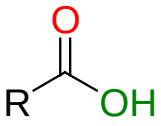
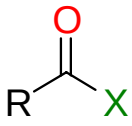
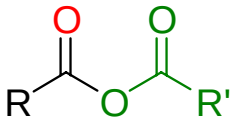
Chapter 10. Carboxylic Acids and Derivatives



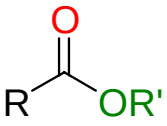
Carboxylic acid



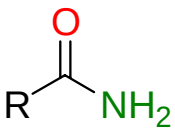
Acid halide



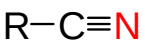
Acid anhydride



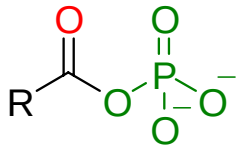
Ester



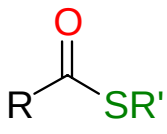
Amide



Nitrile



Acyl phosphate



Thioester

The common structural feature of all these compounds is that they contain an **acyl group** bonded to an electronegative atom or substituent that can act as a **leaving group** in substitution reaction.

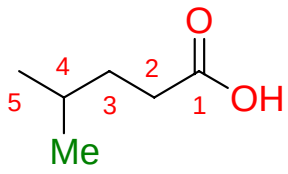
10.1 Naming Carboxylic Acids and Derivatives

Carboxylic Acids: RCO_2H

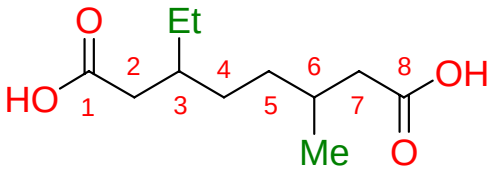
1) Simple open-chain carboxylic acids

Replace the terminal –e of the alkane name with **–oic acid**.

The carboxyl group carbon is always numbered C1.



4-Methylpentanoic acid

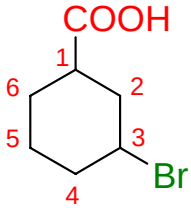


3-Ethyl-6-methyloctanedioic acid

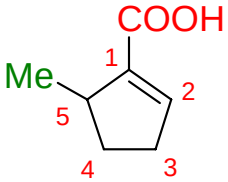
2) Cyclic carboxylic acids

Use the suffix **–carboxylic acid**.

The carboxylic acid carbon is attached to C1 on the ring but is not itself numbered.

