Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

Key Terms

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

- lactam

Study Notes

As the chapter which deals with amino acids and proteins is optional, it is possible for you to complete this course without studying these compounds in detail. However, because of their importance in biological systems, it is essential for all students completing this course to have some knowledge of their structure and properties.

When we talk about amino acids, we are generally referring to $\alpha$-amino acids; that is, compounds in which an amino (NH$_2$) group and a carboxyl group are attached to the same carbon atom:

\[
\begin{align*}
\text{H} & \\
\text{R} & \text{COOH} \\
\text{NH}_2 & 
\end{align*}
\]

Notice that such compounds contain a chiral carbon atom (unless R = H). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in secondary amides.
Note: Although the terms secondary amide and tertiary amide have been used here, this usage is not in agreement with IUPAC recommendations. According to IUPAC, the secondary amide shown above should be referred to as an $N$-substituted primary amide, and the tertiary amide should be referred to as a $N, N$-disubstituted primary amide. IUPAC reserves the term secondary amide for compounds of the type

\[
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{N} \\
\text{O} \\
\text{R} \\
\text{H}
\end{array}
\]

Because of the presence of the amide link in proteins,

\[
\begin{array}{c}
\text{C} \\
\text{O} \\
\text{N} \\
\text{H}
\end{array}
\]

we can expect the properties of these compounds to resemble those of secondary amides.

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:

\[
\begin{array}{c}
\text{C} \\
\text{O} \\
\text{N} \\
\text{H}
\end{array}
\quad\quad
\begin{array}{c}
\text{C} \\
\text{O}
\end{array}
\]

\text{a lactam} \quad \text{a lactone}

Among the most important molecules that contain lactam rings are the penicillins:
Preparation of Amides

Nitriles can be converted to amides. This reaction can be acid or base catalyzed.

\[ \text{R-CN} \xrightarrow{\text{HCl}} \xrightarrow{40 \, ^\circ\text{C}} \text{R-C\text{NH}_2} \]

Nitrile \quad \text{Amide}

Carboxylic acid can be converted to amides by using DCC as an activating agent.

\[ \text{R-COOH} + \text{R'NH}_2 \xrightarrow{\text{DCC}} \text{R-C\text{NH}_2R'} \]

Carboxylic Acid \quad Alcohol \quad Amide

Direct conversion of a carboxylic acid to an amide by reaction with an amine.

\[ \text{R-COOH} + \text{H}_2\text{N-R'} \xrightarrow{\text{DCC}} \text{R'-CONHR'} \xrightarrow{\Delta} \text{R'-CONHR'} + \text{H}_2\text{O} \]

Ammonium Carboxylate Salt

Acid chlorides react with ammonia, $1^0$ amines and $2^0$ amines to form amides.

\[ \text{R-C\text{Cl}} + \text{H-N} \xrightarrow{} \text{R-C\text{NH}_2} + \text{HCl} \]

Acid Chloride \quad Amine \quad Amide

Acid Anhydrides react with ammonia, $1^0$ amines and $2^0$ amines to form amides.
Conversion of Amides into Carboxylic Acids: Hydrolysis

This page describes the hydrolysis of amides under both acidic and alkaline conditions. It also describes the use of alkaline hydrolysis in testing for amides.

What is hydrolysis?

Technically, hydrolysis is a reaction with water. That is exactly what happens when amides are hydrolyzed in the presence of dilute acids such as dilute hydrochloric acid. The acid acts as a catalyst for the reaction between the amide and water. The alkaline hydrolysis of amides actually involves reaction with hydroxide ions, but the result is similar enough that it is still classed as hydrolysis.

Hydrolysis under acidic conditions

Taking ethanamide as a typical amide. If ethanamide is heated with a dilute acid (such as dilute hydrochloric acid), ethanoic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and ethanoic acid.

\[
\text{Acid Anhydride} + 2 \text{H}_2\text{O} \rightarrow \text{Amide} + \text{Acid} + \text{NH}_4^+ \cdot \text{Cl}^-
\]

Hydrolysis under alkaline conditions

Also, if ethanamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium ethanoate.

\[
\text{Acid Anhydride} \rightarrow \text{Amide} + \text{Acid} + \text{NH}_3
\]

Conversion of Amides into Amines: Reduction

Amides can be converted to 1°, 2° or 3° amines using LiAlH₄.
Example 21.7.1: Amide Reductions

Amide

1) \( \text{LiAlH}_4 \)
2) \( \text{H}_2\text{O} \)

1° Amine

Amide

1) \( \text{LiAlH}_4 \)
2) \( \text{H}_2\text{O} \)

2° Amine

Amide

1) \( \text{LiAlH}_4 \)
2) \( \text{H}_2\text{O} \)

3° Amine

Example 21.7.1: Amide Reductions

Alkyl groups attached to the nitrogen do not affect the reaction.

Mechanism

1) Nucleophilic attach by the hydride
2) Leaving group removal

3) Nucleophilic attach by the hydride

Exercises

Questions

Q21.7.1

How would you prepare the following compounds from N-Propyl benzamide?

(a)
Q21.7.2

Propose a synthesis for the following.

S21.7.1

a. NaOH, H₂O
b. NaOH, H₂O, then LAH
c. LAH

S21.7.2
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