CHAPTER 9

Aromatic Nucleophilic Substitution

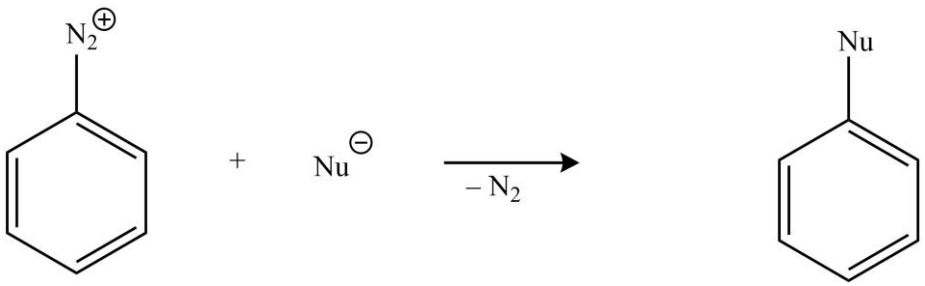
❖ The $ArSN_1$, $ArSN_2$, Benzyne and S_RN_1 Mechanisms

An aromatic nucleophilic substitution in organic chemistry may simply be defined as a chemical reaction where the nucleophile displaces a good leaving group, such as a halide, on an aromatic ring. The aromatic nucleophilic substitution can primarily occur via three different routes as given below.

➢ *$ArSN_1$ or Aryl Cation Mechanism*

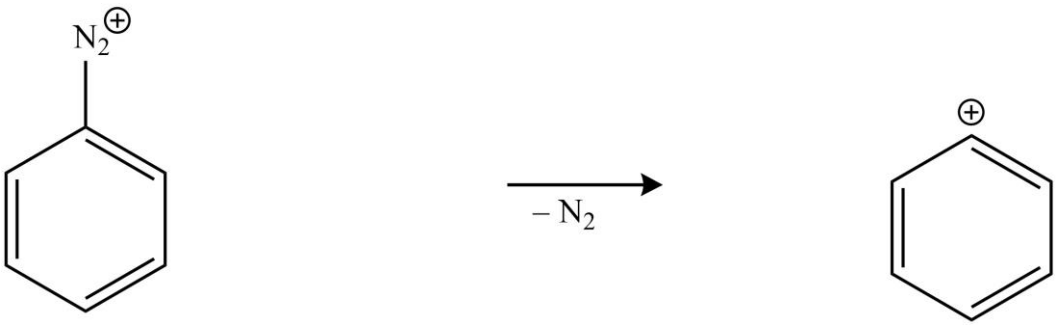
The unimolecular nucleophilic substitution on aromatic rings is mainly given by aromatic diazonium salts. The typical reaction of such type is given below.

Illustrative reaction: The typical reaction involving nucleophilic substitution in aromatic compounds is shown below.



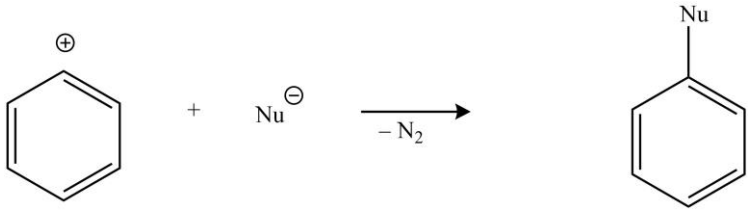
Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) Formation of aryl cation: Now although the aryl carbocation is highly unstable, its formation is still favored due to the high stability of dinitrogen (i.e., good leaving group).



Now although the aryl carbocation is highly unstable, its formation is still favored due to the high stability of dinitrogen (i.e., good leaving group).

ii) Attack by the Nucleophile:



Now since the faces of the carbocations formed are homotopic, the Nu^- can attack from either side to give the same product.

