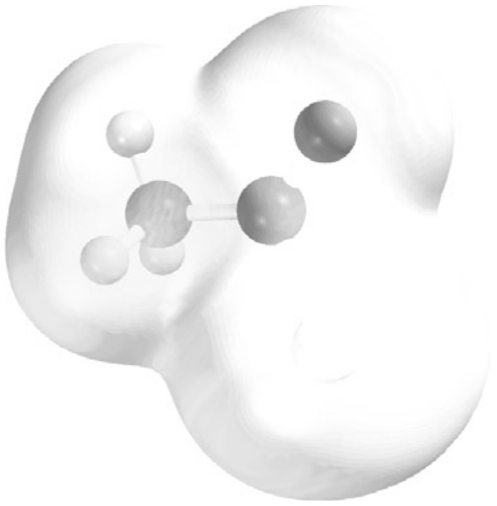
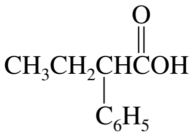


CHAPTER 20

CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION

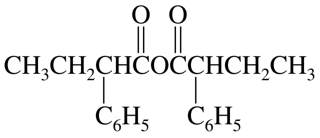
SOLUTIONS TO TEXT PROBLEMS

20.1 (*b*) Carboxylic acid anhydrides bear two acyl groups on oxygen, as in $R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R$. They are named as derivatives of carboxylic acids.



$CH_3CH_2\underset{C_6H_5}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OH$

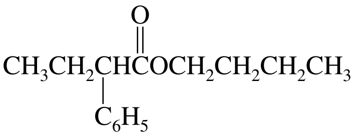
2-Phenylbutanoic acid



$CH_3CH_2\underset{C_6H_5}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}\underset{C_6H_5}{\underset{|}{C}}HCH_2CH_3$

2-Phenylbutanoic anhydride

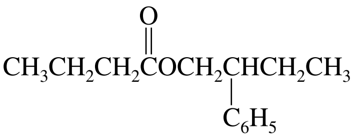
(*c*) Butyl 2-phenylbutanoate is the butyl ester of 2-phenylbutanoic acid.



$CH_3CH_2\underset{C_6H_5}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2CH_3$

Butyl 2-phenylbutanoate

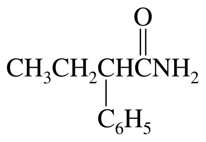
(*d*) In 2-phenylbutyl butanoate the 2-phenylbutyl group is an alkyl group bonded to oxygen of the ester. It is not involved in the acyl group of the molecule.



$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2\underset{C_6H_5}{\underset{|}{C}}HCH_2CH_3$

2-Phenylbutyl butanoate

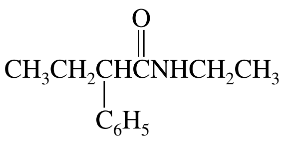
(*e*) The ending -*amide* reveals this to be a compound of the type $R\overset{\substack{O\\ \|}}{C}NH_2$.



$$CH_3CH_2\underset{\substack{|\\ C_6H_5}}{CH}\overset{\substack{O\\ \|}}{C}NH_2$$

2-Phenylbutanamide

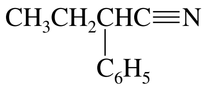
(*f*) This compound differs from 2-phenylbutanamide in part (*e*) only in that it bears an ethyl substituent on nitrogen.



$$CH_3CH_2\underset{\substack{|\\ C_6H_5}}{CH}\overset{\substack{O\\ \|}}{C}NHCH_2CH_3$$

N-Ethyl-2-phenylbutanamide

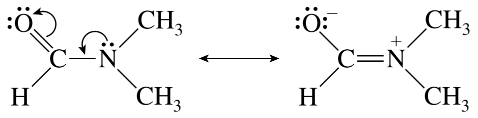
(*g*) The -*nitrile* ending signifies a compound of the type RC≡N containing the same number of carbons as the alkane RCH_3.



$$CH_3CH_2\underset{\substack{|\\ C_6H_5}}{CH}C{\equiv}N$$

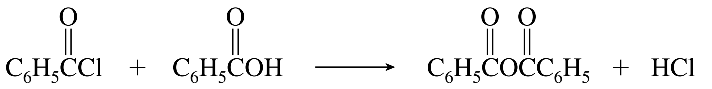
2-Phenylbutanenitrile

20.2 The methyl groups in *N*,*N*-dimethylformamide are nonequivalent; one is cis to oxygen, the other is trans. The two methyl groups have different chemical shifts.



Rotation about the carbon–nitrogen bond is required to average the environments of the two methyl groups, but this rotation is relatively slow in amides as the result of the double-bond character imparted to the carbon–nitrogen bond, as shown by these two resonance structures.

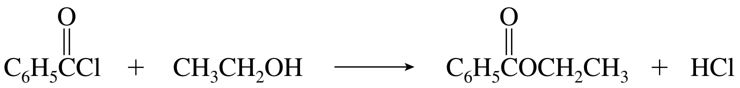
20.3 (*b*) Benzoyl chloride reacts with benzoic acid to give benzoic anhydride.



$$C_6H_5\overset{\substack{O\\ \|}}{C}Cl + C_6H_5\overset{\substack{O\\ \|}}{C}OH \longrightarrow C_6H_5\overset{\substack{O\\ \|}}{C}O\overset{\substack{O\\ \|}}{C}C_6H_5 + HCl$$

Benzoyl chloride | Benzoic acid | Benzoic anhydride | Hydrogen chloride

(*c*) Acyl chlorides react with alcohols to form esters.

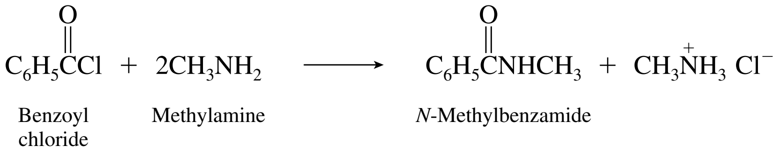


$$C_6H_5\overset{\substack{O\\ \|}}{C}Cl + CH_3CH_2OH \longrightarrow C_6H_5\overset{\substack{O\\ \|}}{C}OCH_2CH_3 + HCl$$

Benzoyl chloride | Ethanol | Ethyl benzoate | Hydrogen chloride

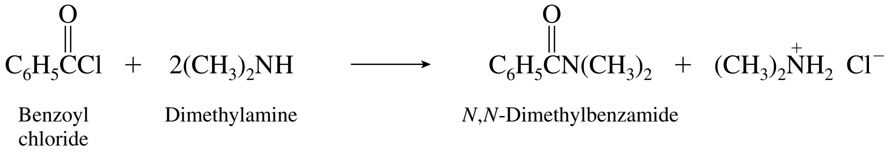
The organic product is the ethyl ester of benzoic acid, ethyl benzoate.

(*d*) Acyl transfer from benzoyl chloride to the nitrogen of methylamine yields the amide *N*-methylbenzamide.



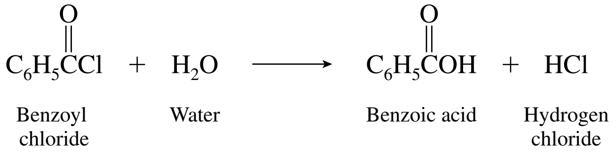
$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + 2CH_3NH_2 \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}NHCH_3 + CH_3\overset{+}{N}H_3\ Cl^-$$

(*e*) In analogy with part (*d*), an amide is formed. In this case the product has two methyl groups on nitrogen.



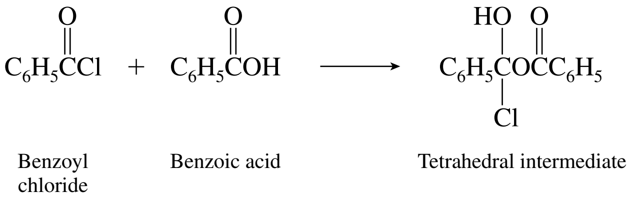
$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + 2(CH_3)_2NH \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}N(CH_3)_2 + (CH_3)_2\overset{+}{N}H_2\ Cl^-$$

(*f*) Acyl chlorides undergo hydrolysis on reaction with water. The product is a carboxylic acid.



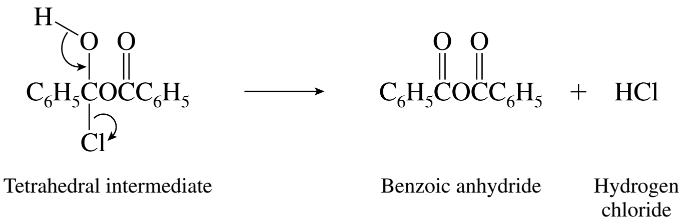
$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + H_2O \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}OH + HCl$$

20.4 (*b*) Nucleophilic addition of benzoic acid to benzoyl chloride gives the tetrahedral intermediate shown.



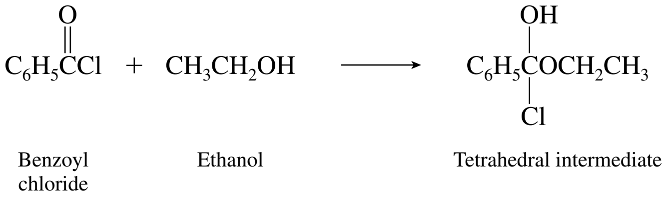
$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + C_6H_5\overset{\overset{O}{\|}}{C}OH \longrightarrow C_6H_5\overset{\overset{HO}{|}}{\underset{\underset{Cl}{|}}{C}}O\overset{\overset{O}{\|}}{C}C_6H_5$$

Dissociation of the tetrahedral intermediate occurs by loss of chloride and of the proton on the oxygen.



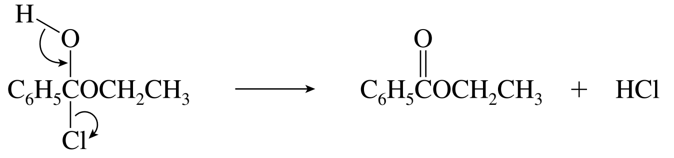
$$C_6H_5\overset{\overset{H-O}{|}}{\underset{\underset{Cl}{|}}{C}}O\overset{\overset{O}{\|}}{C}C_6H_5 \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}C_6H_5 + HCl$$

(*c*) Ethanol is the nucleophile that adds to the carbonyl group of benzoyl chloride to form the tetrahedral intermediate.



$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + CH_3CH_2OH \longrightarrow C_6H_5\overset{\overset{OH}{|}}{\underset{\underset{Cl}{|}}{C}}OCH_2CH_3$$

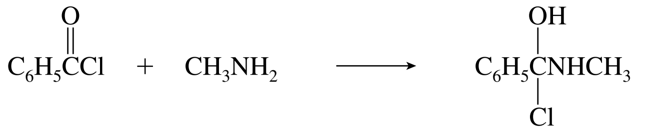
In analogy with parts (*a*) and (*b*) of this problem, a proton is lost from the hydroxyl group along with chloride to restore the carbon–oxygen double bond.



$$\mathrm{C_6H_5\overset{\overset{\displaystyle HO}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}OCH_2CH_3 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3 + HCl}$$

Tetrahedral intermediate — Ethyl benzoate — Hydrogen chloride

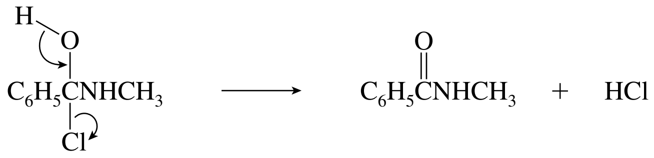
(*d*) The tetrahedral intermediate formed from benzoyl chloride and methylamine has a carbon–nitrogen bond.



$$\mathrm{C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}Cl + CH_3NH_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}NHCH_3}$$

Benzoyl chloride — Methylamine — Tetrahedral intermediate

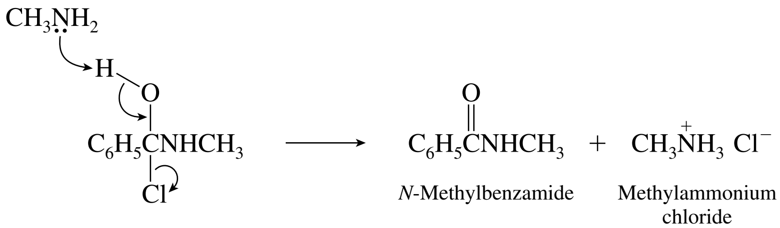
The dissociation of the tetrahedral intermediate may be shown as



$$\mathrm{C_6H_5\overset{\overset{\displaystyle HO}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}NHCH_3 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}NHCH_3 + HCl}$$

Tetrahedral intermediate — *N*-Methylbenzamide — Hydrogen chloride

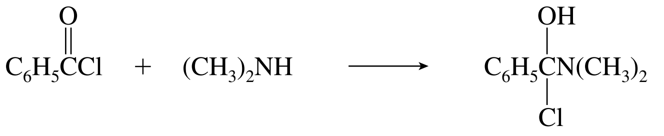
More realistically, it is a second methylamine molecule that abstracts a proton from oxygen.



$$\mathrm{CH_3\ddot{N}H_2 \quad C_6H_5\overset{\overset{\displaystyle HO}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}NHCH_3 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}NHCH_3 + CH_3\overset{+}{N}H_3\ Cl^-}$$

N-Methylbenzamide — Methylammonium chloride

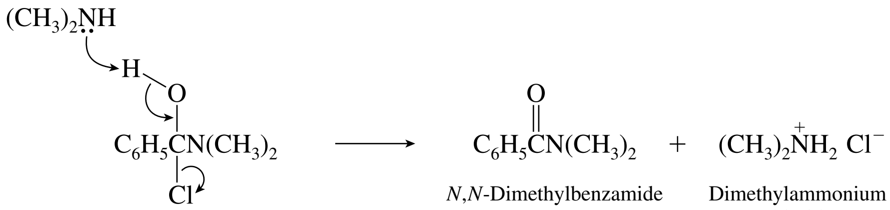
(*e*) The intermediates in the reaction of benzoyl chloride with dimethylamine are similar to those in part (*d*). The methyl substituents on nitrogen are not directly involved in the reaction.



$$\mathrm{C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}Cl + (CH_3)_2NH \longrightarrow C_6H_5\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}N(CH_3)_2}$$

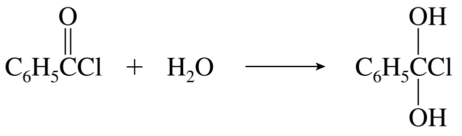
Benzoyl chloride — Dimethylamine — Tetrahedral intermediate

Then



$$\mathrm{(CH_3)_2\ddot{N}H \quad C_6H_5\overset{\overset{\displaystyle HO}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}N(CH_3)_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}N(CH_3)_2 + (CH_3)_2\overset{+}{N}H_2\ Cl^-}$$

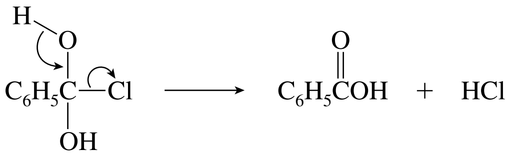
N,*N*-Dimethylbenzamide — Dimethylammonium chloride (*f*) Water attacks the carbonyl group of benzoyl chloride to form the tetrahedral intermediate.



$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + H_2O \longrightarrow C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}Cl$$

Benzoyl chloride Water Tetrahedral intermediate

Dissociation of the tetrahedral intermediate occurs by loss of chloride and the proton on oxygen.



$$C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{HO}{|}}{C}}{-}Cl \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}OH + HCl$$

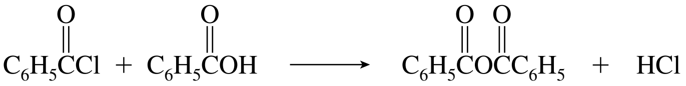
Tetrahedral intermediate Benzoic acid Hydrogen chloride

20.5 One equivalent of benzoyl chloride reacts rapidly with water to yield benzoic acid.

$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + H_2O \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}OH + HCl$$

Benzoyl chloride Water Benzoic acid Hydrogen chloride

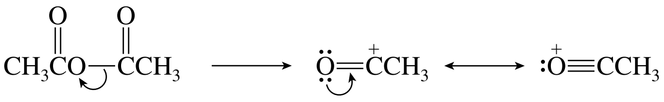
The benzoic acid produced in this step reacts with the remaining benzoyl chloride to give benzoic anhydride.



$$C_6H_5\overset{\overset{O}{\|}}{C}Cl + C_6H_5\overset{\overset{O}{\|}}{C}OH \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}C_6H_5 + HCl$$

Benzoyl chloride Benzoic acid Benzoic anhydride Hydrogen chloride

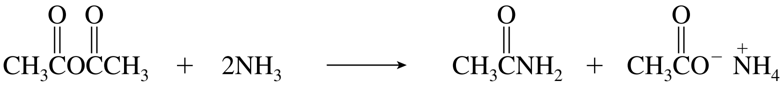
20.6 Acetic anhydride serves as a source of acetyl cation.



$$CH_3\overset{\overset{O}{\|}}{C}O{-}\overset{\overset{O}{\|}}{C}CH_3 \longrightarrow \ddot{O}{=}\overset{+}{C}CH_3 \longleftrightarrow :\overset{+}{O}{\equiv}CCH_3$$

Acetyl cation

20.7 (*b*) Acyl transfer from an acid anhydride to ammonia yields an amide.

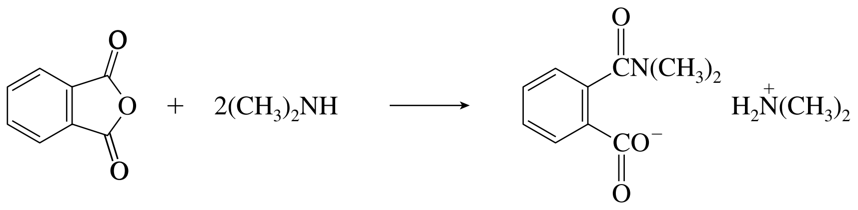


$$CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3 + 2NH_3 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}NH_2 + CH_3\overset{\overset{O}{\|}}{C}O^-\ \overset{+}{N}H_4$$

Acetic anhydride Ammonia Acetamide Ammonium acetate

The organic products are acetamide and ammonium acetate.