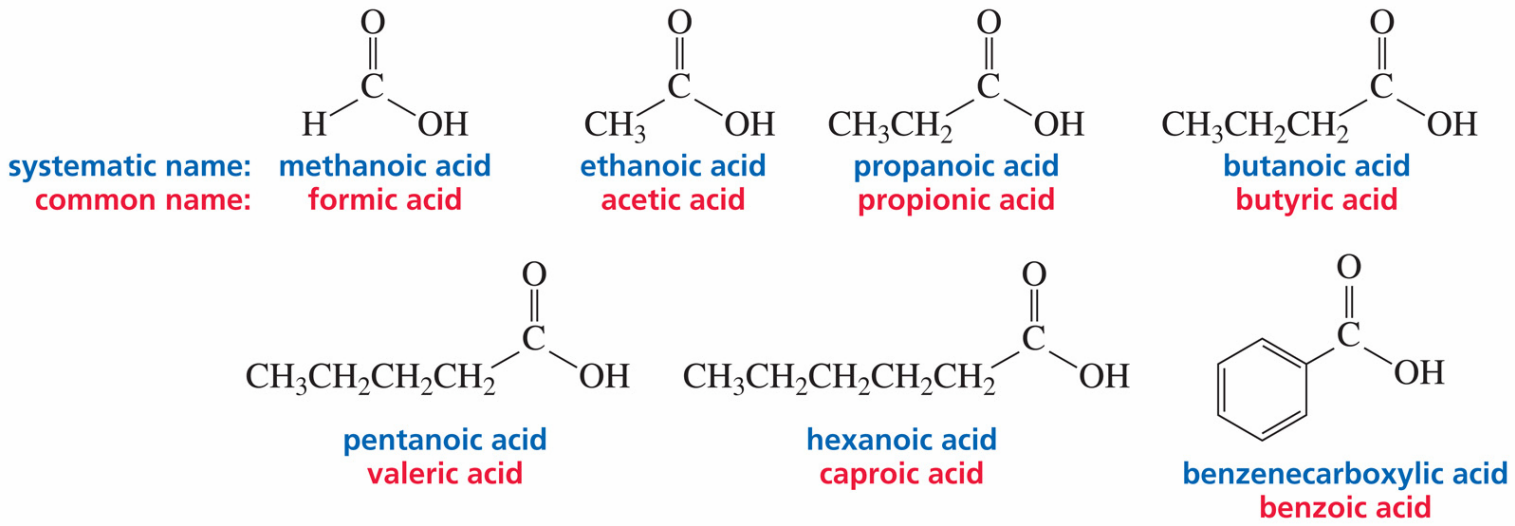


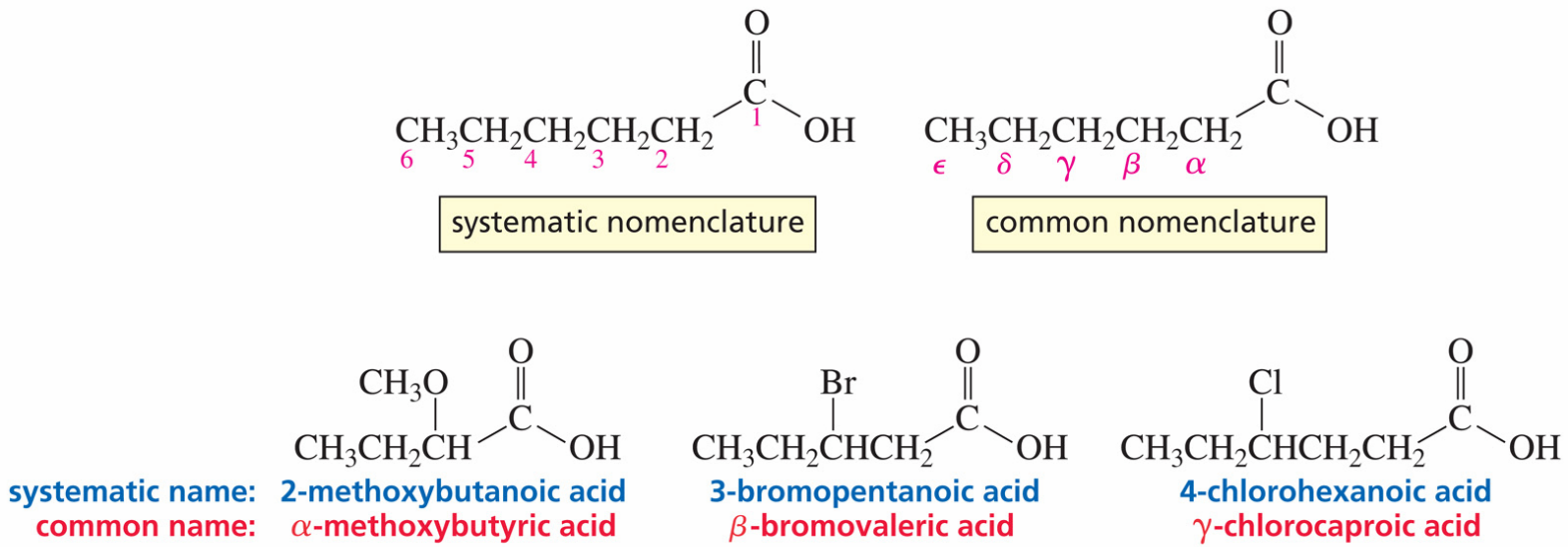
3-Bromocyclohexanecarboxylic acid



5-Methylcyclopent-1-enecarboxylic acid

There are a large number of acids with common names

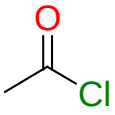




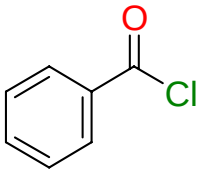
Acid Halides: RCOX

Acid halides are named by identifying first the **acyl group** and then the **halide**.

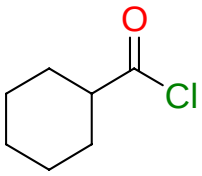
The acyl group name is derived from the acid name by replacing the –ic acid ending with **–yl,** or the –carboxylic acid ending with **–carbonyl**.



Acetyl chloride
(from acetic acid)



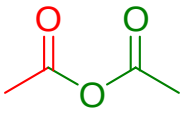
Benzoyl bromide
(from benzoic acid)



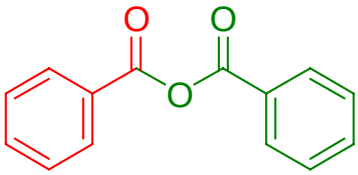
Cyclohexanecarbonyl chloride
(from cyclohexanecarboxylic acid)

Acid Anhydrides: RCO_2COR'

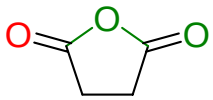
Replace the word acid with **anhydride**.



Acetic anhydride



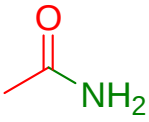
Benzoic anhydride



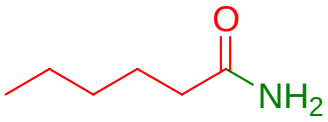
Succinic anhydride

Amides: $RCONH_2$

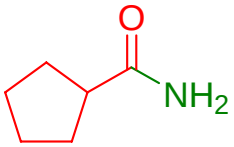
1) Amides with an unsubstituted $–NH_2$ group are named by replacing the –oic acid or –ic acid ending with **–amide**, or by replacing the –carboxylic acid ending with **–carboxamide**.



Acetamide
(from acetic acid)

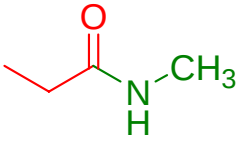


Hexanamide
(from hexanoic acid)

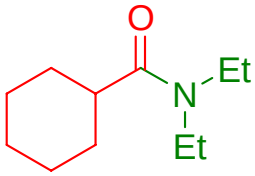


Cyclopentanecarboxamide
(from cyclopentanecarboxylic acid)

2) If the nitrogen atom is substituted, the amide is named by first identifying the substituent group and then the parent. The substituents are preceded by the letter ***N*** to identify them as being directly attached to nitrogen.



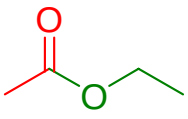
N-methylpropanamide



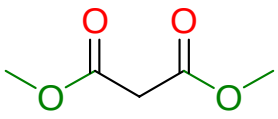
N,N-Diethylcyclohexanecarboxamide

Esters: RCO_2R'

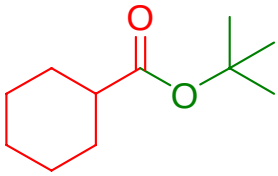
First give the name of the alkyl group attached to oxygen and then identify the carboxylic acid. The –ic acid ending is replaced by **–ate**.



Ethyl acetate



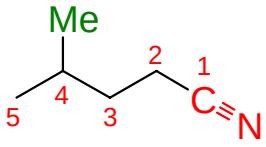
Dimethyl malonate



tert-Butyl cyclohexanecarboxylate

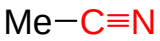
Nitriles: R–C≡N

1) Simple acyclic nitriles are named by adding **–nitrile** as a suffix to the alkane name, with the nitrile carbon numbered C1.

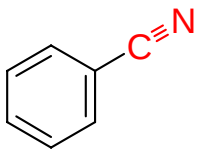


4-Methylpentanenitrile

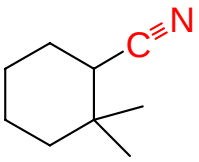
2) Nitriles are named as derivatives of carboxylic acids by replacing the –ic acid or –oic acid ending with **–onitrile**, or by replacing the –carboxylic acid ending with **–carbonitrile**.



Acetonitrile
(from acetic acid)



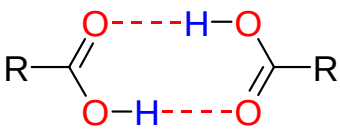
Benzonitrile
(from benzoic acid)



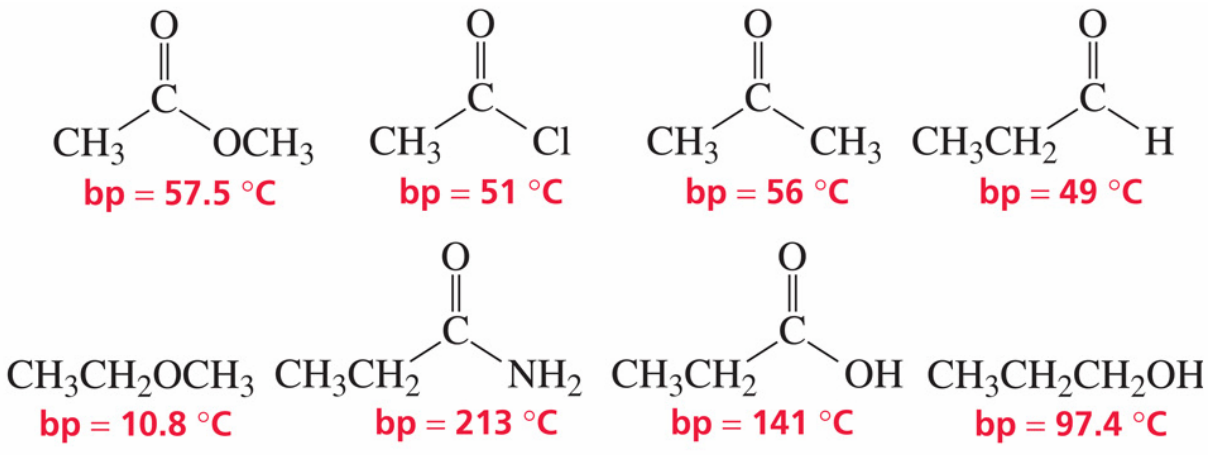
2,2-Dimethylcyclohexanecarbonitrile
(from 2,2-dimethylcyclohexanecarboxylic acid)

10.2 Occurrence and Properties of Carboxylic Acids and Derivatives

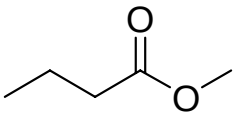
Carboxylic acids are foul in order, and form strong intermolecular hydrogen bonds. Most carboxylic acids exist as dimmers held together by two hydrogen bonds, thereby giving high boiling points.



