Carboxylic Acids and Nitriles

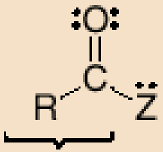
Chapters 20, 21

Organic Chemistry, ***8th Edition***

John McMurry

Carboxylic Acid Derivatives

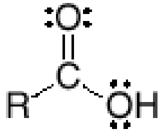
General structure



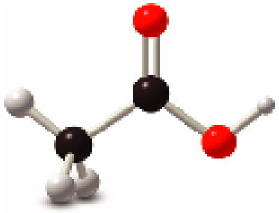
acyl group

Z = electronegative atom

Z = OH

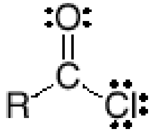


carboxylic acid

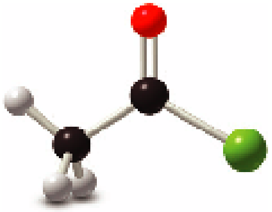


R = CH_3
acetic acid

Z = Cl

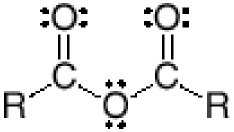


acid chloride

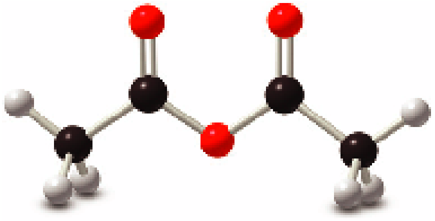


R = CH_3
acetyl chloride

Z = OCOR



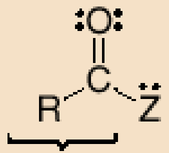
anhydride



R = CH_3
acetic anhydride

Carboxylic Acid Derivatives

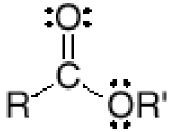
General structure



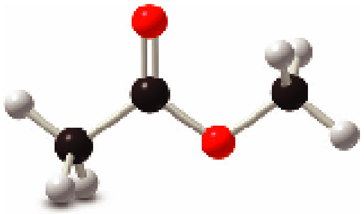
acyl group

Z = electronegative atom

Z = OR'

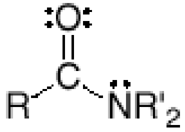


ester

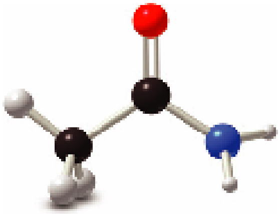


R = R' = CH_3
methyl acetate

Z = NR'_2



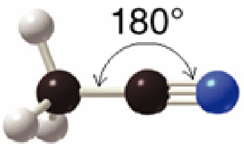
R' = H or alkyl
amide



R = CH_3, R' = H
acetamide

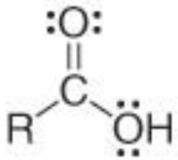
$R-C\equiv N$

nitrile

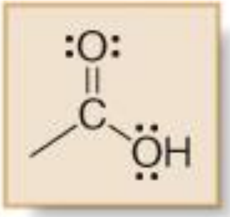


R = CH_3
acetonitrile

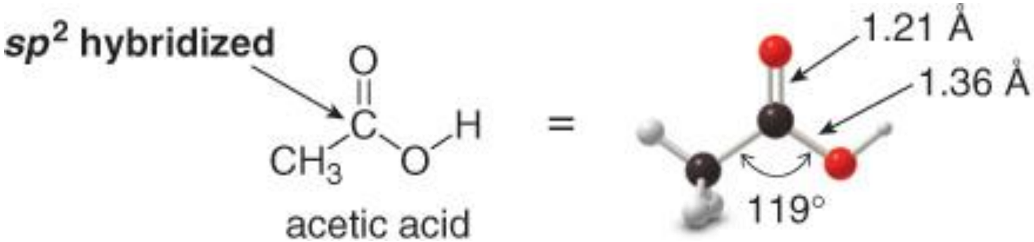
Structure and Bonding



carboxylic acid



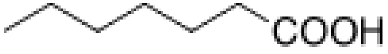
carboxy group



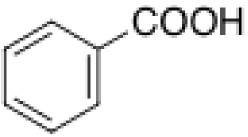
acetic acid

The C=O is shorter than the C–O.

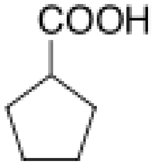
Nomenclature—The IUPAC System



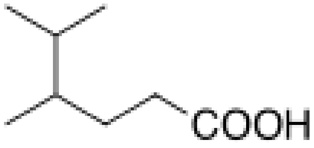
heptanoic acid



benzoic acid

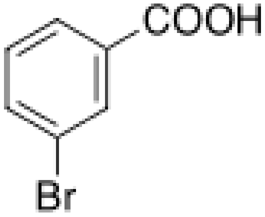


cyclopentane
carboxylic acid

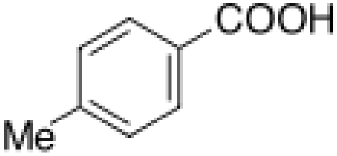


4,5-dimethyl
hexanoic acid

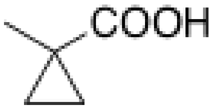
3-pentenoic
acid



3-bromobenzoic
acid



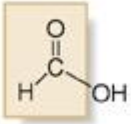
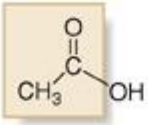
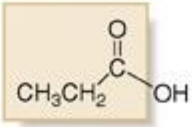
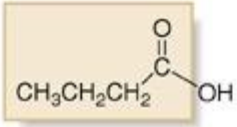
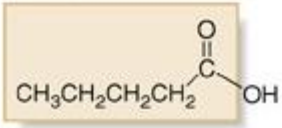
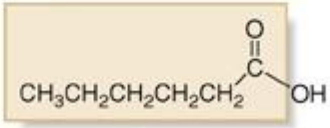
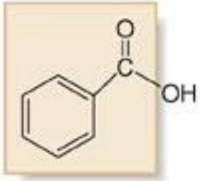
p-toluic
acid



1-methyl-
cyclopropanecarboxylic
acid

Nomenclature-Common Names

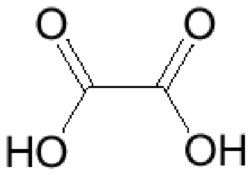
Table 19.1 Common Names for Some Simple Carboxylic Acids

Number of C atoms	Structure	Parent name	Common name
1	 $H\overset{\overset{O}{\|}}{C}OH$	**form-**	formic acid
2	 $CH_3\overset{\overset{O}{\|}}{C}OH$	**acet-**	acetic acid
3	 $CH_3CH_2\overset{\overset{O}{\|}}{C}OH$	**propion-**	propionic acid
4	 $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH$	**butyr-**	butyric acid
5	 $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH$	**valer-**	valeric acid
6	 $CH_3CH_2CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH$	**capro-**	caproic acid
		**benzo-**	benzoic acid

(protos=primo + pion=grasso)

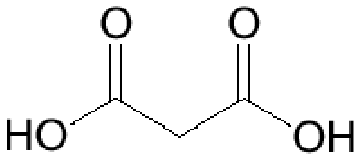
Il primo degli acidi grassi

Nomenclature-Polyiacids



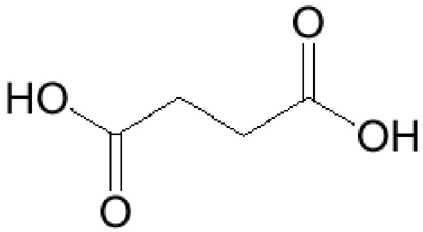
oxalic acid
(ethanedioic acid)

Oxalis acetosella



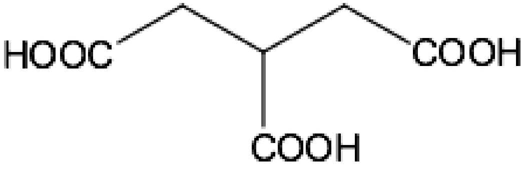
malonic acid
(propanedioic acid)

Malon



succinic acid
(butanedioic acid)

Succinum (ambra)



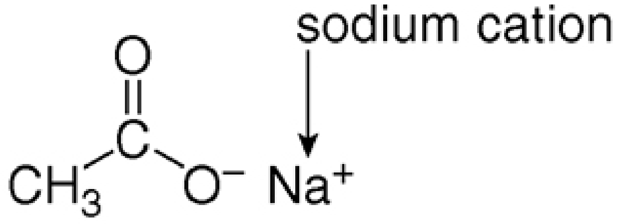
propane-1,2,3-tricarboxylic acid

Nomenclature-Salts

- To name the metal salt of a carboxylate anion, put three parts together:

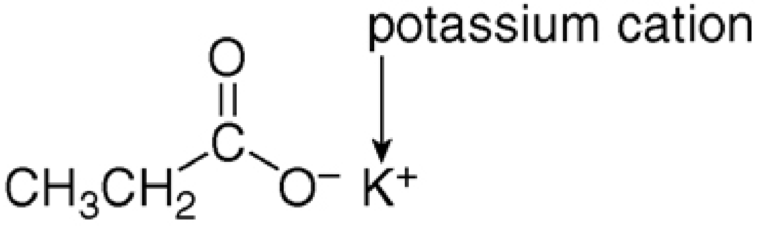
name of the metal cation + parent + suffix

common → ***-ate*** (for a common parent name)
or
IUPAC → ***-oate*** (for an IUPAC parent name)



parent + suffix
acet- -ate

sodium acetate

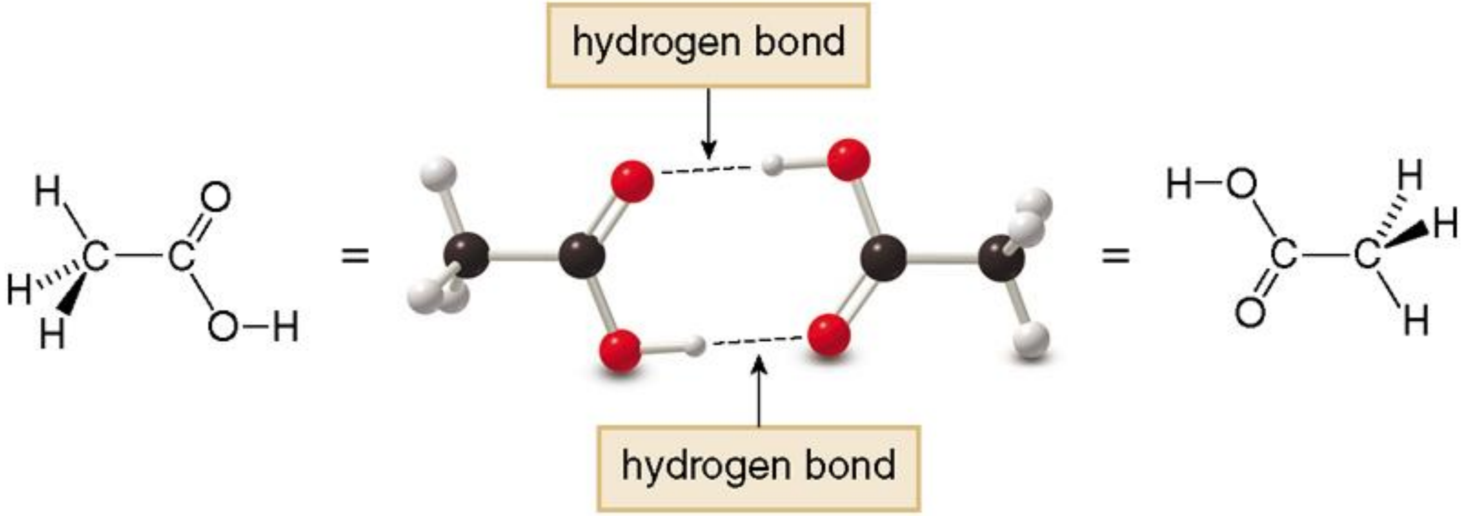


parent + suffix
propan- -oate

potassium propanoate

Physical Properties

- Carboxylic acids exhibit dipole-dipole interactions because they have polar C—O and O—H bonds.
- They also exhibit intermolecular hydrogen bonding.
- In the gas phase and in apolar solvents, carboxylic acids often exist as dimers held together by two intermolecular hydrogen bonds.



Physical Properties

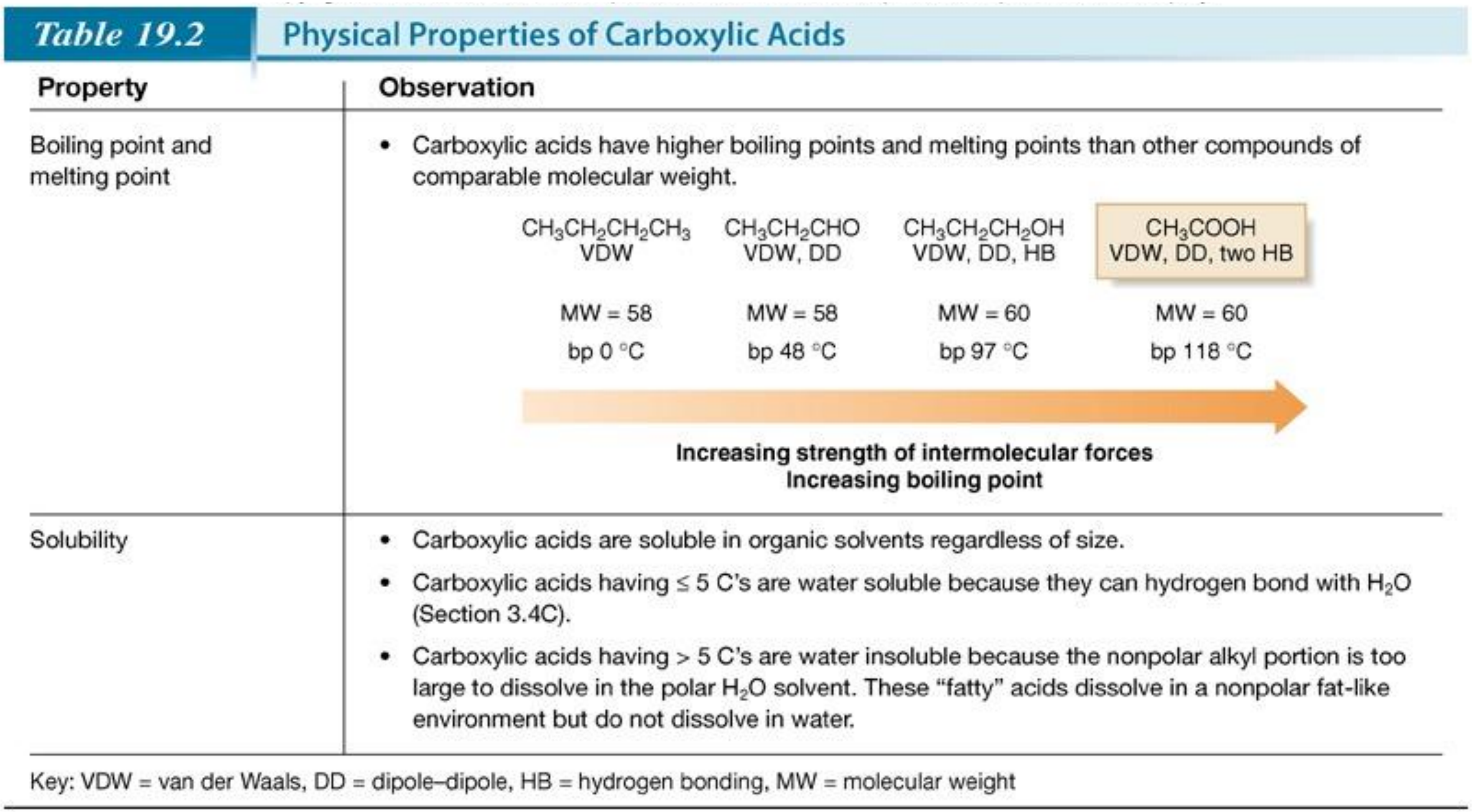


Table 19.2 Physical Properties of Carboxylic Acids

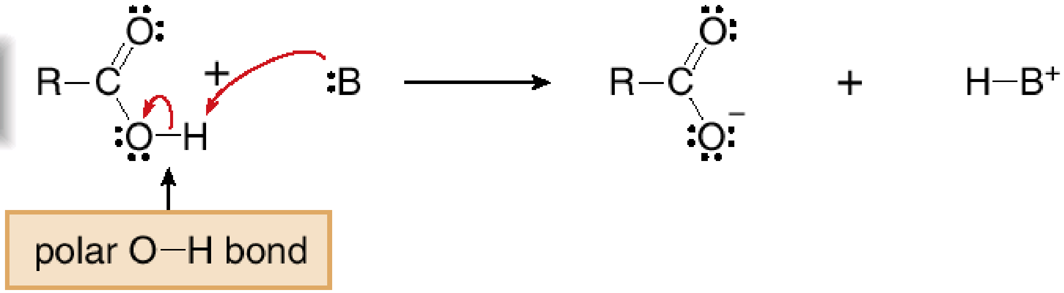
Property	Observation
Boiling point and melting point	- Carboxylic acids have higher boiling points and melting points than other compounds of comparable molecular weight. $CH_3CH_2CH_2CH_3$ VDW, MW = 58, bp 0 °C CH_3CH_2CHO VDW, DD, MW = 58, bp 48 °C $CH_3CH_2CH_2OH$ VDW, DD, HB, MW = 60, bp 97 °C CH_3COOH VDW, DD, two HB, MW = 60, bp 118 °C **Increasing strength of intermolecular forces** **Increasing boiling point**
Solubility	- Carboxylic acids are soluble in organic solvents regardless of size. - Carboxylic acids having ≤ 5 C's are water soluble because they can hydrogen bond with H_2O (Section 3.4C). - Carboxylic acids having > 5 C's are water insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent. These "fatty" acids dissolve in a nonpolar fat-like environment but do not dissolve in water.

Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

Acidity of Carboxylic Acids

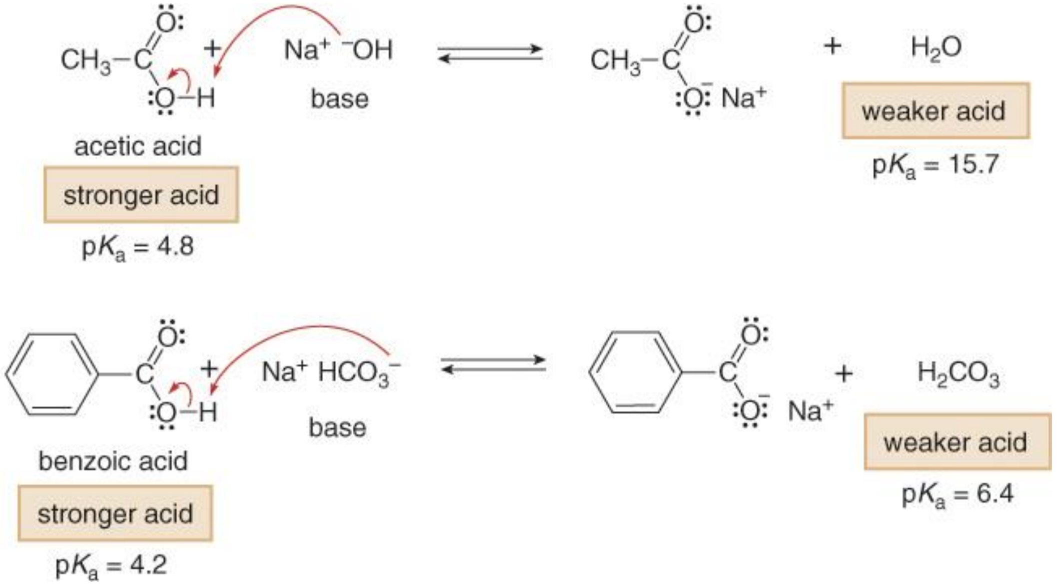
- Carboxylic acids react as Brønsted–Lowry acids—that is, as proton donors.

A Brønsted–Lowry acid–base reaction

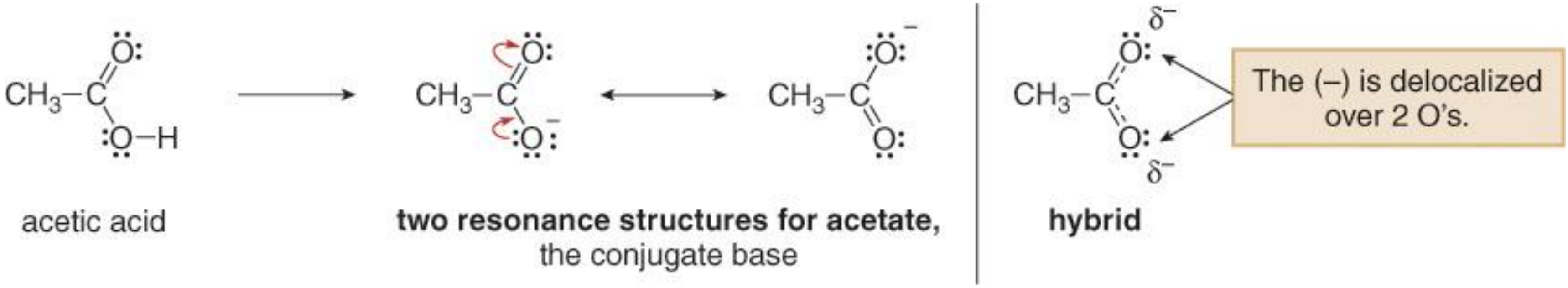


- Because the pK_a values of many carboxylic acids are ~5, bases that have conjugate acids with pK_a values higher than 5 are strong enough to deprotonate them.

Examples



Acidity of Carboxylic Acids



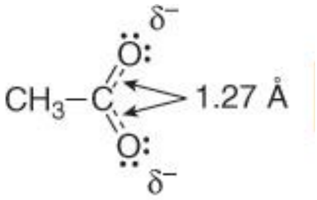
acetic acid

two resonance structures for acetate, the conjugate base

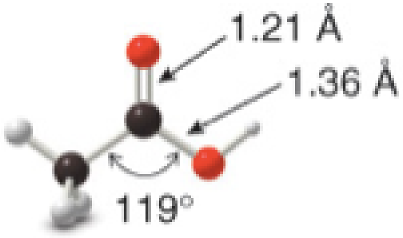
hybrid

The (–) is delocalized over 2 O's.