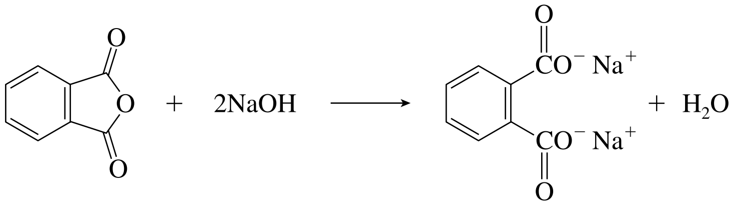
(*c*) The reaction of phthalic anhydride with dimethylamine is analogous to that of part (*b*). The organic products are an amide and the carboxylate salt of an amine.



Phthalic anhydride Dimethylamine Product is an amine salt and contains an amide function.

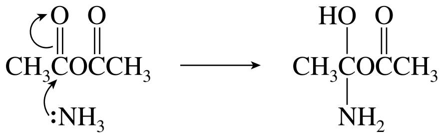
In this case both the amide function and the ammonium carboxylate salt are incorporated into the same molecule.

(*d*) The disodium salt of phthalic acid is the product of hydrolysis of phthalic acid in excess sodium hydroxide.



Phthalic anhydride Sodium hydroxide Sodium phthalate Water

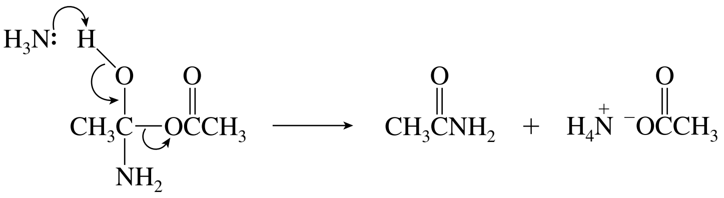
20.8 (*b*) The tetrahedral intermediate is formed by nucleophilic addition of ammonia to one of the carbonyl groups of acetic anhydride.



$$\underset{:NH_3}{CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3} \longrightarrow CH_3\underset{NH_2}{\underset{|}{\overset{HO}{\overset{|}{C}}}}O\overset{O}{\overset{\|}{C}}CH_3$$

Tetrahedral intermediate

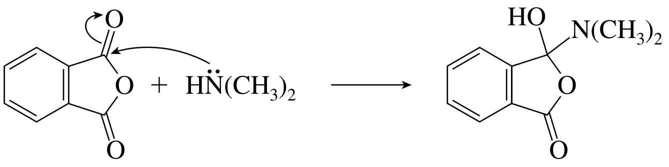
Dissociation of the tetrahedral intermediate occurs by loss of acetate as the leaving group.



$$H_3N\!:\;H\!-\!O\!-\!\underset{NH_2}{\underset{|}{C}}H_3\!-\!O\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}NH_2 + H_4\overset{+}{N}\;{}^{-}O\overset{O}{\overset{\|}{C}}CH_3$$

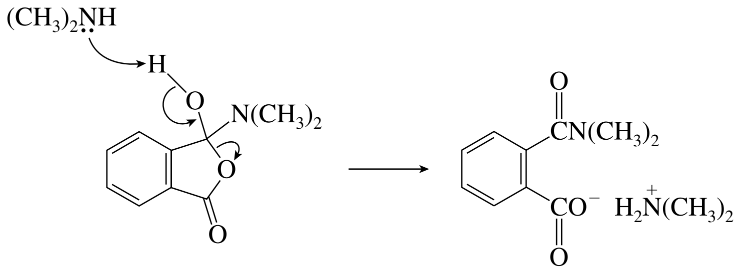
Ammonia + tetrahedral intermediate Acetamide Ammonium acetate

(*c*) Dimethylamine is the nucleophile; it adds to one of the two equivalent carbonyl groups of phthalic anhydride.



Phthalic anhydride Dimethylamine Tetrahedral intermediate

A second molecule of dimethylamine abstracts a proton from the tetrahedral intermediate.

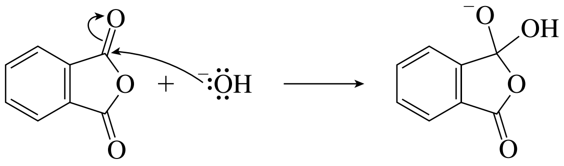


Tetrahedral intermediate + second molecule of dimethylamine

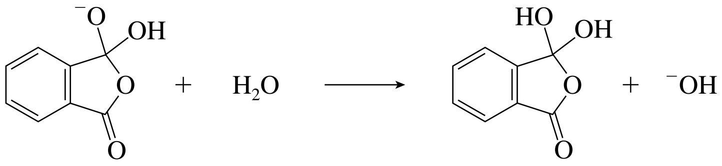
Product of reaction

(*d*) Hydroxide acts as a nucleophile to form the tetrahedral intermediate and as a base to facilitate its dissociation.

Formation of tetrahedral intermediate:

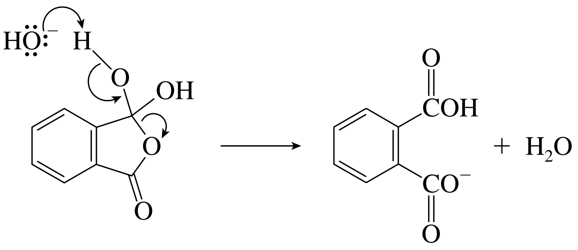


Phthalic anhydride

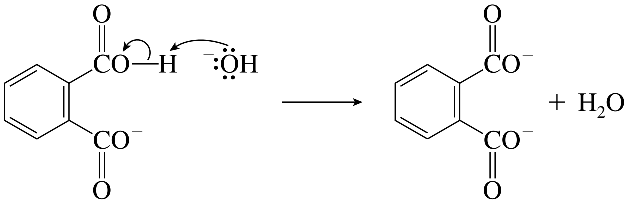


Tetrahedral intermediate

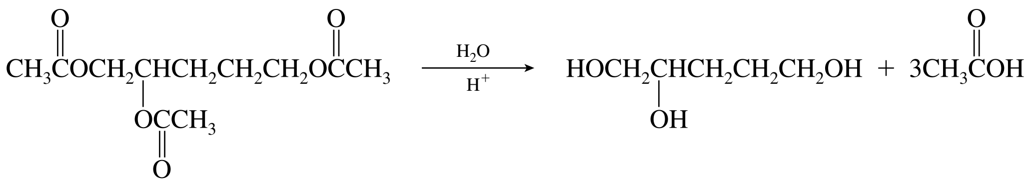
Dissociation of tetrahedral intermediate:



In base, the remaining carboxylic acid group is deprotonated.



20.9 The starting material contains three acetate ester functions. All three undergo hydrolysis in aqueous sulfuric acid.

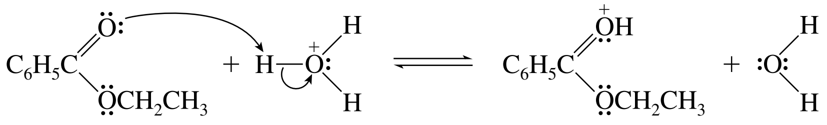


$$CH_3\overset{\overset{O}{\|}}{C}OCH_2\underset{\underset{\underset{\underset{O}{\|}}{OCCH_3}}{|}}{C}HCH_2CH_2CH_2O\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[H^+]{H_2O} HOCH_2\underset{\underset{OH}{|}}{C}HCH_2CH_2CH_2OH + 3CH_3\overset{\overset{O}{\|}}{C}OH$$

1,2,5-Pentanetriol ($C_5H_{12}O_3$) Acetic acid

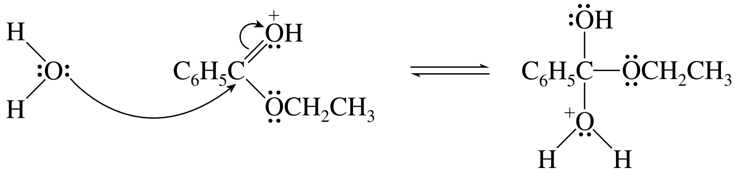
The product is 1,2,5-pentanetriol. Also formed in the hydrolysis of the starting triacetate are three molecules of acetic acid.

20.10 **Step 1: Protonation of the carbonyl oxygen**



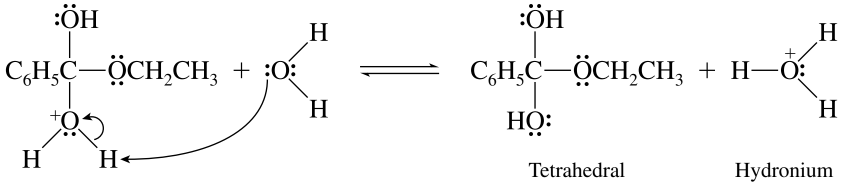
Ethyl benzoate Hydronium ion Protonated form of ester Water

Step 2: Nucleophilic addition of water



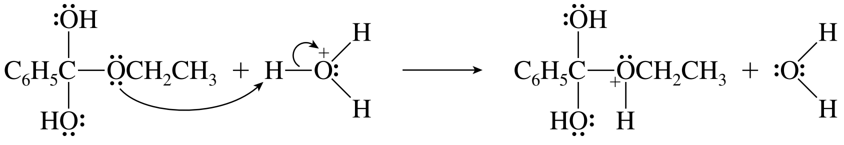
Water Protonated form of ester Oxonium ion

Step 3: Deprotonation of oxonium ion to give neutral form of tetrahedral intermediate



Tetrahedral intermediate Hydronium ion

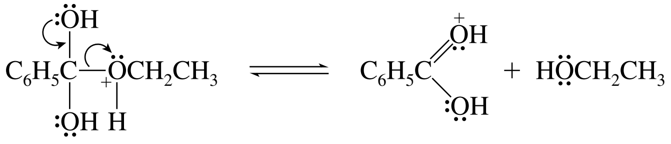
Step 4: Protonation of ethoxy oxygen



Tetrahedral intermediate Hydronium ion Oxonium ion Water

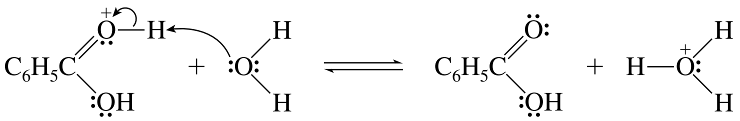
Step 5: Dissociation of protonated form of tetrahedral intermediate

This step yields ethyl alcohol and the protonated form of benzoic acid.



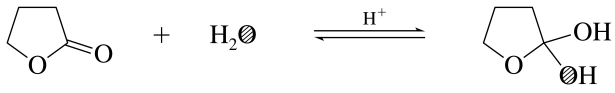
Oxonium ion Protonated form of benzoic acid Ethyl alcohol

Step 6: Deprotonation of protonated form of benzoic acid



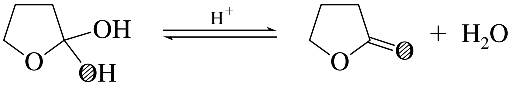
Protonated form of benzoic acid Water Benzoic acid Hydronium ion

20.11 To determine which oxygen of 4-butanolide becomes labeled with ^{18}O, trace the path of ^{18}O-labeled water (▨ = ^{18}O) as it undergoes nucleophilic addition to the carbonyl group to form the tetrahedral intermediate.



4-Butanolide ^{18}O-labeled water Tetrahedral intermediate

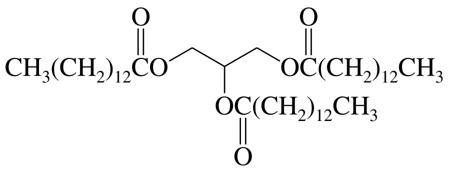
The tetrahedral intermediate can revert to unlabeled 4-butanolide by loss of ^{18}O-labeled water. Alternatively it can lose ordinary water to give ^{18}O-labeled lactone.



Tetrahedral intermediate ^{18}O-labeled 4-butanolide Water

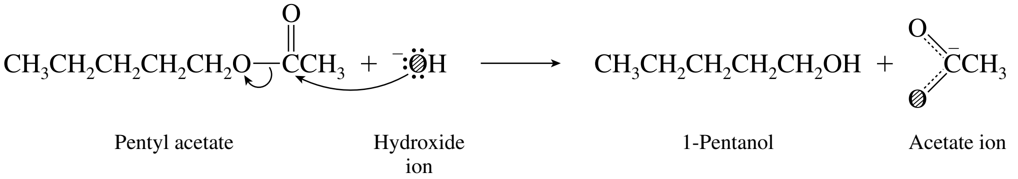
The carbonyl oxygen is the one that is isotopically labeled in the ^{18}O-enriched 4-butanolide.

20.12 On the basis of trimyristin's molecular formula $C_{45}H_{86}O_6$ and of the fact that its hydrolysis gives only glycerol and tetradecanoic acid $CH_3(CH_2)_{12}CO_2H$, it must have the structure shown.

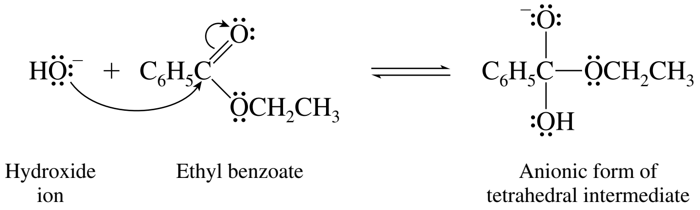


Trimyristin
($C_{45}H_{86}O_6$)

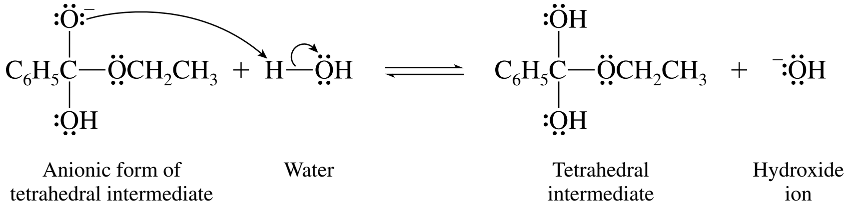
20.13 Because ester hydrolysis in base proceeds by acyl–oxygen cleavage, the ^{18}O label becomes incorporated into acetate ion (◍ = ^{18}O).



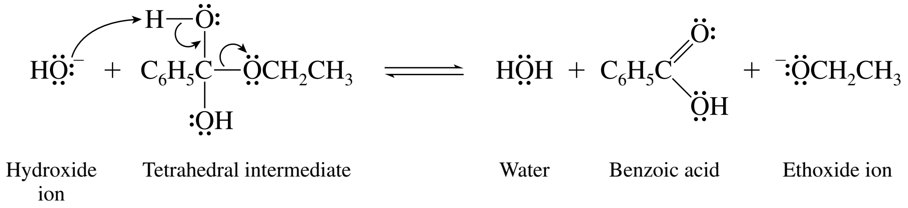
20.14 **Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group**



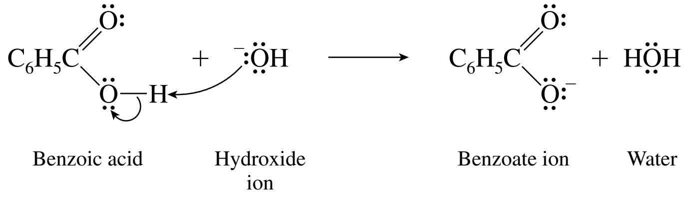
Step 2: Proton transfer from water to give neutral form of tetrahedral intermediate



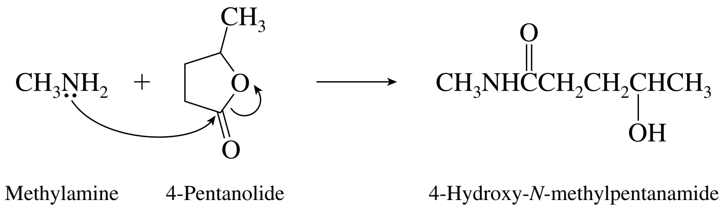
Step 3: Dissociation of tetrahedral intermediate



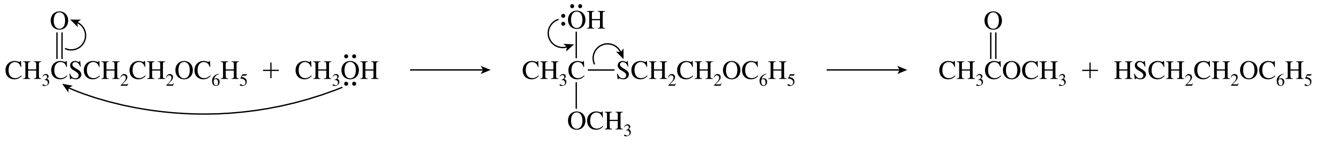
Step 4: Proton transfer from benzoic acid



20.15 The starting material is a lactone, a cyclic ester. The ester function is converted to an amide by nucleophilic acyl substitution.



