sem-I

Mane Madam

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Unit - V

Aromatic nucleophilic substitution,

Introduction :→

In electrophilic aromatic substitution, a strong electrophiles replaces a proton on the aromatic ring

In nucleophilic aromatic substitution a strong nucleophile replaces a leaving group e.g a halid

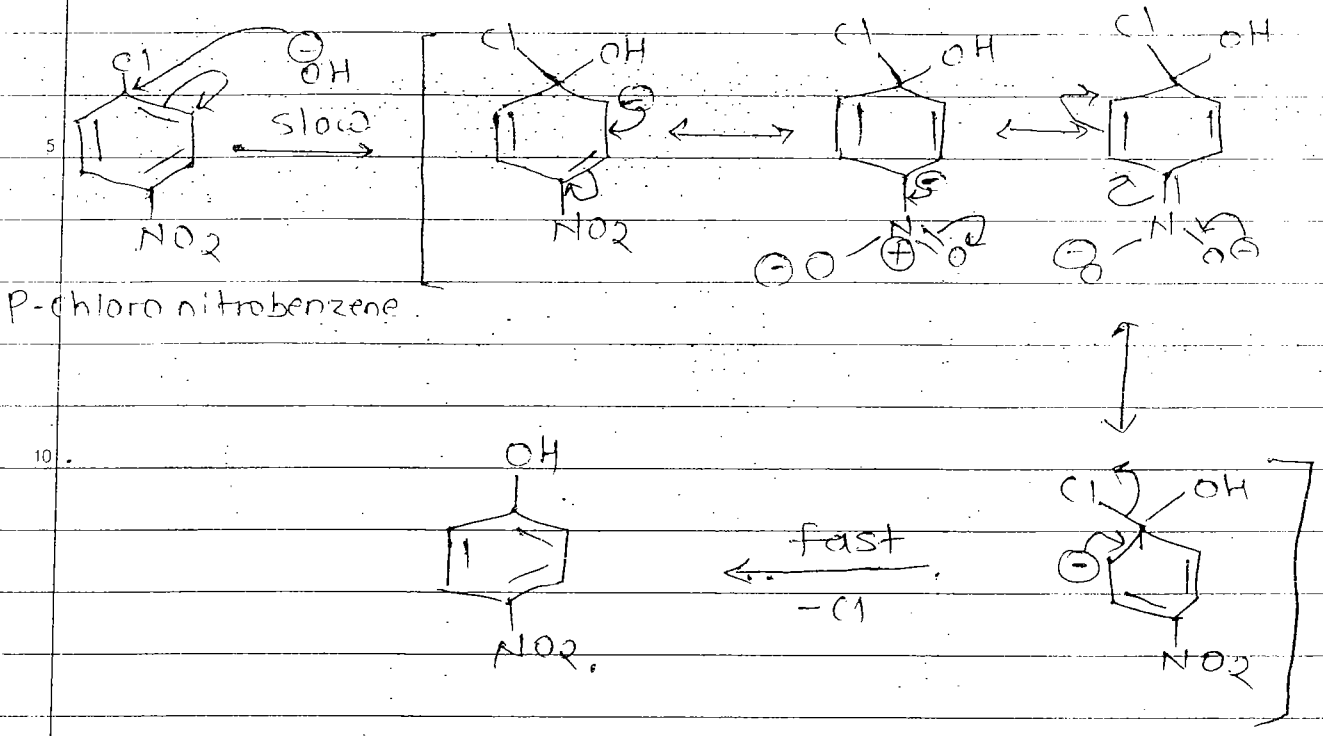
A nucleophile can be introduced into the ring provided it is suffiriently π-electron deficient due to the presence of an electron withdrawing group, i.e NO_2. The more effective leaving groups are halogen

The nucleophile attacks the carbon atom to which the leaving group is attached, the aryl halides undergoes nucleophilic substitution wit great difficulty unless strong electron withdrawi -ng groups are present in the ortho or para position to the halogen atom.

The SNAr mechanism :→

The reaction of P-chloronitrobenzene with nucleophiles e.g hydroxide ion, replaces the halogen with hydroxide ion. this reaction is called as nucleophilic substitution reaction. and the key to its success is the presence of atleast one strong electron withdrawing group on benzene ring at ortho or para to the leaving group. presence of these substitu -ents decreases the electron density in the benzene ring making it more favourable for

nucleophilic attack. A general representation of SNAr mechanism is shown below.



P-chloro nitrobenzene

In this first step is slow step - ipso addition by the nucleophile gives an anion with a high delocalised charge. The important feature of this intermediate is the ability of a negative charge to be delocalised into the electron withdrawing group.

In the second step, the leaving group is eliminated to regenerate the aromatic ring. The reactivity of haloarenes in nucleophilic substitution increases with the no. of electron withdrawing group on the ring. if they are in ortho & para position.

under drastic conditions i.e under high temperature or high pressure or both in the presence or absence of catalysts, aromatic nucleophilic substitution may takes place.

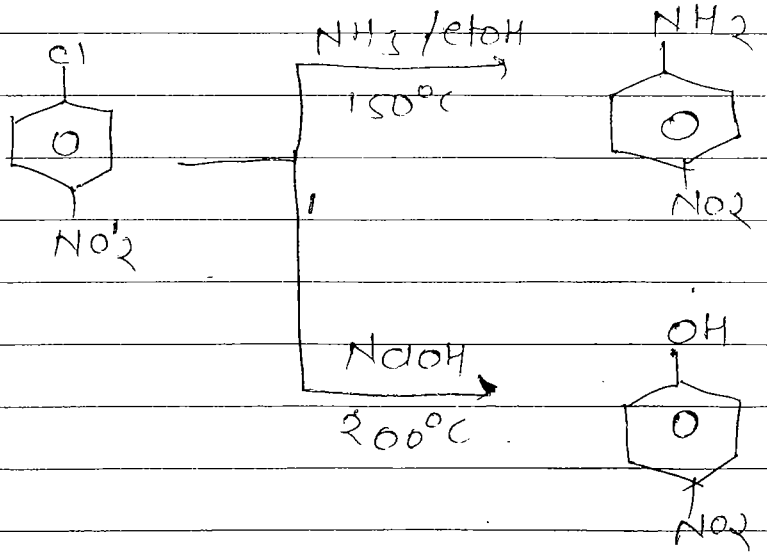
on the other hand properly substituted aromatic compound having -R or -I group at ortho or para or both the positions undergo nucleophilic substitution with less difficulty because -R & -I groups decrease electron density on the aromatic ring and activate it for nucleophilic substitution.

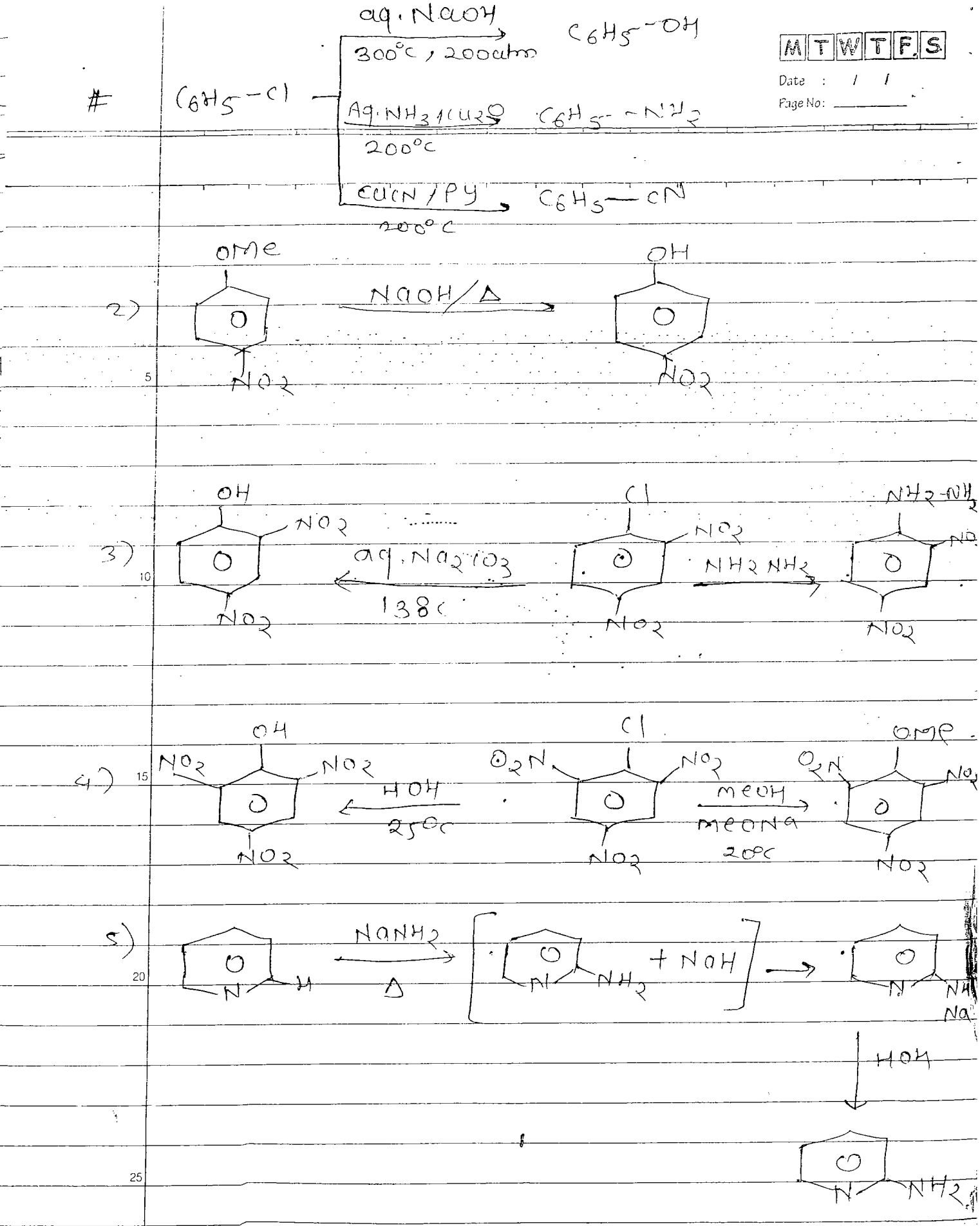
Aromatic compounds undergo the following three types of nucleophilic substitution reaction.

