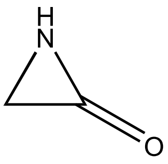
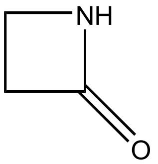
Lactams: Cyclic amides

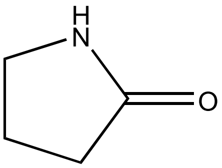
Similar to lactones, the ring size of the lactam is described by starting at the carbonyl carbon and designating the other carbons in the ring with Greek letters until the nitrogen atom is reached.



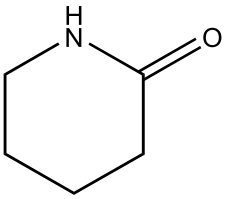
α-lactam



β-lactam



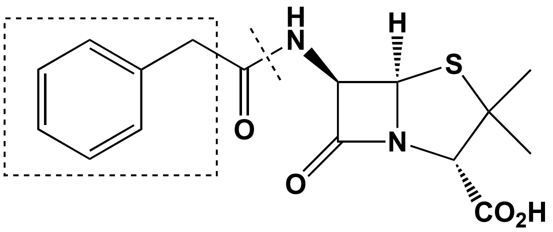
γ-lactam



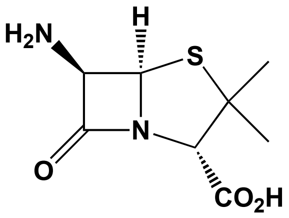
δ-lactam

The four-, five-, and six-member rings appear frequently in nature.

Examples:

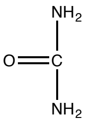


penicillin G

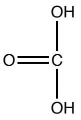


6-aminopenicillanic acid

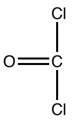
Carbon Dioxide Derivatives:



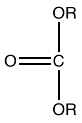
Urea



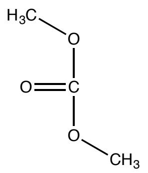
Carbonic acid



Phosgene

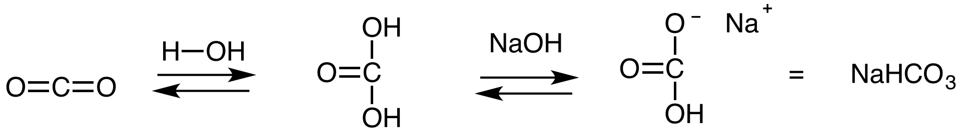


Carbonates



Dimethyl carbonate

Carbon dioxide reacts with water to make carbonic acid:



Carbonic Acid

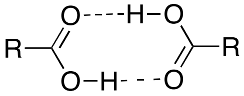
Sodium bicarbonate

Properties of Carboxylic Acids

Since carboxylic acids are structurally related to both ketones and aldehydes, we would expect to see some similar properties. The carbonyl carbon of carboxylic acids is sp^2 hybridized with an approximate bond angle of 120°. The electronegative oxygen also makes the carbonyl carbon partially positively charged and susceptible to nucleophilic attack.

Carboxylic acids with more than six carbons are only slightly soluble in water, but alkali metal salts of carboxylic acids are often quite water soluble because of their ionic nature. Other carboxylic acid derivatives, such as acid chlorides, anhydrides, and esters, are quite insoluble in water. Acid chlorides and anhydrides react with water, as we will see later. Some amide derivatives are also soluble in water.

Like alcohols, carboxylic acids are strongly associated because of hydrogen bonding. Most carboxylic acids can exist as cyclic dimers held together by two hydrogen bonds, which are represented by the dashed lines.

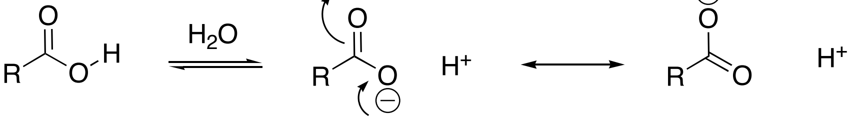


cyclic dimer

This strong hydrogen bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols.

