

# Carboxylic Acids and Their Derivatives

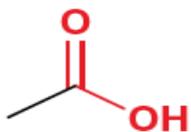


*Organic Chemistry  
Pharmacy College/ 2<sup>nd</sup> Stage  
Dr. Sham Wali Qurban*

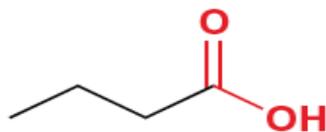
# 20.1 Introduction to Carboxylic Acids

Carboxylic acids, which were introduced in Section 3.4, are compounds with a  $\text{-COOH}$  group.

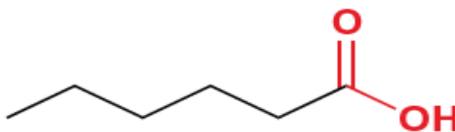
These compounds are abundant in nature, where they are responsible for some familiar odors.



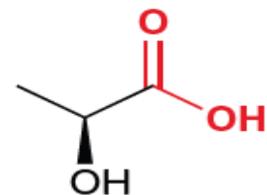
**Acetic acid**  
(Responsible for the pungent smell of vinegar)



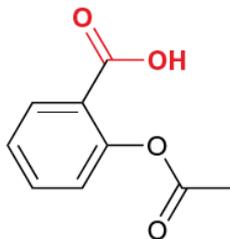
**Butanoic acid**  
(Responsible for the rancid odor of sour butter)



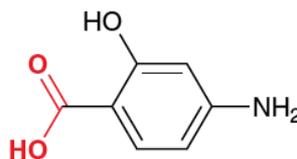
**Hexanoic acid**  
(Responsible for the odor of dirty socks)



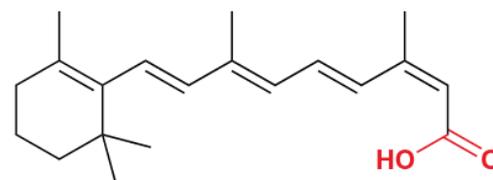
**Lactic acid**  
(Responsible for the taste of sour milk)



**Acetylsalicylic acid**  
(Aspirin, a widely used analgesic)



**4-Aminosalicylic acid**  
(Used in the treatment of tuberculosis)

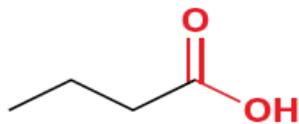


**Isotretinoin**  
(Used in the treatment of acne)

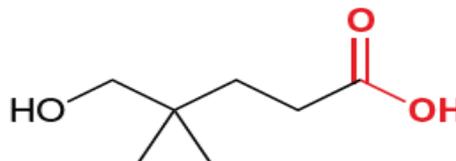
## 20.2 Nomenclature of Carboxylic Acids

### Monocarboxylic Acids

Monocarboxylic acids, compounds containing one carboxylic acid group, are named with the suffix “**oic acid**”:

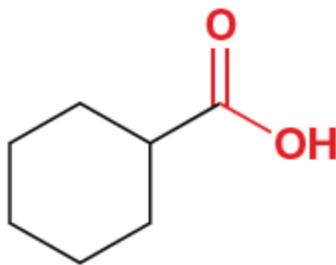


Butano**oic acid**



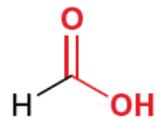
5-Hydroxy-4,4-dimethyl  
pentano**oic acid**

When a carboxylic acid group is connected to a ring, the compound is named as an alkane carboxylic acid; for example:

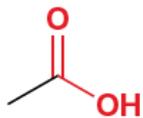


Cyclohexane**carboxylic acid**

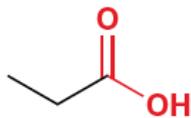
Many simple carboxylic acids have common names accepted by IUPAC.



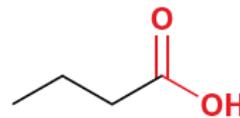
Formic acid



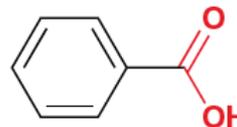
Acetic acid



Propionic acid



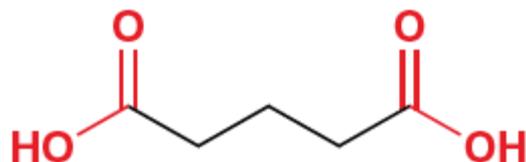
Butyric acid



Benzoic acid

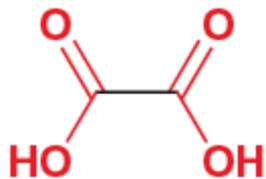
## Diacids

Diacids, compounds containing two carboxylic acid groups, are named with the suffix “**dioic acid**”; for example:

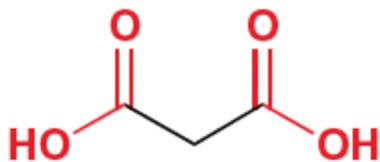


Pentanedioic acid

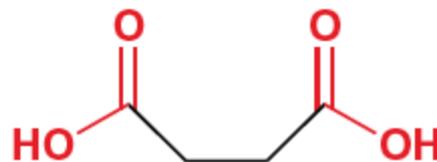
Many diacids have common names accepted by IUPAC.



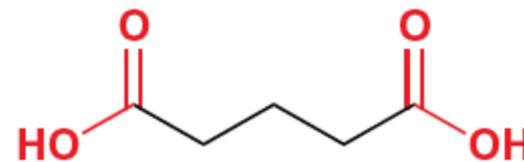
Oxalic acid



Malonic acid

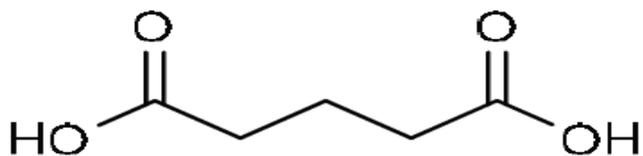


Succinic acid

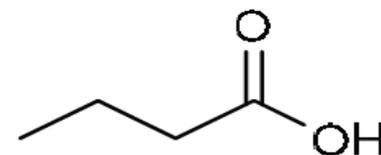
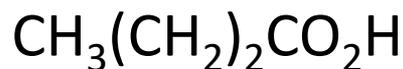


Glutaric acid

**20.1 Provide both an IUPAC name and a common name for each of the following compounds:**



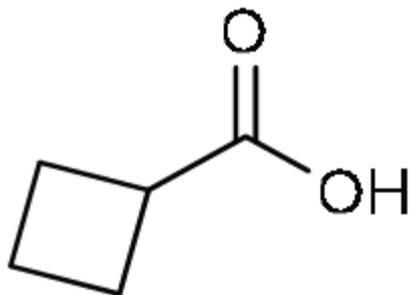
IUPAC name = pentanedioic acid  
Common name = glutaric acid



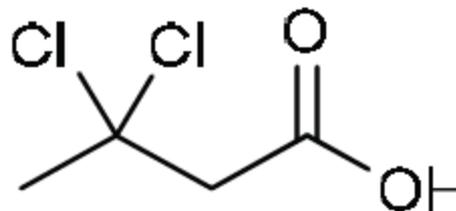
IUPAC name = butanoic acid  
Common name = butyric acid

**20.2 Draw the structure of each of the following compounds:**

Cyclobutanecarboxylic acid



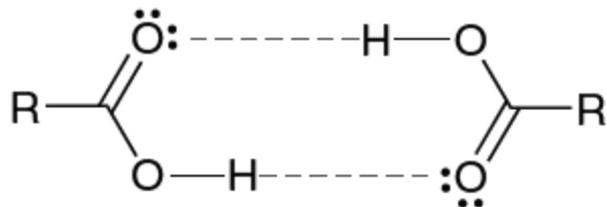
3,3-Dichlorobutyric acid



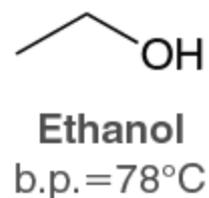
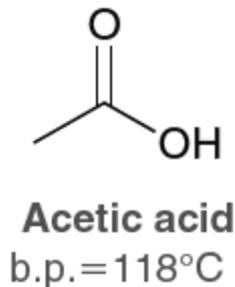
## 20.3 Structure and Properties of Carboxylic Acids

- **Structure**

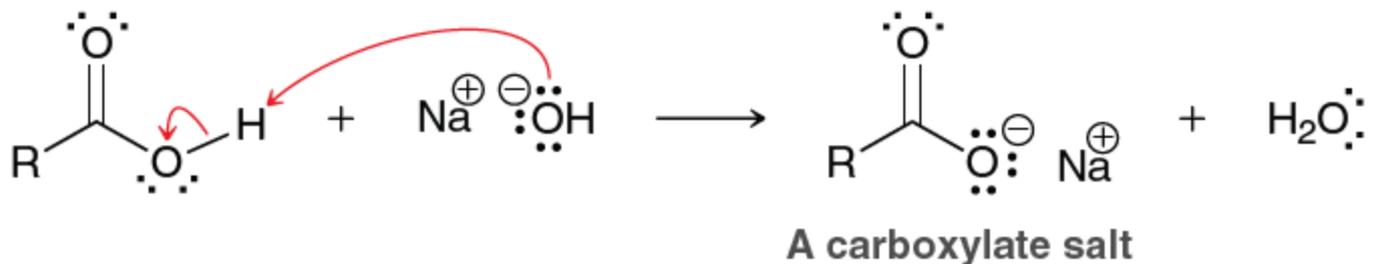
The carbon atom of a carboxylic acid group is  $sp^2$  hybridized and therefore exhibits trigonal planar geometry with bond angles that are nearly  $120^\circ$ .



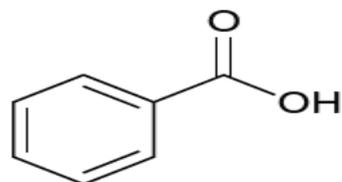
These hydrogen-bonding interactions explain the relatively high boiling points of carboxylic acids.



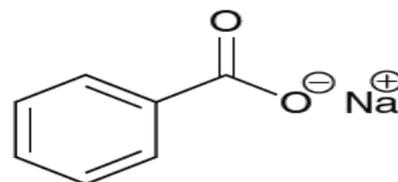
- **Acidity of Carboxylic Acids**



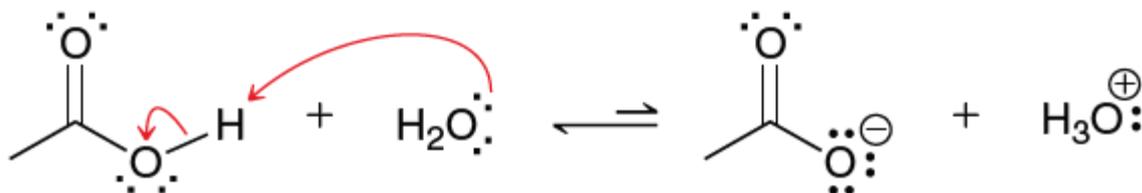
Carboxylate salts are ionic and are therefore more water-soluble than their corresponding carboxylic acids.



