CHEM 322 Organic Chemistry II - Professor Kathleen V. Kilway
"Organic Chemistry" by Maitland Jones, 3rd edition

Chapter 18 - 6, 9, 10, ~~12~~, 21, ~~23~~, 22 (a-c), 24, 25, ~~26~~, 27 (a-g), 28 (no mech d, no g), 29, 30, ~~32, 38~~.

Chapter 18
Carboxylic Acids

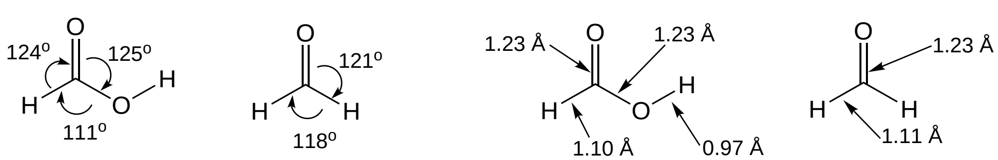
Section 18.1
I. Preview
A- R-COOH
1- In base, always remove the acidic proton first.
2- Will introduce the acid derivatives here but follow up in Chapter 19.

B- Essential Skills
1- Important reaction is the Fisher esterification and then hydrolysis.

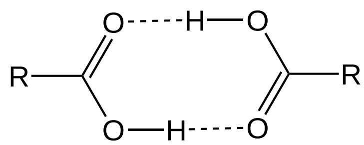
C- Important Details
1- Reaction of a carboxylic acid with two equivalents of R-Li yields a ketone.

Section 18.2
II. Nomenclature and Properties of Carboxylic Acids
A- Systematic Nomenclature
1- Drop the final "e" of the parent alkane and add the suffix "oic."
2- For diacids, use the parent alkane but do not drop the final "e" and add "dioic."
3- Cyclic acids are "cycloalkanecarboxylic acids." (Table 18.1)
4- In numbering substituted acids, the acid itself has the priority in numbering and naming. (Fig. 18.1, p 978)

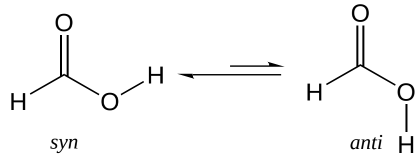
Section 18.3
III. Structure of Carboxylic Acids
A- The structure of carboxylic acids are comparable to other carbonyl compounds with two exceptions.



1- Simple carboxylic acids tend to be dimerized in solution.
a- Hydrogen bonding makes this possible.
b- It also explains why carboxylic acids have high boiling points.



2- Carboxylic acids also have two energy minima: syn and anti. (Fig. 18.4)



Section 18.4

IV. Infrared and Nuclear Magnetic Resonance Spectra of Carboxylic Acids.

A- Both spectra carry similar features of other carbonyl groups.

1- IR Spectra:

a- There is a strong C=O stretch for the dimeric form at ~1710 cm^{-1}.

b- The O-H stretching frequency is very broad at ~3100 cm^{-1}.

2- NMR Spectra:

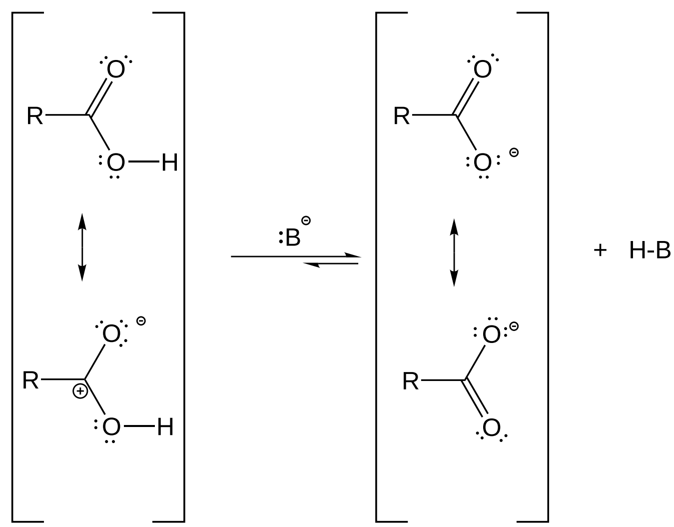
a- Hydrogens in the α-position are deshielded by the carbonyl group and are in approximately the same region as other α-hydrogens, δ 2-2.5 ppm.

b- The carbon of the carboxylic acid is also deshielded and appears at about 180 ppm.

Section 18.5

V. Acidity and Basicity of Carboxylic Acids

A- Carboxylic acids are strong Brønsted acids. (Table 18.2)

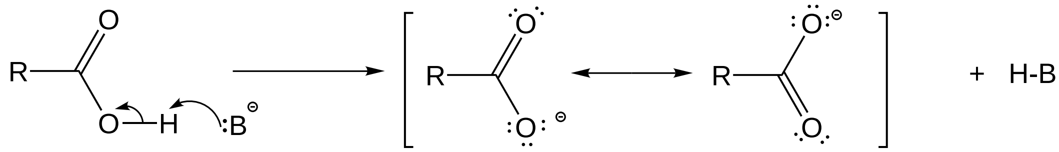


1- Organic acids (pK_a = 3-5) are stronger acids than alcohols (pK_a = 15-20) partly due to resonance effects.

a- Alkoxide is not resonance-stabilized.

b- Other carbonyl compounds are resonance-stabilized, but the negative charge is shared between electronegative oxygen and electropostive carbon.

c- But the **carboxylate anion** is resonance-stabilized *and* the negative charge is shared between two electronegative oxygens. (Fig. 18.6 and 18.7)



pK_a = 3-5
versus ketone pK_a = 15-20
and alcohols pK_a = 15-17

resonance-stabilized
carboxylate anion

2- Organic acids are also strong acids because of inductive effects.

