Chapter 20

Carbonyl Condensation Reactions

Chapter Outline

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Objectives

✔ Know the generalized aldol condensation mechanism
✔ Understand the differences between an $\alpha$ substitution and the aldol condensation reaction
✔ Recognize the predominant product of a mixed aldol condensation reaction
✔ Know what factors influence the formation of product in an intramolecular condensation
✔ Know the differences and similarities of ester substrates and ketone or aldehyde substrates in an aldol condensation
✔ Understand the conjugate addition process in a Michael reaction
✔ Know the Robinson annulation process and be able to write a mechanism for the reaction
✔ Develop your skills in organic synthesis using carbonyl condensation and $\alpha$ substitution reactions

It’s as large as life and twice as natural.
—Lewis Carroll

In a condensation reaction, two, or occasionally more, compounds combine or condense to form a new compound—often releasing a small molecule such as water. The discussion of carbonyl condensation reactions, which is the topic of this chapter, is both a continuation of Chapter 19 and the meeting point of the reactions covered in Chapters 7, 8, and 19. As a continuation of Chapter 19, carbonyl condensation reactions follow the same reaction mechanism as do the $\alpha$ substitution reactions. As the meeting point of Chapters 7, 8, and 19, carbonyl condensation reactions bring together various aspects of the reactions that you studied in these three previous chapters. From Chapters 7 and 8, the condensation reaction uses the carbonyl carbon’s ability to act as an electrophile. From Chapter 19, the condensation reaction uses an enolate ion formed from another carbonyl molecule as a nucleophile.
Carbonyl condensation reactions of ketones and aldehydes are often called aldol condensation reactions. Because the carbonyl compound substrate and the aldol product exist in equilibrium, the aldol product usually reacts further to form an $\alpha,\beta$-unsaturated aldehyde or ketone.

![Chemical structure](image)

Carbonyl condensation reactions are among the most widely applied reactions in organic chemistry. They take place with all kinds of carbonyl compounds, including aldehydes, ketones, esters, amides, thioesters, and nitriles. Carbonyl condensation reactions are very versatile reactions that are used in both organic synthesis and biochemical systems.

### 20.1 The Carbonyl Condensation Mechanism

Most synthetically useful carbonyl, or aldol, condensation reactions are base-catalyzed. The mechanism of a carbonyl condensation is similar to the mechanism of the $\alpha$ substitution reaction. In the first step of a carbonyl condensation reaction, the carbonyl compound forms an enolate ion.

![Enolate ion](image)

In the next step, the nucleophilic enolate ion reacts with the electrophilic carbonyl carbon of another carbonyl compound in a nucleophilic addition reaction such as those you studied in Chapter 7.
The reaction of the enolate ion and the carbonyl compound forms an intermediate alkoxide ion. This alkoxide ion intermediate is then protonated to form the aldol product. Usually carbonyl condensation reactions involve the loss of a small molecule such as water or an alcohol to form the \( \alpha,\beta \)-unsaturated product.

\[
\begin{align*}
\text{Carbonyl compound} & \quad \text{Enolate ion intermediate} \quad \text{Aldol product} \\
\end{align*}
\]

The aldol condensation reaction is a reversible reaction that readily establishes an equilibrium between the reactants and the aldol product. For example, in aqueous base, ethanal (common name: acetaldehyde) forms an equilibrium that involves about 50% aldol product.

\[
\begin{align*}
\text{Acetaldehyde} & \quad \text{Aldol product} \\
\end{align*}
\]

Aldol condensations are sensitive to steric influences, and this factor controls the amount of aldol product present in the equilibrium of a condensation reaction. If you change the substrate from acetaldehyde to acetone, but maintain the same reaction conditions, the reaction equilibrium involves less than 5% of the aldol product. The aldol product that forms from acetone is more sterically crowded than the aldol product that forms from acetaldehyde. Because the acetone aldol product is harder to form, less forms.
Chemists are not often able to isolate the aldol product because it usually spontaneously dehydrates to the \( \alpha, \beta \)-unsaturated aldehyde or ketone product. The dehydration involves two steps. In the first step, the base removes an \( \alpha \) proton to form an enolate ion. Next, the enolate ion intermediate loses the hydroxide group giving the \( \alpha, \beta \)-unsaturated aldehyde or ketone product. The \(-\text{OH}\) group is normally a very poor leaving group, but in this reaction the enolate ion is a stronger base so the \(-\text{OH}\) group readily leaves.