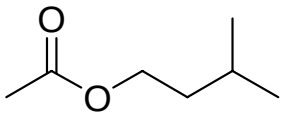
Carboxylic acid dimer



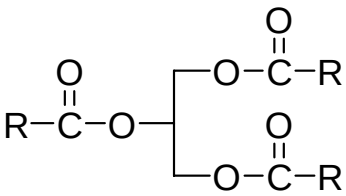
Esters are pleasant-smelling liquids, which are responsible for the fragrant aromas of fruits and flowers.



Methyl butanoate
(from pineapples)

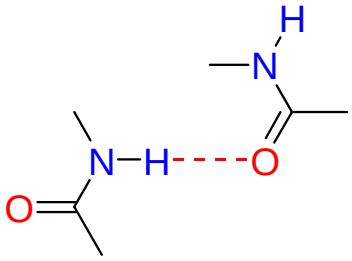


Isopentyl acetate
(from bananas)



Fat (R = $C_{11\sim17}$ chain)

Amides are less reactive than esters; this stability makes amide ideal linkages in peptide and proteins. Hydrogen bonding between amides increases their boiling points. A diverse range of biological events – from protein folding to the action of drugs – depend on hydrogen bonding between amides.



Acyl chlorides and anhydrides are commonly used in the chemical and pharmaceutical industries. These groups are not found in nature due to their reactivity.

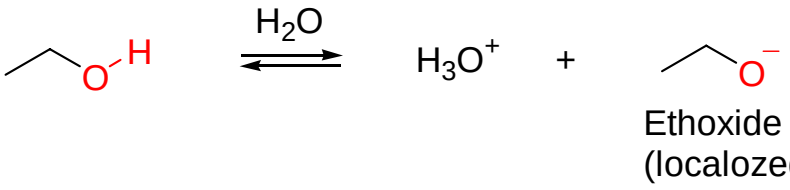
10.3 Acidity of Carboxylic Acids

Acetic acid pK_a = 4.75

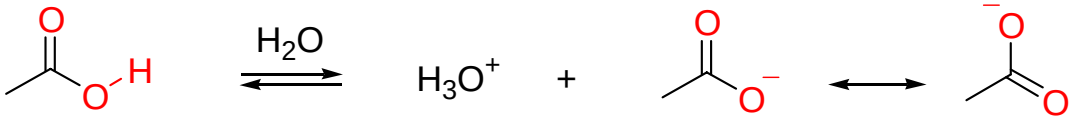
Ethanol pK_a = 16

Why are carboxylic acids so much more acidic than alcohols even though both contain O-H groups?

Compare the relative stabilities of carboxylate anions versus alkoxide anions.

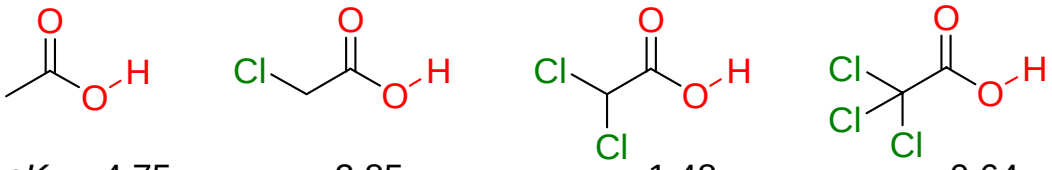


Ethoxide ion
(localozed charge)



Acetate ion
(delocalozed charge)

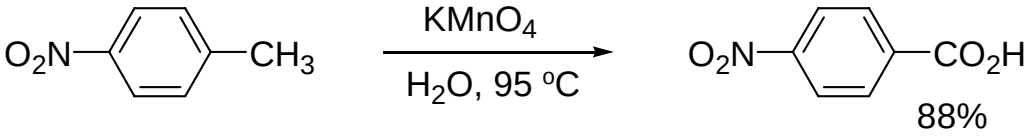
The presence of an electron-withdrawing chlorine atom spreads out the negative charge on the anion and makes chloroacetic acid stronger than acetic acid.



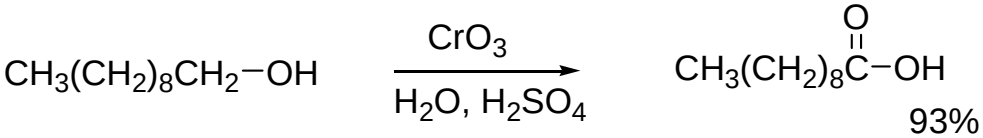
pK_a = 4.75 2.85 1.48 0.64

10.4 Synthesis of Carboxylic Acids

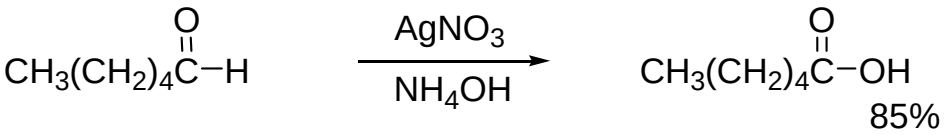
Oxidation reactions



88%



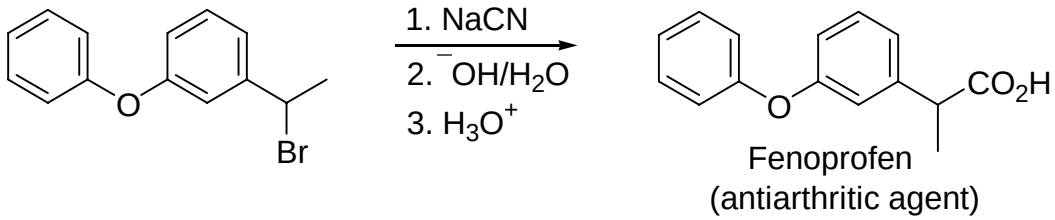
93%



85%

Tollen's reagent

From alkyl halide to carboxylic acid

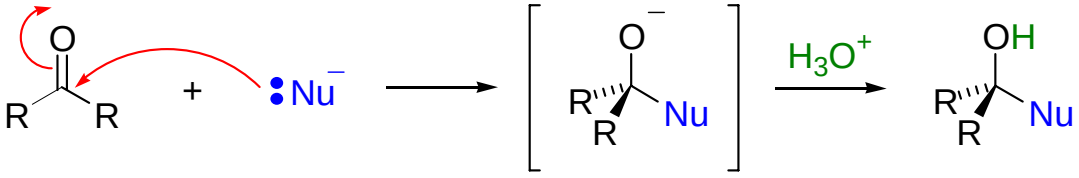


Fenoprofen
(antiarthritic agent)

