Amines

Amines

Amines

bases, substituted ammonia
biologically significant: amino acids,
DNA, RNA bases, alkaloids

General formula

- Primary amine $R\text{-}NH_2$
- Secondary amine $R_2\text{-}NH$
- Tertiary amine $R_3\text{-}N$
- Quarternary $R_4\text{-}N^+ X^-$

Properties of amines

Nitrogen is very electronegative.

Results in

- N-H bond being very polar.
- Hydrogen bonding being possible.
- High boiling points.
- Amines being organic bases.

Nomenclature

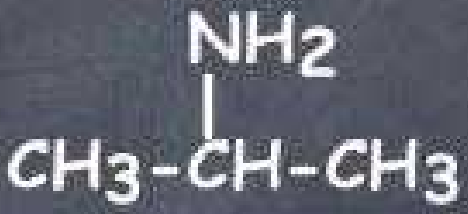
When a primary amine present with another functional group: Use same approach as with any branch or substituent.

4-amino-2-bromo-1-butanol

Examples

$CH_3CH_2CH_2NH_2$

1-aminopropane



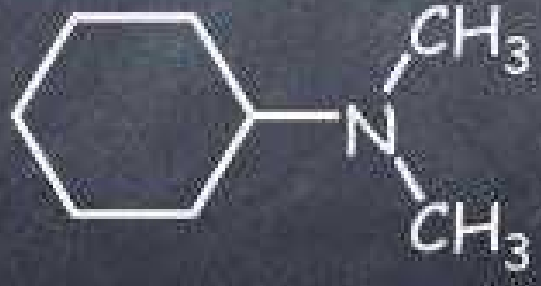
2-aminopropane

2-aminohexane

Examples

$CH_3CH_2CH_2$-NH-CH_3

N-methyl-1-aminopropane



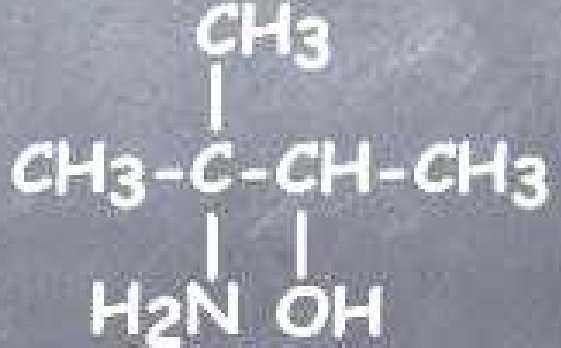
N,N-dimethylaminocyclohexane

Examples

$(CH_3CH_2)_2NCH_3$

N-ethyl-N-methyl-1-aminoethane

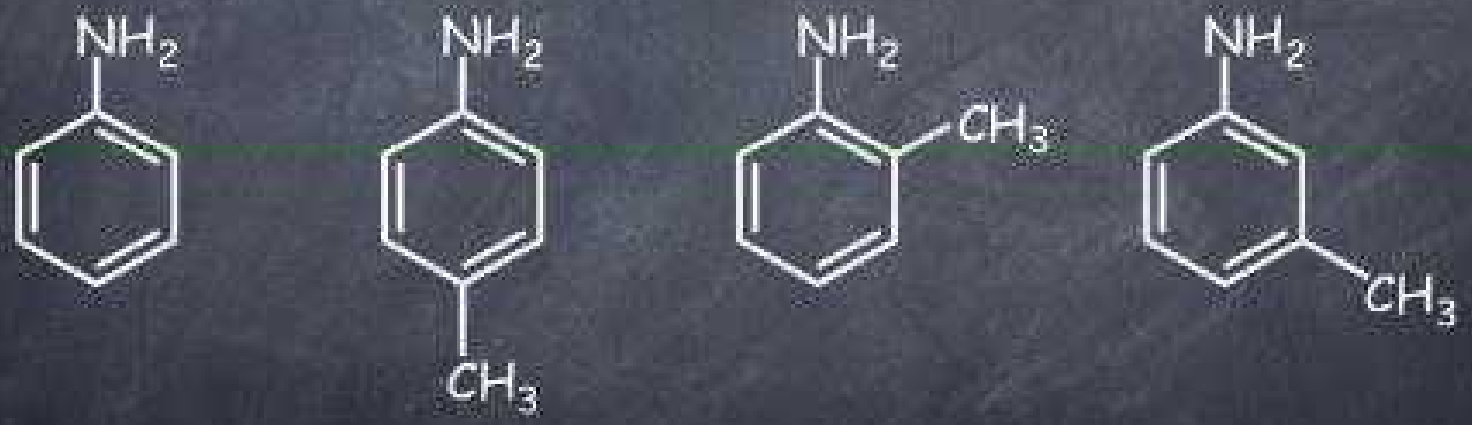
1,2-diaminopropane



3-amino-3-methyl-2-butanol

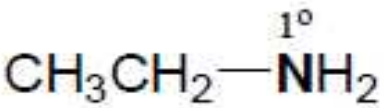
Nomenclature

Many aromatic amines have special names that have been accepted as IUPAC names.

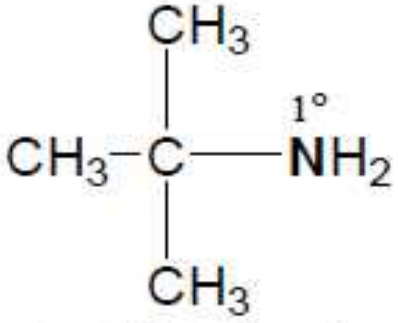


aniline p-toluidine o-toluidine m-toluidine

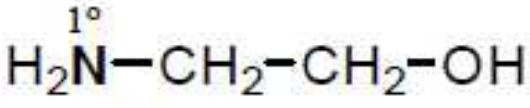
Λ



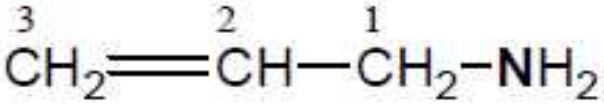
Ethyl amine



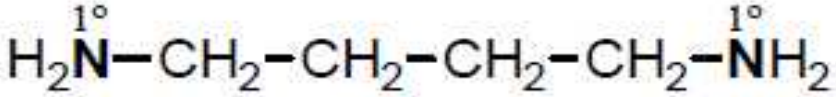
tert-Butyl amine



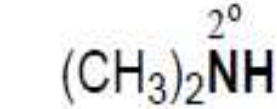
Ethanol amine
[2-Amino ethanol]



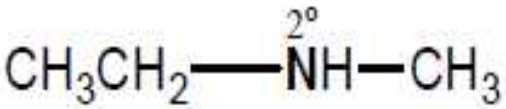
2-Propenamine
[Allyl amine]



1,4-Butanediamine

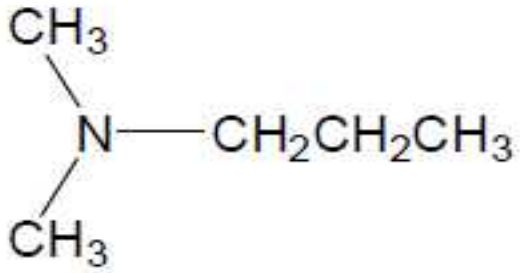


Dimethyl amine

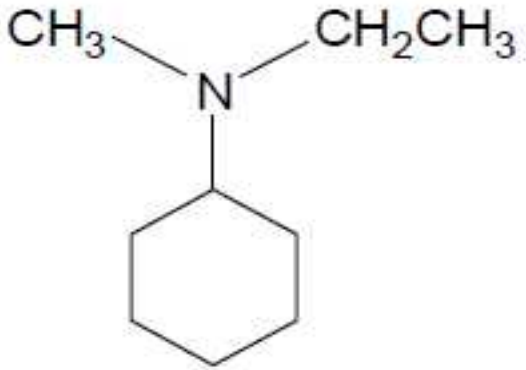


Ethyl methyl amine

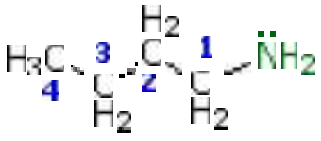
Diisopropyl amine



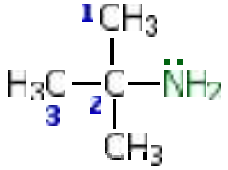
N,N-Dimethyl propyl amine



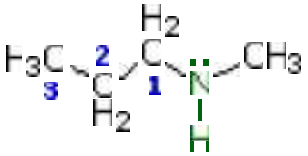
N-Ethyl-*N*-methyl cyclohexane amine



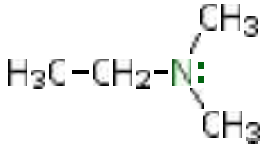
a 1° amine



a 1° amine

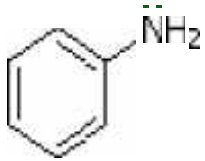


a 2° amine

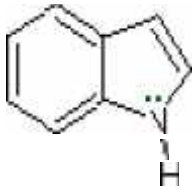


a 3° amine

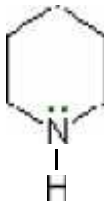
IUPAC name	1-aminobutane	2-amino-2-methylpropane	1-methylaminopropane	dimethylaminoethane
CA name	butanamine	2-methyl-2-propanamine	N-methylpropanamine	N,N-dimethylethanamine
Common name	n-butylamine	tert-butylamine	methylpropylamine	ethyldimethylamine



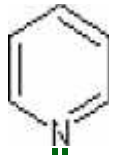
aniline



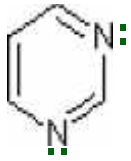
indole



piperidine



pyridine



pyrmicine

pyrrolidine

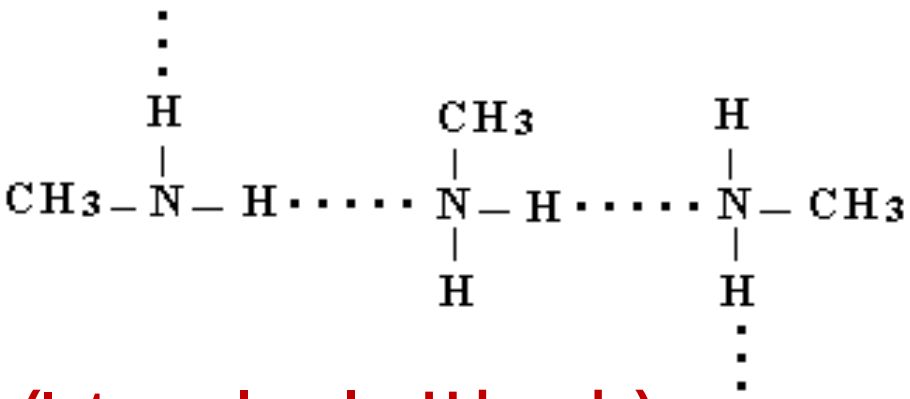
pyrrole

imidazole

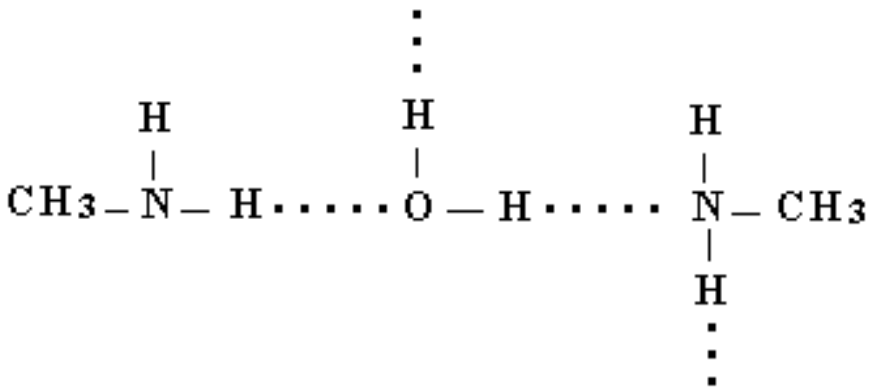
Physical Properties of Amines

- Amines are moderately polar. For this reason the low formula weight amines are readily soluble in water due to the formation of hydrogen bonds with water.

- They have higher boiling points than non-polar compounds of the same molecular weight, because of the formation of intermolecular hydrogen bonds, except for tertiary amines.



(Intermolecular H bonds)



(H bonds with water)

	$CH_3-CH_2-CH_2-CH_2-NH_2$	$(C_2H_5)_2NH$	$CH_3-CH_2-N(CH_3)_2$	$CH_3-CH_2-CH(CH_3)-CH_3$
boiling point :	77.8°C	56.3°C	37.5°C	27.8°C

	$(CH_3CH_2)_2NH$	$(CH_3CH_2)_2O$	$CH_3(CH_2)_3CH_3$
boiling point :	56.3°C	37.5°C	36°C

	$CH_3CH_2CH_2CH_2OH$	$CH_3CH_2CH_2CH_2NH_2$
boiling point :	117.3°C	77.8°C

Physical Properties of Amines

TABLE 11.1 THE BOILING POINTS OF SOME SIMPLE AMINES

Name	Formula	bp, °C
ammonia	NH_3	33.4
methylamine	CH_3NH_2	6.3
dimethylamine	$(CH_3)_2NH$	7.4
trimethylamine	$(CH_3)_3N$	2.9
ethylamine	$CH_3CH_2NH_2$	16.6
propylamine	$CH_3CH_2CH_2NH_2$	48.7
butylamine	$CH_3CH_2CH_2CH_2NH_2$	77.8
aniline	$C_6H_5NH_2$	184.0

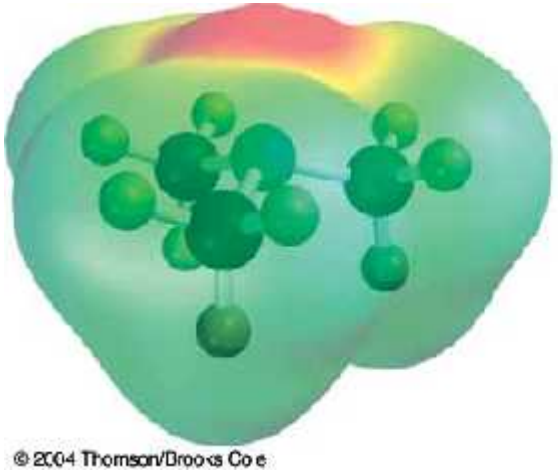
TABLE 11.2 A COMPARISON OF ALKANE, AMINE, AND ALCOHOL BOILING POINTS*

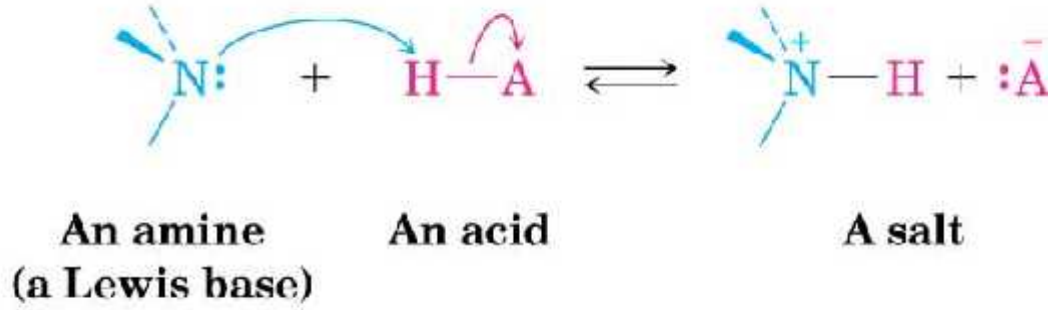
alkane	CH_3CH_3 (30) bp −88.6°C	$CH_3CH_2CH_3$ (44) bp −42.1°C
amine	CH_3NH_2 (31) bp 6.3°C	$CH_3CH_2NH_2$ (45) bp +16.6°C
alcohol	CH_3OH (32) bp +65.0°C	CH_3CH_2OH (46) bp +78.5°C

*Molecular weights (in g/mol) are given in parentheses.