Even in cases with an unfavorable aldol condensation equilibrium, dehydration usually produces a good yield of \( \alpha, \beta \)-unsaturated carbonyl product. Getting a good yield is accomplished by heating the reaction mixture to accelerate the dehydration. Because the \( \alpha, \beta \)-unsaturated carbonyl product is much more stable than the \( \beta \)-ketoalcohol, the heat drives the aldol equilibrium towards the product.

**Exercise 20.1**

The aldol condensation reaction also takes place with an acid catalyst. The enol nucleophile first reacts with the protonated carbonyl. The aldol product then loses water via an E2 elimination. Write a mechanism for this reaction.

**20.2 Carboxyl Condensation versus \( \alpha \) Substitution**
Aldol condensation reactions and $\alpha$ substitution reactions take place under similar conditions. Both reactions usually proceed best in a basic solution, and both involve an enolate ion intermediate. Although the overall reaction conditions for both processes are similar, the details are different.

An $\alpha$ substitution reaction is usually initiated by mixing only the substrate and a full equivalent of a strong base together. This step allows the enolate ion to rapidly and completely form before the electrophile is added to the reaction mixture. Furthermore, an $\alpha$ substitution reaction usually takes place at a low temperature. For example, the alkylation of a ketone works best with one equivalent of LDA in THF at $-78^\circ\text{C}$. Under these conditions, the enolate ion rapidly forms in nearly 100% yield. The reaction proceeds so fast that essentially no ketone is left to react in a condensation reaction with the enolate ion. Immediately after the addition of the LDA, the reaction is ready for the addition of the alkyl halide. The reaction of the enolate ion with the alkyl halide then completes the alkylation.

In contrast to an $\alpha$ substitution reaction, an aldol condensation reaction requires only a catalytic quantity of base. The goal of a condensation reaction is to generate a small amount of enolate ion from the carbonyl compound to maximize the amount of aldol condensation. The concentration of the enolate ion is low compared to the carbonyl compound concentration, but the condensation reaction regenerates the base. The base then forms another molecule of enolate ion that, in turn, brings about another condensation reaction. In practice, approximately 0.05 moles of base is added for each mole of substrate. Finally, aldol condensation reactions are run at higher temperatures than $\alpha$ substitution reactions because higher temperatures speed up the dehydration portion of the reaction.
Exercise 20.2

Two enolate ions form from 2-methylcyclohexanone. Draw them. Which would you expect to form more readily with sodium methoxide in methanol?

[Sidebar]

Borodin and Aldehydes

Aleksander Borodin is best known today as a composer of beautiful Russian music. During his lifetime, however, he was best known as a professor in the Academy of Medicine and Surgery in St. Petersburg. Music was his first love, but chemistry was his profession.

Borodin was born in 1833 in St. Petersburg. At the age of 17, he was admitted to the Academy of Medicine and Surgery where he specialized in medicine. In 1858, he was granted a doctorate in chemistry for his dissertation on the analogy of arsenic acid (H₃AsO₄) with phosphoric acid (H₃PO₄). He was immediately hired as an adjunct professor of chemistry at the Academy and became a full professor in 1864. His work included teaching, research, and administration. In 1872, he helped found a medical course for women.

Borodin's music was never more than a relaxation from his work as a professor of chemistry. He wrote most of his best known compositions in the early years of his work at the Academy. They include two symphonies, two string quartets, several songs, and the early draft of his opera *Prince Igor*. 
Much of Borodin's professional career was spent doing chemical research. Although he was the first to synthesize fluorobenzene, most of his investigations were devoted to the reactions of aldehydes. He showed that aldehydes can be converted to carboxylic acids by reaction with oxygen or to alcohols by reaction with hydrogen in base.

\[
\text{\begin{align*}
\text{O} & \rightarrow \text{O}_2 \\
\text{H} & \rightarrow \text{H}_2 \\
\text{NaOH} & \rightarrow \text{OH}
\end{align*}}
\]

Probably his most important discovery was the aldol condensation reaction of an aldehyde with metallic sodium. Borodin found that pentanal forms a molecule he knew only as $\text{C}_{10}\text{H}_{18}\text{O}$. We now know this molecule was 2-propyl-2-heptenal.

\[
\text{\begin{align*}
\text{O} & \rightarrow \text{Na} \\
\text{H} & \rightarrow \text{2-Propyl-2-heptenal}
\end{align*}}
\]

He also studied the reaction of ethanal with sodium. The aldol condensation product of that reaction is 3-hydroxybutanal, which rapidly dehydrates to form 2-butenal.

\[
\text{\begin{align*}
\text{O} & \rightarrow \text{Na} \\
\text{CH}_3\text{CHCH}_2\text{CH} & \rightarrow \text{CH}_3\text{CH}==\text{CHCH}
\end{align*}}
\]

Borodin considered himself first and foremost a chemist and a professor of chemistry, but he described himself as “always a poet in my soul.” The beautiful music he wrote made him the prototype of the chemist-artist. Although he was neither the first nor the last to make his mark in both science and the arts, he is one of the best known.

