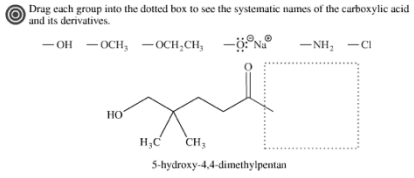
Carboxylic Acid Derivatives

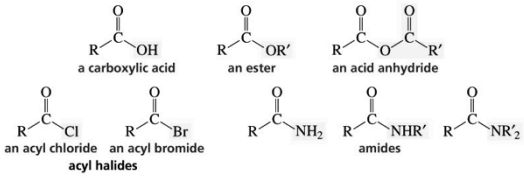
Nucleophilic Substitution: *1)* Addition & *2)* Elimination

GUAR: A General Utilitarian Approach for Reactions of Acid Derivatives (Carbon,Sulfur & Phosphorous)

Systematic Names of Functions

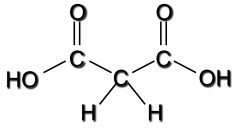


Systematic Names of Acid Functions



Malonic Acid / Condensations and Barbiturates

Malonic Acid

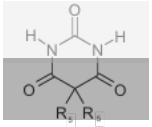


Malonic ester is hydrolyzed to malonic acid, which reacts with urea to produce barbituric acid.

Barbiturates / Condensations

Urea + Malonic Acid & Derivatives ⟶ *>2,500 Compounds*

1864 ⟶ Present Anesthetics / "Sleeping Pills" / "Truth Serum"



DEA Schedule II, III & IV: "bluebirds, downers, goofballs, tooties, yellow jackets"

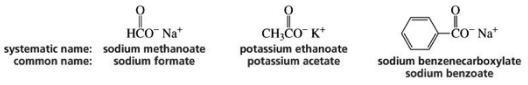
Barbiturates

Short Name	R^5	R^5	Full Name
Allobarbital	CH_2CHCH_2	CH_2CHCH_2	5,5-diallylbarbiturate
Amobarbital	CH_2CH_3	$CH_2CH_2CH(CH_3)_2$	5-ethyl-5-isopentyl-barbiturate
Aprobarbital	CH_2CHCH_2	$CH(CH_3)_2$	5-allyl-5-isopropyl-barbiturate
Alphenal	CH_2CHCH_2	C_6H_5	5-allyl-5-phenyl-barbiturate
Barbital	CH_2CH_3	CH_2CH_3	5,5-diethylbarbiturate
Brallobarbital	CH_2CHCH_2	CH_2CBrCH_2	5-allyl-5-(2-bromo-allyl)-barbiturate
Phenobarbital	CH_2CH_3	C_6H_5	5-phenyl-5-ethylbarbiturate

Nembutal

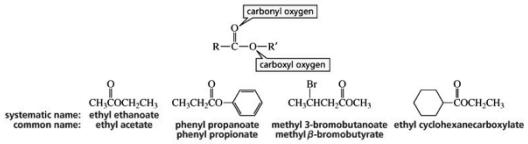
Veronal

Salts of Carboxylic Acids



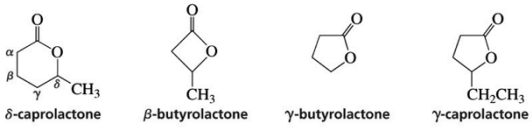
systematic name: sodium methanoate | potassium ethanoate | sodium benzenecarboxylate
common name: sodium formate | potassium acetate | sodium benzoate

Esters



systematic name: ethyl ethanoate | phenyl propanoate | methyl 3-bromobutanoate | ethyl cyclohexanecarboxylate
common name: ethyl acetate | phenyl propionate | methyl β-bromobutyrate

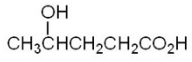
Cyclic Esters:Lactones

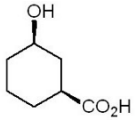


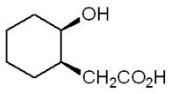
δ-caprolactone | β-butyrolactone | γ-butyrolactone | γ-caprolactone

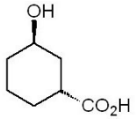
Question

Which compound cannot form a lactone?