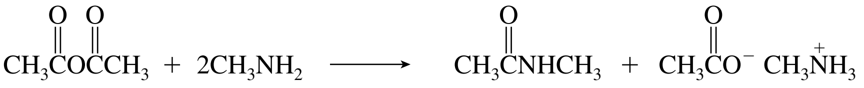
20.16 Methanol is the nucleophile that adds to the carbonyl group of the thioester.



$$CH_3\overset{O}{\overset{\|}{C}}SCH_2CH_2OC_6H_5 + CH_3\ddot{O}H \longrightarrow CH_3\overset{:\ddot{O}H}{\overset{|}{\underset{\underset{OCH_3}{|}}{C}}}—SCH_2CH_2OC_6H_5 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_3 + HSCH_2CH_2OC_6H_5$$

S-2-Phenoxyethyl ethanethiolate — Methanol — Tetrahedral intermediate — Methyl acetate — 2-Phenoxyethanethiol

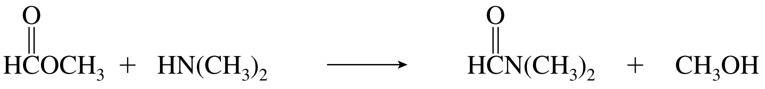
20.17 (*b*) Acetic anhydride is the anhydride that must be used; it transfers an acetyl group to suitable nucleophiles. The nucleophile in this case is methylamine.



$$CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 + 2CH_3NH_2 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3\overset{O}{\overset{\|}{C}}O^- \ CH_3\overset{+}{N}H_3$$

Acetic anhydride — Methylamine — *N*-Methylacetamide — Methylammonium acetate

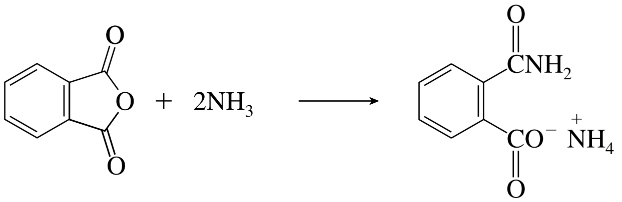
(*c*) The acyl group is $H\overset{O}{\overset{\|}{C}}—$. Because the problem specifies that the acyl transfer agent is a methyl ester, methyl formate is one of the starting materials.



$$H\overset{O}{\overset{\|}{C}}OCH_3 + HN(CH_3)_2 \longrightarrow H\overset{O}{\overset{\|}{C}}N(CH_3)_2 + CH_3OH$$

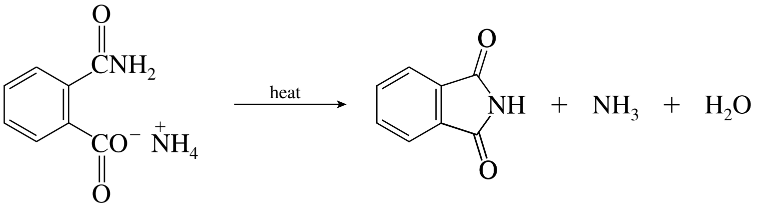
Methyl formate — Dimethylamine — *N*,*N*-Dimethylformamide — Methyl alcohol

20.18 Phthalic anhydride reacts with excess ammonia to give the ammonium salt of a compound known as **phthalamic acid.**



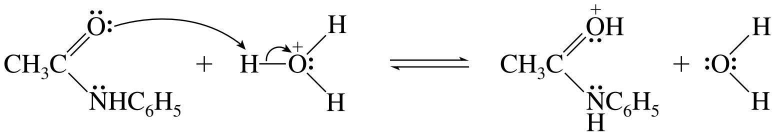
Phthalic anhydride — Ammonia — Ammonium phthalamate ($C_8H_{10}N_2O_3$)

Phthalimide is formed when ammonium phthalamate is heated.



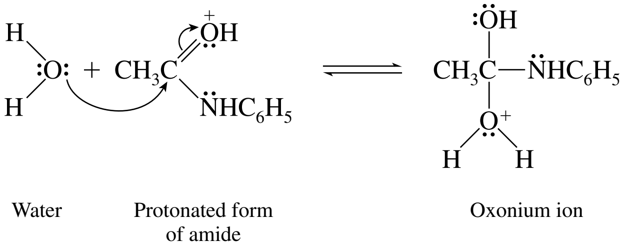
Ammonium phthalamate — Phthalimide — Ammonia — Water

20.19 **Step 1: Protonation of the carbonyl oxygen**

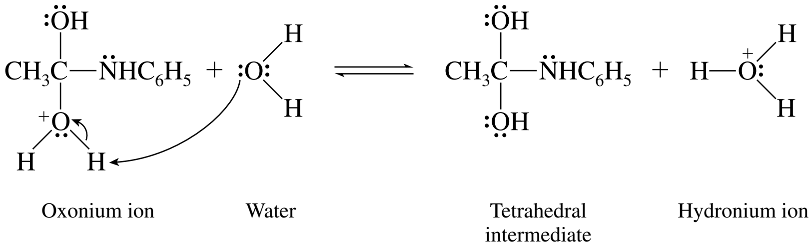


Acetanilide — Hydronium ion — Protonated form of amide — Water

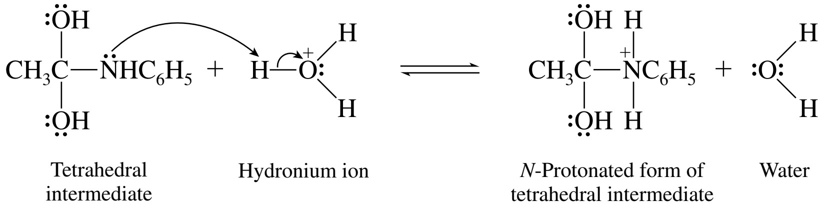
Step 2: Nucleophilic addition of water



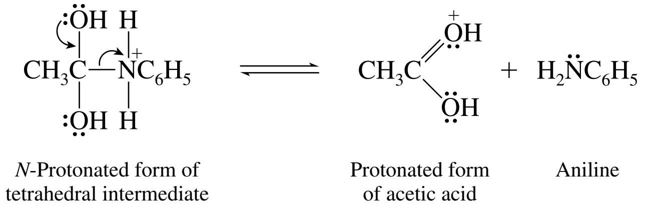
Step 3: Deprotonation of oxonium ion to give neutral form of tetrahedral intermediate



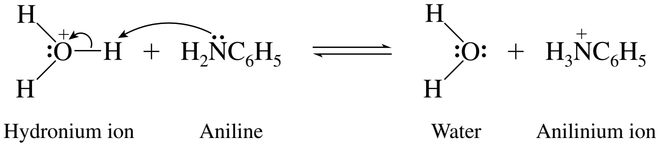
Step 4: Protonation of amino group of tetrahedral intermediate

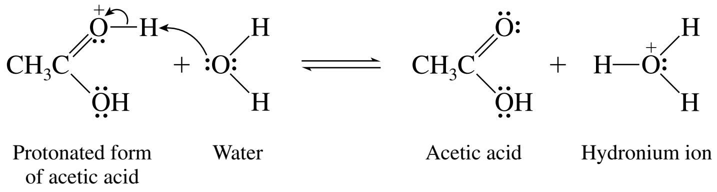


Step 5: Dissociation of *N*-protonated form of tetrahedral intermediate

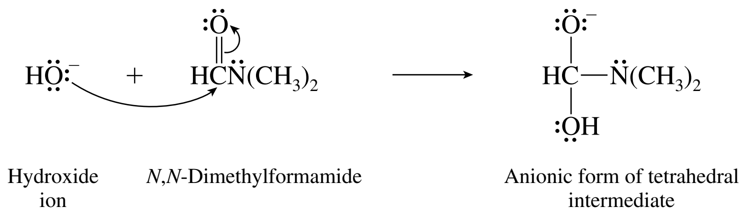


Step 6: Proton-transfer processes

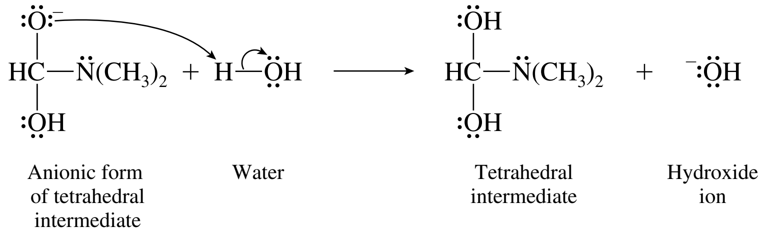




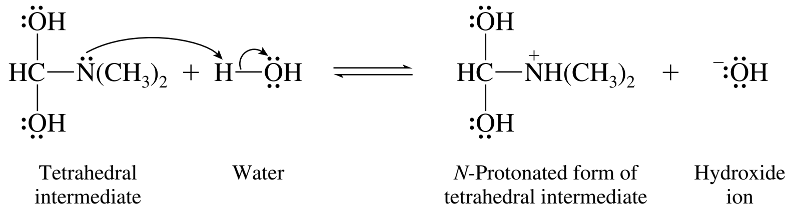
20.20 **Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group**



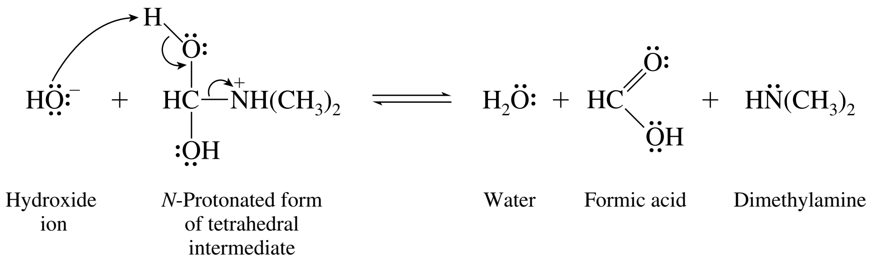
Step 2: Proton transfer to give neutral form of tetrahedral intermediate



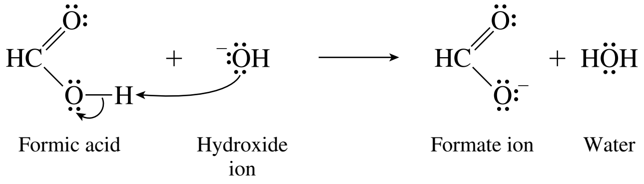
Step 3: Proton transfer from water to nitrogen of tetrahedral intermediate



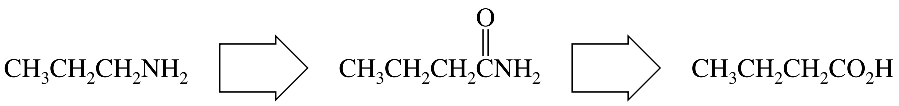
Step 4: Dissociation of *N*-protonated form of tetrahedral intermediate



Step 5: Irreversible formation of formate ion

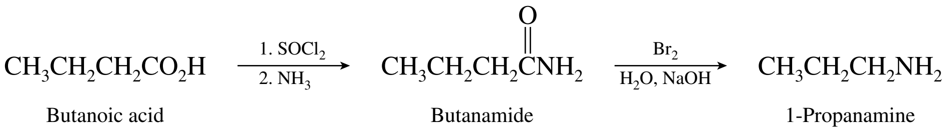


20.21 A synthetic scheme becomes apparent when we recognize that a primary amine may be obtained by Hofmann rearrangement of the primary amide having one more carbon in its acyl group. This amide may, in turn, be prepared from the corresponding carboxylic acid.



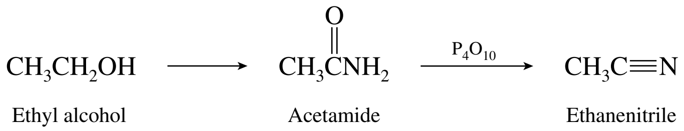
$$CH_3CH_2CH_2NH_2 \Rightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \Rightarrow CH_3CH_2CH_2CO_2H$$

The desired reaction scheme is therefore



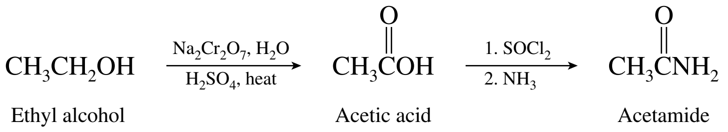
$$CH_3CH_2CH_2CO_2H \xrightarrow[2.\ NH_3]{1.\ SOCl_2} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[H_2O,\ NaOH]{Br_2} CH_3CH_2CH_2NH_2$$

20.22 (*a*) Ethanenitrile has the same number of carbon atoms as ethyl alcohol. This suggests a reaction scheme proceeding via an amide.



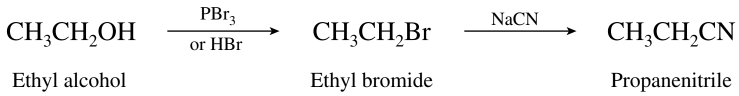
$$CH_3CH_2OH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{P_4O_{10}} CH_3C{\equiv}N$$

The necessary amide is prepared from ethanol.



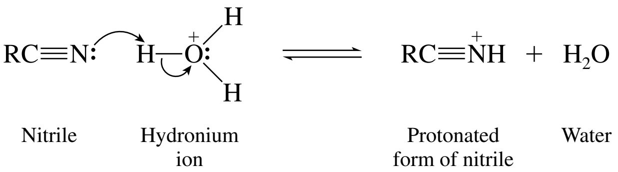
$$CH_3CH_2OH \xrightarrow[H_2SO_4,\ heat]{Na_2Cr_2O_7,\ H_2O} CH_3\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ NH_3]{1.\ SOCl_2} CH_3\overset{O}{\overset{\|}{C}}NH_2$$

(*b*) Propanenitrile may be prepared from ethyl alcohol by way of a nucleophilic substitution reaction of the corresponding bromide.

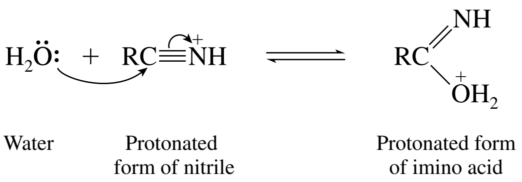


$$CH_3CH_2OH \xrightarrow[or\ HBr]{PBr_3} CH_3CH_2Br \xrightarrow{NaCN} CH_3CH_2CN$$

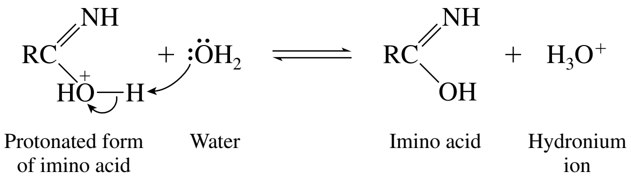
20.23 **Step 1: Protonation of the nitrile**



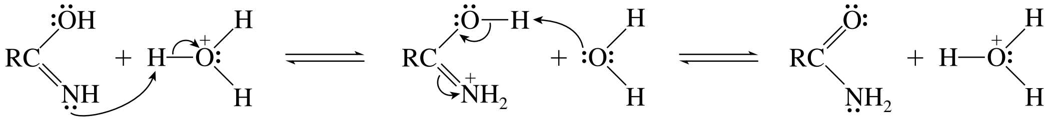
Step 2: Nucleophilic addition of water



Step 3: Deprotonation of imino acid

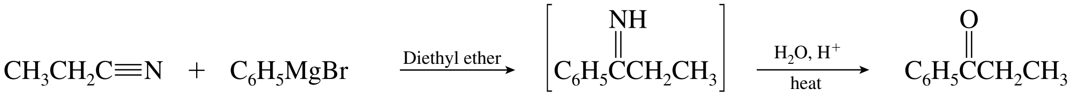


Steps 4 and 5: Proton transfers to give an amide



Imino acid Hydronium ion Conjugate acid of amide Water Amide Hydronium ion

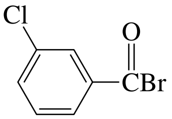
20.24 Ketones may be prepared by the reaction of nitriles with Grignard reagents. Nucleophilic addition of a Grignard reagent to a nitrile produces an imine. The imine is not normally isolated, however, but is hydrolyzed to the corresponding ketone. Ethyl phenyl ketone may be prepared by the reaction of propanenitrile with a phenyl Grignard reagent such as phenylmagnesium bromide, followed by hydrolysis of the imine.



$$CH_3CH_2C{\equiv}N + C_6H_5MgBr \xrightarrow{\text{Diethyl ether}} \left[C_6H_5\overset{\overset{NH}{\|}}{C}CH_2CH_3 \right] \xrightarrow[\text{heat}]{H_2O,\ H^+} C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_3$$

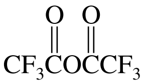
Propanenitrile Phenylmagnesium bromide Imine (not isolated) Ethyl phenyl ketone

20.25 (*a*) The halogen that is attached to the carbonyl group is identified in the name as a separate word following the name of the acyl group.



m-Chlorobenzoyl bromide

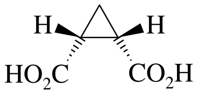
(*b*) Trifluoroacetic anhydride is the anhydride of trifluoroacetic acid. Notice that it contains six fluorines.



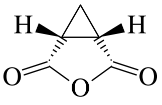
$$CF_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CF_3$$

Trifluoroacetic anhydride

(*c*) This compound is the cyclic anhydride of *cis*-1,2-cyclopropanedicarboxylic acid.

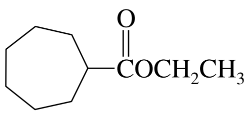


cis-1,2-Cyclopropanedicarboxylic acid



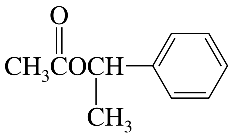
cis-1,2-Cyclopropanedicarboxylic anhydride

(*d*) Ethyl cycloheptanecarboxylate is the ethyl ester of cycloheptanecarboxylic acid.



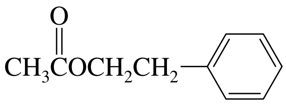
Ethyl cycloheptanecarboxylate

(*e*) 1-Phenylethyl acetate is the ester of 1-phenylethanol and acetic acid.



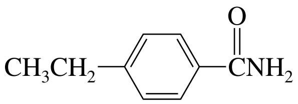
1-Phenylethyl acetate

(*f*) 2-Phenylethyl acetate is the ester of 2-phenylethanol and acetic acid.



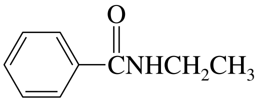
2-Phenylethyl acetate

(*g*) The parent compound in this case is benzamide. *p*-Ethylbenzamide has an ethyl substituent at the ring position para to the carbonyl group.



