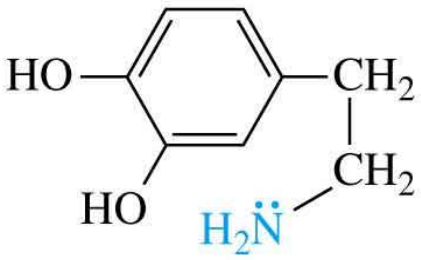
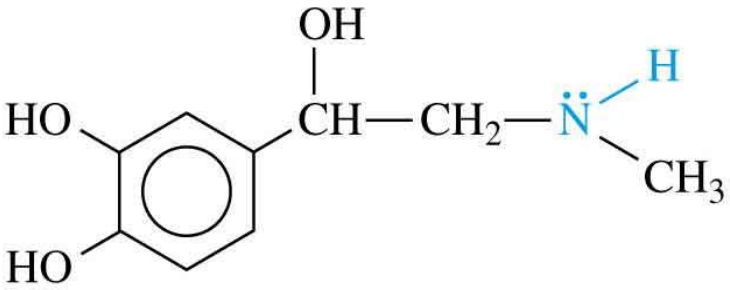
AMINES

Introduction

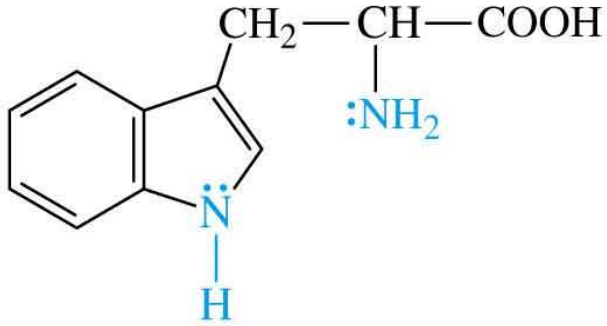
- Organic derivatives of ammonia
- Many are biologically active.



dopamine
a neurotransmitter

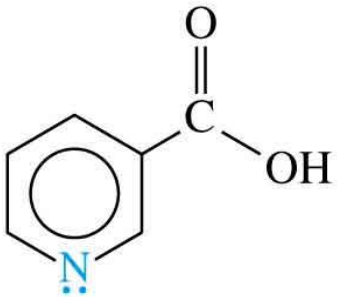


epinephrine
an adrenal hormone

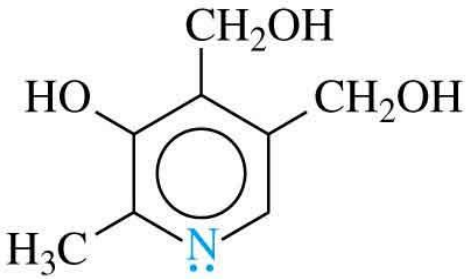


L-tryptophan
an amino acid

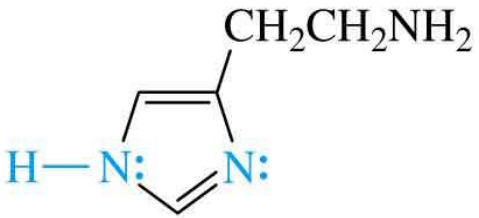
piperazine
kills intestinal worms



nicotinic acid
niacin, a vitamin



pyridoxine
vitamin B_6



histamine
dilates blood vessels

Classes of Amines

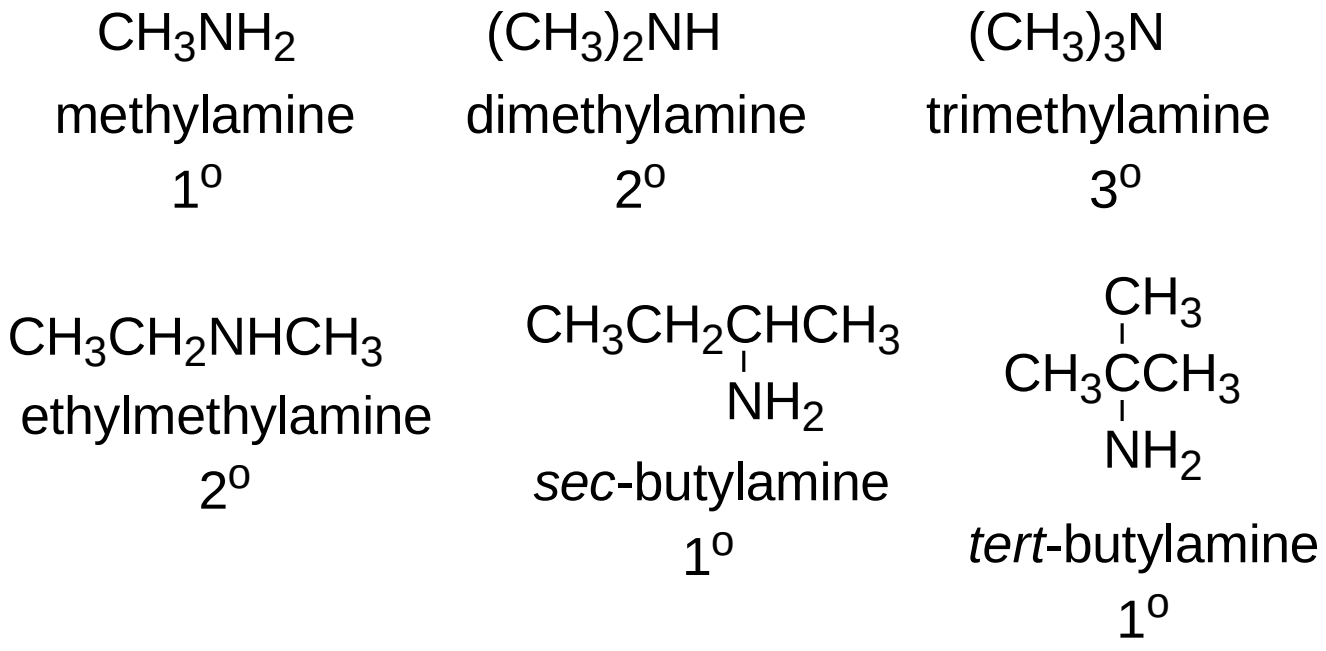
- Primary (1°): one C-N bond, 2 N-H bonds.
- Secondary (2°): two C-N bonds, 1 N-H bond.
- Tertiary (3°): three C-N bonds, no N-H bond.
- Quaternary (4°): four C-N bonds, nitrogen has a + formal charge.

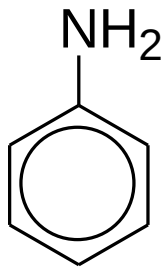
(organic ammonia)		:NH_3	
:NH_2R	or RNH_2	1^o amine	(R may be Ar)
:NHR_2	or R_2NH	2^o amine	
:NR_3	or R_3N	3^o amine	
NR_4^+		4^o ammonium salt	

NB amines are classified by the class of the nitrogen, primary amines have one carbon bonded to N, secondary amines have two carbons attached directly to the N, etc.

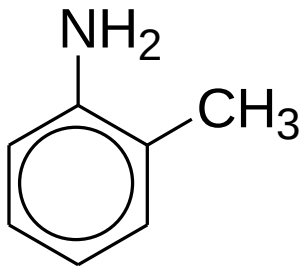
Nomenclature/ trivials

Common aliphatic amines are named as **"alkylamines"**

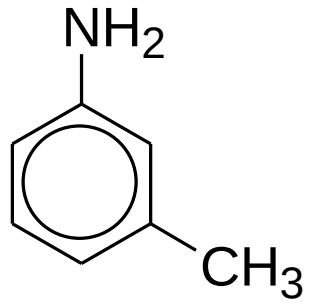




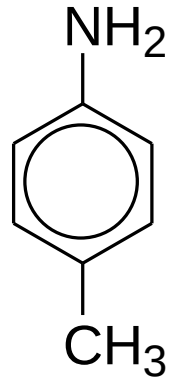
aniline



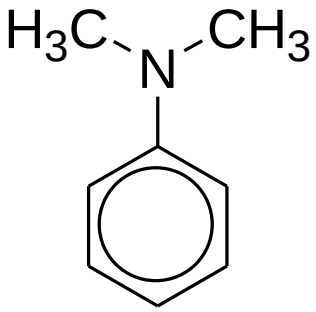
o-toluidine



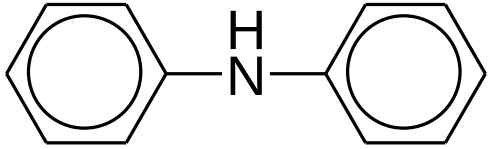
m-toluidine



p-toluidine



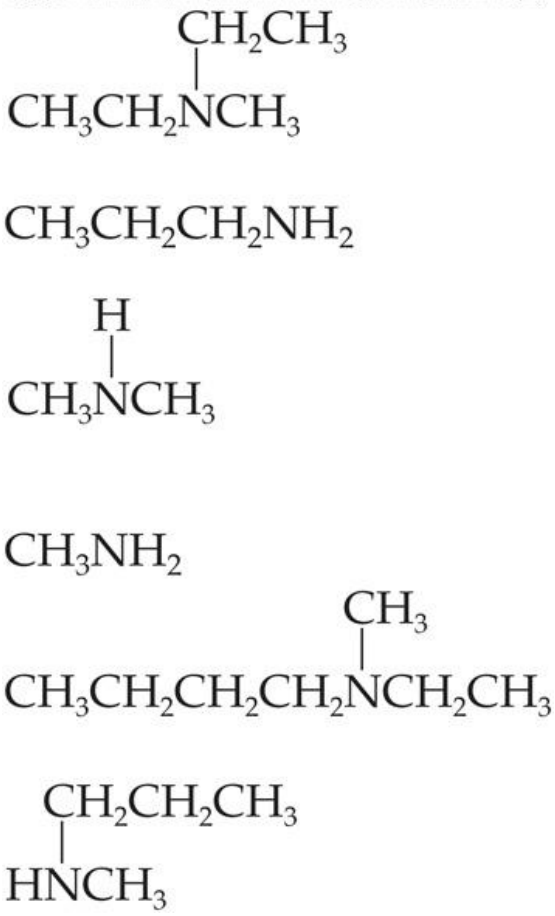
N,N-dimethylaniline

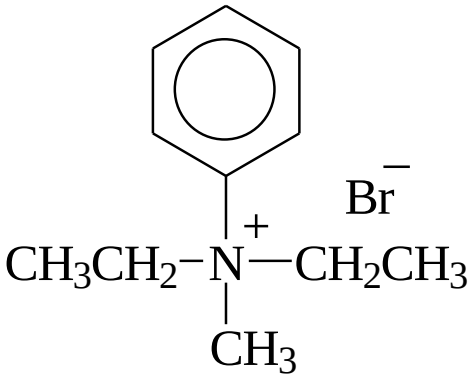


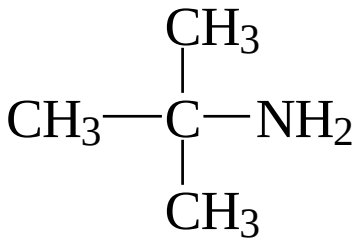
diphenylamine

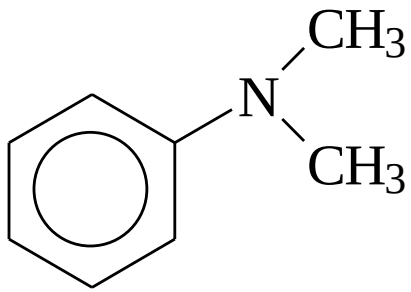
Classify These Amines

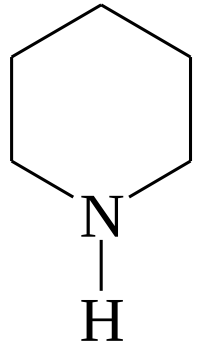
Determine whether the following amines are primary, secondary, or tertiary.







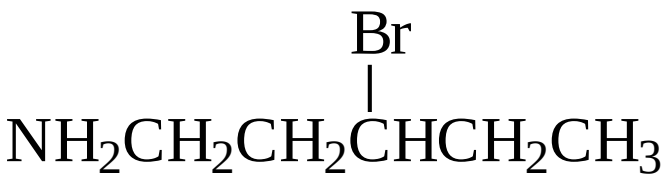




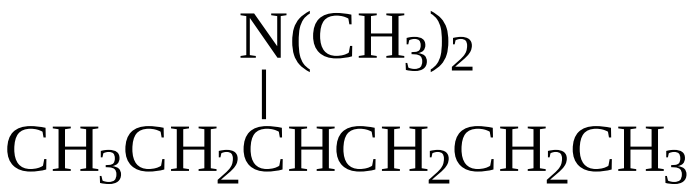
Amine Nomenclature

IUPAC Names

- Name is based on longest carbon chain.
- -*e* of alkane is replaced with -*amine*.
- Substituents on nitrogen have *N*- prefix.



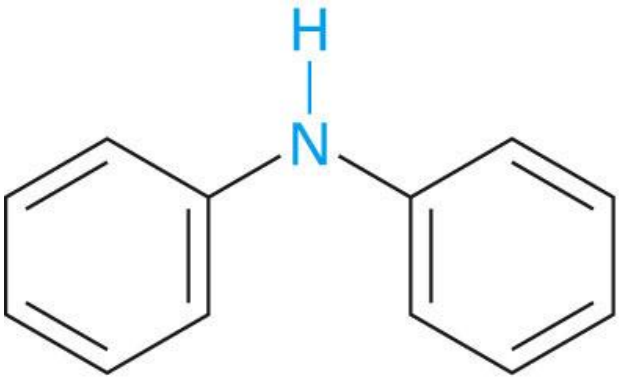
3-bromo-1-pentanamine



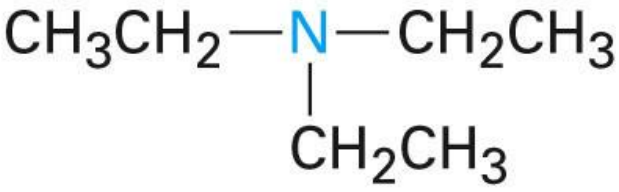
N,*N*-dimethyl-3-hexanamine

IUPAC Names – Multiple Alkyl Groups

- Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group



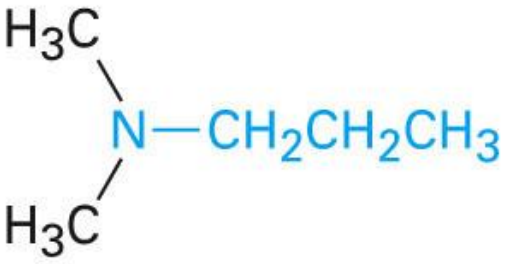
Diphenylamine



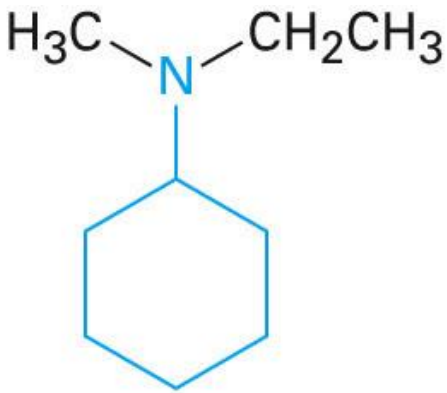
Triethylamine

IUPAC Names – Multiple, Different Alkyl Groups

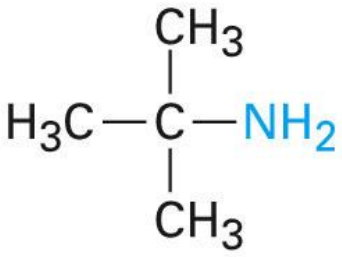
- Named as *N*-substituted primary amines
- Largest alkyl group is the parent name, and other alkyl groups are considered *N*-substituents



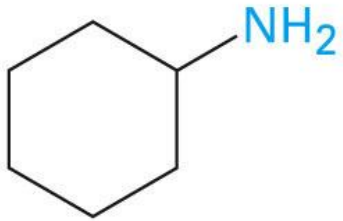
***N,N*-Dimethylpropylamine**



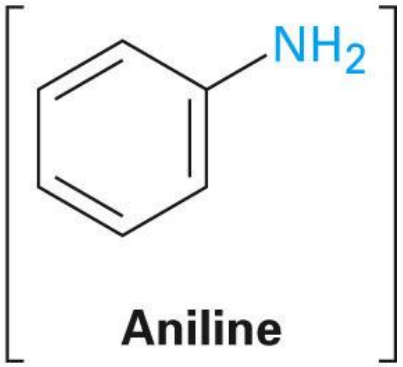
***N*-Ethyl-*N*-methylcyclohexylamine**



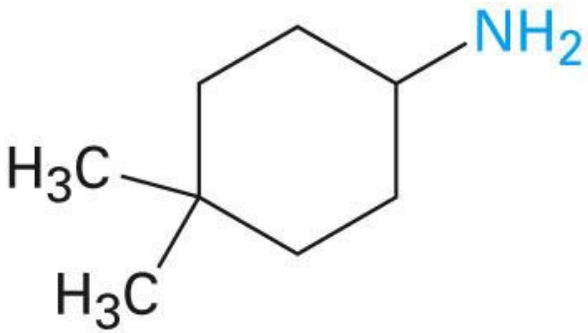
***tert*-Butylamine**



Cyclohexylamine



Aniline



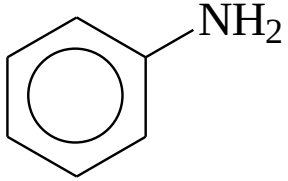
4,4-Dimethylcyclohexanamine

$H_2NCH_2CH_2CH_2CH_2NH_2$

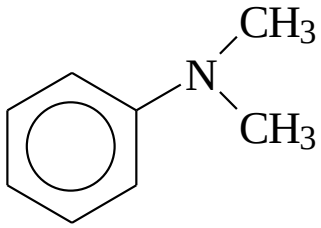
1,4-Butanediamine

Aromatic Amines

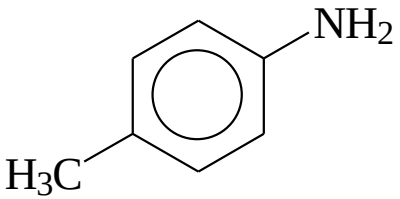
Amino group is bonded to a benzene ring. Parent compound is called aniline.



aniline



N,*N*-dimethylaniline



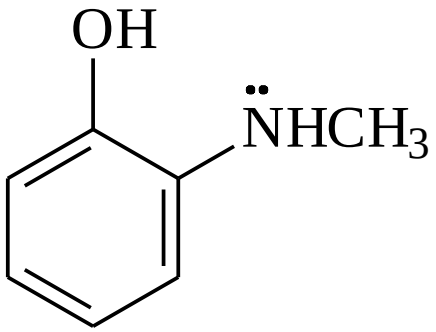
4-methylaniline
or *p*-toluidine

Amine as Substituent

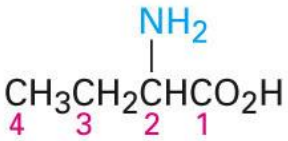
- On a molecule with a higher priority functional group the amine is named as a substituent.

$NH_2CH_2CH_2CH_2COOH$

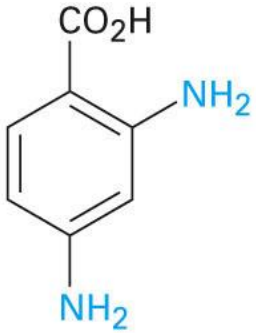
γ-aminobutyric acid or
4-aminobutanoic acid



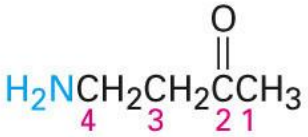
2-methylaminophenol



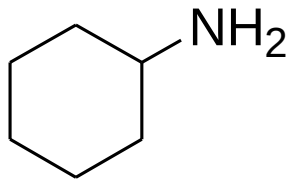
2-Aminobutanoic acid



2,4-Diaminobenzoic acid

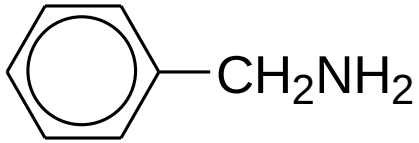


4-Amino-2-butanone



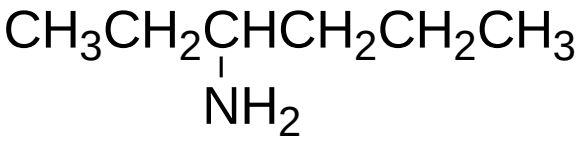
cyclohexylamine

1^{o}

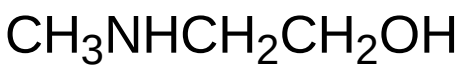


benzylamine

Complex amines are named by prefixing "amino"-" (or *N*-methylamino, *N,N*-dimethyl amino-, etc.) to the parent chain:



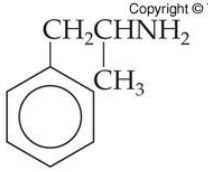
3-aminohexane



2-(*N*-methylamino)ethanol

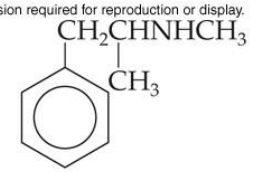
Medically Important Amines

- Amphetamines stimulate the central nervous system



1-Phenyl-2-propanamine
(Amphetamine)

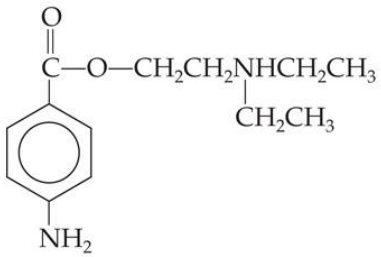
Benzedrine



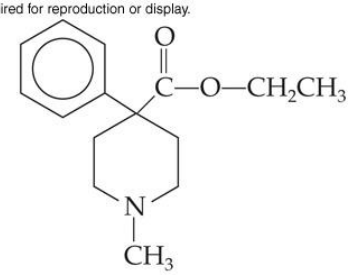
N-Methyl-1-phenyl-2-propanamine
(Methamphetamine)

Methedrine

- Analgesics (pain relievers) and anesthetics (pain blockers)



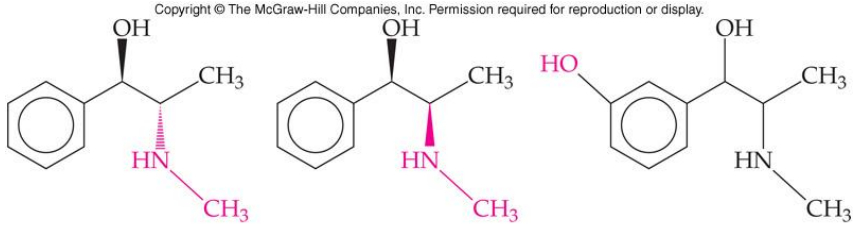
Novocaine



Demerol

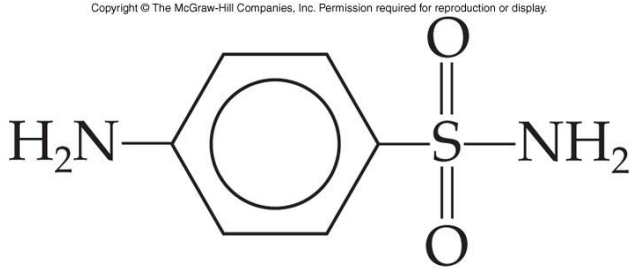
Medically Important Amines

- Decongestants shrink the membranes lining the nasal passages



Ephedrine | Pseudoephedrine | Phenylephrine (neosynephrine)

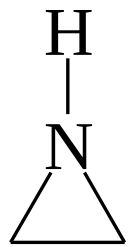
- Sulfa drugs (first chemicals used to fight infections) are also made from amines



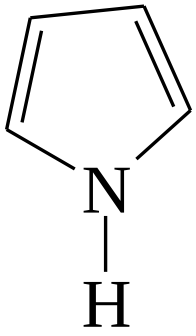
Sulfanilamide—a sulfa drug

Heterocyclic Amines

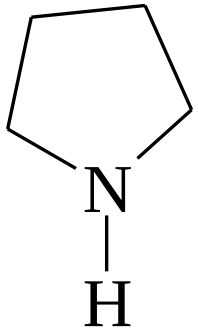
The nitrogen is assigned the number 1.



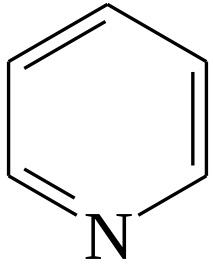
aziridine



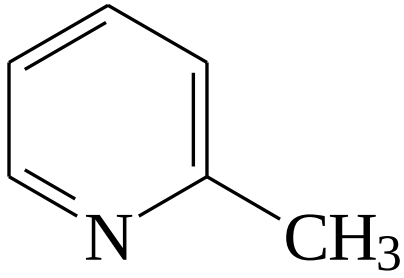
Pyrrole



Pyrrolidine



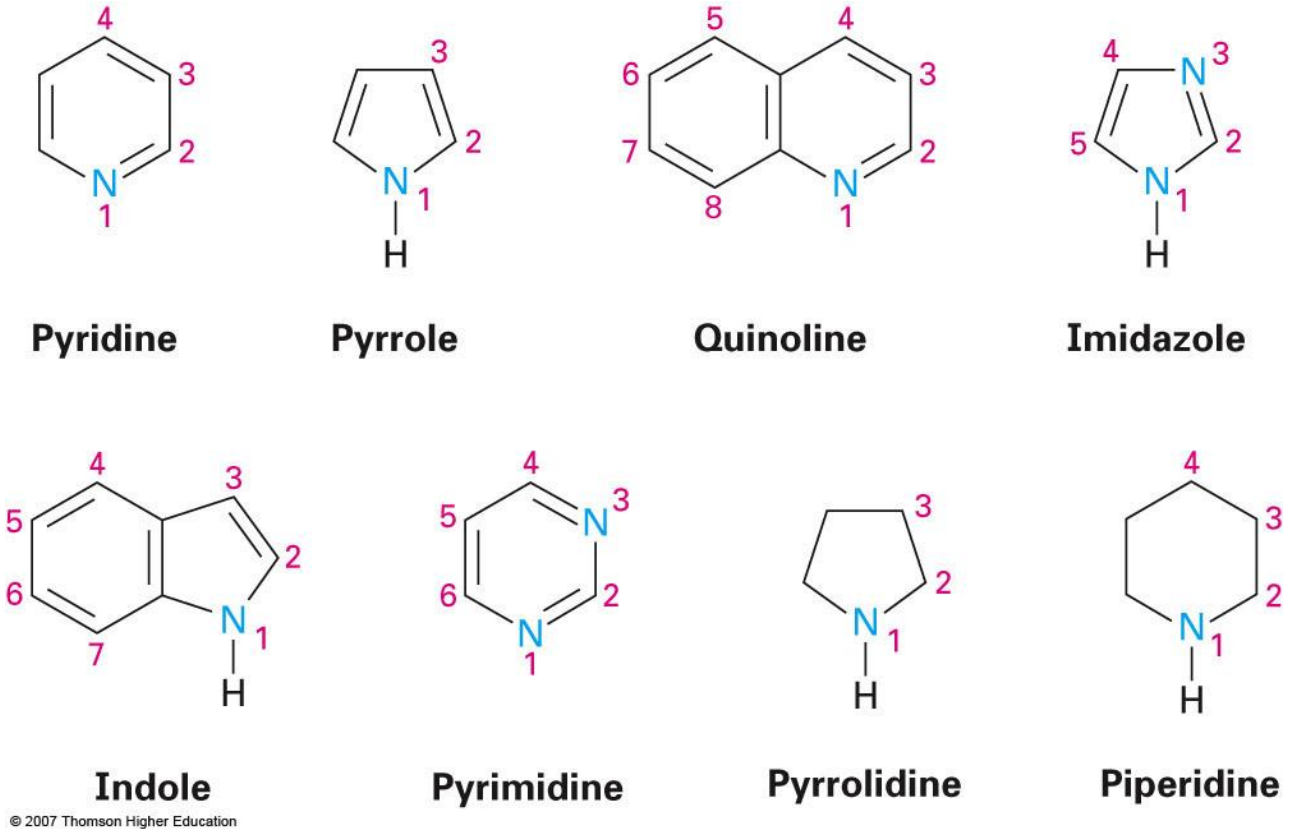
Pyridine



2-methylpyridine

Common Names of Heterocyclic Amines

- If the nitrogen atom occurs as part of a ring, the compound is designated as being heterocyclic
- Each ring system has its own parent name



