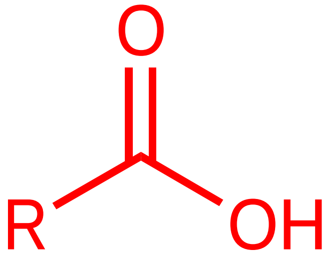
Chapter 17

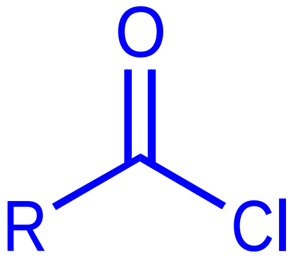
- Carboxylic Acids and Their Derivatives
  Nucleophilic Addition–Elimination
  at the Acyl Carbon

1. Introduction

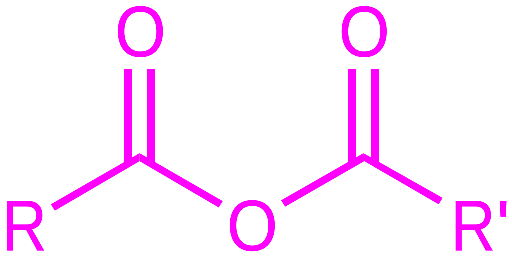
- Carboxylic Acid Derivatives



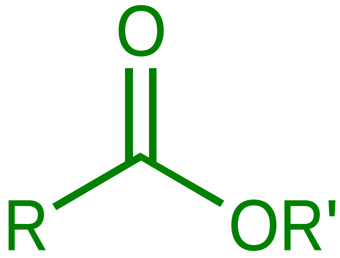
carboxylic acid



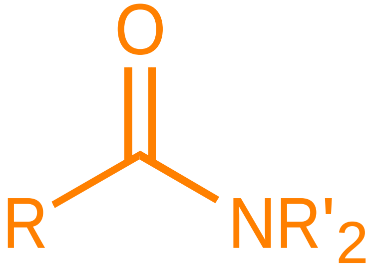
acid chloride



acid anhydride



ester



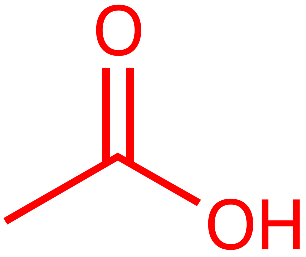
amide

2. Nomenclature and Physical Properties

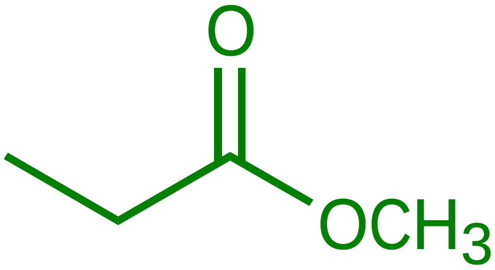
- Nomenclature of Carboxylic Acids and Derivatives
  - Rules
    - Carboxylic acid as parent (suffix): ending with "–oic acid"
    - Carboxylate as parent (suffix): ending with "–oate"

- Most anhydrides are named by dropping the word **acid** from the name of the carboxylic acid and then adding the word “anhydride”
- Acid chloride as parent (suffix): ending with “–oyl chloride”
- Ester as parent (suffix): ending with “–oate”
- Amide as parent (suffix): ending with “amide”
- Nitrile as parent (suffix): ending with “nitrile”

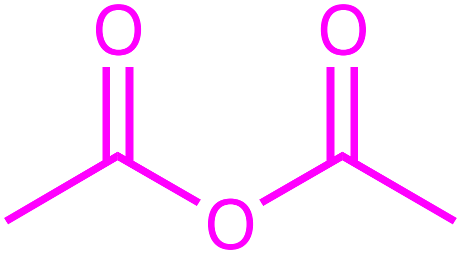
- ❖ Examples



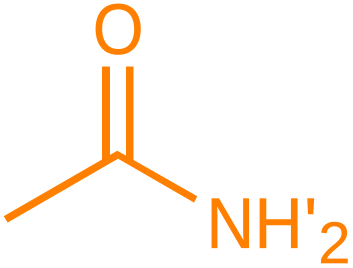
Ethanoic acid
(acetic acid)



Methyl propanoate

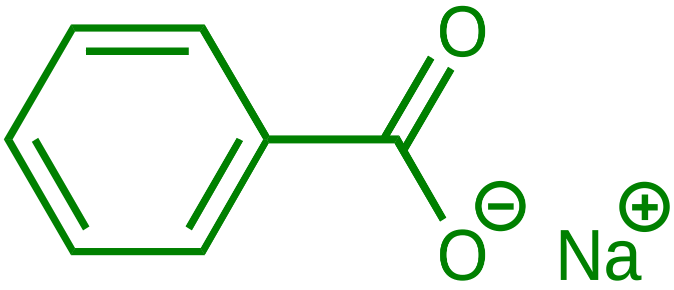


Ethanoic anhydride
(acetic anhydride)

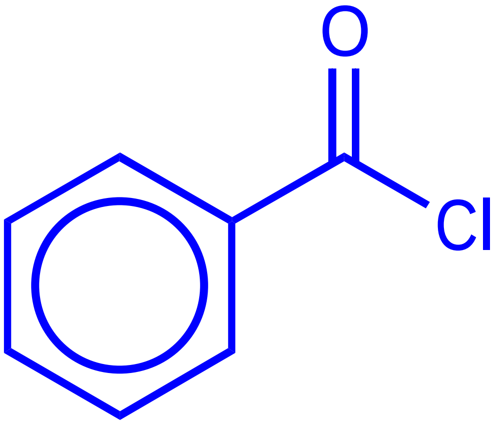


Ethanamide

❖ Examples



Sodium benzoate

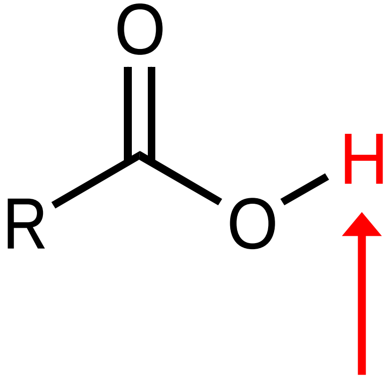


Benzoyl chloride

$H_3C-C\equiv N$

Ethanenitrile

2C. Acidity of Carboxylic Acids

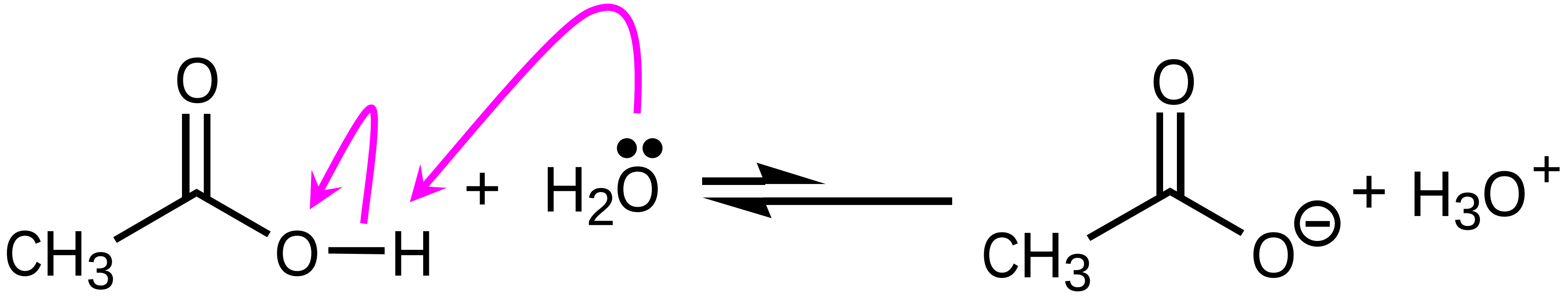


$pK_a \sim$ 4-5

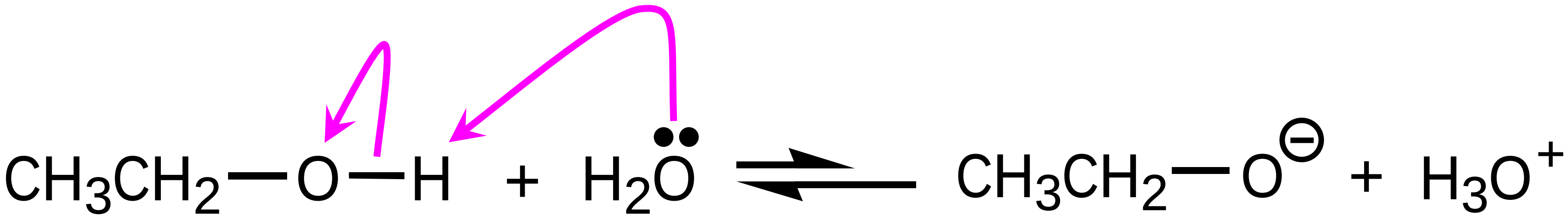
- Compare
  - pK_a of $H_2O \sim 16$
  - pK_a of $H_2CO_3 \sim 7$
  - pK_a of $HF \sim 3$

- When comparing acidity of organic compounds, we compare the stability of their conjugate bases. The more stable the conjugate base, the stronger the acid

	CH_3COOH	CH_3CH_2OH
pK_a	4.75	16

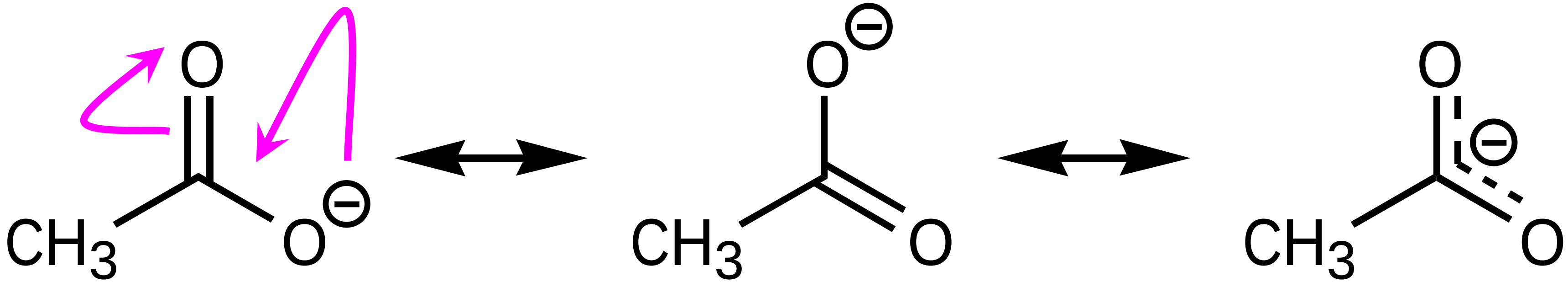


A_1 B_1



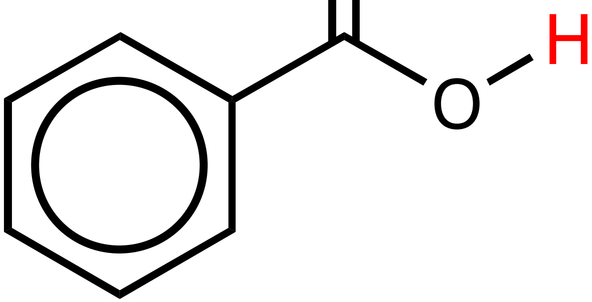
A_2 B_2

- The conjugate base B_1 is more stable (the anion is more delocalized) than B_2 due to resonance stabilization

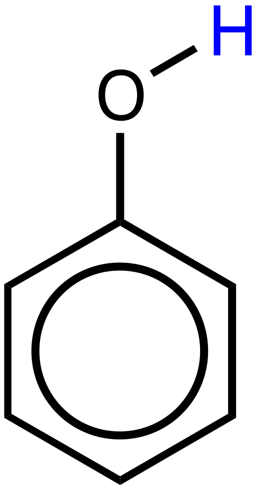


  - **Thus, A_1 is a stronger acid than A_2**

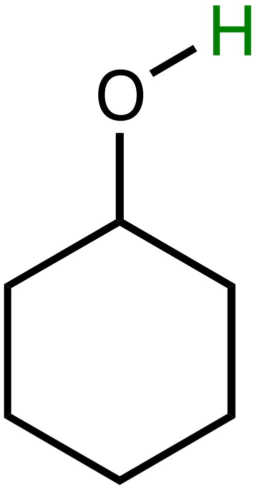
- Acidity of Carboxylic Acids, Phenols and Alcohols



$pK_a = 4.20$

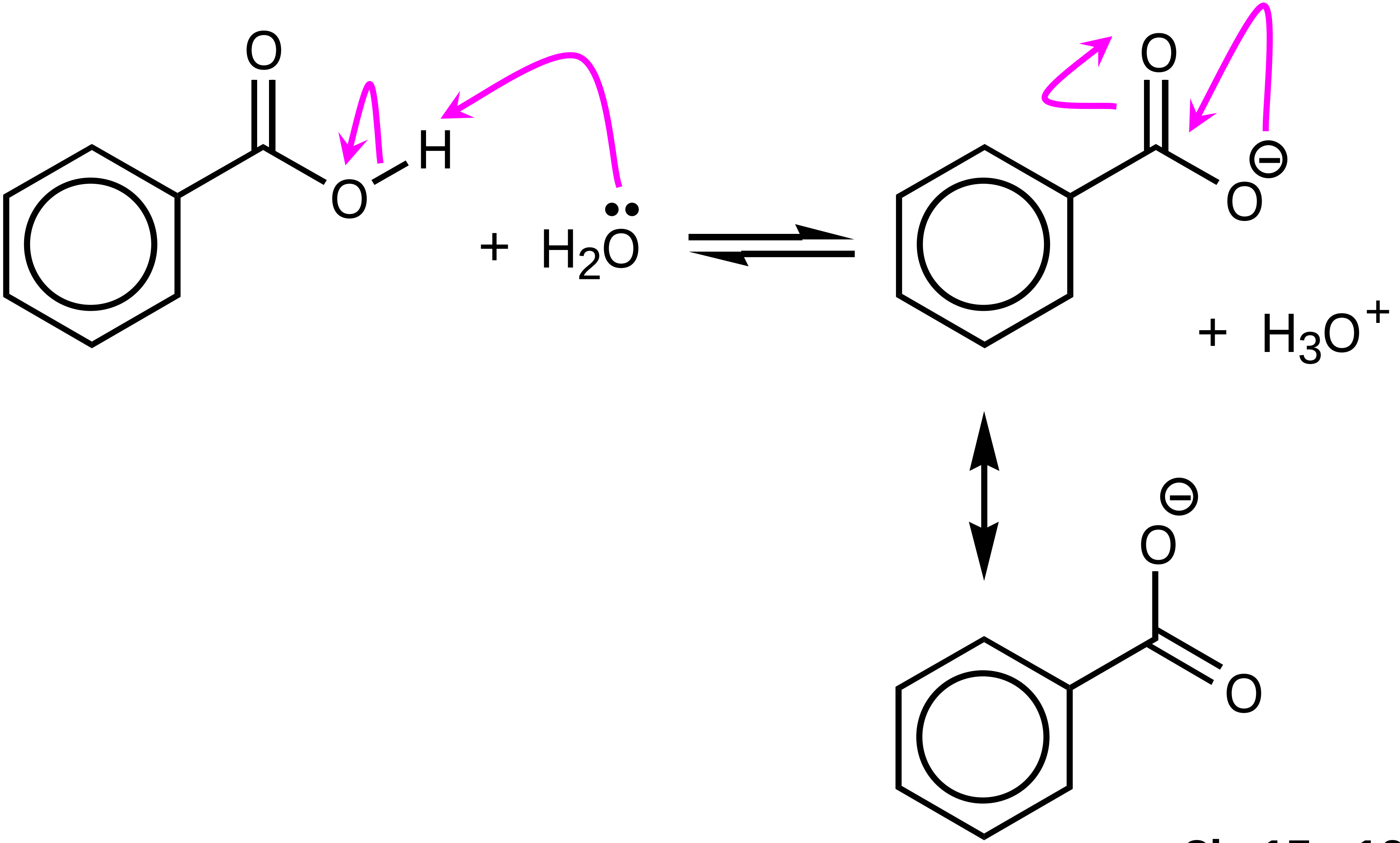


$pK_a = \sim 10$

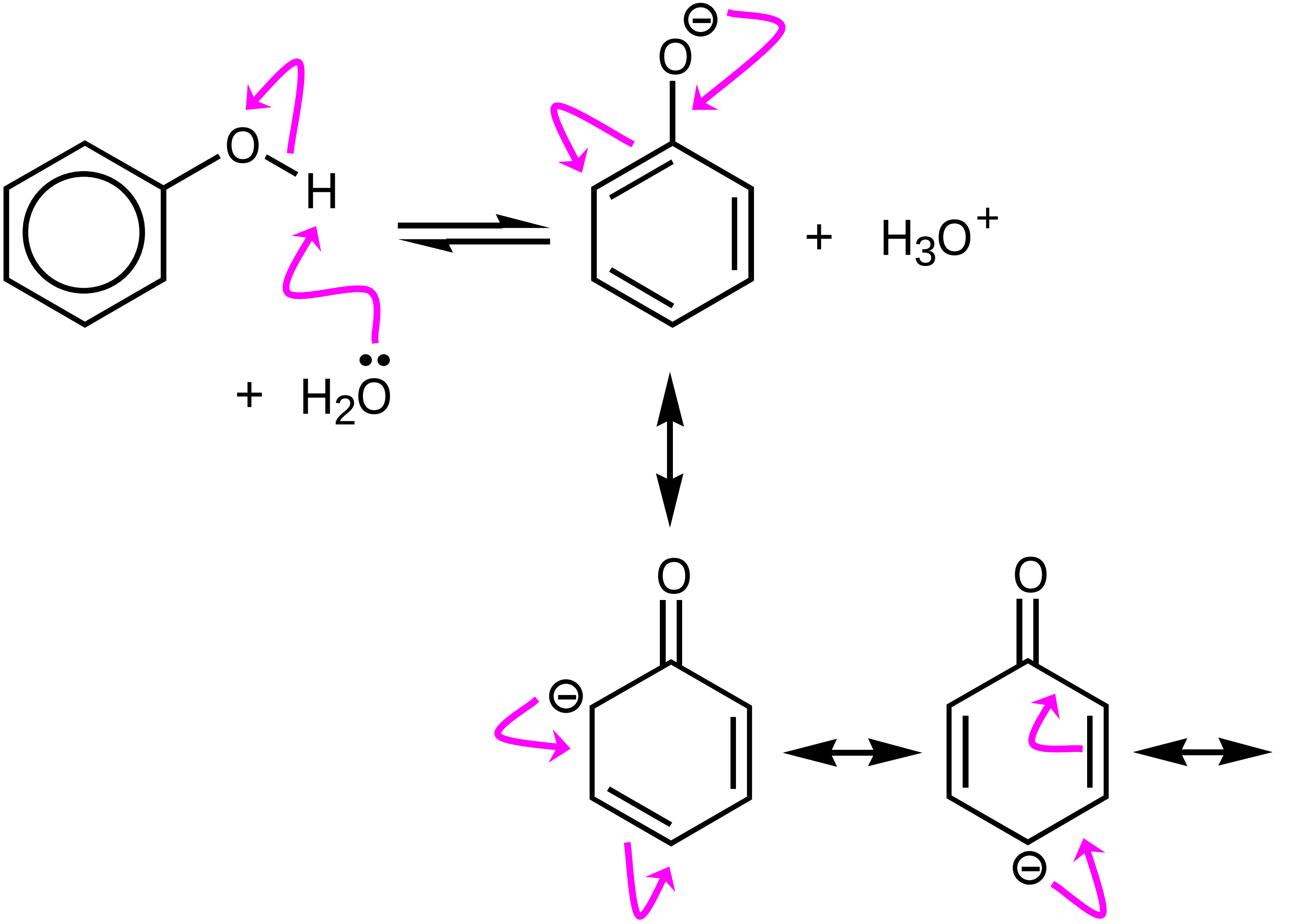


$pK_a = \sim 17$

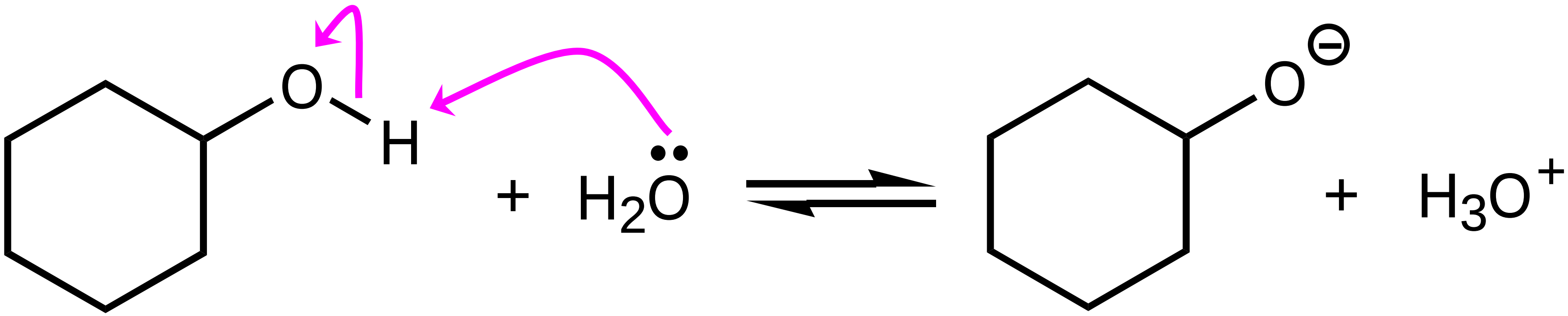
❖ Acidity of Carboxylic Acids, Phenols and Alcohols



❖ Acidity of Carboxylic Acids, Phenols and Alcohols



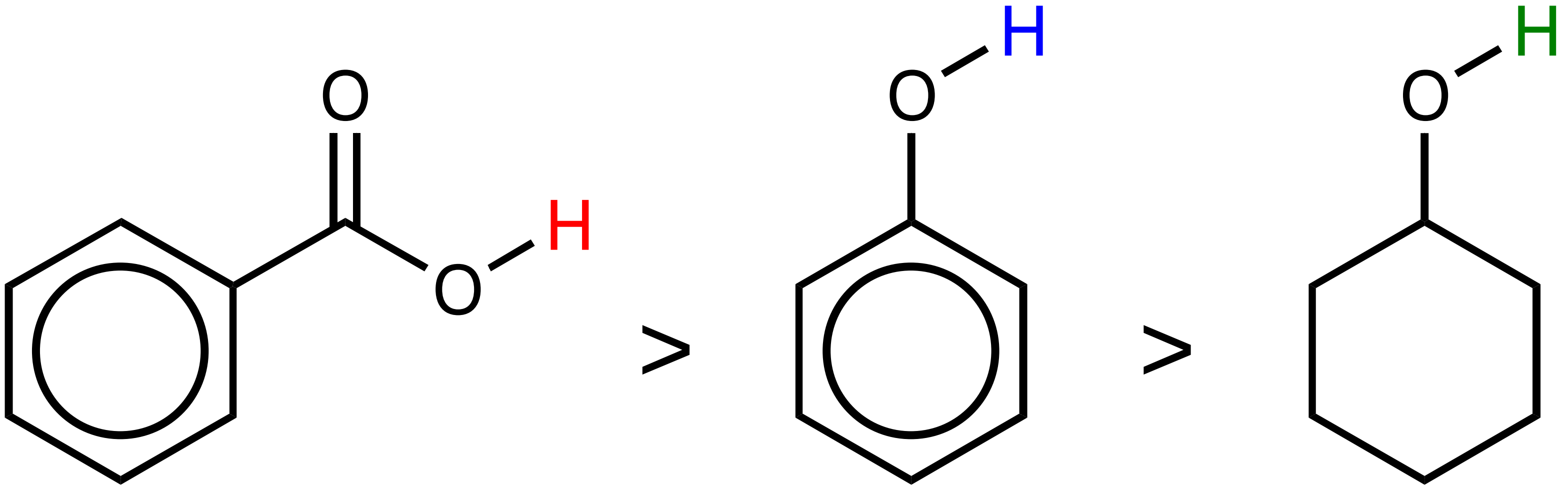
- Acidity of Carboxylic Acids, Phenols and Alcohols

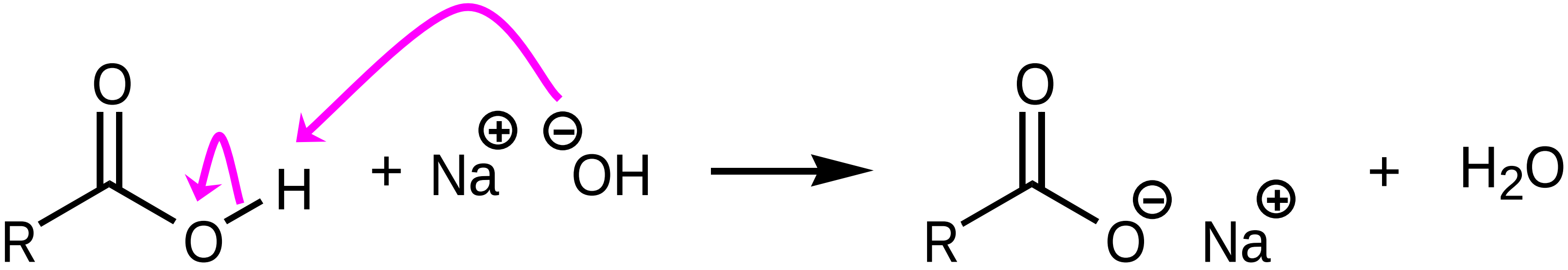


(NO resonance stabilization)

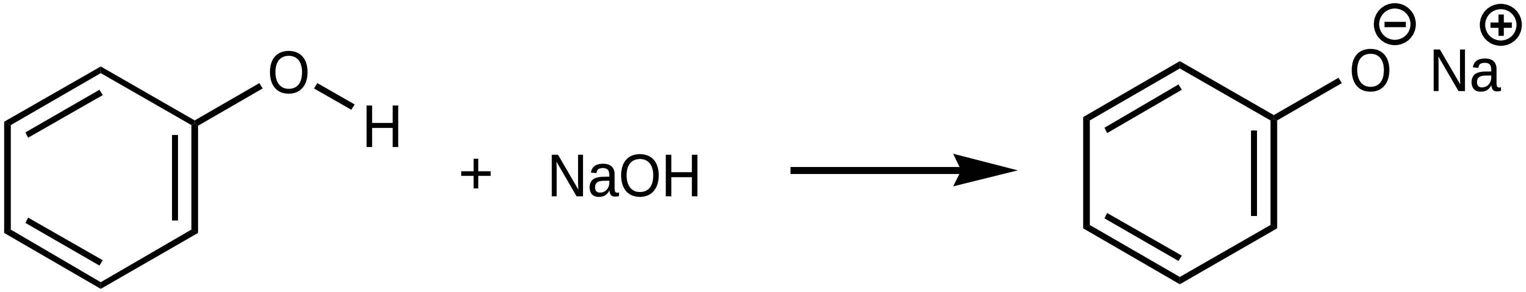
Question

- If you are given three unknown samples: one is benzoic acid; one is phenol; and one is cyclohexyl alcohol; how would you distinguish them by simple chemical tests?
  - Recall: acidity of

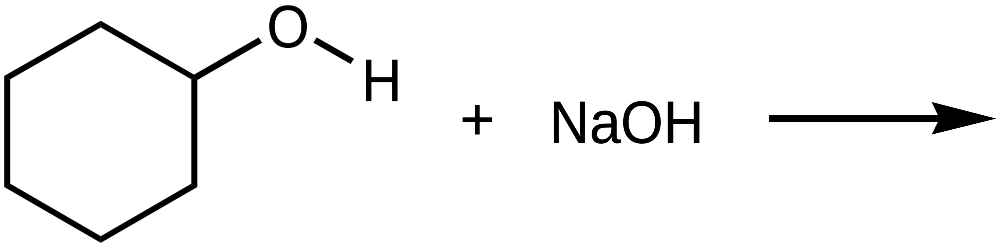




(soluable in water)

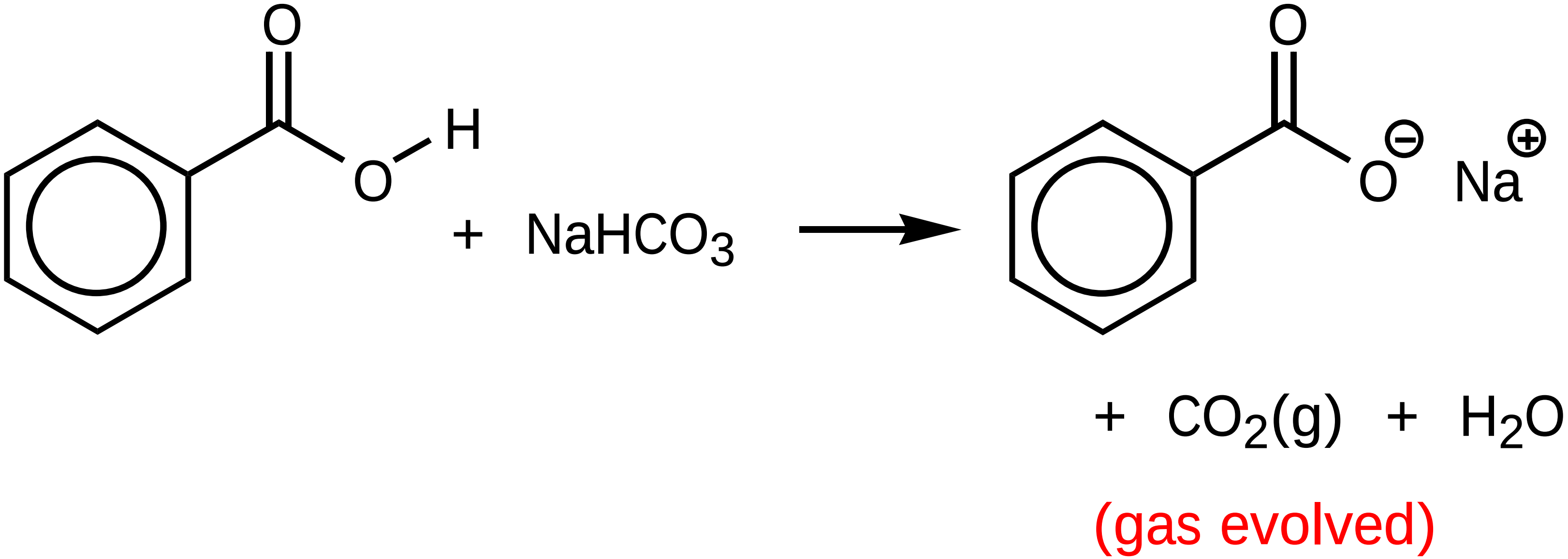


(soluble in water)



No Reaction

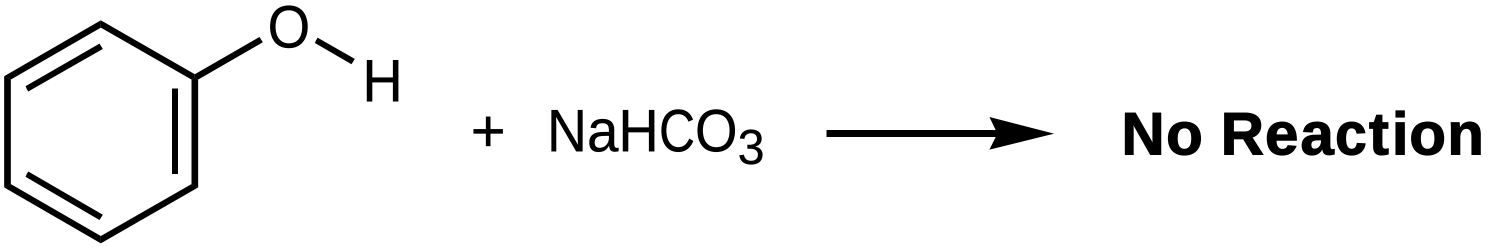
(immiscible with H_2O)



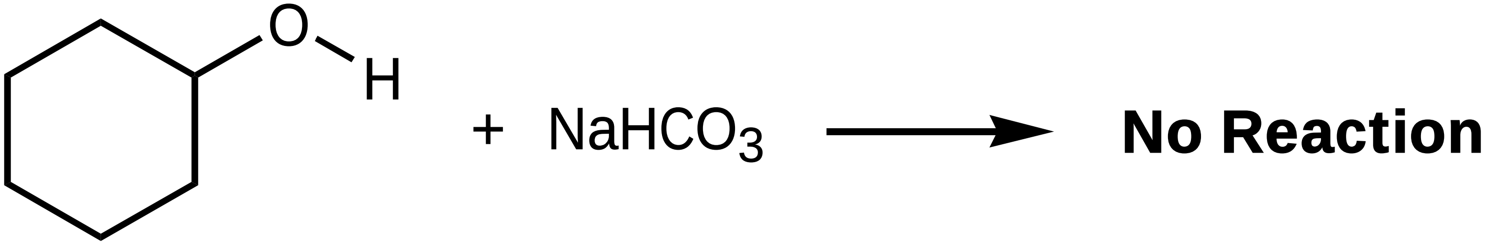
+ $NaHCO_3$ $\longrightarrow$

+ $CO_2(g)$ + H_2O

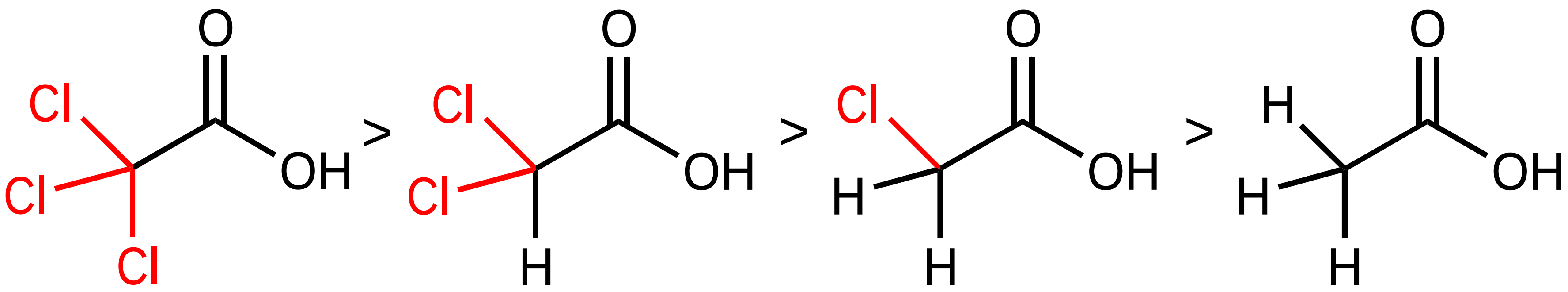
(gas evolved)



+ $NaHCO_3$ $\longrightarrow$ **No Reaction**

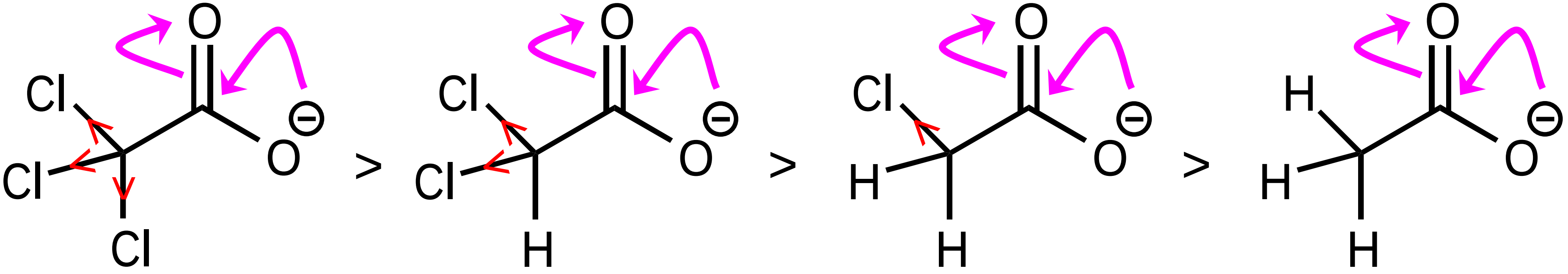


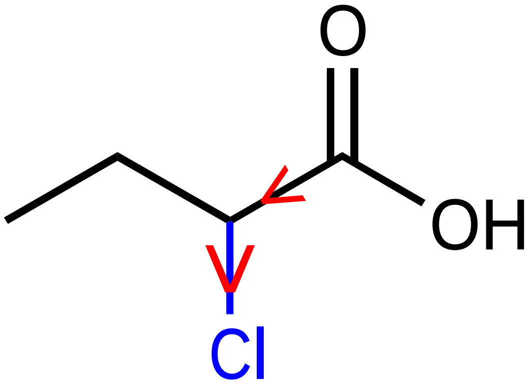
+ $NaHCO_3$ $\longrightarrow$ **No Reaction**



pK_a 0.70 1.48 2.86 4.76

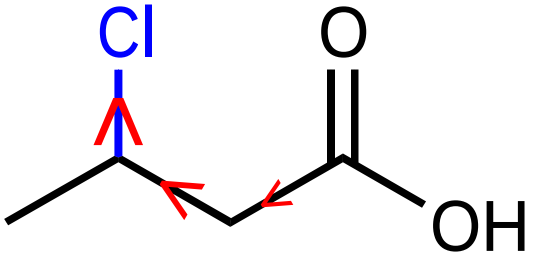
❖ Stability of conjugate bases





2-Chlorobutanoic acid

($pK_a = 2.85$)