i) ArSN1 reaction
ii) ArSN2 reaction
iii) Aromatic nucleophilic substitution reaction via Benzynes.

ArSN2 is the most common aromatic nucleophilic substitution reaction. the reactivity of substrate for ArSN2 also called as SNAr reaction

some example of ArSN2 reactions:



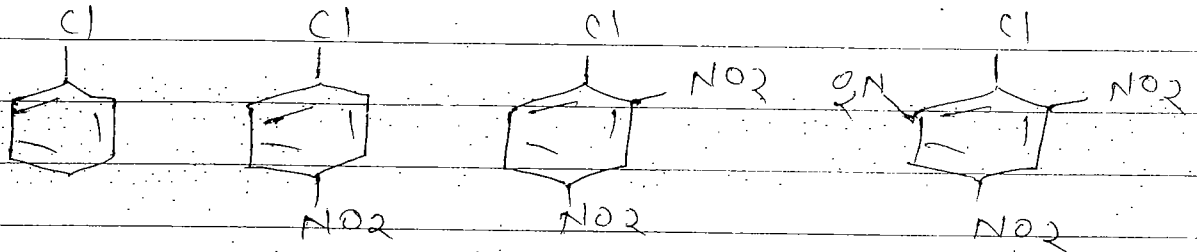


- The following points may be noted.

1) The reaction become facile when two or more nitro group are present in the ortho.

Ipso attack :- Position which is already occupied by non-hydrogen substituent in an aromatic ring called Ipso position, then attack on this position called Ipso attack.

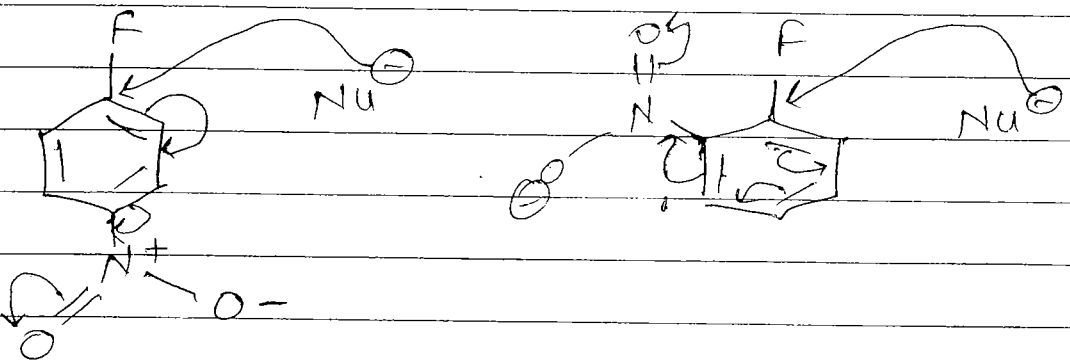
and para position as indicated by rate data.



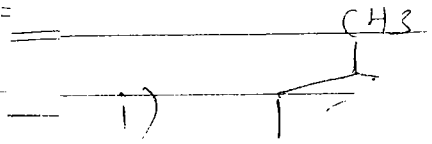
chloroben -zene | 1-chloro- 4-nitroben zene | 1-chloro-2,4 dinitroben zene | 2-chloro-1,3,5 trinitrobenzen

increasing rate of aromatic nucleophilic sub r

2) The presence of electron withdrawing group is essential at the ortho and para positions to the site of nucleophilic attack, only then charge of nucleophile can be delocalised.

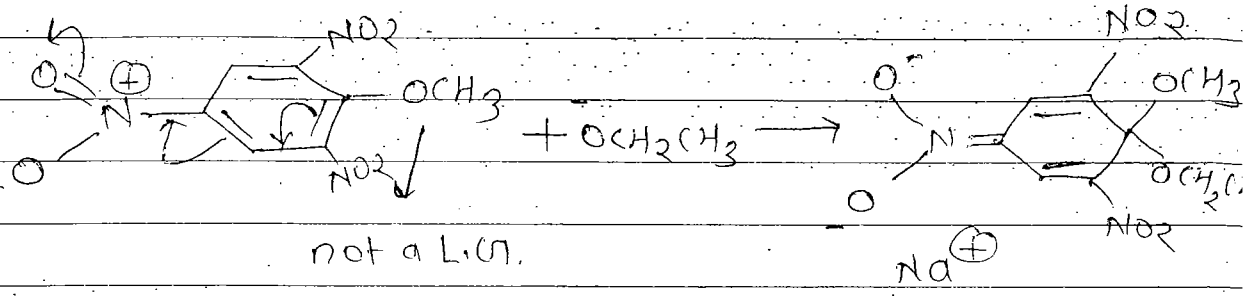


3) 2,4,6-trinitroanisole does not bear a halide leaving group thus its reaction with sodium ethoxide give a Meisenheimer complex. Which corresponds to the product obtained by the nucleophilic addition stage of an SNAr mechanism, this shows that nucleophilic attack on aryl halide initially gives a resonance



1)

stabilised carbanion intermediate known as meisenheimer complex by the initial ipso addition by the nucleophile.



not a L.G.

2,4,6-trinitroanisole

Meisenheimer complex

In case this mechanism is similar to either the SN1 or SN2 mechanism, the Ar-x bond should break in the rate-determining step.

In the SNAr mechanism, the bond is not broken until after the rate-determing step.

As expected a change in L.G. should not effect the rate of reaction and this has been found to be the case

Since the nature of leaving group (x) effects the rate at which nucleophile attacks.

When the electronegativity of Leaving group is more, there would be a decrease in e^- density at the site of attack leading to a faster attack by the nucleophile.

The fact from amongst halogens, fluoro is the best leaving group in several aromatic nucleophilic substitution shows this mechanism to be different from SN1 & SN2 mechanism, where fluro is the poorest of the Leaving groups.