Basicity of Amines

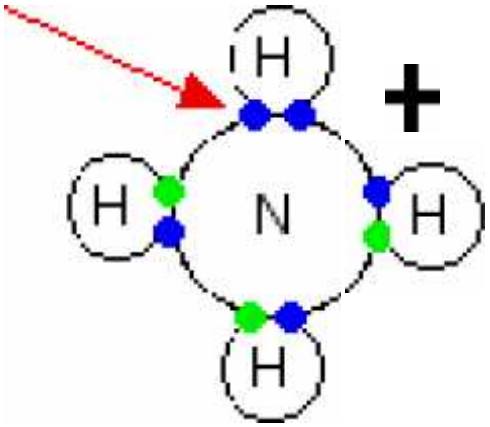
- The lone pair of electrons on nitrogen makes amines basic and nucleophilic
- They react with acids to form acid–base salts and they react with electrophiles
- Amines are stronger bases than alcohols, ethers, or water





Amines as Bases

Incoming hydrogen ion attaches to this lone pair . . .



. . . and forms an ammonium ion.

$$NH_{3(aq)} + H_3O^+_{(aq)} \longrightarrow NH_4^+{}_{(aq)} + H_2O_{(l)}$$

$$NH_{3(g)} + HCl_{(g)} \longrightarrow NH_4^+{}_{(s)} + Cl^-_{(s)}$$

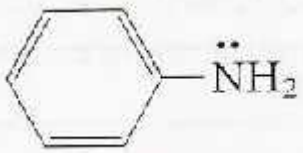
High pKa → weaker acid and stronger conjugate base.

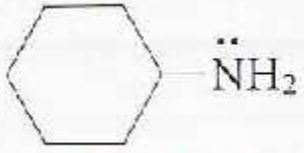
TABLE 11.3 BASICITIES OF SOME COMMON AMINES, EXPRESSED AS pK_a OF THE CORRESPONDING AMMONIUM IONS

	Formula		
Name	**Amine**	**Ammonium ion**	**pK_a of the ammonium ion**
ammonia	$\ddot{N}H_3$	$\overset{+}{N}H_4$	9.30
methylamine	$CH_3\ddot{N}H_2$	$CH_3\overset{+}{N}H_3$	10.64
dimethylamine	$(CH_3)_2\ddot{N}H$	$(CH_3)_2\overset{+}{N}H_2$	10.71
trimethylamine	$(CH_3)_3\ddot{N}$	$(CH_3)_3\overset{+}{N}H$	9.77
ethylamine	$CH_3CH_2\ddot{N}H_2$	$CH_3CH_2\overset{+}{N}H_3$	10.67
propylamine	$CH_3CH_2CH_2\ddot{N}H_2$	$CH_3CH_2CH_2\overset{+}{N}H_3$	10.58
aniline	$C_6H_5\ddot{N}H_2$	$C_6H_5\overset{+}{N}H_3$	4.62
N-methylaniline	$C_6H_5\ddot{N}HCH_3$	$C_6H_5\overset{+}{N}H_2(CH_3)$	4.85
N,N-dimethylaniline	$C_6H_5\ddot{N}(CH_3)_2$	$C_6H_5\overset{+}{N}H(CH_3)_2$	5.04
p-chloroaniline	$p\text{-}ClC_6H_4\ddot{N}H_2$	$p\text{-}ClC_6H_4\overset{+}{N}H_3$	3.98

Aliphatic amines are stronger bases than aromatic amines because of the resonance in aromatic amines

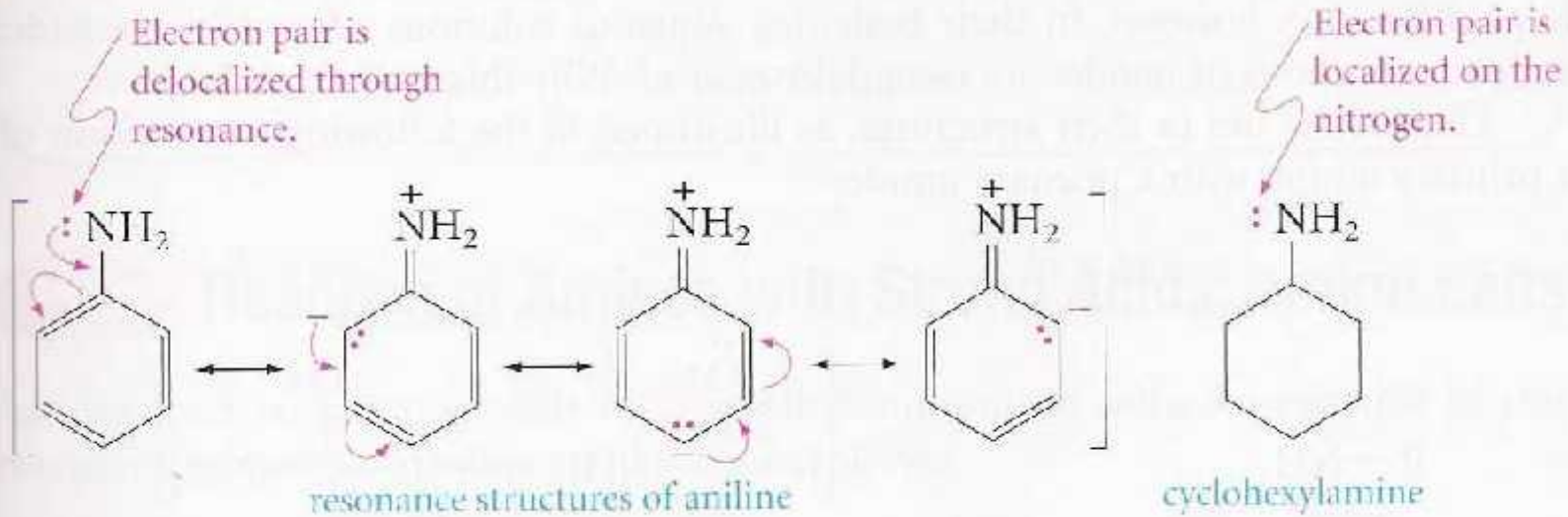
Aromatic amines are much weaker bases than aliphatic amines or ammonia. For example, aniline is less basic than cyclohexylamine by nearly a million times.





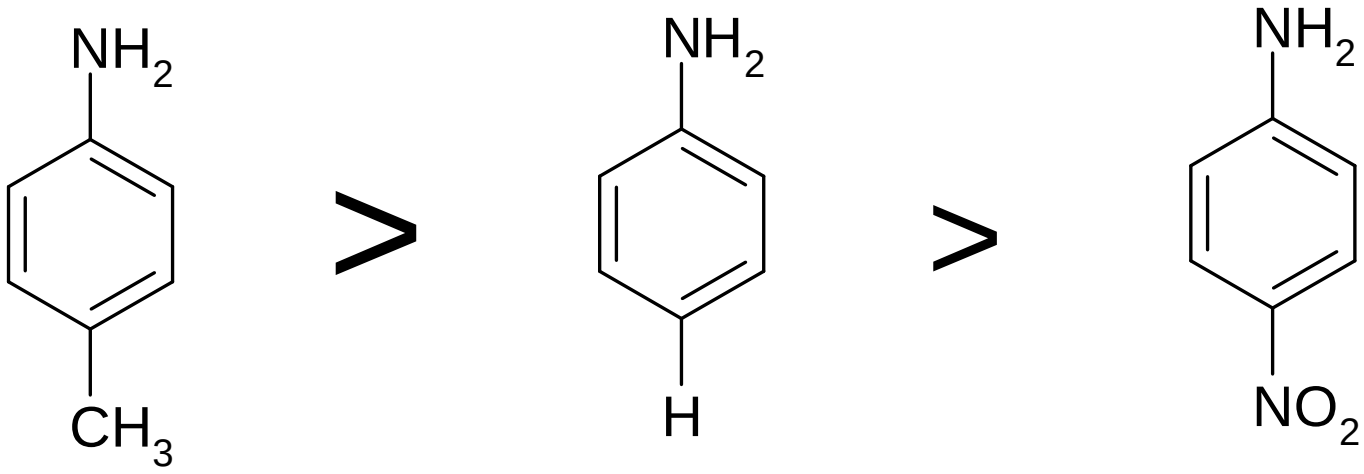
	aniline	cyclohexylamine
pK_a of ammonium ion	4.62	9.8

The reason for this huge difference is the resonance delocalization of the unshared electron pair that is possible in aniline, but not in cyclohexylamine (Figure 11.2).



Electron-donating groups increase the basicity of amines,
Electron-withdrawing groups decrease the basicity of amines

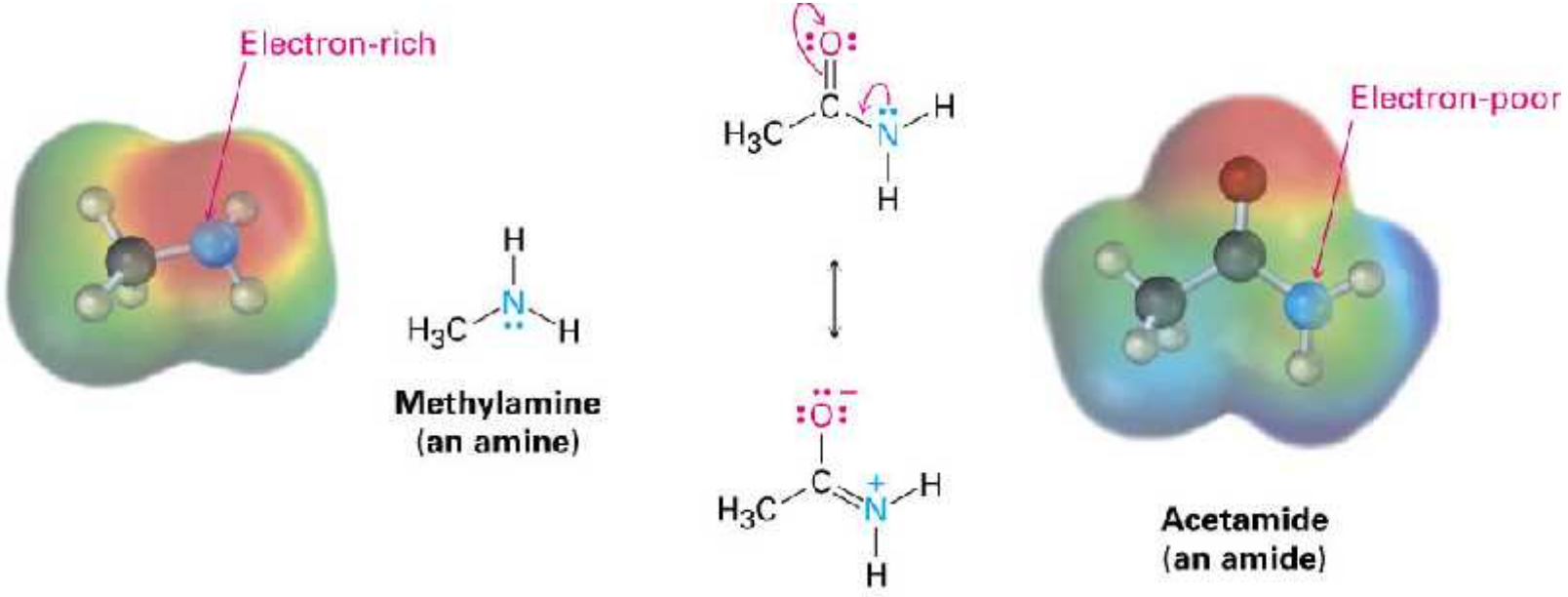
$CH_3CH_2NH_2$ is stronger base than $CH_2(Cl)CH_2NH_2$



