Carboxylic Acids

All carboxylic acids contain the carboxyl group, -COOH.

Depending on whether an R or an Ar. residue is attached to the carboxyl group; Carboxylic acids are classified as aliphatic or aromatic.

Aliphatic Carboxylic Acids.

$R-COOH$ (R = H or alkyl)

Aliphatic acid

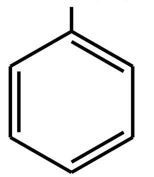
CH_3-COOH

Acetic acid

Aromatic Carboxylic Acids.

$Ar-COOH$ ($R = C_6H_5$-)

Aromatic acid



Benzoic acid

Nomenclature of Carboxylic Acids

The common names of carboxylic acids all end in *-ic acid*.

For example

Formic acid is the acid that gives the characteristic sting to an ant bite (from the Latin *formica*, ant).

Acetic acid is vinegar (from the Latin *acetum*, vinegar).

Butyric acid is the compound that gives rancid butter its putrid smell (from the Latin *butyrum*, butter).

Fatty acids.

Long straight-chain carboxylic acids with even numbers of carbons, which were first isolated from fats and waxes.

IUPAC System

The ending *-e* of the corresponding alkane is replaced by *-oic acid*.

For example

$HCOOH$ is called *methanoic acid*.

CH_3COOH is called *ethanoic acid*.

If substituents are present on the acid chain.

- **Common nomenclature**

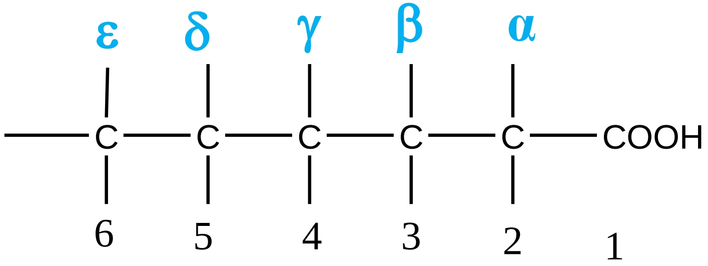
  Their positions are located by Greek letters; α, β, γ, δ, ε,….etc

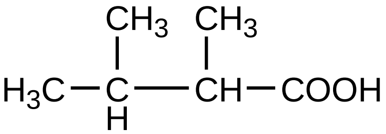
- **IUPAC system**

  Numbers are used and the carboxylic carbon is numbered 1.

Common nomenclature:

IUPAC nomenclature:





Common nome: a,B-Dimethylbutyric acid

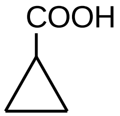
IUPAC nomenclature: 2,3-Dimethylbutanoic acid

IUPAC and Common Names of Some Normal carboxylic Acids.

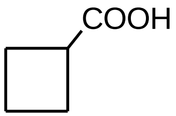
No. of carbon atoms	Formula	IUPAC name	Common name
1	HCOOH	Methanoic acid	Formic acid
2	CH_3COOH	Ethanoic acid	Acetic acid
3	CH_3CH_2COOH	Propanoic acid	Propionic acid
4	$CH_3(CH_2)_2COOH$	Butanoic acid	Butyric acid
5	$CH_3(CH_2)_3COOH$	Pentanoic acid	Valeric acid

Cylcoalkane carboxylic acid

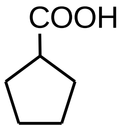
When the carboxyl group is attached to a saturated ring.



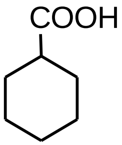
Cyclopropanecarboxylic acid



Cyclobutanecarboxylic acid

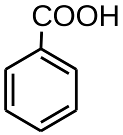


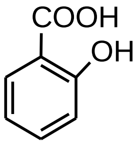
Cyclopentanecarboxylic acid



Cyclohexanecarboxylic acid

Aromatic carboxylic acids are generally called by their common names.



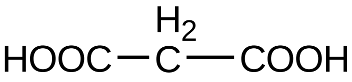


Common name:	Benzoic acid	Salicylic acid
IUPAC name:	Benzenecarboxylic acid (used as germicide and as food preservative)	2-Hydroxybenzenecarboxylic acid (raw material for aspirin)

Dicarboxylic acids (acids that contain two carboxyl groups) are known almost exclusively by their common names.

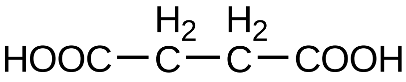
HOOC—COOH

Oxalic acid



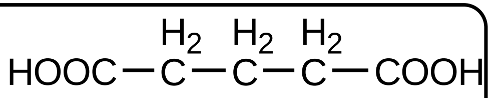
$HOOC{-}\overset{H_2}{C}{-}COOH$

Malonic acid



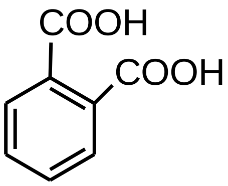
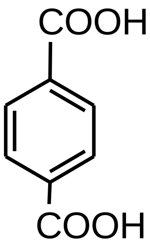
$HOOC{-}\overset{H_2}{C}{-}\overset{H_2}{C}{-}COOH$

Succinic acid



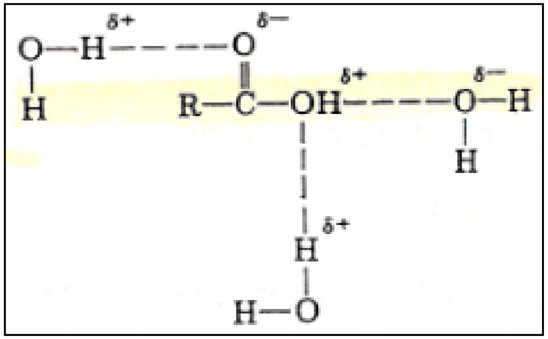
$HOOC{-}\overset{H_2}{C}{-}\overset{H_2}{C}{-}\overset{H_2}{C}{-}COOH$

Glutaric acid

		
Common name:	Phthalic acid	Terephthalic acid
IUPAC name:	Benzene-1,2-dicarboxylic acid	Benzene-1,4-dicarboxylic acid
	(medicinal uses; synthetic perfumes)	(constituent of Dacron)

Physical Properties of Carboxylic Acids

Carboxylic acids are capable of hydrogen bonding .



Solubility in water.

- The first four aliphatic acids (formic through butyric) are completely miscible in water.
- Higher members of the series are less soluble because the long alkyl chain gives them alkane like characteristics.
- Aromatic acids are insoluble in water.

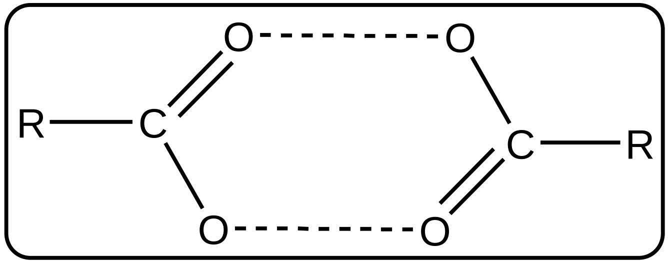
Boiling points.

- The boiling points of carboxylic acids indicate a greater degree of association than for alcohols of comparable molecular weights.
- For example,

  Acetic acid (mol wt = 60) boils at 118°C.

  n-Propyl alcohol (mol wt = 60) boils at only 97° C.

- In fact, simple carboxylic acids exist as *hydrogen-bonded dimers* .



- The first nine aliphatic acids are colorless liquids that have sharp, acrid odors.
- Pure acetic acid is called *glacial acetic acid* because it solidifies into ice-1ike crystals at temperatures slightly below normal room temperature (about 17°C).
- Butyric acid smells like rancid butter and strong cheese.
- Acids of five to ten carbons have goat-like smells because they are present in the skin secretion of goats.
- Higher acids are wax-like solids and are practically odorless.
- Aromatic acids are also high-melting odorless solids.

Some Physical Properties of Acids and Alcohols of Corresponding Molecular Weights.

Structure	Name	Mol. Wt.	b.p. °C	Solubility in H_2O at 25°C
HCOOH CH_3CH_2OH	Formic acid Ethyl alcohol	46 46	100 78	Very soluble Very soluble
CH_3COOH $CH_3CH_2CH_2OH$	Acetic acid *n*-Propyl alcohol	60 60	118 97	Very soluble Very soluble
$CH_3(CH_2)_3COOH$ $CH_3(CH_2)_4CH2OH$	Valeric acid *n*-Hexyl alcohol	102 102	187 156	4.0 g/100 g H_2O 0.6 g/100 g H_2O
Ph-COOH Ph-CH_2CH_2OH	Benzoic acid 3-Phenylethanol	122 122	250 250	Insoluble Insoluble

Acid Strength

- The strength of an acid depends on the extent it ionizes.
- Common mineral acids, such as HCl or HNO_3, ionize completely and are considered therefore to be strong acids.

$$\boxed{HCl \longrightarrow H^+ + Cl^-}$$

- Carboxylic acids are weak acids.

  Because they are incompletely ionized and exist in equilibrium with a solution of their ions.

$$\boxed{RCOOH \longrightarrow H^+ + RCOO^-}$$

Acid Strength and Acid Structure

- **Carboxylic acids are much more acidic than are alcohols even though both classes of compounds contain an OH group.**

  - **Why is this so?**

    The structures of their conjugate bases, the carboxylate anion and the alkoxide anion,

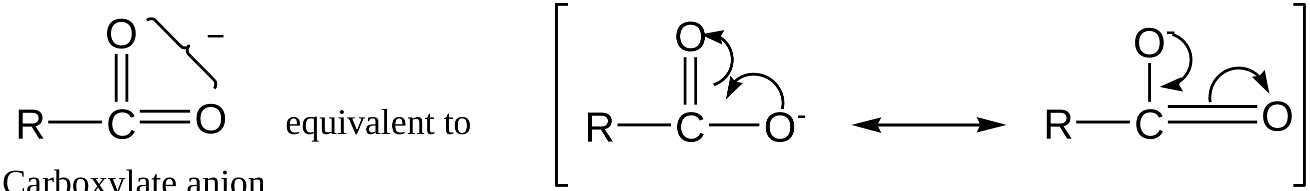
$$RCOOH \longrightarrow RCOO{:}^{-} \quad + \quad H^{+}$$

Carboxylic acid — Carboxylate anion

$$ROH \longrightarrow RO{:}^{-} \quad + \quad H^{+}$$

Carboxylic acid — Alkoxide anion

- **Carboxylic acids are stronger acid than alcohols because *Carboxylate anions are stabilized by resonance* and Alkoxide anions are not.**



Carboxylate anion

- **Acid strength among carboxylic acids.**
  - **Generally, any factor that *stabilizes* the carboxylate anion of an acid will give it *greater* acid strength than an acid lacking that factor.**
  - **Conversely, any factor that *destabilizes* the carboxylate anion of an acid will make that acid *less* strong.**
- **The stronger acid is the one with the electron-withdrawing group compared to unsubstituted acid.**

  By dispersing the negative charge.
- **Examples of common electron-withdrawing, and acid-strengthening, groups are**

F, Cl, Br, NO$_2$, CN, SO$_3$H, COOH

Acid-strengthening substituents

- **Addition of any electron-donating substituent on the R (or Ar) portion of an acid decreases its acid strength relative to the parent unsubstituted acid.**
  - **The electron-donating group destabilizes the carboxylate anion.**

    By intensifying the negative charge.

- **The most common electron-donating, acid-weakening substituent is** *the alkyl group (methyl, ethyl, propyl, and so on.*
- **Formic acid (no alkyl group) is a stronger acid than acetic acid (one alkyl group).**

Comparison of Acid Strengths of Acetic Acid and Chlorinated Acetic Acids

Name	Structure	pK_a	Relative acid strength
Acetic acid	CH_3COOH	4.7	1
Chloroacetic acid	$ClCH_2COOH$	2.8	80
Dichloroacetic acid	$Cl_2CHCOOH$	1.3	2800
Trichloroacetic acid	Cl_3CCOOH	0.7	11000

Comparison of Acid Strengths of Butyric Acid and the Monochlorinated Acids

Name	Structure	pK_a	Relative acid strength
Butyric acid	$CH_3CH_2CH_2COOH$	4.82	1
α-Chlorobutyric acid	$CH_3CH_2CHClCOOH$	2.85	92
β-Chlorobutyric acid	$CH_3CHClCH_2COOH$	4.05	6
γ-Chlorobutyric acid	$ClCH_2CH_2CH_2COOH$	4.52	2

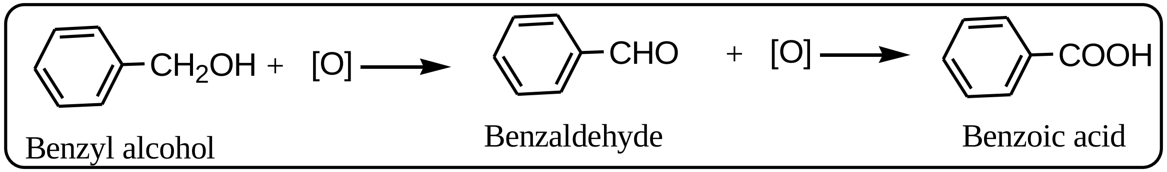
Preparation of Carboxylic Acids

Preparation of Acids by Oxidation

A. Oxidation of Primary Alcohols or Aldehydes

- **Primary alcohols** are oxidized to carboxylic acids by potassium permanganate, $KMnO_4$, or by a mixture of potassium dichromate, $K_2Cr_2O_7$, and sulfuric acid.

$$\underset{\text{Ethyl alcohol}}{CH_3CH_2OH} + [O] \longrightarrow \underset{\text{Acetaldehyde}}{CH_3CHO} + [O] \longrightarrow \underset{\text{Acetic acid}}{CH_3COOH}$$



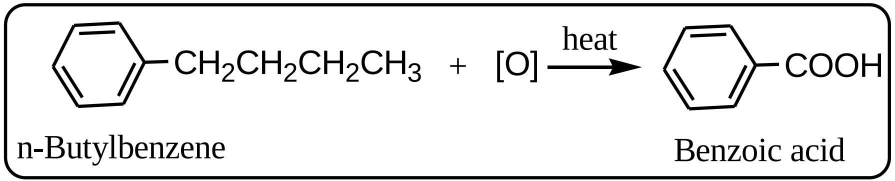
Benzyl alcohol

Benzaldehyde

Benzoic acid

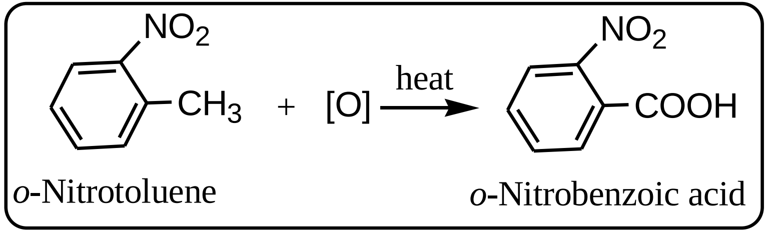
B. Oxidation of Alkylbenzenes

- Vigorous oxidation of alkylbenzenes yields benzoic acid.