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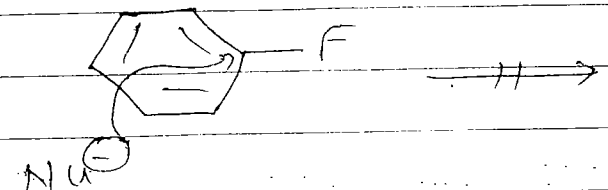
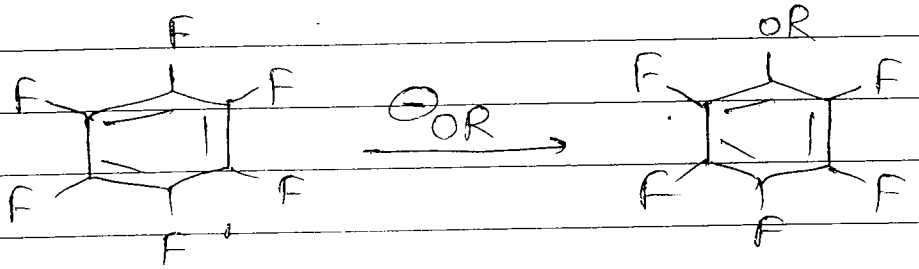


⟶// No reaction.

aryl halides cannot adopt the geometry for a backside attack. since the ring shields the backside of the C–X bond

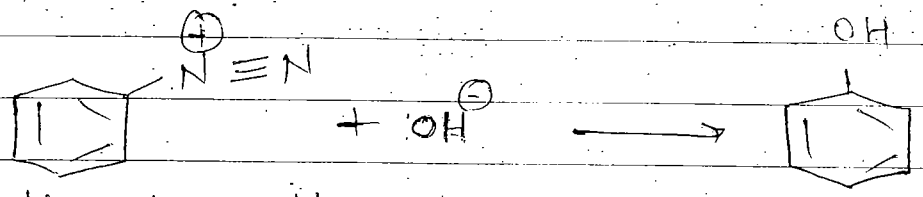
The most common type of reactants in nucleophilic aromatic substitution are those which have o & p NO_2 substitution. However highly fluorinated hydrocarbon's fit the requirements for such a reaction & hexa fluorobenzene undergo substitution of one of its fluorines on reaction with nucleophile



The S_N1 mechanism in nucleophilic aromatic substitution – Diazonium salts :→

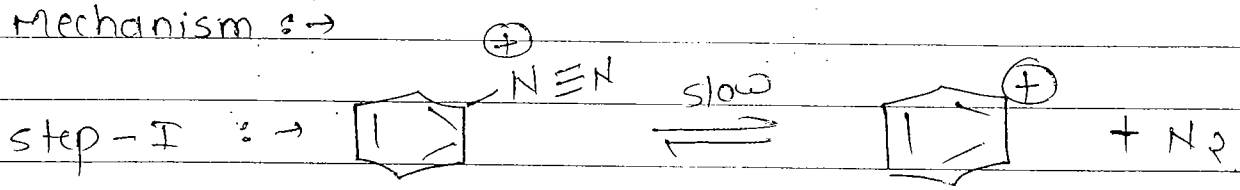
When aryl diazonium salts are hydrolyzed in water these give the corresponding phenol. The net result of the reaction is substitution of the nucleophile for the diazonium group.

There is sufficient evidence that this reaction proce through an aryl cation. In the case of aryl halides and sulphonates a unimolecular mechanism has never been established. However, this mechan -sm is significant only in the case of diazonium salts, the driving force for formation of this reactive cation is departure of the good Leaving group, nitrogen.

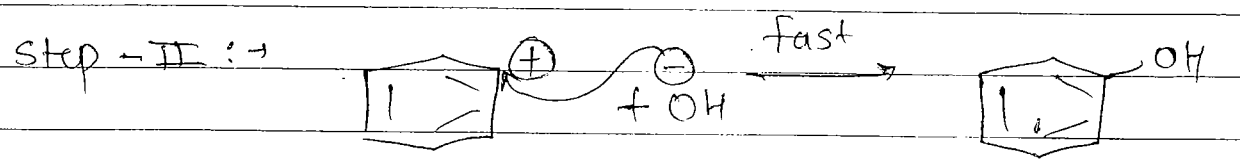


aryl diazonium salt.

Mechanism :→



Aryl cation



The main evidence in support of the above mechanism

i) The rate of decomposition of diazonium salt follows the first order kinetics and is independent of the nature and conc. of the nucleophiles present.

ii) the effect of substituents on the rate are consistent with unimolecular rate-determining cleavage

i.e electron releasing meta substituents (OH, ome, me) increase the rate of reaction & electron-withdrawing meta substituents (COOH, NO_2, Cl) retard the rate of reaction.

Some example of ArSN1 reaction of aromatic diazonium cation are given below:

$$Ar-\overset{\oplus}{N}\equiv N \xrightarrow{H_2O} Ar-OH + N_2 + H^{\oplus}$$

$$Ar-\overset{\oplus}{N}\equiv N \xrightarrow{X^{\ominus}} Ar-X + N_2$$

$$Ar-\overset{\oplus}{N}\equiv N \xrightarrow{N_3^{\ominus}} Ar-N_3 + N_2$$

$$Ar-\overset{\oplus}{N}\equiv N \xrightarrow{CH_3OH} Ar-OCH_3 + N_2 + \overset{\oplus}{H}$$

Presence of Electron donating group at ortho or para or both positions increases the reactivity of substituted diazonium cation for ArSN1 reaction similarly EWG at these position decreases reactivity

3) Isomerization (one molecule converted into another which has exactly same atoms but have diff. arrangement) of isotopically labelled p-toluene-diazonium ^{15}N fluoroborate was observed during hydrolysis. this could be possible only when the nitrogen detaches from the ring & then reattaches.

$$p\text{-}MeC_6H_4-\overset{*}{\overset{\oplus}{N}}\equiv N\,\bar{B}F_4 \underset{}{\overset{H_3O^{\oplus}}{\rightleftharpoons}} p\text{-}MeC_6H_4-\overset{\oplus}{N}\equiv \overset{*}{N}\,BF_4^-$$

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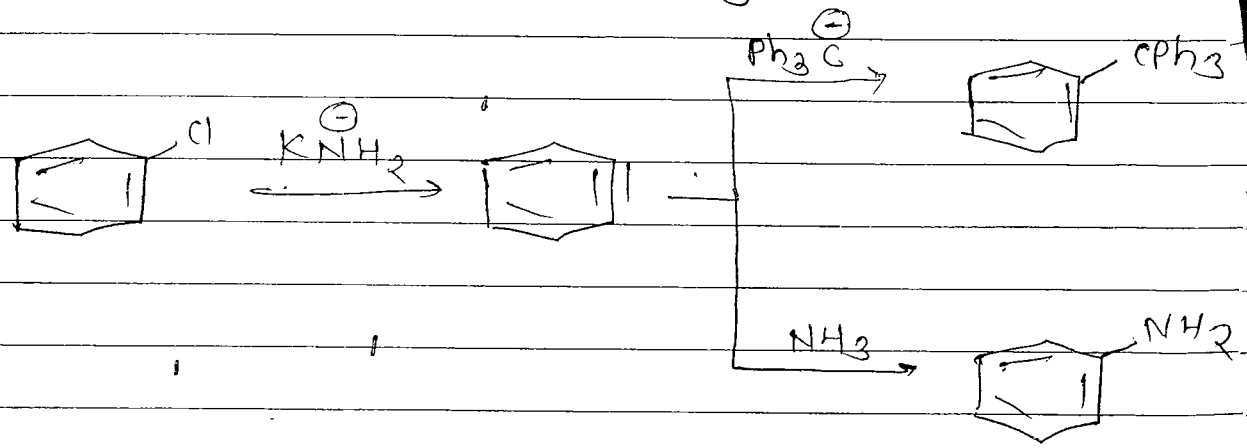
Aromatic nucleophilic substitution reaⁿ VIA Benzynes

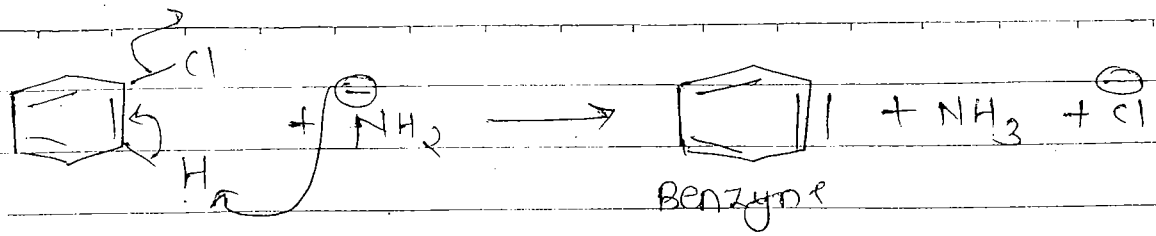
Benzyne is a highly reactive intermediate. The formation of benzyne type of intermediate from a simple haloarene is favoured when the amide ion (NH_2^-) is used as base. due to its strong basic nature it successfully abstracts hydrogens from the aromatic ring as protons with the formation of ammonia. The halide ion X^- departs to give benzyne.

one must have a hydrogen ortho to halogen undergo nucleophilic substitution. With a very strong base like KNH_2 or $NaNH_2$ in liquid ammonia, the reaction also occurs. With base such as PhLi & BuLi. This reaction proceeds via benzyne intermediate & the mechanism is called benzyne mechan. An interesting feature of this reaction is the the incoming nucleophile does not necessarily take the position vacated by the leaving group



