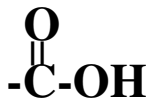
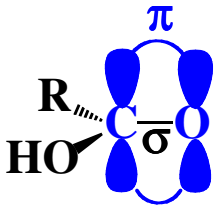
Chapter 18

Carboxylic Acids and Their Derivatives: Nucleophilic Addition-Elimination at the Acyl Carbon

Carboxylic acids are a family of organic compounds with the functional group  **which is also written as -CO_2H or COOH.**

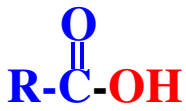
The carbon-oxygen double bond is made up of a σ-bond and a π-bond. The carbon atom is sp^2 hybridized, which explains the trigonal planar geometry at this center.



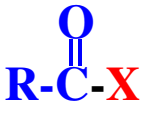
R may be alkyl, aryl or simply H

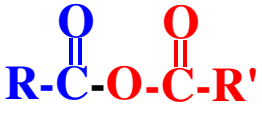
Carboxylic Acid Derivatives

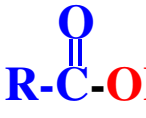
The carboxyl group consists of two parts, the acyl group and the attached hydroxyl group:

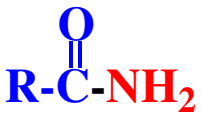


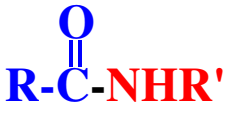
The acid derivatives are compounds in which the hydroxyl group is replaced with another group or a halogen atom. The principal examples are:

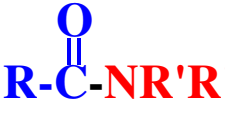
 **Acyl (acid) halides**

 **Acid anhydrides**

 **Esters**

 **Amides**

 ***N*-Monosubstituted Amides**

 ***N*,*N*-Disubstituted Amides**

Another class of carboxylic acid derivatives are the nitriles, which qualify because on hydrolysis, like all of the other derivatives above, they yield carboxylic acids.

 **Nitriles**

Nomenclature of Carboxylic Acids

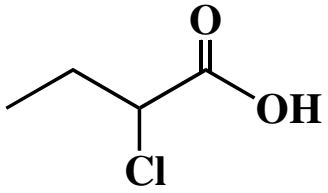
Common names are frequently used for the simpler carboxylic acids that have been known for hundreds of years.

HCOOH	CH_3COOH	$CH_3CH_2CH_2COOH$
Formic acid	**Acetic acid**	**Butyric acid**
(from Latin *formica,* ant)	(from Latin *acetum,* vinegar)	(from Latin *butyrum,* butter)

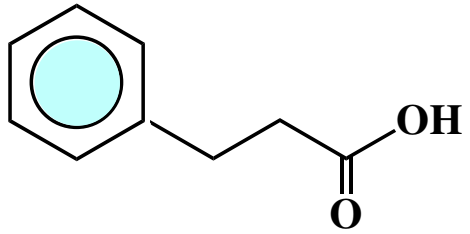
In common names, the positions of substituents are often given by α, β, γ....

δ γ β α
C–C–C–C–COOH

Examples



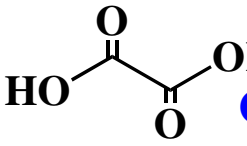
α-Chlorobutyric acid



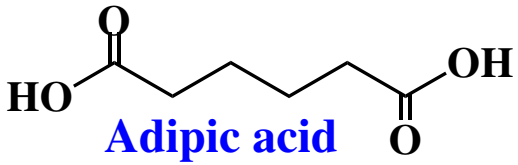
β-Phenylpropionic acid

The simple dicarboxylic acids have common names, they are the ones usually used, and it is advisable to learn them at least through the six-carbon one. These are oxalic, malonic, succinic, glutaric, and adipic acid.

Examples



Oxalic acid



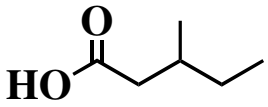
Adipic acid

Systematic Names of Carboxylic Acids

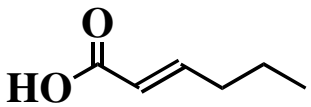
IUPAC systematic names are derived from the name of the longest-chain alkane present (the parent compound), dropping the final *-e*, and adding *-oic acid*.

Note: Count carboxyl carbon as part of the parent chain.

Examples

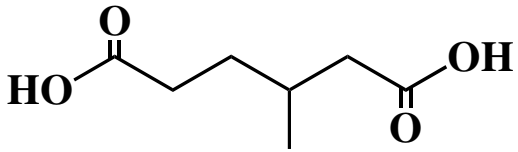


3-Methylpentanoic acid

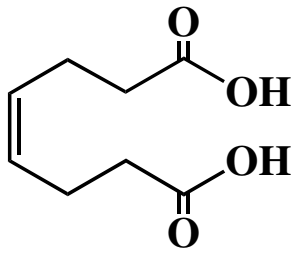


(*E*)-2-Hexenoic acid

Dicarboxylic acids can be named similarly although most have common names that are the ones usually used.



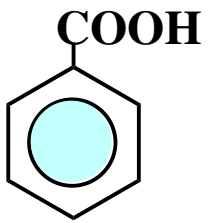
3-Methylhexanedioic acid



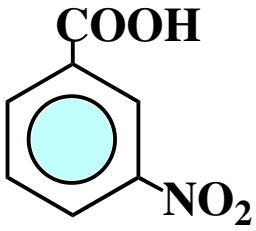
(*Z*)-4-Octenedioic acid

Aromatic Acids: Benzoic Acids

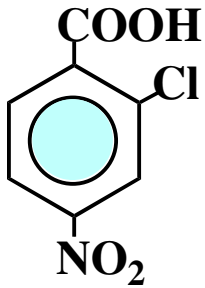
The carboxylic acids derived from benzene are named as derivatives of benzoic acid, using the standard notations to indicate positions of substituent groups.



Benzoic acid



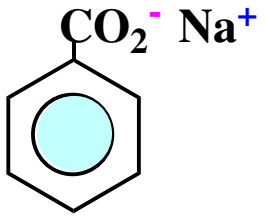
m-Nitrobenzoic acid



2-Chloro-4-nitrobenzoic acid

Salts of Carboxylic Acids

To name a salt, use the name of the cation (sodium, ammonium, etc.) followed by the name of the acid with "ic acid" changed to "ate."



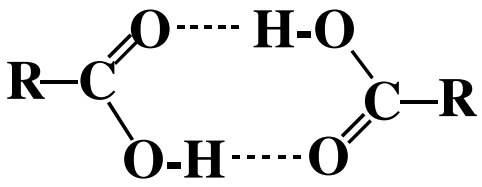
Sodium benzoate

$(CH_3CH_2CO_2^-)_2\ Mg^{2+}$

Magnesium propanoate
or
Magnesium propionate

Physical Properties of Carboxylic acids

Carboxylic acids are polar protic molecules. They form strong hydrogen bonds. One example of this is that they exist as dimers in the liquid state.



The boiling points are about 20 °C higher than alcohols of comparable size.

Carboxylic acids, in neutral solvents, have solubility properties similar to those of alcohols. The first members of the aliphatic series (formic acid through butanoic acid) are miscible with water. Water solubility decreases with increasing chain length, with hexanoic acid being marginally soluble. On neutralization, because of ionic salt formation, most carboxylic acids become water soluble.

The Acid Strength of Carboxylic Acids

Carboxylic acids are weaker acids than mineral acids like HCl, HNO_3, or H_2SO_4, but they are more acidic than organic weak acids such as aliphatic alcohols. Carboxylic acids are converted into their carboxylate salts by aqueous solutions of hydroxide.

$$RCOOH \underset{H_3O^+}{\overset{HO^-/H_2O}{\rightleftharpoons}} RCO_2^-$$

Carboxylate anion of resulting salt

Aqueous solutions of mineral acids convert the salts back into the carboxylic acids.

Large carboxylic acids with limited or no solubility in water (those with 6 or more C's per carboxyl group) may be solubilized through their carboxylate salts:

$$R\text{-}COOH + Na^+ {}^-OH \xrightarrow{H_2O} R\text{-}CO_2^- Na^+ + H_2O$$

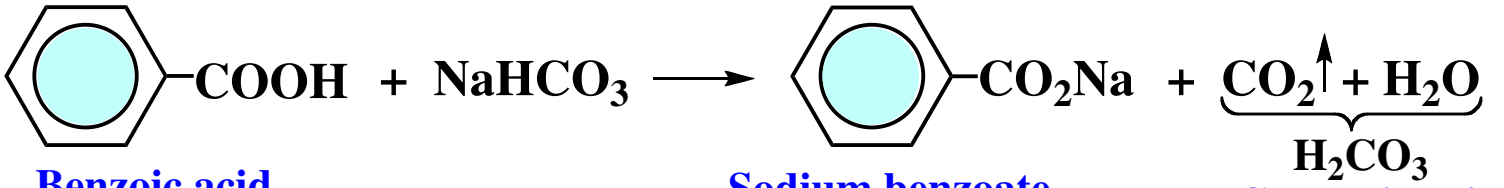
Water insoluble

Water soluble

These solubility properties are the basis for separating carboxylic acids from neutral organic compounds.

Carboxylic Acids: Comparison with Phenols

Carboxylic acids are sufficiently acidic to react with an aqueous solution of sodium bicarbonate to produce their carboxylate salts:



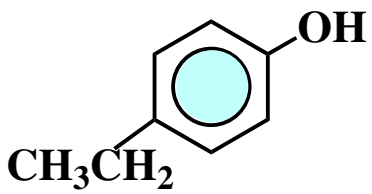
Benzoic acid
$K_a = 6.5 \times 10^{-5}$
stronger acid

stronger base

Sodium benzoate
weaker base

Carbonic acid
$K_a = 4 \times 10^{-7}$
weaker acid

Phenols are the hydroxyl derivatives of aromatic hydrocarbons, an example being:



A classic way to distinguish between carboxylic acids (pK_a ~ 4-5) and phenols (pK_a ~ 10) is by their solubility in an aqueous solution of sodium bicarbonate: Carboxylic acids will dissolve while (water insoluble) phenols will not. Both will dissolve in an aqueous solution of a strong base like NaOH.

A Comparison of the Acid Strength of Carboxylic Acids and Alcohols

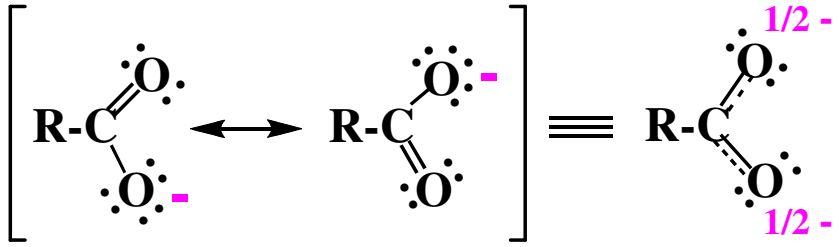
Carboxylic acids are considerably more acidic than alcohols in the absence of special electronic influences.

$$RCOOH + H_2O \rightleftharpoons RCO_2^- + H_3O^+ \qquad pK_a \sim 5$$

$$ROH + H_2O \rightleftharpoons RO^- + H_3O^+ \qquad pK_a \sim 16$$

The enhanced acidity of carboxylic acids is attributed to the greater stability of the carboxylate anion compared with the alkoxide anion, which shifts the equilibrium more to the product side.

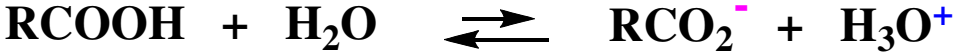
Resonance theory explains this stability through two equivalent resonance structures that contribute to the hybrid.



X-ray analysis of sodium formate shows equivalent C-O bond lengths of 1.27 Å, consistent with this picture of a resonance hybrid.

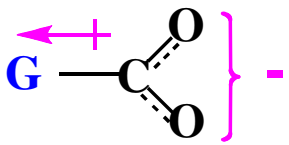
Effect of Substituents on Acidity

Any factor that stabilizes the anion more than it stabilizes the acid should increase acidity (decrease the magnitude of pK_a). Any factor that destabilizes the anion relative to the acid should decrease acidity.



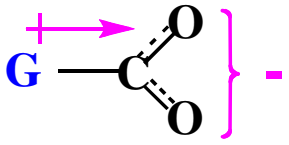
Electronic Influences

The electronic effect of a substituent G operates more strongly on the anion (charged species) than on the carboxylic acid (neutral species).



Electron withdrawal

Stabilizes the anion and increases acidity

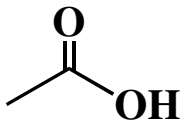


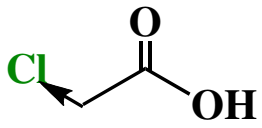
Electron release

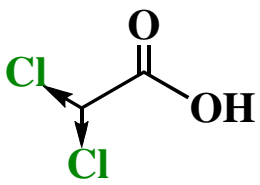
Destabilizes the anion and decreases acidity

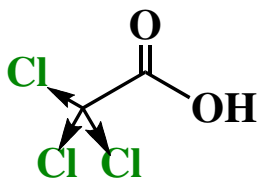
Some Examples of Substituent Effects

Electron-withdrawing α-substituents increase acidity:



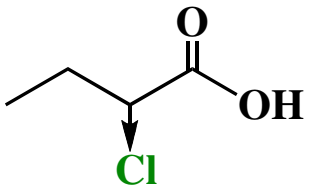


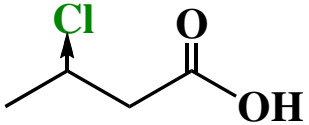


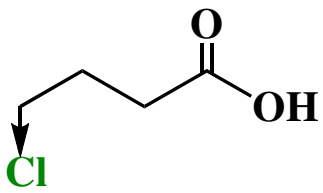


pK_a	4.76	2.86	1.48	0.70

The more remote an electron-withdrawing substituent is from the carbonyl group, the less its effect:



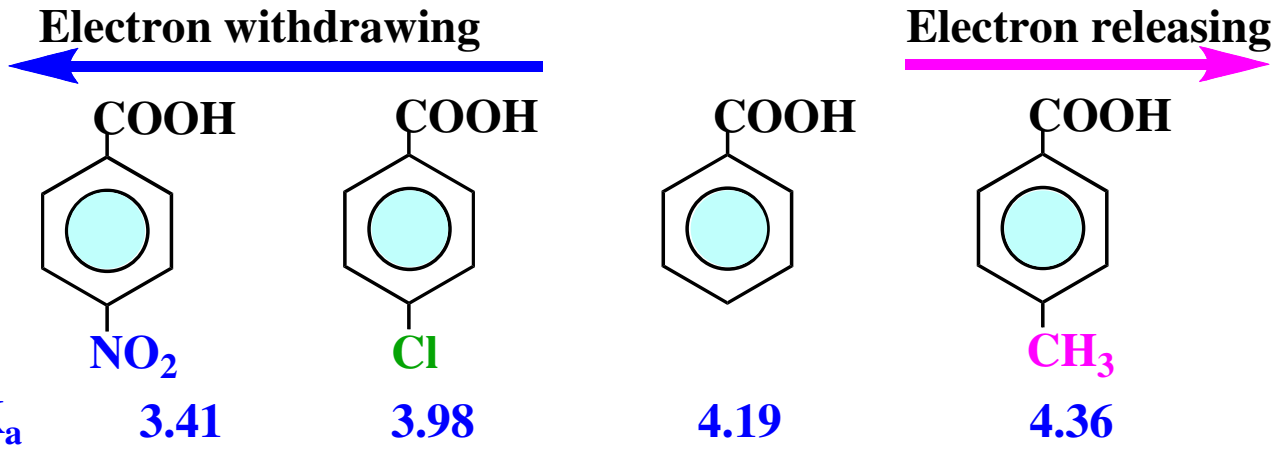




pK_a	2.85	4.05	4.50
	2-Chlorobutanoic acid	3-Chlorobutanoic acid	4-Chlorobutanoic acid

Substituent Effects in Benzoic Acids

Substituents introduced into the *para* position of a benzoic acid affect the acidity as expected for the electronic influence on the stability of the benzoate anion.

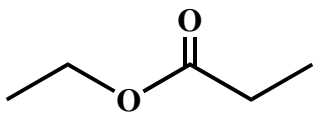


The substituent influence is from a combination of resonance and inductive effects because direct resonance interaction between the benzene ring and the carboxylate anion is not important.

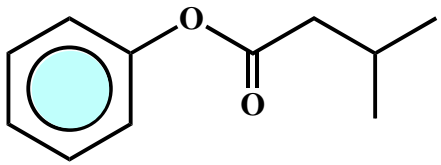
Esters

Their two-part names follow the pattern:
[Name of alkyl or aryl group derived from parent alcohol] [Name of carboxylate ion derived from parent acid]

Examples:



Made from ethanol and propanoic acid, so name is ethyl propanoate.

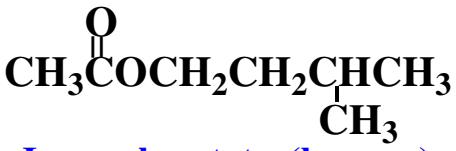


Made from phenol and 3-methylbutanoic acid, so name is phenyl 3-methylbutanoate.

Esters are hydrogen-bond acceptors, enhancing their water solubility, but they are not hydrogen-bond donors, lacking a hydrogen on oxygen. Consequently they cannot associate and so have low boiling points and high volatility. Fortunately, they have pleasant, fruit-like odors.

Esters as Perfumes and Flavoring Agents

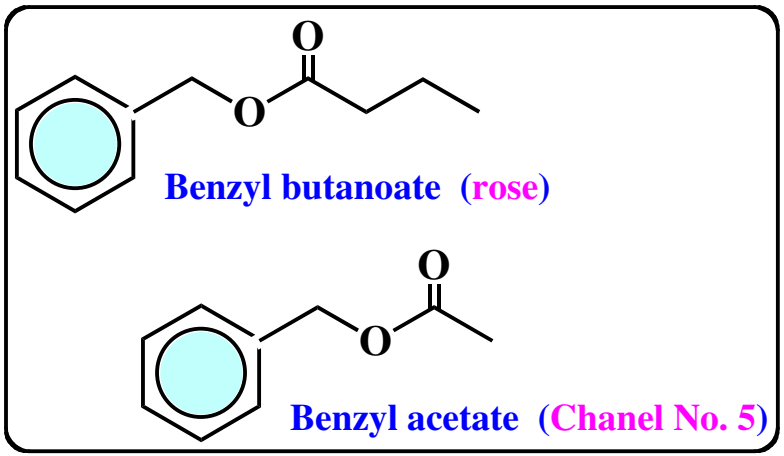
Many esters have pleasant odors and tastes and are used in perfumes and as flavoring agents. A number of these compounds occur in nature where they are responsible for the characteristic odor of fruits.



Isoamyl acetate (banana)

Butyl butanoate (pineapple)

Pentyl butanoate (apricot)



Benzyl butanoate (rose)

Benzyl acetate (Chanel No. 5)

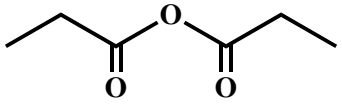
Octyl acetate (orange)

Ethyl formate (rum)

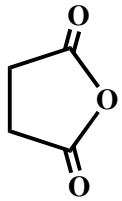
Carboxylic Anhydrides

As the term implies, they are prepared by removing a molecule of water from between two carboxyl groups. They are usually named from the parent acid, simply by replacing the word "acid" with "anhydride."

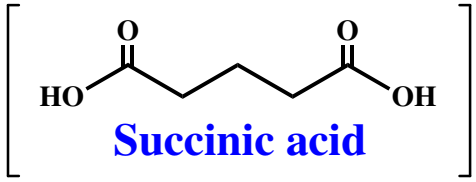
Examples:



Parent acid is propionic acid, so this is propionic anhydride.



Parent acid is succinic acid, so this is succinic anhydride.

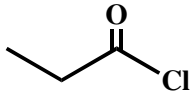


Succinic acid

Acyl Chlorides (Acid Chlorides)

These are named from the parent acid by dropping "-ic acid" from its name and replacing it with "-yl chloride."

Example:



Propionyl chloride

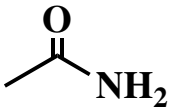
NOTE: Both of the above types of derivatives have intermolecular attractions similar to those of esters, and so they have boiling points in the same range as esters of comparable size.

Both of these types of derivatives are important, powerful donors of their acyl groups and find much use in synthesis.

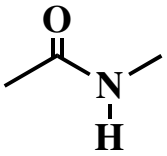
Amides

The amides considered here need to be distinguished from the metal amide bases like $NaNH_2$ and $LiN(i\text{-}Pr)_2$ studied earlier. The present ones are of general structure  where the different R's may be H's, alkyl groups, or aryl groups. They are named by dropping "-ic acid" from the name of the parent acid and adding "amide."

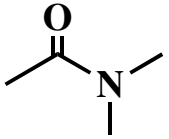
Examples:



Acetamide



N-Methyl-acetamide



N,*N*-Dimethyl-acetamide

MP (°C)	82	28	-20
BP (°C)	221	205	166

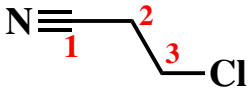
Note how both MP and BP decrease with decreasing opportunity for intramolecular hydrogen bonding.

Nitriles

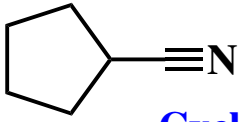
These derivatives are named by adding the suffix "-nitrile" to the name of the parent hydrocarbon, with the C of the CN group counting as part of the parent. Note: chain numbering begins with the nitrile C.

When the CN is attached to a cyclic parent, add "carbonitrile" to the parent name.

Examples:



3-Chloropropanenitrile



Cyclopentanecarbonitrile

Spectroscopic Properties of Acyl Compounds

Infrared Spectroscopy

Acyl compounds show characteristic IR absorption due to C=O stretch. This band is typically very prominent. The exact location (frequency) depends on the type of group (acid, ester, amide, etc.) and its electronic environment.

1) Carboxylic acids are readily identified by a C=O stretch near 1715 cm^{-1} and a broad O-H stretch between 2400-3500 cm^{-1}.

2) Esters show the C=O stretch somewhere between 1735-1750 cm^{-1} and C-O stretch at 1000-1300 cm^{-1}.

3) Acyl chlorides have their C=O band at 1785-1815 cm^{-1}.

4) Anhydrides have two C=O bands in the region 1750-1820 cm^{-1}.

5) Amides have their C=O band at 1640-1650 cm^{-1} and N-H (if present) stretch in the range 3140-3500 cm^{-1} (two bands if has NH_2, one if NH).

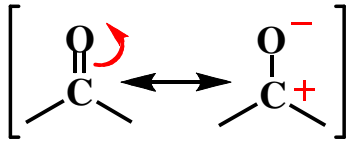
6) The related derivative type nitriles have their characteristic absorption in the triple bond stretching region, at about 2250 cm^{-1}.