A) 

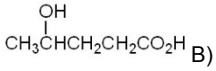
B) 

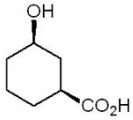
C) 

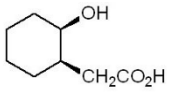
D) 

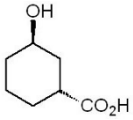
Answer

Which compound cannot form a lactone?

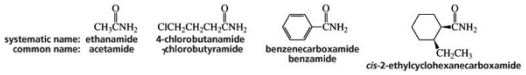
A) 

B) 

C) 

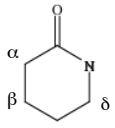
D) 

Amides

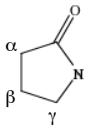


systematic name: ethanamide | 4-chlorobutanamide | | benzenecarboxamide | *cis*-2-ethylcyclohexanecarboxamide
common name: acetamide | γ-chlorobutyramide | | benzamide |

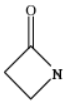
Cyclic Amides: Lactams



2-azacyclohexanone
δ-valerolactam



2-azacyclopentanone
γ-butyrolactam

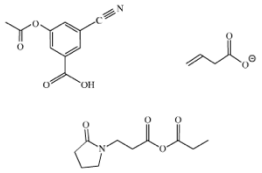


2-azacyclobutanone
β-propiolactam

Recognizing Functions

Touch each label on the left to see the corresponding molecules, substituents, or positions.

nitrile
carboxylic acid
ester
carbonyl oxygens
amide
anhydride
lactam
carboxylate ion



Recognizing Functions

Touch each label on the left to see the corresponding molecules, substituents, or positions.

nitrile
carboxylic acid
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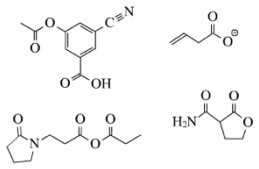
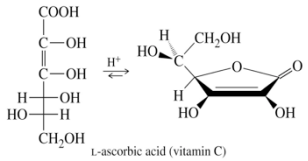
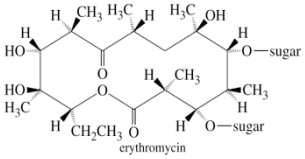
carboxylate ion
lactone

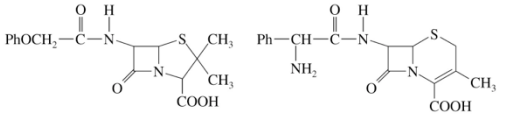




L-ascorbic acid (vitamin C)

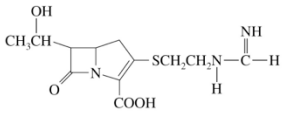


erythromycin



penicillin V
a penicillin

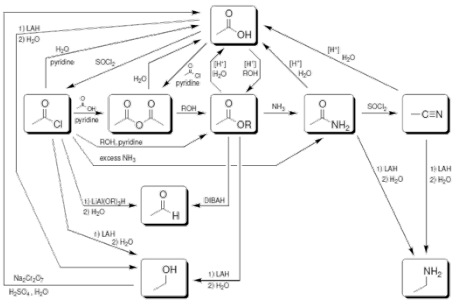
cephalexin (Keflex®)
a cephalosporin



imipenem (Primaxin®)
a carbapenem

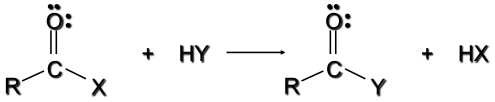
Chemical Reactivity of Carboxylic Acid Derivatives

REACTIONS WITH A COMMON MECHANISM



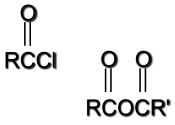
Generic Reaction:
Nucleophilic Substitution

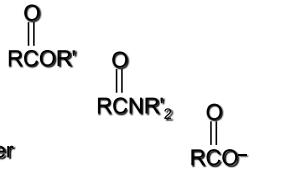
In general:



Reaction is feasible when a less stabilized carbonyl is converted to a more stabilized one (more reactive to less reactive).

most reactive

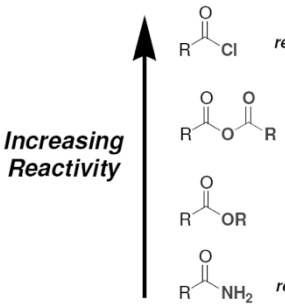




A carboxylic acid derivative can be converted by nucleophilic acyl substitution to any other type that lies below it in this table.

least reactive

Reactivity of Carboxylic Acid Derivatives



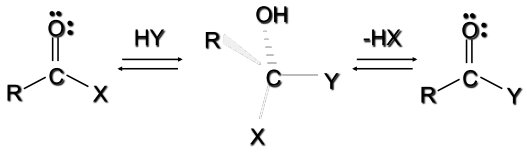
most reactive Reactivity is related to:

- Leaving group
- Induction (R-)
- Resonance (R-)
- Steric effects (R-)

least reactive

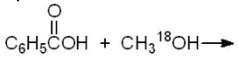
Generic Steps for Nucleophilic Substitution

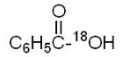
involves formation and dissociation of a tetrahedral intermediate

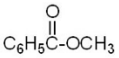


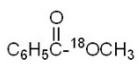
Question

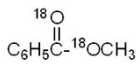
When benzoic acid reacts with ^{18}O-enriched methanol ($CH_3{}^{18}OH$) and an acid catalyst, which product will be obtained?

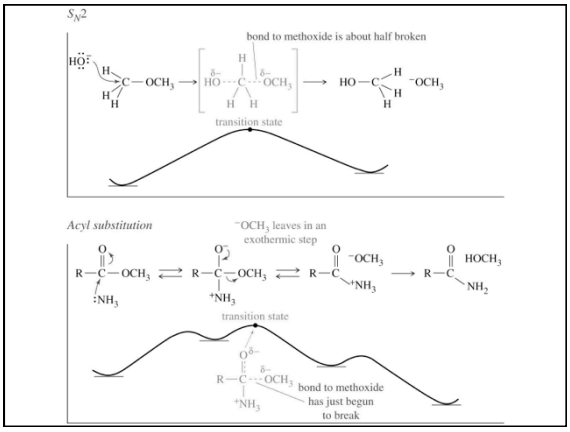


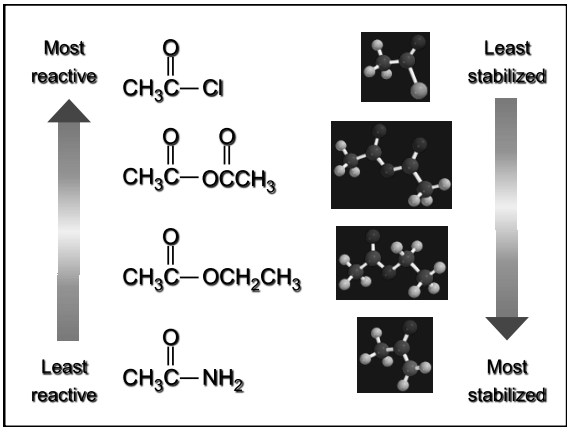
A) 

B) 

C) 

D) 

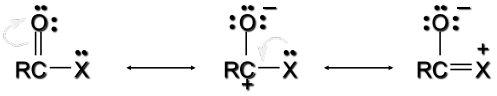




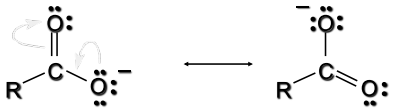
Reactivity, Electron Delocalization & Relative Acidity-Basicity

The extent of delocalization depends on:

1) The electronegativity of X
2) The interaction of X with the π orbital of C=O



Carboxylate Ions



Very efficient electron delocalization and dispersal of negative charge

Maximum stabilization

least stabilized C=O

RCCl

RCOCR'