20.3 Mixed Aldol Condensations
The aldol condensations discussed in Sections 20.1 and 20.2 are **symmetrical aldol condensations**. Their products are called symmetrical products. The reaction discussed in this section is a **mixed aldol condensation**. The product of a mixed aldol condensation is called a mixed product. In most mixed aldol condensations, the reaction of two different carbonyl compounds produces a mixture of four different products. Both carbonyl compounds form an enolate ion, and each of these enolate ions can react with either carbonyl compound. For example, the mixed aldol condensation reaction of acetaldehyde and propanal gives the following four products.

A mixed aldol condensation that involves two carbonyl compounds of similar reactivity is not very useful because of the number of products it produces. However, if one of the carbonyl compounds has no α hydrogens or if one compound forms an enolate ion much more readily than the other, the reaction can be useful. Formaldehyde and benzaldehyde are common examples of carbonyl compounds with no α hydrogens. Neither can form an enolate ion, so neither can initiate a condensation reaction, but both react with an enolate ion in a condensation reaction. Forming an enolate ion with one compound in the presence of another carbonyl compound with no α hydrogens allows the reaction to form only one mixed condensation product.
β-Dicarbonyl compounds, such as acetoacetic ester and malonic ester, are much more acidic than other carbonyl compounds. Thus, they form enolate ions more readily than other carbonyl compounds. In a reaction that involves either acetoacetic ester or malonic ester and another carbonyl compound in the presence of base, the preferred enolate ion forms from the acetoacetic ester or malonic ester. The ester enolate ion then reacts exclusively with the other carbonyl compound in a mixed condensation reaction rather than with the ester in a symmetrical condensation. Because the ethoxide ion is a stronger base than the ester enolate ion, it forms an enolate ion from the ester more quickly than the enolate ion can react with the other unreacted carbonyl compound. Emil Knoevenagle discovered this reaction near the end of the nineteenth century at the University of Heidelberg in Germany. In his honor, the reaction is called the **Knoevenagle reaction**.

*A Knoevenagle reaction is the reaction of a β-dicarbonyl compound with a ketone or aldehyde in the presence of strong base.*
The best method to use to ensure that you get the desired product from a mixed aldol condensation is to form the enolate ion from one of the carbonyl compounds before you add the other carbonyl compound. An efficient technique for doing this is to first form a silyl enol ether, a synthon of an enolate ion, then add the carbonyl compound. This approach allows you to specifically form the desired enolate ion, which then reacts with the other carbonyl compound. In this reaction the titanium is a Lewis acid that forms a complex with the carbonyl oxygen. This complex makes the carbonyl carbon more electrophilic and therefore more reactive.

**Exercise 20.3**

Propose a synthesis for cinnamaldehyde, a widely used flavoring agent in cinnamon confections.
20.4 Intramolecular Aldol Condensations

All the aldol condensation reactions that you have studied to this point have been intermolecular reactions. An intermolecular reaction takes place between two separate carbonyl-containing molecules. This section discusses intramolecular aldol condensation reactions. In an intramolecular aldol condensation, the reaction occurs between two carbonyl groups on the same molecule. The product of an intramolecular aldol condensation is a cyclic molecule. For example, the reaction of 2,6-heptanedione with base produces 3-methyl-2-cyclohexenone.

In principle, the above reaction has two possible products. They are 3-methyl-2-cyclohexenone and methyl (2-methyl-1-cyclobutenyl) ketone.
However, because a four-membered ring has so much ring strain, very little methyl (2-hydroxy-2-methylcyclobutyl) ketone forms. Six-membered rings have very little ring strain, so 2,6-heptanedione readily forms and is the preferred product. It is the thermodynamic, or more stable, product. The regiospecificity of the product is the result of enolate ion involvement in the reaction and the aldol product reversibility. That is, as the methyl (2-hydroxy-2-methylcyclobutyl) ketone reverts back to the enolate ion, it allows more and more of the enolate ion to form 3-methyl-2-cyclohexenone.

