SHORT ANSWER

Exhibit 22-1
Refer to the compounds below to answer the following question(s):

1. Refer to Exhibit 22-1. Indicate all the acidic hydrogens in Compounds I through IV.

ANS:
Acidic hydrogens are underlined.

2. Refer to Exhibit 22-1. Indicate which hydrogens in Compound II are the most acidic. Explain your answer.

ANS:
The methylene hydrogens are the most acidic because they are flanked by two electron-withdrawing groups, −NO₂ and C=O. The enolate generated by their removal is highly resonance stabilized; it has three resonance forms.
In contrast, the enolate generated by the abstraction of a methyl proton is stabilized by only one electron-withdrawing group and has two resonance forms:

\[
\begin{align*}
\text{O}^- & \quad + \quad \text{N}-\text{CH}_2-\text{C} \equiv \text{CH}_2 \\
\text{O}^- & \quad + \quad \text{N}-\text{CH}_2-\text{C} \equiv \text{CH}_2
\end{align*}
\]

3. Refer to Exhibit 22-1. Choose the most acidic compound from Compounds I - IV. Explain your choice.

ANS:
Compound III is the most acidic compound because the methine hydrogen is flanked by three carbonyl groups so the enolate ion generated by its removal has four resonance forms.

4. Refer to Exhibit 22-1. Draw the structures for all enols of Compound I.

ANS:

Exhibit 22-2
Consider the structures below to answer the following question(s).

I

II

III
5. Refer to Exhibit 22-2. Indicate the most acidic hydrogens in each of the molecules.

ANS:

\[ \text{I} \quad \text{II} \quad \text{III} \]

The most acidic hydrogens are underlined.

6. Refer to Exhibit 22-2. Rank the molecules above in order of increasing acidity (least acidic to most acidic).

   a. III, II, I
   b. II, III, I
   c. I, II, III
   d. II, I, III

ANS: b

7. Nitroethane [CH\(_3\)CH\(_2\)NO\(_2\), pK\(_a\) = 8.6] is a much stronger acid than ethane [CH\(_3\)CH\(_3\), pK\(_a\) \approx 60]. Explain.

ANS:
When a proton is removed from the carbon bearing the nitro group in nitroethane, the negative charge is shared by the electron-withdrawing nitro group. Thus, the anion is stabilized by resonance between two forms.

\[
\begin{array}{c}
\text{CH}_3-\text{CH}^+-\text{N}^+&\quad\text{CH}_3-\text{CH}^+-\text{N}^+\\
\begin{array}{c}
\text{O}^-\\
\end{array}&\quad\begin{array}{c}
\text{O}^-\\
\end{array}
\end{array}
\]

When a proton is abstracted from ethane, the carbon atom must bear the full negative charge.

\[ \text{CH}_3\text{CH}_2^- \]
Exhibit 22-3
Consider the reaction below to answer the following question(s).

\[ \text{pK}_a = 26 \quad \text{pK}_a = 40 \]

\[
\begin{array}{ccc}
\text{A} & \xrightarrow{\text{Li}^+} & \text{B} \\
:O: & \xrightarrow{\text{N}} & :O- \\
\text{H} & & \text{Li}^+ \\
& & \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{C} & + & \text{D} \\
\text{H} & + & \text{N} \\
& & \\
\end{array}
\]

8. Refer to Exhibit 22-3. The strongest base in the reaction is:

ANS: B

9. Refer to Exhibit 22-3. The weakest acid in the reaction is:

ANS: D

10. Refer to Exhibit 22-3. The enolate ion in the reaction is:

ANS: C

11. Refer to Exhibit 22-3. On the structures provided above, draw arrows indicating electron flow in the generation of the intermediate C.

ANS:

\[
\begin{array}{ccc}
\text{A} & \xrightarrow{\text{Li}^+} & \text{B} \\
:O: & \xrightarrow{\text{N}} & :O- \\
\text{H} & & \text{Li}^+ \\
& & \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{C} & + & \text{D} \\
\text{H} & + & \text{N} \\
& & \\
\end{array}
\]
Exhibit 22-4
Consider the reaction sequence below to answer the following question(s):

\[
\begin{align*}
\text{Compound X} &\xrightarrow{1.\ NaOEt,\ EtOH} \text{Compound Y} &\xrightarrow{2.\ NaOEt,\ EtOH} \text{Compound Z} \\
\text{EtO} &\text{CO}_2\text{Et} &\text{CO}_2\text{Et}
\end{align*}
\]

12. Refer to Exhibit 22-4. Compound X, diethyl propanedioate, is more commonly known as
   a. ethyl acetoacetate
   b. acetoacetic ester
   c. oxalic ester
   d. malonic ester

ANS: d

13. Refer to Exhibit 22-4. Write the complete stepwise mechanism for the conversion of
    Compound X into Compound Y. Show all electron flow with arrows and draw all
    intermediate structures.