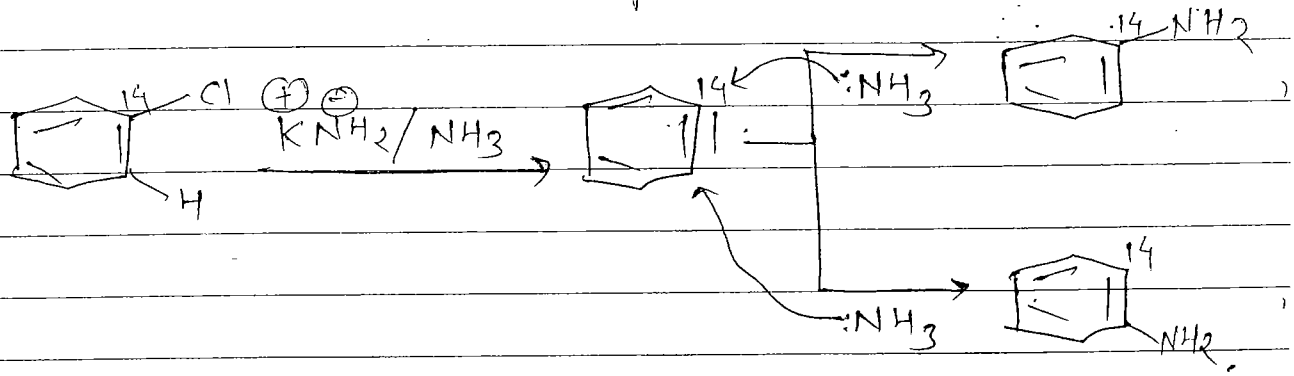
Benzyne mechanism :→

This mechanism involves elimination followed by addition it is also called elimination - addition mechanism of aromatic nucleophilic substitution

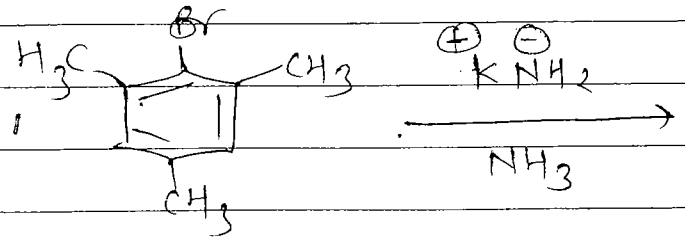


Evidence in support of the benzyne mechanism :→

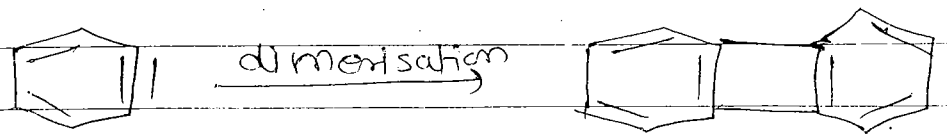
i) 1 - ^{14}C - chlorobenzene on treatment with potassium amide in liquid ammonia gives almost equal amount of 1 - ^{14}C - aniline & 2 - ^{14}C - aniline. The formation of these two products can be explained if the reaction is proceeding through a symmetrical intermediate which can be attacked by ammonia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

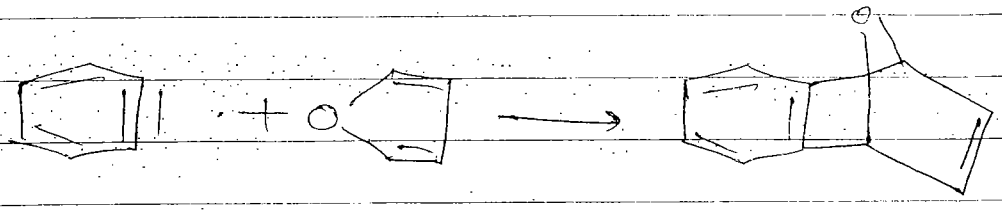


ii) Aryl halides having no hydrogen ortho to the halogen do not react under the same condition



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



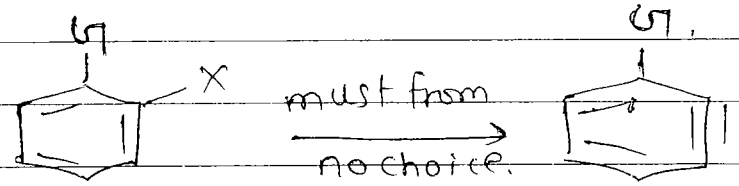


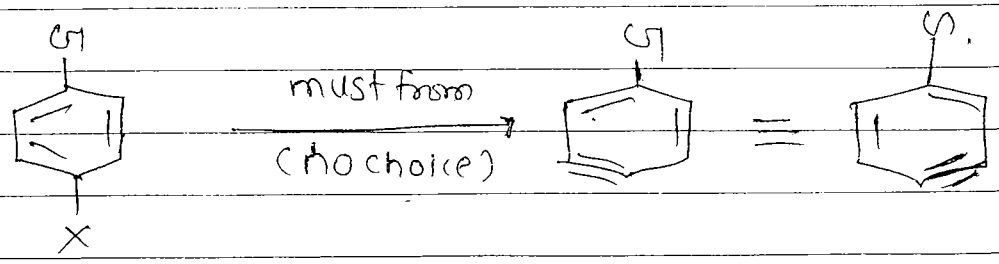
Prediction of major products in the reactions proceeding via benzynes :→

In the case of ortho or para position substituted halobenzenes two products are possible, while meta also gives different 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.

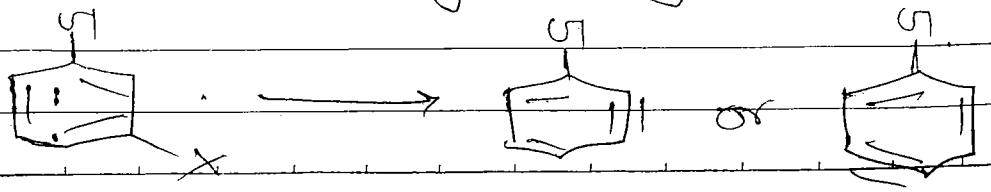
i) direction in which benzyne is formed :→

In the case of ortho or para substituted halob-enzenes there is no choice.





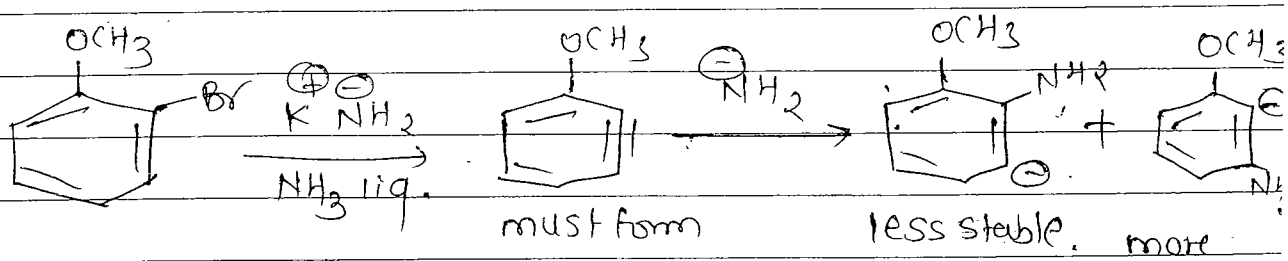
But in the case of meta substituted halobenzenes two different benzynes may be formed.



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 attaked at two position the favoured position of attack is that which give 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.

i)



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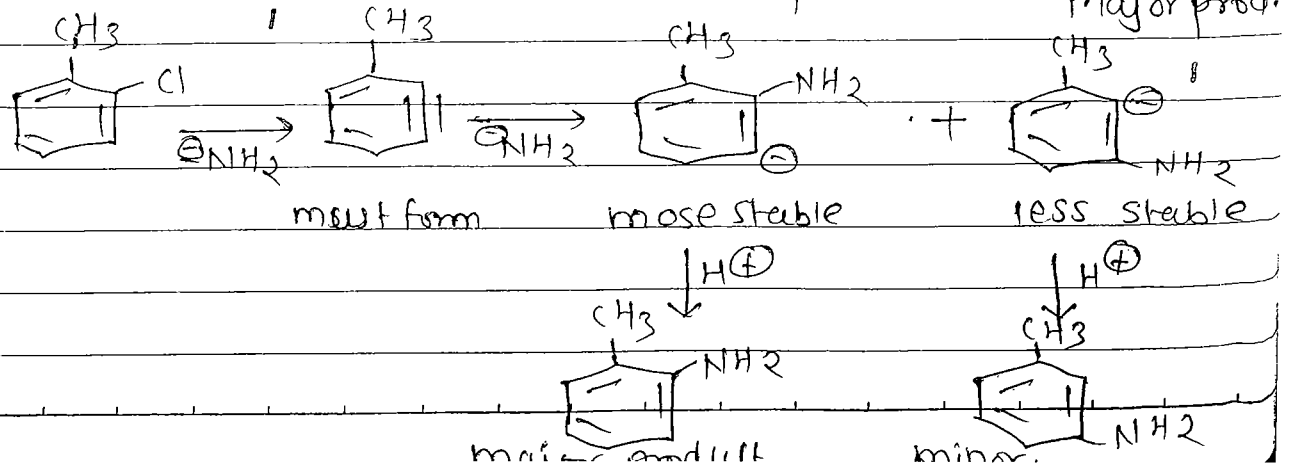