stronger base

amines are stronger bases than amides

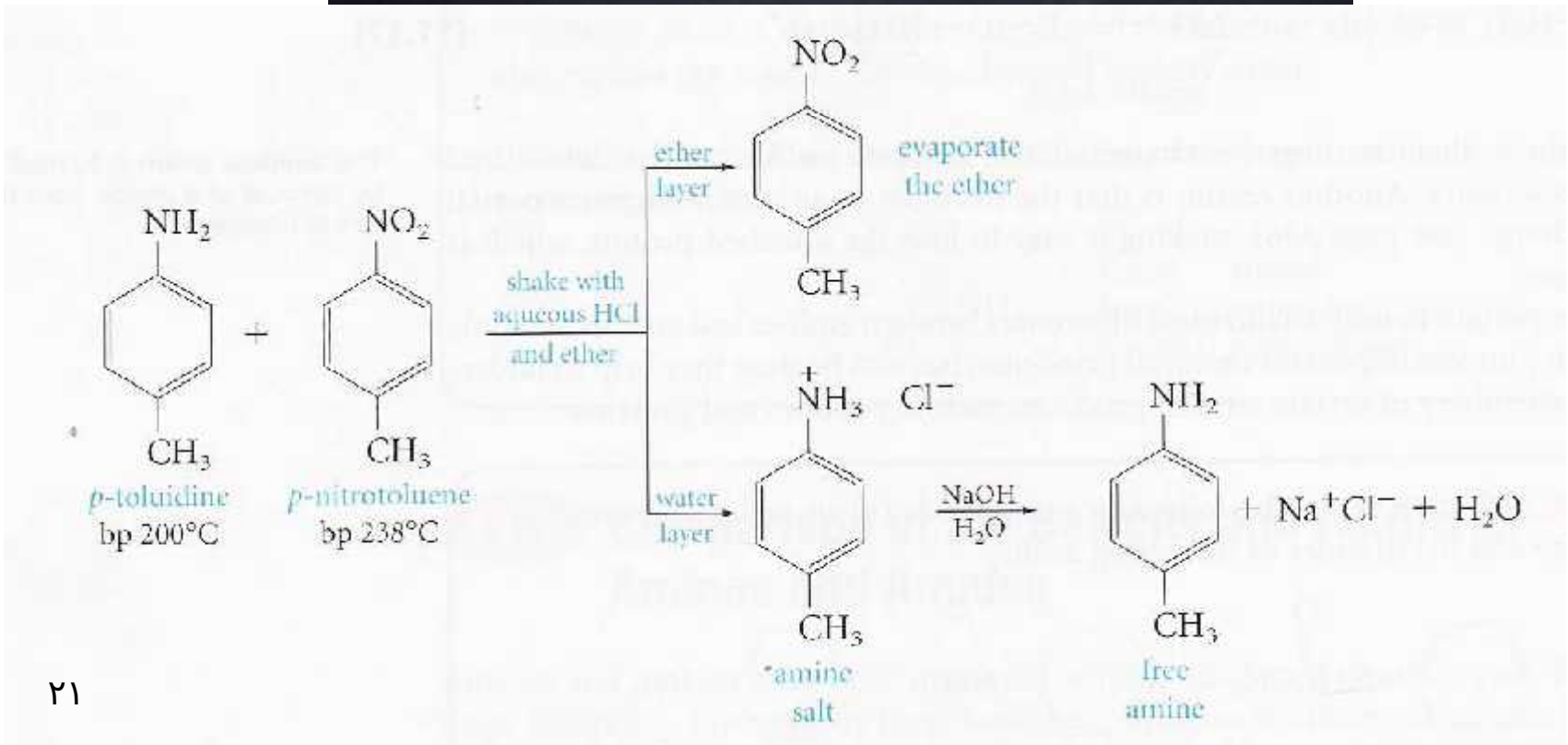
- Amides ($RCONH_2$) in general are not proton acceptors except in very strong acid
- The C=O group is strongly electron-withdrawing, making the N a very weak base
- Addition of a proton occurs on O but this destroys the double bond character of C=O as a requirement of stabilization by N



Basicity of amines

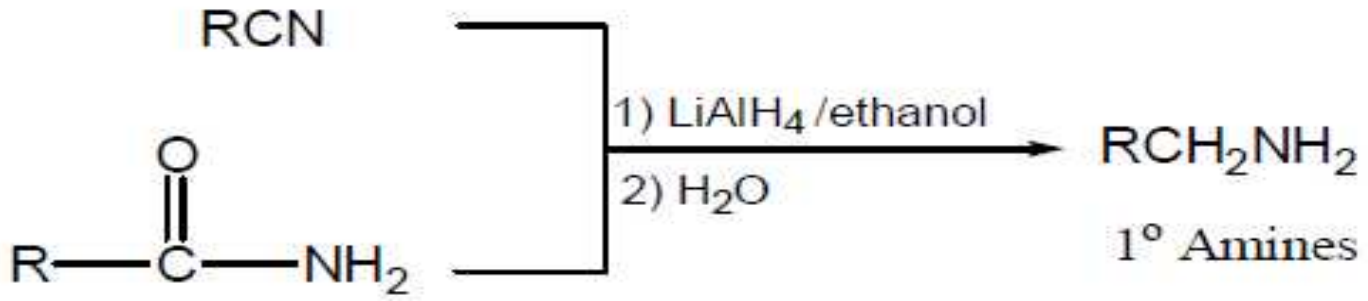
Amines react with acids much like ammonia.

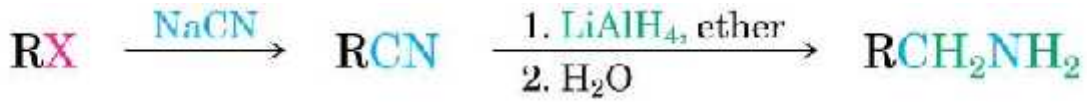
Results in salt formation.



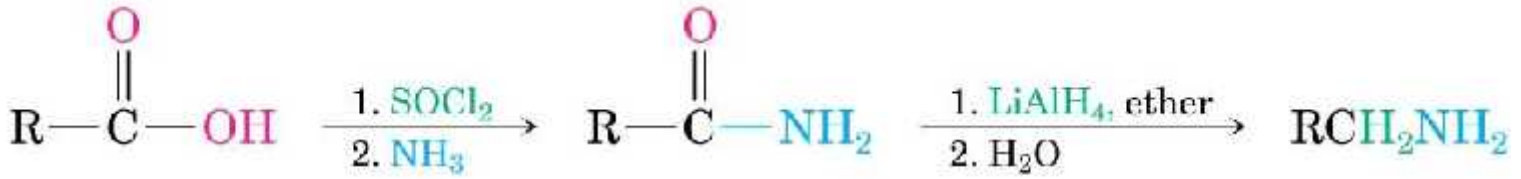
Synthesis of Amines

1- Reduction of Nitriles and Amides

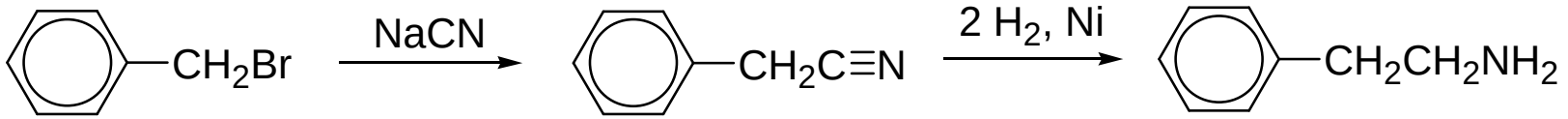




Alkyl halide **1° amine**



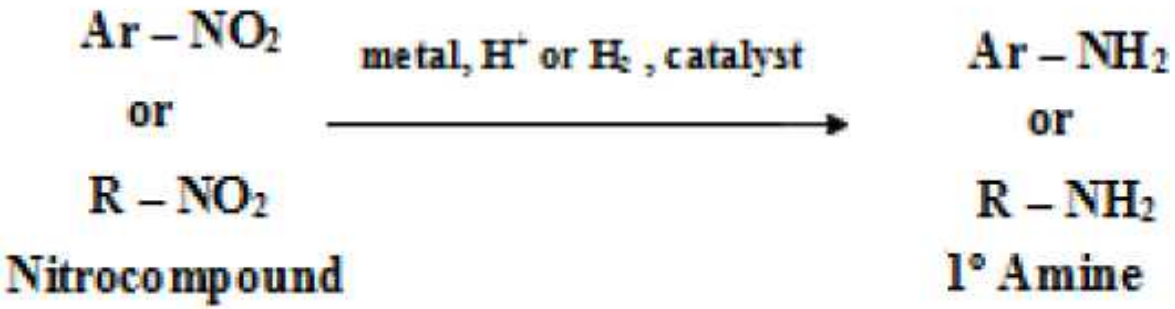
Carboxylic acid **1° amine**



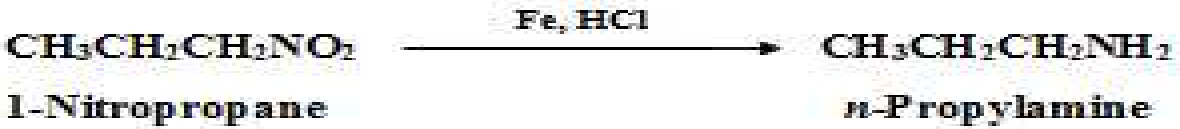
benzyl bromide

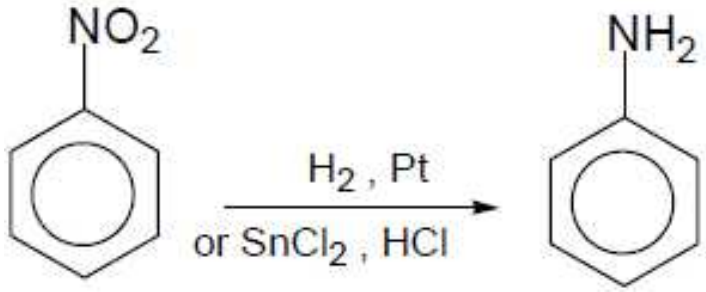
1-amino-2-phenylethane

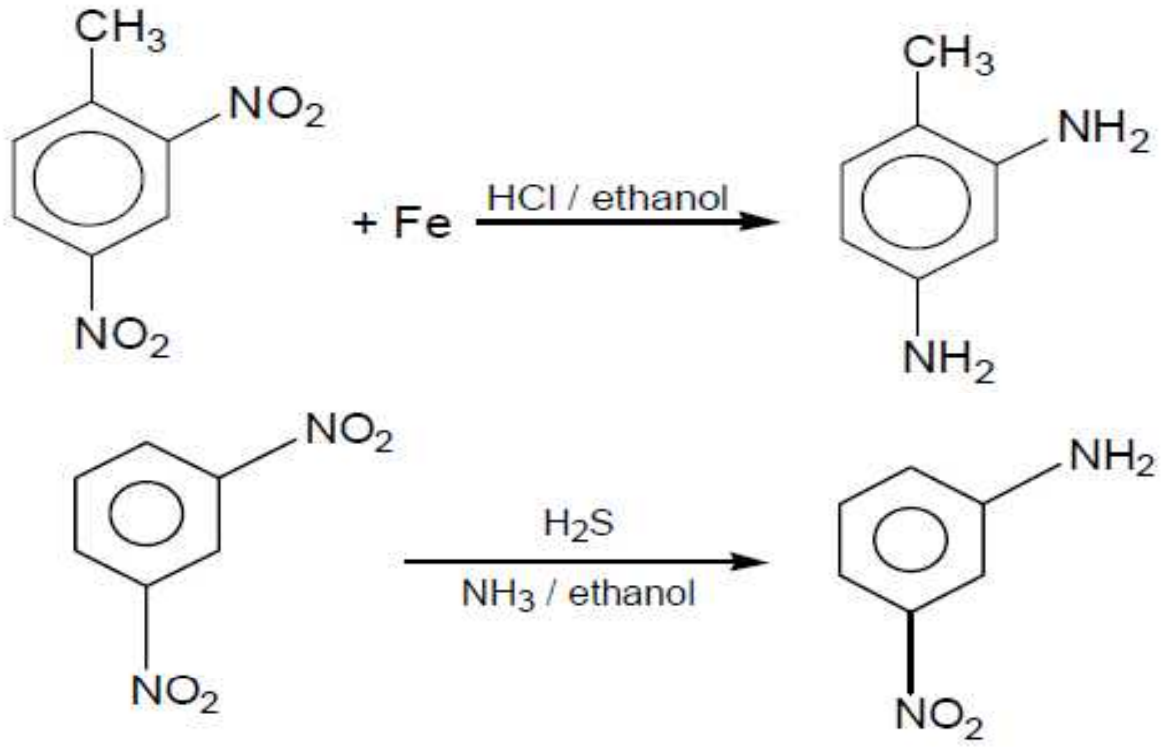
2. Reduction of nitro compounds:

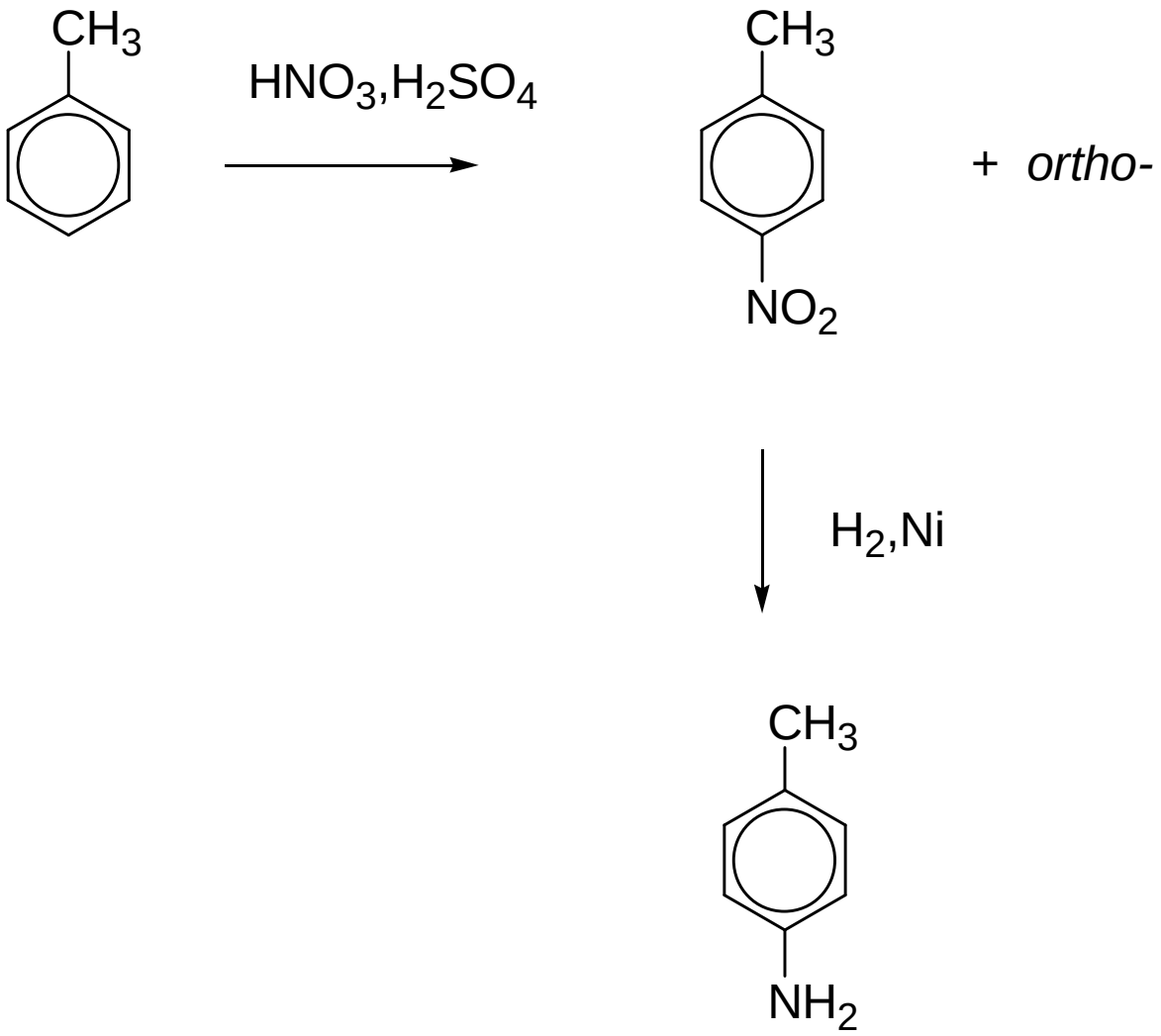


p-Nitroaniline — *p*-Phenylenediamine

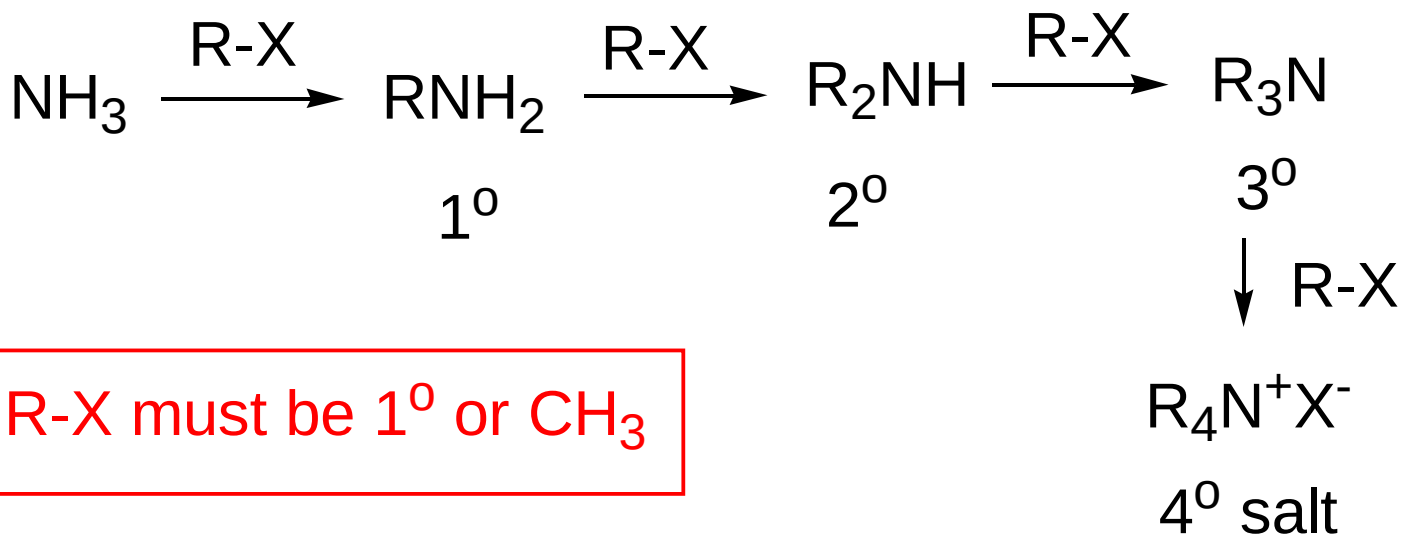




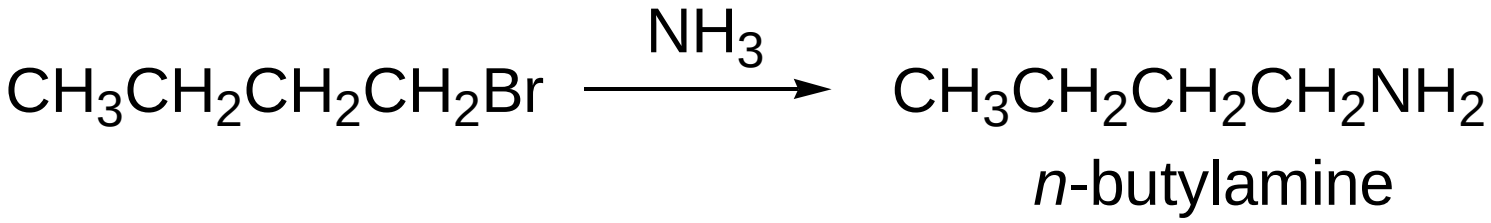

CH3
NO2
NO2
+ Fe
HCl / ethanol
CH3
NH2
NH2
NO2
NO2
H2S
NH3 / ethanol
NH2
NO2

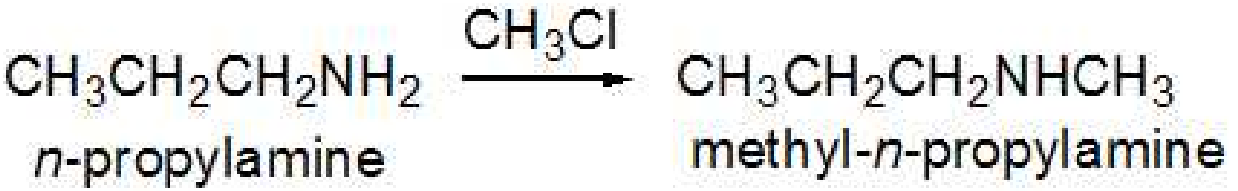

CH3
HNO3,H2SO4
CH3
NO2
+ ortho-
H2,Ni
CH3
NH2
p-toluidine

3- Ammonolysis of 1º or methyl halides.



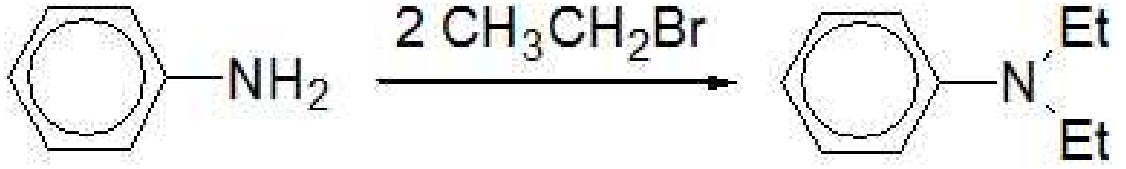
R-X must be 1º or CH_3





n-propylamine

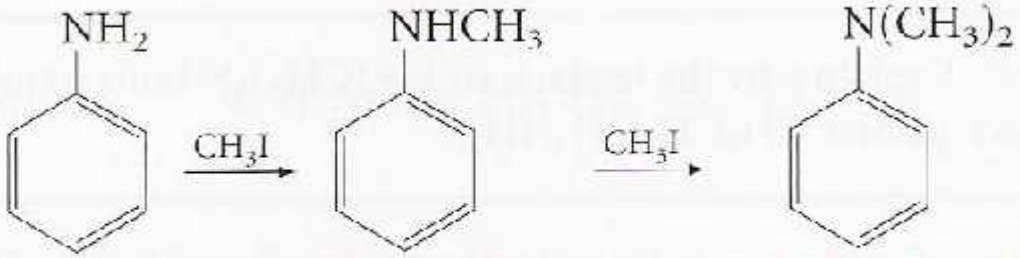
methyl-*n*-propylamine



aniline

N,N-diethylaniline

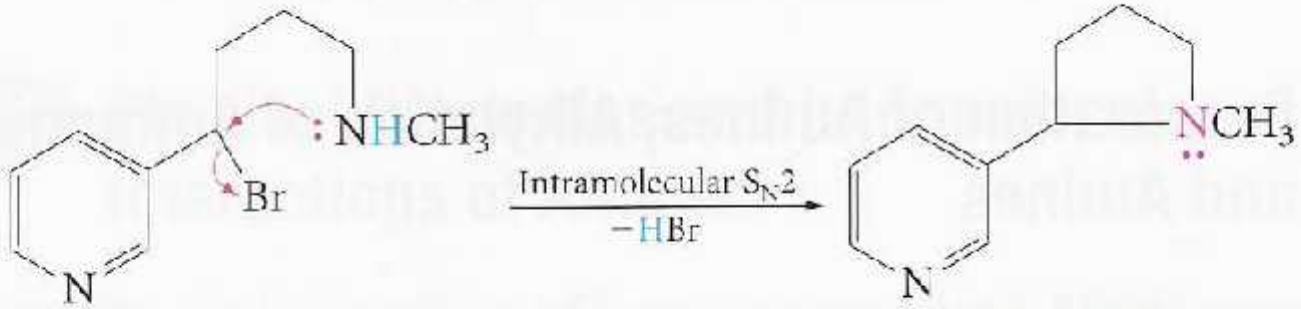
Aromatic amines can often be alkylated selectively.



aniline *N*-methylaniline *N,N*-dimethylaniline

(11.8)

The alkylation can be intramolecular, as in the following final step in a laboratory synthesis of nicotine:

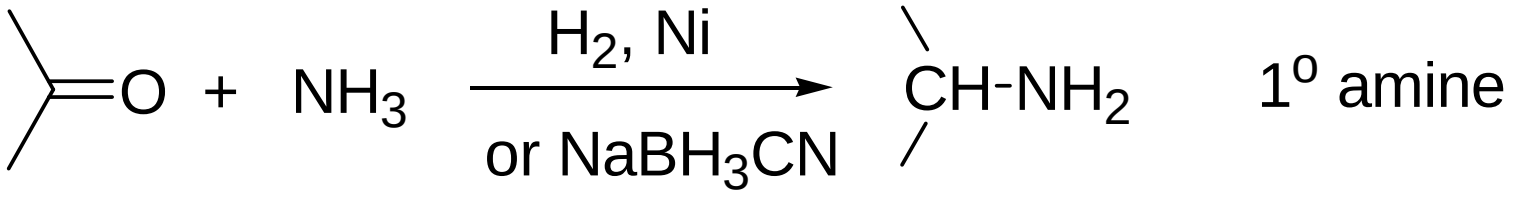


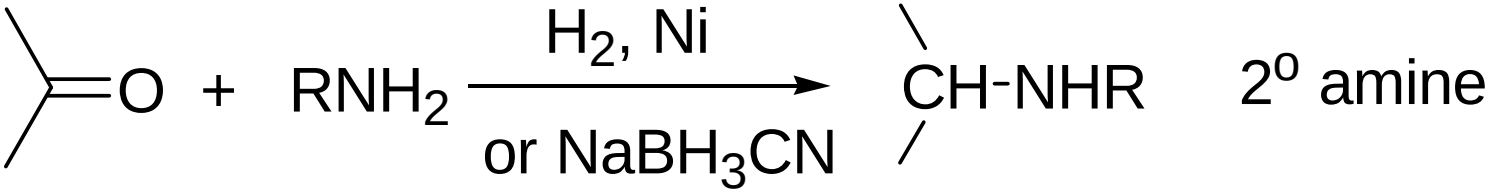
nicotine

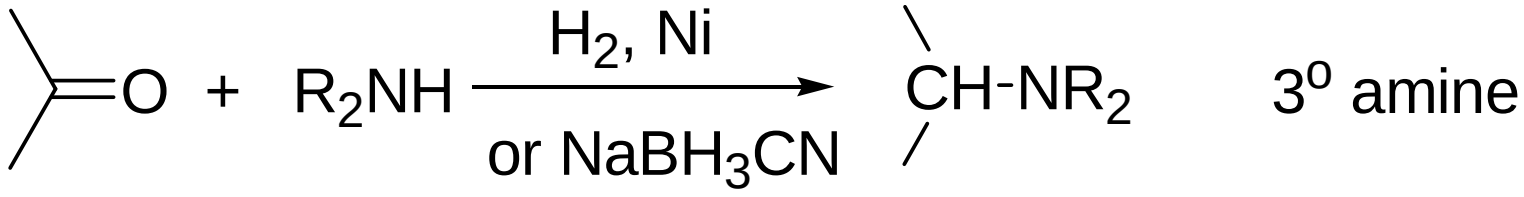
(11.9)

4. Reductive amination:

- Ammonia, primary amines, and secondary amines yield primary, secondary, and tertiary amines, respectively

