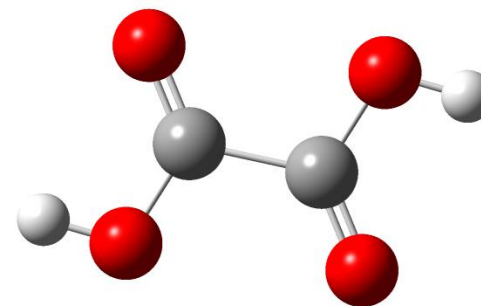
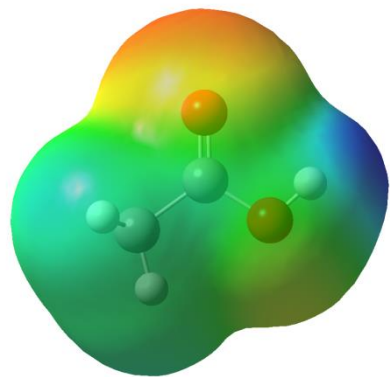


Chapter 10: Carboxylic Acids and Their Derivatives



Carboxylic Acids

Contain a *carboxyl group*: $-\text{CO}_2\text{H}$ or

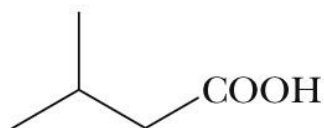


It must be the terminal group on a chain.

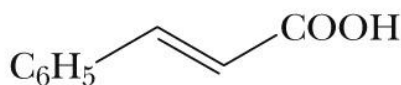
Acid derivatives replace the $-\text{OH}$ (hydroxyl) group with another functional group: *amides* (NH_2), *esters* ($-\text{OR}$), *acyl halides* ($-\text{X}$), *anhydrides* ($-\text{CO}_2\text{R}$).

Nomenclature

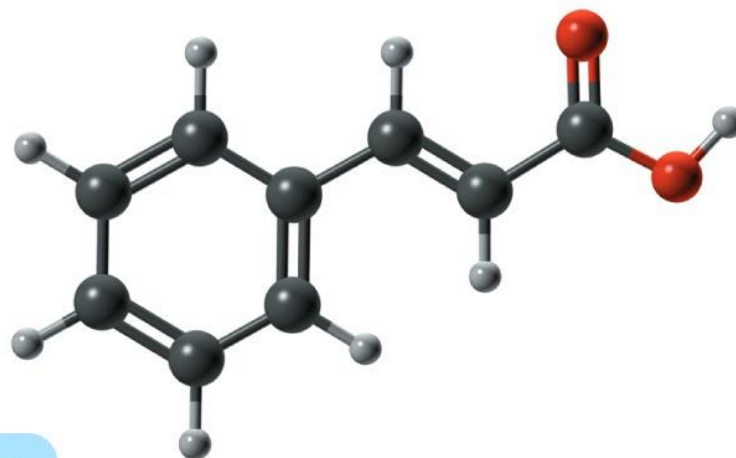
- IUPAC names: drop the **-e** from the parent alkane and add the suffix **-oic acid**.
 - If the compound contains a carbon-carbon double bond, change the infix **-an-** to **-en-**.



3-Methylbutanoic acid
(Isovaleric acid)



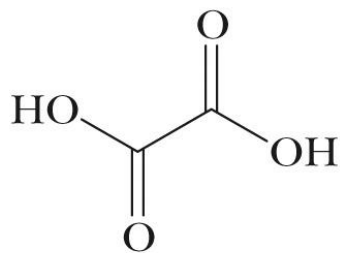
trans-3-Phenylpropenoic acid
(Cinnamic acid)



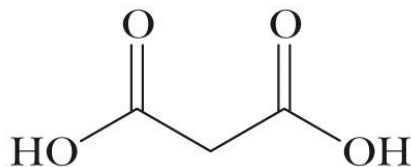
it is not necessary to indicate that the alkene occurs at position 2 because there is no other position where it can occur

Nomenclature

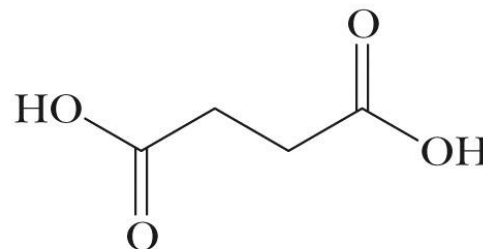
- Dicarboxylic acids: add **-dioic acid** to the name of the parent alkane containing both carboxyl groups.
- There is no need to use numbers to locate the carboxyl groups; they can only be on the ends of the chain.



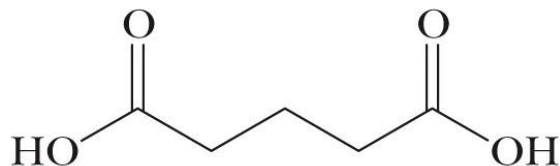
Ethanedioic acid
(Oxalic acid)



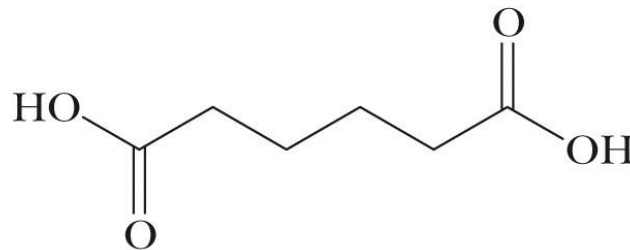
Propanedioic acid
(Malonic acid)



Butanedioic acid
(Succinic acid)



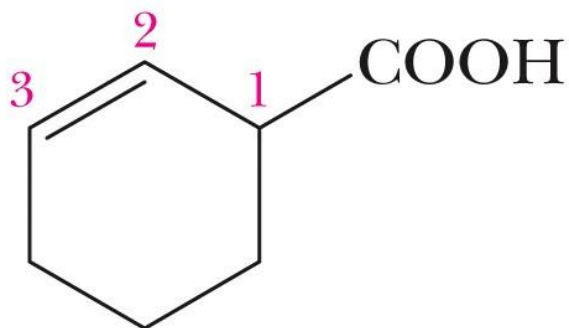
Pentanedioic acid
(Glutaric acid)



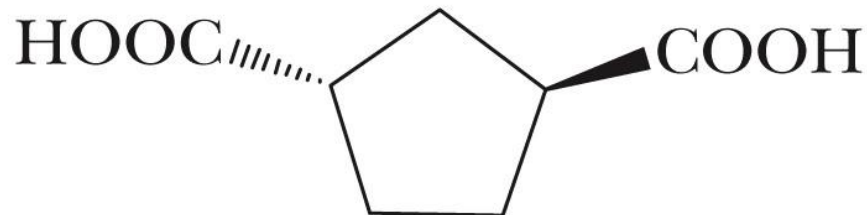
Hexanedioic acid
(Adipic acid)

Nomenclature

- If the carboxyl group is bonded to a ring, name the ring compound and add the suffix **-carboxylic acid**.



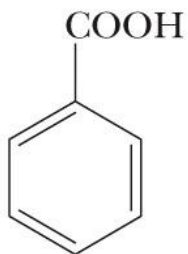
2-Cyclohexenecarboxylic
acid



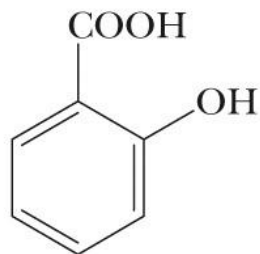
trans-1,3-Cyclopentane-
dicarboxylic acid

Nomenclature

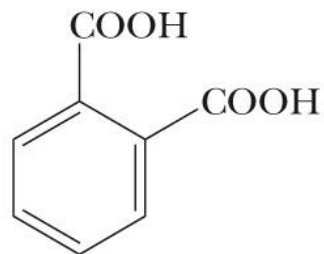
- Benzoic acid is the simplest aromatic carboxylic acid.
- Use numbers to show the location of substituents.



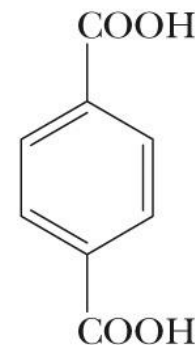
Benzoic acid



2-Hydroxybenzoic acid
(Salicylic acid)



1,2-Benzenedicarboxylic acid
(Phthalic acid)



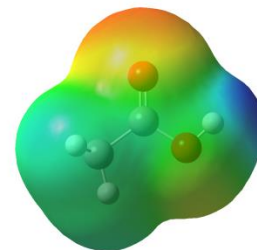
1,4-Benzenedicarboxylic acid
(Terephthalic acid)

TABLE 12.1 Increasing Order of Precedence of Six Functional Groups

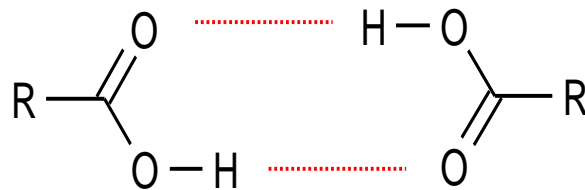
Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Carboxyl	-oic acid	—		
Aldehyde	-al	oxo-	3-Oxopropanoic acid	
Ketone	-one	oxo-	3-Oxobutanal	
Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	
Amino	-amine	amino-	2-Amino-1-propanol	
Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	

Physical Properties of Acids

1) They are acidic, with $pK_a \sim 5$.



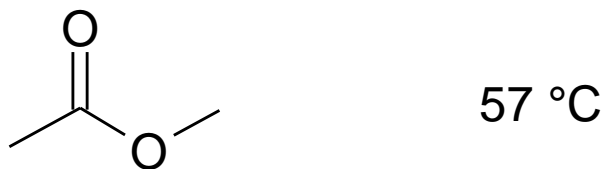
2) As with alcohols, they form strong hydrogen bonds, especially with each other, i.e.



Physical Properties of Acids

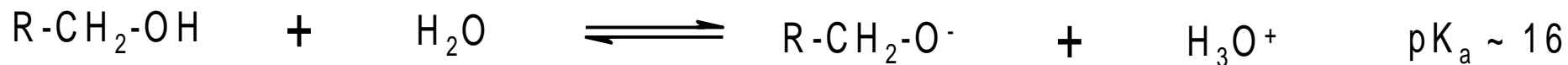
This produces:

1. High BP & MP, higher than equivalent weight alcohols
2. Very soluble in polar protic solvents like water or alcohols



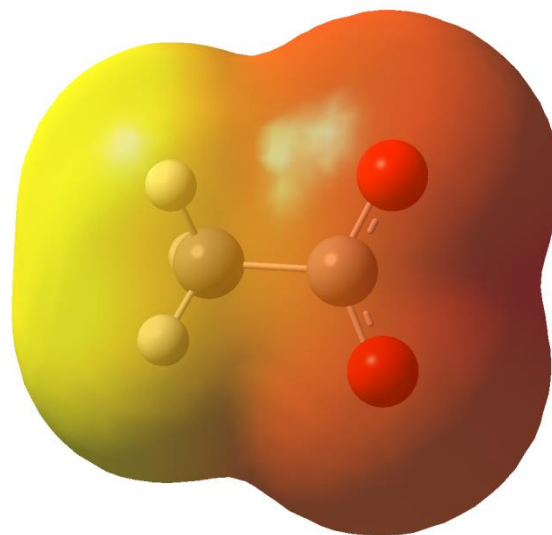
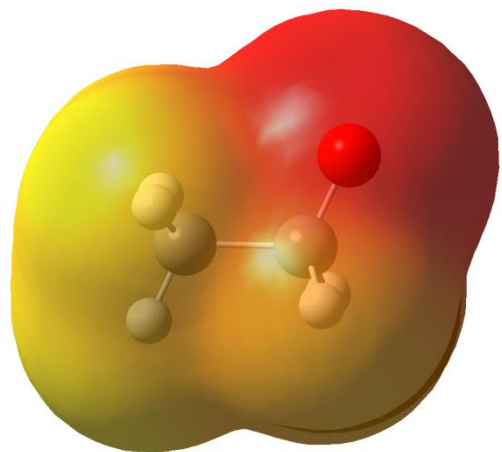
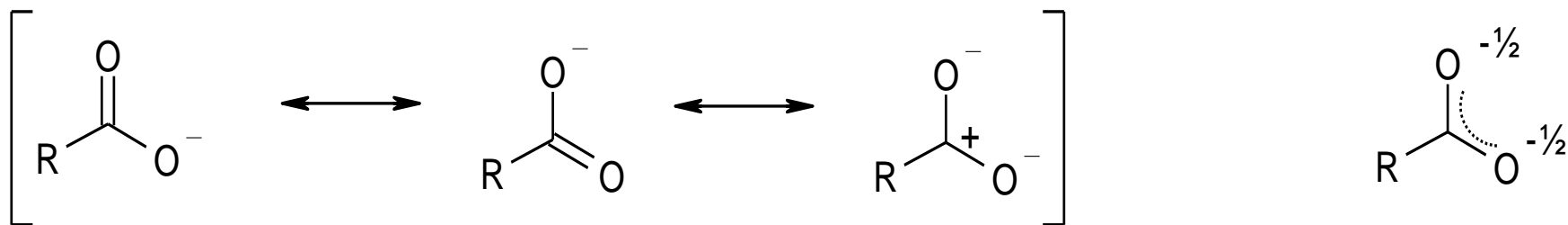
Physical Properties of Acids

K_a & pK_a : the low pK_a of acids compared to alcohols is due to *resonance stabilization* of the conjugate base, i.e.



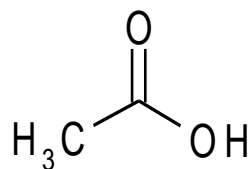
Physical Properties of Acids

Why?

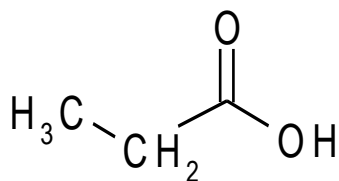


Physical Properties of Acids

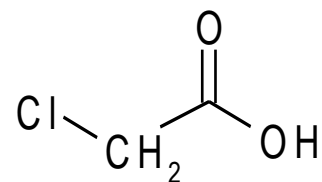
The pK_a can also be affected by *inductive processes* from groups on the α -carbon, i.e.



