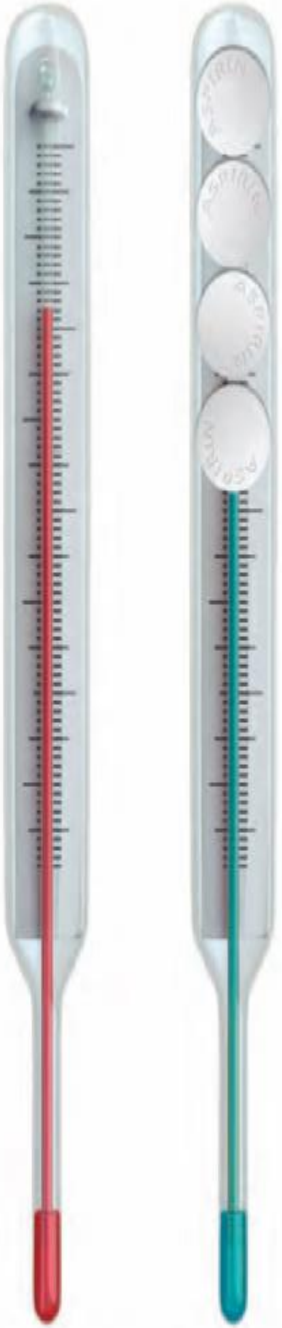
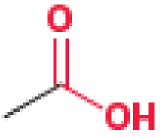
Carboxylic Acids & Their Derivatives



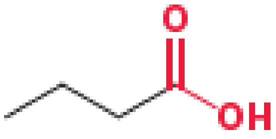
Based on Organic Chemistry, 2nd Edition
David R. Klein

Introduction to Carboxylic Acids

Carboxylic acids are compounds with a -COOH group. These compounds are abundant in nature, where they are responsible for some familiar odors.

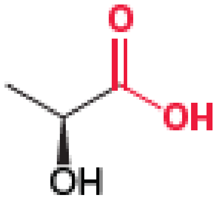


Acetic acid
(Responsible for
the pungent smell
of vinegar)



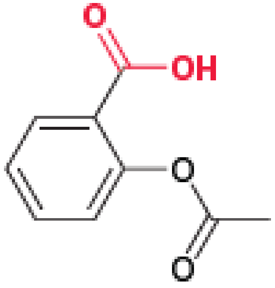
Butanoic acid
(Responsible for
the rancid odor
of sour butter)

Hexanoic acid
(Responsible for
the odor of
dirty socks)

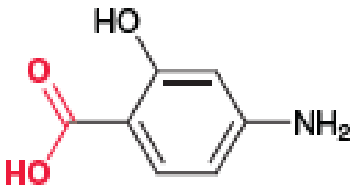


Lactic acid
(Responsible for
the taste of
sour milk)

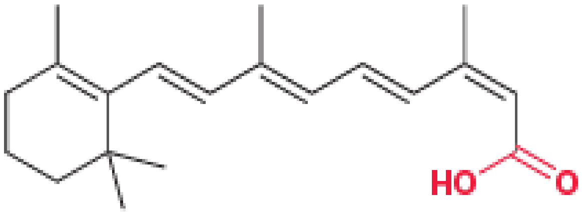
Carboxylic acids are also found in a wide range of pharmaceuticals that are used to treat a variety of conditions.



Acetylsalicylic acid
(Aspirin, a widely used analgesic)



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

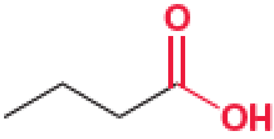


Isotretinoin
(Used in the treatment of acne)

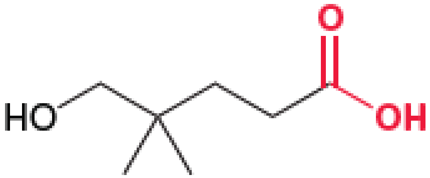
Nomenclature of Carboxylic Acids

Monocarboxylic Acids

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



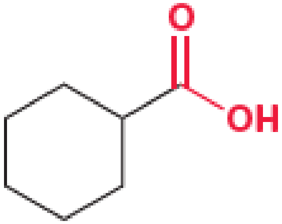
Butanoic acid



5-Hydroxy-4,4-dimethyl
pentanoic acid

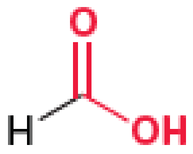
The parent is the longest chain that includes the carbon atom of the carboxylic acid group. That carbon atom is always assigned number 1 when numbering the parent.

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

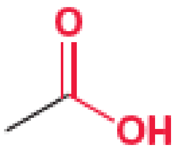


Cyclohexanecarboxylic acid

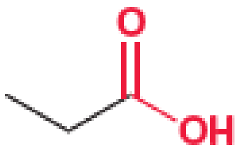
Many simple carboxylic acids have common names accepted by IUPAC.



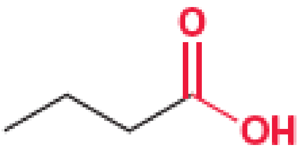
Formic acid



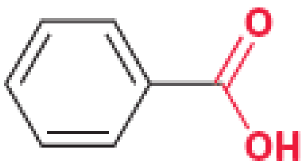
Acetic acid



Propionic acid



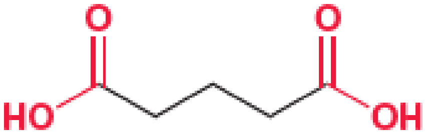
Butyric acid



Benzoic acid

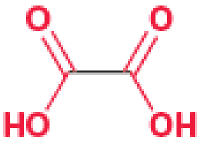
Diacids

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

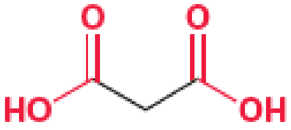


Pentane**dioic acid**

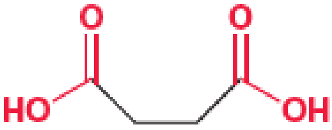
Many diacids have common names accepted by IUPAC.



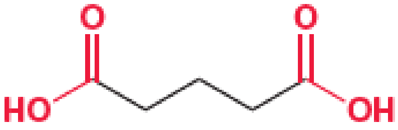
Oxalic acid



Malonic acid



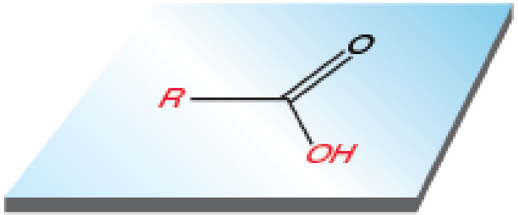
Succinic acid



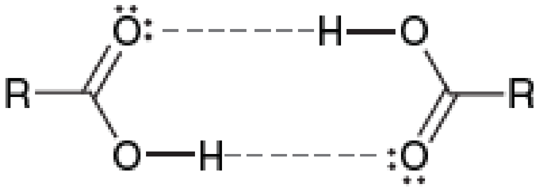
Glutaric acid

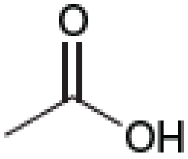
Structure and Properties of Carboxylic Acid

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°

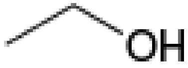


Carboxylic acids can form two hydrogen-bonding interactions, allowing molecules to associate with each other in pairs.



