Lec.4
Conversion into acid chlorides

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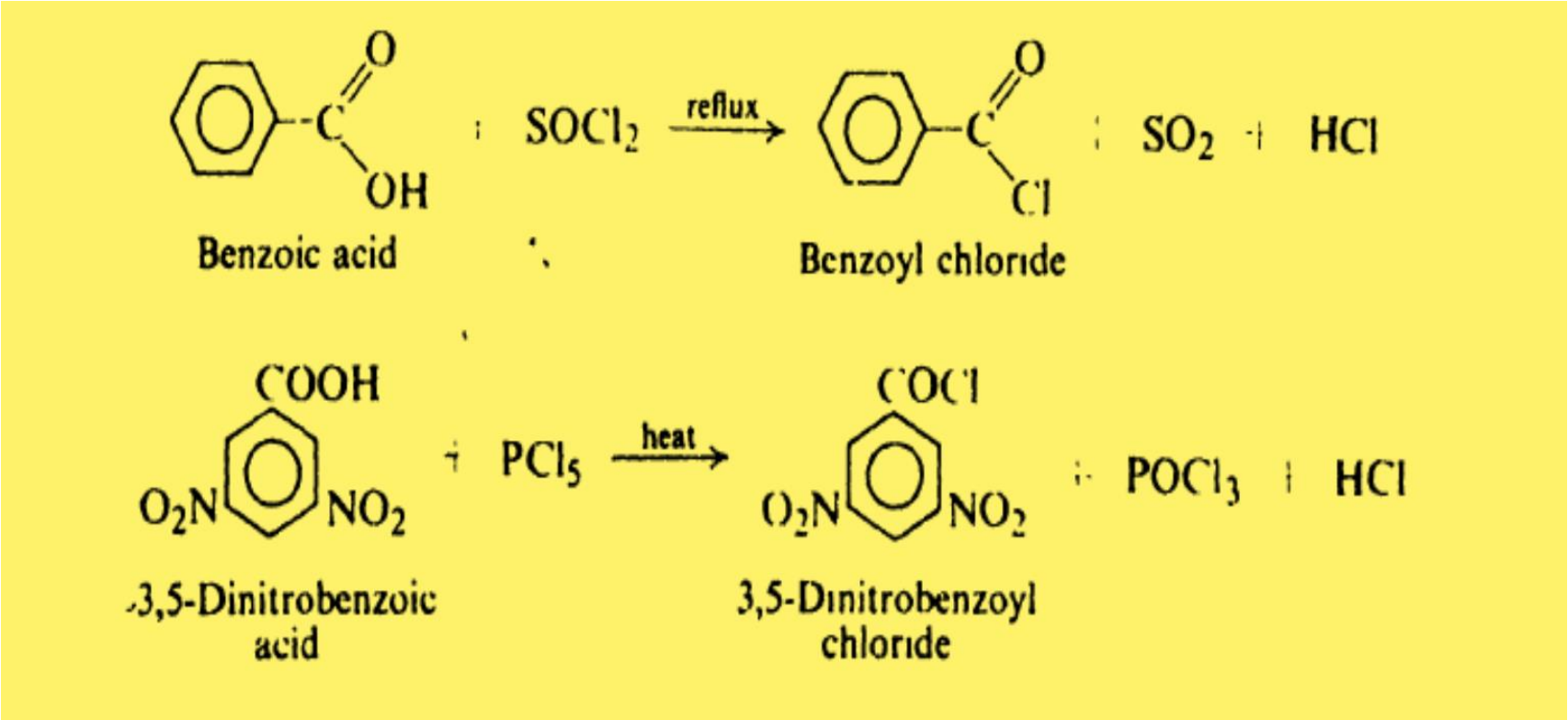
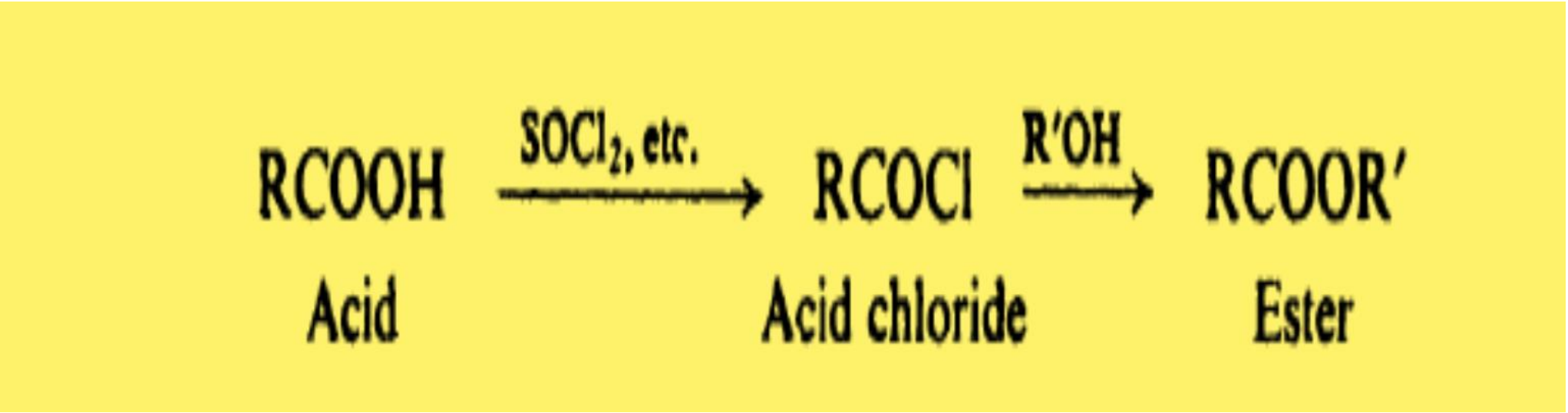
A carboxylic acid is more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride there can then be obtained many other kinds of compounds, including **esters** and **amides**. An acid chloride is prepared by substitution of **Cl** for the **OH** of a carboxylic acid. Three- reagents are commonly used for this purpose: **thionyl chloride, $SOCl_2$; phosphorus trichloride, PCl_3; and phosphorus pentachloride, PCl_5.** For example:



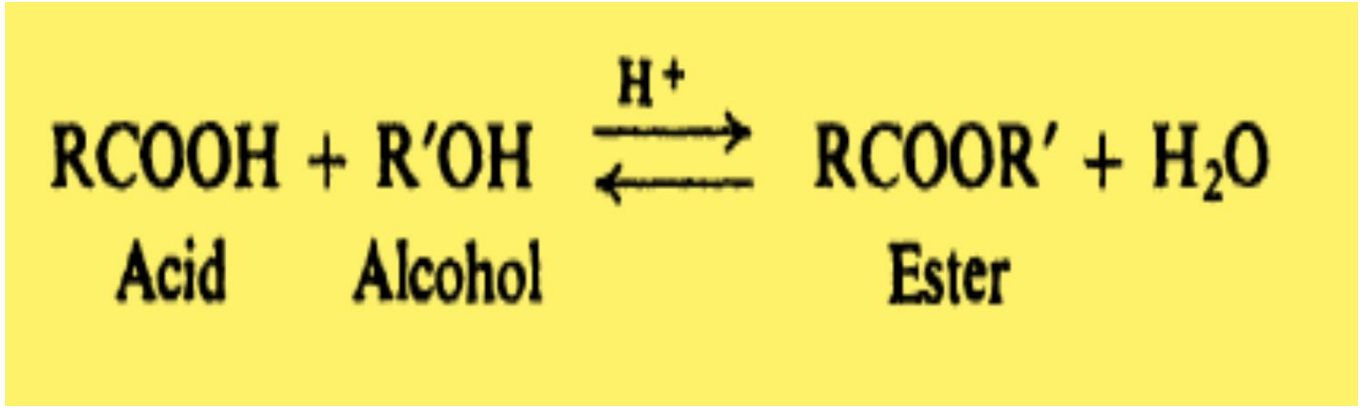
Thionyl chloride is particularly convenient, since the products formed besides the acid chloride are gases and thus easily separated from the acid chloride; any excess of the of the low-boiling thionyl chloride is easily removed by distillation.

Conversion into esters:

Acids are frequently converted into their esters via the acid chlorides.

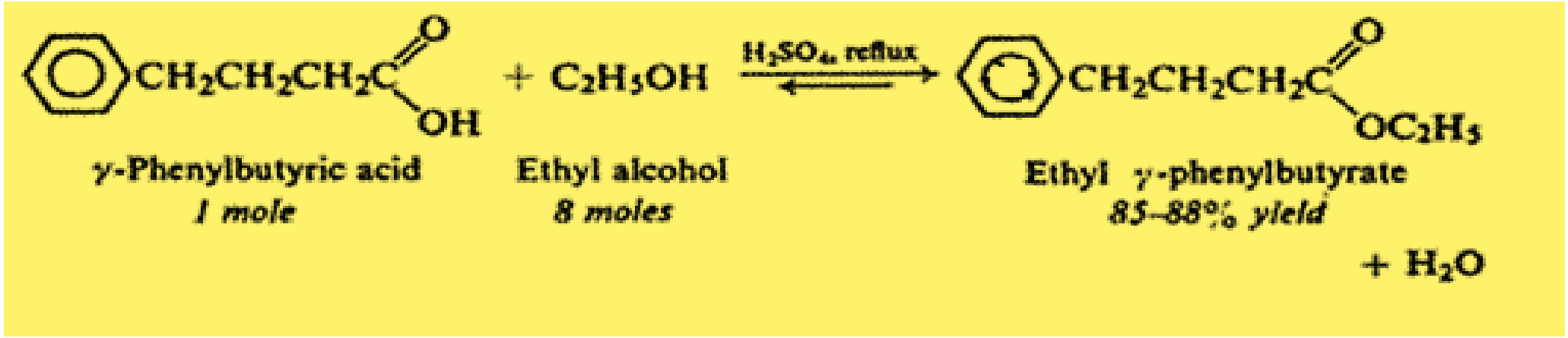


A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is **reversible**, and generally reaches equilibrium when there are appreciable quantities of both reactants and products present.



For example, when we allow one mole of acetic acid and one mole of ethyl alcohol to react in the presence of a little sulfuric acid until equilibrium is reached (after several hours), we obtain a mixture of about two-thirds mole each of ester and water, and one-third mole each of acid and alcohol. We obtain this same equilibrium mixture, of course, if we start with one mole of ester and one mole of water, again in the presence of sulfuric acid. The same catalyst, **hydrogen ion**, that catalyzes the forward reaction, **esterification**, necessarily catalyzes the reverse reaction, **hydrolysis**. This reversibility is a disadvantage in the preparation of an ester directly from an acid; the preference for the acid chloride route is due to the fact that both steps preparation of acid chloride from acid, and preparation of ester from acid chloride are essentially irreversible and go to completion.

Direct esterification, has the advantage of being a **single-step** synthesis; it can often be made useful by application of our knowledge of equilibria. If either the acid or the alcohol is cheap and readily available, it can be used in large excess to shift the equilibrium toward the products and thus to increase the yield of ester. For example, it is worthwhile to use eight moles of cheap ethyl alcohol to convert one mole of valuable γ-phenylbutyric acid more completely into the ester:



γ-Phenylbutyric acid
1 mole

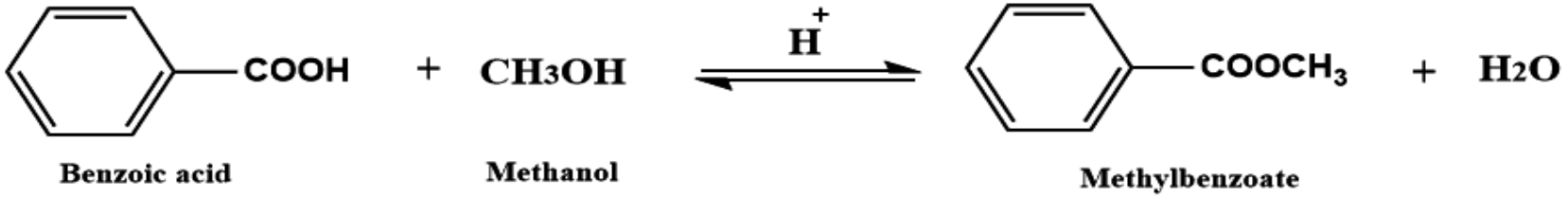
Ethyl alcohol
8 moles

Ethyl γ-phenylbutyrate
85–88% yield

The presence of bulky groups near the site of reaction, whether in the alcohol or in the acid, slows down esterification (as well as its reverse, hydrolysis). This **steric hindrance** can be so marked that special methods are required to prepare esters of tertiary alcohols or esters of acids like 2,4,6-trimethylbenzoic acid (mesitoic acid)