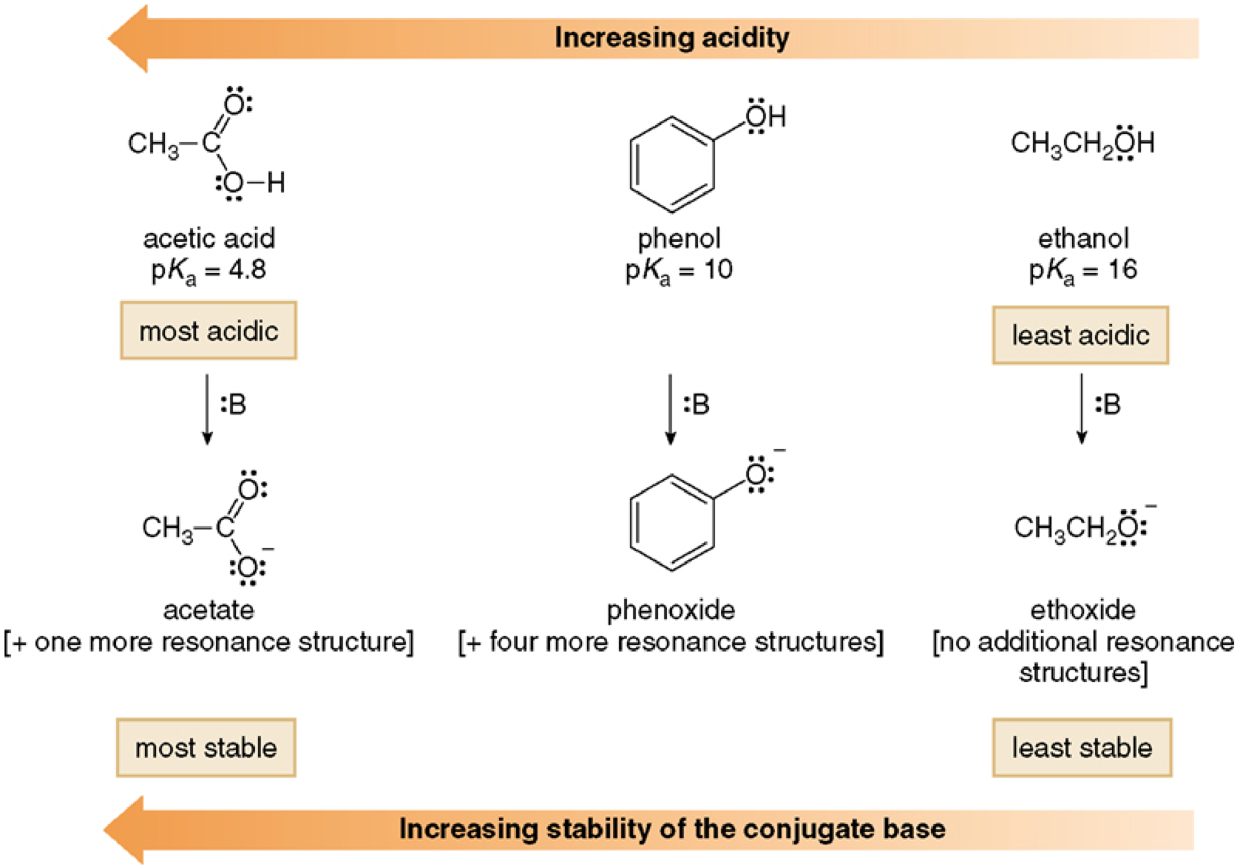
- The acetate anion has two C—O bonds of equal length (1.27 Å) and intermediate between the length of a C—O single bond (1.36 Å) and C=O (1.21 Å).



acetate hybrid



Carboxylic Acids—Strong Organic BrØnsted-Lowry Acids



Increasing acidity

acetic acid
pK_a = 4.8

phenol
pK_a = 10

ethanol
pK_a = 16

most acidic

least acidic

:B

acetate
[+ one more resonance structure]

phenoxide
[+ four more resonance structures]

ethoxide
[no additional resonance structures]

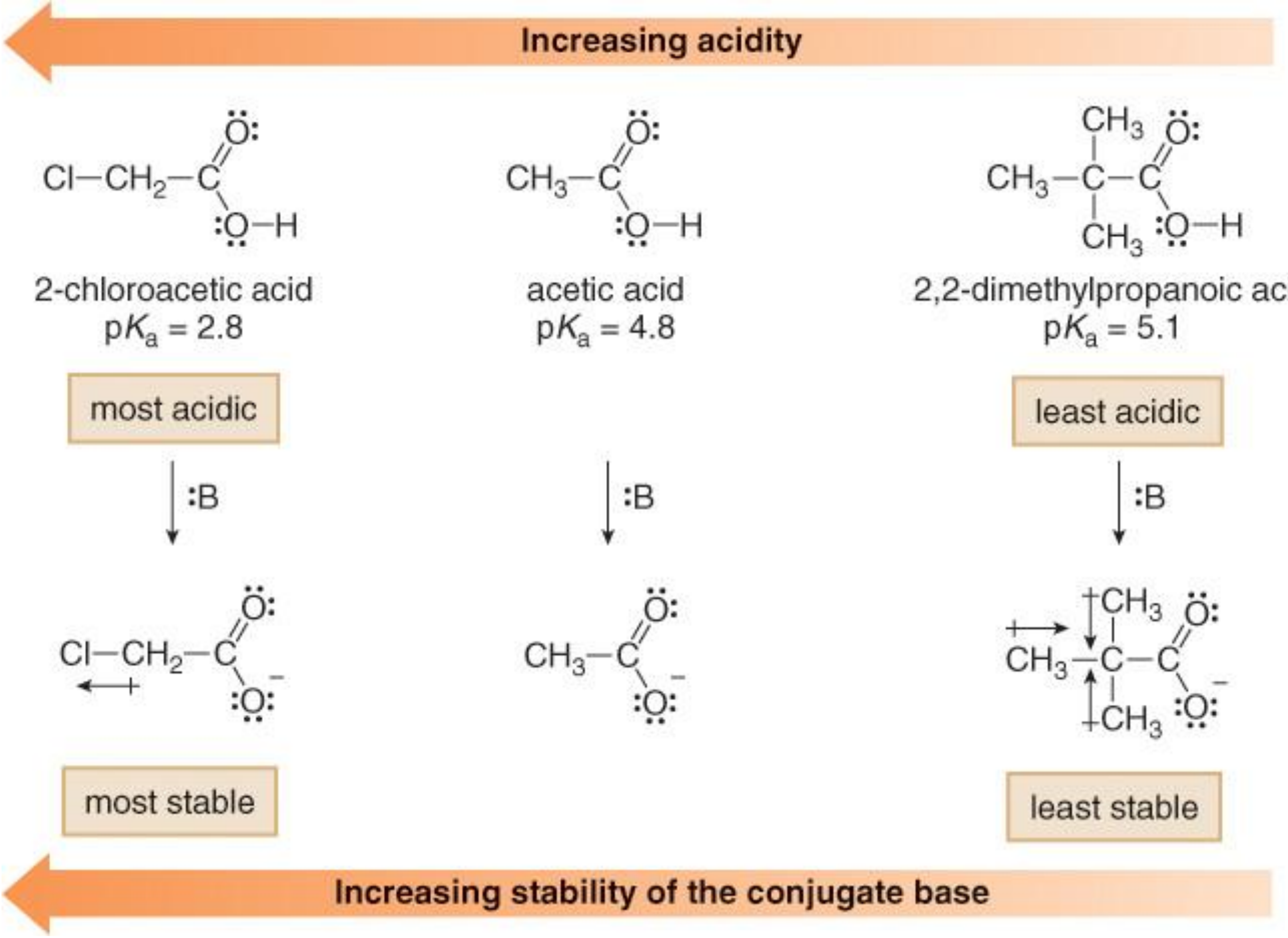
most stable

least stable

Increasing stability of the conjugate base

The Inductive Effect in Aliphatic Carboxylic Acids

- **Electron-withdrawing groups stabilize a conjugate base, making a carboxylic acid more acidic.**
- **Electron-donating groups destabilize the conjugate base, making a carboxylic acid less acidic.**



2-chloroacetic acid
pK_a = 2.8
most acidic
most stable

acetic acid
pK_a = 4.8

2,2-dimethylpropanoic acid
pK_a = 5.1
least acidic
least stable

The Inductive Effect in Aliphatic Carboxylic Acids

- The larger the number of electronegative substituents, the stronger the acid.

$ClCH_2{-}COOH$ pK_a = 2.8

$Cl_2CH{-}COOH$ pK_a = 1.3

$Cl_3C{-}COOH$ pK_a = 0.9

Increasing acidity
Increasing number of electronegative Cl atoms

- The more electronegative the substituent, the stronger the acid.

$ClCH_2{-}COOH$ pK_a = 2.8

$FCH_2{-}COOH$ pK_a = 2.6

stronger acid

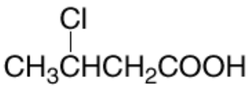
F is more electronegative than Cl.

- The closer the electron-withdrawing group to the COOH, the stronger the acid.

$ClCH_2CH_2CH_2COOH$

4-chlorobutanoic acid

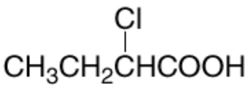
pK_a = 4.5



$CH_3\overset{Cl}{C}HCH_2COOH$

3-chlorobutanoic acid

pK_a = 4.1



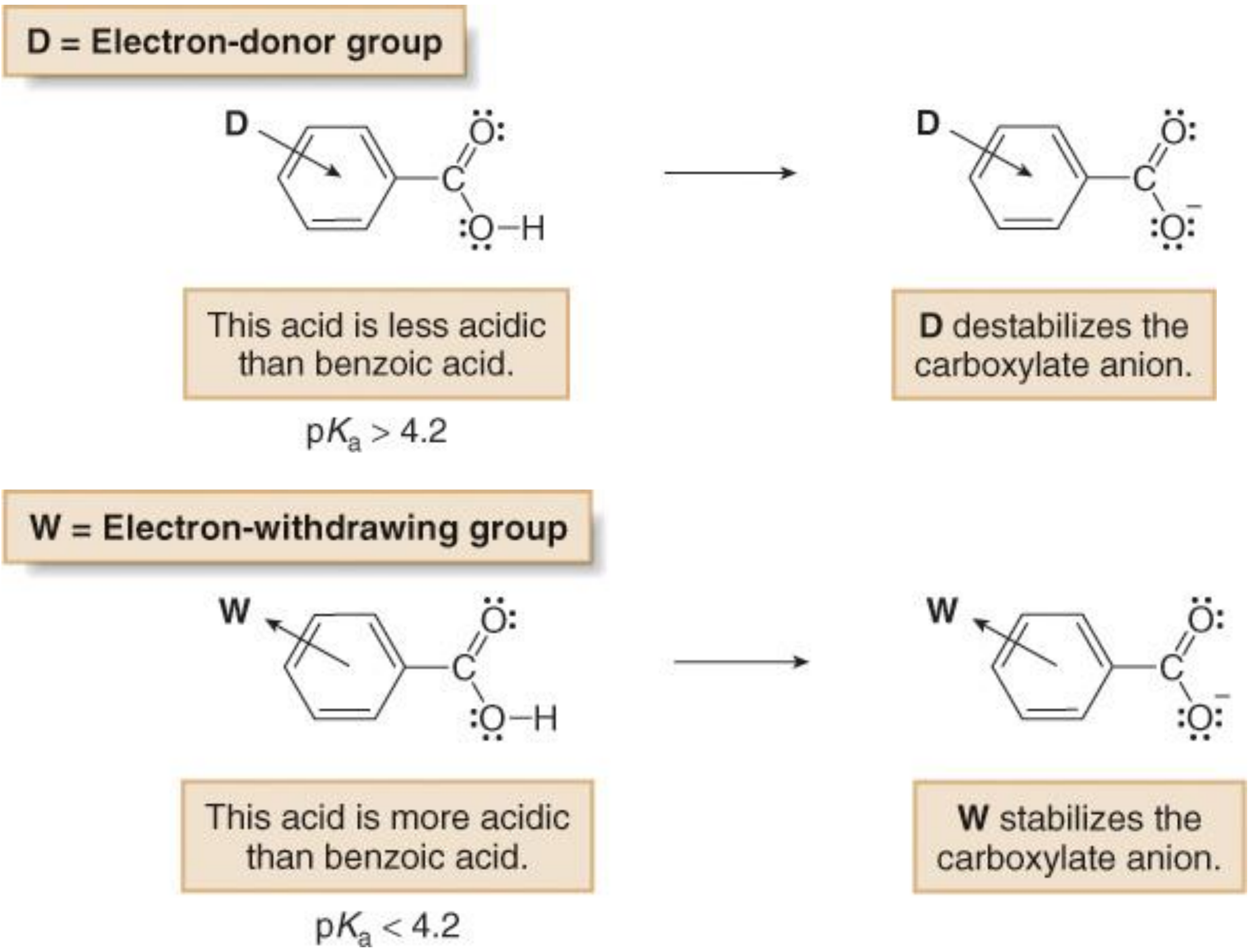
$CH_3CH_2\overset{Cl}{C}HCOOH$

2-chlorobutanoic acid

pK_a = 2.9

Increasing acidity
Increasing proximity of Cl to COOH

Substituted Benzoic Acids



D = Electron-donor group

This acid is less acidic than benzoic acid.

pK_a > 4.2

D destabilizes the carboxylate anion.

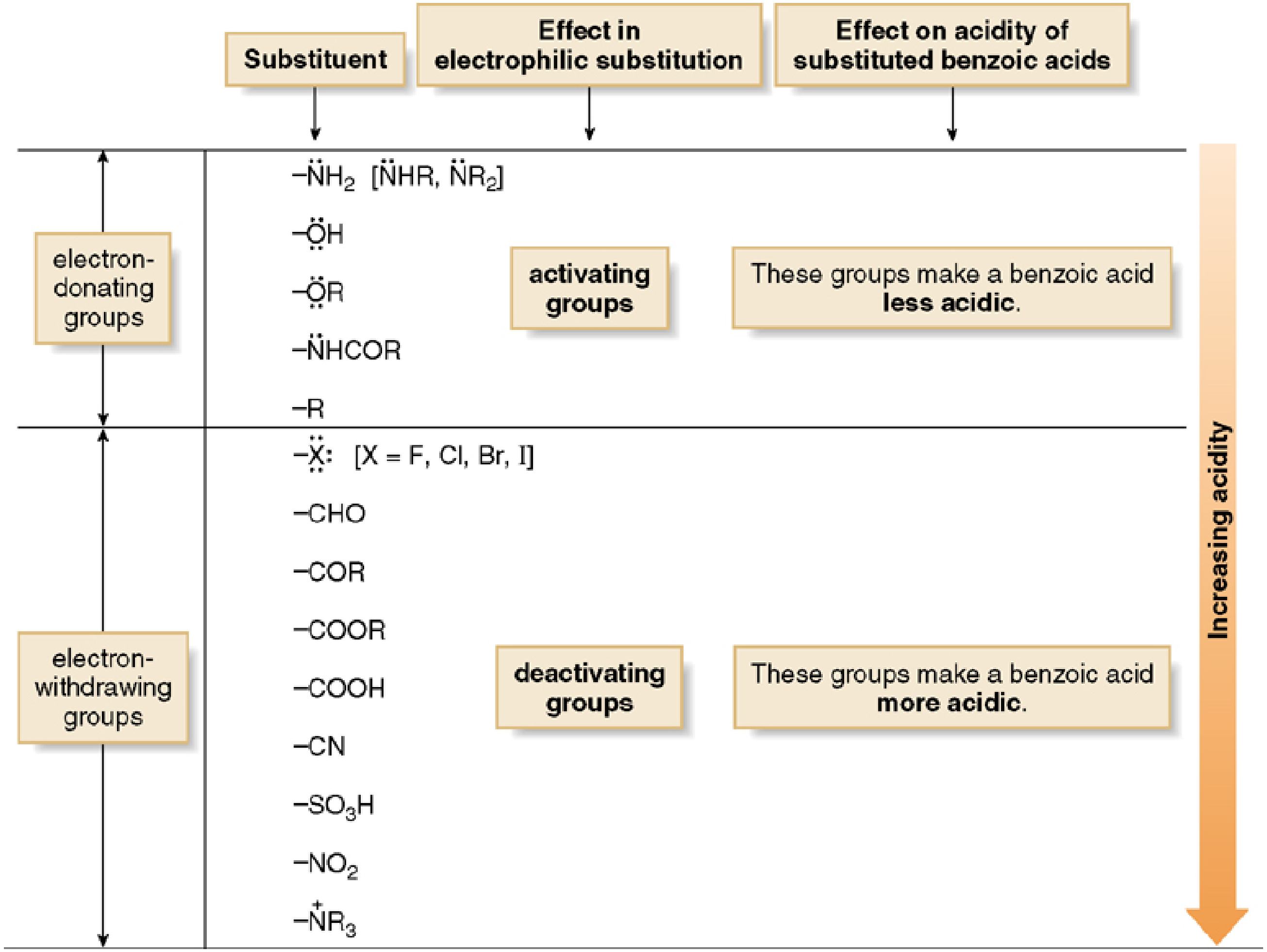
W = Electron-withdrawing group

This acid is more acidic than benzoic acid.

pK_a < 4.2

W stabilizes the carboxylate anion.

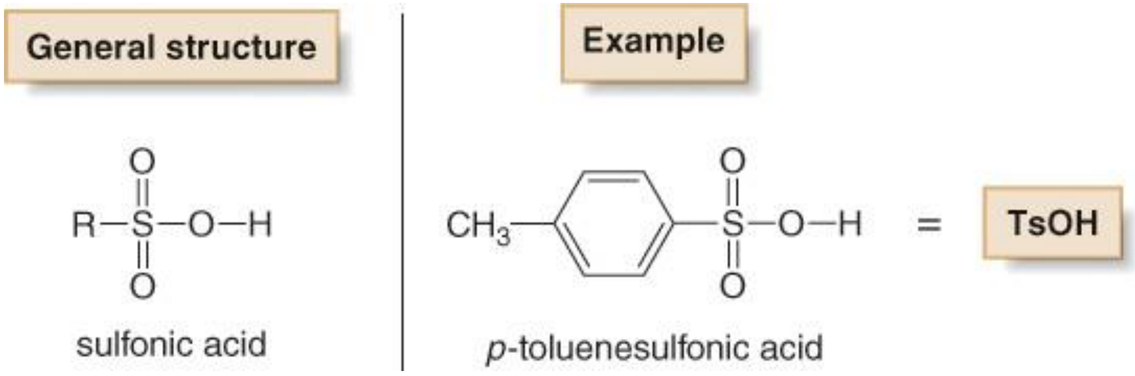
Substituted Benzoic Acids



	Substituent	Effect in electrophilic substitution	Effect on acidity of substituted benzoic acids
electron-donating groups	$-\ddot{N}H_2$ $[\ddot{N}HR, \ddot{N}R_2]$	activating groups	These groups make a benzoic acid **less acidic**.
	$-\ddot{\underset{\cdot\cdot}{O}}H$		
	$-\ddot{\underset{\cdot\cdot}{O}}R$		
	$-\ddot{N}HCOR$		
	$-R$		
electron-withdrawing groups	$-\ddot{\underset{\cdot\cdot}{X}}:$ [X = F, Cl, Br, I]	deactivating groups	These groups make a benzoic acid **more acidic**.
	$-CHO$		
	$-COR$		
	$-COOR$		
	$-COOH$		
	$-CN$		
	$-SO_3H$		
	$-NO_2$		
	$-\overset{+}{N}R_3$		

Sulfonic Acids

- Sulfonic acids have the general structure RSO_3H.
- The most widely used sulfonic acid is *p*-toluenesulfonic acid.



General structure

sulfonic acid

Example

p-toluenesulfonic acid

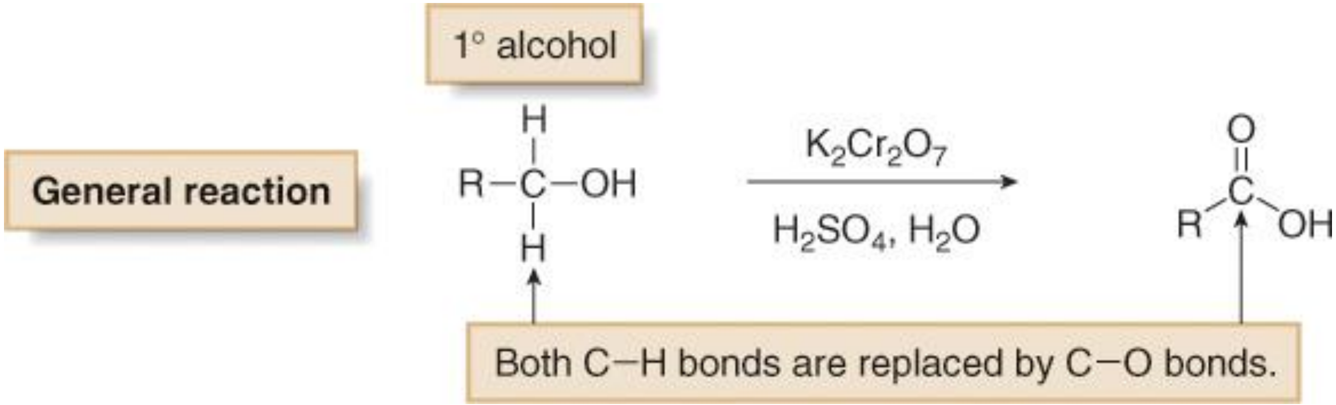
= **TsOH**

strong acid
pK_a ≈ −7

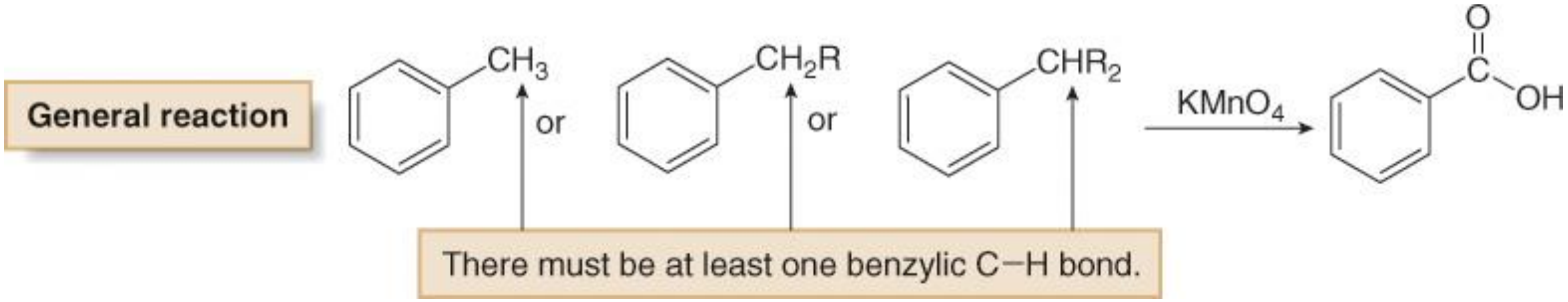
Three resonance structures—
All have a negative charge on oxygen.

