

Chapter 21 – Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

Chapter Outline

- I. Introduction to carboxylic acid derivatives (Sections 21.1 – 21.2).
 - A. Naming carboxylic acid derivatives (Section 21.1).
 1. Acid halides.
 - a. The acyl group is named first, followed by the halide.
 - b. For acyclic compounds, the *-ic acid* of the carboxylic acid name is replaced by *-yl*, followed by the name of the halide.
 - c. For cyclic compounds, the *-carboxylic acid* ending is replaced by *-carbonyl*, followed by the name of the halide.
 2. Acid anhydrides.
 - a. Symmetrical anhydrides are named by replacing *acid* by *anhydride*.
 - b. Unsymmetrical anhydrides are named by citing the two acids alphabetically, followed by *anhydride*.
 3. Amides.
 - a. Amides with an unsubstituted -NH_2 group are named by replacing *-oic acid* by *-amide* or by replacing *-carboxylic acid* with *-carboxamide*.
 - b. If nitrogen is substituted, the nitrogen substituents are named, and an *N-* is put before each.
 4. Esters.

Esters are named by first identifying the alkyl group and then the carboxylic acid group, replacing *-oic acid* by *-ate*.
 5. Thioesters.

Thioesters are named like esters, using the prefix *thio-* before the name of the carboxylic acid.
 6. Acyl phosphates.

Acyl phosphates are named by citing the acyl group and adding the word *phosphate*.
 - B. Nucleophilic acyl substitution reactions (Section 21.2).
 1. Mechanism of nucleophilic acyl substitution reactions.
 - a. A nucleophile adds to the polar carbonyl group.
 - b. The tetrahedral intermediate eliminates one of the two substituents originally bonded to it, resulting in a net substitution reaction.
 - c. Reactions of carboxylic acid derivatives take this course because one of the groups bonded to the carbonyl carbon is a good leaving group.
 - d. The addition step is usually rate-limiting.
 2. Relative reactivity of carboxylic acid derivatives.
 - a. Both steric and electronic factors determine relative reactivity.
 - i. Steric hindrance in the acyl group decreases reactivity.
 - ii. More polarized acid derivatives are more reactive than less polarized derivatives.
 - iii. The effect of substituents on reactivity is similar to their effect on electrophilic aromatic substitution reactions.
 - b. It is possible to convert more reactive derivatives into less reactive derivatives.
 - i. In order of decreasing reactivity: acid chlorides > acid anhydrides > thioesters > esters > amides.
 - ii. Only esters, amides, and carboxylic acids are found in nature.
 3. Kinds of reactions of carboxylic acid derivatives:
 - a. Hydrolysis: reaction with water to yield a carboxylic acid.
 - b. Alcoholysis: reaction with an alcohol to yield an ester.

- c. Aminolysis: reaction with ammonia or an amine to yield an amide.
 - d. Reduction.
 - i. Reaction with a hydride reducing agent yields an aldehyde or an alcohol.
 - ii Amides are reduced to yield amines.
 - e. Reaction with an organometallic reagent to yield a ketone or alcohol.
- II. Reactions of carboxylic acids and their derivatives (Section 21.3 – 21.9).
- A. Nucleophilic acyl substitution reactions of carboxylic acids (Section 21.3).
- 1. Carboxylic acids can be converted to acid chlorides by reaction with SOCl_2 .
The reaction proceeds through a chlorosulfite intermediate.
 - 2. Acid anhydrides are usually formed by heating the corresponding carboxylic acid to remove 1 equivalent of water.
 - 3. Conversion to esters.
 - a. Conversion can be effected by the $\text{S}_{\text{N}}2$ reaction of a carboxylate and an alkyl halide.
 - b. Esters can be produced by the acid-catalyzed reaction of a carboxylic acid and an alcohol.
 - i. This reaction is known as a Fischer esterification.
 - ii. Mineral acid makes the acyl carbon more reactive toward the alcohol.
 - iii. All steps are reversible.
 - iv. The reaction can be driven to completion by removing water or by using a large excess of alcohol.
 - v. Isotopic labelling studies have confirmed the mechanism.
 - 4. Conversion to amides.
 - a. Amides are difficult to form from carboxylic acids because amines convert carboxylic acids to carboxylate salts that no longer have electrophilic carbons.
 - b. The reagent DCC can be used; it is used in the laboratory to form peptide bonds.
 - 5. Reduction of carboxylic acids.
 - a. Reduction to alcohols can be achieved by use of LiAlH_4 .
 - b. BH_3 in THF easily reduces carboxylic acids to alcohols.
- B. Chemistry of carboxylic acid halides (Section 21.4).
- 1. Carboxylic acid halides are prepared by reacting carboxylic acids with either SOCl_2 or PBr_3 .
 - 2. Acyl halides are very reactive.
Most reactions occur by nucleophilic acyl substitution mechanisms.
 - 3. Hydrolysis.
 - a. Acyl halides react with water to form carboxylic acids.
 - b. The reaction mixture usually contains a base to scavenge the HCl produced.
 - 3. Anhydride formation.
Acid halides react with carboxylate ions to form anhydrides.
 - 4. Alcoholysis.
 - a. Acyl halides react with alcohols to form esters.
 - b. Base is usually added to scavenge the HCl produced.
 - c. Primary alcohols are more reactive than secondary or tertiary alcohols.
It's often possible to esterify a less hindered alcohol selectively.
 - 5. Aminolysis.
 - a. Acid chlorides react with ammonia and amines to give amides.
 - b. Either two equivalents of ammonia/amine must be used, or NaOH must be present, in order to scavenge HCl .
 - 6. Reduction.
 LiAlH_4 reduces acid halides to alcohols.
The reaction is a substitution of H^- for Cl^- that proceeds through an intermediate aldehyde, which is then reduced.

7. Reaction with organometallic reagents.
 - a. Reaction with Grignard reagents yields tertiary alcohols and proceeds through an intermediate ketone.
 - b. Reaction with organocopper reagents yields ketones.
 - i. Reaction occurs by a radical mechanism.
 - ii. This reaction doesn't occur with other carboxylic acid derivatives.
- C. Chemistry of carboxylic acid anhydrides (Section 21.5).
 1. Acid anhydrides can be prepared by reaction of carboxylate anions with acid chlorides.

Both symmetrical and unsymmetrical anhydrides can be prepared by this route.
 2. Acid anhydrides react more slowly than acid chlorides.
 - a. Acid anhydrides undergo most of the same reactions as acid chlorides.
 - b. Acetic anhydride is often used to prepare acetate esters.
 - c. In reactions of acid anhydrides, half of the molecule is unused, making anhydrides inefficient to use.
- D. Chemistry of esters (Section 21.6).
 1. Esters can be prepared by:
 - a. S_N2 reaction of a carboxylate anion with an alkyl halide.
 - b. Fischer esterification.
 - c. Reaction of an acid chloride with an alcohol, in the presence of base.
 2. Esters are less reactive than acid halides and anhydrides but undergo the same types of reactions.
 3. Hydrolysis.
 - a. Basic hydrolysis (saponification) occurs through a nucleophilic acyl substitution mechanism.
 - i. Loss of alkoxide ion yields a carboxylic acid which is deprotonated to give a carboxylate anion.
 - ii. Isotope-labelling studies confirm this mechanism.
 - b. Acidic hydrolysis can occur by more than one mechanism.

The usual route is by the reverse of Fischer esterification.
 4. Aminolysis.

Esters can be converted to amides by heating with ammonia/amines, but it's easier to start with an acid chloride.
 5. Reduction.
 - a. $LiAlH_4$ reduces esters to primary alcohols by a route similar to that described for acid chlorides.
 - b. If DIBAL at -78°C is used, reduction yields an aldehyde.
 6. Reaction with Grignard reagents.

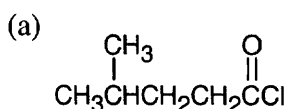
Esters react twice with Grignard reagents to produce tertiary alcohols containing two identical substituents.
- E. Chemistry of amides (Section 21.7).
 1. Amides are prepared by the reaction of acid chlorides with ammonia/amines.
 2. Hydrolysis.
 - a. Hydrolysis occurs under more severe conditions than needed for hydrolysis of other acid derivatives.
 - b. Acid hydrolysis occurs by addition of water to a protonated amide, followed by loss of ammonia or an amine.
 - c. Basic hydrolysis occurs by attack of HO^- , followed by loss of $^-\text{NH}_2$.
 3. Reduction.

$LiAlH_4$ reduces amides to amines.

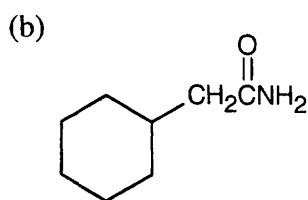
- F. Thiol esters and acyl phosphates (Section 21.8).
1. Nature uses thiol esters and acyl phosphates in nucleophilic acyl substitution reactions because they are intermediate in reactivity between acid anhydrides and esters.
 2. Acetyl CoA is used as an acylating agent.
- III. Polyamides and polyesters (Section 21.9).
- A. Formation of polyesters and polyamides.
1. When a diamine and a diacid chloride react, a polyamide is formed.
 2. When a diacid and a diol react, a polyester is formed.
 3. These polymers are called step-growth polymers because each bond is formed independently of the others.
- B. Types of polymers.
1. Nylons are the most common polyamides.
 2. The most common polyester, Dacron, is formed from dimethylterephthalate and ethylene glycol.
 3. Biodegradable polymers are usually polyesters of naturally-occurring hydroxycarboxylic acids.
- IV. Spectroscopy of carboxylic acid derivatives and nitriles (Section 21.10).
- A. Infrared spectroscopy.
- All of these compounds have characteristic carbonyl absorptions that help identify them; these are listed in Table 21.3.
- B. NMR spectroscopy is of limited usefulness in distinguishing carboxylic acid derivatives.
1. Hydrogens next to carbonyl groups absorb at around 2.1 δ in a ^1H NMR spectrum, but this absorption can't be used to distinguish among carboxylic acid derivatives.
 2. Carbonyl carbons absorb in the range 160–180 δ , but, again, this absorption can't be used to distinguish among carboxylic acid derivatives.

Solutions to Problems

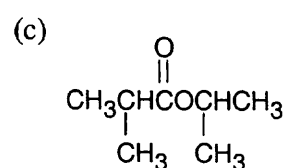
21.1 Table 21.1 lists the suffixes for naming carboxylic acid derivatives. The suffixes used when the functional group is part of a ring are in parentheses.



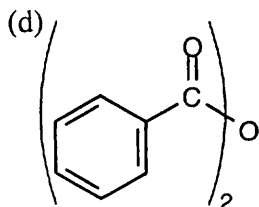
4-Methylpentanoyl chloride



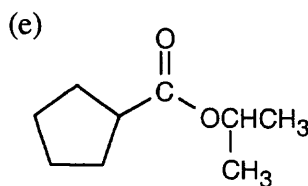
Cyclohexylacetamide



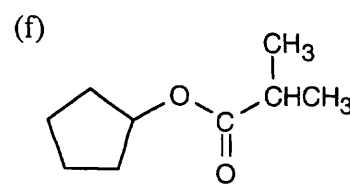
Isopropyl 2-methylpropanoate



Benzoic anhydride

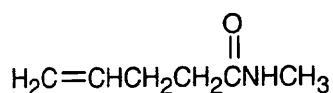


Isopropyl cyclopentanecarboxylate

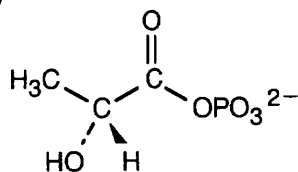


Cyclopentyl 2-methylpropanoate

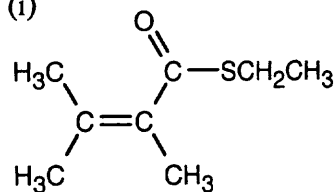
(g)

***N*-Methyl-4-pentenamide**

(h)

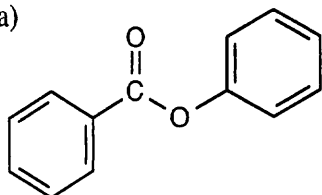
**(*R*)-2-Hydroxypropanoyl phosphate**

(i)

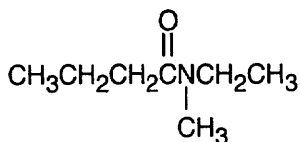
**Ethyl 2,3-dimethyl-2-butenethioate**

21.2

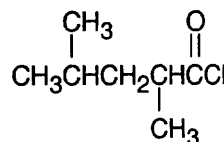
(a)

**Phenyl benzoate**

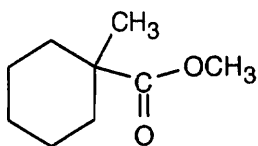
(b)

***N*-Ethyl-*N*-methylbutanamide**

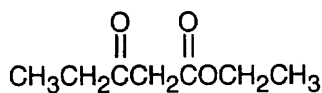
(c)

**2,4-Dimethyl-pentanoyl chloride**

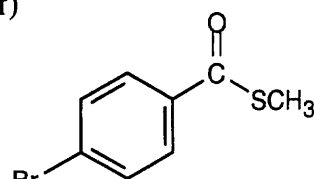
(d)

**Methyl 1-methylcyclohexanecarboxylate**

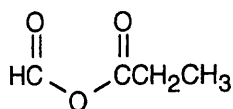
(e)

**Ethyl-3-oxopentanoate**

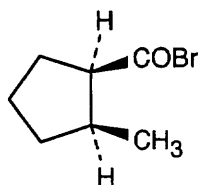
(f)

**Methyl *p*-bromobenzenethioate**

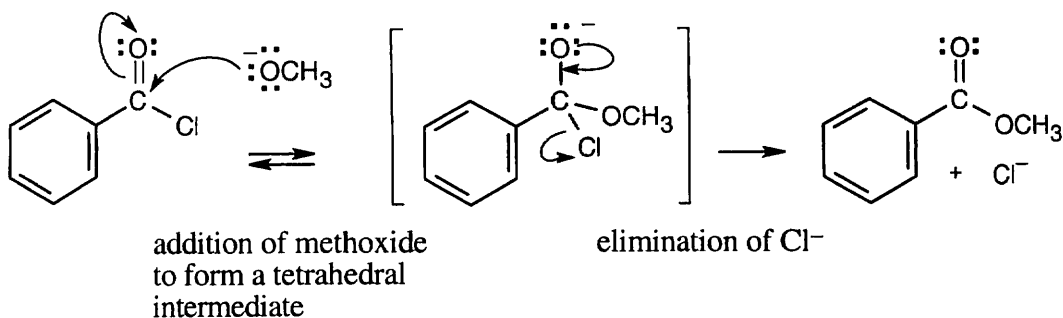
(g)

**Formic propanoic anhydride**

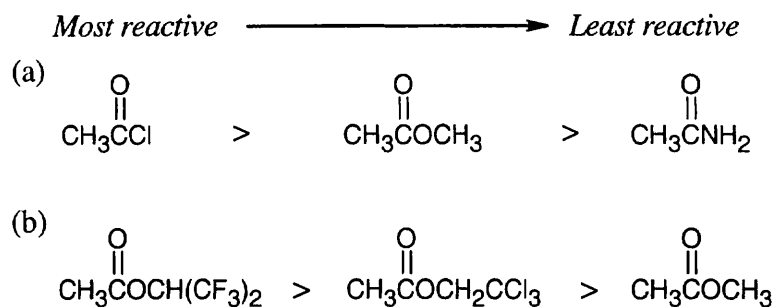
(h)

***cis*-2-Methylcyclopentanecarbonyl bromide**

21.3



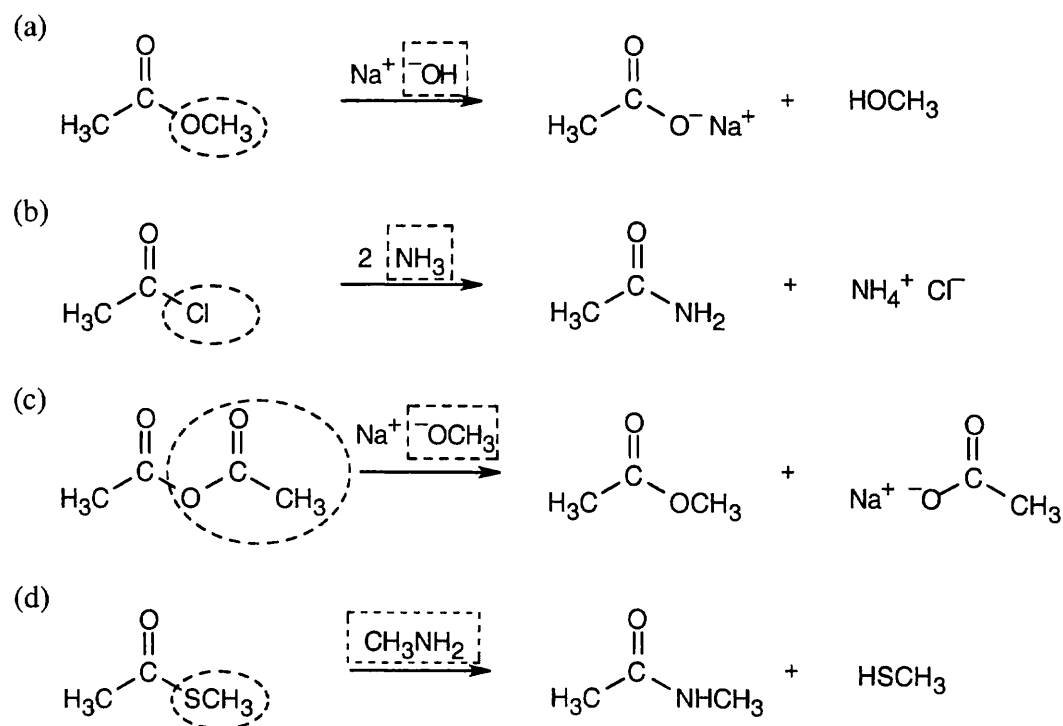
21.4



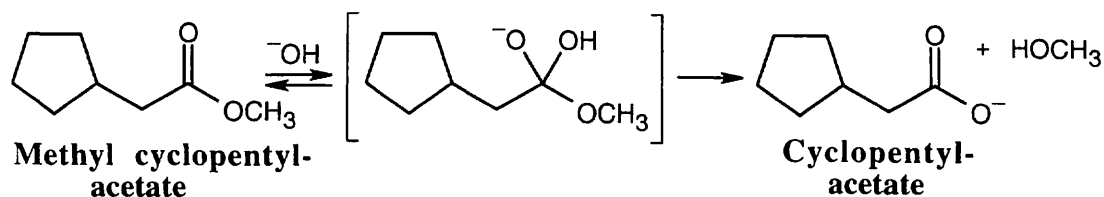
The most reactive acyl derivatives contain strongly electron-withdrawing groups in the part of the structure that is to be the leaving group.

21.5 Strategy: Identify the nucleophile (boxed) and the leaving group (circled), and replace the leaving group by the nucleophile in the product.

