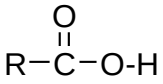
Carboxylic Acids

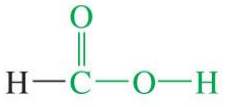
When a carbonyl carbon also bears a hydroxyl group, then these compounds are appreciably acidic, and are called *carboxylic acids*.



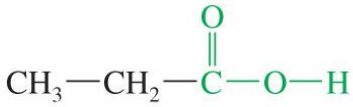
Carboxylic acids are classified according to the substituent that is bonded to the carboxyl carbon:

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

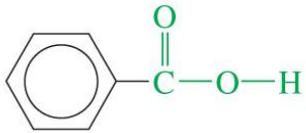
An *aromatic* acid has an *aryl* group bound to the carboxyl group.



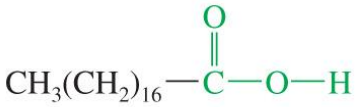
formic acid



propionic acid
(an aliphatic acid)



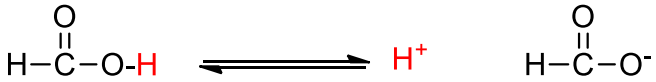
benzoic acid
(an aromatic acid)



stearic acid
(a fatty acid)

The simplest acid is *formic acid*.

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



Nomenclature

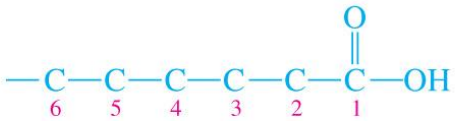
IUPAC formulation

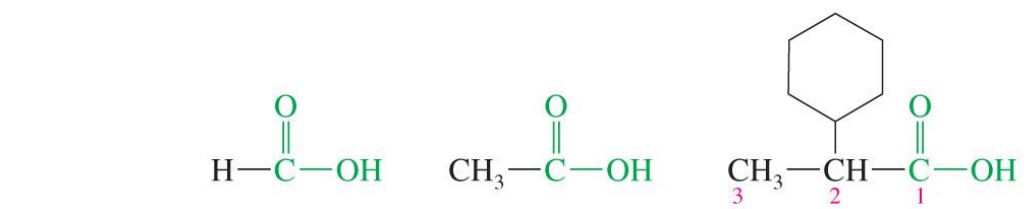
The root name is based on the longest continuous chain of carbon atoms bearing the carboxyl group.

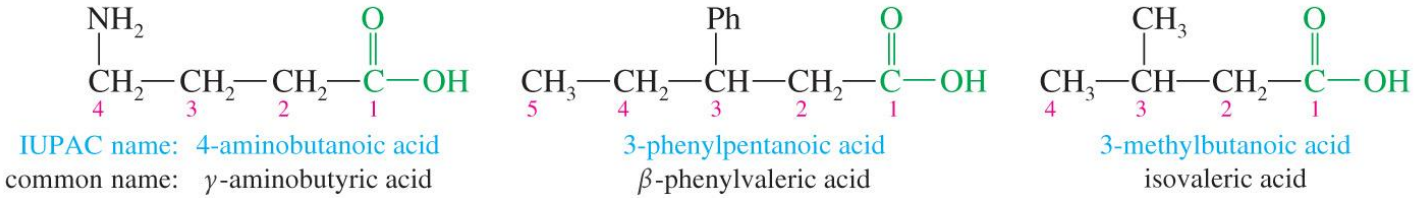
The *-e* is replaced by *-oic acid*.

The chain is numbered **starting with the carboxyl carbon atom**.

The carboxyl group takes priority over any other functional groups previously discussed.
E.g.

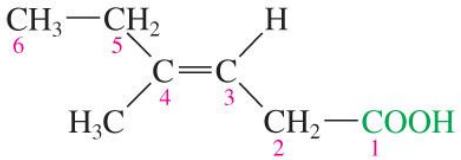


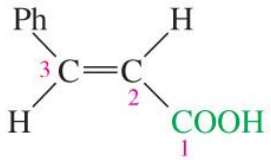




Unsaturated acids are named using the name of the *alkene* with *-e* replaced with *-oic acid*.

The chain is numbered starting with the carboxyl group, and a number designates the location of the multiple bond (and may include Z or E).
E.g.

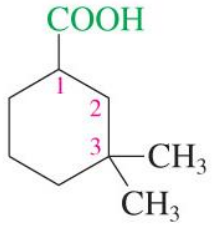




old IUPAC name: (*E*)-4-methyl-3-hexenoic acid
new IUPAC name: (*E*)-4-methylhex-3-enoic acid

trans-3-phenyl-2-propenoic acid
(*E*)-3-phenylprop-2-enoic acid
(cinnamic acid)

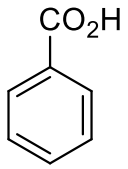
Cycloalkanes with carboxyl substituents are named as *cycloalkanecarboxylic acids*.
E.g.



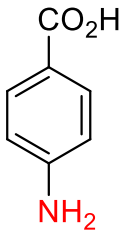
3,3-dimethylcyclohexanecarboxylic acid

(Notice that $-CO_2H$ as a substituent makes the carbon it is **bound** to C-1, not itself).

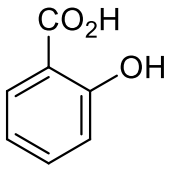
Typically *aromatic* acids of the form **Ar-CO_2H** are named as derivatives of benzoic acids, with *ortho*, *meta* and *para* indicating the location relative to the carboxyl group. (*Recall that this is* ***non-IUPAC***).



benzoic acid



p-aminobenzoic acid



o-hydroxybenzoic acid

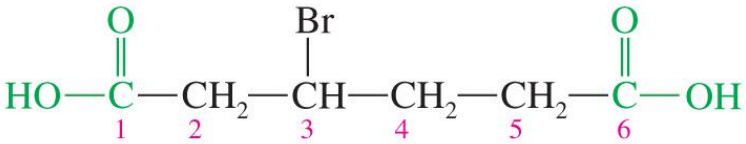
Dicarboxylic Acids

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

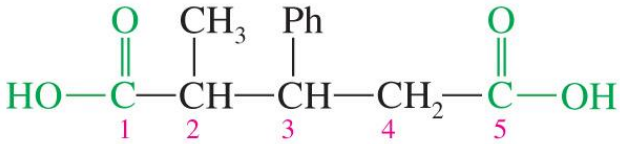
The root name comes from the longest carbon chain containing *both* carboxyl groups.

Numbering starts at the end closest to a substituent.

E.g.



