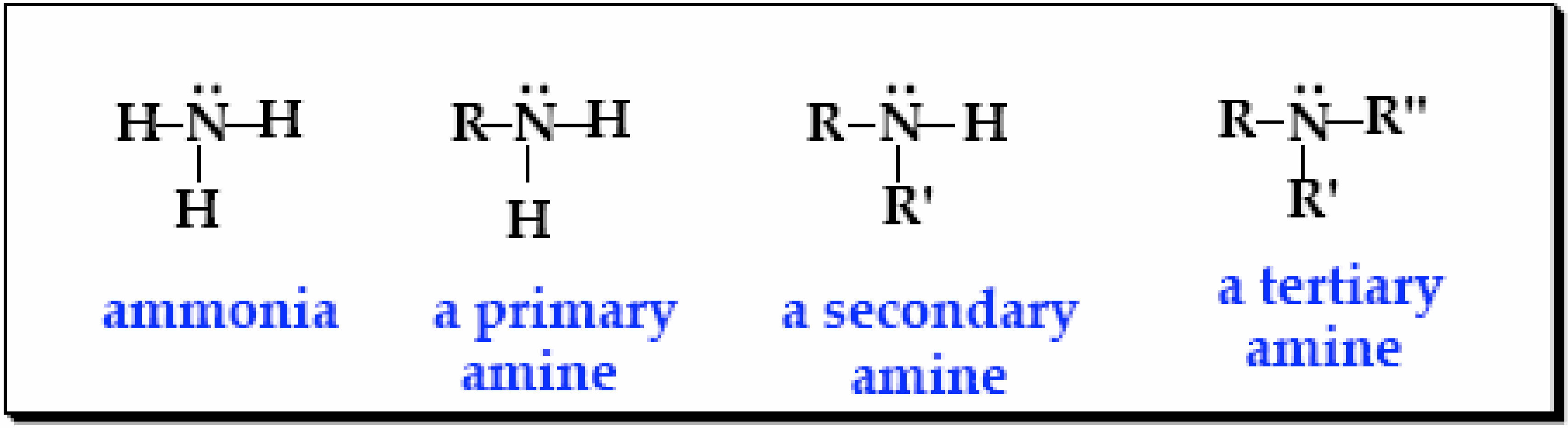
Chapter 18

Amines

Classification of Amines

- Amines are classified as primary, secondary , or tertiary according to the number of alkyl or aryl groups bonded to the nitrogen.



Note: The designation of 1º, 2ºand 3º amine does not depend in any way on the structure of the R group.

Examples

$CH_3CH_2NH_2$

ethylamine

(a 1° amine)

$CH_3NHCH_2CH_3$

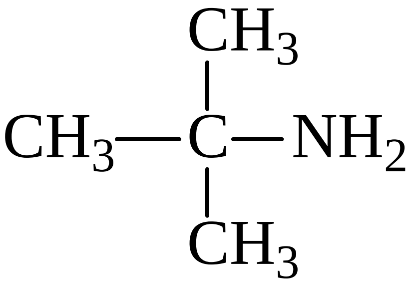
Two alkyl groups attached to N

(a 2° amine)

$(CH_3CH_2)_3N$

Three alkyl groups attached to N

(a 3° amine)

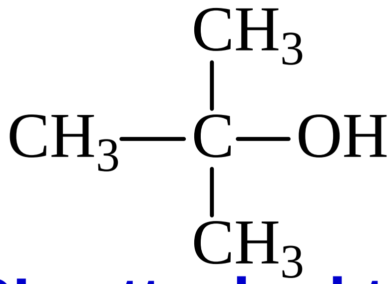


$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-NH_2$$

One C attached to N

(a 1° amine)

tert-butyl amine



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-OH$$

3 C's attached to head C

a 3° alcohol

tert.-Butyl alcohol

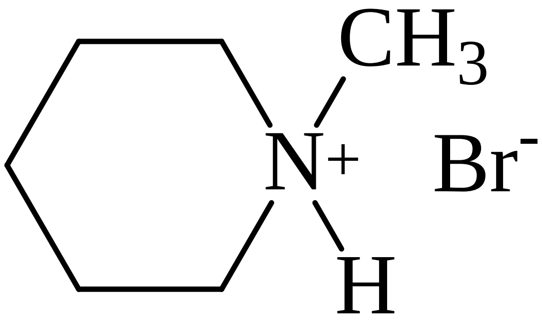
Amine Salt

- If four groups attached to N ➔ amine salt nitrogen is a positive ion

$(CH_3)_2NH_2^+\ Cl^-$

dimethyl ammonium chloride

Salt of 2° amine



N-methylpipridinium bromide

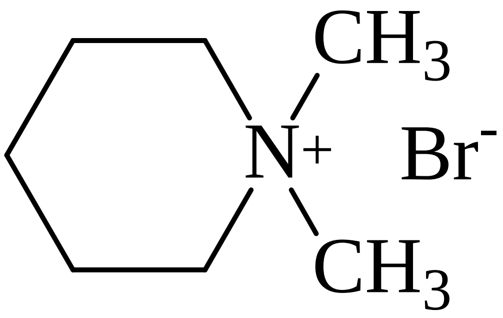
Salt of 3° amine

Quaternary Ammonium Salts

- If all the four groups on N are alkyl or aryl (no H's on N) ➔ the compound is quternary ammonium salt

$(CH_3)_4N^+ Cl^-$

tetramethylammonium chloride



N,N-dimethylpipridinium bromide

Nomenclature of Amines

- *Primary amines* are named by replacing the *-e* of the corresponding parent alkane with *–amine* *(functional group system)*
- Amines may also be named as alkylamines (*substitutive system)*

CH_3NH_2

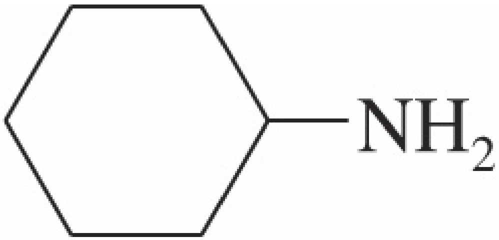
Methylamine

(methanamine)

$$\begin{array}{l} CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2NH_2 \end{array}$$

(2-methyl-1-propanamine)

Isobutylamine



Cyclohexylamine

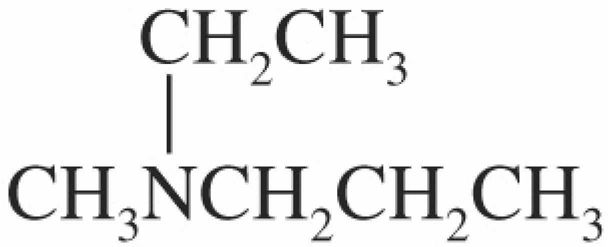
(cyclohexanamine)

If more than one alkyl group is attached to the nitrogen, the largest group is considered the parent. A subsidiary alkyl group is designated by an N-Alkyl- prefix

$(CH_3CH_2)_3N$

Triethylamine

(*N*,*N*-diethylethanamine)



$$\begin{array}{c} CH_2CH_3 \\ | \\ CH_3NCH_2CH_2CH_3 \end{array}$$

N-ethyl-N-methyl propylamine

(*N*-ethyl-*N*-methyl-1-propanamine)

- Diamines are named by the name of the parent alkane followed by ending – diamine.

$H_2NCH_2CH_2CH_2NH_2$

1,3-propanediamine

- The substitutent -NH_2 is called the *amino* group if present with a higher pripority functional group

$H_2NCH_2CH_2OH$

2-Aminoethanol

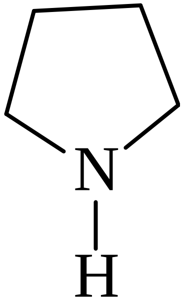
$$H_2NCH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OH$$

3-Aminopropanoic acid

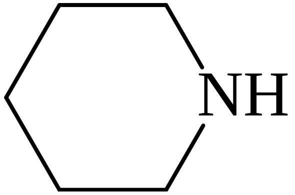
$$CH_3\overset{\overset{\displaystyle NHCH_3}{|}}{C}HCO_2H$$

2-(N-methylamino)-propanoic acid

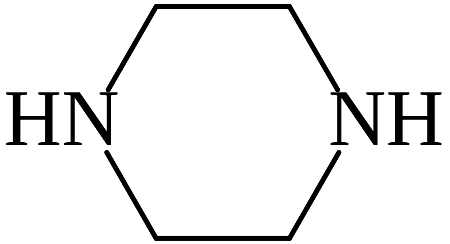
Nonaromatic Heterocylic Amines



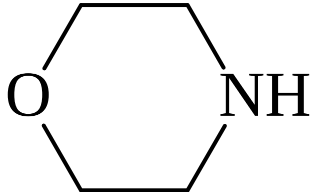
pyrrolidine



pipieridine



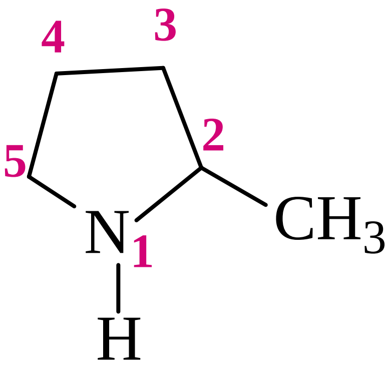
piperizine



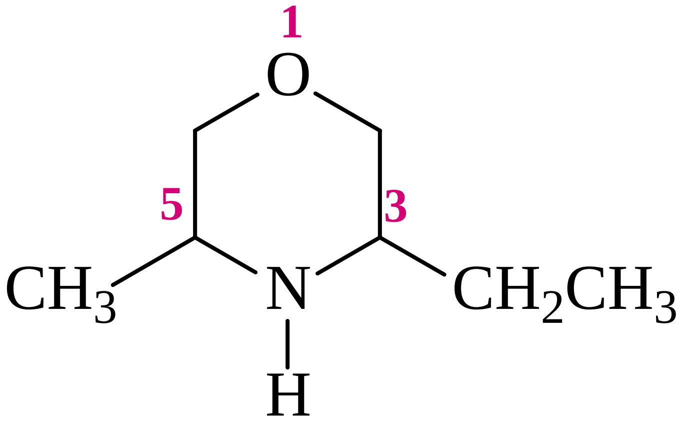
morpholine

Note: in numbering of the heterocyclic rings, the hetroatom is considered position 1. oxygen has a higher priority than nitrogen

Examples



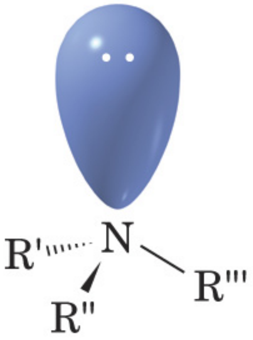
2- methylpyrrolidine



3-ethyl-5-methylmorpholine

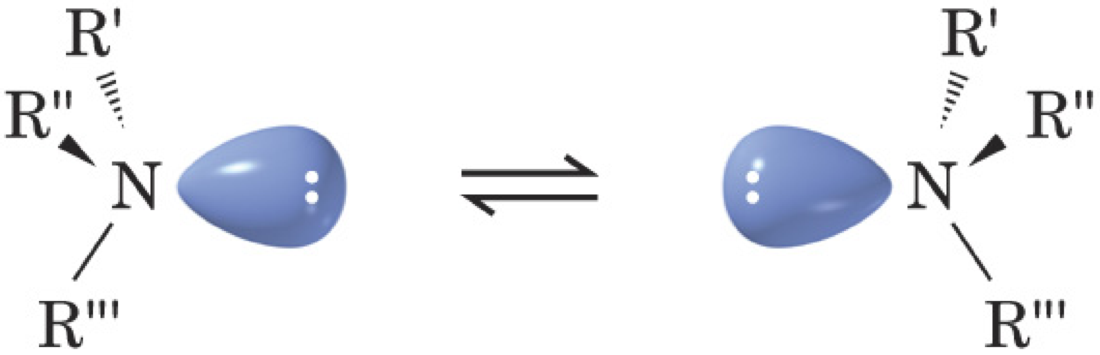
Bonding in Amines

- The nitrogen atom in an amine is *sp*^{3} hybridized
  - The three groups and the unshared electron pair around nitrogen result in a *tetrahedral* geometry
  - If only the location of the groups (and not the unshared electron pair) are considered, the shape of the amine is *trigonal pyramidal*
  - Partial negative charge is localized in the region of the nonbonding electrons



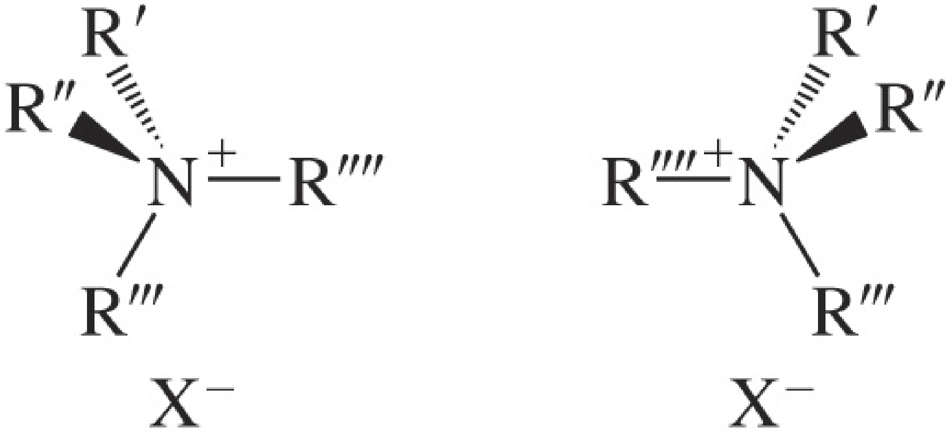
Structure of an amine

- It is usually impossible to resolve amine enantiomers that are chiral at nitrogen because they interconvert rapidly
  - The interconversion occurs through a *pyramidal* or *nitrogen inversion* involving the unshared electron pair