Solution:

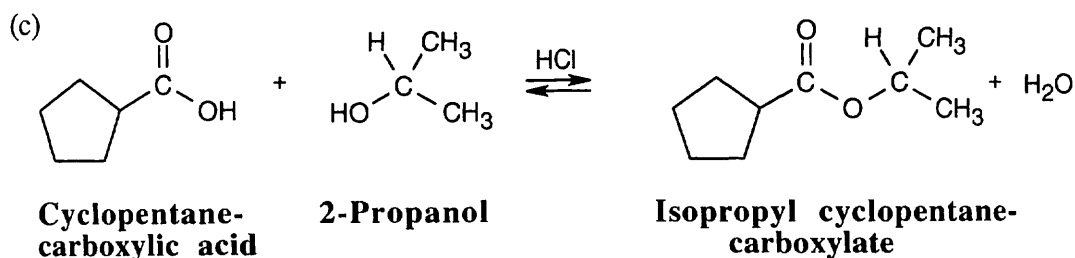
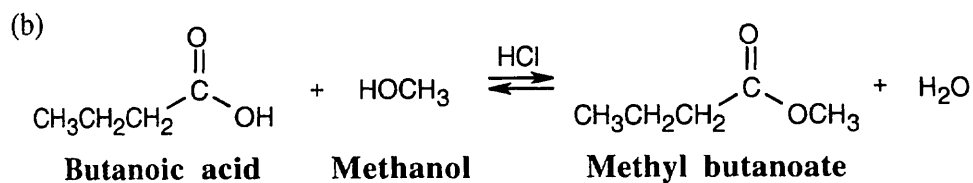
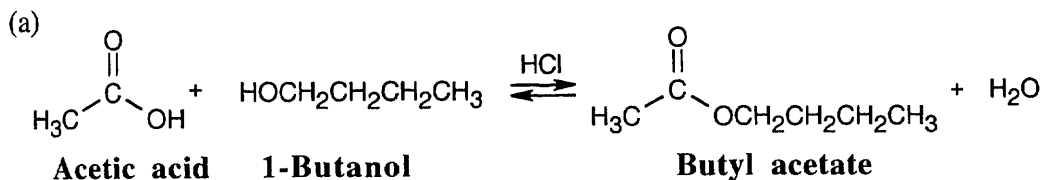


21.6 The structure represents the tetrahedral intermediate in the reaction of methyl cyclopentylacetate with hydroxide, a nucleophile. The products are cyclopentylacetate anion and methanol.

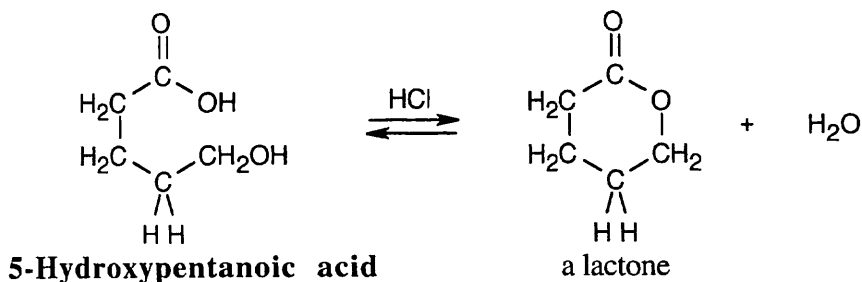


21.7 Strategy: In Fischer esterification, an alcohol undergoes a nucleophilic acyl substitution with a carboxylic acid to yield an ester. The mineral acid catalyst makes the carboxyl group of the acid more electrophilic. Predicting the products is easier if the two reagents are positioned so that the reacting functional groups point towards each other.

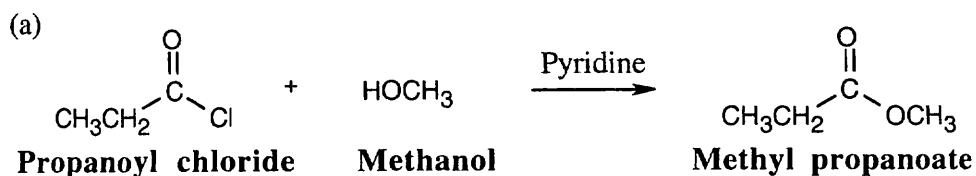
Solution:

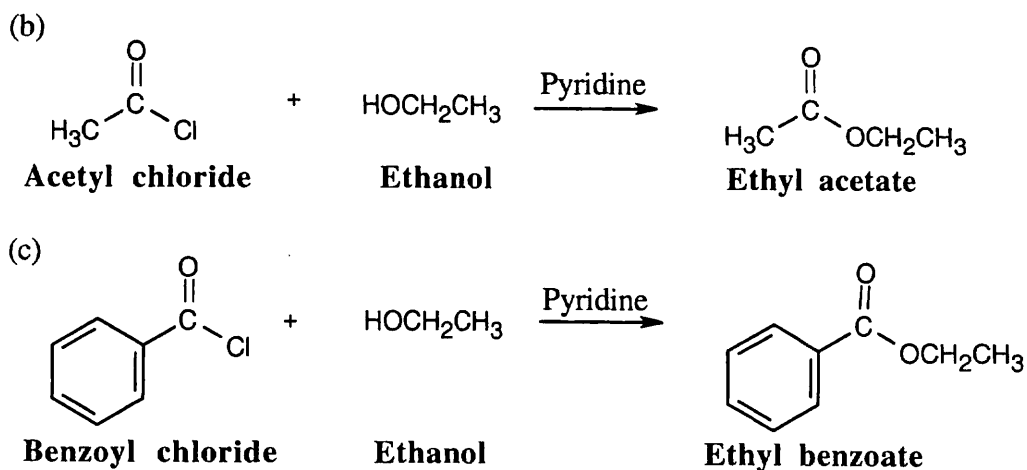


21.8 Under Fischer esterification conditions, many hydroxycarboxylic acids can form intramolecular esters (lactones).

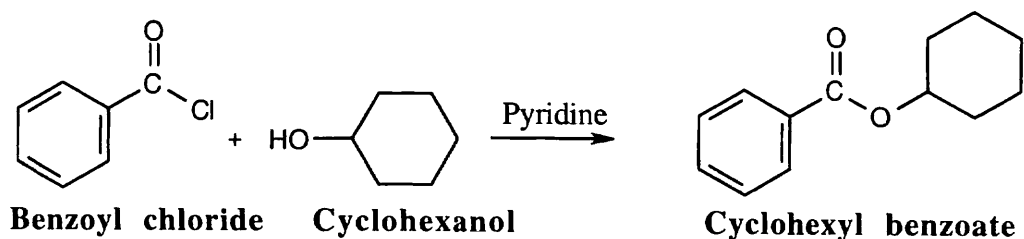


21.9 Pyridine neutralizes the HCl byproduct by forming pyridinium chloride. This neutralization removes from the product mixture acid that might cause side reactions. As mentioned previously, positioning the reacting groups so that they face each other makes it easier to predict the products.

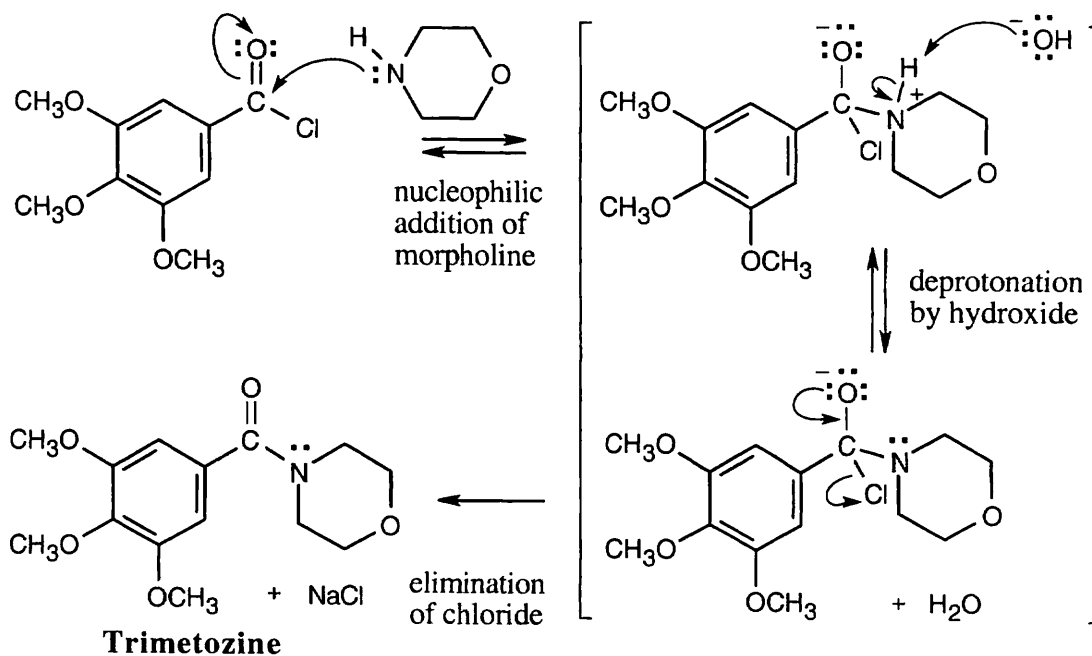




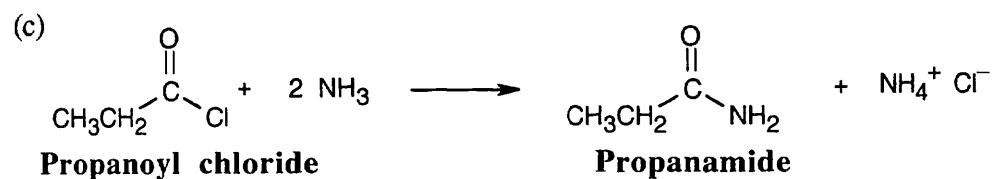
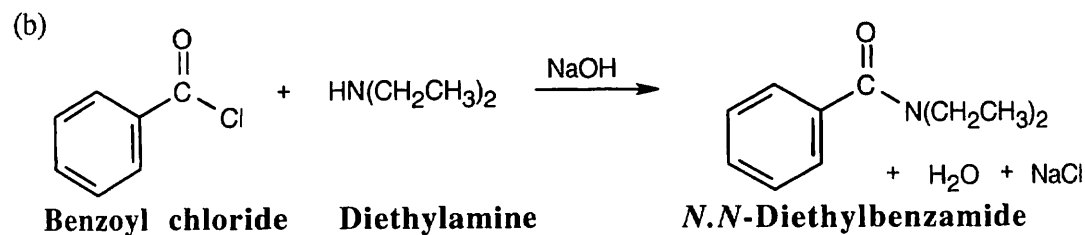
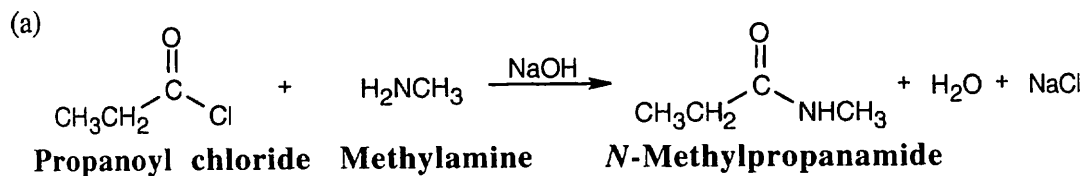
21.10 As explained in the text, only simple, low boiling alcohols are convenient to use in the Fischer esterification reaction. Thus, reaction of cyclohexanol with benzoyl chloride is the preferred method for preparing cyclohexyl benzoate.



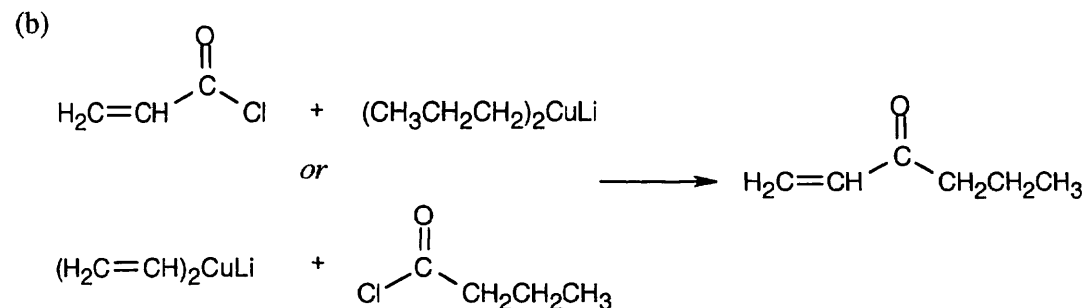
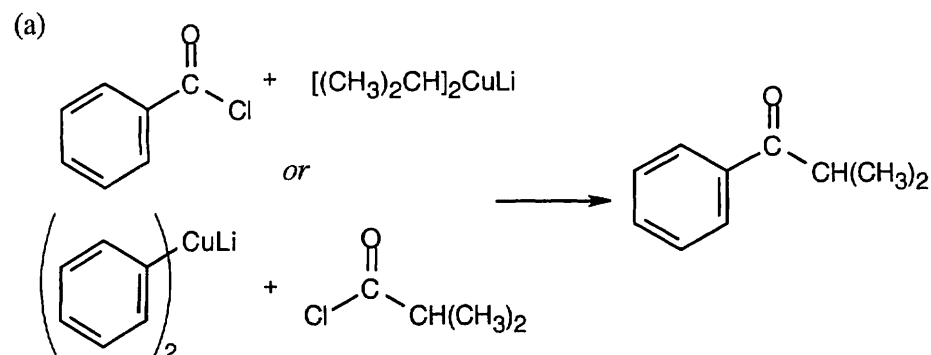
21.11



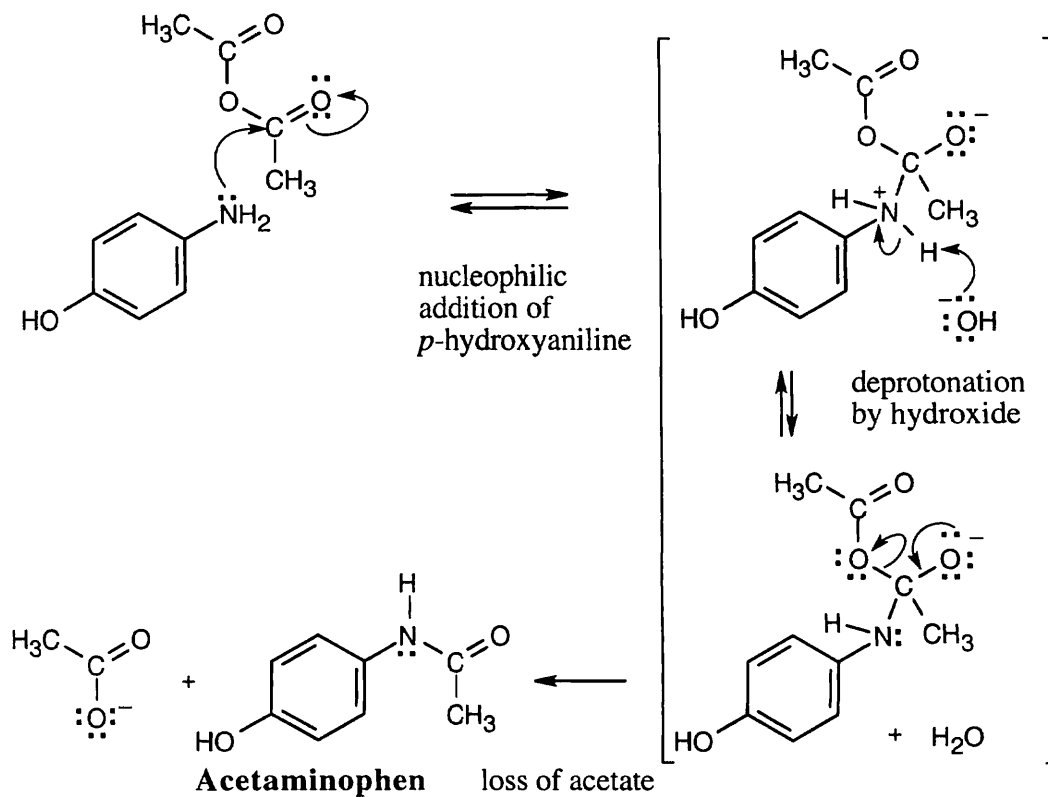
21.12 An extra equivalent of base must be added to neutralize the acid produced in these reactions. In (a) and (b), two equivalents of the amine may be used in place of NaOH.



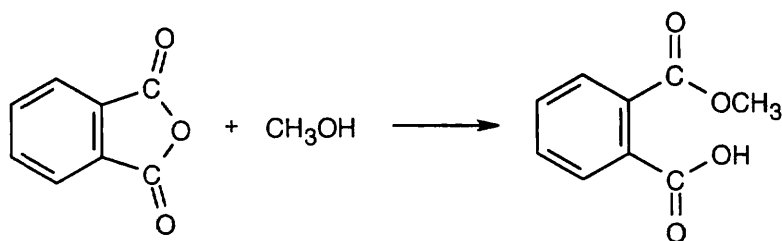
21.13 Two combinations of acid chloride and organocopper reagent are possible.



21.14



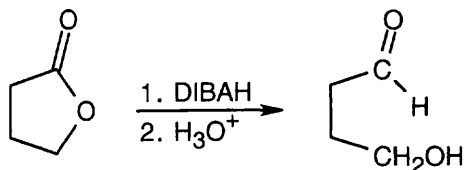
21.15

**Phthalic anhydride**

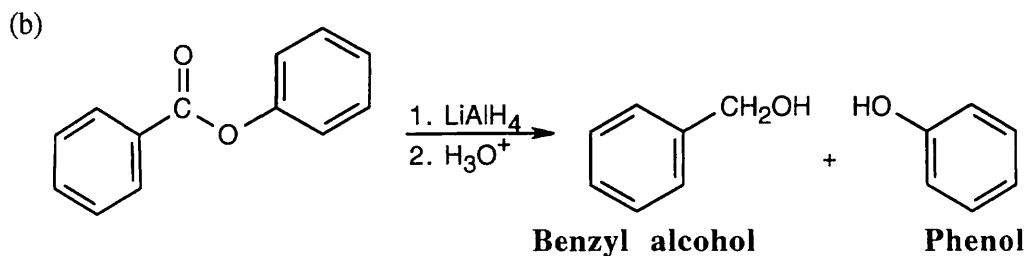
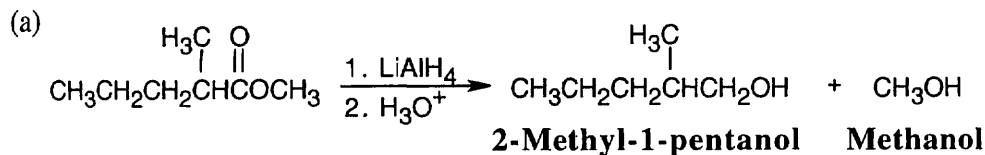
The second half of the anhydride becomes a carboxylic acid.

21.16 Acidic hydrolysis of an ester is a reversible reaction because the products are an alcohol and a carboxylic acid. Basic hydrolysis of an ester is irreversible because its products are an alcohol and a carboxylate anion, which has a negative charge and does not react with nucleophiles.