Reactivity in esterification	$CH_3OH > 1^\circ > 2^\circ (> 3^\circ)$
	$HCOOH > CH_3COOH > RCH_2COOH > R_2CHCOOH > R_3CCOOH$

Examples:



Benzoic acid Methanol Methylbenzoate

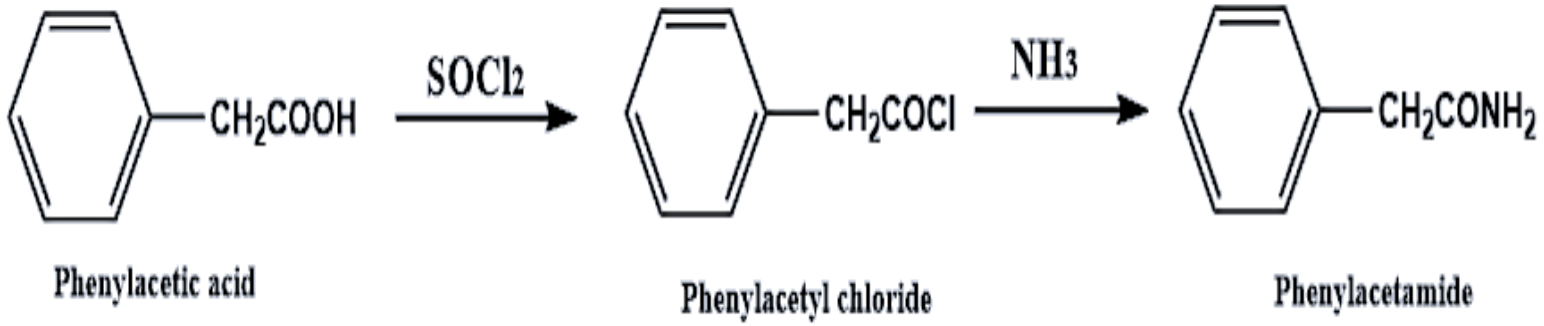
Trimethylacetic acid Ethyl trimethylacetate

Conversion into amides:

Amides are compounds in which the OH of the carboxylic acid has been replaced by NH2

These are generally prepared by reaction of ammonia with acid chlorides.

Example:

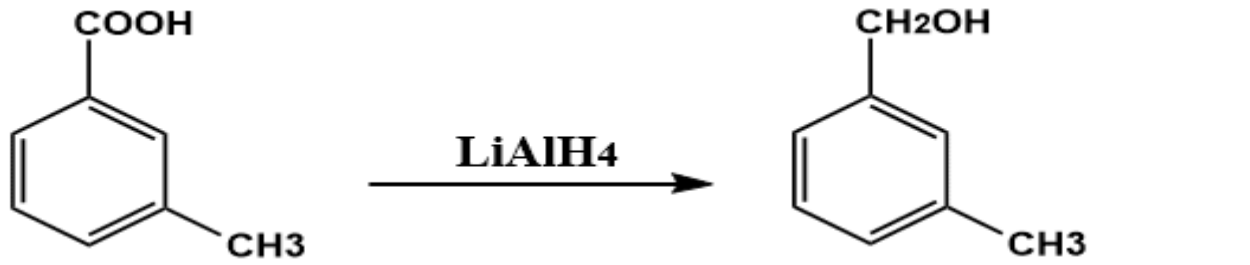


Reduction of acids to alcohols:

Conversion of alcohols into acids is important because, in general, alcohols are more available than acids. This is not always true, however; long straight-chain acids from fats are more available than the corresponding alcohols, and here the reverse process becomes important.

Lithium aluminum hydride, LiAlH4, is one of the few reagents that can reduce an acid to an alcohol; the initial product is an **alkoxide** from which the alcohol is liberated by hydrolysis:

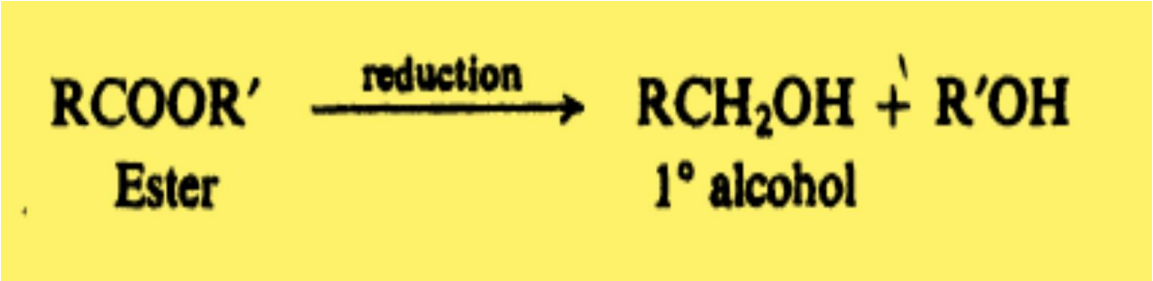
$$4RCOOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{1^\circ \text{ alcohol}}{4RCH_2OH}$$



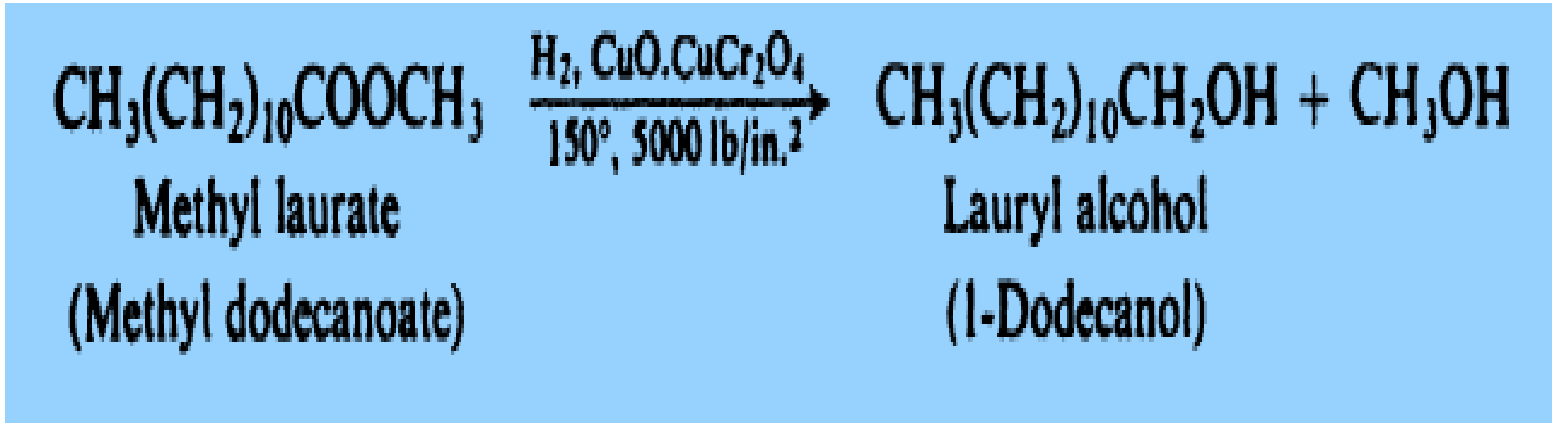
***m*- Toluic acid** ***m*- Methylbenzyl alcohol**

