

Carboxylic Acids

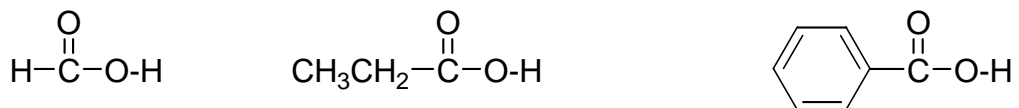
When a carbonyl carbon also bears a hydroxyl group, then these compounds are appreciably acidic, and are called carboxylic acids.



Carboxylic acids are classified according to the substituent that is bonded to the carboxyl carbon:

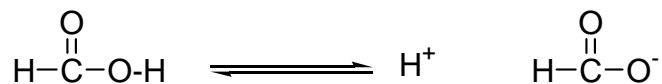
Aliphatic acids have an alkyl group bound to the carboxyl group.

An aromatic acid has an aryl group bound to the carboxyl group.



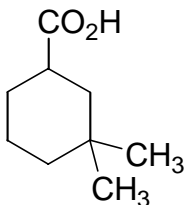
The simplest acid is formic acid.

A carboxylic acid donates protons by the heterolytic cleavage of the O-H bond, generating a carboxylate ion.



Cycloalkanes with carboxyl substituents are named as cycloalkanecarboxylic acids.

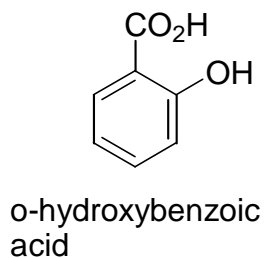
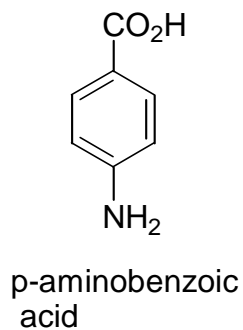
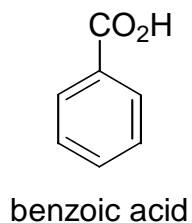
E.g.



3,3-dimethylcyclohexanecarboxylic acid

(Notice that $-\text{CO}_2\text{H}$ as a substituent makes the carbon it is **bound** to C-1, not itself).

Aromatic acids of the form $\text{Ar}-\text{CO}_2\text{H}$ are named as derivatives of benzoic acids, with ortho, meta and para indicating the location relative to the carboxyl group.



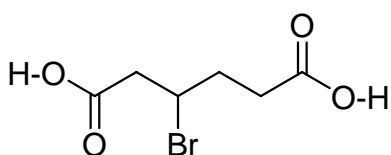
Dicarboxylic Acids

Aliphatic dicarboxylic acids are named by simply adding the suffix -dioic acid to the root name.

The root name comes from the longest carbon chain containing both carboxyl groups.

Numbering starts at the end closest to a substituent.

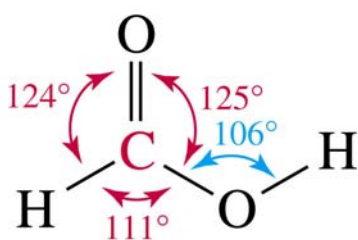
E.g.



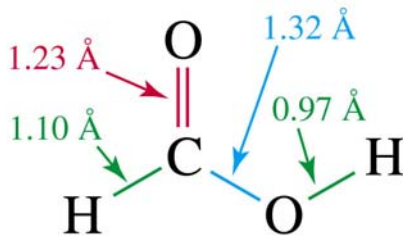
3-bromohexanedioic acid

Structure of the Carboxyl Group

The most stable conformation of formic acid is an almost planar arrangement of the molecule.



bond angles

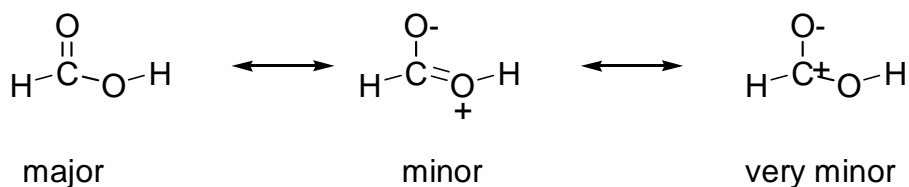


bond lengths

The carbon is sp^2 hybridized, and the O-H bond lies in the plane described by the sp^2 carbon, eclipsing the C=O double bond.

This unexpected geometric arrangement can be explained by resonance (or conjugation).

Three resonance forms can be written for formic acid.



The second structure requires the C-O-H bonds to be co-planar.

