Objectives

After completing this section, you should be able to

1. write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
2. identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
3. identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
4. write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
5. write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
6. explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- 2,4-dinitrophenylhydrozone
- enamine
- imine

Study Notes

An imine is a compound that contains the structural unit

\[ \text{R} \equiv \text{N}: \]

An enamine is a compound that contains the structural unit

\[ \text{R} \equiv \text{N} \equiv \text{R'} \]

Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colourful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and
why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

Reaction with Primary Amines to form Imines

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H₂O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.

Converting reactants to products simply

Examples of imine forming reactions

Mechanism of imine formation

1) Nucleophilic attack
2) Proton transfer

3) Protonation of OH

4) Removal of water

5) Deprotonation
Reversibility of imine forming reactions

Imines can be hydrolyzed back to the corresponding primary amine under acidic conditions.

\[
\begin{align*}
\text{R} - \text{N} = \text{C} - \text{H} & \quad + \quad \text{H}_2\text{O} \quad \xrightarrow{\text{HCl}} \quad \text{R} - \text{NH}_2 \quad + \quad \text{C} = \text{O}
\end{align*}
\]

Reactions involving other reagents of the type Y-NH₂

Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y-NH₂ have been studied, and found to give stable products (R₂C=N–Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed in the following table, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in another module.

\[
\begin{align*}
\text{C} = \text{O} & \quad + \quad \text{H}_2\text{C} - \text{NH}_2 \quad \xrightarrow{\text{1° amine}} \quad \text{H}_2\text{C} - \text{N} \\
\text{C} = \text{O} & \quad + \quad \text{HO} - \text{NH}_2 \quad \xrightarrow{\text{hydroxylamine}} \quad \text{HO} - \text{N} \\
\text{C} = \text{O} & \quad + \quad \text{H}_2\text{N} - \text{NH}_2 \quad \xrightarrow{\text{hydrazine}} \quad \text{H}_2\text{N} - \text{N} \\
\text{C} = \text{O} & \quad + \quad \text{H}_2\text{NHNHNH}_2 \quad \xrightarrow{\text{semicarbazide}} \quad \text{H}_2\text{N} - \text{N} - \text{N} - \text{NH}
\end{align*}
\]

With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has two amino groups (–NH₂) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.
Problems

1) Please draw the products of the following reactions.

\[
\begin{align*}
\text{O} & \hspace{1cm} + \hspace{1cm} \text{NH}_2 \hspace{1cm} \rightarrow \hspace{1cm} A \\
\text{C} & \hspace{1cm} + \hspace{1cm} \text{NH}_3 \hspace{1cm} \rightarrow \hspace{1cm} B \\
\text{C} & \hspace{1cm} + \hspace{1cm} \text{HONH}_2 \hspace{1cm} \rightarrow \hspace{1cm} C \\
\text{O} & \hspace{1cm} + \hspace{1cm} \text{NH}_3 \hspace{1cm} \rightarrow \hspace{1cm} D
\end{align*}
\]

2) Please draw the structure of the reactant needed to produce the indicated product.

\[
\begin{align*}
\text{N} & \hspace{1cm} + \hspace{1cm} \text{H}_2\text{O} \hspace{1cm} \rightarrow \hspace{1cm} I
\end{align*}
\]

3) Please draw the products of the following reactions.

Answers

1)
Reaction with Secondary Amines to form Enamines

Most aldehydes and ketones react with $2^\text{nd}$-amines to give products known as enamines. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.
Mechanism

1) Nucleophilic attack

2) Proton transfer

3) Protonation of OH

4) Removal of water
5) Deprotonation

Reversibility of Enamines

Problems

1) Please draw the products for the following reactions.

2) Please give the structure of the reactant needed to product the following product.
Answers

1)

2)

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