### Thermodynamic Versus Kinetic Control of a Reaction

The intramolecular aldol condensation of 2,6-heptanedione illustrates an important principle concerning the aldol condensation reaction: the outcome of the reaction can be determined by the stability of the product, not by the pathway of the reaction. When the stability of the product determines the outcome of the reaction, chemists say the reaction is thermodynamically controlled. Kinetic control of the reaction occurs when the lowest energy pathway determines the outcome of the reaction. Of the two enolate ions produced from the aldol condensation of 2,6-heptanedione, the one leading to the less stable product is, itself, the more stable enolate ion. This enolate ion is more stable because its double bond is more highly substituted. In general, thermodynamic control of a reaction requires that the reaction be reversible. With kinetic control of a reaction, the reaction is irreversible.
An intramolecular aldol condensation always produces either a five- or a six-membered ring because they are the most stable ring sizes. For example, the reaction of 2,7-octanedione produces a five-membered ring, not a seven-membered ring. In this case, the most stable product forms from the most stable enolate ion intermediate.

**Synthesis of 1,5-Diphenyl-1,4-pentadien-3-one**
Dissolve 0.425 g (4 mmol) of benzaldehyde in 3.2 mL of ethanol in a 25 mL round-bottom flask. Add 4 mL of 3M aqueous sodium hydroxide solution and 0.116 g (2 mmol) of acetone. Put a magnetic stirring bar into the flask. Immediately, cap the flask and shake it vigorously. Stir the initially clear solution for 30 minutes. During this time, pale yellow crystals will separate from the solution. Filter the crystals and wash them with three 4 mL portions of cold water. The crude product may be recrystallized from 70:30 ethanol—water. The yield of product is 0.42 g, m.p. 110-112°C.

Discussion Questions

1. Why is it necessary to cap the reaction vessel as soon as the reagents are added?
2. Besides the peaks for the benzene rings, the NMR spectrum of the product has a pair of doublets at 7.1 and 7.7 ppm. The coupling constant for these peaks is 17 Hz. These are typical peak positions for protons on conjugated double bonds. What geometric isomers are formed in the reaction?

Exercise 20.4

Draw the structure of the products resulting from the reaction of each of the following two cyclodecanediones with base.

20.5 The Claisen Condensation

In a Claisen condensation reaction two esters react in an aldol-like reaction to form a β-ketoester. The Claisen condensation reaction, named for Ludwig Claisen, is widely used as a synthetic tool. Claisen studied the reaction of two esters in the 1870s while he was a professor at the University of Kiel in Germany.
The α hydrogens of an ester are less acidic than the α hydrogens of an aldehyde or ketone because the partial positive charge of an ester carbonyl carbon can be satisfied by the following resonance.

The $pK_a$ for an ester is usually in the range of 23-25, whereas the $pK_a$ for an aldehyde or ketone is 19-20. As a result an ester takes a somewhat stronger base to deprotonate than does a ketone or an aldehyde. Once the ester enolate ion forms, however, it is a stronger nucleophile than a ketone or aldehyde enolate ion.

The ester enolate ion reacts with a molecule of ester in a nucleophilic substitution reaction that, with loss of an alkoxide ion, produces a β-ketoester. This reaction step is a carbonyl substitution reaction like those covered in Chapter 8.

The mechanism for the Claisen condensation is similar to the aldol condensation mechanism. In fact, the only difference between the two is the formation of the tetrahedral intermediate in the Claisen condensation. This intermediate expels an alkoxide ion to generate the β-ketoester.

**Exercise 20.5**

As a rule, the base used for a Claisen condensation is made from the same alcohol as the one used in the synthesis of the ester itself. Thus,
when running a Claisen condensation with an ethyl ester, the ethoxide ion is used as the base. Explain why this is done.

Yields from a Claisen condensation are usually quite good even though all the steps to the β-ketoester product are reversible and all the equilibrium positions favor the reactants, not the products. A Claisen condensation gives good yields because the β-ketoester product is much more acidic than the starting esters. Thus, as soon as the product forms, the base removes a proton from the carbon between the two carbonyl groups forming an enolate ion. This reaction is not reversible. Adding dilute acid to the reaction mixture protonates this enolate ion and restores the β-ketoester.

The deprotonation step is strongly exothermic and is the driving force for the reaction. The Claisen condensation gives good yields of product only when the starting ester has two or more hydrogens on the α carbon.

If the β-ketoester has no hydrogens on the α carbon, then the yield is generally quite low.
Solved Exercise 20.1

Draw the ester that would be used to synthesize the following product:

![Chemical Structure]

Solution

In a Claisen condensation, a new carbon—carbon bond is formed between the \( \alpha \) carbon of one ester molecule and the carbonyl carbon of another ester molecule.