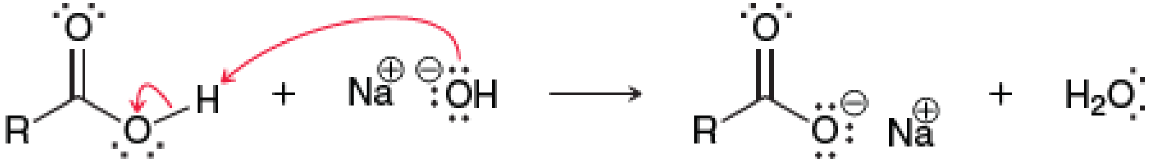


Acetic acid
b.p.=118°C



Ethanol
b.p.=78°C

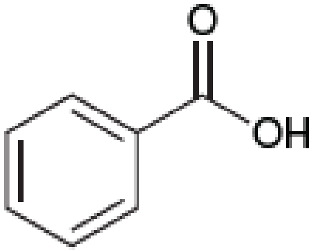
Acidity of Carboxylic Acids



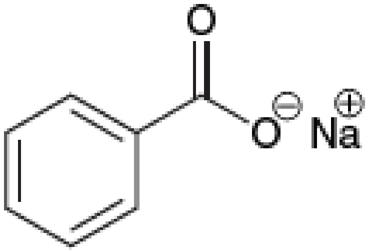
A carboxylate salt

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

Carboxylate ions are named by replacing the suffix “ic acid” with “ate”; for example:

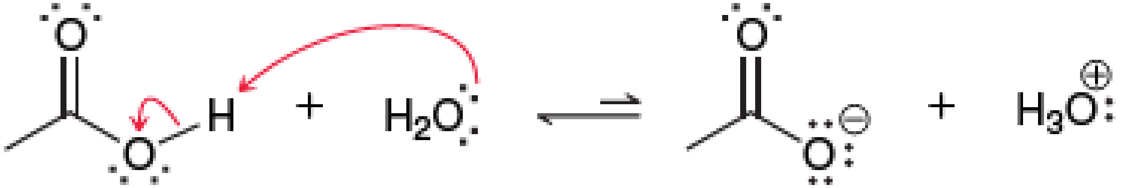


Benzoic acid

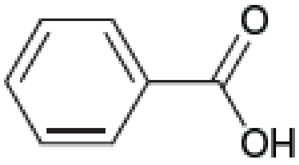


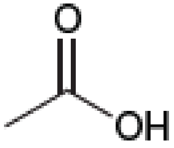
Sodium benzoate

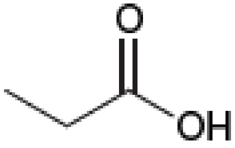
When dissolved in water, an equilibrium is established in which the carboxylic acid and the carboxylate ion are both present.



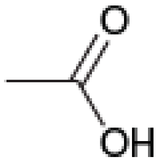
In most cases, the equilibrium significantly favours the carboxylic acid with a *K*a usually around 10^{-4} or 10^{-5}. In other words, the p*K*a of most carboxylic acids is between 4 and 5.

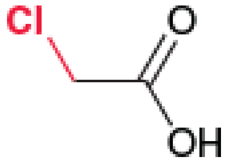

$pK_a=4.19$

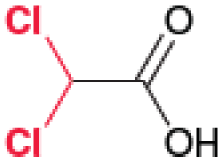

$pK_a=4.76$

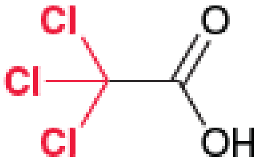

$pK_a=4.87$

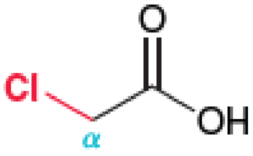
Substituent Effects on Acidity


pK_a = 4.8

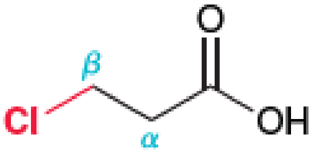

pK_a = 2.9


pK_a = 1.3

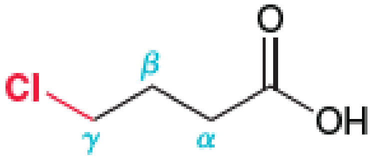

pK_a = 0.9



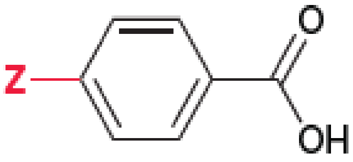
pK_a = 2.9



pK_a = 4.1



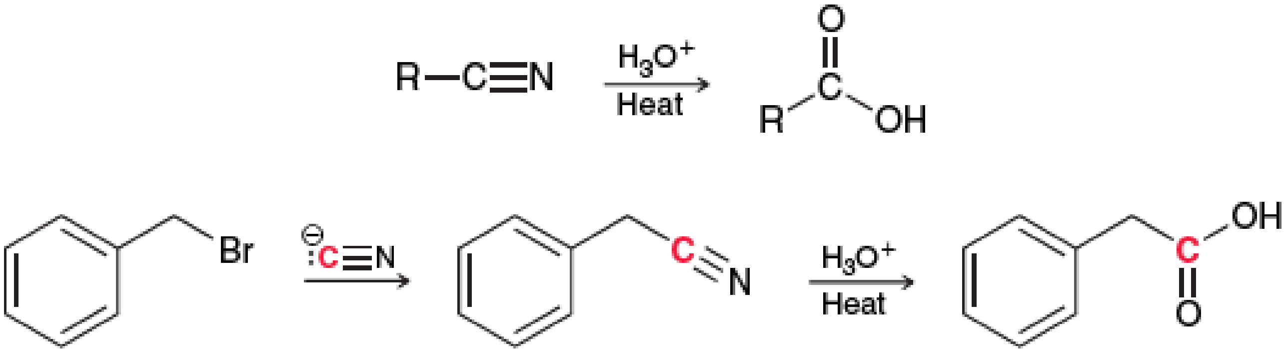
pK_a = 4.5



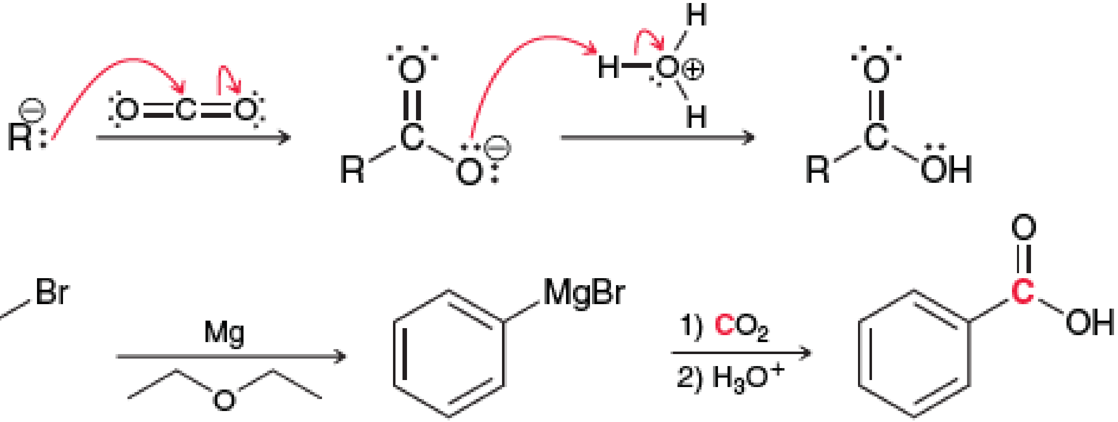
Z	—NO_2	—CHO	—Cl	—H	—CH_3	—OH
pK_a	3.4	3.8	4.0	4.2	4.3	4.5