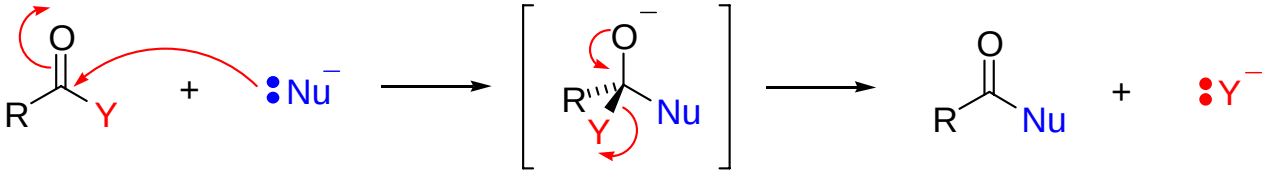
10.5 Nucleophilic Acyl Substitution Reactions

Nucleophilic addition vs. acyl substitution – substrate dependent

ketones and aldehydes: nucleophilic addition



Carboxylic acid derivatives: nucleophilic acyl substitution



The different behavior toward nucleophiles of aldehydes/ketones and carboxylic acid derivatives is a consequence of structure – carboxylic acid derivatives have an acyl carbon bonded to **a group that can leave as a stable anion (Y)**.

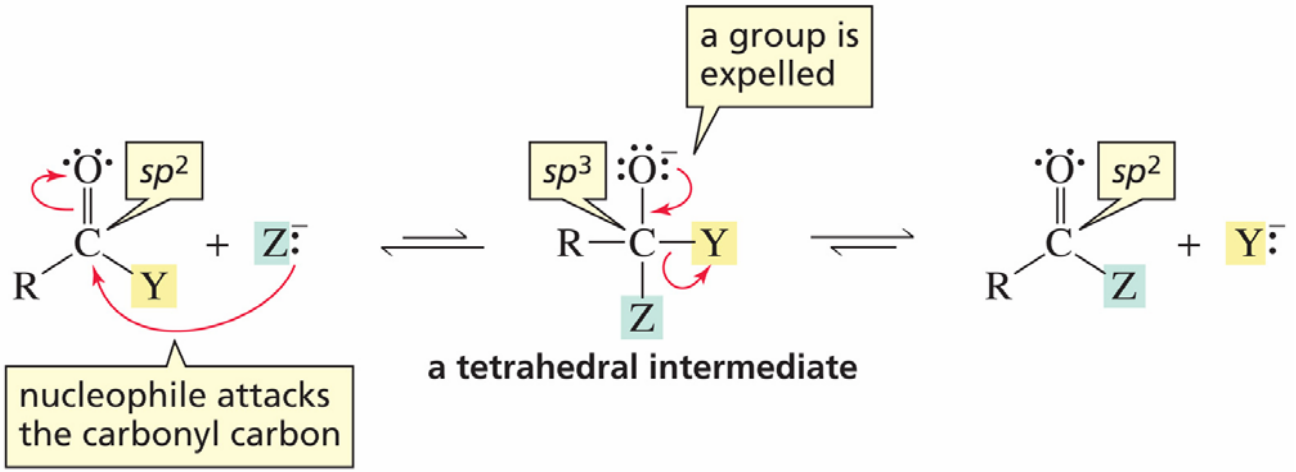
Comparison of the reactivity of different acyl derivatives

The more electron poor the C=O carbon, the more readily the compound reacts with nucleophile.

Reactivity toward nucleophile

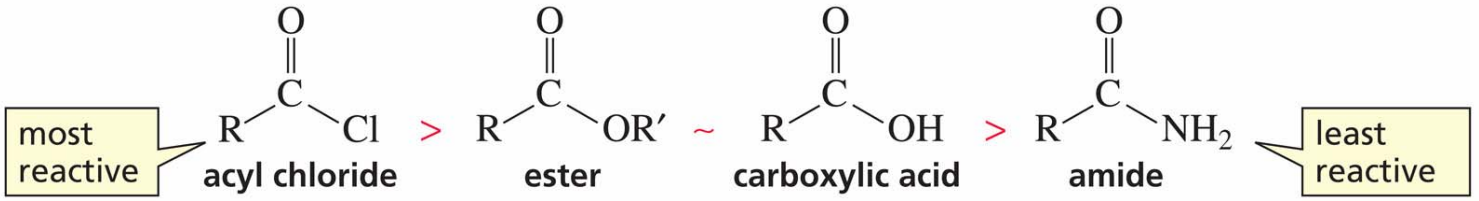
Acid chloride > Anhydride > Ester > Amide

It is possible to convert a more reactive acid derivative into a less reactive one.



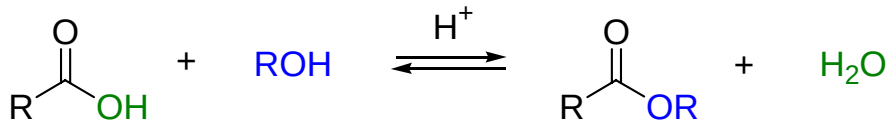
relative basicities of the leaving groups