Salient Features: The main features of the mechanism involved in aromatic nucleophilic substitution unimolecular or $ArSN_1$ type reactions are given below.

i) $ArSN_1$ reactions follow first-order kinetics with the rate law

$$Rate = k[RX]$$

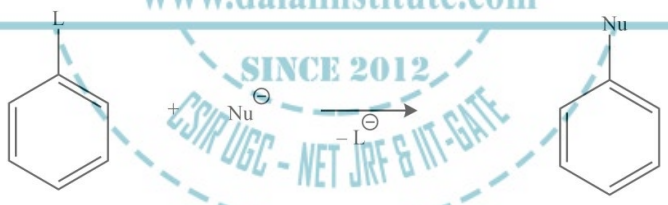
Where k is the rate constant and $[RX]$ represents the molar concentration of the substrate.

ii) The presence of $+R$ groups at *ortho* and *para* positions raises the reactivity of the substrate and vice-versa.

- ***$ArSN_2$ or Addition-Elimination Mechanism***

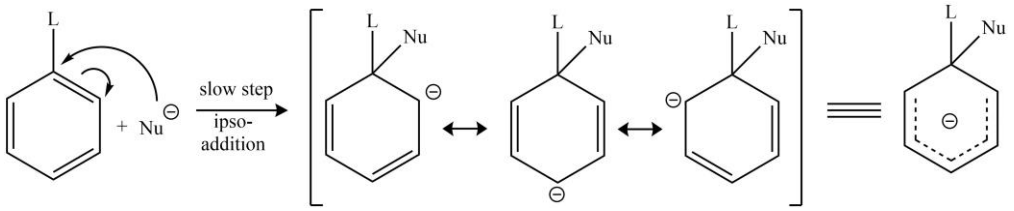
The bimolecular nucleophilic substitution on aromatic rings is most common among the class. The typical reaction of such type is given below.

Illustrative reaction: The typical reaction involving this type of mechanism is given below.



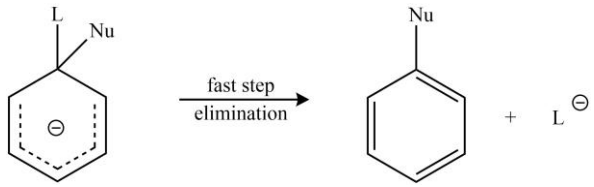
Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) ipso-addition of the nucleophile:



Now although an ion is no longer an aromatic species; however, it is relatively stable due to the delocalization of the negative charge over 3 carbon atoms by the pi system.

ii) Elimination of the leaving group:



Salient Features: The main features of the mechanism involved in aromatic nucleophilic substitution bimolecular or $ArSN_2$ type reactions are given below.

i) $ArSN_2$ reactions follow second-order kinetics with the rate law

$$Rate = k[RX][Nu]$$

Where k is the rate constant. The symbol $[RX]$ and $[Nu]$ represent the molar concentration of the substrate and attacking nucleophiles, respectively.

ii) The reactivity increases as the leaving group gets better.

iii) The rate of the substitution increases as the $-I$ or $-R$ effect of the groups attached *o*- and *p*-positions increases.

iv) The reactivity is also proportional to the electronegativity of the heteroatom (if any) in the ring.

v) The $ArSN_2$ reactions are favored in polar aprotic solvents.

- ***Aryne (Benzyne) or Elimination-Addition Mechanism***

The elimination-addition mechanism involves a highly unstable intermediate called benzyne (dehydrobenzene). A typical reaction of such type is given below.

Illustrative reaction:

Steps involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) First step is the elimination of proton ortho to the substituent present and formation of benzyne:

ii) Attack of amide ion on the benzyne intermediate:

iii) Abstraction of the proton from ammonia:

Salient Features: The main features of the mechanism involved in aromatic nucleophilic substitution via benzyne are given below.

i) At least one hydrogen must be present at ortho position in the inactivated aryl halide.

ii) The incoming group may or may not occupy the position vacated by the leaving group i.e. cine substitution.

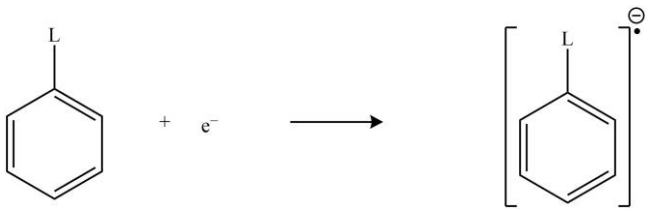
- ***Substitution Radical Nucleophilic Unimolecular ($S_{RN}1$)***

Radical-nucleophilic aromatic substitution or $S_{RN}1$ in organic chemistry is a type of substitution reaction in which a certain substituent on an aromatic compound is replaced by a nucleophile through an intermediary free radical species.