RCOR'

$RCNR'_2$

RCO^-

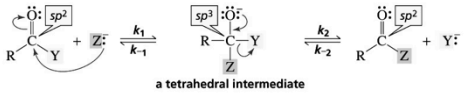
most stabilized C=O

Reactivity is Related to Structure

	Stabilization	Relative rate of hydrolysis
RCCl	very small	10^{11}
RCOCR'	small	10^{7}
RCOR'	moderate	1.0
$RCNR'_2$	large	$< 10^{-2}$

The more stabilized the carbonyl group, the less reactive it is.

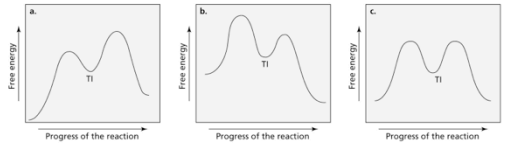
Relative Acidity-Basicity



Z⁻ will be eliminated if it is a much weaker base than **Y**⁻ ($k_{-1} >> k_2$)

Y⁻ will be eliminated if it is a much weaker base than **Z**⁻ ($k_2 >> k_{-1}$)

Reaction Coordinate Diagrams for Nucleophilic Acyl Substitution Reactions

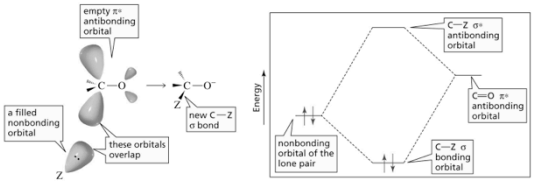


(a) the Nu⁻ is a weaker base
(b) the Nu⁻ is a stronger base
(c) the Nu⁻ and the leaving group have similar basicities

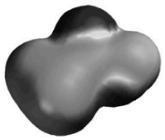
The pK_a Values of the Conjugate Acids of the Leaving Groups of Carbonyl Compounds

Carbonyl compound	Leaving group	Conjugate acid of the leaving group	pK_a
Class I			
	Br^-	HBr	~9
	Cl^-	HCl	~7
			~3–5
	$^-OR'$	R'OH	~15–16
	^-OH	H_2O	15.7
	$^-NH_2$	NH_3	36
Class II			
	H^-	H_2	~40
	R^-	RH	~50

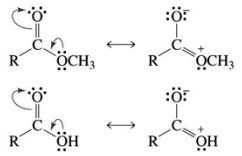
Molecular Orbitals Describe How Compounds React

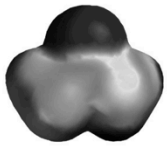


Two major resonance contributors in esters, carboxylic acids, and amides



acetic acid



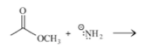


acetamide

Malathion Module: Exploration 3

http://chemconnections.org/organic/chem227/Exploration%203/

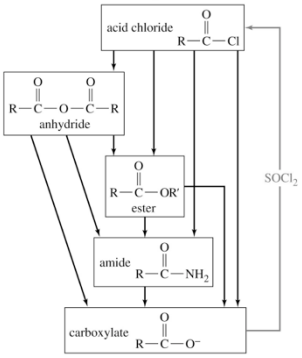
Click "Start" to look at a nucleophilic acyl substitution reaction and the corresponding reaction coordinate diagram.



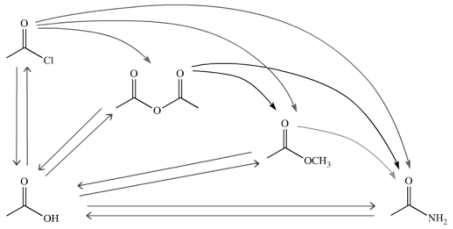
Start

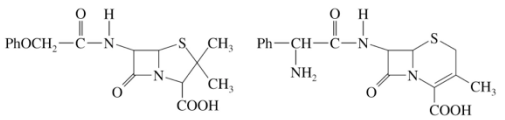
Reactivity	*Derivative*		*Leaving group*	*Basicity*
more reactive	acid chloride	R—C(=O)—Cl	Cl^-	less basic
	anhydride	R—C(=O)—O—C(=O)—R	^-O—C(=O)—R	
	ester	R—C(=O)—O—R′	^-O—R′	
	amide	R—C(=O)—NH_2	$^-NH_2$	
less reactive	carboxylate	R—C(=O)—O^-	—	more basic