relative reactivities of carboxylic acid derivatives

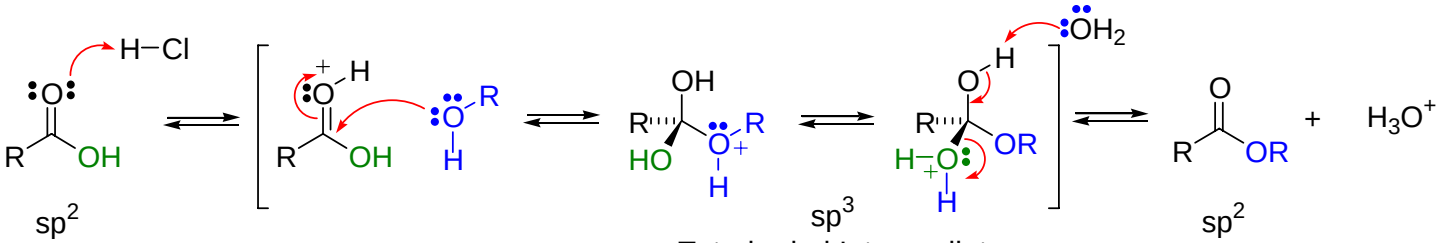


10.6 The Tetrahedral Intermediate

Fischer esterification reaction



Mechanism



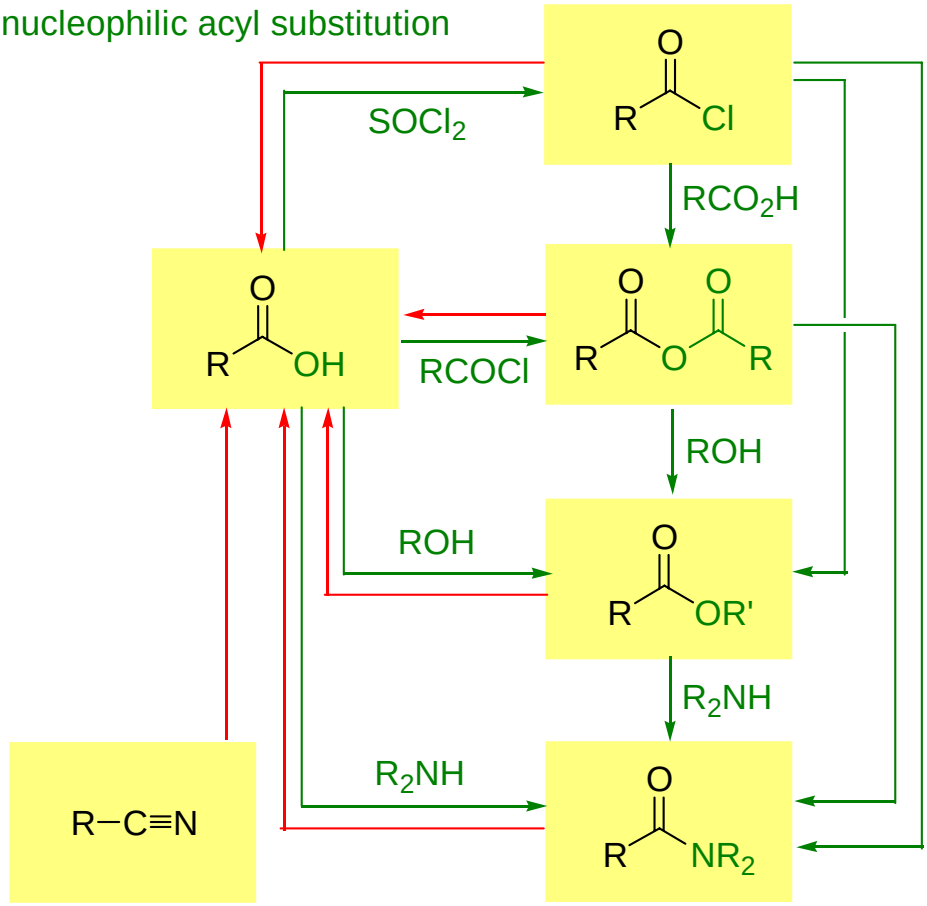
Tetrahedral Intermediate

All steps are reversible, and the position of the equilibrium depends on the reaction conditions. Ester formation is favored when alcohol is used as a solvent, but a carboxylic acid is favored when the solvent is water.

10.7 Overview of Reactions

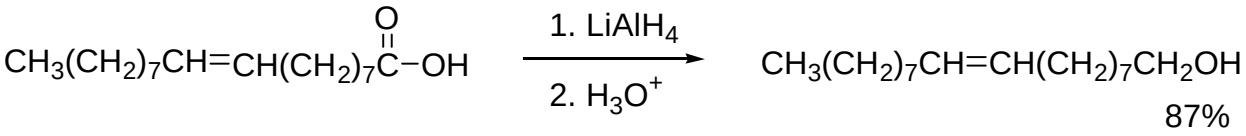
— hydrolysis

— nucleophilic acyl substitution

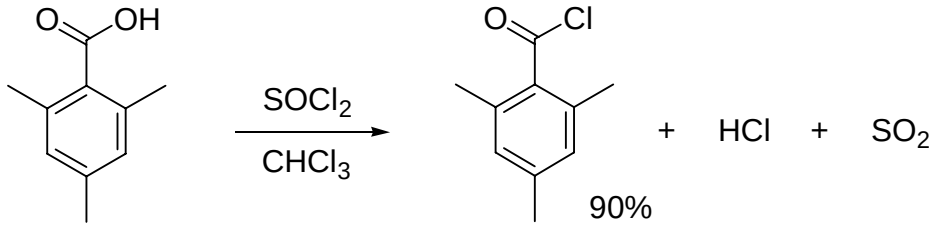


10.8 Reactions of Carboxylic Acids

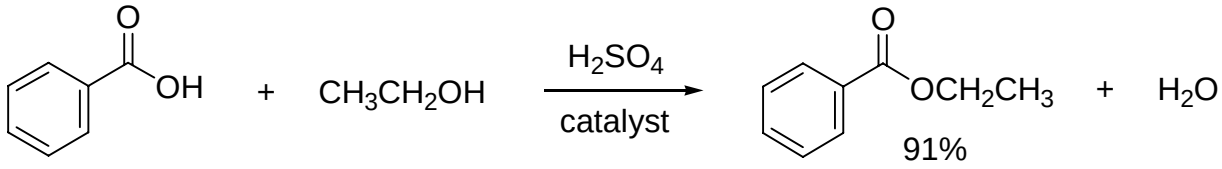
Conversion of Acids into Alcohols by Reduction



Conversion of Acids into Acid Chlorides

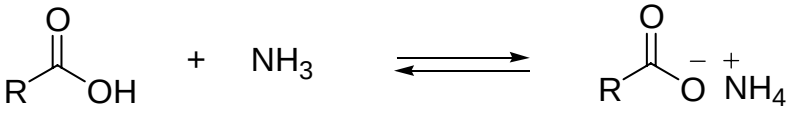


Conversion of Acids into Esters



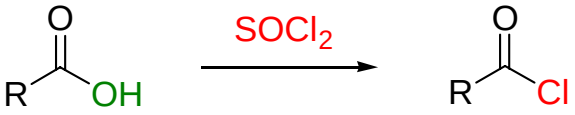
Conversion of Acids into Amides

Amides are difficult to prepare directly from acids by substitution with an amine because amines are bases, which convert acidic carboxyl groups into their carboxylate anions.

