Chapter 21
Carboxylic Acids and Their Derivatives

Review of Concepts

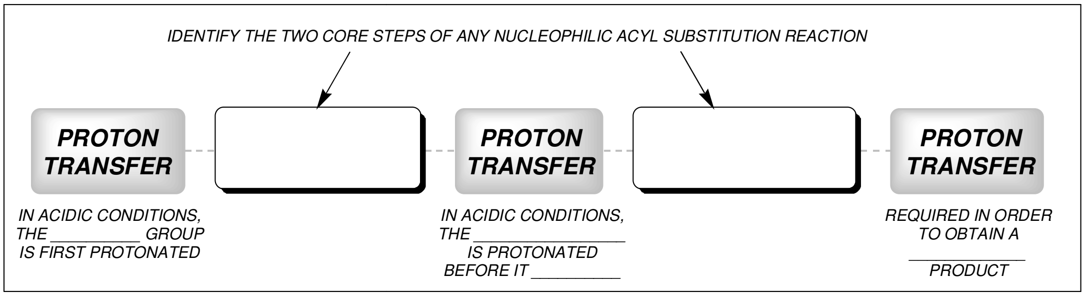
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 21. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Treatment of a carboxylic acid with a strong base yields a _____________ salt.
- The pK_a of most carboxylic acids is between ____ and _____.
- Using the **Henderson-Hasselbalch equation**, it can be shown that carboxylic acids exist primarily _____________________ at **physiological pH**.
- Electron-____________ substituents can increase the acidity of a carboxylic acid.
- When treated with aqueous acid, a nitrile will undergo ___________, yielding a carboxylic acid.
- Carboxylic acids are reduced to ________ upon treatment with lithium aluminum hydride or borane.
- **Carboxylic acid derivatives** exhibit the same ________ state as carboxylic acids.
- Carboxylic acid derivatives differ in reactivity, with _____________ being the most reactive and __________ the least reactive.
- When drawing a mechanism, avoid formation of ___________ charges in acidic conditions, and avoid formation of ____________ charges in alkaline conditions.
- When a nucleophile attacks a carbonyl group to form a tetrahedral intermediate, always reform the carbonyl if possible, but never expel _____ or ______.
- When treated with an alcohol, acid chlorides are converted into _________.
- When treated with ammonia, acid chlorides are converted into _________.
- When treated with a __________ reagent, acid chlorides are converted into alcohols with the introduction of two alkyl groups.
- The reactions of anhydrides are the same as the reactions of ________________ except for the identity of the leaving group.
- When treated with a strong base followed by an alkyl halide, carboxylic acids are converted into __________.
- In a process called the **Fischer esterification**, carboxylic acids are converted into esters when treated with an ____________ in the presence of ________________.
- Esters can be hydrolyzed to yield carboxylic acids by treatment with either aqueous base or aqueous _______. Hydrolysis under basic conditions is also called ________________.
- When treated with lithium aluminum hydride, esters are reduced to yield ___________. If the desired product is an aldehyde, then ________ is used as a reducing agent instead of LAH.
- When treated with a ____________ reagent, esters are reduced to yield alcohols, with the introduction of two alkyl groups.
- When treated with excess LAH, amides are converted into __________.
- Nitriles are converted to amines when treated with _______.

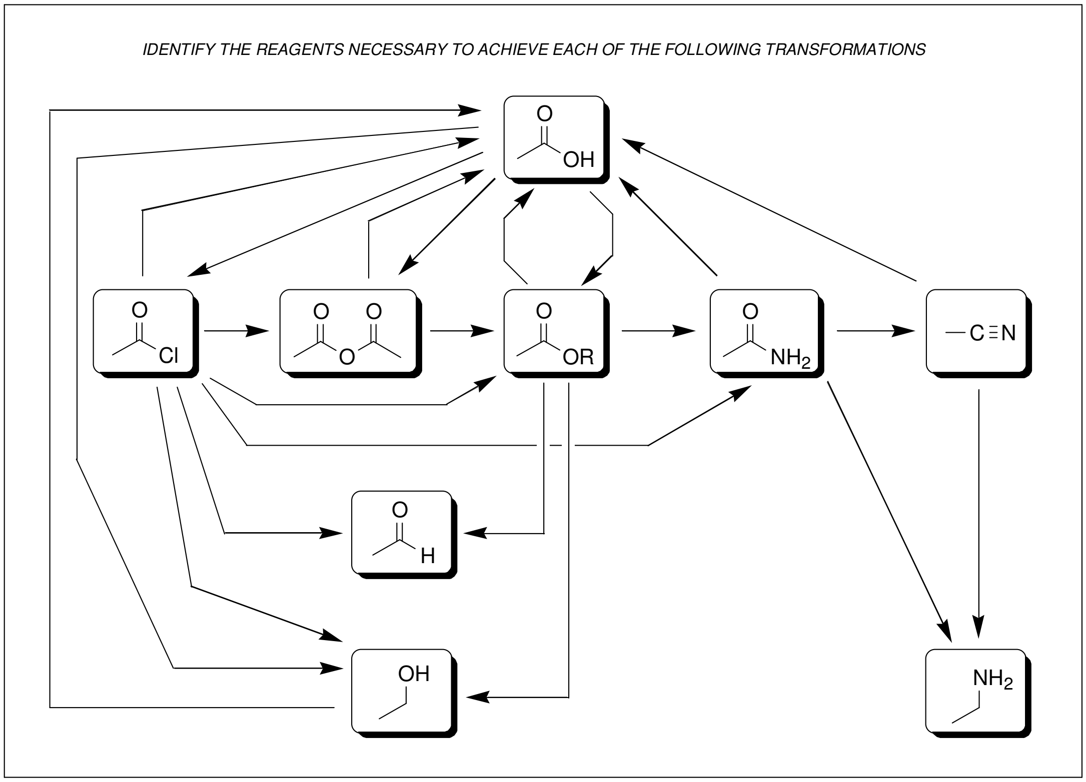
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 21. The answers appear in the section entitled *SkillBuilder Review*.

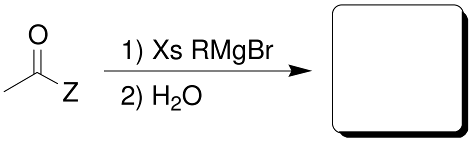
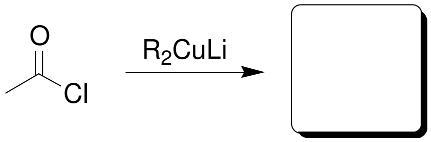
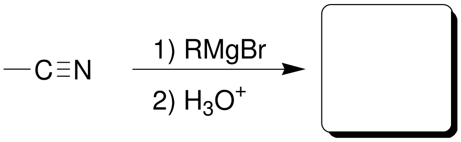
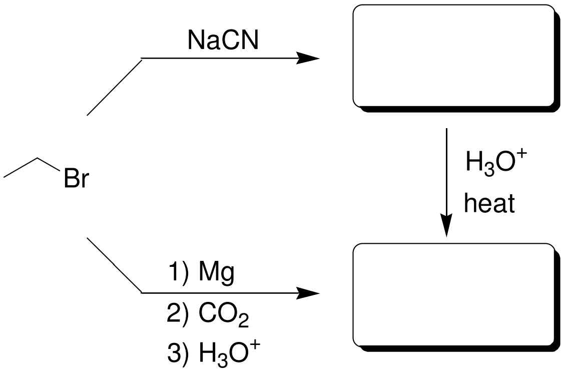
21.1 Drawing the Mechanism of a Nucleophilic Acyl Substitution Reaction



21.2 Interconverting Functional Groups

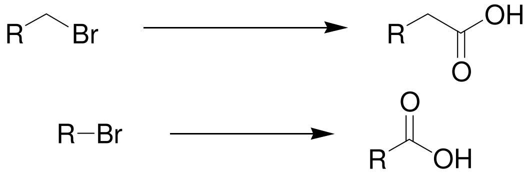
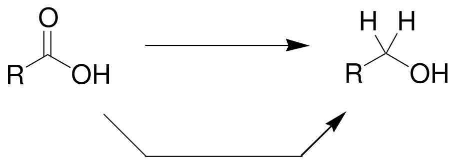


21.3 Choosing the Most Efficient C-C Bond-Forming Reaction

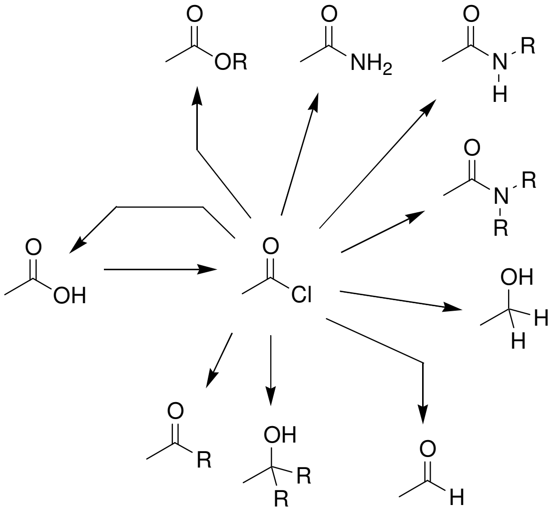
C-C Bond Forming Reactions for which the Functional Group Remains in the Same Location	***C-C Bond Forming Reactions Involving a Change in the Location of the Functional Group***
  	

Review of Reactions

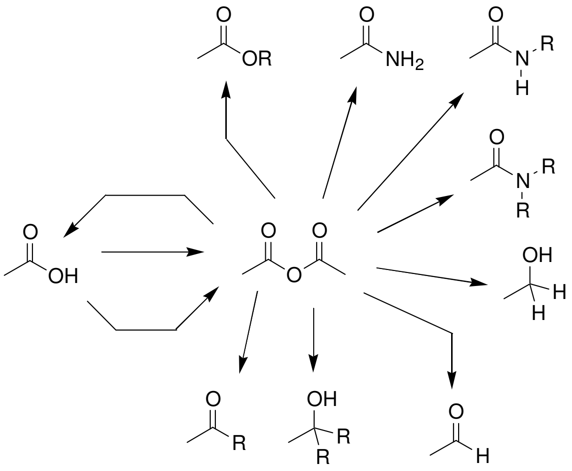
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 21. The answers appear in the section entitled *Review of Reactions*.

Preparation of Carboxylic acids	***Reactions of Carboxylic Acids***
	

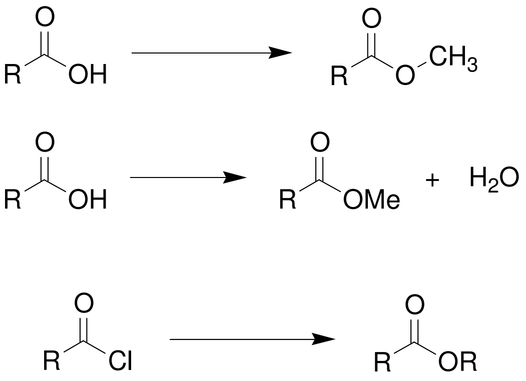
Preparation and Reactions of Acid Chlorides



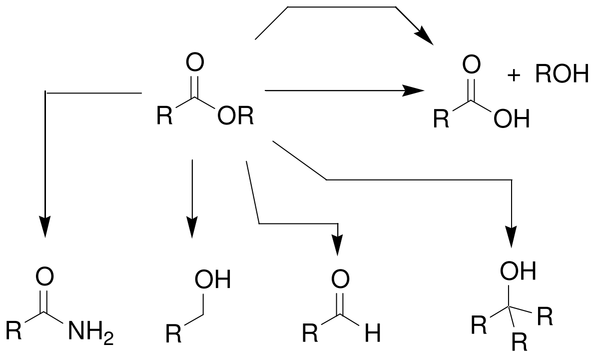
Preparation and Reactions of Acid Anhydrides



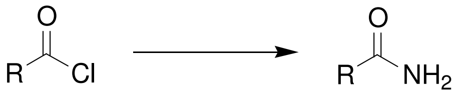
Preparation of Esters



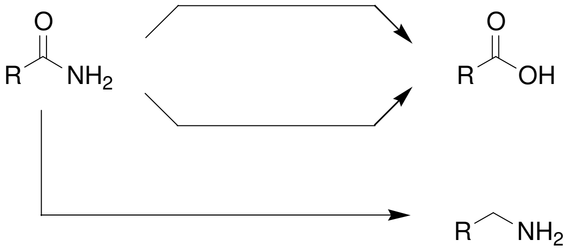
Reactions of Esters

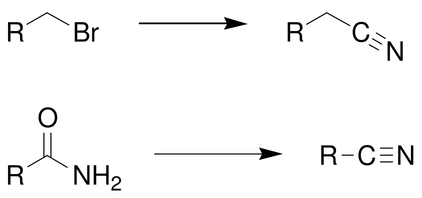
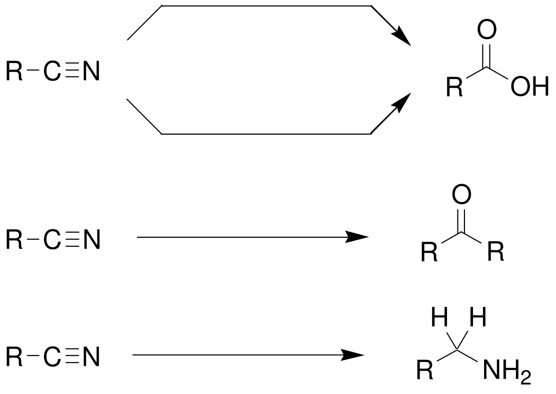


Preparation of Amides



Reactions of Amides



Preparation of Nitriles	***Reactions of Nitriles***
	

Solutions

21.1.

a) IUPAC name = pentanedioic acid
Common name = glutaric acid

b) IUPAC name = butanoic acid
Common name = butyric acid

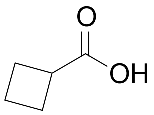
c) IUPAC name = benzene carboxylic acid
Common name = benzoic acid

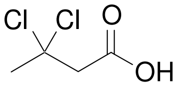
d) IUPAC name = butanedioic acid
Common name = succinic acid

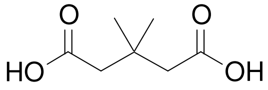
e) IUPAC name = ethanoic acid
Common name = acetic acid

f) IUPAC name = methanoic acid
Common name = formic acid

21.2.

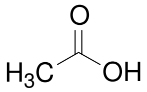
a) 

b) 

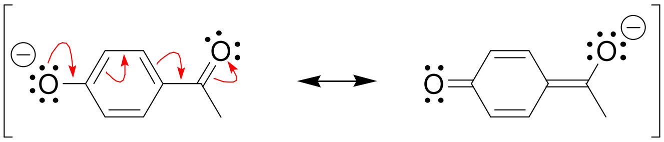
c) 

21.3.
a) 3,3,4,4-tetramethylhexanoic acid
b) 2-propylpentanoic acid
c) (*S*)-2-amino-3-phenylpropanoic acid

21.4. The compound below is more acidic because its conjugate base is resonance stabilized. The conjugate base of the other compound is not resonance stabilized.

