CARBOXYLIC ACIDS AND NITRILES

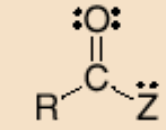
Chapters 20, 21

Organic Chemistry, *8th Edition*

John McMurry

CARBOXYLIC ACID DERIVATIVES

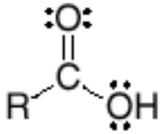
General structure



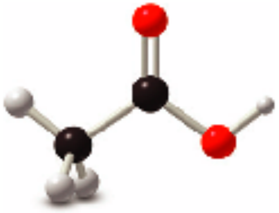
acyl group

Z = electronegative atom

Z = OH

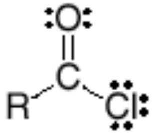


carboxylic acid

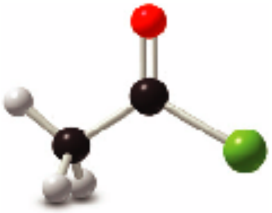


R = CH_3
acetic acid

Z = Cl

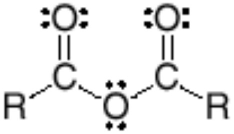


acid chloride

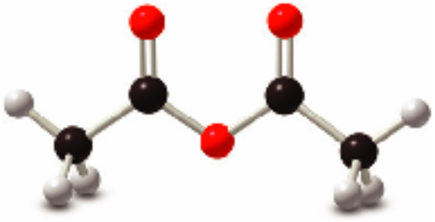


R = CH_3
acetyl chloride

Z = OCOR



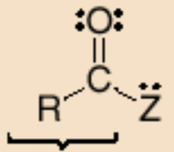
anhydride



R = CH_3
acetic anhydride

CARBOXYLIC ACID DERIVATIVES

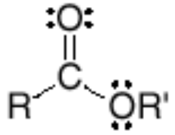
General structure



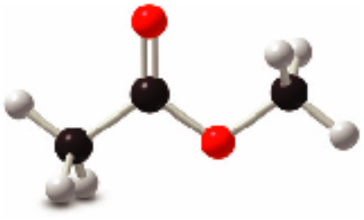
acyl group

Z = electronegative atom

Z = OR'

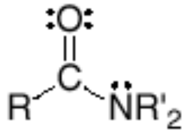


ester

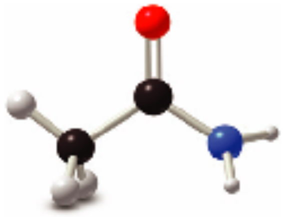


R = R' = CH_3
methyl acetate

Z = NR'_2



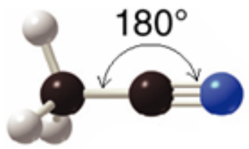
R' = H or alkyl
amide



R = CH_3, R' = H
acetamide

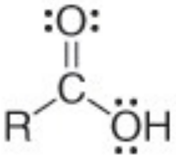
R−C≡N

nitrile

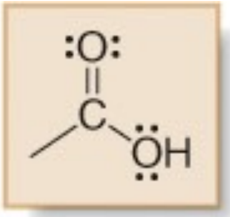


R = CH_3
acetonitrile

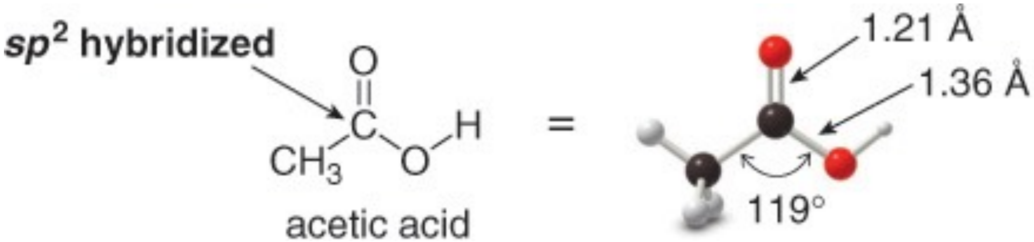
STRUCTURE AND BONDING



carboxylic acid



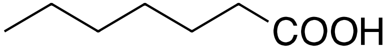
carboxy group



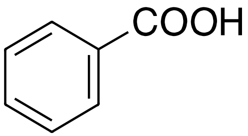
acetic acid

The C=O is shorter than the C−O.

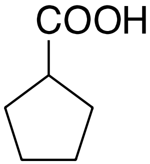
NOMENCLATURE—THE IUPAC SYSTEM



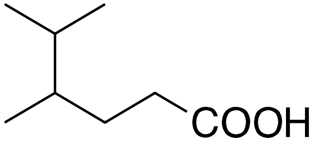
heptanoic acid



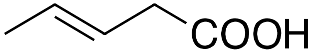
benzoic acid



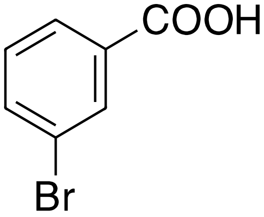
cyclopentane
carboxylic acid



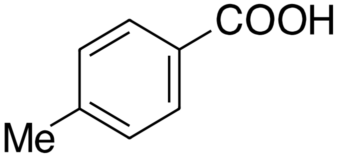
4,5-dimethyl
hexanoic acid



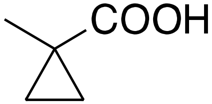
3-pentenoic
acid



3-bromobenzoic
acid



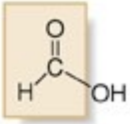
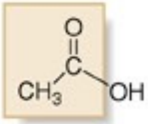
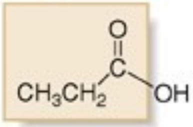
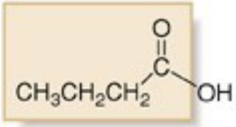
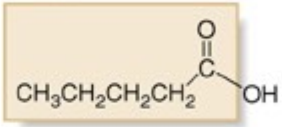
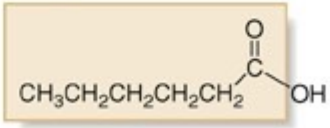
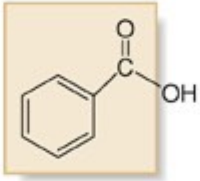
p-toluic
acid



1-methyl-
cyclopropanecarboxylic
acid

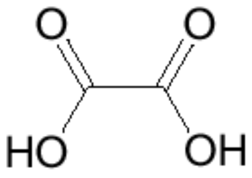
NOMENCLATURE-COMMON NAMES

Table 19.1 Common Names for Some Simple Carboxylic Acids

Number of C atoms	Structure	Parent name	Common name
1		**form-**	formic acid
2		**acet-**	acetic acid
3		**propion-**	propionic acid
4		**butyr-**	butyric acid
5		**valer-**	valeric acid
6		**capro-**	caproic acid
		**benzo-**	benzoic acid

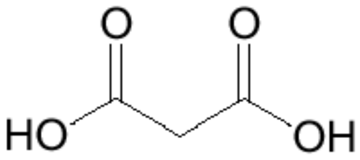
προτοσ πιον

NOMENCLATURE-POLYIACIDS



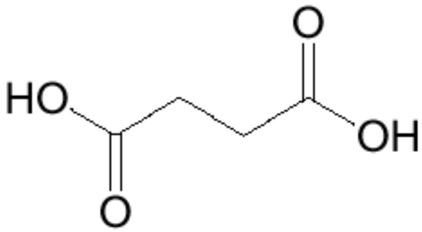
oxalic acid
(ethanedioic acid)

Oxalis acetosella



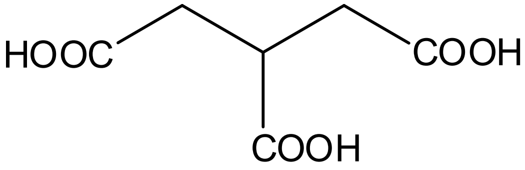
malonic acid
(propanedioic acid)

Malon



succinic acid
(butanedioic acid)

Succinum



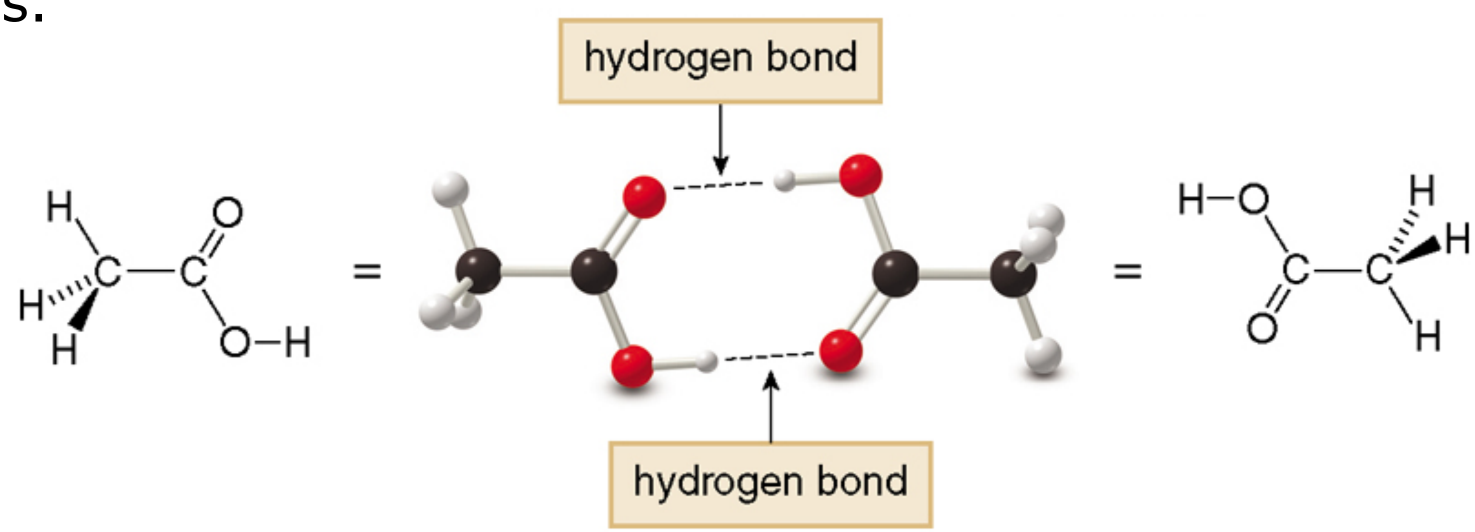
propane-1,2,3-tricarboxylic acid

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

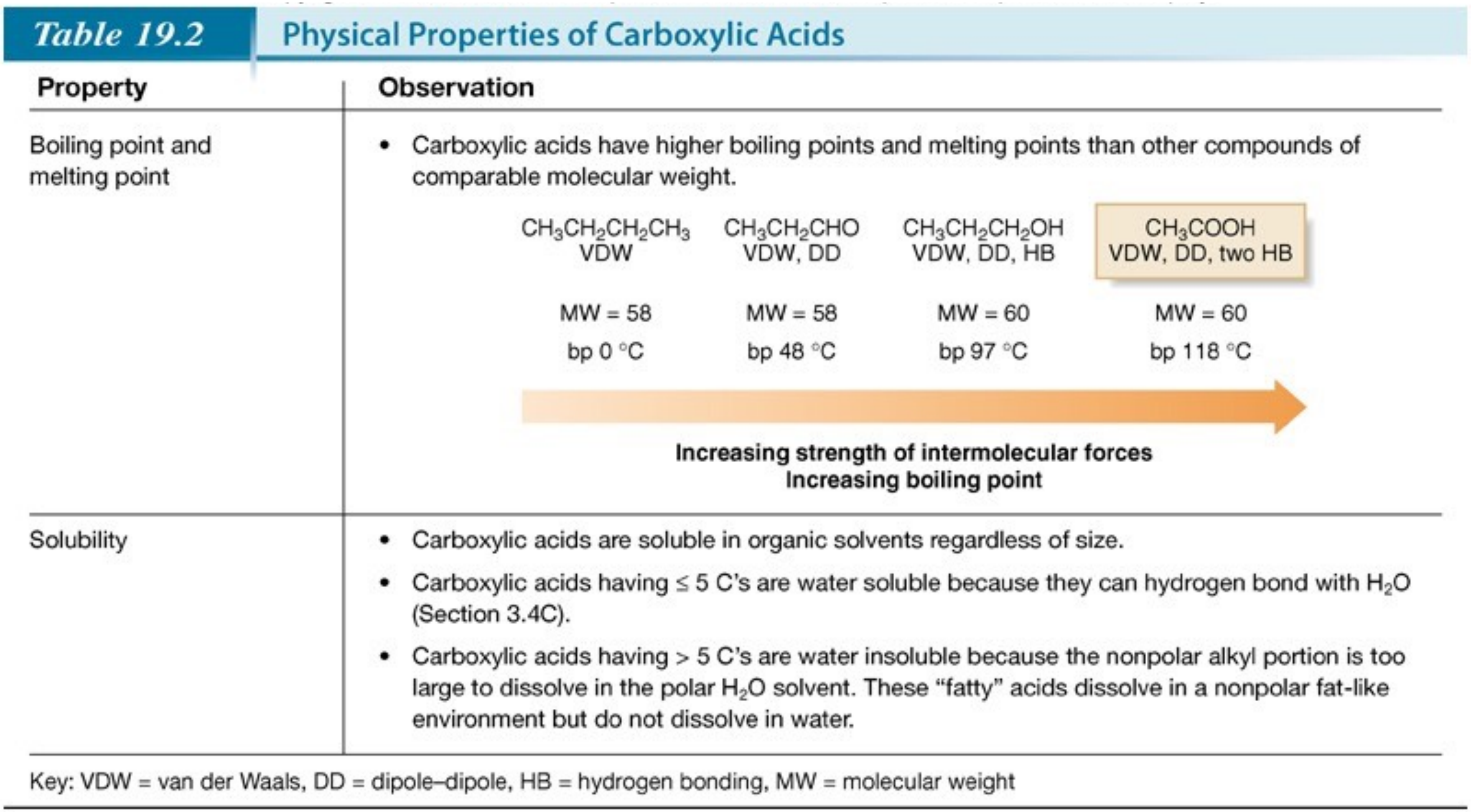
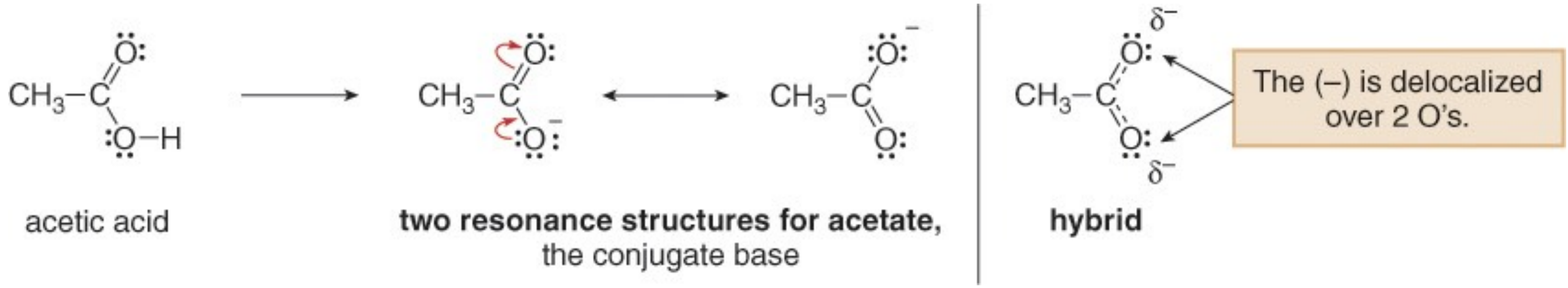


Table 19.2 Physical Properties of Carboxylic Acids

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



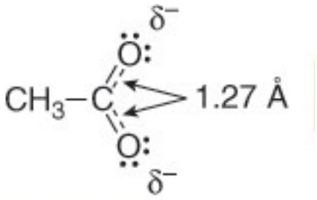
acetic acid

two resonance structures for acetate, the conjugate base

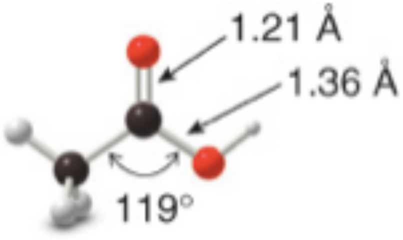
hybrid

The (–) is delocalized over 2 O's.

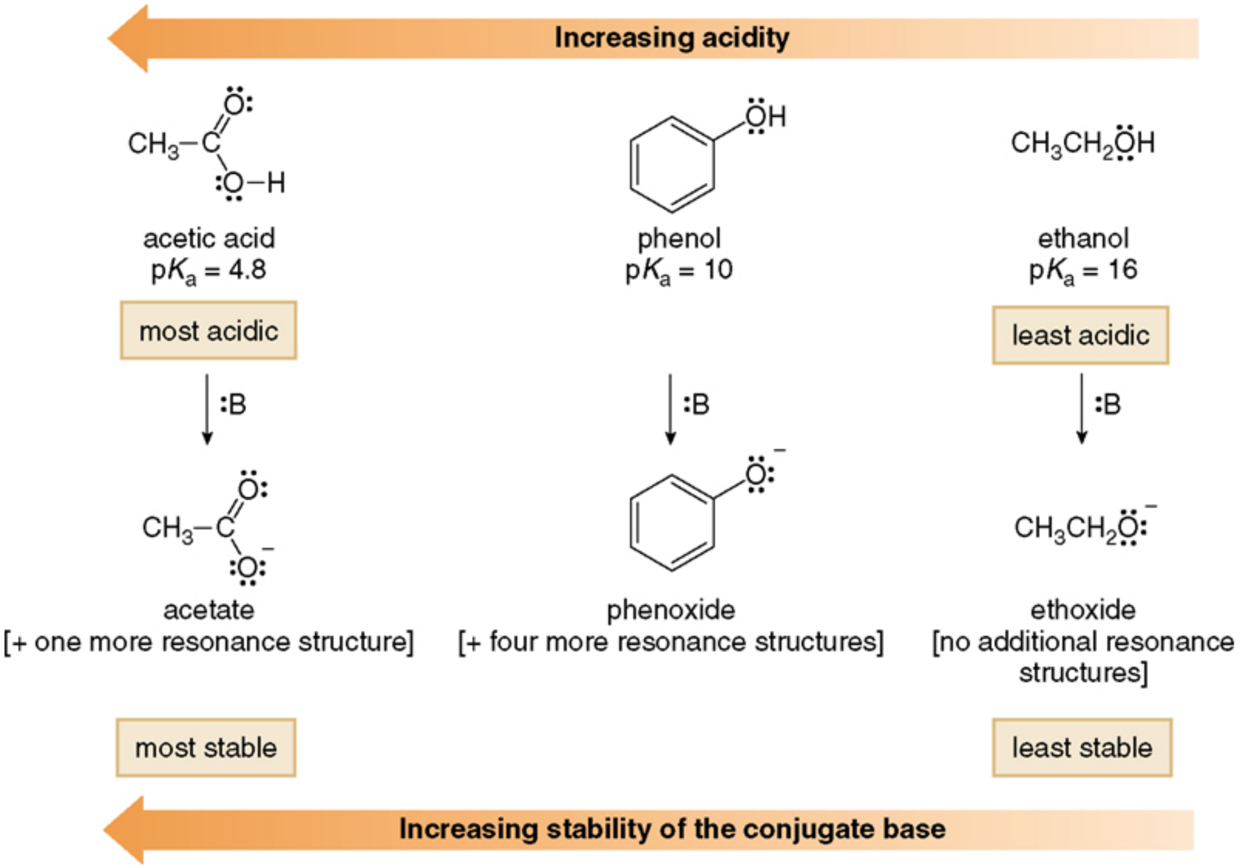
The acetate anion has two C—O bonds of equal length (1.27 Å) and intermediate between the length of a C—O single bond (1.36 Å) and C=O (1.21 Å).



acetate hybrid



CARBOXYLIC ACIDS—STRONG ORGANIC BRØNSTED-LOWRY ACIDS



Increasing acidity

acetic acid
pK_a = 4.8

most acidic

phenol
pK_a = 10

ethanol
pK_a = 16

least acidic

:B

acetate
[+ one more resonance structure]

phenoxide
[+ four more resonance structures]

ethoxide
[no additional resonance structures]

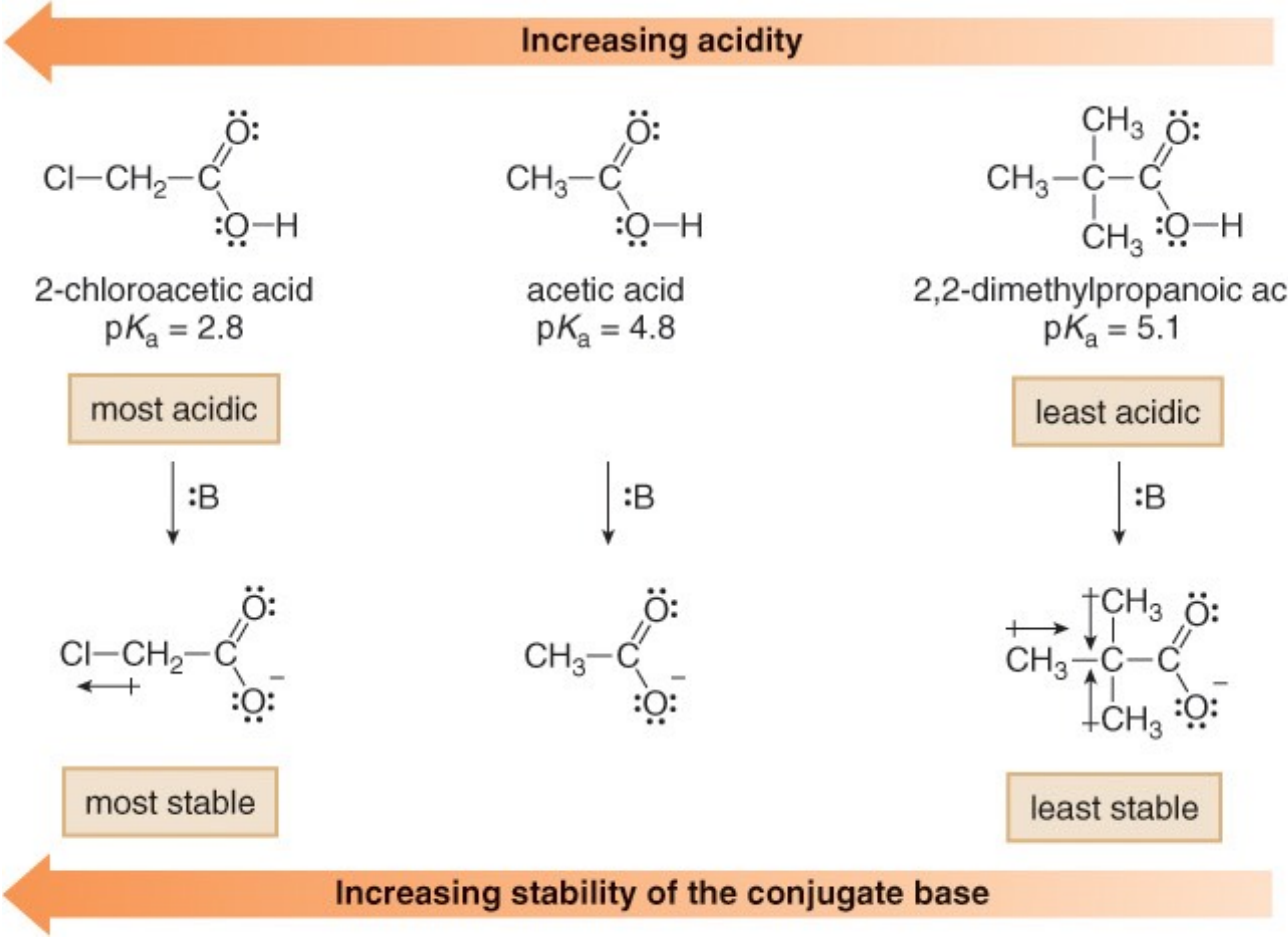
most stable

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.**



Increasing acidity

2-chloroacetic acid
pK_a = 2.8

most acidic

acetic acid
pK_a = 4.8

2,2-dimethylpropanoic acid
pK_a = 5.1

least acidic

most stable

least stable

Increasing stability of the conjugate base

THE INDUCTIVE EFFECT IN ALIPHATIC CARBOXYLIC ACIDS

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

$\mathrm{ClCH_2{-}COOH}$	$\mathrm{Cl_2CH{-}COOH}$	$\mathrm{Cl_3C{-}COOH}$
$\mathrm{p}K_\mathrm{a} = 2.8$	$\mathrm{p}K_\mathrm{a} = 1.3$	$\mathrm{p}K_\mathrm{a} = 0.9$

Increasing acidity
Increasing number of electronegative Cl atoms

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

$\mathrm{ClCH_2{-}COOH}$	$\mathrm{FCH_2{-}COOH}$
$\mathrm{p}K_\mathrm{a} = 2.8$	$\mathrm{p}K_\mathrm{a} = 2.6$
	stronger acid

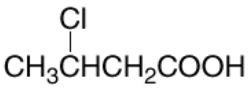
F is more electronegative than Cl.