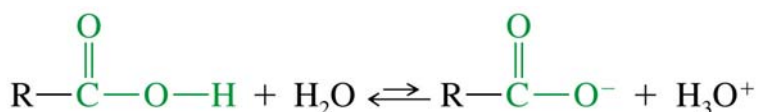
One of the unshared lone pairs of oxygen is delocalized into the electrophilic π system of the carbonyl group.

(One of the lone pairs on the hydroxyl oxygen is conjugated with the C=O double bond).

Acidity

Carboxylic acids can dissociate in aqueous solution into carboxylate ions and protons.

The equilibrium constant for this process is K_a , and more frequently we talk in terms of pK_a .



$$K_a = \frac{[\text{R}-\text{CO}_2^-][\text{H}_3\text{O}^+]}{[\text{R}-\text{CO}_2\text{H}]}$$

$$pK_a = -\log_{10} K_a$$

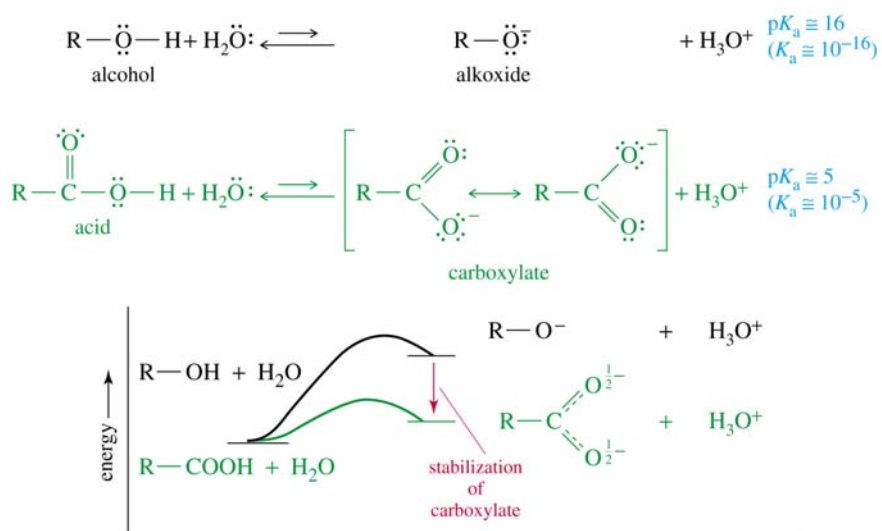
Values of pK_a for common alkyl carboxylic acids are around 5 ($K_a \sim 10^{-5}$).

Table 20-3 (SLIDE)

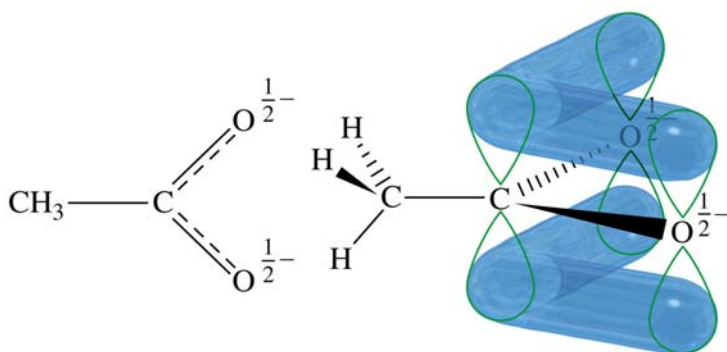
E.g. ethanoic acid has $pK_a = 4.74$, (alcohols have $pK_a \sim 18$, so carboxylic acids are about 10^{13} times more acidic than alcohols).

The reason why carboxylic acids are much more acidic than alcohols is because the carboxylate anion is much more stable than the alkoxide anion.

Both alcohols and carboxylic acids are acidic since their respective O-H bonds can be broken heterolytically, giving a proton and an oxygen anion.



The difference lies in the fact that the carboxylate anion has the negative charge spread out over two oxygen atoms, whereas the alcohol has the negative charge localized on a single oxygen atom.

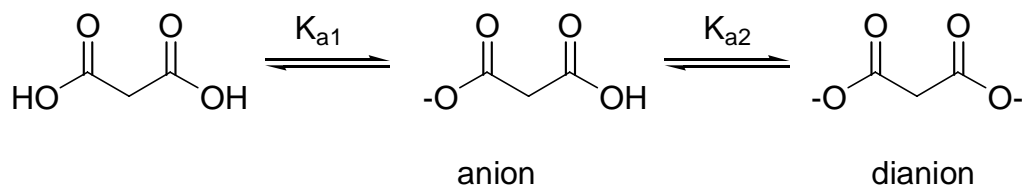


The carboxylate anion can be viewed as a resonance hybrid of the two anionic structures, or as a conjugated system of three interacting p orbitals containing four electrons (like the allylic anion system).