Interconversion of amine enantiomers

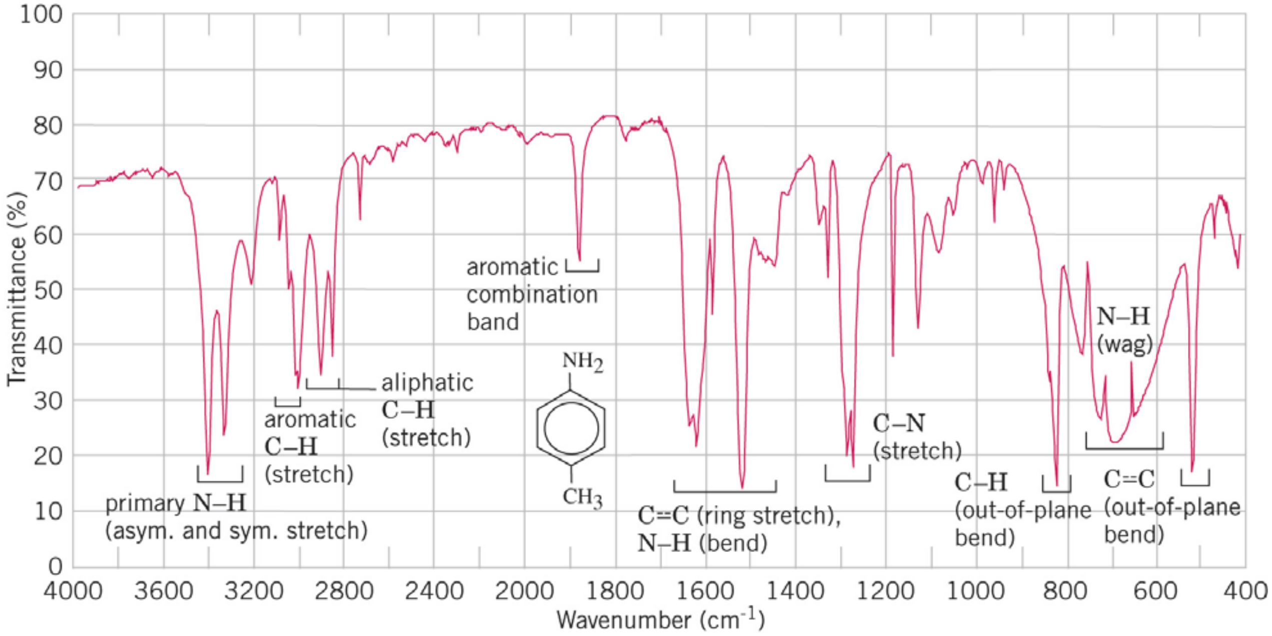
- Quaternary ammonium salts can be resolved into enantiomers
  - Chiral quaternary ammonium salts cannot undergo nitrogen inversion because they lack an unshared electron pair on the nitrogen atom



Quaternary ammonium salts such as these can be resolved.

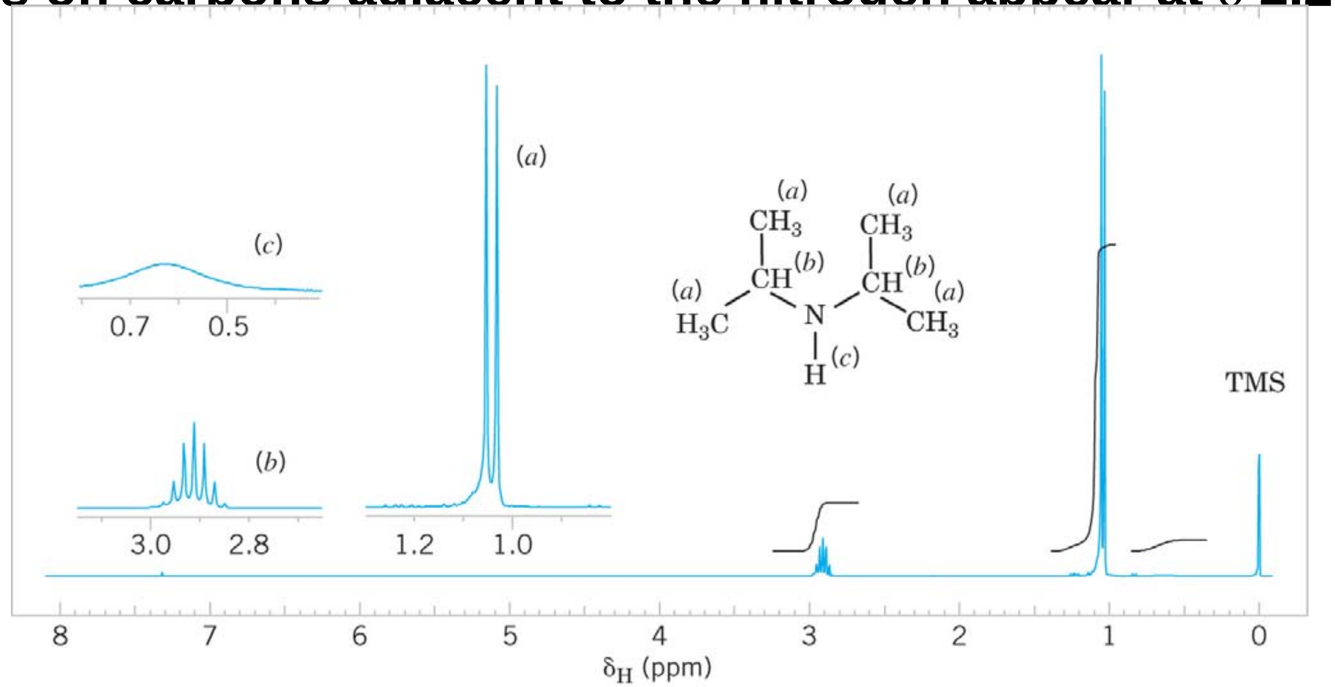
Spectral properties of Amines

- **Infrared Spectra**
  - **Primary and secondary amines are characterized by N-H stretching vibrations in the 3300-3555 cm $^{-1}$ region**
  - **Primary amines give 2 absorptions (from symmetric and asymmetric stretching); secondary amines give one absorption**



Proton NMR

- ^{1}H NMR
  - –**Primary and secondary amines have broad, uncoupled N-H peaks at δ 0.5-5**
  - –**N-H protons will exchange with D_2O and disappear from the ^{1}H spectrum**
  - –**Protons on carbons adjacent to the nitrogen appear at δ 2.2-2.9**



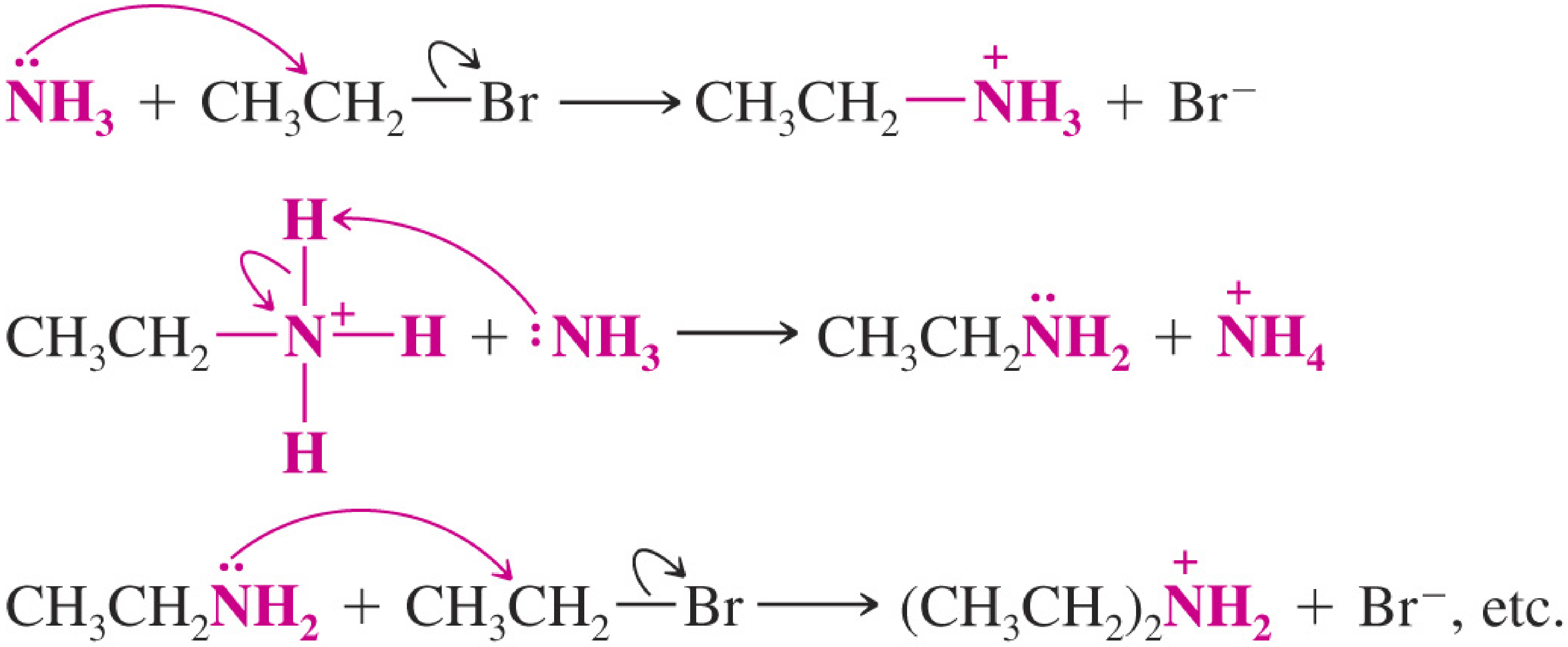
Preparation of Amines

A. Synthesis of Amines by Substitution Reactions

1. By Nucleophilic Substitution Reactions.
   - Alkylation of Ammonia
     - **Reaction of ammonia with an alkyl halide leads to an aminium salt**
     - **The salt is treated with base to give the primary amine**

$$\ddot{N}H_3 + R{-}X \longrightarrow R{-}\overset{+}{N}H_3\ X^- \xrightarrow{OH^-} RNH_2$$

- **The method is limited because multiple alkylations usually occur.**



$$\ddot{N}H_3 + CH_3CH_2{-}Br \longrightarrow CH_3CH_2{-}\overset{+}{N}H_3 + Br^-$$

$$CH_3CH_2{-}\overset{+}{N}H_3 + :NH_3 \longrightarrow CH_3CH_2\ddot{N}H_2 + \overset{+}{N}H_4$$

$$CH_3CH_2\ddot{N}H_2 + CH_3CH_2{-}Br \longrightarrow (CH_3CH_2)_2\overset{+}{N}H_2 + Br^-\text{, etc.}$$

–**Using an excess of ammonia helps to minimize multiple alkylations**

$$CH_3CH_2CH_2Br \;+\; \text{excess } NH_3 \longrightarrow CH_3CH_2CH_2NH_2$$

1-bromopropane **propylamine**

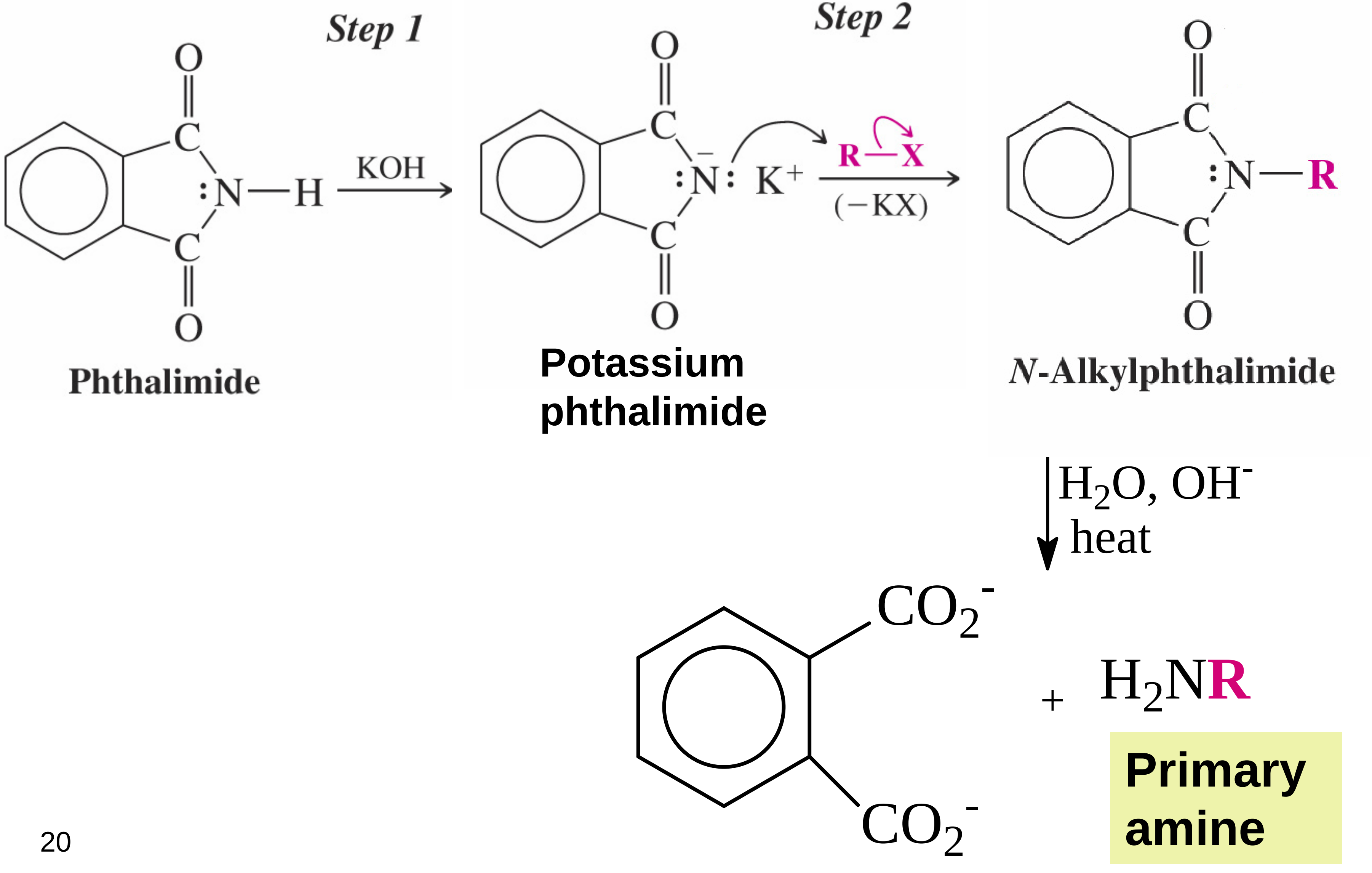
- Using an excess of Alkyl Halides ➔ quaternary ammonium salt

$$NH_3 \xrightarrow{RX} RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4N^+ X^-$$