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

$\mathrm{ClCH_2CH_2CH_2COOH}$

4-chlorobutanoic acid

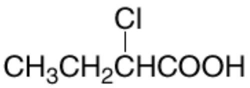
$\mathrm{p}K_\mathrm{a} = 4.5$



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

3-chlorobutanoic acid

$\mathrm{p}K_\mathrm{a} = 4.1$



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

2-chlorobutanoic acid

$\mathrm{p}K_\mathrm{a} = 2.9$

Increasing acidity
Increasing proximity of Cl to COOH

SUBSTITUTED BENZOIC ACIDS

D = Electron-donor group

This acid is less acidic than benzoic acid.

p$K_a > 4.2$

D destabilizes the carboxylate anion.

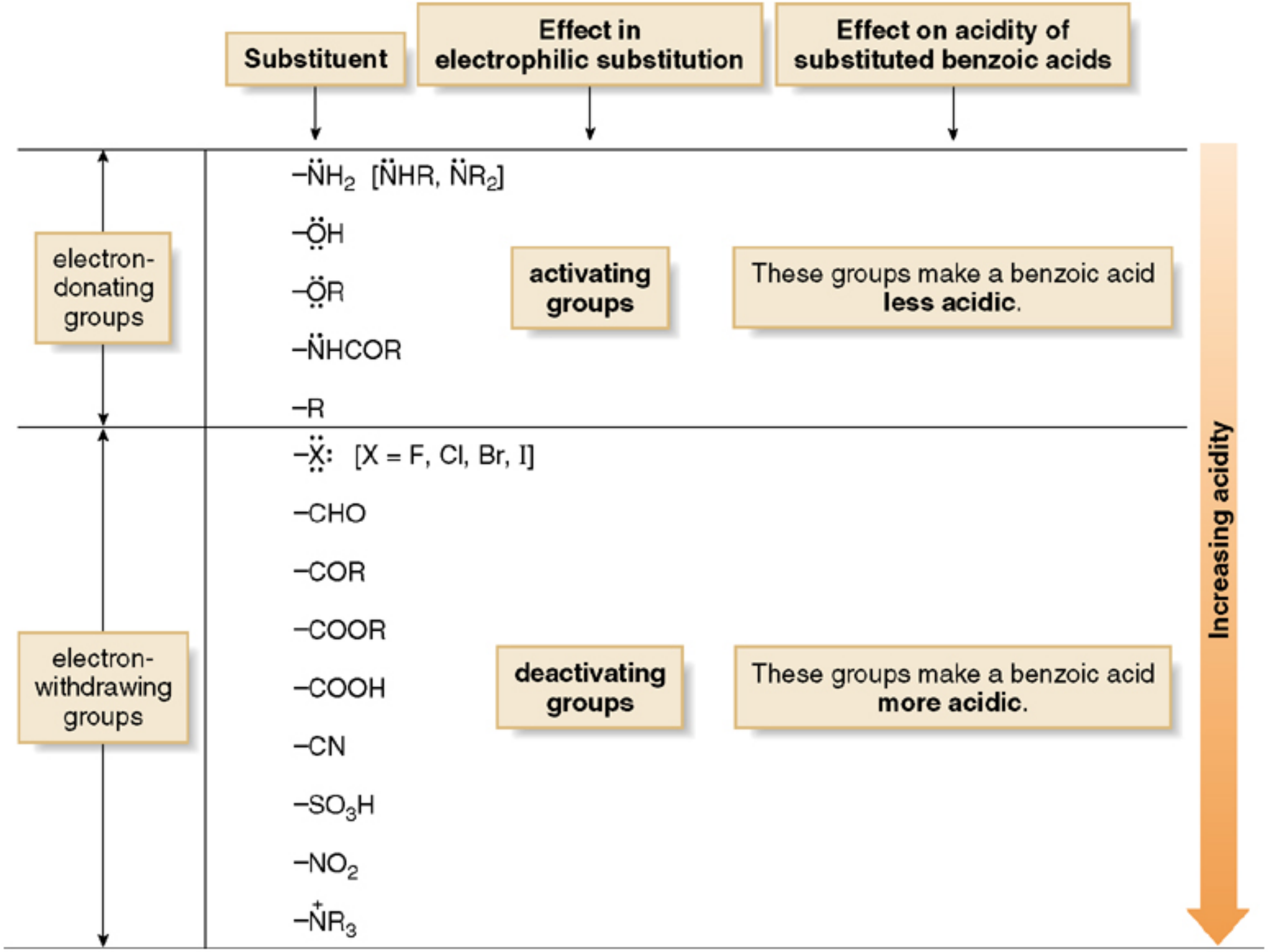
W = Electron-withdrawing group

This acid is more acidic than benzoic acid.

p$K_a < 4.2$

W stabilizes the carboxylate anion.

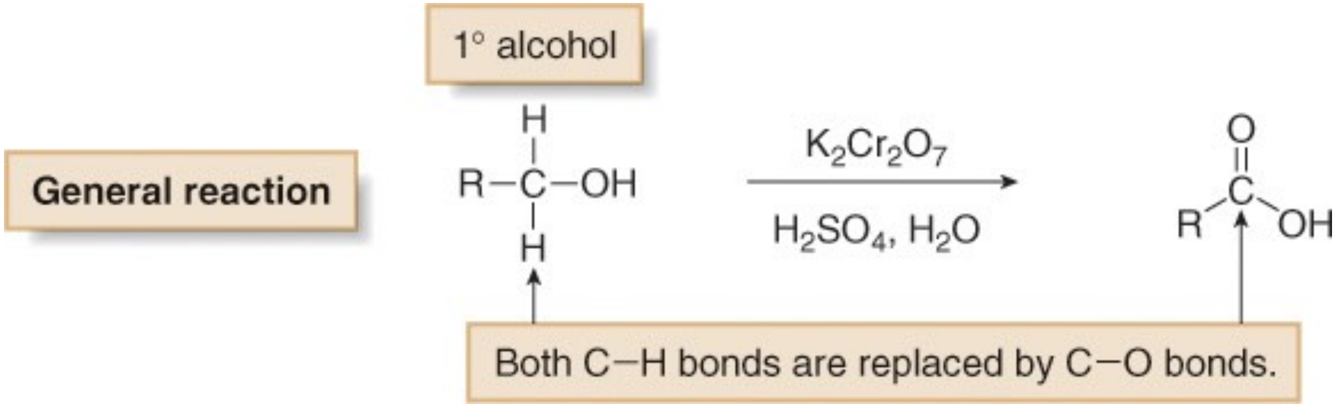
SUBSTITUTED BENZOIC ACIDS



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

PREPARATION OF CARBOXYLIC ACIDS

[1] Oxidation of 1° alcohols

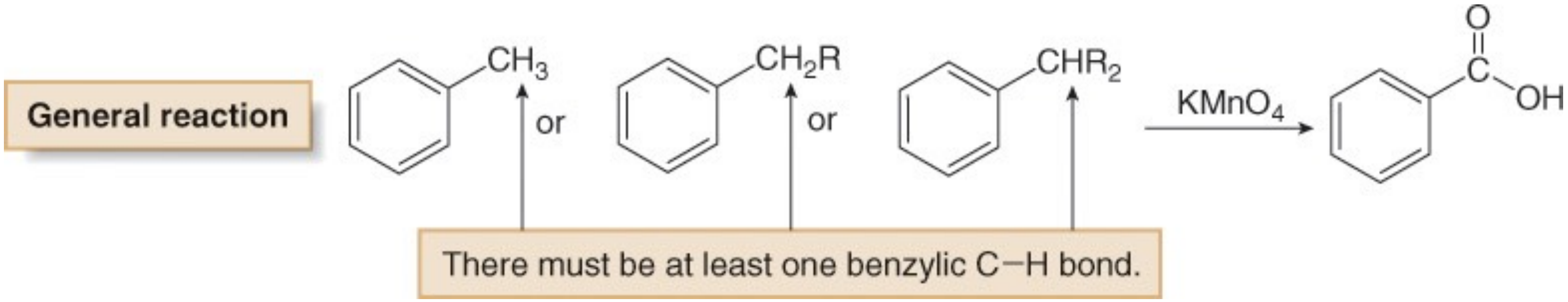


General reaction

1° alcohol

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

[2] Oxidation of alkyl benzenes

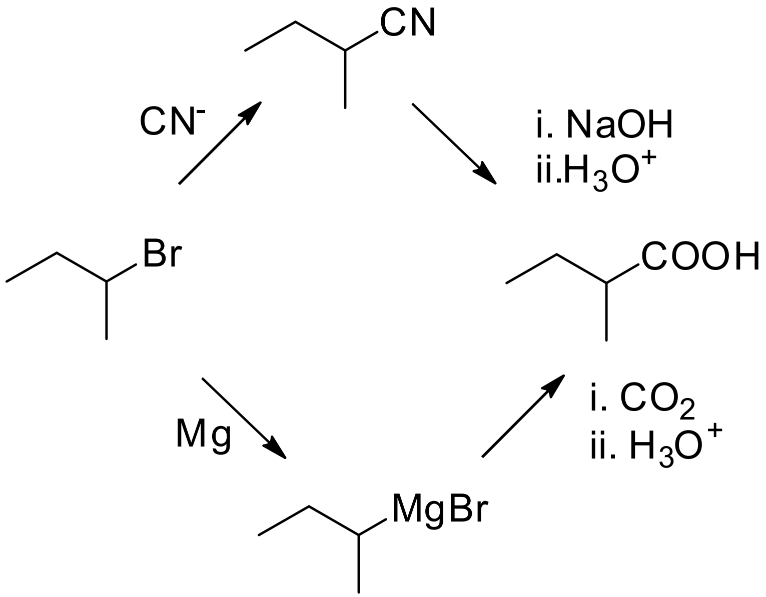


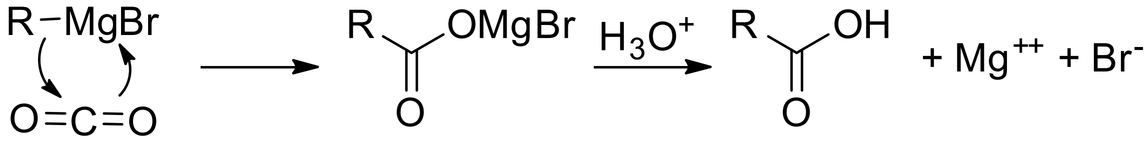
General reaction

There must be at least one benzylic C–H bond.

PREPARATION OF CARBOXYLIC ACIDS

[3] From alkyl halides

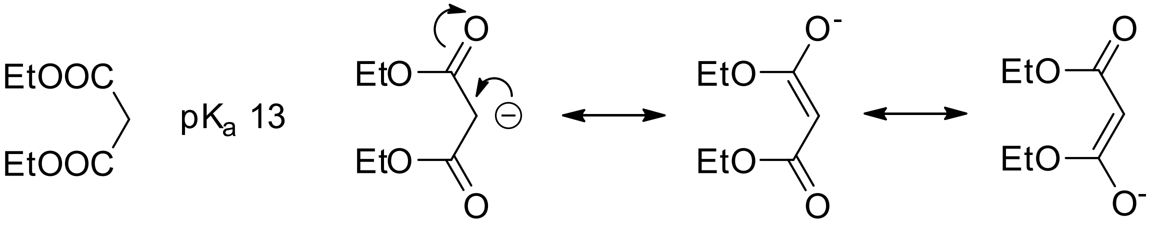




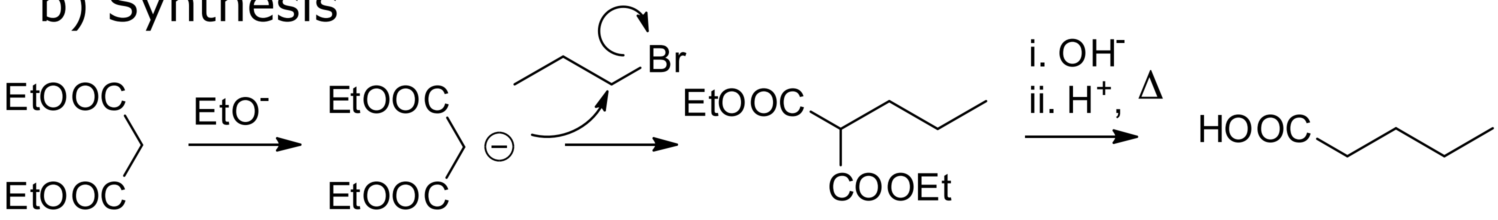
PREPARATION OF CARBOXYLIC ACIDS

[5] From alkyl halides. Malonic ester synthesis

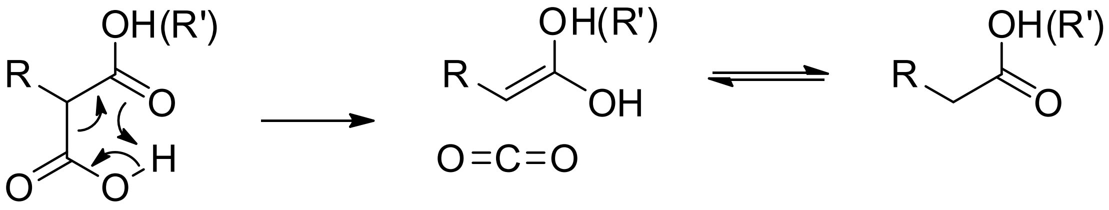
a) Acidity of malonate esters



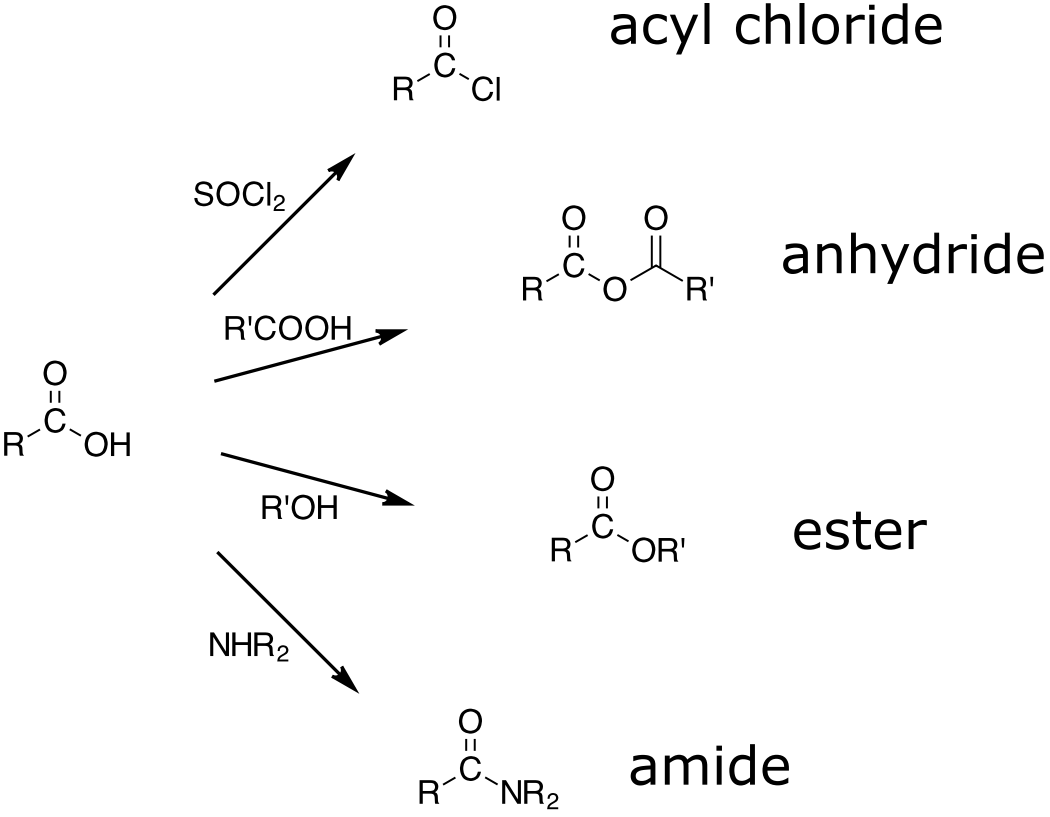
b) Synthesis



c) Mechanism for decarboxylation of β-ketoacids

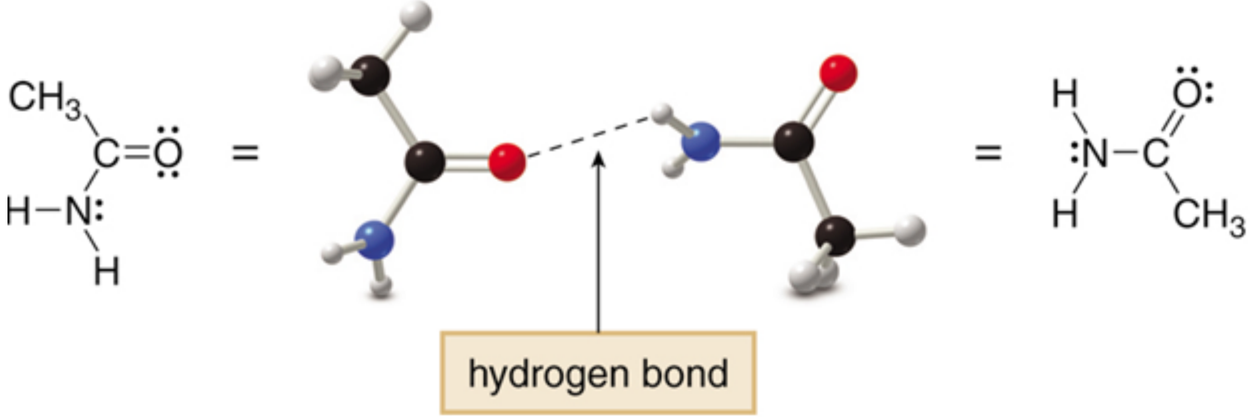


REACTIONS OF CARBOXYLIC ACIDS

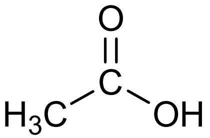


DERIVATIVES: PHYSICAL PROPERTIES

- 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



CH_3COOH

MW = 60 bp 118 °C

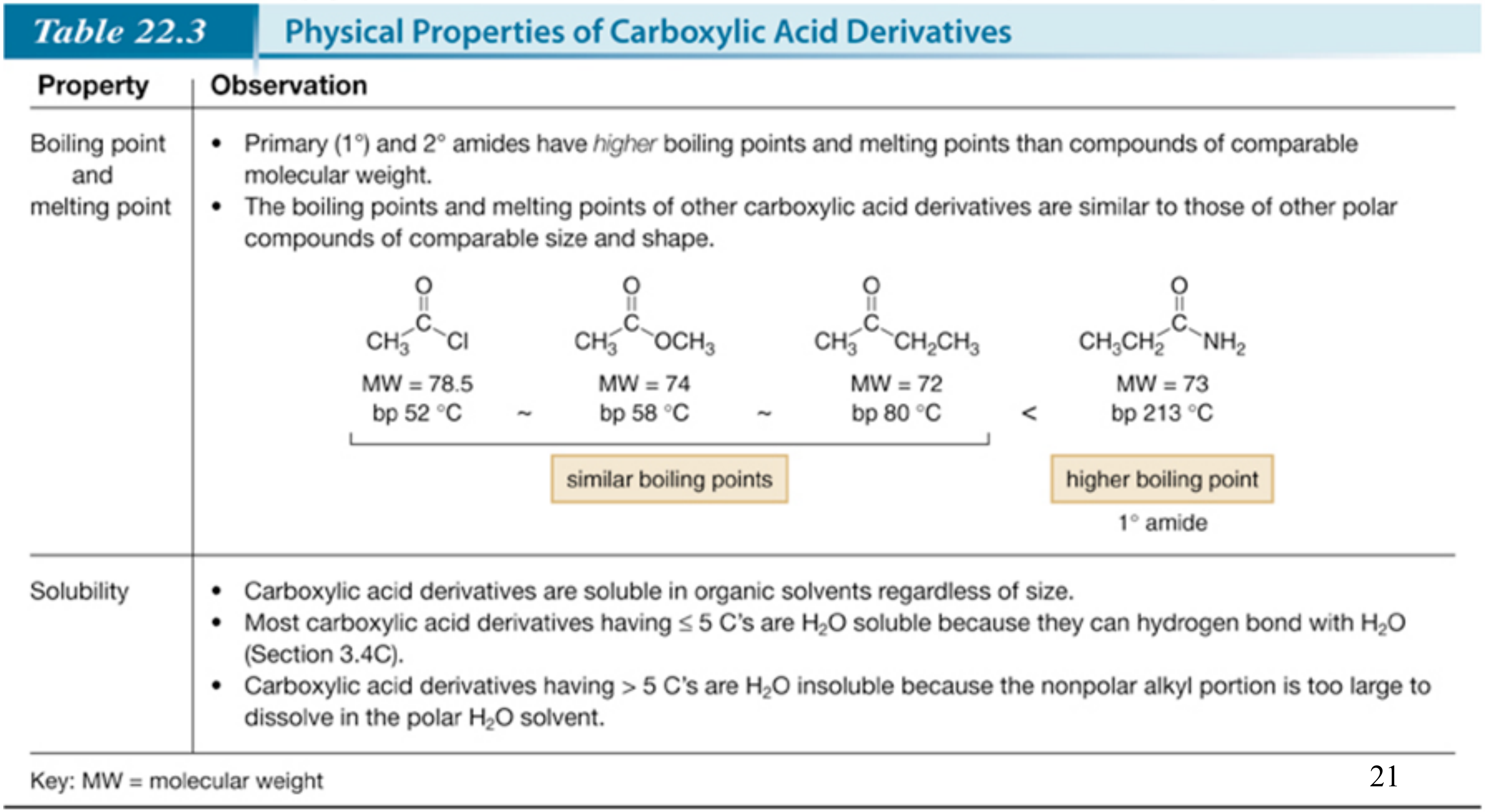
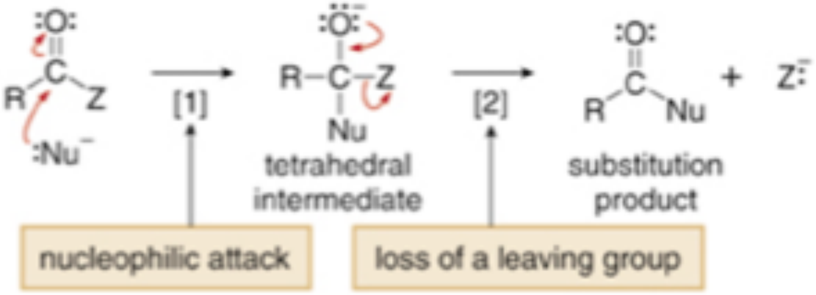


