CHAPTER 19 • THE CHEMISTRY OF ALDEHYDES AND KETONES. CARBONYL-ADDITION REACTIONS

Notice in this synthesis that all steps following acetal formation involve basic or neutral conditions. Acid can be used only when destruction of the acetal is desired. Although any acetal group can in principle be used, the five-membered cyclic acetal is frequently employed as a protecting group because it forms very rapidly (proximity effect; Sec. 11.7) and it introduces relatively little steric congestion into the protected molecule.

A number of reagents that react with carbonyl groups also react with other functional groups. Acetals are commonly used to protect the carbonyl groups of aldehydes and ketones from basic, nucleophilic reagents. Once the protection is no longer needed, the acetal protecting group is easily removed, and the carbonyl group re-exposed, by treatment with dilute aqueous acid. Because acetals are unstable in acid, they do not protect carbonyl groups under acidic conditions.

PROBLEM 19.27 Outline a synthesis of the following compound from \( p \)-bromoacetophenone and any other reagents.

\[
\begin{align*}
\text{HOCH}_2\text{CH}_2\text{OH} + \text{HOCH}_2\text{CH}_2\text{O} & \rightarrow \text{HOCH}_2\text{CH}_2\text{OH} + \text{HOCH}_2\text{CH}_2\text{O} \\
(19.54)
\end{align*}
\]

19.11 REACTIONS OF ALDEHYDES AND KETONES WITH AMINES

A. Reaction with Primary Amines and Other Monosubstituted Derivatives of Ammonia

A primary amine is an organic derivative of ammonia in which only one ammonia hydrogen is replaced by an alkyl or aryl group. An imine is a nitrogen analog of an aldehyde or ketone in which the \( \text{C}=\text{O} \) group is replaced by a \( \text{C}=\text{NR} \) group, where \( R = \text{alkyl}, \text{aryl}, \text{or H} \).
19.11 Reactions of Aldehydes and Ketones with Amines

Imines are sometimes called Schiff bases or Schiff’s bases. Imines are prepared by the reaction of aldehydes or ketones with primary amines. Formation of imines is reversible and generally takes place with acid or base catalysis or with heat. Imine formation is typically driven to completion by precipitation of the imine, removal of water, or both.

The mechanism of imine formation begins as a nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine, which reacts with the aldehyde or ketone to give an unstable addition product called a carbinolamine. A carbinolamine is a compound with an amine group (—NH₂, —NHR, or —NR₂) and a hydroxy group on the same carbon.

Typically, the dehydration of the carbinolamine is the rate-limiting step of imine formation. This is why imine formation is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds, and because protonated amines cannot act as nucleophiles.

Protonation of the amine pulls the equilibrium in Eq. 19.56a to the left; consequently, if the acid concentration is high enough, carbinolamine formation cannot occur. For this reason, many imine syntheses are carried out in very dilute acid.

To summarize: Imine formation is a sequence of two reactions that have close analogies to familiar reactions—namely, carbonyl addition followed by β-elimination.

One use of imines is in the preparation of amines; this is discussed in Sec. 23.7B. Another use, which was more important before the advent of spectroscopy than it is now, is in the characterization of aldehydes and ketones. When a new compound was synthesized, it was typically...
characterized by conversion into two or more crystalline compounds called derivatives. These derivatives served as the basis for subsequent identification of the new compound when it was isolated from another source or from a different reaction. It was important to prepare derivatives because they eliminated the ambiguity that could arise if two compounds have very similar melting points or boiling points. It is relatively improbable that two compounds with the same melting or boiling points will give two crystalline derivatives with the same melting points.

Certain imines are frequently used as solid derivatives of aldehydes and ketones. These imines, and the amines from which they are derived, are listed in Table 19.3. For example, the 2,4-DNP derivative of acetone is prepared by formation of an imine with 2,4-dinitrophenylhydrazine:

\[ \text{H}_3\text{C} - \text{C} = \text{CH}_3 + \text{H}_2\text{N} \rightarrow \text{NH} \underset{\text{C}_2\text{H}_5\text{OH}}{\text{NO}_2} \rightarrow \text{H}_3\text{C} - \text{C} = \text{CH}_3 + \text{H}_2\text{O} \]

(2,4-DNP derivative of acetone)

To illustrate how such derivatives might be used in structure verification, suppose that a chemist has isolated a liquid that could be either 6-methyl-2-cyclohexenone or 2-methyl-2-cyclohexenone. The boiling points of these compounds are too similar for an unambiguous identification. Yet the melting point of either a 2,4-DNP derivative or a semicarbazone (see Table 19.3) would quickly establish which compound has been isolated.

<table>
<thead>
<tr>
<th>Amine</th>
<th>Name</th>
<th>Carbonyl Derivative</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂N-OH</td>
<td>hydroxylamine</td>
<td>R₂C=O-N-H</td>
<td>oxime</td>
</tr>
<tr>
<td>H₂N-NH₂</td>
<td>hydrazine</td>
<td>R₂C=O-N-NH₂</td>
<td>hydrazone</td>
</tr>
<tr>
<td>H₂N-NH-C-C-NH₂</td>
<td>phenylhydrazine</td>
<td>R₂C=O-N-NH-C-C-NH₂</td>
<td>phenylhydrazine</td>
</tr>
<tr>
<td>H₂N-NH-NO₂-NO₂</td>
<td>2,4-dinitrophenylhydrazine (2,4-DNP)</td>
<td>R₂C=O-N-NH-NO₂-NO₂</td>
<td>2,4-dinitrophenylhydrazine (2,4-DNP derivative)</td>
</tr>
<tr>
<td>H₂N-NH-C-C-NH₂</td>
<td>semicarbazide</td>
<td>R₂C=O-N-NH-C-C-NH₂</td>
<td>semicarbazone</td>
</tr>
</tbody>
</table>

**TABLE 19.3**

Some *N*-Substituted Imine Derivatives of Aldehydes and Ketones

<table>
<thead>
<tr>
<th>boiling point</th>
<th>semicarbazone, mp</th>
<th>2,4-DNP derivative, mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>69–71 °C (18 mm)</td>
<td>177–178 °C</td>
<td>162–164 °C</td>
</tr>
<tr>
<td>69–70 °C (16 mm)</td>
<td>207–208 °C</td>
<td>207–208 °C</td>
</tr>
</tbody>
</table>
Although the identity of the compound could be readily established today by spectroscopy (explain how), it is important to be familiar with the imine derivatives in Table 19.3 because references to the use of such derivatives are commonplace in the older chemical literature.