Preparation of Carboxylic Acids

[1] Oxidation of 1° alcohols

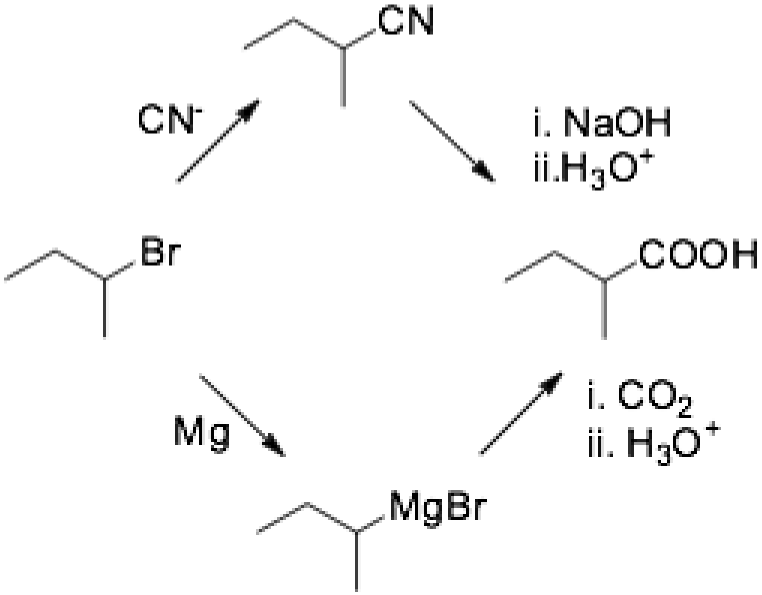


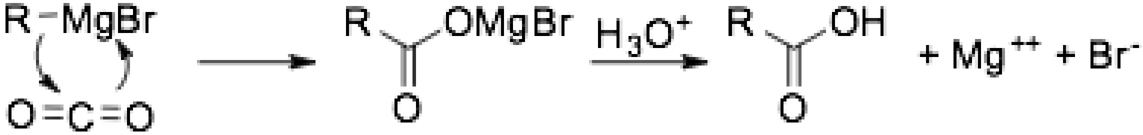
[2] Oxidation of alkyl benzenes



Preparation of Carboxylic Acids

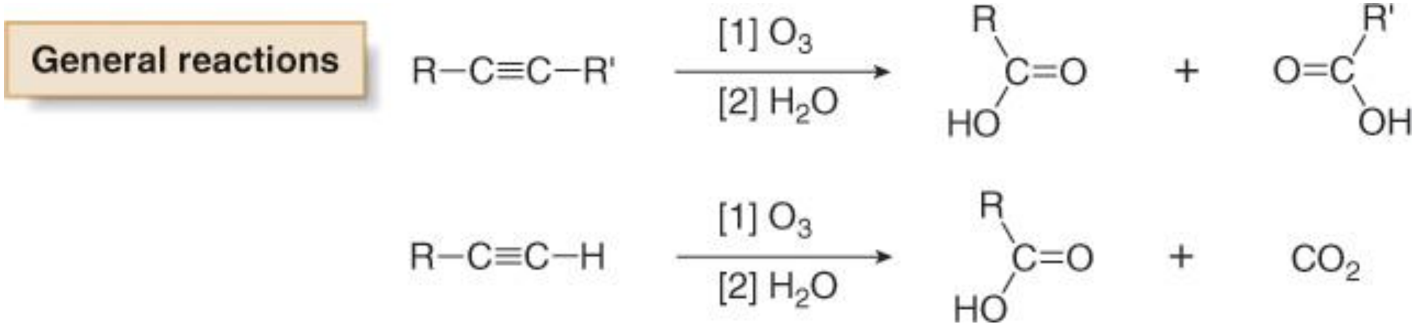
[3] From alkyl halides



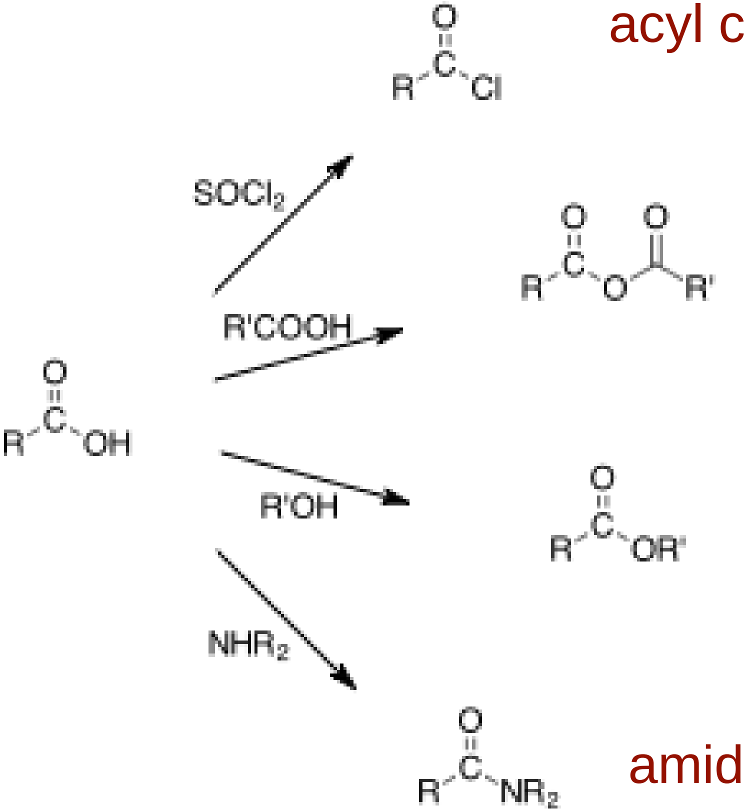


Preparation of Carboxylic Acids

[3] Oxidative cleavage of alkynes



Reactions of Carboxylic Acids



acyl chloride

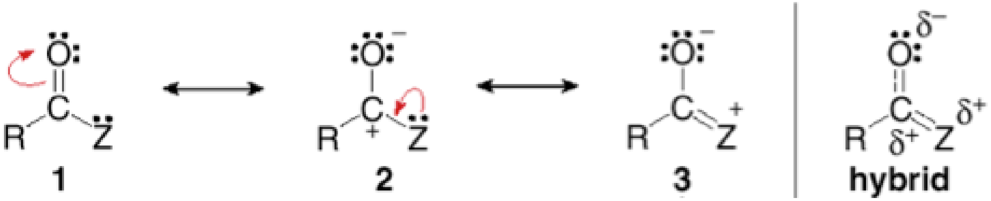
anhydride

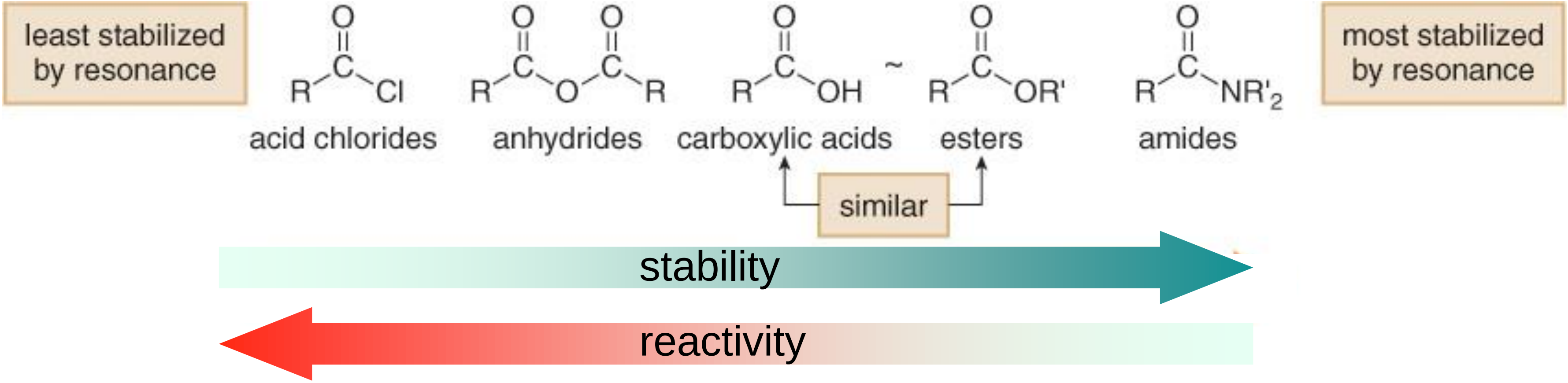
ester

amide

Derivatives: Structure and Bonding

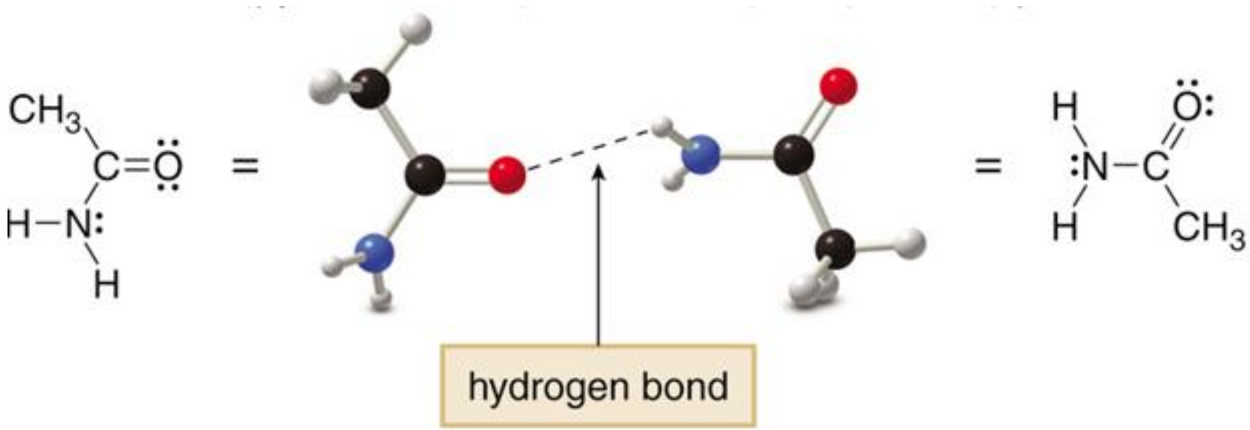
- Three resonance structures stabilize carboxylic acid derivatives (RCOZ) by delocalizing electron density.



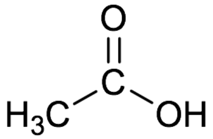


Derivatives: Physical Properties

- Because all carbonyl compounds have a polar carbonyl group, they exhibit dipole-dipole interactions.
- Because they contain one or two N—H bonds, 1° and 2° amides are capable of intermolecular hydrogen bonding.



Derivatives: Physical Properties



MW = 60 bp 118 °C

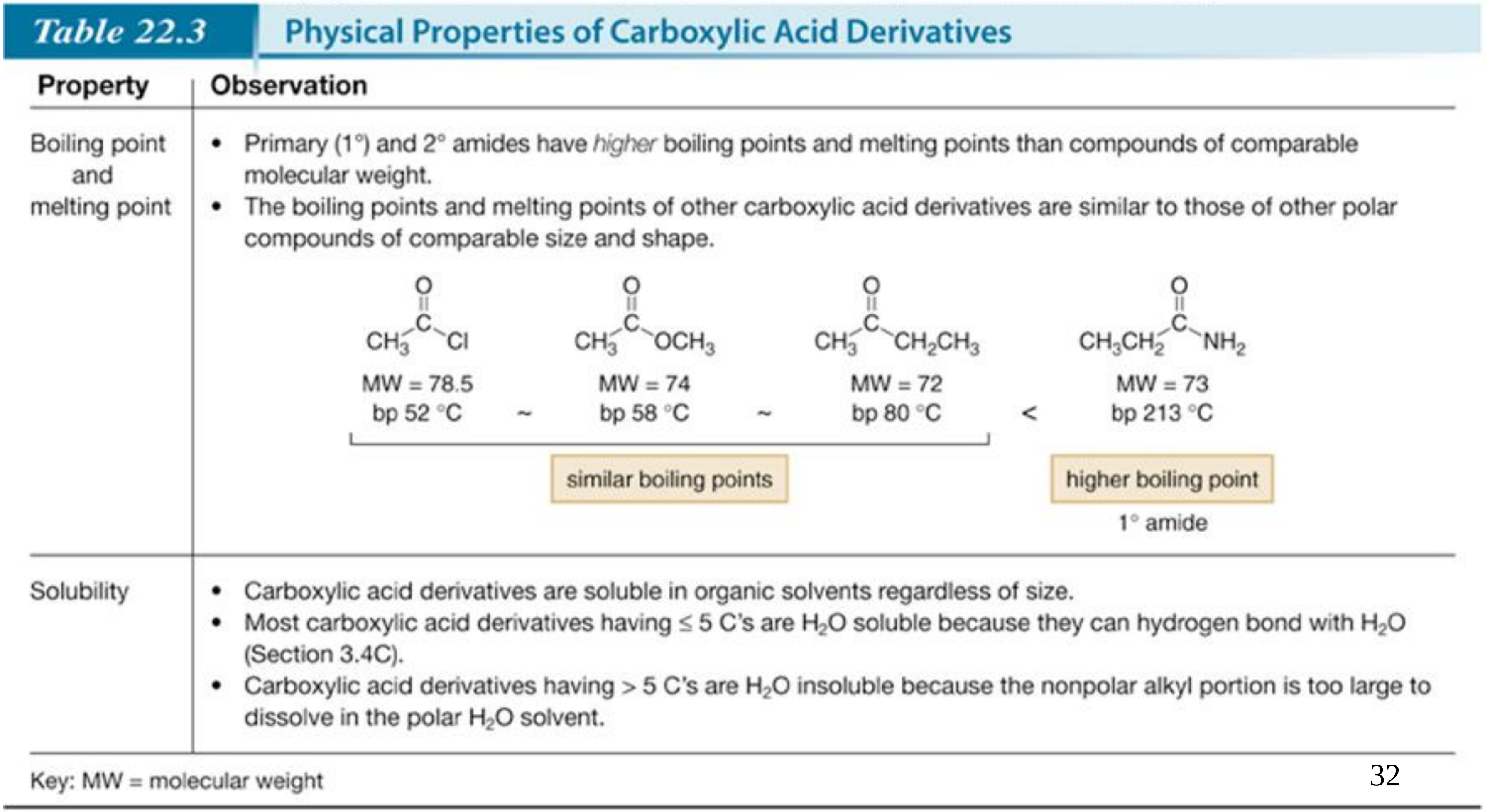
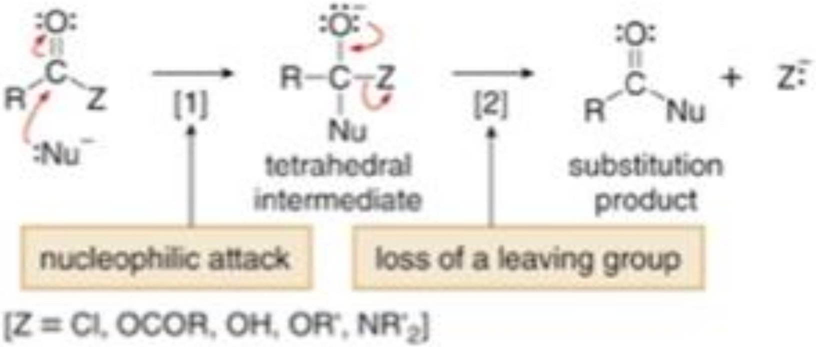


Table 22.3 Physical Properties of Carboxylic Acid Derivatives

Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amides have *higher* boiling points and melting points than compounds of comparable molecular weight. • The boiling points and melting points of other carboxylic acid derivatives are similar to those of other polar compounds of comparable size and shape. CH_3COCl MW = 78.5 bp 52 °C ~ CH_3COOCH_3 MW = 74 bp 58 °C ~ $CH_3COCH_2CH_3$ MW = 72 bp 80 °C < $CH_3CH_2CONH_2$ MW = 73 bp 213 °C similar boiling points higher boiling point 1° amide
Solubility	• Carboxylic acid derivatives are soluble in organic solvents regardless of size. • Most carboxylic acid derivatives having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • Carboxylic acid derivatives having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

Key: MW = molecular weight

Reaction of Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution



Introduction to Nucleophilic Acyl Substitution

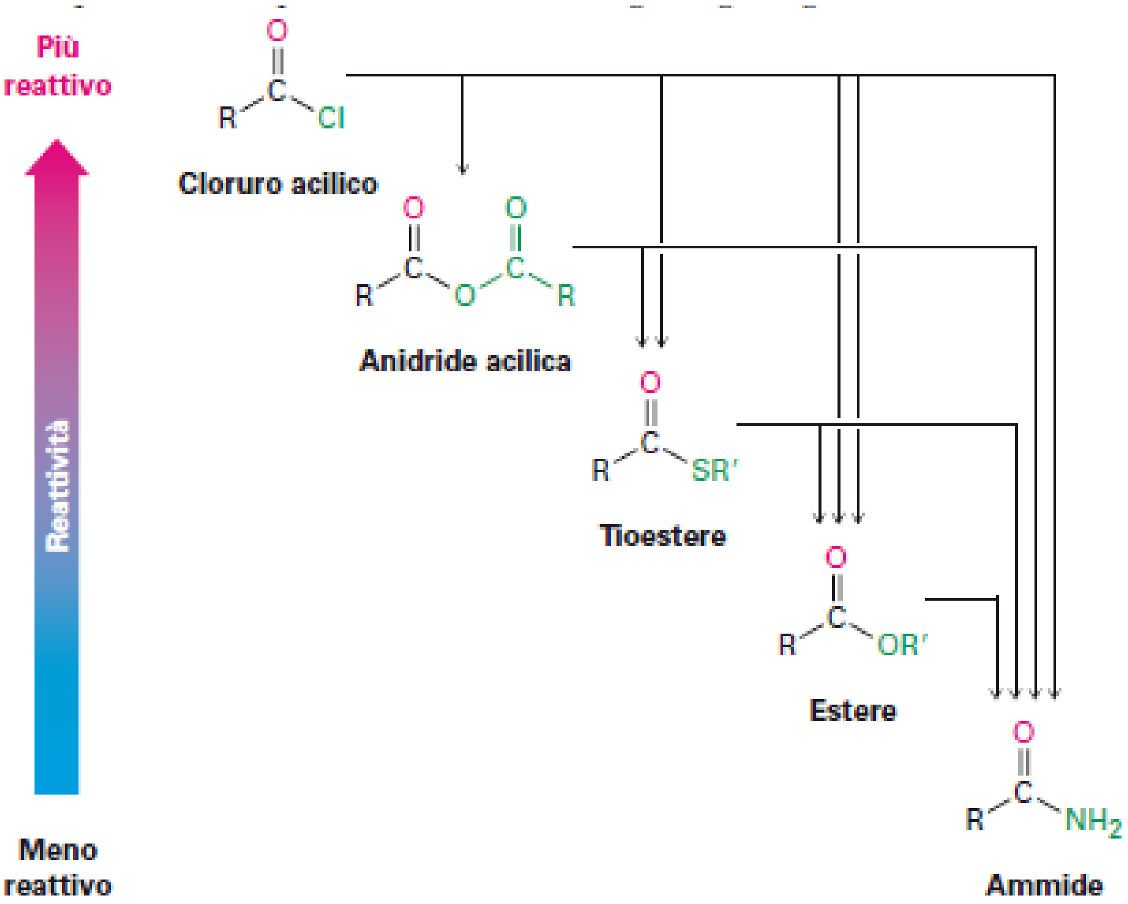
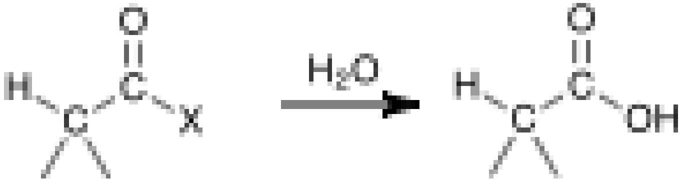


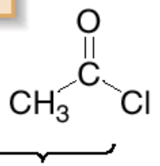
Figura 21.2 Interconversione di derivati degli acidi carbossilici. Un derivato acilico più reattivo può essere trasformato in uno meno reattivo, ma non vale il contrario.

All derivatives are hydrolysed to carboxylic acids



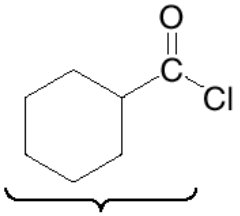
Acid Chlorides: Nomenclature

Naming acid chlorides



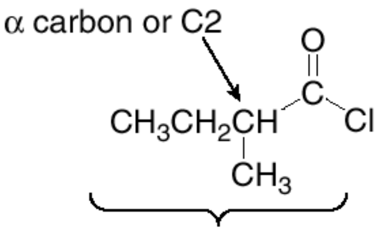
derived from
acet*ic acid*

acetyl chloride



derived from
cyclohexane*carboxylic acid*

cyclohexanecarbonyl chloride

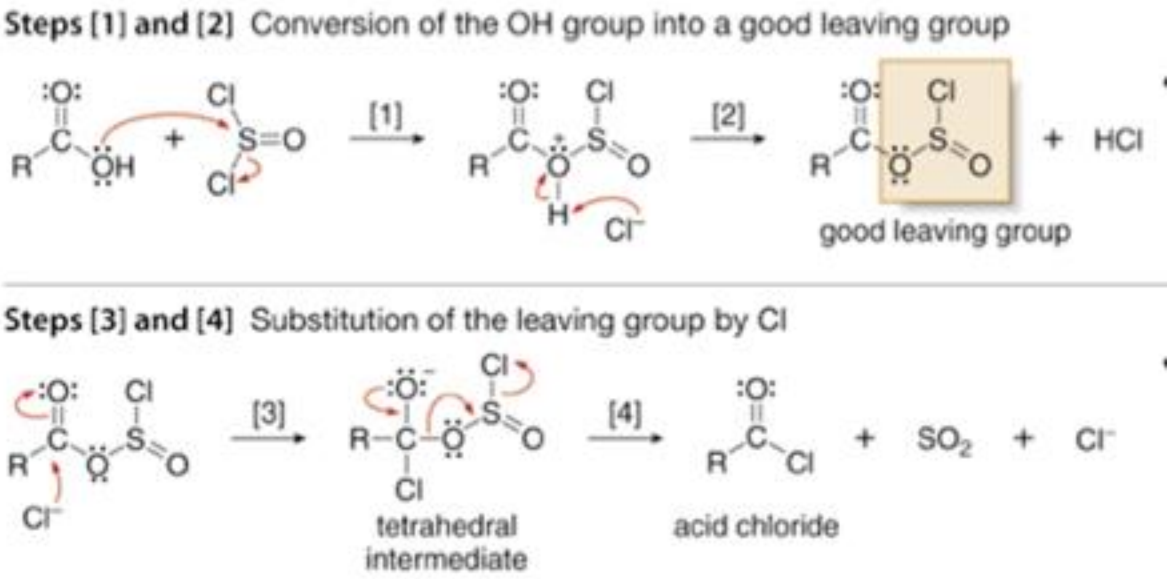


derived from
2-methylbutano*ic acid*
or
α-methylbutyr*ic acid*

2-methylbutanoyl chloride
or
α-methylbutyryl chloride

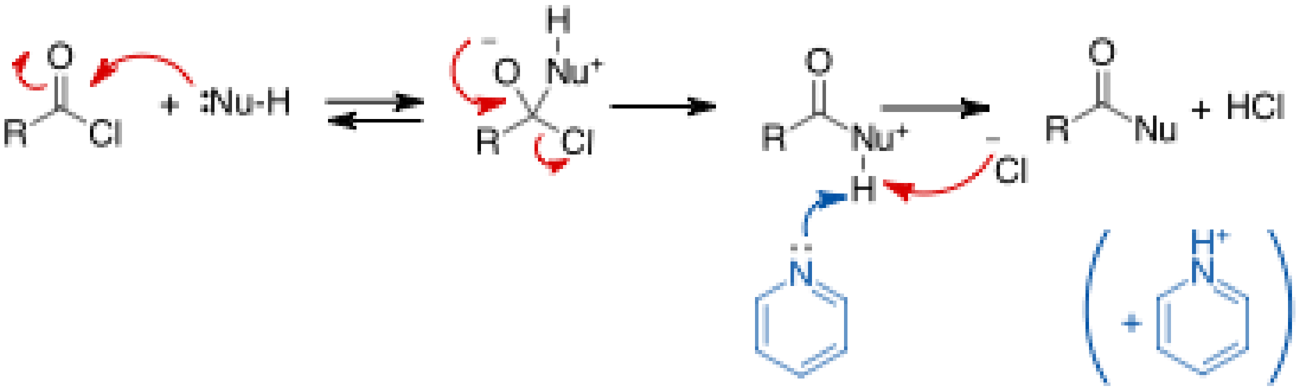
Acid Chlorides: Synthesis

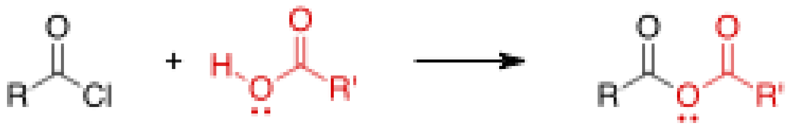
By the reaction of a carboxylic acid with thionyl chloride ($SOCl_2$).



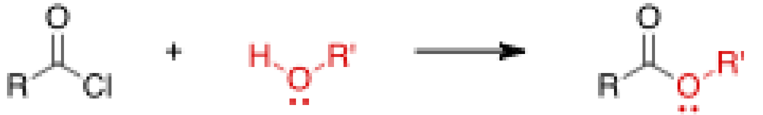
Acid Chlorides: Reactions

- Acyl chlorides are the most reactive among carboxylic acid derivatives
- A weak, non nucleophilic, base like pyridine is often added to the reaction mixture to remove the byproduct HCl.

