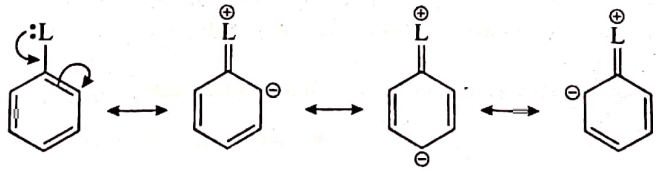
M.Sc. II Semester
Sub - Chemistry
Paper - II (Organic Chemistry)

7 AROMATIC NUCLEOPHILIC SUBSTITUTION

7.0 AROMATIC NUCLEOPHILIC SUBSTITUTION (ArSN)

The replacement of a hydrogen or a substituent on an aromatic ring by a nucleophile is known as aromatic nucleophilic substitution. Unlike aliphatic compounds having a nucleophilic group as a leaving group, aromatic compounds having the same group bonded directly to the aromatic ring do not undergo nucleophilic substitution under ordinary conditions.

The reason for this unusual reactivity of aromatic compounds is the presence of a lone pair of electrons or a π-bond on the key atom of the leaving group. As a result of delocalisation of this lone pair of electrons or the π-bond through conjugation with the π-electrons of the armatic ring, there is partial double bond character between the carbon of the ring and the key atom. Thus, the key atom becomes firmly bonded to the aromatic ring and cannot be replaced easily.



Another factor for the low reactivity is the nucleophilic character of aromatic rings because of the presence of electron cloud above and below the plane of aromatic rings. This shields the ring carbon from the attack of a nucleophile.

Under drastic conditions, *i.e.*, under high temperature or high pressure or both, in the presence or absence of catalysts, aromatic nucleophilic substitution may take place. On the other hand, properly substituted aromatic compounds (compounds having $-R$ or $-I$ group at *o* or *p* or both the positions, or aromatic nucleus having electronegative heteroatom (O, N, S, etc.) undergo nucleophilic substitution with less difficulty because $-R$ and $-I$ groups are activating groups for aromatic nucleophilic substitution. These groups decrease electron density on the aromatic ring and activate it for nucleophilic substitution.

Aromatic compounds undergo the following three types of nucleophilic substitution reactions:

1. ArSN1 reaction (Aromatic Substitution Nucleophilic Unimolecular)
2. ArSN2 reaction (Aromatic Substitution Nucleophilic Bimolecular)
3. Aromatic Nucleophilic Substitution Reaction via Benzynes (Arynes)

The mechanism of each of the above three reactions is similar to one of the aliphatic nucleophilic substitution mechanisms.

7.1 ArSN1 REACTION (AROMATIC SUBSTITUTION NUCLEOPHILIC UNIMOLECULAR)

ArSN1 reactions are very rare. These are mainly given by aromatic diazonium salts.

$$Ar\overset{\oplus}{N}\equiv N + \overset{\ominus}{Nu} \longrightarrow Ar—Nu + N_2$$

Mechanism :

Step I : $$Ar—\overset{\oplus}{N}\equiv N \overset{\text{Slow}}{\rightleftharpoons} \underset{\text{Aryl cation}}{\overset{\oplus}{Ar}} + N_2$$

Step II : $$\overset{\oplus}{Ar} + \overset{\ominus}{Nu} \xrightarrow{\text{Fast}} Ar—Nu$$

Aryl cation ($\overset{\oplus}{Ar}$) is highly unstable but nitrogen is highly stable, hence, very good leaving group. This makes the generation of aryl cation extremely easy.

Evidence in support of the above (ArSN1) mechanism

(i) The reaction rate is first order in diazonium salt and independent of the nature and concentration of the nucleophiles ($\overset{\ominus}{Nu}$) present.

(ii) That the first step is a reversible cleavage of carbon-nitrogen bond has been established by the observation that when $Ar\,{}^{15}\overset{\oplus}{N}\equiv N$ was the reacting species, recovered starting material also contained $Ar\overset{\oplus}{N}\equiv {}^{15}N$. This could be possible only when the nitrogen detaches from the ring and then reattaches.

(iii) The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage, *e.g.*, electron-releasing *m* substituents (OH, OMe, Me, etc.) increase the rate and electron-withdrawing and *m* substituents (COOH, NO_2, Cl, etc.) retard the rate of reaction.

Some examples of ArSN1 reactions of aromatic diazonium cation are given below :

$$Ar—\overset{\oplus}{N}\equiv N \begin{cases} \xrightarrow{H_2O} Ar—OH + N_2 + \overset{\oplus}{H} \\ \xrightarrow[\text{(halide ion)}]{X^{\ominus}} Ar—X + N_2 \\ \xrightarrow{N_3^{\ominus}} Ar—N_3 + N_2 \\ \xrightarrow{CH_3OH} Ar—OCH_3 + N_2 + \overset{\oplus}{H} \end{cases}$$

Presence of electron-donating group (+*R* group) at *ortho* or *para* or both positions increases the reactivity of substituted diazonium cation for ArSN1 reactions. Similarly electron withdrawing-groups at these positions decreases reactivity.

7.2 ArSN2 REACTION (AROMATIC SUBSTITUTION NUCLEOPHILIC BIMOLECULAR)

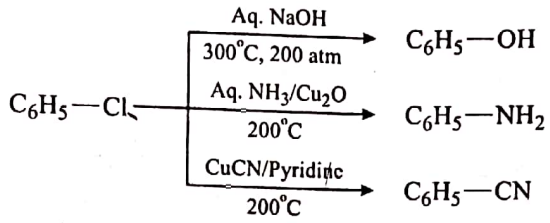
This reaction is the most common among aromatic nucleophilic substitution reactions. The reactivity of substrate for ArSN2 (also called as SNAr) reaction depends on the following factors:

(i) Reactivity $\propto$ leaving power of the leaving group

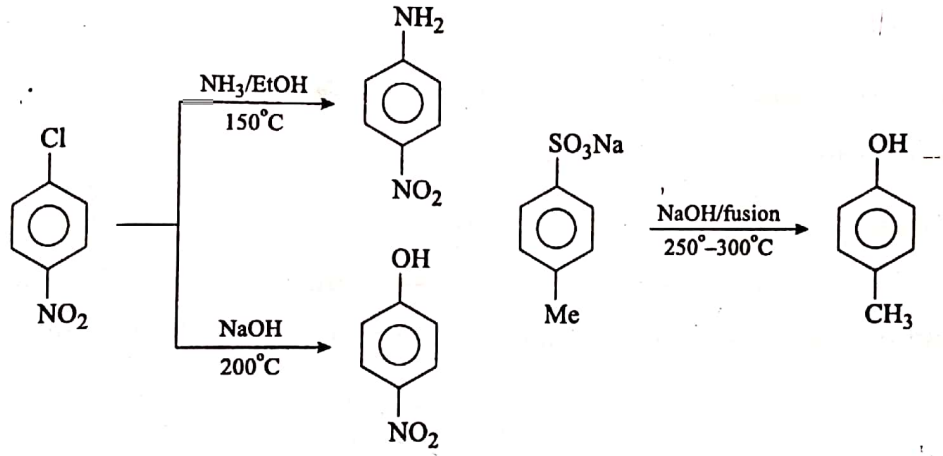
(ii) Reactivity $\propto -R$ and $-I$ powers of the group present at *o*- and/or *p*-position

