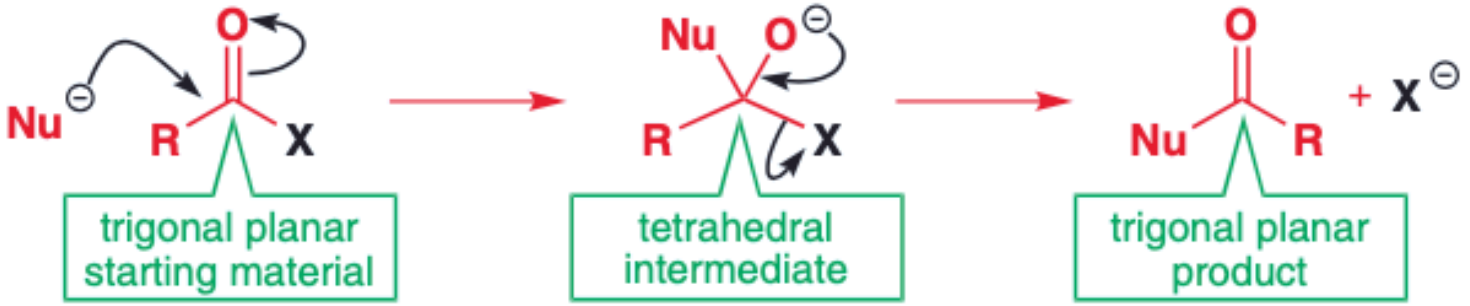
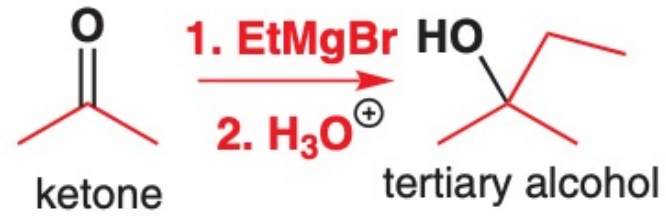
Substituição Nucleofílica no Grupo Carbonila

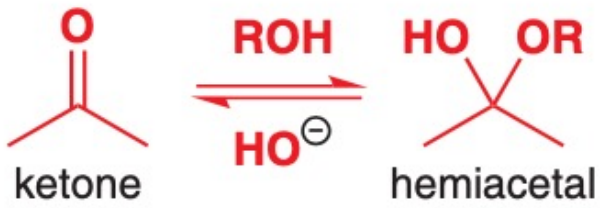
Ácidos Carboxílicos e seus Derivados

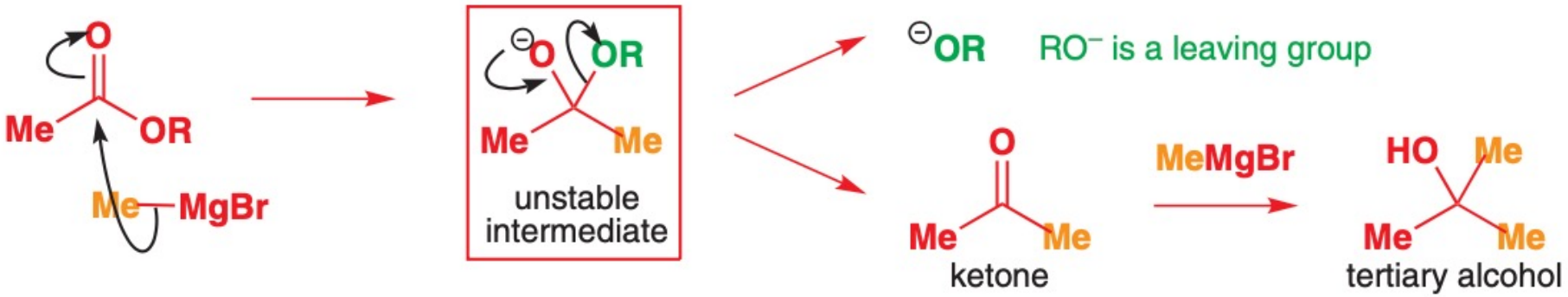


Prof. Dr. Carlos Alberto Montanari
Monitor PAE: Matheus Fernandes Flores

O produto de adição em um grupo carbonila nem sempre é um composto estável

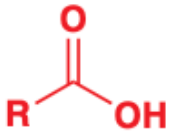
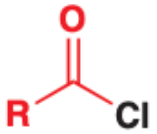
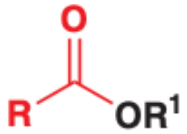
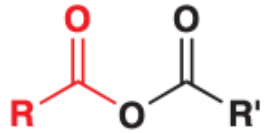
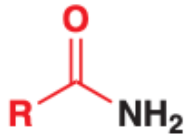




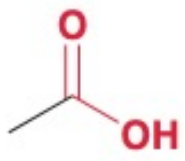


Ácidos Carboxílicos e Derivados

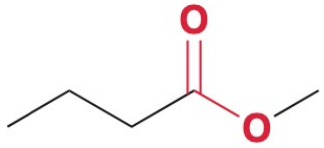
Carboxylic acid derivatives

Carboxylic acid	Derivative of RCO_2H			
	acid chloride or acyl chloride*	ester	acid anhydride	amide
				

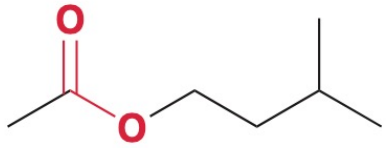
*We shall use these two terms interchangeably.



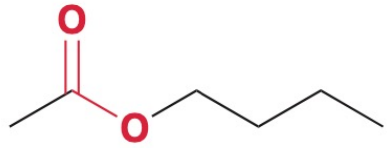
Acetic acid
(Responsible for the pungent smell of vinegar)



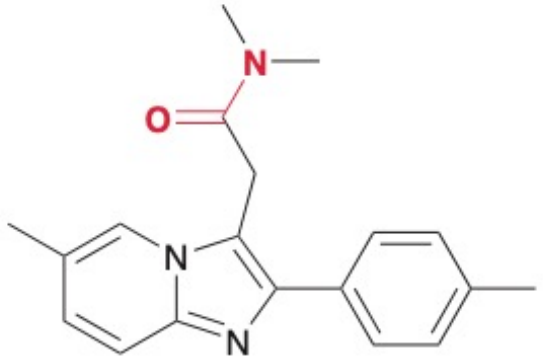
Methyl butanoate
(pineapple)



Isopentyl acetate
(banana)



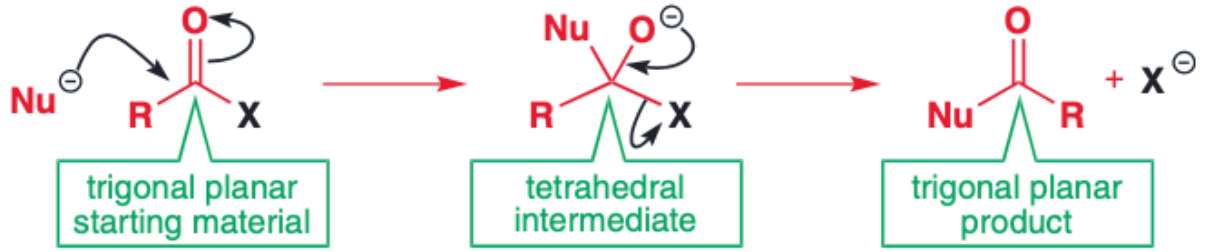
Butyl acetate
(pear)

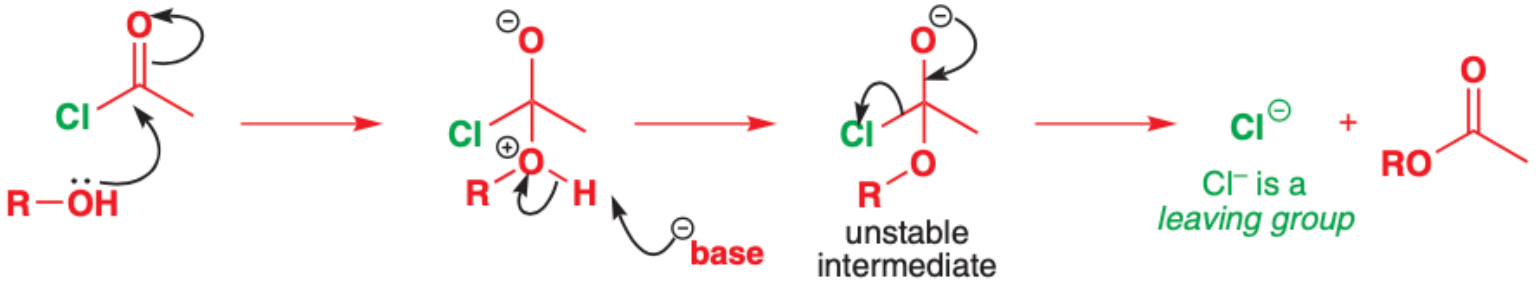


Zolpidem
(Ambien™)

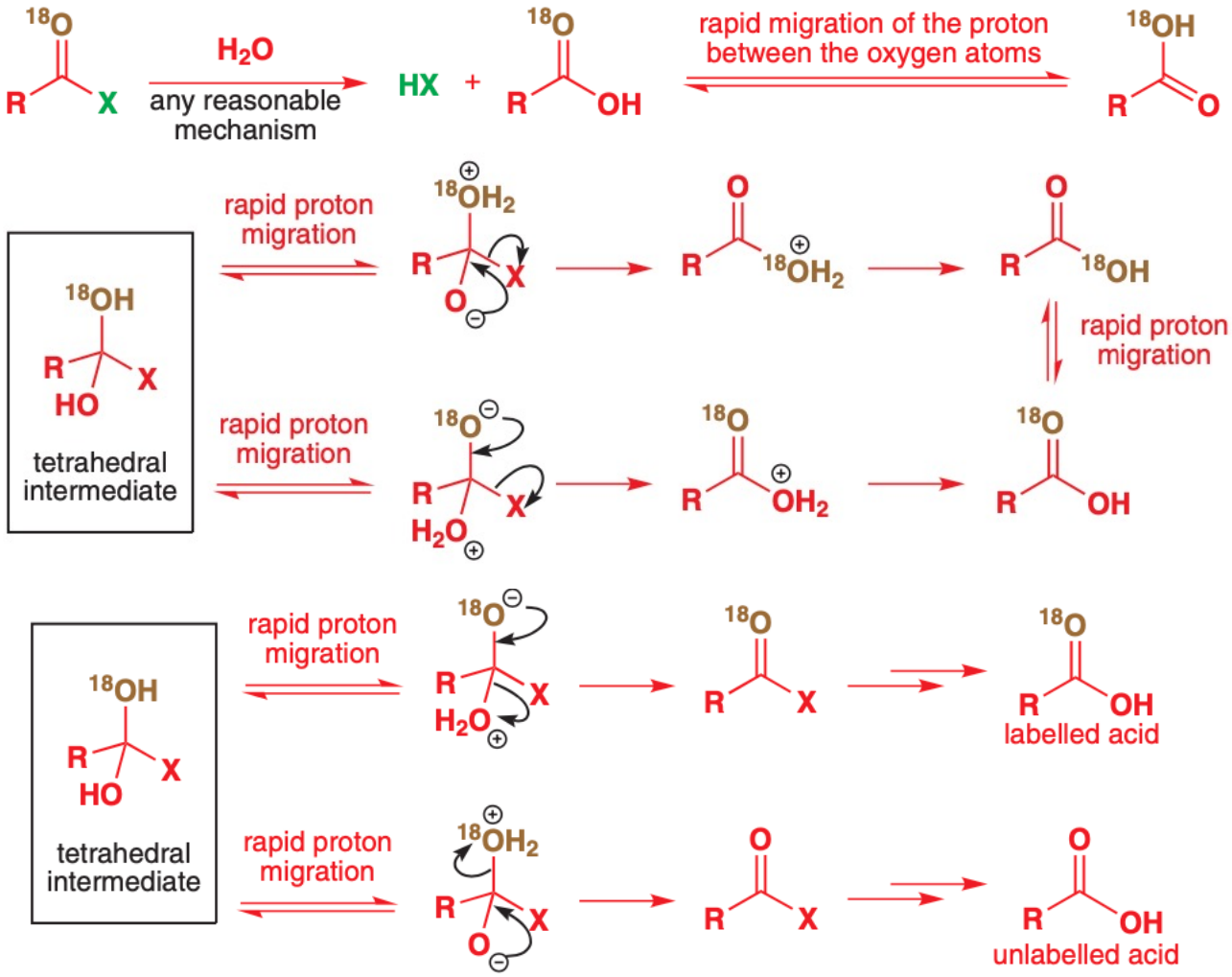
● Tetrahedral intermediates

Substitutions at trigonal carbonyl groups go through a tetrahedral intermediate and then on to a trigonal product.





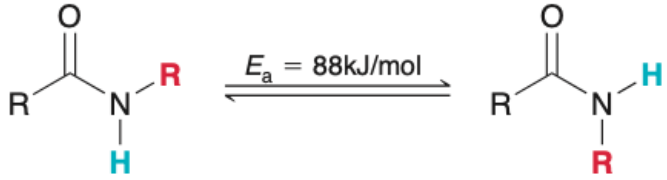
Como sabemos que o intermediário tetraédrico existe?

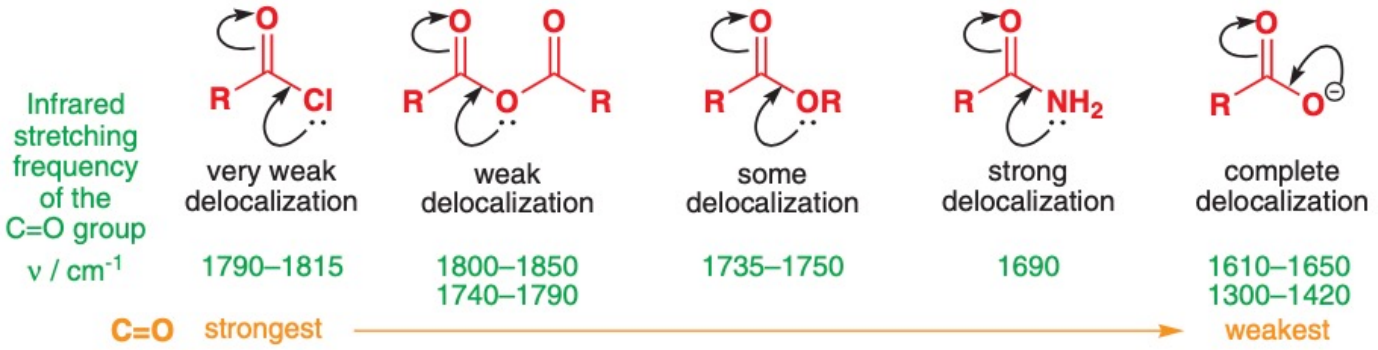


Myron L. Bender.

■ In Bender's original work, X was an alkoxy group (i.e. RCOX was an ester).