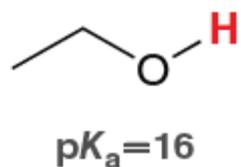
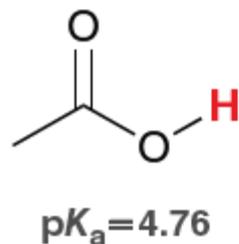
**Benzoic acid**



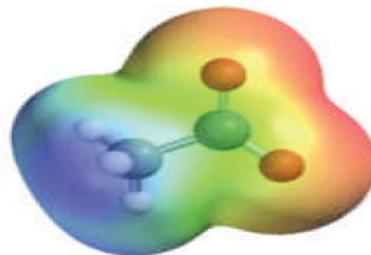
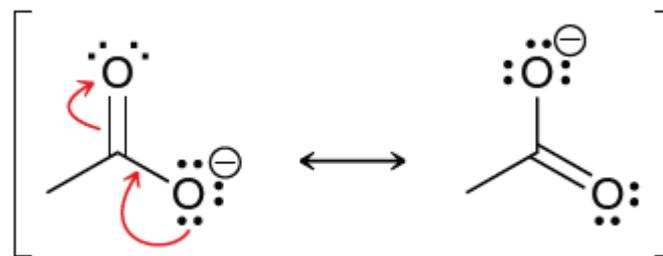
**Sodium benzoate**



When compared to inorganic acids, such as HCl or H<sub>2</sub>SO<sub>4</sub>, carboxylic acids are extremely weak acids. But when compared to most classes of organic compounds, such as alcohols, they are relatively acidic.



The acidity of carboxylic acids is primarily due to the stability of the conjugate base, which is resonance stabilized.



**FIGURE 20.2**

An electrostatic potential map of the acetate ion showing how the electron density is distributed over both oxygen atoms.

- **Carboxylic Acids at Physiological pH**

Our blood is buffered to a pH of approximately 7.3, a value referred to as **physiological pH**. When dealing with buffered solutions.

$$\text{pH} = \text{p}K_a + \log \frac{[\text{conjugate base}]}{[\text{acid}]} \quad \text{Henderson-Hasselbalch equation}$$

$$\frac{[\text{conjugate base}]}{[\text{acid}]} = 10^{(\text{pH} - \text{p}K_a)}$$

This rearranged form of the **Henderson-Hasselbalch** equation provides a method for determining the extent to which an acid will dissociate to form its conjugate base in a buffered solution.

When the **pKa value of an acid is equivalent to the pH of a buffered solution** into which it is dissolved, then

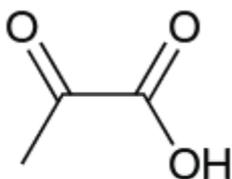
$$\frac{[\text{conjugate base}]}{[\text{acid}]} = 10^{(\text{pH}-\text{p}K_a)} = 10^{(0)} = 1$$

**at physiological pH (7.3),**

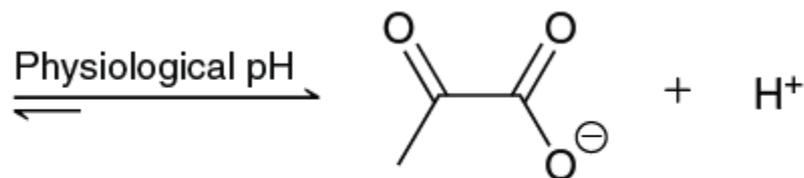
$$\frac{[\text{conjugate base}]}{[\text{acid}]} = 10^{(\text{pH}-\text{p}K_a)} = 10^{(7.3-\text{p}K_a)} \approx 10^3$$

The ratio of the concentrations of the carboxylate ion and the carboxylic acid will be approximately **1000 : 1**.

pyruvic acid exists primarily as pyruvate ion at physiological pH.



Pyruvic acid

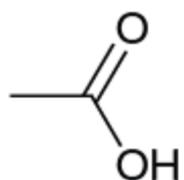


Pyruvate

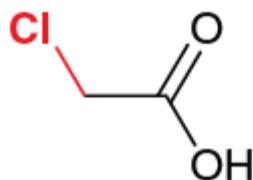
+ H<sup>+</sup>

- Substituent Effects on Acidity**

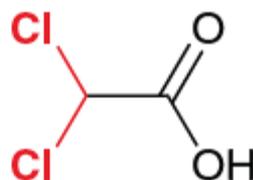
The presence of electron-withdrawing substituents can have a profound impact on the acidity of a carboxylic acid.



$pK_a = 4.8$



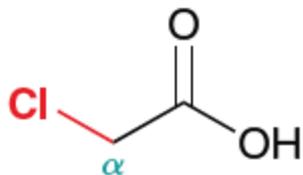
$pK_a = 2.9$



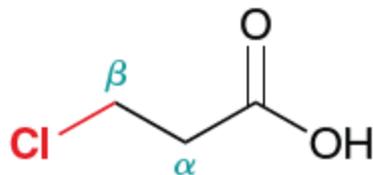
$pK_a = 1.3$



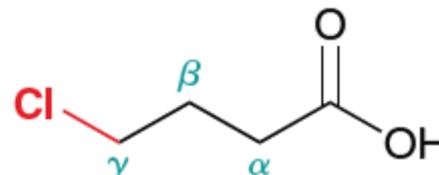
$pK_a = 0.9$



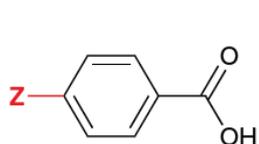
$pK_a = 2.9$



$pK_a = 4.1$



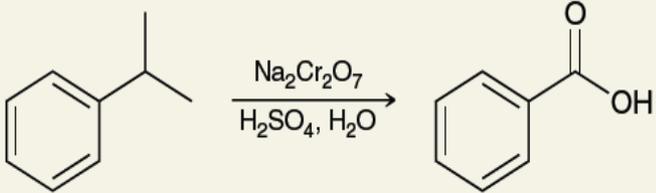
$pK_a = 4.5$



Z	—NO <sub>2</sub>	—CHO	—Cl	—H	—CH <sub>3</sub>	—OH
$pK_a$	3.4	3.8	4.0	4.2	4.3	4.5

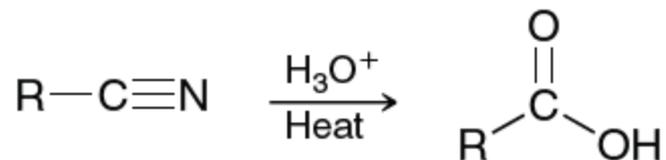
# 20.4 Preparation of Carboxylic Acids

**TABLE 20.1** A REVIEW OF METHODS FOR PREPARING CARBOXYLIC ACIDS

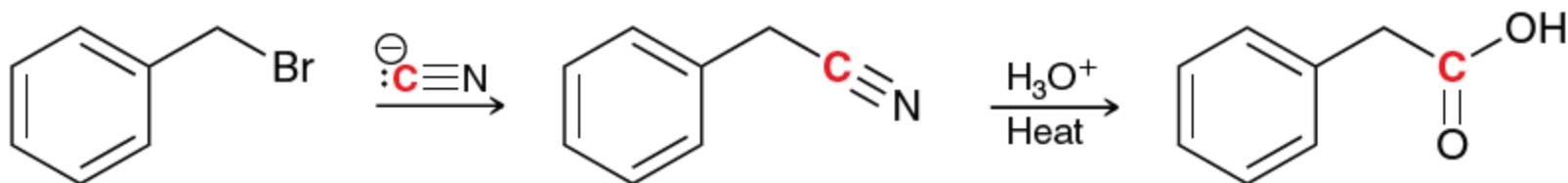
REACTION	SECTION NUMBER	COMMENTS
<p><b>Oxidative Cleavage of Alkynes</b></p> $\text{R}-\text{C}\equiv\text{C}-\text{R} \xrightarrow[2) \text{H}_2\text{O}]{1) \text{O}_3} \begin{array}{c} \text{HO} \\   \\ \text{R}-\text{C}=\text{O} \end{array} + \begin{array}{c} \text{O} \\    \\ \text{C}-\text{OH} \\   \\ \text{R} \end{array}$	9.9	Oxidative cleavage will break a $\text{C}\equiv\text{C}$ triple bond forming two carboxylic acids.
<p><b>Oxidation of Primary Alcohols</b></p> $\text{R}-\text{CH}_2\text{OH} \xrightarrow[\text{H}_2\text{SO}_4, \text{H}_2\text{O}]{\text{Na}_2\text{Cr}_2\text{O}_7} \text{R}-\text{C}(=\text{O})\text{OH}$	12.10	A variety of strong oxidizing agents can be used to oxidize primary alcohols and produce carboxylic acids.
<p><b>Oxidation of Alkylbenzenes</b></p> 	17.6	Any alkyl group on an aromatic ring will be completely oxidized to give benzoic acid, provided that the benzylic position is not quaternary (is not connected to four carbon atoms).

- **Hydrolysis of Nitriles**

When treated with aqueous acid, a *nitrile* (a compound with a cyano group) can be converted into a carboxylic acid.

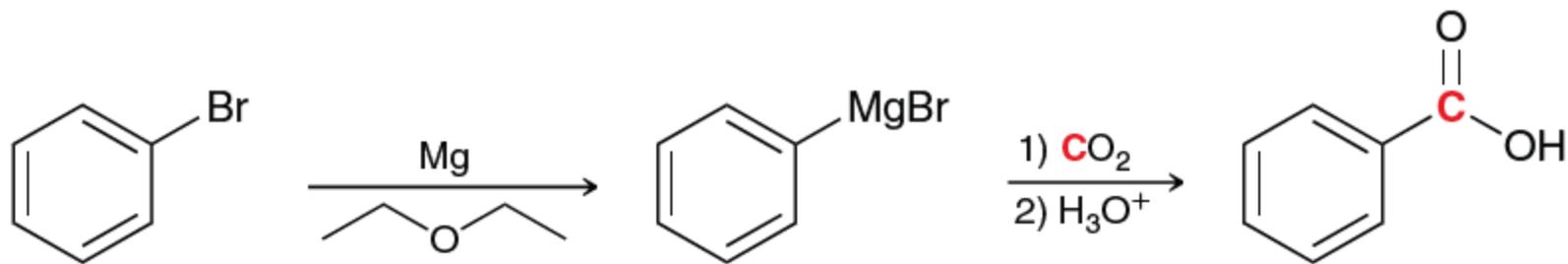
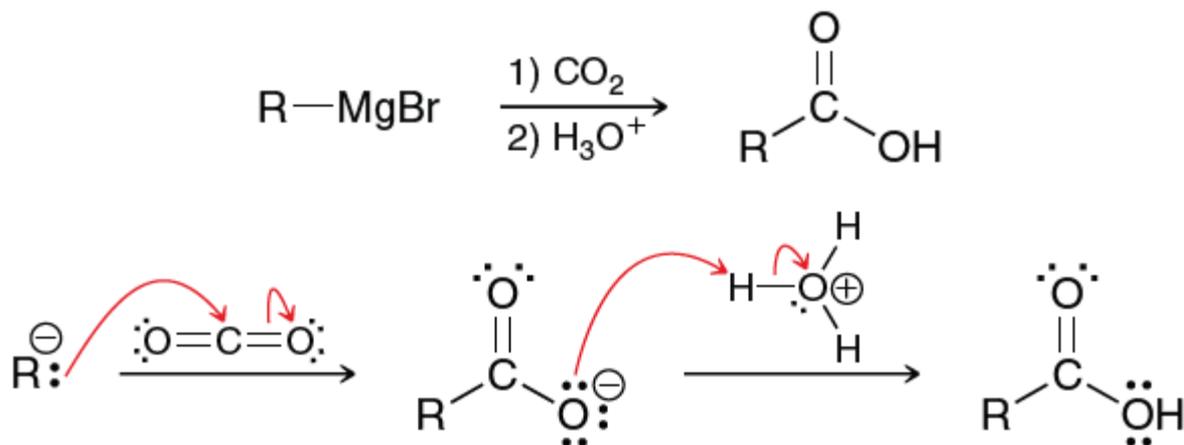


This process is called **hydrolysis**, this reaction provides us with a two-step process for converting an alkyl halide to a carboxylic acid.