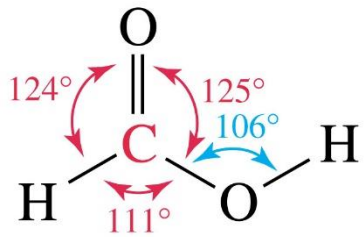
3-bromohexanedioic acid



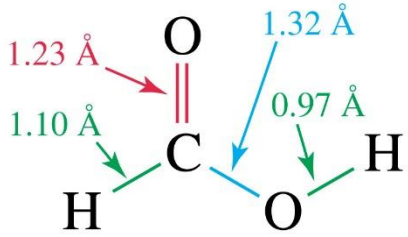
2-methyl-3-phenylpentanedioic acid

Structure of the Carboxyl Group

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



bond angles

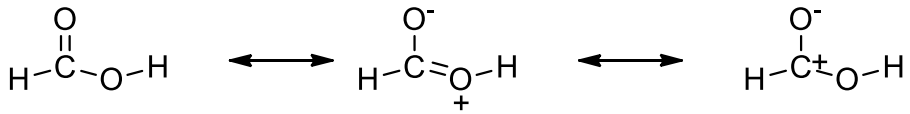


bond lengths

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.



major *minor* *very minor*

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

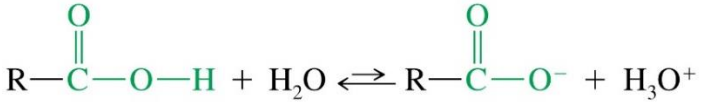
One of the unshared lone pairs of oxygen is delocalized into the electrophilic π system of the carbonyl group.

(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.



$$K_a = \frac{[R—CO_2^-][H_3O^+]}{[R—CO_2H]}$$

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

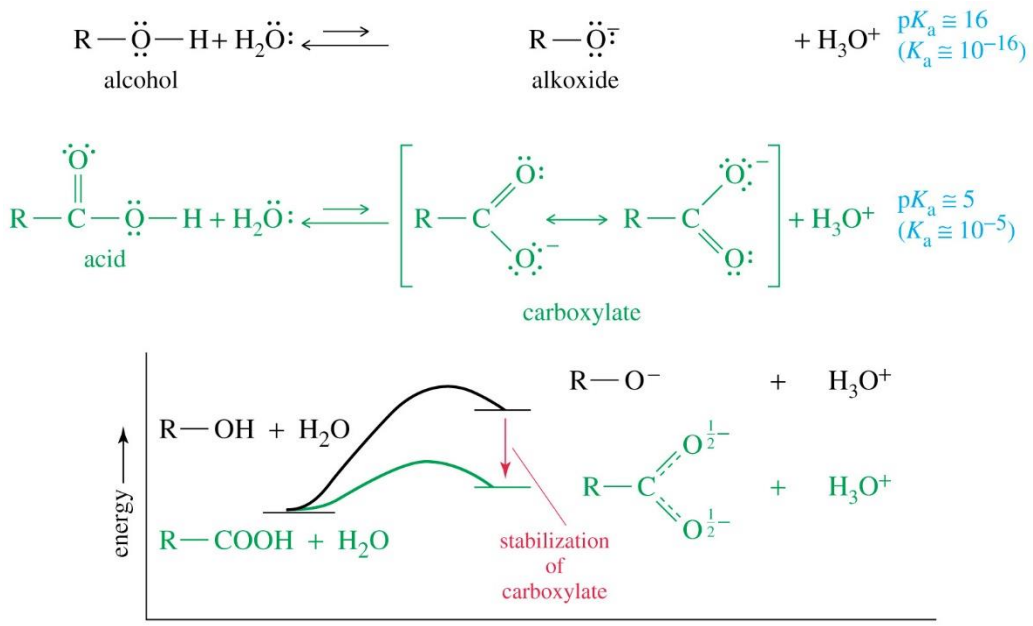
Values of pK_a for common alkyl carboxylic acids are around 5 ($K_a \sim 10^{-5}$).

Formula	Name	Values			
		Simple carboxylic acids			
		K_a (at 25 °C)	pK_a		
HCOOH	formic acid	1.77×10^{-4}	3.75		
CH_3COOH	acetic acid	1.76×10^{-5}	4.74		
CH_3CH_2 COOH	propionic acid	1.34×10^{-5}	4.87		
$CH_3(CH_2)_2COOH$	butyric acid	1.54×10^{-5}	4.82		
$CH_3(CH_2)_3COOH$	pentanoic acid	1.52×10^{-5}	4.81		
$CH_3(CH_2)_4COOH$	hexanoic acid	1.31×10^{-5}	4.88		
$CH_3(CH_2)_6COOH$	octanoic acid	1.28×10^{-5}	4.89		
$CH_3(CH_2)_8COOH$	decanoic acid	1.43×10^{-5}	4.84		
C_6H_5 COOH	benzoic acid	6.46×10^{-5}	4.19		
p-$CH_3C_6H_4COOH$	*p*-toluic acid	4.33×10^{-5}	4.36		
p-ClC_6H_4COOH	*p*-chlorobenzoic acid	1.04×10^{-4}	3.98		
p-$NO_2C_6H_4COOH$	*p*-nitrobenzoic acid	3.93×10^{-4}	3.41		
		Dicarboxylic acids			
		K_{a1}	pK_{a1}	K_{a2}	pK_{a2}
HOOC—COOH	oxalic	5.4×10^{-2}	1.27	5.2×10^{-5}	4.28
$HOOCCH_2COOH$	malonic	1.4×10^{-3}	2.85	2.0×10^{-6}	5.70
$HOOC(CH_2)_2COOH$	succinic	6.4×10^{-5}	4.19	2.3×10^{-6}	5.64
$HOOC(CH_2)_3COOH$	glutaric	4.5×10^{-5}	4.35	3.8×10^{-6}	5.42
$HOOC(CH_2)_4COOH$	adipic	3.7×10^{-5}	4.43	3.9×10^{-6}	5.41
cis-HOOCCH=CHCOOH	maleic	1.0×10^{-2}	2.00	5.5×10^{-7}	6.26
trans-HOOCCH=CHCOOH	fumaric	9.6×10^{-4}	3.02	4.1×10^{-5}	4.39
1,2-$C_6H_4(COOH)_2$	phthalic	1.1×10^{-3}	2.96	4.0×10^{-6}	5.40
1,3-$C_6H_4(COOH)_2$	isophthalic	2.4×10^{-4}	3.62	2.5×10^{-5}	4.60
1,4-$C_6H_4(COOH)_2$	terephthalic	2.9×10^{-4}	3.54	3.5×10^{-5}	4.46

E.g. ethanoic acid has $pK_a = 4.74$, (alcohols have $pK_a \sim 16$, so carboxylic acids are about 10^{11} times *more acidic* than alcohols).

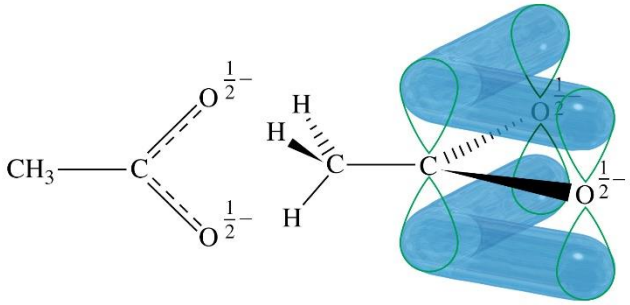
The reason why carboxylic acids are much *more acidic* than alcohols is because the carboxylate <u>anion</u> is much *more stable* than the alkoxide <u>anion</u>.

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 alkoxide has the negative charge localized on a **single** oxygen atom.