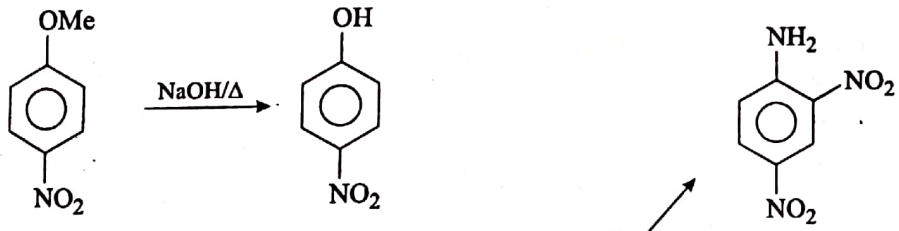
(iii) Reactivity ∝ electronegativity of the heteroatom of the ring
(iv) Nature of the solvent : Polar aprotic solvents favour the reaction.

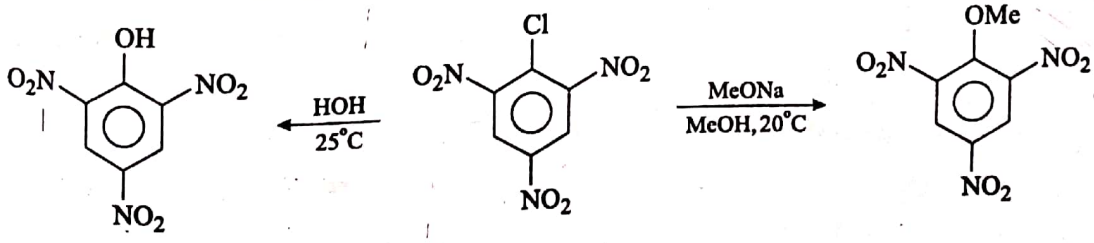
Some examples of ArSN2 reactions : With substrate having no activating group:

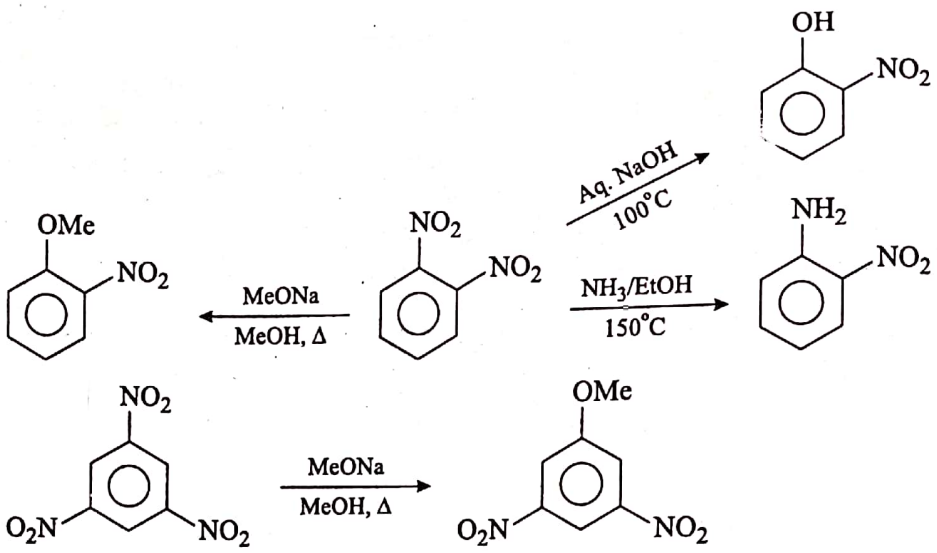


With substrates having activating group(s):

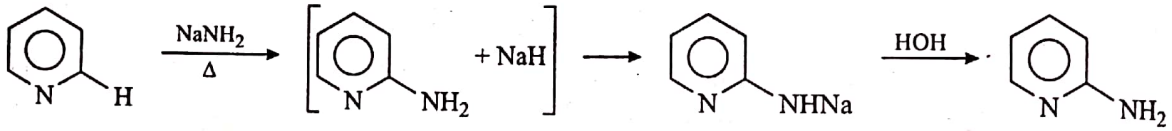




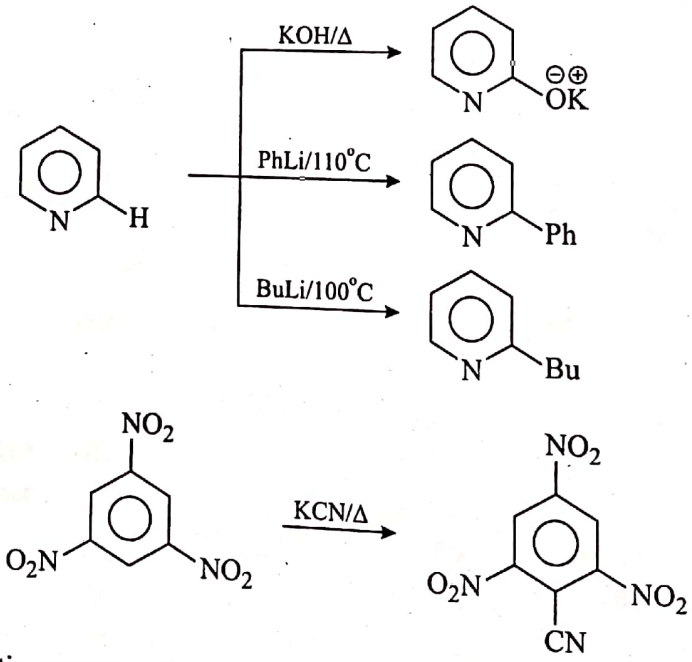




Displacement of hydride ion



This is called Tschitschibabin (chichibabin) reaction.

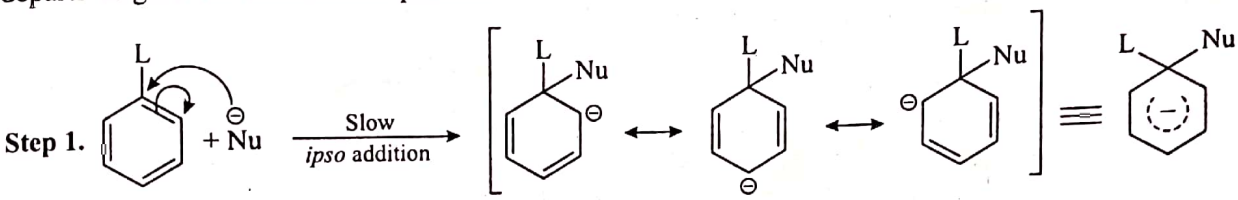


In general, aromatic compounds having the following leaving groups undergo ArSN2 reaction. It should be noted that all of these leaving groups depart as anions, except the $R_3\overset{\oplus}{N}$ group which departs as R_3N.

