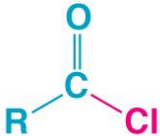
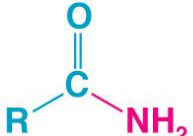
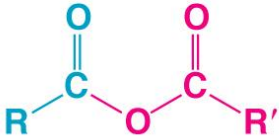
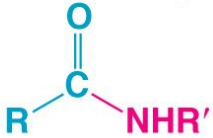
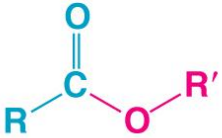
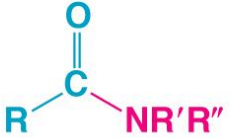



Capítulo 18
Ácidos Carboxílicos e Derivados.
Adição Nucleofílica-Eliminação no
carbono Acila

◆ Introdução

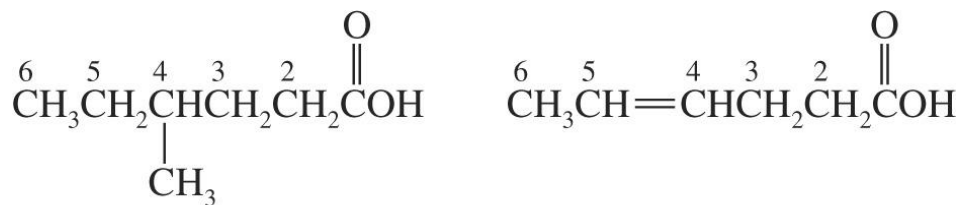
→ O grupo carboxílico (-CO₂H) é da mesma família de compostos denominados de acila ou derivados de ácidos carboxílicos

Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

◆ Nomenclatura e Propriedades Físicas

→ Na nomenclatura IUPAC o nome dos ácidos troca-se o terminal o do alcano por oico

O carbono carboxílico é a posição 1



4-Methylhexanoic acid

4-Hexenoic acid
(or hex-4-enoic acid)


→ Os nomes comuns continuam em uso

☞ Metanoico e etanoico são ácido fórmico e ácido acético

→ Ácidos Carboxílicos formam ligações de hidrogênio fortes entre eles e com a água

Ácidos Carboxílicos com até 4 carbonos são miscíveis em água em qualquer proporção

Tabela 18.2 Ácidos Carboxílicos

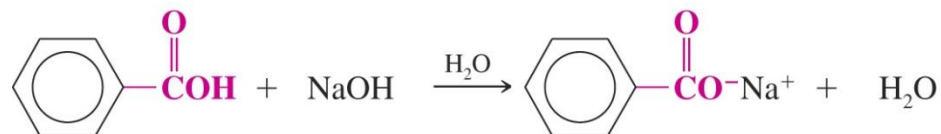
Estrutura	Nome Sistemático	Nome Comum	p.f. (°C)	p.e. (°C)	Solubilidade em Água (g 100 mL ⁻¹ de H ₂ O)		pK _a
					25°C		
HCO ₂ H	Ácido metanóico	Ácido fórmico	8	100,5	∞		3,75
CH ₃ CO ₂ H	Ácido etanóico	Ácido acético	16,6	118	∞		4,76
CH ₃ CH ₂ CO ₂ H	Ácido propanóico	Ácido propiônico	- 21	141	∞		4,87
CH ₃ (CH ₂) ₂ CO ₂ H	Ácido butanóico	Ácido butírico	- 6	164	∞		4,81
CH ₃ (CH ₂) ₃ CO ₂ H	Ácido pentanóico	Ácido valérico	- 34	187	4,97		4,82
CH ₃ (CH ₂) ₄ CO ₂ H	Ácido hexanóico	Ácido capríco	- 3	205	1,08		4,84
CH ₃ (CH ₂) ₆ CO ₂ H	Ácido octanóico	Ácido caprílico	16	239	0,07		4,89
CH ₃ (CH ₂) ₈ CO ₂ H	Ácido decanóico	Ácido cáprico	31	269	0,015		4,84
CH ₃ (CH ₂) ₁₀ CO ₂ H	Ácido dodecanóico	Ácido láurico	44	179 ¹⁸	0,006		5,30
CH ₃ (CH ₂) ₁₂ CO ₂ H	Ácido tetradecanóico	Ácido mirístico	59	200 ²⁰	0,002		
CH ₃ (CH ₂) ₁₄ CO ₂ H	Ácido hexadecanóico	Ácido palmítico	63	219 ¹⁷	0,0007		6,46
CH ₃ (CH ₂) ₁₆ CO ₂ H	Ácido octadecanóico	Ácido esteárico	70	383	0,0003		
CH ₂ ClCO ₂ H	Ácido cloroetanóico	Ácido cloroacético	63	189	Muito solúvel		2,86
CHCl ₂ CO ₂ H	Ácido dicloroetanóico	Ácido dicloroacético	10,8	192	Muito solúvel		1,48
CCl ₃ CO ₂ H	Ácido tricloroetanóico	Ácido tricloroacético	56,3	198	Muito solúvel		0,70
CH ₃ CHClCO ₂ H	Ácido 2-cloropropanóico	Ácido α-cloropropiônico		186	Solúvel		2,83
CH ₂ ClCH ₂ CO ₂ H	Ácido 3-cloropropanóico	Ácido β-cloropropiônico	61	204	Solúvel		3,98
C ₆ H ₅ CO ₂ H	Ácido benzóico	Ácido benzóico	122	250	0,34		4,19
<i>p</i> -CH ₃ C ₆ H ₄ CO ₂ H	Ácido 4-metilbenzóico	Ácido <i>p</i> -toluico	180	275	0,03		4,36
<i>p</i> -ClC ₆ H ₄ CO ₂ H	Ácido 4-clorobenzóico	Ácido <i>p</i> -clorobenzóico	242		0,009		3,98
<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H	Ácido 4-nitrobenzóico	Ácido <i>p</i> -nitrobenzóico	242		0,03		3,41
	Ácido 1-naftóico	Ácido α-naftóico	160	300	Insolúvel		3,70

● Acidez dos Ácidos Carboxílicos

→ O proton carboxílico é o mais ácido e tem $pK_a = 4 - 5$

☞ Ácidos carboxílicos são facilmente desprotonados hidróxido de sódio o bicarbonato de sódio formando sais de carboxilatos

☞ Sais Carboxílicos são mais solúveis em água do que o ácidos

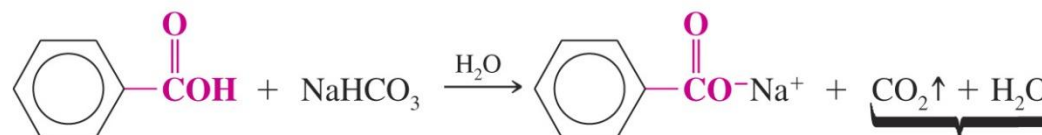


Benzoic acid
(water insoluble)
Stronger acid

Stronger base

Sodium benzoate
(water soluble)
Weaker base

Weaker acid



(water insoluble)
Stronger acid

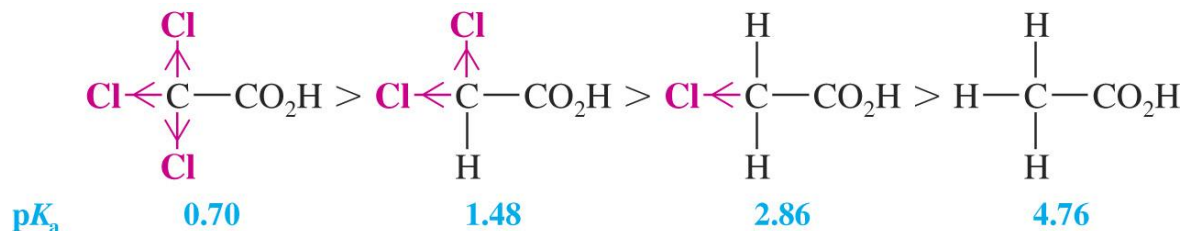
Stronger base

(water soluble)
Weaker base

H_2CO_3
Weaker acid

→ Grupos retiradores de eletrons vizinhos ao grupo carboxílico aumenta a acidez do ácido carboxílico

☞ Eles estabilizam o ânion carboxilato por deslocalização indutiva da carga

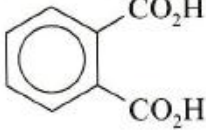
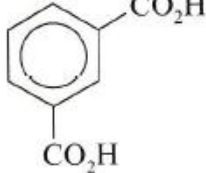
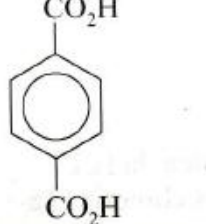


● Ácidos Dicarboxílicos

→ Ácidos Dicarboxylicos são denominados de ácidos alcanodióicos no sistema IUPAC

→ Common names are often used for simple dicarboxylic acids

Tabela 18.3 Ácidos Dicarboxílicos

Estrutura	Nome Comum	p.f. (°C)	pK _a (a 25°C)	
			pK ₁	pK ₂
HO ₂ C—CO ₂ H	Ácido oxálico	189 dec	1,2	4,2
HO ₂ CCH ₂ CO ₂ H	Ácido malônico	136	2,9	5,7
HO ₂ C(CH ₂) ₂ CO ₂ H	Ácido succínico	187	4,2	5,6
HO ₂ C(CH ₂) ₃ CO ₂ H	Ácido glutárico	98	4,3	5,4
HO ₂ C(CH ₂) ₄ CO ₂ H	Ácido adípico	153	4,4	5,6
<i>cis</i> -HO ₂ C—CH=CH—CO ₂ H	Ácido maléico	131	1,9	6,1
<i>trans</i> -HO ₂ C—CH=CH—CO ₂ H	Ácido fumárico	287	3,0	4,4
	Ácido ftálico	206-208 dec	2,9	5,4
	Ácido isoftálico	345-348	3,5	4,6
	Ácido tereftálico	Sublima	3,5	4,8

● Ésteres

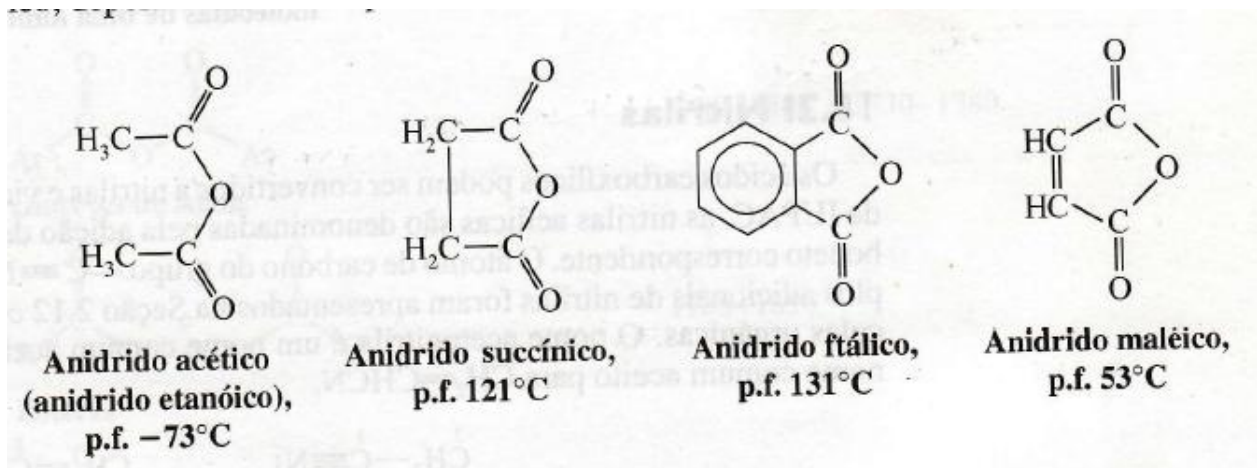
- Os nomes dos ésteres são derivados dos nomes dos ácidos carboxílicos correspondentes e do álcool que esterifica
- Ésteres, não formam ligações de hidrogênio entre eles portanto tem menor ponto de ebulição do que os ácidos carboxílicos e são bastante solúveis em água