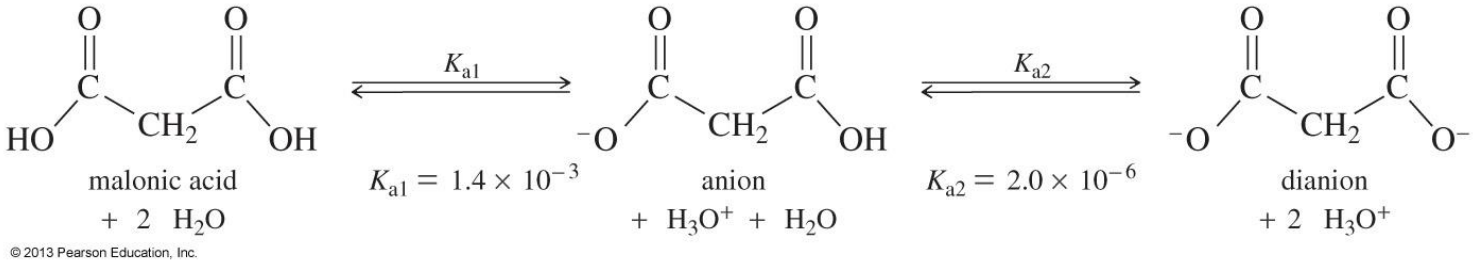
The carboxylate anion can be viewed as a *resonance hybrid* of the two anionic structures, or as a *conjugated* system of three interacting p orbitals containing four electrons (like the allylic anion system).



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.

<u>Dicarboxylic Acids</u>

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



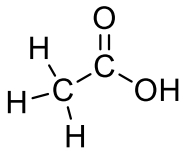
K_{a1} for the first dissociation, and K_{a2} for the second dissociation (which generates a dianion).
K_{a2} is always *less* than K_{a1} (the second carboxyl group is less acidic) since it takes extra energy to overcome the second negative charge being so close to the first negative charge.

Substituent Effects on Acidity

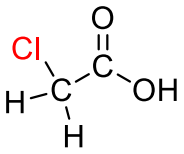
Any substituent that *stabilizes* a negative charge is going to *enhance* the dissociation process, and therefore result in a *stronger* acid.

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

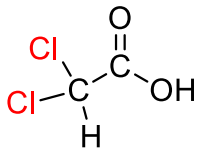
E.g.



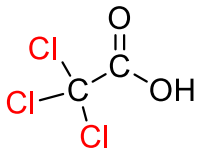
pK_a = 4.74



2.86

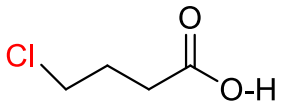


1.26

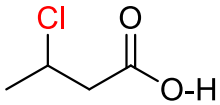


0.64

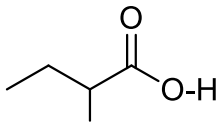
The *closer* the substituent to the anion, the more profound the effect.



pK_a = 4.52



4.05

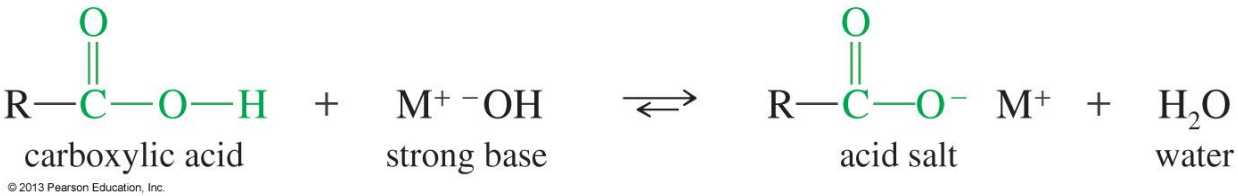


2.86

Salts of carboxylic Acids

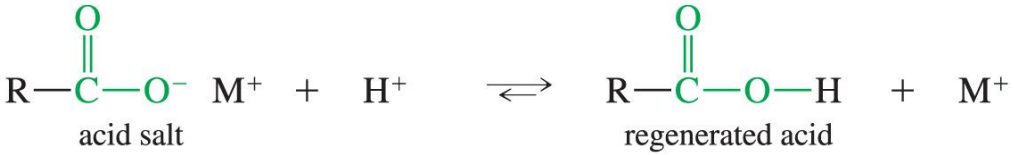
Strong bases can *completely* deprotonate carboxylic acids, thus *salts* of carboxylic acids are formed.

E.g.

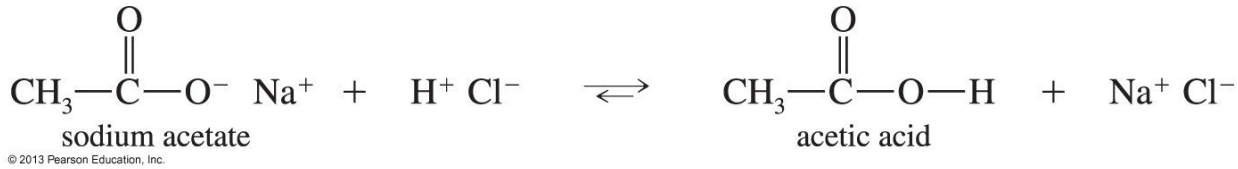


The acid can be *regenerated* by protonation (acidification) of the salt.

E.g.



Example



Syntheses of Carboxylic Acids

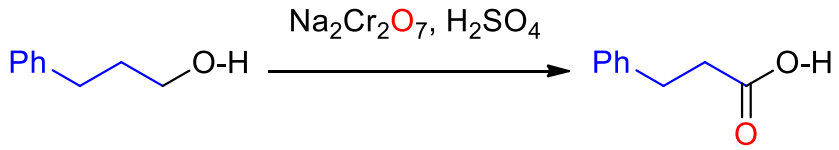
The previously seen syntheses (three) all involved oxidation:

(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 $Na_2Cr_2O_7$ and H_2SO_4).
Potassium permanganate can be used but gives lower yields.

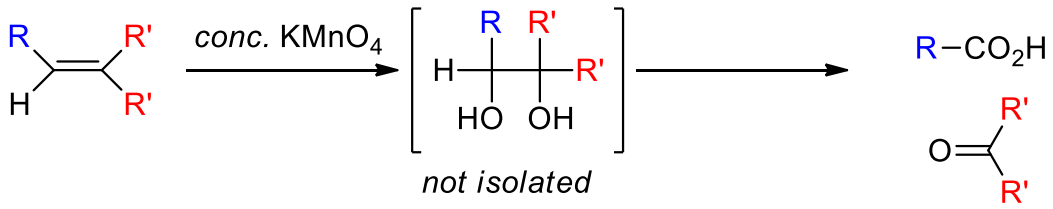
E.g.

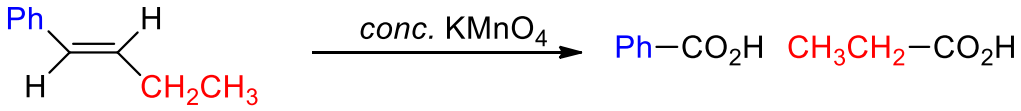


Cleavage of Alkynes and Alkenes

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).

