

AMINES

Amines are organic compounds of ammonia in which one or more than one hydrogen atoms are replaced by other atoms or group of atoms. They are classified as primary (RNH_2 or 1°), secondary (R_2NH or 2°) or tertiary (R_3N or 3°) depending upon one, two or all the three hydrogen atoms of ammonia are replaced by alkyl groups (R).

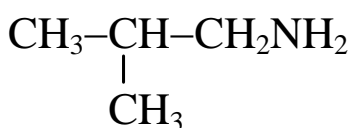
1. Nomenclature

Amines are commonly named as alkyl amines. The alkyl groups attached to N-atom are named in the alphabetical order followed by amine. According to IUPAC system of nomenclature they are named as *Alkanamine*. The longest carbon atom chain attached to N-atom is chosen as the parent compound and in the name of parent hydrocarbon, the last letter 'e' is replaced by the suffix amine. The substituents are named as prefixes in the alphabetical order. The IUPAC names (in bold letters) and common names (in parenthesis) of some of the well known amines are given below.

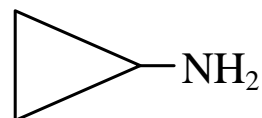
(a) Primary amines:



1-Propanamine
(n-propylamine)



2-methyl-1-propanamine
(isobutylamine)

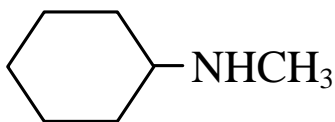


Cyclopropanamine
(cyclopropylamine)

(b) Secondary amines:



N-methylethanamine
(Ethylmethanamine)



N-methylcyclohexanamine
(cyclohexylmethanamine)



N-ethylethanamine
(Diethanamine)

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(c) Tertiary amines:



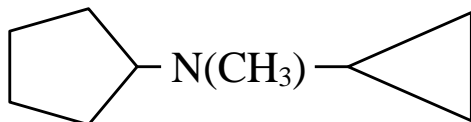
N-ethyl-N-methyl-1-propanamine

(Ethylmethylpropylamine)



N, N-dimethylmethanamine

(Trimethylamine)

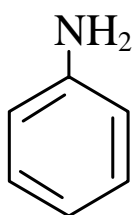


N-methyl-N-cyclopropylcyclopentanamine

(Methylcyclopentylcyclopropylamine)

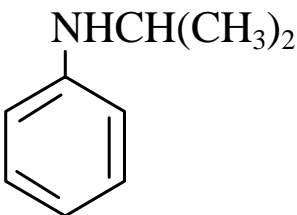
(d) Arylamines:

Arylamines have NH_2 group directly attached to the benzene ring. They are named as derivatives of aniline (common name) or benzenamine (IUPAC name).



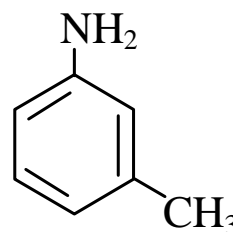
Benzenamine

(Aniline)



N-isopropylbenzenamine

(N-isopropylaniline)



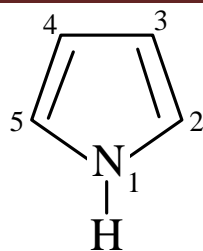
3-methylbenzenamine

(m-toluidine)

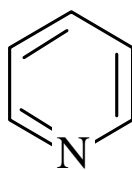
(e) Heterocyclic amines:

IUPAC names of heterocyclic amines have prefixes aza, diaza or triaza to indicate one, two or three nitrogen atoms have replaced carbon atoms in the corresponding hydrocarbons. Numbering of the ring starts from the hetero atom. The names of some of the well known heterocyclic amines are as follows:

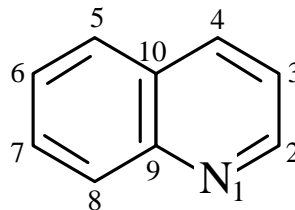
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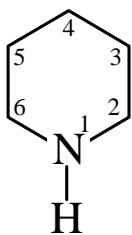
1-Azacyclopenta-2,4-diene
(Pyrrole)



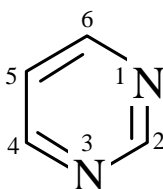
Azabenzene
(Pyridine)



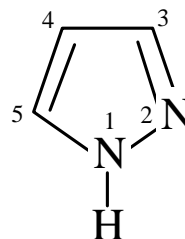
1-Azanaphthalene
(Quinoline)



1-Azacyclohexane
(Piperidine)



1,3-Diazabenzene
(Pyrimidine)

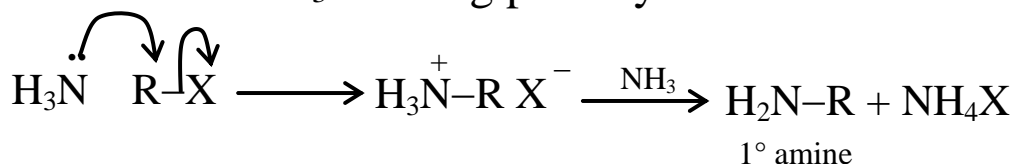


1,2-diazacyclopenta-2,4-diene
(Pyrazole)

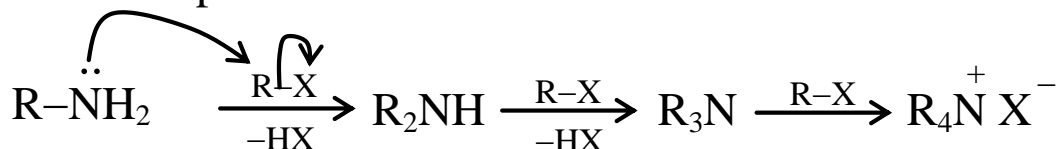
2. Methods of Preparation of Amines

2.1. Alkylation Of Ammonia

Alkyl halides undergo nucleophilic substitution reaction by S_N2 mechanism with NH_3 forming primary amines.

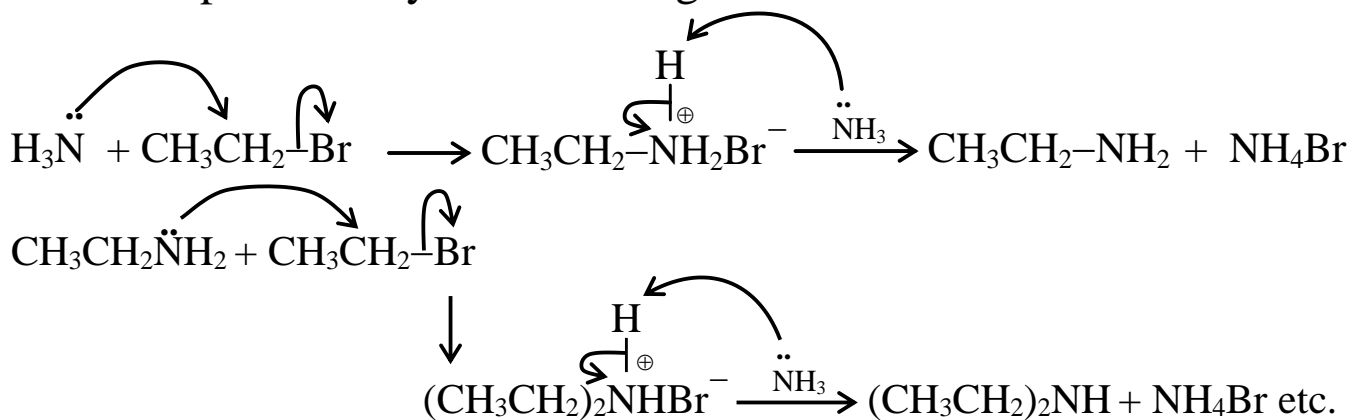


The reaction does not stop at this stage. Primary amine being more basic than ammonia further reacts with alkyl halide forming secondary amine (2°), tertiary amine (3°) and eventually quaternary ammonium salt, if the alkyl halide is present in excess.



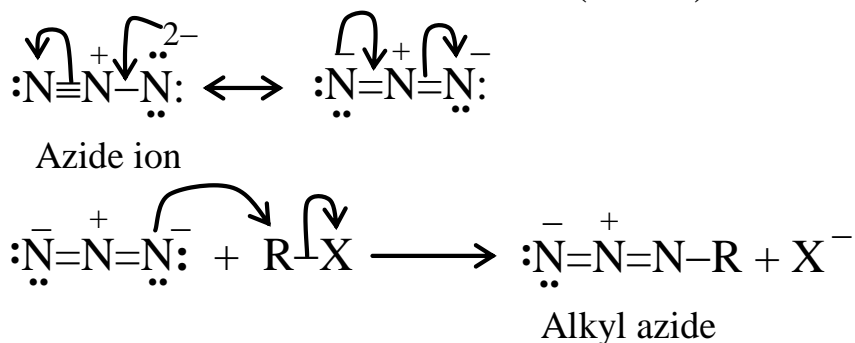
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We can make primary amine as the major product by carrying out the reaction with liquid ammonia. The reaction between ethyl bromide and ammonia proceeds by the following mechanism:

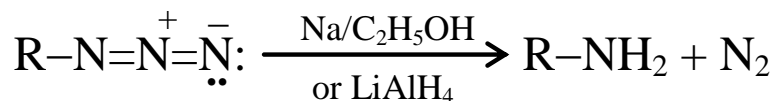


2.2 Alkylation of Azide Ion And Reduction

A much better method for preparing a primary amine from an alkyl halide is first to convert the alkyl halide to an alkyl azide (RN_3) by a nucleophilic substitution reaction with sodium azide (NaN_3).



The alkyl azide is then reduced to a primary amine with $\text{Na/C}_2\text{H}_5\text{OH}$ or LiAlH_4 .

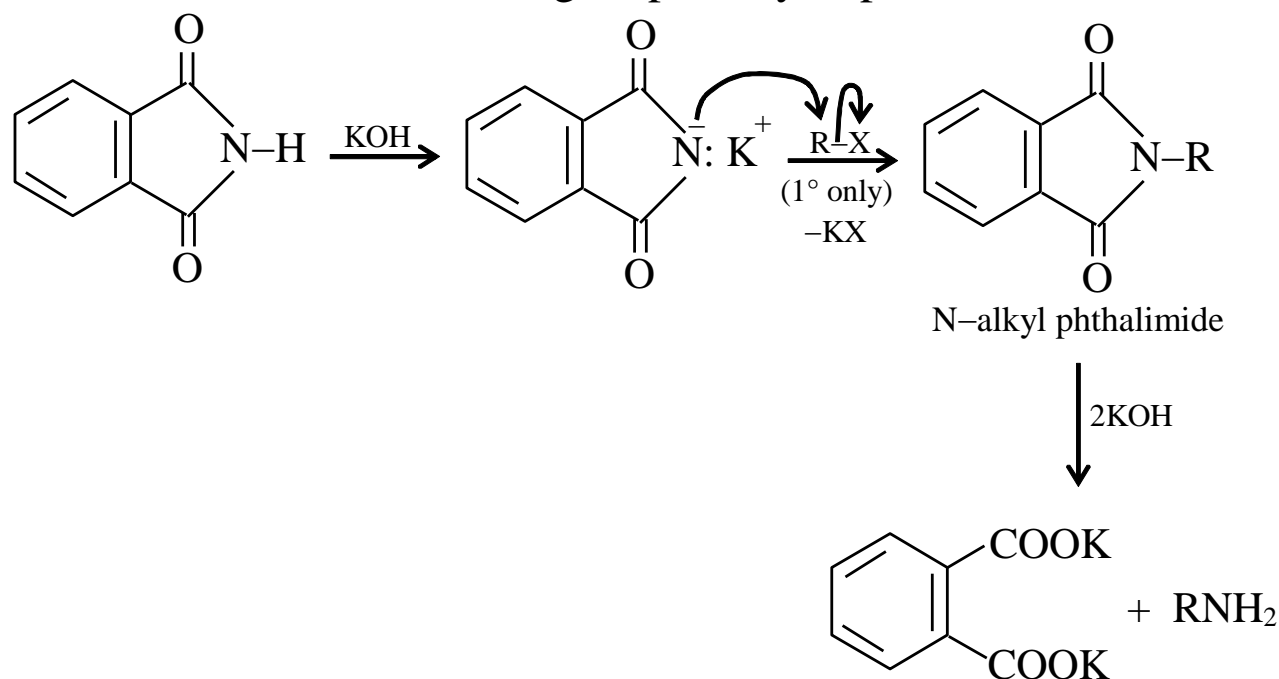


2.3 Gabriel Phthalimide Synthesis

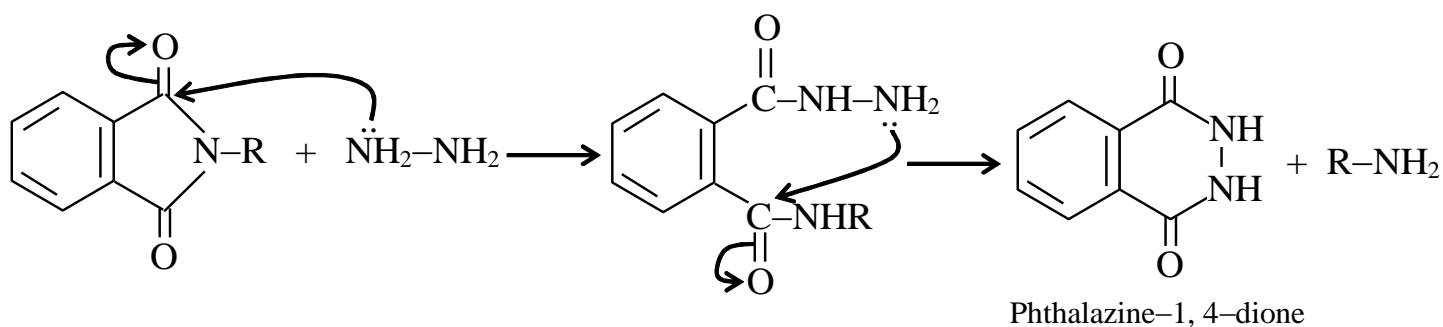
Another method used for the preparation of primary aliphatic amines only is the **Gabriel Phthalimide synthesis**. Phthalimide ($\text{pK}_a = 9$) is quite acidic in nature. It can be converted to potassium phthalimide by its

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reaction with KOH. The phthalimide anion is a strong nucleophile. It reacts with alkyl halide, preferably methyl halide and primary alkyl halide only, by an S_N2 mechanism to give N-alkylphthalimide. The secondary and tertiary alkyl halides are not employed because they undergo elimination reactions also. The N-alkyl phthalimide is hydrolysed with dilute HCl or KOH solution to give primary aliphatic amine.