Example

$$NH_3 \;+\; \text{excess } CH_3CH_2I \longrightarrow \xrightarrow{^-OH} (CH_3CH_2)_4N^+ I^-$$

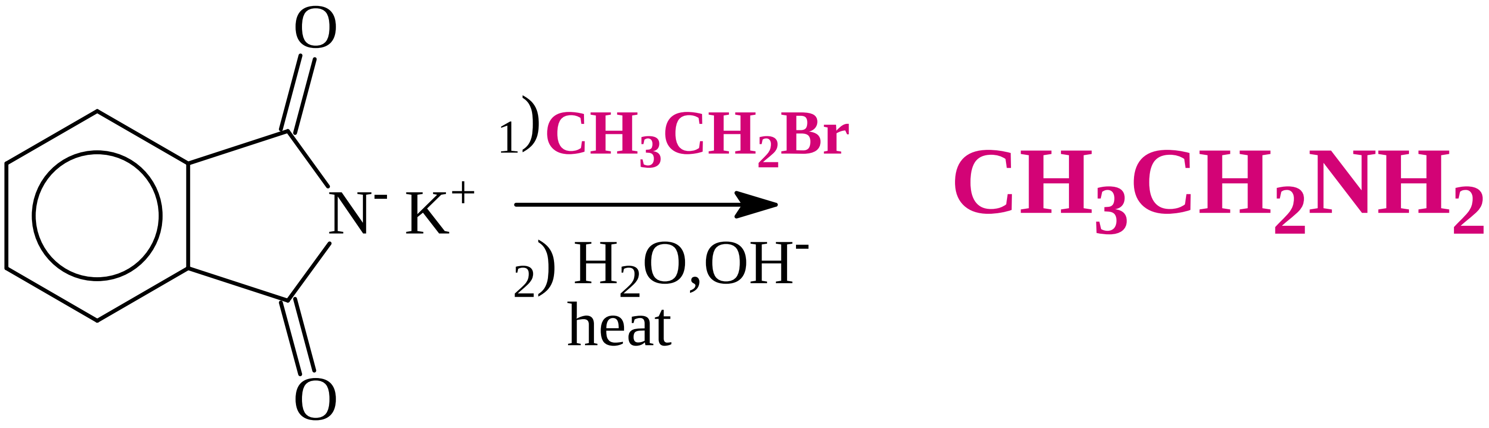
2) Gabrial phthalimide synthesis



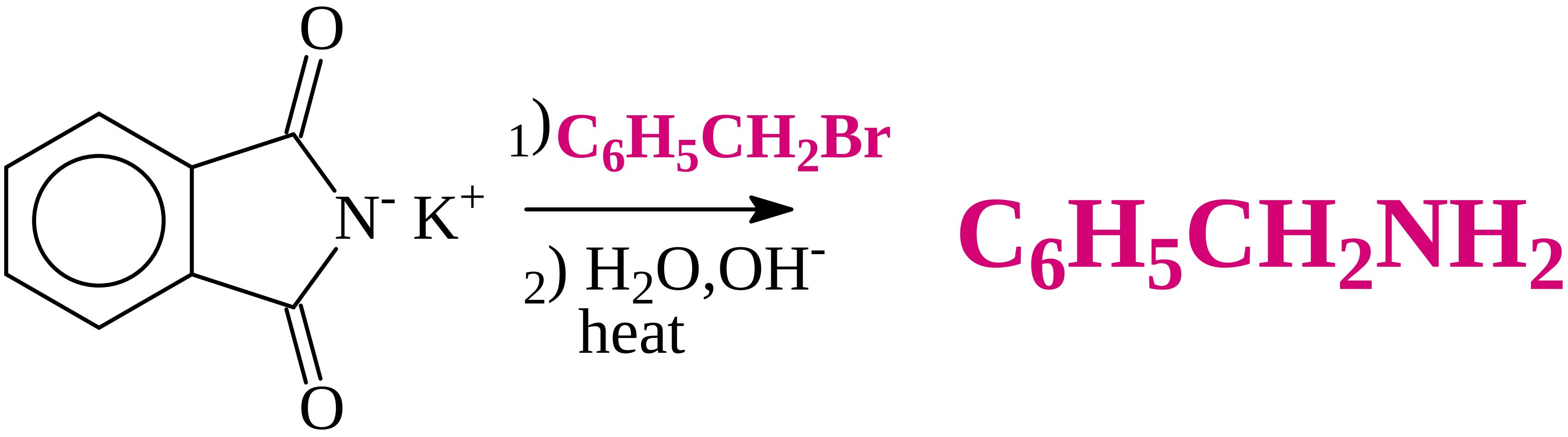
Potassium phthalimide

Primary amine

Examples

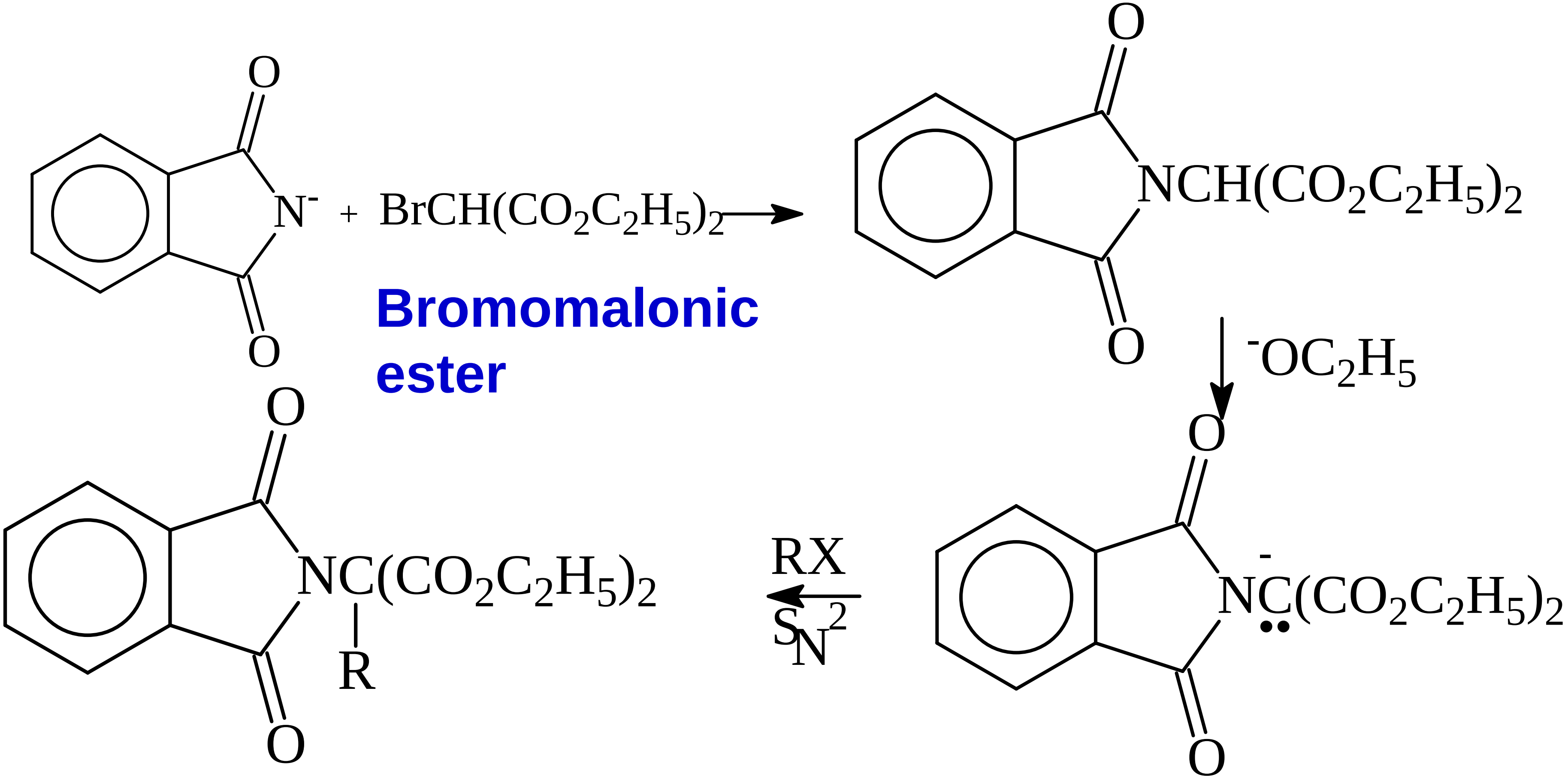


$$\text{N}^-\text{K}^+ \xrightarrow[\text{2) } H_2O, OH^- \text{ heat}]{\text{1) } CH_3CH_2Br} CH_3CH_2NH_2$$



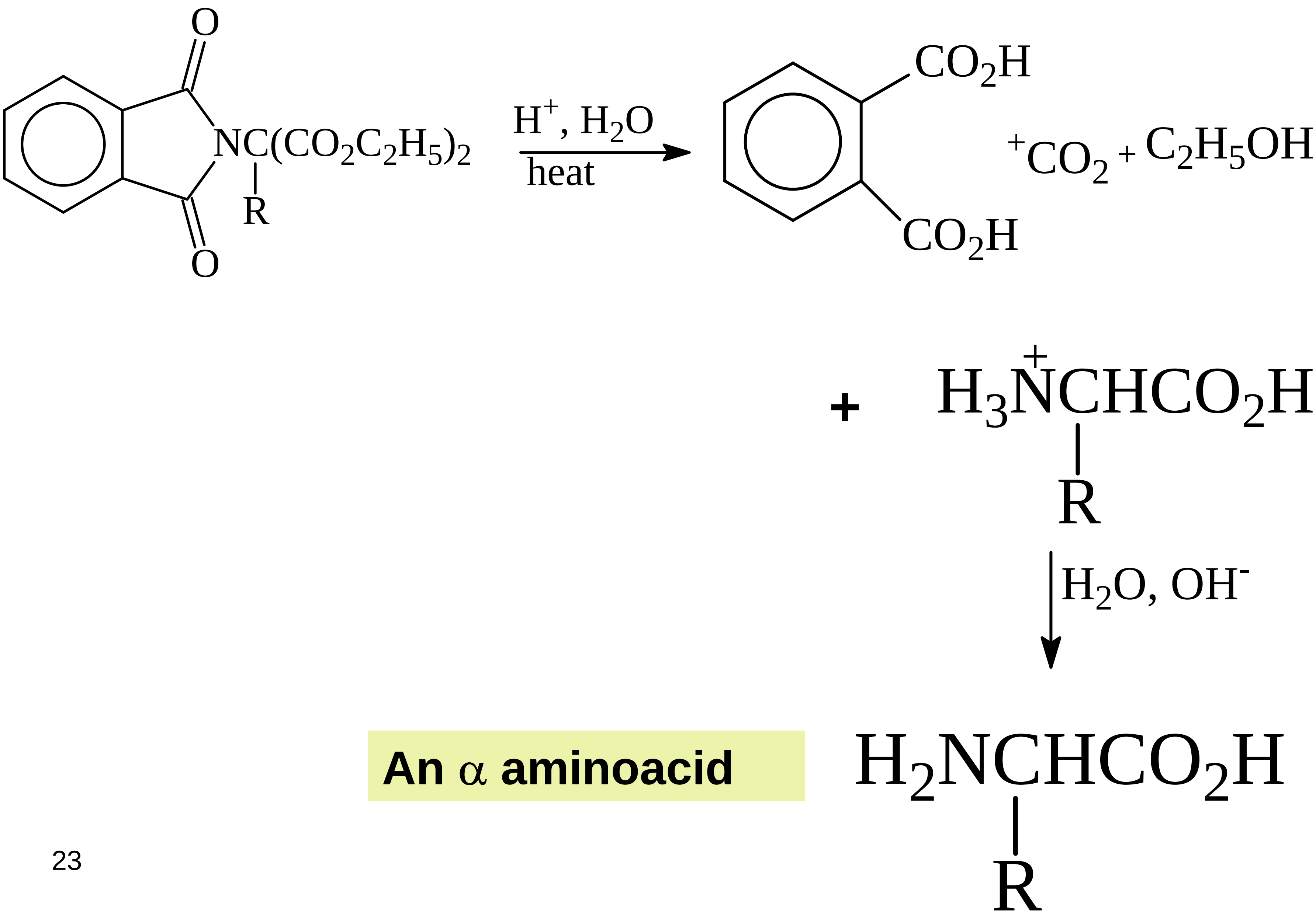
$$\text{N}^-\text{K}^+ \xrightarrow[\text{2) } H_2O, OH^- \text{ heat}]{\text{1) } C_6H_5CH_2Br} C_6H_5CH_2NH_2$$