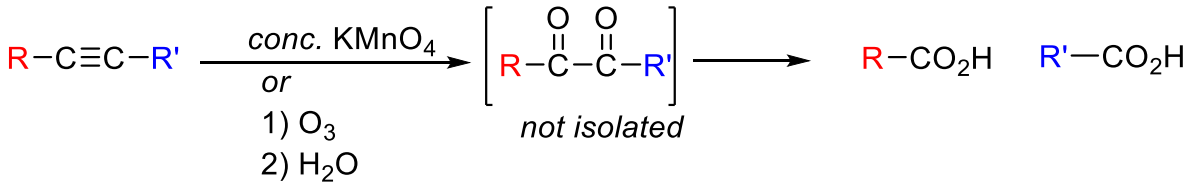
E.g.





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.

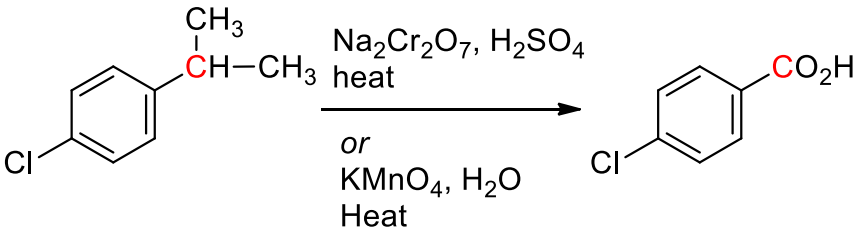


Alkylbenzenes

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.

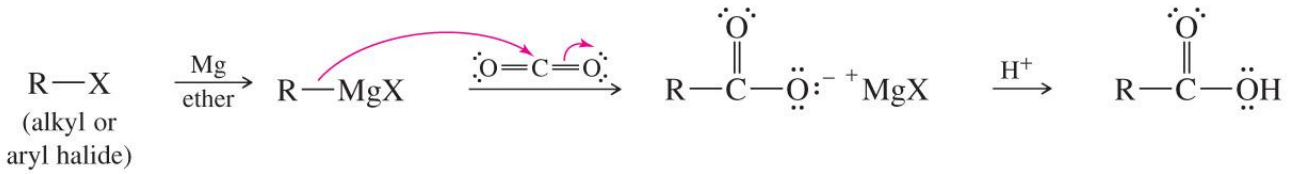
E.g.



New methods

Carboxylation of Grignard Reagents

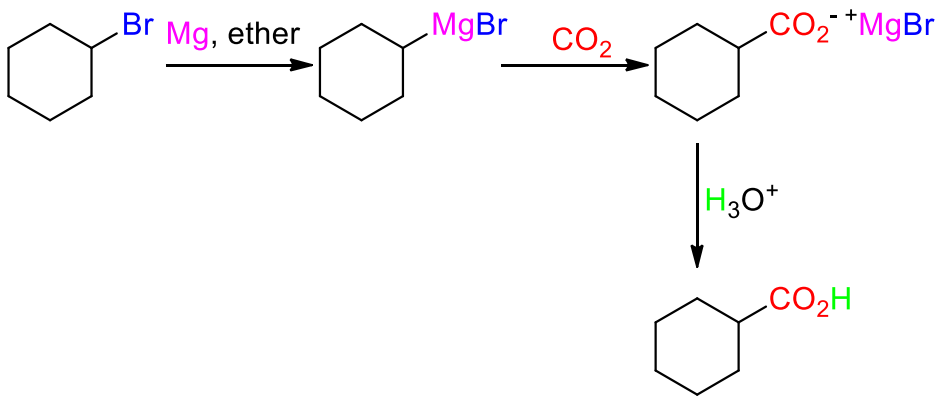
Grignard reagents can react as *nucleophiles* and attack carbon dioxide.



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.

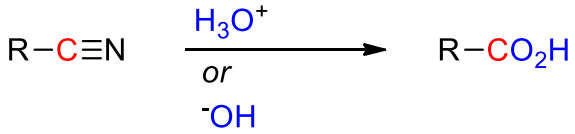
E.g.



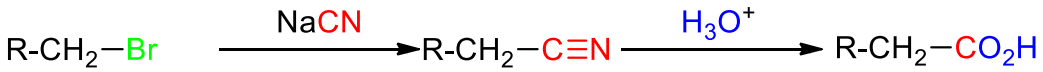
Formation and Hydrolysis of Nitriles

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

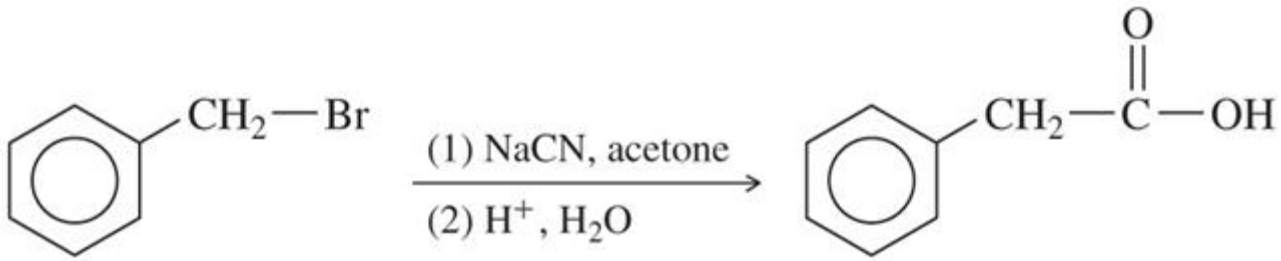
E.g.



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*.



benzyl bromide phenylacetic acid

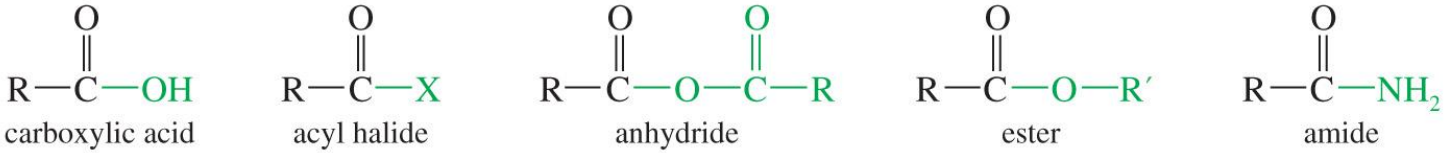
Reactions of Carboxylic Acids (and Derivatives)

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 a leaving group on the acyl carbon.

E.g.

Nucleophilic acyl substitution

Acid derivatives



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

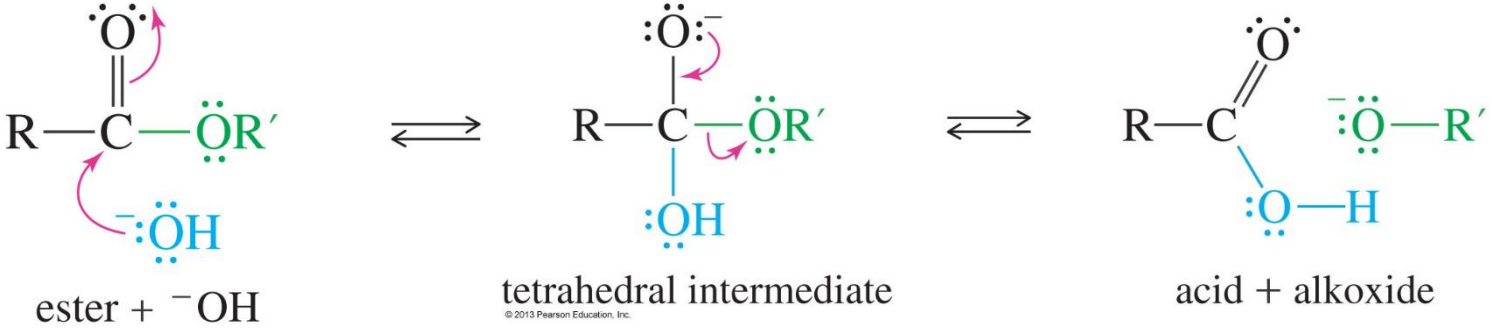
-OH is an *acid*
-Cl is the *acid chloride*
-OCOR' is the *anhydride*
-OR' is the *ester*
-NR_2 is the *amide*

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 addition to aldehydes/ketones).

