UNIT-V: Amines

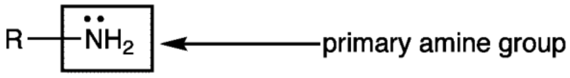
Amines: Nomenclature, structure, and acid/base reactions of amines, Preparation of primary amines: reduction of azides and nitriles, Preparation of secondary and tertiary amines: reductive amination, Synthesis and reactivity of aromatic amines Preparation and reactivity of aryl diazonium salts, Using aryl diazonium salts in synthesis.

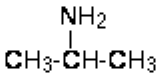
- ***Amines terms refer to the number of alkyl (or aryl) substituents bonded to the nitrogen atom*.**
- ***The different kinds of amines:*** Amines fall into different classes depending on how many of the hydrogen atoms are replaced.

i. Primary amines

✓ In primary amines (**1^0 amine**), only one of the hydrogen atoms in the ammonia molecule has been replaced. That means that the formula of the primary amine will be RNH2 where "R" is an alkyl or aryl group.

$CH_3\text{-}CH_2\text{-}CH_2\text{-}NH_2$ = **1-aminopropane**

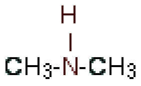




$\overset{NH_2}{CH_3\text{-}CH\text{-}CH_3}$ = **2-aminopropane**

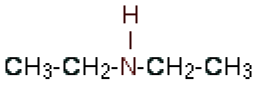
ii. Secondary amines

✓ In a secondary amine (**2^0 amine**), two of the hydrogens in an ammonia molecule have been replaced by alkyl or aryl group or both.



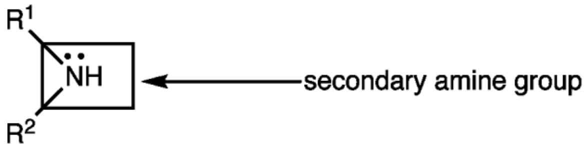
$CH_3\text{-}\overset{H}{N}\text{-}CH_3$

dimethylamine



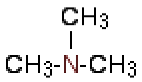
$CH_3\text{-}CH_2\text{-}\overset{H}{N}\text{-}CH_2\text{-}CH_3$

diethylamine



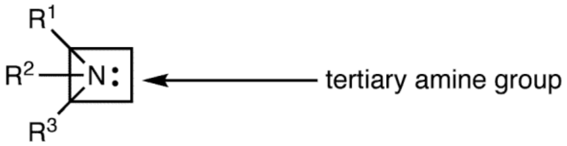
iii. Tertiary amines

✓ In a tertiary amine (**3^0 amine**), all of the hydrogens in an ammonia molecule have been replaced by hydrocarbon groups (alkyl or aryl group or both).



$CH_3\text{-}\overset{CH_3}{N}\text{-}CH_3$

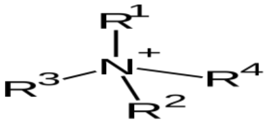
trimethylamine



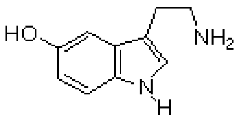
iv. Quaternary amines

✓ Quaternary ammonium cations, also known as quats, are positively charged polyatomic ions of the structure **NR^{+4}**, **R** being an alkyl group or an aryl group. Unlike the ammonium ion (**NH^{+4}**).

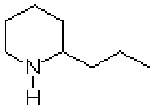
✓ The quaternary ammonium cations are permanently charged, independent of the pH of their solution. Quaternary ammonium salts or quaternary ammonium compounds (called quaternary amines in oilfield parlance) are salts of quaternary ammonium cations.



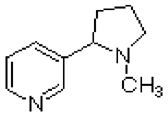
- ***Natural Nitrogen Compounds:*** Nature abounds with nitrogen compounds, many of which occur in plants and are referred to as **alkaloids**.



Serotonin
an important neurochemical



Coniine
poison hemlock



Nicotine (tobacco)

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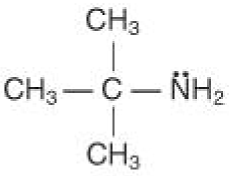
- ***In the IUPAC System, apply the following rules to name amines:***

i. Pick out the longest continuous chain of carbon atoms. The parent name comes from the alkane of the same number of carbons.
ii. Change the **"-e"** of the alkane to "**amine**."
iii. Locate and name any substituents, keeping in mind that the chain is numbered away from the amine group. Substituents, which are attached to the nitrogen atom instead of the carbon of the chain, are designated by a capital **N**.

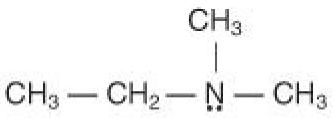
$CH_3-\ddot{N}H_2$

methanamine



$CH_3-C(CH_3)_2-\ddot{N}H_2$

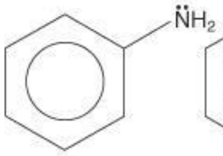
1, 1-dimethylethanamine



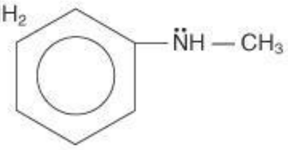
$CH_3-CH_2-\ddot{N}(CH_3)-CH_3$

N, N-dimethylethanamine

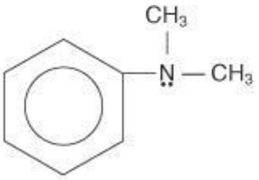
iv. Aromatic amines belong to specific families, which act as parent molecules. For example, an amino group (—NH 2) attached to benzene produces the parent compound aniline.



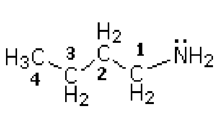
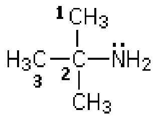
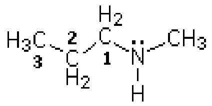
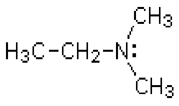
aniline
(parent)

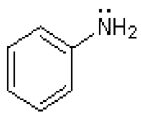


N-methylaniline
(N-substituted)

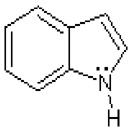


N, N-dimethylaniline
(N, N-disubstituted)

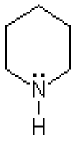
	 a 1° amine	 a 1° amine	 a 2° amine	 a 3° amine
IUPAC name	1-aminobutane	2-amino-2-methylpropane	1-methylaminopropane	dimethylaminoethane
CA name	butanamine	2-methyl-2-propanamine	N-methylpropanamine	N,N-dimethylethanamine
Common name	n-butylamine	tert-butylamine	methylpropylamine	ethyldimethylamine



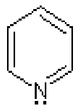
aniline



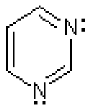
indole



piperidine



pyridine



pyrimidine

pyrrolidine

pyrrole

imidazole

PHYSICAL PROPERTIES AND CHARACTERISTICS OF AMINES

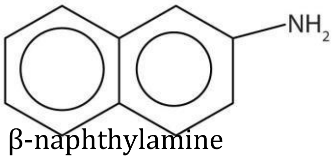
i. General Features of Amines

- The lower aliphatic amines are gaseous in nature with ***fishy smell***.
- Primary amines with three or four carbon atoms are liquids at room temperature whereas higher ones are solids.
- Aniline and other arylamines are generally colourless but they get coloured if stored in open due to atmospheric oxidation.
- Lower aliphatic amines can form hydrogen bonds with water molecules hence they are soluble in water. Increase in size of hydrophobic alkyl part increases the molar mass of amines which results in a decrease in its solubility in water. Higher amines are insoluble in water. Organic solvents like alcohol, benzene and ether readily dissolve amines. Alcohols have higher polarity as compared to amines and hence they form stronger intermolecular hydrogen bonds.
- Primary and secondary amines are often engaged in the intermolecular association as a result of hydrogen bonding between nitrogen of one and hydrogen of the other molecule. The intermolecular association is more prominent in case of primary amines as compared to secondary due to the availability of two hydrogen atoms. In tertiary amines there is no intermolecular association due to absence of free hydrogen atom for bonding.
- The order of boiling point of amines is as follows: **Primary > Secondary > Tertiary**.
- ***Physical Properties of Some Amines and Comparable Oxygen-Containing Compounds***

Name	Condensed Structural Formula	Class	Molar Mass	Boiling Point (°C)	Solubility at 25°C (g/100 g Water)
Butyl amine	$CH_3CH_2CH_2CH_2NH_2$	1°	73	78	miscible
diethyl amine	$(CH_3CH_2)_2NH$	2°	73	55	miscible
Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	—	74	118	8
Dipropyl amine	$(CH_3CH_2CH_2)_2NH$	2°	101	111	4
Triethyl amine	$(CH_3CH_2)_3N$	3°	101	90	14
Dipropyl ether	$(CH_3CH_2CH_2)_2O$	—	102	91	0.25

All three classes of amines can engage in hydrogen bonding with water. Amines of low molar mass are quite soluble in water; the borderline of solubility in water is at five or six carbon atoms.

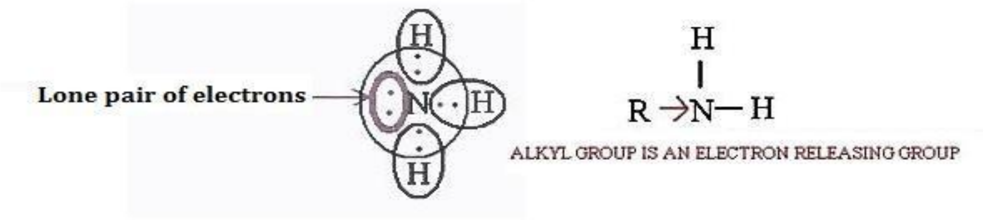
NOTE BY: Aromatic amines generally are quite toxic. They are readily absorbed through the skin, and workers must exercise caution when handling these compounds. Several aromatic amines, including β-naphthylamine, are potent carcinogens.



β-naphthylamine

Ii.Basicity of amines

- Amines are basic because they possess a pair of unshared electrons, which they can share with other atoms. These unshared electrons create an electron density around the nitrogen atom.
- The greater the electron density, the more basic the molecule. Groups that donate or supply electrons will increase the basicity of amines while groups that decrease the electron density around the nitrogen decrease the basicity of the molecule.
- Due to this property of the alkyl group attached to the nitrogen of the amine, the electron density around the nitrogen atom increases due to which its electron releasing ability increases. Due to the greater and easier release of electrons in the alkyl amine, the molecule becomes more basic than ammonia.
- Whereas in ammonia, no such releasing group attached. So, obviously the basicity of ammonia is much less than that of an alkyl amine.



- The basicity amine in the gas phase and aqueous solutions are varies.
  a) In the gas phase, the order of base strength is given below:

$$NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$$

$$\xrightarrow[\text{Increase in Basicity}]{\hspace{6cm}}$$

  b) In aqueous solutions, the order of basicity

$$(CH_3)_2\,NH > CH_3NH_2 > (CH_3)_3N > NH_3$$

$$\xleftarrow[\text{Increase in Basicity}]{\hspace{6cm}}$$

$$\mathbf{NH_3 < \textit{Primary Amine} \sim \textit{Tertiary Amine} < \textit{Secondary Amine}}$$

$$\xrightarrow[\text{Increase in Basicity}]{\hspace{6cm}}$$

- The differences in the basicity order in the ***gas phase*** and ***aqueous solutions*** are the result of ***solvation*** effects. Amines in water solution exist as ammonium ions.
- In water, the ammonium salts of primary and secondary amines undergo ***solvation effects*** (due to hydrogen bonding) to a much greater degree than ammonium salts of tertiary amines. These solvation effects increase the electron density on the amine nitrogen to a greater degree than the inductive effect of alkyl groups.

$$\underset{1^\circ\text{ amine}}{R-\ddot{N}H_2 + H_2O} \longrightarrow \underset{1^\circ\text{ ammonium salt}}{RH\overset{+}{N}H_3\overset{-}{O}H}$$

$$\underset{2^\circ\text{ amine}}{R-\ddot{N}HR + H_2O} \longrightarrow \underset{2^\circ\text{ ammonium salt}}{R\overset{+}{N}H_2R\overset{-}{O}H}$$

$$\underset{3^\circ\text{ amine}}{R\ddot{N}R_2 + H_2O} \longrightarrow \underset{3^\circ\text{ ammonium salt}}{RN\overset{+}{H}R_2\overset{-}{O}H}$$

QUESTION: Comparison in the basicity of the aliphatic amines, the basicity of tertiary amines to be the greatest, followed by secondary amine and then primary amine. But this is not so. The order of basicity is **NH_3 < *primary amine ~ tertiary amine < secondary amine***.....Explain Why?