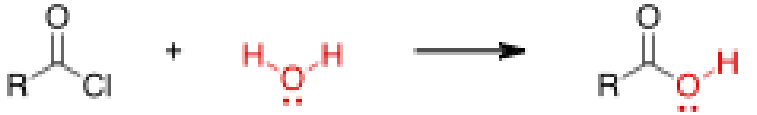




anhydride



ester



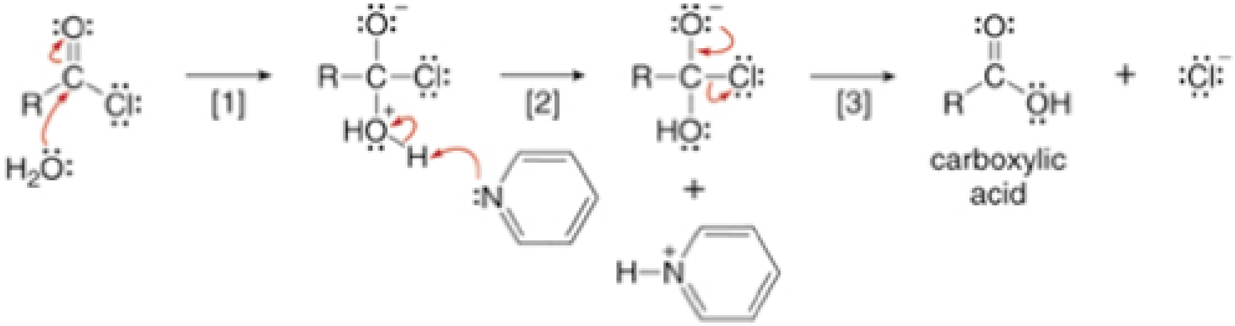
acid

(acid chlorides are readily decomposed by water)

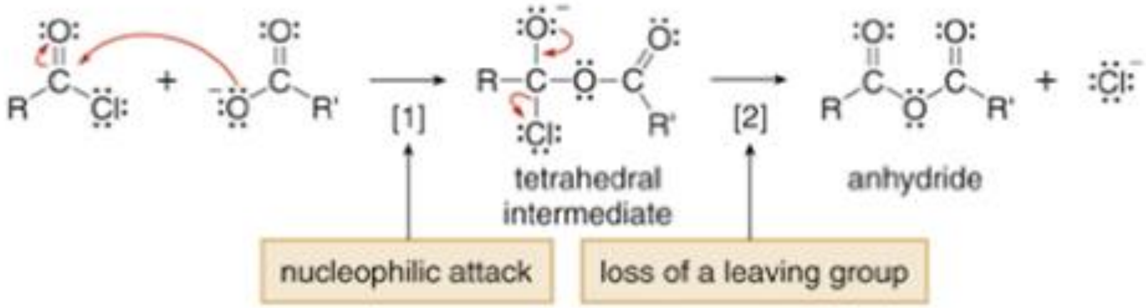
amide

Reactions of Acid Chlorides

Hydrolysis:

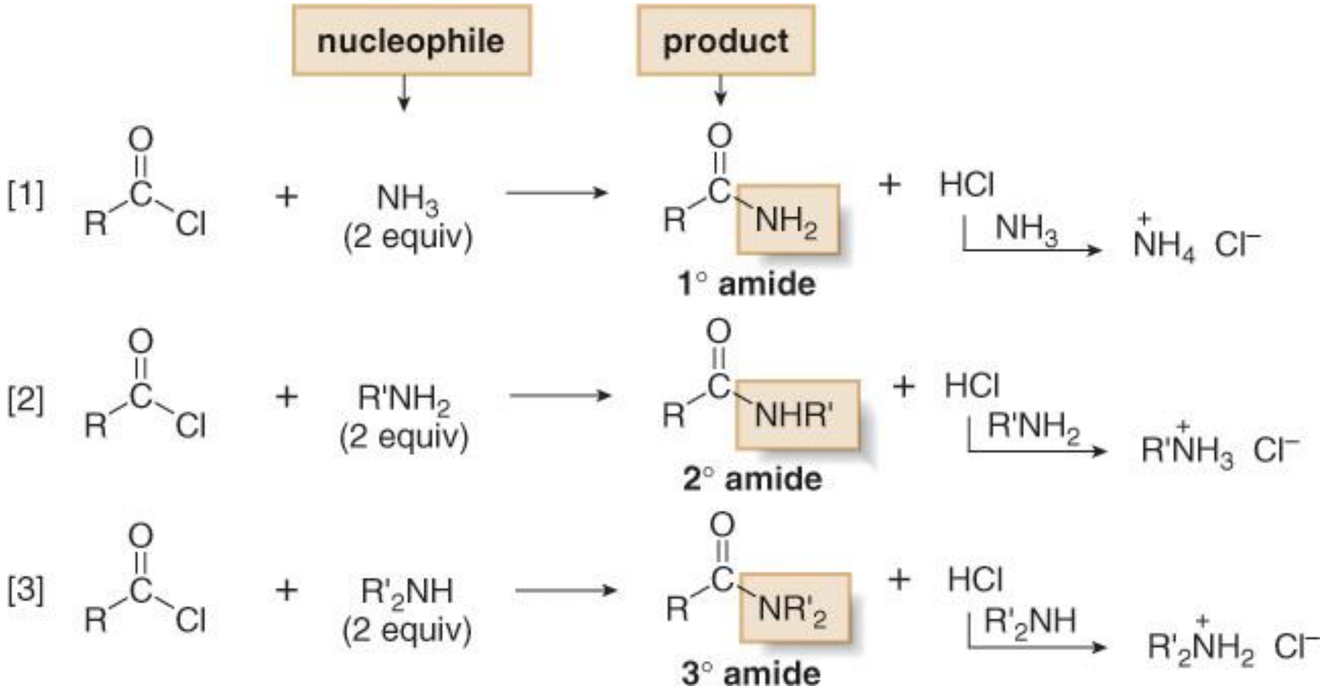


Formation of anhydrides:



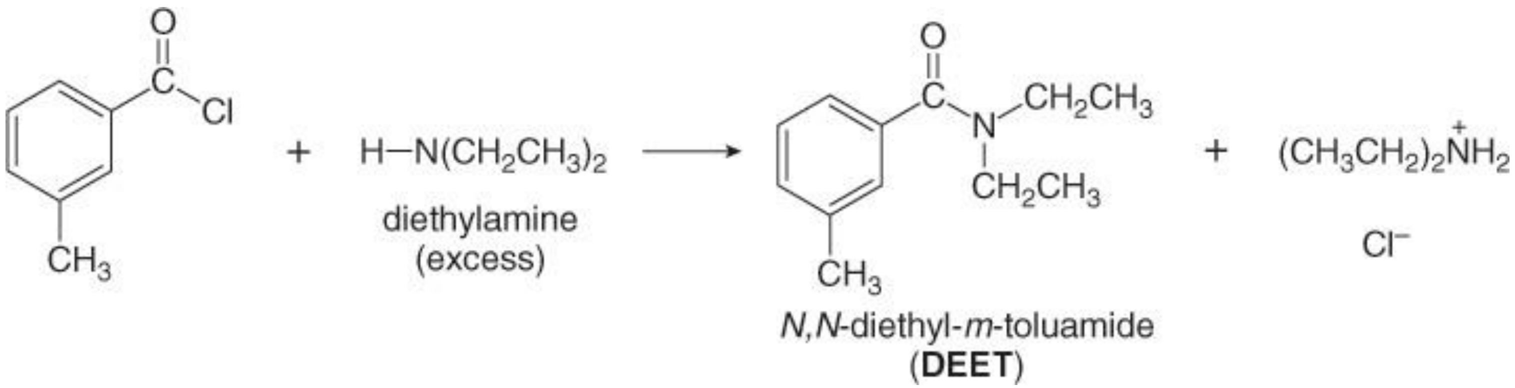
Reactions of Acid Chlorides

- Acid chlorides also react with ammonia and 1° and 2° amines to form 1°, 2° and 3° amides respectively.
- Two equivalents of NH_3 or amine are used.
- One equivalent acts as the nucleophile to replace Cl, while the other reacts as a base with the HCl by-product to form an ammonium salt.



Reactions of Acid Chlorides

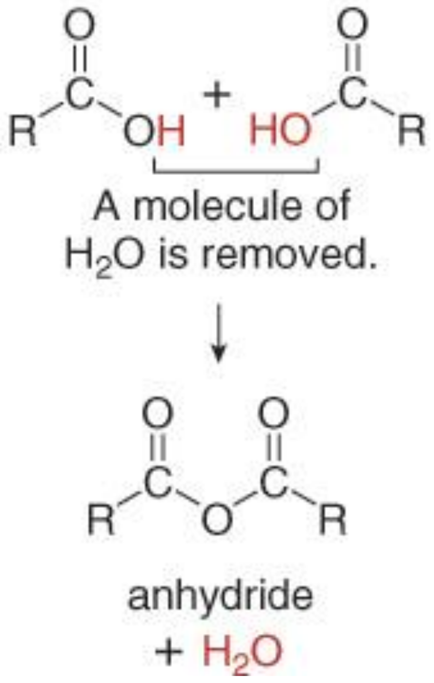
- DEET is the active ingredient in the most widely used insect repellents, and is effective against mosquitoes, fleas and ticks.



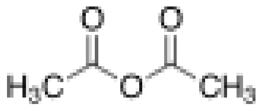
N,*N*-diethyl-*m*-toluamide
(**DEET**)

Anhydrides

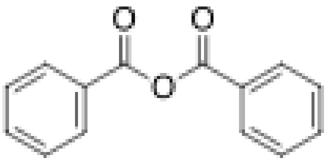
The word anhydride means *without water.* Removing one molecule of water from two molecules of carboxylic acid forms an anhydride.



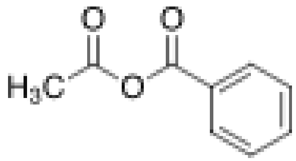
Anydrides: Nomenclature



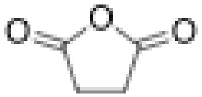
acetic
anhydride



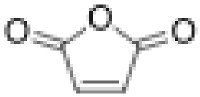
benzoic
anhydride



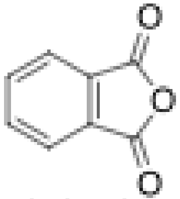
acetic benzoic
anhydride



succinic
anhydride

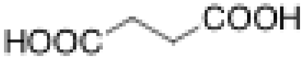


maleic
anhydride



phthalic
anhydride

↑

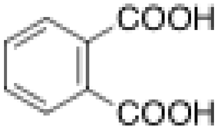


succinic
acid

↑

maleic
acid

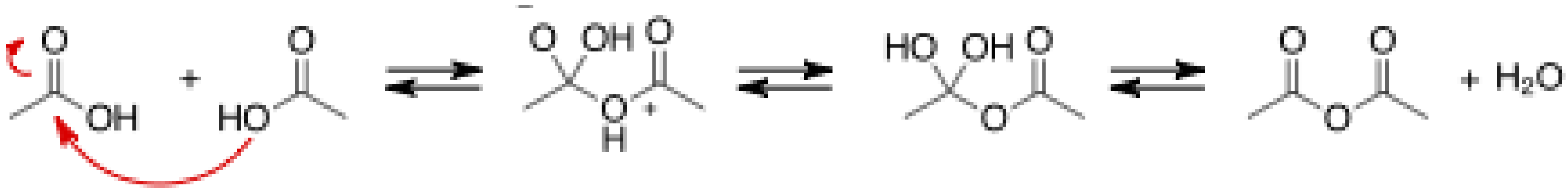
↑



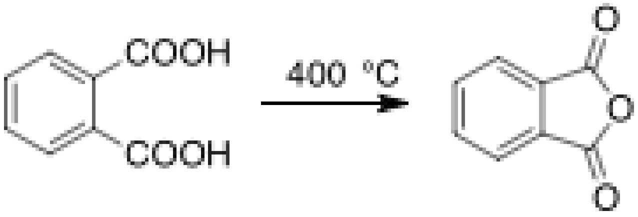
phthalic
acid

Anhydrides: Synthesis

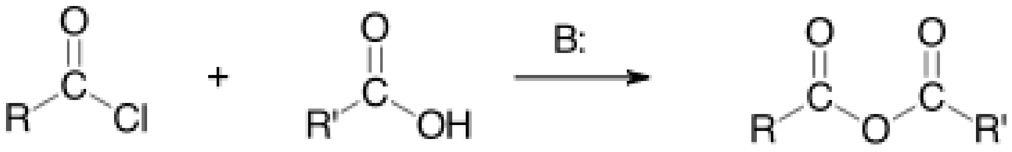
1. By dehydration of carboxylic acids at high temperatures (700-800 °C) and/or in the presence of condensing agents



Formation of cyclic anhydrides is easier

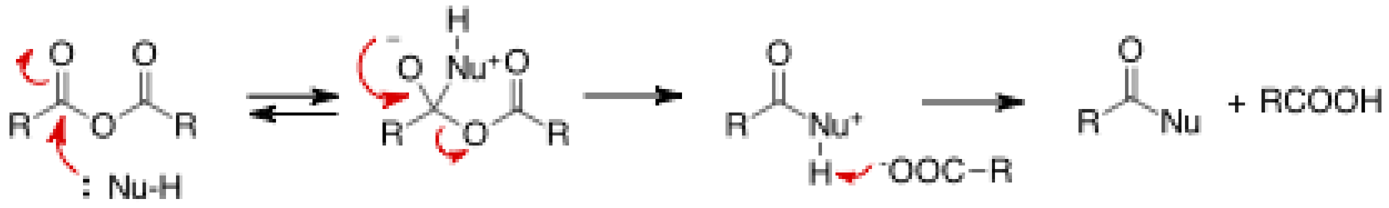


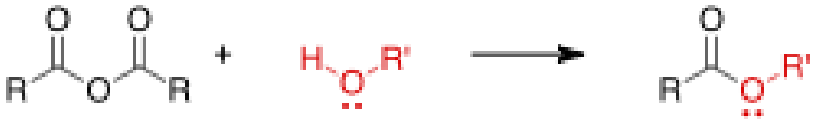
2. From an acid and an acyl chloride



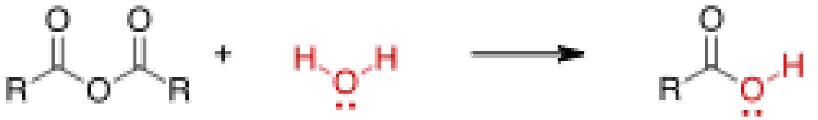
Anhydrides: Reactions

- Anhydrides are strong acylating agents a
- A weak acid is formed as by-product.





ester



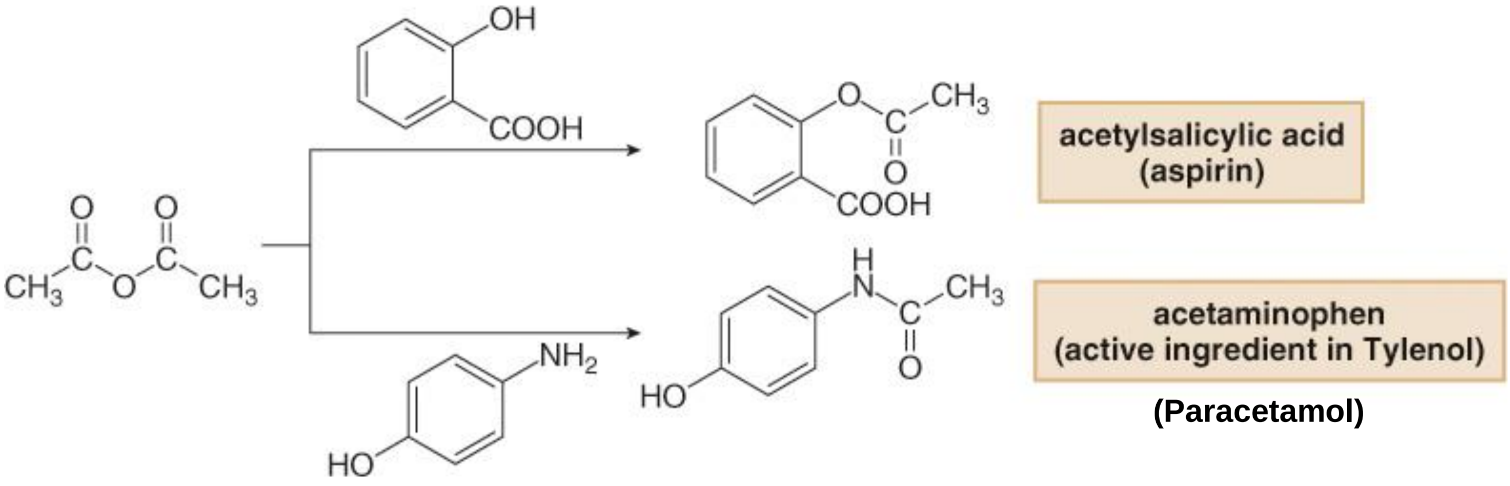
acid

(anhydrides are readily decomposed by water)

amide

Reactions of Anhydrides

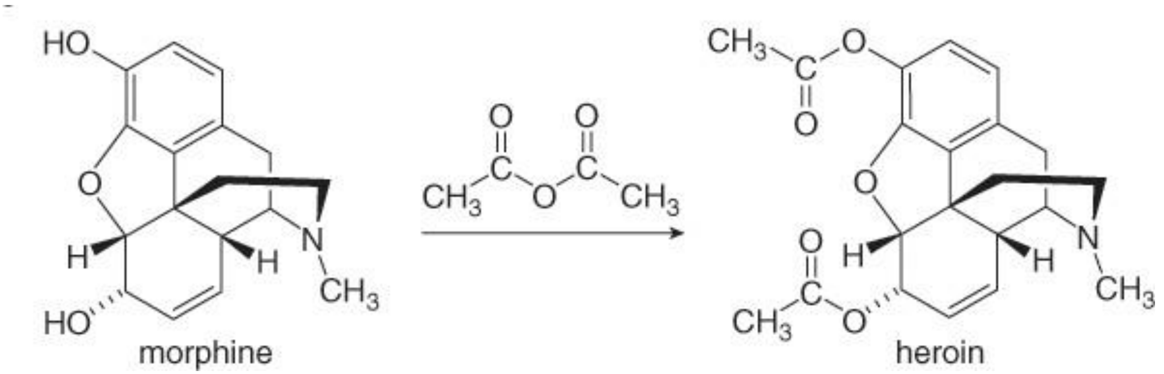
Anhydrides are very common acetylating agents for the synthesis of esters and amides:



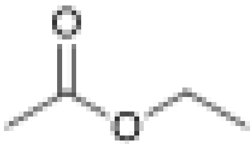
acetylsalicylic acid (aspirin)

acetaminophen (active ingredient in Tylenol)

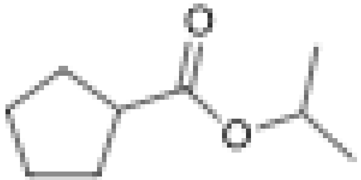
(Paracetamol)



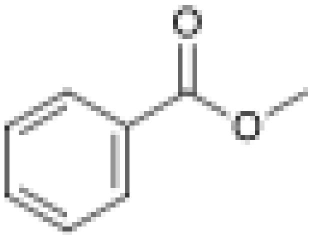
Esters: Nomenclature



Ethyl acetate

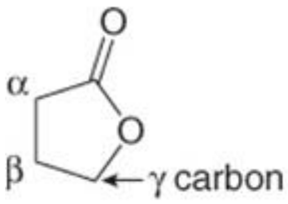


Isopropyl cyclopentanecarboxylate

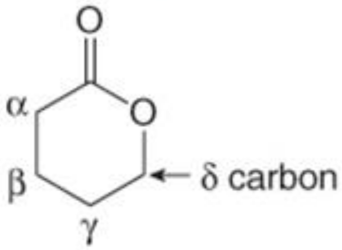


Methyl benzoate

Lactones–Cyclic esters



γ-lactone



δ-lactone

Butyrolactone Valerolactone

Interesting Esters

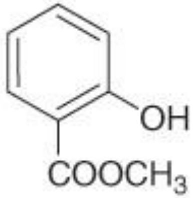
Many low molecular weight esters have pleasant and very characteristic odors.

$CH_3COOCH_2CH_2CH(CH_3)_2$

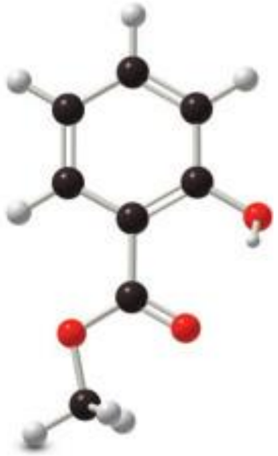
isoamyl acetate
odor of banana

$CH_3CH_2CH_2COOCH_2CH_3$

ethyl butyrate
odor of pineapple

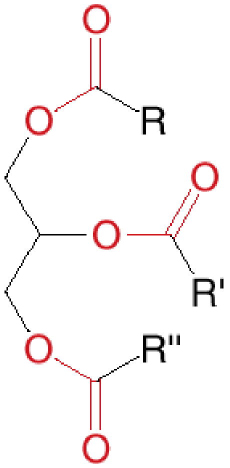


methyl salicylate
oil of wintergreen



Lipids

- Each triacylglycerol is a triester, containing three long hydrocarbon side chains.
- Unsaturated triacylglycerols have one or more double bonds in their long hydrocarbon chains, whereas saturated triacylglycerols have none.



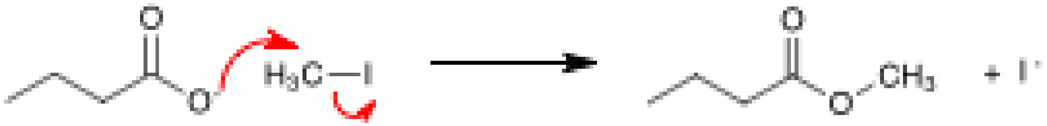
triacylglycerol
the most common type of lipid

R groups have 11–19 C's.

[Three ester groups are labeled in red.]

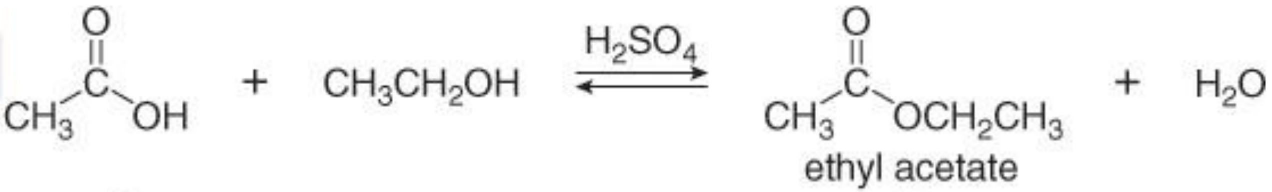
Esters from Carboxylic Acids

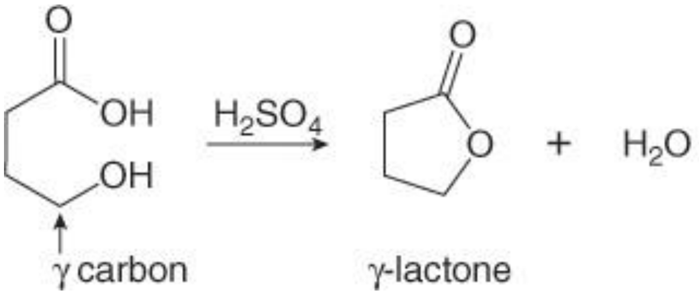
- S_N2 (mainly for methyl esters).

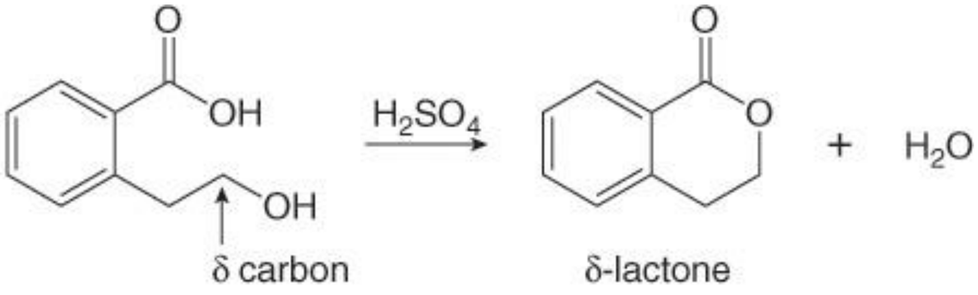


- Fischer esterification.