Interconversions of acid derivatives



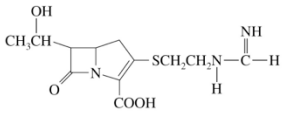
Touch arrows to see the reagents needed to carry out the conversions.





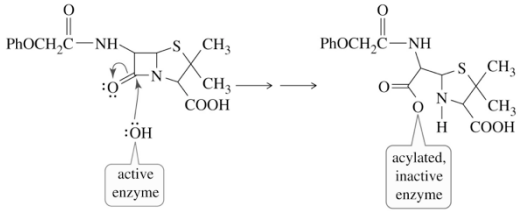
penicillin V
a penicillin

cephalexin (Keflex®)
a cephalosporin

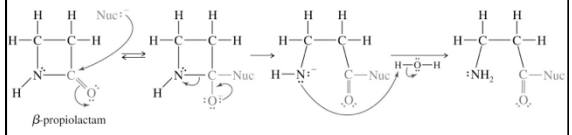


imipenem (Primaxin®)
a carbapenem

β-Lactams & Antibiotic Resistance

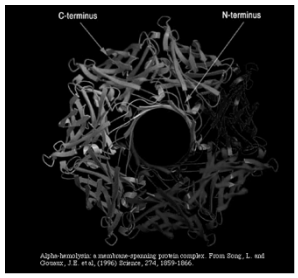


β-Lactams & Antibiotic Resistance

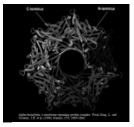


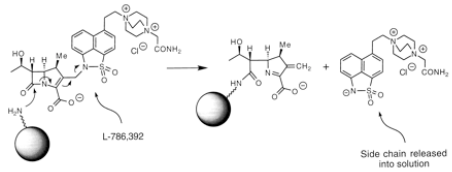
β-propiolactam

http://chemconnections.org/organic/chem227/Staph-infection/index.html

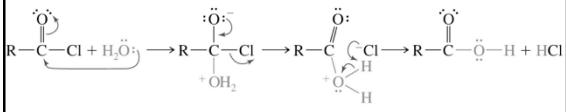


Alpha-hemolysin: a membrane-spanning protein complex. From Song, L. and Gouaux, J.E. et al, (1996) Science, 274, 1859-1866.

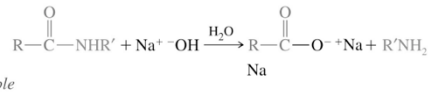




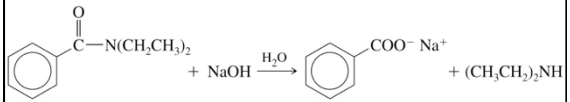
http://chemconnections.org/organic/chem227/Staph-infection/index.html



Basic hydrolysis

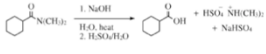


Example



N,N-diethylbenzamide — sodium benzoate — diethylamine

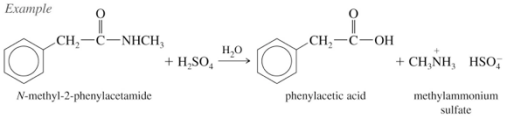
The basic hydrolysis of carboxylic acid derivatives is accomplished by heating the carboxylic acid derivative in the presence of aqueous hydroxide. To view its mechanism click "Begin".