21.17

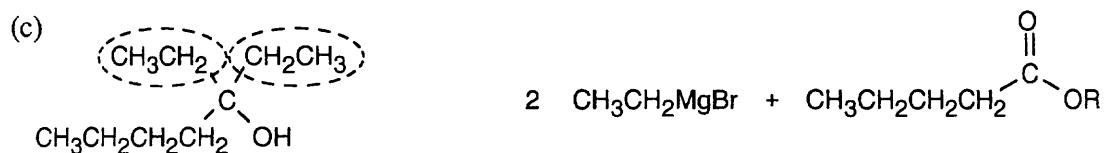
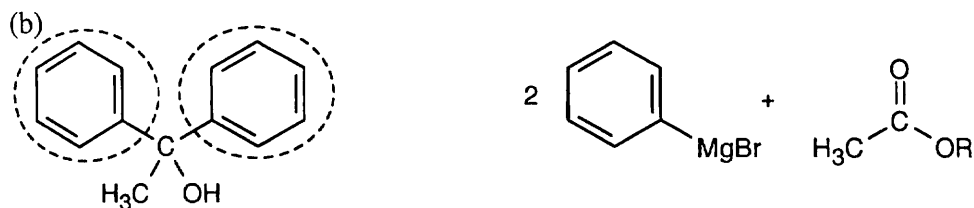
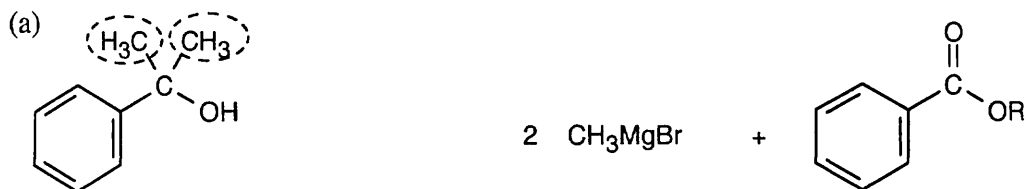
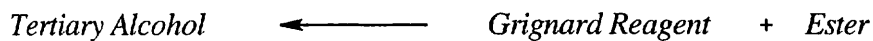


21.18 Lithium aluminum hydride reduces an ester to form two alcohols.

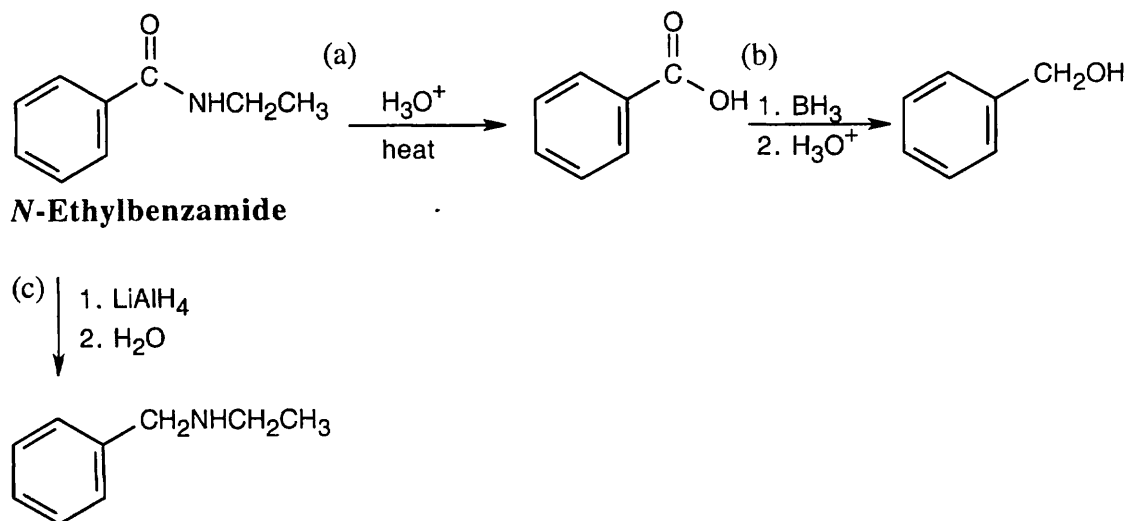


21.19 **Strategy:** Remember that Grignard reagents can only be used with esters to form a tertiary alcohol that has two identical substituents. Identify these two substituents, which come from the Grignard reagent, and work backward to select the ester (the alkyl group of the ester is unimportant).

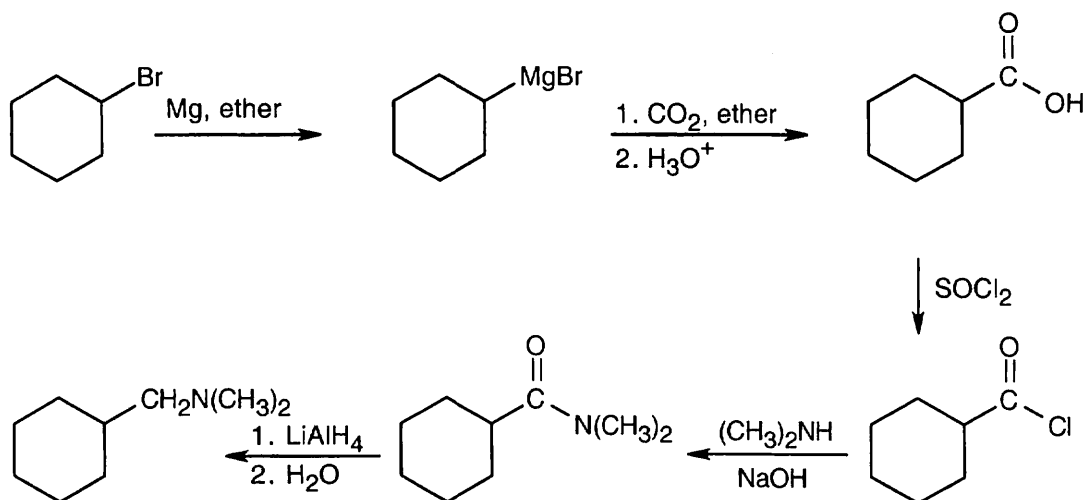
Solution:



21.20

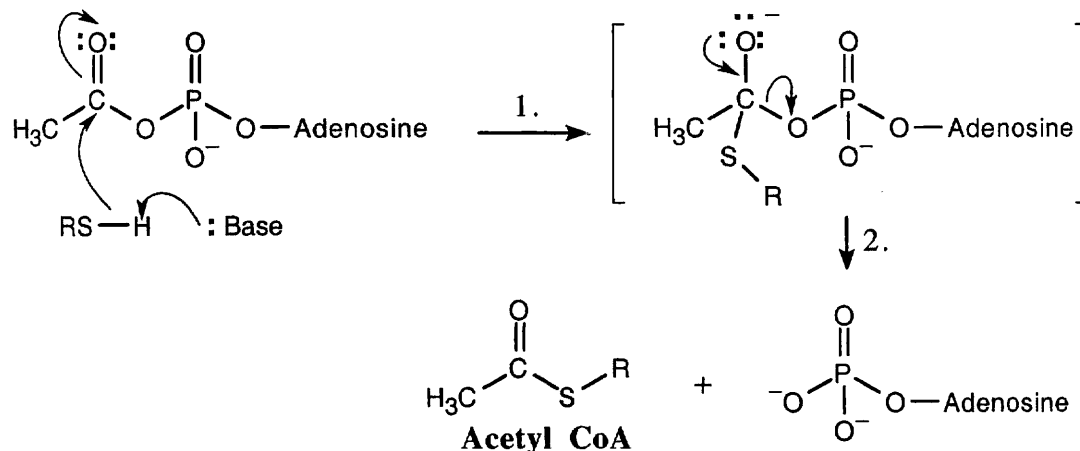


21.21



The product is a *N,N*-disubstituted amine, which can be formed by reduction of an amide. The amide results from treatment of an acid chloride with the appropriate amine. The acid chloride is the product of the reaction of SOCl_2 with a carboxylic acid that is formed by carboxylation of the Grignard reagent synthesized from the starting material.

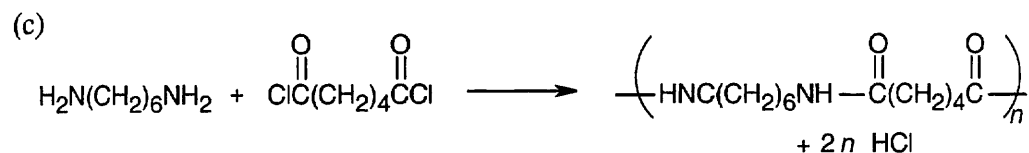
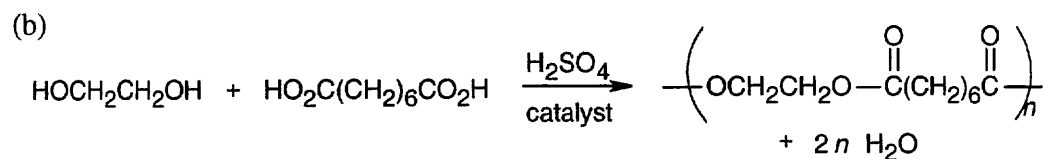
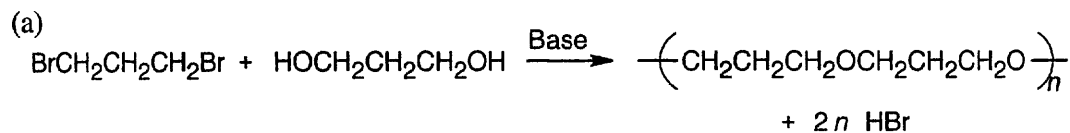
21.22 Even though the entire molecule of coenzyme A is biologically important, we are concerned in this problem only with the $-\text{SH}$ group. The remainder of the structure is represented here as "R".



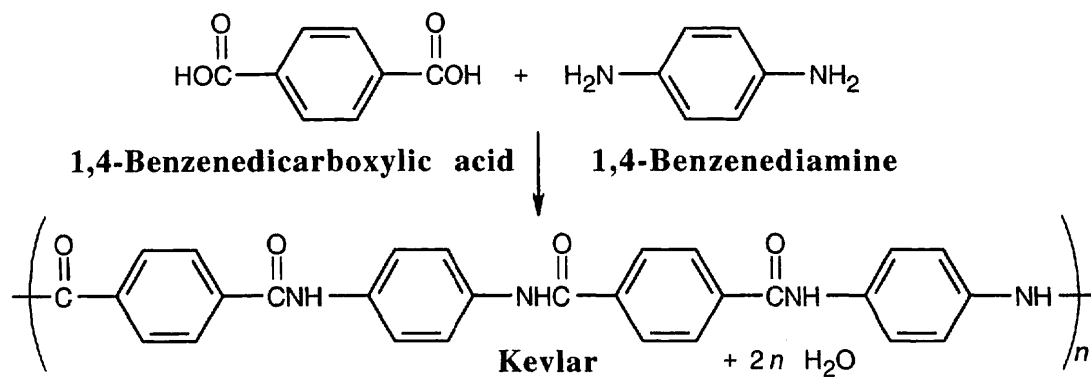
Step 1: Nucleophilic addition of the $-\text{SR}$ group of CoA (after deprotonation) to acetyl adenylate to form a tetrahedral intermediate.

Step 2: Loss of adenosine monophosphate.

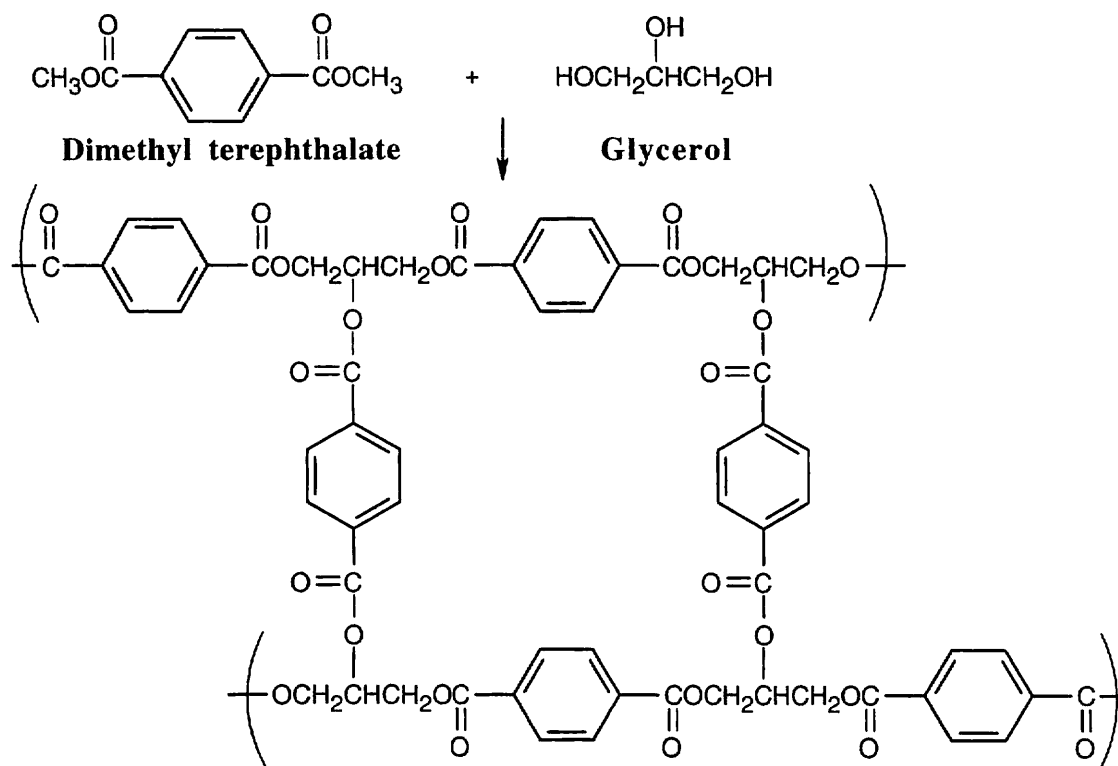
21.23 In each example, if n molecules of one component react with n molecules of the other component, a polymer with n repeating units is formed, and $2n$ small molecules are formed as byproducts; these are shown in each reaction.



21.24



21.25



The product of the reaction of dimethyl terephthalate with glycerol has a high degree of cross-linking and is more rigid than Dacron.

21.26 Use Table 21.3 if you need help.

Absorption

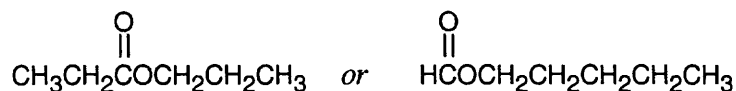
- (a) 1735 cm^{-1}
 (b) 1810 cm^{-1}
 (c) $2500 - 3300\text{ cm}^{-1}$ and 1710 cm^{-1}
 (d) 1715 cm^{-1}

Functional group present

- Saturated ester *or* 6-membered ring lactone
 Saturated acid chloride
 Carboxylic acid
 Saturated ketone *or* 6-membered ring ketone

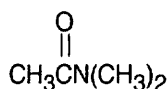
21.27 (a) IR 1735 cm^{-1} corresponds to a saturated ester.

The remaining five carbons and twelve hydrogens can be arranged in a number of ways to produce a structure for this compound. For example:

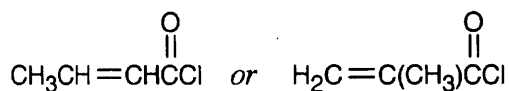


The structural formula indicates that this compound can't be a lactone.

(b)



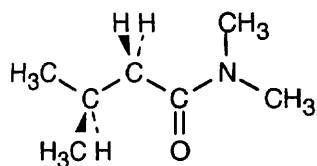
(c)



Visualizing Chemistry

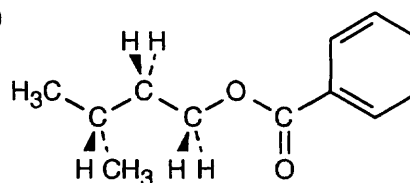
21.28

(a)



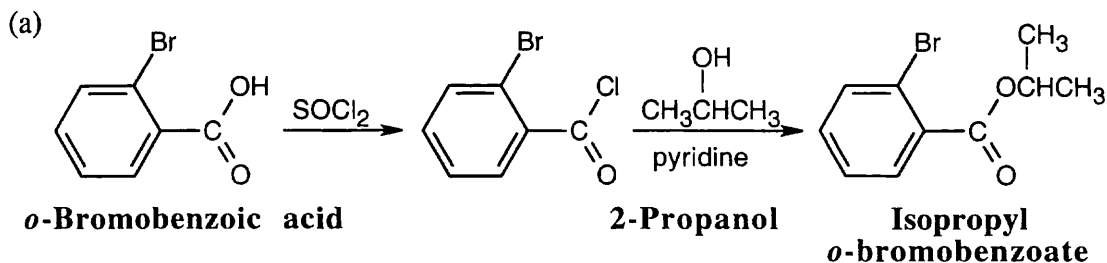
***N,N*-Dimethyl-3-methylbutanamide**

(b)

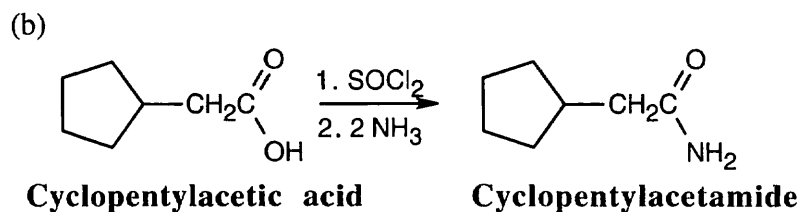


3-Methylbutyl benzoate

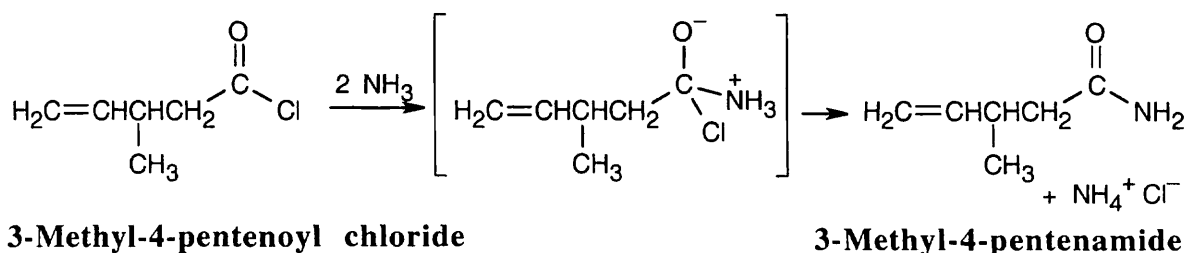
21.29



This compound can also be synthesized by Fischer esterification of *o*-bromobenzoic acid with 2-propanol and an acid catalyst.