Preparation of Carboxylic Acids

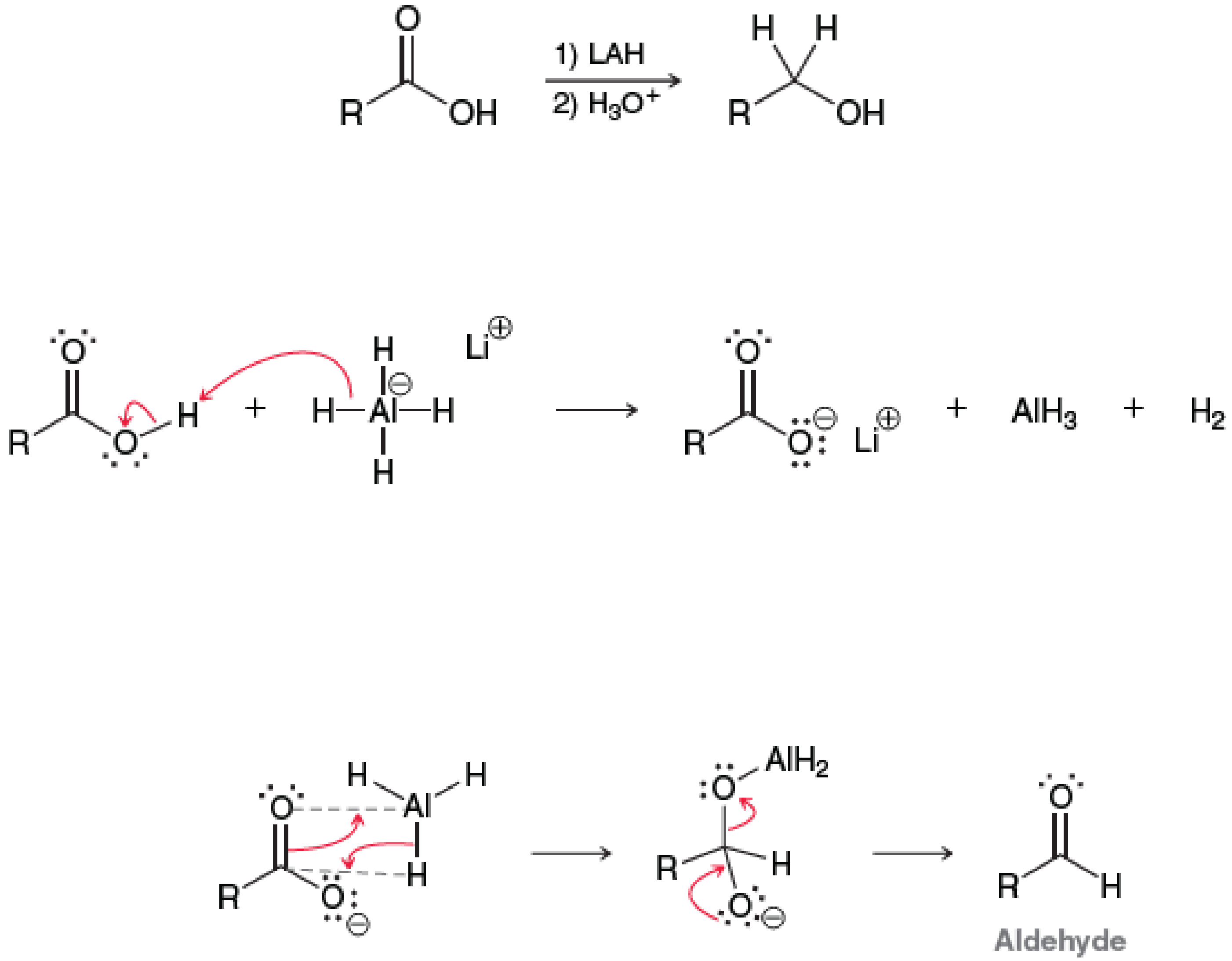
Hydrolysis of Nitriles



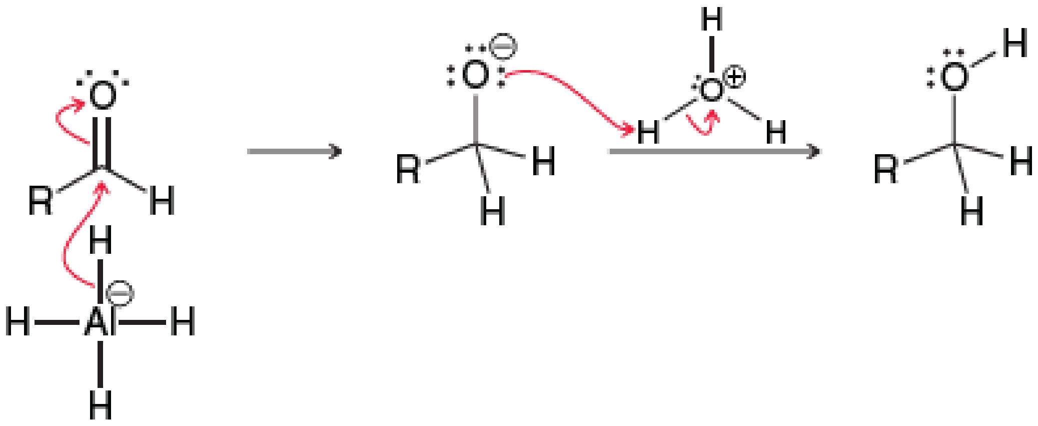
Carboxylation of Grignard Reagents



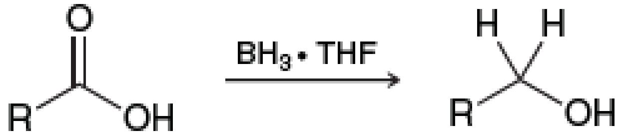
Reactions of Carboxylic Acids



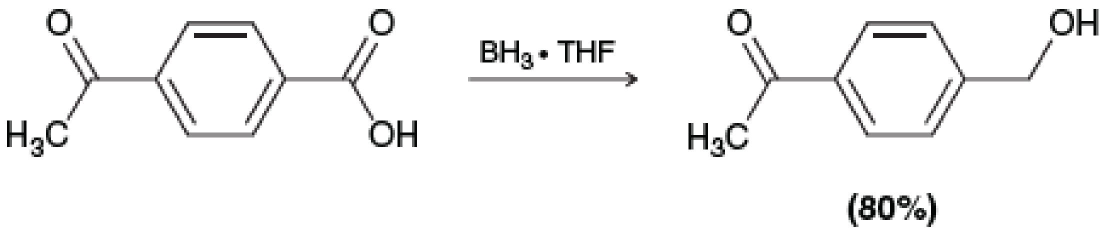
Under such conditions, the aldehyde cannot be isolated. Instead, it is further attacked by LAH to form an alkoxide, which is then protonated when H3O+ is introduced into the reaction flask.



An alternative method for reducing carboxylic acids involves the use of borane (BH_3).



Selectivity

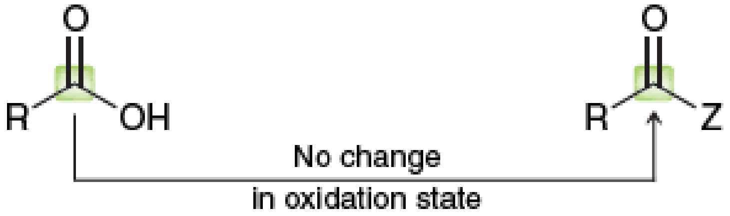


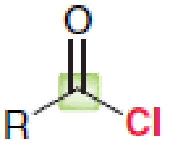
Introduction to Carboxylic Acid Derivatives

Classes of Carboxylic Acid Derivatives

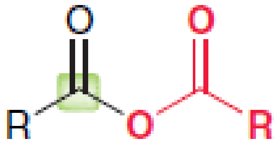
In the previous section, we learned about the reaction between a carboxylic acid and LAH. This reaction is a reduction, because the carbon atom of the carboxylic acid group is reduced in the process:

Carboxylic acids also undergo many other reactions that do not involve a change in oxidation state:

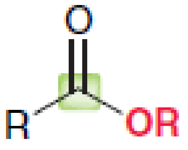




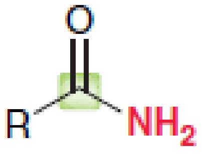
Acid halide



Acid anhydride



Ester

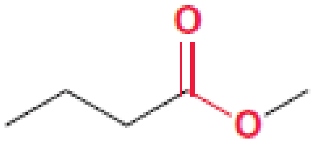


Amide

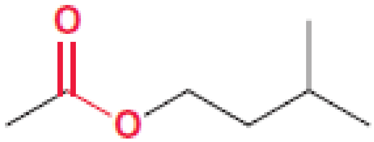
$R-C\equiv N$

A nitrile

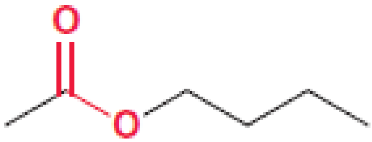
Carboxylic Acid Derivatives in Nature



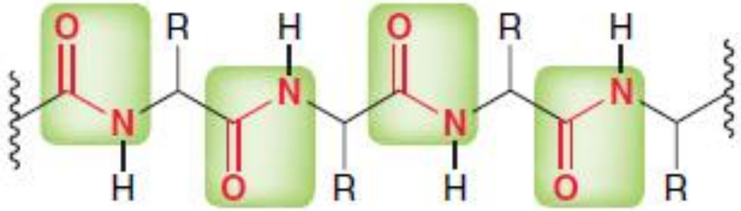
Methyl butanoate
(pineapple)