n-Butylbenzene

Benzoic acid

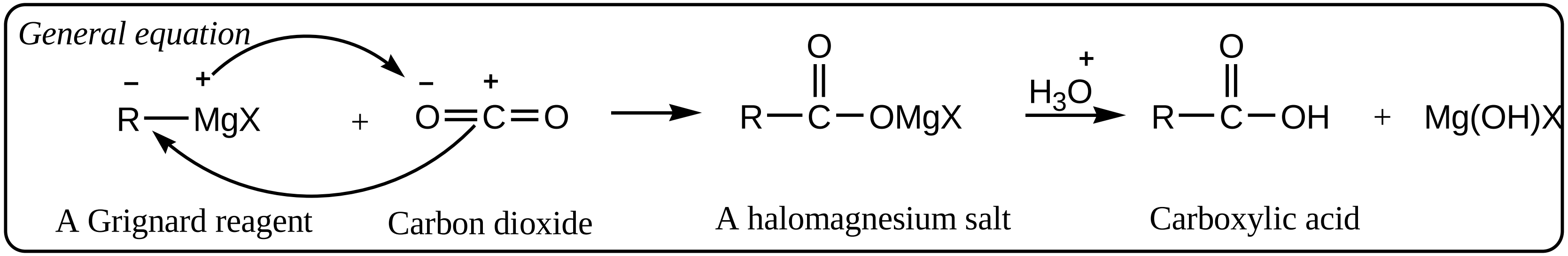


o-Nitrotoluene

o-Nitrobenzoic acid

Carbonation of Grignard Reagents

- **The addition of Grignard reagents to CO_2 in the form of dry ice proceeds in a similar fashion and yields the halomagnesium salt of a carboxylic acid.**
- **Hydrolysis of the salt gives an acid with one carbon more than the original Grignard reagent**



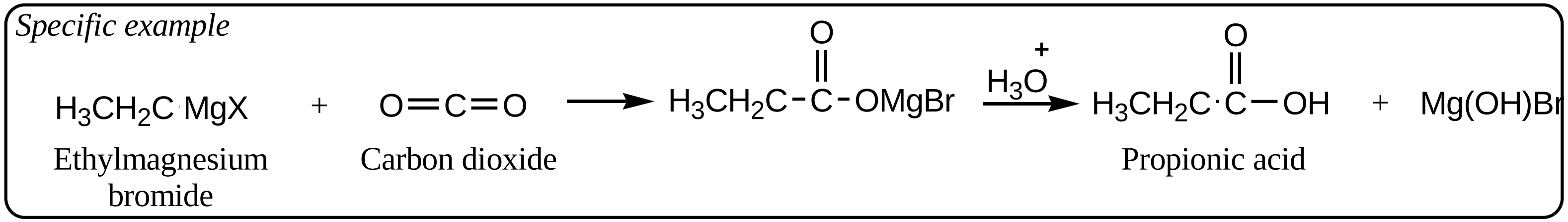
General equation

A Grignard reagent

Carbon dioxide

A halomagnesium salt

Carboxylic acid



Specific example

Ethylmagnesium bromide

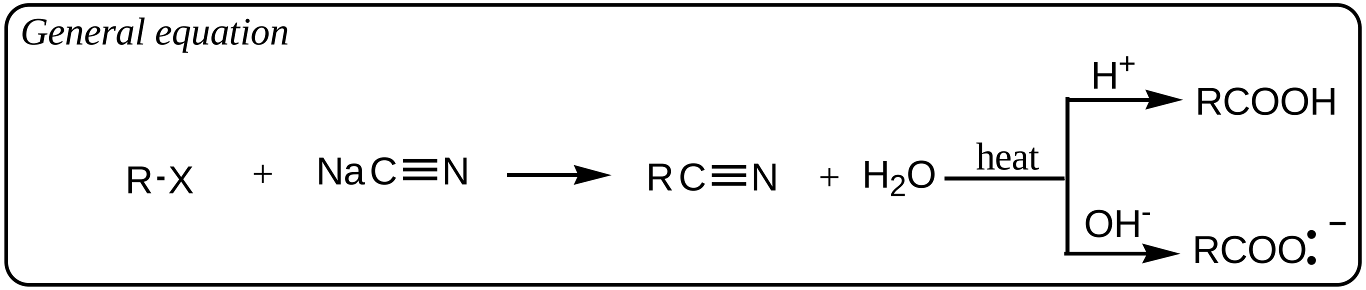
Carbon dioxide

Propionic acid

Hydrolysis of Nitriles

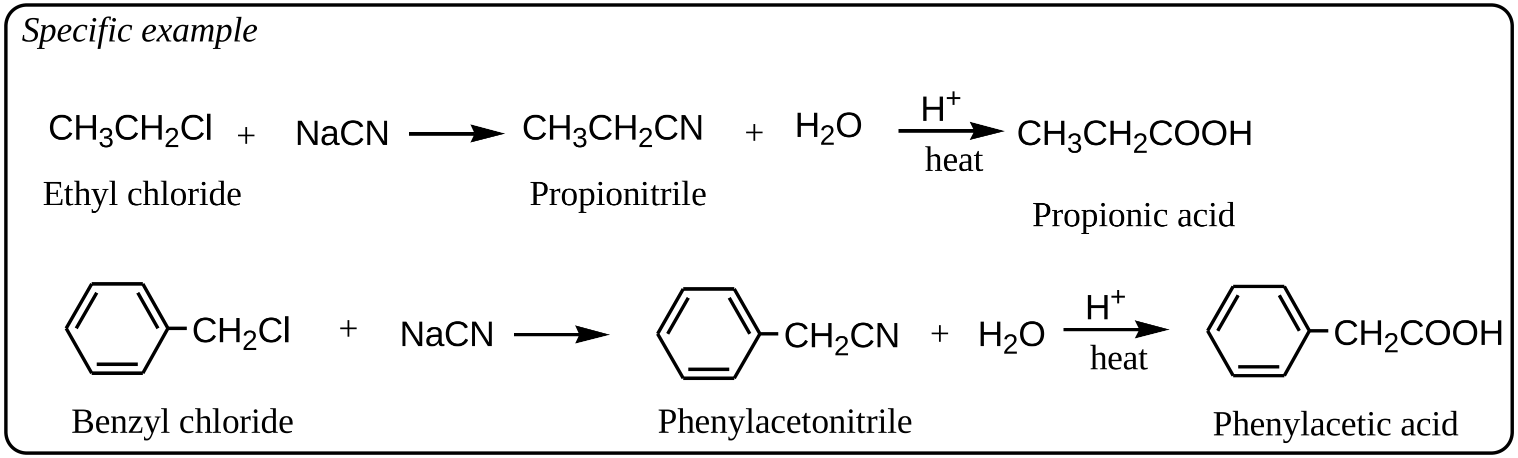
- **Nitriles are compounds with the general formula RCN or ArCN.**
- **They are prepared by reacting a 1° or 2° alkyl halide with a cyanide salt.**

- **Acid hydrolysis of a nitrile yields a carboxylic acid. Alkaline hydrolysis yields a carboxylate salt.**
- **The carboxylate acid or salt contain one carbon more than the starting alkyl halide.**



General equation

$$R\text{-}X + NaC{\equiv}N \longrightarrow RC{\equiv}N + H_2O \xrightarrow{heat} \begin{cases} \xrightarrow{H^+} RCOOH \\ \xrightarrow{OH^-} RCOO\!:^- \end{cases}$$



Specific example

$$CH_3CH_2Cl + NaCN \longrightarrow CH_3CH_2CN + H_2O \xrightarrow[heat]{H^+} CH_3CH_2COOH$$

Ethyl chloride, Propionitrile, Propionic acid

Benzyl chloride, Phenylacetonitrile, Phenylacetic acid

Reactions of Carboxylic Acids

Reactions with Bases: Salt Formation

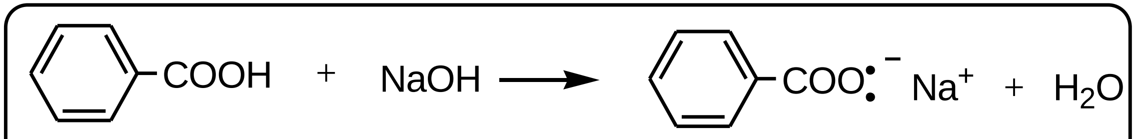
- Carboxylic acids react quantitatively with bases to form water-soluble salts.
- The metal cation is named first, followed by the name of the carboxylate anion.
- The latter is named by dropping the *-ic acid* ending from the name of the parent acid and replacing it with *–ate*.

$$HCOOH + KOH \longrightarrow HCOO^{-}\ K^{+} + H_2O$$

Formic acid — Potassium formate

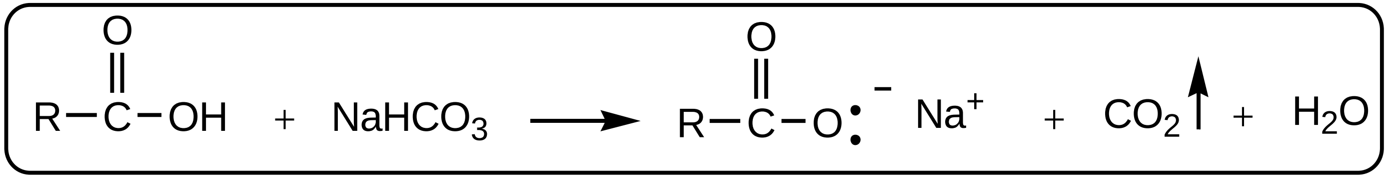
$$CH_3COOH + NaOH \longrightarrow CH_3COO^{-}\ K^{+} + H_2O$$

Acetic acid — Sodium acetate



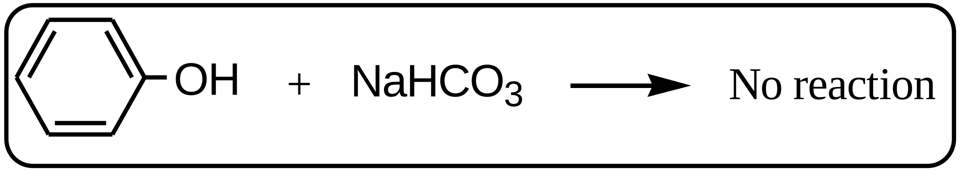
Benzoic acid — Sodium benzoate

- **Sodium acetate** is used in dyeing.
- **Sodium propionate, $CH_3CH_2COO:^{-}Na^{+}$, and calcium propionate, $(CH_3CH_2COO:^{-})_2Ca^{2+}$,** are used in bread to prevent molding.
- **Sodium benzoate** is a food preservative.
- **Carboxylic acids** will also react with a weak base like sodium bicarbonate, $NaHCO_3$, to form
  - Water-soluble salts.
  - Carbon dioxide is liberated as a by-product.



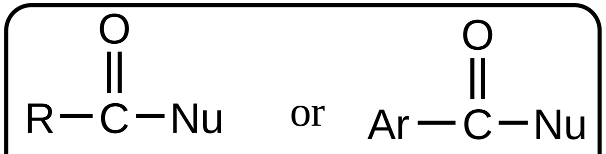
$$R-\overset{\overset{O}{\|}}{C}-OH + NaHCO_3 \longrightarrow R-\overset{\overset{O}{\|}}{C}-O:^{-}\ Na^{+} + CO_2\uparrow + H_2O$$

- **Weaker acids like phenols** react only with strong bases (NaOH or KOH) and will not react with $NaHCO_3$.



Carboxylic Acid Derivatives

- **When the OH of a carboxylic acid is replaced by a nucleophile, : Nu, a carboxylic acid derivative is produced.**

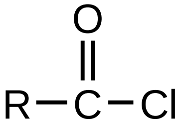


$R-\overset{\overset{O}{\|}}{C}-Nu$ or $Ar-\overset{\overset{O}{\|}}{C}-Nu$

Carboxylic acid derivatives

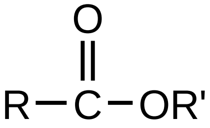
- **The RCO- portion of acid derivatives is called the acyl group.**
  Aromatic acid derivatives contain the aryl group.

- **The carboxylic acid derivatives are**



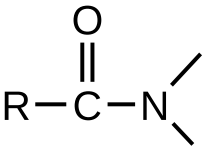
$R-\overset{\overset{O}{\|}}{C}-Cl$

Acyl chloride
Acid chloride

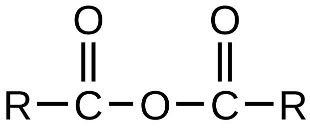


$R-\overset{\overset{O}{\|}}{C}-OR'$

Ester



Amide

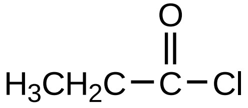


$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R$

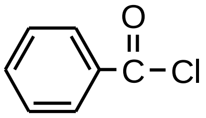
Acid anhydride

Nomenclature of Acid Derivatives

- **Acyl chlorides, or acid chlorides**, are named by replacing the *-ic acid* ending of the parent acid by *-yl chloride*.



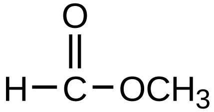
$H_3CH_2C-\overset{O}{\overset{\|}{C}}-Cl$



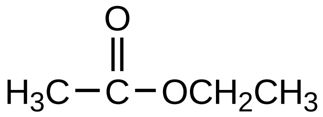
IUPAC name:	Propanoyl chloride	Benzoyl chloride
Common name:	Propionyl chloride	

- **Esters** are named as if they were formed from replacement of the carboxyl hydrogen by an alkyl group.

  - The alkyl group is named first followed by the name of the parent acid with the ending *-ate* in place of *-ic acid*.

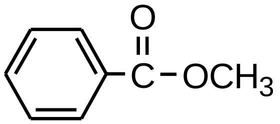


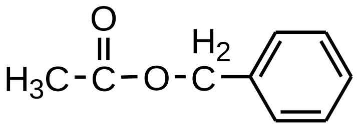
$H-\overset{O}{\overset{\|}{C}}-OCH_3$



$H_3C-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$

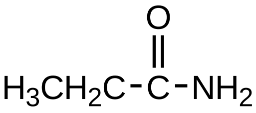
IUPAC name:	Methyl methanoate	Ethyl ethanoate
Common name:	Methyl formate	Ethyl acetate



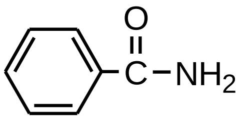


IUPAC name:	Methyl benzoate	Benzoyl ethanoate
Common name:		Benzyl acetate

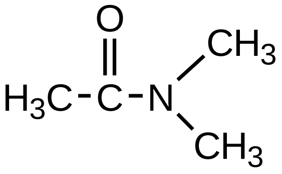
- **Amides** are named by replacing the *-oic acid* or *-ic acid* of the parent acid's name by *–amide*.