Synthesis of aminoacids by Gabrial Phthalimide method



Bromomalonic ester

continued



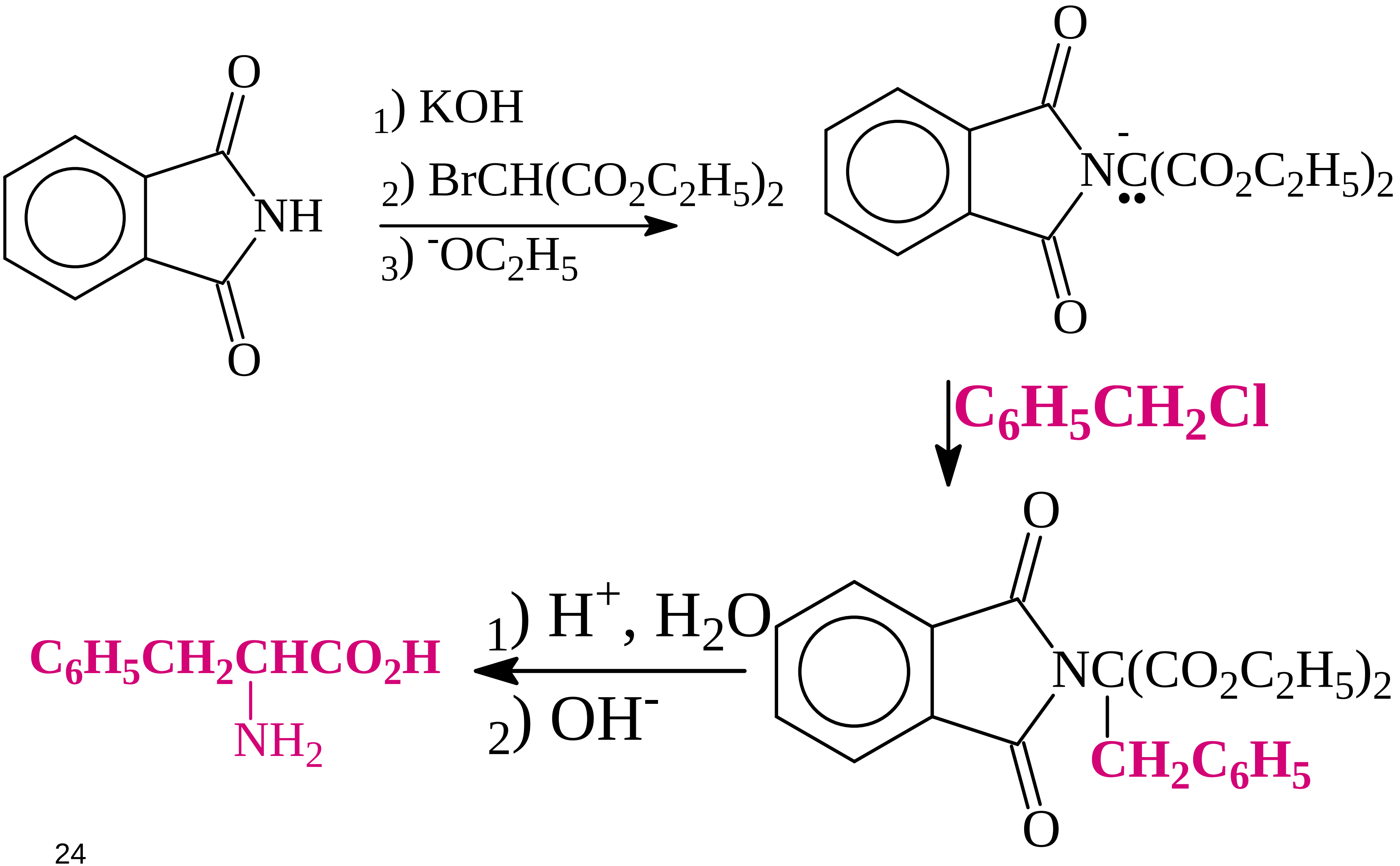
$$\mathrm{NC(CO_2C_2H_5)_2} \xrightarrow[\text{heat}]{H^+,\ H_2O} + CO_2 + C_2H_5OH$$

$$+ \quad H_3\overset{+}{N}CHCO_2H$$

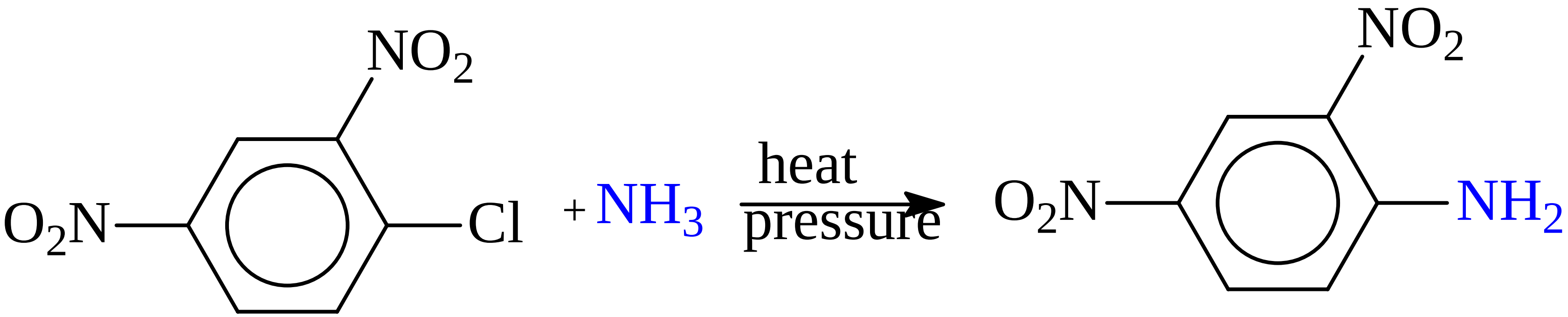
$$\xrightarrow{H_2O,\ OH^-} H_2NCHCO_2H$$

An α aminoacid

Example

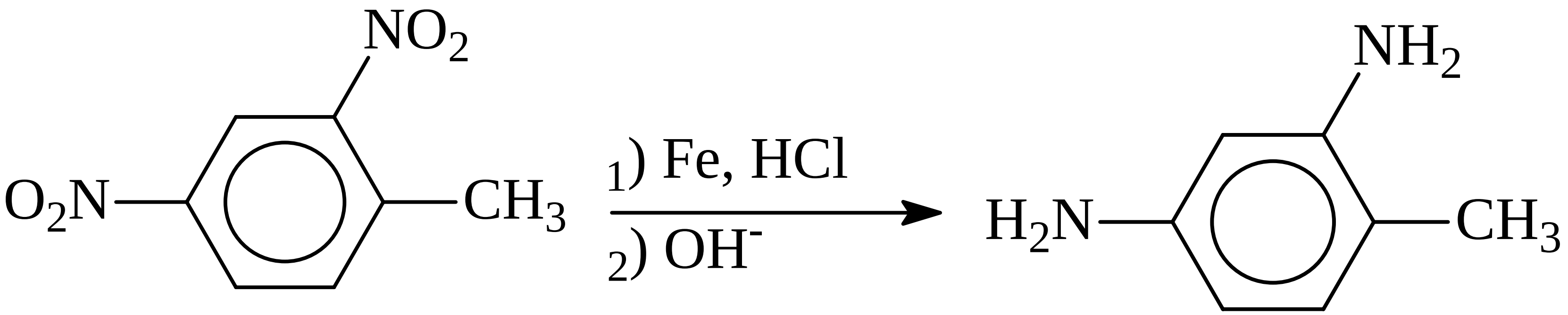

O
O
NH
1) KOH
2) BrCH(CO2C2H5)2
3) -OC2H5
O
O
NC(CO2C2H5)2
-
C6H5CH2Cl
O
O
NC(CO2C2H5)2
CH2C6H5
1) H+, H2O
2) OH-
C6H5CH2CHCO2H
NH2

3) Nucleophilic Aromatic Substitution



B. Synthesis By Reduction

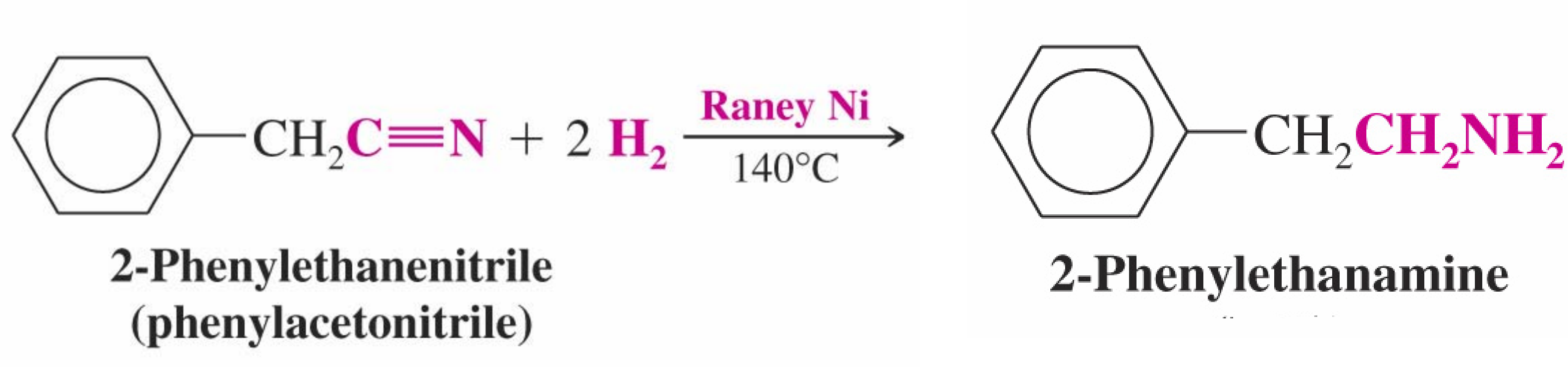
1) Reduction of aromatic nitro compounds to aryl amines



2,4-dinitrotoluene **2,4-toluenediamine**

2) Reduction of Nitriles

- Nitriles undergo hydrogenation or reduction with $LiAlH_4$ to yield primary amines



2-Phenylethanenitrile (phenylacetonitrile)

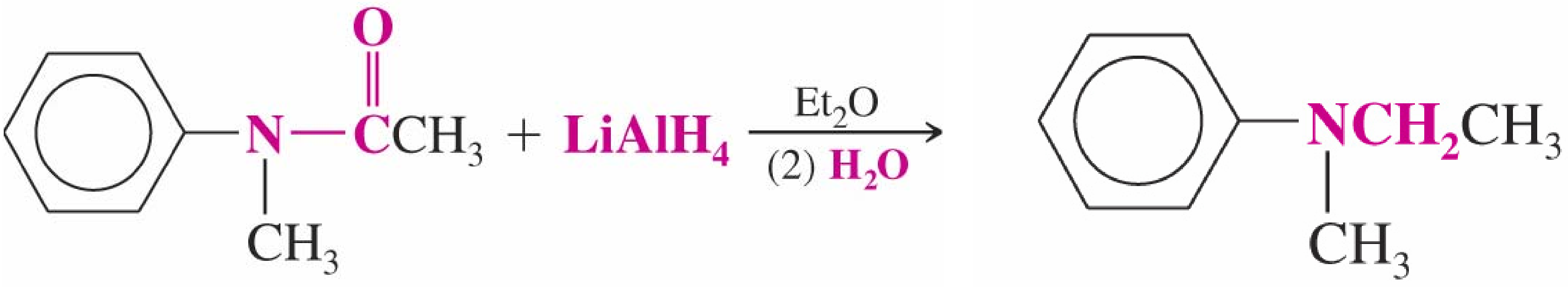
2-Phenylethanamine

$$CH_3CH_2CH_2Br \xrightarrow{CN^-} CH_3CH_2CH_2\mathbf{CN} \xrightarrow[2)\ H^+,\ H_2O]{1)\ LiAlH_4}$$

$$CH_3CH_2CH_2\mathbf{CH_2NH_2}$$

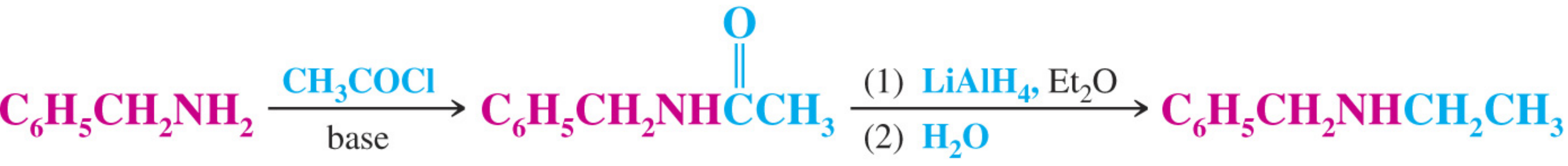
3) Reduction of amides

- Reduction of amides can yield primary, secondary or tertiary amines using $LiAlH_4$.