The C and two oxygens are all sp^2 hybridized, and the remaining p orbitals create the π MO system giving rise to the half π bond between each C and O, and the half negative charge on the end oxygens.

Dicarboxylic Acids

These have two dissociation constants, since they can lose two protons.



$$K_{a1} = 1.4 \times 10^{-3}$$
$$K_{a2} = 2.0 \times 10^{-6}$$

K_{a1} for the first dissociation and K_{a2} for the second dissociation, which generates a dianion.

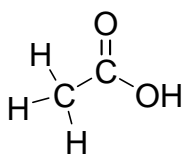
K_{a2} is always less than K_{a1} (the second carboxyl group is less acidic) since it takes extra energy to overcome the second negative charge being so close to the first negative charge.

Substituent Effects on Acidity

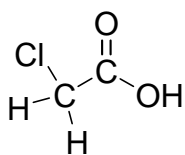
Any substituent that stabilizes a negative charge is going to enhance the dissociation process, and therefore result in a stronger acid.

Thus electronegative elements can enhance the acid strength, through inductive effects.

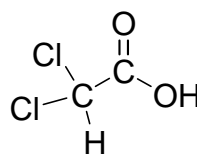
E.g.



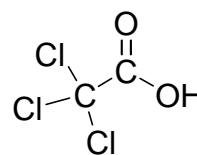
$pK_a = 4.74$



2.86

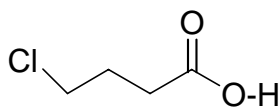


1.26

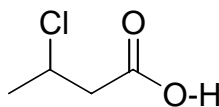


0.64

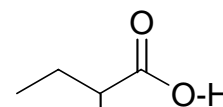
The closer the substituent to the anion, the more profound the effect.



$pK_a = 4.52$



4.05



2.86

Salts of carboxylic Acids

Strong bases can completely deprotonate carboxylic acids, thus salts of carboxylic acids are formed.

E.g.



Syntheses of Carboxylic Acids

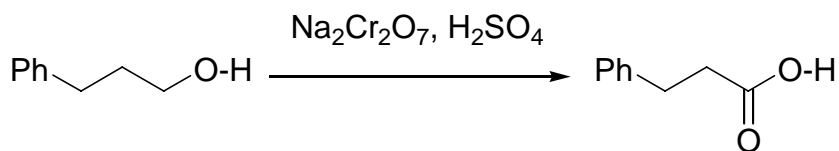
The previously seen syntheses (three) all involved oxidation:

- (a) oxidation of primary alcohols and aldehydes
- (b) oxidative cleavage of alkenes and alkynes
- (c) side chain oxidation of alkyl benzenes

Oxidation of Primary Alcohols and Aldehydes

These oxidations are best performed using chromic acid (made from $\text{Na}_2\text{Cr}_2\text{O}_7$ and H_2SO_4). Potassium permanganate can be used but gives lower yields.

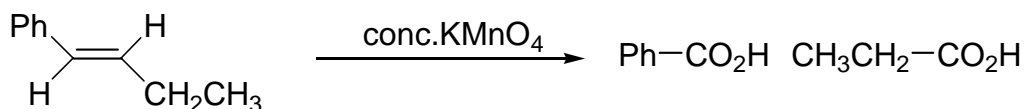
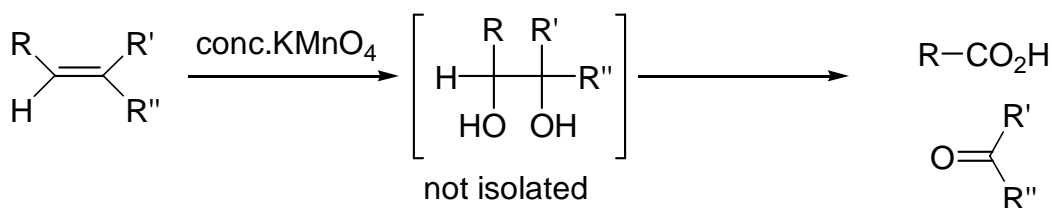
E.g.



Cleavage of Alkenes and Alkynes

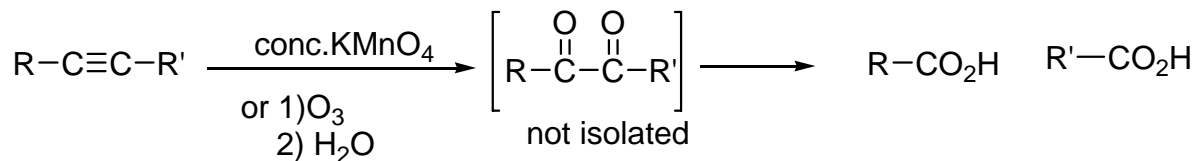
Alkenes react with concentrated KMnO_4 to produce intermediate glycols which react further to produce either carboxylic acids or ketones (depending on the original alkene substituents).