Dissociation of Carboxylic Acids

As the name implies, carboxylic acids are acidic. They therefore react with bases such as sodium hydroxide to give metal carboxylate salts. Like other Bronsted-Lowry acids discussed in previous courses, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ ($H^+ + H_2O$) and carboxylate anions, $RCOO^-$. The carboxylate anion is stabilized by resonance where the negative charge is delocalized over both oxygen atoms. Remember that we use a double-headed arrow only when electrons are being moved (resonance forms) and not when atoms are moving.



As with all acids, we can define an acidity constant K_a which equals the concentration of the carboxylate salt multiplied by the concentration of (H^+) divided by the concentration of the carboxylic acid.

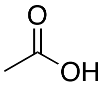
$$K_a = \frac{[RCOO^-][H^+]}{[RCOOH]}$$

For most carboxylic acids, K_a is approximately 10^{-5}. Acetic acid, for example, has $K_a = 10^{-4.5}$, which corresponds to a pK_a of 4.5 ($pK_a = -\log K_a$). In practical terms, K_a values near 10^{-5} mean that only about one part in 100,000 is dissociated, as opposed to 100% dissociation found with strong mineral acids such as HCl and H_2SO_4.

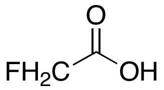
Substituent Effects on Acidity

The pK_a value of a carboxylic acid is quite different when it is substituted. Since the dissociation of a carboxylic acid is an equilibrium reaction, any factor that stabilizes the carboxylate anion relative to the undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. For example, an electron-withdrawing group attached to the carboxyl should inductively withdraw electron density, thereby stabilizing the carboxylate anion and increase acidity. An electron-donating group would conversely do the opposite.

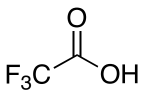
Electronegative substituents, such as halogens, make the carboxylate anion more stable. Fluoroacetic acid and trifluoroacetic acid are both stronger acids than acetic acid because they stabilize the carboxylate anion by inductively withdrawing electron density.



pKa = 4.5



pKa = 2.6

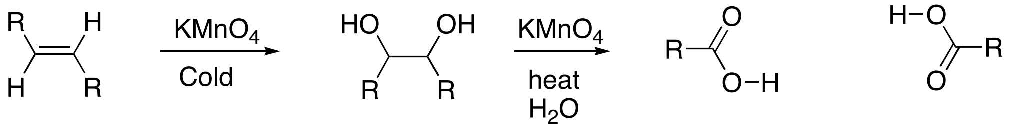


pKa = 0.2

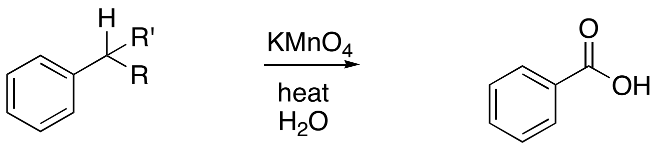
Preparation of Carboxylic Acids - Review

You have already seen most of the methods for the preparation of carboxylic acids so here is a review.

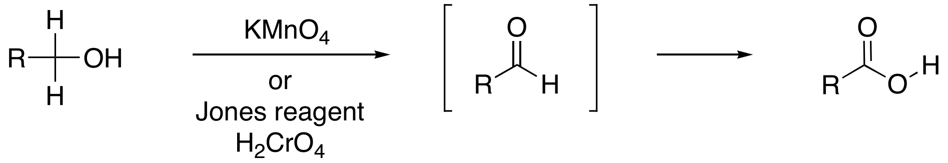
Oxidative cleavage of an alkene with aqueous $KMnO_4$ gives a carboxylic acid if the alkene has at least one vinylic hydrogen.



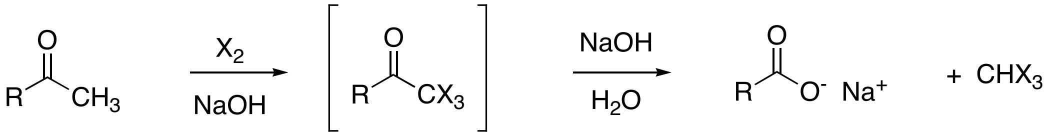
Oxidation of an alkylbenzene derivative with $KMnO_4$ gives a substituted benzoic acid derivative. Both primary and secondary alkyl groups can be oxidized but tertiary groups cannot.



