

Chapter 22 – Carbonyl Alpha-Substitution Reactions

Chapter Outline

I. Keto-enol tautomerism (Section 22.1).

A. Nature of tautomerism.

1. Carbonyl compounds with hydrogens bonded to their α carbons equilibrate with their corresponding enols.
2. This rapid equilibration is called tautomerism, and the individual isomers are tautomers.
3. Unlike resonance forms, tautomers are isomers.
4. Despite the fact that very little of the enol isomer is present at room temperature, enols are very important because they are reactive.

B. Mechanism of tautomerism.

1. In acid-catalyzed enolization, the carbonyl carbon is protonated to form an intermediate that can lose a hydrogen from its α carbon to yield a neutral enol.
2. In base-catalyzed enol formation, an acid-base reaction occurs between a base and an α hydrogen.
 - a. The resultant enolate ion is protonated to yield an enol.
 - b. Protonation can occur either on carbon or on oxygen.
 - c. Only hydrogens on the α positions of carbonyl compounds are acidic.

II. Enols (Sections 22.2 – 22.4).

A. Reactivity of enols (Section 22.2).

1. The electron-rich double bonds of enols cause them to behave as nucleophiles.

The electron-donating enol $-OH$ groups make enols more reactive than alkenes.
2. When an enol reacts with an electrophile, the initial adduct loses $-H$ from oxygen to give a substituted carbonyl compound.

B. Reactions of enols (Sections 22.3 – 22.4).

1. Alpha halogenation of aldehydes and ketones (Section 22.3).
 - a. Aldehydes and ketones can be halogenated at their α positions by reaction of X_2 in acidic solution.
 - b. The reaction proceeds by acid-catalyzed formation of an enol intermediate.
 - c. Halogen isn't involved in the rate-limiting step; the rate doesn't depend on the identity of the halogen, but only on $[ketone]$ and $[H^+]$.
 - d. α -Bromo ketones are useful in syntheses because they can be dehydrobrominated by base treatment to form α,β -unsaturated ketones.
2. Alpha-bromination of carboxylic acids (Section 22.4).
 - a. In the Hell–Volhard–Zelinskii (HVZ) reaction, a mixture of Br_2 and PBr_3 can be used to brominate carboxylic acids in the α position.
 - b. The initially formed acid bromide reacts with Br_2 to form an α -bromo acid bromide, which is hydrolyzed by water to give the α -bromo carboxylic acid.
 - c. The reaction proceeds through an acid bromide enol.

III. Enolates (Sections 22.5 – 22.7).

A. Enolate ion formation (Section 22.5).

1. Hydrogens α to a carbonyl group are weakly acidic.
 - a. This acidity is due to overlap of a filled p orbital with the carbonyl group p orbitals, allowing the carbonyl group to stabilize the negative charge by resonance.
 - b. The two resonance forms aren't equivalent; the form with the negative charge on oxygen is of lower energy.

2. Strong bases are needed for enolate ion formation.
 - a. Alkoxide ions are often too weak to use in enolate formation.
 - b. Lithium diisopropylamide can be used to form the enolates of many different carbonyl compounds.
 3. When a hydrogen is flanked by two carbonyl groups, it is much more acidic.

Both carbonyl groups can stabilize the negative charge.
- B. Reactivity of enolate ions (Section 22.6).
1. Enolates are more useful than enols for two reasons:
 - a. Unlike enols, stable solutions of enolates are easily prepared.
 - b. Enolates are more reactive than enols because they are more nucleophilic.
 2. Enolates can react either at carbon or at oxygen.
 - a. Reaction at carbon yields an α -substituted carbonyl compound.
 - b. Reaction at oxygen yields an enol derivative.
- C. Reactions of enolate ions (Sections 22.6 – 22.7).
1. Base-promoted α -halogenation.
 - a. Base-promoted halogenation of aldehydes and ketones proceeds readily because each halogen added makes the carbonyl compound more reactive.
 - b. Consequently, polyhalogenated compounds are usually produced.
 - c. This reaction is only useful with methyl ketones, which form HCX_3 when reacted with halogens.
 - d. This reaction is known as the haloform reaction.
 - i. The HCX_3 is a solid that can be identified.
 - ii. The last step of the reaction involves a carbanion leaving group.
 2. Alkylation reactions of enolates (Section 22.7).
 - a. General features.
 - i. Alkylations are useful because they form a new C–C bond.
 - ii. Alkylations have the same limitations as $\text{S}_{\text{N}}2$ reactions; the alkyl groups must be methyl, primary, allylic or benzylic.
 - b. The malonic ester synthesis.
 - i. The malonic ester synthesis is used for preparing a carboxylic acid from a halide while lengthening the chain by two carbon atoms.
 - ii. Diethyl malonate is useful because its enolate is easily prepared by reaction with sodium ethoxide.
 - iii. Since diethyl malonate has two acidic hydrogens, two alkylations can take place.
 - iv. Heating in aqueous HCl causes hydrolysis and decarboxylation of the alkylated malonate.

Decarboxylations are common only to β -keto acids and malonic acids.
 - v. Cycloalkanecarboxylic acids can also be prepared.
 - c. The acetoacetic ester synthesis.
 - i. The acetoacetic ester synthesis is used for converting an alkyl halide to a methyl ketone, while lengthening the carbon chain by 3 atoms.
 - ii. As with malonic ester, acetoacetic ester has two acidic hydrogens which are flanked by a ketone and an ester, and two alkylations can take place.
 - iii. Heating in aqueous HCl hydrolyzes the ester and decarboxylates the acid to yield the ketone.
 - iv. Most β -keto esters can undergo this type of reaction.
 - d. Direct alkylation of ketones, esters, and nitriles.
 - i. LDA in a nonprotic solvent can be used to convert the above compounds to their enolates.
 - ii. Alkylation of an unsymmetrical ketone leads to a mixture of products, but the major product is alkylated at the less hindered position.

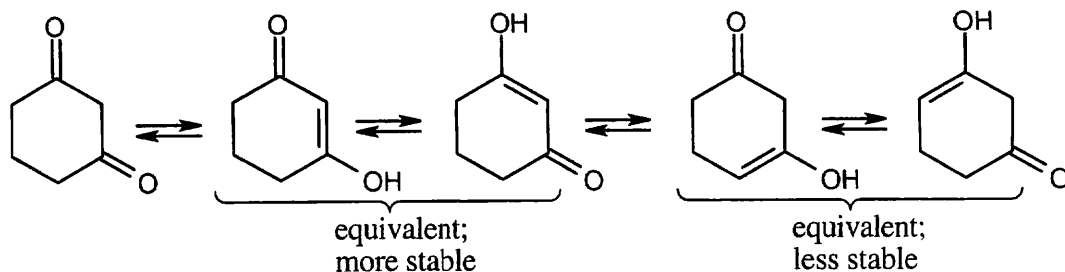
Solutions to Problems

22.1–22.2 Acidic hydrogens in the keto form of each of these compounds are bold.

	<i>Keto Form</i>	<i>Enol Form</i>	<i>Number of Acidic Hydrogens</i>
(a)			4
(b)			3
(c)			3
(d)			2
(e)			4
(f)			5

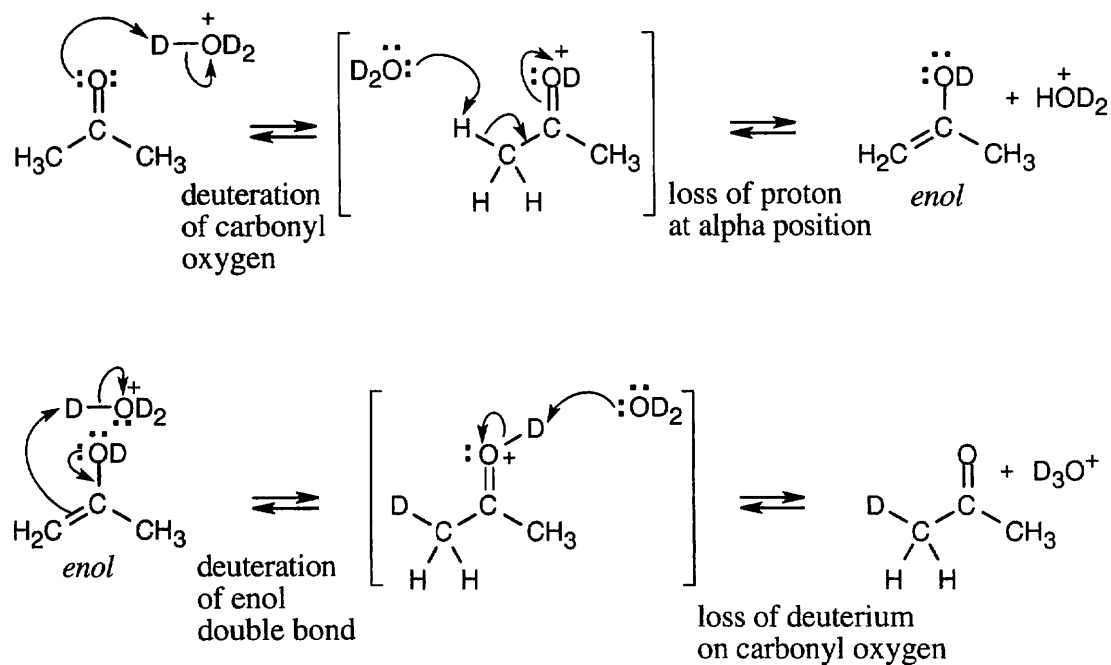
In (d) and (f), cis and trans enolates are possible.

22.3

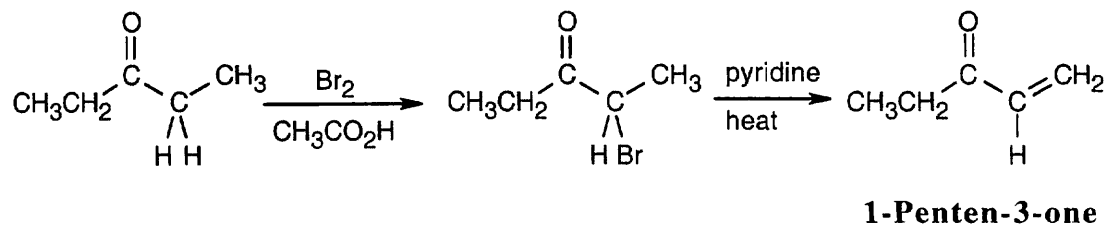


The first two monoenols are more stable because the enol double bond is conjugated with the carbonyl group.

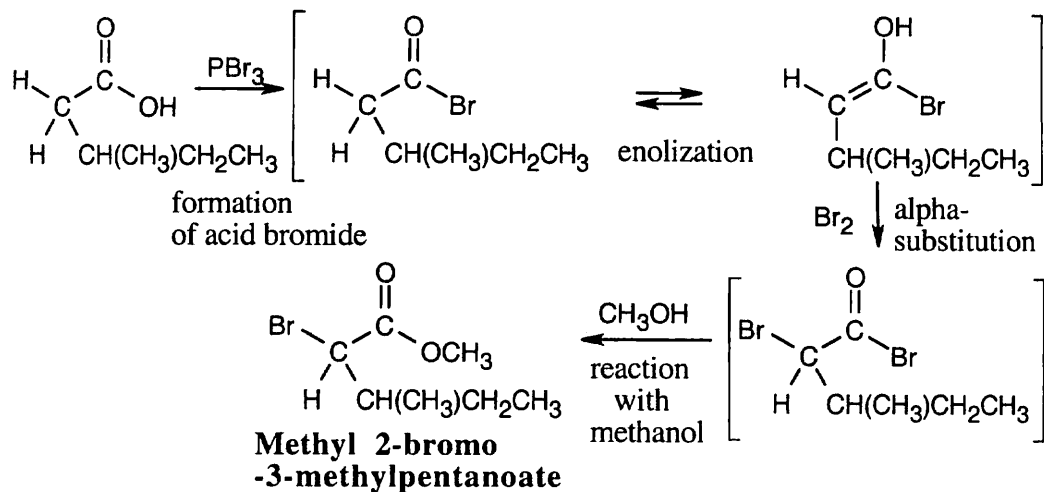
22.4



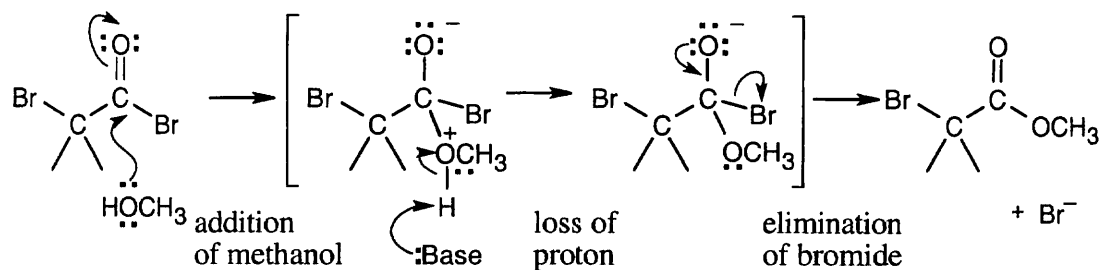
22.5 Alpha-bromination, followed by dehydration using pyridine, yields the enone pictured.