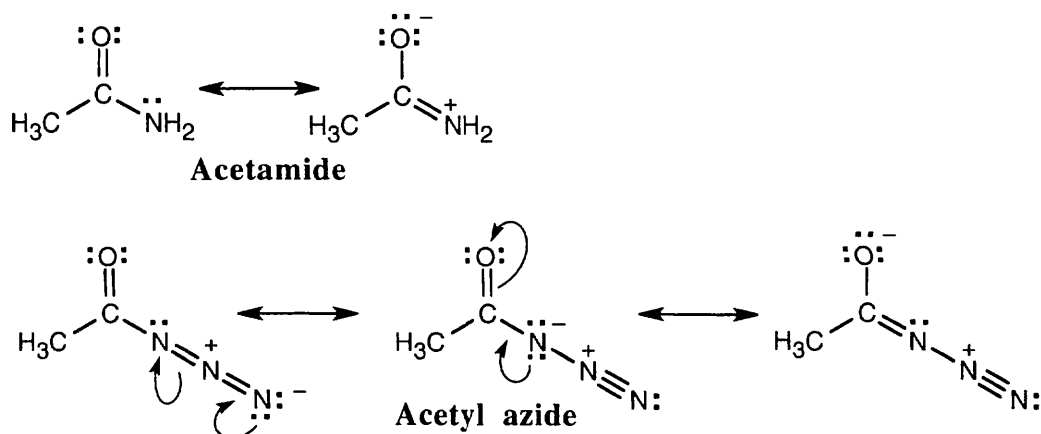


21.30



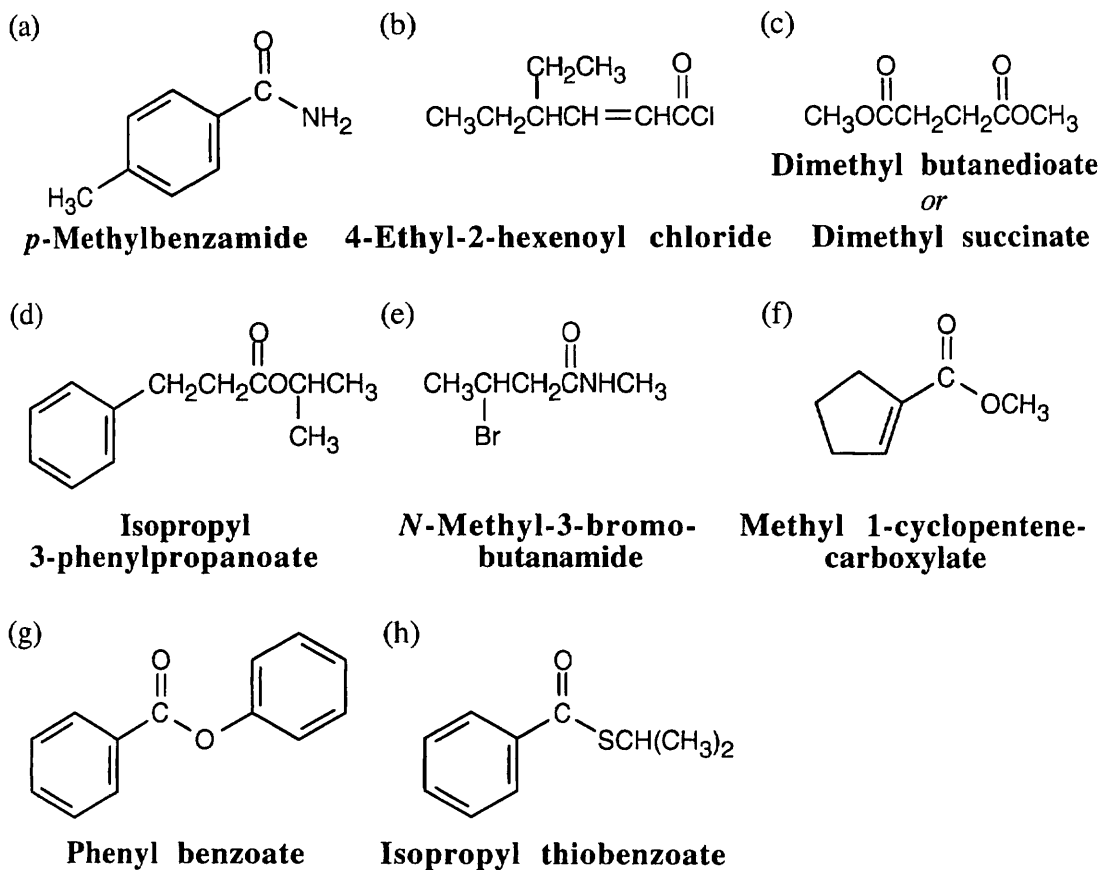
The starting material is 3-methyl-4-pentenoyl chloride. Ammonia adds to give the observed tetrahedral intermediate, which eliminates Cl^- to yield the above amide.

21.31 According to the electrostatic potential maps, the carbonyl carbon of acetyl azide is more electron-poor and therefore more reactive in nucleophilic acyl substitution reactions. Resonance donation of nitrogen lone-pair electrons to the carbonyl group is greater in an amide than in an acyl azide.

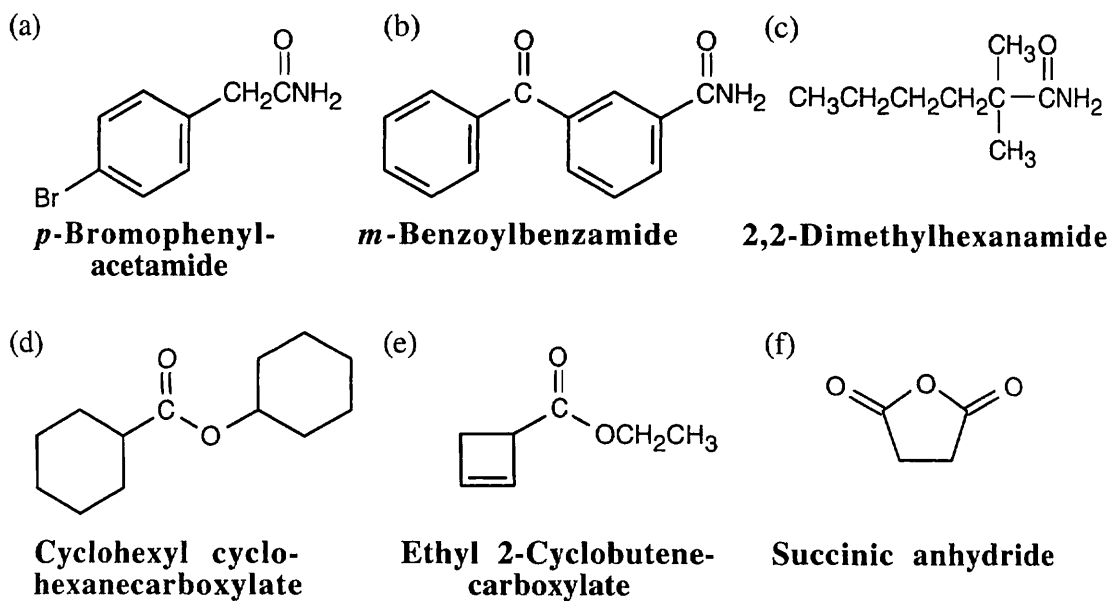


Additional Problems

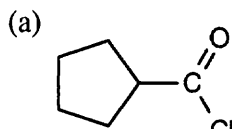
21.32



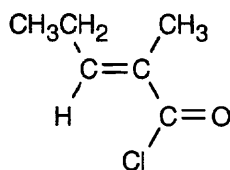
21.33



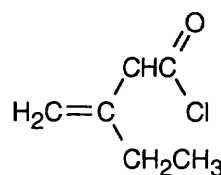
21.34 Many structures can be drawn for each part of this problem.



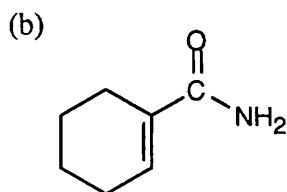
Cyclopentanecarbonyl chloride



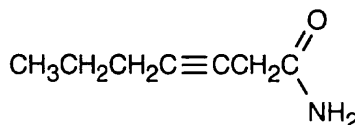
E-2-Methyl-2-pentenoyl chloride



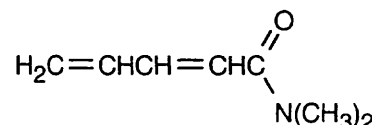
3-Ethyl-3-butenoyl chloride



1-Cyclohexenecarboxamide

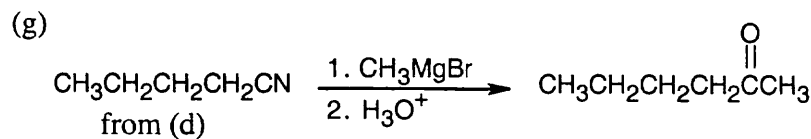
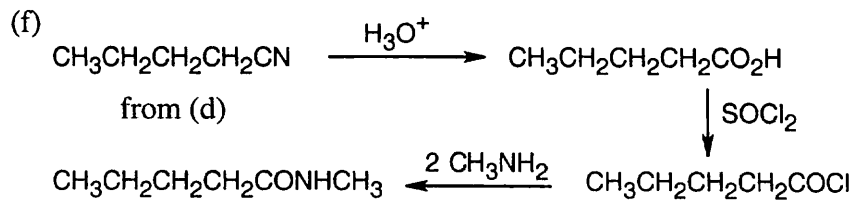
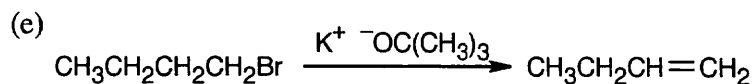
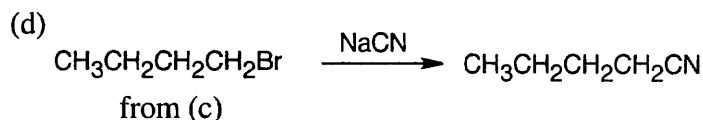
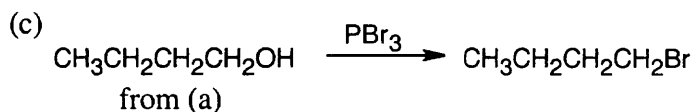
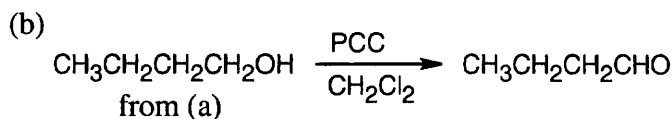
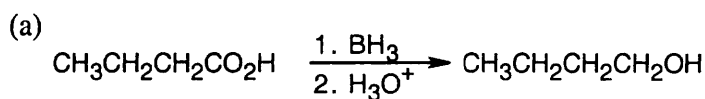


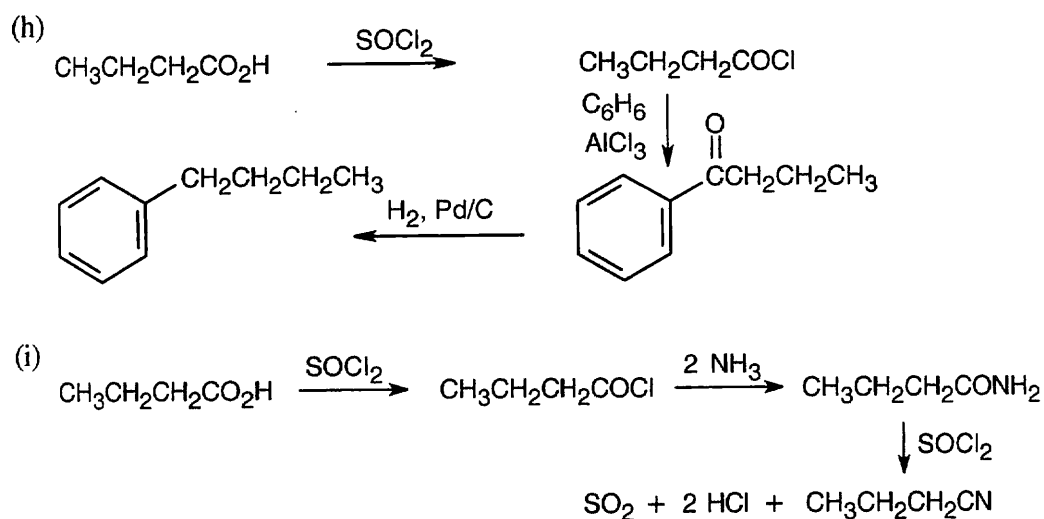
3-Heptynamide



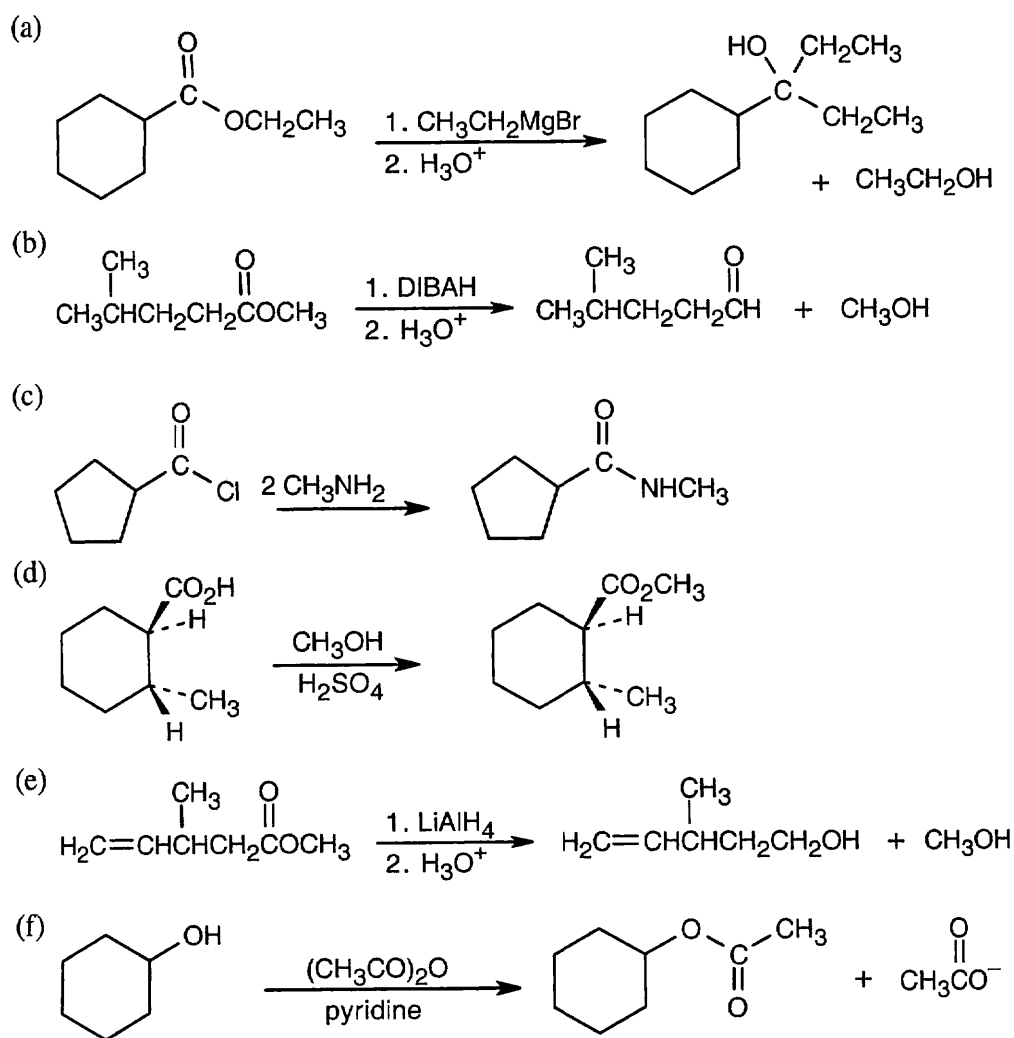
N,N-Dimethyl-2,4-pentadienamide

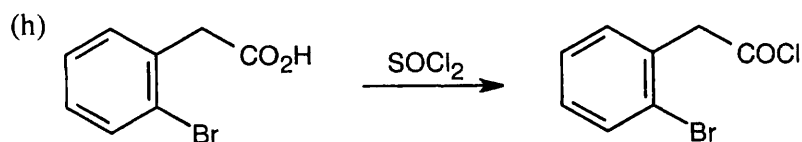
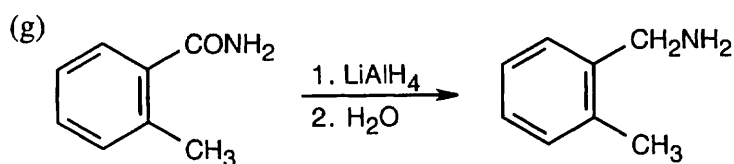
21.35



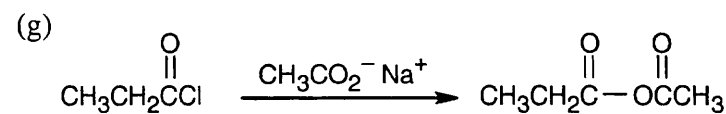
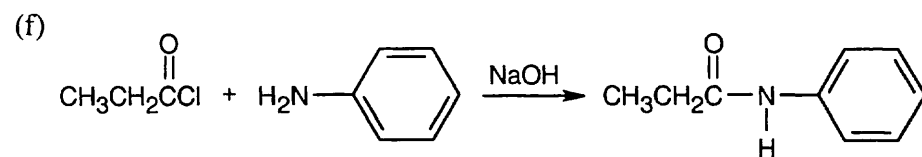
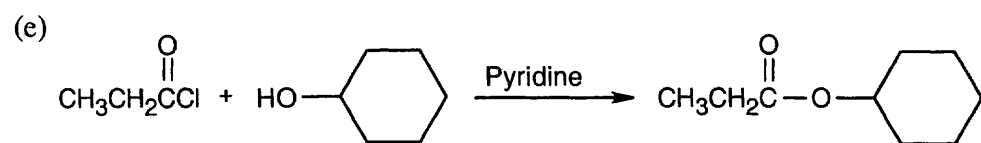
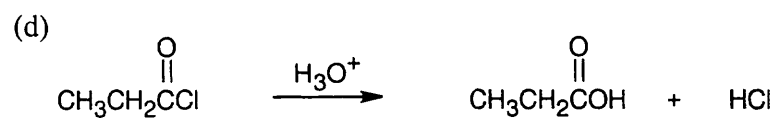
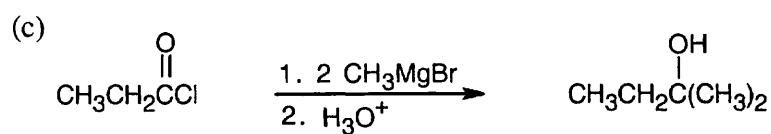
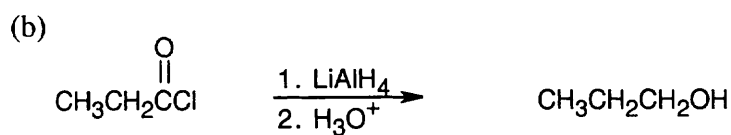
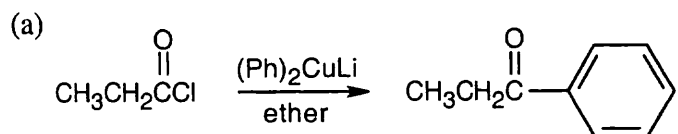