Table 22.3 Physical Properties of Carboxylic Acid Derivatives

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

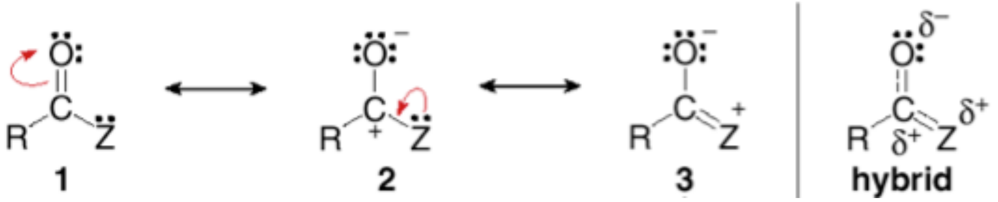
REACTION OF CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION

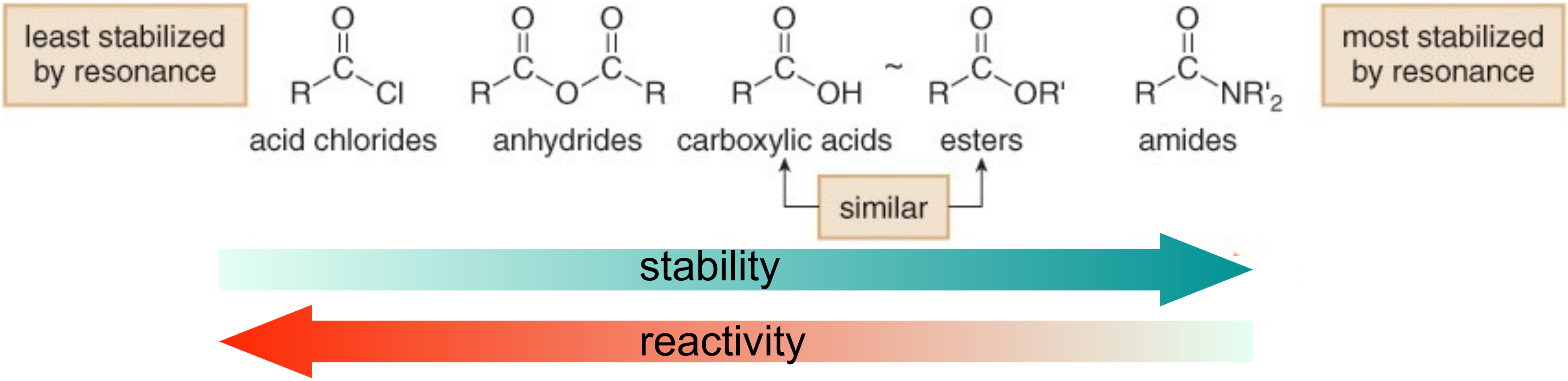


[$Z = Cl, OCOR, OH, OR', NR'_2$]

DERIVATIVES: STRUCTURE AND BONDING

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





INTRODUCTION TO NUCLEOPHILIC ACYL SUBSTITUTION

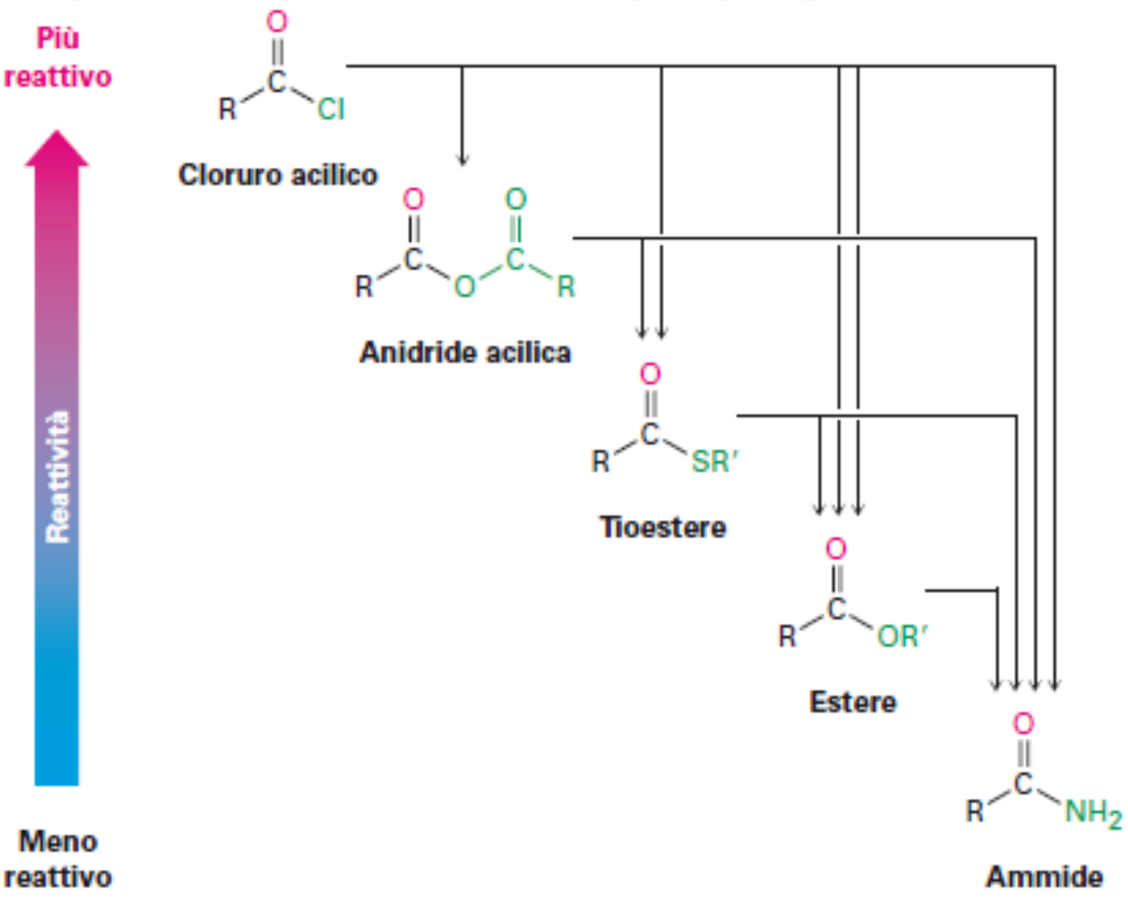
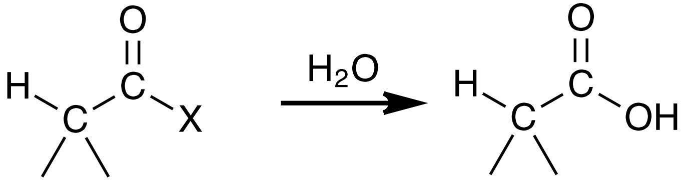


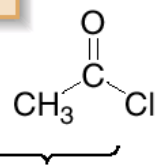
Figura 21.2 Interconversione di derivati degli acidi carbossilici. Un derivato acilico più reattivo può essere trasformato in uno meno reattivo, ma non vale il contrario.

All derivatives are hydrolysed to carboxylic acids



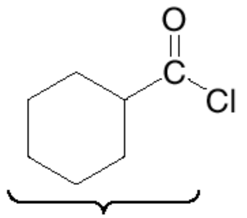
ACID CHLORIDES: NOMENCLATURE

Naming acid chlorides



derived from acet*ic acid*

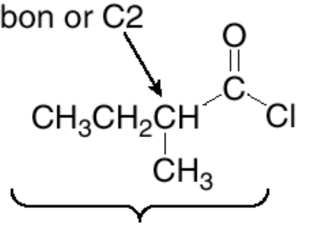
acetyl chloride



derived from cyclohexane*carboxylic acid*

cyclohexanecarbonyl chloride

α carbon or C2

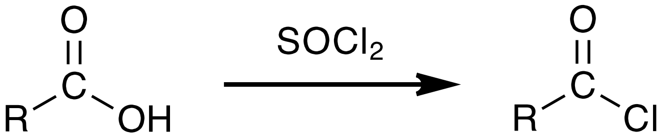


derived from
2-methylbutano*ic acid*
or
α-methylbutyr*ic acid*

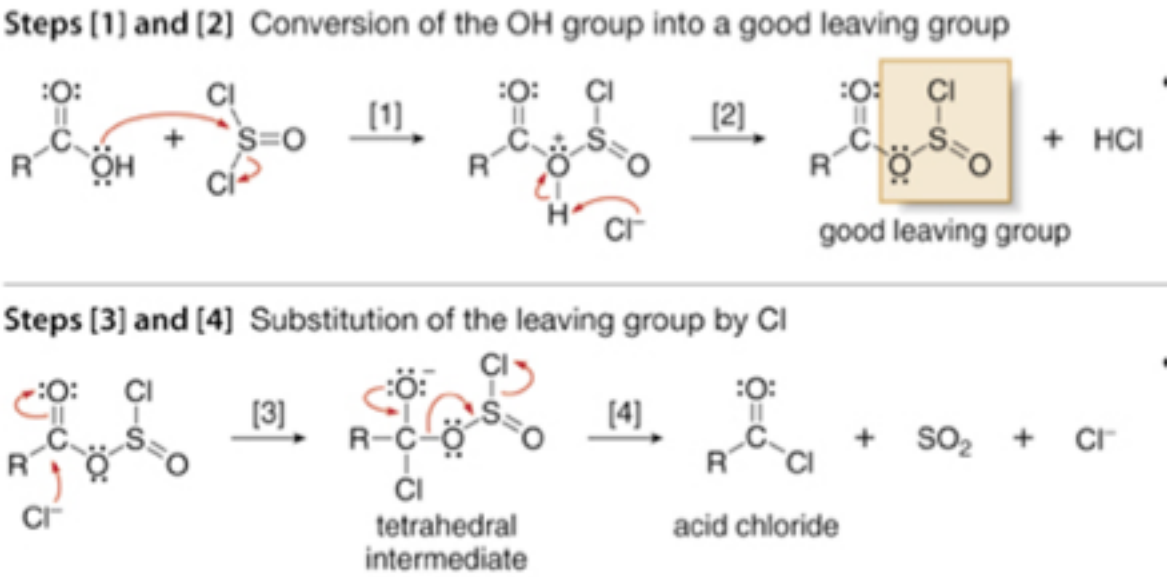
2-methylbutanoyl chloride
or
α-methylbutyryl chloride

ACID CHLORIDES: SYNTHESIS

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

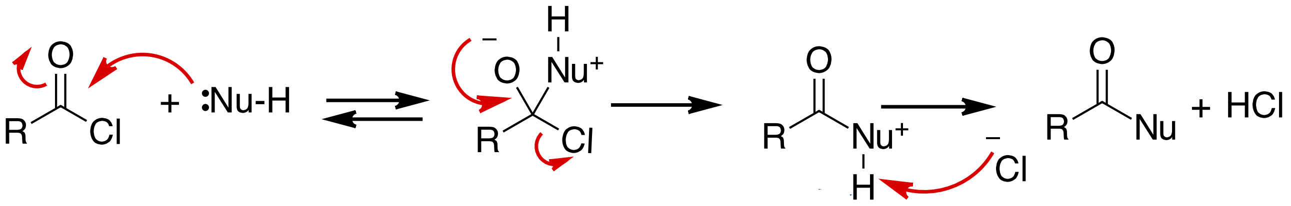


$$RCOOH \xrightarrow{SOCl_2} RCOCl$$

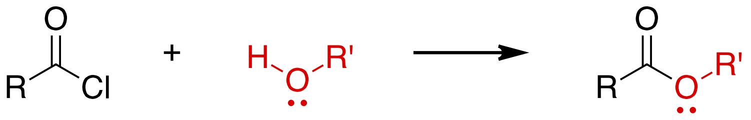


ACID CHLORIDES: REACTIONS

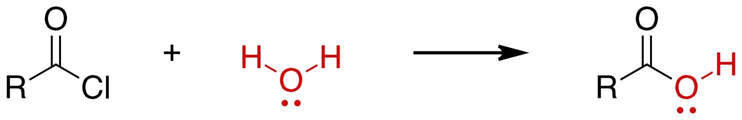
- Acyl chlorides are the most reactive among carboxylic acid derivatives
- A weak, non nucleophilic, base like pyridine is often added to the reaction mixture to remove the byproduct HCl.



anhydride

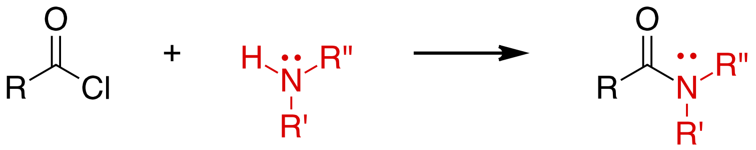


ester



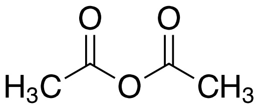
acid

(acid chlorides are readily decomposed by water)

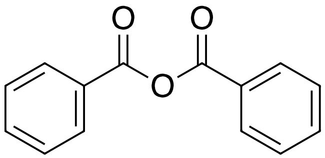


amide

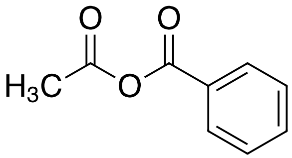
ANYDRIDES: NOMENCLATURE



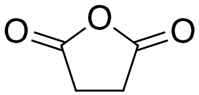
acetic
anhydride



benzoic
anhydride

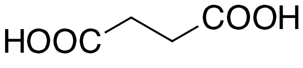


acetic benzoic
anhydride

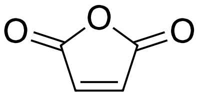


succinic
anhydride

↑

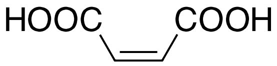


succinic
acid

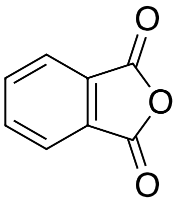


maleic
anhydride

↑

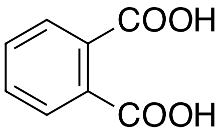


maleic
acid



phthalic
anhydride

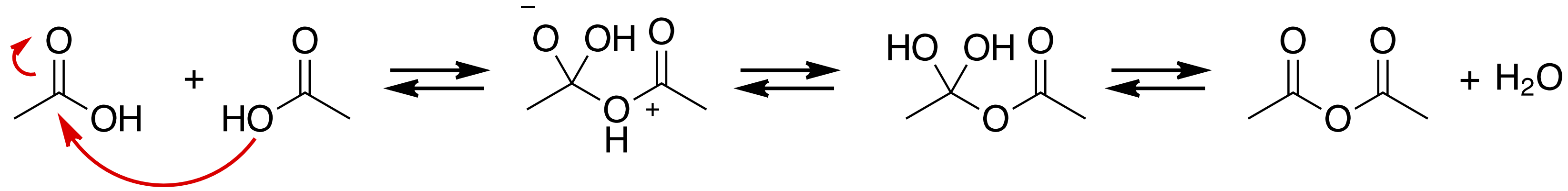
↑



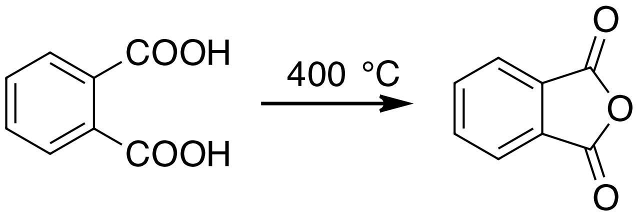
phthalic
acid

ANHYDRIDES: SYNTHESIS

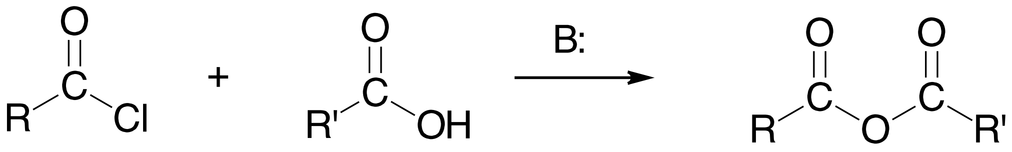
1. By dehydration of carboxylic acids at high temperatures (700-800 °C) and/or in the presence of condensing agents



Formation of cyclic anhydrides is easier

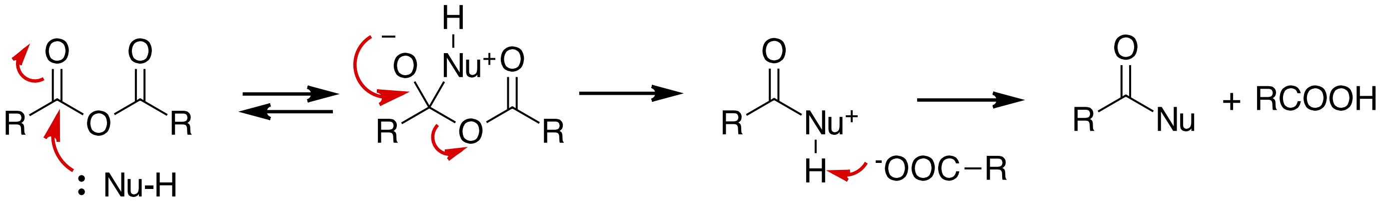


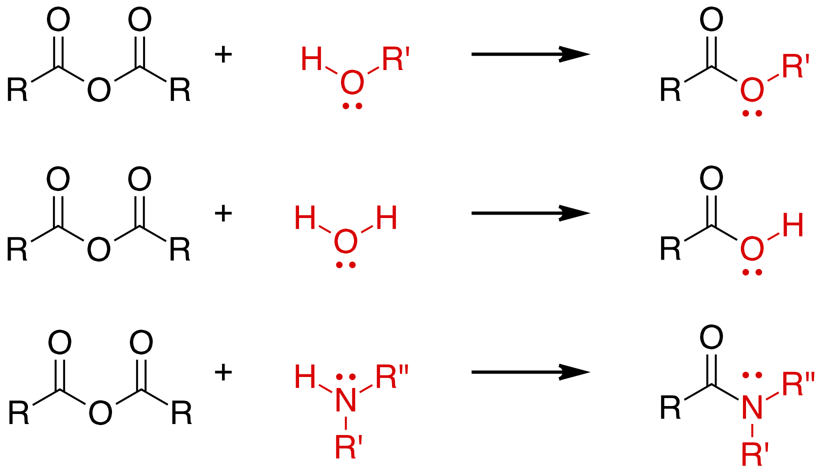
2. From an acid and an acyl chloride



ANHYDRIDES: REACTIONS

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





ester

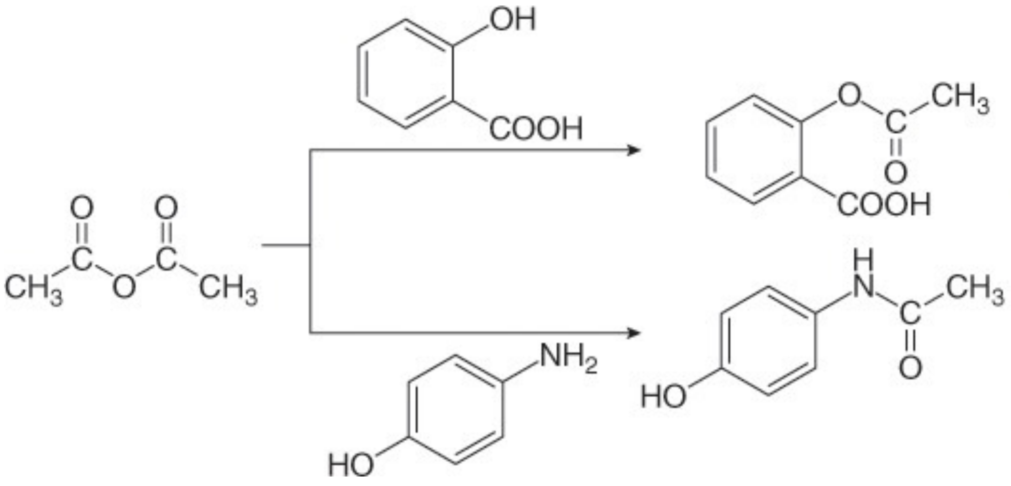
acid

(anhydrides are readily decomposed by water)

amide

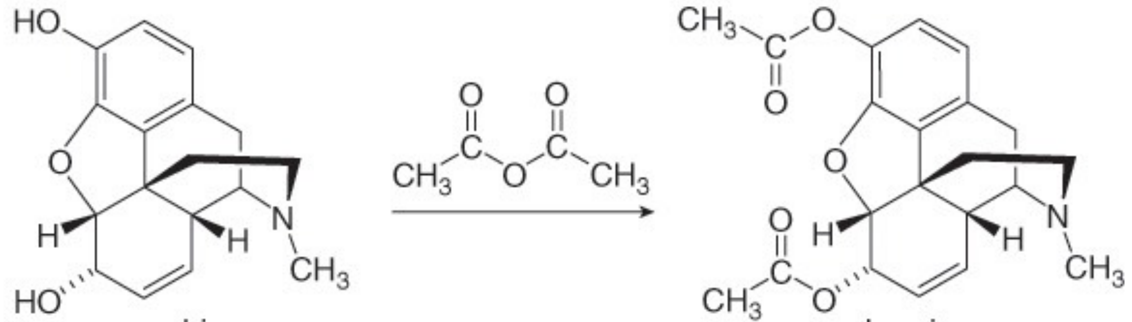
REACTIONS OF ANHYDRIDES

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



acetylsalicylic acid (aspirin)