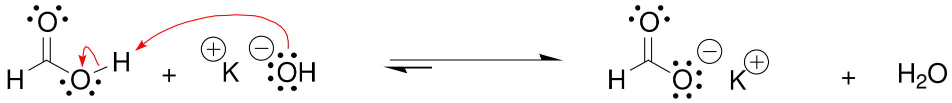


21.5.
The conjugate base is resonance stabilized, with the negative charge spread over two oxygen atoms, just like with carboxylic acids:



21.6. *meta*-Hydroxyacetophenone should be less acidic than *para*-hydroxyacetophenone, because in the conjugate base of the former, the negative charge is spread over only one oxygen atoms (and three carbon atoms). In contrast, the conjugate base of *para*-hydroxyacetophenone has the negative charge spread over two oxygen atoms (more stable).

21.7.



formic acid

potassium formate

21.8. The conjugate base predominates under these conditions:

$$\frac{[\text{conjugate base}]}{[\text{acid}]} = 10^{(\text{pH - p}K_\text{a})} = 10^{(5.76 - 4.76)} = 10^{1} = 10$$

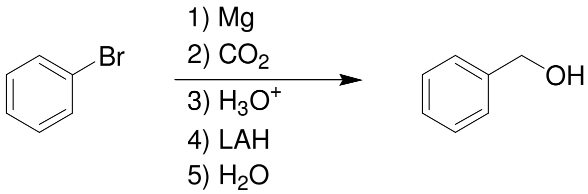
21.9.
a) 2,3-dichlorobutyric acid is the most acidic and 3,4-dimethylbutyric acid is the least acidic.
b) 2,2-dibromopropionic acid is the most acidic and 3-bromopropionic acid is the least acidic.

21.10.

a) $Na_2Cr_2O_7$, H_2SO_4, H_2O
b) $Na_2Cr_2O_7$, H_2SO_4, H_2O
c) CH_3Cl, $AlCl_3$ followed by $Na_2Cr_2O_7$, H_2SO_4, H_2O
d) NaCN, followed by H_3O^+, heat
  or Mg, followed by CO_2, followed by H_3O^+
e) $Na_2Cr_2O_7$, H_2SO_4, H_2O
f) Mg, followed by CO_2, followed by H_3O^+

21.11.

a)



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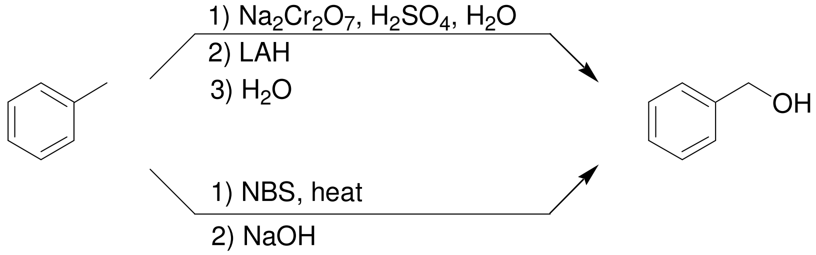
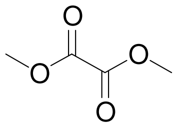


21.12.

a) propionic anhydride
b) *N,N*-diphenyl-propionamide
c) dimethylsuccinate
d) *N*-ethyl-*N*-methylcyclobutanecarboxamide
e) butyronitrile
f) propyl butyrate
g) succinic anhydride
h) methyl benzoate
i) phenyl acetate

21.13.

a)



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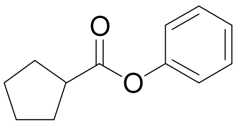

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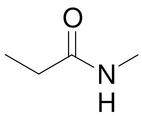

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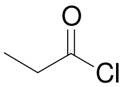
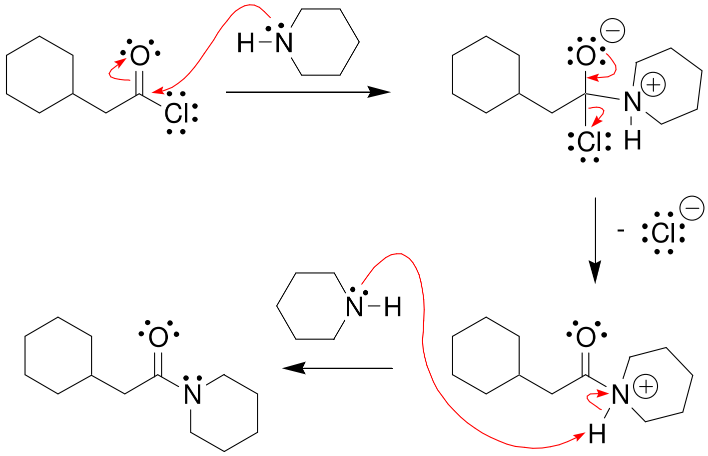


21.14.

a)



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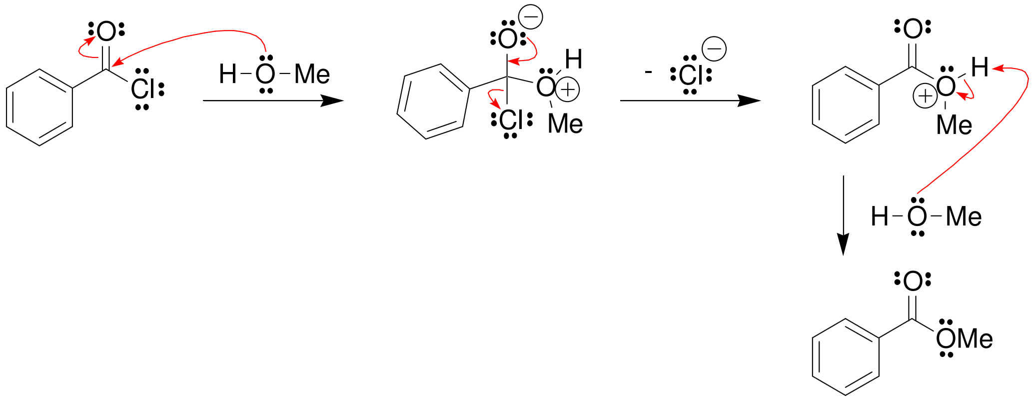

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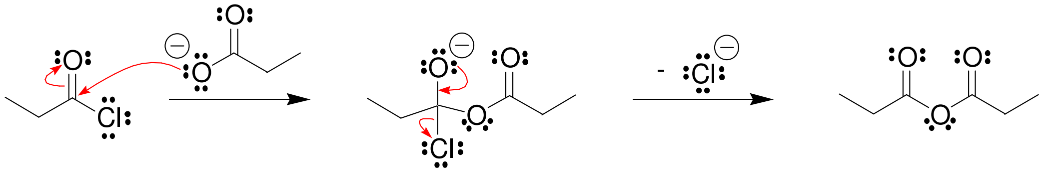

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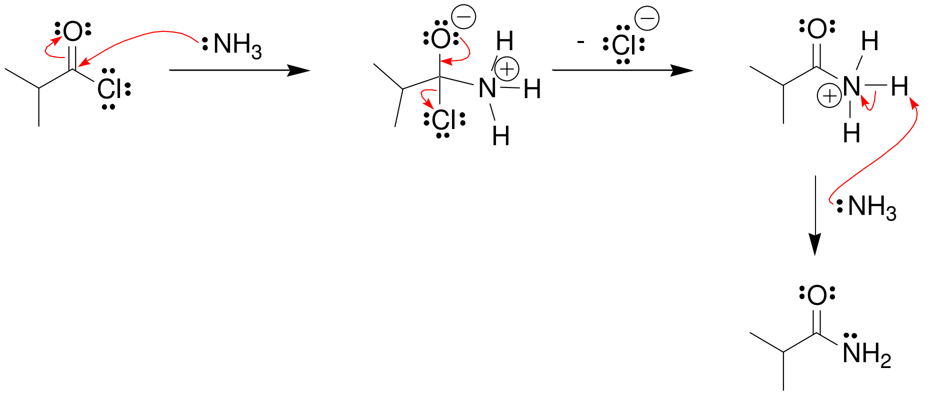
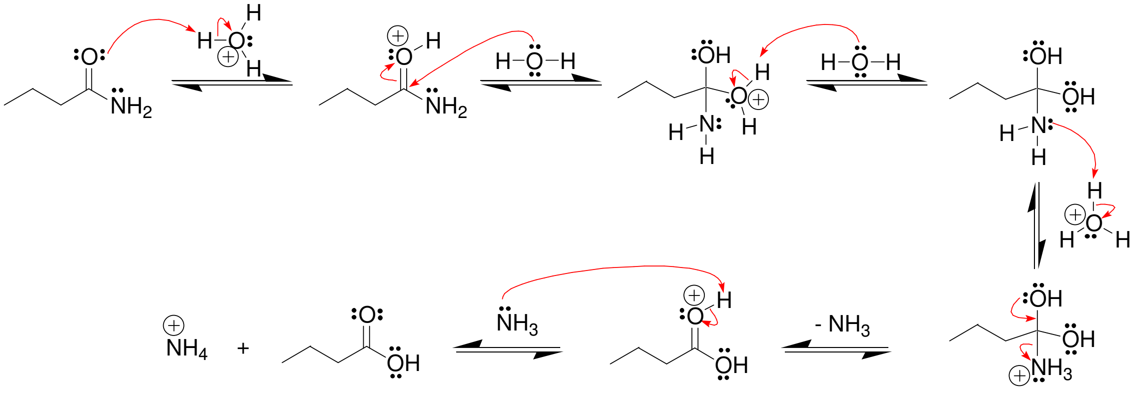
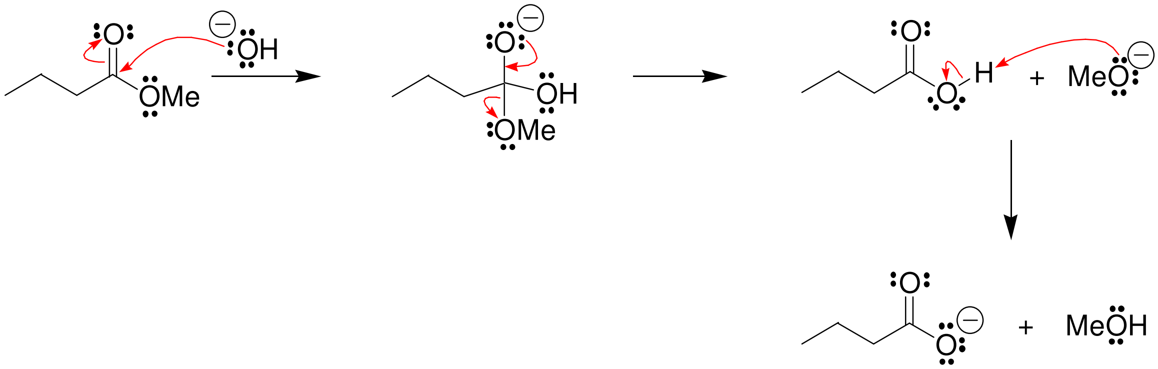


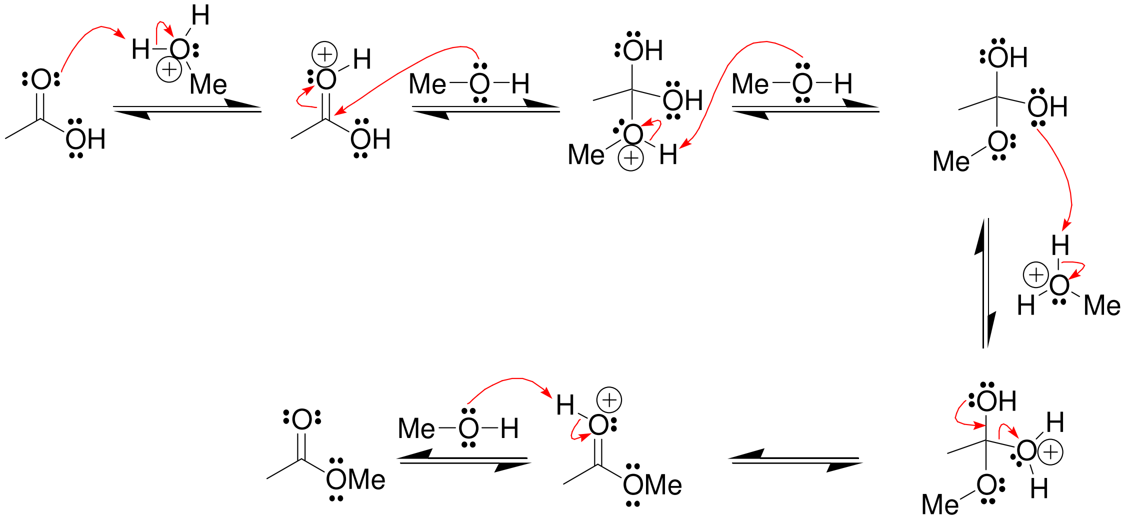
e)


NH2
H–O–H
H–O–H
- NH3
NH3
NH4 +
OH

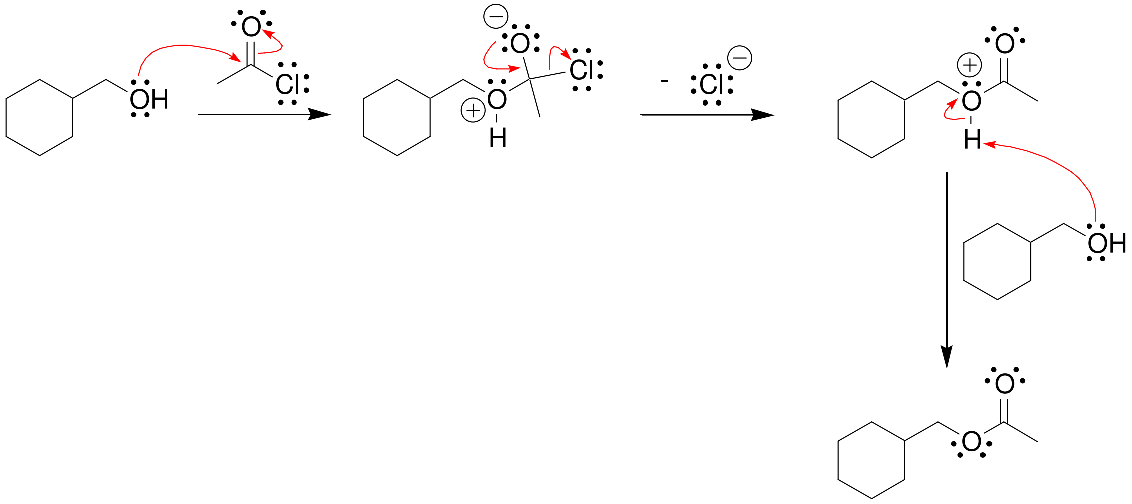
f)


OH
OMe
H
+
MeO
MeOH

g)


Me
OH
Me–O–H
Me–O–H
Me–O–H
H
OMe

21.15.



