster still).

The Effect Of The Leaving Group

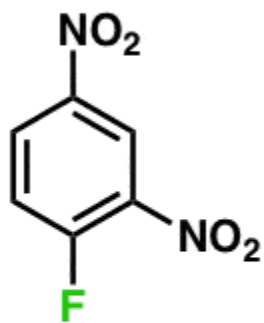
One of the most eye-opening aspects of nucleophilic aromatic substitution is noting that fluorine is often used as a leaving group. This is seen in Sanger's reagent for sequencing peptides, to take one example (more on that below).

After all, given the stern tones we instructors use in Org 1 on this subject, the words "FLUORINE IS NEVER A LEAVING GROUP IN SN2 AND SN1 REACTIONS" may as well have been carved on one of the stone tablets handed down to Moses on Mt. Sinai.

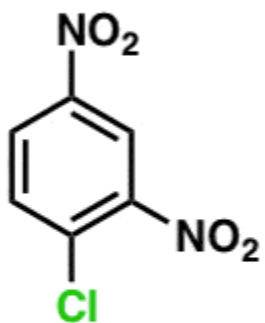
Here's a thought: if even a "bad" leaving group like fluorine works in nucleophilic aromatic substitution, then surely a "better" leaving group like bromine or iodine would work even better. Right?

This is a good hunch. It is also wrong – which does not make it a dumb idea, only that organic chemistry is deep.

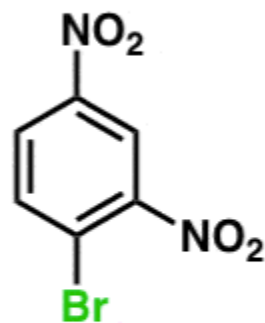
Fluorine is actually a better leaving group than Cl, Br, and I



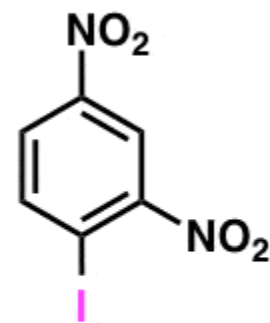
3300



4.3



4.3

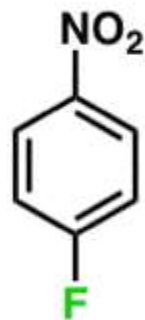


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suggests that C–F bond cleavage is not involved in the rate-determining step!

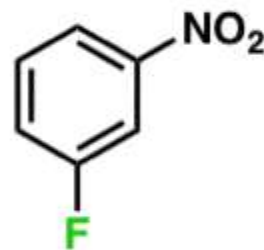
The effect of substitution pattern

Nucleophilic aromatic substitution on *p*-nitrofluorobenzene is faster than *m*-nitrofluorobenzene. **Why?**