- Carboxylation of Grignard Reagents**

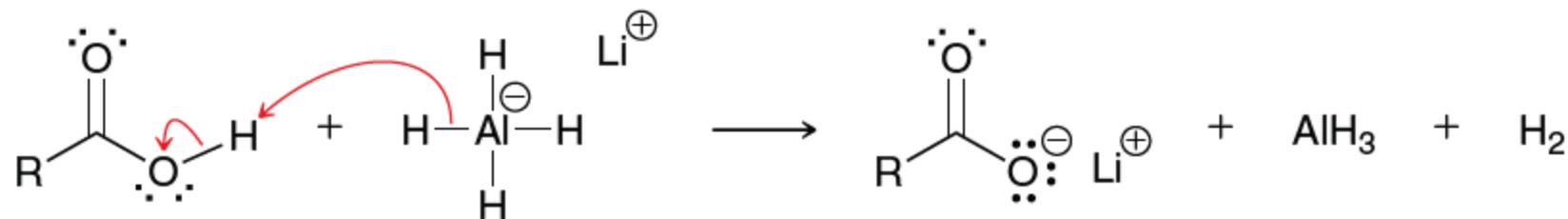
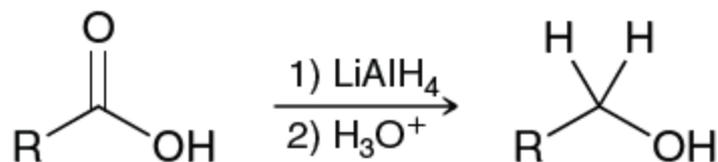
Carboxylic acids can also be prepared by treating a Grignard reagent with carbon dioxide:



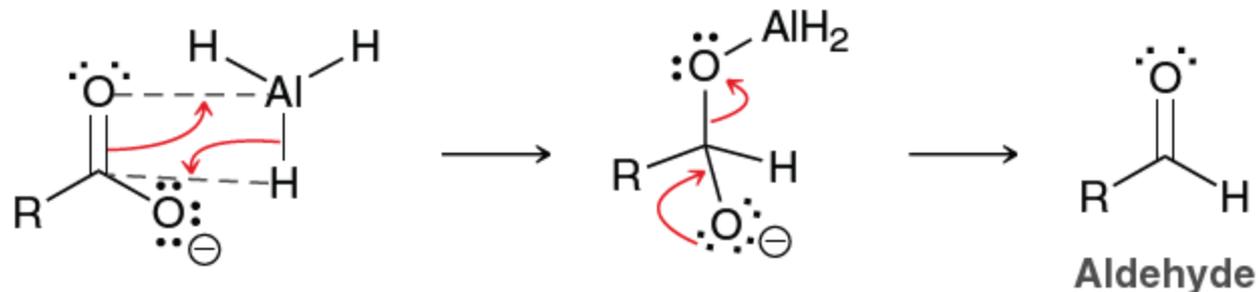
# 20.5 Reactions of Carboxylic Acids

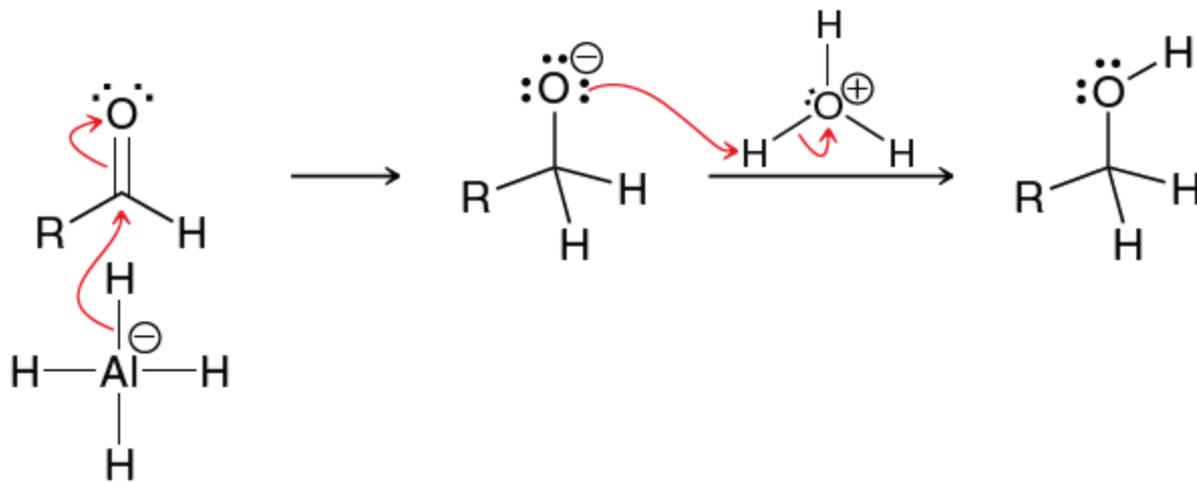
- Reduction**

Carboxylic acids are reduced to alcohols upon treatment with lithium aluminum hydride.

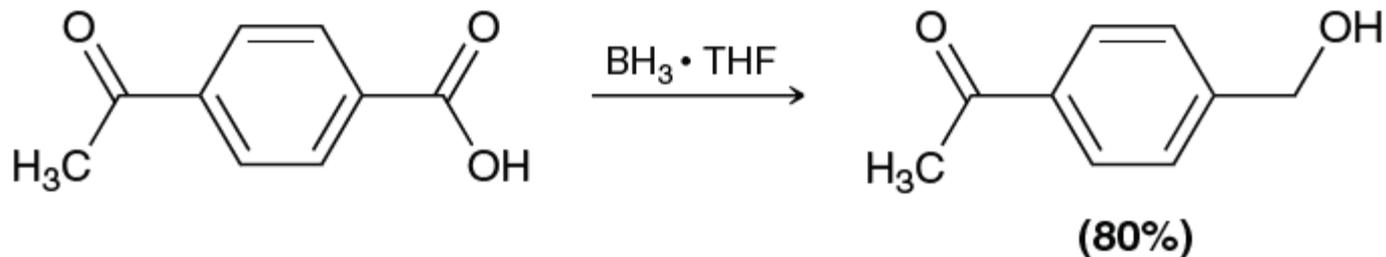
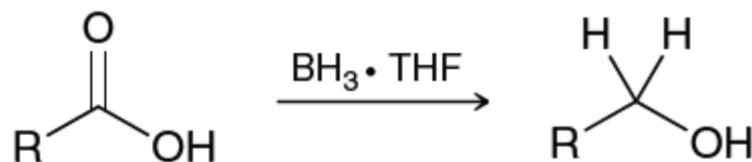


One possibility involves a reaction of the carboxylate ion with AlH<sub>3</sub> followed by elimination to form an aldehyde:

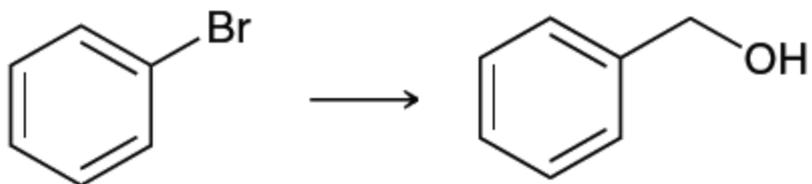




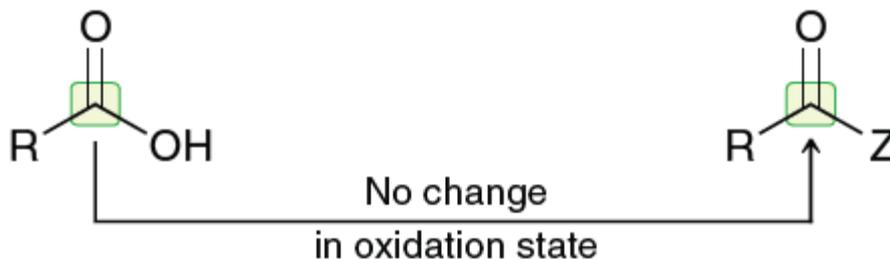
An alternative method for reducing carboxylic acids involves the use of borane ( $\text{BH}_3$ ).



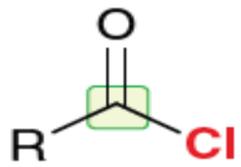
**20.11 Identify the reagents you would use to achieve each of the following transformations:**



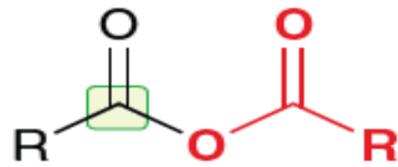
- **Classes of Carboxylic Acid Derivatives**



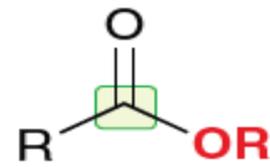
Replacement of the **OH** group with a different group (**Z**) does not involve a change in oxidation state if **Z** is a heteroatom (**Cl, O, N**, etc.). Compounds of this type are called **carboxylic acid derivatives**,



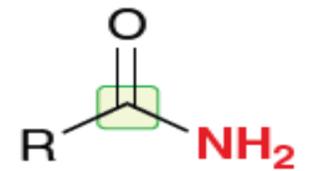
Acid halide



Acid anhydride

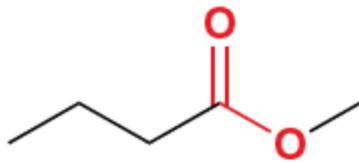


Ester

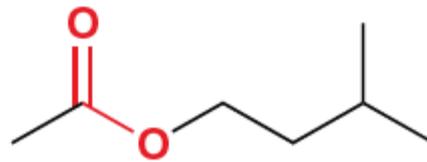


Amide

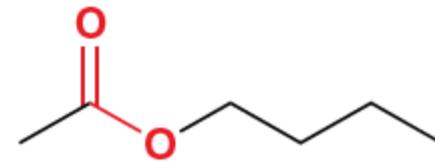
- Carboxylic Acid Derivatives in Nature



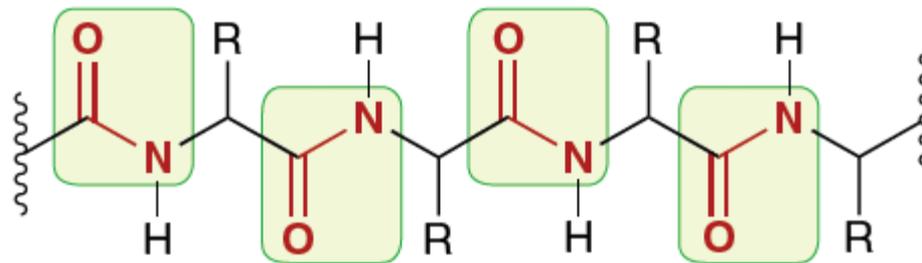
Methyl butanoate  
(pineapple)



Isopentyl acetate  
(banana)