X (halogens), NO_2, N_3, $\overset{\oplus}{N}R_3$, *OR*, *SR*, *SOR*, SO_2R, SO_3H, OAr, H

ArSN2 mechanism

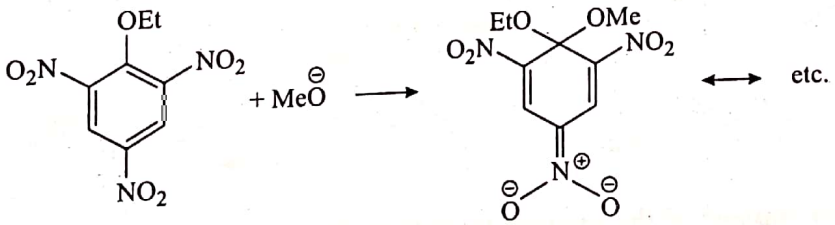
It resembles the arenium ion mechanism of aromatic electrophilic substitution. In both the cases the attacking species forms a bond with the substrate, giving an intermediate, and then the leaving group departs, *i.e.*, both involve an addition elimination process. ArSN2 reaction involves two steps, the first step is slow *ipso* addition by the nucleophile to give intermediate anion (Meisenheimer (salt) complex, σ-complex or cyclohexadienyl carbanion) which is stabilised by resonance, especially when $-R$ group(s) are present either at *o* or *p* or both positions. In the second fast step the leaving group departs to give the substitution product.



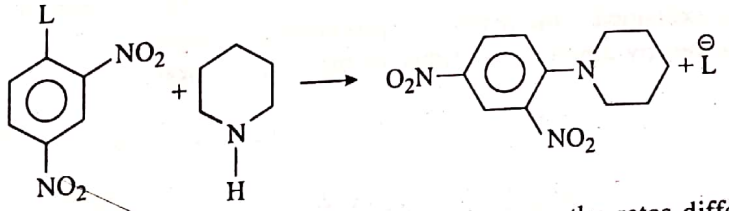
General aromatic nucleophilic ipso substitution

Evidence in support of the above mechanism :

(i) In many cases salts of the postulated intermediate (Meisenheimer salts) have been isolated and characterized.



(ii) In the reaction :

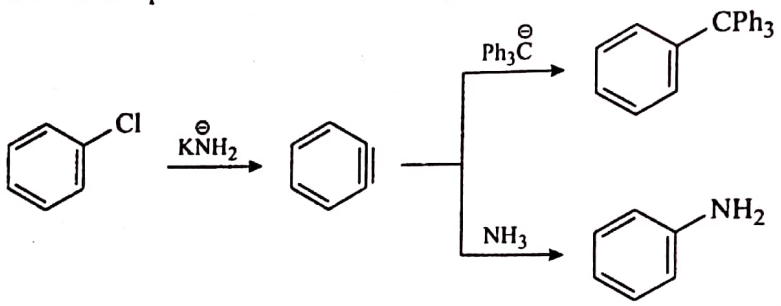


When *L* was Cl, Br, I, SOPh, SO_2Ph or *p*-nitrophenoxy, the rates differed only by a factor of about 5. This shows that the Ar—L bond is not broken in the rate-determining step. We do not expect the rates to be identical because the nature of *L* affects the rate at which a nucleophile attacks.

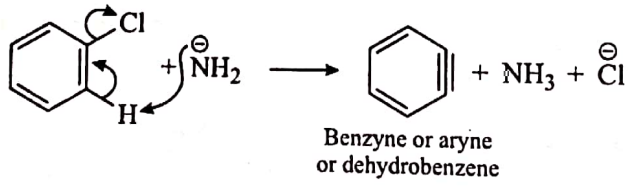
(iii) When $L{=}F$ the relative rate was 3300 (compared with 1 when $L = I$). The fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions shows that the mechanism is different from the SN1 and SN2 mechanism, where fluoro group is the poorest leaving group among the halogens.

7.3 AROMATIC NUCLEOPHILIC SUBSTITUTION REACTION VIA BENZYNES (ARYNES)

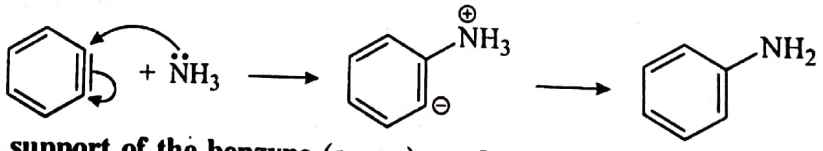
Unactivated aryl halides having at least one hydrogen in *ortho* position undergo nucleophilic substitution with a very strong base like KNH_2 or $NaNH_2$ in liquid ammonia. The reaction also occurs with bases such as PhLi and BuLi. This reaction proceeds via benzyne (aryne) intermediate and the mechanism is called benzyne (aryne) mechanism. An interesting feature of this reaction is that the incoming nucleophile does not necessarily take the position vacated by the leaving group. This is called *cine substitution*. In the presence of other nucleophiles mixed products are obtained.



Benzyne (Aryne) Mechanism : This mechanism involves elimination followed by addition, hence, it is also called elimination-addition mechanism of aromatic nucleophilic substitution.

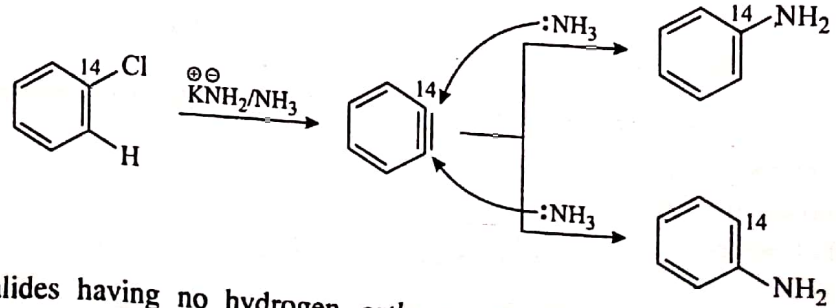


Benzyne or aryne
or dehydrobenzene

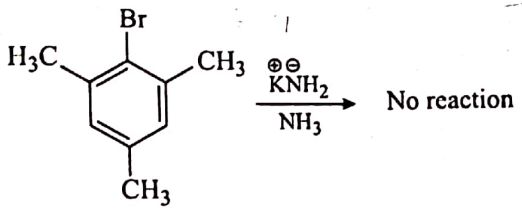


Evidence in support of the benzyne (aryne) mechanism :