Isopentyl acetate
(banana)



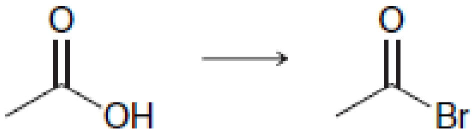
Butyl acetate
(pear)



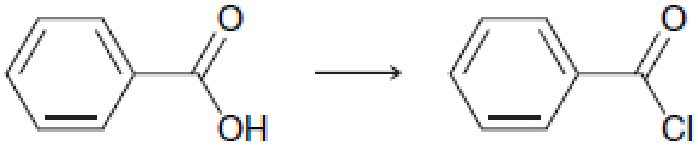
The structure of proteins

Naming Acid Halides

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

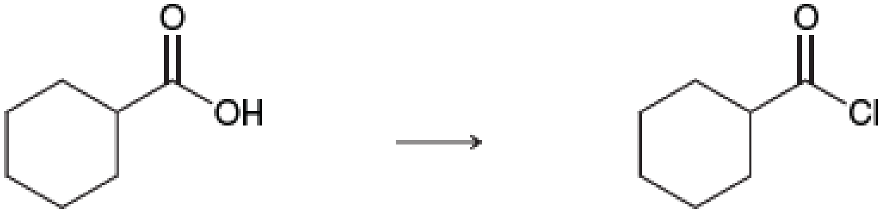


Acetic acid Acetyl bromide



Benzoic acid Benzoyl chloride

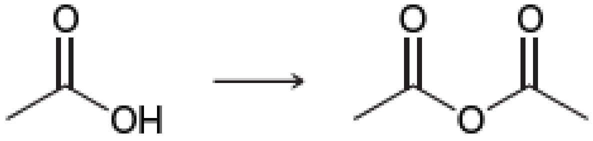
When an acid halide group is connected to a ring, the suffix “carboxylic acid” is replaced with “carbonyl halide”; for example:



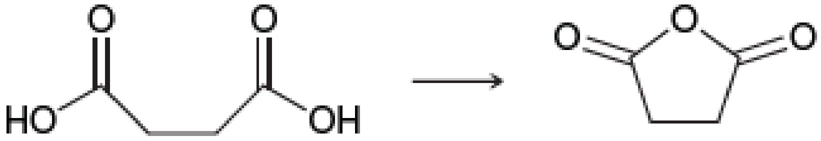
Cyclohexanecarboxylic acid Cyclohexanecarbonyl chloride

Naming Acid Anhydrides

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

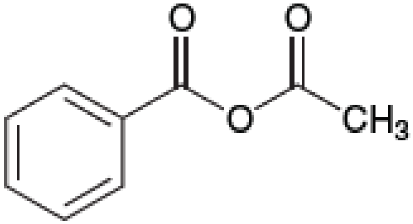


Acetic acid Acetic anhydride



Succinic acid Succinic anhydride

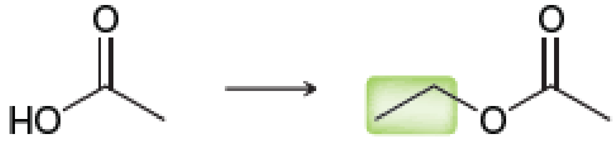
Unsymmetrical anhydrides are prepared from two different carboxylic acids and are named by indicating both acids alphabetically followed by the suffix “anhydride”:



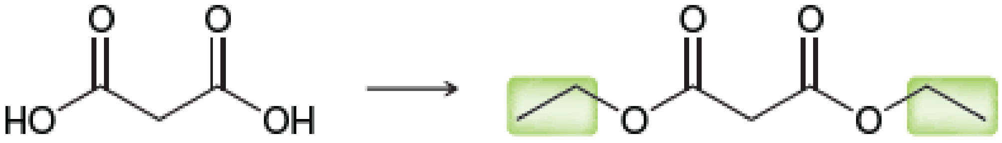
Acetic benzoic anhydride

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."

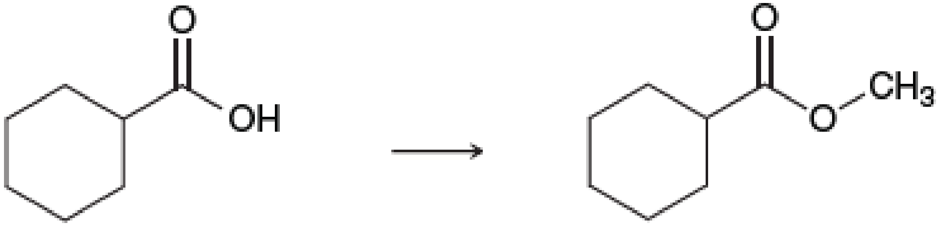


Acetic acid **Ethyl acetate**



Malonic acid **Diethyl malonate**

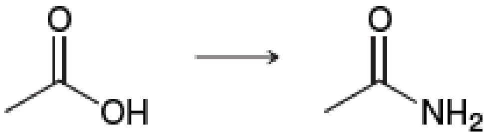
The same methodology is applied when the ester group is connected to a ring; for example:



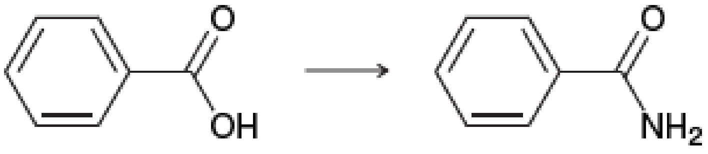
Cyclohexanecarboxylic acid **Methyl cyclohexanecarboxylate**

Naming Amides

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

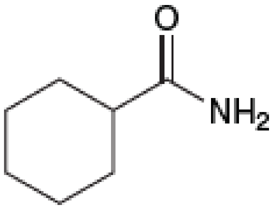


Acetic acid **Acetamide**



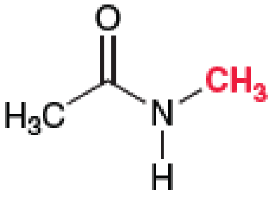
Benzoic acid **Benzamide**

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

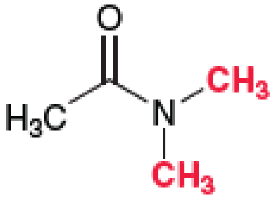


Cyclohexanecarboxamide

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.



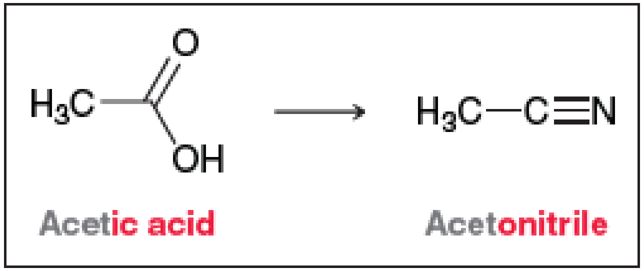
***N*-Methylacetamide**

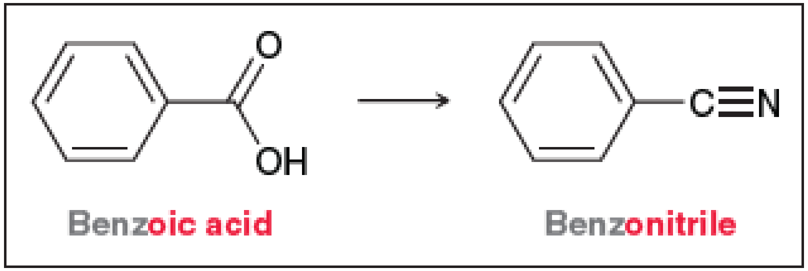


***N*,*N*-Dimethylacetamide**

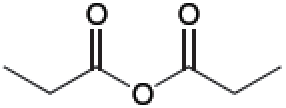
Naming Nitriles

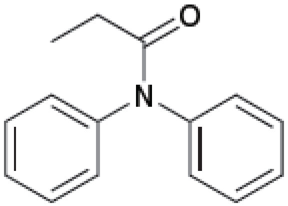
Nitriles are named as derivatives of carboxylic acids by replacing the suffix “ic acid” or “oic acid” with “onitrile.”