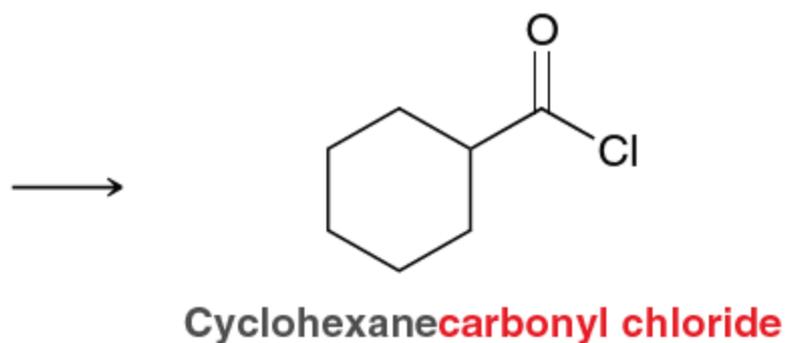
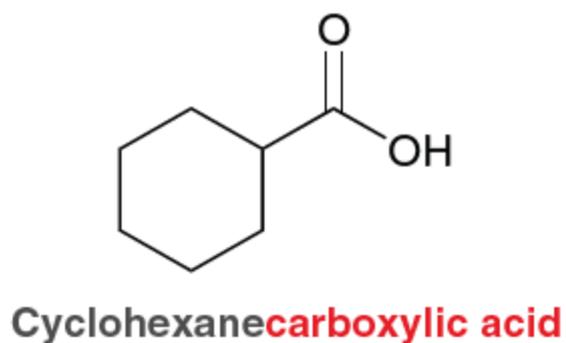
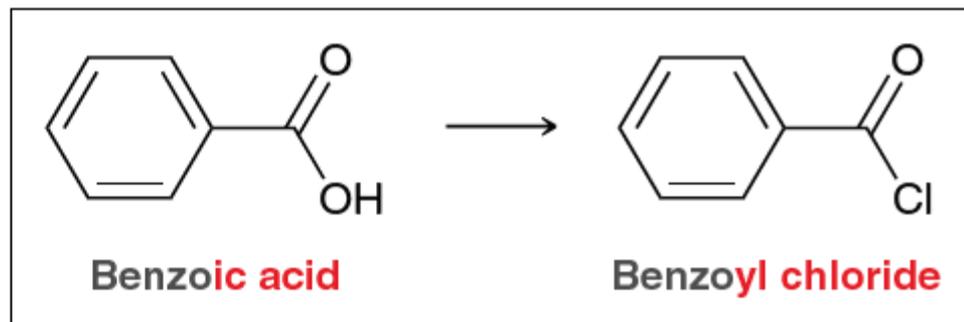
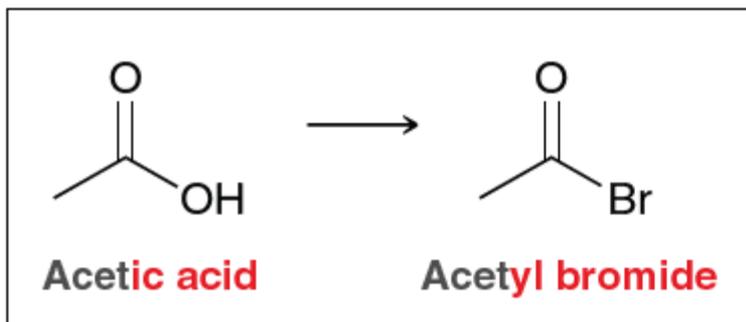
Butyl acetate  
(pear)



The structure of proteins

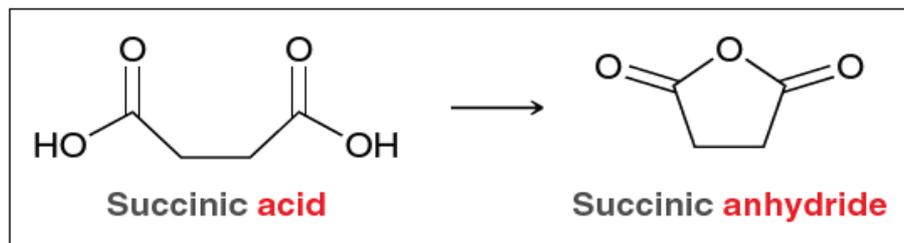
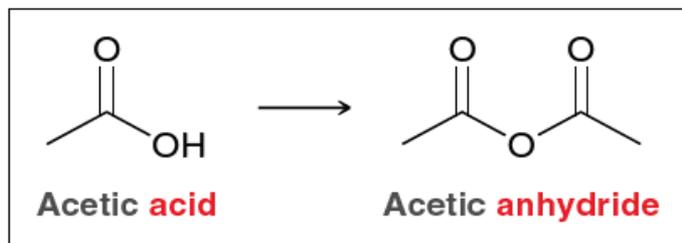
## Naming Acid Halides

Acid halides are named as derivatives of carboxylic acids by replacing the suffix “ic acid” with “yl halide”:

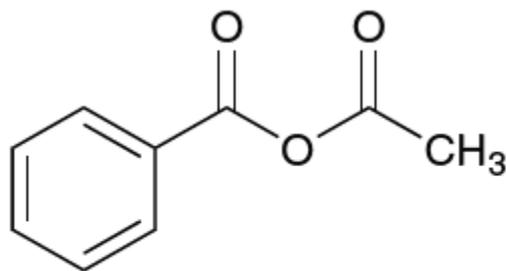


## Naming Acid Anhydrides

Acid anhydrides are named as derivatives of carboxylic acids by replacing the suffix “**acid**” with “**anhydride**.”



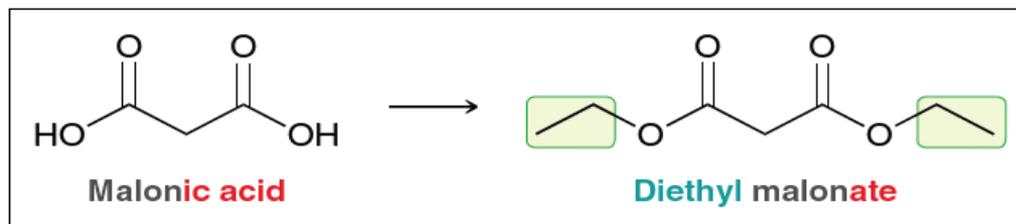
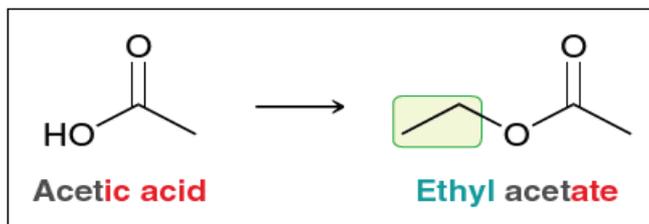
**Unsymmetrical anhydrides** are prepared from two different carboxylic acids and are named by indicating both acids alphabetically followed by the suffix “**anhydride**”:



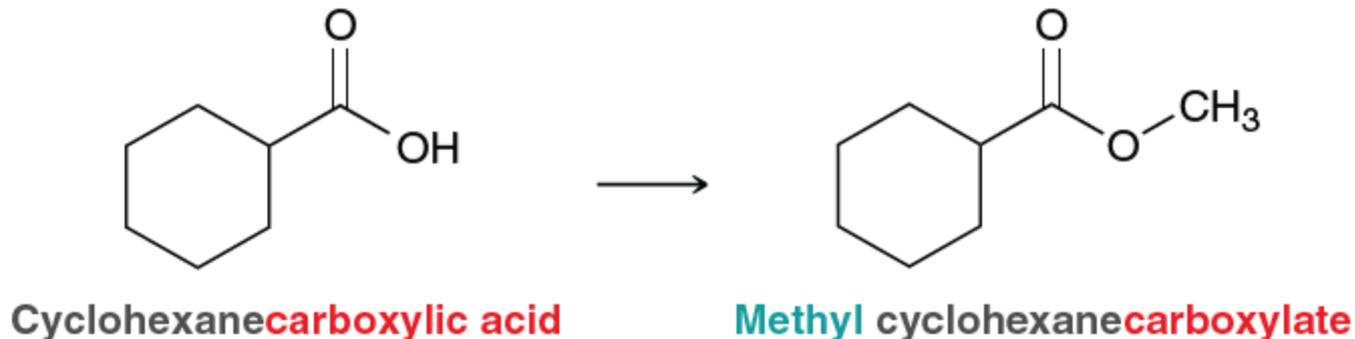
Acetic benzoic **anhydride**

## Naming Esters

Esters are named by first indicating the alkyl group attached to the oxygen atom followed by the carboxylic acid, for which the suffix “**ic acid**” is replaced with “**ate.**”

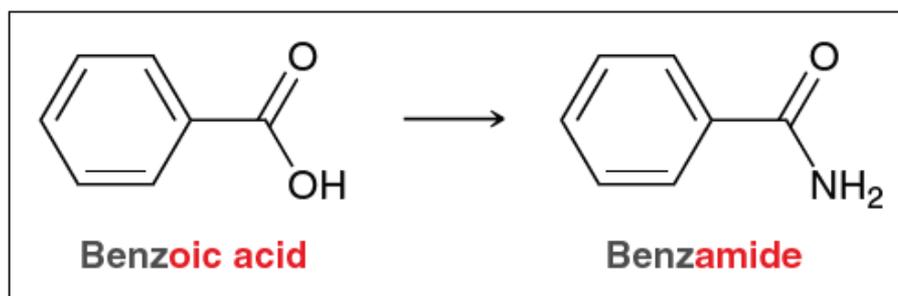
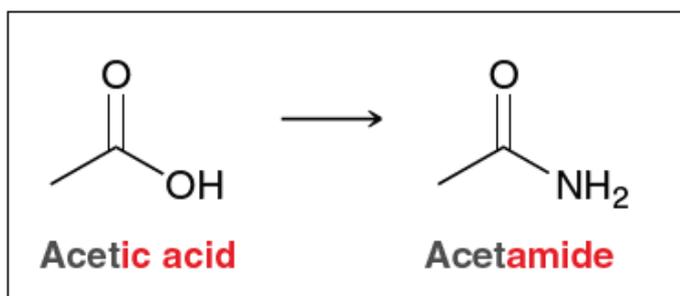


The same methodology is applied when the ester group is connected to a ring; for example:

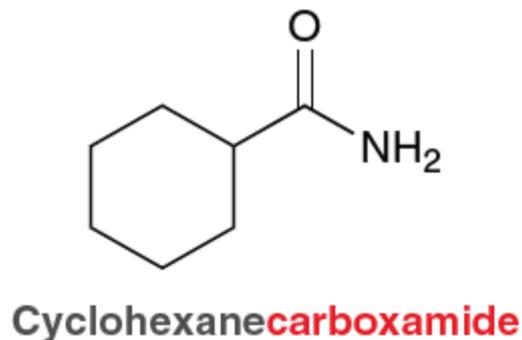


# Naming Amides

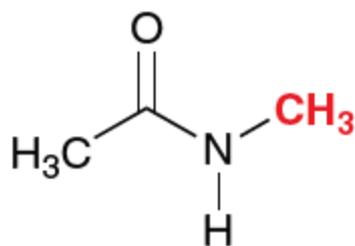
Amides are named as derivatives of carboxylic acids by replacing the suffix “**ic acid**” or “**oic acid**” with “**amide**.”



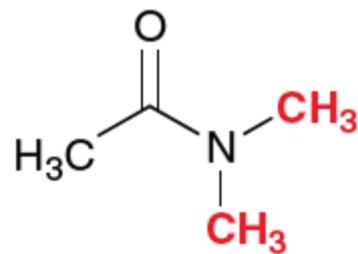
When an amide group is connected to a ring, the suffix “carboxylic acid” is replaced with “carboxamide.”



If the nitrogen atom bears alkyl groups, these groups are indicated at the beginning of the name, and the letter “**N**” is used as a locant to indicate that they are attached to the nitrogen atom.