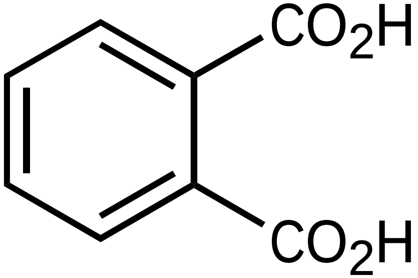
3-Chlorobutanoic acid

($pK_a = 4.05$)

4-Chlorobutanoic acid

($pK_a = 4.50$)

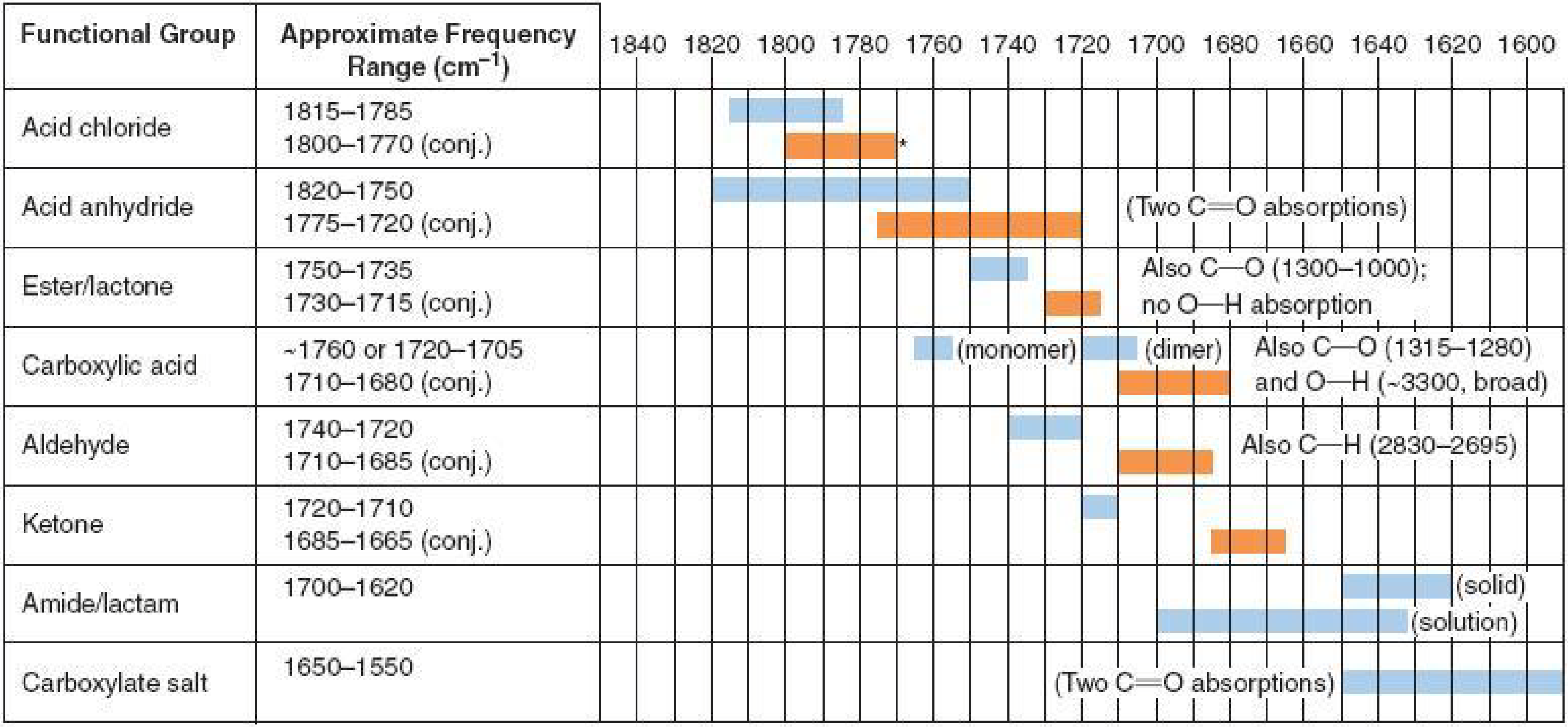
2D. Dicarboxylic Acids

Structure	Common Name	mp (°C)	pK_a (at 25°C)	
			pK_1	pK_2
HO_2C-CO_2H	Oxalic acid	189 dec	1.2	4.2
$HO_2CCH_2CO_2H$	Malonic acid	136	2.9	5.7
$HO_2C(CH_2)_4CO_2H$	Adipic acid	153	4.4	5.6
	Phthalic acid	206-208 dec	2.9	5.4

2J. Spectroscopic Properties of Acyl Compounds

- IR Spectra
  - The C=O stretching band occurs at different frequencies for acids, esters, and amides, and its precise location is often helpful in structure determination
  - Conjugation and electron-donating groups bonded to the carbonyl shift the location of the C=O absorption to lower frequencies

- IR Spectra
  - Electron-withdrawing groups bonded to the carbonyl shift the C=O absorption to higher frequencies
  - The hydroxyl groups of carboxylic acids also give rise to a broad peak in the 2500-3100-cm^{-1} region arising from O–H stretching vibrations
  - The N–H stretching vibrations of amides absorb between 3140 and 3500 cm^{-1}



Functional Group	Approximate Frequency Range (cm^{-1})
Acid chloride	1815–1785 1800–1770 (conj.)
Acid anhydride	1820–1750 1775–1720 (conj.)
Ester/lactone	1750–1735 1730–1715 (conj.)
Carboxylic acid	~1760 or 1720–1705 1710–1680 (conj.)
Aldehyde	1740–1720 1710–1685 (conj.)
Ketone	1720–1710 1685–1665 (conj.)
Amide/lactam	1700–1620
Carboxylate salt	1650–1550

*Orange bars represent absorption ranges for conjugated species.

Figure 17.2 Approximate carbonyl IR absorption frequencies. (Frequency ranges based on Silverstein and Webster, reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds, Sixth Edition*. Copyright 1998.)

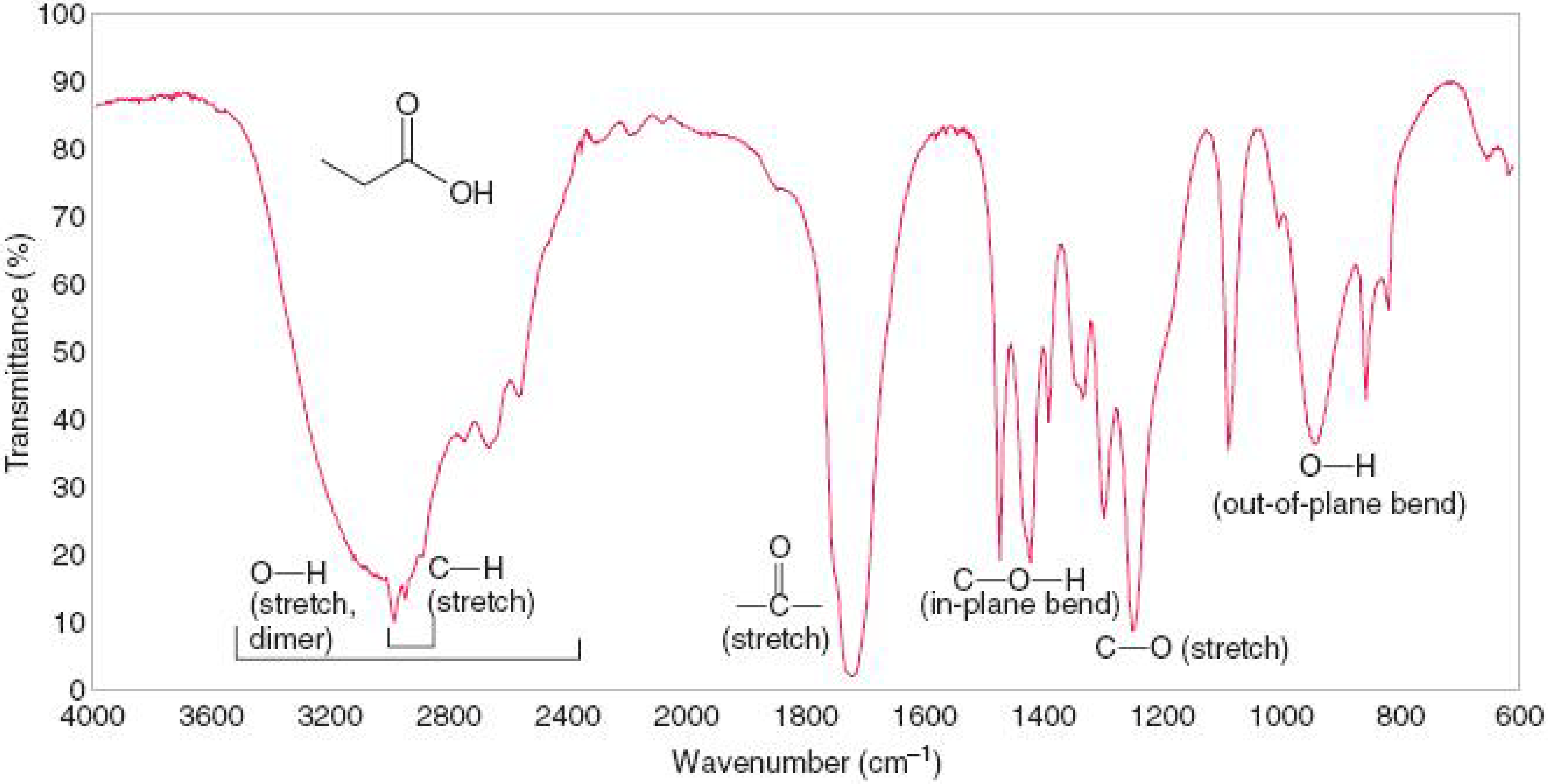


Figure 17.3 The infrared spectrum of propanoic acid.

- ^{1}H NMR Spectra
  - The acidic protons of carboxylic acids are highly deshielded and absorb far downfield in the δ 10-12 region
  - The protons of the a carbon of carboxylic acids absorb in the δ 2.0-2.5 region

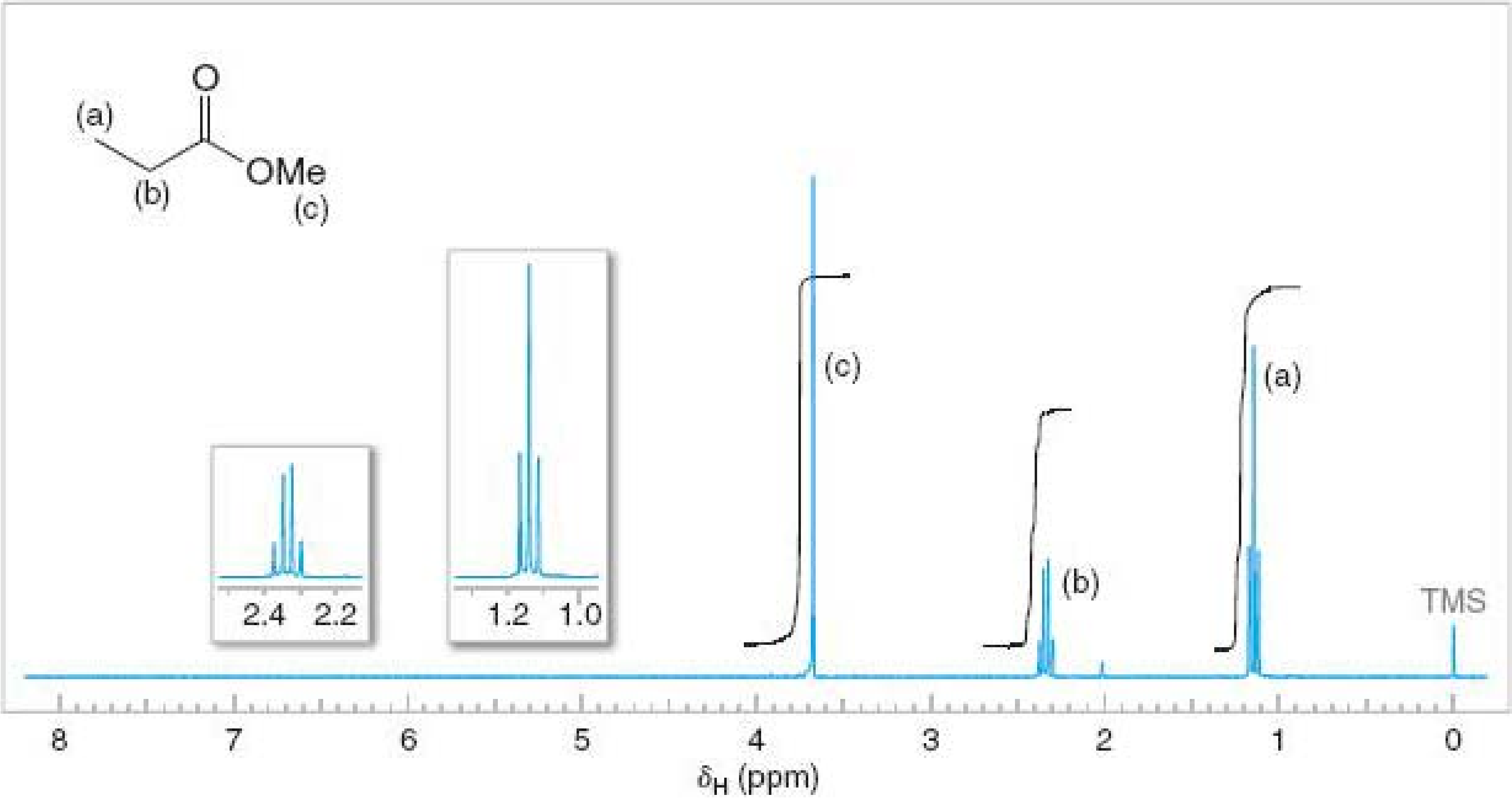
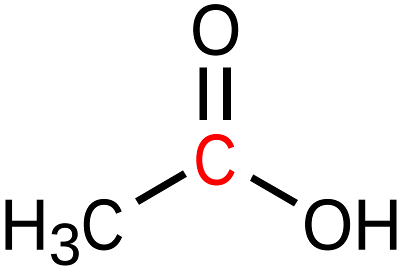


Figure 17.4 The 300-MHz ^1H NMR spectrum of methyl propanoate. Expansions of the signals are shown in the offset plots.

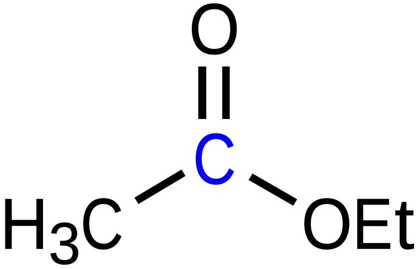
❖ ^{13}C NMR Spectra

- The carbonyl carbon of carboxylic acids and their derivatives occurs downfield in the δ 160-180 region (see the following examples), but not as far downfield as for aldehydes and ketones (δ 180-220)
- The nitrile carbon is not shifted so far downfield and absorbs in the δ 115-120 region

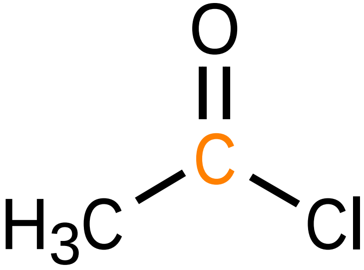
- ^{13}C NMR chemical shifts for the carbonyl or nitrile carbon atom



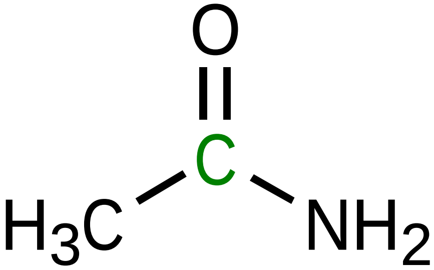
δ 177.2



δ 170.7



δ 170.3



δ 172.6

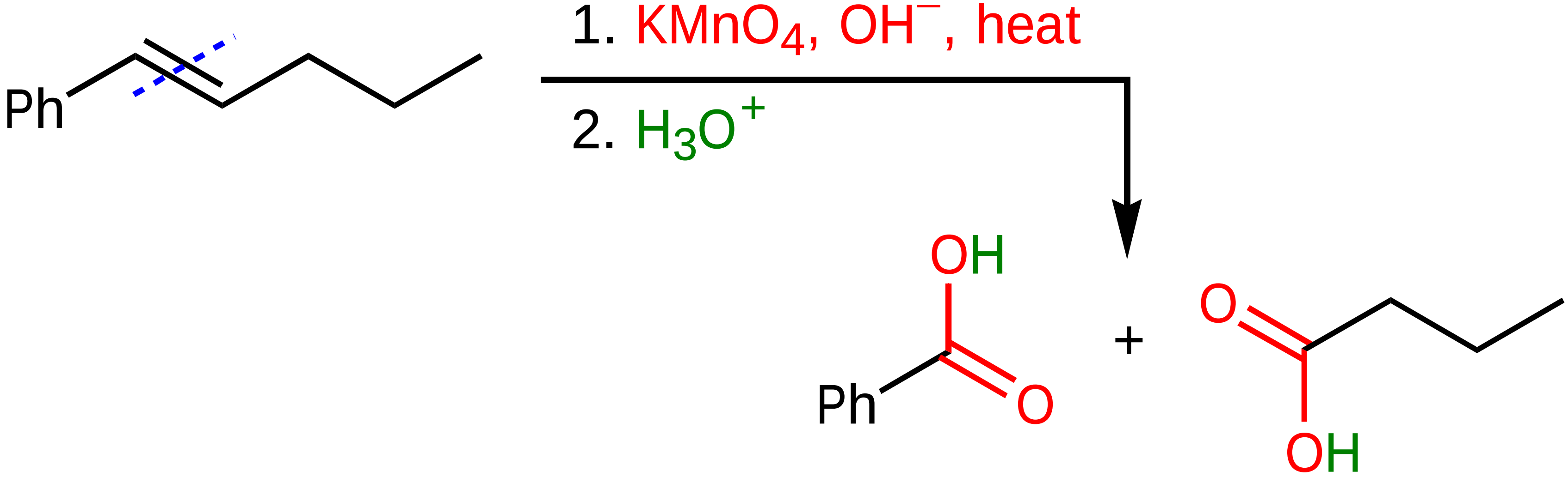
$H_3C{-}C{\equiv}N$

δ 117.4

3. Preparation of Carboxylic Acids

❖ By oxidation cleavage of alkenes

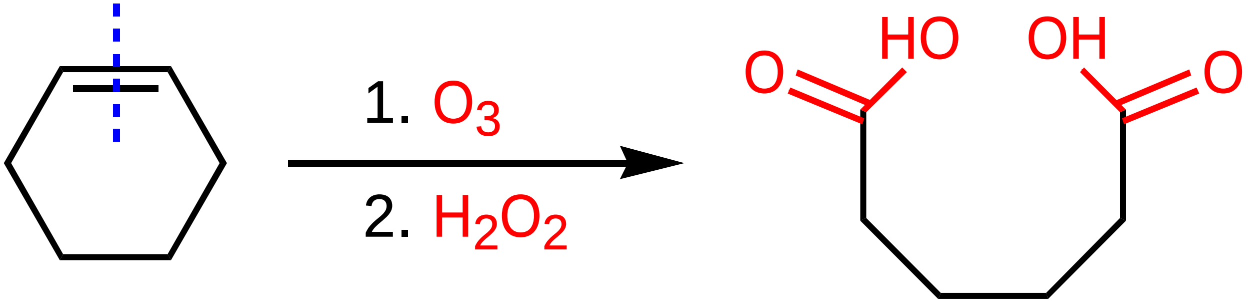
- Using $KMnO_4$



1. $KMnO_4$, OH^-, heat

2. H_3O^+

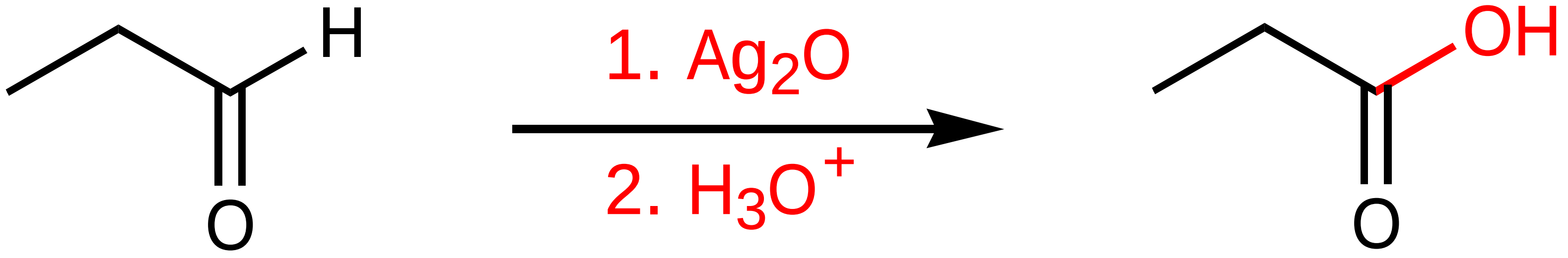
- Using ozonolysis

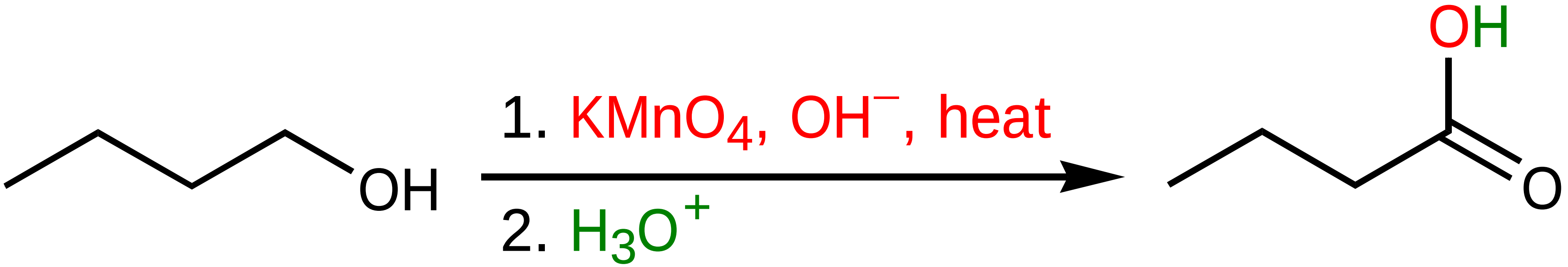


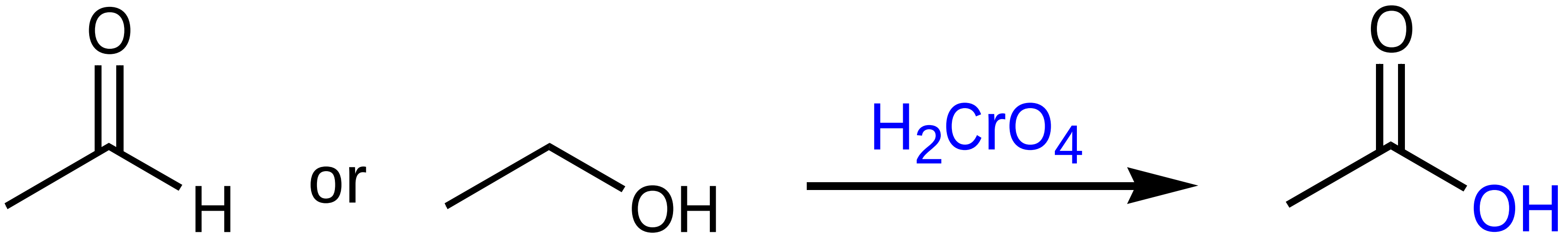
1. O_3

2. H_2O_2

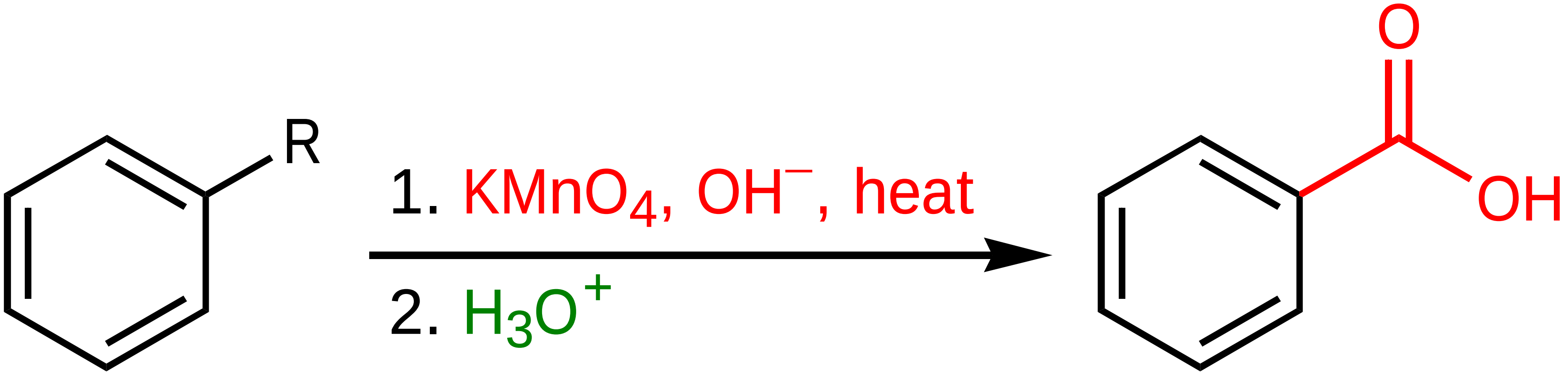
- ❖ By oxidation of aldehydes & 1° alcohols
  - e.g.







- By oxidation of alkyl benzene

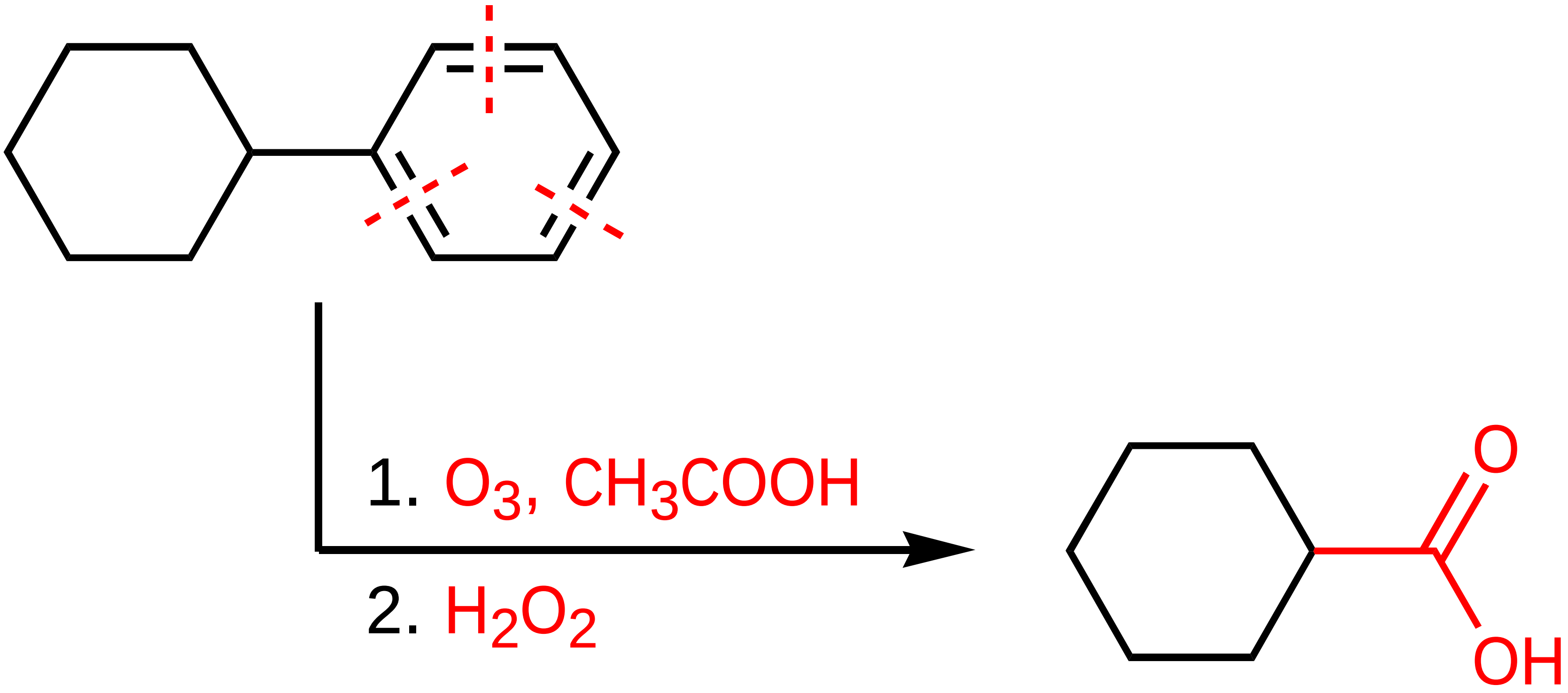


1. $KMnO_4$, OH^-, heat

2. H_3O^+

(R = 1° or 2° alkyl groups)

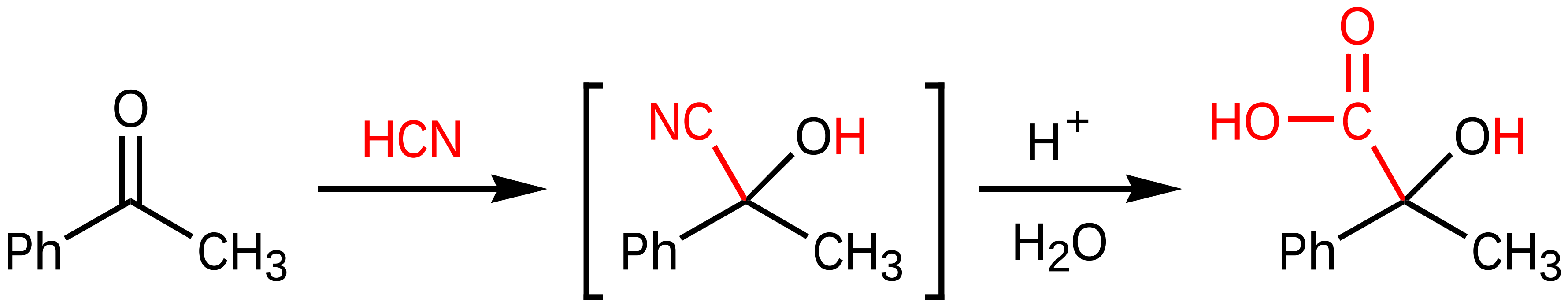
- By oxidation of benzene ring
  - e.g.

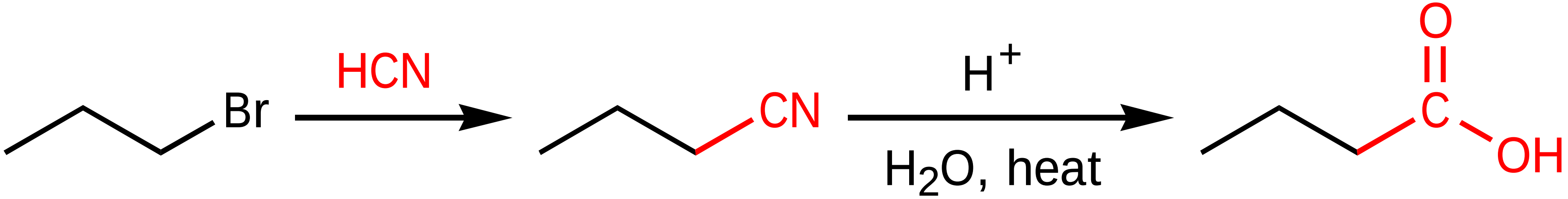


1. O_3, CH_3COOH

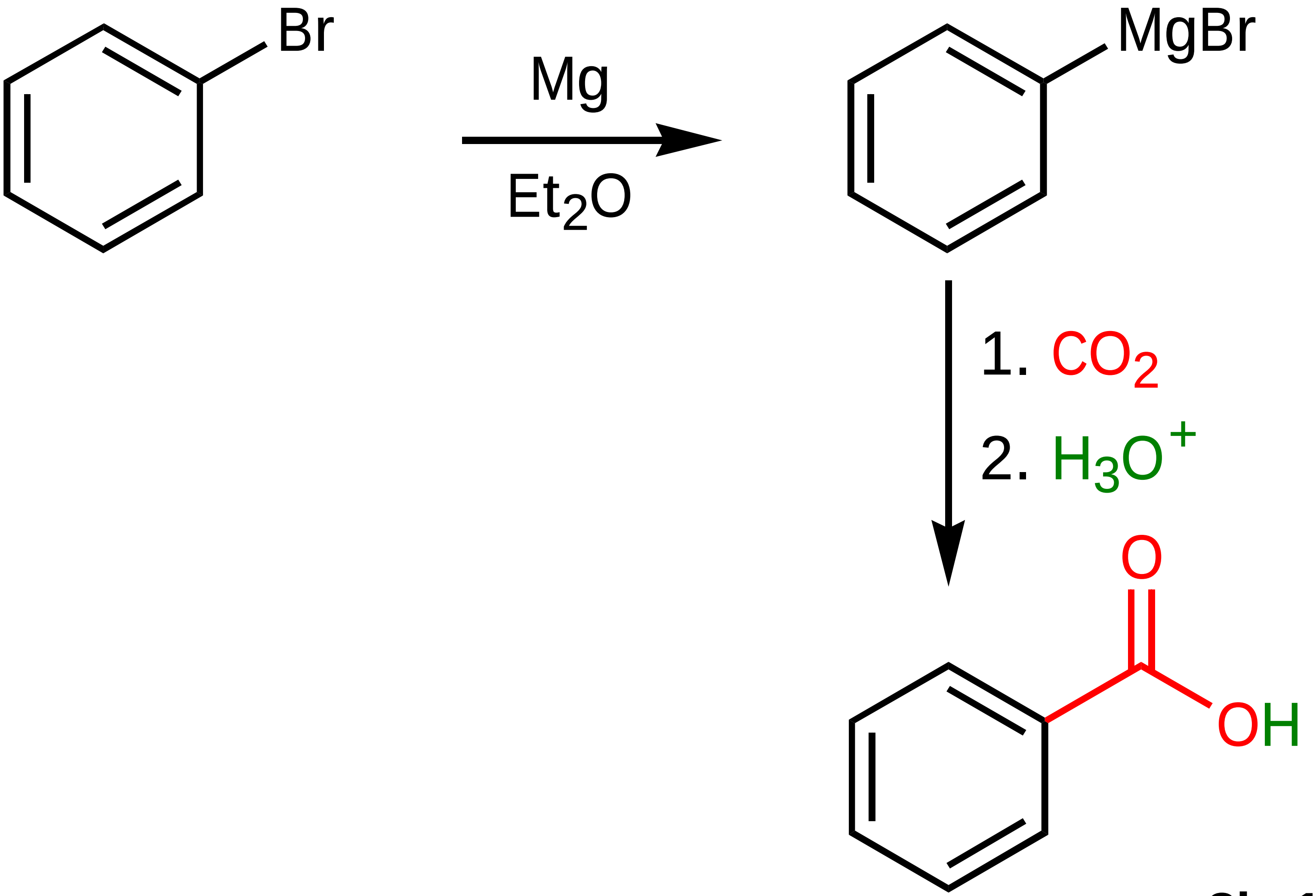
2. H_2O_2

- By hydrolysis of cyanohydrins and other nitriles
  - e.g.