ANSWER:

- This is due to (i) *Steric hindrance effect* and (ii) *Solvation of ions effect*

i. *This "unexpected" order of basicity is due to Steric hindrance*:

- The size of an alkyl group is more than that of a hydrogen atom. So, an alkyl group would hinder the attack of a hydrogen atom, thus decreasing the basicity of the molecule.
- So, the more the number of alkyl groups attached, lesser will be its basicity. So, the decreasing order of basicity will be: ***Primary amine > secondary amine > tertiary amine.***

ii. Solvation of ions

- When amines are dissolved in water, they form protonated amines. Also, the number of possibilities of hydrogen bonding also increases. More the number of hydrogen bonding, more is the hydration that is released in the process of the formation of hydrogen bonds.
- The more the hydration energy of the molecule, more is the stability of the amine. Experiments have indicated, in terms of hydration energy, that the tertiary amines are the least stable followed by the secondary amines followed by the primary amines.
- This can be explained on the basis of the following reactions.

  In primary amine: $RNH_2 + H_2O \rightarrow\rightarrow RNH_3^+ + OH^-$

  In secondary amine: $R_2NH + H_2O \rightarrow\rightarrow R_2NH_2^+ + OH^-$

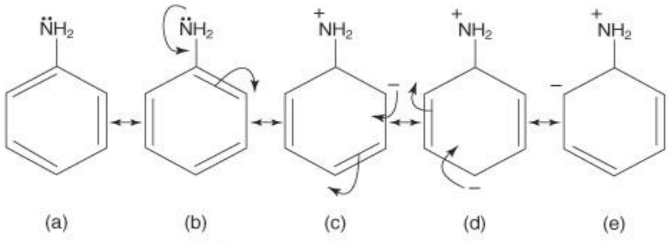
  In tertiary amine: $R_3N + H_2O \rightarrow\rightarrow R_2NH^+ + OH^-$
- So, the number of hydrogen bonds possible when primary amines are dissolved in water is the greatest, implying that they are most stable species of amine, the least being the tertiary amines.
- The combined effect of the pushing effect of the alkyl group **(+I effect)**, steric hindrance and the salvation of amines causes the basicity order to be: (basicity of tertiary is almost the same as that of primary).

NH_3< *primary amine ~ tertiary amine < secondary amine*

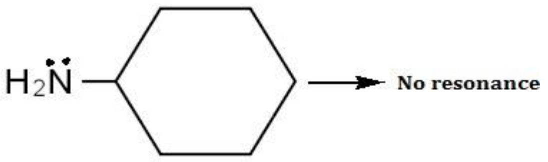
QUESTION: WHY ARYLAMINES ARE WEAKER BASES THAN CYCLOHEXYLAMINES?

ANSWER:

In **Aniline (Arylamines)**, the lone pair on nitrogen (which is free for protonation in a cyclohexylamines) is present in conjugation with the benzene ring, so **aniline** can't lose electrons as easily as a cyclohexylamines can. The basicity of **amines** is due to the nitrogen of the **amine** donating its lone pair of electrons.



Aniline (Arylamines)

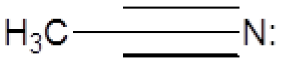


Cyclohexylamines

QUESTION: WHAT IS THE RELATIONSHIP BETWEEN HYBRIDIZATION AND ACIDITY OR BASICITY?

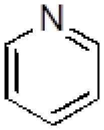
ANSWER:

- For **acidity**, the hydrogen should be attached to an electronegative atom. The more electronegative the atom is, the more acidic that hydrogen is.
- Electronegativity depends on **%s** character.
- More the **%s** character, more the electronegativity of central atom. So, **sp^3** ordital has the least electronegativity and "**sp**" orbital is most electronegative.
- Hence, it follows that alkynes (**sp** hybridised carbon) are more acidic than alkenes
- The reason for this is that since the <u>**s-orbital**</u> is spherical, electrons in it experience more force of attraction from the nucleus. Since electronegativity is largely associated by how tightly valence electrons are held, as s character of a hybrid orbital increases, its electronegativity increases and hence its acidity increases.
- Order of **basicity** is reverse order of acidity. This result is realised when the Electronegativity of **sp**-carbon is greater than that of **sp^3** nitrogen.
- **The greater the % of "S" character, The closer the lone pair is to N- atom, The weaker the base**



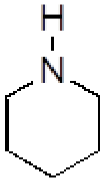
sp- *Hybridization*

(24% ***S***-Character)



sp^2- *Hybridization*

(8.75% ***S***-Character)



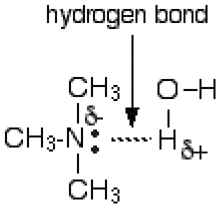
sp^3- *Hybridization*

(2.88% ***S***-Character)

→ Increase in Basicity

iii. Solubility of Amines in water

- The small amines of all types are very soluble in water.
- All of the amines can form hydrogen bonds with water - even the tertiary ones. Although the tertiary amines don't have a hydrogen atom attached to the nitrogen and so can't form hydrogen bonds with themselves, they can form hydrogen bonds with water molecules just using the lone pair on the nitrogen.



- Solubility falls off as the hydrocarbon chains get longer - noticeably so after about **6 carbons**. The hydrocarbon chains have to force their way between water molecules, breaking hydrogen bonds between water molecules. However, they don't replace them by anything as strong, and so the process of forming a solution becomes less and less energetically feasible as chain length grows.
- The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. These comparisons, however, are valid only for pure compounds in neutral water.

QUESTION: BETWEEN ALCOHOLS & AMINES, WHICH ONE IS MORE SOLUBLE & WHY?

ANSWER:

- Alcohols are more soluble in water due to the electron availability of the two electron pairs in the oxygen which can accept a proton.
- And simultaneously, The hydrogen bonds between the **Oxygen** (lone pair of electrons) in the alcohol and the water molecules is stronger because **Oxygen** (lone pair) is more electronegative than the **Nitrogen** (lone pair) in the **NH_2** group in the amines

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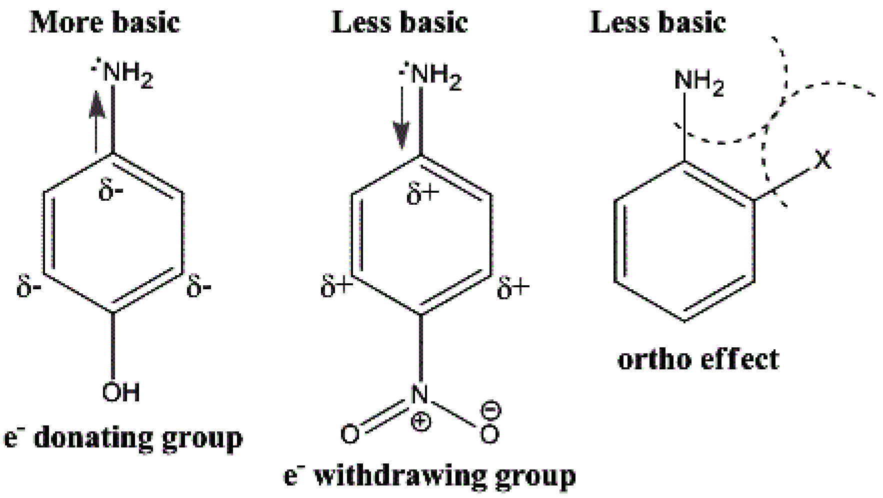
QUESTION: WHY ARE AROMATIC AMINES LESS BASIC THAN ALIPHATIC AMINES?

ANSWER:

- The basicity of amines is due to the nitrogen of the amine donating its lonepair of electrons. In aromatic amines this lone pair is in conjugation (delocalized) with the aromatic ring. While in aliphatic mine this doesn't happen and thus the lone pair is ready to be donated.
- Aromatic amines are weaker bases than aliphatic amines. This is because the amine donates its electron density to the aromatic ring. Also, the amine forms stable resonance structures with the aromatic ring, which is absent once the amine becomes protonated.
- Electron donating groups on the aromatic amine increase the basicity of aromatic amines. This is because the electron donating groups contribute to the electron density on the nitrogen.
- Electron withdrawing groups on the aromatic amine decrease the basicity of aromatic amines. This is because the electron withdrawing groups steal electron density from the nitrogen.
- Anything ortho to the amine, no matter whether it is electron donating or withdrawing, will decrease the basicity of the aromatic amine. This is because of the ortho effect, which is basically sterics. The protonated amine will have a greater steric interaction with the ortho group, so it will be less stable.



iv.Boiling Point of Amines

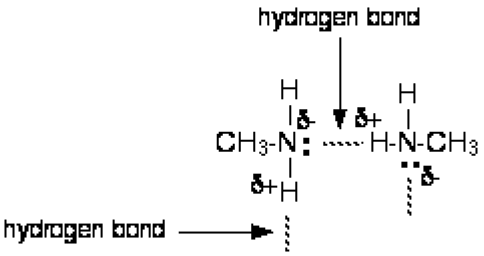
- The boiling points and water solubility of amines is depend on hydrogen bonding.
- The powerful intermolecular attraction that results from **-O-H---O-** hydrogen bonding in alcohols whereas **-N-H---N-** hydrogen bonding is weaker, as the lower boiling points of similarly sized amines.

Compound	**CH_3CH_3**	**CH_3OH**	**CH_3NH_2**	**$CH_3CH_2CH_3$**	**CH_3CH_2OH**	**$CH_3CH_2NH_2$**
Mol.Wt.	30	32	31	44	46	45
Boiling Point ^{0}C	-88.6^{0}	65^{o}	-6.0^{0}	-42^{0}	78.5^{0}	16.6^{0}

- Whereas **1^{0}, 2^{0}** & **3^{0}-amines**, has different boiling point, Since **1^{0} amines** have two hydrogens available for hydrogen bonding, to have higher boiling points than isomeric **2^{0} amines**, which in turn should boil higher than isomeric **3^{0} amines** (no hydrogen bonding).
- Indeed, **3^{0} amines** have boiling points similar to equivalent sized **ethers**; and in all but the smallest compounds, corresponding **ethers**, **3^{0} amines** and **alkanes** have similar boiling points.

Compound	**$(CH_3)_3CH$**	**$(CH_3)_2CHOH$**	**$(CH_3)_2CHNH_2$**	**$(CH_3)_3N$**
Mol.Wt.	58	60	59	59
Boiling Point ^{0}C	-12^{0}	82^{0}	34^{0}	3^{0}

- The reason for the higher boiling points of the **primary amines** is that they can form *hydrogen bonds* with each other as well as *van der Waals dispersion forces* and *dipole-dipole interactions*. Hydrogen bonds can form between the lone pair on the very electronegative nitrogen atom and the slightly positive hydrogen atom in another molecule.

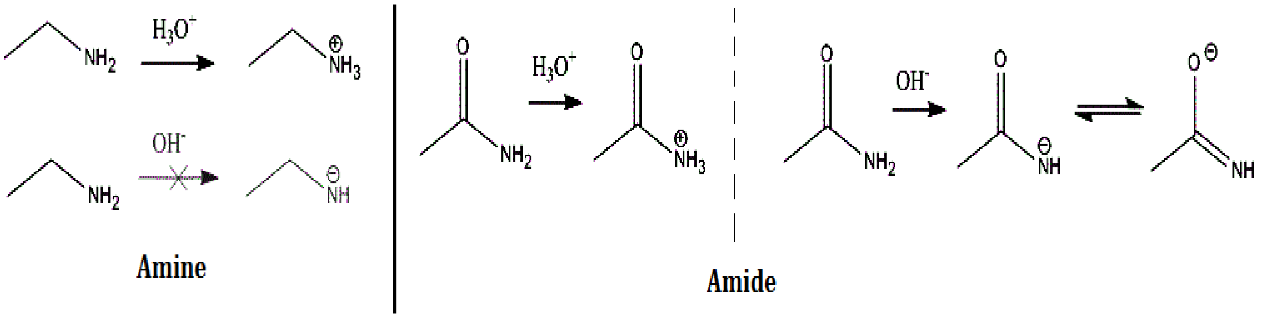


- The boiling point of the **secondary amine** is a little lower than the corresponding **primary amine** with the same number of carbon atoms. Secondary amines still form hydrogen bonds, but having the nitrogen atom in the middle of the chain rather than at the end makes the permanent dipole on the molecule slightly less. The lower boiling point is due to the lower dipole-dipole attractions in the ***dimethyl amine*** compared with ***ethylamine***.
- The ***trimethyl amine*** has a much lower boiling point ($3.5^{0}C$) than 1-aminopropane ($48.6^{0}C$). In a **tertiary amine** there aren't any hydrogen atoms attached directly to the nitrogen. That means that hydrogen bonding between tertiary amine molecules is impossible. That's why the boiling point is much lower.