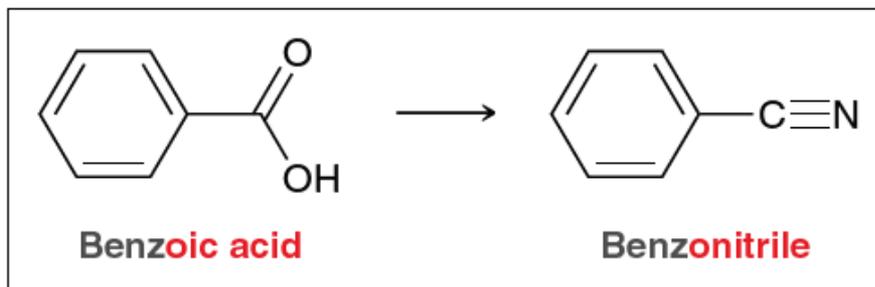
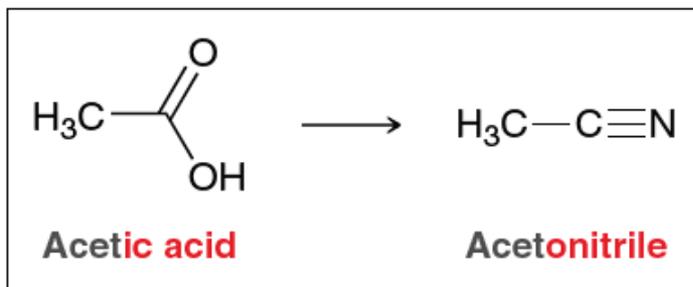
**N-Methylacetamide**



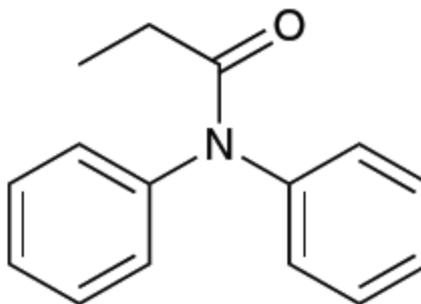
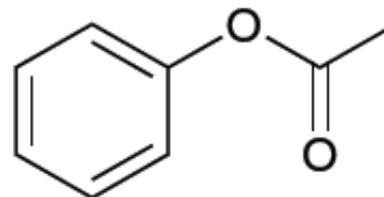
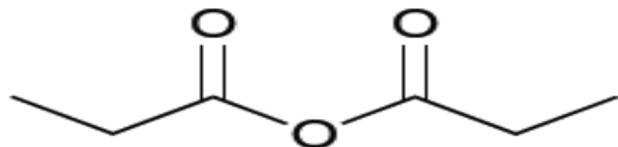
**N,N-Dimethylacetamide**

## Naming Nitriles

Nitriles are named as derivatives of carboxylic acids by replacing the suffix “**ic acid**” or “**oic acid**” with “**onitrile**.”



**20.12 Provide a name for each of the following compounds:**

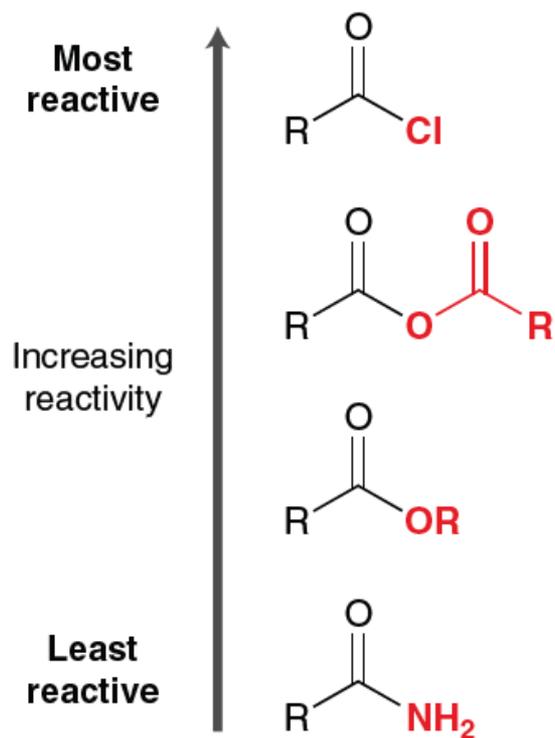


**20.13 Draw a structure for each of the following compounds:**

- (a) Dimethyl oxalate
- (b) Propionyl chloride

# 20.7 Reactivity of Carboxylic Acid Derivatives

## • Electrophilicity of Carboxylic Acid Derivatives



**FIGURE 20.4**

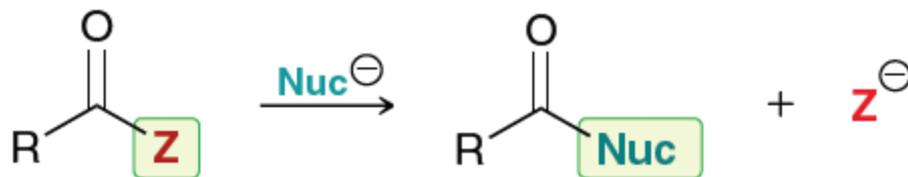
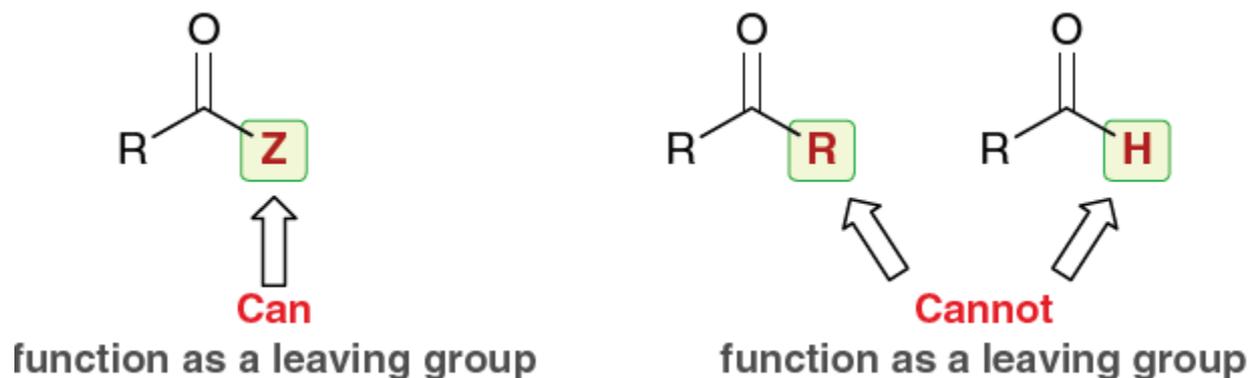
The relative order of reactivity of carboxylic acid derivatives.

- **Chlorine** is an electronegative atom and therefore withdraws electron density from the carbonyl group via induction.
- **Amides** are the least reactive of the carboxylic acid derivatives.
- **Nitrogen** is less electronegative than chlorine or oxygen and is not an effective electron-withdrawing group. The nitrogen atom does not withdraw much electron density from the carbonyl group, and inductive effects are not significant.

# Nucleophilic Acyl Substitution

The reactivity of carboxylic acid derivatives is similar to the reactivity of aldehydes and ketones in a number of ways.

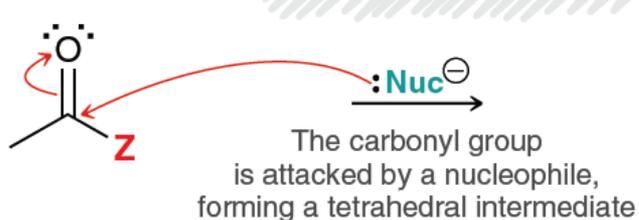
**Nevertheless**, there is one critical difference between carboxylic acid derivatives and aldehydes/ketones.



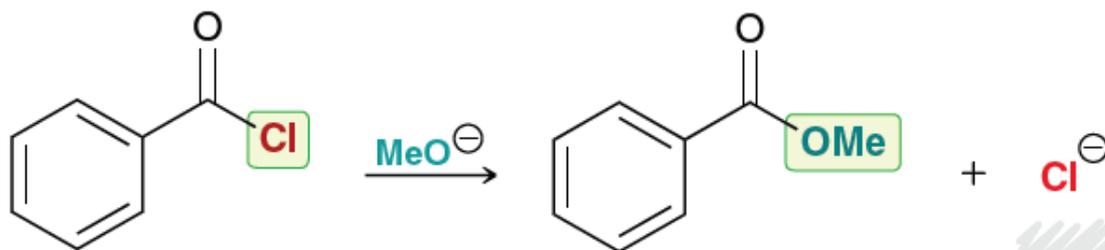
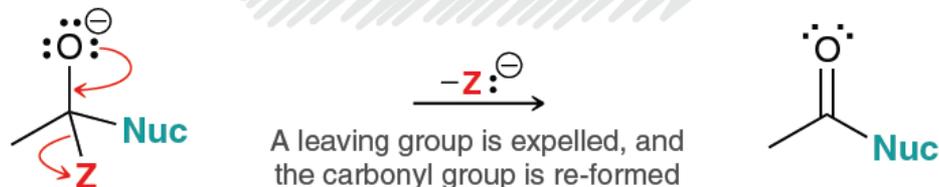
This type of reaction is called a **nucleophilic acyl substitution**

# MECHANISM 20.1 NUCLEOPHILIC ACYL SUBSTITUTION

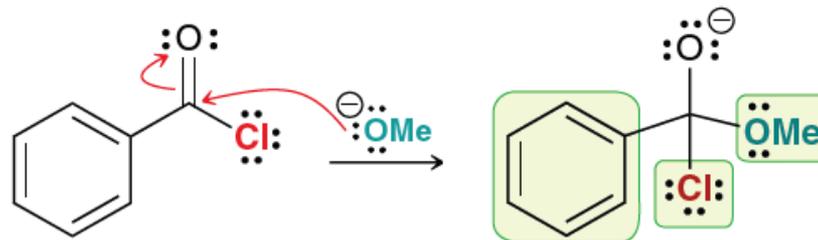
## Nucleophilic attack



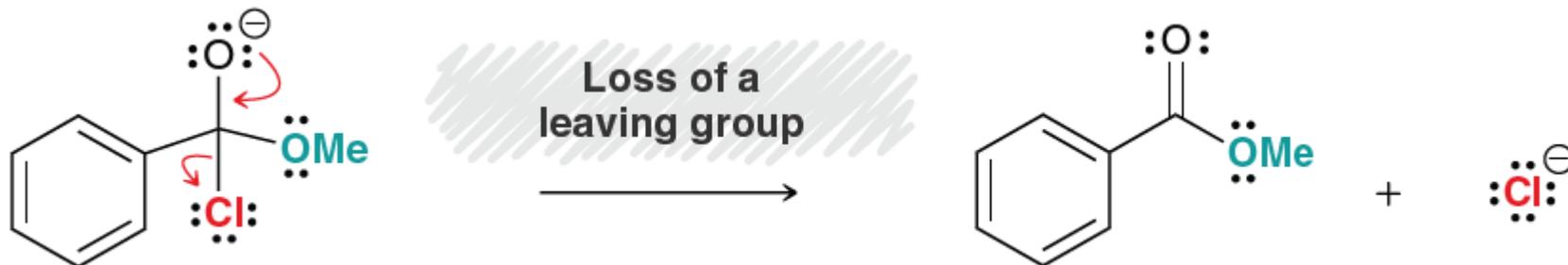
## Loss of a leaving group



## Nucleophilic attack



## Loss of a leaving group



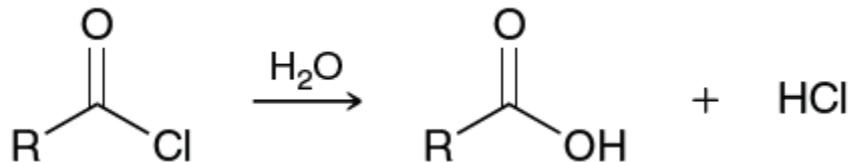
Proton transfer

Nucleophilic attack

Proton transfers

Loss of a leaving group

Proton transfer



Nucleophilic attack

Loss of a leaving group

Proton transfer



X

Nucleophilic attack

X

Loss of a leaving group

Proton transfer

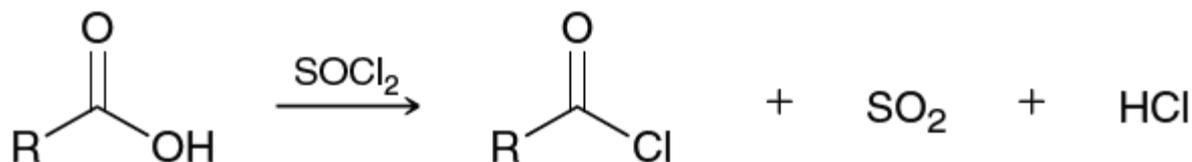
(No proton transfer)