Salts of amines: change amine → ammonium + anion

change aniline → anilinium + anion

$CH_3CH_2CH_2NH_3^+Cl^-$

n-propylammonium chloride

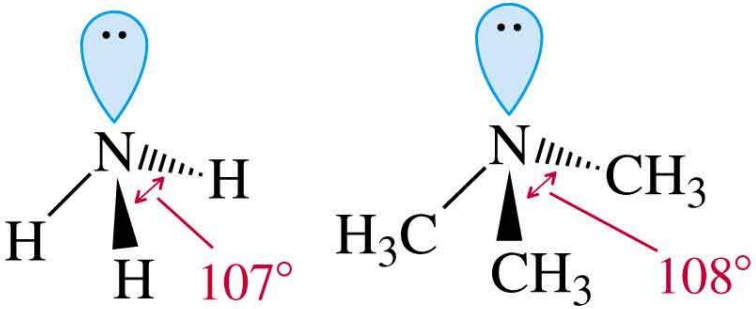
$(C_6H_5NH_3)_2SO_4$

anilinium sulfate

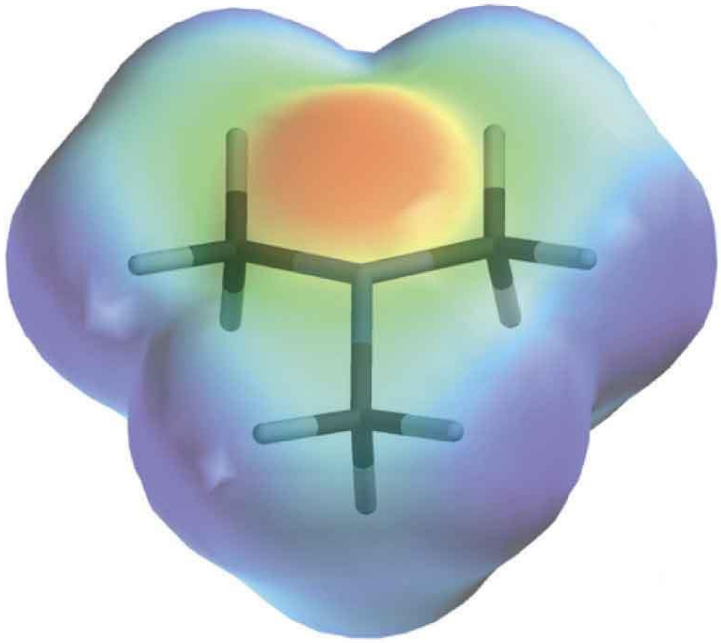
Structure and Bonding of Amines

Structure of Amines

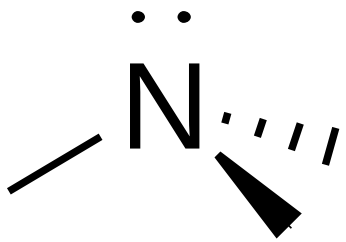
Nitrogen is sp^3 hybridized with a lone pair of electrons in an sp^3 orbital.



ammonia trimethylamine



electrostatic potential map of trimethylamine



Amines, physical properties:

Nitrogen is sp^3 hybridized, amines are polar

and can hydrogen bond.

mp/bp are relatively high for covalent substances

amines are basic and will turn litmus blue

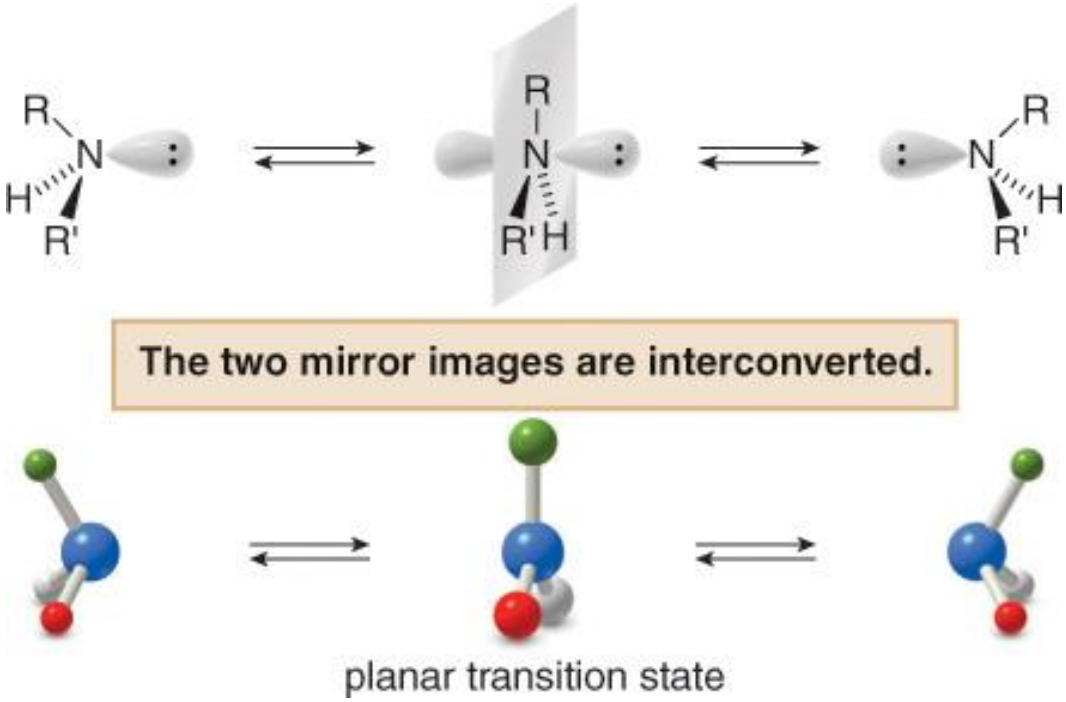
insoluble in water (except for four-carbons or less)

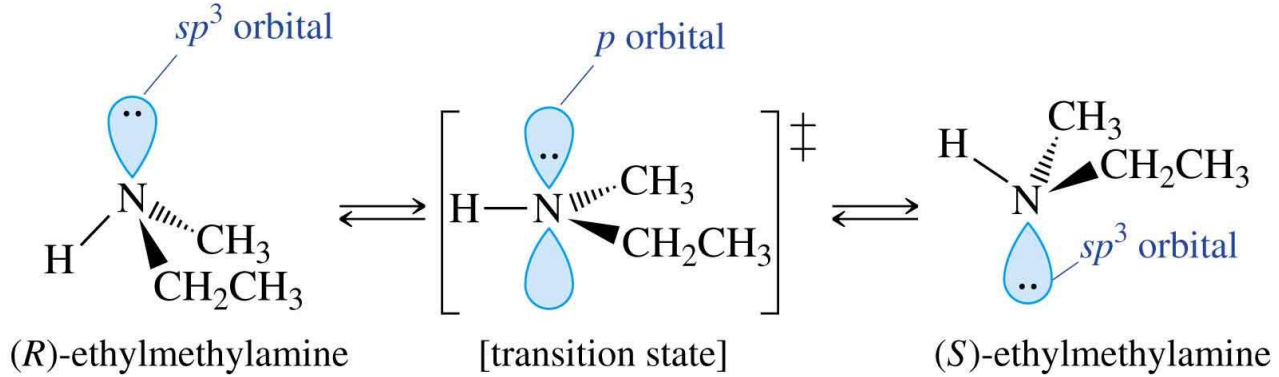
soluble in 5% HCl

"fishy" smell ☹

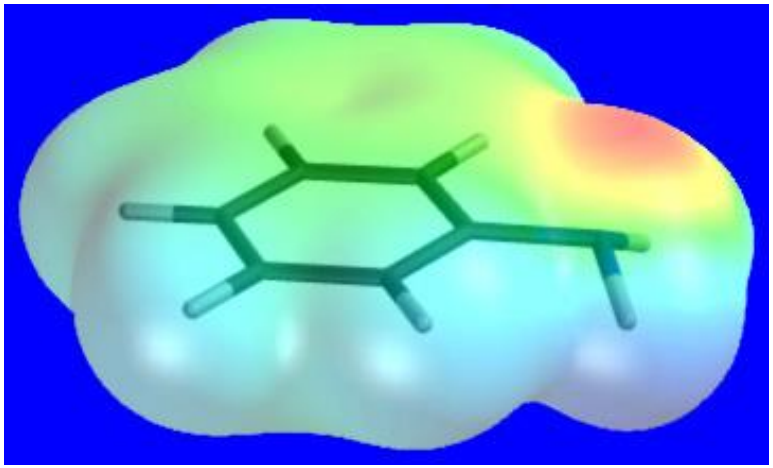
Chirality of Amines

Nitrogen may have 3 different groups and a lone pair, but enantiomers cannot be isolated due to inversion around N.



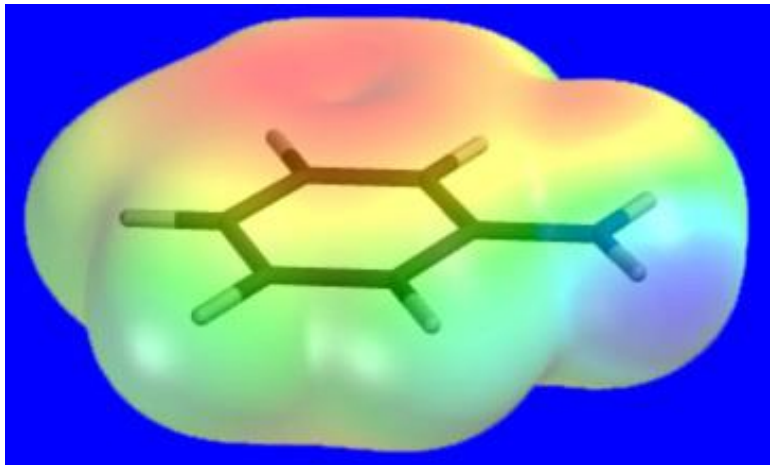


Aniline - Distribution of Electron Density



Enforce a non-planar geometry (sp^3-like) at the nitrogen center

- highest negative potential is on nitrogen.



Enforce a planar geometry (sp^2-like) at the nitrogen center

- negative potential is shared by both nitrogen and ring.

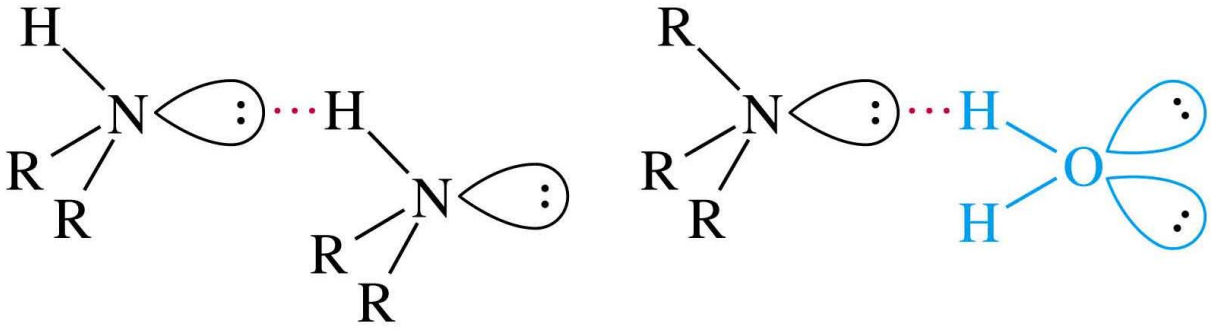
Physical Properties of Amines

Physical Properties

- Amines are polar compounds
  - both 1° and 2° amines form intermolecular hydrogen bonds
  - N-H----N hydrogen bonds are weaker than O-H----O hydrogen bonds because the difference in electronegativity between N and H (3.0 - 2.1 =0.9) is not as great as that between O and H (3.5 - 2.1 = 1.4)

Boiling Points

- N-H less polar than O-H.
- Weaker hydrogen bonding.
- Tertiary amines cannot hydrogen bond.



1° or 2° amine: hydrogen bond donor and acceptor

3° amine: hydrogen bond acceptor only

	CH_3CH_3	CH_3NH_2	CH_3OH
MW (g/mol)	**30.1**	**31.1**	**32.0**
bp (°C)	**-88.6**	**-6.3**	**65.0**

- Amines have boiling points between alkanes and alcohols

$CH_3CH_2CH_3$	$CH_3CH_2NH_2$	CH_3CH_2OH
Propane	Ethanamine	Ethanol
M.W. = 44 g/mol	M.W. = 45 g/mol	M.W. = 46 g/mol
b.p. = −42.2° C	b.p. = 16.6° C	b.p. = 78.5° C

- Tertiary amines boil lower then 1º or 2º of similar molecular weight

$CH_3CH_2CH_2—NH_2$	$CH_3CH_2—\underset{\displaystyle H}{\overset{\displaystyle \vert}{N}}—CH_3$	$CH_3—\underset{\displaystyle CH_3}{\overset{\displaystyle \vert}{N}}—CH_3$
Propanamine (propylamine)	*N*-Methylethanamine (ethylmethylamine)	*N,N*-Dimethylmethanamine (trimethylamine)
M.W. = 59 g/mol	M.W. = 59 g/mol	M.W. = 59 g/mol
b.p. = 48.7° C	b.p. = 36.7° C	b.p. = 2.9° C

Comparison of Alcohol and Amine Boiling Points

TABLE 15.2 Comparison of the Boiling Points of Selected Alcohols and Amines

Name	Molecular Weight (g/mol)	Boiling Point (°C)
Methanol	32	64.5
Methanamine	31	−6.3
Ethanol	46	78.5
Ethanamine	45	16.6
Propanol	60	97.2
Propanamine	59	48.7

Boiling Points

Which molecule in each pair will have the higher boiling point?

- Methanol or Methylamine
- Dimethylamine or Water
- Methylamine or Ethylamine
- Propylamine or Butane

Solubility and Odor

- Small amines (<6 C) soluble in water.
- All amines accept hydrogen bonds from water and alcohol.
- Branching increases solubility.
- Most amines smell like rotting fish.

$NH_2CH_2CH_2CH_2CH_2CH_2NH_2$

1,5-pentanediamine or cadaverine

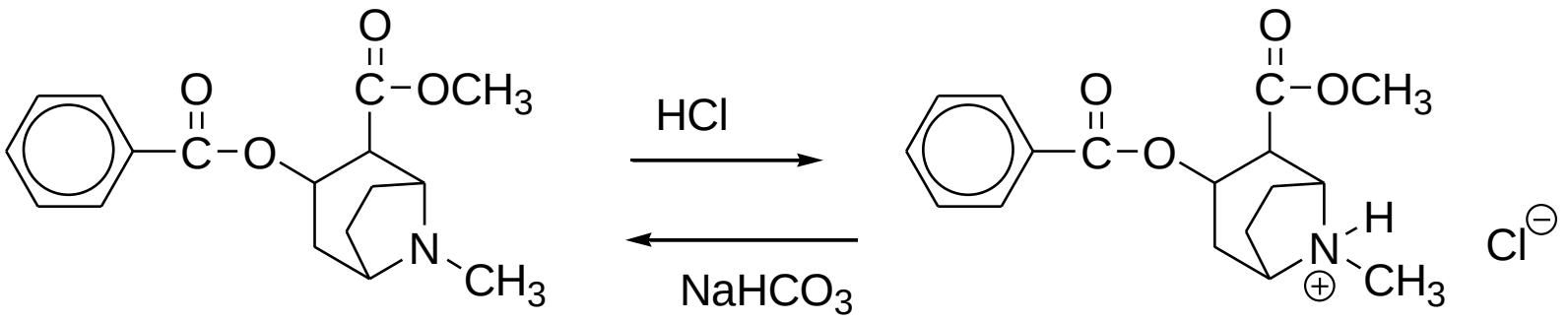
RNH_2 + HCl → RNH_3^+ + Cl^-

water insoluble → water soluble

RNH_3^+ + OH^- → RNH_2 + H_2O

water soluble → water insoluble

1. **test for amines**
2. **can be used to separate amines from neutral or acidic organic compounds**

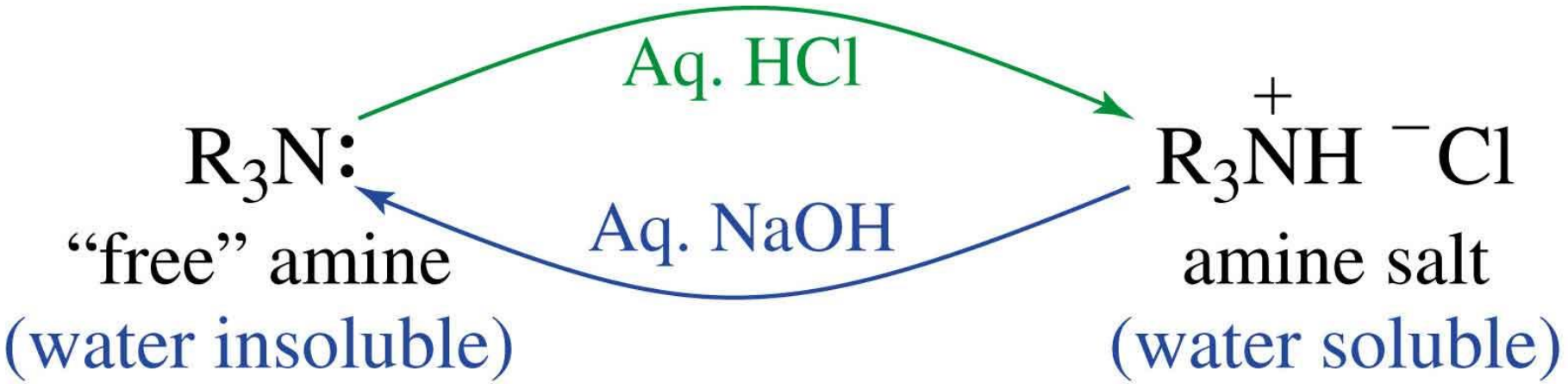


cocaine
3^{o} amine
m 98^{o} C
water insoluble
volatile
"free base"
"crack"
smoked
shorter "high"
lower dose, cheaper
5 g = 5 years

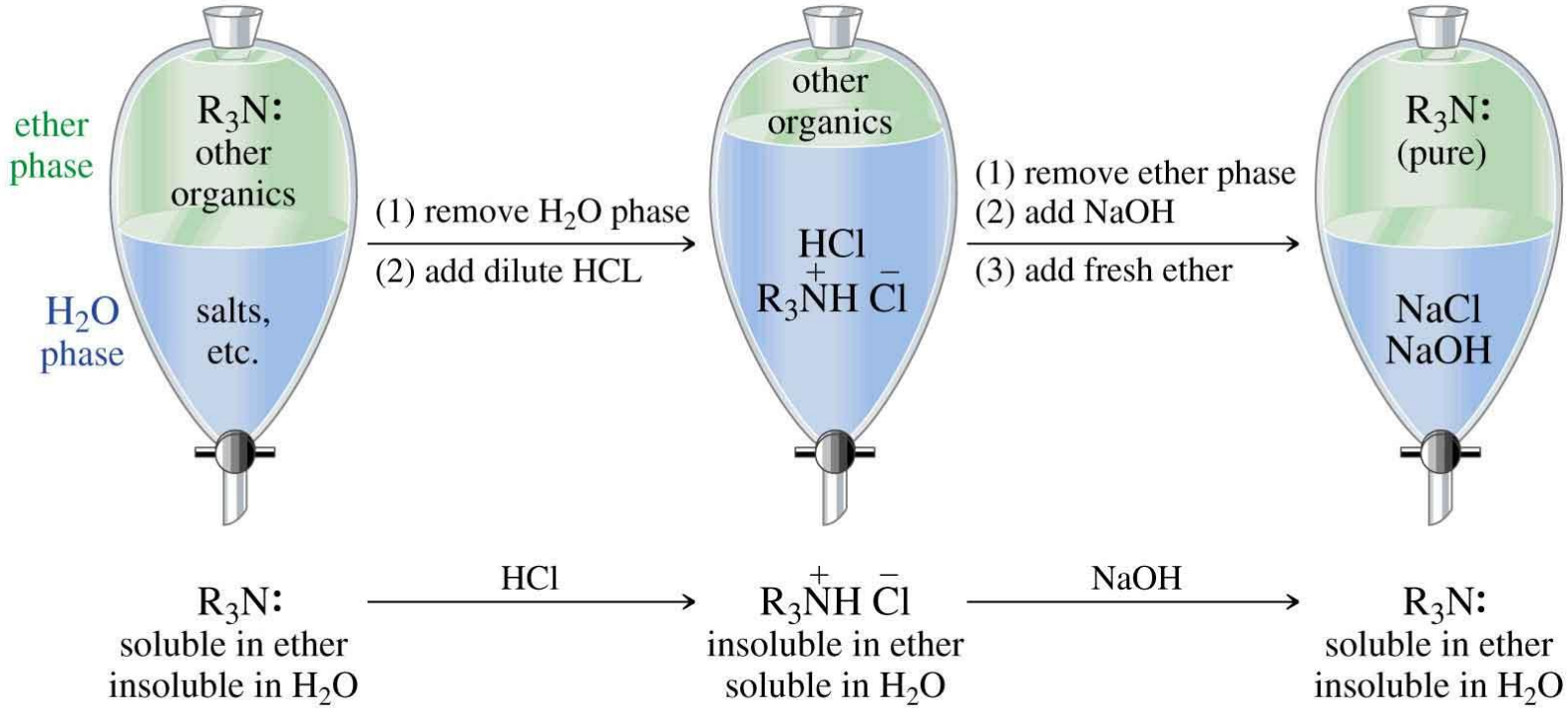
cocaine·HCl
HCl salt of 3^{o} amine
m 195^{o} C
water soluble
non-volatile
"powder", "blow"
"snow"
snorted
longer "high"
higher dose, expensive
500 g = 5 years

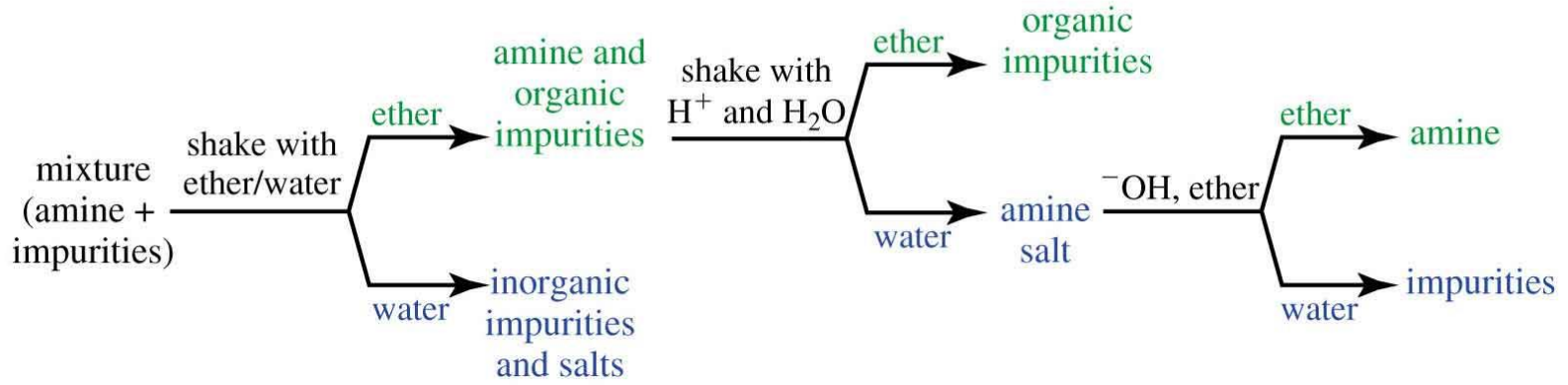
Amine Salts

- Ionic solids with high melting points
- Soluble in water
- No fishy odor



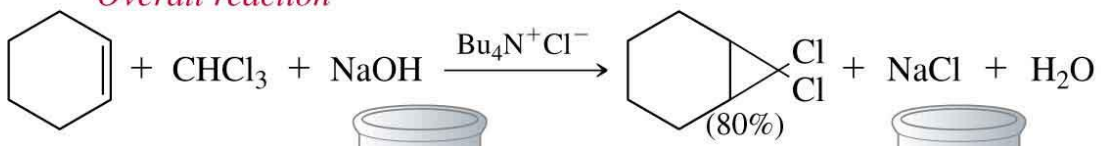
Purifying an Amine

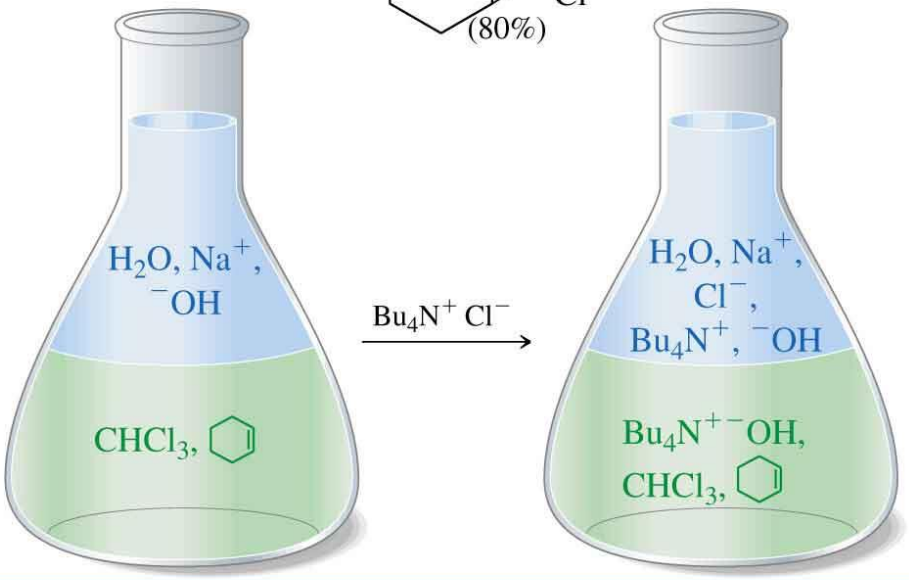




Phase Transfer Catalysts

Overall reaction





Mechanism

1. Aqueous phase

$$Bu_4N^+\ {}^-Cl + Na^+\ {}^-OH \rightleftharpoons Bu_4N^+\ {}^-OH + Na^+\ {}^-Cl$$

tetrabutylammonium chloride — (ion pair)

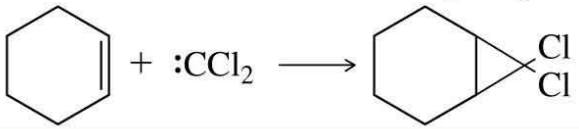
2. Organic phase

$$Bu_4N^+\ {}^-OH + CHCl_3 \rightleftharpoons Bu_4N^+\ {}^-CCl_3 + H_2O$$

organic soluble

$$Bu_4N^+\ {}^-CCl_3 \rightleftharpoons Bu_4N^+\ {}^-Cl + :CCl_2$$

catalyst regenerated — dichlorocarbene



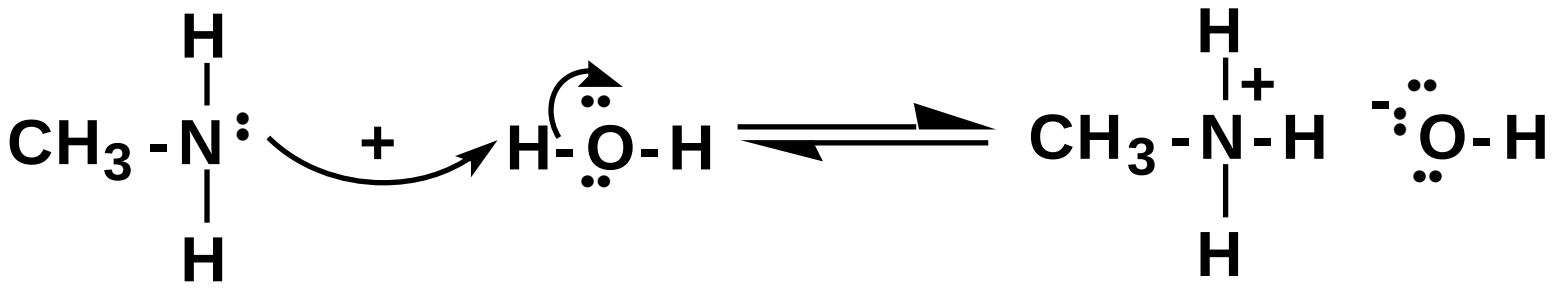
Basicity of Amines

Basicity of Amines

- Lone pair of electrons on nitrogen can accept a proton from an acid
- Aqueous solutions are basic to litmus.
- Ammonia pK_b = 4.74
- Alkyl amines are usually stronger bases than ammonia. Increasing the number of alkyl groups decreases solvation of ion, so 2° and 3° amines are similar to 1° amines in basicity.

