

Organic Chemistry

Chapter 16

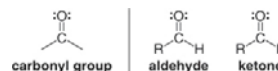
Aldehydes and Ketones

Nucleophilic Addition

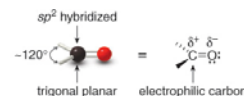
Aldehydes and Ketones—Nucleophilic Addition

Introduction

Aldehydes and ketones contain a carbonyl group. An aldehyde contains at least one H atom bonded to the carbonyl carbon, whereas the ketone has two alkyl or aryl groups bonded to it.



Two structural features determine the chemistry and properties of aldehydes and ketones.

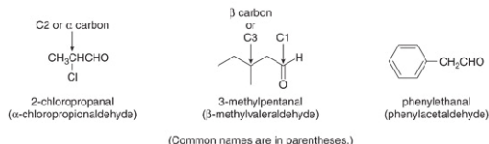


- The carbonyl group is sp^2 hybridized and trigonal planar, making it relatively uncrowded.
- The electronegative oxygen atom polarizes the carbonyl group, making the carbonyl carbon electrophilic.

Aldehydes and Ketones

Nomenclature of Aldehydes

- If the CHO is bonded to a chain of carbons, find the longest chain containing the CHO group, and change the $-e$ ending of the parent alkane to the suffix $-al$.
- Number the chain or ring to put the CHO group at C1, but omit this number from the name. Apply all the other usual rules of nomenclature.
- If the CHO group is bonded to a ring, name the ring and add the suffix $-carbaldehyde$.

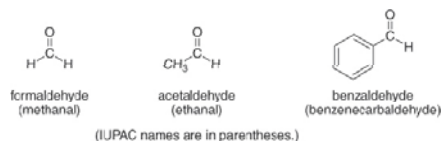


Aldehydes and Ketones

Nomenclature of Aldehydes

Many simple aldehydes have common names that are widely used.

- A common name for an aldehyde is formed by taking the common parent name and adding the suffix $-aldehyde$.



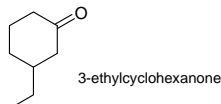
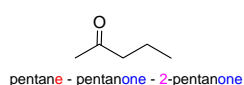
- Greek letters are used to designate the location of substituents in common names.



Aldehydes and Ketones

Nomenclature of Ketones

- In the IUPAC system, all ketones are identified by the suffix "one".
- Find the longest continuous chain containing the carbonyl group, and change the -e ending of the parent alkane to the suffix -one.
- Number the carbon chain to give the carbonyl carbon the lowest number. Apply all of the usual rules of nomenclature.

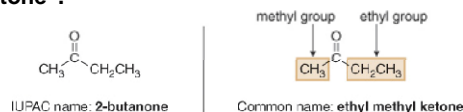


- With cyclic ketones, numbering always begins at the carbonyl carbon, but the "1" is usually omitted from the name. The ring is then numbered clockwise or counterclockwise to give the first substituent the lower number.

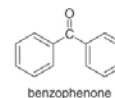
Aldehydes and Ketones

Nomenclature of Ketones

- Most common names for ketones are formed by naming both alkyl groups on the carbonyl carbon, arranging them alphabetically, and adding the word "ketone".

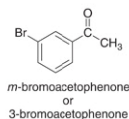
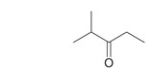


- Three widely used common names for some simple ketones do not follow this convention:

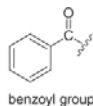


Aldehydes and Ketones

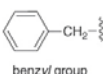
Nomenclature of Ketones



- Sometimes, acyl groups must be named as substituents.
- The three most common acyl groups are shown below:

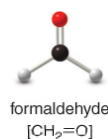


Do not confuse a benzyl group with a benzoyl group.

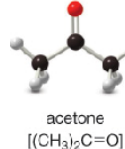


Aldehydes and Ketones

Interesting Aldehydes and Ketones



Billions of pounds of formaldehyde are produced annually for the oxidation of methanol. It is sold as a 37% solution called formalin which is used as a disinfectant, antiseptic, and preservative for biological specimens. It is a product of incomplete combustion of coal, and is partly responsible for the irritation caused by smoggy air.