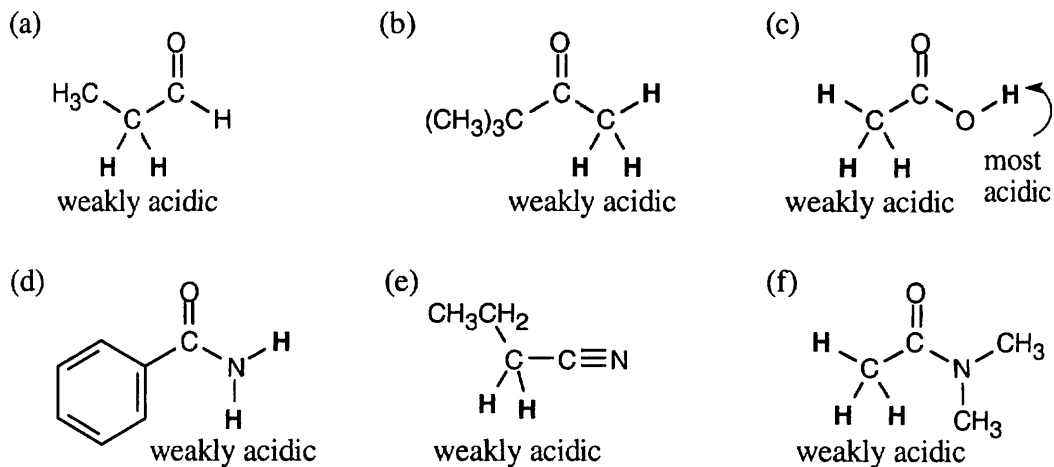
22.6



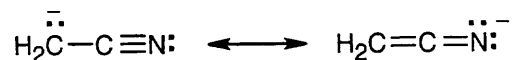
The mechanism of the ester-forming step is a nucleophilic acyl substitution, which was described in Chapter 21.



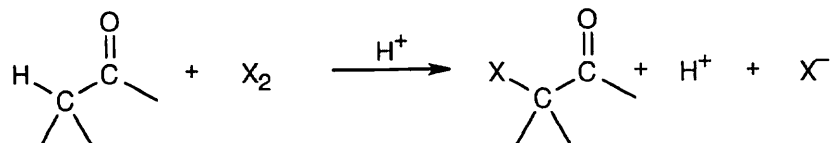
22.7 Hydrogens α to one carbonyl group are weakly acidic. Hydrogens α to two carbonyl groups are much more acidic, but they are not as acidic as carboxylic acid protons.



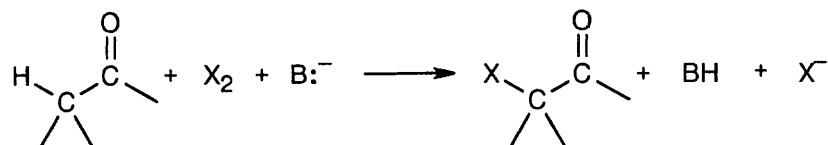
- 22.8** Nitriles are weakly acidic because the nitrile anion can be stabilized by resonance involving the π bond of the nitrile group.



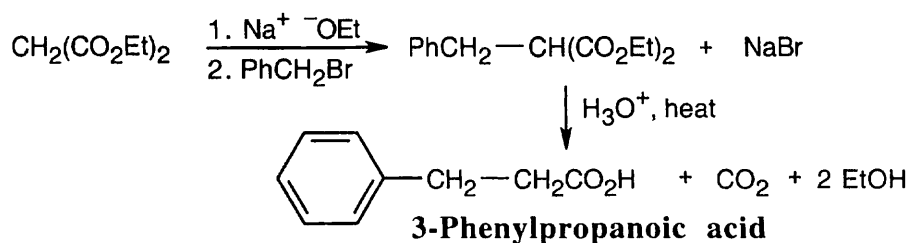
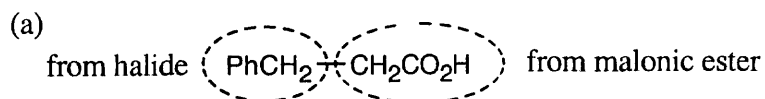
- 22.9** Halogenation in acid medium is acid-*catalyzed* because hydrogen ions are regenerated:

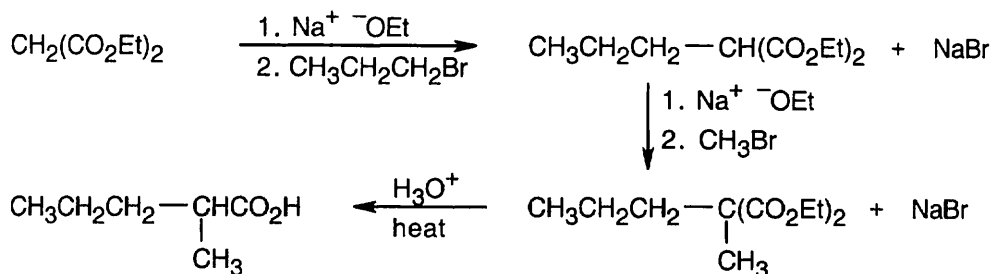
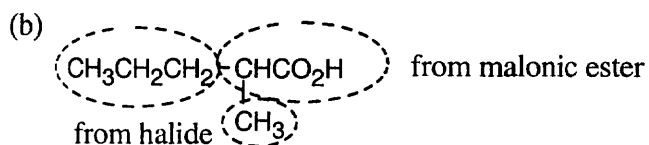
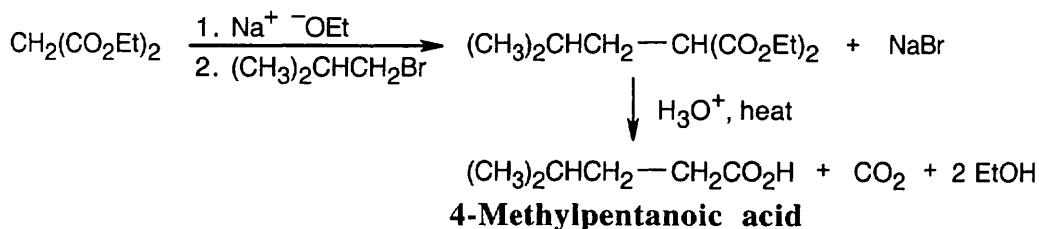
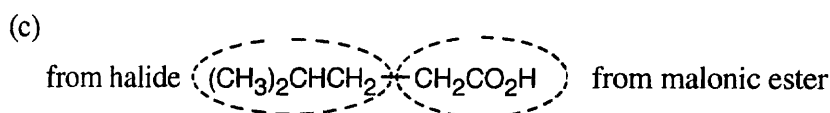
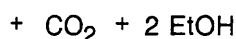


Halogenation in basic medium is base-*promoted* because a stoichiometric amount of base is consumed:



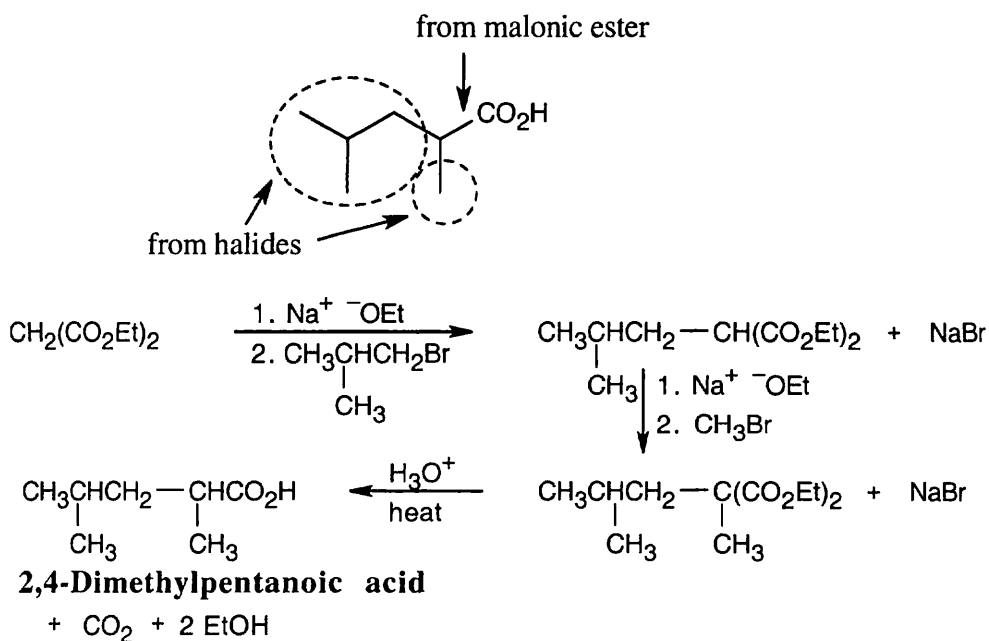
- 22.10** The malonic ester synthesis converts a primary or secondary alkyl halide into a carboxylic acid with two more carbons (a substituted acetic acid). Identify the component that originates from malonic ester (the acid component). The rest of the molecule comes from the alkyl halide, which should be primary or methyl.



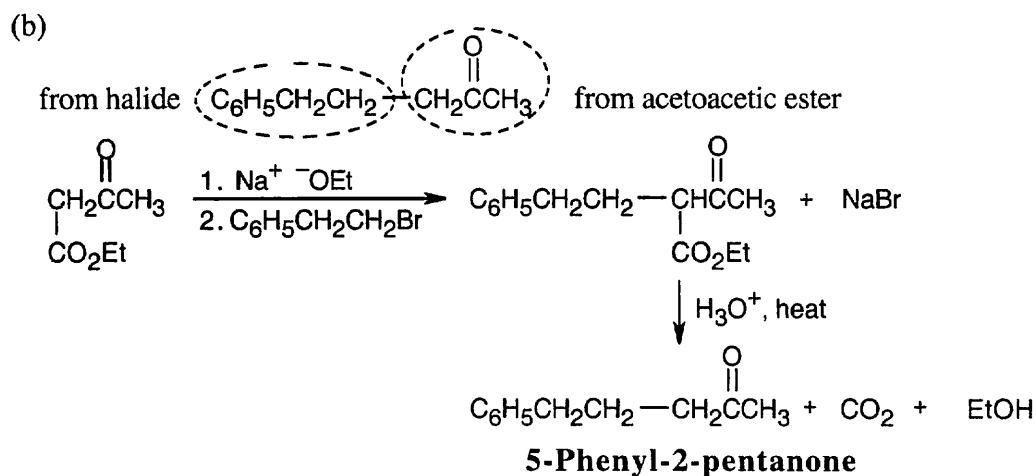
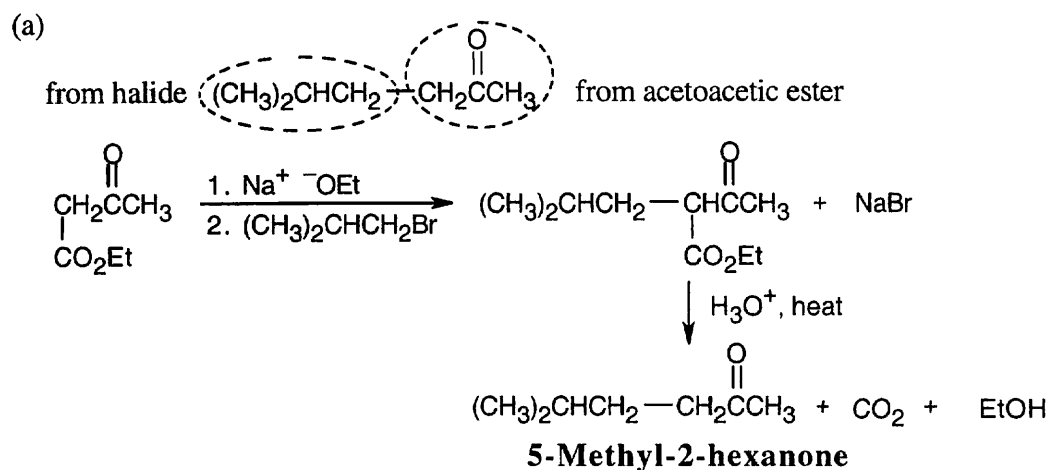
**2-Methylpentanoic acid**

22.11 Since malonic ester has only two acidic hydrogen atoms, it can be alkylated only two times. Formation of trialkylated acetic acids is thus not possible.