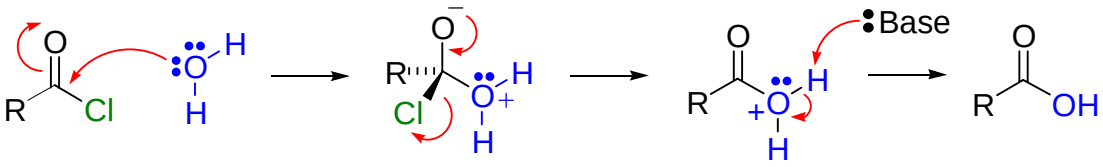


10.9 Chemistry of Acid Halides

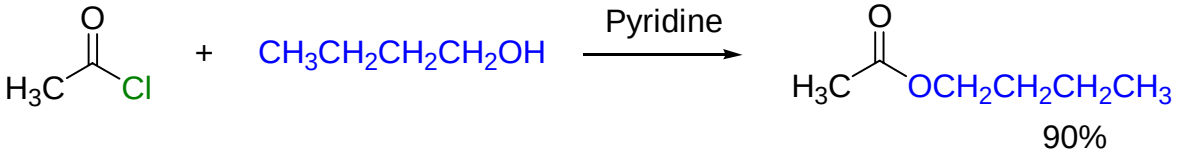
Preparations



Conversion of Acid Chlorides into Acids

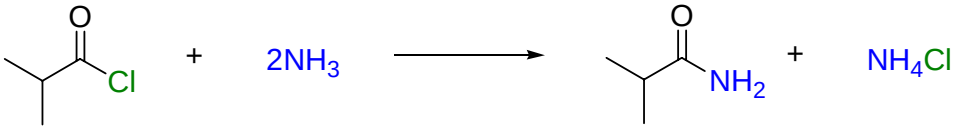


Conversion of Acid Chlorides into Esters



Since HCl is generated as a byproduct, the reaction is carried out in the presence of amine base such as pyridine.

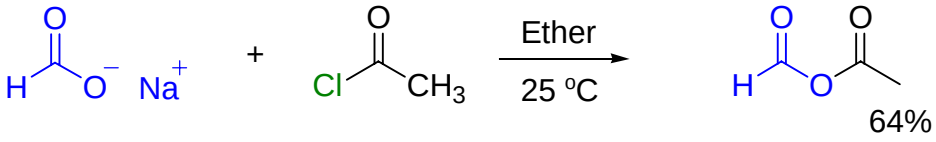
Conversion of Acid Chlorides into Amides



One extra equivalent of ammonia is added to react with the HCl generated.

10.10 Chemistry of Acid Anhydrides

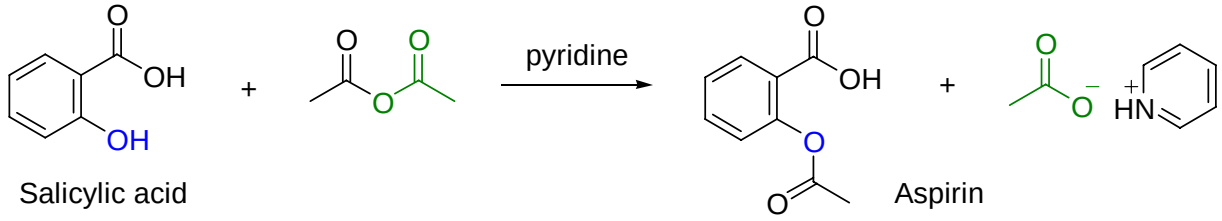
Preparations



Reactions

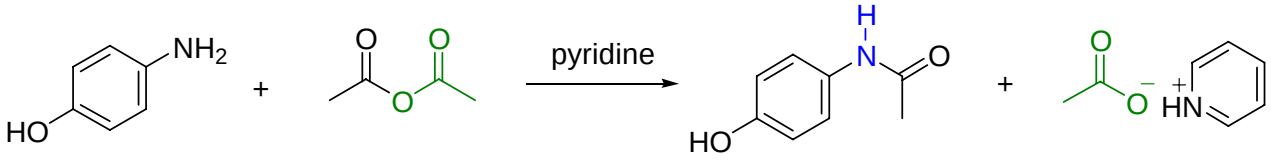
The chemistry of acid anhydrides is similar to that of acid chlorides.
Acid anhydrides react with water to form acids.

Ester formation



Salicylic acid — Aspirin

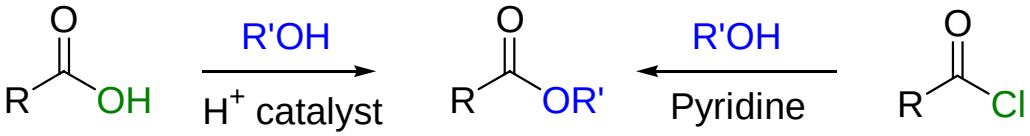
Amide formation



p-Hydroxyaniline — Acetaminophen (Tylenol)

10.11 Chemistry of Esters

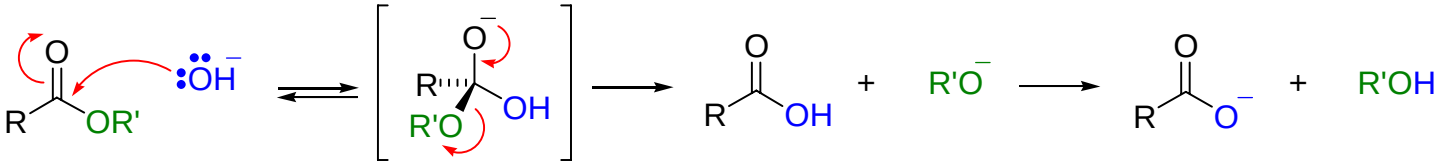
Preparations



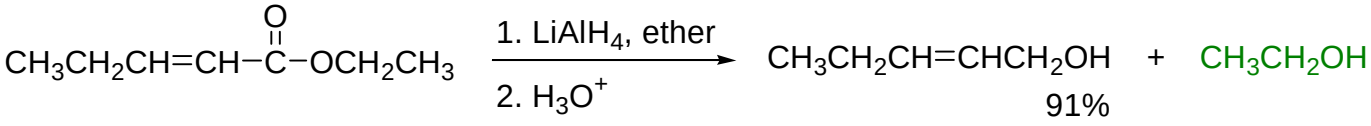
Conversion of Esters into Acids

Esters are hydrolyzed either by aqueous base or aqueous acid to yield a carboxylic acid and an alcohol.

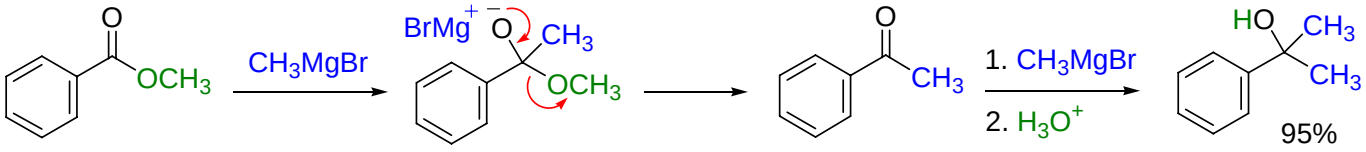
Mechanism of the base hydrolysis (saponification – soap making)



Conversion of Esters into Alcohols by Reduction



Conversion of Esters into Alcohols by Reaction with Grignard Reagents

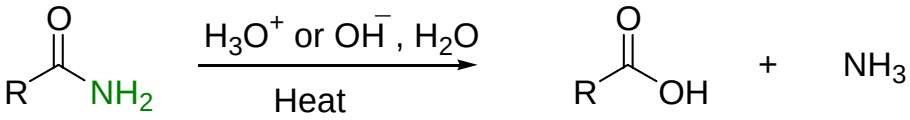


10.12 Chemistry of Amides

Preparations

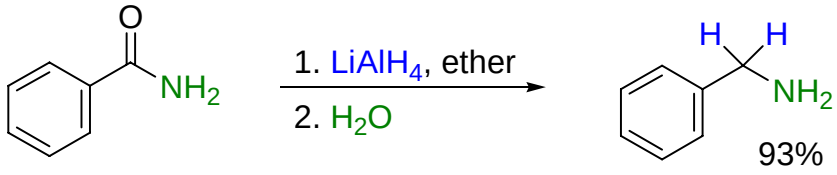
Nucleophilic acyl substitution reaction of acid chloride, acid anhydride, or ester with ammonia, monosubstituted amine, and disubstituted amine.