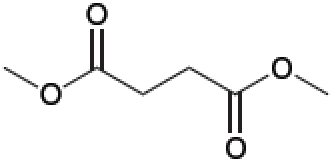


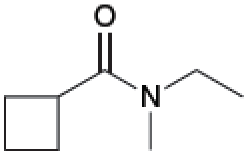


Provide a name for each of the following compounds:

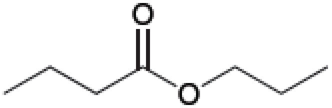
(a)


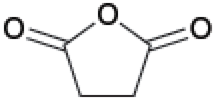
(b)


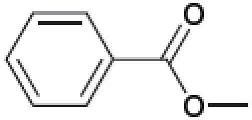
(c)


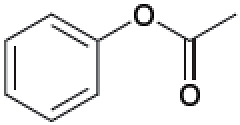
(d)


(e)


(f)


(g)


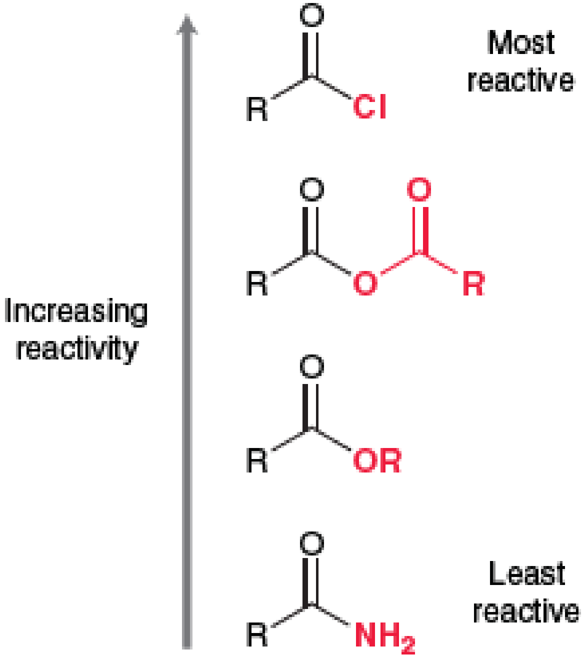
(h)


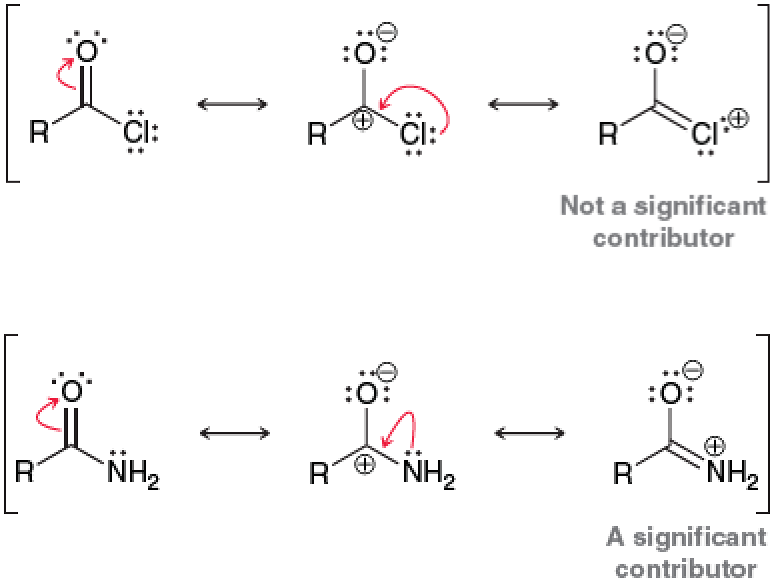
(i)


Draw a structure for each of the following compounds:

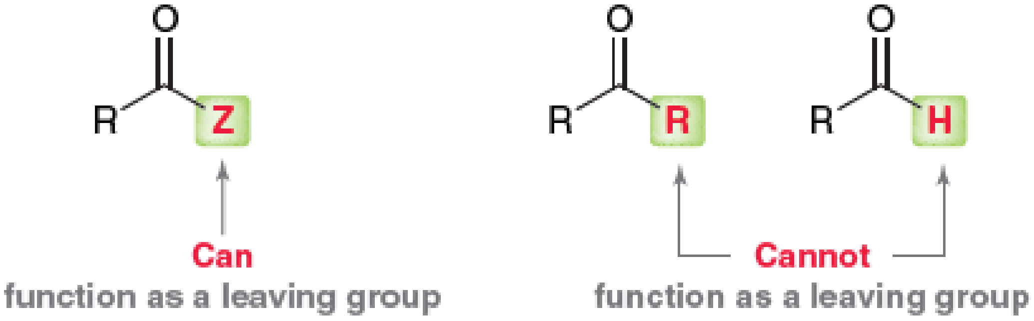
(a) Dimethyl oxalate
(b) Phenyl cyclopentanecarboxylate
(c) *N*-Methylpropionamide
(d) Propionyl chloride

Reactivity of Carboxylic Acid Derivatives



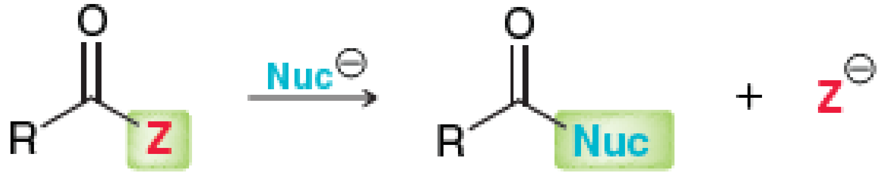


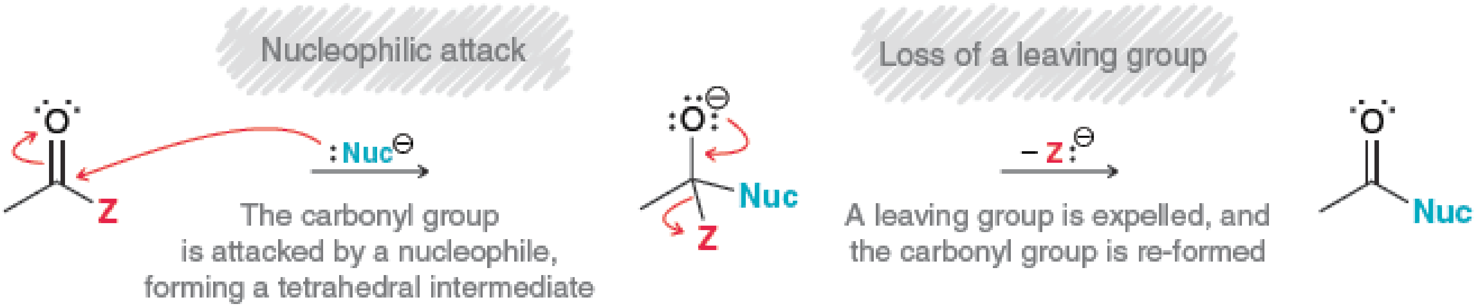
Nucleophilic Acyl Substitution



Can
function as a leaving group

Cannot
function as a leaving group





Nucleophilic attack

The carbonyl group is attacked by a nucleophile, forming a tetrahedral intermediate