22.12



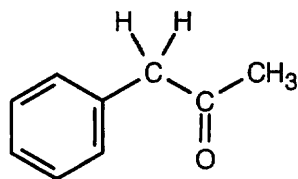
22.13 As in the malonic ester synthesis, you should identify the structural fragments of the target compound. The acetoacetic ester synthesis converts an alkyl halide to a methyl ketone ("substituted acetone"). The methyl ketone component comes from acetoacetic ester; the other component comes from a halide.



22.14 The acetoacetic ester synthesis can only be used for certain products:

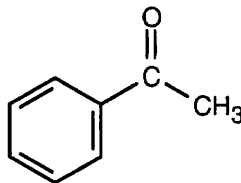
- (1) Three carbons must originate from acetoacetic ester. In other words, compounds of the type RCOCH_3 can't be synthesized by the reaction of RX with acetoacetic ester.
- (2) Alkyl halides must be primary or methyl.
- (3) The acetoacetic ester synthesis can't be used to prepare compounds that are trisubstituted at the α position.

(a)



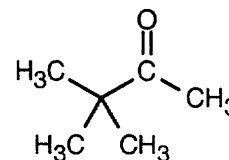
Phenylacetone

(b)



Acetophenone

(c)

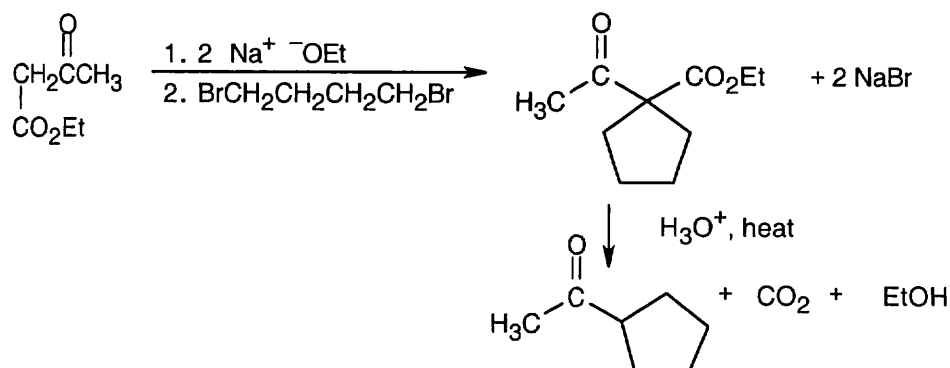


3,3-Dimethylbutan-2-one

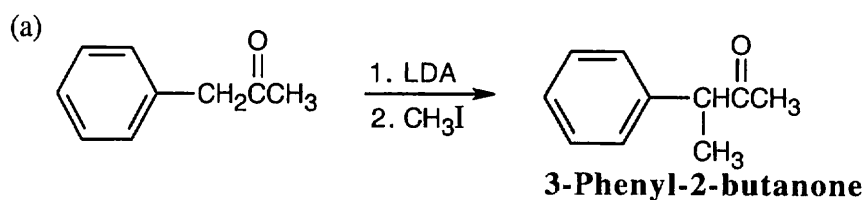
- (a) Phenylacetone can't be produced by an acetoacetic ester synthesis because bromobenzene, the necessary halide, does not enter into $\text{S}_{\text{N}}2$ reactions. [See (2) above.]

(b) Acetophenone can't be produced by an acetoacetic ester synthesis. [See (1) above.]

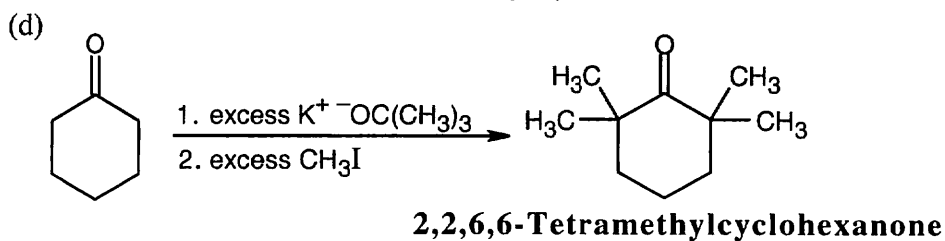
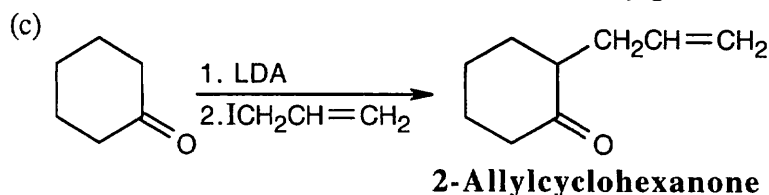
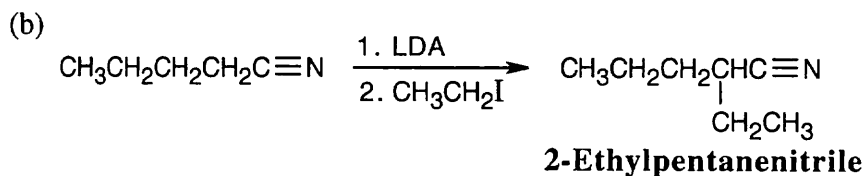
(c) 3,3-Dimethyl-2-butanone can't be prepared because it is trisubstituted at the α position. [See (3) above.]

22.15

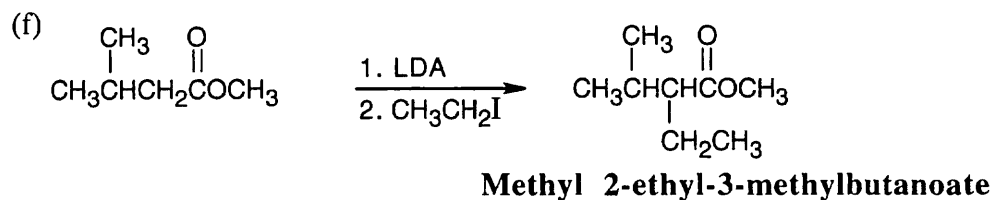
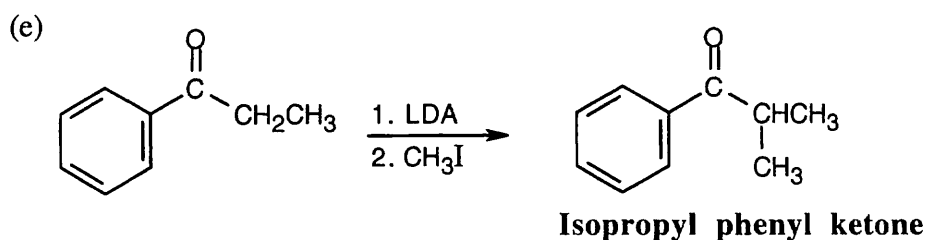
22.16 Direct alkylation is used to introduce substituents α to an ester, ketone or nitrile. Look at the target molecule to identify these substituents. Alkylation is achieved by treating the starting material with LDA, followed by a primary halide.



Alkylation occurs at the carbon next to the phenyl group because the phenyl group can help stabilize the enolate anion intermediate.

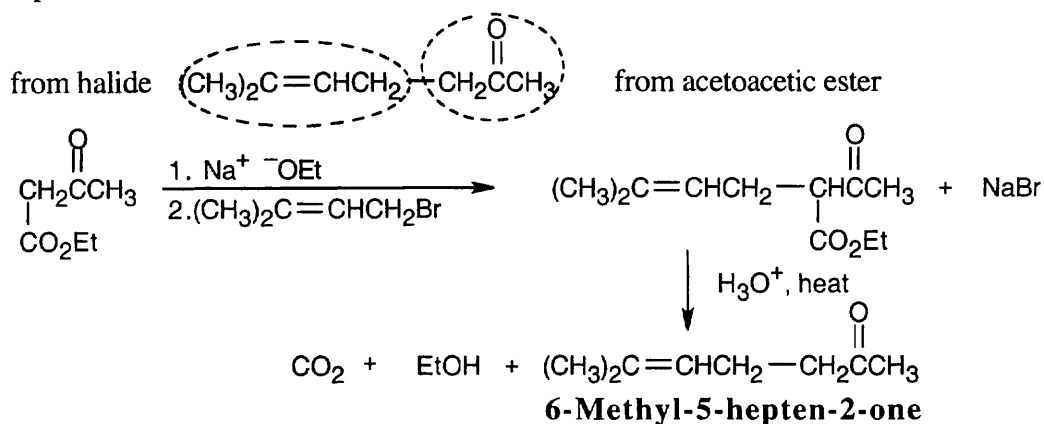


This alkylation can also be carried out using LDA as the base.

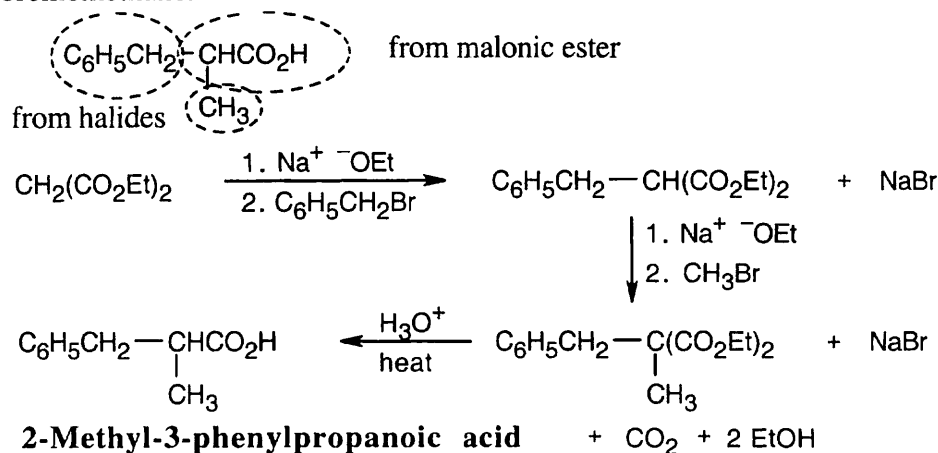


Visualizing Chemistry

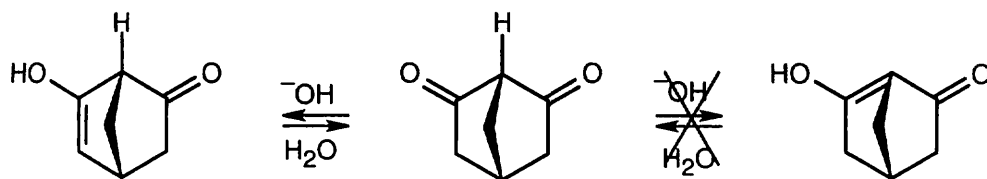
22.17 (a) Check to see if the target molecule is a methyl ketone or a substituted carboxylic acid. (The target molecule is a methyl ketone, and the reaction is an acetoacetic ester synthesis.) Next, identify the halide or halides that react with acetoacetic ester. (The halide is 1-bromo-3-methyl-2-butene.) Formulate the reaction, remembering to include a decarboxylation step.



(b) This product is formed from the reaction of malonic ester with both benzyl bromide and bromomethane.

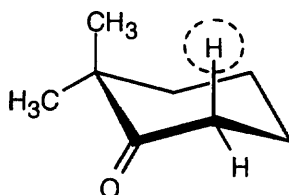


22.18



Ordinarily, β -diketones are acidic because they can form enolates that can be stabilized by delocalization over both carbonyl groups. In this case, loss of the proton at the bridgehead carbon doesn't occur because the strained ring system doesn't allow formation of the bridgehead double bond. Instead, enolization takes place in the opposite direction, and the diketone resembles acetone, rather than a β -diketone, in its pK_a and degree of dissociation.

