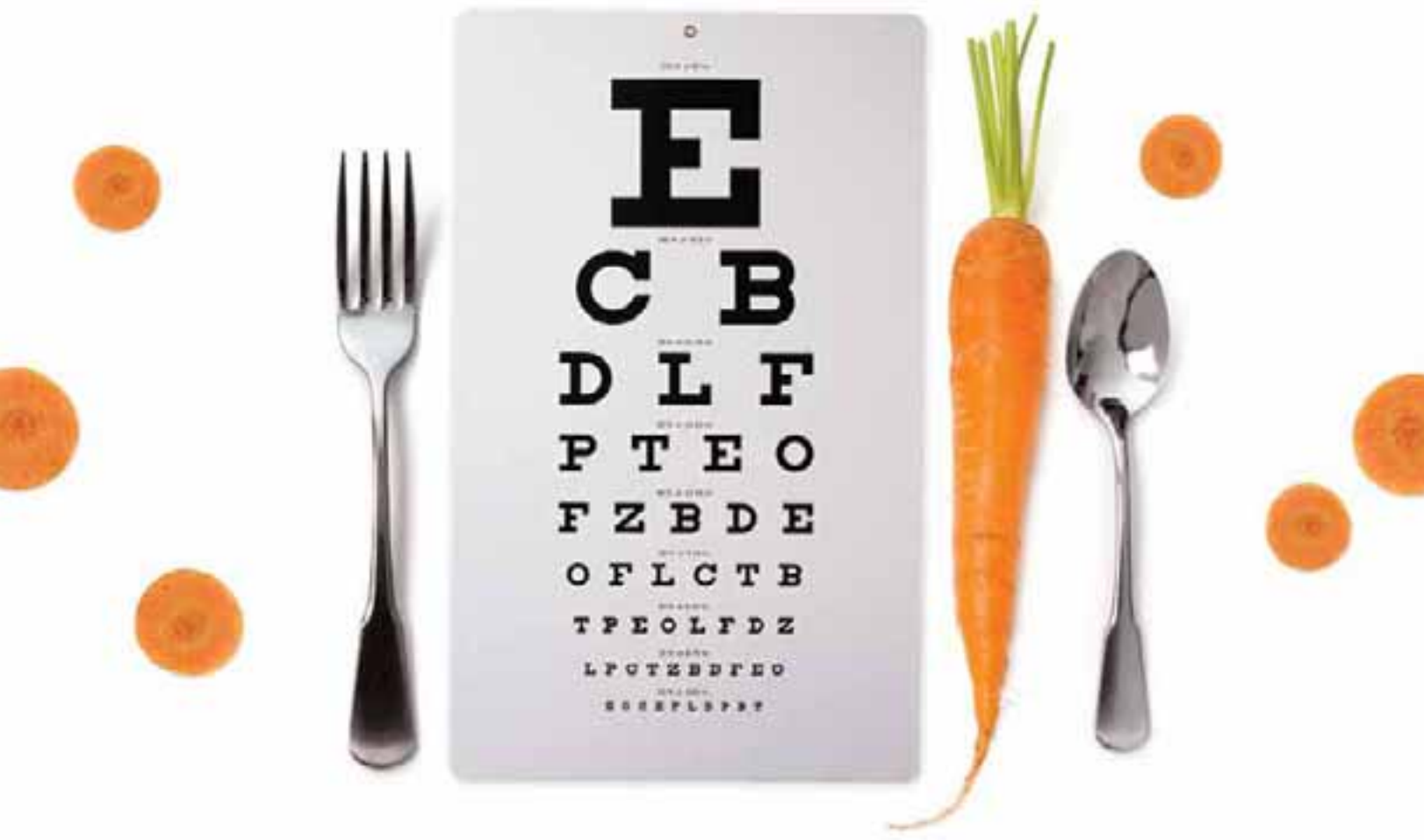
Aldehydes and Ketones

20

DID YOU EVER WONDER...

***why* beta-carotene, which makes carrots orange, is reportedly good for your eyes?**

This chapter will explore the reactivity of aldehydes and ketones. Specifically, we will see that a wide variety of nucleophiles will react with aldehydes and ketones. Many of these reactions are common in biological pathways, including the role that beta-carotene plays in promoting healthy vision. As we will see several times in this chapter, the reactions of aldehydes and ketones are also cleverly exploited in the design of drugs. The reactions and principles outlined in this chapter are central to the study of organic chemistry and will be used as guiding principles throughout the remaining chapters of this textbook.



DO YOU REMEMBER?

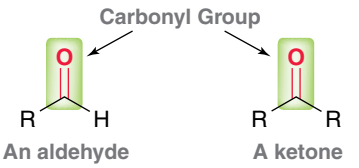
Before you go on, be sure you understand the following topics. If necessary, review the suggested sections to prepare for this chapter:

- Grignard reagents (Section 13.6)
- Oxidation of alcohols (Section 13.10)
- Retrosynthetic analysis (Section 12.3)

Visit www.wileyplus.com to check your understanding and for valuable practice.

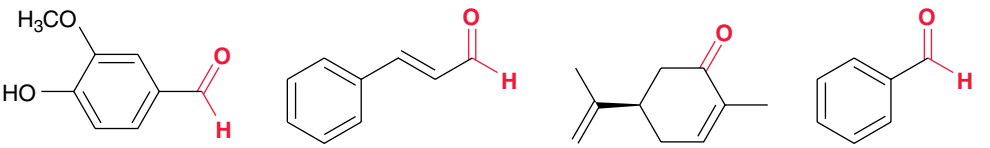
20.1 Introduction to Aldehydes and Ketones

Aldehydes (RCHO) and ketones (R_2CO) are similar in structure in that both classes of compounds possess a C═O bond, called a **carbonyl group:**



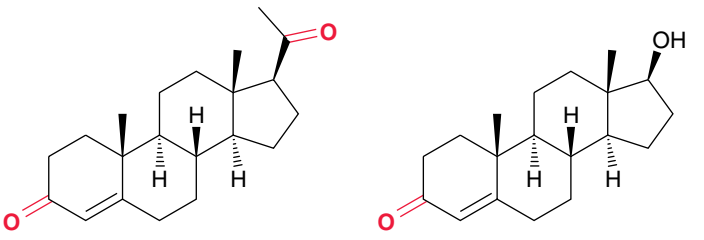
The carbonyl group of an aldehyde is flanked by one carbon atom and one hydrogen atom, while the carbonyl group of a ketone is flanked by two carbon atoms.

Aldehydes and ketones are responsible for many flavors and odors that you will readily recognize:



Vanillin (Vanilla flavor) | **Cinnamaldehyde** (Cinnamon flavor) | **(*R*)-Carvone** (Spearmint flavor) | **Benzaldehyde** (Almond flavor)

Many important biological compounds also exhibit the carbonyl moiety, including progesterone and testosterone, the female and male sex hormones.



Progesterone | **Testosterone**

Simple aldehydes and ketones are industrially important; for example:

Formaldehyde | **Acetone**

Acetone is used as a solvent and is commonly found in nail polish remover, while formaldehyde is used as a preservative in some vaccine formulations. Aldehydes and ketones are also used as building blocks in the syntheses of commercially important compounds, including pharmaceuticals and polymers. Compounds containing a carbonyl group react with a large variety of nucleophiles, affording a wide range of possible products. Due to the versatile reactivity of the carbonyl group, aldehydes and ketones occupy a central role in organic chemistry.

20.2 Nomenclature

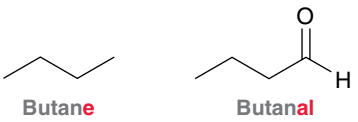
Nomenclature of Aldehydes

Recall that four discrete steps are required to name most classes of organic compounds (as we saw with alkanes, alkenes, alkynes, and alcohols):

1. Identify and name the parent.
2. Identify and name the substituents.
3. Assign a locant to each substituent.
4. Assemble the substituents alphabetically.

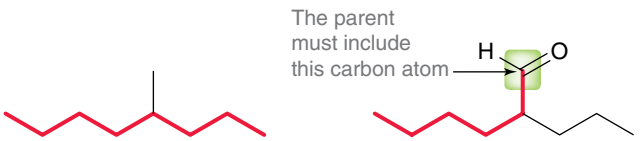
Aldehydes are also named using the same four-step procedure. When applying this procedure for naming aldehydes, the following guidelines should be followed:

When naming the parent, the suffix "-al" indicates the presence of an aldehyde group:



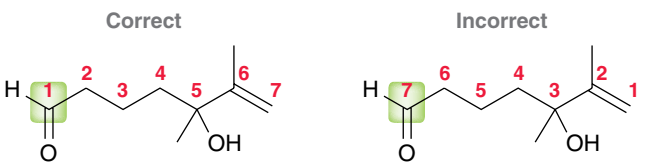
Butane Butanal

When choosing the parent of an aldehyde, identify the longest chain *that includes the carbon atom of the aldehydic group*:



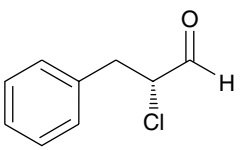
Parent = Octane Parent = Hexanal

When numbering the parent chain of an aldehyde, the aldehydic carbon is assigned number 1, despite the presence of alkyl substituents, π bonds, or hydroxyl groups:



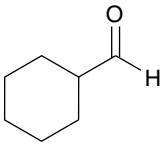
It is not necessary to include the locant in the name, because it is understood that the aldehydic carbon is the number 1 position.

As with all compounds, when a chirality center is present, the configuration is indicated at the beginning of the name; for example:



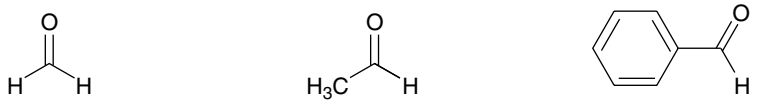
(*R*)-2-chloro-3-phenylpropanal

A cyclic compound containing an aldehyde group immediately adjacent to the ring is named as a carbaldehyde:



Cyclohexanecarbaldehyde

The International Union of Pure and Applied Chemistry (IUPAC) nomenclature also recognizes the common names of many simple aldehydes, including the three examples shown below:



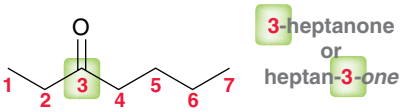
Formaldehyde Acetaldehyde Benzaldehyde

Nomenclature of Ketones

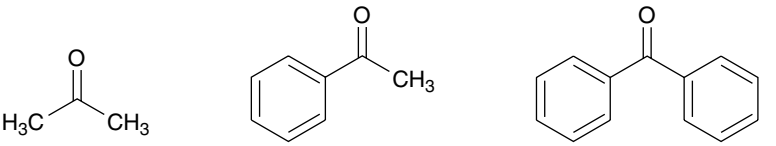
Ketones, like aldehydes, are named using the same four-step procedure. When naming the parent, the suffix "-one" indicates the presence of a ketone group:

Butane Butanone

The position of the ketone group is indicated using a locant. The IUPAC rules published in 1979 dictate that this locant be placed immediately before the parent, while the IUPAC recommendations released in 1993 and 2004 allow for the locant to be placed immediately before the suffix "-one":

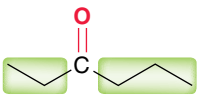


Both names above are acceptable IUPAC names. IUPAC nomenclature recognizes the common names of many simple ketones, including the three examples shown below:



Acetone Acetophenone Benzophenone

Although rarely used, IUPAC rules also allow simple ketones to be named as *alkyl alkyl ketones*. For example, 3-hexanone can also be called ethyl propyl ketone:



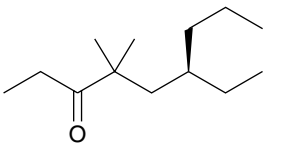
Ethyl propyl ketone

SKILLBUILDER

20.1 NAMING ALDEHYDES AND KETONES

LEARN the skill

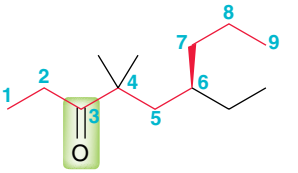
Provide a systematic (IUPAC) name for the following compound:



SOLUTION

STEP 1
Identify and name the parent.

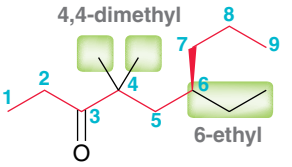
The first step is to identify and name the parent. Choose the longest chain that includes the carbonyl group, and then number the chain to give the carbonyl group the lowest number possible:



3-nonanone

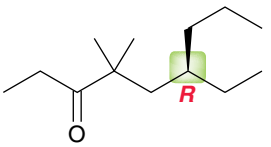
STEP 2
Identify and name the substituents.
STEP 3
Assign a locant to each substituent.

Next, identify the substituents and assign locants:



STEP 4
Assemble the substituents alphabetically.
STEP 5
Assign the configuration of any chirality centers.

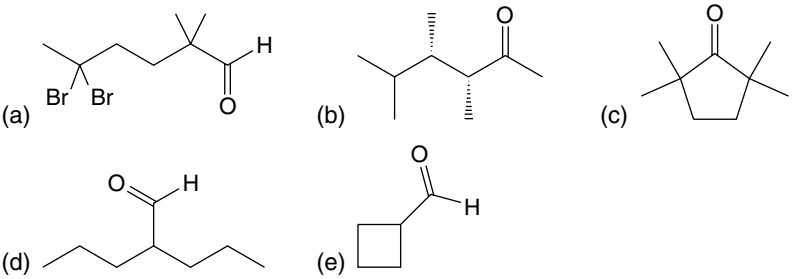
Finally, assemble the substituents alphabetically: 6-ethyl-4,4-dimethyl-3-nonanone. Before concluding, we must always check to see if there are any chirality centers. This compound does exhibit one chirality center. Using the skills from Section 5.3, the *R* configuration is assigned to this chirality center:



Therefore, the complete name is **(*R*)-6-ethyl-4,4-dimethyl-3-nonanone.**

PRACTICE the skill

20.1 Assign a systematic (IUPAC) name to each of the following compounds:



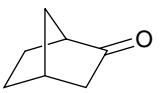
APPLY the skill

20.2 Draw the structure of each of the following compounds:

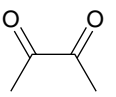
(a) (*S*)-3,3-dibromo-4-ethylcyclohexanone (b) 2,4-dimethyl-3-pentanone

(c) (*R*)-3-bromobutanal

20.3 Provide a systematic (IUPAC) name for the compound below. Be careful: This compound has two chirality centers (can you find them?).

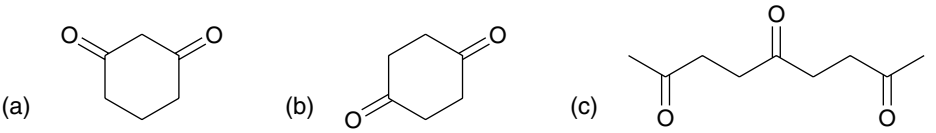


20.4 Compounds with two carbonyl moieties are named as alkane diones; for example:



2,3-butanedione

The compound above is an artificial flavor added to microwave popcorn and movie-theater popcorn to simulate the butter flavor. Interestingly, this very same compound is also known to contribute to body odor. Name the following compounds:



need more **PRACTICE?** **Try Problems 20.44–20.49**

20.3 Preparing Aldehydes and Ketones: A Review

In previous chapters, we have studied a variety of methods for preparing aldehydes and ketones, which are summarized in Tables 20.1 and 20.2, respectively.

TABLE 20.1 A SUMMARY OF ALDEHYDE PREPARATION METHODS COVERED IN PREVIOUS CHAPTERS

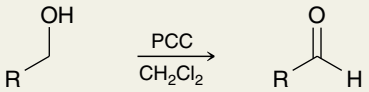
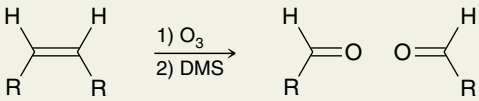
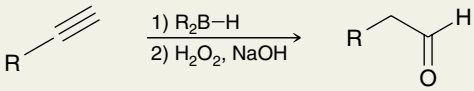
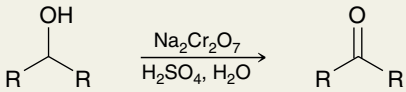
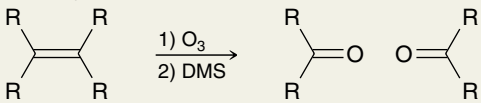
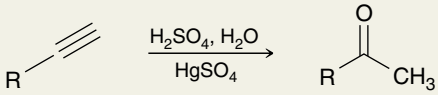
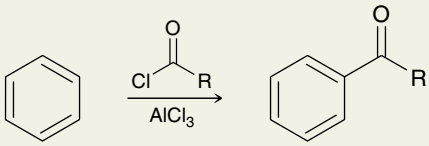
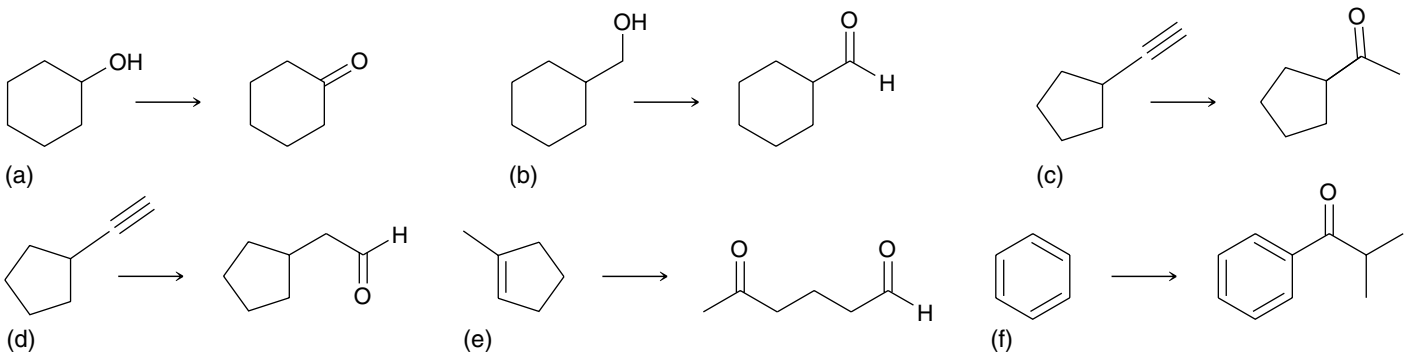
REACTION	SECTION
Oxidation of Primary Alcohols	13.10
	
When treated with a strong oxidizing agent, primary alcohols are oxidized to carboxylic acids. Formation of an aldehyde requires an oxidizing agent, such as PCC, that will not further oxidize the resulting aldehyde.	
Ozonolysis of Alkenes	9.19
	
Ozonolysis will cleave a C═C double bond. If either carbon atom bears a hydrogen atom, an aldehyde will be formed.	
Hydroboration-Oxidation of Terminal Alkynes	10.8
	
Hydroboration-oxidation results in an anti-Markovnikov addition of water across a π bond, followed by tautomerization of the resulting enol to form an aldehyde.	

TABLE 20.2 A SUMMARY OF KETONE PREPARATION METHODS COVERED IN PREVIOUS CHAPTERS

REACTION	SECTION
Oxidation of Secondary Alcohols	13.10
	
A variety of strong or mild oxidizing agents can be used to oxidize secondary alcohols. The resulting ketone does not undergo further oxidation.	
Ozonolysis of Alkenes	9.19
	
Tetrasubstituted alkenes are cleaved to form ketones.	
Acid-Catalyzed Hydration of Terminal Alkynes	10.8
	
This procedure results in a Markovnikov addition of water across the π bond, followed by tautomerization to form a methyl ketone.	
Friedel-Crafts Acylation	19.6
	
Aromatic rings that are not too strongly deactivated will react with an acid halide in the presence of a Lewis acid to produce an aryl ketone.	

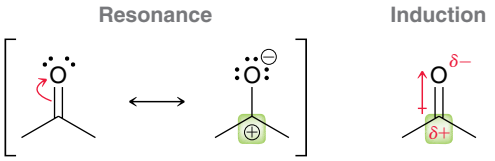
CONCEPTUAL CHECKPOINT

20.5 Identify the reagents necessary to achieve each of the following transformations:



20.4 Introduction to Nucleophilic Addition Reactions

The electrophilicity of a carbonyl group derives from resonance effects as well as inductive effects:



One of the resonance structures exhibits a positive charge on the carbon atom, indicating that the carbon atom is deficient in electron density (δ+). Inductive effects also render the carbon atom deficient in electron density. As a result, this carbon atom is particularly electrophilic and is susceptible to attack by a nucleophile. Molecular orbital calculations suggest that nucleophilic attack occurs at an angle of approximately 107° to the plane of the carbonyl group, and in the process, the hybridization state of the carbon atom changes (Figure 20.1).

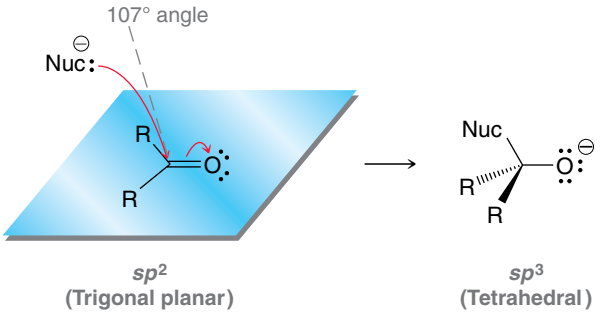


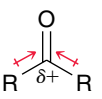
FIGURE 20.1
When a carbonyl group is attacked by a nucleophile, the carbon atom undergoes a change in hybridization and geometry.

The carbon atom is originally sp^2 hybridized with a trigonal planar geometry. After the attack, the carbon atom is sp^3 hybridized with a tetrahedral geometry. In recognition of this geometric change, the resulting alkoxide ion is often called a **tetrahedral intermediate.** This term appears many times throughout the remainder of this chapter.

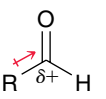
In general, aldehydes are more reactive than ketones toward nucleophilic attack. This observation can be explained in terms of both steric and electronic effects:

1. *Steric effects*. A ketone has two alkyl groups (one on either side of the carbonyl) that contribute to steric hindrance in the transition state of a nucleophilic attack. In contrast, an aldehyde has only one alkyl group, so the transition state is less crowded and lower in energy.

2. *Electronic effects*. Recall that alkyl groups are electron donating. A ketone has two electron-donating alkyl groups that can stabilize the δ+ on the carbon atom of the carbonyl group. In contrast, aldehydes have only one electron-donating group:



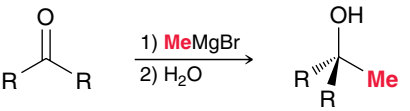
A ketone
has **two** electron-donating alkyl groups
that stabilize the partial positive charge



An aldehyde
has **only one** electron-donating alkyl group
that stabilizes the partial positive charge

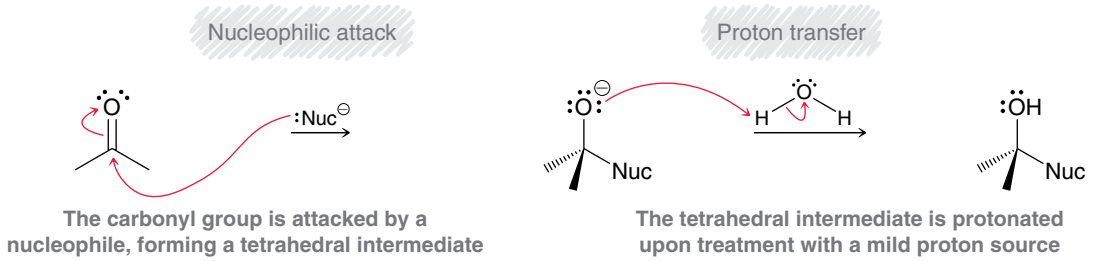
The δ+ charge of an aldehyde is less stabilized than a ketone. As a result, aldehydes are more electrophilic than ketones and therefore more reactive.

Aldehydes and ketones react with a wide variety of nucleophiles. As we will see in the coming sections of this chapter, some nucleophiles require basic conditions, while others require acidic conditions. For example, recall from Chapter 13 that Grignard reagents are very strong nucleophiles that will attack aldehydes and ketones to produce alcohols:



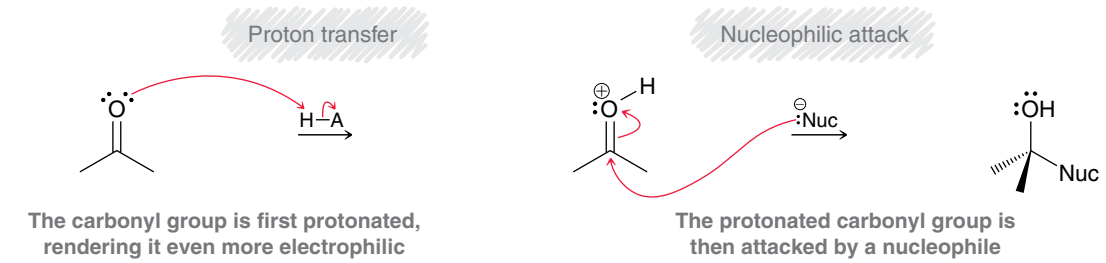
The Grignard reagent itself provides for strongly basic conditions, because Grignard reagents are both strong nucleophiles and strong bases. This reaction cannot be achieved under acidic conditions, because, as explained in Section 13.6, Grignard reagents are destroyed in the presence of an acid. The Grignard reaction above follows a general mechanism for the reaction between a nucleophile and a carbonyl group under basic conditions (Mechanism 20.1). This general mechanism has two steps: (1) nucleophilic attack followed by (2) proton transfer.

MECHANISM 20.1 NUCLEOPHILIC ADDITION UNDER BASIC CONDITIONS

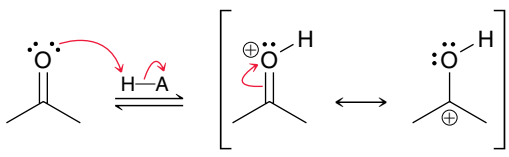


Aldehydes and ketones also react with a wide variety of other nucleophiles under acidic conditions. In acidic conditions, the same two mechanistic steps are observed, but in reverse order—that is, the carbonyl group is first protonated and then undergoes a nucleophilic attack (Mechanism 20.2).

MECHANISM 20.2 NUCLEOPHILIC ADDITION UNDER ACIDIC CONDITIONS



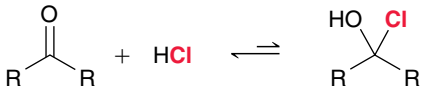
In acidic conditions, the first step plays an important role. Specifically, protonating the carbonyl group generates a very powerful electrophile:



It is true that the carbonyl group is already a fairly strong electrophile; however, a protonated carbonyl group bears a full positive charge, rendering the carbon atom even more electrophilic. This is especially important when weak nucleophiles, such as H_2O or ROH, are employed, as we will see in the upcoming sections.