N-Methylacetanilide

N-Ethyl-*N*-methylaniline

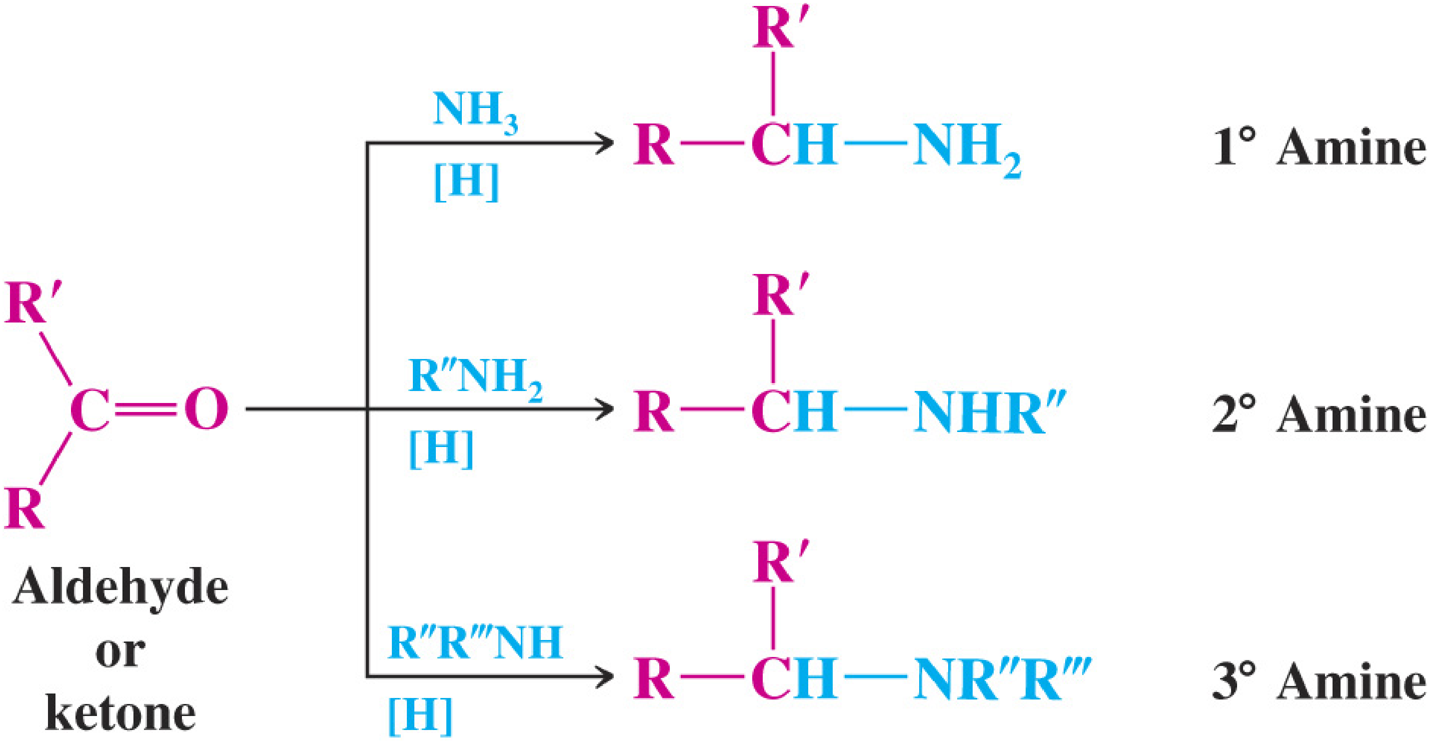


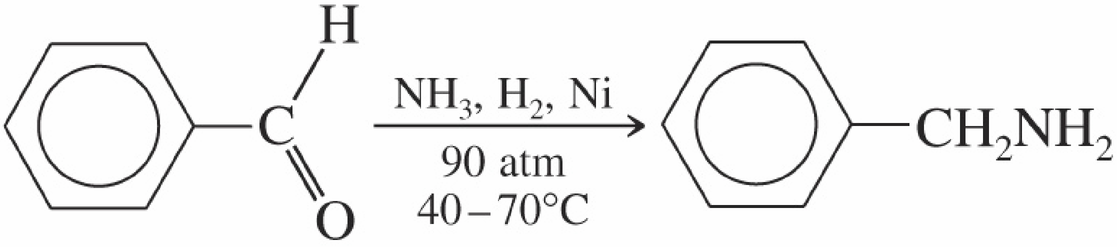
$$C_6H_5CH_2NH_2 \xrightarrow[\text{base}]{CH_3COCl} C_6H_5CH_2NH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4,\ Et_2O} C_6H_5CH_2NHCH_2CH_3$$

Benzylamine

Benzylethylamine

4) Reductive Amination

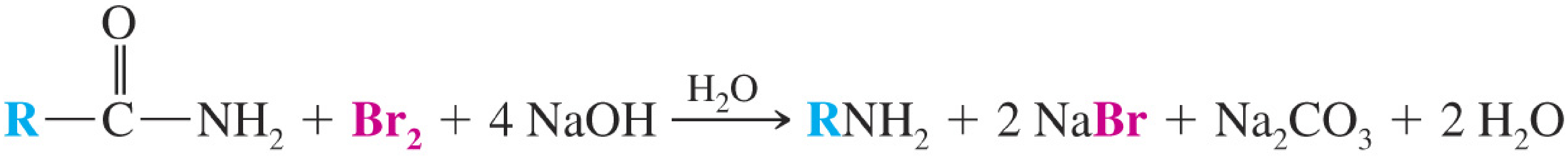




Benzaldehyde **Benzylamine**

C. Synthesis by Amide Rearrangement

- An unsubstituted amide can be converted to a primary amine(*Hofmann rearrangement*)



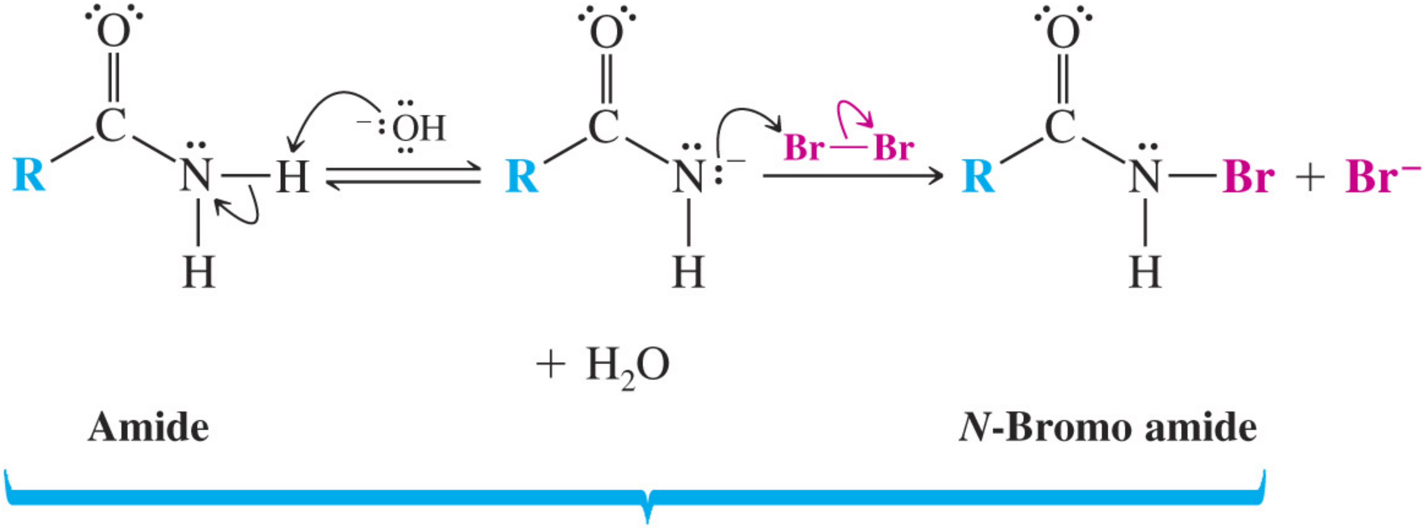
$$R-\overset{\overset{O}{\|}}{C}-NH_2 + Br_2 + 4\,NaOH \xrightarrow{H_2O} RNH_2 + 2\,NaBr + Na_2CO_3 + 2\,H_2O$$

1. The first two steps of the mechanism result in *N*-bromination of the amide.

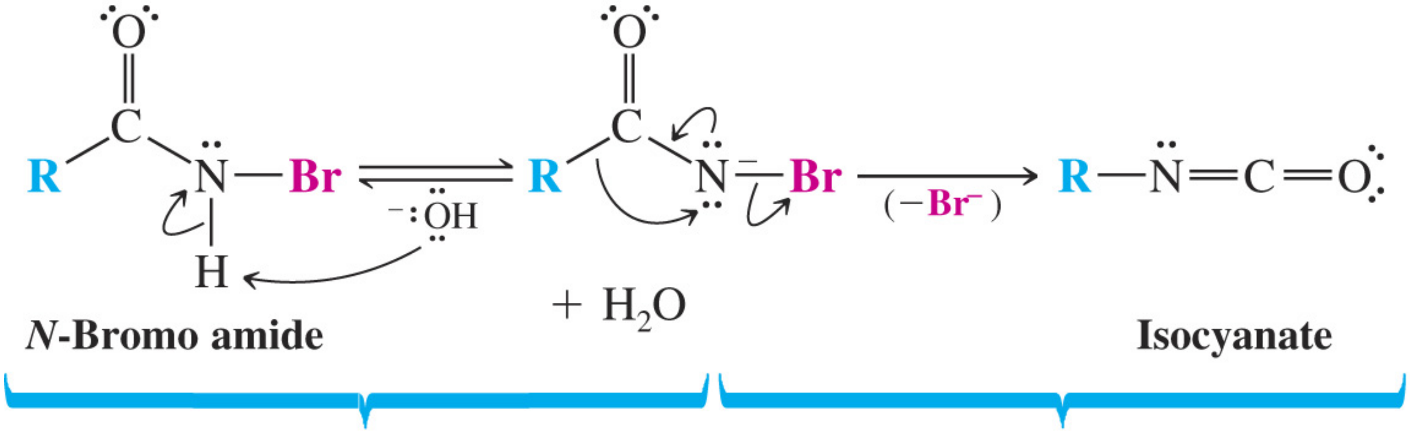
2. The *N*-bromoamide is deprotonated and rearranges to an isocyanate.

3. The isocyanate is hydrolyzed to a carbamate which decarboxylates to the amine.

Mechanism



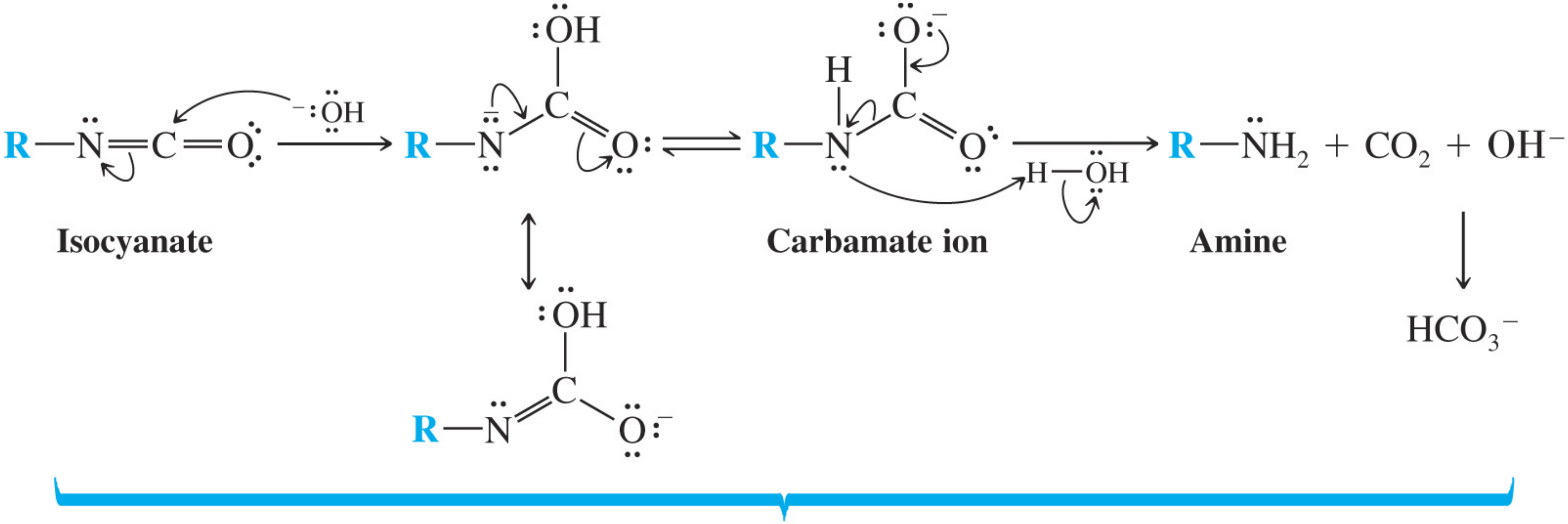
Base-promoted *N*-bromination of the amide occurs.