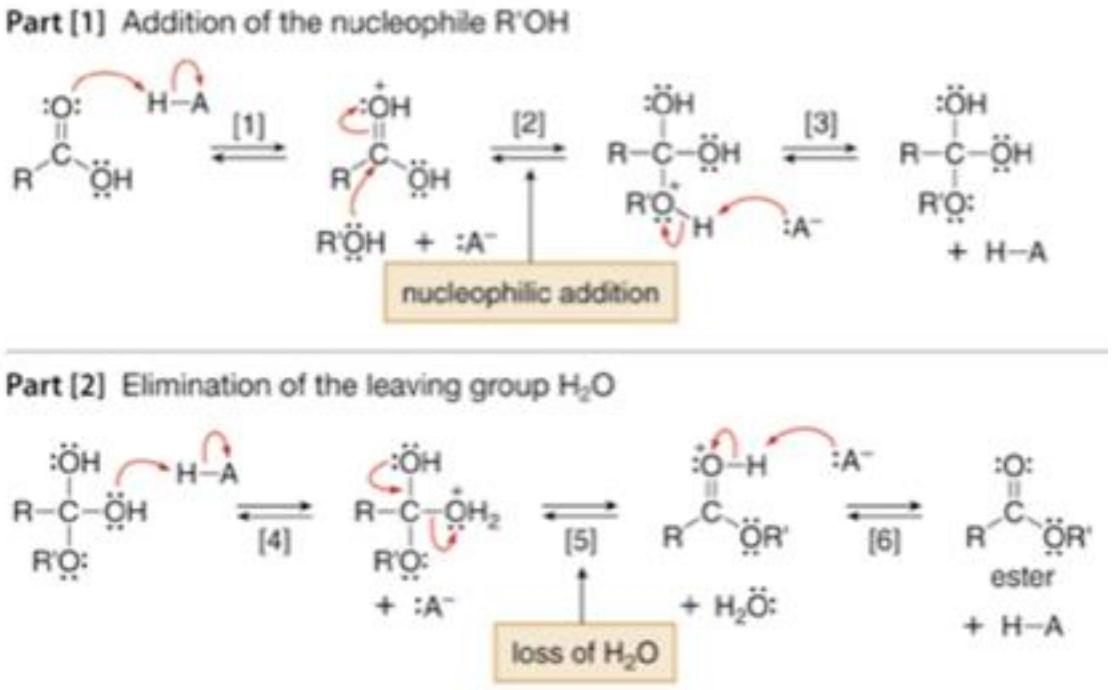
Examples





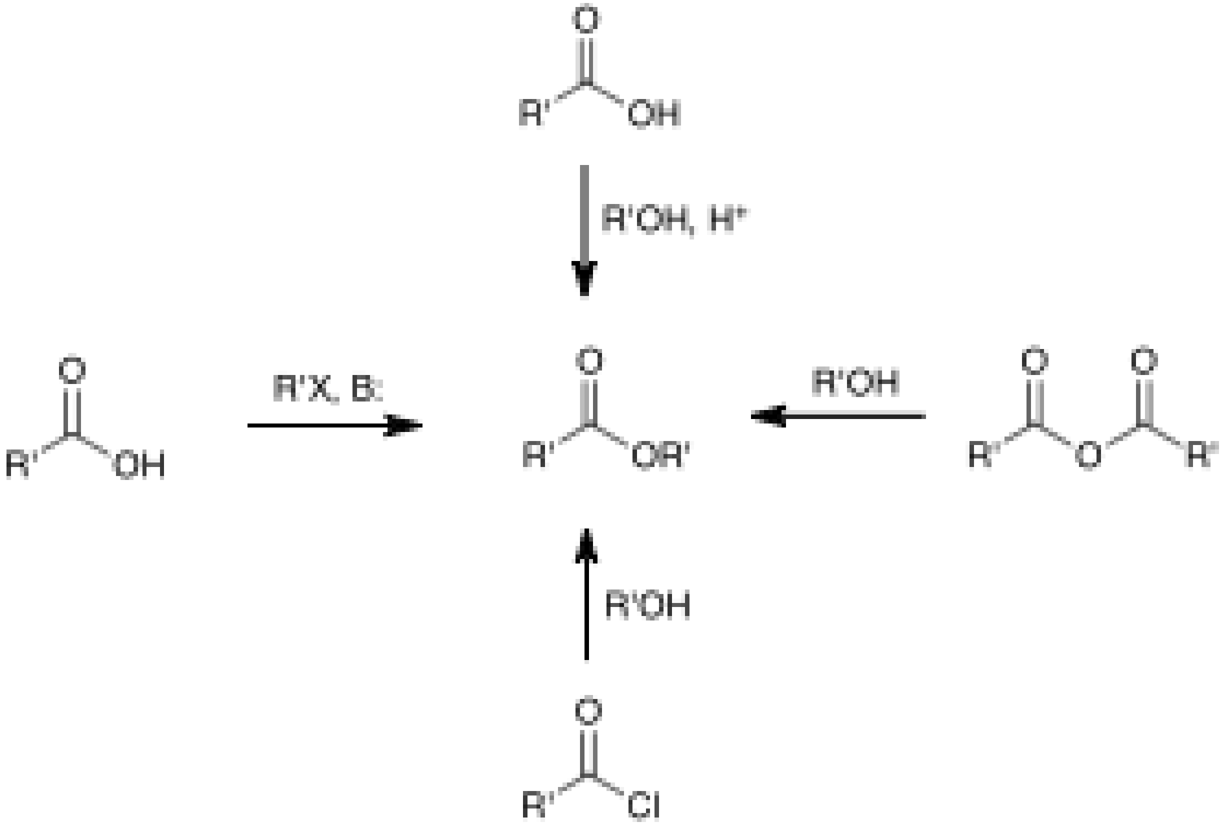


Fischer Esterification



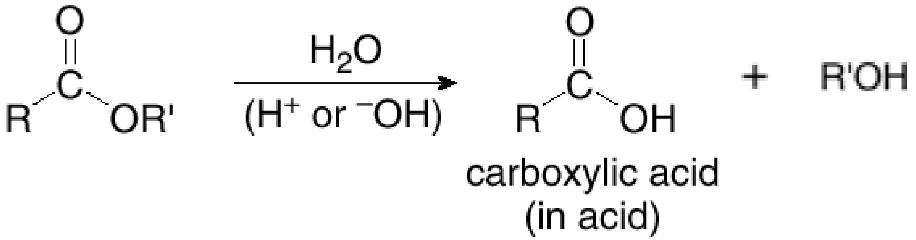
- The reaction is an equilibrium, so it is driven to the right by using excess alcohol or by removing water as it is formed.

Esters: Synthesis

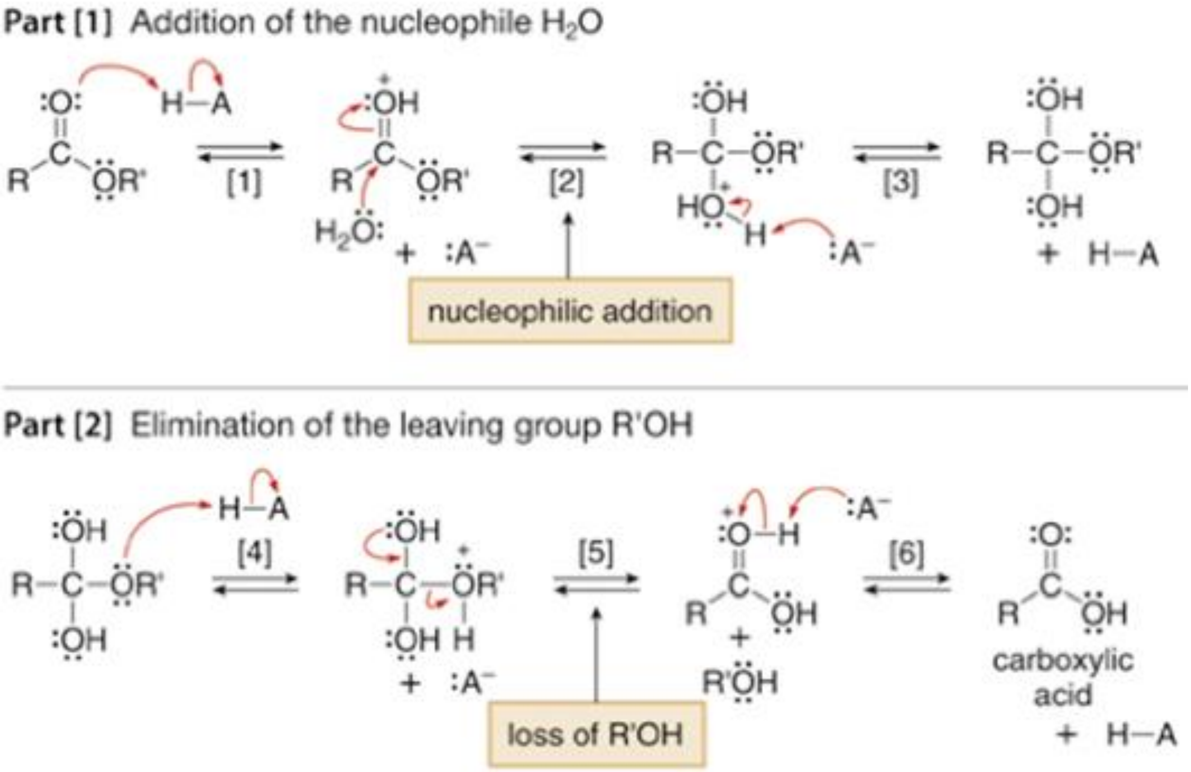


Esters: Reactions

Ester hydrolysis

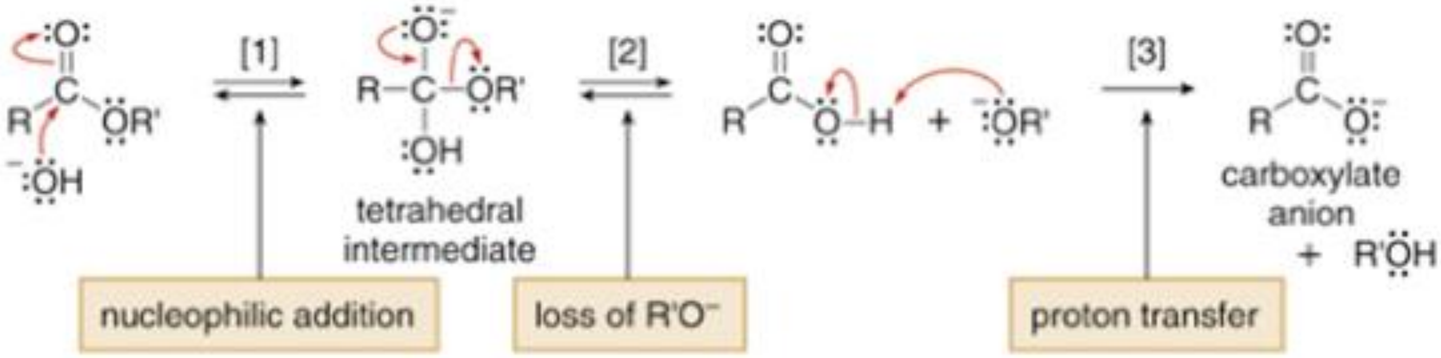


Acid hydrolysis



Esters: Reactions

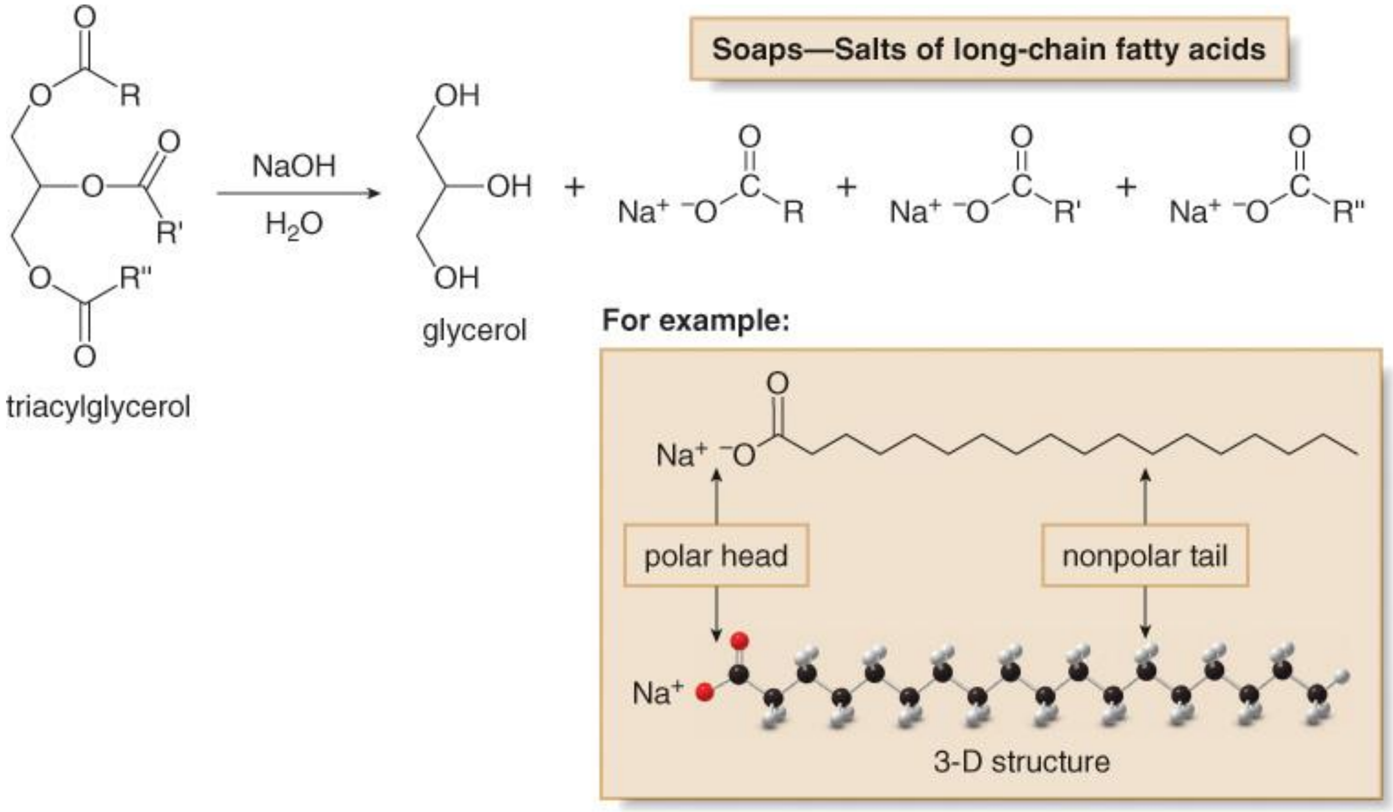
- Basic hydrolysis of an ester is also called saponification.



- Hydrolysis is base promoted, <u>not</u> base catalyzed, because the base (OH⁻) is the nucleophile that adds to the ester and forms part of the product. It participates in the reaction and is not regenerated later.

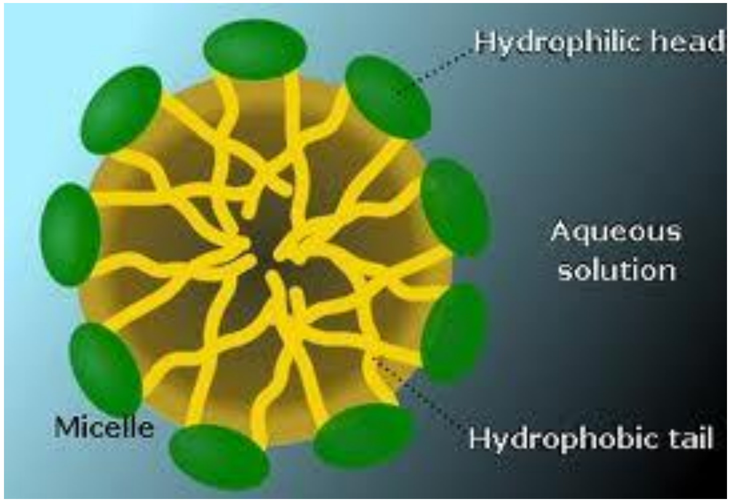
Lipid Hydrolysis

- Soap is prepared by the basic hydrolysis or saponification of a triacylglycerol. Heating an animal fat or vegetable oil with aqueous base hydrolyzes the three esters to form glycerol and sodium salts of three fatty acids. These carboxylate salts are soaps.



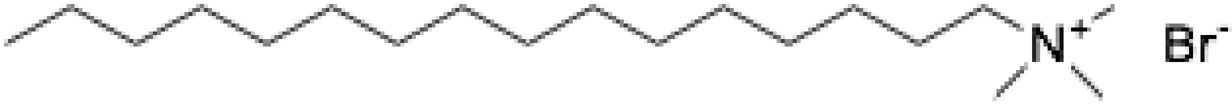
Soap

- Soap molecules self-aggregate in water to form micelles



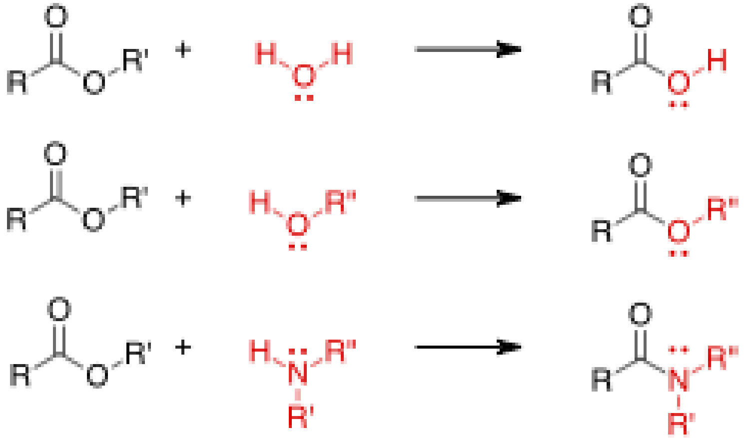
- Synthetic detergents

sodium laurylsulfate
SDS



cetyltrimethylammonium bromide
CTAB

Esters: Other Reactions

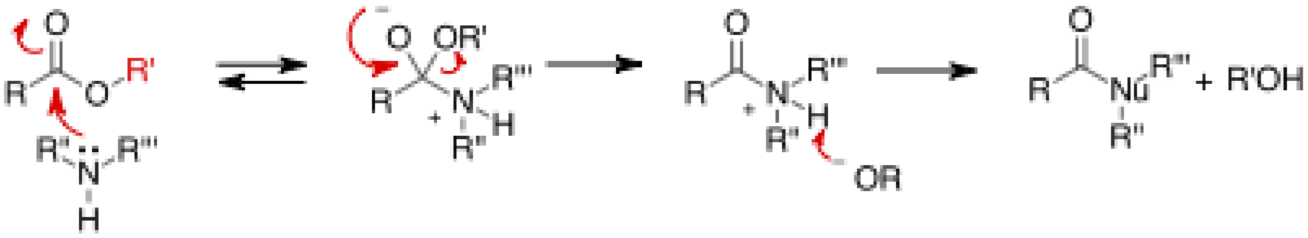


acid — H^+, H_2O or OH^-

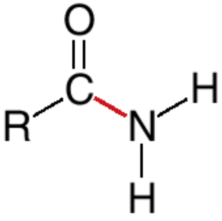
transeserification — H^+, ROH or RO^-

amide

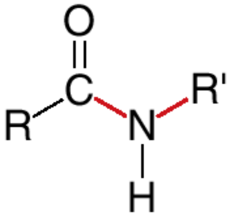
Mechanism of amide formation



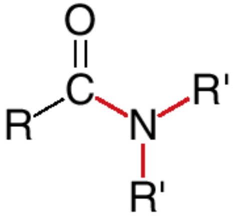
Amides: Structure



1° amide
1 C—N bond

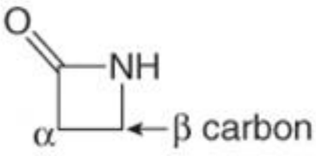


2° amide
2 C—N bonds

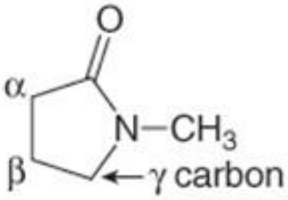


3° amide
3 C—N bonds

Lactams–Cyclic amides



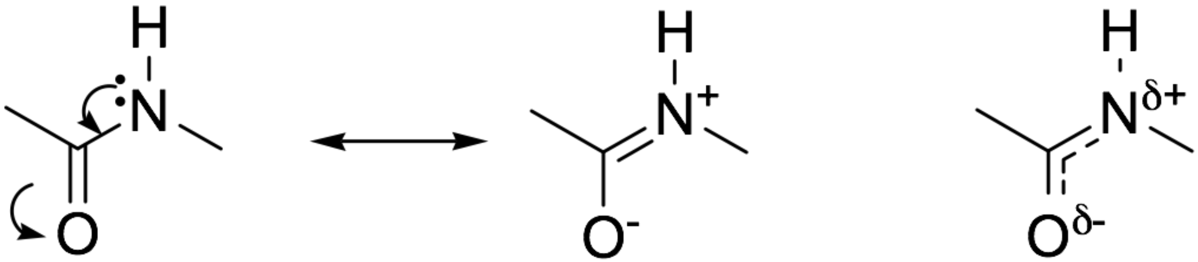
β-lactam



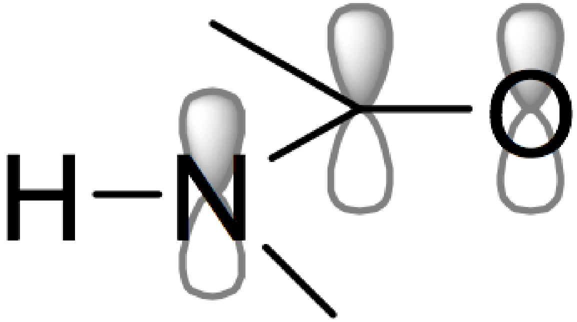
γ-lactam

Amides: Structure

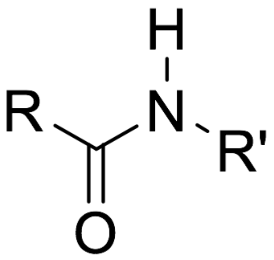
Amide resonance

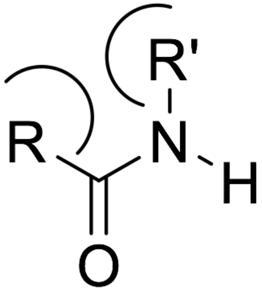


C, N, O: sp^2
planar
Restricted rotation

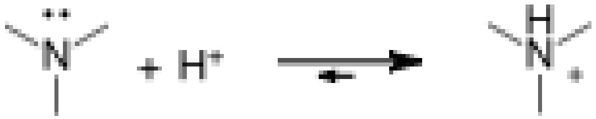


Trans amides are more stable than cis amides





Amides: Basicity

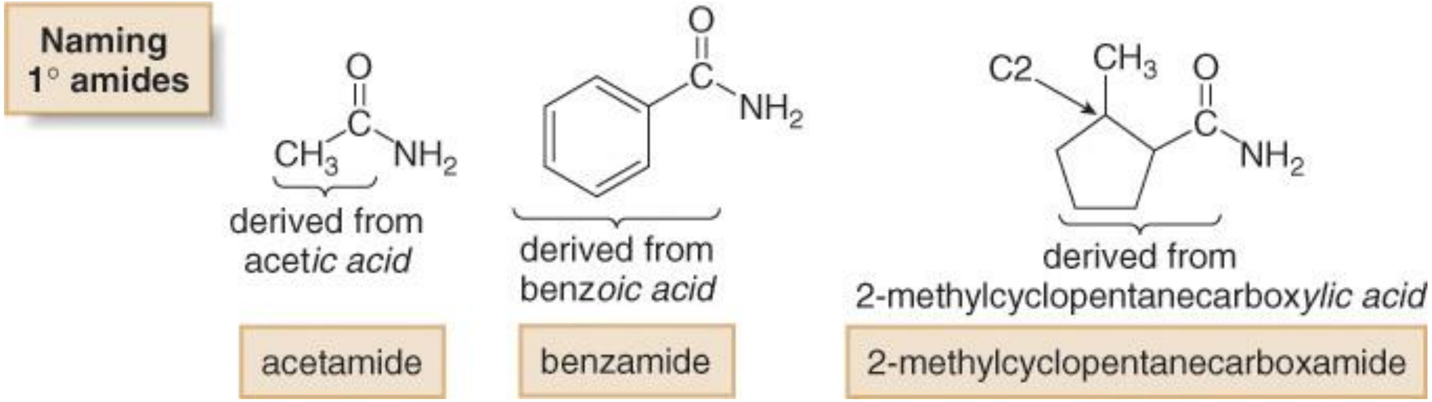


pKa = 9

pKa = -1

Amides: Nomenclature

- All 1° amides are named by replacing the *-ic acid*, *-oic acid*, or *-ylic acid* ending with the suffix amide.



Naming 1° amides

derived from acet*ic acid*

derived from benz*oic acid*

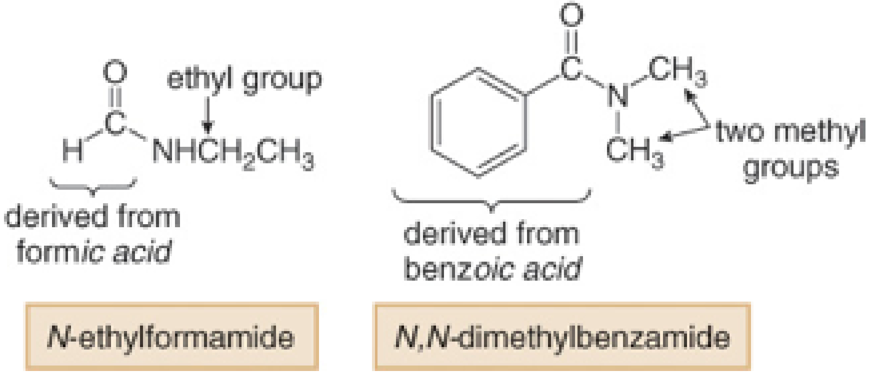
derived from 2-methylcyclopentanecarbox*ylic acid*

acetamide

benzamide

2-methylcyclopentanecarboxamide

- 2° and 3° amides are named as N-substituted (2°) or N,N-disubstituted (3°) derivatives of 1° amides



derived from form*ic acid*

derived from benz*oic acid*

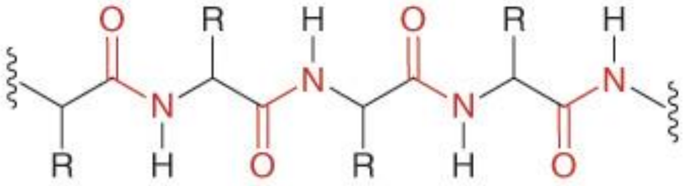
N-ethylformamide

N,N-dimethylbenzamide

Interesting Amides

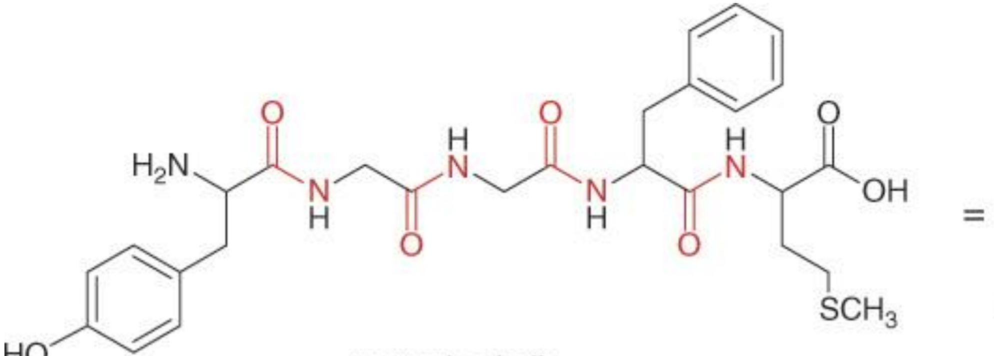
An important group of naturally occurring amides consists of proteins, polymers of amino acids joined together by amide linkages.