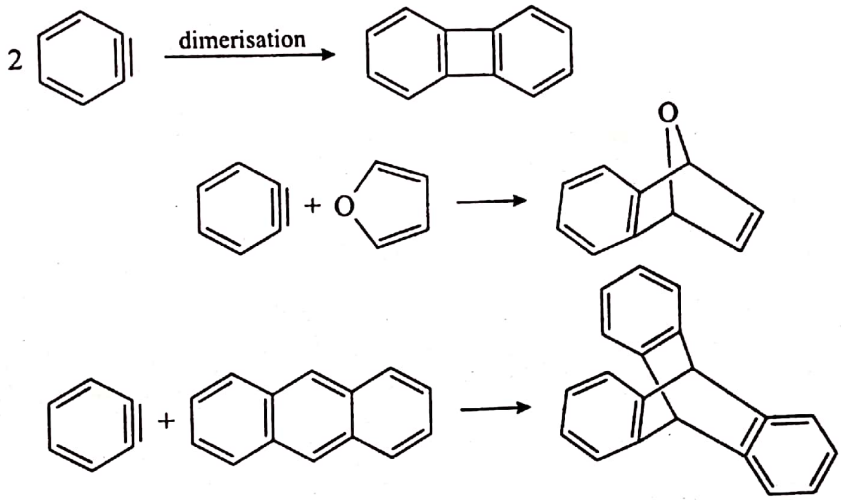
(i) 1—^{14}C-chlorobenzene on treatment with potassium amide in liquid ammonia gives almost equal amounts of 1—^{14}C-aniline and 2—^{14}C-aniline. The formation of these two products can only be explained if the reaction is proceeding through a symmetrical intermediate which can be attacked by ammonia at either of the two positions as follows:



(ii) Aryl halides having no hydrogen *ortho* to the halogen do not react under the same conditions.

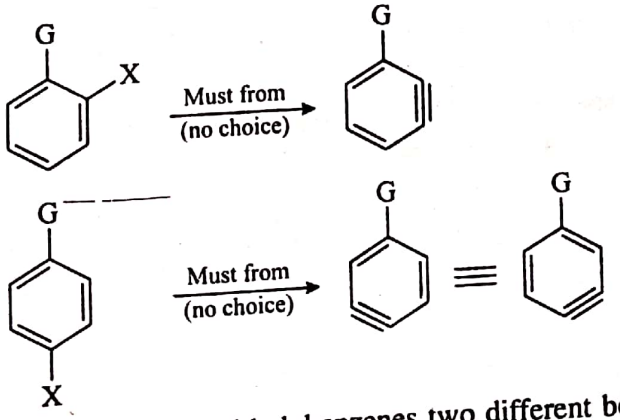


(iii) Benzynes are usually detected by spectroscopy or by their participation in dimerisation, and by trapping through cycloaddition to compounds such as furan and anthracene.

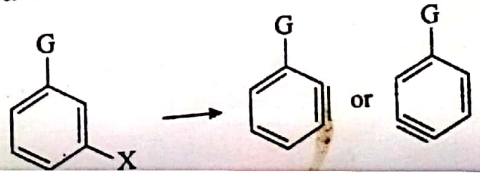


Prediction of major products in the reactions proceeding via benzynes (arynes) : In the case of *ortho* or *para* substituted halobenzenes two products are possible, while *meta* substituted halobenzenes may give three products. One can predict the major product in these product mixtures. Two factors govern the position of the incoming group in reactions involving benzyne intermediates:

1. **Direction in which benzyne is formed :** In the case of *ortho* or *para* substituted halobenzenes there is no choice:

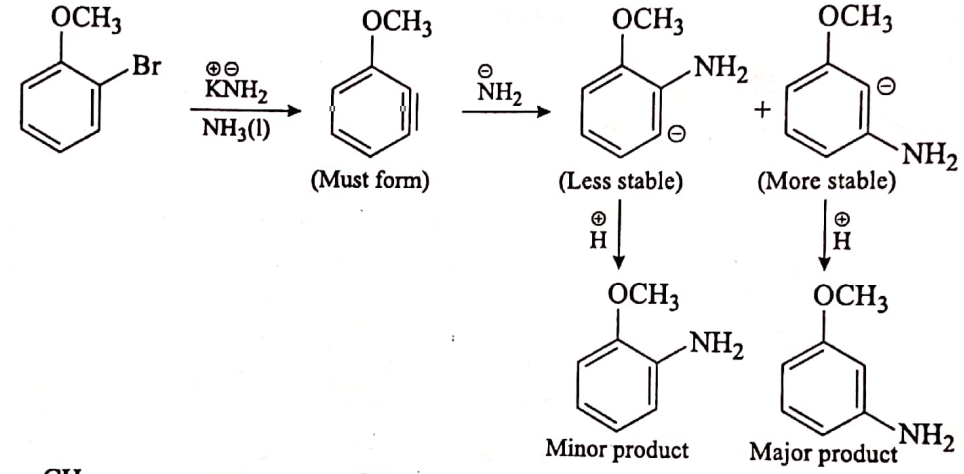


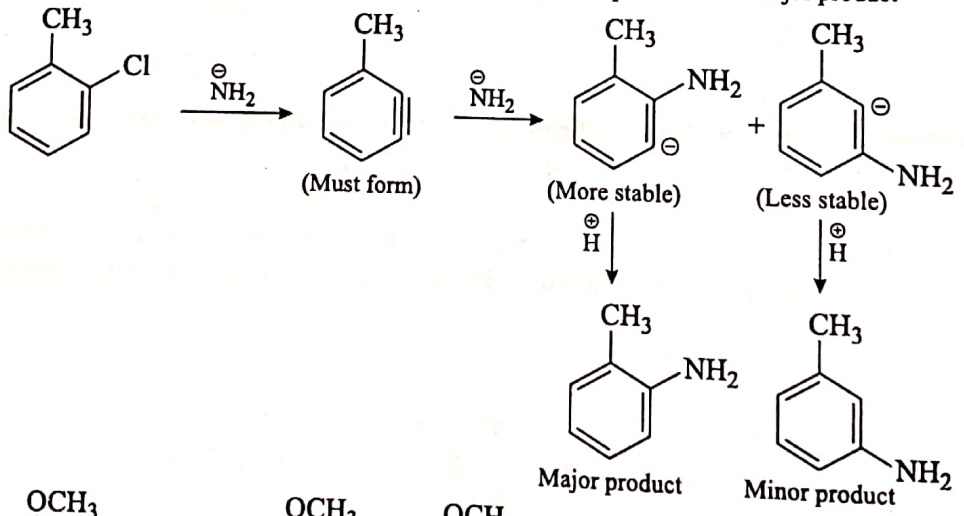
But in the case of *meta* substituted halobenzenes two different benzynes may be formed :