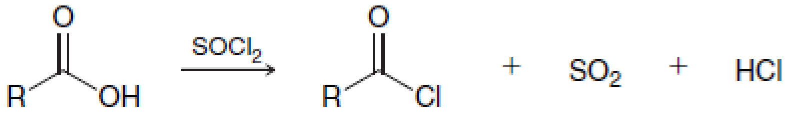
Loss of a leaving group

A leaving group is expelled, and the carbonyl group is re-formed

Preparation and Reactions of Acid Chlorides

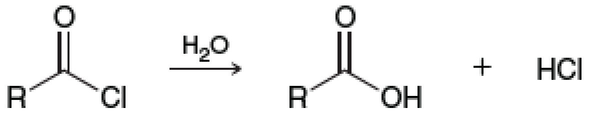
Preparation of Acid Chlorides

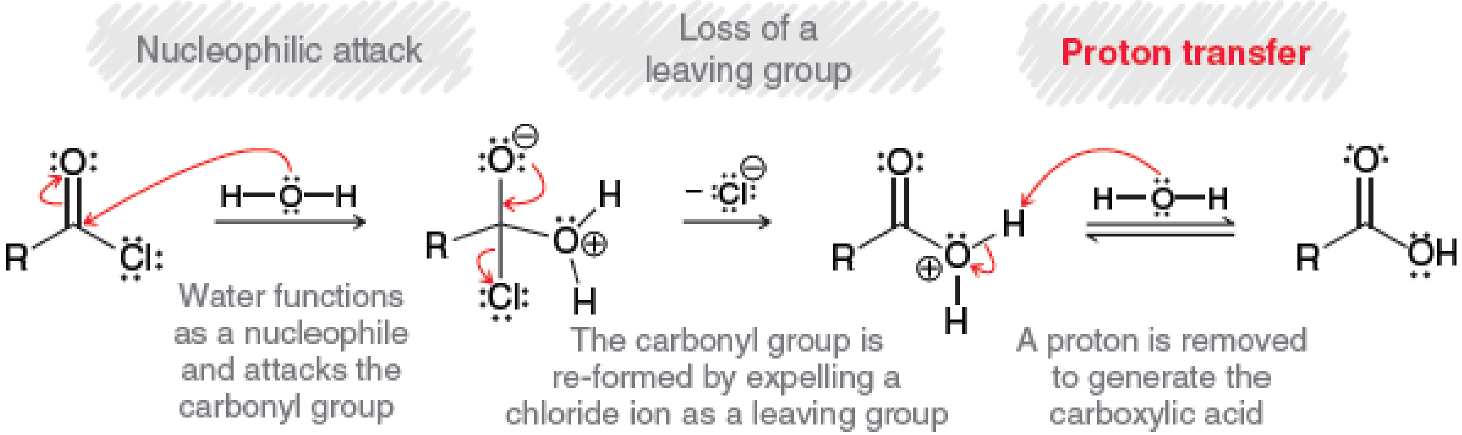
Acid chlorides can be formed by treating carboxylic acids with thionyl chloride ($SOCl_2$):



Hydrolysis of Acid Chlorides

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




Nucleophilic attack

Loss of a leaving group

Proton transfer

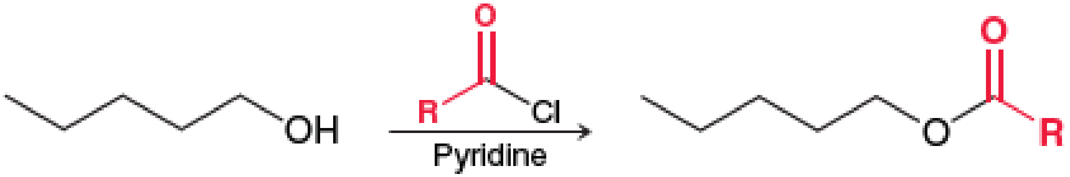
Water functions as a nucleophile and attacks the carbonyl group

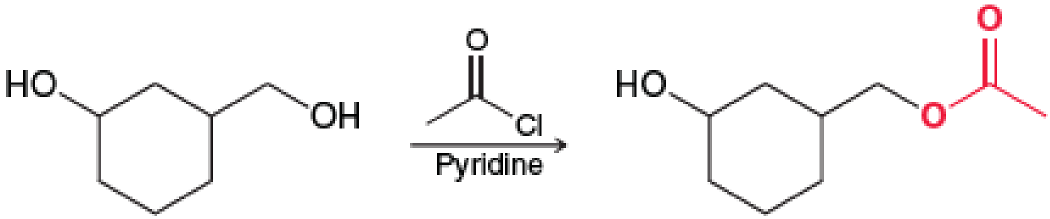
The carbonyl group is re-formed by expelling a chloride ion as a leaving group

A proton is removed to generate the carboxylic acid

Alcoholysis of Acid Chlorides

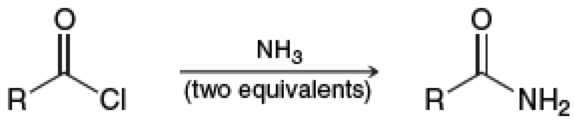
When treated with an alcohol, acid chlorides are converted into esters.

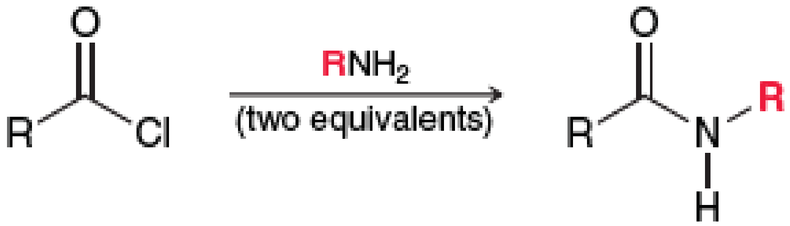


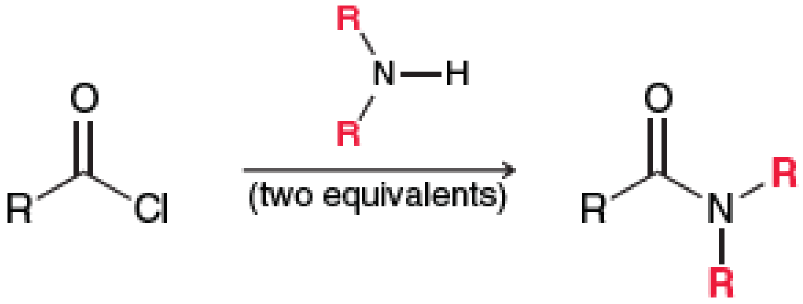


Aminolysis of Acid Chlorides

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

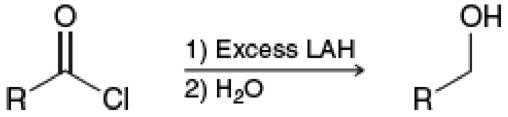


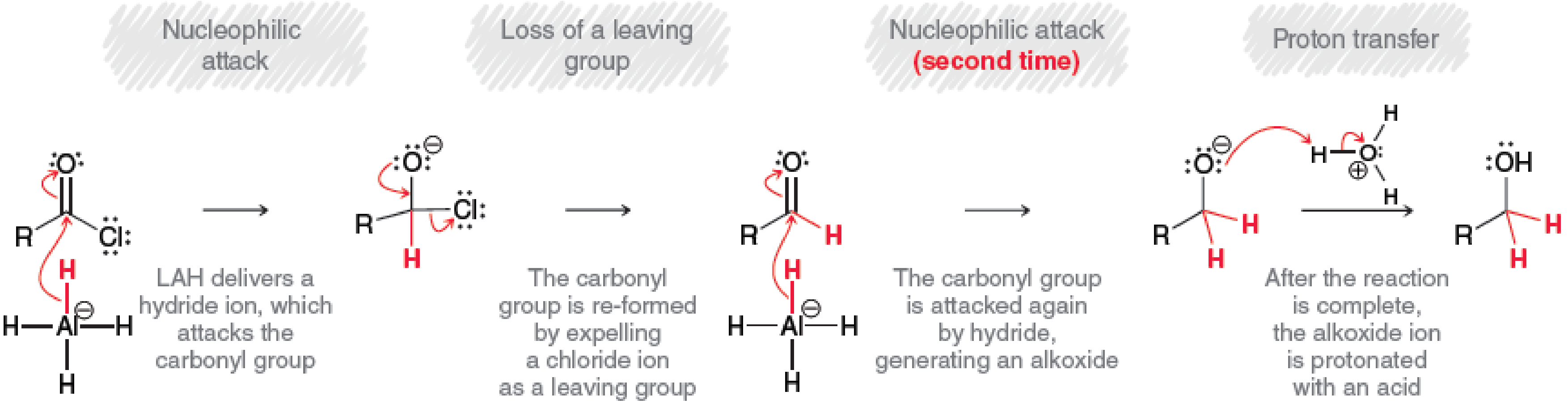




Reduction of Acid Chlorides

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





Nucleophilic attack

LAH delivers a hydride ion, which attacks the carbonyl group

Loss of a leaving group

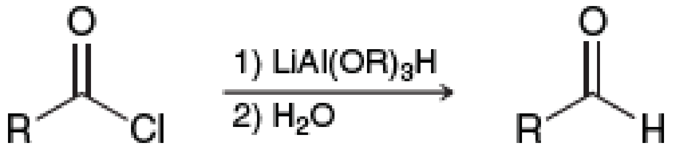
The carbonyl group is re-formed by expelling a chloride ion as a leaving group