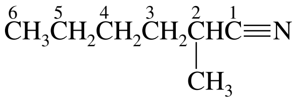
p-Ethylbenzamide

(*h*) The parent compound is benzamide. In *N*-ethylbenzamide the ethyl substituent is bonded to nitrogen.



N-Ethylbenzamide

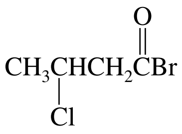
(*i*) Nitriles are named by adding the suffix *-nitrile* to the name of the alkane having the same number of carbons. Numbering begins at the nitrile carbon.



$$\overset{6}{\mathrm{C}}\mathrm{H_3}\overset{5}{\mathrm{C}}\mathrm{H_2}\overset{4}{\mathrm{C}}\mathrm{H_2}\overset{3}{\mathrm{C}}\mathrm{H_2}\underset{\mathrm{CH_3}}{\overset{2}{\mathrm{C}}}\mathrm{H}\overset{1}{\mathrm{C}}{\equiv}\mathrm{N}$$

2-Methylhexanenitrile

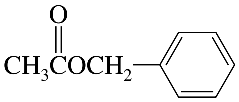
20.26 (*a*) This compound, with a bromine substituent attached to its carbonyl group, is named as an acyl bromide. It is 3-chlorobutanoyl bromide.



$$\mathrm{CH_3}\underset{\mathrm{Cl}}{\mathrm{C}}\mathrm{HCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Br}$$

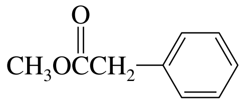
3-Chlorobutanoyl
bromide

(*b*) The group attached to oxygen, in this case **benzyl,** is identified first in the name of the ester. This compound is the benzyl ester of acetic acid.



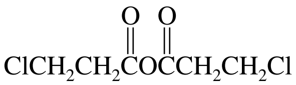
Benzyl acetate

(*c*) The group attached to oxygen is methyl; this compound is the methyl ester of phenylacetic acid.



Methyl phenylacetate

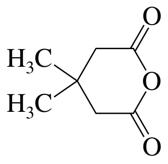
(*d*) This compound contains the functional group $-\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}-$ and thus is an anhydride of a carboxylic acid. We name the acid, in this case 3-chloropropanoic acid, drop the *acid* part of the name, and replace it by *anhydride.*



$$ClCH_2CH_2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_2CH_2Cl$$

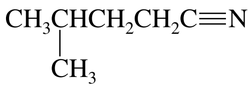
3-Chloropropanoic anhydride

(*e*) This compound is a cyclic anhydride, whose parent acid is 3,3-dimethylpentanedioic acid.



3,3-Dimethylpentanedioic anhydride

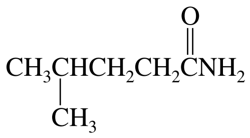
(*f*) Nitriles are named by adding *-nitrile* to the name of the alkane having the same number of carbons. Remember to count the carbon of the C≡N group.



$$CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2C\equiv N$$

4-Methylpentanenitrile

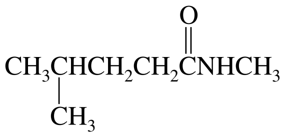
(*g*) This compound is an amide. We name the corresponding acid and then replace the *-oic acid* suffix by *-amide.*



$$CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}NH_2$$

4-Methylpentanamide

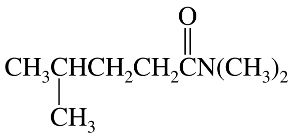
(*h*) This compound is the *N*-methyl derivative of 4-methylpentanamide.



$$CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_3$$

N-Methyl-4-methylpentanamide

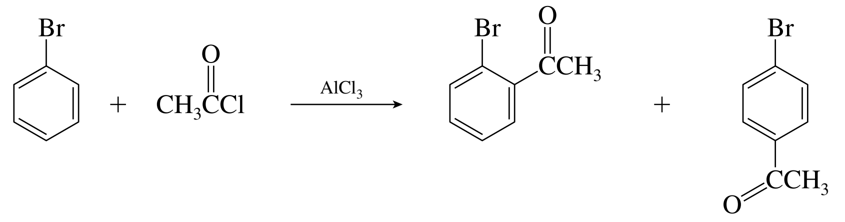
(*i*) The amide nitrogen bears two methyl groups. We designate this as an *N*,*N*-dimethyl amide.



$$\mathrm{CH_3\underset{\underset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{O}{\|}}{C}N(CH_3)_2}$$

N,*N*-Dimethyl-4-methylpentanamide

20.27 (*a*) Acetyl chloride acts as an acyl transfer agent to the aromatic ring of bromobenzene. The reaction is a Friedel–Crafts acylation. Bromine is an ortho, para-directing substituent.



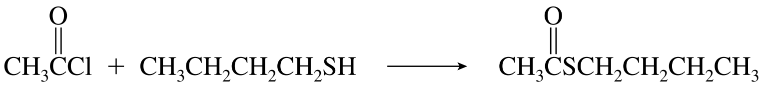
Bromobenzene

Acetyl chloride

o-Bromoacetophenone

p-Bromoacetophenone

(*b*) Acyl chlorides react with thiols to give thioesters.



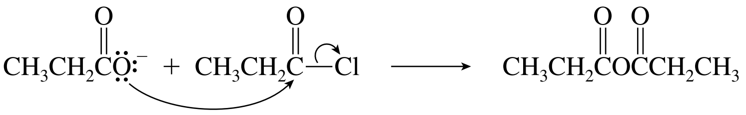
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}Cl + CH_3CH_2CH_2CH_2SH \longrightarrow CH_3\overset{\overset{O}{\|}}{C}SCH_2CH_2CH_2CH_3}$$

Acetyl chloride

1-Butanethiol

S-Butyl ethanethioate

(*c*) Sodium propanoate acts as a nucleophile toward propanoyl chloride. The product is propanoic anhydride.



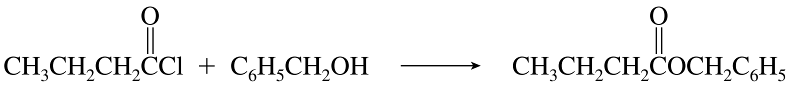
$$\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}\ddot{\underset{..}{O}}{:}^{-} + CH_3CH_2\overset{\overset{O}{\|}}{C}{-}Cl \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_2CH_3}$$

Propanoate anion

Propanoyl chloride

Propanoic anhydride

(*d*) Acyl chlorides convert alcohols to esters.



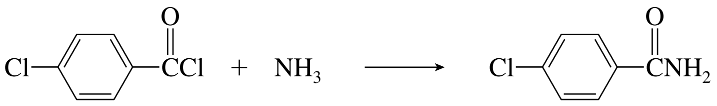
$$\mathrm{CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}Cl + C_6H_5CH_2OH \longrightarrow CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2C_6H_5}$$

Butanoyl chloride

Benzyl alcohol

Benzyl butanoate

(*e*) Acyl chlorides react with ammonia to yield amides.

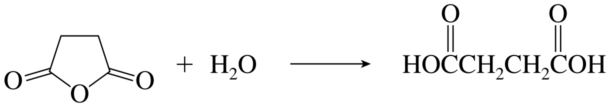


p-Chlorobenzoyl chloride

Ammonia

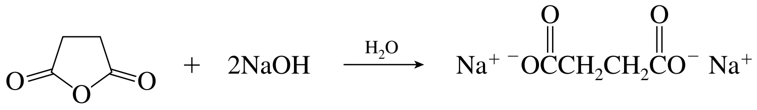
p-Chlorobenzamide

(*f*) The starting material is a cyclic anhydride. Acid anhydrides react with water to yield two carboxylic acid functions; when the anhydride is cyclic, a dicarboxylic acid results.



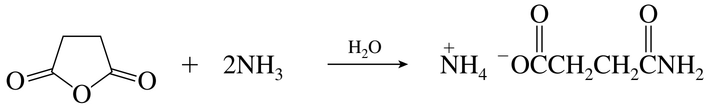
Succinic anhydride Water Succinic acid

(*g*) In dilute sodium hydroxide the anhydride is converted to the disodium salt of the diacid.



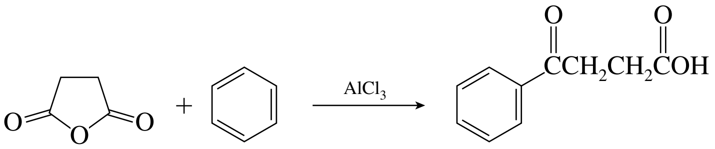
Succinic anhydride Sodium hydroxide Sodium succinate

(*h*) One of the carbonyl groups of the cyclic anhydride is converted to an amide function on reaction with ammonia. The other, the one that would become a carboxylic acid group, is converted to an ammonium carboxylate salt.



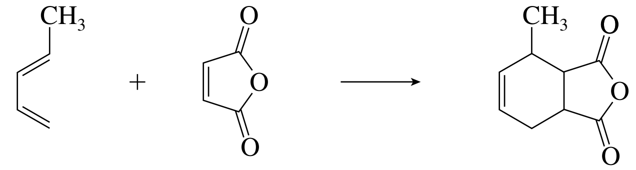
Succinic anhydride Ammonia Ammonium succinamate

(*i*) Acid anhydrides are used as acylating agents in Friedel–Crafts reactions.



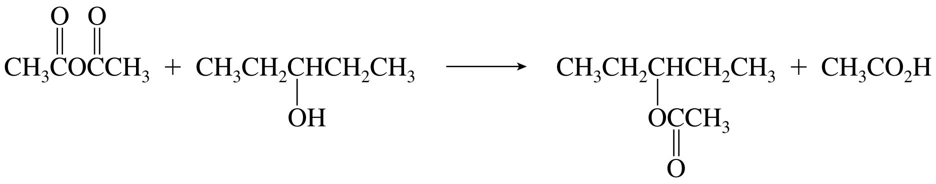
Succinic anhydride Benzene 3-Benzoylpropanoic acid

(*j*) The reactant is maleic anhydride; it is a good dienophile in Diels–Alder reactions.



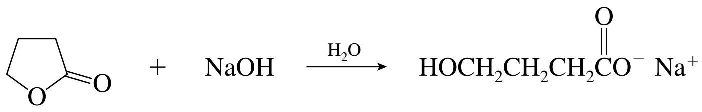
1,3-Pentadiene Maleic anhydride 3-Methylcyclohexene-4,5-dicarboxylic anhydride

(*k*) Acid anhydrides react with alcohols to give an ester and a carboxylic acid.



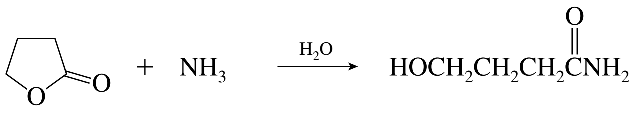
$$CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3 + CH_3CH_2\underset{\underset{OH}{|}}{C}HCH_2CH_3 \longrightarrow CH_3CH_2\underset{\underset{O\underset{\underset{O}{\|}}{C}CH_3}{|}}{C}HCH_2CH_3 + CH_3CO_2H$$

Acetic anhydride 3-Pentanol 1-Ethylpropyl acetate Acetic acid (*l*) The starting material is a cyclic ester, a lactone. Esters undergo saponification in aqueous base to give an alcohol and a carboxylate salt.



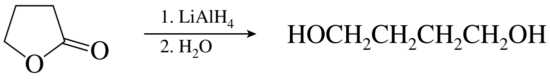
4-Butanolide Sodium hydroxide Sodium 4-hydroxybutanoate

(*m*) Ammonia reacts with esters to give an amide and an alcohol.



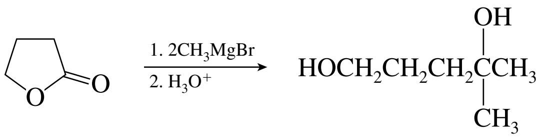
4-Butanolide Ammonia 4-Hydroxybutanamide

(*n*) Lithium aluminum hydride reduces esters to two alcohols; the one derived from the acyl group is a primary alcohol. Reduction of a cyclic ester gives a diol.



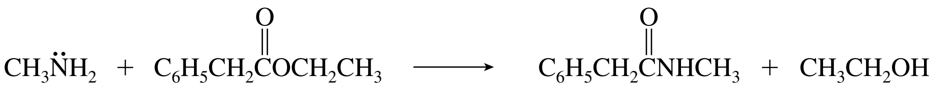
4-Butanolide 1,4-Butanediol

(*o*) Grignard reagents react with esters to give tertiary alcohols.



4-Butanolide 4-Methyl-1,4-pentanediol

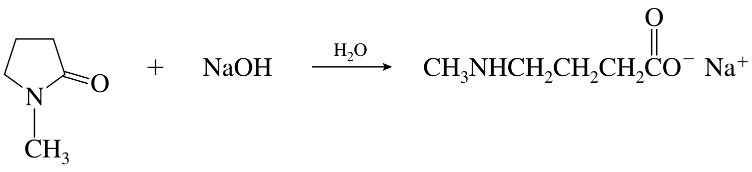
(*p*) In this reaction methylamine acts as a nucleophile toward the carbonyl group of the ester. The product is an amide.



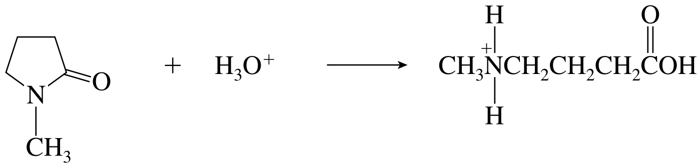
$$CH_3\ddot{N}H_2 + C_6H_5CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \longrightarrow C_6H_5CH_2\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3CH_2OH$$

Methylamine Ethyl phenylacetate *N*-Methylphenylacetamide Ethyl alcohol

(*q*) The starting material is a lactam, a cyclic amide. Amides are hydrolyzed in base to amines and carboxylate salts.



N-Methylpyrrolidone Sodium hydroxide Sodium 4-(methylamino)butanoate (*r*) In acid solution amides yield carboxylic acids and ammonium salts.

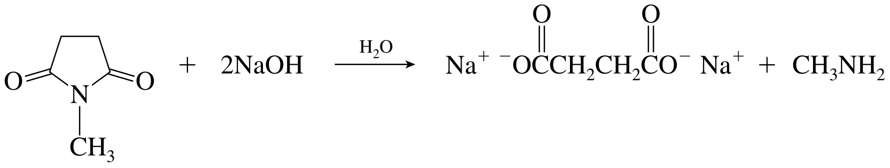


N-Methylpyrrolidone

Hydronium ion

4-(Methylammonio)butanoic acid

(*s*) The starting material is a cyclic imide. Both its amide bonds are cleaved by nucleophilic attack by hydroxide ion.



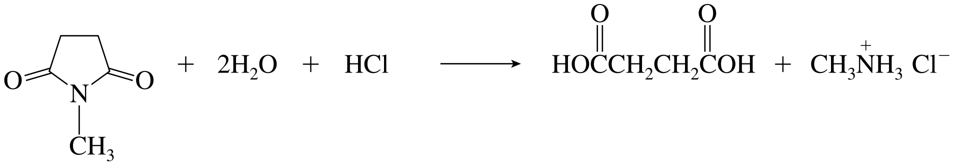
N-Methylsuccinimide

Sodium hydroxide

Disodium succinate

Methylamine

(*t*) In acid the imide undergoes cleavage to give a dicarboxylic acid and the conjugate acid of methylamine.



N-Methylsuccinimide

Water

Hydrogen chloride

Succinic acid

Methylammonium chloride

(*u*) Acetanilide is hydrolyzed in acid to acetic acid and the conjugate acid of aniline.

$$C_6H_5NH\overset{O}{\overset{\|}{C}}CH_3 + H_2O + HCl \longrightarrow C_6H_5\overset{+}{N}H_3\ Cl^- + CH_3\overset{O}{\overset{\|}{C}}OH$$

Acetanilide

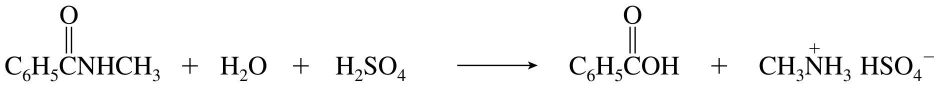
Water

Hydrogen chloride

Anilinium chloride

Acetic acid

(*v*) This is another example of amide hydrolysis.



$$C_6H_5\overset{O}{\overset{\|}{C}}NHCH_3 + H_2O + H_2SO_4 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}OH + CH_3\overset{+}{N}H_3\ HSO_4^-$$

N-Methylbenzamide

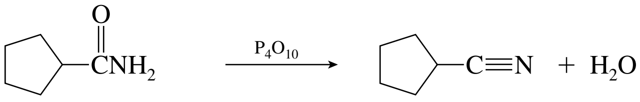
Water

Sulfuric acid

Benzoic acid

Methylammonium hydrogen sulfate

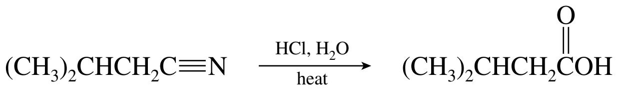
(*w*) One way to prepare nitriles is by dehydration of amides.