E.g.



Alkynes also react with conc. KMnO_4 to give carboxylic acids, and the same transformation can be achieved by the use of ozonolysis.

E.g.

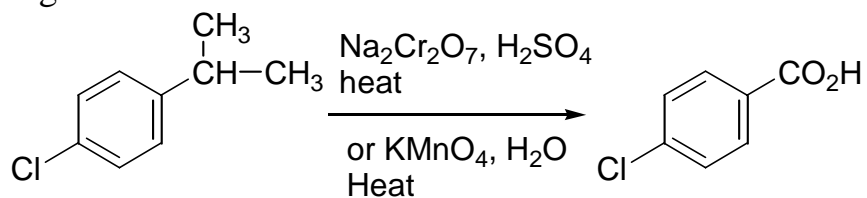


Alkylbenzenes

Benzoic acid derivatives can be made by the oxidation of alkylbenzenes with either hot KMnO_4 or hot chromic acid.

The vigorous conditions means this can only be used when there are no oxidizable groups present in the molecule.

E.g.



New methods

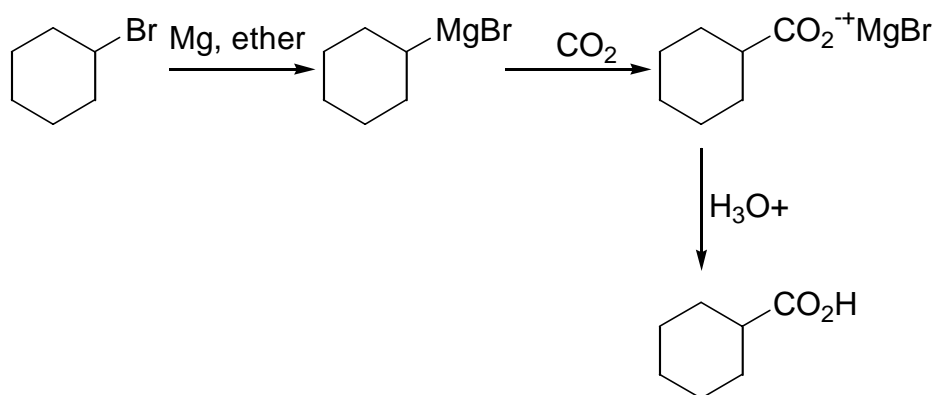
Carboxylation of Grignard Reagents

Grignard reagents can react as nucleophiles and attack carbon dioxide.

This results in magnesium salts of carboxylic acids, and treatment with dilute acid produces a carboxylic acid.

The overall transformation is from alkyl halide to a carboxylic acid with an extra carbon atom.

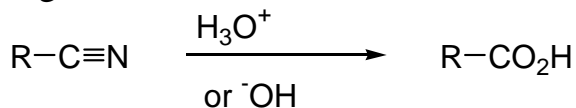
E.g.



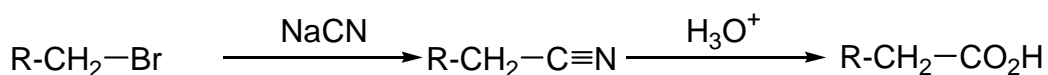
Formation and Hydrolysis of Nitriles

Nitriles can be hydrolyzed by dilute acid to generate carboxylic acids.

E.g.



Nitriles are easily made by the action of cyanide ion as a nucleophile on alkyl halides (or tosylates).

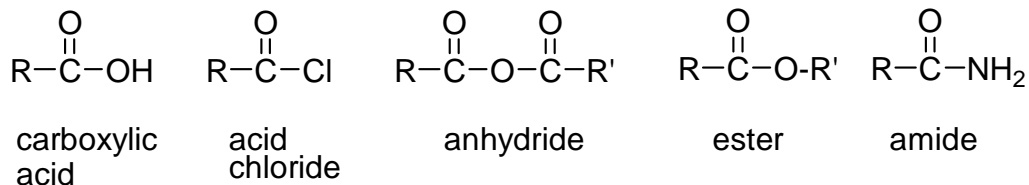


Again the overall transformation is from alkyl halide to a carboxylic acid with an extra carbon atom.

Reactions of Carboxylic Acids (and Derivatives)

Ketones and aldehydes have a carbonyl group and undergo nucleophilic addition, whereas carboxylic acids (and their derivatives) undergo nucleophilic acyl substitution - this is where one nucleophile replaces another on the acyl carbon.

E.g.



Carboxylic acid derivatives differ in the nature of the group bound to the acyl group.