Begin

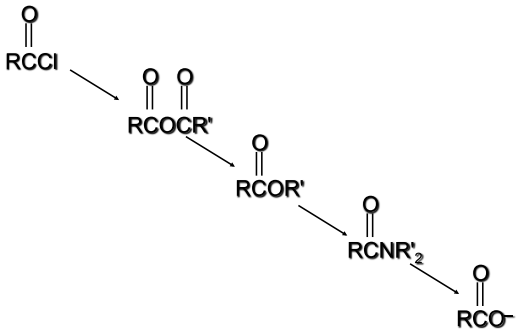
Acid hydrolysis

Example



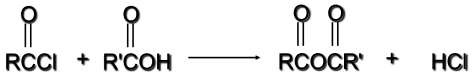
N-methyl-2-phenylacetamide — phenylacetic acid — methylammonium sulfate

Reactions of Acyl Chlorides



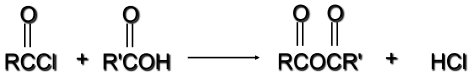
Reactions of Acyl Chlorides

Acyl chlorides react with carboxylic acids to give acid anhydrides:

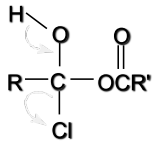


Reactions of Acyl Chlorides

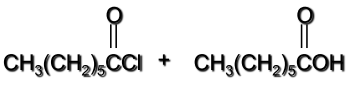
Acyl chlorides react with carboxylic acids to give acid anhydrides:



via:



Example

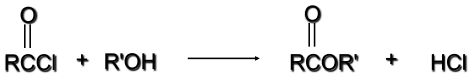


pyridine

(78-83%)

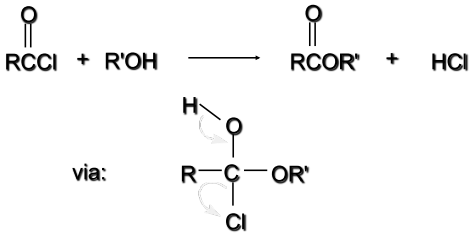
Reactions of Acyl Chlorides

Acyl chlorides react with alcohols to give esters:

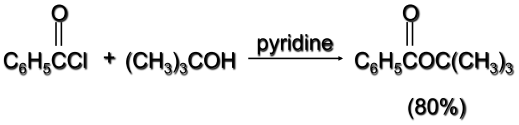


Reactions of Acyl Chlorides

Acyl chlorides react with alcohols to give esters:



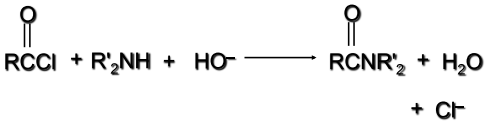
Example



(80%)

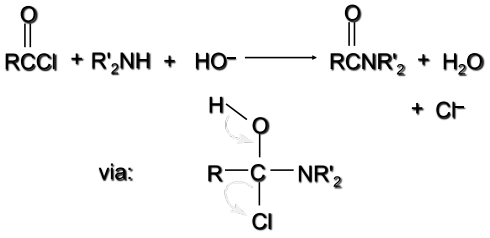
Reactions of Acyl Chlorides

Acyl chlorides react with ammonia and amines to give amides:

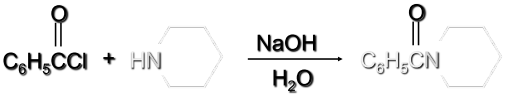


Reactions of Acyl Chlorides

Acyl chlorides react with ammonia and amines to give amides:



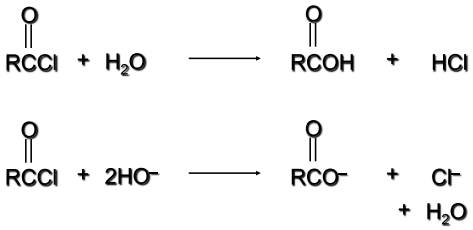
Example



(87-91%)