Under <u>basic</u> 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 <u>acidic</u> conditions, the carbonyl group becomes protonated, and thus activated toward nucleophilic acyl substitution.

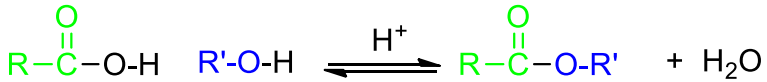
Then attack by a weak nucleophile generates the tetrahedral intermediate.

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

The Fischer Esterification

Recall that *acid* and *alcohol* → *ester* and *water*

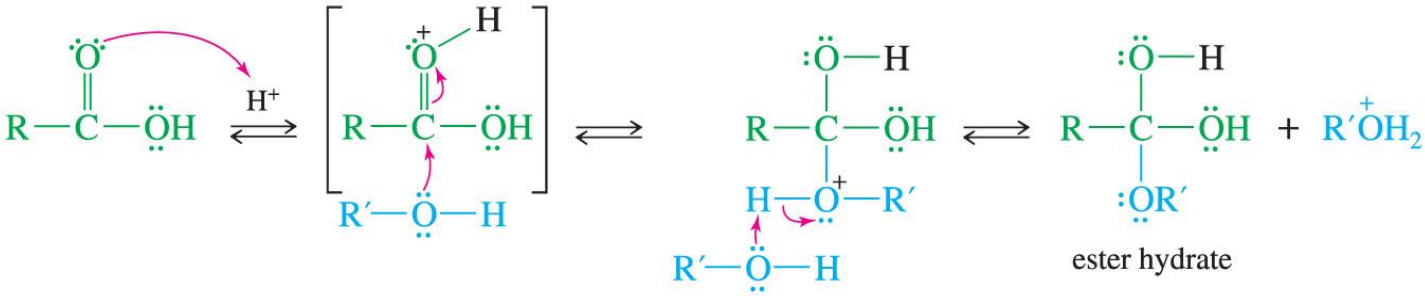
The overall transformation is that the -OH of an acid is replaced by the -OR' of an alcohol.



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.

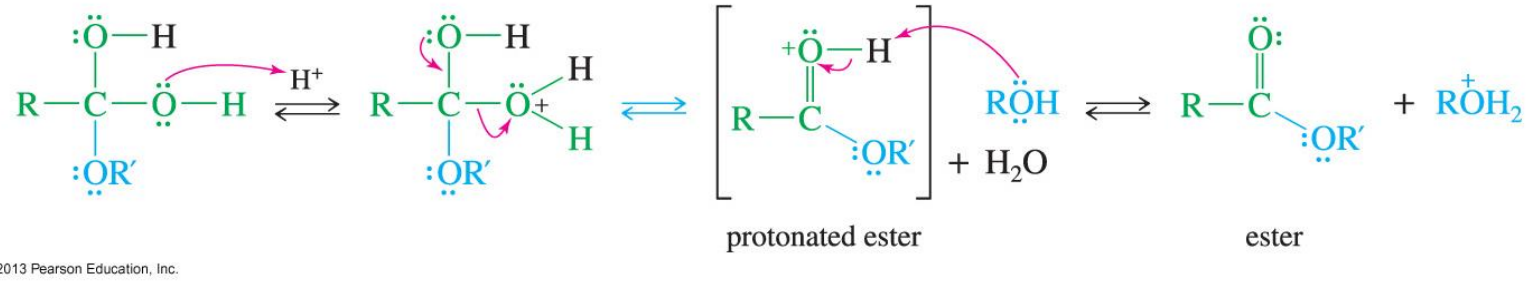


(Species in brackets are resonance-stabilized.)

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.
As usual, the hydroxyl oxygen is protonated, thus creating a good leaving group.

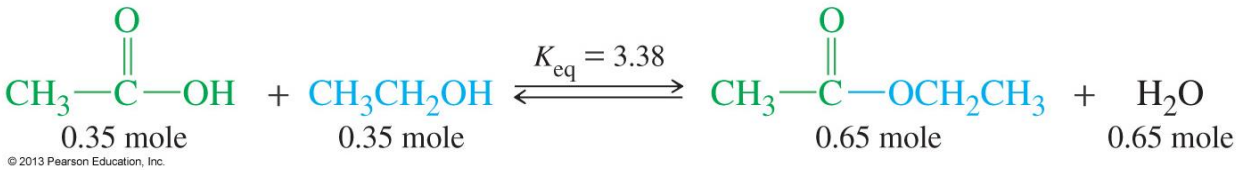


This leaves with assistance from the neighboring hydroxyl oxygen.

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_{eq} = 3.4, so this would be a good case.

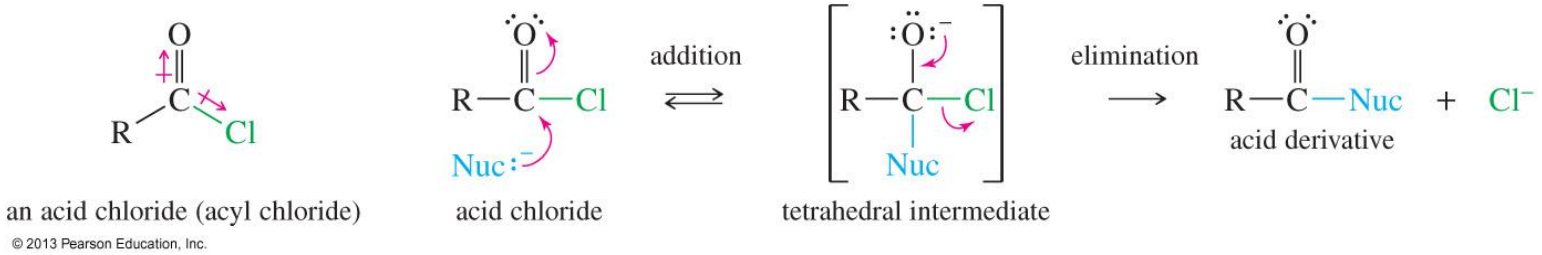
To drive the reaction to completion we can either use an *excess* of one of the reagents, or *remove* one of the products.

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

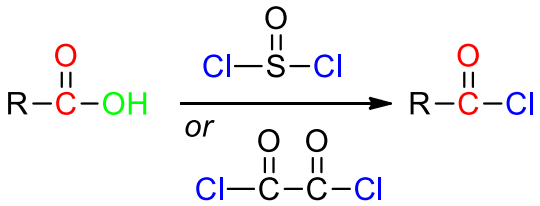
Both the carbonyl oxygen and the chlorine are *electron withdrawing*, and thus make the carbonyl carbon very *electrophilic*.