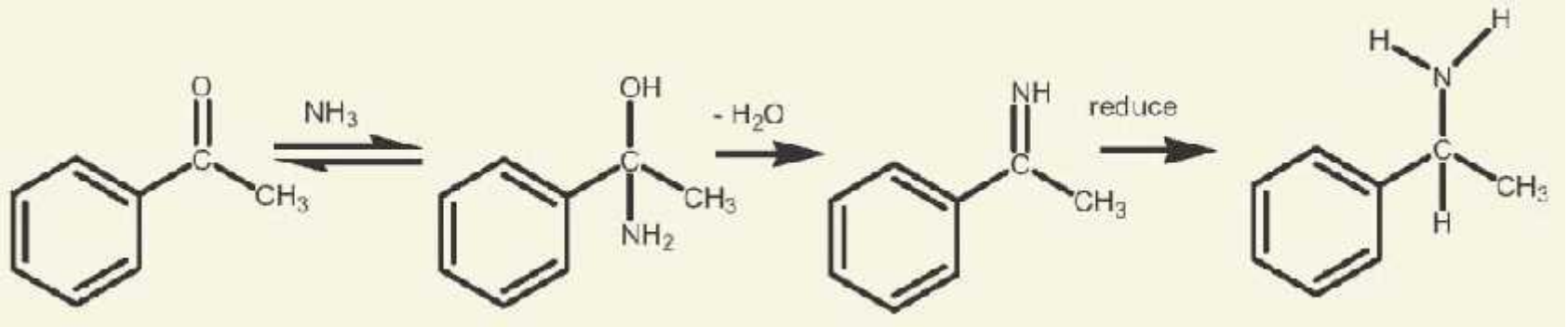


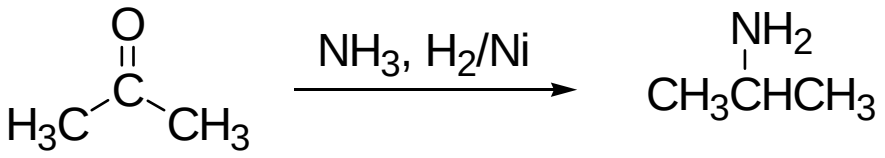




Mechanism of Reductive Amination

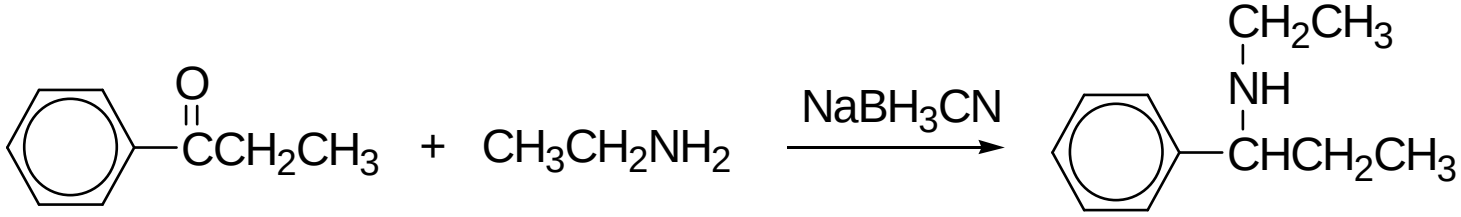
- Imine is intermediate





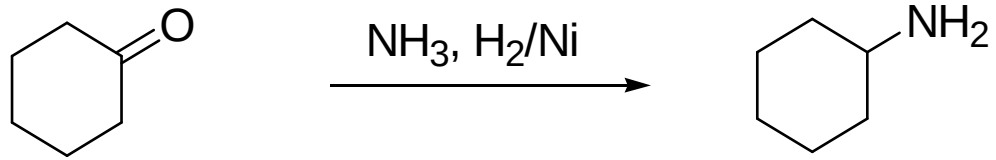
acetone

isopropylamine



propiophenone

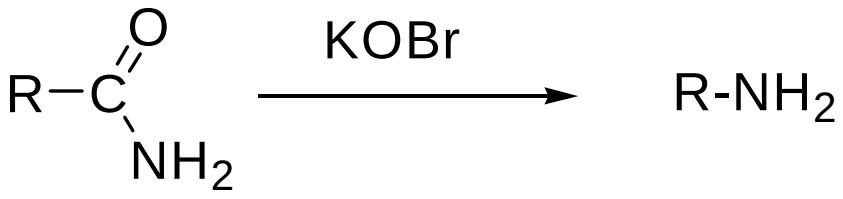
1-(*N*-ethylamino)-1-phenylpropane



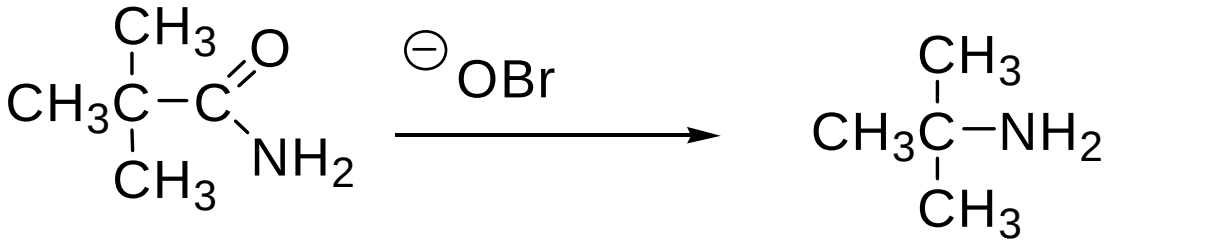
cyclohexanone

cyclohexylamine

5. Hofmann degradation of amides

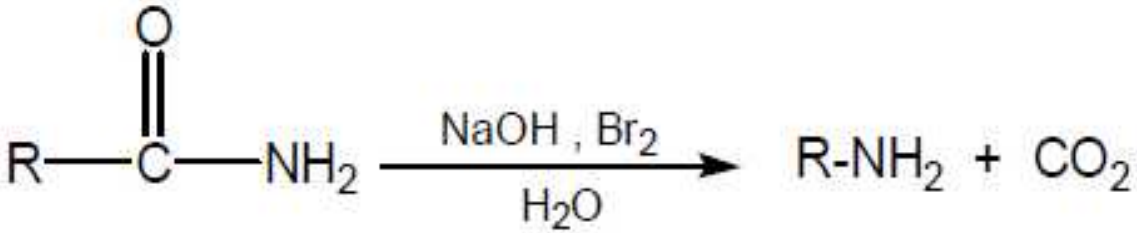


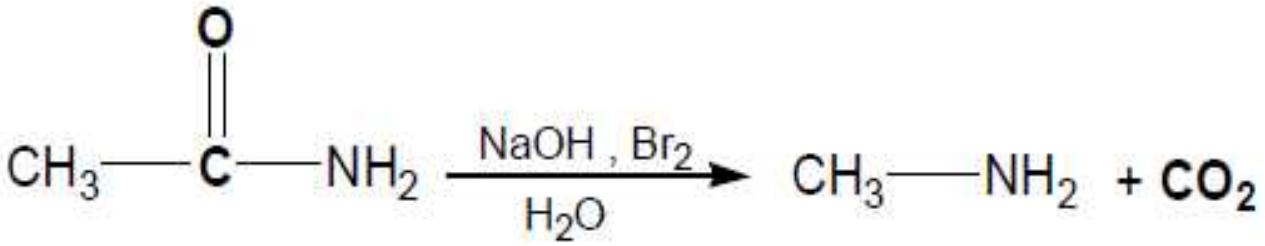
Removes one carbon!



2,2-dimethylpropanamide

tert-butylamine





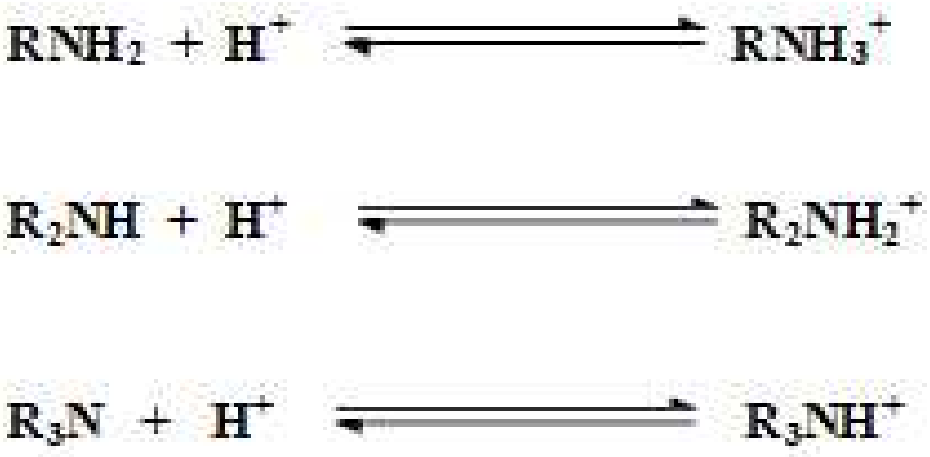
m-Bromobenzamide **m-Bromoaniline**

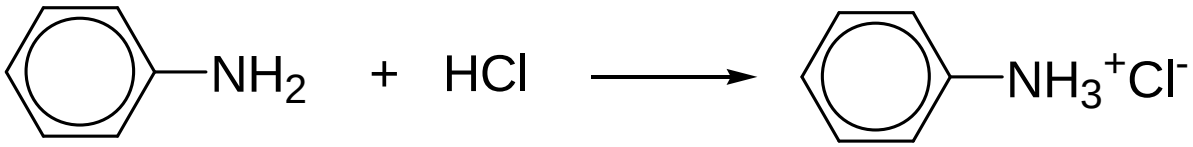
Hexanamide (Caproamide) ***n*-Pentylamine**

Reactions of Amines

- The lone-pair of electrons on the nitrogen atom dominates the chemistry of the amines and cause them to function as Lewis bases or nucleophiles

1- Basicity. Salt formation

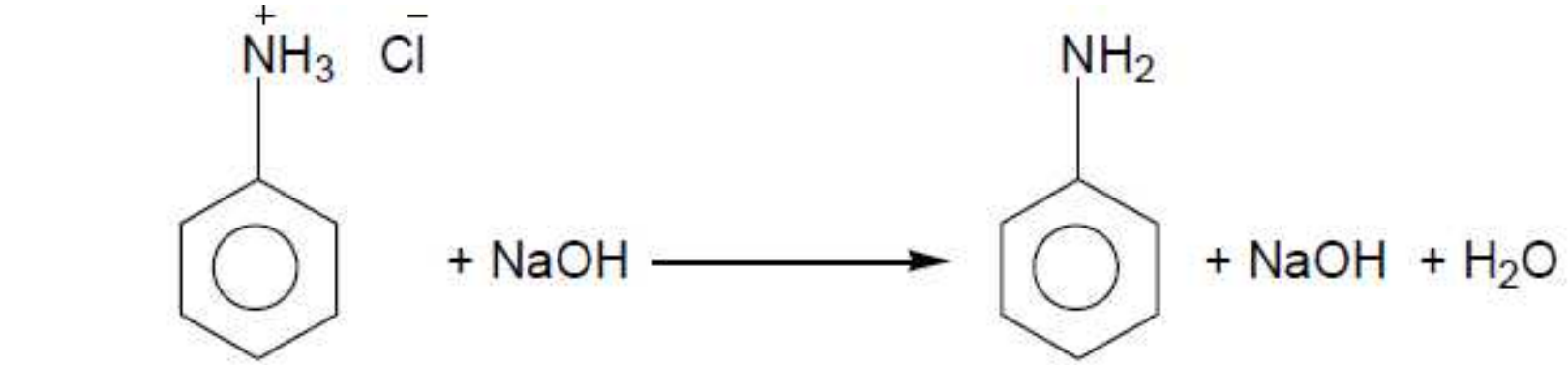




anilinium chloride

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

diethylammonium acetate

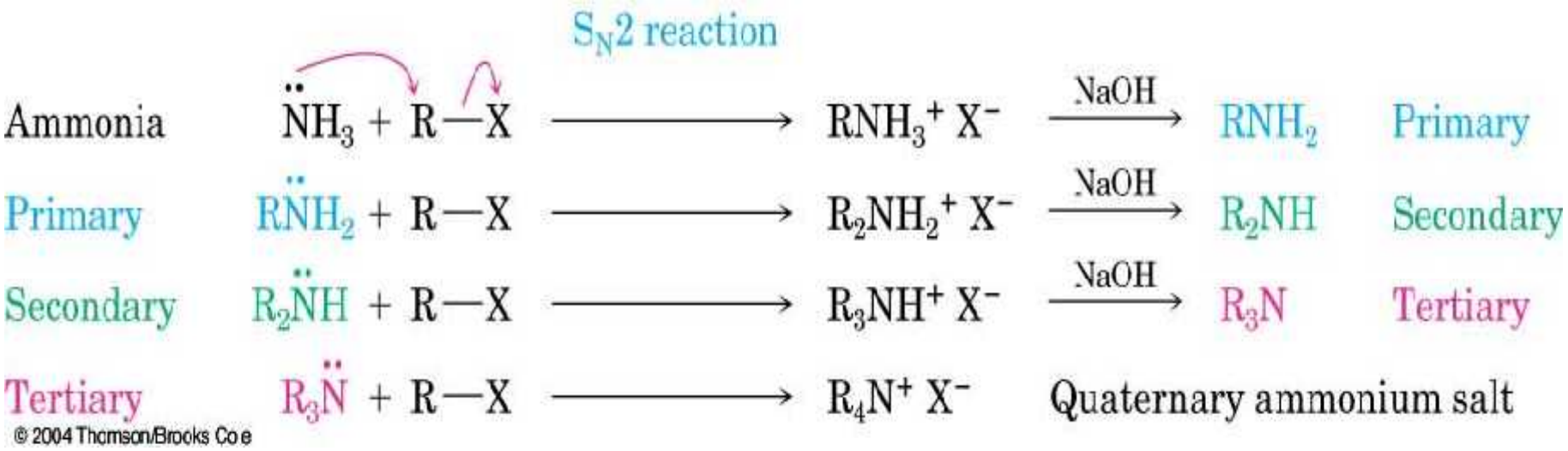


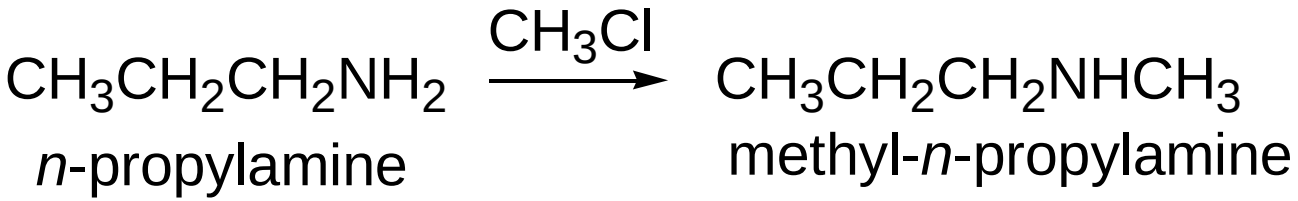
Phenyl ammonium chloride

Aniline

2. Alkylation (ammonolysis of alkyl halides)

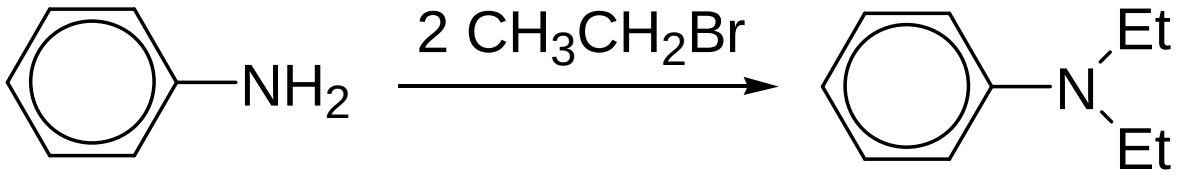
- Ammonia and other amines are good nucleophiles