QUESTION: COMPARING THE BASICITY OF ALKYL AMINES TO AMIDES.

ANSWER:

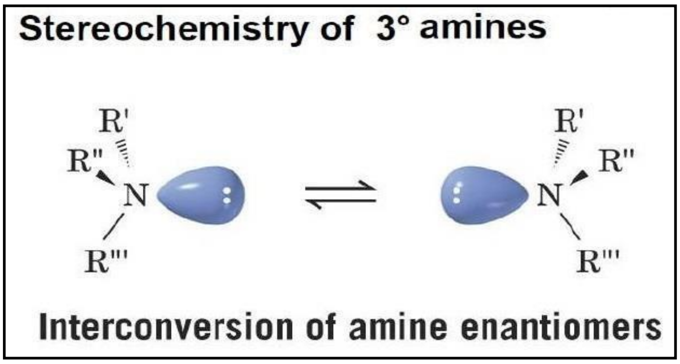
- The **basicity** of **alkyl amines** to **amides**, with an alkyl **amine** the lone pair electron is localized on the nitrogen. However, the lone pair electrons on an **amide** are delocalized between the nitrogen and the oxygen through resonance. This makes **amides** much less basic compared to **alkyl amines**.
- *General principles of basicity*
  - ✓ **Amines** are basic. They like to gain a proton. $R\text{-}NH_2 \rightarrow R\text{-}NH_3^+$. It is very difficult for neutral amines to lose a proton.
  - ✓ An **amide**, however, can lose a proton much more easily. This is because the carbonyl group next to the nitrogen contributes to a resonance structure that places the negative charge on the oxygen. Thus, the negative charge of the conjugate base is distributed over both nitrogen and oxygen.



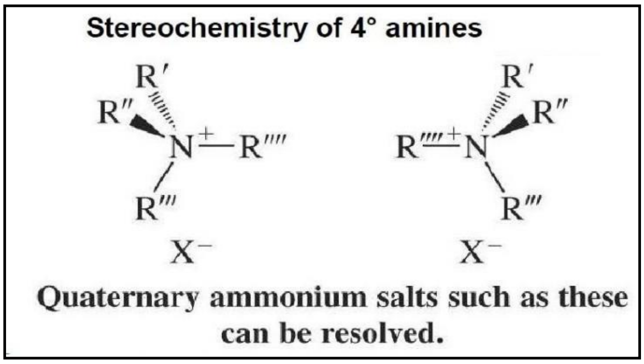
QUESTION: EXPLAIN THE STEREOCHEMISTRY OF AMINE.

ANSWER:

- **3^0 amines** can be chiral. But they are always racemic because of spontaneous inversions at room temperature. Even protonated **3^0 amines** undergo inversion because the proton comes on and off in an acid-base equilibrium.
- **4^0 amines** can be chiral and they stay chiral because they don't undergo inversion.


Stereochemistry of 3° amines

Interconversion of amine enantiomers


Stereochemistry of 4° amines

Quaternary ammonium salts such as these can be resolved.

Note By:
INFRARED ABSORPTION OF AMINES
Primary amines = $R\text{-}NH_2$ = 2 N-H bonds = 2 peaks around 3300 cm^{-1}.
Secondary amines = $R_2\text{-}NH$ = 1 N-H bonds = 1 peak around 3300 cm^{-1}.
Tertiary amines = $R_3\text{-}N$ = no N-H bonds = 0 peak around 3300 cm^{-1}.

PREPARATION OF AMINES

- ***The methods commonly used for preparing amines are***
  1. Alkylation of ammonia
  2. Gabriel synthesis
  3. Reduction of amides
  4. Reduction of nitriles
  5. Reduction of nitro compounds
  6. Reductive amination of aldehydes and ketones.
  7. Reduction of azides

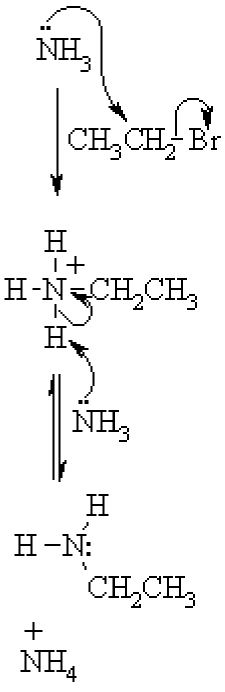
1. Alkylation of ammonia (Alkylation of Amines by Alkyl Halides)

- Ammonia reacts as a nucleophile with alkyl halides to give primary amines in a Nucleophilic substitution reaction.
- Yields are often poor as the product, a primary amine, RNH_2, are itself a nucleophile and can react with more alkyl halide.
- The results are mixtures containing primary amines, secondary amines, tertiary amines and quaternary ammonium salts.
- This can be avoided if a large excess of ammonia is used.
- As aryl halides do not undergo simple nucleophilic substitution, they cannot be prepared using this method.
- ***General reaction:***

$$R-X \quad + \quad 2\,NH_3 \longrightarrow R-NH_2 \quad + \quad \overset{+}{N}H_4X^-$$

$$\underset{\text{primary}}{R\ddot{N}H_2} \xrightarrow{R'CH_2X} \underset{\text{secondary}}{R\ddot{N}H(CH_2R')} \xrightarrow{R'CH_2X} \underset{\text{tertiary}}{R\ddot{N}(CH_2R')_2} \xrightarrow{R'CH_2X} \underset{\text{quaternary}}{R\overset{+}{N}(CH_2R')_3\bar{X}}$$

- ***Mechanism of ammonia alkylation***

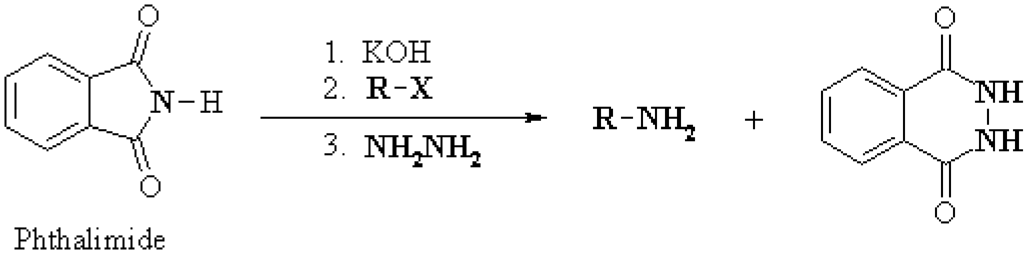


Step 1:
The N in ammonia functions as the nucleophile and attacks the electrophilic C of the alkyl halide displacing the bromide and creating the new C-N bond.

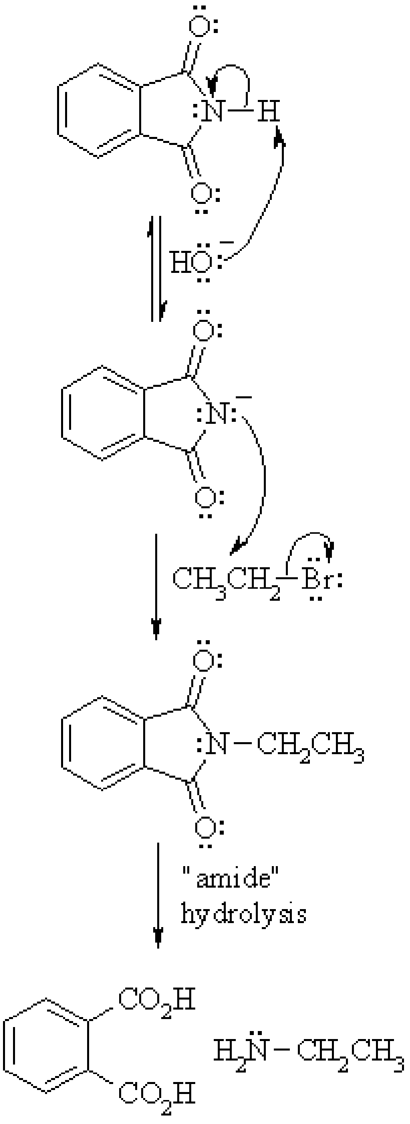
Step 2:
An acid/base reaction. The base (excess ammonia) deprotonates the positive **N** (ammonium) center creating the alkylation product, the primary amine

2.Gabriel synthesis

- ***Reaction type:*** Nucleophilic substitution then Nucleophilic Acyl Substitution.
- The advantage of this method is that over alkylation is avoided.
- Reaction of phthalimide with KOH removes the N-H proton giving an imide ion, a good nucleophile.
- Nucleophilic substitution by the imide ion (**[HN]**$^{2-}$) on the alkyl halide generates an intermediate, N-alkyl phthalimide.
- Hydrolysis or hydrazinolysis liberates a primary alkyl amine.
- Aryl amines **cannot** be prepared via this method since aryl halides **do not** undergo simple nucleophilic substitution.
- ***General reaction:***



- ***Mechanism of the Gabriel Synthesis***



Step 1:

An acid/base reaction. Deprotonation of the imide N-H proton by the base, hydroxide. This proton is more acidic than a simple amine due to the resonance stabilization by the two adjacent C=O groups. This generates a strong nucleophile, the -ve N.

Step 2:

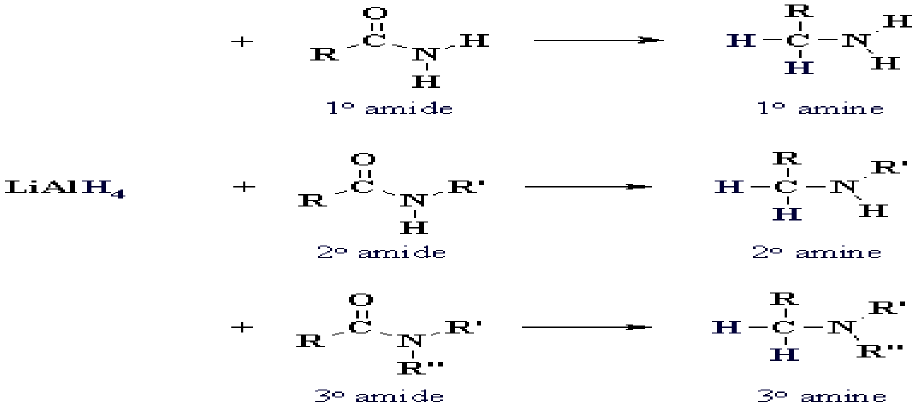
The N nucleophile attacks the electrophilic C of the alkyl halide displacing the bromide and creating the new C-N bond. This product can be compared to an N-alkyl amide.

Step 3:

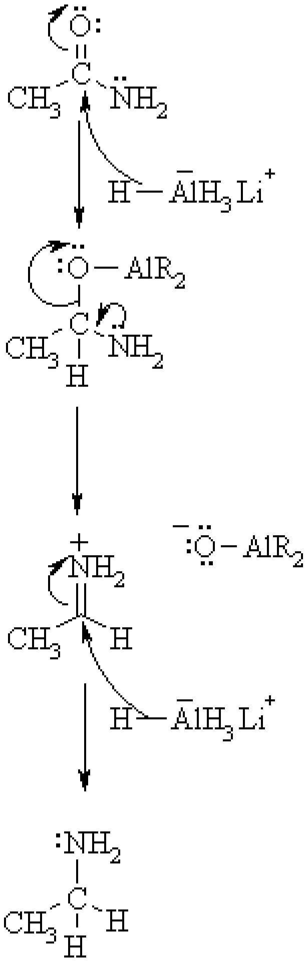
Hydrolysis creates the dicarboxylic acid and the required amine.