ANS:

14. Refer to Exhibit 22-4. Below are the structures and electron flow for the conversion of
    Compound Y into Compound Z. Draw the structure of Compound Z. (Hint: Compound Z is
    an alcohol.)

ANS:
Exhibit 22-5
Consider the reaction sequence below to answer the following question(s):

15. Refer to Exhibit 22-5. The starting material A in this reaction sequence is called _____.
   a. a β-keto ester
   b. an α-carboethoxy ketone
   c. a malonic ester
   d. an acetoacetic ester

ANS: a

16. Refer to Exhibit 22-5. Conversion of A into B is a type of reaction termed _____.
   a. an acylation
   b. an enolation
   c. an alkylation
   d. a phenylation

ANS: c

17. Refer to Exhibit 22-5. Conversion of B into C involves hydrolysis of the ester followed by
decarboxylation. On the structures provided below, show the electron flow for the
decarboxylation step.

ANS:
18. Refer to Exhibit 22-5. The initial product formed on decarboxylation is an enol, which rapidly equilibrates to its keto form under the acidic reaction conditions. Write the complete stepwise mechanism for the acid-catalyzed conversion of the enol into its keto form, Compound C.

\[
\text{O} \quad \text{H} \quad \text{Ph} \quad \overset{\text{H}_3\text{C}^+}{\underset{\text{H} \quad \text{OH}_2}{\text{Ph}}} \quad \overset{\text{H} \quad \text{H}}{\underset{\text{OH}_2}{\text{Ph}}} \quad \overset{\text{O}}{\text{O}} \quad \text{Ph}
\]

ANS:

Exhibit 22-6
Consider the reaction below to answer the following question(s):

\[
\text{CH}_3 \quad \overset{1. \text{LiN}[\text{CH}(\text{CH}_3)_2]_2, \text{THF}}{\text{2. PhCH}_2\text{Br}} \quad \overset{\text{90\%}}{\text{PhCH}_2} \quad \overset{\text{10\%}}{\text{CH}_3} \quad + \quad \overset{\text{CH}_3}{\text{CH}_3} \quad \overset{\text{CH}_3\text{Ph}}{\text{CH}_3\text{Ph}}
\]
19. Refer to Exhibit 22-6. Write the complete stepwise mechanism for the reaction above. Show all intermediate structures and all electron flow with arrows.

ANS:

20. Refer to Exhibit 22-6. Explain the product ratio in this reaction.

ANS:
Lithium diisopropylamide is a sterically hindered base, so abstraction of a proton is more favorable at the less sterically crowded side of the ketone. Hence, the substitution occurs primarily at position 6 rather than position 2.

21. Write the complete stepwise mechanism for the reaction of cyclopentanone with bromine in acetic acid to give 2-bromocyclopentanone. Show all intermediate structures and all electron flow with arrows.

ANS:
Exhibit 22-7
Give the major organic product(s) of each of the following reactions or sequences of reactions. Show all relevant stereochemistry.

22.
\[
\text{O} \quad \text{CH}_3 \quad \xrightarrow{\text{Br}_2, \text{CH}_3\text{COOH}} \quad \text{O} \quad \text{CH}_2\text{Br}
\]

ANS:

23.
\[
\text{OH} \quad \xrightarrow{1. \text{Br}_2, \text{FBr}_3, 2. \text{H}_2\text{O}} \quad \text{Br}
\]

ANS:

24.
\[
\text{CH}_3 \quad \xrightarrow{1. \text{I}_2, \text{NaOH} \text{ (excess)} \text{H}_2\text{O}} \quad \text{CH}_3 \text{OH}
\]

ANS:
Carbonyl Alpha-Substitution Reactions

25. \[
\text{EtO} \quad \begin{array}{c}
\text{OEt} \\
\text{EtO}
\end{array}
\quad \xrightarrow{1.2 \text{ equiv. NaOEt, EtOH}} \\
\xrightarrow{2. \text{Br}} \\
\xrightarrow{2. \text{Br}}
\]