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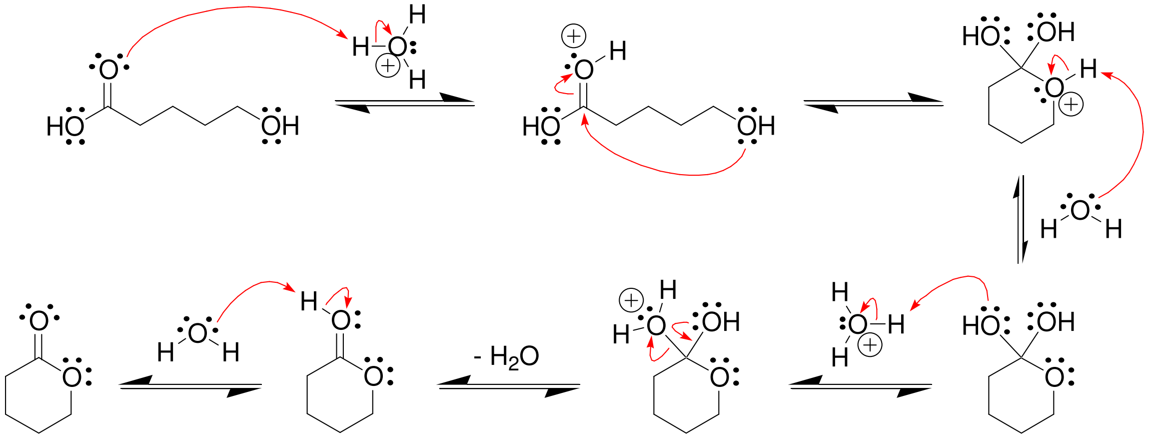

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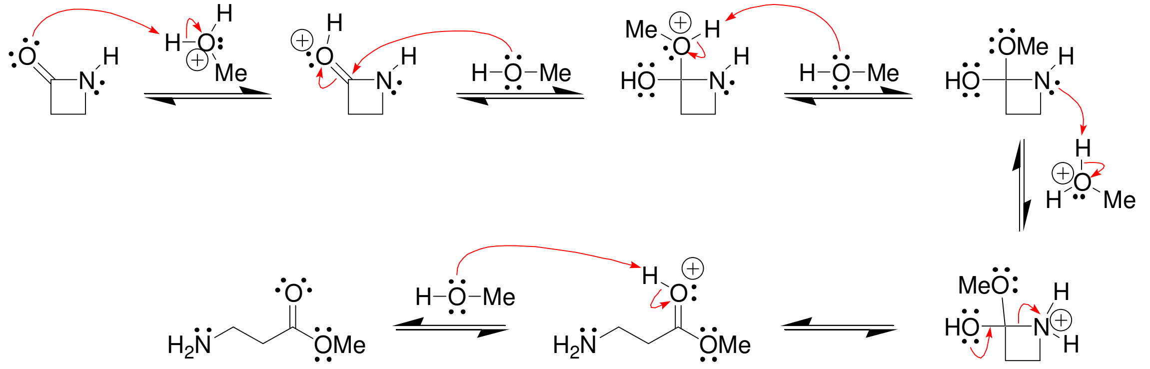

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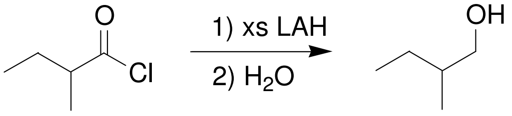
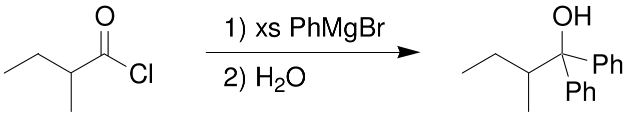
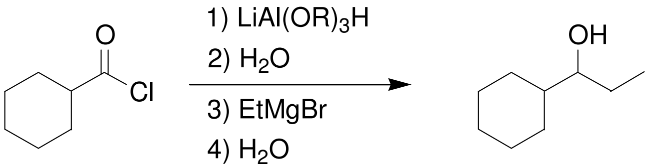
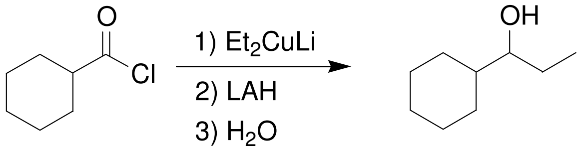
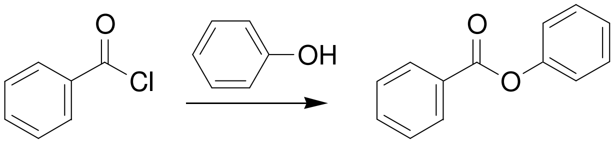
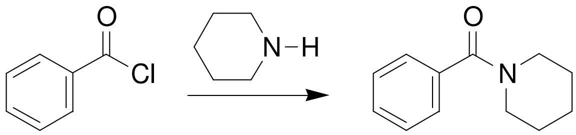
a) 

b) 

c) 

d) 

e) 

f) 

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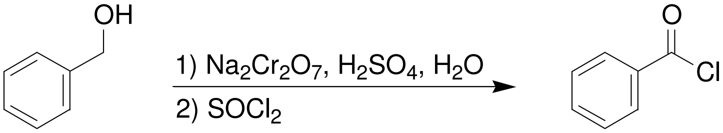

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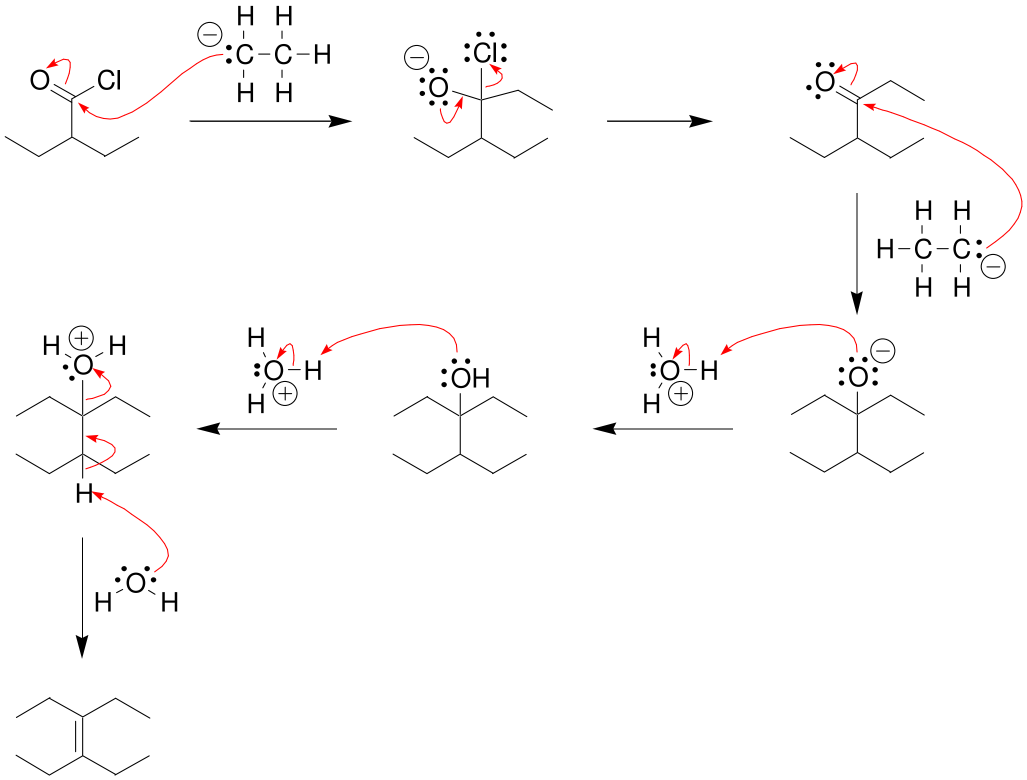
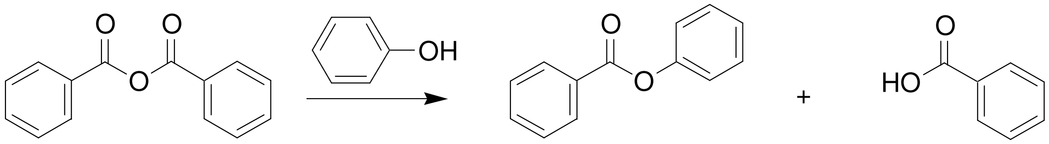


21.21.

a)



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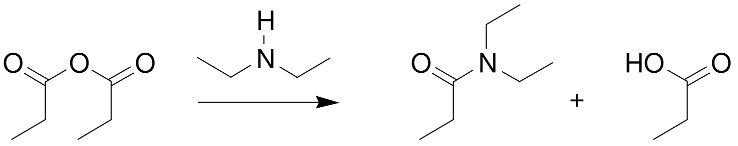

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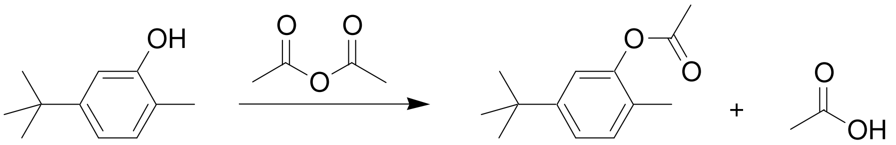

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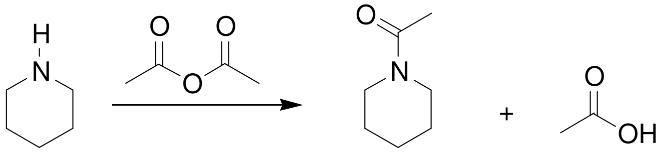

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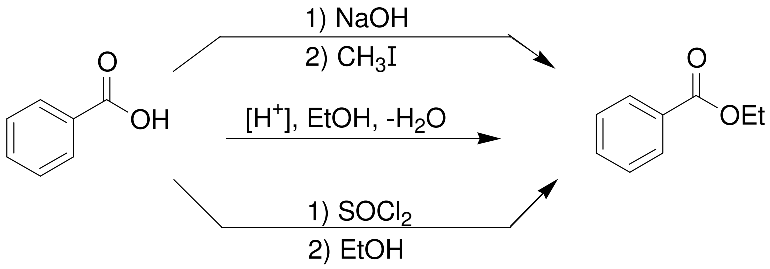

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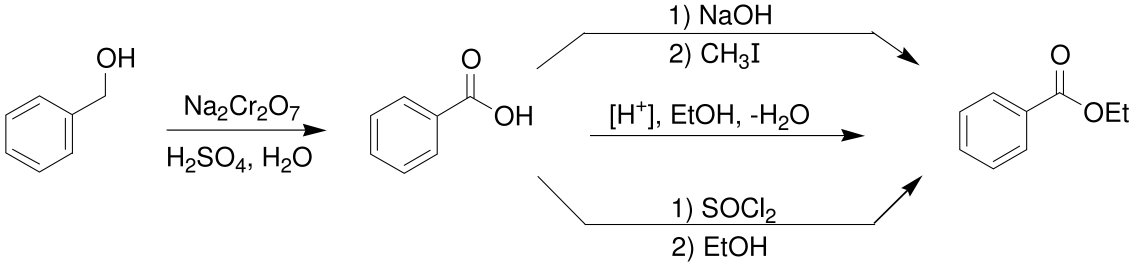

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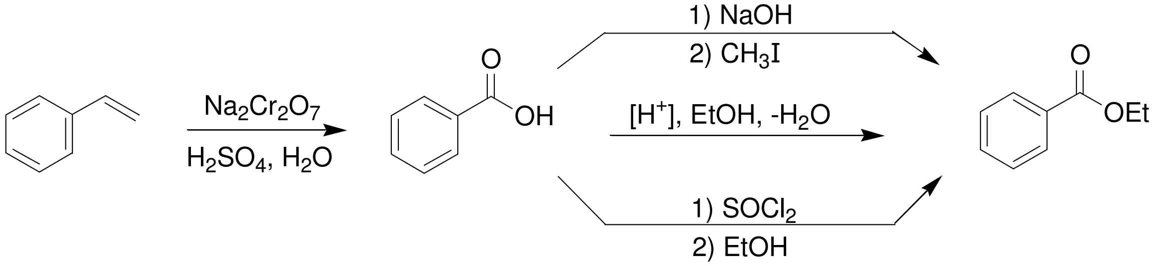

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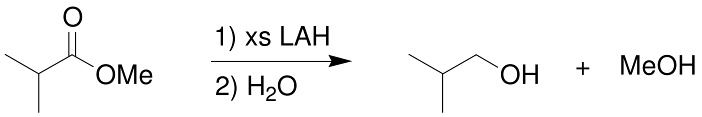

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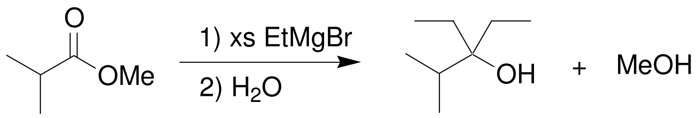

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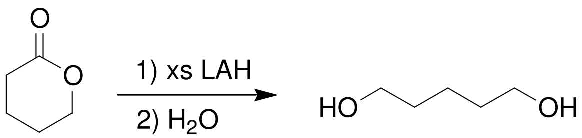

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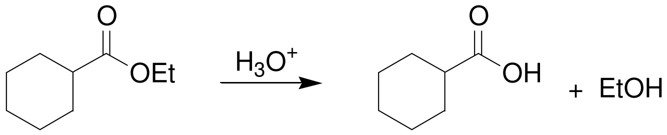

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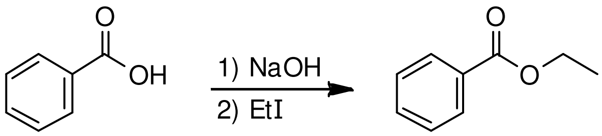

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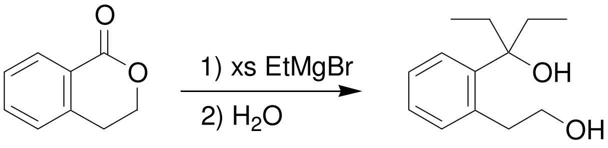
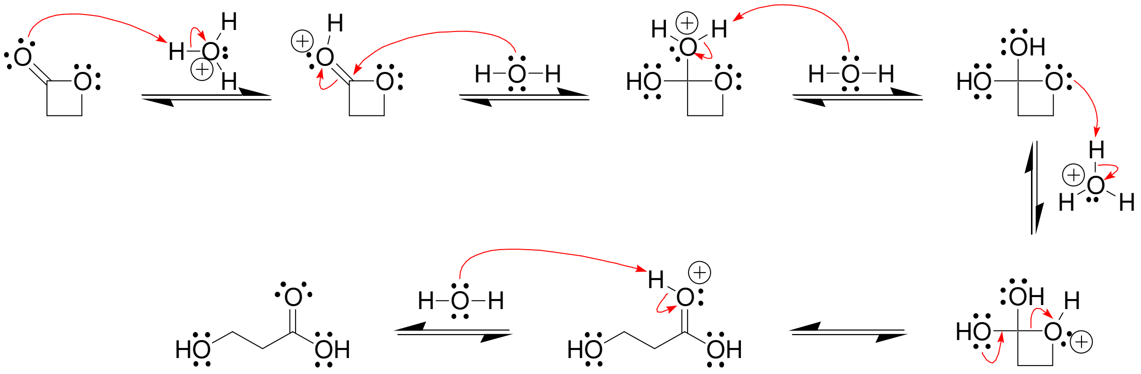
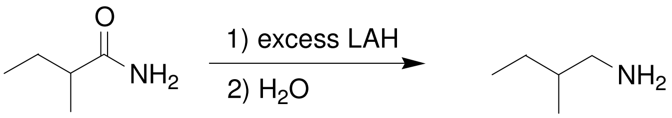


21.25.