2.Reduction of amides

- ***Reaction type:*** Nucleophilic Acyl Substitution then Nucleophilic Addition.
- Amides (**RCONR'$_2$**) can be reduced to the amine
- Amides can be reduced by **LiAlH$_4$** but NOT the less reactive **NaBH$_4$**
- ***Typical reagents :*** LiAlH$_4$ / ether solvent followed by aqueous
- **R**, **R'** or **R"** may be either alkyl or aryl substituents.
- ***General reaction:***



- ***Reaction mechanism of* LiAlH$_4$ *with an amide***



Step 1:

The nucleophilic H from the hydride reagent adds to the electrophilic C in the polar carbonyl group of the ester. Electrons from the C=O move to the electronegative O creating an intermediate metal alkoxide complex.

Step 2:

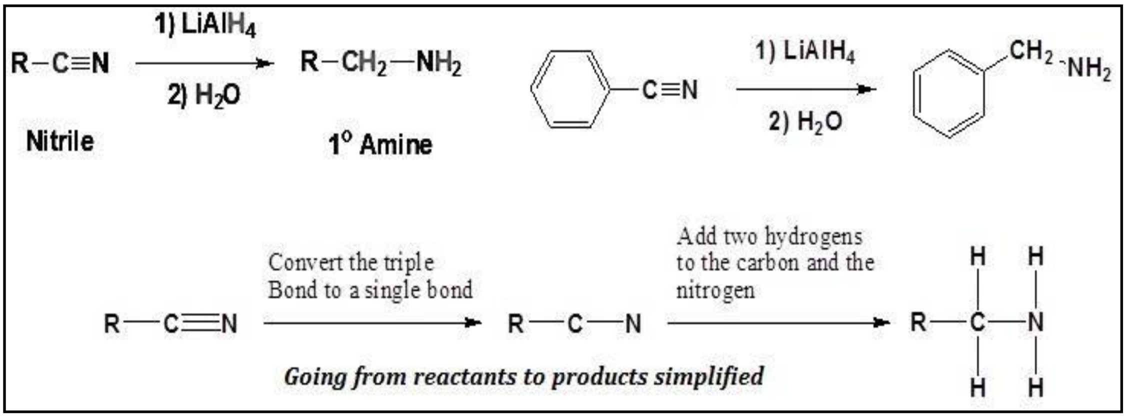
The tetrahedral intermediate collapses and displaces the O as part of a metal alkoxide leaving group, this produces a highly reactive iminium ion an intermediate.

Step 3:

Rapid reduction by the nucleophilic H from the hydride reagent as it adds to the electrophilic C in the iminium system. p electrons from the C=N move to the cationic N neutralizing the charge creating the amine product.

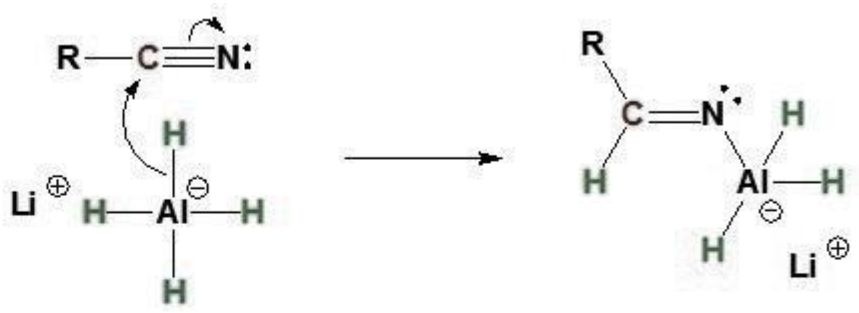
2.<u>Reduction of nitriles</u>

- Nitriles can be converted to **1° amines** by reaction with $LiAlH_4$. During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.
- ***General Reaction***

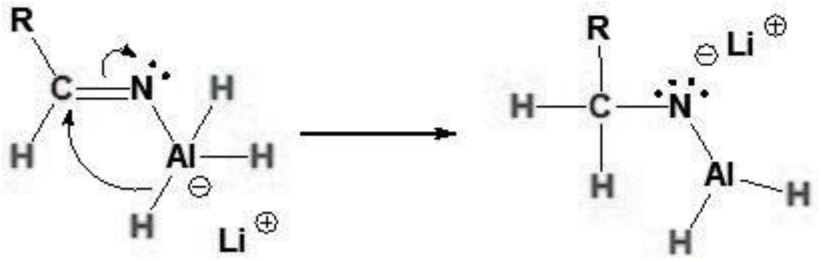


- ***Reaction mechanism***

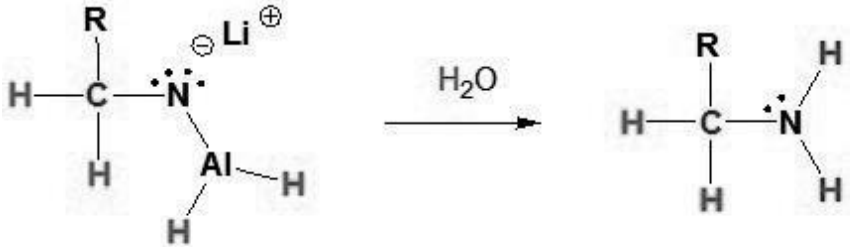
Step I: *Nucleophilic Attack by the Hydride*



Step II: *Second nucleophilic attack by the hydride*



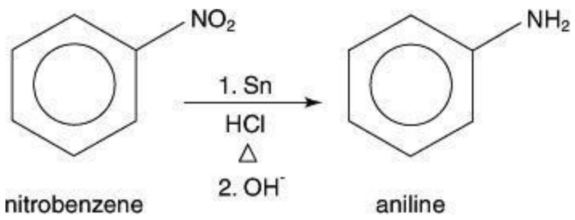
Step III: *Protonation by addition of water to give an amine*



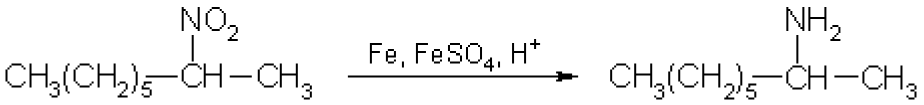
R
H
C
N
Li
H
Al
H
H
H₂O
R
H
C
N
H
H
H

2.Reduction of nitro compounds

- Aromatic amines are normally prepared by reduction of the corresponding aromatic nitro compound.



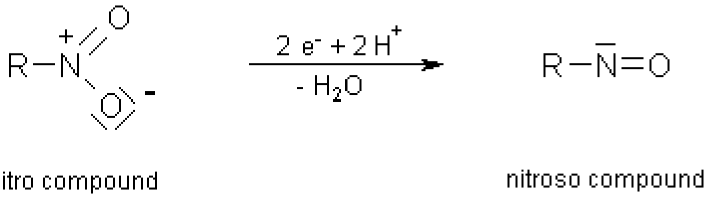
- Nitro groups can be easily reduced to amino groups with metals, such as zinc, tin and iron, in acidic solution. Additional methodologies involve catalytic hydrogenation and the use of reducing agents, such as hydrazine and titanium trichloride.



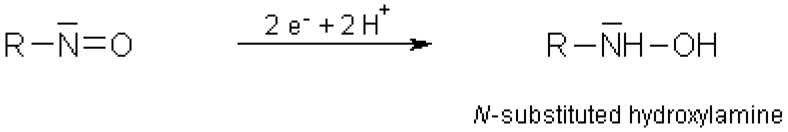
$$CH_3(CH_2)_5-\overset{NO_2}{\overset{|}{C}}H-CH_3 \xrightarrow{Fe,\ FeSO_4,\ H^+} CH_3(CH_2)_5-\overset{NH_2}{\overset{|}{C}}H-CH_3$$

- ***Reaction Mechanism:*** *Reduction of Nitro Compounds to Amines*

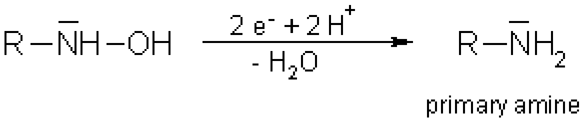
Step I: *Initially, the nitro group is reduced to the nitroso group.*



Step II: *The initial step is followed by the reductive addition of two hydrogen atoms to form the hydroxylamine.*

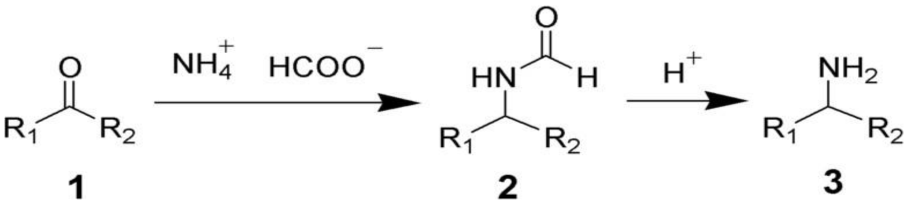


Step III: *The last step is again a reduction; water is eliminated and the amine is isolated.*

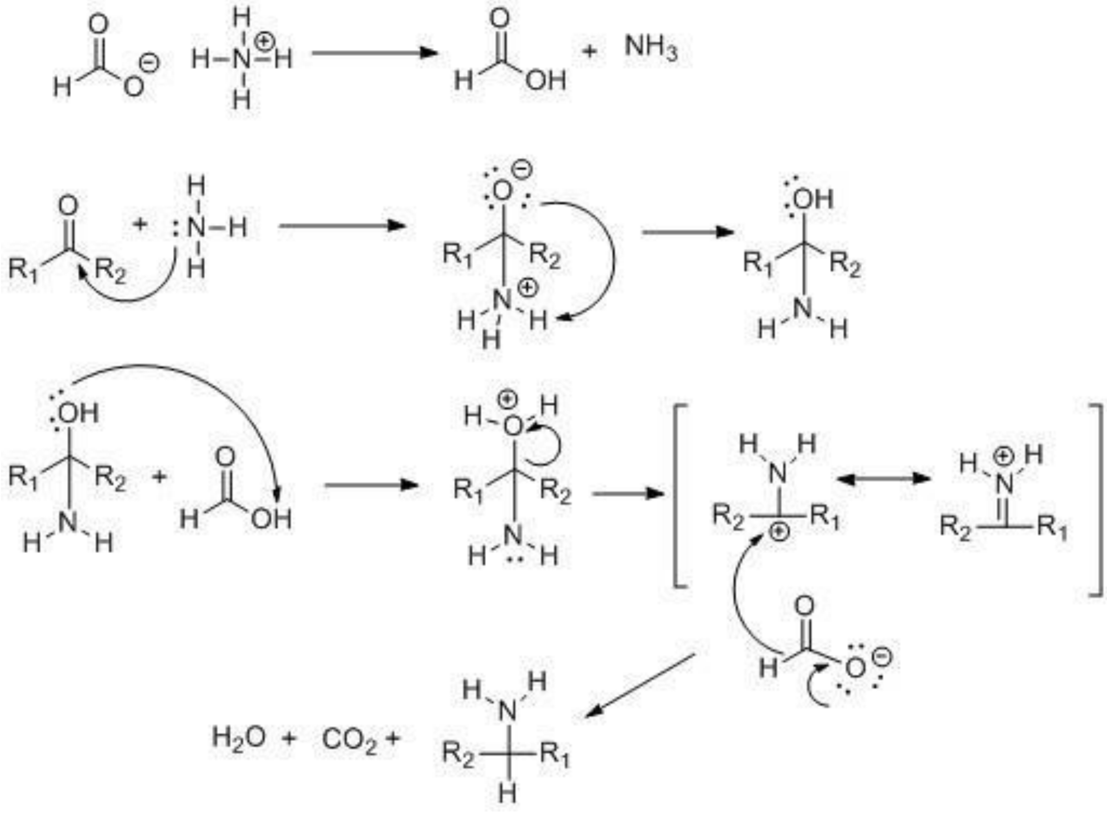


2.Reductive amination of aldehydes and ketones.

- Aldehydes or ketones can be reduced by catalytic or chemical reductions in the presence of ammonia or primary or secondary amines, producing primary, secondary, or tertiary amines.
- ***LEUCKART REACTION:*** The Leuckart reaction is the chemical reaction that converts aldehydes or ketones to amines by reductive amination in the presence of heat. The reaction, named after ***Sir Rudolf Leuckart***, proceeds via two mechanisms: one using ammonium formate and the other using formamide as the reducing agent. It requires high temperatures, usually between 120 and 130^{0}C, although under the presence of formamide, the temperature can be greater than 165^{0}C.
- ***General Reaction***



- ***Reaction mechanism:***

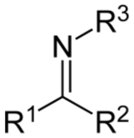


REDUCTIVE AMINATION

- ***Reductive amination*** (also known as *reductive alkylation*) is a form of amination that involves the conversion of a carbonyl group to an amine via an intermediate imine. The carbonyl group is most commonly a ketone or an aldehyde. It is considered the most important way to make amines, and a majority of amines made in the pharmaceutical industry are made this way.