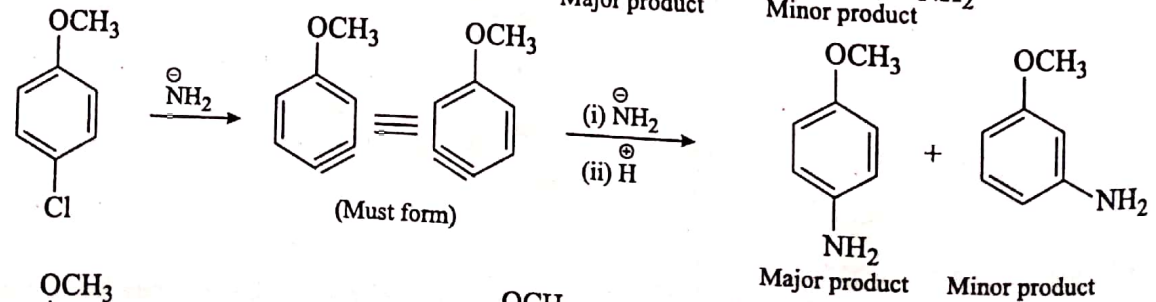


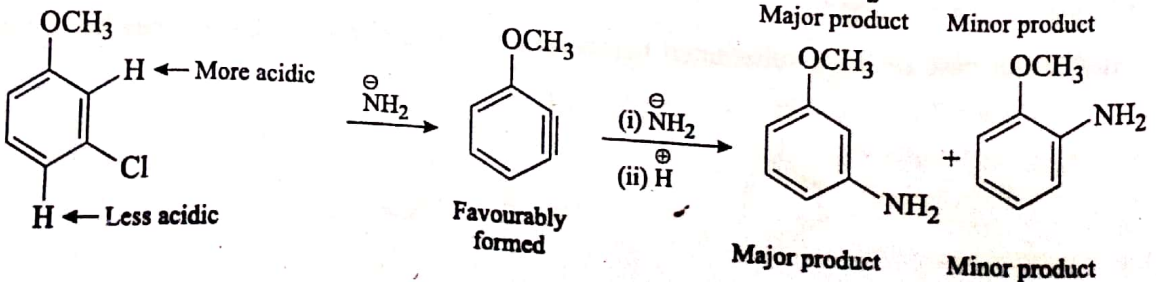
In such cases the more acidic hydrogen is removed, *i.e.*, if *G* is a *–I* group then it will favour removal of hydrogen *ortho* to it, when *G* is a *+I* group, it will favour removal of the hydrogen *para* to it.

2. The benzyne formed may be attacked at two positions. The favoured position of attack is that which gives stabler carbanion. If group *G* is a *–I* group then the more stable carbanion is that in which the negative charge is closer to the substituent (*G*). The following reactions illustrate the above generalisations:



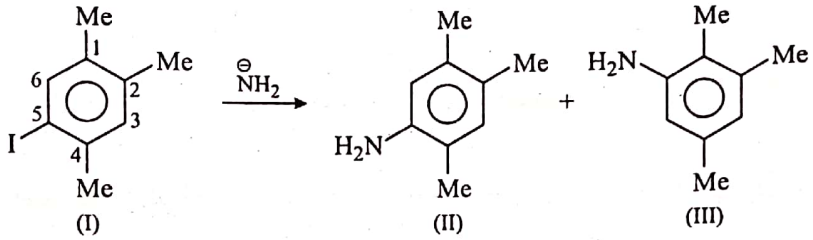






7.4 SRN1 MECHANISM

5-Iodo-1,2,4-trimethylbenzene **I** on treatment with KNH_2 in liquid NH_3 gives **II** and **III** in the ratio 0.63 : 1. The presence of an unactivated substrate, strong base and the formation of *cine* along



(I) (II) (III)

with normal substitution product indicate that the reaction proceeds through a benzyne mechanism. However, the 6-iodo isomer of **I** should have given **II** and **III** in the same ratio (because the same aryne intermediate would be formed in both the cases), but in this case the ratio of **II** to **III** was 5.9 : 1 (the chloro and bromo analogues did give the same ratio, 1.46 : 1 showing that the benzyne mechanism may be taking place there).

To explain the result of iodo analogue **I**, it has been proposed that besides the benzyne mechanism, the following mechanism (called as SRN1 mechanism) is also operating :

$$ArI \xrightarrow{\text{Electron donor}} ArI^{\bullet -} \longrightarrow Ar^{\bullet} + I^{-}$$

$$Ar^{\bullet} + NH_2^{-} \longrightarrow ArNH_2^{\bullet -} \xrightarrow{ArI} ArNH_2 + ArI^{\bullet -}$$

The reaction involves a chain mechanism. An electron donor is required to initiate the reaction. In the above case it was solvated electrons from KNH_2 in liquid NH_3.

Evidence in support of the SRN1 mechanism

(i) The addition of potassium metal (a good producer of solvated electrons in liquid NH_3) completely suppressed the cine substitution.

(ii) Addition of radical scavengers (which would suppress a free radical mechanism) led to **II** : **III** ratio much closer to 1.46 : 1.

(iii) Some 1,2,4-trimethylbenzene was found among the products, which could easily be formed by abstraction of H by Ar from the solvent liquid NH_3.

(iv) Besides, initiation by solvated electrons, SRN1 reactions have been initiated photochemically, electrochemically, and even thermally.

SRN1 reactions have wide scope. Cine substitution is not observed in these reactions. There is no requirement for activating groups or strong bases. Alkyl, alkoxy, aryl, and $\overset{\ominus}{C}OO$ groups do not interfere, although Me_2N, $\overset{\ominus}{O}$ and NO_2 groups do interfere.

7.5 FACTORS AFFECTING REACTIVITY IN AROMATIC NUCLEOPHILIC SUBSTITUTIONS

Effect of substrate structure : As we have noted, ArSN2 reactions are accelerated by electron-withdrawing groups, especially in the *o* and *p*-positions to the leaving group, and retarded by electron-donating groups. Heteroatoms of the ring are also strongly activating, *e.g.*, nitrogen, which is more activating when quaternized. The decreasing order of activating power of some groups in ArSN2 reaction is given below :

$\overset{\oplus}{N}H_3 > NO_2 > CF_3 > CN > SO_3H > CHO > CO > COOH > COOR > CONH_2 > F > Cl > Br > I$

Effect of leaving group : The following is an approximate decreasing order of leaving group power :

$$F > NO_2 > OTs > SOPh > Cl > Br > I > N_3 > \overset{\oplus}{N}R_3 > OAr, OR, SR, NH_2$$

Effect of the attacking nucleophile : The following is an approximate decreasing order of nucleophilicity :

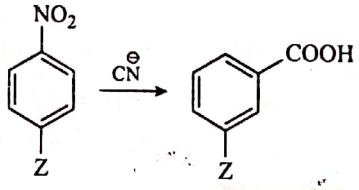
$\overset{\oplus}{N}H_2 > Ph_3\overset{\ominus}{C} > PhN\overset{\ominus}{H}$ (aryne mechanism) $> Ar\overset{\ominus}{S} > R\overset{\ominus}{O} > R_2NH > Ar\overset{\ominus}{O} > \overset{\ominus}{O}H > ArNH_2 > NH_3 > \overset{\ominus}{I} > \overset{\ominus}{Br} > \overset{\ominus}{Cl} > H_2O > ROH$

As in aliphatic nucleophilic substitutions, nucleophilicity is generally dependant on basicity, and nucleophilicity increases as the attacking atom moves down a coloumn of the periodic table.