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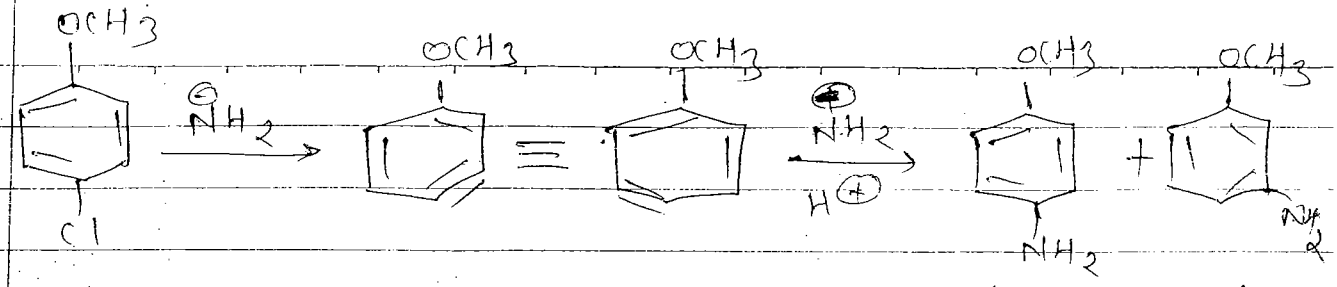
iii)



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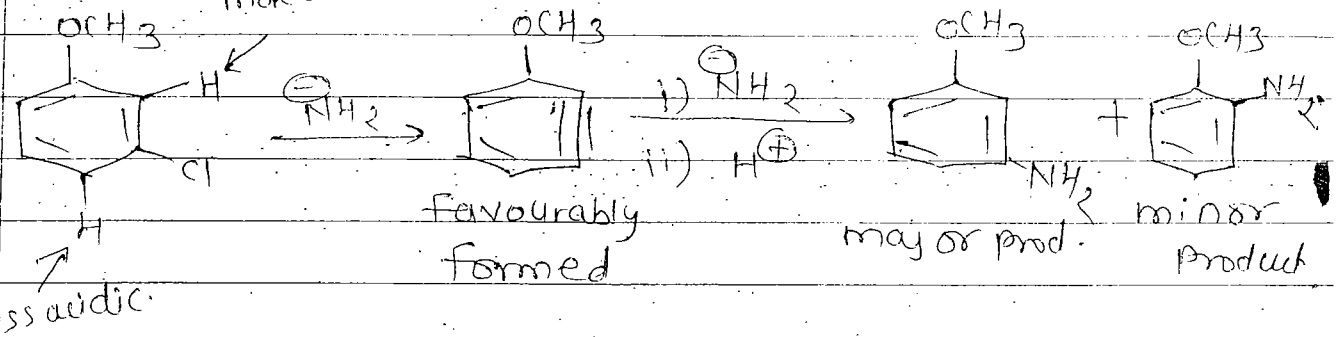
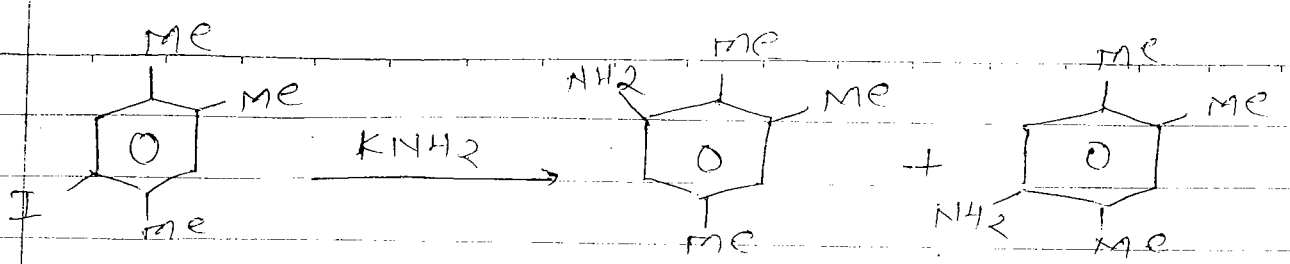


SRN1 mechanism :→

When 5-Iodo-1,2,4-trimethylbenzene on treatment with KNH_2 in liq. NH_3 give II & III in the ratio 0.63 : 1. The presence of an unactivated substrate, strong base and the formation of cine along with normal substitution product indicate that the reaction proceeds through a benzyne mechanism. However, the 6-Iodo isomer of (I) should have given II, & III in the same ratio because the same aryne intermediate would be formed in both cases but in this case the ratio of II to III was 5.9:1 To explain the result of Iodo, It has been proposed that besides the benzyne mechanism, the following mechanism called as SRN1 mechanism is also operating here.



I

5-Iodo-1,2,4-trimethylbenzene

II

III

$$ArI \xrightarrow[\text{donor}]{\text{electron}} ArI^{\cdot-} \longrightarrow Ar^{\cdot} + I^{-}$$

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

this is called the SRN1 mechanism. the last step of the mechanism produce $ArI^{\cdot-}$ radical ion, so the process is a chain mechanism. e^- donor is required to initiate the reaction. in the above case it was solvated electron from KNH_2 in liq. NH_3.

Evidence in support of the SRN1 mechanism,

1) addition of potassium metal. (a good producer of solvated electrons in liq. NH_3) completely suppressed the cine substitution.

2) Addition of radical scavengers. (which could supress a free radical mechanism) led to II : III ratio much closer to 1 : 46 : 1

3) Some 1,2,4-trimethylbenzene was found among the products which could easily be formed.

by abstraction of H by Ar from the solvent liq. NH_3.

4) Besides, initiation by solvated electrons SRN1 reactions have been initiated photochemically, electrochemically & even thermally.

SRN1 reactions have a fairly wide scope. there is no requirement for activating group or strong bases. Alkyl, Alkoxy, aryl & COO^- group do not interfere, although Me_2N, O^- & NO_2 groups do interfere. cine substitution is not found

effect of substrate, leaving group & Nucleophile

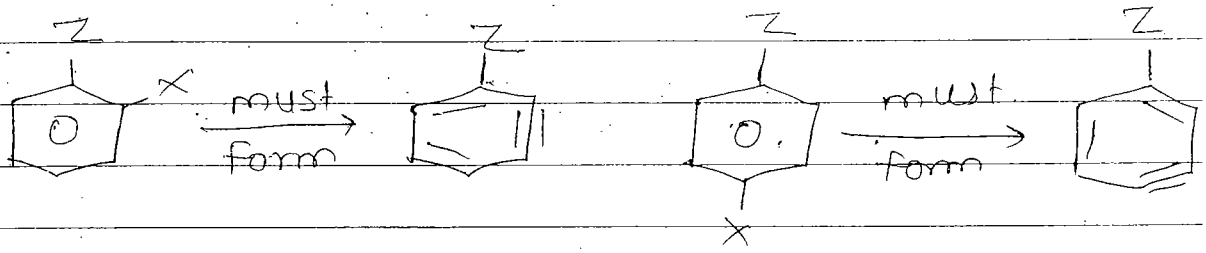
(I) effect of substrate :→

SNAr mechanism are accelarated by electron-withdrawing groups, especially in the o & p position to the leaving group & retarted by electron donating group. Heteroatoms of the ring are also strongly activating e.g. nitrogen which is more activating when quaternized. thus 2- & 4-chloropyridine for example are used as substrate Heterocyclic N-oxides are readily attacked by nucleophiles in the 2 & 4 positions but the oxygen is generally lost in these reactions. decreasing order of activating power of some groups in ArSN reaⁿ is given below.