Cyclopentanecarboxamide

Cyclopentyl cyanide

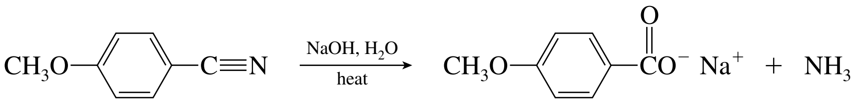
(*x*) Nitriles are hydrolyzed to carboxylic acids in acidic media.



$$(CH_3)_2CHCH_2C{\equiv}N \xrightarrow[\text{heat}]{\text{HCl, }H_2O} (CH_3)_2CHCH_2\overset{\overset{\displaystyle O}{\|}}{C}OH$$

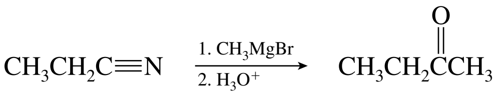
3-Methylbutanenitrile 3-Methylbutanoic acid

(*y*) Nitriles are hydrolyzed in aqueous base to salts of carboxylic acids.



p-Methoxybenzonitrile Sodium *p*-methoxybenzoate Ammonia

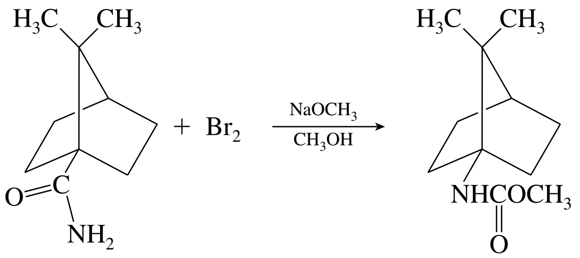
(*z*) Grignard reagents react with nitriles to yield ketones after addition of aqueous acid.



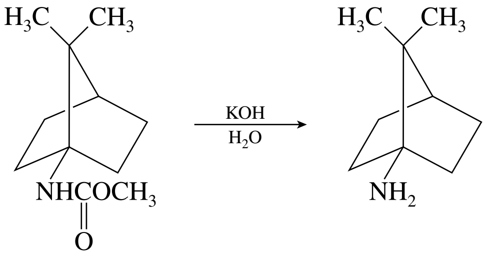
$$CH_3CH_2C{\equiv}N \xrightarrow[\text{2. }H_3O^+]{\text{1. }CH_3MgBr} CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

Propanenitrile 2-Butanone

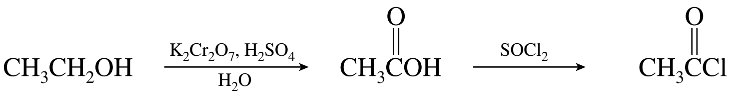
(*aa*) Amides undergo the Hofmann rearrangement on reaction with bromine and base. A methyl carbamate is the product isolated when the reaction is carried out in methanol.



(*bb*) Saponification of the carbamate in part (*aa*) gives the corresponding amine.



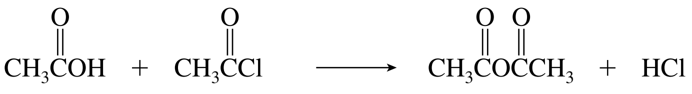
20.28 (*a*) Acetyl chloride is prepared by reaction of acetic acid with thionyl chloride. The first task then is to prepare acetic acid by oxidation of ethanol.



$$CH_3CH_2OH \xrightarrow[H_2O]{K_2Cr_2O_7,\ H_2SO_4} CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH \xrightarrow{SOCl_2} CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl$$

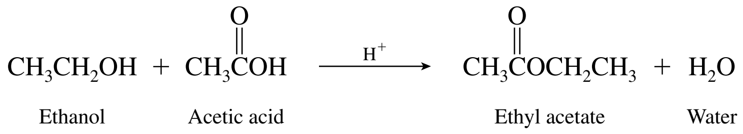
Ethanol Acetic acid Acetyl chloride

(*b*) Acetic acid and acetyl chloride, available from part (*a*), can be combined to form acetic anhydride.



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH + CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}O\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + HCl$$

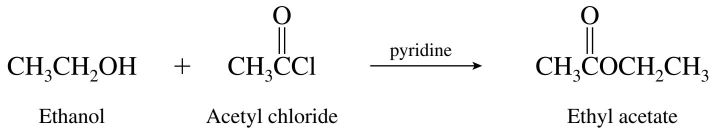
Acetic acid Acetyl chloride Acetic anhydride Hydrogen chloride (*c*) Ethanol can be converted to ethyl acetate by reaction with acetic acid, acetyl chloride, or acetic anhydride from parts (*a*) and (*b*).



$$CH_3CH_2OH + CH_3\overset{\overset{O}{\|}}{C}OH \xrightarrow{H^+} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 + H_2O$$

Ethanol Acetic acid Ethyl acetate Water

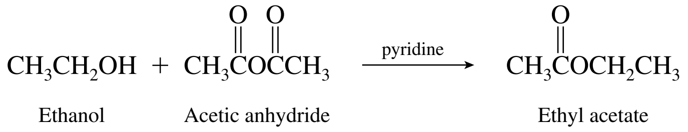
or



$$CH_3CH_2OH + CH_3\overset{\overset{O}{\|}}{C}Cl \xrightarrow{\text{pyridine}} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Ethanol Acetyl chloride Ethyl acetate

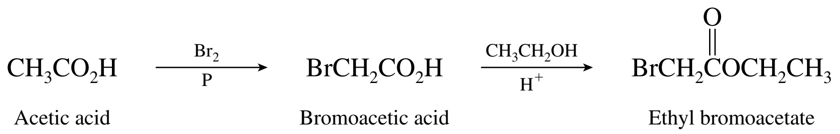
or



$$CH_3CH_2OH + CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{\text{pyridine}} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Ethanol Acetic anhydride Ethyl acetate

(*d*) Ethyl bromoacetate is the ethyl ester of bromoacetic acid; thus the first task is to prepare the acid. We use the acetic acid prepared in part (*a*), converting it to bromoacetic acid by the Hell–Volhard–Zelinsky reaction.



$$CH_3CO_2H \xrightarrow[P]{Br_2} BrCH_2CO_2H \xrightarrow[H^+]{CH_3CH_2OH} BrCH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Acetic acid Bromoacetic acid Ethyl bromoacetate

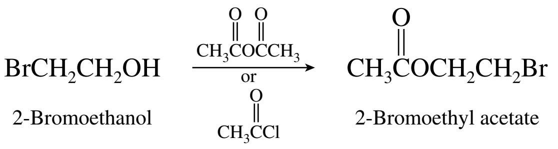
Alternatively, bromoacetic acid could be converted to the corresponding acyl chloride, then treated with ethanol. It would be incorrect to try to brominate ethyl acetate; the Hell–Volhard–Zelinsky method requires an acid as starting material, not an ester.

(*e*) The alcohol $BrCH_2CH_2OH$, needed in order to prepare 2-bromoethyl acetate, is prepared from ethanol by way of ethylene.

$$CH_3CH_2OH \xrightarrow[\text{heat}]{H_2SO_4} CH_2{=}CH_2 \xrightarrow[H_2O]{Br_2} BrCH_2CH_2OH$$

Ethanol Ethylene 2-Bromoethanol

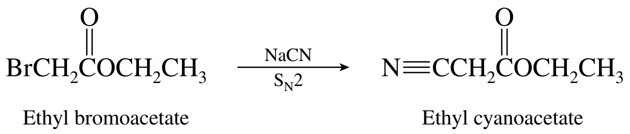
Then



$$BrCH_2CH_2OH \xrightarrow[\substack{\text{or} \\ CH_3\overset{\overset{O}{\|}}{C}Cl}]{CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_2Br$$

2-Bromoethanol 2-Bromoethyl acetate

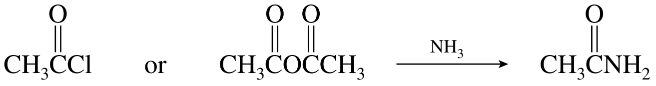
(*f*) Ethyl cyanoacetate may be prepared from the ethyl bromoacetate obtained in part (*d*). The bromide may be displaced by cyanide in a nucleophilic substitution reaction.



$$BrCH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[S_N2]{NaCN} N{\equiv}CCH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Ethyl bromoacetate Ethyl cyanoacetate

(*g*) Reaction of the acetyl chloride prepared in part (*a*) or the acetic anhydride from part (*b*) with ammonia gives acetamide.



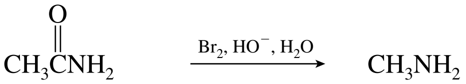
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}Cl} \quad \text{or} \quad \mathrm{CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3} \xrightarrow{\mathrm{NH_3}} \mathrm{CH_3\overset{\overset{O}{\|}}{C}NH_2}$$

Acetyl chloride

Acetic anhydride

Acetamide

(*h*) Methylamine may be prepared from acetamide by a Hofmann rearrangement.

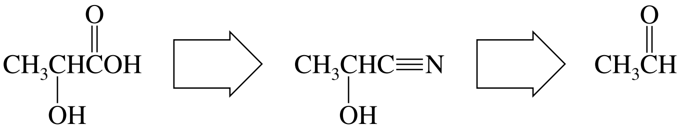


$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}NH_2} \xrightarrow{\mathrm{Br_2,\ HO^-,\ H_2O}} \mathrm{CH_3NH_2}$$

Acetamide [prepared as in part (*g*)]

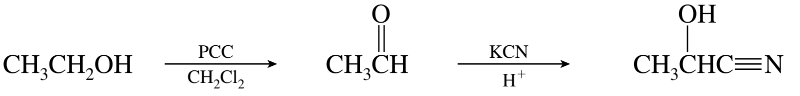
Methylamine

(*i*) The desired hydroxy acid is available from hydrolysis of the corresponding cyanohydrin, which may be prepared by reaction of the appropriate aldehyde with cyanide ion.



$$\mathrm{CH_3\underset{\underset{OH}{|}}{C}H\overset{\overset{O}{\|}}{C}OH} \Longrightarrow \mathrm{CH_3\underset{\underset{OH}{|}}{C}HC{\equiv}N} \Longrightarrow \mathrm{CH_3\overset{\overset{O}{\|}}{C}H}$$

In this synthesis the cyanohydrin is prepared from ethanol by way of acetaldehyde.

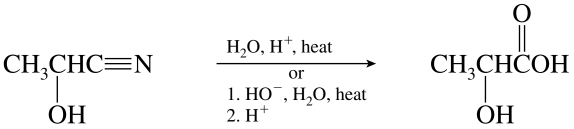


$$\mathrm{CH_3CH_2OH} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{PCC}} \mathrm{CH_3\overset{\overset{O}{\|}}{C}H} \xrightarrow[\mathrm{H^+}]{\mathrm{KCN}} \mathrm{CH_3\overset{\overset{OH}{|}}{C}HC{\equiv}N}$$

Ethanol

Acetaldehyde

2-Hydroxypropanenitrile

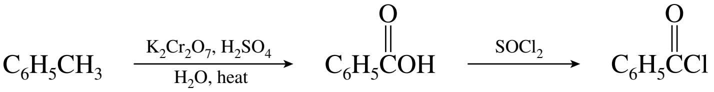


$$\mathrm{CH_3\underset{\underset{OH}{|}}{C}HC{\equiv}N} \xrightarrow[\substack{\text{or} \\ 1.\ \mathrm{HO^-,\ H_2O,\ heat} \\ 2.\ \mathrm{H^+}}]{\mathrm{H_2O,\ H^+,\ heat}} \mathrm{CH_3\underset{\underset{OH}{|}}{C}H\overset{\overset{O}{\|}}{C}OH}$$

2-Hydroxypropanenitrile

2-Hydroxypropanoic acid

20.29 (*a*) Benzoyl chloride is made from benzoic acid. Oxidize toluene to benzoic acid, and then treat with thionyl chloride.



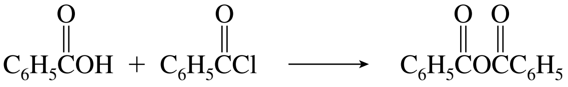
$$\mathrm{C_6H_5CH_3} \xrightarrow[\mathrm{H_2O,\ heat}]{\mathrm{K_2Cr_2O_7,\ H_2SO_4}} \mathrm{C_6H_5\overset{\overset{O}{\|}}{C}OH} \xrightarrow{\mathrm{SOCl_2}} \mathrm{C_6H_5\overset{\overset{O}{\|}}{C}Cl}$$

Toluene

Benzoic acid

Benzoyl chloride

(*b*) Benzoyl chloride and benzoic acid, both prepared from toluene in part (*a*), react with each other to give benzoic anhydride.



$$\mathrm{C_6H_5\overset{\overset{O}{\|}}{C}OH} + \mathrm{C_6H_5\overset{\overset{O}{\|}}{C}Cl} \longrightarrow \mathrm{C_6H_5\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}C_6H_5}$$

Benzoic acid

Benzoyl chloride

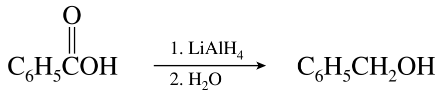
Benzoic anhydride

(*c*) Benzoic acid, benzoyl chloride, and benzoic anhydride have been prepared in parts (*a*) and (*b*) of this problem. Any of them could be converted to benzyl benzoate on reaction with benzyl alcohol. Thus the synthesis of benzyl benzoate requires the preparation of benzyl alcohol from toluene. This is effected by a nucleophilic substitution reaction of benzyl bromide, in turn prepared by halogenation of toluene.

$$C_6H_5CH_3 \xrightarrow[\text{or } Br_2\text{, light}]{N\text{-bromosuccinimide (NBS)}} C_6H_5CH_2Br \xrightarrow[HO^-]{H_2O} C_6H_5CH_2OH$$

Toluene — Benzyl bromide — Benzyl alcohol

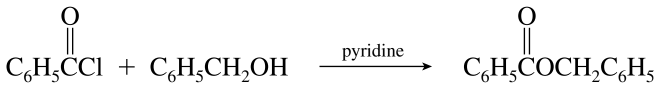
Alternatively, recall that primary alcohols may be obtained by reduction of the corresponding carboxylic acid.



$$C_6H_5\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} C_6H_5CH_2OH$$

Benzoic acid — Benzyl alcohol

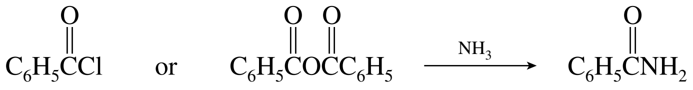
Then



$$C_6H_5\overset{O}{\overset{\|}{C}}Cl + C_6H_5CH_2OH \xrightarrow{\text{pyridine}} C_6H_5\overset{O}{\overset{\|}{C}}OCH_2C_6H_5$$

Benzoyl chloride — Benzyl alcohol — Benzyl benzoate

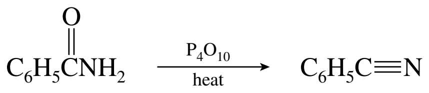
(*d*) Benzamide is prepared by reaction of ammonia with either benzoyl chloride from part (*a*) or benzoic anhydride from part (*b*).



$$C_6H_5\overset{O}{\overset{\|}{C}}Cl \quad \text{or} \quad C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}C_6H_5 \xrightarrow{NH_3} C_6H_5\overset{O}{\overset{\|}{C}}NH_2$$

Benzoyl chloride — Benzoic anhydride — Benzamide

(*e*) Benzonitrile may be prepared by dehydration of benzamide.



$$C_6H_5\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\text{heat}]{P_4O_{10}} C_6H_5C{\equiv}N$$

Benzamide — Benzonitrile

(*f*) Benzyl cyanide is the product of nucleophilic substitution by cyanide ion on benzyl bromide or benzyl chloride. The benzyl halides are prepared by free-radical halogenation of the toluene side chain.

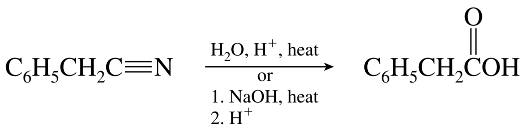
$$C_6H_5CH_3 \xrightarrow[\text{light or heat}]{Cl_2} C_6H_5CH_2Cl \xrightarrow{NaCN} C_6H_5CH_2C{\equiv}N$$

Toluene — Benzyl chloride — Benzyl cyanide

or

$$C_6H_5CH_3 \xrightarrow[\text{or } Br_2\text{, light}]{NBS} C_6H_5CH_2Br \xrightarrow{NaCN} C_6H_5CH_2C{\equiv}N$$

Toluene — Benzyl bromide — Benzyl cyanide (*g*) Hydrolysis of benzyl cyanide yields phenylacetic acid.

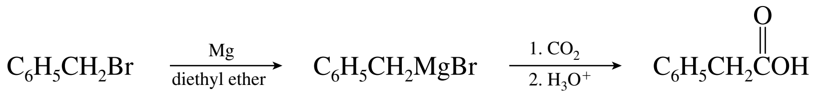


$$C_6H_5CH_2C{\equiv}N \xrightarrow[\text{1. NaOH, heat}\ \ \text{2. }H^+]{H_2O,\ H^+,\ \text{heat}\ \ \text{or}} C_6H_5CH_2\overset{\overset{O}{\|}}{C}OH$$

Benzyl cyanide

Phenylacetic acid

Alternatively, the Grignard reagent derived from benzyl bromide may be carboxylated.



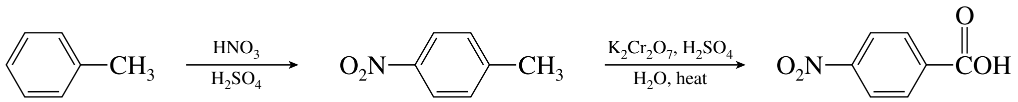
$$C_6H_5CH_2Br \xrightarrow[\text{diethyl ether}]{Mg} C_6H_5CH_2MgBr \xrightarrow[\text{2. }H_3O^+]{\text{1. }CO_2} C_6H_5CH_2\overset{\overset{O}{\|}}{C}OH$$

Benzyl bromide

Benzylmagnesium bromide

Phenylacetic acid

(*h*) The first goal is to synthesize *p*-nitrobenzoic acid because this may be readily converted to the desired acyl chloride. First convert toluene to *p*-nitrotoluene; then oxidize. Nitration must precede oxidation of the side chain in order to achieve the desired para orientation.