(No proton transfer)

## 20.8 Preparation and Reactions of Acid Chlorides

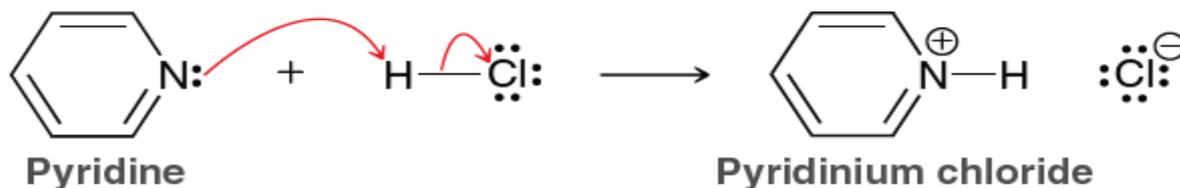
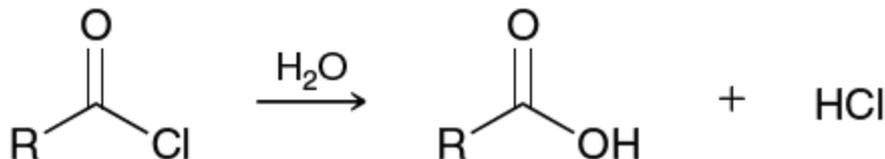
- Preparation of Acid Chlorides**

Acid chlorides can be formed by treating carboxylic acids with thionyl chloride ( $\text{SOCl}_2$ ):



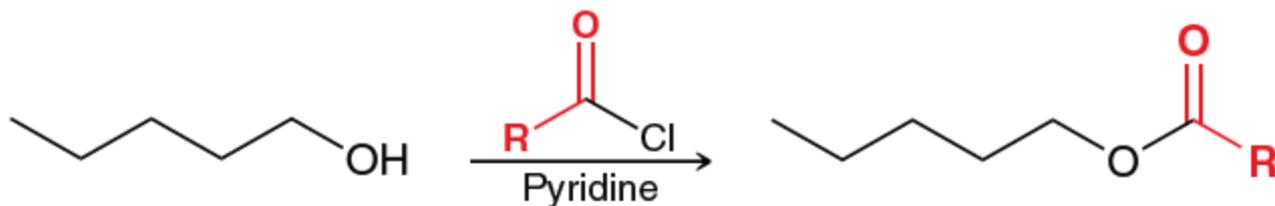
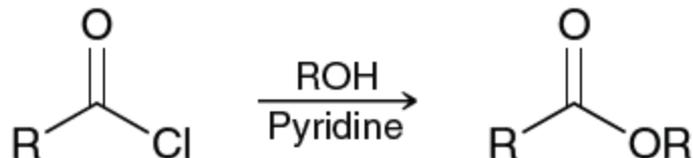
- Hydrolysis of Acid Chlorides**

When treated with water, acid chlorides are hydrolyzed to give carboxylic acids.

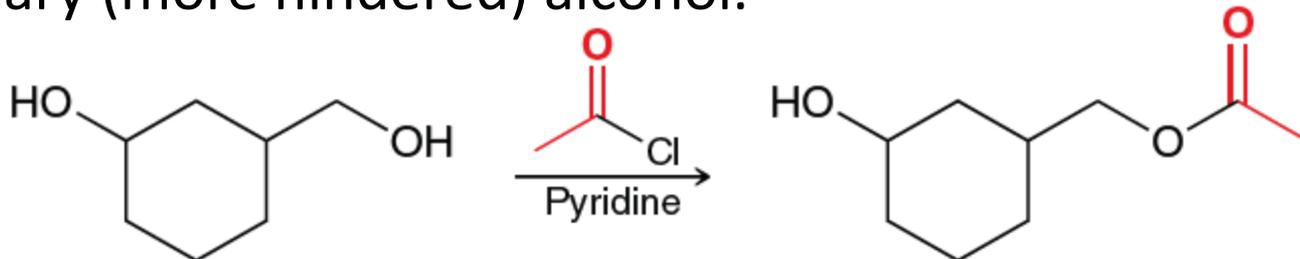


- Alcoholysis of Acid Chlorides**

When treated with an alcohol, acid chlorides are converted into esters.

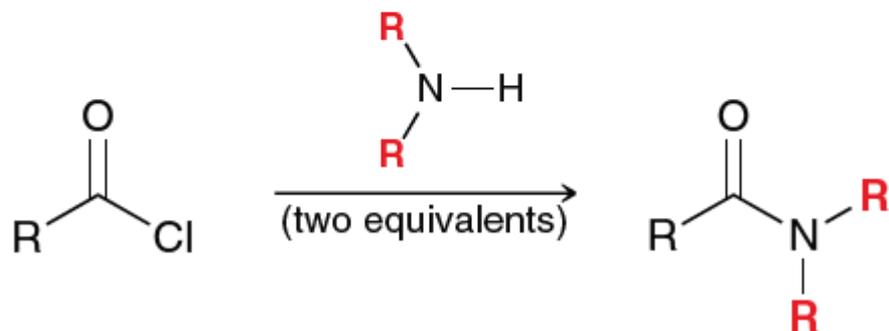
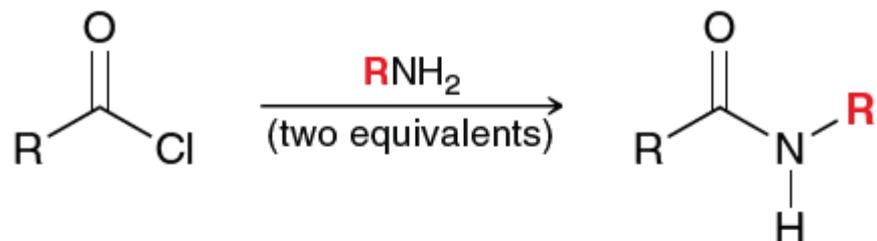
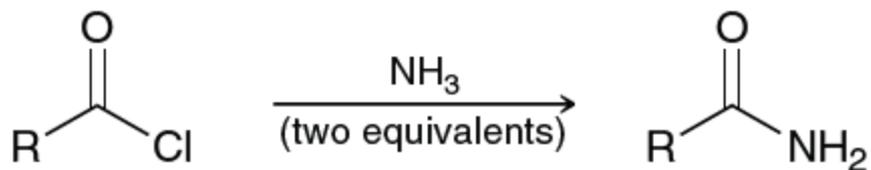


This process is sensitive to steric effects, which can be exploited to selectively acylate a primary alcohol in the presence of a secondary (more hindered) alcohol.



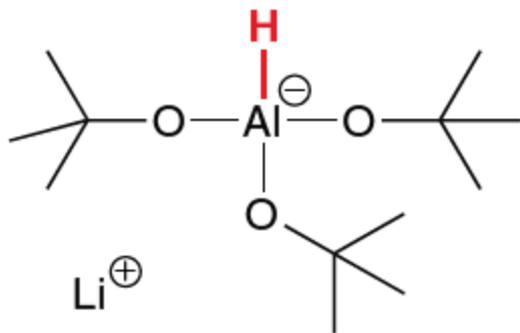
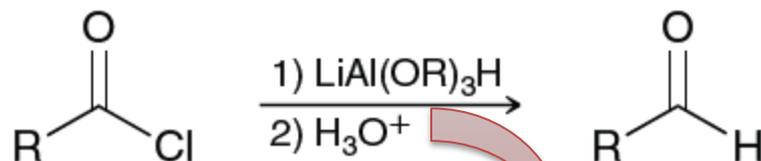
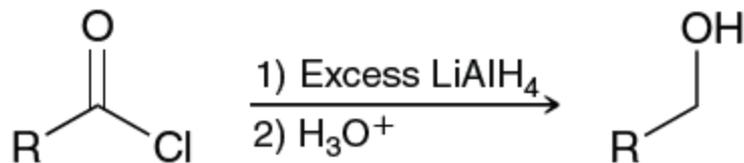
- Aminolysis of Acid Chlorides**

When treated with ammonia, acid chlorides are converted into amides.



- **Reduction of Acid Chlorides**

When treated with lithium aluminum hydride, acid chlorides are reduced to give alcohols:

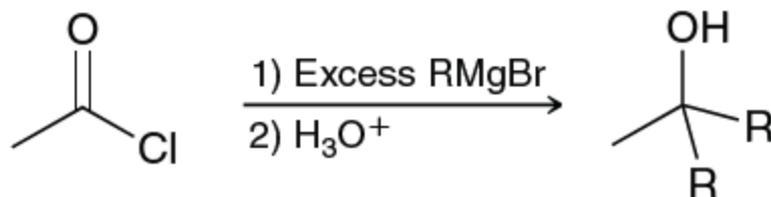


Lithium tri(*t*-butoxy) aluminum hydride

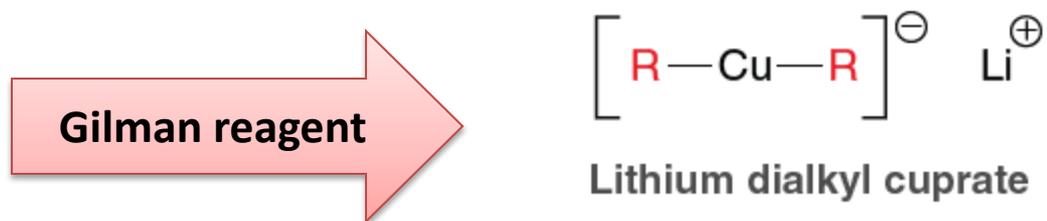
This reducing agent will react with the acid chloride rapidly but will react with the aldehyde more slowly, allowing the aldehyde to be isolated. These conditions can be used to convert an acid chloride into an aldehyde.

## • Reactions between Acid Chlorides and Organometallic Reagents

When treated with a Grignard reagent, acid chlorides are converted into alcohols, with the introduction of two alkyl groups.

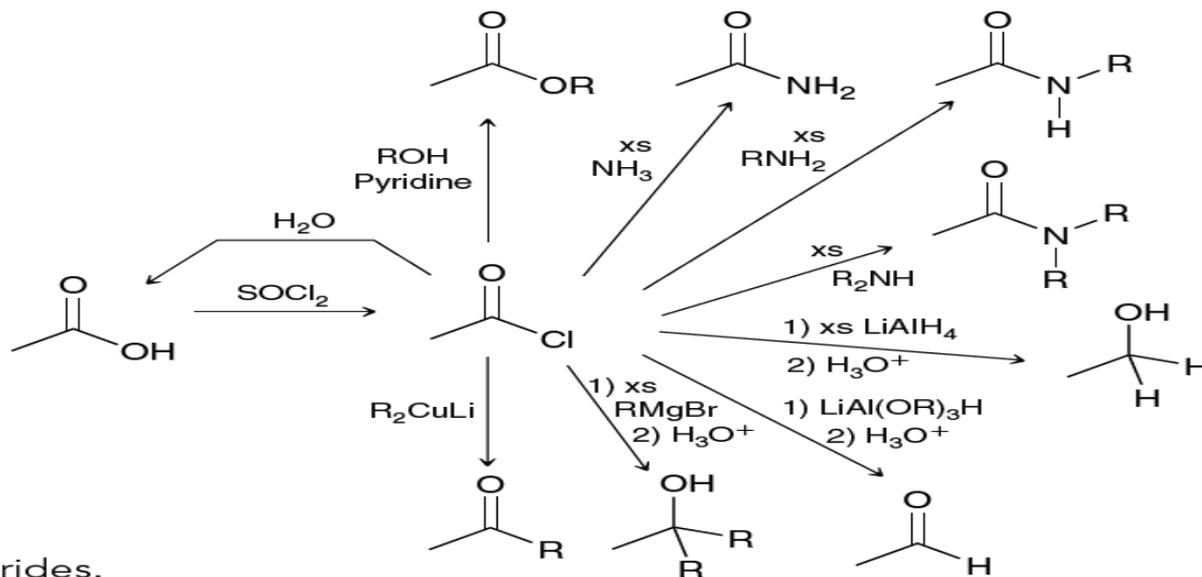


Producing the ketone requires the use of a more selective carbon nucleophile that will react with acid chlorides but not with ketones.