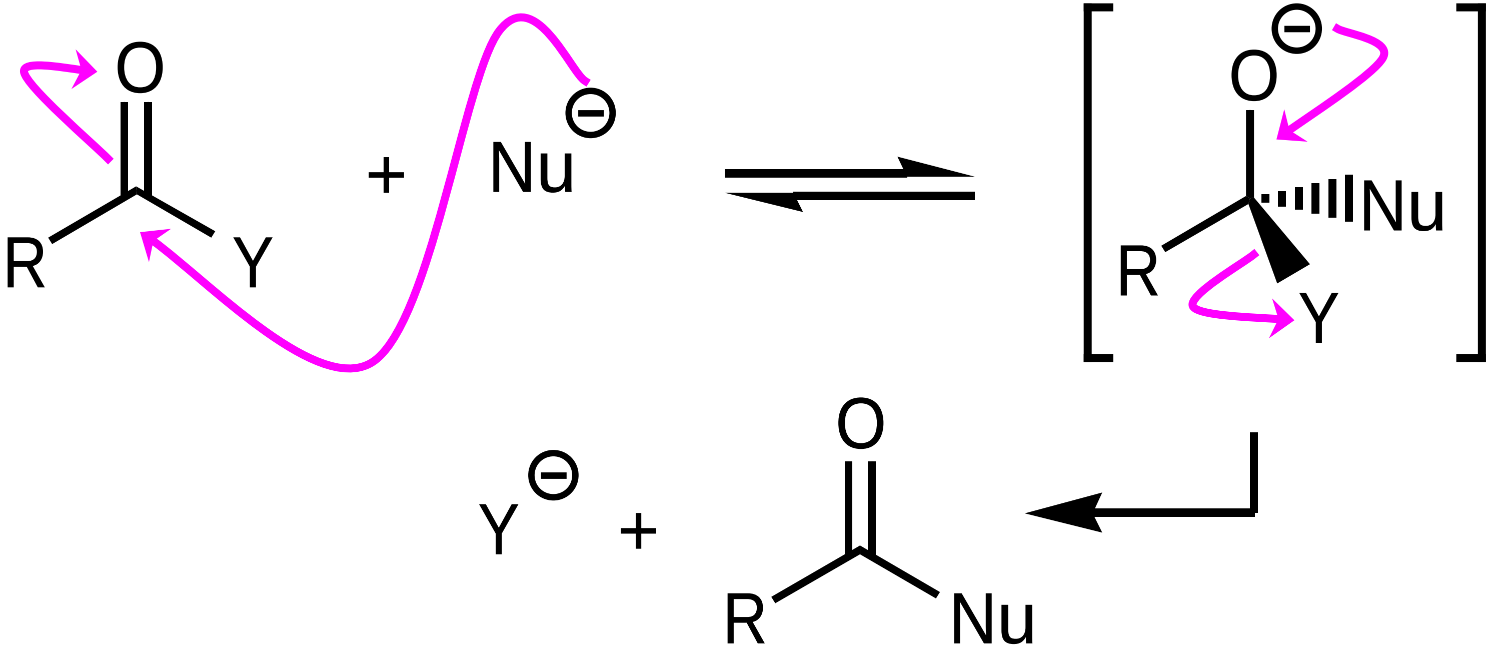




- By carbonation of Grignard reagents
  - e.g.



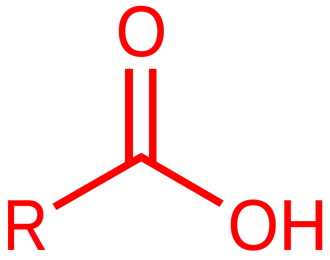
4. Acyl Substitution: Nucleophilic Addition-Elimination at the Acyl Carbon



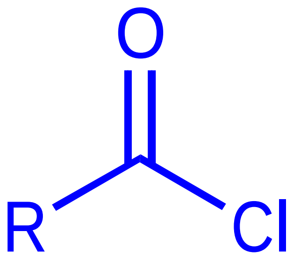
(Y = leaving group, e.g. OR, NR_2, Cl)

- This nucleophilic acyl substitution occurs through a nucleophilic addition-elimination mechanism

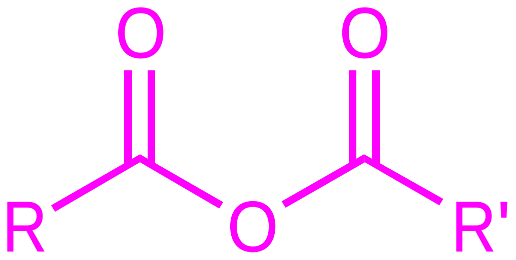
- This type of nucleophilic acyl substitution reaction is common for carboxylic acids and their derivatives



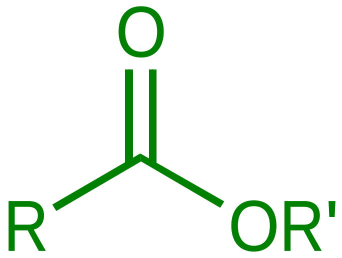
carboxylic acid



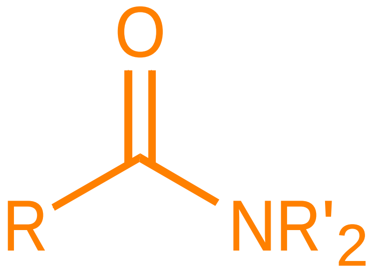
acid chloride



acid anhydride

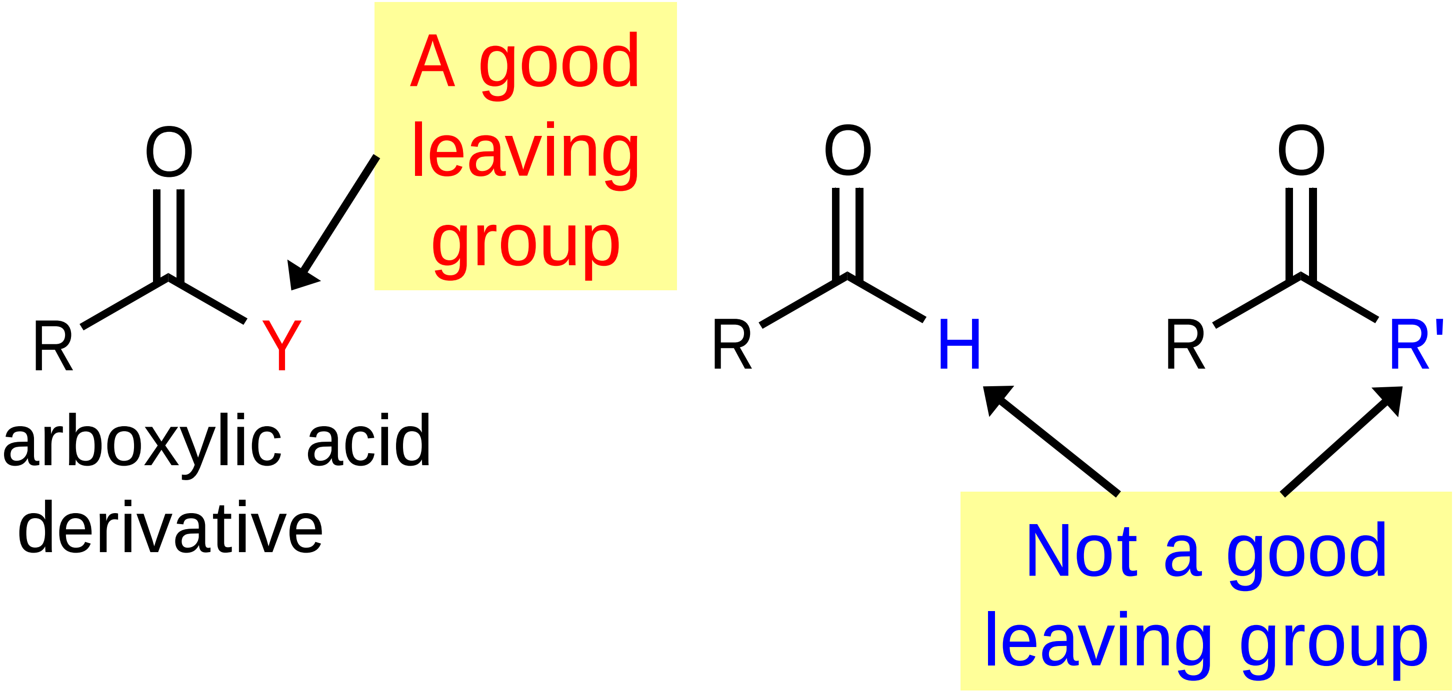


ester



amide

- Unlike carboxylic acids and their derivatives, aldehydes & ketones usually do not undergo this type of nucleophilic acyl substitution, due to the lack of an acyl leaving group



A good leaving group

a carboxylic acid derivative

Not a good leaving group

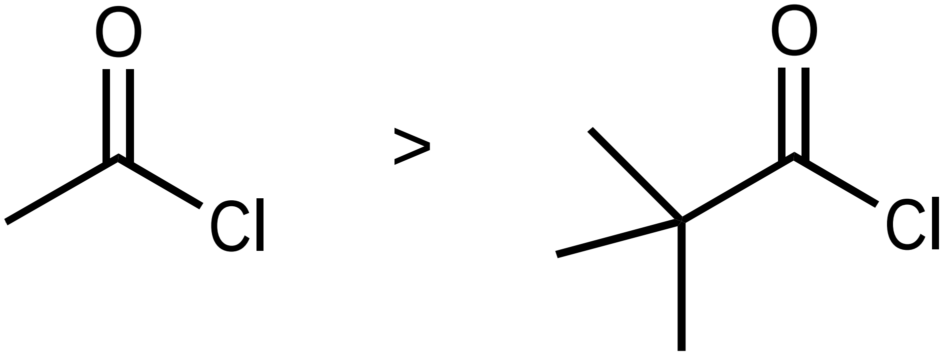
- Relative reactivity of carboxylic acid derivatives towards nucleophilic acyl substitution reactions
  - There are 2 steps in a nucleophilic acyl substitution
    - The addition of the nucleophile to the carbonyl group
    - The elimination of the leaving group in the tetrahedral intermediate

- Usually the addition step (the first step) is the rate-determining step (r.d.s.). As soon as the tetrahedral intermediate is formed, elimination usually occurs spontaneously to regenerate the carbonyl group
- Thus, both steric and electronic factors that affect the rate of the addition of a nucleophile control the reactivity of the carboxylic acid derivative

- Steric factor

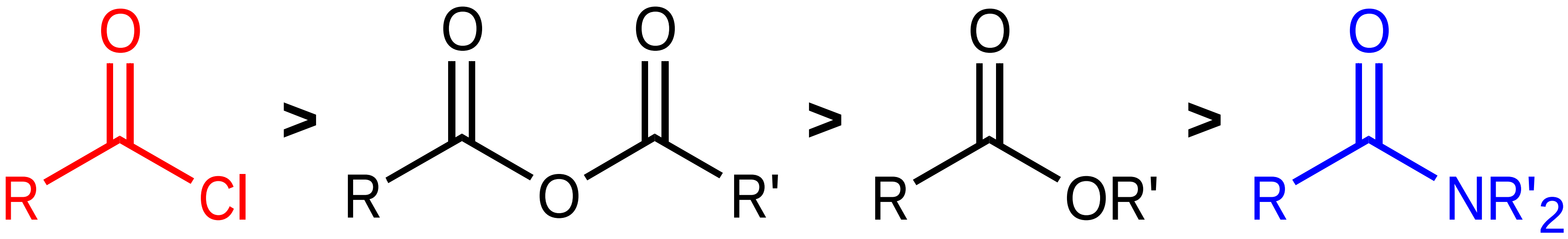
e.g.

reactivity of



- Electronic factor
  - ♦ The strongly polarized acid derivatives react more readily than less polar ones

- Thus, reactivity of



most reactive

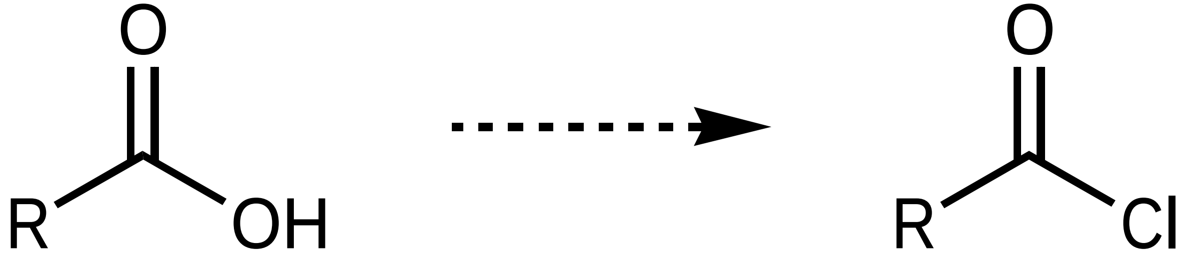
least reactive

- An important consequence of this reactivity
    - It is usually possible to convert a more reactive acid derivative to a less reactive one, but not vice versa

5. Acyl Chlorides

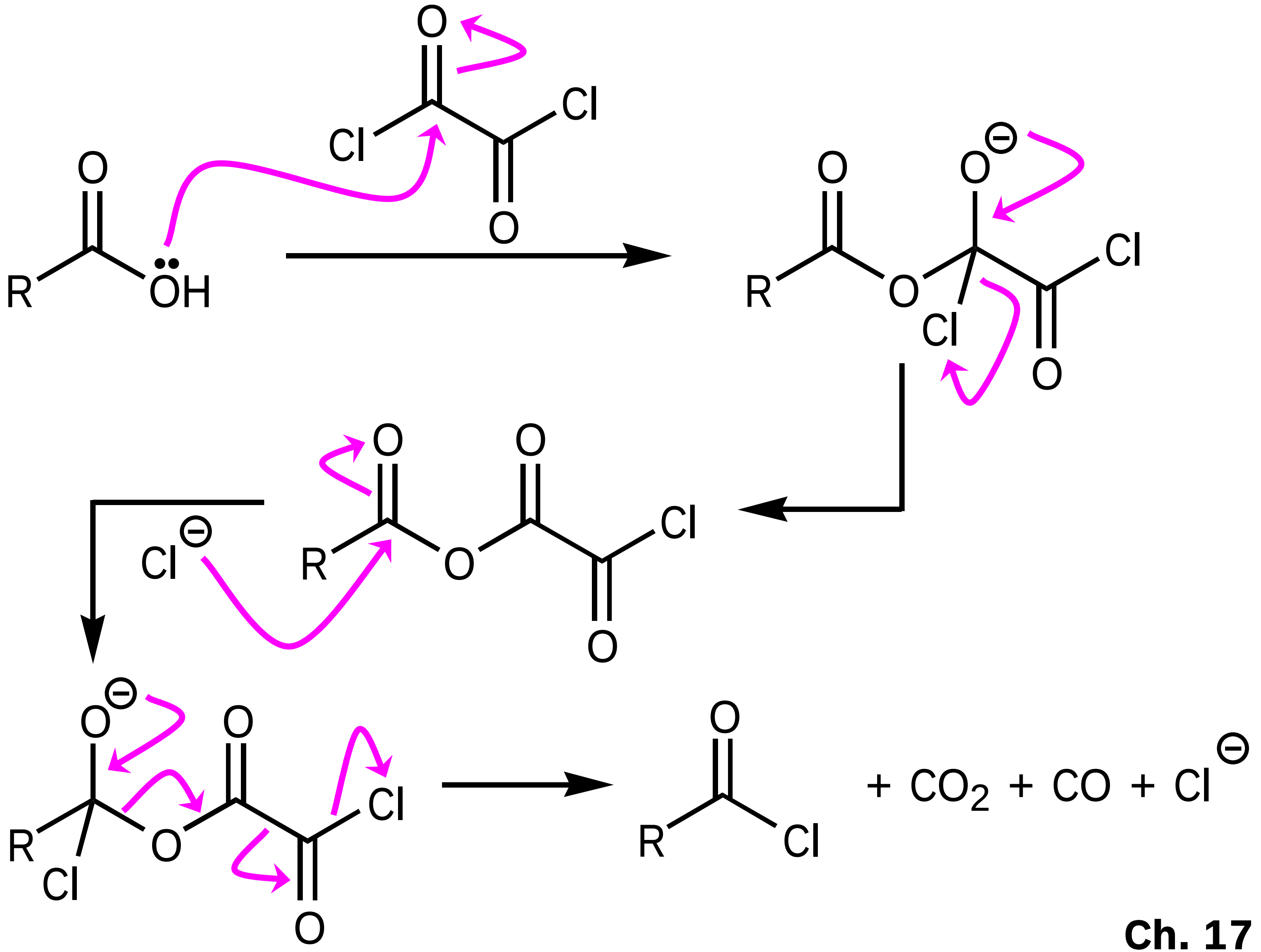
5A. Synthesis of Acyl Chlorides

- Conversion of carboxylic acids to acid chlorides

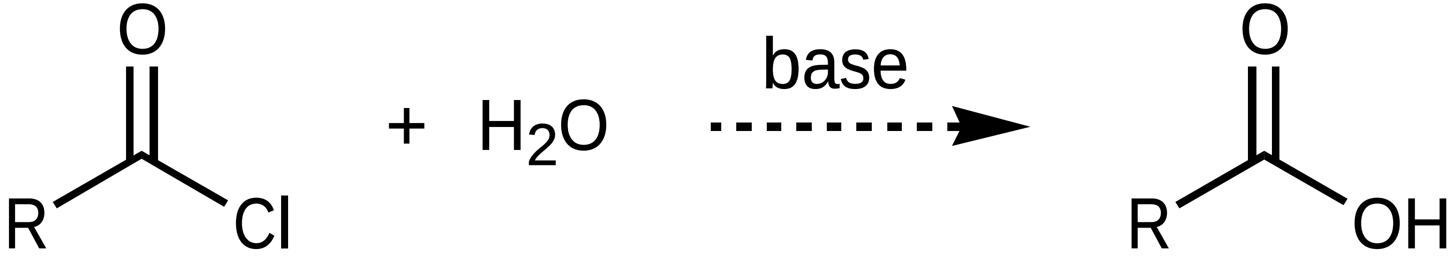


- Common reagents
  - $SOCl_2$
  - $(COCl)_2$
  - PCl_3 or PCl_5

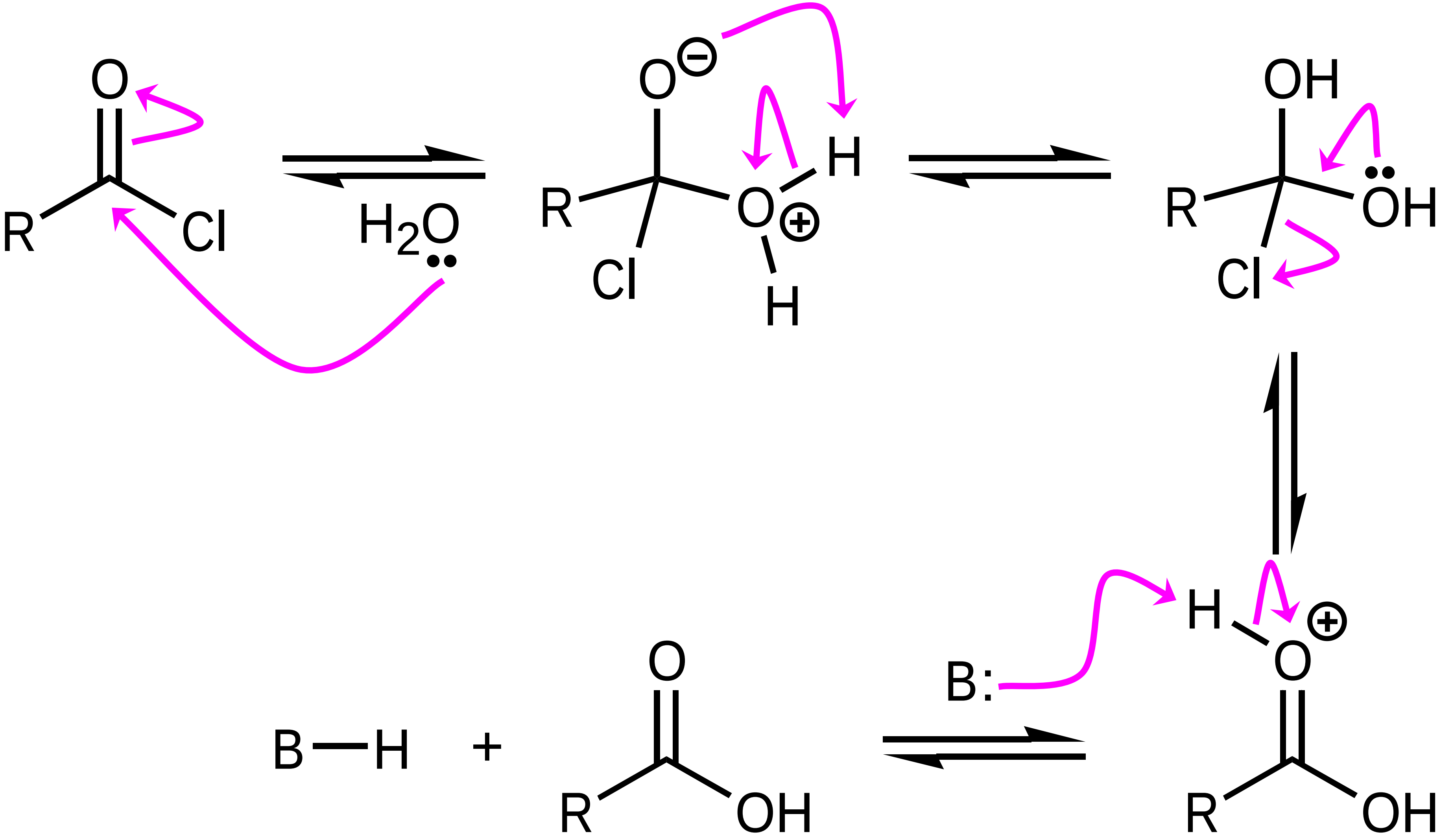
- Mechanism



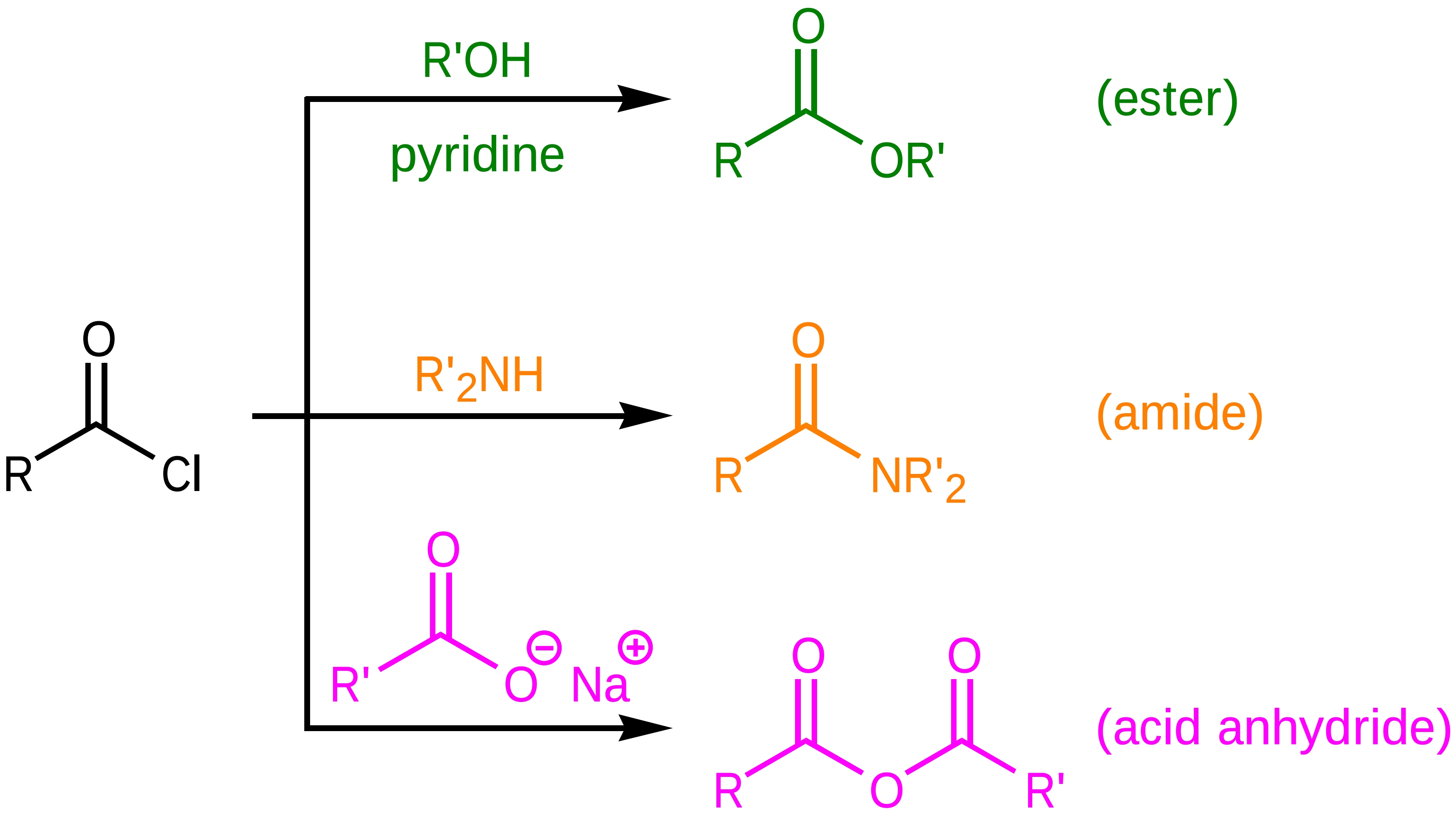
- Nucleophilic acyl substitution reactions of acid chlorides
    - Conversion of acid chlorides to carboxylic acids



- Mechanism



- Conversion of acid chlorides to other carboxylic derivatives



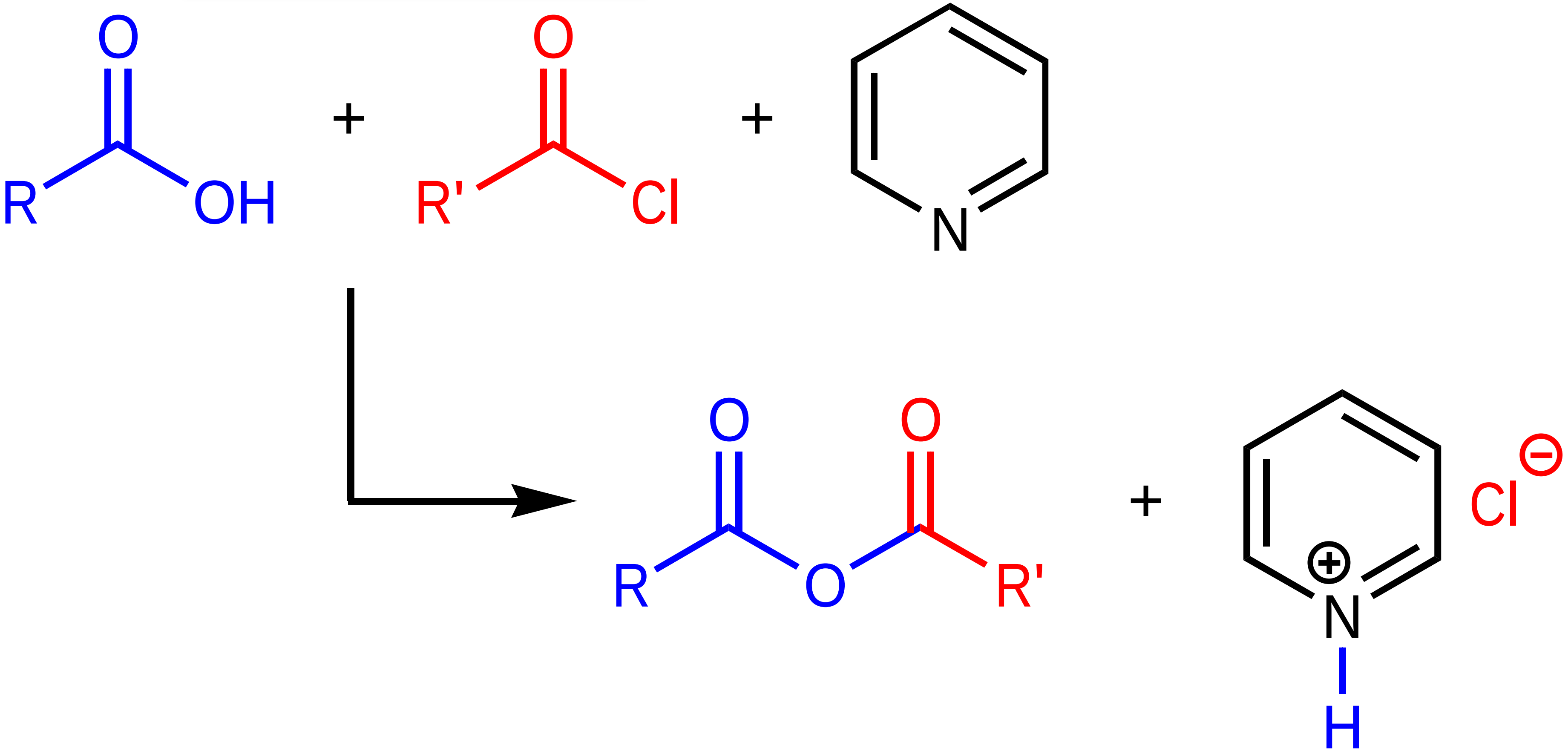
(ester)

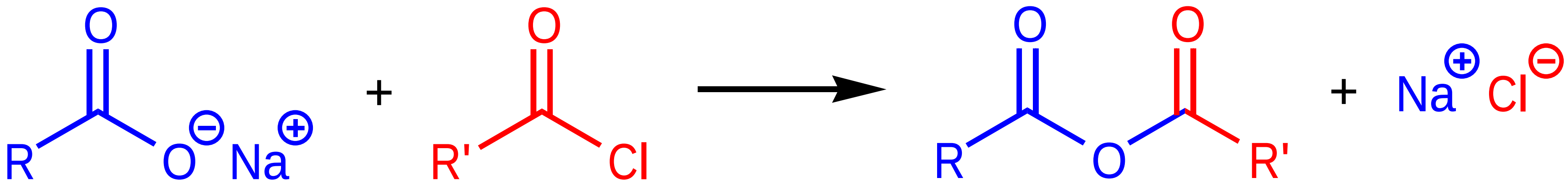
(amide)

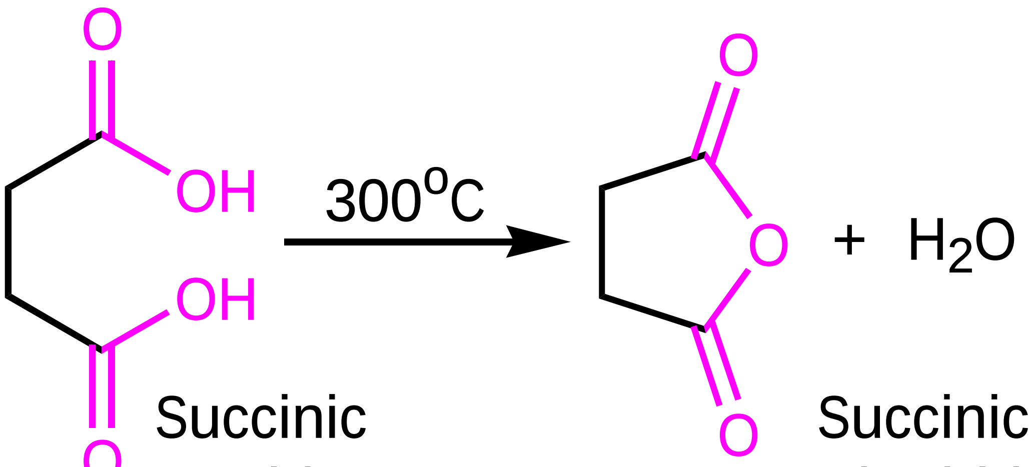
(acid anhydride)