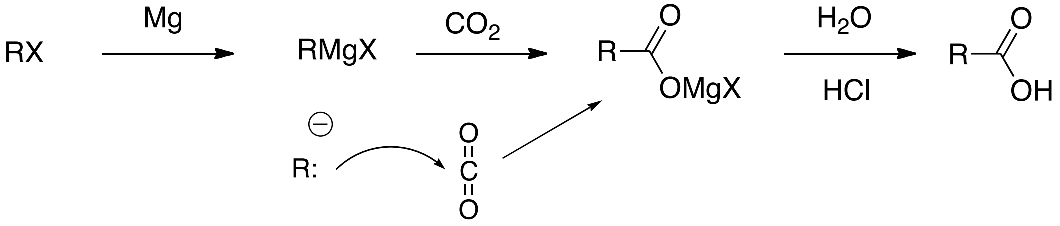
Oxidation of primary alcohols and aldehydes yields carboxylic acids when oxidized with $KMnO_4$, H_2CrO_4 or Jones reagent (CrO_3, H_2O, H_2SO_4). The oxidation of primary alcohols proceeds via an aldehyde intermediate, which is further oxidized to the carboxylic acid.



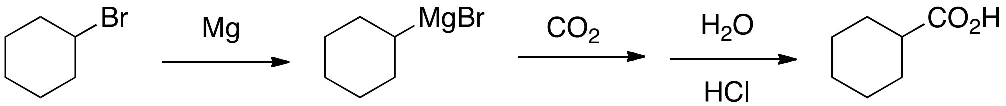
Not discussed in class:
The haloform reaction converts a methyl ketone into a carboxylate salt plus a haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3) and is the qualitative test for methyl ketones.



Not discussed in class:
From alkyl halide (or Grignard reagent) and CO_2:



Example:

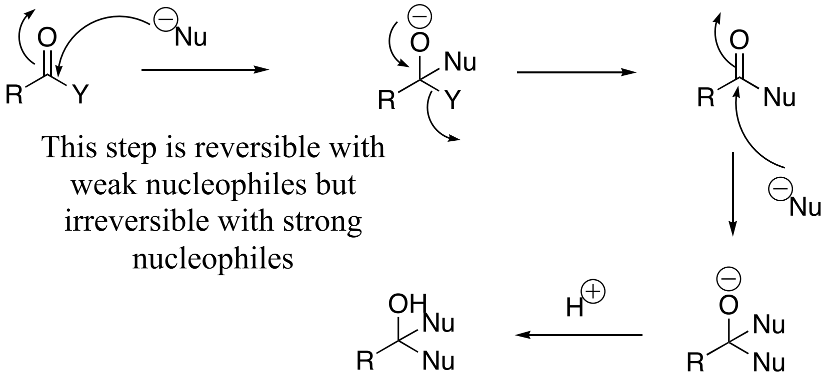


Reactions of Carboxylic Acids and Derivatives: Strong Nucleophiles

The strong nucleophiles ($Nu:^-$) that we have learned in this course are either hydride anion (H^-) or alkyl anion (R^-). Remember, attack by strong nucleophiles is not reversible.

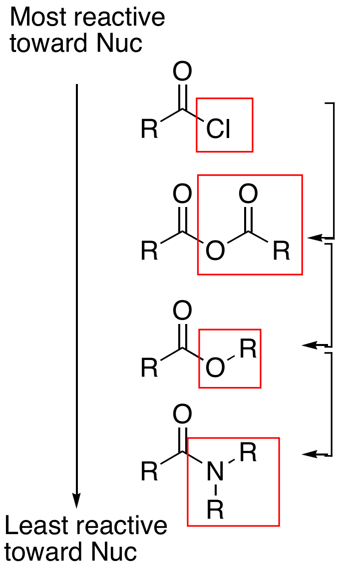
Hydride anion comes from hydride donors such as $LiAlH_4$ or $NaBH_4$ (however, $NaBH_4$ is not strong enough reaction on carboxylic acid derivatives except for acid chlorides). Alkyl anion comes from RM, where R is an alkyl group and M is a metal (these reagents include Grignard reagents (RMgX) and alkyl lithium reagents RLi). Grignard reagents fail with carboxylic acids, but alkyl lithium reagents can be used.