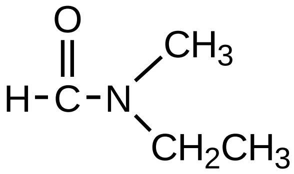


$H_3CH_2C-\overset{\overset{O}{\|}}{C}-NH_2$



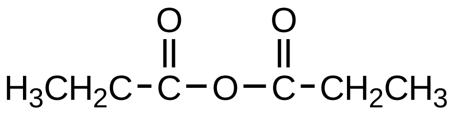
IUPAC name:	Propanamide	Benzamide
Common name:	Propionamide	



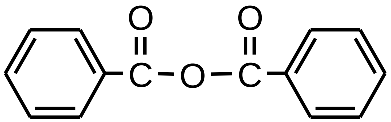


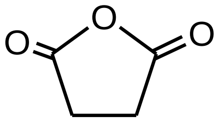
IUPAC name:	*N*,*N*-Dimethylethanamide	*N*-Ethyl-*N*-methylmethanamide
Common name:	*N*,*N*-Dimethylacetamide	*N*-Ethyl-*N*-methylformamide

- **An anhydride is named by replacing the word *acid* with *anhydride* in the name of the acid from which it was formed.**



$H_3CH_2C-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-CH_2CH_3$

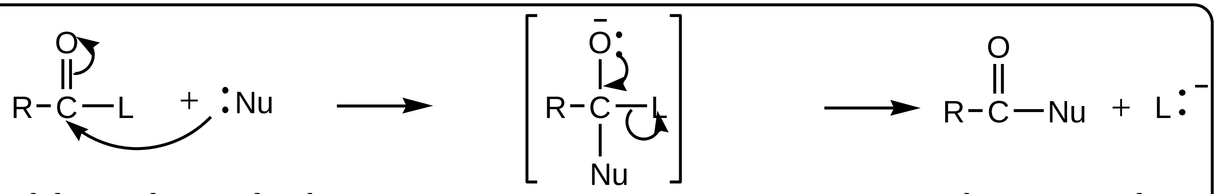




IUPAC name:	Propanoic anhydride	Benzoic anhydride	Succinic anhydride
Common name:	Propionic anhydride		

Nucleophilic Substitution of Acid Derivatives

- Most reactions of acids and acid derivatives proceed by a common mechanism: **nucleophilic substitution**.



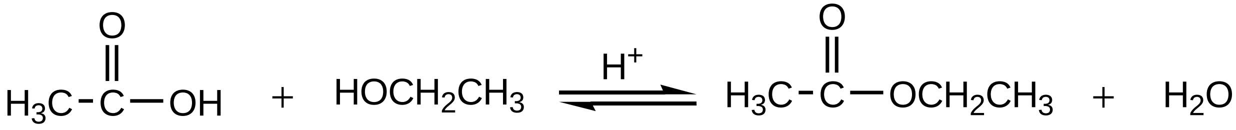
Nucleophilic attach on acyl carbon — Elimination of leaving group, L — Substitution product

- The **leaving group, L**, may be **OH, OR, Cl, OCOR or NH_2**.

Esters from Carboxylic Acids: Esterfication

- **Esters** are formed by treatment a carboxylic acid with a primary or secondary alcohol.
- A small amount of mineral acid catalyst (H^+) is required to speed up esterification.

Specific example

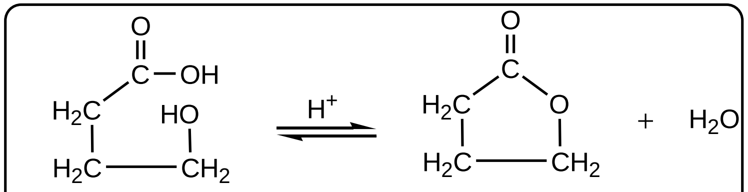


$$H_3C-\overset{\overset{O}{\|}}{C}-OH + HOCH_2CH_3 \overset{H^+}{\rightleftharpoons} H_3C-\overset{\overset{O}{\|}}{C}-OCH_2CH_3 + H_2O$$

Acetic acid — Ethyl alcohol — Ethyl acetate

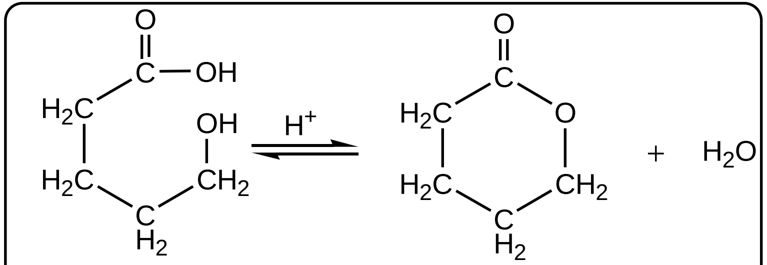
Intramolecular esterification.

- **If the acid and alcohol functions are part of the same molecule.**
- **The product, in such cases, is *a cyclic ester* or lactone.**



C-Hydroxbutyric acid
(OH on fourth carbon)

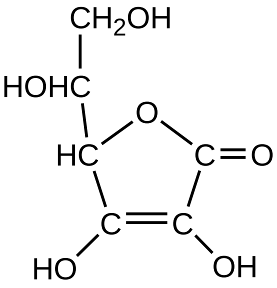
C-Butyrolactone
(five-membred lactone)



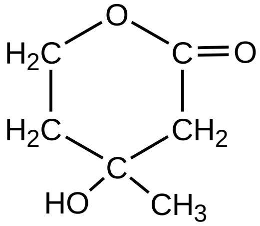
d-Hydroxvaleric acid

d-Valeroolactone
(six-membred lactone)

- **Ascorbic acid (vitamin C) and the lactone of mevalonic acid are two naturally occurring lactones.**



L-Ascorbic acid
(Vitamin C)

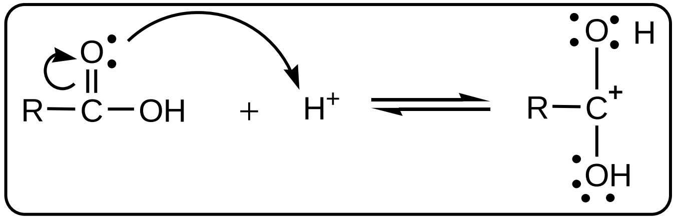


Lactone of mevalonic acid
(precursor of cholesterol)

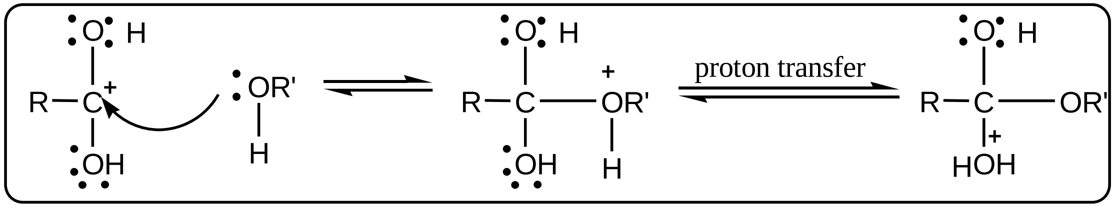
Mechanism of Esterfication

- **Esterification is a nucleophiic substitution reaction.**
- **The steps in the mechanism are**

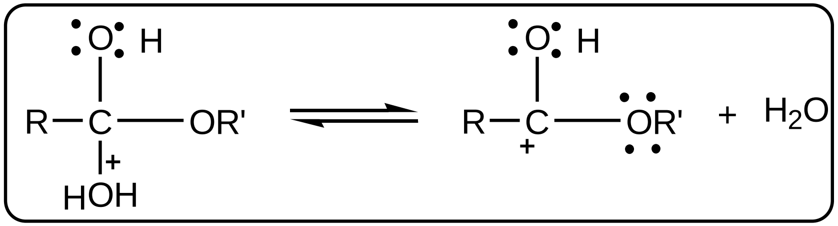
Step 1. Protonation of the acyl group oxygen.



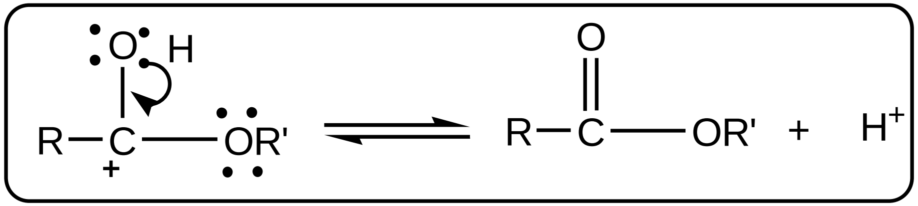
Step 2. Attack by alcohol nucleophile on positively charged carbon, followed by proton transfer.



Step 3. Elimination of H_2O.

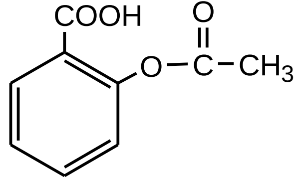


Step 4. Regeneration of proton catalyst and formation of ester.



Sources and Uses of Esters

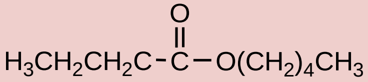
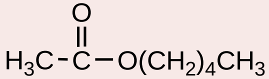
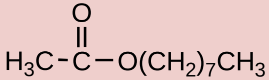
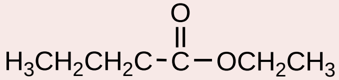
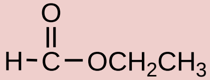
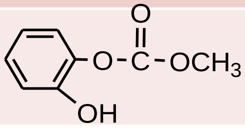
- **Fats**, **oils**, **and** **waxes** **are naturally occurring esters of high molecular weight.**
- **A very common ester of medicinal importance is acetylsalicylic acid (aspirin).**



Acetylsalicylic acid
(Aspirin)

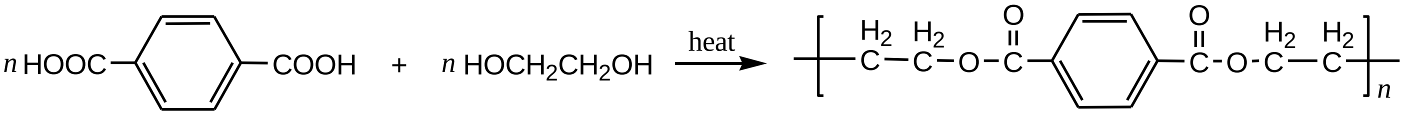
- **Lower-molecular-weight esters are excellent solvents for many organic compounds.**

Low-molecular-weight esters are pleasant-smelling substances.

Flavor	Name	Structure
Apricot	*n*-Pentyl butyrate	 $H_3CH_2CH_2C-\overset{\overset{O}{\|}}{C}-O(CH_2)_4CH_3$
Banana	*n*-Pentyl acetate	 $H_3C-\overset{\overset{O}{\|}}{C}-O(CH_2)_4CH_3$
Orange	*n*-Octyl acetate	 $H_3C-\overset{\overset{O}{\|}}{C}-O(CH_2)_7CH_3$
Pineapple	Ethyl butyrate	 $H_3CH_2CH_2C-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$
Rum	Ethyl formate	 $H-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$
Wintergreen	Methyl salicylate	

Other esters are suitable textile fibers.

The best-known polyester, Dacron, is polyethylene terephthalate, formed from the polymerization of ethylene glycol and terephthalic acid



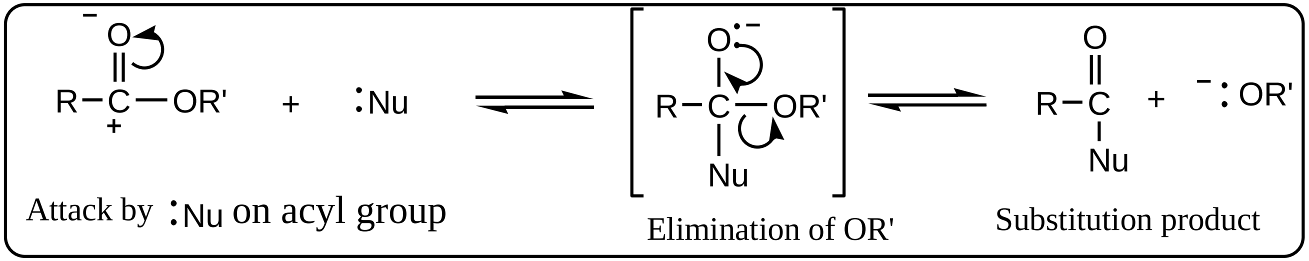
Terephthalic acid

Ethylene glycol

Polethylene terephthalate
(Terylene; Dacron)

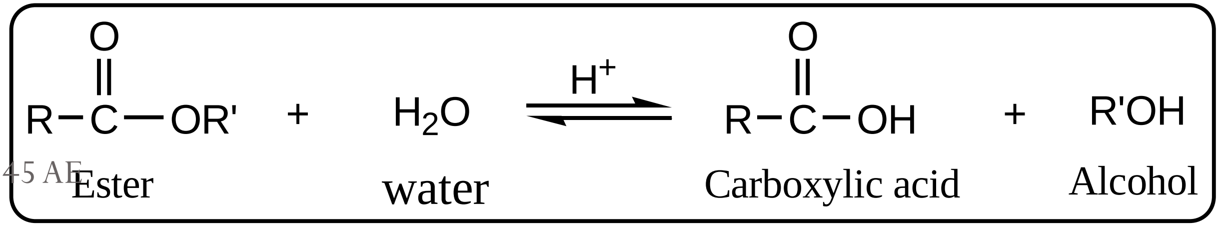
Reactions of Esters

- Nucleophilic attack on the acyl carbon followed by elimination of the OR group.



A. Acid-Catalyzed Hydrolysis of Esters

- When a compound is broken down by the action of water, the reaction is called hydrolysis.
- The hydrolysis of an ester gives a carboxylic acid and an alcohol.
- The reaction is catalyzed by strong mineral acids H^+.
- Acid-catalyzed hydrolysis, like acid-catalyzed esterification, is an equilibrium reaction that does not go to completion

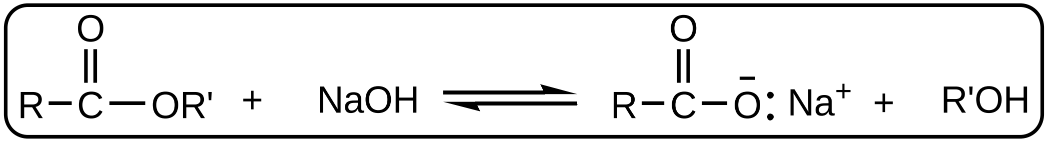


$$R-C(=O)-OR' + H_2O \overset{H^+}{\rightleftharpoons} R-C(=O)-OH + R'OH$$

B. *Alkaline Hydrolysis of Esters: Saponification*

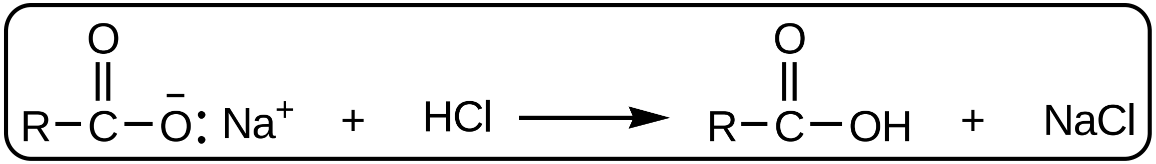
- **Alkaline hydrolysis** of an ester is called **saponification.**

  because soap is the product of alkaline hydrolysis of esters of glycerol and long- chain fatty acids.