![New bond formed]

Mixed Claisen condensation reactions involving two different esters are similar to mixed aldol condensations. A mixed Claisen condensation works well only if one of the esters has no \( \alpha \) hydrogens. Having no \( \alpha \) hydrogens means that the ester cannot form an enolate ion.
Ethyl formate can be used in a mixed Claisen-like condensation reaction because it contains no α hydrogens. The reaction product is unique because it is an aldehyde. Particularly good product yields are obtained when the other reactant is a ketone.

**Exercise 20.6**

What product would you get from diethyl oxalate \((CO_2Et)_2\) in a mixed Claisen reaction with ethyl acetate?

**Exercise 20.7**

Predict the products from the reaction of the following compounds with ethoxide ion in ethanol.

a) Ethyl cyclohexylacetate  
b) Ethyl pentanoate  
c) Ethyl 2,2-dimethylpropanoate and ethyl acetate  
d) Ethyl 3-methylbutanoate

**Sample solution**

b) 

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COEt} \quad \overset{\text{1) EtO}^- , \text{EtOH}}{\longrightarrow} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CCHCOEt} \quad \overset{\text{2) H}_2\text{O}^-}{\longrightarrow} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COEt}
\]

Ethyl pentanoate
[Sidebar]

Biochemical Carbonyl Condensation Reactions

The Claisen condensation is an important reaction in various biochemical systems. One of these systems is acetyl coenzyme (often abbreviated as acetyl CoA). Acetyl coenzyme A is a thioester of acetic acid and coenzyme A.

Instead of writing out the whole structure of coenzyme A, chemists often abbreviate it as HSCoA. They then write acetyl CoA as follows:

![Coenzyme A]

The sulfur in acetyl CoA makes both $\alpha$ substitution and nucleophilic substitution at the carbonyl group easier than with an ester because sulfur does not donate as much electron density to the carbonyl carbon as does oxygen. Thus, the $\alpha$ protons of a thioester are more acidic than the $\alpha$ protons of an ester. In addition, the sulfur anion is a better leaving group than an oxygen analog. The $\beta$-ketothiolase enzyme-catalyzed condensation reaction of acetyl CoA with itself illustrates these points:
Subsequent steps reduce the ketone to a —CH$_2$— group. Repeating this process several times produces the long chain carboxylic acids known as fatty acids found in biochemical systems.

This reaction is an example of nature using a familiar chemical process, in this case a Claisen condensation, to selectively achieve a goal. The second, and subsequent, steps in this sequence are mixed Claisen condensations. The mixed Claisen condensation steps are achieved with a selectivity that chemists normally can only dream of achieving. For example, the reaction of acetyl CoA and butanoyl CoA
could produce two different products. However, Nature produces only the product as shown on the right below.

\[
\begin{align*}
\text{CH}_3\text{COSCoA} + \text{CH}_2\text{CH}_2\text{COSCoA} & \quad \text{or} \quad \text{CH}_3\text{CH}_2\text{COSCoA} + \text{CH}_2\text{CHCH}_3\text{OSCoA} \\
\text{None produced}
\end{align*}
\]

### 20.6 The Dieckmann Cyclization

The Dieckmann cyclization was named after Walter Dieckmann, who discovered it in Germany early in the twentieth century. The Dieckmann cyclization, an intramolecular Claisen condensation, forms a \(\beta\)-ketoester with the ketone on the ring and the ester group attached as a side chain to the ring. Similar to the intramolecular aldol condensation, the Dieckmann cyclization works best when it forms a five- or six-membered ring. A 1,6-diester gives a five-membered ring; a 1,7-diester gives a six-membered ring.

The mechanism of the Dieckmann cyclization reaction is analogous to the Claisen condensation mechanism. One of the two ester groups converts to an enolate ion. The enolate ion then attacks the second ester group at the other end of the molecule to form a cyclic tetrahedral intermediate. The cyclic tetrahedral intermediate loses an alkoxide ion to form the \(\beta\)-ketoester with the attached ester side chain. These three steps are reversible, as are the analogous steps in the Claisen condensation. Once a base removes the acidic proton from the carbon between the two carbonyl groups, however, the product is
removed from the equilibrium. This step is also analogous to the final step in the Claisen condensation. To recover the product, simply add dilute acid.

![Chemical structure](image)

**Exercise 20.8**

A Dieckmann cyclization reaction involving diethyl 3-methylheptanedioate produces two β-ketoester products. These two products form in approximately equal amounts. Draw their structures. A Dieckmann cyclization reaction involving diethyl 2-methylheptanedioate produces only one major product. What is its structure? Why does it not also form the other possible product?