N-alkylphthalimide can also be converted to primary amine and phthalazine-1, 4-dione by treating it with hydrazine.

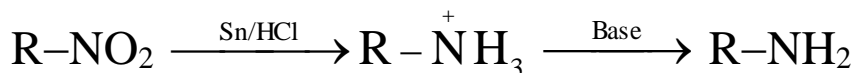
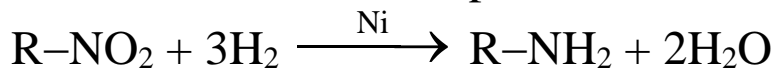


This method is not suitable for preparing aromatic primary amines as aryl halides are not good substrates for nucleophilic substitution.

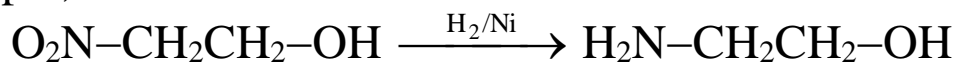
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2.4 Reduction of Nitro Compounds

Aliphatic primary amines can be synthesised by reducing nitroalkanes with metal and acid or with H_2 in presence of nickel as a catalyst.



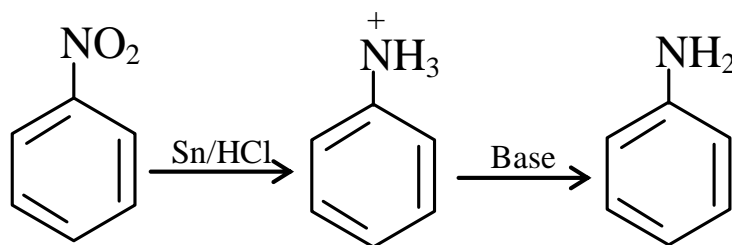
For example,



2-nitro ethanol

2-amino ethanol

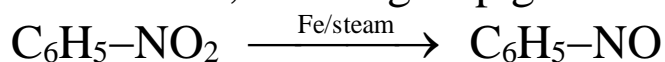
Primary aromatic amines are also prepared by the reduction of corresponding nitro compounds.



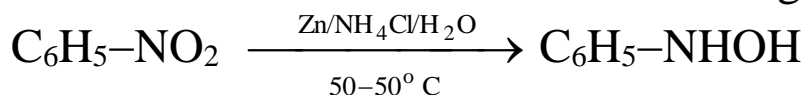
Other reducing agents such as LiAlH_4 and H_2/Pt also reduce nitrobenzene to aniline.

Reduction in neutral medium

1. With Fe and steam, a nitro group gets reduced to nitroso group.

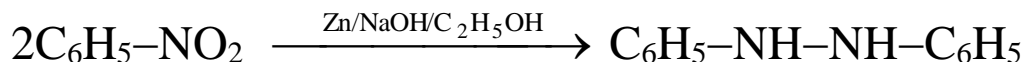


2. $\text{Zn}/\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ or $\text{Zn}/\text{CaCl}_2/\text{H}_2\text{O}$ reduces nitro group to hydroxylamine.



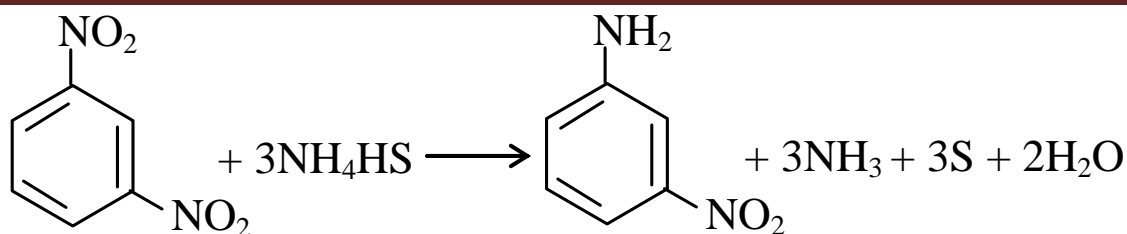
Reduction in alkaline medium

Nitro benzene when reduced with $\text{Zn}/\text{NaOH}/\text{C}_2\text{H}_5\text{OH}$ gives hydroazobenzene.

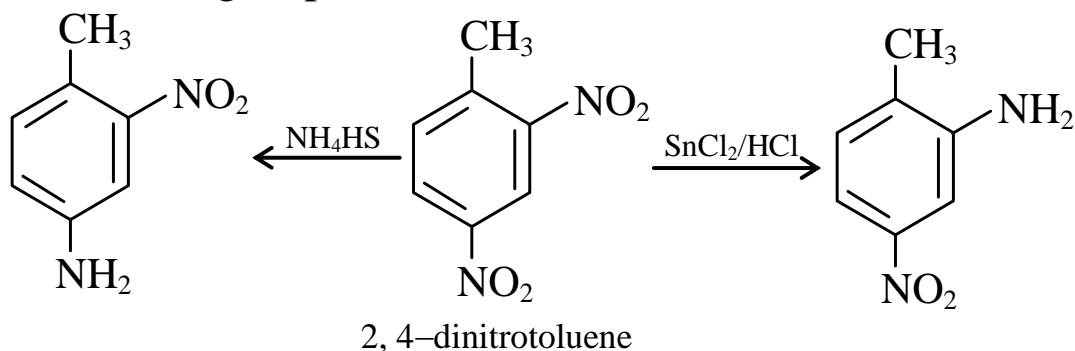


By means of aqueous ethanolic NH_4HS , aqueous Na_2S or SnCl_2 in HCl , nitro groups in a polynitro compound can be reduced one at a time. For example, *m*-dinitrobenzene can be reduced to *m*-nitroaniline.

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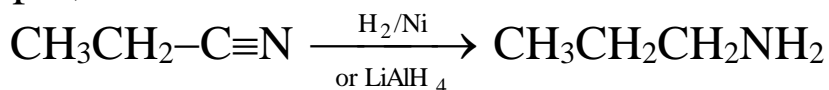
It is not always possible to predict that which nitro group will be reduced first. For instance, 2, 4–dinitrotoluene when treated with NH_4HS , the 4–nitro group is reduced whereas treatment with SnCl_2/HCl results in the reduction of 2–nitro group.



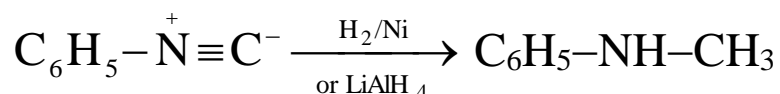
2.5 Reduction of Nitriles, Isonitriles And Oximes

Both aliphatic and aromatic amines can be synthesised by reduction of cyanides (or nitriles), isocyanides (or isonitriles) and oximes by H_2 in the presence of a catalyst or LiAlH_4 .

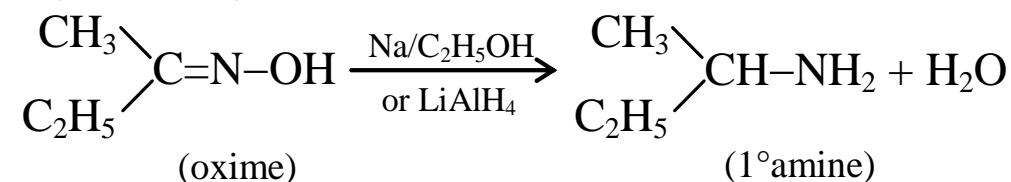
For example,



(1° amine)



(2° amine)

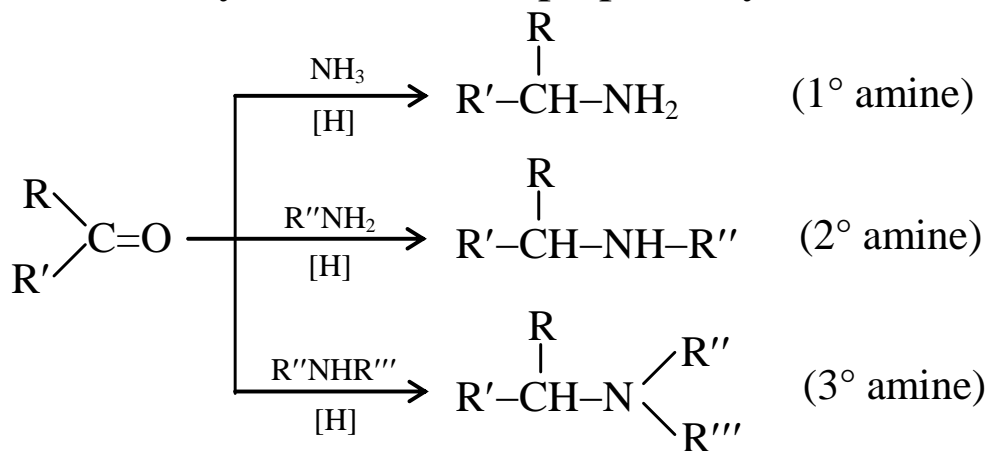


Cyanides and oximes on reduction gives 1° amines while isocyanide on reduction gives 2° amines.

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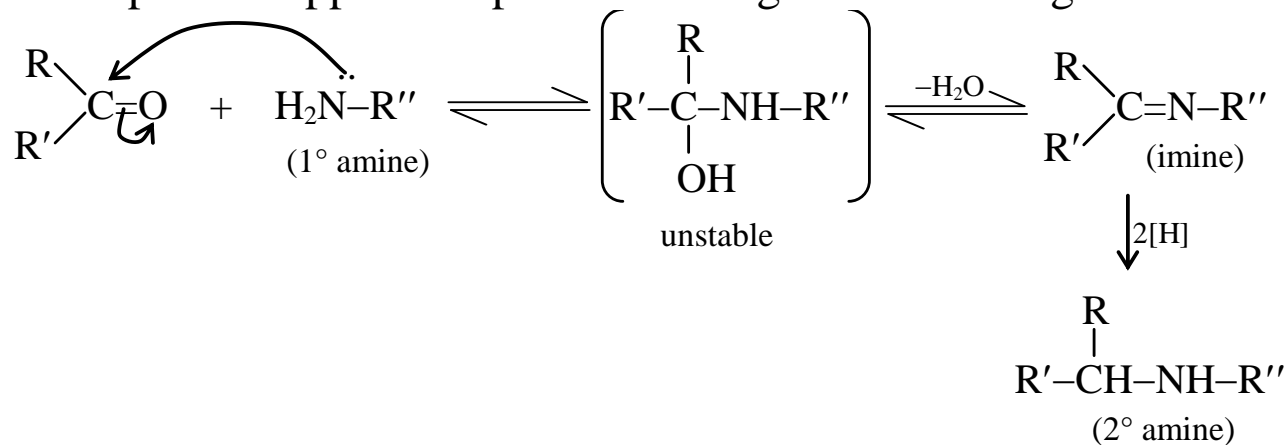
2.6 Reductive Amination of Carbonyl Compounds

Aldehydes and ketones are converted to amines through catalytic or chemical reduction in the presence of ammonia or amine. Primary, secondary and tertiary amines can be prepared by this method.



(R' may be hydrogen or an alkyl group)

The above process appears to proceed through the following mechanism.