21.36



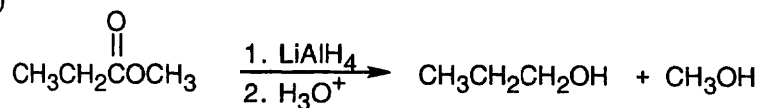


21.37

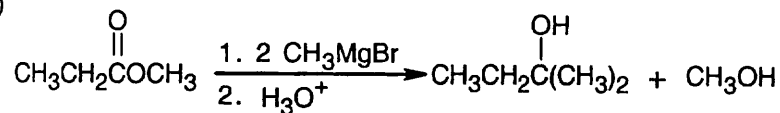


21.38 The reagents in parts (a), (e), and (g) don't react with methyl propanoate.

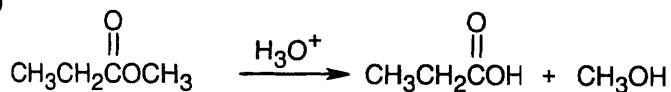
(b)



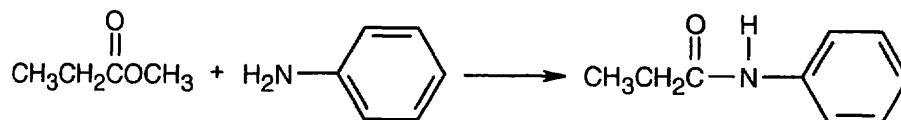
(c)



(d)

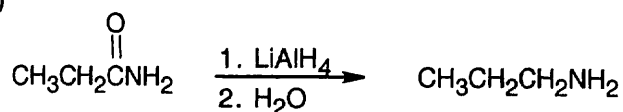


(f)

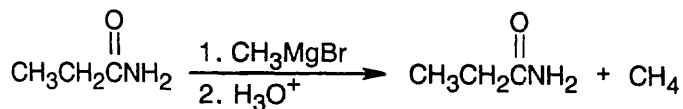


21.39 The reagents in parts (a), (e), (f), and (g) don't react with propanamide.

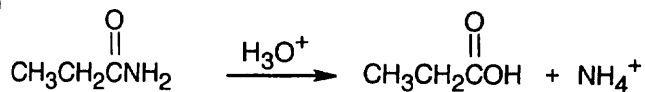
(b)



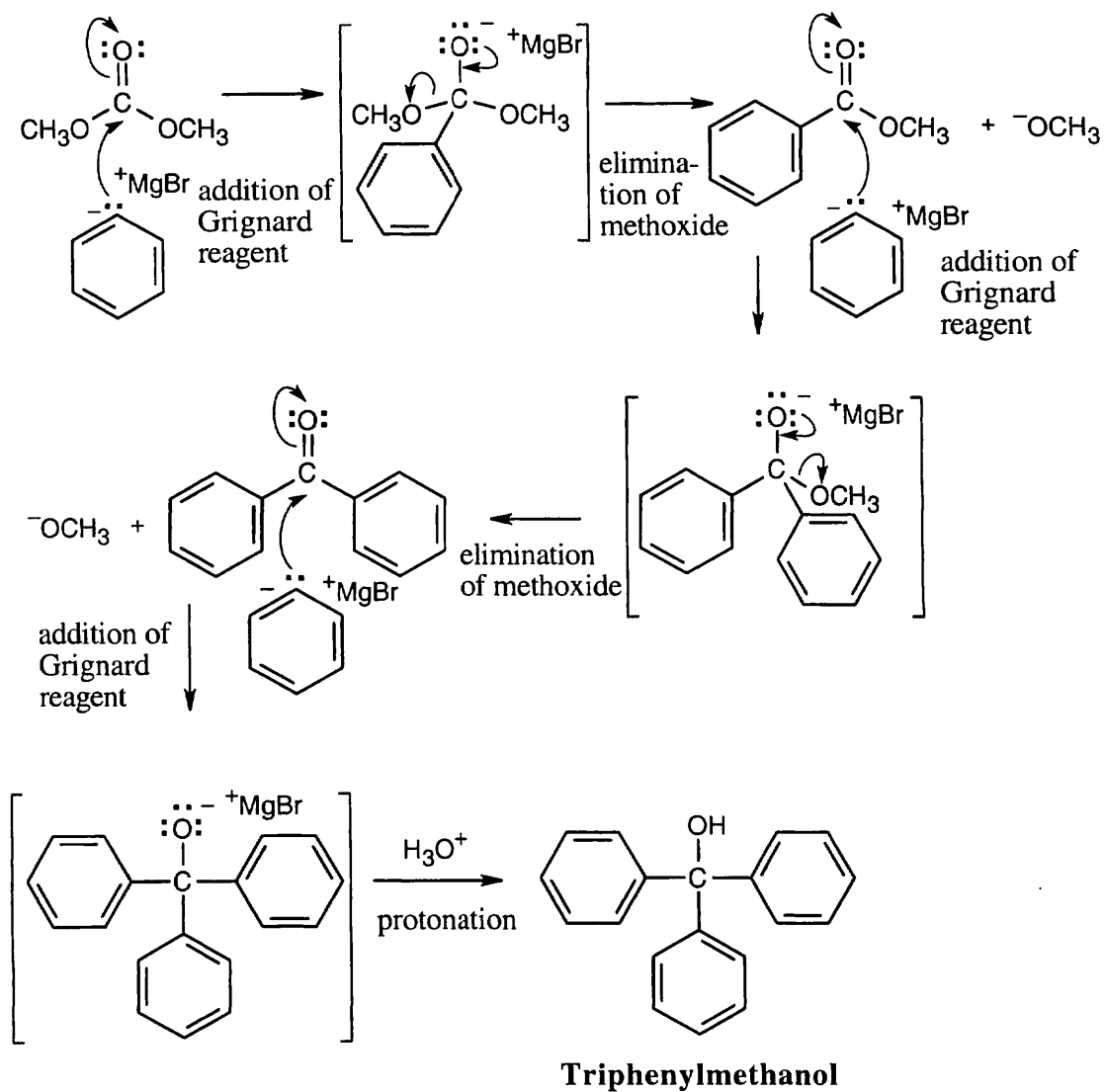
(c)



(d)

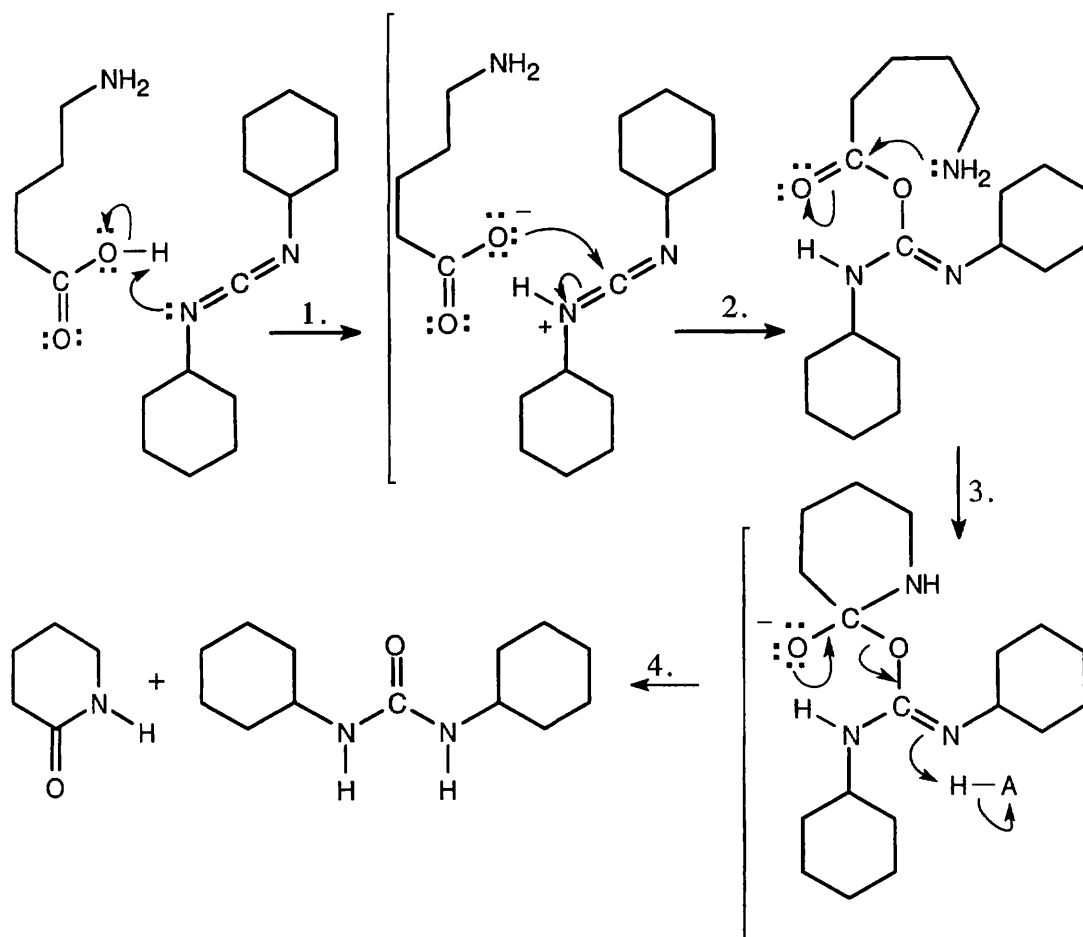


21.40 Dimethyl carbonate is a diester. Use your knowledge of the Grignard reaction to work your way through this problem.



The overall reaction consists of three additions of phenylmagnesium bromide, two eliminations of methoxide and one protonation.

21.41



Step 1: The carboxylic acid protonates DCC.

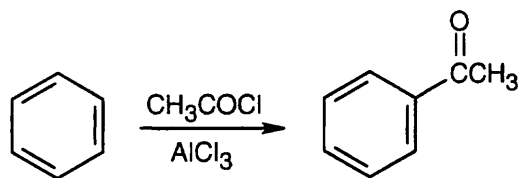
Step 2: The carboxylate oxygen adds to DCC to form a reactive intermediate.

Step 2: The amine nitrogen adds to the carbonyl group to yield a tetrahedral intermediate.

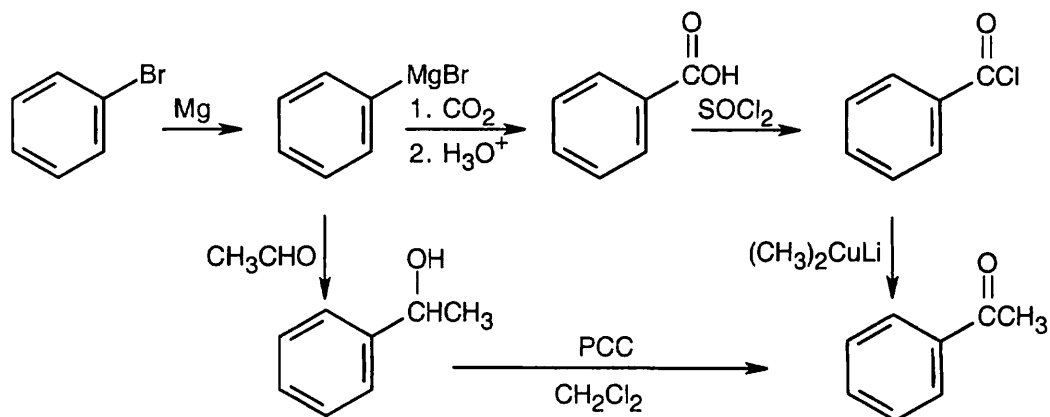
Step 3: The intermediate loses dicyclohexylurea to produce the lactam.

21.42

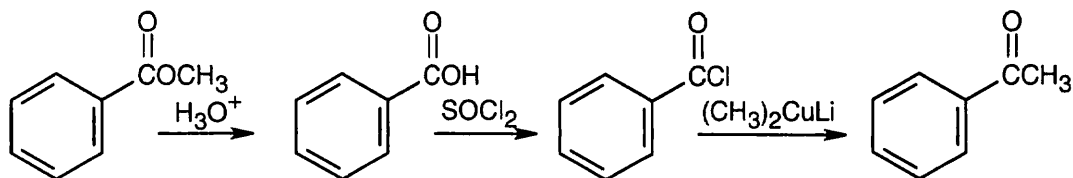
(a)



(b)

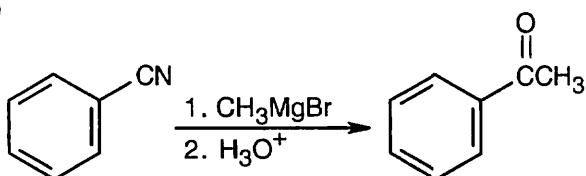


(c)

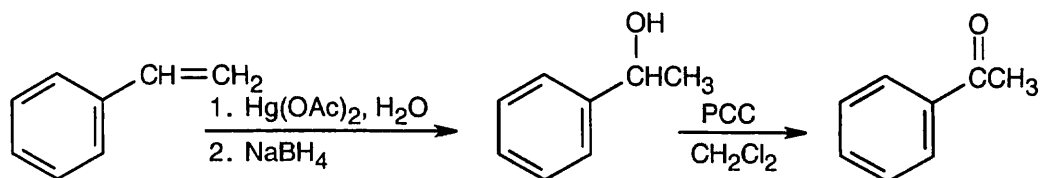


Reaction of an ester with Grignard reagent produces a tertiary alcohol, not a ketone.

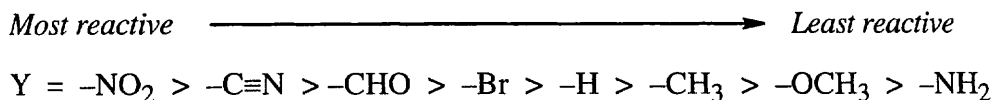
(d)



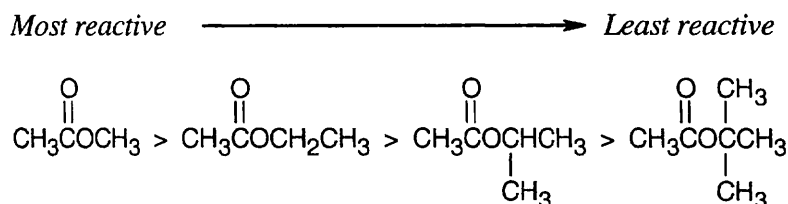
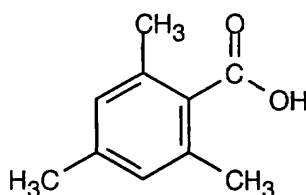
(e)



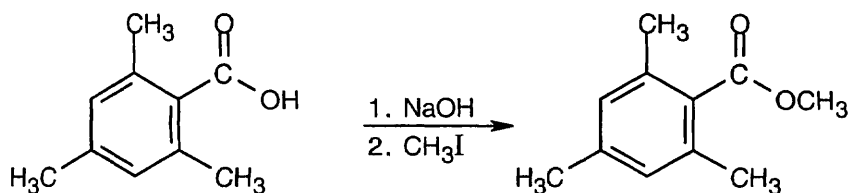
- 21.43** A negatively charged tetrahedral intermediate is formed when the nucleophile OH^- attacks the carbonyl carbon of an ester. An electron-withdrawing substituent can stabilize this negatively charged tetrahedral intermediate and increase the rate of reaction. (Contrast this effect with substituent effects in electrophilic aromatic substitution, in which positive charge developed in the intermediate is stabilized by electron-*donating* substituents.) Substituents that are deactivating in electrophilic aromatic substitution are activating in ester hydrolysis, as the observed reactivity order shows. The substituents $-\text{CN}$ and $-\text{CHO}$ are electron-withdrawing; $-\text{NH}_2$ is strongly electron-donating.



- 21.44** The reactivity of esters in saponification reactions is influenced by steric factors. Branching in both the acyl and alkyl portions of an ester hinders attack of the hydroxide nucleophile. This effect is less dramatic in the alkyl portion of the ester than in the acyl portion because alkyl branching is one atom farther away from the site of attack, but it is still significant.

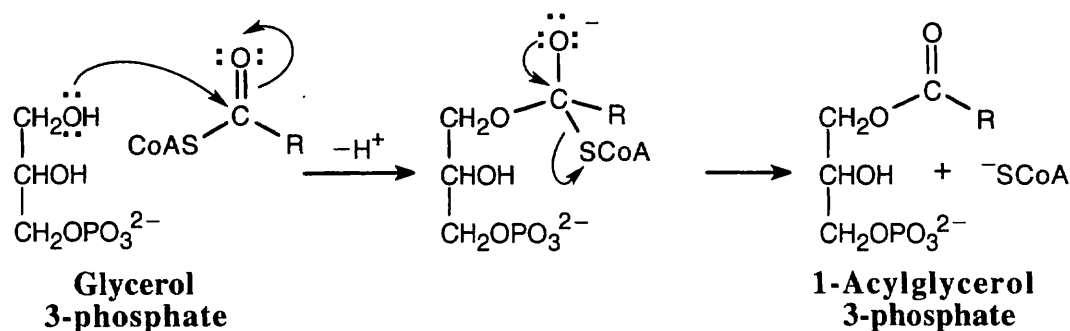
**21.45****2,4,6-Trimethylbenzoic acid**

2,4,6-Trimethylbenzoic acid has two methyl groups ortho to the carboxylic acid functional group. These bulky methyl groups block the approach of the alcohol and prevent esterification from occurring under Fischer esterification conditions. A possible route to the methyl ester:



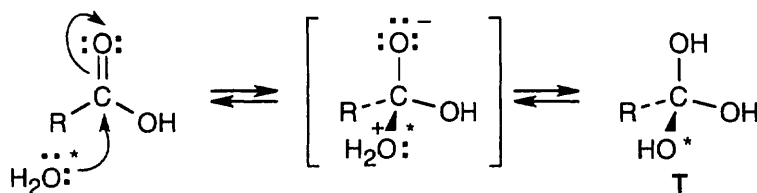
This route succeeds because reaction occurs farther away from the site of steric hindrance. It is also possible to form the acid chloride of 2,4,6-trimethylbenzoic acid and react it with methanol and pyridine.