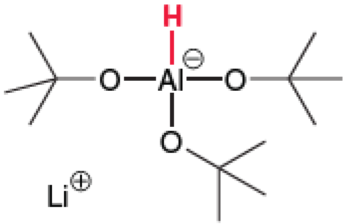
Nucleophilic attack **(second time)**

The carbonyl group is attacked again by hydride, generating an alkoxide

Proton transfer

After the reaction is complete, the alkoxide ion is protonated with an acid

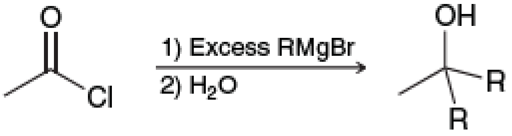


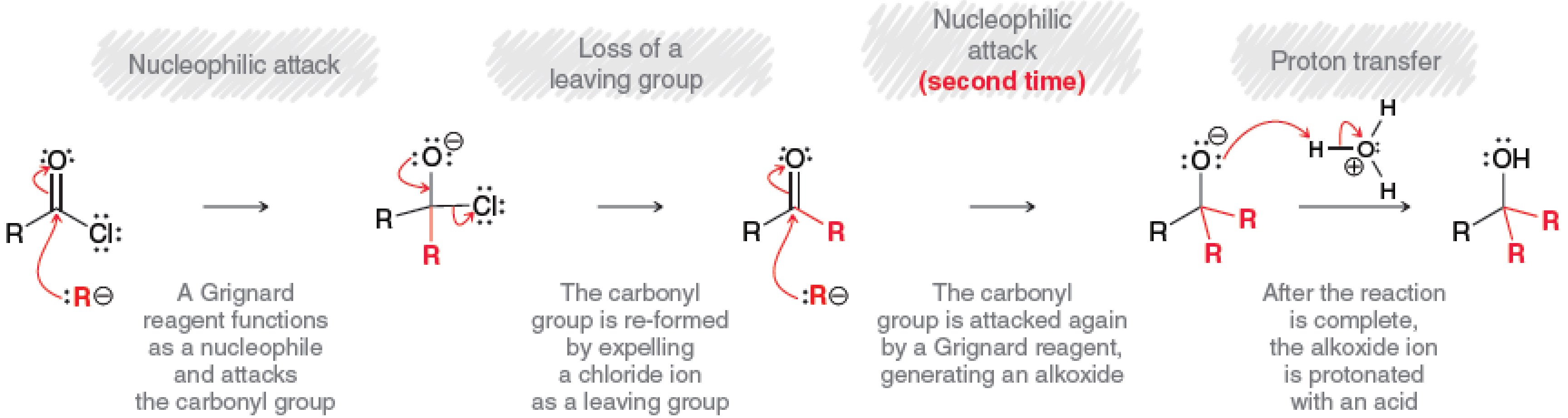


Lithium tri(*t*-butoxy) aluminum hydride

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.





Nucleophilic attack

A Grignard reagent functions as a nucleophile and attacks the carbonyl group

Loss of a leaving group

The carbonyl group is re-formed by expelling a chloride ion as a leaving group

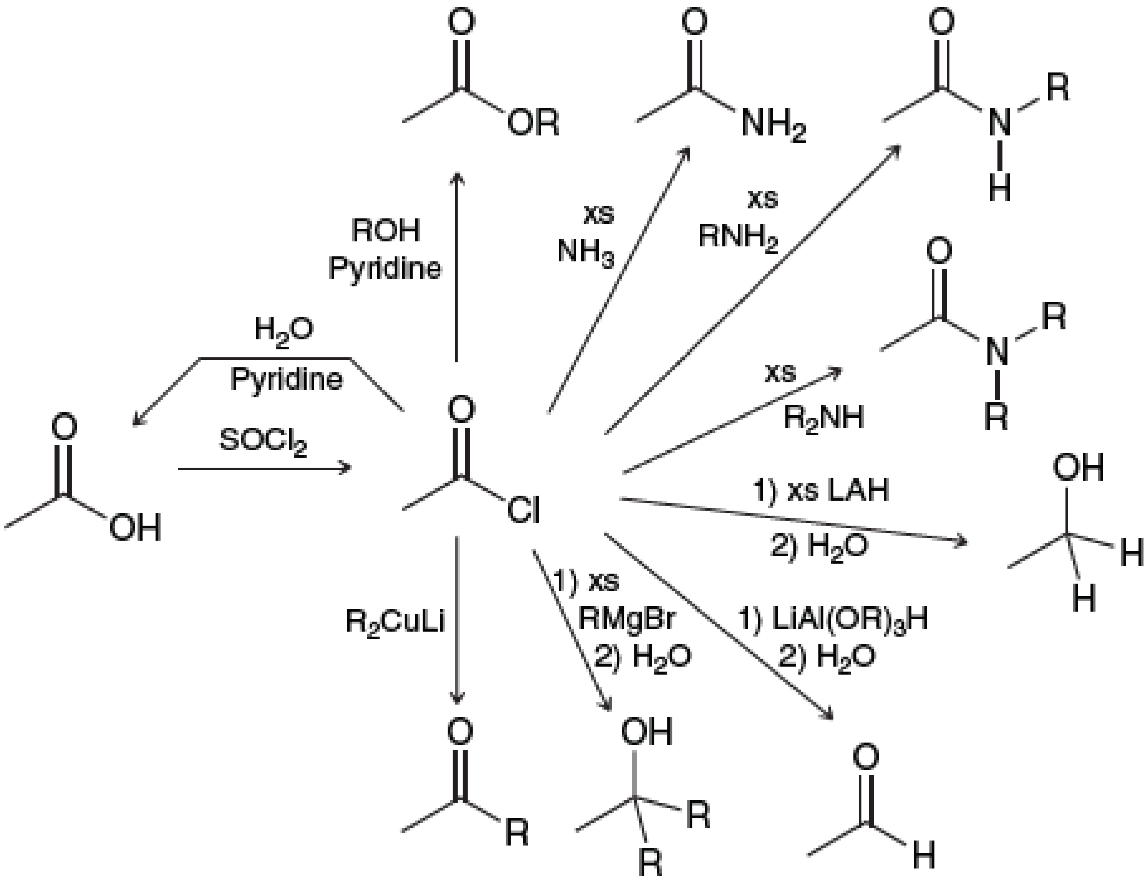
Nucleophilic attack **(second time)**

The carbonyl group is attacked again by a Grignard reagent, generating an alkoxide