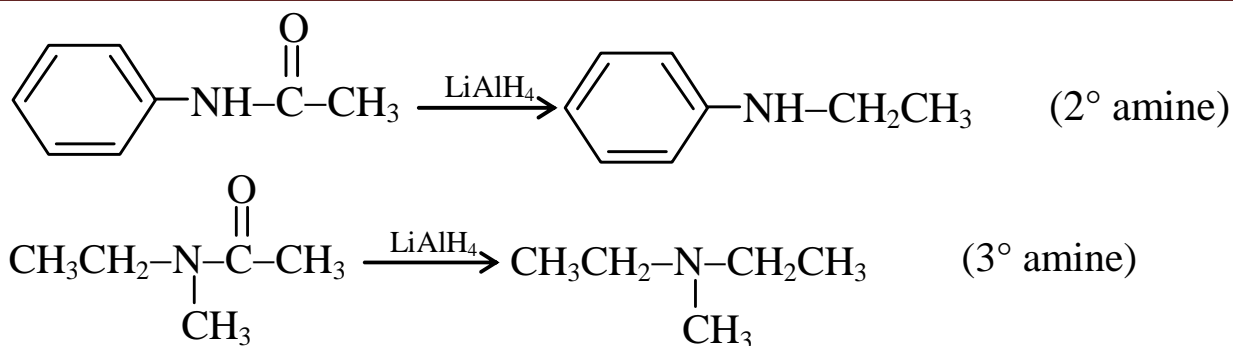


2.7 From Amides

Amides with or without any substituent on the nitrogen can be reduced with LiAlH_4 to the corresponding amines having same number of carbon atoms. For example,

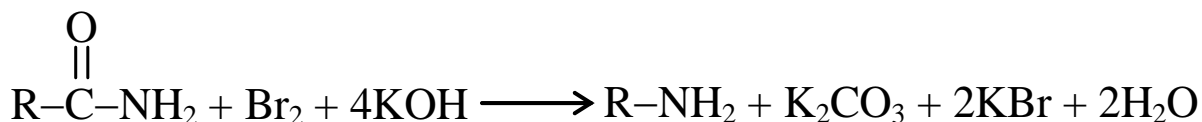


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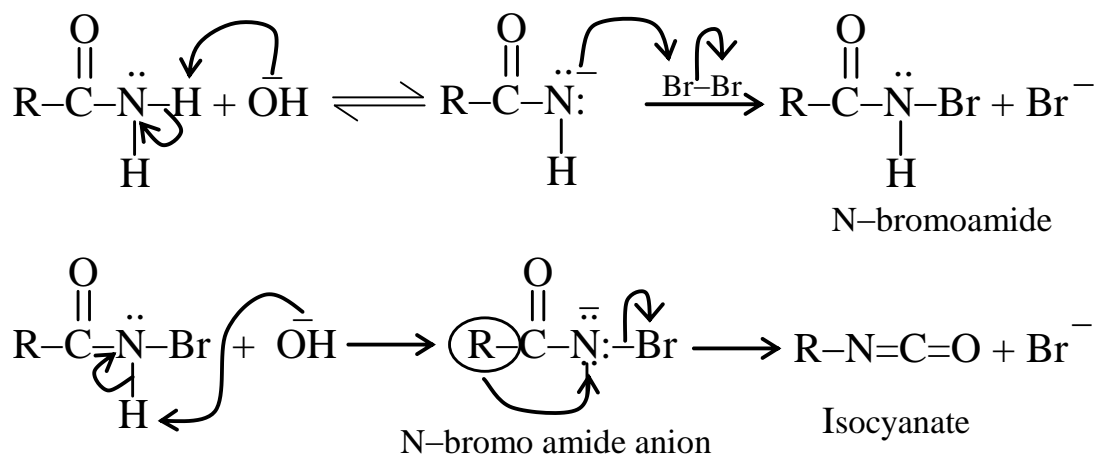


2.8 Hoffmann Bromamide Degradation

Amides with no substituent on the nitrogen when treated with a solution of Br_2 or Cl_2 in KOH yield only primary amines having one carbon atom less than the amides.

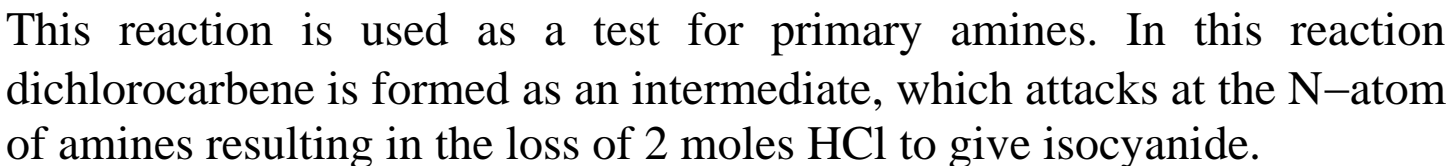


The reaction mechanism involves base-promoted N-bromination yielding N-bromo amide as an intermediate. The N-bromo amide then reacts with hydroxide ion to produce N-bromamide anion, which rearranges with the migration of R group and loss of Br^- ion to produce isocyanate. Base catalysed hydrolysis of isocyanate formed in the reaction mixture produces carbamate ion, which undergoes spontaneous decarboxylation resulting in the formation of amine.



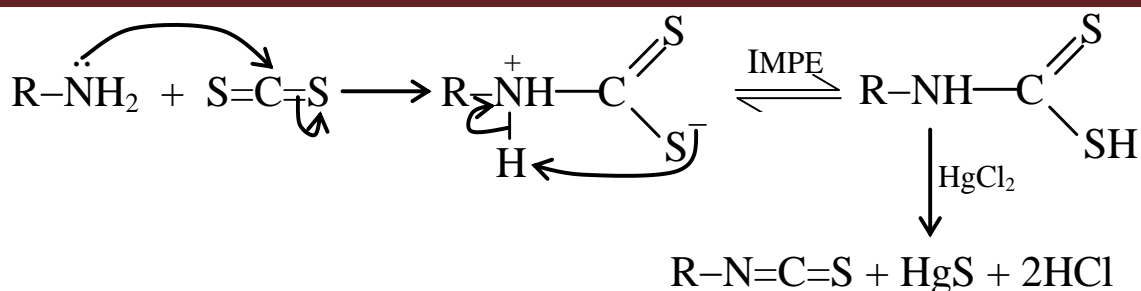


Both aliphatic and aromatic amines when heated with chloroform and ethanolic KOH form isocyanide, also called carbylamine, a foul smelling compound.



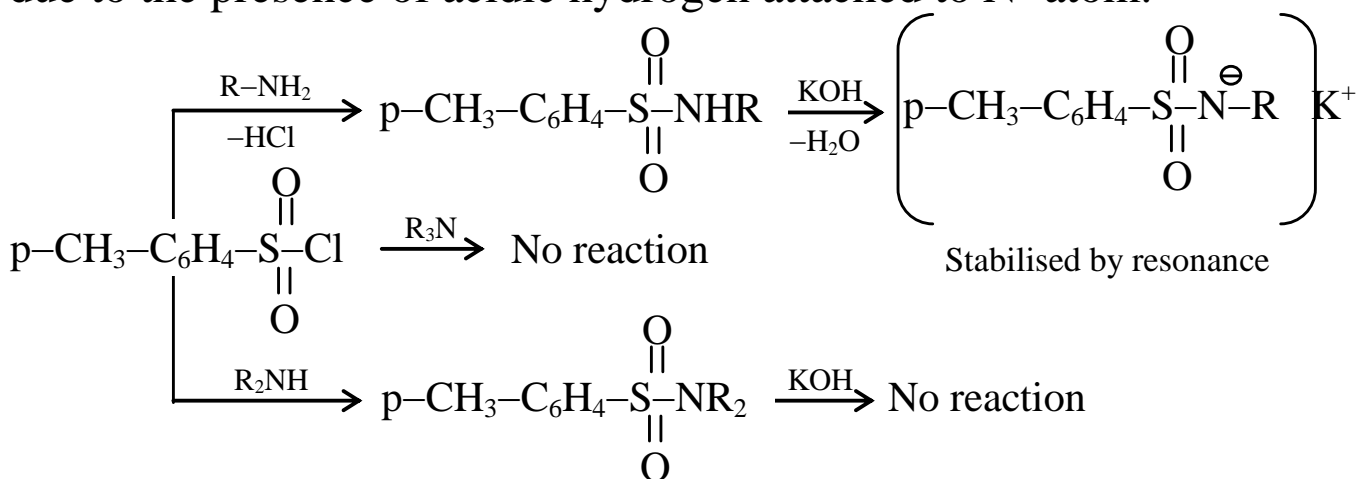
When warmed with carbon disulphide, primary amines form dithiocarbamic acid, which is decomposed by mercuric chloride to the alkyl isothiocyanate.

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3.3 Hinsberg Reaction:

This reaction is used for the separation of amines from a mixture. The mixture containing primary, secondary and tertiary amines is treated with an aromatic sulphonyl chloride. Originally benzenesulphonyl chloride, $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ was used, but has now been replaced by p-toluene sulphonyl chloride, $\text{p-CH}_3\text{-C}_6\text{H}_4\text{-SO}_2\text{Cl}$. After treatment with this acid chloride, the solution is made alkaline with KOH. Primary amines form N-alkylsulphonamides, which dissolve in KOH forming potassium salt due to the presence of acidic hydrogen attached to N-atom.

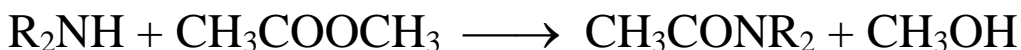
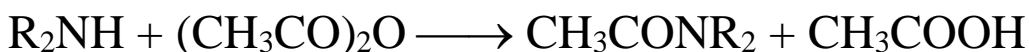
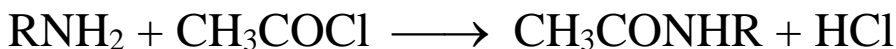


Secondary amines form N, N-dialkylsulphonamides, which do not dissolve in KOH because there is no hydrogen atom attached to N. Tertiary amines do not react with p-toluenesulphonyl chloride.

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3.4 Reaction With Carboxylic Acid Derivatives:

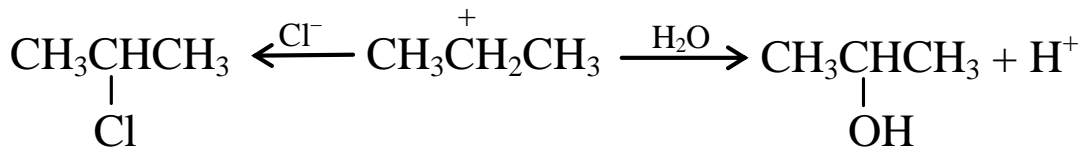
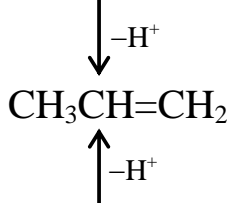
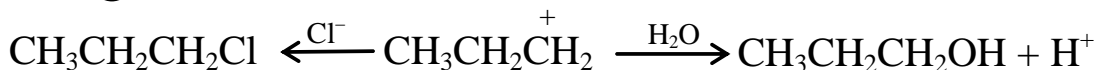
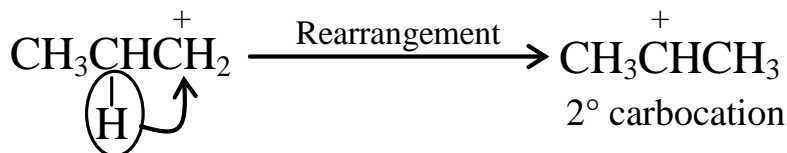
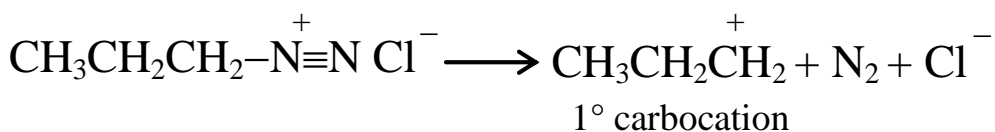
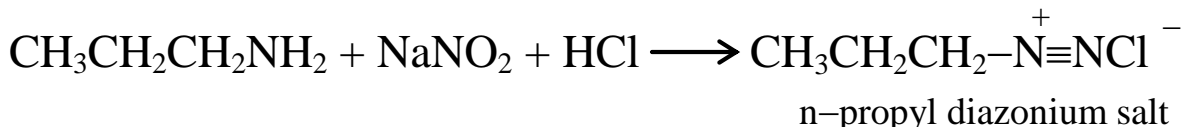
Primary and secondary amines react with acid chlorides, anhydrides or esters to form substituted acid amides; primary amines forming N-alkyl amides and secondary amines forming N, N-dialkyl amides.



3.5 Reaction With Nitrous Acid:

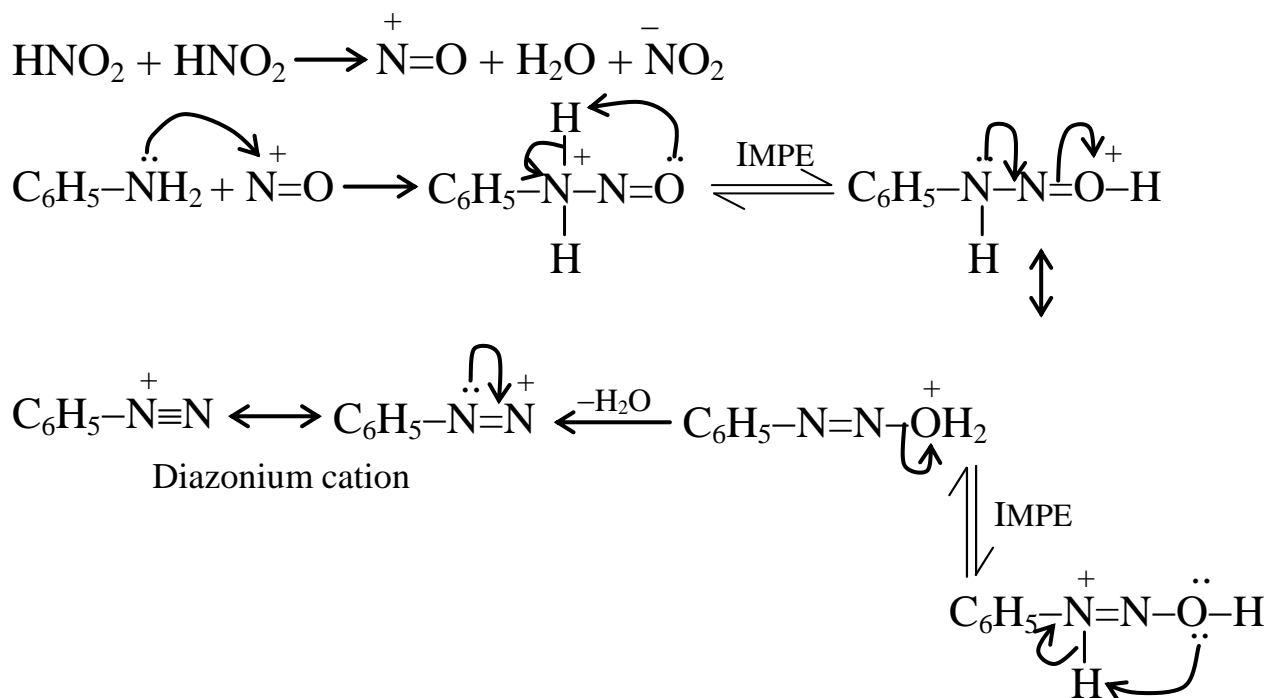
Primary amines:

Aliphatic primary amines react with HNO_2 with the evolution of N_2 . Nitrous acid is aliphatic produced in the reaction mixture by adding NaNO_2 and dilute HCl . The reaction proceeds via diazonium salt, which is not stable and decomposes to yield a carbocation as one of the intermediates. This carbocation gives variety of products. For example,

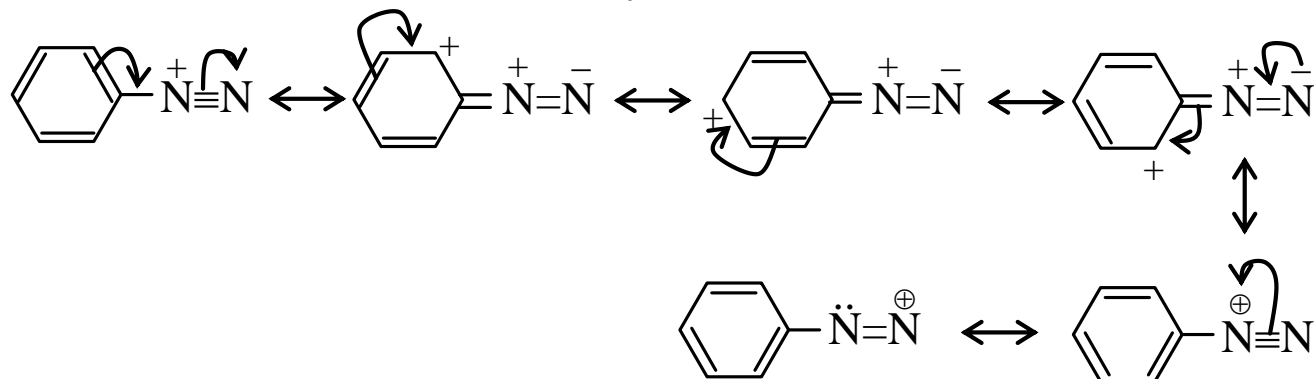


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Diazonium salts of aromatic amines are stable at low temperature ($0-5^{\circ}\text{C}$) but decompose with the evolution of N_2 on heating. The mechanism involved in the formation of diazonium salt is as follows:



Aromatic diazonium chlorides, sulphates, nitrates etc. are reasonably stable in aqueous solution at room temperature or below but cannot be readily isolated without decomposition. The π -orbital system of benzene ring stabilises the diazonium cation by resonance.

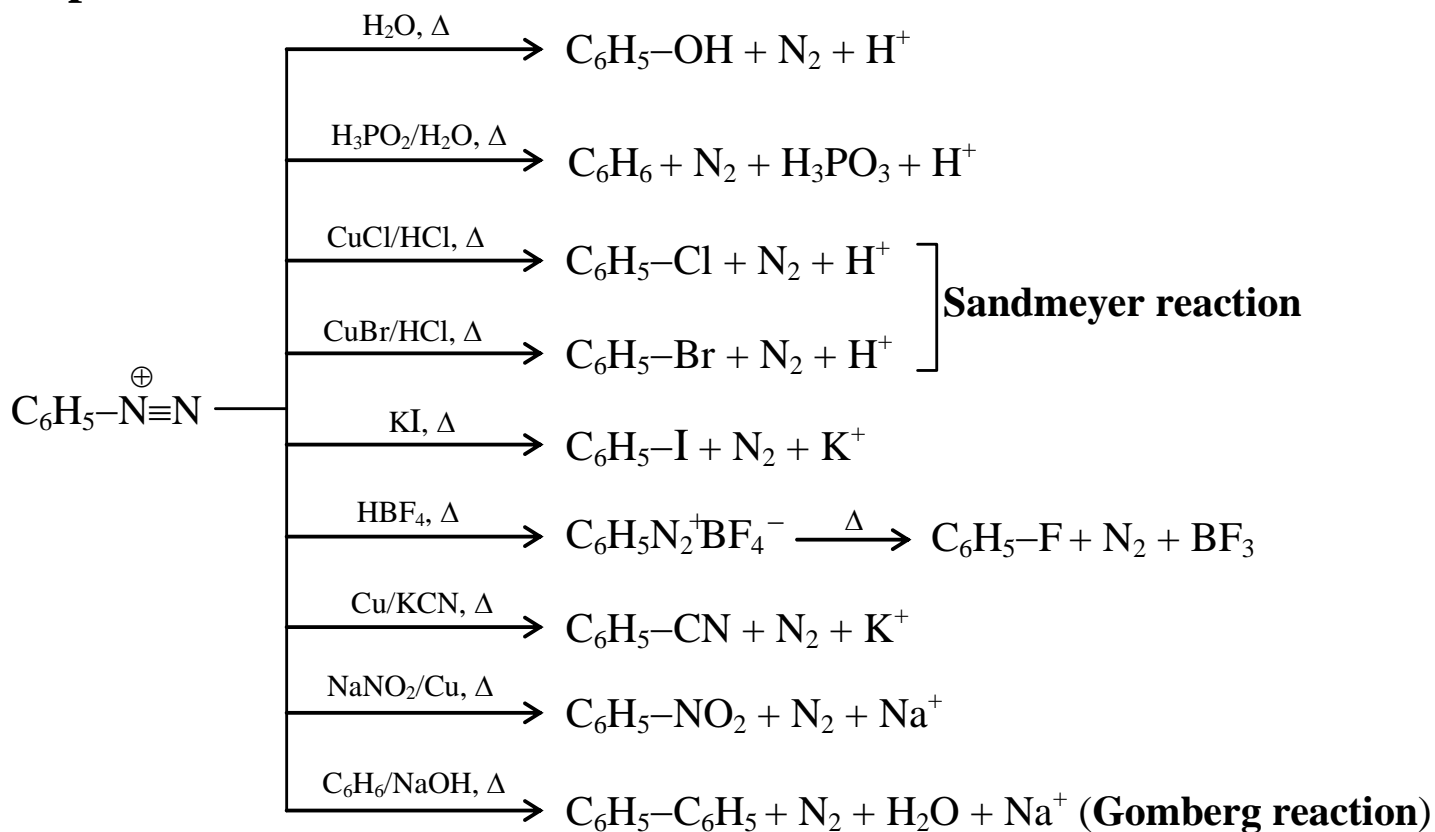


The diazonium salts are very important synthetic reagents, being the starting point in the preparation of various aromatic compounds. Their reactions may be divided into two groups; those which involve the liberation of N_2 gas and the displacement of the diazo group $-\text{N}_2^+$, by

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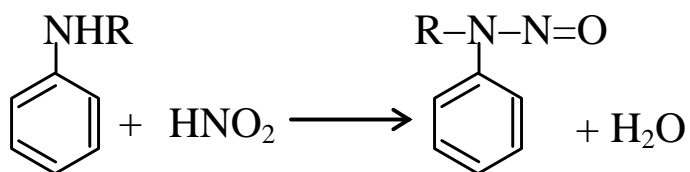
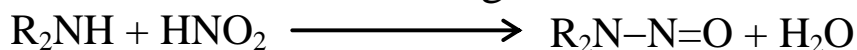
another univalent group and those in which the two N-atoms are retained (coupling reactions).

Replacement reactions:



Secondary amines

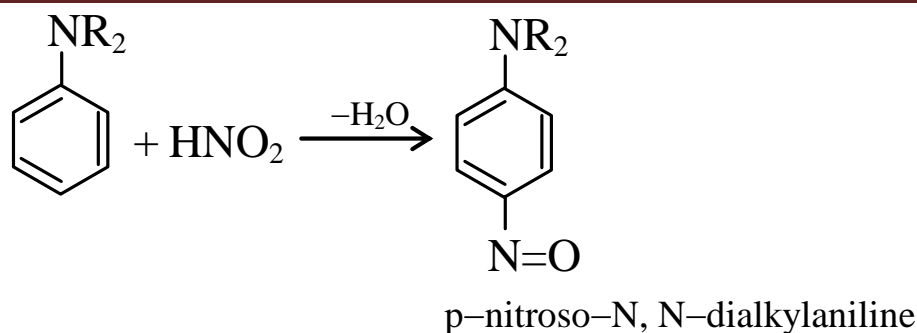
Both the aliphatic and aromatic amines react with HNO_2 in which NO^+ ion attacks the N-atom of the amine forming N-nitrosamine.



Tertiary amines

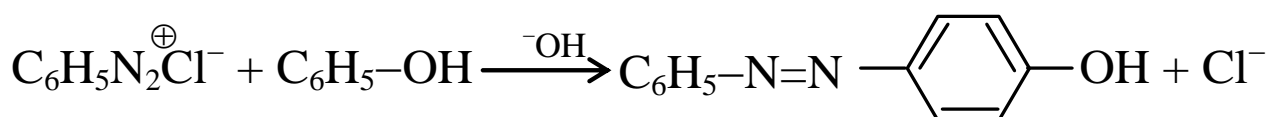
Aliphatic tertiary amines (3°) do not react with HNO_2 whereas aromatic tertiary amines react with HNO_2 forming p-nitroso-N, N-dialkylaniline as the major product.

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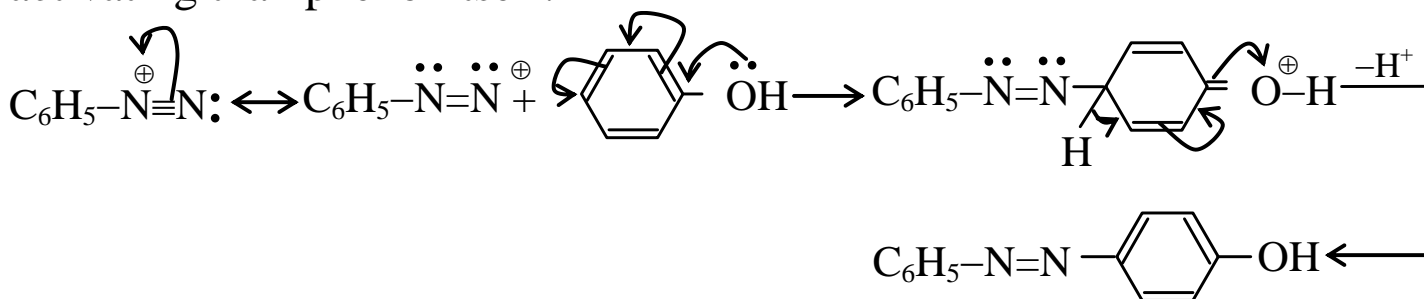


3.6 Azo Coupling

Diazonium salts readily undergo coupling reactions with phenols, naphthols and aromatic amines to form highly coloured azo-compounds. For example, benzenediazonium chloride couples with phenol in weakly alkaline solution to form p-hydroxyazobenzene.

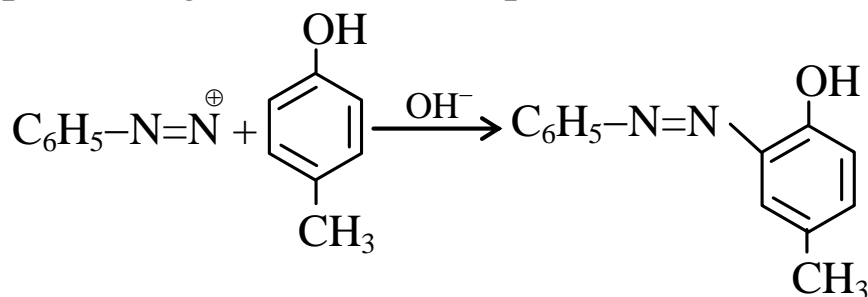


The rate of reaction increases as the pH change from 5 to 8. Under mildly alkaline conditions, phenol behaves as phenoxide ion, which is much more activating than phenol itself.



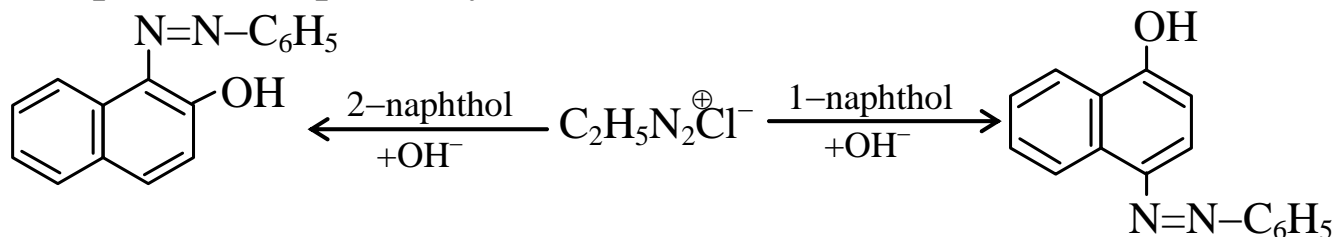
Coupling with benzene substrates occurs preferentially in the para position to the hydroxyl group. But if this position is blocked, then the coupling occurs at the ortho position.

For example, p-cresol gives o-azo compound.



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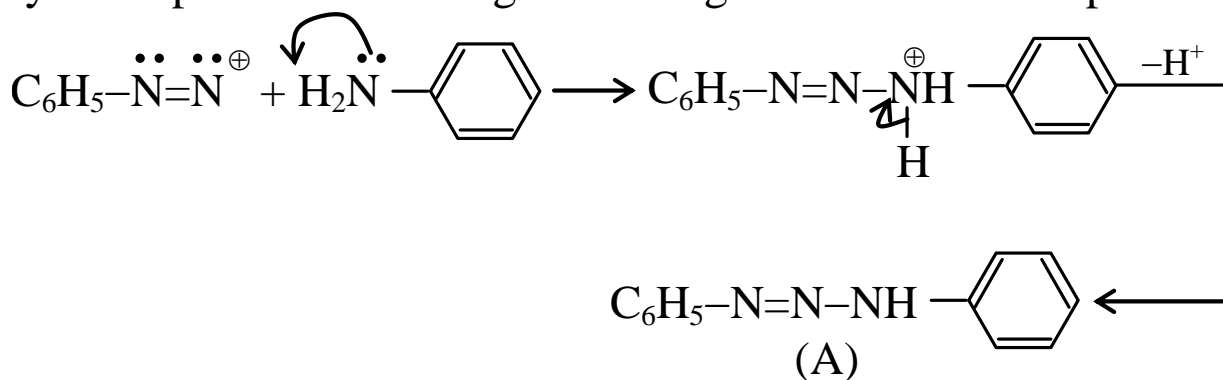
1- and 2-naphthols in alkaline solution couple with diazonium salt in the 4- and 1-position respectively.