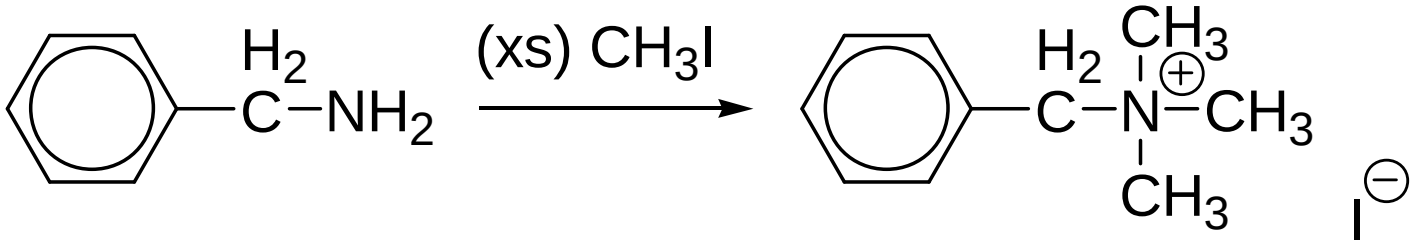
n-propylamine

methyl-*n*-propylamine



aniline

N,N-diethylaniline

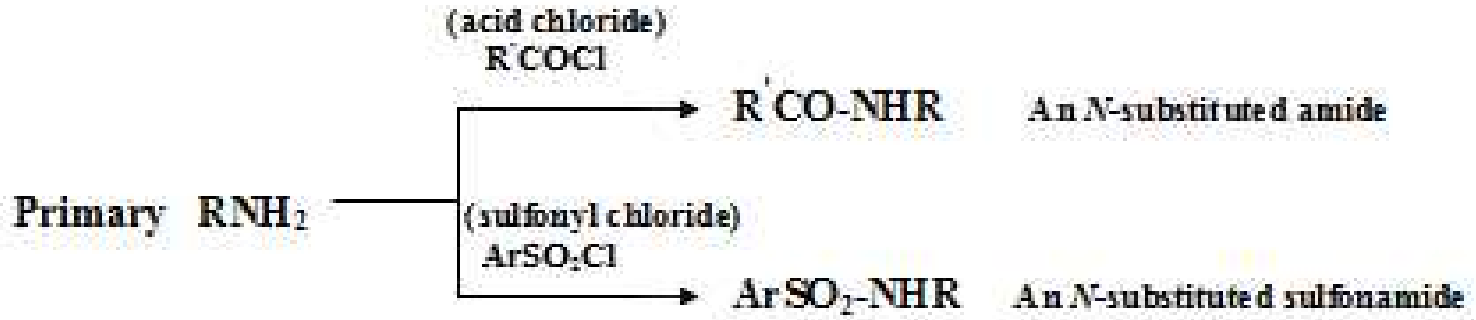


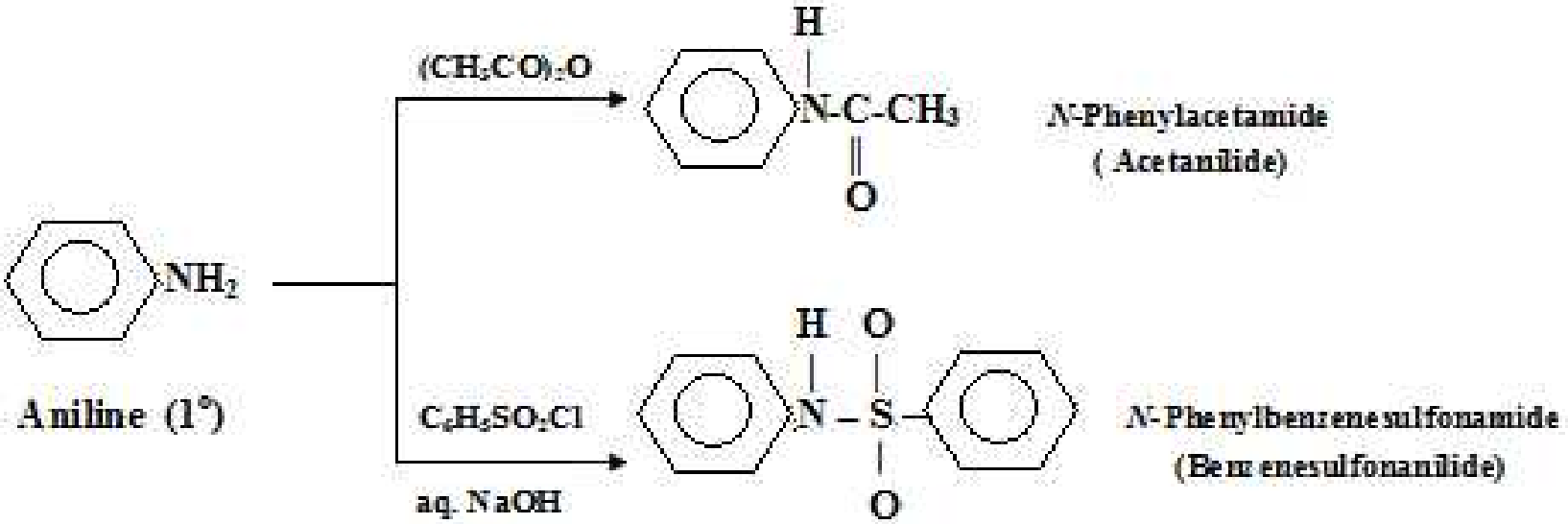
benzylamine

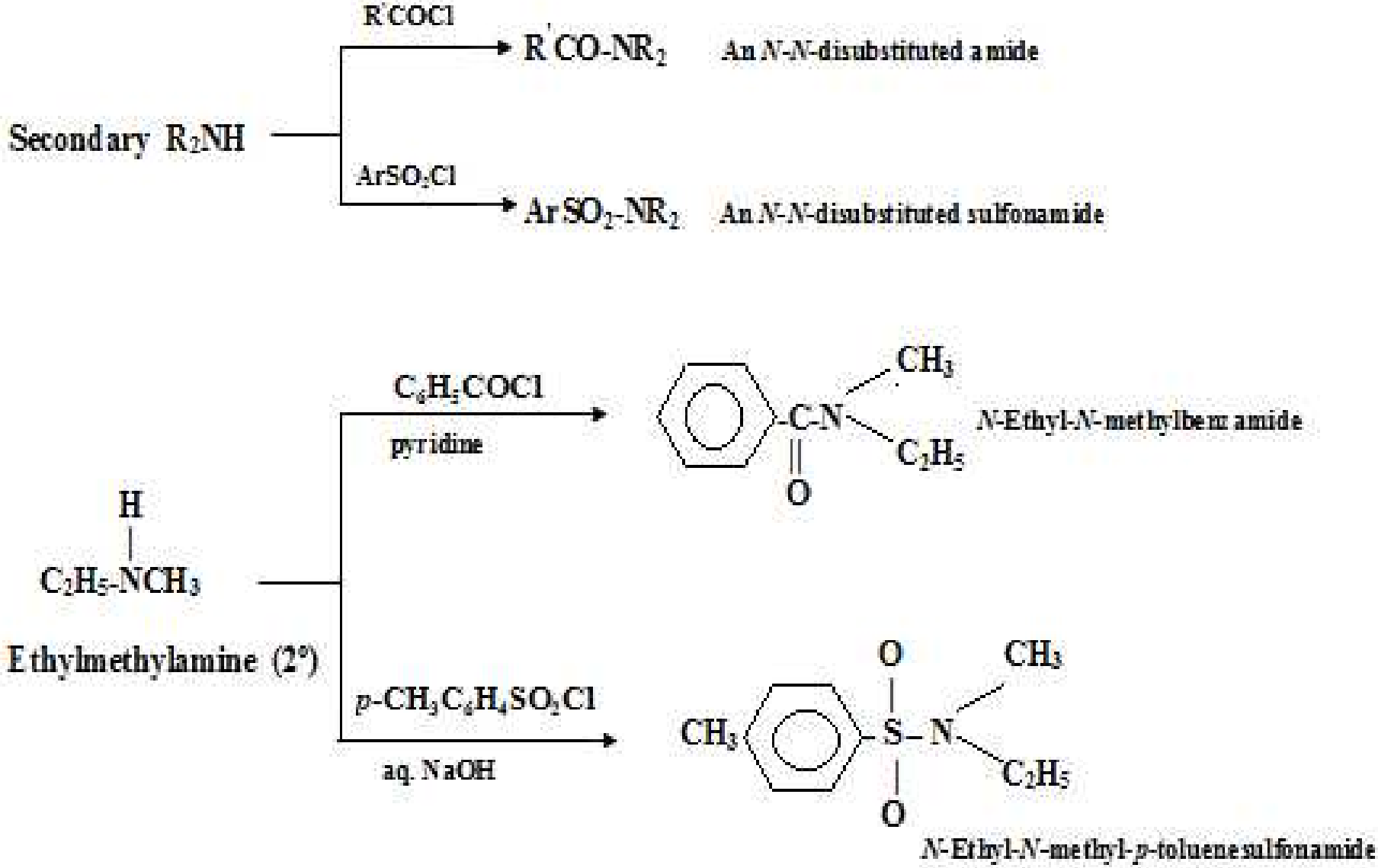
benzyltrimethylammonium iodide

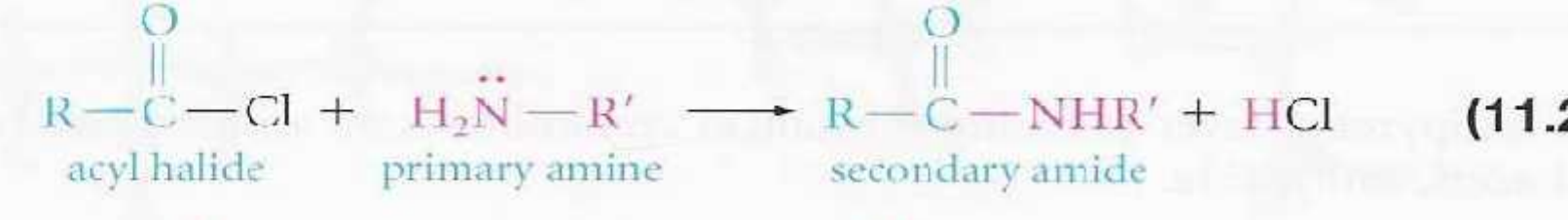
3- Conversion into amides

-Primary and secondary amines react readily with acid chlorides and acid anhydrides to form N-substituted amides.

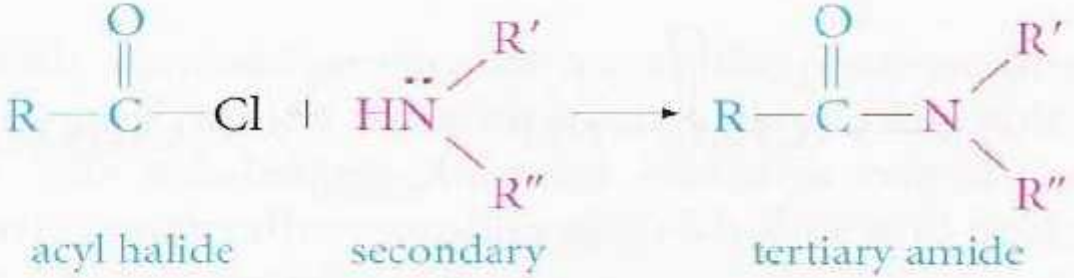




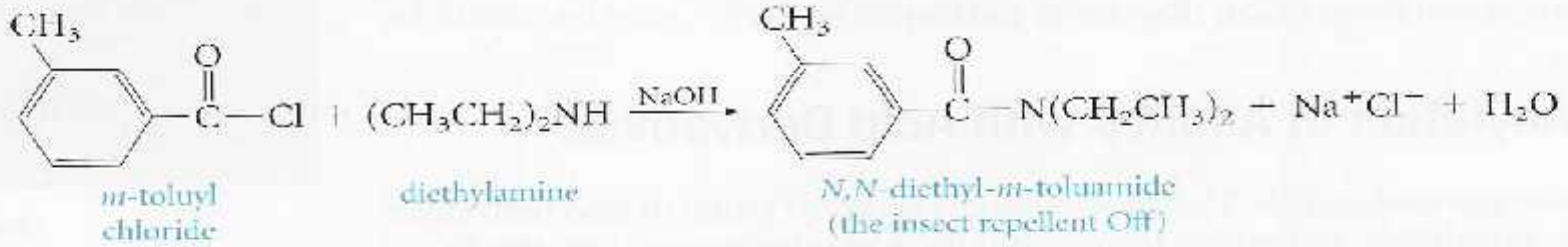

R'COCl
R'CO-NR2
An N-N-disubstituted amide
Secondary R2NH
ArSO2Cl
ArSO2-NR2
An N-N-disubstituted sulfonamide
C6H5COCl
pyridine
CH3
C-N
C2H5
O
N-Ethyl-N-methylbenzamide
H
C2H5-NCH3
Ethylmethylamine (2°)
p-CH3C6H4SO2Cl
aq. NaOH
O
CH3
CH3
S
N
C2H5
O
N-Ethyl-N-methyl-p-toluenesulfonamide



(11.22)



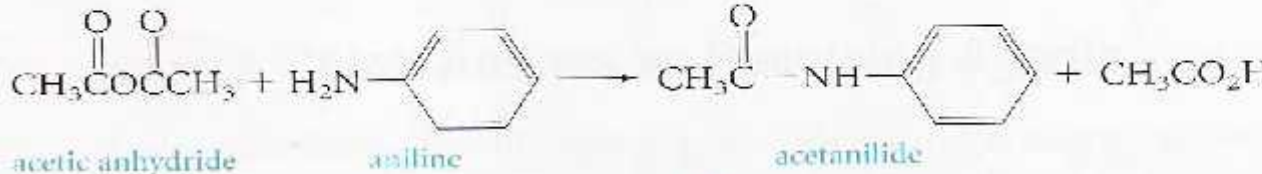
(11.23)



(11.24)

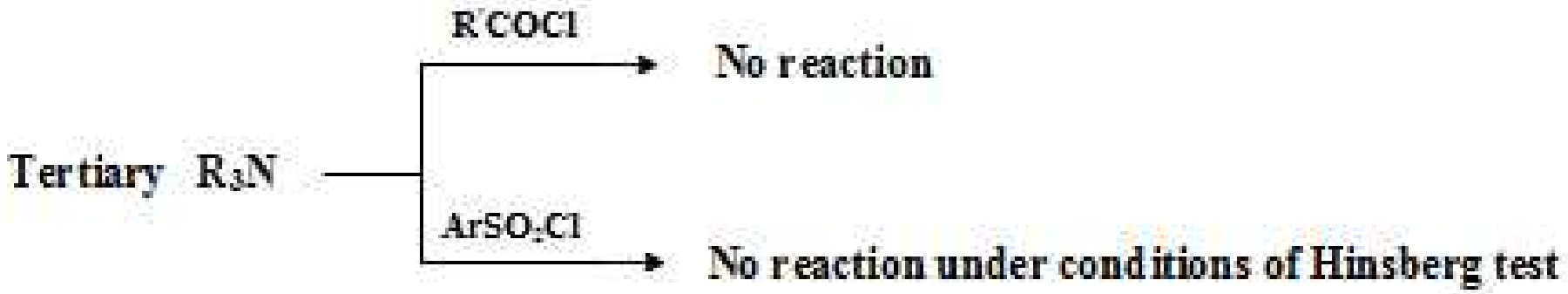
PROBLEM 11.18 Write out the steps in the mechanism for the synthesis of Off (eq. 11.24).