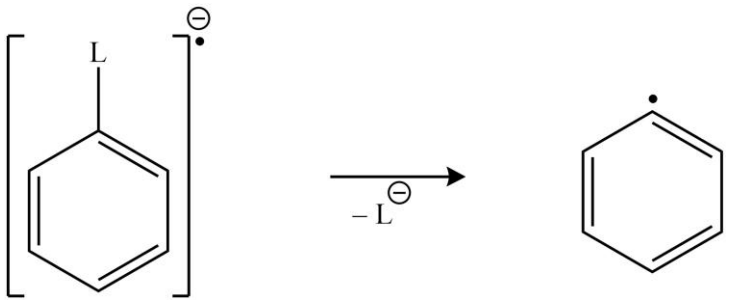
Illustrative reaction:

Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) Formation of radical anion: The aryl halide accepts an electron from a radical initiator to form a radical anion.



ii) Transformation of radical anion into aryl radical:



iii) Attack of the nucleophile on the aryl radical:

iv) Transfer of electron to new aryl halide:

Salient Features: The main features of the mechanism involved in S_RN1 (substitution radical nucleophilic unimolecular) type reactions are given below.

i) $S_{RN}1$ reactions follow first-order kinetics with the rate law

$$Rate = k[RX]$$

Where k is the rate constant and $[RX]$ represents the molar concentration of the substrate.

ii) The phenyl radical can also abstract any loose proton to form arene in a chain termination reaction to yield the final product.

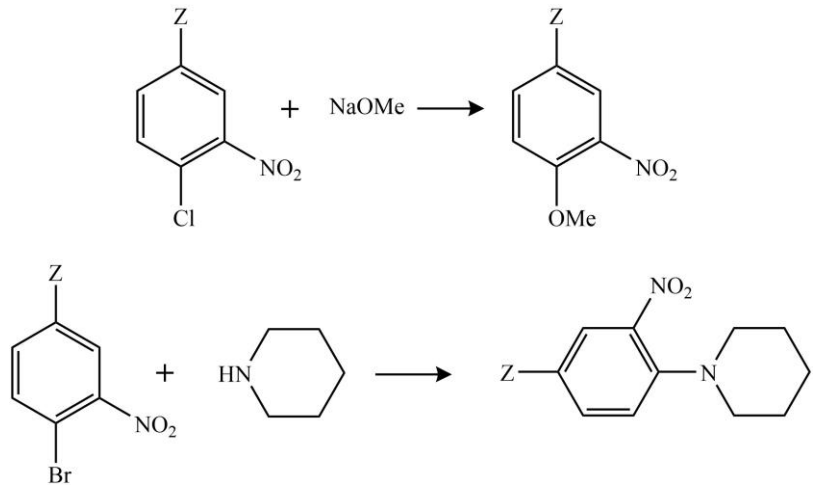
❖ Reactivity – Effect of Substrate Structure, Leaving Group and Attacking Nucleophile

In this section, we will discuss the effect of substrate structure, leaving the group and attacking nucleophiles on the reactivity of nucleophilic substitution in aromatic compounds.

➢ *Effect of Substrate Structure on the Reactivity of Aromatic Electrophilic Substitution*