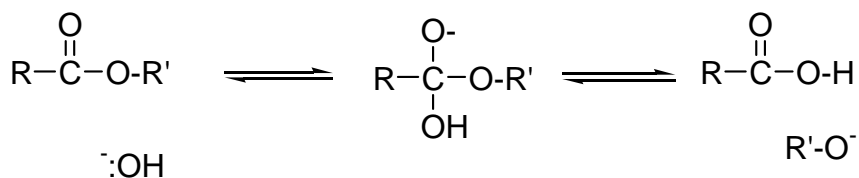
- OH is an acid
- Cl is the acid chloride
- OCOR' is the anhydride
- OR' is the ester
- NR₂ is the amide

Nucleophilic acyl substitution can interconvert all of these different acid derivatives.

The mechanism for nucleophilic acyl substitution varies depending if it occurs under acidic or basic conditions (similar to acid and base varieties of nucleophilic attack on aldehydes/ketones).

Under basic conditions, a strong nucleophile can attack the carbonyl carbon, thus generating a tetrahedral intermediate.

This intermediate can then expel its leaving group.



E.g. the above ester hydrolysis to a carboxylic acid.

Under acidic conditions, the carbonyl group becomes protonated, and thus activated toward nucleophilic acyl substitution.

Attack by a weak nucleophile generates the tetrahedral intermediate.

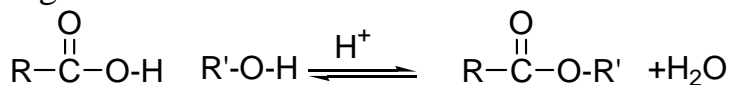
The leaving group (often in its protonated form) is then expelled (often as a neutral molecule). (See below).

The Fischer Esterification

Recall that acid and alcohol → ester and water

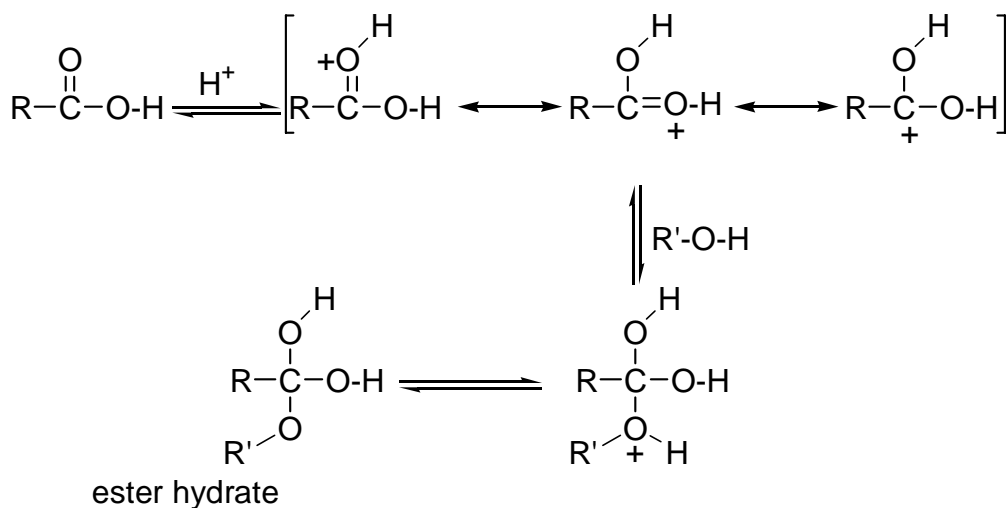
The overall transformation is that the -OH of an acid is replaced by the -OR' of an alcohol.

E.g.



The Fischer esterification is an example of acid catalyzed nucleophilic acyl substitution.

The carbonyl group of a carboxylic acid is not sufficiently electrophilic to be attacked by the alcohol.