The antipyretic (fever-reducing substance) acetanilide is an amide made from aniline and acetic anhydride.



(11.25)

-Tertiary amines do not possess a hydrogen atom bonded to nitrogen and do not form amides with acid chlorides and acid anhydrides.



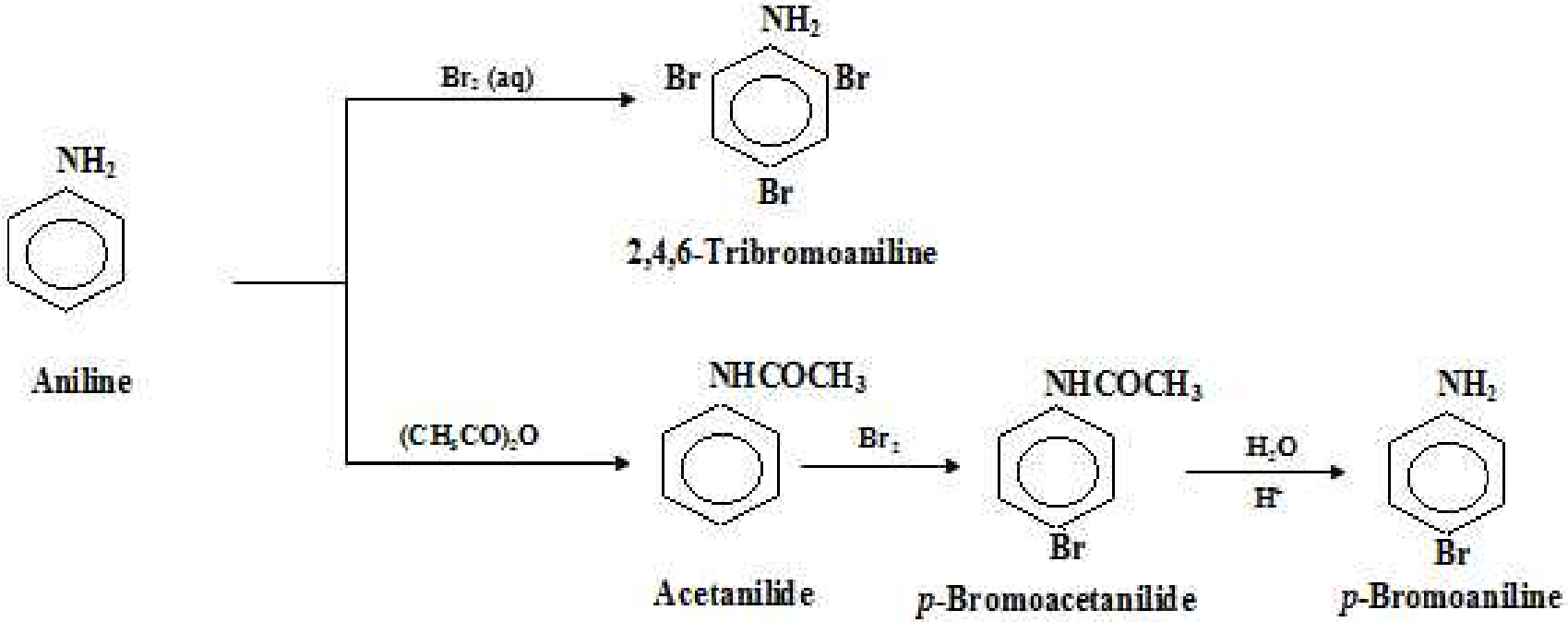
Hinsberg Test:

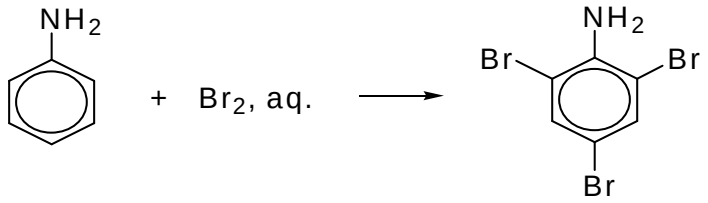
unknown amine + benzenesulfonyl chloride, KOH (aq)

- Reacts to produce a clear solution and then gives a ppt upon acidification → primary amine.
- Reacts to produce a ppt → secondary amine.
- Doesn't react → tertiary amine.

4- Ring substitution in aromatic amines

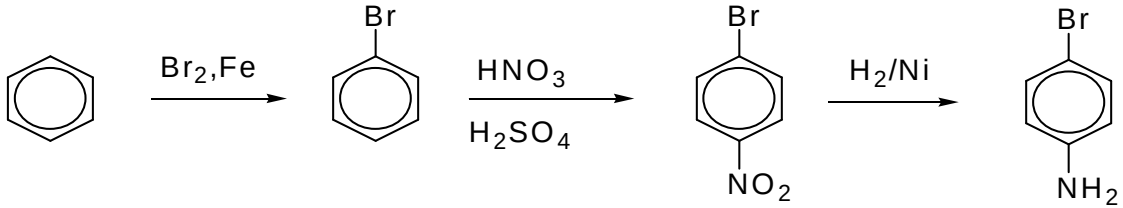
- Aromatic amines can undergo substitutions on the ring.
- The amino group forms a Lewis acid–base complex with the $AlCl_3$ catalyst, preventing further reaction
- -NH2, -NHR, -NR2 are powerful activating groups and ortho/para directors
- -NHCOR less powerful activator than NH2



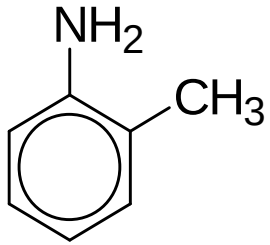


polyhalogenation!

no catalyst needed
use polar solvent

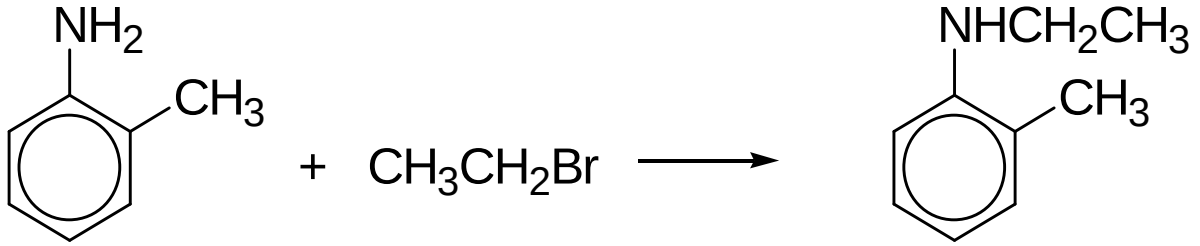


+ *ortho-*



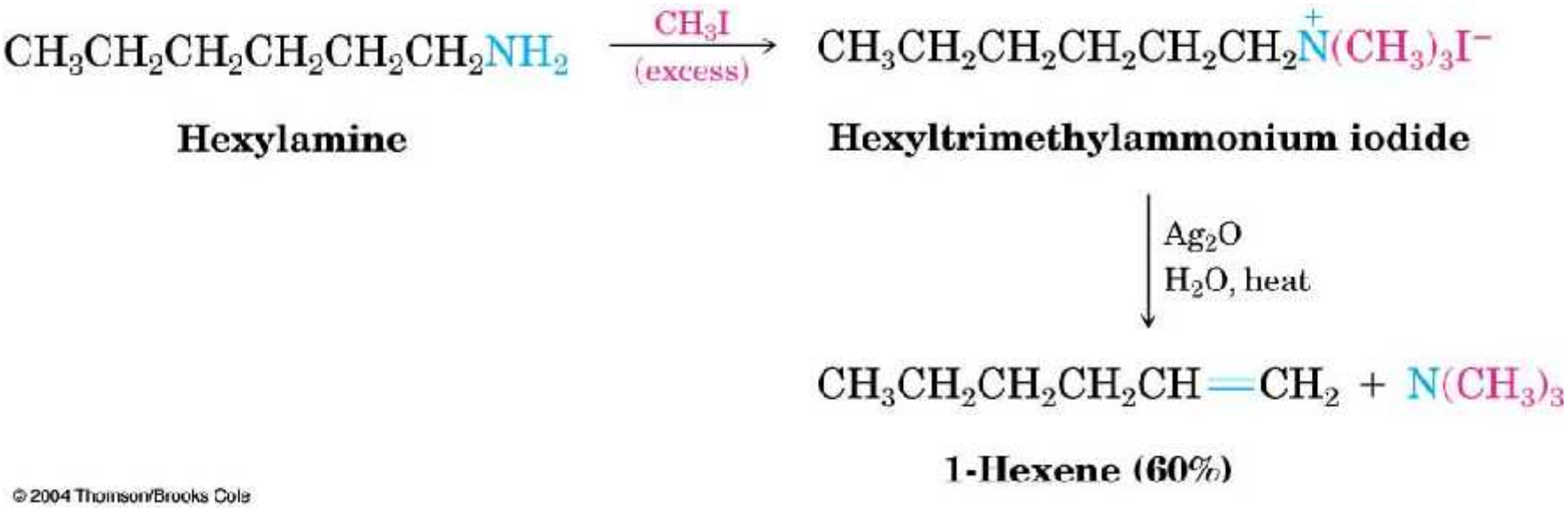
+ CH_3CH_2Br, $AlCl_3$ ⟶ NR

Do not confuse the above with the alkylation reaction:



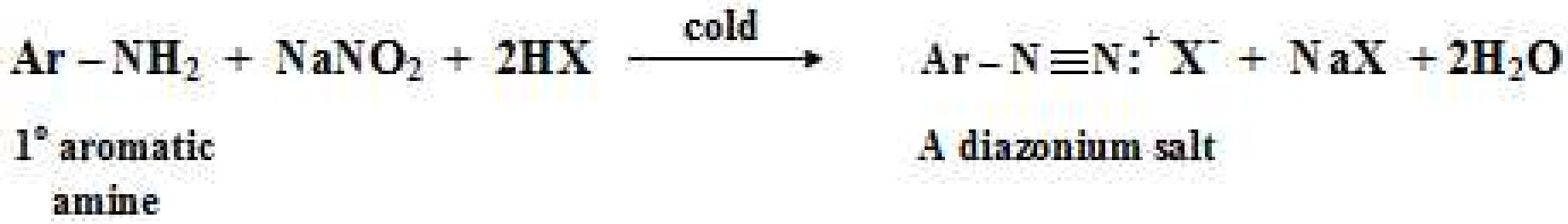
5- Hofmann Elimination

- Converts amines into alkenes
- NH_2^- is very a poor leaving group so it converted to an alkylammonium ion, which is a good leaving group



6- Diazonium salts

Primary aromatic amines react with nitrous acid at 0°C to yield **aryldiazonium ions.** The process is called **diazotization.**

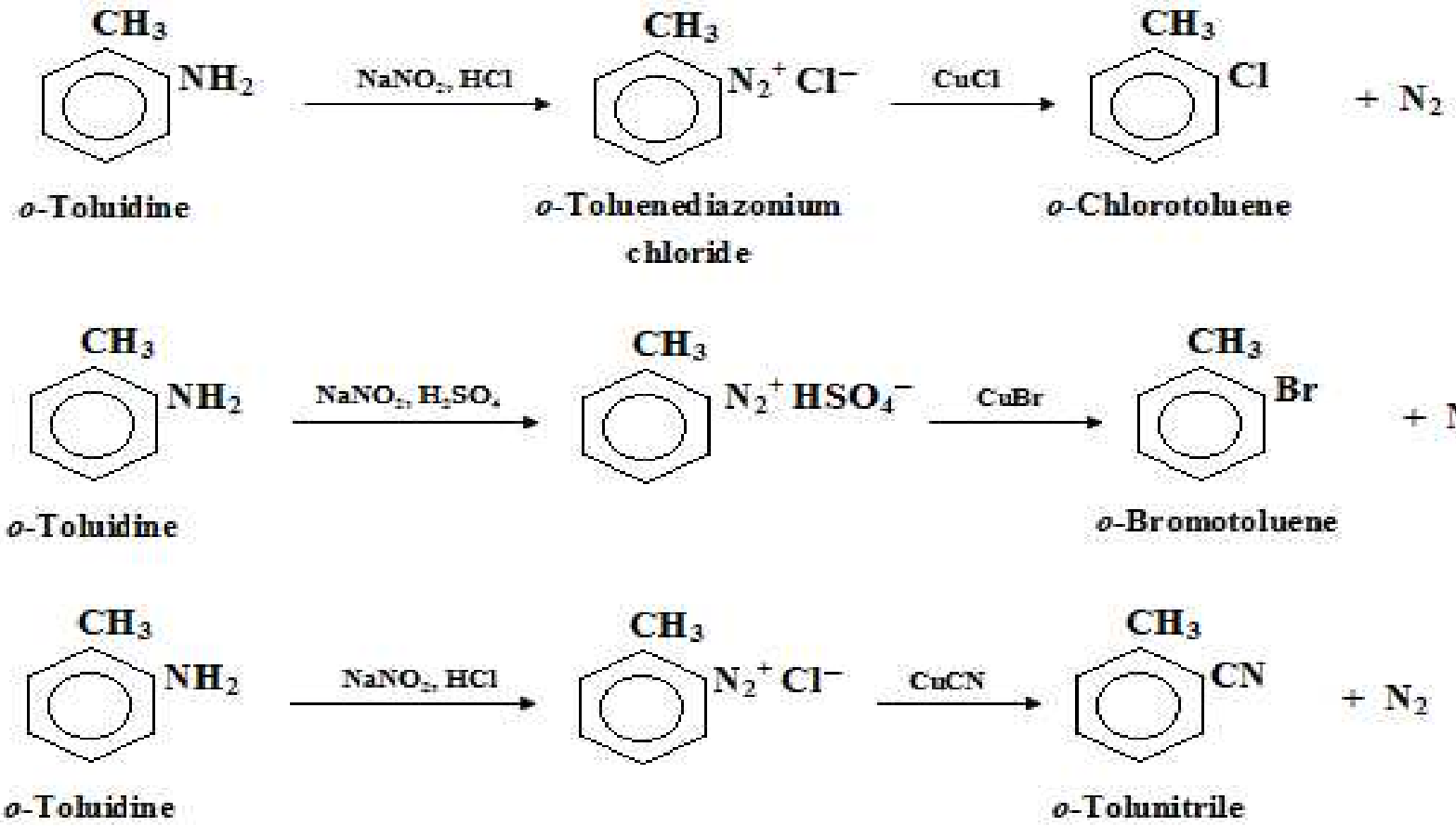


i- Reactions of Diazonium Salts

1- Replacement of nitrogen

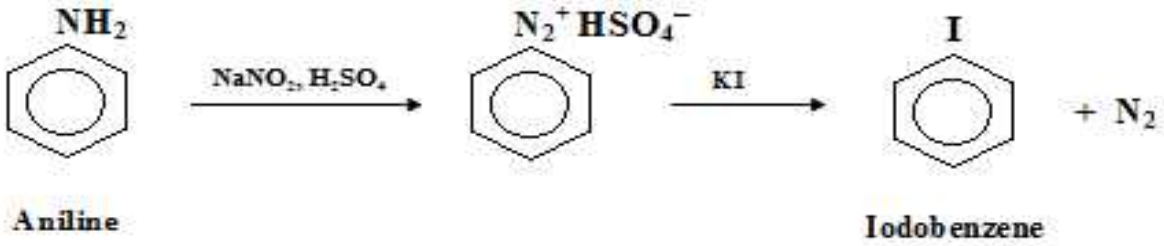
-Replacement of the diazonium group is the best general way of introducing F, Cl, Br, I, CN, OH, and H into an aromatic ring.