When a nucleophile attacks a carbonyl group under either acidic or basic conditions, the position of equilibrium is highly dependent on the ability of the nucleophile to function as a leaving group. A Grignard reagent is a very strong nucleophile, but it does not function as a leaving group (a carbanion is too unstable to leave). As a result, the equilibrium so greatly favors products that the reaction effectively occurs in only one direction. With a sufficient amount of nucleophile present, the ketone is not observed in the product mixture. In contrast, halides are

good nucleophiles, but they are also good leaving groups. Therefore, when a halide functions as the nucleophile, the equilibrium actually favors the starting ketone:



Once equilibrium has been achieved, the mixture consists primarily of the ketone, and only small quantities of the addition product.

In this chapter, we will explore a wide variety of nucleophiles, which will be classified according to the nature of the attacking atom. Specifically, we will see nucleophiles based on oxygen, sulfur, nitrogen, hydrogen, and carbon (Figure 20.2).

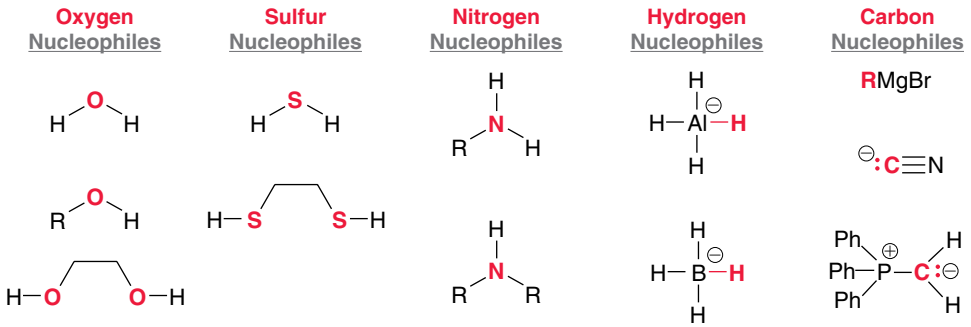
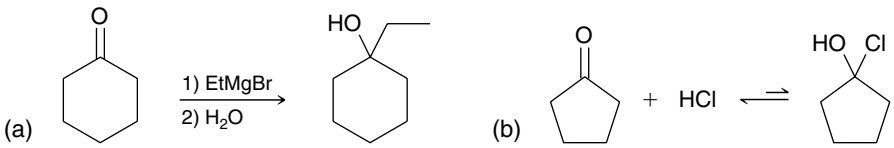


FIGURE 20.2
Various nucleophiles that can attack a carbonyl group.

The remainder of the chapter will be a methodical survey of the reactions that occur between the reagents in Figure 20.2 and ketones and aldehydes. We will begin our survey with oxygen nucleophiles.

CONCEPTUAL CHECKPOINT

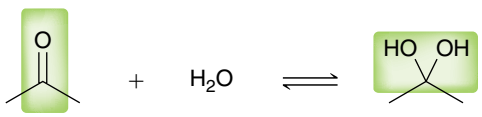
20.6 Draw a mechanism for each of the reactions below:



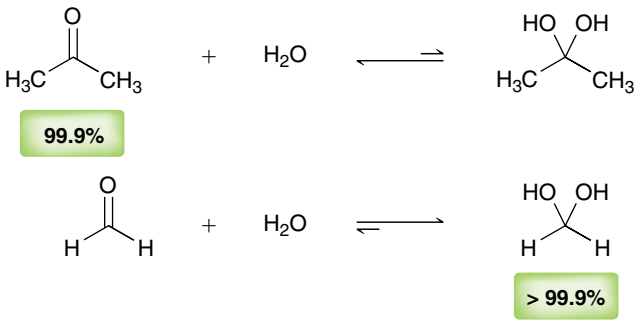
20.5 Oxygen Nucleophiles

Hydrate Formation

When an aldehyde or ketone is treated with water, the carbonyl group can be converted into a **hydrate:**

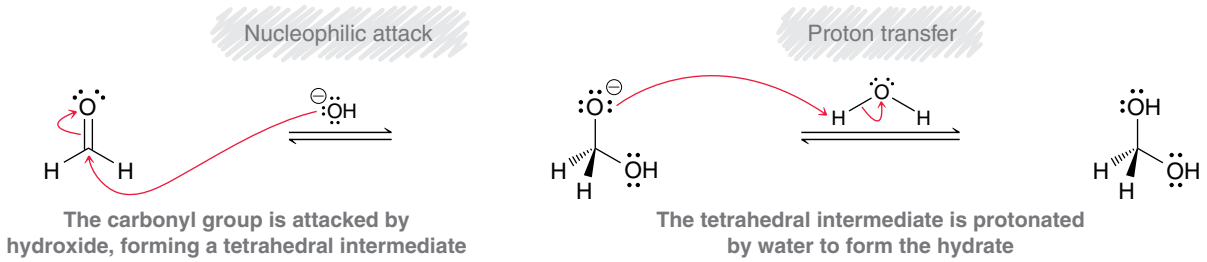


The position of equilibrium generally favors the carbonyl group rather than the hydrate, except in the case of very simple aldehydes, such as formaldehyde:



The rate of reaction is relatively slow under neutral conditions but is readily enhanced in the presence of either acid or base. That is, the reaction can be either acid catalyzed or base catalyzed, allowing the equilibrium to be achieved much more rapidly. Consider the base-catalyzed hydration of formaldehyde (Mechanism 20.3).

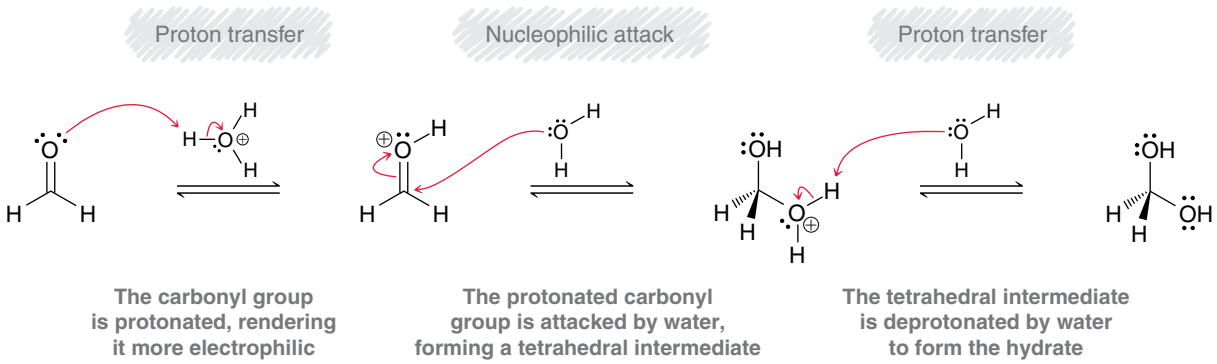
MECHANISM 20.3 BASE-CATALYZED HYDRATION



In the first step, a hydroxide ion (rather than water) functions as a nucleophile. Then, in the second step, the tetrahedral intermediate is protonated with water, regenerating a hydroxide ion. In this way, hydroxide serves as a catalyst for the addition of water across the carbonyl group.

Now consider the acid-catalyzed hydration of formaldehyde (Mechanism 20.4).

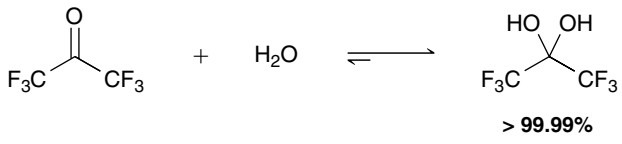
MECHANISM 20.4 ACID-CATALYZED HYDRATION



Under acid-catalyzed conditions, the carbonyl group is first protonated, generating a positively charged intermediate that is extremely electrophilic (it bears a full positive charge). This intermediate is then attacked by water to form a tetrahedral intermediate, which is deprotonated to give the product.

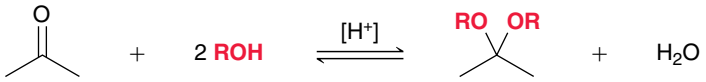
CONCEPTUAL CHECKPOINT

20.7 For most ketones, hydrate formation is unfavorable, because the equilibrium favors the ketone rather than the hydrate. However, the equilibrium for hydration of hexafluoroacetone favors formation of the hydrate: Provide a plausible explanation for this observation.



Acetal Formation

The previous section discussed a reaction that can occur when water attacks an aldehyde or ketone. This section will explore a similar reaction, in which an alcohol attacks an aldehyde or ketone:

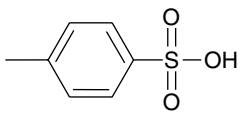


Acetal

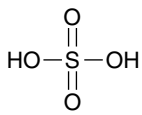
BY THE WAY

When the starting compound is a ketone, the product can also be called a "ketal." *Acetal* is a more general term, and it will be used exclusively for the remainder of this discussion.

In acidic conditions, an aldehyde or ketone will react with two molecules of alcohol to form an **acetal.** The brackets surrounding the H^+ indicate that the acid is a catalyst. Common acids used for this purpose include *para*-toluenesulfonic acid (TsOH) and sulfuric acid (H_2SO_4):



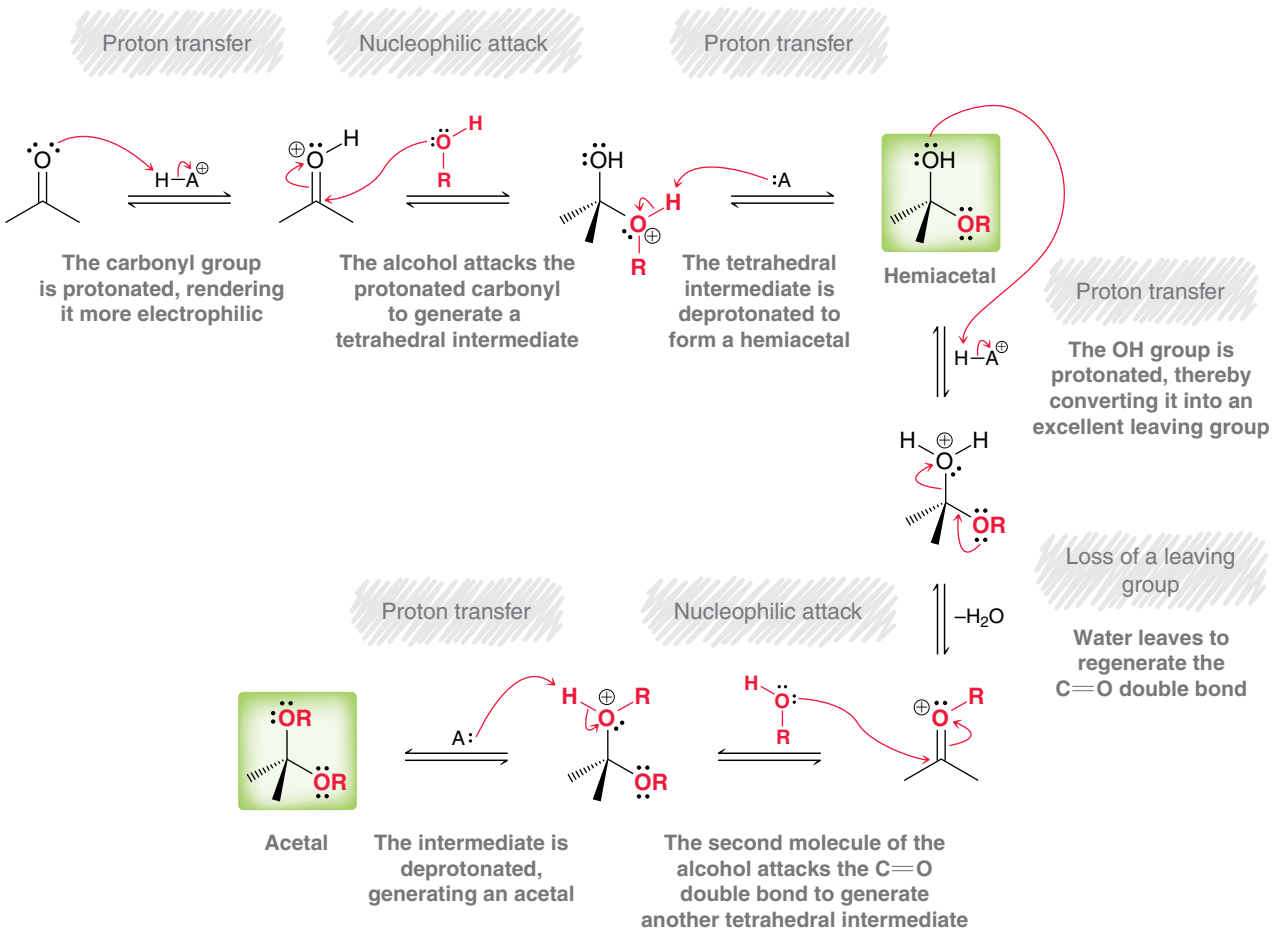
***p*-toluenesulfonic acid**
(TsOH)



Sulfuric acid

As mentioned earlier, the acid catalyst serves an important role in this reaction. Specifically, in the presence of an acid, the carbonyl group is protonated, rendering the carbon atom even more electrophilic. This is necessary because the nucleophile (an alcohol) is weak; it reacts with the carbonyl group more rapidly if the carbonyl group is first protonated. A mechanism for acetal formation is shown in Mechanism 20.5. This mechanism has many steps, and it is best to divide it conceptually into two parts: (1) The first three steps produce an intermediate called a **hemiacetal** and (2) the last four steps convert the hemiacetal into an acetal:

MECHANISM 20.5 ACETAL FORMATION



Let's begin our analysis of this mechanism by focusing on the first part: formation of the hemiacetal, which involves the three steps in Figure 20.3.

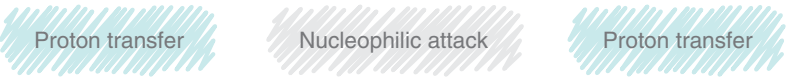
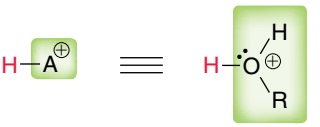


FIGURE 20.3
The sequence of steps involved in formation of a hemiacetal.

Notice that the sequence of steps begins and ends with a proton transfer. This will be a recurring pattern in this chapter. Let's focus on the details of these three steps:

1. The carbonyl is protonated in the presence of an acid. The identity of the acid, HA^+, is most likely a protonated alcohol, which received its extra proton from the acid catalyst:



2. The protonated carbonyl is a very powerful electrophile and is attacked by a molecule of alcohol (ROH) to form a tetrahedral intermediate that bears a positive charge.
3. The tetrahedral intermediate is deprotonated by a weak base (A), which is likely to be a molecule of alcohol present in solution.

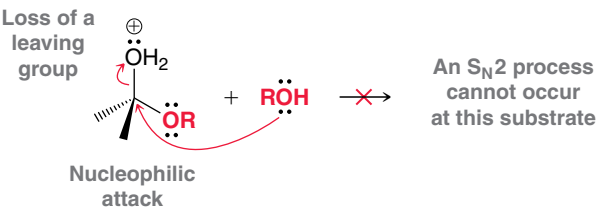
Notice that the acid is not consumed in this process. A proton is used in step 1 and then returned in step 3, confirming the catalytic nature of the proton in the reaction.

It is important to remember the specific order of these three steps, as we will soon encounter many other reactions that begin with the same three steps. These three steps are typical of reactions involving acid-catalyzed nucleophilic attack.

Now let's focus on the second part of the mechanism, conversion of the hemiacetal into an acetal, which is accomplished with the four steps in Figure 20.4.

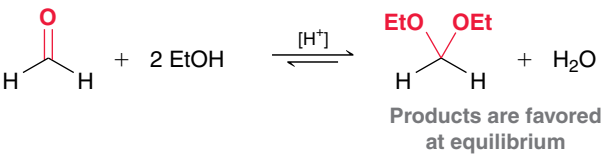
FIGURE 20.4
The sequence of steps that convert a hemiacetal into an acetal.

Notice, once again, that the sequence of steps begins and ends with a proton transfer. A proton is used in the first step and then returned in the last step, but this time there are two middle steps rather than just one. When drawing the mechanism of acetal formation, make sure to draw these two steps separately. Combining these two steps is incorrect and represents one of the most common student errors when drawing this mechanism:



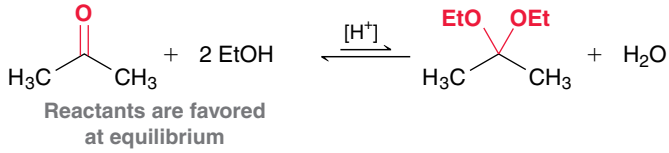
These two steps cannot occur simultaneously, because that would represent an S_N2 process occurring at a sterically hindered substrate. Such a process is disfavored and does not occur at an appreciable rate. Instead, the leaving group leaves first to form a resonance-stabilized intermediate, which is then attacked by the nucleophile in a separate step.

The equilibrium arrows in the full mechanism of acetal formation indicate that the process is governed by an equilibrium. For many simple aldehydes, the equilibrium favors formation of the acetal, so aldehydes are readily converted into acetals by treatment with two equivalents of alcohol in acidic conditions:



BY THE WAY
This technique exploits Le Châtelier's principle, which was covered in your general chemistry course. According to Le Châtelier's principle, if a system at equilibrium is upset by some disturbance, the system will change in a way that restores equilibrium.

However, for most ketones, the equilibrium favors reactants rather than products:

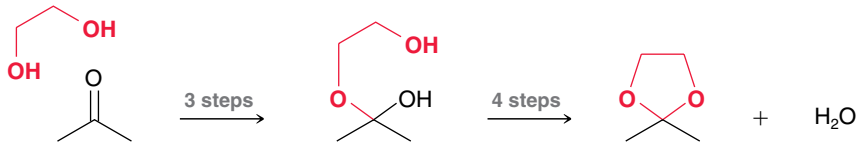


Reactants are favored at equilibrium

In such cases, formation of the acetal can be accomplished by removing one of the products (water) via a special distillation technique. By removing water as it is formed, the reaction can be forced to completion.

Notice that acetal formation requires two equivalents of the alcohol. That is, two molecules of ROH are required for every molecule of ketone. Alternatively, a compound containing two OH groups can be used, forming a cyclic acetal.

This reaction proceeds via the regular seven-step mechanism for acetal formation: three steps for formation of the hemiacetal followed by four steps for formation of the cyclic acetal:



Hemiacetal — Cyclic acetal

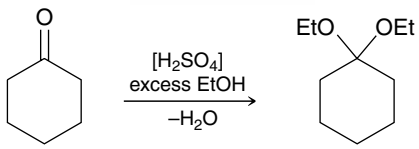
The seven-step mechanism for acetal formation is very similar to other mechanisms that we will explore. It is therefore critical to master these seven steps. To help you draw the mechanism properly, remember to divide the entire mechanism into two parts, where each part begins and ends with proton transfers. Let's get some practice.

SKILLBUILDER

20.2 DRAWING THE MECHANISM OF ACETAL FORMATION

LEARN the skill

Draw a plausible mechanism for the following transformation:



SOLUTION

The reaction above is an example of acid-catalyzed acetal formation, in which the product is favored by the removal of water. The mechanism can be divided into two parts: (1) formation of the hemiacetal and (2) formation of the acetal. Formation of the hemiacetal involves three mechanistic steps:

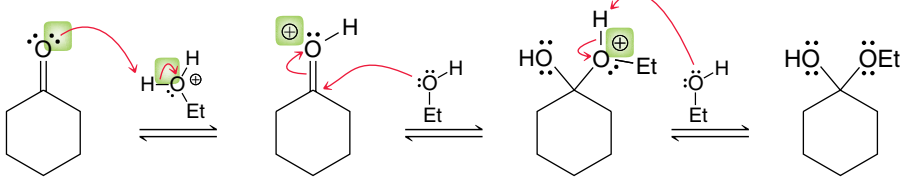
Proton transfer — Nucleophilic attack — Proton transfer

STEP 1
Draw the three steps necessary for hemiacetal formation.

When drawing these three steps, make sure to focus on proper arrow placement (as described in Chapter 6), and make sure to place all positive charges in their appropriate locations. Notice that every step requires two curved arrows.

The tail of this arrow should be placed on a lone pair

Don't forget the positive charges



Don't forget the second curved arrow that shows release of the proton

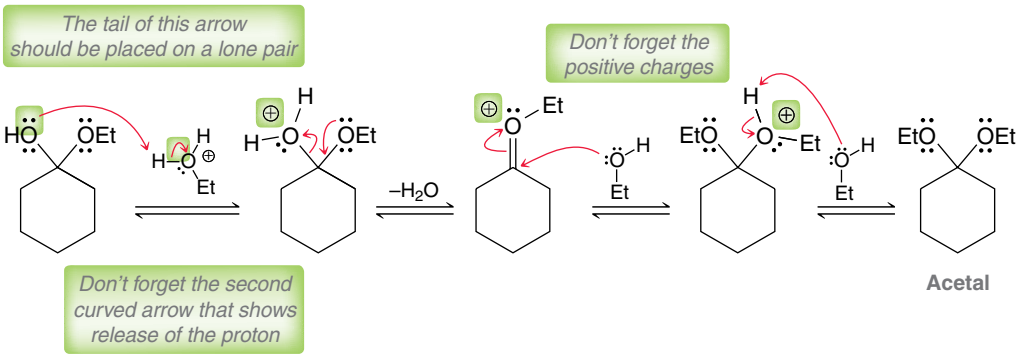
Hemiacetal

STEP 2
Draw the four steps necessary to convert the hemiacetal into an acetal.

Now let's focus on the last four steps of the mechanism, in which the hemiacetal is converted into an acetal:

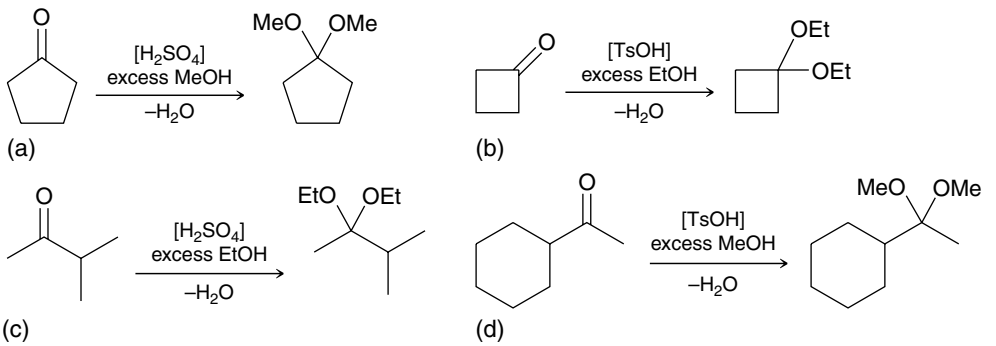
Proton transfer | Loss of a leaving group | Nucleophilic attack | Proton transfer

Once again, this sequence of steps begins with a proton transfer and ends with a proton transfer. When drawing these four steps, make sure to draw the middle two steps separately, as discussed earlier. In addition, make sure to focus on proper arrow placement, and make sure to place all positive charges in their appropriate locations:



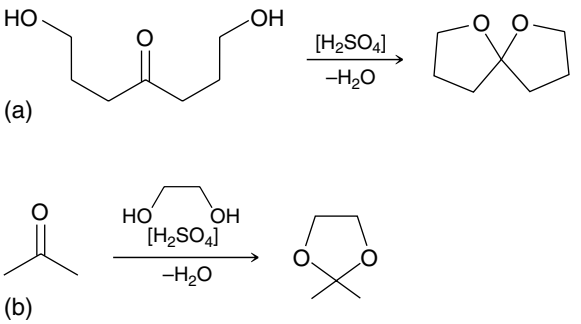
PRACTICE the skill

20.8 Draw a plausible mechanism for each of the following transformations:

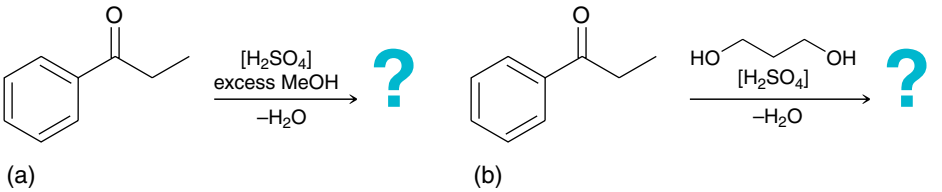


APPLY the skill

20.9 Draw a plausible mechanism for each of the following reactions:



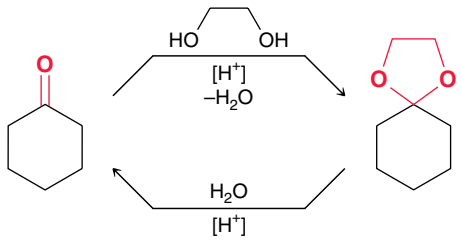
20.10 Predict the product of each of the following reactions:



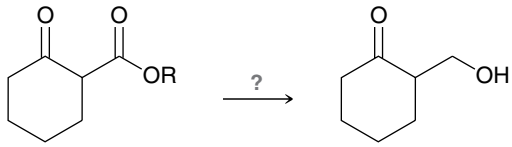
need more **PRACTICE?** **Try Problems 20.57, 20.62, 20.67**

Acetals as Protecting Groups

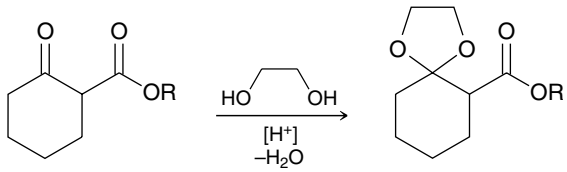
Acetal formation is a reversible process that can be controlled by carefully choosing reagents and conditions:



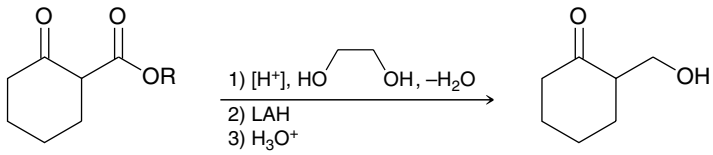
As mentioned in the previous section, acetal formation is favored by removal of water. To convert an acetal back into the corresponding aldehyde or ketone, it is simply treated with water in the presence of an acid catalyst. In this way, acetals can be used to protect ketones or aldehydes. For example, consider how the following transformation might be accomplished:



This transformation involves reduction of an ester to form an alcohol. Recall that lithium aluminum hydride (LAH) can be used to accomplish this type of reaction. However, under these conditions, the ketone moiety will also be reduced. The problem above requires reduction of the ester moiety without also reducing the ketone moiety. To accomplish this, a protecting group can be used. The first step is to convert the ketone into an acetal:

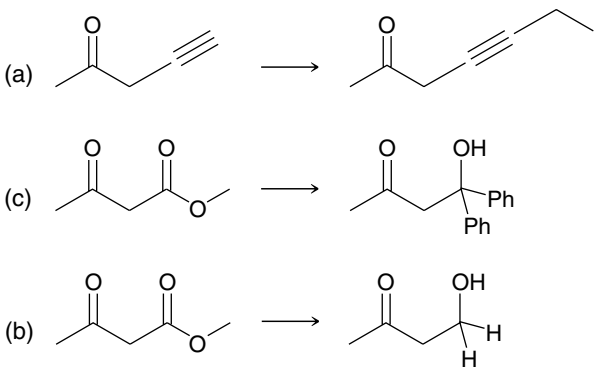


Notice that the ketone moiety is converted into an acetal, but the ester moiety is not. The resulting acetal group is stable under strongly basic conditions and will not react with LAH. This makes it possible to reduce only the ester, after which the acetal can be removed to regenerate the ketone: The three steps are summarized below:

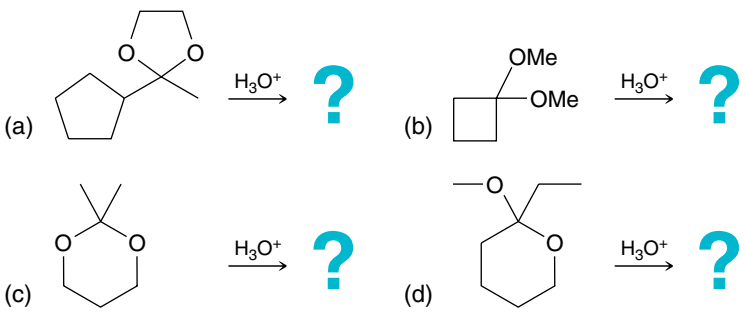


CONCEPTUAL CHECKPOINT

20.11 Propose an efficient synthesis for each of the following transformations:



20.12 Predict the product(s) for each reaction below:



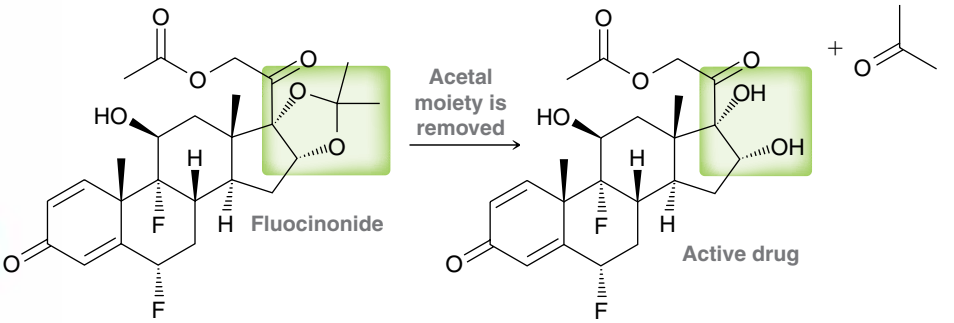
MEDICALLYSPEAKING

Acetals as Prodrugs

In Chapter 19 we explored the concept of prodrugs—pharmacologically inactive compounds that are converted by the body into active compounds. Many strategies are used in the design of prodrugs. One such strategy involves an acetal moiety.