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR'} \;+\; \mathrm{NaOH} \;\rightleftharpoons\; \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{-}{O}\colon\, Na^{+}} \;+\; \mathrm{R'OH}$$

- **Treatment of the salt with mineral acid regenerates the organic acid.**

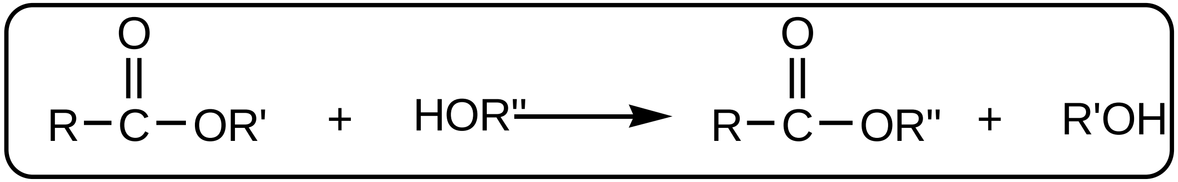


$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{-}{O}\colon\, Na^{+}} \;+\; \mathrm{HCl} \;\longrightarrow\; \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} \;+\; \mathrm{NaCl}$$

C. *Alcoholysis: Transesterfication*

- **Alcoholysis is the acid-catalyzed reaction between an ester and an alcohol to give an equilibrium mixture with another ester and another alcohol.**

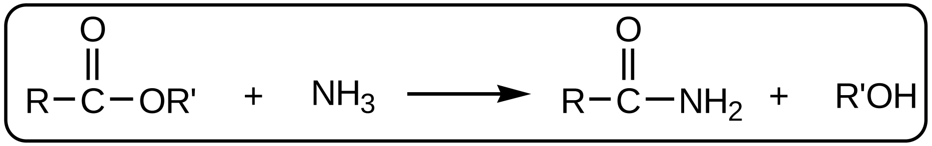
Ester interchange, or transesterification.



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR'} \;+\; \mathrm{HOR''} \;\longrightarrow\; \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR''} \;+\; \mathrm{R'OH}$$

D. *Ammonolysis of Esters*

- **Ammonolysis** is the reaction of esters with ammonia to form an amide and an alcohol.

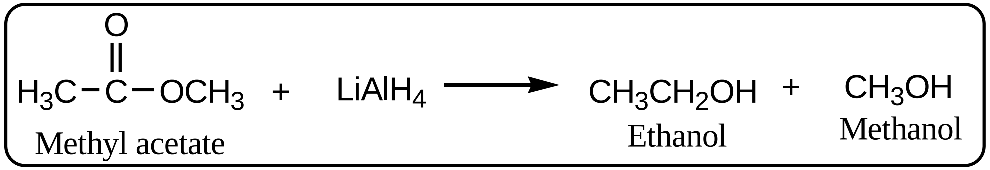


$$R-\overset{O}{\overset{\|}{C}}-OR' + NH_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}-NH_2 + R'OH$$

- The amide group, -CON-, is widely distributed in nature, especially in protein molecules

E. *Reduction of Esters*

- The reduction of esters with lithium aluminum hydride, $LiAlH_4$ produces two moles of alcohol:



$$H_3C-\overset{O}{\overset{\|}{C}}-OCH_3 + LiAlH_4 \longrightarrow CH_3CH_2OH + CH_3OH$$

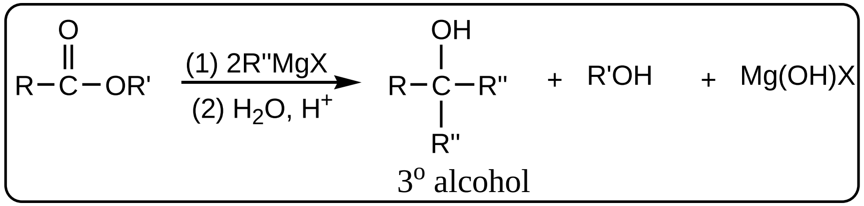
Methyl acetate

Ethanol

Methanol

F. *Esters and Grignard Reagents*

- The carbonyl group of an ester can react with a Grignard reagent to form a *tertiary alcohol.*



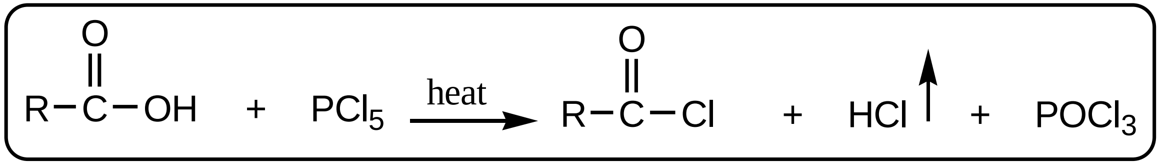
$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow[(2)\ H_2O,\ H^+]{(1)\ 2R''MgX} R-\overset{OH}{\overset{|}{\underset{R''}{\underset{|}{C}}}}-R'' + R'OH + Mg(OH)X$$

3^o alcohol

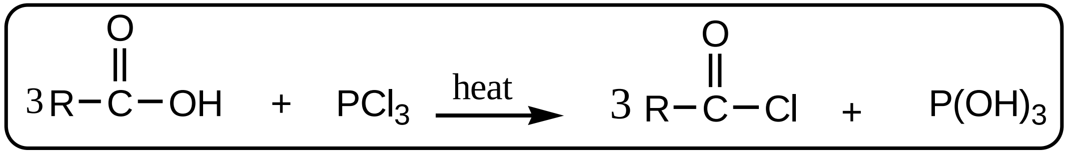
Acid Chlorides: Preparation

- Acid chlorides are reactive compounds and are important intermediates for the synthesis of other acid derivatives.

- They are prepared by reaction of a carboxylic acid with phosphorus chlorides (PCl_5 or PCl_3) or with thionyl chloride ($SOCl_2$).



$$\mathrm{R-\overset{\overset{O}{\|}}{C}-OH} + \mathrm{PCl_5} \xrightarrow{\text{heat}} \mathrm{R-\overset{\overset{O}{\|}}{C}-Cl} + \mathrm{HCl}\uparrow + \mathrm{POCl_3}$$

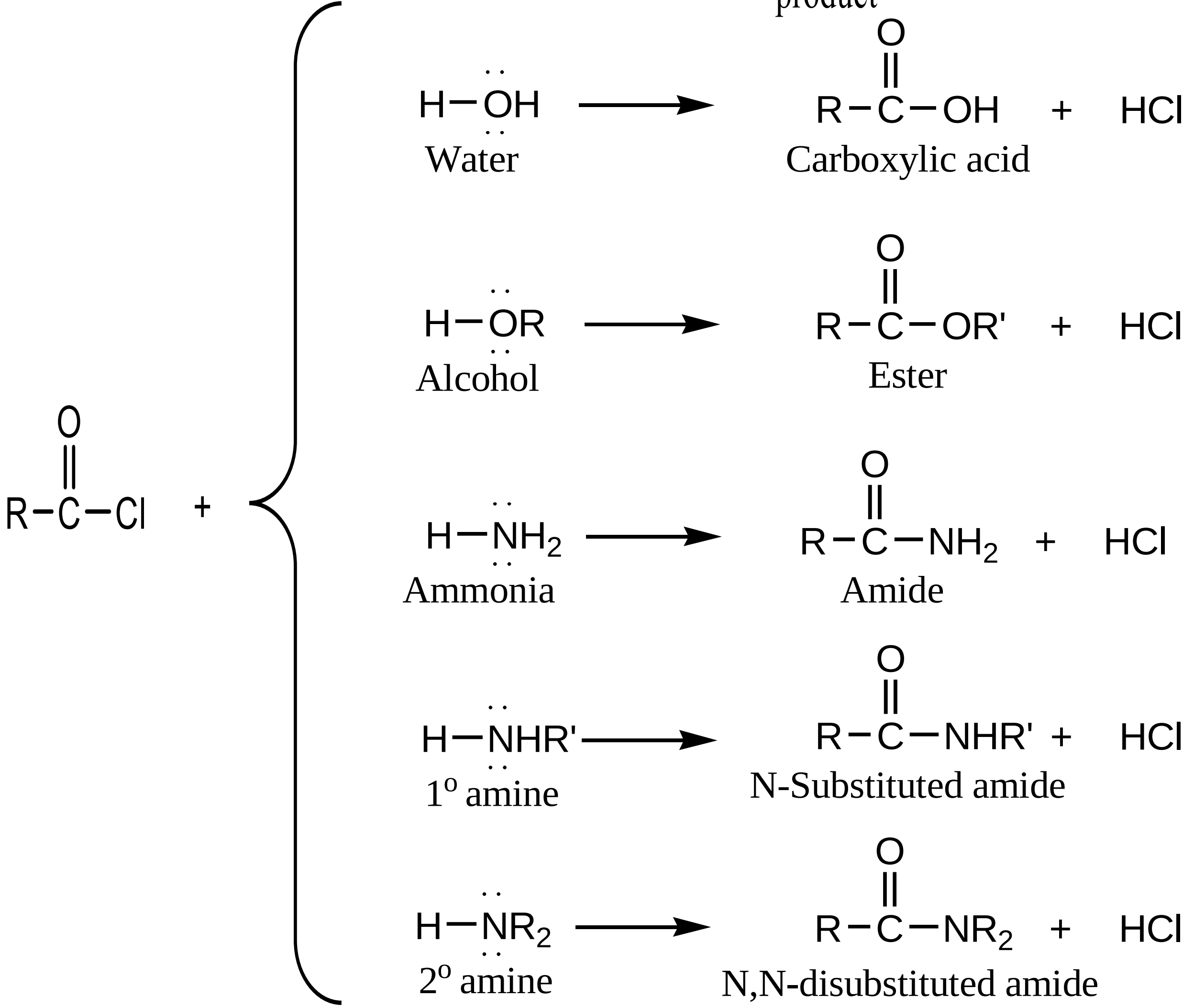


$$3\,\mathrm{R-\overset{\overset{O}{\|}}{C}-OH} + \mathrm{PCl_3} \xrightarrow{\text{heat}} 3\,\mathrm{R-\overset{\overset{O}{\|}}{C}-Cl} + \mathrm{P(OH)_3}$$

$$\mathrm{R-\overset{\overset{O}{\|}}{C}-OH} + \mathrm{SOCl_2} \xrightarrow{\text{heat}} \mathrm{R-\overset{\overset{O}{\|}}{C}-Cl} + \mathrm{SO_2}\uparrow + \mathrm{HCl}\uparrow$$

- Acid chlorides are low-boiling liquids of irritating odors.

- Acid chlorides also form aromatic ketones *via* the Friedel-Crafts acylation.

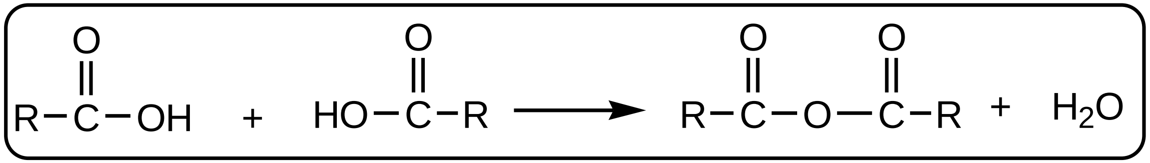


$R-\overset{O}{\overset{\|}{C}}-Cl$ +

Nucleophile		Substitution product		By-product
$H-\ddot{\underset{..}{O}}H$ Water	$\longrightarrow$	$R-\overset{O}{\overset{\|}{C}}-OH$ Carboxylic acid	+	HCl
$H-\ddot{\underset{..}{O}}R$ Alcohol	$\longrightarrow$	$R-\overset{O}{\overset{\|}{C}}-OR'$ Ester	+	HCl
$H-\ddot{\underset{..}{N}}H_2$ Ammonia	$\longrightarrow$	$R-\overset{O}{\overset{\|}{C}}-NH_2$ Amide	+	HCl
$H-\ddot{\underset{..}{N}}HR'$ 1° amine	$\longrightarrow$	$R-\overset{O}{\overset{\|}{C}}-NHR'$ N-Substituted amide	+	HCl
$H-\ddot{\underset{..}{N}}R_2$ 2° amine	$\longrightarrow$	$R-\overset{O}{\overset{\|}{C}}-NR_2$ N,N-disubstituted amide	+	HCl

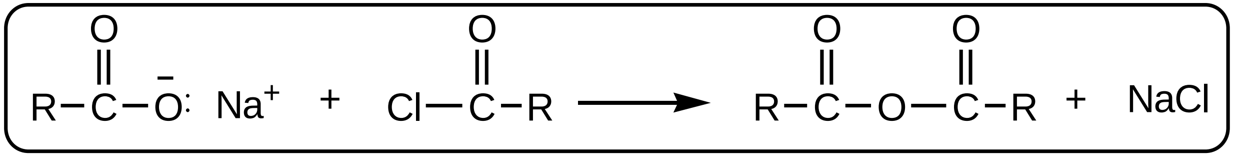
Acid Anhydrides: Preparation

- **Anhydrides are compounds that may be thought of as being formed by loss of water between two molecules of an acid.**



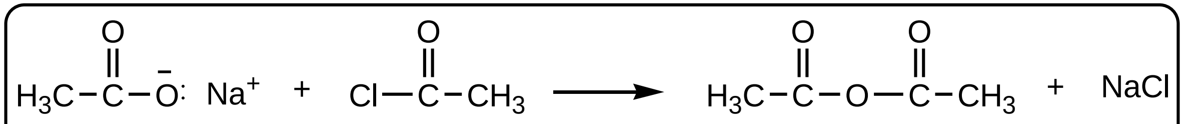
$$R-\overset{O}{\overset{\|}{C}}-OH + HO-\overset{O}{\overset{\|}{C}}-R \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R + H_2O$$

- **Most anhydrides are prepared by reaction between the sodium salt of the acid and an acid chloride.**



$$R-\overset{O}{\overset{\|}{C}}-\overset{-}{O}{:}\ Na^+ + Cl-\overset{O}{\overset{\|}{C}}-R \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R + NaCl$$

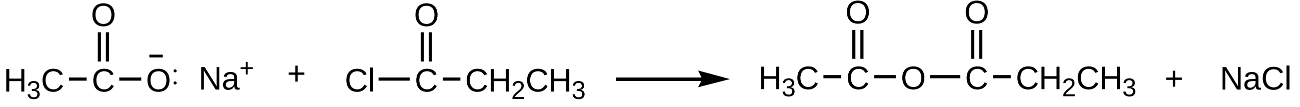
- **If the R groups of the acid salt and acid chloride are identical, we get a *anhydride*.**



$$H_3C-\overset{O}{\overset{\|}{C}}-\overset{-}{O}{:}\ Na^+ + Cl-\overset{O}{\overset{\|}{C}}-CH_3 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3 + NaCl$$

Acetic anhydride
(a simple anhydride)

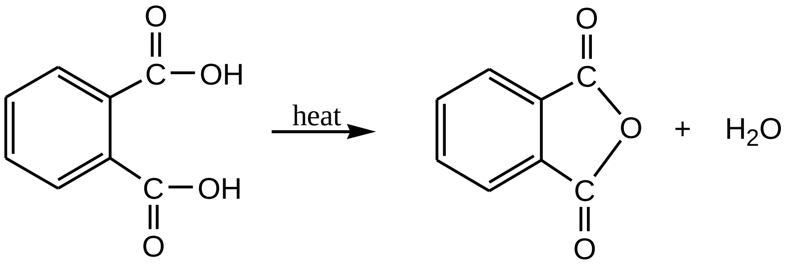
- If the R groups are not the same, we get a *mixed anhydride*



$$H_3C-\overset{O}{\overset{\|}{C}}-\overset{-}{O}{:}\ Na^+ + Cl-\overset{O}{\overset{\|}{C}}-CH_2CH_3 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_2CH_3 + NaCl$$

Acetic propionic anhydride
(a mixed anhydride)

- **Cyclic anhydrides** are prepared by **intramolecular dehydration**.