(a) Replacement by – Cl, - Br, - CN. Sandmeyer reaction



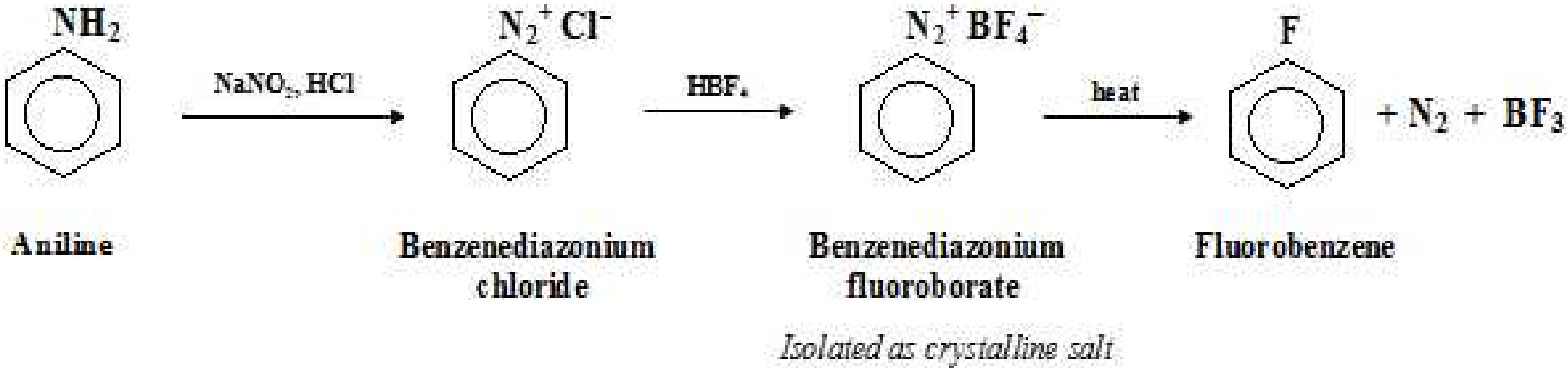
(b) Replacement by – I

$$Ar-N_2^+ \; + \; I^- \longrightarrow Ar-I \; + N_2$$

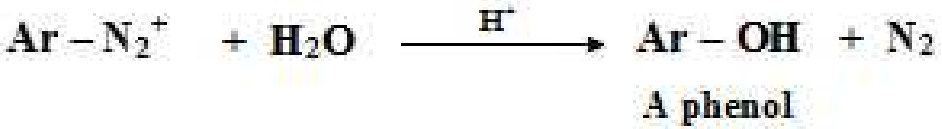


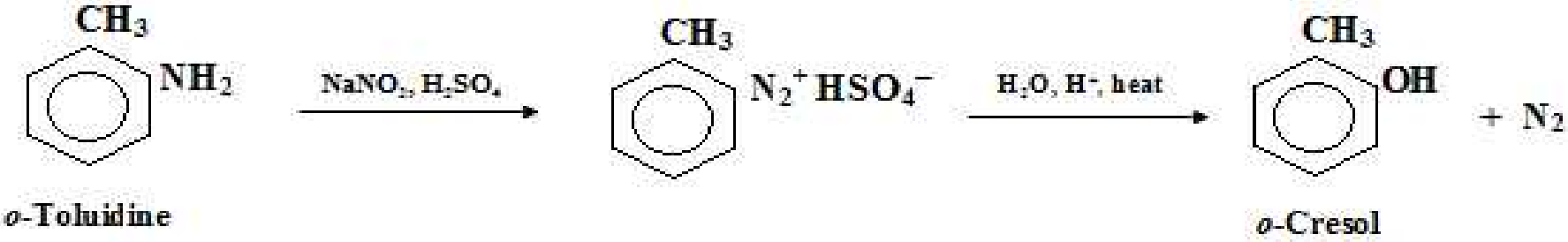
(c) Replacement by – F

$$Ar-N_2^+BF_4^- \xrightarrow{\text{heat}} Ar-F \; + N_2 \; + BF_3$$

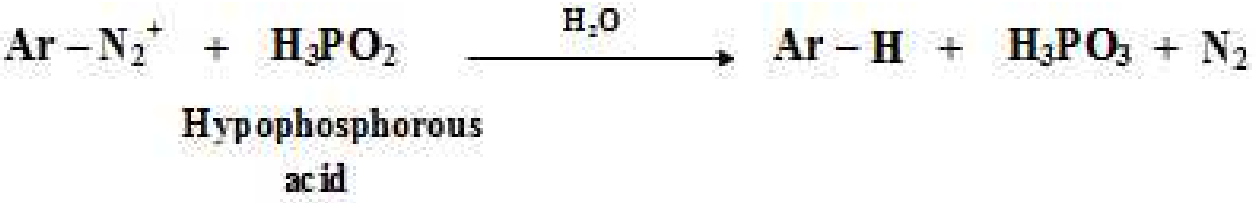


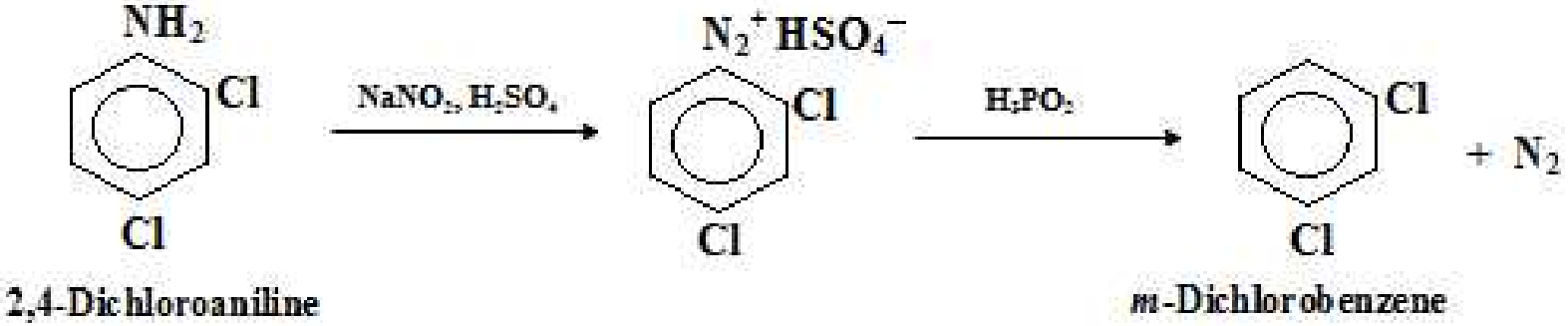
(d) Replacement by – OH





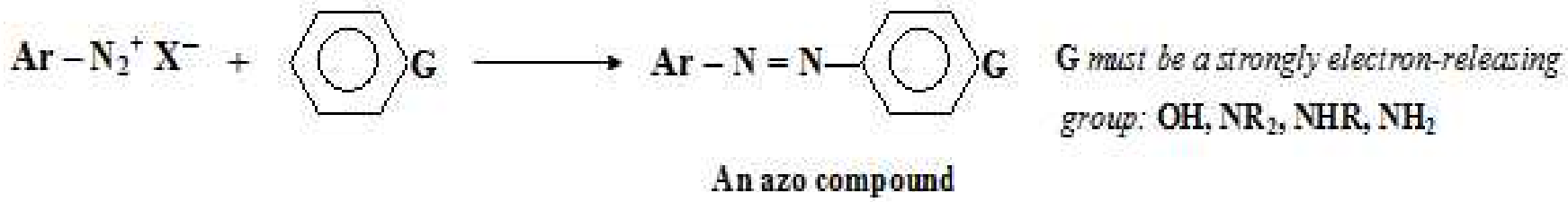
(e) Replacement by – H

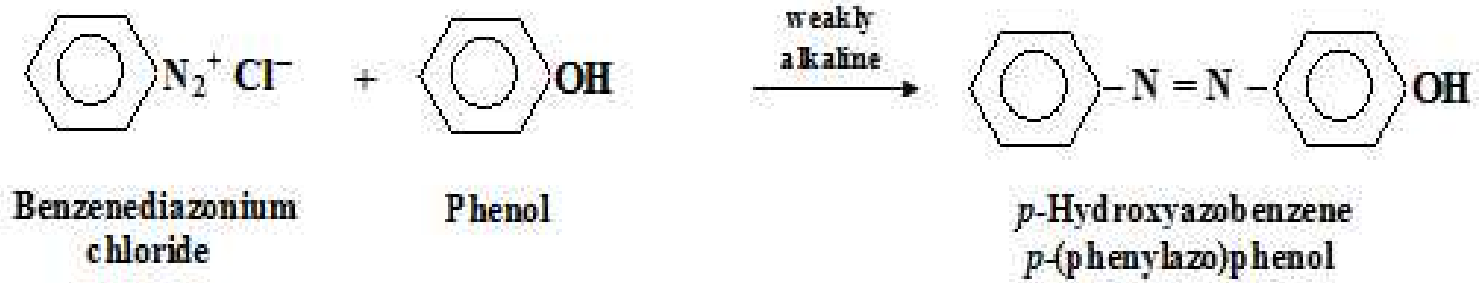


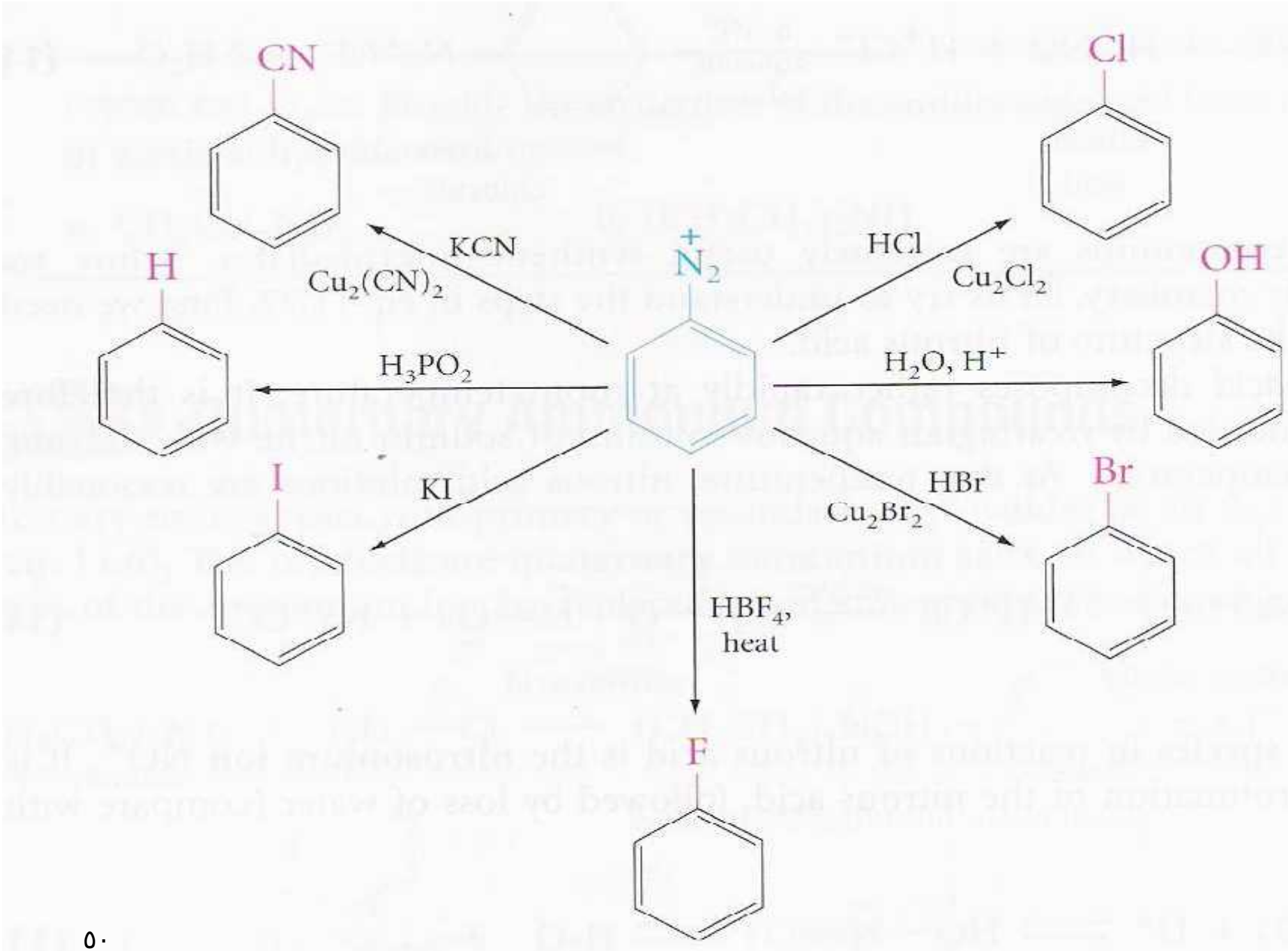


ii- Coupling

- Under the proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula Ar – N = N – Ar', called **azo compounds**, this reaction, known as coupling.






CN
KCN
$Cu_2(CN)_2$
Cl
HCl
Cu_2Cl_2
H
H_3PO_2
N_2^+
OH
H_2O, H^+
I
KI
HBr
Cu_2Br_2
Br
HBF_4,
heat
F