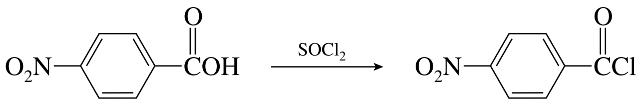


Toluene

p-Nitrotoluene
(separate from ortho isomer)

p-Nitrobenzoic acid

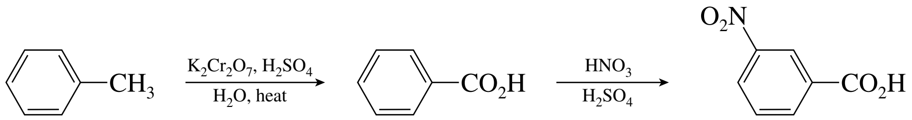
Treatment of *p*-nitrobenzoic acid with thionyl chloride yields *p*-nitrobenzoyl chloride.



p-Nitrobenzoic acid

p-Nitrobenzoyl chloride

(*i*) In order to achieve the correct orientation in *m*-nitrobenzoyl chloride, oxidation of the methyl group must precede nitration.

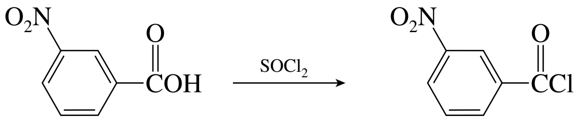


Toluene

Benzoic acid

m-Nitrobenzoic acid

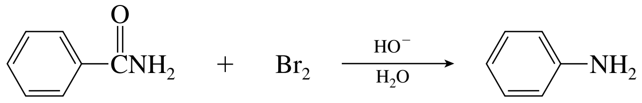
Once *m*-nitrobenzoic acid has been prepared, it may be converted to the corresponding acyl chloride.



m-Nitrobenzoic acid

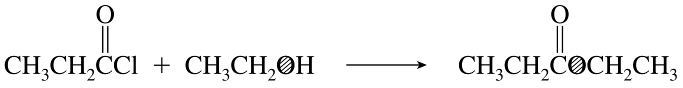
m-Nitrobenzoyl chloride

(*j*) A Hofmann rearrangement of benzamide affords aniline.



Benzamide [prepared as in part (*d*)]
Bromine
Aniline

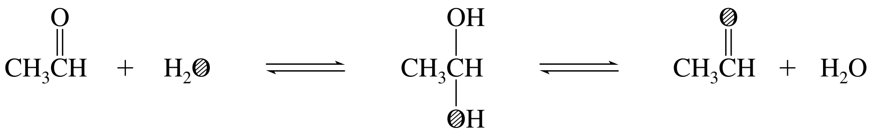
20.30 The problem specifies that $CH_3CH_2\overset{O}{\overset{\|}{C}}\oslash CH_2CH_3$ is to be prepared from ^{18}O-labeled ethyl alcohol ($\oslash = {}^{18}O$) .



$$CH_3CH_2\overset{O}{\overset{\|}{C}}Cl + CH_3CH_2\oslash H \longrightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}\oslash CH_2CH_3$$

Propanoyl chloride
Ethyl alcohol
Ethyl propanoate

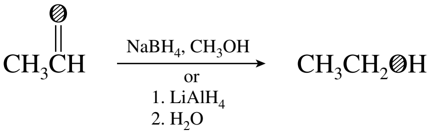
Thus, we need to prepare ^{18}O-labeled ethyl alcohol from the other designated starting materials, acetaldehyde and ^{18}O-enriched water. First, replace the oxygen of acetaldehyde with ^{18}O by the hydration–dehydration equilibrium in the presence of ^{18}O-enriched water.



$$CH_3\overset{O}{\overset{\|}{C}}H + H_2\oslash \rightleftharpoons CH_3\underset{\oslash H}{\underset{|}{\overset{OH}{\overset{|}{C}}}}H \rightleftharpoons CH_3\overset{\oslash}{\overset{\|}{C}}H + H_2O$$

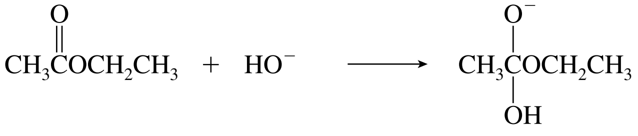
Acetaldehyde
^{18}O-enriched water
Hydrate of acetaldehyde
^{18}O-enriched acetaldehyde
Water

Once ^{18}O-enriched acetaldehyde has been obtained, it can be reduced to ^{18}O-enriched ethanol.



$$CH_3\overset{\oslash}{\overset{\|}{C}}H \xrightarrow[\substack{\text{or}\\ 1.\ LiAlH_4\\ 2.\ H_2O}]{NaBH_4,\ CH_3OH} CH_3CH_2\oslash H$$

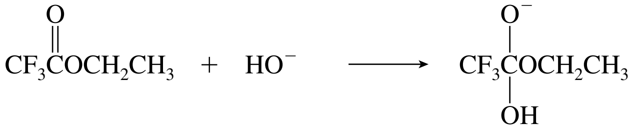
20.31 (*a*) The rate-determining step in basic ester hydrolysis is nucleophilic addition of hydroxide ion to the carbonyl group. The intermediate formed in this step is negatively charged.



$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 + HO^- \longrightarrow CH_3\underset{OH}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}OCH_2CH_3$$

Ethyl acetate
Hydroxide ion
Rate-determining intermediate

The electron-withdrawing effect of a CF_3 group stabilizes the intermediate formed in the rate-determining step of ethyl trifluoroacetate saponification.

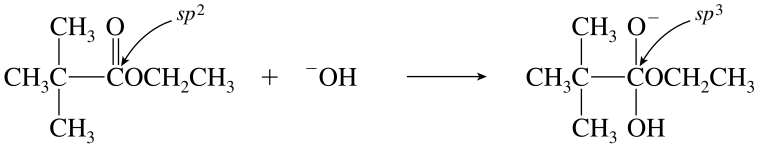


$$CF_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 + HO^- \longrightarrow CF_3\underset{OH}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}OCH_2CH_3$$

Ethyl trifluoroacetate
Hydroxide ion
Rate-determining intermediate

Because the intermediate is more stable, it is formed faster than the one from ethyl acetate.

(*b*) Crowding is increased as the transition state for nucleophilic addition to the carbonyl group is approached. The carbonyl carbon undergoes a change in hybridization from sp^2 to sp^3.



$$CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\overset{\overset{O}{\|}}{C}OCH_2CH_3 + {}^{-}OH \longrightarrow CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}OCH_2CH_3$$

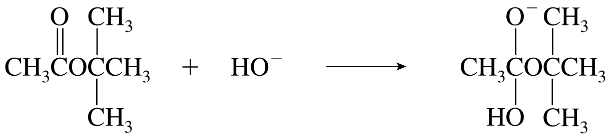
Ethyl 2,2-dimethylpropanoate

Hydroxide ion

Rate-determining intermediate; crowded

The *tert*-butyl group of ethyl 2,2-dimethylpropanoate causes more crowding than the methyl group of ethyl acetate; the rate-determining intermediate is less stable and is formed more slowly.

(*c*) We see here another example of a steric effect of a *tert*-butyl group. The intermediate formed when hydroxide ion adds to the carbonyl group of *tert*-butyl acetate is more crowded and less stable than the corresponding intermediate formed from methyl acetate.

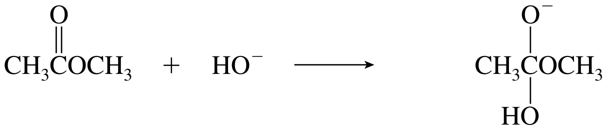


$$CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3 + HO^- \longrightarrow CH_3\overset{\overset{O^-}{|}}{\underset{\underset{HO}{|}}{C}}O\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3$$

tert-Butyl acetate

Hydroxide ion

Rate-determining intermediate; crowded



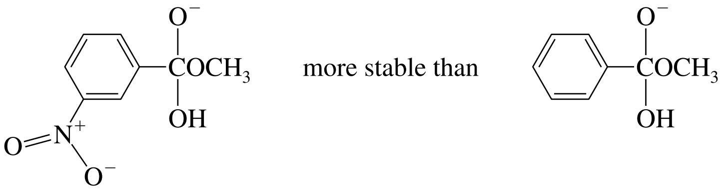
$$CH_3\overset{\overset{O}{\|}}{C}OCH_3 + HO^- \longrightarrow CH_3\overset{\overset{O^-}{|}}{\underset{\underset{HO}{|}}{C}}OCH_3$$

Methyl acetate

Hydroxide ion

Rate-determining intermediate; less crowded than intermediate from *tert*-butyl acetate

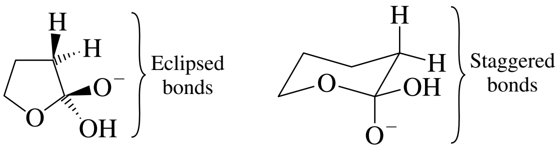
(*d*) Here, as in part (*a*), we have an electron-withdrawing substituent increasing the rate of ester saponification. It does so by stabilizing the negatively charged intermediate formed in the rate-determining step.



Rate-determining intermediate from methyl *m*-nitrobenzoate

Rate-determining intermediate from methyl benzoate

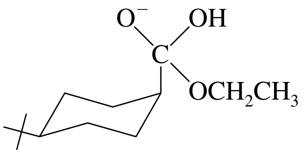
(*e*) Addition of hydroxide to 4-butanolide introduces torsional strain in the intermediate because of eclipsed bonds. The corresponding intermediate from 5-butanolide is more stable because the bonds are staggered in a six-membered ring.



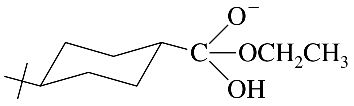
Less stable; formed more slowly

More stable; formed faster

(*f*) Steric crowding increases more when hydroxide adds to the axial carbonyl group.

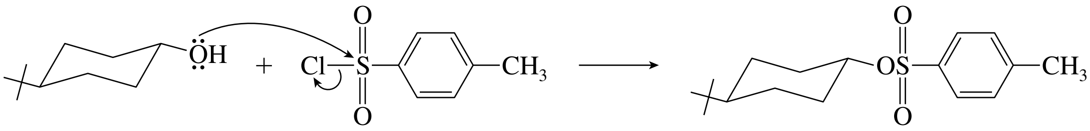


Cis diastereomer: greater increase in crowding when carbon changes from sp^2 to sp^3; formed more slowly



Trans diastereomer: smaller increase in crowding when carbon changes from sp^2 to sp^3; formed more rapidly

20.32 Compound A is the *p*-toluenesulfonate ester (tosylate) of *trans*-4-*tert*-butylcyclohexanol. The oxygen atom of the alcohol attacks the sulfur of *p*-toluenesulfonyl chloride, and so the reaction proceeds with retention of configuration.

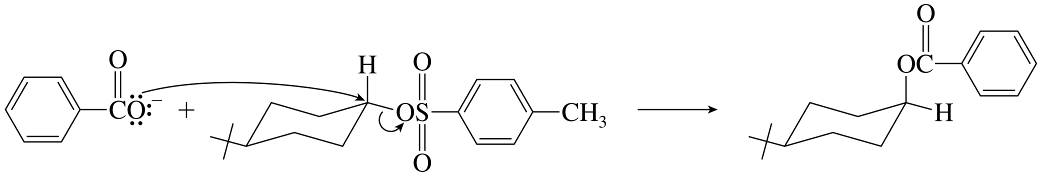


trans-4-*tert*-Butylcyclohexanol

p-Toluenesulfonyl chloride

trans-4-*tert*-Butylcyclohexyl *p*-toluenesulfonate (compound A)

The second step is a nucleophilic substitution in which benzoate ion displaces *p*-toluenesulfonate with inversion of configuration.



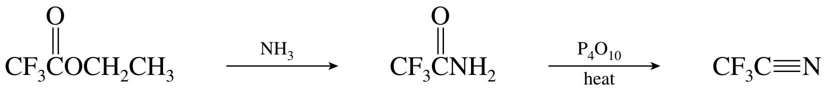
Benzoate ion

trans-4-*tert*-Butylcyclohexyl *p*-toluenesulfonate (compound A)

cis-4-*tert*-Butylcyclohexyl benzoate (compound B)

Saponification of *cis*-4-*tert*-butylcyclohexyl benzoate in step 3 proceeds with acyl–oxygen cleavage to give *cis*-4-*tert*-butylcyclohexanol.

20.33 Reaction of ethyl trifluoroacetate with ammonia yields the corresponding amide, compound A. Compound A undergoes dehydration on heating with P_4O_{10} to give trifluoroacetonitrile, compound B. Grignard reagents react with nitriles to form ketones. *tert*-Butyl trifluoromethyl ketone is formed from trifluoroacetonitrile by treatment with *tert*-butylmagnesium chloride followed by aqueous hydrolysis.

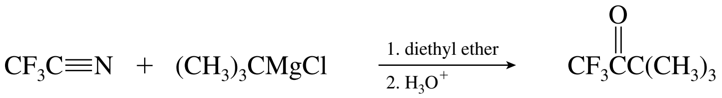


$$CF_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow{NH_3} CF_3\overset{\overset{O}{\|}}{C}NH_2 \xrightarrow[\text{heat}]{P_4O_{10}} CF_3C\equiv N$$

Ethyl trifluoroacetate

Trifluoroacetamide (compound A)

Trifluoroacetonitrile (compound B)



$$CF_3C\equiv N + (CH_3)_3CMgCl \xrightarrow[\text{2. } H_3O^+]{\text{1. diethyl ether}} CF_3\overset{\overset{O}{\|}}{C}C(CH_3)_3$$

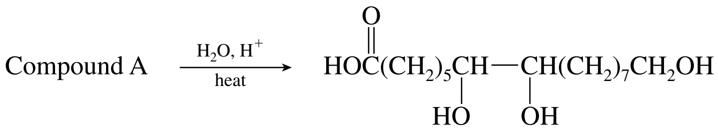
Compound B

tert-Butylmagnesium chloride

tert-Butyl trifluoromethyl ketone

20.34 The first step is acid hydrolysis of an acetal protecting group.

Step 1:

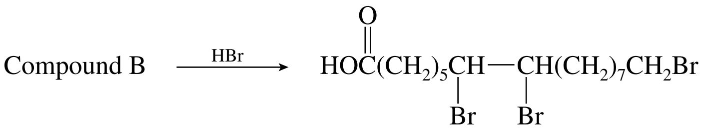


$$\text{Compound A} \xrightarrow[\text{heat}]{H_2O,\ H^+} HO\overset{\overset{O}{\|}}{C}(CH_2)_5\underset{\underset{HO}{|}}{CH}-\underset{\underset{OH}{|}}{CH}(CH_2)_7CH_2OH$$

Compound B
($C_{16}H_{32}O_5$)

All three alcohol functions are converted to bromide by reaction with hydrogen bromide in step 2.

Step 2:

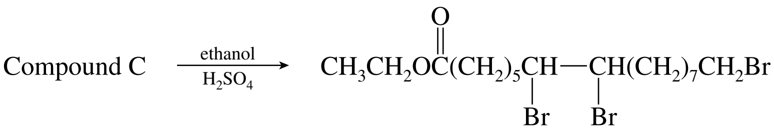


$$\text{Compound B} \xrightarrow{HBr} HO\overset{\overset{O}{\|}}{C}(CH_2)_5\underset{\underset{Br}{|}}{CH}-\underset{\underset{Br}{|}}{CH}(CH_2)_7CH_2Br$$

Compound C
($C_{16}H_{29}Br_3O_2$)

Reaction with ethanol in the presence of an acid catalyst converts the carboxylic acid to its ethyl ester in step 3.

Step 3:

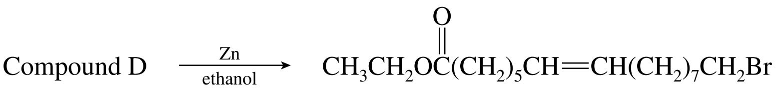


$$\text{Compound C} \xrightarrow[H_2SO_4]{\text{ethanol}} CH_3CH_2O\overset{\overset{O}{\|}}{C}(CH_2)_5\underset{\underset{Br}{|}}{CH}-\underset{\underset{Br}{|}}{CH}(CH_2)_7CH_2Br$$

Compound D
($C_{18}H_{33}Br_3O_2$)

The problem hint points out that zinc converts vicinal dibromides to alkenes. Of the three bromine substituents in compound D, two of them are vicinal. Step 4 is a dehalogenation reaction.

Step 4:

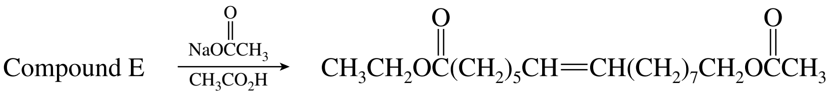


$$\text{Compound D} \xrightarrow[\text{ethanol}]{Zn} CH_3CH_2O\overset{\overset{O}{\|}}{C}(CH_2)_5CH{=}CH(CH_2)_7CH_2Br$$

Compound E
($C_{18}H_{33}BrO_2$)

Step 5 is a nucleophilic substitution of the S_N2 type. Acetate ion is the nucleophile and displaces bromide from the primary carbon.

Step 5:

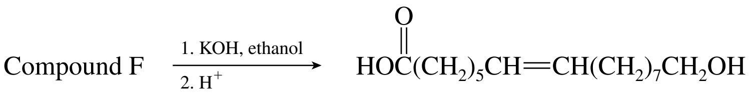


$$\text{Compound E} \xrightarrow[CH_3CO_2H]{NaO\overset{\overset{O}{\|}}{C}CH_3} CH_3CH_2O\overset{\overset{O}{\|}}{C}(CH_2)_5CH{=}CH(CH_2)_7CH_2O\overset{\overset{O}{\|}}{C}CH_3$$

Compound F
($C_{20}H_{36}O_4$)

Step 6 is ester saponification. It yields a 16-carbon chain having a carboxylic acid function at one end and an alcohol at the other.

Step 6:

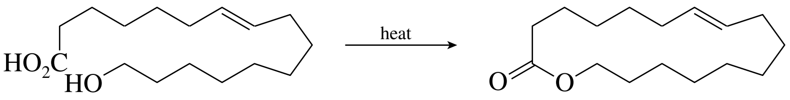


$$\text{Compound F} \xrightarrow[\text{2. H}^+]{\text{1. KOH, ethanol}} \mathrm{HO\overset{\displaystyle O}{\overset{\|}{C}}(CH_2)_5CH{=}CH(CH_2)_7CH_2OH}$$

Compound G
($C_{16}H_{30}O_3$)

In step 7, compound G cyclizes to ambrettolide on heating.