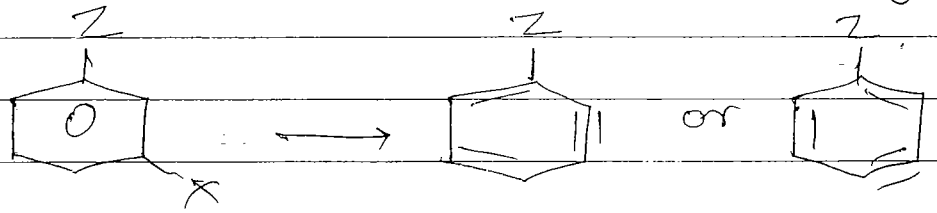
(F)
$NH_3 > NO_2 > CF_3 > CN > SO_3H > CHO > CO > COOH > COO$
$> CONH_2 > F > Cl > Br > I$.

- Benzyne mechanism :→

too factors affect the position of the incoming group. the first being the direction in which the aryne forms. where there are groups orth or para to the leaving group. there is no choice



but when a meta group is present, the aryne can form in too different ways:



in such cases, the more acidic hydrogen is removed.

(2) effect of leaving group :→

The common leaving groups in aliphatic nucleo-philic substitution ~~are~~ halide, sulfate, sulfo-nate etc. are also common leaving group in aromatic nucleophilic substitution, but the group NO_2, OR, OAr, SO_2R and SR which are not generally lost in aliphatic system, ~~are leaving~~

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if these groups when attached to aromatic rings are leaving group. NO_2 is particularly good leaving group. order of leaving group ability is. $F > NO_2 > OTS > SOPh > Cl > Br > I > N_3 > NR_3^+ > OAr, OR, SR, NH_2$. However this depends greatly on the nature of the nucleophile.

- The four halogen as well as SPh, $NMe_3^{\oplus}$ & $OPO(OEt)_2$ have been shown to be leaving groups in the SRN1 mechanism.
- The only important leaving group in the SN1 mechanism is N_2.

(3) effect of the attacking nucleophile.

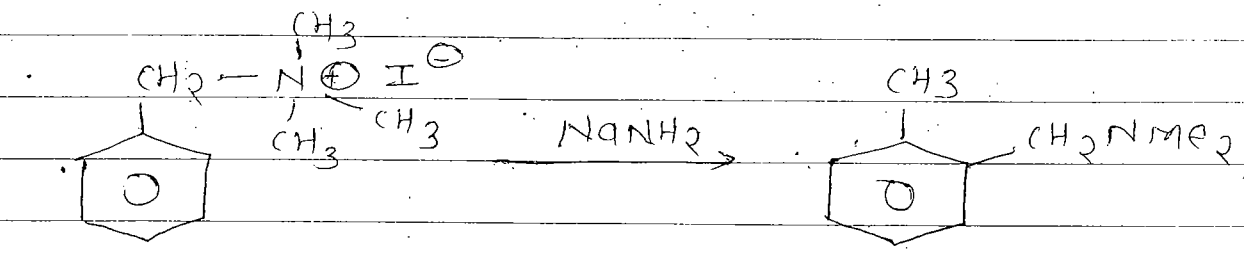
It is not possible to construct the nucleophilicity order because different substrate and different conditions lead to different of of nucleophilicity, but an overall approximate order is.

$NH_2^- > PH_3C^- > PhNH^- > ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.

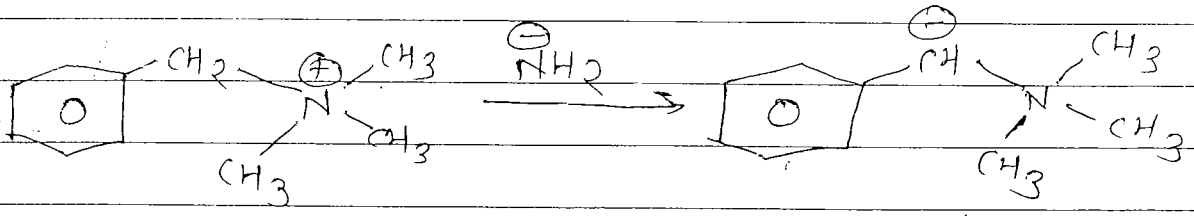
- CN ion is not a nucleophile for aromatic system, except for sulfonic acid salts.

Sommelet-Hauser rearrangment :→

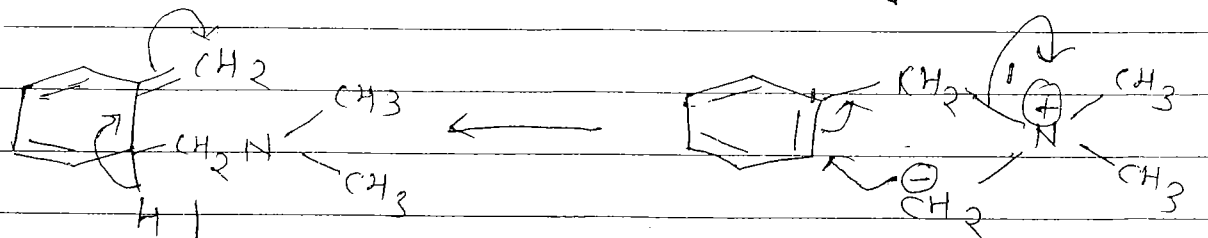
When benzylic quaternary ammonium salts are treated with alkali-metal amides, undergo a rearrangment called Sommelet-Hauser rearrangment. Since, the product is a benzylic tertiary amine it can be further alkylated and the product again subjected to the rearrangement. this process can be continued around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



Mechanism :→

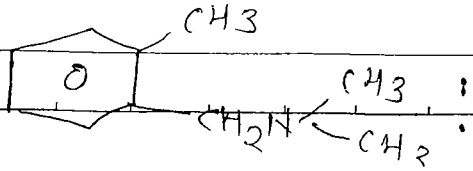


ylide (A)



Tautomerisation or aromatisation

ylide (B)



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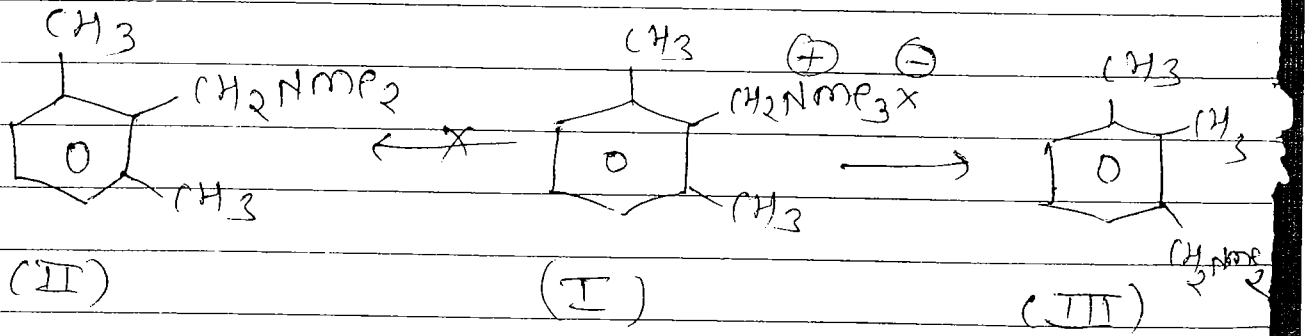
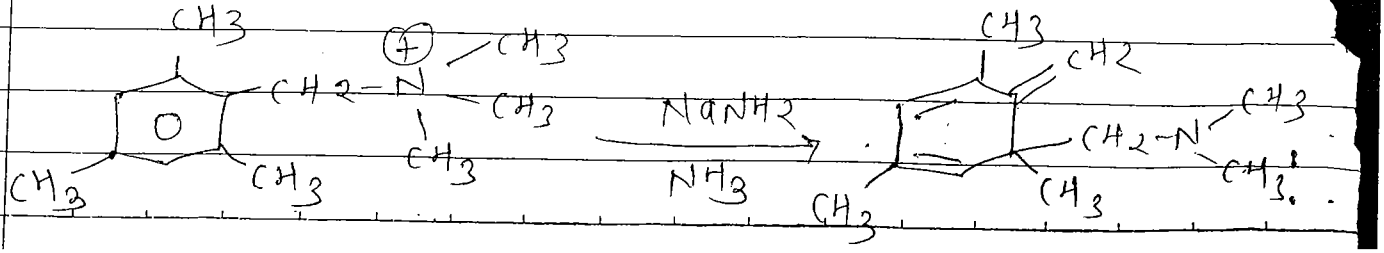
The reaction is most often carried out with three methyl group on nitrogen but other groups can also be used.