General mechanism:

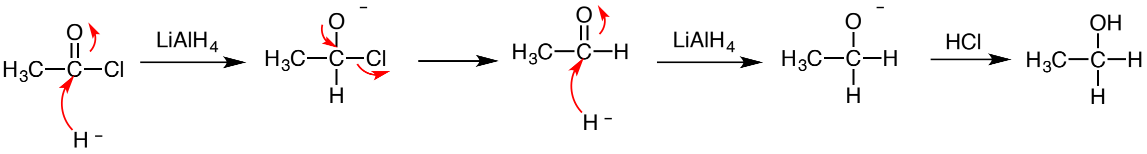


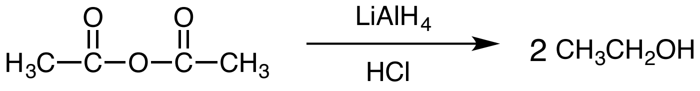
This step is reversible with weak nucleophiles but irreversible with strong nucleophiles

Addition of a nucleophile depends on stability of the leaving group. You can easily transform the most reactive carboxylic acid derivatives to less reactive carboxylic acid derivatives but you cannot easily transform the least reactive derivative to the most reactive derivative.

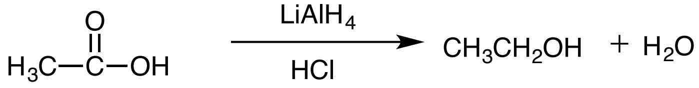


Examples:

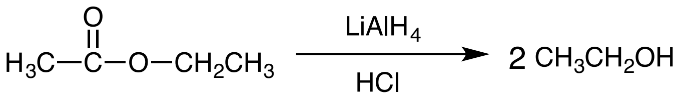




$$\mathrm{H_3C-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3} \xrightarrow[\text{HCl}]{\text{LiAlH}_4} 2\ \mathrm{CH_3CH_2OH}$$

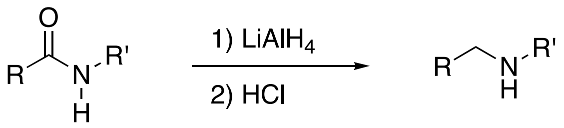


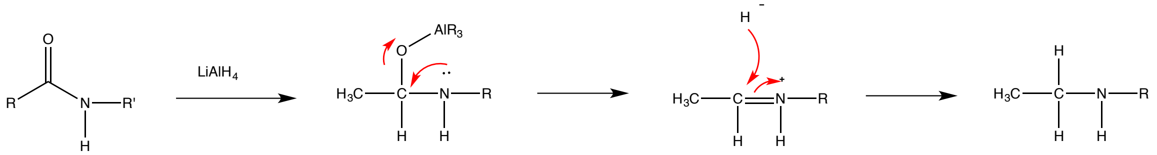
$$\mathrm{H_3C-\overset{O}{\overset{\|}{C}}-OH} \xrightarrow[\text{HCl}]{\text{LiAlH}_4} \mathrm{CH_3CH_2OH} + \mathrm{H_2O}$$



$$\mathrm{H_3C-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3} \xrightarrow[\text{HCl}]{\text{LiAlH}_4} 2\ \mathrm{CH_3CH_2OH}$$