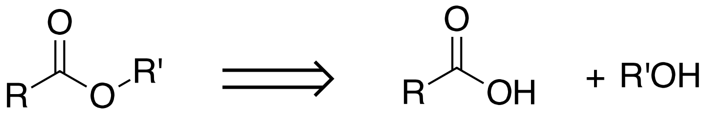
acetaminophen (active ingredient in Tylenol)



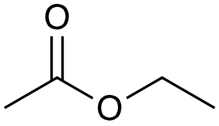
morphine

heroin

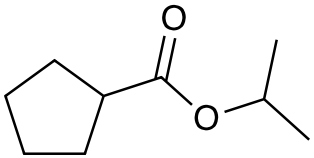
ESTERS: NOMENCLATURE



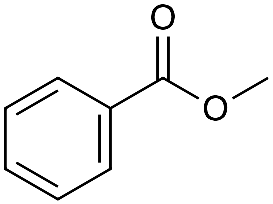
Esters are the (formal) condensation products of an acid and an alcohol



Ethyl acetate

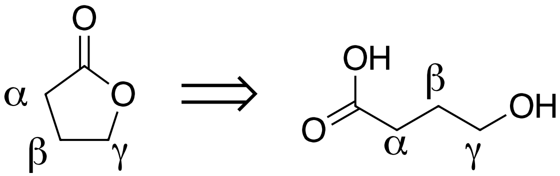


Isopropyl cyclopentanecarboxylate



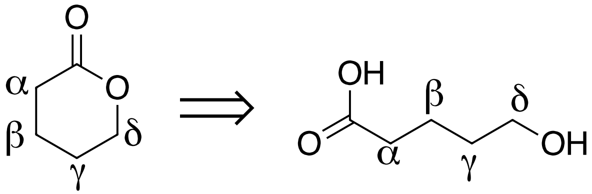
Methyl benzoate

Lactones are cyclic esters



Butyrolactone
(a γ-lactone)

4-hydroxybutanoic acid
(a γ-hydroxyacid)



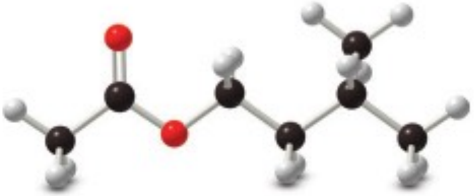
Valerolactone
(a δ-lactone)

5-hydroxypentanoic (valeric) acid
(a δ-hydroxyacid)

INTERESTING ESTERS

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

$CH_3COOCH_2CH_2CH(CH_3)_2$



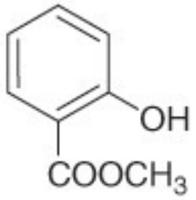
isoamyl acetate

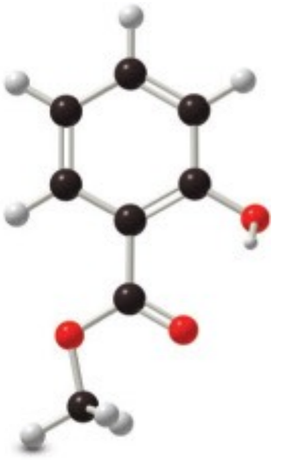
odor of banana

$CH_3CH_2CH_2COOCH_2CH_3$

ethyl butyrate

odor of pineapple

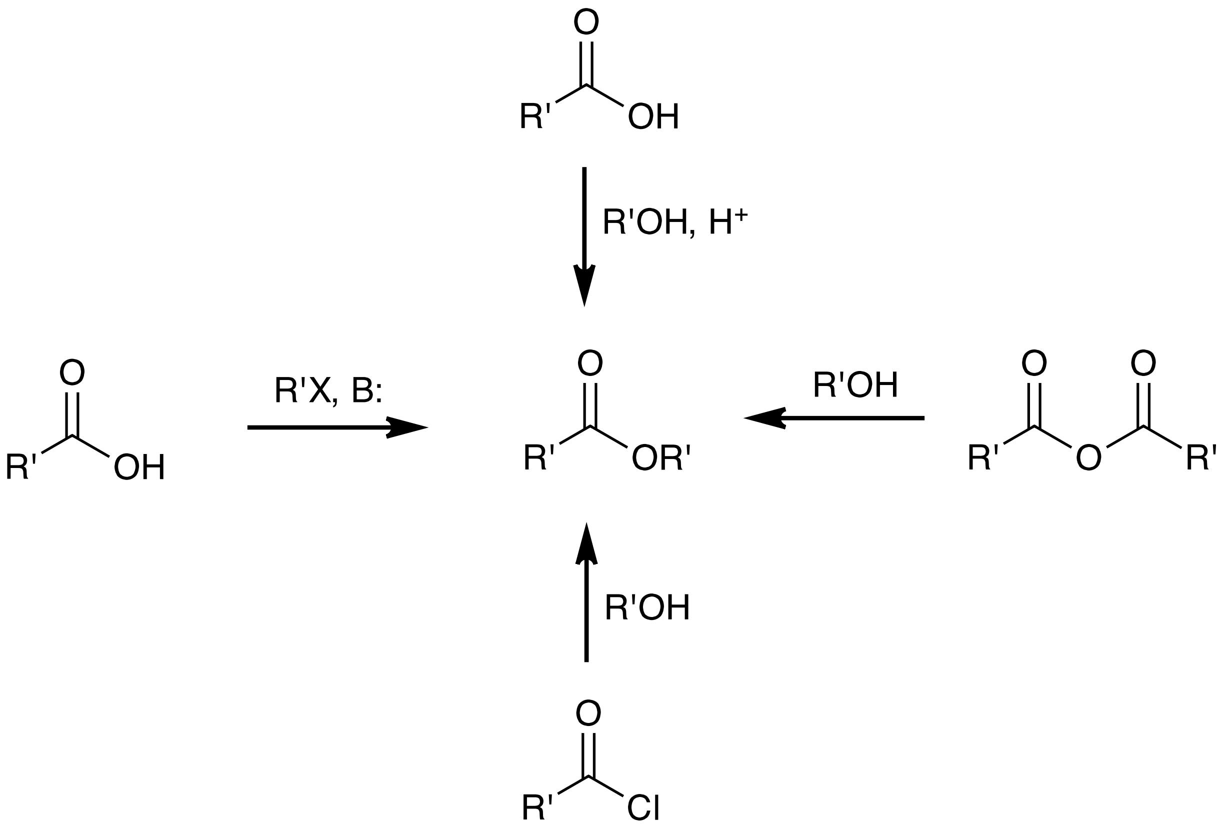




methyl salicylate

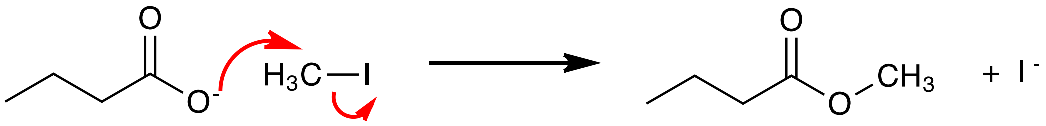
oil of wintergreen

ESTERS: SYNTHESIS



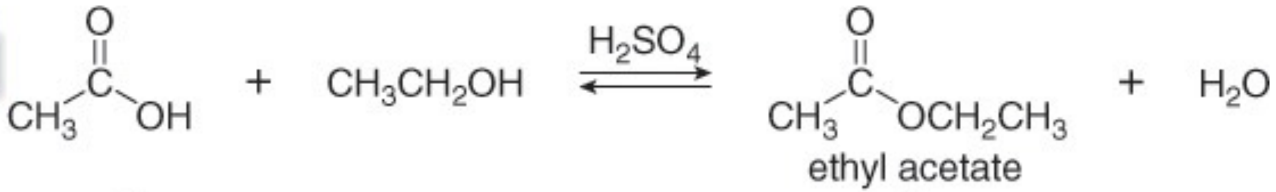
ESTERS FROM CARBOXYLIC ACIDS

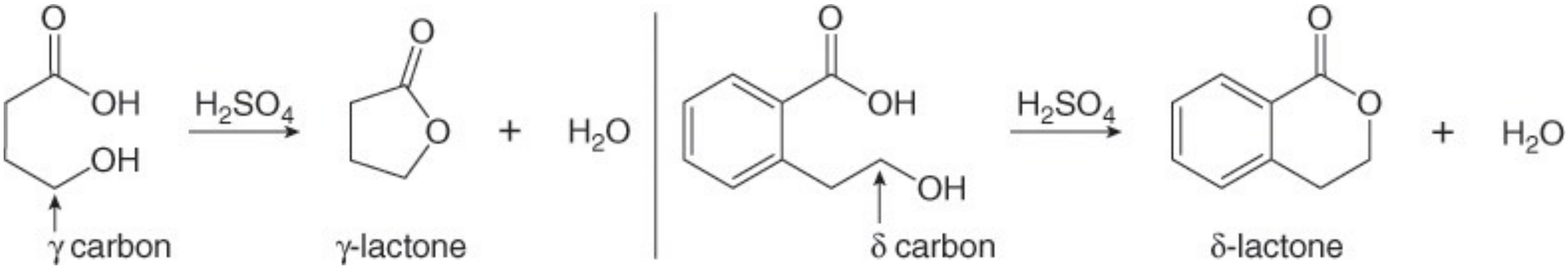
- SN2 (mainly for methyl esters).



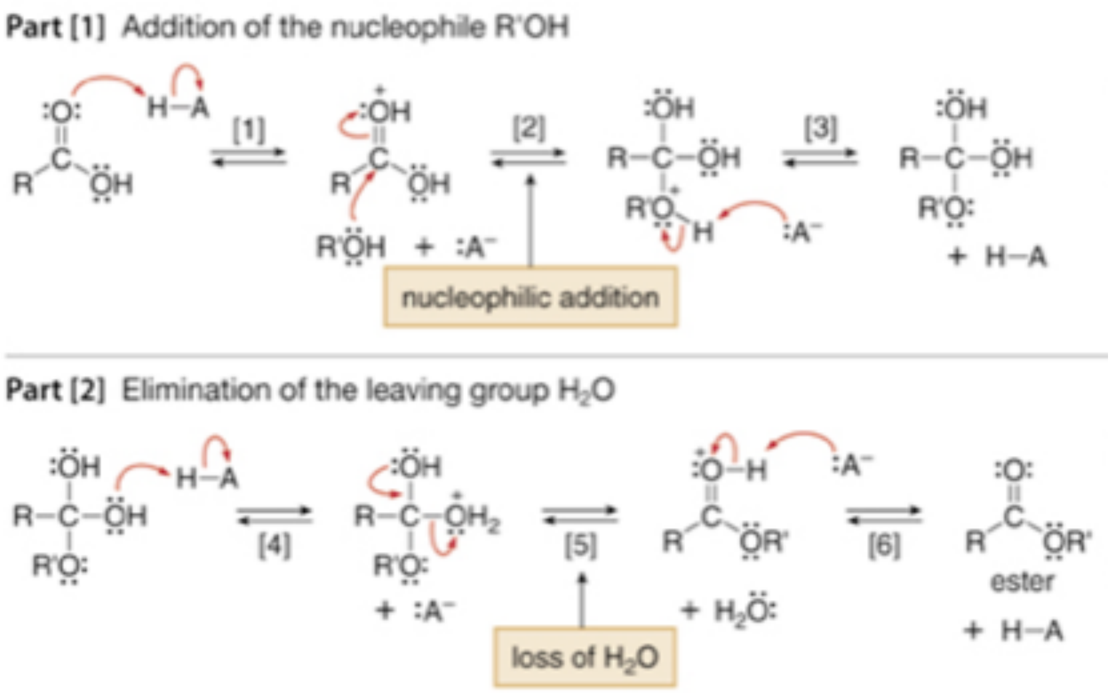
- Fischer esterification.

Examples





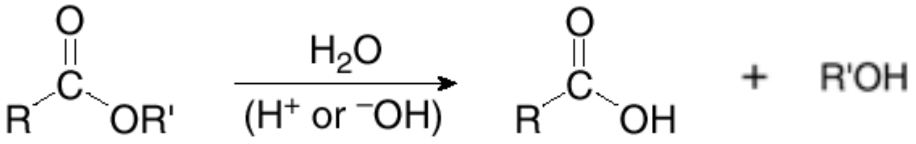
FISCHER ESTERIFICATION



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

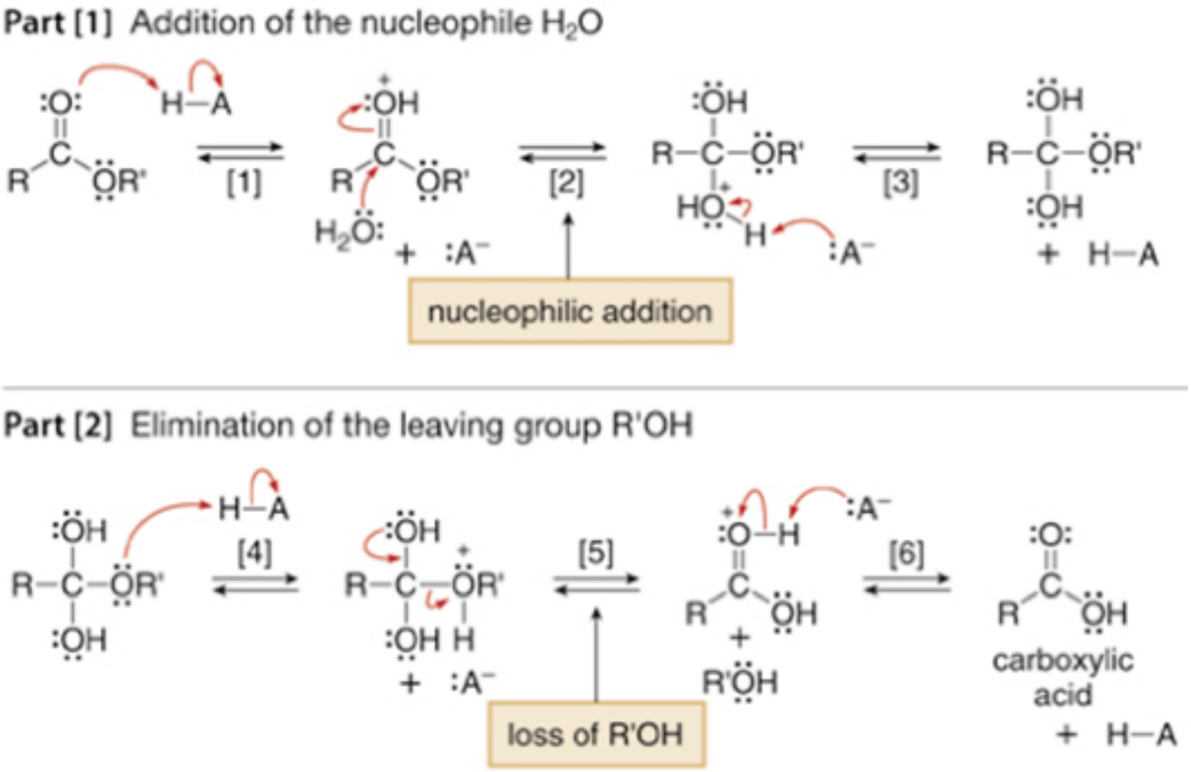
ESTERS: REACTIONS

Ester hydrolysis



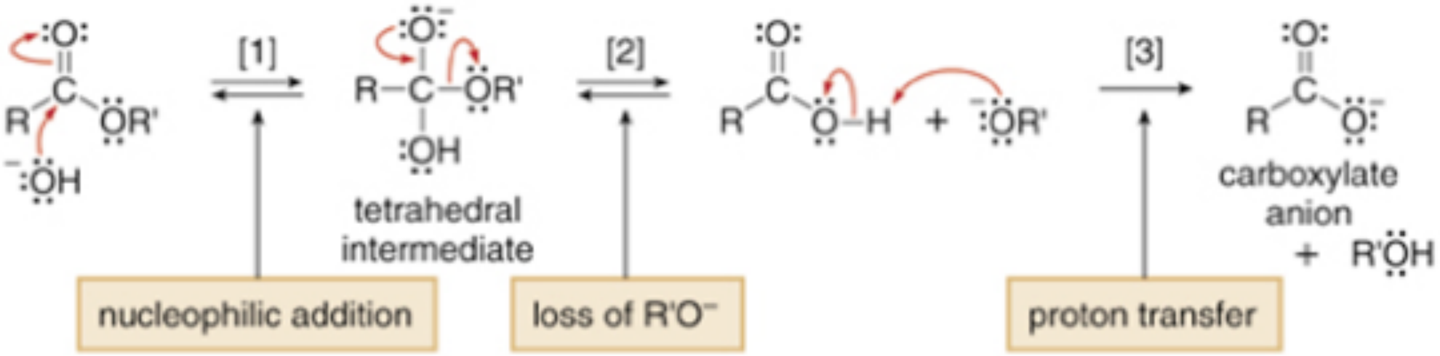
carboxylic acid
(in acid)

Acid hydrolysis



ESTERS: REACTIONS

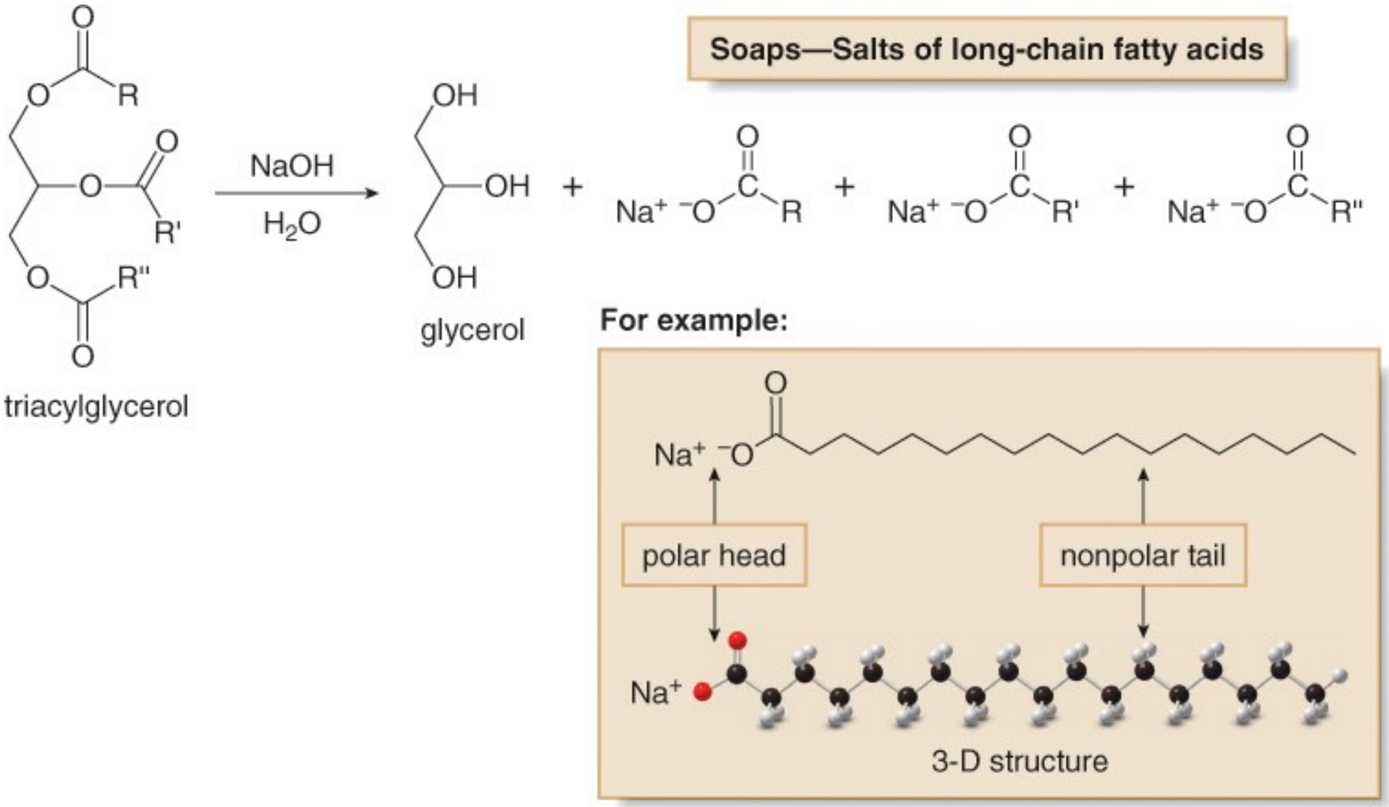
- Basic hydrolysis of an ester is also called saponification.



- 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.

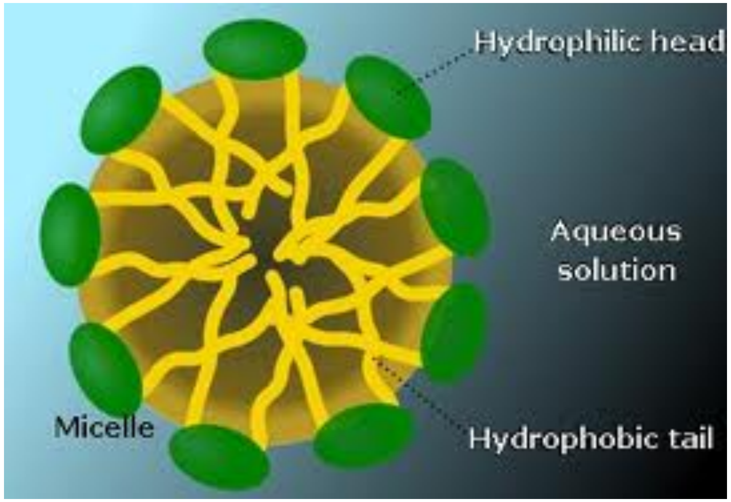
LIPID HYDROLYSIS

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.