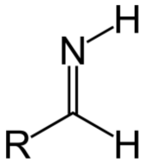
IMINE

- An ***imine*** is a functional group or chemical compound containing a ***carbon–nitrogen double bond***.

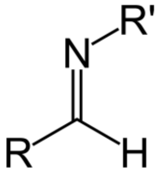


Imine

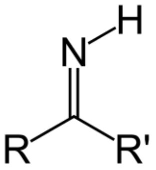
- A **primary imine** in which C is attached to both a hydrocarbyl and a H is called a **primary aldimine**.
- A **secondary imine** with such groups is called a **secondary aldimine**.
- A **primary imine** in which C is attached to **two hydrocarbyls** is called a **primary ketimine**; a **secondary imine** with such groups is called a **secondary ketamine**.



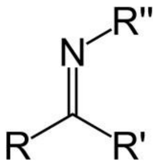
Primary aldimine



Secondary aldimine



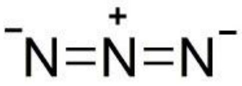
Primary ketimine



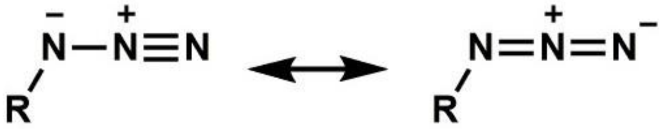
Secondary ketimine

AZIDE

- Azide is the anion with the formula N^{3-}. It is the conjugate base of hydrazoic acid (HN_3). N^{3-} is a linear anion.
- The dominant application of azides is as a propellant in air bags.



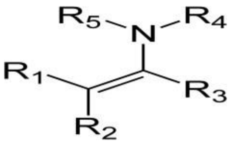
The azide anion



The azide functional group can be shown by two resonance structures

ENAMINE

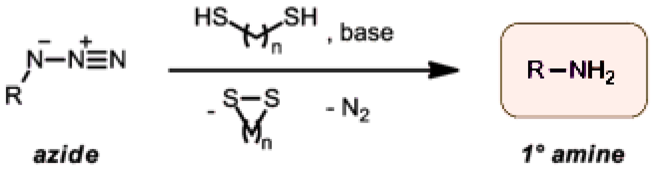
- An **ENAMINE** is an unsaturated compound derived by the condensation of an aldehyde or ketone with a secondary amine

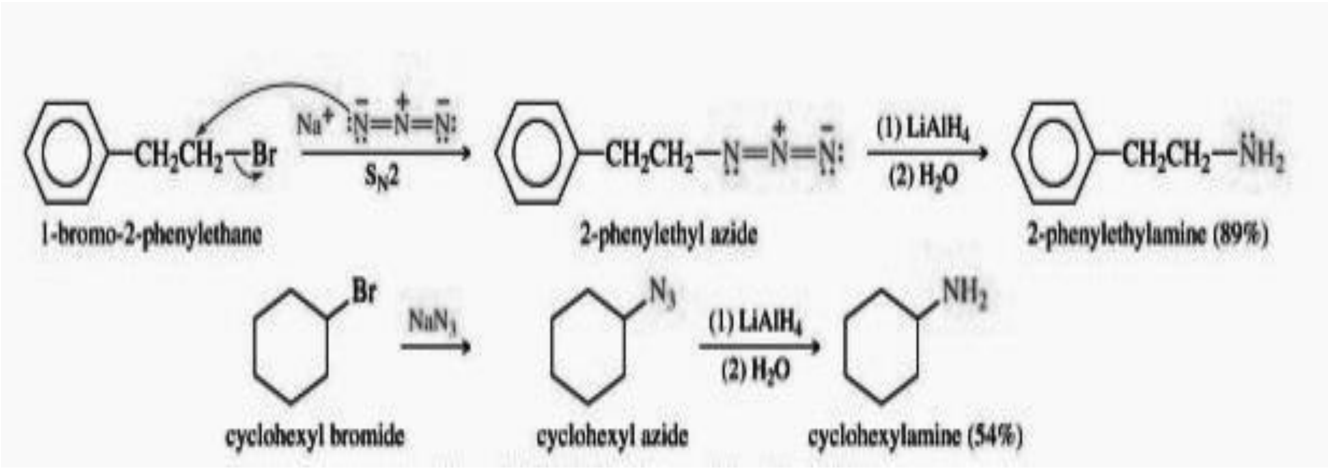


Reduction of azides

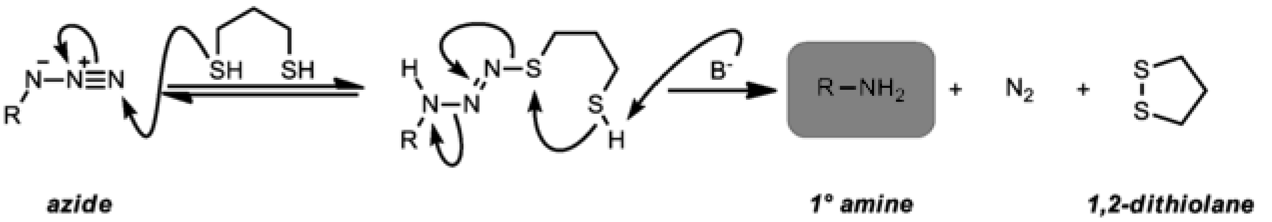
- Azide ion is a good nucleophile.

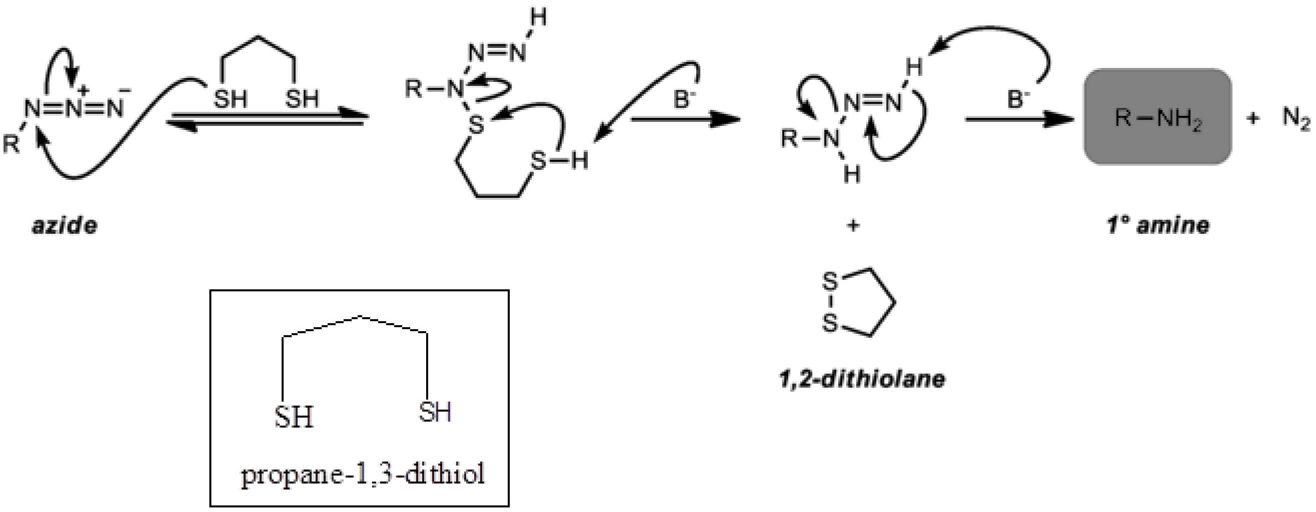
- Reaction with Unhindered **1^0** or **2^0** halide through **S_N2** mechanism
- ***General Reaction:***





- ***Reaction mechanism:***



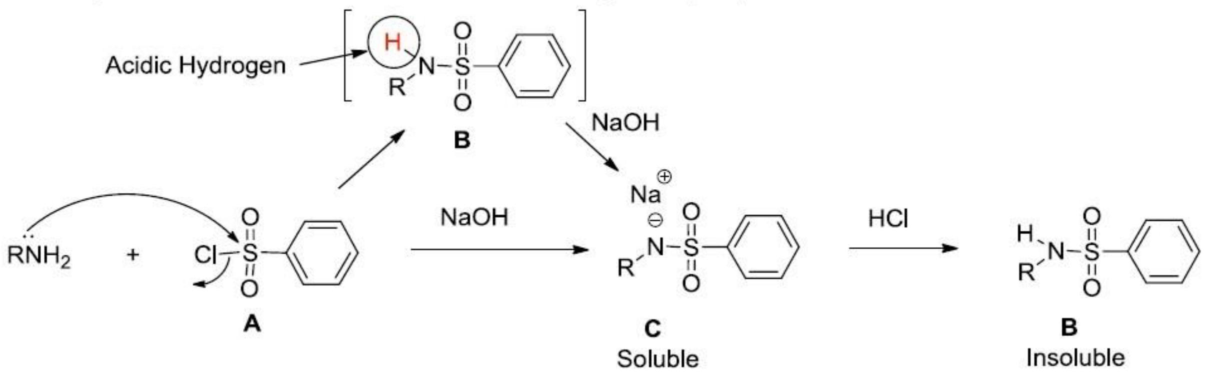


TEST FOR AMINES

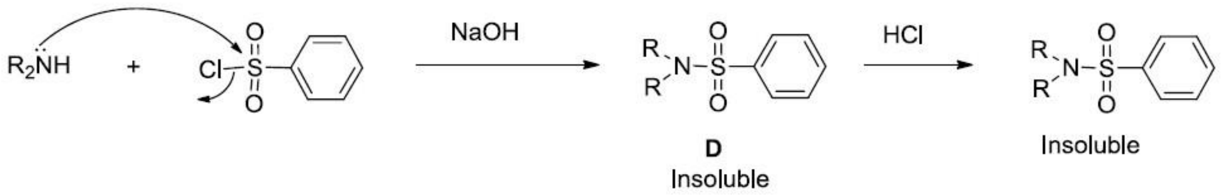
1. *Hinsberg Test* (Test for Primary, Secondary and Tertiary Amines)

Principle:- Treatment of an amine with benzenesulfonyl chloride in aqueous sodium hydroxide is useful for determining whether an unknown amine is primary, secondary or tertiary.

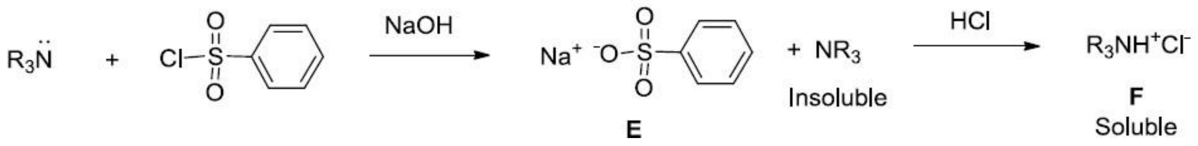
Primary Amines react with benzenesulfonyl chloride **A** to give sulfonamides **B** which have an acidic amide hydrogen that reacts with sodium hydroxide to form the sodium salt of the sulfonamide **C**. **C** is soluble in the aqueous sodium hydroxide solution. Acidification of the solution gives a precipitate of the sulfonamide **B**.



Secondary Amines react with benzenesulfonyl chloride to form a sulfonamide **D** that does not contain an acidic amide hydrogen and thus is not soluble in the aqueous sodium hydroxide solution. Acidification of the mixture does not dissolve the insoluble sulfonamide.



Tertiary Amines do not react with benzenesulfonyl chloride; however, the sodium hydroxide eventually will react with the sulfonyl chloride to form a salt of benzenesulfonic acid **E**. The amine does not dissolve (unless it is a low molecular weight water soluble amine) in the initial reaction mixture, but will dissolve on acidification with HCl since a water soluble amine hydrochloride salt **F** is formed.