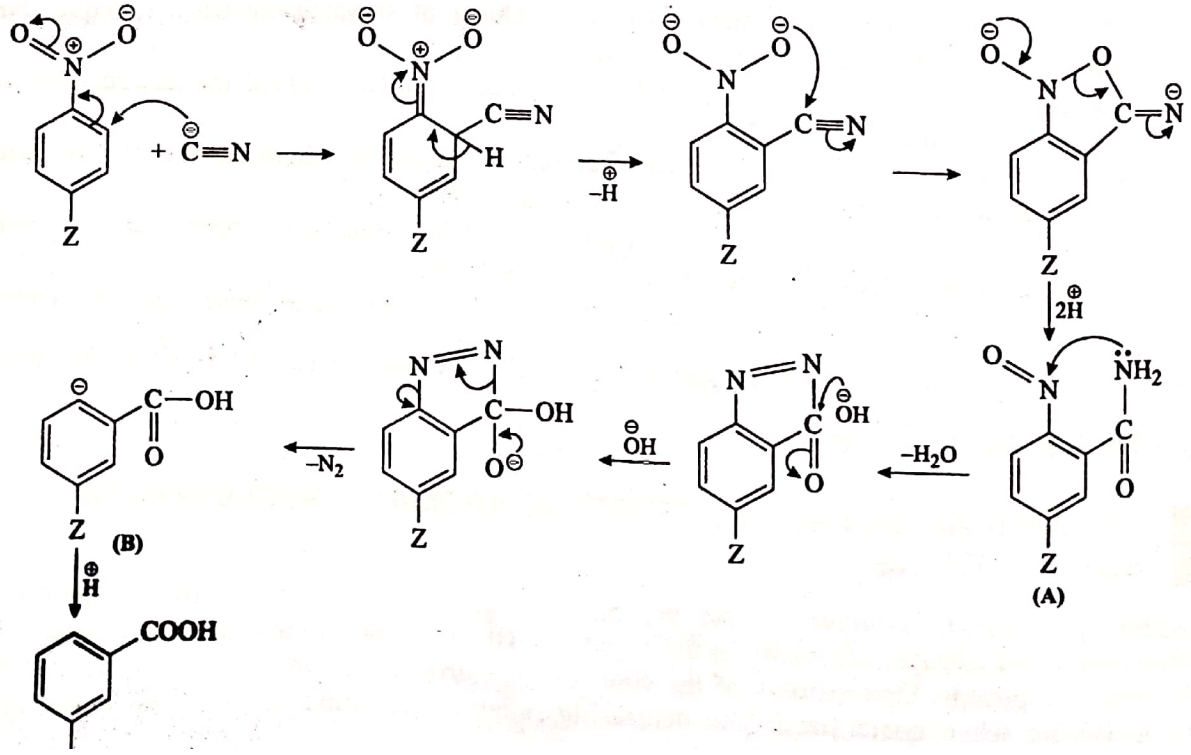
7.6 SOME IMPORTANT NAME REACTIONS INVOLVING AROMATIC NUCLEOPHILIC SUBSTITUTION MECHANISM

(1) von Richter rearrangement

When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters always *ortho* to the displaced group. This reaction is called ***von Richter rearrangement***, and is an example of cine substitution. As with other aromatic nucleophilic substitutions, the reaction gives best results when an electron-withdrawing group (Z) is present in *o*- and/or *p*-positions.



Mechanism :



Evidence in support of the above mechanism :

(i) N_2 is a major product of the reaction. This indicates that nitrogen-nitrogen bond must be formed during the course of the reaction.

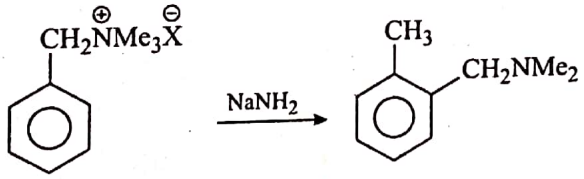
(ii) **(A)** is a stable compound which has been prepared independently, and it gives the product of von Richter rearrangement when subjected to the conditions of this reaction.

(iii) When the reaction was performed in $H_2{}^{18}O$ with $\overset{\ominus}{CN}$, the half oxygen in the product was labeled, showing that one of the oxygen of the carboxyl group came from the NO_2 group, and one from the solvent as required by the above mechanism.

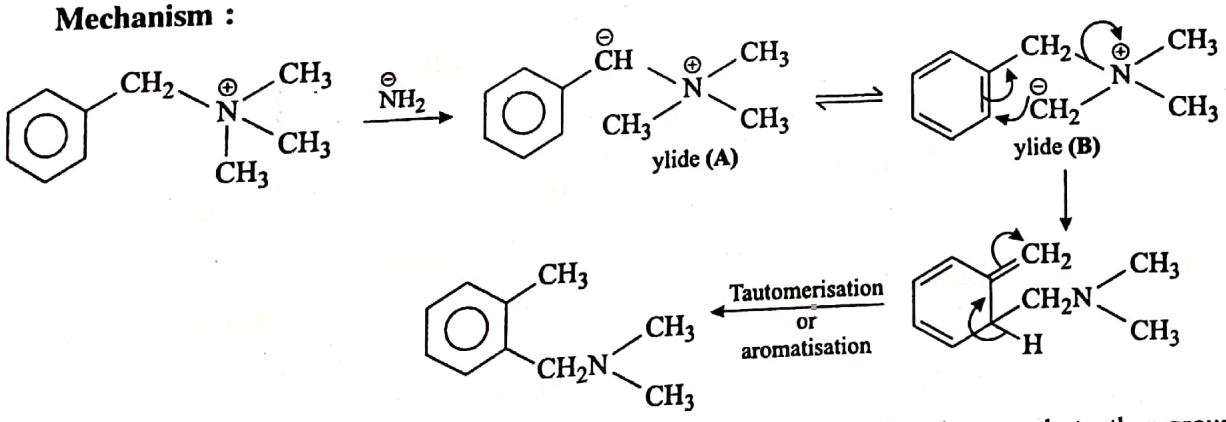
(iv) When the reaction is carried out in the presence of D_2O/C_2H_5OD, the carboxylic acid formed contains the deuterium at the position originally occupied by the NO_2 group. This confirms the formation of the species **(B)**.