Inductive and Resonance Effects

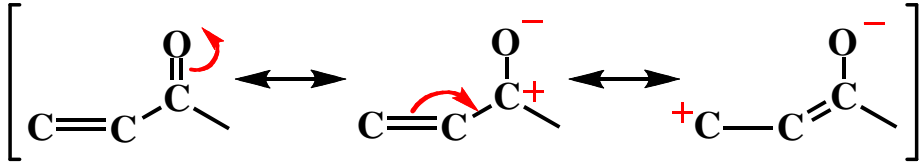
The electronic environment of a carbonyl affects its vibrational frequency, often in a predictable way. The frequency is a measure of a C=O group's bond multiplicity. As usual in IR spectrometry, as bond order decreases, C=O vibrational frequency decreases.

Examples of how to predict aproximately where a C=O absorption will be:

A simple ketone (or carboxyl) C=O absorbs at about 1715 cm^{-1} and may be represented by these resonance forms, which indicate the carbonyl bond order is between single and double.

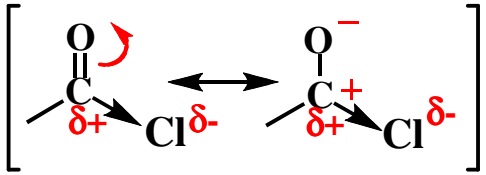


Conjugation effect: This introduces a contribution by one additional



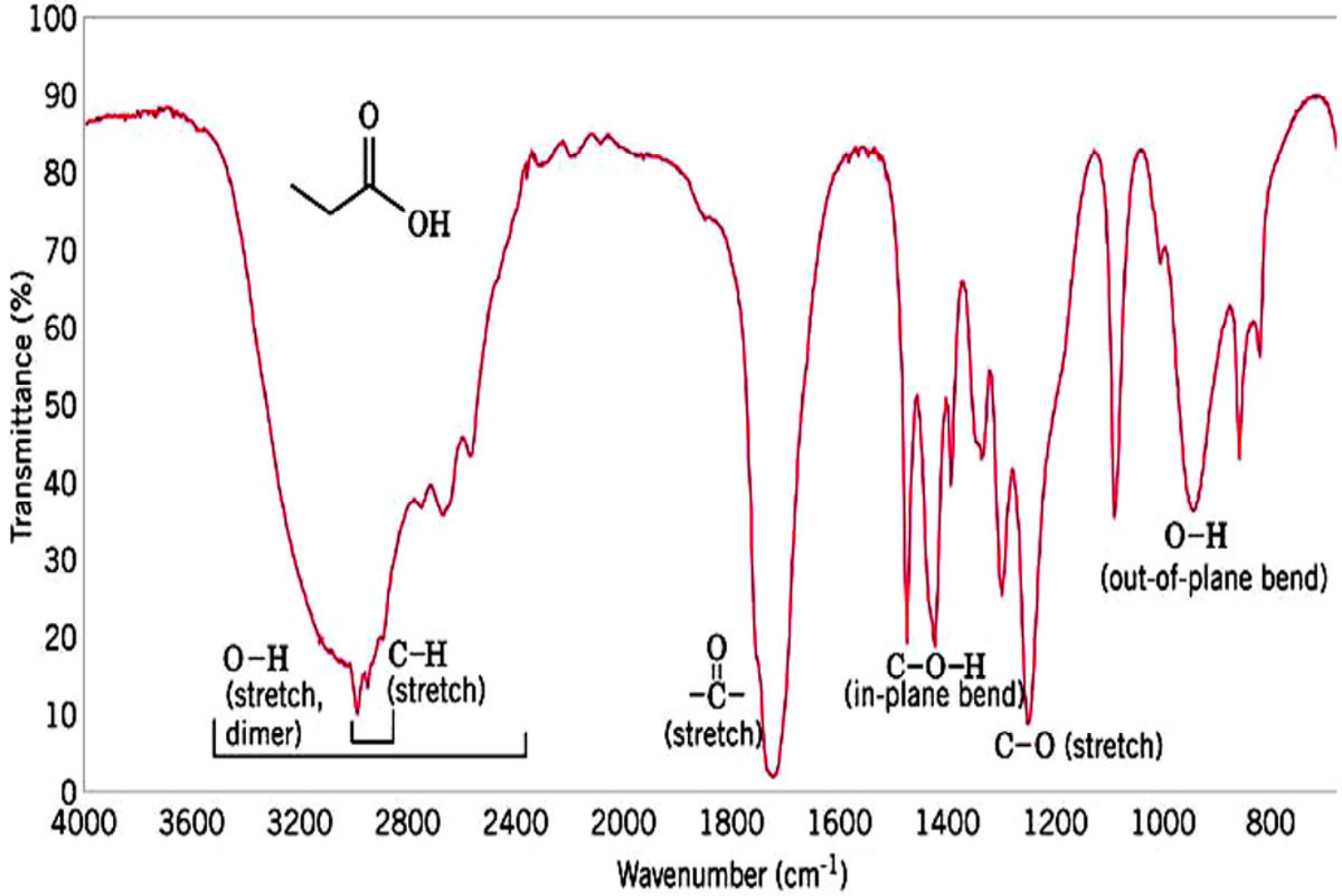
resonance form, one that decreases the bond multiplicity. So the vibrational frequency of the C=O group is decreased (to about 1695 cm^{-1}).

Inductive effect: Bonding a chlorine to the carbonyl, as in an acyl chloride, decreases the contribution of the C-O resonance form, and thus increases the multiplicity of the carbonyl. This increases its vibrational frequency (to about 1800 cm^{-1}).



IR Spectrum of Propanoic Acid ("neat", i.e., without dilution)

The C=O stretch frequency is at 1715 cm^{-1}; in the absence of hydrogen bonding (which enhances carbonyl single-bond character) it would be at about 1760 cm^{-1}.

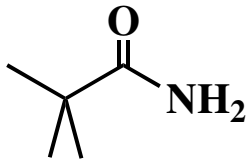


Ethyl Acetate

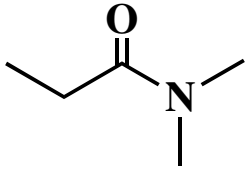
Note C=O stretch at about 1740 cm^{-1}, C-O stretch at about 1050 and 1200 cm^{-1}, and the absence of O-H stretch bands in the 3200-3600 cm^{-1} region.

Amides

2,2-Dimethyl-propanamide

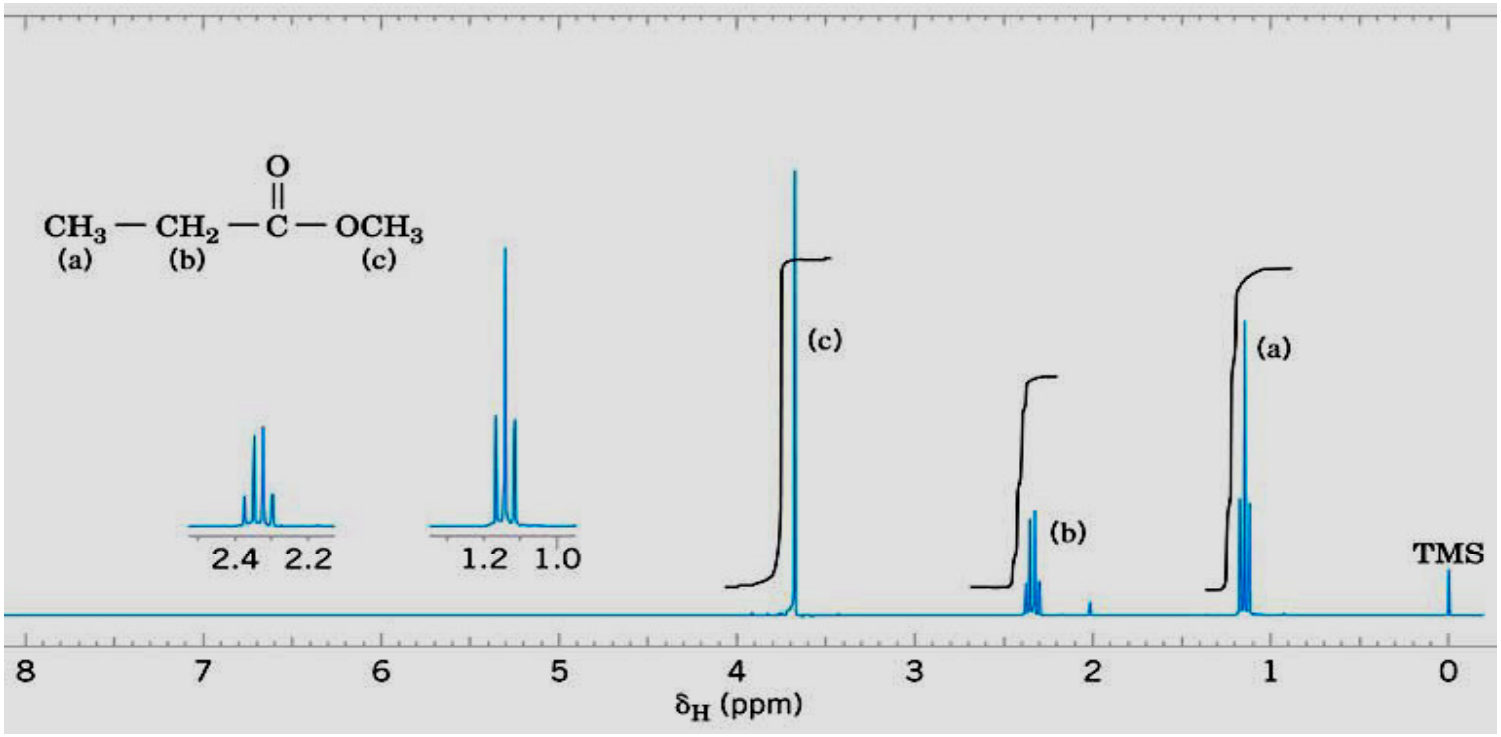


***N,N*-Dimethyl-propanamide**



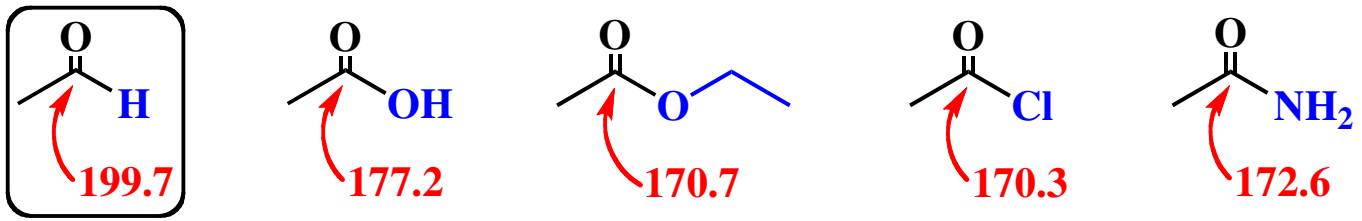
^{1}H NMR Spectroscopy

The acidic proton of a carboxylic acid is highly deshielded and appears far downfield in the range δ 10-12. Protons on a carbon α to a carbonyl appear in the δ 2.0-2.5 region. The chemical shifts, splitting patterns, and relative intensities of the H resonances of a typical ester are depicted in this methyl propionate spectrum.

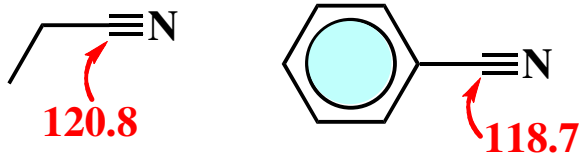


^{13}C NMR Spectroscopy

The carbonyl carbons of aldehydes and ketones appear at δ 180-220. When an O, N, or Cl is attached in place of the aldehyde H, the carbonyl carbon absorbs at a higher field position, δ 160-180.



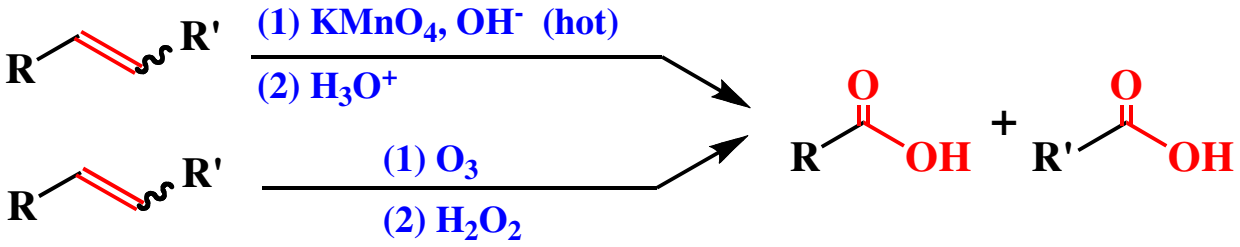
A nitrile carbon absorbs even further upfield, at δ 115-120.



Preparation of Carboxylic Acids

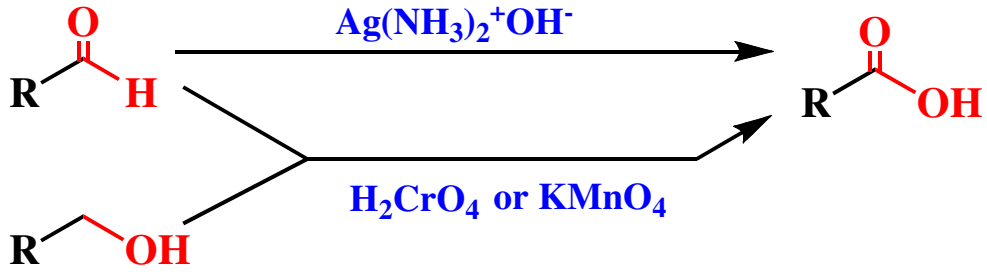
Oxidation of Alkenes

Alkenes can be oxidatively cleaved to carboxylic acids by use of either $KMnO_4$ or ozone.



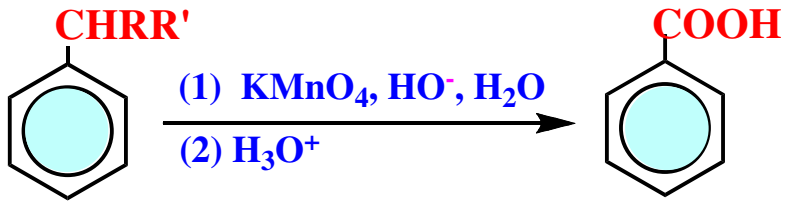
Oxidation of Aldehydes and 1º Alcohols

Aldehydes are easily oxidized to carboxylic acids, even by mild oxidants such as $Ag(NH_3)_2^+OH^-$, which is used in the Tollens' test for distinguishing aldehydes from ketones. Stronger reagents such as chromic acid (H_2CrO_4) or $KMnO_4$ can oxidize either aldehydes or 1º alcohols to carboxylic acids.



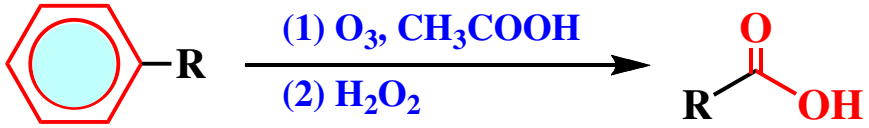
Oxidation of Alkylbenzenes

Vigorous oxidation by $KMnO_4$ of primary and secondary (but not tertiary) alkyl groups directly attached to a benzene ring produces aromatic acids.



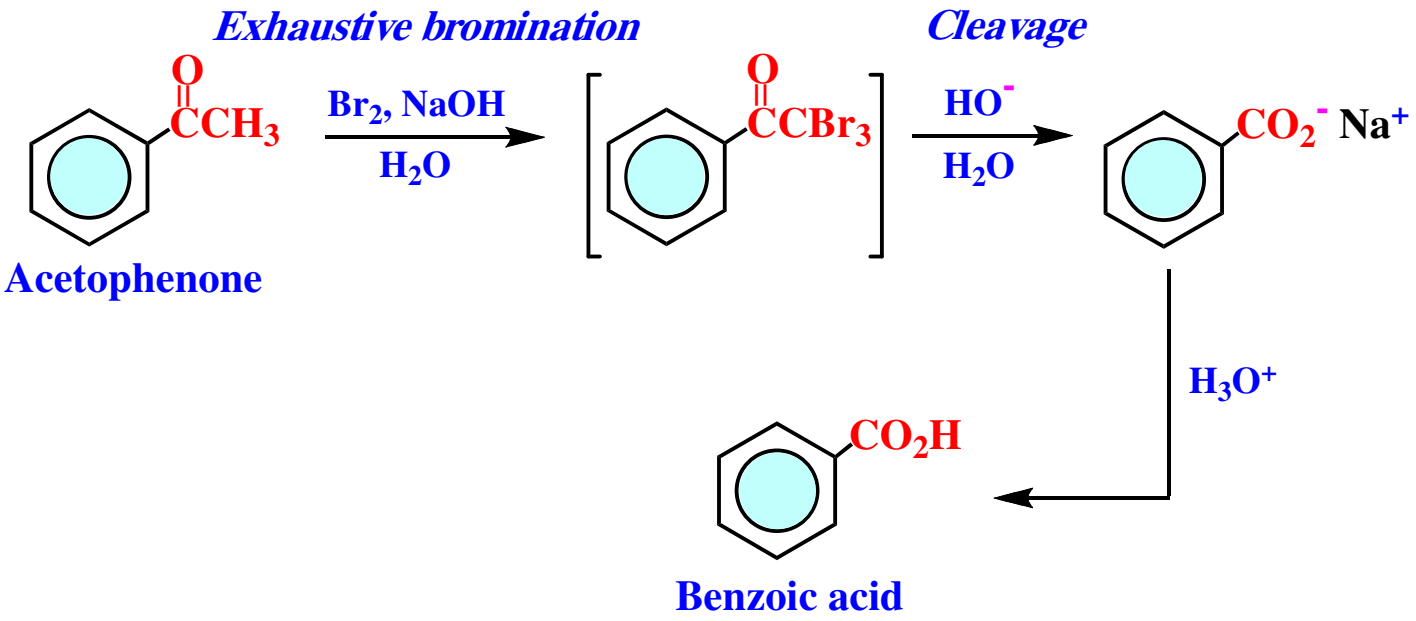
Oxidation of Alkylbenzenes

The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis.



Oxidative Cleavage of Methyl Ketones

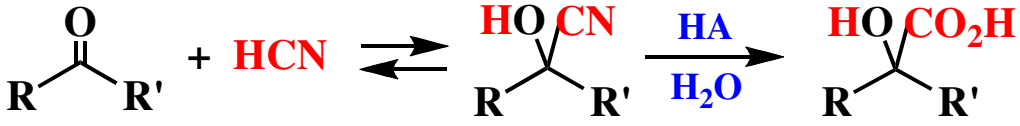
The haloform reaction converts methylketones to carboxylic acids (on acidification of the product).

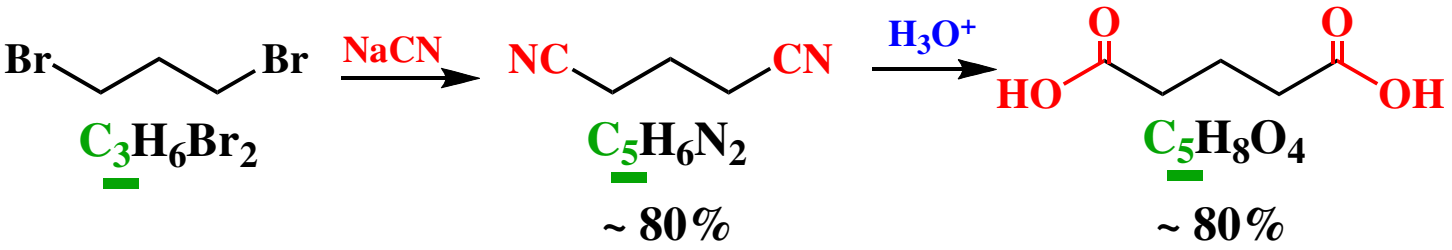


Hydrolysis of Cyanohydrins and Other Nitriles

Cyanohydrins, prepared by addition of HCN to aldehydes or ketones, can be hydrolyzed to α-hydroxy acids.

Nitriles can also be prepared by nucleophilic substitution reactions of 1° alkyl halides with sodium cyanide. Hydrolysis then provides a carboxylic acid of increased chain length .

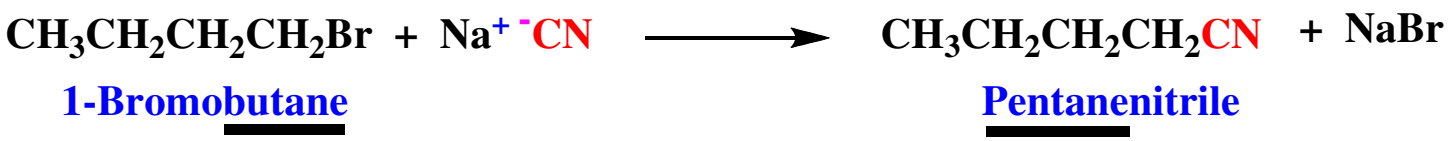




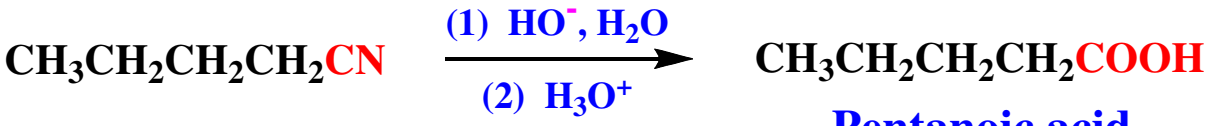
Because of the elimination-promoting basicity of cyanide ion, the S_N2 reaction proceeds in good yield only with CH_3X and 1° halides. Aryl halides (except for those with *o*- or *p*-nitro groups) do not readily undergo nucleophilic substitution reactions.

Hydrolysis of nitriles may be carried out under either basic or acidic conditions.

An Example: The Synthesis of Pentanoic Acid from 1-Bromobutane



1-Bromobutane — Pentanenitrile



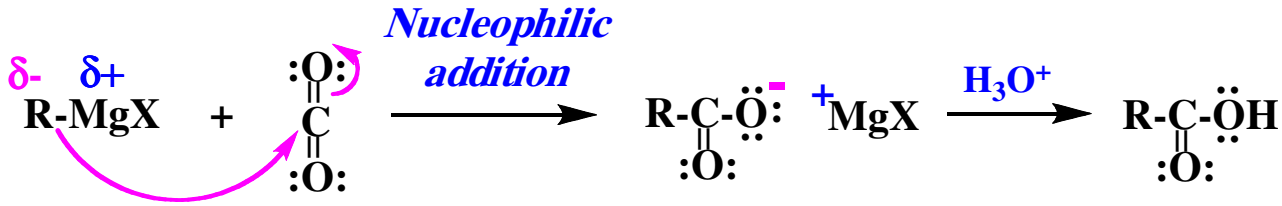
Pentanoic acid

(valeric acid)

Carbonation of Grignard Reagents

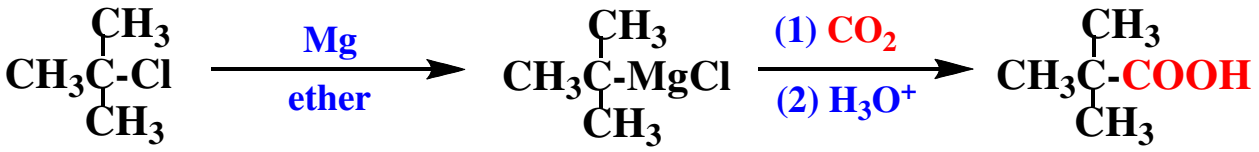
A more general way to prepare carboxylic acids from alkyl or aryl halides is by carbonation (reaction with CO_2) of the corresponding Grignard reagents.