p-fluoronitrobenzene

Fast

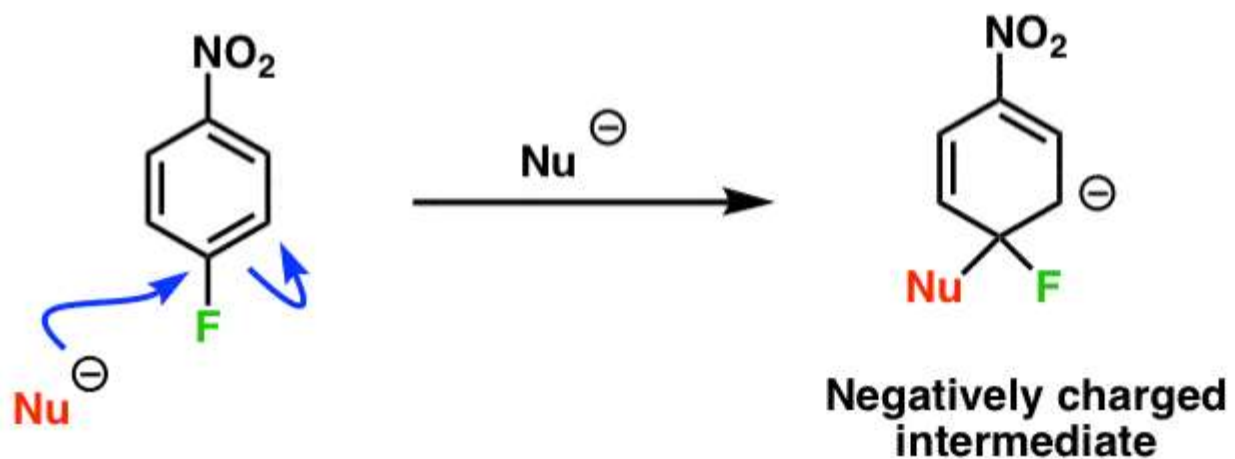


m-fluoronitrobenzene

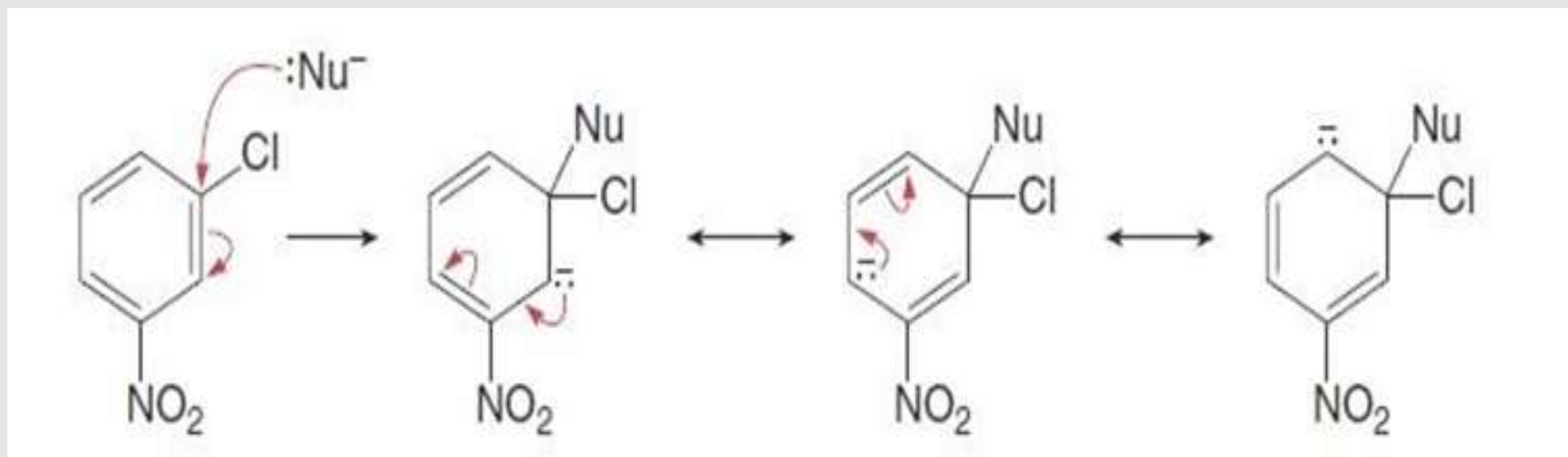
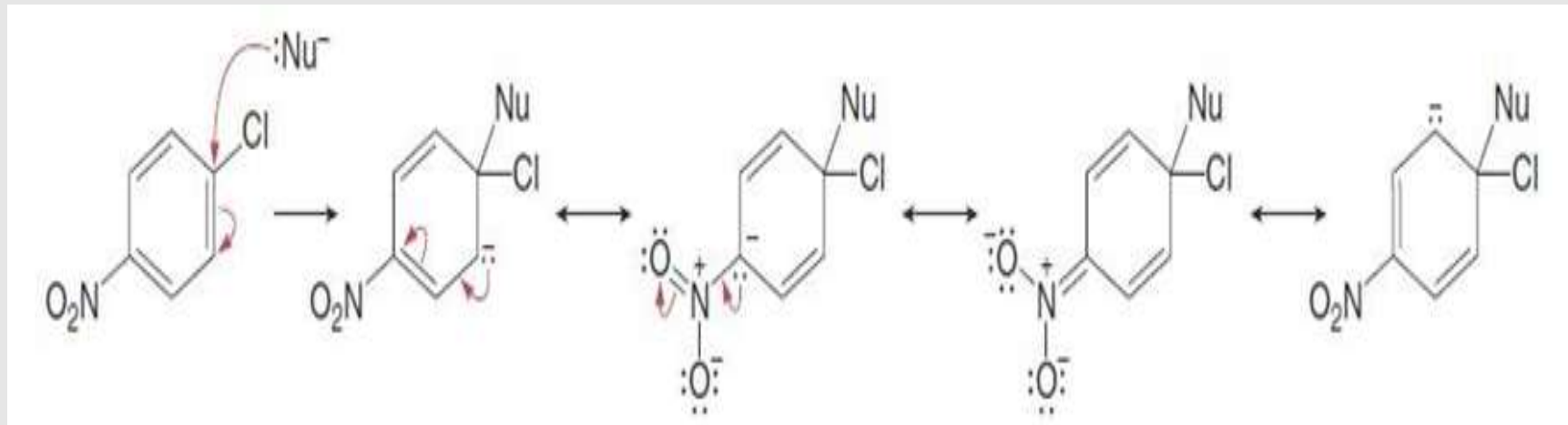
Slow