Aromatic amines are in general somewhat less readily attacked than phenols and coupling is often carried out in slightly acid solution. Under these conditions not only the concentration of $\text{C}_6\text{H}_5\text{N}_2^+$ is high but also the

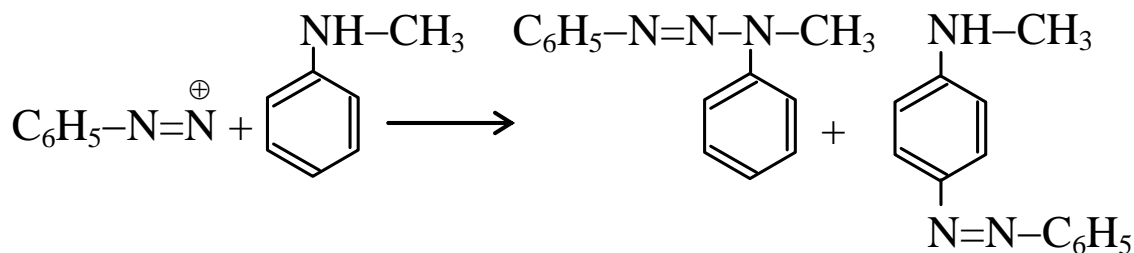
amine $\text{Ar}\ddot{\text{N}}\text{H}_2$ is not significantly converted into the unreactive protonated cation, $\text{Ar}\overset{+}{\text{N}}\text{H}_3$. The initial diazotisation of aromatic primary amines is carried out in strongly acidic media to ensure that as yet unreacted amine is converted to the cation and so prevented from coupling with diazonium salt as it is formed.

With aromatic amines, there is the possibility of attack on either nitrogen or carbon. In the case of primary amines, the attack of diazonium ion mainly takes place at the nitrogen forming diazo-amino compound (A).

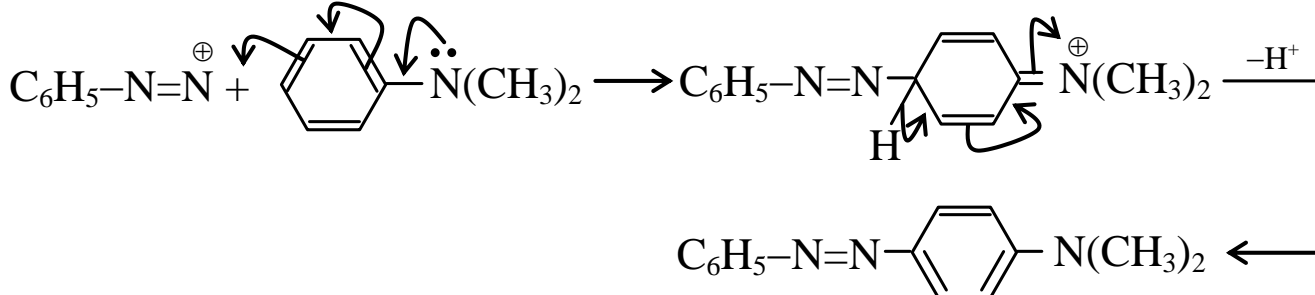


With secondary amines (e.g., N-alkyl anilines), two products are formed; one due to N-N coupling and the other due to N-C coupling. For example,

AMINES

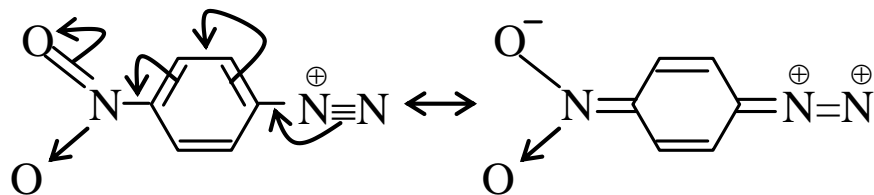


Tertiary amines (e.g. N, N-dialkylaniline) show only N–C coupling.



Diazonium cation, $\text{C}_6\text{H}_5\text{N}_2^+$ is a relatively weak electrophile and reacts with only highly reactive aromatic compounds such as phenols, aniline and substituted anilines.

It does not react with less reactive compound $\text{C}_6\text{H}_5-\text{OCH}_3$ (anisole), mesitylene etc. Its reactivity can be increased by introducing strongly electron withdrawing groups such as NO_2 at the ortho or para position. This will enhance positive charge at the diazo group making it a better electrophile.



Thus, the 2,4-dinitrophenyl diazonium cation will react with $\text{C}_6\text{H}_5-\text{OCH}_3$ and 2,4,6-trinitrophenyl diazonium cation will even react with the hydrocarbon 1,3,5-trimethyl benzene (mesitylene).

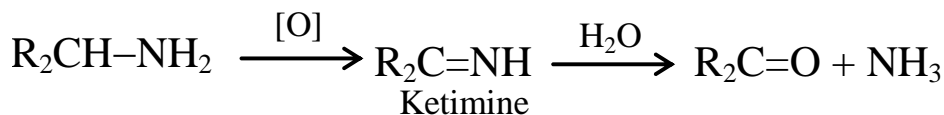
3.7 Oxidation Reactions

Both the primary and secondary amines undergo oxidation. The oxidation products obtained depend on the oxidising agent used and on the nature of alkyl group.

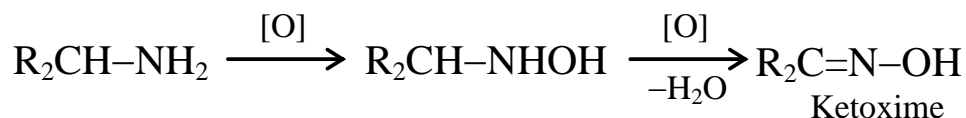
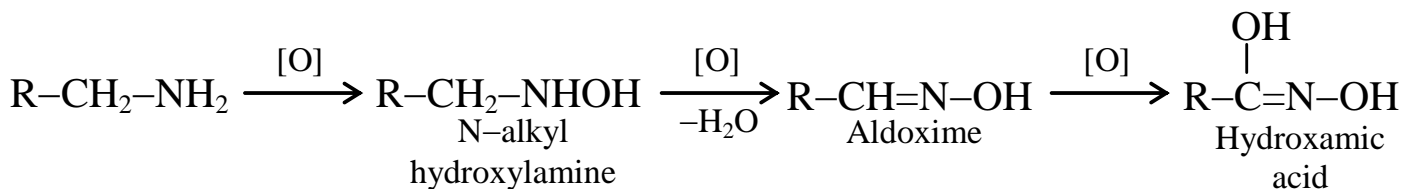
AMINES

Primary amines

(i) With KMnO_4 :

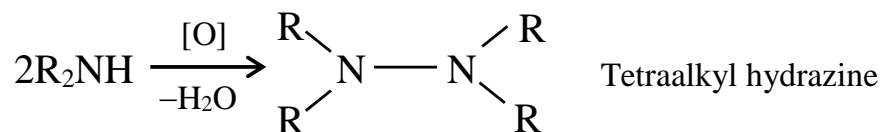


(ii) With Caro's acid (H_2SO_5)/ H_2O_2 /Peroxy carboxylic acid:

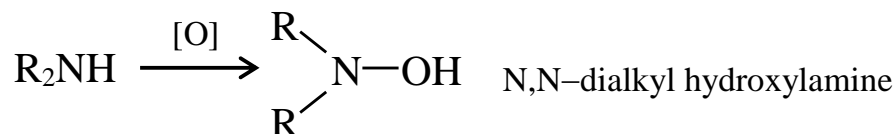


Secondary amines

(i) With KMnO_4 :



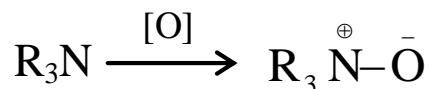
(ii) With Caro's acid (H_2SO_5)/ H_2O_2 /Peroxy carboxylic acid:



Tertiary amines

(i) With H_2O_2 /Peroxy carboxylic acid

Tertiary amines are oxidised to amine oxide, $\text{R}_3\text{N}^{\oplus}\text{-}\bar{\text{O}}$ (a dipolar ion or Zwitterion).

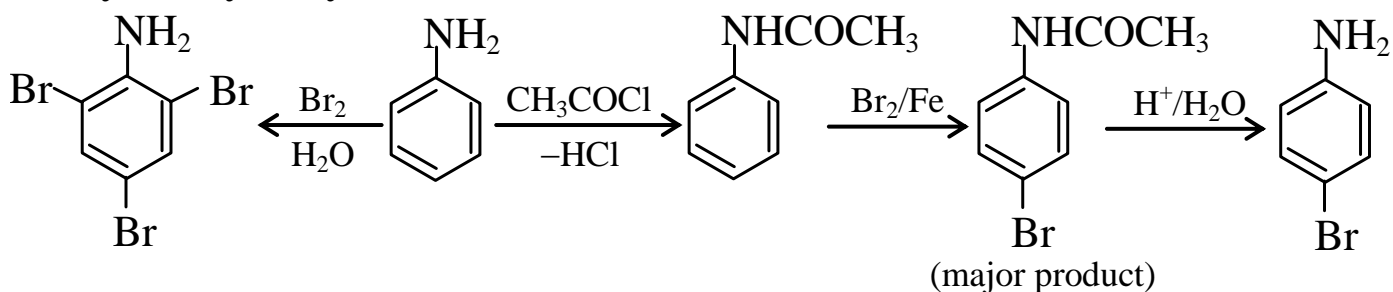


3.8 Ring Substitution Reactions

$-\text{NH}_2$, $-\text{NHR}$ and $-\text{NR}_2$ groups when attached to benzene strongly increases its electron density, making it highly reactive towards electrophilic aromatic substitution.

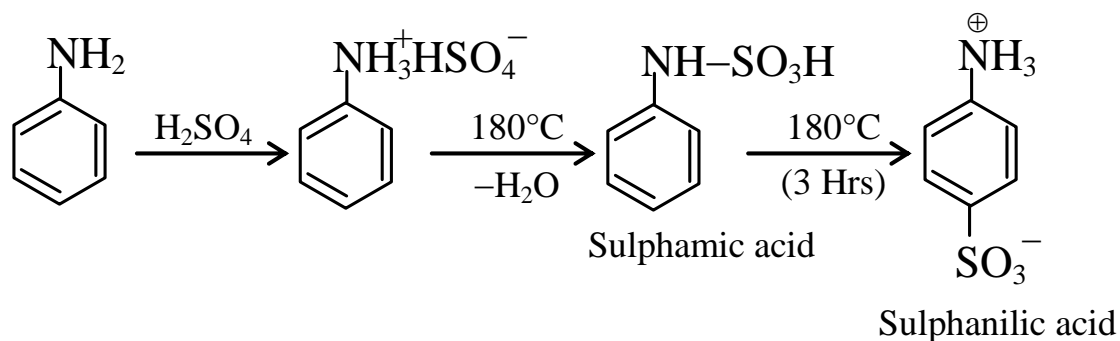
(i) Halogenation

When aniline is treated with bromine water, the substitution takes place at all the three places (two ortho and one para) yielding the solo product 2,4,6-tribromoaniline. In order to carry out monobromination, the $-\text{NH}_2$ group is first converted to moderately activating acetanilide group $-\text{NHCOR}$ and then subjecting it to bromination followed by acid or base catalysed hydrolysis.



(ii) Sulphonation

Aniline reacts with H_2SO_4 forming a salt, which on heating at 180°C yields sulphamic acid. If the heating is continued at 180°C for 3 hours, sulphamic acid undergoes rearrangement to give sulphanilic acid, which exists as a dipolar ion.

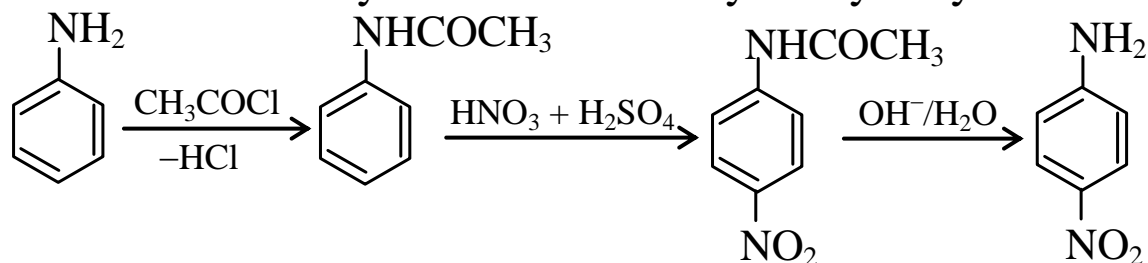


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In contrast, p-amino benzoic acid does not exist as a dipolar ion because $-\text{COOH}$ is a very weak acid in comparison to $-\text{SO}_3\text{H}$ and is unable to transfer proton to the weakly basic $-\text{NH}_2$ group.