21.46



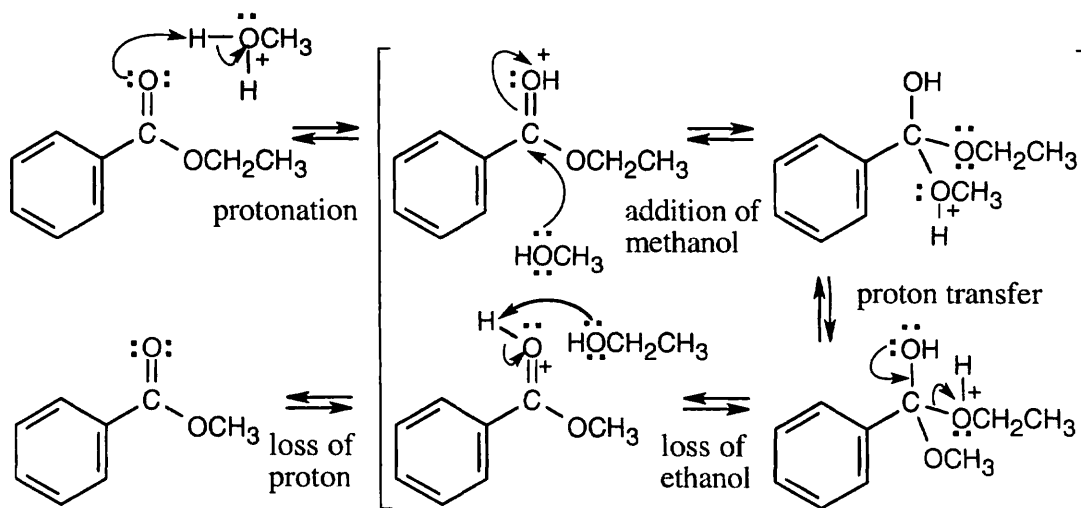
Addition of $-\text{OH}$ to the fatty acyl CoA, followed by loss of $-\text{SCoA}$ from the tetrahedral intermediate, produces 1-acylglycerol 3-phosphate.

21.47



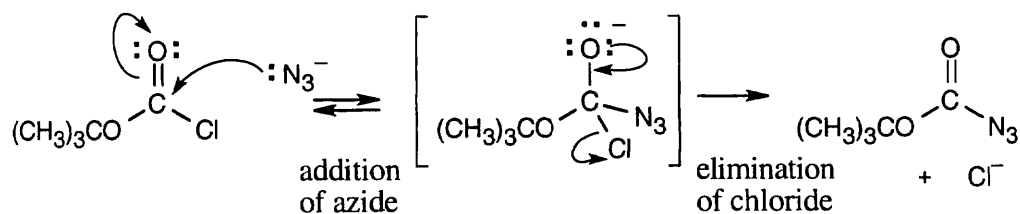
The tetrahedral intermediate **T** can eliminate any one of the three $-\text{OH}$ groups to reform either the original carboxylic acid or labeled carboxylic acid. Further reaction of water with mono-labeled carboxylic acid leads to the doubly labeled product.

21.48



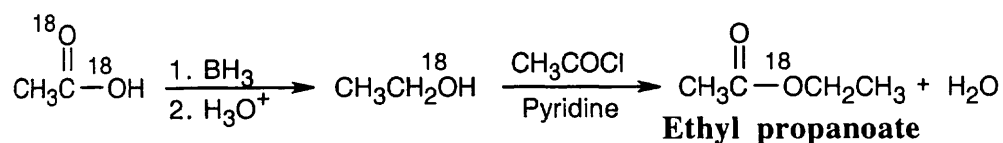
In acidic methanol, the ethyl ester reacts by a nucleophilic acyl substitution mechanism to yield a methyl ester. The equilibrium favors the methyl ester because of the large excess of methanol present.

21.49



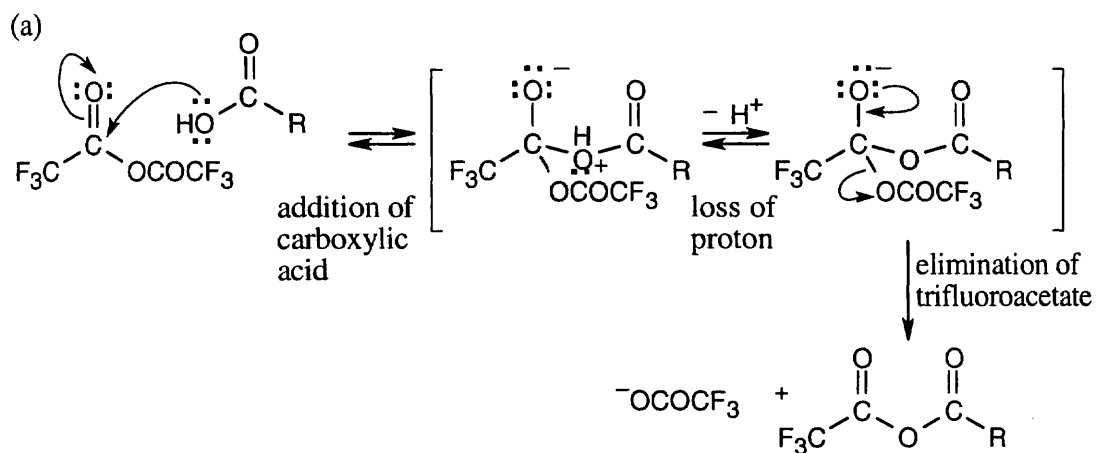
This reaction is a typical nucleophilic acyl substitution reaction, with azide as the nucleophile and chloride as the leaving group.

21.50

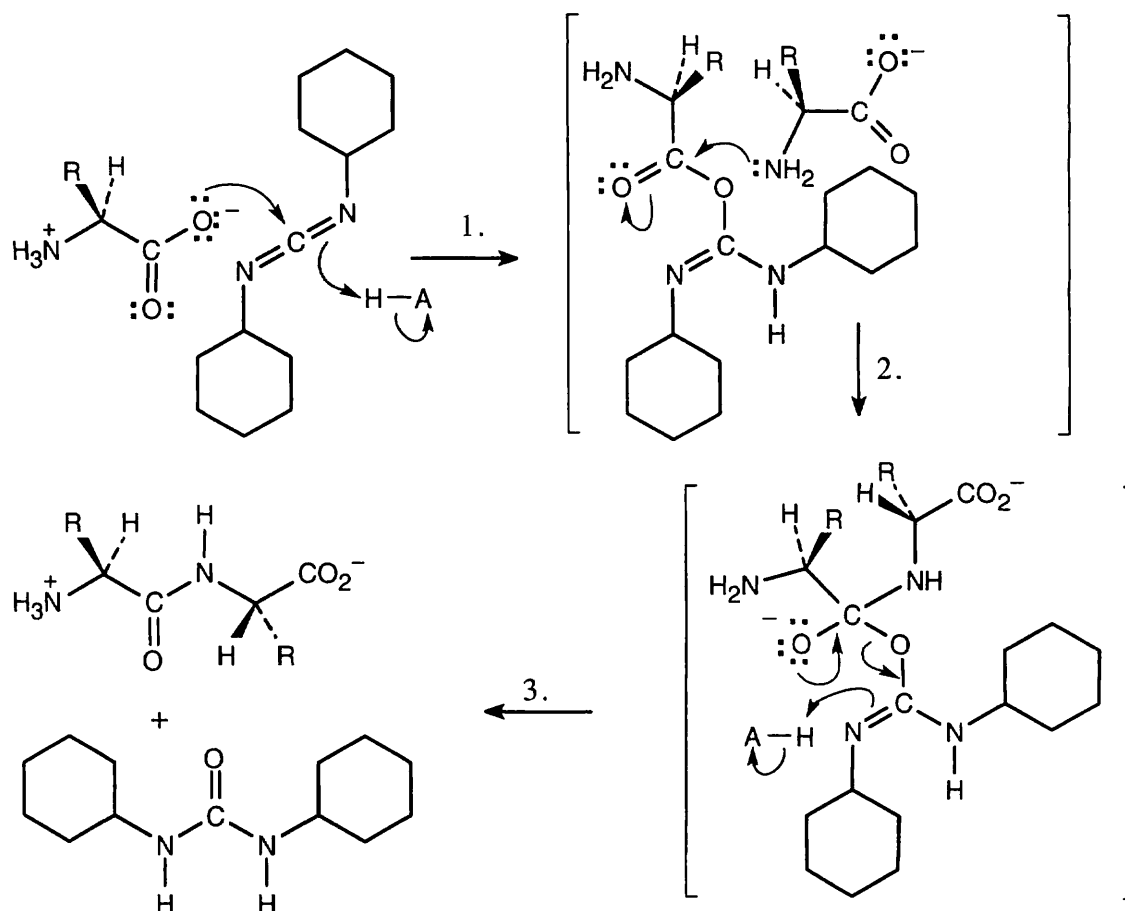


Remember that the ^{18}O label appears in both oxygens of the acetic acid starting material.

21.51



- (b) The electron-withdrawing fluorine atoms polarize the carbonyl group, making it more reactive toward nucleophiles.
- (c) Because trifluoroacetate is a better leaving group than other carboxylate anions, the reaction proceeds as indicated.

21.52 Formation of the dipeptide:

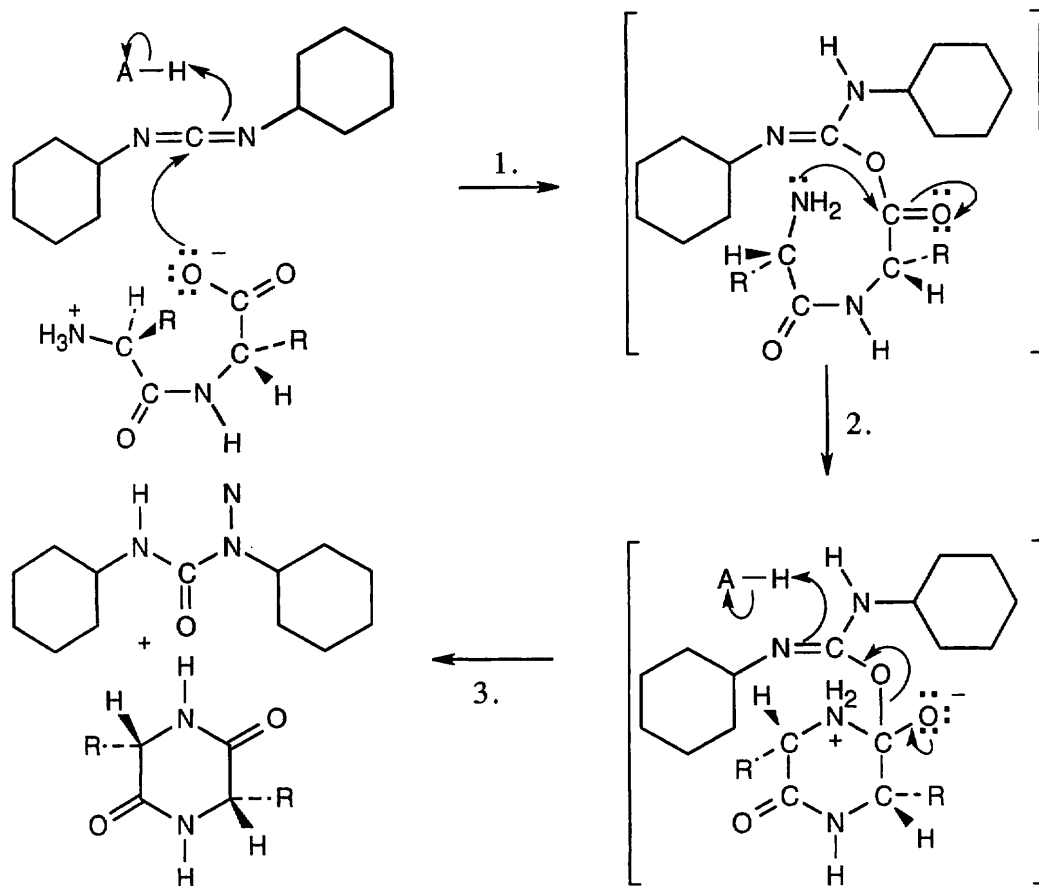
Step 1: The carboxylate group from one amino acid adds to DCC to form a reactive intermediate.

Step 2: The amino group of the second amino acid adds to the carbonyl group to yield a tetrahedral intermediate.

Step 3: The intermediate loses dicyclohexylurea to produce the amide.

Proton transfers occur in steps 1 and 3.

Formation of the 2,5-diketopiperazine:



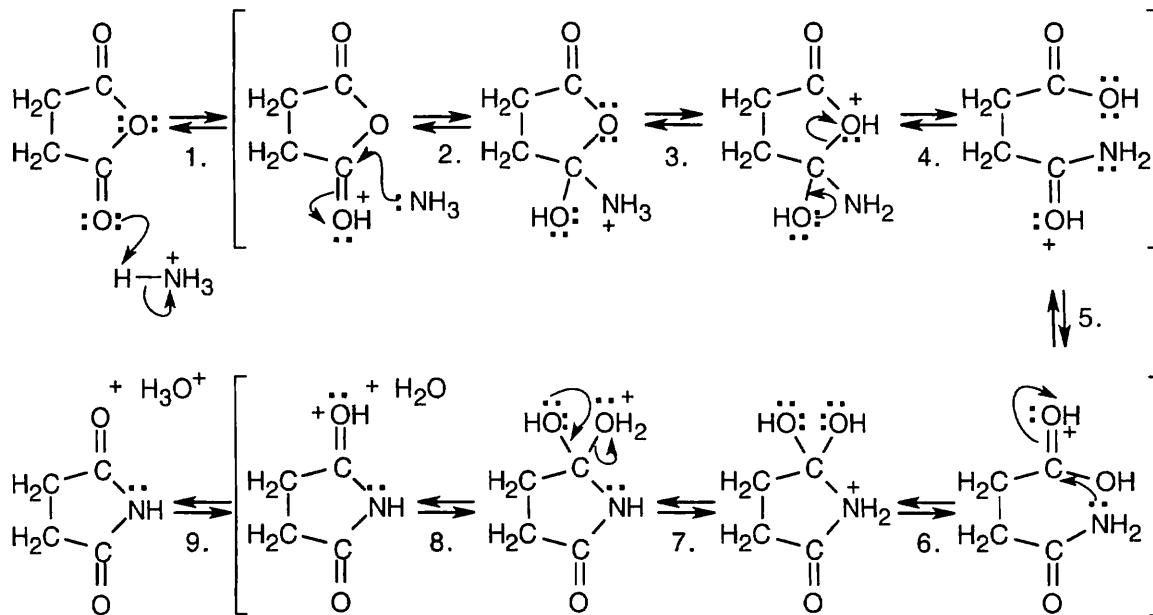
Step 1: Addition of carboxylate to DCC.

Step 2: Intramolecular nucleophilic attack of the amino terminal end of the amide on the acylating agent.

Step 3: Loss of dicyclohexylurea.

Proton transfers occur in steps 1 and 2.

21.53



A summary of steps:

Step 1: Protonation

Steps 3,5,7,9: Proton transfers

Step 6: Nucleophilic addition of -NH_2

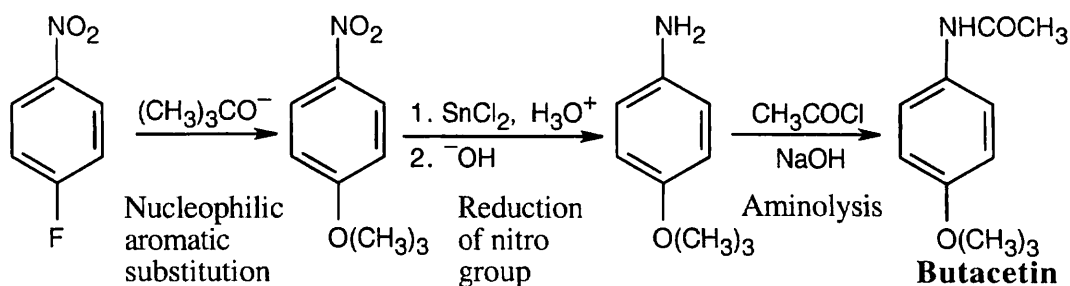
Step 2: Nucleophilic addition of NH_3

Step 4: Ring opening

Step 8: Loss of H_2O

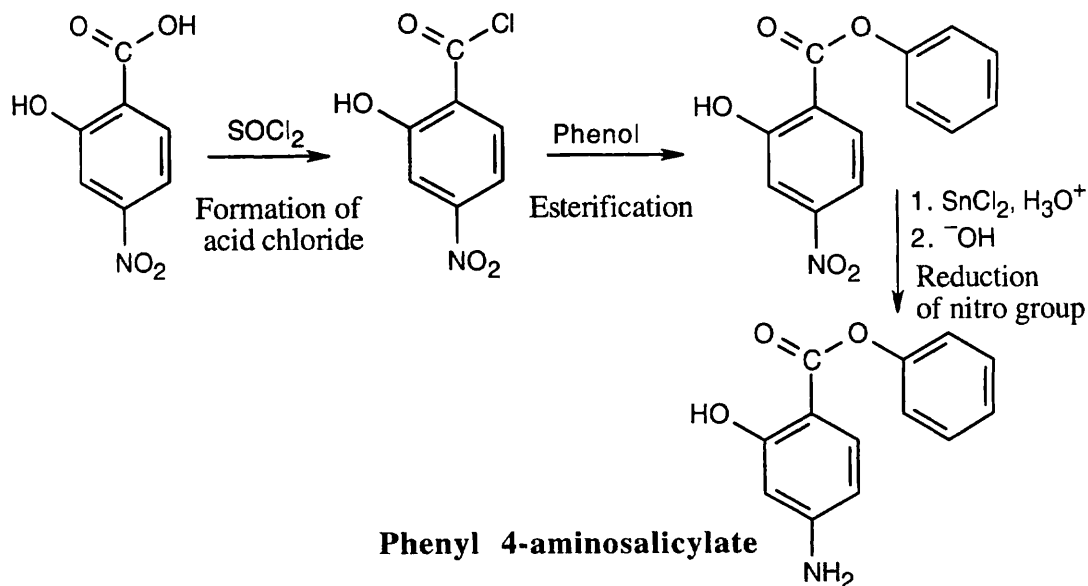
This reaction requires high temperatures because the intermediate amide is a poor nucleophile and the carboxylic acid carbonyl group is unreactive.

21.54 This synthesis requires a nucleophilic aromatic substitution reaction, explained in Section 16.7.

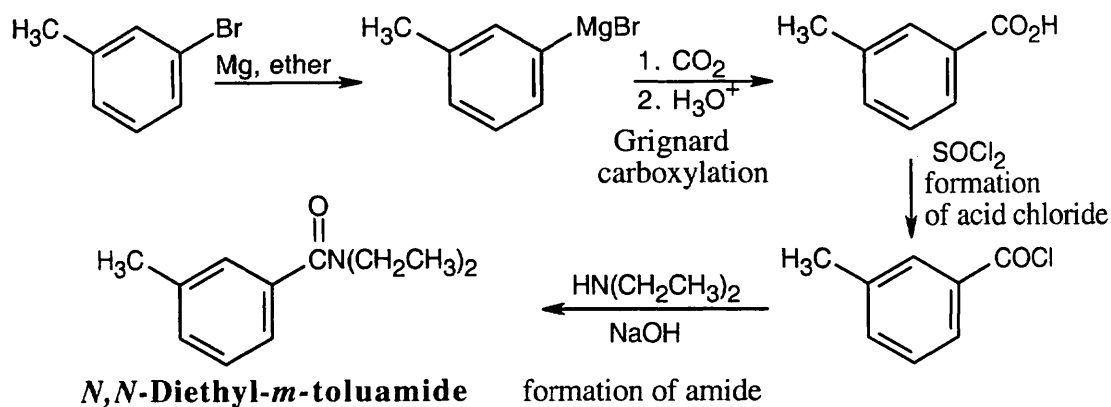


The amide can be formed by the reaction of acetyl chloride with the appropriate amine, which is produced by reduction of the nitro group of the starting material. A nucleophilic aromatic substitution of -F by $\text{-O}(\text{CH}_3)_3$ can take place because the ring has an electron-withdrawing nitro group para to the site of substitution. Acetic anhydride can also be used to acetylate the amine.