Portion of a protein molecule



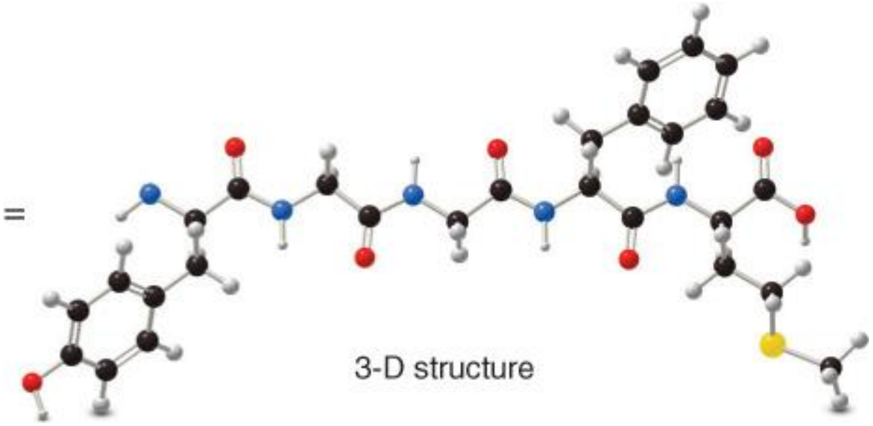
[Amide bonds are shown in red.]

The R groups come from amino acids joined together to form the protein.



met-enkephalin

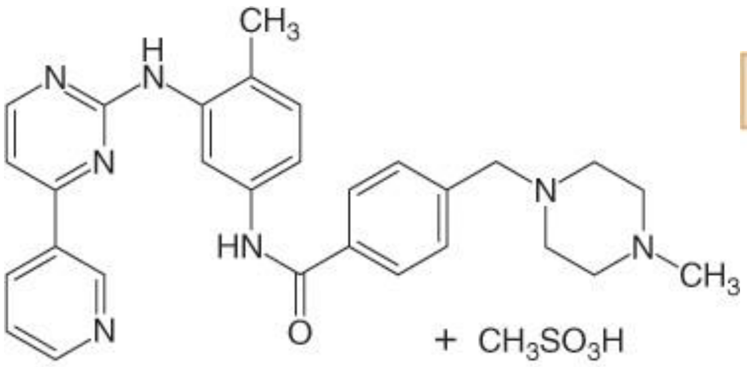
[The four amide bonds are shown in red.]



3-D structure

Interesting Amides

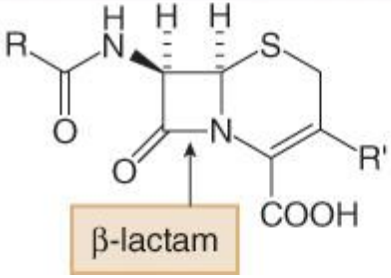
Several useful drugs are amides.

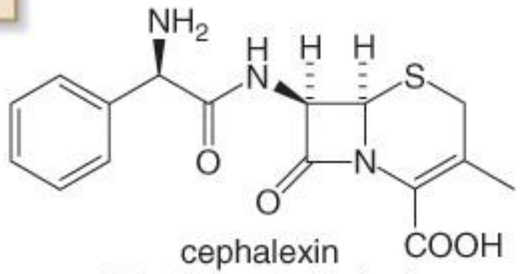


+ CH_3SO_3H

Trade name: Gleevec
Generic name: imatinib mesylate

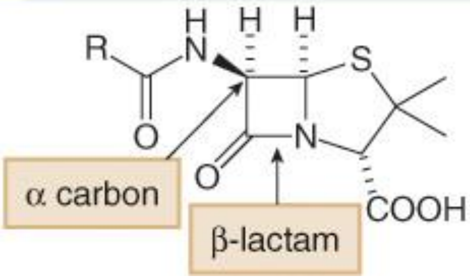
General structure—Cephalosporin

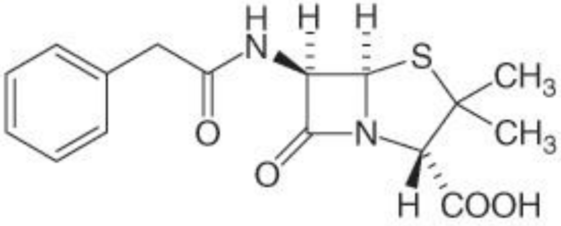




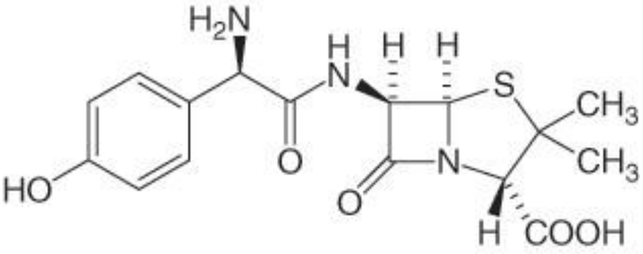
cephalexin
(Trade name: Keflex)

General structure—Penicillin





penicillin G

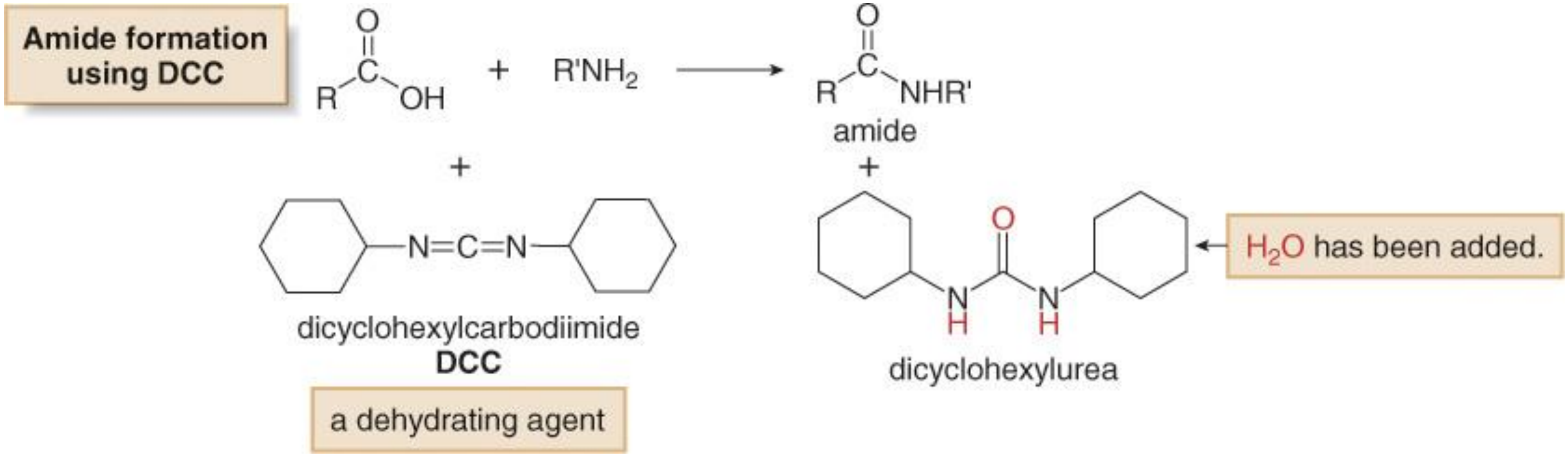


amoxicillin

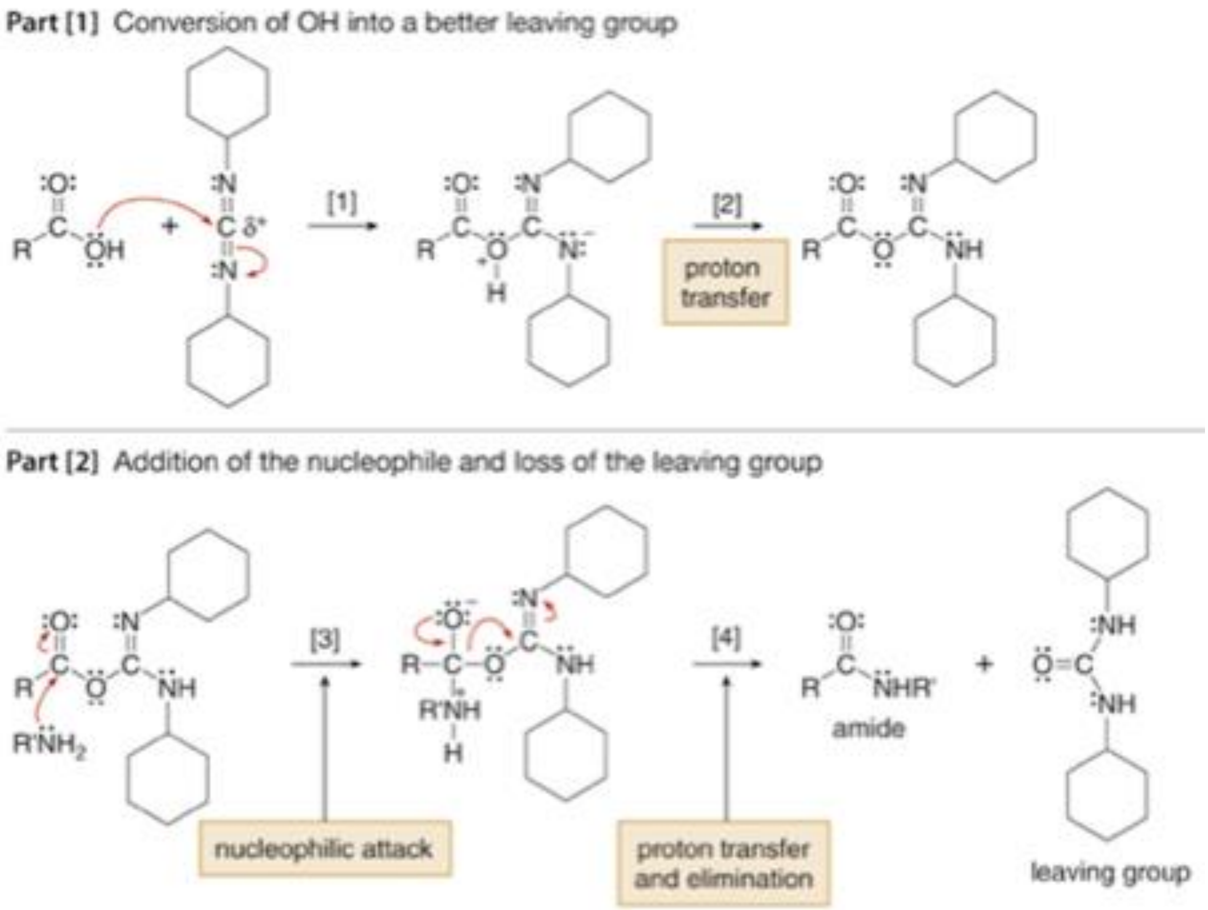
Amides from Carboxylic Acids

- Carboxylic acids cannot be converted into amides by reaction with NH_3 or an amine.

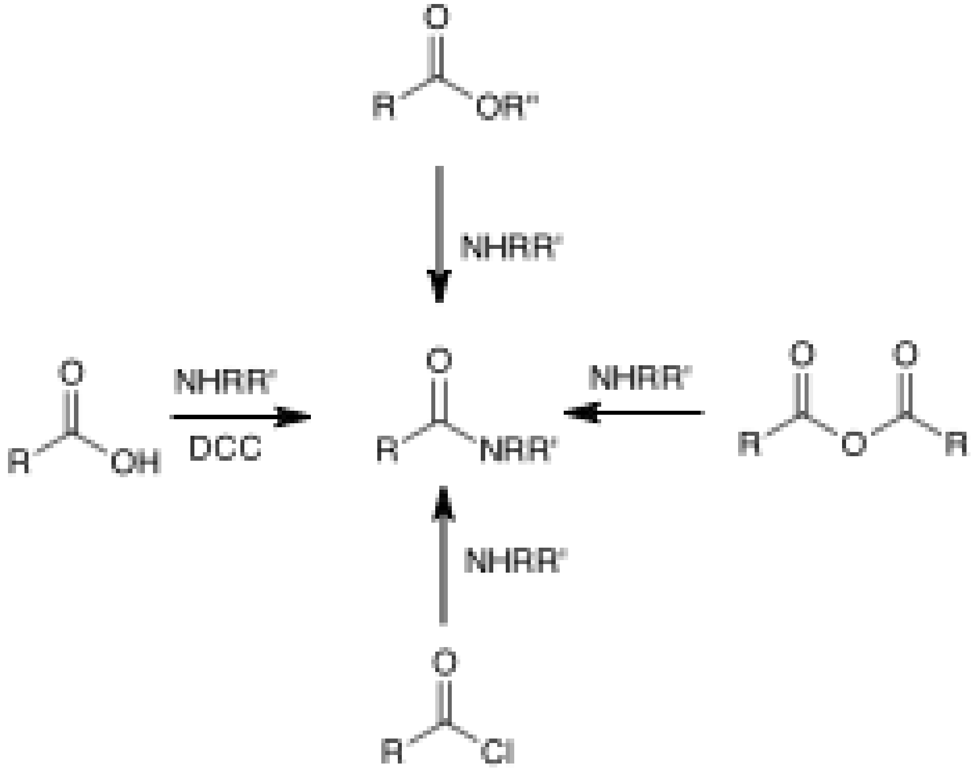
- Carboxylic acids are converted into amides by reaction with NH_3 or an amine in the presence of a condensing agent (DCC).



Reactions of Carboxylic Acids: Amides



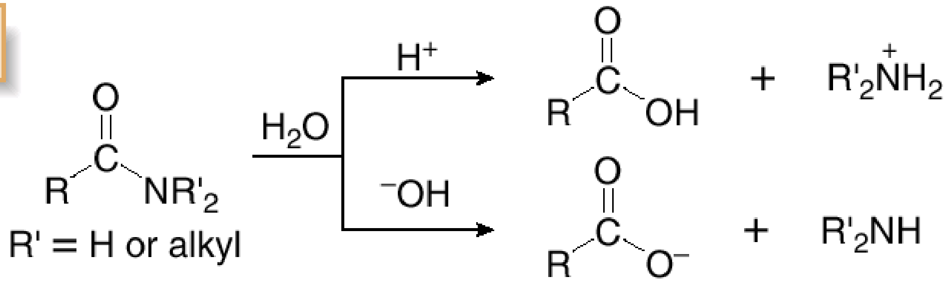
Synthesis of Amides



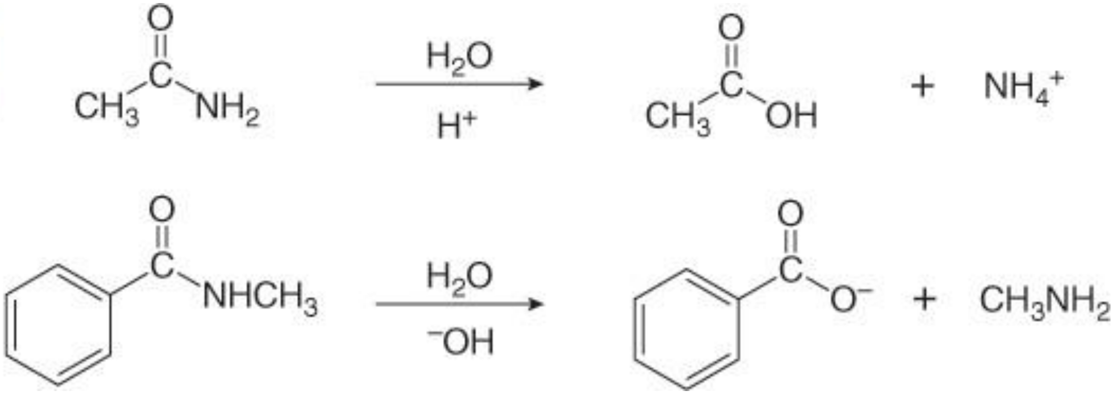
Amides: Reactions

- Amides are the least reactive of the carboxylic acid derivatives.

Amide hydrolysis

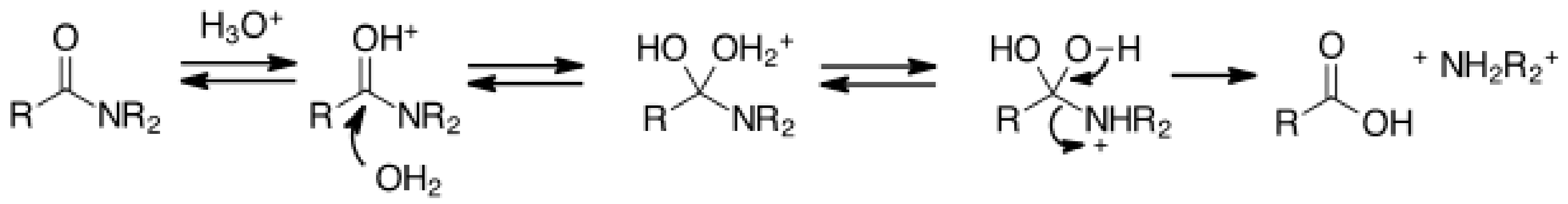


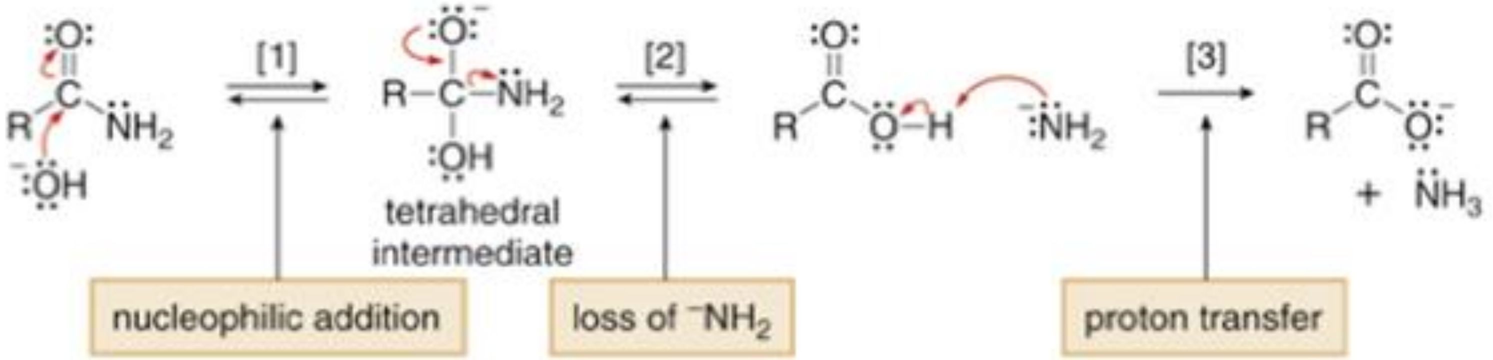
Examples



Amides: Reactions

- The mechanism of amide hydrolysis is exactly the same as the mechanism of ester hydrolysis.



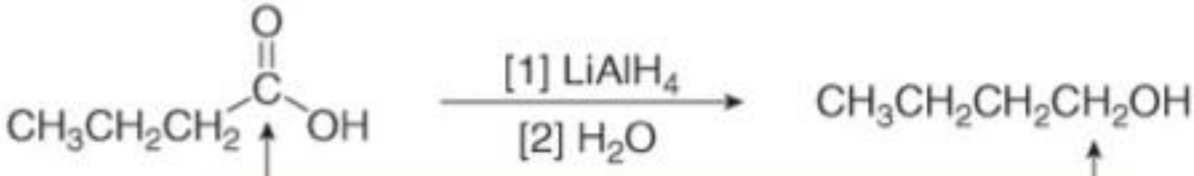


Amide hydrolysis is hard in acid because the nucleophile (H_2O) and the electrophile (amide) are poor.
Amide hydrolysis is hard in base because the electrophile and the leaving group (NR_2^-) are poor.

Reduction of Carboxylic Acids

Carboxylic acids are reduced to 1° alcohols with $LiAlH_4$.

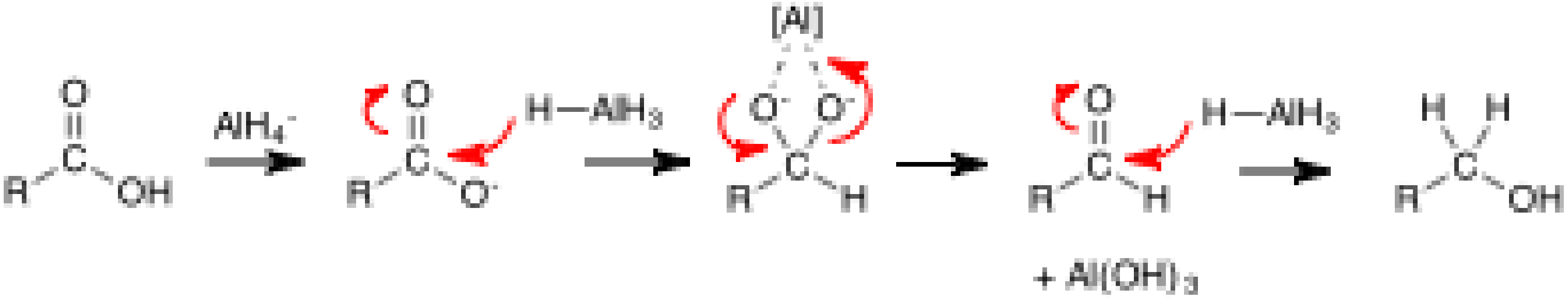
Example



$$CH_3CH_2CH_2COOH \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} CH_3CH_2CH_2CH_2OH$$

Two C–O bonds are replaced by C–H bonds.

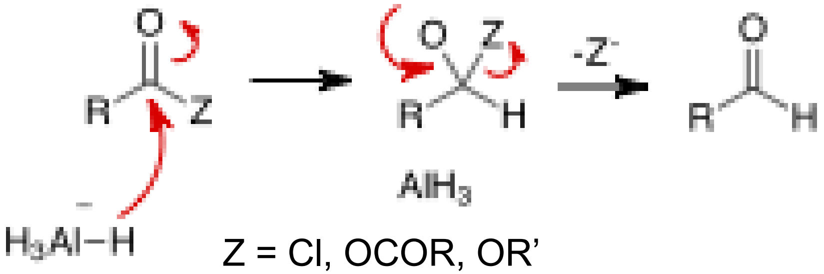
Mechanism:



Reduction: acid chlorides, anhydrides and esters

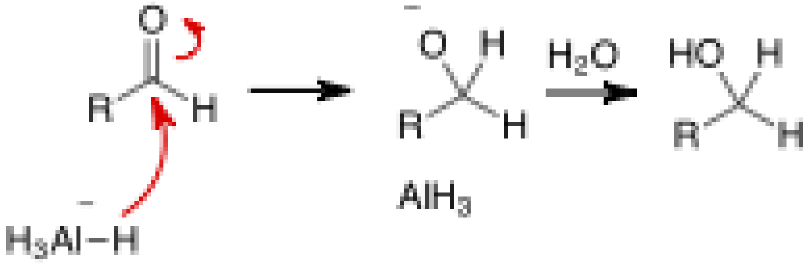
- Acid chlorides, anhydrides and esters are reduced to 1^{ry} alcohols by Al hydrides, e.g. $LiAlH_4$
- A two-step reaction:

1. Nucleophilic acyl substitution



Z = Cl, OCOR, OR’

2. Nucleophilic addition

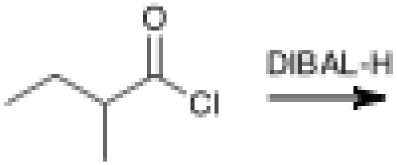


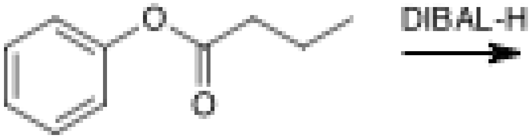
Reduction of acid chlorides, anhydrides and esters

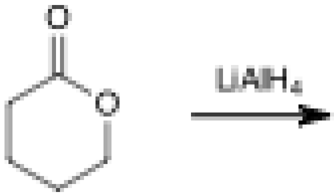
- $LiAlH_4$ is a strong reducing agent that reduces acids, acid chlorides, anhydrides and esters to primary alcohols.
- Diisobutylaluminum hydride ($[(CH_3)_2CHCH_2]_2AlH$, abbreviated DIBAL-H, has two bulky isobutyl groups which makes this reagent less reactive than $LiAlH_4$.
- DIBAL-H reduces acid chlorides, anhydrides and esters **to aldehydes**.