To summarize of Hinsberg test:

1. ***Primary amines*** – Adding a primary amine to the Hinsberg test solution should give a clear solution which, on acidification with HCl, would form a precipitate.
2. ***Secondary amines*** - React to form a suspension of an insoluble solid or oil which does not dissolve on acidification with HCl.
3. ***Tertiary amines*** – Do not react with the benzenesulfonyl chloride in the Hinsberg test solution and thus initially provide an insoluble solid or oil (the unreacted amine) which, on acidification with HCl, dissolves to give a clear solution of the amine salt.

2. Nitrous acid test

- *Primary amine* reacts with nitrous acid to give nitrogen gas.: $\mathbf{RNH_2 + HONO \rightarrow ROH + H_2O + N_2}$
- *Secondary amine* reacts with nitrous acid to form a yellow oily nitrosamine.: $\mathbf{R_2NH + HONO \rightarrow R_2N\text{-}NO + H_2O}$
- *Tertiary amine* reacts with nitrous acid to form soluble nitrite salt.: $\mathbf{R_3N + HONO \rightarrow R_3NH{+}ONO^-}$ (trialkyl ammonium nitrite)
- *Principle:*
  - Nitrous acid is a source of electrophilic nitrosonium ion ($O = N^+$), which reacts with amines. Nitrous acid being unstable is generated in situ from a mineral acid and sodium nitrite.
  - Primary aromatic amine reacts with nitrous acid to form a diazonium salt which is stable but low temperatures.
  - On reaction with phenol, an aromatic diazonium salt undergoes a coupling reaction to form a dye.

$$ArNH_2Cl + NaNO_2 + HCl \xrightarrow{4.85^0C} ArN_2^+\ Cl^- + NaCl + 2H_2O$$

$$ArN_2Cl + Ar^-OH \longrightarrow \underset{\text{dye}}{Ar - N = N - Ar}$$

  - Primary aliphatic amines form diazonium salts which are unstable and liberate nitrogen to form a carbonium ion which in aqueous reaction medium forms an alcohol or on proton elimination gives an alkene.

$$RNH_2 + HNO_2 \longrightarrow \left[\overset{+}{R} + N_2\right] \longrightarrow ROH \ / \ \text{alkene} + N_2$$

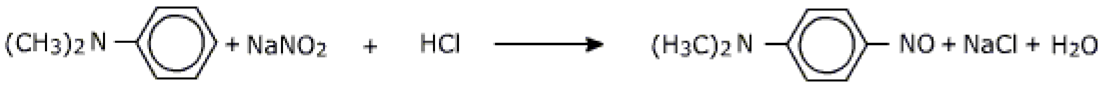
  - So primary amines liberate $\mathbf{N_2}$ with nitrous acid unlike $\mathbf{2^0}$and $\mathbf{3^0}$ amines. So this can be used to distinguish $\mathbf{1^0}$ amines from $\mathbf{2^0}$ and $\mathbf{3^0}$amines.
  - Secondary amines, both aliphaptic and aromatic on reaction with nitrous acid give yellow colored oily N-nitrosoamines which unlike amines are insoluble in aqueous mineral acids. This is used as a test for $\mathbf{2^0}$ amines.

$$R_2NH + NaNO_2 + HCl \longrightarrow R_2N - N = O + NaCl + H_2O$$

  - Aliphatic tertiary amines form water soluble salts with nitrous acid.

$$R_3N + NaNO_2 + HCl \longrightarrow R_3\overset{+}{N}H\overset{-}{N}O_2 + NaCl$$

- Aromatic tertiary amines on reaction with nitrous acid undergo electrophilic substitution with nitro sonium ion at the *p*-position of the phenyl ring.



QUESTION: DISTINGUISH BETWEEN ALIPHATIC PRIMARY AMINES & AROMATIC PRIMARY AMINES.

ANSWER:

- At low temperature (0 - 5^0C) aromatic primary amines dissolved in strong acids (HCl & H_2SO_4) reacts with nitrous acid ($NaNO_2$ +HCl) to form water soluble diazonium salts.
- Aliphatic primary amines do not form stable diazonium salts under similar condition. They react with nitrous acid to yield alcohols and nitrogen (causes rapid foaming).

$$ArNH_2 \xrightarrow[HCl]{NaNO_2} \underset{\textit{Aryl diazonium chloride}}{ArN_2^+Cl^-} + NaCl + 2H_2O$$

$$RNH_2 \xrightarrow[HCl]{NaNO_2} ROH + N_2\uparrow$$

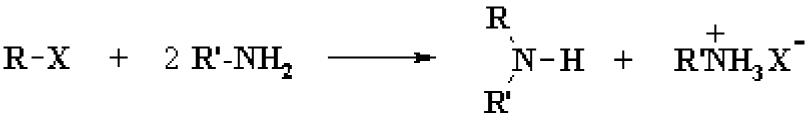
AMINE REACTIONS

- **Ammonia** and many **amines** are not only bases in the Brønsted sense, they are also nucleophiles that bond to and form products with a variety of electrophiles. A general equation for such **electrophilic substitution of nitrogen** is $\mathbf{2R_2NH + E^{(+)} \rightleftharpoons R_2NHE^{(+)} \rightleftharpoons R_2NE + H^{(+)}}$ **(bonded to a base)**
- A list of some electrophiles that are known to react with amines (**bold** are the electrophilic atom)

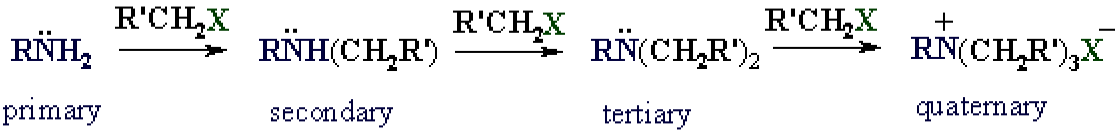
Electrophile	$R\mathbf{C}H_2{-}X$	$R\mathbf{C}H_2{-}OSO_2R$	$R_2\mathbf{C}{=}O$	$R(\mathbf{C}{=}O)X$	$R\mathbf{S}O_2{-}Cl$	$HO{-}\mathbf{N}{=}O$
Name	*Alkyl Halide*	*Alkyl Sulfonate*	*Aldehyde or Ketone*	*Acid Halide or Anhydride*	*Sulfonyl Chloride*	*Nitrous Acid*

1. ALKYLATION OF AMINE BY ALKYL HALIDES

- **Reaction type :** *Nucleophilic Substitution*
- Amines can react as a nucleophiles with alkyl halides via substitution reactions (**S$_N$2**)
- The result is often a mixture of amines in various states of alkylation.



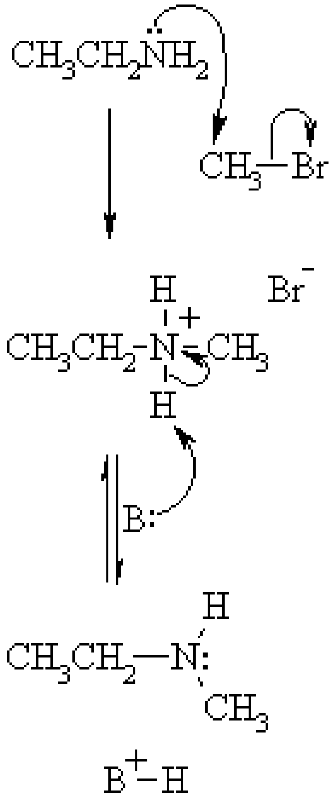
$$R{-}X + 2\,R'{-}NH_2 \longrightarrow R(R')N{-}H + R'\overset{+}{N}H_3X^-$$



- ***Reaction Mechanism***

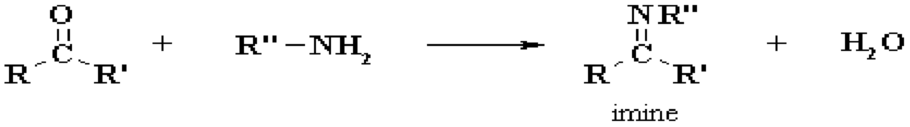
Step 1:
The amine N functions as the nucleophile and attacks the electrophilic C of the alkyl halide displacing the bromide and creating the new C-N bond.

Step 2:
An acid/base reaction. The base (excess amine) deprotonates the positive N (ammonium) center creating the alkylation product, here a secondary amine.

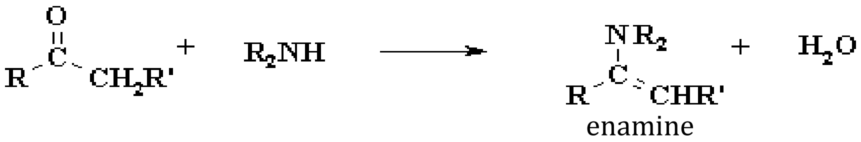


REACTIONS OF AMINES WITH ALDEHYDES AND KETONES

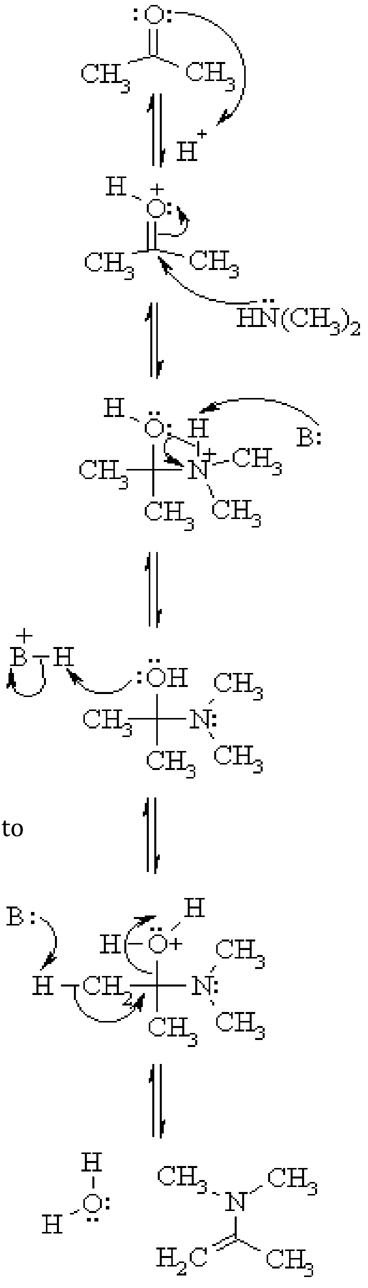
- **Reaction type:** *Nucleophilic Addition then Elimination*
- ***Primary amines*** (R-NH_2 or $ArNH_2$) undergo nucleophilic addition with aldehydes or ketones to give carbinolamines which then dehydrate to give substituted **IMINES**.



- ***Secondary amines*** (R_2NH) react with aldehydes or ketones to give carbinolamines which then dehydrate to give **ENAMINES**.



- ***Nucleophilic Addition of a Secondary Amine Giving an ENAMINE***



Step 1:
An acid/base reaction. Protonation of the carbonyl activates it and makes it more susceptible to attack by a neutral nucleophilic like the N of a secondary amine.

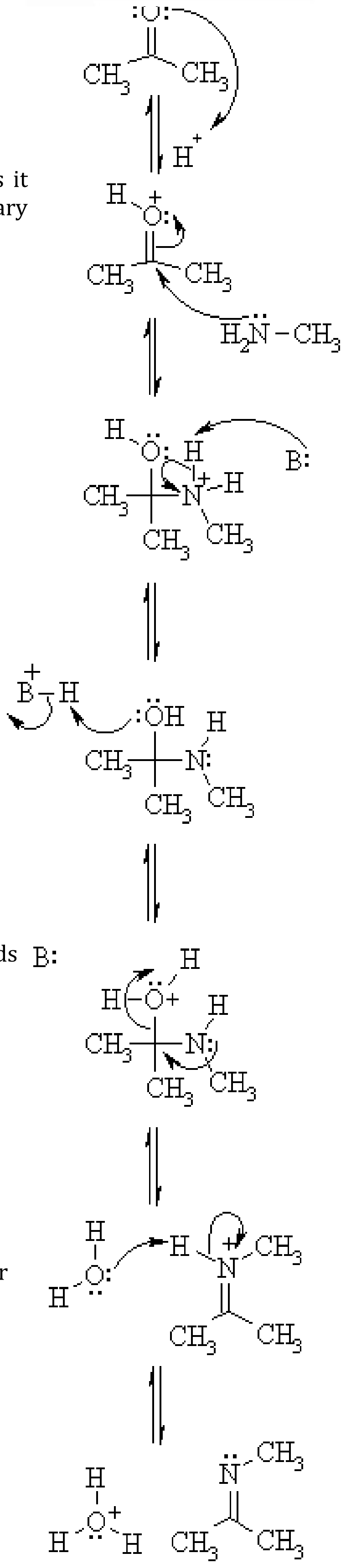
Step 2:
Attack of the N nucleophile at the electrophilic **C** of the **C=O** group with the electrons from the p bond going to the +ve O.