21.55

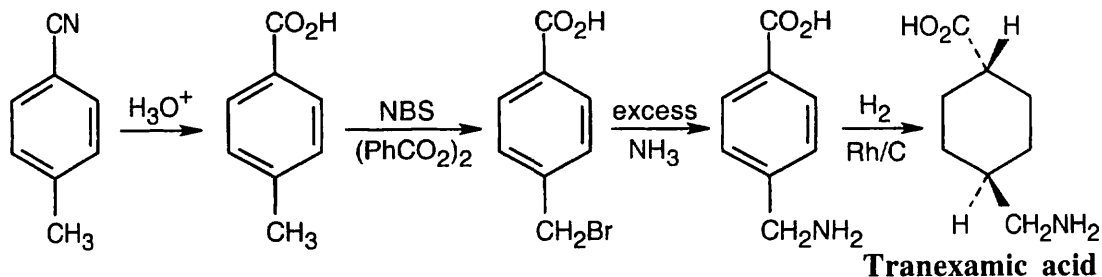


21.56



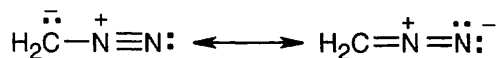
Grignard carboxylation yields *m*-methylbenzoic acid, which can be converted to an acid chloride and treated with diethylamine.

21.57

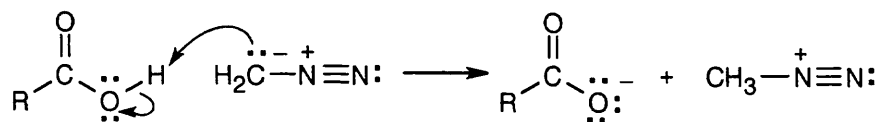


Using a rhodium catalyst, the aromatic ring is hydrogenated to form the cis-substituted cyclohexane, which is converted to the trans isomer by heating to 300°. The nitrile starting material is hydrolyzed to form a carboxylic acid, and the methyl group is brominated and treated with ammonia to form the amine.

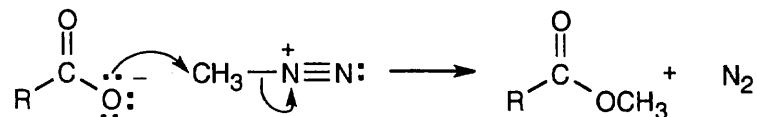
21.58 (a)



Resonance forms show that the carbon of diazomethane is basic, and reaction with an acid can occur to form a methyldiazonium ion.

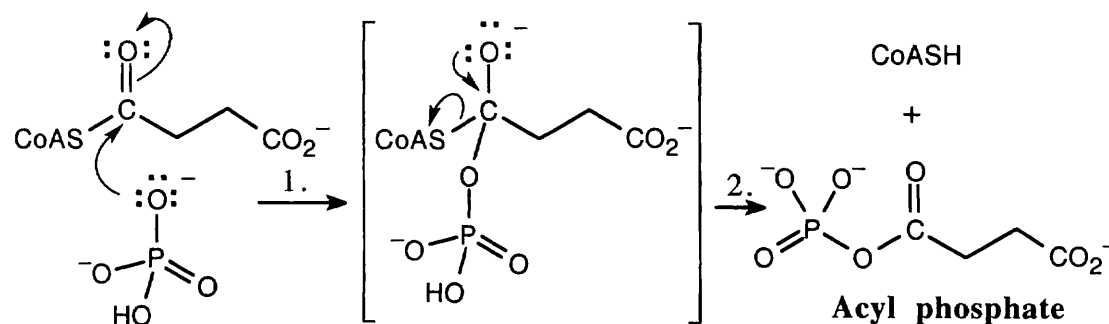


(b)



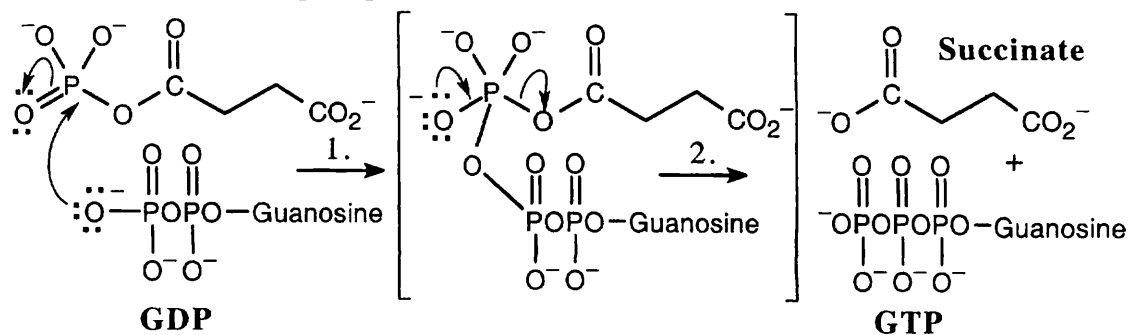
An $\text{S}_{\text{N}}2$ reaction takes place in which the carboxylate ion displaces N_2 as the leaving group to form the methyl ester.

21.59 Both steps involve nucleophilic acyl substitutions.

Formation of acyl phosphate:

Step 1: Reaction of the phosphate oxygen with the carbonyl carbon of succinyl CoA.

Step 2: Loss of $^-\text{SCoA}$ from the tetrahedral intermediate, yielding acyl phosphate.

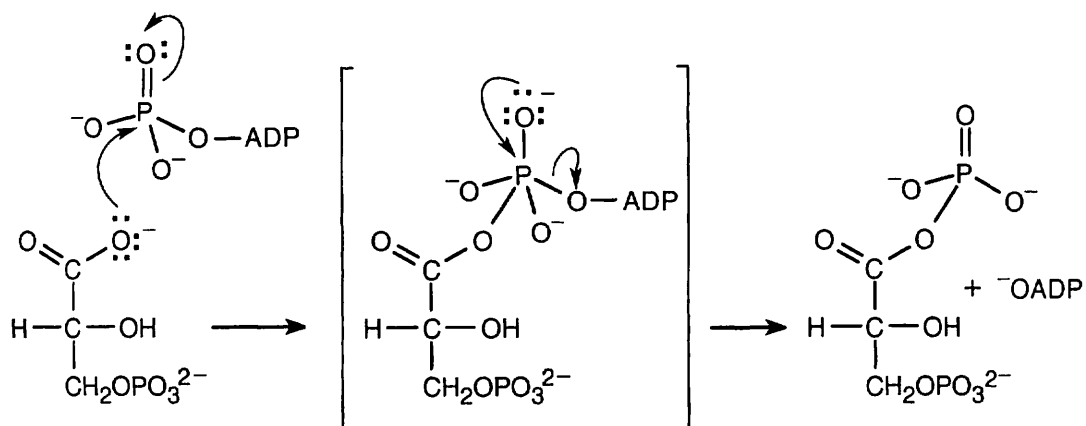
Conversion of acyl phosphate to succinate:

Step 1: Reaction of the diphosphate oxygen of GDP with the phosphorus of the acyl phosphate to produce an intermediate similar to the intermediates formed in nucleophilic acyl substitutions of carboxylic acid derivatives.

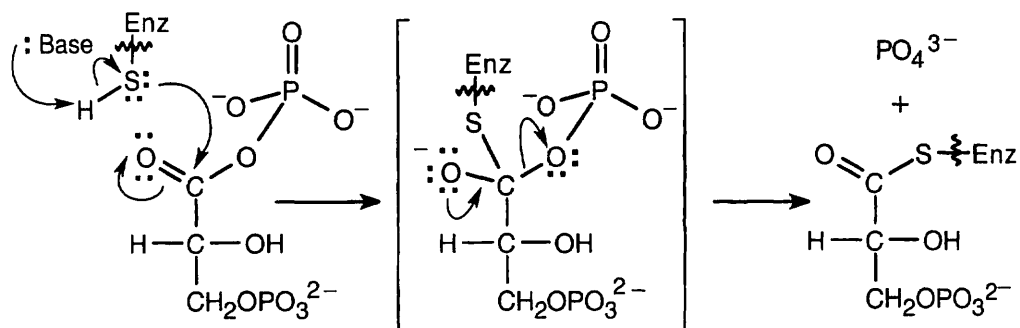
Step 2: Loss of phosphate to form GTP and succinate.

21.60 In all of these reactions, a nucleophile adds to either carbon or phosphorus to form an intermediate that expels a leaving group to give the desired product.

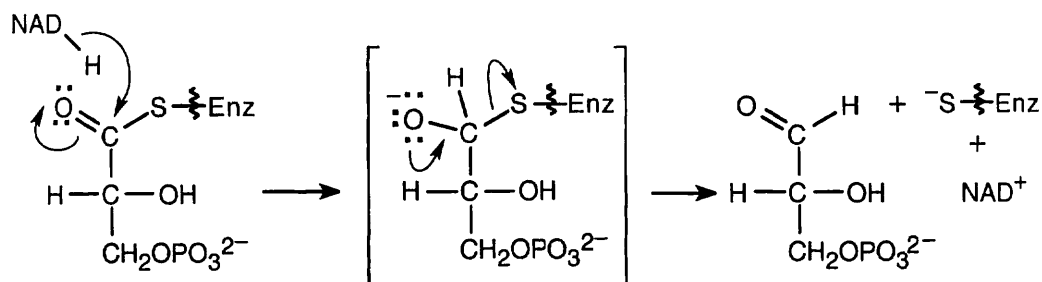
Formation of 1,3-bisphosphoglycerate:



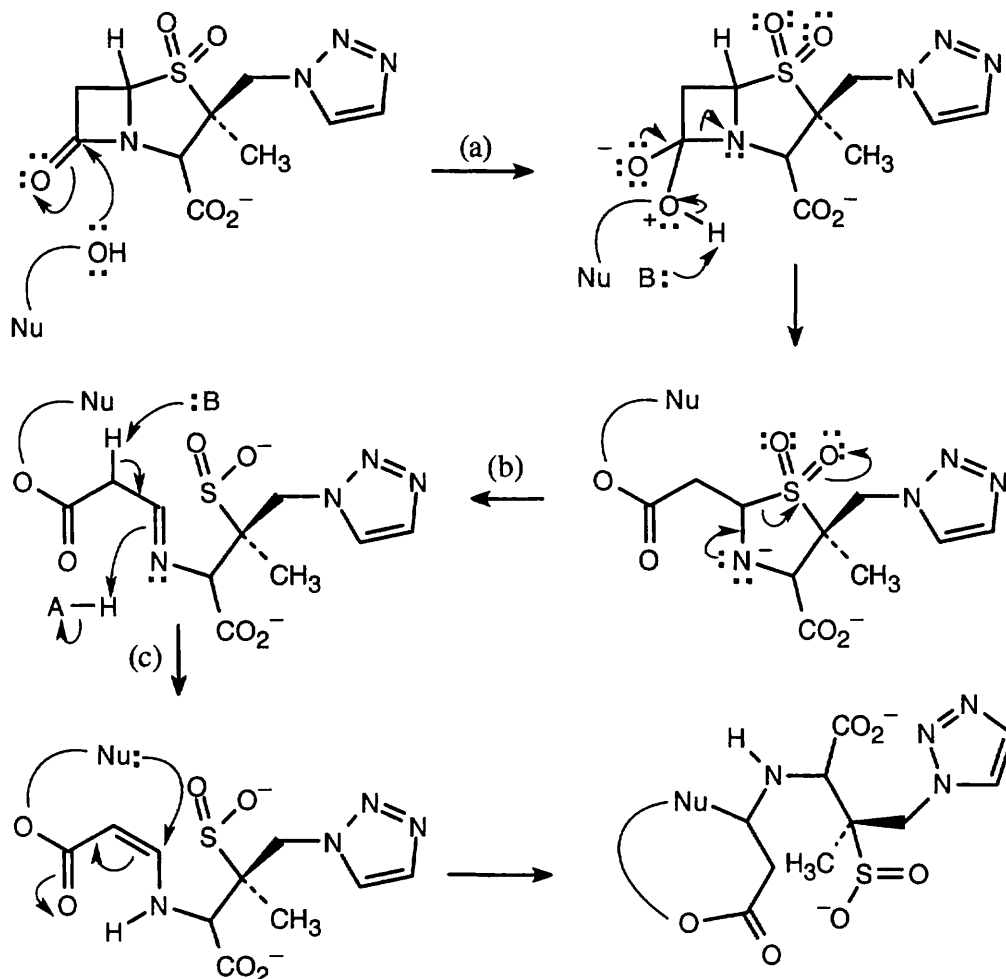
Route to enzyme-bound thioester:



Reduction to glyceraldehyde 3-phosphate:

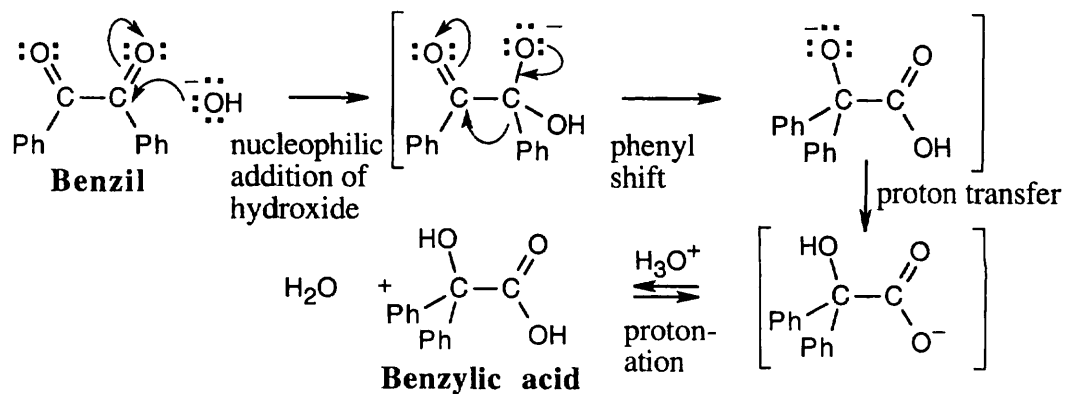


21.61



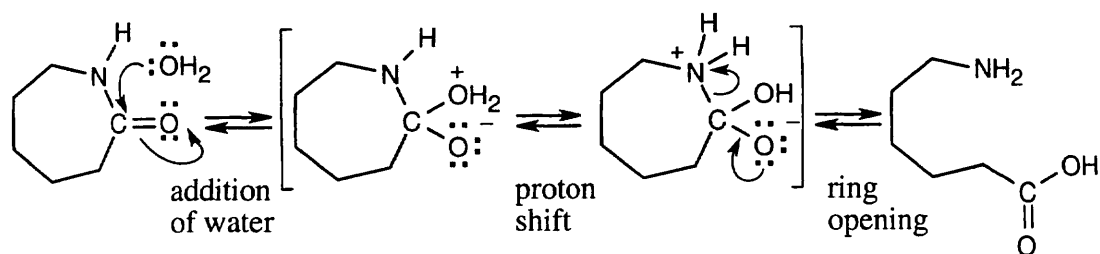
In (c), the imine rearranges to an α,β -unsaturated ester, to which the nucleophile adds to give the trapped β -lactamate.

21.62

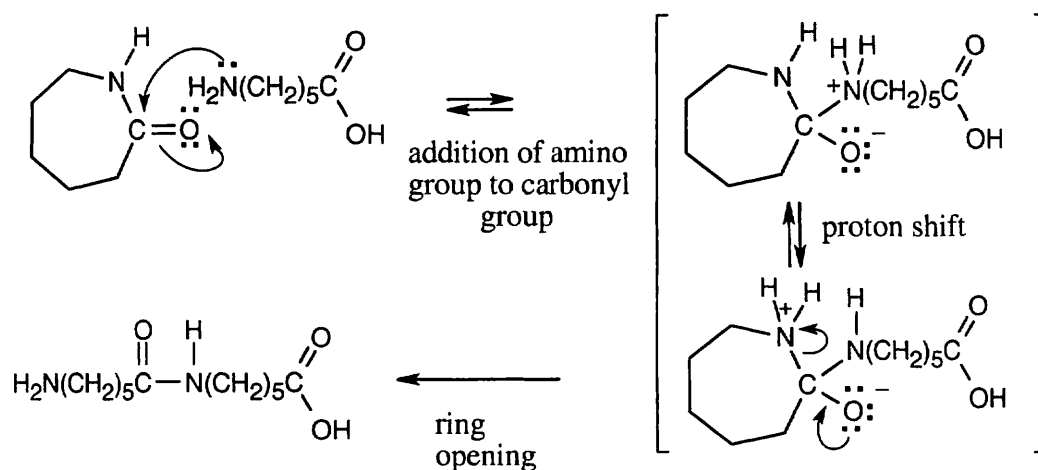


21.63

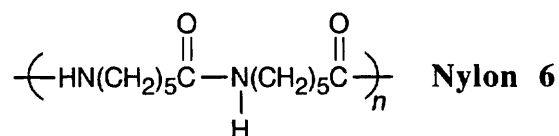
Step 1: Water opens the caprolactam ring to form the amino acid intermediate.



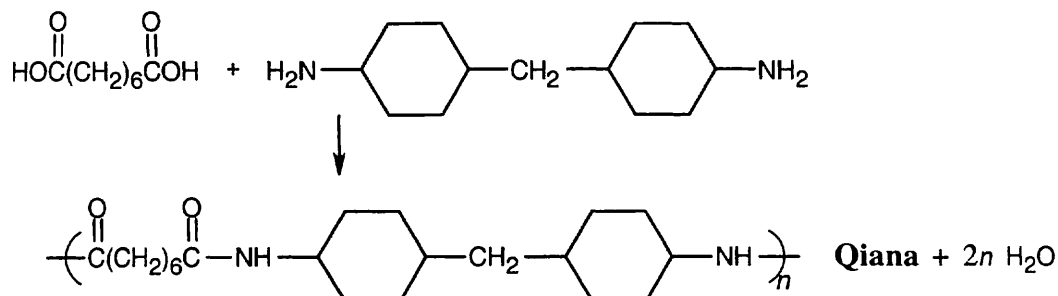
Step 2: Reaction of the intermediate with a second molecule of caprolactam forms a dimer.