As an alternative to direct reduction, acids are often converted into alcohols by a two-step process: **esterification, and reduction of the ester.**

Esters can be reduced in a number of ways that are adaptable to both laboratory and industry



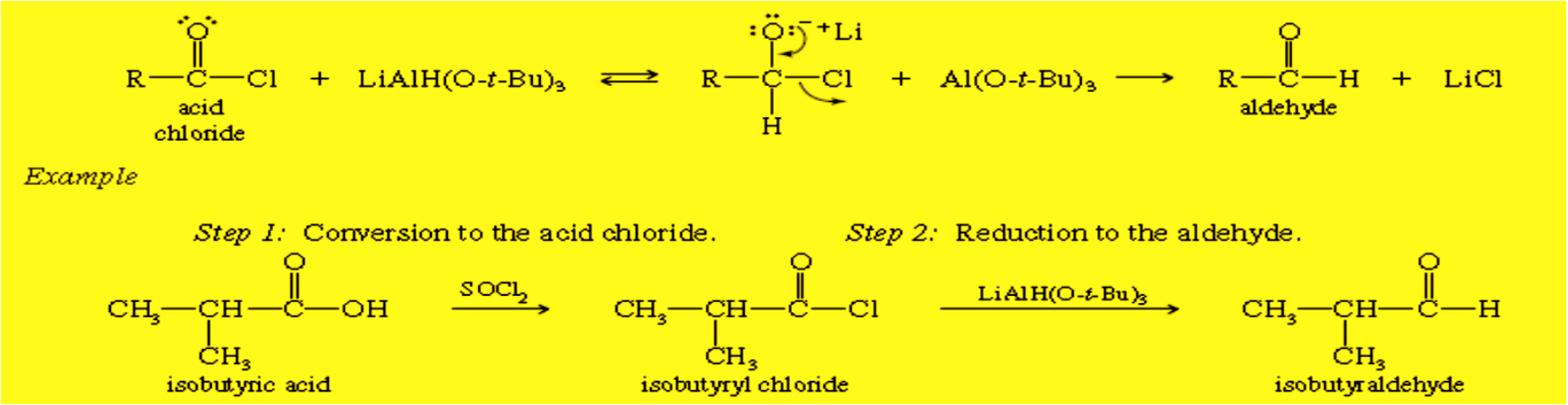
Example:



Reduction to Aldehydes:

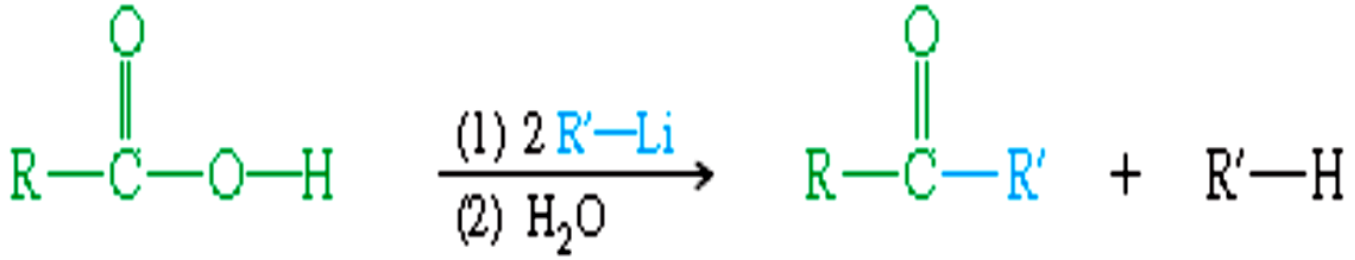
Reduction of carboxylic acids to aldehydes is difficult ***because aldehydes are more reactive than carboxylic acids toward most reducing agents.*** Almost any reagent that reduces acids to aldehydes also reduces aldehydes to primary alcohols.

Lithium tri-tert-butoxyaluminum hydride, $LiAlH(O\text{-}t\text{-}Bu)_3$ a **weaker** reducing agent than lithium aluminium hydride. It reduces acid chlorides to aldehydes because acid chlorides are strongly activated toward nucleophilic addition of a hydride ion. Under these conditions, the aldehyde reduces **more slowly** and can be **isolated**. Therefore, reduction of an acid to an aldehyde is a two-step process: **Convert the acid to the acid chloride, then reduce using lithium tri-tert-butoxyaluminum hydride.**

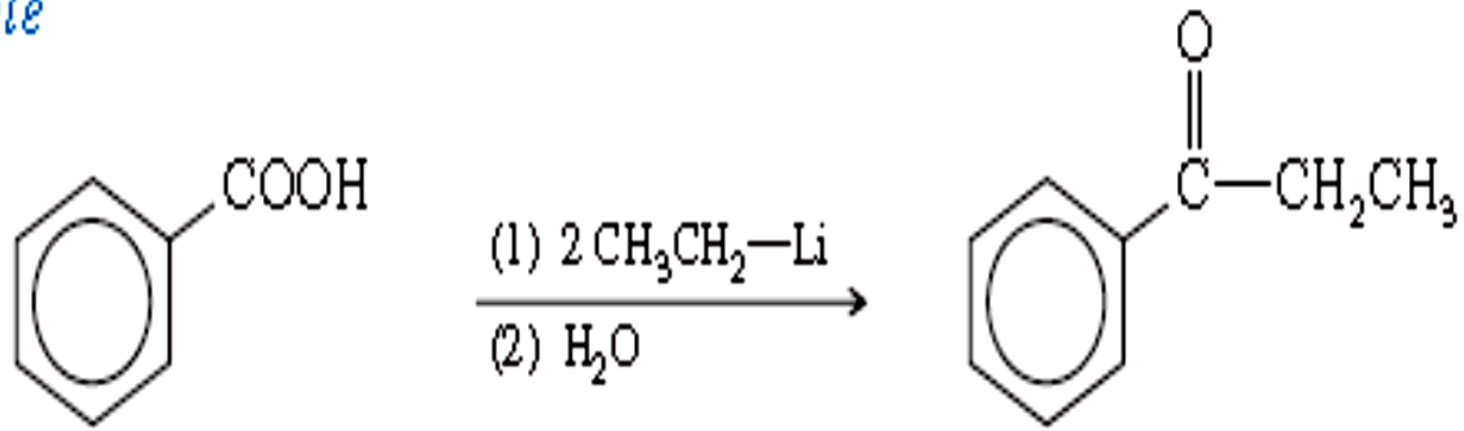


Alkylation of carboxylic acids to form ketones:

Carboxylic acids react with 2 equivalents of an organolithium reagent to give ketones



Example

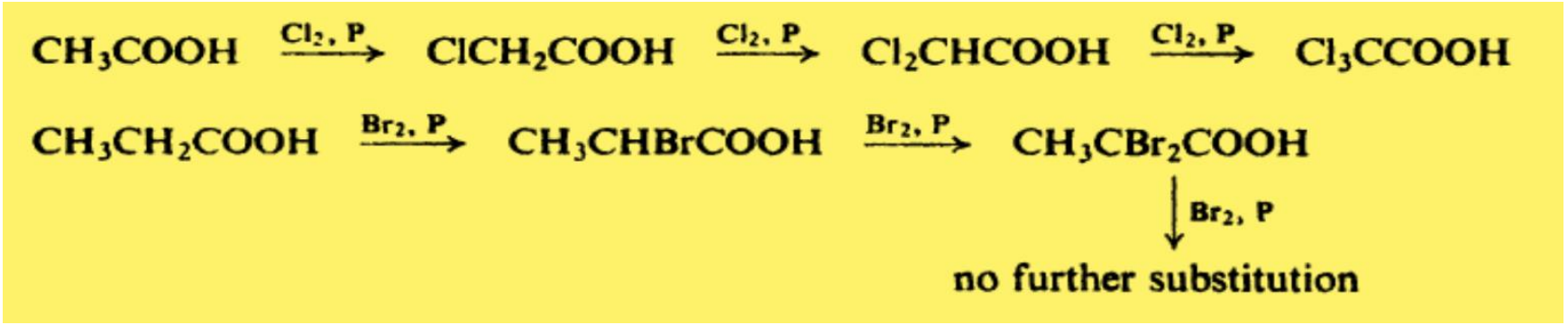


benzoic acid

propiophenone

Halogenation of aliphatic acids: Substituted acids

In the presence of a small amount of phosphorus, aliphatic carboxylic acids react smoothly with chlorine or bromine to yield a compound in which a hydrogen has been replaced by halogen. This is the **Hell-Volhard-Zelinsky** reaction. Because of its specificity only alpha halogenation- -and the readiness with which it takes place, it is of considerable importance in synthesis.



The function of the phosphorus is ultimately to convert a little of the acid into **acid halide**. In this form each molecule of acid sooner or later undergoes a-halogenation.

$$P + X_2 \longrightarrow PX_3$$

$$RCH_2COOH + PX_3 \longrightarrow RCH_2COX$$

$$RCH_2COX + X_2 \longrightarrow RCHCOX + HX$$

(X on the α-carbon)

$$RCHCOX + RCH_2COOH \rightleftharpoons RCHCOOH + RCH_2COX$$

(X on the α-carbon)

α-Haloacid

Examples:

$CH_3COOH \xrightarrow{Cl_2, P} ClCH_2COOH \xrightarrow{Cl_2, P} Cl_2CHCOOH \xrightarrow{Cl_2, P} Cl_3CCOOH$

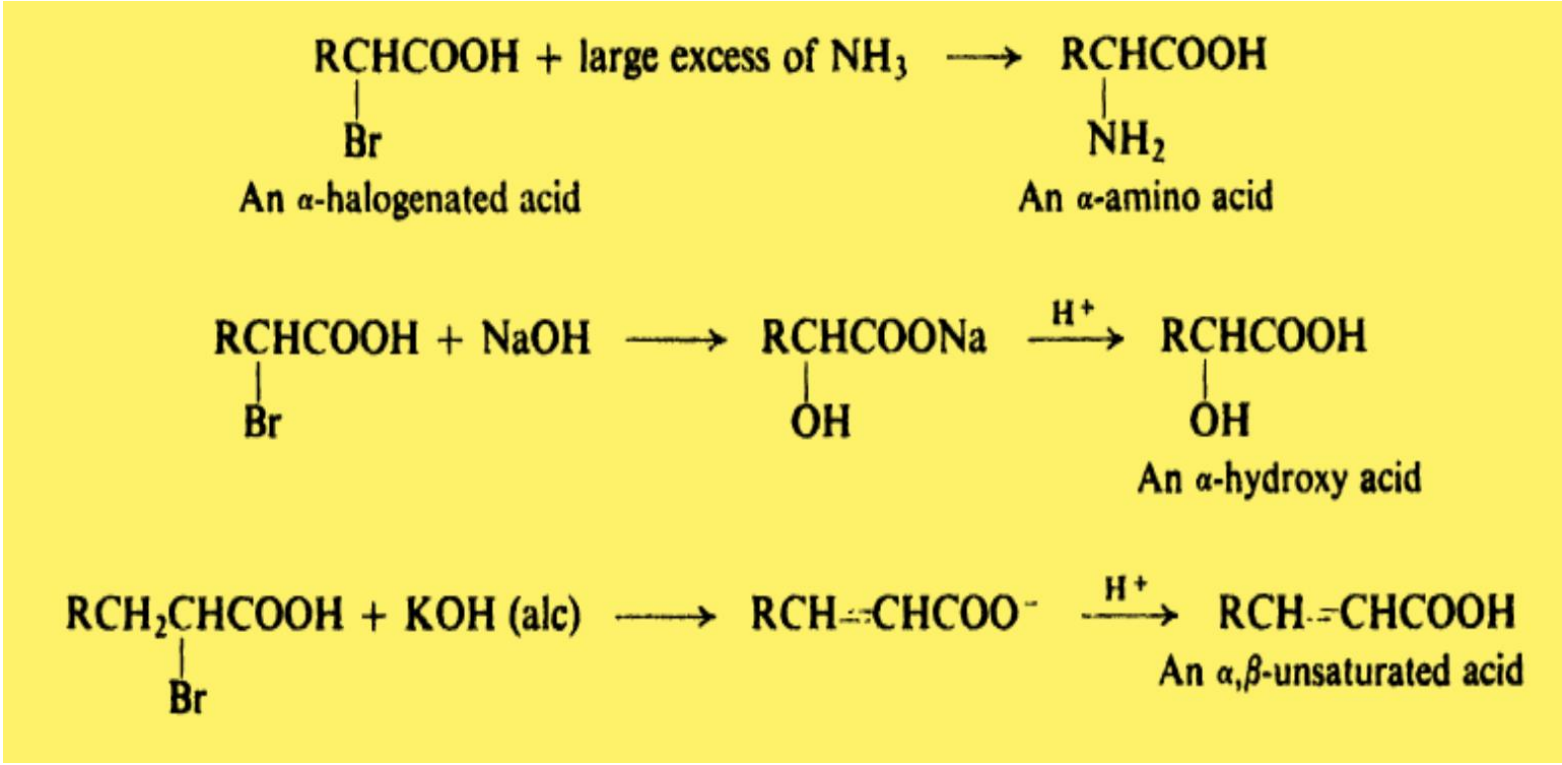
Acetic acid — **Chloroacetic acid** — **Dichloroacetic acid** — **Trichloroacetic acid**