$pK_a = 4.72$

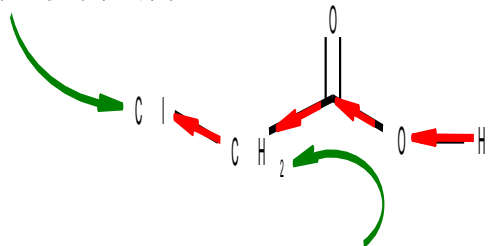


$pK_a = 4.82$



$pK_a = 2.86$

Cl atom pulls electron density towards itself

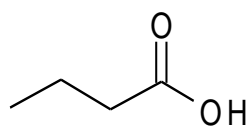


electron density is pulled towards the O atom

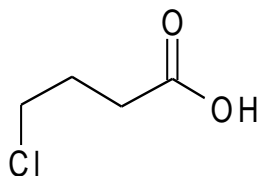
electron density is pulled towards the C atom

Physical Properties of Acids

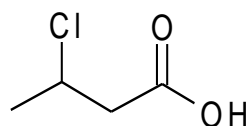
This helps stabilize the conjugate base by shifting the charge density away from the O atom, but is distance dependent, i.e.



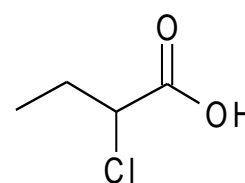
$$pK_a = 4.82$$



$$pK_a = 4.52$$

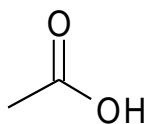


$$pK_a = 4.05$$

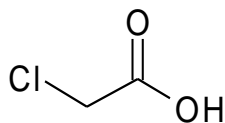


$$pK_a = 3.15$$

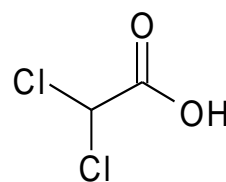
The effect is cumulative so the greater the number of electron withdrawing atoms the greater the effect, i.e.



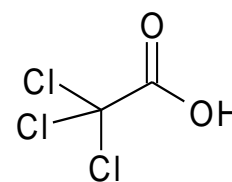
$$pK_a = 4.74$$



$$pK_a = 2.82$$



$$pK_a = 1.30$$

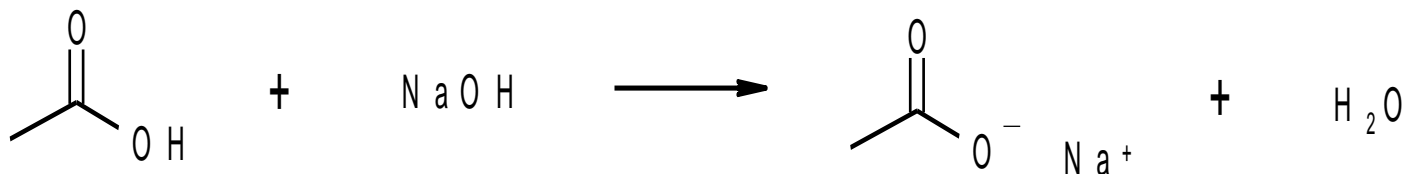


$$pK_a = 0.70$$

Formation of Salts

A salt is an ionic compound containing the conjugate base of an acid and a group I or II metal.

They are generated by treating an organic acid with NaOH or KOH, the OH⁻ combines with the acidic proton in a neutralization reaction to form water. The conjugate base and metal ion form an ionic solid, i.e.

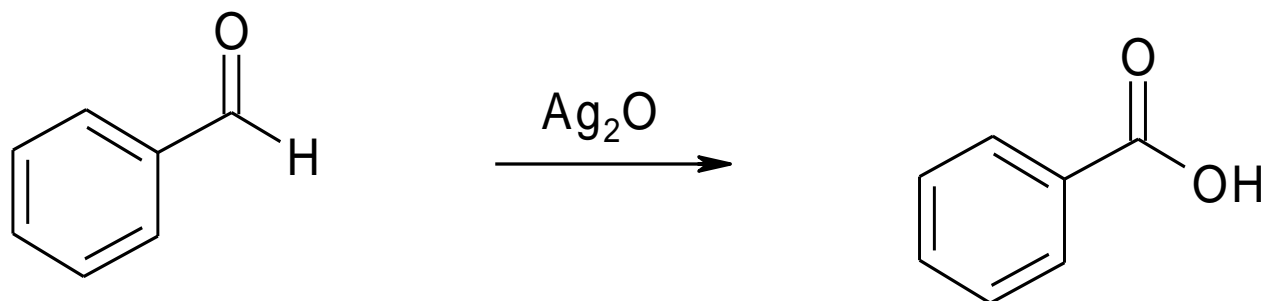
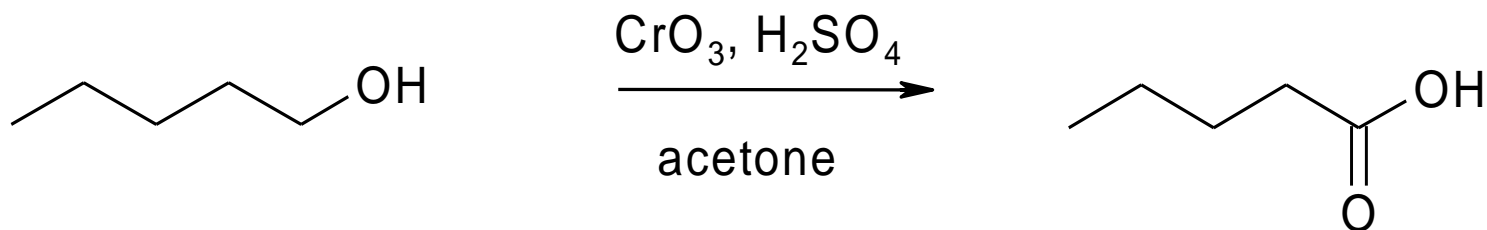


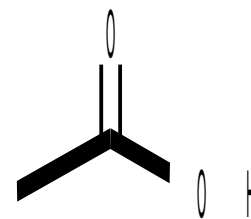
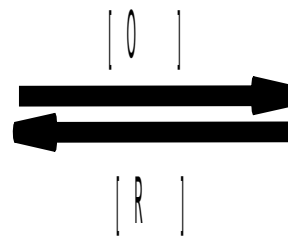
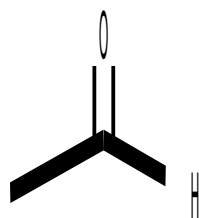
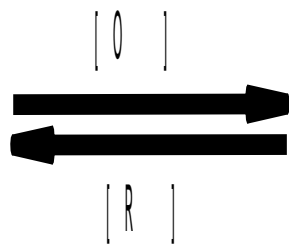
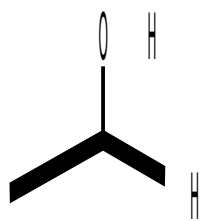
Preparation of Acids

There are a number of ways to create carboxylic acids:

1. Oxidation of 1° alcohols or aldehydes:

Common reagents include; CrO_3 , H_2SO_4 in acetone (Jones' reagent), KMnO_4 , HNO_3 , and for aldehydes Ag_2O , i.e.

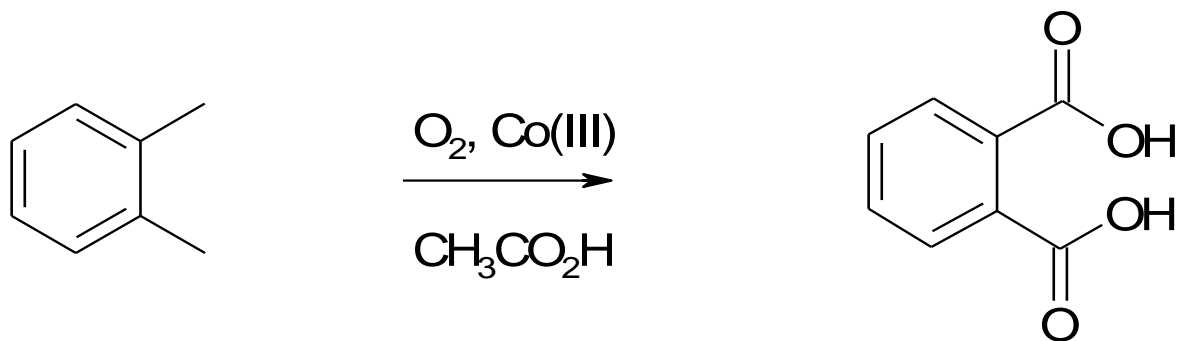
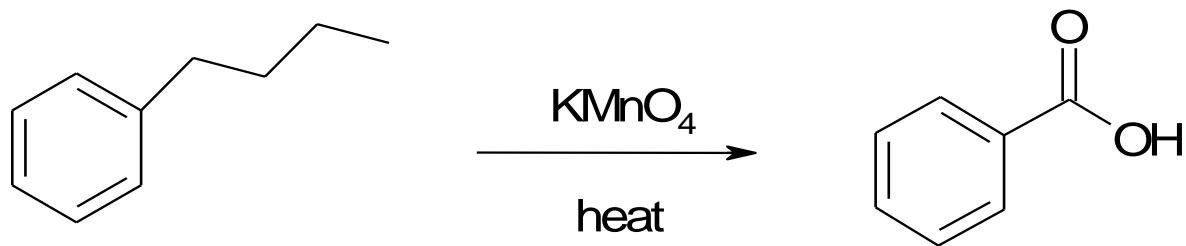




Preparation of Acids

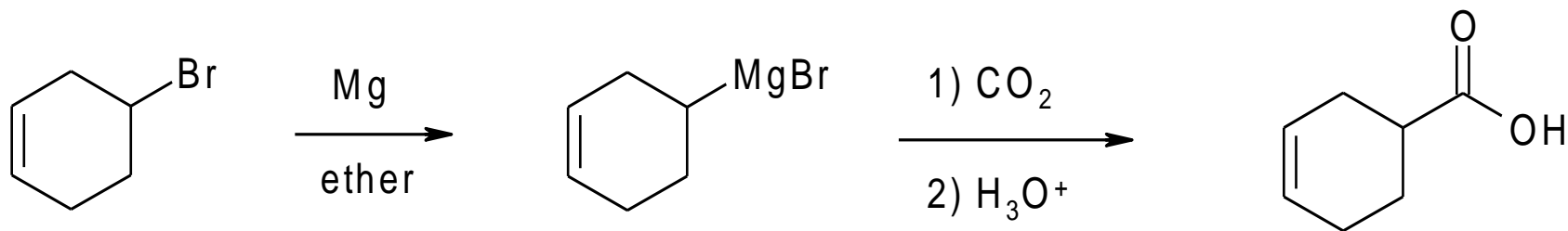
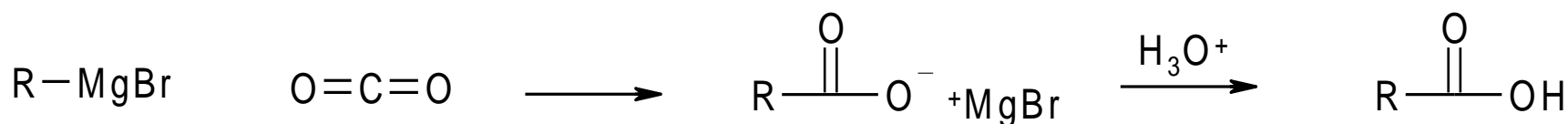
2. *Oxidation of aromatic alkyl side chains:*

Common reagents include; KMnO_4 , commercially: O_2 , Co(III) in $\text{CH}_3\text{CO}_2\text{H}$, i.e.



Preparation of Acids

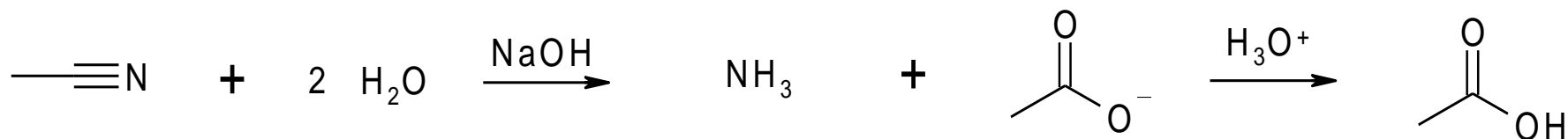
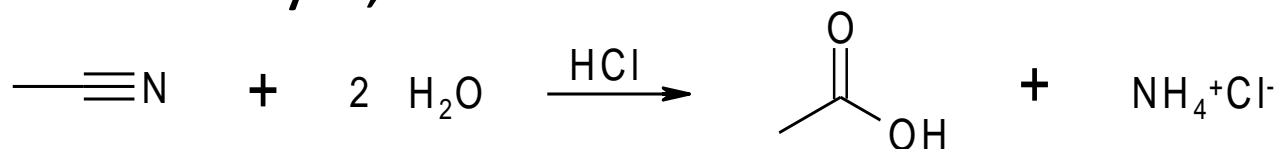
3. Grignard reagents with CO_2 :



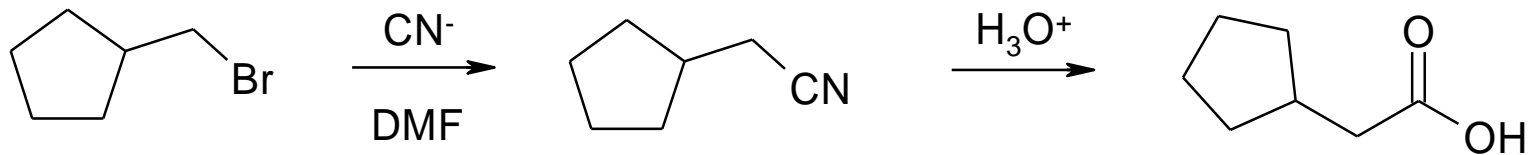
Note: the acid is one carbon atom longer than the Grignard reagent.

Preparation of Acids

4. *Hydrolysis of nitriles*: need either an acid or base catalyst, i.e.