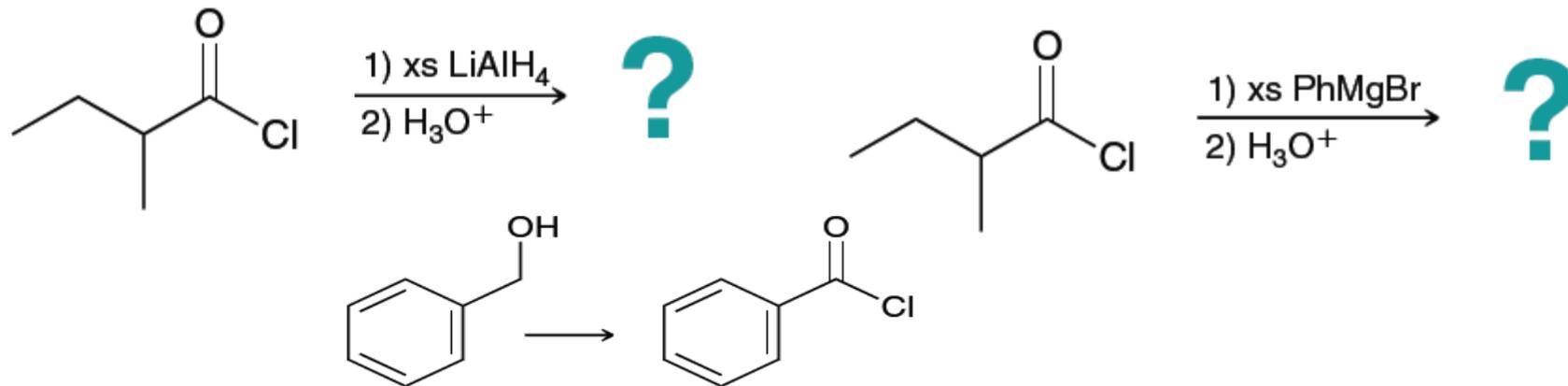
## Summary of Reactions of Acid Chlorides

Figure 20.9 summarizes the reactions of acid chlorides discussed in this section.



**FIGURE 20.9**  
Reactions of acid chlorides.

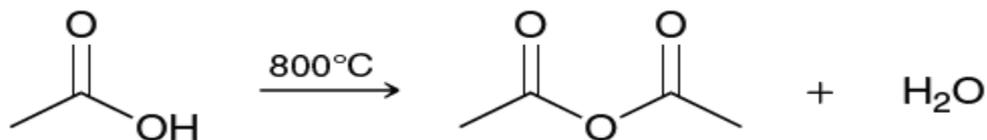
**20.16 Predict the major product for each of the following reactions:**



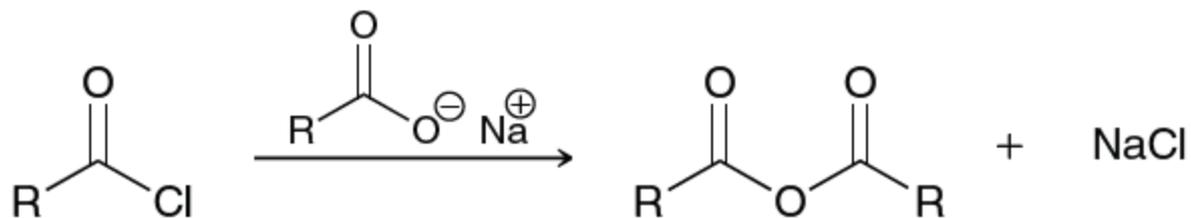
## 20.9 Preparation and Reactions of Acid Anhydrides

- Preparation of Acid Anhydrides**

Carboxylic acids can be converted into acid anhydrides with excessive heating.

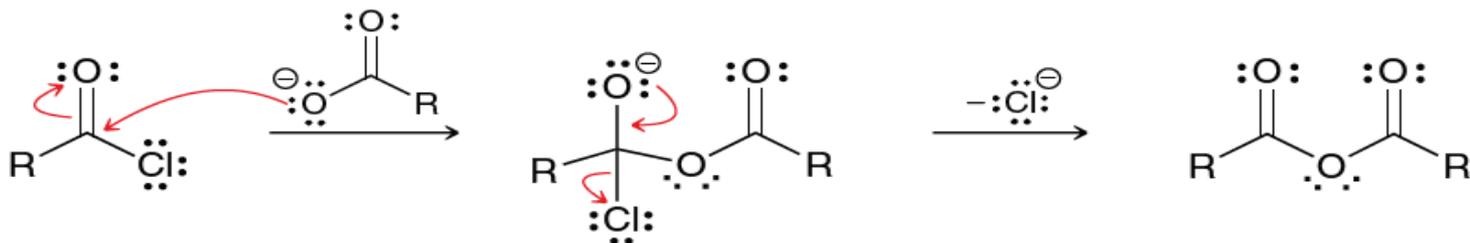


An alternative method for preparing acid anhydrides, used to prepare symmetrical or unsymmetrical anhydrides.



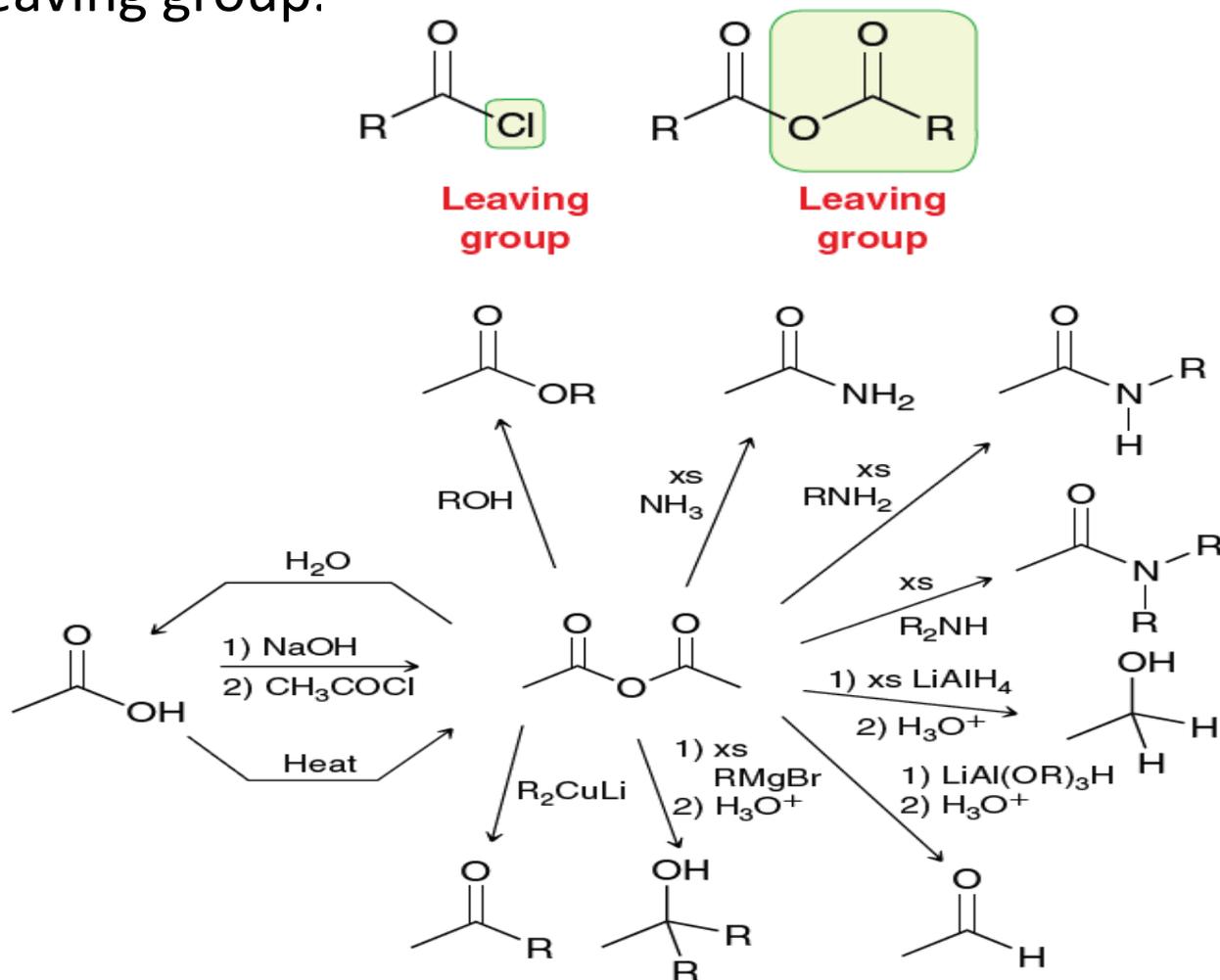
Nucleophilic attack

Loss of a leaving group



## • Reactions of Acid Anhydrides

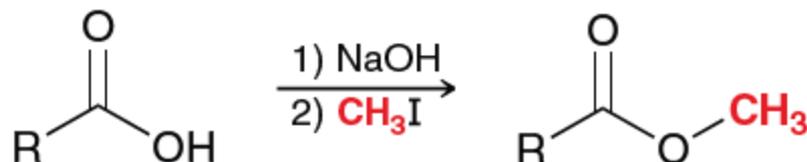
The reactions of anhydrides are directly analogous to the reactions of acid chlorides. The only difference is in the identity of the leaving group.



## 20.10 Preparation of Esters

- **Preparation of Esters via  $S_N2$  Reactions**

When treated with a strong base followed by an alkyl halide, carboxylic acids are converted into esters:

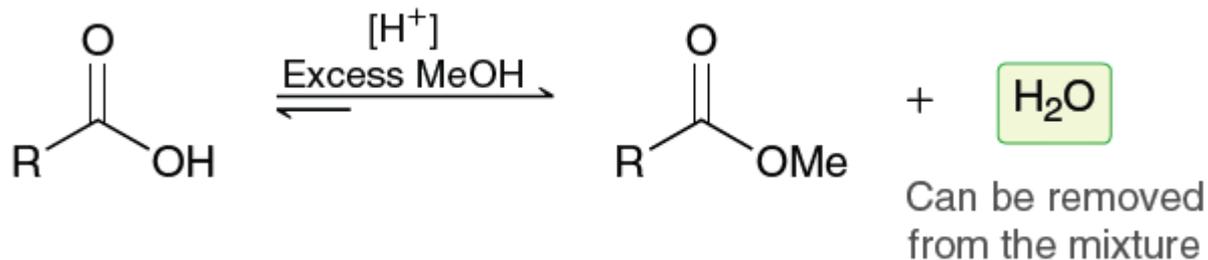


- **Preparation of Esters via Fischer Esterification**

Carboxylic acids are converted into esters when treated with an alcohol in the presence of an acid catalyst. This process is called the **Fischer esterification**

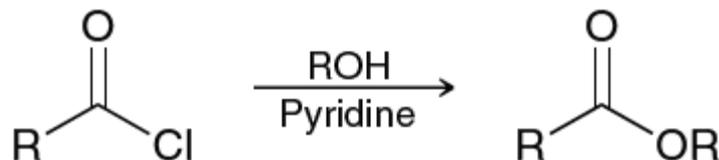


The Fischer esterification process is reversible and can be controlled by exploiting Le Châtelier's principle.