**B. Reaction with Secondary Amines**

A secondary amine has the general structure \( R_2NH \), in which two ammonia hydrogens are replaced by alkyl or aryl groups. An enamine (pronounced ənˈeɪmənˈeɪnə) has the following general structure:

The name enamine is a contraction of the word amine (a compound of the form \( R_3N \)) and the suffix ene, which is used for naming alkenes. The name recognizes that an amine nitrogen is bonded to a carbon that is part of a double bond (that is, an alkene).

Formation of an enamine occurs when a secondary amine reacts with an aldehyde or ketone, provided that the carbonyl compound has an \( \alpha \)-hydrogen.

\[
\text{H}_3\text{C} - \text{CH} = \text{O} + \text{H} - \text{N} - \text{Ph} \xrightarrow{} \text{H}_3\text{C} \xrightarrow{\text{C}} \text{CH} = \text{N} - \text{Ph} + \text{H}_2\text{O} \quad (19.59)
\]

As Eq. 19.60 illustrates, the two alkyl groups of a secondary amine may be part of a ring.

Like imine formation, enamine formation is reversible and must be driven to completion by the removal of one of the reaction products (usually water; see Eq. 19.60). Enamines, like imines, revert to the corresponding carbonyl compounds and amines in aqueous acid.
The mechanism of enamine formation begins, like the mechanism of imine formation, as a nucleophilic addition to give a carbinolamine intermediate. (Write the mechanism of this reaction.)

\[ R_2\tilde{N}-H + \begin{array}{c} O \\ \end{array} \xrightleftharpoons{} \begin{array}{c} HO \tilde{N}R_2 \\ \end{array} \]  

(19.61a)

Because no hydrogen remains on the nitrogen of this carbinolamine, imine formation cannot occur. Instead, dehydration of the carbinolamine involves loss of a hydrogen from an adjacent carbon.

\[ \text{acid} \xrightarrow{} \begin{array}{c} \tilde{N}R_2 \\ \end{array} + H-\text{OH} \]  

(19.61b)

Why don’t primary amines react with aldehydes or ketones to form enamines rather than imines? The answer is the enamines bear the same relationship to imines that enols bear to ketones.

\[ \begin{array}{c} \text{an enamine} \\ \end{array} \xrightleftharpoons{} \begin{array}{c} \text{the isomeric imine} \\ \text{(more stable)} \end{array} \]  

(19.62a)

\[ \begin{array}{c} \text{an enol} \\ \end{array} \xrightleftharpoons{} \begin{array}{c} \text{the isomeric ketone} \\ \text{(more stable)} \end{array} \]  

(19.62b)

Just as most aldehydes and ketones are more stable than their corresponding enols (Sec. 14.5A), most imines are more stable than their corresponding enamines. Because secondary amines cannot form imines, they form enamines instead.

To summarize: Aldehydes and ketones react with primary amines (RNH₂) to give imines, and with secondary amines (R₂NH) to give enamines. In a third type of amine, a tertiary amine (R₃N), all hydrogens of ammonia are replaced by alkyl or aryl groups. Tertiary amines do not react with aldehydes and ketones to form stable derivatives. Although most tertiary amines are good nucleophiles, they have no NH hydrogens and therefore cannot even form carbinolamines. Their adducts with aldehydes and ketones are unstable and can only break down to starting materials.

\[ R_3N: + \begin{array}{c} O: \\ \end{array} \xrightleftharpoons{} \begin{array}{c} O^-: \\ \end{array} \]  

(19.63)
19.12 REDUCTION OF CARBONYL GROUPS TO METHYLENE GROUPS

The most common reductive transformation of aldehydes or ketones is their conversion into alcohols (Sec. 19.8). But it is also possible to reduce the carbonyl group of an aldehyde or ketone completely to a methylene (—CH₂—) group. One procedure for effecting this transformation involves heating the aldehyde or ketone with hydrazine (H₂N—NH₂) and strong base.

This reaction, called the Wolff–Kishner reduction, typically uses ethylene glycol or similar high-boiling compounds as co-solvents. (Triethylene glycol, which has the structure HOCH₂CH₂OCH₂CH₂OCH₂CH₂OH, and a boiling point of 278 °C, is used in Eqs. 19.64 and 19.65.) The high boiling points of these solvents allow the reaction mixtures to reach the high temperatures required for the reduction to take place at a reasonable rate.

The Wolff–Kishner reduction is an extension of imine formation (Sec. 19.11A) because a hydrazone (Table 19.3) is an intermediate in the reaction. A series of Brønsted acid–base reactions (see Study Guide Link 19.9) lead ultimately to expulsion of dinitrogen gas and formation of the product.

The Wolff–Kishner reduction takes place under strongly basic conditions. The same overall transformation can be achieved under acidic conditions by a reaction called the Clemmensen reduction. In this reaction, an aldehyde or ketone is reduced with zinc amalgam (a solution of zinc metal in mercury) in the presence of HCl.