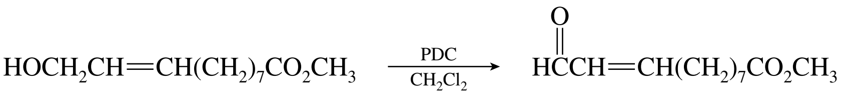
Step 7:



Compound G

Ambrettolide

20.35 (*a*) This step requires the oxidation of a primary alcohol to an aldehyde. As reported in the literature, pyridinium dichromate in dichloromethane was used to give the desired aldehyde in 84% yield.

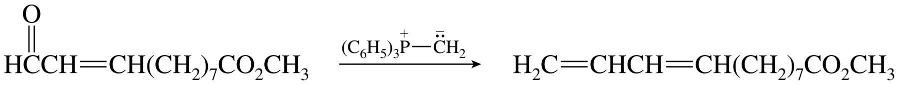


$$\mathrm{HOCH_2CH{=}CH(CH_2)_7CO_2CH_3} \xrightarrow[\mathrm{CH_2Cl_2}]{\text{PDC}} \mathrm{H\overset{\displaystyle O}{\overset{\|}{C}}CH{=}CH(CH_2)_7CO_2CH_3}$$

Compound A

Compound B

(*b*) Conversion of $\overset{\displaystyle O}{\overset{\|}{\text{—CH}}}$ to $\text{—CH{=}CH}_2$ is a typical case in which a Wittig reaction is appropriate.



$$\mathrm{H\overset{\displaystyle O}{\overset{\|}{C}}CH{=}CH(CH_2)_7CO_2CH_3} \xrightarrow{(C_6H_5)_3\overset{+}{P}\text{—}\ddot{\overset{-}{C}}H_2} \mathrm{H_2C{=}CHCH{=}CH(CH_2)_7CO_2CH_3}$$

Compound B

Compound C
(observed yield, 53%)

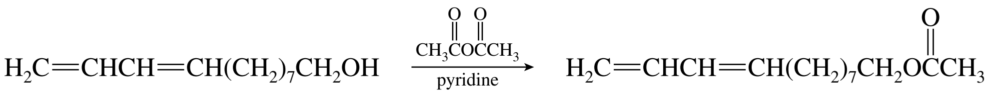
(*c*) Lithium aluminum hydride was used to reduce the ester to a primary alcohol in 81% yield.

$$\mathrm{H_2C{=}CHCH{=}CH(CH_2)_7CO_2CH_3} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4} \mathrm{H_2C{=}CHCH{=}CH(CH_2)_7CH_2OH}$$

Compound C

Compound D

(*d*) The desired sex pheromone is the acetate ester of compound D. Compound D was treated with acetic anhydride to give the acetate ester in 99% yield.



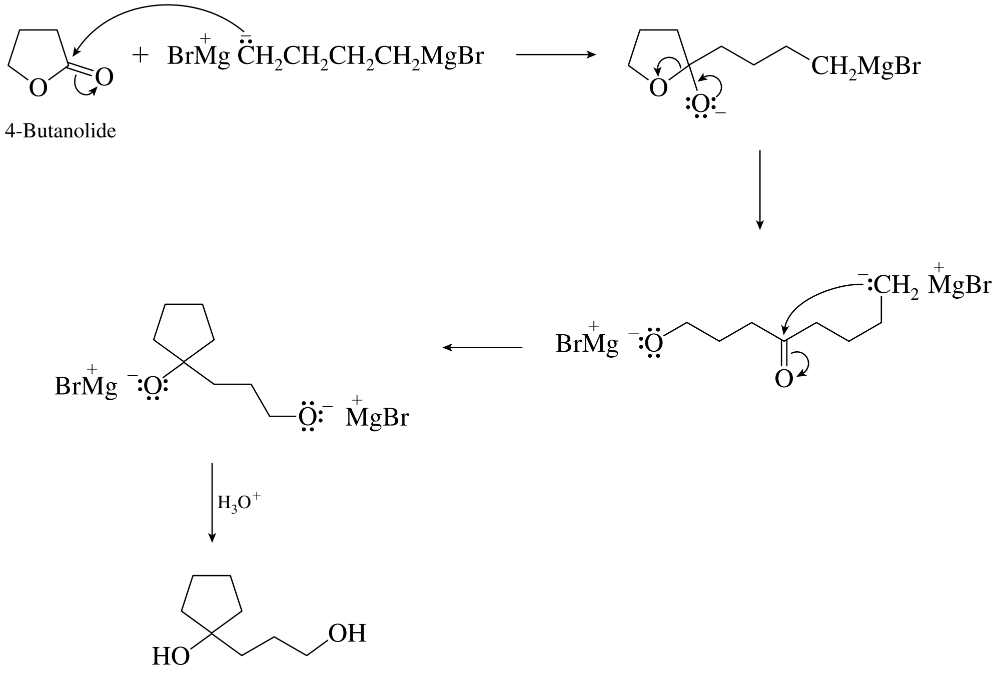
$$\mathrm{H_2C{=}CHCH{=}CH(CH_2)_7CH_2OH} \xrightarrow[\text{pyridine}]{\mathrm{CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3}} \mathrm{H_2C{=}CHCH{=}CH(CH_2)_7CH_2O\overset{\displaystyle O}{\overset{\|}{C}}CH_3}$$

Compound D

(*E*)-9,11-Dodecadien-1-yl acetate

Acetyl chloride could have been used in this step instead of acetic anhydride.

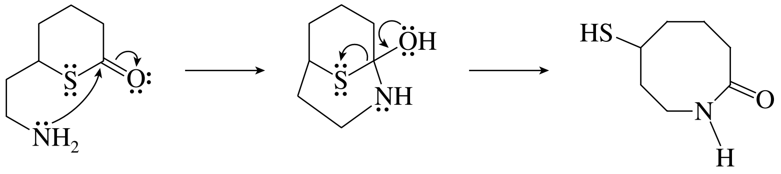
20.36 (*a*) The reaction given in the problem is between a lactone (cyclic ester) and a difunctional Grignard reagent. Esters usually react with 2 moles of a Grignard reagent; in this instance both Grignard functions of the reagent attack the lactone. The second attack is intramolecular, giving rise to the cyclopentanol ring of the product.



4-Butanolide

1-(3-Hydroxypropyl)-
cyclopentanol (88%)

(*b*) An intramolecular acyl transfer process takes place in this reaction. The amine group in the thiolactone starting material replaces sulfur on the acyl group to form a lactam (cyclic amide).

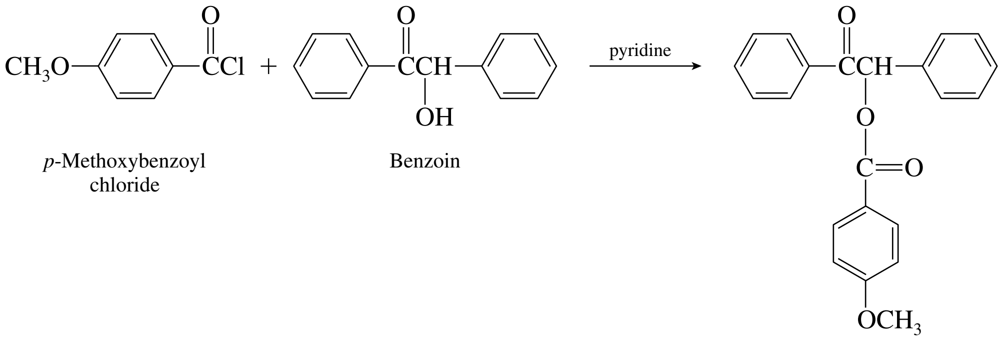


Thiolactone

Tetrahedral
intermediate

Lactam

20.37 (*a*) Acyl chlorides react with alcohols to form esters.

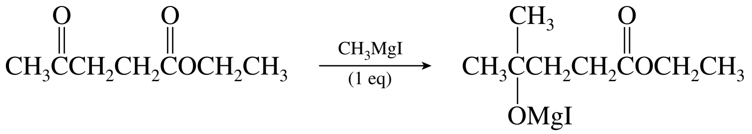


p-Methoxybenzoyl
chloride

Benzoin

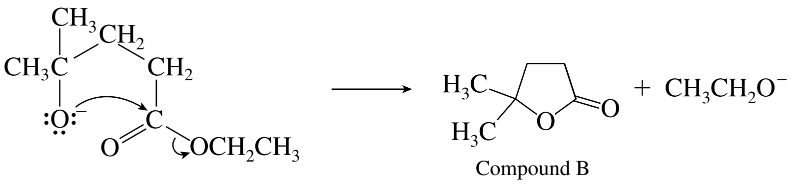
Benzoin *p*-methoxybenzoate
(compound A; 95%)

(*b*) Of the two carbonyl groups in the starting material, the ketone carbonyl is more reactive than the ester. (The ester carbonyl is stabilized by electron release from oxygen.)



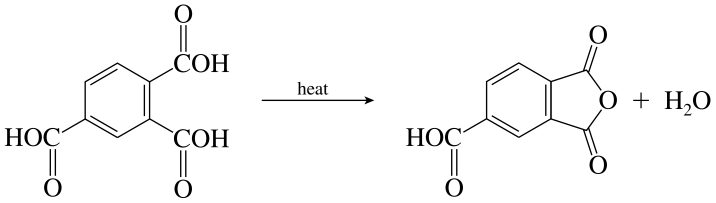
$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[\text{(1 eq)}]{CH_3MgI} CH_3\underset{OMgI}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

Compound B has the molecular formula $C_6H_{10}O_2$. The initial product forms a cyclic ester (lactone), with elimination of ethoxide ion.



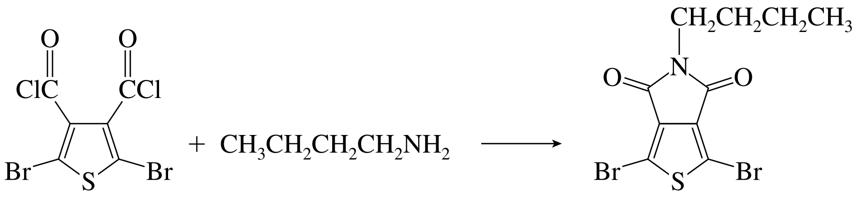
Compound B

(*c*) Only carboxyl groups that are ortho to each other on a benzene ring are capable of forming a cyclic anhydride.



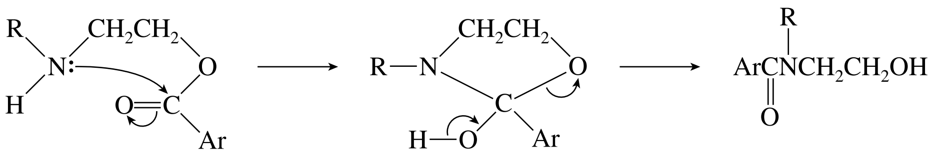
Compound C

(*d*) The primary amine can react with both acyl chloride groups of the starting material to give compound D.



Compound D

20.38 Compound A is an ester but has within it an amine function. Acyl transfer from oxygen to nitrogen converts the ester to a more stable amide.



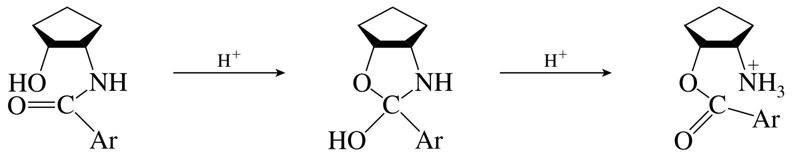
Compound A
(Ar = *p*-nitrophenyl)

Tetrahedral
intermediate

Compound B
(Ar = *p*-nitrophenyl)

The tetrahedral intermediate is the key intermediate in the reaction.

20.39 (*a*) The rearrangement in this problem is an acyl transfer from nitrogen to oxygen.

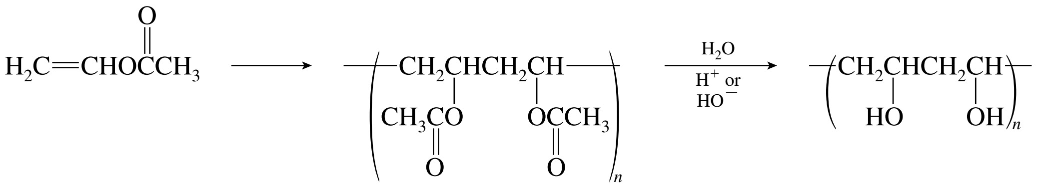


Compound A (Ar = *p*-nitrophenyl) Tetrahedral intermediate Compound B (Ar = *p*-nitrophenyl)

This rearrangement takes place in the indicated direction because it is carried out in acid solution. The amino group is protonated in acid and is no longer nucleophilic.

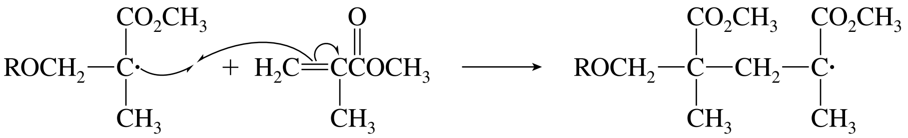
(*b*) The trans stereoisomer of compound A does not undergo rearrangement because when the oxygen and nitrogen atoms on the five-membered ring are trans, the necessary tetrahedral intermediate cannot form.

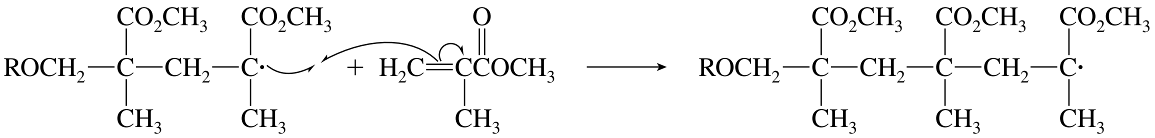
20.40 The ester functions of a polymer such as poly(vinyl acetate) are just like ester functions of simple molecules; they can be cleaved by hydrolysis under either acidic or basic conditions. To prepare poly(vinyl alcohol), therefore, polymerize vinyl acetate to poly(vinyl acetate), and then cleave the ester groups by hydrolysis.



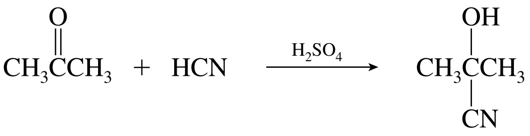
Vinyl acetate Poly(vinyl acetate) Poly(vinyl alcohol)

20.41 (*a*) Each propagation step involves addition of the free-radical species to the β-carbon of a molecule of methyl methacrylate.



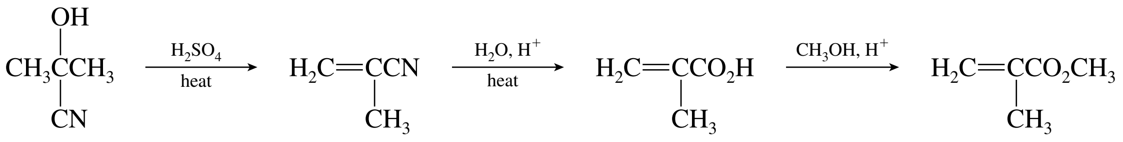


(*b*) The correct carbon skeleton can be constructed by treating acetone with sodium cyanide in the presence of H_2SO_4 to give acetone cyanohydrin.



Acetone Hydrogen cyanide Acetone cyanohydrin

Dehydration of the cyanohydrin followed by hydrolysis of the nitrile group and esterification of the resulting carboxylic acid yields methyl methacrylate.



$$CH_3\underset{\underset{CN}{|}}{\overset{\overset{OH}{|}}{C}}CH_3 \xrightarrow[\text{heat}]{H_2SO_4} H_2C{=}\underset{\underset{CH_3}{|}}{C}CN \xrightarrow[\text{heat}]{H_2O,\ H^+} H_2C{=}\underset{\underset{CH_3}{|}}{C}CO_2H \xrightarrow{CH_3OH,\ H^+} H_2C{=}\underset{\underset{CH_3}{|}}{C}CO_2CH_3$$

Acetone cyanohydrin

Methyl methacrylate

20.42 The compound contains nitrogen and exhibits a prominent peak in the infrared spectrum at 2270 cm^{-1}; it is likely to be a nitrile. Its molecular weight of 83 is consistent with the molecular formula C_5H_9N. The presence of four signals in the δ 10 to 30-ppm region of the ^{13}C NMR spectrum suggests an unbranched carbon skeleton. This is confirmed by the presence of two triplets in the ^1H NMR spectrum at δ 1.0 ppm (CH_3 coupled with adjacent CH_2) and at δ 2.3 ppm (CH_2CN coupled with adjacent CH_2). The compound is pentanenitrile.

$$CH_3CH_2CH_2CH_2C{\equiv}N$$

Pentanenitrile

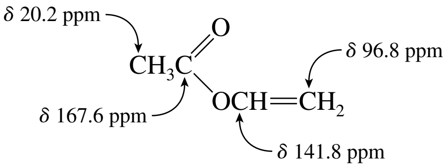
20.43 The compound has the characteristic triplet–quartet pattern of an ethyl group in its ^1H NMR spectrum. Because these signals correspond to 10 protons, there must be two equivalent ethyl groups in the molecule. The methylene quartet appears at relatively low field (δ 4.1 ppm), which is consistent with ethyl groups bonded to oxygen, as in $—OCH_2CH_3$. There is a peak at 1730 cm^{-1} in the infrared spectrum, suggesting that these ethoxy groups reside in ester functions. The molecular formula $C_8H_{14}O_4$ reveals that if two ester groups are present, there can be no rings or double bonds. The remaining four hydrogens are equivalent in the ^1H NMR spectrum, and so two equivalent CH_2 groups are present. The compound is the diethyl ester of succinic acid.

$$CH_3CH_2O\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Diethyl succinate

20.44 Compound A ($C_4H_6O_2$) has an index of hydrogen deficiency of 2. With two oxygen atoms and a peak in the infrared at 1760 cm^{-1}, it is likely that one of the elements of unsaturation is the carbon–oxygen double bond of an ester. The ^1H NMR spectrum contains a three-proton singlet at δ 2.1 ppm, which is consistent with a $\underset{\underset{O}{\|}}{CH_3C}$ unit. It is likely that compound A is an acetate ester.