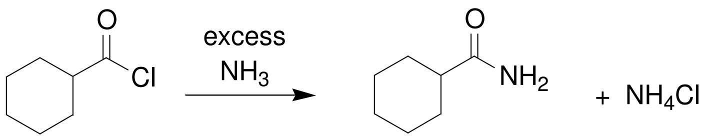


21.26.

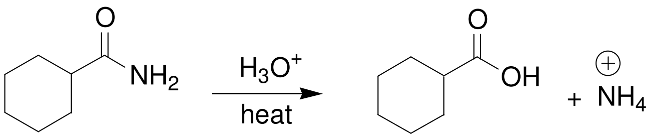
a)



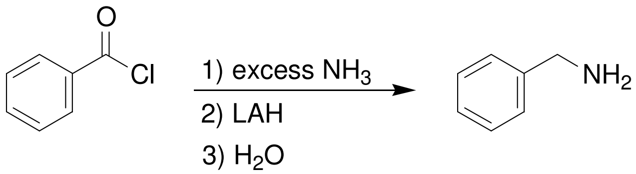
b)



c)

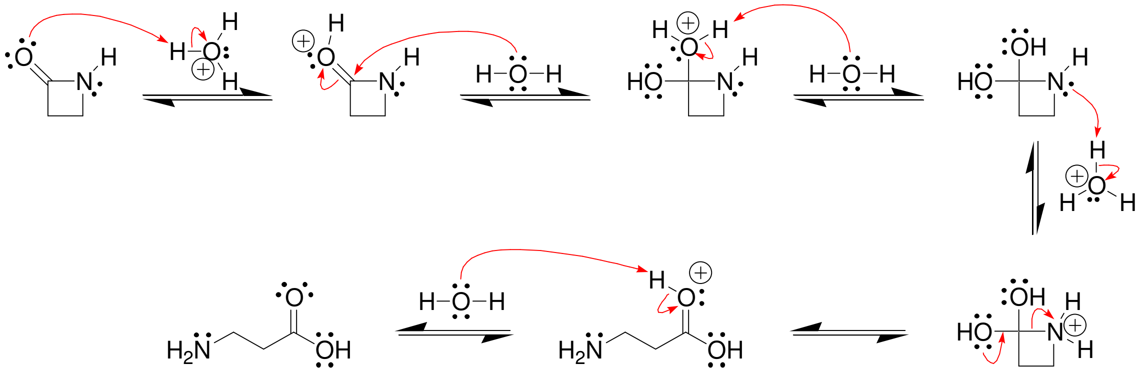


21.27.

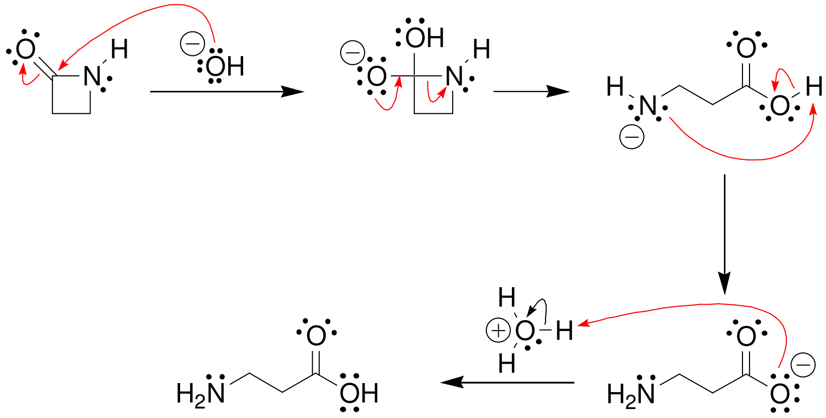

O
Cl
1) excess NH$_3$
2) LAH
3) H$_2$O
NH$_2$

21.28.

a)

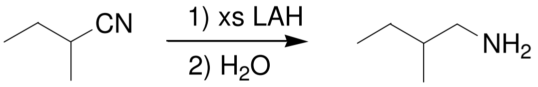

H–O–H
H–O–H
H–O–H
HO
OH
H$_2$N
OH

b)

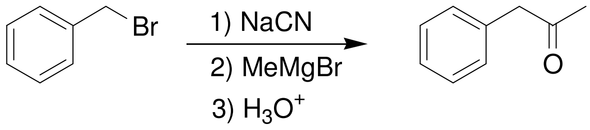

OH
OH
H
H$_2$N
OH
H$_2$N

21.29.

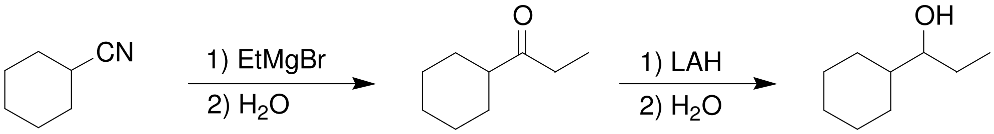
a)



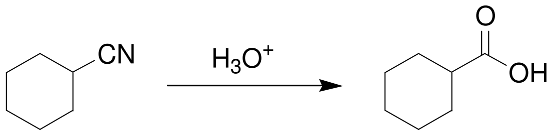
b)



c)

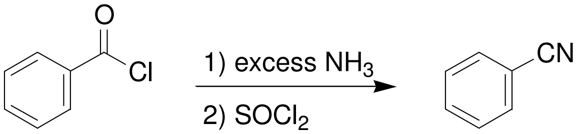


d)

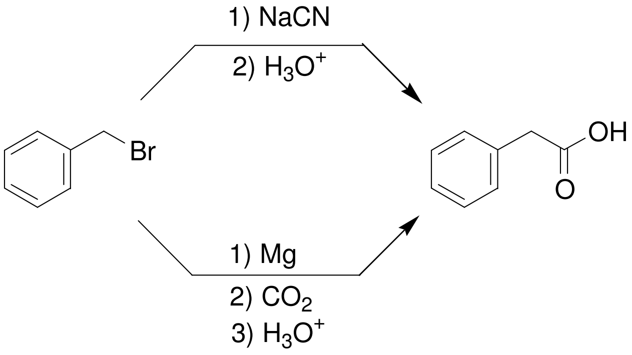


21.30.

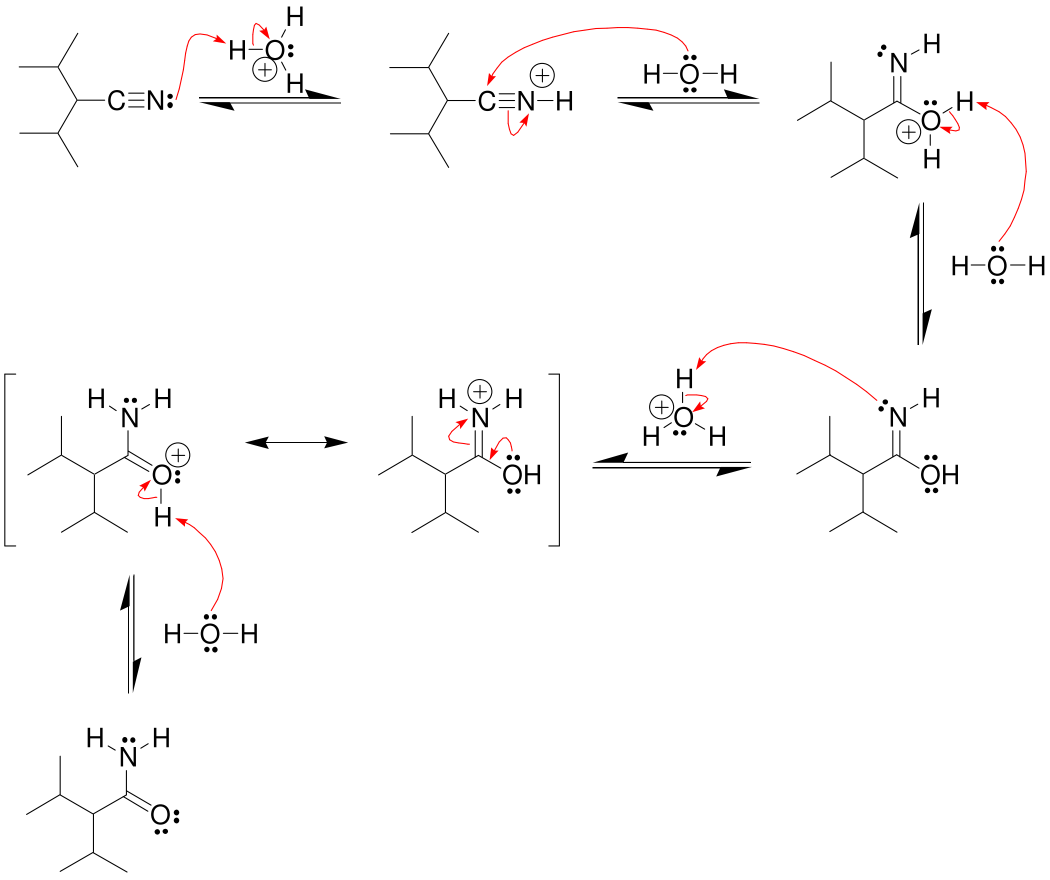
a)



b)

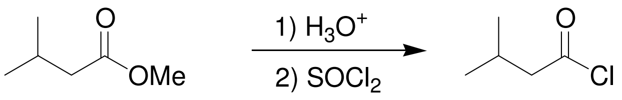


21.31.

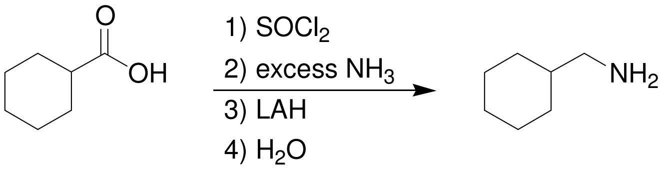


21.32.

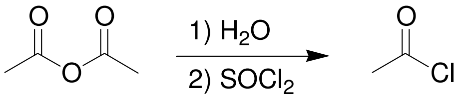
a)



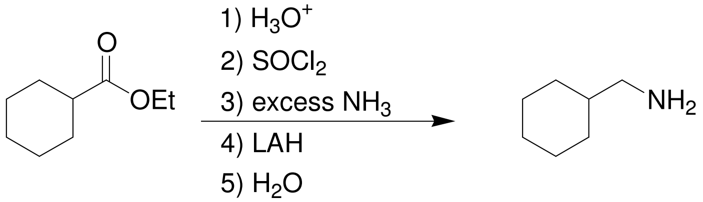
b)



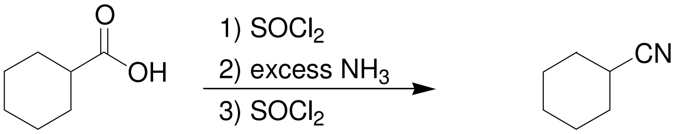
c)



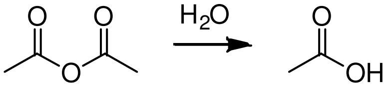
d)



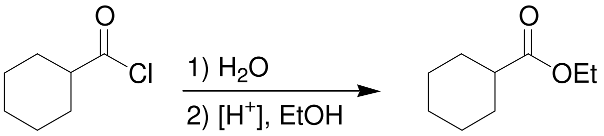
e)



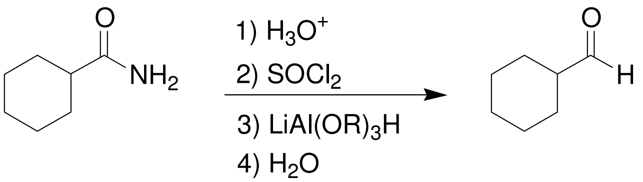
f)



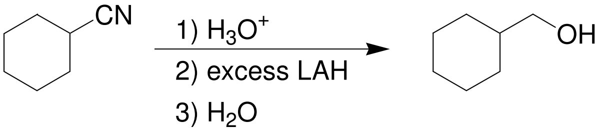
g)



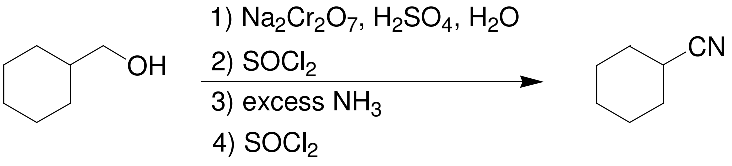
h)



i)

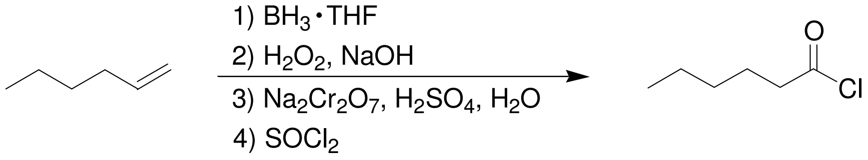


j)

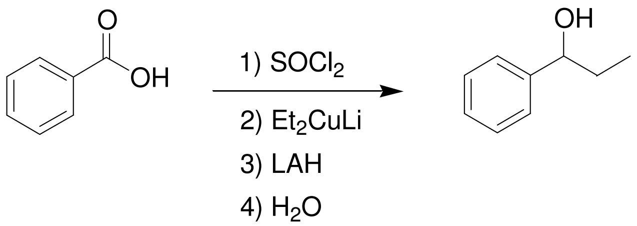


21.33. Four steps: 1) oxidize to a carboxylic acid, 2) convert into an acid halide, 3) convert into an amide, and 4) reduce to give an amine.

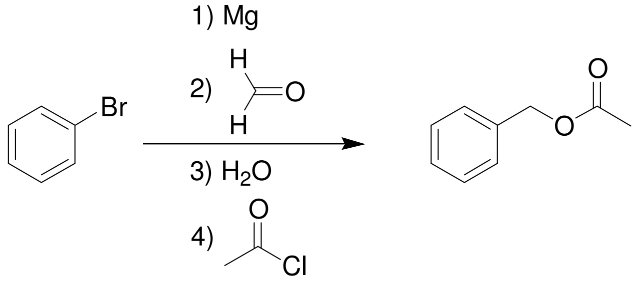
21.34.