“Exception” for $\mathrm{LiAlH_4}$





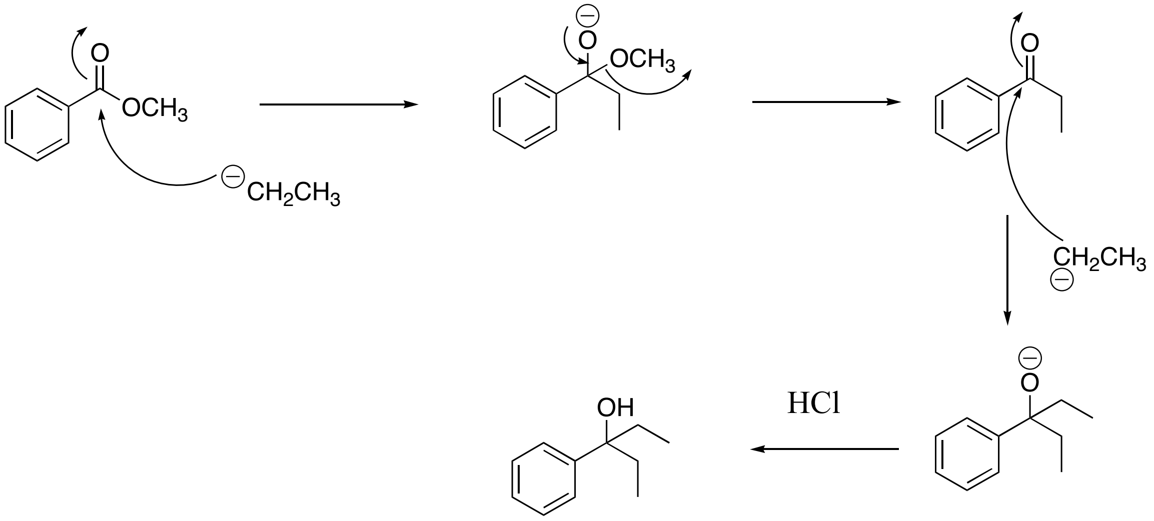
Alkyl anion as nucleophile

$$\text{R-X} \xrightarrow[\text{or Mg}]{\text{Li}} \text{R-Li} + \text{LiX}$$

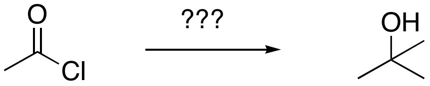
X= Cl, Br, I

Behaves like R⊖

Example:



Example:

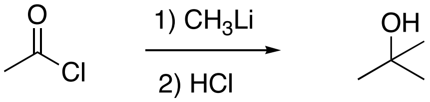


What reagent would you use for this reaction?

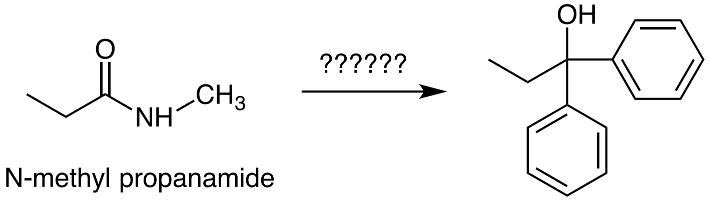
Let's analyze this: *What has changed between the two molecules?*
The Cl group has gone, there are three methyl groups attached to the center carbon, and carbon oxygen double bond is singly bonded. Methyl anion is used in this reaction.

Analysis of the problem:

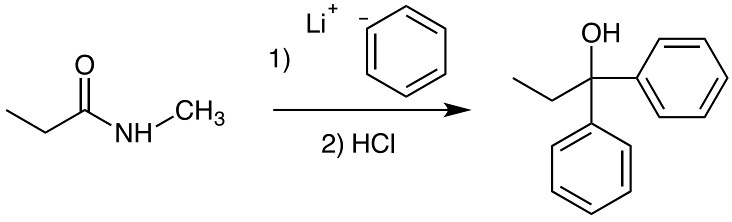
Add	Reagent	Remove
H+	HCl	
CH_3^-	CH_3Li	
CH_3^-	CH_3Li	- Cl



Example:



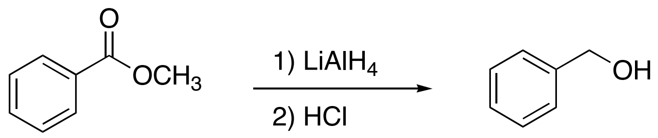
Answer:

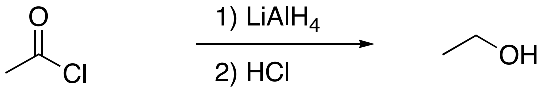


H^- ($LiAlH_4$) as a nucleophile:

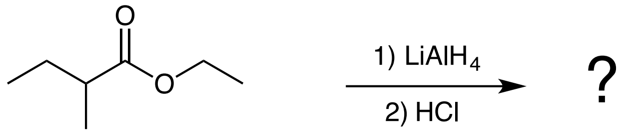
The mechanism of hydride anion attack on carboxylic acid derivatives is the same as shown above for the alkyl anion attack.

Example:



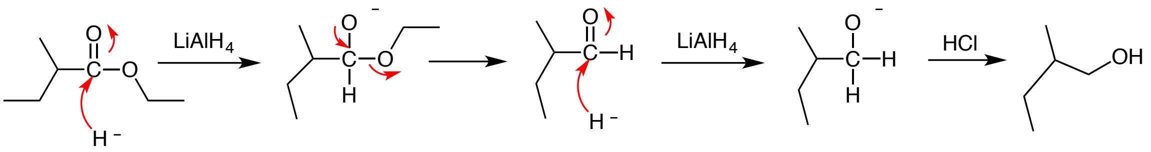


Example:



Ethyl-2-methylbutanoate

Answer:

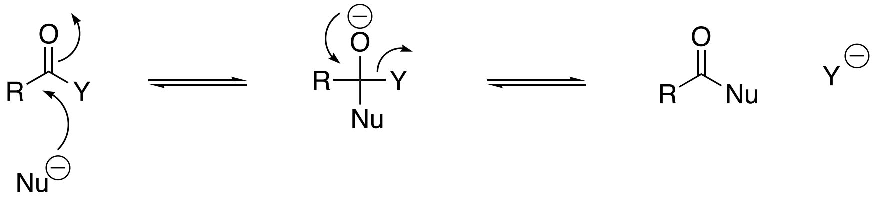


and ethanol

General Reaction of any Carboxylic Acid Derivative with a Weak Nucleophile

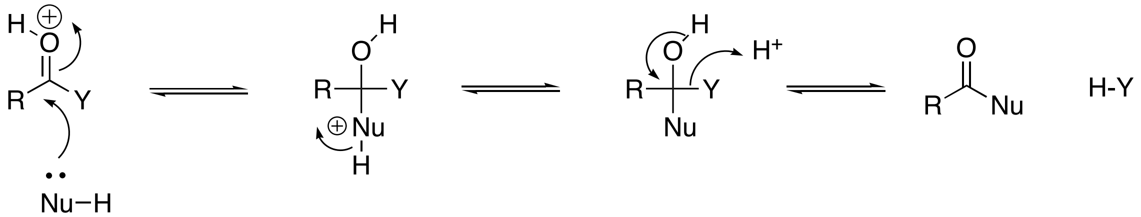
The chemistry of carboxylic acid derivatives is dominated by the nucleophilic acyl substitution reaction. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative, followed by expulsion of a leaving group from the tetrahedral intermediate. These reactions takes place in both acidic and basic environments and have slight mechanistic differences. These reactions are also reversible with weak nucleophiles.

Under basic conditions, the anionic nucleophile will attack the carbonyl of the carboxylic acid derivative to form the tetrahedral intermediate. This intermediate will then displace the leaving group (shown as Y) to yield the substituted carboxylic acid and the Y anion. If the Y anion is quite basic (e.g. amide anion $R_2N:^-$ or alkoxide/hydroxide anion RO^-) it will leave only as a neutral species after protonation of the nitrogen or oxygen.



tetrahedral intermediate

Under acidic conditions, a lone pair of electrons from the nucleophile will attack the protonated carbonyl group of the carboxylic acid derivative to form a positively charged tetrahedral intermediate. Loss of a proton then yields the neutral species. The intermediate then expels the leaving group, which is protonated to yield the substituted carboxylic acid and the protonated leaving group.



Reactivity of carboxylic acid derivatives