The strongly nucleophilic organomagnesium reagents add to CO_2 to produce magnesium carboxylates. Acidification of these salts yields the carboxylic acids.



All alkyl (1º, 2º, 3º) and aryl Grignard reagents undergo the carboxylation reaction. This reaction is accomplished by either bubbling dry gaseous CO_2 through an ether solution of the Grignard reagent or by pouring the Grignard reagent onto crushed dry ice (solid CO_2).

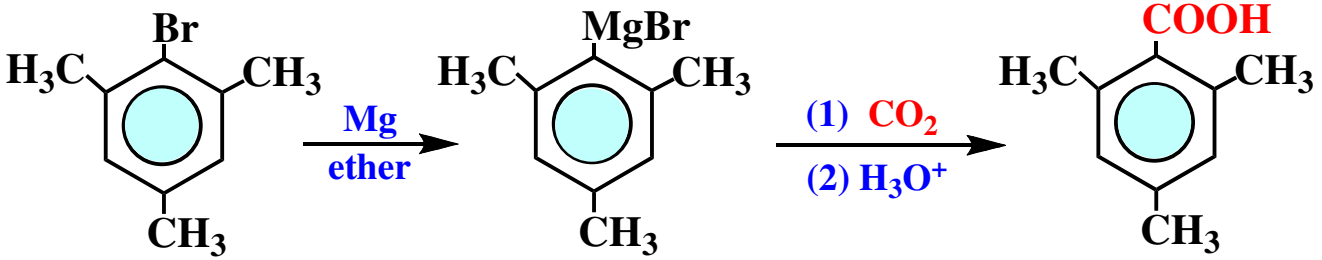
Syntheses Using the Grignard Carbonation Reaction



tert-Butyl chloride

tert-Butylmagnesium chloride

2,2-Dimethyl-propanoic acid



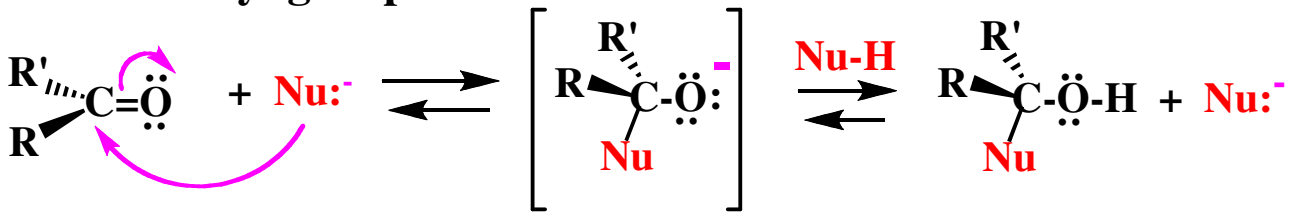
2,4,6-Trimethyl-bromobenzene

2,4,6-Trimethylphenyl-magnesium bromide

2,4,6-Trimethylbenzoic acid

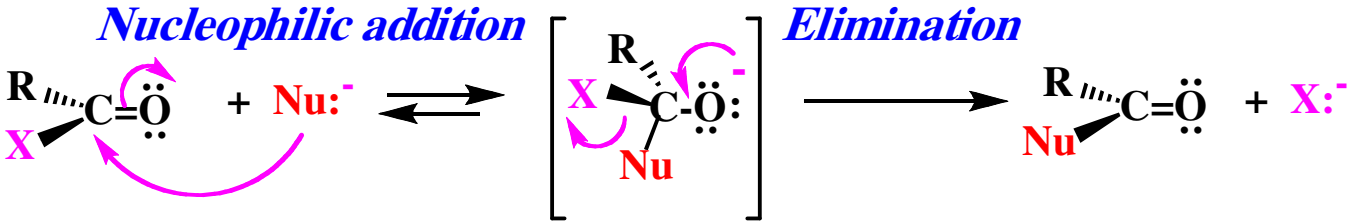
Nucleophilic Addition-Elimination at Acyl Carbon

Aldehydes and ketones undergo nucleophilic additions to the carbonyl group:



Tetrahedral intermediate

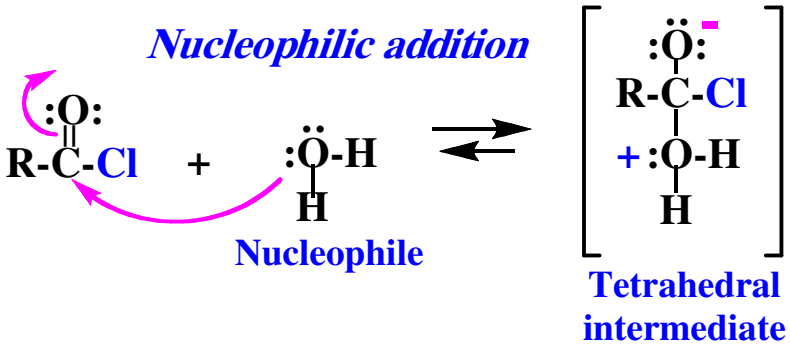
A typical reaction of carboxylic acids and their derivatives is nucleophilic addition-elimination. The first step is nucleophilic addition to the carbonyl to give a tetrahedral intermediate, but the presence of a good leaving group (X) at this site results in an elimination that regenerates the trigonal carbonyl.

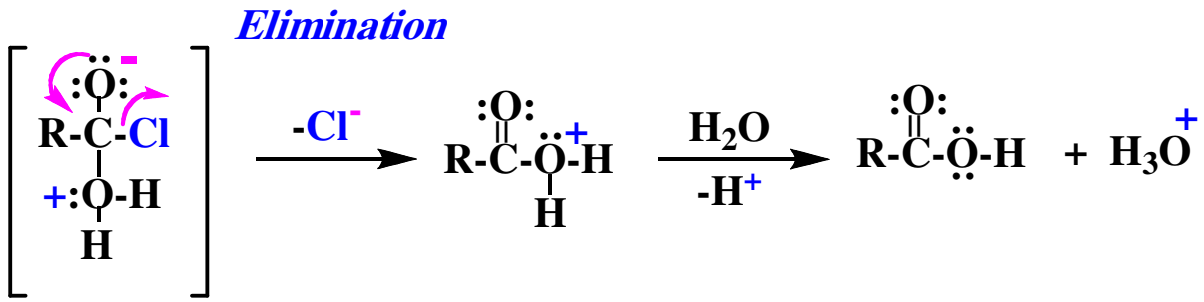


Tetrahedral intermediate

This reaction mechanism is employed in many biological systems, and biochemists call them acyl transfer reactions.

Example: Hydrolysis of an Acyl Chloride



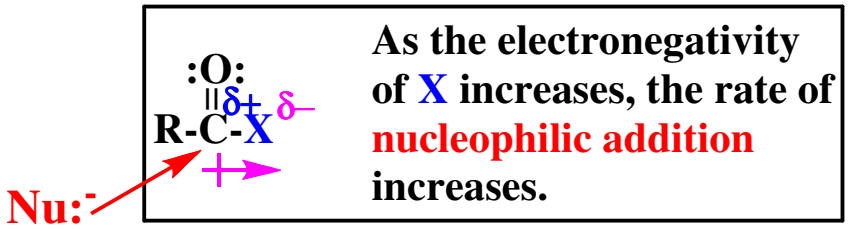


This reaction proceeds well because of the great reactivity of the acyl chloride towards nucleophilic addition and the good leaving group ability of Cl^- in the cleavage step.

Important Factors in the Addition-Elimination Reaction

Reactivity of the Acyl Carbon

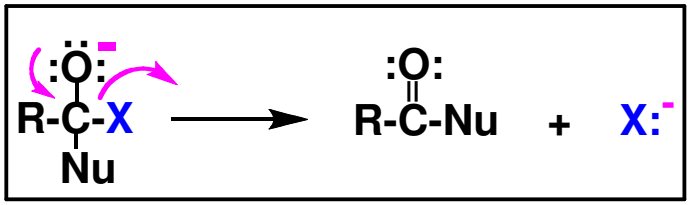
Electronic influences that increase the electropositive character of the acyl carbon enhance the rate of nucleophilic addition.



As the electronegativity of X increases, the rate of nucleophilic addition increases.

Stability of the Leaving Group

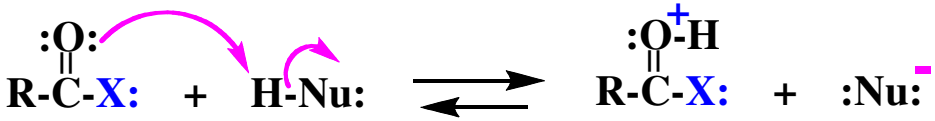
As the stability of $X:^-$ increases, it becomes a better leaving group.



Acid Catalysis

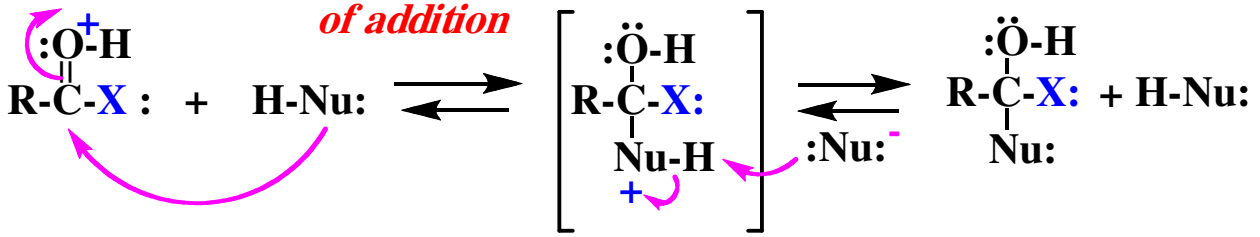
Acid catalysis is important in both the addition and elimination steps.

Protonation of the carbonyl



Provides electrophilic catalysis of addition

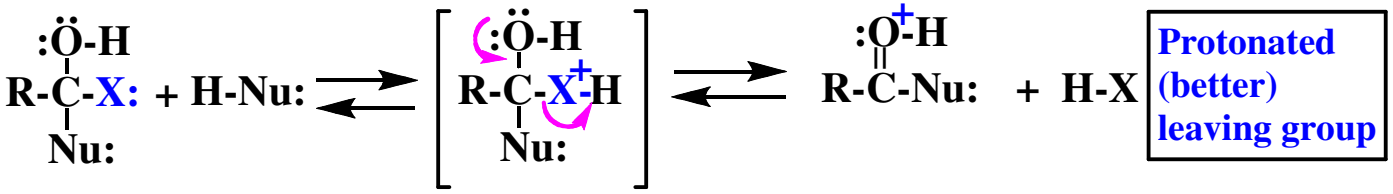
deprotonation



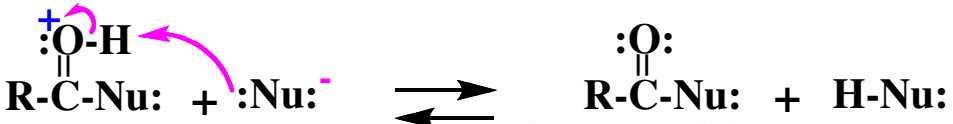
Tetrahedral intermediate

Protonation of leaving group

Electrophilic catalysis of elimination



Deprotonation



Acyl addition-elimination product

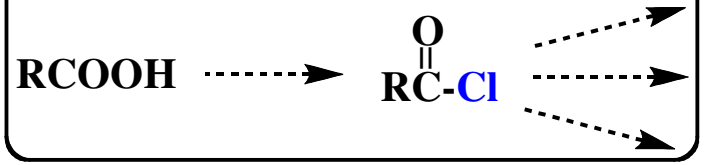
Relative Reactivity of Acyl Compounds

The basicity of the leaving group can explain the relative reactivity of acid derivatives below. The weaker the basicity of the leaving group, the more reactive the acid derivative.

Acyl chloride Acid anhydride Ester Amide

In general, a less reactive acyl compound can be prepared from more reactive acyl compounds. The reverse is usually difficult and, when possible, requires special reagents.

General Synthetic Scheme

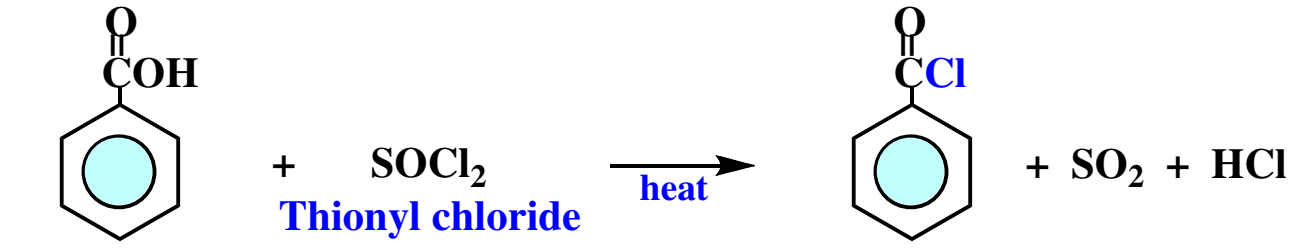


Synthesis of Acyl Chlorides

Because of their reactivity, acyl chlorides must be prepared under conditions that exclude exposure to good nucleophiles like water. Common reagents that convert carboxylic acids into acyl chlorides are phosphorus trichloride (PCl_3) phosphorus pentachloride (PCl_5), and thionyl chloride ($SOCl_2$).

Typical Synthetic Procedures

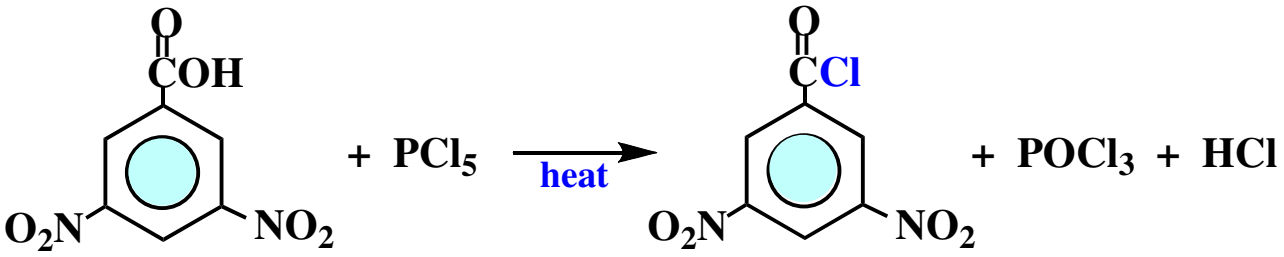
The carboxylic acid is heated with the reagent, with or without the presence of an inert solvent.



Benzoic acid **Thionyl chloride (bp 75-76 °C)** **Benzoyl chloride**

Thionyl chloride is an especially convenient reagent because the byproducts are gases and easily removed. Excess thionyl chloride is easy to remove by distillation.

Use of Phosphorus Pentachloride



3,5-Dinitrobenzoic acid

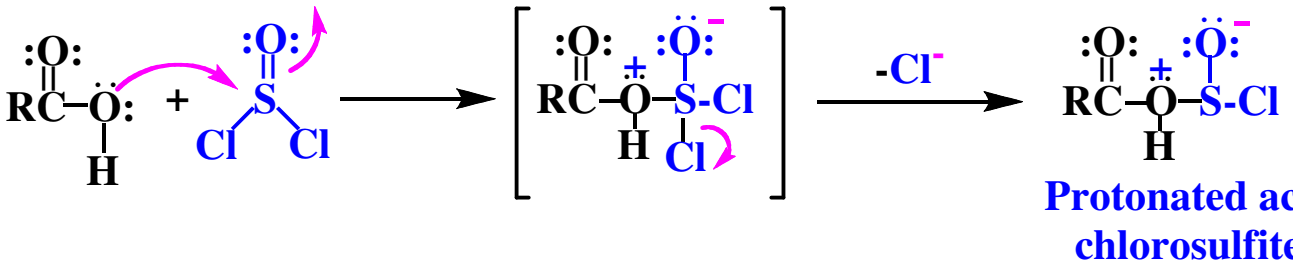
3,5-Dinitrobenzoyl chloride

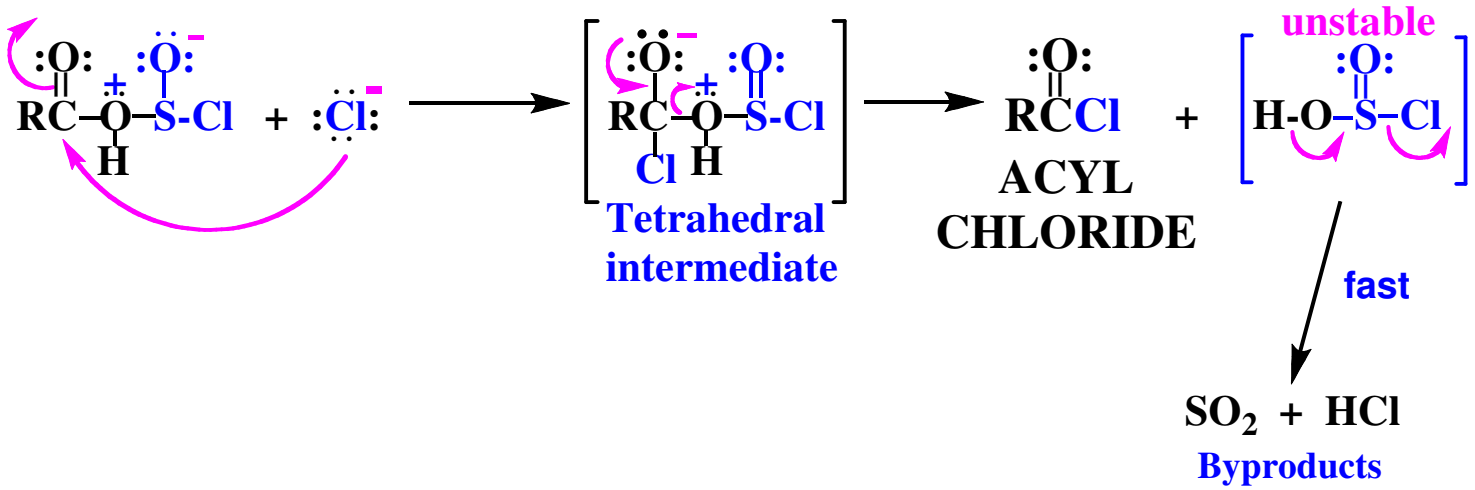
Phosphorus oxychloride

The acyl chlorides are usually isolated and purified, often by distillation. They are reasonably stable in the absence of water and other nucleophiles.

Both $SOCl_2$ and PCl_5 are strong electrophiles that transform the hydroxyl into a much better leaving group, thereby promoting substitution at the acyl carbon.

Mechanism for Acyl Chloride Synthesis Using Thionyl Chloride

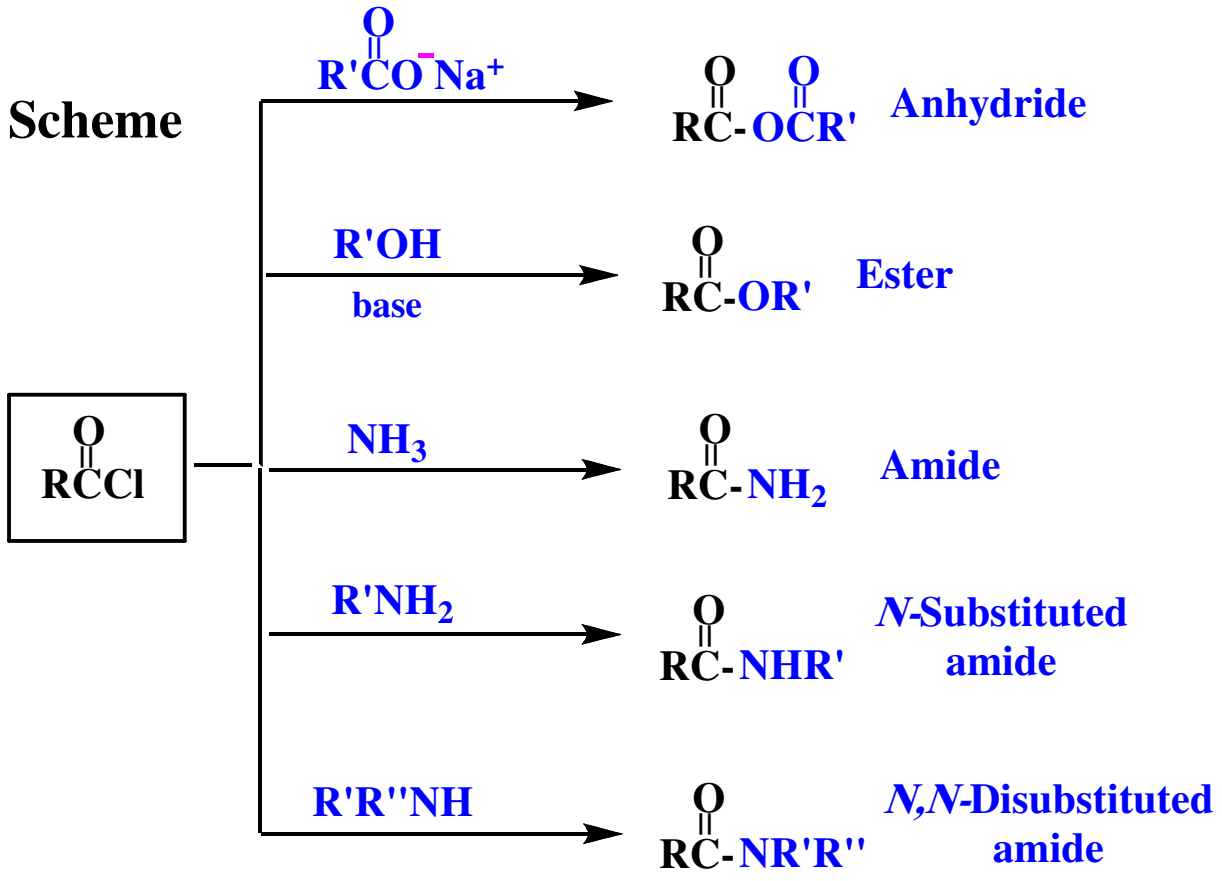




Reactions of Acyl Chlorides

Acyl chlorides are easily converted into other acyl compounds (acid anhydrides, esters, amides, etc.) by reaction with the appropriate nucleophile.