Tabela 18.4 Ésteres Carboxílicos

Nome	Estrutura	p.f. (°C)	p.e. (°C)	Solubilidade em Água (g 100 mL ⁻¹ a 20°C)
Formato de metila	HCO ₂ CH ₃	- 99	31,5	Muito solúvel
Formato de etila	HCO ₂ CH ₂ CH ₃	- 79	54	Solúvel
Acetato de metila	CH ₃ CO ₂ CH ₃	- 99	57	24,4
Acetato de etila	CH ₃ CO ₂ CH ₂ CH ₃	- 82	77	7,39 (25°C)
Acetato de propila	CH ₃ CO ₂ CH ₂ CH ₂ CH ₃	- 93	102	1,89
Acetato de butila	CH ₃ CO ₂ CH ₂ (CH ₂) ₂ CH ₃	- 74	125	1,0 (22°C)
Propanoato de etila	CH ₃ CH ₂ CO ₂ CH ₂ CH ₃	- 73	99	1,75
Butanoato de etila	CH ₃ (CH ₂) ₂ CO ₂ CH ₂ CH ₃	- 93	120	0,51
Pentanoato de etila	CH ₃ (CH ₂) ₃ CO ₂ CH ₂ CH ₃	- 91	145	0,22
Hexanoato de etila	CH ₃ (CH ₂) ₄ CO ₂ CH ₂ CH ₂	- 68	168	0,063
Benzoato de metila	C ₆ H ₅ CO ₂ CH ₃	- 12	199	0,15
Benzoato de etila	C ₆ H ₅ CO ₂ CH ₂ CH ₃	- 35	213	0,08
Acetato de fenila	CH ₃ CO ₂ C ₆ H ₅		196	Pouco solúvel
Salicilato de metila	<i>o</i> -HOC ₆ H ₄ CO ₂ CH ₃	- 9	223	0,74 (30°C)

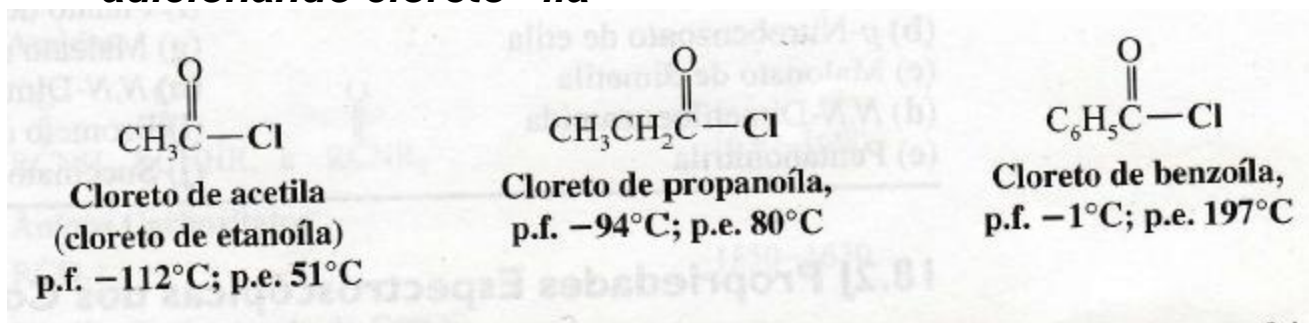
● Anidridos de ácidos carboxílicos

→ Esses são denominados retirando o termo ácido e substituindo-o por anidrido



Cloretos de ácidos

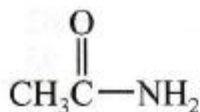
→ Os cloretos de acila são denominados retirando *-ico do* e *adicionando cloreto -ila*



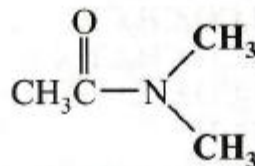
● Amidas

→ Amidas sem substituintes no nitrogênio são nomeadas substituindo ácido *-ico* ou *oico* por *amida*

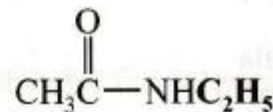
☞ Grupos no nitrogênio são nomeados como substituindo localizando –os no N ou *N,N*-



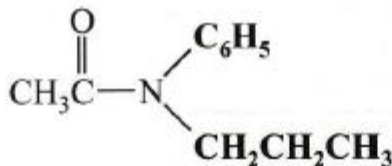
Acetamida
(etanamida),
p.f. 82°C; p.e. 221°C



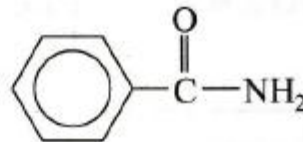
N,N-Dimetilacetamida,
p.f. -20°C; p.e. 166°C



N-Etilacetamida,
p.e. 205°C



N-fenil-*N*-propilacetamida,
p.f. 49°C; p.e. 266°C a 712 torr

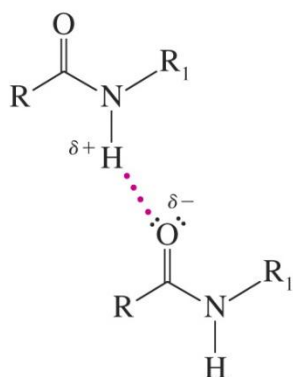


Benzamida,
p.f. 130°C; p.e. 290°C

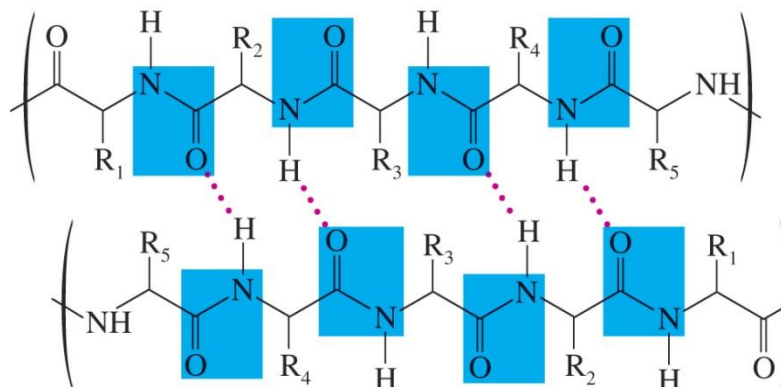
→ Amidas com um ou dois hidrogênios no nitrogênio formam ligações de hidrogênio muito fortes e tem alto ponto de fusão e ebulição

☞ Amidas *N,N*-dissubstituídas não formam ligações de hidrogênio entre si e tem menor ponto de fusão e ebulição.

→ Ligação de hidrogênio entre amidas em proteínas e peptideos são importantes na determinação da estrutura terciária dos mesmos.



Hydrogen bonding (red dots) between amide molecules



Hydrogen bonding between amide groups of peptide chains. This interaction between chains (called a β sheet) is important to the structure of many proteins.

● Nitrilas

→ Nitrilas acíclicas são denominadas adicionando o sufixo *-nitrila* ao nome do alcano

→ A nitrila é o carbono 1

☞ Nome popular da Etanenitrila é a acetoneitrila



Ethanenitrile
(acetoneitrile)

Propenenitrile
(acrylonitrile)

● Propriedades Espectroscópicas do compostos Acilas

→ Espectros no infravermelho

- ☞ Estiramento da carbonila varia de frequência de acordo com o tipo do derivado de ácido carboxílico
- ☞ Estiramento O-H do ácido carboxílico dá uma banda larga entre 2500-3100 cm^{-1}
- ☞ Estiramento N-H de amidas acontecem em 3140-3500 cm^{-1}

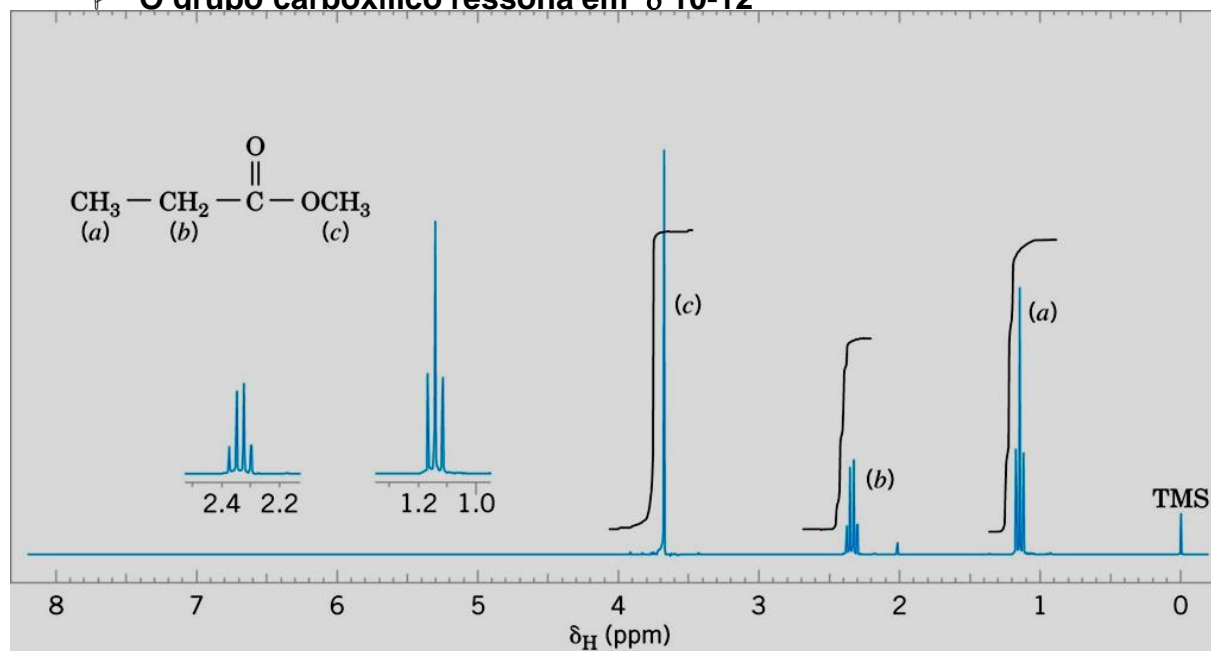
Functional Group	Approximate Frequency Range (cm^{-1})	1840	1820	1800	1780	1760	1740	1720	1700	1680	1660	1640	1620	1600
Acid chloride	1815–1785 1800–1770 (conj.)													
Acid anhydride	1820–1750 1775–1720 (conj.)													
Ester/Lactone	1750–1735 1730–1715 (conj.)													
Carboxylic acid	~1760 or 1720–1705 1710–1680 (conj.)													
Aldehyde	1740–1720 1710–1685 (conj.)													
Ketone	1720–1710 1685–1665 (conj.)													
Amide/lactam	1650–1640													
Carboxylate salt	1650–1550													

*Orange bars represent absorption ranges for conjugated species.