As an example, fluocinonide is a prodrug that contains an acetal moiety, and is sold in a cream used for the topical treatment of eczema and other skin conditions.

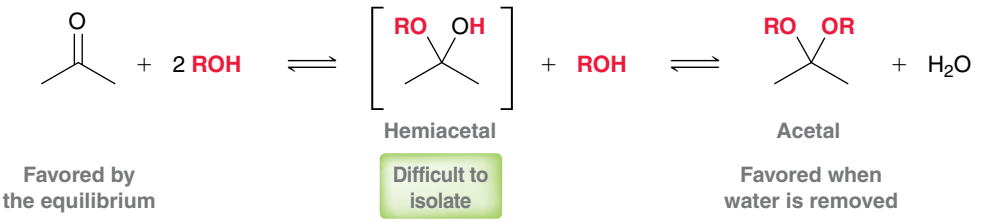
Skin has several important functions, including preventing the absorption of foreign substances into the general circulation. This feature protect us from harmful substances, but it also prevents beneficial drugs from penetrating deep into the skin. This effect is most pronounced for drugs containing OH groups that can interact with binding sites on the skin's surface. To circumvent this problem, two OH groups can be temporarily converted into an acetal. The acetal prodrug is capable of penetrating the skin more deeply, because it lacks the OH groups that bind to the skin. Once the prodrug reaches its target, the acetal moiety is slowly hydrolyzed, thereby releasing the active drug:



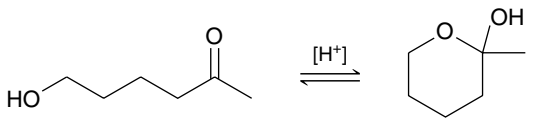
Treatment with fluocinonide is significantly more effective than direct treatment with the active drug, because the latter cannot reach all of the affected areas.

Stable Hemiacetals

In the previous section, we saw how to convert an aldehyde or ketone into an acetal. In most cases, it is very difficult to isolate the intermediate hemiacetal:

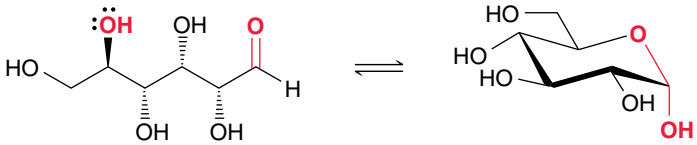


For ketones we saw that the equilibrium generally favors the reactants unless water is removed, which enables formation of the acetal. The hemiacetal is not favored under either set of conditions (with or without removal of water). However, when a compound contains both a carbonyl group and a hydroxyl group, the resulting cyclic hemiacetal can often be isolated; for example:



Cyclic hemiacetal

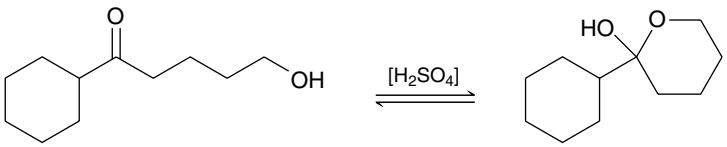
This will be important when we learn about carbohydrate chemistry in Chapter 24. Glucose, the major source of energy for the body, exists primarily as a cyclic hemiacetal:



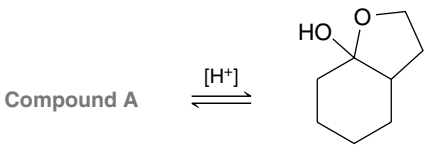
Glucose (Open-chain) Glucose (Cyclic hemiacetal)

CONCEPTUAL CHECKPOINT

20.13 Draw a plausible mechanism for the following transformation:



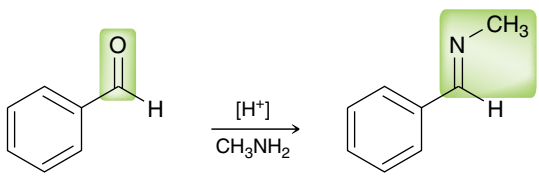
20.14 Compound A has molecular formula $C_8H_{14}O_2$. Upon treatment with catalytic acid, compound A is converted into the cyclic hemiacetal. Identify the structure of compound A.



20.6 Nitrogen Nucleophiles

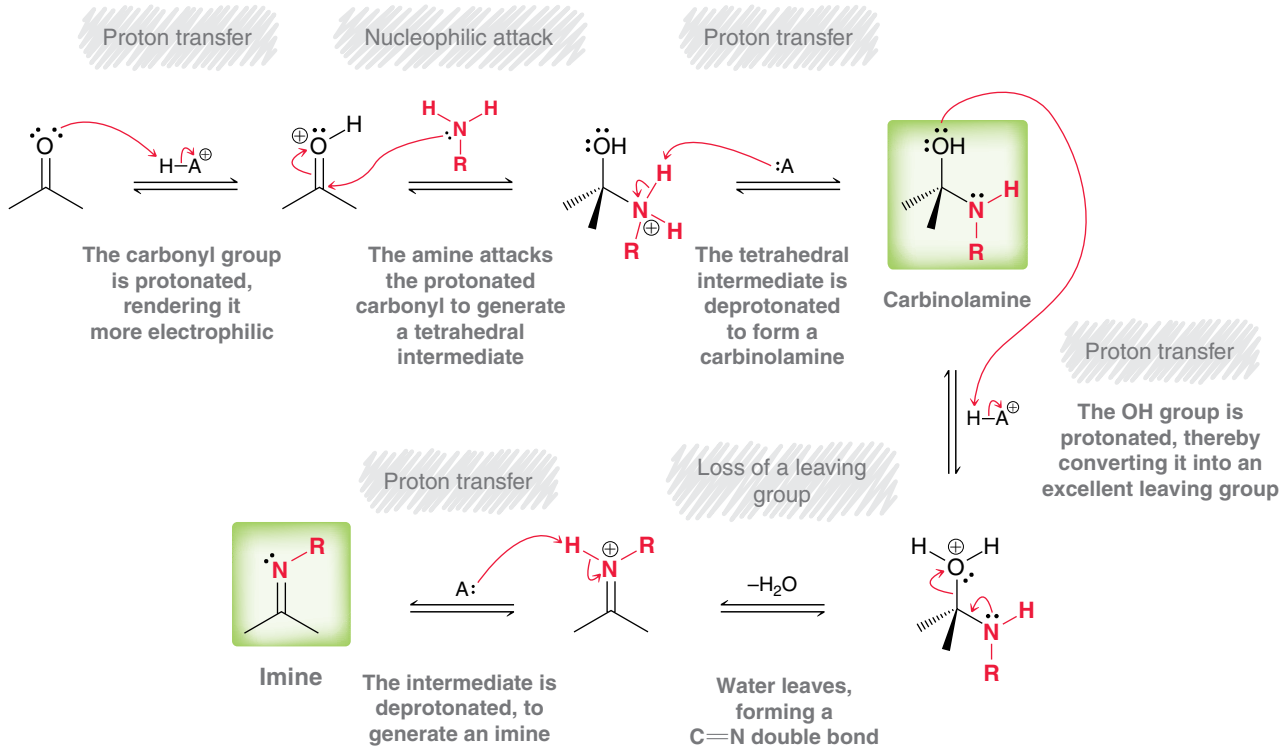
Primary Amines

In mildly acidic conditions, an aldehyde or ketone will react with a primary amine to form an **imine:**



Imines are compounds that possess a C═N double bond and are common in biological pathways. Imines are also called Schiff bases, named after Hugo Schiff, a German chemist who first described their formation. A six-step mechanism for imine formation is shown in Mechanism 20.6. It is best to divide the mechanism conceptually into two parts (just as we did to conceptualize the mechanism of acetal formation): (1) The first three steps produce an intermediate called a **carbinolamine** and (2) the last three steps convert the carbinolamine into an imine:

MECHANISM 20.6 IMINE FORMATION



Note: There is experimental evidence that the first two steps of this mechanism (protonation and nucleophilic attack) more likely occur either simultaneously *or* in the reverse order of what is shown above. Most nitrogen nucleophiles are sufficiently nucleophilic to attack a carbonyl group directly, before protonation occurs. Nevertheless, the first two steps of the mechanism above have been drawn in the order shown (which only rarely occurs), because this sequence enables a more effective comparison of all acid-catalyzed mechanisms in this chapter and also unifies the rationale behind proton transfers, as we will discuss in Sections 20.6 and 20.7. Interested students can learn more from the following literature references:

1. *J. Am. Chem. Soc.*, **1974**, 96(26), 7998–09
2. *J. Org. Chem.*, **2007**, 72(22), 8202–8215

FIGURE 20.5
The sequence of steps involved in formation of a carbinolamine.

Let's begin our analysis of this mechanism by focusing on the first part: formation of the carbinolamine, which involves the three steps in Figure 20.5. Notice that these three steps are identical to the first three steps of acetal formation. Specifically, this sequence of steps involves a nucleophilic attack that is sandwiched between proton transfer steps. The identity of the acid, HA^+, is most likely a protonated amine, which received its extra proton from the acid source:

Once the carbinolamine has been formed, formation of the imine is accomplished with three steps (Figure 20.6). Notice again that this reaction sequence begins and ends with proton transfers.

FIGURE 20.6
The sequence of steps that convert a carbinolamine into an imine.

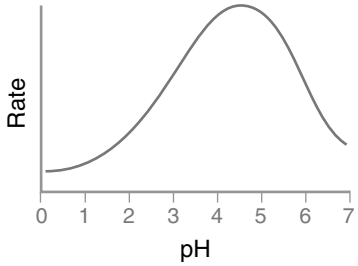
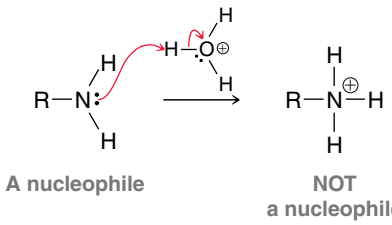


FIGURE 20.7
The rate of imine formation as a function of pH.

The pH of the solution is an important consideration during imine formation, with the rate of reaction being greatest when the pH is around 4.5 (Figure 20.7). If the pH is too high (i.e., if no acid catalyst is used), the carbonyl group is not protonated (step 1 of the mechanism) and the carbinolamine is also not protonated (step 4 of the mechanism); so the reaction occurs more slowly. If the pH is too low (too much acid is used), most of the amine molecules will be protonated:



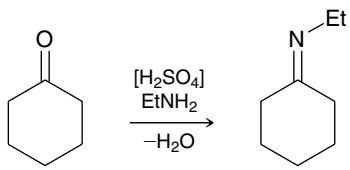
Under these conditions, step 2 of the mechanism occurs too slowly. As a result, care must be taken to ensure optimal pH of the solution during imine formation.

SKILLBUILDER

20.3 DRAWING THE MECHANISM OF IMINE FORMATION

LEARN the skill

Draw a plausible mechanism for the following transformation:



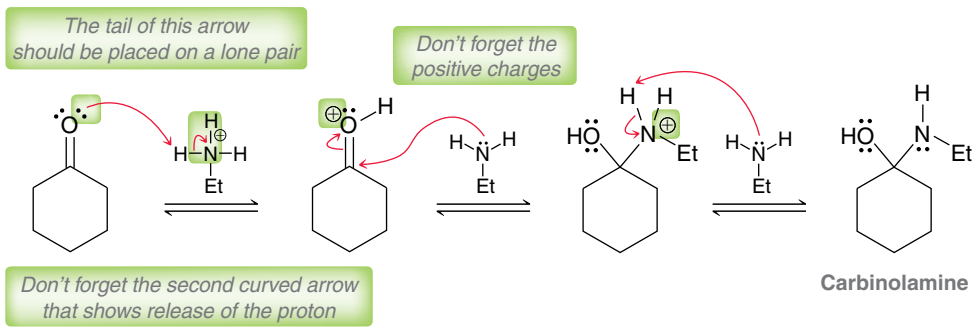
SOLUTION

The reaction above is an example of imine formation. The mechanism can be divided into two parts: (1) formation of the carbinolamine and (2) formation of the imine.
Formation of the carbinolamine involves three mechanistic steps:

Proton transfer | Nucleophilic attack | Proton transfer

When drawing these three steps, make sure to place the head and tail of every curved arrow in its precise location, and make sure to place all positive charges in their appropriate locations. Notice that every step requires two curved arrows.

STEP 1
Draw the three steps necessary to form a carbinolamine.

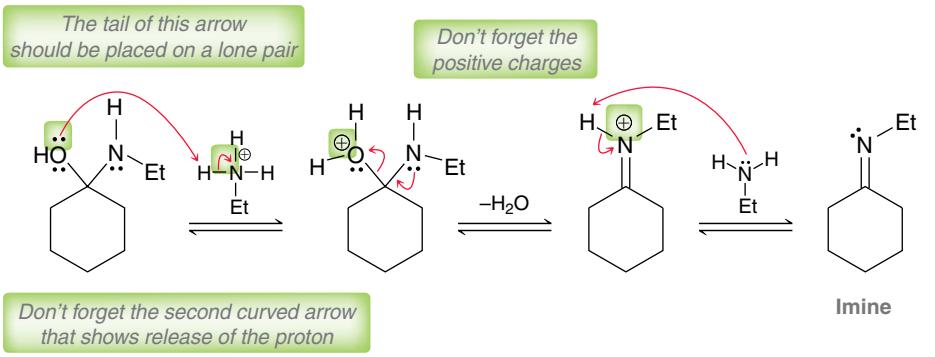


Now let's focus on the second part of the mechanism, in which the carbinolamine is converted into an imine. This requires three steps:

Proton transfer | Loss of a leaving group | Proton transfer

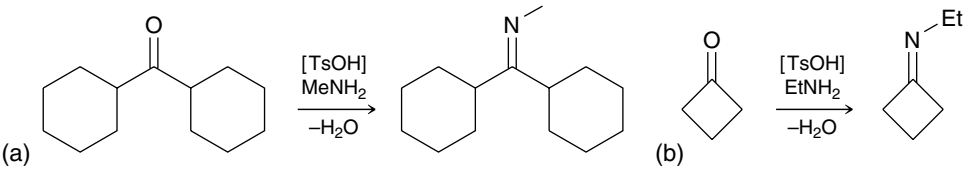
Once again, this sequence of steps begins with a proton transfer and ends with a proton transfer. Make sure to place the head and tail of every curved arrow in its precise location, and make sure to place all positive charges in their appropriate locations:

STEP 2
Draw the three steps necessary to convert the carbinolamine into an imine.



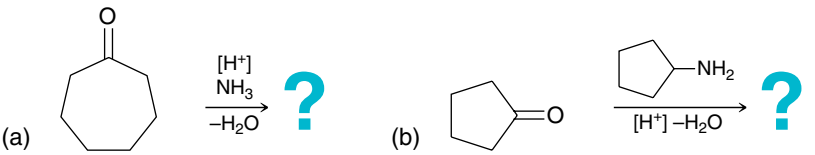
PRACTICE the skill

20.15 Draw a plausible mechanism for each of the following transformations:

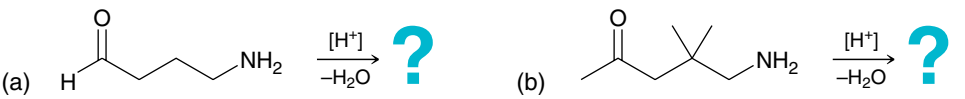


APPLY the skill

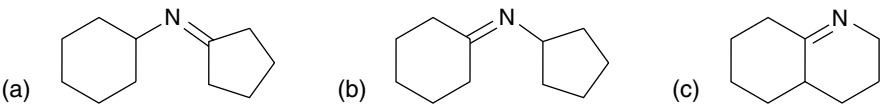
20.16 Predict the major product for each of the following reactions:



20.17 Predict the major product for each of the following intramolecular reactions:

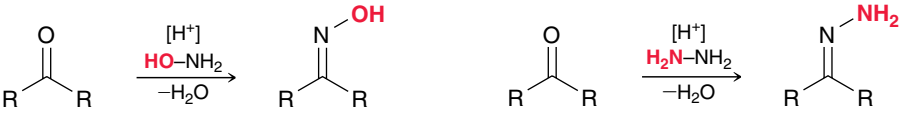


20.18 Identify the reactants that you would use to make each of the following imines:



need more **PRACTICE?** **Try Problems 20.72, 20.86**

Many different compounds of the form RNH_2 will react with aldehydes and ketones, including compounds in which R is not an alkyl group. In the following examples, the R group of the amine has been replaced with a group that has been highlighted in red:



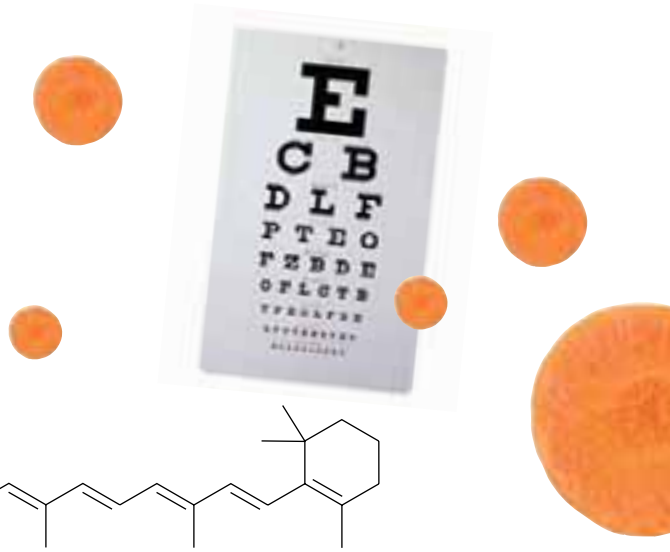
LOOKING AHEAD
Hydrazones are synthetically useful, as we will see in the discussion of the Wolff-Kishner reduction later in this chapter.

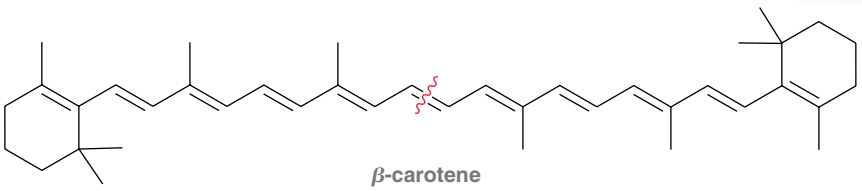
When hydroxylamine (NH_2OH) is used as a nucleophile, an **oxime** is formed. When hydrazine (NH_2NH_2) is used as a nucleophile, a **hydrazone** is formed. The mechanism for each of these reactions is directly analogous to the mechanism of imine formation.

PRACTICALLYSPEAKING

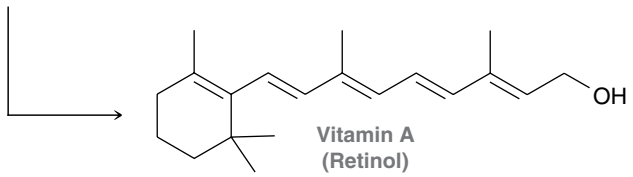
Beta-Carotene and Vision

Beta-carotene is a naturally occurring compound found in many orange-colored fruits and vegetables, including carrots, sweet potatoes, pumpkins, mangoes, cantaloupes, and apricots. As mentioned in the chapter opener, beta-carotene is known to be good for your eyes. To understand why, we must explore what happens to beta-carotene in your body. Imine formation plays an important role in the process.

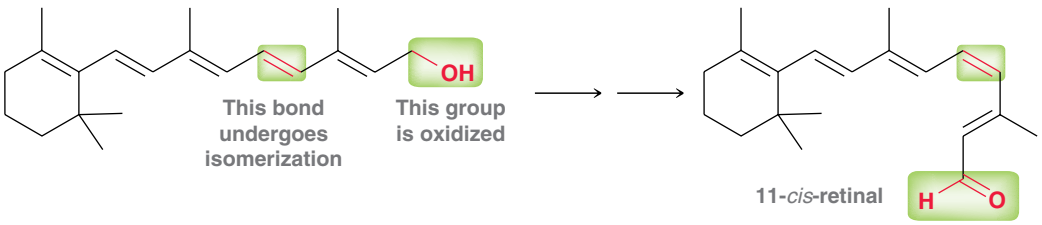




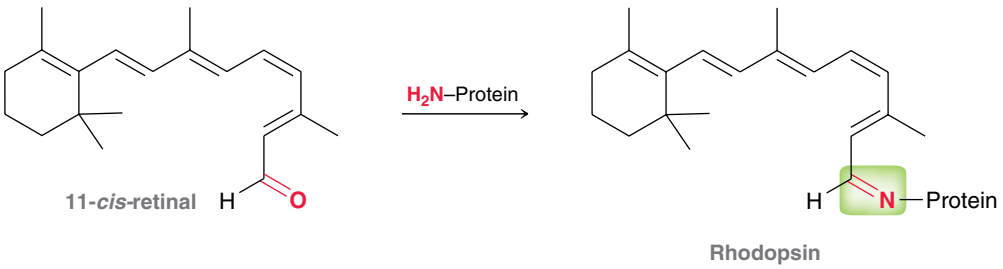
Beta-carotene is metabolized in the liver to produce vitamin A (also called retinol):



Vitamin A is then oxidized, and one of the double bonds undergoes isomerization to produce 11-*cis*-retinal:



The resulting aldehyde then reacts with an amino group of a protein (called opsin) to produce rhodopsin, which possesses an imine moiety:

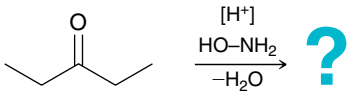


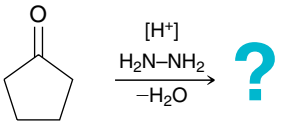
As described in Section 17.13, rhodopsin can absorb a photon of light, initiating a photoisomerization of the *cis* double bond to form a *trans* double bond. The resulting change in geometry triggers a signal that is ultimately detected by the brain and interpreted as vision.

A deficiency of vitamin A can lead to "night blindness," a condition that prevents the eyes from adjusting to dimly lit environments.