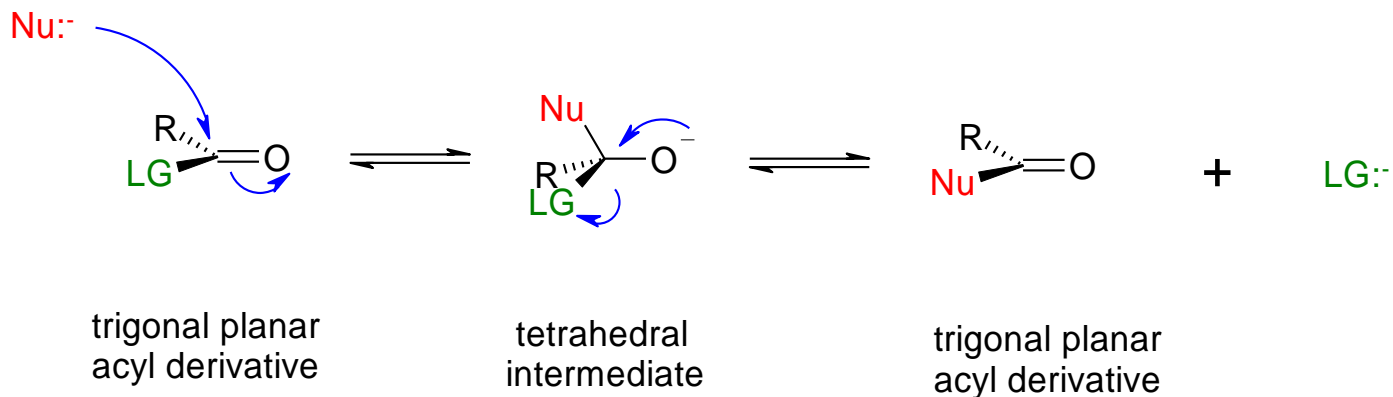
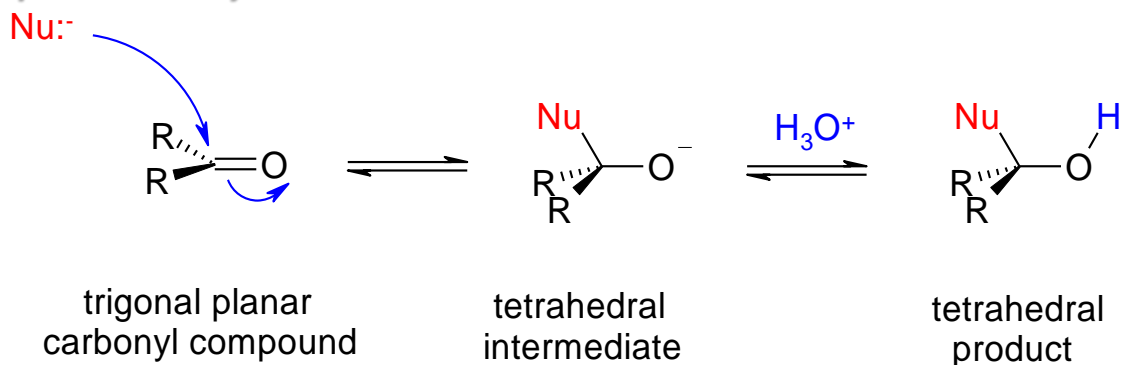


Note: the nitrile can be made from an alkyl halide, i.e.



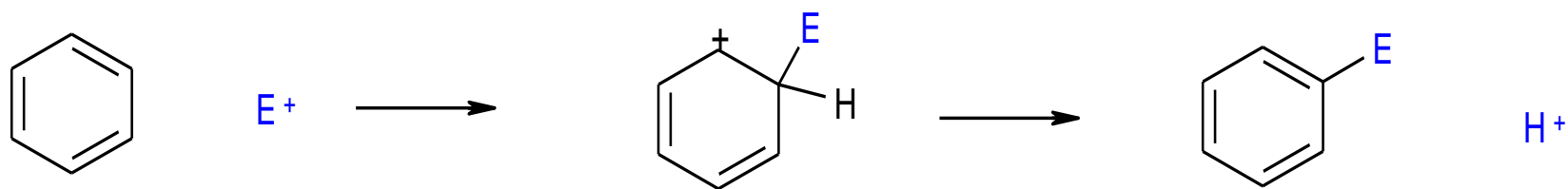
Nucleophilic Acyl Substitution

In contrast to aldehydes and ketones, which react by *nucleophilic (acyl) addition*, carboxylic acids (and derivatives) react by *nucleophilic acyl substitution*, i.e.

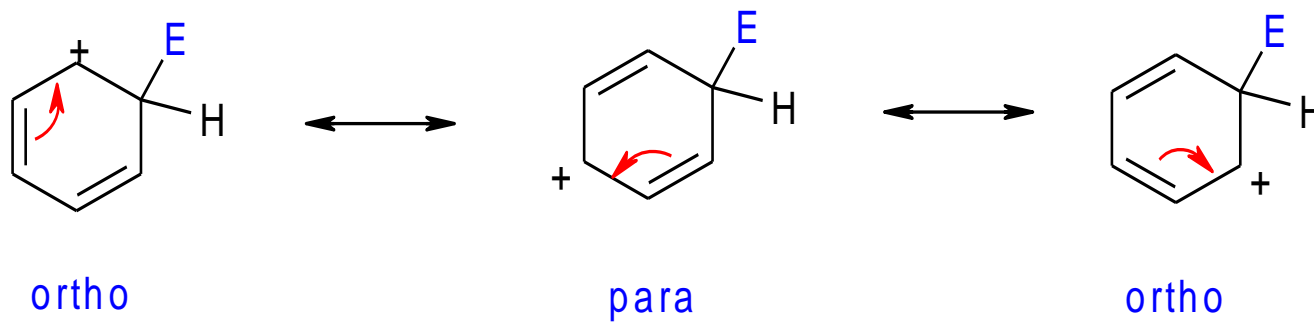


Mechanism of Electrophilic Aromatic Substitution (EArS)

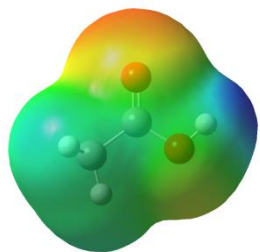
In general all EArS reactions proceed by the same mechanism:



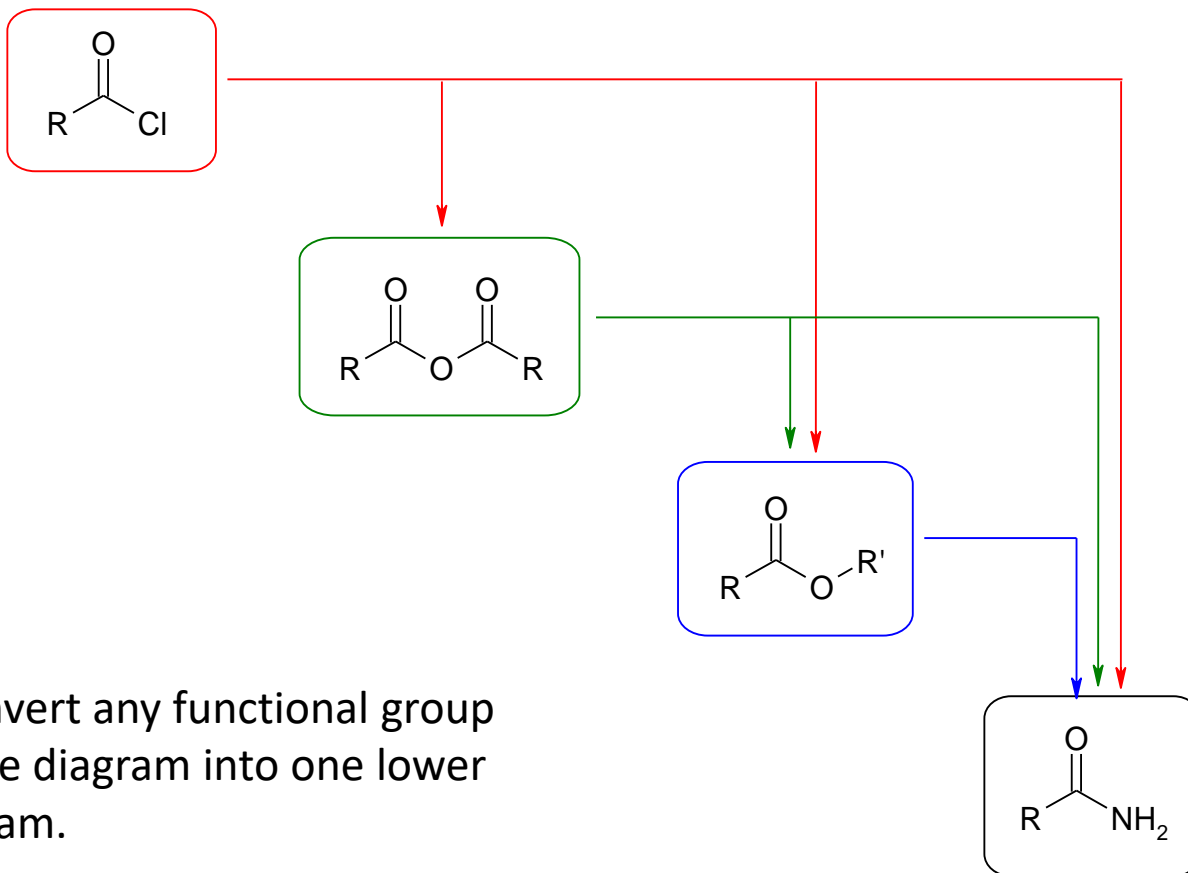
benzenonium ion
(a carbocation)



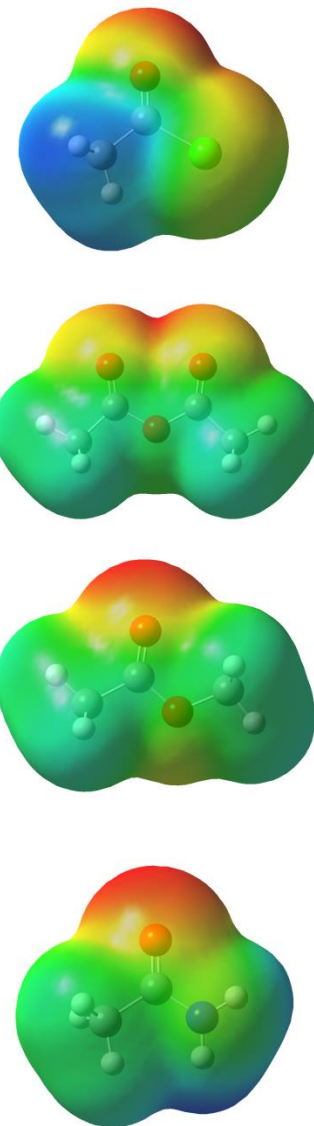
Benzenonium resonance structures



Relative Reactivities

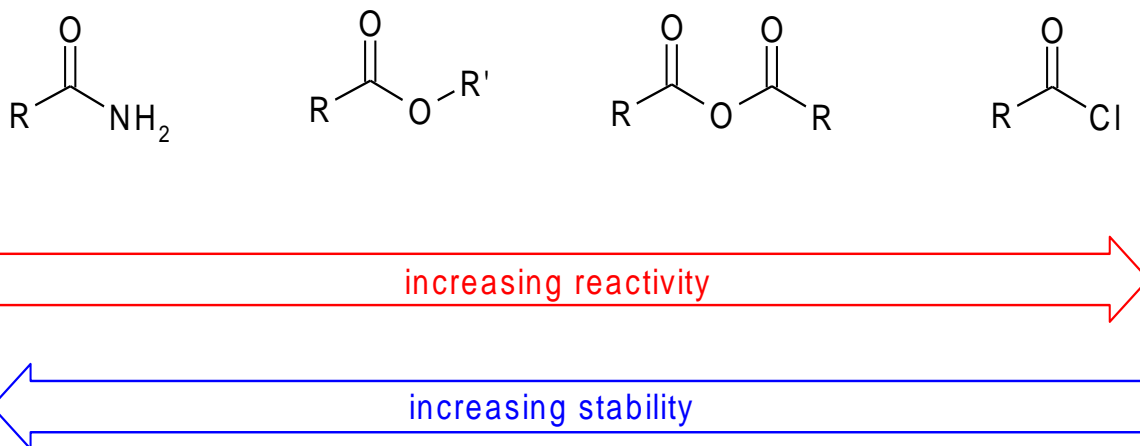


You can convert any functional group higher in the diagram into one lower in the diagram.



Nucleophilic Acyl Substitution

The reaction proceeds by a substitution since the acid / derivative has a leaving group in place of an H atom or alkyl group of the aldehyde or ketone, neither of which is a good leaving group. The relative reactivity of the derivatives depends on the leaving group ability, i.e.



Acid Derivatives

The -OH group of the acid has been replaced by another functional group.

All of the derivatives can be hydrolyzed back to the carboxylic acid.

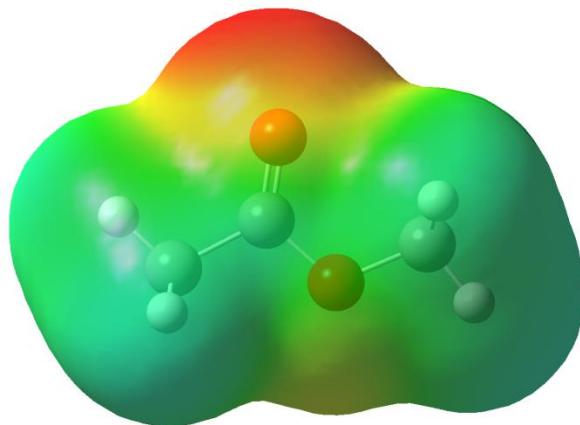
Types of derivatives:

1. *Esters*: $R-CO_2-R'$
2. *Acyl halides*: $R-CO-Cl$
3. *Anhydrides*: $R-CO_2CO-R$
4. *Amides*: $R-CO-NH_2$

Esters

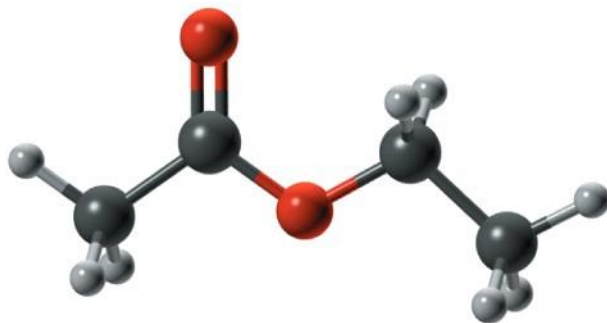
The -OH of an acid has been replaced by a $\text{-OR}'$ from an alcohol.

Very common compounds in nature and a wide variety are produced commercially.

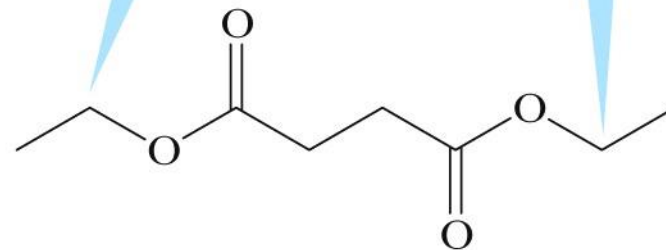


Esters

- The functional group of an ester is an acyl group bonded to -OR or -OAr.
 - Name the alkyl or aryl group bonded to oxygen followed by the name of the acid.
 - Change the suffix **-ic acid** to **-ate**.