Basicity

- **All amines are weak bases and aqueous solutions of amines are basic**



$$K_b = K_{eq}[H_2O] = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]} = 4.37 \times 10^{-4}$$

Basicity

- It is also common to discuss the basicity of amines by reference to the acid ionization constant of the corresponding conjugate acid

$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$$

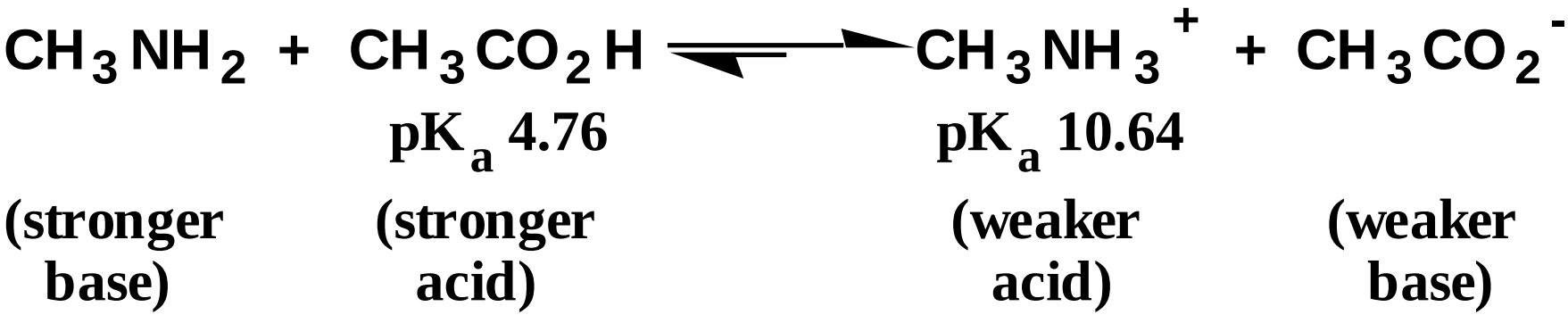
$$K_a = \frac{[CH_3NH_2][H_3O^+]}{[CH_3NH_3^+]} = 2.29 \times 10^{-11} \qquad pK_a = 10.64$$

- For any acid-conjugate base pair

$$pK_a + pK_b = 14.00$$

Basicity

- Using values of pK_a, we can compare the acidities of amine conjugate acids with other acids



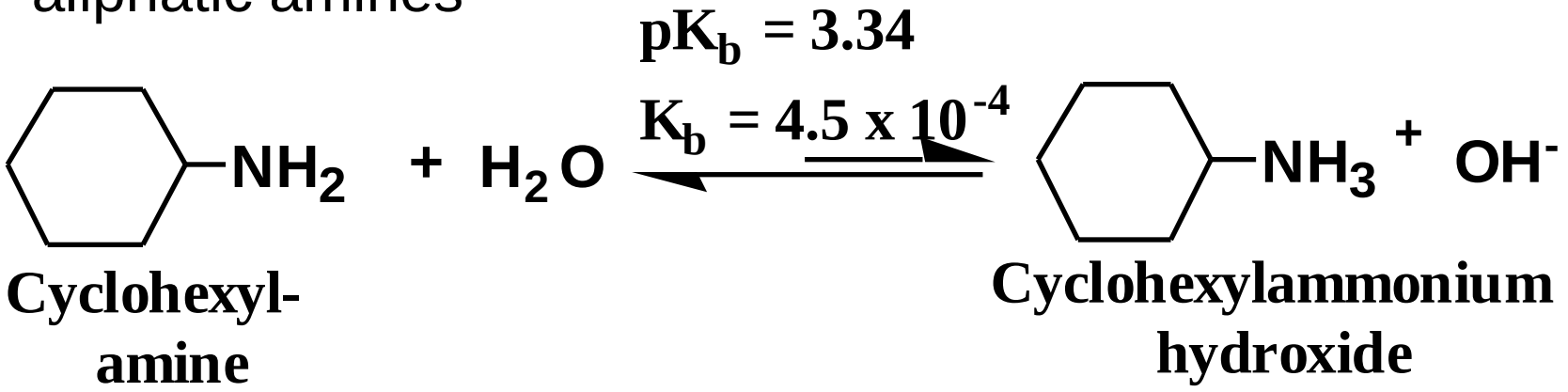
  - acetic acid is the stronger acid and, therefore, the position of this equilibrium lies to the right
- All aliphatic amines have about the same base strength, pK_b 3.0 - 4.0, and are slightly stronger bases than ammonia

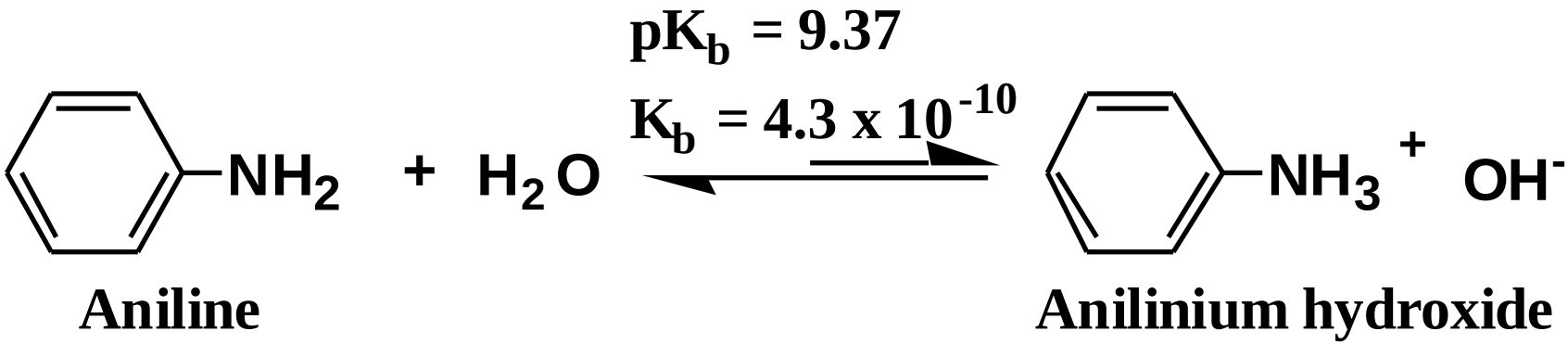
Basicity-Aliphatic Amines

Amine	Structure	pK_b	pK_a
Ammonia	NH_3	**4.74**	**9.26**
Primary Amines			
methylamine	CH_3NH_2	**3.36**	**10.64**
ethylamine	$CH_3CH_2NH_2$	**3.19**	**10.81**
cyclohexylamine	$C_6H_{11}NH_2$	**3.34**	**10.66**
Secondary Amines			
dimethylamine	$(CH_3)_2NH$	**3.27**	**10.73**
diethylamine	$(CH_3CH_2)_2NH$	**3.02**	**10.98**
Tertiary Amines			
trimethylamine	$(CH_3)_3N$	**4.19**	**9.81**
triethylamine	$(CH_3CH_2)_3N$	**3.25**	**10.75**

Basicity-Aromatic Amines

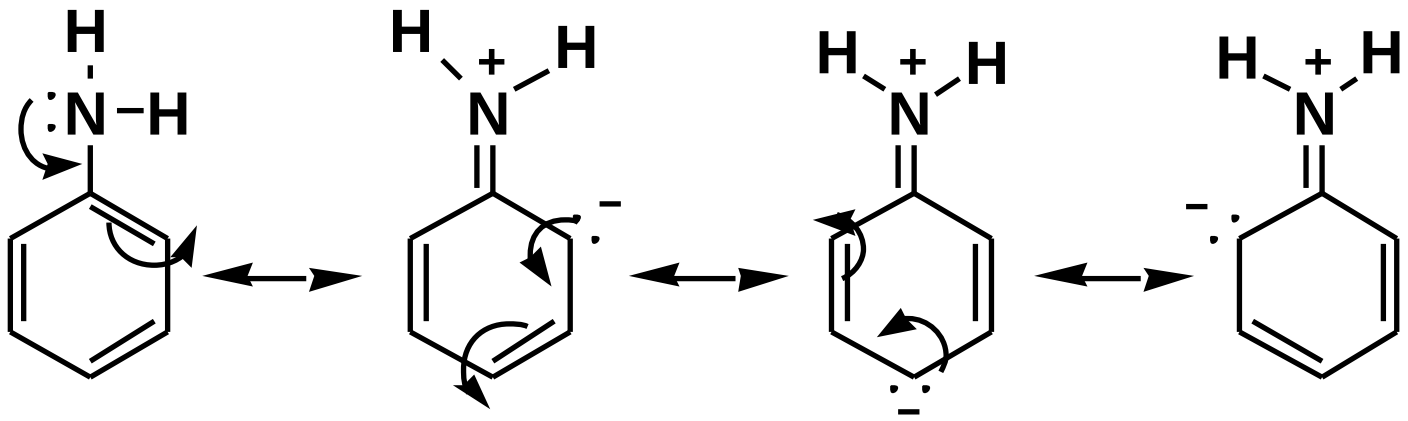
- Aromatic amines are considerably weaker bases than aliphatic amines





Basicity-Aromatic Amines

- Aromatic amines are weaker bases than aliphatic amines because of the resonance stabilization of the free base, which is lost on protonation



Interaction of the electron pair on nitrogen with the pi system of the aromatic ring

The greater the availability of the lone pair electrons on nitrogen, the greater the base.

In the old days, pK_b was a measure of base strength.

$Kb = [RNH_3^+]\,[OH^-] / RNH_2$ $\qquad$ $pK_b = -\log K_b$

The stronger the base the lower the pK_b

EFFECTS ON AMINE BASICITY

1. INDUCTIVE EFFECT - ALKYL SUBSTITUTION

CH_3

$CH_3\text{-}NH_2 < CH3\text{-}NH$

3.36 3.28

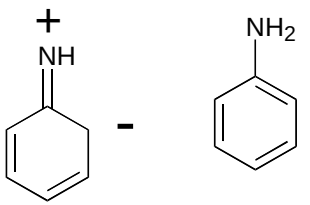
METHYL GROUP INCREASES ELECTRON DENSITY ON N

2 METHYLS ARE BETTER THAN ONE

WATCH OUT THREE METHYL GROUPS DECREASES BASICITY $pK_b = 4.26$ - Steric inhibition of solvation of HOH with the NH^+ of the $R3NH^+$ cation.

2. RESONANCE EFFECT

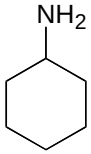
Base weakening Why? Delocalizes electron pair on N!!



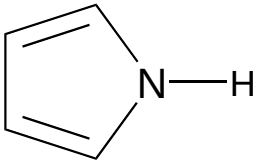
-

9.4

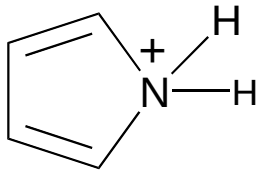
vs.



3.3



aromatic 6 pi system

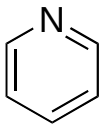


not aromatic

$pK_b = 15$

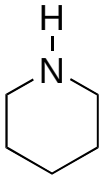
3. Hybridization

The greater the % of s character-The closer the lone pair is to N-The weaker the base



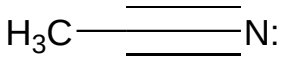
sp_2

8.75



sp_3

2.88

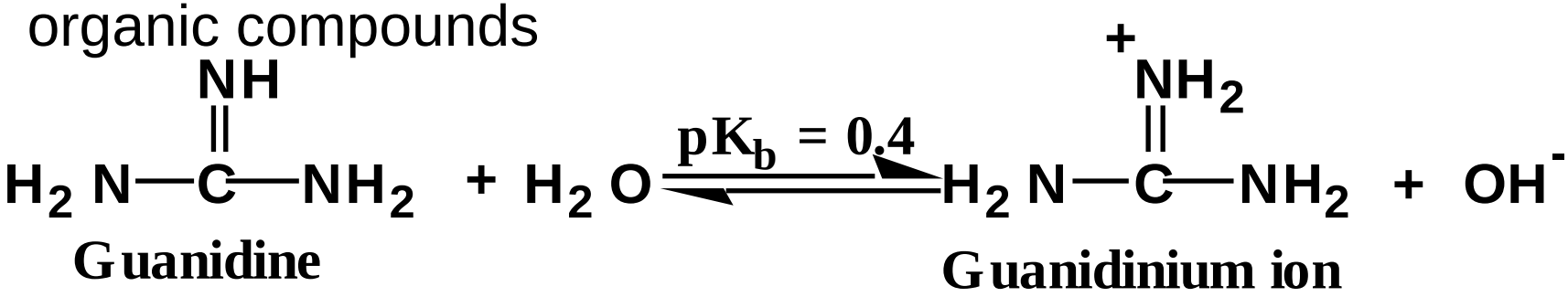


sp

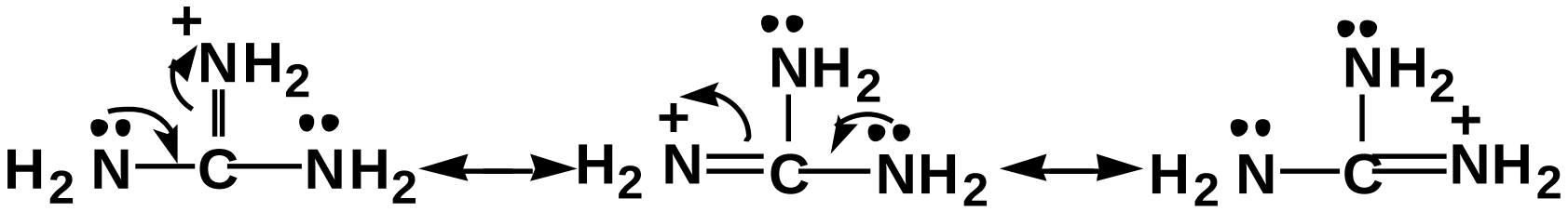
24

Basicity-Guanidine

- Guanidine, pK_b 0.4, is the strongest base among neutral organic compounds



  - its basicity is due to the delocalization of the positive charge over the three nitrogen atoms

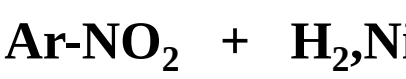


Three equivalent contributing structures

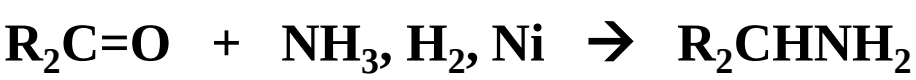
Preparation of Amines

Amines, syntheses:

1. **Reduction of nitro compounds**

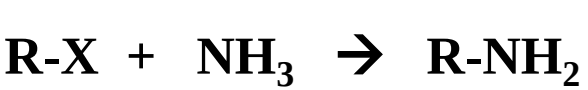


2. **Reductive amination**



3. **Reduction of nitriles**

4. **Amminolysis of 1º or methyl halides → alkilation**



5. **Hofmann rearrangement of amides**

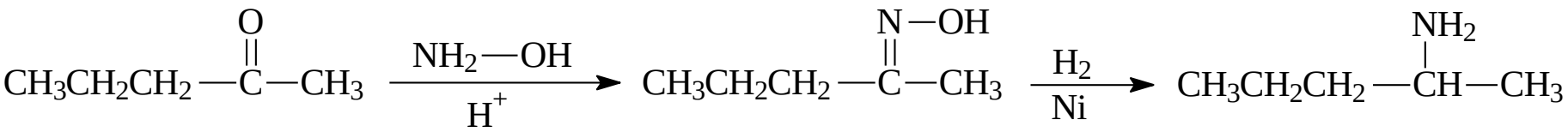
6. **Gabriel Synthesis**

Reduction

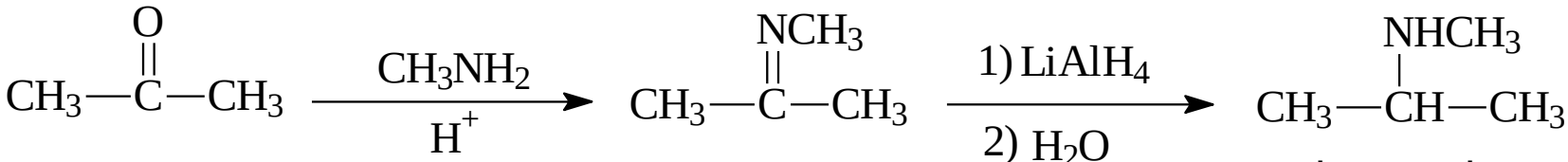
1. Synthesis by Reductive Amination

- To produce a 1° amine, react an aldehyde or ketone with hydroxylamine, then reduce the oxime.
- To produce a 2° amine, react an aldehyde or ketone with a 1° amine, then reduce the imine.
- To produce a 3° amine, react an aldehyde or ketone with a 2° amine, then reduce the imine salt.

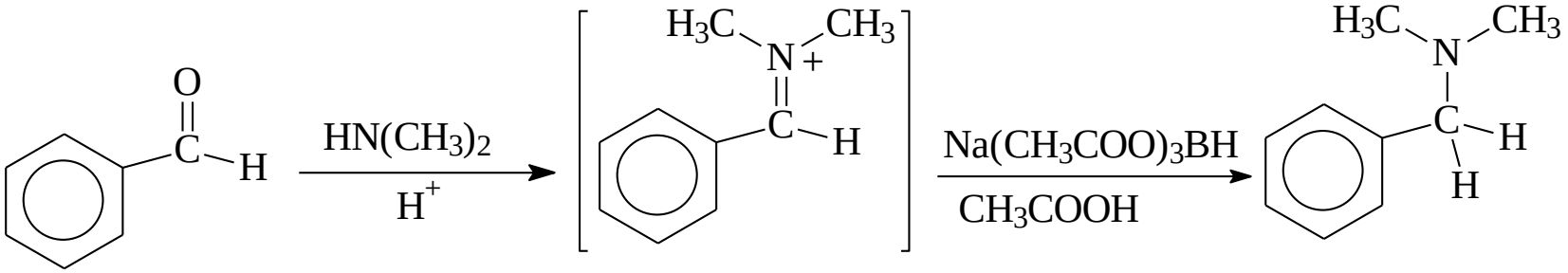
Examples



primary amine



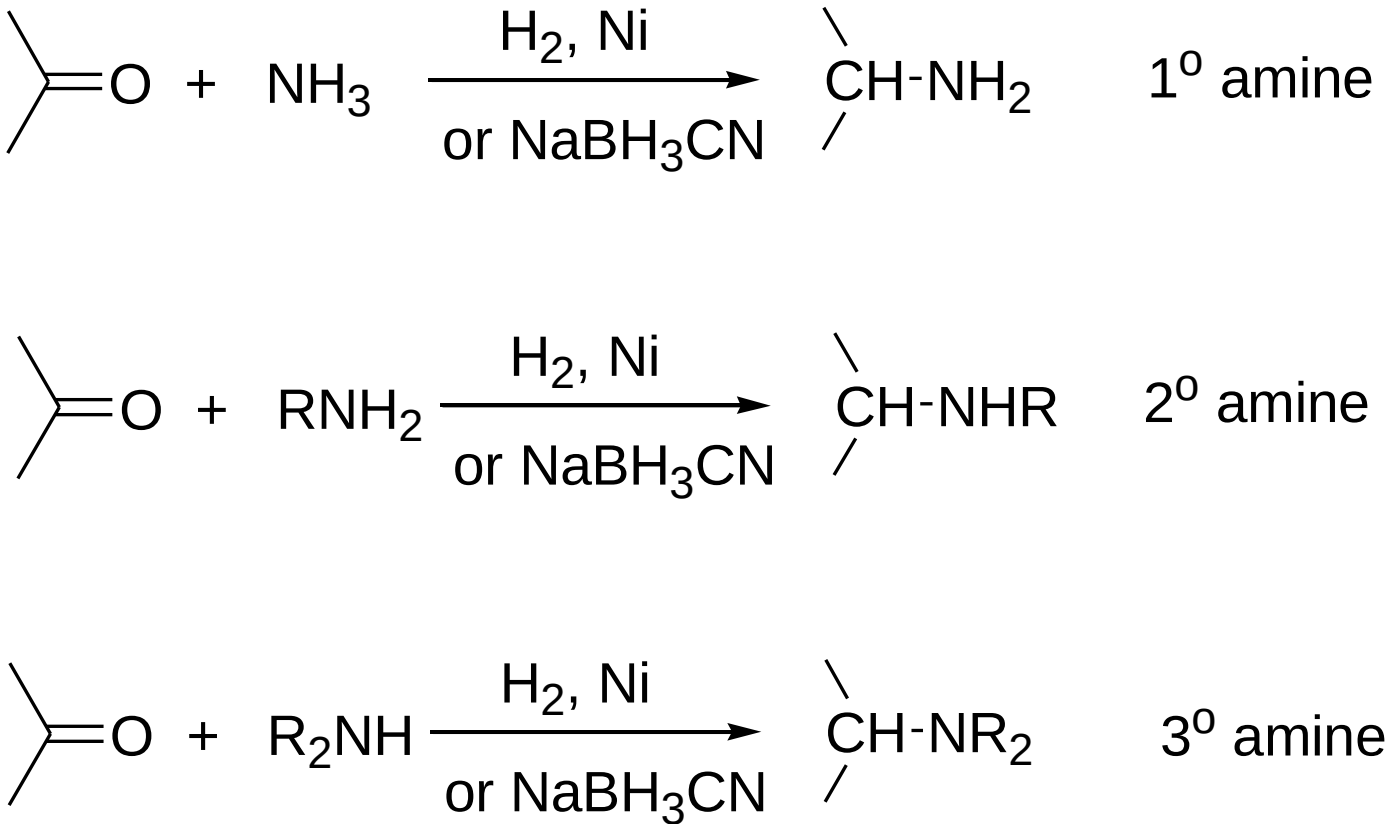
secondary amine



tertiary amine

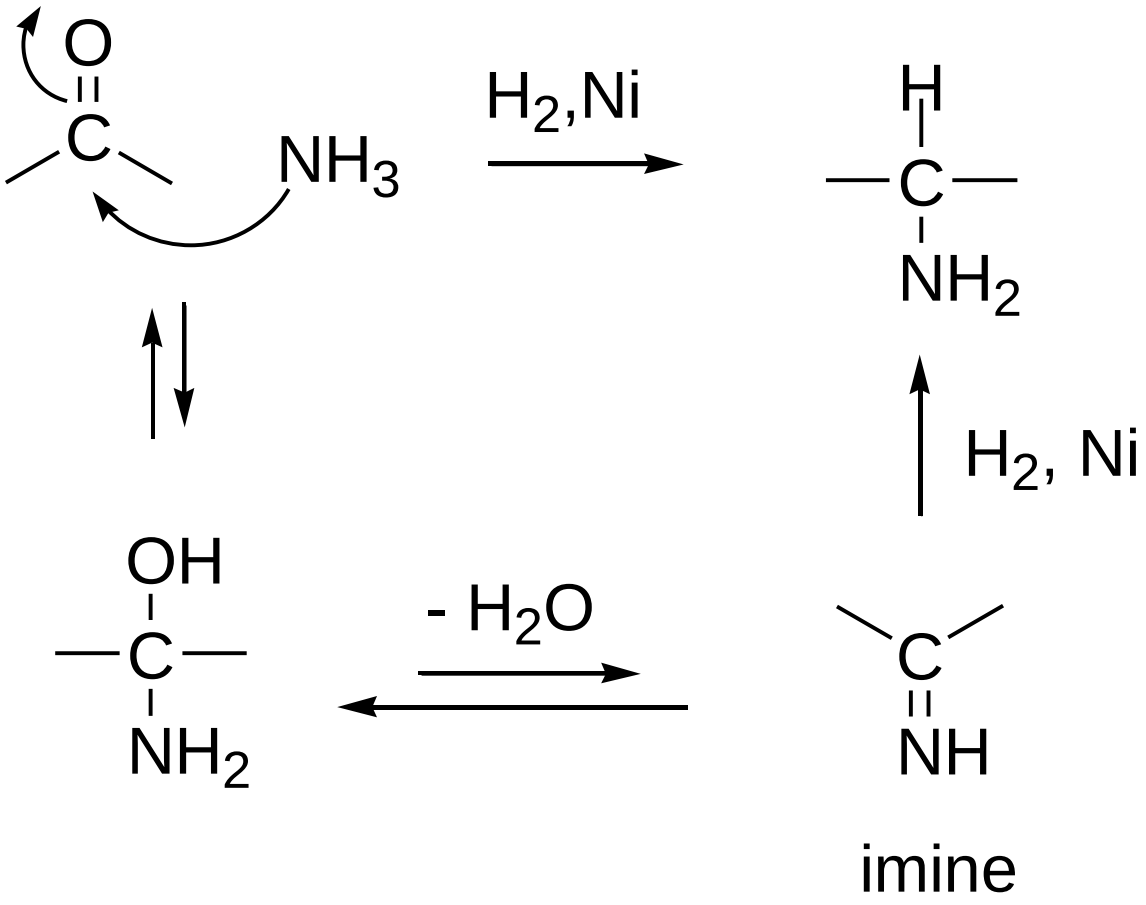
=>

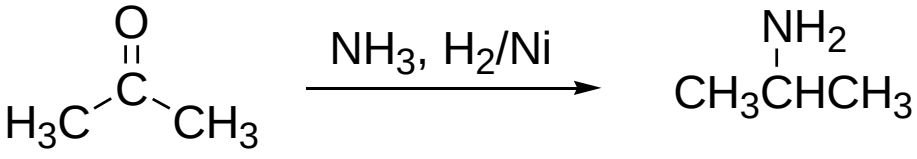
Reductive amination:



Avoids E2

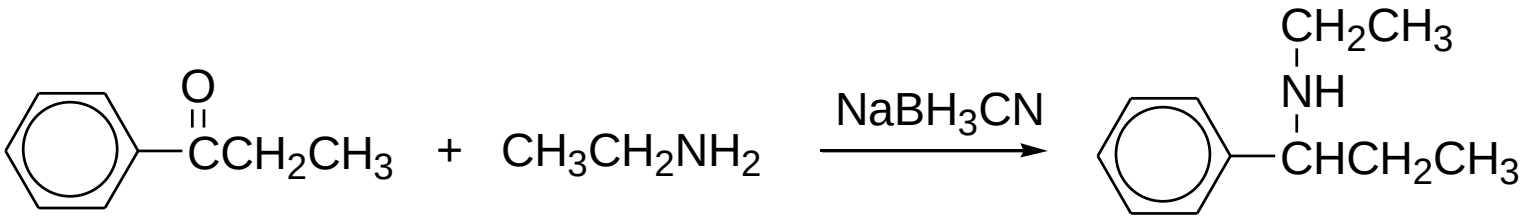
Reductive amination via the imine.





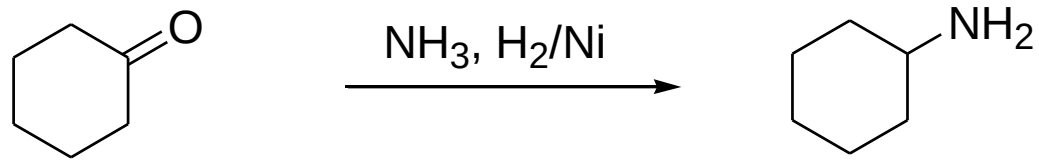
acetone

isopropylamine



propiophenone

1-(*N*-ethylamino)-1-phenylpropane



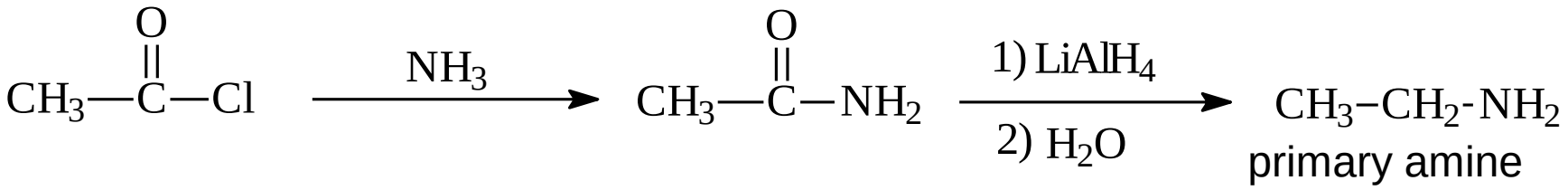
cyclohexanone

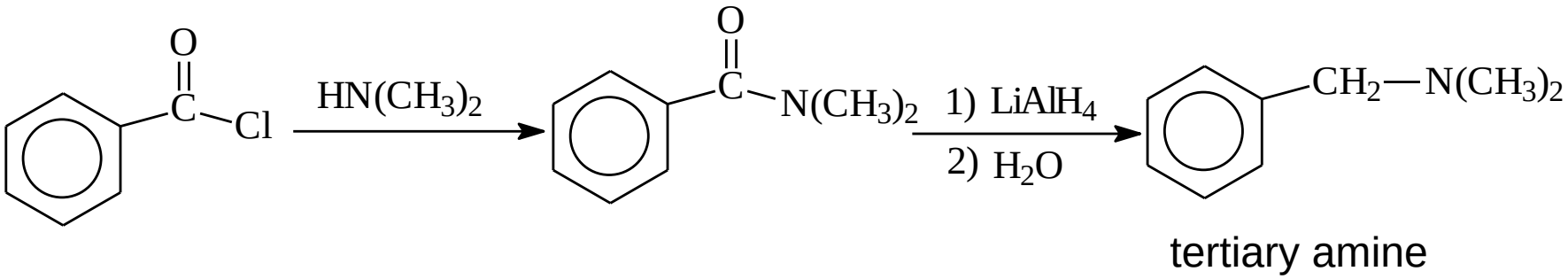
cyclohexylamine

2. Acylation-Reduction

- An acid chloride reacts with ammonia or a 1° amine or a 2° amine to form an amide.
- The C=O of the amide is reduced to CH_2 with lithium aluminum hydride.
- Ammonia yields a 1° amine.
- A 1° amine yields a 2° amine.
- A 2° amine yields a 3° amine.