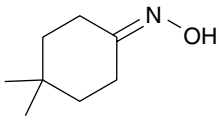
CONCEPTUAL CHECKPOINT

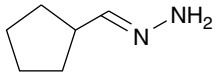
20.19 Predict the product of each of the following reactions:

(a) 

(b) 

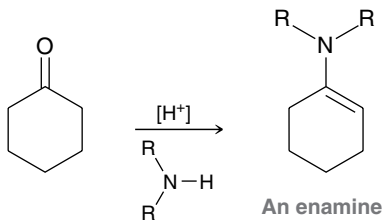
20.20 Identify the reactants that you would use to make each of the following compounds:

(a) 

(b) 

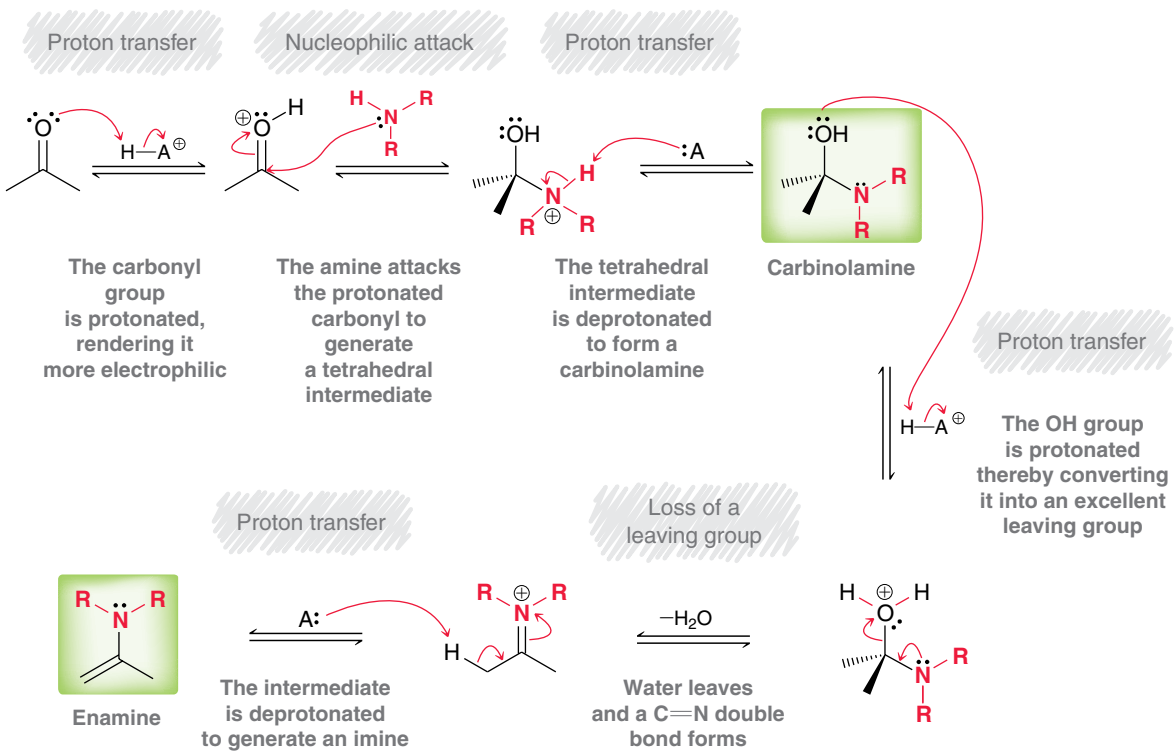
Secondary Amines

In acidic conditions, an aldehyde or ketone will react with a secondary amine to form an **enamine:**



Enamines are compounds in which the nitrogen lone pair is delocalized by the presence of an adjacent C=C double bond. A mechanism for enamine formation is shown in Mechanism 20.7

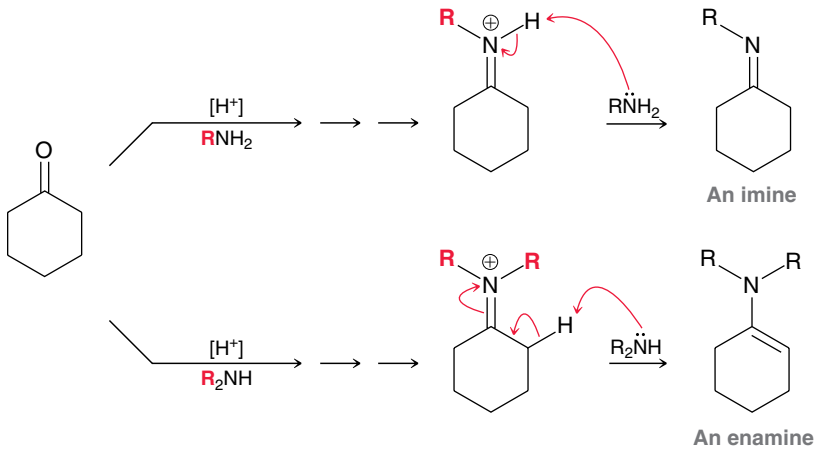
MECHANISM 20.7 ENAMINE FORMATION



Note: There is experimental evidence that the first two steps of this mechanism (protonation and nucleophilic attack) more likely occur either simultaneously *or* in the reverse order of what is shown above. Most nitrogen nucleophiles are sufficiently nucleophilic to attack a carbonyl group directly, before protonation occurs. Nevertheless, the first two steps of the mechanism above have been drawn in the order shown (which only rarely occurs), because this sequence enables a more effective comparison of all acid-catalyzed mechanisms in this chapter and also unifies the rationale behind proton transfers, as we will discuss in Sections 20.6 and 20.7. Interested students can learn more from the following literature references:

1. *J. Am. Chem. Soc.*, **1974**, 96(26), 7998–09
2. *J. Org. Chem.*, **2007**, 72(22), 8202–8215

This mechanism of enamine formation is identical to the mechanism of imine formation except for the last step:



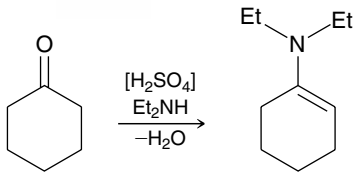
The difference in the iminium ions explains the different outcomes for the two reactions. During imine formation, the nitrogen atom of the iminium ion possesses a proton that can be removed as the final step of the mechanism. In contrast, during enamine formation, the nitrogen atom of the iminium ion does not possess a proton. As a result, elimination from the adjacent carbon is necessary in order to yield a neutral species.

SKILLBUILDER

20.4 DRAWING THE MECHANISM OF ENAMINE FORMATION

LEARN the skill

Draw a plausible mechanism for the following reaction:



SOLUTION

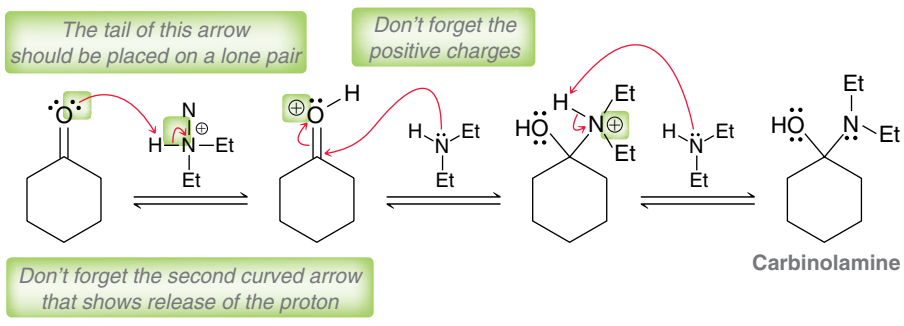
The reaction above is an example of enamine formation. The mechanism can be divided into two parts: (1) formation of the carbinolamine and (2) formation of the enamine.

Formation of the carbinolamine involves three mechanistic steps:

Proton transfer | Nucleophilic attack | Proton transfer

When drawing these three steps, make sure to place the head and tail of every curved arrow in its precise location, and make sure to place all positive charges in their appropriate locations. Notice that every step requires two curved arrows.

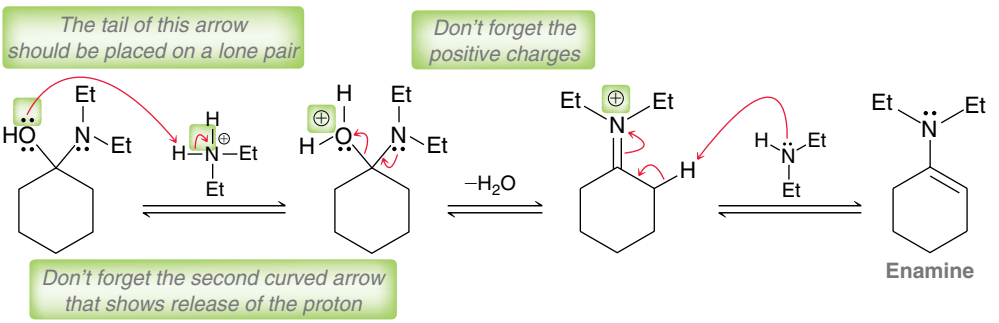
STEP 1
Draw the three steps necessary to form a carbinolamine.



In the second part of the mechanism, the carbinolamine is converted into an enamine via a three-step process. Once again, this sequence begins and ends with proton transfers:

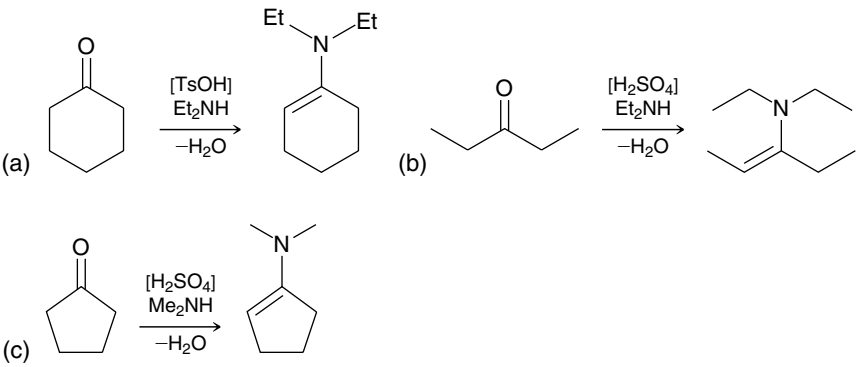
Proton transfer | Loss of a leaving group | Proton transfer

STEP 2
Draw the three steps necessary to convert the carbinolamine into an enamine.



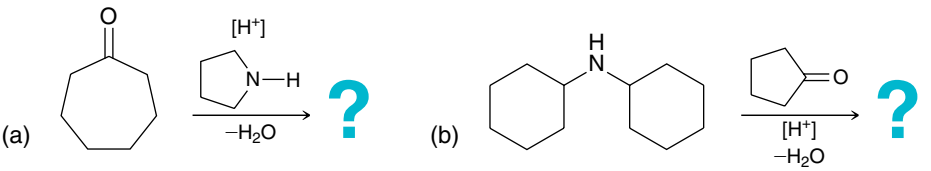
PRACTICE the skill

20.21 Draw a plausible mechanism for each of the following reactions:

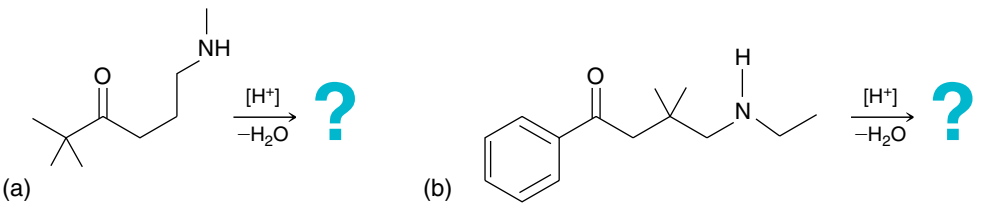


APPLY the skill

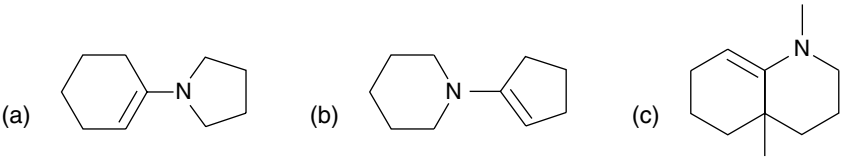
20.22 Predict the major product for each of the following reactions:



20.23 Predict the major product for each of the following intramolecular reactions:



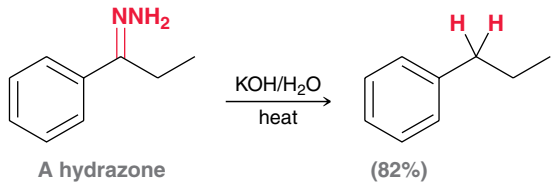
20.24 Identify the reactants that you would use to make each of the following enamines:



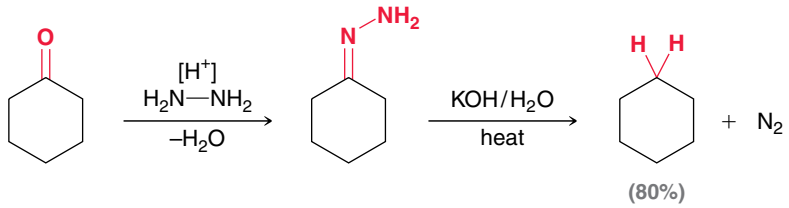
need more **PRACTICE?** **Try Problem 20.72**

Wolff-Kishner Reduction

At the end of the previous section, we noted that ketones can be converted into hydrazones. This transformation has practical utility, because hydrazones are readily reduced under strongly basic conditions:

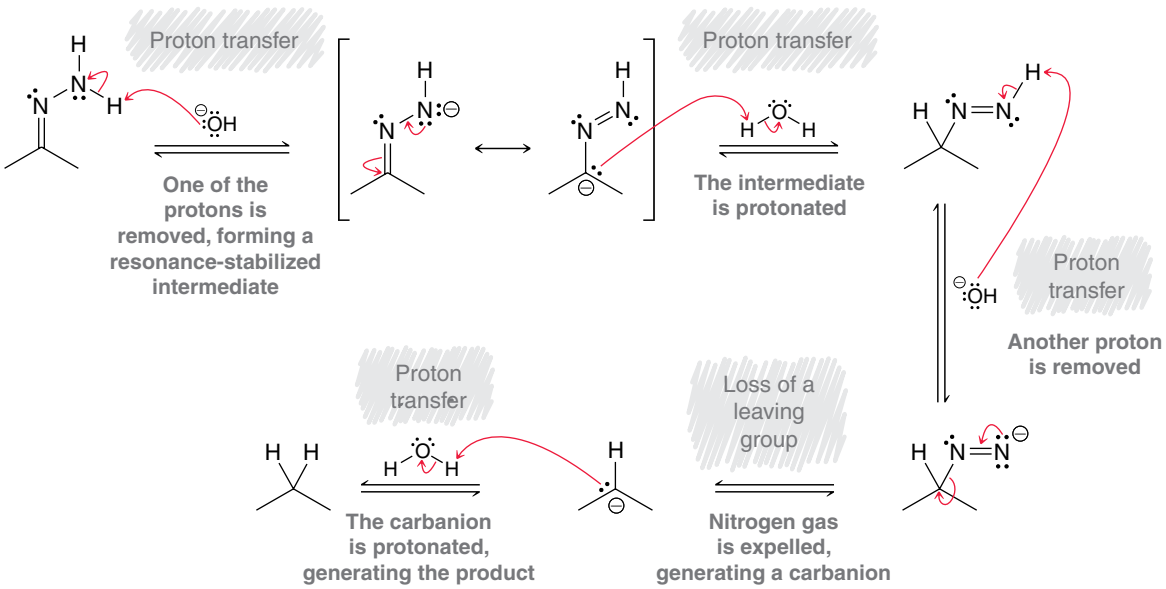


This transformation is called the **Wolff-Kishner reduction,** named after the German chemist Ludwig Wolff (University of Jena) and the Russian chemist N. M. Kishner (University of Moscow). This provides a two-step procedure for reducing a ketone to an alkane:



The second part of the Wolff-Kishner reduction is believed to proceed via Mechanism 20.8.

MECHANISM 20.8 THE WOLFF-KISHNER REDUCTION

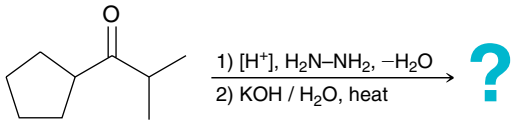


Notice that four of the five steps in the mechanism are proton transfers, the exception being the loss of N_2 gas to generate a carbanion. This step warrants special attention, because formation of a carbanion in a solution of aqueous hydroxide is thermodynamically unfavorable (*significantly* uphill in energy). Why, then, does this step occur? It is true that the equilibrium for this step greatly disfavors formation of the carbanion, and therefore, only a very small number of molecules will initially lose N_2 to form the carbanion. However, the resulting N_2 gas then

bubbles out of the reaction mixture, and the equilibrium is adjusted to form more nitrogen gas, which again leaves the reaction mixture. The evolution of nitrogen gas ultimately renders this step irreversible and forces the reaction to completion. As a result, the yields for this process are generally very good.

CONCEPTUAL CHECKPOINT

20.25 Predict the product of the two-step procedure below, and draw a mechanism for its formation:



20.7 Mechanism Strategies

Compare the mechanistic steps for the formation of acetals, imines, and enamines (Figure 20.8). Each of the mechanisms has been divided into two parts, and in all cases, the first part consists of the same three steps. In addition, even the second part of each mechanism begins with the same first two steps (proton transfer followed by loss of a leaving group). In other words, these three mechanisms are identical until the fifth step, in which water is lost (loss of a leaving group), shown in red in Figure 20.8. Rather than viewing these reactions as three separate, unrelated reactions, it is best to view them as nearly identical with different endings. Acetal formation has one additional nucleophile attack, giving a total of seven steps. In contrast, imine formation and enamine formation do not exhibit a nucleophilic attack during the second part of the mechanism, giving a total of only six steps.

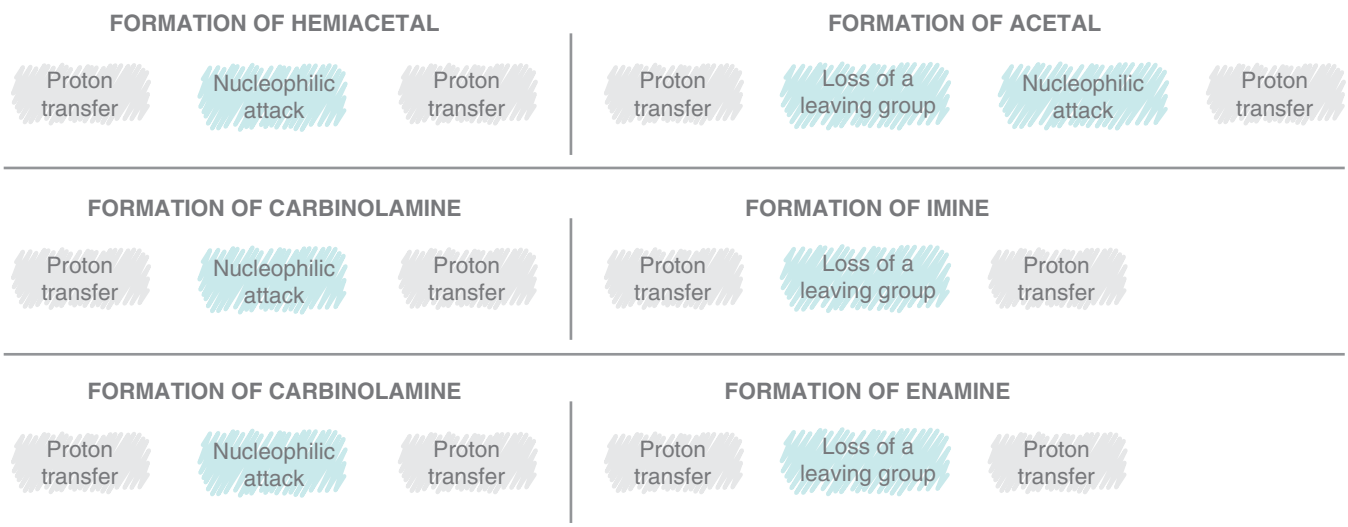


FIGURE 20.8
A comparison of the sequence of steps for acetal, imine, and enamine formation.

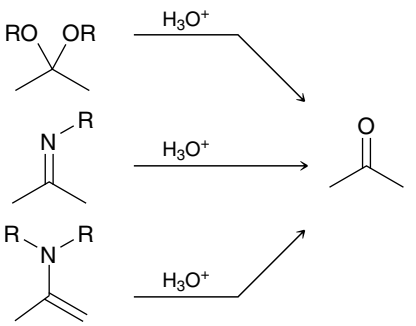
In each of these mechanisms, there are four proton transfer steps. In order to draw the mechanism correctly, it is critical to draw these proton transfers properly. To do so, it will be helpful to remember the following rules that dictate when and why proton transfers occur in acid-catalyzed conditions:

- The carbonyl group should be protonated before it is attacked. This generates a more powerful electrophile, and it avoids formation of a negative charge that would occur if the nucleophile attacked the carbonyl directly.

- Avoid formation of two positive charges on a single intermediate. This type of intermediate will generally be too high in energy to form.
- The leaving group should become neutral when it leaves. Do not expel hydroxide as a leaving group; rather, it should first be protonated so that it can leave as water.
- At the end of the mechanism, a proton transfer is used to form a neutral product.

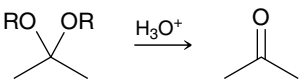
The four rules above correspond with each of the four proton transfers, respectively. These four rules can be consolidated into one master rule that defines when and why proton transfer steps are utilized: *In acidic conditions, all reagents, intermediates, and leaving groups should either be neutral (no charge) or bear one positive charge.* All of the proton transfers in the mechanism occur in order to fulfill this requirement.

Acetals, imines, and enamines can be converted back into ketones by treatment with excess water under acid-catalyzed conditions:

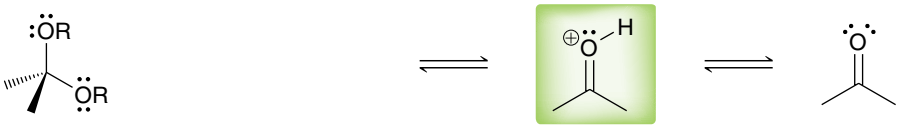


Each of the reactions above is called a **hydrolysis** reaction, because in each case bonds are cleaved by treatment with water. These three reactions are essentially the reverse of the reactions we have seen. The following procedure should be used in drawing the mechanisms for the above hydrolysis reactions:

1. Begin by drawing all of the intermediates without any curved arrows. For example, suppose that we want to draw the mechanism for hydrolysis of an acetal to form a ketone:



We did not learn the mechanism for this reaction; however, we did learn the mechanism for acetal formation. Think about the first intermediate in acetal formation (a protonated carbonyl), and then draw that intermediate as the last intermediate of the hydrolysis reaction:



The last intermediate should be a protonated carbonyl

Continue working backward until you have drawn all of the intermediates.

2. Then, working forward, draw the curved arrows that are necessary to transform each intermediate into the next intermediate. At each stage, make sure you are following the master rule for proton transfers in acid-catalyzed conditions.

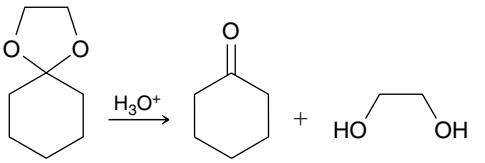
The skill of being able to draw the reverse of a known mechanism is incredibly important and will be used again for other reactions in the remaining chapters of this book. The following example illustrates this procedure.

SKILLBUILDER

20.5 DRAWING THE MECHANISM OF A HYDROLYSIS REACTION

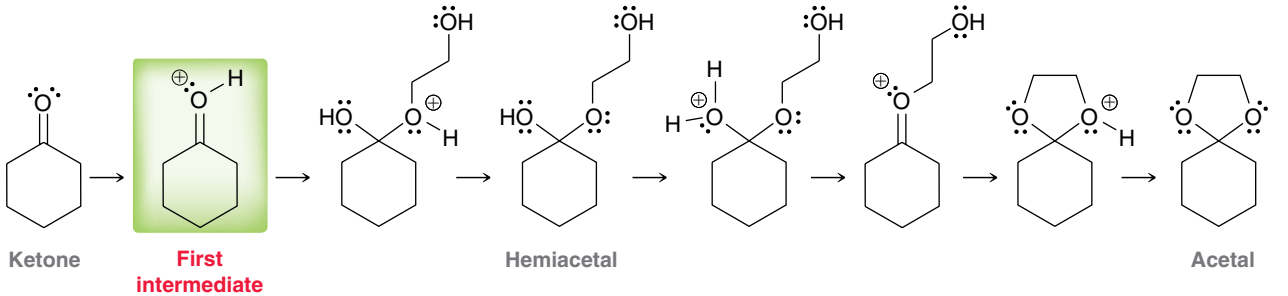
LEARN the skill

Propose a mechanism for the following transformation:



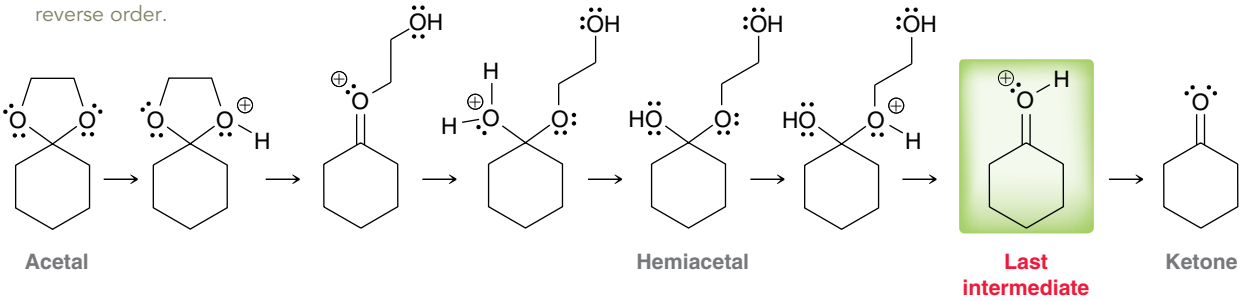
SOLUTION

This is a hydrolysis reaction in which a cyclic acetal is opened to form a ketone. We therefore expect the mechanism to be the reverse of acetal formation. Begin by considering all of the intermediates involved in acetal formation:



STEP 1
Draw all intermediates for acetal formation in reverse order.

We simply draw all of these intermediates in reverse order so that the first intermediate above (highlighted) becomes the last intermediate of the hydrolysis mechanism:

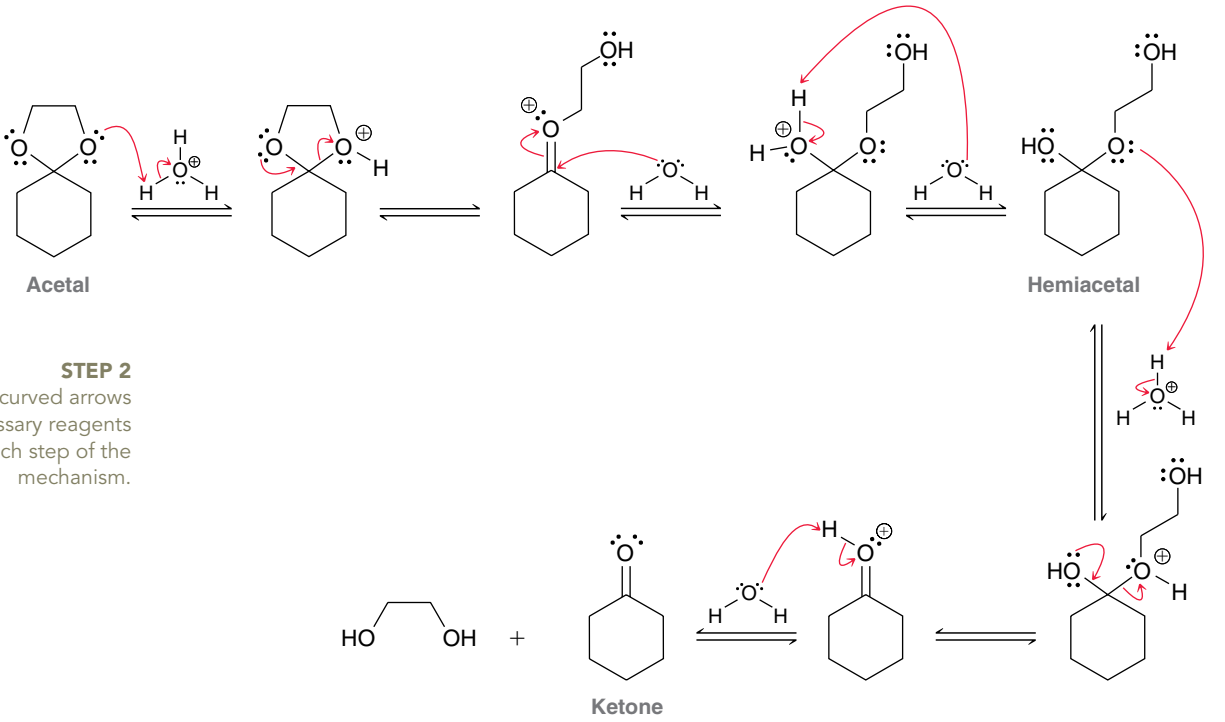


Hydrolysis of the acetal must involve these intermediates, in the order shown above. If any of the intermediates has a negative charge, then you have made a mistake.