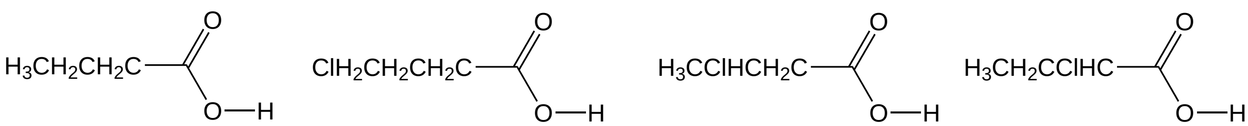
a- The carbonyl group is polar and increases the stability of the carboxylate anion. (Fig. 18.8)

b- The carbonyl oxygen already carries much of the negative charge, even before the O-H bond begins to break. (Fig. 18.9)

c- Electron withdrawing groups increase overall acidity.

i- The closer they are to the acid, the stronger the effect.

ii- See Table 18.2.



pK_a = 4.81
Butyric acid
Butanoic acid

pK_a = 4.54
4-Chlorobutyric acid
4-Chlorobutanoic acid

pK_a = 4.06
3-Chlorobutyric acid
3-Chlorobutanoic acid

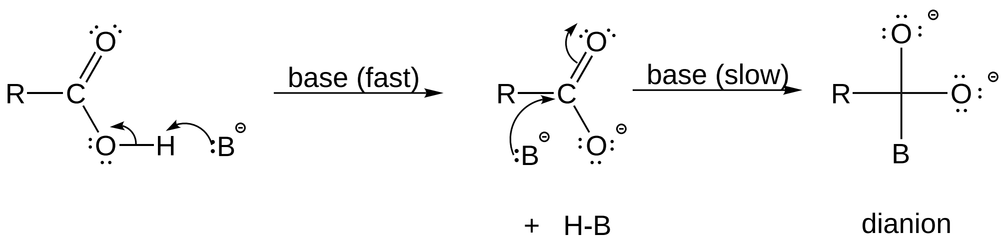
pK_a = 2.84
2-Chlorobutyric acid
2-Chlorobutanoic acid

B- Carboxylic acids are Lewis acids.

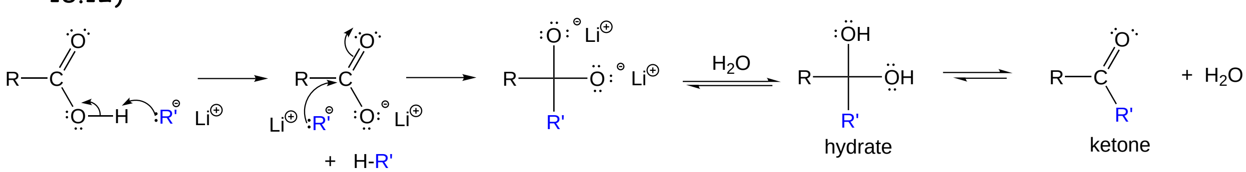
1- The Lewis acid quality is difficult to express. (Fig. 18.11)

a- The fastest reaction in base is usually the removal of hydroxyl hydrogen.

b- The carboxylate anion resists addition of base, which would give a dianion.



2- There are some strong nucleophiles that are capable of adding to the carboxylate anion. (Fig. 18.12)



C- Carboxylic acids are Lewis bases.

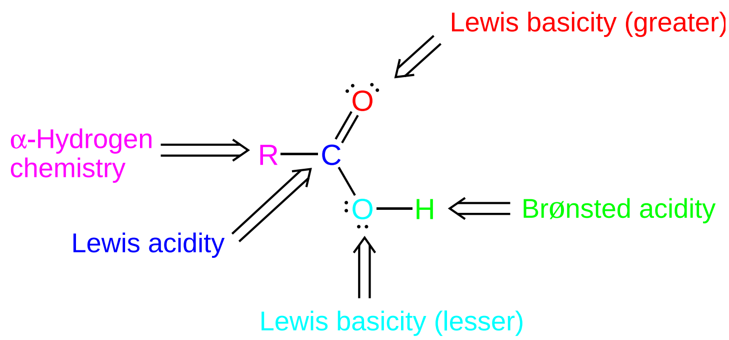
1- It is more energetically favorable to protonate the carbonyl oxygen.

a- Protonation at the carbonyl oxygen is resonance-stabilized.

b- Protonation at the hydroxyl oxygen is not.

c- Protonation at the hydroxyl oxygen is destabilized by the dipole in the carbonyl which puts a partial positive charge on carbon.

2- Although the hydroxyl group can be protonated, carboxylic acids are more strongly basic at the carbonyl oxygen and reactions there will be favored, and faster. (Fig. 18.15)

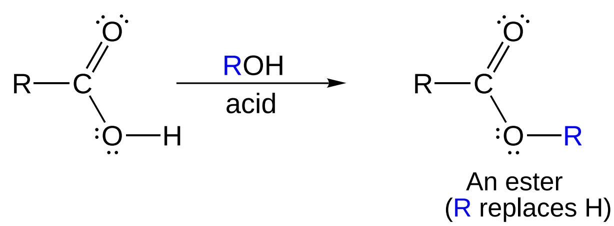


Section 18.6

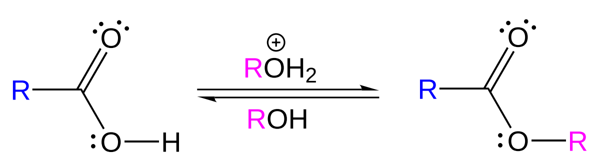
VI. Reactions of Carboxylic Acids

A- Formation of Esters: Fischer Esterification

1- When the hydrogen of the hydroxyl group of a carboxylic acid is replaced by an R group, it is called an **ester**.



a- The acid-catalyzed reaction of a carboxylic acid with excess alcohol is called **Fischer esterification**.



i- Step 1 is protonation of the carbonyl group.