Acetone is an industrial solvent. It is also produced in vivo during breakdown of fatty acids. Diabetics often have unusually high levels of acetone in their blood streams. Thus, its characteristic odor can be detected on the breath of diabetic patients when the disease is poorly controlled.

Aldehydes and Ketones

Interesting Aldehydes and Ketones

Many aldehydes and ketones with characteristic odors occur in nature.

Figure 21.6 Some naturally occurring aldehydes and ketones with strong odors

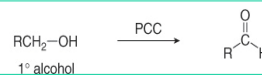


Aldehydes and Ketones

Preparation of Aldehydes and Ketones

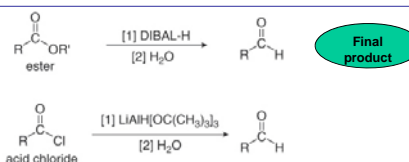
Methods to synthesize aldehydes:

- By oxidation of 1° alcohols with PCC



Recall Chapter 12: PCC stops oxidation of 1° alcohols at aldehyde level but most oxidative method will further oxidize aldehyde to the carboxylic acids RCOOH

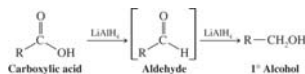
- By reduction of esters and acid chlorides



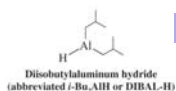
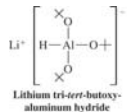
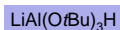
Synthesis of Aldehydes

- Aldehydes by Reduction of Acyl Chlorides, Esters and Nitriles
- Reduction of carboxylic acid to aldehyde is impossible to stop at the aldehyde stage since Aldehydes are much more easily reduced than carboxylic acids

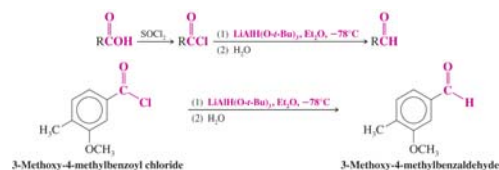
Same dilemma like in the oxidation



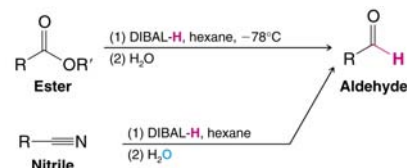
An approach: (1) Reduction to an aldehyde can be accomplished by using a **more reactive carboxylic acid derivatives** such as an acyl chloride, ester or nitrile, and (2) Use a less reactive hydride source than LiAlH₄ (LAH). The use of a **sterically hindered and less reactive** aluminum hydride reagent is important. They would stop reduction on an aldehyde level



Reduction of an Acid Chloride to an Aldehyde

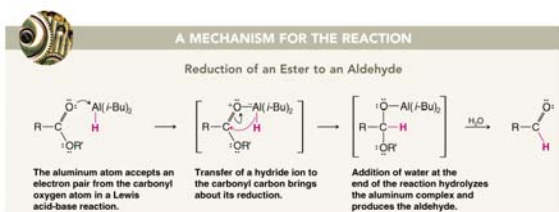


Reduction of an Esters and Nitriles are reduced to an Aldehydes with DIBAL-H



Reduction of an Ester to an Aldehyde with DIBAL-H

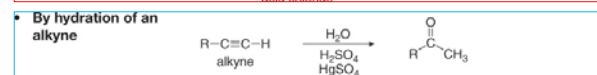
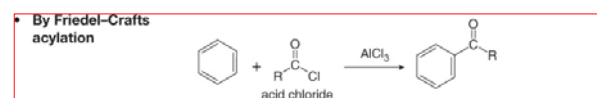
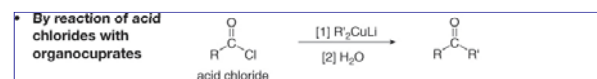
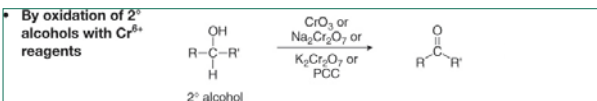
Please note that DIBAL-H is a source of hydride anion, which is an actual reducing agent



Aldehydes and Ketones

Preparation of Aldehydes and Ketones

Methods to synthesize ketones:

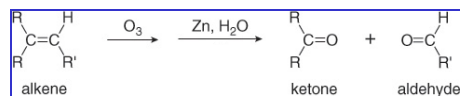


Aldehydes and Ketones

Ketones from nitriles: Nitriles react with Grignard reagent or an organolithium reagent followed by hydrolysis affording ketones



Aldehydes and ketones are also both obtained as products of the oxidative cleavage of alkenes.