With the intermediates placed in the correct order, the final step is to draw the reagents and curved arrows that show how each intermediate is transformed into the next intermediate. Begin with the acetal, and work forward until reaching the ketone. This requires that your arrow-pushing skills are in good shape.

Make sure to use only the reagents that are provided, and obey the master rule for proton transfers. For example, this problem indicates that H_3O^+ is available. This means that H_3O^+ should be used for protonating, and H_2O should be used for deprotonating. Do not use hydroxide ions, as they are not present in sufficient quantity under acid-catalyzed conditions. Application of these rules gives the following answer:

LOOKING BACK
If you need to polish your arrow-pushing skills, go to Section 6.8.

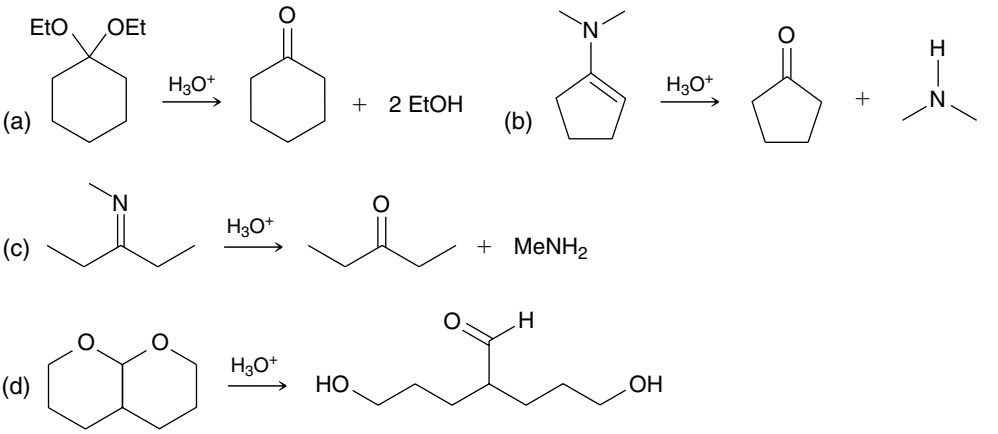


STEP 2
Draw the curved arrows and necessary reagents for each step of the mechanism.

Notice the use of equilibrium arrows, because the process is governed by an equilibrium, as noted in previous sections.

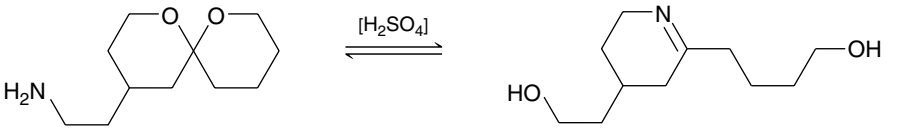
PRACTICE the skill

20.26 Propose a plausible mechanism for each of the following hydrolysis reactions:



APPLY the skill

20.27 Propose a plausible mechanism for the reaction below:



Hint: It is not necessary to open the acetal into a ketone (7 steps) followed by closing the imine (6 steps). A plausible mechanism can be drawn with fewer than 13 steps. Start working with the acetal (using the steps necessary to open an acetal), and look for an intermediate that can be attacked by the amino group. Make sure to avoid drawing an S_N2 process at a sterically hindered substrate!

need more **PRACTICE?** **Try Problem 20.65**

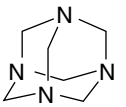
The Medically Speaking box below provides two examples of hydrolysis reactions that are exploited in drug design.

MEDICALLY SPEAKING

Prodrugs

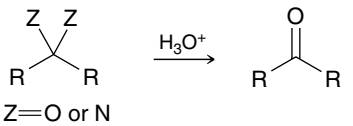
Methenamine as a Prodrug of Formaldehyde

Formaldehyde has antiseptic properties and can be employed in the treatment of urinary tract infections due to its ability to react with nucleophiles present in urine. However, formaldehyde can be toxic when exposed to other regions of the body. Therefore, the use of formaldehyde as an antiseptic agent requires a method for selective delivery to the urinary tract. This can be accomplished by using a prodrug called methenamine:

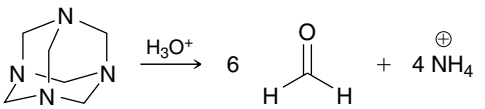


Methenamine

This compound is a nitrogen analogue of an acetal. That is, each carbon atom is connected to two nitrogen atoms, very much like an acetal in which a carbon atom is connected to two oxygen atoms. A carbon atom that is connected to two heteroatoms (O or N) can undergo acid-catalyzed hydrolysis:



Each of the carbon atoms in methenamine can be hydrolyzed, releasing formaldehyde:

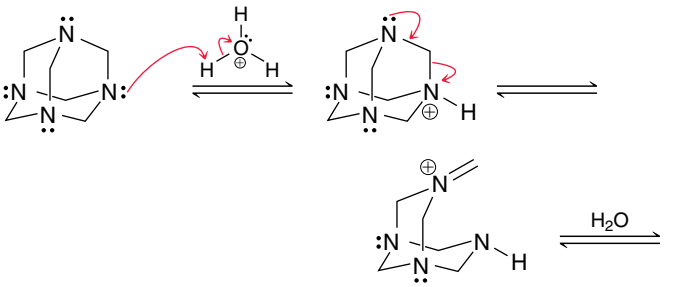


Formaldehyde

Methenamine is placed in special tablets that do not dissolve as they travel through the acidic environment of the stomach but do dissolve once they reach the basic environment of the intestinal tract. Methenamine is thereby released in the intestinal tract, where it is stable under basic conditions. Once it reaches the acidic environment of the urinary tract, methenamine is hydrolyzed, releasing formaldehyde, as shown above. In this way, methenamine is used as a prodrug that enables delivery of formaldehyde specifically to the urinary tract. This method prevents the systemic release of formaldehyde in other organs of the body where it would be toxic.

CONCEPTUAL CHECKPOINT

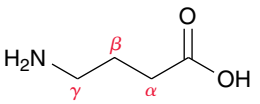
20.28 As shown above, methenamine is hydrolyzed in aqueous acid to produce formaldehyde and ammonia. Draw a mechanism showing formation of one molecule of formaldehyde (the remaining five molecules of formaldehyde are each released via a similar sequence of steps). The release of each molecule of formaldehyde is directly analogous to the hydrolysis of an acetal. To get you started, the first two steps are provided below:



Imines as Prodrugs

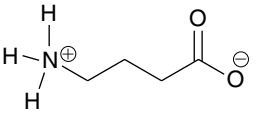
The imine moiety is used in the development of many prodrugs. Here we will explore one such example.

The compound below, γ-aminobutyric acid, is an important neurotransmitter:

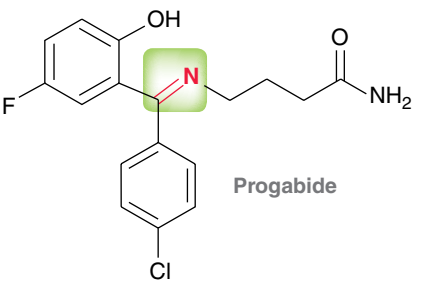


γ-aminobutyric acid

A deficiency of this compound can cause convulsions. Administering γ-aminobutyric acid directly to a patient is not an effective treatment, because the compound does not readily cross the blood-brain barrier. Why not? At physiological pH, the amino group is protonated and the carboxylic acid moiety is deprotonated:



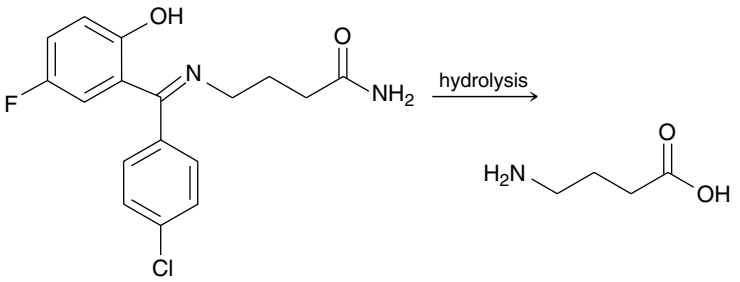
The compound exists primarily in this ionic form, which cannot cross the nonpolar environment of the blood-brain barrier. Progabide is a prodrug derivative used to treat patients who exhibit the symptoms of a deficiency of γ-aminobutyric acid:



Progabide

The carboxylic acid has been converted to an amide, and the amino group has been converted into an imine (highlighted). At physiological pH, this compound exists primarily as a neutral compound (uncharged), and it can therefore cross the blood-brain bar-

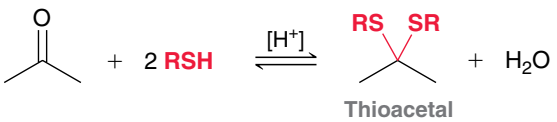
rier. Once in the brain, it is converted to γ-aminobutyric acid via hydrolysis of the imine and amide moieties:



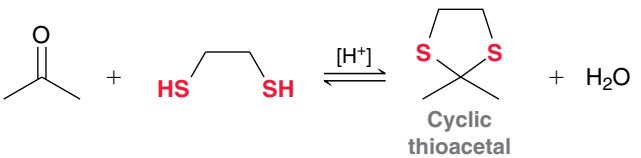
Progabide is just one example in which the imine moiety has been used in the development of a prodrug.

20.8 Sulfur Nucleophiles

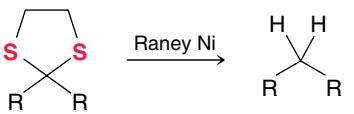
In acidic conditions, an aldehyde or ketone will react with two equivalents of a thiol to form a **thioacetal:**



The mechanism of this transformation is directly analogous to acetal formation, with sulfur atoms taking the place of oxygen atoms. If a compound with two SH groups is used, a cyclic thioacetal is formed:

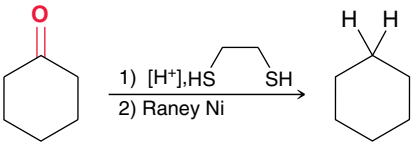


When treated with Raney nickel, thioacetals undergo **desulfurization,** yielding an alkane:



Raney Ni is a spongy form of nickel that has adsorbed hydrogen atoms. It is these hydrogen atoms that ultimately replace the sulfur atoms, although a discussion of the mechanism for desulfurization is beyond the scope of this text.

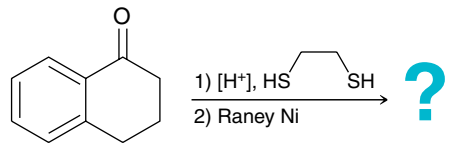
The reactions above provide us with another two-step method for the reduction of a ketone:

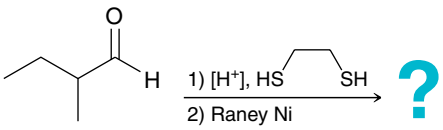


This method involves formation of the thioacetal followed by desulfurization with Raney nickel. It is the third method we have encountered for achieving this type of transformation. The other two methods are the Clemmensen reduction (Section 19.6) and the Wolff-Kishner reduction (Section 20.6).

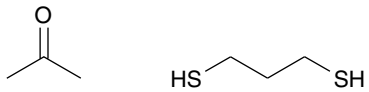
CONCEPTUAL CHECKPOINT

20.29 Predict the major product for each reaction below:

(a) 

(b) 

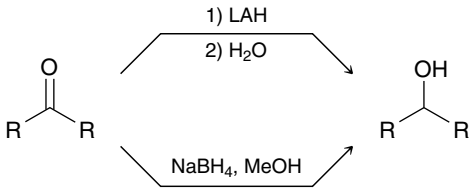
20.30 Draw the structure of the cyclic compound that is produced when acetone is treated with 1,3-propanedithiol in the presence of an acid catalyst.



Acetone 1,3-propanedithiol

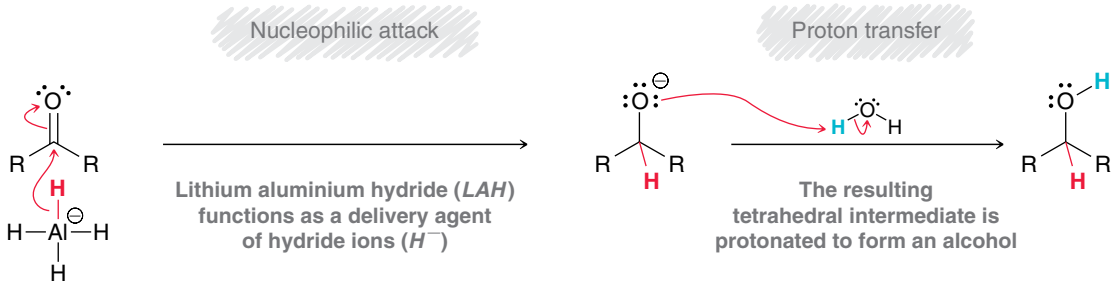
20.9 Hydrogen Nucleophiles

When treated with a hydride reducing agent, such as LAH or sodium borohydride ($NaBH_4$), aldehydes and ketones are reduced to alcohols:



These reactions were discussed in Section 13.4, and we saw that LAH and $NaBH_4$ both function as delivery agents of hydride (H^-). The precise mechanism of action for these reagents has been heavily investigated and is somewhat complex. Nevertheless, the simplified version shown in Mechanism 20.9 will be sufficient for our purposes.

MECHANISM 20.9 THE REDUCTION OF KETONES OR ALDEHYDES WITH HYDRIDE AGENTS



In the first step of the mechanism, the reducing agent delivers a hydride ion, which attacks the carbonyl group, producing a tetrahedral intermediate. This intermediate is then treated with a proton source to yield the product. This simplified mechanism does not take into account many important observations, such as the role of the lithium cation (Li^+). For example, when

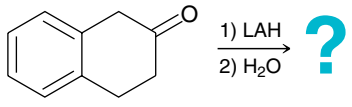
LOOKING BACK
Hydride cannot function as a leaving group because it is too strongly basic. (See Section 7.8.)

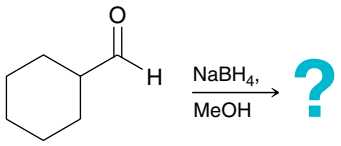
12-crown-4 is added to the reaction mixture, the lithium ions are solvated (as described in Section 14.4), and reduction does not occur. Clearly, the lithium cation plays a pivotal role in the mechanism. However, a full treatment of the mechanism of hydride reducing agents is beyond the scope of this text, and the simplified version above will suffice.

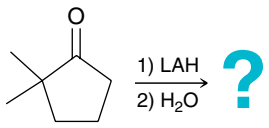
The reduction of a carbonyl group with LAH or $NaBH_4$ is not a reversible process, because hydride does not function as a leaving group. Notice that the mechanism above employs one-way arrows (rather than equilibrium arrows) to signify that the reverse process is insignificant.

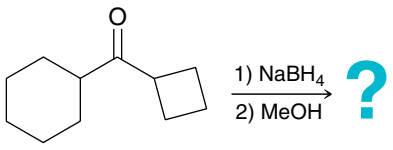
CONCEPTUAL CHECKPOINT

20.31 Predict the major product for each of the following reactions:

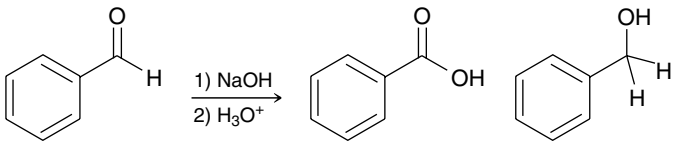
(a) 

(b) 

(c) 

(d) 

20.32 When 2 moles of benzaldehyde are treated with sodium hydroxide, a reaction occurs in which 1 mole of benzaldehyde is oxidized (giving benzoic acid) while the other mole of benzaldehyde is reduced (giving benzyl alcohol):



This reaction, called the Cannizzaro reaction, is believed to occur via the following mechanism: A hydroxide ion serves as a nucleophile to attack the carbonyl group of benzaldehyde, generating a tetrahedral intermediate. This tetrahedral intermediate then functions as a hydride reducing agent by delivering a hydride ion to another molecule of benzaldehyde. In this way, one molecule is reduced while the other is oxidized.

(a) Using the explanation above, draw the mechanism of the Cannizzaro reaction.

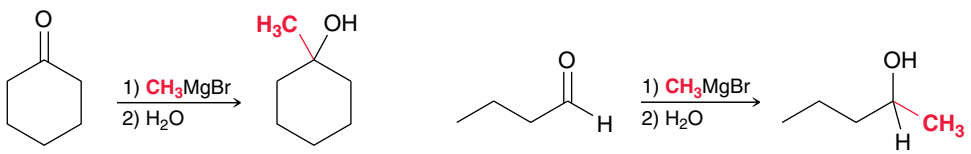
(b) What is the function of H_3O^+ in the second step?

(c) Water alone is not sufficient to accomplish the function of the second step. Explain.

20.10 Carbon Nucleophiles

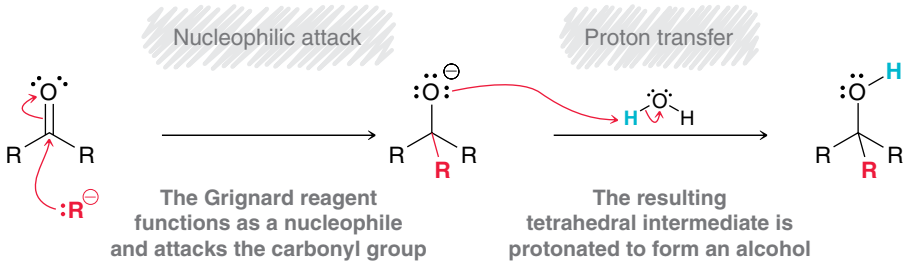
Grignard Reagents

When treated with a Grignard reagent, aldehydes and ketones are converted into alcohols, accompanied by the formation of a new C–C bond:



Grignard reactions were discussed in more detail in Section 13.6. The precise mechanism of action for these reagents has been heavily investigated and is fairly complex. The simplified version shown in Mechanism 20.10 will be sufficient for our purposes.

MECHANISM 20.10 THE REACTION BETWEEN A GRIGNARD REAGENT AND A KETONE OR ALDEHYDE



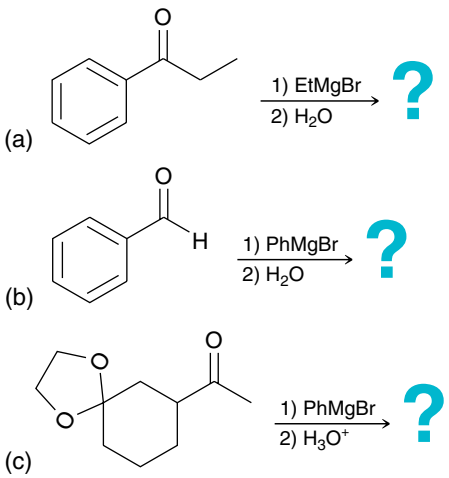
LOOKING BACK

Carbanions rarely function as leaving groups because they are generally strongly basic. (See Section 7.8.)

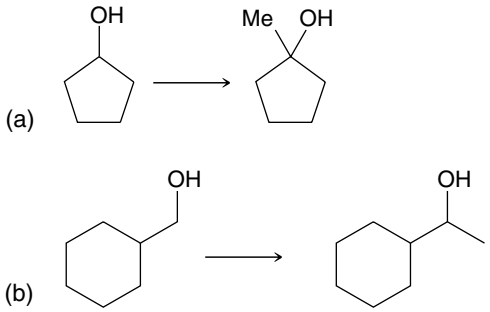
Grignard reactions are not reversible because carbanions generally do not function as leaving groups. Notice that the mechanism above employs one-way arrows (rather than equilibrium arrows) to signify that the reverse process is insignificant.

CONCEPTUAL CHECKPOINT

20.33 Predict the major product of each reaction below:



20.34 Identify the reagents necessary to accomplish each of the transformations below:



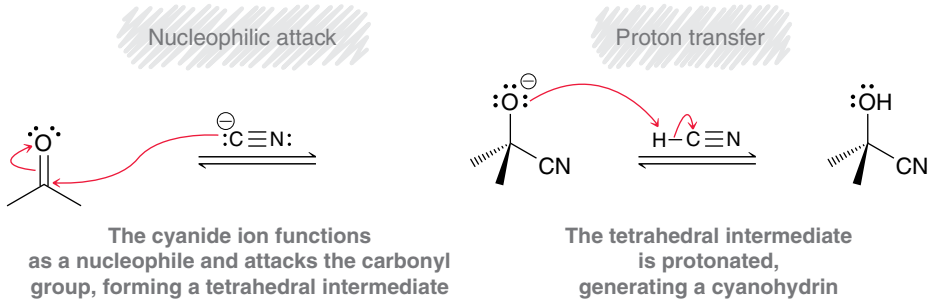
Cyannohydrin Formation

When treated with hydrogen cyanide (HCN), aldehydes and ketones are converted into **cyanohydrins,** which are characterized by the presence of a cyano group and a hydroxyl group connected to the same carbon atom:

A cyanohydrin

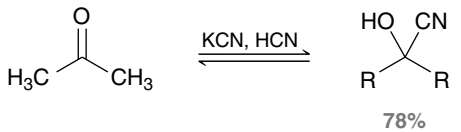
This reaction was studied extensively by Arthur Lapworth (University of Manchester) and was found to occur more rapidly in mildly basic conditions. In the presence of a catalytic amount of base, a small amount of hydrogen cyanide is deprotonated to give cyanide ions, which catalyze the reaction (Mechanism 20.11).

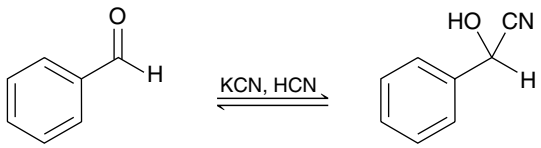
MECHANISM 20.11 CYANOHYDRIN FORMATION



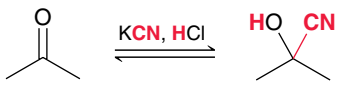
In the first step, a cyanide ion attacks the carbonyl to produce a tetrahedral intermediate. This intermediate then abstracts a proton from HCN, regenerating a cyanide ion. In this way, cyanide functions as a catalyst for the addition of HCN to the carbonyl group.

Rather than using a catalytic amount of base to form cyanide ions, the reaction can simply be performed in a mixture of HCN and cyanide ions (from KCN). The process is reversible, and the yield of products is therefore determined by equilibrium concentrations. For most aldehydes and unhindered ketones, the equilibrium favors formation of the cyanohydrin:

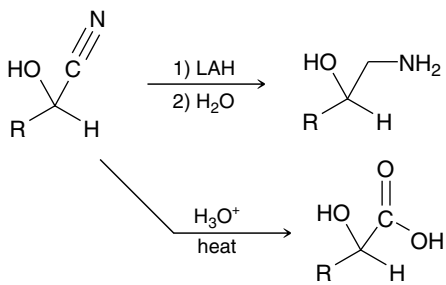




HCN is a liquid at room temperature and is extremely hazardous to handle because it is highly toxic and volatile (b.p. = 26°C). To avoid the dangers associated with handling HCN, cyanohydrins can also be prepared by treating a ketone or aldehyde with potassium cyanide and an alternate source of protons, such as HCl:



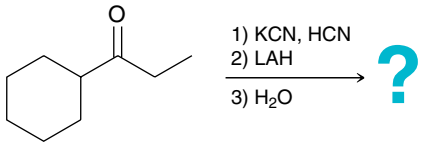
Cyanohydrins are useful in syntheses, because the cyano group can be further treated to yield a range of products. Two examples are shown below:

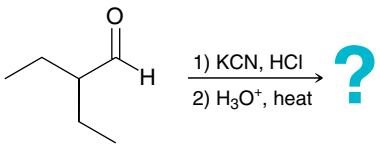


In the first example, the cyano group is reduced to an amino group. In the second example, the cyano group is hydrolyzed to give a carboxylic acid. Both of these reactions and their mechanisms will be explored in more detail in the next chapter.

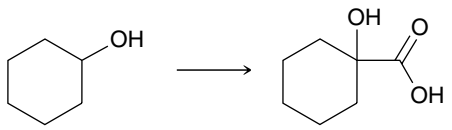
CONCEPTUAL CHECKPOINT

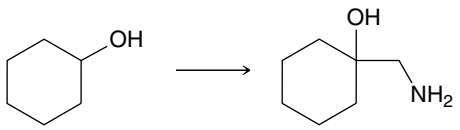
20.35 Predict the major product for each reaction below:

(a) 

(b) 

20.36 Identify the reagents necessary to accomplish each of the transformations below:

(a) 

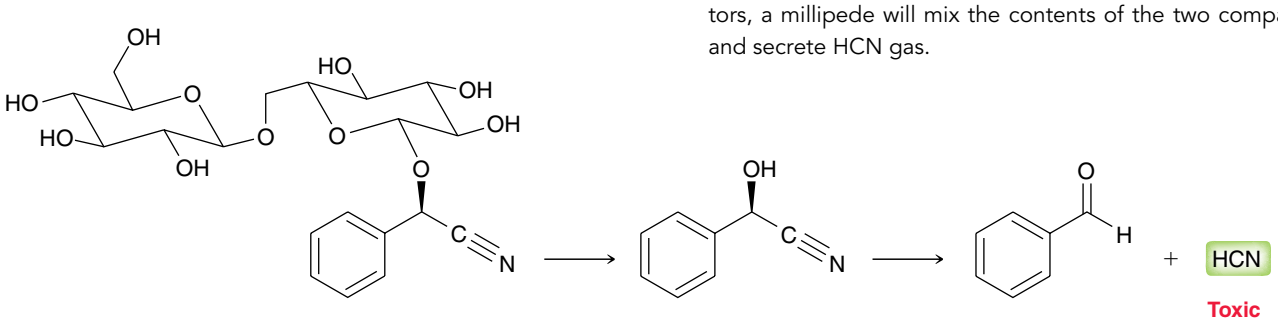
(b) 

PRACTICALLYSPEAKING

Cyanohydrin Derivatives in Nature

Amygdalin is a naturally occurring compound found in the pits of apricots, wild cherries, and peaches.