Base removes a proton from the nitrogen to give a bromo amide anion.

The R— group migrates to the nitrogen as a bromide ion departs. This produces an isocyanate.

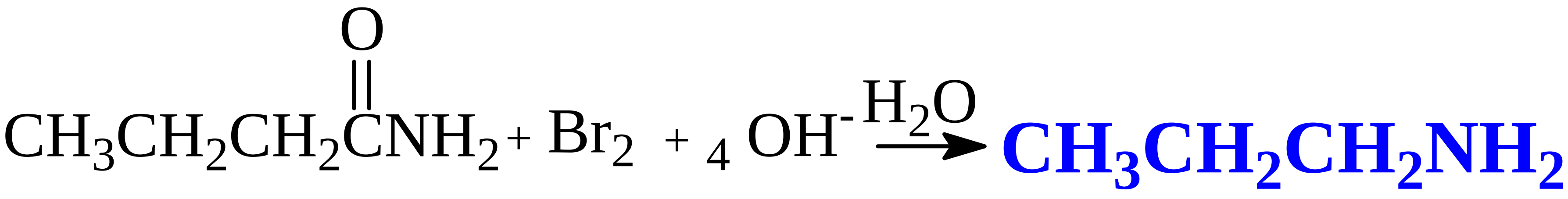
Mechanism continued



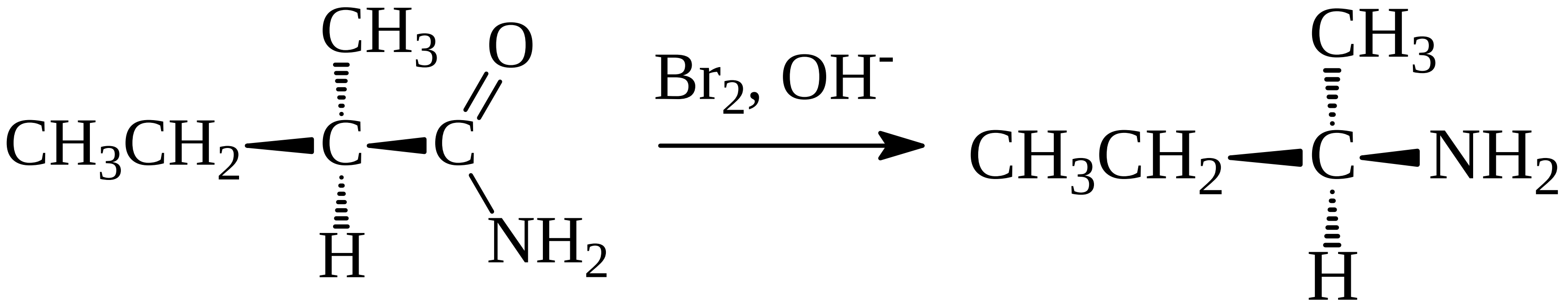
The isocyanate undergoes hydrolysis and decarboxylation to produce the amine.

Notice: the amine contain one less carbon than the starting amide.

Exampels



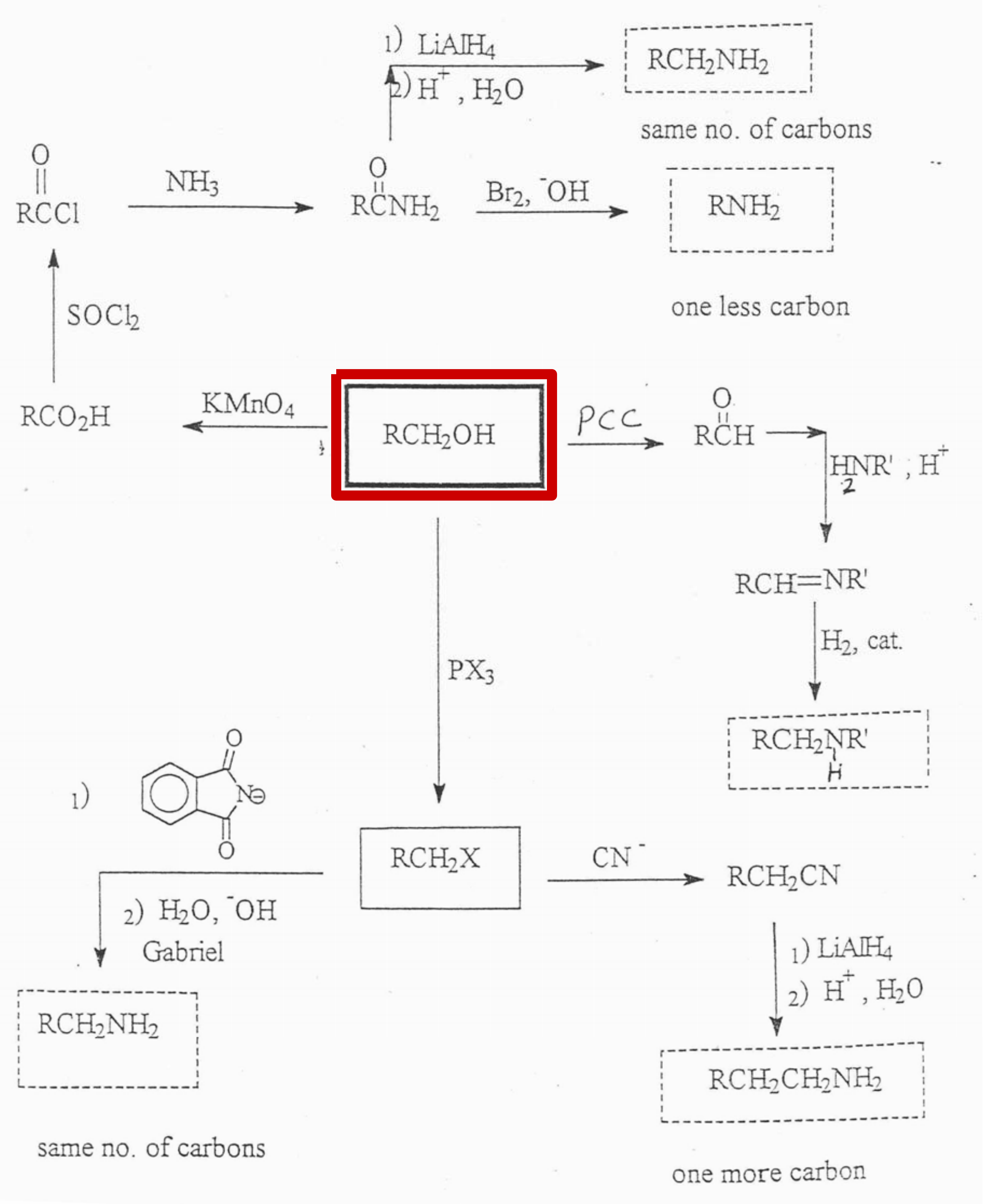
$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}NH_2 + Br_2 + 4\ OH^- \xrightarrow{H_2O} CH_3CH_2CH_2NH_2$$



(R)-2-methylbutanamide

(R)-2-butylamine

Migration proceeds with retention of configuration


1) LiAlH4
2) H+, H2O
RCH2NH2
same no. of carbons
RCCl
NH3
RCNH2
Br2, -OH
RNH2
one less carbon
SOCl2
RCO2H
KMnO4
RCH2OH
PCC
RCH
HNR'2, H+
RCH=NR'
H2, cat.
RCH2NHR'
PX3
1)
2) H2O, -OH
Gabriel
RCH2X
CN-
RCH2CN
1) LiAlH4
2) H+, H2O
RCH2NH2
same no. of carbons
RCH2CH2NH2
one more carbon

Basicity of Amines

$$R_3N\!: + H_2O \rightleftharpoons R_3NH^+ + OH^-$$

If the amine is stabilized relative to the cation → the amine is less basic

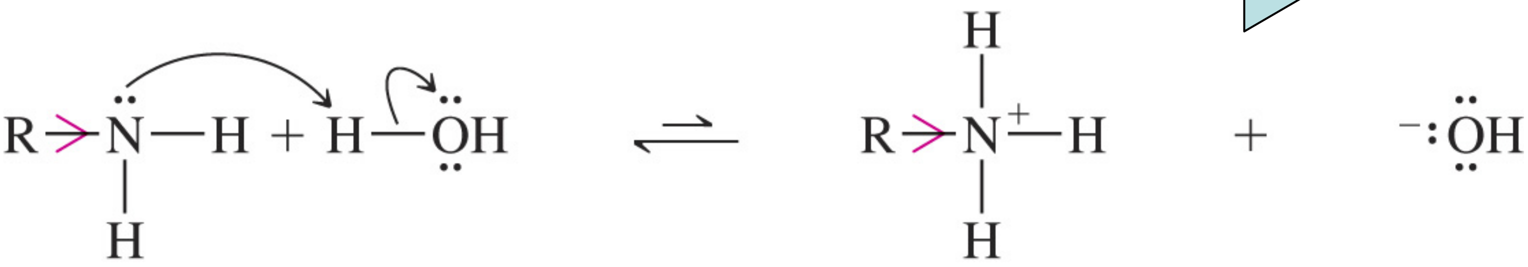
If the cation is stabilized relative to the free amine → the amine is a stronger base

Factors affect the relative base strength

1. An electron releasing group on the nitrogen increases basicity by dispersing the positive charge in the cation.

	NH_3	CH_3NH_2	CH_3NHCH_3
pK_b	**4.75**	**3.34**	**3.27**

Increasing Basicity →



By releasing electrons, R→ stabilizes the alkylaminium ion through dispersal of charge.

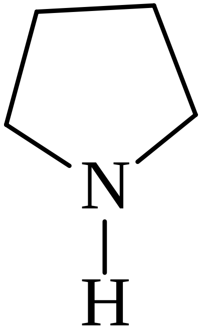
2. The cation is stabilized by increasing solvation (the solvent help disperse the positive charge)

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

pK_b 3.27 3.34 4.19 4.75

The trimethylaminium ion is solvated less well (and therefore stabilized less) than the dimethylaminium ion due to steric hinderance.

$CH_3CH_2NHCH_2CH_3$ is weaker base than

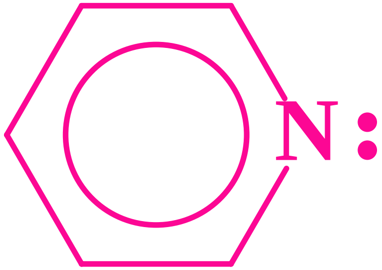


pKb 3.01

pKb= 2.73

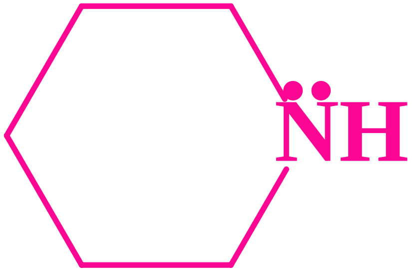
3. Hybridization of the nitrogen atom

An sp^2 orbital contain more s character than an sp^3 orbital ➔ An sp^2-hybridized nitrogen is less basic than sp^3-hybridized because its unshared electrons are more tightly held



pyridine (sp^2)

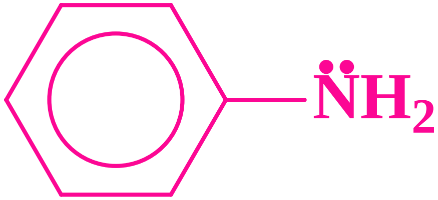
pK_b= 8.75



piperidine (sp^3)

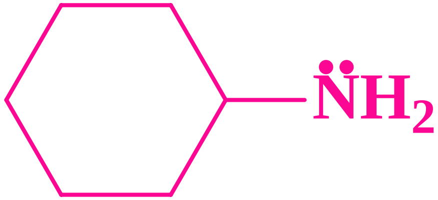
pK_b = 2.88

4. Resonance



aniline

$pK_b = 9.37$

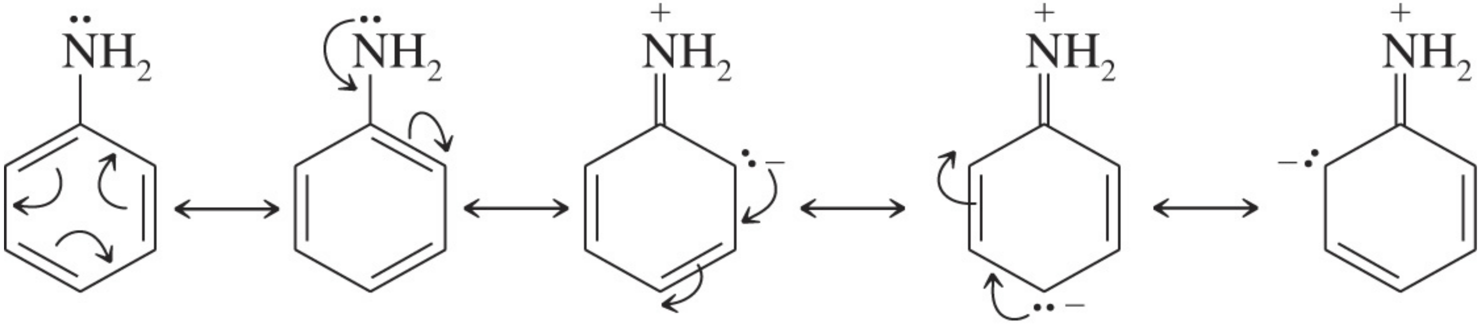


cyclohexylamine

$pK_b = 3.3$

No resonance stabilization

The unshared electron pair on nitrogen of an arylamine is *delocalized* ➔ the lone pair is less available for protonation, *i.e.*, it is less basic