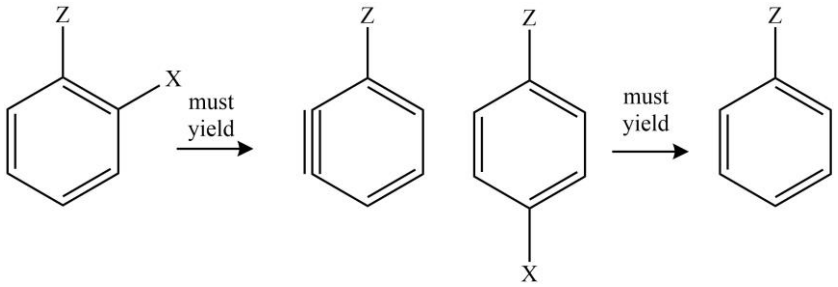
Just like the case of aromatic electrophilic substitution, substrate structure also affects the reactivity of aromatic nucleophilic substitution w.r.t orientation as well as ring-activation. However, orientation-effect was of more importance in the electrophilic case four or five hydrogens were able that act as leaving groups in comparison to the nucleophilic-case where the typical number of leaving group one. Consequently, substrate reactivity is primarily studied w.r.t other molecules rather than the same species.

Aromatic nucleophilic substitution reactions are typically opposed by electron attracting groups but enhanced by electron-withdrawing groups mainly at ortho and para positions to the leaving group, which is just the reverse order for electrophilic substitutions. Therefore, all the groups can be arranged in ascending or descending order of their activating (or deactivating) abilities.

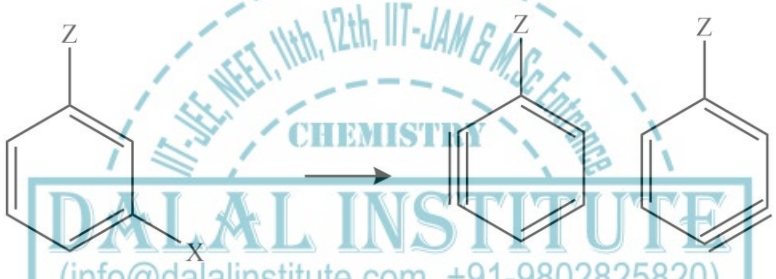


Groups with nitrogen atoms activating in nature w.r.t to *o*- and *p*-position with N_2^+ as the strongest activator. Also, $-NO_2$ is the most common activating group; whereas 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides are considered as the most common substrates. Furthermore, substrates without activating groups are largely useless to serve in $ArSN_{1,2}$ pathways, which can be attributed to the presence of 2 antibonding electrons in the ring. If attached groups are electron-withdrawing, they can activate the reaction by withdrawing electron density, and therefore, will stabilize the transition states (or intermediate). Aromatic electrophilic substitutions of type $ArSN_{1,2}$ are also supported if a transition metal is connected to the aromatic ring. Finally, the Hammett equation can also be modified for aromatic electrophilic substitution with the difference of σ^- instead of σ^+.

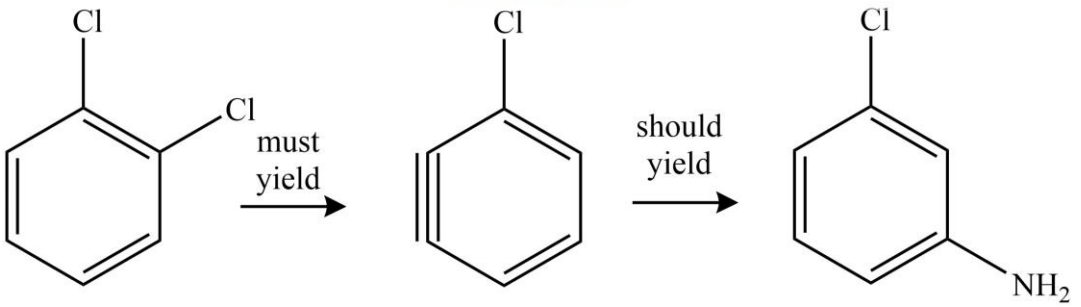
As far as the benzyne pathway is concerned, the reactivity w.r.t to the substrate can be factored in categories; one is the direction the aryne forms in, and the second is the presence of groups at ortho or para positions to the leaving group.



However, if the aryne substrate is *m*-substituted, the nucleophilic substitution can occur via two different routes as shown below.



These types of attacks occur via the removal of more acidic hydrogen; and because the acidity is correlated to the magnitude of field effect of the −Z group, we can conclude that Z with more electron-attracting character will support the removal of the o-hydrogen whereas the Z with electron-donating character will elimination of the *p*-hydrogen atom. On the other hand, the other route says that though the aryne attacked at two sites, the favored site for the nucleophile to attack will be the one that gives rise to a stabler carbanion (which is also a function of Z's field effect).