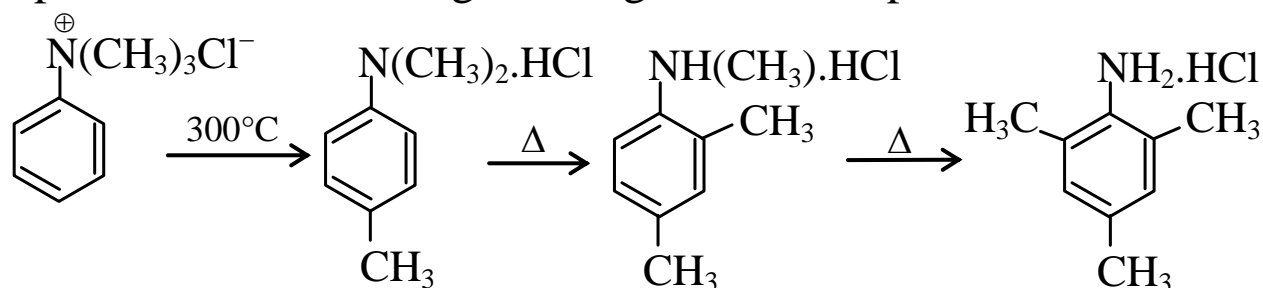
(iii) Nitration

Aniline is very reactive towards nitration and much of it gets oxidised by HNO_3 . In order to carry out mononitration of aniline, the aniline is first converted to acetanilide and then acetanilide is subjected to nitration by nitrating mixture followed by acid or base catalysed hydrolysis.



3.9 Rearrangement Reactions

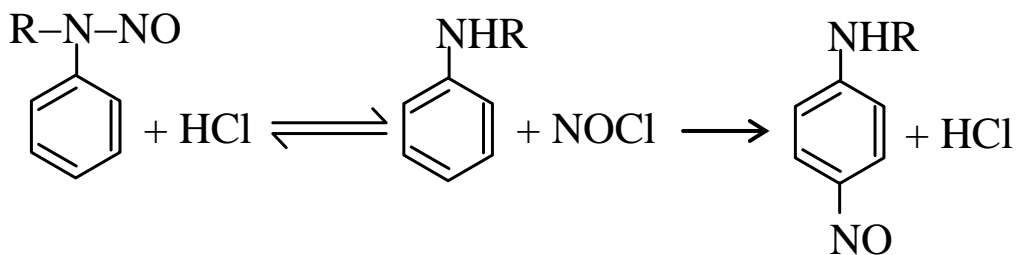
A remarkable property of mono-, di-, and trialkyl anilinium chlorides (or bromides) is their ability to undergo rearrangement on strong heating, an alkyl group migrating from the N-atom and entering preferentially the p-position. If this position is occupied, then the alkyl group migrates to the o-position. For example, when trimethyl anilinium chloride is heated under pressure, the following rearrangement takes place.



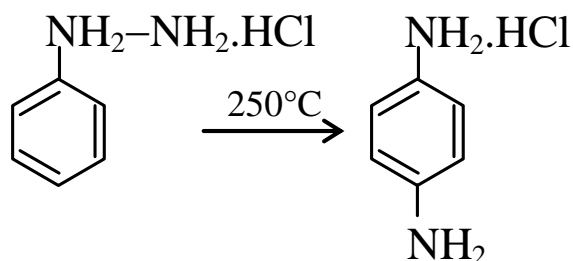
This reaction is known as the **Hoffmann–Martius rearrangement**.

Rearrangements of this kind have been observed to take place with aniline derivatives of the type $\text{C}_6\text{H}_5\text{--NH--Z}$ where Z is R, X, NH_2 , OH, NO or NO_2 . For example,

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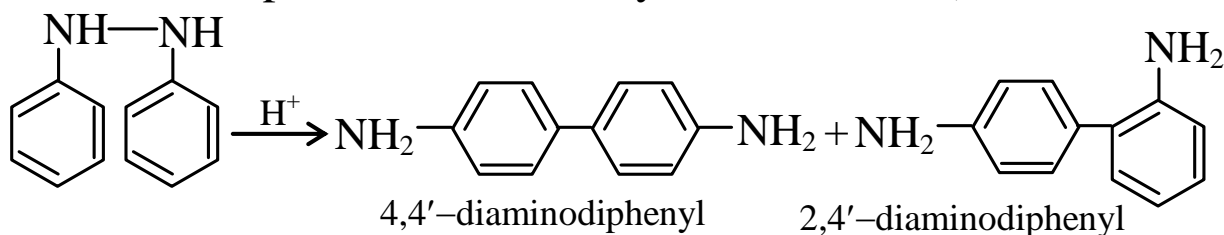


This reaction is called **Fischer-Hepp rearrangement**.



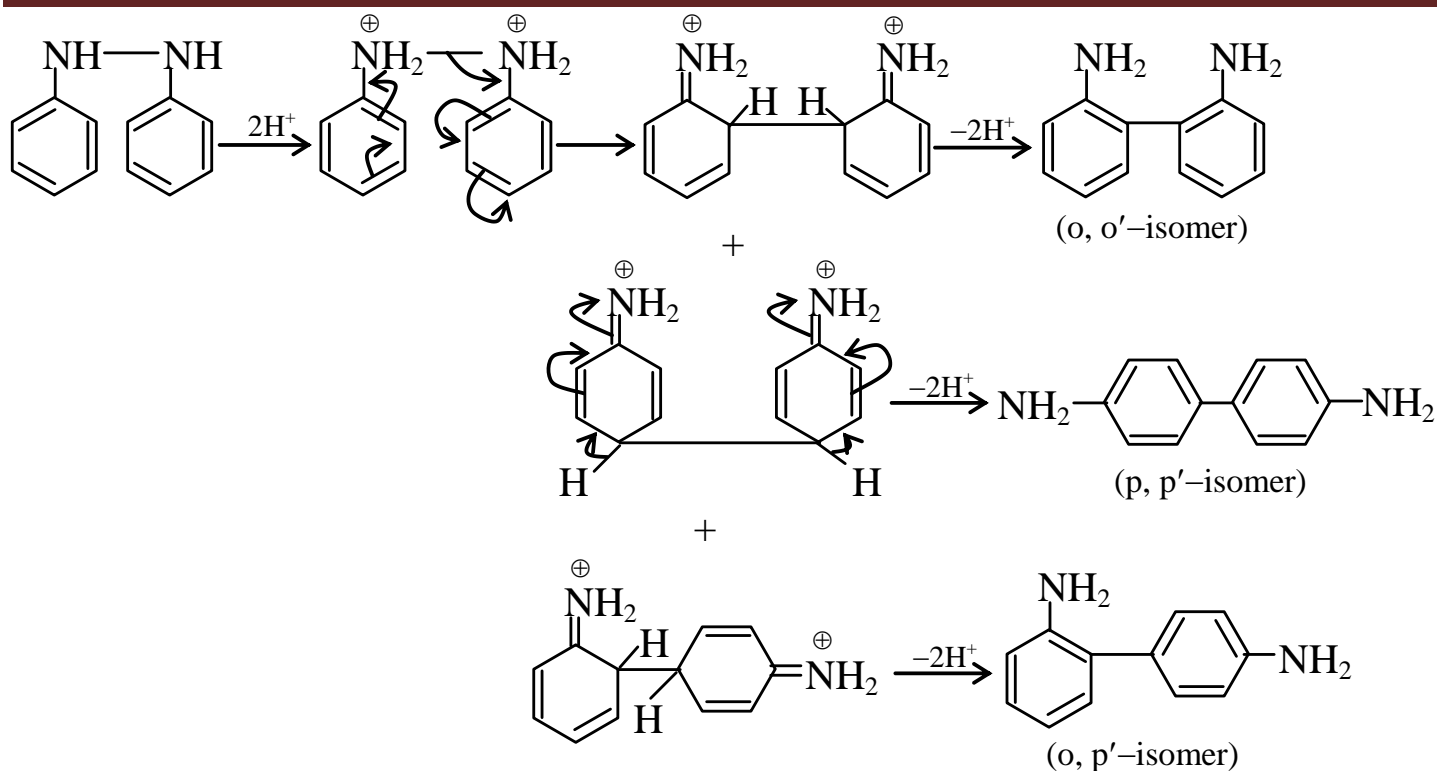
Benzidine Rearrangement

Hydroazobenzene, $\text{C}_6\text{H}_5\text{NH}-\text{NHC}_6\text{H}_5$ undergoes rearrangement when heated in the presence of acid to yield benzidine (4, 4'-diamino diphenyl).



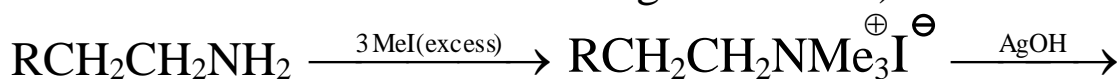
This is known as benzidine rearrangement. The p, p'-isomer is the major product (70%) and the rest is o, p' and o, o'-isomer. The reaction probably follows the given mechanism.

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3.10 Exhaustive Methylation

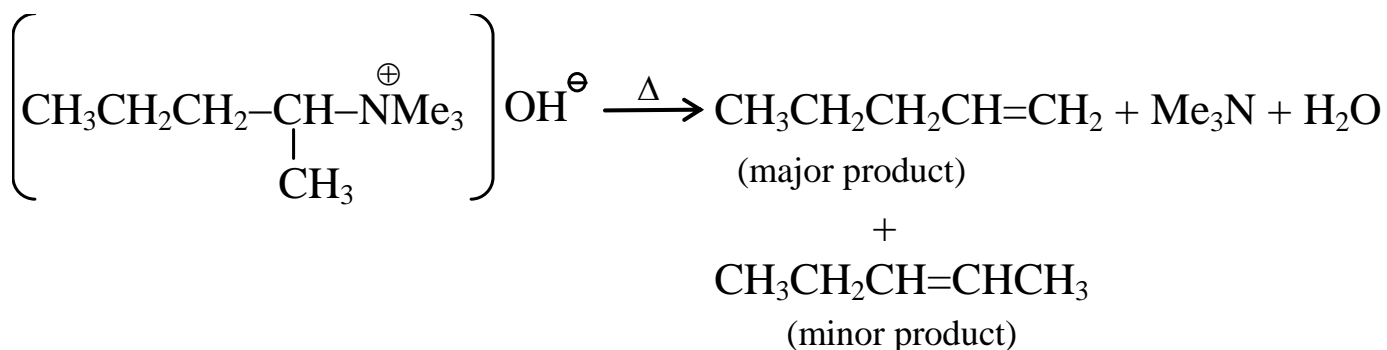
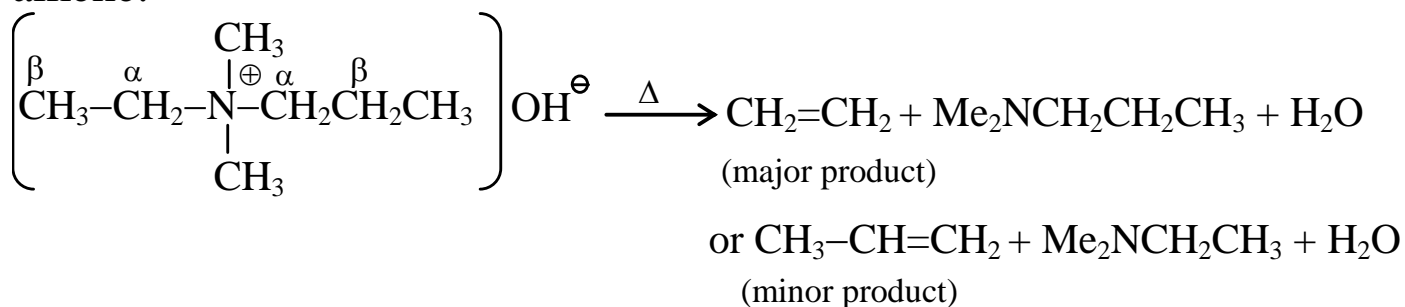
Primary, amine $\text{RCH}_2\text{CH}_2\text{NH}_2$ undergoes exhaustive methylation with the MeI to give quaternary ammonium iodide $\text{RCH}_2\text{CH}_2\text{NMe}_3^+\text{I}^-$. The quaternary ammonium iodide on treatment with AgOH gives quaternary ammonium hydroxide $\text{RCH}_2\text{CH}_2\text{NMe}_3^+\text{OH}^-$ along with precipitate of AgI . When quaternary ammonium hydroxide is heated, it undergoes Hoffmann elimination (Hoffmann degradation) to give mostly less substituted alkene. The alkene formation is governed by the loss of most acidic $\beta\text{-H}$ ($1^\circ > 2^\circ > 3^\circ$). The transition state has more C-H^β bond breaking than bond making (double bond formation) because the leaving group is a relatively poor one. Thus, the acidity of $\beta\text{-H}$ becomes more important than the stability of alkene that forms. This is called **Hoffmann rule** (less substituted alkene is formed in higher amount).



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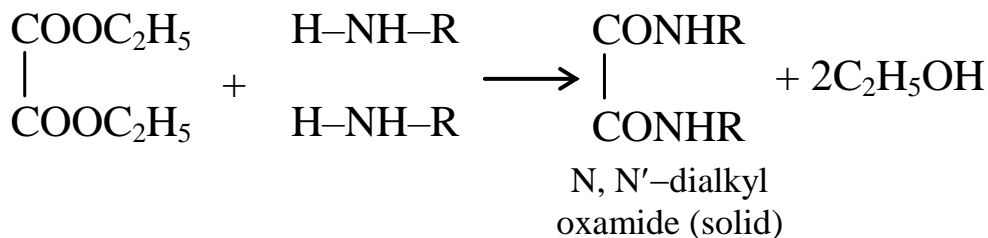


But when there are two alkyl groups, each having β -hydrogens, that alkyl part forms alkene, whose β -H is more acidic to give least substituted alkene.