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

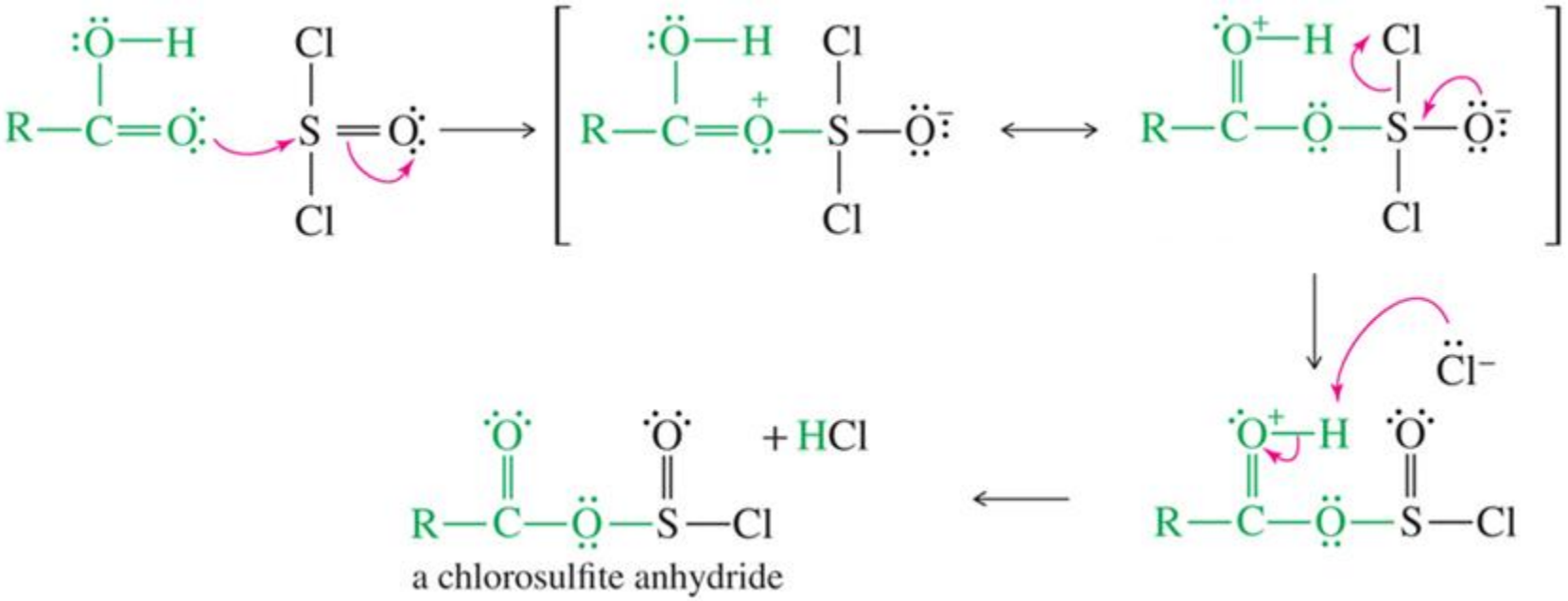
The best way to make acid chlorides is the reaction of a carboxylic acid with either thionyl chloride ($SOCl_2$) or $(COCl)_2$, which is called oxalyl chloride.

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.

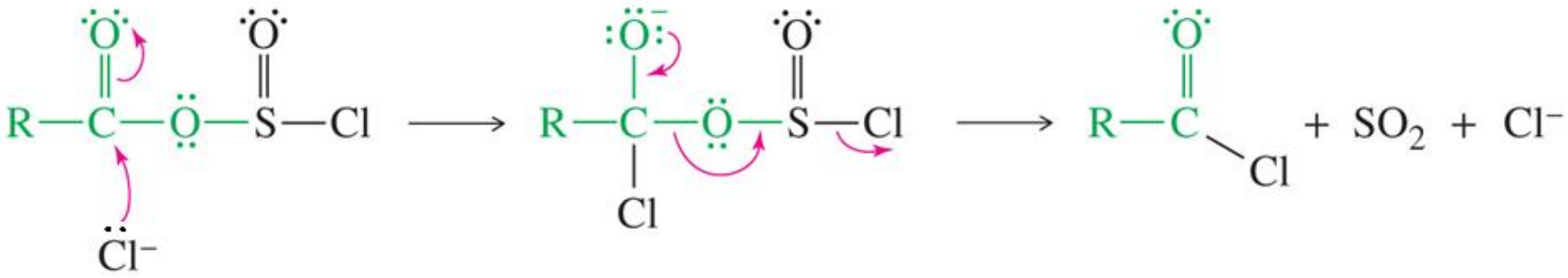


The lone pair of the acid carbonyl oxygen attacks the electrophilic sulfur (sulfur analogue of an acid chloride), and chloride is expelled from the tetrahedral intermediate.

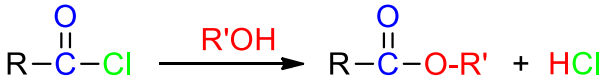
Deprotonation yields a *chlorosulfite anhydride*.

The liberated chloride ion now attacks the electrophilic carbon of the mixed anhydride.

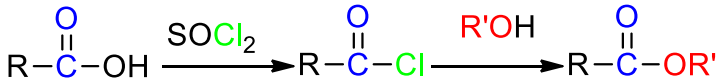
This tetrahedral intermediate then expels the leaving group which fragments into SO_2 and chloride ion.



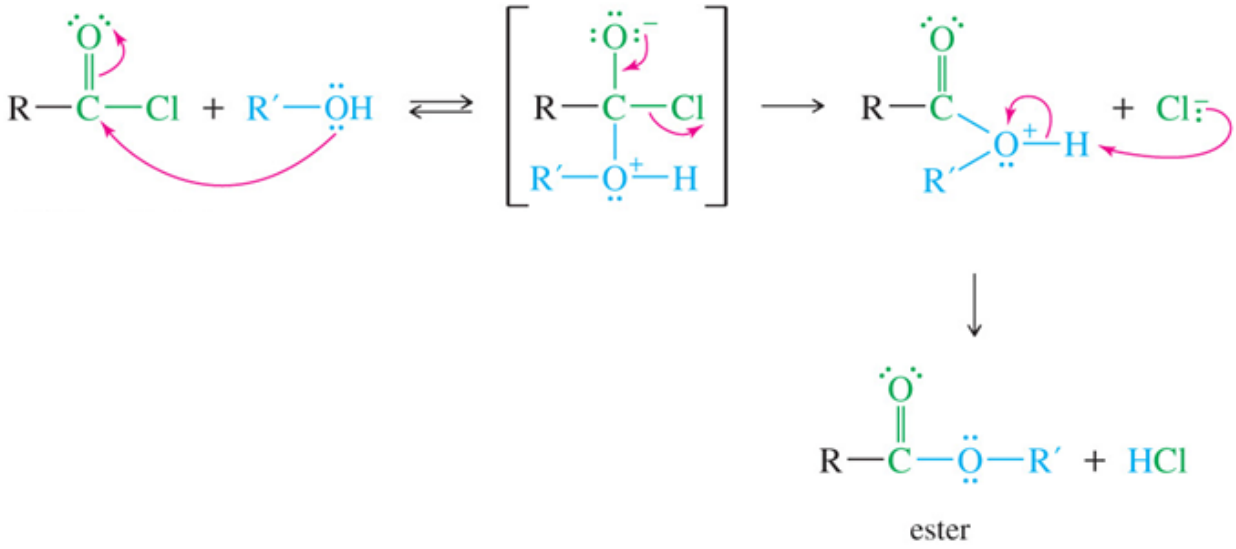
Acid chlorides react with alcohols to give esters through a nucleophilic acyl substitution by the addition elimination mechanism.