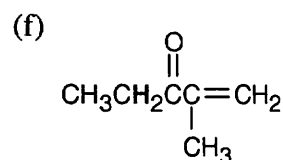
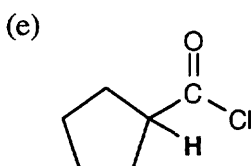
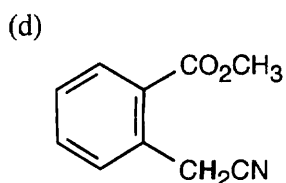
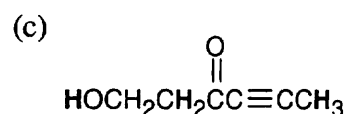
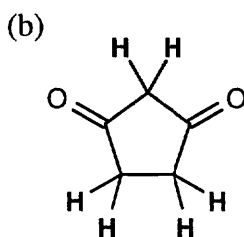
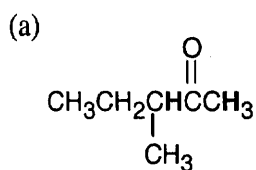
22.19



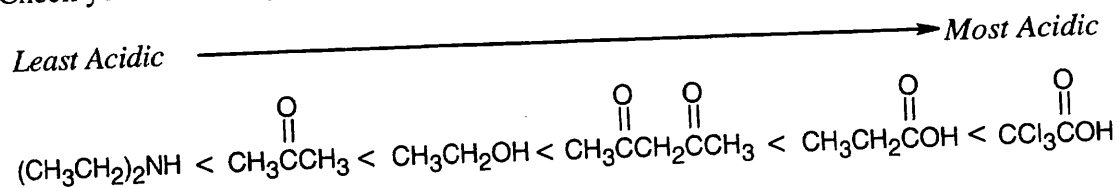
Enolization can occur on only one side of the carbonyl group because of the two methyl groups on the other side. The circled axial hydrogen is more acidic because the p orbital that remains after its removal is aligned for optimum overlap with the π electrons of the carbonyl oxygen.

Additional Problems

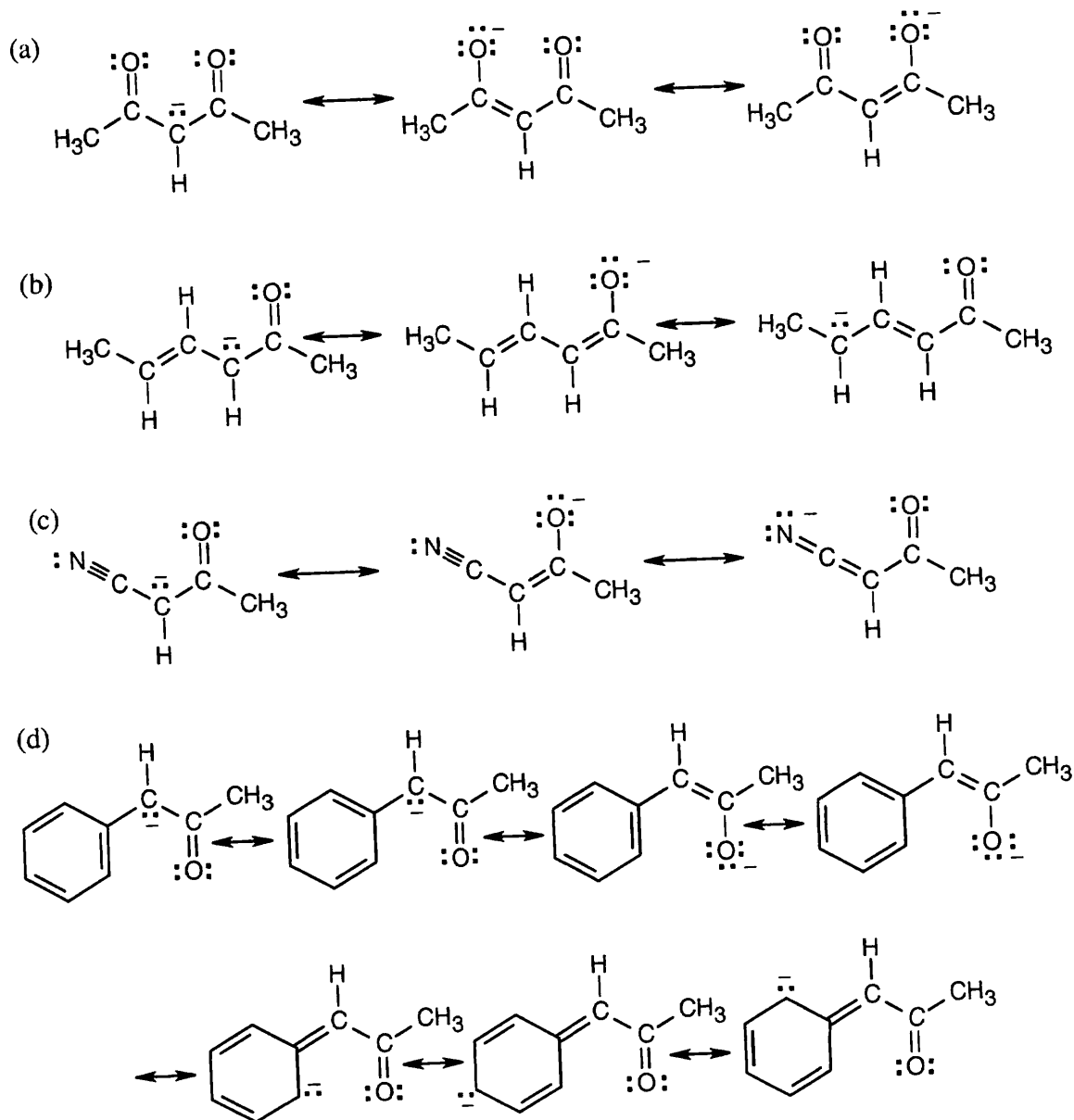
22.20 Acidic hydrogens are bold. The most acidic hydrogens are the two between the carbonyl groups in (b) and the hydroxyl hydrogen in (c). The hydrogens in (c) that are bonded to the methyl group are acidic (draw resonance forms to prove it).

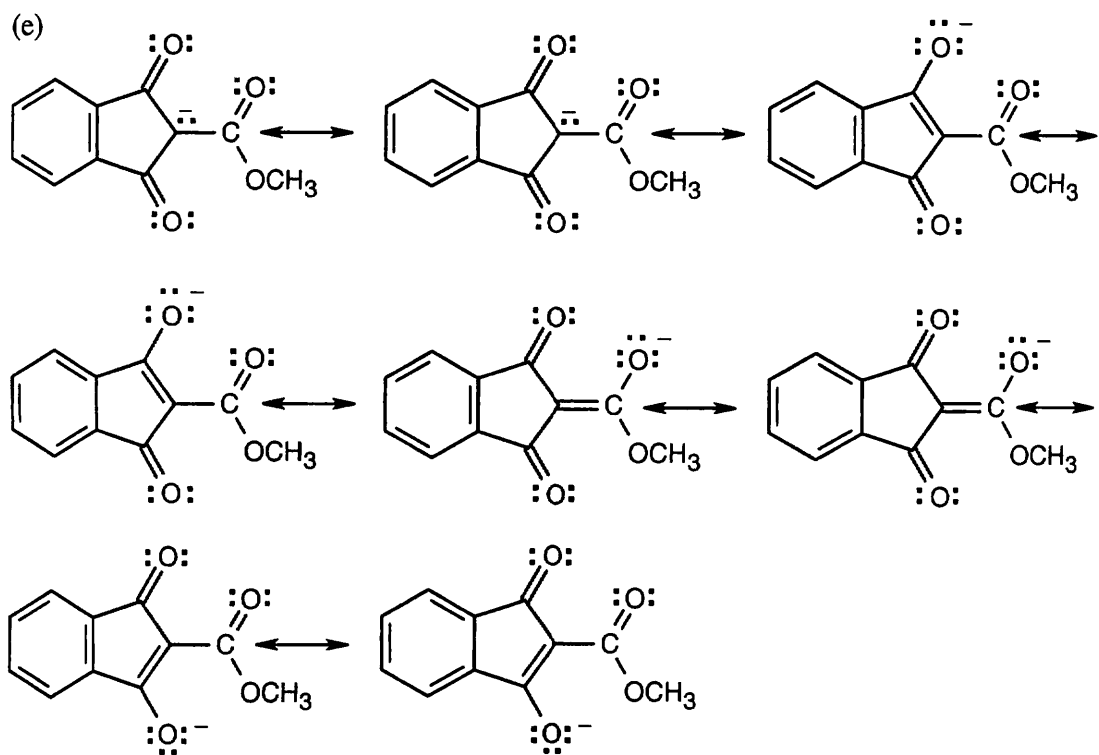


22.21 Check your answer by using Table 22.1.

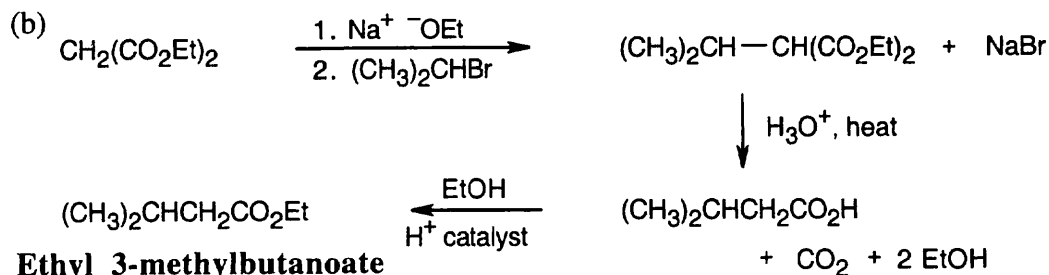
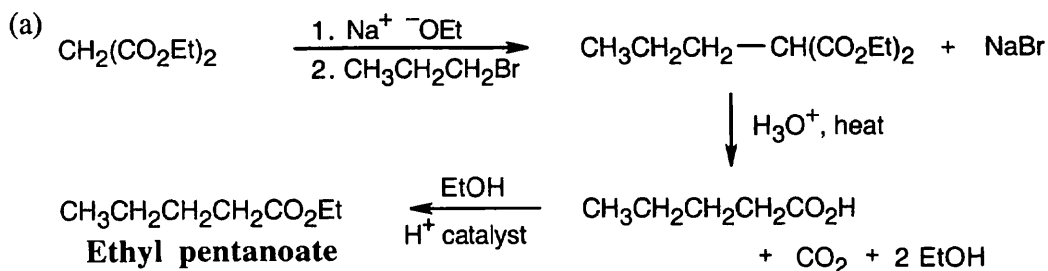


22.22

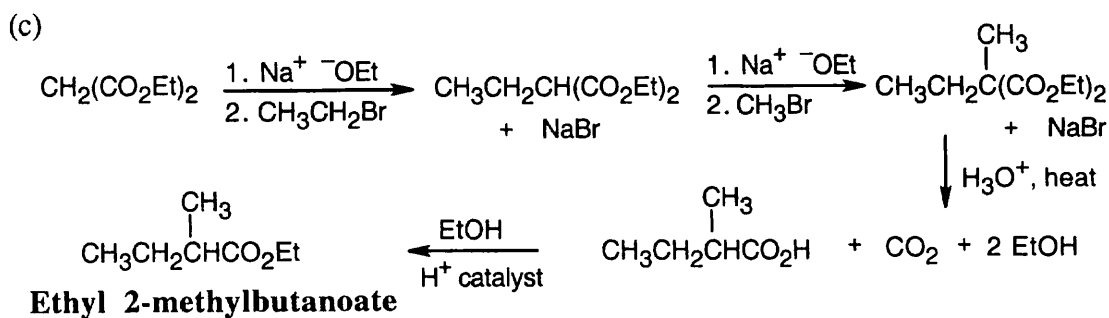




22.24



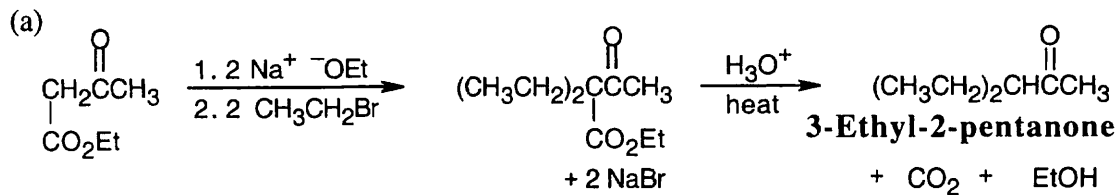
Some elimination product will also be formed.