6. Carboxylic Acid Anhydrides

6A. Synthesis of Carboxylic Acid Anhydrides

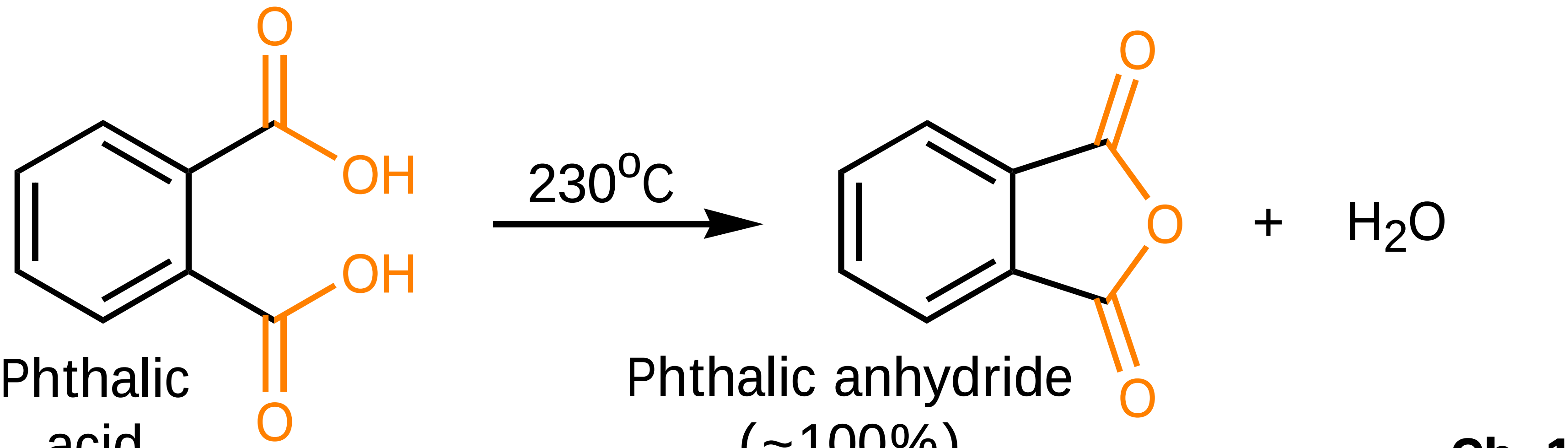






Succinic acid

Succinic anhydride

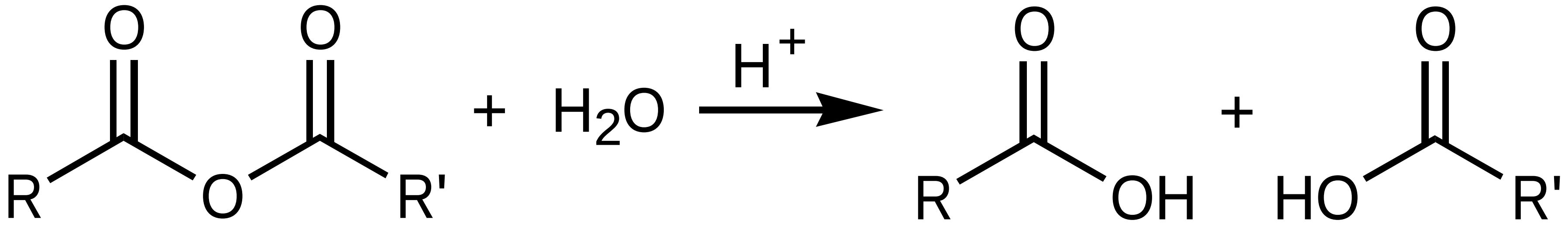


Phthalic acid

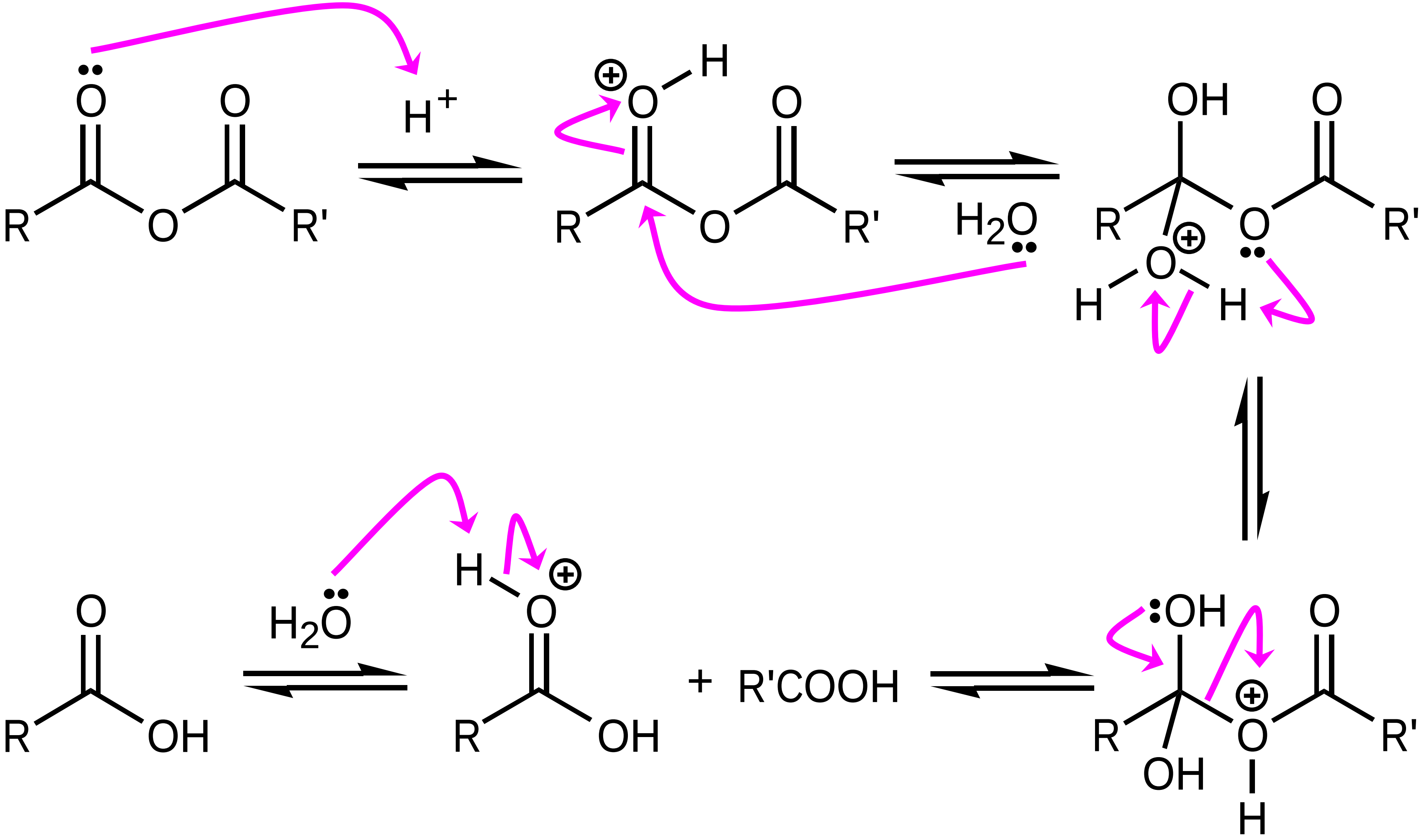
Phthalic anhydride (~100%)

6B. Reactions of Carboxylic Acid Anhydrides

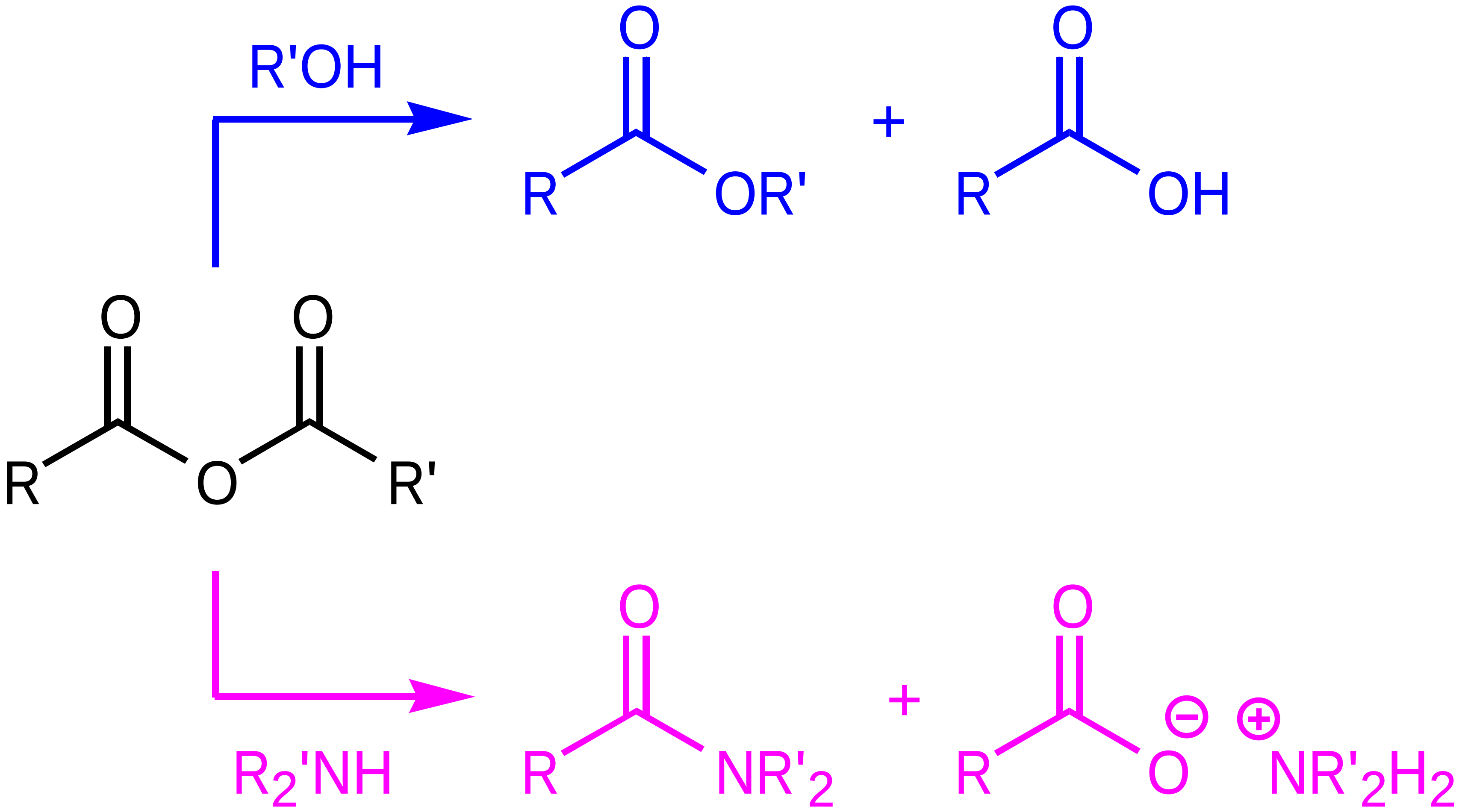
- Conversion of acid anhydrides to carboxylic acids



- Mechanism

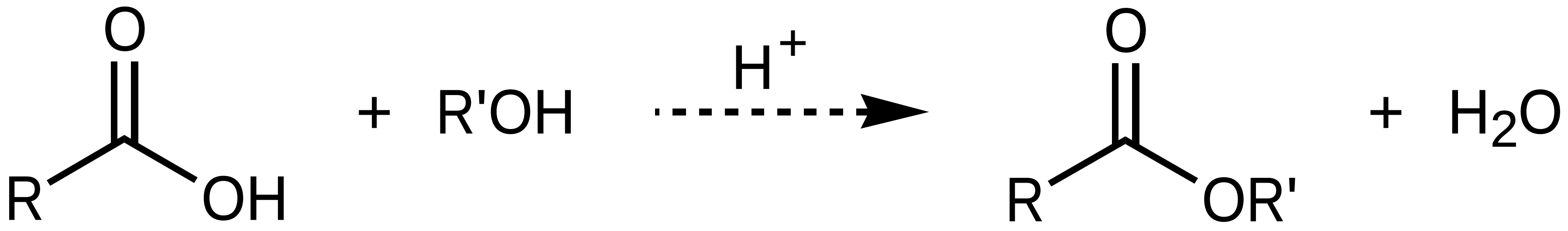


❖ Conversion of acid anhydrides to other carboxylic derivatives

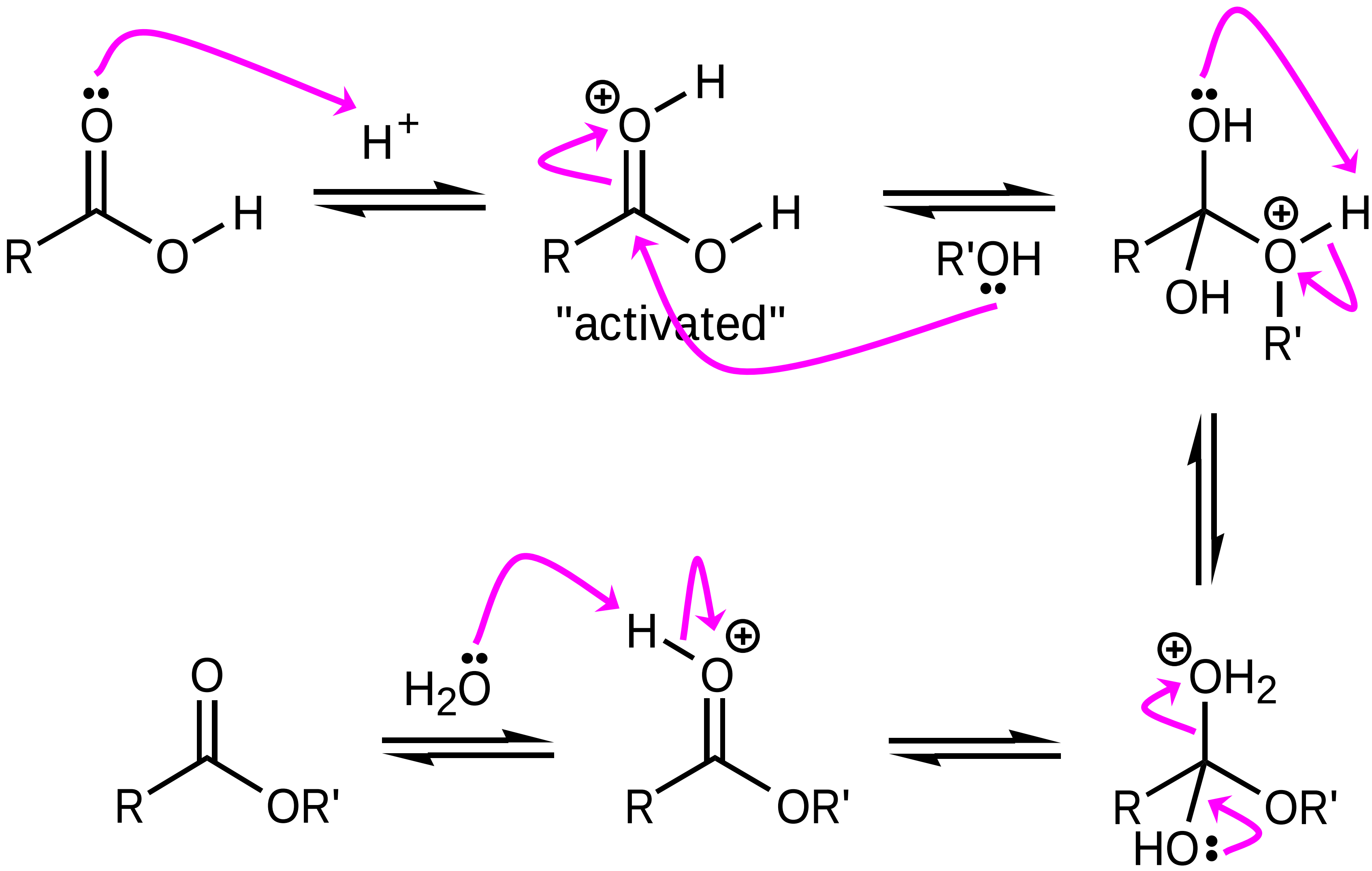


7. Esters

7A. Synthesis of Esters: Esterification



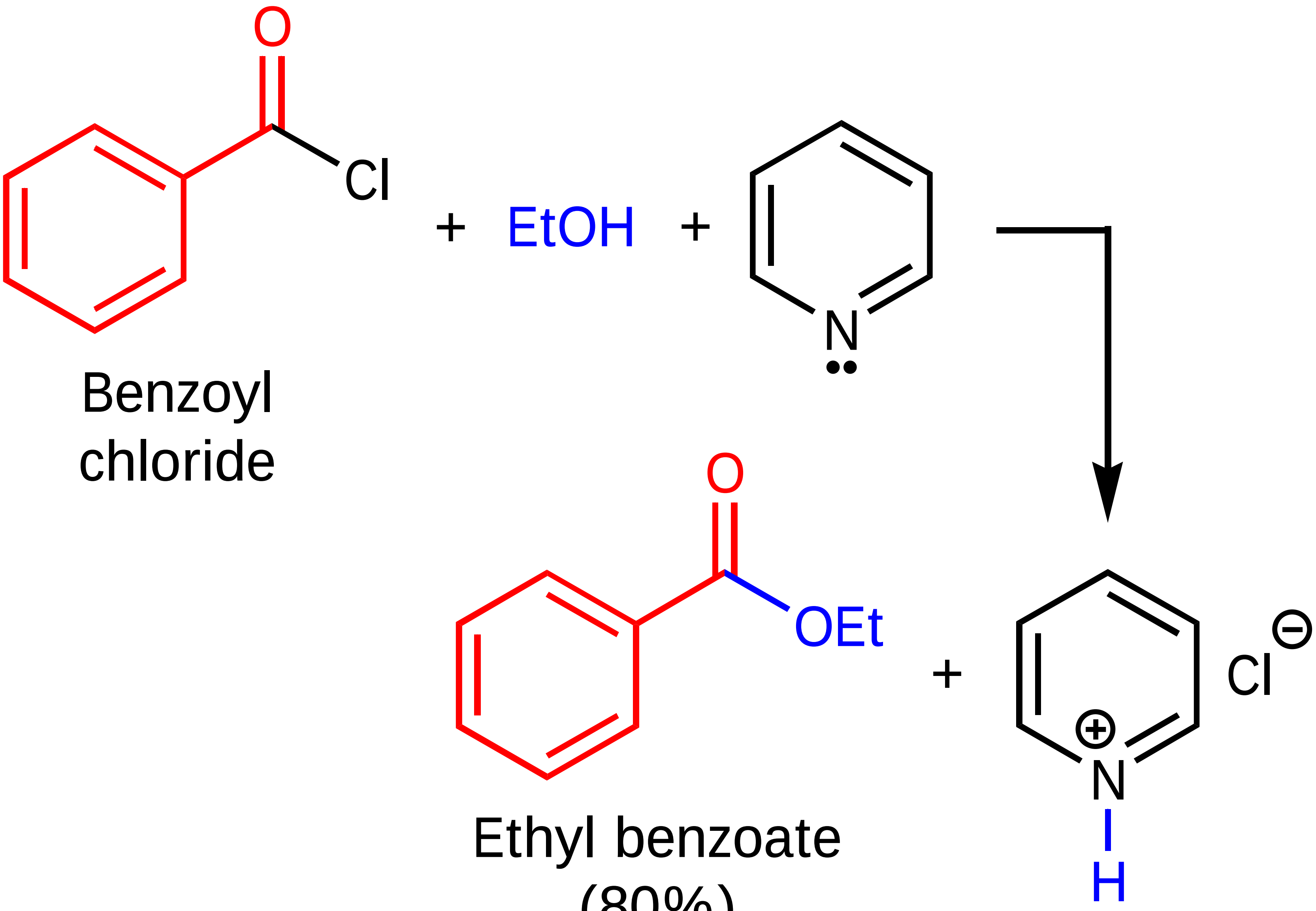
- Mechanism



O
R
O
H
H+
O
H
R
O
H
"activated"
R'OH
OH
R
OH
O
H
R'
OH2
R
OR'
HO
H
O
R
OR'
H2O
O
R
OR'

Esters from acyl chlorides

e.g.

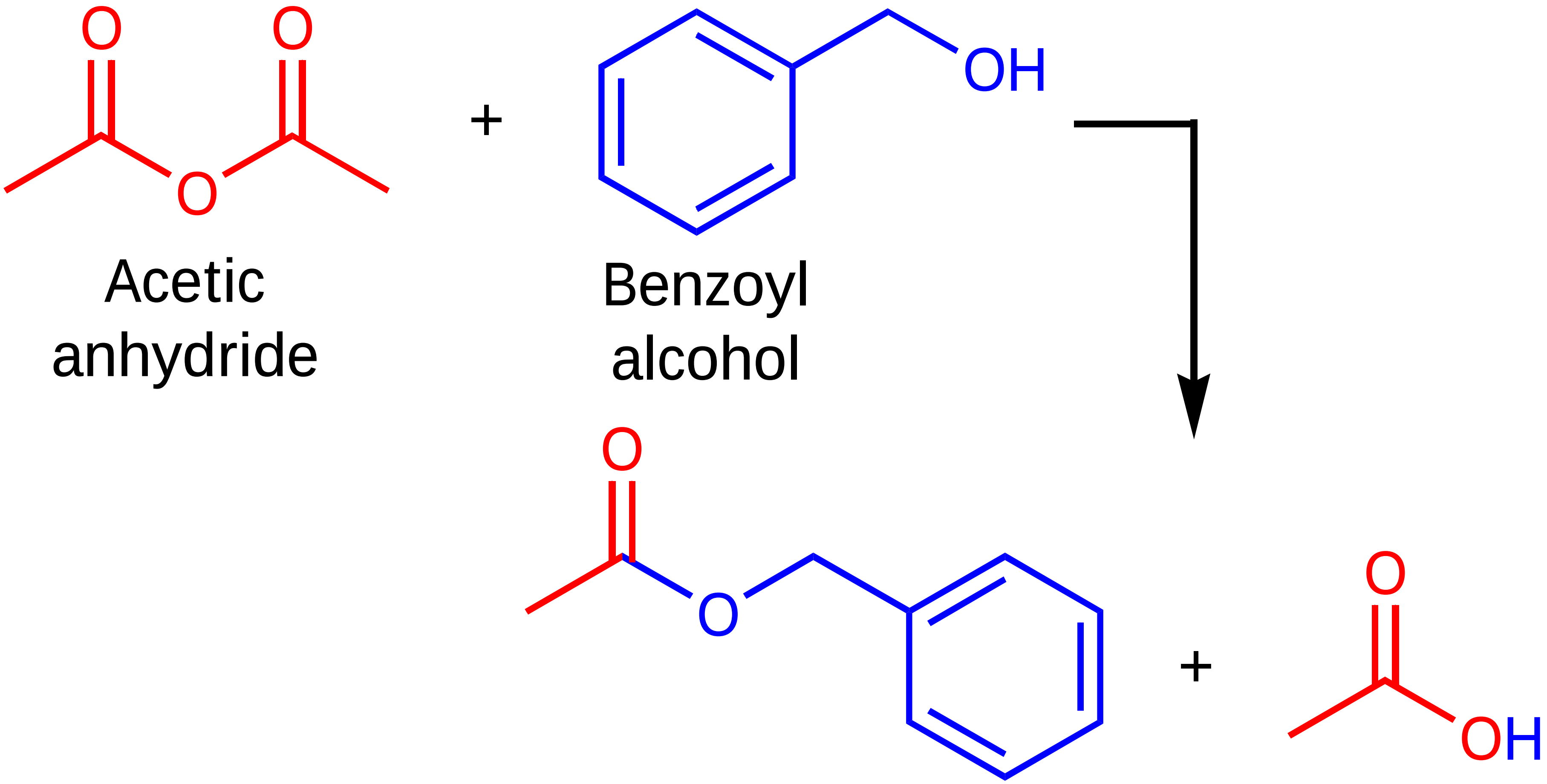


Benzoyl chloride

Ethyl benzoate (80%)

❖ Esters from carboxylic acid anhydrides

e.g.



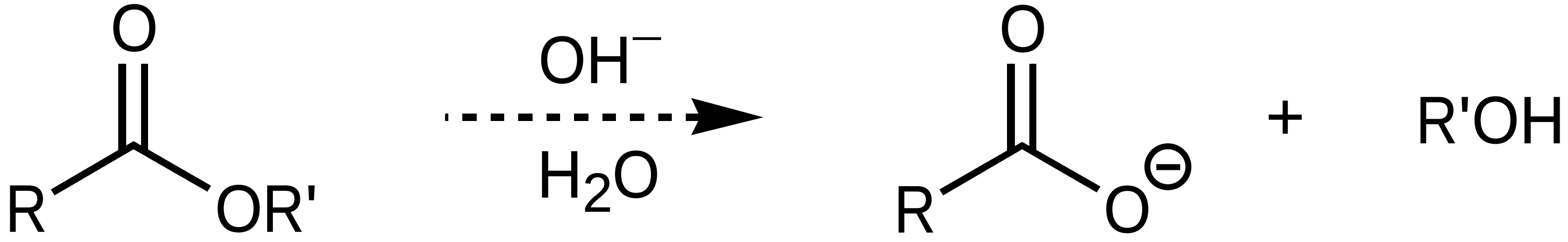
Acetic anhydride

Benzoyl alcohol

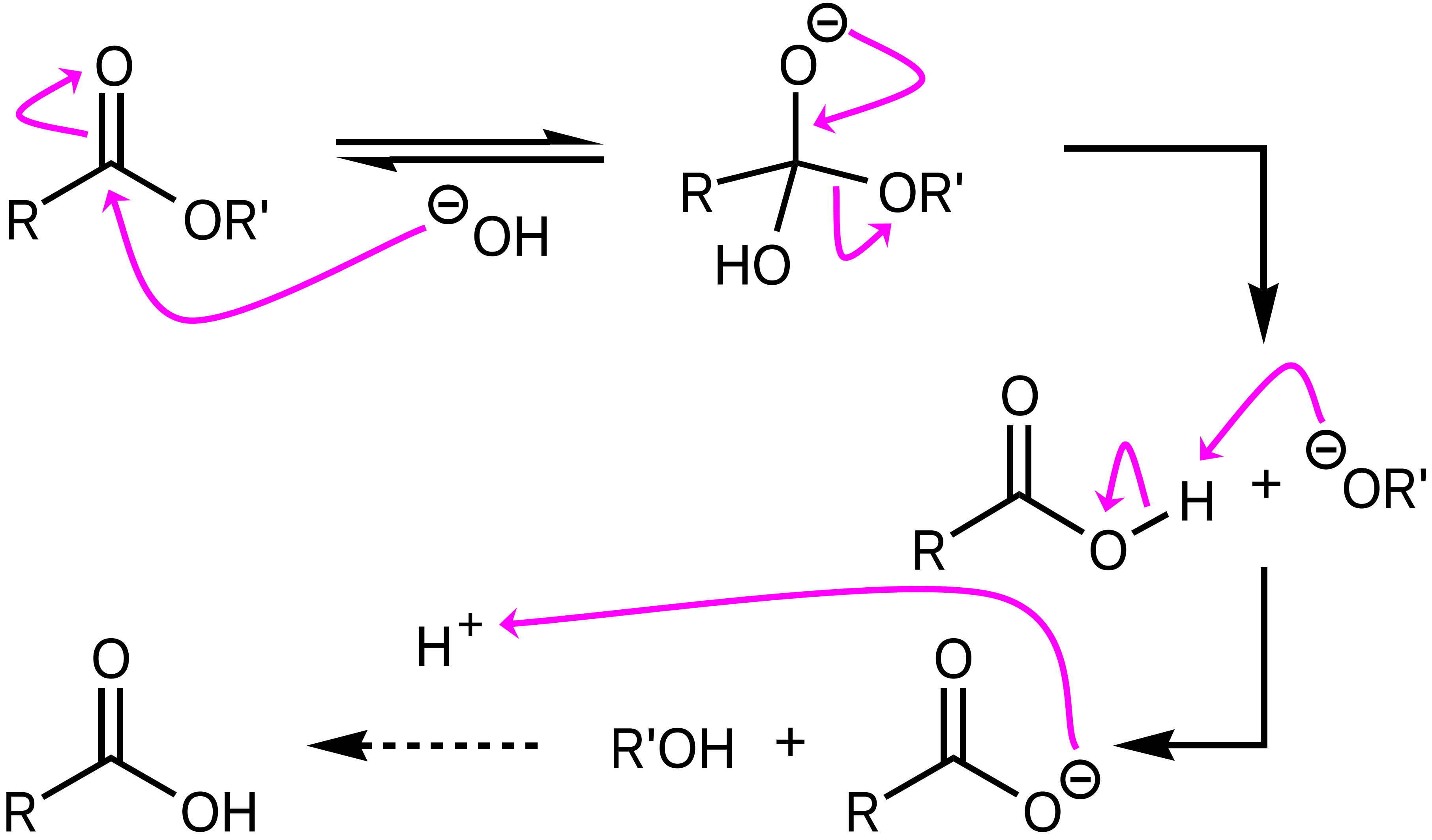
Benzoyl acetate

7B. Base-Promoted Hydrolysis of Esters: Saponification

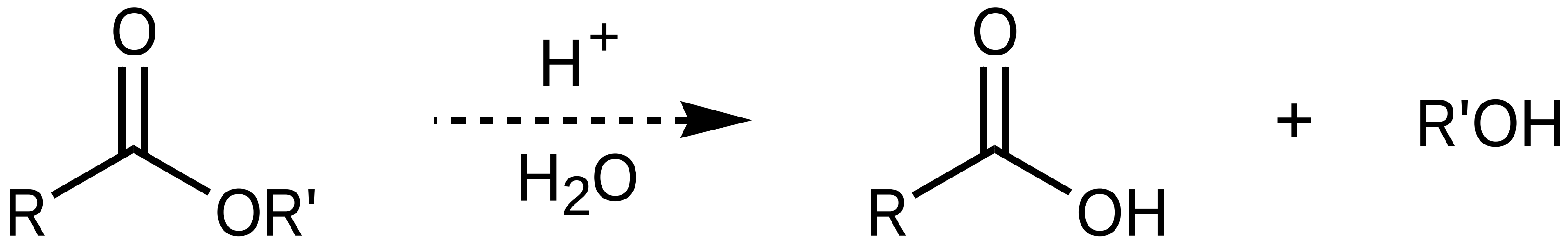
- Hydrolysis of esters under basic conditions: saponification



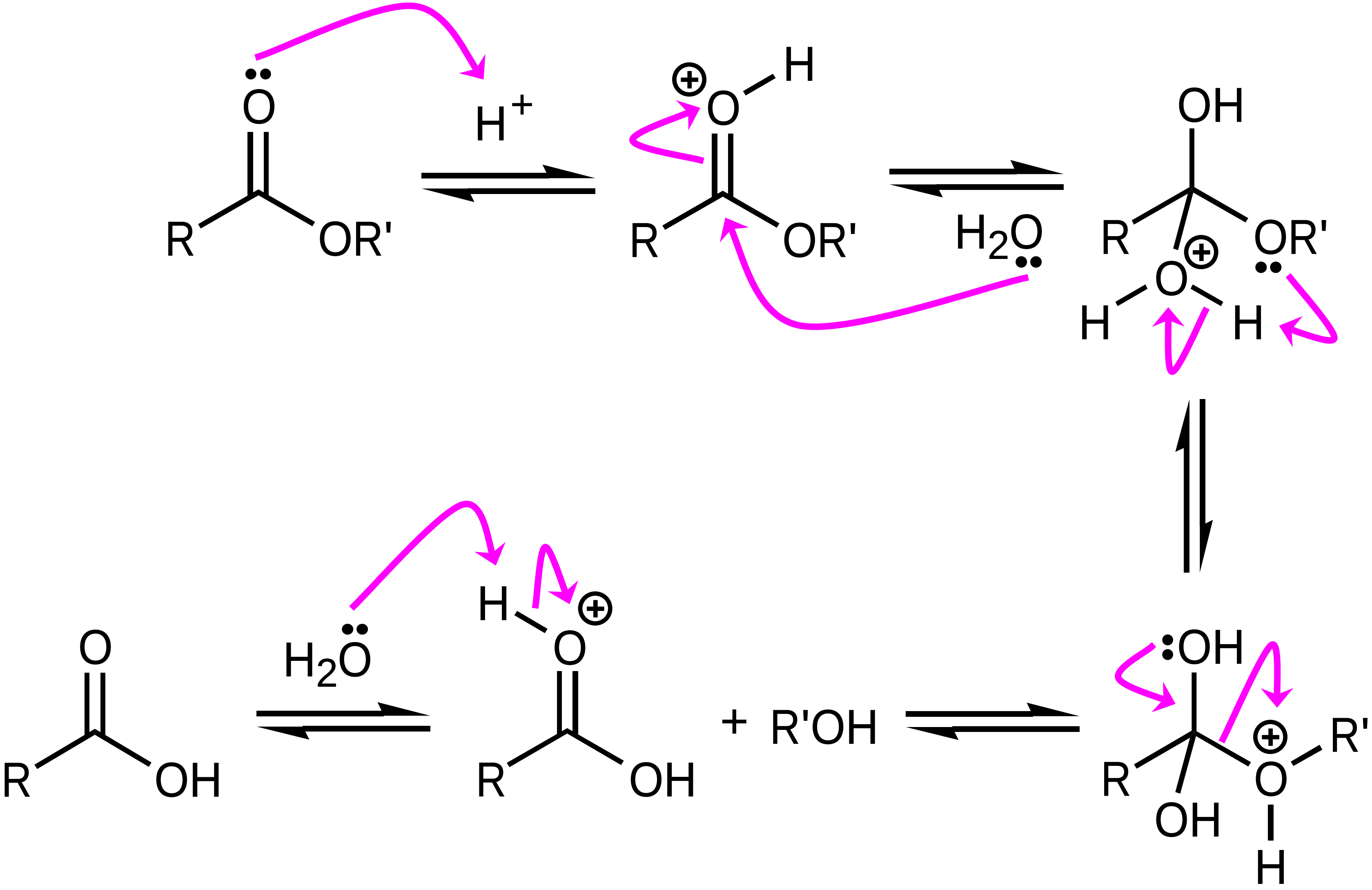
❖ Mechanism



❖ Hydrolysis of esters under acidic conditions

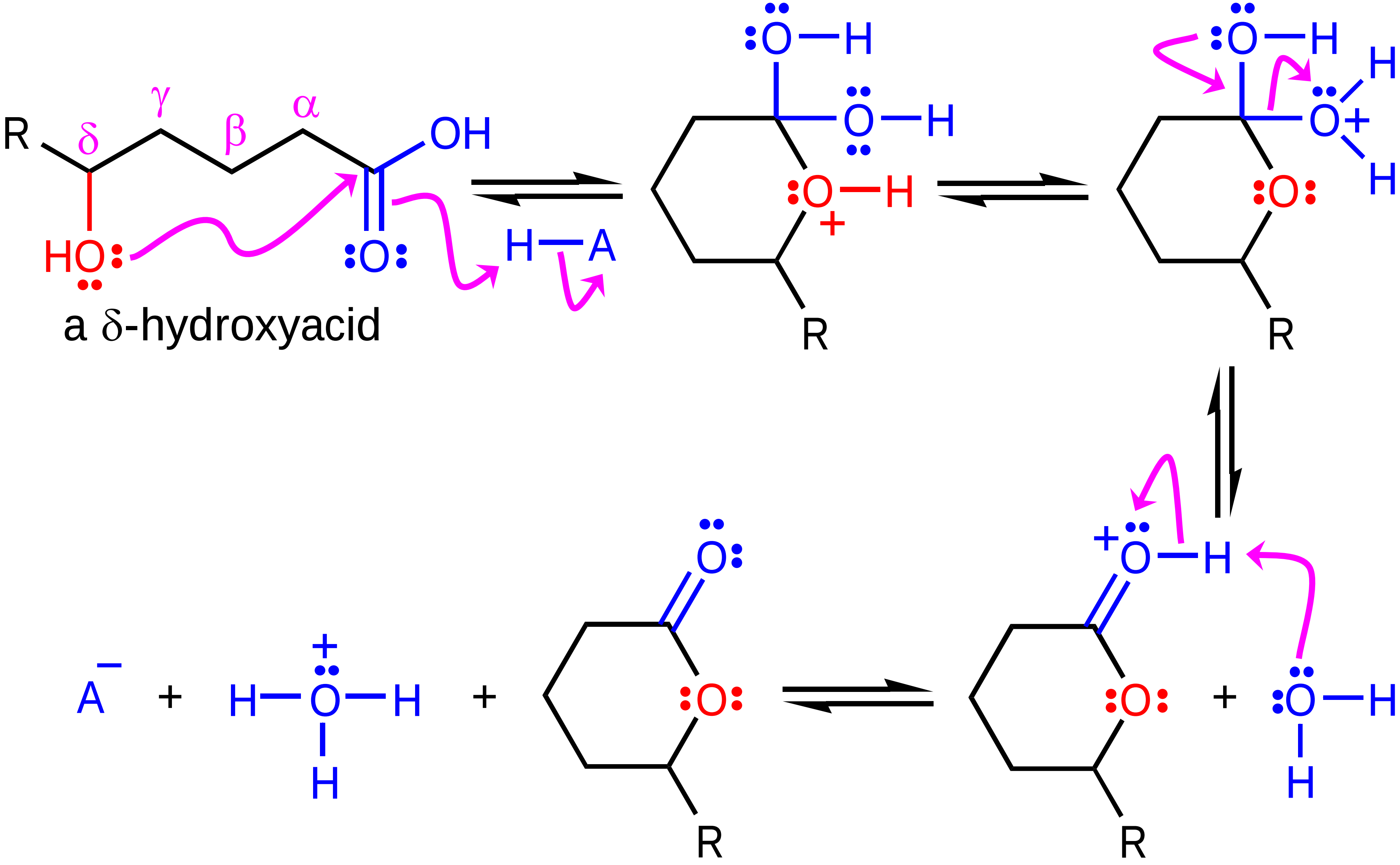


- # Mechanism


Ö
R
OR'
H^+
⊕
O
H
R
OR'
$H_2\ddot{O}$
OH
R
OR'
⊕
O
H
H
:OH
R
OH
⊕
O
R'
H
+ R'OH
H
⊕
O
R
OH
$H_2\ddot{O}$
O
R
OH

7C. Lactones

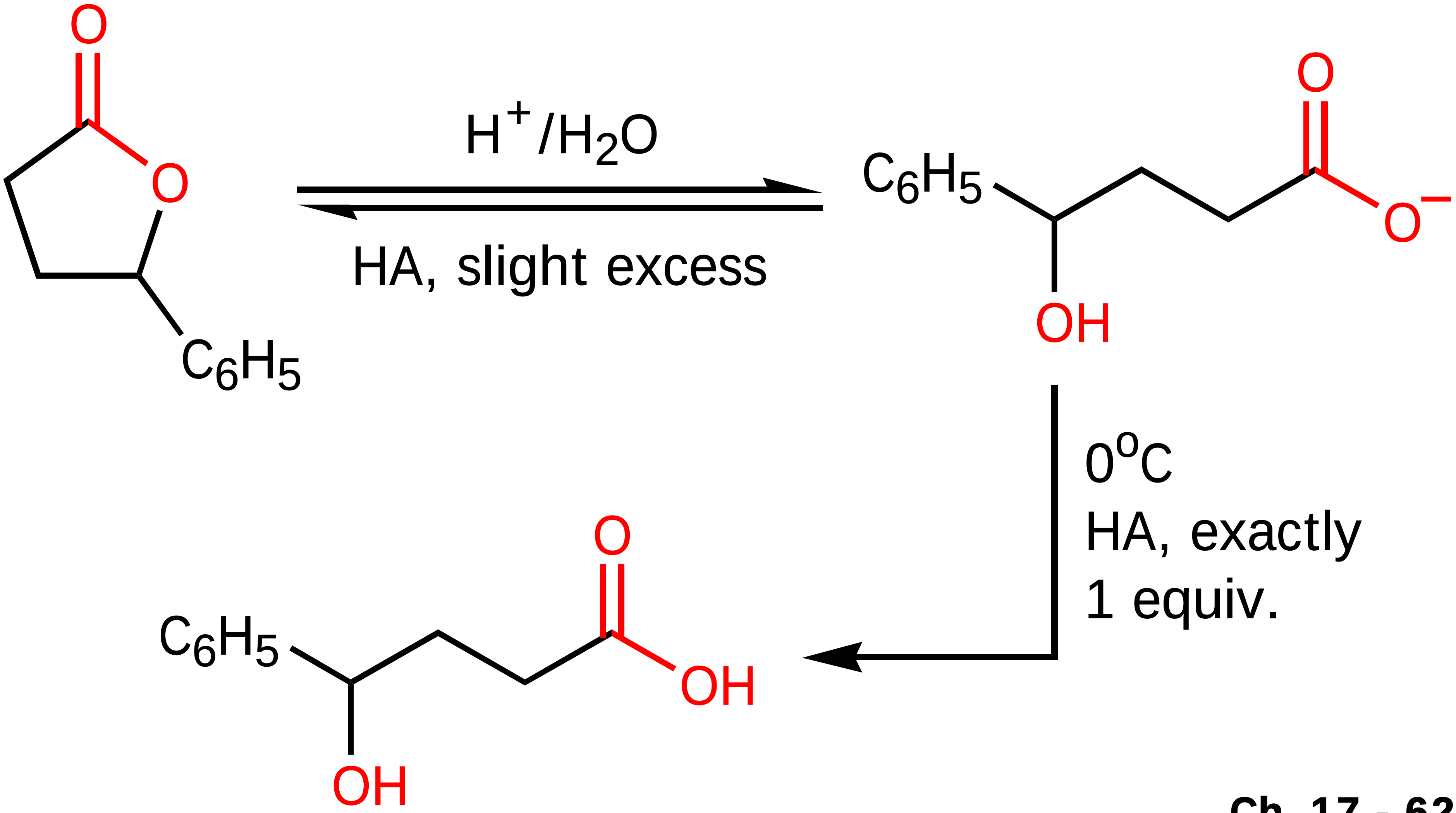
- Carboxylic acids whose molecules have a hydroxyl group on a γ or δ carbon undergo an intramolecular esterification to give cyclic esters known as γ- or δ-*lactones*