The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (I) This ylide is in equilibrium with (II) ylide that is formed by deproton-ation of one of the ammonium methyl group. Though the second ylide is undergoes a 2,3 – sigmatropic rearrangment and subseq-uent aromatization to form the final Product. 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

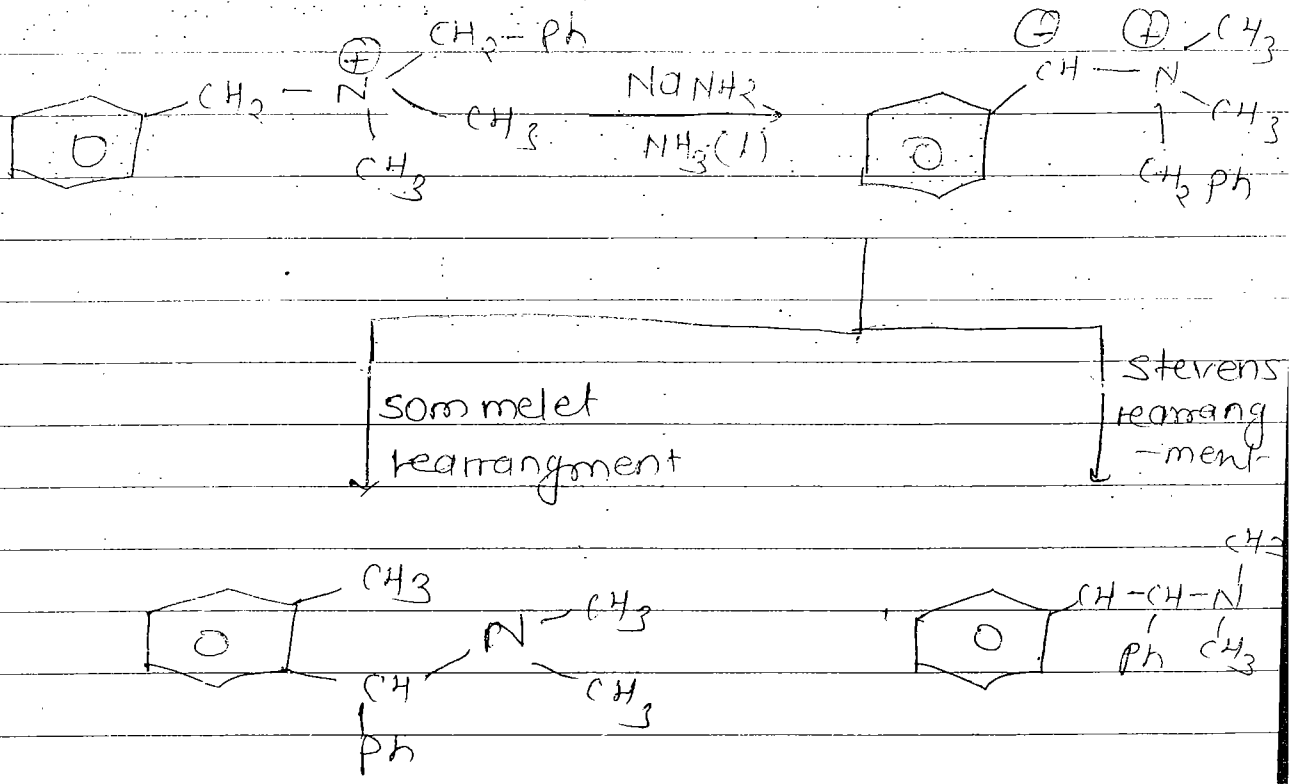


(II) (I) (III)

Geomethylene derivatives VI has been isolated this clearly indicates that the formation of the ylide B in the above mechanism.

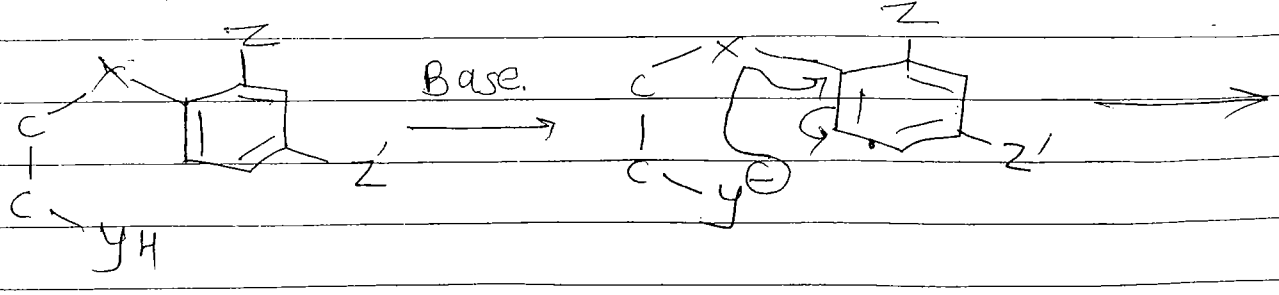


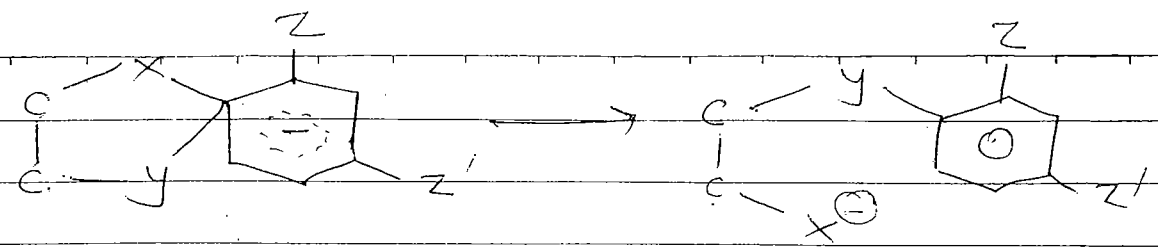
the main drawback of sommelet rearrangment is that it is accompanied by stevens rearrang-ement. when both rearrangments are possible the stevens is favored at high temperatures and the sommelet-Hauser at low temp.



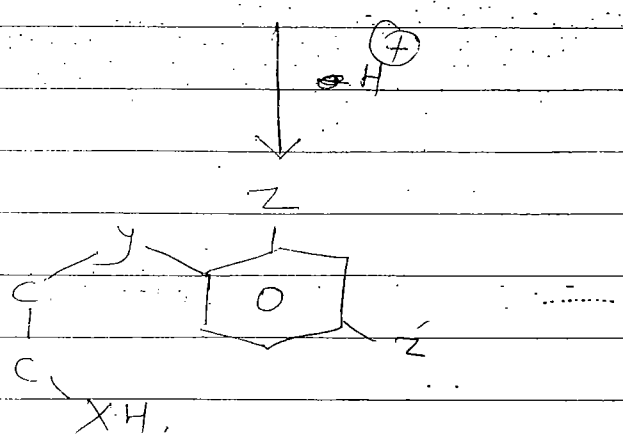
Smiles Rearrangment :-

Smiles rearrangments are simply intramolecular nucleophilic substitutions.

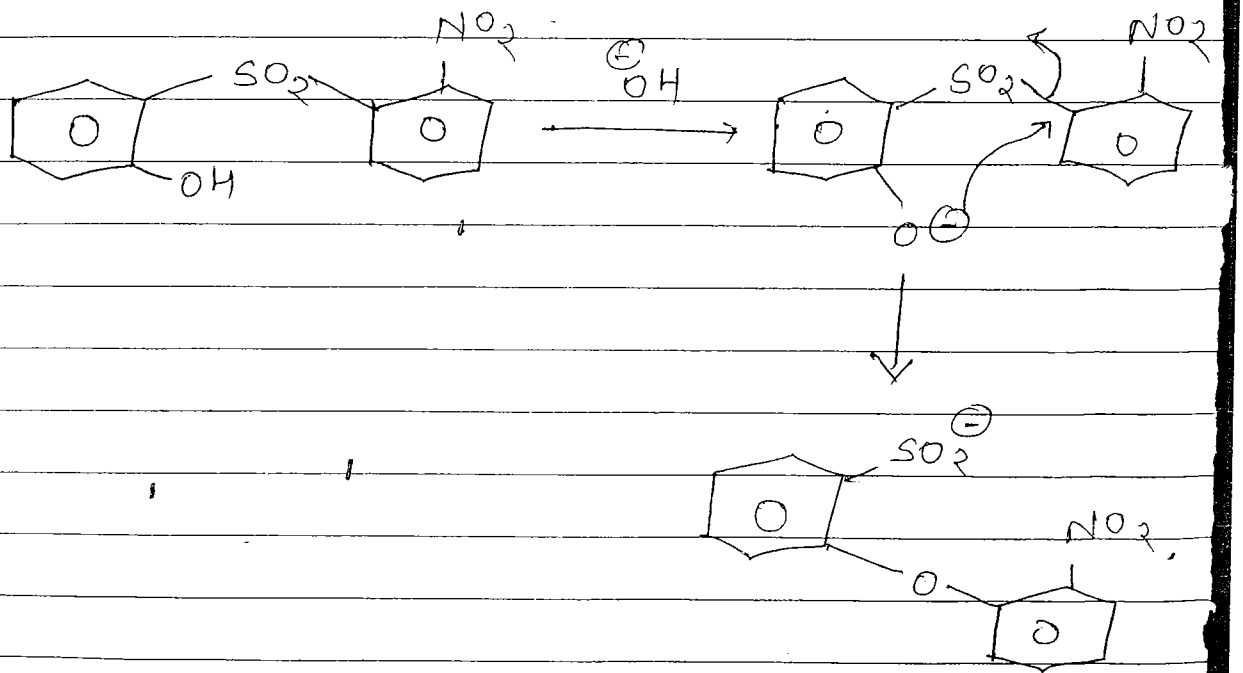




cyclohexadienylide anion.