Nucleophilic Aromatic Substitution

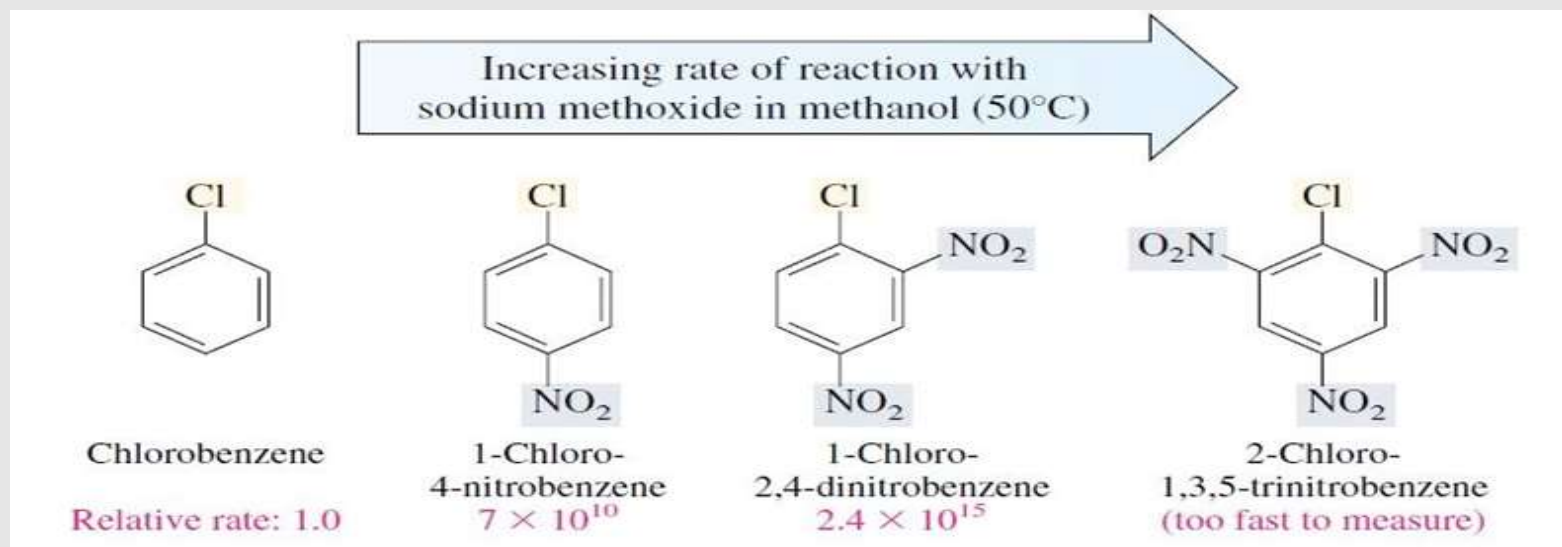
First step: Attack of electron-poor aromatic ring by nucleophile, forming a negatively charged intermediate:



- **The position of substituent that best facilitate the reaction is -ortho or -para substitution, this is because only then the negative charge acquired by the ring may get accommodated by the substituent as shown below. In contrast if the substituent is present on the meta position, no stabilization is achieved. This becomes clearer from the following resonating structures.**



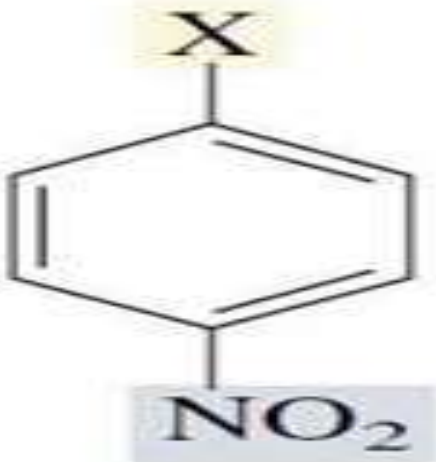
- Increasing the number of electron-withdrawing groups also increase the reactivity of the aryl halides drastically towards nucleophilic substitutions as shown below:



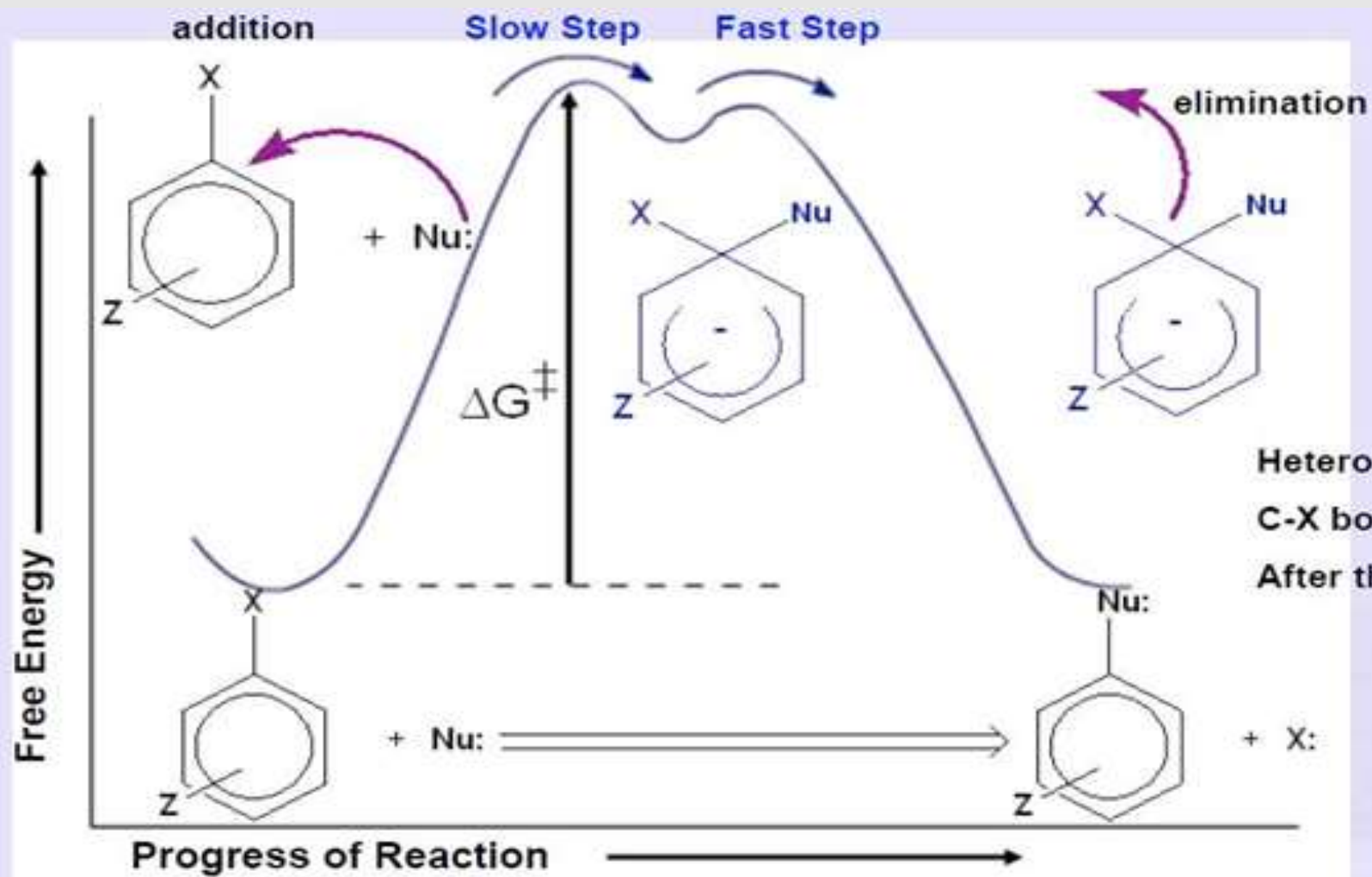
- **According to the Hammond postulate, electron-withdrawing groups stabilize the intermediate carbanion by lowering the energy of the transition state.**
- **Interestingly, increasing the electronegativity of the halogen atom in substrates increases the reactivity of the aryl halide.**

- **This trend is opposite to reactivity for aliphatic nucleophilic substitution, but the reason behind this is that a more electronegative halogen stabilizes the intermediate carbanion better by an inductive effect. Thus, aryl fluorides (ArF) are much more reactive than other alkyl halides, which contain less electronegative halogens**

- **The S_NAr reactions follow a second order kinetics according to the following equation:**
- **Rate = k[aryl halide] [nucleophile]**
- **Following data illustrates the significant differences observed between reactivity of alkyl halides.**

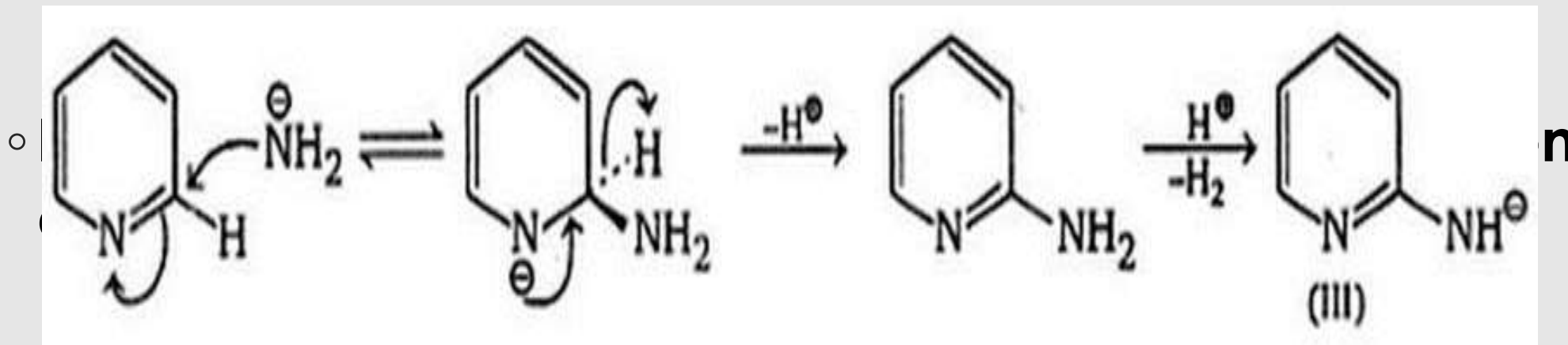
	Relative reactivity toward sodium methoxide in methanol (50°C):	
	X = F	312
	X = Cl	1.0
	X = Br	0.8
	X = I	0.4

As can be seen, the reactivity of substituted aryl fluoride is almost 780 times more as compared to aryl iodide. Following diagram presents the reaction co-ordinates for a general ArNuSub



The Chichibabin reaction : Amination of Pyridine

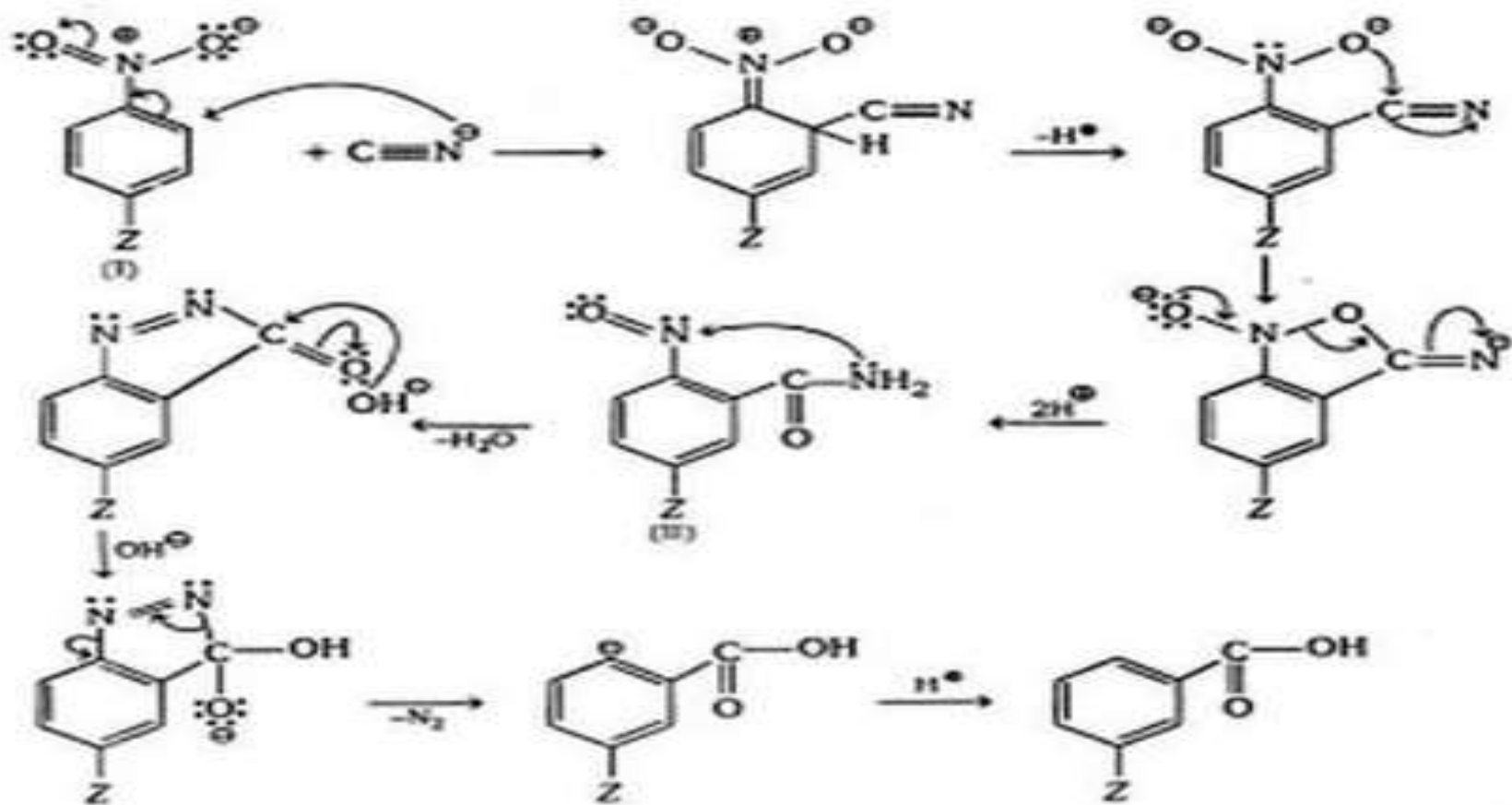
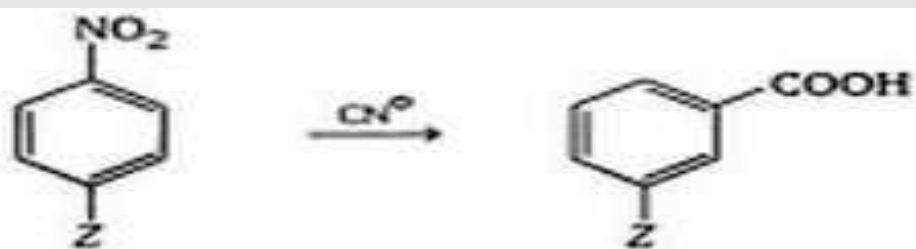
In the reaction pyridine is attacked by a strong nucleophile NH_2^- which displaces hydride ion. On treatment with water the desired 2-amino pyridine is obtained.