a δ-hydroxyacid

a δ-lactone

- **Lactones** are hydrolyzed by aqueous base just as other esters are



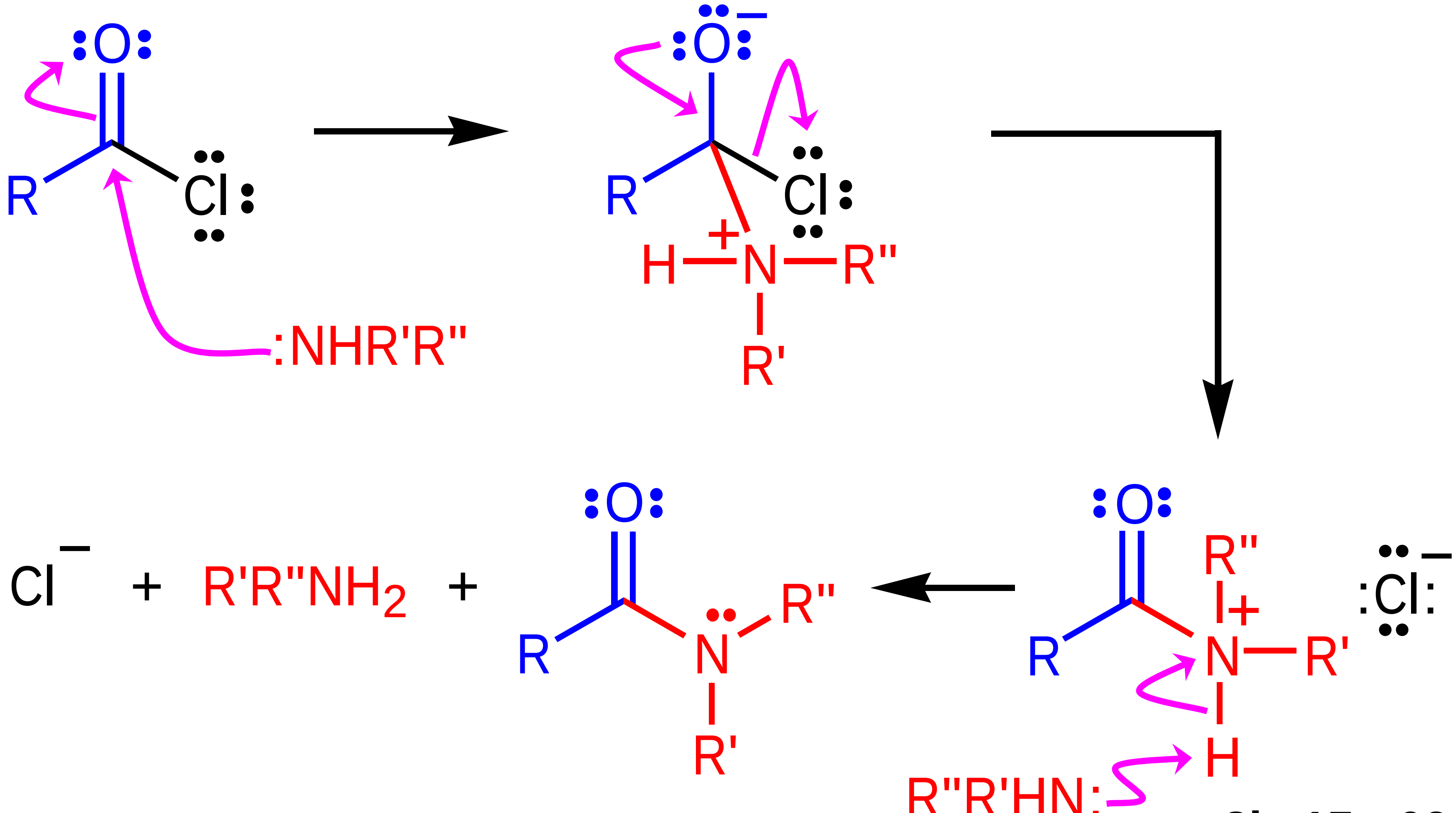
H^+/H_2O

HA, slight excess

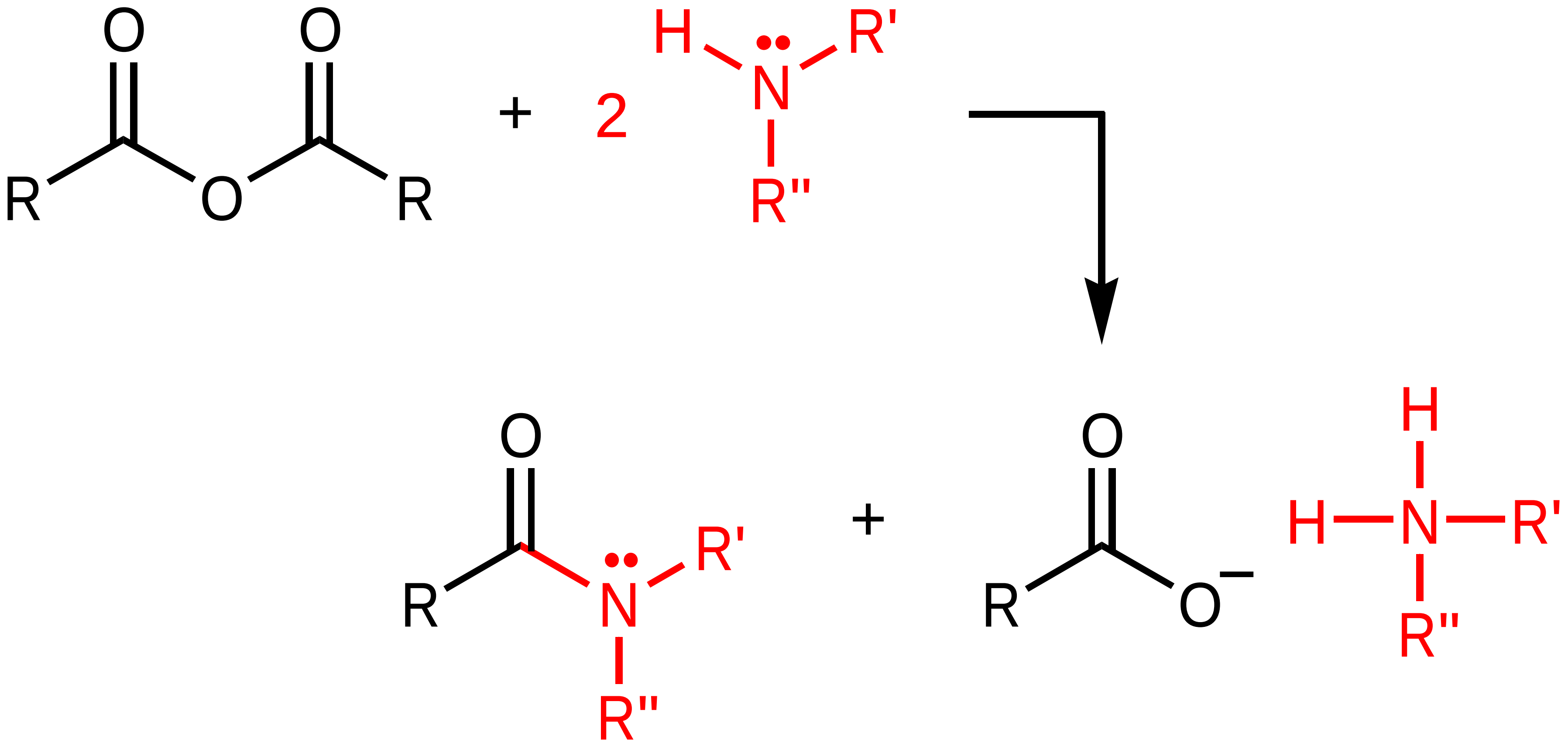
0°C
HA, exactly
1 equiv.

8. Amides

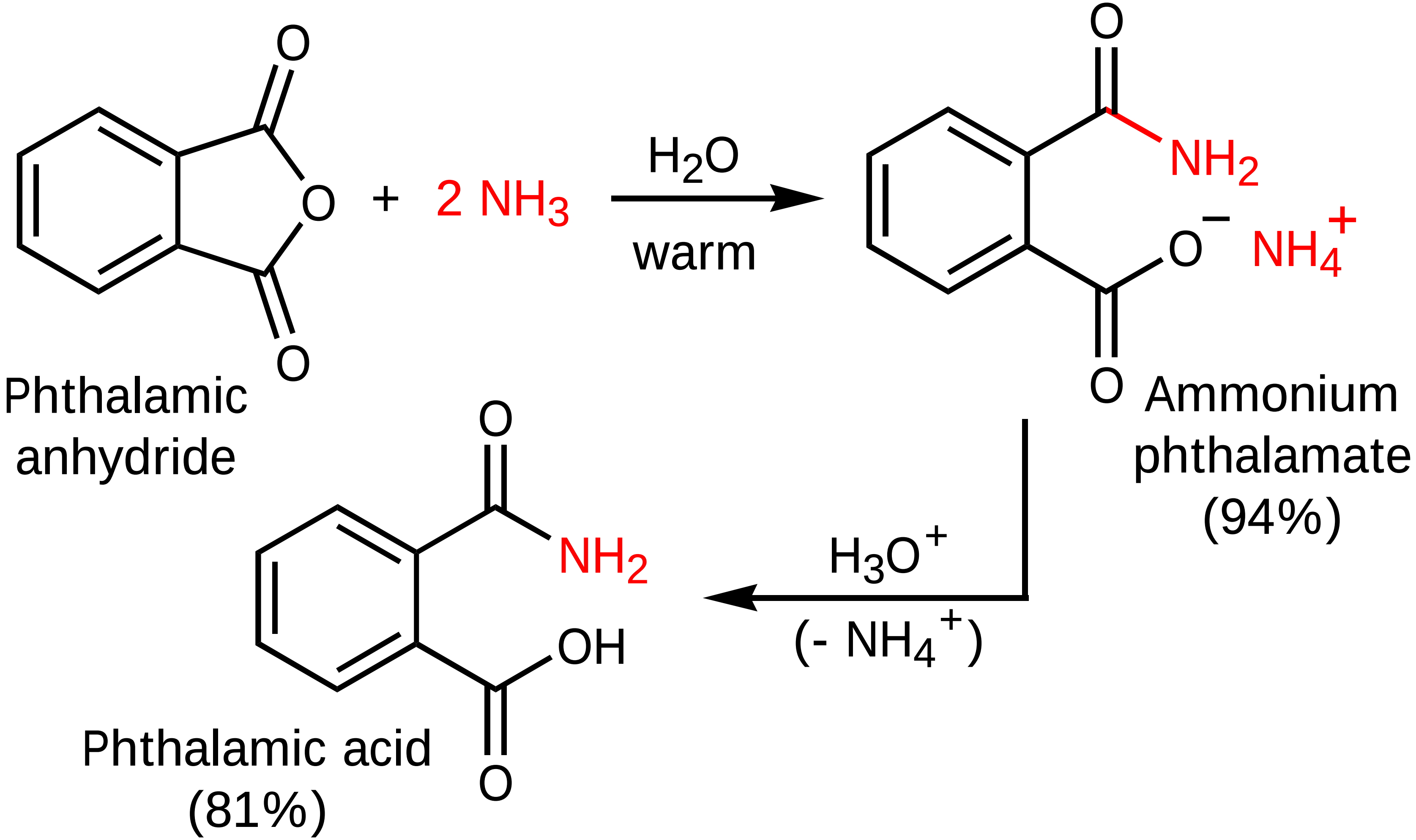
8B. Amides from Acyl Chlorides



8C. Amides from Carboxylic Anhydrides



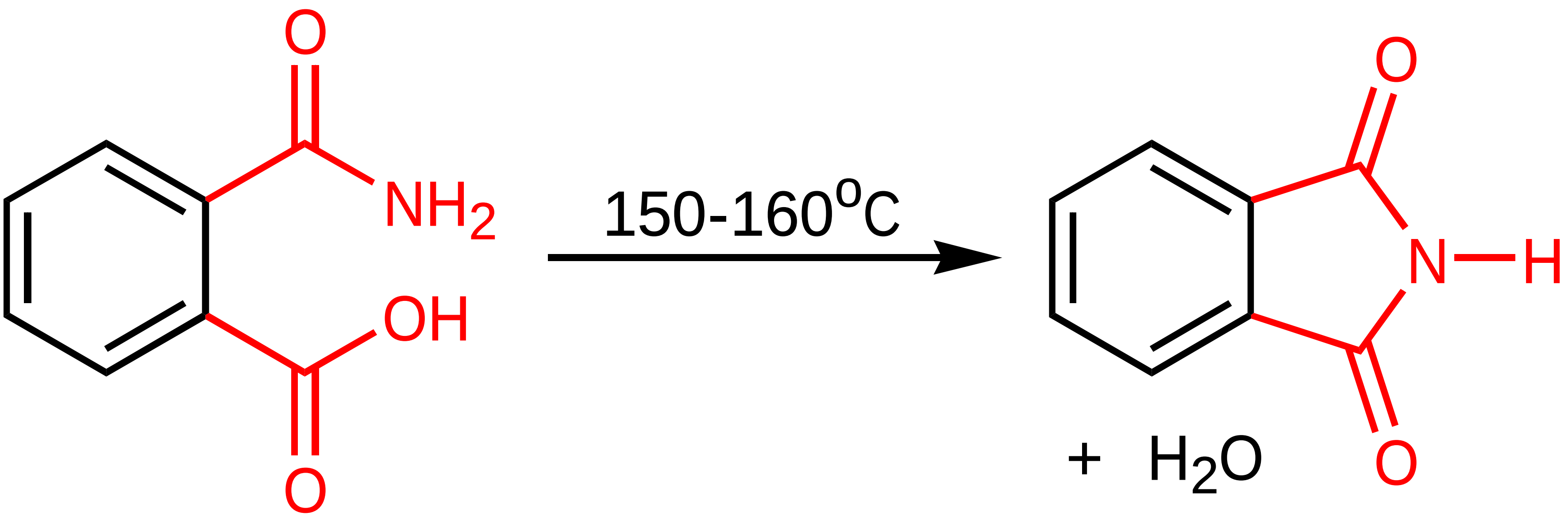
R', R'' can be H, alkyl, or aryl.



Phthalamic anhydride

Ammonium phthalamate (94%)

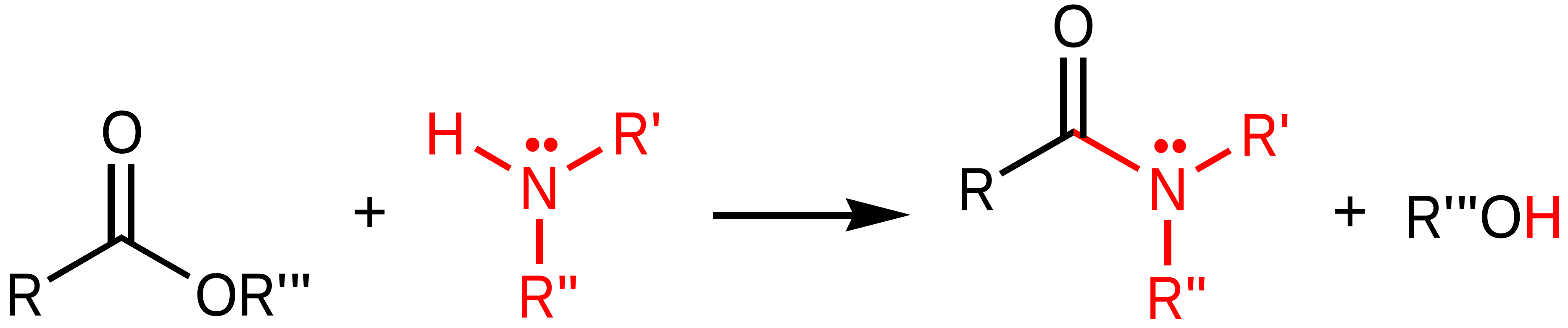
Phthalamic acid (81%)



Phthalamic acid

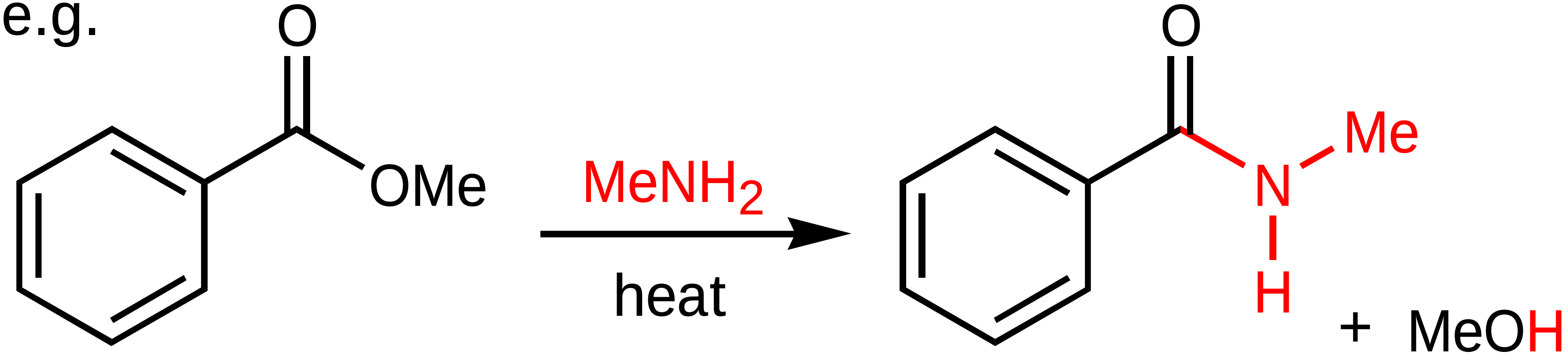
Phthalimide
(~ 100%)

8D. Amides from Esters

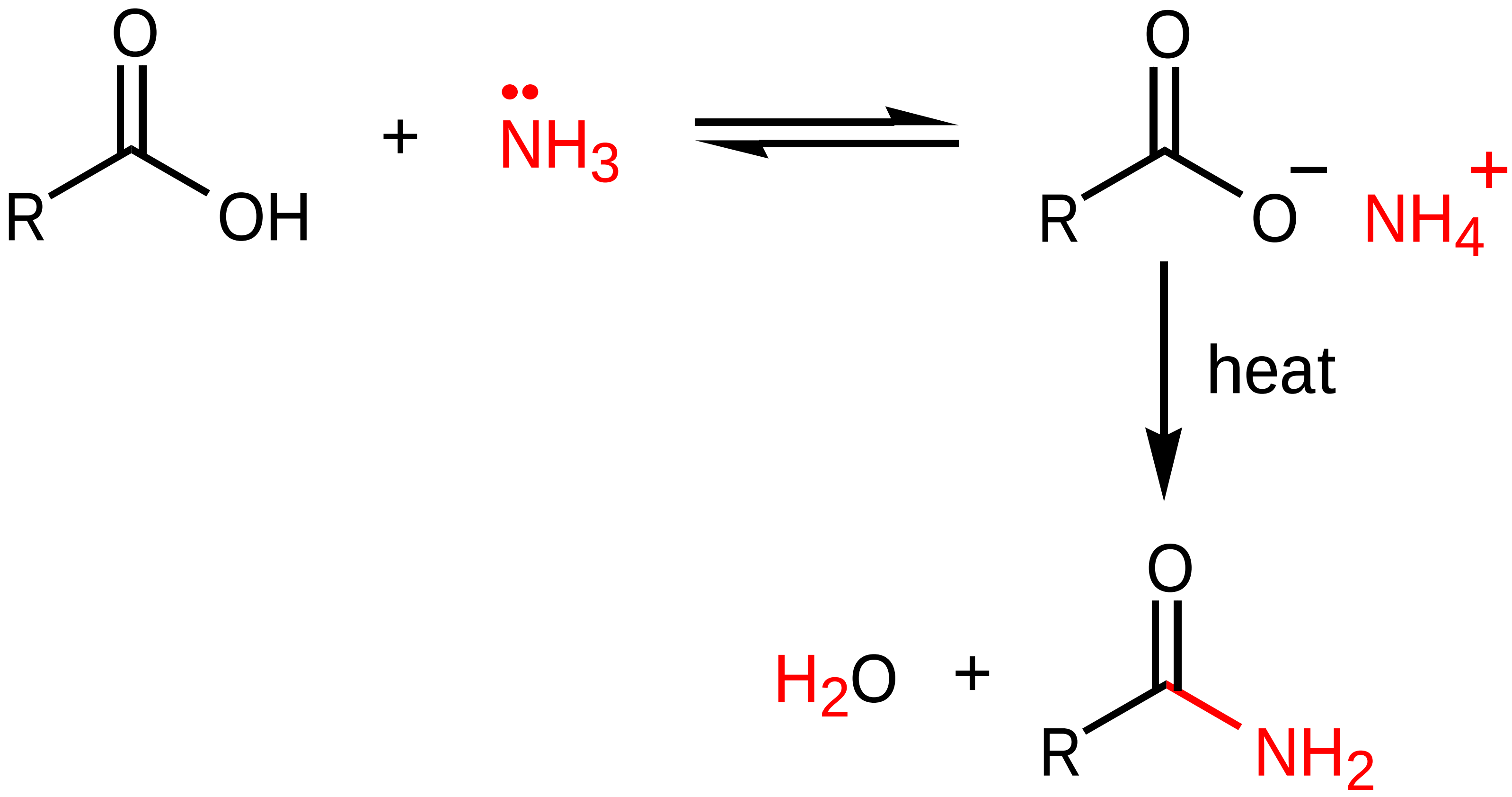


R' and / or R'' may be H.

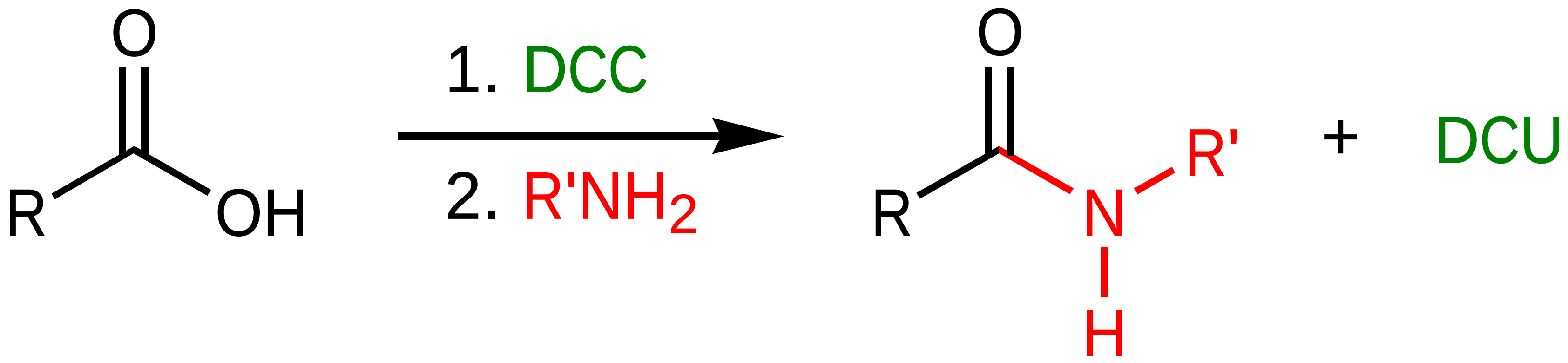
e.g.



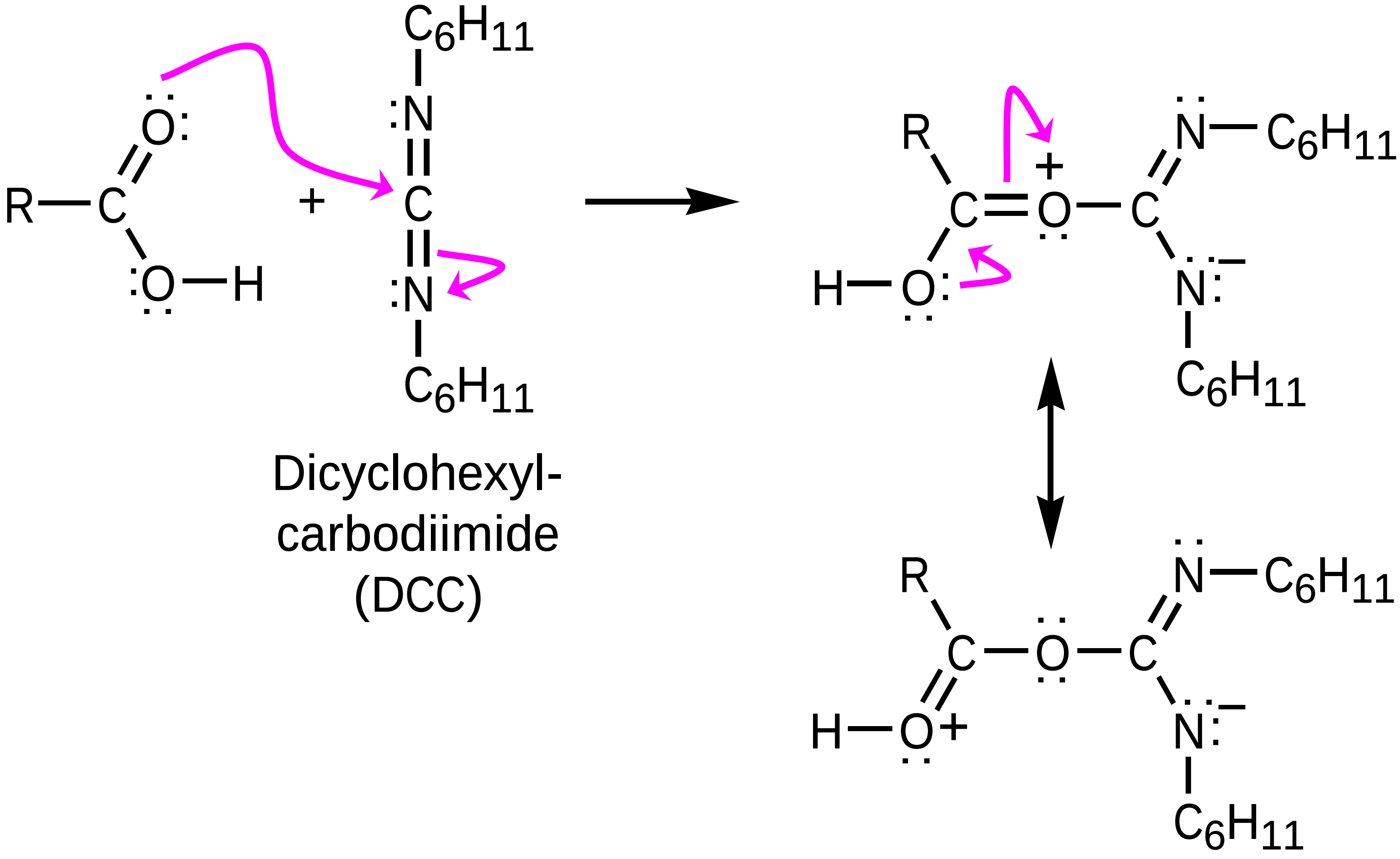
8E. Amides from Carboxylic Acids and Ammonium Carboxylates



❖ DCC-Promoted amide synthesis

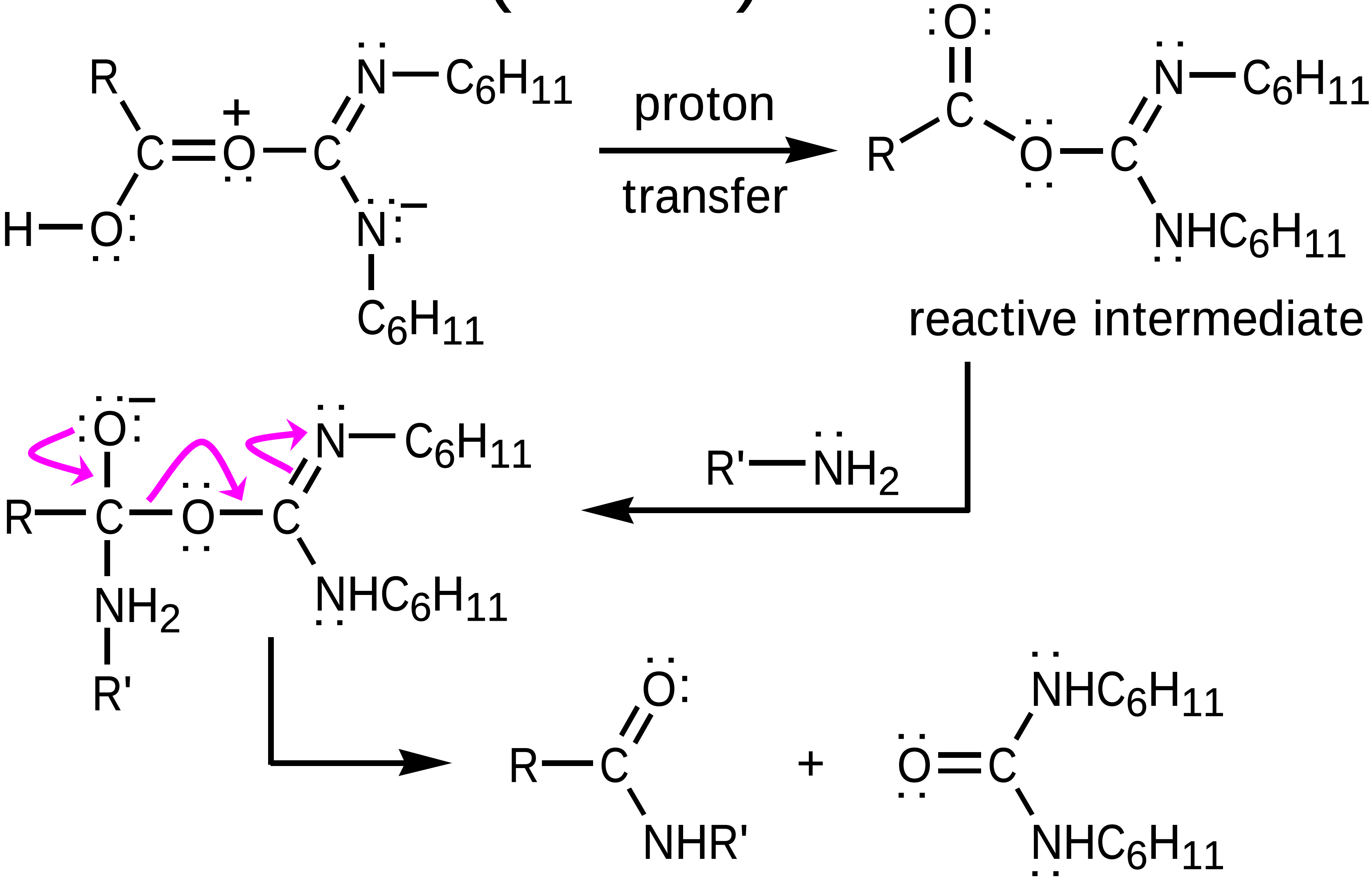


❖ Mechanism



Dicyclohexyl-
carbodiimide
(DCC)