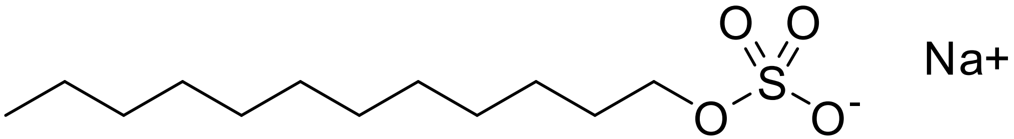
SOAP

- Soap molecules self-aggregate in water to form micelles

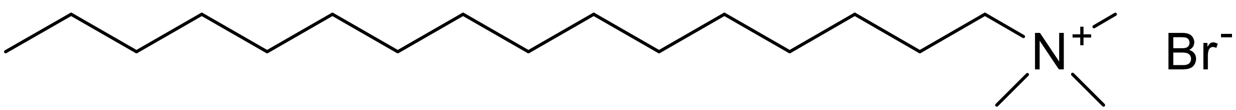


Micelles are water-soluble because the heads are hydrophilic.
Fats and oils from dirt dissolve in the hydorphobic core and are taken into solution

- Synthetic detergents

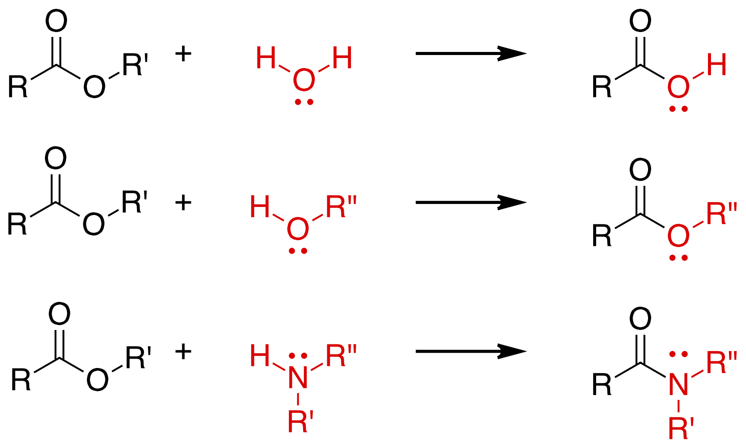


sodium laurylsulfate
SDS



cetyltrimethylammonium bromide
CTAB

ESTERS: OTHER REACTIONS

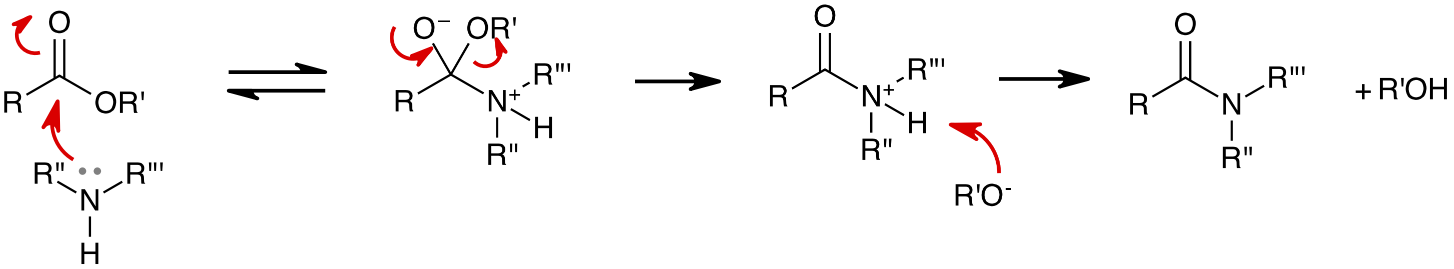


acid H^+, H_2O or OH^-

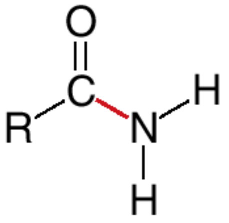
transesterification H^+, ROH or RO^-

amide

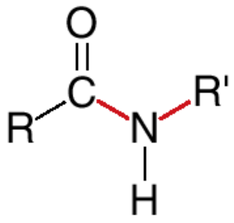
Mechanism of amide formation



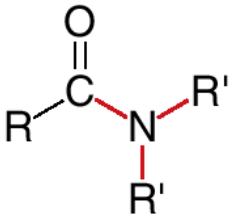
AMIDES: STRUCTURE



1° amide
1 C—N bond

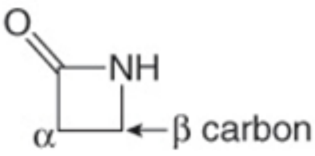


2° amide
2 C—N bonds

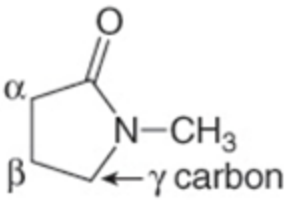


3° amide
3 C—N bonds

Lactams–Cyclic amides



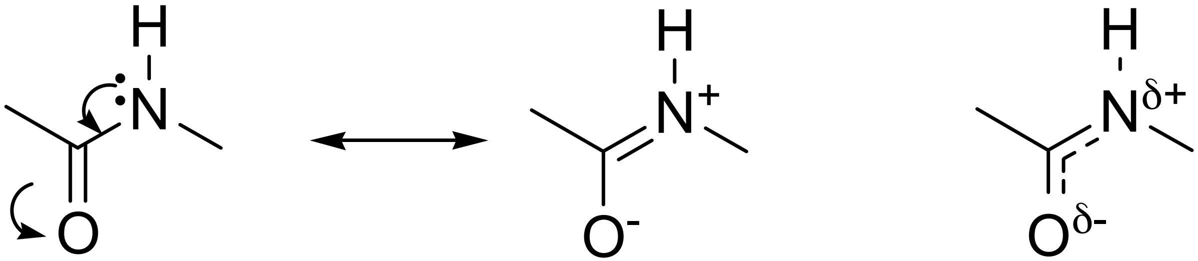
β-lactam



γ-lactam

AMIDES: STRUCTURE

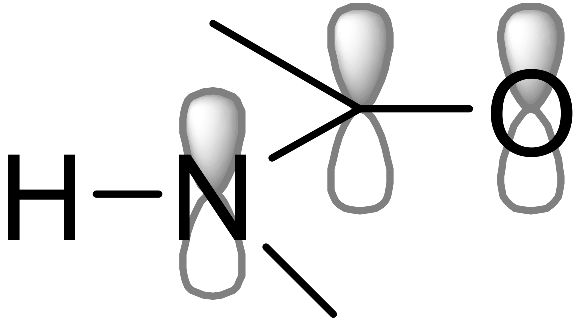
Amide resonance



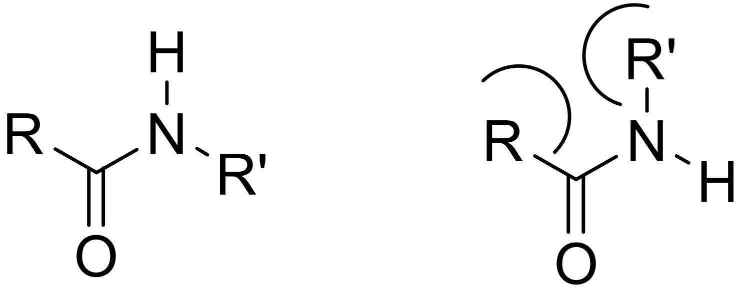
C, N, O: sp2

planar

restricted rotation

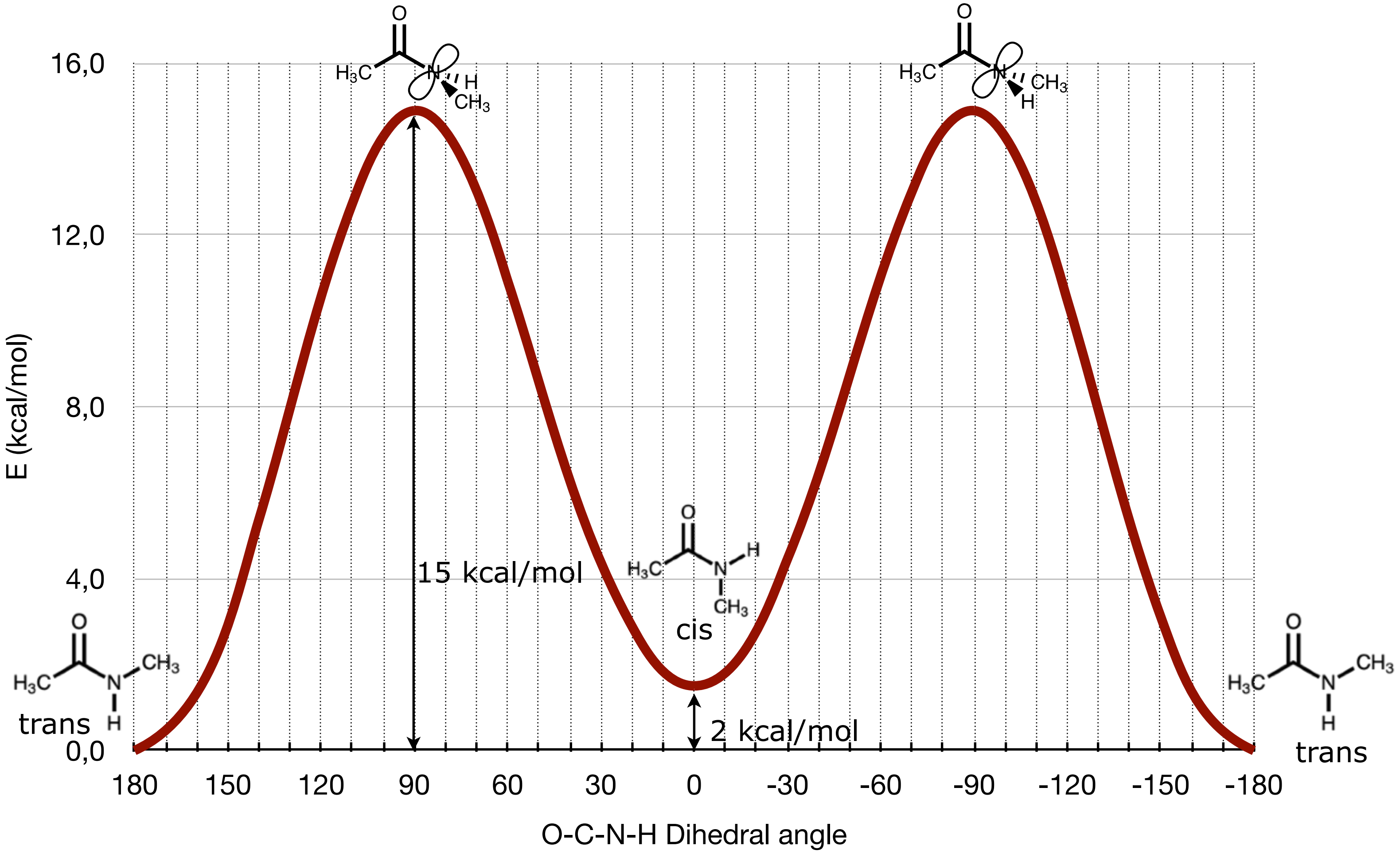


Trans amides are more stable than cis amides

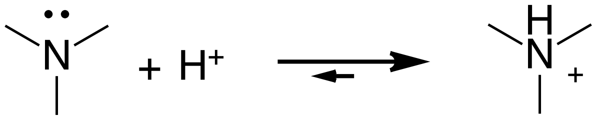


N-METHYLACETAMIDE

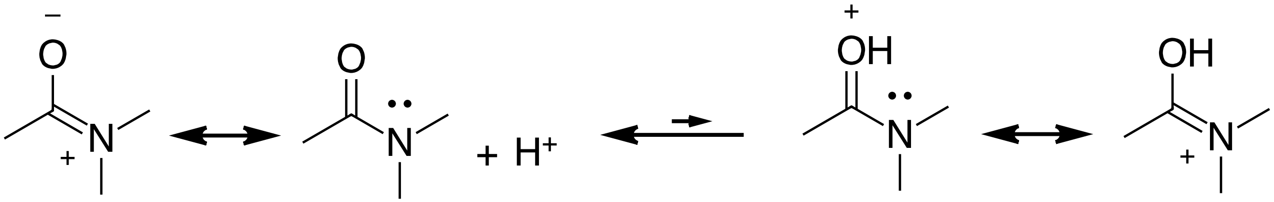
- The rotational barrier is unusually high in amides (15-20 kcal/mol) due to the partia double bond character of the C-N bond.
- Trans-amides are more stable than cis-amides.



AMIDES: BASICITY



pKa = 9

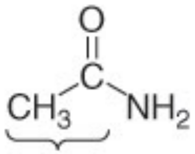


pKa = -1

AMIDES: NOMENCLATURE

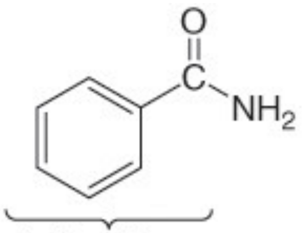
All 1° amides are named by replacing the *-ic acid*, *-oic acid*, or *-ylic acid* ending with the suffix amide.

Naming 1° amides



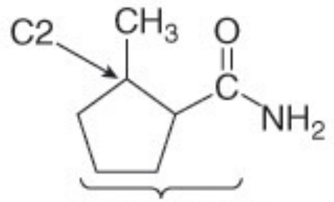
derived from acetic acid

acetamide



derived from benzoic acid

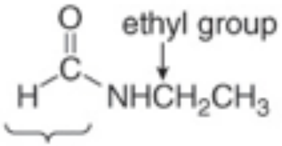
benzamide



derived from 2-methylcyclopentanecarbox*ylic acid*

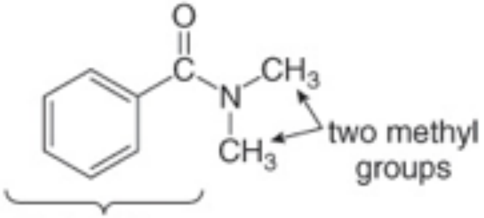
2-methylcyclopentanecarboxamide

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



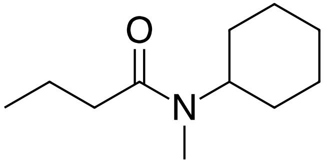
derived from form*ic acid*

N-ethylformamide



derived from benzo*ic acid*

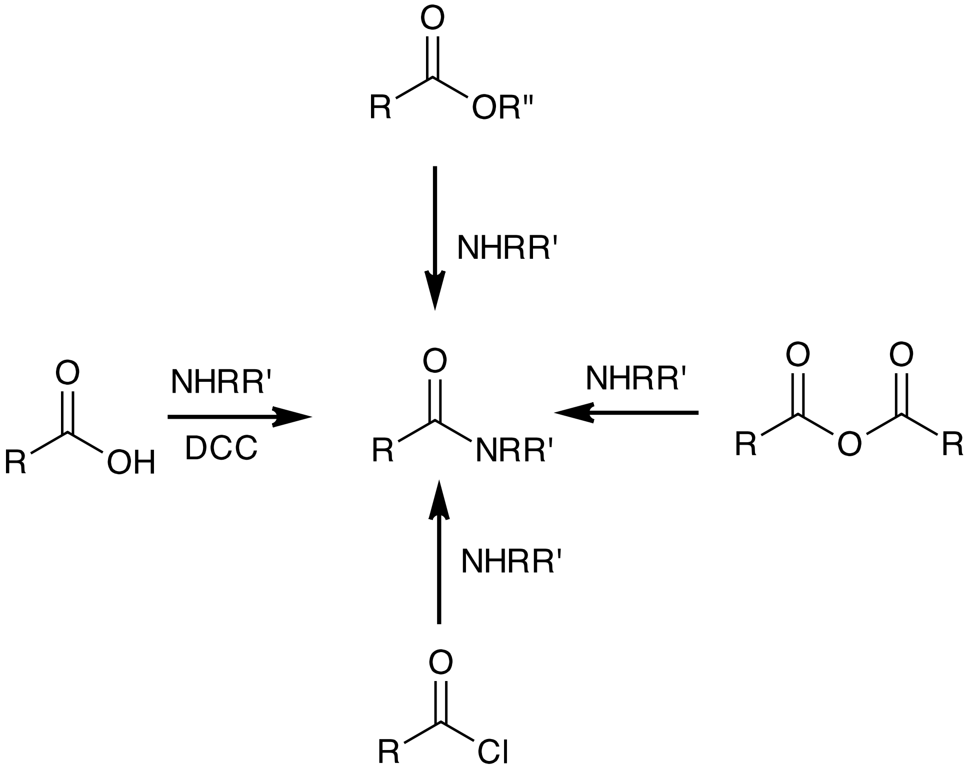
N,N-dimethylbenzamide



derived from butanoic acid

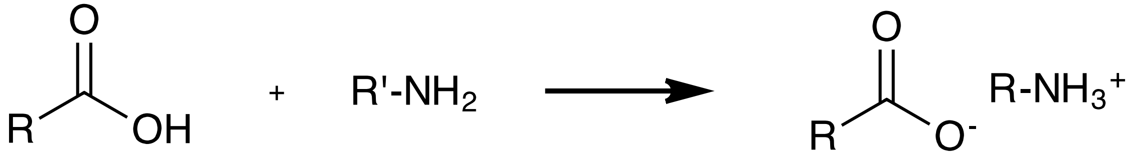
N-cyclohexyl-*N*-methylbutanamide

SYNTHESIS OF AMIDES

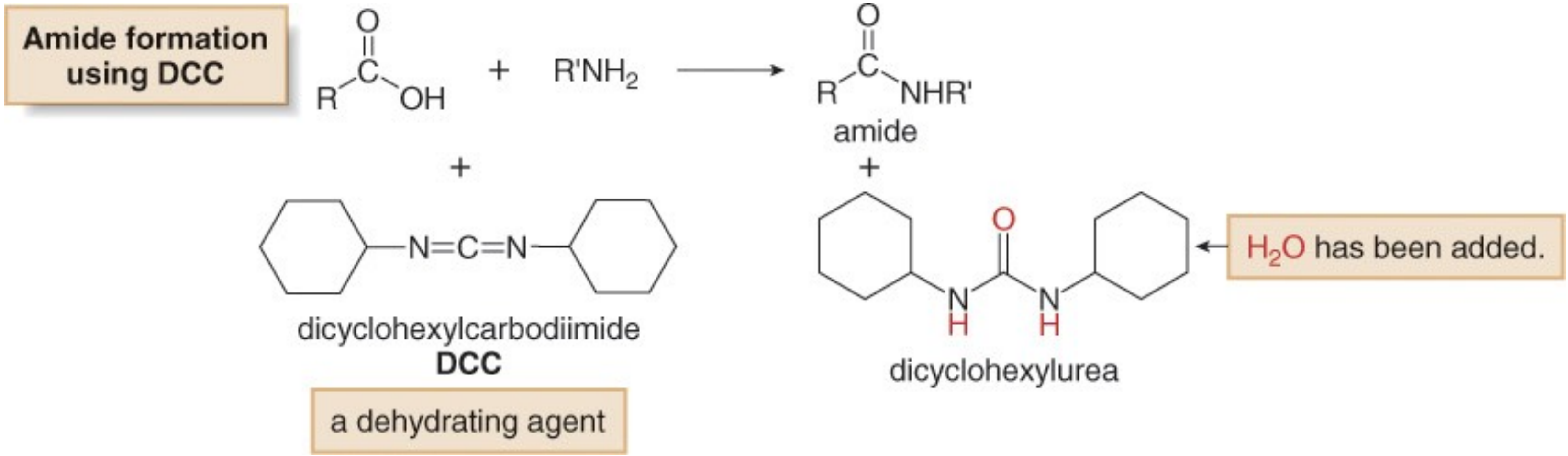


AMIDES FROM CARBOXYLIC ACIDS

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

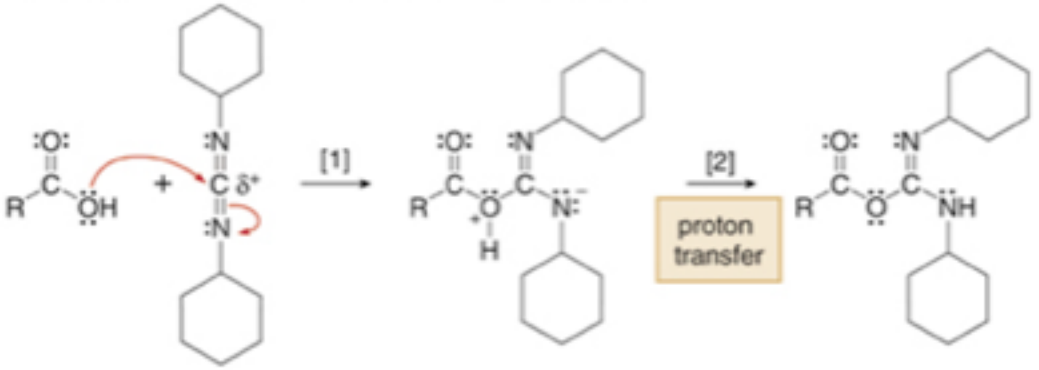


Carboxylic acids are converted into amides by reaction with NH_3 or an amine in the presence of a condensing agent (DCC).