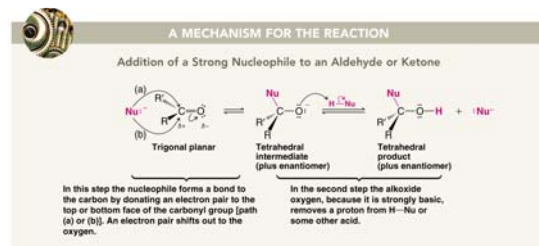
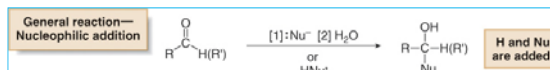


Aldehydes and Ketones—Nucleophilic Addition

Important General Reaction of Aldehydes and Ketones

Reaction at the carbonyl carbon

Overall, the elements of H and Nu are added to the carbonyl group.



Aldehydes and Ketones— Acid-catalyzed Nucleophilic Addition

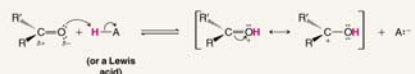
- With some neutral nucleophiles, nucleophilic addition only occurs if an acid is present—In this mechanism, protonation precedes nucleophilic attack as shown below.



A MECHANISM FOR THE REACTION

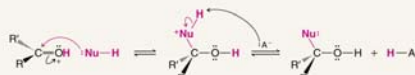
Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone

Step 1



In this step an electron pair of the carbonyl oxygen accepts a proton from the acid (or associates with a Lewis acid), producing an oxonium cation. The carbon of the oxonium cation is more susceptible to nucleophilic attack than the carbonyl of the starting ketone.

Step 2



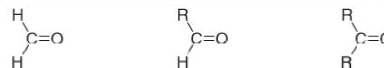
In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.

Aldehydes and Ketones—Nucleophilic Addition

Relative reactivity

- As the number of R groups around the carbonyl carbon increases, the reactivity of the carbonyl compound decreases, resulting in the following order of reactivity:

Increasing reactivity towards nucleophiles



Increasing steric hindrance

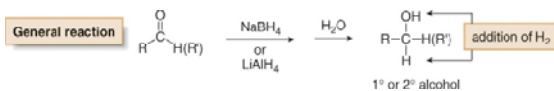


The Ketone carbonyl carbon is less positive because it has two electron-releasing alkyl groups.

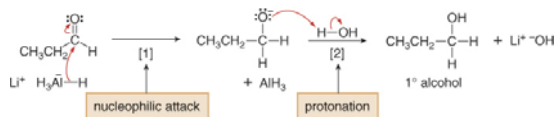
Aldehydes and Ketones—Nucleophilic Addition

Nucleophilic Addition of H^- —Review problem 16.6

For example reduction an aldehyde or ketone with either NaBH_4 or LiAlH_4 followed by protonation forms a 1° or 2° alcohol is an nucleophilic addition reaction. The nucleophile in these reactions is H^- .



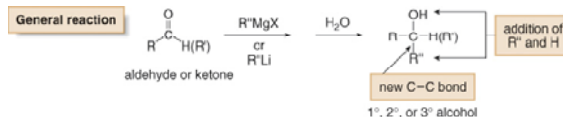
Hydride reduction occurs via a two-step mechanism.



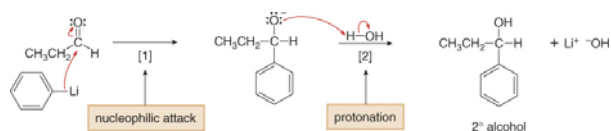
Aldehydes and Ketones—Nucleophilic Addition

Nucleophilic Addition of R^- —Review problem 16.5

Treatment of an aldehyde or ketone with either an **organolithium** (R^-Li) or **Grignard reagent** (R^-MgX) followed by water forms a 1°, 2°, or 3° alcohol containing a new C—C bond. In these reactions, R^- is the nucleophile.