❖ Mechanism (Cont’d)



proton transfer

reactive intermediate

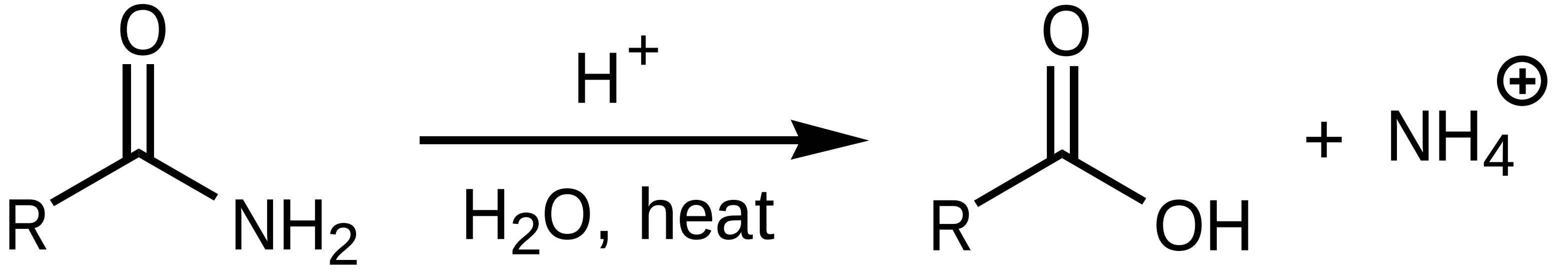
$R'-\ddot{N}H_2$

an amide

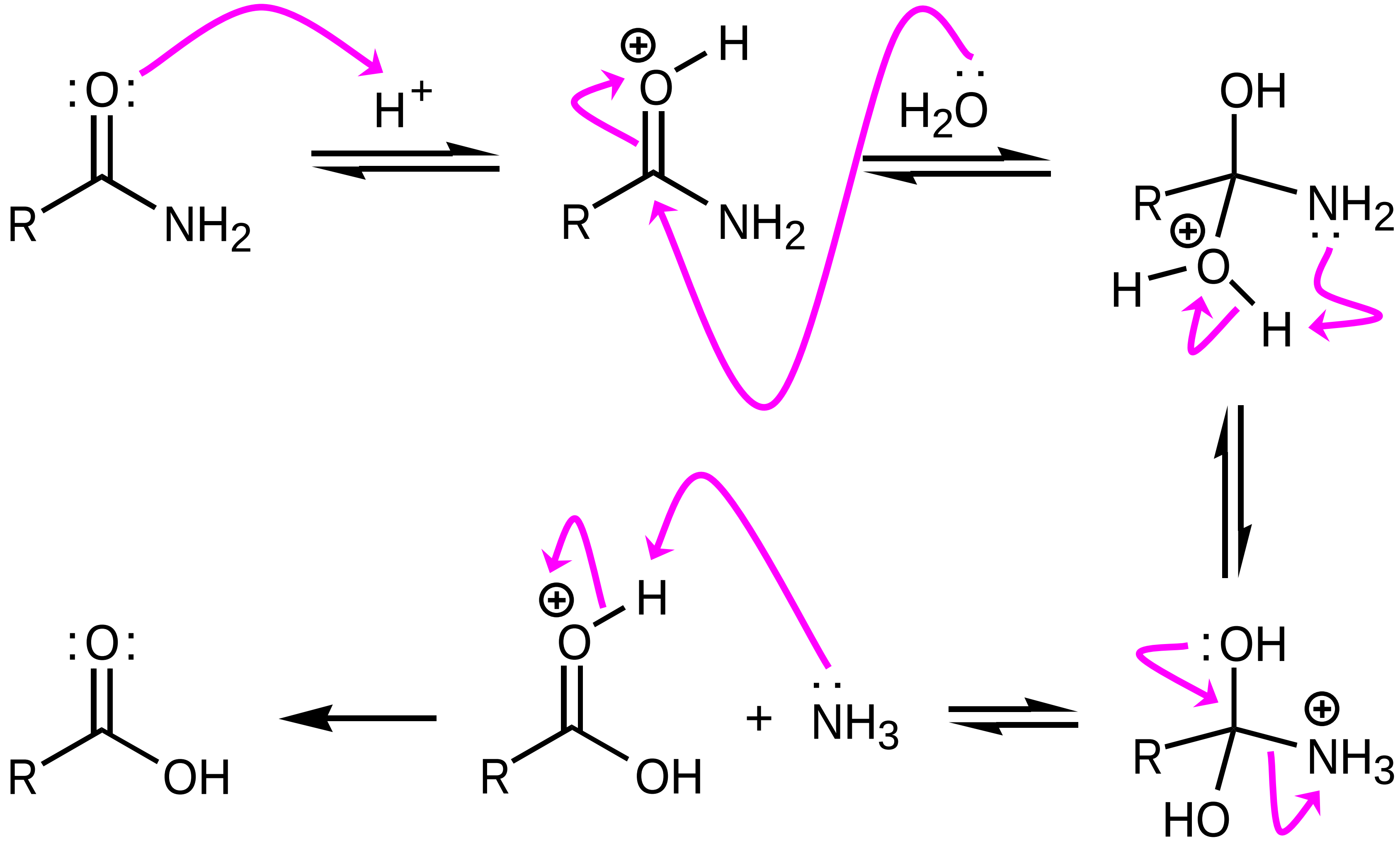
N,N'-Dicyclohexylurea
(DCU)

8F. Hydrolysis of Amides

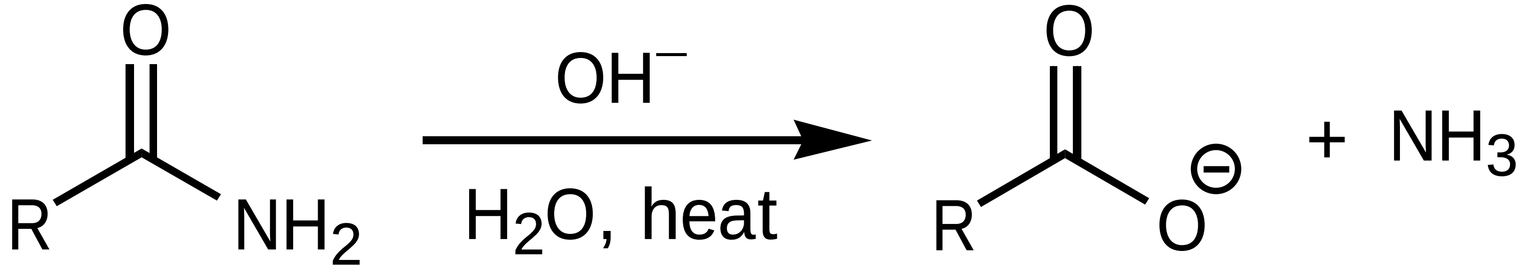
- Acid hydrolysis of amides



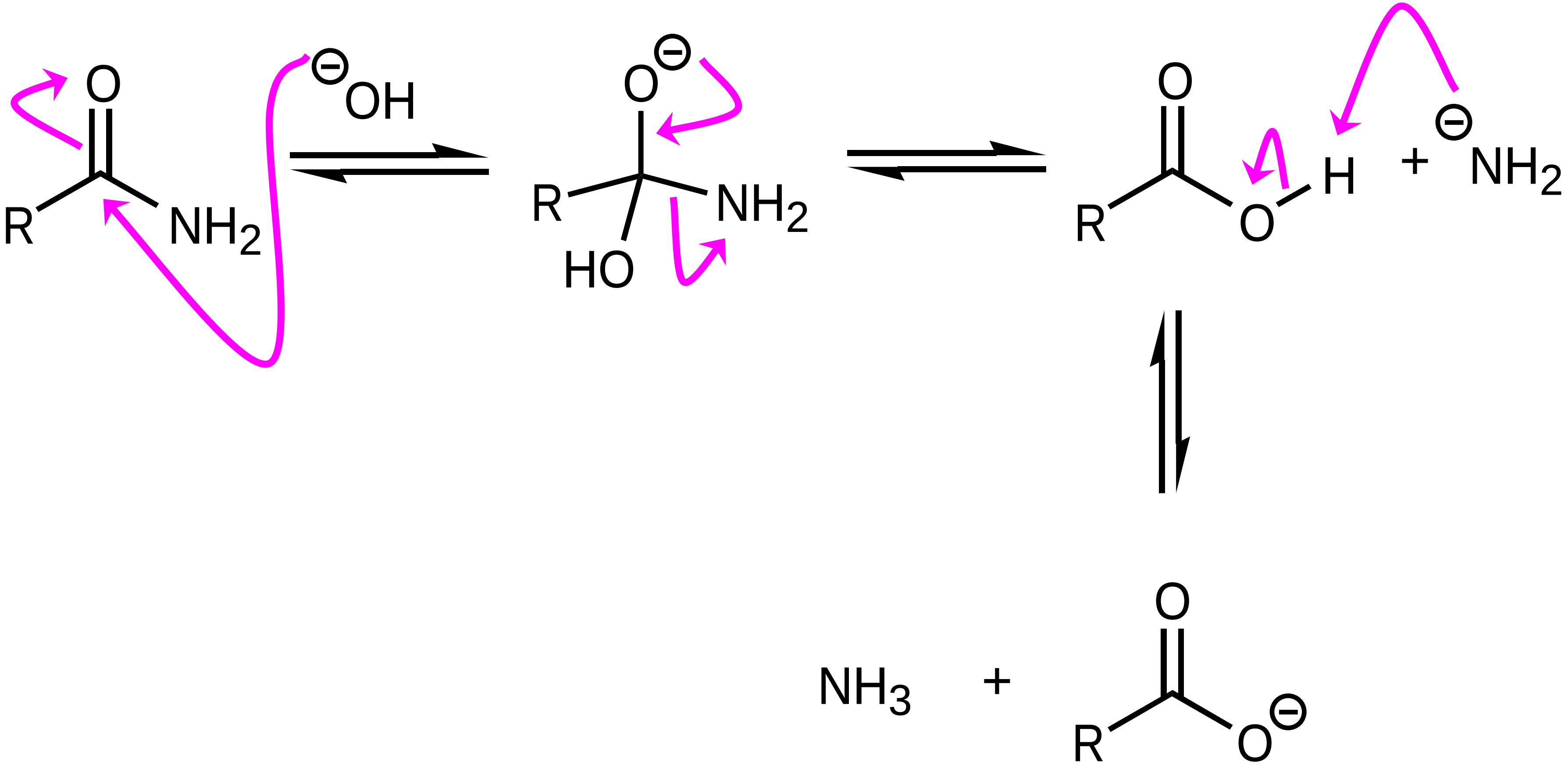
❖ Mechanism



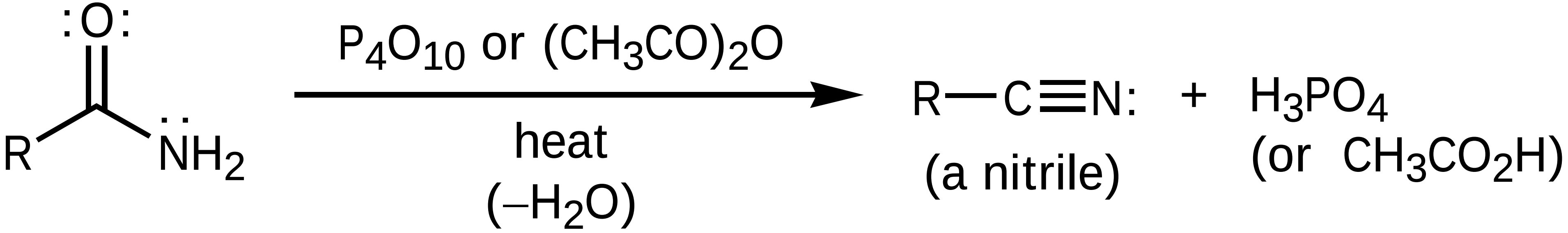
- Basic hydrolysis of amides



❖ Mechanism

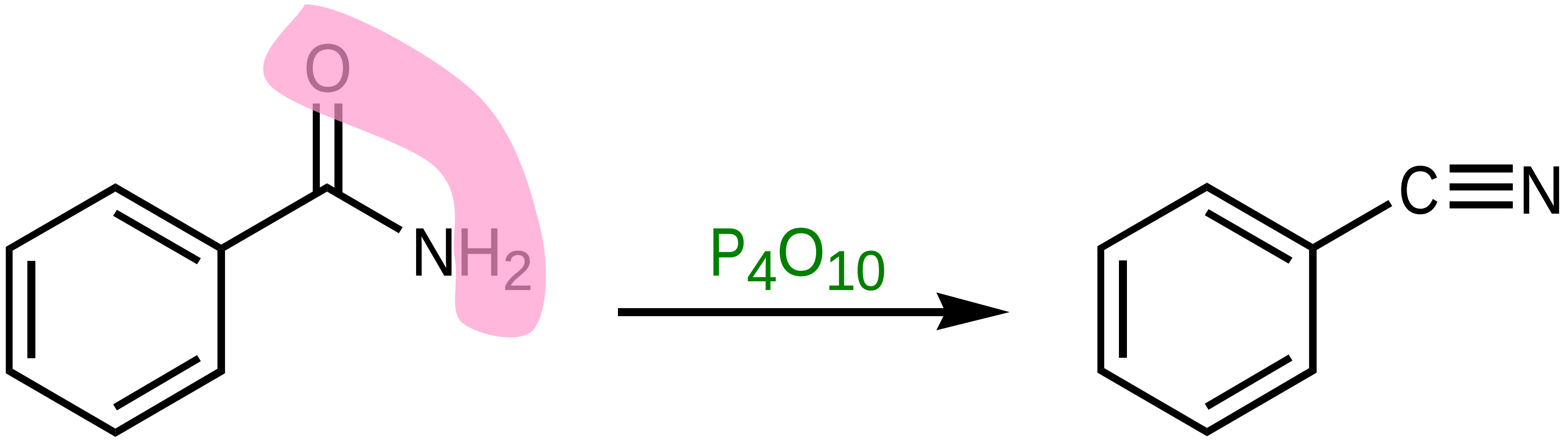


8G. Nitriles from the Dehydration of Amides

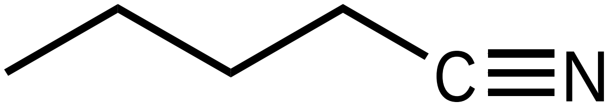


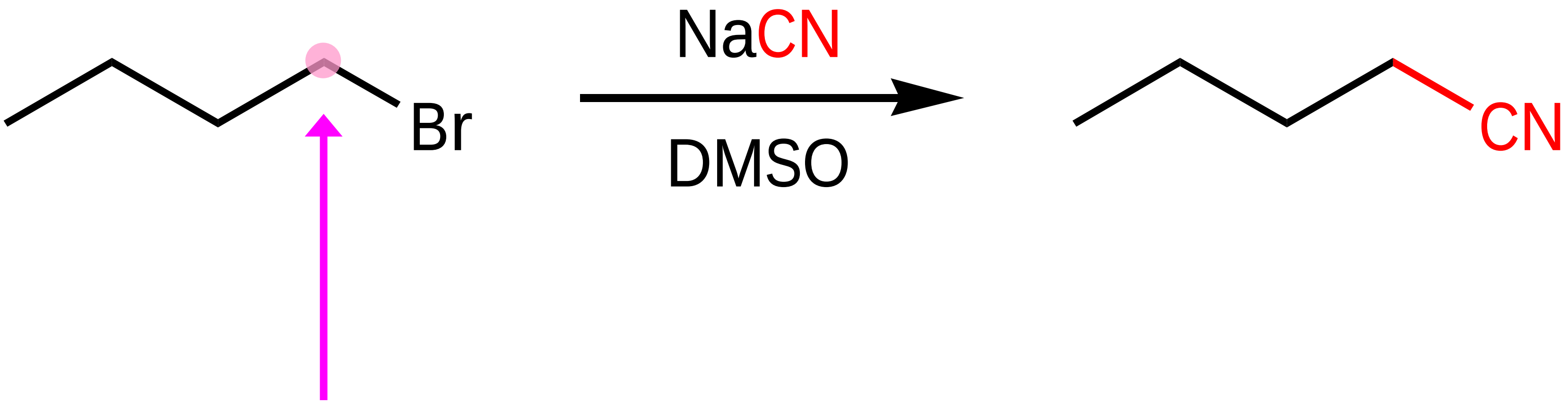
- This is a useful synthetic method for preparing nitriles that are not available by nucleophilic substitution reactions between alkyl halides and cyanide ions

- e.g.

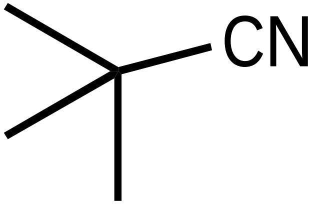


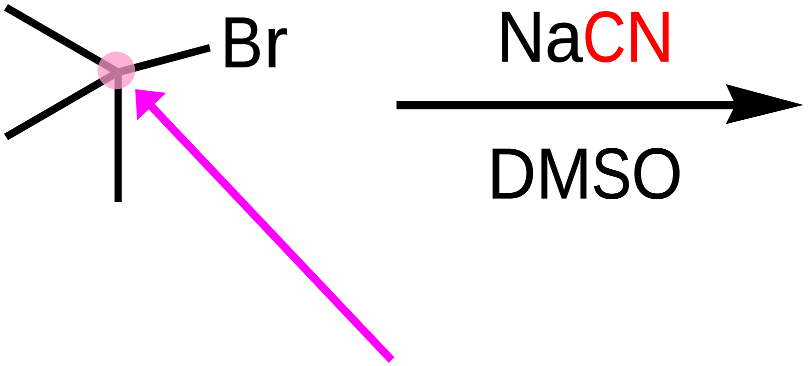
dehydration

- Example
  - Synthesis of 



1^{o} alkyl bromide
⇒ S_N2 reaction with
$^{\ominus}$CN works fine

But synthesis of 



NaCN

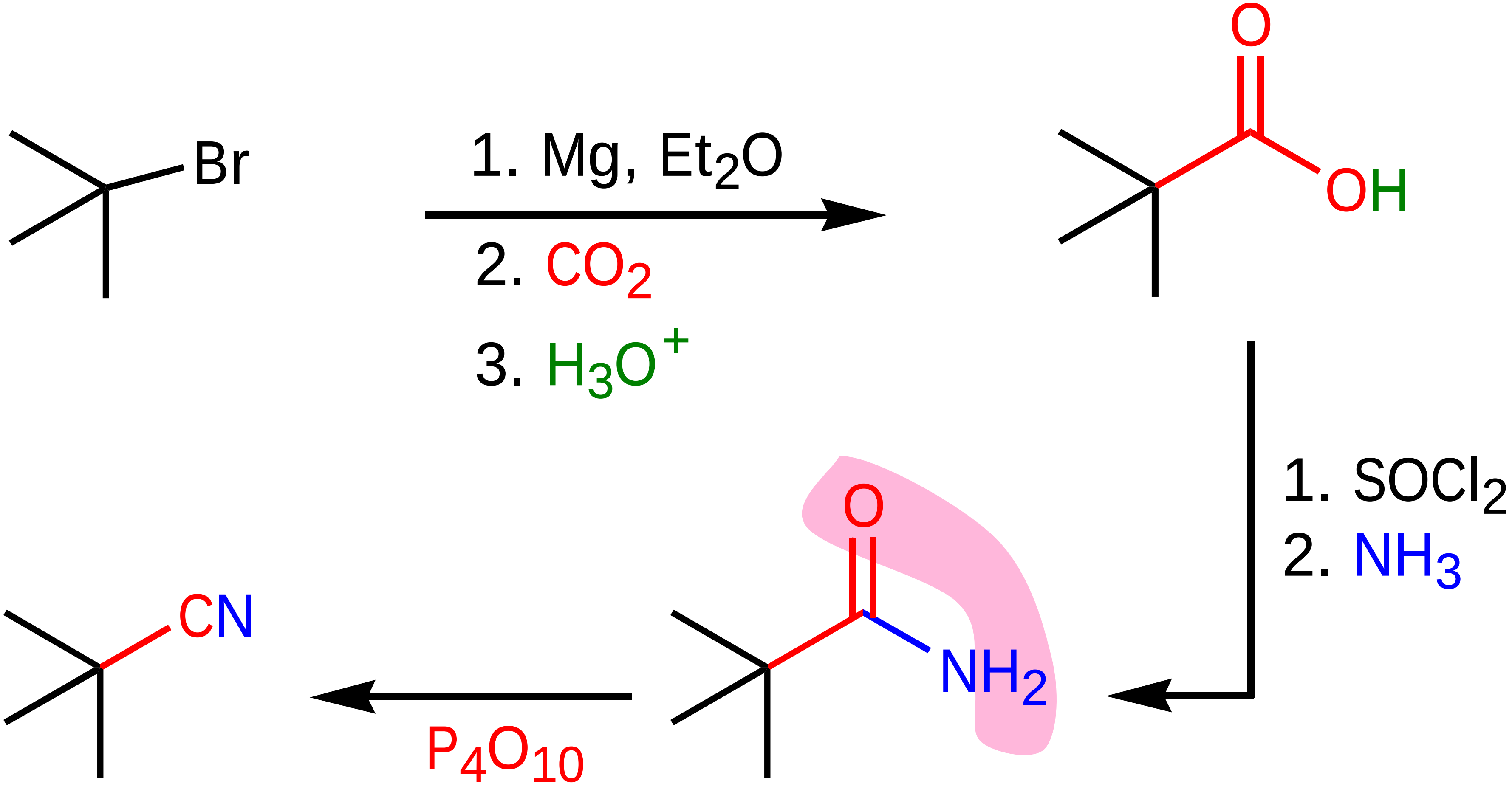
DMSO

No Reaction!

3^o alkyl bromide

⇒ No S_N2 reaction

Solution



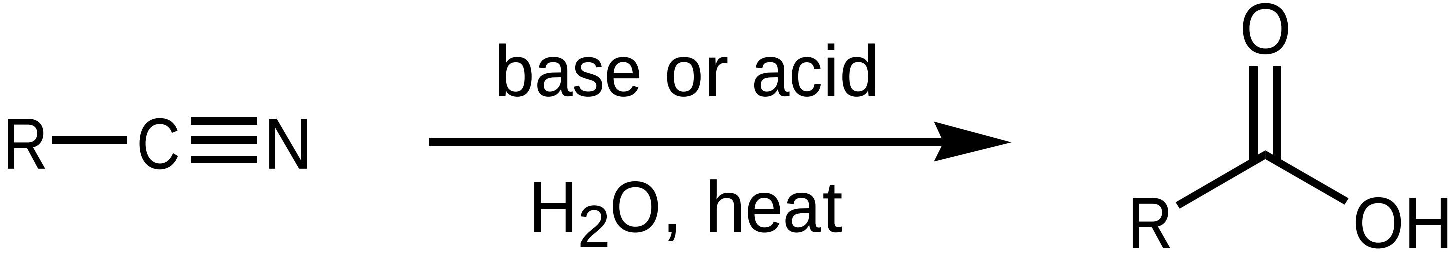
1. Mg, Et_2O
2. CO_2
3. H_3O^+

1. $SOCl_2$
2. NH_3

P_4O_{10}

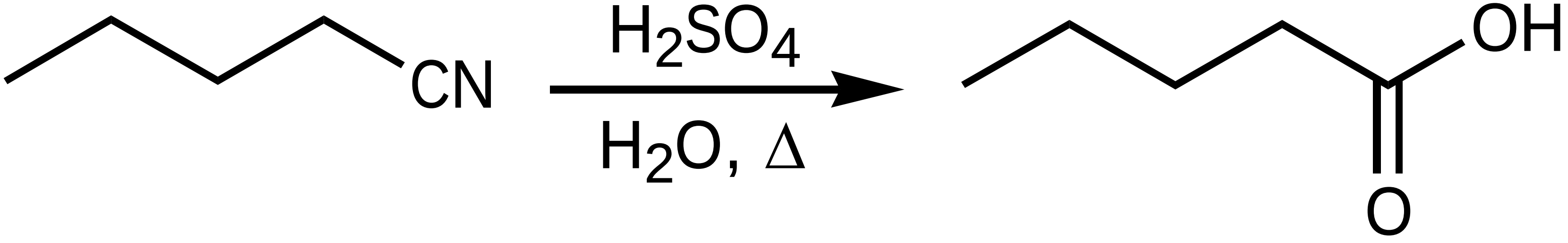
dehydration

8H. Hydrolysis of Nitriles



- ❖ Catalyzed by both acid and base

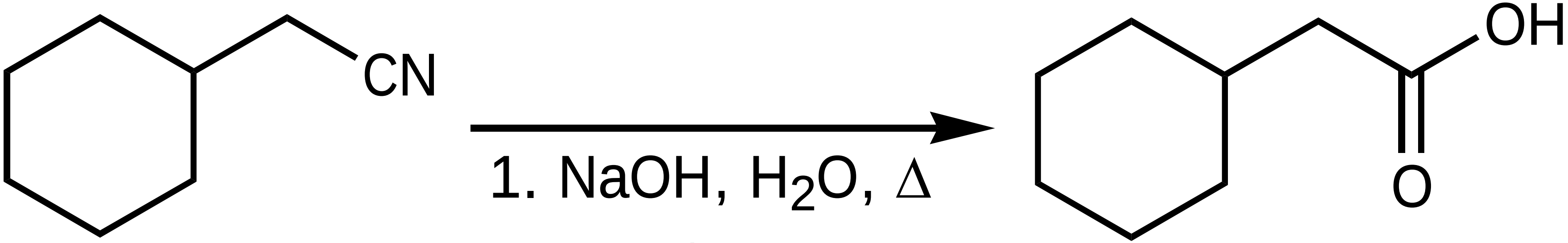
❖ Examples



H_2SO_4

H_2O, Δ

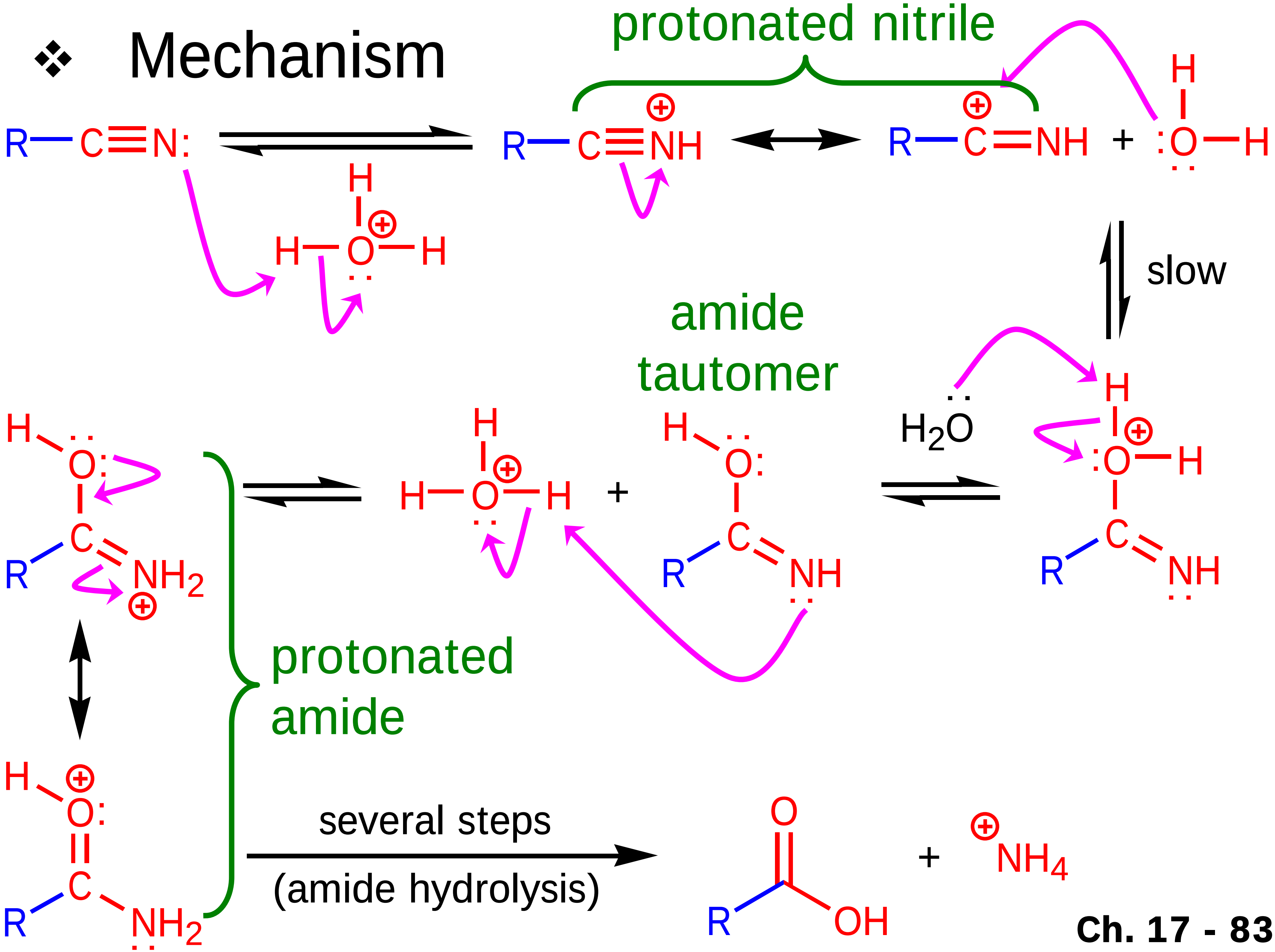
(82%)



1. NaOH, H_2O, Δ
2. H_3O^+

(68%)

❖ Mechanism



protonated nitrile

slow

amide tautomer

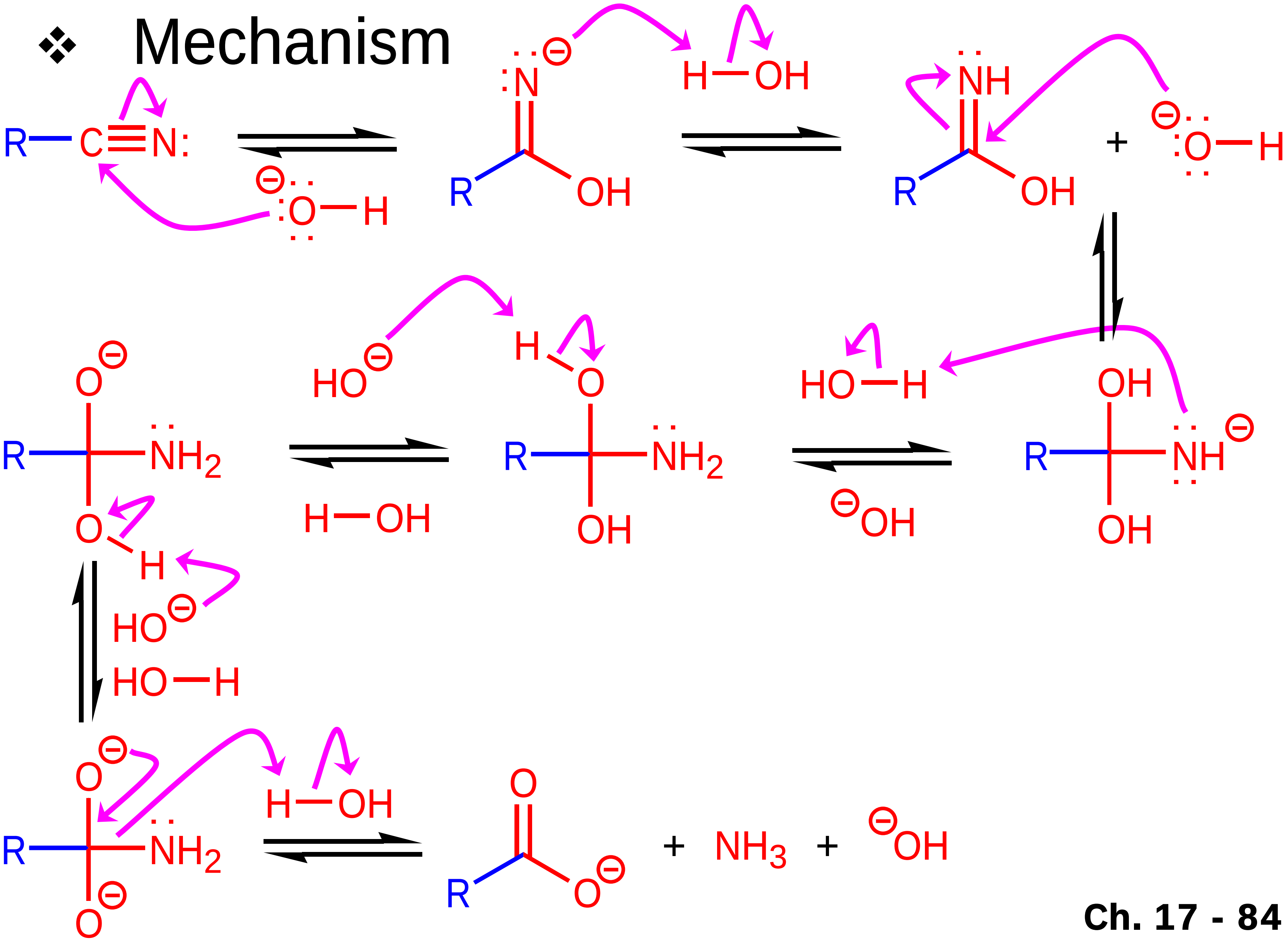
protonated amide

several steps

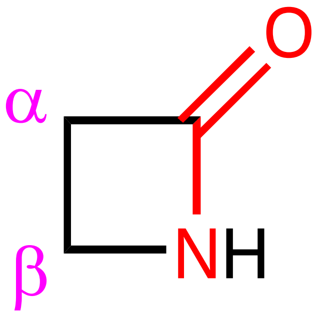
(amide hydrolysis)

+ NH_4^+

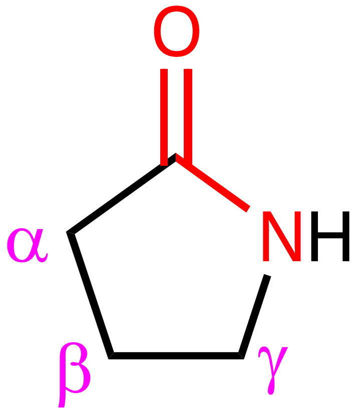
❖ Mechanism


R—C≡N:
⊖:O—H
:N⊖
R OH
H—OH
NH
R OH
+
⊖:O—H
O⊖
R NH₂
O—H
HO⊖
H—OH
H
O
R NH₂
OH
HO—H
⊖OH
OH
R NH⊖
OH
HO⊖
HO—H
O⊖
R NH₂
O⊖
H—OH
O
R O⊖
+ NH₃ + ⊖OH

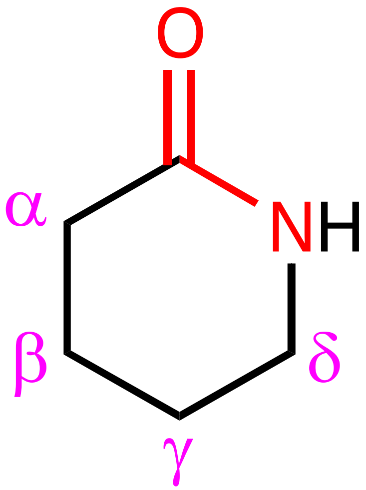
8I. Lactams



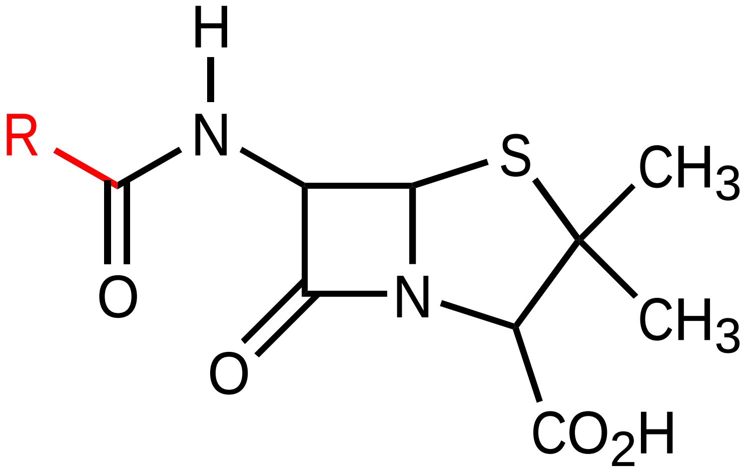
a β-lactam



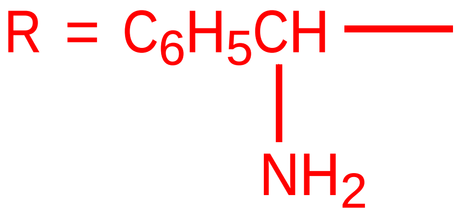
a γ-lactam



a δ-lactam



R = $C_6H_5CH_2$— Penicillin G



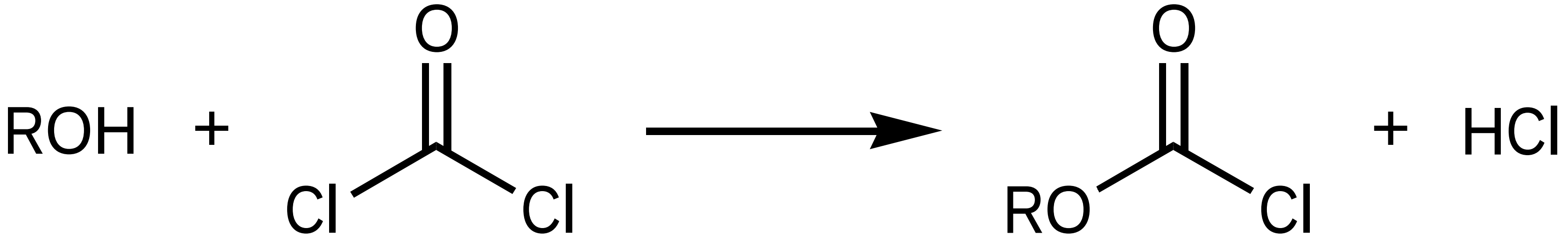
R = $C_6H_5\underset{\displaystyle NH_2}{CH}$— Ampicillin

R = $C_6H_5OCH_2$— Penicillin V

9. Derivatives of Carbonic Acid

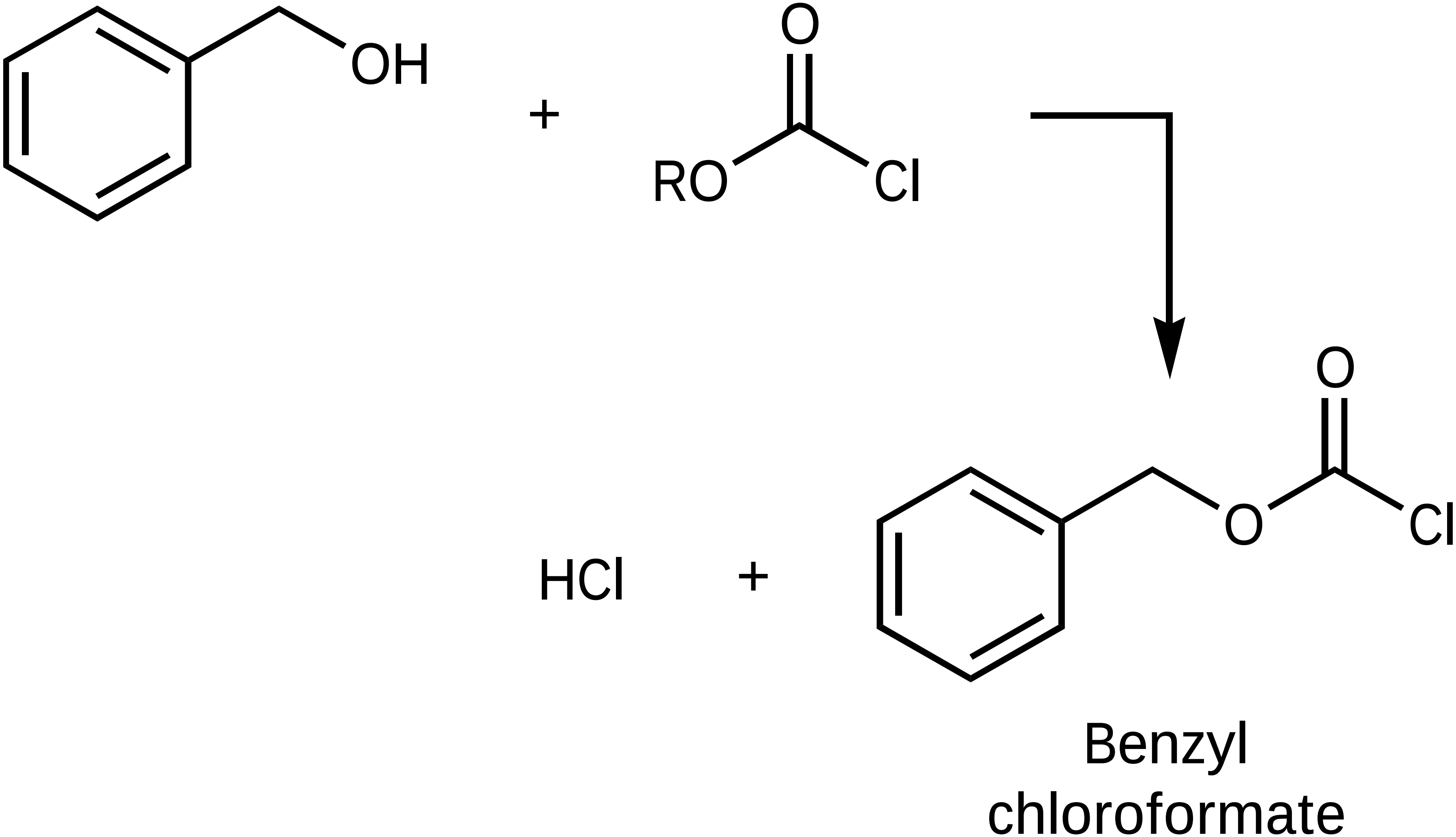
9A. Alkyl Chloroformates and Carbamates (Urethanes)

- Alkyl chloroformate



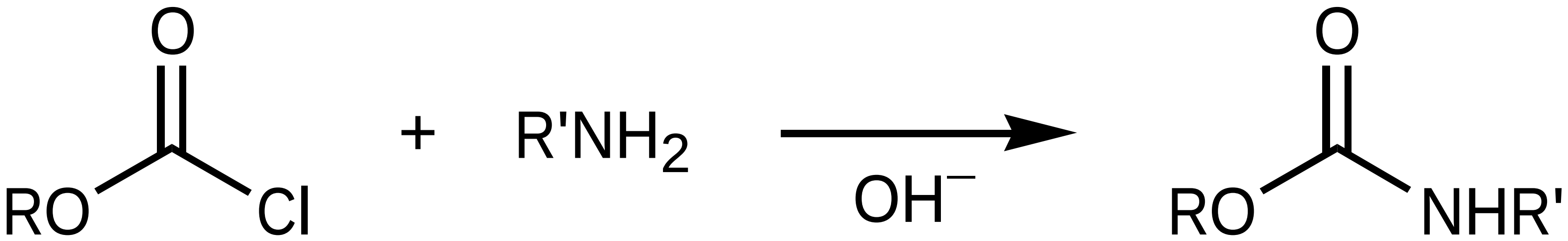
alkyl chloroformate

- e.g.