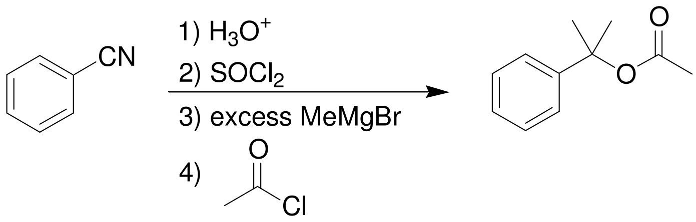
21.35.



a)

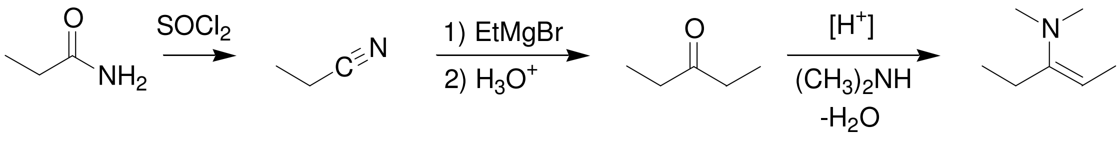


b)



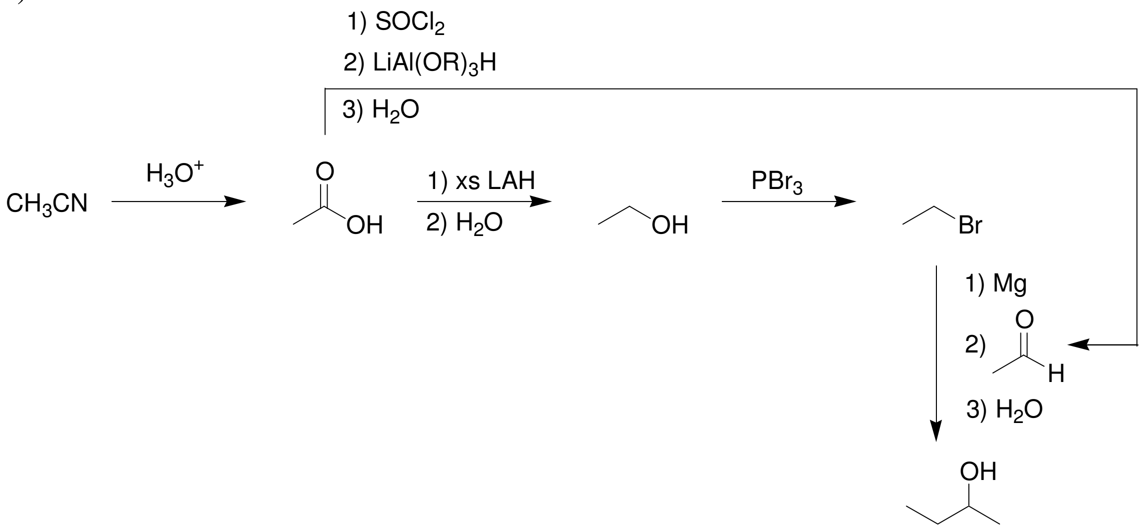
c)

21.36.

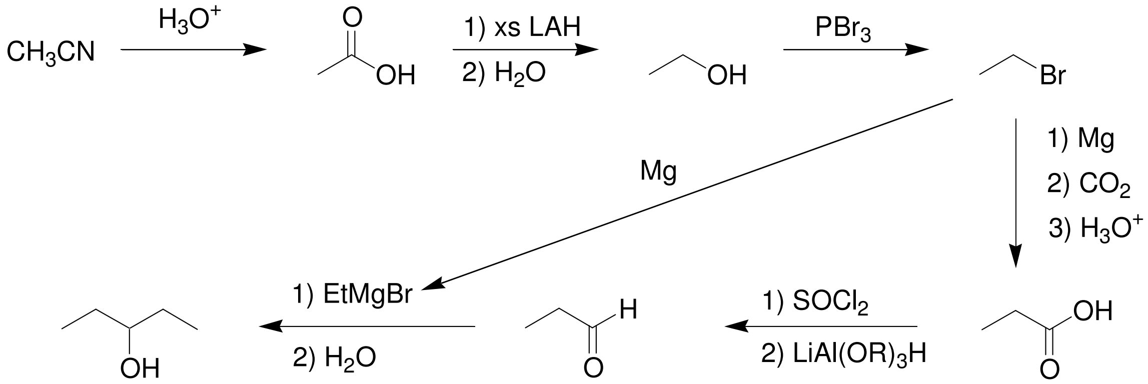


21.37.

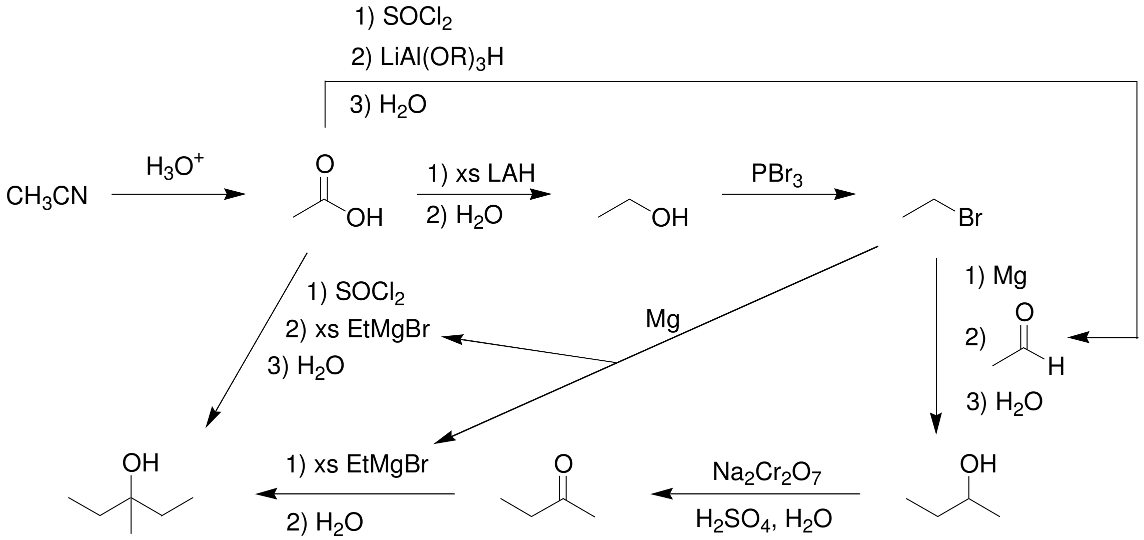
a)


1) SOCl2
2) LiAl(OR)3H
3) H2O
CH3CN
H3O+
O
OH
1) xs LAH
2) H2O
OH
PBr3
Br
1) Mg
2)
O
H
3) H2O
OH

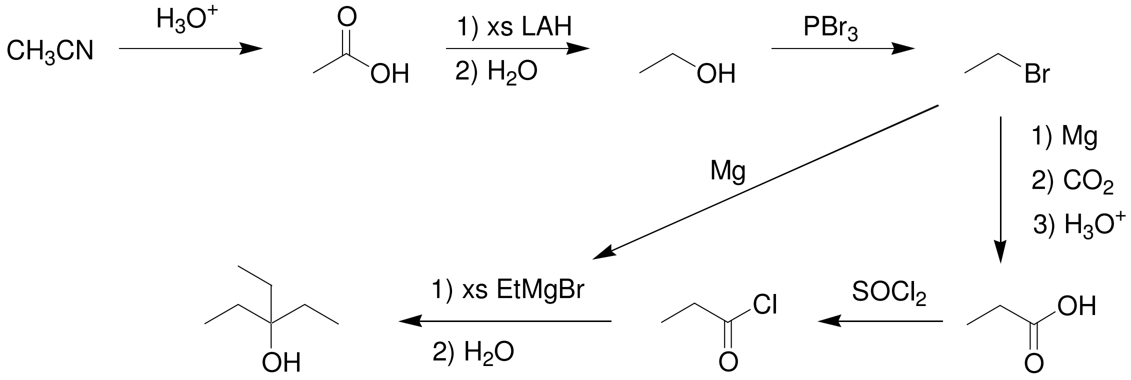
b)


CH3CN
H3O+
O
OH
1) xs LAH
2) H2O
OH
PBr3
Br
Mg
1) Mg
2) CO2
3) H3O+
1) EtMgBr
2) H2O
OH
H
O
1) SOCl2
2) LiAl(OR)3H
OH
O

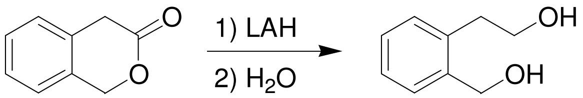
c)


1) SOCl2
2) LiAl(OR)3H
3) H2O
CH3CN
H3O+
O
OH
1) xs LAH
2) H2O
OH
PBr3
Br
1) SOCl2
2) xs EtMgBr
3) H2O
Mg
1) Mg
2)
O
H
3) H2O
OH
1) xs EtMgBr
2) H2O
O
Na2Cr2O7
H2SO4, H2O
OH

d)

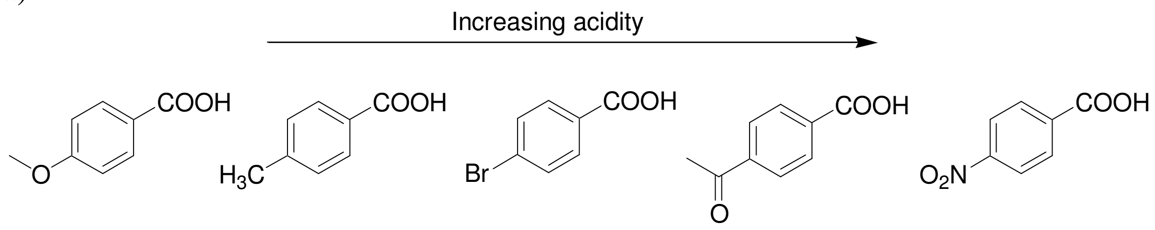


21.38. The signal at 1740 cm^{-1} indicates that the carbonyl group is not conjugated with the aromatic ring (it would be at a lower wavenumber if it was conjugated),

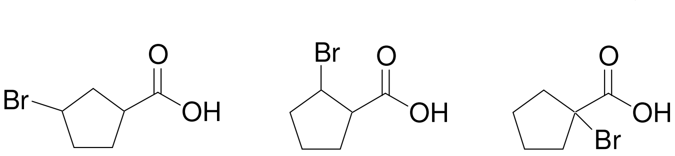


21.39.

a)



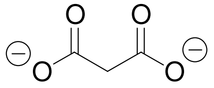
b)



21.40.

a) The second carboxylic acid moiety is electron withdrawing, and stabilizes the conjugate base that is formed when the first proton is removed.

b) The carboxylate ion is electron rich and it destabilizes the conjugate base that is formed when the second proton is removed.

c) .

d) The number of methylene groups (CH_2) separating the carboxylic acid moieties is greater in succinic acid than in malonic acid. Therefore, the inductive effects are not as strong.

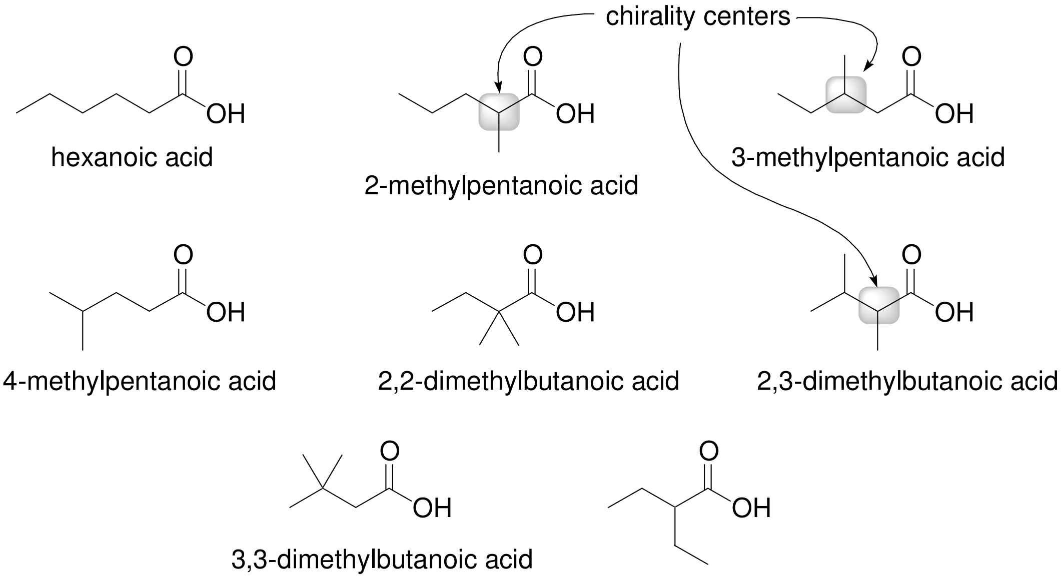
21.41.

a) cyclopentanecarboxylic acid
b) cyclopentanecarboxamide
c) benzoyl chloride
d) ethyl acetate
e) hexanoic acid
f) pentanoyl chloride
g) hexanamide

21.42.

a) acetic anhydride
b) benzoic acid
c) formic acid
d) oxalic acid

21.43.



hexanoic acid

2-methylpentanoic acid

3-methylpentanoic acid

4-methylpentanoic acid

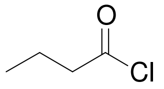
2,2-dimethylbutanoic acid

2,3-dimethylbutanoic acid

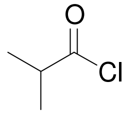
3,3-dimethylbutanoic acid

2-ethylbutanoic acid

21.44.



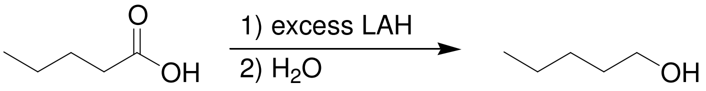
butanoyl chloride



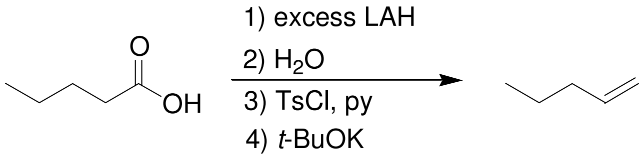
2-methylpropanoyl chloride

21.45.

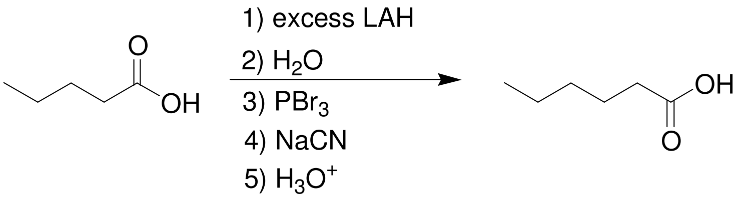
a)



b)

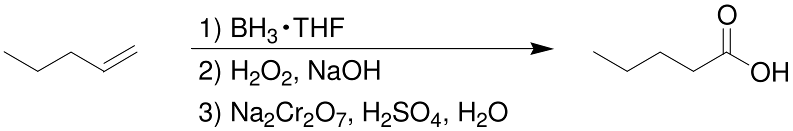


c)

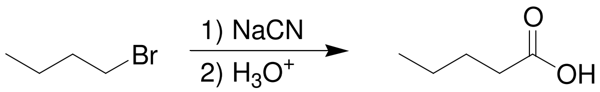


21.46.

a)

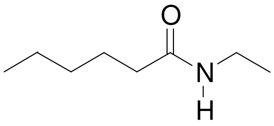


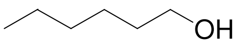
b)

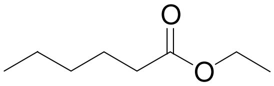


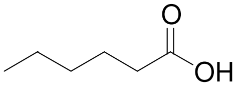
21.47. As discussed in Chapter 19, the methoxy group is electron donating via resonance, but electron withdrawing via induction. The resonance effect is stronger, but only occurs when the methoxy group is in an *ortho* or *para* position.

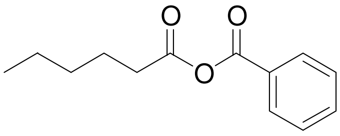
21.48.

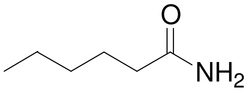
a) 

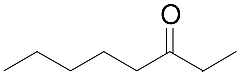
b) 

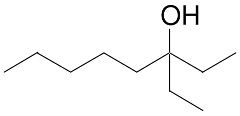
c) 

d) 

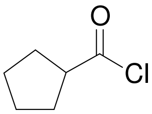
e) 

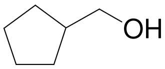
f) 

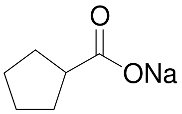
g) 

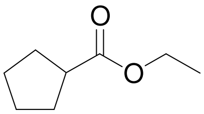
h) 

21.49.