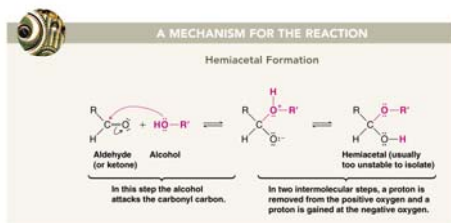


Nucleophilic addition occurs via a two-step mechanism.



Aldehydes and Ketones: Addition of Alcohols: Hemiacetals

- Aldehydes and ketones react with **one** equivalent of alcohol to form **hemiacetals**
- Note that hemiacetals (or acetals) are not ethers.

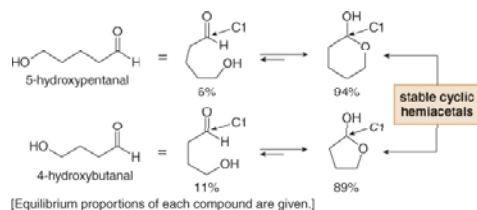


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Aldehydes and Ketones: Cyclic Hemiacetals

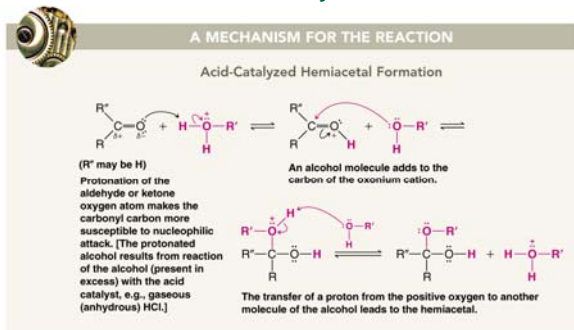
Cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.



Such intramolecular reactions to form five- and six-membered rings are faster than the corresponding intermolecular reactions. The two reacting functional groups (OH and C=O), are held in close proximity, increasing the probability of reaction.

Cyclic hemiacetals containing five- and six-membered rings are stable compounds that are readily isolated

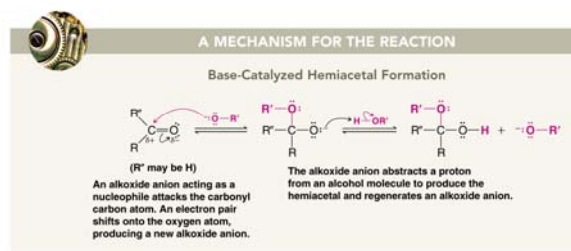
Aldehydes and Ketones: Addition of Alcohols: Acid-catalyzed Hemiacetal Formations



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Aldehydes and Ketones: Addition of Alcohols: Base-catalyzed Hemiacetal Formations

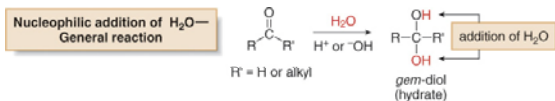


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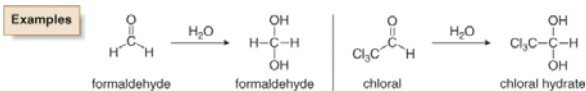
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Aldehydes and Ketones—Addition of H₂O: Hydration

- Treatment of a carbonyl compound with H₂O in the presence of an acid or base catalyst adds the elements of H and OH across the C=O π bond, forming a *gem*-diol or hydrate.

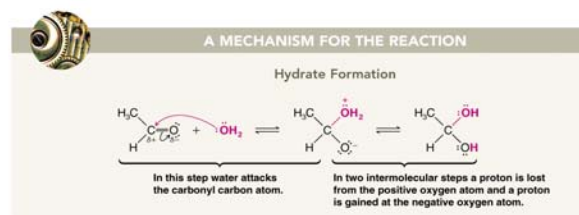


- Gem*-diol product yields are good only when unhindered aldehydes or aldehydes with nearby electron withdrawing groups are used.