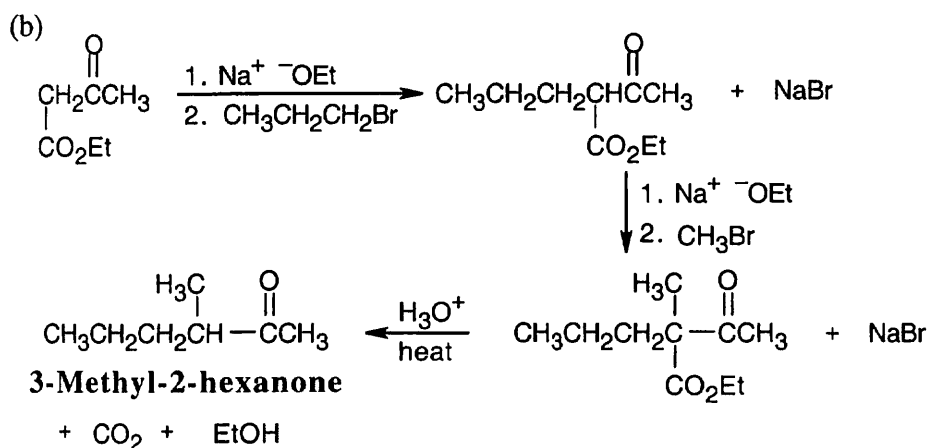


(d) The malonic acid synthesis can't be used to synthesize carboxylic acids that are trisubstituted at the alpha position.

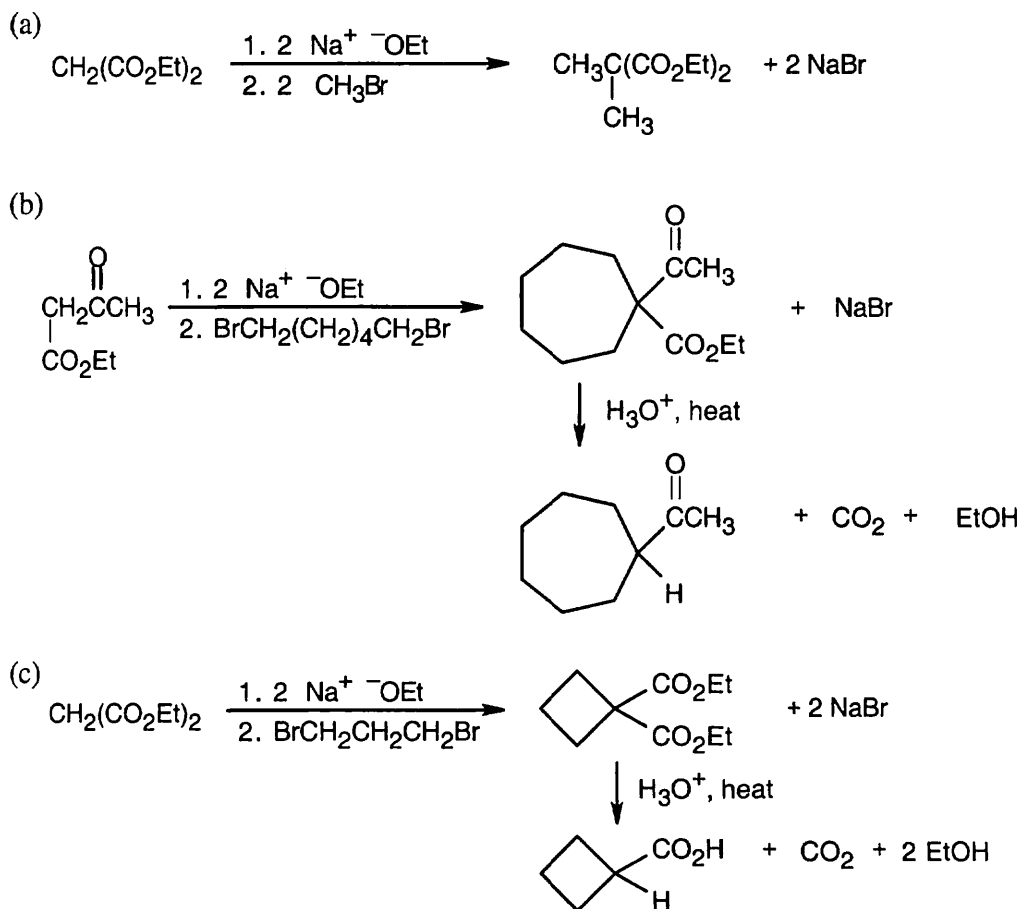
22.25 Look back to Problem 22.14, which describes compounds that can be prepared by an acetoacetic ester synthesis. Neither (a) or (c) are products of an acetoacetic ester synthesis because the halide component that would be needed for each synthesis doesn't undergo $\text{S}_{\text{N}}2$ reactions. Compound (b) can be prepared by the reaction of acetoacetic ester with 1,5-dibromopentane.

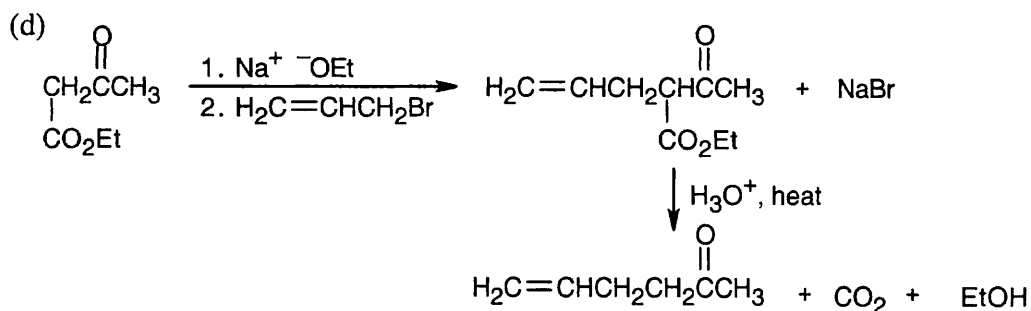
22.26





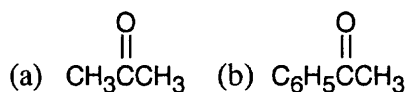
22.27 Use a malonic ester synthesis if the product you want is an α -substituted carboxylic acid or derivative. Use an acetoacetic acid synthesis if the product you want is an α -substituted methyl ketone.



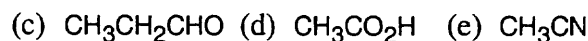


22.28 The haloform reaction (Problem 22.23d) is an alpha-substitution reaction in which a methyl ketone is trihalogenated at the alpha position, and the trihalomethyl group is displaced by $-\text{OH}$. It is a test for methyl ketones.

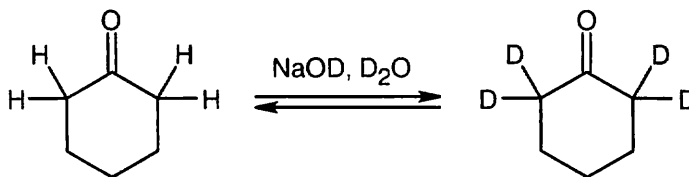
Positive haloform reaction:



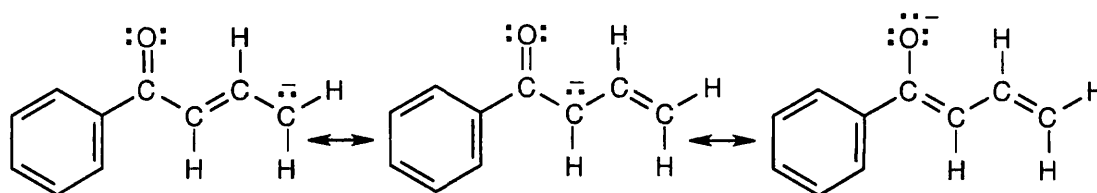
Negative haloform reaction:



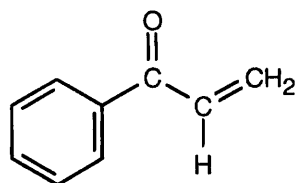
22.29 When a compound containing acidic hydrogen atoms is treated with NaOD in D_2O , all acidic hydrogens are gradually replaced by deuteriums. For each proton (atomic weight 1) lost, a deuteron (atomic weight 2) is added. Since the molecular weight of cyclohexanone increases by four after $\text{NaOD}/\text{D}_2\text{O}$ treatment (from 98 to 102), cyclohexanone contains four acidic hydrogen atoms.



22.30 Enolization at the γ position produces a conjugated enolate anion that is stabilized by delocalization of the negative charge over the π system of five atoms.

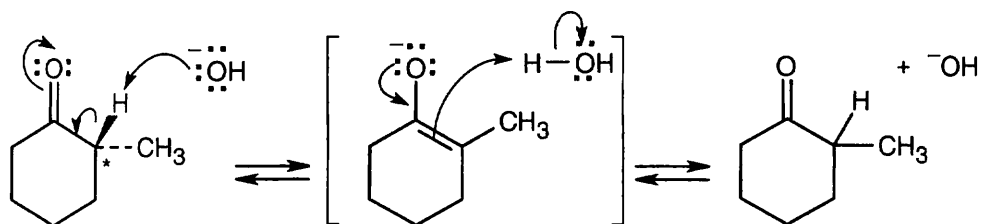


22.31 The illustrated compound, 1-phenyl-2-propenone, doesn't yield an anion when treated with base because the hydrogen on the α carbon is vinylic and isn't acidic (check Table 22.1 for acidity constants).



1-Phenyl-2-propenone

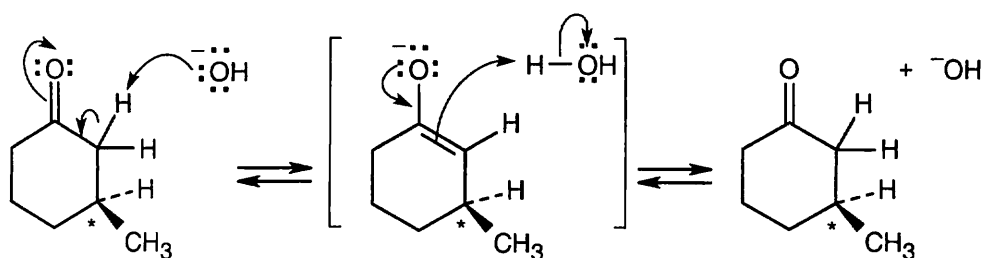
22.32 Reaction of (*R*)-2-methylcyclohexanone with aqueous base is shown below. Reaction with aqueous acid proceeds by a related mechanism through an enol, rather than an enolate ion, intermediate.



(*R*)-2-Methylcyclohexanone

Carbon 2 loses its chirality when the enolate ion double bond is formed. Protonation occurs with equal probability from either side of the planar sp^2 -hybridized carbon 2, resulting in a racemic product.

22.33

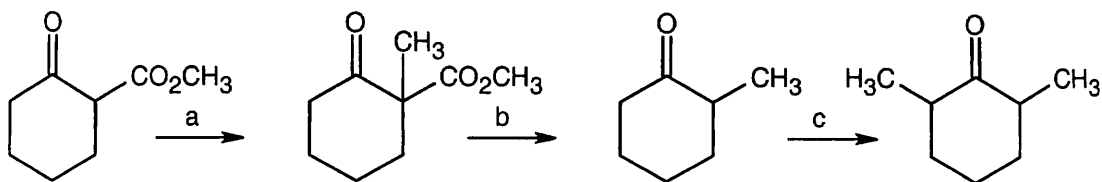


(*S*)-3-Methylcyclohexanone

(*S*)-3-Methylcyclohexanone isn't racemized by base because its chirality center is not involved in the enolization reaction.

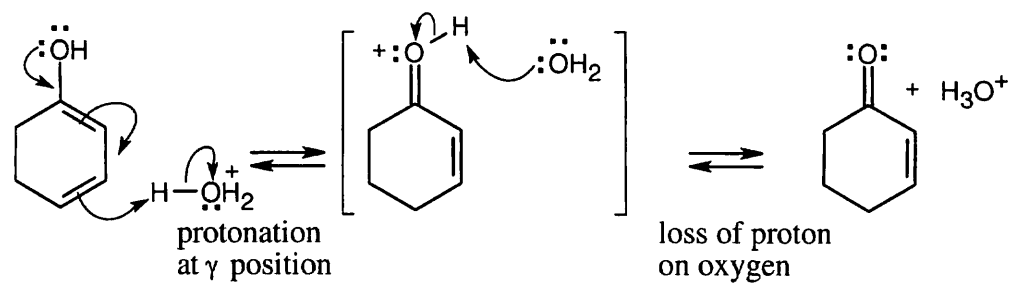
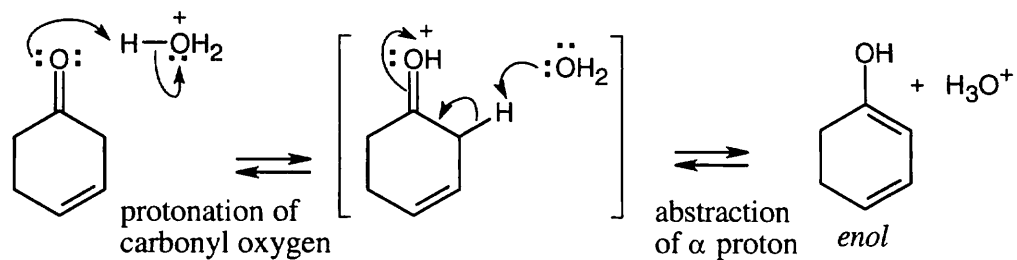
22.34 The Hell–Volhard–Zelinskii reaction involves formation of an intermediate acid bromide enol, with loss of stereochemical configuration at the chirality center. Bromination of (*R*)-2-phenylpropanoic acid can occur from either face of the enol double bond, producing racemic 2-bromo-2-phenylpropanoic acid. If the molecule had a chirality center that didn't take part in enolization (Problem 22.33), the product would be optically active.