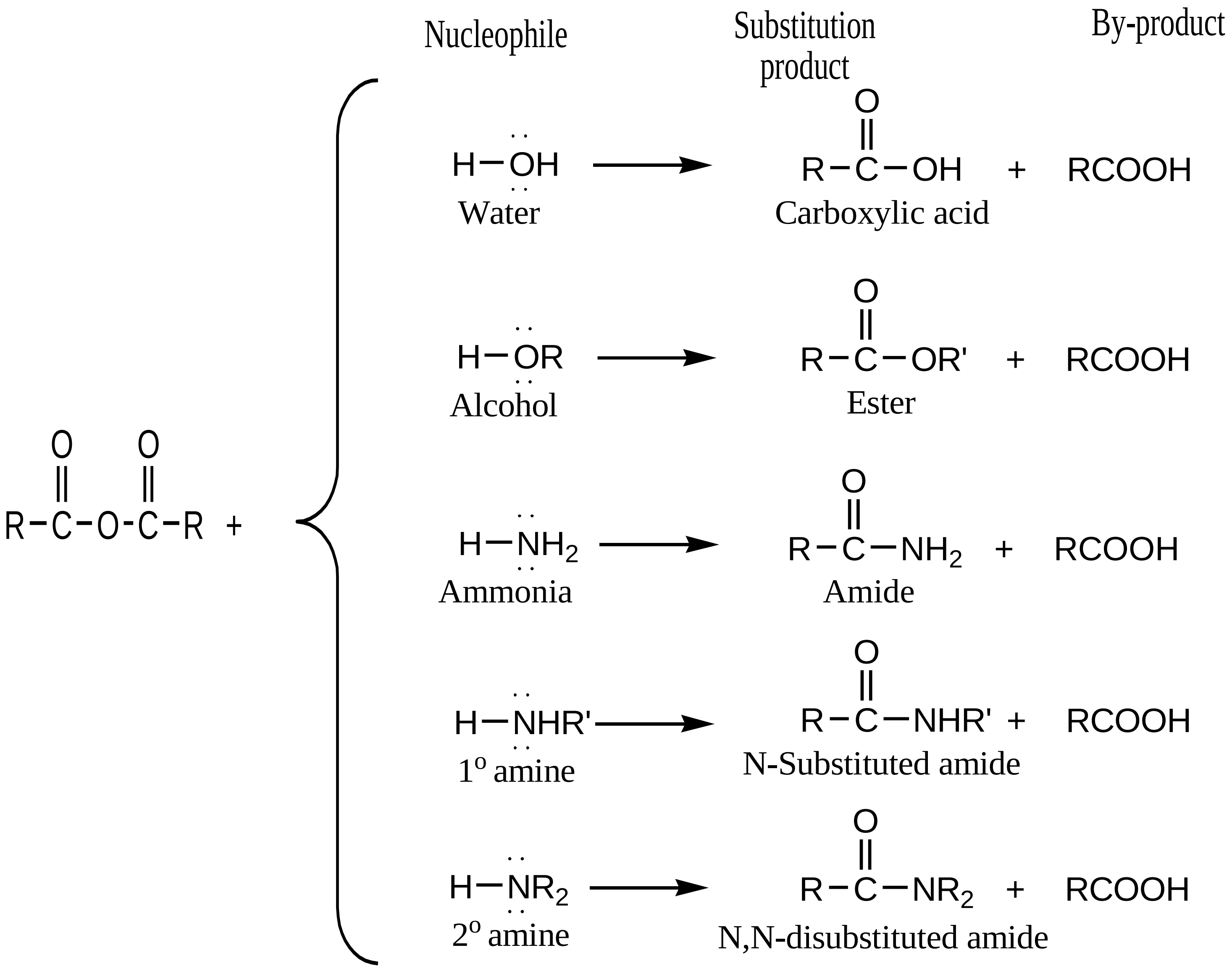


Phthalic acid

Phthalic anhydride

- The reactions of acid anhydrides with water, alcohols, ammonia, or amines parallel those already shown for the acid chlorides.

- The by-product in all reactions of acid anhydrides is always a carboxylic acid

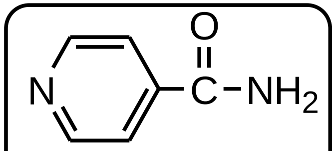


$R-C(=O)-O-C(=O)-R$ +

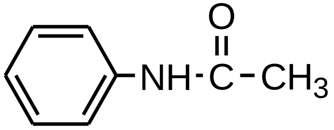
Nucleophile	Substitution product	By-product
$H-\ddot{O}H$ Water	$R-C(=O)-OH$ Carboxylic acid	+ RCOOH
$H-\ddot{O}R$ Alcohol	$R-C(=O)-OR'$ Ester	+ RCOOH
$H-\ddot{N}H_2$ Ammonia	$R-C(=O)-NH_2$ Amide	+ RCOOH
$H-\ddot{N}HR'$ 1^o amine	$R-C(=O)-NHR'$ N-Substituted amide	+ RCOOH
$H-\ddot{N}R_2$ 2^o amine	$R-C(=O)-NR_2$ N,N-disubstituted amide	+ RCOOH

Amides

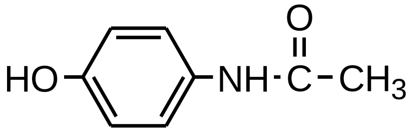
- **Amides** are commonly prepared in the laboratory by the ammonolysis of acid chlorides or acid anhydrides .
- **For example,**
  - **Nicotinamide**, the amide of nicotinic acid (niacin), is essential in the diet to prevent pellagra.
  - **Acetanilide** and a **derivative *p*-hydroxyacetanilide**, are used as pain killers.
  - **Lidocaine** is a widely used local anesthetic.



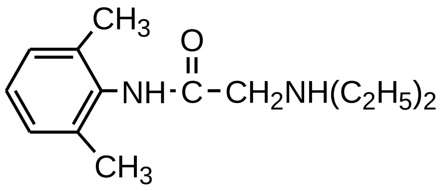
Nictonamide
(prvents pellagra)



Acetanilide
(a pain killer)

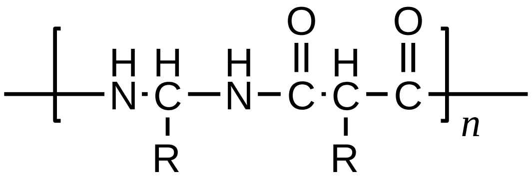


p-Hydroxyacetanilide
(a pain killer)



Lidocaine
(a local anesthetic)

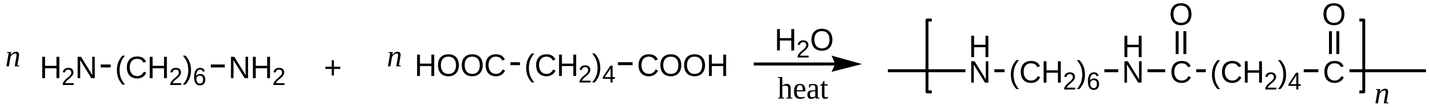
- **Proteins are polyamides containing amide linkage.**



$$-\left[\overset{H}{N}-\underset{R}{\overset{H}{C}}-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-\underset{R}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}\right]_n-$$

Polyamide polymer

- **Simpler polyamides make up the industrially important Nylon 6,6, used in the production of stockings and other textiles, and in the manufacture of brushes and plastic toys.**
- **Nylon 6,6 is made from the reaction of hexamethylenediamine and adipic acid.**



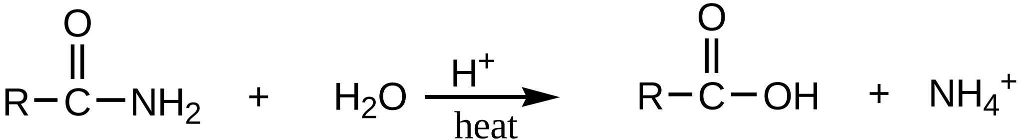
$$n\ H_2N-(CH_2)_6-NH_2 + n\ HOOC-(CH_2)_4-COOH \xrightarrow[\text{heat}]{H_2O} -\left[\overset{H}{N}-(CH_2)_6-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-(CH_2)_4-\overset{O}{\overset{\|}{C}}\right]_n-$$

Hexamethylenediamine

Adipic acid

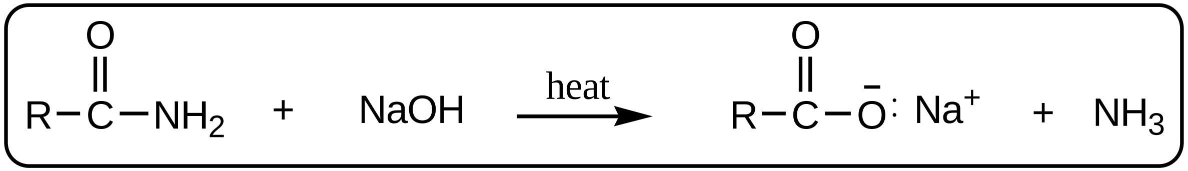
Nylon 6,6
(a polyamide)

- **Amides can be hydrolyzed in acid or in alkaline solution.**
- **Acid-catalyzed hydrolysis produces the free organic acid and an ammonium salt.**



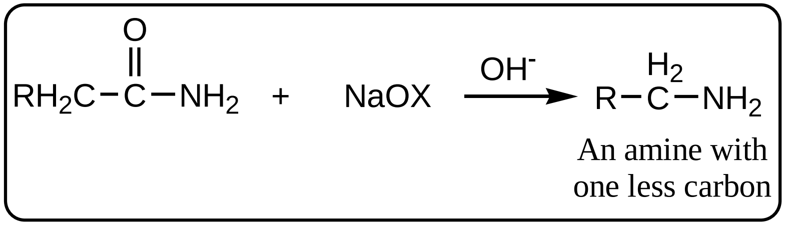
$$R-\overset{O}{\overset{\|}{C}}-NH_2 + H_2O \xrightarrow[\text{heat}]{H^+} R-\overset{O}{\overset{\|}{C}}-OH + NH_4^+$$

- **Base-catalyzed hydrolysis produces a carboxylate salt and free ammonia.**



$$R-\overset{O}{\overset{\|}{C}}-NH_2 + NaOH \xrightarrow{\text{heat}} R-\overset{O}{\overset{\|}{C}}-\overset{-}{O}\!:\ Na^+ + NH_3$$

- **Simple amides can be reduced to amines containing *one less carbon atom* by reaction with alkaline hypohalite solution.**

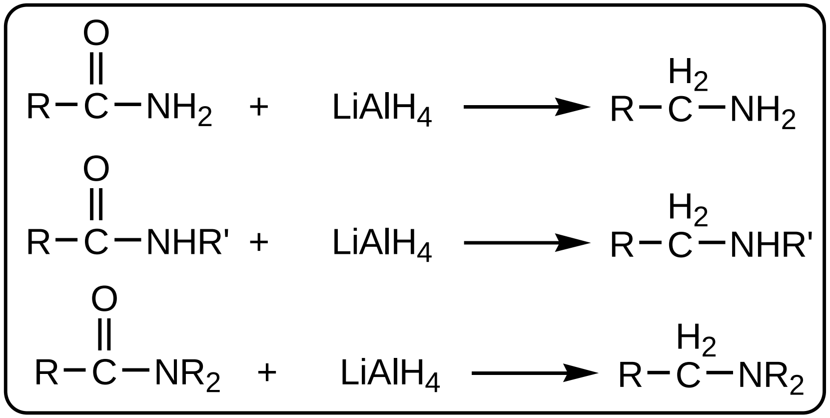


$$RH_2C-\overset{O}{\overset{\|}{C}}-NH_2 + NaOX \xrightarrow{OH^-} R-\overset{H_2}{C}-NH_2$$

An amine with one less carbon

- **Amides, when treated with lithium aluminum hydride, are reduced to amines.**

- **The net reaction is the conversion of the C=O in amides to CH_2.**



$$R-\overset{O}{\overset{\|}{C}}-NH_2 + LiAlH_4 \longrightarrow R-\overset{H_2}{C}-NH_2$$

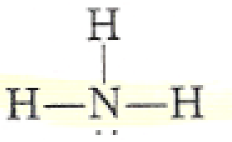
$$R-\overset{O}{\overset{\|}{C}}-NHR' + LiAlH_4 \longrightarrow R-\overset{H_2}{C}-NHR'$$

$$R-\overset{O}{\overset{\|}{C}}-NR_2 + LiAlH_4 \longrightarrow R-\overset{H_2}{C}-NR_2$$

Amines and other Nitrogen Compounds

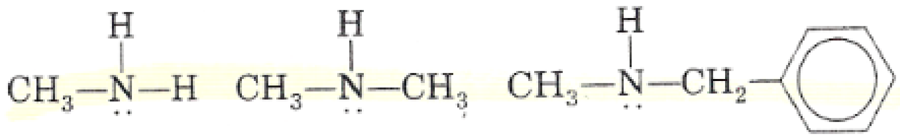
Structure and Classification of Amines

- **Amines** are compounds that derived from **ammonia** by replacement of one, two, or three hydrogens by alkyl or aryl groups.



Ammonia

- **Aliphatic amines** contain *only alkyl* groups bonded directly to the nitrogen atom.

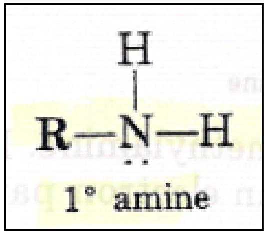


Aliphatic amines

- **Aromatic amines** are those in which one or more aryl groups are bonded directly to nitrogen.