Conversion of Amides into Acids



Amides undergo hydrolysis to yield carboxylic acids and amine on heating in either aqueous acid or base. The reaction is slow and requires prolonged heating.

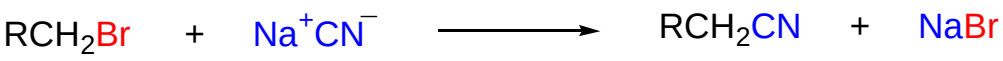
Conversion of Amides into Amines by Reduction



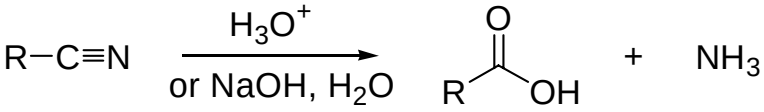
Notice that the product is an amine instead of an alcohol.

10.13 Chemistry of Nitriles

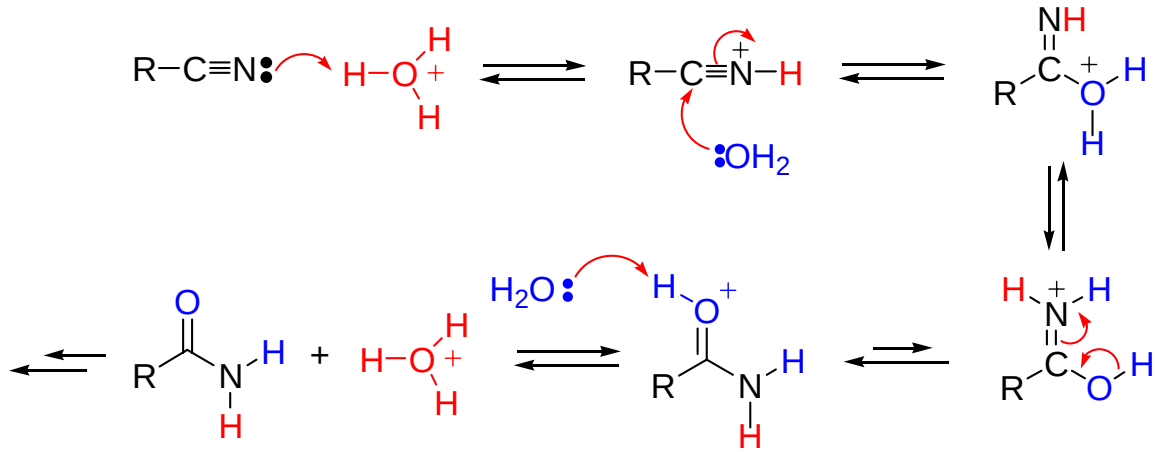
Preparation



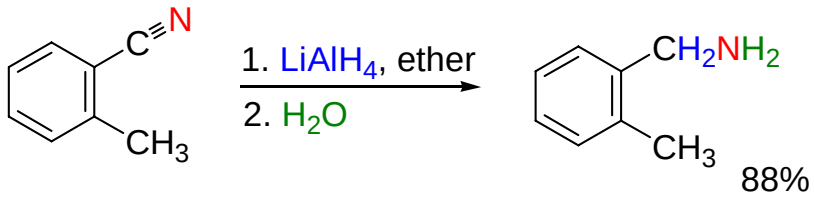
Conversion of Nitriles into Carboxylic Acids



Mechanism

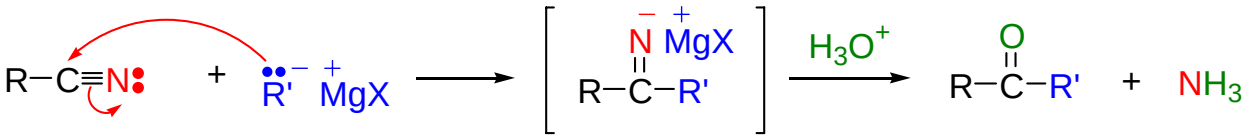


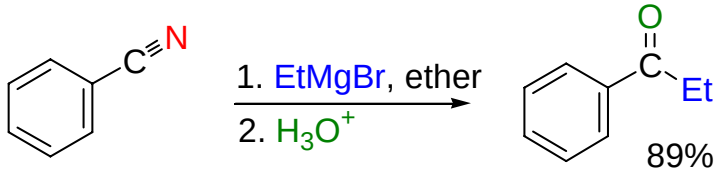
Conversion of Nitriles into Amines by Reduction