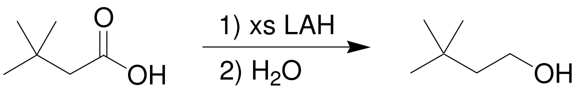
a) 

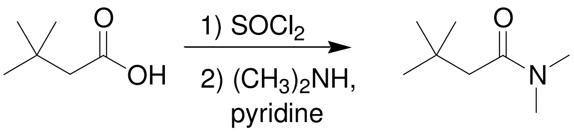
b) 

c) 

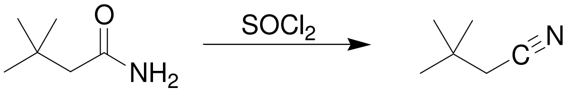
d) 

21.50.

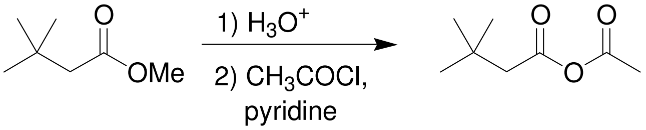
a) 


O
OH
1) $SOCl_2$
2) $(CH_3)_2NH$,
pyridine
O
N

b)


O
NH_2
$SOCl_2$
C≡N

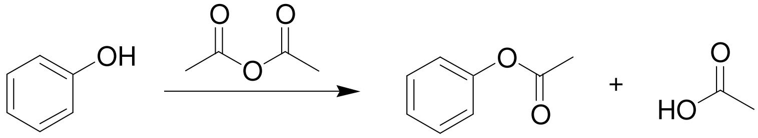
c)


O
OMe
1) H_3O^+
2) CH_3COCl,
pyridine
O
O
O

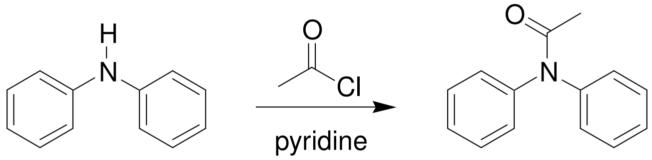
d)


O
OMe
DIBAH
O
H

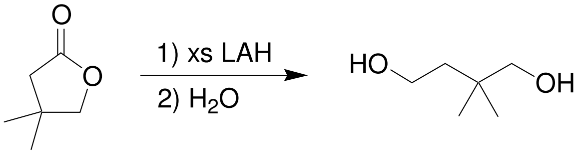
e)


OH
O
O
O
O
O
+
O
HO

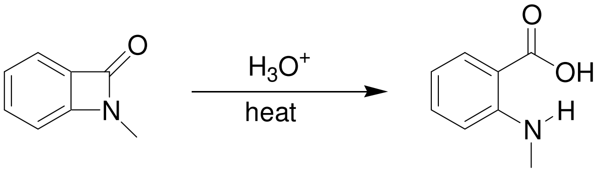
f)


H
N
O
Cl
pyridine
O
N

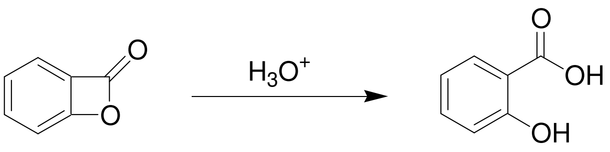
g)


O
O
1) xs LAH
2) H_2O
HO
OH

h)

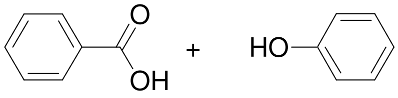

O
N
H_3O^+
heat
O
OH
N
H

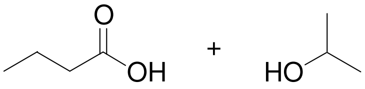
i)


O
O
H_3O^+
O
OH
OH

j)

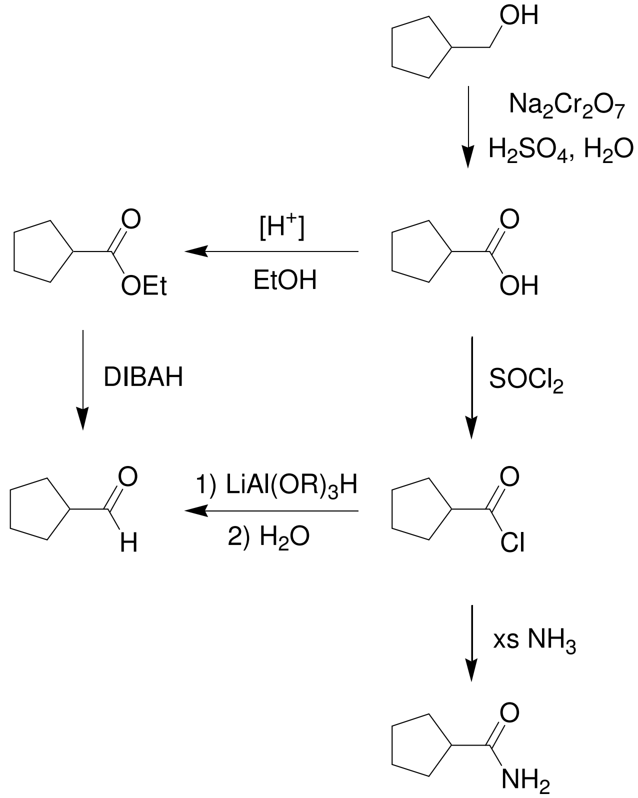
21.51.

a) 

b) 

c) $CH_3CH_2CO_2H$ + $(CH_3)_3COH$

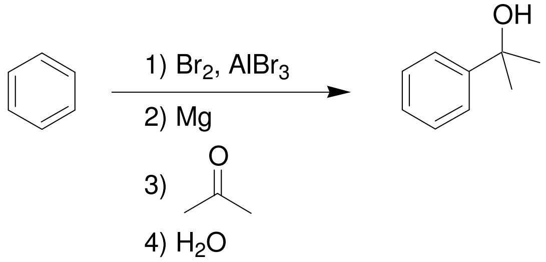
21.52.

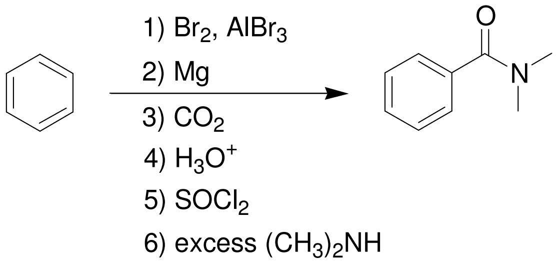


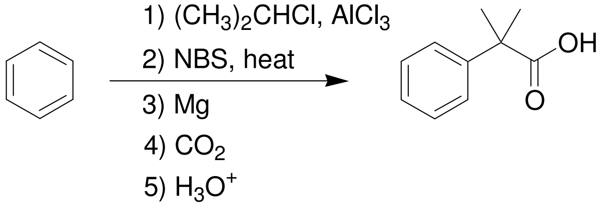
21.53.

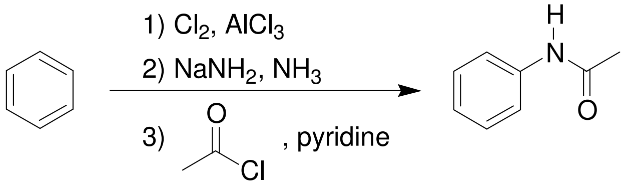
a) NaOH, followed by $Na_2Cr_2O_7$, H_2SO_4, H_2O
b) NaCN followed by H_3O^+
c) NaOH, followed by $Na_2Cr_2O_7$, H_2SO_4, H_2O, followed by $SOCl_2$
d) NaCN, followed by H_3O^+, followed by $SOCl_2$, followed by xs NH_3
e) NaOH, followed by $Na_2Cr_2O_7$, H_2SO_4, H_2O, followed by $SOCl_2$, followed by xs NH_3
f) NaCN followed by H_3O^+, followed by [H^+], EtOH (with removal of water)

21.54.

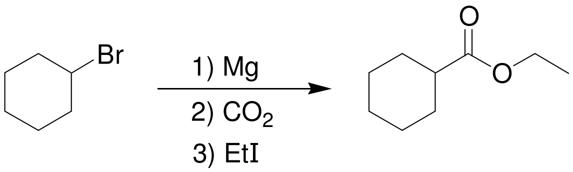
a) 

b) 

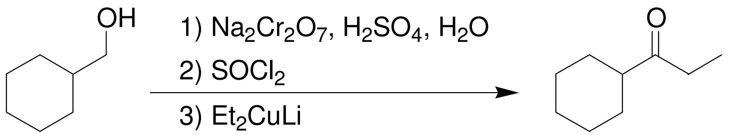
c) 

d) 

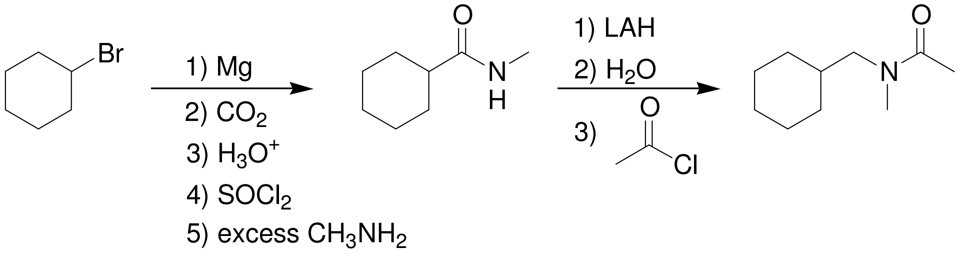
21.55.

a) 

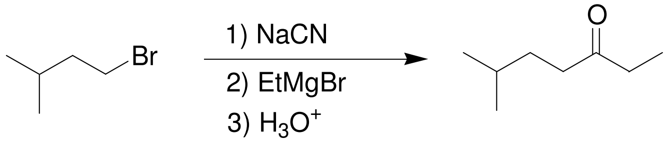
b)



c)

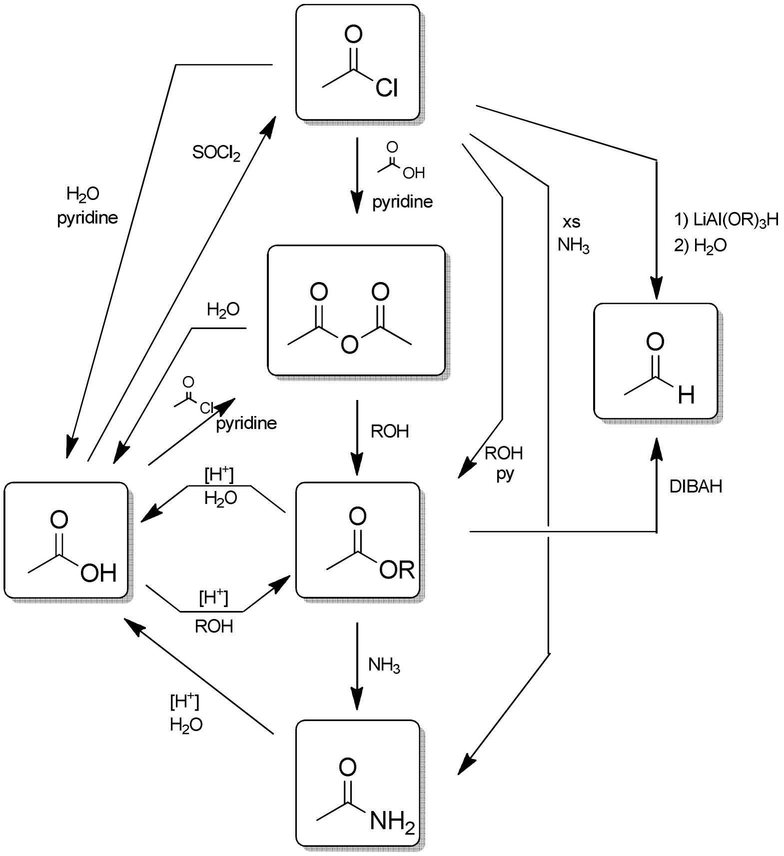


d)

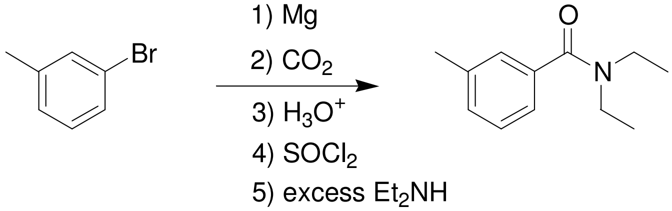


21.56. A methoxy group is electron donating, thereby decreasing the electrophilicity of the ester moiety. A nitro group is electron withdrawing, thereby increasing the electrophilicity of the ester group.

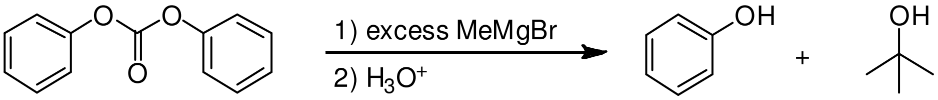
21.57.



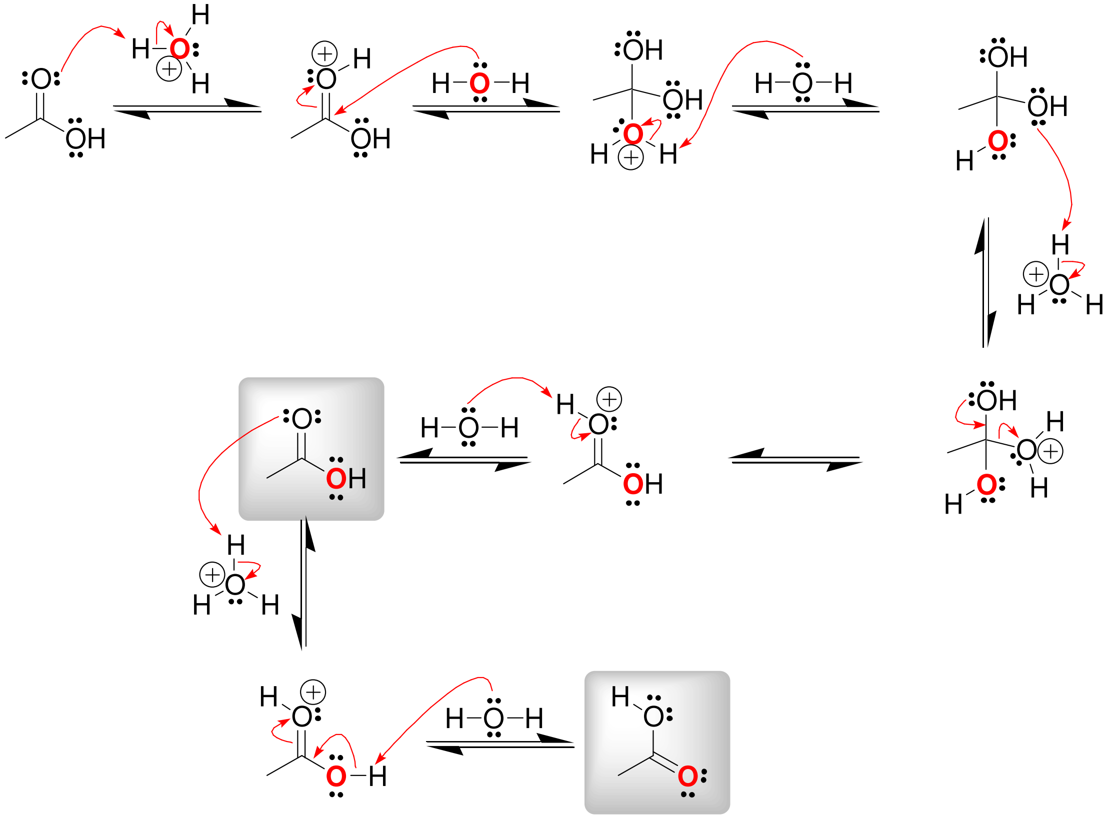
21.58.