Ethyl ethanoate
(Ethyl acetate)

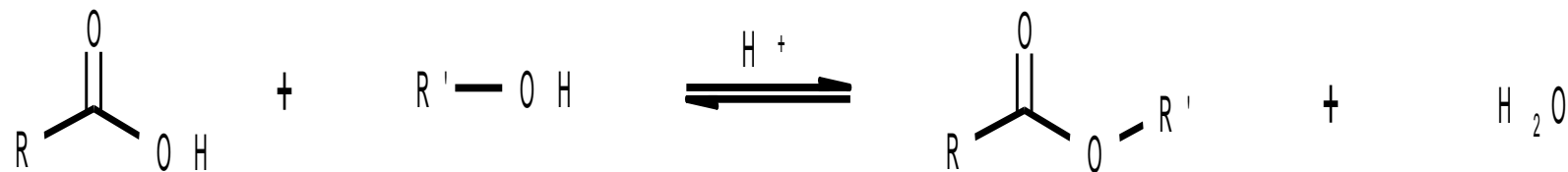


Diethyl butanedioate
(Diethyl succinate)

Preparation of Esters

The most common method is a “*Fisher esterification*”.

The general reaction is:

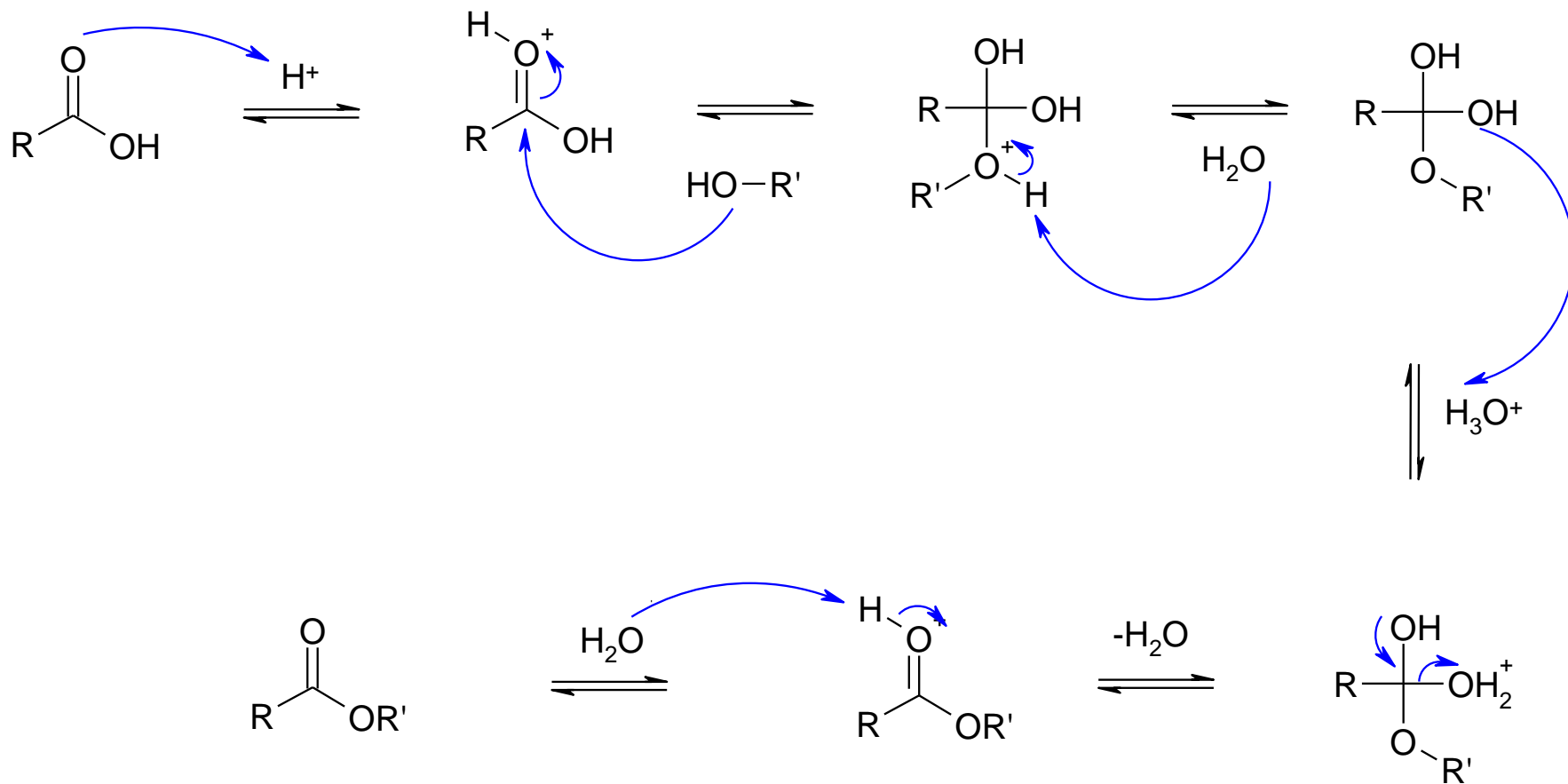


Note: you need an acid catalyst.

it is an equilibrium reaction, to drive it forward use excess alcohol or acid, or distill off the ester or water.

Preparation of Esters

The mechanism:



Preparation of Esters

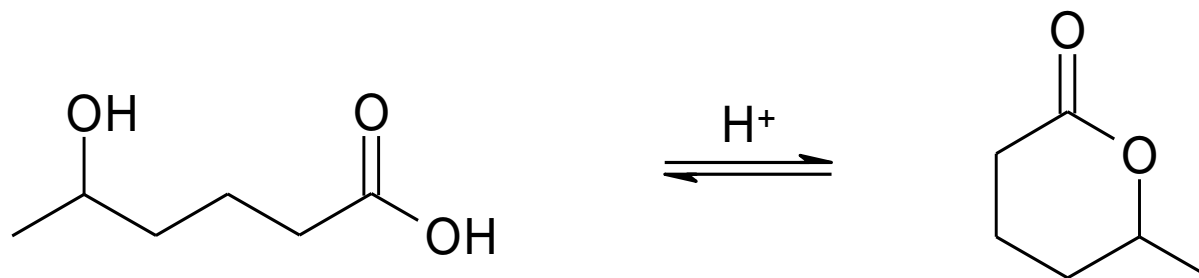
Note:

- i. Every step is reversible so the entire reaction is reversible
- ii. The $-OR'$ comes from the alcohol, i.e. it is a nucleophilic attack by the alcohol O atom on the carboxylate C atom (this is confirmed by radioisotopic labeling).
- iii. Substitution occurs rather than addition as we generate a very good leaving group, a water molecule.

Lactones

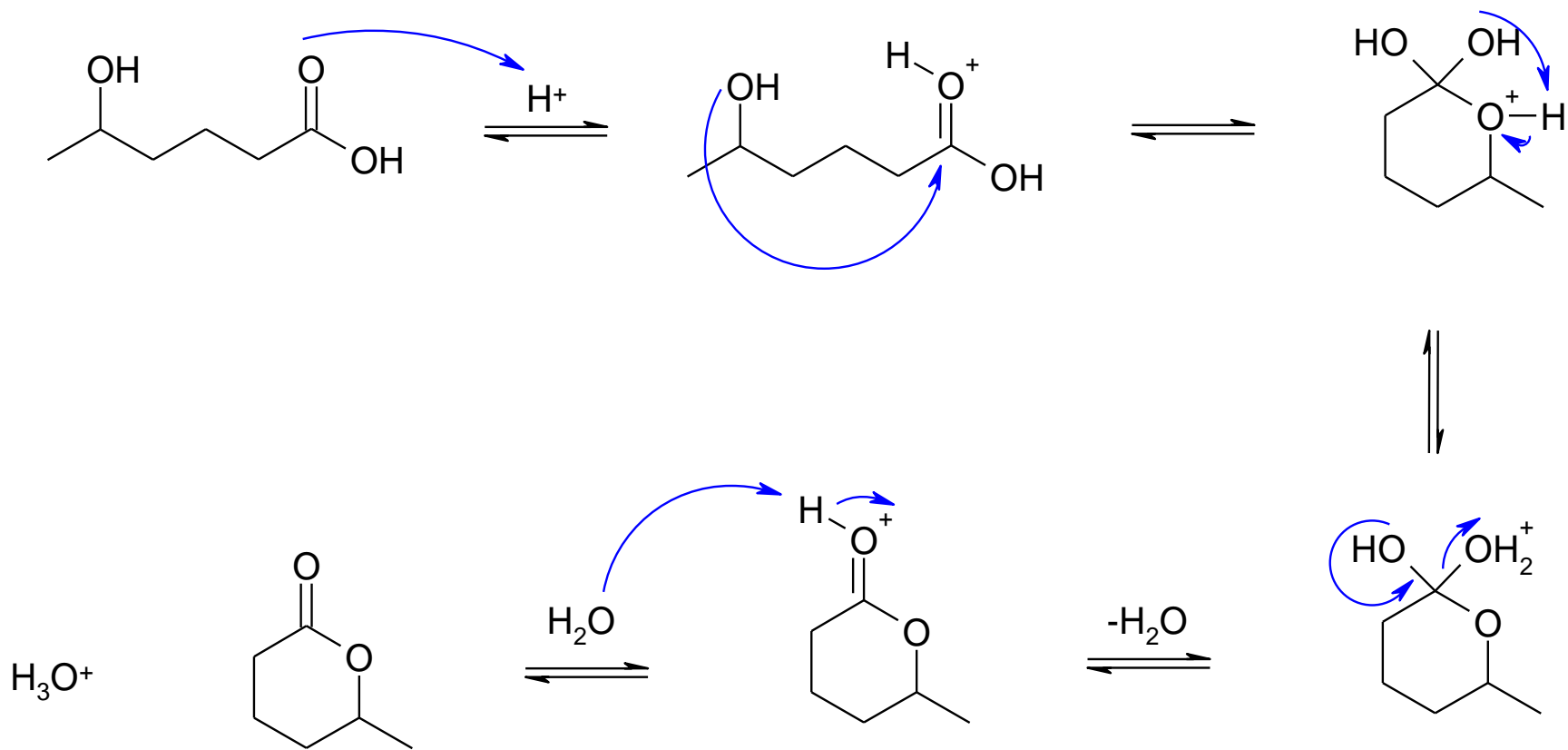
Lactones are cyclic esters made from γ or δ hydroxy acids.

Common reaction produces a 5 or 6 membered ring which are stable, i.e.



Lactones

Mechanism:



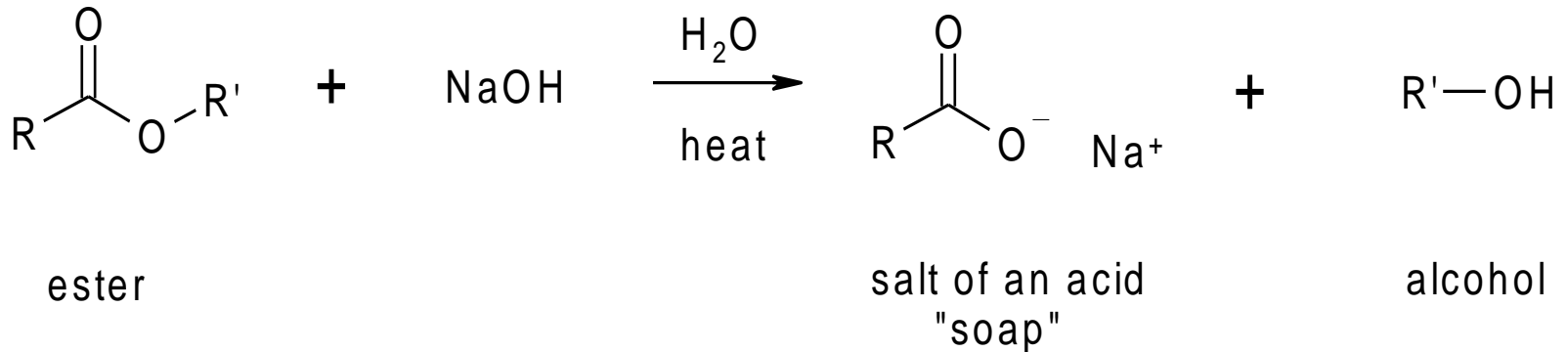
Saponification

Generally done on esters but acids work also.

Used to make soap (or in structure determination to remove the alcohol group).

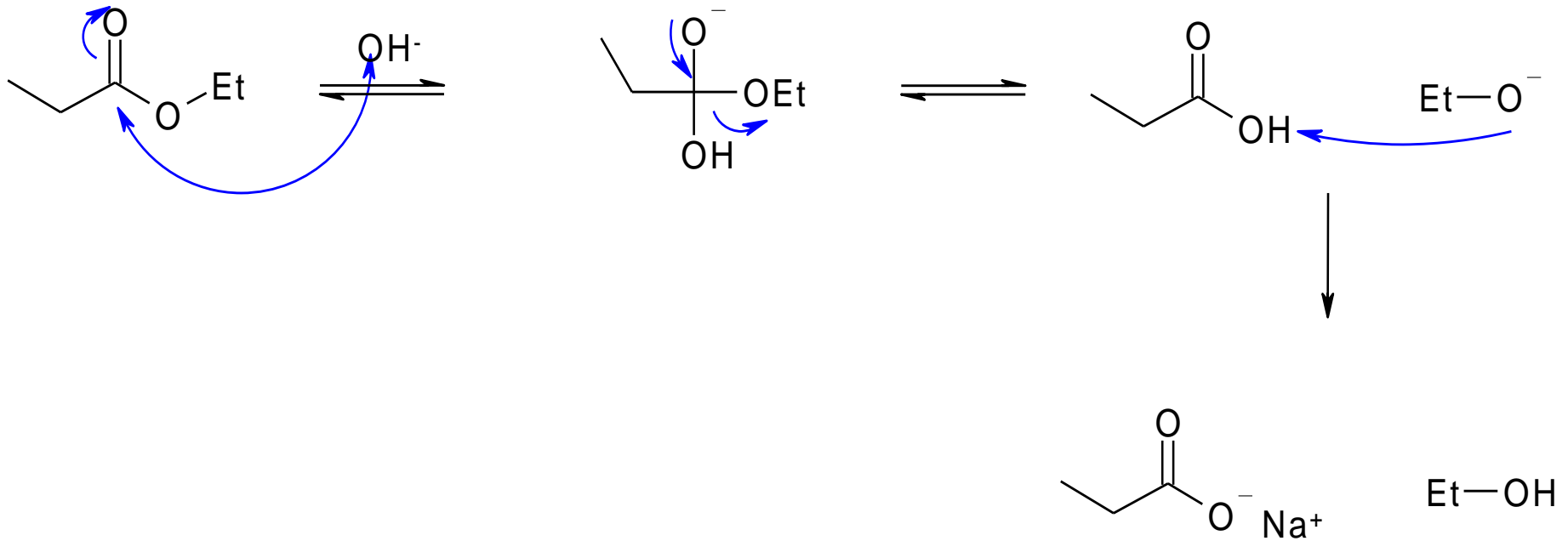
This is a *base hydrolysis* reaction

It is irreversible!