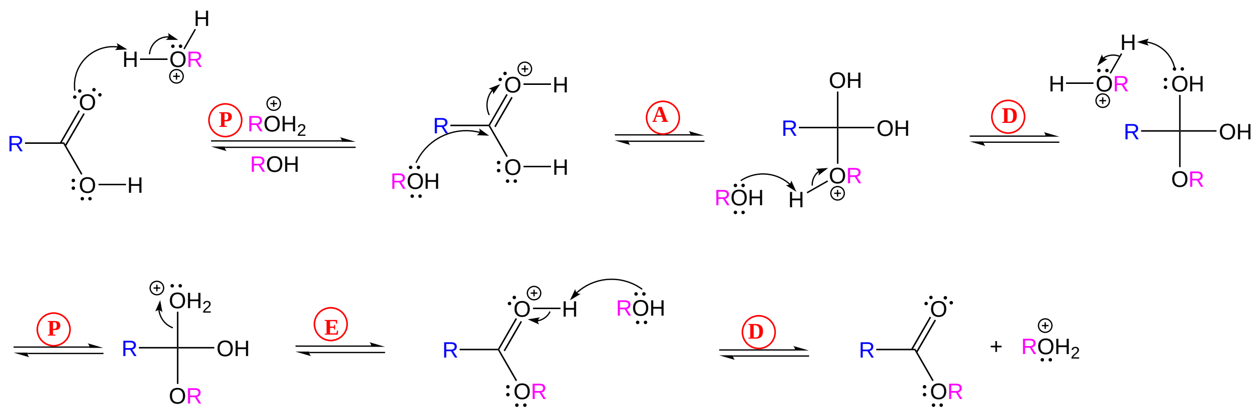
ii- Step 2 is addition of alcohol to the protonated carbonyl.

iii- Step 3 is deprotonation of the alcohol. This forms the tetrahedral intermediate.

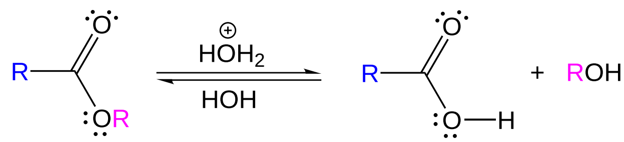
iv- Step 4 is protonation of one of the hydroxyl groups.

v- Step 5 is loss of water to give a resonance-stabilized carbocation.

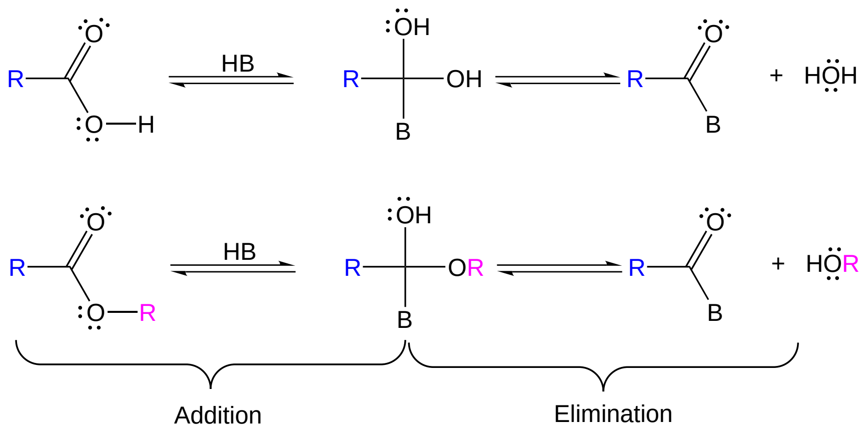
vi- Step 6 is deprotonation of one of the resonance forms to give the carbonyl group, forming the ester. (Fig. 18.18)



b- This is a reversible reaction. The reverse reaction is hydrolysis of ester to carboxylic acid.

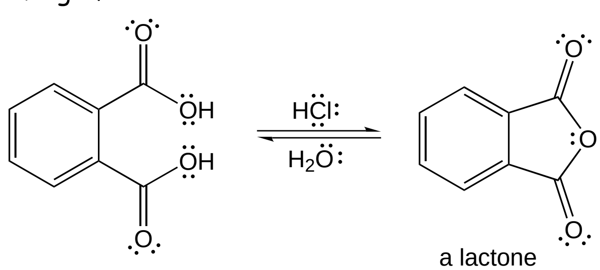


c- Fischer esterification is the prototype for other **addition-elimination reactions**.



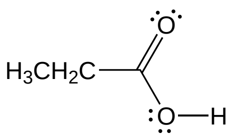
2- The intramolecular Fischer esterification gives a cyclic ester, called a **lactone**.

a- The common naming of lactones relates to the acid with the same number of carbons.

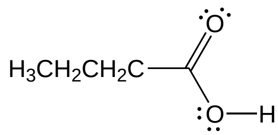


b- A Greek letter starting with the a-carbon designates the size of the ring.

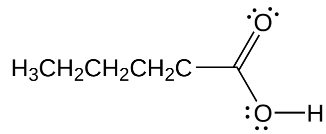
c- In IUPAC, lactones are called "oxacycloalkanones." (Fig. 18.24)



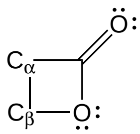
Propionic acid
(propanioc acid)



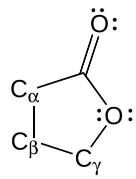
Butyric acid
(butanioc acid)



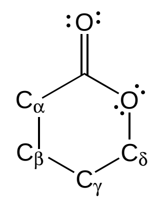
Pentanoic acid



A propanolide
(a β-lactone)
(2-oxacyclobutanone)

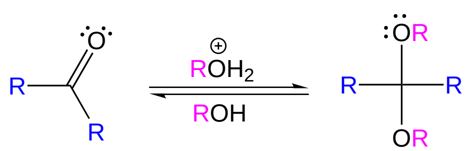


A butanolide
(a γ-lactone)
(2-oxacyclopentanone)

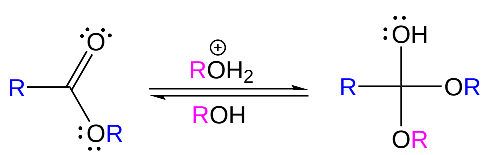


A pentanolide
(a δ-lactone)
(2-oxacyclohexanone)

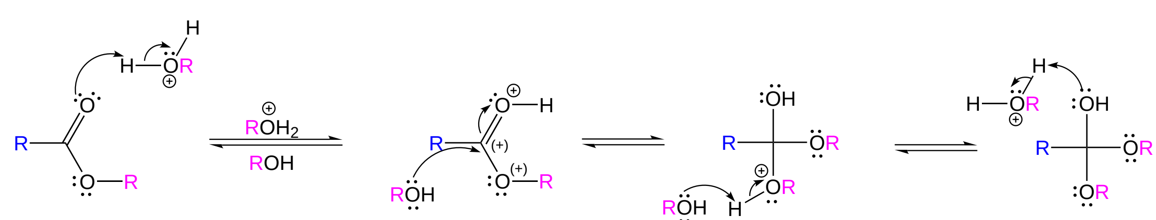
3- Esters can also be made in an S_N2 reaction.