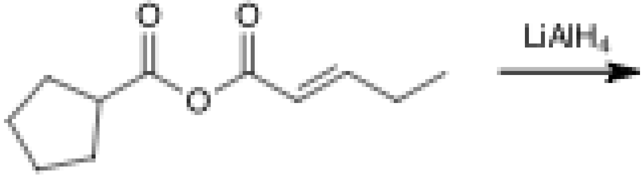
DIBAL-H

Reduction of acid chlorides, anhydrides and esters









Reduction of Carboxylic Acids and Their Derivatives

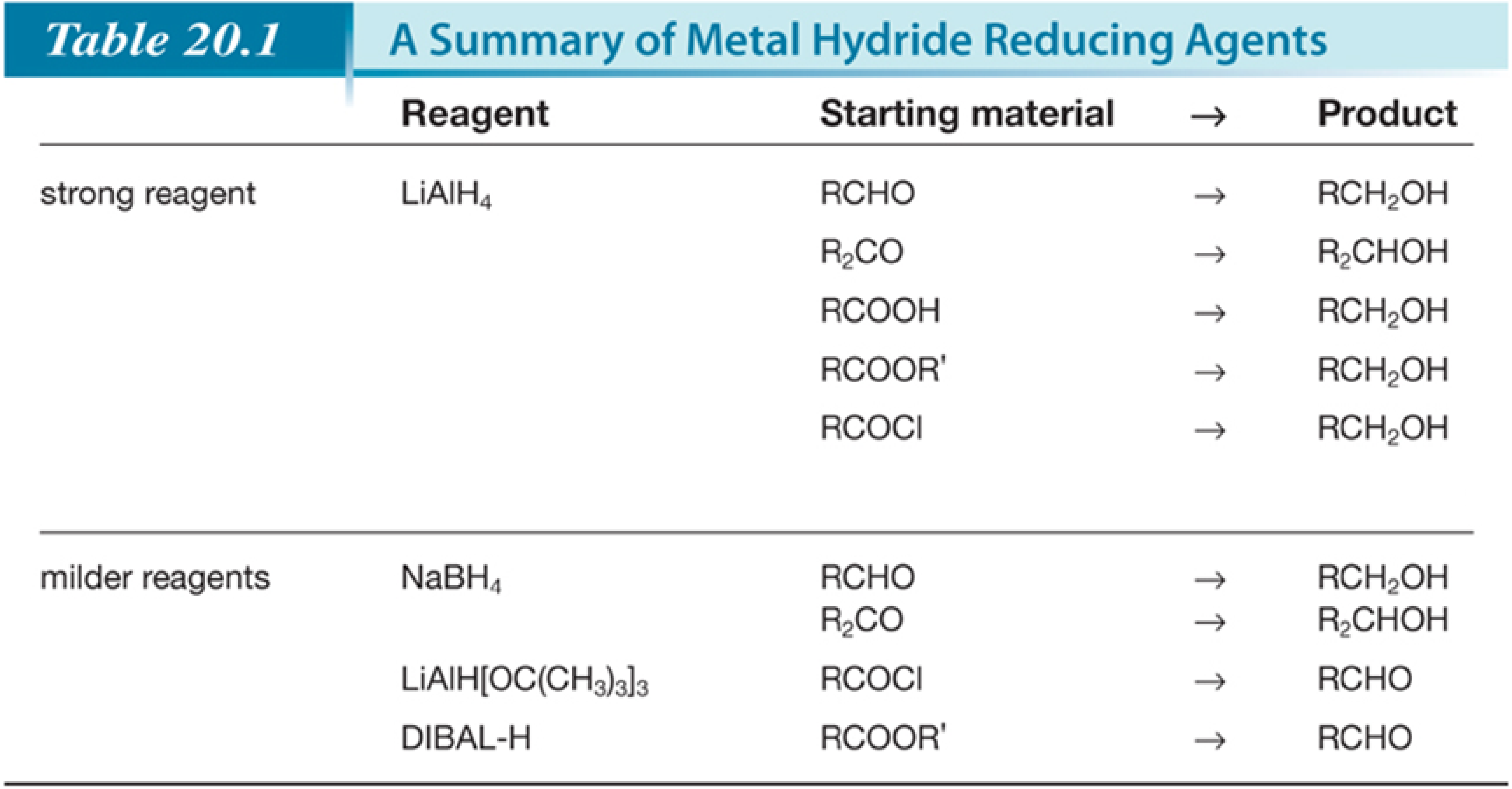


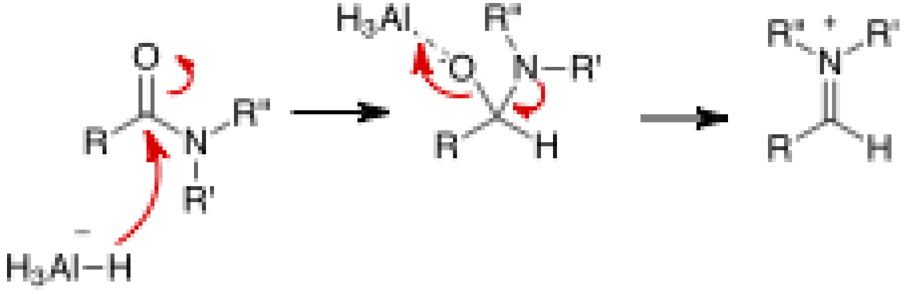
Table 20.1 A Summary of Metal Hydride Reducing Agents

	Reagent	Starting material	→	Product
strong reagent	$LiAlH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
		RCOOH	→	RCH_2OH
		RCOOR'	→	RCH_2OH
		RCOCl	→	RCH_2OH
milder reagents	$NaBH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
	$LiAlH[OC(CH_3)_3]_3$	RCOCl	→	RCHO
	DIBAL-H	RCOOR'	→	RCHO

Reduction of Amides

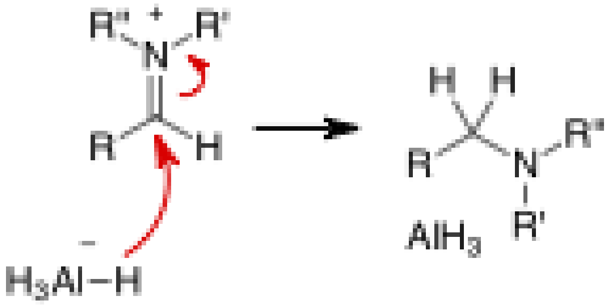
- Amides are reduced to amines by Al hydrides, e.g. $LiAlH_4$
- A two-step reaction:

1. Nucleophilic addition-elimination

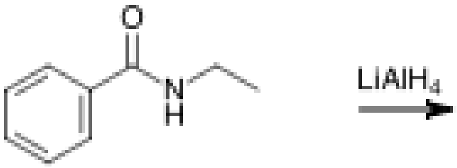


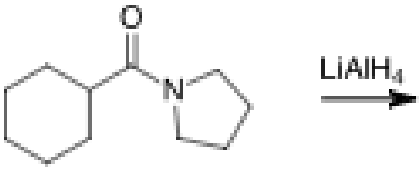
imminium ion

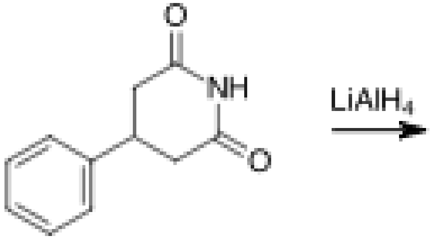
2. Nucleophilic addition



Reduction of Amides



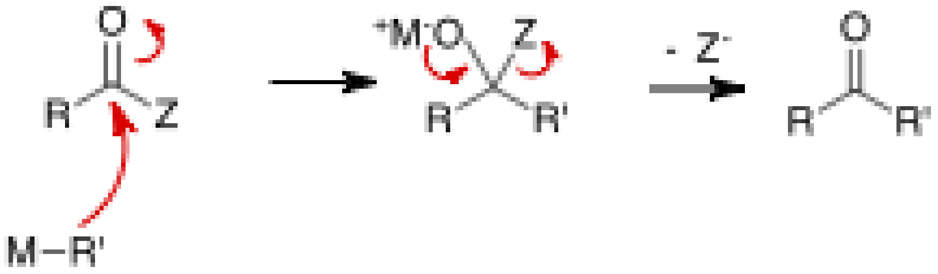




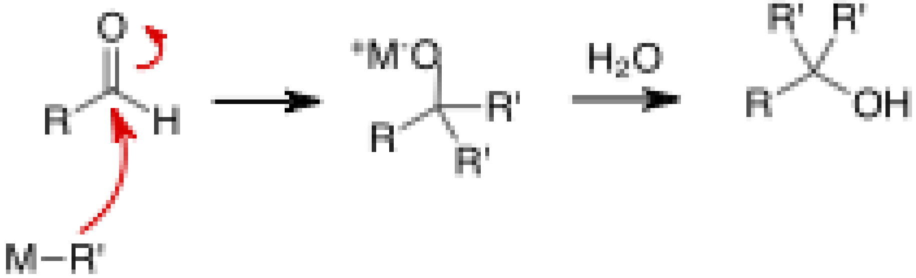
Reaction of Organometallic Reagents with Carboxylic Acid Derivatives.

- Both esters and acid chlorides form 3° alcohols when treated with two equivalents of either Grignard or organolithium reagents.
- A two-step reaction:

1. Nucleophilic acyl substitution



2. Nucleophilic addition

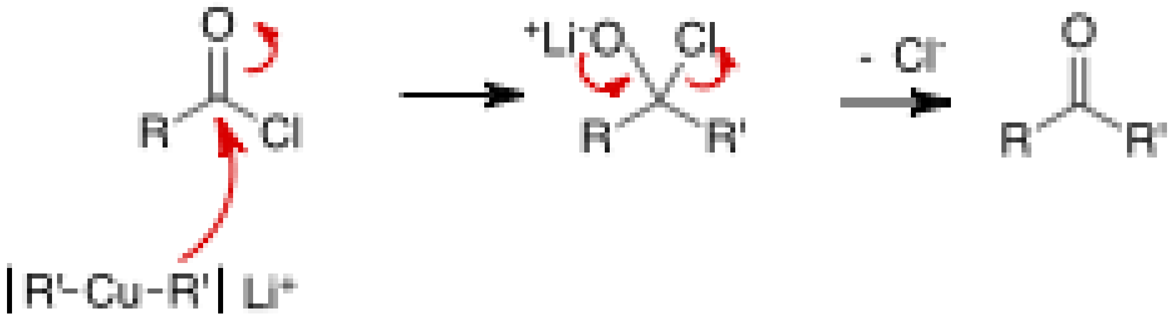


Reaction of Organometallic Reagents with Carboxylic Acid Derivatives.

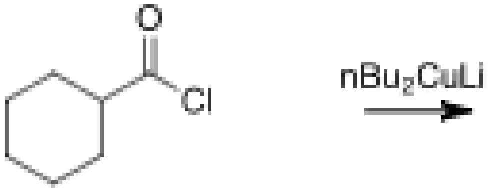
- Organocuprates (R'_2CuLi) are less reactive than organolithium and organomagnesium compounds.

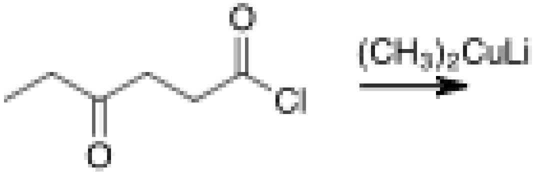
- R'_2CuLi react only with acid chlorides, which are the more reactive among carboxylic acid derivatives, to give a ketone as the product.

- Esters do not react with R'_2CuLi.



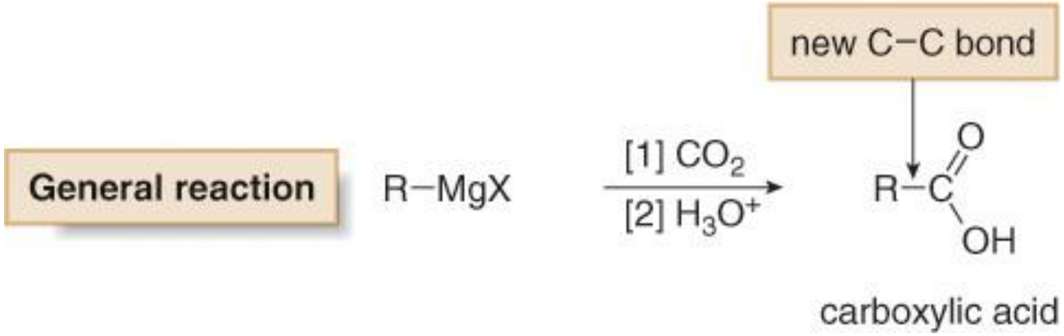
Reaction of Organometallic Reagents with Carboxylic Acid Derivatives.

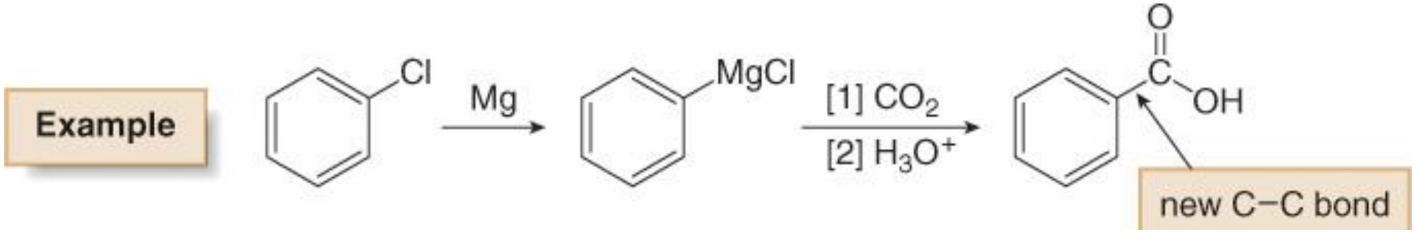




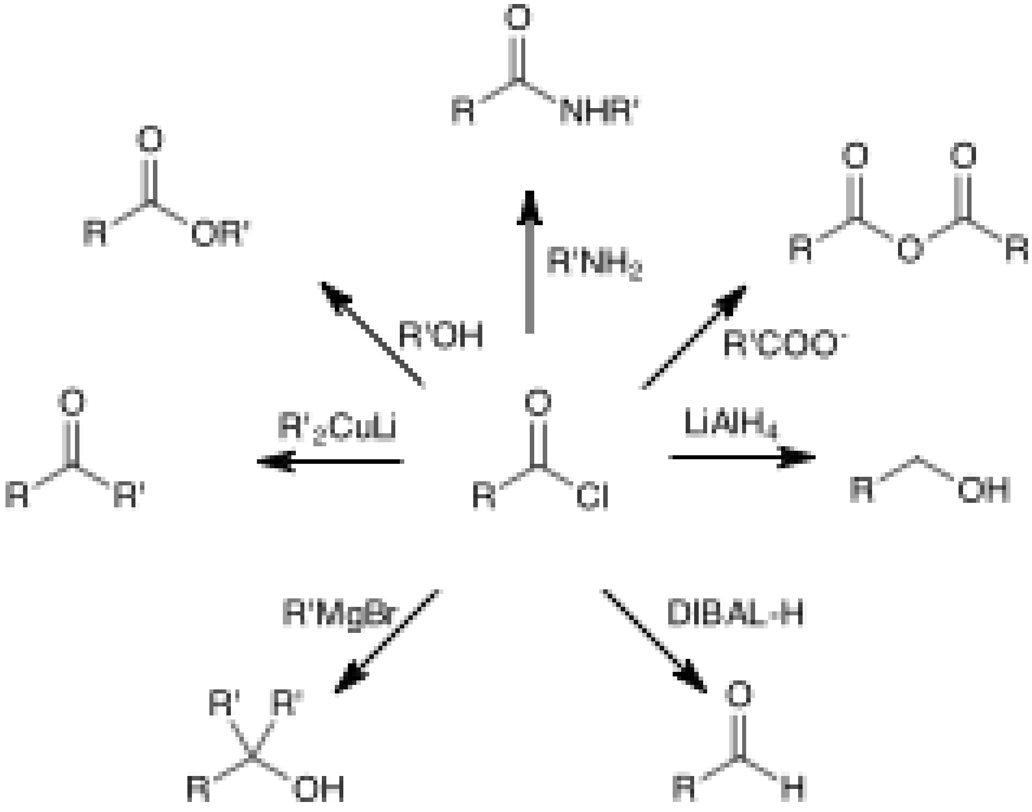
Reaction of Organometallic Reagents with CO_2

- Grignards react with CO_2 to give carboxylic acids after protonation with aqueous acid.
- This reaction is called carboxylation.
- The carboxylic acid formed has one more carbon atom than the Grignard reagent from which it was prepared.

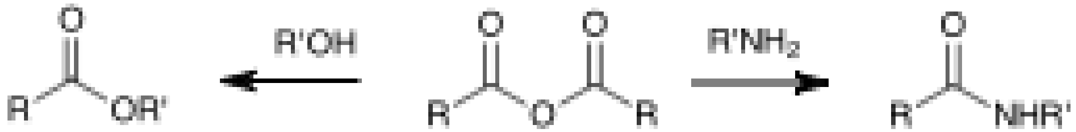




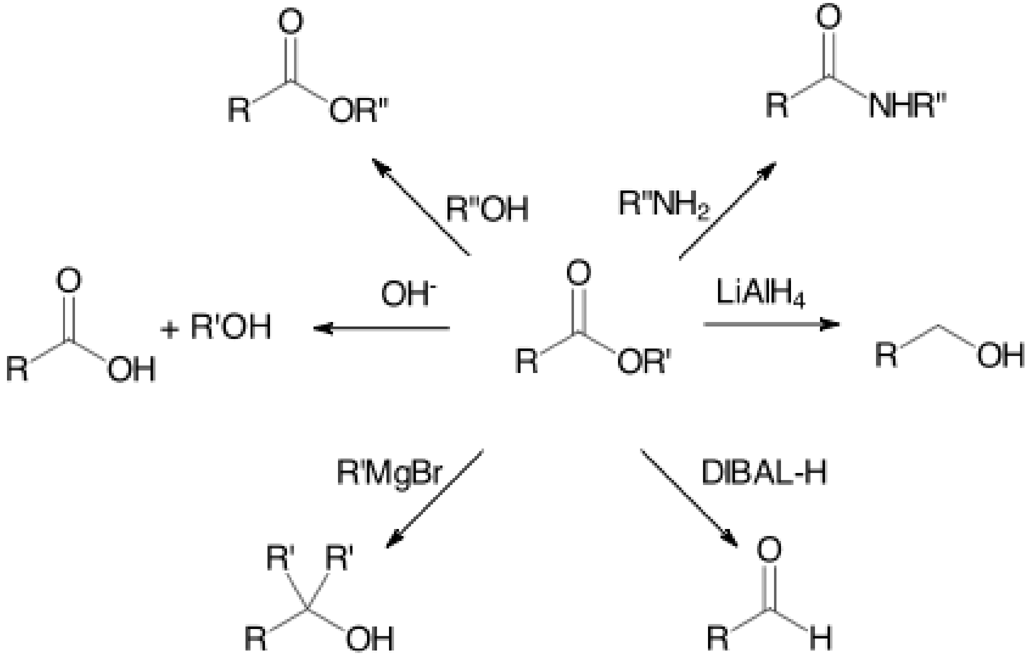
Summary: important reactions of acid chlorides.



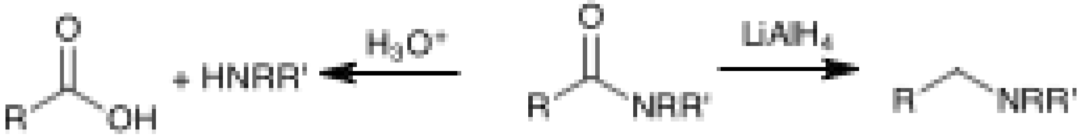
Summary: important reactions of anhydrides.



Summary: important reactions of esters.



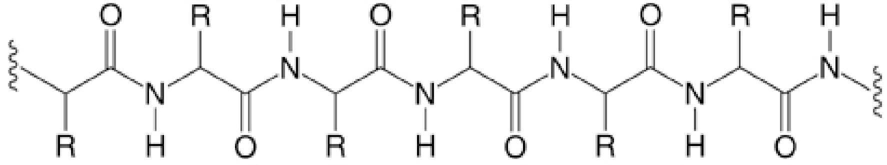
Summary: important reactions of amides.



Natural and Synthetic Fibers

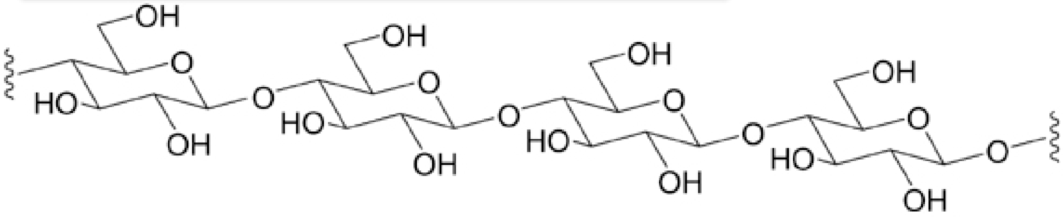
- Fibers like wool and silk are proteins obtained from animals.
- Cotton and linen are derived from carbohydrates having the general structure of cellulose.

Wool and silk—Proteins with many amide bonds



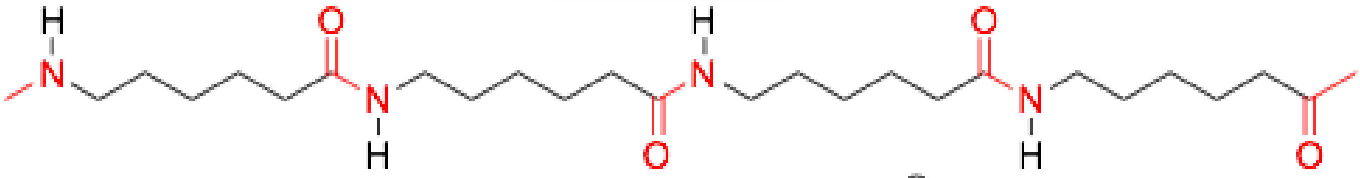
R groups contain C, H, and functional groups like NH_2, COOH, OH, and SH.