ANS:

26. \[
\text{EtO} \quad \begin{array}{c}
\text{OEt} \\
\text{EtO}
\end{array}
\quad + \quad \text{(CH}_2\text{)}_2\text{CHCH}_2\text{CH}_2\text{Br}
\quad \xrightarrow{1. \text{NaOEt, EtOH}}
\quad \xrightarrow{2. \text{H}_2\text{O}^+, \text{heat}}
\]

ANS:

27. \[
\text{Cl}_2
\quad \xrightarrow{\text{HCl}}
\]

ANS:

28. \[
\text{CH}_2\text{CO}_2\text{Et}
\quad \xrightarrow{1. \text{LDA, THF}}
\quad \xrightarrow{2. \text{CH}_3\text{CH}_2\text{Br}}
\]

ANS:
29. ANS:

30. Diethyl malonate can be prepared by the following reaction sequence. Draw the structures of each of the missing intermediates in the boxes provided.
Exhibit 22-8
How would you prepare each of the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis? Show all intermediate structures and all reagents.

31.

**ANS:**

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{COOH} & \\
\text{EtO} & \quad \text{EtO} \\
\end{align*}
\]

\[1. \text{NaOEt, EtOH} \]
\[2. \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \]

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{COOH} & \\
\text{EtO} & \quad \text{EtO} \\
\end{align*}
\]

\[1. \text{NaOEt, EtOH} \]
\[2. \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \]

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{COOH} & \\
\text{EtO} & \quad \text{EtO} \\
\end{align*}
\]

\[\text{H}_2\text{O}^+ \text{ heat} \]

32.

**ANS:**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \\
\text{O} & \\
\text{Ph} & \\
\end{align*}
\]

\[1. \text{NaOEt, EtOH} \]
\[2. \text{PhCH}_2\text{Br} \]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \\
\text{O} & \\
\text{Ph} & \\
\end{align*}
\]

\[1. \text{NaOEt, EtOH} \]
\[2. \text{CH}_3\text{I} \]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \\
\text{O} & \\
\text{Ph} & \\
\end{align*}
\]

\[\text{H}_2\text{O}^+ \text{ heat} \]
33. ANS:

\[
\text{EtO} \quad \text{EtO}_2 \quad \text{EtO}
\]

\[
\text{EtO} \quad \text{EtO}_2 \quad \text{EtO}
\]

\[
\text{EtO} \quad \text{EtO}_2 \quad \text{EtO}
\]

34. ANS:

\[
\text{O} \quad \text{C} \quad \text{CH}_3
\]

\[
\text{O} \quad \text{C} \quad \text{CH}_3
\]

\[
\text{O} \quad \text{C} \quad \text{CH}_3
\]
35. \( H_2C\equiv CHCH_2CH_2CH_3 \)

ANS:

\[
\begin{align*}
\text{CH}_3\text{C\equiv CCH}_2\text{CH}_2\text{Br} & \xrightarrow{1. \text{NaOEt, EtOH}} \text{CH}_3\text{C\equiv CCH}_2\text{CH}_2\text{Et} \\
& \xrightarrow{2. H_2C\equiv CHCH_2Br} \text{CH}_3\text{C\equiv CCH}_2\text{CH}_2\text{CH}_2\text{Br} \\
& \xrightarrow{\text{H}_2\text{O}^+, \text{heat}} \text{CH}_3\text{C\equiv CCH}_2\text{CH}_2\text{CO}_2\text{CH}_3
\end{align*}
\]

Exhibit 22-9
Show how you would accomplish each of the following transformations. More than one step may be required. Show all reagents and all intermediate structures.

36.

ANS:

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{Mg, ether}} \text{MgBr} \\
& \xrightarrow{\text{NaCN}} \text{CN} \\
& \xrightarrow{\text{H}_2\text{O}^+, \text{heat}} \text{COOH} \\
& \xrightarrow{1. \text{CO}_2} \text{COOH} \\
& \xrightarrow{2. \text{H}_2\text{O}^+} \text{Br} \\
& \xrightarrow{\text{Br}_2, \text{PBr}_3} \text{Br} \\
& \xrightarrow{\text{CH}_3\text{OH, HCl}} \text{COOH} \\
& \xrightarrow{\text{pyridine, heat}} \text{CO}_2\text{CH}_3
\end{align*}
\]

37. \( \text{CH}_3 \xrightarrow{} \text{CH}_2\text{CH}_2\text{C\equiv N} \)
38. Mechanistically like halogenation, acetone can be deuterated by treatment with D₃O⁺. Describe how an H NMR could be used to verify that deuteration actually occurs.