22.35

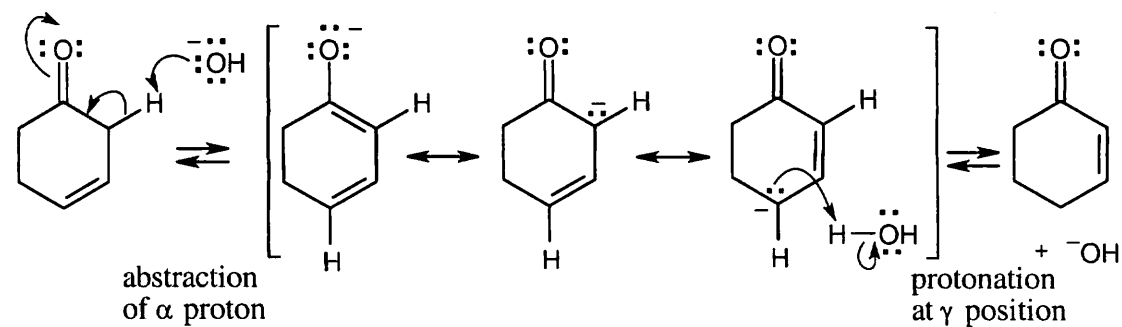


(a) $\text{Na}^+ \text{OEt}^-$, then CH_3I ; (b) H_3O^+ , heat; (c) LDA, then CH_3I

22.36

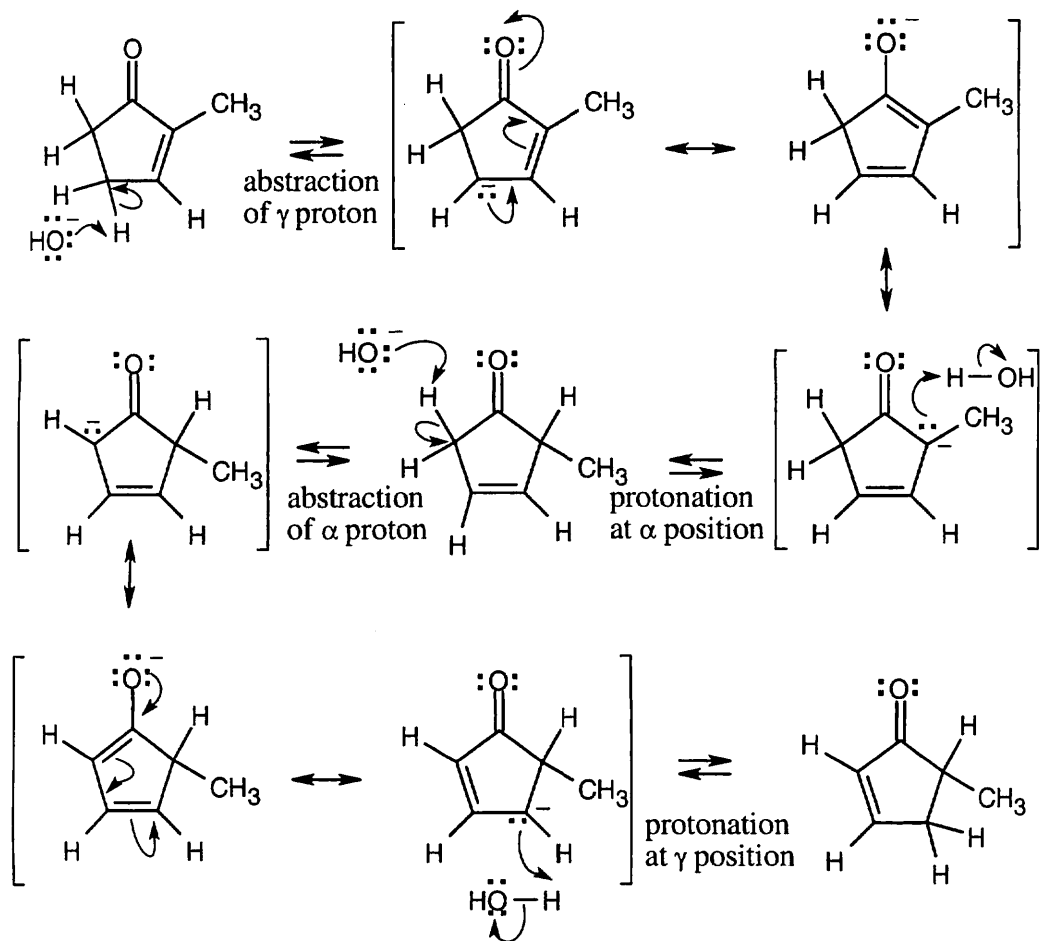


22.37



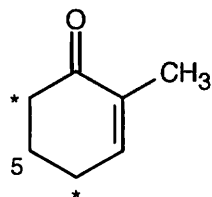
The enolate of 3-cyclohexenone can be protonated at three different positions. Protonation at the γ position yields the α,β -unsaturated ketone.

22.38



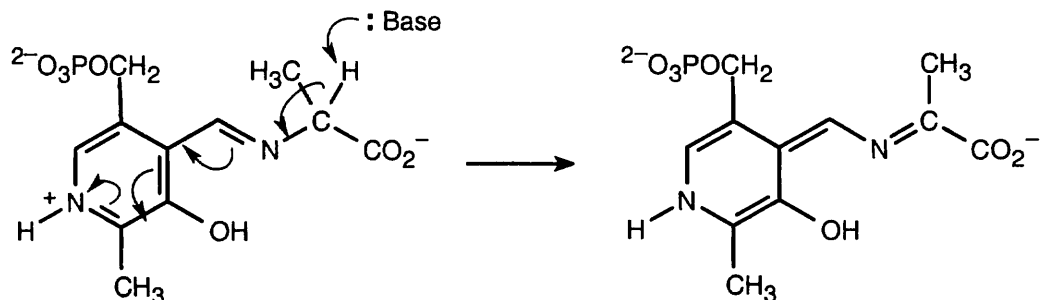
All protons in the five-membered ring can be exchanged by base treatment.

22.39 Protons α to a carbonyl group or γ to an enone carbonyl group are acidic (Problem 22.37). Thus for 2-methyl-2-cyclohexenone, protons at the starred positions are acidic.

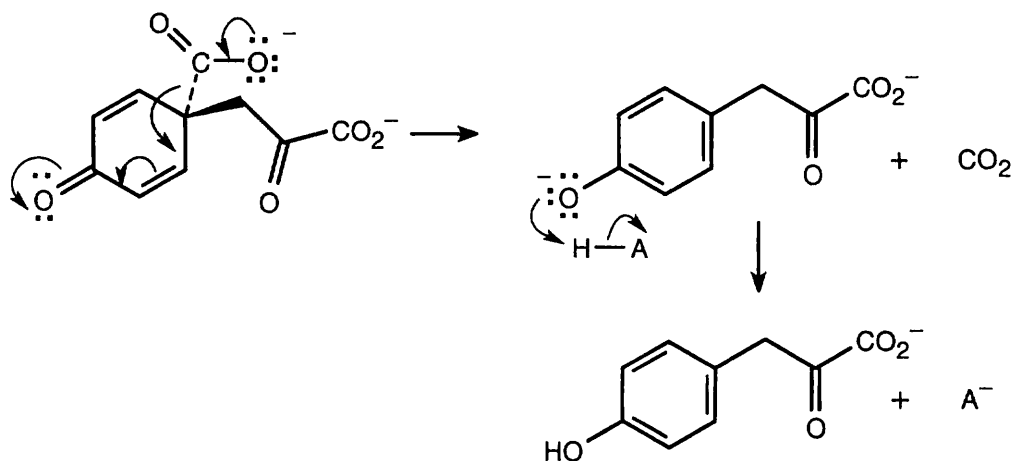


Isomerization of a 2-substituted 2-cyclohexenone to a 6-substituted 2-cyclohexenone requires removal of a proton from the 5-position of the 2-substituted isomer. Since protons in this position are not acidic, double bond isomerization does not occur.

22.40



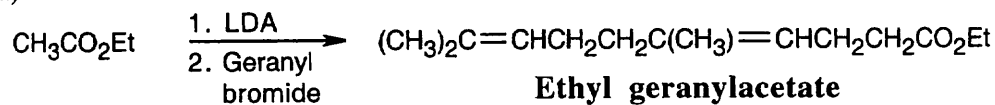
22.41 Decarboxylation, which takes place because of the stability of the resulting anion, is followed by protonation.



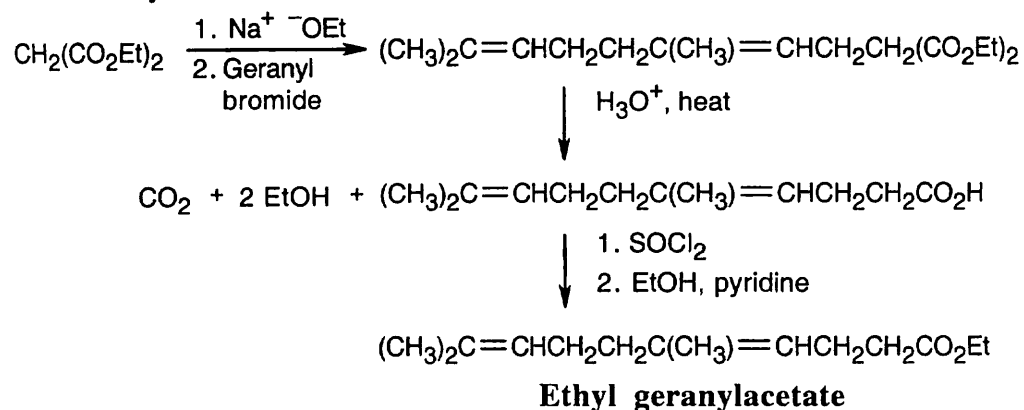
22.42 A nitroso compound is analogous to a carbonyl compound. If there are hydrogens α to the nitroso group, enolization similar to that observed for carbonyl compounds can occur, leading to formation of an oxime. If no hydrogens are adjacent to the nitroso group, enolization to the oxime can't occur, and the nitroso compound is stable.

22.43 First, treat geraniol with PBr_3 to form $(\text{CH}_3)_2\text{C}=\text{CHCH}_2\text{CH}_2\text{C}(\text{CH}_3)=\text{CHCH}_2\text{Br}$ (geranyl bromide).