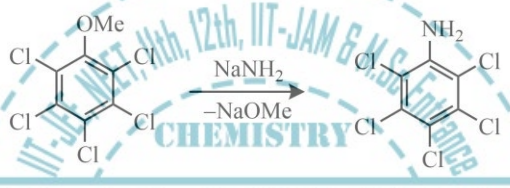
In other words, we may conclude that the carbanion with the negative charge closer to Z will be more stable than others.

➢ ***Effect of Leaving Group on the Reactivity of Aromatic Electrophilic Substitution***

Typical leaving groups for nucleophilic substitutions in aromatic compounds are X^- (halides), sulfonate, sulfate, NR_3^+, etc., which also act as a leaving-group for nucleophilic substitution in aliphatic compounds. Nevertheless, some groups are common; for instance, OAr, SO_2R, NO_2, OR, and SR, which do not act as leaving-group in aliphatic compounds but exclusively in aromatic systems. The typical order of leaving group power in aromatic nucleophilic substitution is given below.

$$F > NO_2 > OTs > SOPh > Cl > Br > I > N_3 > NR_3^+ > OAr, OR, SR, NH_2$$

It is obvious from the order given above that F and NO_2 are exceptionally good leaving groups in the aromatic nucleophilic substitution. Nonetheless, it should also be kept in mind that a better leaving group doesn't always lead to the preferred product because the nature of attacking nucleophile also decide the final departed result. For example, Cl is better a better leaving group than OR but the attack of NH_2^- on $C_6Cl_5OCH_3$ always results in $C_6Cl_5NH_2$ which is contrary to expectations.



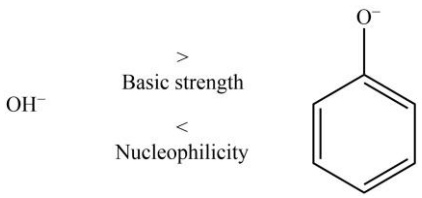
Routinely, the formation of an inorganic ester can also make OH act like a leaving group. It can also be seen that leaving group order give here different than aliphatic nucleophilic substitution because the first step (rate-determining) in the present case is assisted by prevalent $-I$ effects.

➢ ***Effect of Attacking Nucleophile on the Reactivity of Aromatic Electrophilic Substitution***

Just like the order of leaving groups, the manifestation of a universal nucleophilicity order is very hard; though an approximation can still be made.

$$NH_2 > Ph_3C > PhNH^- > ArS > RO > R_2NH > ArO > OH > ArNH_2 > NH_3 > I > Br > Cl > H_2O > ROH.$$

The nucleophilic strength also depends upon the base strength and shows an increase we select the attacking atom more down the group. Nevertheless, like other physical concepts, some exceptions are always present like a stronger basic character of OH than ArO but weaker nucleophilicity.



It is also worthy to remember that even though the nucleophilicity order is not invariant, it still finds application in a wide range of synthetic and practical applications including the assignment of electrophilicity parameters in the case of electron-short heteroarenes.

❖ The von Richter, Sommelet-Hauser, and Smiles Rearrangements

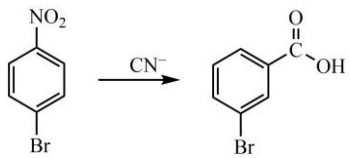
In this section, we will discuss some common types of rearrangement reactions that involve aromatic electrophilic substitution.