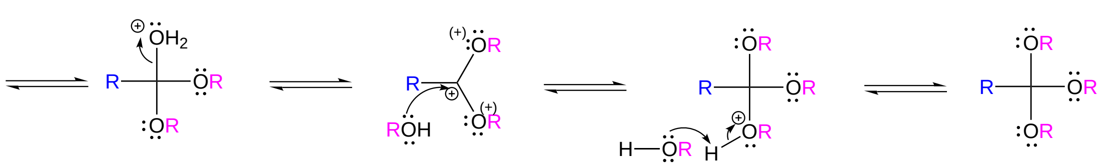


A ketal (acetal)



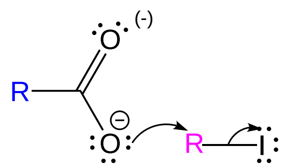
An ortho ester

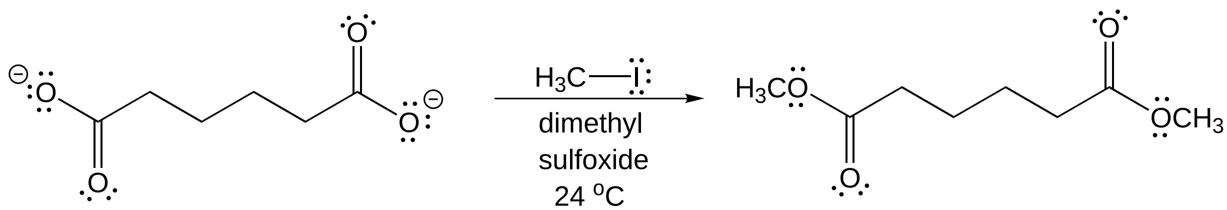




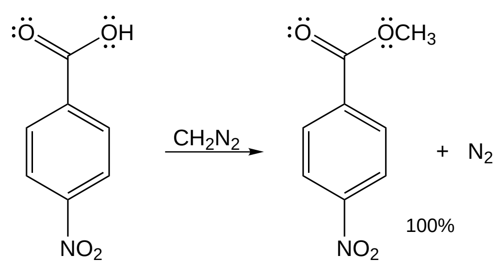
An ortho ester

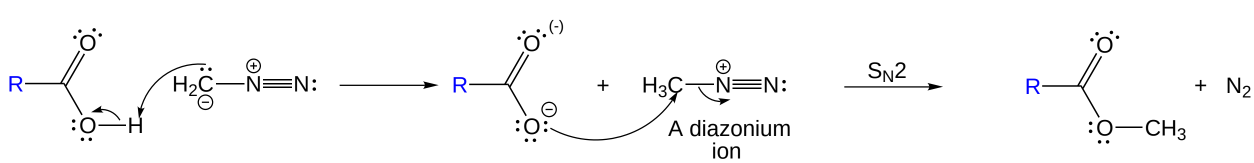
a- The carboxylate anion must act as nucleophile.
b- The partner in the replacement reaction has to be very reactive.
c- Primary halides or a more reactive species is required. (Fig. 18.30)





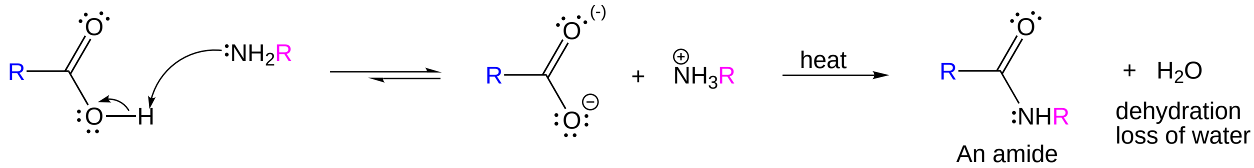
4- The carboxylate anion can be used as nucleophile to make methyl esters.
a- First, the acid is deprotonated by the basic carbon of diazomethane.
b- This gives the carboxylate anion and diazonium ion, which is an extremely reactive alkylating agent. (Fig. 18.32-18.33)
c- Then nitrogen is diplaced by the carboxylate anion to give the methyl ester.





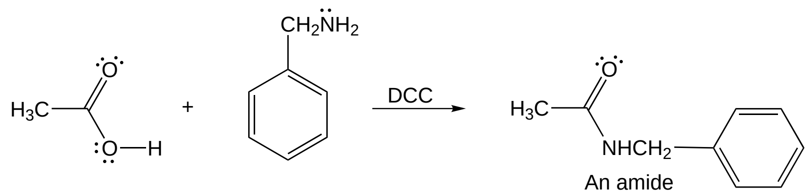
B- Formation of Amides

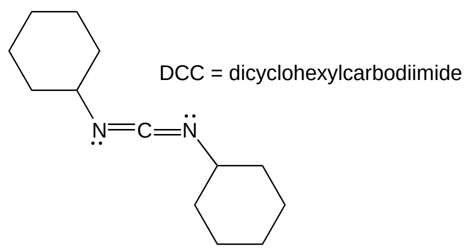
1- Carboxylic acids can react with amines to form **amides**.
a- A proton transfer gives an ammonium salt of the acid.



b- Heating causes loss of water (dehydration reaction) to give the amide. (Fig. 18.434)

2- A better way is to use a dehydrating agent, such as **dicyclohexylcarbodiimide (DCC)**.





a- The poor leaving group, OH, is converted to a good leaving group, giving two possible mechanistic pathways. (Fig. 18.37)

i- The amine can add to C=O to give the tetrahedral intermediate. A stable ion is expelled to generate the amide.

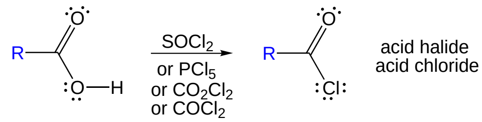
ii- Or, another molecule of carboxylic acid can add to C=O to give anhydride. The anhydride can then react with the amine to give the amide.