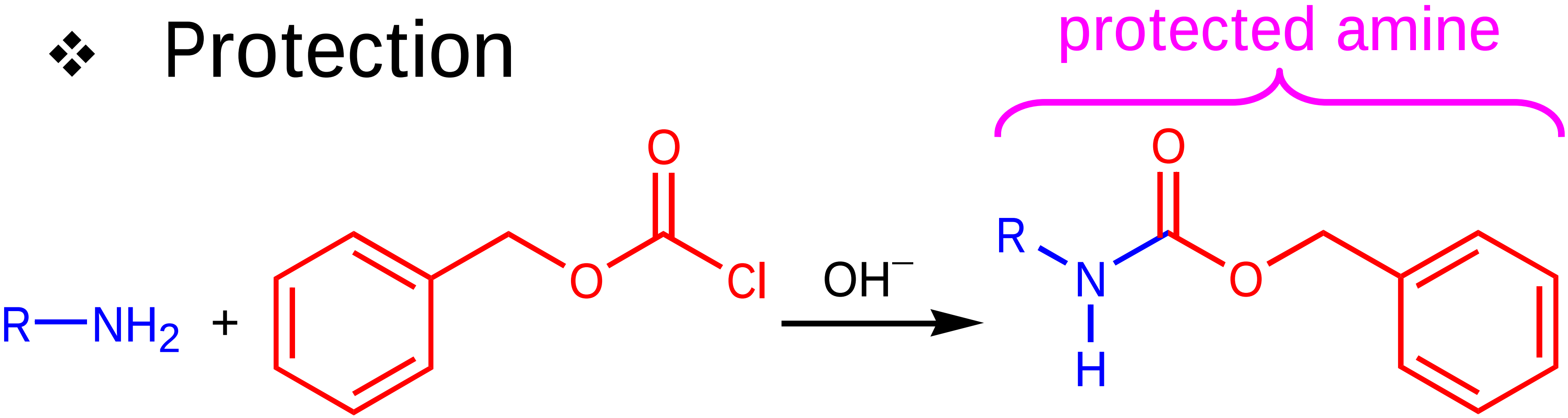
Benzyl chloroformate

- Carbamates or urethanes

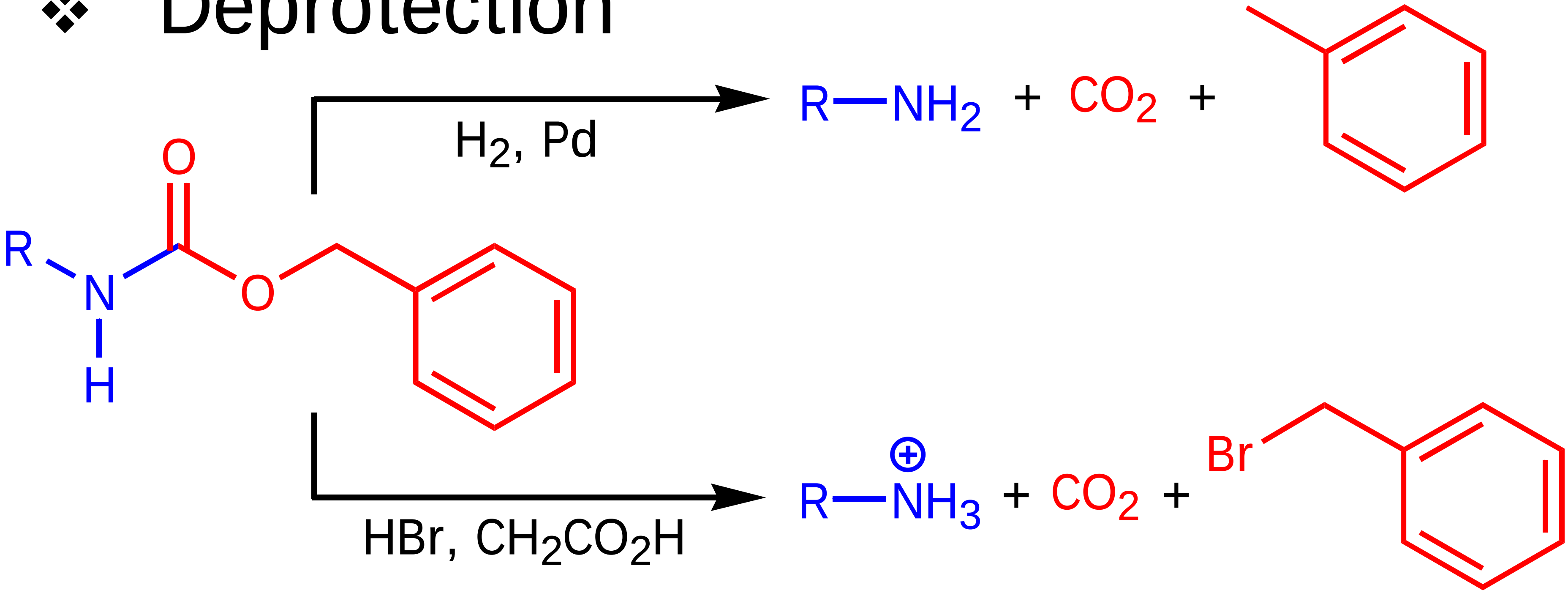


a carbamate
(or urethane)

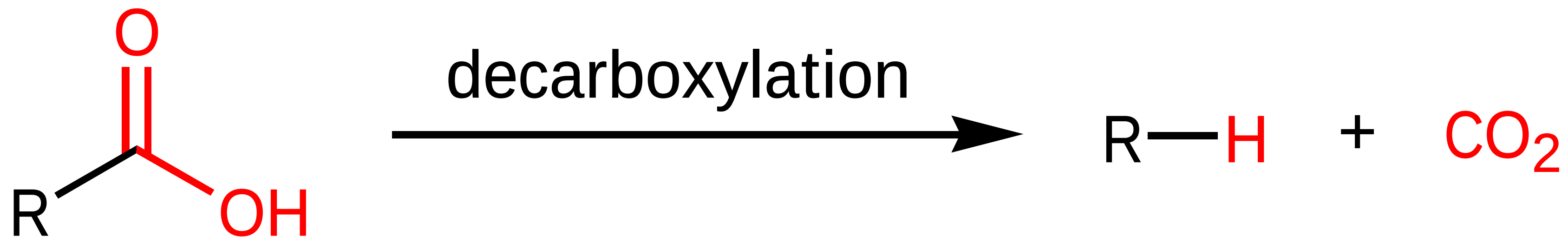
❖ Protection

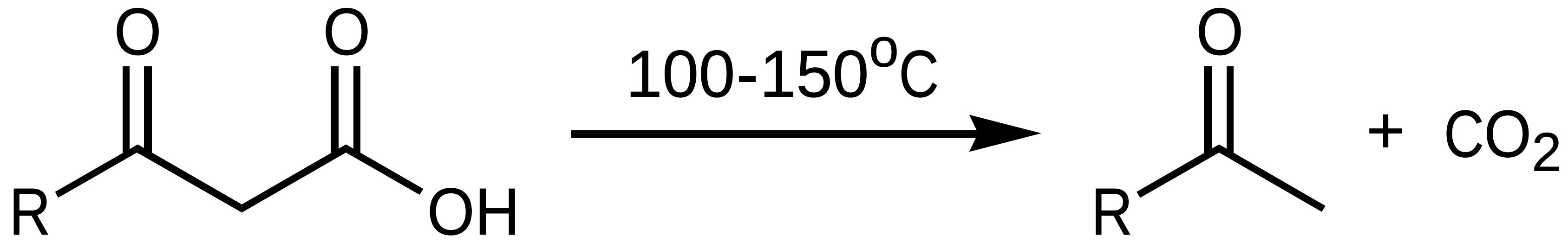


❖ Deprotection



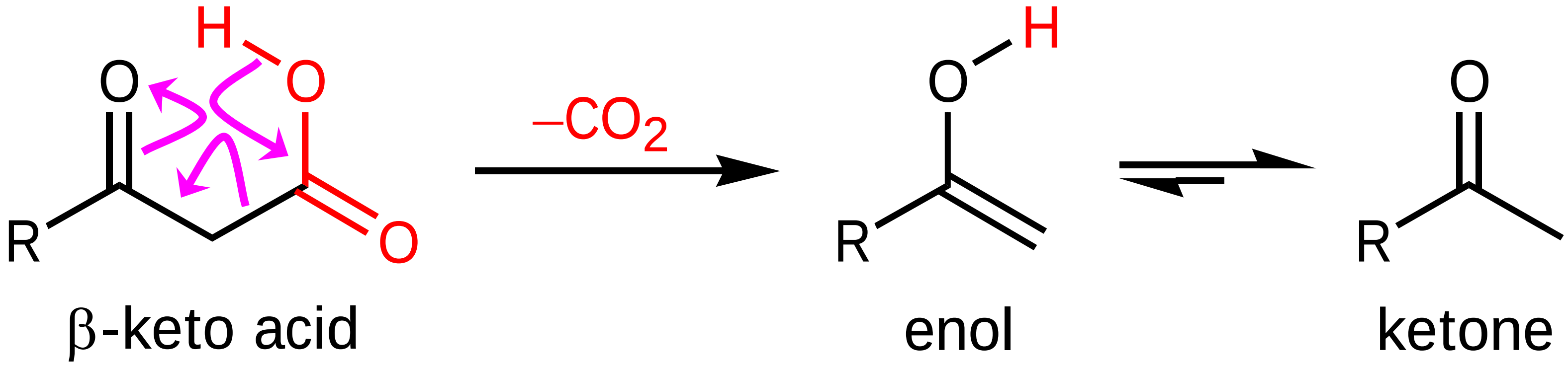
10. Decarboxylation of Carboxylic Acids

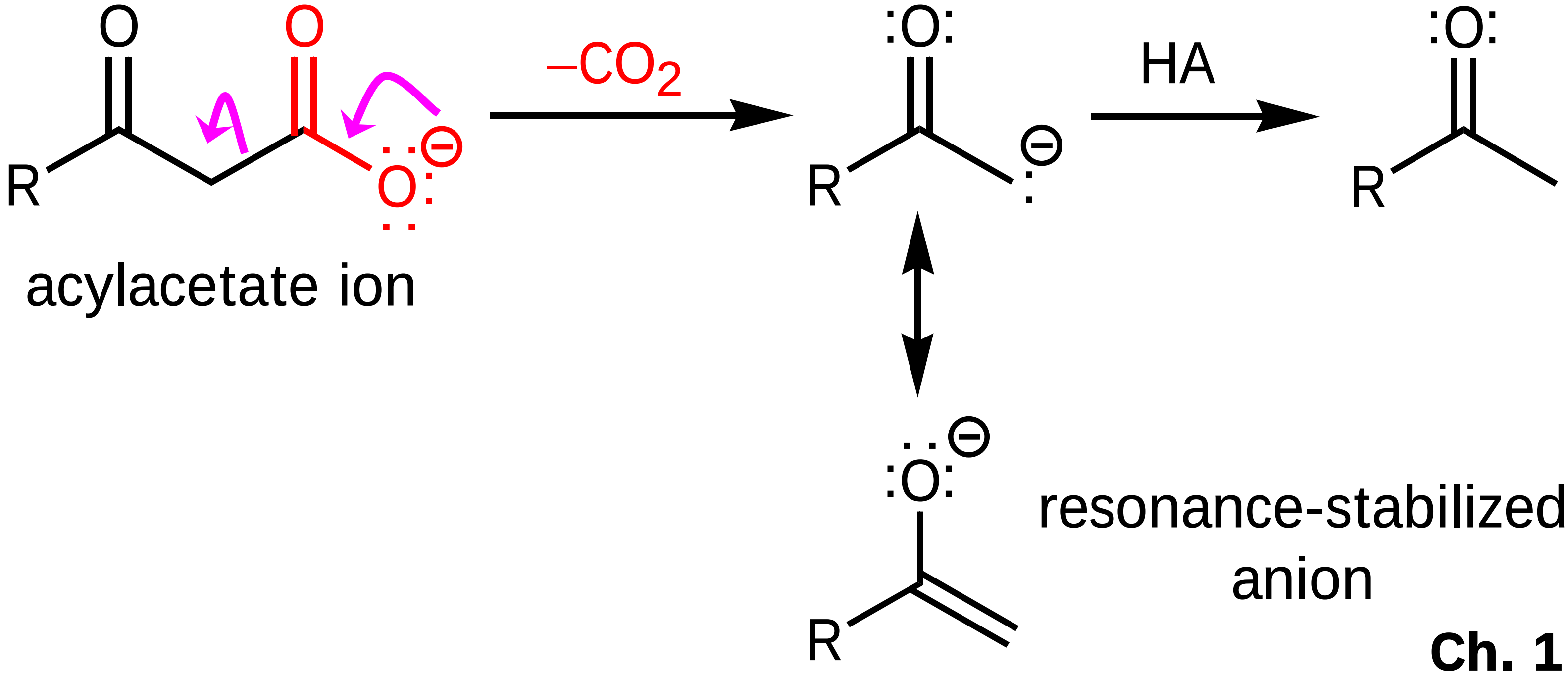




A β-keto acid

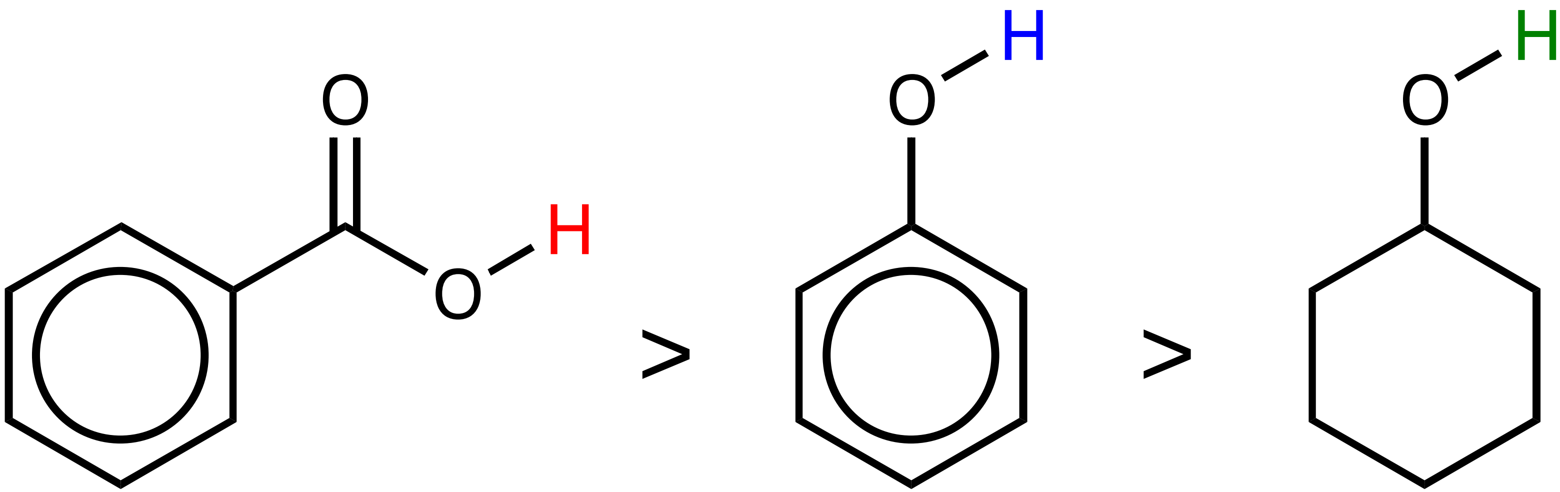
- There are two reasons for this ease of decarboxylation

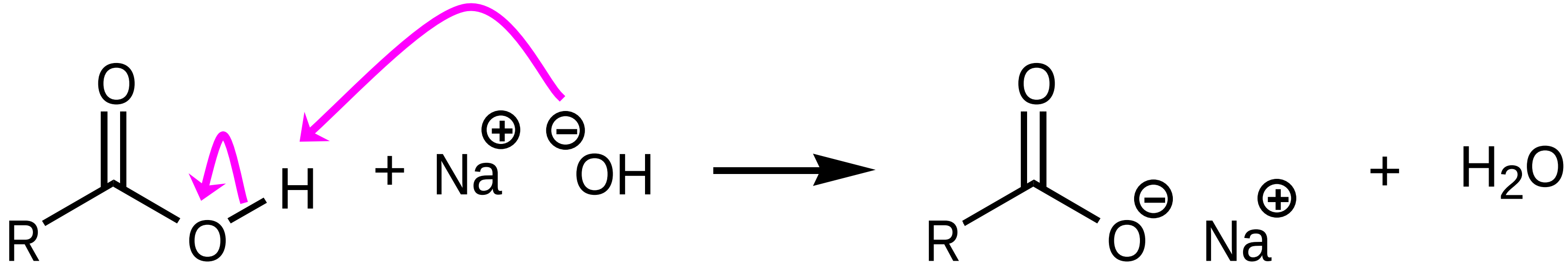




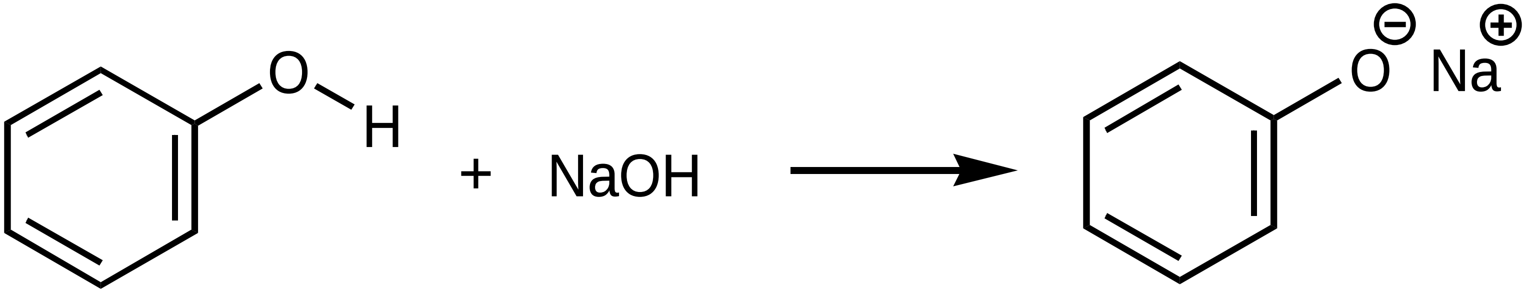
11. Chemical Tests for Acyl Compounds

- Recall: acidity of

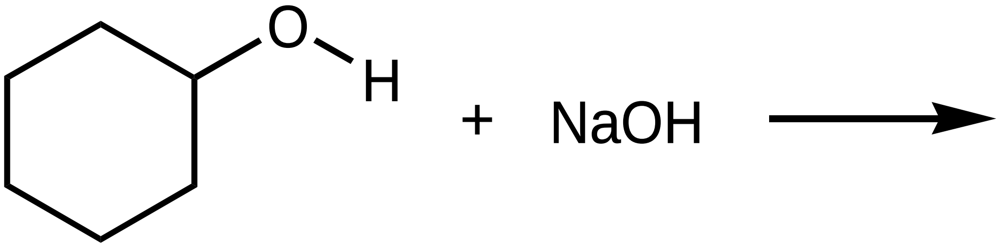




(soluable in water)

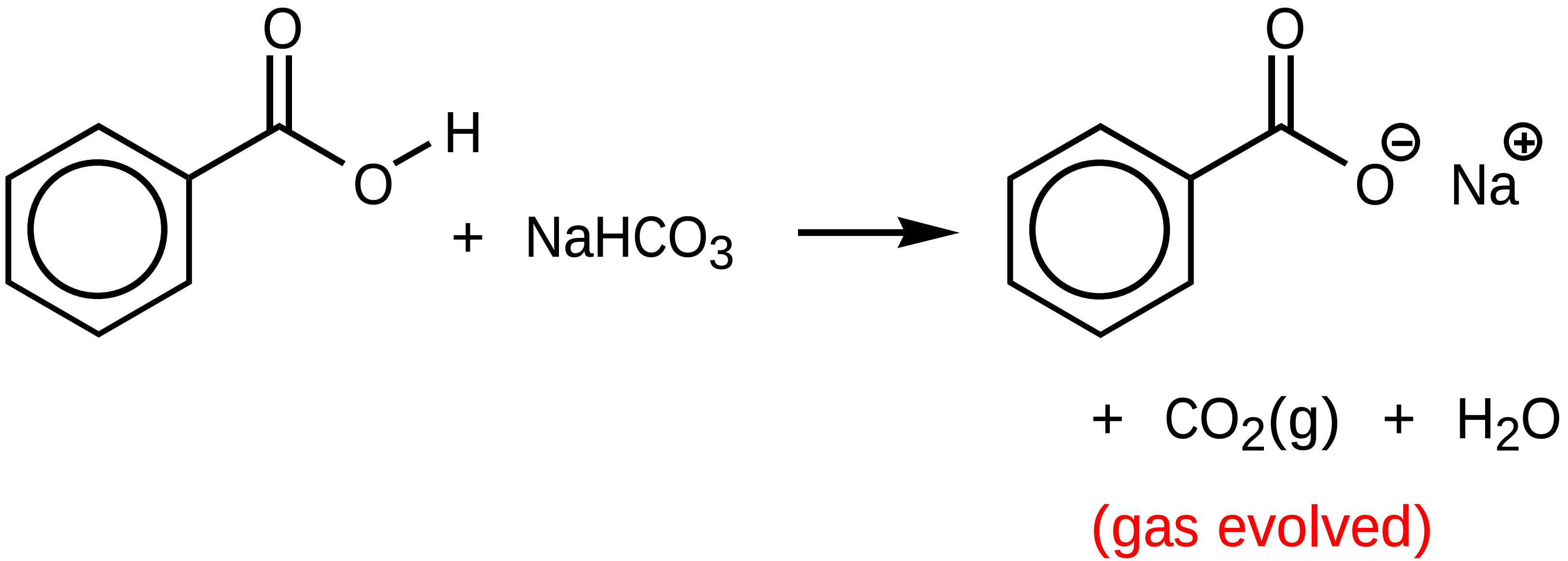


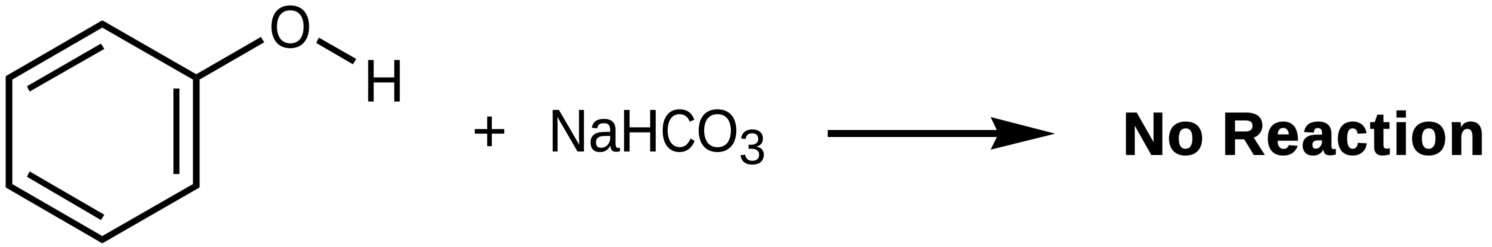
(soluble in water)

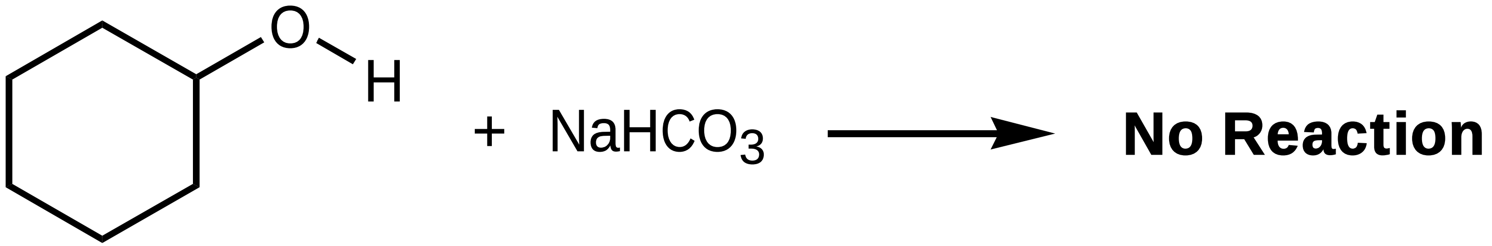


No Reaction

(immiscible with H_2O)

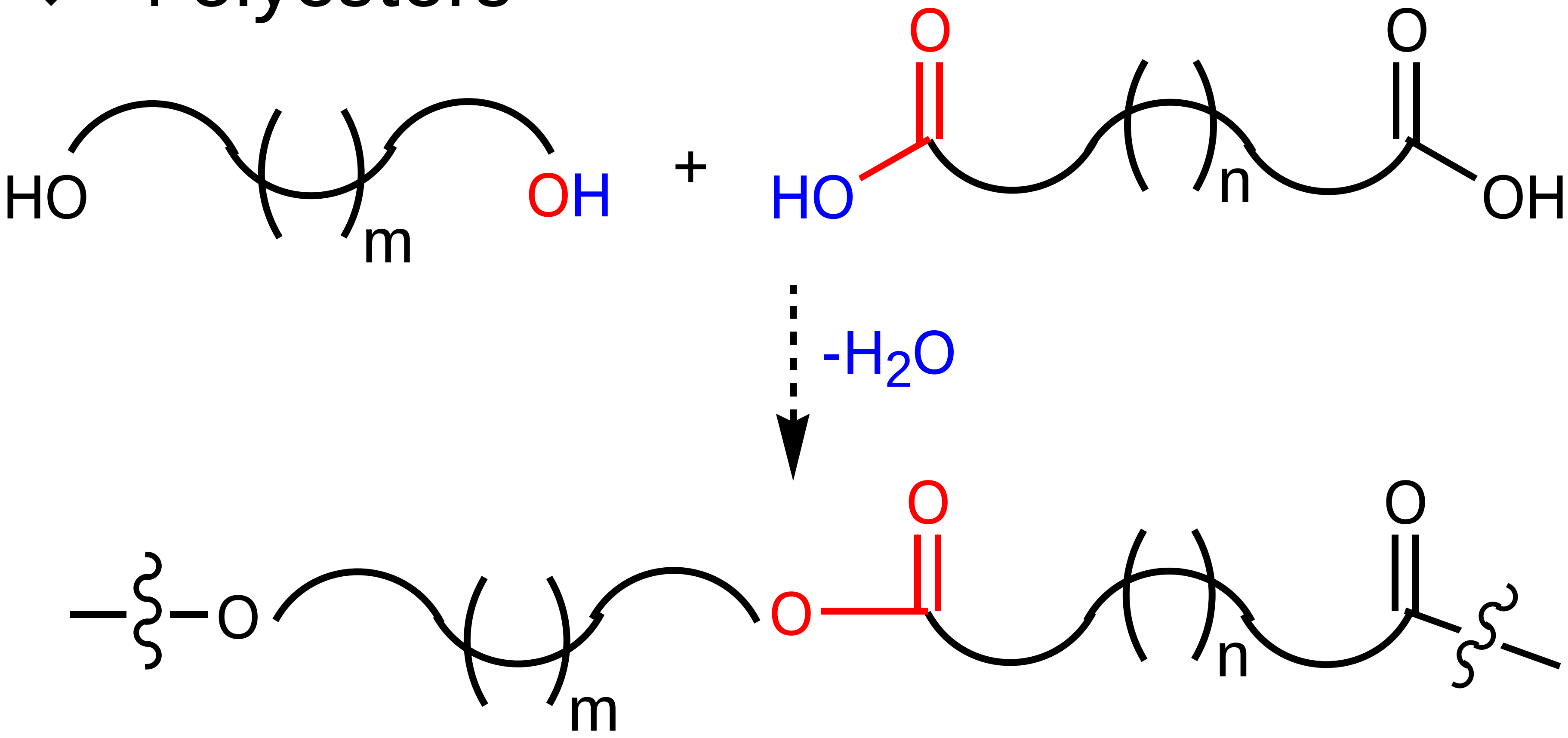

O
O
H
+ NaHCO3
O
O
Na
+ CO2(g) + H2O
(gas evolved)


O
H
+ NaHCO3
No Reaction


O
H
+ NaHCO3
No Reaction

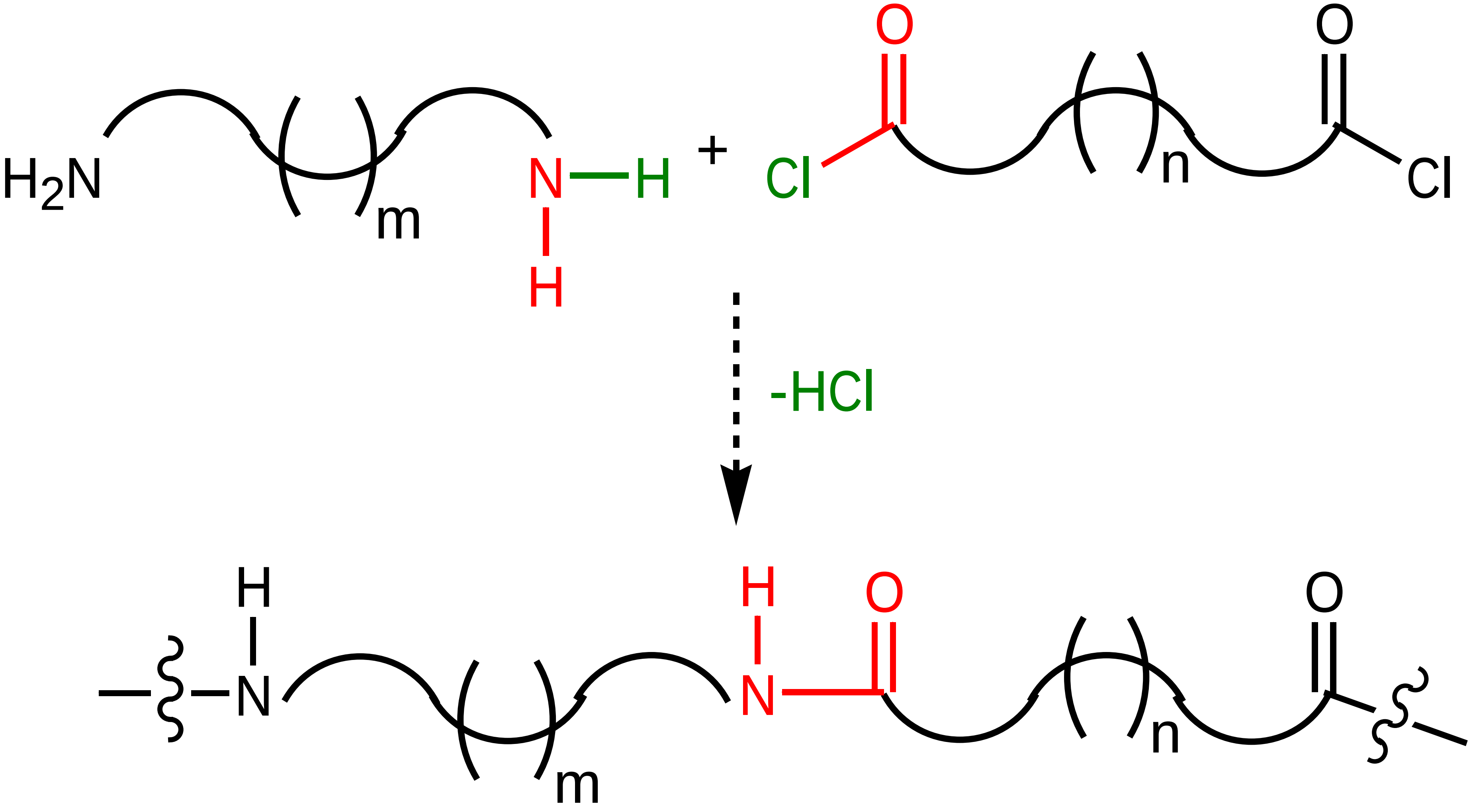
12. Polyesters and Polyamides: Step-Growth Polymers