Saponification

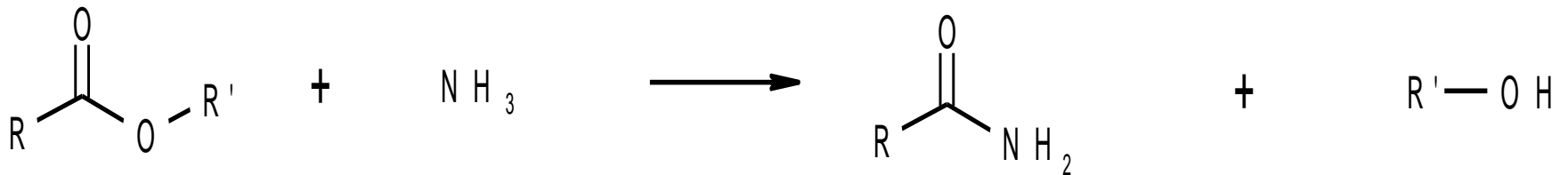
Mechanism:



Ammonolysis of Esters

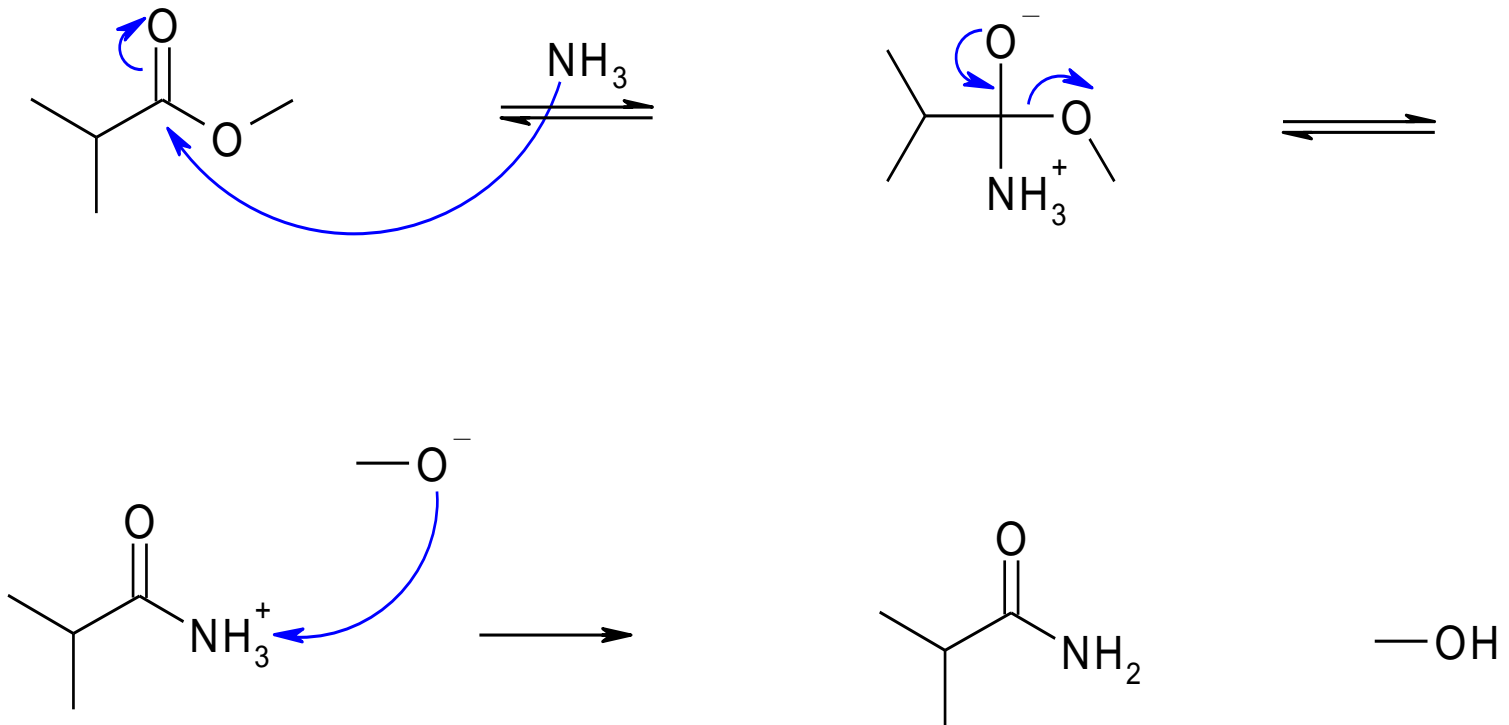
Used to make amides

Ammonia is the nucleophile, i.e.



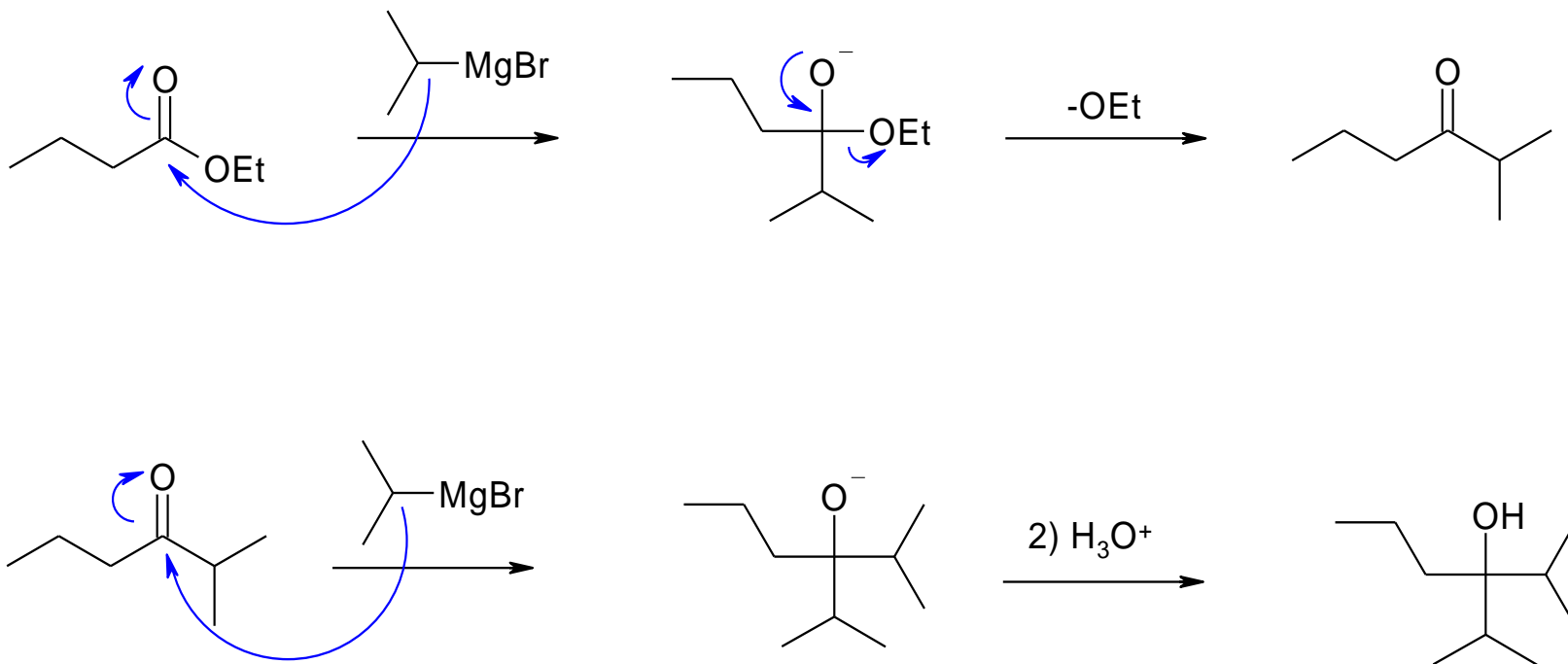
Ammonolysis of Esters

Mechanism:



Ester Reactions with Grignard Reagents

Esters will react with 2 equivalents of a Grignard reagent to produce a 3° alcohol, i.e.



Ester Reactions with Grignard Reagents

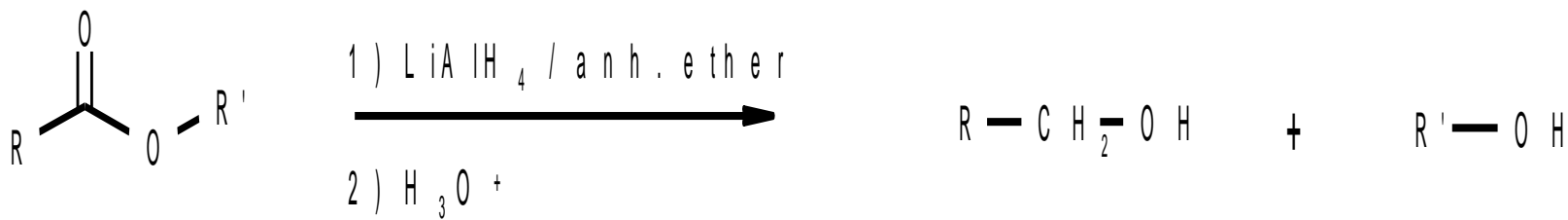
The second addition occurs since the ketone is still reactive to the Grignard reagent.

This is a good method to make 3° alcohol where two of the alkyl groups are the same.

Reduction of Esters

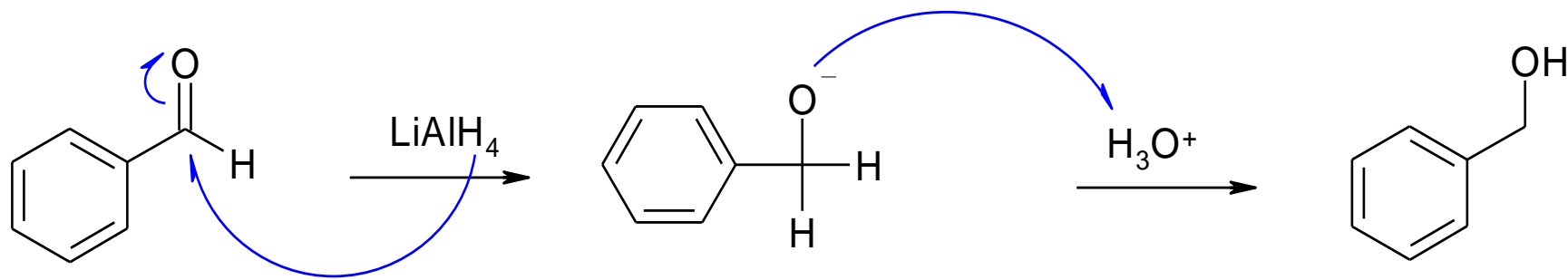
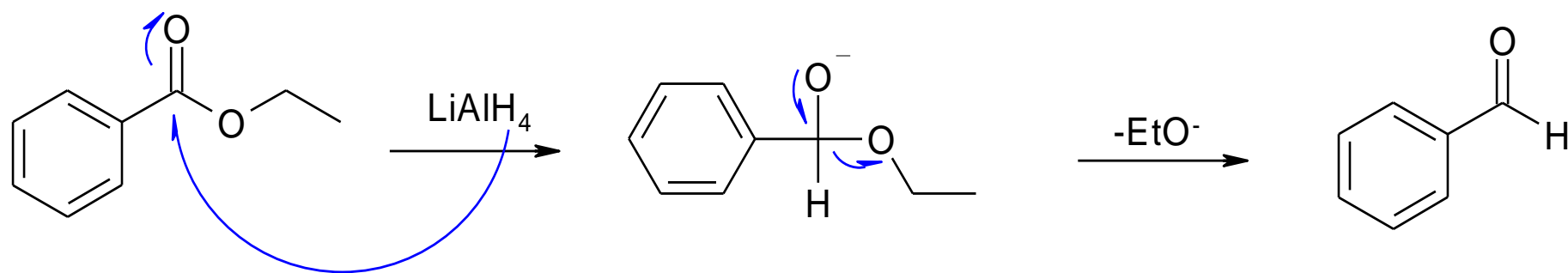
Product is a 1° alcohol.

Reagent: LiAlH_4 in anhydrous ether



Reduction of Esters

Mechanism:



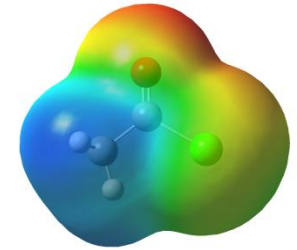
Reduction of Esters

Note:

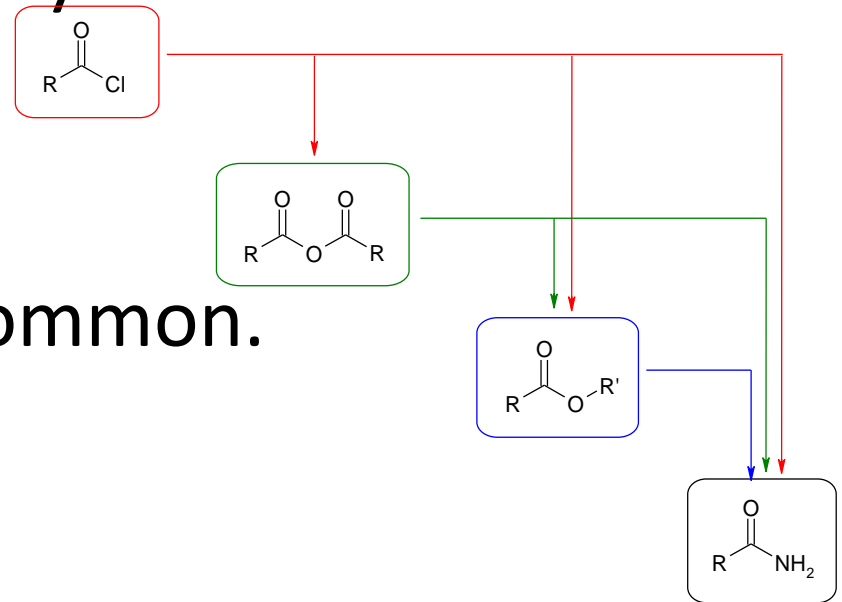
1. You can not isolate the aldehyde as it is still reactive to the LiAlH_4
2. LiAlH_4 does not reduce $\text{C}=\text{C}$ so you can selectively reduce an acyl group without reducing a $\text{C}=\text{C}$ π bond.
3. NaBH_4 is not strong enough to reduce acids or acid derivatives, this allows for the selective reduction of aldehyde or ketone groups.