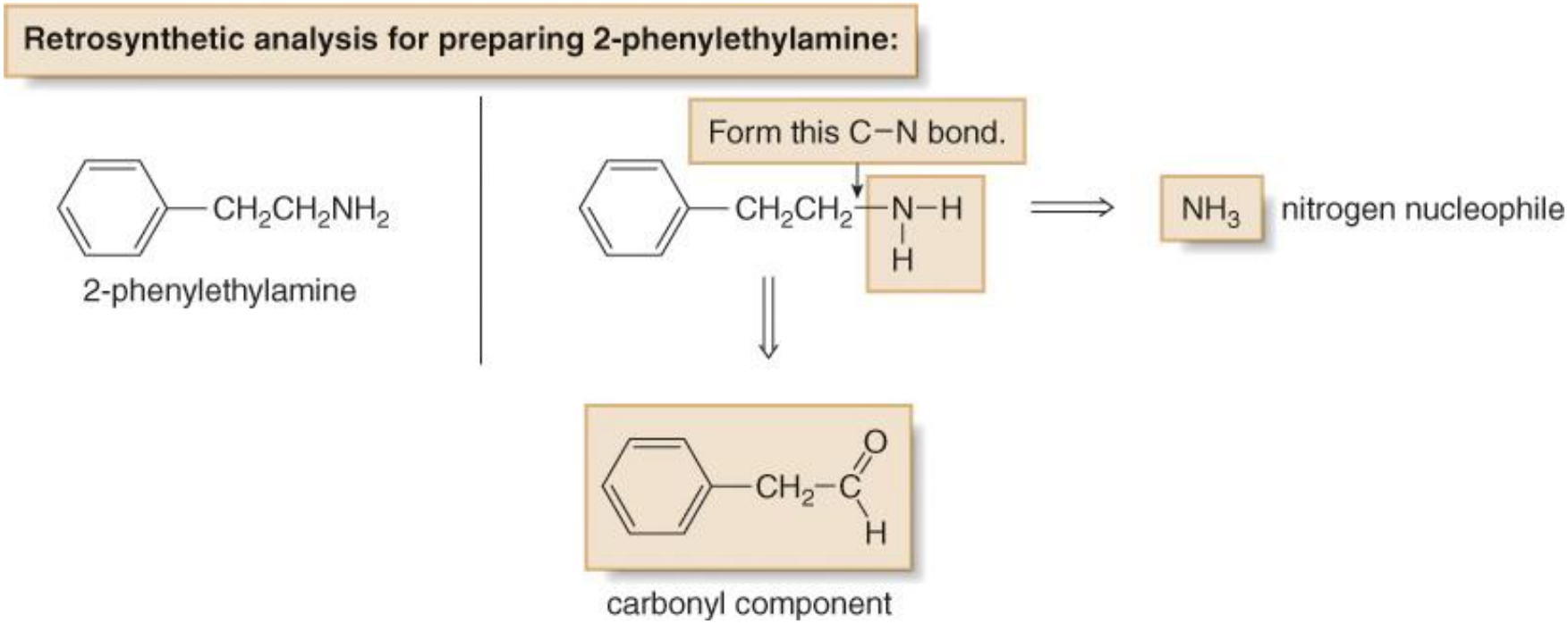
Examples


O
CH3—C—Cl
NH3
O
CH3—C—NH2
1) LiAlH4
2) H2O
CH3−CH2-NH2
primary amine


O
C
Cl
HN(CH3)2
O
C
N(CH3)2
1) LiAlH4
2) H2O
CH2—N(CH3)2
tertiary amine

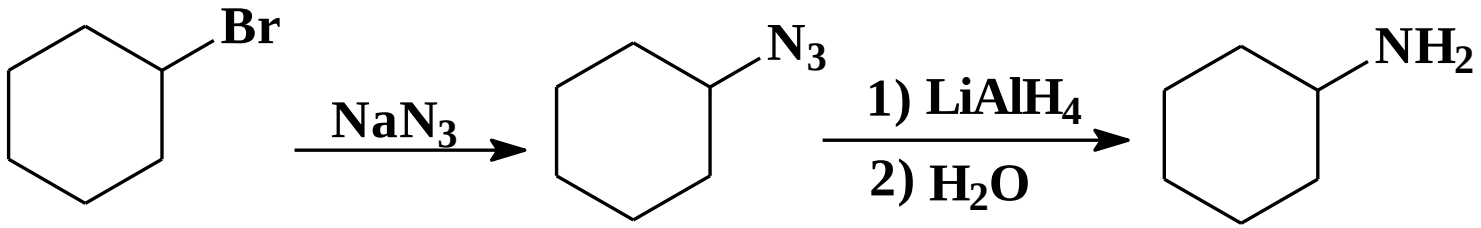
Preparation of Amines—Reductive Amination

- For a 1^0 amine, the nitrogen component must be NH_3.



3. Azide Reduction (1°)

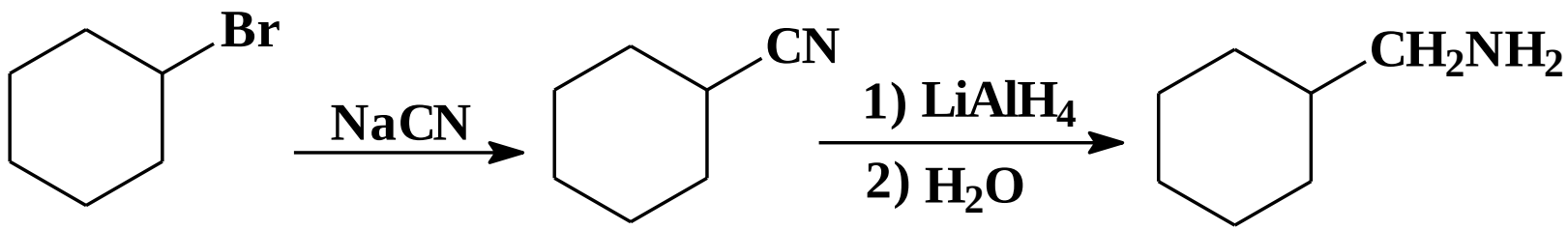
- Azide ion, N_3^-, is a good nucleophile.
- React azide with unhindered 1° or 2° halide or tosylate (S_N2).
- Alkyl azides are explosive! Do not isolate.



=>

4. Nitrile Reduction (1°)

- Nitrile, -C≡N, is a good S_N2 nucleophile.
- Reduction with H_2 or $LiAlH_4$ adds $-CH_2NH_2$.



=>

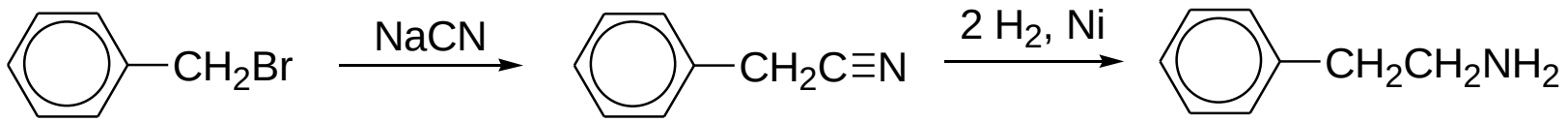
$$R\text{-}C{\equiv}N + 2\,H_2, \text{catalyst} \rightarrow R\text{-}CH_2NH_2$$

1^o amine

$$R\text{-}X + NaCN \rightarrow R\text{-}CN \rightarrow RCH_2NH_2$$

primary amine with one additional carbon

(R must be 1^o or methyl)

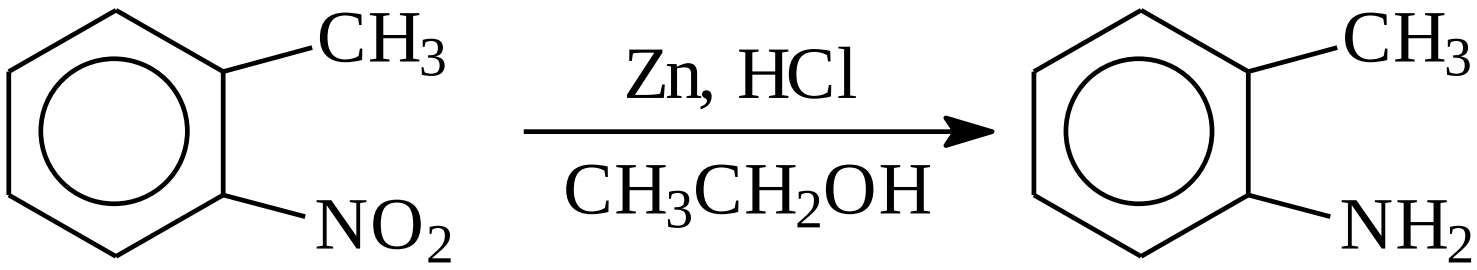


benzyl bromide

1-amino-2-phenylethane

5. Reduction of Nitro Compounds (1°)

- -NO_2 is reduced to -NH_2 by catalytic hydrogenation, or active metal with acid.
- Commonly used to synthesize anilines.



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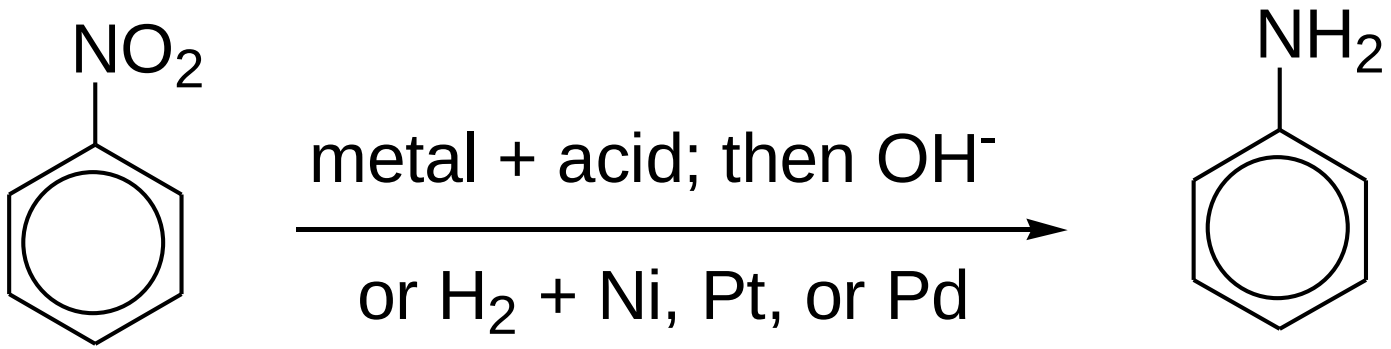
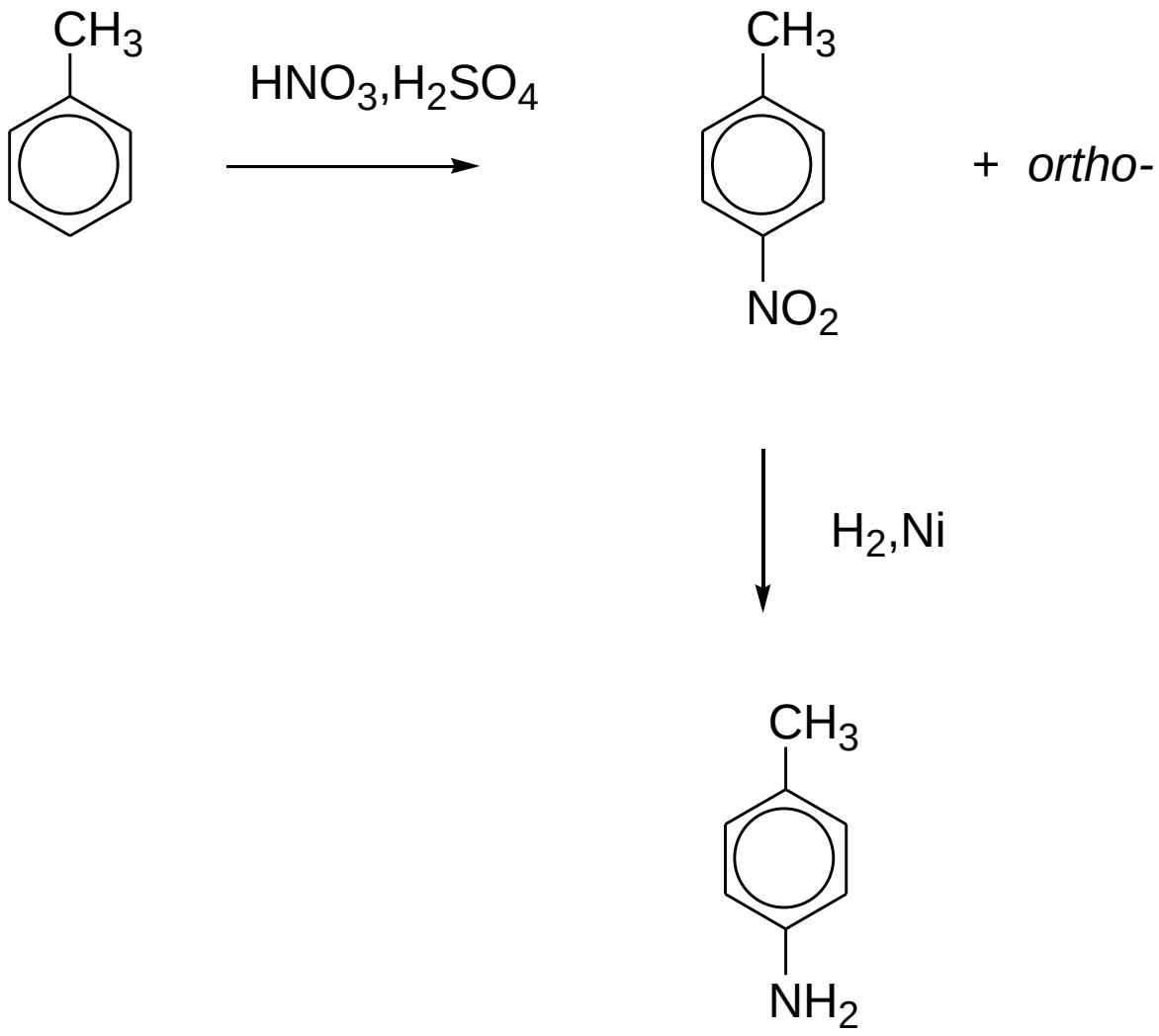
Reduction of nitro compounds:



Chiefly for primary **aromatic** amines.

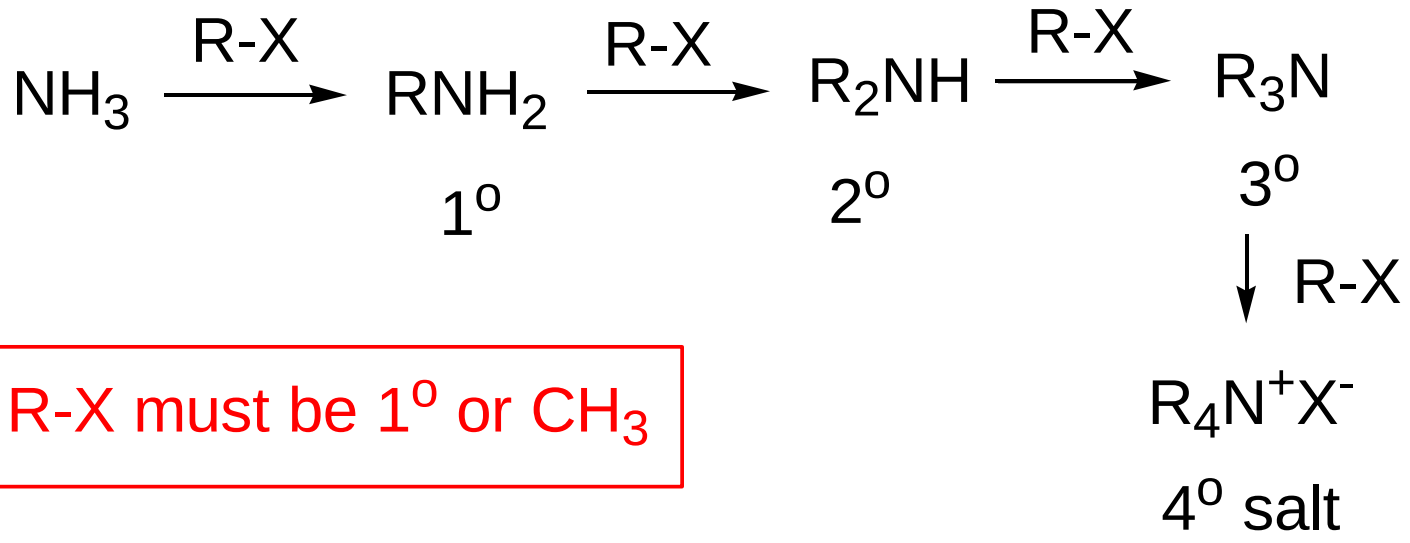


p-toluidine

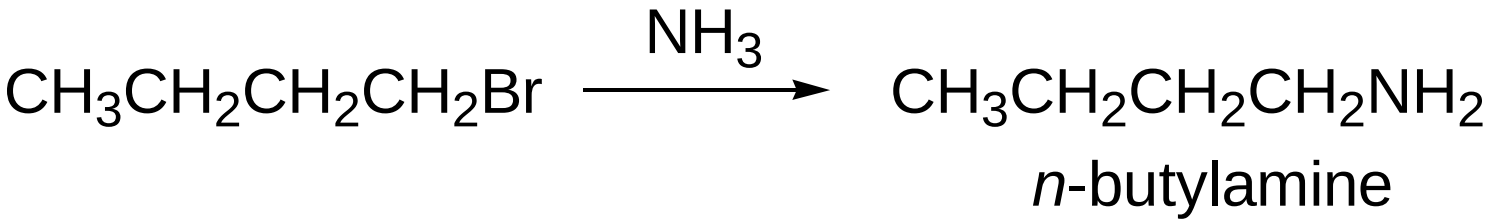
2. Direct Alkylation (1°)

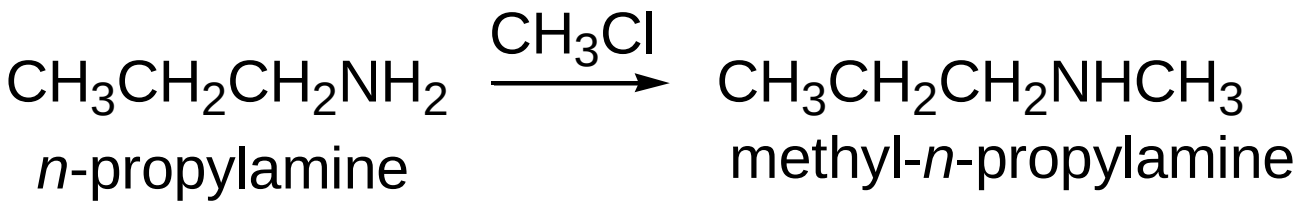
- Use a large excess (10:1) of ammonia with a primary alkyl halide or tosylate.
- Reaction mechanism is S_N2.

Ammonolysis of 1° or methyl halides.



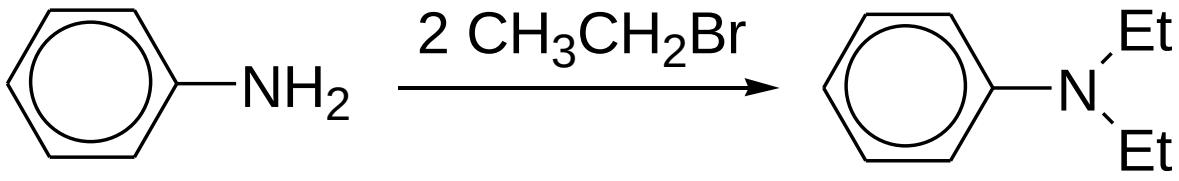
R-X must be 1° or CH_3





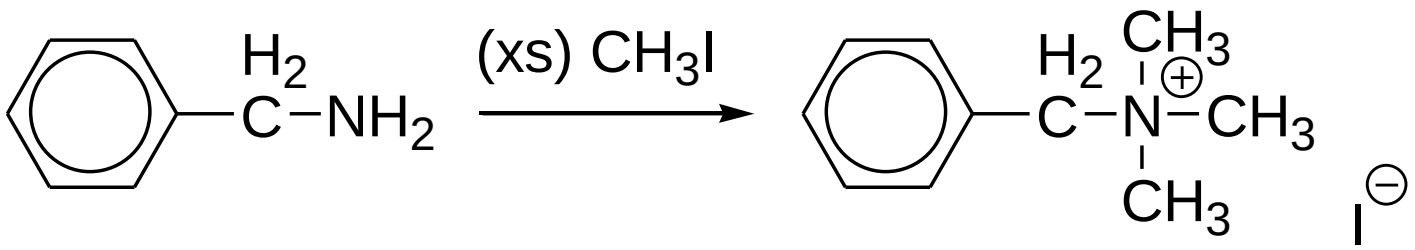
n-propylamine

methyl-*n*-propylamine



aniline

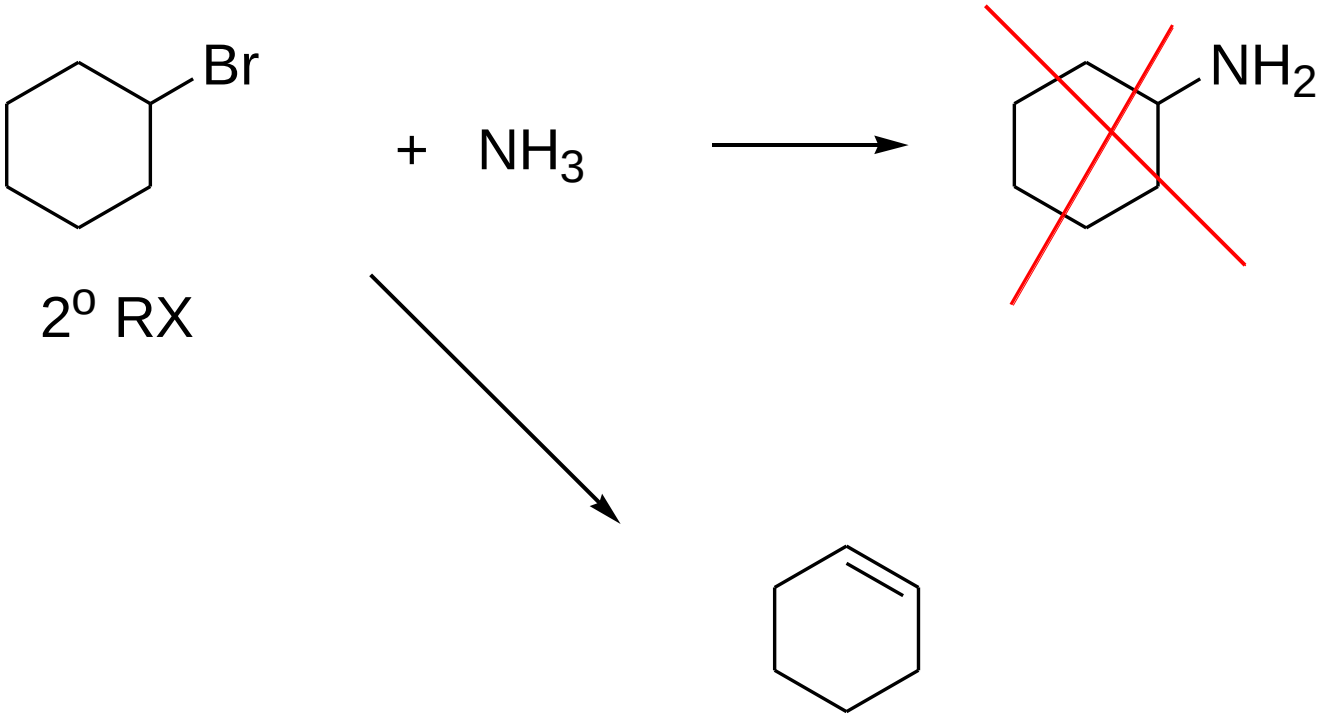
N,N-diethylaniline



benzylamine

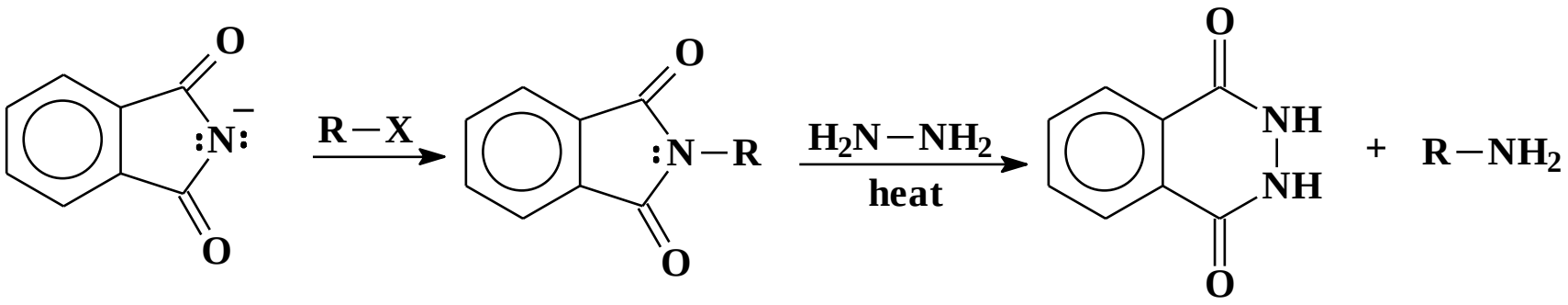
benzyltrimethylammonium iodide

Ammonolysis of alkyl halides is an S_N2 reaction. The alkyl halide must be primary or methyl. If the alkyl halide is secondary or tertiary, then an E2 reaction will take place and the product will be an alkene!



3. Gabriel Synthesis (1°)

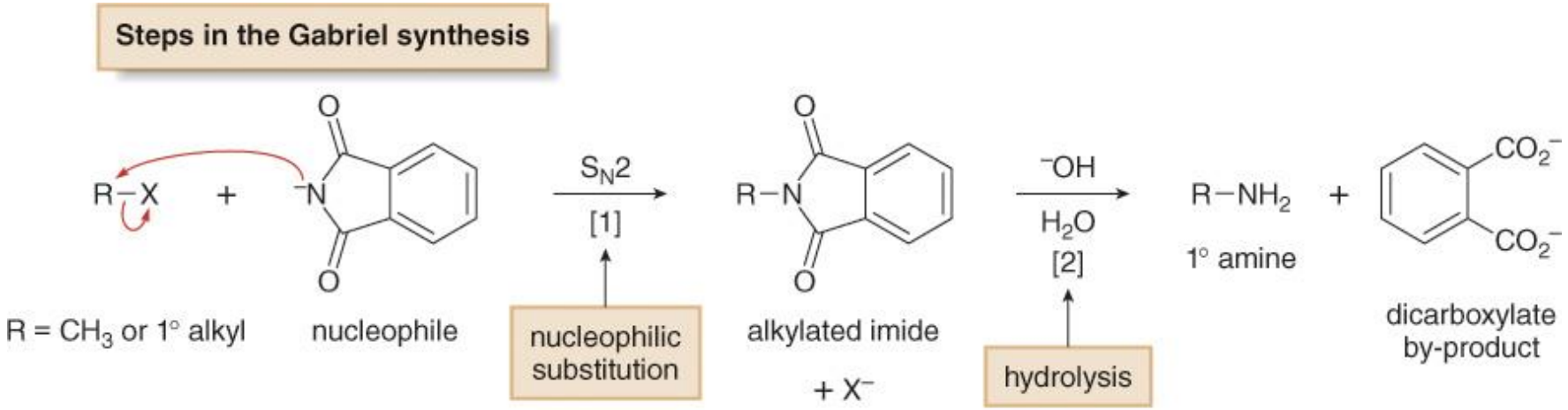
- Use the phthalimide anion as a form of ammonia that can only alkylate once.
- React the anion with a good S_N2 substrate, then heat with hydrazine.



phthalimide

Preparation of Amines—Gabriel Synthesis of 1^0 Amines

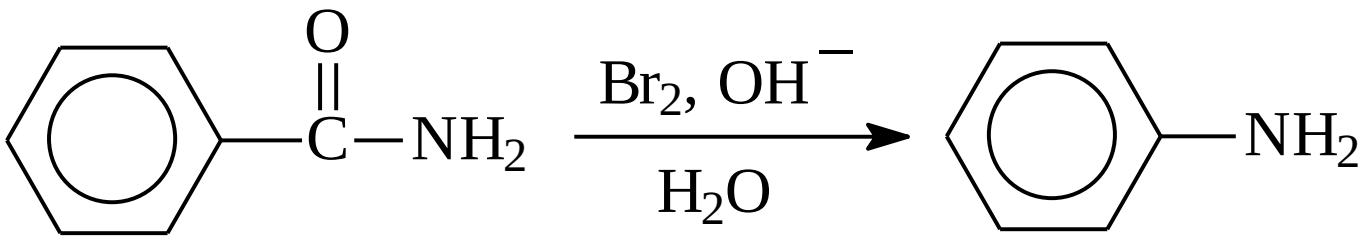
- The alkylated imide is then hydrolyzed with aqueous base to give a 1^0 amine and a dicarboxylate.