Cotton and linen—Carbohydrates like cellulose



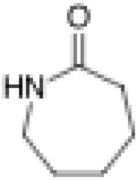
Natural and Synthetic Fibers: Nylon—A Polyamide

Nylon 6



monomers:

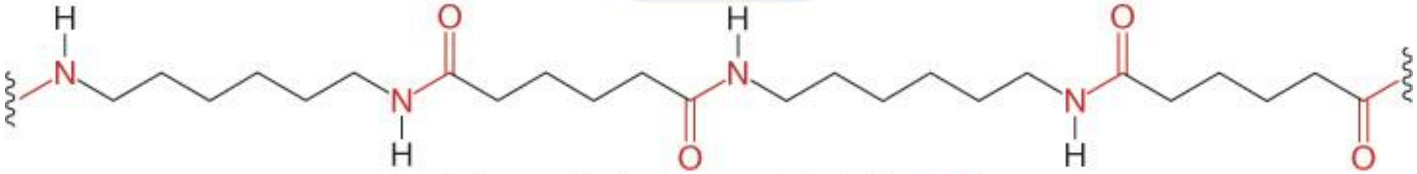
or



6-aminohexanoic acid

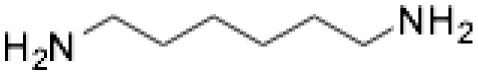
∑-caprolactam

Nylon 6,6

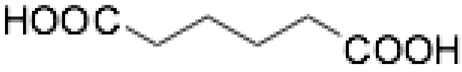


[The amide bonds are labeled in red.]

monomers:



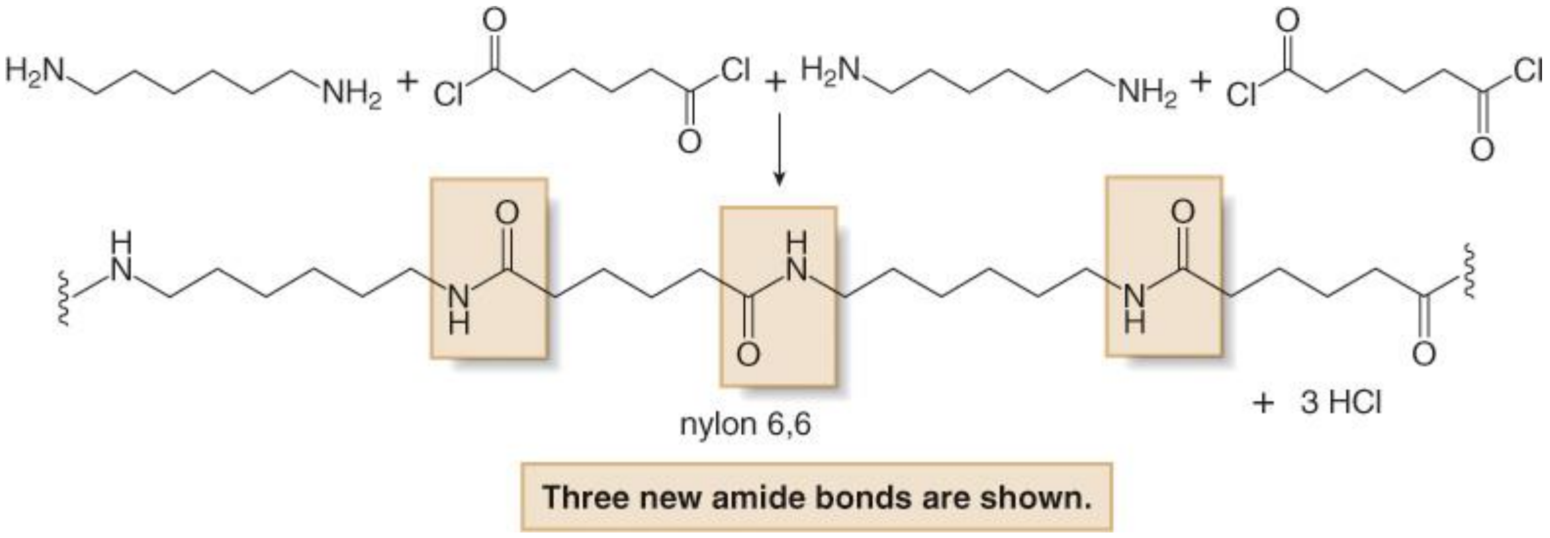
hexamethylenediamine



adipic acid

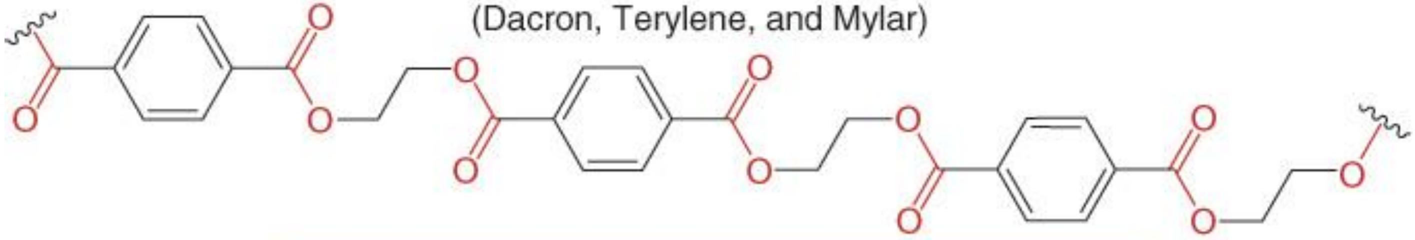
Natural and Synthetic Fibers: Nylon—A Polyamide

- Nylon is a condensation polymer



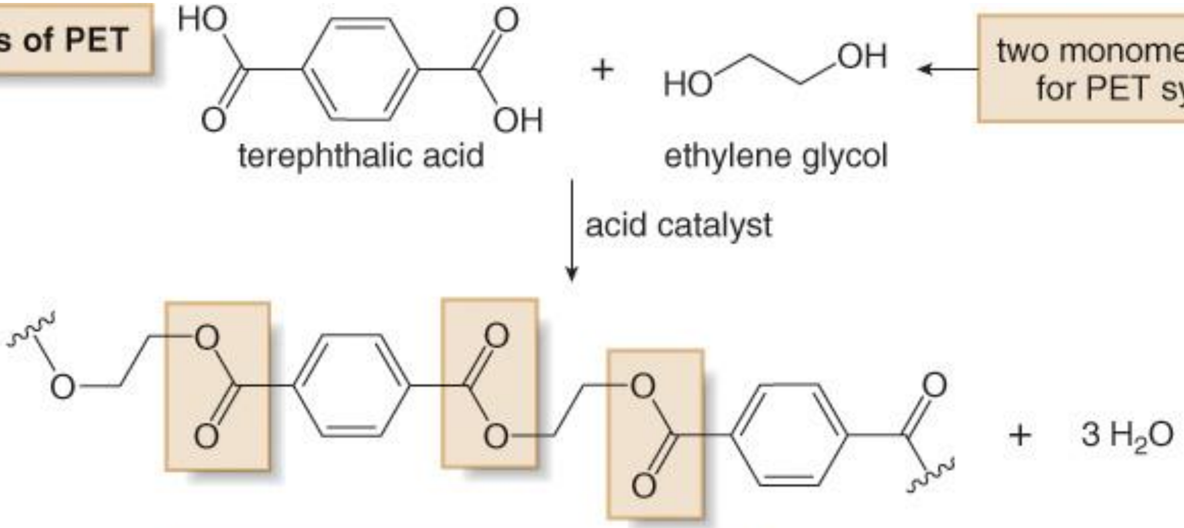
Natural and Synthetic Fibers: Polyesters

Polyethylene terephthalate
PET
(Dacron, Terylene, and Mylar)



Ester bonds (in red) join the carbon skeleton together.

Synthesis of PET



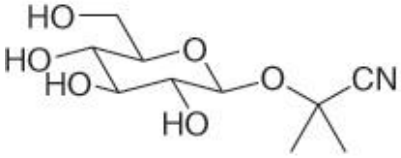
two monomers needed for PET synthesis

Three new ester bonds are shown.

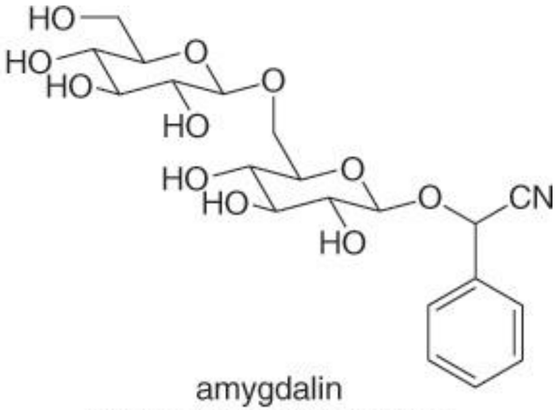
Nitriles

- Nitriles are not common in nature.

- Cianohydrins are the most common nitriles.

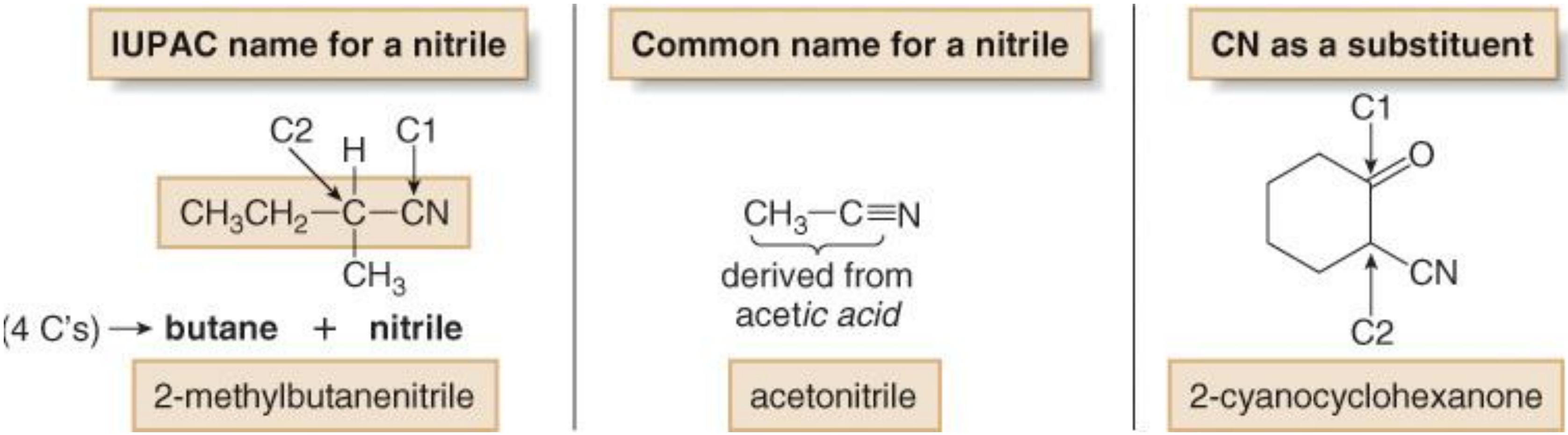


linamarin
(found in cassava root)



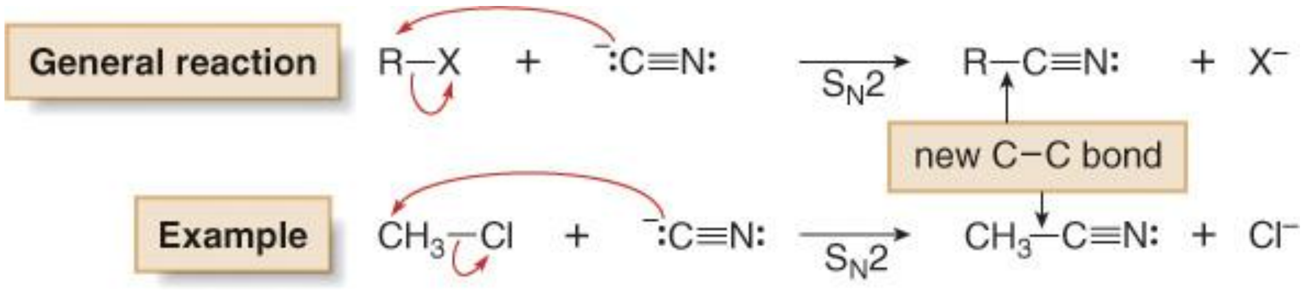
amygdalin
(commonly called laetrile)

Nomenclature—Nitriles

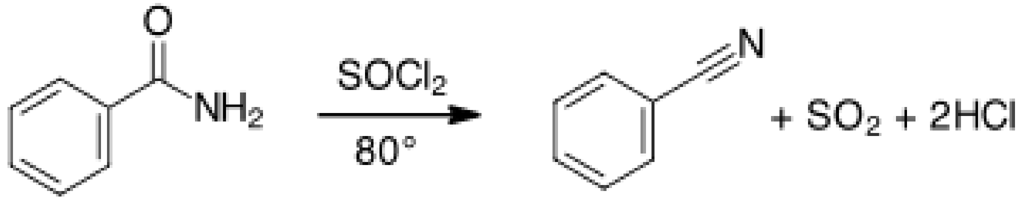


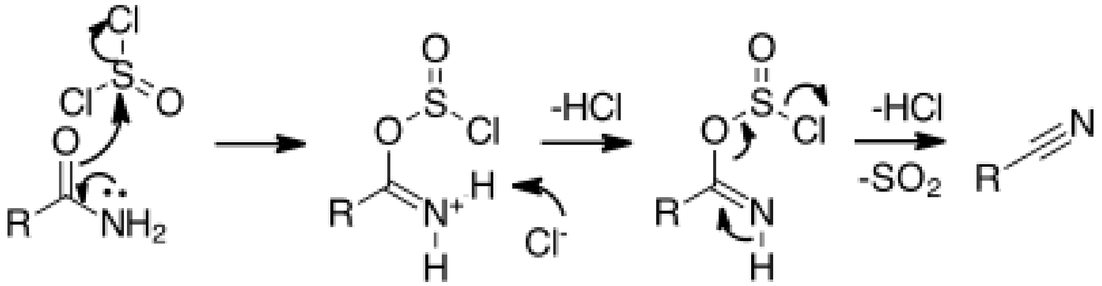
Nitriles

- Nitriles are prepared by S_N2 reactions of unhindered methyl and 1° alkyl halides with ^{-}CN.

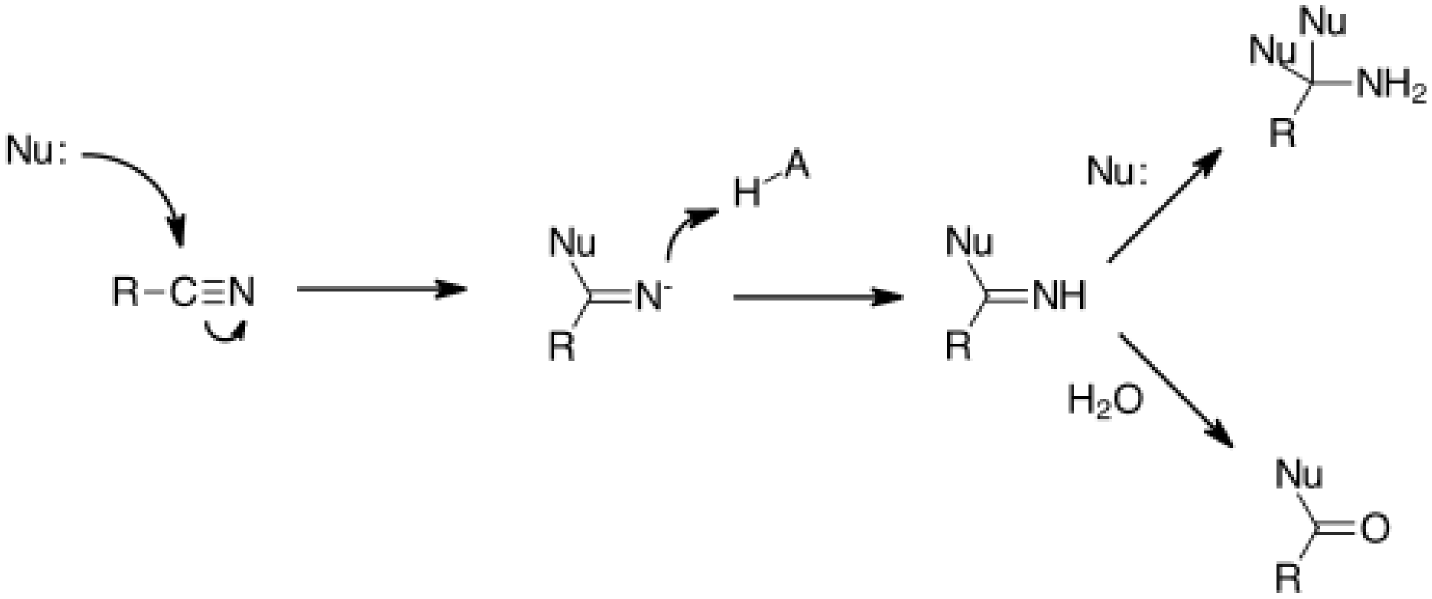


- Nitriles are prepared by dehydration of amides (more general).





Reactions of Nitriles – Nucleophilic Addition to the CN Group

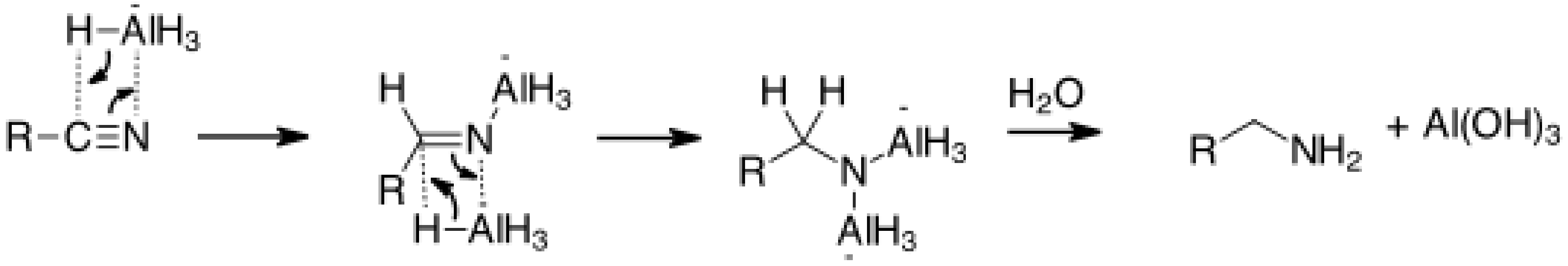


Nu: = H^- ([Al]-H); R^- (R-[M]); H_2O

Reactions of Nitriles—Reduction

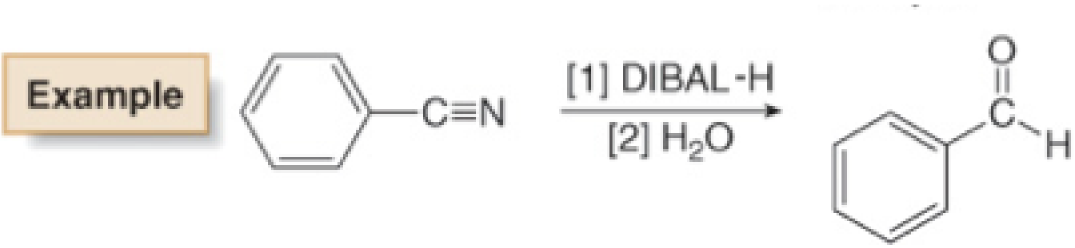
$LiAlH_4$ (more reactive)

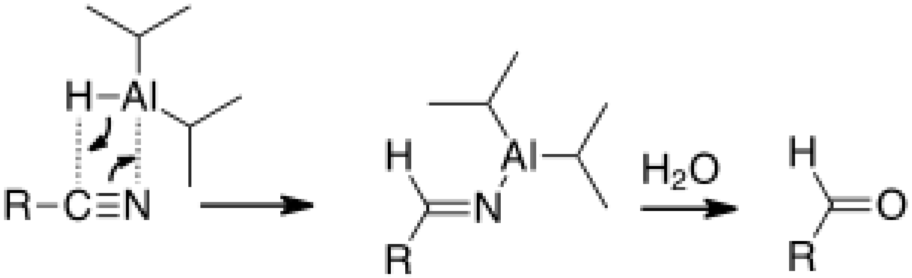
Example $(CH_3)_3C-C\equiv N \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} (CH_3)_3C-CH_2NH_2$



Reactions of Nitriles—Reduction

DIBAL-H (less reactive)

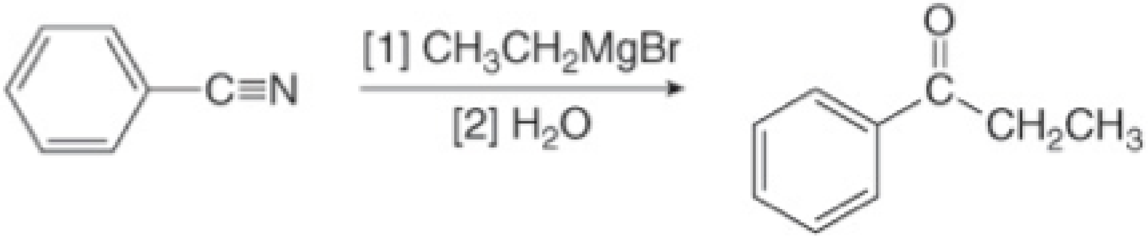


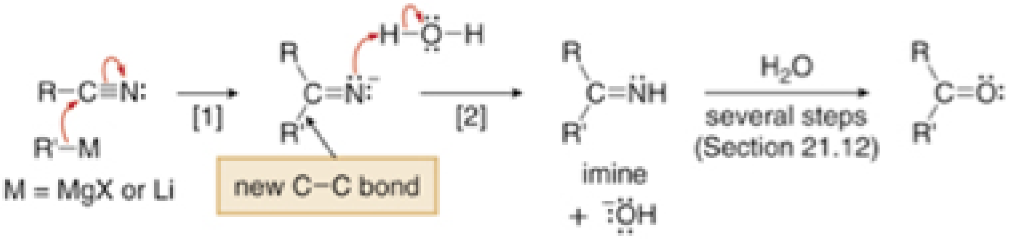


Addition of Organometallic reagents

- Both Grignard and organolithium reagents react with nitriles to form ketones with a new C—C bond.

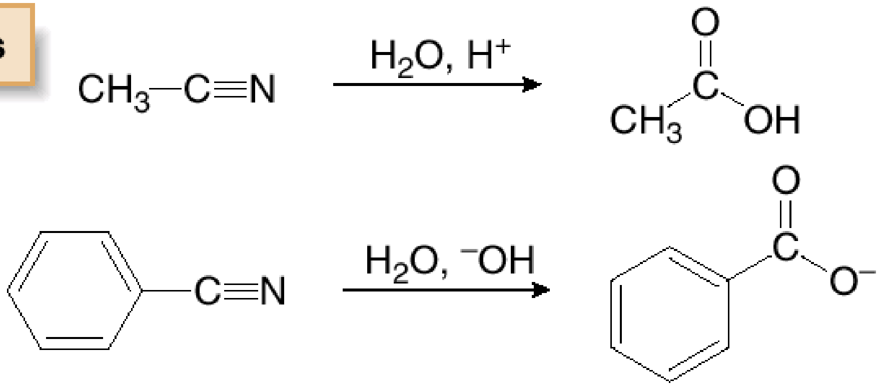
Example



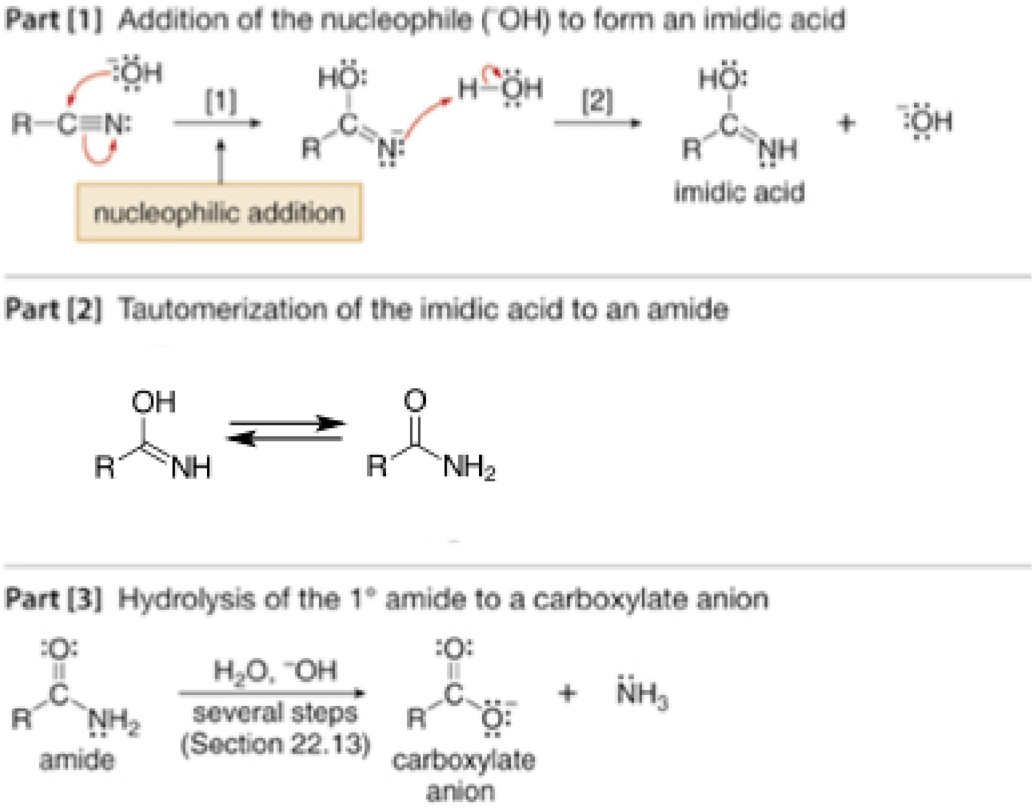


Reactions of Nitriles—Hydrolysis

Examples



Reactions of Nitriles—Hydrolysis


Part [1] Addition of the nucleophile (^-OH) to form an imidic acid

Part [2] Tautomerization of the imidic acid to an amide

Part [3] Hydrolysis of the 1° amide to a carboxylate anion

Summary: important reactions of nitriles.