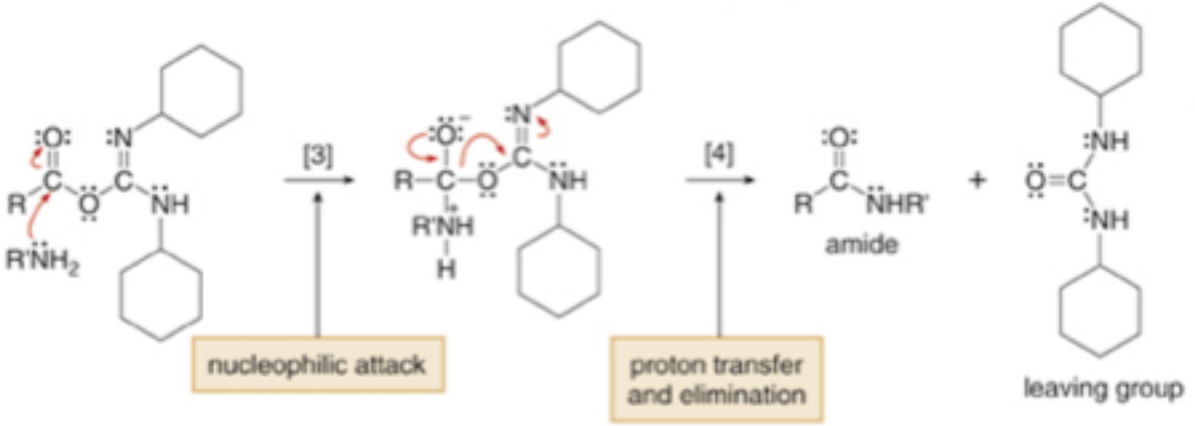


REACTIONS OF CARBOXYLIC ACIDS: AMIDES

Part [1] Conversion of OH into a better leaving group



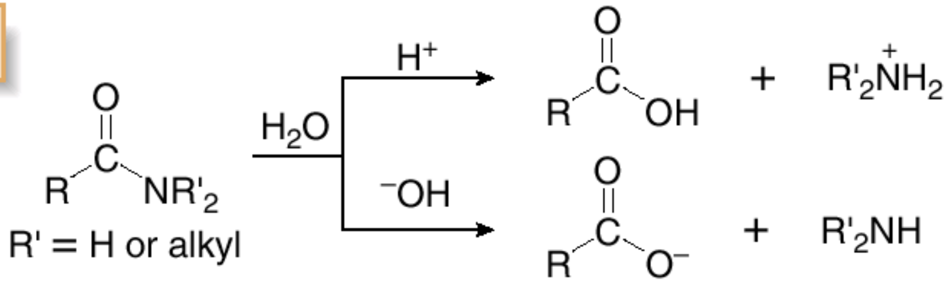
Part [2] Addition of the nucleophile and loss of the leaving group



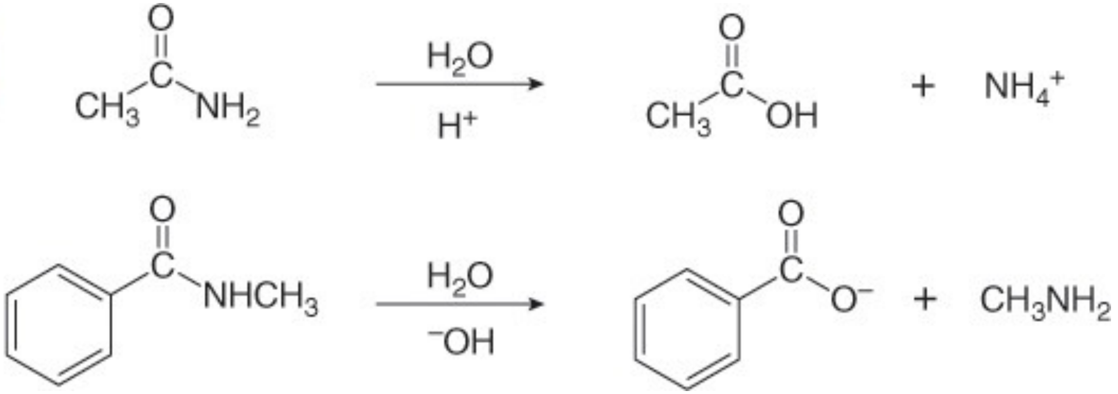
AMIDES: REACTIONS

Amides are the least reactive of the carboxylic acid derivatives.

Amide hydrolysis

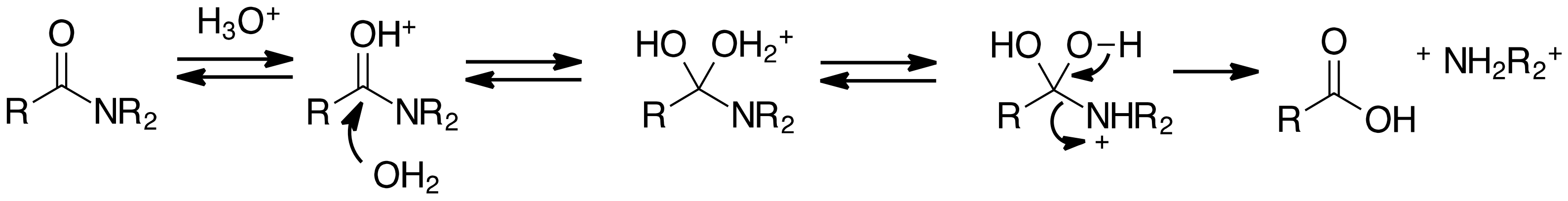


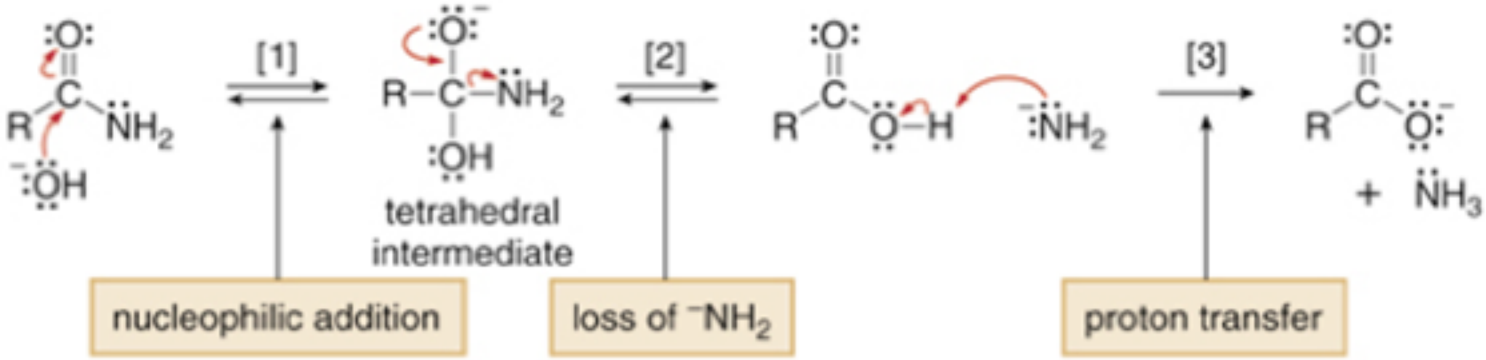
Examples



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.

SUMMARY OF NUCLEOPHILIC ACYL SUBSTITUTIONS

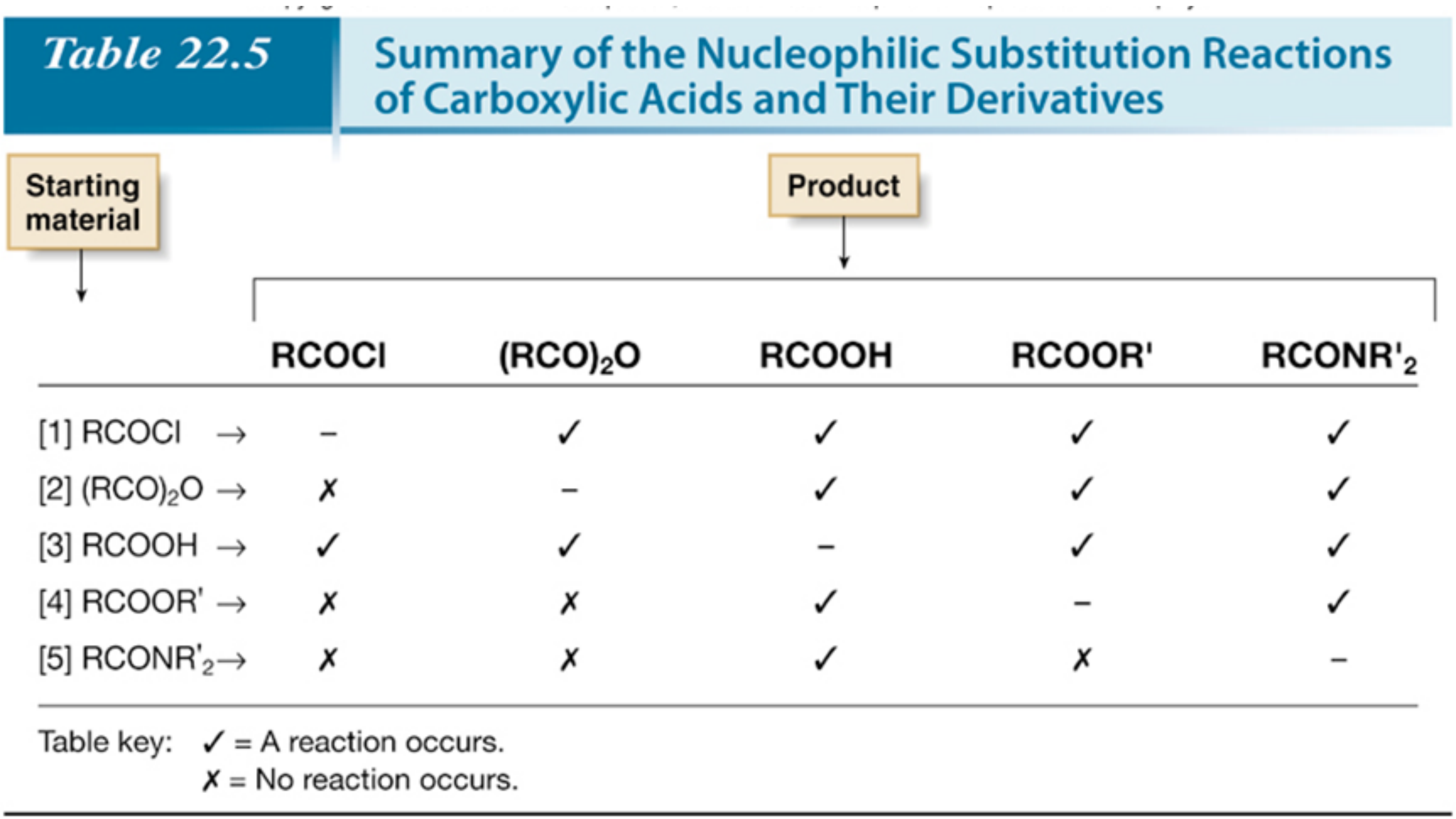


Table 22.5 Summary of the Nucleophilic Substitution Reactions of Carboxylic Acids and Their Derivatives

Starting material	Product: RCOCl	$(RCO)_2O$	RCOOH	RCOOR'	$RCONR'_2$
[1] RCOCl →	–	✓	✓	✓	✓
[2] $(RCO)_2O$ →	✗	–	✓	✓	✓
[3] RCOOH →	✓	✓	–	✓	✓
[4] RCOOR' →	✗	✗	✓	–	✓
[5] $RCONR'_2$ →	✗	✗	✓	✗	–

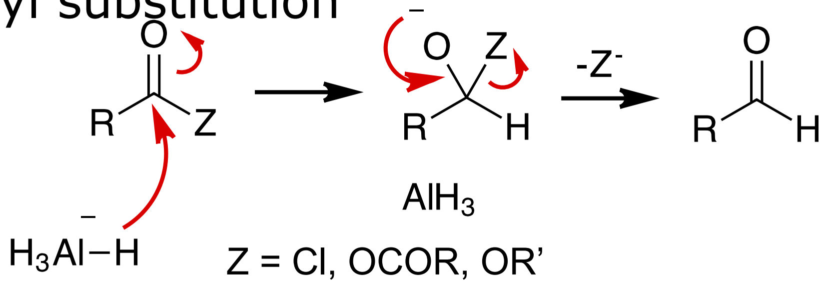
Table key: ✓ = A reaction occurs.
✗ = No reaction occurs.

REDUCTION: ACID CHLORIDES, ANHYDRIDES AND ESTERS

Acid chlorides, anhydrides and esters are reduced to 1^{ry} alcohols by Al hydrides, e.g. $LiAlH_4$

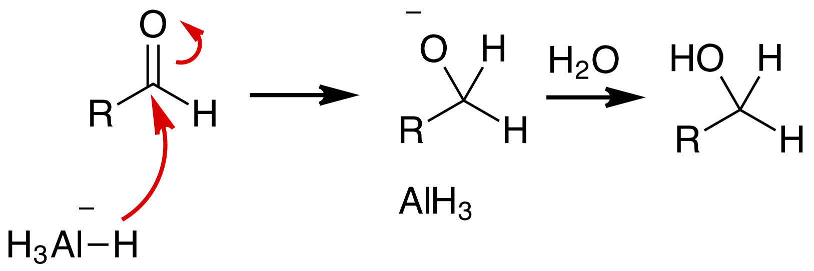
A two-step reaction:

1. Nucleophilic acyl substitution



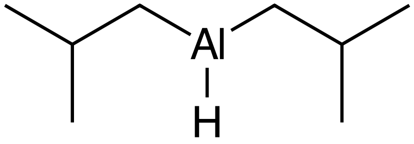
Z = Cl, OCOR, OR’

2. Nucleophilic addition



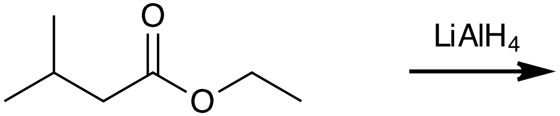
REDUCTION OF ACID CHLORIDES, ANHYDRIDES AND ESTERS

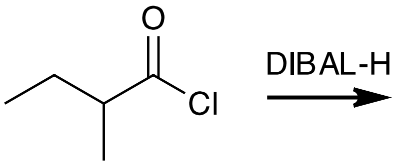
- $LiAlH_4$ is a strong reducing agent that reduces acids, acid chlorides, anhydrides and esters to primary alcohols.
- Diisobutylaluminum hydride ($[(CH_3)_2CHCH_2]_2AlH$, abbreviated DIBAL-H, has two bulky isobutyl groups which makes this reagent less reactive than $LiAlH_4$.
- DIBAL-H reduces acid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

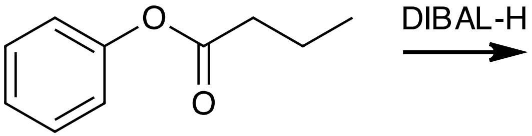


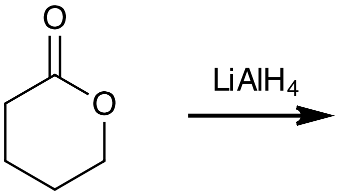
DIBAL-H

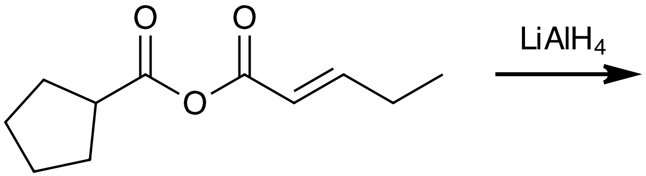
REDUCTION OF ACID CHLORIDES, ANHYDRIDES AND ESTERS

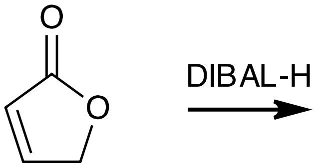












REDUCTION OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

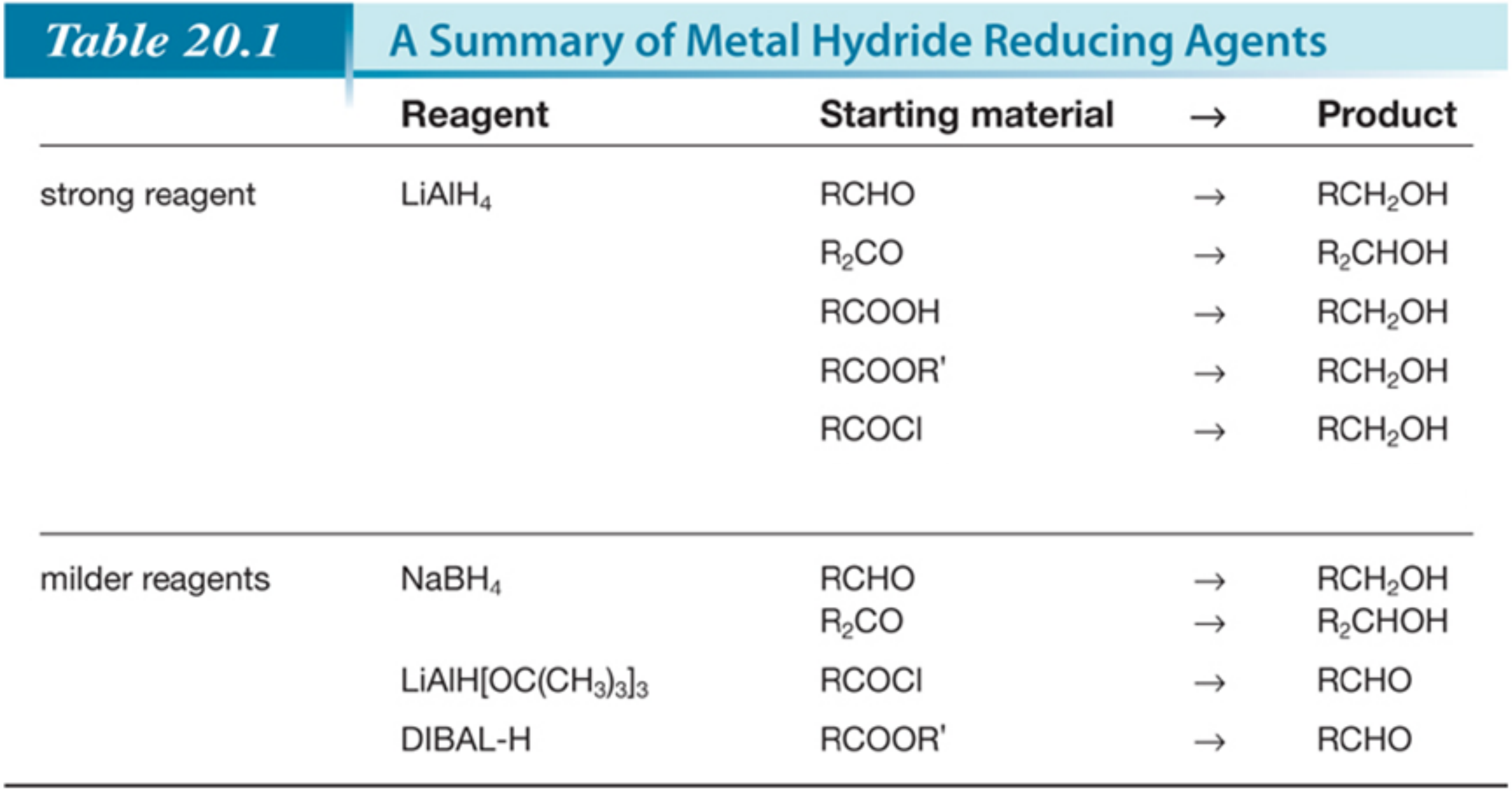
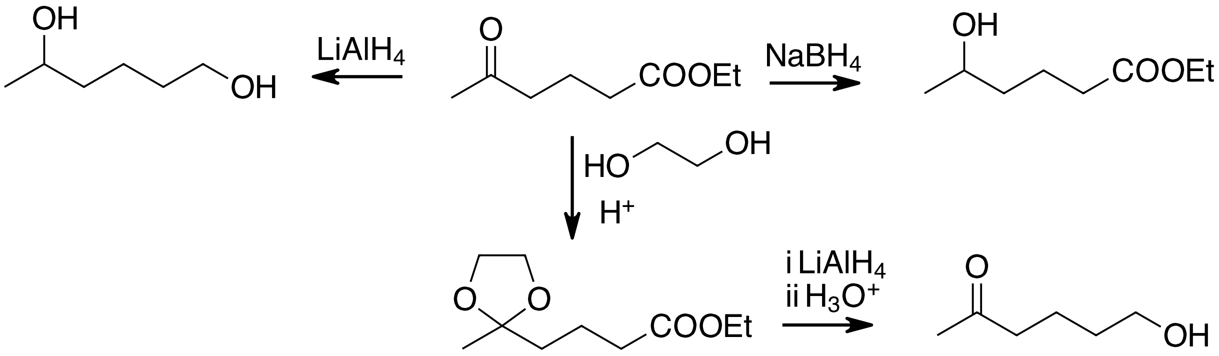


Table 20.1 A Summary of Metal Hydride Reducing Agents

	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 R_2CO	→ →	RCH_2OH R_2CHOH
	$LiAlH[OC(CH_3)_3]_3$	RCOCl	→	RCHO
	DIBAL-H	RCOOR'	→	RCHO

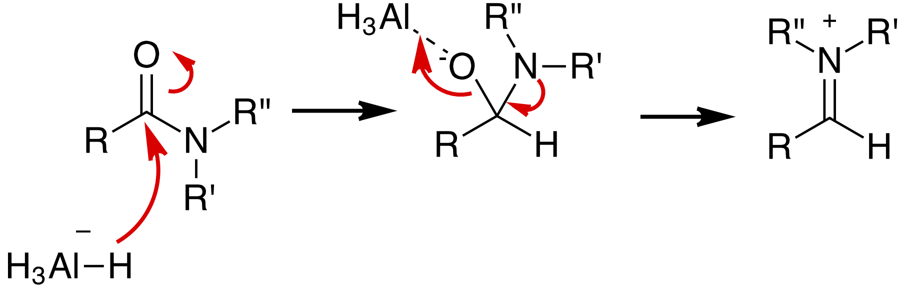
SELECTIVE REDUCTION OF CARBONYL COMPOUNDS



REDUCTION OF AMIDES

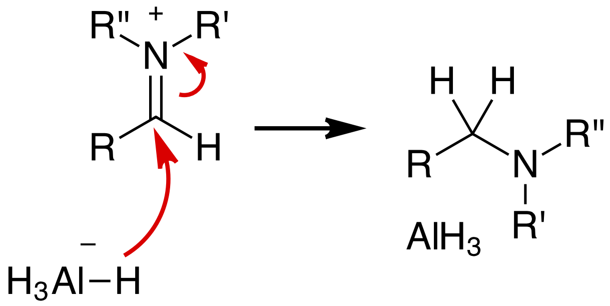
- Amides are reduced to amines by Al hydrides, e.g. $LiAlH_4$
- A two-step reaction:

Nucleophilic addition-elimination

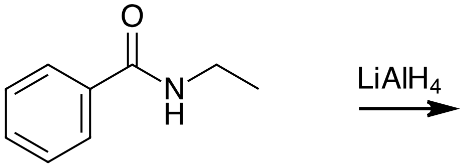


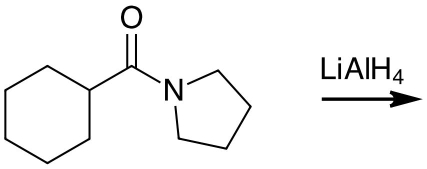
imminium ion

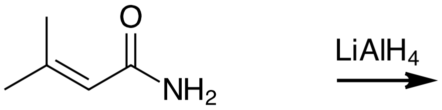
Nucleophilic addition

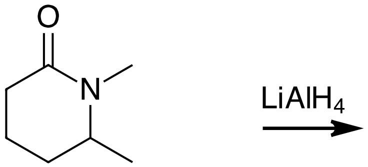


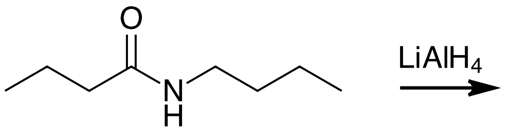
REDUCTION OF AMIDES

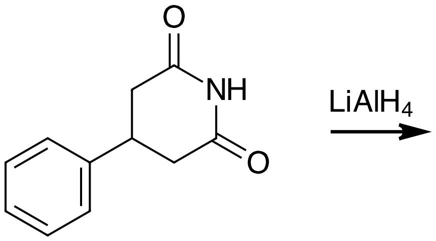








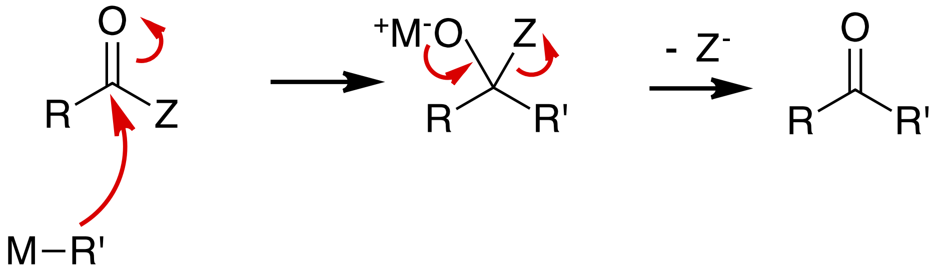




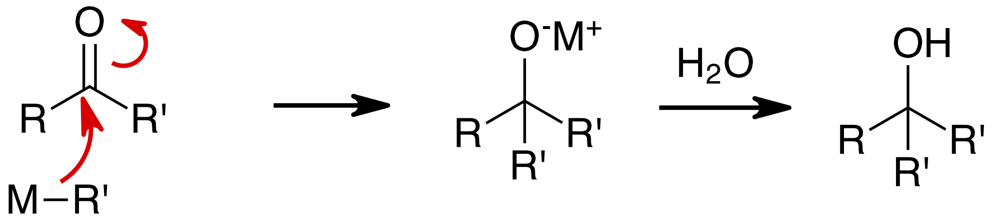
REACTION OF ORGANOMETALLIC REAGENTS WITH CARBOXYLIC ACID DERIVATIVES.