Acyl Halides

More reactive than acids or esters.



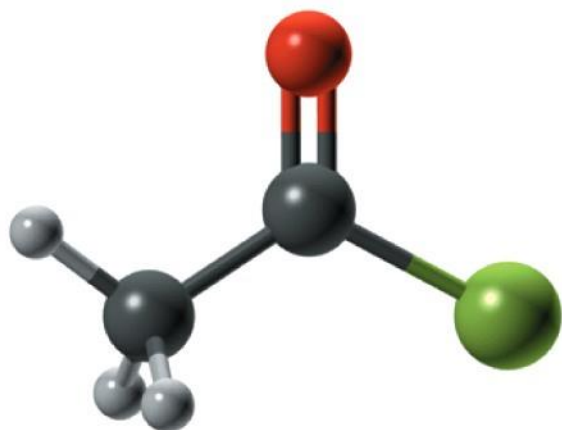
Man made compounds, they do not exist in nature.



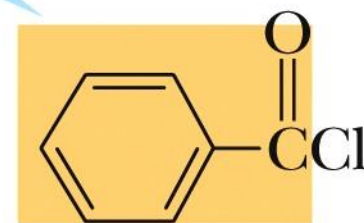
The chloride is the most common.

Acid Chlorides

- The functional group of an acid halide is an acyl group bonded to a halogen.
 - The most widely used are the acid chlorides.
 - To name, change the suffix **-ic acid** to **-yl chloride**.



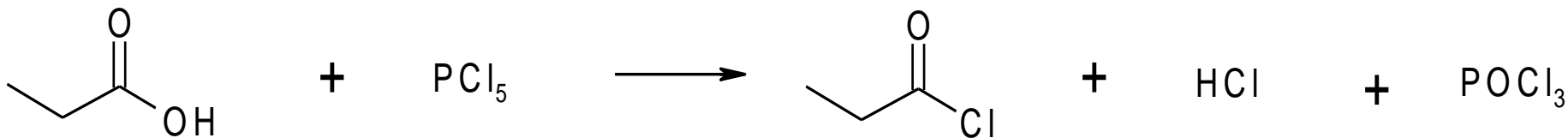
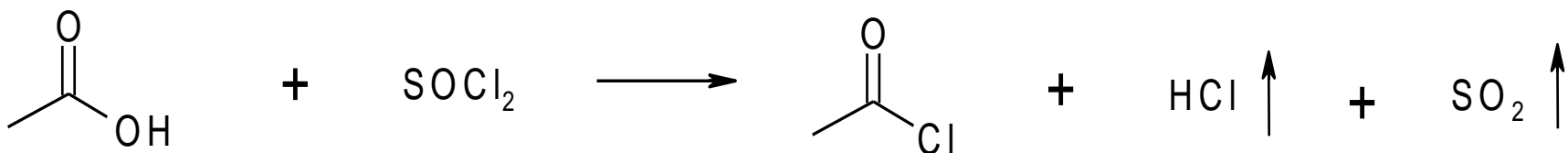
Ethanoyl chloride
(Acetyl chloride)



Benzoyl chloride

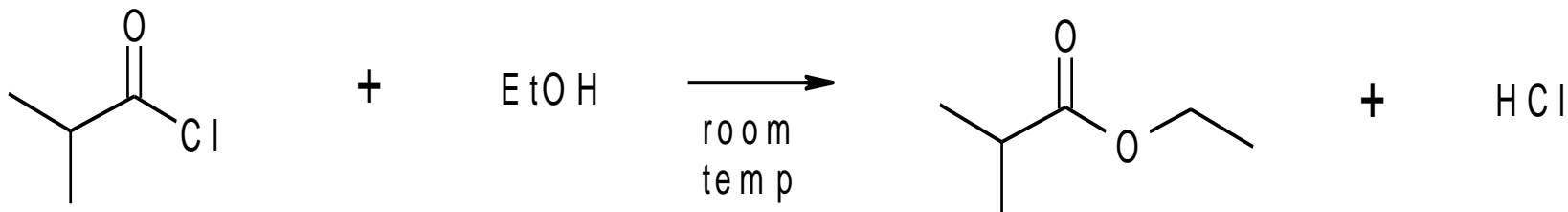
Acyl Halides: Preparation

Prepared from acids using thionyl chloride or phosphorus pentachloride, i.e.



Acyl Halides

Acyl halides are much more reactive than acids or esters, therefore reactions occur in milder conditions, don't normally need to heat or use acid catalysts.

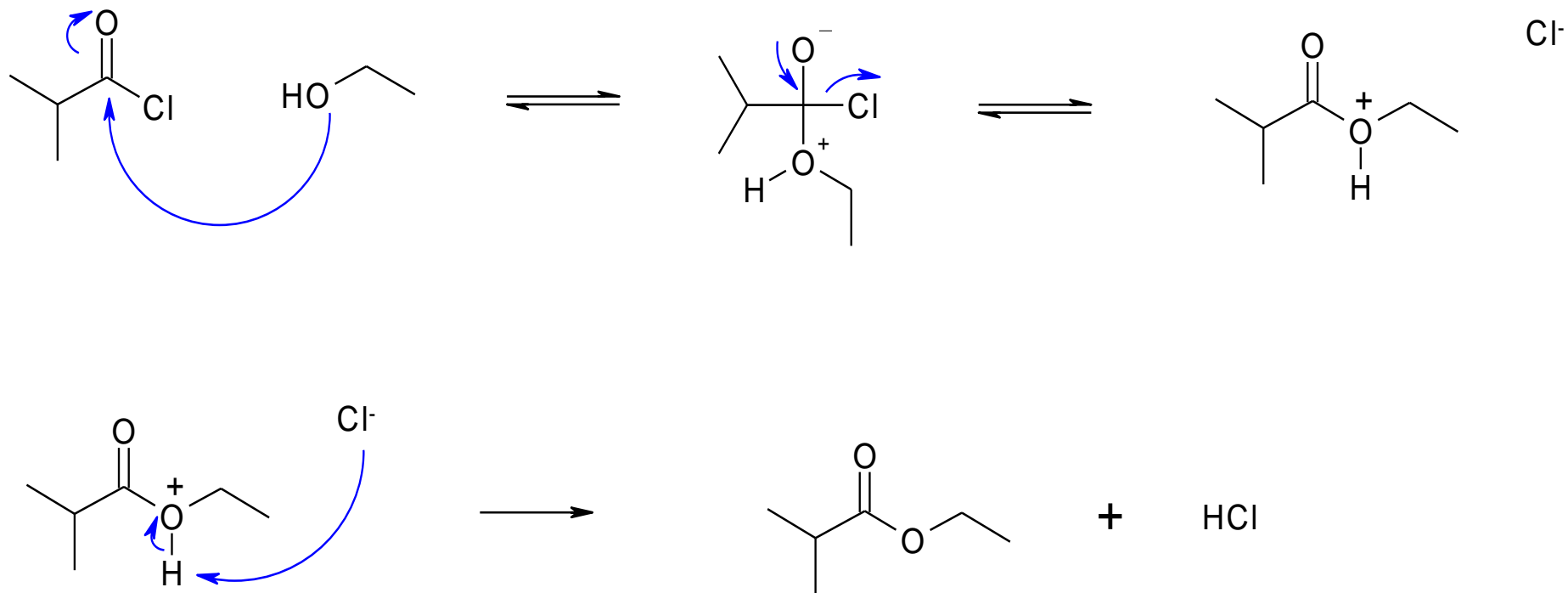


Better way to make esters, no catalyst needed, and a Fischer is an equilibrium.

Note: the HCl normally fumes and is an irritant.

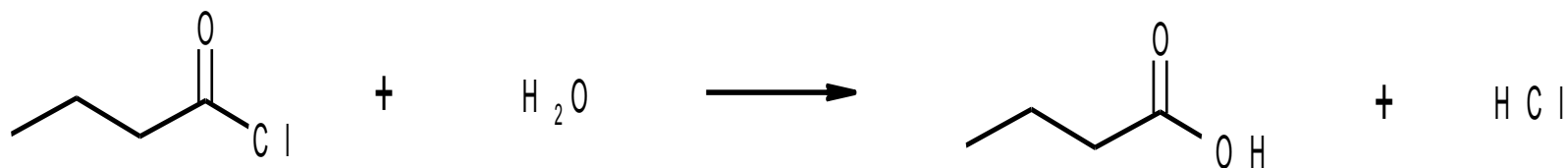
Acyl Halides

Mechanism:



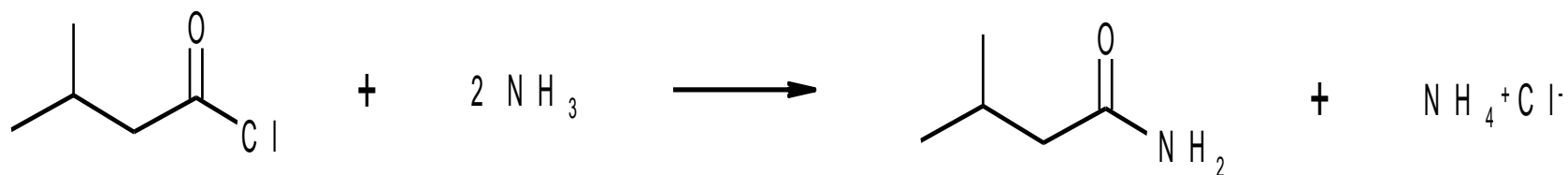
Acyl Halides

Hydrolysis will produce the acid, i.e.



Acyl Halides

Ammonolysis will produce the amide, i.e.

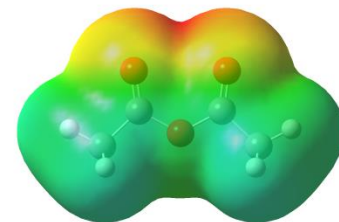


Need 2 equivalents of NH_3 , 1 makes the amide, the other neutralizes the HCl .

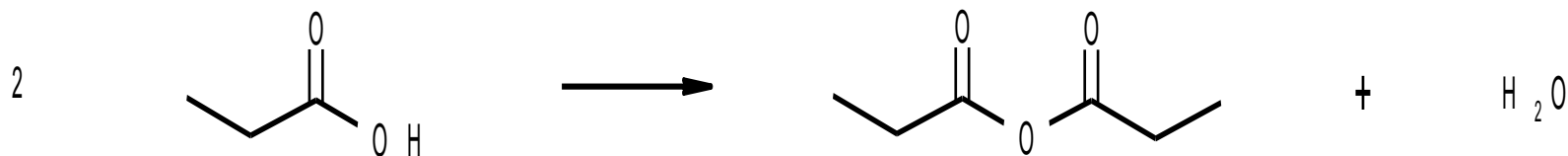
Acyl halides are also used in Friedel-Crafts acylation reactions.

Acid Anhydrides

Another more reactive form is the *anhydride*.

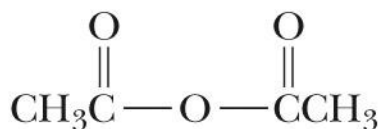


Made by reacting two acid molecules together with the loss of a water molecule, i.e.

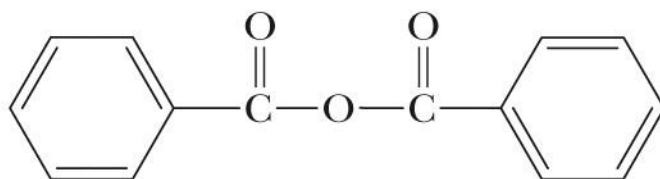


Acid Anhydrides

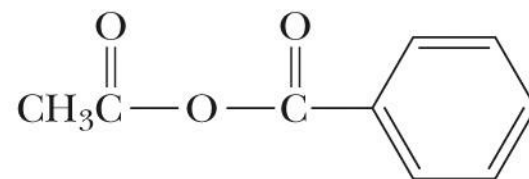
- The functional group of an acid anhydride is two acyl groups bonded to an oxygen atom.
 - Anhydrides may be symmetrical (two identical acyl groups) or mixed (two different acyl groups).
 - To name, replace **acid** of the parent acid by **anhydride**.



Acetic anhydride



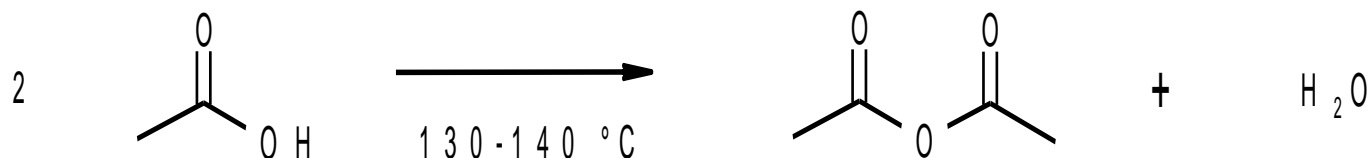
Benzoic anhydride



Acetic benzoic anhydride
(a mixed anhydride)

Acid Anhydrides: Preparation

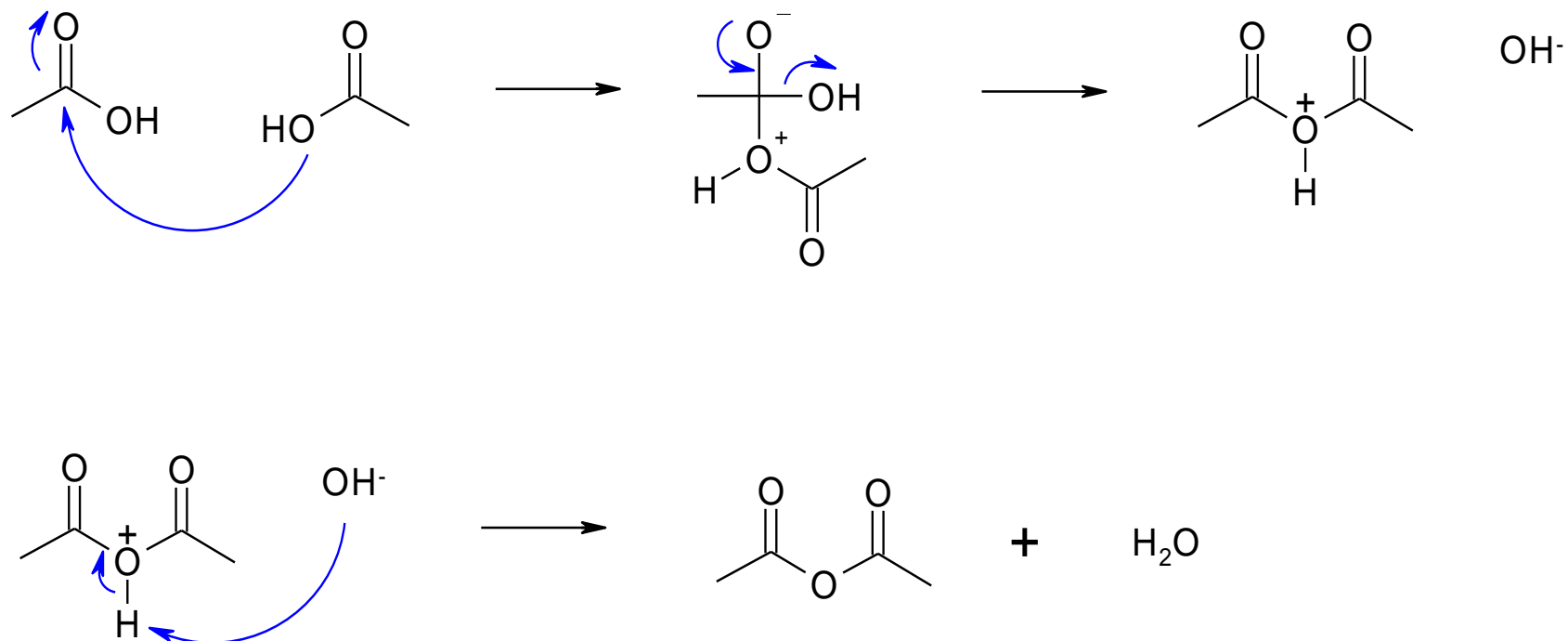
Anhydrides can be made by heating an acid, i.e.