Aromatic amines

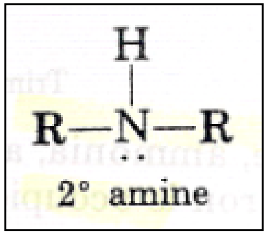
According to the number of R or Ar groups *attached to the nitrogen atom*, Amines are classified as;



$$R-\ddot{N}(H)-H$$

1° amine

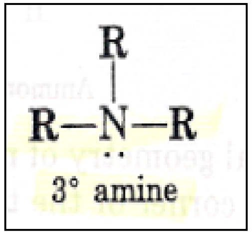
Primary (1°)



$$R-\ddot{N}(H)-R$$

2° amine

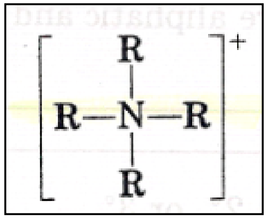
Secondary (2°)



$$R-\ddot{N}(R)-R$$

3° amine

Tertiary (3°)

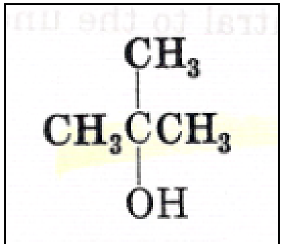


$$[R_4N]^+$$

Quaternary ammonium salt

Note

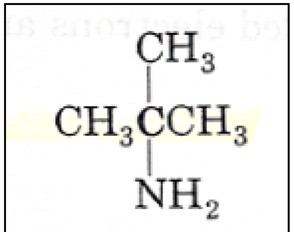
- ***t*-butyl alcohol is a tertiary alcohol (because three carbons are attached to the carbinol carbon),**



$$CH_3C(CH_3)_2OH$$

t-Butyl alcohol
(3° alcohol)

- ***t*-butyl amine is a primary amine (because only one carbon is attached directly to the nitrogen atom).**



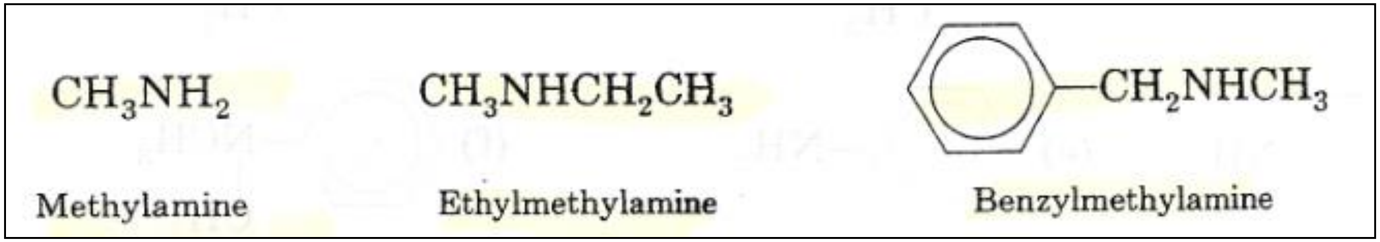
$$CH_3C(CH_3)_2NH_2$$

t-Butylamine
(1° amine)

Nomenclature of Amines

- **Simple aliphatic amines** are named by listing, in alphabetical order, the alkyl groups attached to the nitrogen atom and adding the suffix *–amine.*

Alkylamine

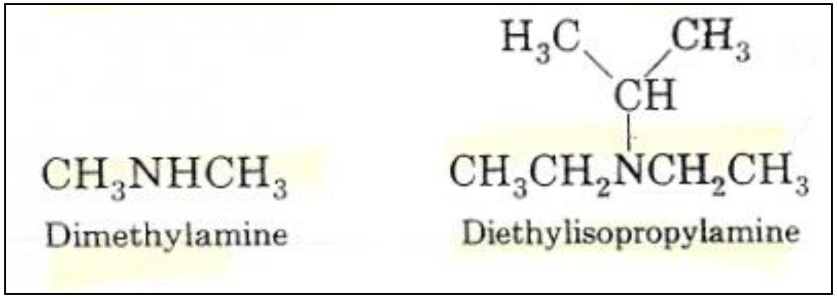


CH_3NH_2 Methylamine

$CH_3NHCH_2CH_3$ Ethylmethylamine

$C_6H_5CH_2NHCH_3$ Benzylmethylamine

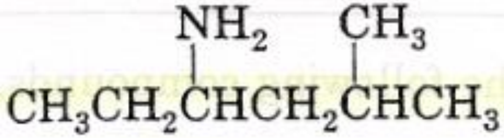
- If **two or three identical alkyl groups** are attached to the nitrogen, the prefix *di-* or *tri-* is added to the name of the amine.



CH_3NHCH_3 Dimethylamine

$CH_3CH_2N(CH(CH_3)_2)CH_2CH_3$ Diethylisopropylamine

- If the amine is complicated, the IUPAC system is used.
    - In this system the amino group (—NH_2) is considered the substituent,
    - Its position on the chain is indicated by the lowest possible number.



$CH_3CH_2\overset{\overset{NH_2}{|}}{C}HCH_2\overset{\overset{CH_3}{|}}{C}HCH_3$

3-Amino-5-methylhexane

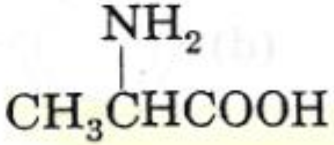
- The amino group is also considered a substituent if it is part of a molecule that contains another functional group.

$H_2NCH_2CH_2OH$

2-Aminoethanol

$H_2NCH_2CH_2CH_2OH$

3-Amino-1-propanol

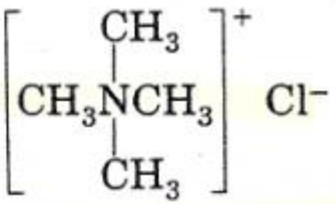


$CH_3\overset{\overset{NH_2}{|}}{C}HCOOH$

2-Aminopropanoic acid
(Alanine)

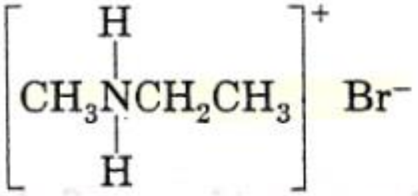
- Amine salts are named by replacing the suffix *-amine* by *ammonium*, followed by the name of the anion, which is written as a second word.

Alkylammonium + name of anion



$\left[CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{N}}CH_3\right]^+ Cl^-$

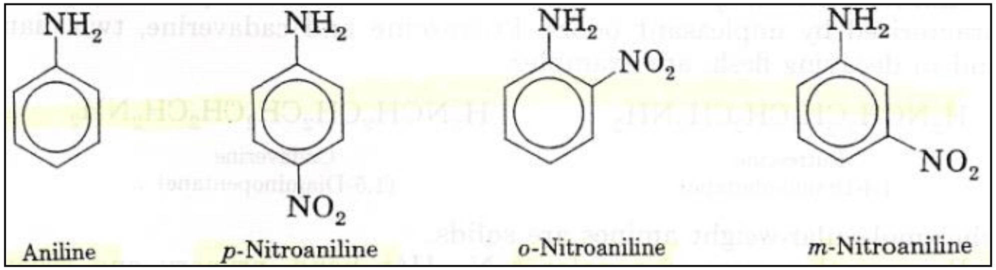
Tetramethylammonium chloride



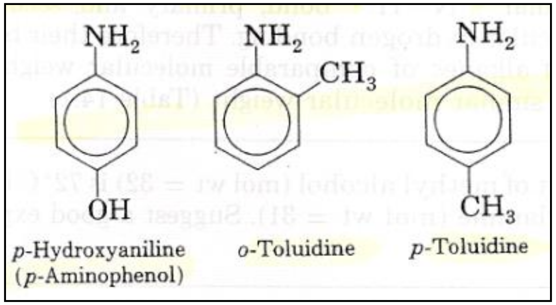
$\left[CH_3\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{N}}CH_2CH_3\right]^+ Br^-$

Ethylmethylammonium bromide

- **Aromatic amines** are usually named as **derivatives of aniline.**
  - The prefixes **ortho (*o*-), meta (*m*-), and para (*p*-)** are used to locate the position of a substituent.

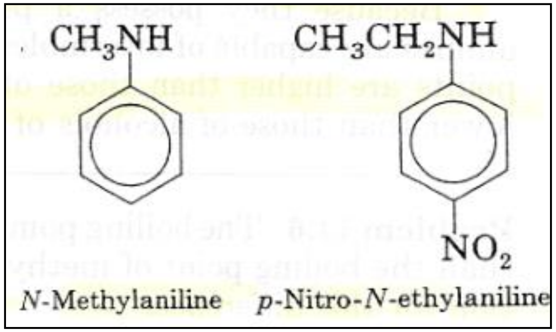


Aniline | *p*-Nitroaniline | *o*-Nitroaniline | *m*-Nitroaniline



p-Hydroxyaniline (*p*-Aminophenol) | *o*-Toluidine | *p*-Toluidine

- **If hydrocarbon groups are attached on the nitrogen atom,**
  - The letter ***N*** is prefixed to the alkyl or aryl group name.



N-Methylaniline | *p*-Nitro-*N*-ethylaniline

Physical Properties of Amines

- Low-molecular-weight aliphatic amines (methyl-, dimethyl-, and trimethylamines) are
    - Colorless gases.
    - Soluble in water.
- Amines containing 4 to 11 carbons atoms are liquids.
- Higher-molecular-weight amines are solids.
- Like ammonia, they form basic solutions.
- They have characteristically unpleasant odors that resemble the odors of ammonia and dead fish.
- Because they possess a polar $^{\delta-}\text{N—H}^{\delta+}$ bond, primary and secondary amines are capable of intermolecular hydrogen bonding.
    - Therefore their boiling points are
        - Higher than those of alkanes of comparable molecular weight.
        - Lower than those of alcohols of similar molecular weight.

- **Tertiary amines** are also polar compounds, but because hydrogen is not bonded to nitrogen, these amines are incapable of **intermolecular hydrogen bonding**.
  - Therefore their **boiling points** are
    - **Lower** than **primary** and **secondary amines** of identical **molecular weights**.
    - **Higher** than those of **alkanes** of similar **molecular weight**.
- **All amines** are capable of forming hydrogen bonds with water.
- **Amines** with up to six carbons show appreciable solubility in water.

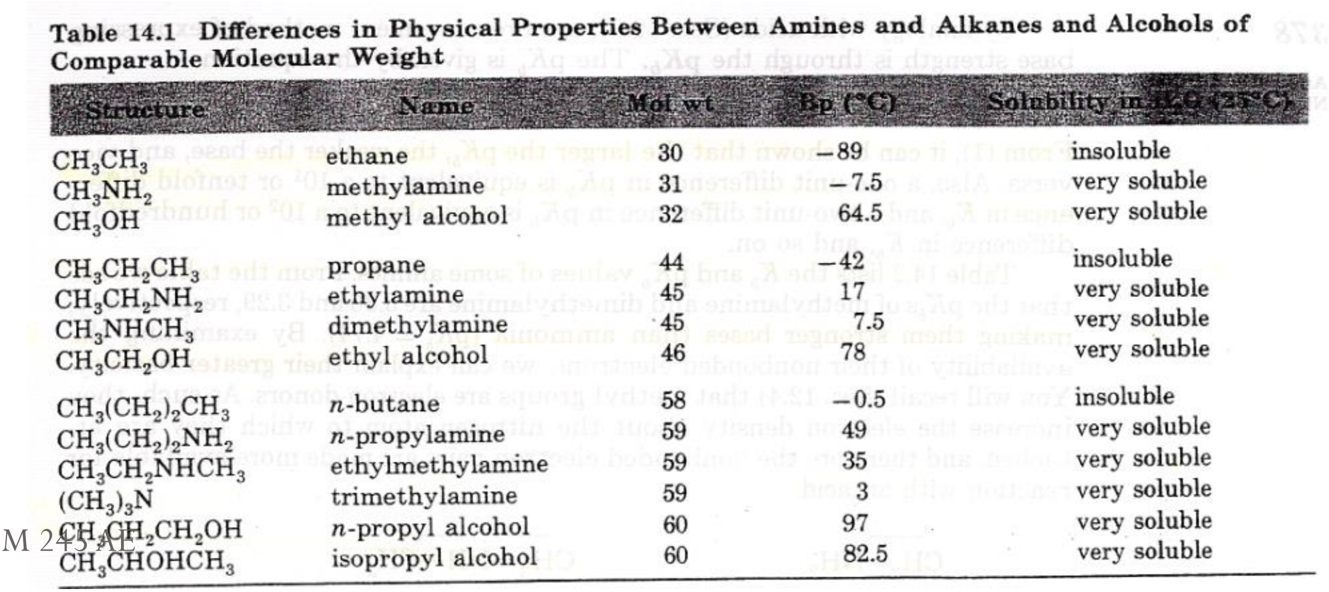
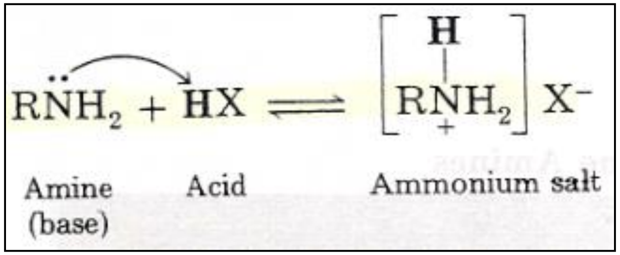


Table 14.1 Differences in Physical Properties Between Amines and Alkanes and Alcohols of Comparable Molecular Weight

Structure	Name	Mol wt	Bp (°C)	Solubility in H_2O (25°C)
CH_3CH_3	ethane	30	−89	insoluble
CH_3NH_2	methylamine	31	−7.5	very soluble
CH_3OH	methyl alcohol	32	64.5	very soluble
$CH_3CH_2CH_3$	propane	44	−42	insoluble
$CH_3CH_2NH_2$	ethylamine	45	17	very soluble
CH_3NHCH_3	dimethylamine	45	7.5	very soluble
CH_3CH_2OH	ethyl alcohol	46	78	very soluble
$CH_3(CH_2)_2CH_3$	*n*-butane	58	−0.5	insoluble
$CH_3(CH_2)_2NH_2$	*n*-propylamine	59	49	very soluble
$CH_3CH_2NHCH_3$	ethylmethylamine	59	35	very soluble
$(CH_3)_3N$	trimethylamine	59	3	very soluble
$CH_3CH_2CH_2OH$	*n*-propyl alcohol	60	97	very soluble
$CH_3CHOHCH_3$	isopropyl alcohol	60	82.5	very soluble

Basicity of Amines

- **Amines** are **bases** because the nitrogen atom has a nonbonded pair of electrons.
  - This nonbonded electron pair can be donated to an acid's proton to form an ammonium salt.



$$R\ddot{N}H_2 + HX \rightleftharpoons \left[R\overset{H}{\underset{+}{N}}H_2\right] X^-$$

- The **more available the electron pair on *N*** is to an acid, **the stronger the base, and vice versa.**
- We can explain their greater basicity.

Methyl groups are electron donors, they increase the electron density about the nitrogen atom to which they are attached, and therefore the non-bonded electron pairs are made more available for reaction with an acid

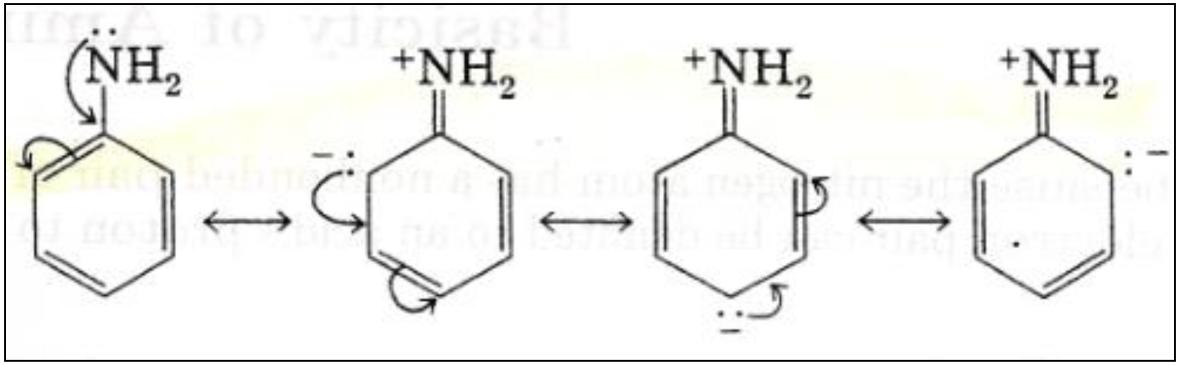
$$\overset{+\!\!\longrightarrow}{CH_3}-\ddot{N}H_2 \qquad \overset{+\!\!\longrightarrow}{CH_3}-\ddot{N}H-\overset{\longleftarrow\!\!+}{CH_3}$$

- **Aliphatic amines** are more basic than **aromatic amines**.
- For example;

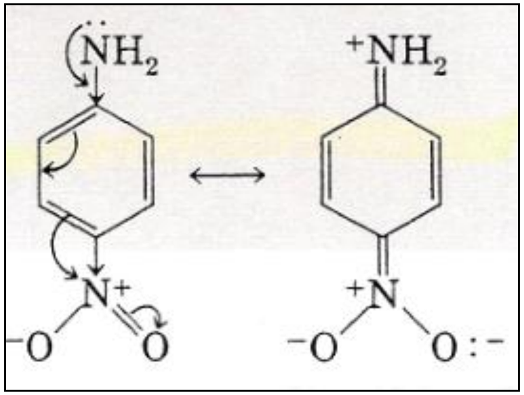
The basicity of **aniline** turns out to be almost a million times weaker than that of **methylamine**.

is attributed to resonance interactions.