21.59.

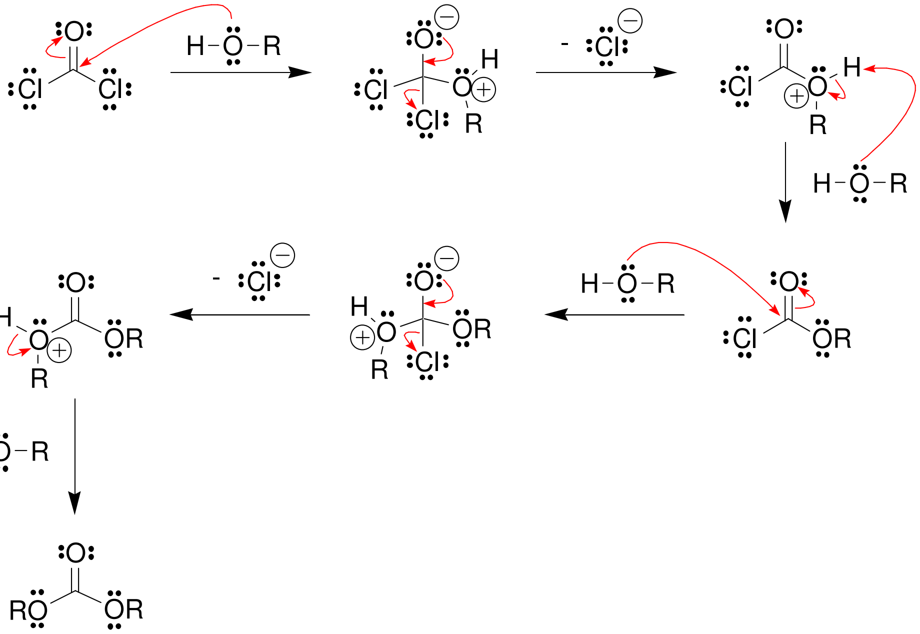


21.60.

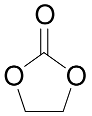


21.61.

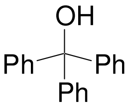
a)



b)

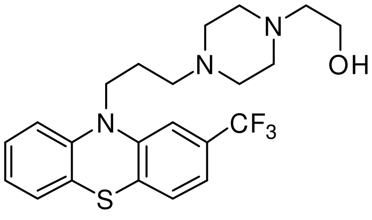


c)

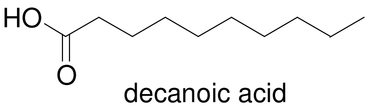


21.62.

a)

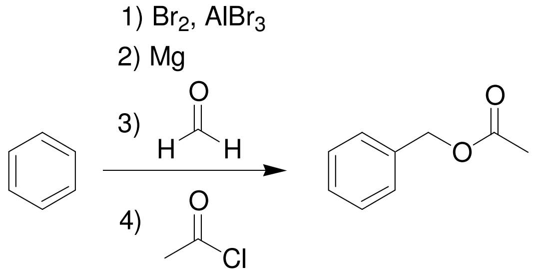


b)

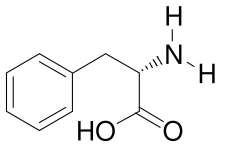


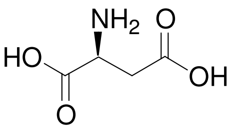
decanoic acid

21.63.



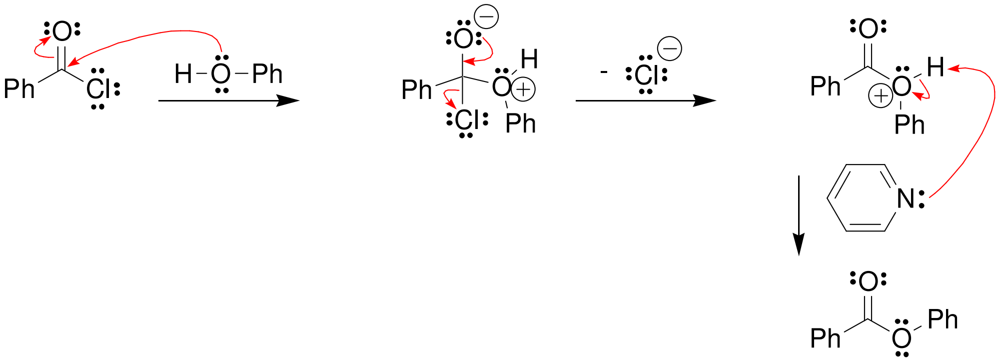
21.64.


phenylalanine

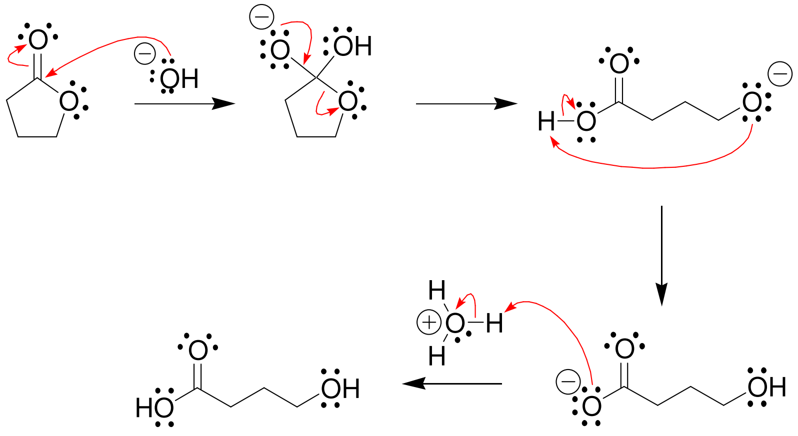

aspartic acid

21.65.

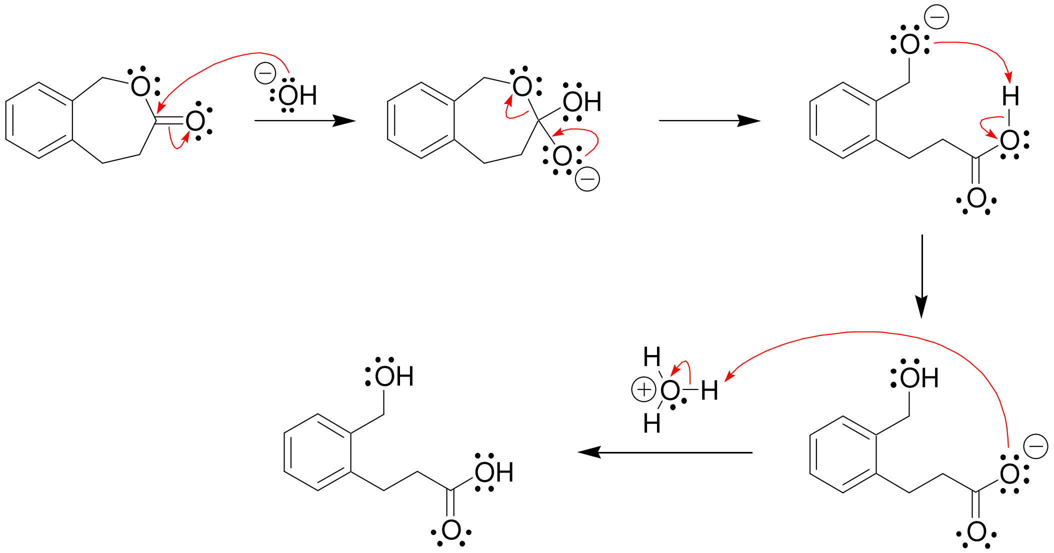
a)



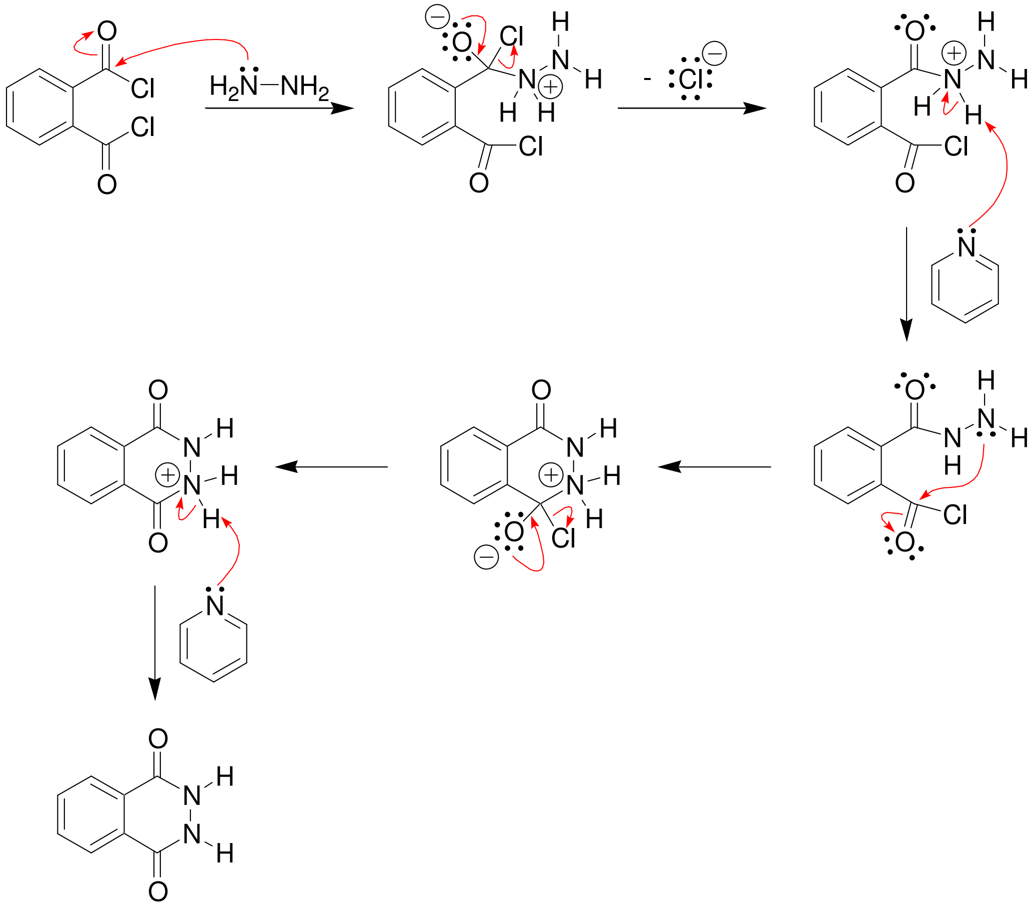
b)



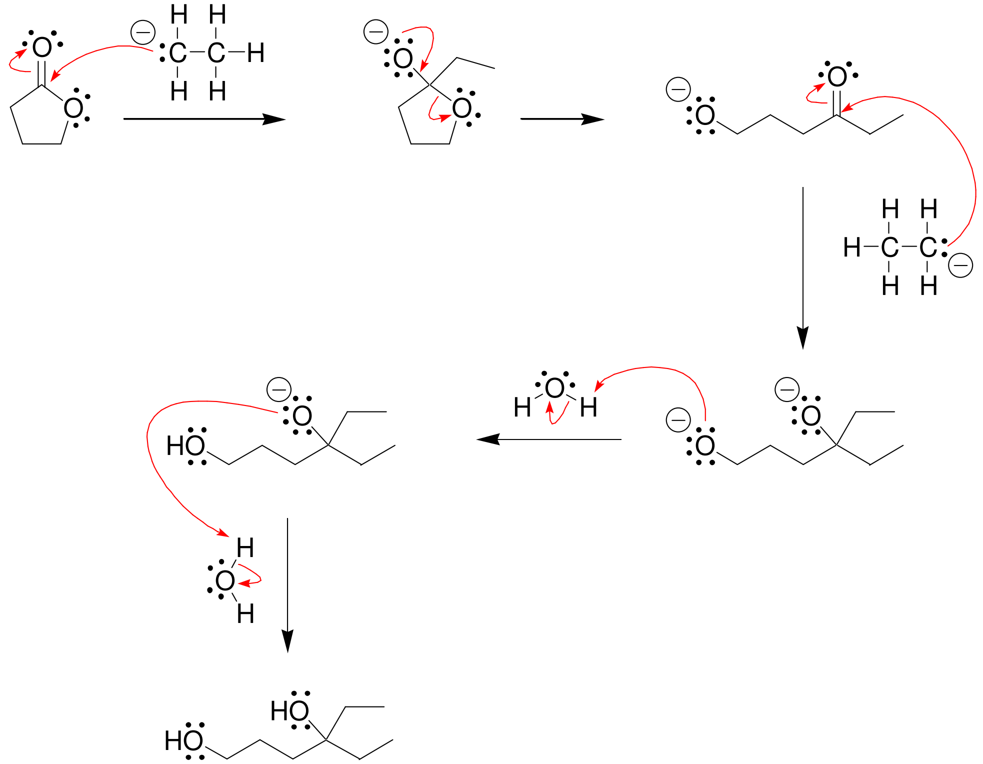
c)



d)

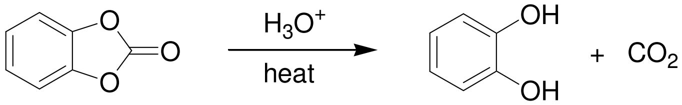


e)

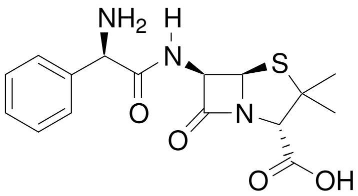


21.66. The three chlorine atoms withdraw electron density via induction. This effect renders the carbonyl group more electrophilic.

21.67.



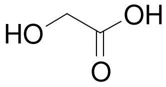
21.68



a)

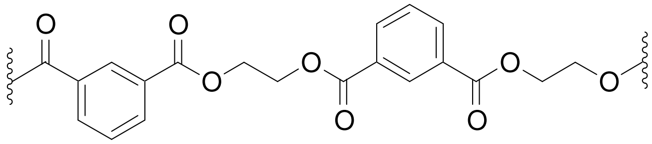
b) Ampicillin

21.69.