◆ The Gabriel synthesis converts an alkyl halide into a 1° amine by a two-step process: nucleophilic substitution followed by hydrolysis.

4. Hofmann Rearrangement of Amides (1°)

In the presence of a strong base, primary amides react with chlorine or bromine to form amines with one less C.



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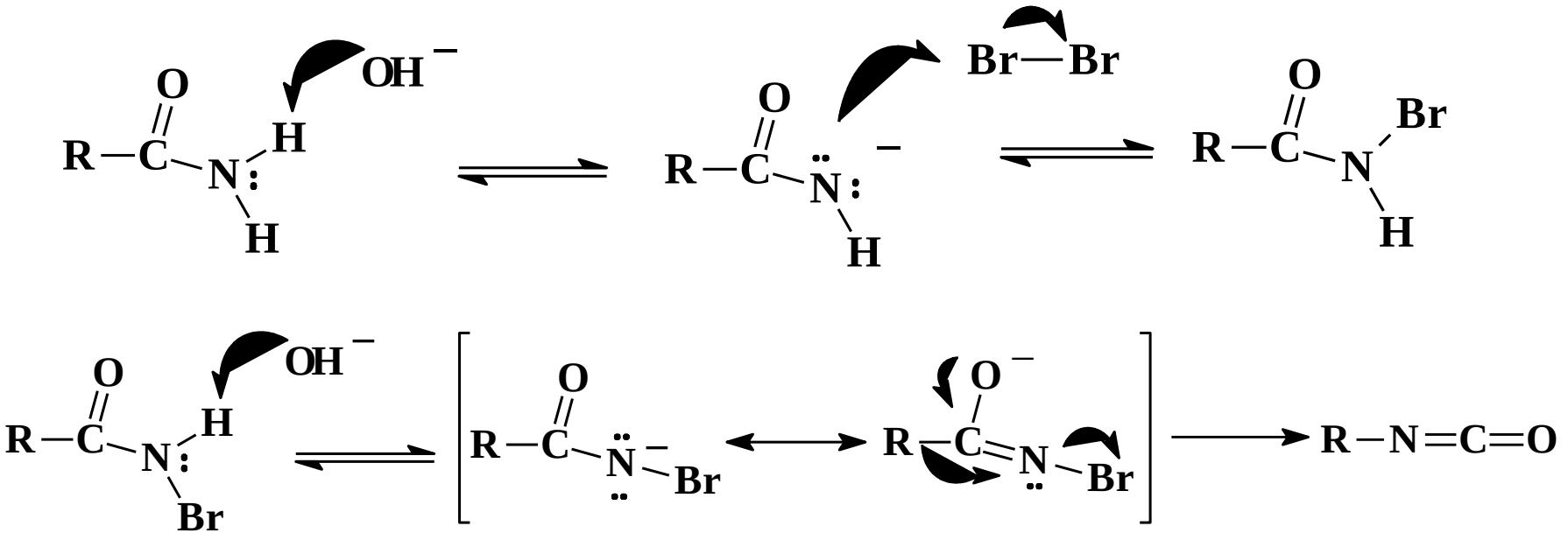
Hofmann Mechanism (1)

- N-H protons of amide are abstracted.
- Rearrangement forms an isocyanate.



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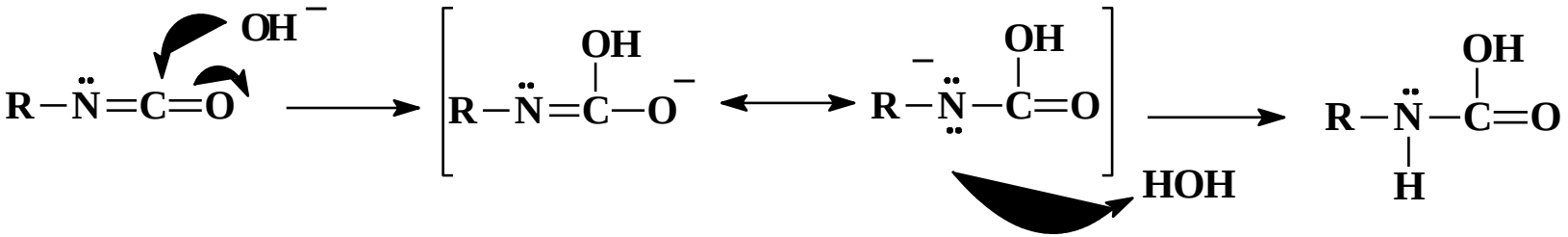
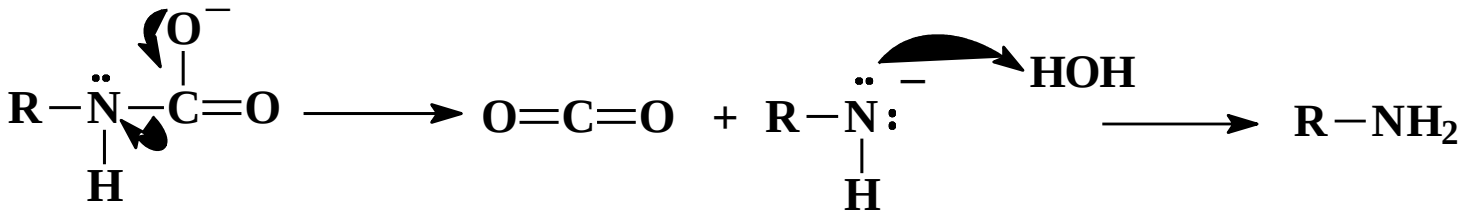
Hofmann Mechanism (2)

- Isocyanate reacts with water to form carbamic acid, which loses CO_2.





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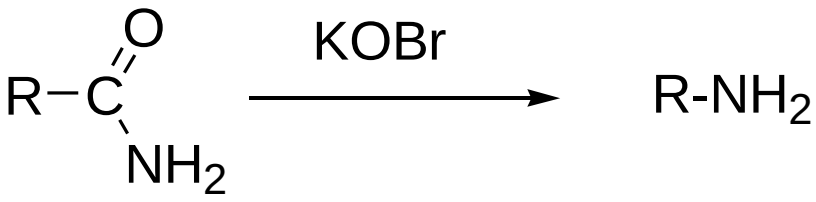
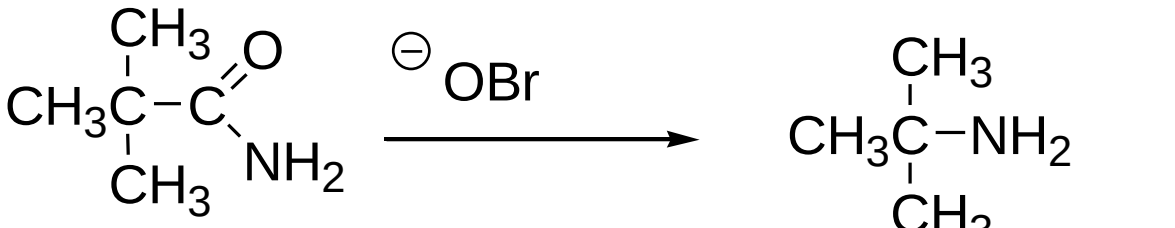


Removes one carbon!



2,2-dimethylpropanamide

tert-butylamine

Summary of Amines syntheses:

1. **Reduction of nitro compounds** — **1º Ar**

   $Ar\text{-}NO_2 + H_2,Ni \rightarrow Ar\text{-}NH_2$

2. **Ammonolysis of 1º or methyl halides** — **R-X = 1º,CH_3**

   $R\text{-}X + NH_3 \rightarrow R\text{-}NH_2$

3. **Reductive amination** — **avoids E2**

   $R_2C{=}O + NH_3, H_2, Ni \rightarrow R_2CHNH_2$

4. **Reduction of nitriles** — **+ 1 carbon**

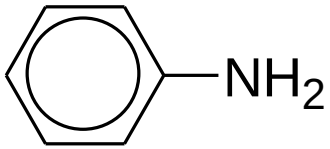
   $R\text{-}C{\equiv}N + 2\ H_2, Ni \rightarrow RCH_2NH_2$

5. **Hofmann degradation of amides** — **- 1 carbon**

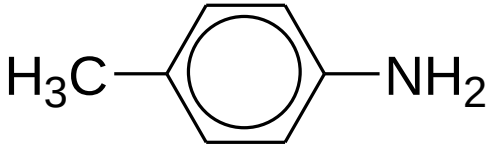
   $RCONH_2 + KOBr \rightarrow RNH_2$

Question :

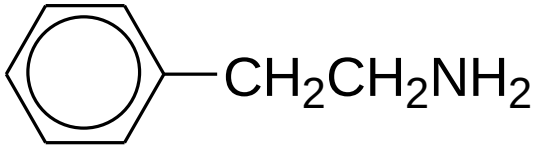
Outline possible laboratory syntheses for each of the following amines, starting with **toluene**. Use a <u>different</u> method for each compound.



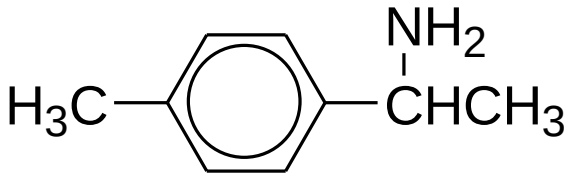
aniline



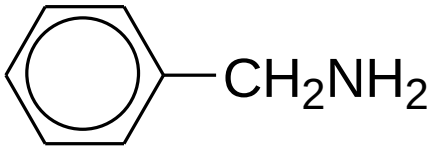
p-toluidine



1-amino-2-phenylethane

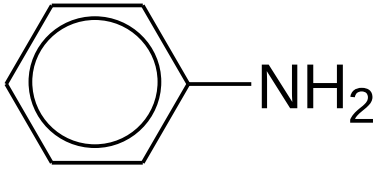


1-amino-1-(*p*-tolyl)ethane

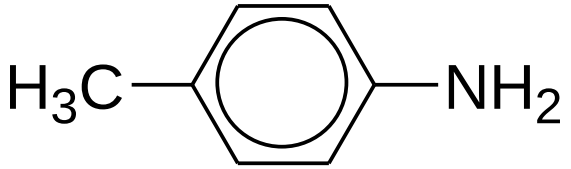


benzylamine

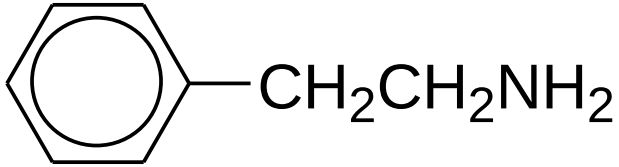
First decide which method you are going to use for which compound…



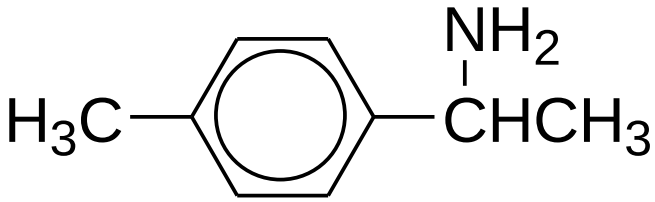
5. Hofmann degradation



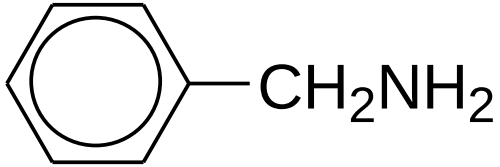
1. nitration



4. Reduction of nitrile

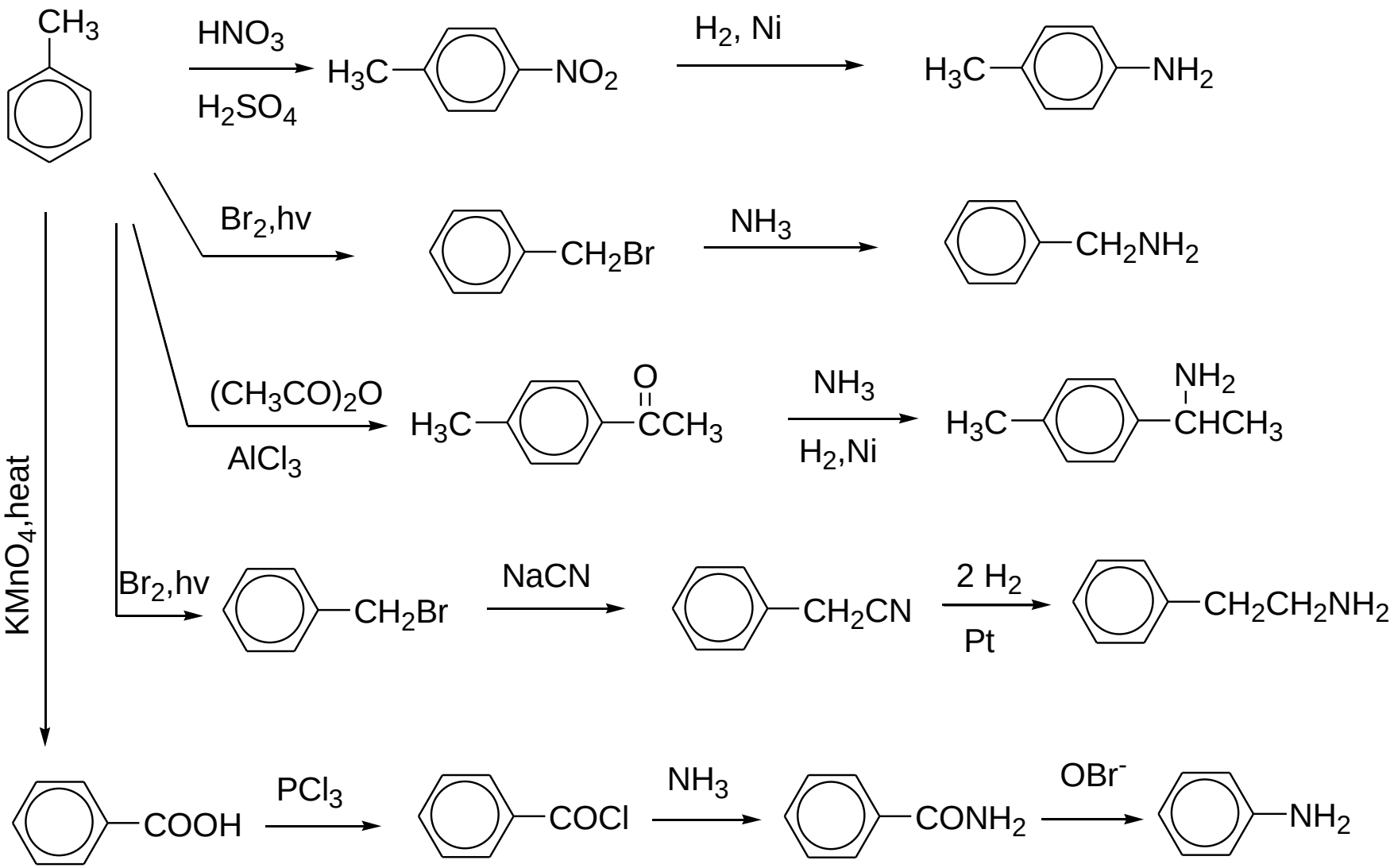


3. Reductive amination



2. ammonolysis

Answer :


CH3
HNO3
H2SO4
H3C
NO2
H2, Ni
H3C
NH2
Br2,hv
CH2Br
NH3
CH2NH2
KMnO4,heat
(CH3CO)2O
AlCl3
H3C
O
CCH3
NH3
H2,Ni
H3C
NH2
CHCH3
Br2,hv
CH2Br
NaCN
CH2CN
2 H2
Pt
CH2CH2NH2
COOH
PCl3
COCl
NH3
CONH2
OBr-
NH2

Reactions of Amines

Amines, reactions

Amines are similar to ammonia in their reactions.

Like ammonia, amines are basic.

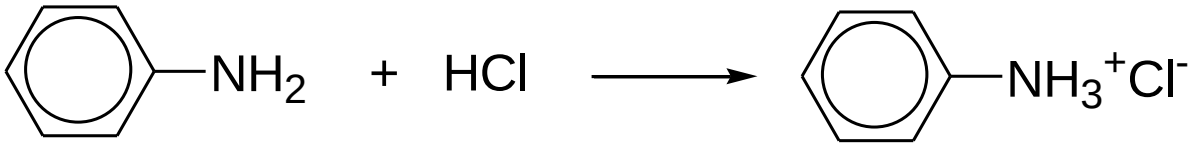
Like ammonia, amines are nucleophilic and react with alkyl halides, acid chlorides, and carbonyl compounds.

The aromatic amines are highly reactive in electrophilic aromatic substitution.

Amine, reactions:

1. Acid- bases
2. Alkylation – substitution reaction
3. Reductive amination
4. Conversion into amides
5. Electrophilic Aromatic Substitution
6. Hofmann elimination from quarternary ammonium salts
7. Reactions with nitrous acid – diazonium salt

1. Acids-base reactions



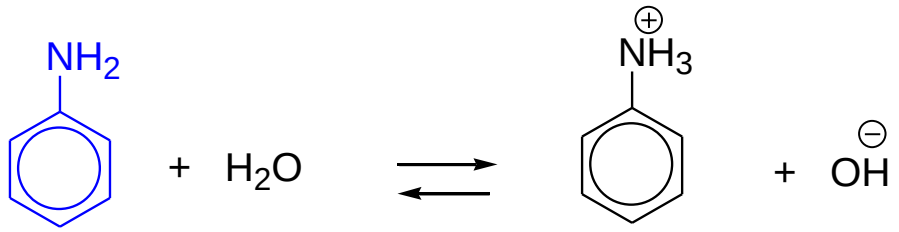
anilinium chloride

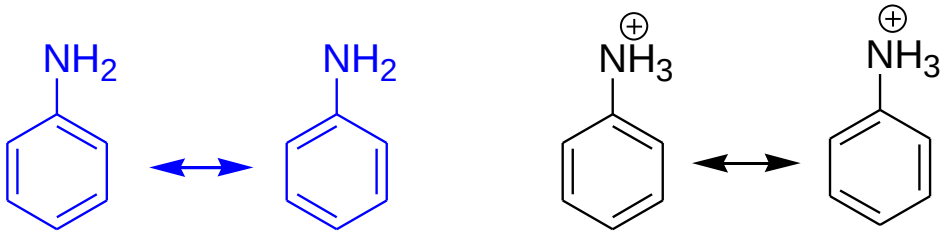
$(CH_3CH_2)_2NH + CH_3COOH \longrightarrow (CH_3CH_2)_2NH_2^+, {}^-OOCCH_3$

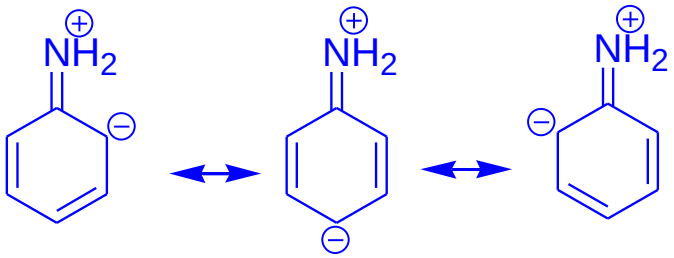
diethylammonium acetate

Why are aromatic amines less basic than aliphatic amines?

$$R\text{-}NH_2 + H_2O \leftrightarrows R\text{-}NH_3^+ + OH^-$$

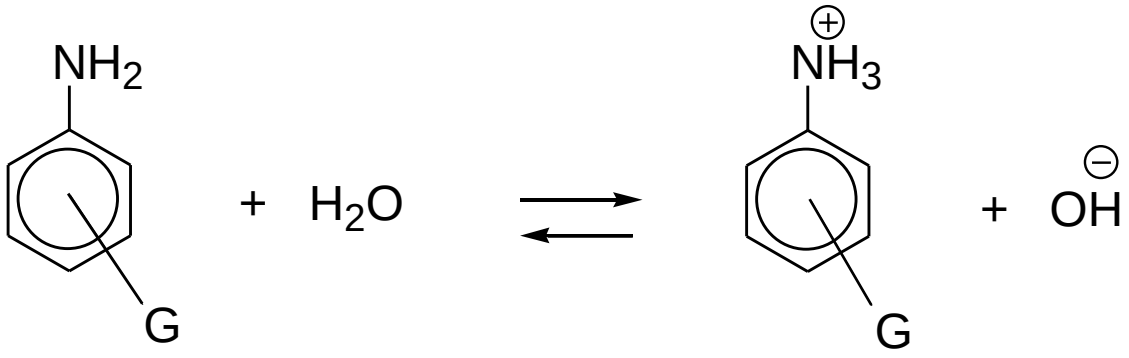






resonance stabilization of the free base, increases the ΔH, shifts the ionization to the left, decreasing base strength.

Effect of substituent groups on base strength:



Electron donating groups will stabilize the anilinium ion, decreasing the ΔH, shifting the ionization farther to the right and making the compound a stronger base.

Electron withdrawing groups destabilize the anilinium ion, increasing the ΔH, shifting the ionization towards the reactants, making the compound a weaker base.

Common substituent groups:

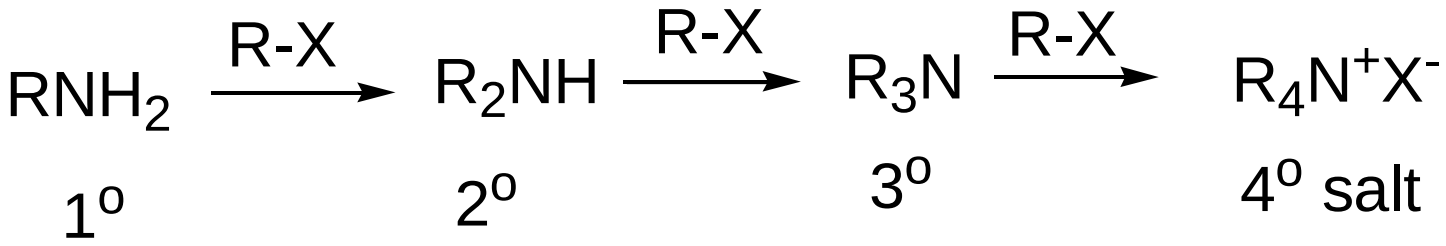
- $-NH_2$, $-NHR$, $-NR_2$
- $-OH$
- $-OR$
- $-NHCOCH_3$
- $-C_6H_5$
- $-R$
- $-H$

electron donating groups

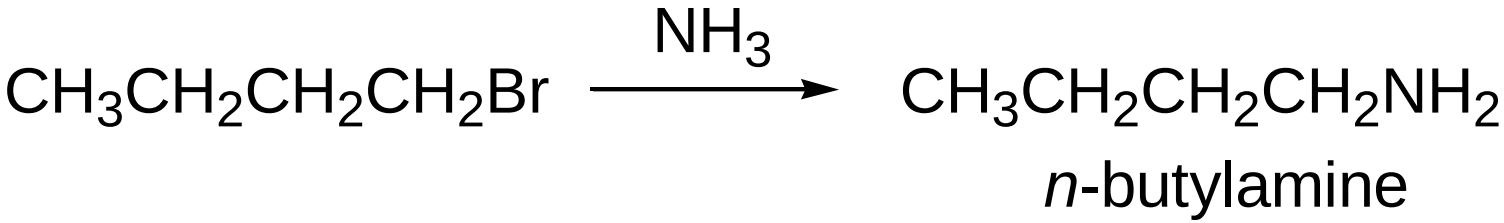
- $-X$
- $-CHO$, $-COR$
- $-SO_3H$
- $-COOH$, $-COOR$
- $-CN$
- $-NR_3^+$
- $-NO_2$

electron withdrawing groups

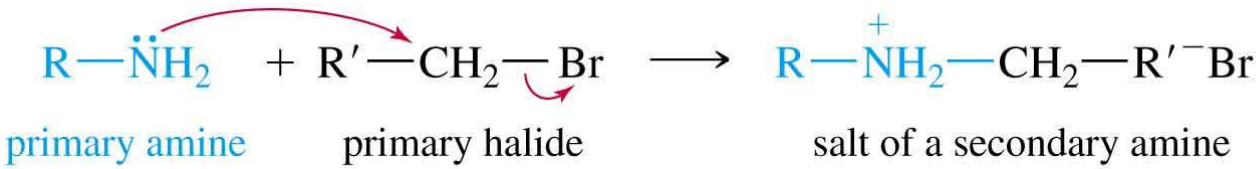
2. Alkylation (amminolysis of alkyl halides)

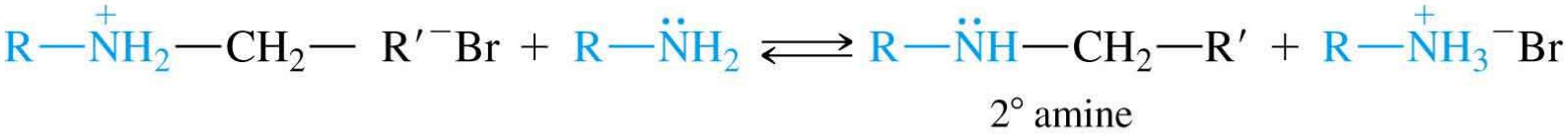


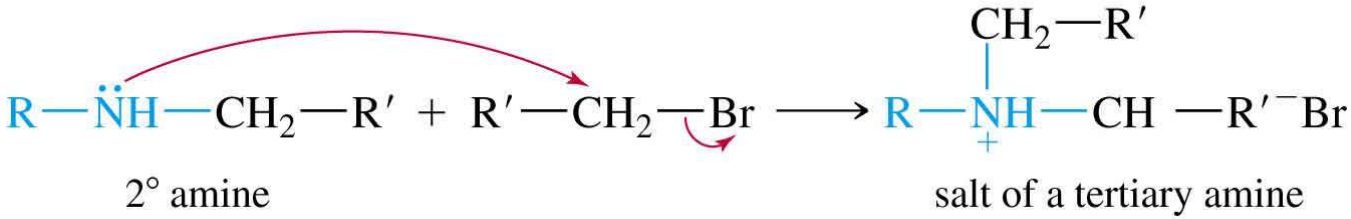
S_N2: R-X must be 1^o or CH_3



- Amines react with 1° alkyl halides via the S_N2 mechanism.
- Mixtures of the mono-, di-, and tri-alkylated products are obtained.

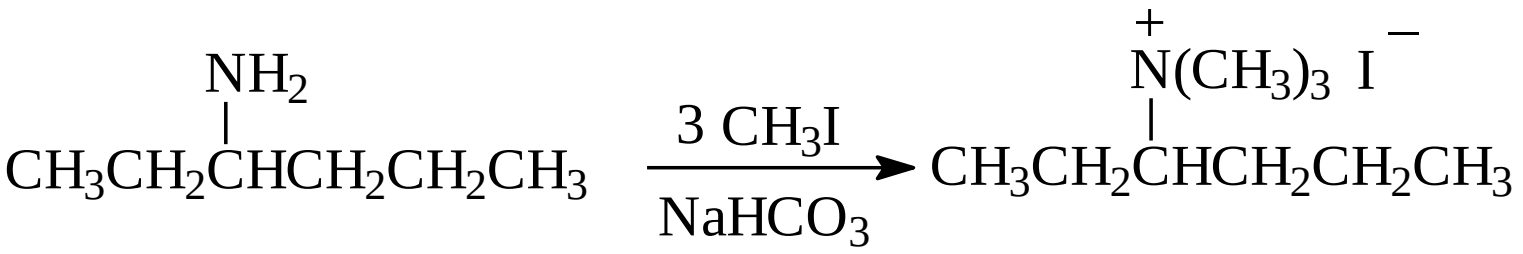




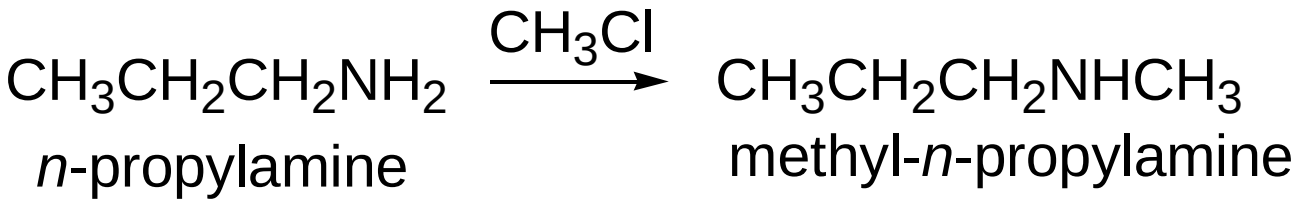


Useful Alkylations

- Exhaustive alkylation to form the tetraalkylammonium salt.

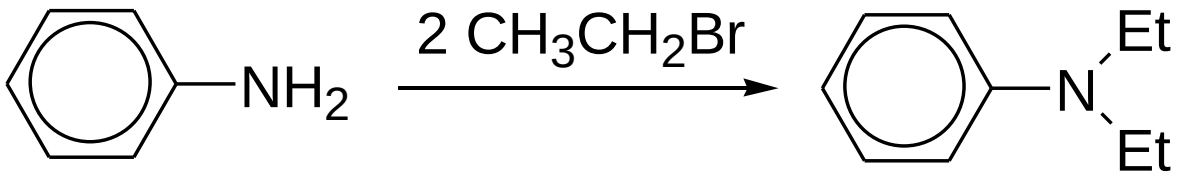


- Reaction with large excess of NH_3 to form the primary amine.