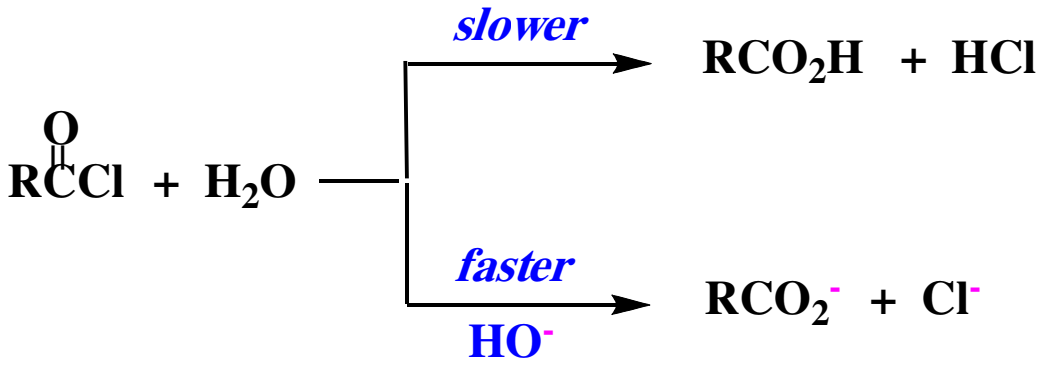
General Scheme



Hydrolysis of Acyl Chlorides

Hydrolysis converts acyl chlorides into carboxylic acids. Note that reaction with water yields HCl as a byproduct. Alkaline hydrolysis proceeds faster than acid hydrolysis.

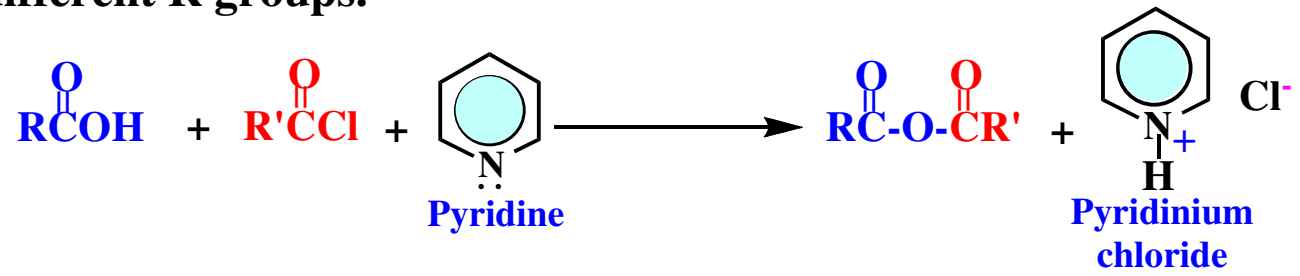
These reactions are rarely useful; usually they are accidental and need to be guarded against.



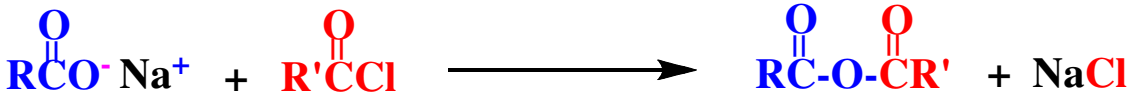
Carboxylic Acid Anhydrides

Synthesis

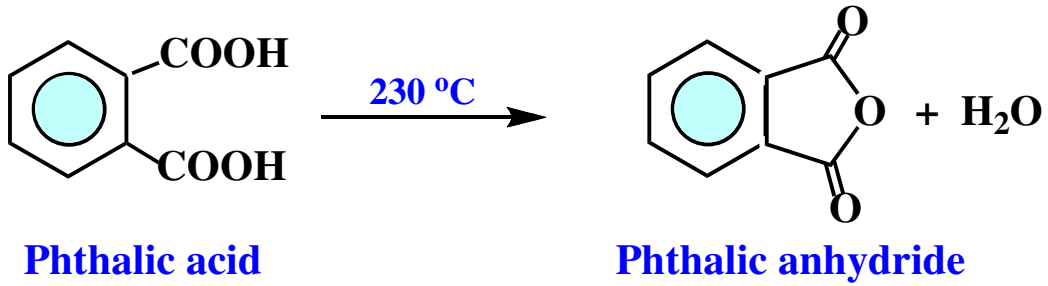
The reaction of a carboxylic acid and an acyl chloride in the presence of pyridine (a base) gives carboxylic acid anhydrides that may contain different R groups.



Alternatively, carboxylate salts may be reacted with acyl chlorides:

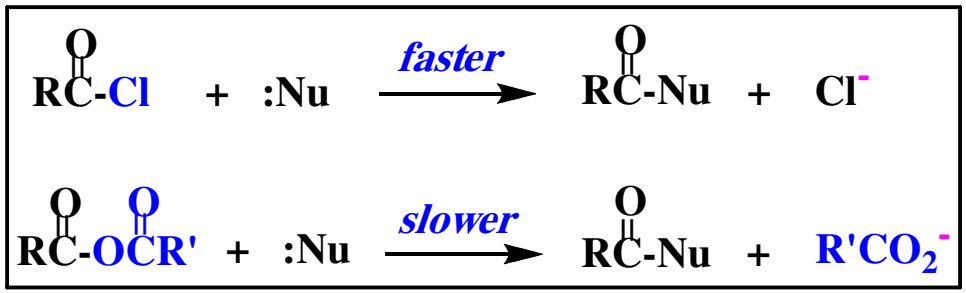


On heating, dicarboxylic acids yield cyclic anhydrides, if they have 5- or 6-membered rings.

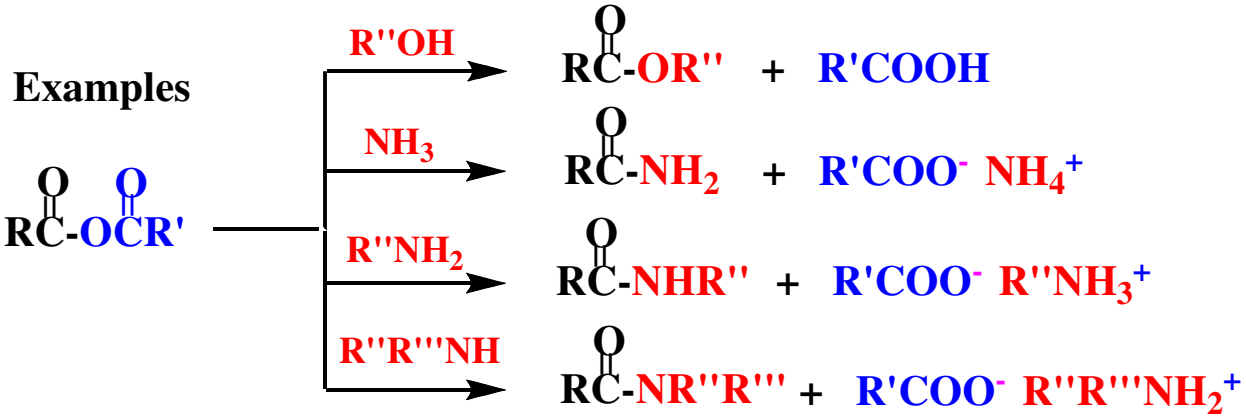


Reactions of Carboxylic Acid Anhydrides

Carboxylic acid anhydrides and acyl chlorides show parallel patterns of reactions. The latter react faster because of the better leaving group ability of Cl^-.



Examples

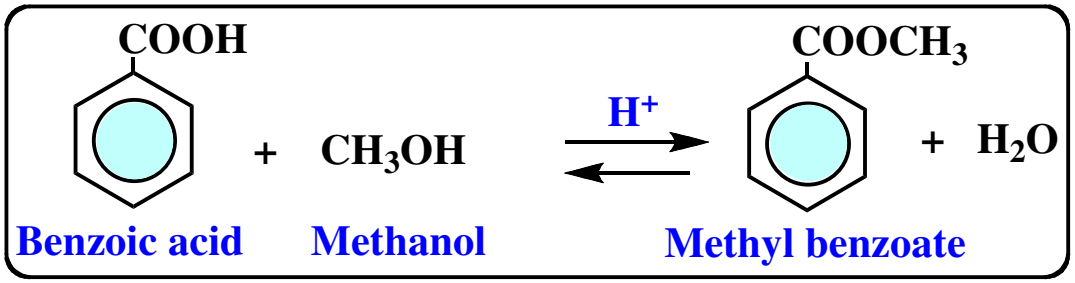


Esters

Synthesis of Esters

Direct Esterification of Carboxylic Acids

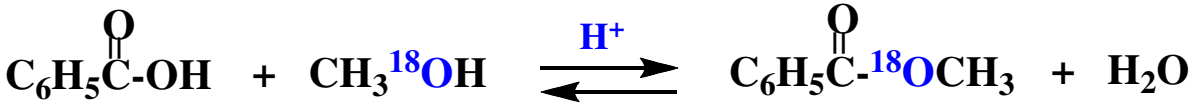
Carboxylic acids and alcohols react in the presence of a small amount of strong acid to give esters.



Esterifications are acid-catalyzed equilibrium reactions. Catalytic amounts of concentrated sulfuric acid or hydrochloric acid are used. Usually a large excess of the alcohol (10- or 15-fold) is used to drive the equilibrium to the product side. Product formation can also be promoted by removing the water as it is formed.

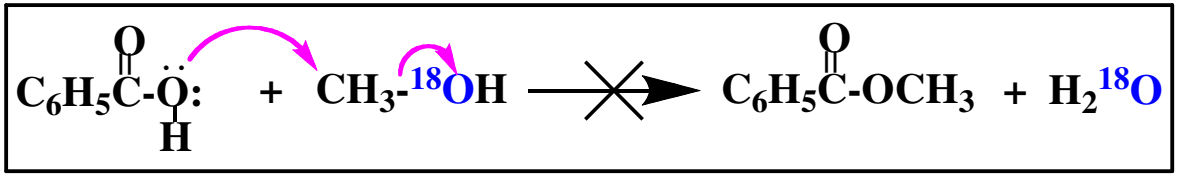
Mechanistic Studies by Isotopic Labeling

Insight into the key bonding changes during esterification was obtained by studies using isotopically enriched methanol.

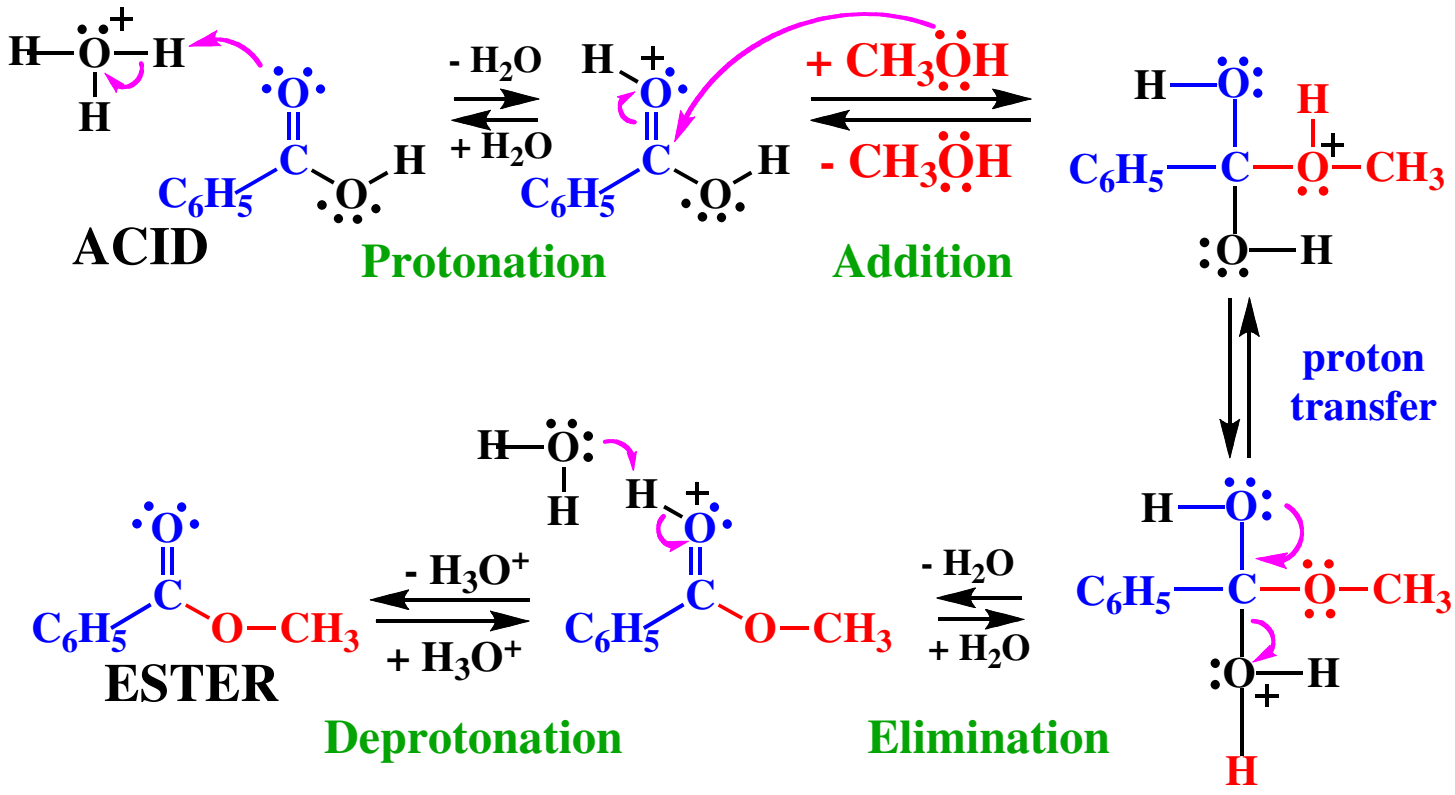


All the isotopic label appears in the methoxy oxygen.

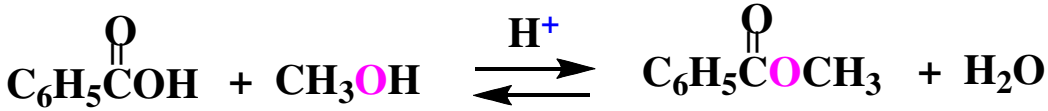
This result rules out an S_N2 mechanism:



The Mechanism of Acid-Catalyzed Esterification

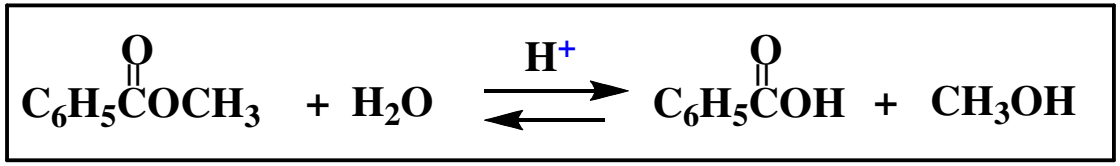


This mechanism for esterification is consistent with the incorporation of the isotopic label:



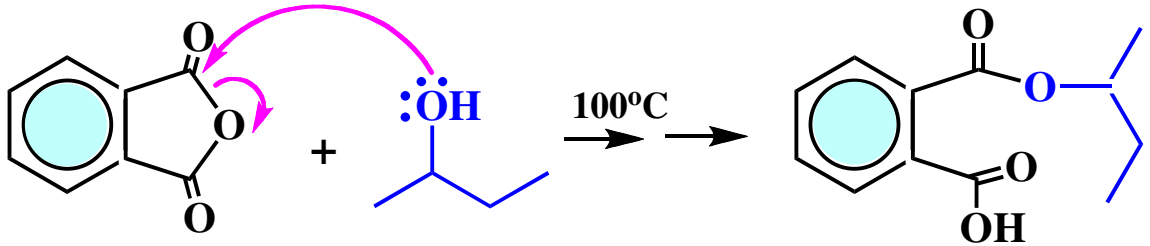
A Mechanism for Acid-Catalyzed Hydrolysis of Esters

Since every step is reversible, the reverse of the esterification scheme is the mechanism for the acid-catalyzed hydrolysis of esters.



The direction of the reaction is controlled by the relative concentrations of water versus alcohol.

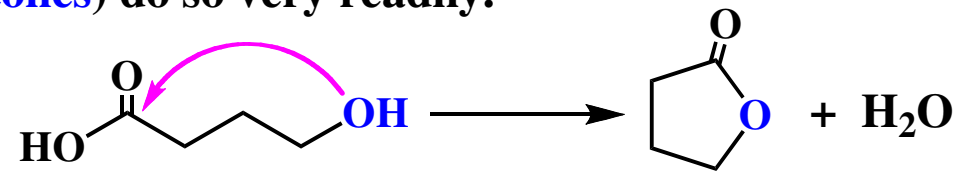
Cyclic Anhydrides Undergo Similar Reactions



Phthalic anhydride *sec*-Butyl alcohol *sec*-Butyl hydrogen phthalate

Intramolecular Esterification: Lactone Formation

Carboxylic acids that contain alcohol functions that can react intramolecularly to form 5- or 6-membered cyclic esters (lactones) do so very readily.

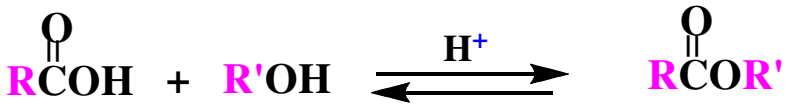


4-Hydroxybutanoic acid (γ-Hydroxybutyric acid) γ-Butyrolactone

A trace of strong acid catalyst hastens the conversion.

Steric Factors in Direct Esterification

The rate of esterification slows down as bulky groups are introduced into the structure near the carbonyl group of the acid or in the alcohol.



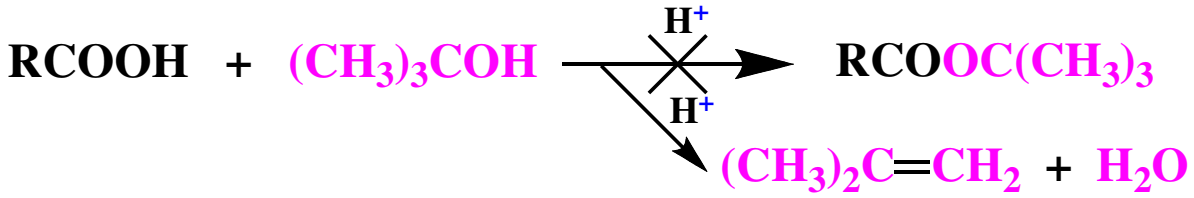
***Relative reactivity* of RCOOH**

HCOOH > CH_3COOH > $R'CH_2COOH$ > $R'_2CHCOOH$ > R'_3CCOOH

***Relative reactivity* of R'OH**

CH_3OH > $R''CH_2OH$ > R''_2CHOH > R''_3COH (no reaction)

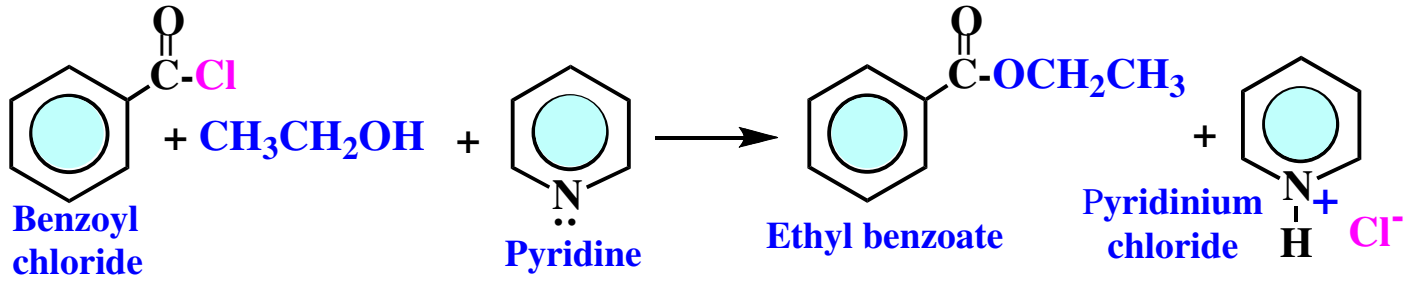
In the presence of strong acids, tertiary alcohols tend to dehydrate rather than undergo esterification reactions.



Sterically hindered esters have to be prepared by other methods.

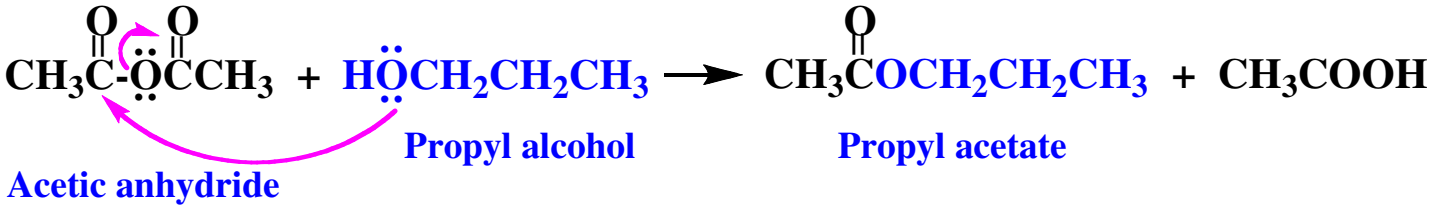
Esters from Acyl Chlorides

The reaction of alcohols with acyl chlorides gives esters. No acid catalysis is needed, but a tertiary amine, usually pyridine, is usually added to capture the HCl formed and drive the reaction to completion. These bases also appear to enhance the reactivity of acyl halides.



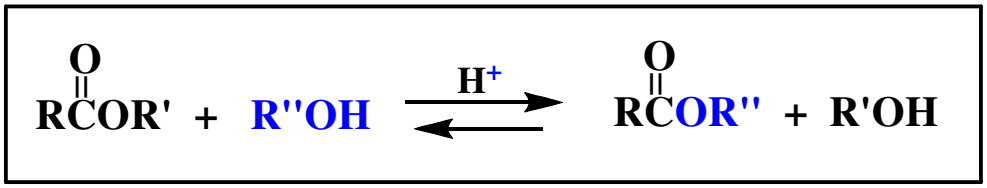
Esters from Carboxylic Acid Anhydrides

Alcohols react with acid anhydrides to give esters. As seen earlier, acyl chlorides and carboxylic acid anhydrides often undergo similar nucleophilic substitution reactions at the acyl carbon.