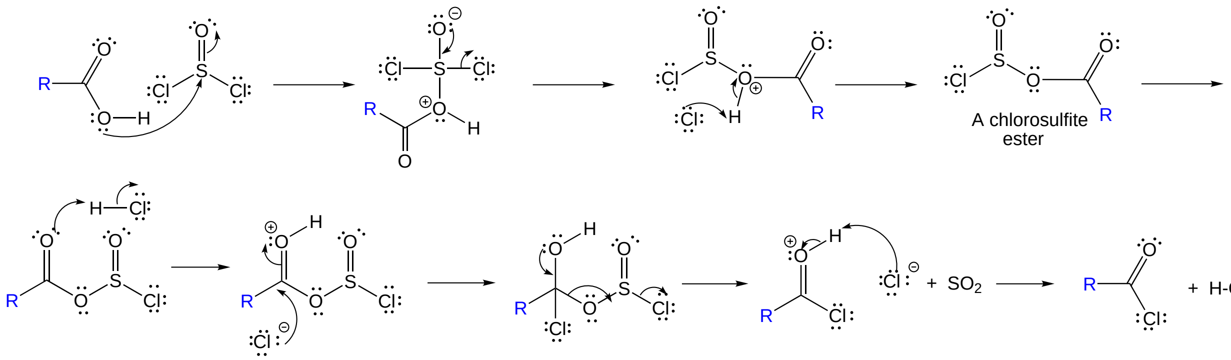
b- All these reactions are just variations of the addition-elimination reactions.

~~C- Polyamides (nylon) and Polysesters~~

D- Formation of Acid Chlorides - No mechanism

1- The **acid chloride** can be made by reacting carboxylic acid with thionyl chloride or phosphorus pentachloride.





a- First OH is replaced with a good leaving group to form an ester, such as chlorosulfinic acid. (Fig. 18.46)

b- Then the HCl that is generated protonates the oxygen of the carbonyl group.

c- The chloride ion then adds to the strong Lewis acid (the protonated carbonyl group).

d- This intermediate breaks down into chloride, sulfur dioxide and the protonated acid chloride.

e- Finally, chloride ion deprotonates the carbonyl oxygen to give the acid chloride. (Fig. 18.42)

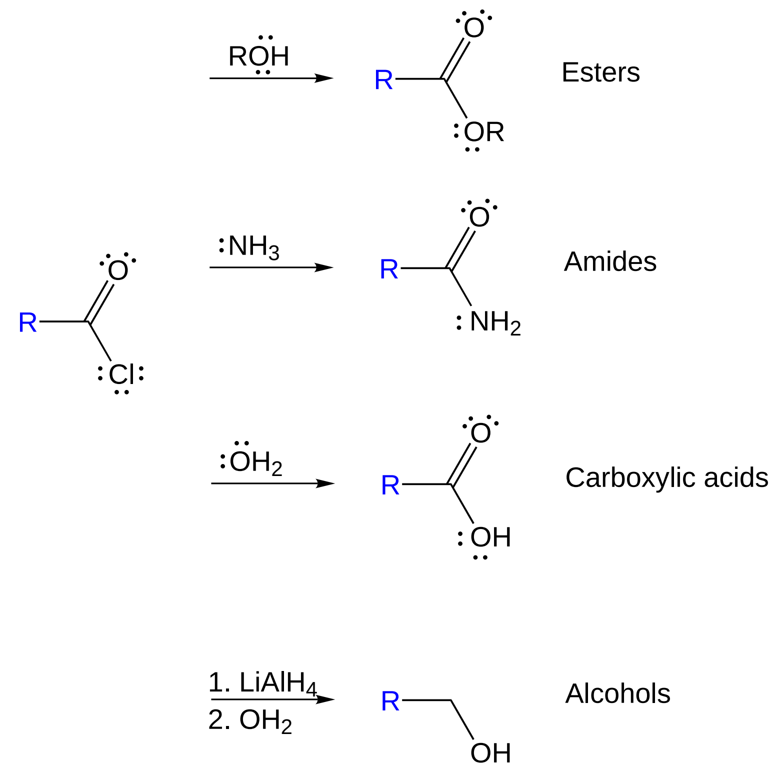
2- Acid chlorides have a good leaving group (chloride) and addition-elimination reactions can give many acyl derivatives. (R-CO-X) - Further explained in Chapter 19.

a- Use ROH to get esters.

b- Use NH_3 to to get amides.

c- Use H_2O to get carboxylic acids.

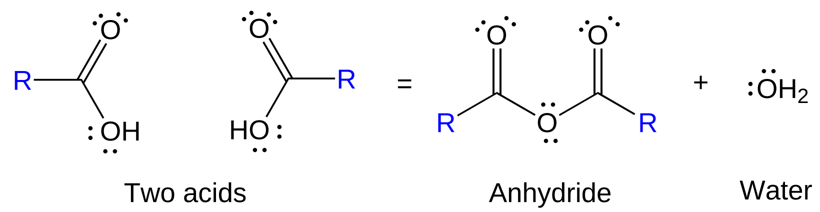
d- Use Li$_A$lH_4/H_2O to get alcohols.



3- Acid chlorides can also be synthesized from carboxylic acids using:
   a- Phogene (Cl-CO-Cl)
   b- oxalyl chloride (Cl-CO-CO-Cl)

E- Anhydride Formation - Mechanism not required.

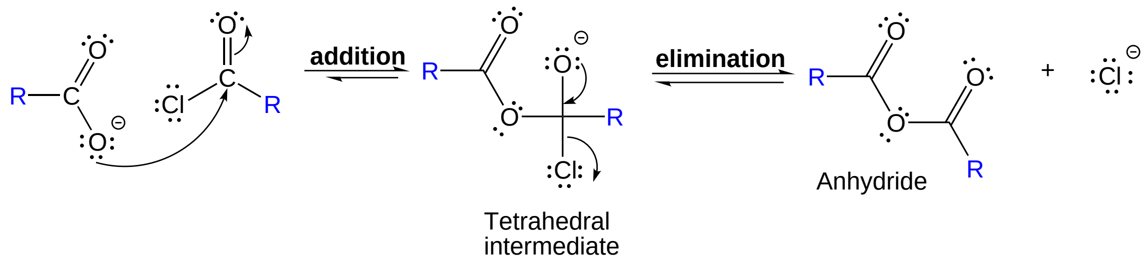
1- Two carboxylic acids that are joined with loss of water form a molecule called an **anyhdride**.