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VON RICHTER REARRANGEMENT

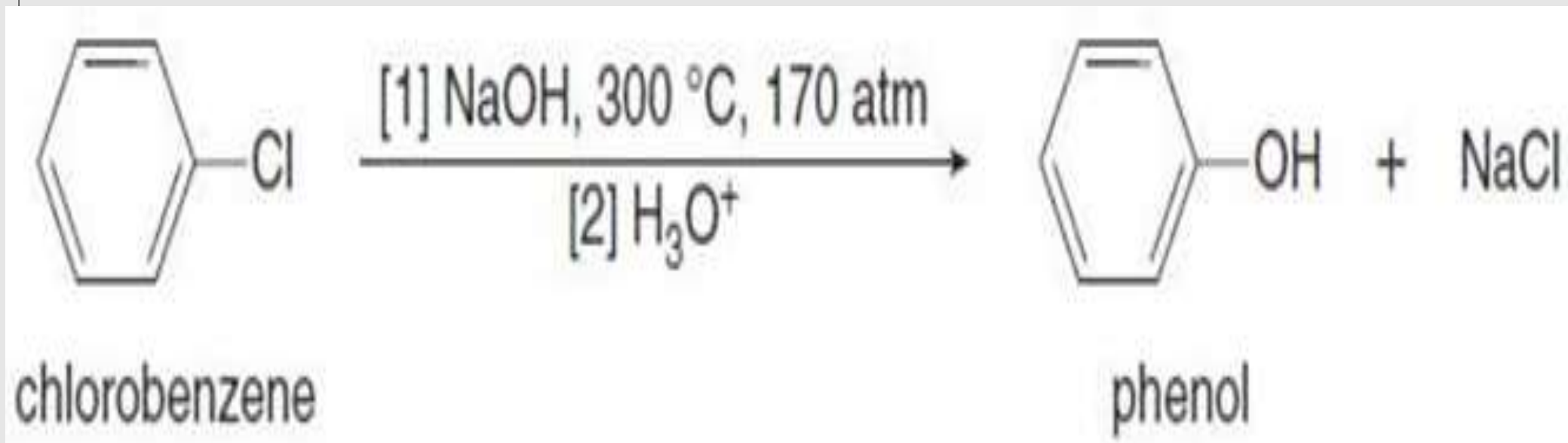
- **Another name reaction involving nucleophilic aromatic substitution is Von Richter rearrangement. It involves reaction of substituted aromatic nitro compounds with potassium cyanide to give rise to carboxylation of ortho position relative to the leaving nitro group.**



Elimination/addition Mechanism

- **Without a substituent it is hard for aryl halides to undergo nucleophilic substitution and only under drastic conditions they react with nucleophiles. For example, chlorobenzene can be converted into phenol by heating it with NaOH above 300 °C and at 170 atmosphere pressures.**