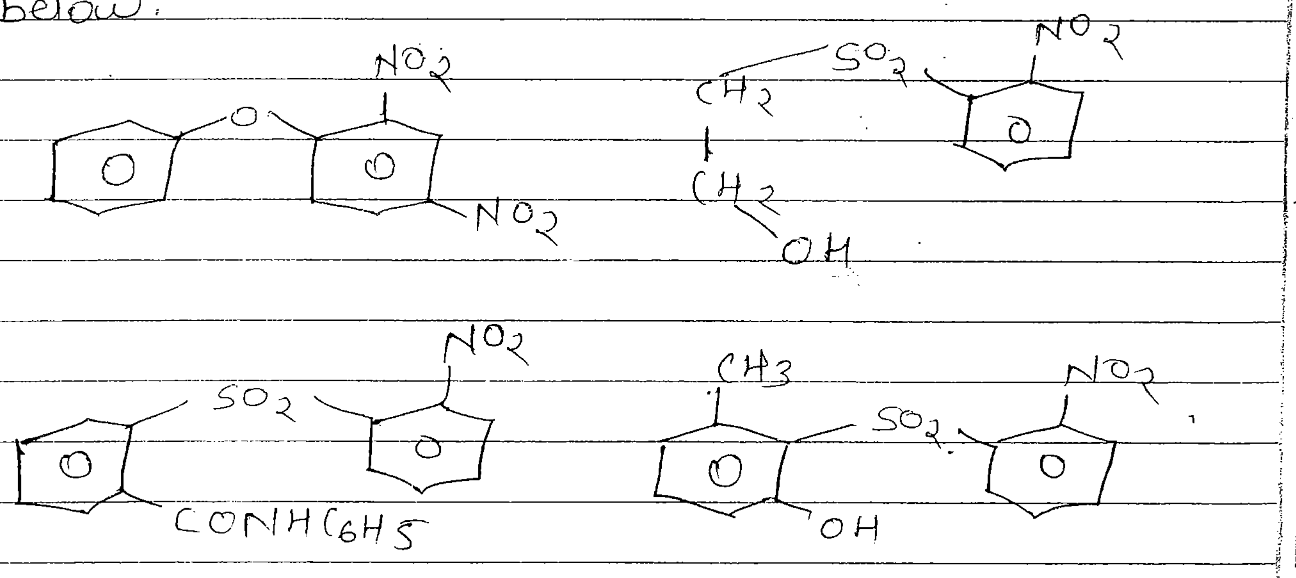


The smiles rearrangments actually comprises a group of rearrangments that follow the pattern given above. A specific example is.

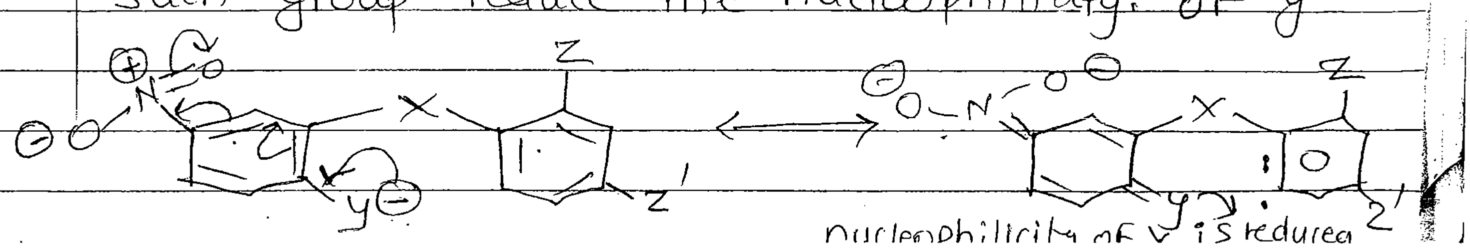


In the above example. $ArSO_2$ is the leaving group & $ArO^{\ominus}$ is the nucleophile and nitro activates the ortho position or para position.

X is usually S, SO, SO_2, O or COO.
y is usually conjugate base of OH, NH_2, NHR, SH, $\bar{C}H_2$, & the reaction has also been carried out with Y = PhLi, BuLi. in this particular case the rearrangment is known as Truce - Smiles rearrangment.
Z & Z' are activating group for nucleophilic aromatic substitution reaction. Z and Z' should be an electron-withdrawing group such as NO_2, CN or CF_3 to stabilise the cyclohexa-dienylide anion formed.
In this rearrangment the chain linking X & Y can be aromatic as well as aliphatic. the rearrangment also takes place in heterocyclic aromatic system. some example of substrates that undergo smiles rearrangment are given below.



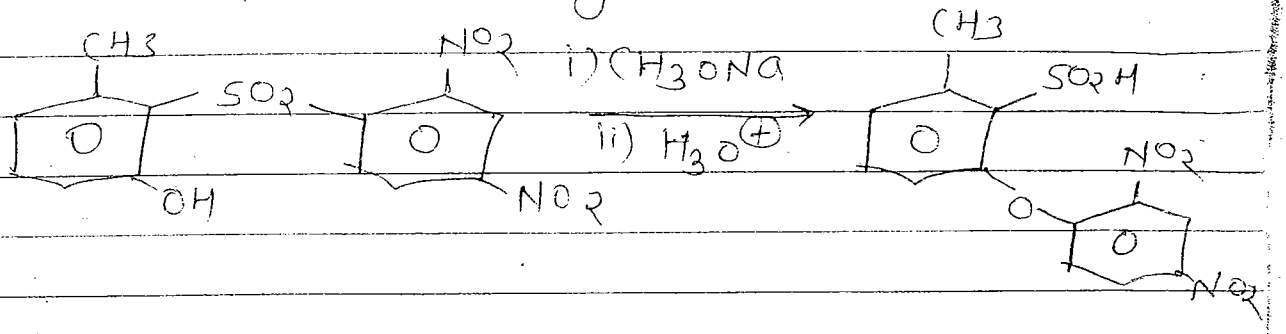
The presence of an electron withdrawing group para to the YH in the substrate retards the rate of the smiles rearrangments because such group reduce the nucleophilicity of $y^{\ominus}$



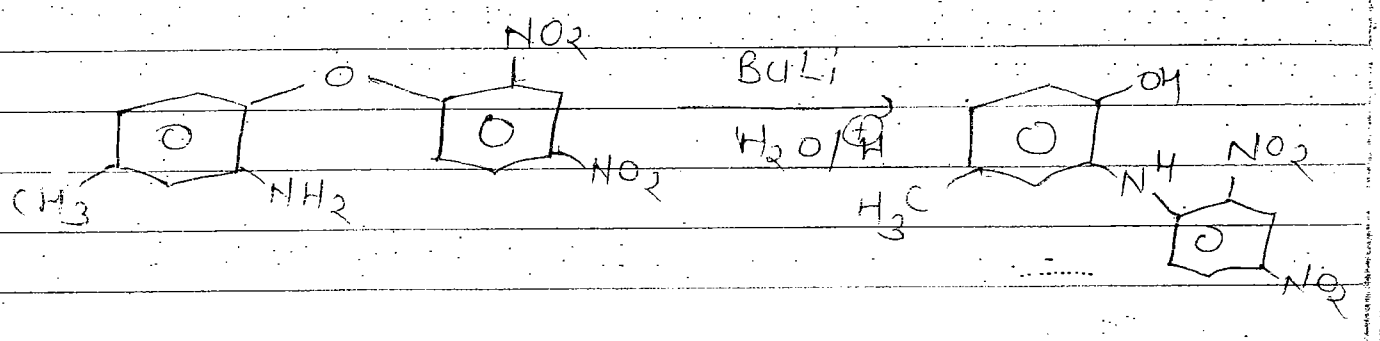
nucleophilicity of Y is reduced

examples of Smiles rearrangment:-

i)



ii)



iii)