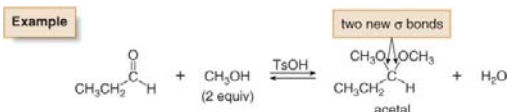
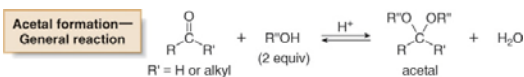
Aldehydes and Ketones—Addition of H₂O: Hydration

Please note that all the reactions between aldehydes and ketones with water and alcohols are reversible



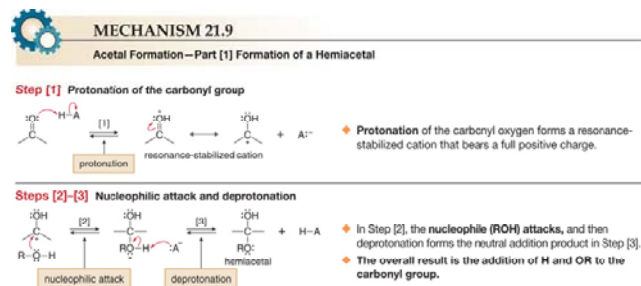
Aldehydes and Ketones: Addition of Alcohols: Acetals

- Aldehydes and ketones can react with **two** equivalents of alcohols to form **acetals**.
- Acetal formation is **catalyzed by acids**, such as TsOH.
- Because conversion of an aldehyde or ketone to an acetal is a **reversible reaction**, an acetal can be hydrolyzed to an aldehyde or ketone by treatment with aqueous acid (**but are stable in basic solutions**).



Aldehydes and Ketones—Acetal Formation: Mechanism

- The mechanism for acetal formation can be divided into two parts, the first of which is addition of one equivalent of alcohol to form the hemiacetal.



Aldehydes and Ketones—Acetal Formation: Mechanism

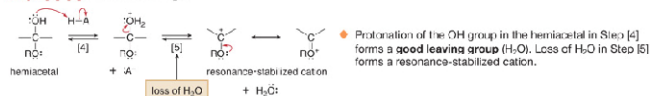
- The second part of the mechanism involves conversion of the hemiacetal into the acetal.



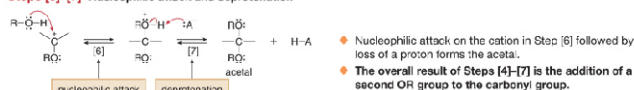
MECHANISM 21.10

Acetal Formation—Part [2] Formation of the Acetal

Steps [4]–[5] Elimination of H₂O



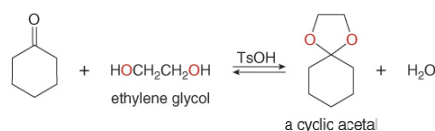
Steps [6]–[7] Nucleophilic attack and deprotonation



Please note that hemiacetals can be hydrolyzed back to aldehydes or ketones in acidic and basic solutions while acetals can be only hydrolyzed to carbonyl compounds in acidic conditions and are stable in basic solutions. **Why?**

Aldehydes and Ketones—Cyclic Acetals

- When a diol such as ethylene glycol is used in place of two equivalents of ROH, a cyclic acetal is formed.



- Like gem-diol formation, the synthesis of acetals is reversible, and often, the equilibrium favors the reactants.
- In acetal synthesis, since water is formed as a by-product, the equilibrium can be driven to the right by removing H₂O as it is formed using distillation or other techniques.

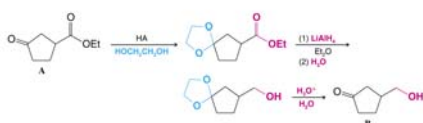
Aldehydes and Ketones—Acetals as Protecting Groups

- Acetals are valuable protecting groups for aldehydes and ketones:
- Suppose we wish to selectively reduce the ester group in compound A to an alcohol to give compound B, leaving the ketone untouched.
- Because ketones are more readily reduced than ester we have to protect ketone group in A as **acetal** (stable in basic conditions),



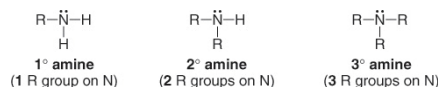
General Protection Strategy
[1] Protect the interfering functional group.
[2] Carry out the desired reaction.
[3] Remove the protecting group.

Three steps synthesis: (1) protection of the ketone group as acetal; (2) reduction of the ester to alcohol; (3) deprotection (hydrolysis of acetal to ketone)

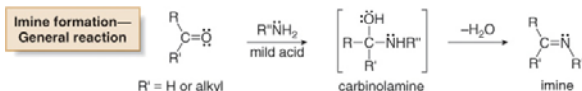


Aldehydes and Ketones—Addition 1° Amines: Imines

- Amines are classified as 1°, 2°, or 3° by the number of alkyl groups bonded to the nitrogen atom.