ANS: Acetone containing only ¹H nuclei would show one singlet in the ¹HNMR. Upon deuteration, all of the hydrogen atoms will no longer exist in chemically equivalent environments and splitting of the signal may occur. If the deuteration goes to completion, CD₃COCD₃, the ¹HNMR signal will be lost because ²H (D) is a nonmagnetic nucleus possessing an even number of nucleons.

39. Explain why the following reaction does not occur to any significant extent respect when the reactant is treated with bromine in the presence of acetic acid. Atoms other than carbon and hydrogen are labeled.

ANS: Carboxylic acids, like esters and amides, do not enolize to any appreciable extent. The enol tautomer is the necessary intermediate in alpha substitution using Br₂ in acetic acid.
Carbonyl Alpha-Substitution Reactions

40. Draw the structure of the major product formed when the substance represented by the following molecular model is treated with: 1. Br<sub>2</sub>/acetic acid, 2.) pyridine/heat. Atoms of other than carbon and hydrogen are labeled.

![Molecular Model]

ANS:

\[
\text{O} \\
\text{CH}_3\text{CH}=\text{CH}_2
\]

41. Explain how to use an alkylation reaction to produce:

![Molecular Model]

from

![Molecular Model]

Atoms other than carbon and hydrogen are labeled.

ANS:

Treatment of 3-methylbutanenitrile with LDA/THF followed by the alkylation using iodoethane, CH<sub>3</sub>CH<sub>2</sub>I, will yield 2-ethyl-3-methylbutanenitrile via deprotonation and alkylation of the \( \alpha \)-carbon.
MULTIPLE CHOICE

1. Which of the following is **not** correct?
   a. Tautomers are constitutional isomers.
   b. Tautomers rapidly interconvert.
   c. The enol form is generally more stable.
   d. Tautomerization is catalyzed by both acids and bases.
   e. All of the above are correct with respect to tautomers.

   ANS: C

2. Examine the following generalized structure.

   ![Generalized Structure](image)

   This represents
   a. the acid catalyzed intermediate between an keto and enol tautomer.
   b. the base catalyzed intermediate between an keto and enol tautomer.
   c. one of the resonance forms of the acid catalyzed intermediate between an keto and enol tautomer.
   d. one of the resonance forms of the acid catalyzed intermediate between an keto and enol tautomer.

   ANS: C

3. Consider the following molecular model. Atoms other than carbon and hydrogen are labeled.

   ![Molecular Model](image)

   Bromination of the substance represented would be dependent on the concentration of:
   a. ketone.
   b. acid.
   c. halogen.
   d. a and b
   e. a and c
   f. b and c
   g. a, b, d.

   ANS: D
4. The alkyl halide that should be used to produce octanoic acid via the malonic ester synthesis is:
   a. 1-bromooctane
   b. 1-bromohexane
   c. 1-bromopentane
   d. 1-bromodecane
   e. 1-bromoundecane
   ANS: B

5. Using the acetoacetic ester synthesis, to produce 5-methyl-2-heptanone, the alkyl halide that should be used is:
   a. 1-bromo-2-methylpentane
   b. 1-bromo-2-methylnonane
   c. 1-bromo-2-methylbutane
   d. 1-bromo-2-methyldecane
   e. 1-bromo-5-methylheptane
   ANS: C

6. The following substance is produced using a acetoacetic ester synthesis. Atoms other than carbon and hydrogen are labeled.

   ![Chemical Structure](image)

   Which of the following regions of an IR spectrum could be used to monitor the progress of the reaction?
   a. 2850 - 29060 cm\(^{-1}\)
   b. 2500 - 3100 cm\(^{-1}\)
   c. 1670 - 1780 cm\(^{-1}\)
   d. 500 - 600 cm\(^{-1}\)
   e. either c or d
   ANS: E
7. Which of the hydrogen atoms indicated by a number is the most acidic in the structure below? Atoms other than carbon and hydrogen are labeled.

a. 1  
b. 2  
c. 3  
d. 4  

ANS: A