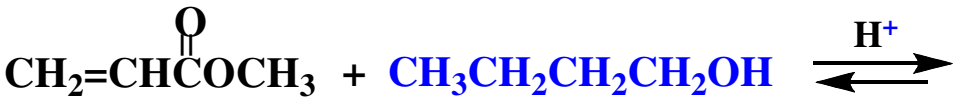


Transesterification

This is a process whereby the ester of one alcohol may be converted into the ester of a second alcohol by the equilibrium:

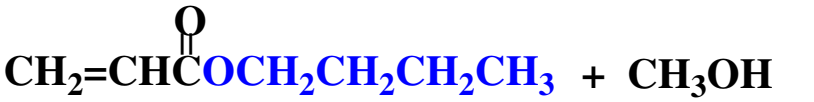


An example



Methyl acrylate

Butyl alcohol



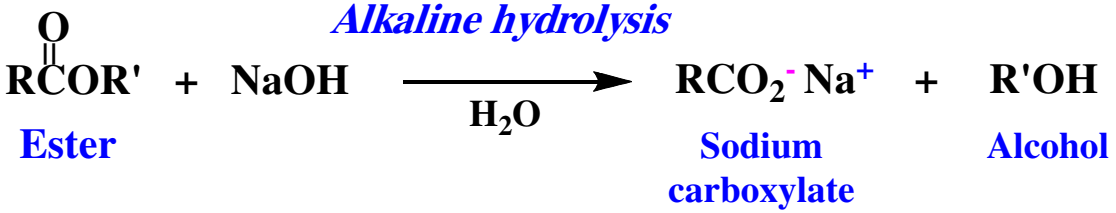
Butyl acrylate

Methyl alcohol

The equilibrium is shifted to the product side by using an excess of butyl alcohol and/or distilling out the lower boiling methanol from the reaction mixture.

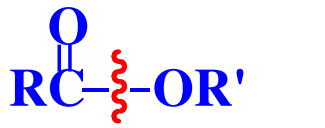
Base-Promoted Hydrolysis of Esters: Saponification

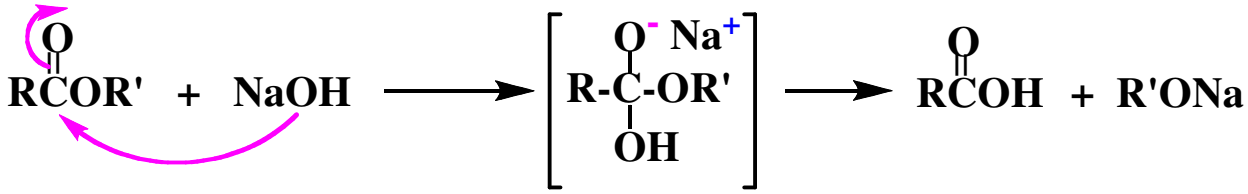
Base-promoted hydrolysis of esters is called saponification (from the Latin *sapo*, soap) because traditional soap-making involves the alkaline hydrolysis of fats (esters of glycerol).



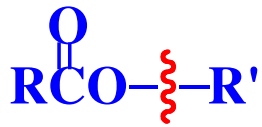
In the case of soaps, the R in the carboxylate ion typically is a straight-chain alkyl containing eleven to seventeen carbon atoms.

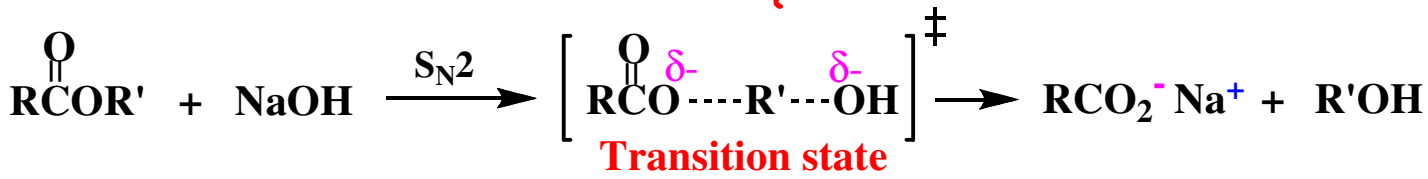
Two Possible Mechanisms for the Alkaline Hydrolysis of Esters

(1) ***Addition-Elimination:*** 



Tetrahedral Intermediate

(2) ***S_N2 Nucleophilic Substitution:*** 



Transition state

To distinguish between these possibilities, information on the mechanism was obtained by carefully designed experiments using stereochemical and isotopic probes.

Some Observations

Kinetic Studies

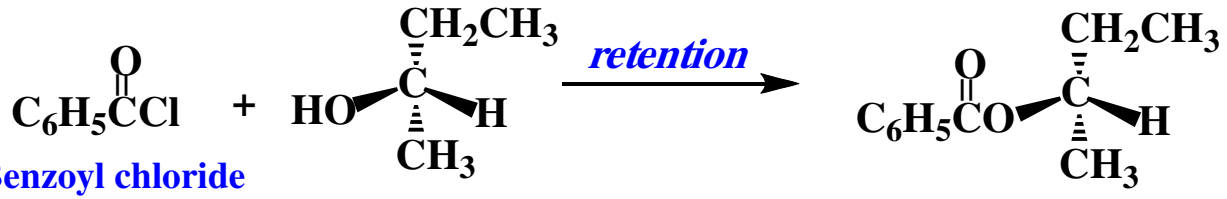
The rate of alkaline hydrolysis follows the second-order rate expression:

$$\text{rate} = k\,[RCO_2R']\,[HO^-]$$

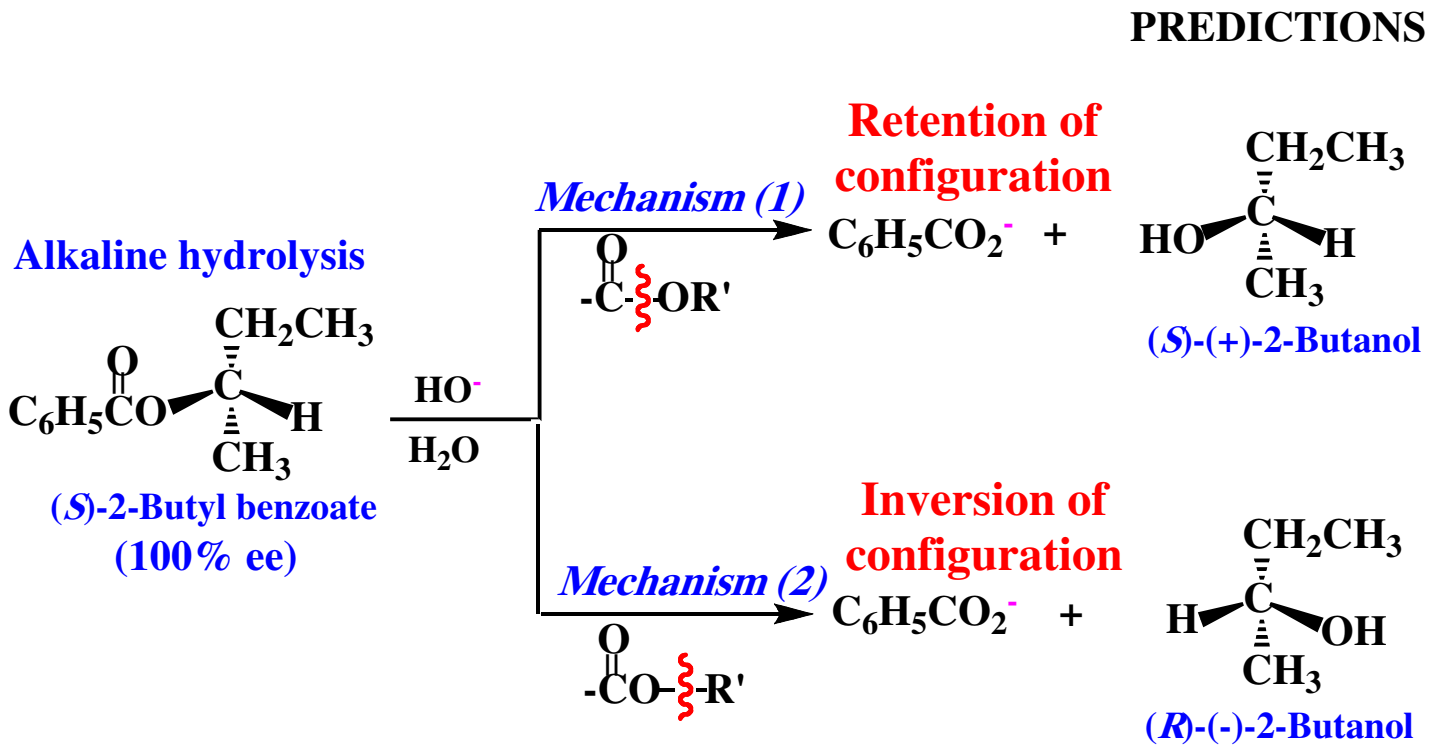
Since this result is consistent with either mechanism, it cannot elucidate the operating pathway for alkaline hydrolysis.

Stereochemical Probe

An ester with a stereocenter at the alkyl carbon can serve as a stereochemical probe of the mechanism. Such a probe molecule may be synthesized by the following stereospecific reaction.



Predictions of Stereochemical Outcomes

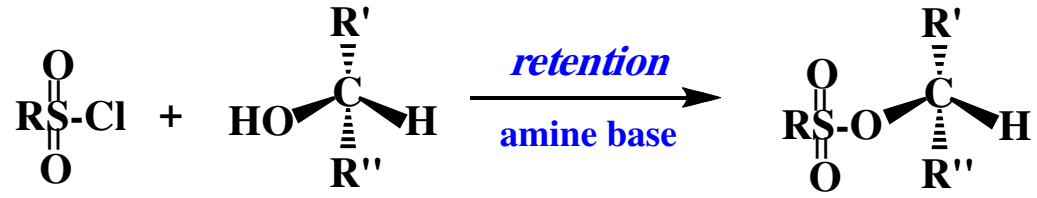


Stereochemical Outcome

Alkaline hydrolysis of (*S*)-2-butyl benzoate produced only (*S*)-(+)-2-butanol which is consistent with mechanism (1), cleavage at the acyl carbon.

Alkaline Hydrolysis of Sulfonate Esters

In contrast, stereochemical studies on esters of sulfonic acids indicate that alkaline hydrolysis proceeds by the S_N2 mechanism:

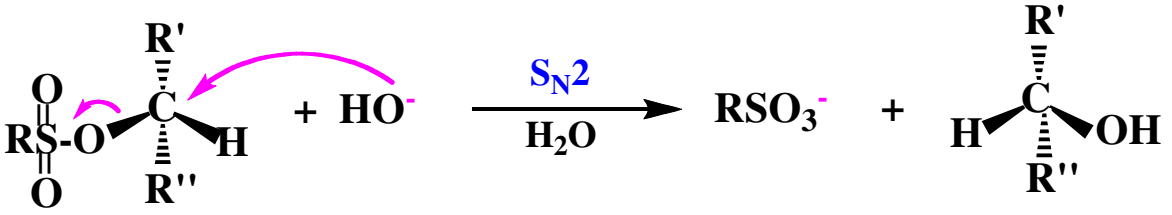


Sulfonyl chloride

Chiral alcohol (100% ee)

Alkyl sulfonate (100% ee)

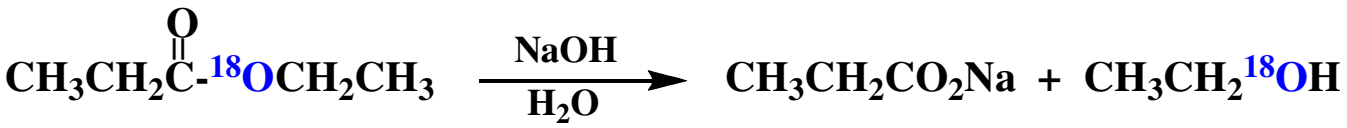
Alkaline hydrolysis



Inverted alcohol (100% ee)

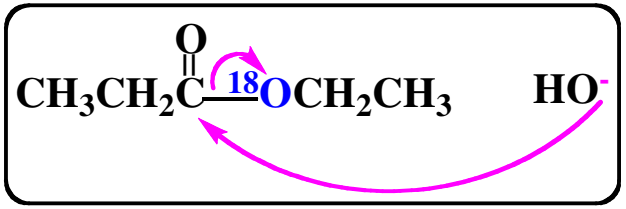
Isotopic Probe

It is possible to prepare esters enriched with oxygen-18 in either the carbonyl or alkoxy oxygen position. The location of the isotopic label after alkaline hydrolysis provides mechanistic information.



Ethyl propanoate **Sodium propanoate** **Ethanol**

The recovery of all the isotopic label in the ethanol product is consistent with nucleophilic attack by the hydroxide ion at the acyl carbon followed by cleavage of the acyl carbon-alkoxy oxygen bond.



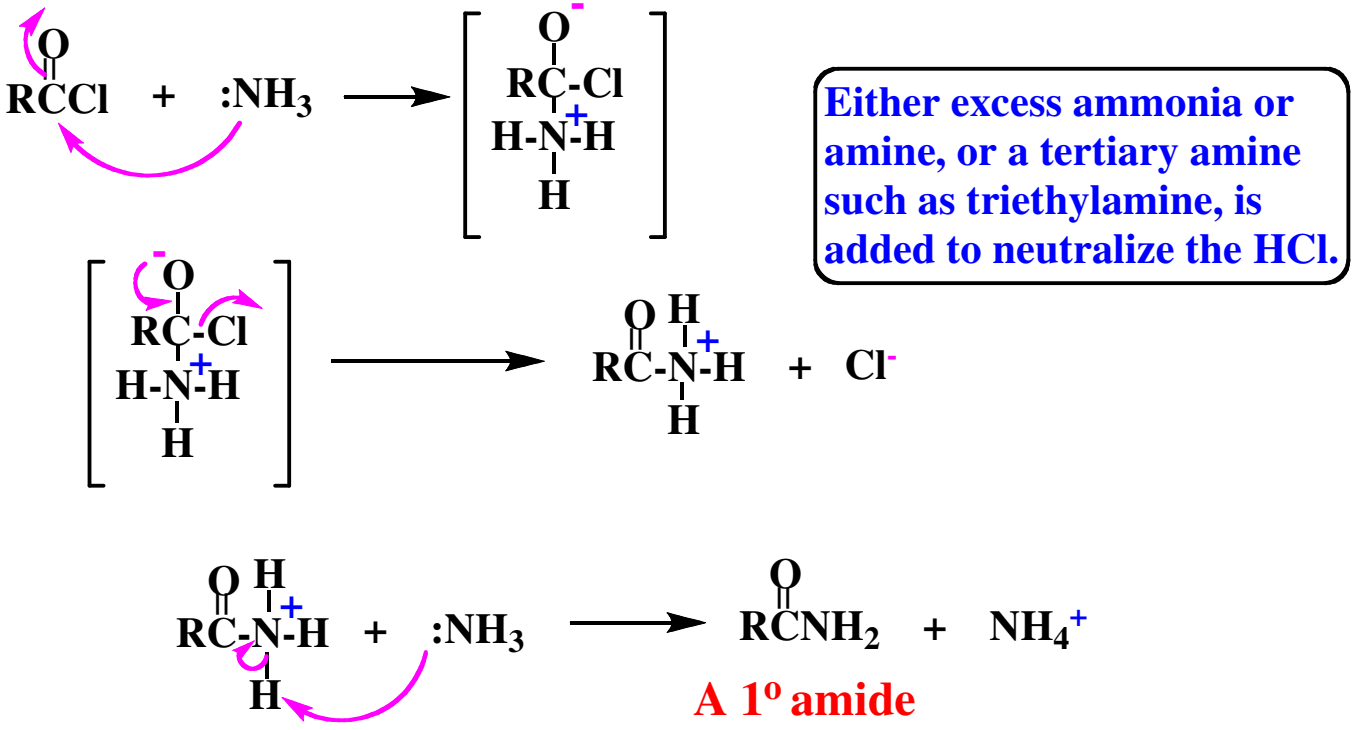
That is, the addition-elimination mechanism is employed.

Amides

Amides like amines are classified according to the number of substituents on the ammonia-type nitrogen:

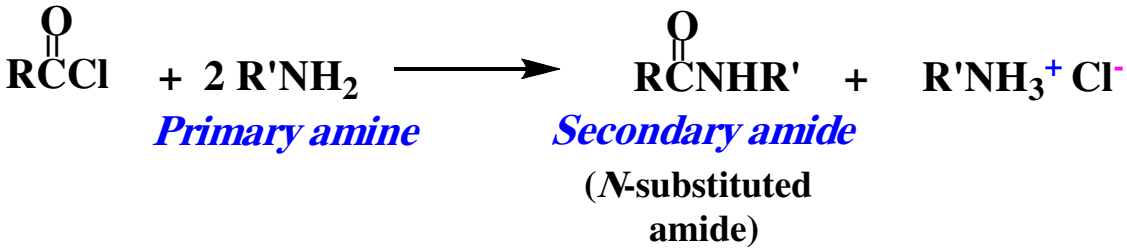
Synthesis of Amides from Acyl Chlorides

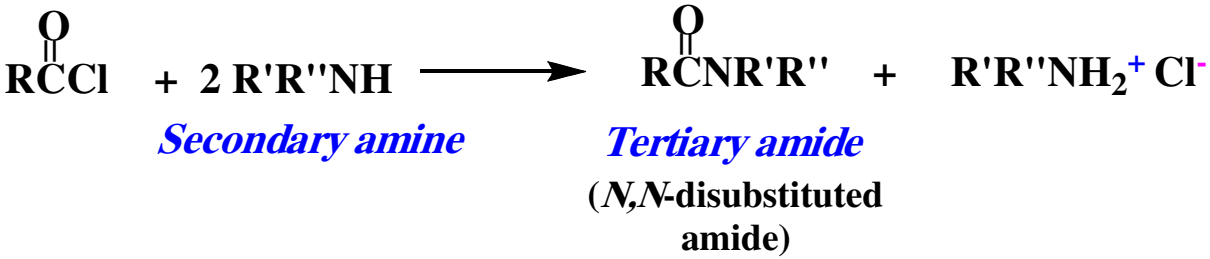
The nucleophiles ammonia and primary and secondary amines all react rapidly with acyl chlorides to produce amides. For complete reaction, the byproduct HCl must be neutralized.



Secondary and Tertiary Amides

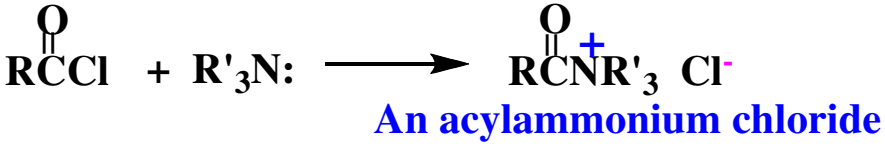
The reaction of acyl chlorides with primary and secondary amines yields secondary and tertiary amides, respectively.





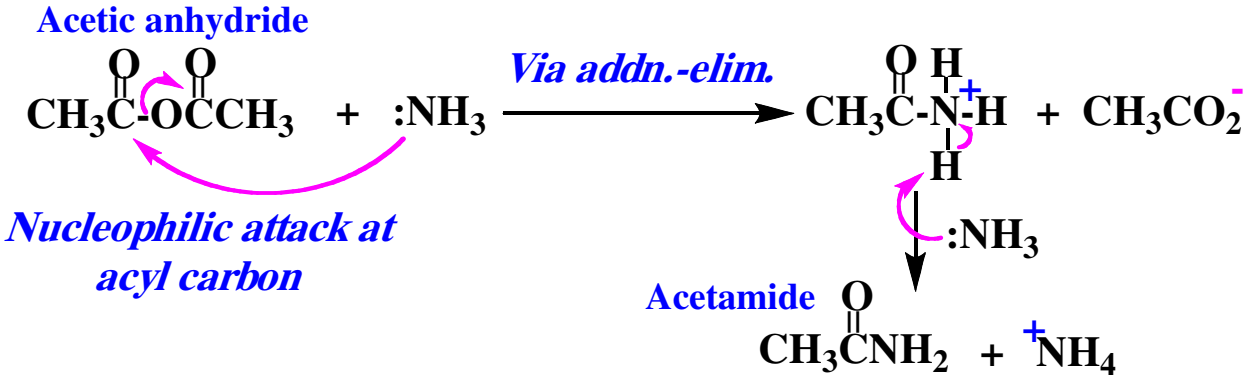
Note: Two equivalents of the amine are required for complete reaction.

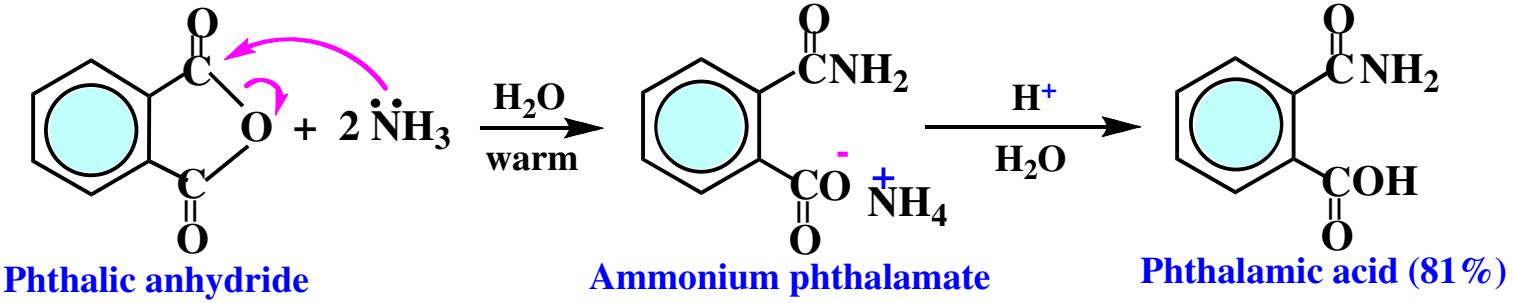
Tertiary amines react with acyl chlorides to produce salts, not stable amide products.



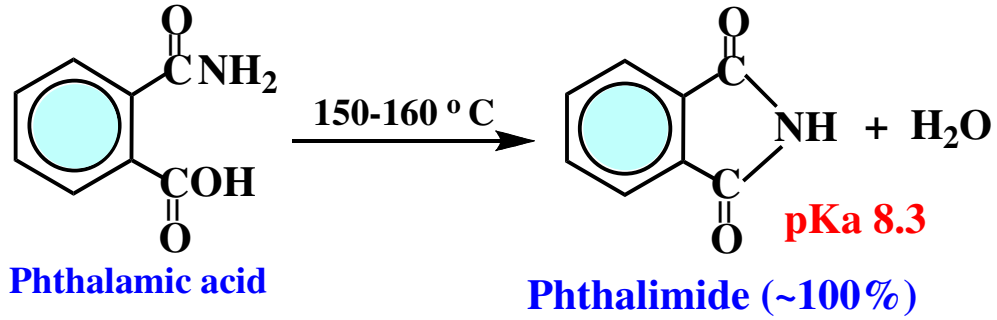
Amides from Carboxylic Acid Anhydrides

Analogous reactions occur between acid anhydrides and ammonia or amines.