- 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

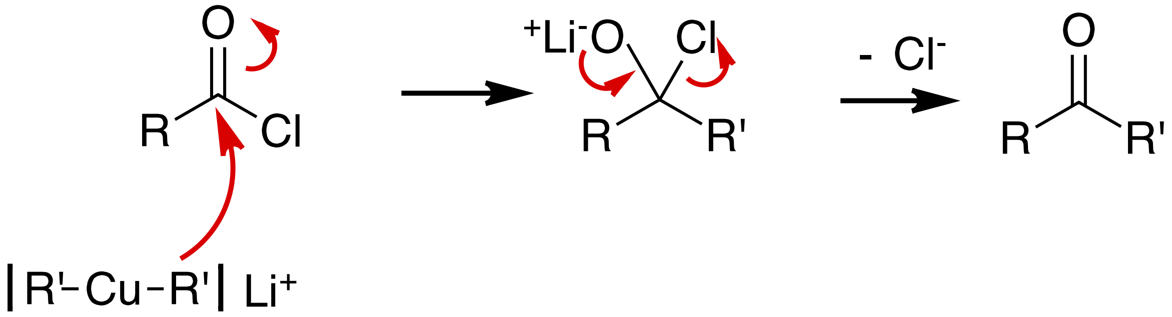


REACTION OF ORGANOMETALLIC REAGENTS WITH CARBOXYLIC ACID DERIVATIVES.

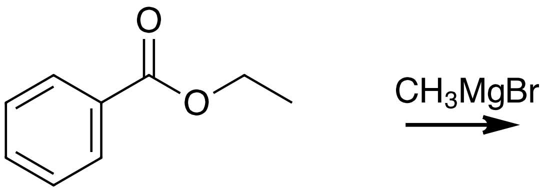
- Organocuprates (R'_2CuLi) are less reactive than organolithium and organomagnesium compounds.

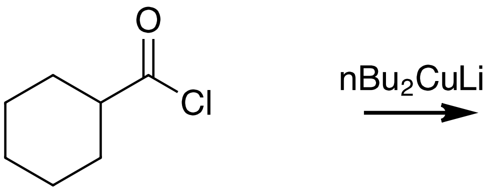
- R'_2CuLi react only with acid chlorides, which are the more reactive among carboxylic acid derivatives, to give a ketone as the product.

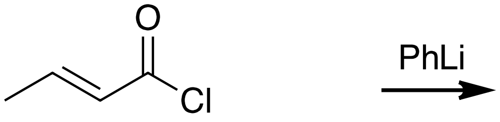
- Esters do not react with R'_2CuLi.

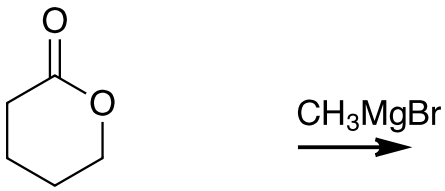


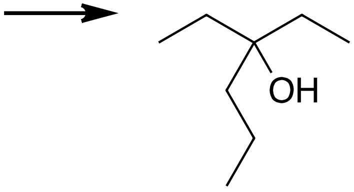
REACTION OF ORGANOMETALLIC REAGENTS WITH CARBOXYLIC ACID DERIVATIVES.

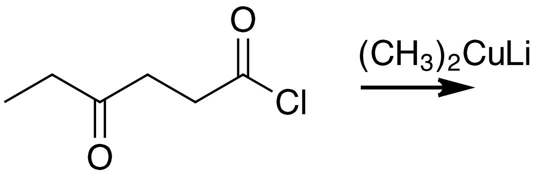




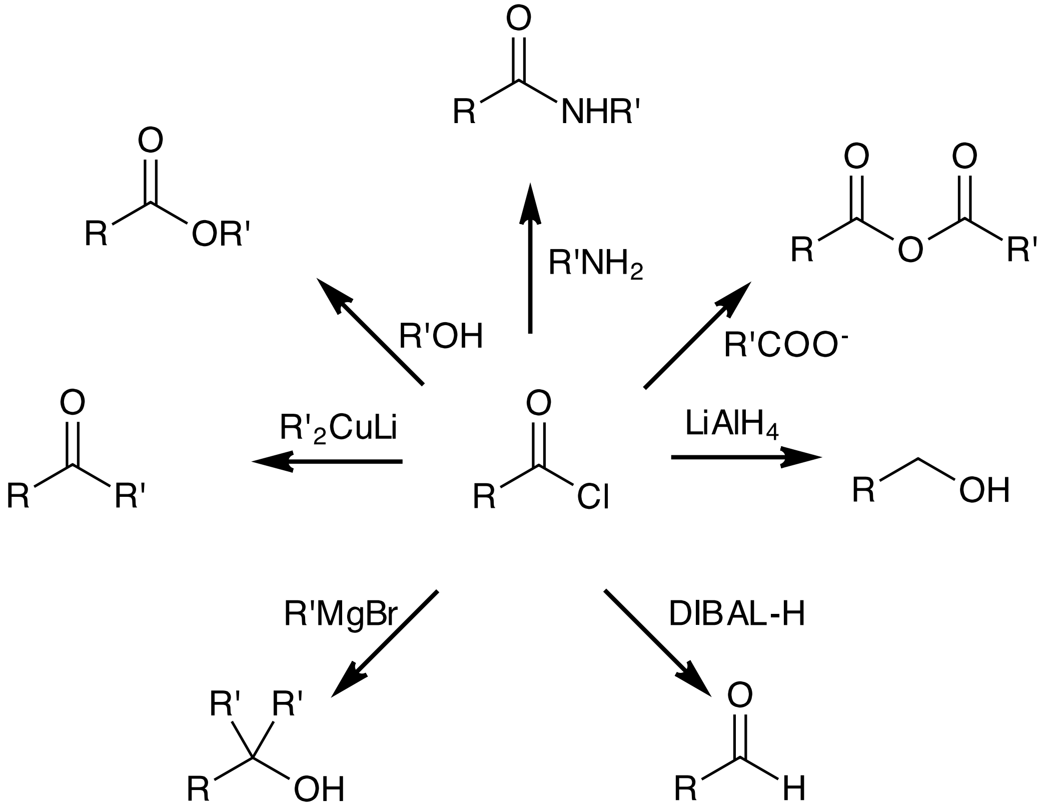




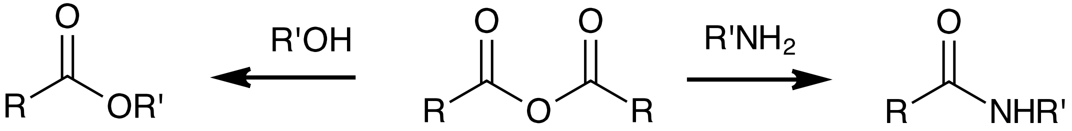




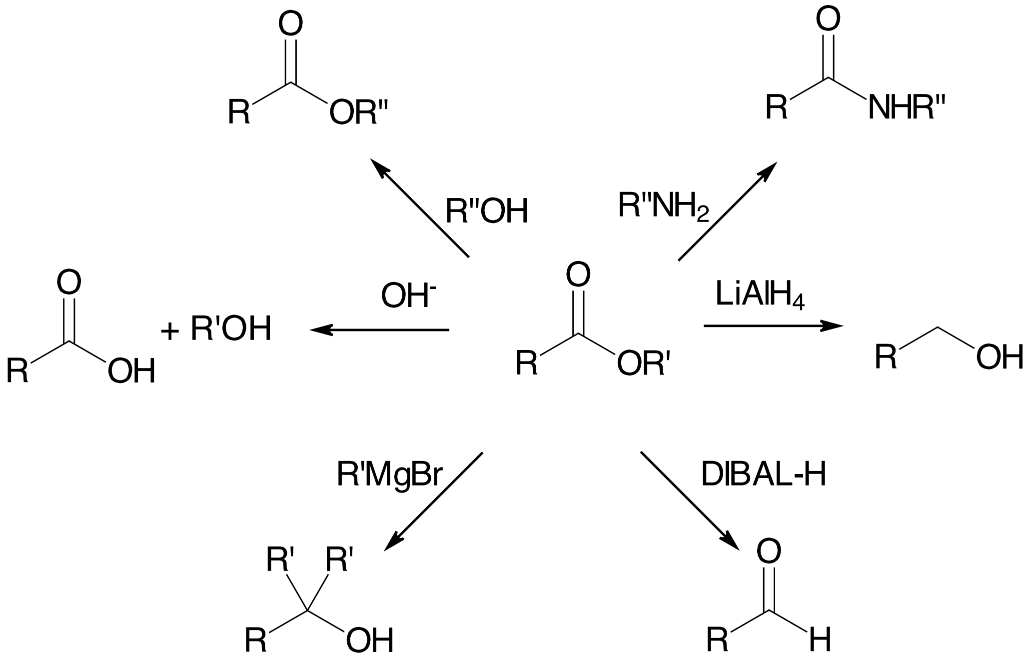
SUMMARY: IMPORTANT REACTIONS OF ACID CHLORIDES.



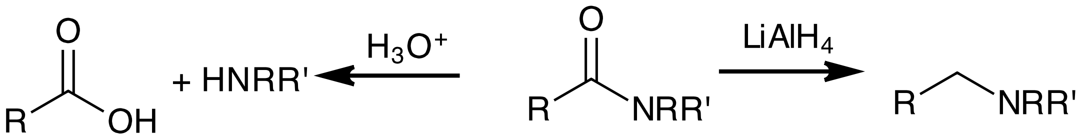
SUMMARY: IMPORTANT REACTIONS OF ANHYDRIDES.



SUMMARY: IMPORTANT REACTIONS OF ESTERS.



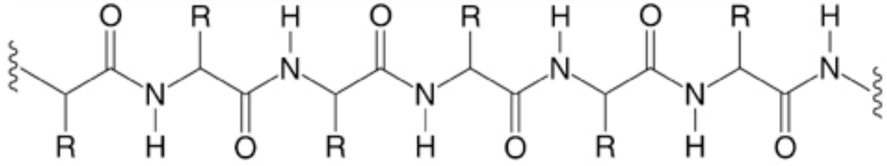
SUMMARY: IMPORTANT REACTIONS OF AMIDES.



NATURAL AND SYNTHETIC FIBERS

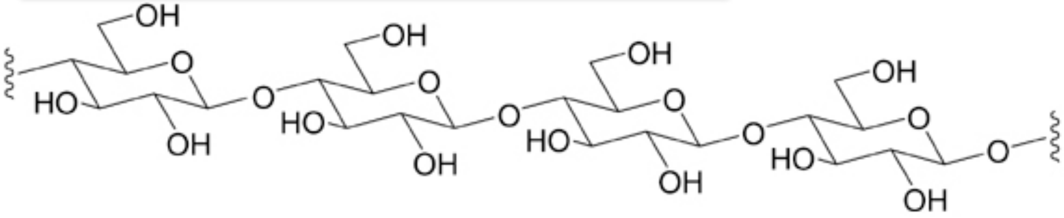
- Fibers like wool and silk are proteins obtained from animals.
- Cotton and linen are derived from carbohydrates having the general structure of cellulose.

Wool and silk—Proteins with many amide bonds



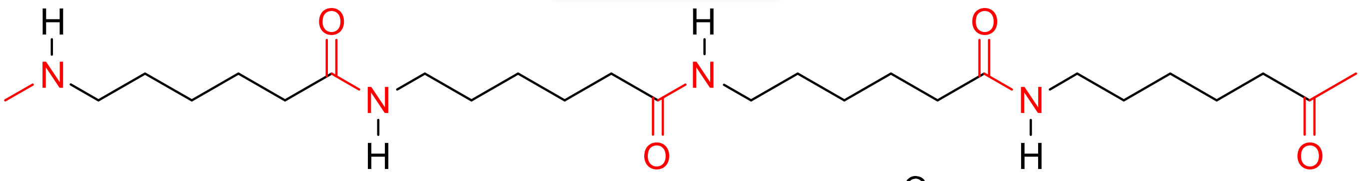
R groups contain C, H, and functional groups like NH_2, COOH, OH, and SH.

Cotton and linen—Carbohydrates like cellulose

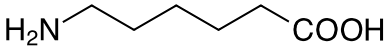


NATURAL AND SYNTHETIC FIBERS: NYLON—A POLYAMIDE

Nylon 6

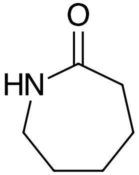


monomers:



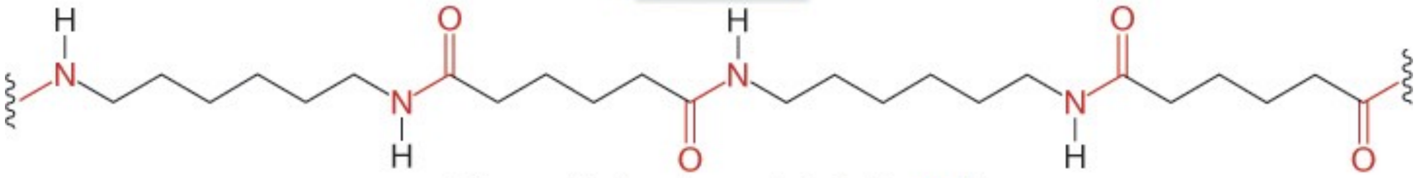
6-aminohexanoic acid

or



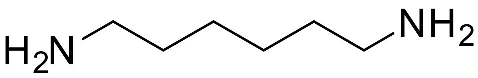
ε-caprolactam

Nylon 6,6

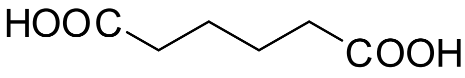


[The amide bonds are labeled in red.]

monomers:



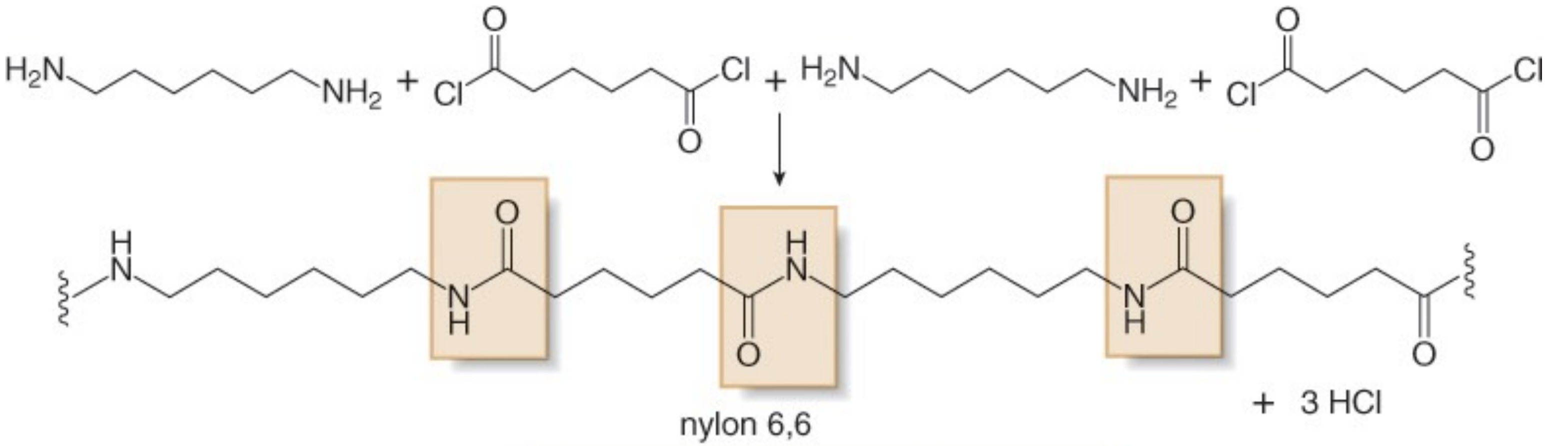
hexamethylenediamine



adipic acid

NATURAL AND SYNTHETIC FIBERS: NYLON—A POLYAMIDE

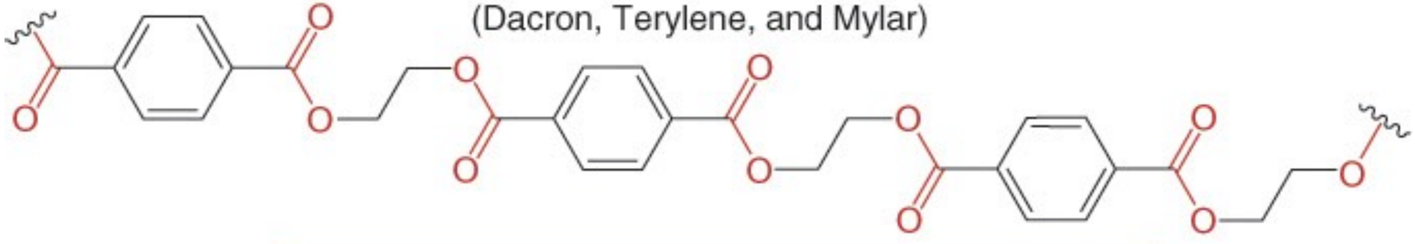
- Nylon is a condensation polymer



Three new amide bonds are shown.

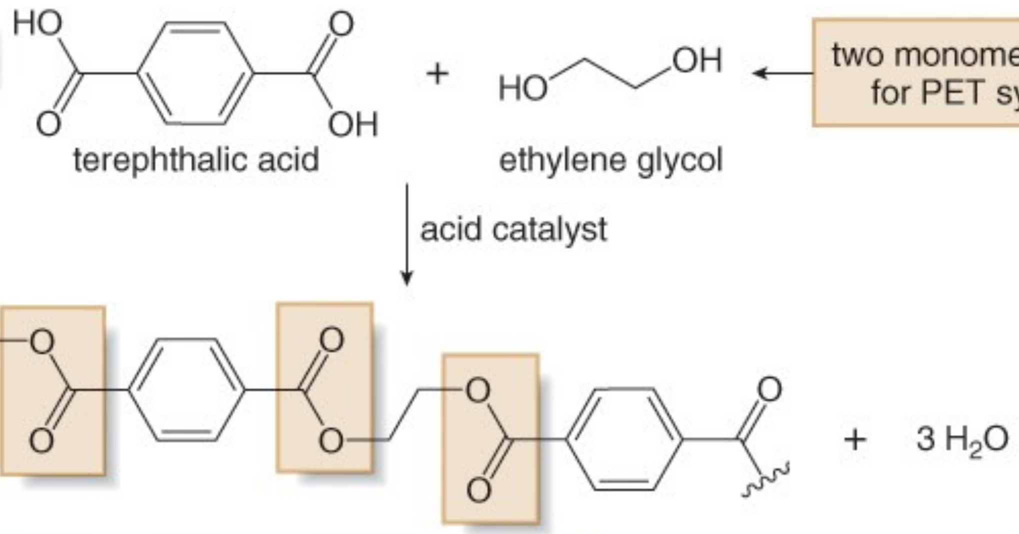
NATURAL AND SYNTHETIC FIBERS: POLYESTERS

Polyethylene terephthalate
PET
(Dacron, Terylene, and Mylar)



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

Synthesis of PET

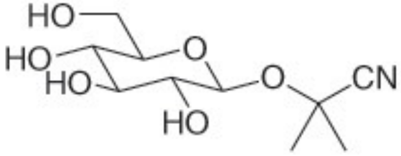


two monomers needed for PET synthesis

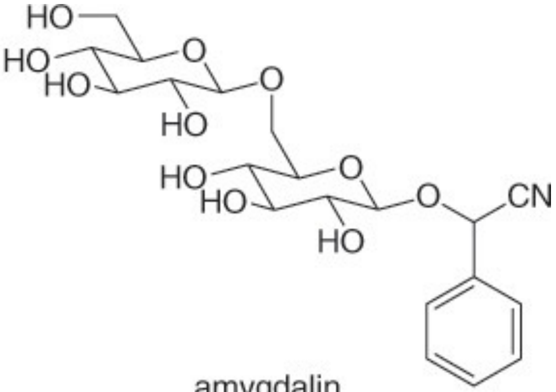
Three new ester bonds are shown.

NITRILES

- Nitriles are not common in nature.
- Cyanohydrins are the most common natural nitriles.