$CH_3CH(CH_3)CH_2COOH \xrightarrow{Br_2, P} CH_3CH(CH_3)CH(Br)COOH$

Isovaleric acid

α-Bromoisovaleric acid

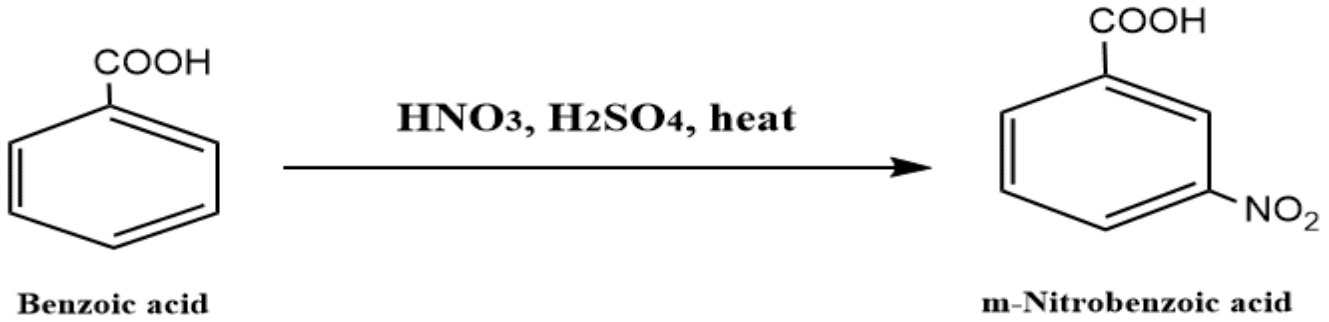
The halogen of these halogenated acids undergoes nucleophilic displacement and elimination much as it does in the simpler alkyl halides Halogenation is therefore the first step in the conversion of a carboxylic acid into many important substituted carboxylic acids:



These new substituents can, in turn, undergo their characteristic reactions.

Ring substitution in aromatic acids:

-COOH is a deactivating group and directs toward **meta** position in electrophilic substitution.



Benzoic acid

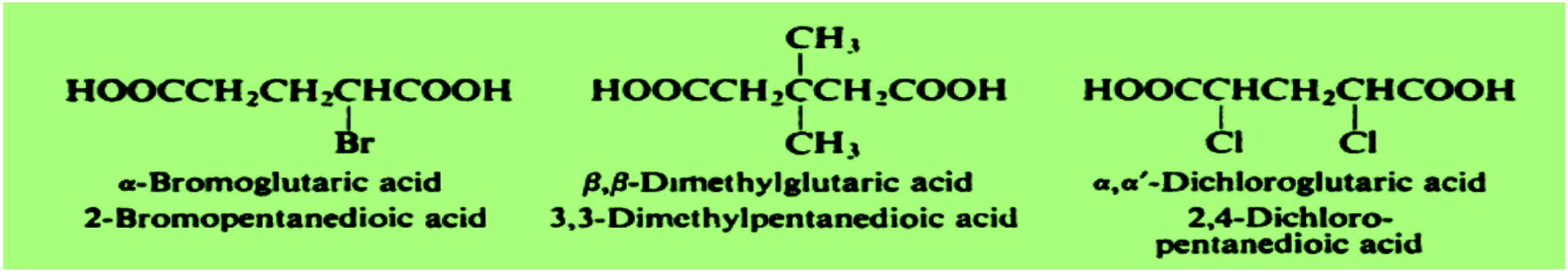
m-Nitrobenzoic acid

The deactivation is so strong that the Friedel-Crafts reaction does not take place.

Dicarboxylic acids:

If the substituent is a second carboxyl group, we have a dicarboxylic acid. For example

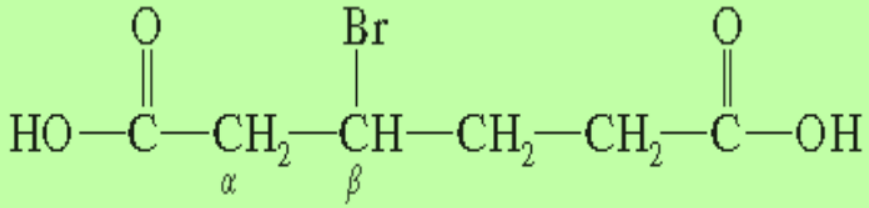
$HOOCCH_2COOH$	$HOOCCH_2CH_2COOH$	$HOOCCH_2CH_2CH_2CH_2COOH$
Malonic acid	Succinic acid	Adipic acid
Propanedioic acid	Butanedioic acid	Hexanedioic acid



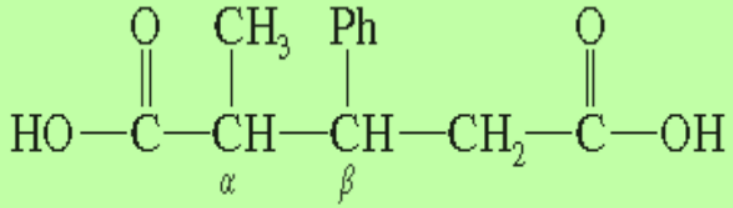
Common Names of Dicarboxylic Acids:

IUPAC Name	Common Name	Formula
ethanedioic	oxalic	HOOC—COOH
propanedioic	malonic	$HOOCCH_2COOH$
butanedioic	succinic	$HOOC(CH_2)_2COOH$
pentanedioic	glutaric	$HOOC(CH_2)_3COOH$
hexanedioic	adipic	$HOOC(CH_2)_4COOH$
heptanedioic	pimelic	$HOOC(CH_2)_5COOH$
cis-but-2-enedioic	maleic	*cis*-HOOCCH=CHCOOH
trans-but-2-enedioic	fumaric	*trans*-HOOCCH=CHCOOH
benzene-1,2-dicarboxylic	phthalic	$1,2\text{-}C_6H_4(COOH)_2$
benzene-1,3-dicarboxylic	isophthalic	$1,3\text{-}C_6H_4(COOH)_2$
benzene-1,4-dicarboxylic	terephthalic	$1,4\text{-}C_6H_4(COOH)_2$

Substituted dicarboxylic acids are given common names using Greek letters, as with the simple carboxylic acids. Greek letters are assigned beginning with the carbon atom next to the carboxyl group that is closer to the substituents.

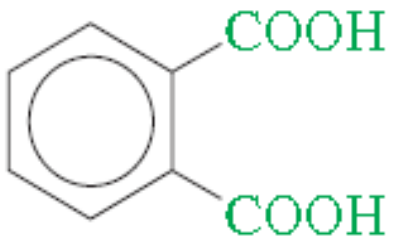


β-bromoadipic acid

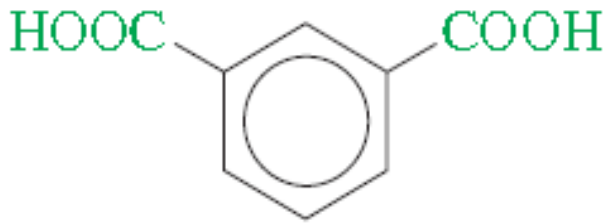


α-methyl-β-phenylglutaric acid

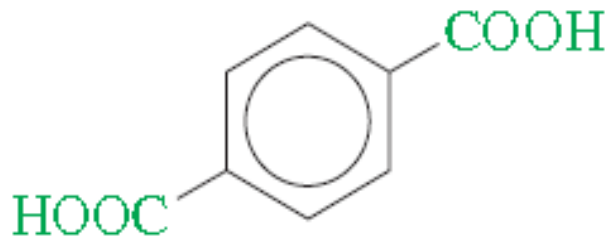
Benzenoid compounds with two carboxyl groups are named **phthalic acids.** *Phthalic acid* itself is the ortho isomer. The meta isomer is called *isophthalic acid*, and the para isomer is called *terephthalic acid*.



o-phthalic acid
phthalic acid

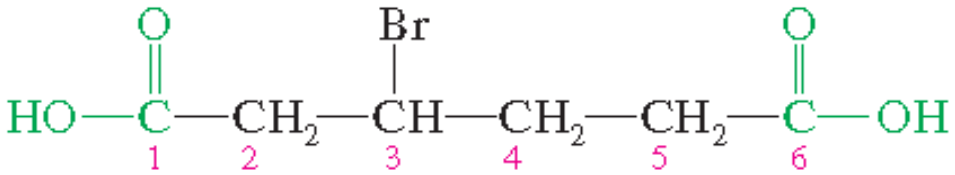


m-phthalic acid
isophthalic acid

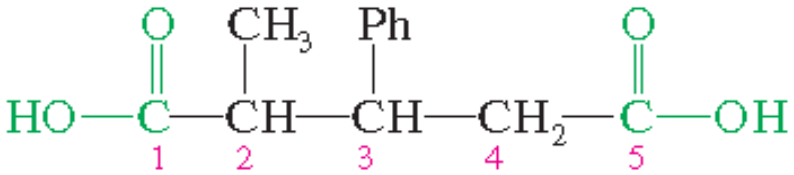


p-phthalic acid
terephthalic acid

IUPAC Names of Dicarboxylic Acids Aliphatic dicarboxylic acids are named simply by adding the suffix *-dioic acid* to the name of the parent alkane. For straight-chain dicarboxylic acids, the parent alkane name is determined by using the longest continuous chain that contains both carboxyl groups. The chain is numbered beginning with the carboxyl carbon atom that is closer to the substituents, and these numbers are used to give the positions of the substituents.

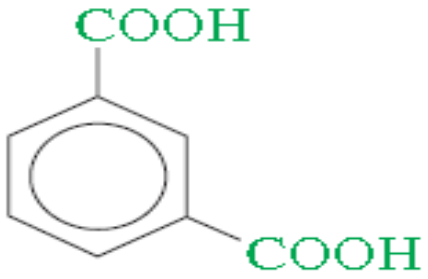


3-bromohexanedioic acid

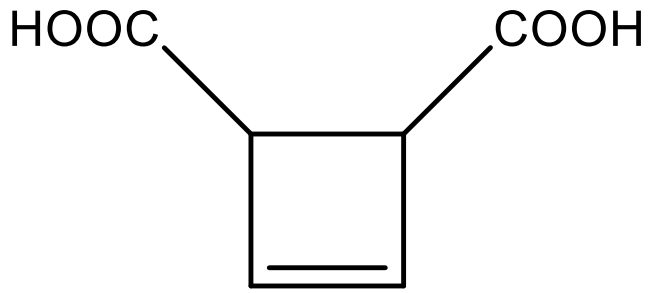


2-methyl-3-phenylpentanedioic acid

The system for naming cyclic dicarboxylic acids treats the carboxyl groups as substituents on the cyclic structure.