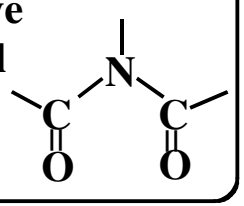




Vigorous heating of phthalamic acid results in dehydration and formation of phthalimide, which is used in a classic method of amine synthesis.

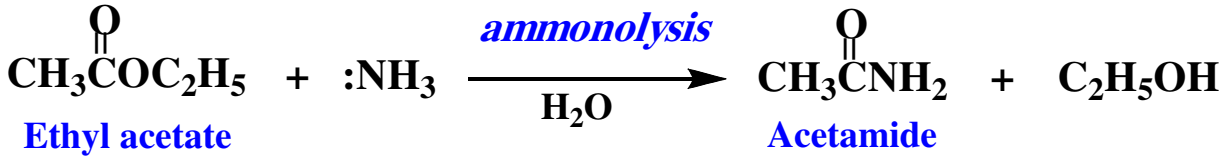


Imides have the general structure:



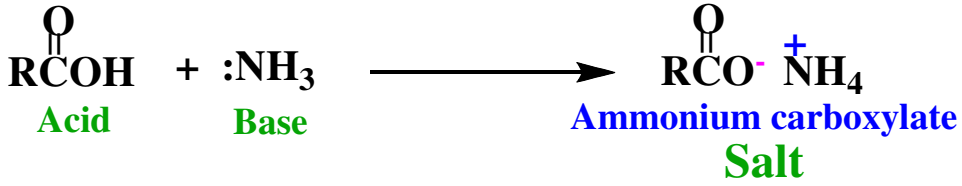
Amides from Esters

Esters undergo nucleophilic addition-elimination at the acyl carbon with nitrogen nucleophiles such as ammonia (ammonolysis) or amines (amination).

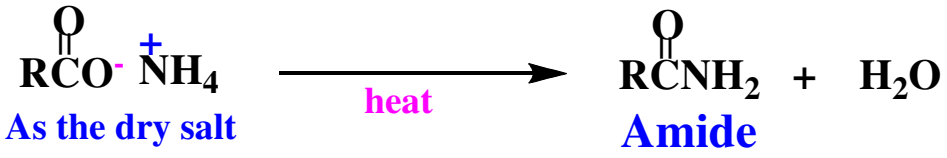


Amides from Carboxylic Acids

Carboxylic acids react with aqueous ammonia to produce ammonium carboxylates in an acid-base reaction:



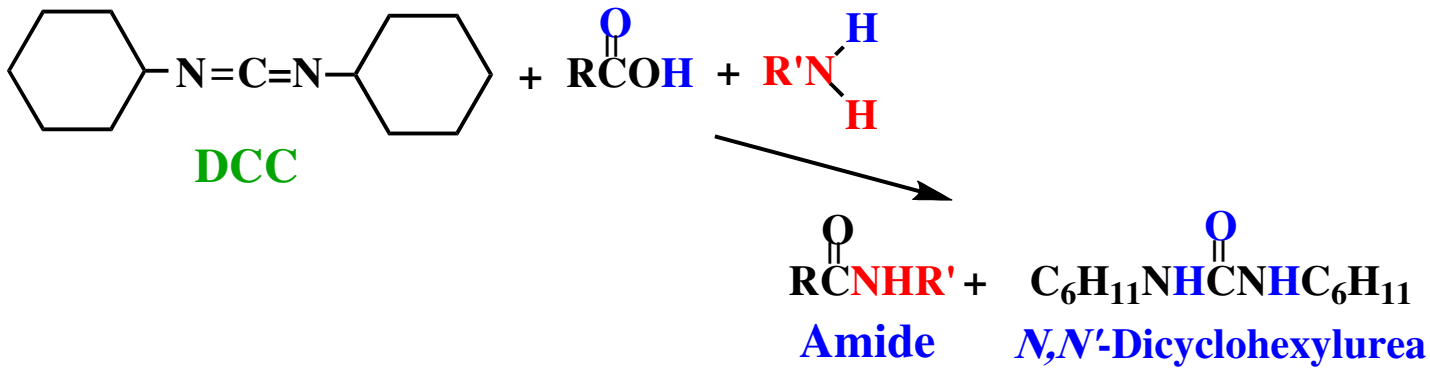
Recovery of the ammonium carboxylate and heating of the dry salt leads to dehydration and formation of the amide.



This method is generally not used in organic synthesis because the vigorous heating required will often decompose the sample.

Amides by a Condensation Synthesis Using Dicyclohexylcarbodiimide (DCC)

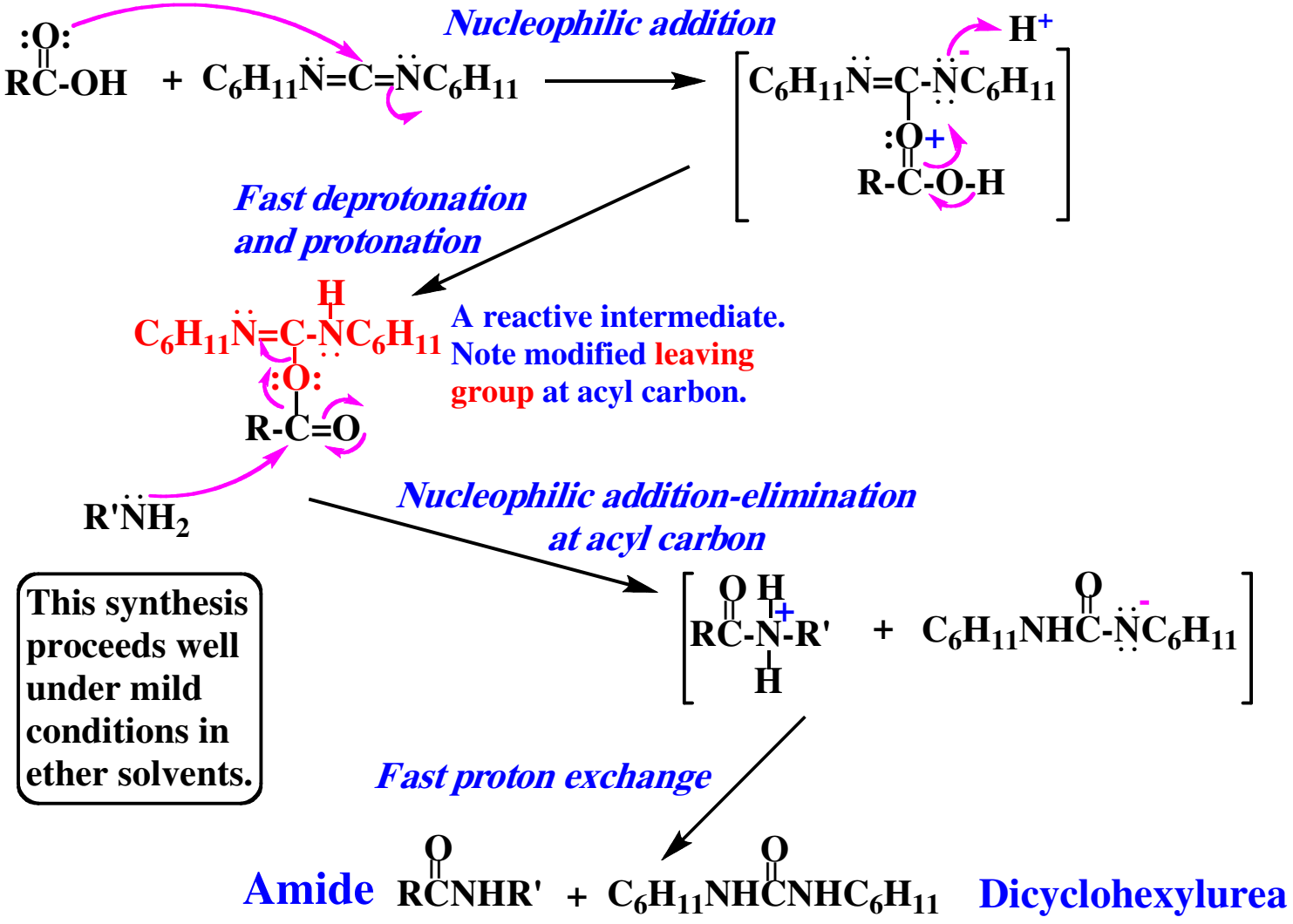
Amides may be prepared from carboxylic acids and amines in an indirect dehydration synthesis using DCC. This method was developed for synthesizing the amide bond in biological systems under very mild conditions.



Note that the H_2O byproduct ends up hydrating the diimide function to an urea compound.

A Proposed Mechanism for the DCC Synthesis of Amides

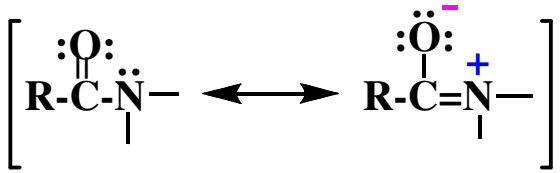
The central carbon of the diimide function is electropositive and subject to nucleophilic attack.



Hydrolysis of Amides

Amides hydrolyze much more slowly than other acyl derivatives of carboxylic acids such as acyl chlorides, esters, or anhydrides. This decreased reactivity is associated with the greater stability of the amide functional group compared with the other acyl derivatives.

This enhanced stability is explained by resonance theory through these contributors to a hybrid structure:

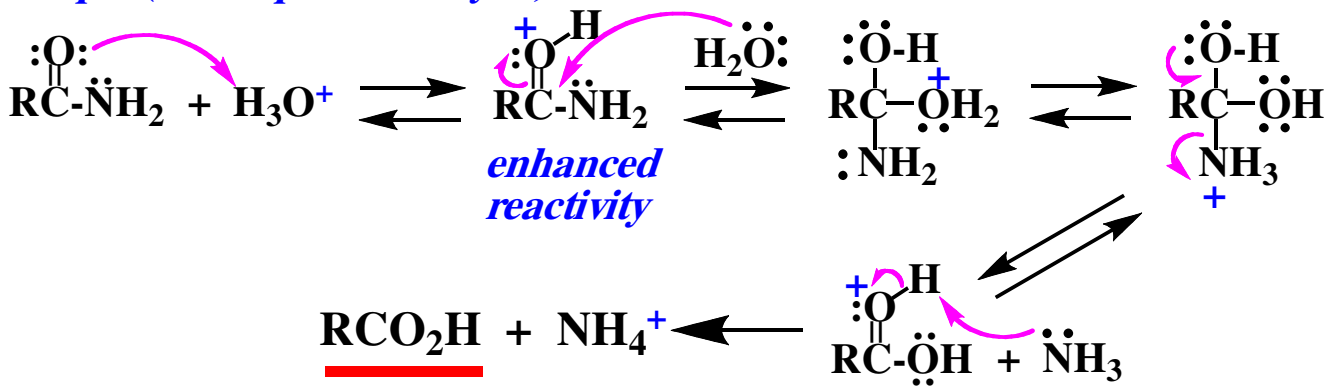


Amides are neutral compounds despite the presence of the amino-type nitrogen. Their decreased base strength compared with amines is also explained by the resonance stabilization of the amide function illustrated above, which much diminishes the electron density on the nitrogen. Much of this resonance stabilization is lost when the amide group is protonated.

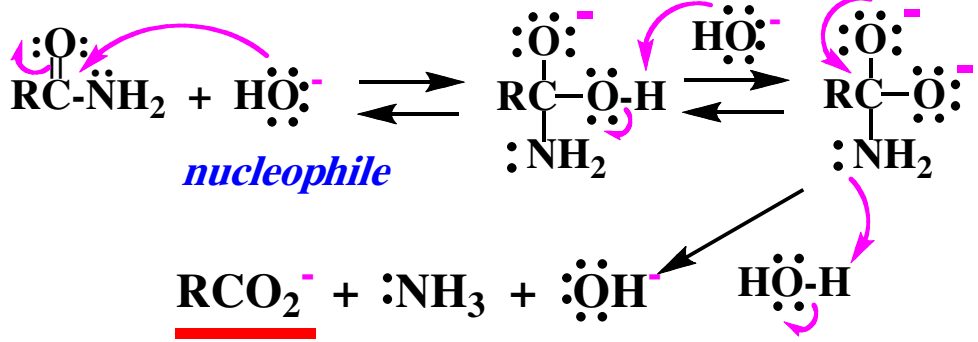
Hydrolysis of Amides: Mechanisms

The rate of hydrolysis of amides is faster at lower or higher pH than at pH 7.

At low pH (electrophilic catalysis)



At high pH (a better nucleophile)

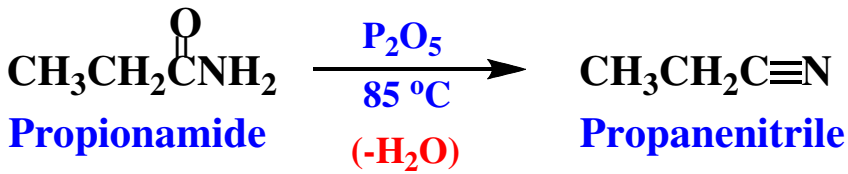


***N*-Substituted and *N,N*-disubstituted amides react similarly.**

Typical hydrolysis conditions involve extensive heating of the amide in 6 *M* HCl or 40% aqueous NaOH.

Nitriles

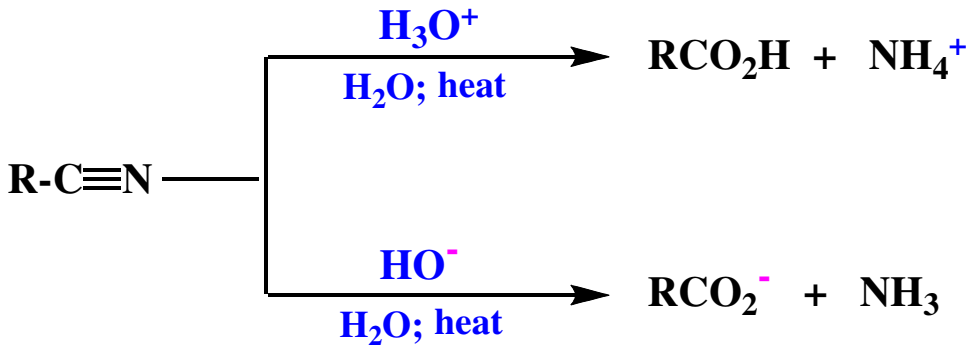
One standard way of preparing a nitrile is by dehydration of the corresponding primary amide with reagents such as P_4O_{10} (usually called phosphorus pentoxide, from its empirical formula P_2O_5) or refluxing acetic anhydride.



This synthesis is an alternative to the reaction of an alkyl halide with cyanide ion, which proceeds by an S_N2 mechanism.

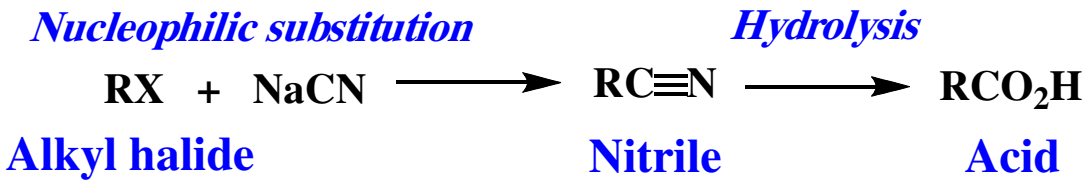
Hydrolysis of Nitriles

Nitriles are considered derivatives of carboxylic acids because hydrolysis of a nitrile produces an acid. As with amides, the rate of hydrolysis is faster under either acidic or basic conditions than at neutral pH.



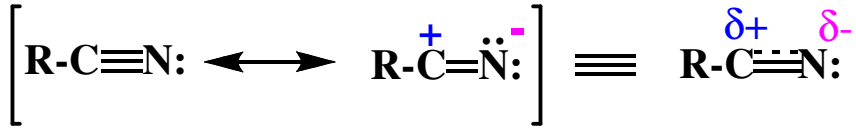
Use in a Synthetic Sequence

The hydrolysis of nitriles to carboxylic acids is synthetically useful when linked with the readily available alkyl halides by the sequence:

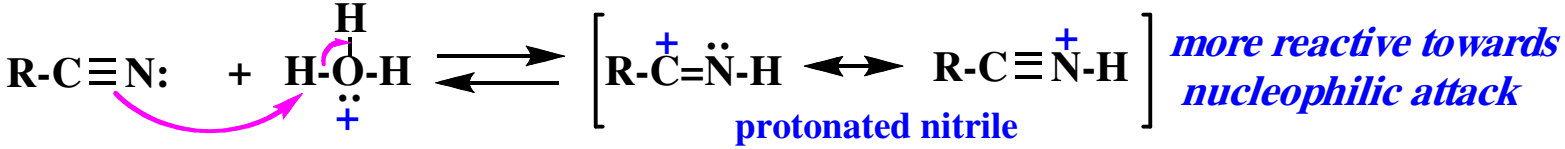


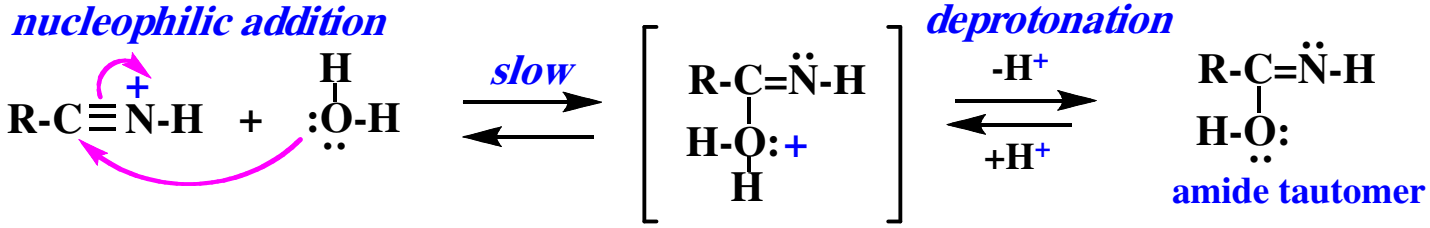
A Mechanism for the Acidic Hydrolysis of Nitriles

The nitrile is a polar functional group similar to a carbonyl:

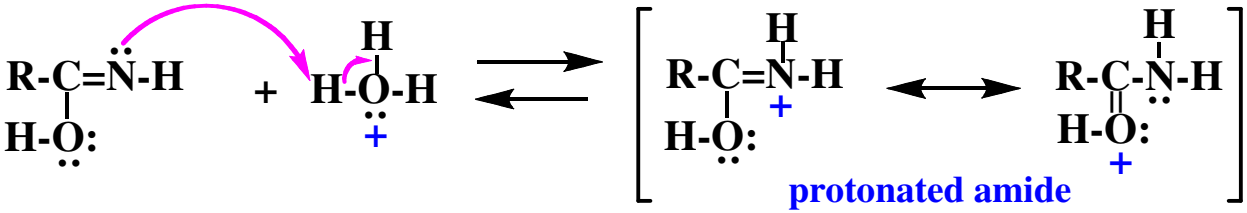


Stage 1: Hydrolysis of nitrile to amide

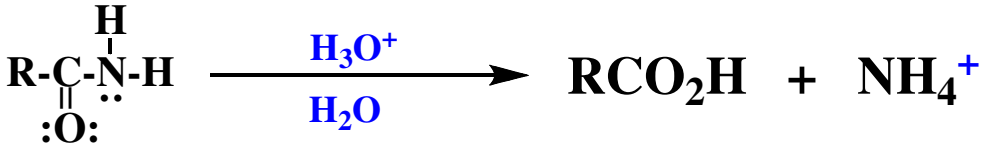




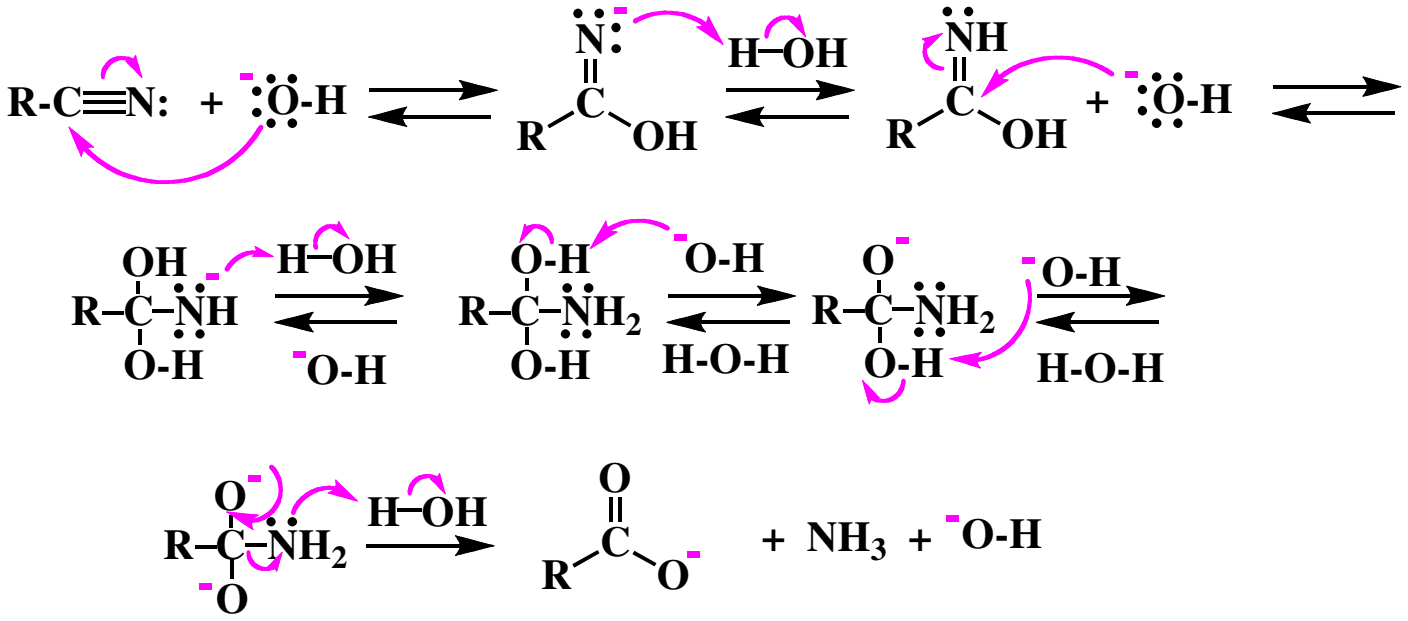
acid-catalyzed tautomerization (isomerization)



Stage 2: Continued hydrolysis yields carboxylic acid

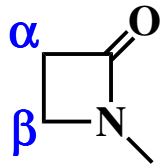


A Mechanism for the Basic Hydrolysis of Nitriles



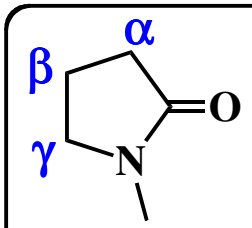
Lactams: Cyclic Amides

Cyclic amides are called lactams. The size of the ring is given by a Greek letter that indicates the relative positions of the carbonyl and amino functions.