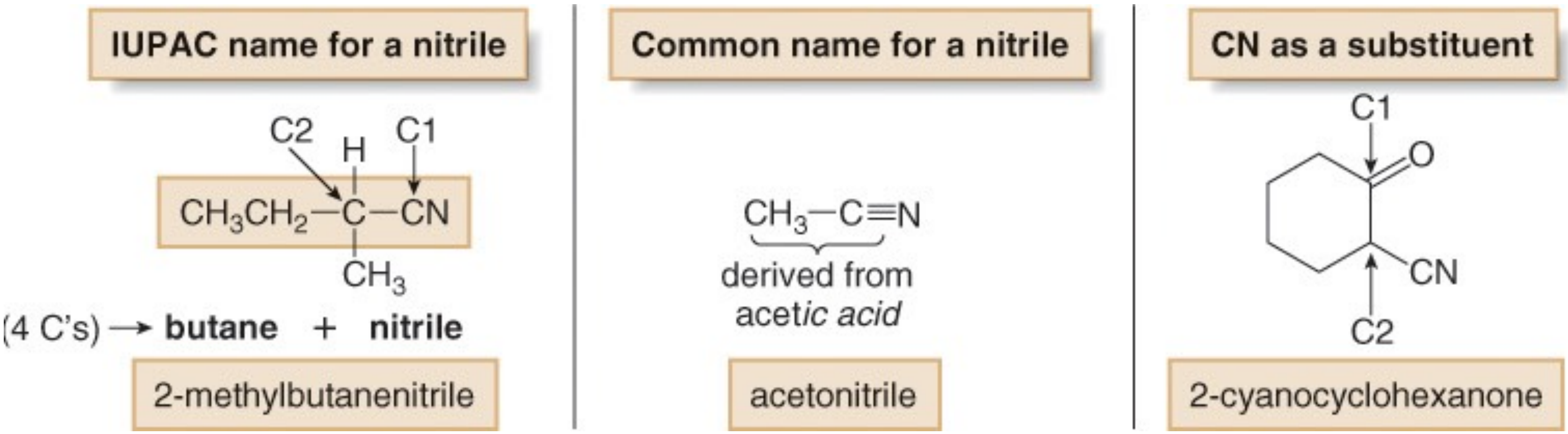


linamarin
(found in cassava root)



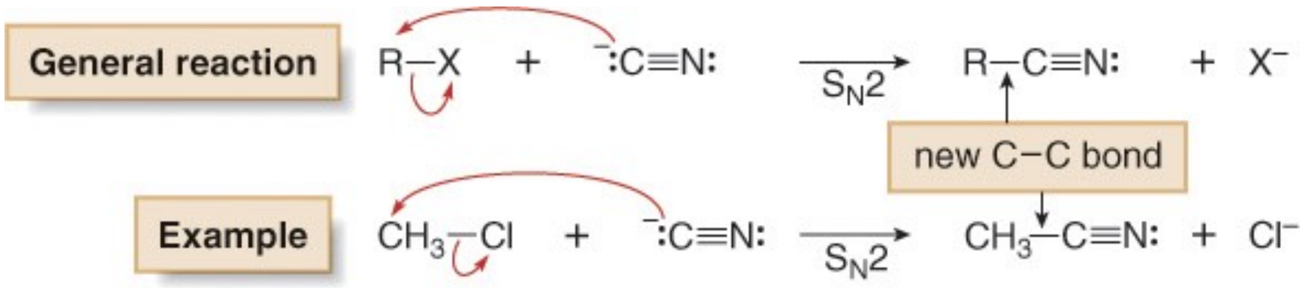
amygdalin
(commonly called laetrile)

NOMENCLATURE — NITRILES

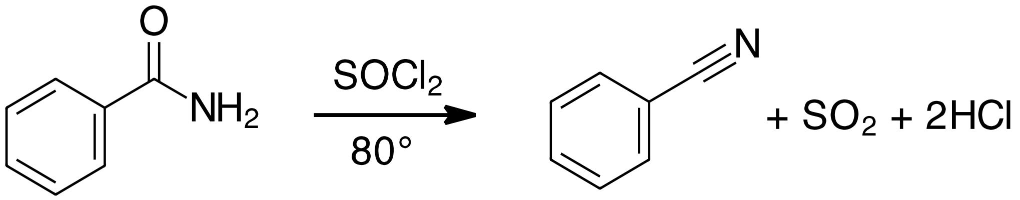


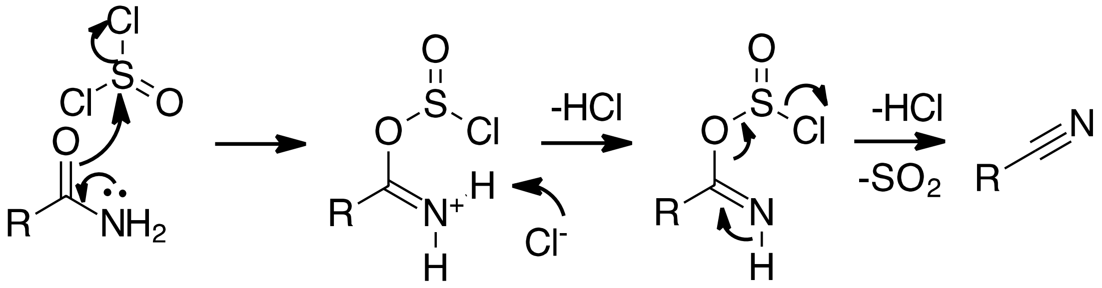
NITRILES

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



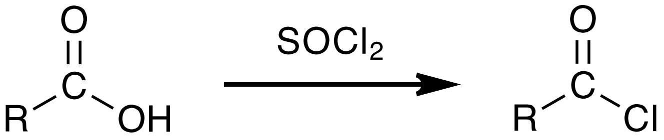
- Nitriles are prepared by dehydration of amides (more general).

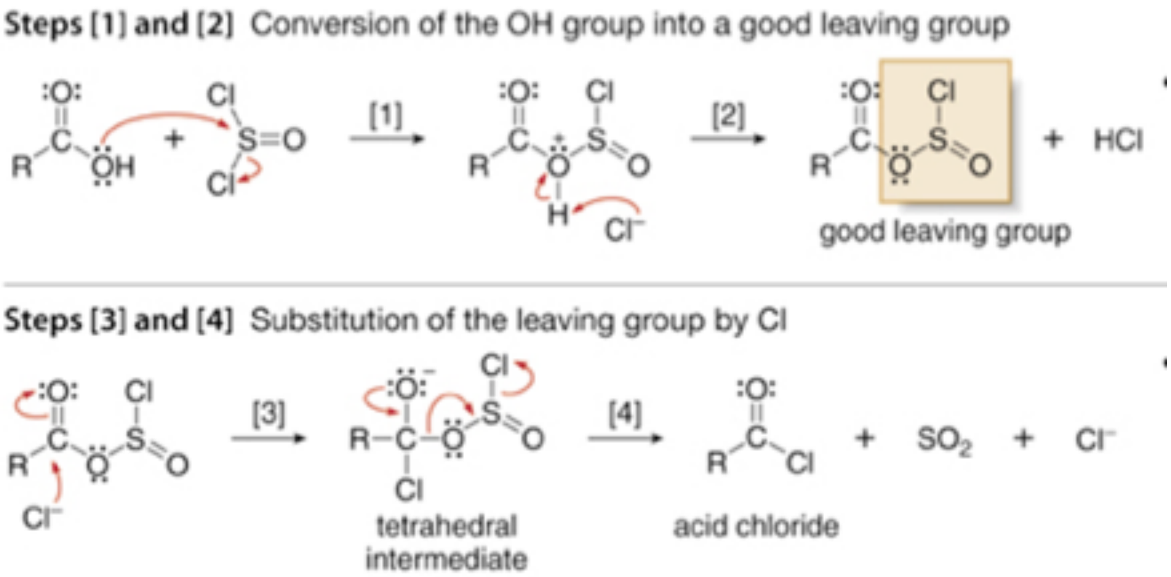




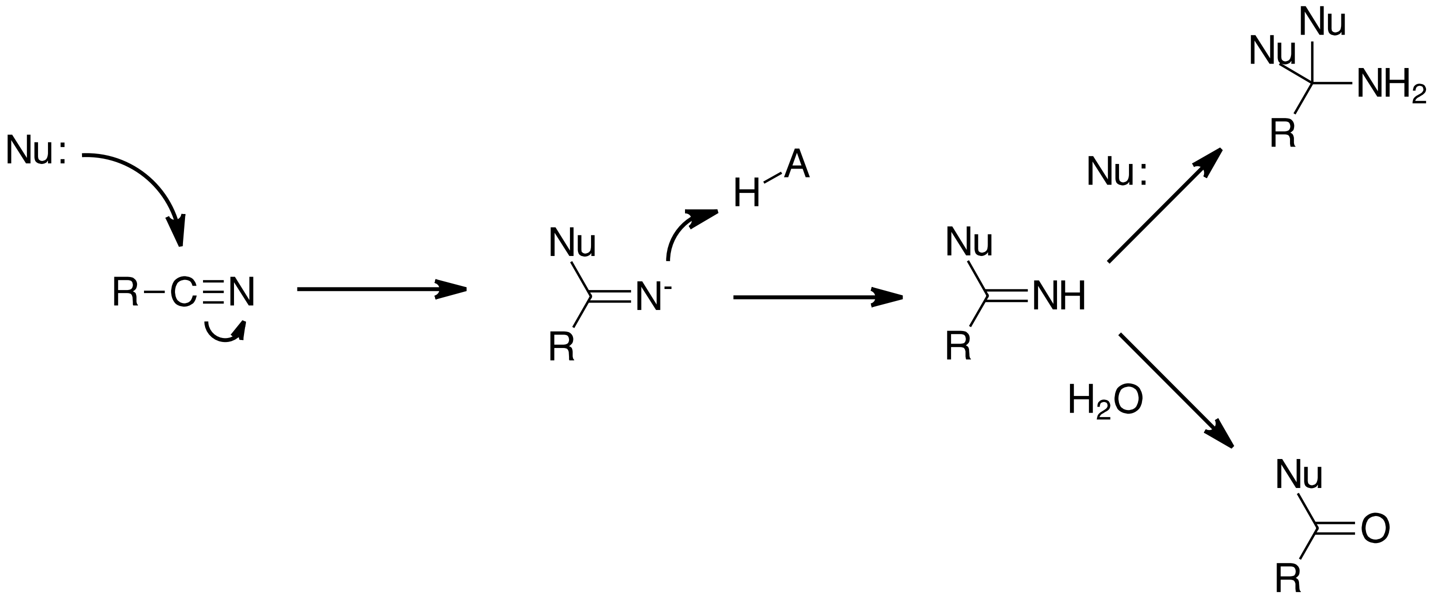
ACID CHLORIDES: SYNTHESIS

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



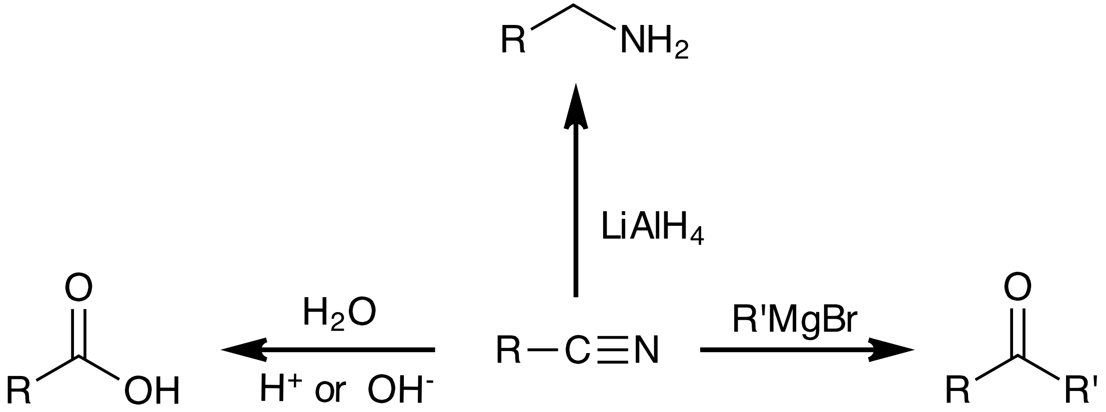


REACTIONS OF NITRILES – NUCLEOPHILIC ADDITION TO THE CN GROUP



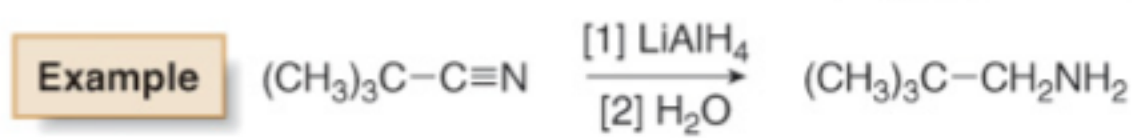
Nu: = H^- ([Al]-H); R^- (R-[M]); H_2O

SUMMARY: IMPORTANT REACTIONS OF NITRILES.

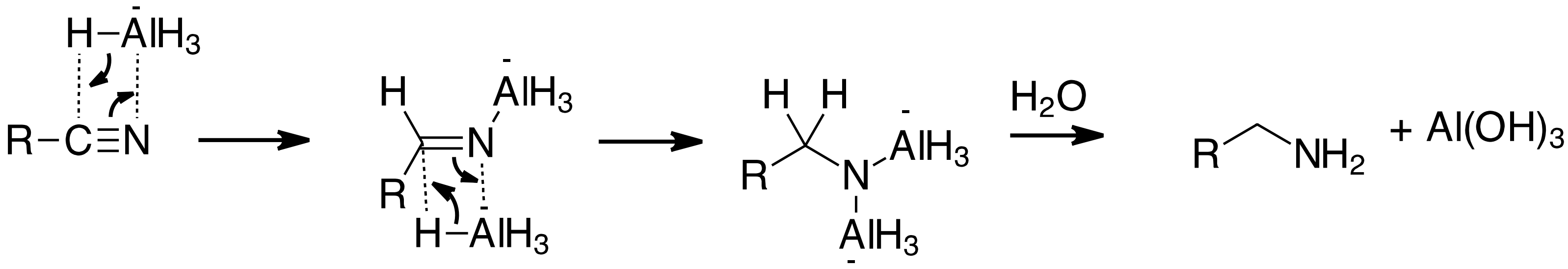


REACTIONS OF NITRILES — REDUCTION

$LiAlH_4$ (more reactive)



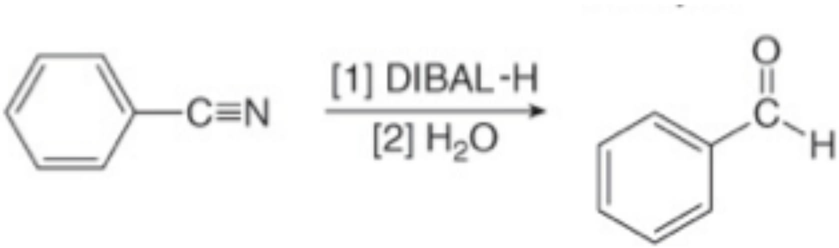
Example $(CH_3)_3C{-}C{\equiv}N \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} (CH_3)_3C{-}CH_2NH_2$

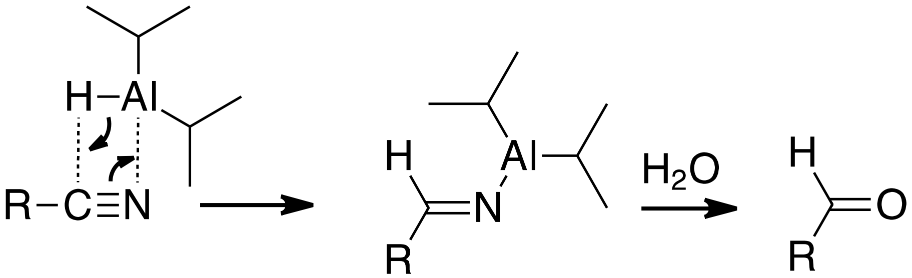


REACTIONS OF NITRILES — REDUCTION

DIBAL-H (less reactive)

Example

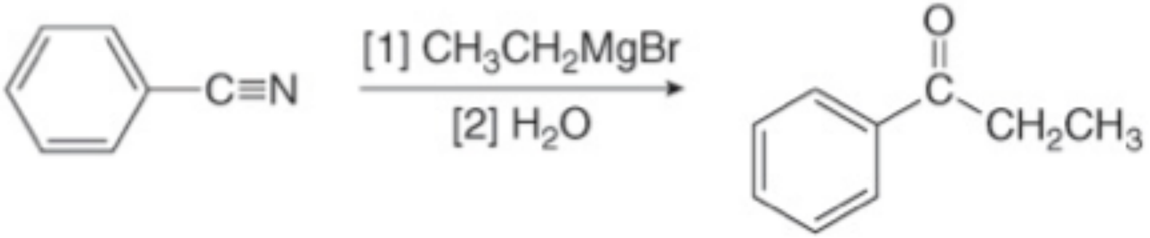


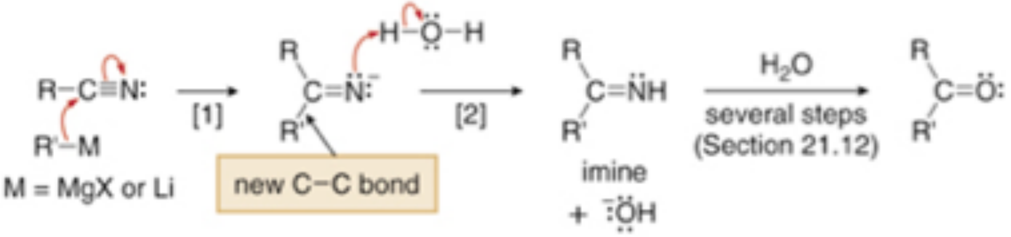


ADDITION OF ORGANOMETALLIC REAGENTS

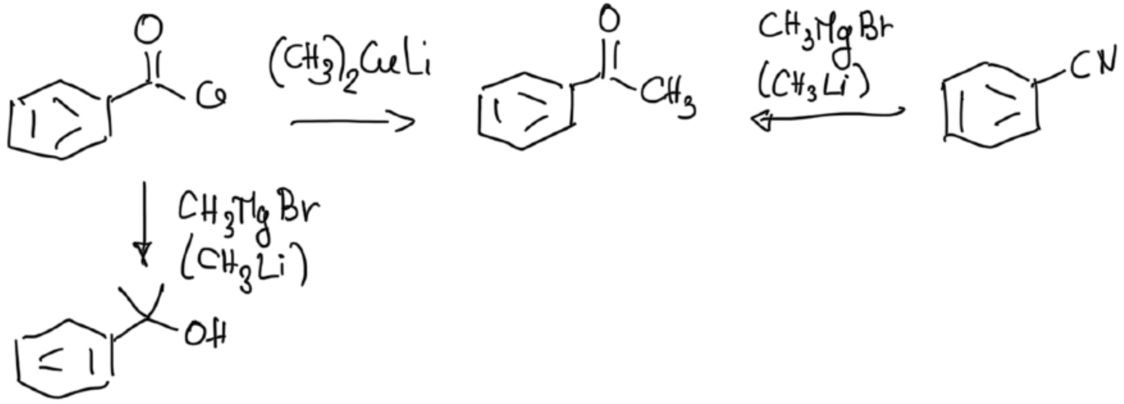
Both Grignard and organolithium reagents react with nitriles to form ketones with a new C—C bond.

Example



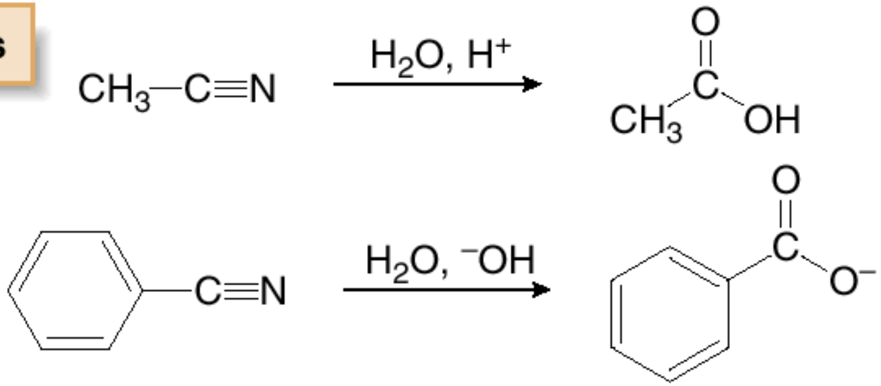


ADDITION OF ORGANOMETALLIC REAGENTS

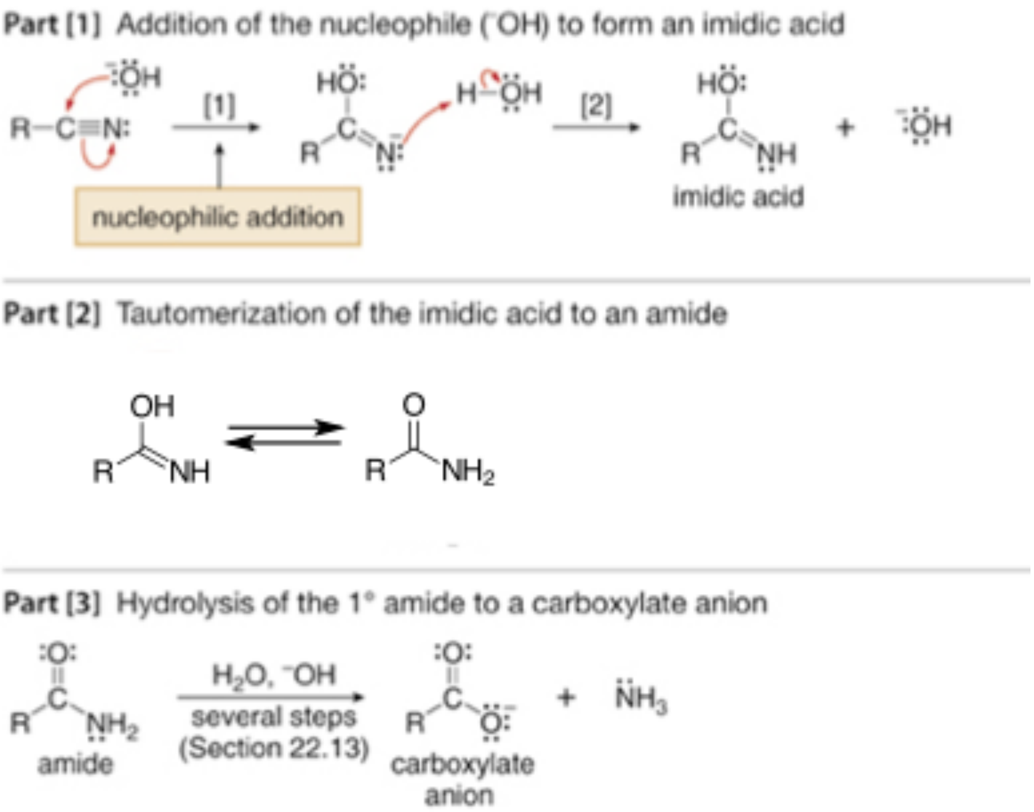


REACTIONS OF NITRILES—HYDROLYSIS

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