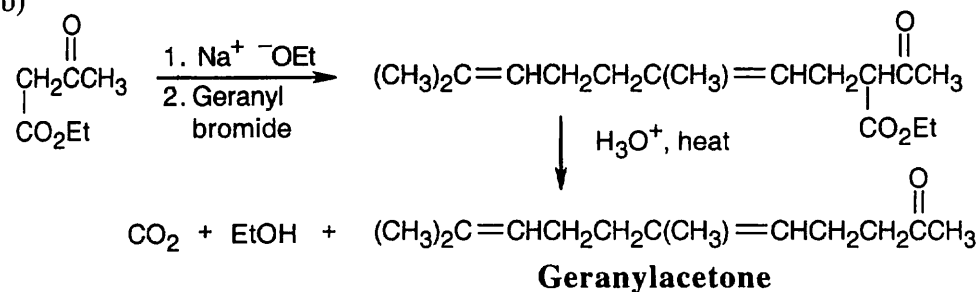
(a)



Alternatively:

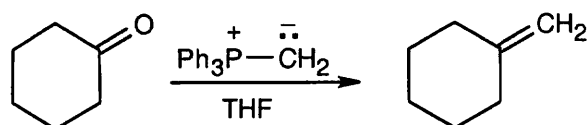


(b)

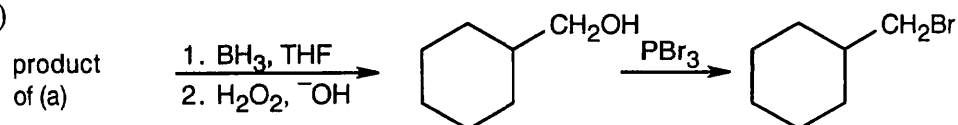


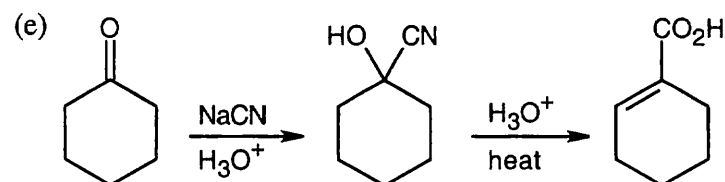
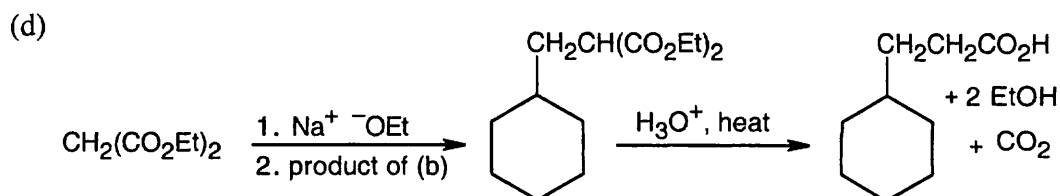
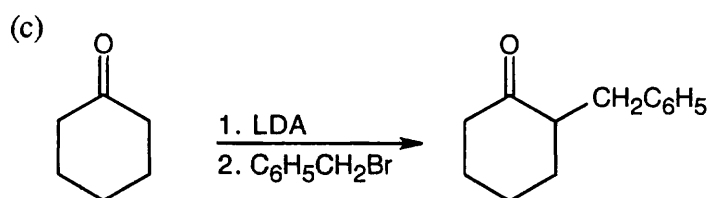
22.44

(a)

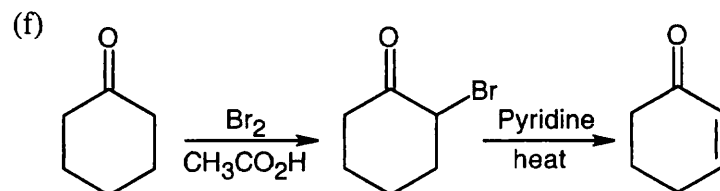


(b)

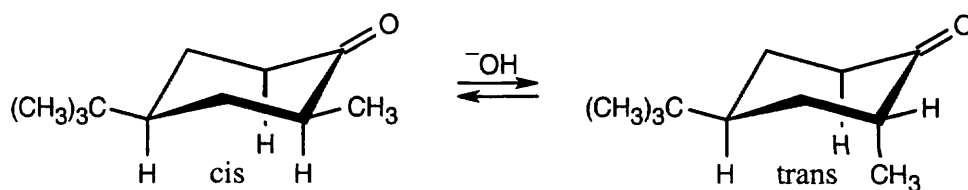




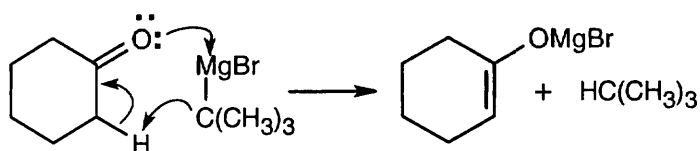
Warm aqueous acid both hydrolyzes the nitrile and dehydrates the alcohol.



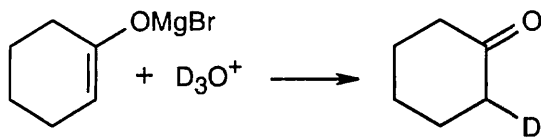
22.45 Treatment of either the *cis* or *trans* isomer with base causes enolization α to the carbonyl group and results in loss of configuration at the α position. Reprotonation at carbon 2 produces either of the diastereomeric 4-*tert*-butyl-2-methylcyclohexanones. In both diastereomers the *tert*-butyl group of carbon 4 occupies the equatorial position for steric reasons. The methyl group of the *cis* isomer is also equatorial, but the methyl group of the *trans* isomer is axial. The *trans* isomer is less stable because of 1,3-diaxial interactions of the methyl group with the ring hydrogens.



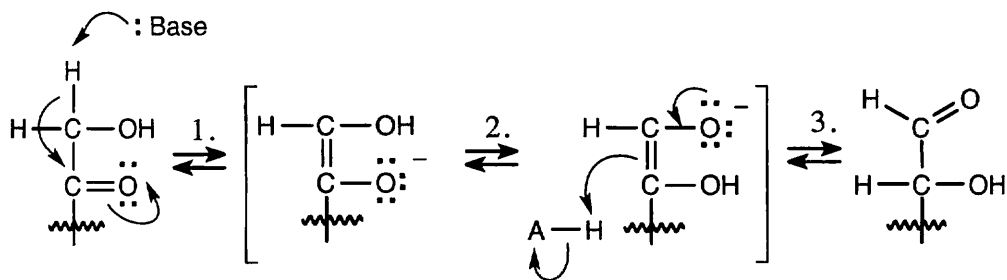
- 22.46** (a) Reaction with Br_2 at the α position occurs only with aldehydes and ketones, not with esters.
- (b) Aryl halides can't be used in malonic ester syntheses because they don't undergo $\text{S}_{\text{N}}2$ reactions.
- (c) The product of this reaction sequence, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COCH}_3$, is a methyl ketone, not a carboxylic acid.
- 22.47** The reaction of cyclohexanone and *tert*-butylmagnesium bromide gives the expected carbonyl addition product. The yield of the *tert*-butylmagnesium bromide addition product is very low, however, because of the difficulty of approach of the bulky *tert*-butyl Grignard reagent to the carbonyl carbon. More favorable is the acid-base reaction between the Grignard reagent and a carbonyl α proton.



When D_3O^+ is added to the reaction mixture, the deuterated ketone is produced.



22.48

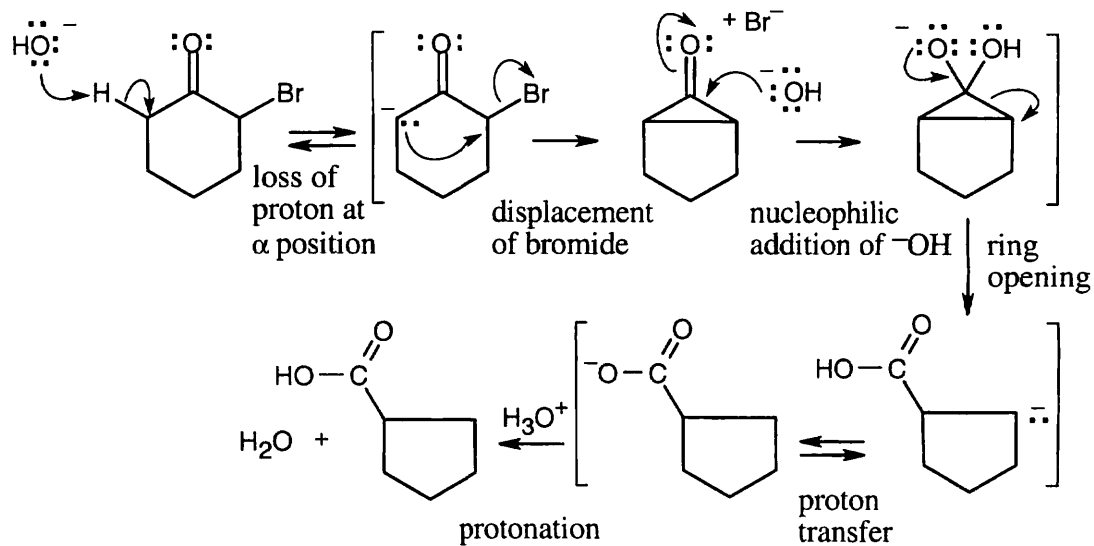


Step 1: Base-catalyzed enolization.

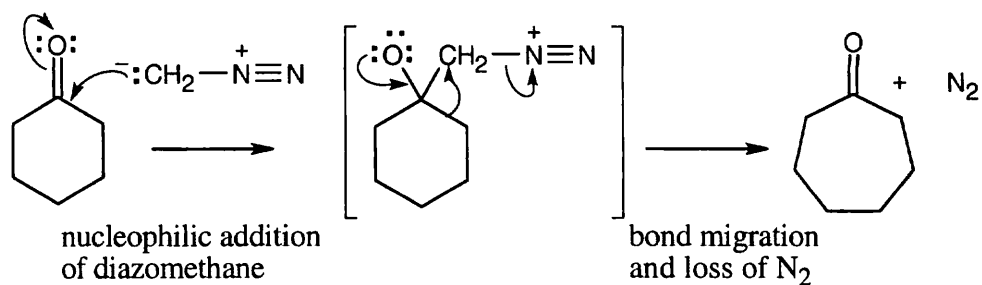
Step 2: Equilibration of two enolates by proton transfer.

Step 3: Protonation.

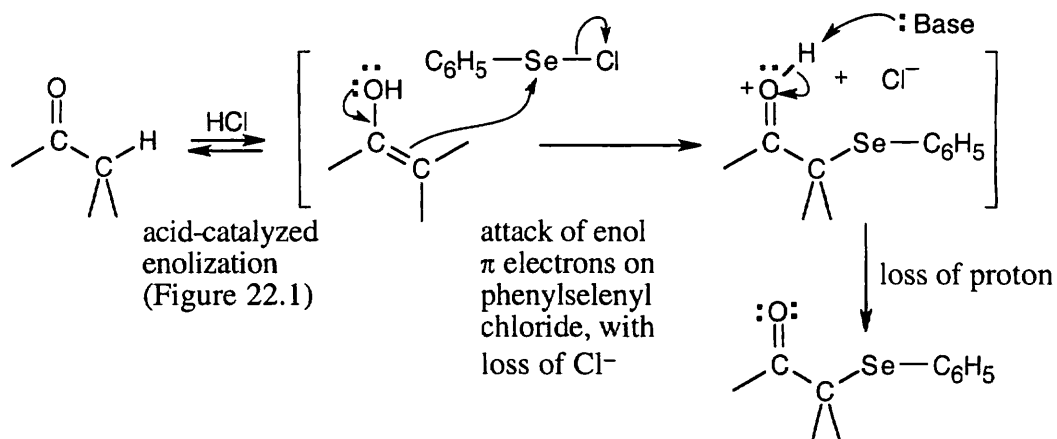
22.49



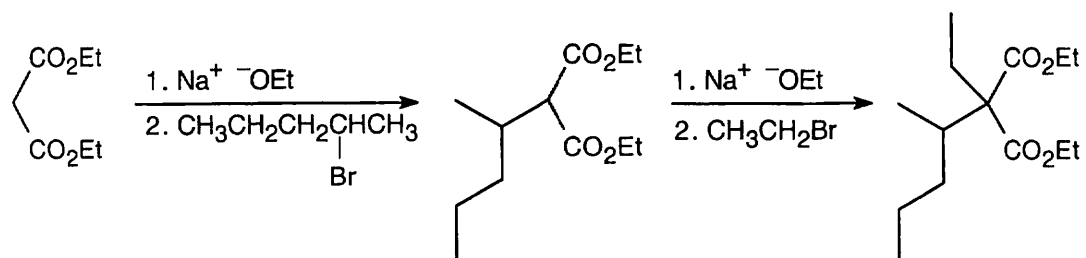
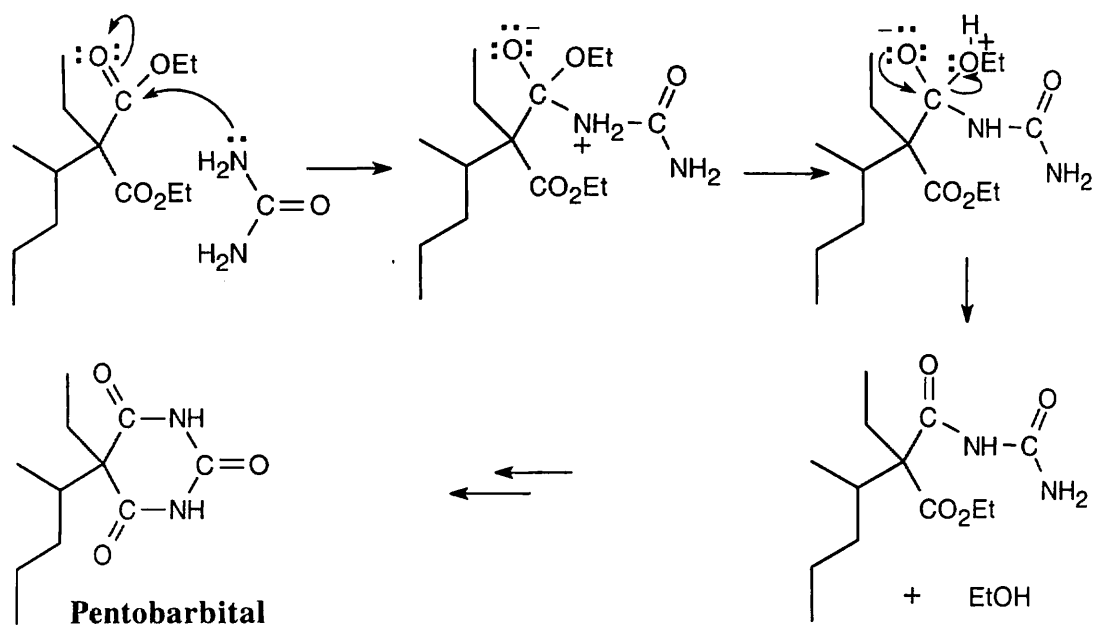
22.50