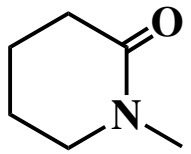


a β lactam

Highly reactive; ring opens easily on nucleophilic attack because of bond-angle strain.



a γ lactam

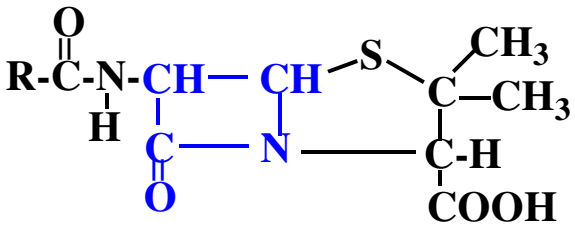


a δ lactam

Stable; often form spontaneously from γ- and δ-amino acids.

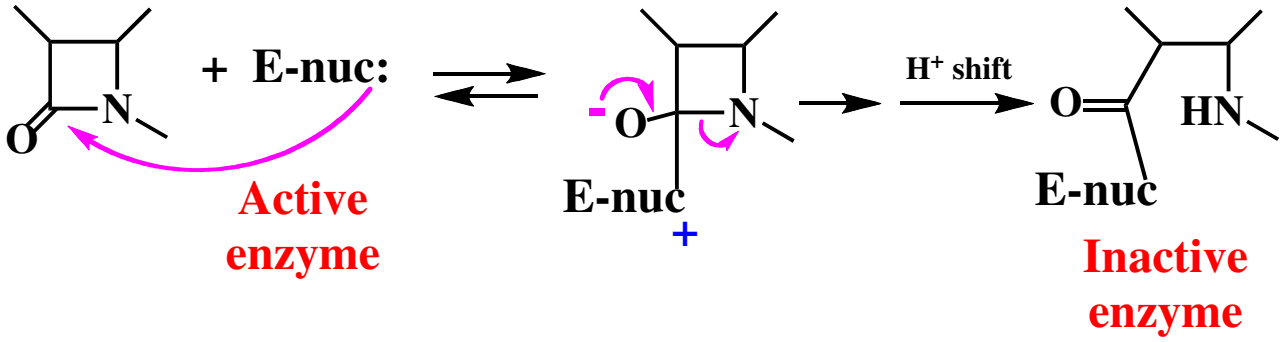
The Penicillin Antibiotics

The medicinally important penicillins contain a β-lactam structure.



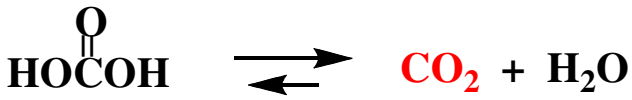
R Group	
$C_6H_5CH_2$-	*Penicillin G*
$C_6H_5\underset{\displaystyle NH_2}{\underset{\vert}{C}}H$-	*Ampicillin*
$C_6H_5OCH_2$-	*Penicillin V*

The penicillins apparently act by reaction with an enzyme vital to the synthesis of bacterial cell walls, inactivating it. This reaction is dependent on the high reactivity of the β-lactam ring:



Derivatives of Carbonic Acid

Carbonic acid (H_2CO_3) is unstable and dissociates to CO_2 and H_2O. The reaction is reversible so when CO_2 dissolves in water some H_2CO_3 is formed.



Carbonic acid

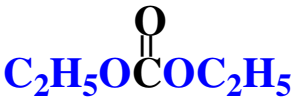
Carbonic acid is a weak acid, pK_a 6.35. Solutions of carbonated water (including natural rainwater) are slightly acidic.

Carbonic acid is a hydrate of a carbonyl portion of  **and has two hydroxyl groups on one carbon, like the hydrates of aldehydes and ketones. They also are unstable and present only in small amount at equilibrium. (There are some stable exceptions, like the hydrate of trichloroacetaldehyde.)**

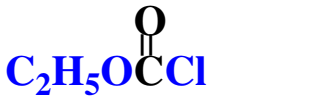
Many stable derivatives of carbonic acid are known:

Phosgene
(carbonyl chloride)

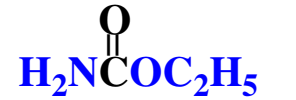
Urea
(carbamide)



Ethyl carbonate

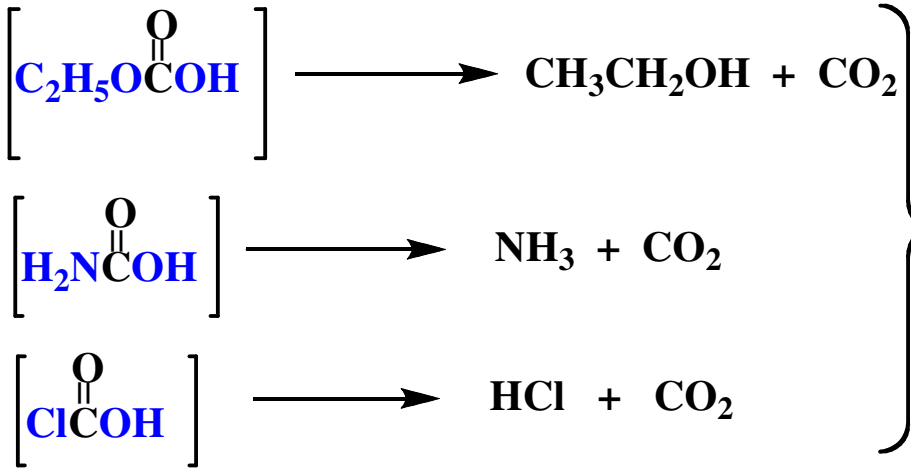


Ethyl chlorocarbonate



Ethyl carbamate
(a "urethane")

Monoderivatives of Carbonic Acid Are Unstable



This is true also of the corresponding derivatives of aldehydes and ketones.

Industrial Production of Phosgene

Phosgene, ClCOCl, is an important industrial chemical used in producing many other materials. It is produced on a large scale from carbon monoxide and chlorine.

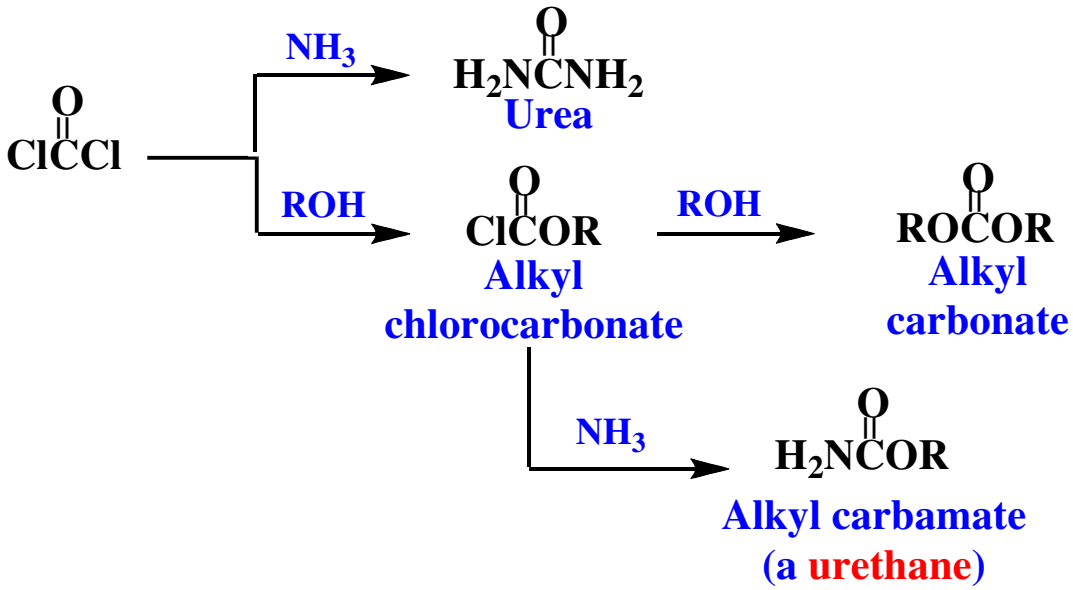
$$CO\ (g) + Cl_2\ (g) \xrightarrow[200\ ^oC]{\text{activated charcoal}} ClC(=O)Cl\ (g)$$

The above gas phase reaction is actually a very favorable equilibrium. At 100 ^oC,

$$K = \frac{[COCl_2]}{[CO]\,[Cl_2]} = 4.6 \times 10^9$$

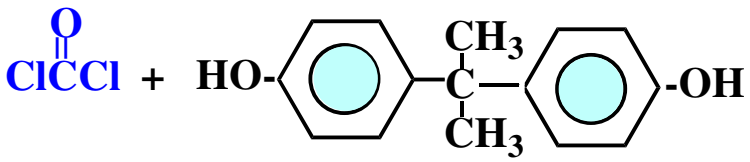
Phosgene is a colorless, highly toxic gas (bp 8.2 ^oC). It causes pulmonary edema (pneumonia) and has been used as a chemical warfare agent.

Because of its chemical reactivity, phosgene is easily turned into other derivatives of carbonic acid.



Polycarbonates

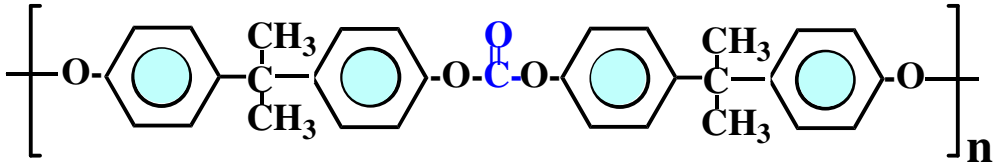
Polycarbonates are an important class of polymers produced from the reaction of phosgene with bifunctional alcohols.



"bisphenol A"

heat

-HCl

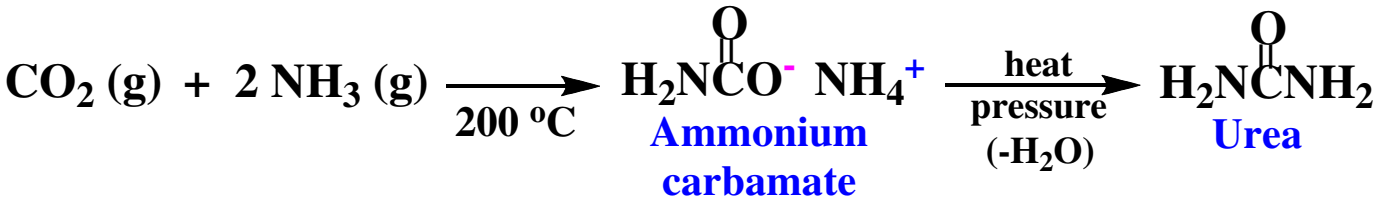


Lexan

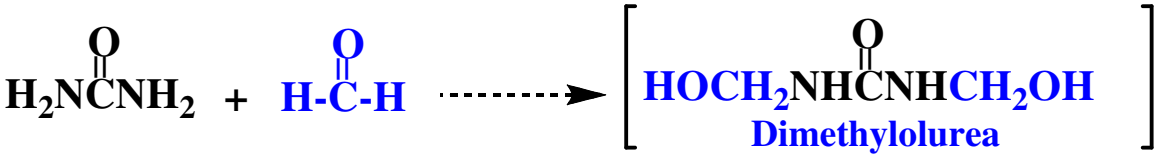
A strong, clear material used for, e.g., bullet-proof "glass."

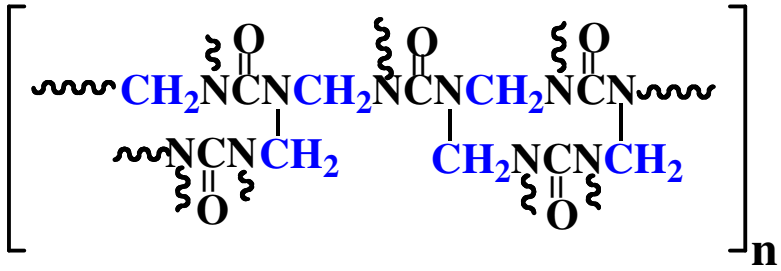
Urea

Urea is excreted in urine as the end product of protein metabolism. It is produced industrially (over 8 billion pounds per year in the United States). Although it can be produced from phosgene, a cheaper, more direct method is from ammonium carbamate.



An important condensation polymer (over one billion pounds per year in the United States) is produced from urea and formaldehyde:

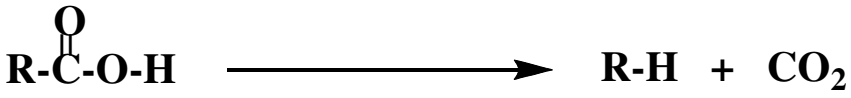




A very strong three dimensional structure

Decarboxylation of Carboxylic Acids

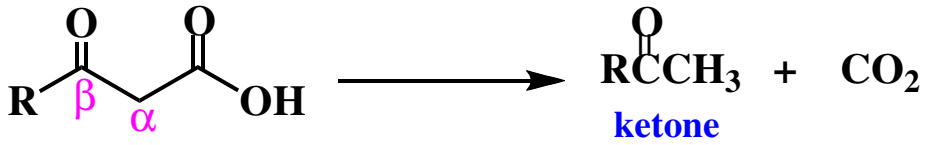
The loss of CO_2 from a carboxylic acid is called decarboxylation.



Although the loss of CO_2 is usually exothermic (because of the stability of CO_2), the reaction is kinetically slow. However, certain structural features promote decarboxylation.

β-Keto Acids

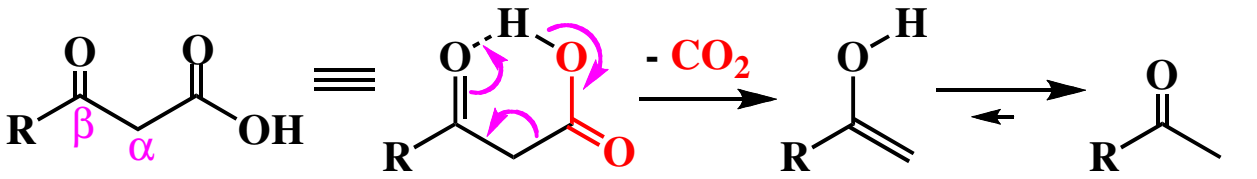
β-Keto acids decarboxylate rapidly when heated to 100-150 °C.



The decarboxylation reaction occurs with either the acid or its carboxylate salt.

Decarboxylation of the Acid

This reaction of the acid involves a six-membered cyclic transition state that initially produces the enol of the ketone product.

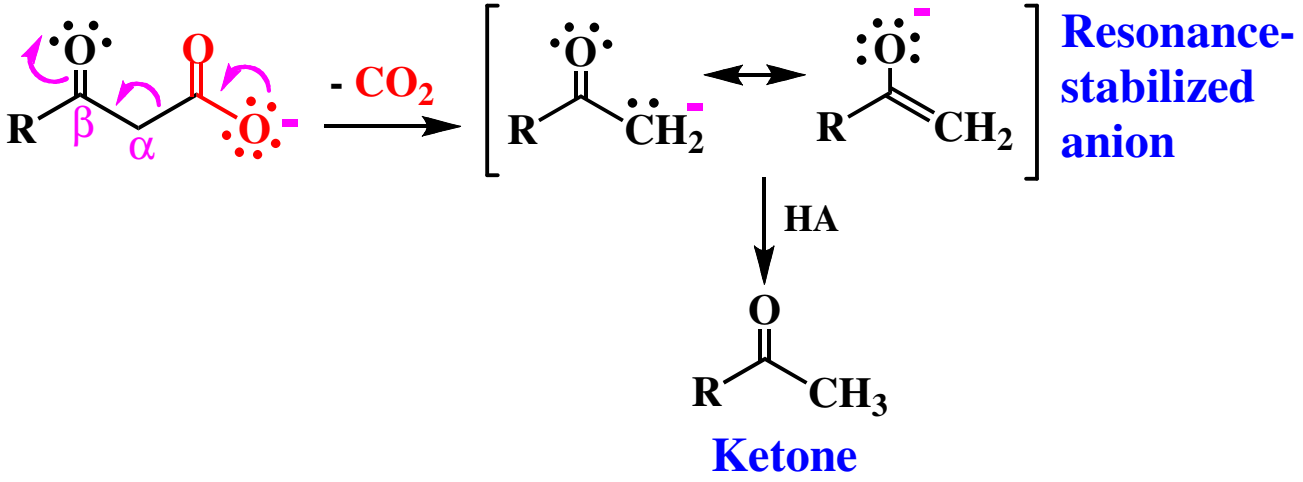


β-Keto acid | Conformer favored by hydrogen-bonding | Enol | Ketone

This decarboxylation reaction proceeds well because of a mechanism that avoids high energy intermediates. It is believed that bond-making and bond-breaking in the cyclic transition state proceed more or less at the same rate, producing an enol product that subsequently isomerizes to the more stable ketone.

Decarboxylation of the Carboxylate Salt

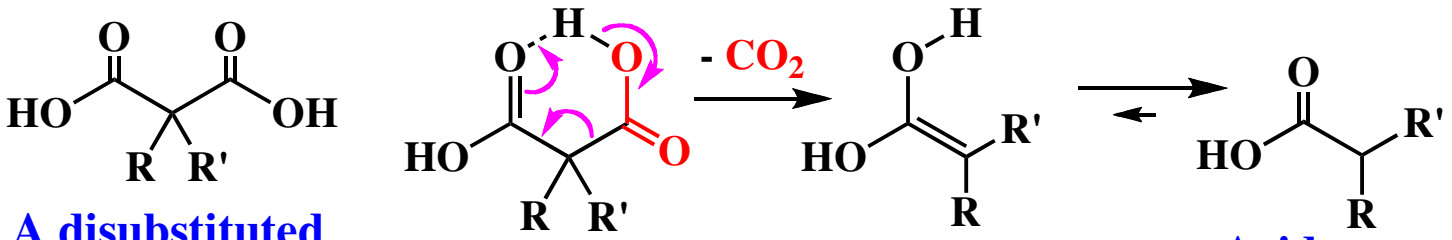
Decarboxylation of the carboxylate anion produces a resonance stabilized enolate anion:



This decarboxylation reaction proceeds well because a resonance stabilized enolate anion is formed in contrast to a high energy carbanion, the result of decarboxylation of a simple carboxylic acid.

Decarboxylation of Malonic Acids

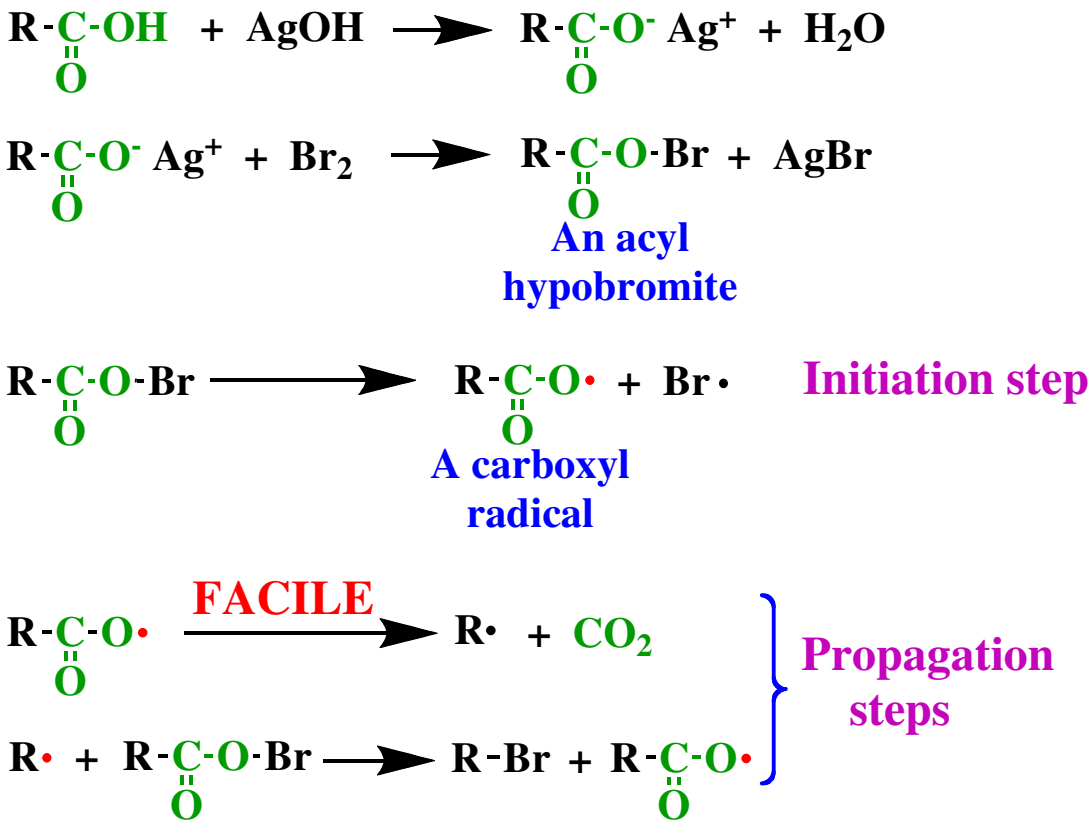
Malonic acids (1,1-dicarboxylic acids) decarboxylate rapidly when heated above 100 °C, like β-ketoacids. A similar six-membered cyclic transition state is believed to be involved that directly yields the enol form of a carboxylic acid.



This is the final part of a valuable synthetic method because of the ease of introducing specific R and R' groups into the starting malonic acid.

Decarboxylation of Carboxyl Radicals

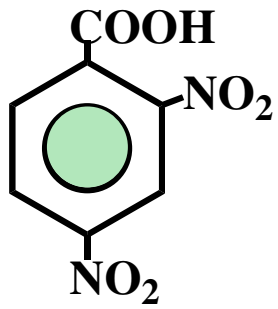
This is the essential step in the Hunsdiecker-Borodin method for replacing a carboxyl group with a bromine atom.



Quiz 18.01

Provide IUPAC (systematic) names for the following carboxylic acids.

2-Chloro-4-methylpentanoic acid

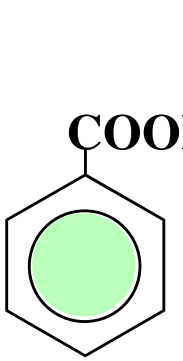


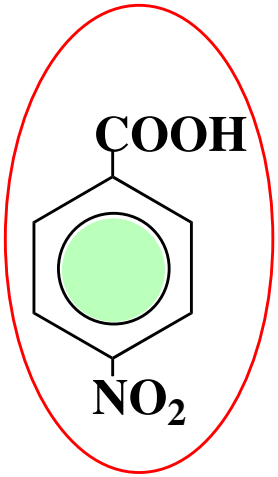
2,4-Dinitrobenzoic acid

Quiz 18.02

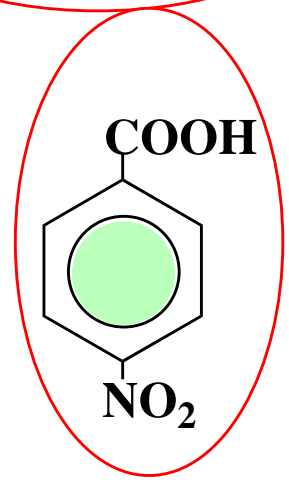
In each pair of compounds below, circle the stronger carboxylic acid.