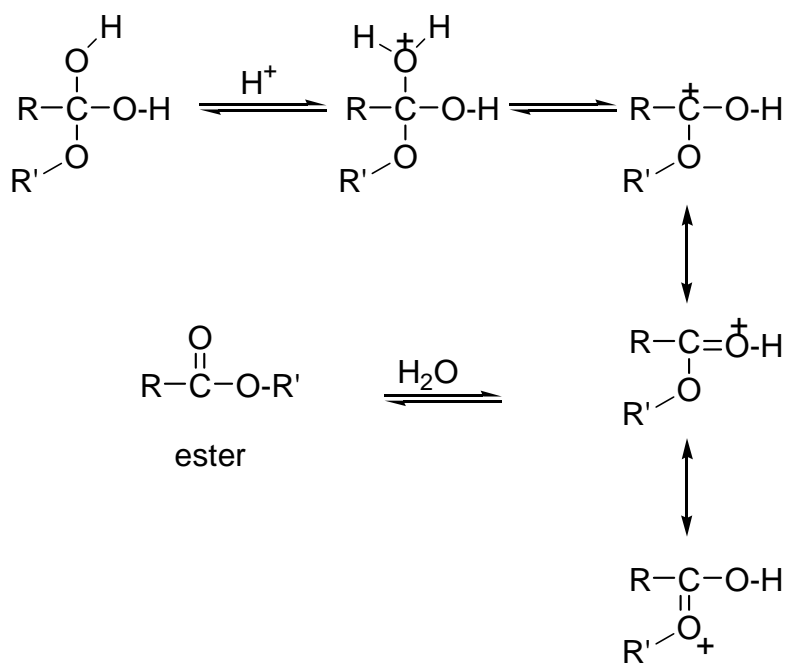


The acid catalyst protonates the carbonyl oxygen, and activates it toward nucleophilic attack.

The alcohol attacks and after deprotonation of the alcohol oxygen, the hydrate of an ester is formed.

The ester is produced via acid catalyzed dehydration of the ester hydrate.

The hydroxyl oxygen is protonated, thus creating a good leaving group.

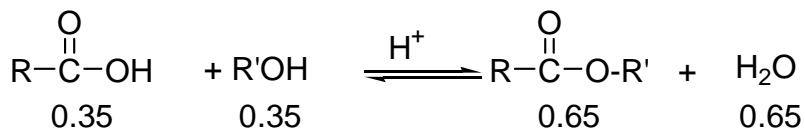


This leaves with assistance from the neighboring hydroxyl oxygen.

The cation remaining is resonance stabilized, and deprotonation yields the desired ester.

The overall mechanism is quite long, but both steps have been seen before (acid catalyzed addition to a carbonyl; acid catalyzed dehydration), and so should not be viewed as difficult, or as new work to learn.

Esterification reactions such as this one are equilibrium reactions, and the equilibrium normally will lie to the left.



$K_a = 3.4$, so this would be a good case.

To drive the reaction to completion we can either use an excess of one or the reagents, or remove one of the products.

Often it is the water produced which is removed by a dehydrating agent such as MgSO_4 , or molecular sieves.

A simpler (yet more expensive) way to make esters in the laboratory (not industrially) is to react an alcohol with an acid chloride.

Synthesis of Acid Chlorides

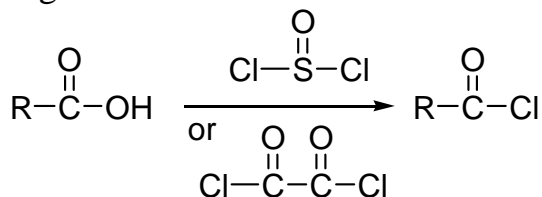
Both the carbonyl oxygen and the chlorine are electron withdrawing, and thus make the carbonyl carbon very electrophilic.

Diagrams

Therefore acid chlorides are very reactive with nucleophiles, usually through the nucleophilic acyl substitution mechanism.

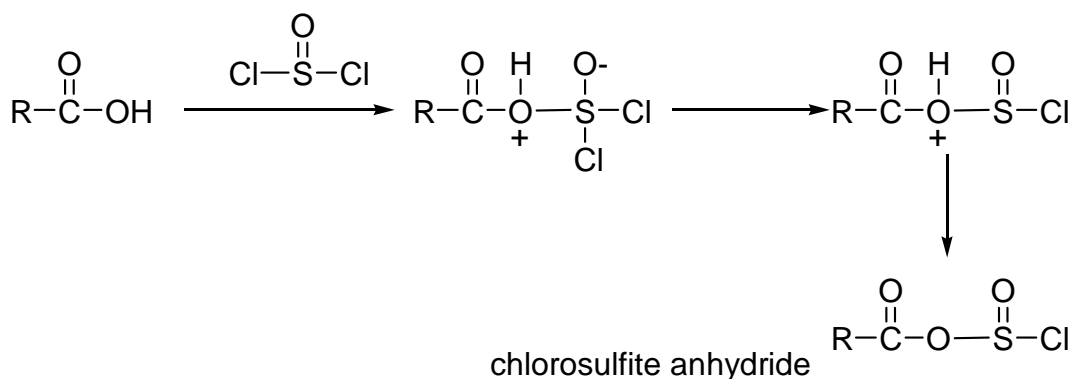
The best way to make acid chlorides is the reaction of a carboxylic acid with either thionyl chloride (SOCl_2) or $(\text{COCl})_2$, which is called oxalyl chloride.

E.g.



Both these methods are good since they generate gaseous by-products, and thus do not contaminate the acid chloride product.