![Chemical structure](image)

**20.7 The Michael Addition Reaction**

Chapter 16 presents a variety of nucleophiles that react with conjugated carbonyl groups to give 1,4-, or conjugated, addition products. When the nucleophile is an enolate ion, the reaction is called the **Michael addition reaction**. The reaction is named for Arthur Michael who first published a description of the reaction in 1887 while he was a professor at Tufts University.
The best enolate nucleophiles, often called **Michael donors**, are those nucleophiles derived from β-dicarbonyl compounds. Other good nucleophiles are ones that contain an electron-withdrawing group, such as a nitrile or a nitro group instead of the carbonyl group of a β-dicarbonyl compound. Table 20.1 lists some common Michael donors. The electrophiles, often called **Michael acceptors**, contain conjugated carbonyl, nitro, or nitrile groups.

<table>
<thead>
<tr>
<th>Michael Donor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enamine</td>
<td><img src="image" alt="Enamine" /></td>
</tr>
<tr>
<td>β-Dicarbonyl</td>
<td>EtOCCH₂COEt</td>
</tr>
<tr>
<td>Nitro alkane</td>
<td>CH₃NO₂</td>
</tr>
<tr>
<td>β-Cyanocarbonyl</td>
<td>N≡CCH₂COEt</td>
</tr>
<tr>
<td>Dialkylcuprates</td>
<td>(CH₃)₂CuLi</td>
</tr>
</tbody>
</table>

**Table 20.1.** Examples of some typical Michael donors.
In the product of a Michael reaction, the two electron-withdrawing functional groups, either carbonyl, nitrile, or nitro groups, are separated by three carbons. For example, either carbonyl compound that you derive from the donor in the previous reaction has three carbons between it and the carbonyl derived from the acceptor molecule.

The enamine group also makes an excellent Michael donor.

**Solved Exercise 20.2**

Show how a Michael addition reaction synthesizes the following product.

**Solution**
There are three carbons between the two carbonyl groups. The best synthesis is via an enamine.

Exercise 20.9

Complete each of the following reactions.

a)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NH} & \quad \text{H}^+ \\
\text{1)} & \quad \text{H}_2\text{O}^+ \\
\text{2)} & \quad \text{H}_2\text{O}^+ \\
\end{align*}
\]

b)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_3\text{CCH}_2\text{OEt} & \quad \text{CH}_2=\text{CHCCH}_3 \\
\text{1)} & \quad \text{EtO}^- , \text{EtOH} \\
\text{2)} & \quad \text{H}_2\text{O} \\
\end{align*}
\]

c)

\[
? \quad \text{O} \quad \text{O} \quad \text{CH}_2\text{CH}_3 \\
\quad \text{O} \quad \text{O} \quad \text{OCH}_2\text{CH}_3 \\
\quad \text{O} \quad \text{O} \quad \text{OCH}_2\text{CH}_3
\]

d)

\[
? \quad \text{O} \quad \text{CN} \quad \text{NO}_2 \\
\text{O} \quad \text{O} \quad \text{OEt}
\]

e)

\[
\text{O} \quad \text{O} \\
\text{1)} & \quad \text{(CH}_3)_2\text{CuLi}
\]

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**20.8 The Robinson Annulation Reaction**

A Michael addition that takes place in either strongly acidic or strongly basic conditions does not stop with the 1,5-dicarbonyl Michael product. It continues on in an intramolecular aldol condensation to form a cyclic product between the two carbonyl groups. This reaction sequence, called the **Robinson annulation** reaction, is named for British chemist Robert Robinson who won the Nobel Prize in 1947.

As with other ring forming reactions, the product of a Robinson annulation depends on the amount of ring strain in that product. The previous Michael reaction has three possible enolate ions, but the ring strain of the products formed from enolate ion A and enolate ion B is so great that very little of either forms. Following are the three possible
enolate ions and the products that each would produce. As you examine the relative stabilities of these three possible enolate ions, note that enolate ion C, the enolate ion that produces the major product, is actually the least stable intermediate.

![Diagram of enolate ions and products]

Exercise 20.10

One other product could result from the enolate ion A above. However, its elimination product violates Bredt’s rule. Draw its structure. (Hint: see Section 3.13, page 000.)

As the reaction proceeds, all three enolate ions are in equilibrium. However, neither enolate ion A nor enolate ion B, the two most stable enolate ions of the three, produces a stable product. Although enolate ion A forms a six-membered ring product, the ring is more sterically strained than the six-membered ring product formed from enolate ion C. This strain is the result of the bridge in the bicyclic
compound. The product from enolate ion B is a four-membered ring and is not stable due to its small size. Whether a reaction stops at the Michael product or continues on to form the Robinson annulation product depends on the structure of the Michael product and whether or not the Robinson annulation product is stable enough to form. Thus, the outcome is determined by the stability of the product, so the reaction is thermodynamically controlled.

The differences in stabilities of the three enolate ions (A, B, and C) discussed previously are very small. All three protons that are removed to form the enolate ions have similar pKₐs. However, if you ran the same reaction using 1,3-cyclohexanediione instead of 2-methyl-1,3-cyclohexanediione, you would observe a much greater difference in the stability of one of the enolate ions that it forms.

Structurally, the only difference between 2-methyl-1,3-cyclohexanediione and 1,3-cyclohexanediione occurs at the carbon between the two carbonyl groups. 2-Methyl-1,3-cyclohexanediione has a methyl group where 1,3-cyclohexanediione has a hydrogen. The lack of a methyl group in 1,3-cyclohexanediione allows the formation of a fourth possible enolate ion. This fourth enolate ion is much more stable than the other three enolate ions, so it predominates.

![Diagram of Michael product and Robinson annulation product formation]

The only possible ring that could form from this enolate ion in a Robinson annulation reaction is a four-membered ring. Because the reaction is an equilibrium reaction with the outcome controlled by the stability of the product, forming a four-membered ring is very unlikely. Thus, no Robinson annulation reaction product forms.

The Robinson annulation has been used widely to synthesize steroid molecules. The synthesis of the hormone estrone is particularly
significant, because estrone is a metabolite of estrogen and can be used in the preparation of other steroids.

![Chemical structures](image)

**Synthesis of 4,4-Dimethyl-2-cyclohexen-1-one**

To a 100 mL round bottom flask, add 30 mL of toluene, 3.2 g (0.045 mol) of 3-buten-2-one, and 4.2 g (0.058 mol) of 2-methylpropanal. Add 0.1 g of p-toluenesulfonic acid. Fit the flask with a Dean-Stark trap and a reflux condenser. Reflux for at least 2.5 hours. When the theoretical amount of water (0.8 mL) is collected, discontinue the reflux. Cool the reaction mixture and transfer it to a separatory funnel. Wash with 25 mL of saturated sodium bicarbonate solution. Separate the layers and dry the organic layer over anhydrous sodium sulfate for at least 0.5 hour. Distill the solvent and unreacted starting materials, then distill the product under reduced pressure. Yield of product is 4.3 g (77%), b.p. 75-78°C/15mm.

**Discussion Question**

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Reaction of 3-buten-2-one with propanal in an attempt to form 4-methyl-2-cyclohexenone does not give a good yield of the desired product. What alternate product is formed? Why does this alternate product form?

Exercise 20.11

Propose a detailed mechanism for the formation of the following product of a Robinson annulation reaction.

20.9 Carbonyl Condensations in Synthesis

Carbonyl condensation reactions are among the most widely used reactions in organic synthesis. For example, the perfumery industry around the world uses thousands of pounds of jasmone each year as a fragrance, and the synthesis of jasmone involves a carbonyl condensation.

Chemists first isolated jasmone from jasmine flowers in 1933. Since then, they have made a number of efforts to synthesize it. Using the retrosynthetic method of developing a synthesis, this section examines two of those syntheses.

Recall that in a retrosynthesis, you begin with the final product and work backward to the starting material. Your goal is to propose a synthetic plan that you could then use in the laboratory to actually prepare the product—in this case jasmone. The structure of jasmone suggests that there are two possible main routes to synthesize it. The first route begins with a pre-formed five-membered ring to which you add the appropriate functional groups, and the second route forms the
five-membered ring by the cyclization of a properly substituted 1,4-
dicarbonyl substrate. Although both approaches appear in the chemical
literature, the first approach uses chemistry not yet familiar to you, so
this section considers only the second approach.

Exercise 20.12

Before proceeding to the published syntheses, you will benefit from
proposing a synthesis yourself. Do it now, then compare your ideas
with those presented here. Concentrate on a synthesis of the
appropriate 1,4-dicarbonyl that could be cyclized using an
intramolecular aldol condensation.

The first step in the retrosynthesis is an intramolecular aldol
cyclization of a substituted 1,4-dicarbonyl compound. In the laboratory
synthesis, this step is the final, key step in the reaction. The reported
yield of the intramolecular aldol cyclization is nearly 90%.

The 1,4-dicarbonyl compound used in the intramolecular aldol
cyclization is Z-8-undecene-2,5-dione and can be synthesized in two
ways. The first synthesis involves making an unsaturated dione by an
acid-catalyzed ring opening reaction of a substituted furan—a reaction
that you have not yet studied. Furan, an aromatic heterocyclic
compound with a very small resonance energy, is the equivalent of a
di-enol ether. When furan is hydrolyzed, it forms a 1,4-dicarbonyl
compound.

The previous illustration shows the hydrolysis of furan to form 1,4-
butanediol. To make jasmone, however, you must have the methyl and
Z-3-hexenyl side chains on C2 and C5, before you hydrolyze.
The next step in the retrosynthesis is the synthesis of the unsaturated side chain on the furan ring. This step involves two reactions, a Wittig reaction and a Michael addition. The Wittig reaction changes an aldehyde side chain to the unsaturated side chain. Conveniently, the Wittig reaction gives a 65% product yield—85% of which is the desired \( Z \) isomer and 15% the \( E \) isomer.

The other reaction places the aldehyde side chain on the furan via a Michael addition of 2-methylfuran with propenal. 2-Methylfuran is readily available commercially, so you don't need to synthesize it. Because you go back no further than 2-methylfuran in your retrosynthesis, 2-methylfuran is your beginning substrate for the laboratory synthesis.

This Michael addition reaction uses 2-methylfuran as the nucleophile according to the following mechanism.
The overall yield of this synthetic pathway is 35%. Note that although most of the reactions give yields much higher than this, every step in the reaction does cause an overall reduction in the yield. Because this is a multistep synthesis, a 35% overall yield is reasonable. Following is the complete synthesis.
The second synthesis of Z-8-undecene-2,5-dione is very different from the first and has two significant advantages. The synthesis gives an overall yield of 61%, and the formation of the double bond is stereospecific for the desired cis double bond.

The synthetic uses for 1,3-dithiane is introduced in Section 19.9, page 000.

To prepare the 1,3-dithianyl derivative, you react an acetal with a dithiol in acid to form a thioacetal. The acetal is available commercially. Thus, this is the last step in the retrosynthesis and the first step in the laboratory synthesis.

Exercise 20.13

In the second synthesis discussed above, the alkylation reaction with 1,3-dithiane to form Z-8-undecene-2,5-dione requires the reagent Z-1-bromo-3-hexene. Propose a synthesis for this reagent.

Key Ideas from Chapter 20

In a carbonyl condensation reaction, an enolate ion nucleophile reacts with the electrophilic carbon of a carbonyl group. The product, with an aldehyde or ketone substrate, is an α,β-unsaturated carbonyl compound. As a group, these reactions are called aldol condensations.
The mechanism for an aldol condensation reaction combines the mechanisms of the nucleophilic addition to a carbonyl from Chapter 7 and the enolate ion reactions in Chapter 19. The nucleophile in these reactions is the enolate ion.

Although aldol condensations can be either acid- or base-catalyzed, most often they are base-catalyzed.

The reaction conditions for $\alpha$ substitution reactions are similar to the reaction conditions for aldol condensations, but aldol condensations require smaller amounts of base and usually require higher temperatures.

A mixed aldol condensation reaction occurs when two different carbonyl compounds are present in the reaction mixture. For this reaction to be useful, however, one of the reactants must have no enolizable hydrogens or one of the reactants must be much more acidic than the other.

In an intramolecular aldol condensation reaction, two carbonyl groups that are present in the same molecule react to form a five- or six-membered ring.

The Claisen condensation is an aldol-like condensation reaction that uses an ester substrate, instead of an aldehyde or ketone to form a $\beta$-dicarbonyl compound.

The mechanism of the Claisen condensation is a combination of the mechanism for a nucleophilic substitution on a carbonyl presented in Chapter 8 and the mechanism of the enolate ion reactions presented in Chapter 19. The nucleophile in these reactions is the enolate ion.

The Claisen condensation has an unfavorable equilibrium constant. However, if the product has a hydrogen located on the carbon between both carbonyl groups, the product reacts with the base. This reaction prevents the product from undergoing the reverse reaction.

The Dieckmann cyclization is an intramolecular Claisen condensation that gives excellent yields when the product forms a five- or six-membered ring.
The Michael reaction is a conjugate addition of a nucleophile to an α,β-unsaturated carbonyl compound. The best nucleophiles for a Michael reaction are stabilized enolate ions.

The Robinson Annulation reaction is a two step reaction. Step 1 is a Michael reaction, and step 2 is an aldol condensation.

Carbonyl condensations are among the most useful synthetic procedures in organic synthesis because they form new carbon—carbon bonds and leave reactive functional groups in the region of the new bond.