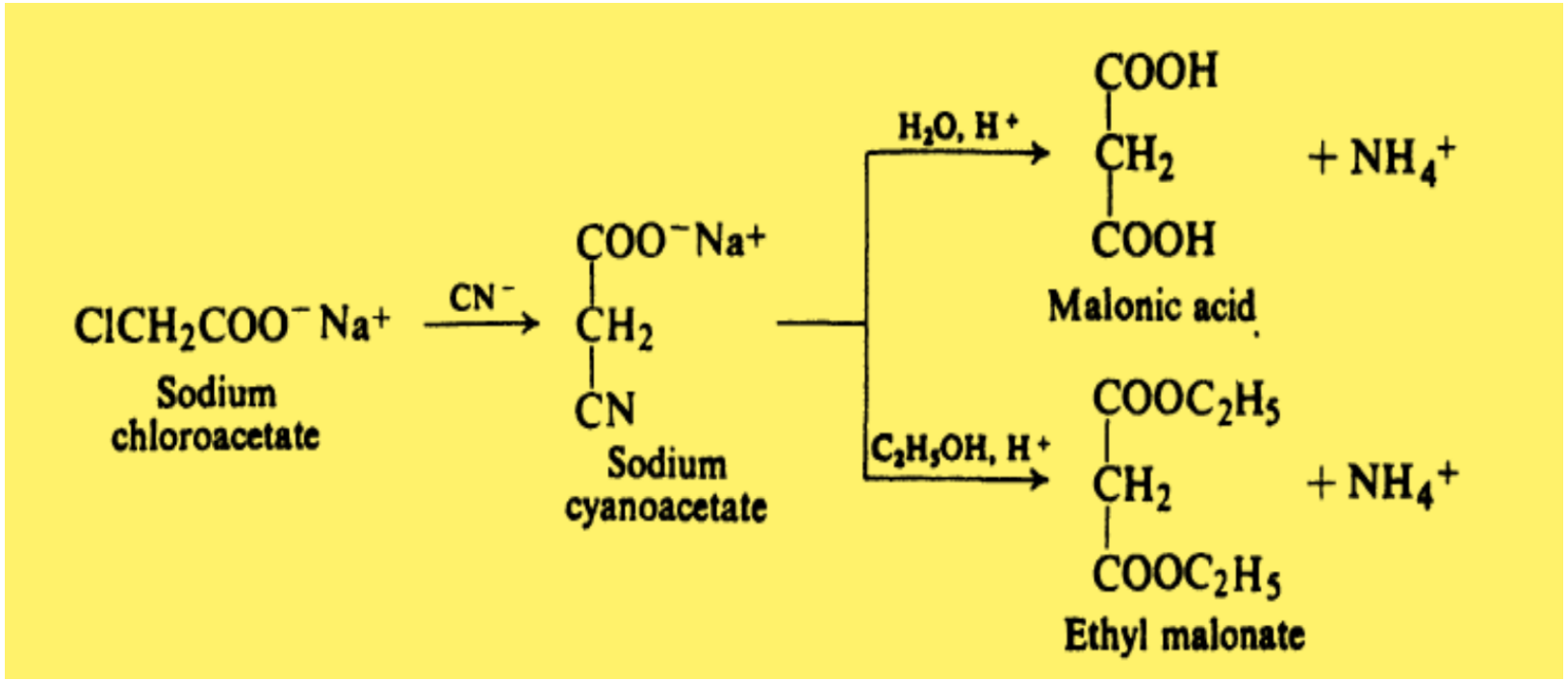
1,3-benzenedicarboxylic acid
benzene-1,3-dicarboxylic acid



cyclobut-3-ene-1,2-dicarboxylic acid

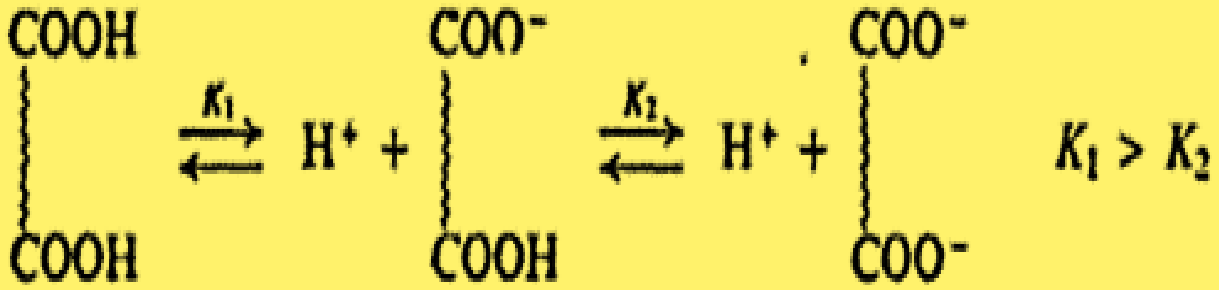
Most dicarboxylic acids are prepared by adaptation of methods used to prepare monocarboxylic acids. Where hydrolysis of a nitrile yields a monocarboxylic acid, hydrolysis of a **dinitrile** or a **cyanocarboxylic acid** yields a dicarboxylic acid; where oxidation of a methylbenzene yields a benzoic acid, oxidation of a **dimethylbenzene yields a phthalic acid**.

For example :



In general, dicarboxylic acids show the same chemical behaviour as monocarboxylic acids. It is possible to prepare compounds in which only one of the carboxyl groups has been converted into a derivative; it is possible to prepare compounds in which the two carboxyl groups have been converted into different derivatives.

As with other acids containing more than one ionizable hydrogen (H_2SO_4, H_2CO_3, H_3PO_4, etc.), ionization of the second carboxyl group occurs less readily than ionization of the first.



More energy is required to separate a positive hydrogen ion from the doubly charged anion than from the singly charged anion.

Analysis of carboxylic acids: Neutralization equivalent:

Carboxylic acids are recognized through their acidity. They dissolve in aqueous sodium hydroxide and in aqueous sodium bicarbonate. The reaction with bicarbonate releases bubbles of carbon dioxide. Once characterized as a carboxylic acid, an unknown is identified as a particular acid on the usual basis of its physical properties and the physical properties of derivatives. The derivatives commonly used are amides and esters.

Particularly useful both in identification of previously studied acids and in proof of structure of new ones is the **neutralization equivalent**: *the equivalent weight of the acid as determined by titration with standard base*. A weighed sample of the acid is dissolved in water or aqueous alcohol, and the volume of standard base needed to neutralize the solution is measured. For example, a 0.224-g sample of an unknown acid (m.p. 139–140°) required 13.6 ml of 0.104 N sodium hydroxide solution for neutralization (to a phenolphthalein end point). Since each 1000 ml of the base contains 0.104 equivalents, and since the number of equivalents of base required equals the number of equivalents of acid present,

Number of equivalents of the acid = Number of equivalents of the base

$$\frac{wt}{eq.wt} \times 1000 = N \times V$$

$$\frac{0.224}{eq.wt} \times 1000 = 13.6 \times 0.104$$

$$eq.wt = \frac{0.224 \times 1000}{13.6 \times 0.104}$$

$$eq.wt = 158\ g$$

A metal salt of a carboxylic acid is recognized through these facts: (a) it leaves a residue when strongly heated (*ignition test*); (b) it decomposes at a fairly high temperature, instead of melting; and (c) it is converted into a carboxylic acid upon treatment with dilute mineral acid.