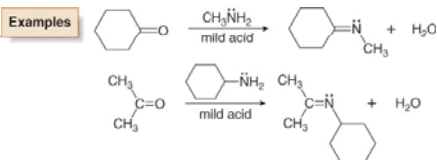


- Treatment of an aldehyde or a ketone with a **1° amine** affords an **imine** (also called a **Schiff base**).



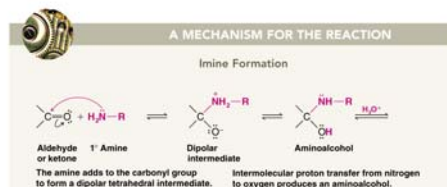
Aldehydes and Ketones— Imines

- Because the N atom of an imine is surrounded by three groups (two atoms and a lone pair), it is sp^2 hybridized, making the C—N—R bond angle 120° , (not 180°).
- Imine formation is fastest when the reaction medium is weakly acidic (pH 4-5).

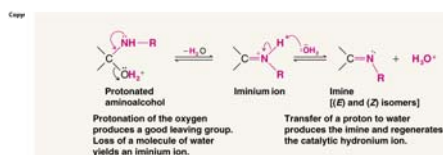


Aldehydes and ketones react with hydroxylamine (NH_2OH) to form **oximes**. They also react with or hydrazines (RNHNH_2) to form **hydrazones**. (see Table 16.2 on p. 752) Oximes and hydrazones are useful to identify unknown aldehydes and ketones

Aldehydes and Ketones: Addition 1° Amines: Imine formation mechanism

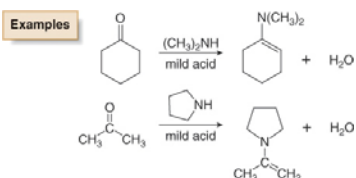
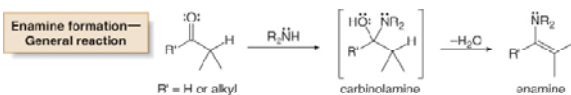


In imine formation, mild acid is needed for protonation of the hydroxy group in step 3 to form a good leaving group. However, under strongly acidic conditions, the reaction rate decreases because the amine nucleophile is protonated



Aldehydes and Ketones—Addition of 2° : Enamines

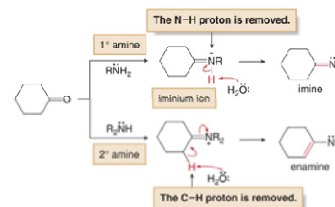
- A 2° amine reacts with an aldehyde or ketone to give an enamine. Enamines have a nitrogen atom bonded to a C—C double bond.



Aldehydes and Ketones

Difference between addition of 1° Amine (to form imine) and a 2° amine (to form enamine)

Figure 21.10 The formation of imines and enamines compared



- With a 1° amine, the intermediate iminium ion still has a proton on the N atom that may be removed to form a C=N.
- With a 2° amine, the intermediate iminium ion has no proton on the N atom. A proton must be removed from an adjacent C—H bond, and this forms a C=C.

Aldehydes and Ketones

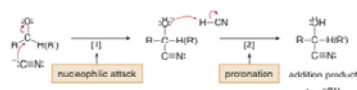
Nucleophilic Addition of ^-CN : Formation of Cyanohydrin

- Treatment of an aldehyde or ketone with NaCN and a strong acid such as HCl adds the elements of HCN across the C=O π bond, forming a cyanohydrin.
- The mechanism involves the usual two steps of nucleophilic addition—nucleophilic attack followed by protonation.



MECHANISM 21.3

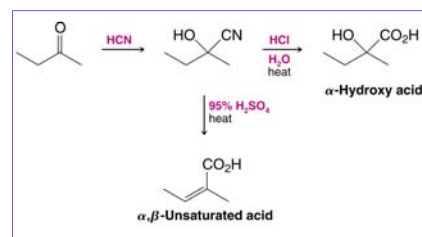
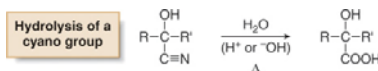
Nucleophilic Addition of ^-CN —Cyanohydrin Formation



- In Step [1], nucleophilic attack of ^-CN forms a new carbon-carbon bond with cleavage of the C=O π bond.
- In Step [2], protonation of the negatively charged O atom by HCN forms the addition product. The hydrogen cyanide (HCN) used in this step is formed by the acid-base reaction of cyanide (^-CN) with the strong acid, HCl.