- The unshared pair of electrons in the resonance hybrid is not localized on the nitrogen atom in ammonia and aliphatic amines.
- It is distributed over the aromatic ring, thus making it less available for sharing in reaction with a Lewis acid.



- **Nitroaniline** is even *more weakly basic* than **aniline**.
  - **because the *electron-withdrawing effect* of the *–NO_2* group on the ring.**
    - **lowers the electron density on the nitrogen atom,**
    - **making the electrons even less available for sharing with a Lewis acid**



Summary

- **Electron-releasing groups on the nitrogen atom of amines increase the basicity of amines,**
  and electron-withdrawing groups decrease the basicity.
- **Resonance effects in aromatic amines lower their basicity.**
- **Electron-withdrawing groups on the aromatic ring lower the basicity even more.**

Preparation of Amines

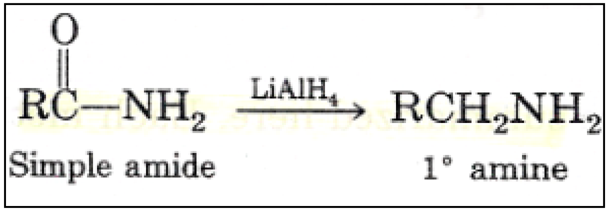
Reduction of Nitro Compounds, Nitriles and Amides;

- Catalytic hydrogenation works well with nitro compounds and nitriles to give *primary amines*.

$$CH_3CH_2NO_2 \xrightarrow{H_2/Pt} CH_3CH_2NH_2$$

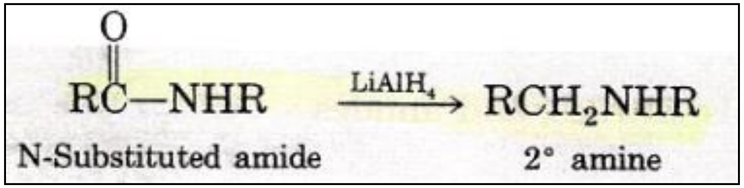
$$CH_3CH_2CN \xrightarrow{H_2/Pt} CH_3CH_2CH_2NH_2$$

- The carbonyl function of amides is reduced by **lithium aluminum hydride, $LiAlH_4$**.



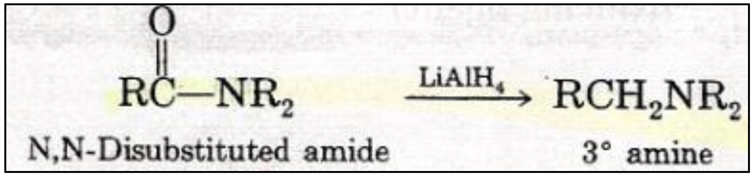
$$R\overset{O}{\overset{\|}{C}}{-}NH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

Simple amide → 1° amine



$$R\overset{O}{\overset{\|}{C}}{-}NHR \xrightarrow{LiAlH_4} RCH_2NHR$$

N-Substituted amide → 2° amine

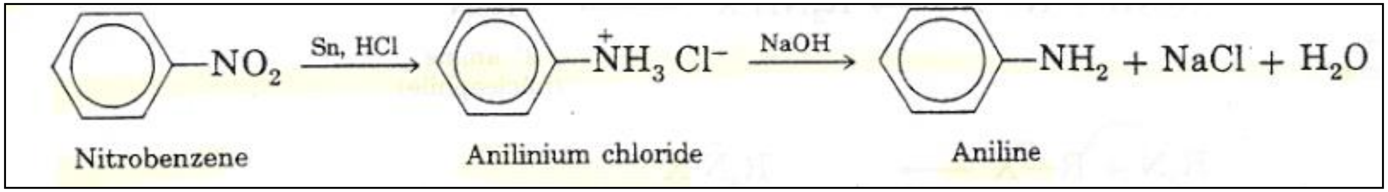


$$R\overset{O}{\overset{\|}{C}}{-}NR_2 \xrightarrow{LiAlH_4} RCH_2NR_2$$

N,N-Disubstituted amide → 3° amine

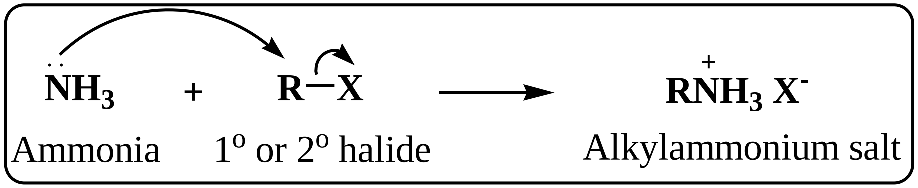
- **Aniline** is prepared by reduction of nitrobenzene.

The reducing agent most frequently used is tin and hydrochloric acid,



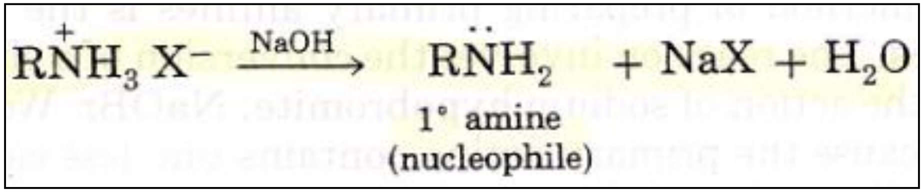
Alkylation of Ammonia;

- The non-bonded electron pair on the nitrogen makes ammonia an excellent nucleophile.
- Ammonia is capable of attacking primary or secondary alkyl halides in an S_N2 reaction to give an alkylammonium salt.



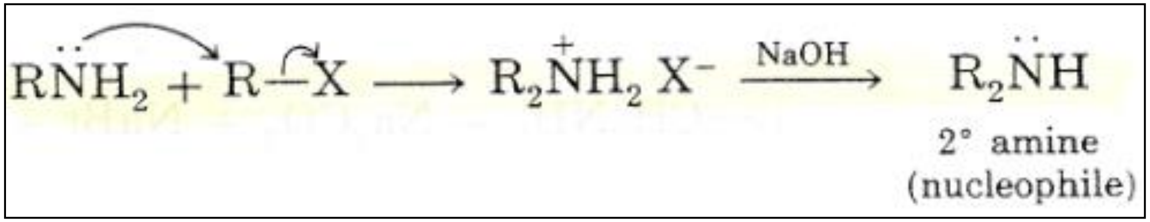
$$\ddot{N}H_3 + R-X \longrightarrow R\overset{+}{N}H_3\,X^-$$

- Treatment of the alkylammonium salt with a strong base (NaOH) liberates the free amine.

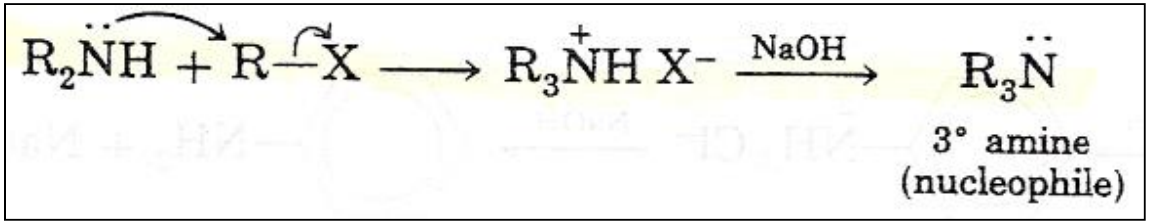


$$R\overset{+}{N}H_3\,X^- \xrightarrow{NaOH} R\ddot{N}H_2 + NaX + H_2O$$

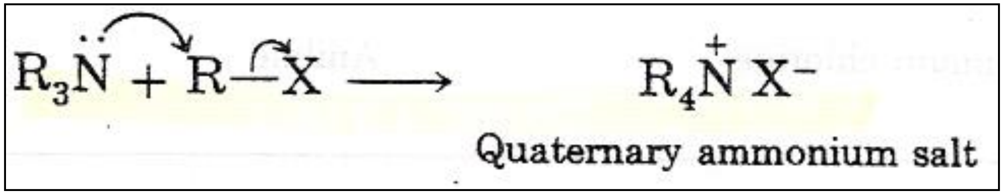
➦ **The net result is the replacement of a hydrogen of ammonia by an alkyl group, the reaction is called *alkylation of ammonia*.**



2° amine
(nucleophile)



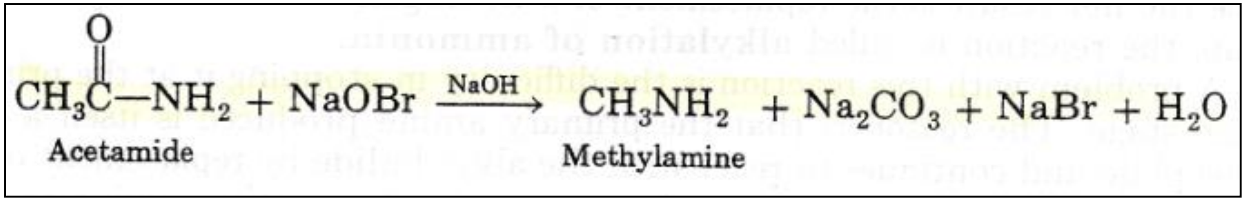
3° amine
(nucleophile)



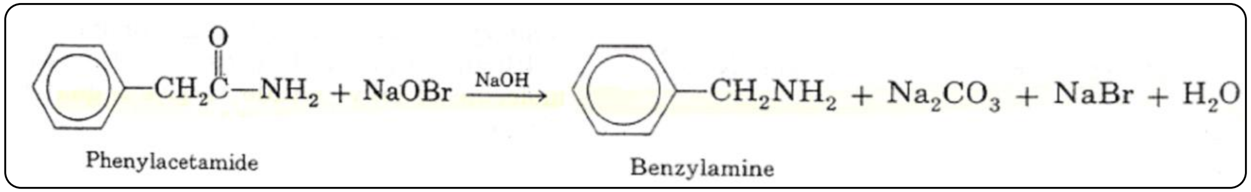
Quaternary ammonium salt

Hofmann Degradation of Amides

- **The reaction involves the conversion of a simple amide to a primary amine** *by the action of sodium hypobromite, NaOBr.*



$$CH_3\overset{\overset{O}{\parallel}}{C}-NH_2 + NaOBr \xrightarrow{NaOH} CH_3NH_2 + Na_2CO_3 + NaBr + H_2O$$



- **We call the reaction a degradation because** *the primary amine contains one less carbon atom than the parent amide.*

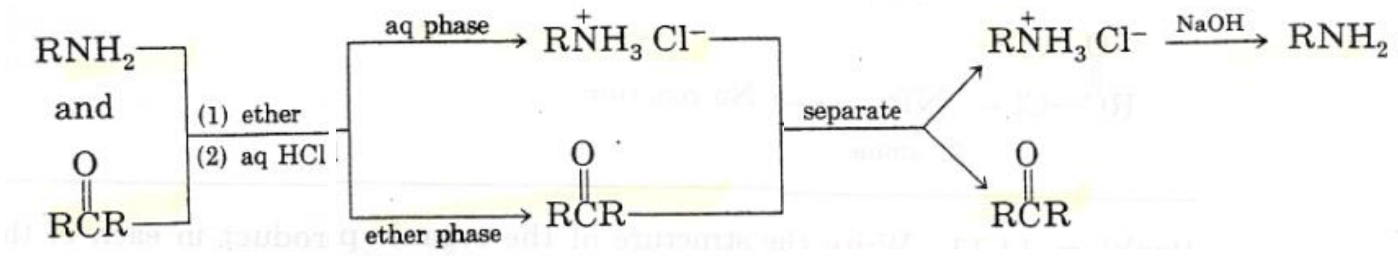
Familiar Reactions of Amines

Salt Formation;

- They react with acids to form ammonium salts.

  Ammonium salts are soluble in water but insoluble in organic solvents such as ethyl ether.

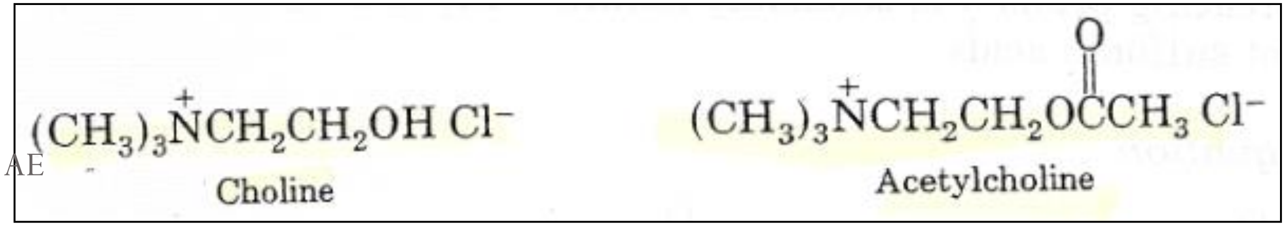
- Separation of amine from nonbasic organic compounds.



Alkylation;

- Amines, like ammonia, react with primary and secondary alkyl halides to give *alkylated* amines.

- Complete alkylation eventually leads to a quaternary ammonium salt.