➢ *Von Richter Reaction*

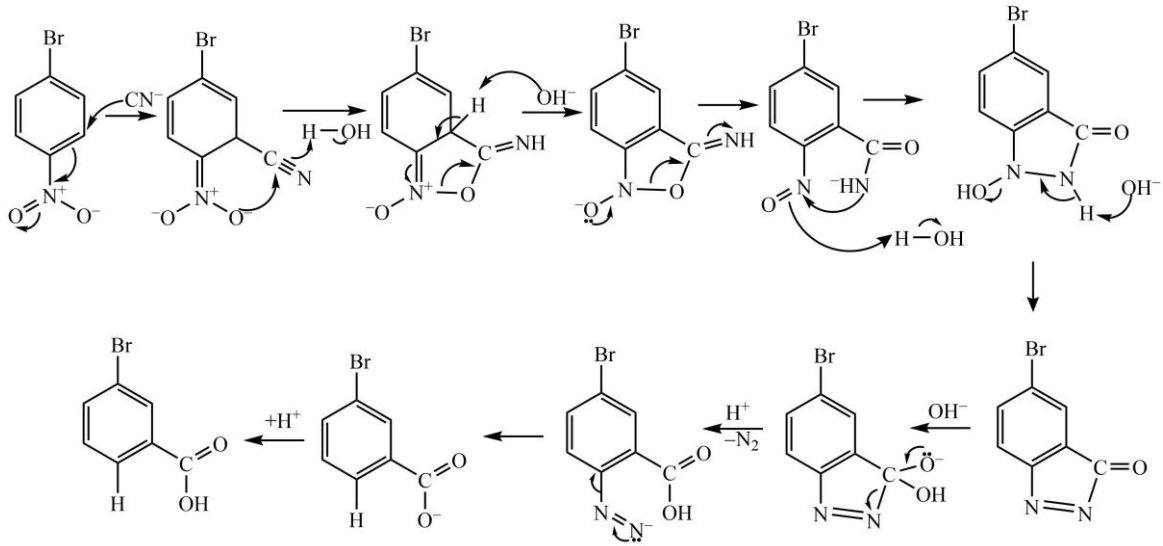
The von Richter reaction may simply be defined as the chemical transformation where aromatic nitro compounds react with KCN in aqueous ethanol to yield cine substitution product by a carboxyl group.

This reaction was invented by a German chemist Victor von Richter in 1871; and therefore, it is also named after him; and It is practically unimportant because of low yield and by-products formation.

Illustrative reaction: Common example is the conversion of *p*-bromonitrobenzene into m-bromobenzoic acid.



Mechanism involved: The most widely accepted mechanism for the von Richter reaction was given by Rosenblum in 1960 when he employed ^{15}N labeling experiments.



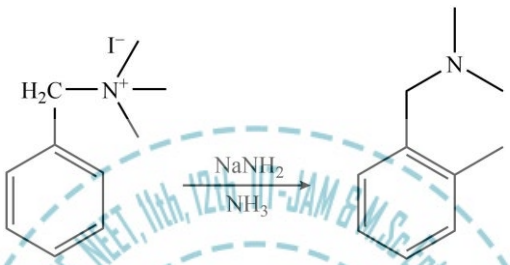
In the first step, the carbon ortho to the nitro group is attacked by cyanide; which is followed by ring-closing through nucleophilic invasion at the cyano group; finally resulting in the rearomatization of the imidate intermediate. The opening of the cycle via nitrogen-oxygen bond-breaking gives rise to an ortho-nitroso benzamide that recyclizes to yield a compound with a nitrogen-nitrogen bond. The elimination of H_2O results in a cyclic azoketone, which undergoes nucleophilic invasion by OH^- to result in a tetrahedral intermediate. This intermediate breakdowns with the removal of the azo group to give an aryldiazene with an o-carboxylate group, which squeezes out dinitrogen gas to be able to have the anionic form of the benzoic acid.