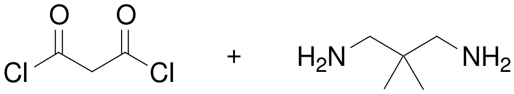


(glycolic acid)
hydroxyacetic acid

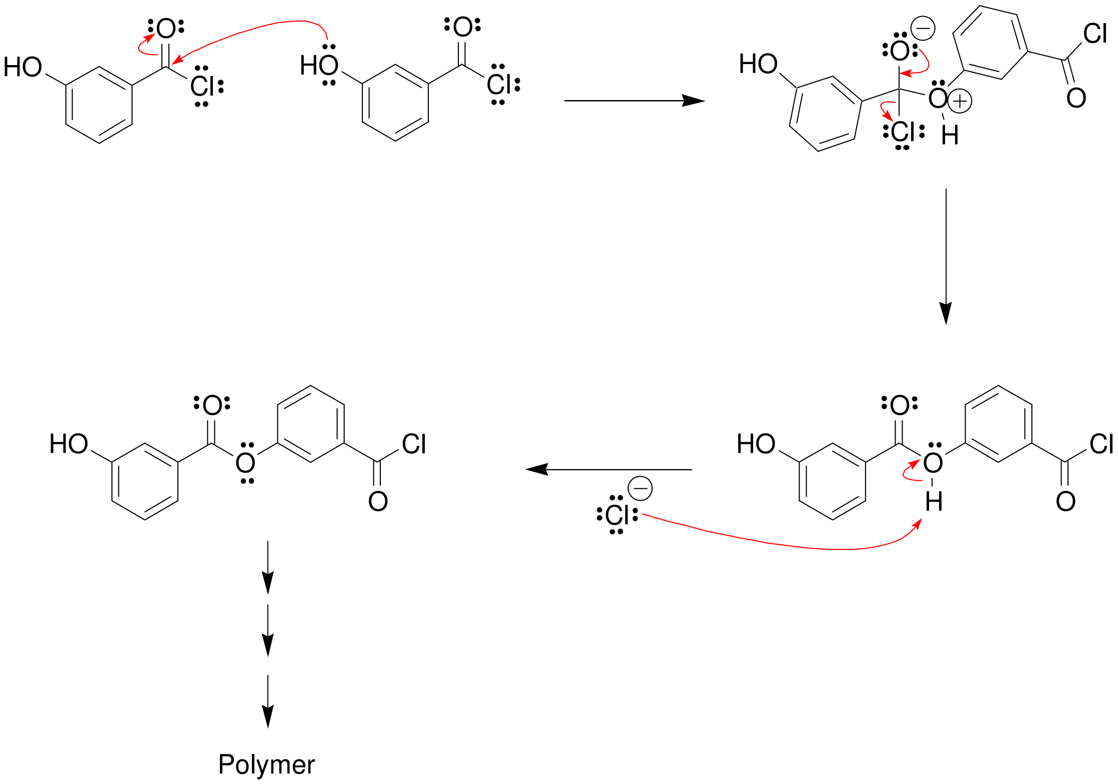
21.70.



21.71.

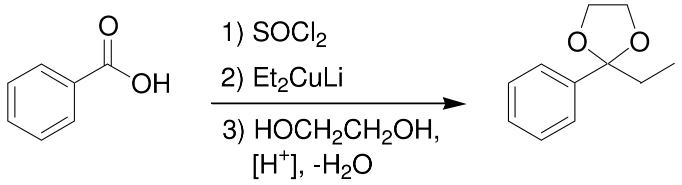


21.72.

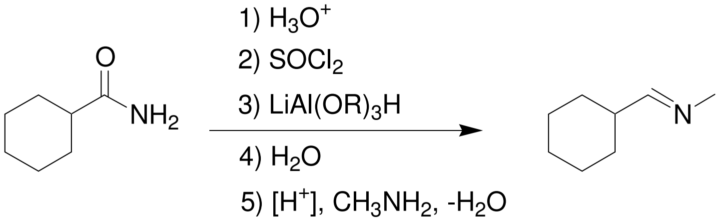


21.73.

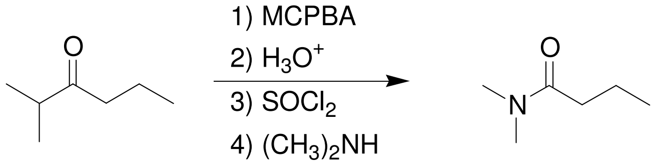
a)



b)



c)



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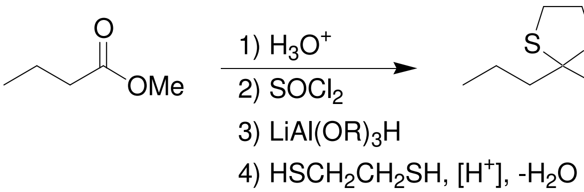
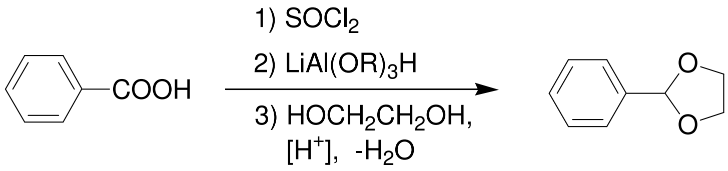
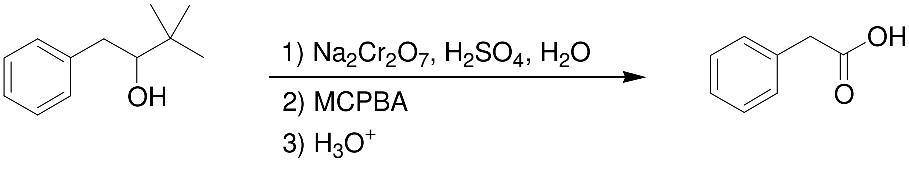


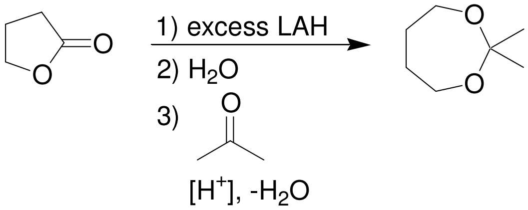
e)



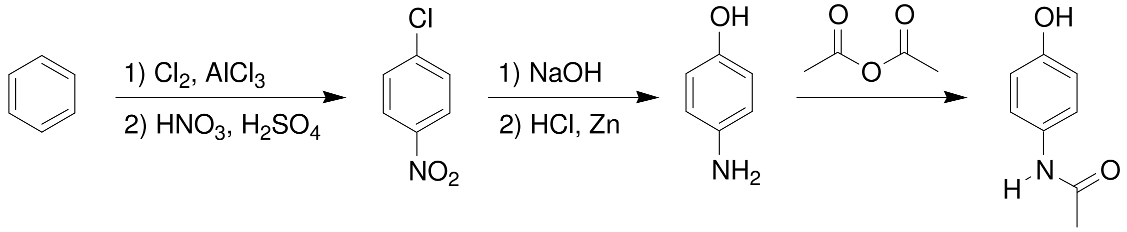
f)



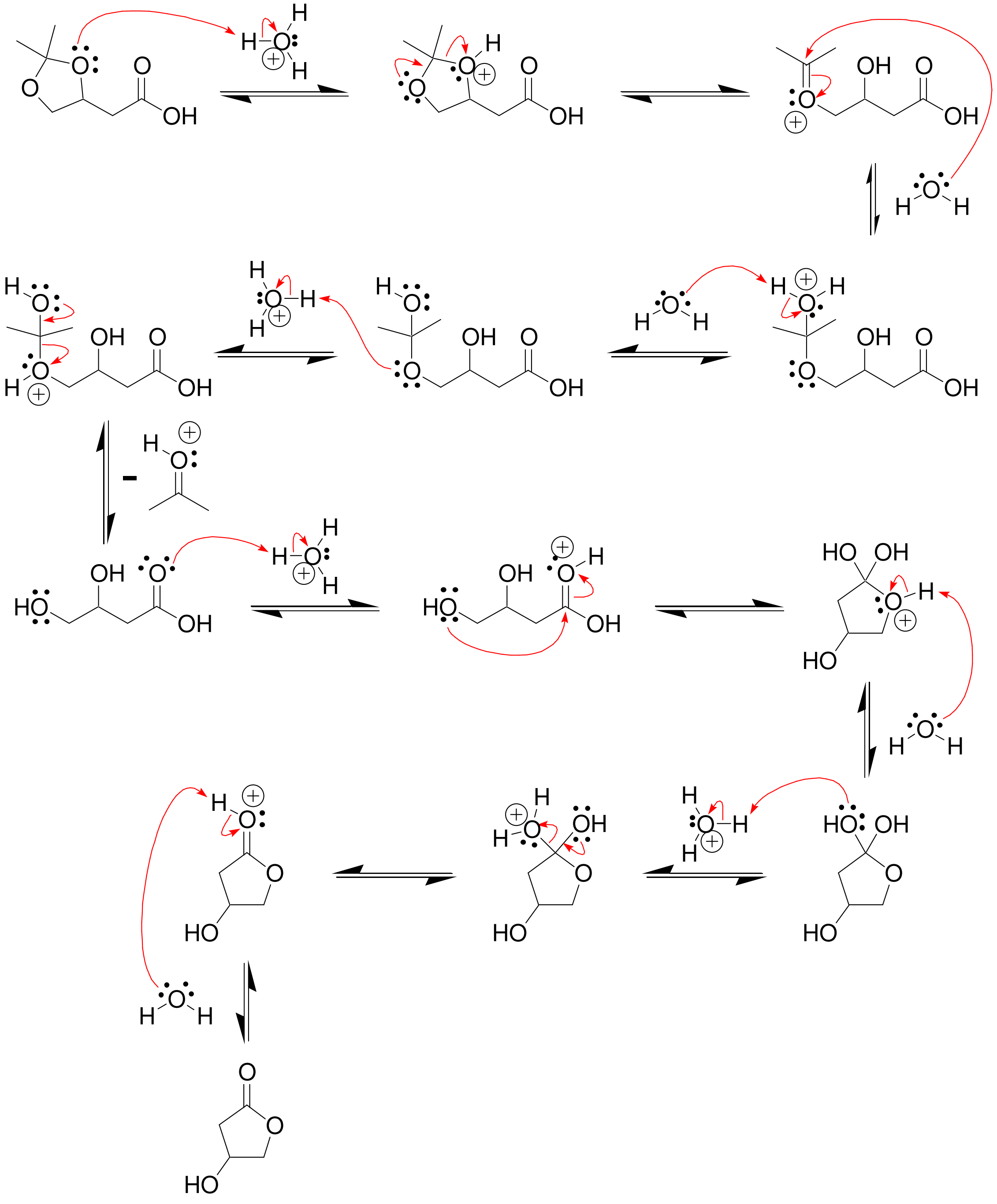
g)



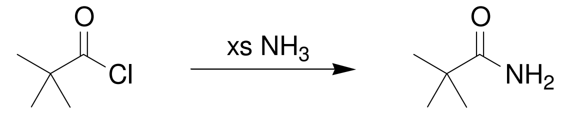
21.74.



21.75.

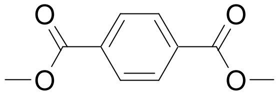


21.76.



Compound A

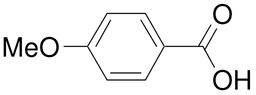
21.77.



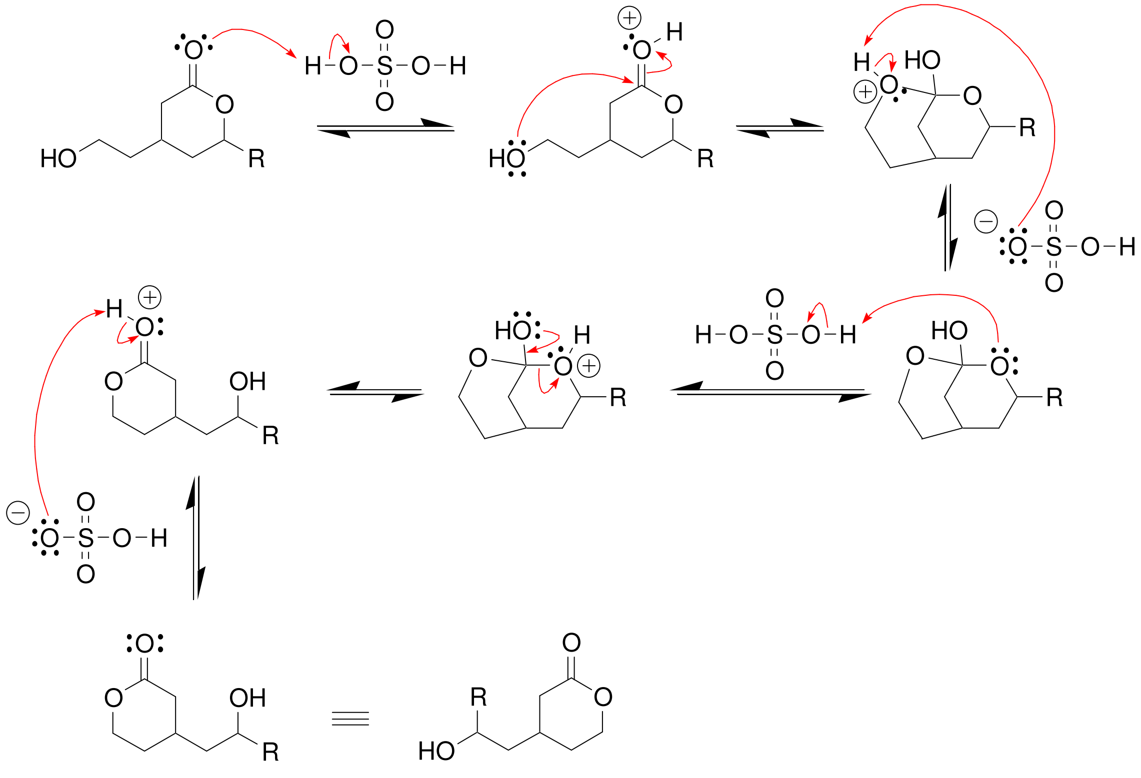
21.78. An IR spectrum of butyric acid should have a broad signal between 2500 cm^{-1} and 3600 cm^{-1}. An IR spectrum of ethyl acetate will not have this signal.

21.79. The ^{1}H NMR spectrum of *para*-chlorobenzaldehyde should have a signal at approximately 10 ppm corresponding to the aldehydic proton. The ^{1}H NMR spectrum of benzoyl chloride should not have a signal near 10 ppm.

21.80.



21.81. If the oxygen atom of the OH group in the starting material is an isotopic label, then we would expect the label to be incorporated into the ring of the product:



21.82. The lone pair of the nitrogen atom in this case is participating in resonance and is less available to donate electron density to the carbonyl group. As a result, the carbonyl group is more electrophilic than the carbonyl group of a regular amide (where the lone pair contributes significant electron density to the carbonyl group). Also, when this compound functions as an electrophile in a nucleophilic acyl substitution reaction, the leaving group is particularly stable because it is an aromatic anion. With a good leaving group, this compound more closely resembles the reactivity of an acid halide than an amide.

21.83.

a) DMF, like most amides, exhibits restricted rotation about the bond between the carbonyl group and the nitrogen atom. This restricted rotation causes the methyl groups to be in different electronic environments. They are not chemically equivalent, and will therefore produce two different signals (in addition to the signal from the other proton in the compound). Upon treatment with excess LAH followed by water, DMF is reduced to an amine that does not exhibit restricted rotation. As such, the methyl groups are now chemically equivalent and will together produce only one signal.

b) Restricted rotation causes the methyl groups to be in different electronic environments. As a result, the ^{13}C NMR spectrum of DMF should have three signals.