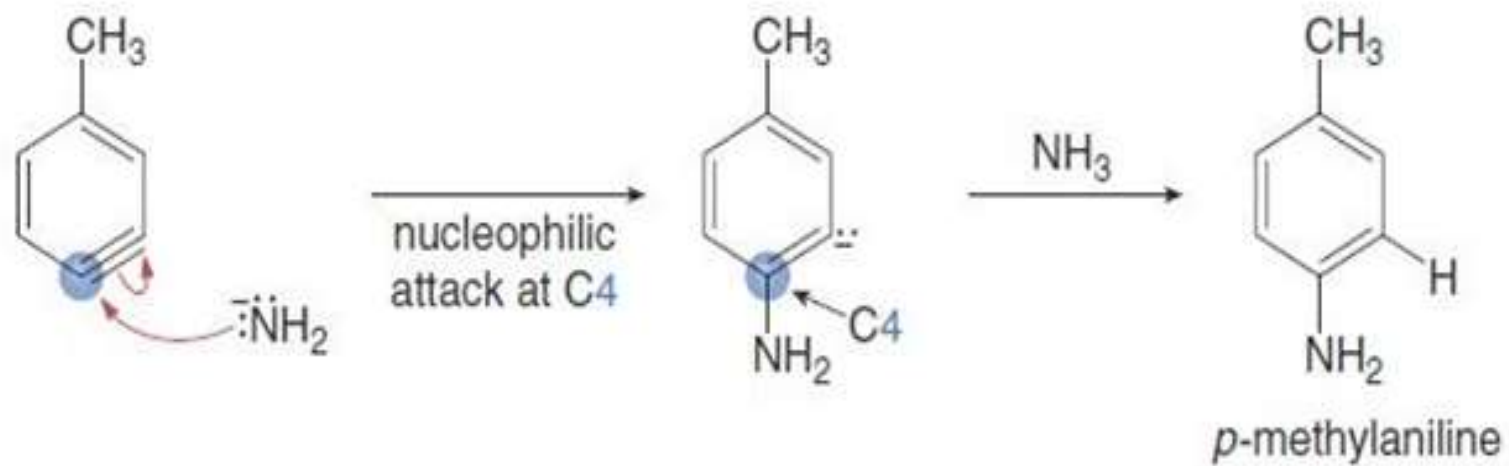
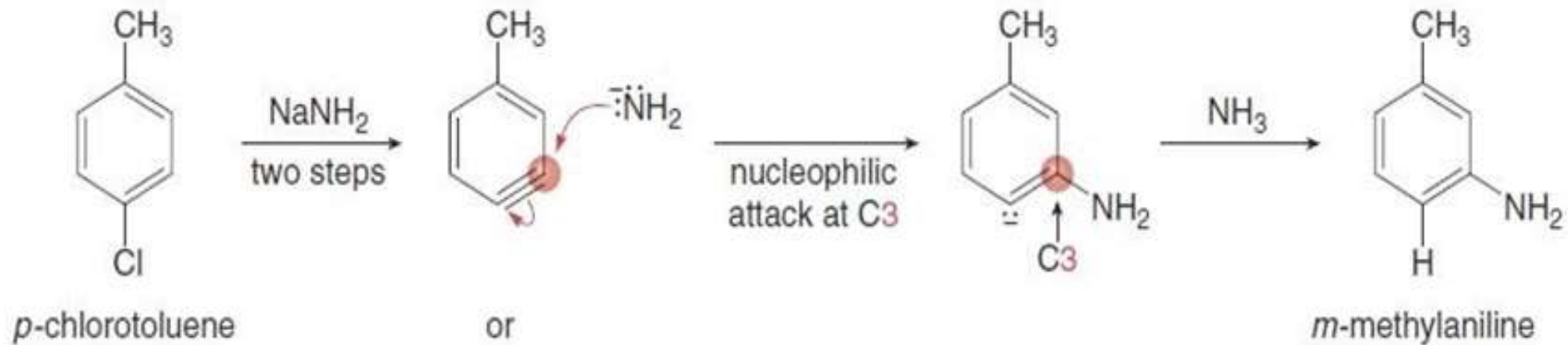
S_NAr1



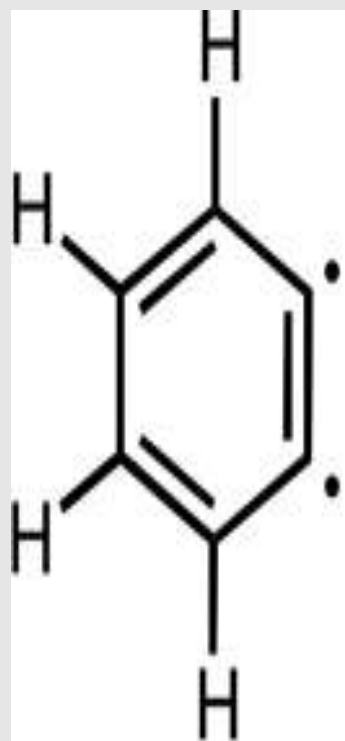
Reaction of p-chlorotoluene with strong base NaNH₂