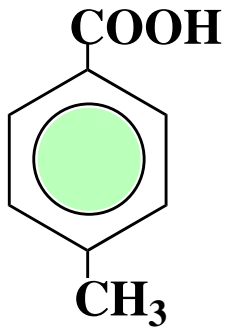
Cl_3CCOOH CH_3COOH





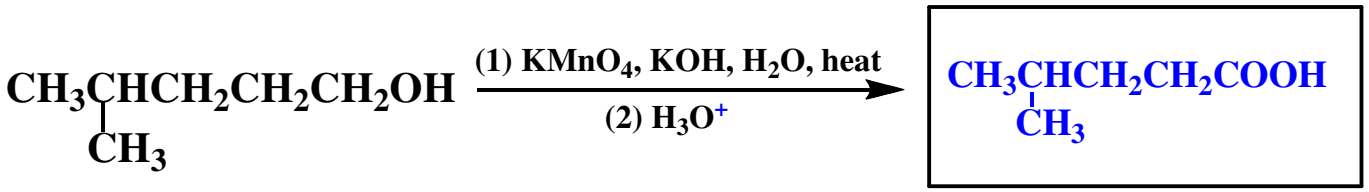
Cl_2CHCH_2COOH CH_3CCl_2COOH

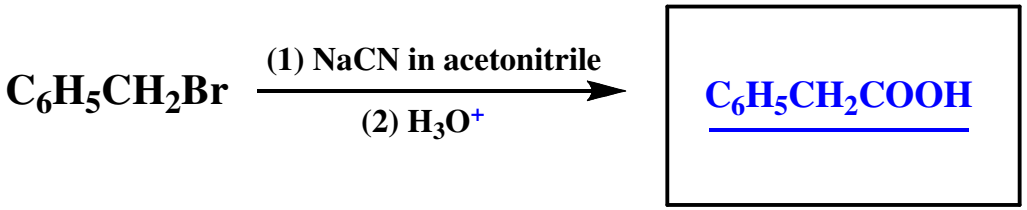


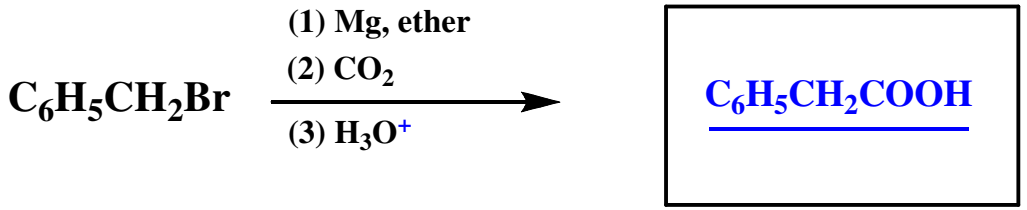


Quiz 18.03

Draw the structures of the products of the following synthetic procedures.

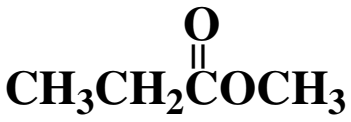




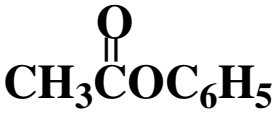


Quiz 18.04

Provide IUPAC names for the following acid derivatives.

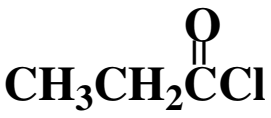


Methyl propanoate

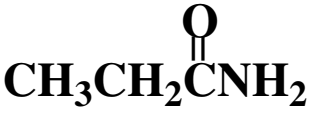


Phenyl ethanoate (phenyl acetate)

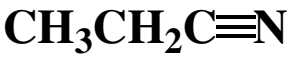
Ethanoic anhydride (acetic anhydride)



Propanoyl chloride



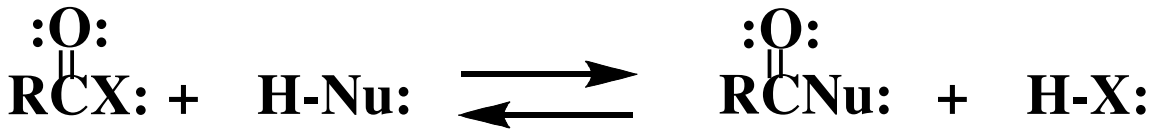
Propanamide



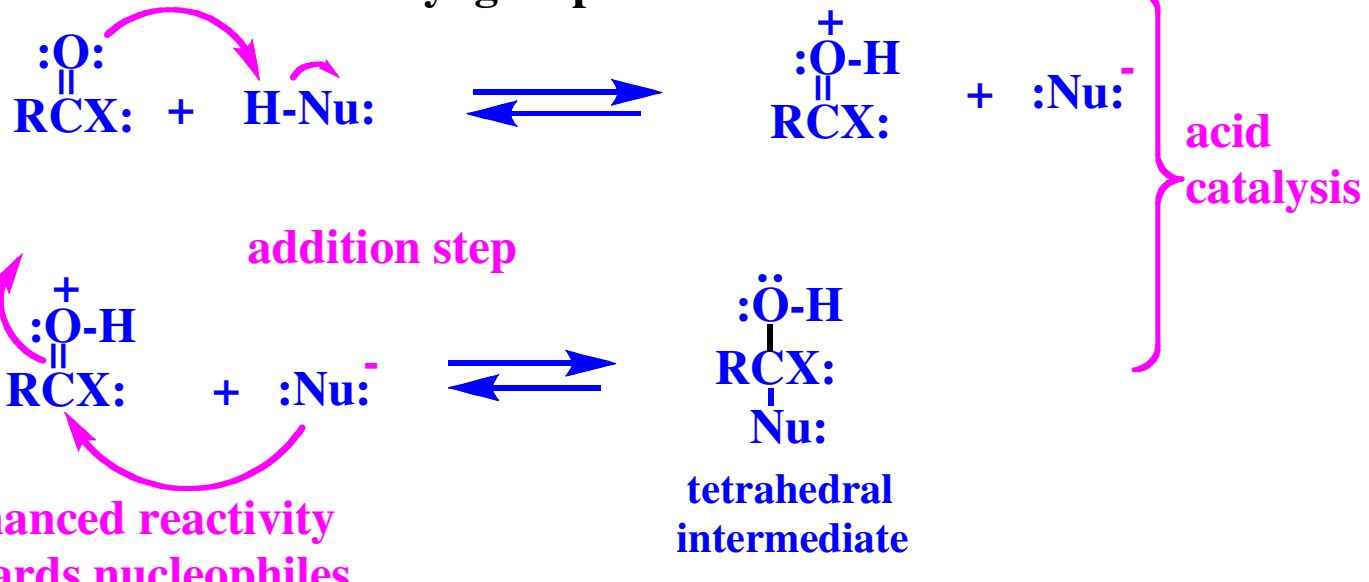
Propanenitrile

Quiz 18.05

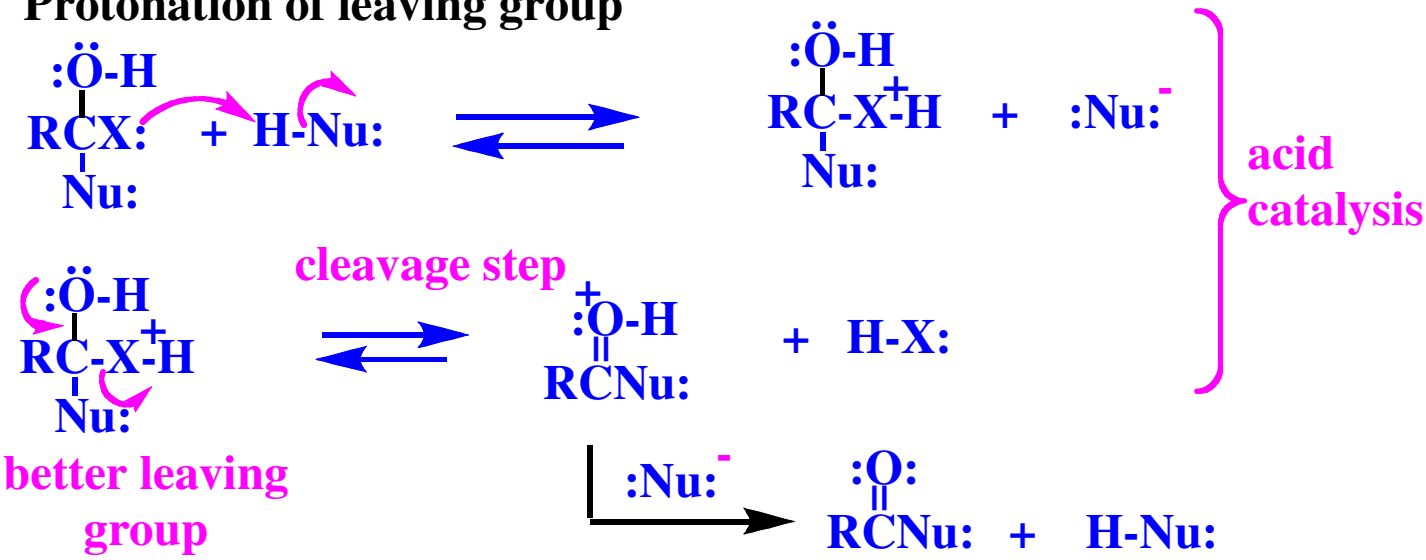
Acid catalysis is important in nucleophilic addition-elimination at acyl carbon. Sketch the general mechanism for this reaction, indicating where the catalysis occurs.



Protonation of carbonyl group



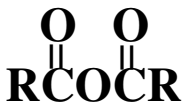
Protonation of leaving group



Quiz 18.06

Circle the least reactive acid derivative among those below.

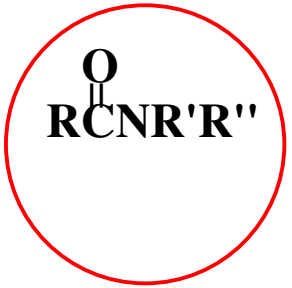
ester



acid anhydride

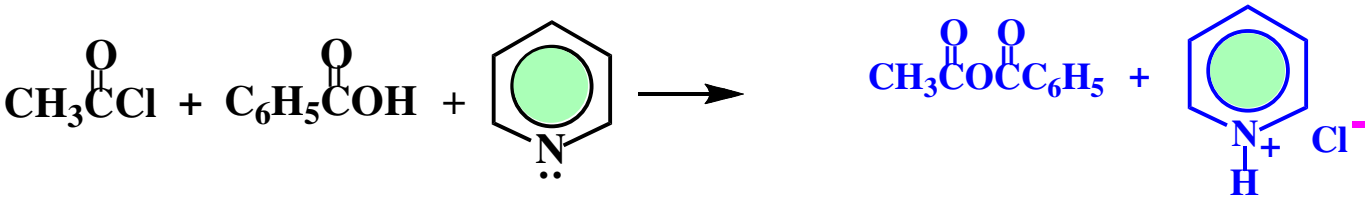
acyl chloride

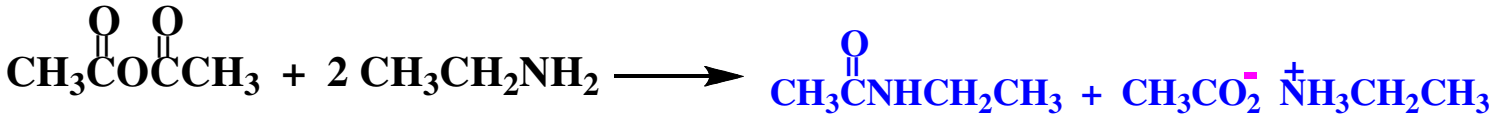
amide



Quiz 18.07

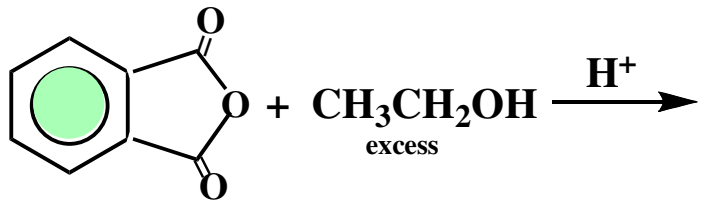
Draw the structures of the products of the following reactions.

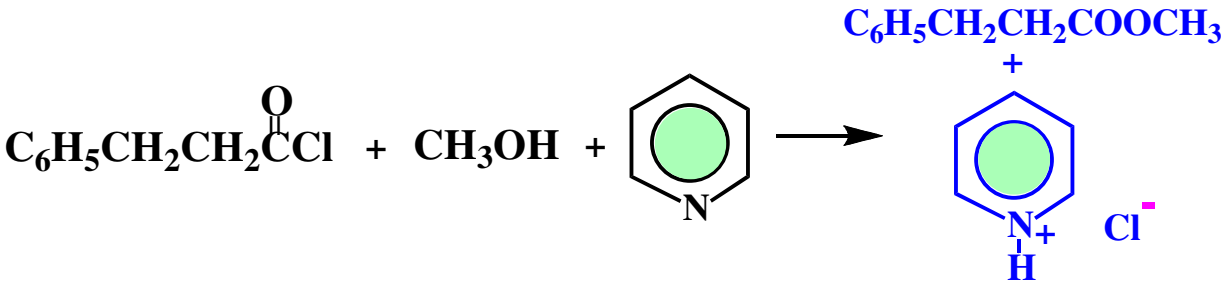




Quiz 18.08

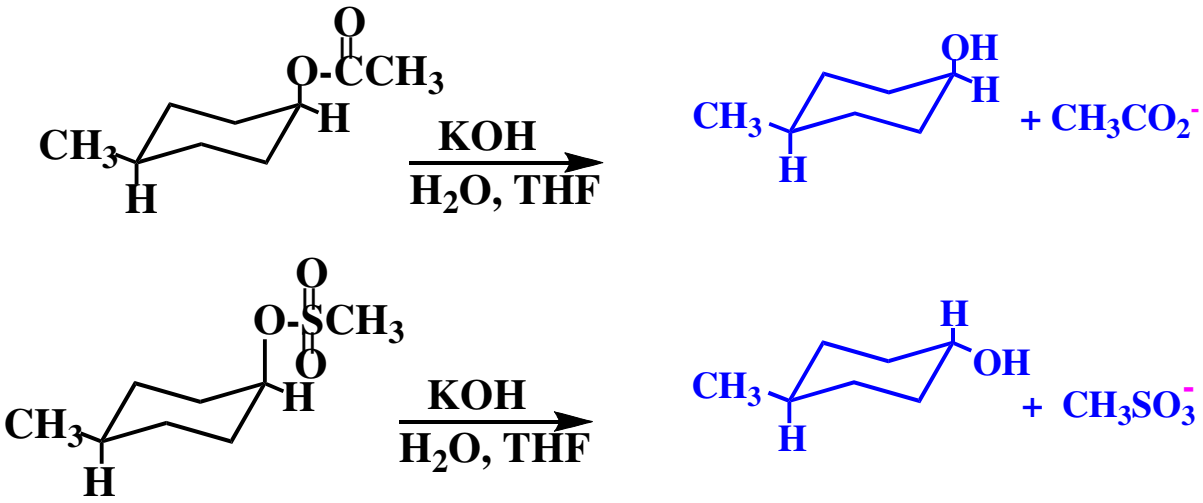
Draw the structures of the products of the following reactions.





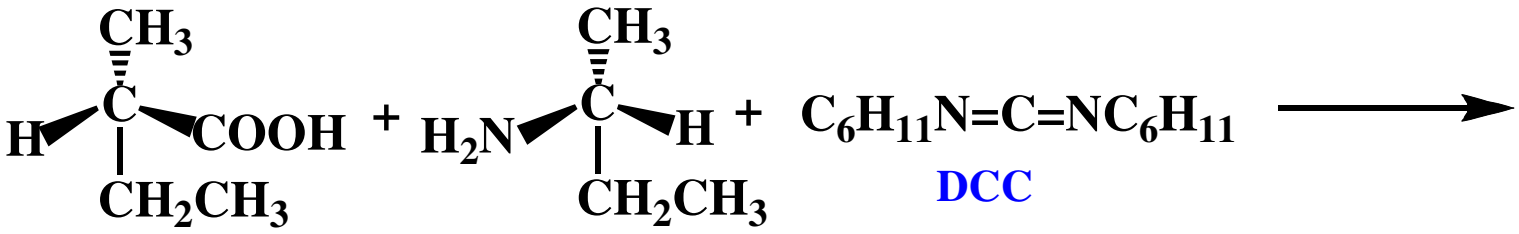
Quiz 18.09

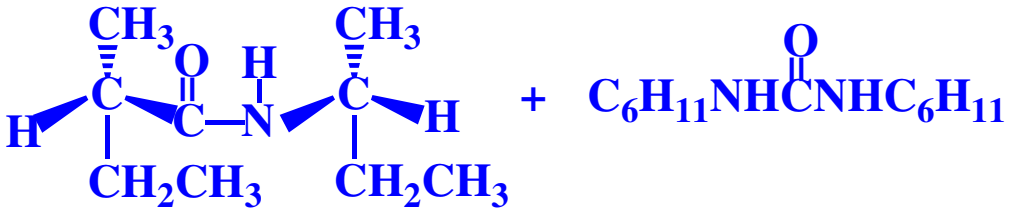
Draw the structures of the products of the following alkaline hydrolysis reactions.



Quiz 18.010

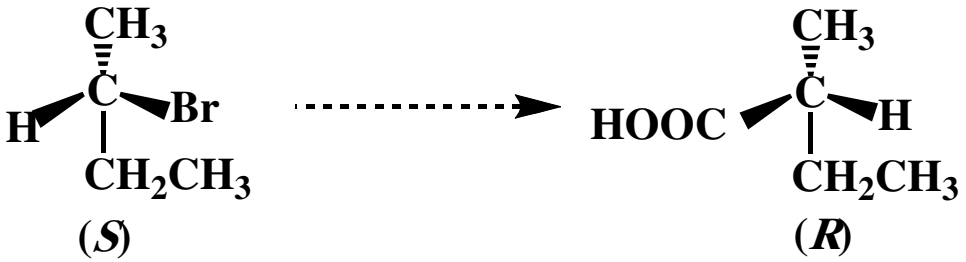
Draw the structures of the products of the following reaction. Show stereochemical details.

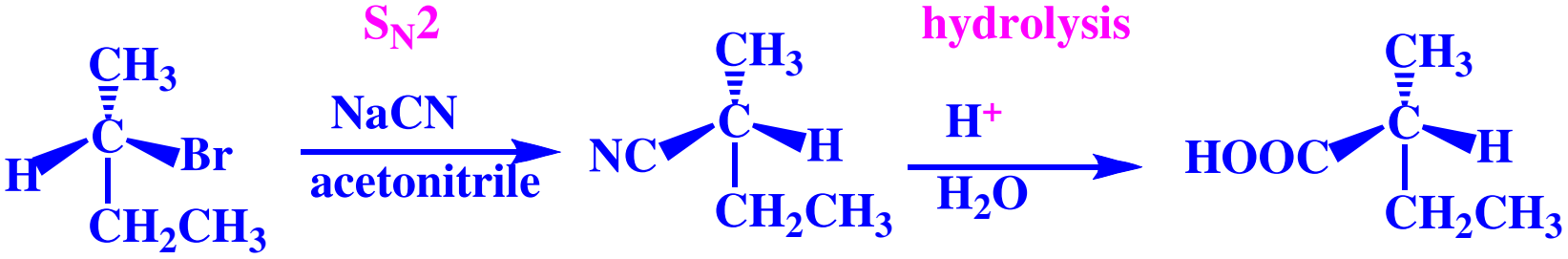




Quiz 18.011

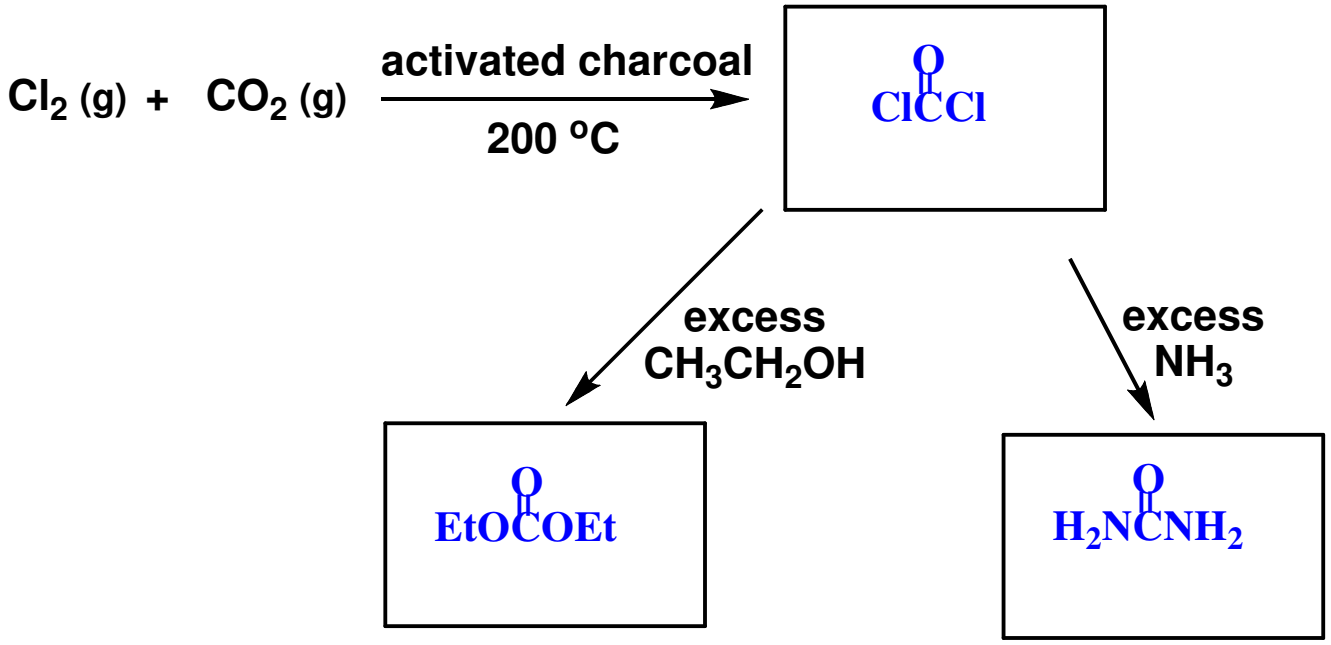
Design a two-step synthesis of (*R*)-2-methylbutanoic acid from (*S*)-2-bromobutane.





Quiz 18.012

Provide the missing structures in the scheme below.



Quiz 18.013

Circle the carboxylic acids below that will decarboxylate when heated to ~100 ^{o}C.