(2) Sommelet-Hauser rearrangement

When benzylic quaternary ammonium salts are treated with alkali-metal amides, undergo a rearrangement called *Sommelet-Hauser* rearrangement. Since, the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an *ortho* position is blocked.

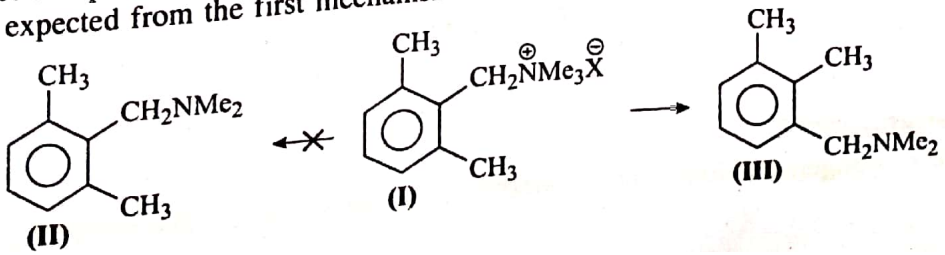


Mechanism :

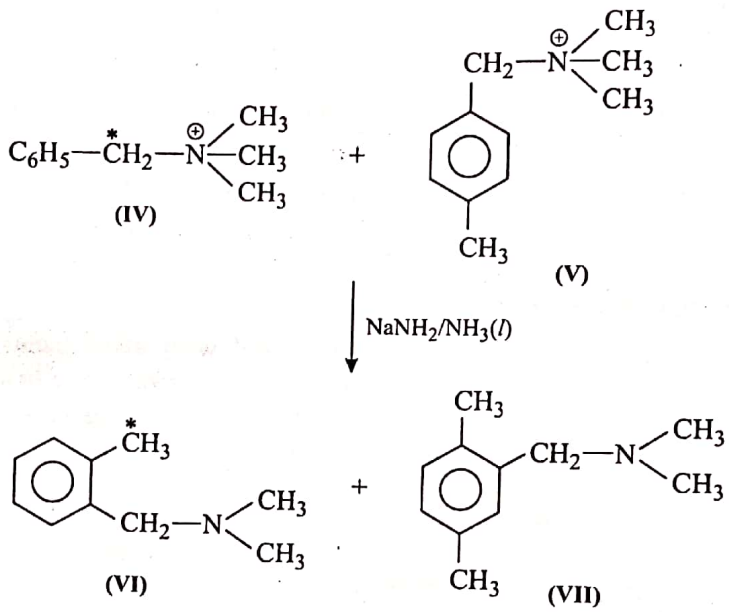


The reaction is most often carried out with three methyl groups on nitrogen, but other groups can also be used. However, if a β hydrogen is present, Hofmann elimination often competes. This mechanism is an example of [2,3] sigmatropic rearrangement.

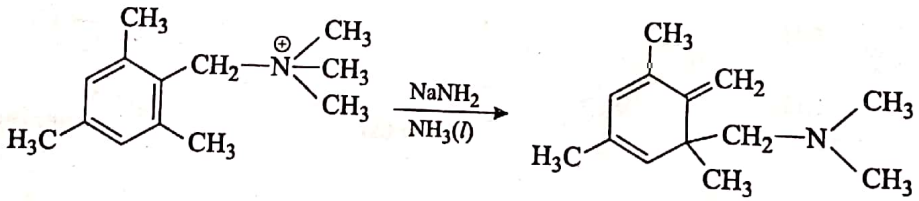
A mechanism in which a methyl group is detached from the nitrogen and then attaches itself to the ring is not acceptable. This is because in the following reaction **II** is not formed from **I**, but **III** is formed as expected from the first mechanism.



Crossover experiment showed that the Sommelet rearrangement is intramolecular in nature. This has been confirmed by isotopic labelling experiment. When **IV** and **V** are rearranged together, no radioactivity at all could be found in the product **VII**.

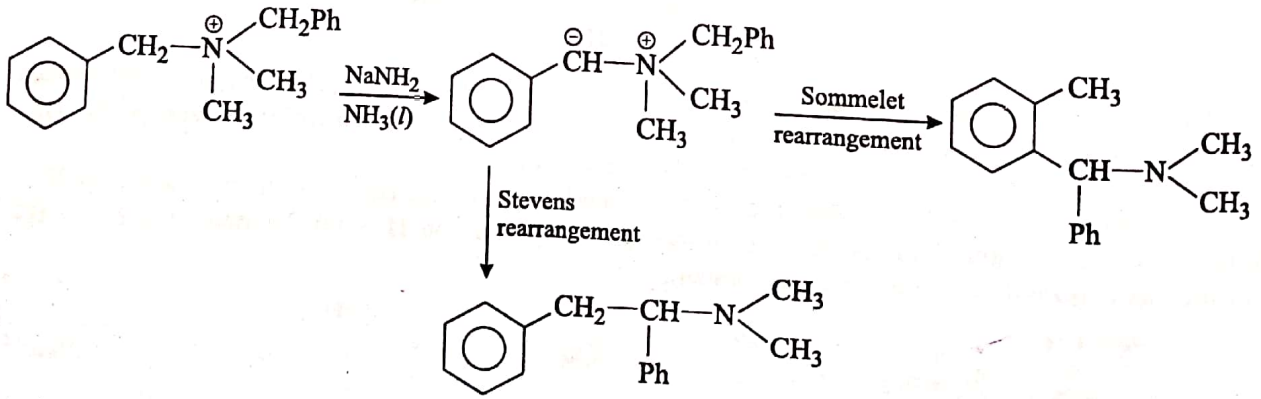


Exomethylene derivative **VIII** has been isolated. This clearly indicates the formation of the ylide **B** in the above mechanism.



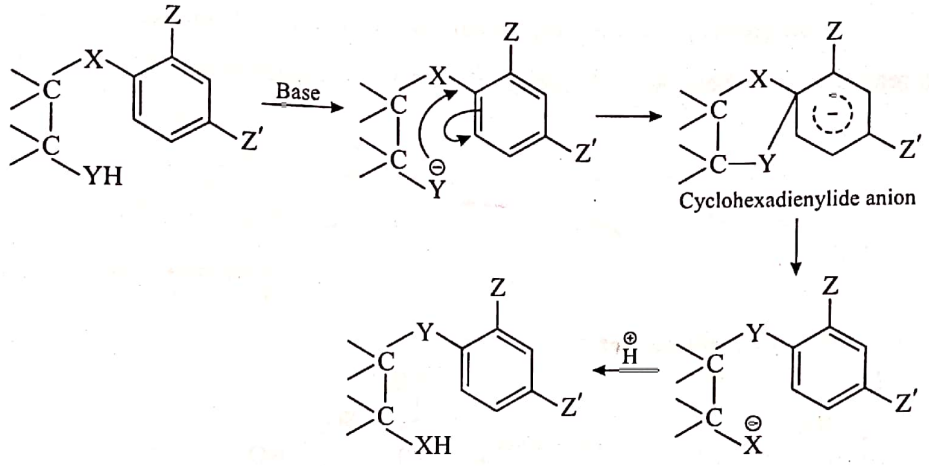
(VIII)

The main drawback of Sommelet rearrangement is that it is accompanied by Stevens rearrangement.