The high temperature drives off the water and drives the reaction forward.

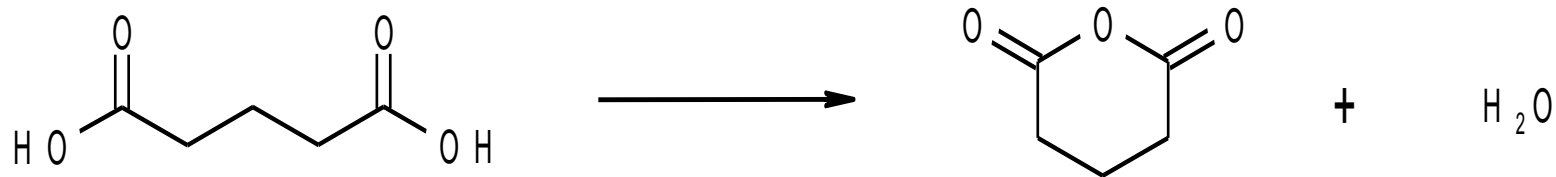
Acid Anhydrides: Preparation

Mechanism:



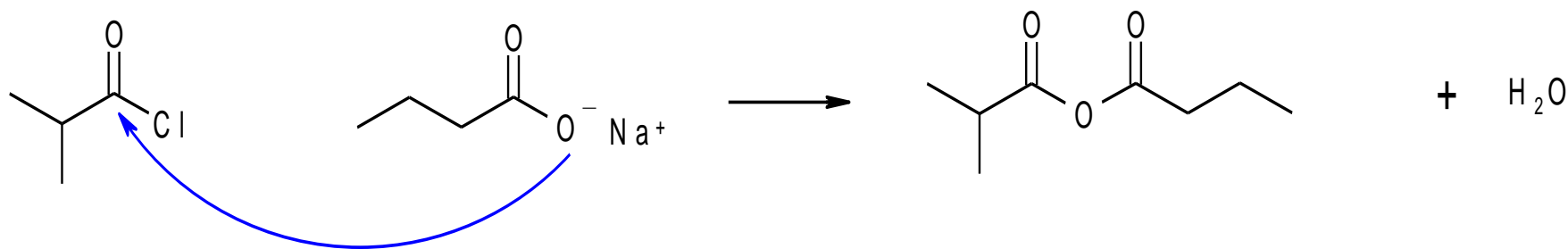
Acid Anhydrides: Preparation

Diacids form cyclic anhydrides, i.e.



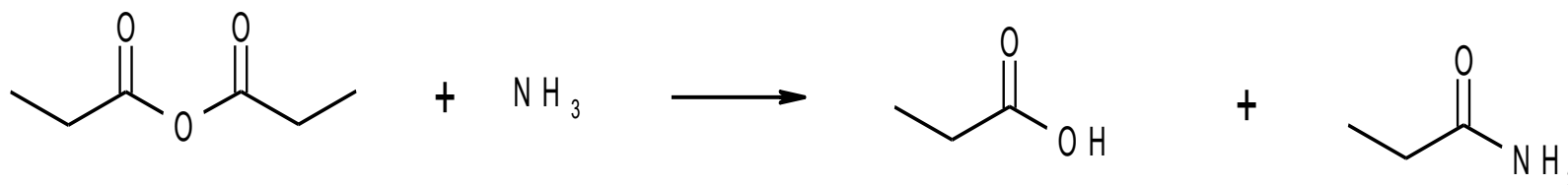
Acid Anhydrides: Preparation

Mixed anhydrides can be made, but you need to use an acyl halide and an acid (or salt) otherwise you get a mixture of products, this way only the acid (or salt) can act as the nucleophile, i.e.



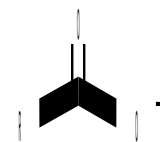
Acid Anhydrides

Anhydrides undergo nucleophilic acyl substitution and are more reactive than acids or esters, but not acyl halides, i.e.



Alcohol and water react the same way as ammonia.

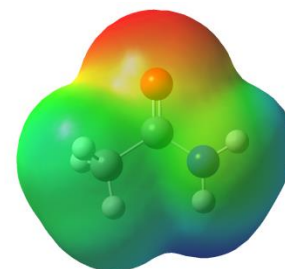
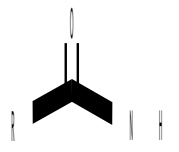
The “leaving group” is a carboxylate ion which will get protonated to form the acid.



Amides

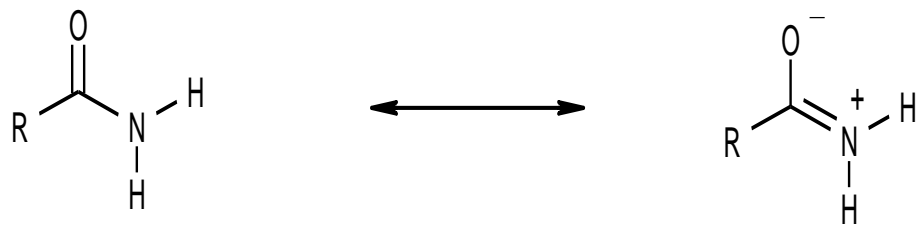
Amides are the least reactive of the acid derivatives.

1° amides: $\text{RCONH}_2 =$



Amides

The N atom in an amide is sp^2 hybridized (and planar). This allows the lone pair electrons on the amide N to interact with the carbonyl π system, i.e.



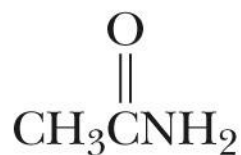
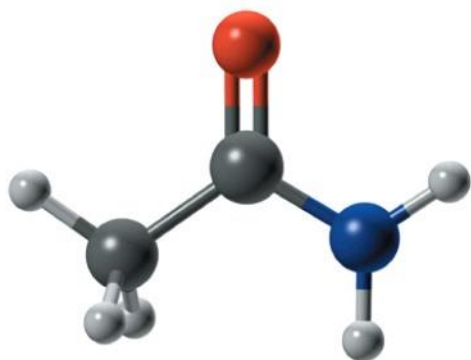
This means the amide bond is rigid to rotation the same as a $C=C$ π bond.

Amides

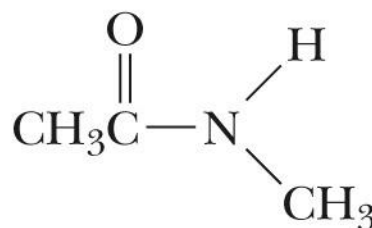
The amide group possess both a hydrogen bond donor and acceptors so form strongly H-bonded complexes similar to alcohols and acids. This means they are soluble in water and have high MP & BP for their size.

Amides

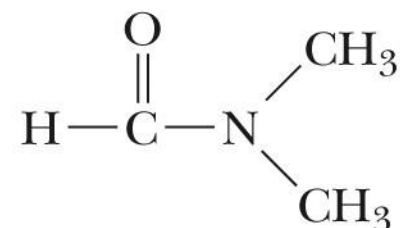
- The functional group of an amide is an acyl group bonded to a trivalent nitrogen.
 - IUPAC: drop **-ic acid** from the name of the parent acid and add **-amide**.
 - If the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by **N-**.



Acetamide
(a 1° amide)



N-Methylacetamide
(a 2° amide)



N,N-Dimethylformamide (DMF)
(a 3° amide)

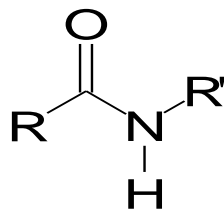
Amides: Preparation

1° amides can be prepared by: reacting NH_3 with esters, acyl halides or anhydrides. They can also be prepared from acids but require heating, i.e.

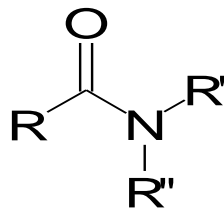


Amides:

2° amides have one H atom replaced by an alkyl group



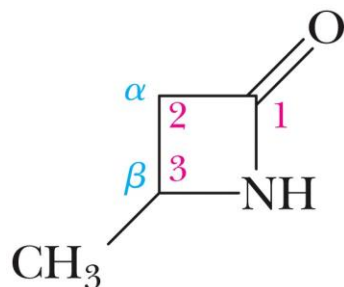
3° amides have both H atom replaced by alkyl groups



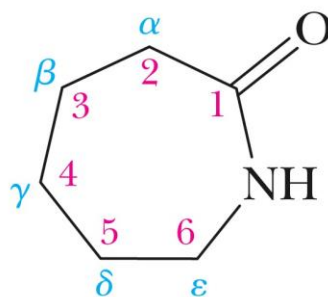
Note: no longer has a H-bond donor

Lactam

- **Lactam**: a cyclic amide.
 - Name the parent carboxylic acid, drop the suffix -ic acid and add **-lactam**.
 - The location of the nitrogen atom in the ring is commonly indicated by a Greek letter, α , β , etc.



3-Butanolactam
(A β -lactam)

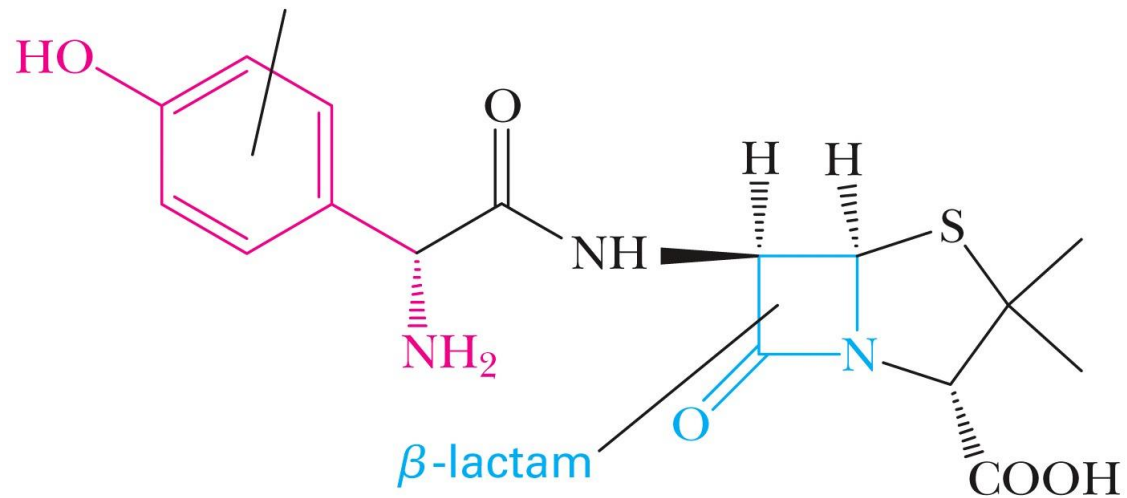


6-Hexanolactam
(An ϵ -lactam)

The Penicillins

- The penicillins are a family of β -lactam antibiotics.
 - The structural feature common to all penicillins is a β -lactam ring fused to a five-membered ring containing one S atom and one N atom.

The penicillins differ in the group bonded to the carbonyl carbon



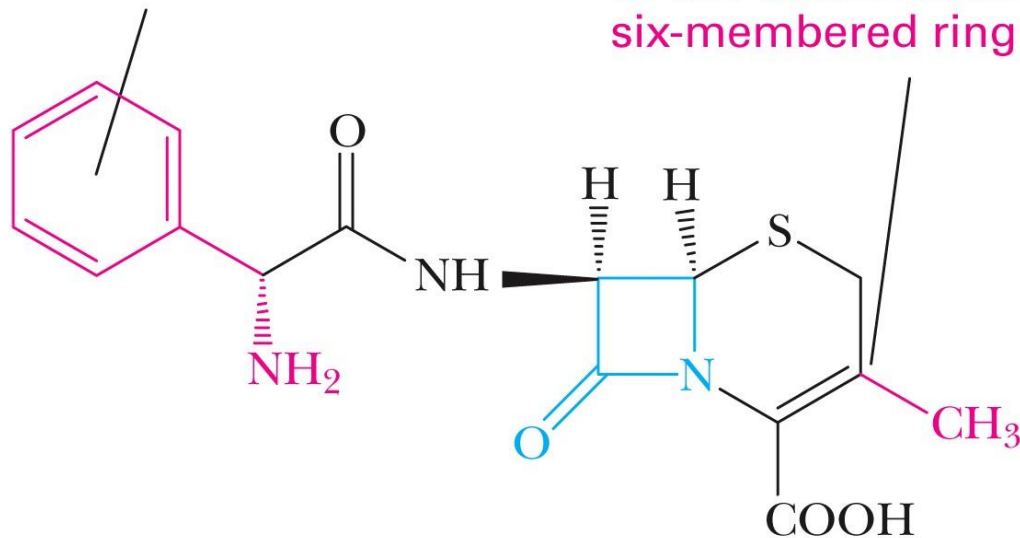
Amoxicillin
(a β -lactam antibiotic)

Cephalosporins

- The cephalosporins are also β -lactam antibiotics.

The cephalosporins differ in the group bonded to the carbonyl carbon...