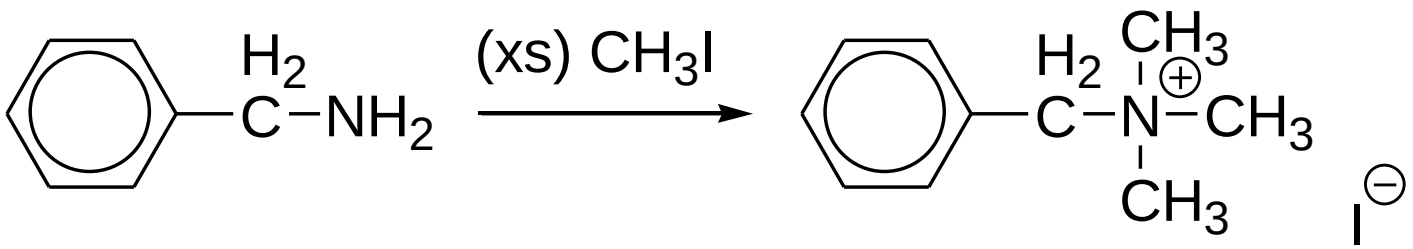
n-propylamine

methyl-*n*-propylamine



aniline

N,N-diethylaniline

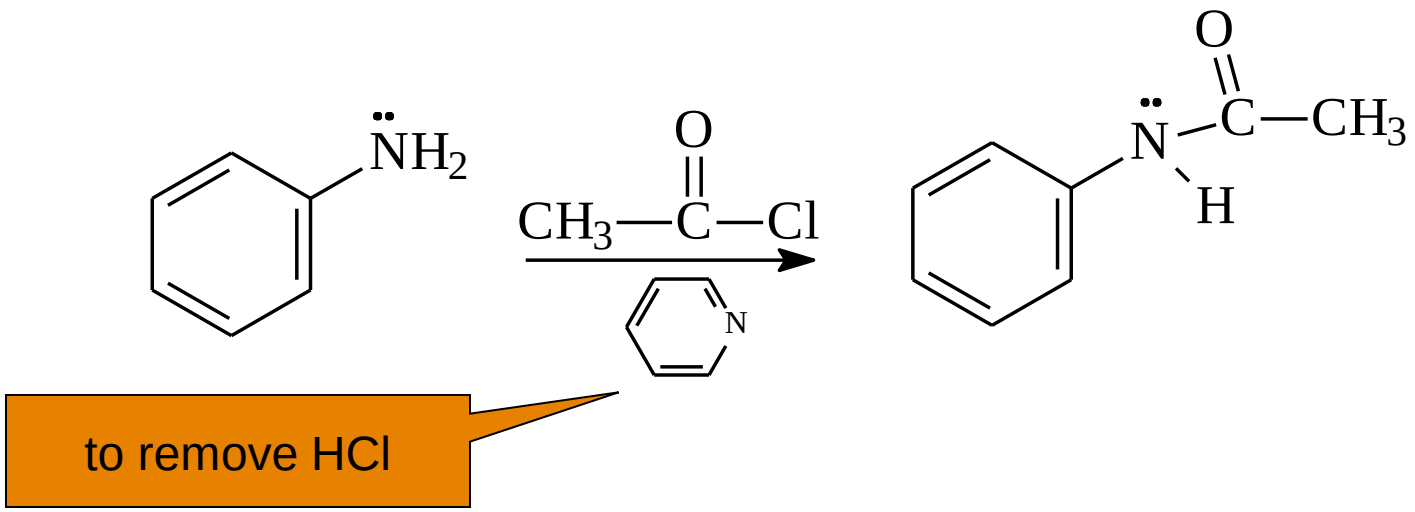


benzylamine

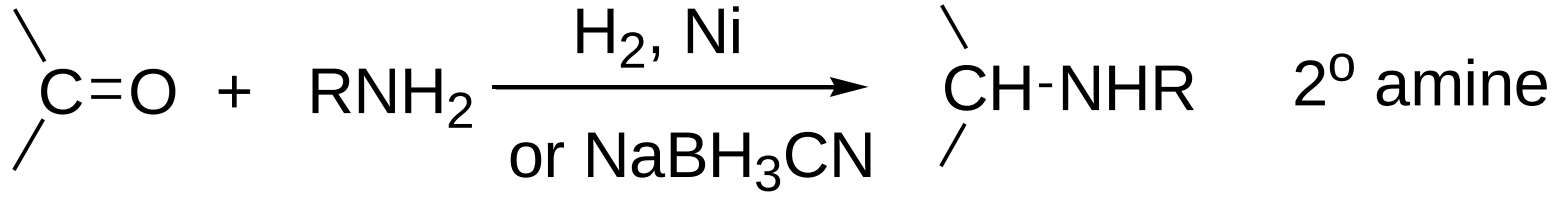
benzyltrimethylammonium iodide

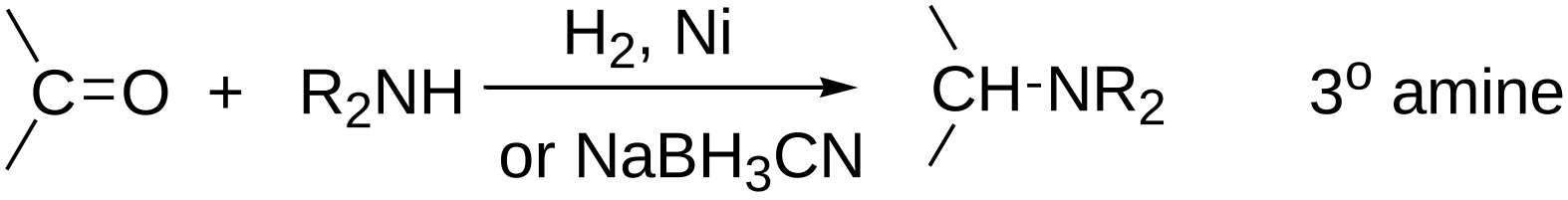
Acylation of Amines by Acid Chlorides

- Amine attacks C=O, chloride ion leaves.
- Product is amide, neutral, not basic.
- Useful for decreasing activity of aniline toward electrophilic aromatic substitution.



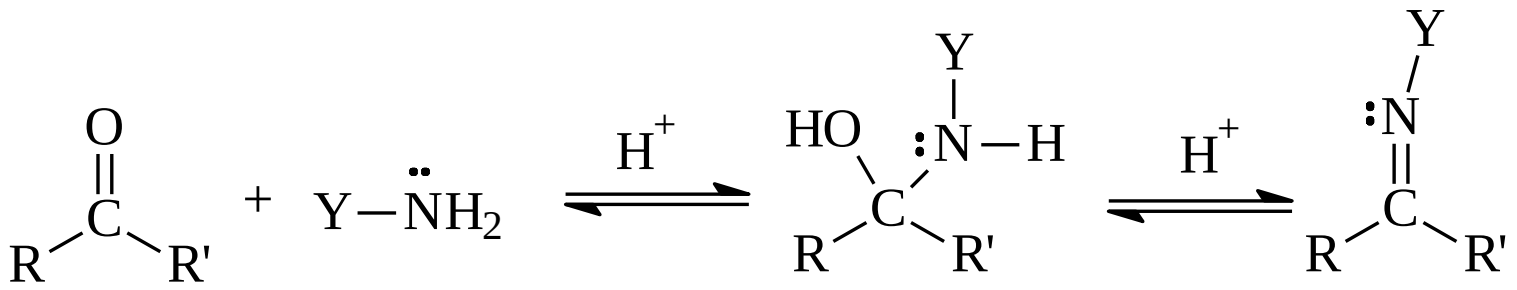
3. Reductive amination





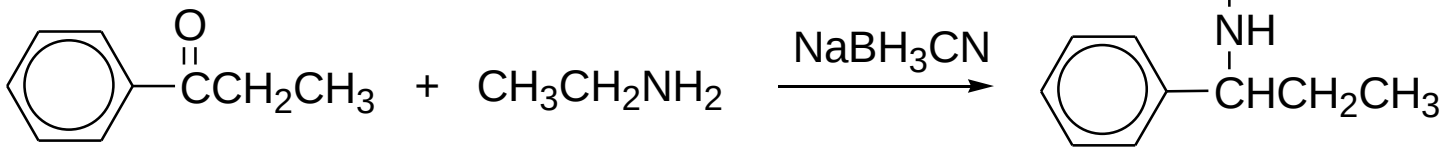
Reactions with C=O

- Ammonia and primary amines react with carbonyls to give an imine (Schiff base).



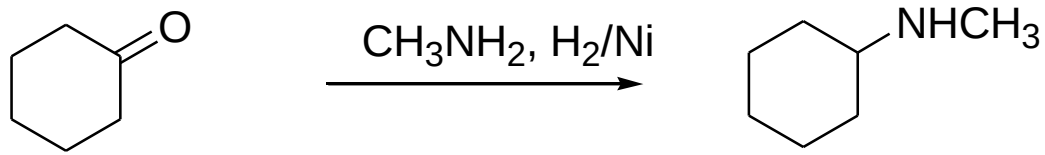
Y = H or alkyl gives an imine
Y = OH gives an oxime
Y = NHR gives a hydrazone

=>



propiophenone

1-(*N*-ethylamino)-1-phenylpropane



cyclohexanone

cyclohexylmethylamine

4. Conversion into amides

$R\text{-}NH_2$ + RCOCl → RCONHR + HCl

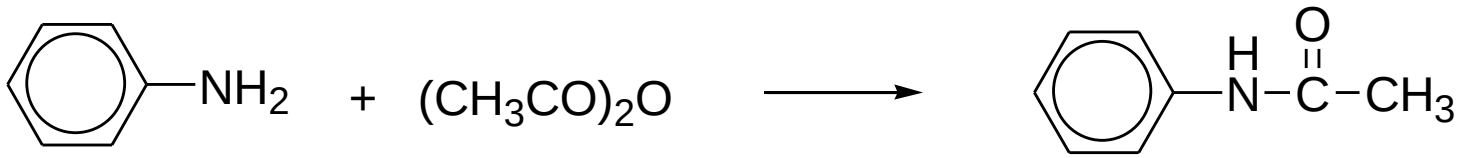
1^o *N*-subst. amide

R_2NH + RCOCl → $RCONR_2$ + HCl

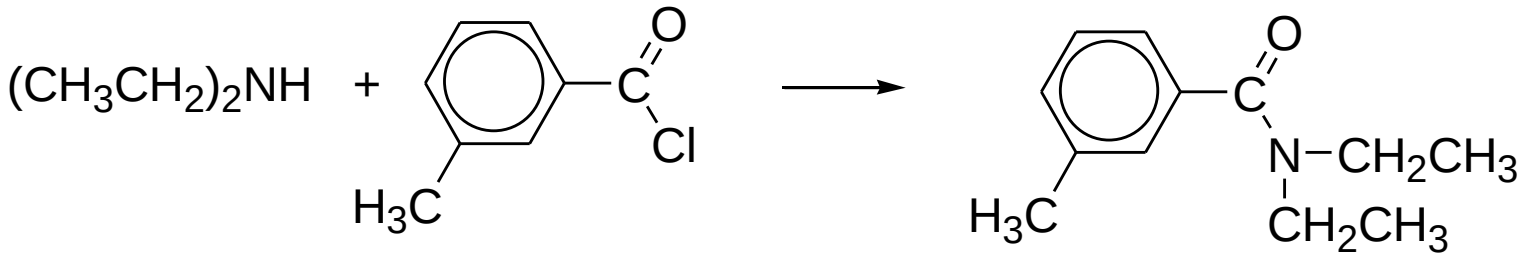
2^o *N*,*N*-disubst. amide

R_3N + RCOCl → NR

3^o

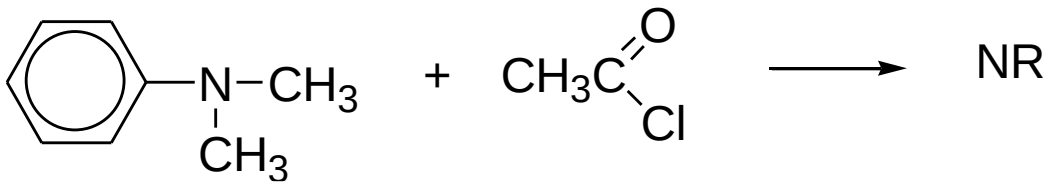


N-phenylacetamide



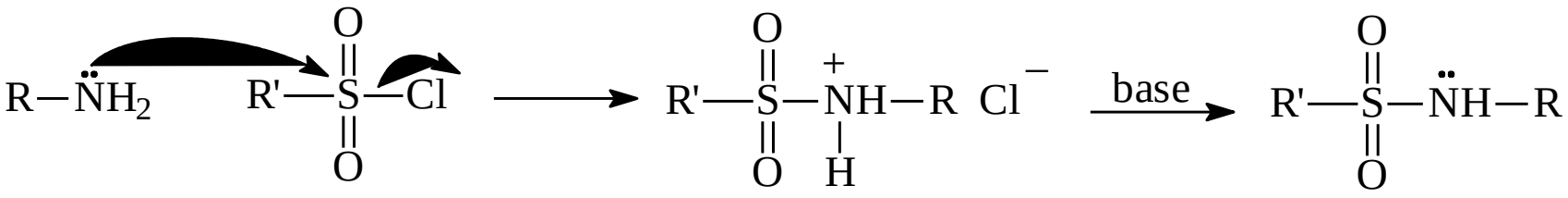
N.N-diethyl-*m*-toluamide

DEET

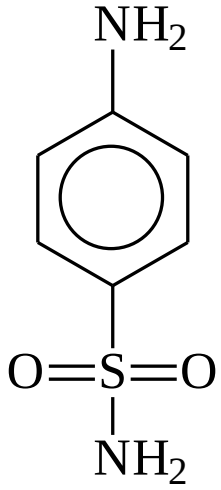


Formation of Sulfonamides

- Primary or secondary amines react with sulfonyl chloride.



- Sulfa drugs are sulfonamides that are antibacterial agents.



Conversion into sulfonamides

$R\text{-}NH_2 + ArSO_2Cl \rightarrow ArSO_2NHR + HCl$

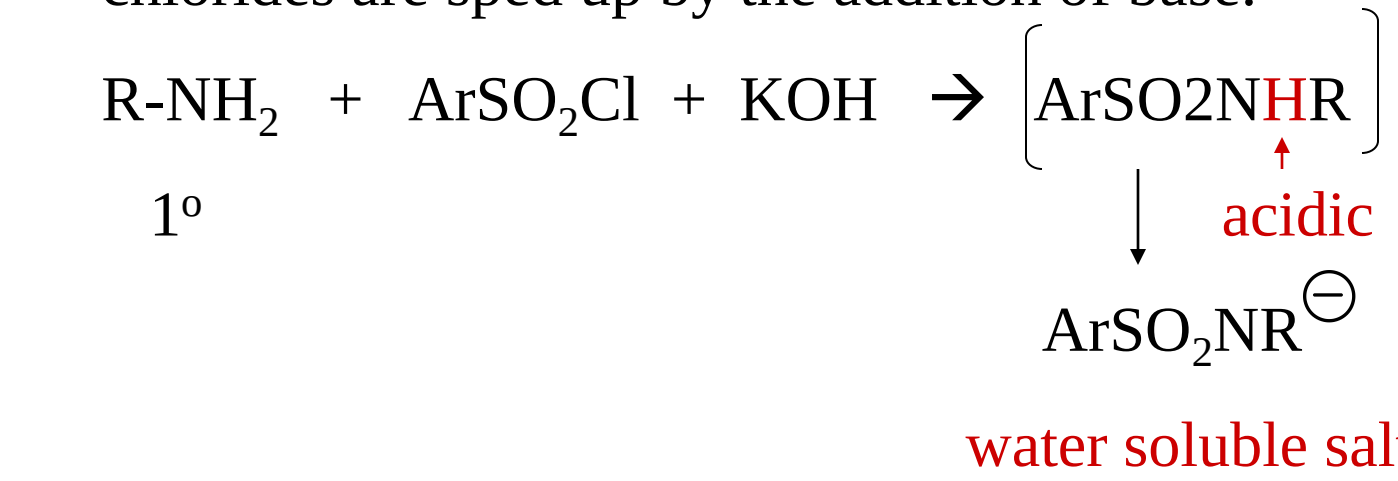
1^o *N*-subst.sulfonamide

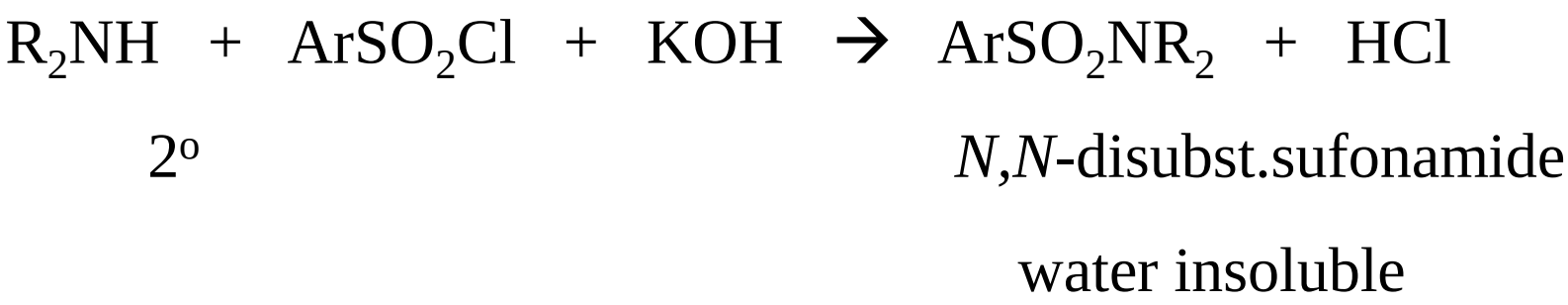
$R_2NH + ArSO_2Cl \rightarrow ArSO_2NR_2 + HCl$

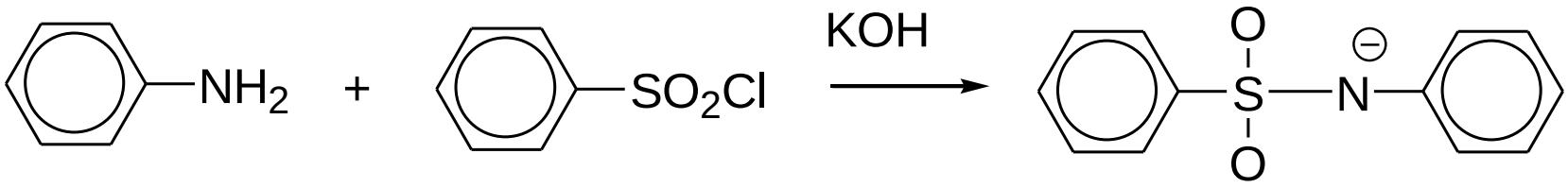
2^o *N*,*N*-disubst.sufonamide

$R_3N + ArSO_2Cl \rightarrow NR$

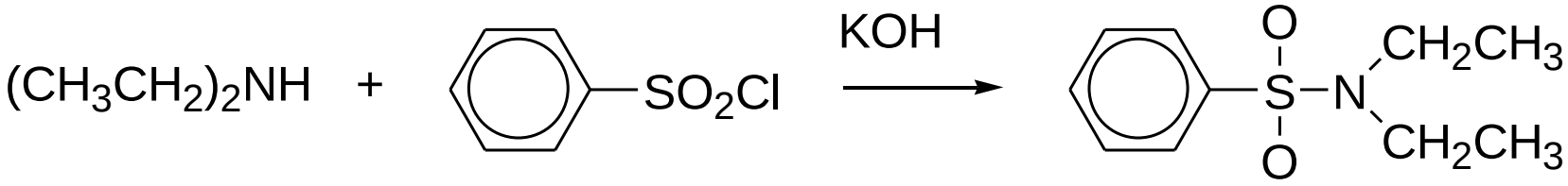
Schotten-Baumann technique: reactions of aromatic acid chlorides are sped up by the addition of base.



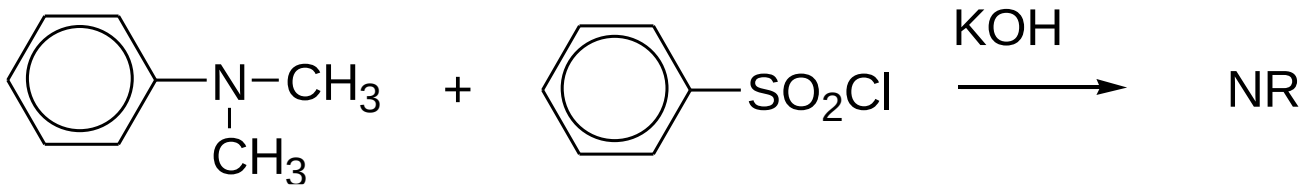


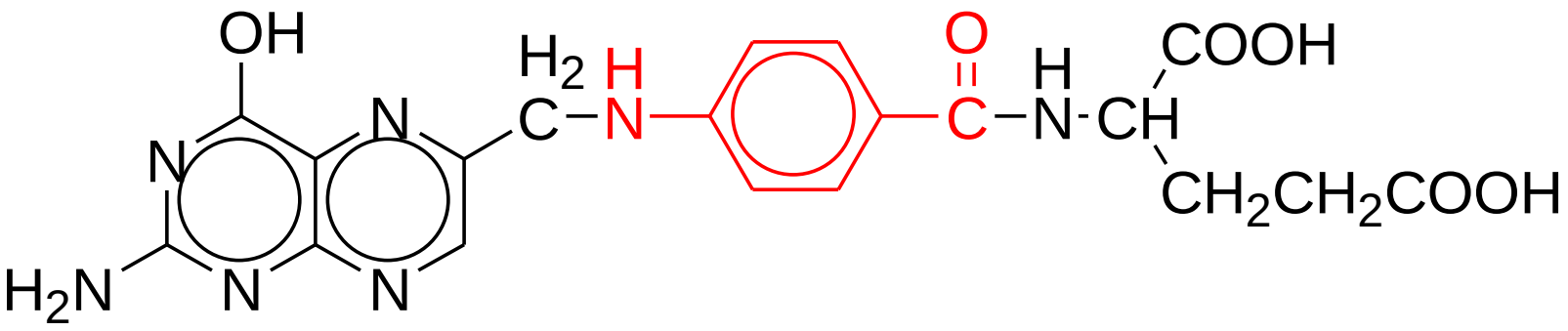


water sol.

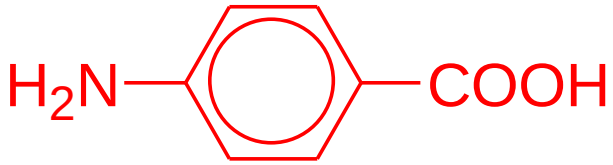


ppt

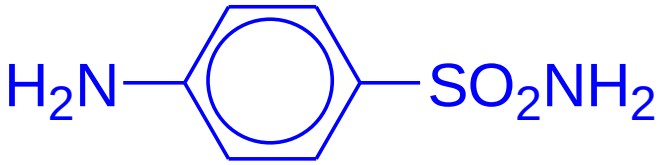




folic acid



p-aminobenzoic acd



sulfanilamide

5. Electrophilic Aromatic Substitution

$-NH_2$, $-NHR$, $-NR_2$ are powerful activating groups and *ortho/para* directors

a) nitration

b) sulfonation

c) halogenation

d) Friedel-Crafts alkylation

e) Friedel-Crafts acylation

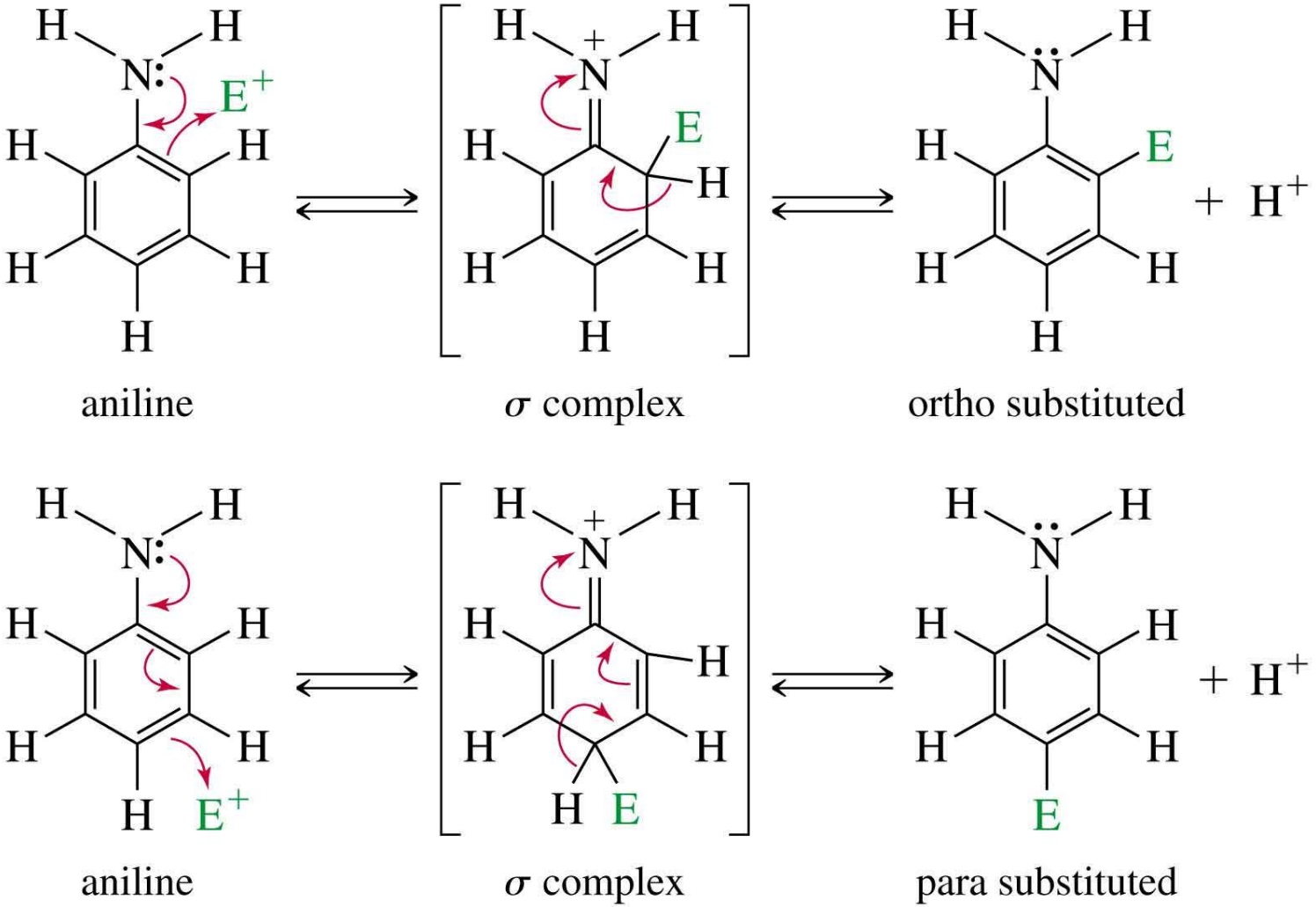
f) coupling with diazonium salts

g) nitrosation

Electrophilic Substitution of Aniline

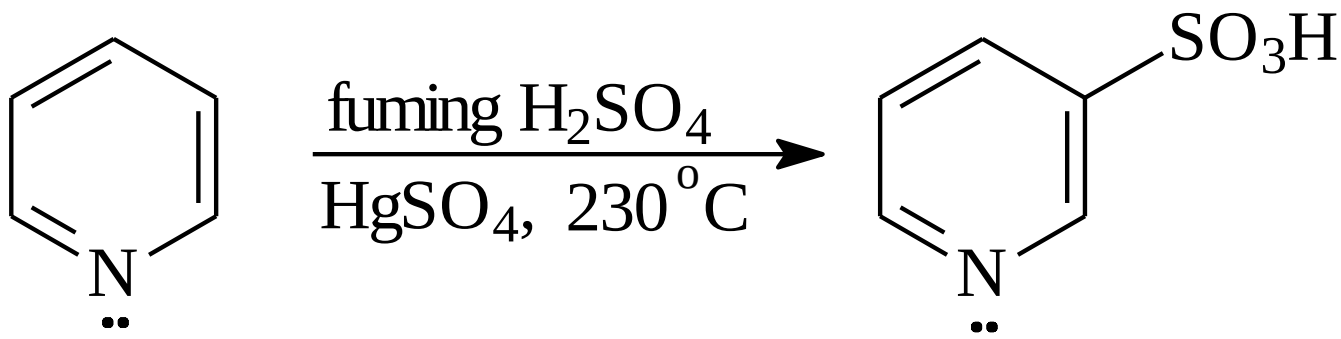
- -NH_2 is strong activator, *o*-,*p*-directing.
- May trisubstitute with excess reagent.
- H^+ changes -NH_2 to -NH_3^+, a *meta*-directing deactivator.
- Attempt to nitrate aniline may explode.