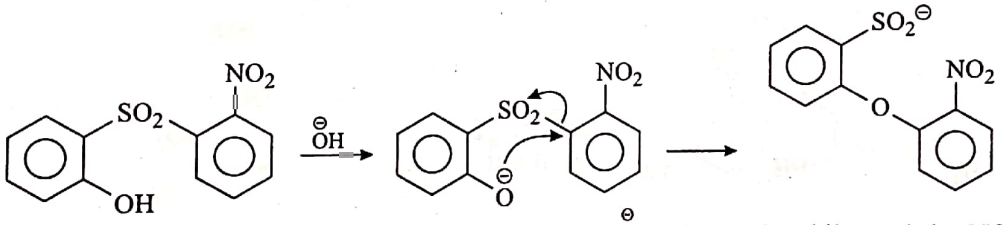


(3) Smiles rearrangement

A group of rearrangements following the mechanism given below is called *Smiles* rearrangement.



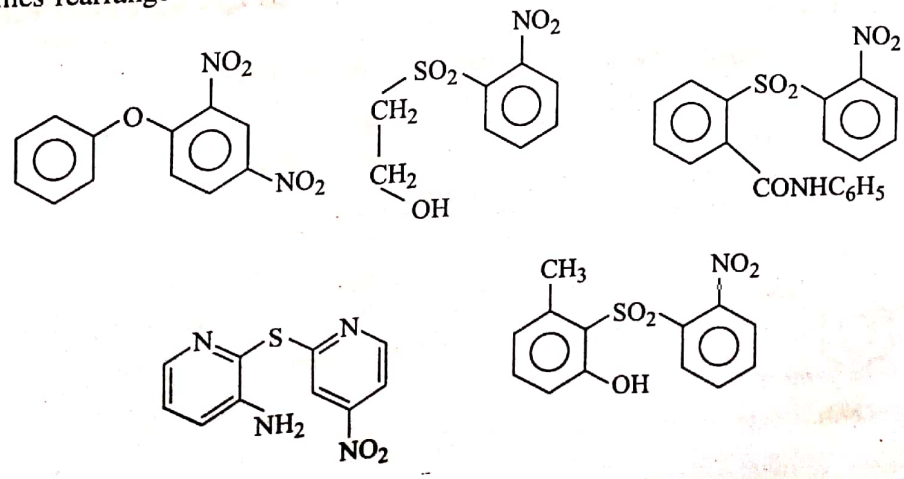
Smiles rearrangements are simply intramolecular nucleophilic substitutions. A particular example is given below:



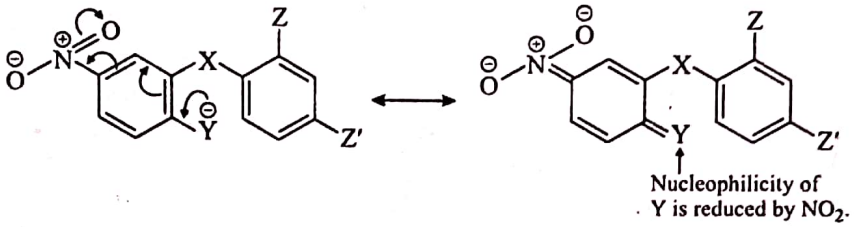
In the above example $ArSO_2$ is the leaving group, $ArO^{\ominus}$ is the nucleophile, and the NO_2 group activates the *ortho* position. In this reaction $X = S, SO, SO_2, O,$ or COO. $YH = OH, NH_2, NHR$ or SH. The reaction has also been carried out with $YH = CH_3$ (PhLi was used as the base here) ; in this particular case the rearrangement is known as Truce-Smiles rearrangement.

Z and Z' are activating groups for nucleophilic aromatic substitution reaction. Z and /or Z' should be an electron-withdrawing group such as $—NO_2$, —CN or CF_3 to stabilise the cyclohexadienylide anion formed.

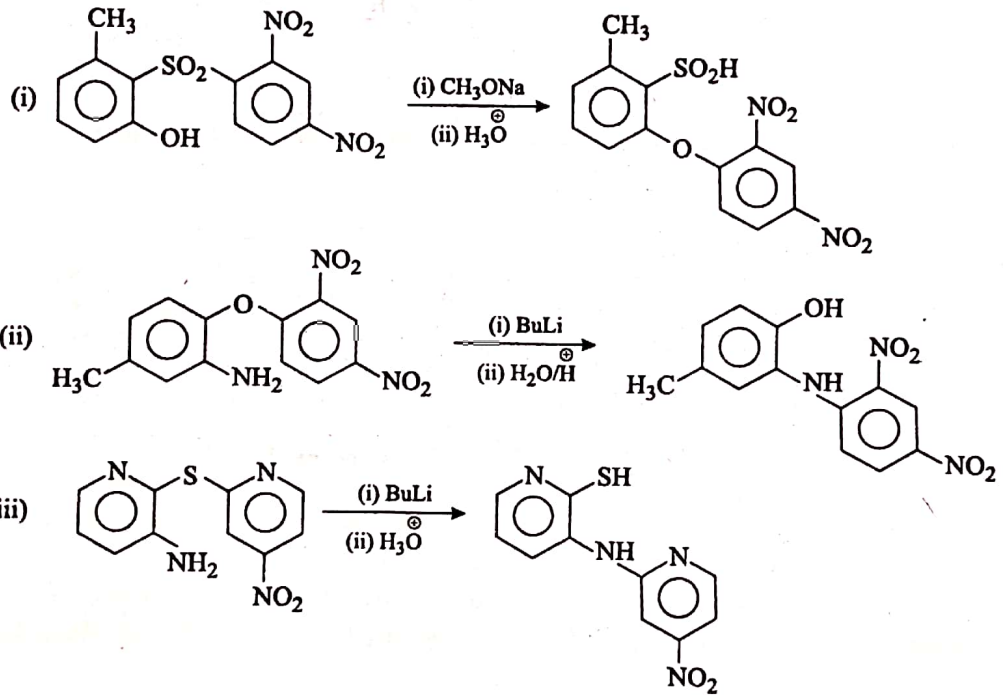
In this rearrangement the chain linking X and Y can be aromatic as well as aliphatic. The rearrangement also takes place in heterocyclic aromatic systems. Some examples of substrates that undergo Smiles rearrangement are given below :



The presence of an electron-withdrawing group *para* to the *YH* in the substrate retards the rate of the Smiles rearrangement because such groups reduce the nucleophilicity of $\overset{\ominus}{Y}$.



Examples of Smiles rearrangement :



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