The ^{13}C NMR spectrum reveals that the four carbon atoms of the molecule are contained in one each of the fragments CH_3, CH_2, and CH, along with the carbonyl carbon. In addition to the two carbons of the acetate group, the remaining two carbons are the CH_2 and CH carbons of a vinyl group, $CH{=}CH_2$. Compound A is vinyl acetate.



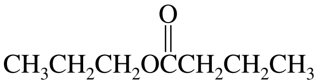
Each vinyl proton is coupled to two other vinyl protons; each appears as a doublet of doublets in the ^1H NMR spectrum.

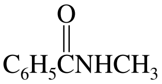
20.45 Solutions to molecular modeling exercises are not provided in this *Study Guide and Solutions Manual.* You should use *Learning By Modeling* for this exercise.

SELF-TEST

PART A

A-1. Give a correct IUPAC name for each of the following acid derivatives:

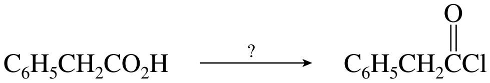
(*a*) 
$CH_3CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

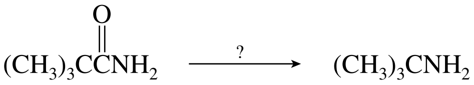
(*b*) 
$C_6H_5\overset{O}{\overset{\|}{C}}NHCH_3$

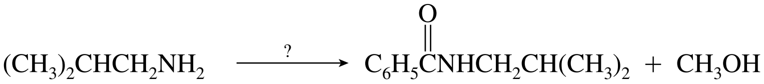
(*c*) 
$(CH_3)_2CHCH_2CH_2\overset{O}{\overset{\|}{C}}Cl$

A-2. Provide the correct structure of
(*a*) Benzoic anhydride
(*b*) *N*-(1-Methylpropyl)acetamide
(*c*) Phenyl benzoate

A-3. What reagents are needed to carry out each of the following conversions?

(*a*) 
$C_6H_5CH_2CO_2H \xrightarrow{?} C_6H_5CH_2\overset{O}{\overset{\|}{C}}Cl$

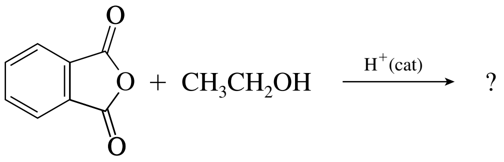
(*b*) 
$(CH_3)_3C\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{?} (CH_3)_3CNH_2$

(*c*) 
$(CH_3)_2CHCH_2NH_2 \xrightarrow{?} C_6H_5\overset{O}{\overset{\|}{C}}NHCH_2CH(CH_3)_2 + CH_3OH$

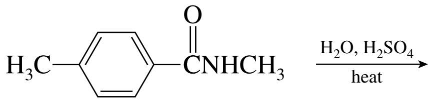
A-4. Write the structure of the product of each of the following reactions:

(*a*) Cyclohexyl acetate $\xrightarrow[2.\ H^+]{1.\ NaOH,\ H_2O}$? (two products)

(*b*) Cyclopentanol + benzoyl chloride $\xrightarrow{\text{pyridine}}$?

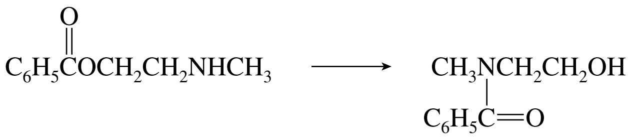
(*c*) 

(*d*) Ethyl propanoate + dimethylamine $\longrightarrow$? (two products)

(*e*) 

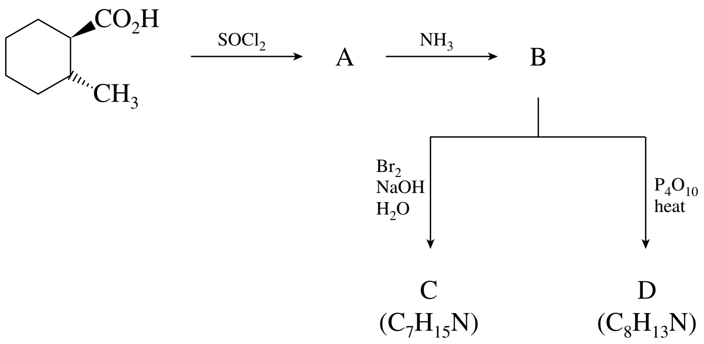
? (two products)

A-5. The following reaction occurs when the reactant is allowed to stand in pentane. Write the structure of the key intermediate in this process.



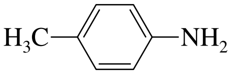
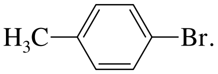
$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_2NHCH_3 \longrightarrow \underset{\underset{\displaystyle C_6H_5C{=}O}{|}}{CH_3N}CH_2CH_2OH$$

A-6. Give the correct structures, clearly showing stereochemistry, of each compound, A through D, in the following sequence of reactions:

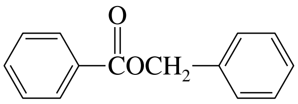


A-7. Write the structure of the neutral form of the tetrahedral intermediate in the

(*a*) Acid-catalyzed hydrolysis of methyl acetate
(*b*) Reaction of ammonia with acetic anhydride

A-8. Write the steps necessary to prepare  from .

A-9. Outline a synthesis of benzyl benzoate using toluene as the source of all the carbon atoms.

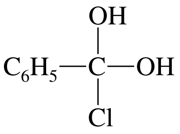


Benzyl benzoate

A-10. The infrared spectrum of a compound (C_3H_6ClNO) has an intense peak at 1680 cm^{-1}. Its ^{1}H NMR spectrum consists of a doublet (3H, δ 1.5 ppm), a quartet (1H, δ 4.1 ppm), and a broad singlet (2H, δ 6.5 ppm). What is the structure of the compound? How would you prepare it from propanoic acid?

PART B

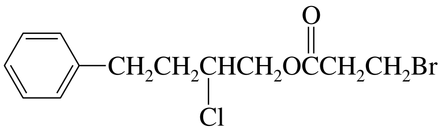
B-1. What are the products of the most favorable mode of decomposition of the intermediate species shown?



$$C_6H_5{-}\underset{\underset{\displaystyle Cl}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}OH$$

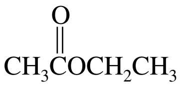
(*a*) Benzoic acid and HCl
(*b*) Benzoyl chloride and H_2O
(*c*) Both (*a*) and (*b*) equally likely
(*d*) Neither (*a*) nor (*b*)

B-2. What is the correct IUPAC name for the compound shown?

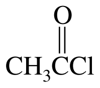


- (*a*) 3-Bromopropyl 2-chloro-4-butylbutanoate
- (*b*) 2-Chloro-4-phenylbutyl 3-bromopropanoate
- (*c*) 3-Chloro-1-phenylbutyl 1-bromopropanoate
- (*d*) 3-Chloro-1-phenylbutyl 3-bromopropanoate
- (*e*) 7-Bromo-3-chloro-1-phenylbutyl propanoate

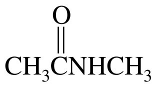
B-3. Rank the following in order of increasing reactivity (least → most) toward acid hydrolysis:


$\mathrm{CH_3}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{OCH_2CH_3}$

1


$\mathrm{CH_3}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{Cl}$

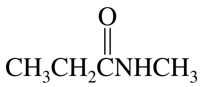
2


$\mathrm{CH_3}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{NHCH_3}$

3

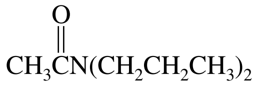
- (*a*) $1 < 2 < 3$
- (*b*) $3 < 1 < 2$
- (*c*) $1 < 3 < 2$
- (*d*) $2 < 1 < 3$

B-4. The structure of *N*-propylacetamide is

(*a*)

$\mathrm{CH_3CH_2}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{NHCH_3}$

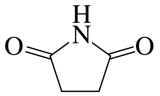
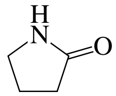
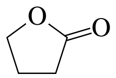
(*c*)

$\mathrm{CH_3}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{NHCH_2CH_2CH_3}$

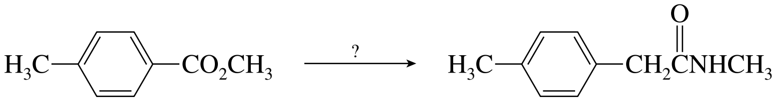
(*b*)

$\mathrm{CH_3}\overset{O}{\overset{\|}{\mathrm{C}}}\mathrm{N(CH_2CH_2CH_3)_2}$

(*d*) $\mathrm{CH_3CH{=}NCH_2CH_2CH_3}$

B-5. Choose the response that matches the correct functional group classification with the following group of structural formulas.

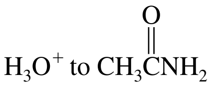
			
(*a*)	Anhydride	Lactam	Lactone
(*b*)	Lactam	Imide	Lactone
(*c*)	Imide	Lactone	Anhydride
(*d*)	Imide	Lactam	Lactone

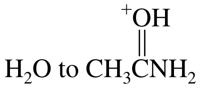
B-6. Choose the best sequence of reactions for the transformation given. Semicolons indicate separate reaction steps to be used in the order shown.

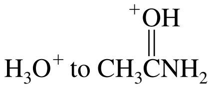


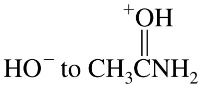
- (*a*) $\mathrm{H_3O^+}$; $\mathrm{SOCl_2}$; $\mathrm{CH_3NH_2}$
- (*b*) $\mathrm{HO^-/H_2O}$; $\mathrm{PBr_3}$; Mg; $\mathrm{CO_2}$; $\mathrm{H_3O^+}$; $\mathrm{SOCl_2}$; $\mathrm{CH_3NH_2}$
- (*c*) $\mathrm{LiAlH_4}$; $\mathrm{H_2O}$; HBr; Mg; $\mathrm{CO_2}$; $\mathrm{H_3O^+}$; $\mathrm{SOCl_2}$; $\mathrm{CH_3NH_2}$
- (*d*) None of these would yield the desired product.

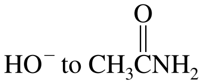
B-7. A key step in the hydrolysis of acetamide in aqueous acid proceeds by nucleophilic addition of

(*a*)

H_3O^+ to $CH_3\overset{O}{\overset{\|}{C}}NH_2$

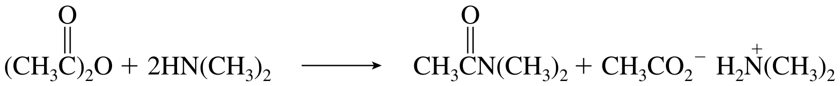
(*d*)

H_2O to $CH_3\overset{^+OH}{\overset{\|}{C}}NH_2$

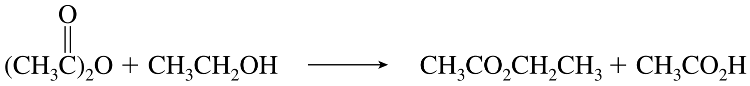
(*b*)

H_3O^+ to $CH_3\overset{^+OH}{\overset{\|}{C}}NH_2$

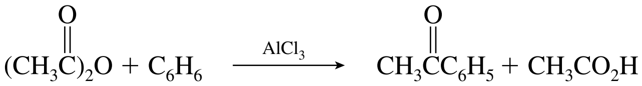
(*e*)

HO^- to $CH_3\overset{^+OH}{\overset{\|}{C}}NH_2$

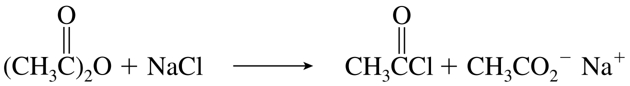
(*c*)

HO^- to $CH_3\overset{O}{\overset{\|}{C}}NH_2$

B-8. Which reaction is *not* possible for acetic anhydride?

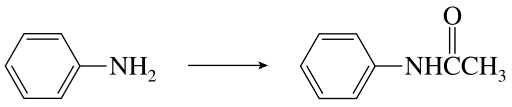
(*a*)

$(CH_3\overset{O}{\overset{\|}{C}})_2O + 2HN(CH_3)_2 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}N(CH_3)_2 + CH_3CO_2^-\ H_2\overset{+}{N}(CH_3)_2$

(*b*)

$(CH_3\overset{O}{\overset{\|}{C}})_2O + CH_3CH_2OH \longrightarrow CH_3CO_2CH_2CH_3 + CH_3CO_2H$

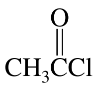
(*c*)

$(CH_3\overset{O}{\overset{\|}{C}})_2O + C_6H_6 \xrightarrow{AlCl_3} CH_3\overset{O}{\overset{\|}{C}}C_6H_5 + CH_3CO_2H$

(*d*)

$(CH_3\overset{O}{\overset{\|}{C}})_2O + NaCl \longrightarrow CH_3\overset{O}{\overset{\|}{C}}Cl + CH_3CO_2^-\ Na^+$

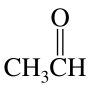
B-9. All but one of the following compounds react with aniline to give acetanilide. Which one does *not?*



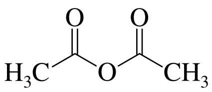
Aniline Acetanilide


$CH_3\overset{O}{\overset{\|}{C}}Cl$

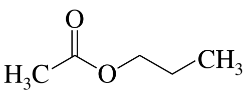
(*a*)


$CH_3\overset{O}{\overset{\|}{C}}H$

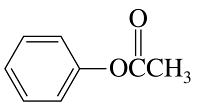
(*b*)



(*c*)



(*d*)



(*e*)

B-10. Identify product Z in the following reaction sequence:

$$H_2C{=}CHCH_2Br \xrightarrow{NaCN} Y \xrightarrow[2.\ H_3O^+]{1.\ C_6H_5MgBr,\ \text{diethyl ether}} Z$$

(*a*) 
$H_2C{=}CHCH_2\overset{\overset{O}{\|}}{C}C_6H_5$

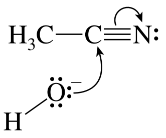
(*d*) 
$H_2C{=}CHCH_2NH\overset{\overset{O}{\|}}{C}C_6H_5$

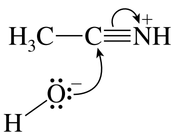
(*b*) 
$H_2C{=}CHCH_2\overset{\overset{OH}{|}}{C}HC_6H_5$

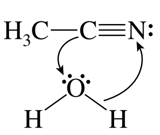
(*e*) 
$H_2C{=}CHCH_2\overset{\overset{NH_2}{|}}{C}HC_6H_5$

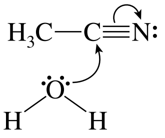
(*c*) 
$H_2C{=}CHCH_2\overset{\overset{O}{\|}}{C}NHC_6H_5$

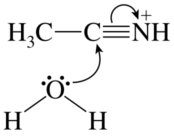
B-11. Which of the following best describes the nucleophilic addition step in the acid-catalyzed hydrolysis of acetonitrile (CH_3CN)?

(*a*) 

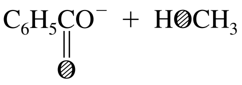
(*c*) 

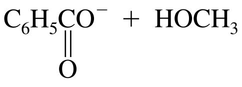
(*e*) 

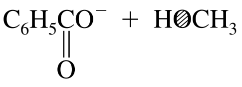
(*b*) 

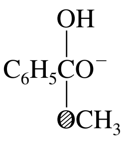
(*d*) 

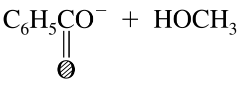
B-12. Saponification (basic hydrolysis) of $C_6H_5\underset{\underset{O}{\|}}{C}⊘CH_3$ will yield: [⊘ = mass-18 isotope of oxygen]

(*a*) 
$C_6H_5\underset{\underset{⊘}{\|}}{C}O^- + H⊘CH_3$

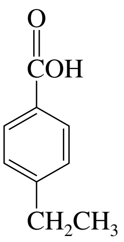
(*d*) 
$C_6H_5\underset{\underset{O}{\|}}{C}O^- + HOCH_3$

(*b*) 
$C_6H_5\underset{\underset{O}{\|}}{C}O^- + H⊘CH_3$

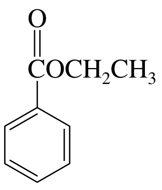
(*e*) 
$C_6H_5\overset{\overset{OH}{|}}{\underset{\underset{⊘CH_3}{|}}{C}}O^-$

(*c*) 
$C_6H_5\underset{\underset{⊘}{\|}}{C}O^- + HOCH_3$

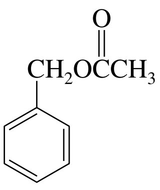
B-13. An unknown compound, $C_9H_{10}O_2$, did not dissolve in aqueous NaOH. The infrared spectrum exhibited strong absorption at 1730 cm^{-1}. The ^1H NMR spectrum had signals at δ 7.2 ppm (multiplet), 4.1 ppm (quartet), and 1.3 ppm (triplet). Which of the following is most likely the unknown?



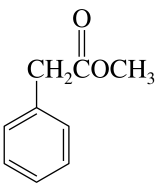
(*a*)



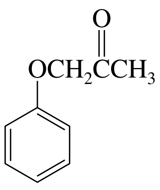
(*b*)



(*c*)



(*d*)



(*e*)