Proton transfer

After the reaction is complete, the alkoxide ion is protonated with an acid

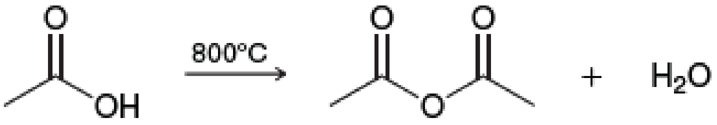
Summary of Reactions of Acid Chlorides



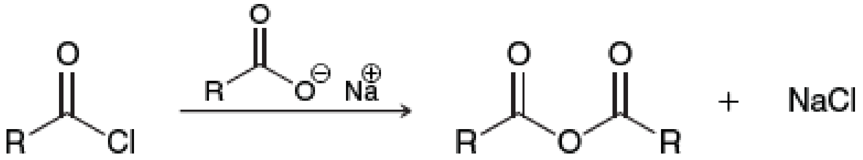
Preparation and Reactions of Acid Anhydrides

Preparation of Acid Anhydrides

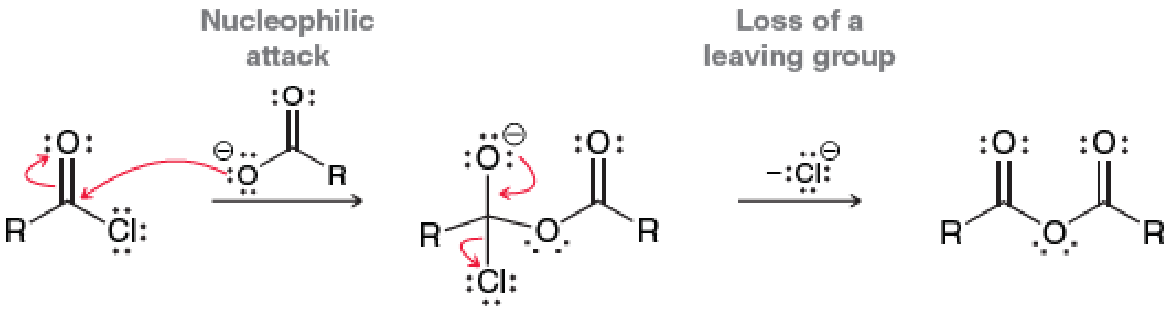
Carboxylic acids can be converted into acid anhydrides with excessive heating.



This method is only practical for acetic acid, as most other acids cannot survive the excessive heat. An alternative method for preparing acid anhydrides involves treating an acid chloride with a carboxylate ion, which functions as a nucleophile.



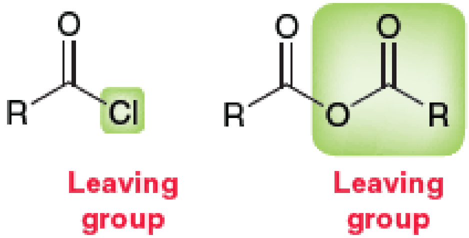
As we might expect, the mechanism of this transformation involves only two steps:

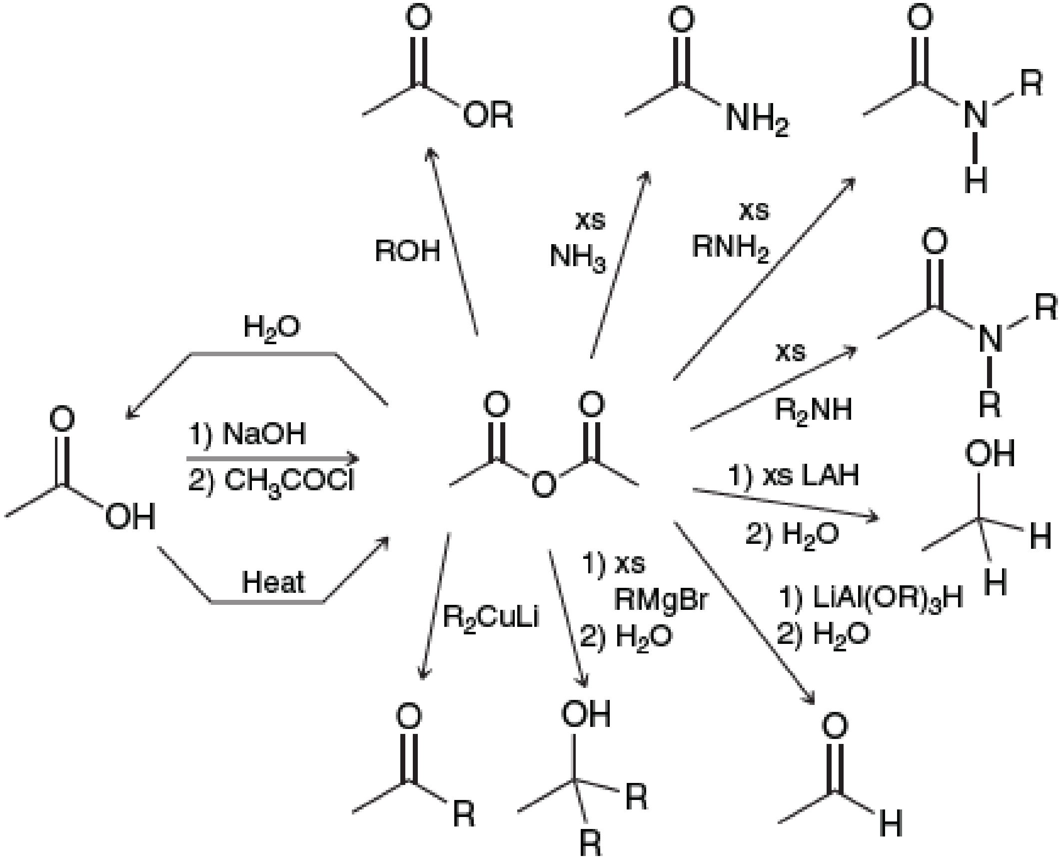


This method can be used to prepare symmetrical or unsymmetrical anhydrides.

Reactions of Acid Anhydrides

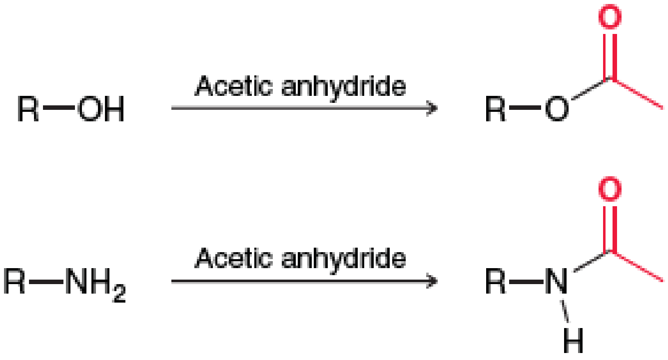
The reactions of anhydrides are directly analogous to the reactions of acid chlorides. The only difference is in the identity of the leaving group.



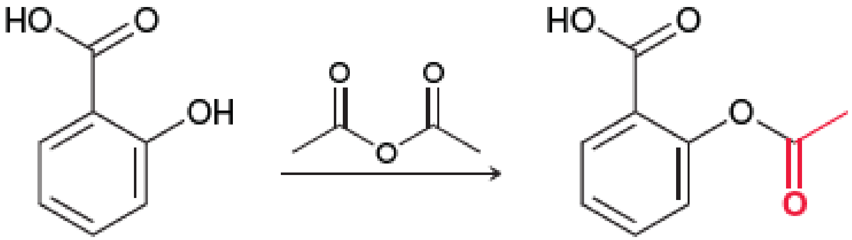


Acetylation with Acetic Anhydride

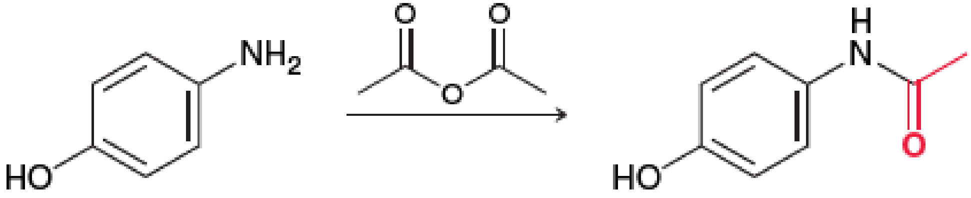
Acetic anhydride is often used to acetylate an alcohol or an amine.



These reactions are utilized in the commercial preparation of aspirin and Tylenol.



Aspirin



Tylenol