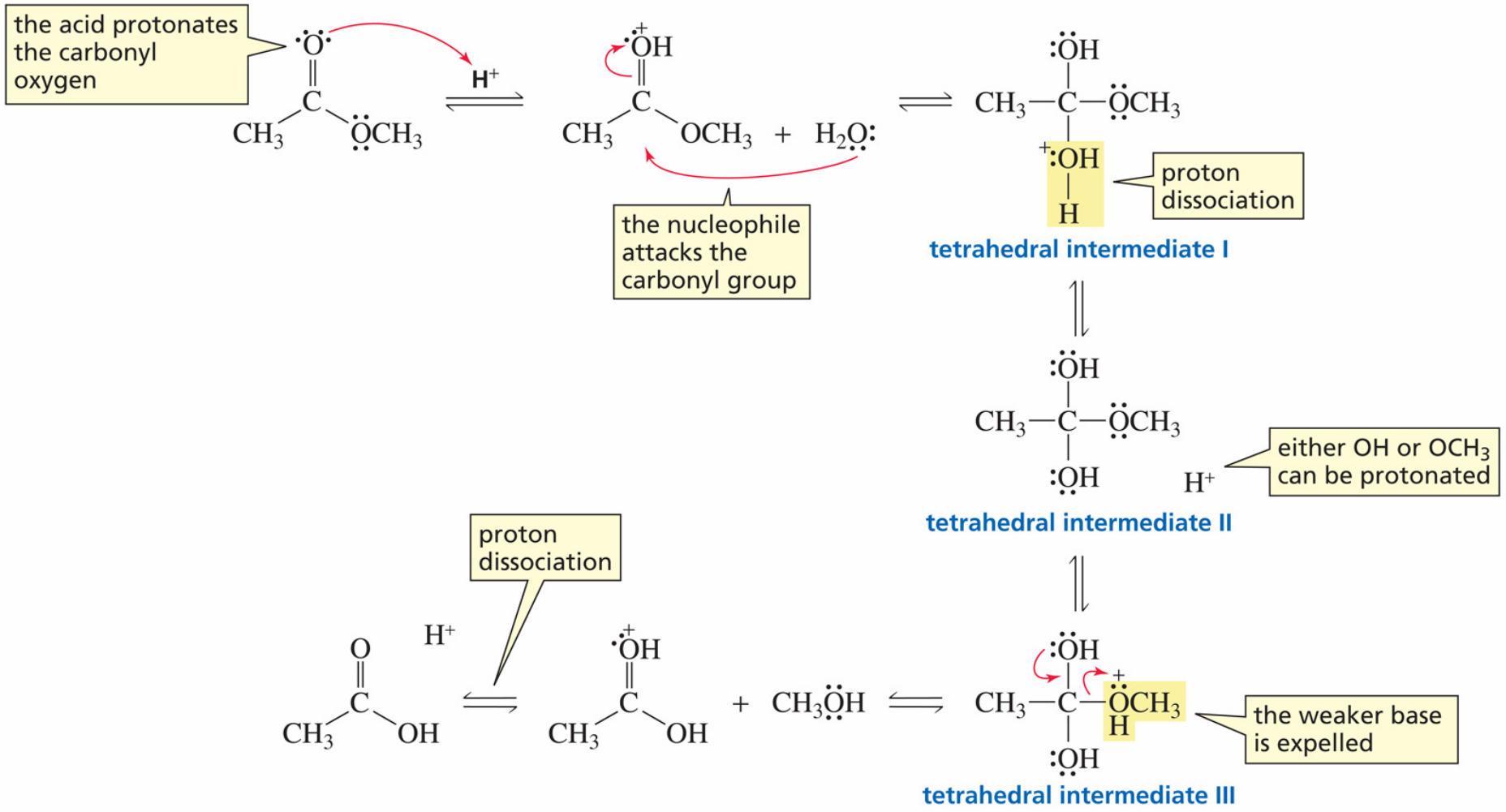
Conversion of Nitriles into Ketones by Reaction with Grignard Reagents

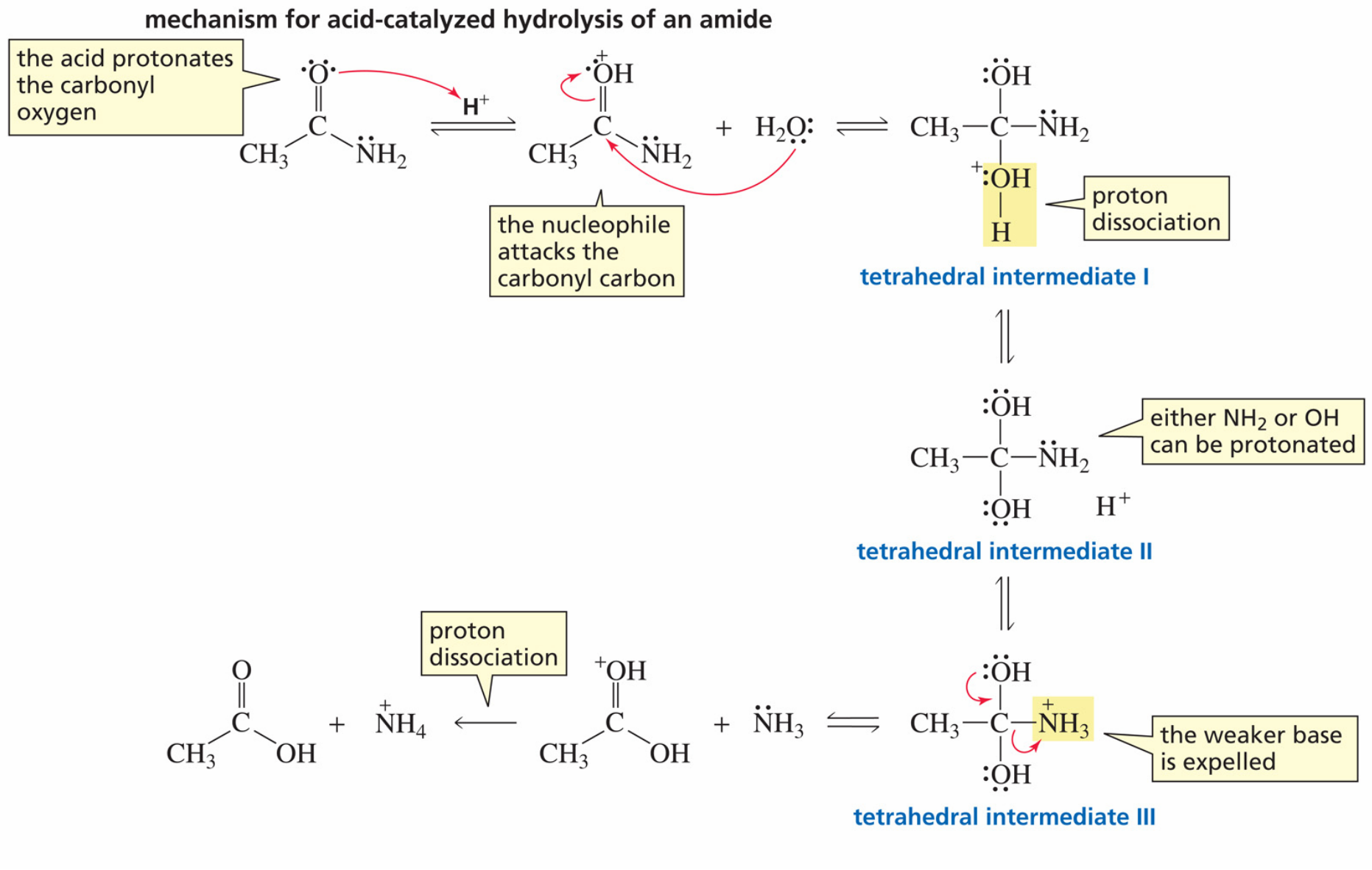
Grignard reagents, RMgX, add to nitrile to give intermediate imine anions that can be hydrolyzed to yield ketones.


R–C≡N:
+
R'
MgX
N
MgX
R–C–R'
H3O+
O
R–C–R'
+
NH3


C≡N
1. EtMgBr, ether
2. H3O+
O
C
Et
89%

mechanism for acid-catalyzed ester hydrolysis




mechanism for acid-catalyzed hydrolysis of an amide
the acid protonates the carbonyl oxygen
the nucleophile attacks the carbonyl carbon
proton dissociation
tetrahedral intermediate I
either NH2 or OH can be protonated
tetrahedral intermediate II
proton dissociation
the weaker base is expelled
tetrahedral intermediate III