- Polyesters



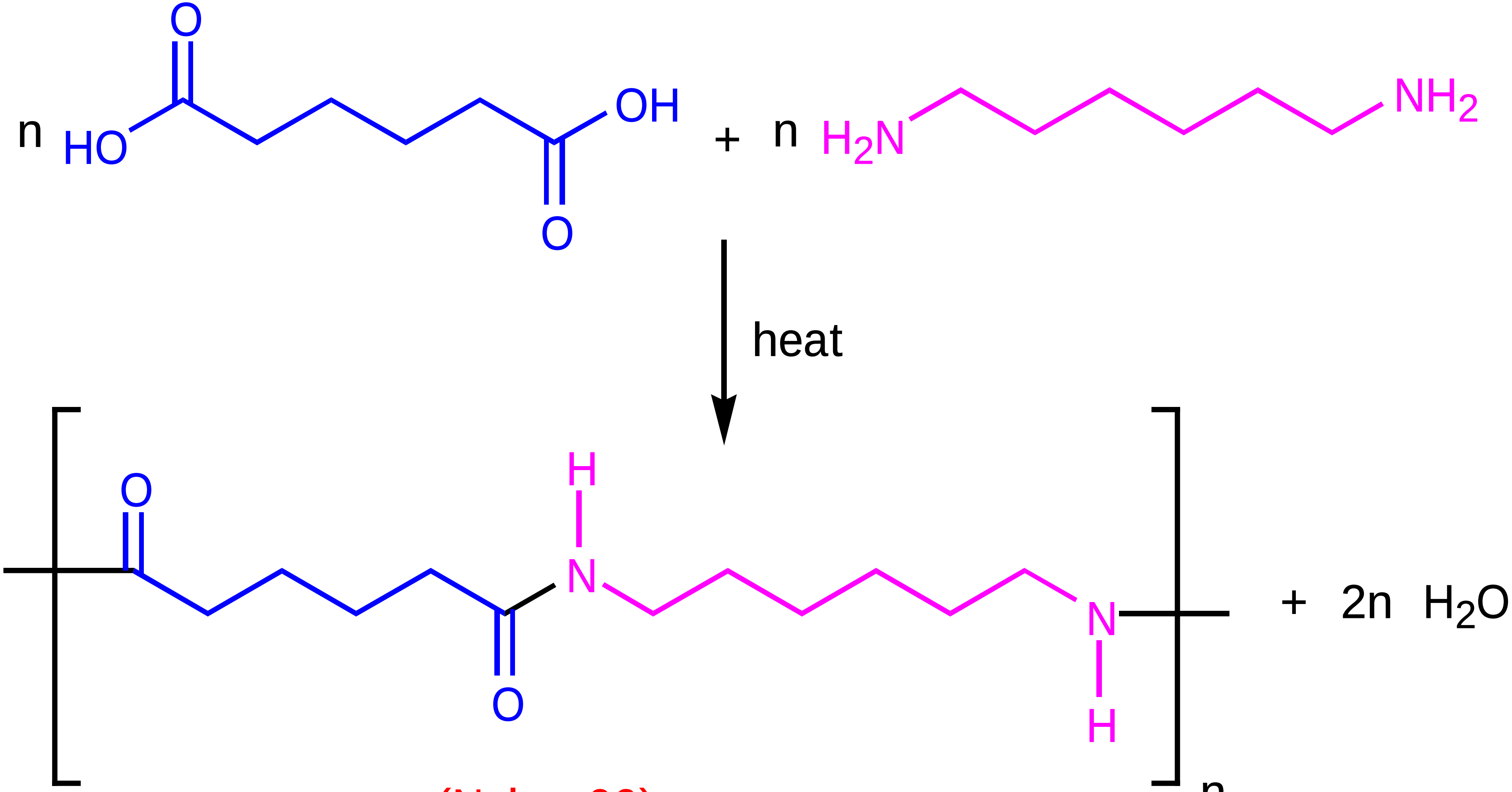
(a polyester)

❖ Polyamides



(a polyamide)

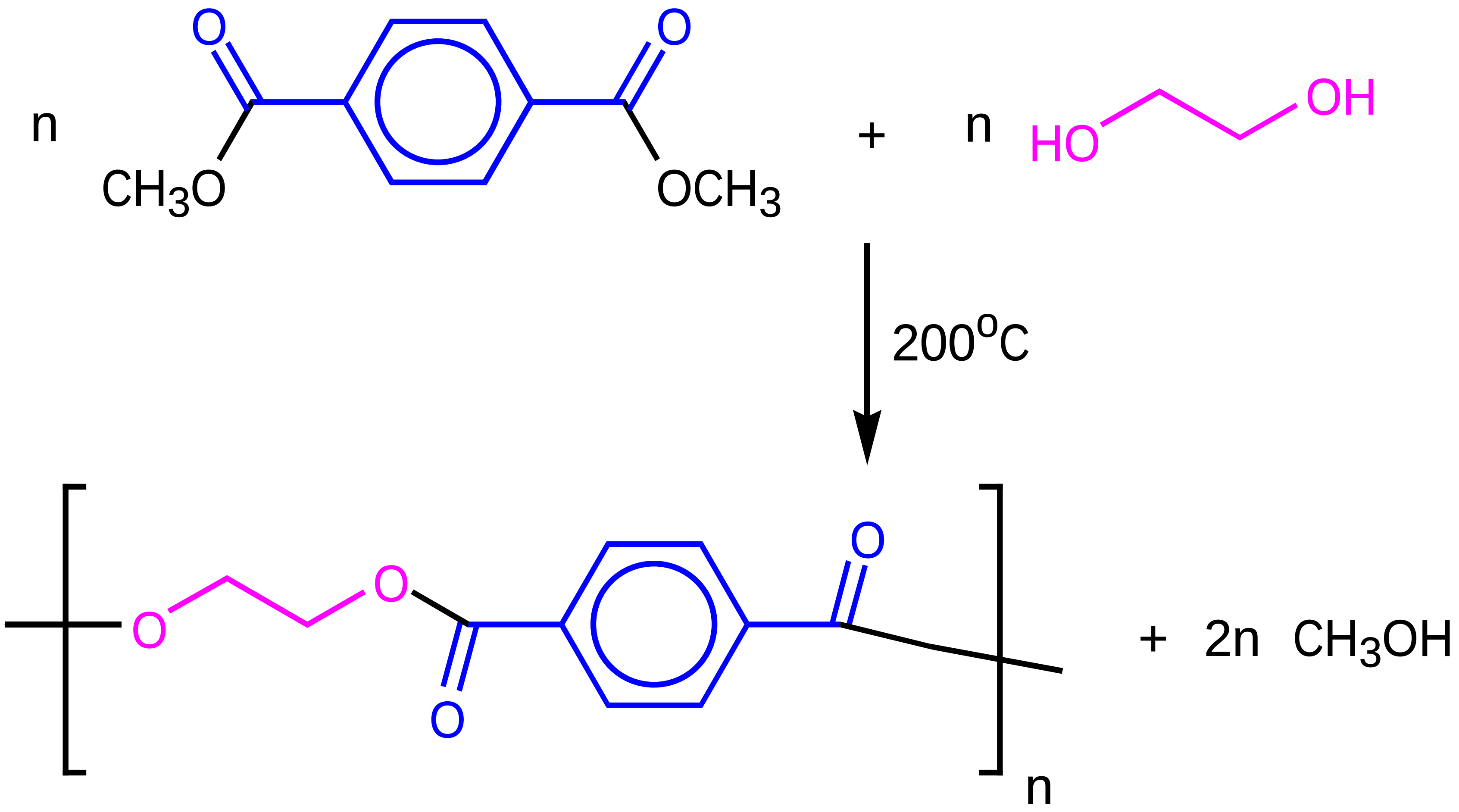
❖ Example: Nylon 66



(Nylon 66)

- Applications: clothing, fibers, bearings

❖ Example: Dacron (Mylar)

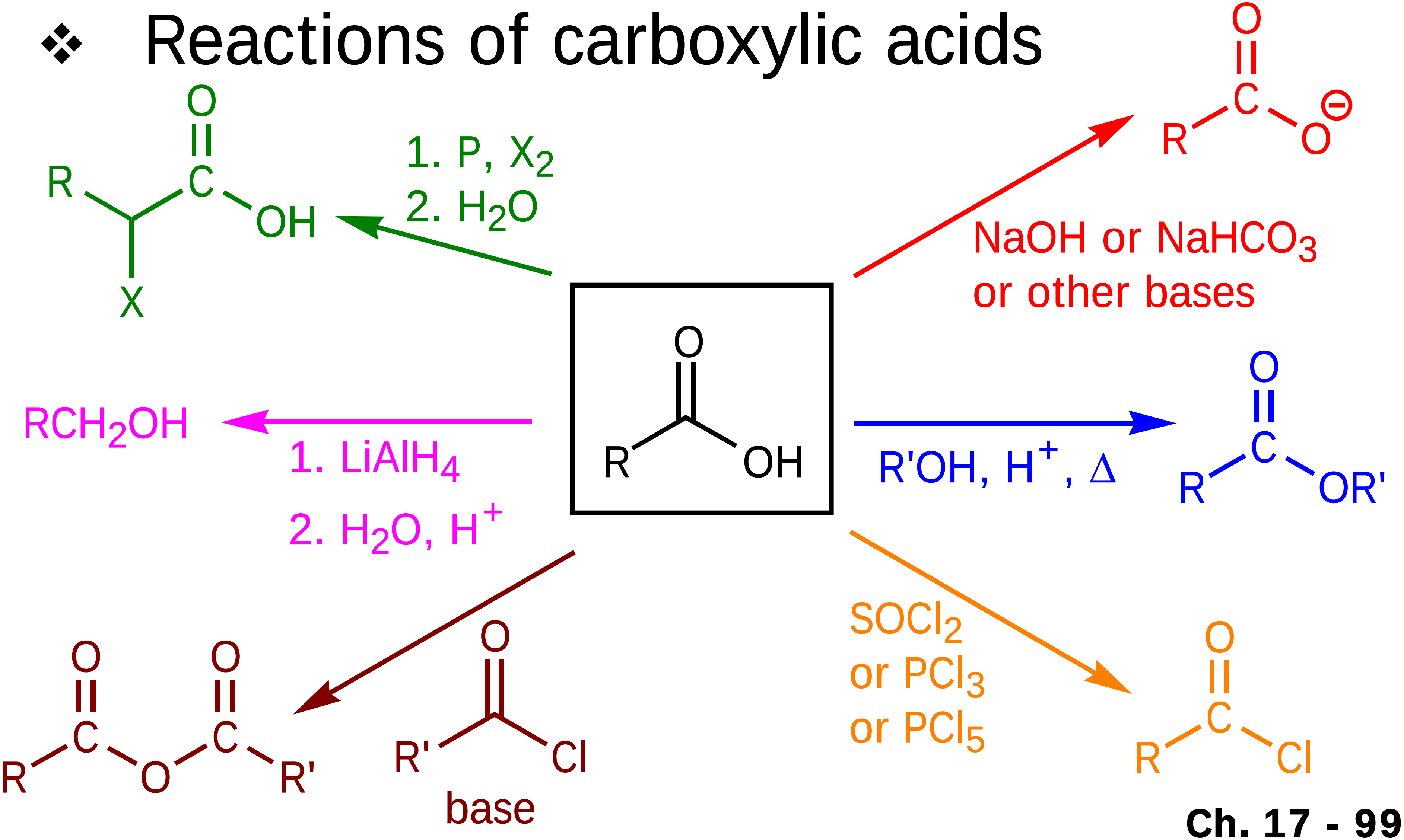


(Dacron)

- Applications: film, recording tape

13. Summary of the Reactions of Carboxylic Acids and Their Derivatives

- Reactions of carboxylic acids



1. P, X_2
2. H_2O

NaOH or $NaHCO_3$
or other bases

RCH_2OH

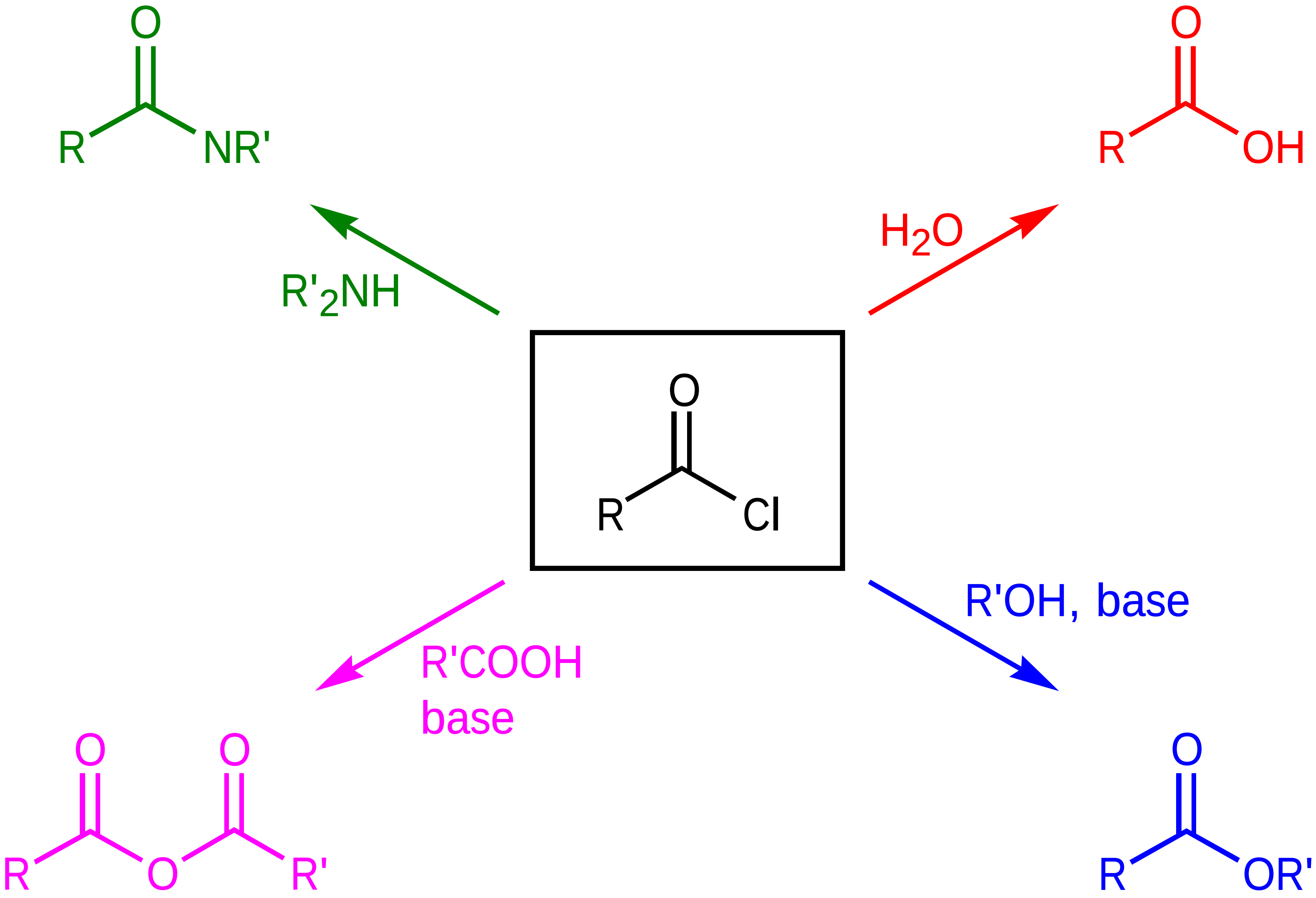
1. $LiAlH_4$
2. H_2O, H^+

$R'OH$, H^+, Δ

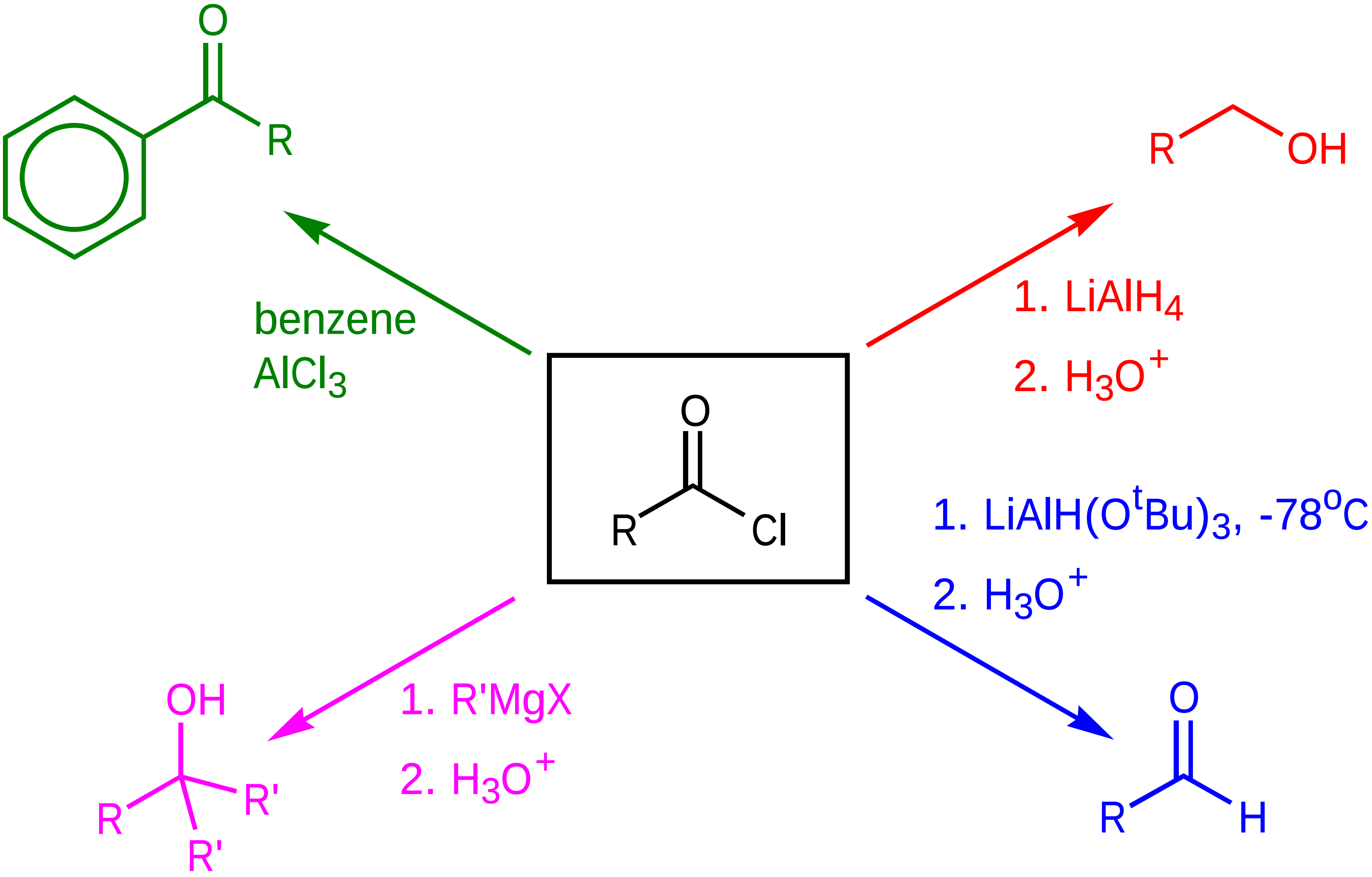
base

$SOCl_2$
or PCl_3
or PCl_5

❖ Reactions of acyl chlorides



❖ Reactions of acyl chlorides (Cont'd)



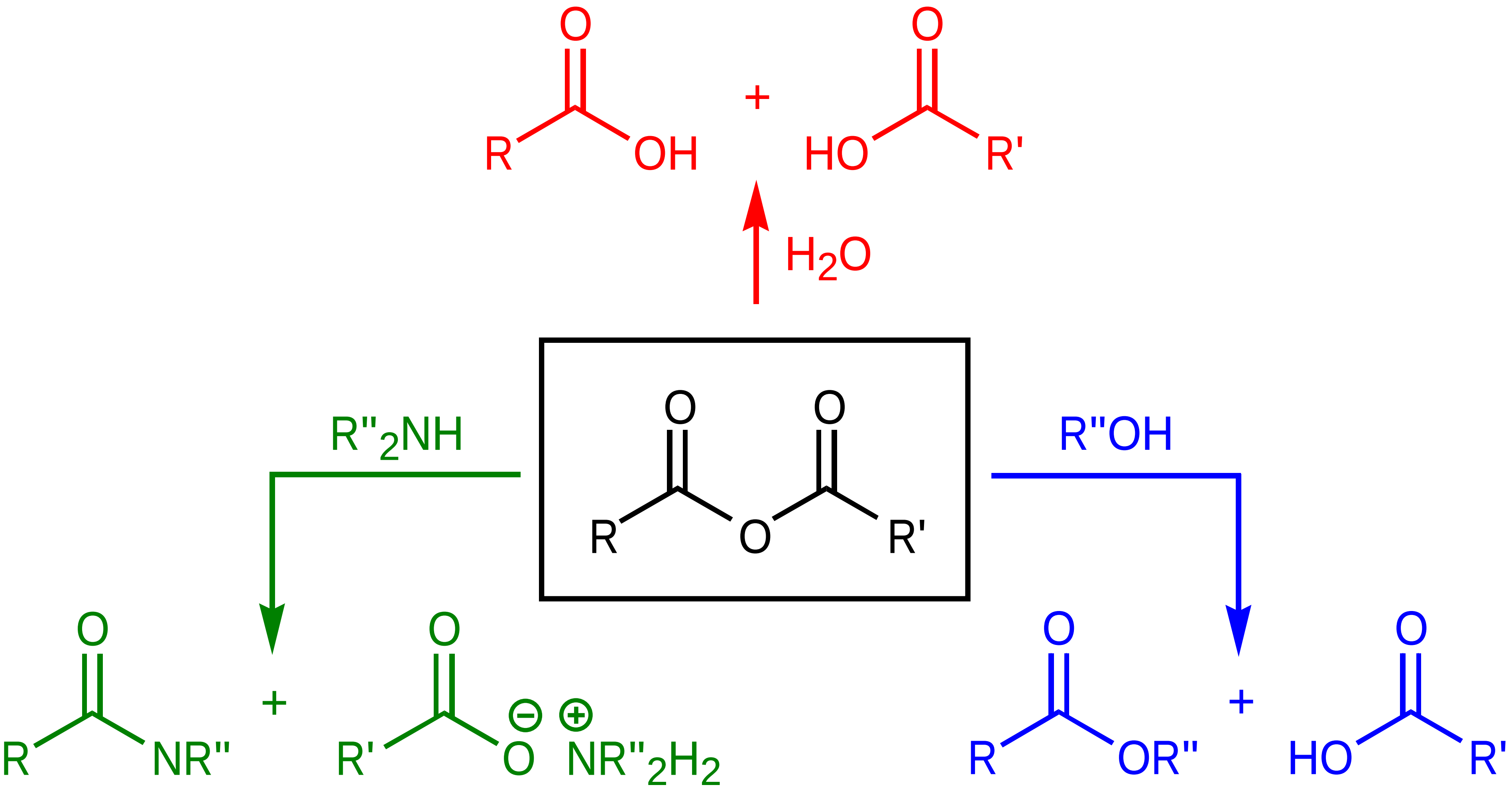
benzene
$AlCl_3$

1. $LiAlH_4$
2. H_3O^+

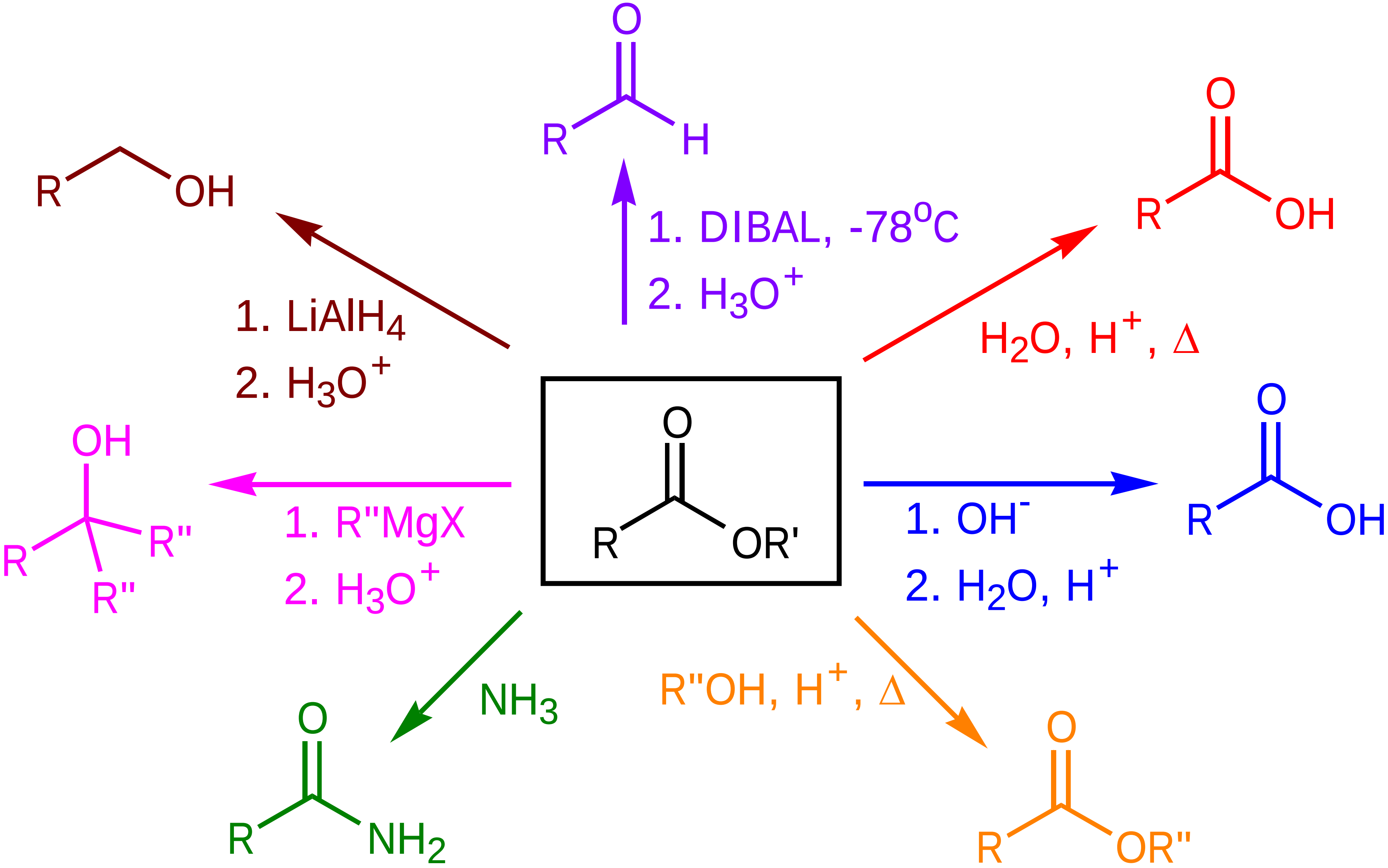
1. $LiAlH(O^tBu)_3$, -78°C
2. H_3O^+

1. R'MgX
2. H_3O^+

❖ Reactions of acid anhydrides



Reactions of esters



1. $LiAlH_4$
2. H_3O^+

1. DIBAL, -78°C
2. H_3O^+

H_2O, H^+, Δ

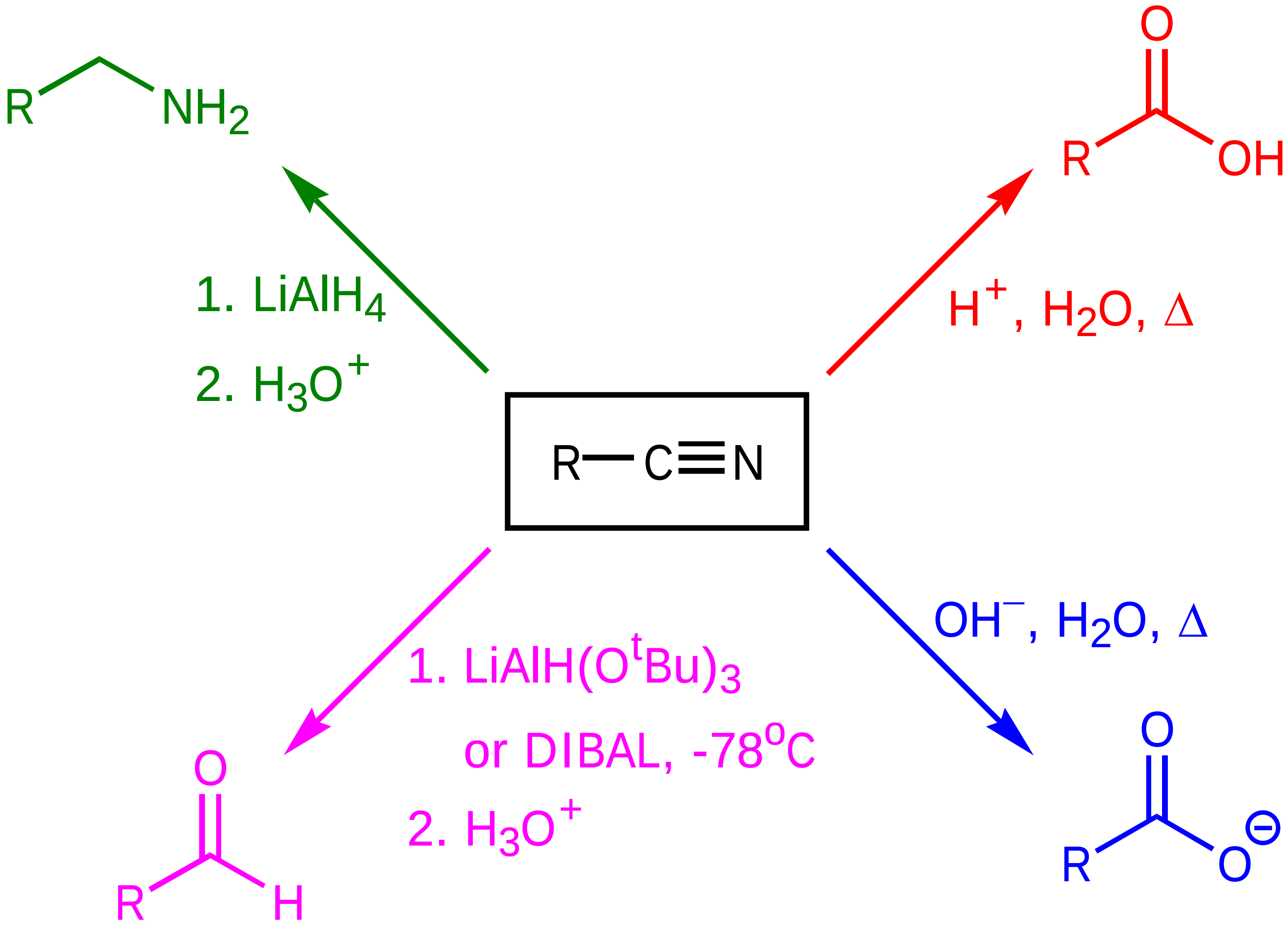
1. R''MgX
2. H_3O^+

1. OH^-
2. H_2O, H^+

NH_3

$R''OH, H^+, \Delta$

❖ Reactions of nitriles



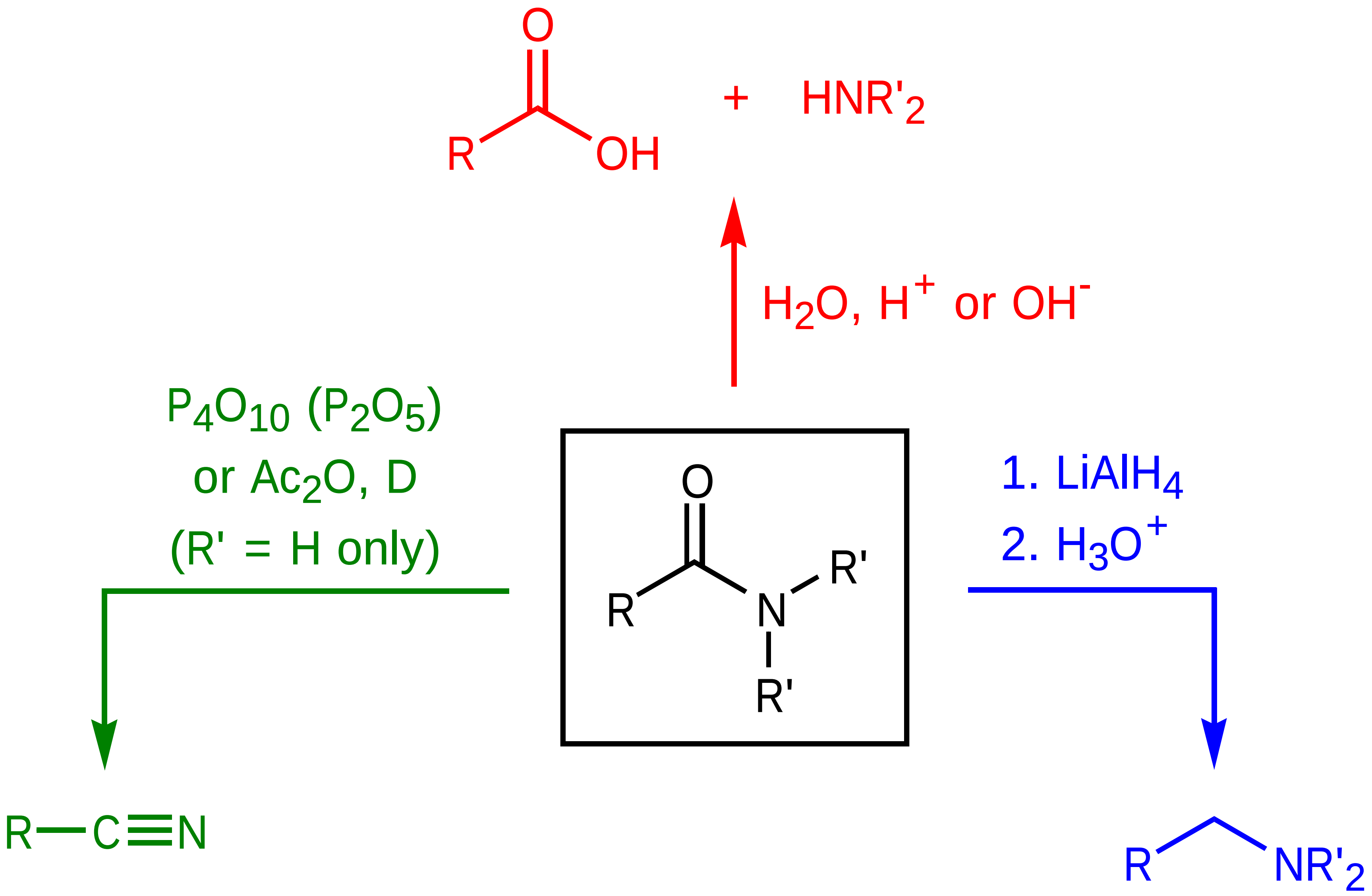
1. $LiAlH_4$
2. H_3O^+

H^+, H_2O, Δ

1. $LiAlH(O^tBu)_3$
or DIBAL, -78^{o}C
2. H_3O^+

OH^-, H_2O, Δ

❖ Reactions of amides



H_2O, H^+ or OH^-

P_4O_{10} (P_2O_5)
or Ac_2O, D
(R' = H only)

1. $LiAlH_4$
2. H_3O^+

🔔 END OF CHAPTER 17 🔔