Aniline Substitution



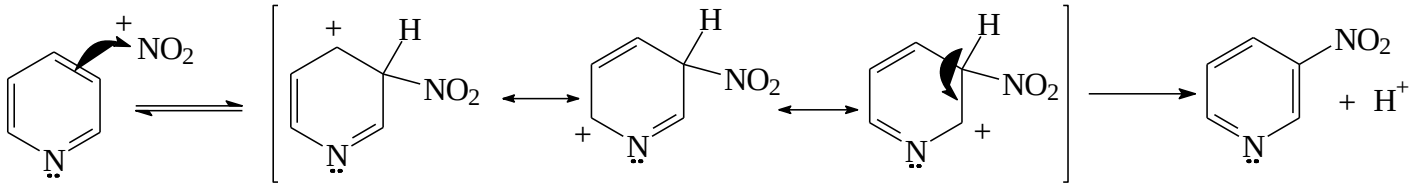
Electrophilic Substitution of Pyridine

- Strongly deactivated by electronegative N.
- Substitutes in the 3-position.
- Electrons on N react with electrophile.

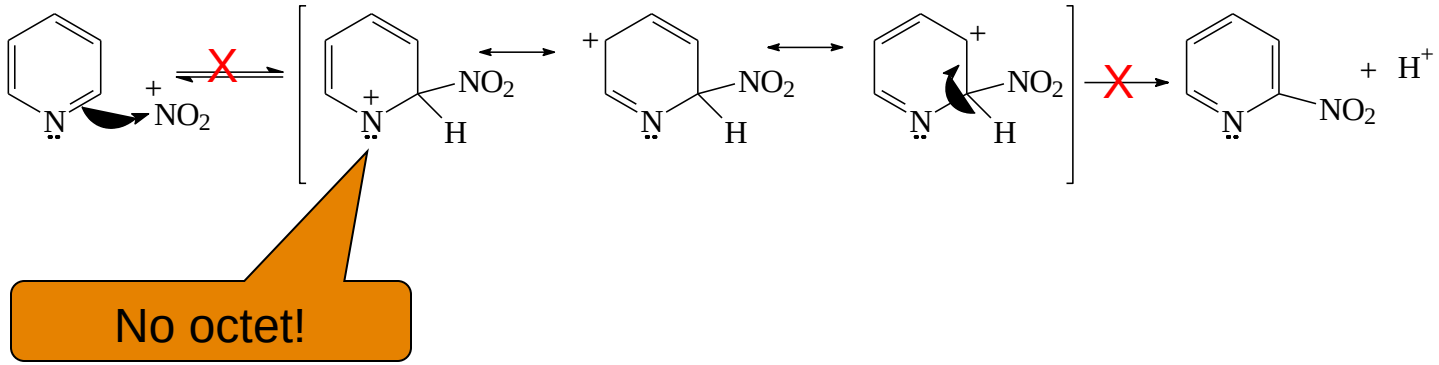


Mechanism for Electrophilic Substitution

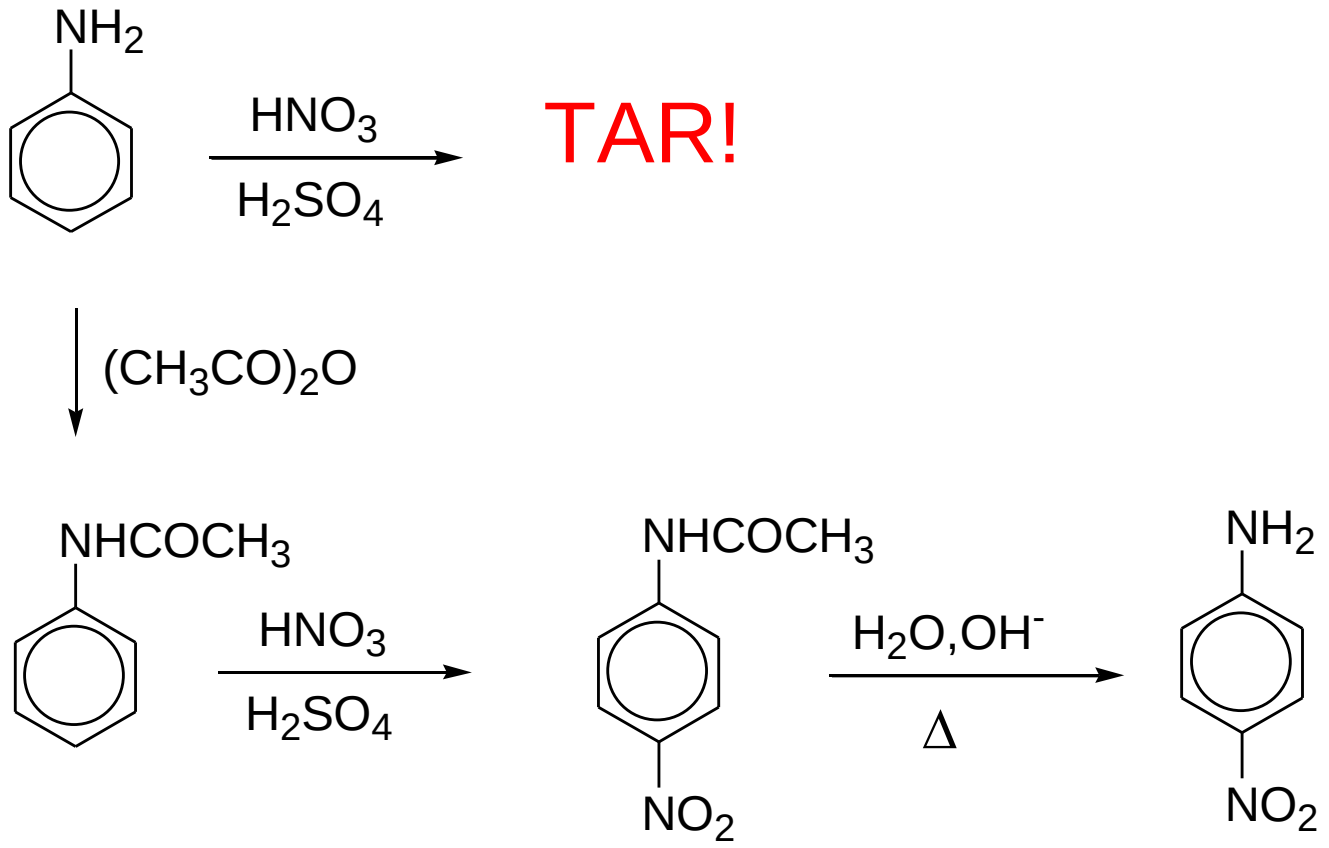
Attack at the 3-position (observed)



Attack at the 2-position (not observed)

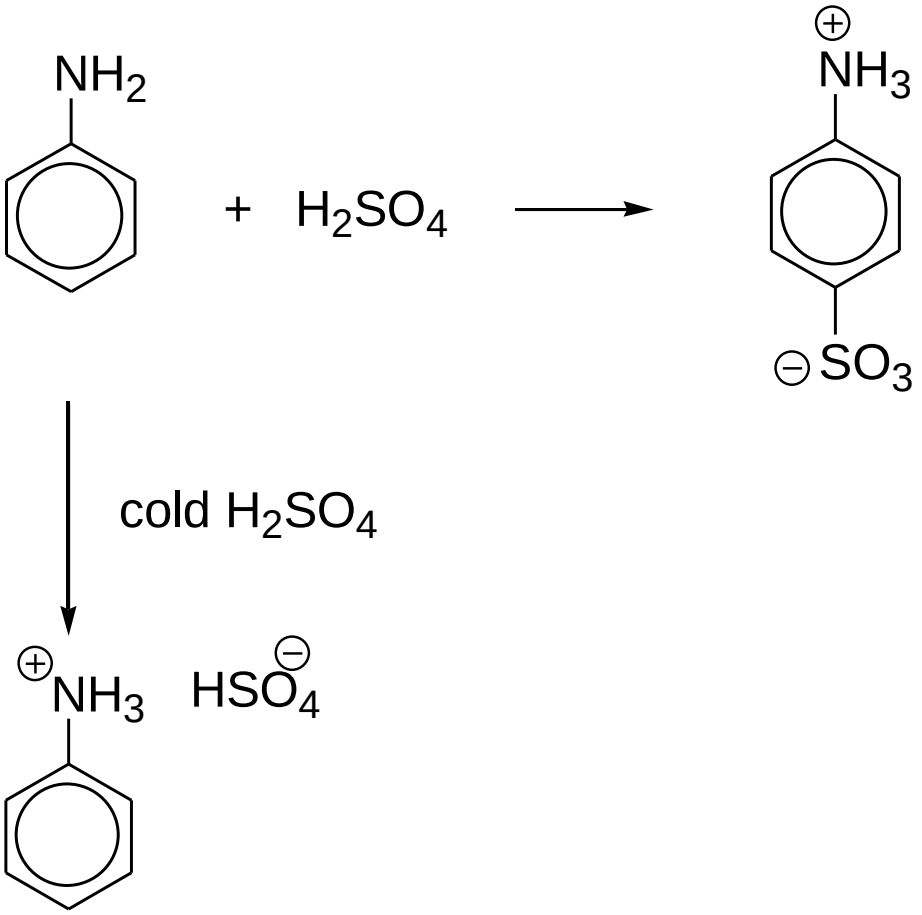


a) nitration

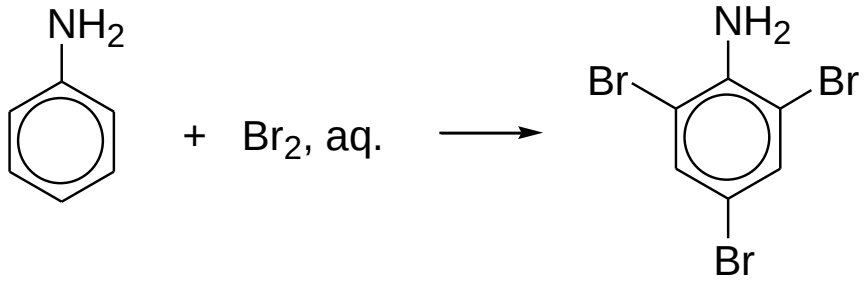


\+ *ortho-*

b) sulfonation

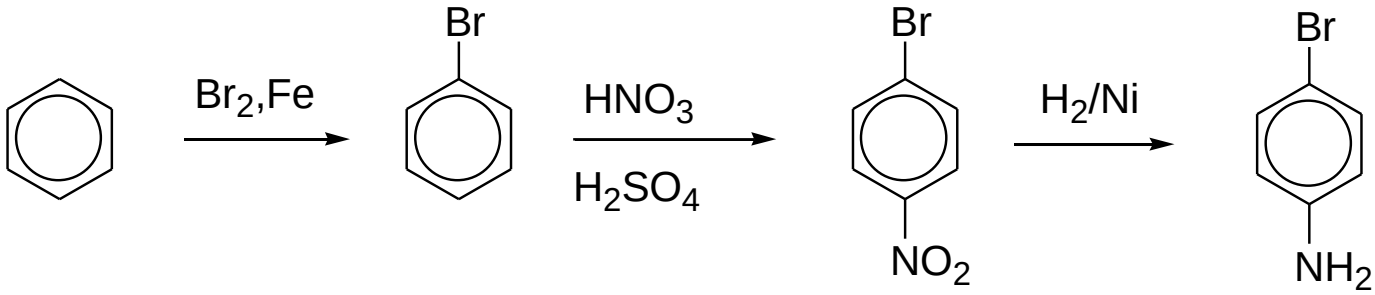


c) halogenation



polyhalogenation!

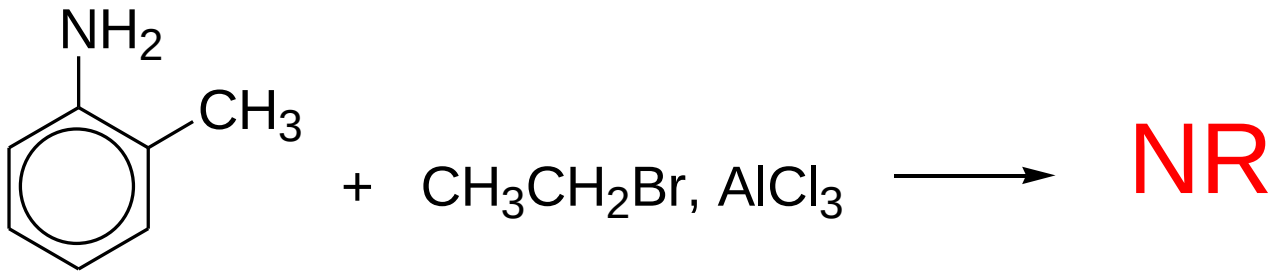
no catalyst needed
use polar solvent



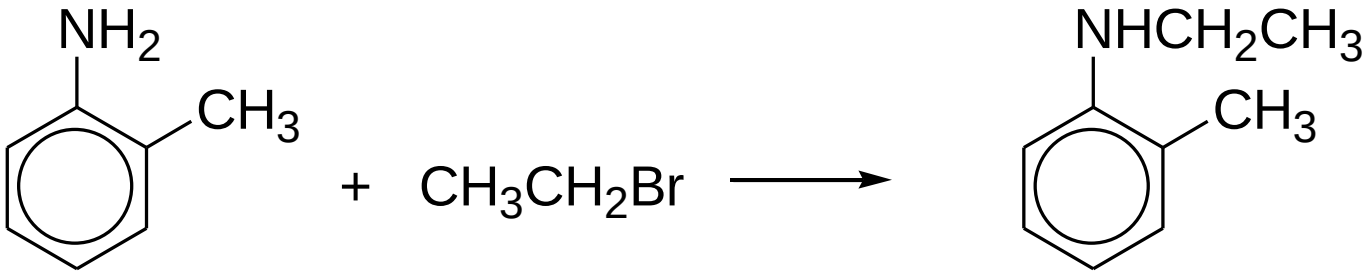
+ *ortho-*

e) Friedel-Crafts alkylation

NR with $-NH_2$, $-NHR$, $-NR_2$

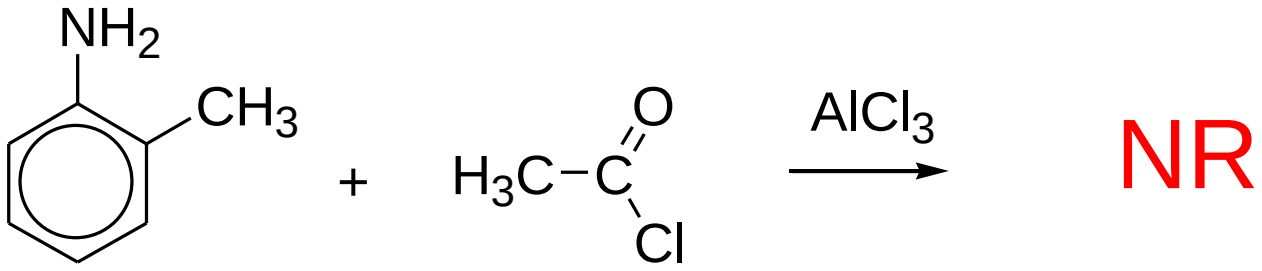


Do not confuse the above with the alkylation reaction:

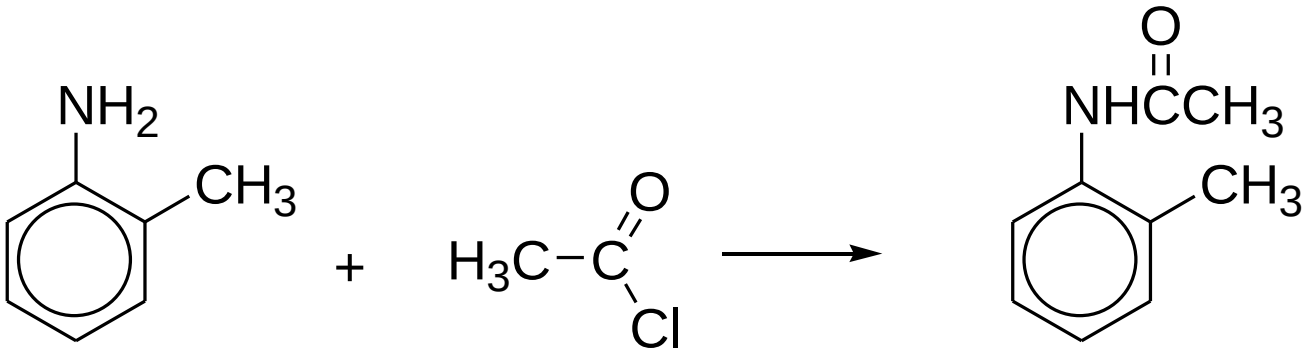


f) Friedel-Crafts acylation

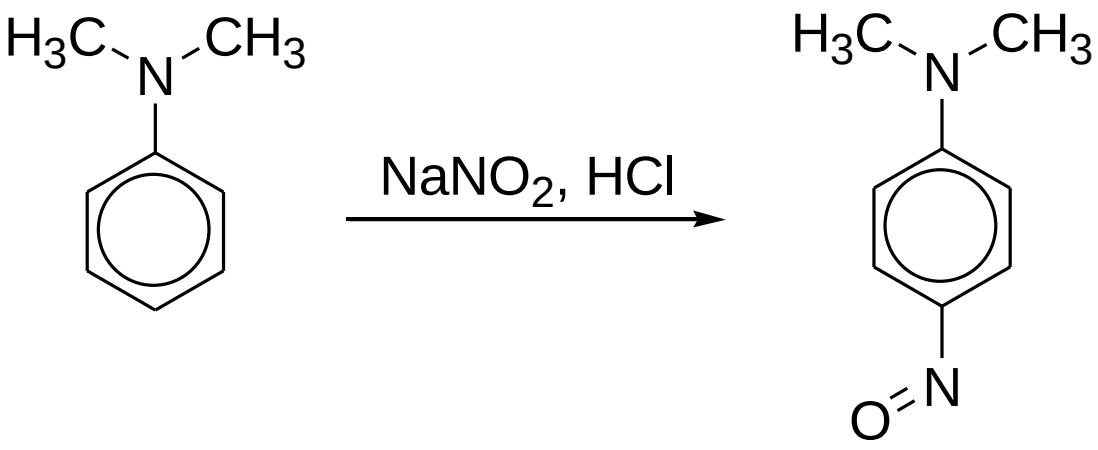
NR with $-NH_2$, $-NHR$, $-NR_2$



Do not confuse the above with the formation of amides:

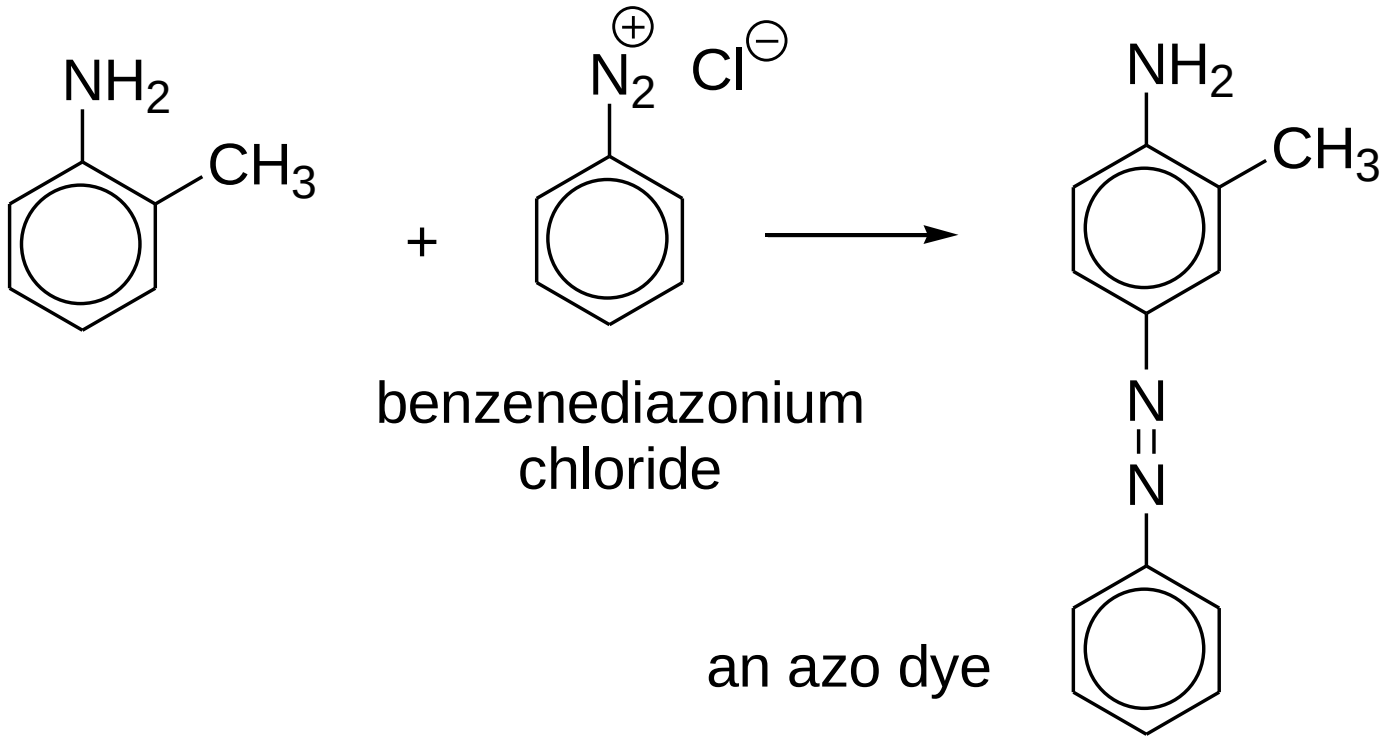


g) nitrosation



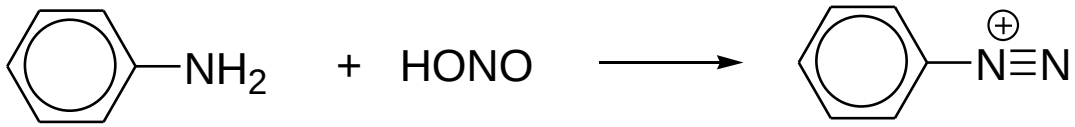
The ring is sufficiently activated towards EAS to react with the weak electrophile NO+

h) coupling with diazonium salts → azo dyes

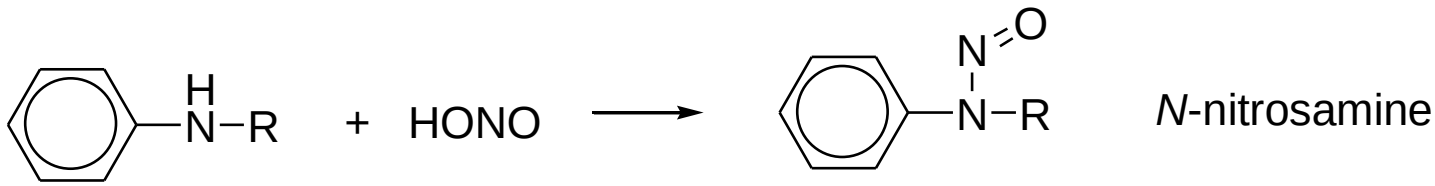


Reactions with nitrous acid

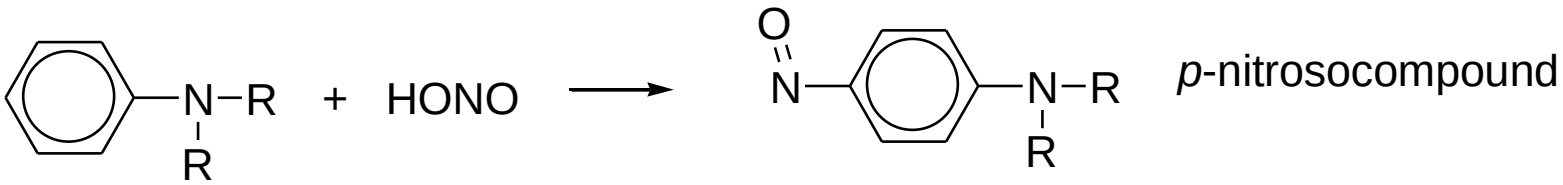
primary amines



secondary amines

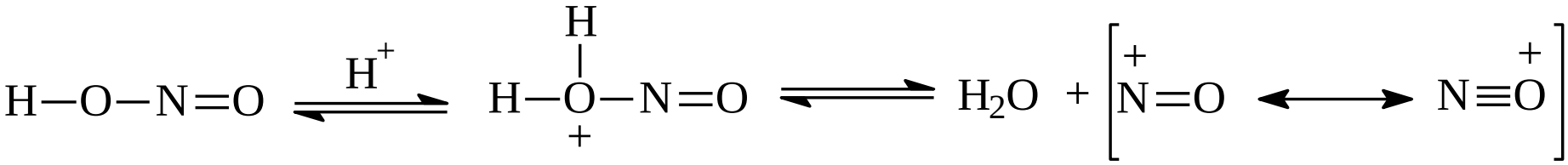


tertiary amines



Nitrous Acid Reagent

- Nitrous acid is produced *in situ* by mixing sodium nitrite with HCl.
- The nitrous acid is protonated, loses water to form the nitrosonium ion.

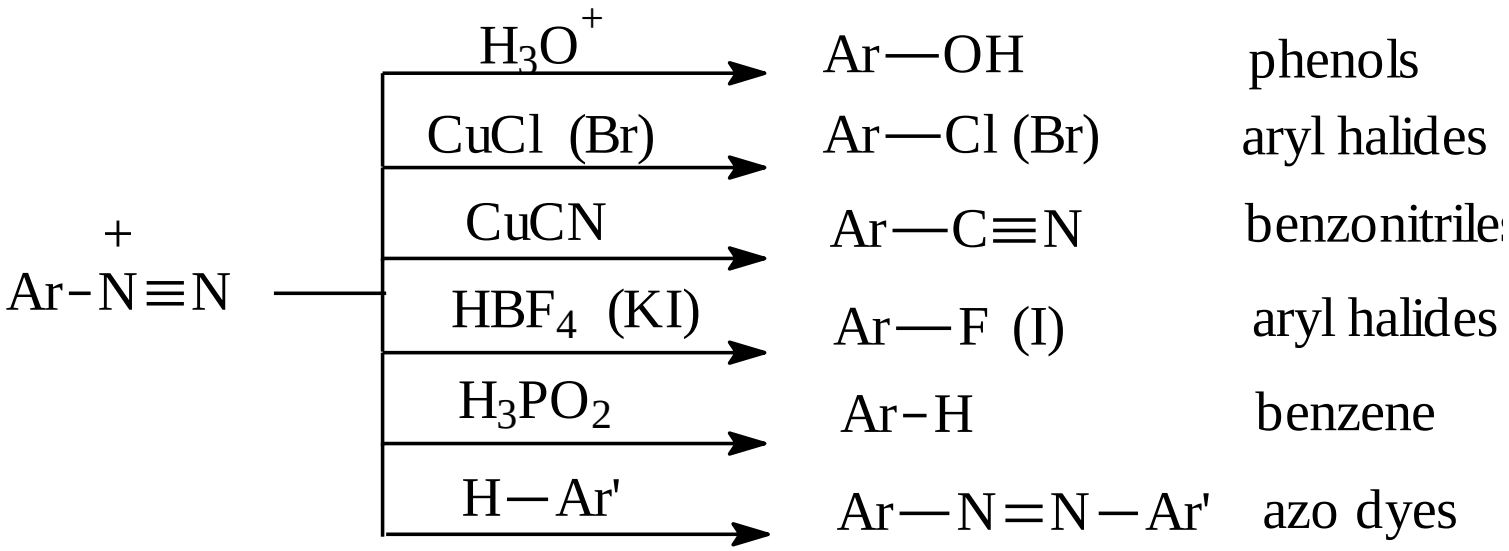


Reaction with Nitrous Acid

- 1° Amines form diazonium salts, $R\text{-}N^{+}\equiv N$.
- Alkyldiazonium salts are unstable, but arenediazonium salts are widely used for synthesis.
- 2° Amines form *N*-nitrosoamines, $R_2N\text{-}N{=}O$, found to cause cancer in laboratory animals.

Arenediazonium Salts

- Stable in solution at 0°–10°C.
- The -$^{+}$N≡N group is easily replaced by many different groups.
- Nitrogen gas, N_2, is a by-product.