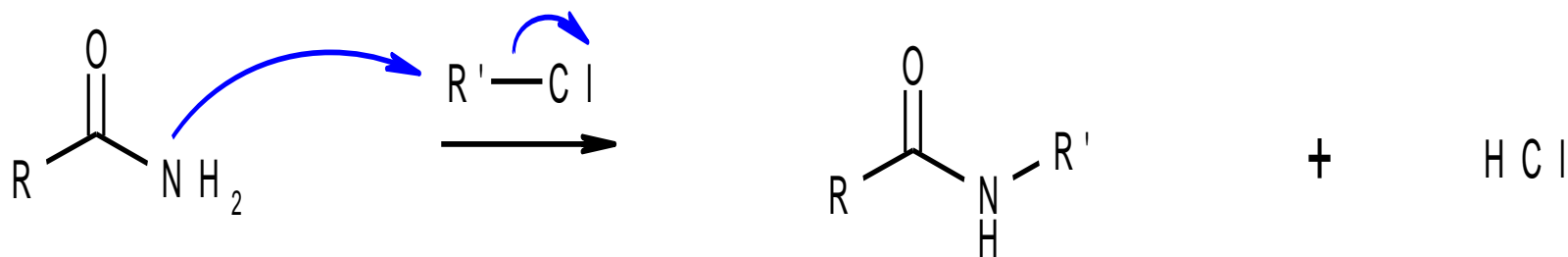
...and the group bonded to this carbon of the six-membered ring



Keflex
(a β -lactam antibiotic)

Amides: Preparation

The N atom is weakly nucleophilic due to the lone pair electrons, but less than expected as they are conjugated to the carbonyl group. 2° amides can be prepared by reacting a 1° amide with an alkyl halide, i.e.

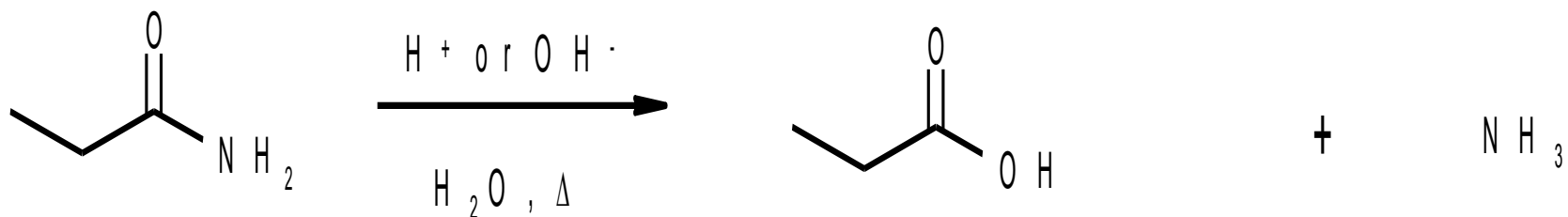


This is an S_N type reaction on the alkyl halide.

The initial product can react again to produce a 3° amide.

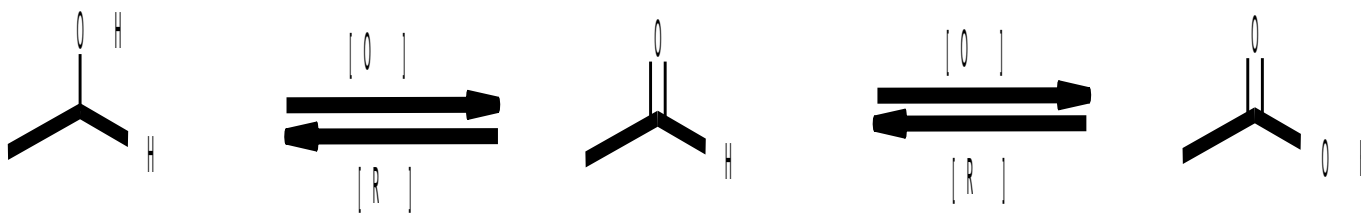
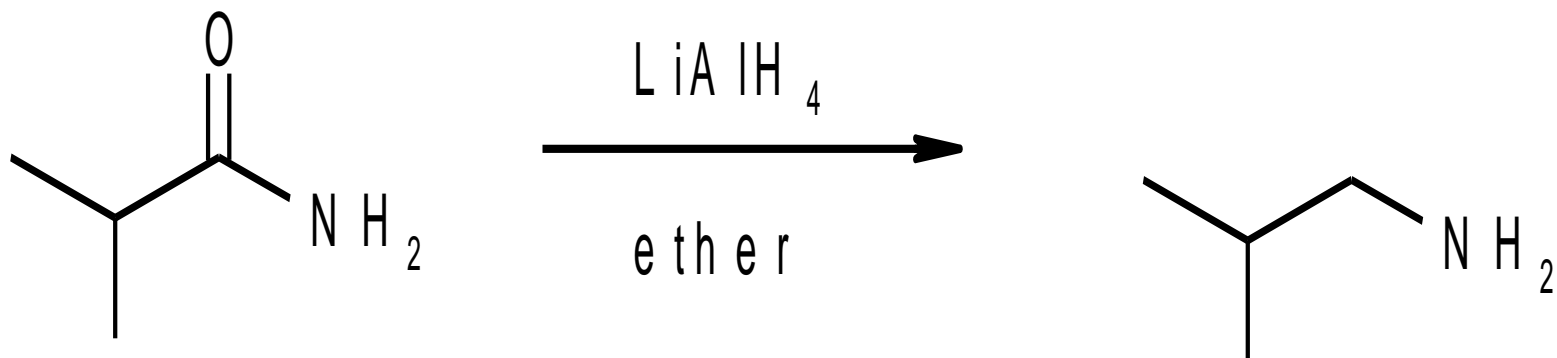
Amides: Hydrolysis

Hydrolysis of an amide leads back to a carboxylic acid.
Requires the use of an acid or base catalyst, i.e.



Amides: Reduction

Reduction of an amide leads to 1° amines, i.e.



α -Hydrogen of Esters

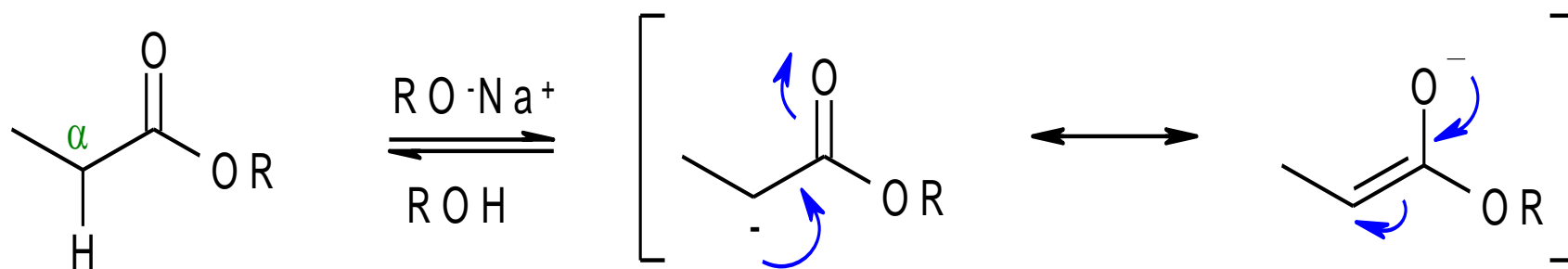
Similar to aldehydes and ketones, the α -H atoms of esters and other acid derivatives are weakly acidic and can be removed by strong bases such as alkoxides.

The products are β -ketoesters.

Note: the reaction will not work with an acid as the base will react with the more acidic acid proton not the α -H atom.

α -Hydrogen of Esters

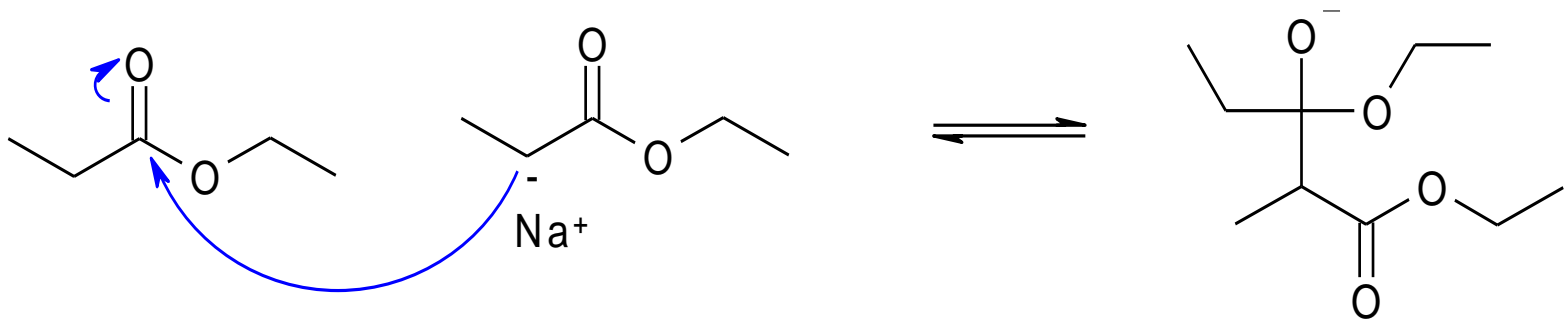
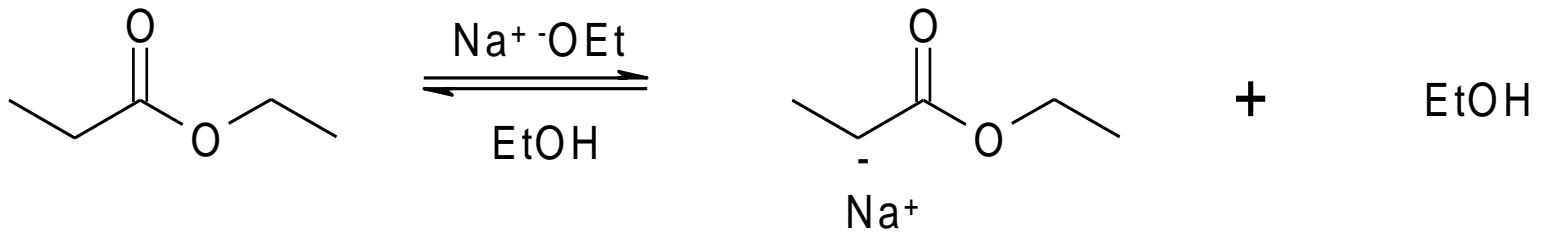
The removal of the α -H produces an ester enolate, i.e.



The resulting enolate is nucleophilic!

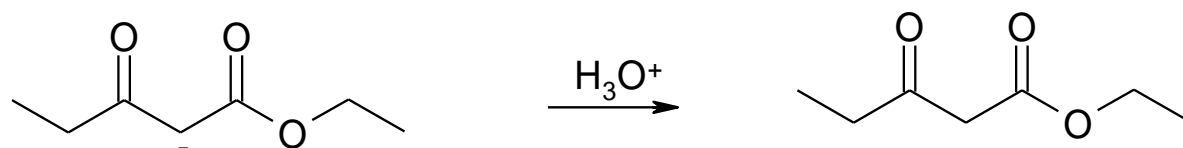
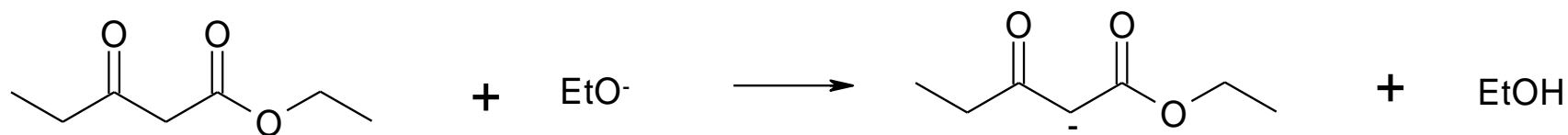
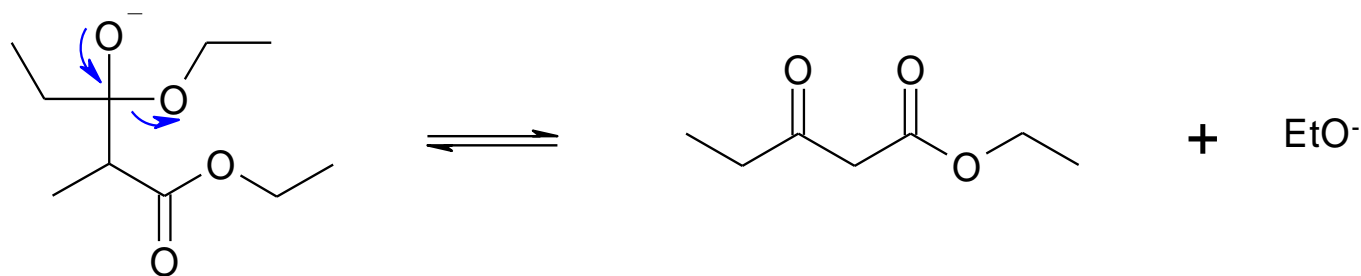
The Claisen Reaction

The *Claisen reaction* makes use of the acidic α -H to produce a β -keto ester, i.e.



The Claisen Reaction

The Claisen reaction continued

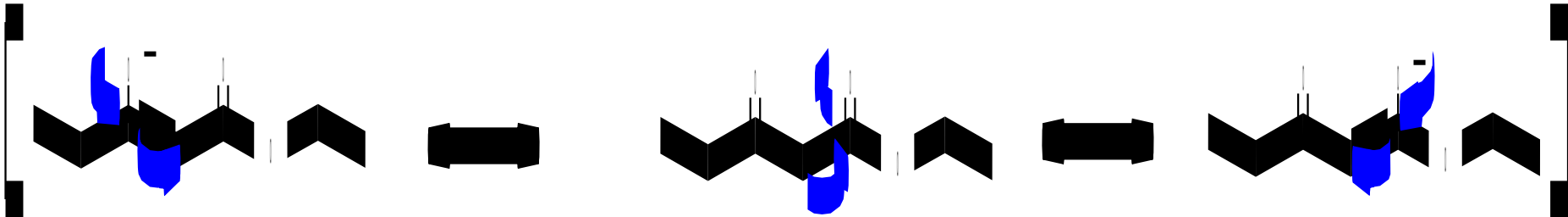


The Claisen Reaction

Overall reaction:



Note: the product is very reactive to the base and can form an enoate easily, i.e.



The Claisen Reaction

The acid is required to destroy any remaining alkoxide and proton the β -keto enolate.

The two carbonyl groups are not equivalent, the ketone is more reactive than the ester and can be reduced selectively with NaBH_4 and will react first to a nucleophile.

The Claisen Reaction

i.e.