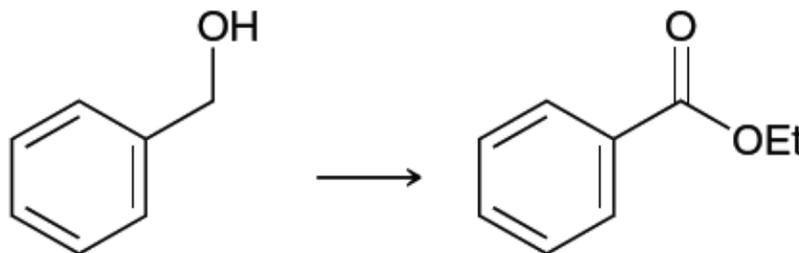


- **Preparation of Esters via Acid Chlorides**

Esters can also be prepared by treating an acid chloride with an alcohol.



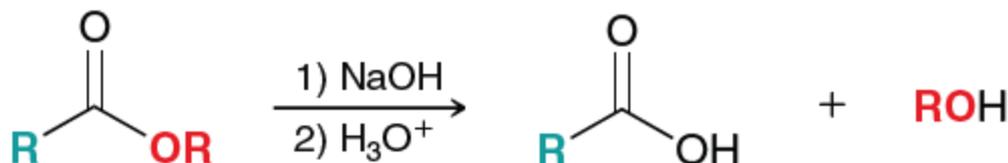
**20.21 Identify reagents that can be used to accomplish each of the following transformations:**



## 20.11 Reactions of Esters

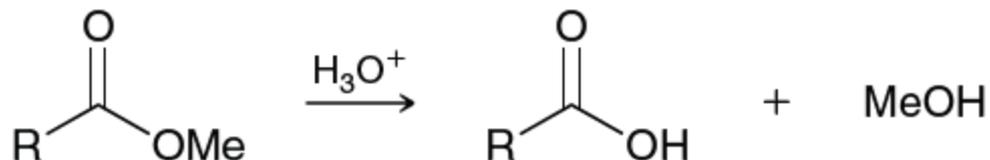
- **Saponification**

Esters can be converted into carboxylic acids by treatment with sodium hydroxide followed by an acid. This process is called **saponification**



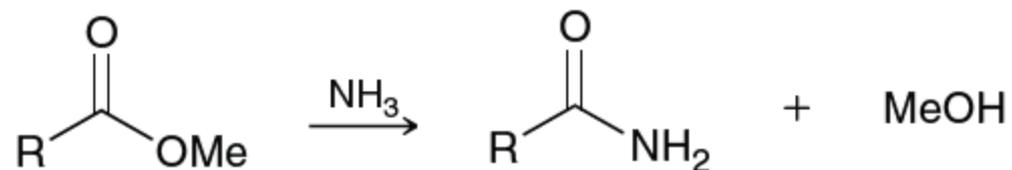
- **Acid-Catalyzed Hydrolysis of Esters**

Esters can also be hydrolyzed under acidic conditions.



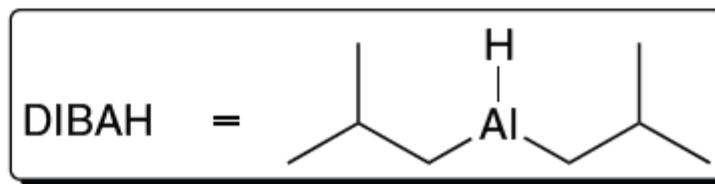
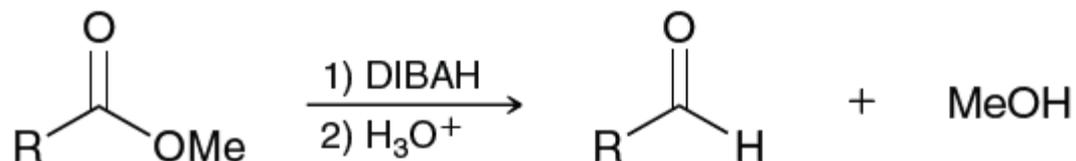
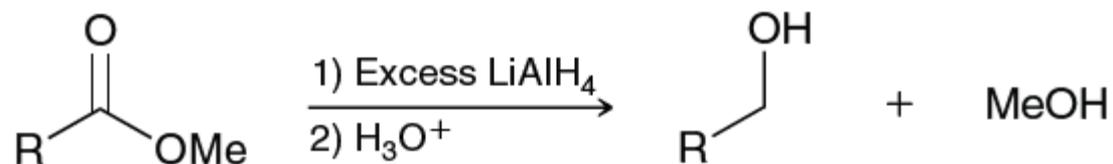
- Aminolysis of Esters**

Esters react slowly with amines to yield amides.



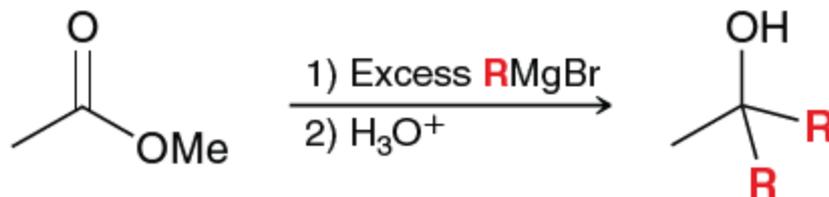
- Reduction of Esters with Hydride-Reducing Agents**

When treated with lithium aluminum hydride, esters are reduced to yield alcohols.

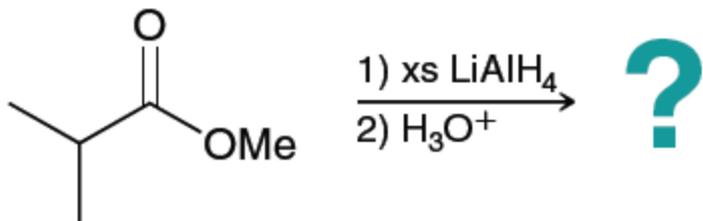


- Reactions between Esters and Grignard Reagents**

When treated with a Grignard reagent, esters are reduced to yield alcohols with the introduction of two alkyl groups.

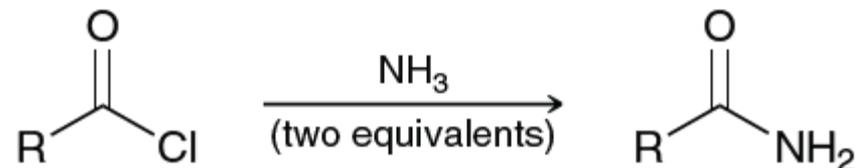


**20.22 Predict the major organic product(s) for each of the following reactions:**



## 20.12 Preparation and Reactions of Amides

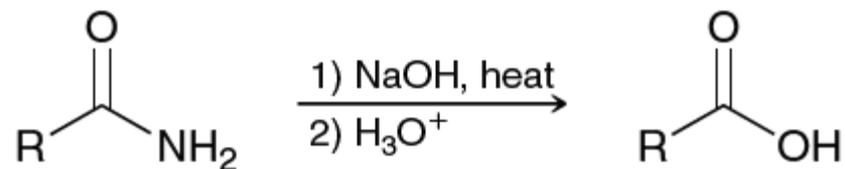
- **Preparation of Amides**



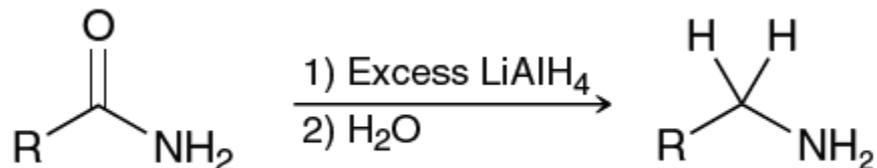
- **Acid-Catalyzed Hydrolysis of Amides**



- **Hydrolysis of Amides under Basic Conditions**

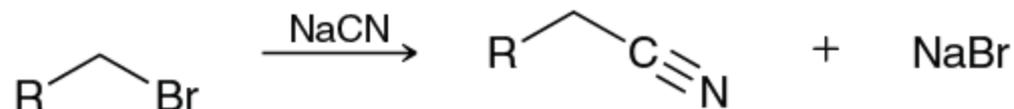


- **Reduction of Amides**

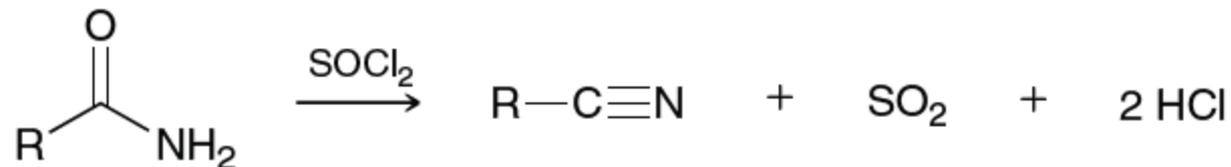


## 20.13 Preparation and Reactions of Nitriles

- Preparation of Nitriles via  $S_N2$  Reactions

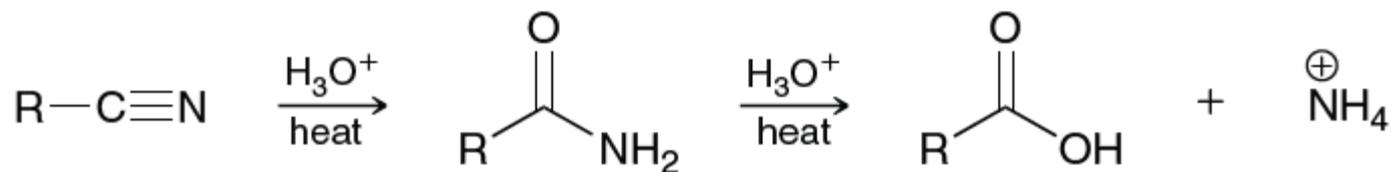


- Preparation of Nitriles from Amides

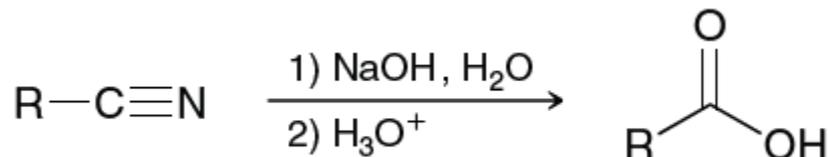


- Hydrolysis of Nitriles

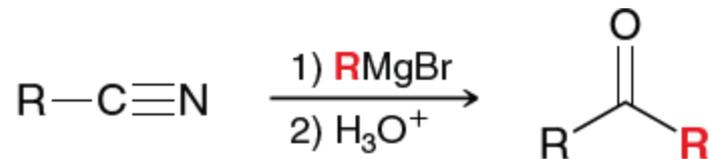
In aqueous acidic conditions



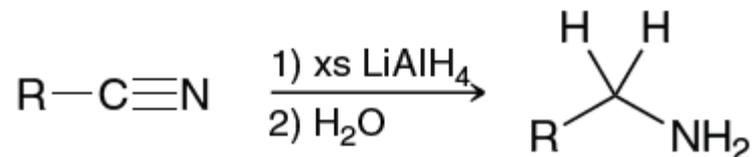
in aqueous base



- **Reactions between Nitriles and Grignard Reagents**



- **Reduction of Nitriles**



**20.27 Predict the major product for each of the following reactions:**