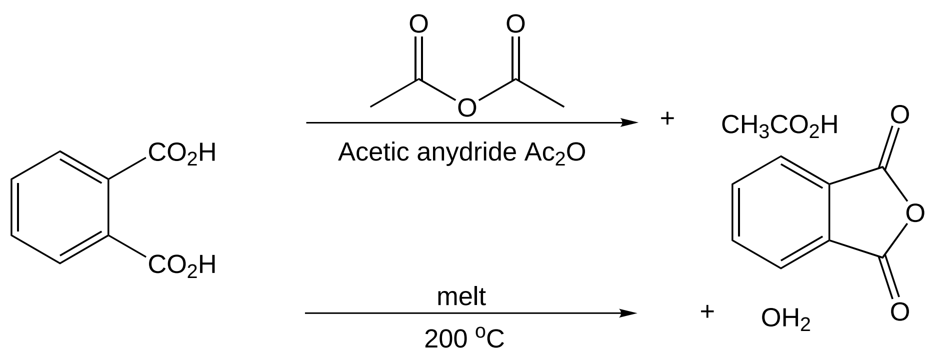
a- Carboxylic acids and their conjugate bases (the carboxylate anion) can react with acid halides to give anhydrides.

b- The carboxylate anion adds to the carbonyl group of the acid chloride.

c- The tetrahedral intermediate loses the chloride, a good leaving group, to generate the anhydride. (Fig. 18.46)

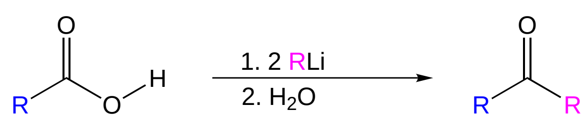


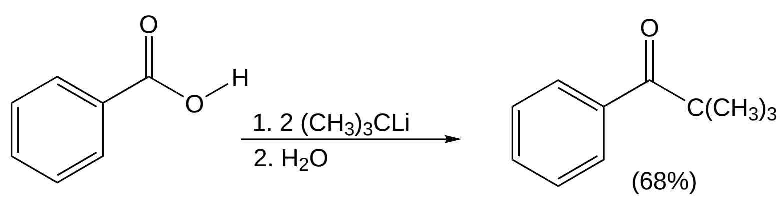
2- Other **dehydrating agents** such as DCC or P_2O_5 can give anhydrides.
3- Anhydrides can react with another anhydride or by heating the diacid to give a cyclic anhydride. (Fig. 18.47)



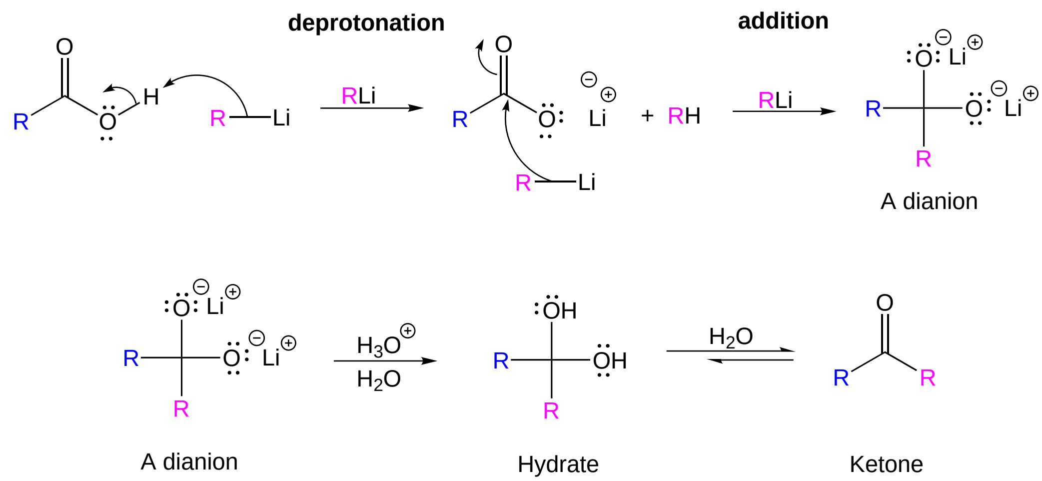
F- Reactions with Organolithium Reagents and Metal Hydrides

1- Ketones can be synthsized from carboxylic acids using 2 equivalents of organolithium reagent.

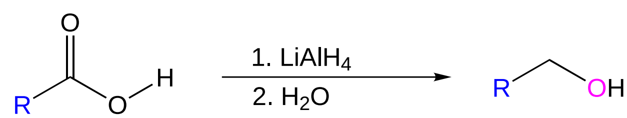


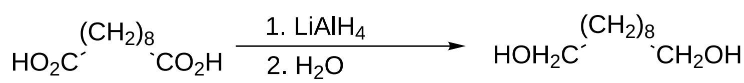


a- In the first step, R-Li deprotonates to give carboxylate anion.
b- Organolithium is strong enough to add to the anion to give a dianion. (Fig. 18.49)
c- The second step (adding water) hydrolyzes the dianion to give hydrate which is unstable relative to the ketone. (Fig. 18.50)

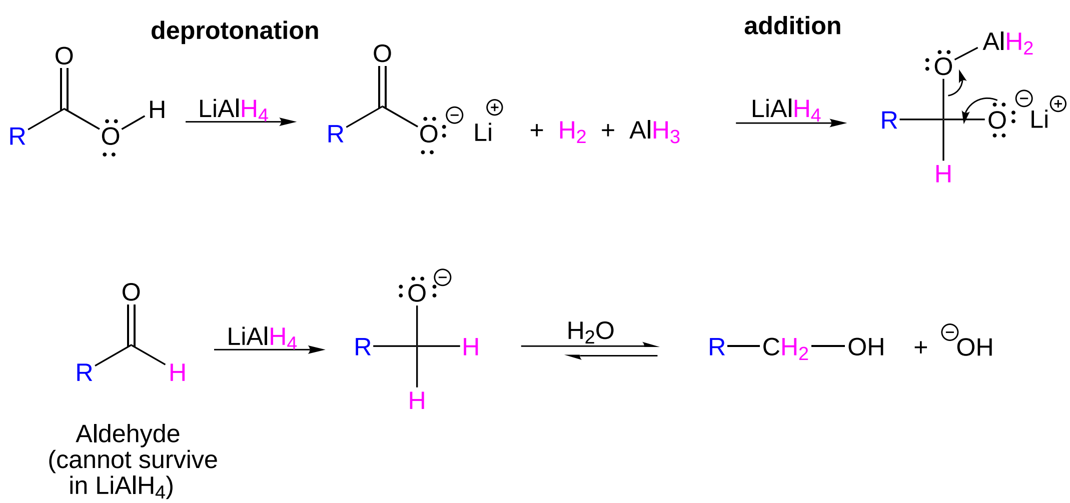


2- Carboxylic acids can be reduced by lithium aluminum hydride to the related primary alcohol. (Fig. 18.52)