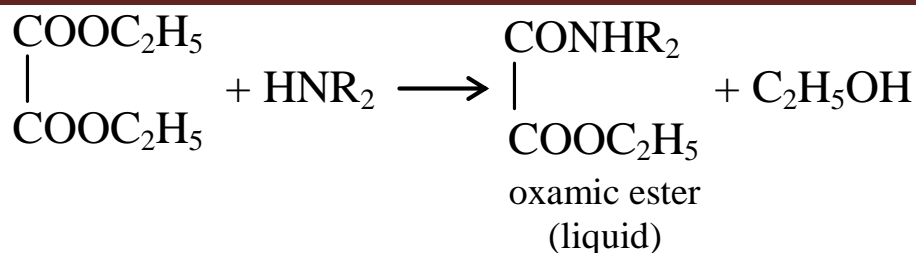
3.11 Reaction With Diethyl Oxalate

1° , 2° and 3° amines can be distinguished by their reaction with diethyl oxalate. Primary (1°) amines react with diethyl oxalate forming N, N'-oxamide, which is a solid.



Secondary (2°) amines react with diethyl oxalate forming oxamic ester, which is a liquid.

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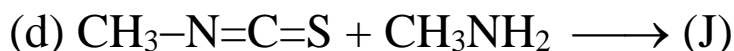
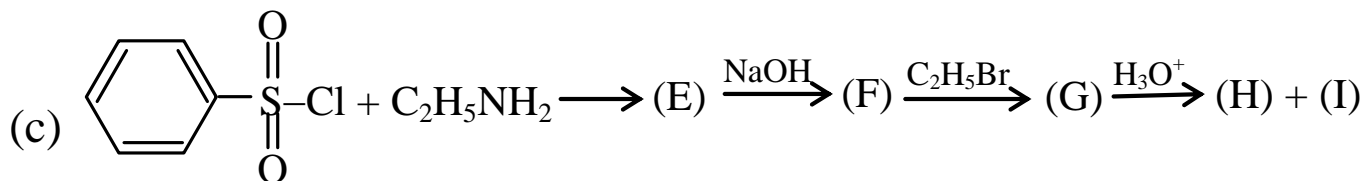
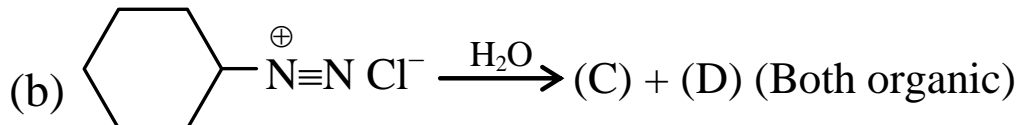
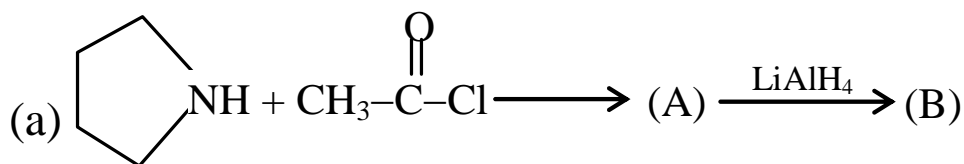


Tertiary (3°) amines donot react with diethyl oxalate.

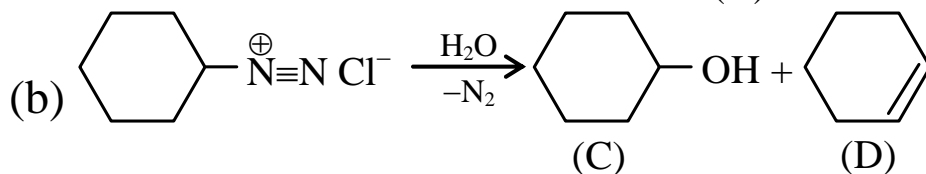
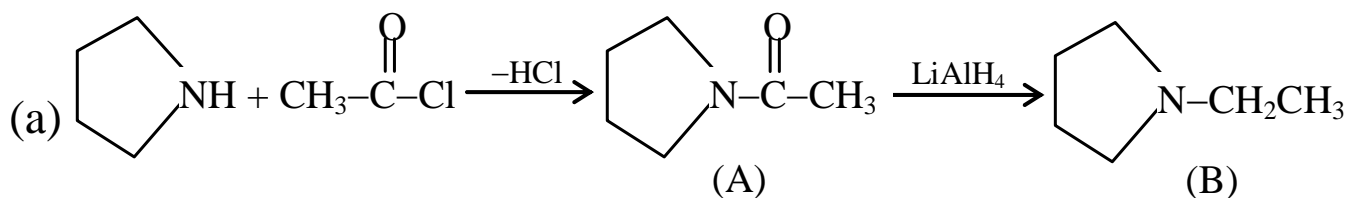
Fundamental Solved Examples

Example 1.

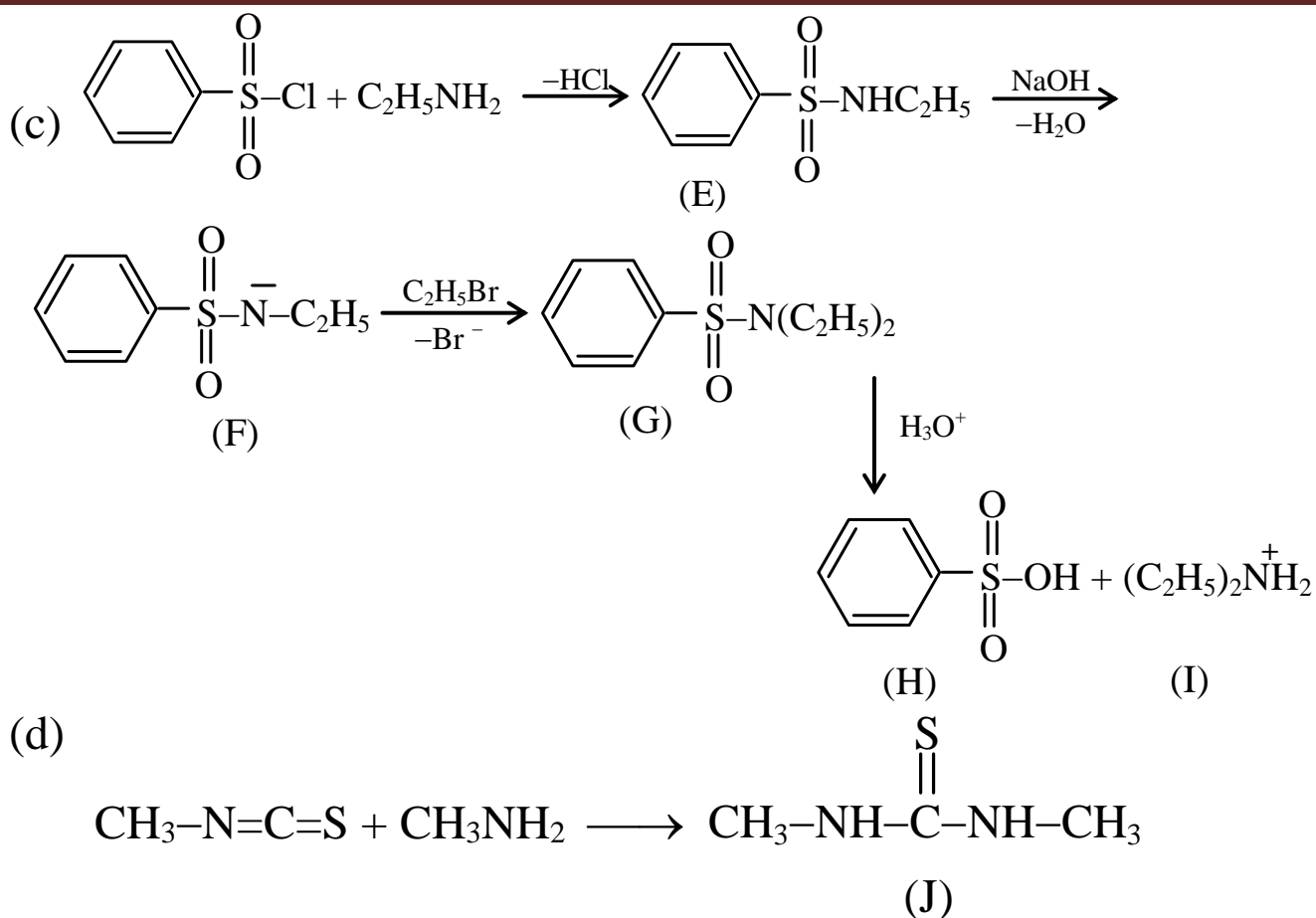
Complete the following reactions:



Solution:



AMINES



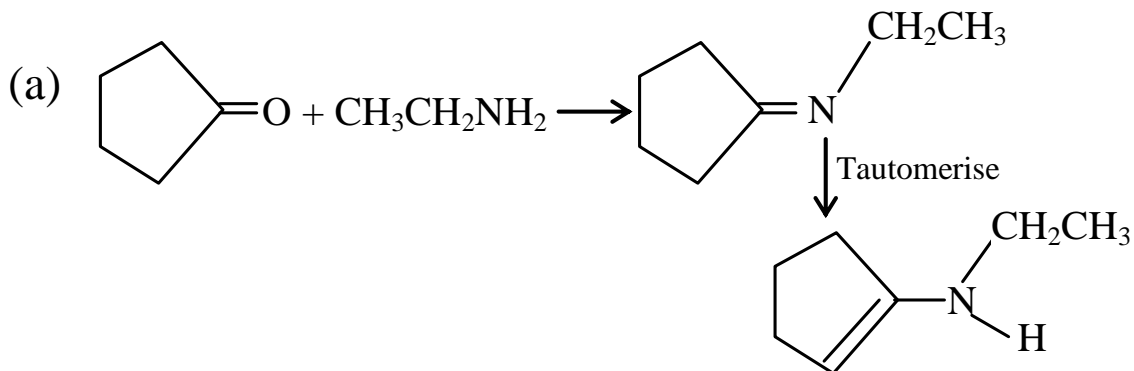
Example 2.

What happens when cyclopentanone reacts with

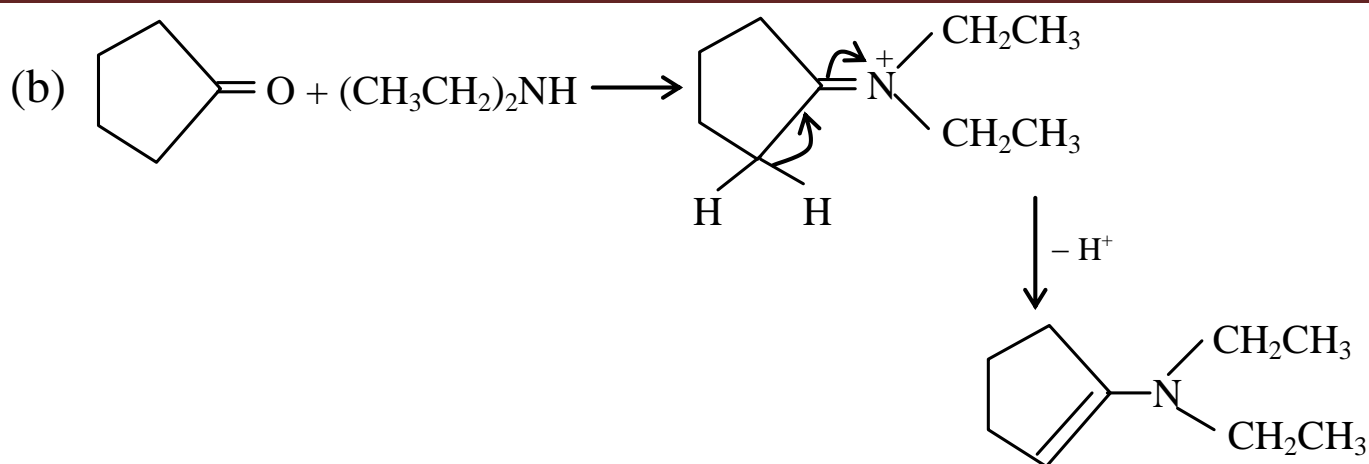
(a) $\text{CH}_3\text{CH}_2\text{NH}_2$ (1° amine)

(b) $(\text{CH}_3\text{CH}_2)_2\text{NH}$ (2° amine)

Solution:

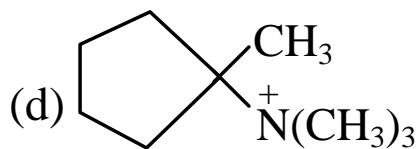
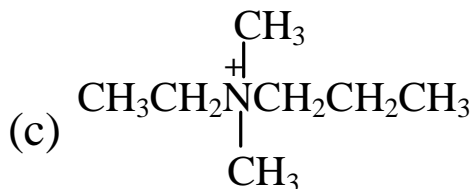
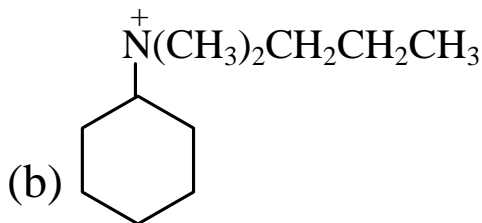
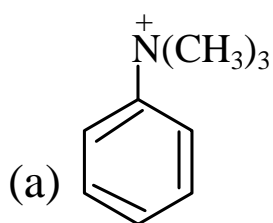


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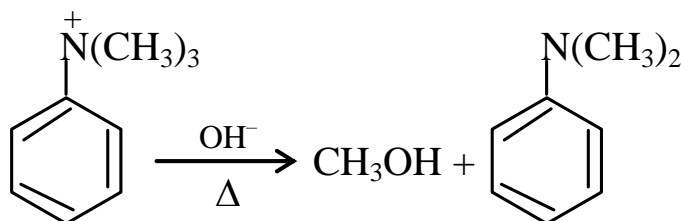
Example 3.

Give product of the thermal decomposition of hydroxide of the following quaternary salts.