➢ ***Sommelet-Hauser Rearrangement***

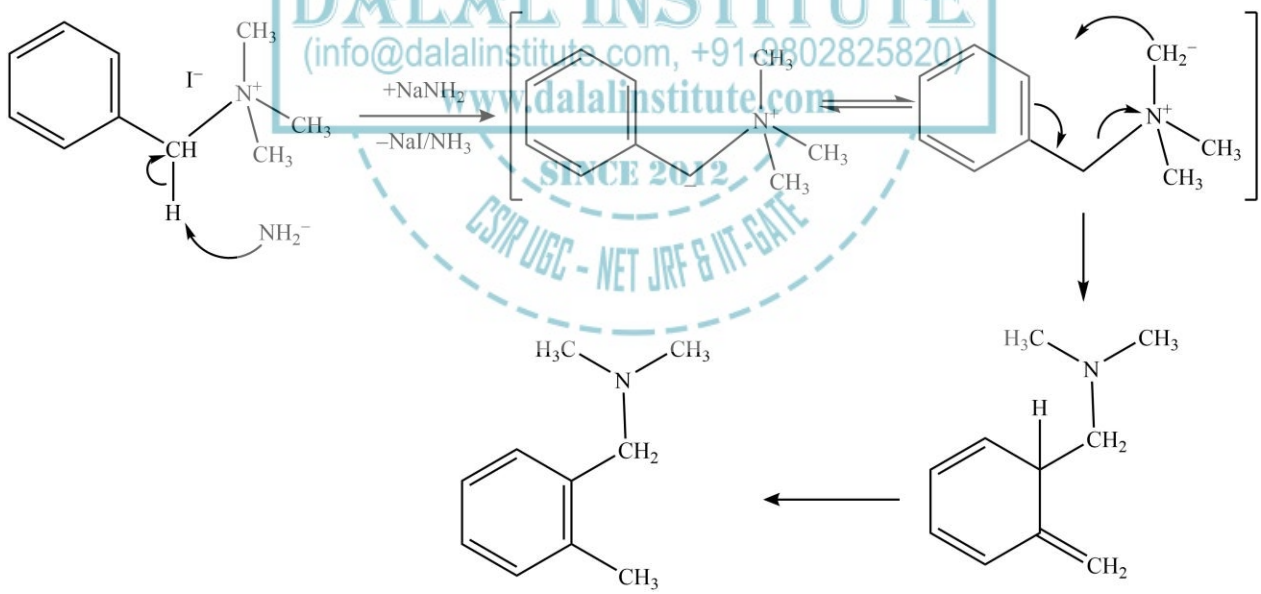
The Sommelet-Hauser rearrangement may simply be defined as the rearrangement reaction of certain benzyl quaternary ammonium salts where the reagent used is sodium amide (or alkali amide) and the reaction results in the N,N-dialkylbenzylamine with a new alkyl substituent in the aromatic o-position.

Now because the final product is a benzylic tertiary amine, it can further undergo alkylation followed by reoccurring rearrangement, and then repeating the process until the blockage of o-site.

Illustrative reaction: The common type of this type of rearrangement is benzyltrimethylammonium iodide that rearranges in the presence of $NaNH_2$ to give the o-methyl derivative of N,N-dimethylbenzylamine.



Mechanism involved: The widely accepted mechanism for the Sommelet-Hauser mechanism is depicted below clear the propagation picture.



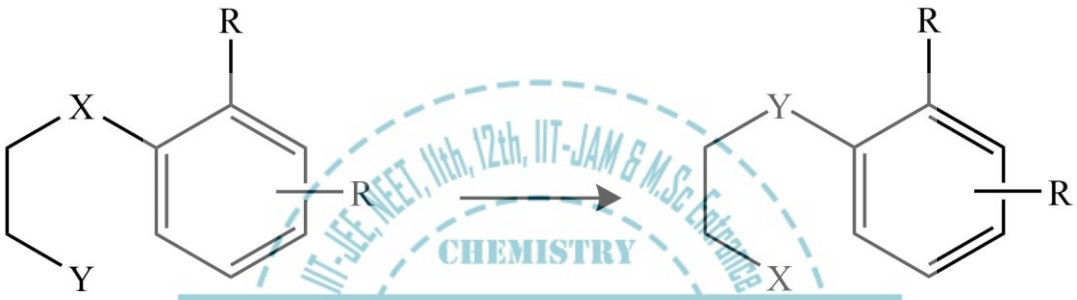
The benzylic methylene hydrogen is acidic and deprotonation occurs to give the benzylic ylide, which is in equilibrium with another ylide formed via deprotonation of one ammonium methyl substituent. Nevertheless, the second ylide is available in much minor quantity, it shows a 2,3-sigmatropic rearrangement as it has a more reactive character than the initial one, and will show subsequent aromatization to give rise to the end product.