→ Espectros de RMN de ^1H

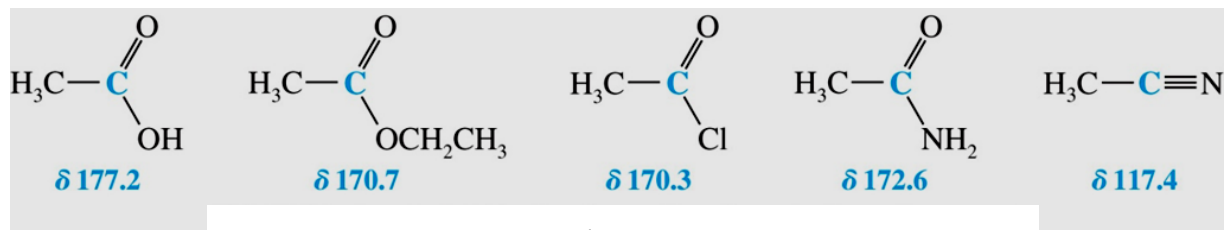
→ Os hidrogênios α dos ácidos carboxílicos e seus derivados em δ 2.0-2.5

☞ O grupo carboxílico ressona em δ 10-12



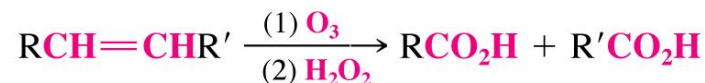
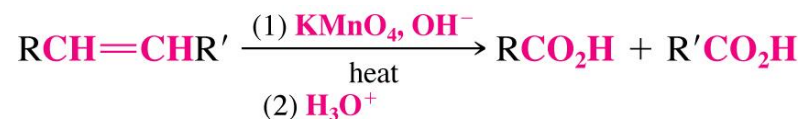
→ Espectros de RMN de ^{13}C

☞ O sinal do carbono carbonílico de ácidos carboxílicos e seus derivados aparecem em δ 160 to 180

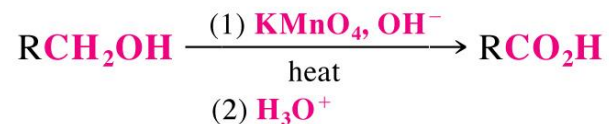


◆ Preparação de ácidos carboxílicos

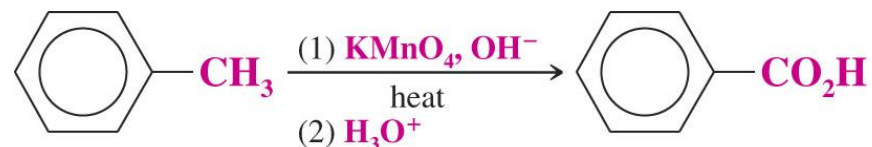
● Oxidação de alcenos



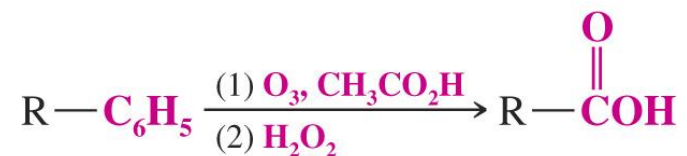
● Oxidação de aldeídos e álcoois primários



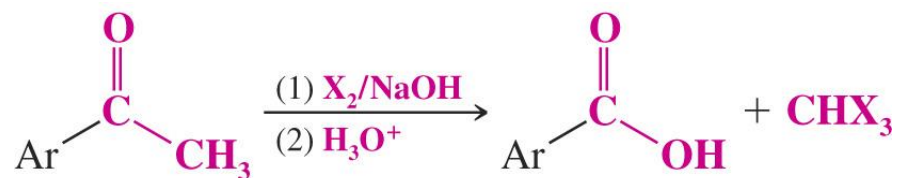
● Oxidação de alquilbenzenos



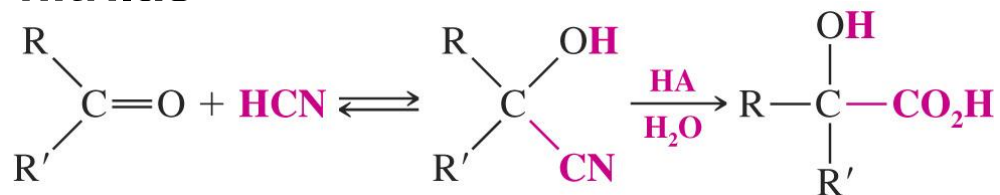
- Por oxidação do anel benzênico



- Por oxidação de metil cetonas (reação do Haloformio)



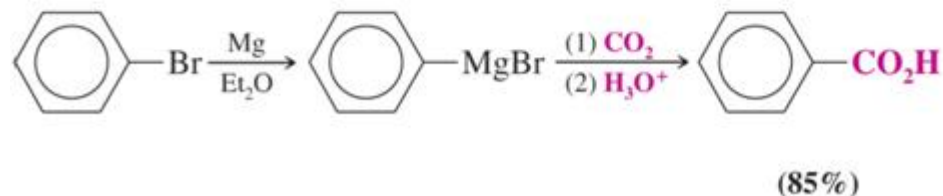
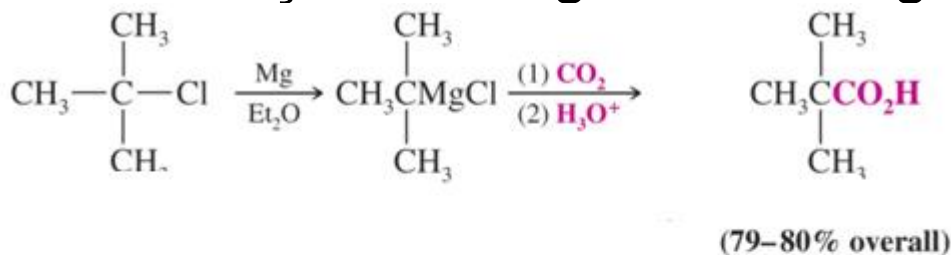
- Por hidrólise de cianoidrinas (alfa hidroxí ácidos) e outras nitrilas



- ☞ Haletos de alquila primários podem reagir com cianeto e formar nitrilas e estas hidrolizam a ácido carboxílicos

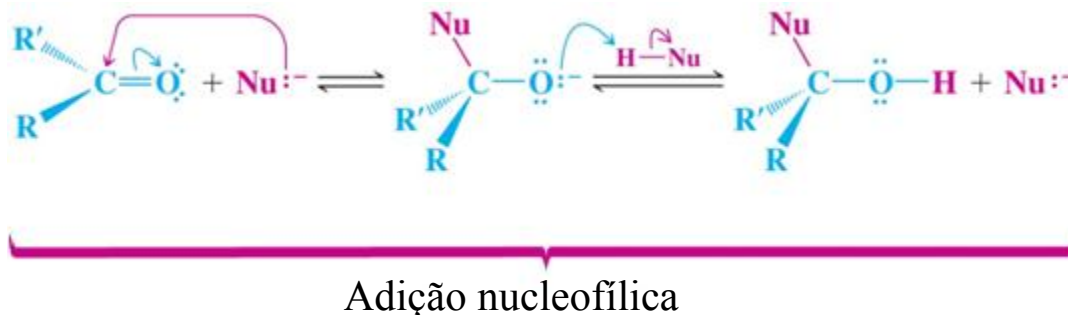


● Por carbonilação de Reagentes de Grignard



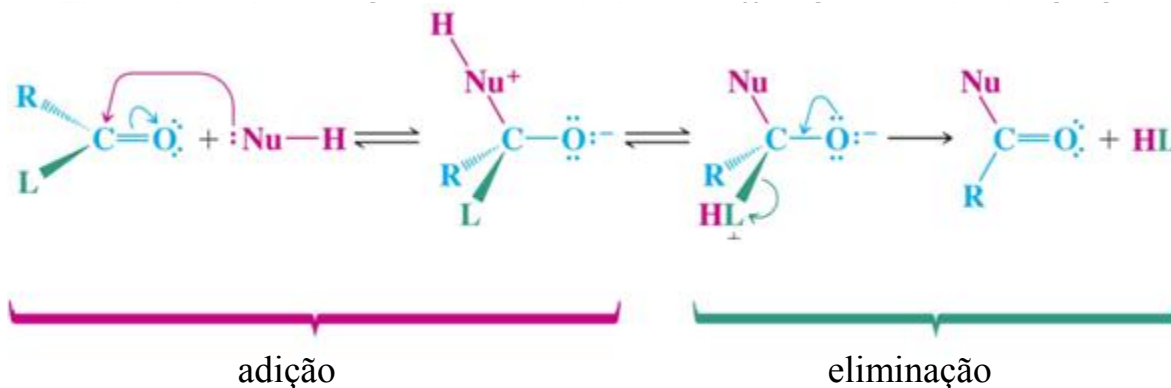
◆ Adição Nucleofílica – Eliminação no carbono acila

→ Lembramos que os aldeídos e cetona sofre adição nucleofílica na dupla ligação carbono oxigênio



→ O grupo carbonílico dos ácidos e seus derivados sofrem adição-eliminação

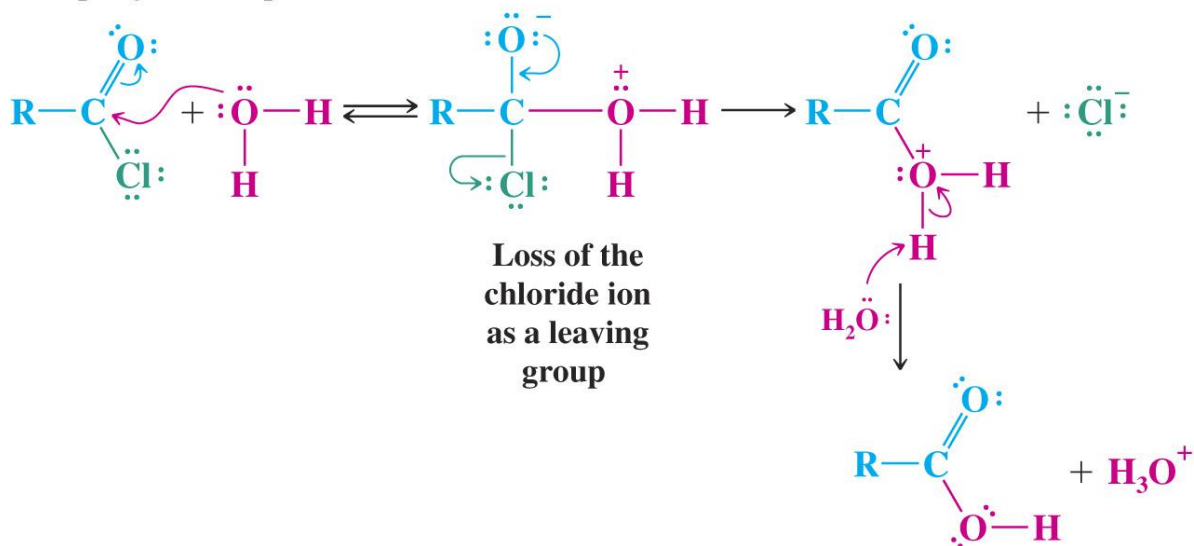
- ☞ The nucleophile reacts at the carbonyl group to form a tetrahedral intermediate
- ☞ The tetrahedral intermediate eliminates a leaving group (L)



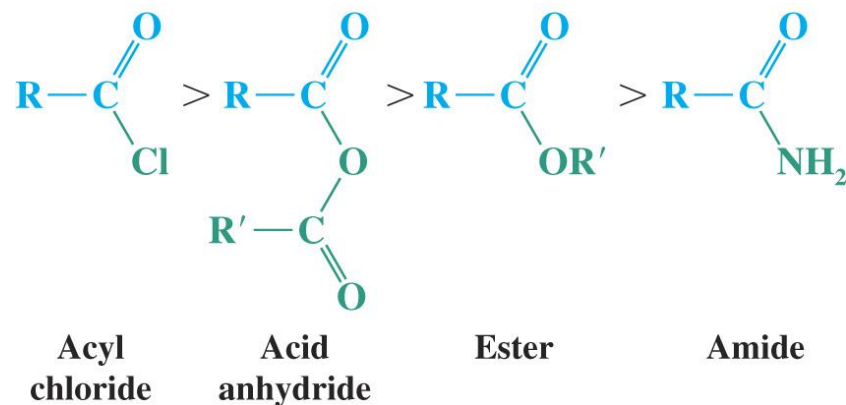
→ Para sofrer adição-eliminação nucleofílica o composto acila tem que ter um bom grupo de saída