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

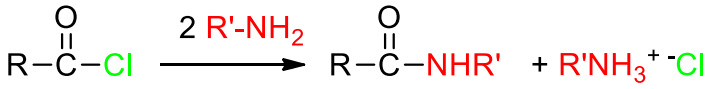


The *acid chloride* to *ester* transformation is standard *nucleophilic acyl substitution*.



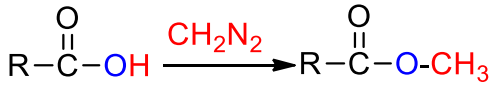
Ammonia and amines react with acid chlorides to give *amides*, also through this addition-elimination version of nucleophilic acyl substitution.

E.g.



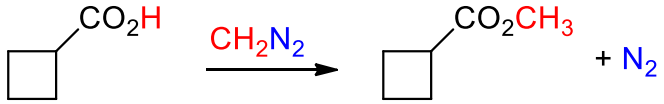
Esterification using Diazomethane

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



The only by-product is nitrogen gas.

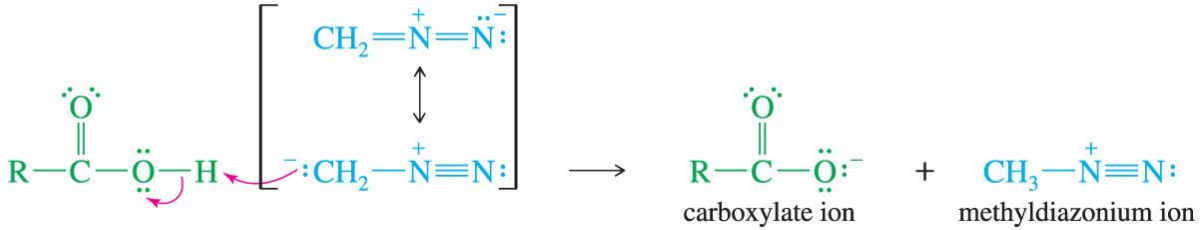
E.g.



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

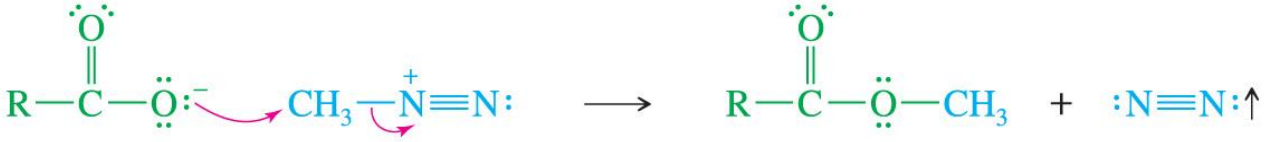
The mechanism involves the deprotonation of the hydroxyl oxygen, which generates a *methyldiazonium salt*, which is a potent methylating agent.

Step 1: Proton transfer, forming a carboxylate ion and a methyldiazonium ion.



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

Step 2: Nucleophilic attack on the methyl group displaces nitrogen.

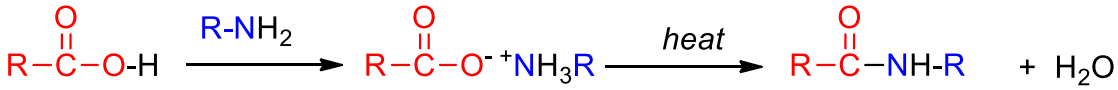


<u>Condensations of Acids with Amines (→ Amides)</u>
Although the acid chloride/amine reaction generates amides, it is also possible (and cheaper) to synthesize amides directly from carboxylic acids.

The direct reaction of an amine and a carboxylic acid <u>initially</u> forms 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.

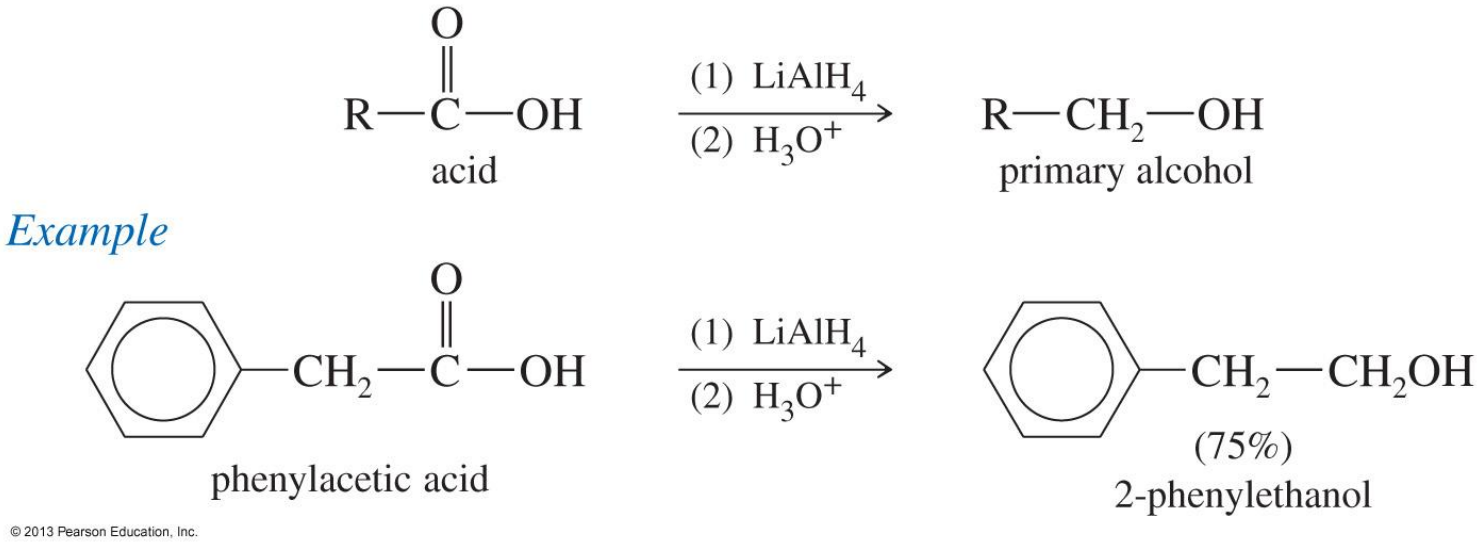
E.g.



This is an important commercial process.