Nucleophilic attacks on reaction intermediate (Benzyne) at either C3 or C4 position (meta- or para-position)

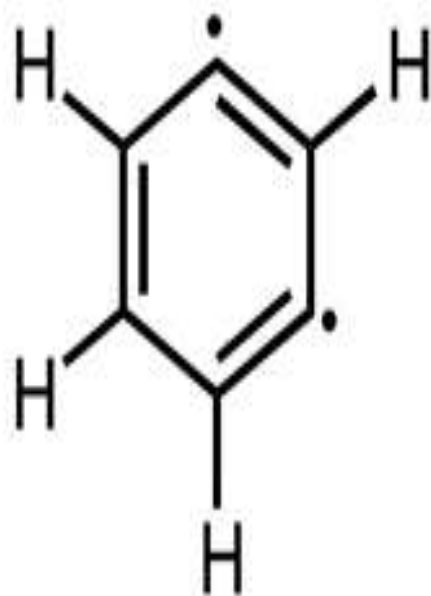
Reactions indicate that nucleophilic aromatic substitution by an elimination-addition mechanism lead to products with substitution on the carbon directly bonded to the leaving group or to the carbon adjacent to



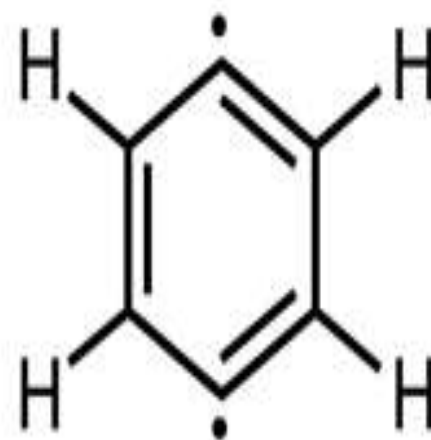
- **These elimination/addition reactions proceed via benzyne intermediates.**
- **The benzyne intermediate has a triple bond in benzene ring. The triple bond in benzyne is unusual as each carbon of the six-member ring is sp^2 hybridized.**
- **Benzyne is best described as to having a strained triple bond, a biradical representation is also useful and describes properties of the system.**



o-benzyne

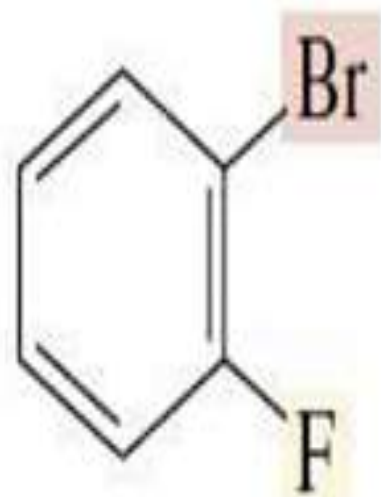


m-benzyne



p-benzyne

- **Benzyne intermediates are highly reactive and readily undergo Nucleophilic substitution reactions. Due to their high reactivity benzyne intermediates are synthetically useful to prepare various useful products. There are alternate ways to prepare benzyne and thus formed benzyne are used as diene component for the Diels Alder reaction**

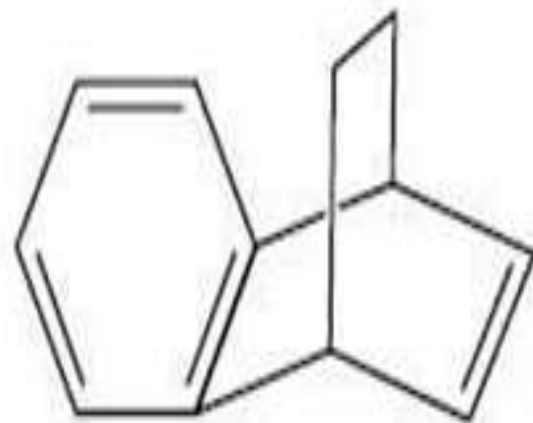


o-Bromo-
fluorobenzene

+



1,3-Cyclohexadiene



5,6-Benzobicyclo[2.2.2]-
octa-2,5-diene (46%)

SANDMEYER REACTION

SN1 mechanism represent first order nucleophilic substitution reactions, where, the rate of reaction depends only upon the nature of substrate and there is no effect of concentration of incoming nucleophile. Such substrates are rare to find unless highly substituted benzene rings are present or with diazonium salts. When primary aromatic amines are treated with nitrous acid (HONO) under cold conditions, they gave diazonium salts.

- **These diazonium salts are good substrates for reactions proceeding via SN1 mechanisms. This is because in diazonium salts the leaving group is di-nitrogen, which is an excellent leaving group, and on leaving it affords a positive charge on benzene ring, making it available for attack by incoming nucleophiles.**

Aniline with HNO₂