1 2 3 4 5

Amine Salts

The reaction of amine with acids ➔ amine salts.

$$(CH_3)_3N: \quad + \quad HCl \rightarrow (CH_3)_3NH^+Cl^-$$

triethylamine

triethylammonium chloride

(triethylamine hydrochloride)

$$CH_3CH_2NH_2 \quad + \quad CH_3CO_2H \rightarrow CH_3CH_2NH_3^+ \, {}^-O_2CCH_3$$

ethylamie

ethylammonium acetate

(ethylamine acetate)

Applications of Quaternary Ammonium Salts

1. Quaternary Ammonium Salts with along hydrocarbon chain are used as detergents.
2. Quaternary Ammonium Salts can act as phase-transfer agents.

$$(C_4H_9)_4N^+Cl^- \;+\; CN^- \rightarrow (C_4H_9)_4N^+CN^- + Cl^-$$

Soluble in organic phase

S_N2 reaction in the organic phase

$$CH_3(CH_2)_7Cl + (C_4H_9)_4N^+CN^- \rightarrow CH_3(CH_2)_7CN$$

Reactions of Amines

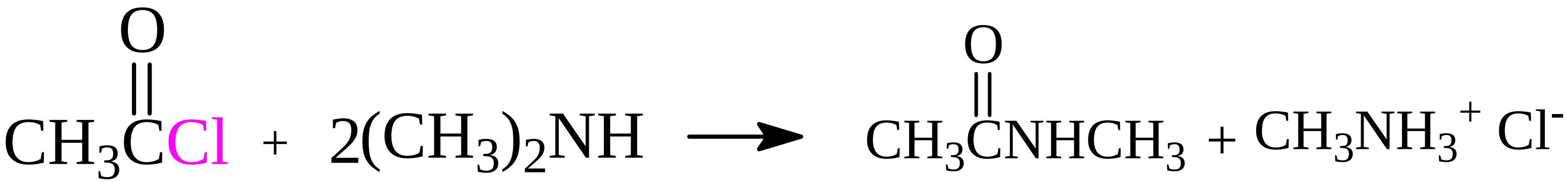
1) Substitution Reactions with Amines

1. S_N2 (alkyl halides + amines)

$RNH_2 + R'Cl \rightarrow RR'NH_2^+Cl^- + RR'_2NH^+Cl^-$

2. Acylation of amines

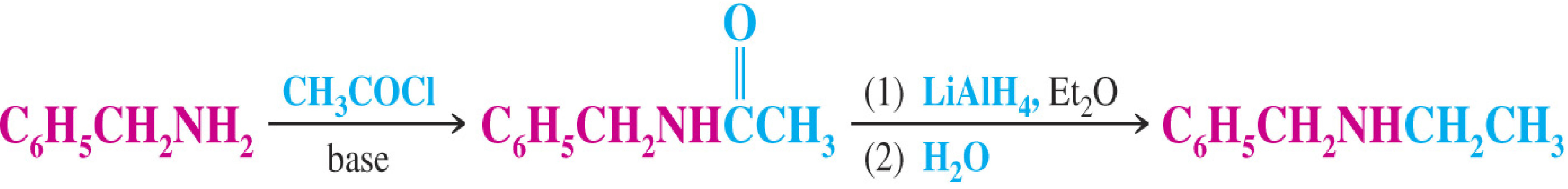
(amine + acid chloride) ➔ synthesis of amides



$$CH_3\overset{O}{\overset{\|}{C}}Cl + 2(CH_3)_2NH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3NH_3^+ Cl^-$$

N-methylacetamide

Amines can be used to synthesize other amines by conversion to amides followed by reduction



$$C_6H_5CH_2NH_2 \xrightarrow[\text{base}]{CH_3COCl} C_6H_5CH_2NH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{(2) } H_2O]{\text{(1) } LiAlH_4,\ Et_2O} C_6H_5CH_2NHCH_2CH_3$$

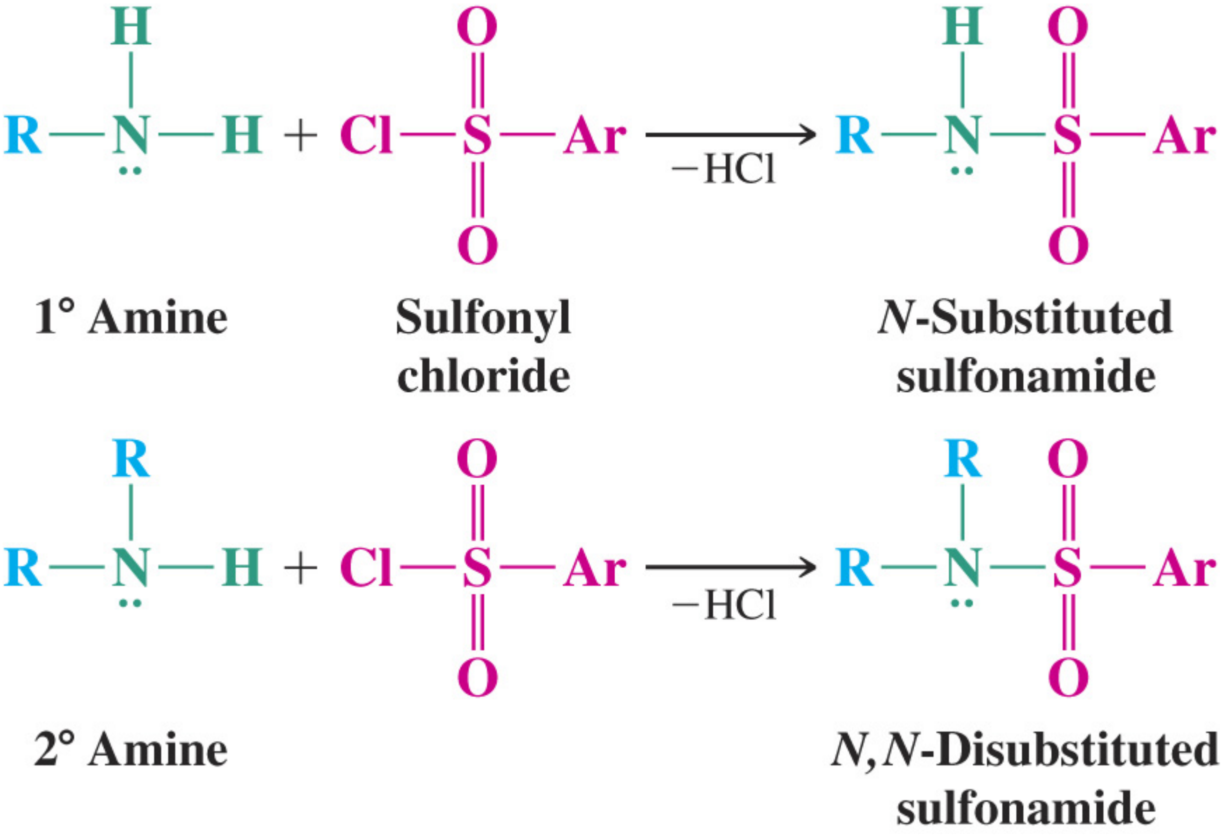
Benzylamine

Benzylethylamine

a new amine

Reactions of Amines with Sulfonyl Chlorides

Primary and secondary amines react with sulfonyl chlorides to produce *sulfonamides*



$$R{-}NH{-}H + Cl{-}SO_2{-}Ar \xrightarrow[-HCl]{} R{-}NH{-}SO_2{-}Ar$$

1° Amine

Sulfonyl chloride

N-Substituted sulfonamide

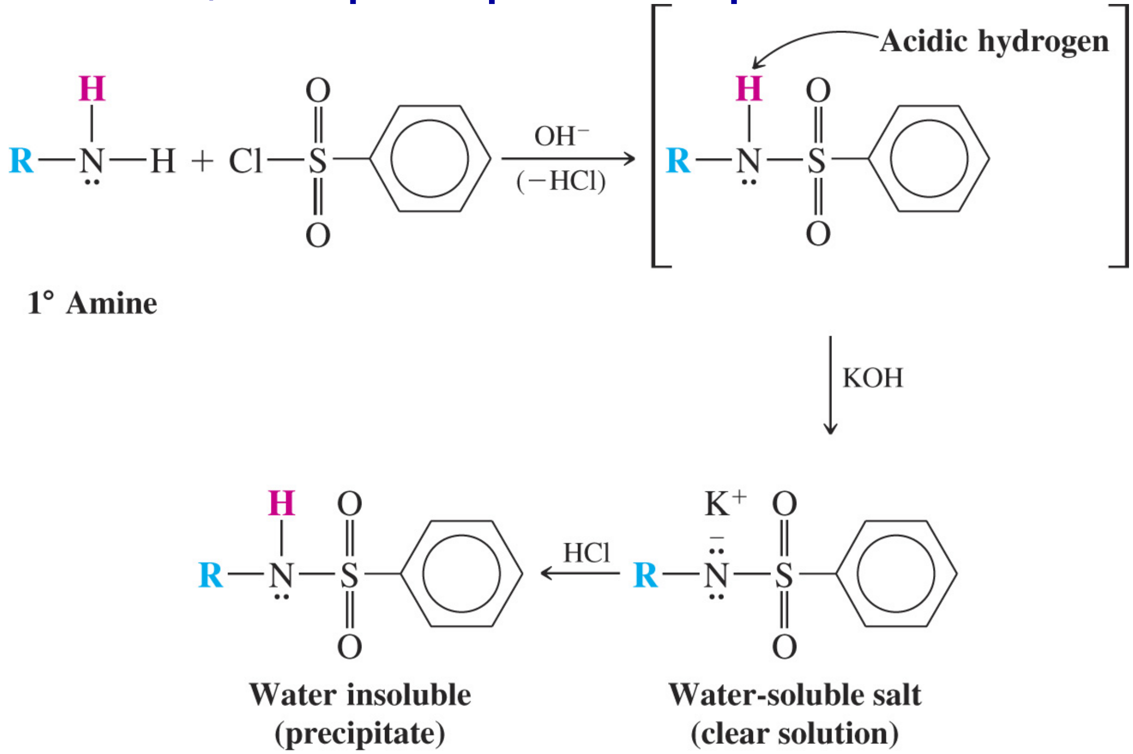
$$R{-}NR{-}H + Cl{-}SO_2{-}Ar \xrightarrow[-HCl]{} R{-}NR{-}SO_2{-}Ar$$

2° Amine

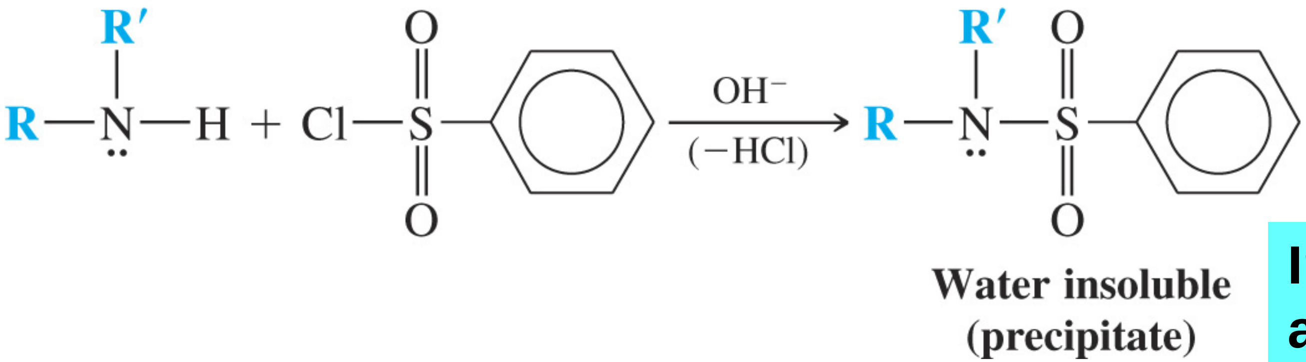
N,*N*-Disubstituted sulfonamide

The Hinsberg Test

- This test can distinguish between 1°, 2° and 3° amines.
- A benzenesulfonamide from a ***primary amine*** is soluble in basic solution, but precipitates upon acidification



- A secondary amine forms a precipitate directly because an *N,N*-disubstituted sulfonamide remains insoluble in basic solution.
- There is no acidic hydrogen in an *N,N*-disubstituted sulfonamide



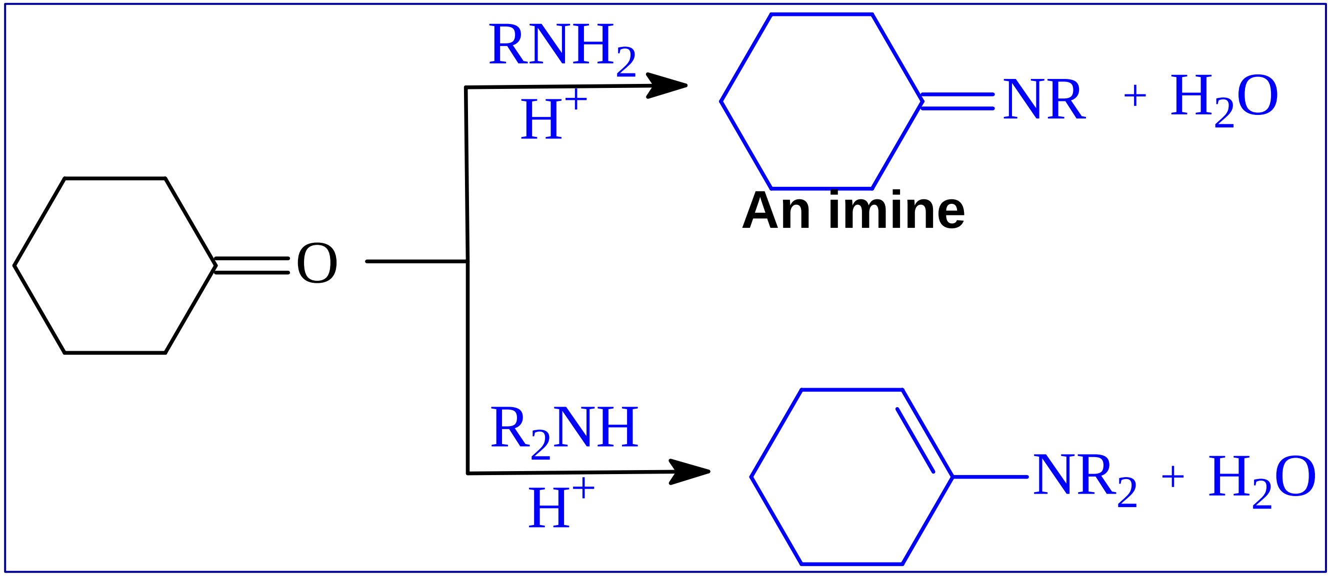
Insoluble in acid or base

A tertiary amine will not react to form a sulfonamide, but will dissolve upon acidification.