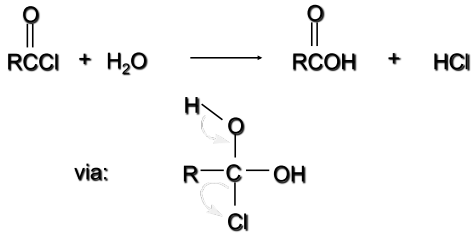
Reactions of Acyl Chlorides

Acyl chlorides react with water to give carboxylic acids (carboxylate ion in base):



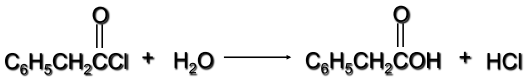
Reactions of Acyl Chlorides

Acyl chlorides react with water to give carboxylic acids (carboxylate ion in base):



via:

Example

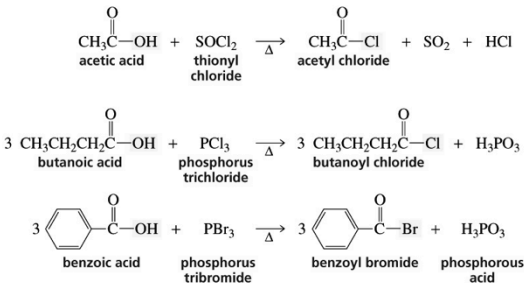


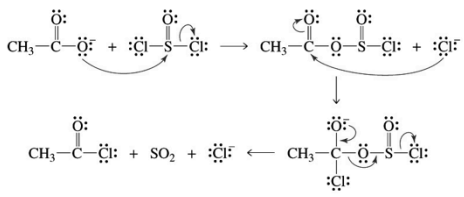
Reactivity

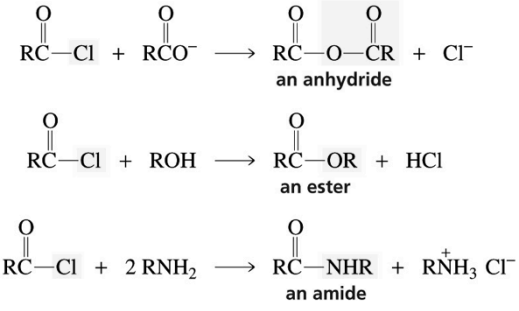
Acyl chlorides undergo nucleophilic substitution much faster than alkyl chlorides.

	C_6H_5CCl	$C_6H_5CH_2Cl$
Relative rates of hydrolysis (25°C)	1,000	1

Activation of Carboxylic Acids

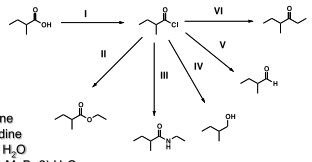






Question

Match the reagents to the corresponding reaction.

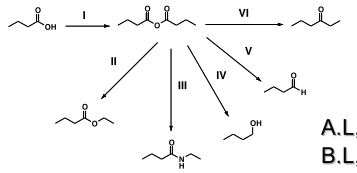


A. $SOCl_2$, pyridine
B. Ethanol, pyridine
C. 1) xs LAH 2) H_2O
D. 1) xs CH_3CH_2MgBr 2) H_2O
E. 1) NaOH 2) H_3O^+
F. 1) DIBAH 2) H_2O
G. H_2O
H. xs $CH_3CH_2NH_2$
I. 1) $LiAl(OR)_3H$ 2) H_2O
J. $(CH_3CH_2)_2CuLi$
K. xs NH_3
L. 1) NaOH 2) $CH_3CH_2CH_2COCl$
M. Butanol, H^+

A. A, M, K, C, F, D
B. A, B, K, C, I, D
C. G, B, H, F, I, J
D. A, M, H, F, F, J
E. A, B, H, C, I, J

Question

Match the reagents to the corresponding reaction.