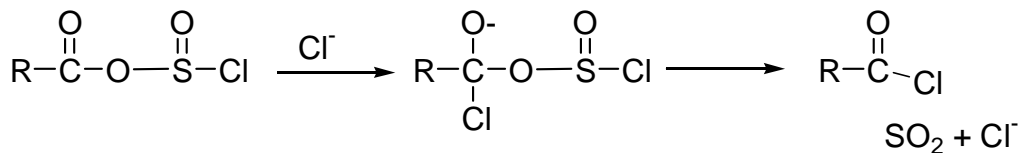
The mechanism of formation of acid chloride is similar to the reaction of alcohols with thionyl chloride.



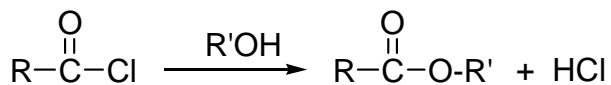
The lone pair of the acid carbonyl oxygen attacks the electrophilic sulfur (sulfur analogue of an acid chloride), and chloride is expelled from the tetrahedral intermediate.

Deprotonation yields a chlorosulfite anhydride, and the liberated chloride ion now attacks the electrophilic carbon of the mixed anhydride.

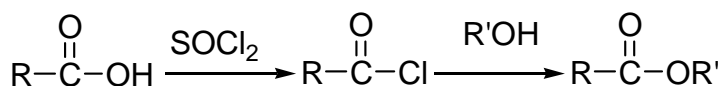
This tetrahedral intermediate then expels leaving group which fragments into SO_2 and chloride ion.



Acid chlorides react with alcohols to give esters through a nucleophilic acyl substitution by the addition elimination mechanism.

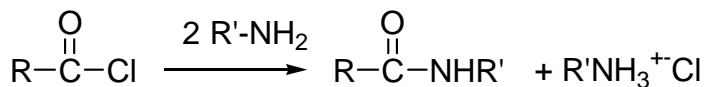


The overall transformation of this two step scheme is a carboxylic acid is converted into an acid chloride, then into an ester.



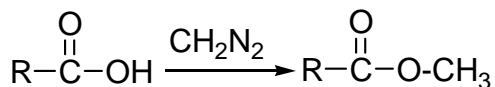
Ammonia and amines react with acid chlorides to give amides, also through this addition-elimination version of nucleophilic acyl substitution.

E.g.



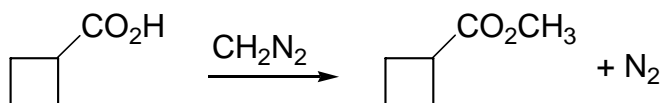
Esterification using Diazomethane

The addition of an ethereal solution of diazomethane smoothly converts carboxylic acids to their methyl esters.



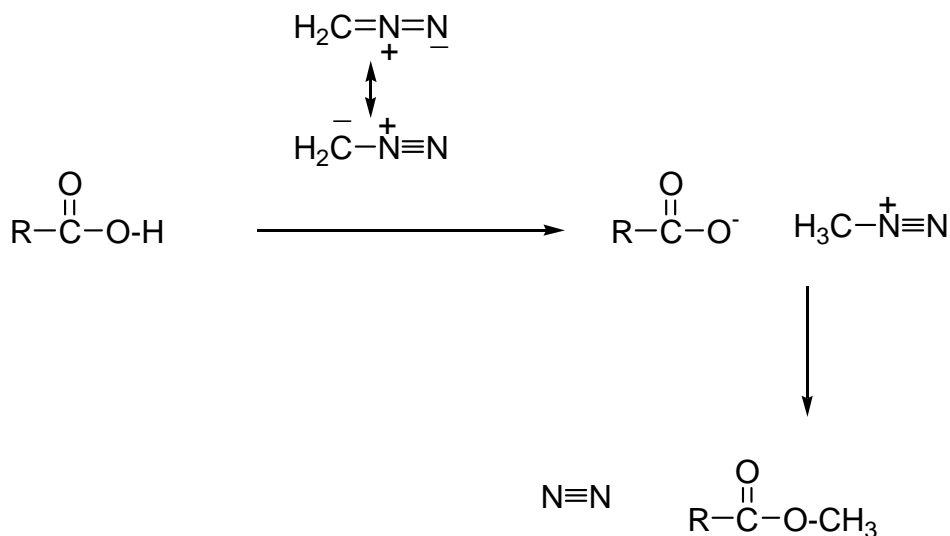
The only by-product is nitrogen gas.

E.g.



Diazomethane is a toxic, explosive yellow gas that dissolves in ether, and requires special glassware.

The mechanism involves the deprotonation of the hydroxyl oxygen, which generates a methyldiazonium salt, which is a potent methylating agent.



The carboxylate anion becomes methylated, thus generating the methyl ester, and nitrogen gas is evolved.