Reatividade dos derivados de ácido



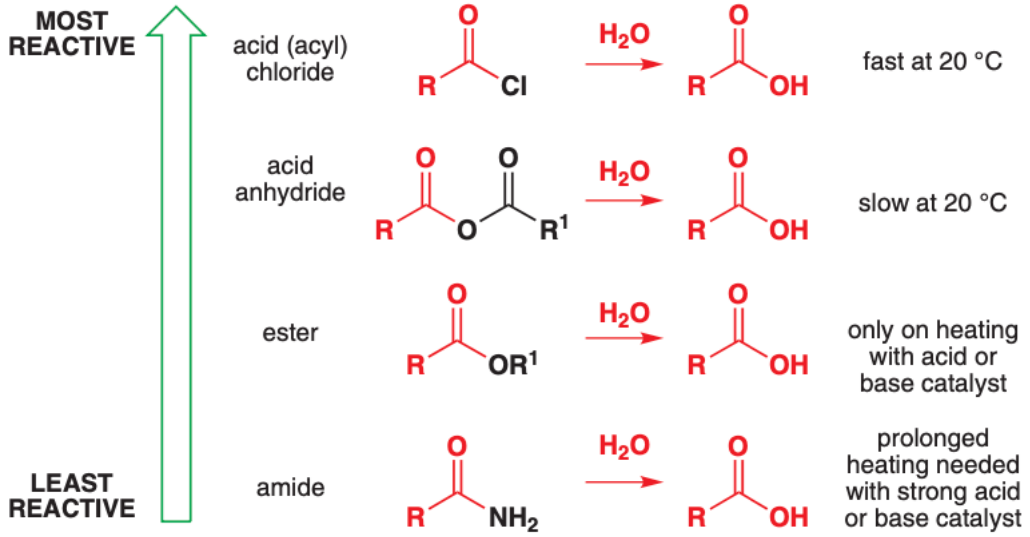


pK_a e a reatividade dos derivados de ácido

● Leaving group ability

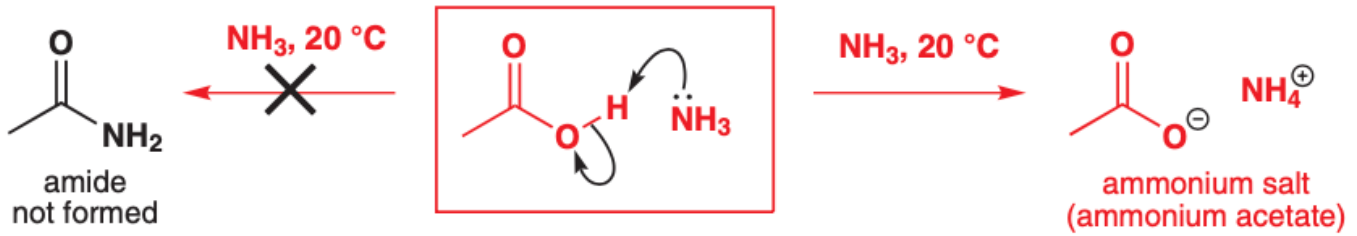
The lower the pK_a of HX, the better the leaving group of X^- in carbonyl substitution reactions.

carboxylic acid derivative	leaving group, X^-	conjugate acid, HX	p*K*a of HX	leaving group?
acyl chloride	Cl^-	HCl	<0	excellent
anhydride	$RCOO^-$	RCO_2H	about 5	good
ester	RO^-	ROH	about 15	poor
amide	NH_2^-	NH_3	about 25	very poor
alkyl or aryl derivative	R^-	RH	>40	not a leaving group

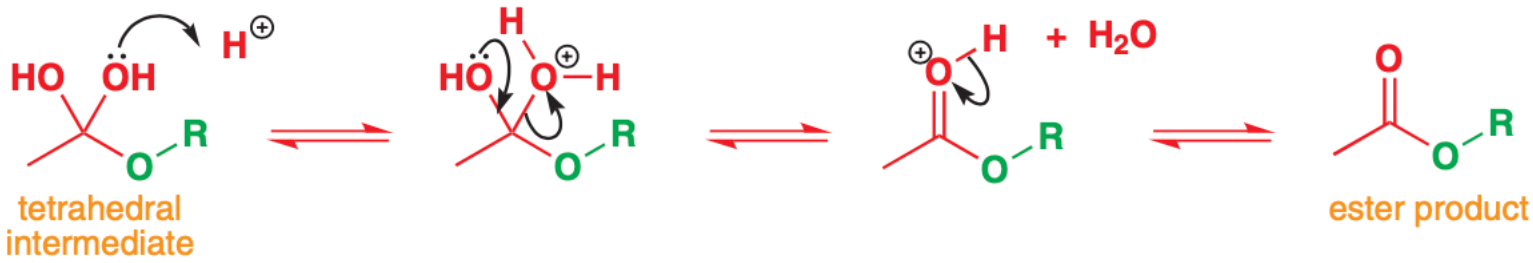


pH e a reatividade dos derivados de ácido

Ácidos carboxílicos não experimentam substituição nucleofílica em meio básico:

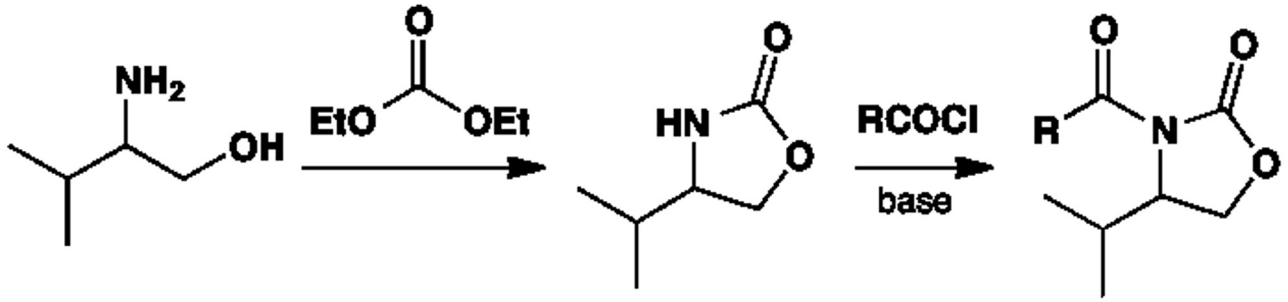


Catálise ácida pode transformar um péssimo grupo de saída em um bom:

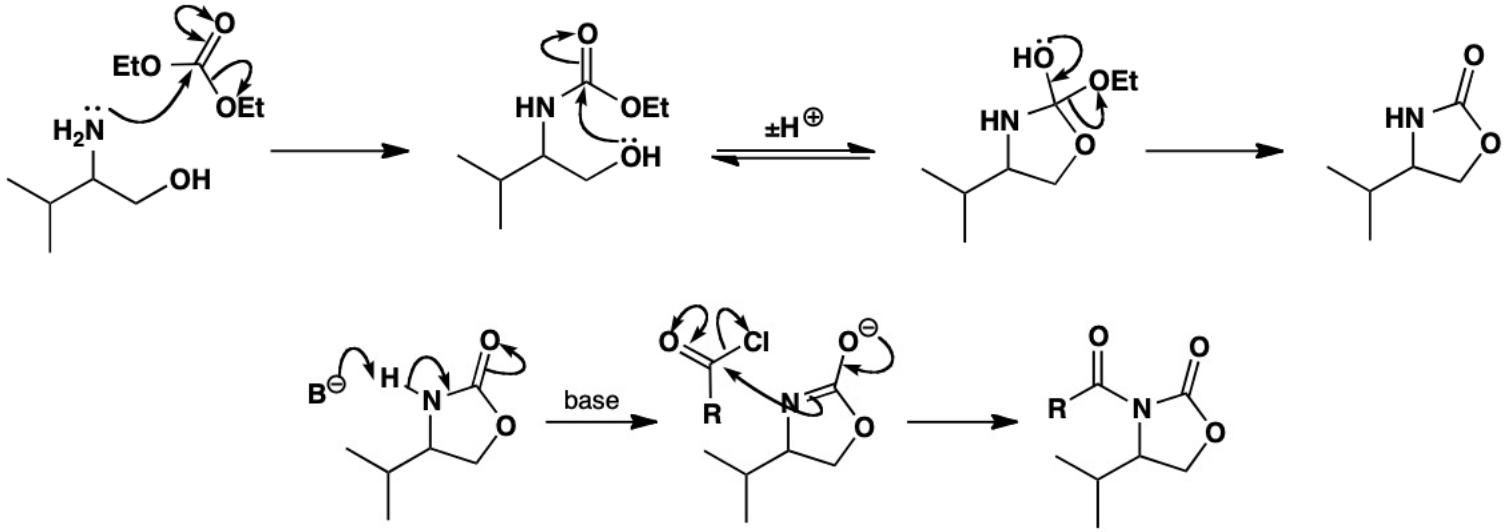


DESAFIO!

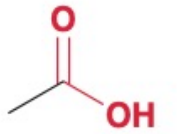
Sugira um mecanismo para esta transformação:



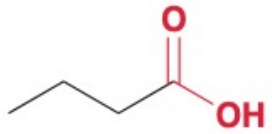
Resposta:



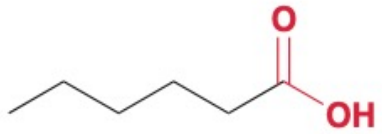
Ácidos carboxílicos, estrutura e propriedades



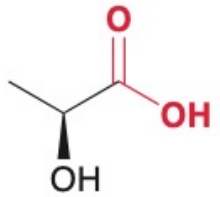
Acetic acid
(Responsible for the pungent smell of vinegar)



Butanoic acid
(Responsible for the rancid odor of sour butter)



Hexanoic acid
(Responsible for the odor of dirty socks)



Lactic acid
(Responsible for the taste of sour milk)

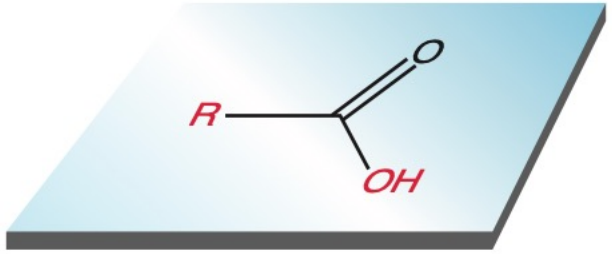
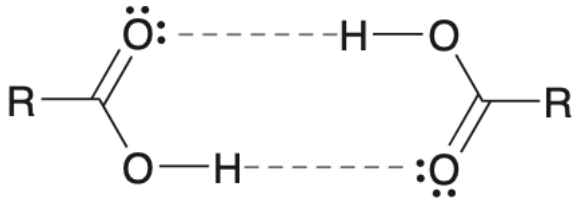
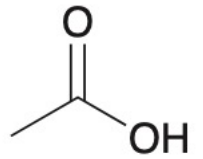
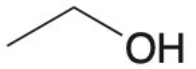


FIGURE 21.1
The carbonyl group as well as the two atoms attached to the carbonyl carbon all reside in a plane.



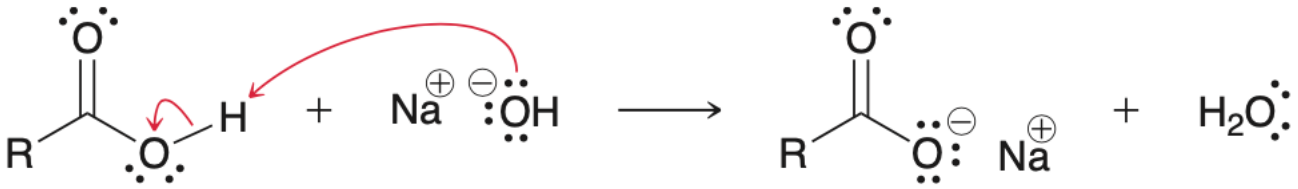


Acetic acid
b.p. = 118°C



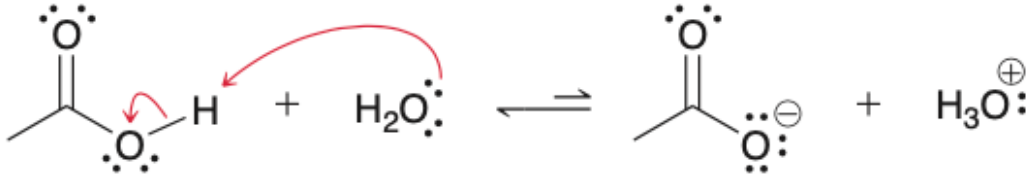
Ethanol
b.p. = 78°C

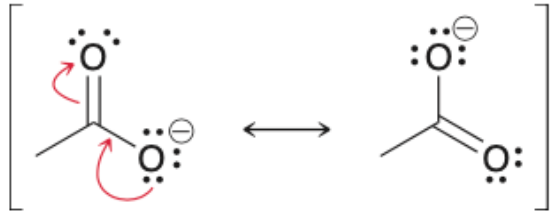
Ácidos carboxílicos, estrutura e propriedades

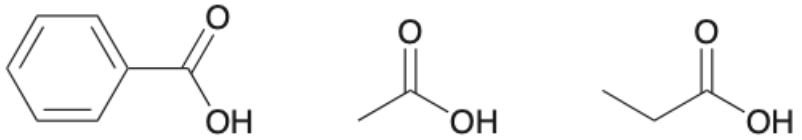


A carboxylate salt

$pK_a = 4.76$ $pK_a = 16$





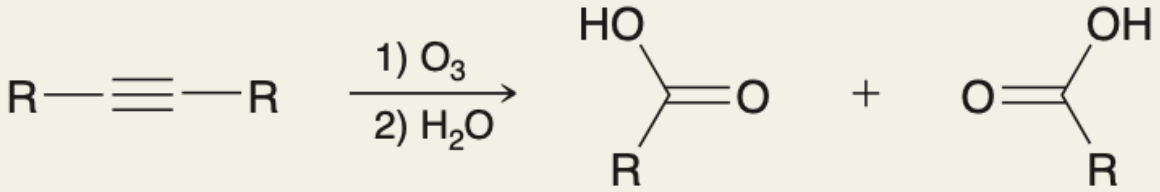


$pK_a = 4.19$ $pK_a = 4.76$ $pK_a = 4.87$

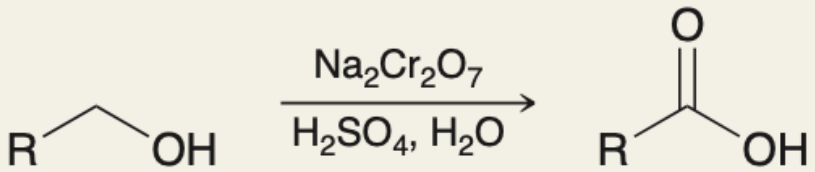
Preparo de ácidos carboxílicos

REACTION

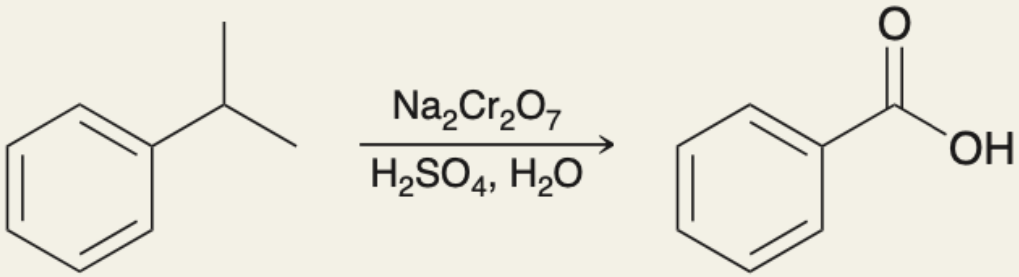
Oxidative Cleavage of Alkynes



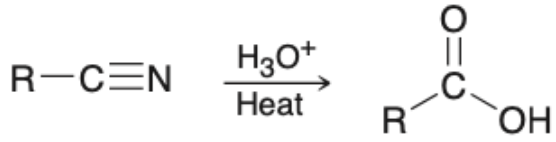
Oxidation of Primary Alcohols



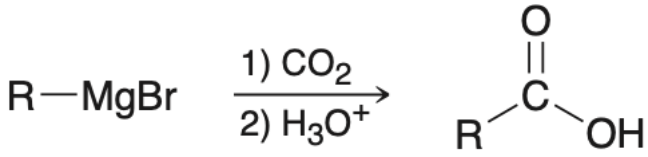
Oxidation of Alkylbenzenes



Hidrólise de nitrilas:



Carboxilação de reagentes de Grignard:



Reações de ácidos carboxílicos

Redução:

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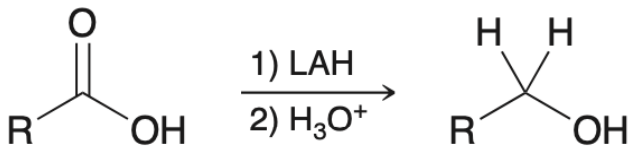

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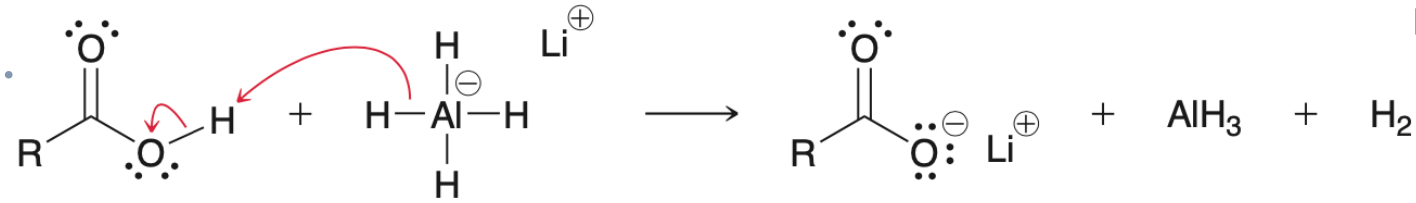