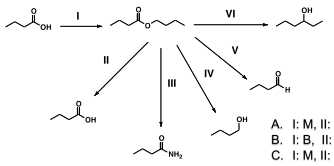


A. $SOCl_2$, pyridine
B. Ethanol, pyridine
C. 1) xs LAH 2) H_2O
D. 1) xs CH_3CH_2MgBr 2) H_2O
E. 1) NaOH 2) H_3O^+
F. 1) DIBAH 2) H_2O
G. H_2O
H. xs $CH_3CH_2NH_2$
I. 1) $LiAl(OR)_3H$ 2) H_2O
J. $(CH_3CH_2)_2CuLi$
K. xs NH_3
L. 1) NaOH 2) $CH_3CH_2CH_2COCl$
M. Butanol, H^+

A.L, B, K, I, C, J
B.L, B, H, C, I, J
C.J, M, K, I, C, D
D.J, M, H, C, I, D
E.J, B, K, I, D, J

Question

Match the reagents to the corresponding reaction.

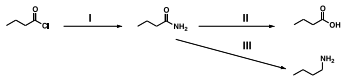


A. I: M, II: E, III: K, IV: C, V: F, VI: F,D
B. I: B, II: G, III: H, IV: C, V: I, VI: D
C. I: M, II: G, III: K, IV: I, V: C, VI: F, D
D. I: B, II: E, III: H, IV: I, V: F, VI: D
E. I: M, II: G, III: H, IV: I, V: F, VI: D

A. $SOCl_2$, pyridine
B. Ethanol, pyridine
C. 1) xs LAH 2) H_2O
D. 1) xs CH_3CH_2MgBr 2) H_2O
E. 1) NaOH 2) H_3O^+
F. 1) DIBAH 2) H_2O
G. H_2O
H. xs $CH_3CH_2NH_2$
I. 1) $LiAl(OR)_3H$ 2) H_2O
J. $(CH_3CH_2)_2CuLi$
K. xs NH_3
L. 1) NaOH 2) $CH_3CH_2CH_2COCl$
M. Butanol, H^+

Question

Match the reagents to the corresponding reaction.

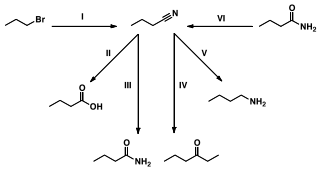


A. $SOCl_2$, pyridine
B. Ethanol, pyridine
C. 1) xs LAH 2) H_2O
D. 1) xs CH_3CH_2MgBr 2) H_2O
E. 1) NaOH 2) H_3O^+
F. 1) DIBAH 2) H_2O
G. H_2O
H. xs $CH_3CH_2NH_2$
I. 1) $LiAl(OR)_3H$ 2) H_2O
J. $(CH_3CH_2)_2CuLi$
K. xs NH_3
L. 1) NaOH 2) $CH_3CH_2CH_2COCl$
M. Butanol, H^+

A.K, G, F
B.K, E, C
C.H, E, F
D.A, G, F
E.H, G, C

Question

Match the reagents to the corresponding reaction.

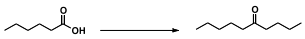


A. $SOCl_2$
B. Ethanol, pyridine
C. 1) xs LAH 2) H_2O
D. 1) xs CH_3CH_2MgBr 2) H_2O
E. 1) NaOH, H_2 2) H_3O^+
F. NaCN
G. H_2O
H. xs $CH_3CH_2NH_2$
I. H_3O^+/Heat
J. $(CH_3CH_2)_2CuLi$
K. NH_3
L. 1) NaOH 2) $CH_3CH_2CH_2COCl$
M. Butanol, H

A. F, G, E, J, C, K
B. F, E, G, J, C, F
C. A, E, I, J, D, K
D. A, G, E, D, C, F
E. F, E, I, D, C, A

Question

Identify the reagents needed for the following synthesis.



A. $SOCl_2$, pyridine
B. H_2O
C. 1) xs LAH 2) H_2O
D. 1) $(CH_3CH_2)_2CuLi$ 2) H_2O
E. 1) $(CH_3CH_2CH_2)_2CuLi$ 2) H_2O
F. 1) $(CH_3CH_2CH_2CH_2)_2CuLi$ 2) H_2O

A.A, C
B.A, D
C.A, E
D.A, F
E.B, E

Activated Carboxylic Acid Derivatives in Living Organisms