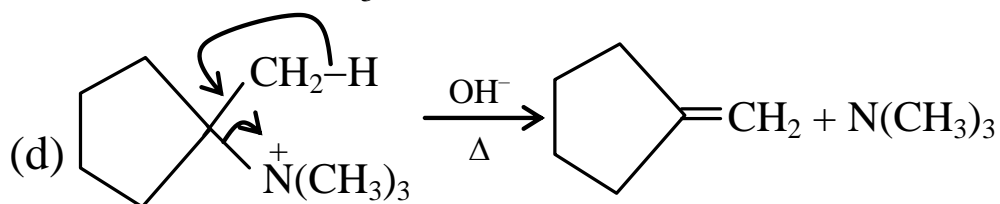
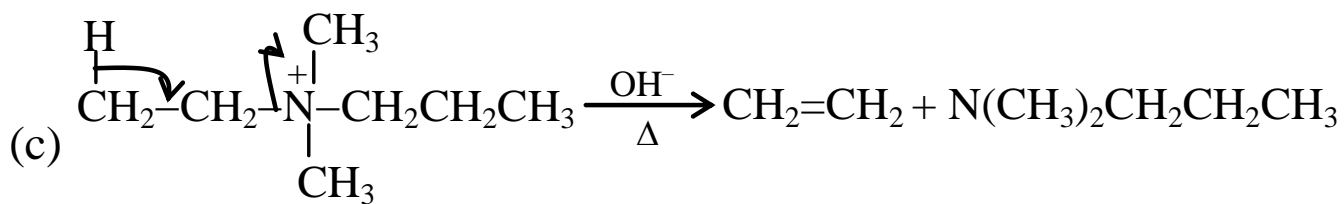
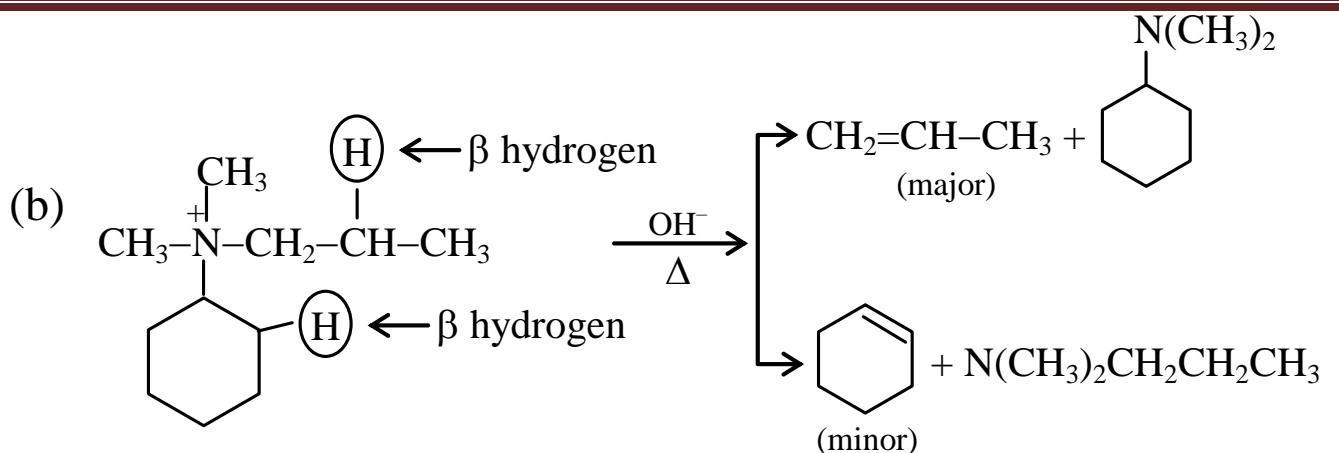


Solution:

(a) As there is no β hydrogen atom, alkene is not formed. Instead methanol is formed.

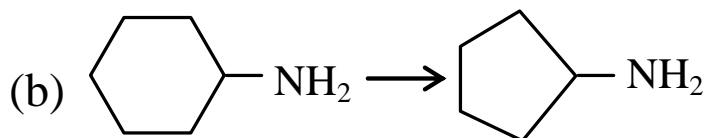
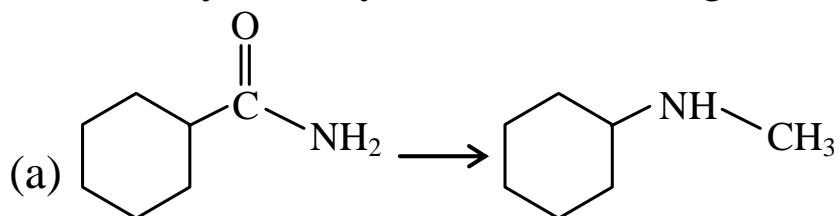


AMINES



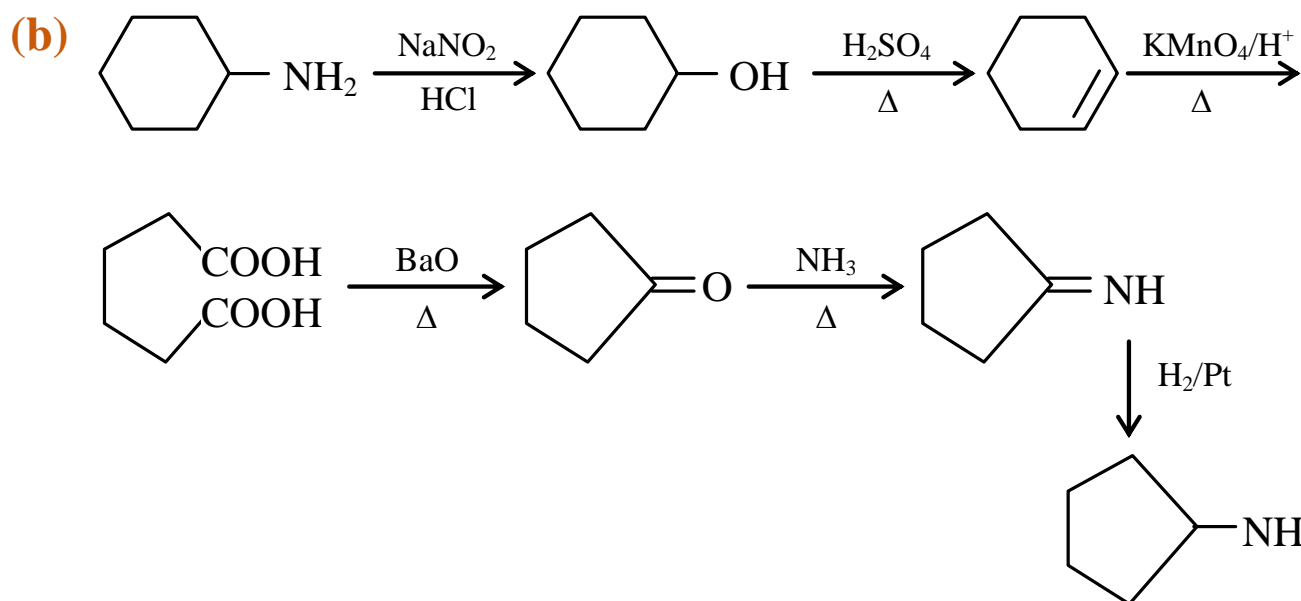
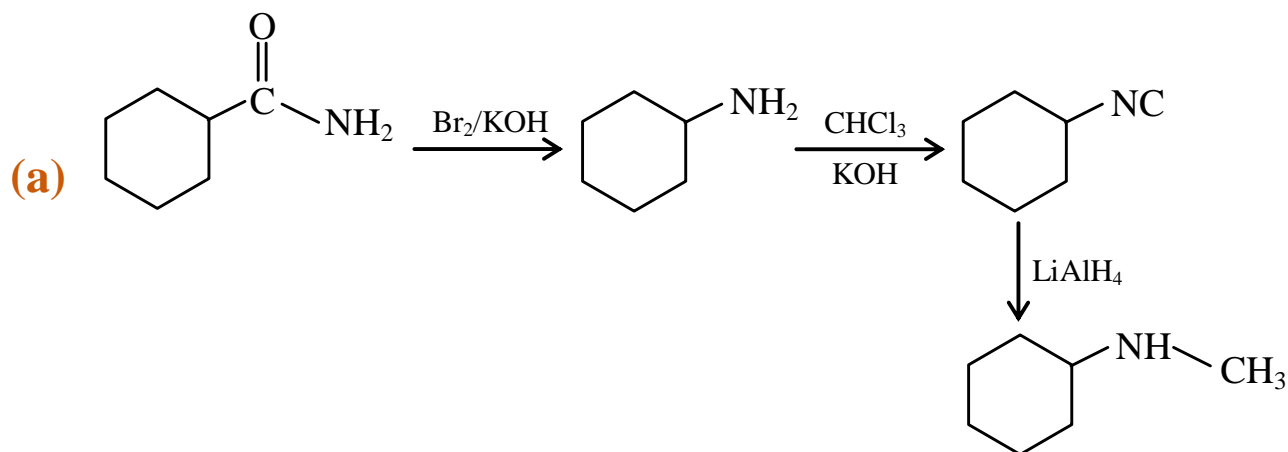
Example 4.

How will you carry out the following conversions?



Solution:

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Example 5.

An optically active compound (A), $\text{C}_3\text{H}_7\text{O}_2\text{N}$ forms a hydrochloride but dissolves in water to give a neutral solution. On heating with soda lime (A) yields (B) $\text{C}_2\text{H}_7\text{N}$. Both (A) and (B) react with NaNO_2 and HCl , the former yielding a compound (C) $\text{C}_3\text{H}_6\text{O}$, which on heating is converted to (D), $\text{C}_6\text{H}_8\text{O}_4$ while the latter yields (E), $\text{C}_2\text{H}_6\text{O}$. Account for the above reactions and suggest how (A) may be synthesized.

Solution:

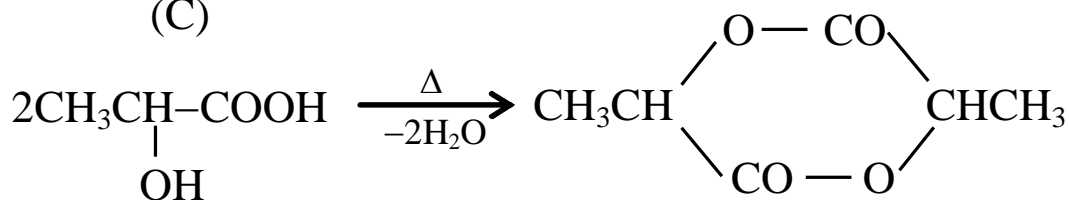
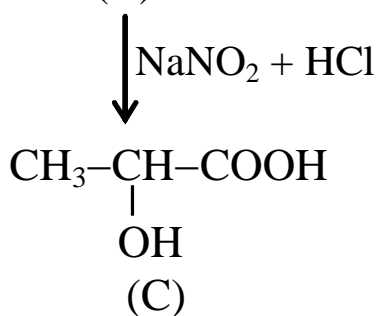
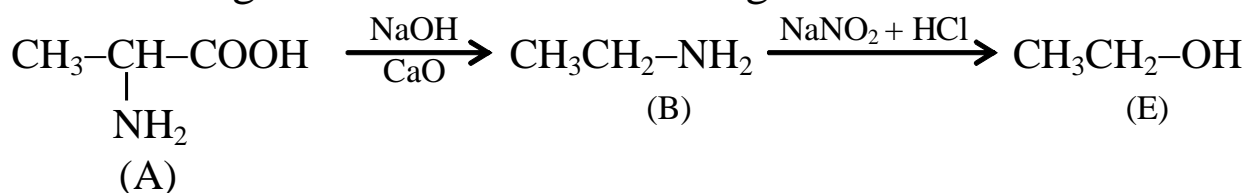
Degree of unsaturation of (A) = 2.

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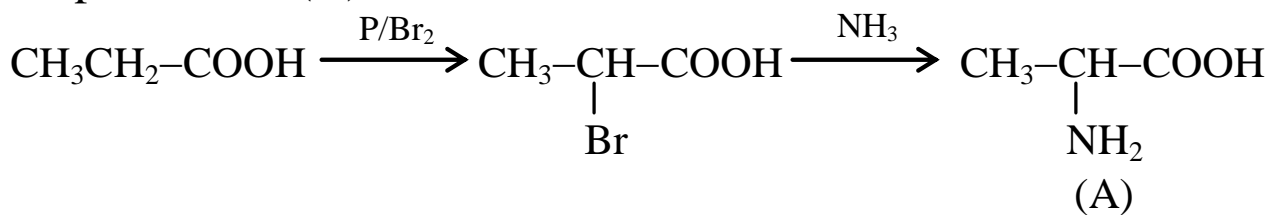
Since (A) forms hydrochloride and dissolves in water to give a neutral solution, it contains both a basic and an acidic functional group. It is likely to be amino acid as the molecular formula contains one N and 2 O-atoms. On decarboxylation it forms an amine (B).

Degree of unsaturation of (B) = 0

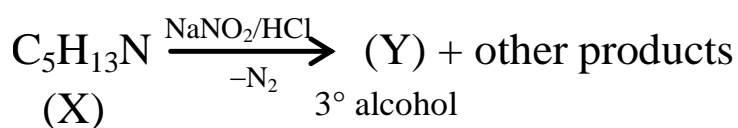
Therefore, (B) is a saturated amine. (B) reacts with NaNO_2 and dilute HCl forming (E) $\text{C}_2\text{H}_5\text{OH}$. Thus, (B) is $\text{CH}_3\text{CH}_2\text{NH}_2$. (A) also reacts with NaNO_2 and dilute HCl forming (C), a hydroxy acid, which forms a cyclic diester on heating. All the reactions can be given as



Preparation of (A):



Example 6.



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(X) is optically active. Identify the structure of (X) and (Y). Explain the formation of (Y) from (X). Will (Y) also be optically active? Justify your answer. Draw the structure of important intermediates, if any.

Solution:

