Carboxylic acids and **Nitriles**

Part B

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to describe

Carboxylic acids and Nitriles

- ❑ **Methods for the preparation of Carboxylic acids**
- ❑ **Reactions of Carboxylic acids**
- ❑ **Preparation of Nitriles**
- ❑ **Reactions of Nitriles**
- ❑ **Spectroscopy of Carboxylic acids and Nitriles**

Objective

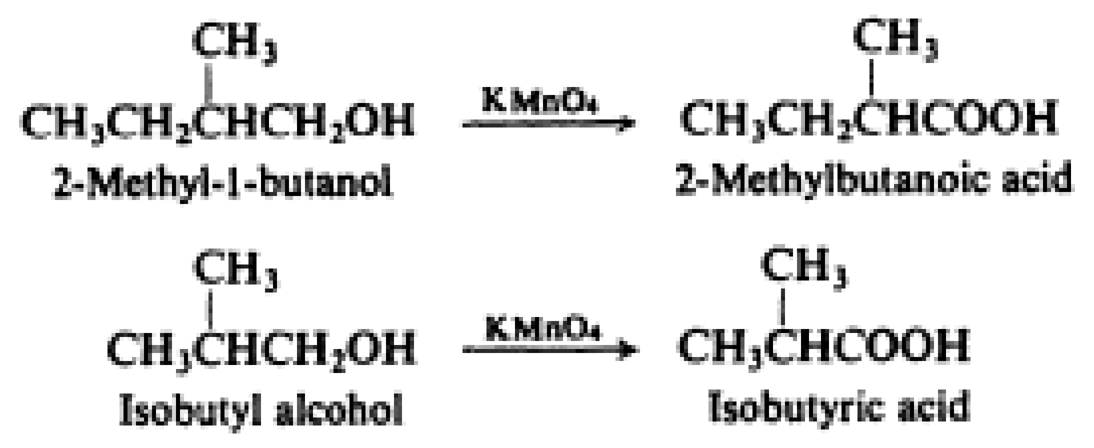
The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Methods for the preparation of Carboxylic acids (R-COOH)

1. **Oxidation of primary alcohols**
2. **Oxidation of alkyl benzenes**
3. **Carbonation of Grignard reagents**
4. **Hydrolysis of nitriles**
5. **Malonic ester synthesis**
6. **Special methods for phenolic acids**

1. Oxidation of primary alcohols

$$RCH_2OH \xrightarrow{KMnO_4} RCOOH$$



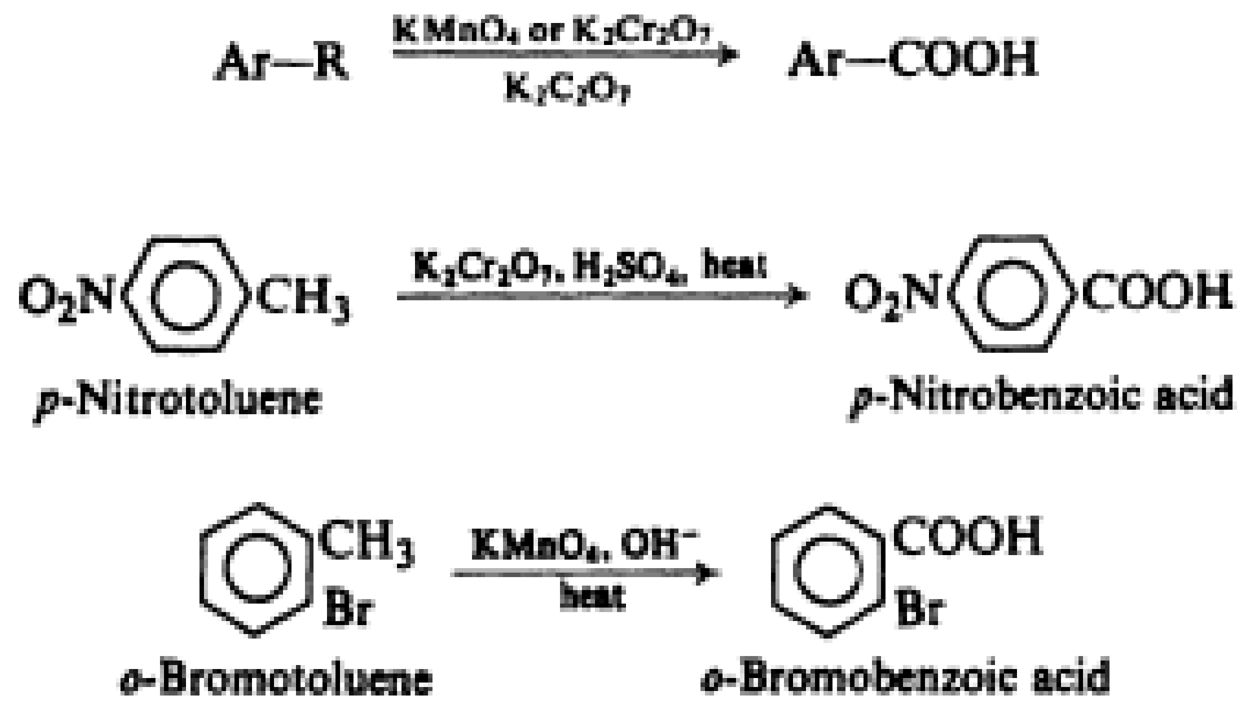
$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2OH \xrightarrow{KMnO_4} CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCOOH$$

2-Methyl-1-butanol → 2-Methylbutanoic acid

$$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2OH \xrightarrow{KMnO_4} CH_3\overset{\overset{CH_3}{|}}{C}HCOOH$$

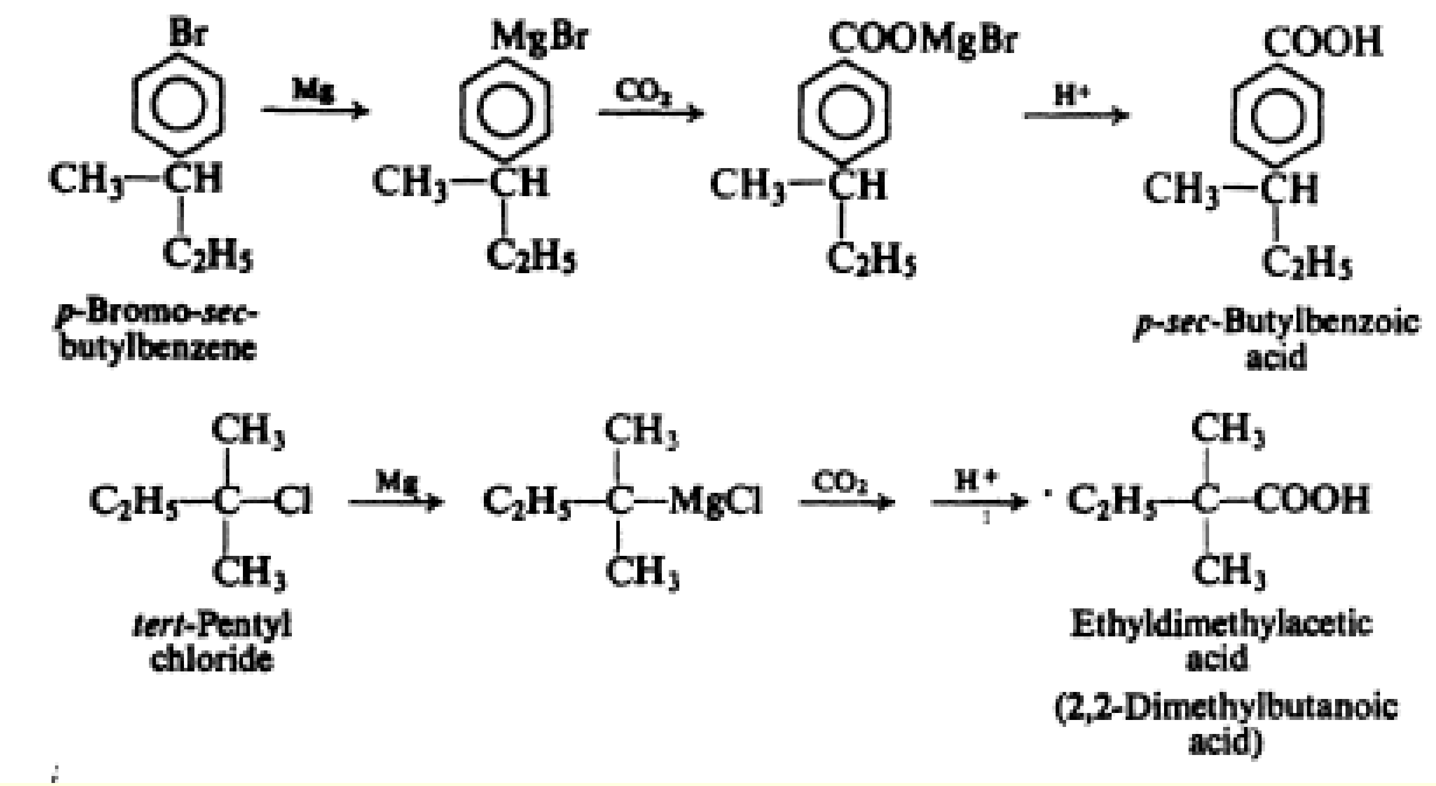
Isobutyl alcohol → Isobutyric acid

2. Oxidation of alkyl benzenes



3. Carbonation of Grignard reagents

$$\underset{\text{(or ArX)}}{RX} \xrightarrow{Mg} RMgX \xrightarrow{CO_2} RCOOMgX \xrightarrow{H^+} \underset{\text{(or ArCOOH)}}{RCOOH}$$



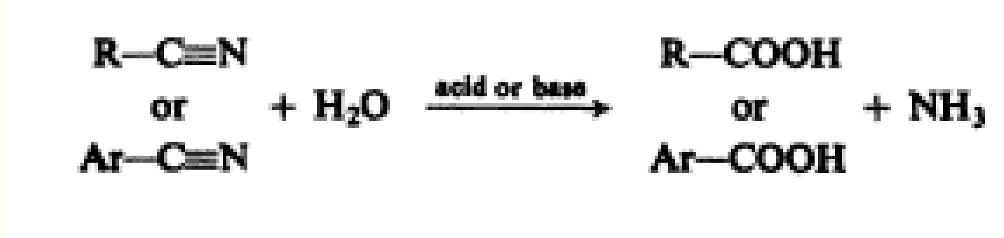
p-Bromo-*sec*-butylbenzene

p-*sec*-Butylbenzoic acid

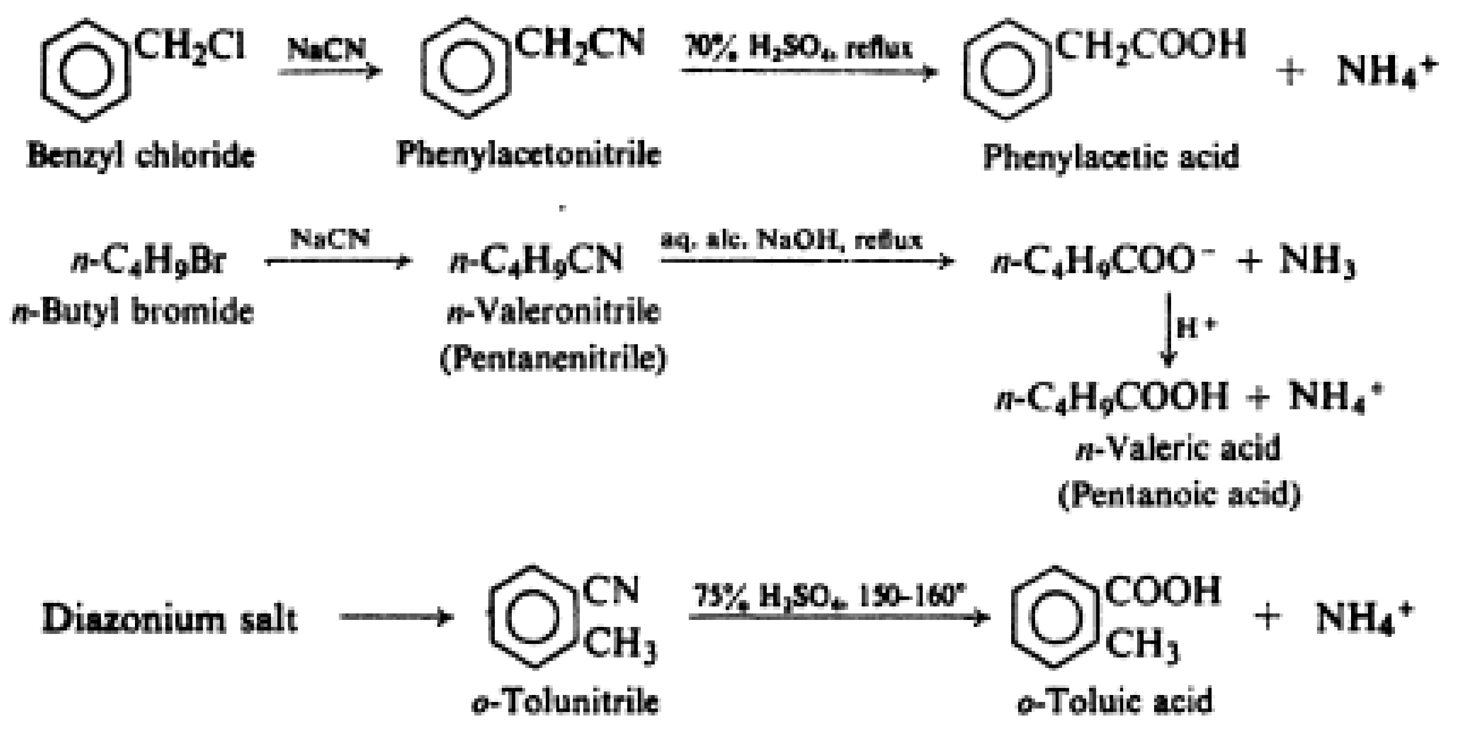
tert-Pentyl chloride

Ethyldimethylacetic acid (2,2-Dimethylbutanoic acid)

4. Hydrolysis of nitriles



$$\begin{matrix} R{-}C{\equiv}N \\ \text{or} \\ Ar{-}C{\equiv}N \end{matrix} + H_2O \xrightarrow{\text{acid or base}} \begin{matrix} R{-}COOH \\ \text{or} \\ Ar{-}COOH \end{matrix} + NH_3$$



Benzyl chloride

Phenylacetonitrile

Phenylacetic acid

n-Butyl bromide

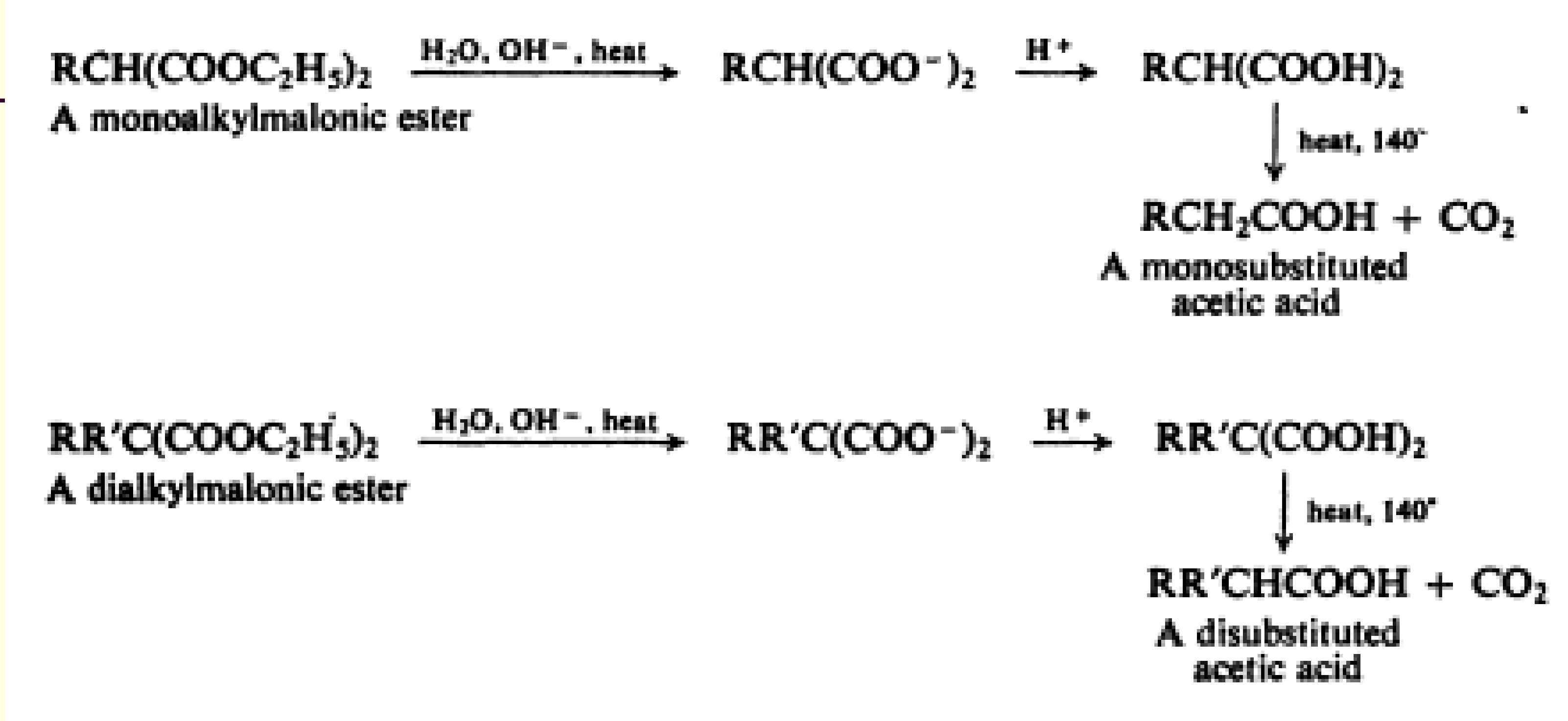
n-Valeronitrile (Pentanenitrile)

n-Valeric acid (Pentanoic acid)

o-Tolunitrile

o-Toluic acid

5. Malonic ester synthesis



- One of the most valuable methods of preparing carboxylic acids makes use of diethyl malonate (malonic ester), $CH_2(COOC_2H_5)_2$ and is called the malonic ester synthesis.
- This synthesis depends upon the high acidity of the α-hydrogens of malonic ester, and in the extreme ease with which malonic acid and substituted malonic acids undergo decarboxylation

5. Malonic ester synthesis: Mechanism

Step-1: Treatment of sodium ethoxide in absolute ethanol, malonic ester is converted into its salt (sodium malonic ester).

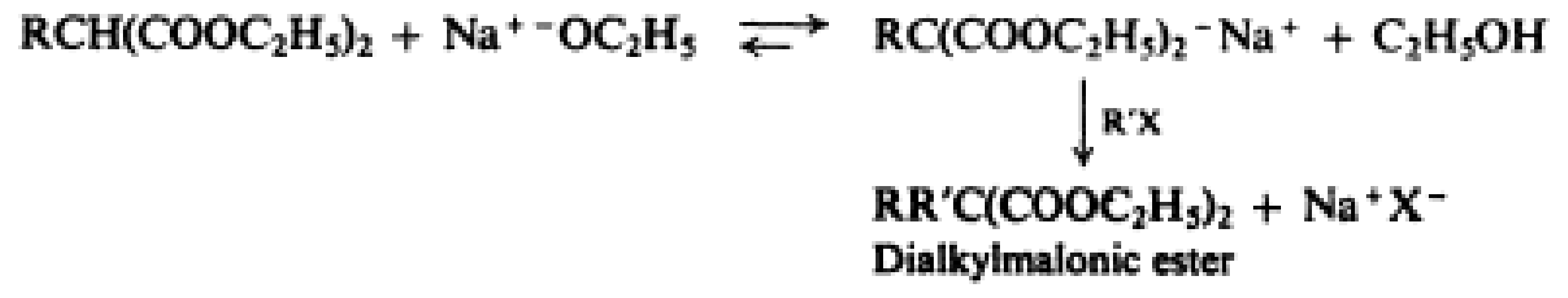
$$\underset{\text{Stronger acid}}{CH_2(COOC_2H_5)_2} + Na^{+}\,{}^{-}OC_2H_5 \rightleftharpoons \underset{\text{Sodiomalonic ester}}{CH(COOC_2H_5)_2^{-}\,Na^{+}} + \underset{\text{Weaker acid}}{HOC_2H_5}$$

Step-2: Reaction of this salt with an alkyl halide yields a substituted malonic ester, an ethyl alkylmalonate, often called an alkylmalonic ester.

$$CH(COOC_2H_5)_2^{-}\,Na^{+} + RX \longrightarrow \underset{\substack{\text{Ethyl alkylmalonate}\\ \text{Alkylmalonic ester}}}{RCH(COOC_2H_5)_2} + Na^{+}X^{-}$$

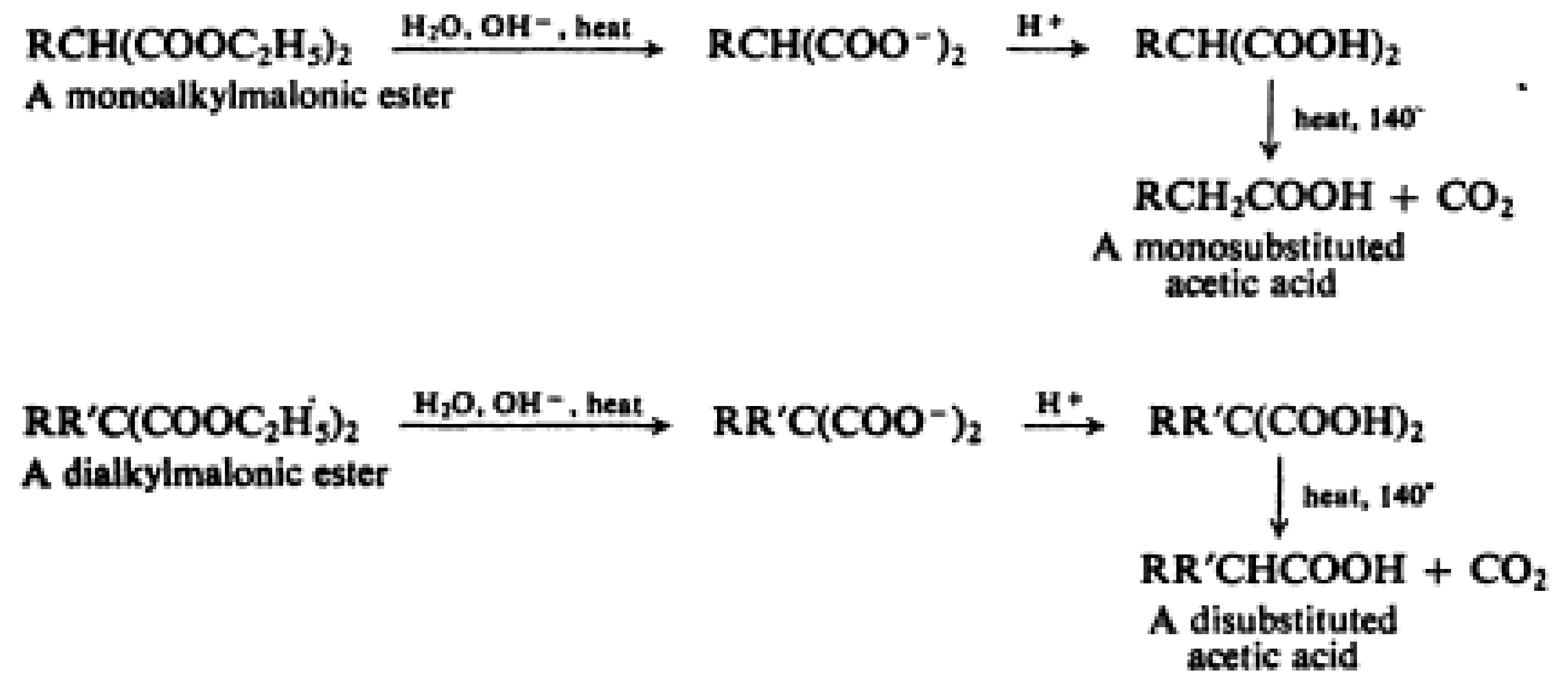
5. Malonic ester synthesis: Mechanism

Step-3: The alkylmalonic ester still contains one ionizable hydrogen, and on treatment with sodium ethoxide it, too, can be converted into its salt; this salt can react with an alkyl halide which may be same as, or different from, the first alkyl halide to yield a dialkylmalonic ester.



Step-4: The monoalkylmalonic ester or the dialkylmalonic ester are readily converted into monocarboxylic acids by hydrolysis, acidification, and heat.

5. Malonic ester synthesis: Mechanism



$$\begin{tikzcd}
\mathrm{RCH(COOC_2H_5)_2} \arrow[r, "\mathrm{H_2O,\ OH^-,\ heat}"] & \mathrm{RCH(COO^-)_2} \arrow[r, "\mathrm{H^+}"] & \mathrm{RCH(COOH)_2} \arrow[d, "\mathrm{heat,\ 140^\circ}"] \\
 & & \mathrm{RCH_2COOH + CO_2}
\end{tikzcd}$$

A monoalkylmalonic ester

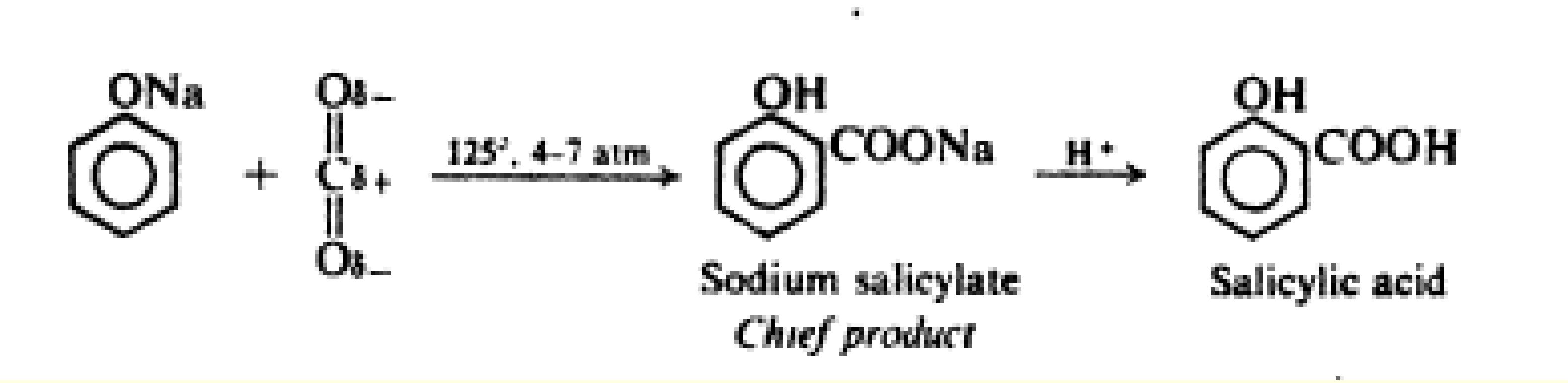
A monosubstituted acetic acid

$$\begin{tikzcd}
\mathrm{RR'C(COOC_2H_5)_2} \arrow[r, "\mathrm{H_2O,\ OH^-,\ heat}"] & \mathrm{RR'C(COO^-)_2} \arrow[r, "\mathrm{H^+}"] & \mathrm{RR'C(COOH)_2} \arrow[d, "\mathrm{heat,\ 140^\circ}"] \\
 & & \mathrm{RR'CHCOOH + CO_2}
\end{tikzcd}$$

A dialkylmalonic ester

A disubstituted acetic acid

6. Special methods for phenolic acids

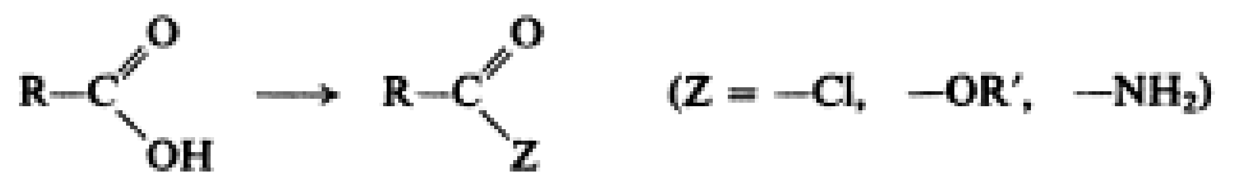


Reactions of Carboxylic acids (R-COOH)

1. **Conversion into functional derivatives of Carboxylic acids**
2. **Reduction**
3. **Substitution in alkyl or aryl group**

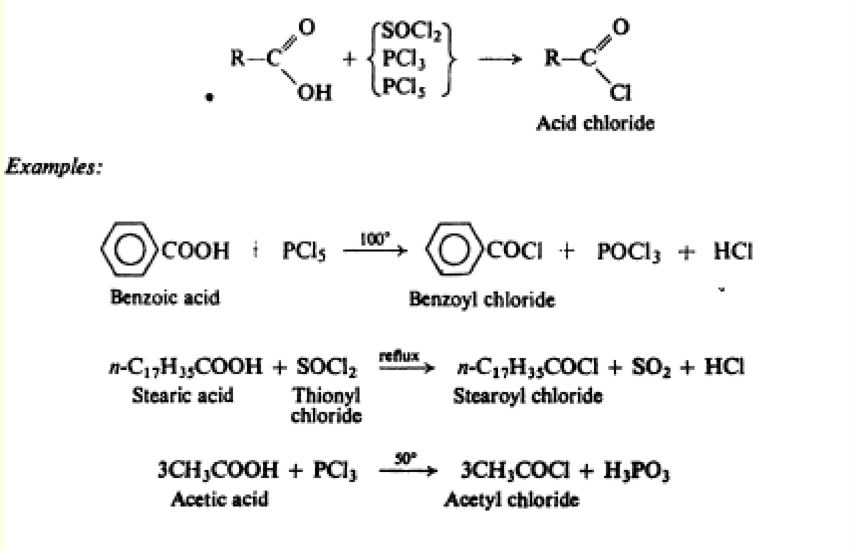
1. Conversion into functional derivatives of Carboxylic acids

General Reaction



$(Z = —Cl,\ —OR',\ —NH_2)$

I. Conversion to acid chlorides



Acid chloride

Examples:

$C_6H_5COOH + PCl_5 \xrightarrow{100°} C_6H_5COCl + POCl_3 + HCl$

Benzoic acid → Benzoyl chloride

$n\text{-}C_{17}H_{35}COOH + SOCl_2 \xrightarrow{\text{reflux}} n\text{-}C_{17}H_{35}COCl + SO_2 + HCl$

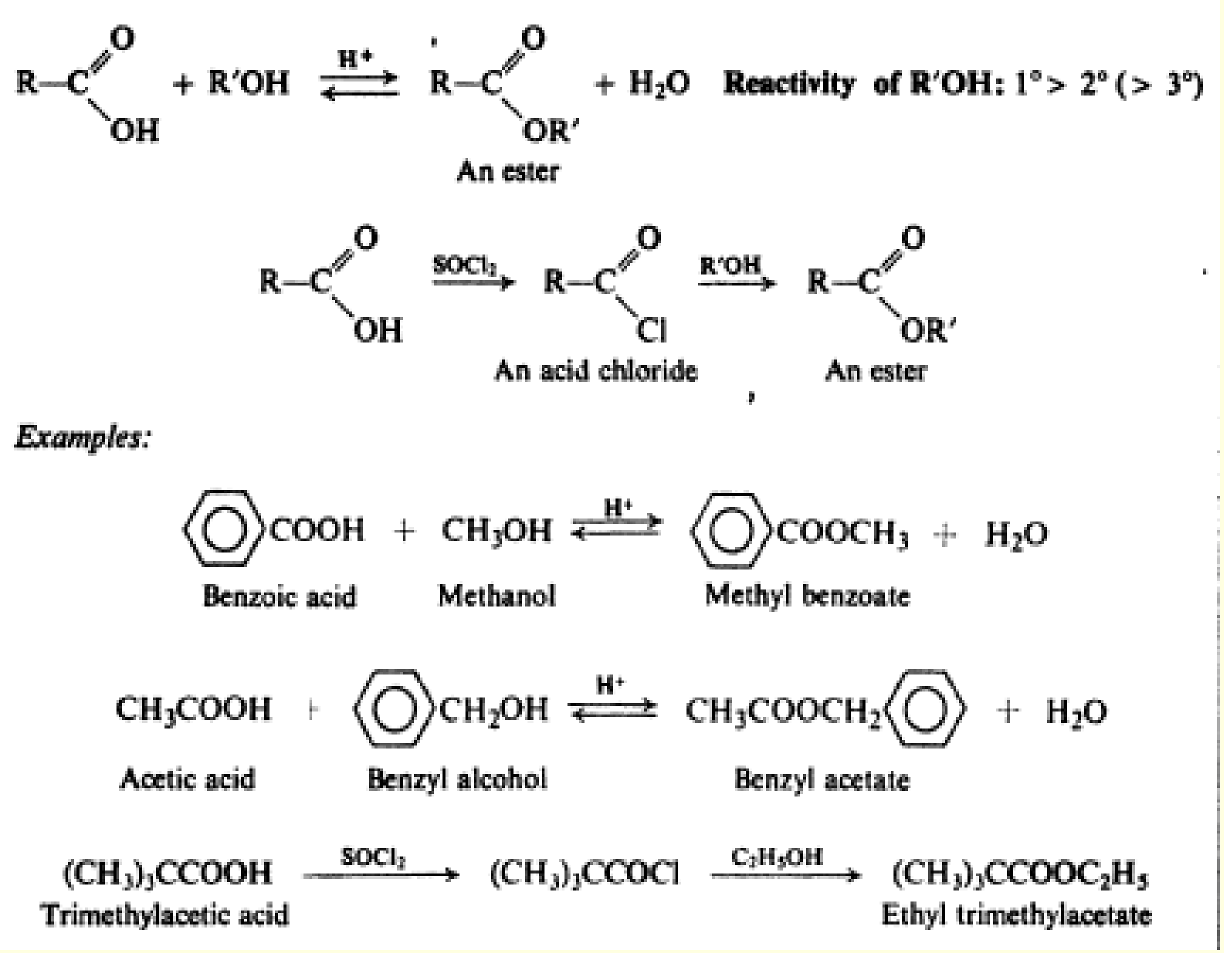
Stearic acid, Thionyl chloride → Stearoyl chloride

$3CH_3COOH + PCl_3 \xrightarrow{50°} 3CH_3COCl + H_3PO_3$

Acetic acid → Acetyl chloride

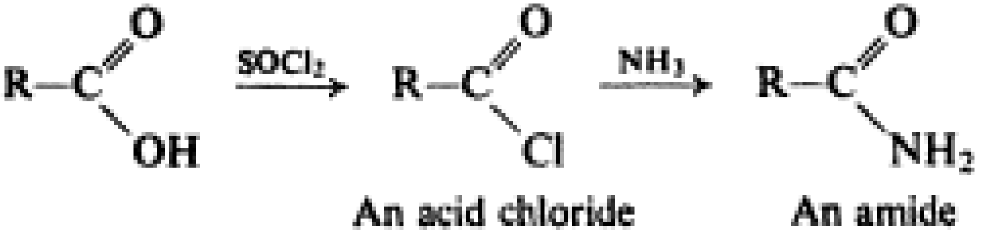
1. Conversion into functional derivatives of Carboxylic acids

II. Conversion to acid esters



1. Conversion into functional derivatives of Carboxylic acids

III. Conversion to amides



Example:

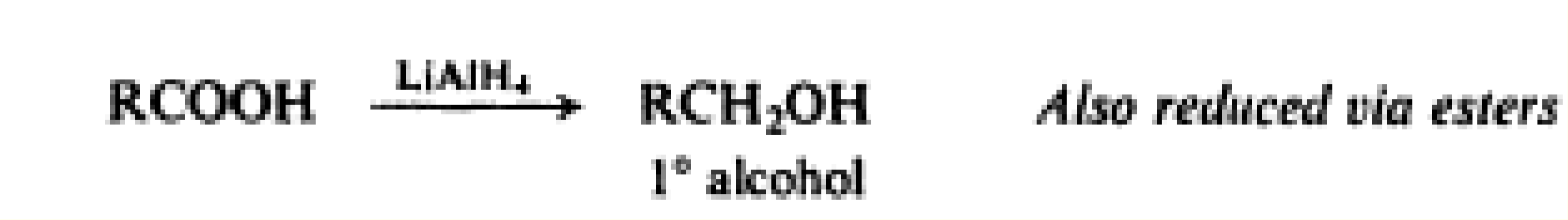
$C_6H_5CH_2COOH \xrightarrow{SOCl_2} C_6H_5CH_2COCl \xrightarrow{NH_3} C_6H_5CH_2CONH_2$

Phenylacetic acid — Phenylacetyl chloride — Phenylacetamide

2. Reduction of Carboxylic acids

Lithium aluminum hydride is the strong reducing agent that reduces the acid to alcohol.

This reaction involves the formation of an alkoxide ion which undergoes hydrolysis to yield the final product alcohol.



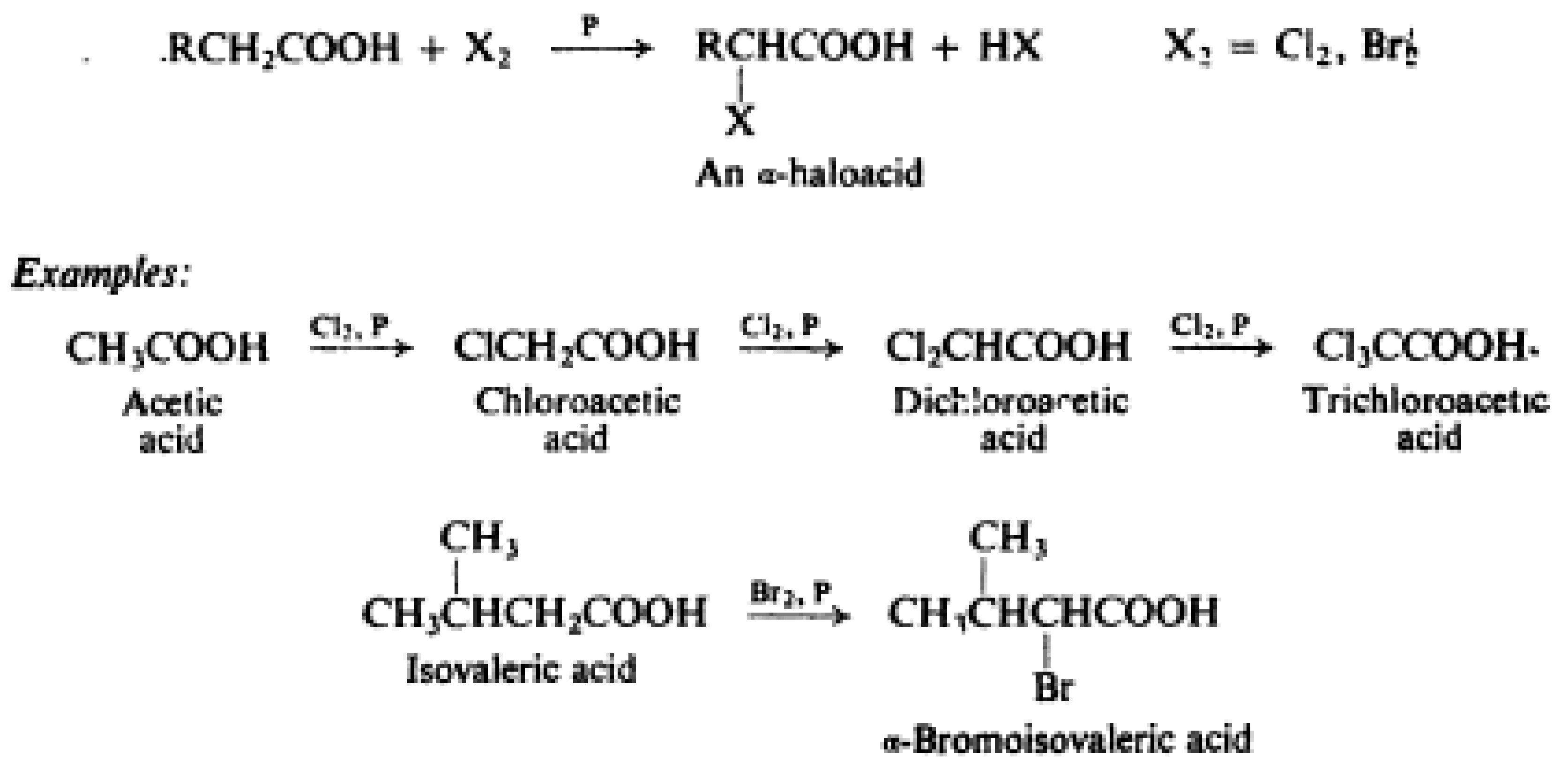
$$RCOOH \xrightarrow{LiAlH_4} \underset{1^\circ \text{ alcohol}}{RCH_2OH}$$

Also reduced via esters

$$4RCOOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{1^\circ \text{ alcohol}}{4RCH_2OH}$$

3. Substitution in alkyl or aryl group

A. α-halogenation of aliphatic acids:
Hell-Volhard-Zelinsky reaction



$$RCH_2COOH + X_2 \xrightarrow{P} \underset{\displaystyle X}{\underset{|}{RCHCOOH}} + HX \qquad X_2 = Cl_2, Br_2$$

An α-haloacid

Examples:

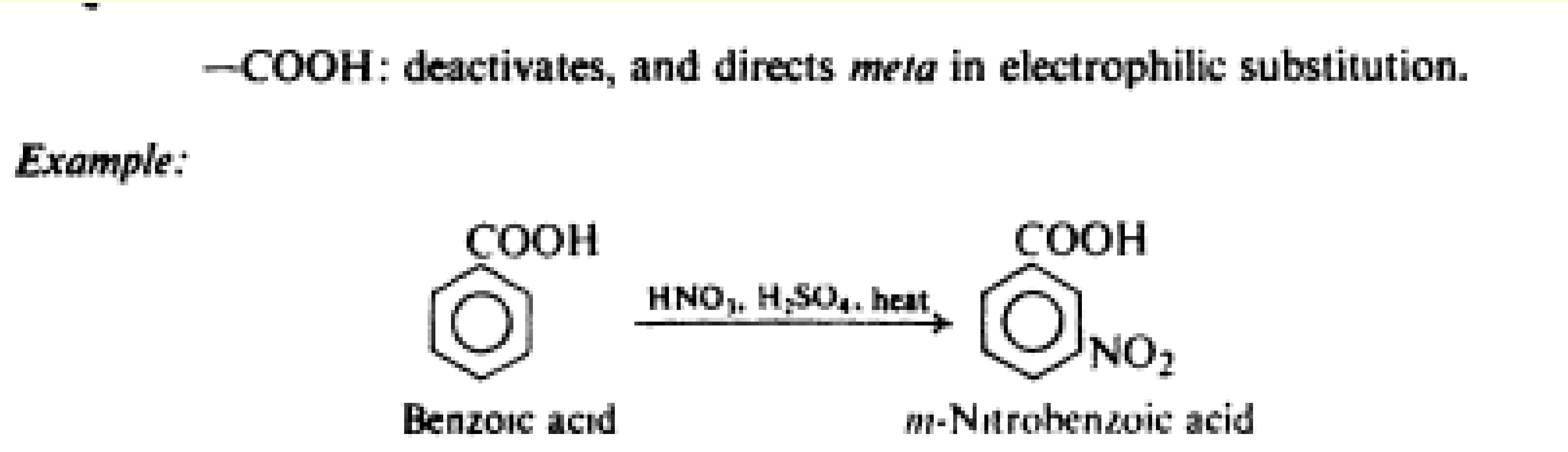
$$\underset{\text{Acetic acid}}{CH_3COOH} \xrightarrow{Cl_2,\ P} \underset{\text{Chloroacetic acid}}{ClCH_2COOH} \xrightarrow{Cl_2,\ P} \underset{\text{Dichloroacetic acid}}{Cl_2CHCOOH} \xrightarrow{Cl_2,\ P} \underset{\text{Trichloroacetic acid}}{Cl_3CCOOH}$$

$$\underset{\text{Isovaleric acid}}{CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOH} \xrightarrow{Br_2,\ P} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCOOH$$

α-Bromoisovaleric acid

3. Substitution in alkyl or aryl group

B. Ring substitution in aromatic acid



—COOH: deactivates, and directs *meta* in electrophilic substitution.

Example:

COOH

$\xrightarrow{HNO_3,\ H_2SO_4,\ heat}$

COOH

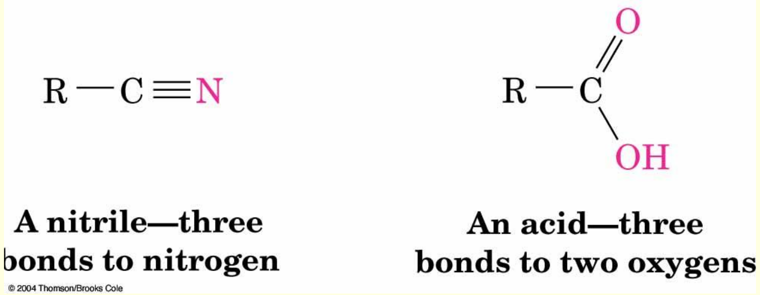
NO_2

Benzoic acid

m-Nitrobenzoic acid

Preparation of Nitriles

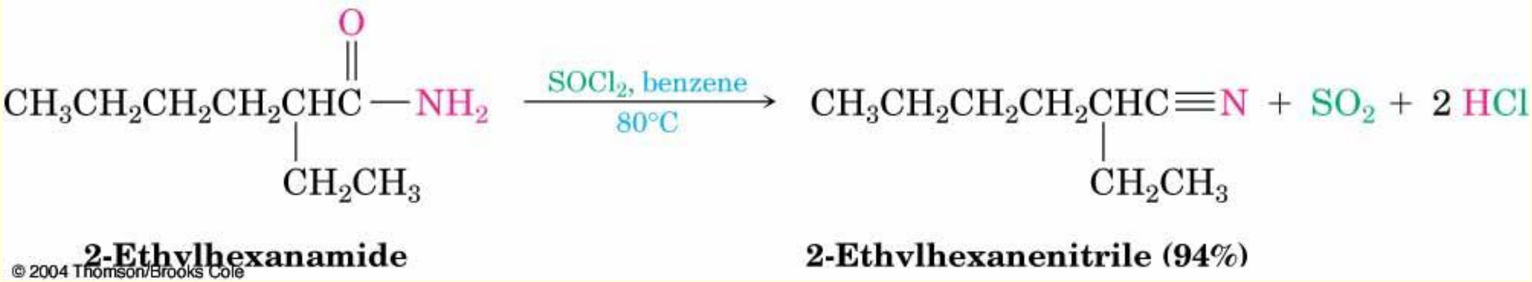
Nitriles and carboxylic acids both have a carbon atom with three bonds to an electronegative atom, and both contain a π-bond and are electrophiles.



A nitrile—three bonds to nitrogen

An acid—three bonds to two oxygens

Nitriles can be prepared by dehydration amides using primary amides ($RCONH_2$) with $SOCl_2$ or $POCl_3$



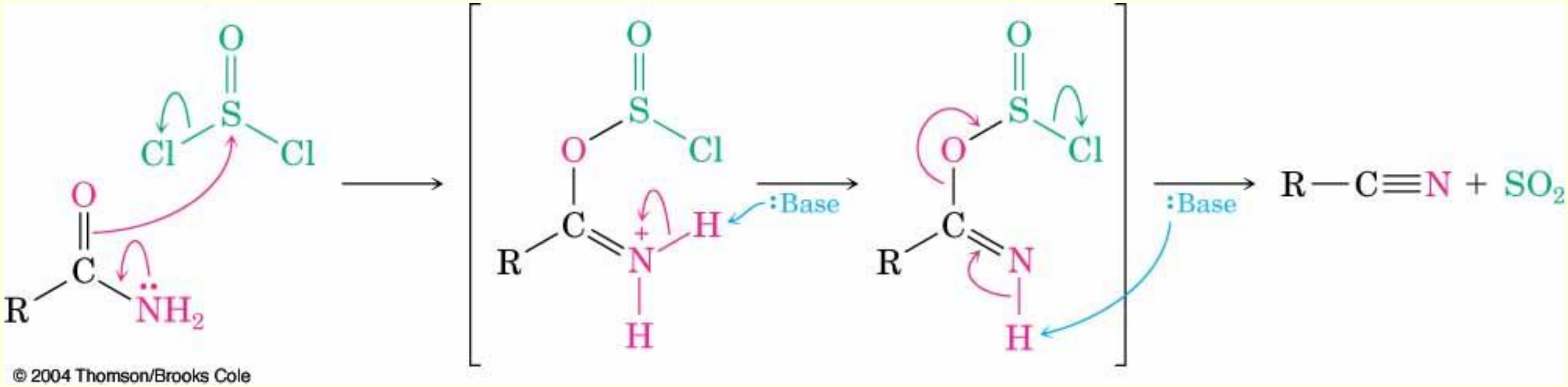
$$CH_3CH_2CH_2CH_2CH(CH_2CH_3)C(=O){-}NH_2 \xrightarrow[80^\circ C]{SOCl_2,\ benzene} CH_3CH_2CH_2CH_2CH(CH_2CH_3)C{\equiv}N + SO_2 + 2\,HCl$$

2-Ethylhexanamide

2-Ethylhexanenitrile (94%)

Preparation of Nitriles: Mechanism

Nucleophilic amide oxygen atom attacks $SOCl_2$ followed by deprotonation and elimination.



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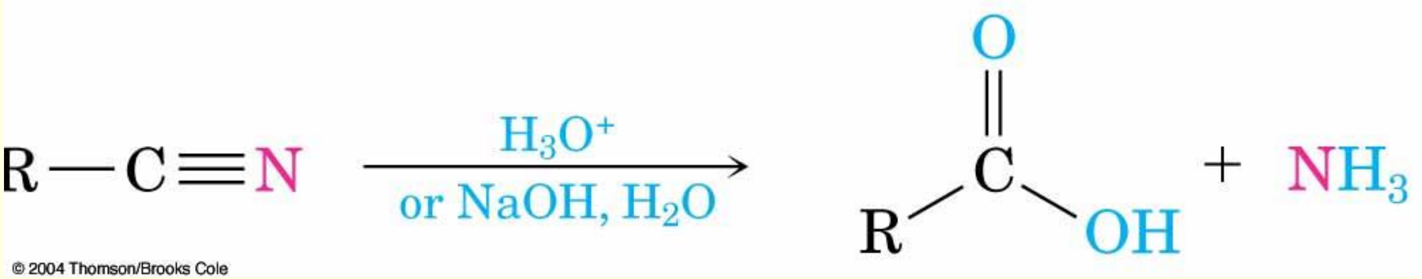
Reaction of Nitriles: Hydrolysis

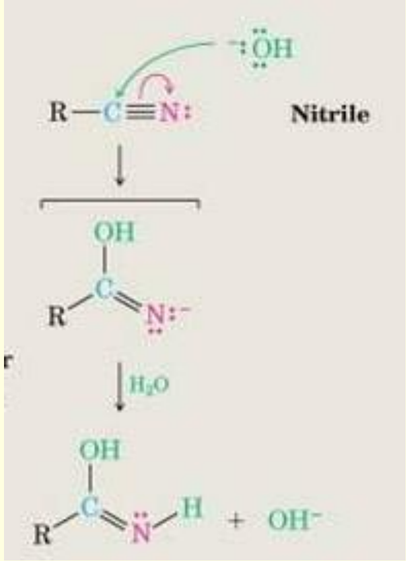
Nitriles can be hydrolyzed with acid or base catalyst to a carboxylic acid and ammonia or an amine.

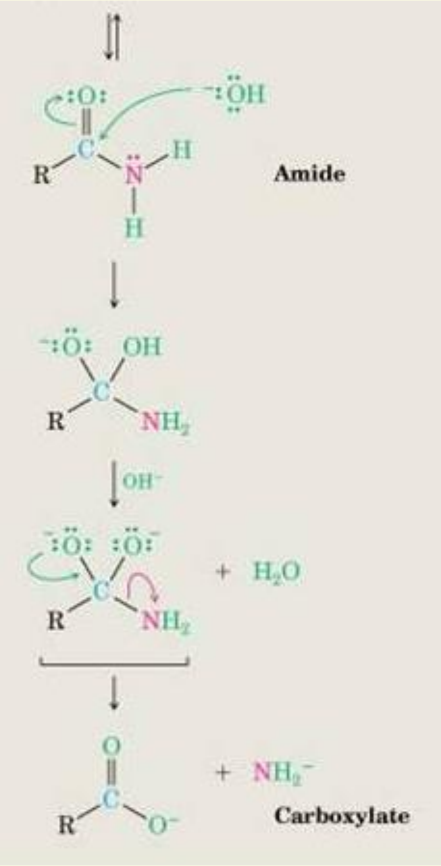


Reaction of Nitriles: Hydrolysis: Mechanism

Nucleophilic addition of hydroxide to C≡N bond Protonation gives a hydroxy imine, which tautomerizes to an amide.

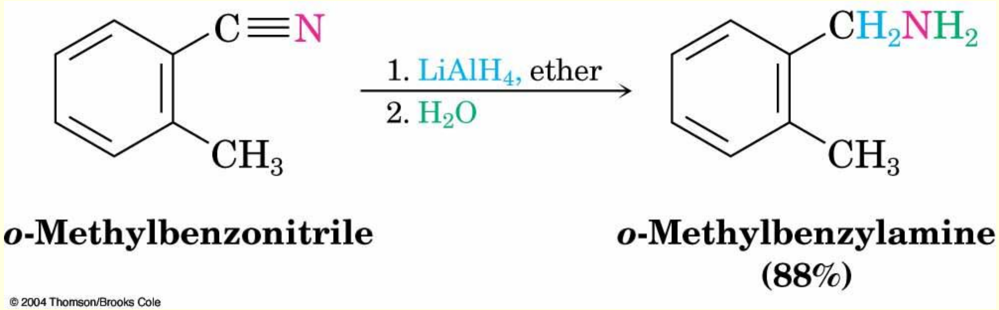
A second hydroxide adds to the amide carbonyl group and loss of a proton gives a dianion, Expulsion of NH_2– gives the carboxylate.



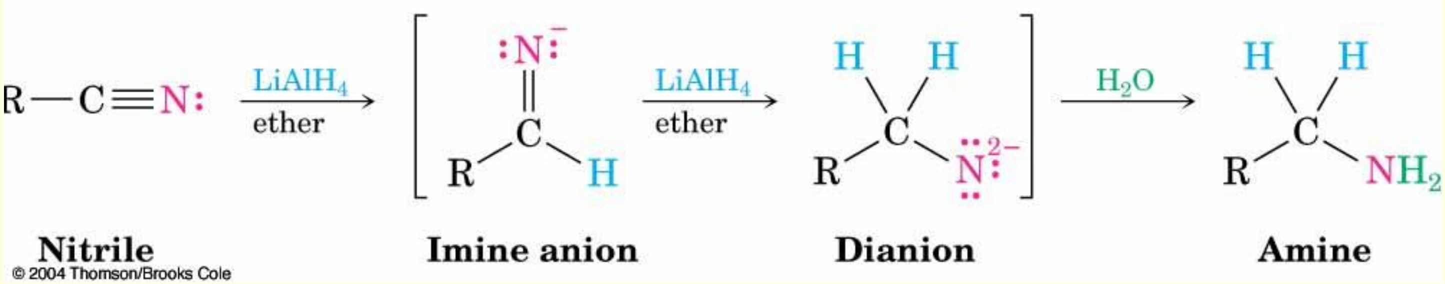


Reaction of Nitriles: Reduction

Reduction of a nitrile with $LiAlH_4$ gives a primary amine.

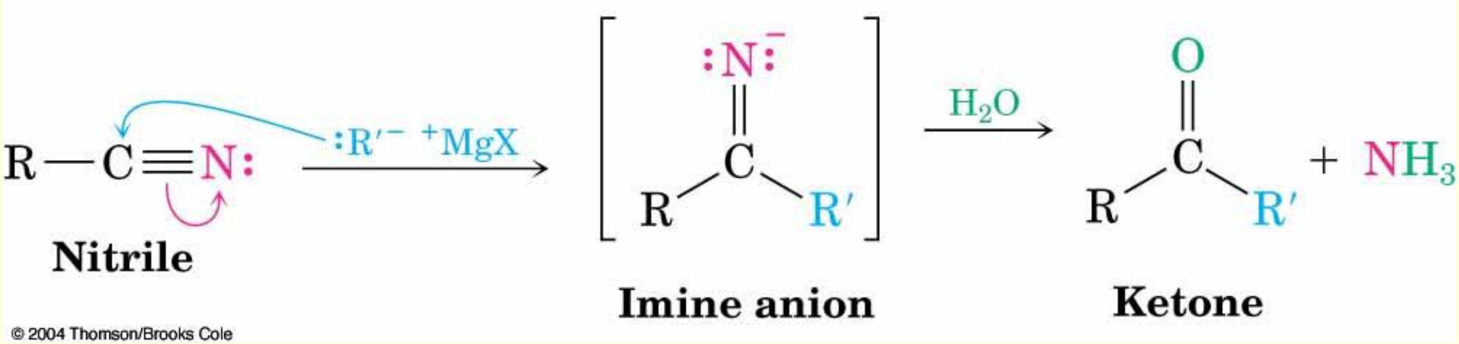


Mechanism: Nucleophilic addition of hydride ion to the polar C≡N bond, yields an imine anion.
The C=N bond undergoes a second nucleophilic addition of hydride to give a dianion, which is protonated by water.



Reaction of Nitriles with organometallic reagents

Grignard reagents add to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone.



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Spectroscopy of Carboxylic acids and Nitriles

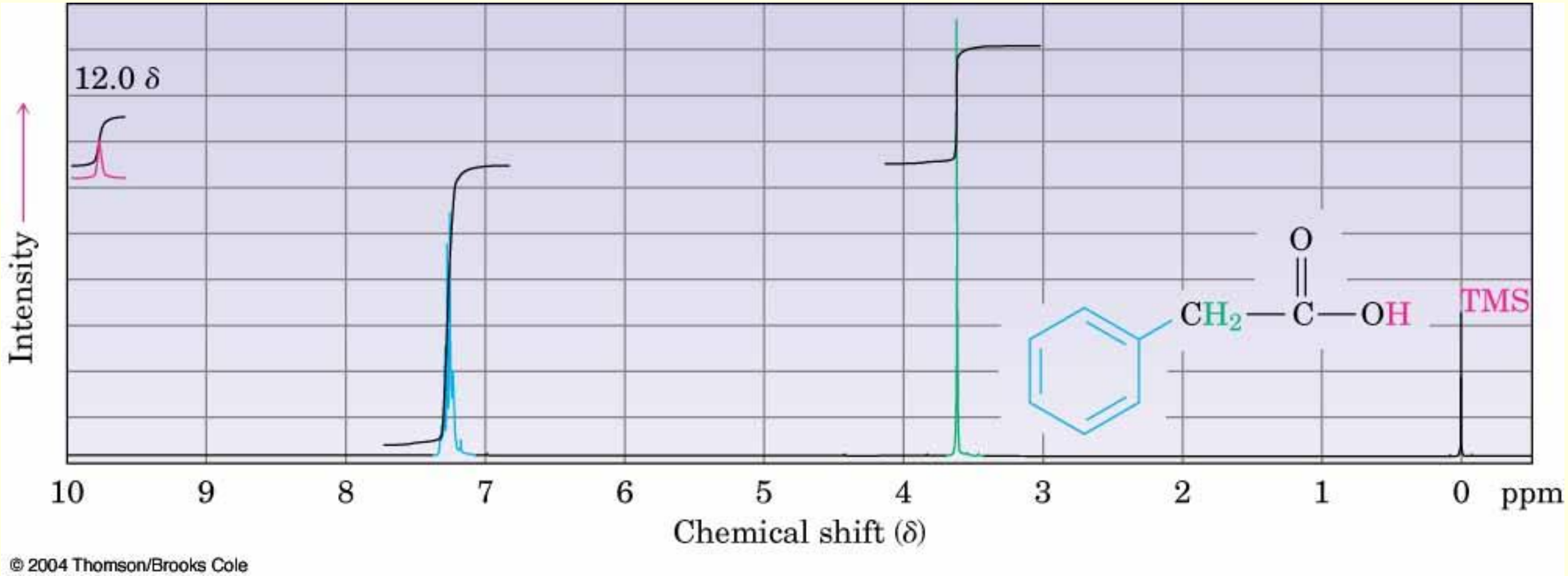
IR Spectroscopy

- O–H bond of the **carboxyl group** gives a very broad absorption 2500 to 3300 cm^{-1}
- C=O bond absorbs sharply between 1710 and 1760 cm^{-1}
- Free carboxyl groups absorb at 1760 cm^{-1}
  - Commonly encountered dimeric carboxyl groups absorb in a broad band centered around 1710 cm^{-1}.

Nitriles show an intense C≡N bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules.
This is highly diagnostic peak for nitriles.

^{1}H-NMR Spectroscopy of Carboxylic acids

- The acidic $-CO_2H$ proton is a singlet near δ 12 ppm
- When D_2O is added to the sample the $-CO_2H$ proton is replaced by Deuterium causing the absorption to disappear from the NMR spectrum.



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^{13}C-NMR Spectroscopy of Carboxylic acids

- The Carboxyl ^{13}COOH signals appear at δ165 to δ185 ppm.
- Aromatic and α,β-unsaturated acids are near δ 165 ppm and saturated aliphatic acids are near δ185 ppm.
- $^{13}C \equiv N$ signal appears at δ 115 to δ 130 ppm.

REFERENCES

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