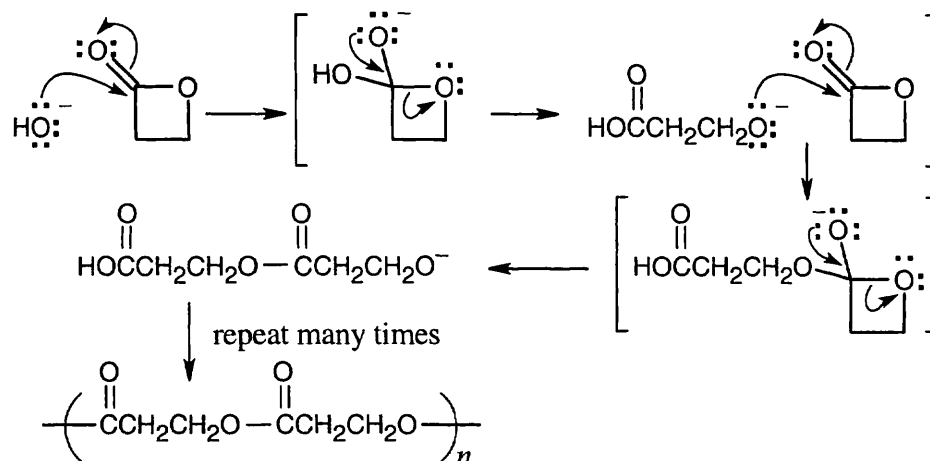
Steps 3 and beyond: Reaction of the dimer with caprolactam. This process repeats itself many, many times until the polymer stops growing. Remember that each new bond is formed in a discrete step. Heat forces the equilibrium in the direction of polymer formation.



21.64

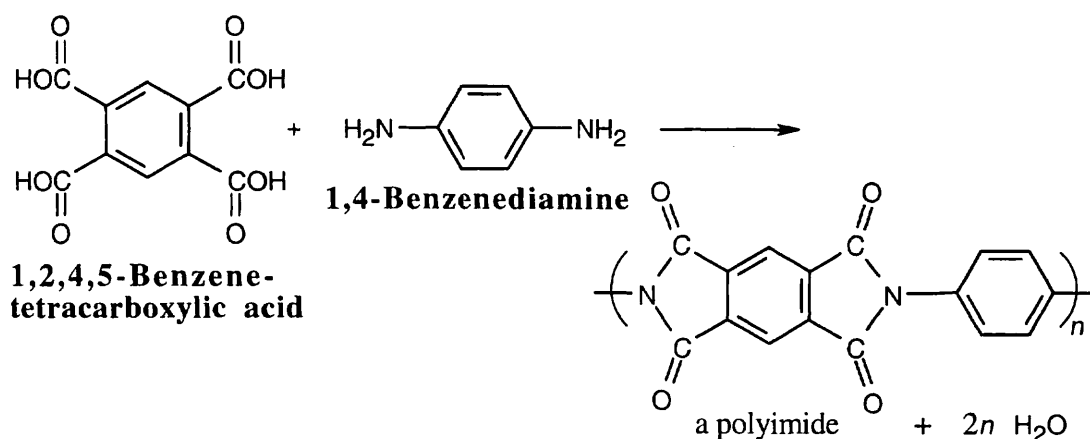


21.65



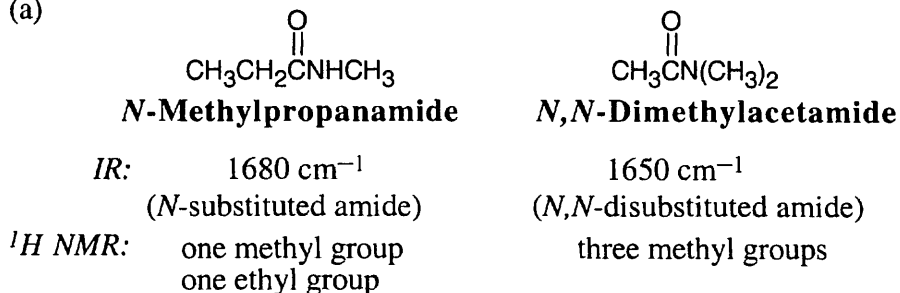
The polymer is a polyester.

21.66 The polyimide pictured is a step-growth polymer of a benzene tetracarboxylic acid and an aromatic diamine.



21.67 In some of these pairs, IR spectroscopy alone can differentiate between the isomers. For others, either ^1H NMR or a combination of ^1H NMR and IR data is necessary.

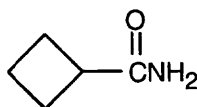
(a)



(b)

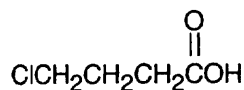
**5-Hydroxypentanenitrile**

IR: 3300–3400 cm^{-1}
(hydroxyl)
2250 cm^{-1}
(nitrile)

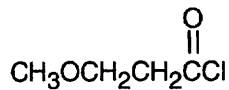
**Cyclobutanecarboxamide**

1690 cm^{-1}
(amide)

(c)

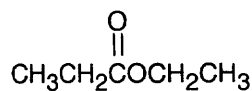
**4-Chloropentanoic acid**

IR: 2500–3300 cm^{-1}
(hydroxyl)
1710 cm^{-1}
(carboxylic acid)

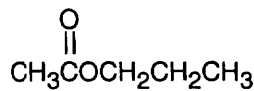
**3-Methoxypropanoyl chloride**

1810 cm^{-1}
(carboxylic acid chloride)

(d)

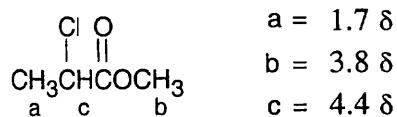
**Ethyl propanoate**

^1H NMR: two triplets
two quartets

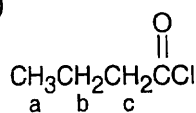
**Propyl acetate**

one singlet
one triplet
one quartet
one multiplet

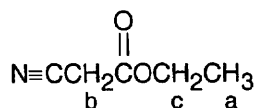
21.68 The IR spectrum indicates that this compound has a carbonyl group.

a = 1.7 δ b = 3.8 δ c = 4.4 δ **21.69**

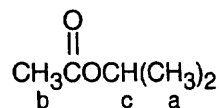
(a)

a = 1.0 δ b = 1.7 δ c = 2.8 δ

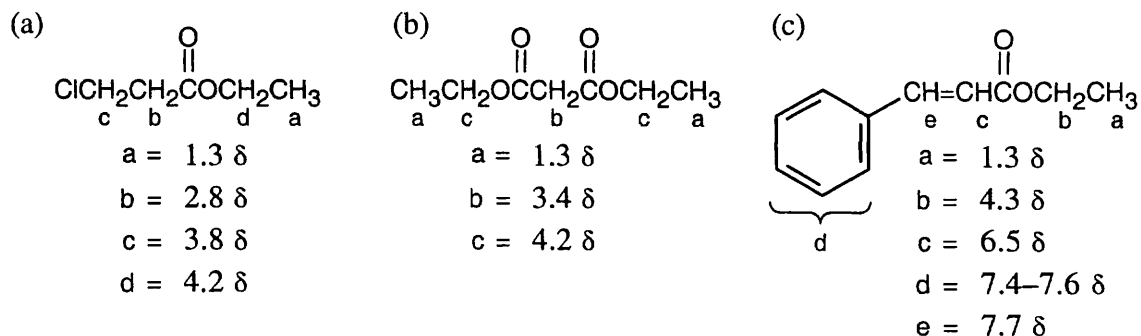
(b)

a = 1.3 δ b = 3.6 δ c = 4.3 δ

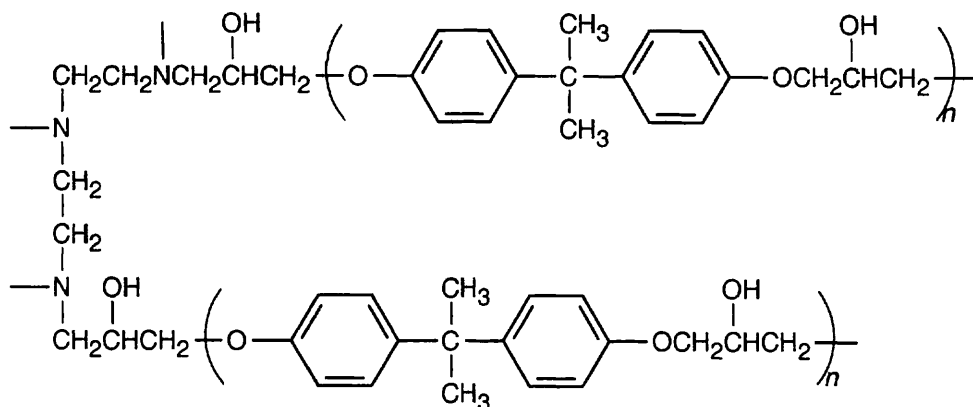
(c)

a = 1.3 δ b = 2.0 δ c = 5.0 δ

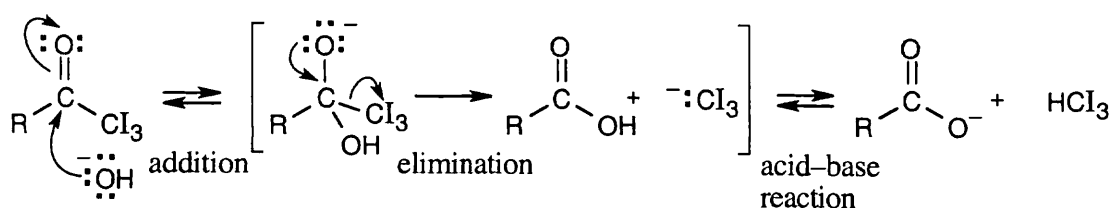
21.70



21.71 Addition of the triamine causes formation of cross-links between prepolymer chains.



21.72 This is a nucleophilic acyl substitution reaction whose mechanism is similar to others we have studied.



I_3C^- can act as a leaving group because the electron-withdrawing iodine atoms stabilize the carbanion.

Review Unit 8: Carbonyl Compounds 1.

Reaction at the Carbonyl Group

Major Topics Covered (with vocabulary);

Aldehydes and ketones:

-carbaldehyde acyl group acetyl group formyl group benzoyl group hydrate Tollens reagent

Reactions of aldehydes and ketones:

nucleophilic addition reaction gem diol cyanohydrin imine enamine carbinolamine
2,4-dinitrophenylhydrazone Wolff-Kishner reaction acetal hemiacetal Wittig reaction ylide
betaine Cannizzaro reaction conjugate addition α,β -unsaturated carbonyl compound

Carboxylic acids and their derivatives:

carboxylation carboxylic acid derivative acid halide acid anhydride amide ester nitrile
-carbonitrile

Reactions of carboxylic acids and their derivatives:

nucleophilic acyl substitution hydrolysis alcoholysis aminolysis Fischer esterification reaction
lactone saponification DIBAH lactam thiol ester acyl phosphate polyamide polyester
step-growth polymer chain-growth polymer nylon

Types of Problems:

After studying these chapters you should be able to:

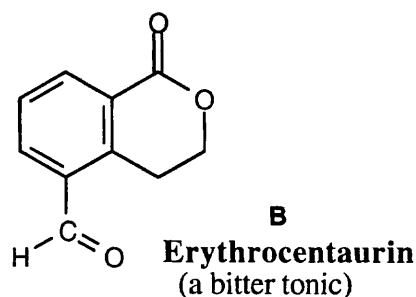
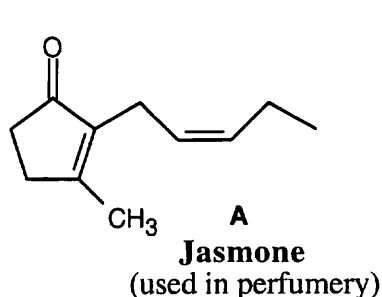
- Name and draw aldehydes, ketones, carboxylic acids and their derivatives.
- Prepare all of these compounds.
- Explain the reactivity difference between aldehydes and ketones and between carboxylic acids and all their derivatives.
- Calculate dissociation constants of carboxylic acids, and predict the relative acidities of substituted carboxylic acids.
- Formulate mechanisms for reactions related to the reactions we have studied.
- Predict the products of the reactions for all functional groups we have studied.
- Use spectroscopic techniques to identify these compounds.
- Draw representative segments of step-growth polymers.

Points to Remember:

- * In all of these reactions, a nucleophile adds to a positively polarized carbonyl carbon to form a tetrahedral intermediate. There are three possible fates for the tetrahedral intermediate: (1) The intermediate can be protonated, as occurs in Grignard reactions, reductions, and cyanohydrin formation. (2) The intermediate can lose water (or ^-OH), as happens in imine and enamine formation. (3) The intermediate can lose a leaving group, as occurs in most reactions of carboxylic acid derivatives.
- * Many of the reactions in these three chapters require acid or base catalysis. An acid catalyst, protonates the carbonyl oxygen, making the carbonyl carbon more reactive toward nucleophiles, and/or protonates the tetrahedral intermediate, making loss of a leaving group easier. A base catalyst deprotonates the nucleophile, making it more nucleophilic. The pH optimum for these reactions is a compromise between the two needs.

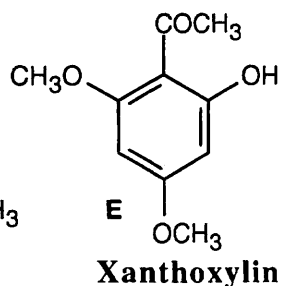
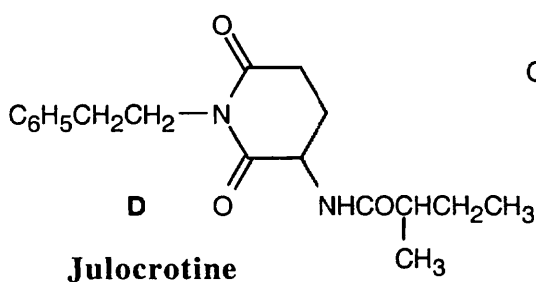
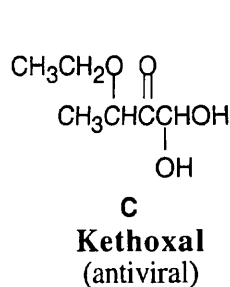
- * Here are a few reminders for drawing the mechanisms of nucleophilic addition and substitution reactions. (1) When a reaction is acid-catalyzed, none of the intermediates are negatively charged, although, occasionally, a few may be neutral. Check your mechanisms for charge balance. (2) Make sure you have drawn arrows correctly. The point of the arrow shows the new location of the electron pair at the base of the arrow. (3) In a polar reaction, two arrows never point at each other. If you find two arrows pointing at each other, redraw the mechanism.
- * Reactions of acyl halides are almost always carried out with an equivalent of base present. The base is used to scavenge the protons produced when a nucleophile adds to an acyl halide. If base were not present, hydrogen ions would protonate the nucleophile and make it unreactive.
- * The products of acidic cleavage of an amide are a carboxylic acid and a protonated amine. The products of basic cleavage of an amide are a carboxylate anion and an amine.
- * In some of the mechanisms shown in the answers, a series of protonations and deprotonations occur. These steps convert the initial tetrahedral intermediate into an intermediate that more easily loses a leaving group. These deprotonations may be brought about by the solvent, by the conjugate base of the catalyst, by other molecules of the carbonyl compound or may occur intramolecularly. When a "proton transfer" is shown as part of a mechanism, the base that removes the proton has often not been shown. However, it is implied that the proton transfer is assisted by a base: the proton doesn't fly off the intermediate unassisted.
- * The most useful spectroscopic information for identifying carbonyl compounds comes from IR spectroscopy and ^{13}C NMR spectroscopy. Carbonyl groups have distinctive identifying absorptions in their infrared spectra. ^{13}C NMR is also useful for identifying aldehydes, ketones, and nitriles, although other groups are harder to distinguish. The ^1H NMR absorptions of aldehydes and carboxylic acids are also significant. Look at mass spectra for McLafferty rearrangements and alpha-cleavage reactions of aldehydes and ketones.

Self-Test:



Predict the products of the reaction of **A** with: (a) LiAlH_4 , then H_3O^+ ; (b) $\text{C}_6\text{H}_5\text{MgBr}$, then H_3O^+ ; (c) $(\text{CH}_3)_2\text{NH}$, H_3O^+ ; (d) CH_3OH , H^+ catalyst (e) $(\text{C}_6\text{H}_5)_3\text{P}^+ - \text{CH}_2^-$; (f) 1 equiv. $\text{CH}_3\text{CH}_2\text{NH}_2$, H_3O^+ . How would you reduce **A** to yield a saturated hydrocarbon? Where would you expect the carbonyl absorption of **A** to occur in its IR spectrum?

Predict the products of **B** with the reagents (a) – (d) above. What product(s) would be formed if **B** was treated with Br_2 , FeBr_3 ? Where do the carbonyl absorptions occur in the IR spectrum of **B**? Describe the ^{13}C NMR spectrum of **B**.



Kethoxal (**C**) exists in solution as an equilibrium mixture. With what compound is it in equilibrium. Why does the equilibrium lie on the side of kethoxal?

Identify the carboxylic acid derivatives present in **D**. Show the products of treatment of **D** with (a) ^-OH , H_2O (b) $LiAlH_4$, then H_2O .

Name **E**. Describe the IR spectrum and 1H NMR spectrum of **E**.

Multiple Choice:

- In which of the following nucleophilic addition reactions does the equilibrium lie on the side of the products?
(a) Propanal + HCN (b) Acetone + H_2O (c) Acetaldehyde + HBr
(d) 2,2,4,4-Tetramethyl-3-pentanone + HCN
- Which alcohol can be formed by three different combinations of carbonyl compound + Grignard reagent?
(a) 2-Butanol (b) 3-Methyl-3-hexanol (c) Triphenylmethanol (d) 1-Phenylethanol
- A nitrile can be converted to all of the following except:
(a) an aldehyde (b) an amide (c) an amine (d) A nitrile can be converted to all of the above compounds.
- Which of the following *p*-substituted benzoic acids is the least acidic?
(a) $CH_3COC_6H_5CO_2H$ (b) $CH_3OC_6H_5CO_2H$ (c) $BrC_6H_5CO_2H$ (d) $NCC_6H_5CO_2H$
- A carboxylic acid can be reduced by all of the following except:
(a) $LiAlH_4$, then H_3O^+ (b) BH_3 , THF, then H_3O^+ (c) $NaBH_4$, then H_3O^+ (d) All of these reagents can reduce a carboxylic acid.
- Which of the following carboxylic acids can be formed by both Grignard carboxylation and by nitrile hydrolysis?
(a) Phenylacetic acid (b) Benzoic acid (c) Trimethylacetic acid (d) 3-Butynoic acid
- Acid anhydrides are used mainly for:
(a) synthesizing carboxylic acids (b) forming alcohols (c) introducing acetyl groups
(d) forming aldehydes
- A ketone is formed from an acid halide by reaction with:
(a) DIBAL (b) $LiAlH_4$ (c) $RMgBr$ (d) $(CH_3CH_2)CuLi$

9. From which carboxylic acid derivative can you form a ketone as the product of a Grignard reaction?
(a) acid chloride (b) ester (c) nitrile (d) amide
10. An infrared absorption at 1650 cm^{-1} indicates the presence of:
(a) aromatic acid chloride (b) *N,N*-disubstituted amide (c) α,β -unsaturated ketone
(d) aromatic ester