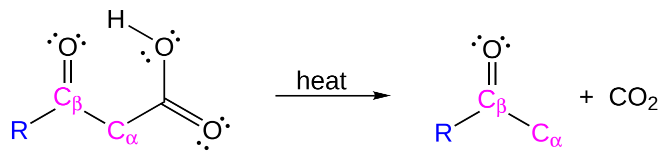


a- Reaction mechanism is uncertain, but carboxylate anion and hydrogen must be formed first.
b- Addition of hydride to the carbonyl gives another dianion.
c- Metal oxide can now be lost to give the aldehyde. (Fig. 18.53)
d- Aldehydes cannot last long in the presence of reducing agents, so further addition of hydride generates the alkoxide.
e- The final hydrolysis step gives the alcohol. (Fig. 18.54)

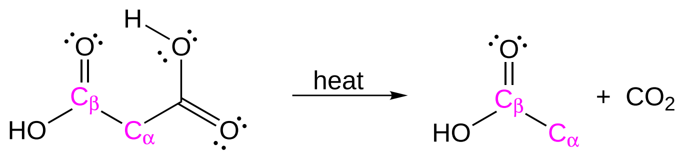


G- Decarboxylation

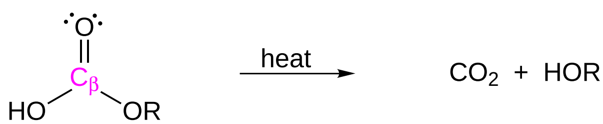
1- Carboxylic acids that have a carbonyl group β to the acid (β-ketoacids and 1,3-diacids such as malonic acid) lose CO_2 easily.



β-Keto acids   Ketones

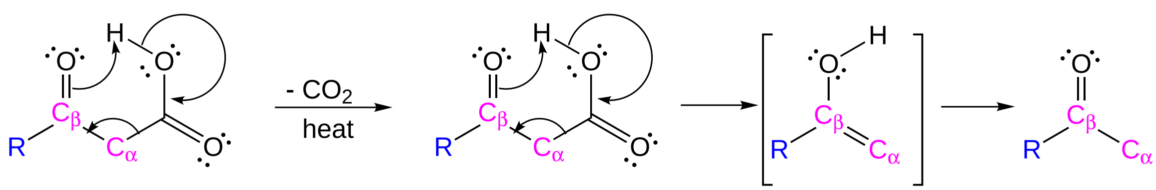


Malonic acids   Acids



Monoester of carbonic acid   Alcohols

2- This is called **decarboxylation** and provides another way to make ketones and acids.



Enol   Ketones

~~H- Formation of Alkyl Bromides: The Hunsdiecker Reaction~~

1- Alkyl bromides can be made from acids in the **Hunsdiecker reaction**.

a- The silver salt of the acid reacts with bromine to give a hypobromite.

b- With heat, a carboxyl radical and Bromine atom are formed when the weak O-Br bond breaks homolytically.

c- The carboxyl radical loses carbon dioxide to give an alkyl radical.

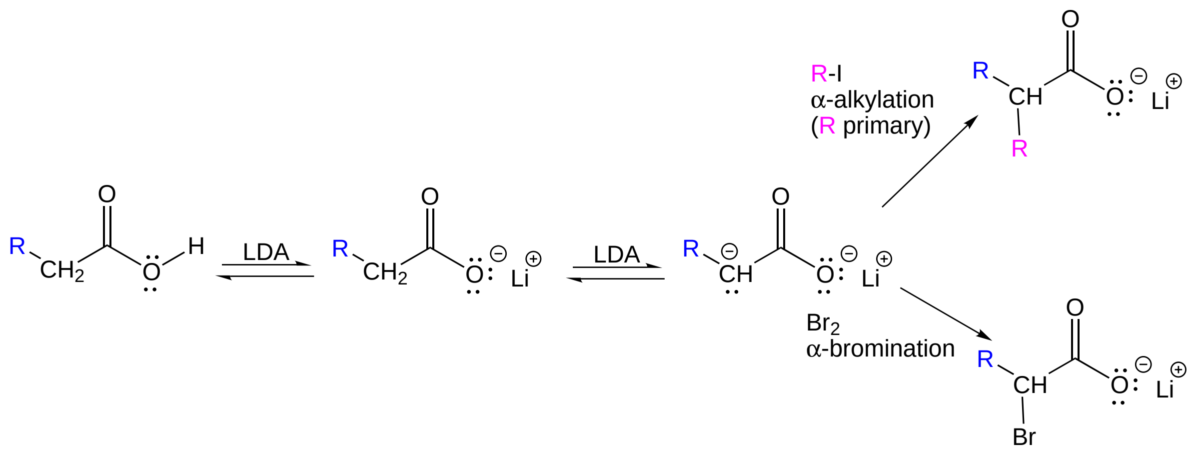
d- The alkyl radical recycles to react with the hypobromite to produce the alkyl bromide and another carboxyl radical. (Fig. 18.60)

Section 18.7

VII. Reactivity of Carboxylic Acids at the α-Position

A- Formation and Reactions of α-Halo Derivatives: Alkylation at the α-Position

1- Carboxylic acids can be alkylated at the I-position.



a- Two equivalents of base are required because the reaction proceeds through a dianion.

i- The first equivalent removes the carboxyl hydrogen.

ii- If a base like LDA, which is a strong base but weak nucleophile is used, a second hydrogen is removed from the α-position.

b- The dianion can be brominated or alkylated at the α-position if the alkylating agent is sufficiently reactive.