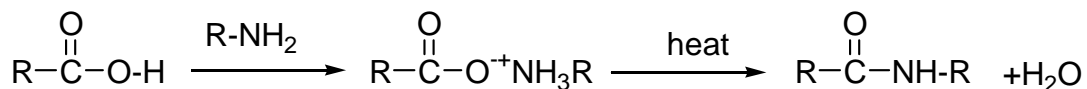
Condensations of Acids with Amines (→ Amides)

Although the acid chloride/amine reaction generates amides, it is also possible (and cheaper) to synthesize amides directly from carboxylic acids.

The direct reaction of an amine and a carboxylic acid initially formed a carboxylate anion and an ammonium cation.

Normally the reaction would stop at this point since the carboxylate anion is a poor electrophile, but by heating the reaction to over 100°C, the water can be driven off as steam, and amide products are formed.

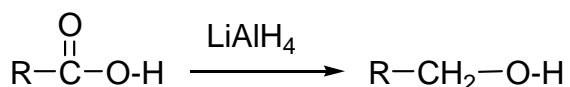
E.g.



This is an important commercial process.

Reduction of Carboxylic Acids

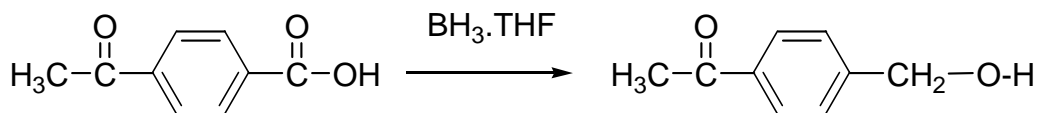
Lithium aluminum hydride reduces carboxylic acids back to primary alcohols.



The reaction proceeds through an aldehyde but it cannot be stopped at that stage since aldehydes are more easily reduced than the carboxylic acid.

Carboxylic acids are also reduced by borane (BH₃) to generate primary alcohols.

This reaction has good selectivity since the carboxyl group reacts faster than any other carbonyl derivative.



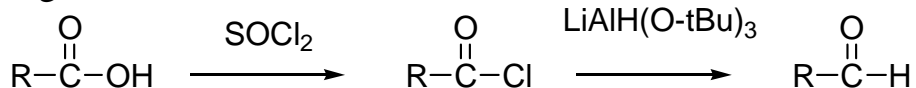
Therefore carboxylic acids can be reduced in the presence of ketone functionalities using borane.

Reduction to Aldehydes

(We have seen this before, Ch18). The carboxylic acid must first be converted into a group more easily reduced than an aldehyde.

The reactive acid derivative is the acid chloride, and the mild reducing agent is lithium aluminum tri(^tbutoxy)hydride.

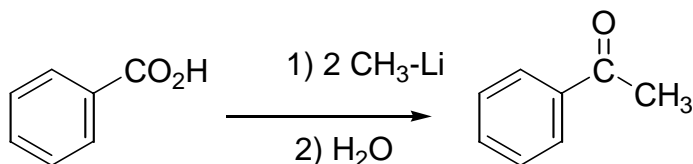
E.g.



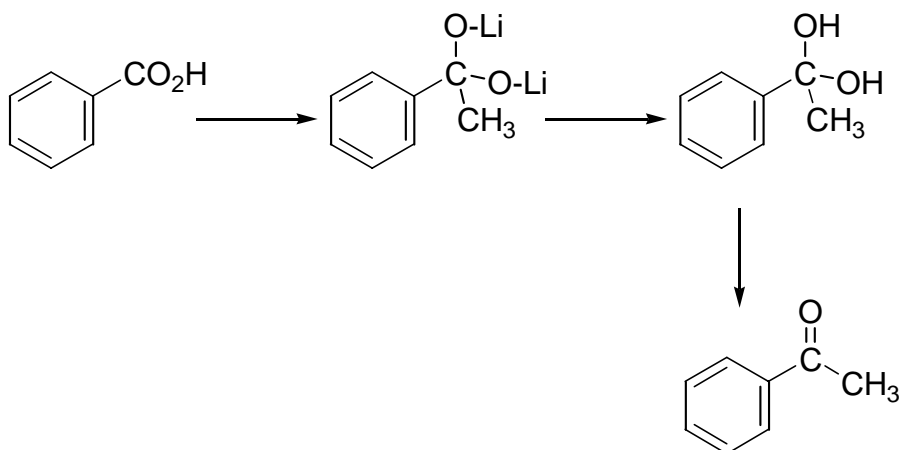
Alkylation of Carboxylic Acids (→ Ketones)

(Also seen this before, Ch18). A general method to form ketones is the reaction of a carboxylic acid with two equivalent of organolithium reagent.

E.g.



The first equivalent just deprotonates the carboxylic acid, and then the second performs a nucleophilic attack to generate a dianion.



On acid hydrolysis a ketone hydrate is formed, which loses water to yield the ketone.