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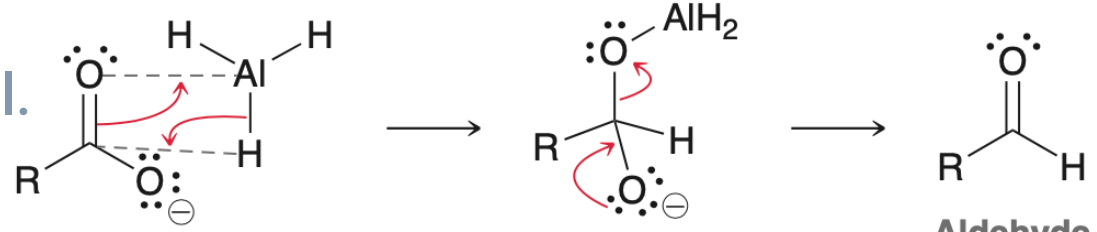

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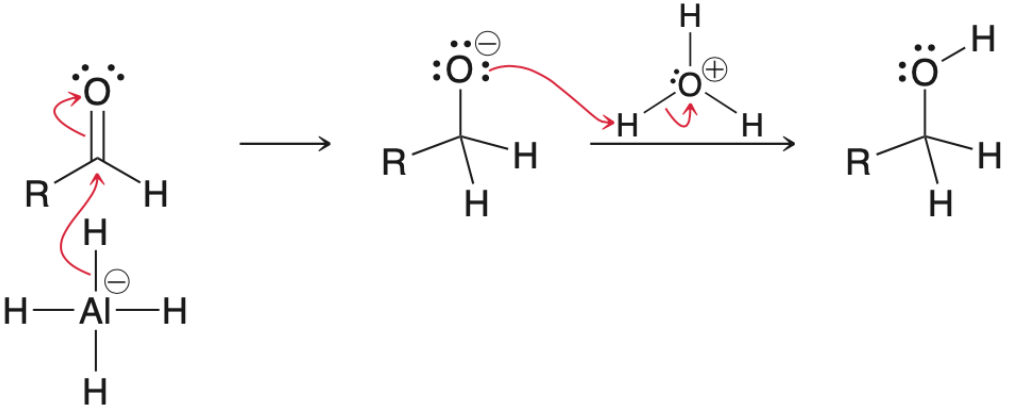
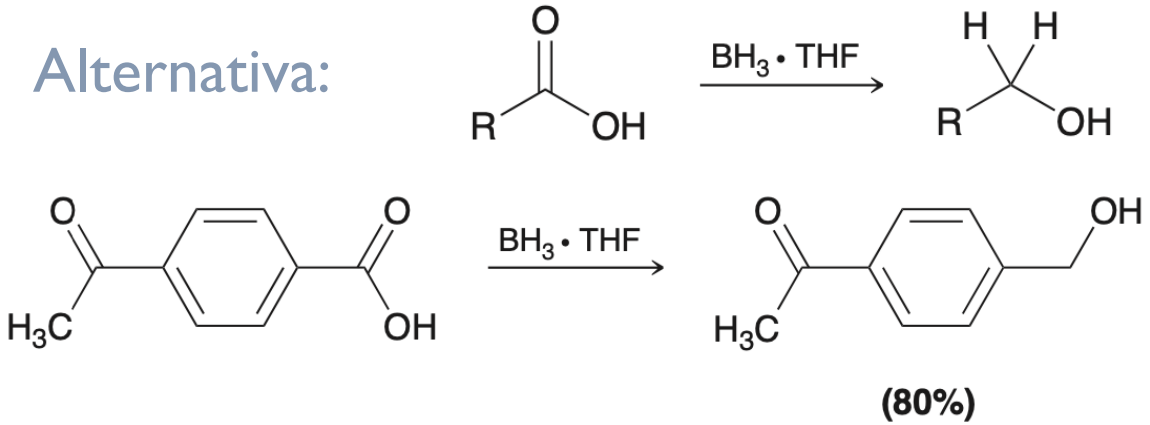
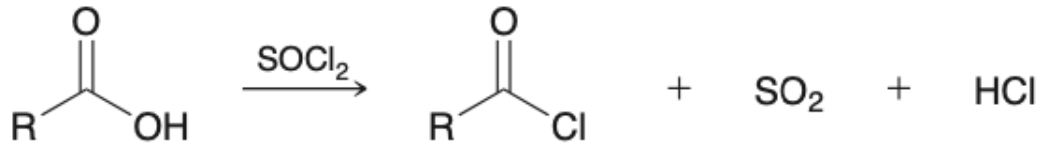


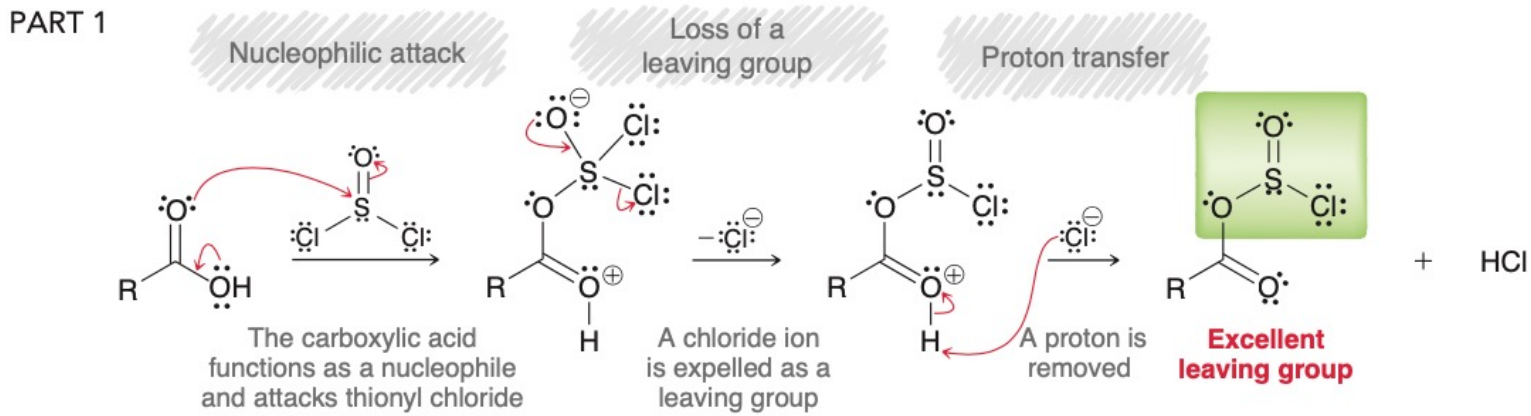
Alternativa:



Preparo de Cloretos de Ácido

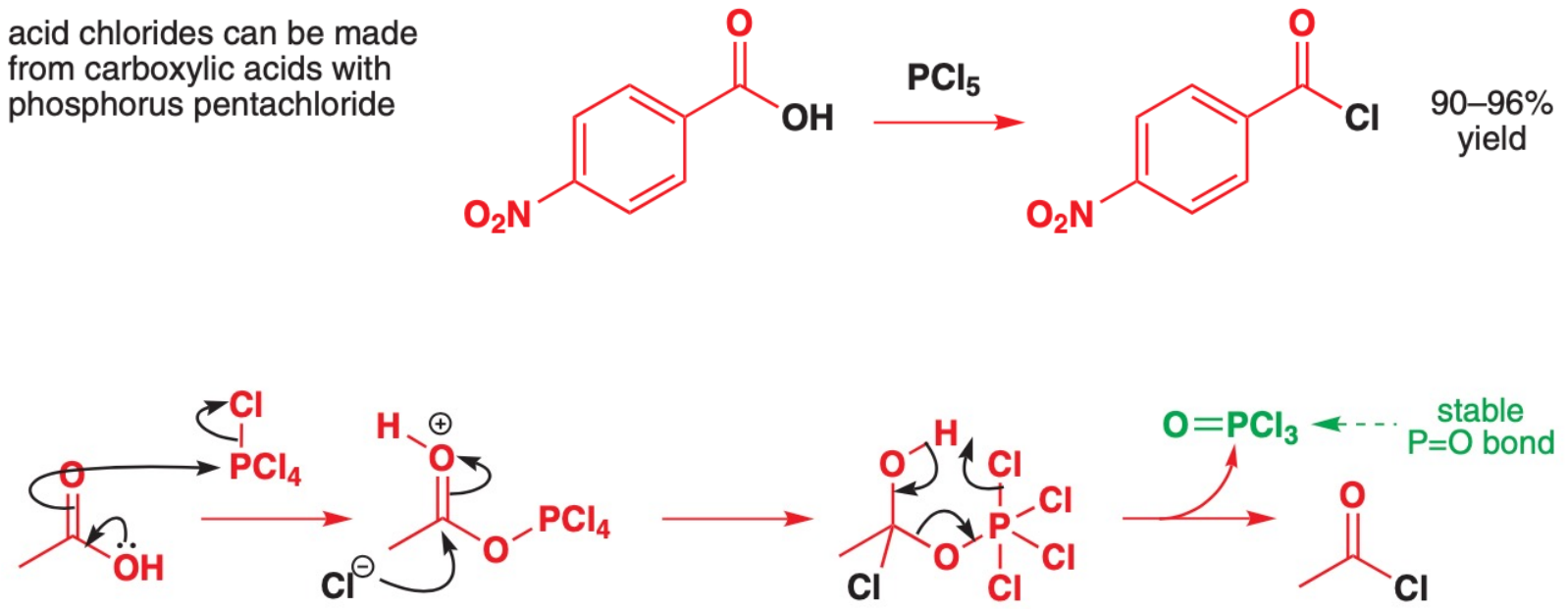
Reação com cloreto de tionila:





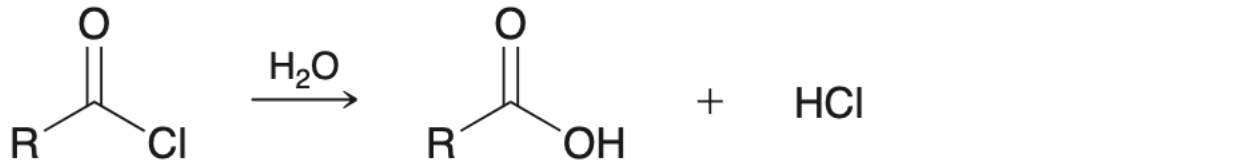
Preparo de Cloretos de Ácido

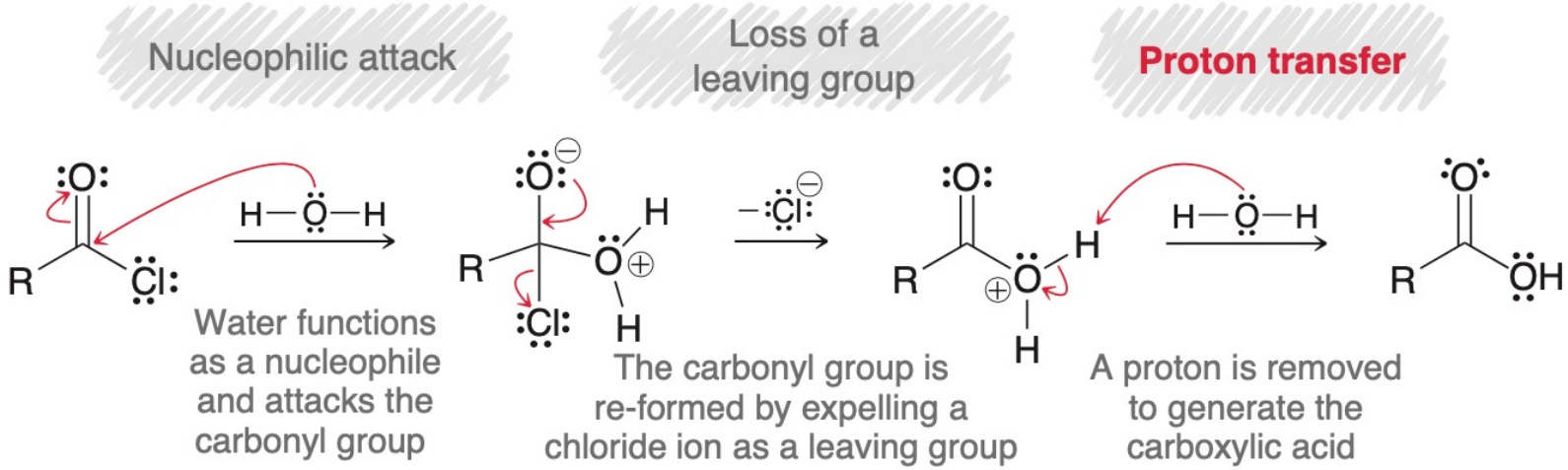
Reação com pentacloreto de fósforo:

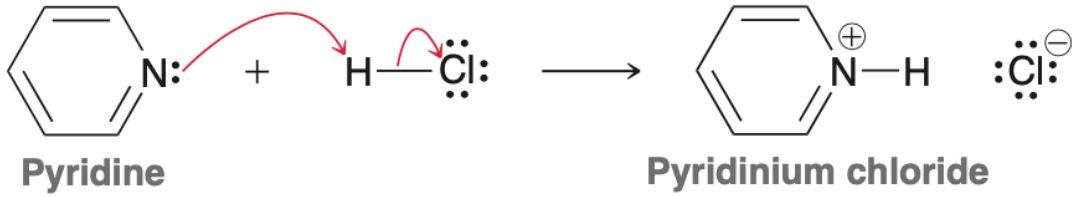


Reações de Cloretos de Ácido

Hidrólise do cloretos de ácido:

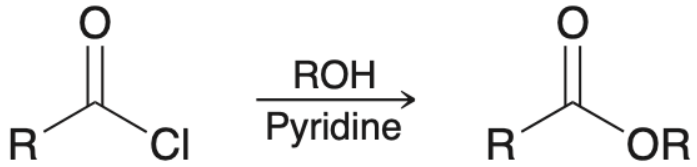




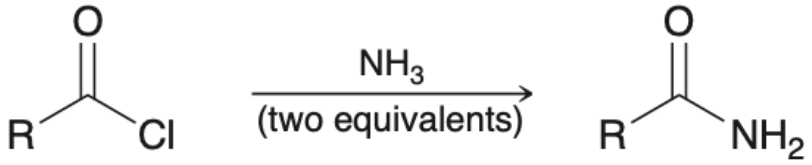


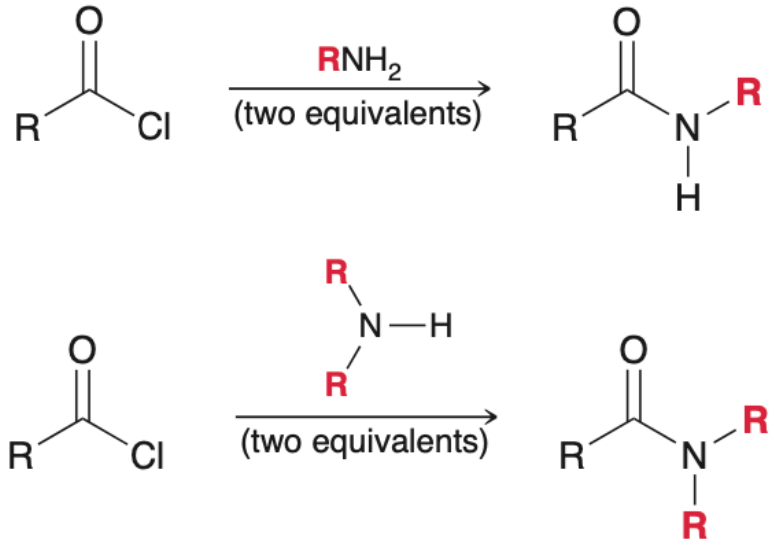
Reações de Cloreto de Ácidos

Alcóolise de cloretos de ácido:



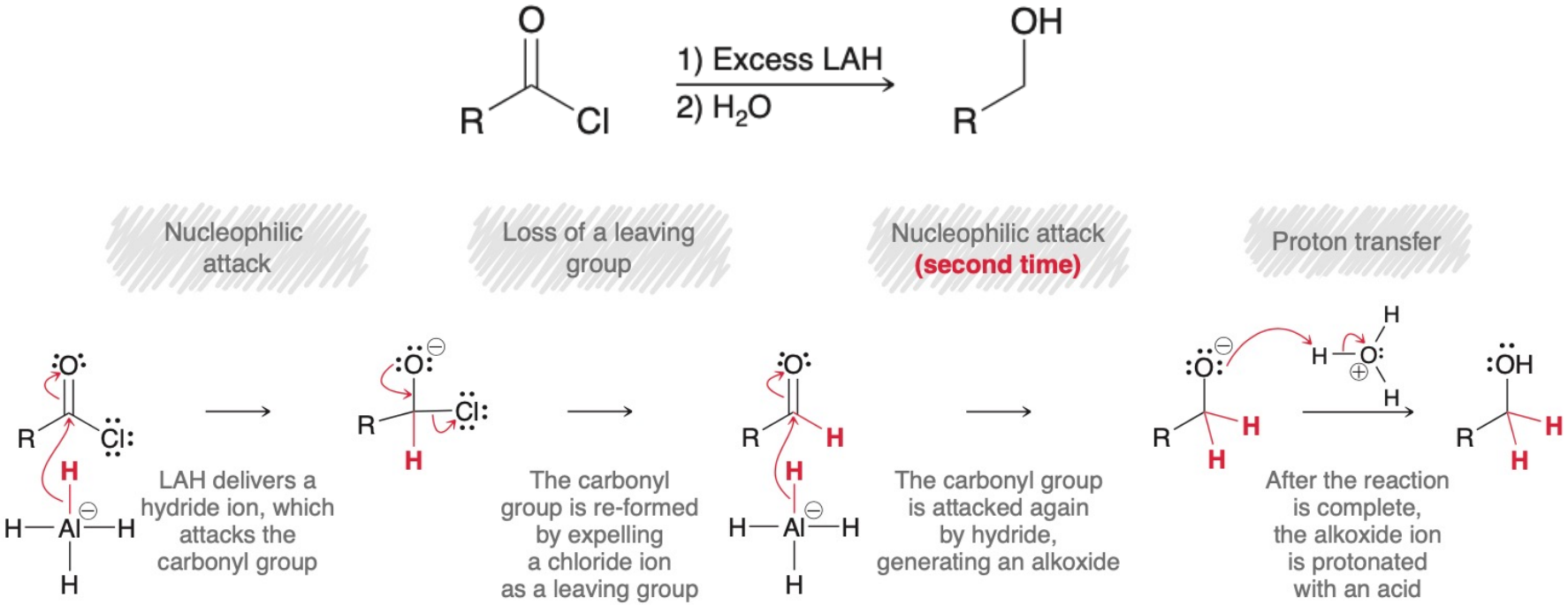
Aminólise de cloretos de ácido:





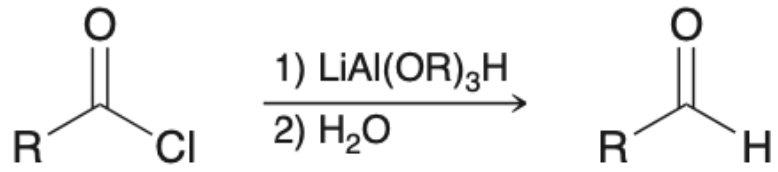
Reações de Cloreto de Ácidos

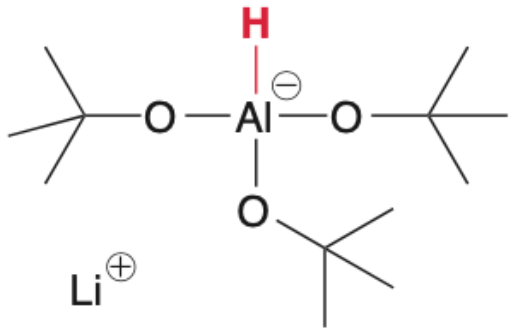
Redução de cloretos de ácido:



Reações de Cloreto de Ácidos

Redução de cloretos de ácido para aldeídos:



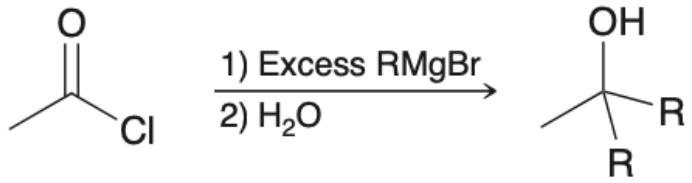


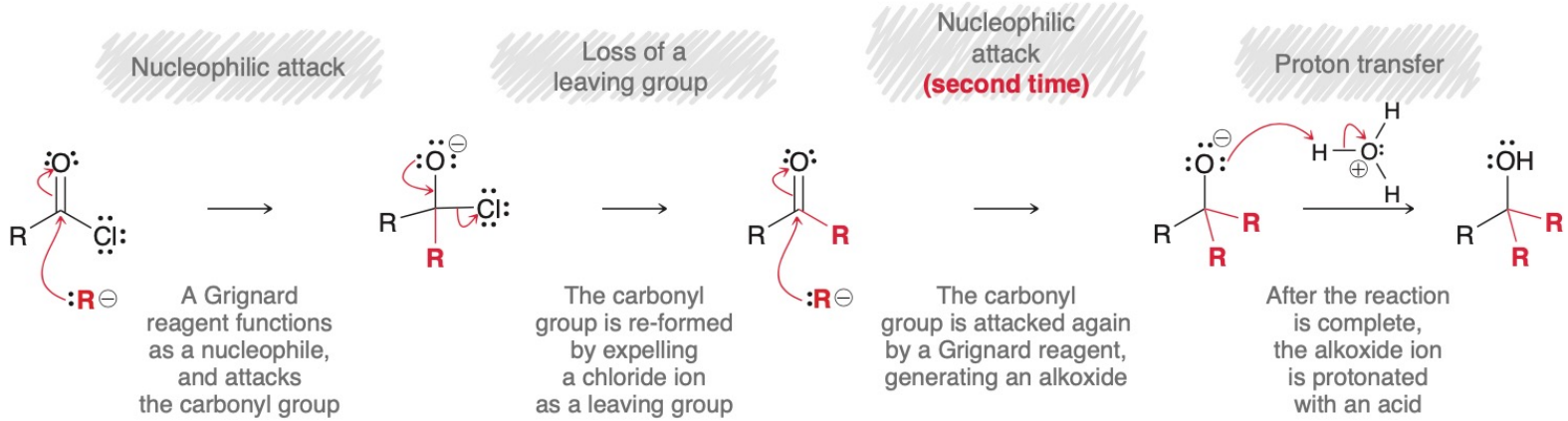
Lithium tri(*t*-butoxy) aluminium hydride

Reações de Cloreto de Ácidos

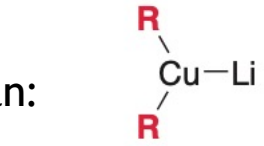
Reagentes Organometálicos:

Reagente de Grignard:





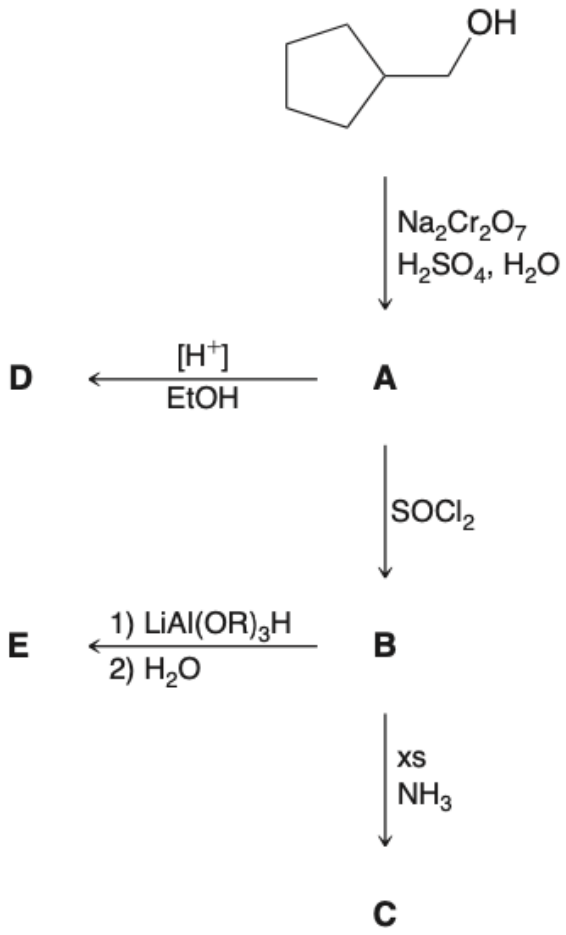
Reagente de Gilman:



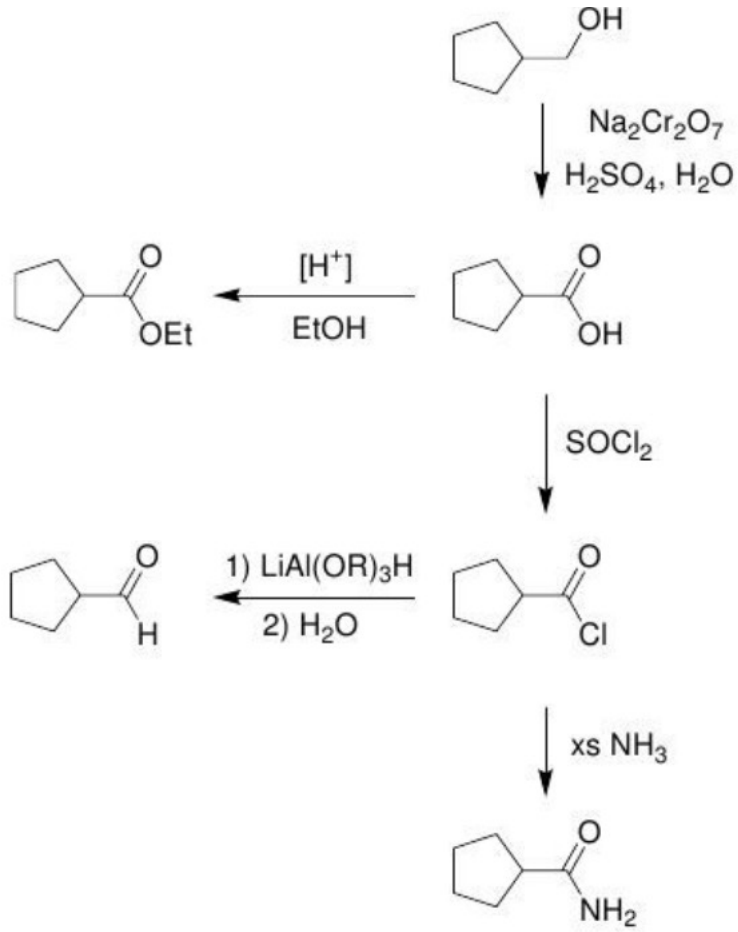
Lithium dialkyl cuprate

DESAFIO!

Sugira quais são os compostos A, B, C, D e E:

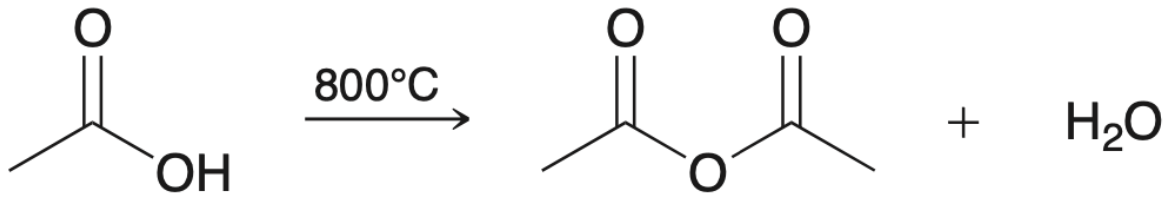


Resposta:

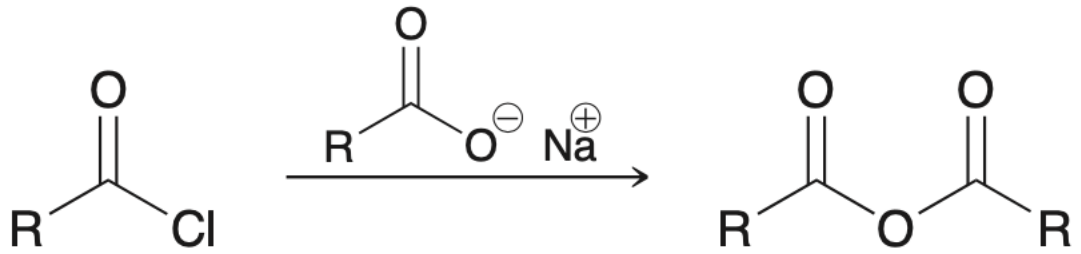


Preparo de Anidridos Ácidos

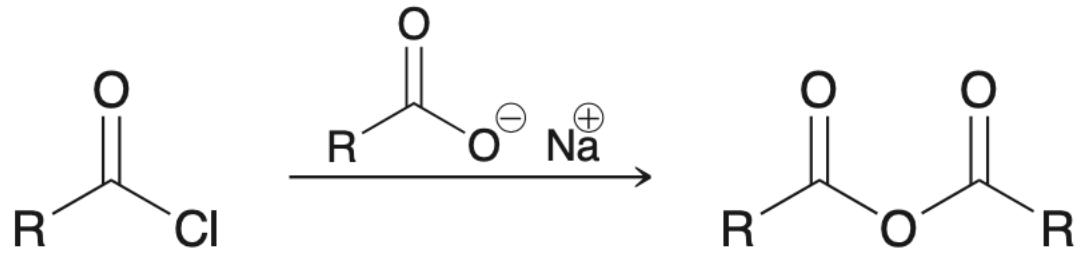
A partir do ácido carboxílico:

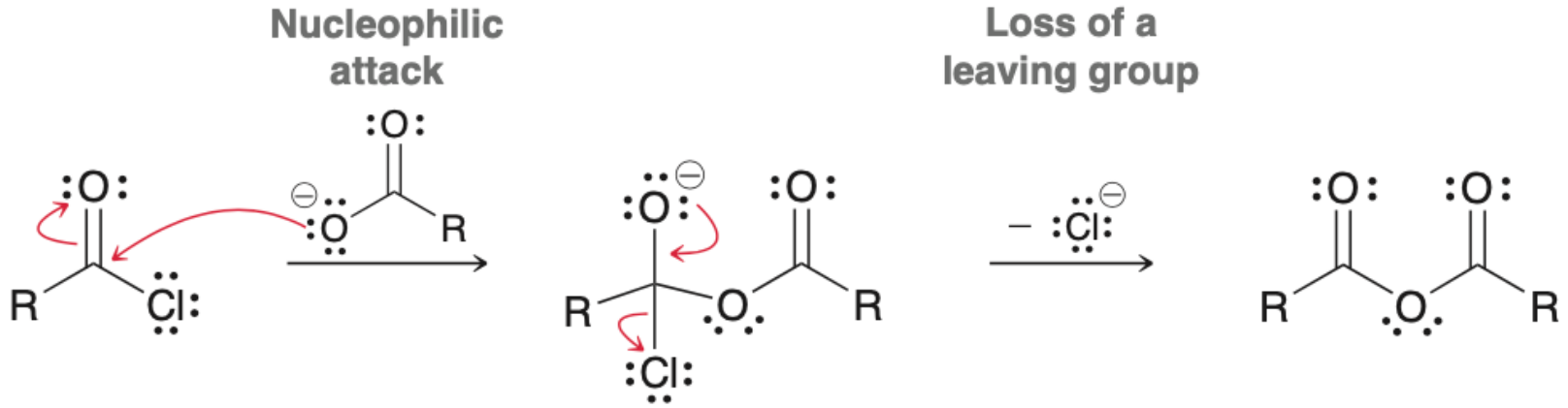


A partir do cloreto de ácido:

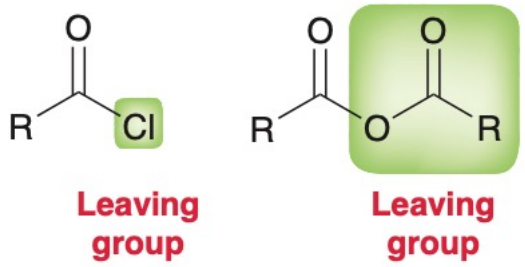


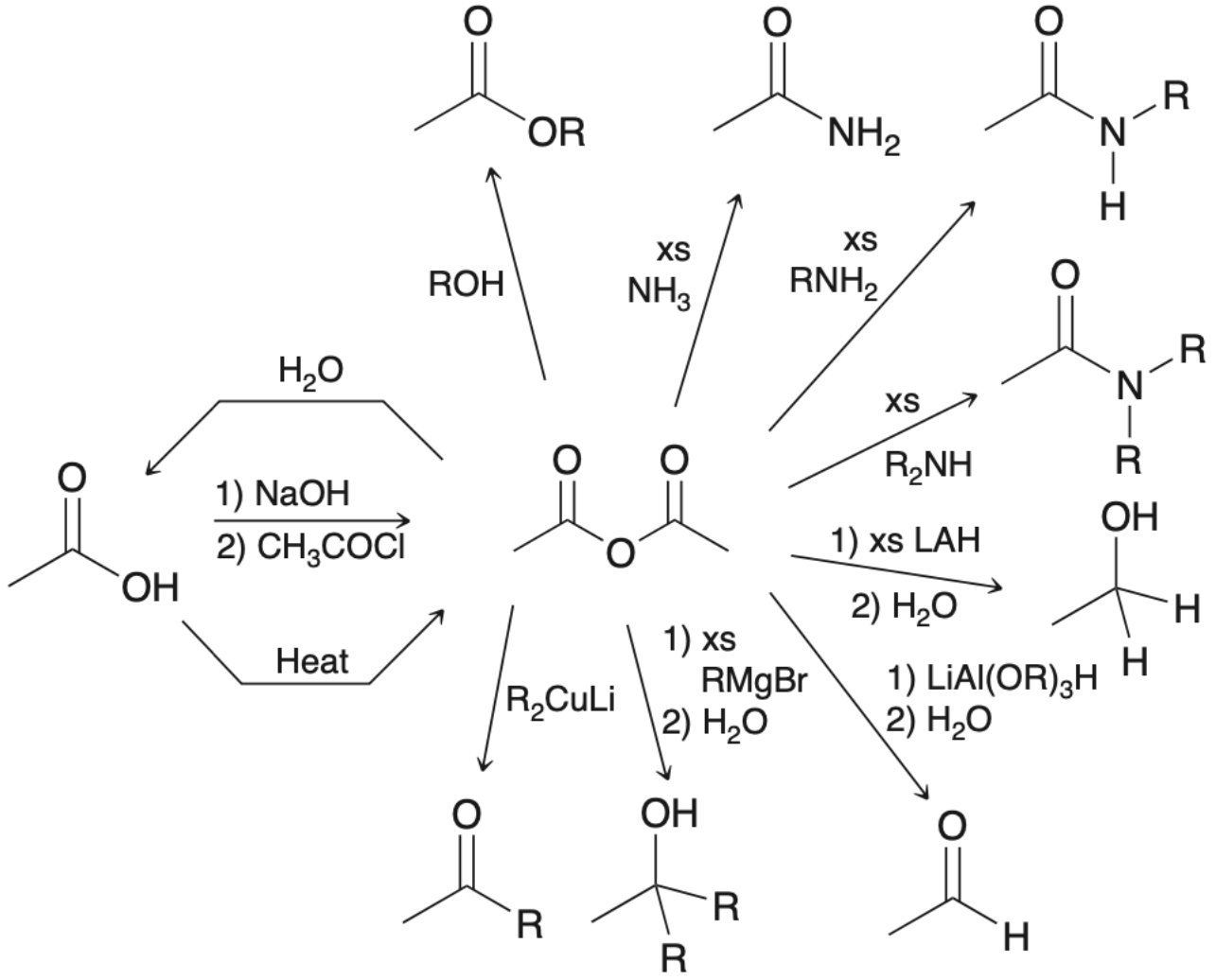
Preparo de Anidridos Ácidos





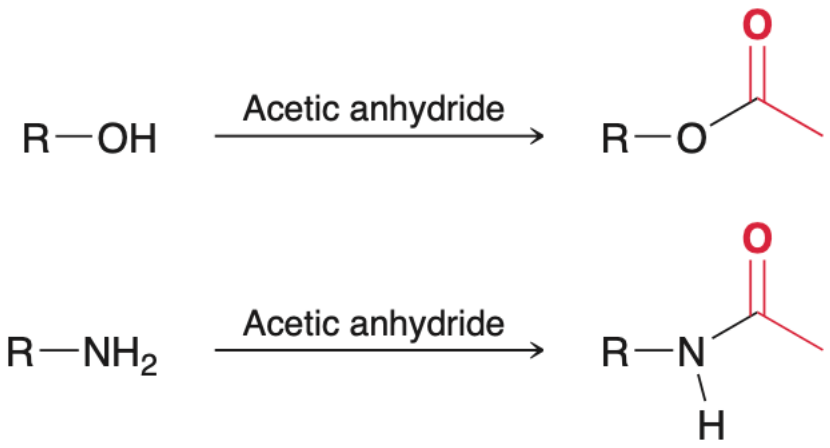
Reações de Anidridos Ácidos

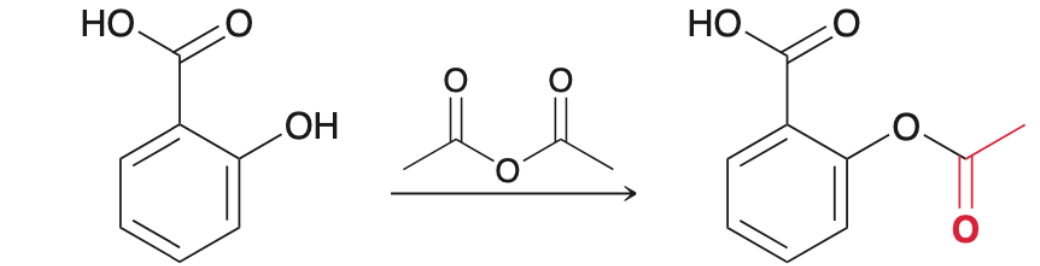




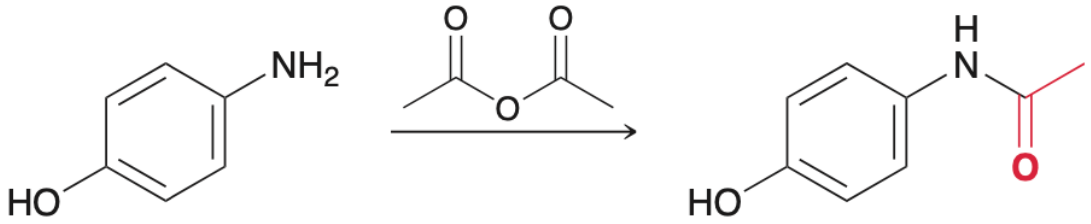
Reações de Anidridos Ácidos

Acetilação:





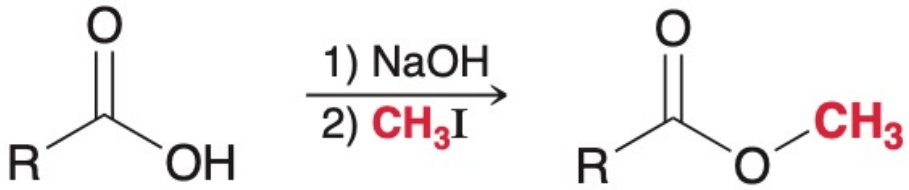
Aspirin



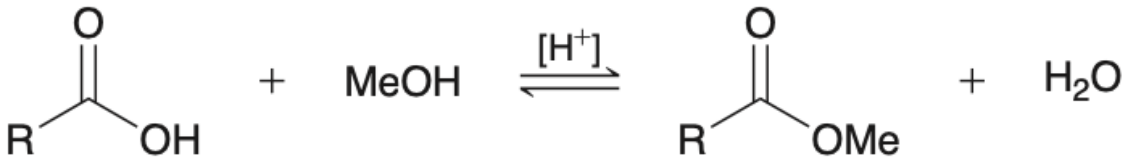
Tylenol™

Preparo de Ésteres

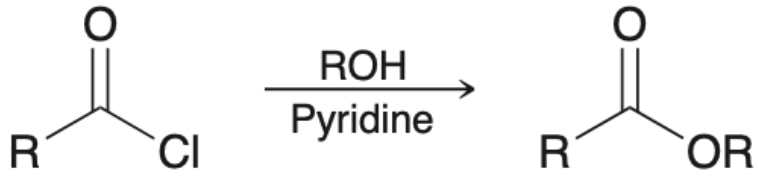
Via S_N2:



Via Esterificação de Fischer:

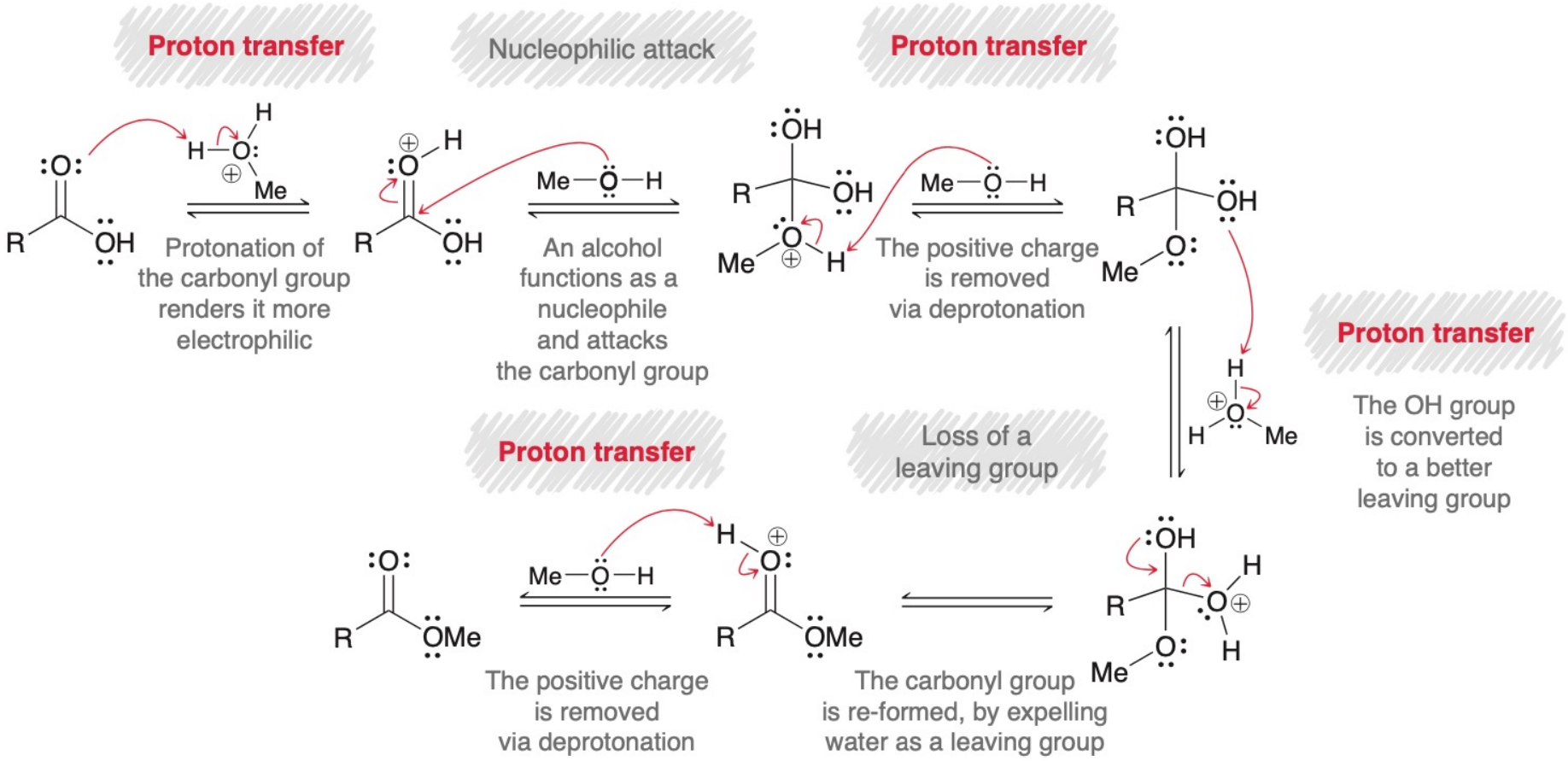


Via Cloreto de Ácidos:



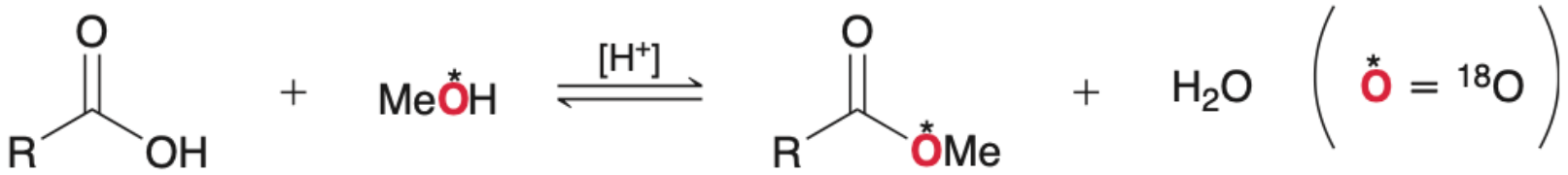
Preparo de Ésteres

Esterificação de Fischer:

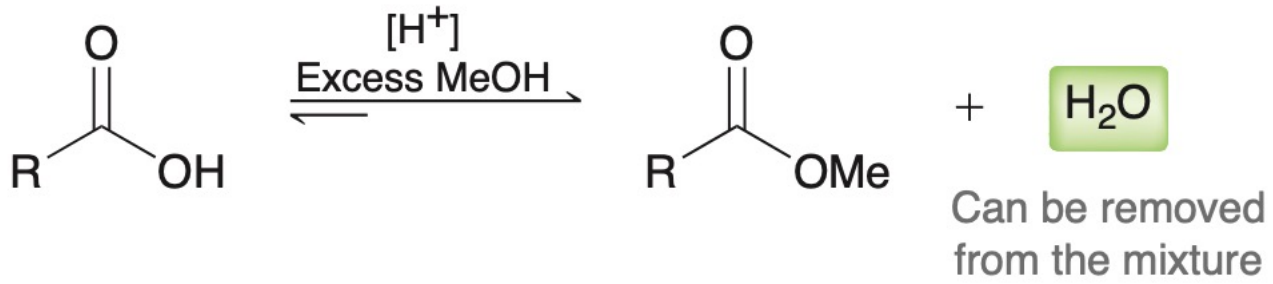


Preparo de Ésteres

Evidência para o mecanismo proposto:

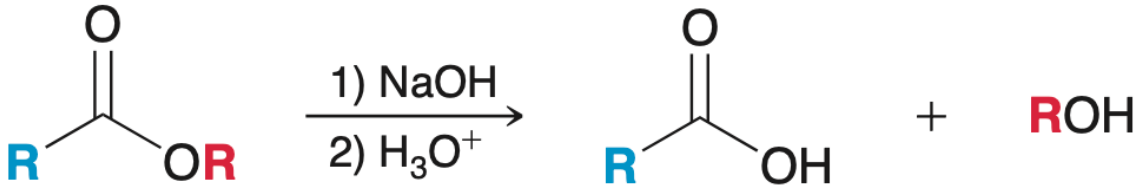


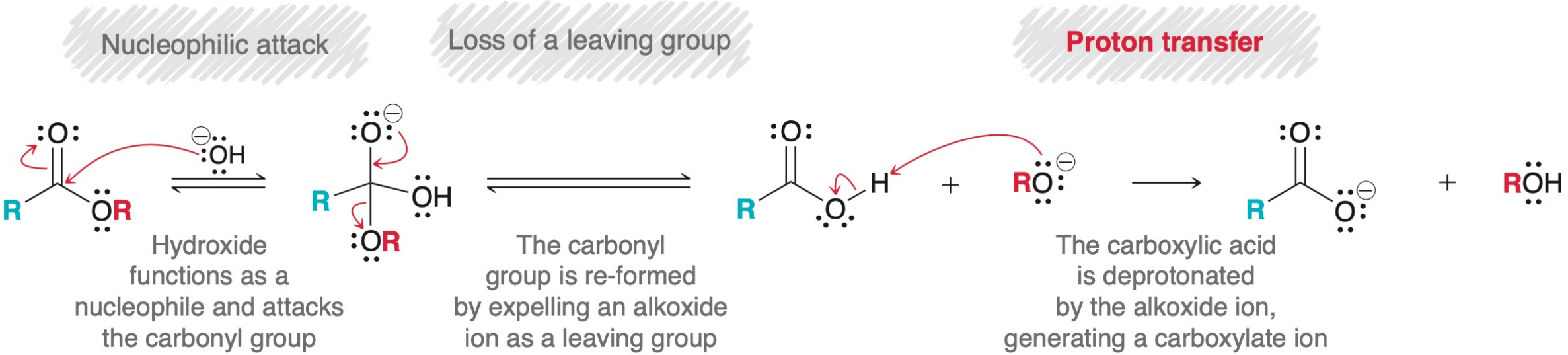
Reversibilidade do processo:



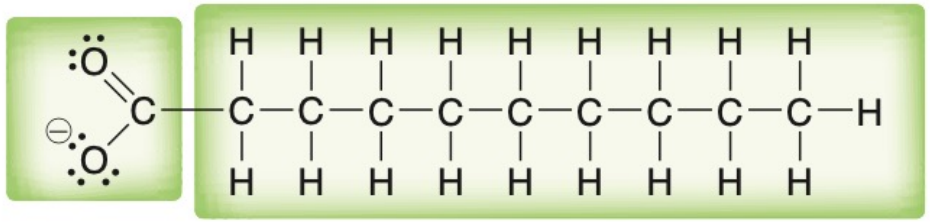
Reações de Ésteres

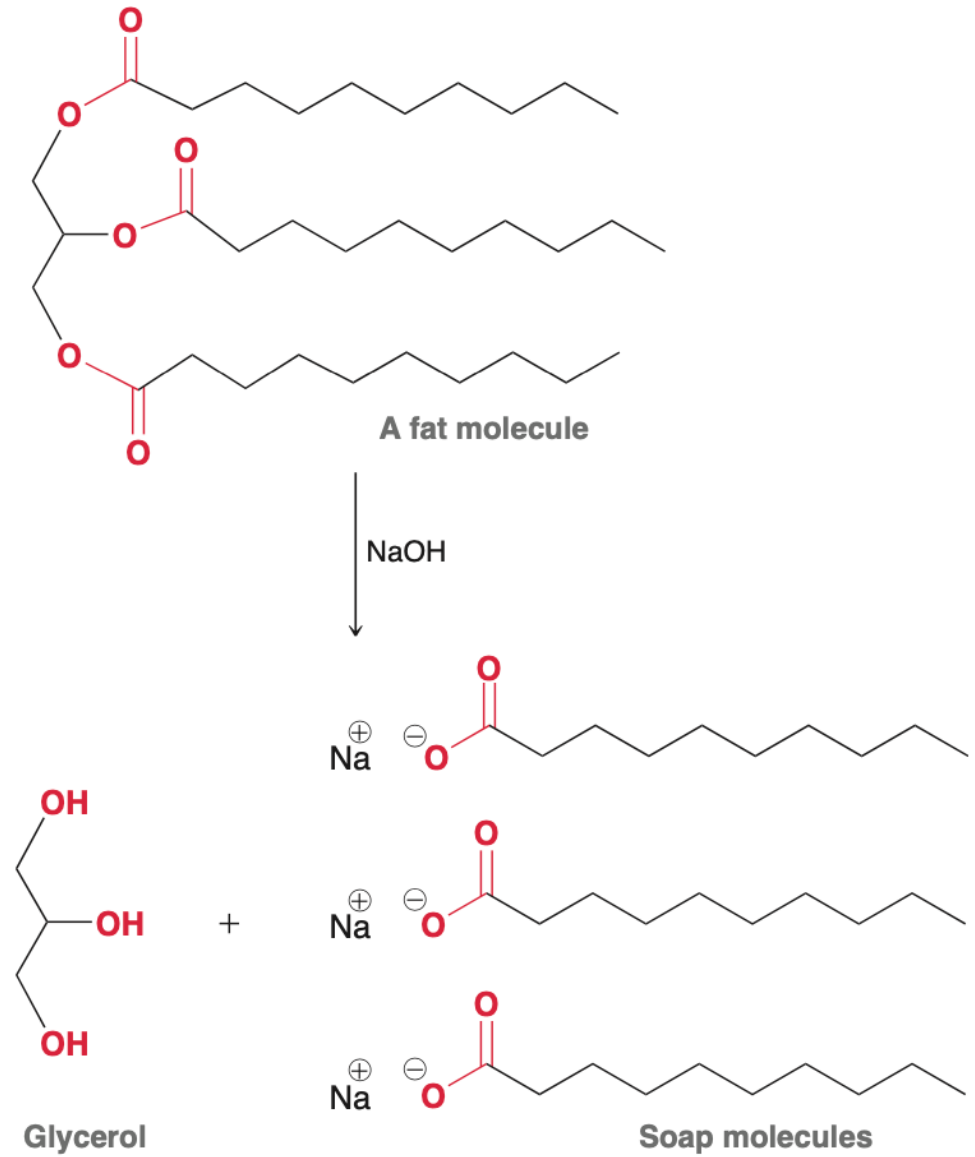
Saponificação:





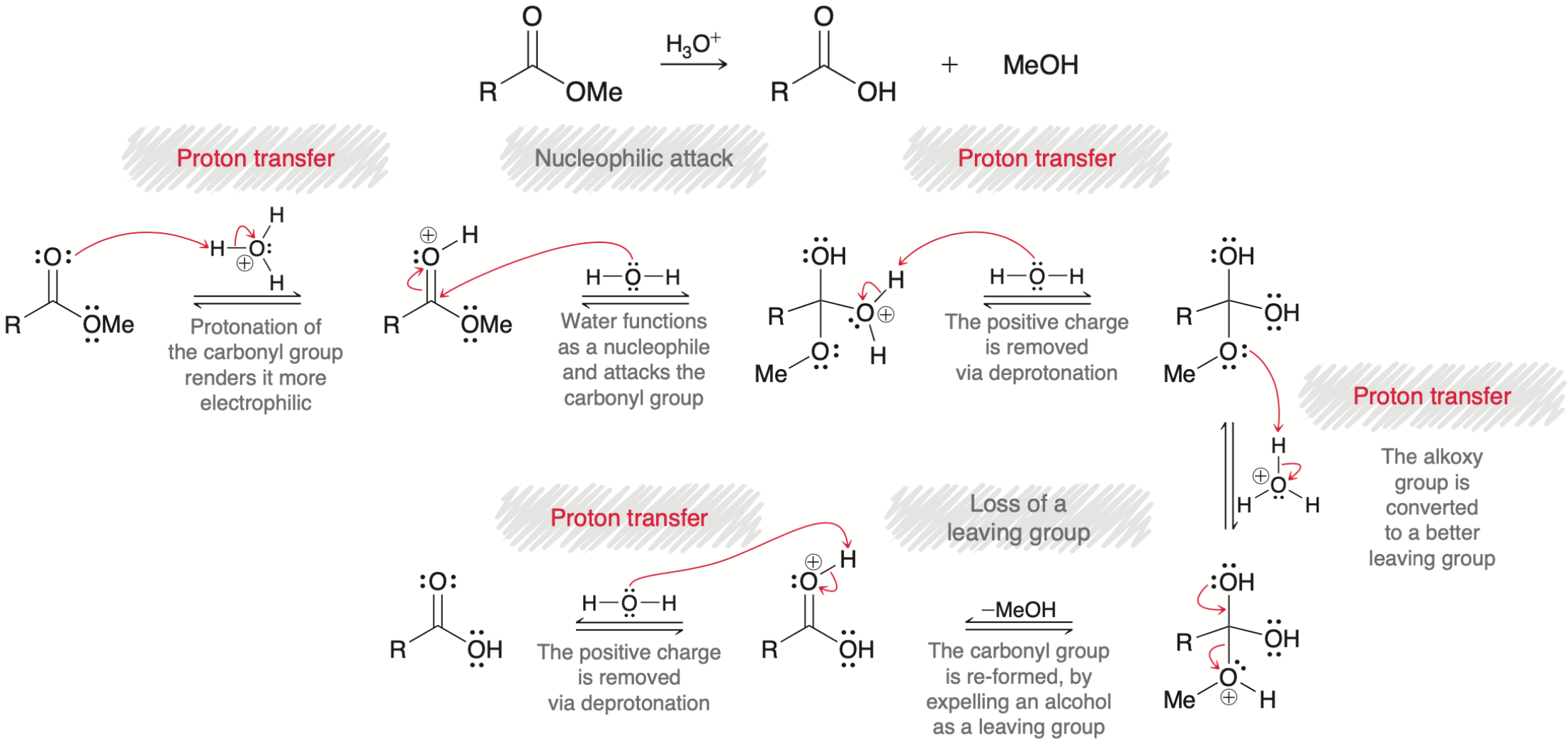
Reações de Ésteres





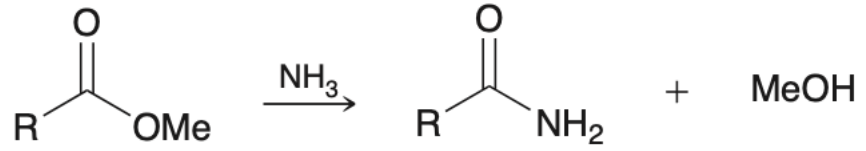
Reações de Ésteres

Hidrólise de Ésteres Catalisada por Ácido:

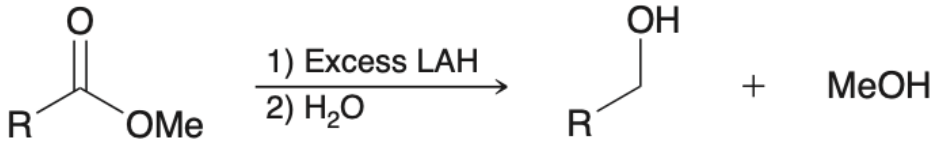


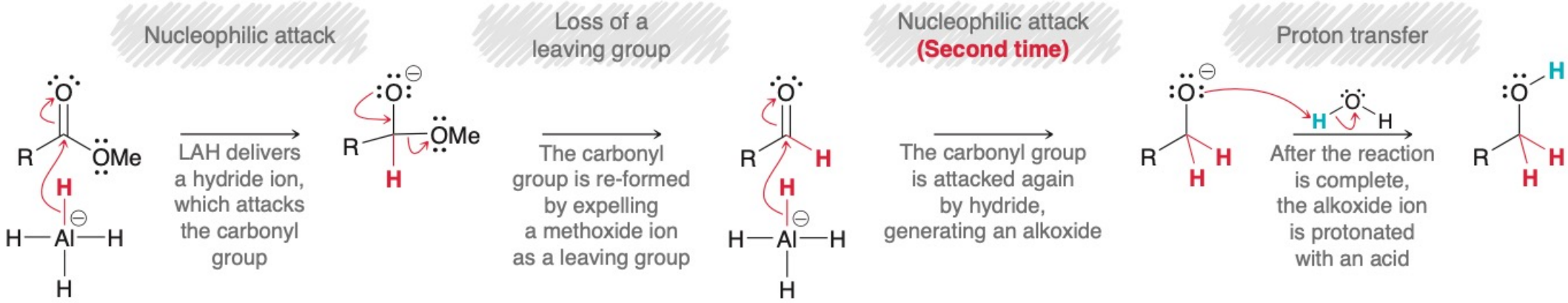
Reações de Ésteres

Aminólise de ésteres:



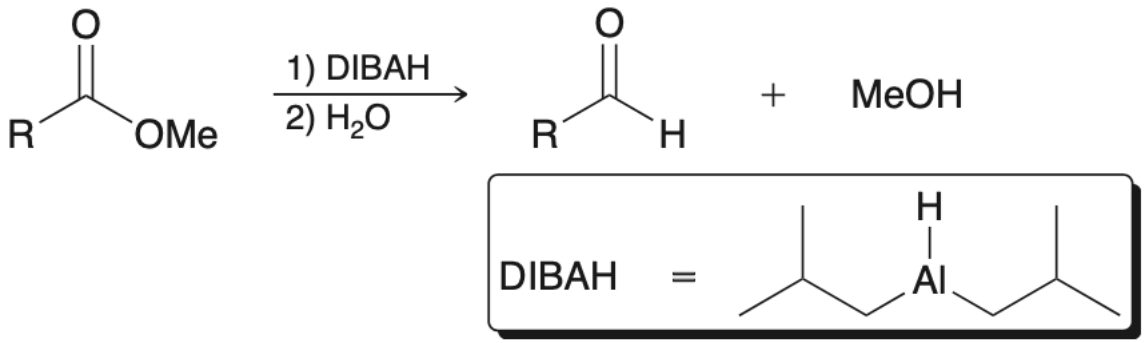
Redução de ésteres:





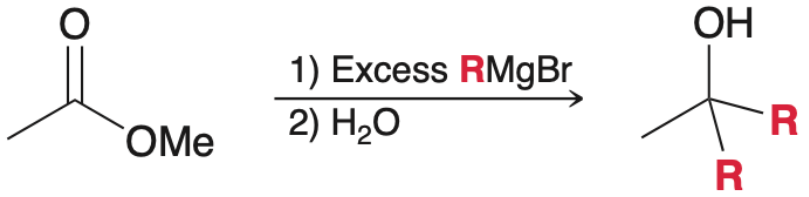
Reações de Ésteres

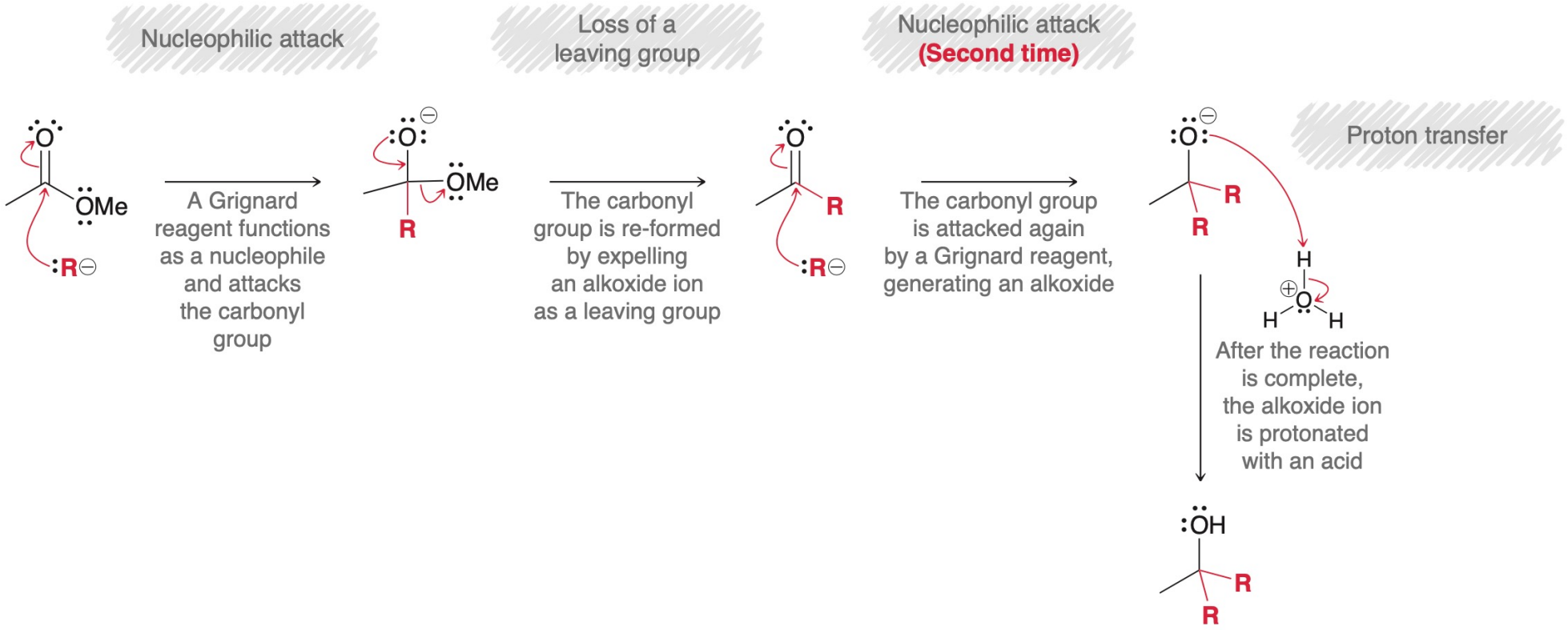
Redução de ésteres a aldeídos:



Reações de Ésteres

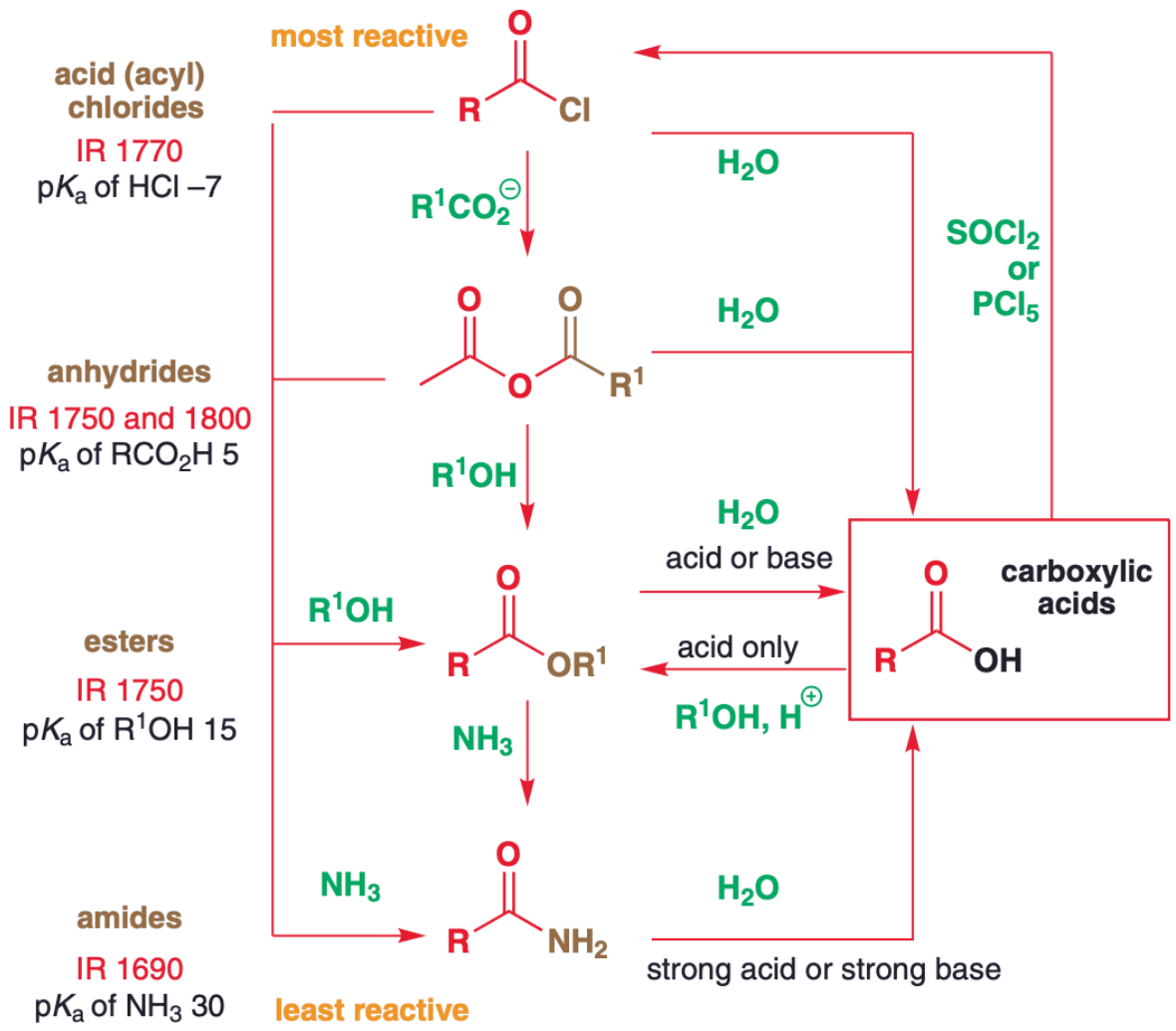
Reagentes de Grignard:





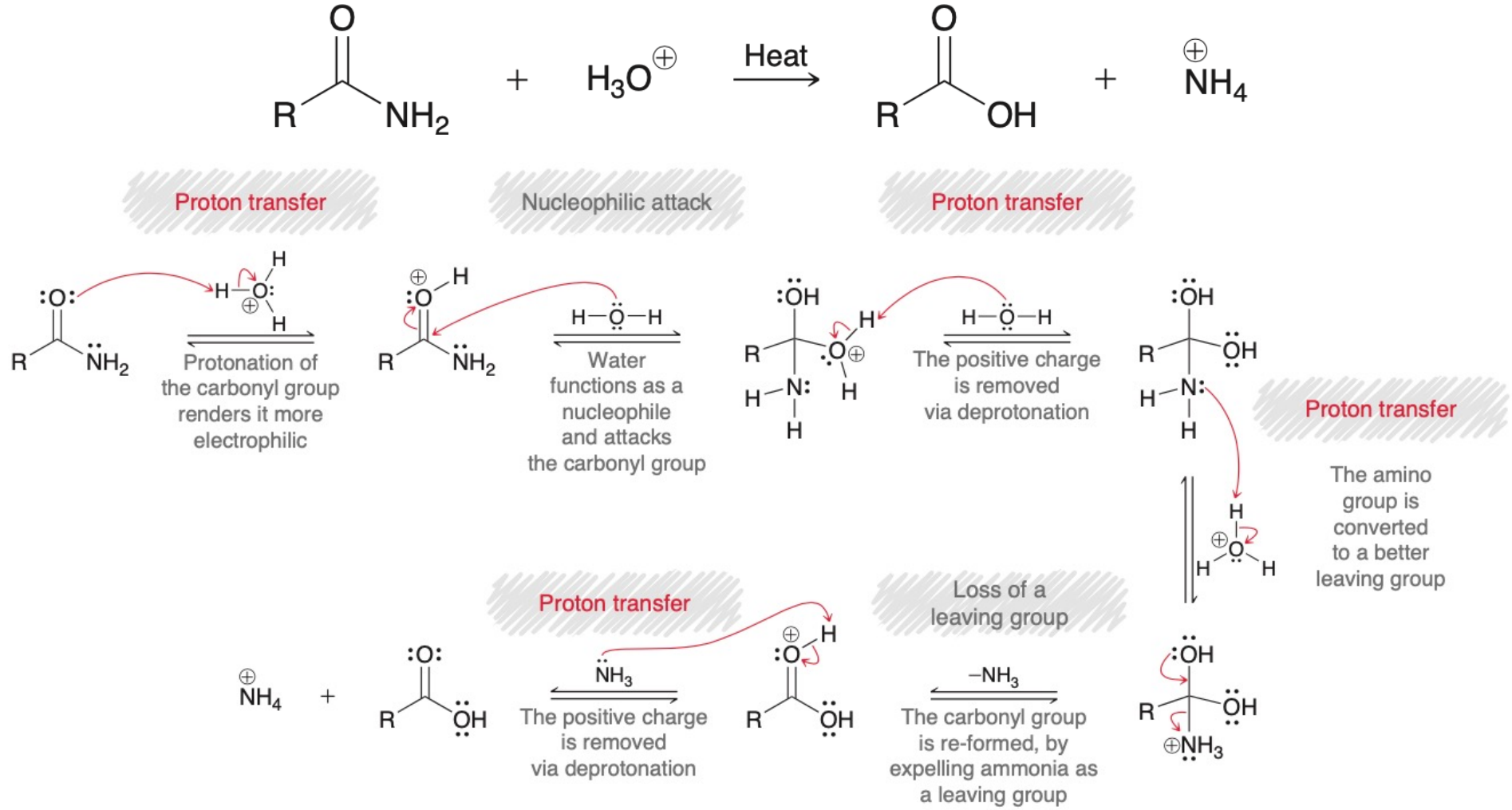
Preparo de Amidas

- **Interconversion of carboxylic acid derivatives**



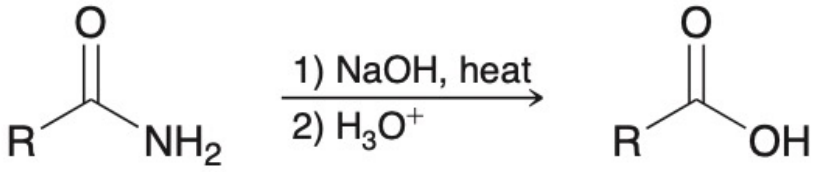
Reações de Amidas

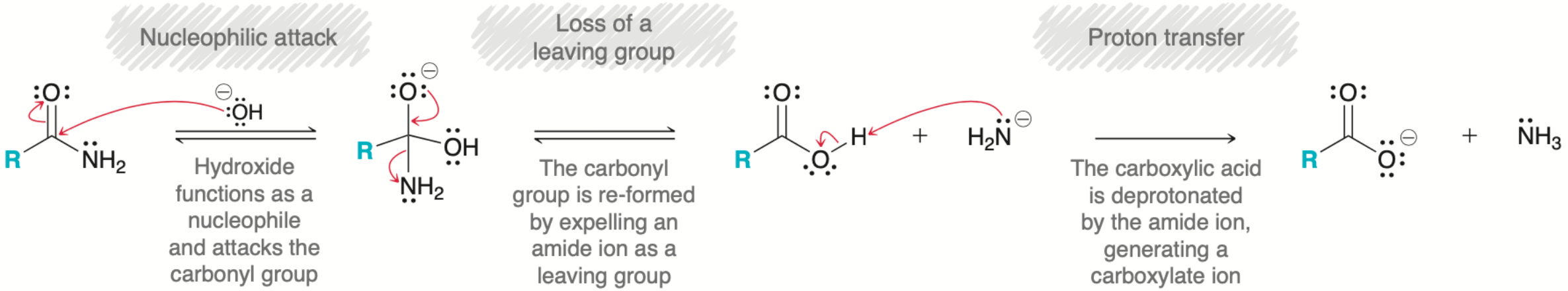
Hidrólise de Amidas Catalisada por Ácido:



Reações de Amidas

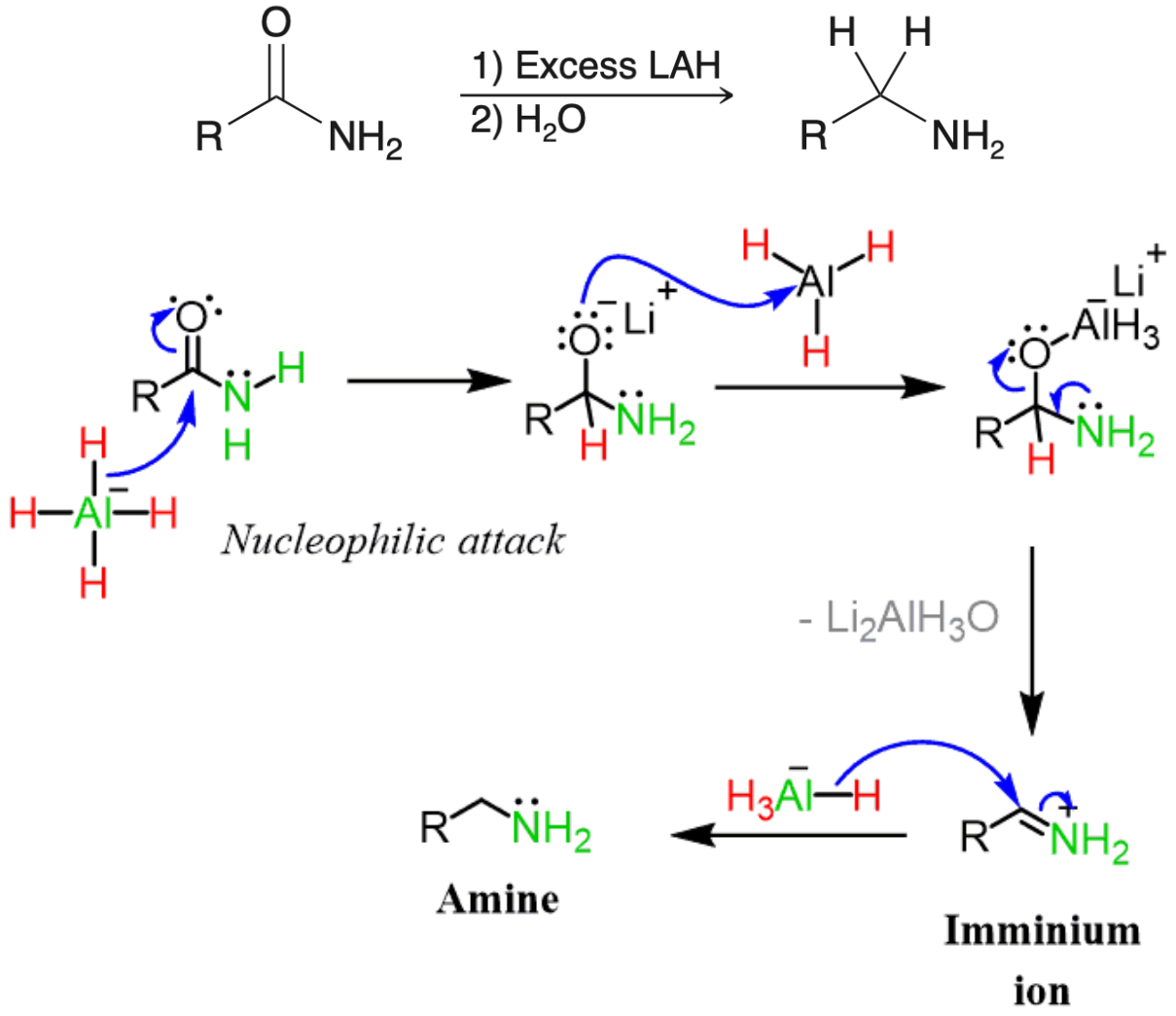
Hidrólise de Amidas Catalisada por Base:





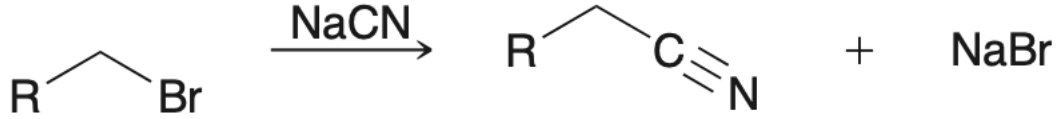
Reações de Amidas

Redução de Amidas:

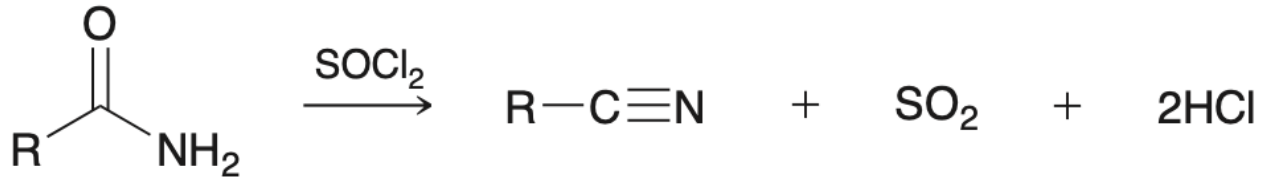


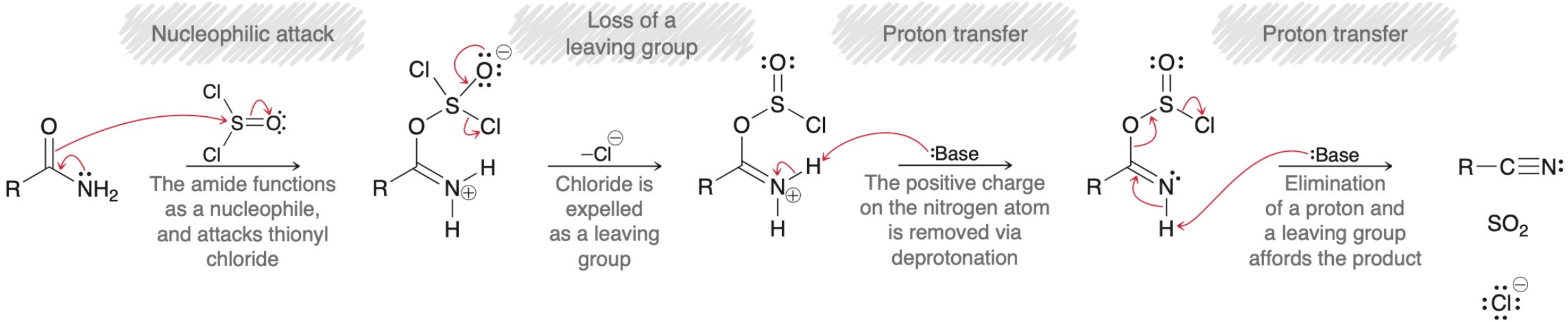
Preparo de Nitrilas

Via reações S_N2:



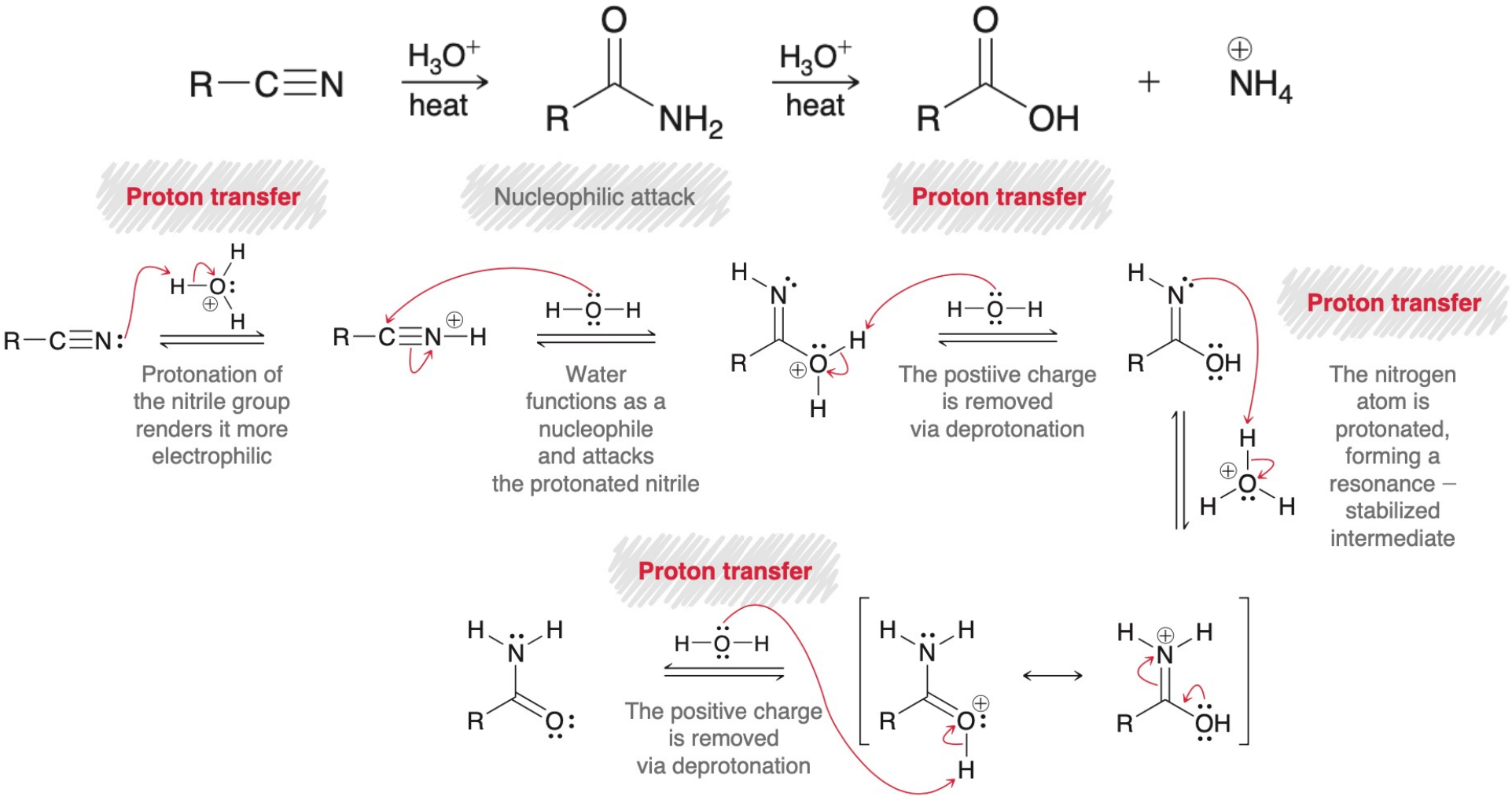
A partir de Amidas (desidratação):





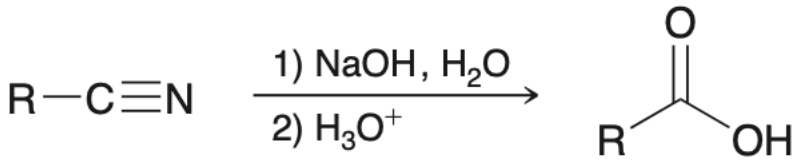
Reações de Nitrilas

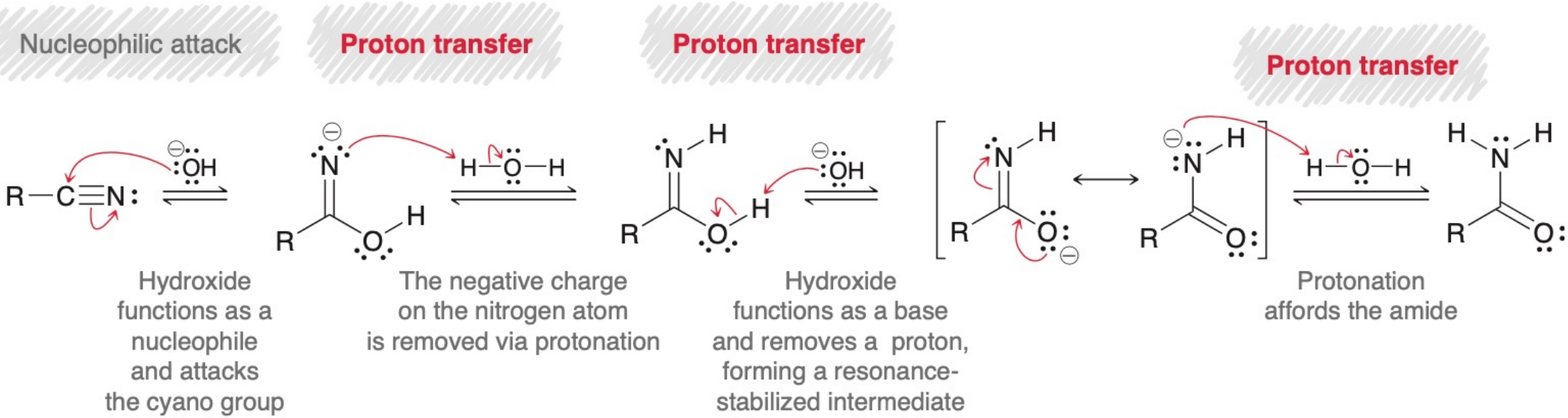
Hidrólise de Nitrilas Catalisada por Ácido:



Reações de Nitrilas

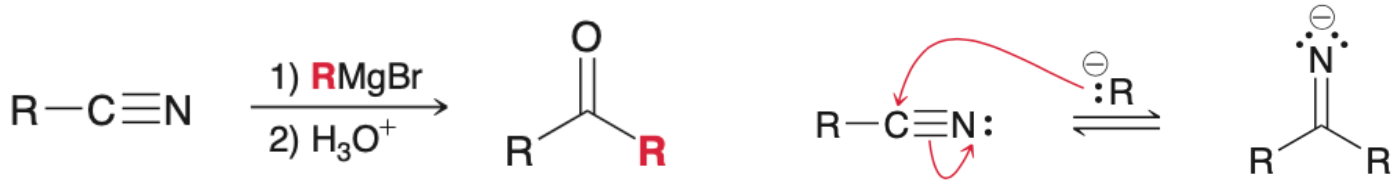
Hidrólise de Nitrilas Catalisada por Base:

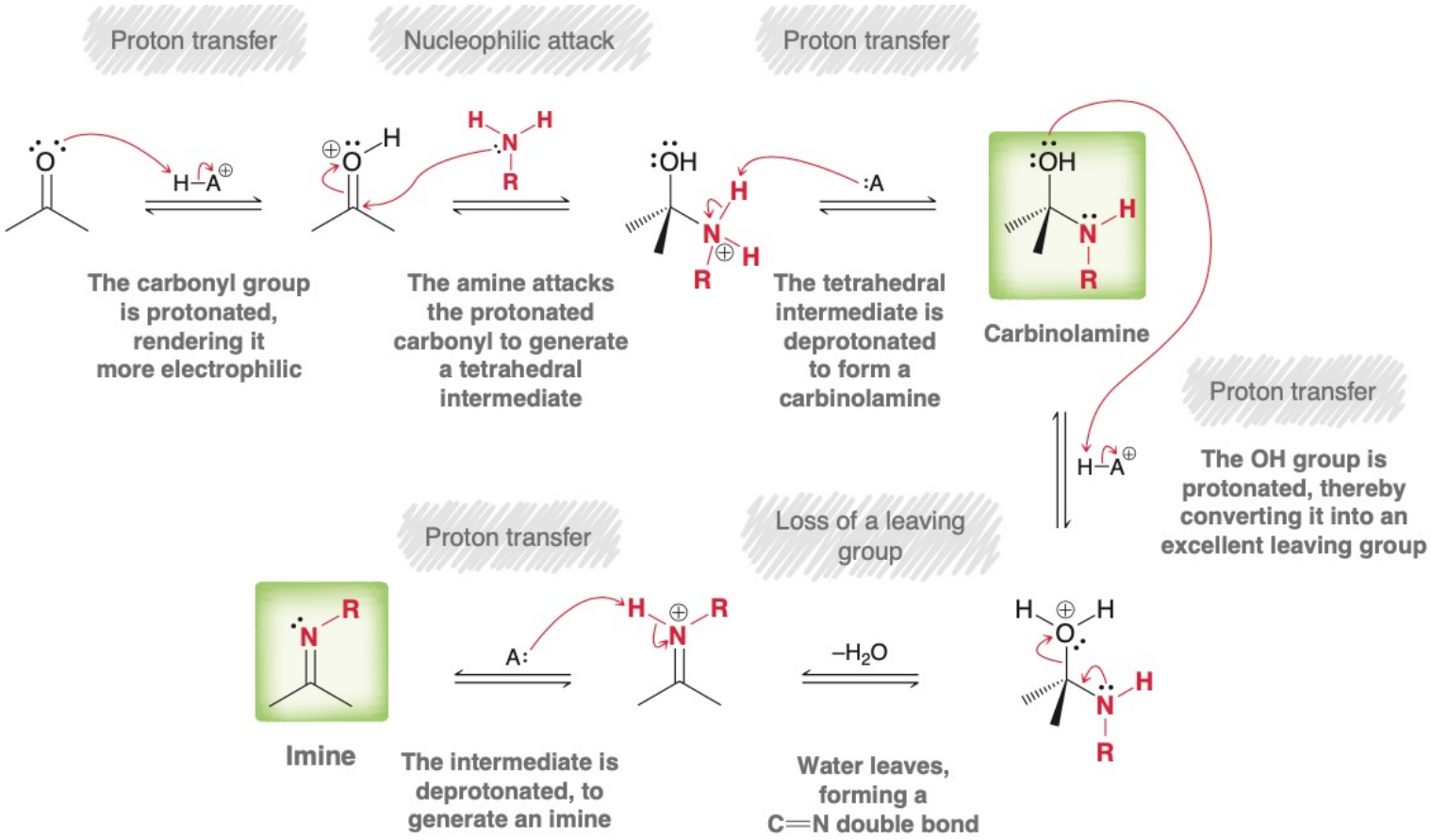




Reações de Nitrilas

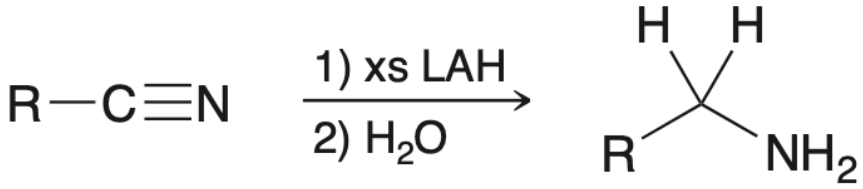
Reagentes de Grignard:





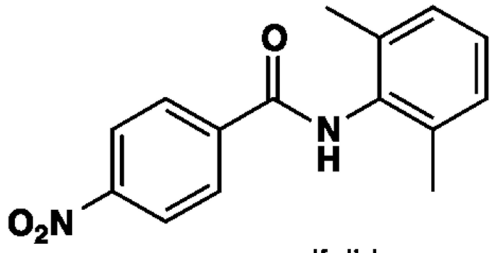
Reações de Nitrilas

Redução de Nitrilas:

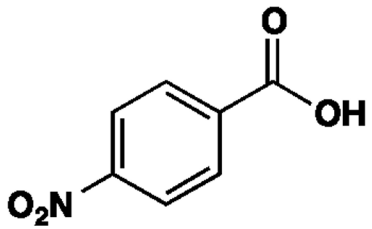


Desafio!

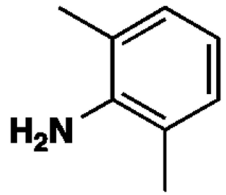
Amelfolide é um medicamento usado para tratar arritmia cardíaca. Sugira como ele poderia ser produzido a partir do ácido 4-nitrobenzóico e da 2,5-dimetilanilina.



amelfolide

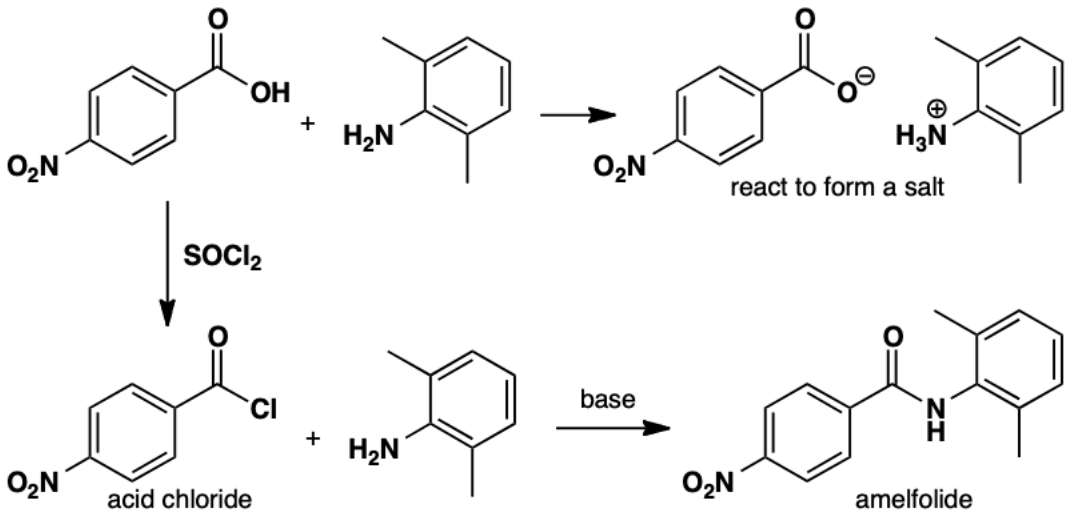


4-nitrobenzoic acid



2,6-dimethylaniline

Resposta:

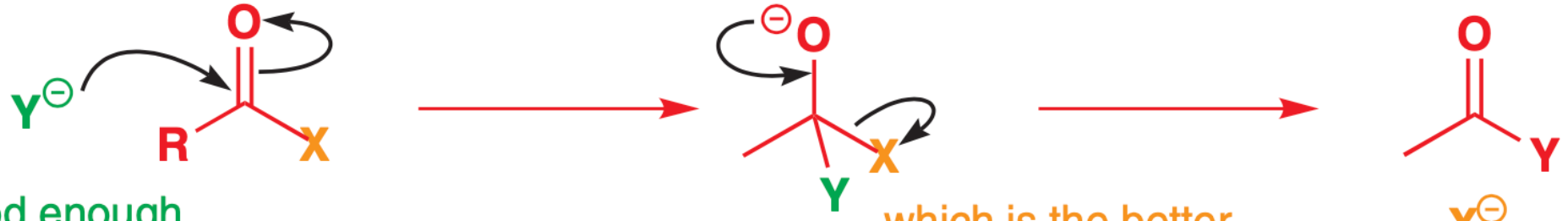


Concluindo

is this carbonyl group electrophilic enough?

tetrahedral intermediate

is this product more, or less, reactive than the starting material?



is Y a good enough nucleophile?

which is the better leaving group: X or Y?