Step 3:
An acid/base reaction. Removal of the proton neutralizes the **+ve** charge on the **N** and forms the **carbinolamines** intermediate.

Step 4:
To form the enamine we need to dehydrate. However, before -OH leaves it needs to be protonated, so a simple acid/base reaction.

Step 5:
Removal of a proton from an adjacent C allows the p bond to form and loss of the leaving group, a neutral water molecule, creating the enamine.

-
- Nucleophilic Addition of a Primary Amine Giving an IMINE



Step 1:
An acid/base reaction. Protonation of the carbonyl activates it and makes it more susceptible to attack by a neutral nucleophilic like the N of a primary amine.

Step 2:
Attack of the N nucleophile at the electrophilic C of the C=O group with the electrons from the p bond going to the +ve O.

Step 3:
An acid/base reaction. Removal of the proton neutralizes the +ve charge on the N and forms the carbinolamine intermediate.

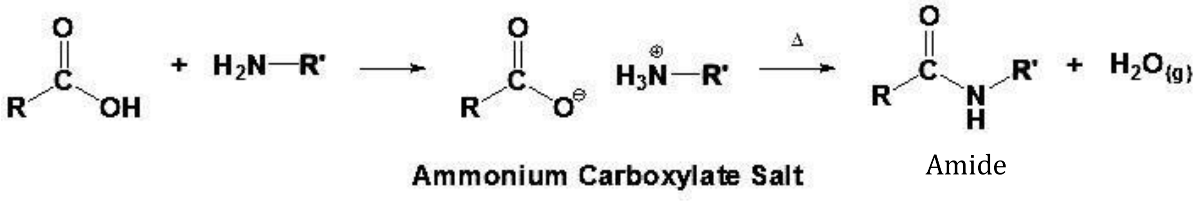
Step 4:
To form the imine we need to dehydrate. However, before -OH leaves it needs to be protonated, so a simple acid/base reaction.

Step 5:
Use the electrons of the N to help push out the leaving group, a neutral water molecule, this leaves us with an iminium ion.

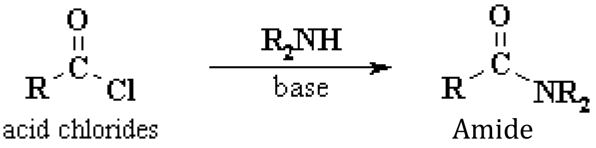
Step 6:
An acid/base reaction. Deprotonation of the iminium N reveals the imine product and regenerates the acid catalyst.

3.CONVERSION OF CARBOXYLIC ACID/ACID CHLORIDE/ ACIDANHYDRIDES TO AN AMIDE BY REACTION WITH AN AMINE

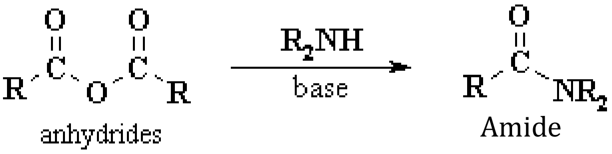
- **Reaction type:** *Nucleophilic Acyl Substitution*
- ***Primary amines*** (**R-NH$_2$**) and ***secondary amines*** (**R$_2$-NH**) undergo nucleophilic acyl substitution with carboxylic acid derivatives to give amides.
- Direct conversion of a ***carboxylic acid*** to an ***amide*** by reaction with an ***amine***.



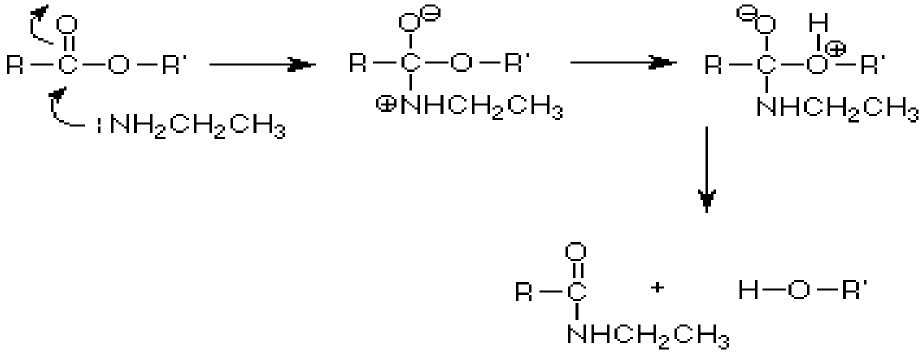
- **Acid chlorides** react with **ammonia**, **1⁰ amines** and **2⁰ amines** to form **amides**



- **Acid Anhydrides** react with **ammonia**, **1⁰ amines** and **2⁰ amines** to form **amides**

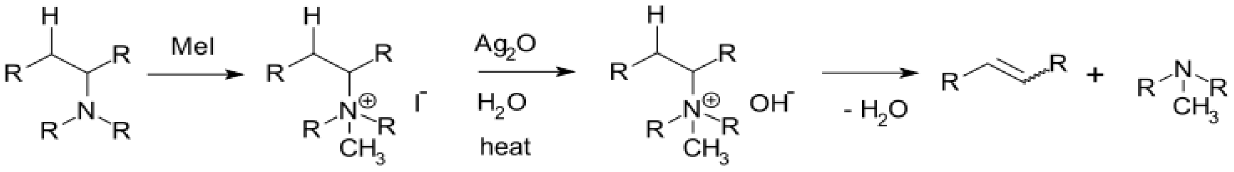


- ***Reaction mechanism***

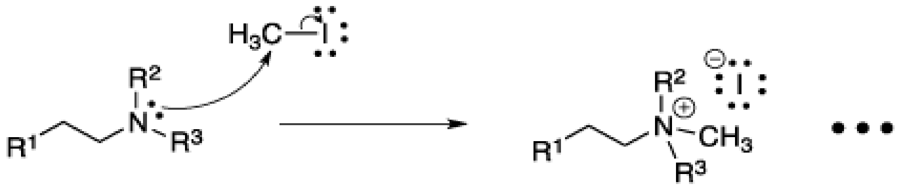


2.HOFMANN ELIMINATION

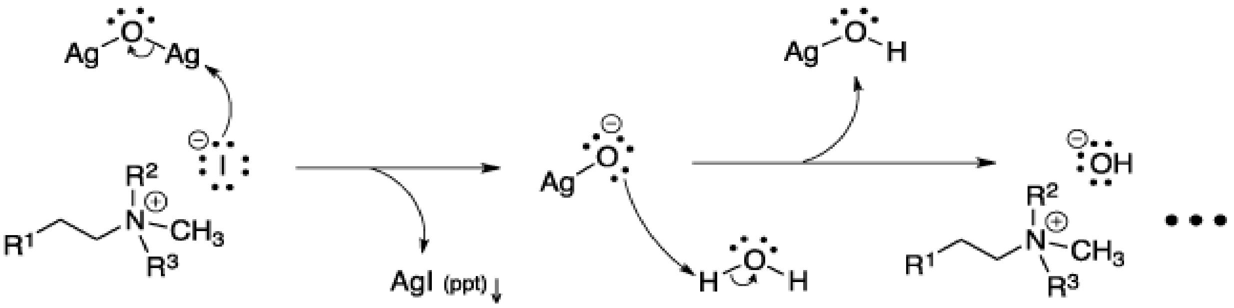
- ***Hofmann elimination***, also known as exhaustive methylation, is a process where a **quaternary amine** is reacted to create a **Tertiary amine** and an alkene by treatment with excess **methyl iodide** followed by treatment with **silver oxide**, **water**, and **heat**.
- Quaternary ammonium salts undergo an **E2** elimination when heated with silver oxide, Ag_2O, in water.
- Amines can readily be converted into quaternary ammonium iodides by treating them with excess methyl iodide.
- Ag_2O / H_2O reacts giving the quaternary ammonium hydroxide, silver iodide precipitates.
- ***Reaction Mechanism***



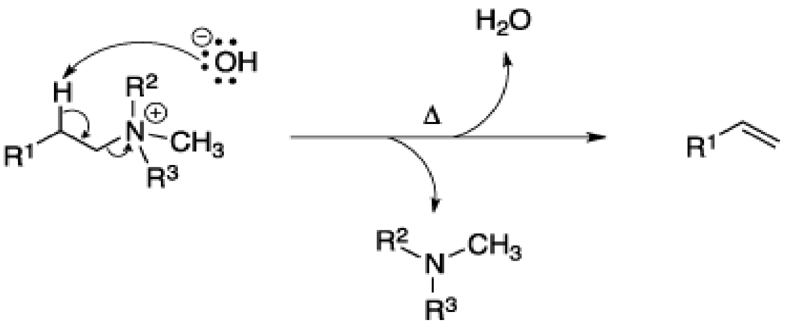
1. Formation of the ammonium iodide salt



2. Substitution of iodide anion with hydroxide

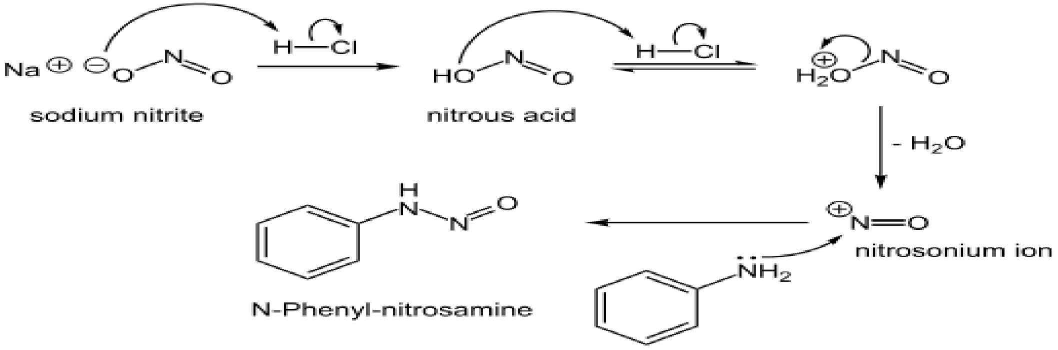


3. Heat mediated elimination leading to product

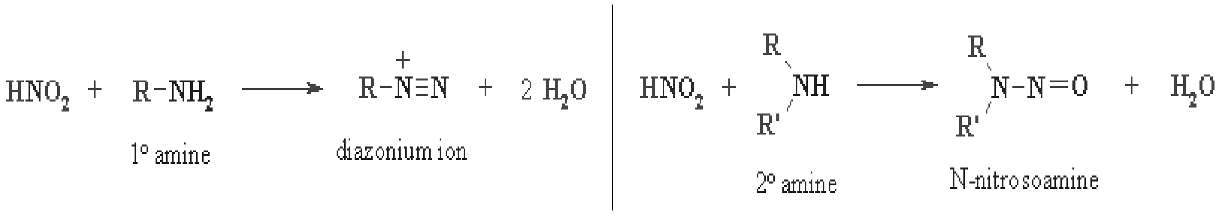


NITROSATION OF AMINES

- **Nitrosation** is a process of converting organic compounds into **nitroso derivatives**, i.e. compounds containing the **R-NO** functionality.