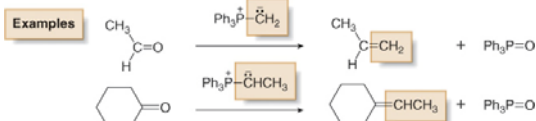
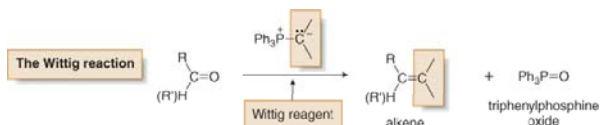
Cyanohydrin; Hydrolysis to the carboxylate group

- The cyano group of a cyanohydrin is readily hydrolyzed to a carboxy group by heating with aqueous acid or base.



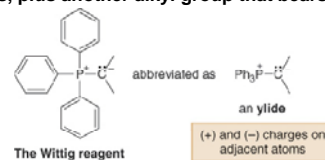
Aldehydes and Ketones— The Wittig Reaction

- The Wittig reaction uses a carbon nucleophile (the Wittig reagent) to form alkenes. A very general and useful reaction: **Nobel Prize 1970**
- The carbonyl group is converted to a C=C.



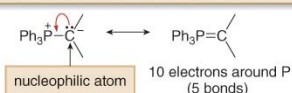
Aldehydes and Ketones— The Wittig Reaction

- The Wittig reagent is an organophosphorus reagent.
- A typical Wittig reagent has a phosphorus atom bonded to three phenyl groups, plus another alkyl group that bears a negative charge.



- A Wittig reagent is an **ylide**, a species that contains two oppositely charged atoms bonded to each other, with both atoms having octets.

Two resonance structures for the Wittig reagent



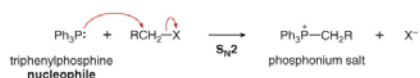
Regardless of which resonance structure is drawn, a Wittig reagent has overall no net charge

10 electrons around P (5 bonds)

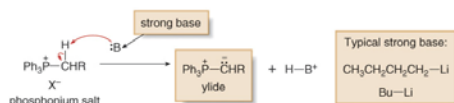
Aldehydes and Ketones— The Wittig Reaction

Wittig reagents are synthesized by a two-step procedure from alkyl halides.

Step [1] S_N2 reaction of triphenylphosphine with an alkyl halide forms a phosphonium salt.



Step [2] Deprotonation of the phosphonium salt with strong base forms the ylide.



Aldehydes and Ketones— The Wittig Reaction

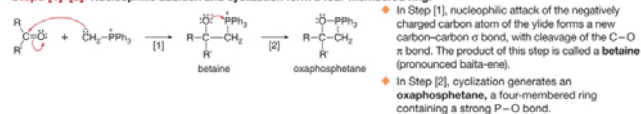
Wittig reactions occur by an addition-elimination sequence that involves three steps.



MECHANISM 21.4

The Wittig Reaction

Steps [1]–[2] Nucleophilic addition and cyclization form a four-membered ring.

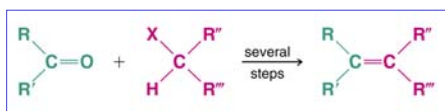


Step [3] Elimination of $\text{Ph}_3\text{P=O}$ forms the alkene.

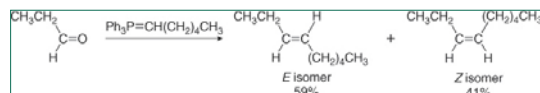


Aldehydes and Ketones— The Wittig Reaction

So the overall effect of a Wittig synthesis is formation of alkene



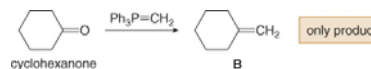
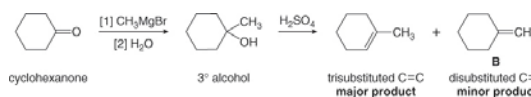
One limitation of the Wittig reaction is that a mixture of *E* and *Z* stereoisomers sometimes forms.