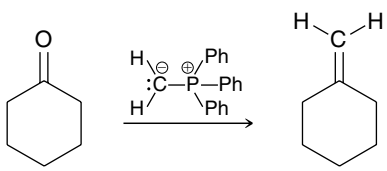
If ingested, this compound is metabolized to produce mandelonitrile, a cyanohydrin, which is converted by enzymes into benzaldehyde and HCN gas, a toxic compound:



This last step (generation of HCN gas) is used as a defense mechanism by many species of millipedes. The millipedes manufacture and store mandelonitrile, and in a separate compartment, they store enzymes that are capable of catalyzing the conversion of mandelonitrile into benzaldehyde and HCN. To ward off predators, a millipede will mix the contents of the two compartments and secrete HCN gas.

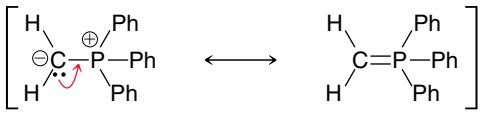
Wittig Reaction

Georg Wittig, a German chemist, was awarded the 1979 Nobel Prize in Chemistry for his work with phosphorous compounds and his discovery of a reaction with enormous synthetic utility. Below is an example of this reaction, called the **Wittig reaction** (pronounced Vittig):



This reaction can be used to convert a ketone into an alkene by forming a new C–C bond at the location of the carbonyl moiety. The phosphorus-containing reagent that accomplishes this transformation is called a **phosphorane,** and it belongs to a larger class of compounds called **ylides.** An ylide is a compound with two oppositely charged atoms adjacent to each

other. The phosphorane above exhibits a negative charge on the carbon atom and a positive charge on the phosphorous atom. This ylide does, in fact, have a resonance structure that is free of any charges:

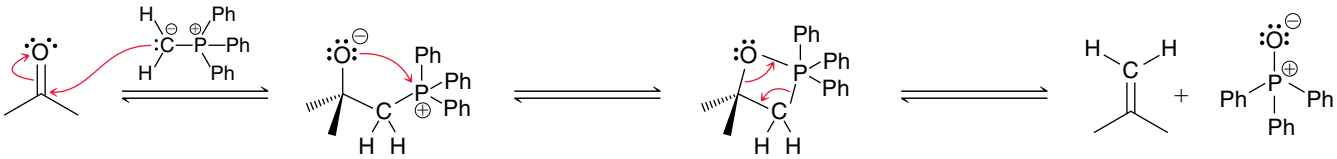


However, this resonance structure (with a C═P double bond) does not contribute much character to the overall resonance hybrid, because the *p* orbitals on C and P are vastly different in size and do not effectively overlap. A similar argument was used in describing S═O bonds in the previous chapter (Section 19.3). Despite this fact, the phosphorus ylide above, also called a **Wittig reagent,** is often drawn using either of the resonance structures shown above.

A mechanism for the Wittig reaction is shown in Mechanism 20.12.

MECHANISM 20.12 THE WITTIG REACTION

Nucleophilic attack | Nucleophilic attack | Rearrangement



A Betaine | An Oxaphosphetane

The Wittig reagent functions as a nucleophile and attacks the carbonyl group, forming a tetrahedral intermediate

A lone pair on the oxygen atom functions as a nucleophile and attacks the phosphorus atom in an intramolecular attack

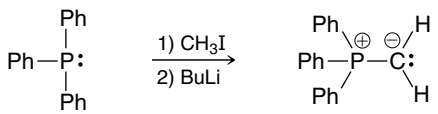
The oxaphosphetane decomposes to produce an alkene and triphenylphosphine oxide

BY THE WAY

Experimental evidence suggests that the intermediate betaine is only formed in limited cases. In other cases, it appears that the Wittig reagent may react with the carbonyl compound in a [2+2] cycloaddition process, directly generating the oxaphosphetane. The mechanism for this reaction is still under investigation.

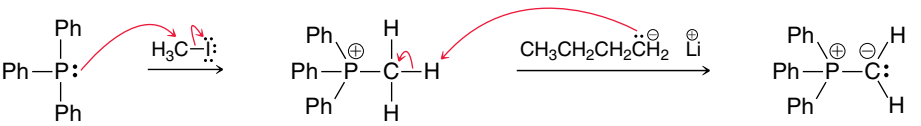
The Wittig reagent is a carbanion and can attack the carbonyl group in the first step of the mechanism, generating an intermediate called a **betaine** (pronounced "bay-tuh-een"). A betaine is a neutral compound with two oppositely charged atoms that are not adjacent to each other. The negatively charged oxygen atom then attacks the positively charged phosphorous atom in an intramolecular nucleophilic attack, generating an **oxaphosphetane.** This compound then rearranges to give the alkene product.

Wittig reagents are easily prepared by treating triphenylphosphine with an alkyl halide followed by a strong base:



Triphenylphosphine | Wittig reagent

The mechanism of formation for Wittig reagents involves an S_N2 reaction followed by deprotonation:



Triphenylphosphine

Since the first step is an S_N2 process, the regular restrictions of S_N2 processes apply. Specifically, primary alkyl halides will react more readily than secondary alkyl halides, and tertiary alkyl halides cannot be used. The Wittig reaction is useful for preparing mono-, di-, or trisubstituted alkenes. Tetrasubstituted alkenes are more difficult to prepare due to steric hindrance in the transition states.

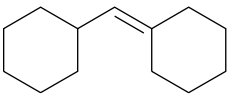
The following exercise illustrates how to choose the reagents for a Wittig reaction.

SKILLBUILDER

20.6 PLANNING AN ALKENE SYNTHESIS WITH A WITTIG REACTION

LEARN the skill

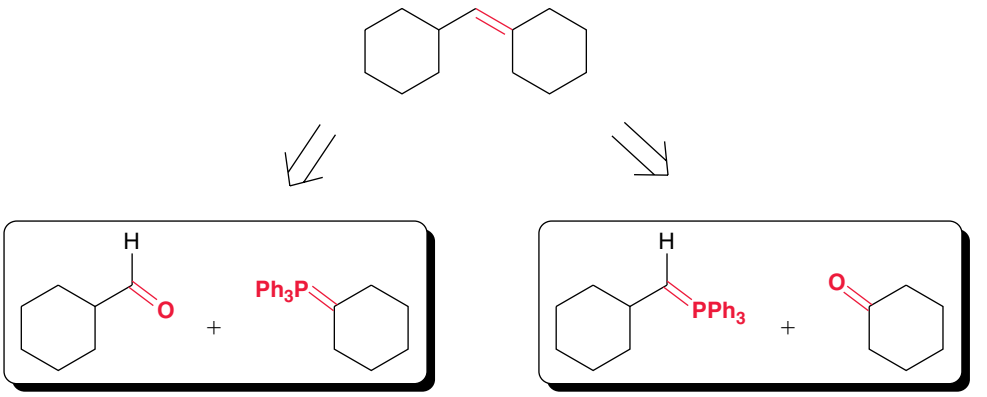
Identify the reagents necessary to prepare the compound below using a Wittig reaction:



SOLUTION

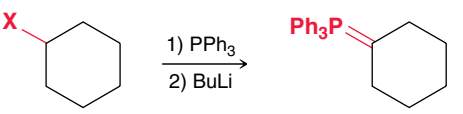
Begin by focusing on the two carbon atoms of the double bond. One carbon atom must have been a carbonyl group, while the other must have been a Wittig reagent. This gives two potential routes to explore:

STEP 1
Using a retrosynthetic analysis, determine the two possible sets of reactants that could be used to form the C=C bond.



Method 1 Method 2

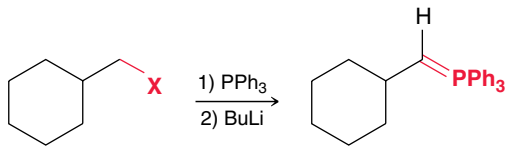
Let's compare these two methods by focusing on the Wittig reagent in each case. Recall that the Wittig reagent is prepared by an S_N2 process, and we therefore must consider steric factors during its preparation. Method 1 requires the use of a secondary alkyl halide:



2° Alkyl halide

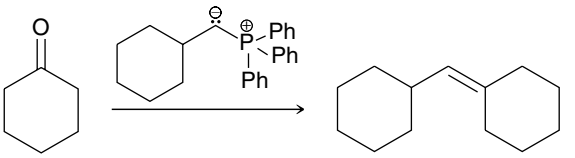
but method 2 requires the use of a primary alkyl halide:

STEP 2
Consider how you would make each possible Wittig reagent, and determine which method involves the less substituted alkyl halide.



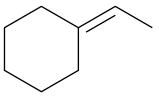
1°
Alkyl halide

Method 2 is likely to be more efficient, because a primary alkyl halide will undergo S_N2 more rapidly than a secondary alkyl halide. Therefore, the following would be the preferred synthesis:

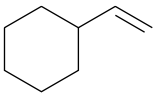


PRACTICE the skill

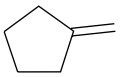
20.37 Identify the reagents necessary to prepare each of the following compounds using a Wittig reaction:



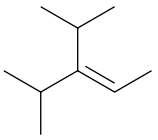
(a)



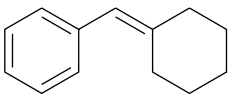
(b)



(c)



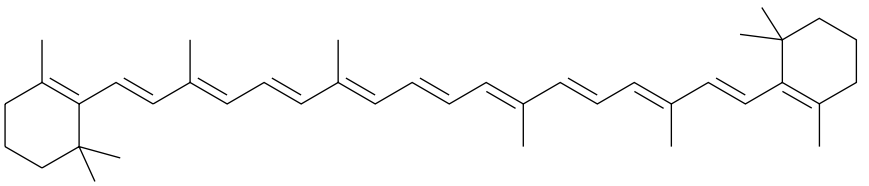
(d)



(e)

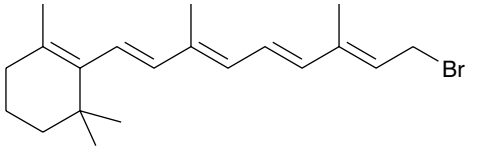
APPLY the skill

20.38 Consider the structure of beta-carotene, mentioned earlier in this chapter:

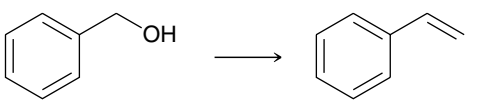


***β*-carotene**

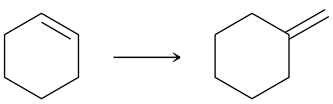
Design a synthesis of beta carotene using the compound below as your only source of carbon atoms:



20.39 Identify the reagents necessary to accomplish each of the transformations below:



(a)

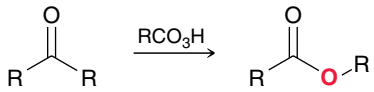


(b)

need more **PRACTICE?** **Try Problems 20.51–20.53**

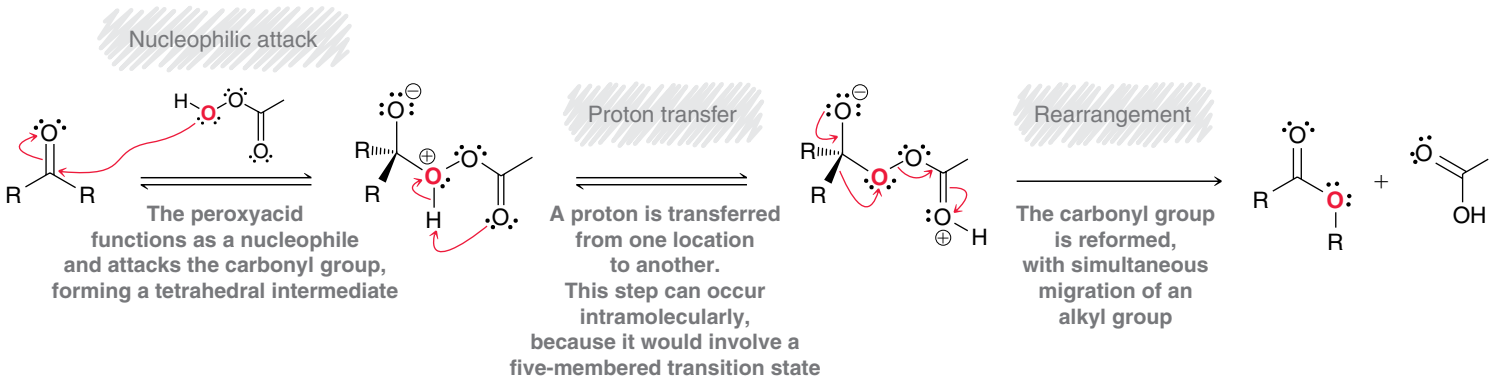
20.11 Baeyer-Villiger Oxidation of Aldehydes and Ketones

When treated with a peroxy acid, ketones can be converted into esters via the insertion of an oxygen atom:



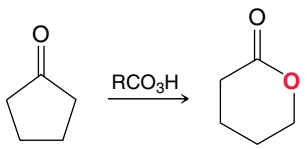
This reaction, discovered by Adolf von Baeyer and Victor Villiger in 1899, is called the **Baeyer-Villiger oxidation.** This process is believed to proceed via Mechanism 20.13.

MECHANISM 20.13 THE BAEYER-VILLIGER OXIDATION



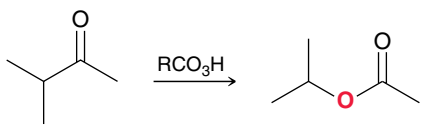
The peroxy acid attacks the carbonyl group of the ketone, giving a tetrahedral intermediate that then undergoes an intramolecular proton transfer (or two successive intermolecular proton transfers). Finally, the C═O double bond is re-formed by migration of an R group. This rearrangement produces the ester.

In much the same way, treatment of a cyclic ketone with a peroxy acid yields a cyclic ester, or **lactone.**



A lactone

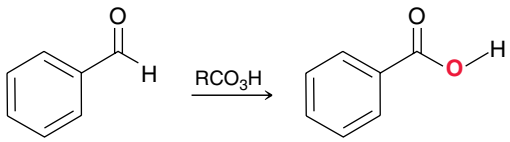
When an unsymmetrical ketone is treated with a peroxy acid, formation of the ester is regioselective; for example:



In this case, the oxygen atom is inserted on the left side of the carbonyl group, rather than the right side. This occurs because the isopropyl group migrates more rapidly than the methyl group during the rearrangement step of the mechanism. The migration rates of different groups, or **migratory aptitude,** can be summarized as follows:

$$H > 3° > 2°, Ph > 1° > methyl$$

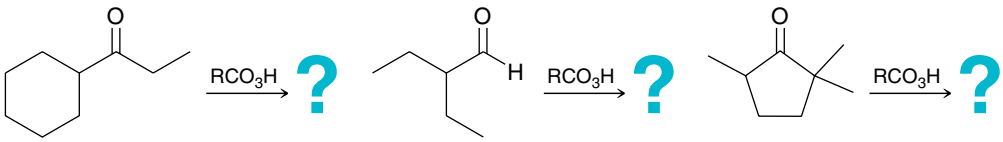
A hydrogen atom will migrate more rapidly than a tertiary alkyl group, which will migrate more rapidly than a secondary alkyl group or phenyl group. Below is one more example that illustrates this concept:



In this example, the oxygen atom is inserted on the right side of the carbonyl, because the hydrogen atom exhibits a greater migratory aptitude than the phenyl group.

CONCEPTUAL CHECKPOINT

20.40 Predict the major product of each reaction below:



(a) (b) (c)

20.12 Synthesis Strategies

Recall from Chapter 12 that there are two main questions to ask when approaching a synthesis problem:

1. *Is there any change in the carbon skeleton?*
2. *Is there any change in the functional group?*

Let's focus on these issues separately, beginning with functional groups.

Functional Group Interconversion

In previous chapters, we learned how to interconvert many different functional groups (Figure 20.9). The reactions in this chapter expand the playing field by opening up the frontier of aldehydes and ketones. You should be able to fill in the reagents for each transformation in Figure 20.9. If you are having trouble, refer to Figure 13.13 for help. Then, you should be able to make a list of the various products than can be made from aldehydes and ketones and identify the required reagents in each case.

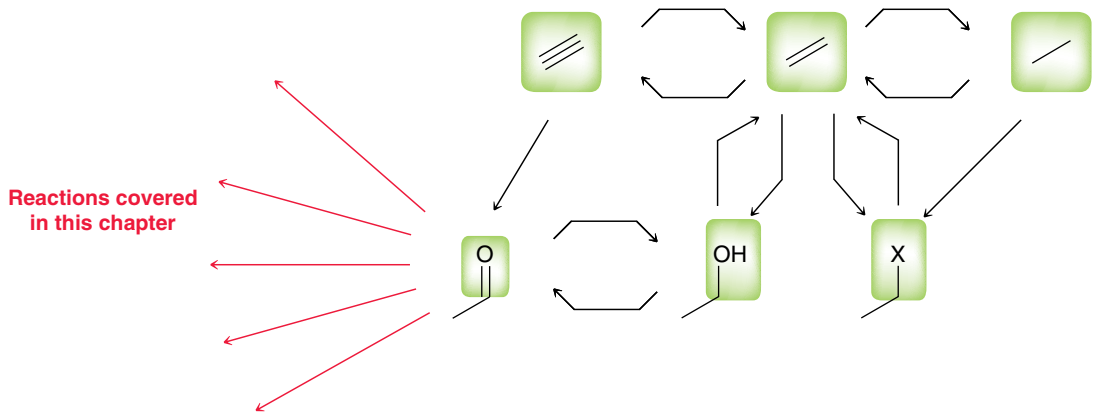
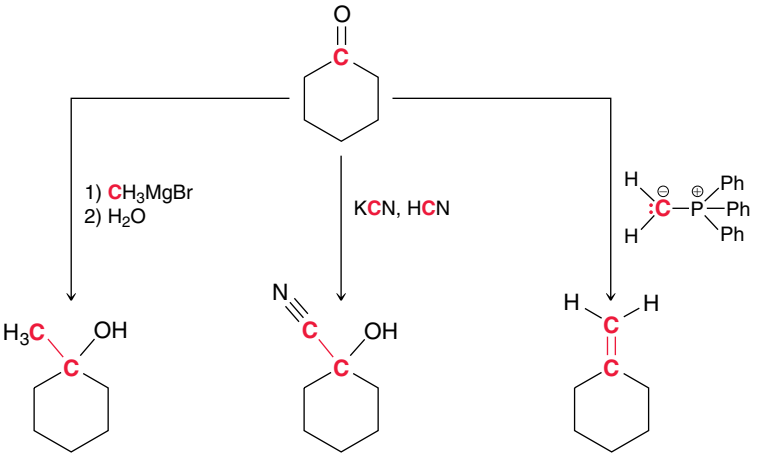


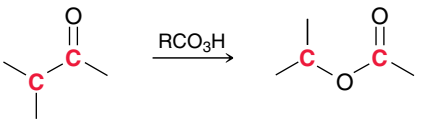
FIGURE 20.9
Functional groups that can be interconverted using reactions that we have learned thus far.

Reactions Involving a Change in Carbon Skeleton

In this chapter, we have seen three C–C bond-forming reactions: (1) a Grignard reaction, (2) cyanohydrin formation, and (3) a Wittig reaction:



We have only seen one C–C bond-breaking reaction: the Baeyer-Villiger oxidation:



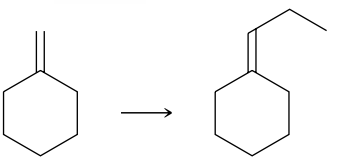
These four reactions should be added to your list of reactions that can change a carbon skeleton. Let's get some practice using these reactions.

SKILLBUILDER

20.7 PROPOSING A SYNTHESIS

LEARN the skill

Propose an efficient synthesis for the following transformation:



SOLUTION

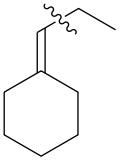
STEP 1
Inspect whether there is a change in the carbon skeleton and/or a change in the identity or location of the functional groups.

Always begin a synthesis problem by asking the following two questions:

1. *Is there any change in the carbon skeleton?* Yes. The product has two additional carbon atoms.

2. *Is there any change in the functional groups?* No. Both the starting material and the product have a double bond in the exact same location. If we destroy the double bond in the process of adding the two carbon atoms, we will need to make sure that we do so in such a way that we can restore the double bond.

Now let's consider how we might install the additional two-carbon atoms. The following C–C bond is the one that needs to be made:

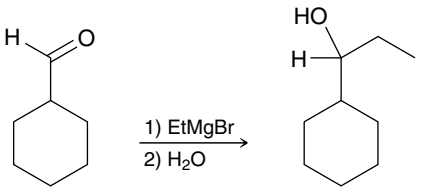


In this chapter, we have seen three C–C bond-forming reactions. Let's consider each one as a possibility.

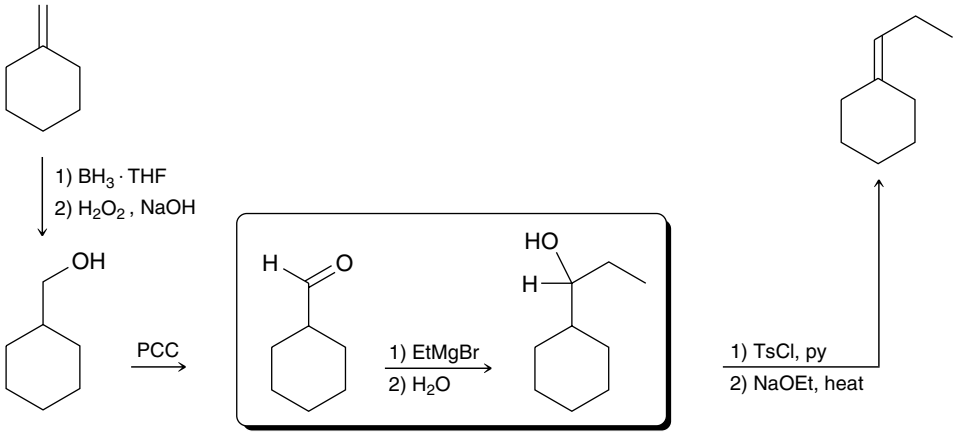
STEP 2
When there is a change in the carbon skeleton, consider all of the C–C bond-forming reactions and all of the C–C bond-breaking reactions that you have learned so far.

We can immediately rule out cyanohydrin formation, as that process installs only one carbon atom, not two. So let's consider forming the C–C bond with either a Grignard reaction or a Wittig reaction.

A Grignard reagent won't attack a C═C double bond, so using a Grignard reaction would require first converting the C═C double bond into a functional group that can be attacked by a Grignard reagent, such as a carbonyl group:



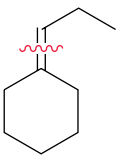
This reaction can indeed be used to form the crucial C–C bond. To use this method of C–C bond formation, we must first form the necessary aldehyde, then perform the Grignard reaction, and then finally restore the double bond in its proper location. This can be accomplished with the following reagents:



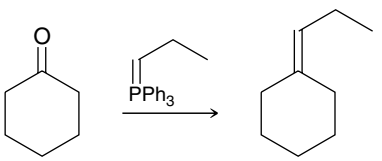
C—C bond-forming reaction

This provides us with a four-step procedure, and this answer is certainly reasonable.

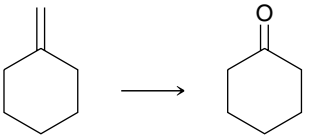
Let's now explore the possibility of proposing a synthesis with a Wittig reaction. Recall that a Wittig reaction can be used to form a C═C bond, so we focus on formation of this bond:



This bond can be formed if we start with a ketone and use the following Wittig reagent:

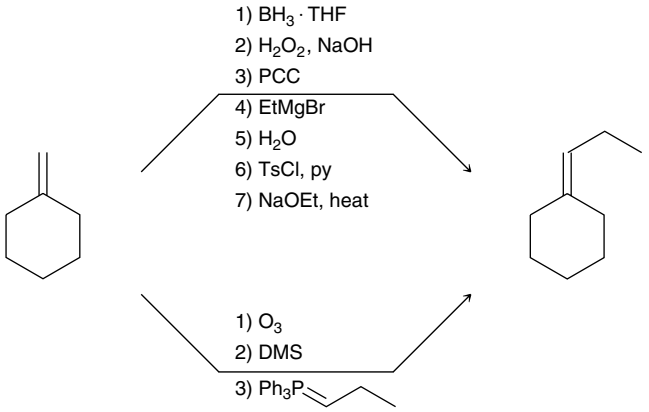


To use this reaction, we must first form the necessary ketone from the starting alkene:

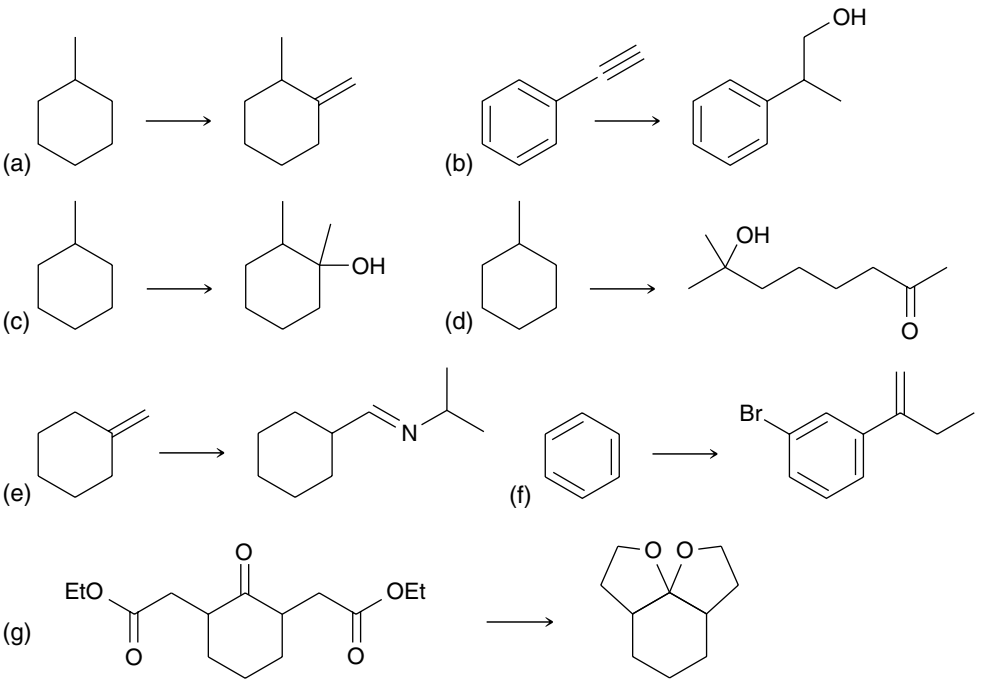


This can be accomplished with ozonolysis. This gives a two-step procedure for accomplishing the desired transformation: ozonolysis followed by a Wittig reaction. This approach is different than our first answer. In this approach, we are not attaching a two-carbon chain, but rather, we are first expelling a carbon atom and then attaching a three-carbon chain.

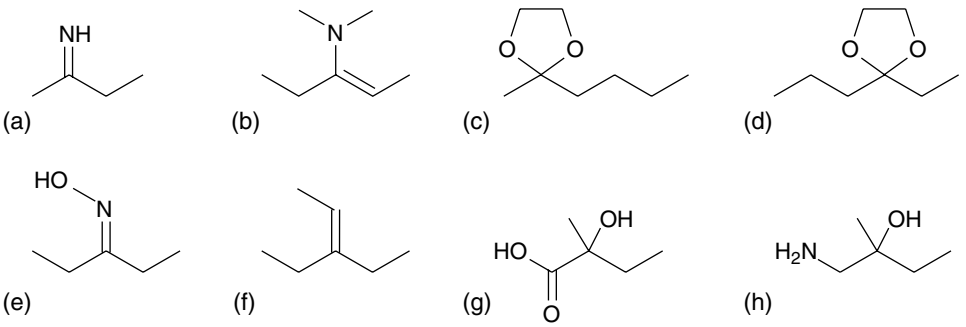
In summary, we have discovered two plausible methods. Both methods are correct answers to this problem, but the method employing the Wittig reaction is likely to be more efficient, because it requires fewer steps.



PRACTICE the skill **20.41** Propose an efficient synthesis for each of the following transformations:



APPLY the skill **20.42** Using any compounds of your choosing, identify a method for preparing each of the following compounds. *Your only limitation is that the compounds you use can have no more than two carbon atoms.* For purposes of counting carbon atoms, you may ignore the phenyl groups of a Wittig reagent. That is, you are permitted to use Wittig reagents.



need more **PRACTICE?** **Try Problems 20.55, 20.58, 20.67–20.69, 20.71, 20.75**

20.13 Spectroscopic Analysis of Aldehydes and Ketones

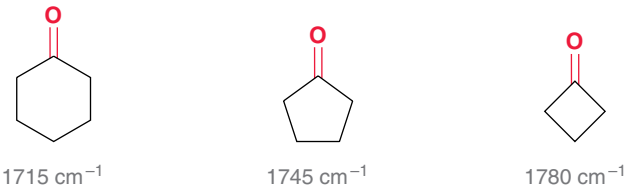
Aldehydes and ketones exhibit several characteristic signals in their infrared (IR) and nuclear magnetic resonance (NMR) spectra. We will now summarize these characteristic signals.

IR Signals

The carbonyl group produces a strong signal in an IR spectrum, generally around 1715 or 1720 cm^{-1}. However, a conjugated carbonyl will produce a signal at a lower wavenumber as a result of electron delocalization via resonance effects:

LOOKING BACK
For an explanation of this effect, see Section 15.3.

Ring strain has the opposite effect on a carbonyl group. That is, increasing ring strain tends to increase the wavenumber of absorption:



Aldehydes generally exhibit one or two signals (C–H stretching) between 2700 and 2850 cm^{-1} (Figure 20.10).

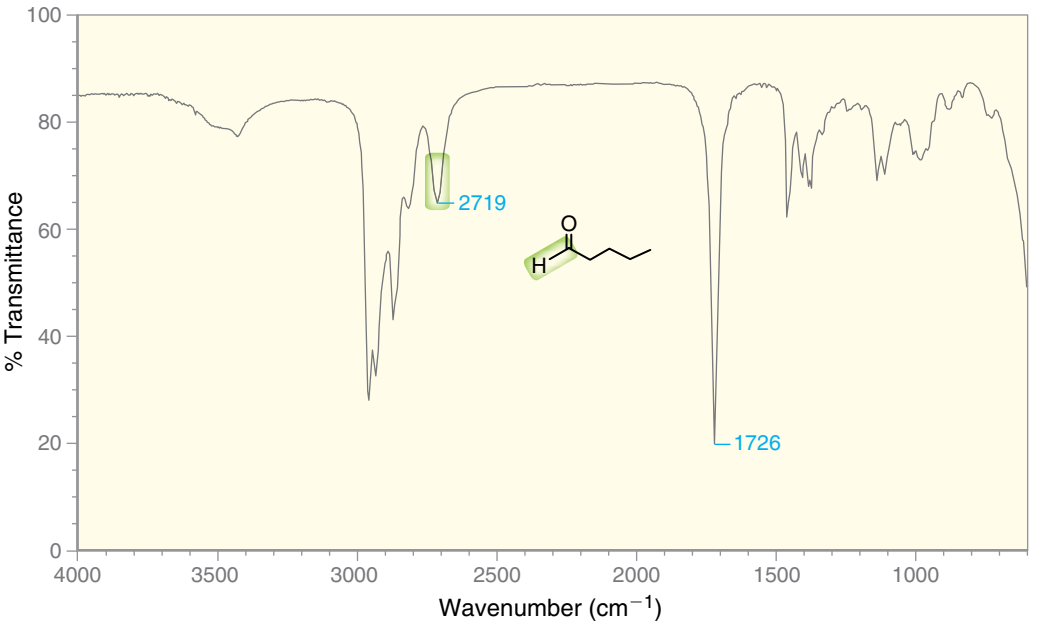
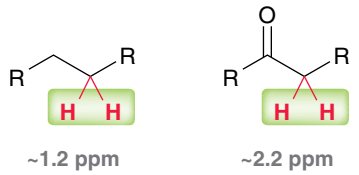


FIGURE 20.10
An IR spectrum of an aldehyde.

^{1}H NMR Signals

In a ^{1}H NMR spectrum, the carbonyl group itself does not produce a signal. However, it has a pronounced effect on the chemical shift of neighboring protons. We saw in Section 16.5 that a carbonyl group adds +1 ppm to the chemical shift of its neighbors:



Aldehydic protons generally produce signals around 10 ppm. These signals can usually be identified with relative ease, because very few signals appear that far downfield in a ^{1}H NMR spectrum (Figure 20.11).

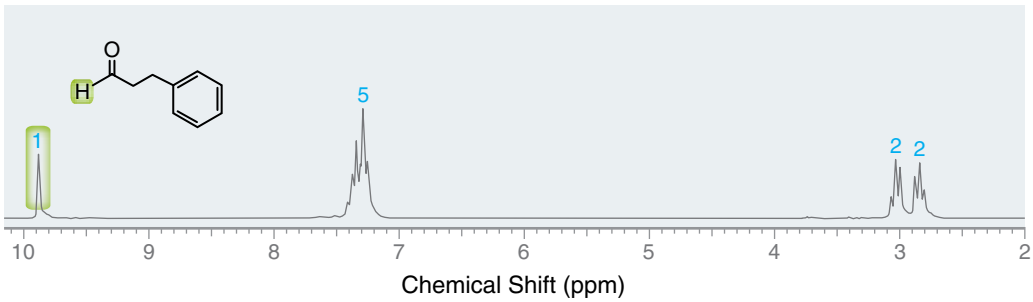


FIGURE 20.11
A ^{1}H NMR spectrum of an aldehyde.

^{13}C NMR Signals

In a ^{13}C NMR spectrum, the carbon atom of a carbonyl group will generally produce a weak signal near 200 ppm. This signal can often be identified with relative ease, because very few signals appear that far downfield in a ^{13}C NMR spectrum (Figure 20.12).

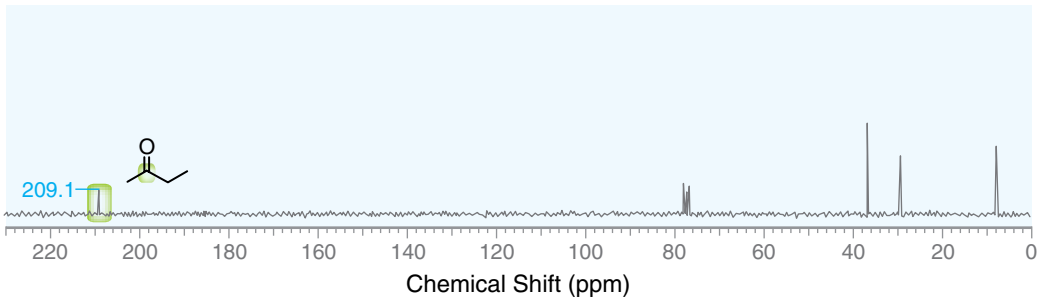
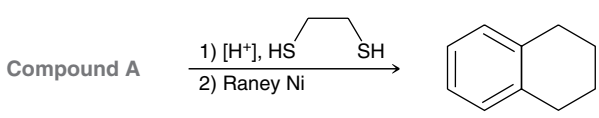


FIGURE 20.12
A ^{13}C NMR spectrum of a ketone.

CONCEPTUAL CHECKPOINT

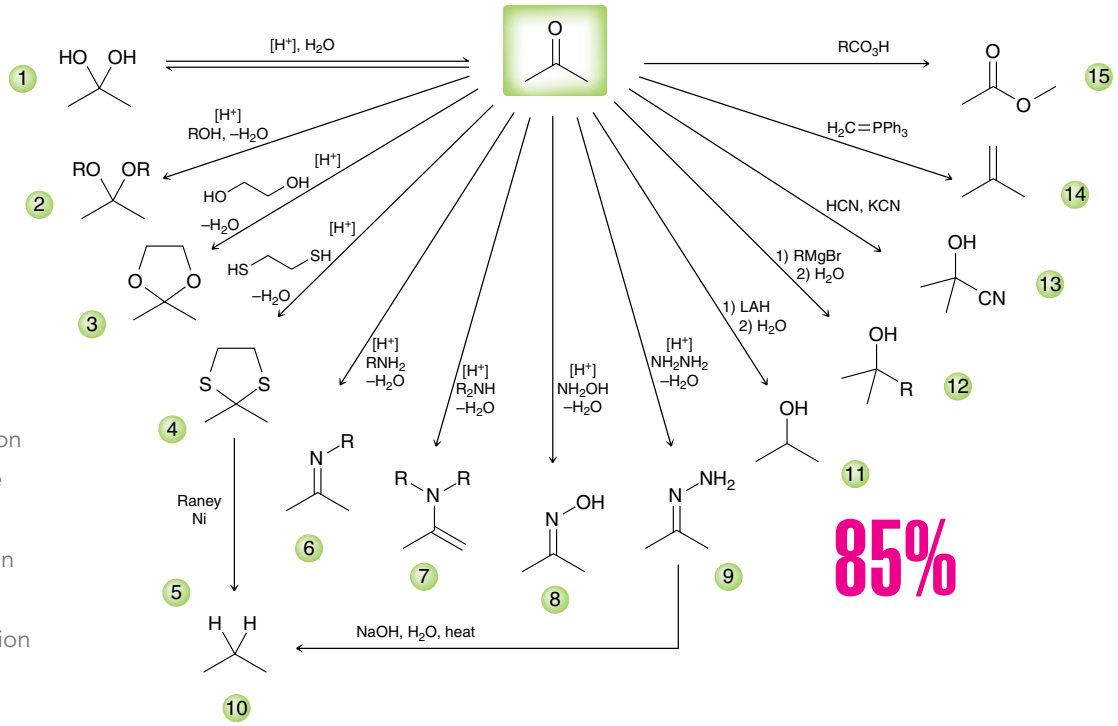
20.43 Compound A has molecular formula $C_{10}H_{10}O$ and exhibits a strong signal at 1720 cm^{-1} in its IR spectrum. Treatment with 1,2-ethanedithiol followed by Raney nickel affords the product shown below. Identify the structure of compound A.



REVIEW OF REACTIONS

SYNTHETICALLY USEFUL REACTIONS

1. Hydrate Formation
2. Acetal Formation
3. Cyclic Acetal Formation
4. Cyclic Thioacetol Formation
5. Desulfurization
6. Imine Formation
7. Enamine Formation
8. Oxime Formation
9. Hydrazone Formation
10. Wolff-Kishner Reduction
11. Reduction of a Ketone
12. Grignard Reaction
13. Cyanohydrin Formation
14. Wittig Reaction
15. Baeyer-Villiger Oxidation



REVIEW OF CONCEPTS AND VOCABULARY

SECTION 20.1

- Both aldehydes and ketones contain a **carbonyl group**, and both are common in nature and industry and occupy a central role in organic chemistry.

SECTION 20.2

- The suffix "-al" indicates an aldehydic group, and the suffix "-one" is used for ketones.
- In naming aldehydes and ketones, locants should be assigned so as to give the carbonyl group the lowest number possible.

SECTION 20.3

- Aldehydes can be prepared via oxidation of primary alcohols, ozonolysis of alkenes, or hydroboration-oxidation of terminal alkynes.
- Ketones can be prepared via oxidation of secondary alcohols, ozonolysis of alkenes, acid-catalyzed hydration of terminal alkynes, or Friedel-Crafts acylation.

SECTION 20.4

- The electrophilicity of a carbonyl group derives from resonance effects as well as inductive effects.
- Aldehydes are more reactive than ketones as a result of steric effects and electronic effects.
- A general mechanism for nucleophilic addition under basic conditions involves two steps:
  1. Nucleophilic attack to generate a **tetrahedral intermediate**.
  2. Proton transfer
- The position of equilibrium is dependent on the ability of the nucleophile to function as a leaving group.

SECTION 20.5

- When an aldehyde or ketone is treated with water, the carbonyl group can be converted into a **hydrate**. The equilibrium generally favors the carbonyl group, except in the case of very simple aldehydes, or ketones with strong electron-withdrawing substituents.
- In acidic conditions, an aldehyde or ketone will react with two molecules of alcohol to form an **acetal**.
- In the presence of an acid, the carbonyl group is protonated to form a very powerful electrophile.
- The mechanism for acetal formation can be divided into two parts:
  1. The first three steps produce a **hemiacetal**.
  2. The last four steps convert the hemiacetal to an acetal.
- For many simple aldehydes, the equilibrium favors formation of the acetal; however, for most ketones, the equilibrium favors reactants rather than products.
- An aldehyde or ketone will react with one molecule of a diol to form a cyclic acetal.
- The reversibility of acetal formation enables acetals to function as protecting groups for ketones or aldehydes. Acetals are stable under strongly basic conditions.
- Hemiacetals are generally difficult to isolate unless they are cyclic.

SECTION 20.6

- In acidic conditions, an aldehyde or ketone will react with a primary amine to form an **imine**.
- The first three steps in imine formation produce a **carbinolamine**, and the last three steps convert the carbinolamine into an imine.
- Many different compounds of the form RNH_2 will react with aldehydes and ketones; for example:
  1. When hydrazine is used as a nucleophile (NH_2NH_2), a **hydrazone** is formed.
  2. When hydroxylamine is used as a nucleophile (NH_2OH), an **oxime** is formed.
- In acidic conditions, an aldehyde or ketone will react with a secondary amine to form an **enamine**. The mechanism of enamine formation is identical to the mechanism of imine formation except for the last step.
- In the **Wolff-Kishner reduction**, a hydrazone is reduced to an alkane under strongly basic conditions.

SECTION 20.7

- In acidic conditions, all reagents, intermediates, and leaving groups either should be neutral (no charge) or should bear one positive charge.
- **Hydrolysis** of acetals, imines, and enamines under acidic conditions produces ketones or aldehydes.

SECTION 20.8

- In acidic conditions, an aldehyde or ketone will react with two equivalents of a thiol to form a **thioacetal**. If a compound with two SH groups is used, a cyclic thioacetal is formed.
- When treated with Raney nickel, thioacetals undergo **desulfurization** to yield a methylene group.

SECTION 20.9

- When treated with a hydride reducing agent, such as lithium aluminum hydride (LAH) or sodium borohydride ($NaBH_4$), aldehydes and ketones are reduced to alcohols.
- The reduction of a carbonyl group with LAH or $NaBH_4$ is not a reversible process, because hydride does not function as a leaving group.

SECTION 20.10

- When treated with a Grignard agent, aldehydes and ketones are converted into alcohols, accompanied by the formation of a new C–C bond.
- Grignard reactions are not reversible, because carbanions do not function as leaving groups.
- When treated with hydrogen cyanide (HCN), aldehydes and ketones are converted into **cyanohydrins**. For most aldehydes and unhindered ketones, the equilibrium favors formation of the cyanohydrin.
- The **Wittig reaction** can be used to convert a ketone to an alkene. The **Wittig reagent** that accomplishes this transformation is called a **phosphorane**, which belongs to a larger class of compounds called **ylides**.
- The mechanism of a Wittig reaction involves initial formation of a **betaine**, which undergoes an intramolecular nucleophilic attack, generating an **oxaphosphetane**. Rearrangement gives the product.
- Preparation of Wittig reagents involves an S_N2 reaction, and the regular restrictions of S_N2 processes apply.

SECTION 20.11

- A **Baeyer-Villiger oxidation** converts a ketone to an ester by inserting an oxygen atom next to the carbonyl group. Cyclic ketones produce cyclic esters called **lactones**.
- When an unsymmetrical ketone is treated with a peroxy acid, formation of the ester is regioselective, and the product is determined by the **migratory aptitude** of each group next to the carbonyl.

SECTION 20.12

- This chapter explored three C–C bond-forming reactions: (1) a Grignard reaction, (2) cyanohydrin formation, and (3) a Wittig reaction.
- This chapter explored only one C–C bond-breaking reaction: the Baeyer-Villiger oxidation.

SECTION 20.13

- Carbonyl groups produce a strong IR signal around 1715 cm^{-1}. A conjugated carbonyl produces a signal at a lower wavenumber, while ring strain increases the wavenumber of absorption.
- Aldehydic C–H bonds exhibit one or two signals between 2700 and 2850 cm^{-1}.
- In a ^1H NMR spectrum, a carbonyl group adds +1 ppm to the chemical shift of its neighbors, and an aldehydic proton produces a signal around 10 ppm.
- In a ^{13}C NMR spectrum, a carbonyl group produces a weak signal near 200 ppm.

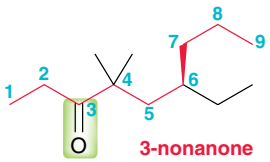
KEY TERMINOLOGY

acetal •••
Baeyer-Villiger oxidation •••
betaine •••
carbinolamine •••
carbonyl group •••
cyanohydrins •••
desulfurization •••
enamine •••
hemiacetal •••
hydrate •••
hydrazone •••
hydrolysis •••
imine •••
lactone •••
migratory aptitude •••
oxaphosphetane •••
oxime •••
phosphorane •••
tetrahedral intermediate •••
thioacetal •••
Wittig reaction •••
Wittig reagent •••
Wolff-Kishner reduction •••
ylide •••

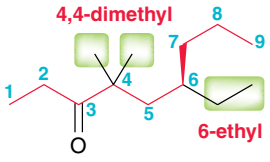
SKILLBUILDER REVIEW

20.1 NAMING ALDEHYDES AND KETONES

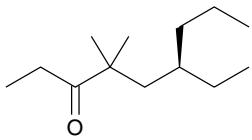
STEP 1 Choose the longest chain containing the carbonyl group, and number the chain starting from the end closest to the carbonyl group.



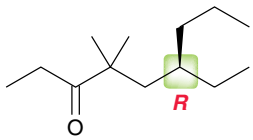
STEP 2 AND 3 Identify the substituents, and assign locants.



STEP 4 Assemble the substituents alphabetically.



STEP 5 Assign the configuration of any chirality center.

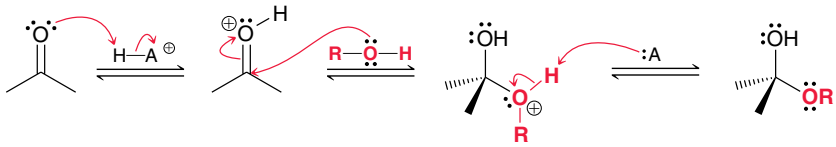


Try problems 20.1–20.4, 20.44–20.49

20.2 DRAWING THE MECHANISM OF ACETAL FORMATION

STEP 1 Draw the three steps necessary for hemiacetal formation.

Proton transfer | Nucleophilic attack | Proton transfer

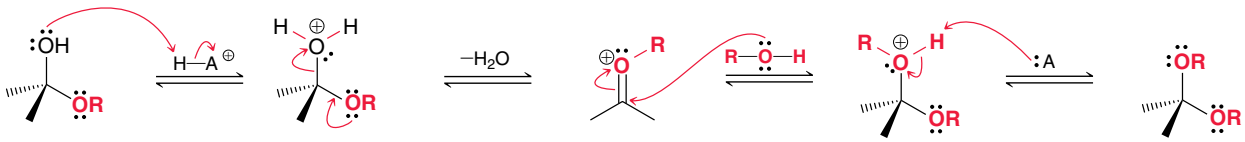


COMMENTS

- Every step has two curved arrows. Draw them precisely.
- Do not forget the charges.
- Draw each step separately.

STEP 2 Draw the four steps that convert the hemiacetal into an acetal.

Proton transfer | Loss of a leaving group | Nucleophilic attack | Proton transfer

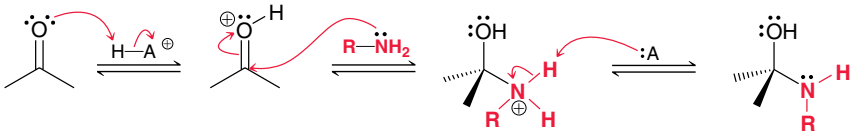


Try Problems 20.8–20.10, 20.57, 20.62, 20.67

20.3 DRAWING THE MECHANISM OF IMINE FORMATION

STEP 1 Draw the three steps necessary for carbinolamine formation.

Proton transfer | Nucleophilic attack | Proton transfer

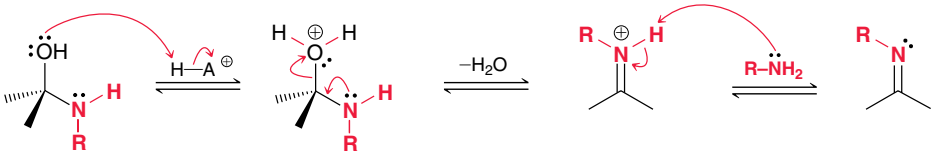


COMMENTS

- Each part of the mechanism begins with a proton transfer and ends with a proton transfer.
- Every step has two curved arrows. Make sure to draw them precisely.
- Do not forget the positive charges. There should be no negative charges.
- Draw each step separately, following the precise order of steps.

STEP 2 Draw the three steps that convert the carbinolamine into an imine.

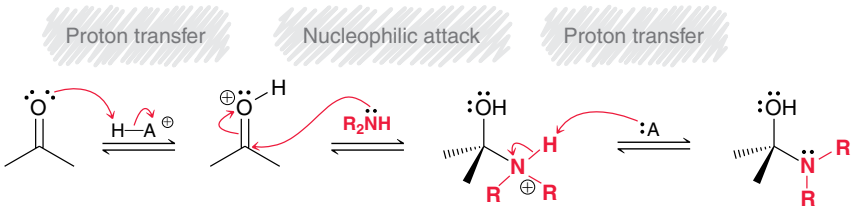
Proton transfer | Loss of a leaving group | Proton transfer



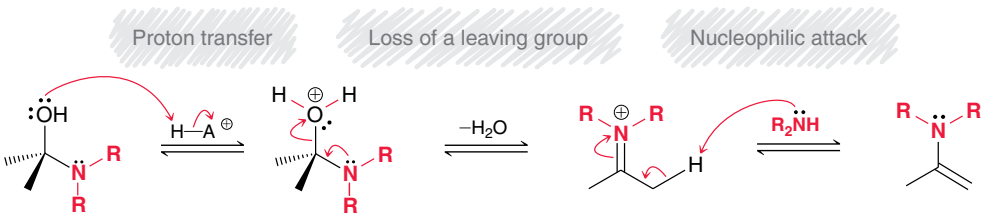
Try Problems 20.15–20.18, 20.72, 20.86

20.4 DRAWING THE MECHANISM OF ENAMINE FORMATION

STEP 1 Draw the three steps necessary for carbinolamine formation.



STEP 2 Draw the three steps that convert the carbinolamine into an enamine.



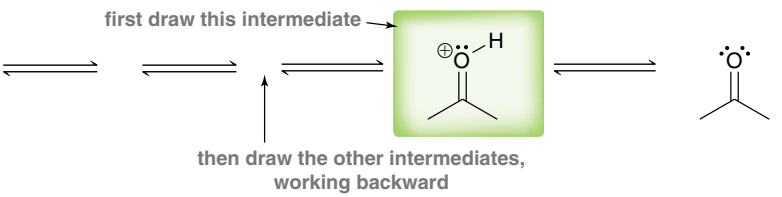
COMMENTS

- Each part of the mechanism begins with a proton transfer and ends with a proton transfer.
- Every step has two curved arrows. Make sure to draw them precisely.
- Do not forget the positive charges. There should be no negative charges.
- Draw each step separately following the precise order of steps.

Try Problems 20.21–20.24, 20.72

20.5 DRAWING THE MECHANISM OF A HYDROLYSIS REACTION

STEP 1 Working backwards, draw all intermediates.



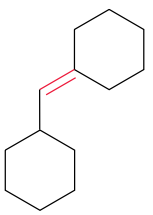
STEP 2

- After drawing all intermediates, then draw all reagents and curved arrows using the following rules:
- In acidic conditions, all reagents, intermediates, and leaving groups either should be neutral or should bear one positive charge.
- Use only those reagents that are already present.

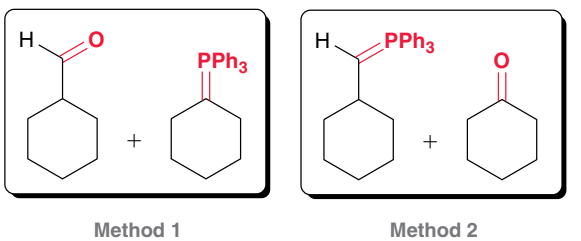
Try Problems 20.26, 20.27, 20.65

20.6 PLANNING AN ALKENE SYNTHESIS WITH A WITTIG REACTION

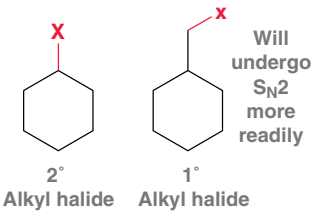
EXAMPLE Identify the reactants you would use to prepare this compound via a Wittig reaction.



STEP 1 Using a retrosynthetic analysis, determine the two possible sets of reactants that could be used to form the C=C bond.



STEP 2 Consider how you would make each possible Wittig reagent, and determine which method involves the less substituted alkyl halide.



Try Problems 20.37–20.39, 20.51–20.53

20.7 PROPOSING A SYNTHESIS

STEP 1 Begin by asking the following two questions:

1. Is there a change in the carbon skeleton?
2. Is there a change in the functional groups?

STEP 2 If there is a change in the carbon skeleton, consider all of the C–C bond-forming reactions and all of the C–C bond-breaking reactions that you have learned so far

C–C bond-forming reactions in this chapter

- Grignard reaction
- Cyanohydrin formation
- Witting reaction

C–C bond-breaking reactions in this chapter

- Baeyer-Villiger oxidation

CONSIDERATIONS

Remember that the desired product should be the major product of your proposed synthesis.