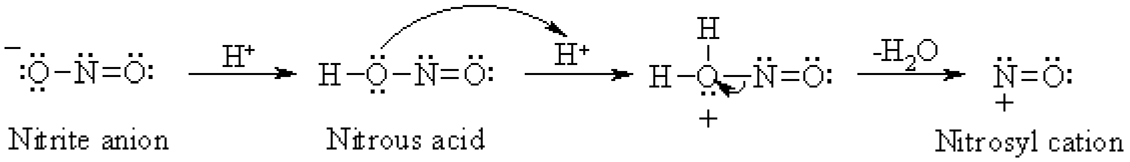
- **Primary alkyl** or **aryl amines** yield diazonium salts (hence the diazotisation reaction). **Tertiary alkyl** amines do not react in a useful fashion.
- ***General Reaction:***



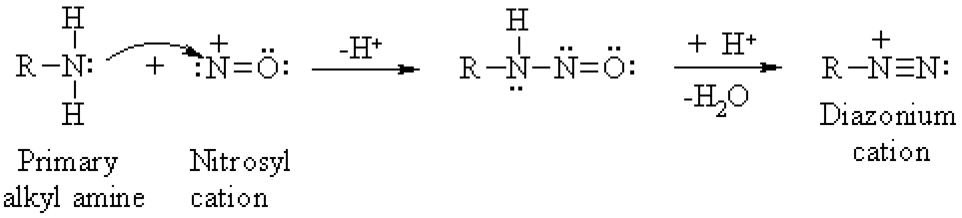
- **Reagents: Sodium Nitrite** (**$NaNO_2$**) and **aq. HCl** or **H_2SO_4** [this mixture yields **nitrous acid** (**HNO_2**)]

> In chemistry, ***in situ*** typically means "*in the reaction mixture.*" There are numerous situations in which chemical intermediates are synthesized ***in situ*** in various processes. This may be done because the species is unstable, and cannot be isolated, or simply out of convenience.

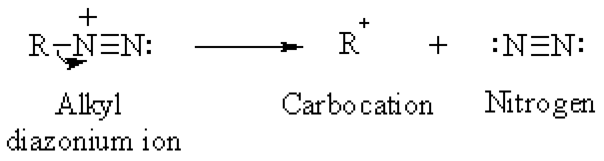
- The most useful reactions are probably those of **primary aryl amines** (**$Ar-NH_2$**), which give aryl diazonium salts, **$Ar-N_2^+$** which can then be used to prepare substituted benzenes.
- The actual nitrosation reagent is the **nitrosyl cation** (**NO^+)** which is formed ***in situ***



- The nature of the product depends on the nature of the initial amine, such as Primary alkyl or aryl amines yield diazonium salts



- **Alkyl diazonium salts** are very unstable and yield **carbocation-derived products** by loss of the very good leaving group, **N_2**



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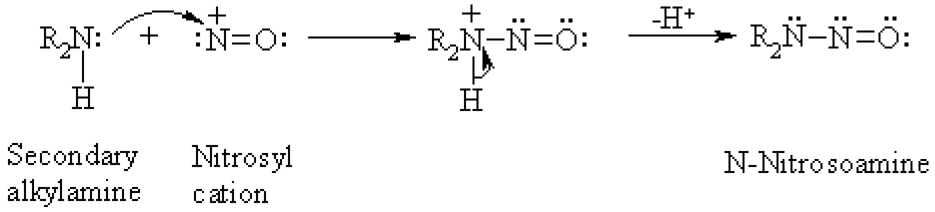
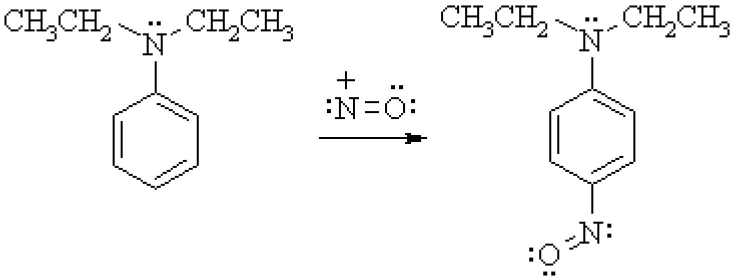
- **Secondary alkyl** or **aryl amines** yield **N-nitrosoamines**



- **Tertiary aryl amines** undergo **nitrosation** of the ring (an electrophilic aromatic substitution reaction).



QUESTION: WHAT IS DIAZONIUM SALTS OF AMINES?

ANSWER:

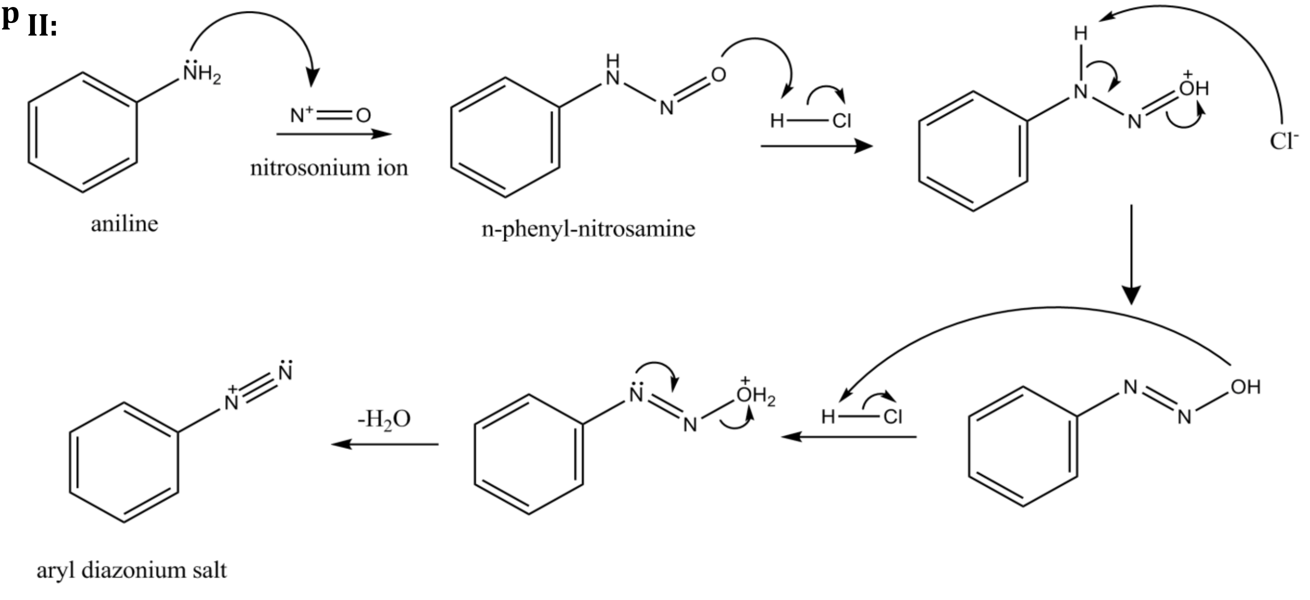
- These diazonium salts are prepared by treating a **primary amine** with **$NaNO_2$** in presence of **con. HCl**; the temperature being **0°C**. (Here the temperature has to be taken care of and if the temperature exceeds **5°C**, the reaction will not take place.)
- ***General Reaction:***

$$RNH_2/Ar\text{-}NH_2 \xrightarrow[HCl,0°C]{HONO} RN_2^+Cl^-$$

- ***Mechanism for Diazotization:***

Step I: $H-\ddot{O}NO + H_3\overset{+}{O} \rightleftharpoons H_2O^+ - \ddot{N}O + H_2O \rightleftharpoons 2H_2O + \overset{+}{\ddot{N}}=0$

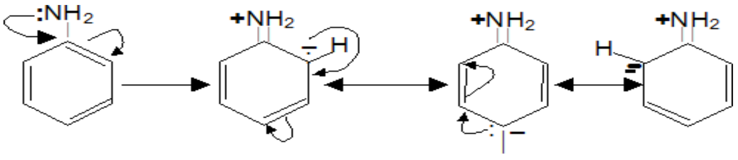
Step II:



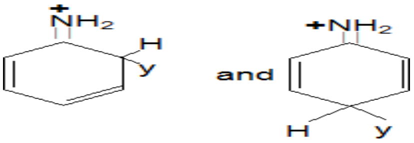
ELECTROPHILIC AROMATIC SUBSTITUTION OF ARYL AMINES

➢ Ring Substitution in Aromatic Amines

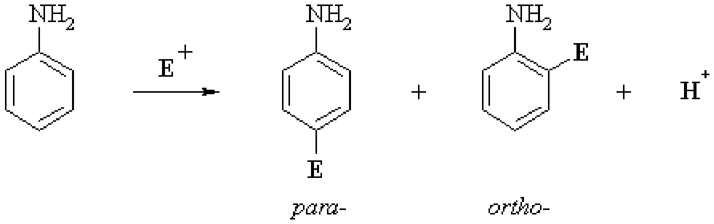
- The **–NH₂, – NHR** and **–NR₂** are benzene activating groups through resonance effect of nitrogen where the lone one pair of electron of nitrogen is shifted to the benzene ring making **ortho** and **para**, position available for electrophilic attack.



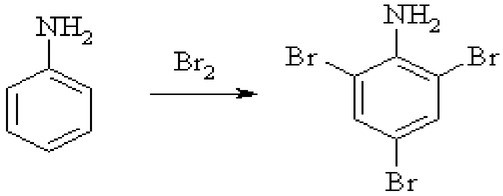
- The carbocation formed as intermediate are



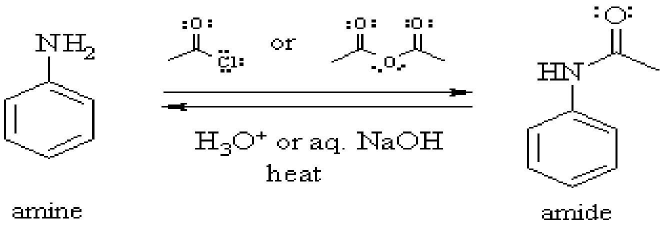
- ***Electrophilic Aromatic Substitution of Aryl Amines***



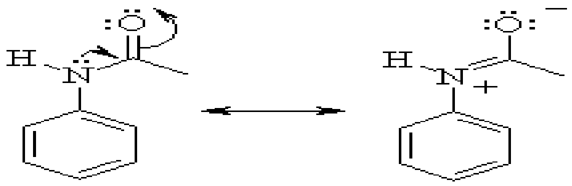
- Polysubstitution can also be a problem. For example, bromination is very rapid, even in the absence of a catalyst, leading to bromination in all available **ortho**- and **para**- positions:



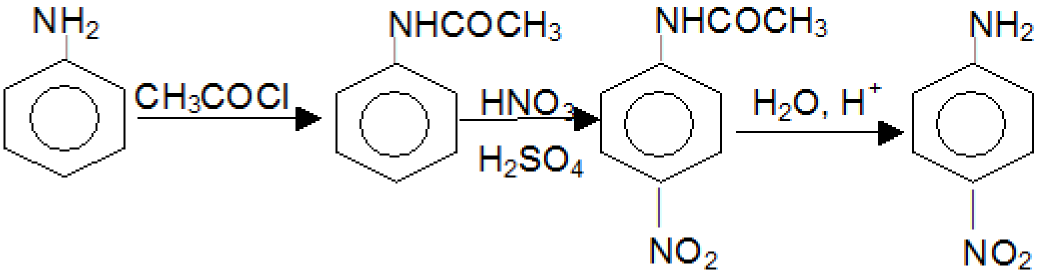
- To avoid these problems, it is customary to "protect" **aryl amines** as their **N-acyl derivatives**. The protecting group (**an amide**) can later be removed by either acid or base hydrolysis.



- The **amide** is a <u>less powerful activating group</u> than the **simple amino group**, **-NH₂** since resonance within the **N-acetyl group** of the amide competes with delocalization of the **N** *lone pair* into the ring and **Steric effects** in the amide also often lead to a decrease in the amount of the ortho-products.


H
N
O
H
N
+
O
−

- The group **–NHCOCH₃** is less powerful ortho and para director because of the electron-withdrawing character of oxygen makes nitrogen a poor source of electrons. This fact is made use in preparing mono substituted aniline. The **–NH₂** group is such a powerful activator, that substitution occurs at all available ortho and para positions of aniline. If, however, $-NH_2$ group is converted to **–NHCOCH₃**, the molecule becomes less powerful activator. Hence only mono substitution products are obtained. Finally **–NHCOCH₃** is converted back to **–NH₂** by hydrolyzing with acid. This technique is especially used while nitrating aniline as strong oxidizing agent destroys the highly reactive ring.



❖ FISCHER–HEPP REARRANGEMENT

- The ***Fischer–Hepp rearrangement*** is a rearrangement reaction in which an aromatic **N-nitroso** or **nitrosamine** converts to a **carbon nitroso** compound
- The rearrangement reaction takes place by reacting the nitrosamine precursor with hydrochloric acid.
- The exact reaction mechanism is unknown but there is evidence suggesting an intramolecular reaction.