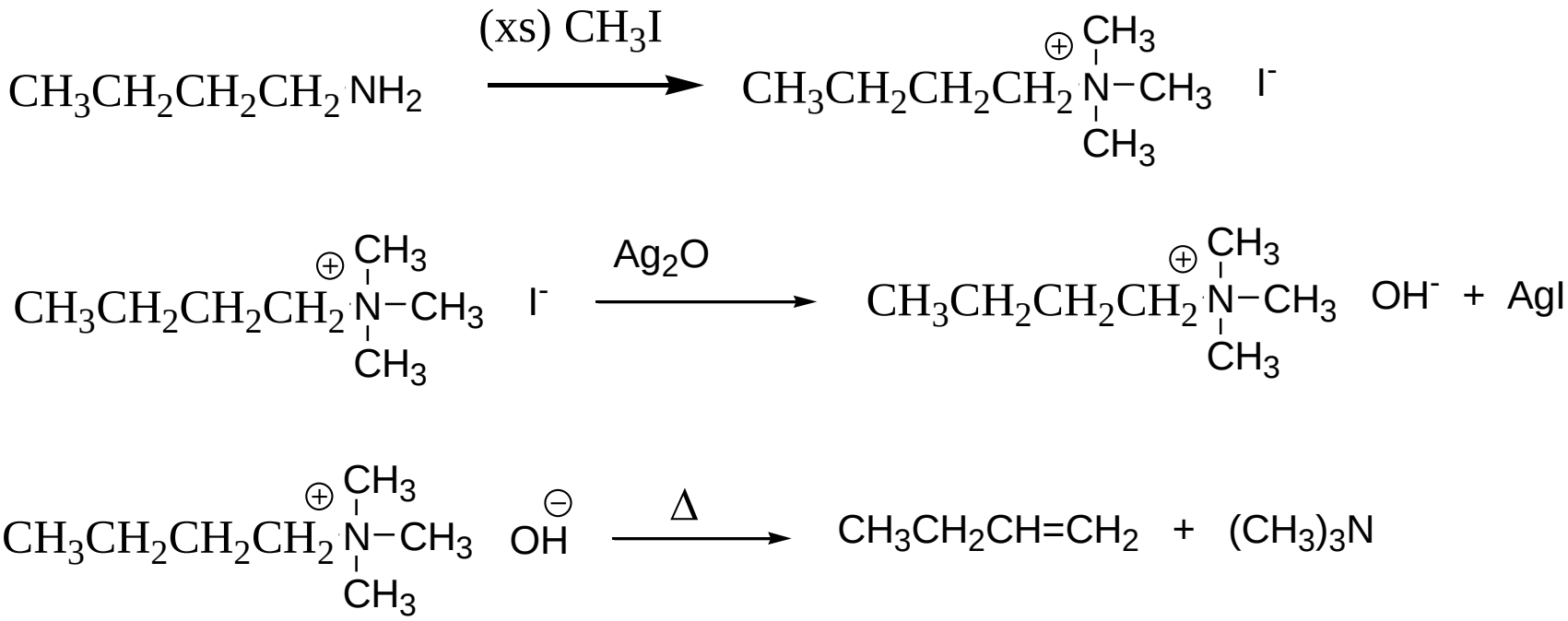


6. Hofmann elimination from quarternary hydroxides

step 1, exhaustive methylation → 4° salt

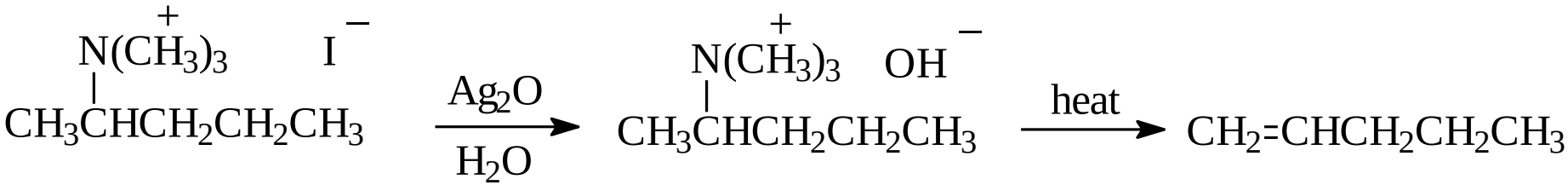
step 2, reaction with Ag_2O → 4° hydroxide + AgX

step 3, heat to eliminate → alkene(s) + R_3N



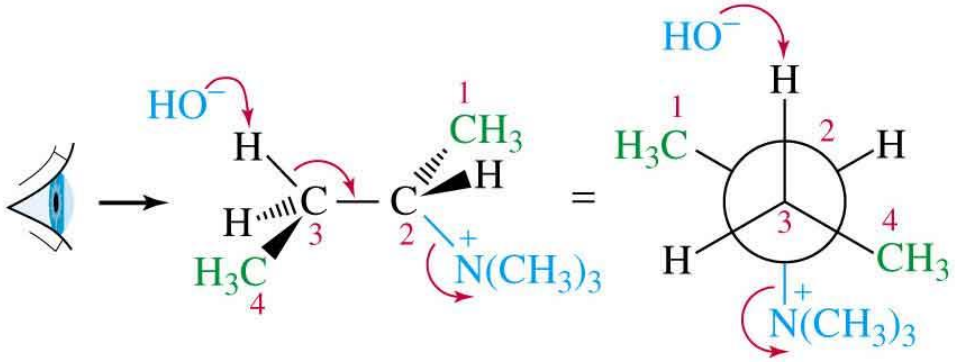
Hofmann Elimination

- A quaternary ammonium salt has a good leaving group - a neutral amine.
- Heating the hydroxide salt produces the least substituted alkene.



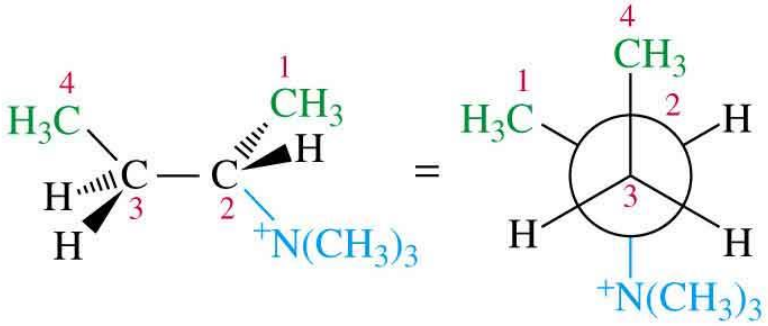
E2 Mechanism

Looking along the C2—C3 bond



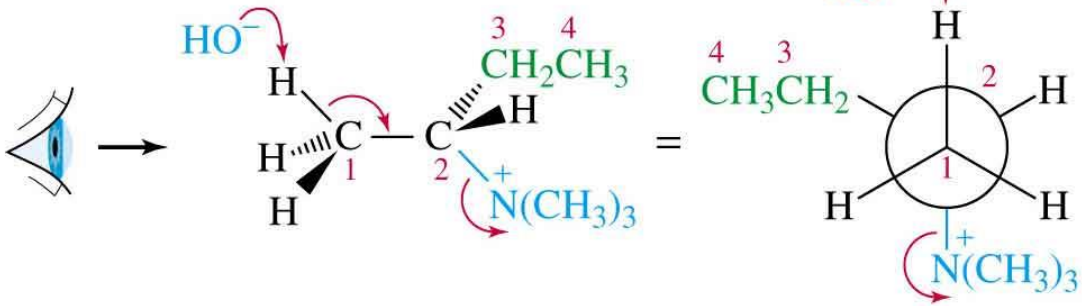
needed for E2 (less stable)

The most stable C2—C3 conformation



more stable (E2 is impossible in this conformation)

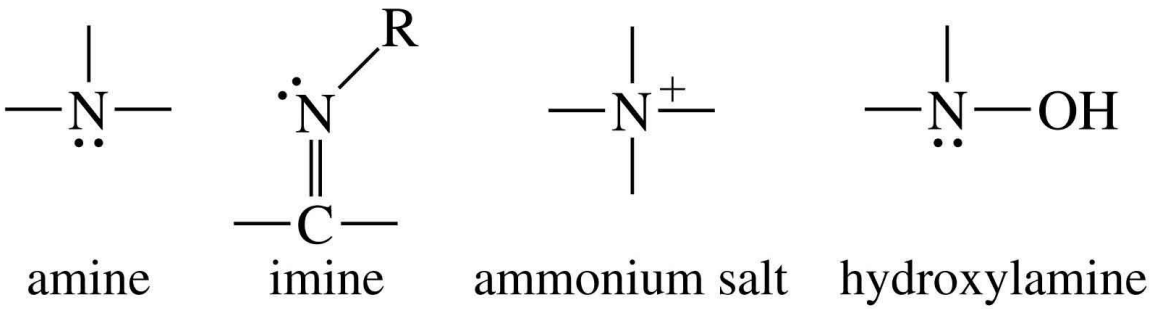
Looking along the C1—C2 bond

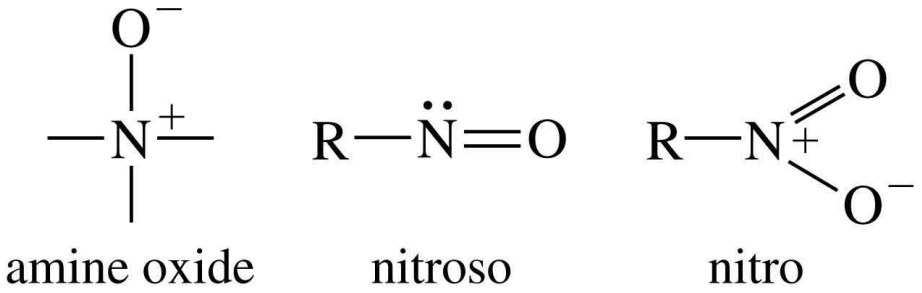


(any of the three staggered conformations is suitable for the E2)

7. Oxidation of Amines

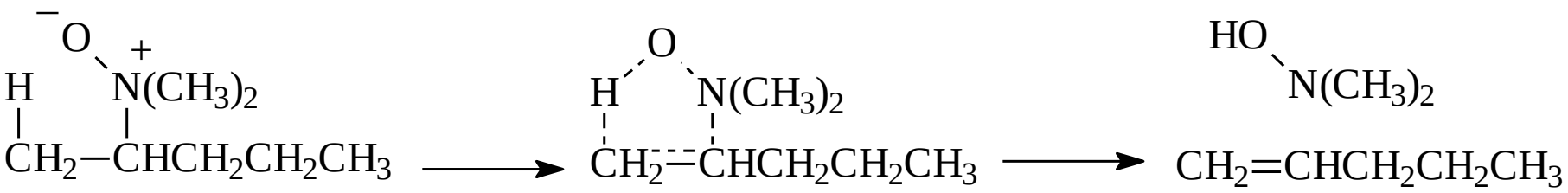
- Amines are easily oxidized, even in air.
- Common oxidizing agents: H_2O_2 , MCPBA.
- 2° Amines oxidize to hydroxylamine (-NOH)
- 3° Amines oxidize to amine oxide ($-N^+-O^-$)





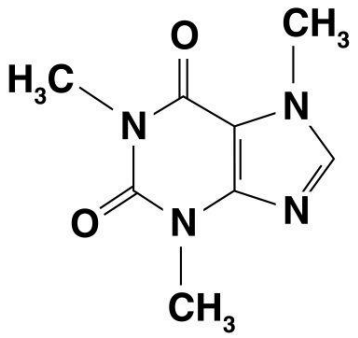
8. Cope Elimination

Amine oxides undergo elimination to form the least substituted alkene under milder conditions than the Hofmann reaction.

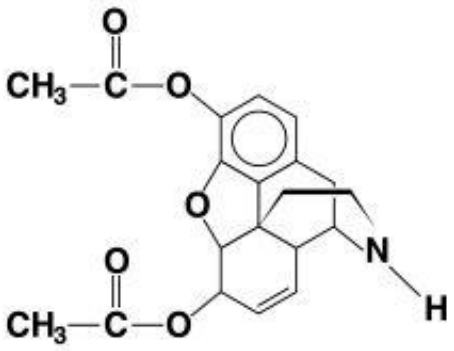


Alkaloids

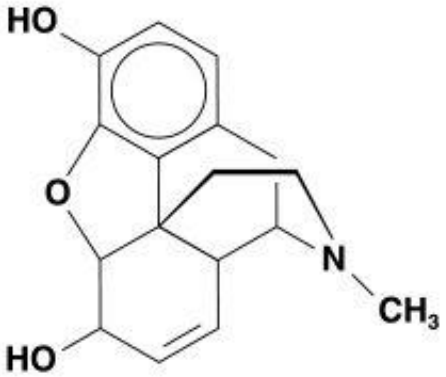
- Alkaloids are naturally occurring compounds that contain nitrogen and have basic properties
- They have a wide variety of structures, including simple amines, aromatic amines, and heterocyclic amines
- Some examples of alkaloids are caffeine and the opiates



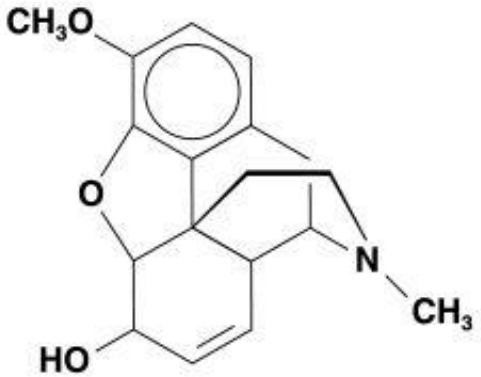
Caffeine



Heroin



Morphine

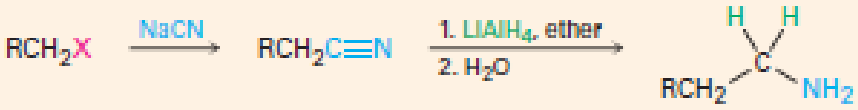


Codeine

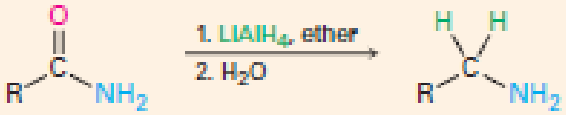
Summary of Reactions

1. Synthesis of amines (Section 24.6)

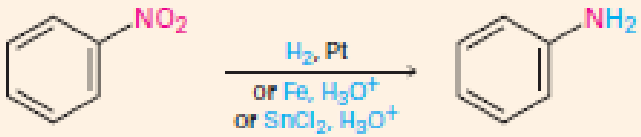
(a) Reduction of nitriles



(b) Reduction of amides



(c) Reduction of nitrobenzenes

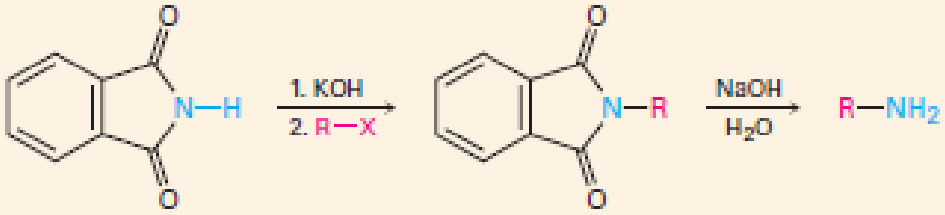


(d) S_N2 Alkylation of alkyl halides

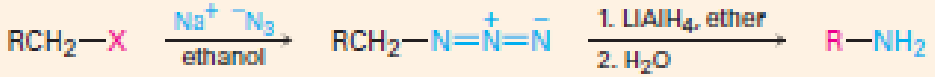
Ammonia	$\ddot{N}H_3$	+ R—X	⟶	$R\overset{+}{N}H_3\ X^-$	NaOH ⟶	RNH_2	Primary
Primary	$R\ddot{N}H_2$	+ R—X	⟶	$R_2\overset{+}{N}H_2\ X^-$	NaOH ⟶	R_2NH	Secondary
Secondary	$R_2\ddot{N}H$	+ R—X	⟶	$R_3\overset{+}{N}H\ X^-$	NaOH ⟶	R_3N	Tertiary
Tertiary	$R_3\ddot{N}$	+ R—X	⟶	$R_4\overset{+}{N}\ X^-$			Quaternary ammonium

(continued)

(e) Gabriel amine synthesis

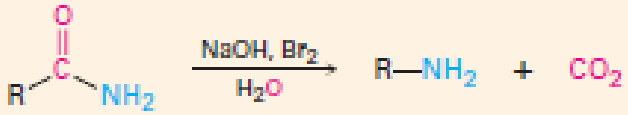


(f) Reduction of azides

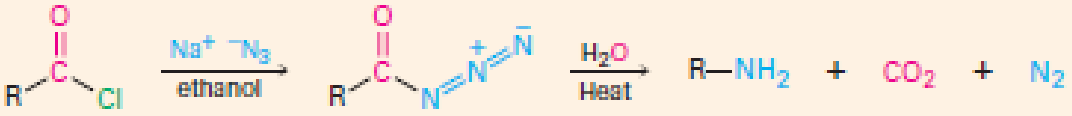


(g) Reductive amination of aldehydes/ketones

(h) Hofmann rearrangement of amides



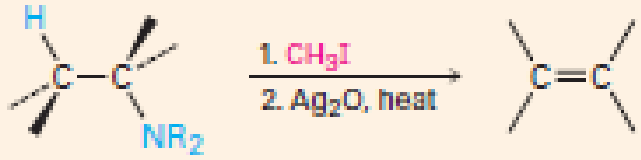
(i) Curtius rearrangement of acyl azides



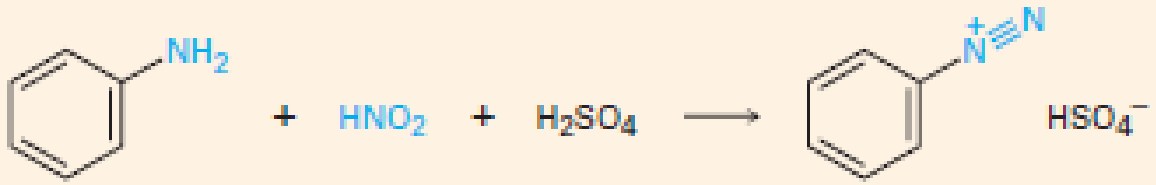
2. Reactions of amines

(a) Alkylation with alkyl halides; see reaction 1(d)

(b) Hofmann elimination (Section 24.7)

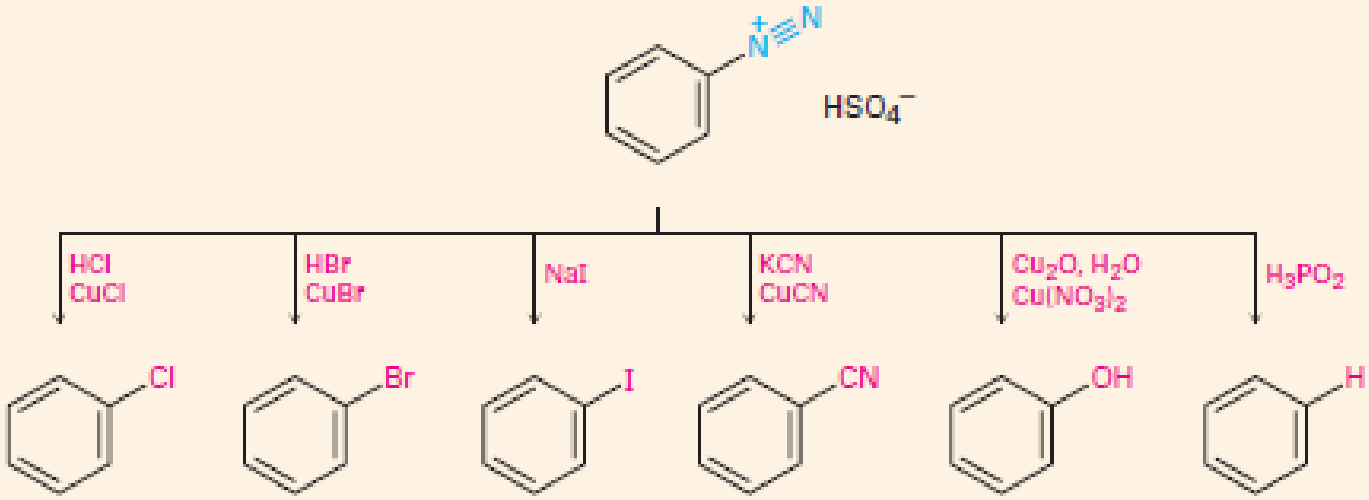


(c) Diazotization (Section 24.8)

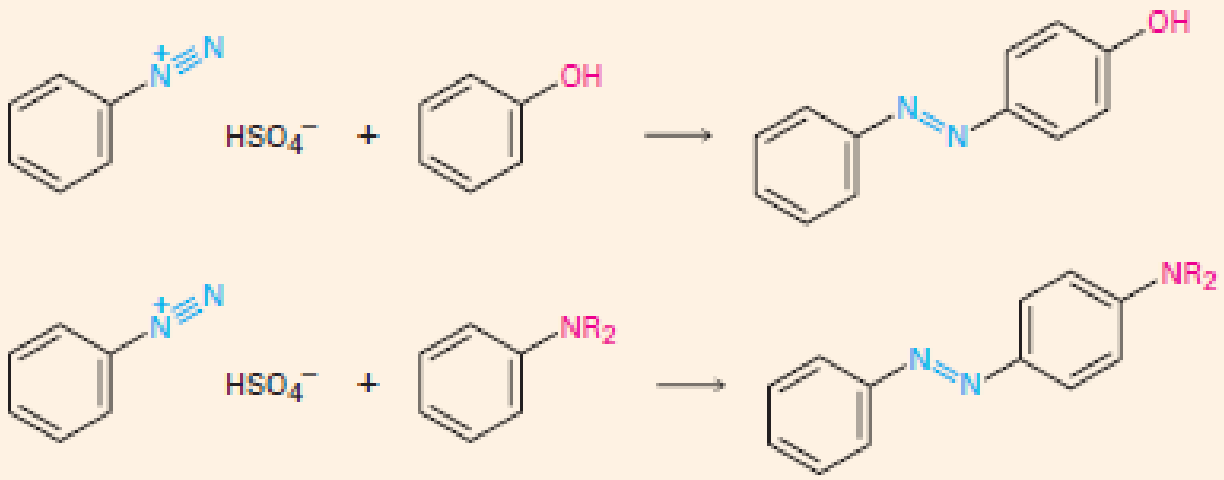


3. Reactions of arenediazonium salts (Section 24.8)

(a) Nucleophilic substitutions



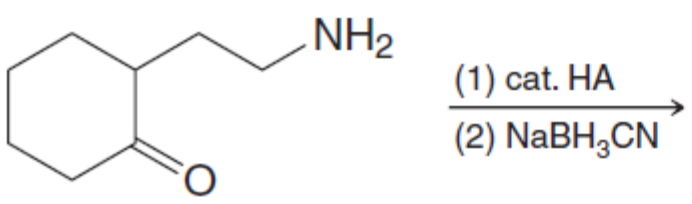
(b) Diazonium coupling



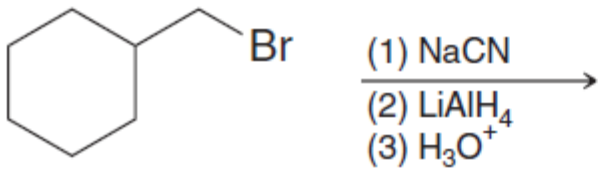
Exercise

1. Provide the major organic product from each of the following reactions

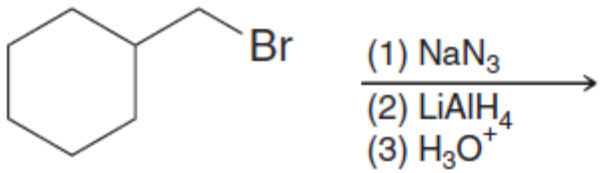
(a)



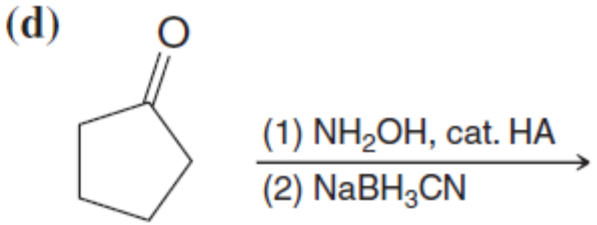
(b)



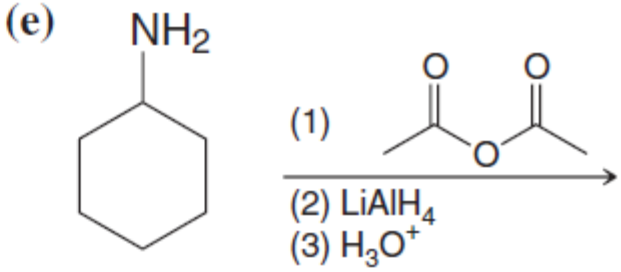
(c)



(d)

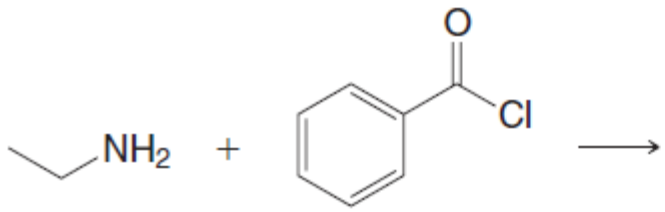


(e)

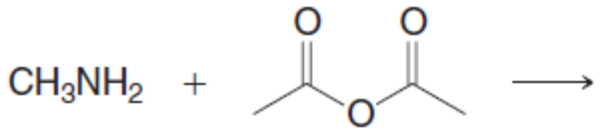


2. Give structures for the products of each of the following reactions:

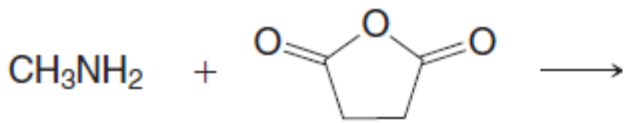
(a)



(b)

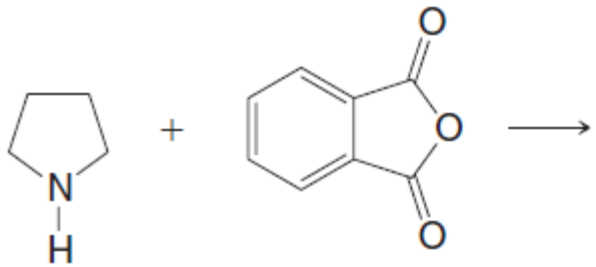


(c)

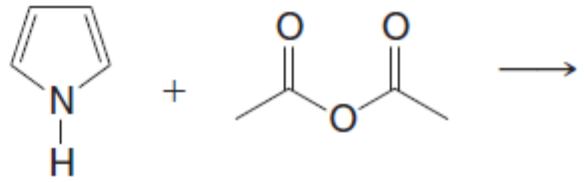


(d) Product of (c) $\xrightarrow{\text{heat}}$

(e)



(f)

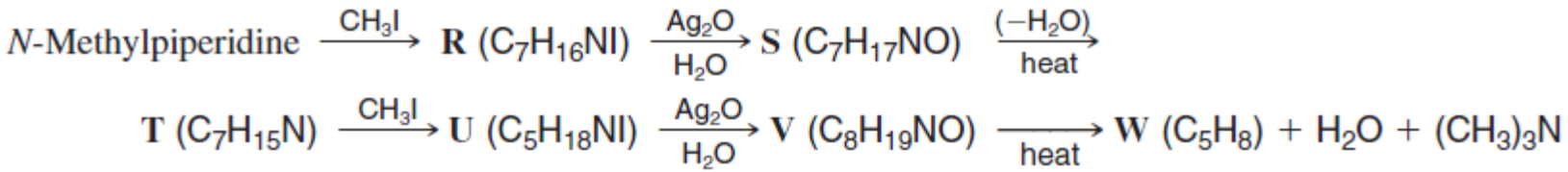


(g) Aniline + propanoyl chloride $\longrightarrow$

(h) Tetraethylammonium hydroxide $\xrightarrow{\text{heat}}$

(i) *p*-Toluidine + Br_2 (excess) $\xrightarrow[H_2O]{}$

3. Give structures for compounds **R–W:**



What products are formed when *N*-ethylaniline ($C_6H_5NHCH_2CH_3$) is treated with each reagent?

a. HCl
b. CH_3COOH
c. $(CH_3)_2C=O$
d. CH_2O, $NaBH_3CN$
e. CH_3I (excess)
f. CH_3I (excess), followed by Ag_2O and Δ
g. CH_3CH_2COCl
h. The product in (g), then HNO_3, H_2SO_4
i. The product in (g), then [1] $LiAlH_4$; [2] H_2O
j. The product in (h), then H_2, Pd-C

Draw the products formed when *p*-methylaniline (*p*-$CH_3C_6H_4NH_2$) is treated with each reagent.

a. HCl
b. CH_3COCl
c. $(CH_3CO)_2O$
d. excess CH_3I
e. $(CH_3)_2C=O$
f. CH_3COCl, $AlCl_3$
g. CH_3COOH
h. $NaNO_2$, HCl
i. Step (b), then CH_3COCl, $AlCl_3$
j. CH_3CHO, $NaBH_3CN$

How would you convert $CH_3CH_2CH_2CH_2NH_2$ into each compound?

a. $CH_3CH_2CH_2CH_2NHCOC_6H_5$
b. $CH_3CH_2CH_2CH_2N=C(CH_2CH_3)_2$
c. $CH_3CH_2CH=CH_2$
d. $CH_3CH_2CH_2CH_2NHCH_2C_6H_5$
e. $CH_3CH_2CH_2CH_2NHCH_2CH_3$
f. $[CH_3CH_2CH_2CH_2N(CH_3)_3]^+I^-$