Make sure that the regiochemical outcome of each step is correct.

Always think backward (retrosynthetic analysis) as well as forward, and then try to bridge the gap.

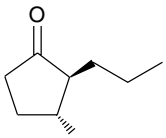
Most synthesis problems will have multiple correct answers. Do not feel that you have to find the "one" correct answer.

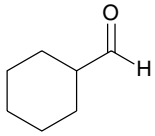
Try Problems 20.41, 20.42, 20.55, 20.58, 20.67–20.69, 20.71, 20.75

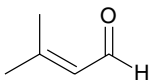
PRACTICE PROBLEMS

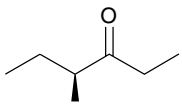
Note: Most of the Problems are available within **WileyPLUS**, an online teaching and learning solution.

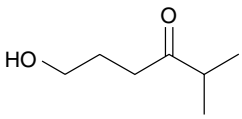
20.44 Provide a systematic (IUPAC) name for each of the following compounds:

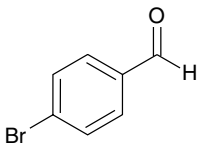
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

20.45 Draw the structure for each compound below:

(a) propanedial

(b) 4-phenylbutanal

(c) *(S)*-3-phenylbutanal

(d) 3,3,5,5-tetramethyl-4-heptanone

(e) *(R)*-3-hydroxypentanal

(f) meta-hydroxyacetophenone

(g) 2,4,6-trinitrobenzaldehyde

(h) tribromoacetaldehyde

(i) *(3R,4R)*-3,4-dihydroxy-2-pentanone

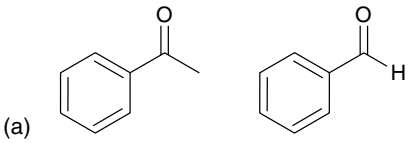
20.46 Draw all constitutionally isomeric aldehydes with molecular formula C_4H_8O, and provide a systematic (IUPAC) name for each isomer.

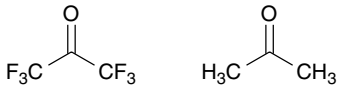
20.47 Draw all constitutionally isomeric aldehydes with molecular formula $C_5H_{10}O$, and provide a systematic (IUPAC) name for each isomer. Which of these isomers possesses a chirality center?

20.48 Draw all constitutionally isomeric ketones with molecular formula $C_6H_{12}O$, and provide a systematic (IUPAC) name for each isomer.

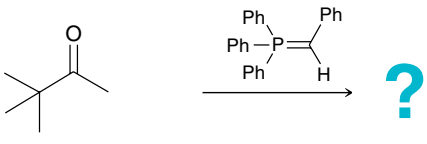
20.49 Explain why the IUPAC name of a compound will never end with the suffix "-1-one."

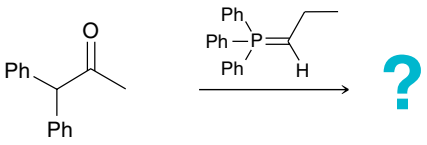
20.50 For each pair of the following compounds, identify which compound would be expected to react more rapidly with a nucleophile:

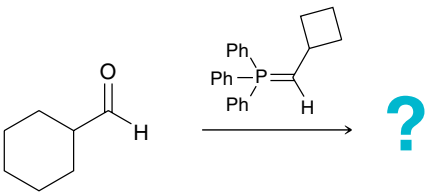
(a) 

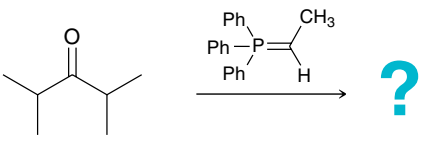
(b) 

20.51 Draw the products of each Wittig reaction below. If two stereoisomers are possible, draw both stereoisomers:

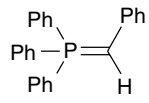
(a) 

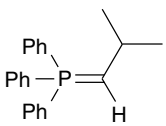
(b) 

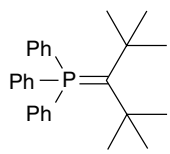
(c) 

(d) 

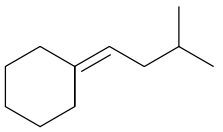
20.52 Draw the structure of the alkyl halide needed to prepare each of the following Wittig reagents, and then determine which Wittig reagent will be the most difficult to prepare. Explain your choice:

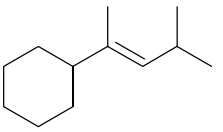
(a) 

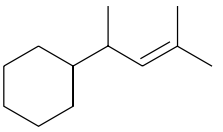
(b) 

(c) 

20.53 Show how a Wittig reaction can be used to prepare each of the following compounds. In each case, also show how the Wittig reagent would be prepared:

(a) 

(b) 

(c) 

20.54 Choose a Grignard reagent and a ketone that can be used to produce each of the following compounds:

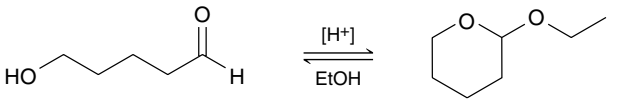
(a) 3-methyl-3-pentanol
(b) 1-ethylcyclohexanol
(c) triphenylmethanol
(d) 5-phenyl-5-nonanol

20.55 You are working in a laboratory, and you are given the task of converting cyclopentene into 1,5-pentanediol. Your first thought is simply to perform an ozonolysis followed by reduction with LAH, but your lab is not equipped for an ozonolysis reaction. Suggest an alternative method for converting cyclopentene into 1,5-pentanediol. For help, see Section 13.4 (reduction of esters to give alcohols).

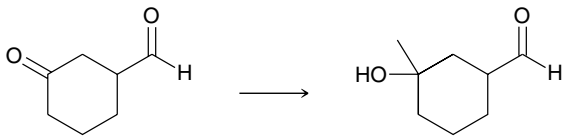
20.56 Predict the major product(s) from the treatment of acetone with the following compounds:

(a) $[H^+]$, NH_3 , $(-H_2O)$
(b) $[H^+]$, CH_3NH_2 , $(-H_2O)$
(c) $[H^+]$, excess EtOH, $(-H_2O)$
(d) $[H^+]$, $(CH_3)_2NH$, $(-H_2O)$
(e) $[H^+]$, NH_2NH_2 , $(-H_2O)$
(f) $[H^+]$, NH_2OH , $(-H_2O)$
(g) $NaBH_4$, MeOH
(h) MCPBA
(i) HCN, KCN
(j) EtMgBr followed by H_2O
(k) $(C_6H_5)_3P{=}CHCH_2CH_3$
(l) LAH followed by H_2O

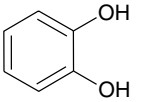
20.57 Propose a plausible mechanism for the following transformation:



20.58 Devise an efficient synthesis for the following transformation (recall that aldehydes are more reactive than ketones):

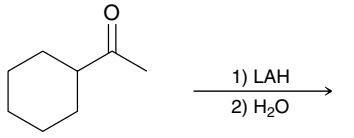


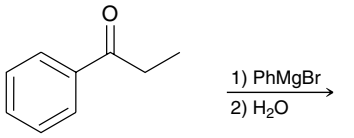
20.59 Treatment of catechol with formaldehyde in the presence of an acid catalyst produces a compound with molecular formula $C_7H_6O_2$. Draw the structure of this product.

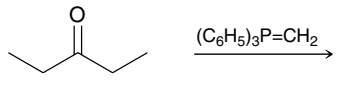


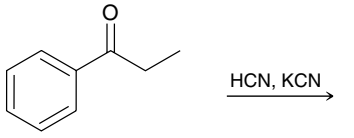
Catechol

20.60 Predict the major product(s) for each reaction below.

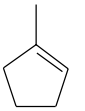
(a) 

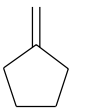
(b) 

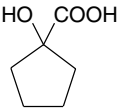
(c) 

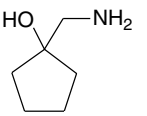
(d) 

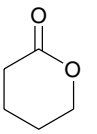
20.61 Starting with cyclopentanone and using any other reagents of your choosing, identify how you would prepare each of the following compounds:

(a) 

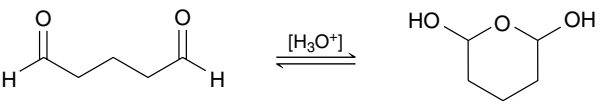
(b) 

(c) 

(d) 

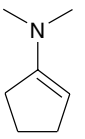
(e) 

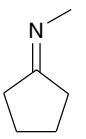
20.62 Glutaraldehyde is a germicidal agent that is sometimes used to sterilize medical equipment too sensitive to be heated in an autoclave. In mildly acidic conditions, glutaraldehyde exists in a cyclic form (below right). Draw a plausible mechanism for this transformation:

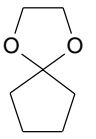


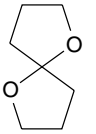
Glutaraldehyde

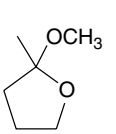
20.63 Predict the major product(s) obtained when each of the following compounds undergoes hydrolysis in the presence of H_3O^+:

(a) 

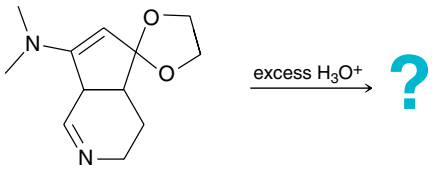
(b) 

(c) 

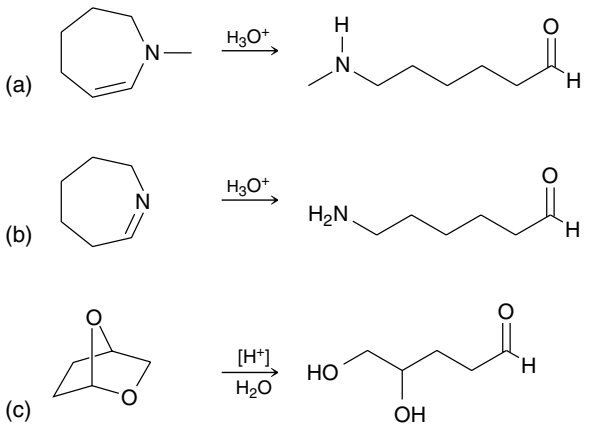
(d) 

(e) 

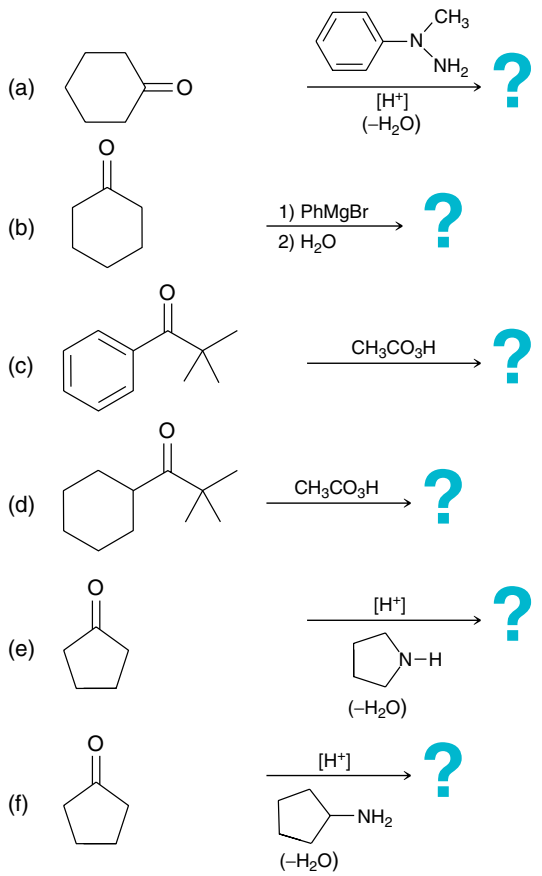
20.64 Identify all of the products formed when the compound below is treated with aqueous acid:

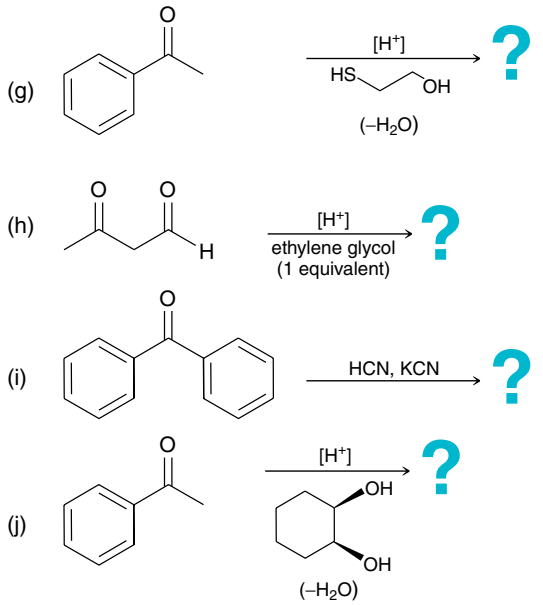


20.65 Draw a plausible mechanism for each of the following transformations:

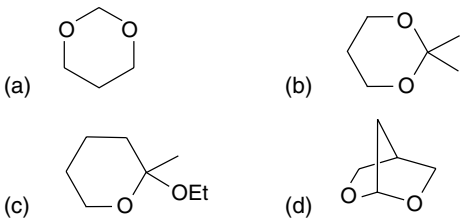


20.66 Predict the major product(s) for each of the following reactions:

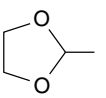




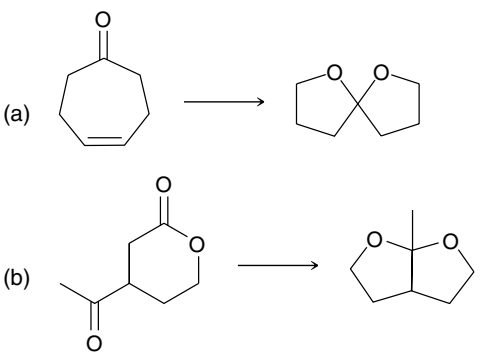
20.67 Identify the starting materials needed to make each of the following acetals:



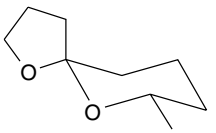
20.68 Using ethanol as your only source of carbon atoms, design a synthesis for the following compound:



20.69 Propose an efficient synthesis for each of the following transformations:

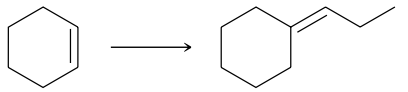


20.70 The compound below is believed to be a wasp pheromone. Draw the major product formed when this compound is hydrolyzed in aqueous acid:

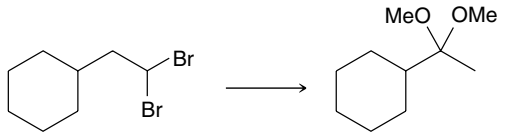


20.71 Propose an efficient synthesis for each of the following transformations:

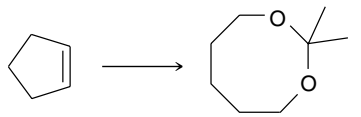
(a)



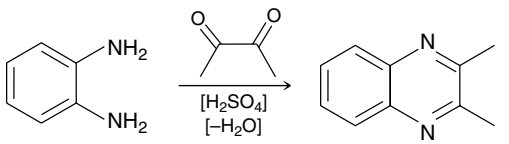
(b)



(c)

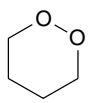


20.72 Draw a plausible mechanism for the following transformation:

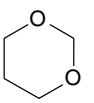


20.73 When cyclohexanone is treated with H_2O, an equilibrium is established between cyclohexanone and its hydrate. This equilibrium greatly favors the ketone, and only trace amounts of the hydrate can be detected. In contrast, when cyclopropanone is treated with H_2O, the resulting hydrate predominates at equilibrium. Suggest an explanation for this curious observation.

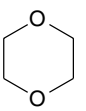
20.74 Consider the three constitutional isomers of dioxane ($C_4H_8O_2$):



1,2-dioxane



1,3-dioxane

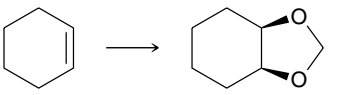


1,4-dioxane

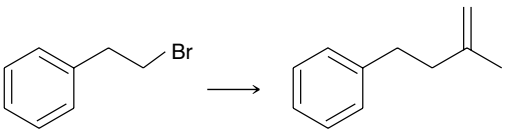
One of these constitutional isomers is stable under basic conditions as well as mildly acidic conditions and is therefore used as a common solvent. Another isomer is only stable under basic conditions but undergoes hydrolysis under mildly acidic conditions. The remaining isomer is extremely unstable and potentially explosive. Identify each isomer, and explain the properties of each compound.

20.75 Propose an efficient synthesis for each of the following transformations:

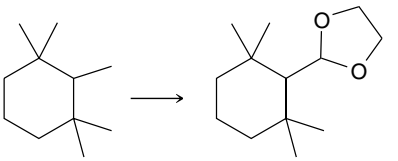
(a)



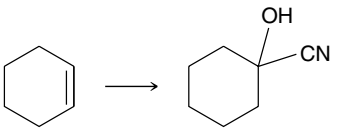
(b)



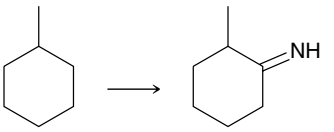
(c)



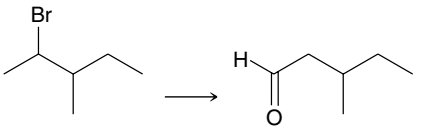
(d)



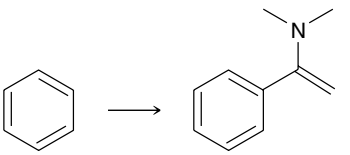
(e)



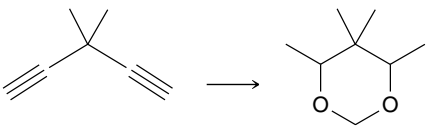
(f)



(g)



(h)



INTEGRATED PROBLEMS

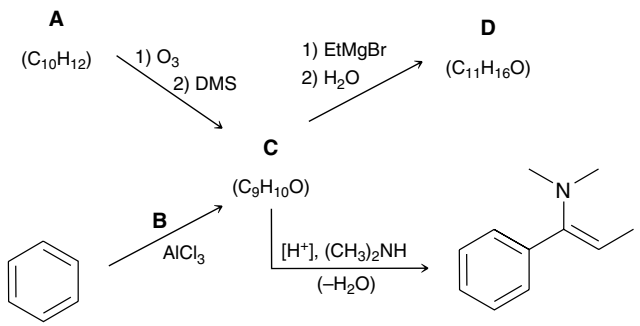
20.76 Compound A has molecular formula $C_7H_{14}O$ and reacts with sodium borohydride in methanol to form an alcohol. The ^1H NMR spectrum of compound A exhibits only two signals: a doublet (J = 12) and a septet (J = 2). Treating compound A with 1,2-ethanedithiol ($HSCH_2CH_2SH$) followed by Raney nickel gives compound B.

(a) How many signals will appear in the ^1H NMR spectrum of compound B?

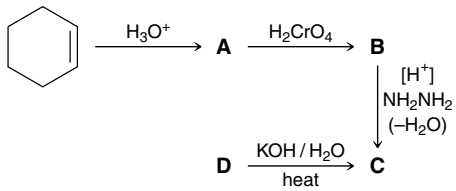
(b) How many signals will appear in the ^{13}C NMR spectrum of compound B?

(c) Describe how you could use IR spectroscopy to verify the conversion of compound A to compound B.

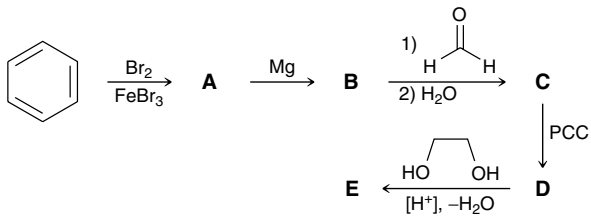
20.77 Using the information provided below, deduce the structures of compounds A, B, C, and D:



20.78 Identify the structures of compounds A to D below, and then identify the reagents that can be used to convert cyclohexene into compound D in just one step.



20.79 Identify the structures of compounds A to E below:

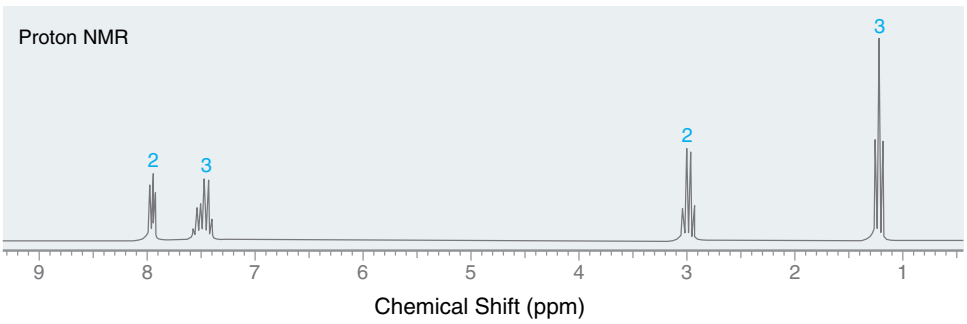


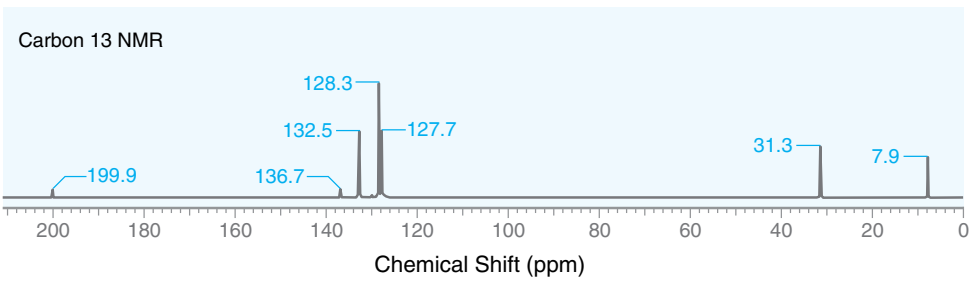
20.80 An aldehyde with molecular formula C_4H_6O exhibits an IR signal at 1715 cm^{-1}.

(a) Propose two possible structures that are consistent with this information.

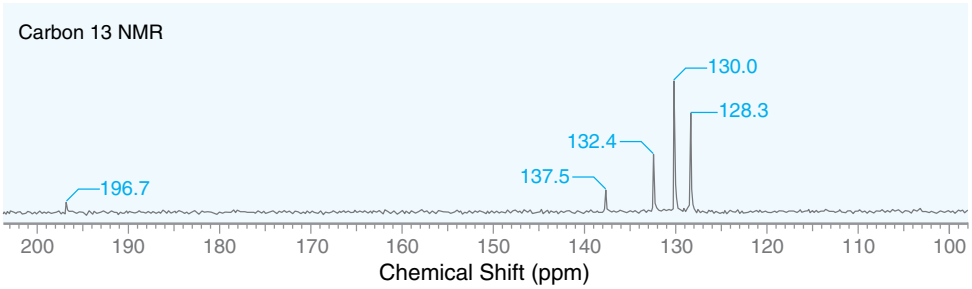
(b) Describe how you could use ^{13}C NMR spectroscopy to determine which of the two possible structures is correct.

20.81 A compound with molecular formula $C_9H_{10}O$ exhibits a strong signal at 1687 cm^{-1} in its IR spectrum. The ^1H and ^{13}C NMR spectra for this compound are shown below. Identify the structure of this compound.





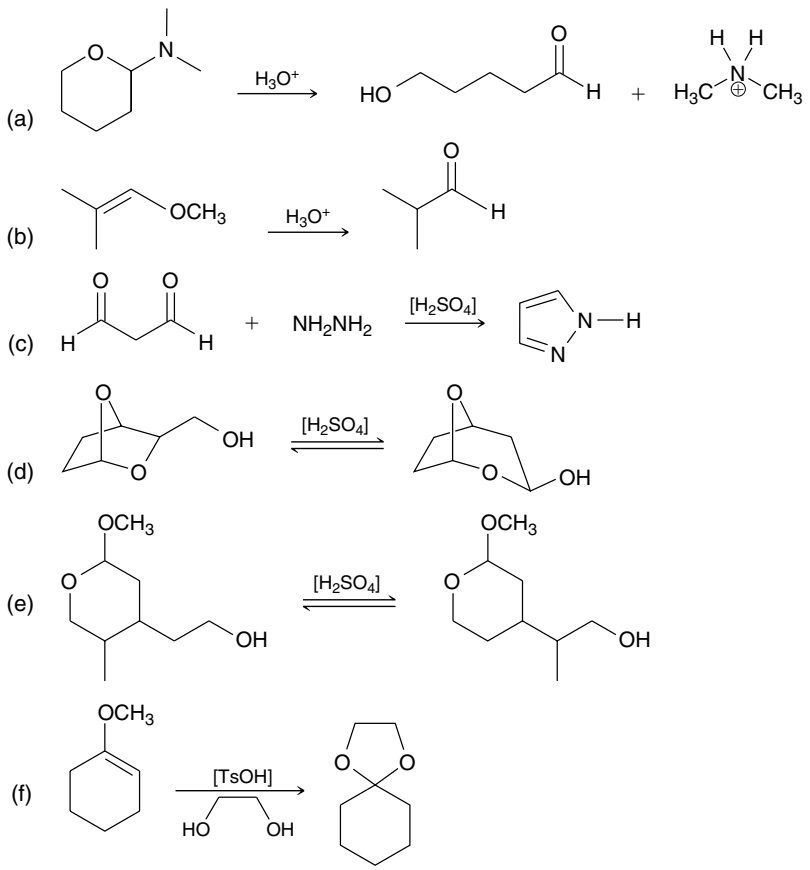
20.82 A compound with molecular formula $C_{13}H_{10}O$ produces a strong signal at 1660 cm^{-1} in its IR spectrum. The ^{13}C NMR spectrum for this compound is shown below. Identify the structure of this compound.



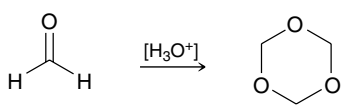
20.83 A ketone with molecular formula $C_9H_{18}O$ exhibits only one signal in its ^1H NMR spectrum. Provide a systematic (IUPAC) name for this compound.

CHALLENGE PROBLEMS

20.84 Draw a plausible mechanism for each of the following transformations:



20.85 Under acid-catalyzed conditions, formaldehyde polymerizes to produce a number of compounds, including paraformaldehyde. Draw a plausible mechanism for this transformation:



Paraformaldehyde