- ☞ Cloreto de acila reage com perda do ion cloreto
- ☞ Anidridos reagem com perda de ion carboxilato

Specific Example



● **Reatividade relativa dos compostos de acila:**



→ **Em geral a reatividade está relacionada a facilidade de saída do grupo abandonador (L)**

- ☞ Facilidade de saída é inversamente relacionada a basicidade
- ☞ Cloreto é mais fraco e o melhor grupo de saída
- ☞ Aminas são bases mais fortes e os piores grupos de saída

→ **Via de regra os compostos acilas podem ser sintetizados a partir dos mais reativos.**

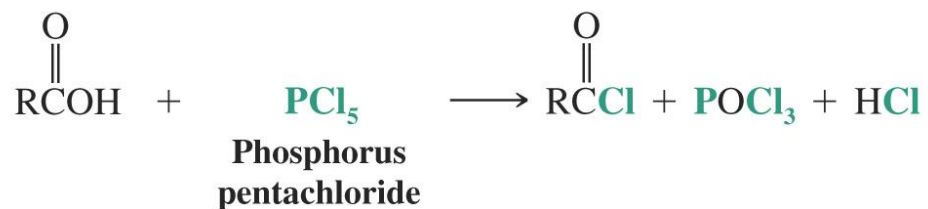
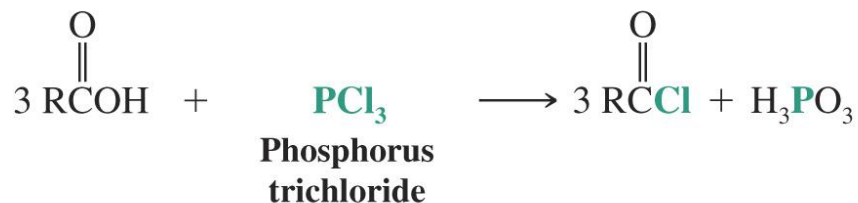
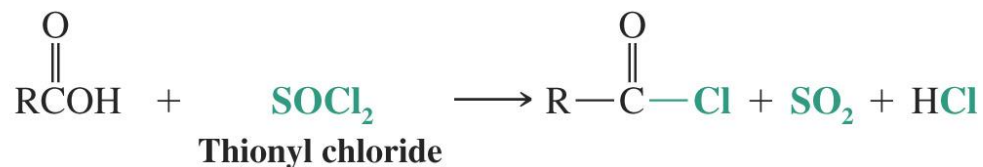
- ☞ Sínteses de derivados de acila a partir de derivados de acila menos reativos é difícil e necessita de reagentes especiais.

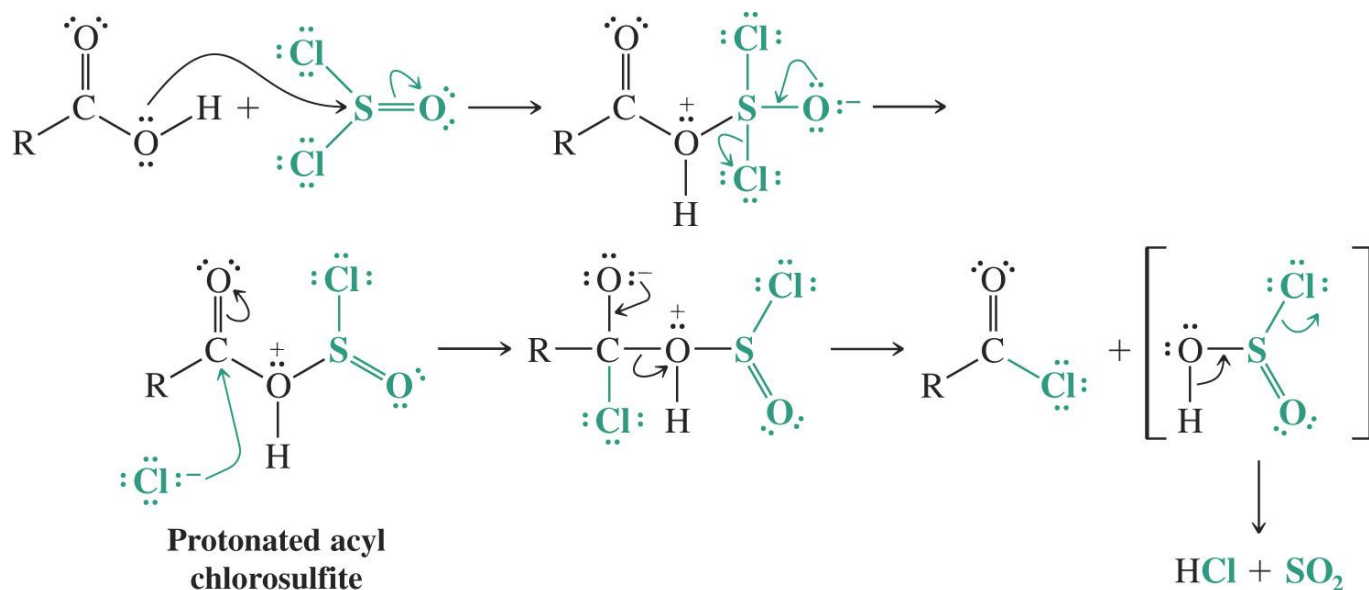
◆ Cloretos de acila

● Síntese de cloretos de acila

→ Cloretos de acila são feitos de ácidos carboxílicos por reação com cloreto de tionila, tricloreto de fósforo ou pentacloreto de fósforo

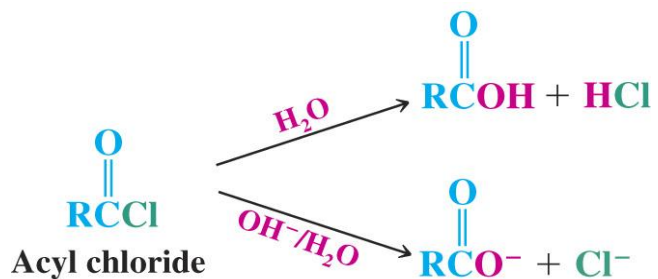
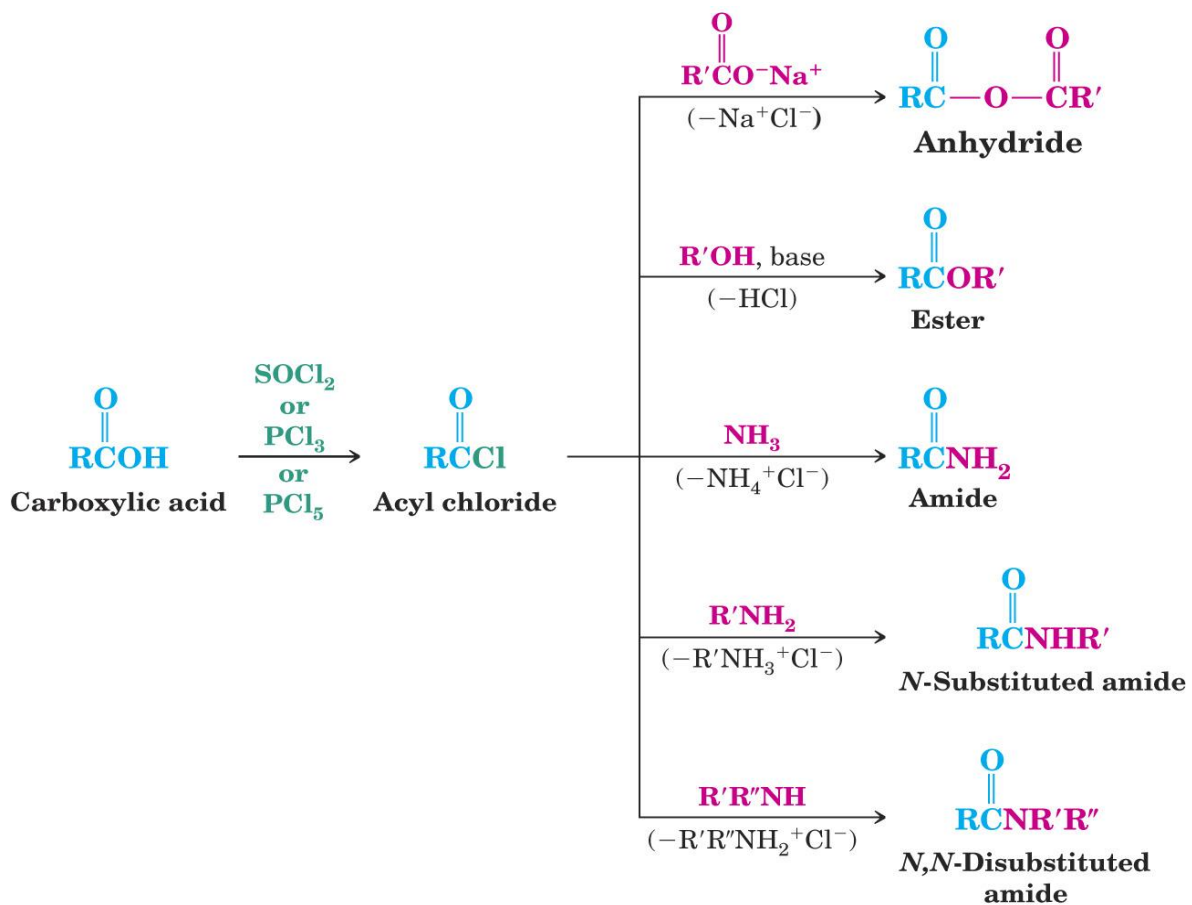
☞ Eses reagentes agem pois transformam o grupo hidroxila do ácido num bom grupo de saída





● Reações de cloretos de acila

- Cloretos de acila são os derivados de acila mais reativos e podem ser utilizados para fazer qualquer outro derivado.
- Como cloretos de acila são obtidos a partir de ácidos carboxílicos eles dão uma via para síntese de compostos acilas a parti de ácidos carboxílicos
- Cloretos de Aila regem violentamente com água dando ácidos carboxílico mas não é uma eação importante.

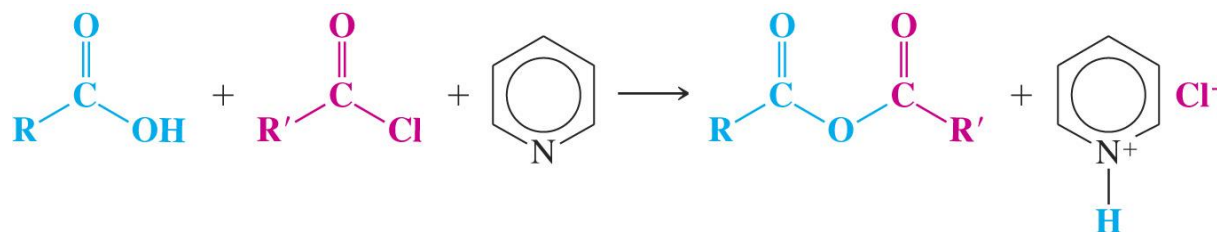


◆ Anidridos de ácidos

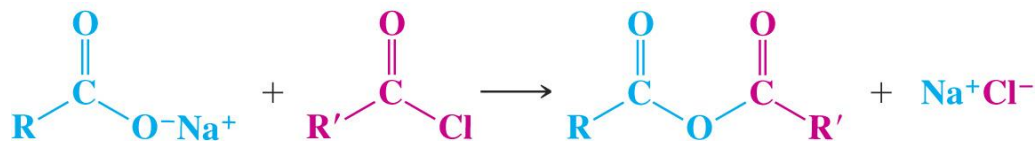
● Síntese de anidridos de ácidos carboxílicos

→ Cloretos de acila reagem com ácidos carboxílicos formando anidridos mistos ou simétricos

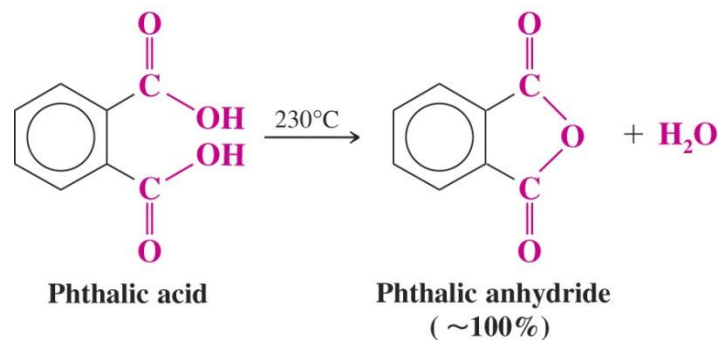
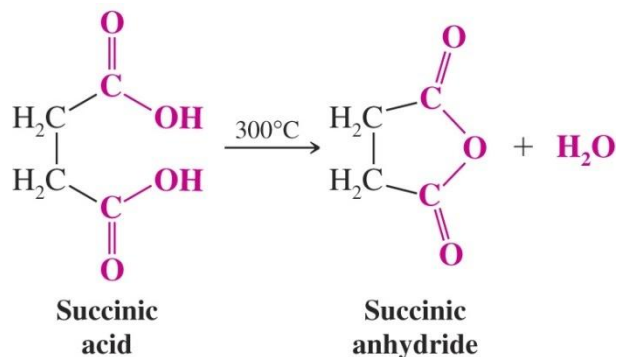
✎ É necessário utilizar bases como piridina



→ Carboxilatos de sódio reagem com cloretos de acila formando anidridos.



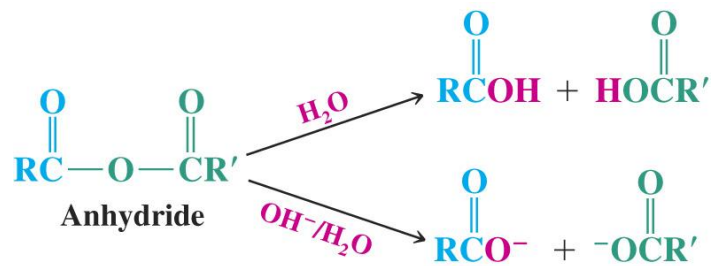
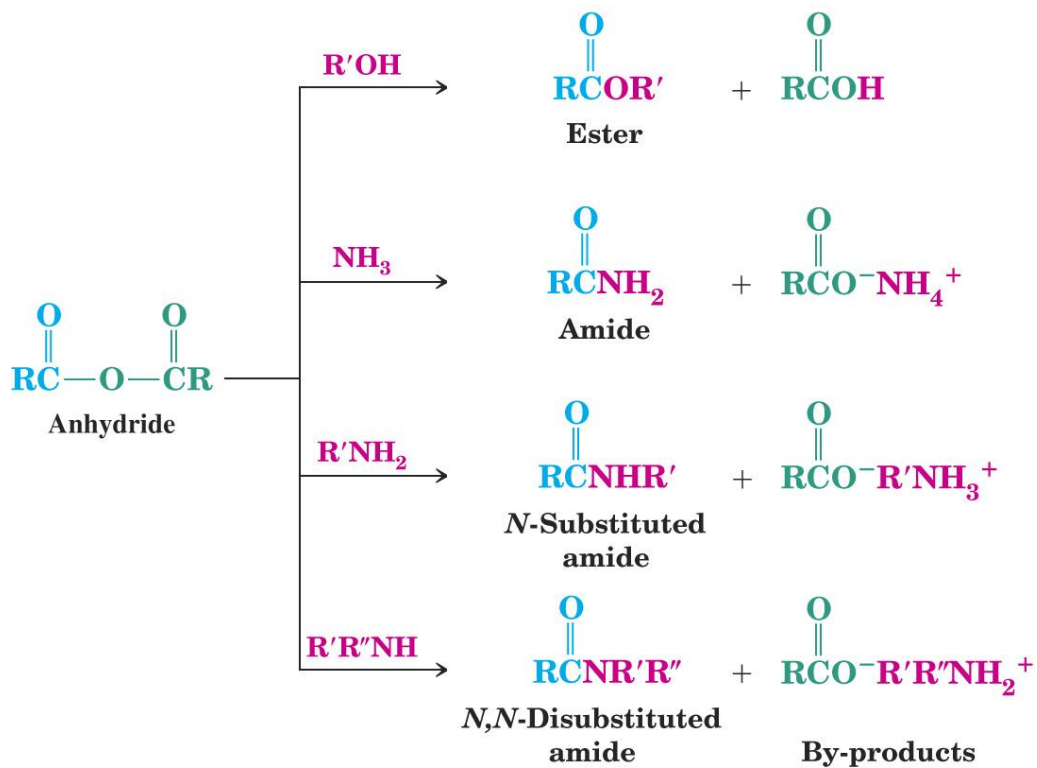
→ Anidridos cíclicos de 5 e 6 membros podem ser formados aquecendo o diácido apropriado



● Reações de anidridos de ácidos carboxílicos

→ Anidridos de ácidos carboxílicos são bem reativos e podem ser utilizados para sintetizar esteres e amidas

☞ Hidrólise de um anidrido fornece os ácidos carboxílicos correspondentes



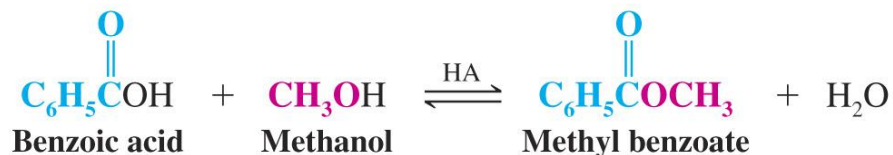
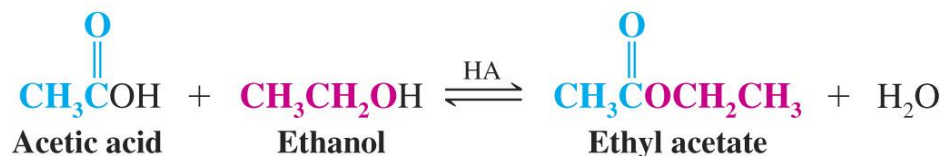
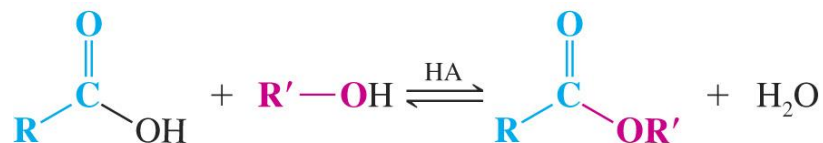
◆ Ésteres

● Síntese de ésteres: Esterificação

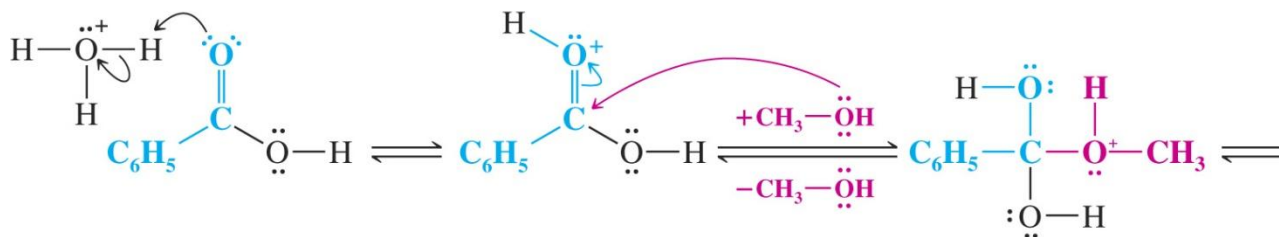
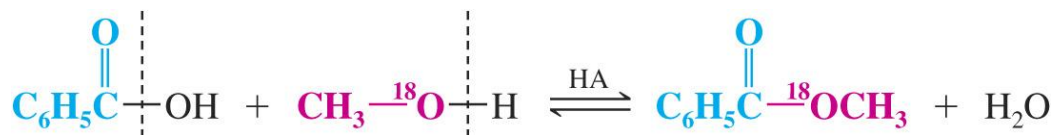
→ Reações catalisadas por ácidos com álcoois e ácidos carboxílicos dando esteres são denominadas de esterificação de Fischer

→ Esterificação de Fischer é um equilíbrio

- ☞ A formação do ester é favorecida pelo uso de excesso de álcool ou ácido carboxílico.
- ☞ Formação de ester é também favorecida pela remoção de água;



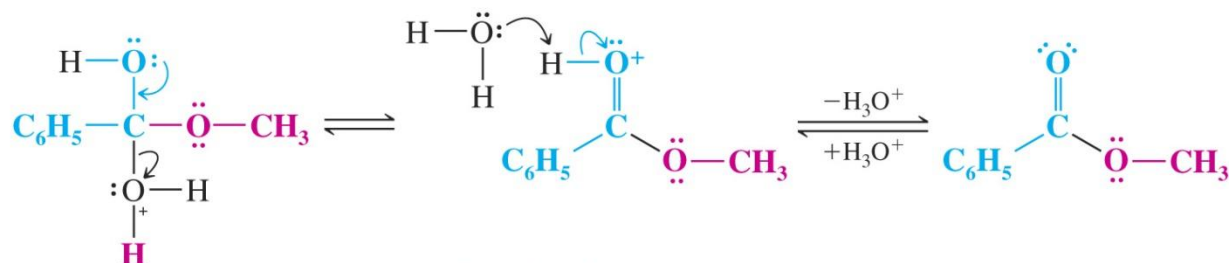
→ Esterificação com metanol marcado fornece um produto marcado no oxigênio ligado ao grupo metílico . O mecanismo consistente com essa observação está abaixo.



The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.

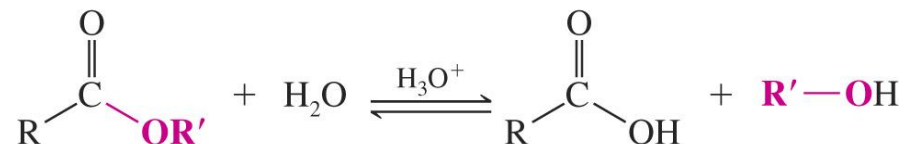


Loss of a molecule of water gives a protonated ester.

Transfer of a proton to a base leads to the ester.

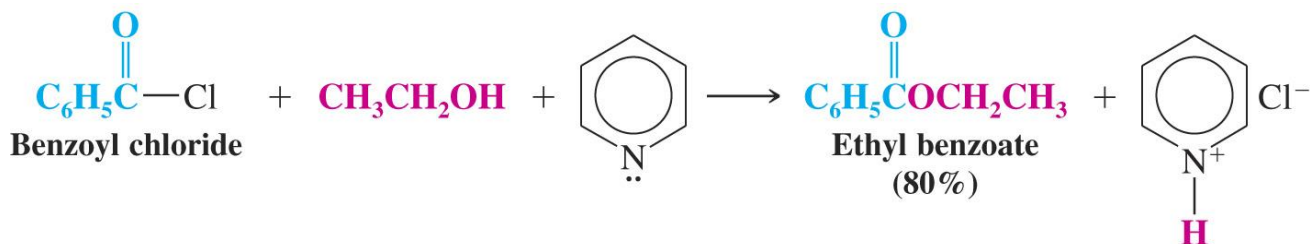
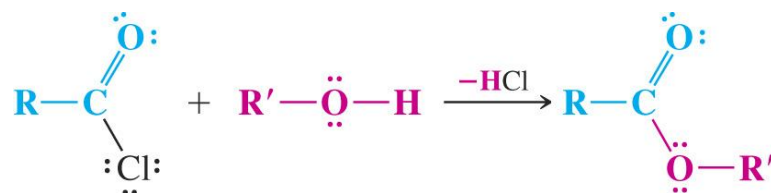
→ The reverse reaction is acid-catalyzed ester hydrolysis

☞ Ester hydrolysis is favored by use of dilute aqueous acid



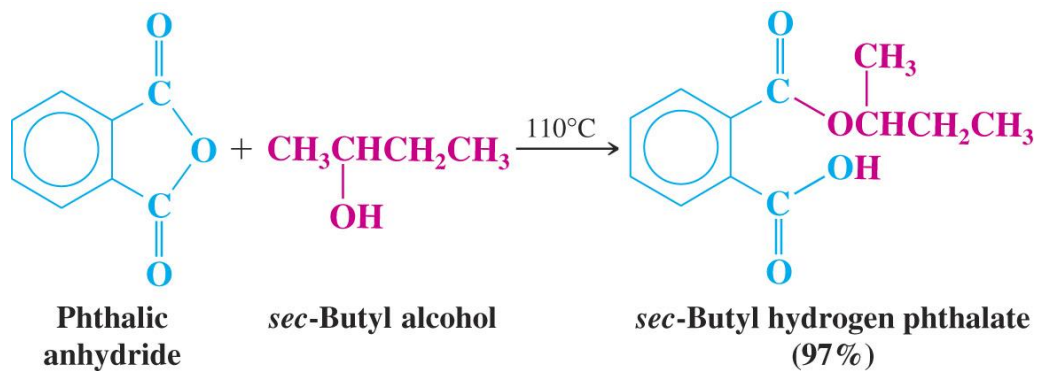
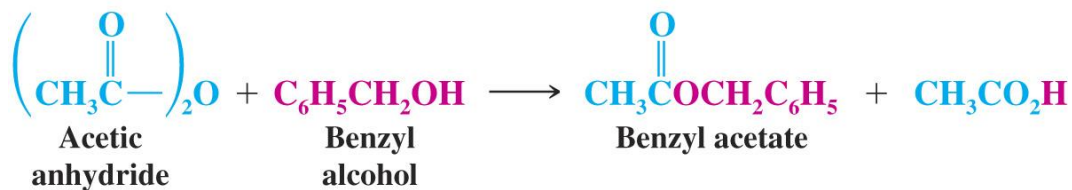
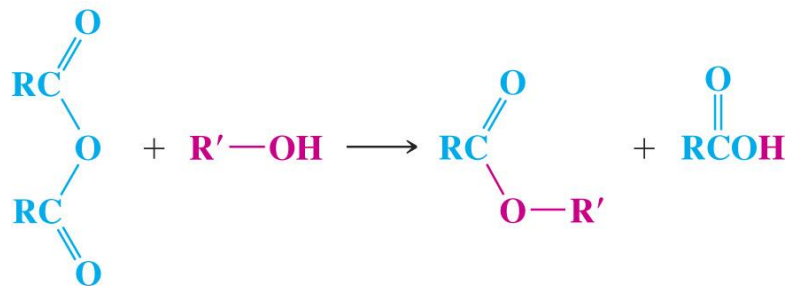
→ Esters from Acid Chlorides

☞ Acid chlorides react readily with alcohols in the presence of a base (e.g. pyridine) to form esters



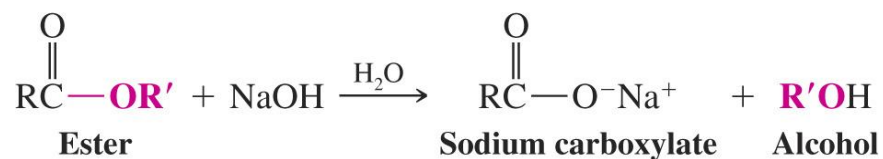
→ Esters from Carboxylic Acid Anhydrides

☞ Alcohols react readily with anhydrides to form esters



● Base-Promoted Hydrolysis of Esters: Saponification

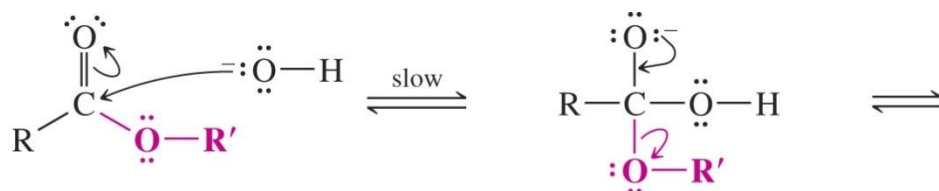
→ Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol



→ The mechanism is reversible until the alcohol product is formed

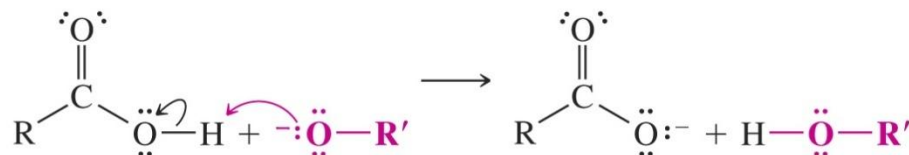
→ Protonation of the alkoxide by the initially formed carboxylic acid is irreversible

☞ This step draws the overall equilibrium toward completion of the hydrolysis



A hydroxide ion attacks the carbonyl carbon atom.

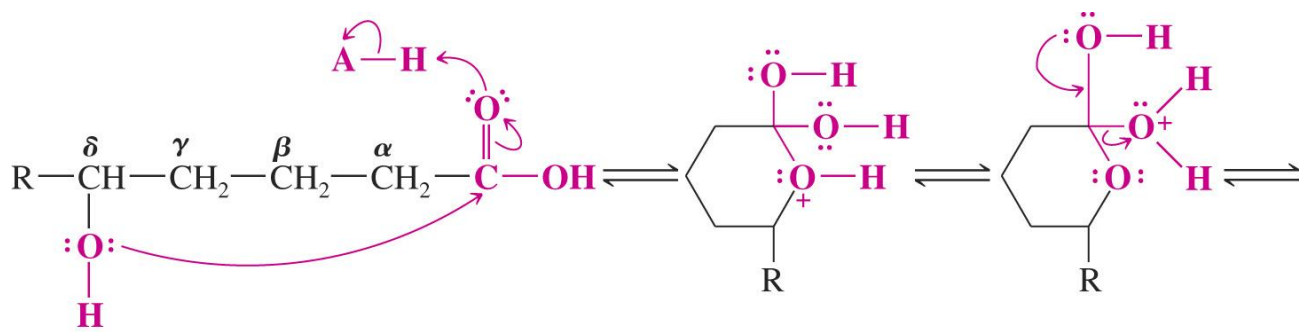
The tetrahedral intermediate expels an alkoxide ion.



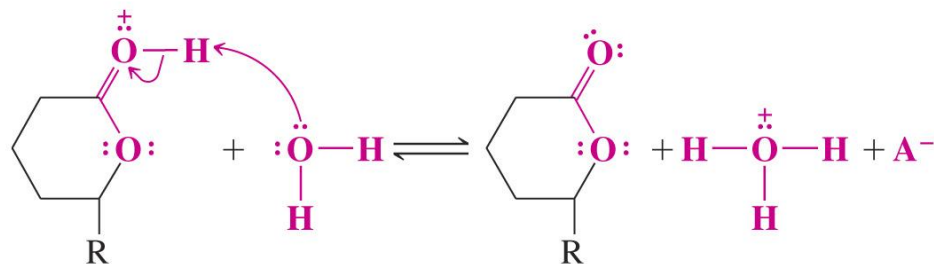
Transfer of a proton leads to the products of the reaction.

● Lactones

→ γ - or δ -Hydroxyacids undergo acid catalyzed reaction to give cyclic esters known as γ - or δ -lactones, respectively



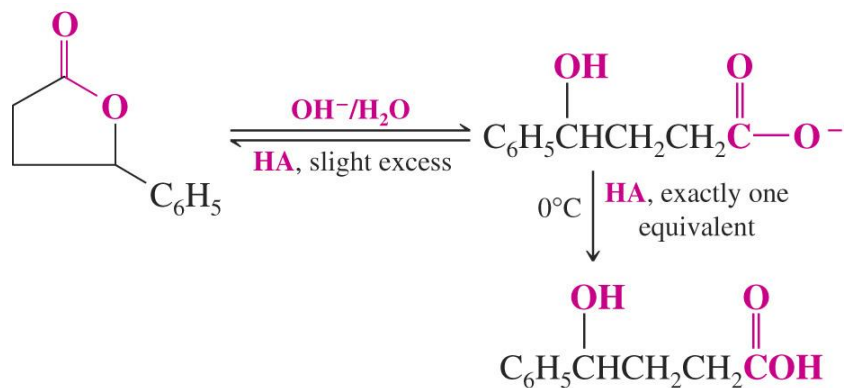
A δ -hydroxy acid



A δ -lactone

→ Lactones can be hydrolyzed with aqueous base

⚡ Acidification of the carboxylate product can lead back to the original lactone if too much acid is added

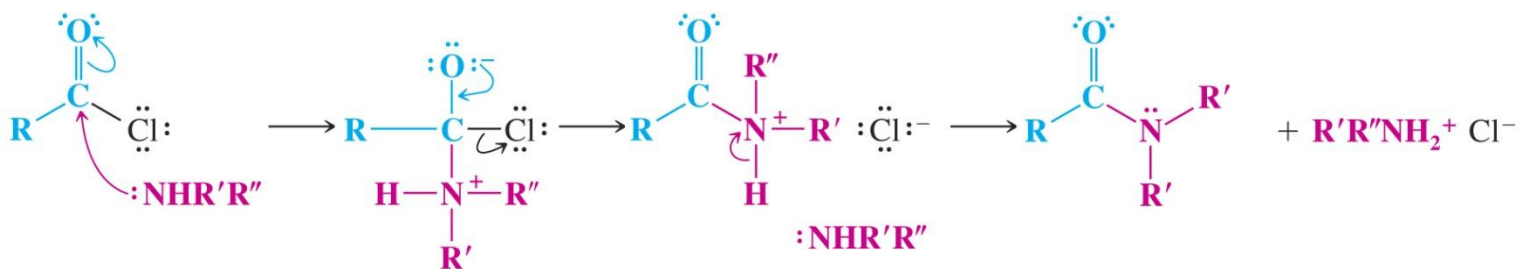


◆ Amides

● Synthesis of Amides

→ Amides From Acyl Chlorides

- ☞ Ammonia, primary or secondary amines react with acid chlorides to form amides
- ☞ An excess of amine is added to neutralize the HCl formed in the reaction
- ☞ Carboxylic acids can be converted to amides via the corresponding acid chloride



Reactant

Ammonia; $\text{R}', \text{R}'' = \text{H}$

1° Amine; $\text{R}' = \text{H}, \text{R}'' = \text{alkyl, aryl}$

2° Amine; $\text{R}', \text{R}'' = \text{alkyl, aryl}$

Product

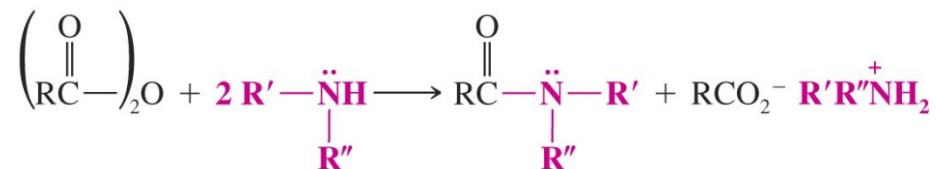
Unsubstituted amide; $\text{R}', \text{R}'' = \text{H}$

N-Substituted amide; $\text{R}' = \text{H}, \text{R}'' = \text{alkyl, aryl}$

N,N-Disubstituted amide; $\text{R}', \text{R}'' = \text{alkyl, aryl}$

→ Amides from Carboxylic Anhydrides

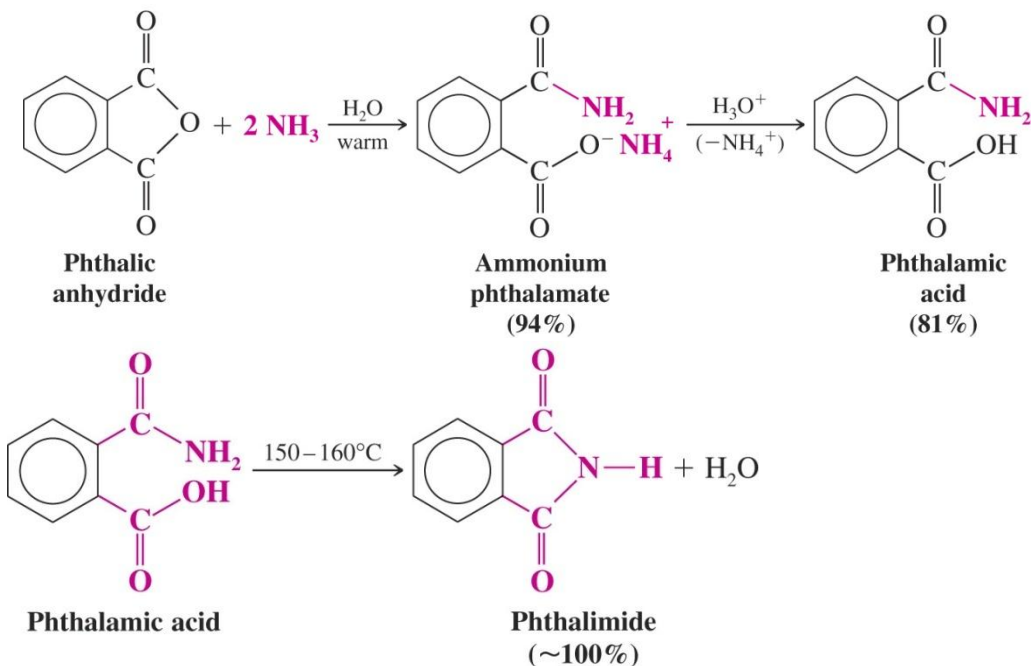
- ☞ Anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate



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

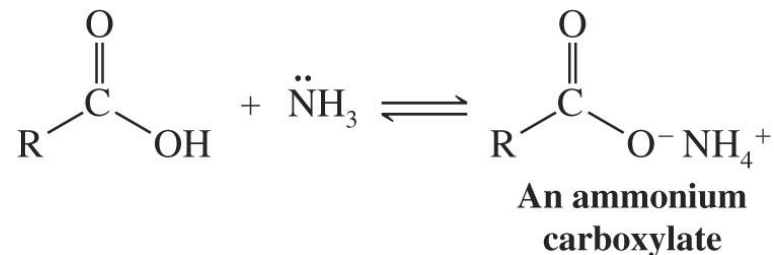
- ☞ Reaction of a cyclic anhydride with an amine, followed by acidification yields a product containing both amide and carboxylic acid functional groups

- ☞ Heating this product results in the formation of a cyclic imide

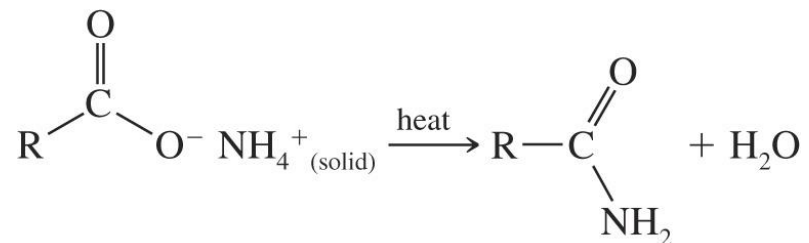


→ Amides from Carboxylic Acids and Ammonium Carboxylates

- ☞ Direct reaction of carboxylic acids and ammonia yields ammonium salts

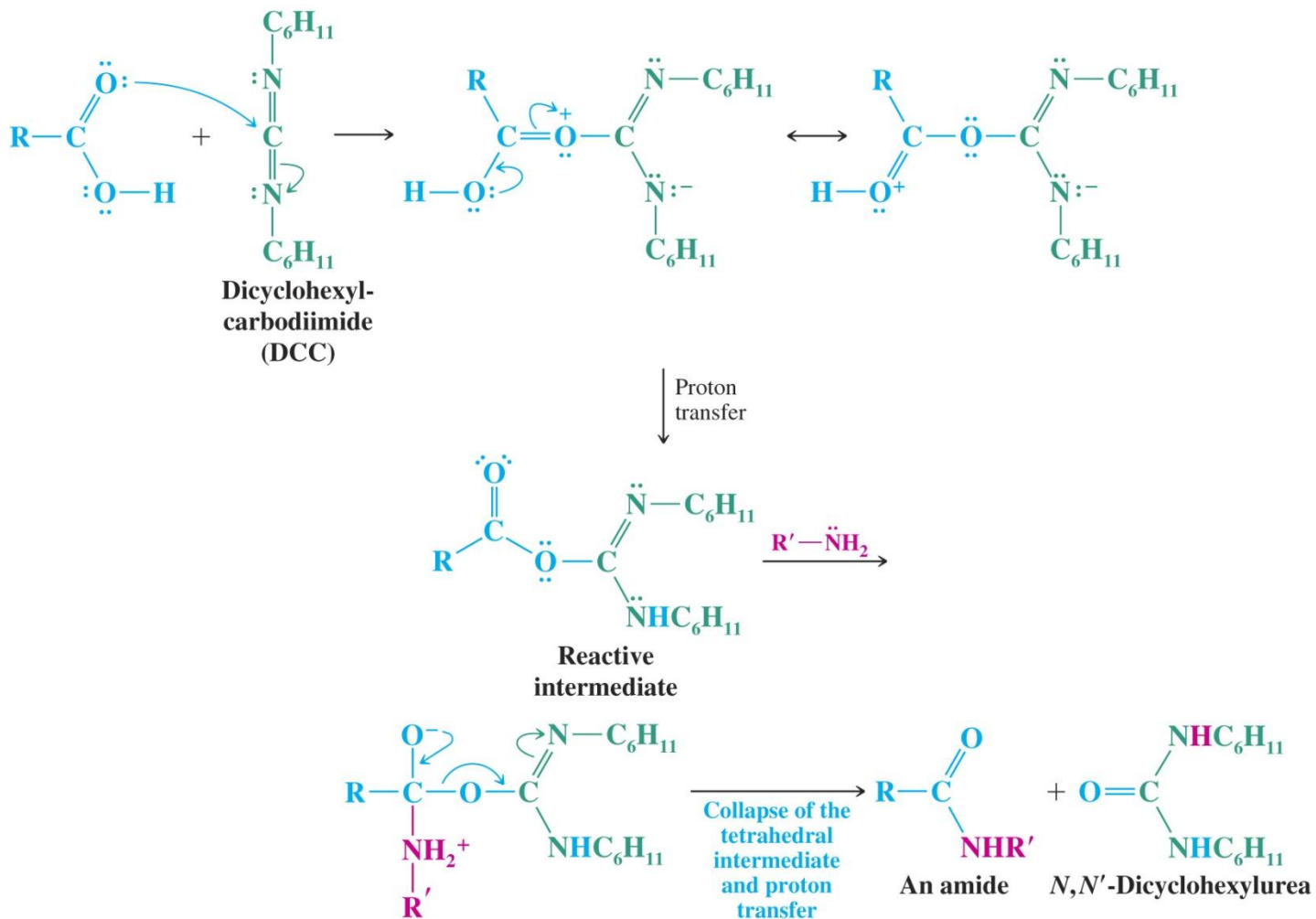


- ☞ Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures
- ☞ This is generally a poor method of amide synthesis



- ☞ A good way to synthesize an amide is to convert a carboxylic acid to an acid chloride and to then to react the acid chloride with ammonia or an amine

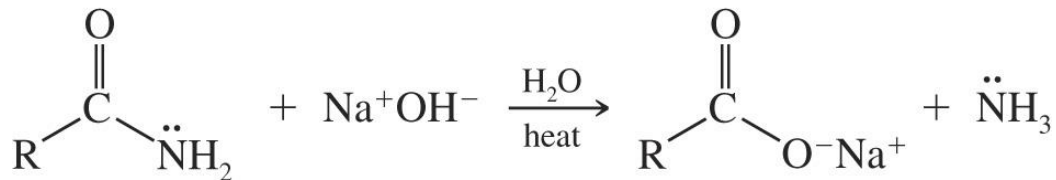
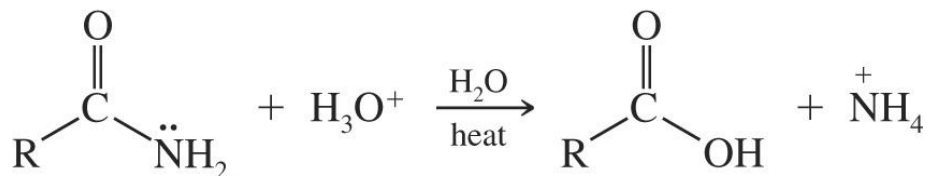
- ☞ Dicyclohexylcarbodiimide (DCC) is a reagent used to form amides from carboxylic acids and amines
- ☞ DCC activates the carbonyl group of a carboxylic acid toward nucleophilic addition-elimination

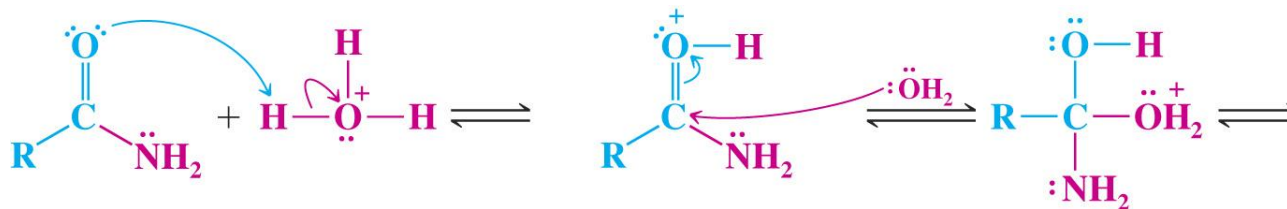


● Hydrolysis of Amides

→ Heating an amide in concentrated aqueous acid or base causes hydrolysis

☞ Hydrolysis of an amide is slower than hydrolysis of an ester

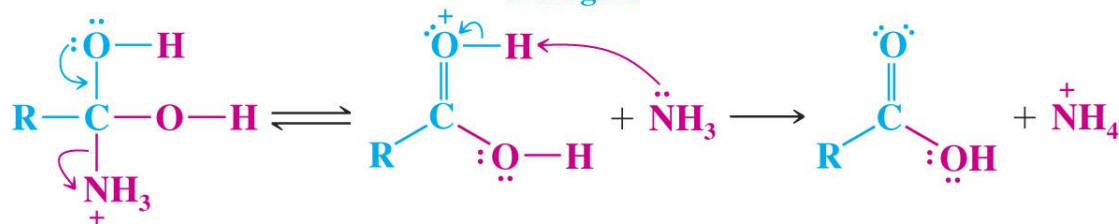




The amide carbonyl accepts a proton from the aqueous acid.