22.51



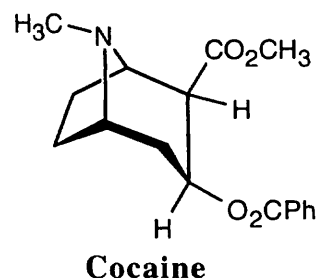
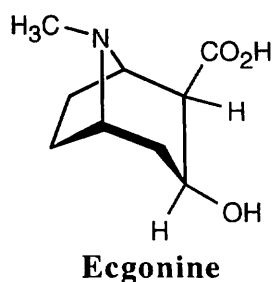
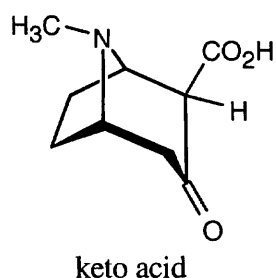
22.52

Dialkylation of diethylmalonate:**Nucleophilic acyl substitution:**

The series of steps is repeated to form the 6-membered ring.

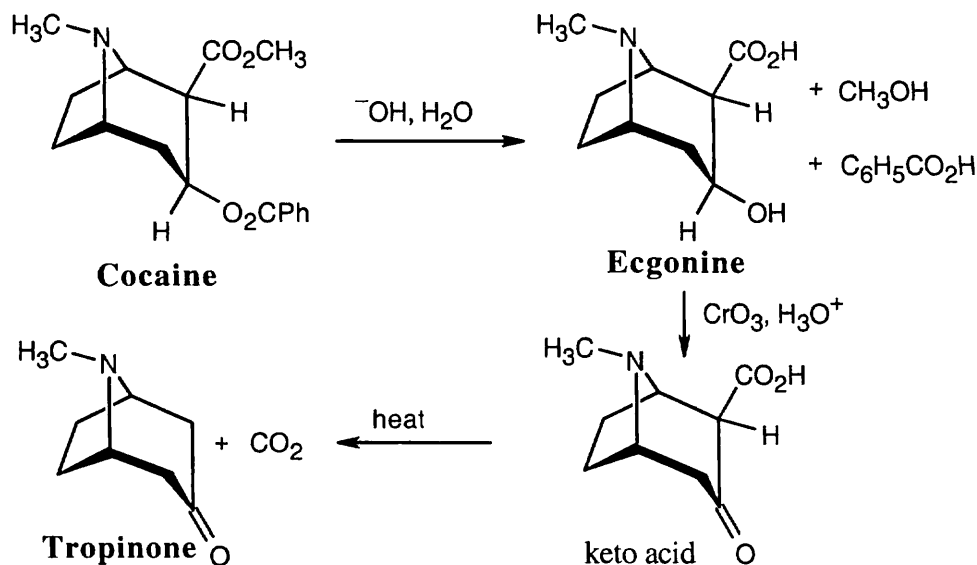
22.53 Start at the end of the sequence of reactions and work backwards.

- (a) Because the keto acid $C_9H_{13}NO_3$ loses CO_2 on heating, it must be a β -keto acid. Neglecting stereoisomerism, we can draw the structure of the β -keto acid as:



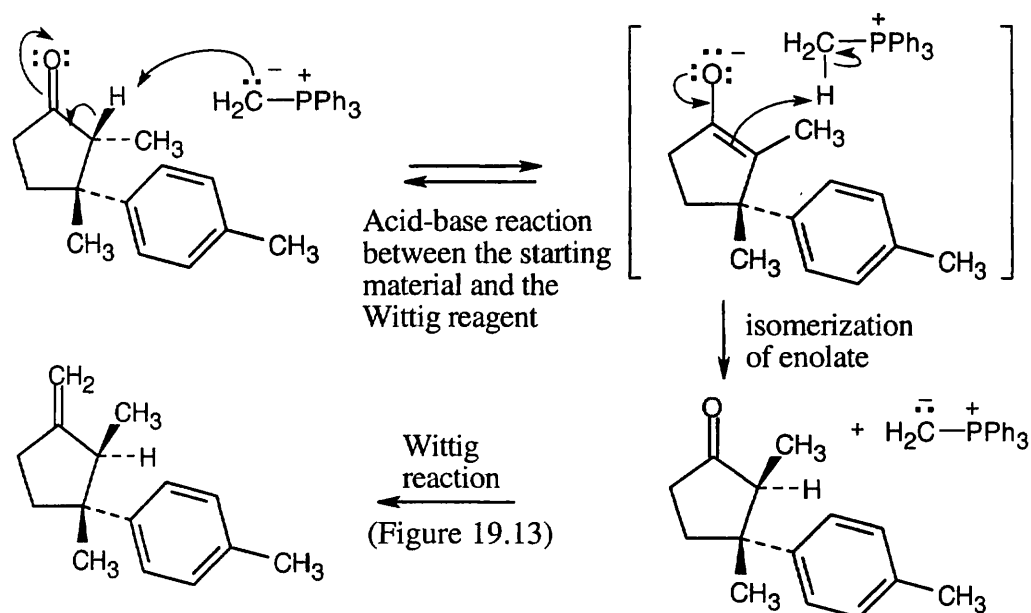
- (b) When ecgonine ($C_9H_{15}NO_3$) is treated with CrO_3 , the keto acid $C_9H_{13}NO_3$ is produced. Since CrO_3 is used for oxidizing alcohols to carbonyl compounds, ecgonine has the structure shown above. Again, the stereochemistry is unspecified.
- (c) Ecgonine contains carboxylic acid and alcohol functional groups. The other products of hydroxide treatment of cocaine are a carboxylic acid (benzoic acid) and an alcohol (methanol). Cocaine thus contains two ester functional groups, which are saponified on reaction with hydroxide.

The complete reaction sequence:

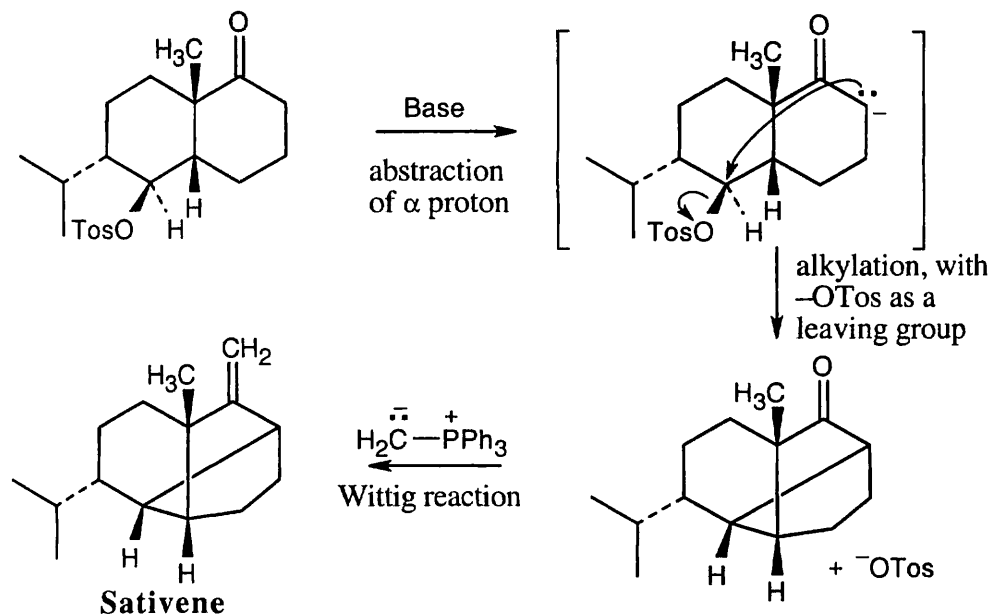


22.54 Laurene differs in stereochemical configuration from the observed product at the carbon α to the methylene group. Since this position is α to the carbonyl group in the precursor to laurene, enolization and isomerization must have occurred during the reaction.

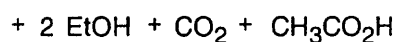
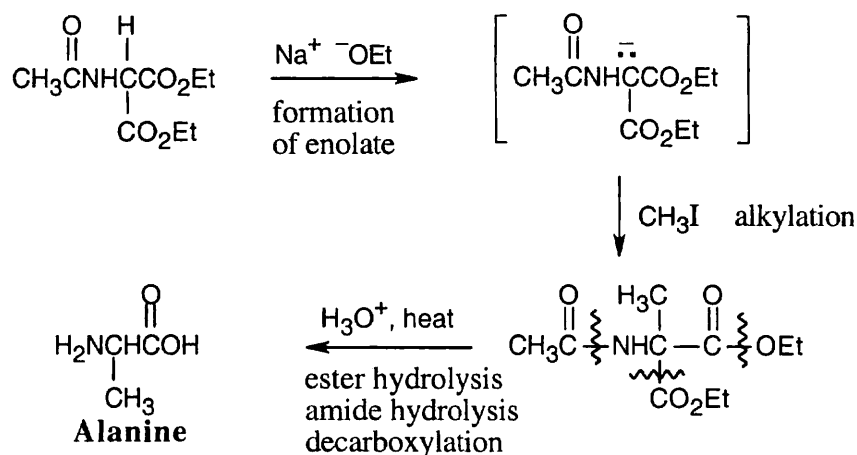
Isomerization of the ketone precursor is brought about by a reversible reaction with the basic Wittig reagent, which yields an equilibrium mixture of two diastereomeric ketones. One of the ketone isomers then reacts preferentially with the Wittig reagent to give only the observed product.



22.55 The key step is an intramolecular alkylation reaction of the ketone α -carbon, with the tosylate in the adjacent ring serving as the leaving group.

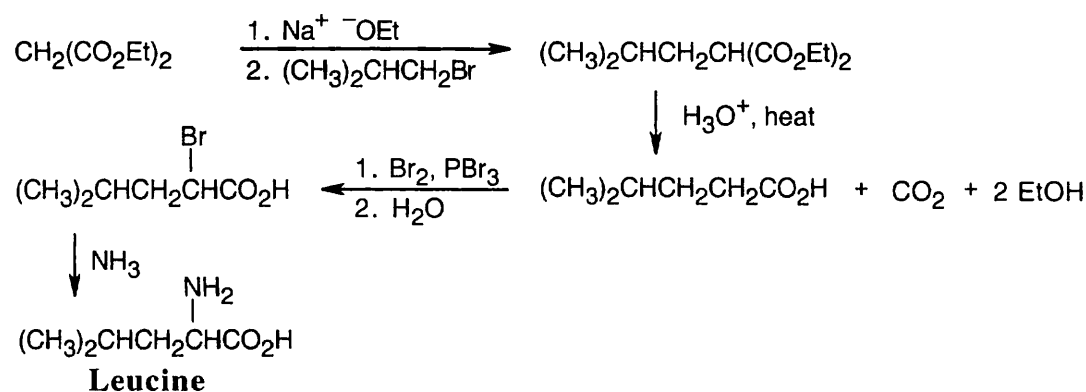


22.56



Acid hydrolyzes both ester bonds, as well as the amide bond, by mechanisms that were shown in Figure 21.8 and Section 21.6. Decarboxylation of the β -keto acid produces alanine.

22.57



A malonic ester synthesis is used to form 4-methylpentanoic acid. Hell-Volhard-Zelinskii bromination of the acid, followed by reaction with ammonia, yields leucine. The last reaction is an $\text{S}_{\text{N}}2$ displacement of bromide by ammonia.

22.58