The Wittig reaction has been used to synthesize many natural products.

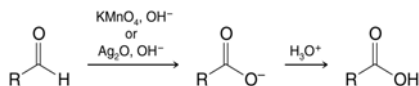
Aldehydes and Ketones— The Wittig Reaction

- An advantage of the Wittig reaction over elimination methods used to synthesize alkenes is that you always know the location of the double bond—the Wittig reaction always gives a single constitutional isomer.
- Consider the two methods that can be used to convert cyclohexanone into cycloalkene B.

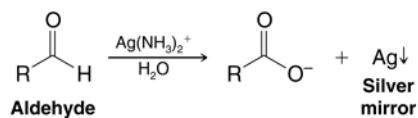


Aldehydes vs. Ketones — Chemical Analysis

Oxidation of aldehydes: Decolorization of permanganate



Tollens' Test (Silver mirror test)



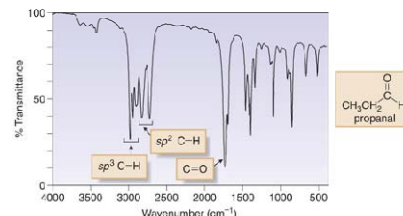
Both reactions are specific only to aldehydes

Aldehydes and Ketones

Spectroscopic Properties—IR Spectra

- Aldehydes and ketones give a strong peak at $\sim 1700 \text{ cm}^{-1}$ due to the $\text{C}=\text{O}$ (THE MOST DIAGNOSTIC PEAK IN IR).
- The sp^2 hybridized $\text{C}-\text{H}$ bond of an aldehyde shows one or two peaks at $\sim 2700 - 2830 \text{ cm}^{-1}$.

Figure 21.3 The IR spectrum of propanal, $\text{CH}_3\text{CH}_2\text{CHO}$



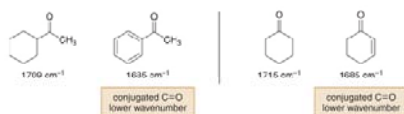
- A strong $\text{C}=\text{O}$ occurs at 1700 cm^{-1} .
- The $\text{sp}^2 \text{ C}-\text{H}$ of the CHO appears as two peaks at 2813 and 2716 cm^{-1} .

Aldehydes and Ketones

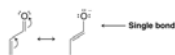
Spectroscopic Properties—IR Spectra

- Conjugation affects the carbonyl absorption in a predictable manner.

Figure 21.4 The effect of conjugation on the carbonyl absorption in an IR spectrum



This shift to lower frequencies occurs because the carbonyl double bond of the conjugated compound has more single bond character (resonance effect?), and single bonds are easier to stretch



Aldehydes and Ketones

Spectroscopic Properties—NMR Spectra

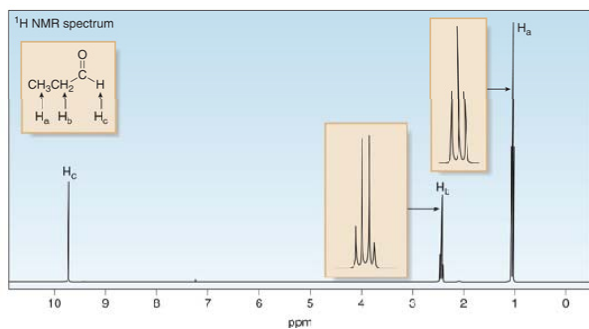
Aldehydes and ketones exhibit the following ^1H -NMR absorptions.

- The sp^2 hybridized $\text{C}-\text{H}$ proton of an aldehyde is highly deshielded and absorbs far downfield at 9-10 ppm. Splitting occurs with protons on the α carbon, but the coupling constant is often very small ($J = 1-3 \text{ Hz}$).
- Protons on the α carbon to the carbonyl group absorb at 2-2.5 ppm. Methyl ketones, for example, give a characteristic singlet at $\sim 2.1 \text{ ppm}$.

Aldehydes and Ketones

Spectroscopic Properties—NMR Spectra

Figure 21.5 The ^1H and ^{13}C NMR spectra of propanal, $\text{CH}_3\text{CH}_2\text{CHO}$



Summary