Acidification converts the amine to a water soluble amine salt

Imines and Enamines

- Amines react with aldehydes and ketones to form imines or enamines.



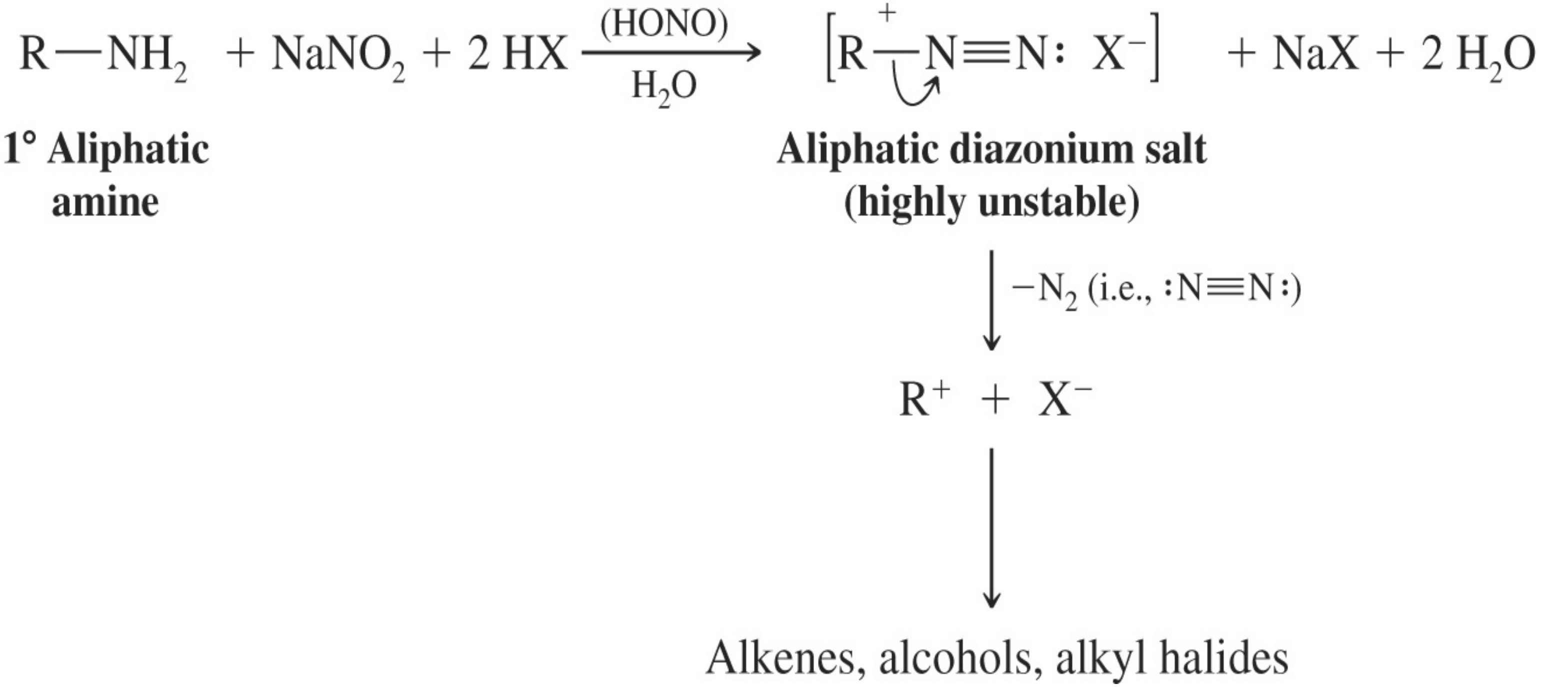
An imine

An enamine

Reactions of Amines with Nitrous Acid

- Primary amines undergo *diazotization* with nitrous acid.

General Reaction



$$R{-}NH_2 + NaNO_2 + 2\,HX \xrightarrow[H_2O]{(HONO)} \left[R{-}\overset{+}{N}{\equiv}N\!:\ X^-\right] + NaX + 2\,H_2O$$

$$\downarrow -N_2 \text{ (i.e., } :N{\equiv}N:)$$

$$R^+ + X^-$$

$$\downarrow$$

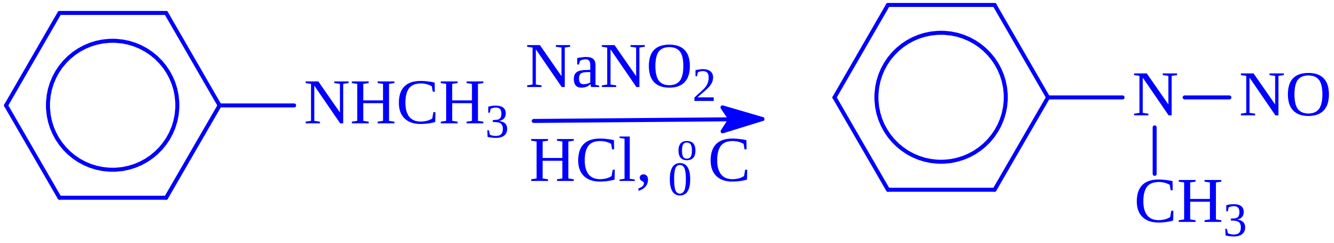
Alkenes, alcohols, alkyl halides

Example

$$(CH_3)_2CHNH_2 \xrightarrow[HCl,\ 0^{o}C]{NaNO_2} (CH_3)_2CHN_2^+\ Cl^- \xrightarrow[-Cl]{-N_2}$$

$$\left[(CH_3)_2CH^+\right] \xrightarrow{H_2O} (CH_3)_2CHOH + CH_3CH{=}CH_2$$

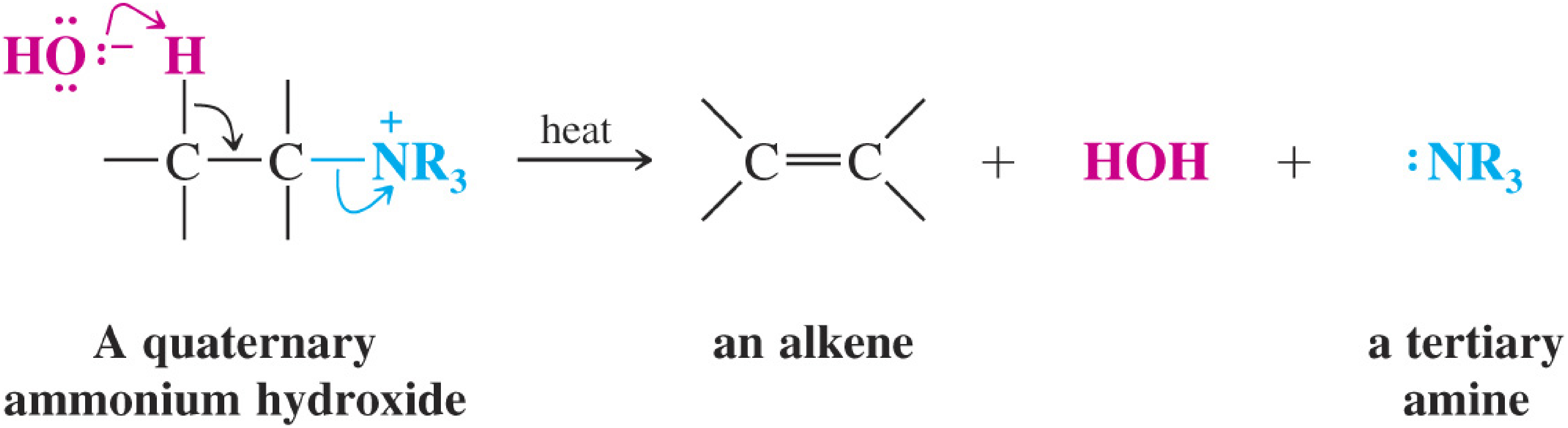
Secondary amines yield N-nitrosoamines when treated with nitrous acid



An N-nitrosoamine

The Hofmann Elimination

- An E2-type reaction occurs when a quaternary ammonium hydroxide is heated.
- An amine is a relatively good leaving group



Formation of Quaternary Ammonium Hydroxides

A quaternary ammonium hydroxide can be made from a quaternary ammonium halide using silver oxide

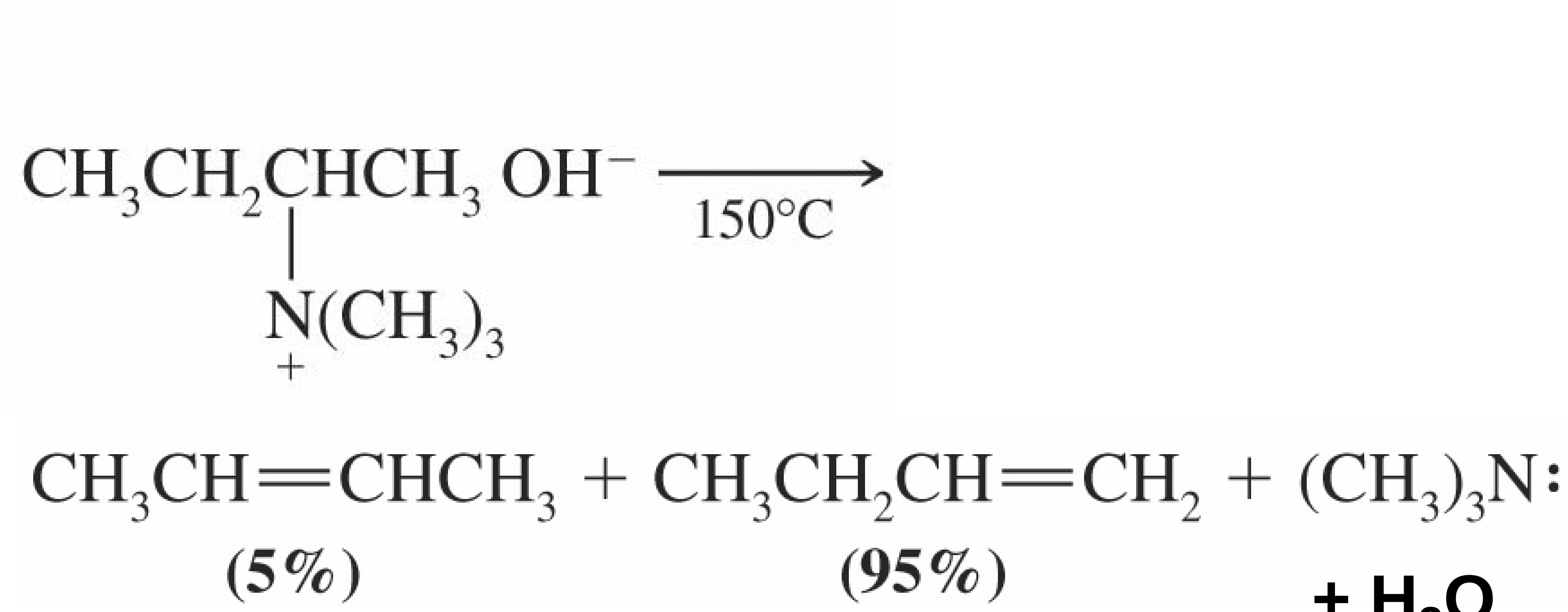
$$2\ \mathrm{RCH_2CH_2\overset{+}{N}(CH_3)_3\ X^-} + \mathrm{Ag_2O} + \mathrm{H_2O} \longrightarrow 2\ \mathrm{RCH_2CH_2\overset{+}{N}(CH_3)_3\ OH^-} + 2\ \mathrm{AgX}\downarrow$$

A quaternary ammonium halide

A quaternary ammonium hydroxide

Example

- Hofmann elimination proceeds to give the least substituted double bond



$$\underset{\underset{+}{N}(CH_3)_3}{CH_3CH_2\overset{}{C}HCH_3}\ OH^- \xrightarrow[150^\circ C]{}$$

$$\underset{(5\%)}{CH_3CH{=}CHCH_3} + \underset{(95\%)}{CH_3CH_2CH{=}CH_2} + (CH_3)_3N\!:$$

+ H_2O