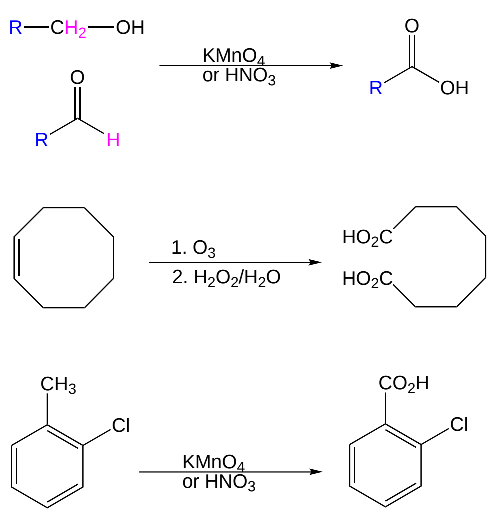
i- Primary halides work very well, due to S_N2 demands.

ii- More substituted halides give mostly E2 reaction products. (Fig. 18.62)

Section 18.8

IIX. Syntheses of Carboxylic Acids

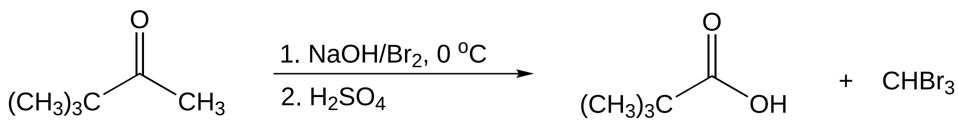
A- Oxidative Routes



1- Alcohols and aldehydes can be oxidized to acids. (Ch. 16)

2- If 18-crown-6 ether is used to make KmnO4 soluble in benzene, alkenes can be form 2 acids.
3- Alkenes can also be ozonized with an oxidative workup to form acids. (Ch. 10)
4- The side chain of an alkyl aromatic compound can be oxidized to an acid group (Ch. 13)

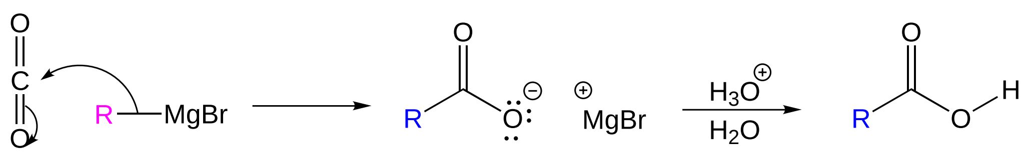
B- Haloform Reaction



1- The reaction of methyl ketones in base with iodine, bromine or chlorine produces the acid and the haloform. (Fig. 18.65)
2- Review Chapter 17, p 912.

C- Reaction of Organometallic Reagents with Carbon Dioxide

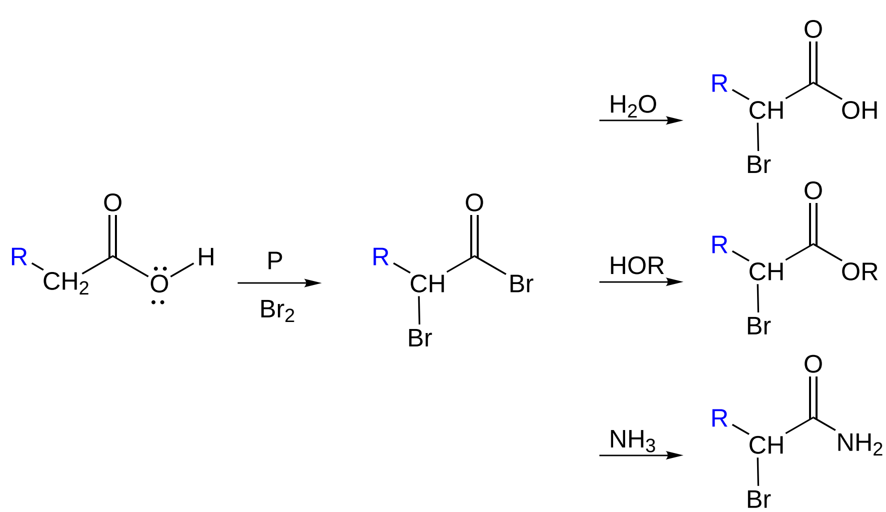
1- Carbon dioxide can react with an organometallic reagent such as the Grignard through an addition reaction.
2- A carboxylate salt is produced first, then converted to the acid after acidification.



3- This is a good source of many acids. (Fig. 18.6)

~~Section 18.9~~

~~IIX. Special Topic: Another Bromination at the α-Position, The Hell-Volhard-Zelinsky Reaction~~



1- If a carboxylic acid is treated with Br_2 and PBr_3, α-bromo acid is formed and the reaction is called the **Hell-Volhard-Zelinsky reaction**.

a- First the acid bromide is formed through reaction with PBr_3.

b- Because the acid bromide is in equilibrium with its enol form, α-bromo acid bromide is produced.

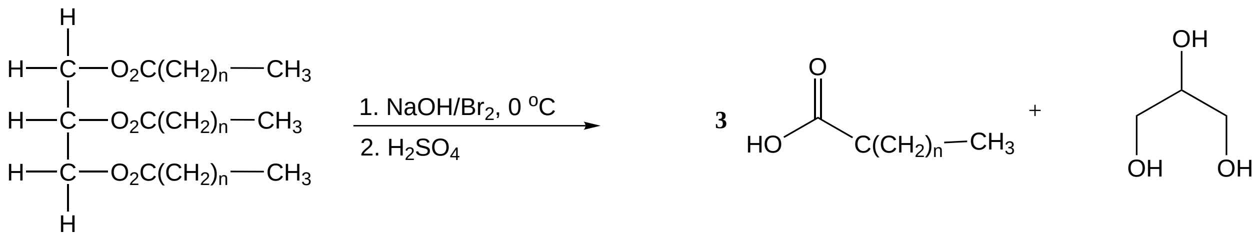
2- The α-bromo acid halide can be used to give α-bromo acid, ester, and amide.

Section 18.10

X. Fatty Acids - even numbered long-chain acids

A- Ester Hydrolysis

1- Base-induced ester hydrolysis or saponification



2- Detergents and soaps