$(CH_3)_3\overset{+}{N}CH_2CH_2OH\ Cl^-$

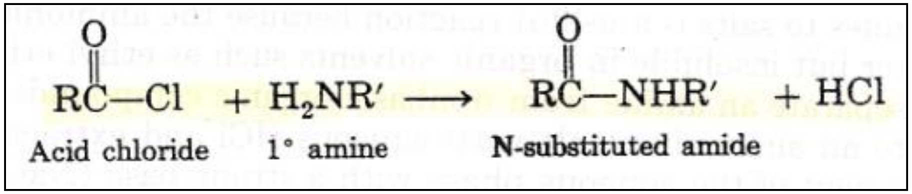
Choline

$(CH_3)_3\overset{+}{N}CH_2CH_2O\overset{\overset{O}{\|}}{C}CH_3\ Cl^-$

Acetylcholine

Amide Formation;

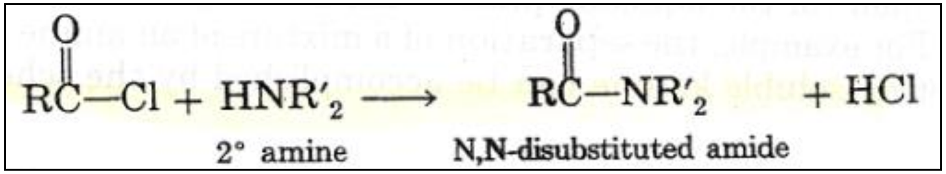
- **Primary amines** yield **N-substituted amides.**



$$R\overset{\overset{\displaystyle O}{\|}}{C}-Cl + H_2NR' \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}-NHR' + HCl$$

Acid chloride 1° amine N-substituted amide

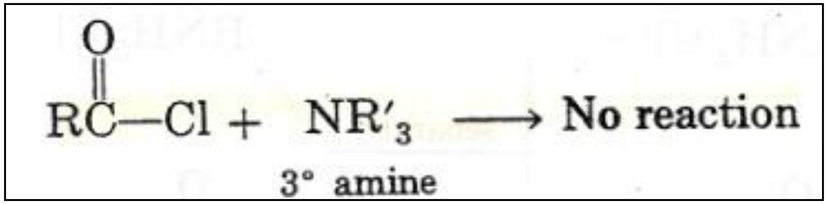
- **Secondary amines** yield **N,N-disubstituted amides.**



$$R\overset{\overset{\displaystyle O}{\|}}{C}-Cl + HNR'_2 \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}-NR'_2 + HCl$$

2° amine N,N-disubstituted amide

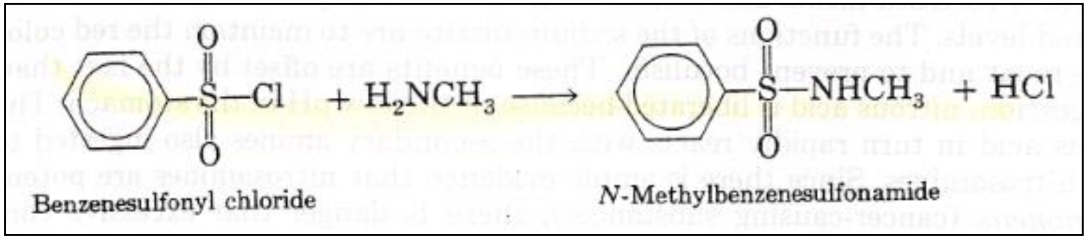
- **Tertiary amines**, which have no H atom on the nitrogen, *cannot be converted to amides*.



$$R\overset{\overset{\displaystyle O}{\|}}{C}-Cl + NR'_3 \longrightarrow \text{No reaction}$$

3° amine

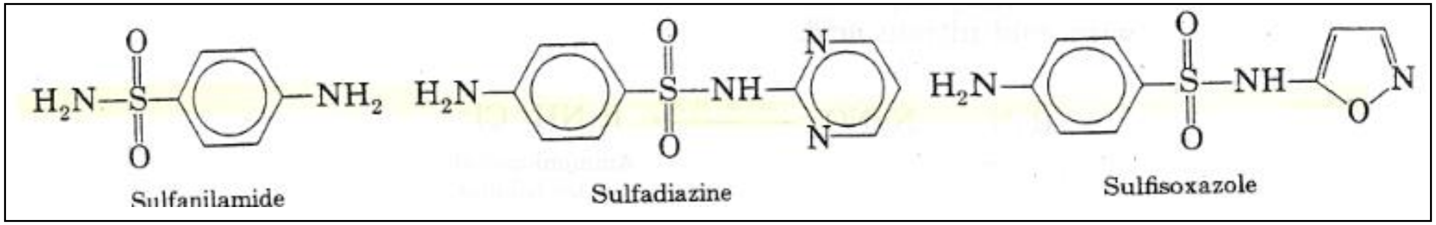
- An interesting class of amides are the *sulfonamides*.
  - *Sulfonamides* are prepared by treating primary or secondary amines with sulfonyl chlorides, the acid chlorides of sulfonic acids.
  - *Specific example*



Benzenesulfonyl chloride

N-Methylbenzenesulfonamide

  - A biologically important sulfonamide used to prevent bacterial infection is sulfanilamide, *the first* sulfa drug.



Sulfanilamide

Sulfadiazine

Sulfisoxazole

Visual Test for Amines: Reaction with Nitrous Acid

- **Differentiation between (1°, 2°, and 3°) amines;**
  - **Treatment with nitrous acid, HNO_2 at (0-5°C).**

$$NaNO_2 + HCl \xrightarrow{H_2O} \underset{\text{Nitrous acid}}{HNO_2} + NaCl$$

- **Primary aliphatic amines yield nitrogen gas (seen as bubbles) and a mixture of other products.**

$$\underset{1^\circ\ \text{amine}}{RNH_2} + HNO_2 \xrightarrow{\text{cold}} N_2\uparrow + \text{Mixture of products}$$

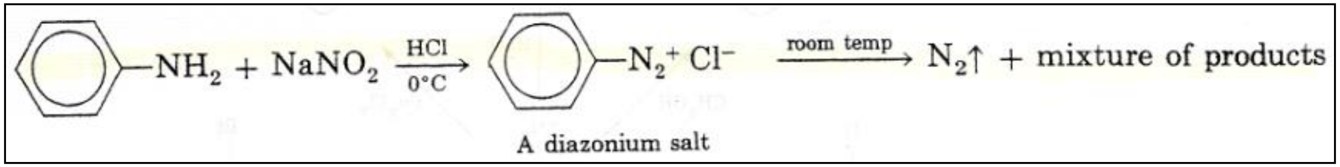
- **Secondary aliphatic amines react more slowly under the same conditions and form water-insoluble, oily yellow derivatives called nitrosamines ($R_2N{-}N{=}O$).**

- **Tertiary aliphatic amines form water-soluble ammonium salts when treated with cold nitrous acid.**

$$\underset{3^\circ\ \text{amine}}{R_3N} + NaNO_2 \xrightarrow{\text{cold dil HCl}} \underset{\substack{\text{Ammonium salt}\\ \text{(water soluble)}}}{R_3NH^+Cl^-}$$

Differentiation between Aromatic and Aliphatic primary amines;

- Aromatic primary amines can react with cold nitrous acid to form *diazonium salts* *without evolution of nitrogen gas.*
- When the *diazonium salt* is warmed to room temperature will bubbles of nitrogen gas appear.



Summary, Treatment of amines with nitrous acid

- If nitrogen gas is produced at 0°C,

  The amine is 1° aliphatic amine.
- If an oily yellow layer separates from the aqueous layer,

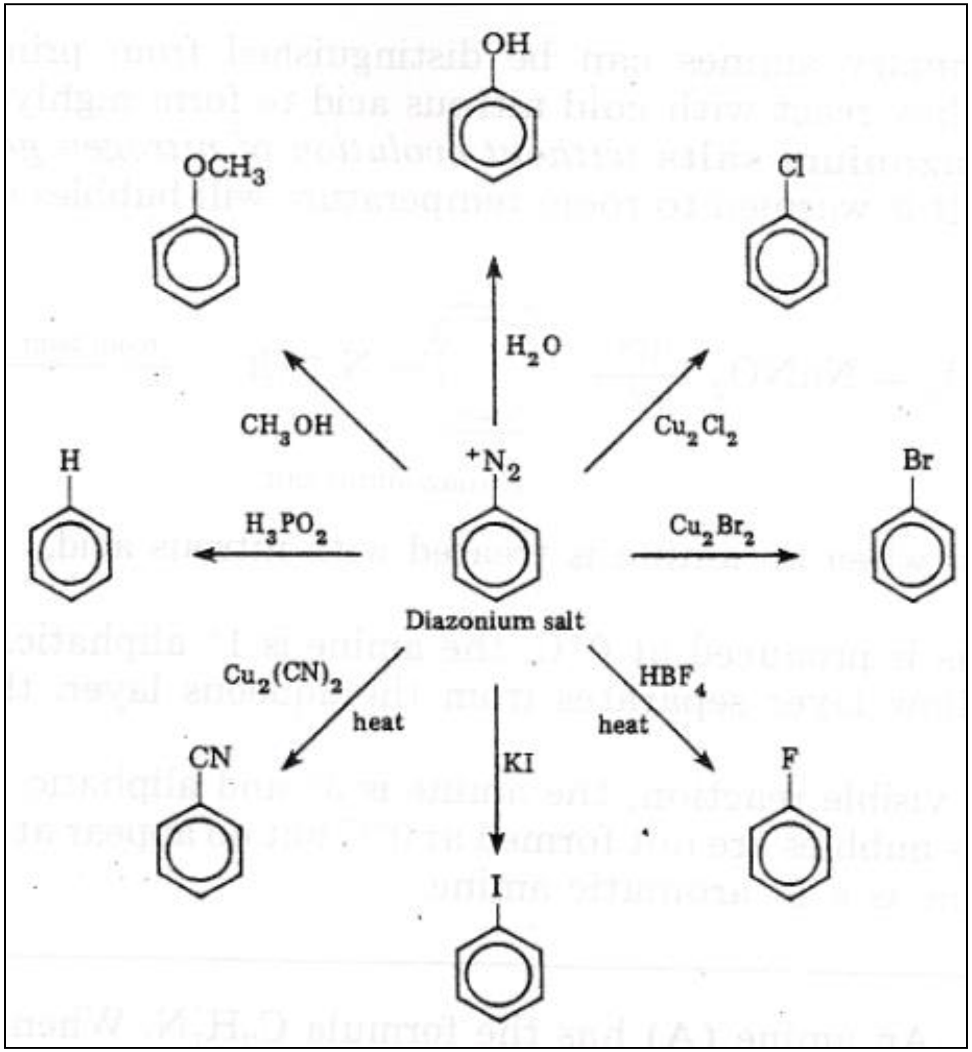
  The amine is 2° aliphatic amine.
- If there is no visible reaction,

  The amine is 3° aliphatic amine.
- If nitrogen gas bubbles are not formed at 0°C but do appear at room temperature,

  The amine is 1° aromatic amine.

Conversion of Diazonium Salts

- **Aromatic diazonium salts** are useful for preparing a host of **substituted benzene derivatives**.

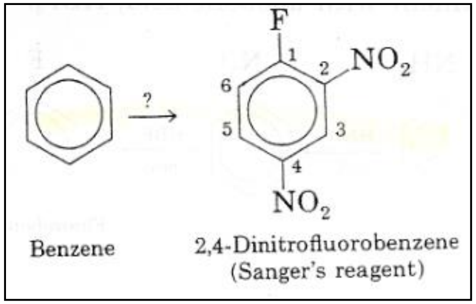


Example;

Starting from benzene,

synthesize 2,4-dinitrofluorobenzene (also known as *Sanger's reagent*).

- **First draw the structure of the starting material and that of the product.**

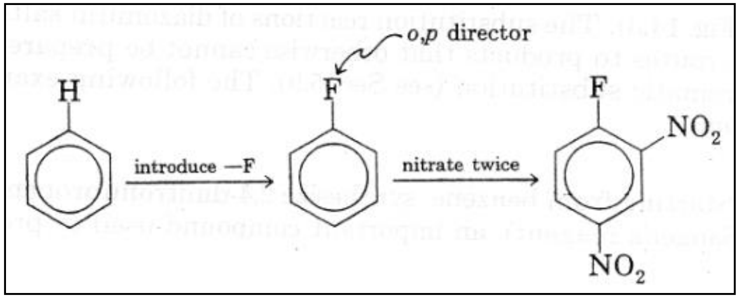


- **The problem here is to introduce three substituents, one -F and two -NO_2, in the proper sequence.**

You know that —F is an ortho, para director,

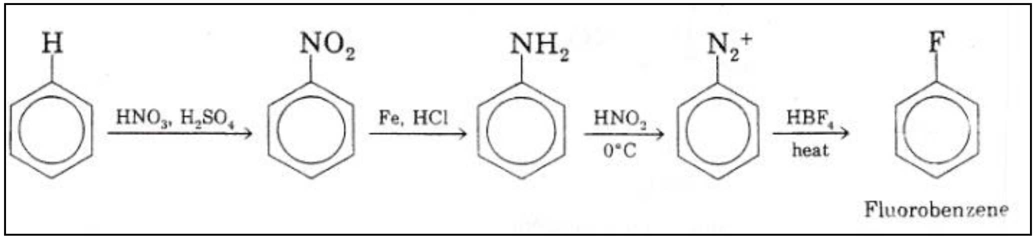
the —NO_2 group have a meta-directing effect.

- **Obviously, the —F group must be introduced first, followed by nitration of fluorobenzene.**



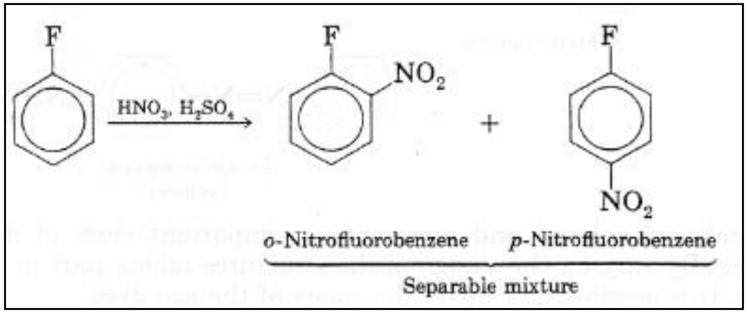
Synthesis of *fluorobenzene*,

- The fluoro group can be introduced by nitration of benzene, reduction of the nitro group to the amine, formation of the diazonium compound, and treatment with fluoboric acid, HBF_4.

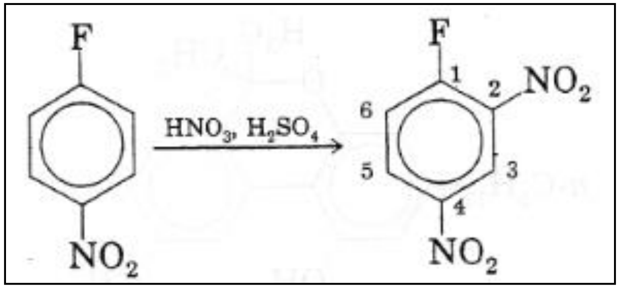


Nitration of *fluorobenzene*,

- Fluorobenzene is nitrated, giving a mixture of *o*- and *p*-nitrofluorobenzene.

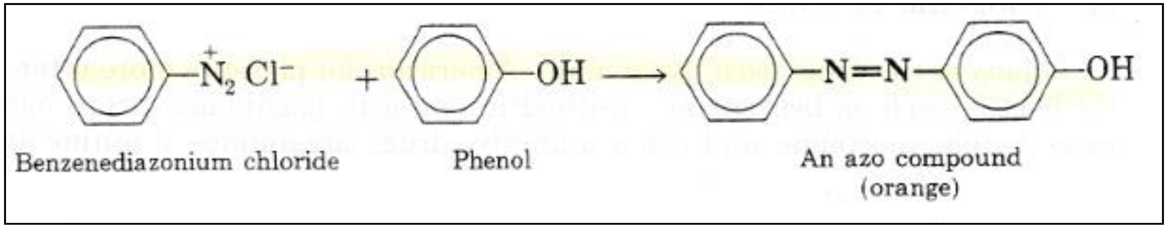


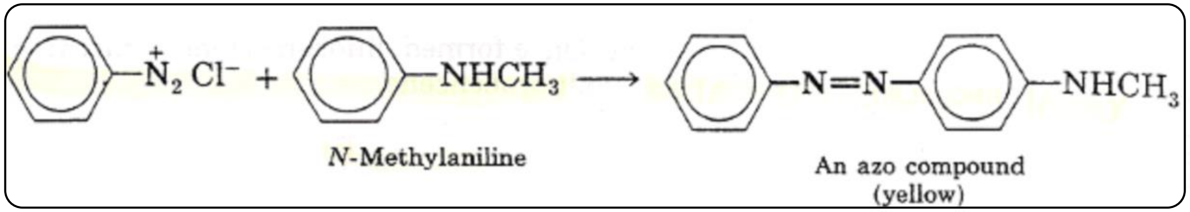
Nitration of *p-nitrofluorobenzene*,



Azo Compounds

- When aromatic diazonium salts are treated with phenols or aromatic amines, a reaction takes place *without the loss of nitrogen*.
- The result is an azo compound, formed by the coupling of the two aromatic rings through the *azo group,* -N=N-.





- Azo compounds are colored and represent one important class of dyes known as *azo dyes*.
- By varying the design of the structures taking part in the coupling reaction,

it is possible to control the colors of the azo dyes.