➢ *Smiles Rearrangements*

The Smiles rearrangement may simply be defined as an intramolecular aromatic nucleophilic substitution (ArSN) reaction, where the breaking of a C−X single bond and creation of a new C−C or C−X bond take place via ipso substitution.

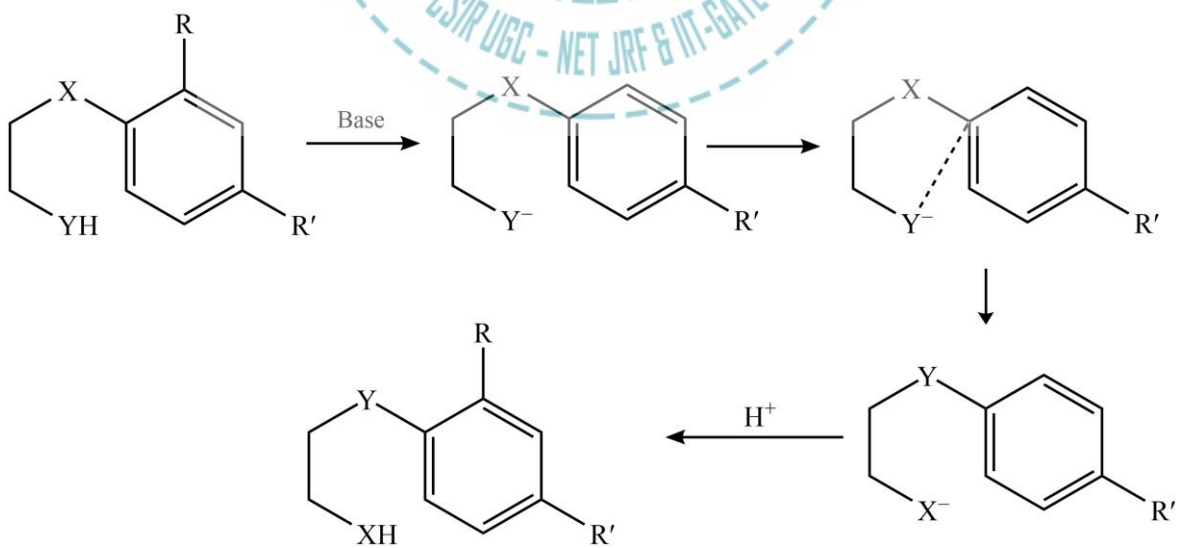
This reaction was invented by a British chemist Samuel Smiles; and therefore, it is also named after him. Its dependence upon leaving group, nucleophile, and the cycle-size of transition state makes it suitable for arene functionalization.

Illustrative reaction: The general reaction showing this type of transformation (Smiles rearrangement) is shown below.



where X represents a sulfide, a sulfone, an ether, or any group capable of displacing from a negatively charged arene. On the other hand, Y represents a group that is capable to act as a strong nucleophile (like alcohol, thiol, or amine).

Mechanism involved: The widely accepted mechanism for the Smiles mechanism is depicted below clear the propagation picture.



Just like other aromatic nucleophilic substitutions, an electron-withdrawing group at ortho position is also required for activation. However, in Truce-Smiles rearrangement, no additional activation is required because the income g nucleophile is enough strong (i.e., organolithium).

❖ Problems

Q 1. What is aromatic nucleophilic substitution? Explain with special reference to the benzyne mechanism.

Q 2. Give five points of differences between $ArSN_1$ and $ArSN_2$ mechanism.

Q 3. Discuss the effect of Substrate Structure, Leaving Group, and Attacking Nucleophile on the overall Reactivity of aromatic nucleophilic substitution reactions.

Q 4. Define von Richter reaction. Also, explain its mechanism.

Q 5. Discuss Smiles rearrangement in detail.

Q 6. What is the Sommelet-Hauser reaction?

Q 7. Give SRN_1 mechanism of nucleophilic substitution reactions.

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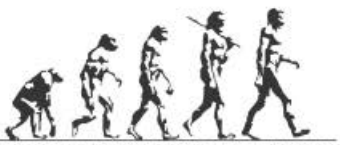

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