Reduction of Carboxylic Acids

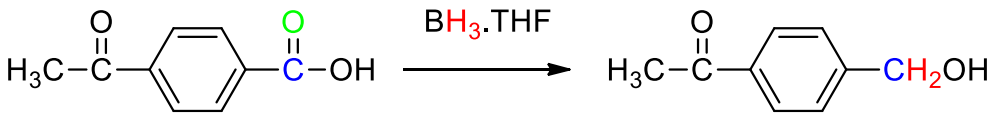
Lithium aluminum hydride reduces carboxylic acids back to primary alcohols.



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

Carboxylic acids are also reduced by borane (BH_3) to generate primary alcohols.

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

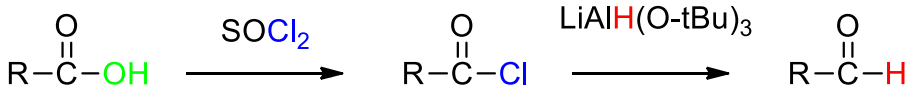


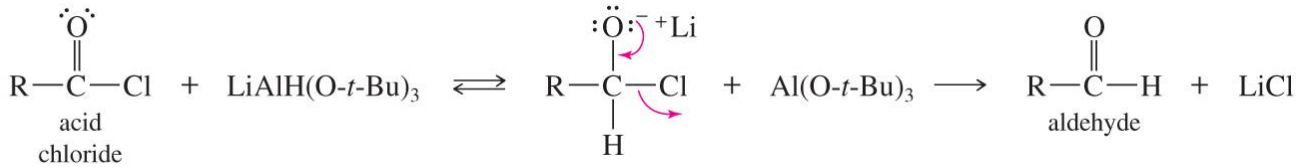
Therefore carboxylic acids can be reduced in the presence of *ketone* functionalities using borane.

<u>Reduction to Aldehydes</u>
(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(*^{t}*butoxy)hydride*.

E.g.

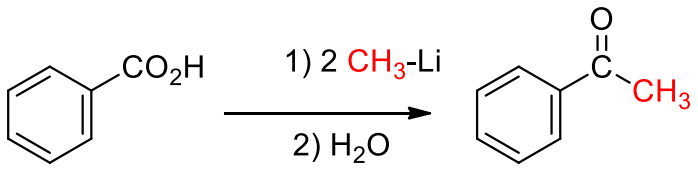




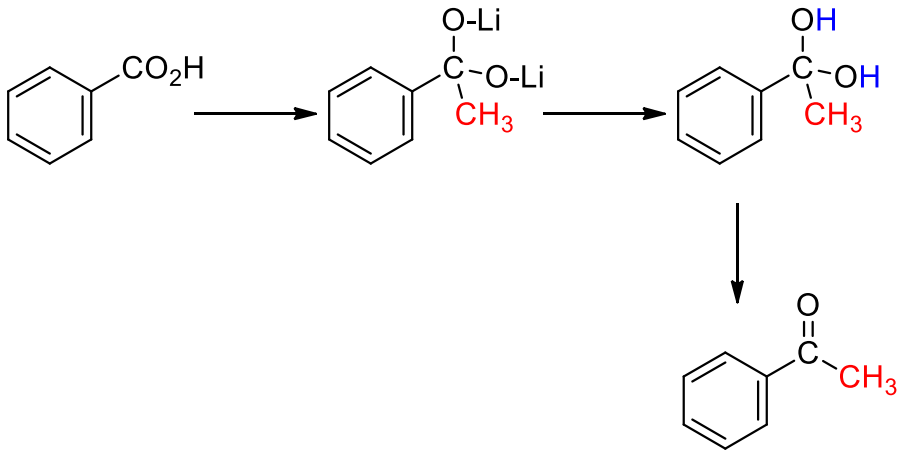
Alkylation of Carboxylic Acids (→ Ketones)

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

E.g.



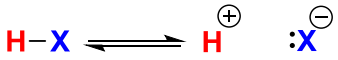
The first equivalent just deprotonates the carboxylic acid, and then the second performs a nucleophilic attack to generate a dianion.



On acid hydrolysis a *ketone hydrate* is formed, which loses water (H_2O) to yield the ketone.

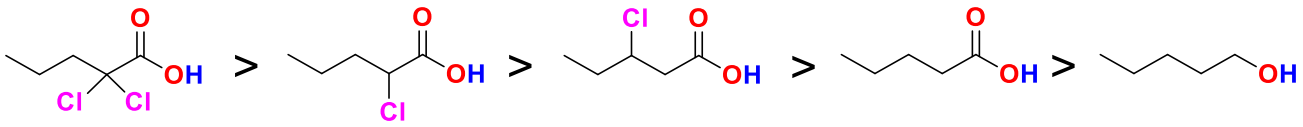
CARBOXYLIC ACIDS

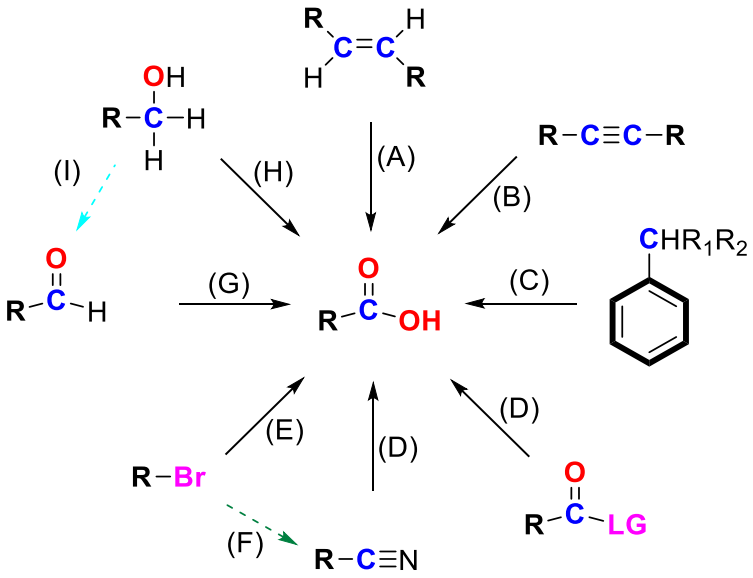
Acid Strength



Factors: (a) **Resonance** (e.g. RCO_2^- *vs.* RO^-)

(b) **Electron Withdrawing Groups** (Number and Location)





(**A**) conc. $KMnO_4$
(**B**) O_3 then H_3O^+; or *conc.* $KMnO_4$
(**C**) $KMnO_4$, H_2O, heat; or $Na_2Cr_2O_7$, H_2SO_4, heat
(**D**) H_2O (*H^+ or ^-OH with heat, if needed*)
(**E**) Mg; CO_2; H_3O^+
(**F**) NaCN
(**G**) Ag_2O (or H_2CrO_4 or $KMnO_4$)
(**H**) H_2CrO_4 (or $KMnO_4$)
(**I**) PCC

(**A**) R'COCl (or $R'CO_2H$, heat)
(**B**) R'OH, H^+ (*or CH_2N_2 for methyl esters*)
(**C**) $R'NH_2$, heat
(**D**) 2 R'Li then H_3O^+
(**E**) $LiAlH_4$ then H_3O^+; (or BH_3.THF)
(**F**) PCC
(**G**) $SOCl_2$ (or ClCOCOCl)
(**H**) $LiAl(OBu)_3H$