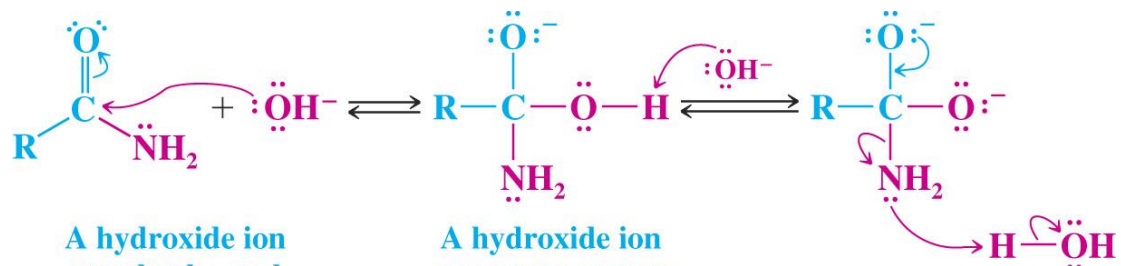
A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.



Loss of a molecule of ammonia gives a protonated carboxylic acid.

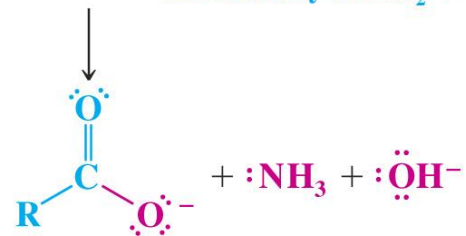
Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.



A hydroxide ion attacks the acyl carbon of the amide.

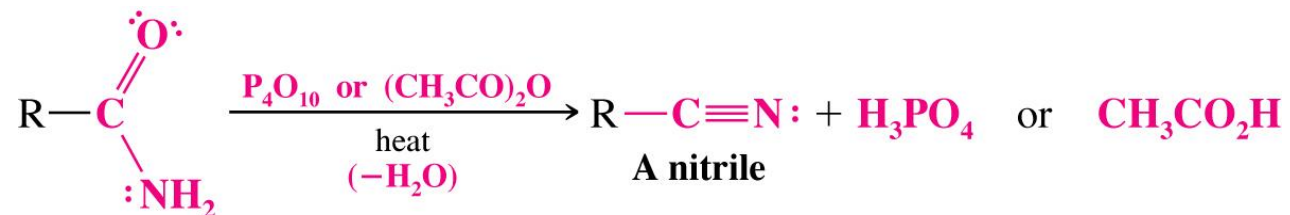
A hydroxide ion removes a proton to give a dianion.

The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^- .



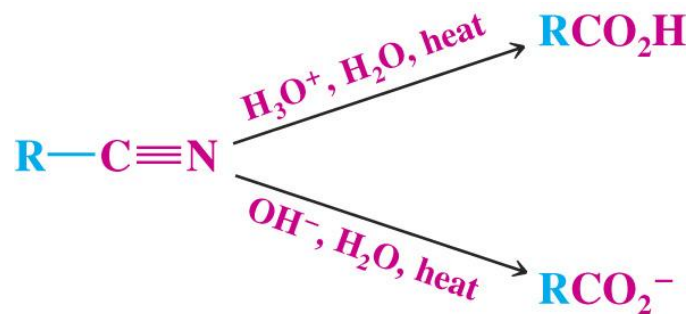
- **Nitriles from the Dehydration of Amides**

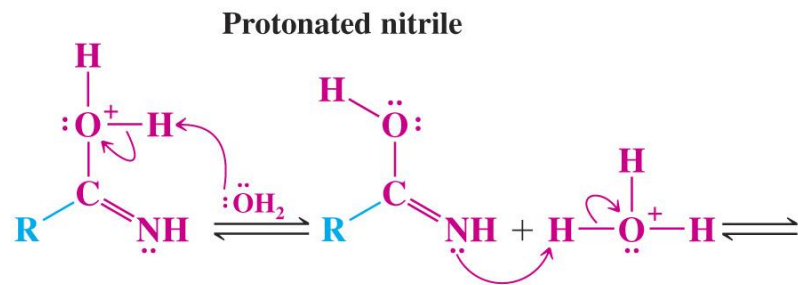
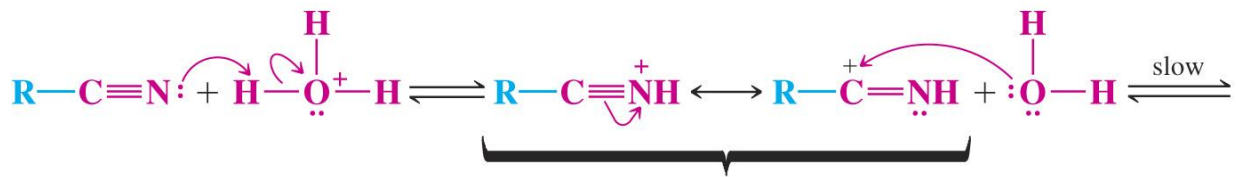
→ A nitrile can be formed by reaction of an amide with phosphorous pentoxide or boiling acetic anhydride



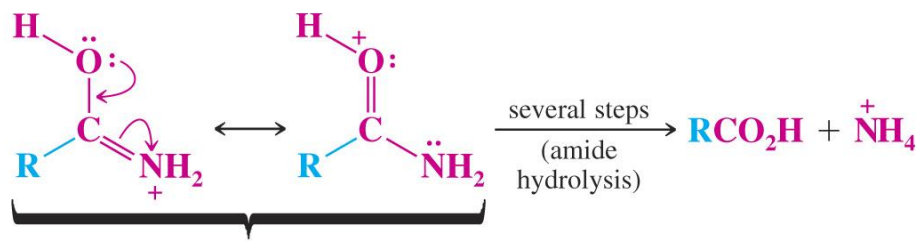
- **Hydrolysis of Nitriles**

→ A nitrile is the synthetic equivalent of a carboxylic acid because it can be converted to a carboxylic acid by hydrolysis

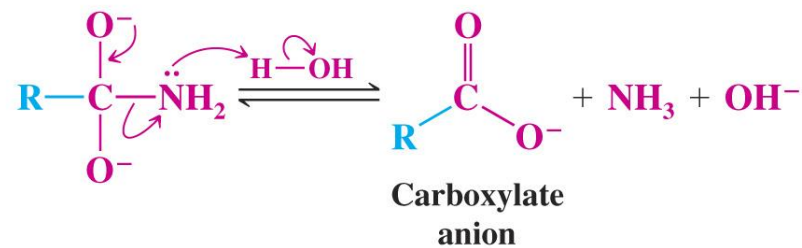
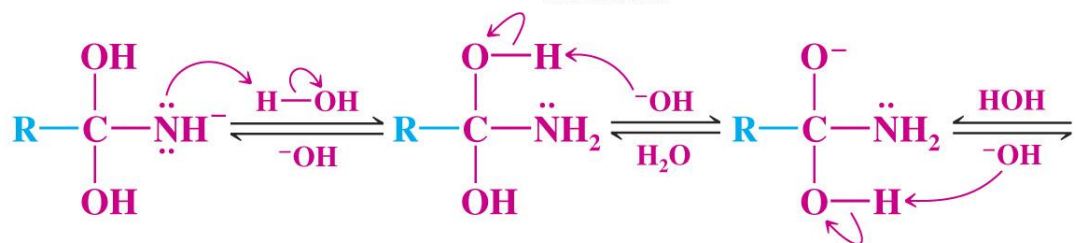
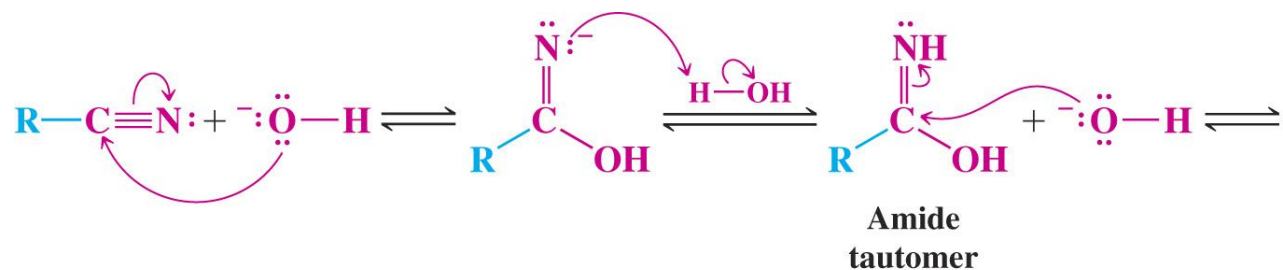




Amide tautomer



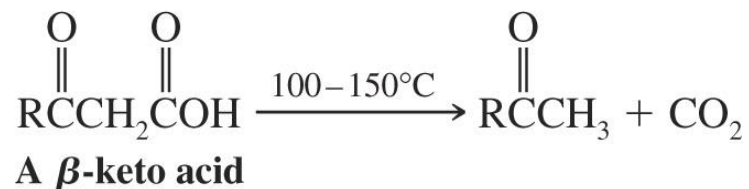
Protonated amide



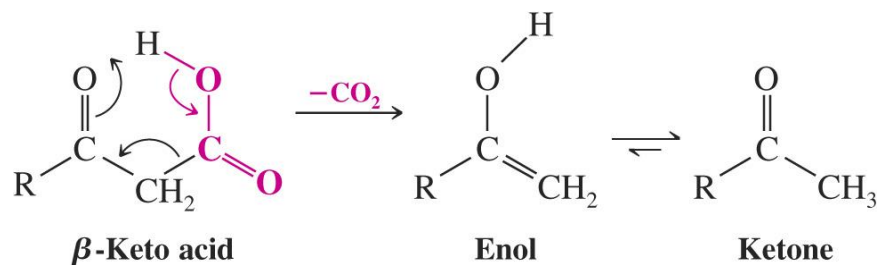
◆ Decarboxylation of Carboxylic Acids

→ β -Keto carboxylic acids and their salts decarboxylate readily when heated

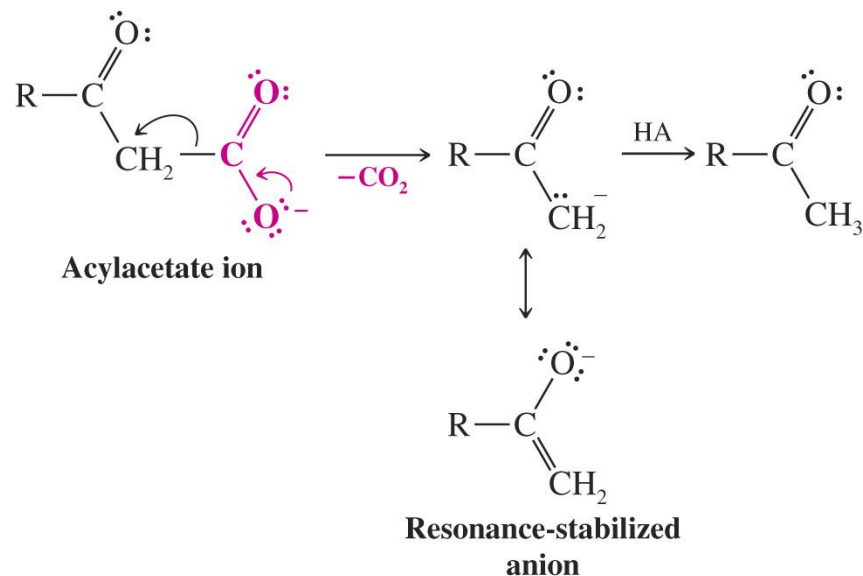
☞ Some even decarboxylate slowly at room temperature



→ The mechanism of β -keto acid decarboxylation proceeds through a 6-membered ring transition state



→ Carboxylate anions decarboxylate rapidly because they form a resonance-stabilized enolate



→ Malonic acids also decarboxylate readily

