Objectives

After completing this section, you should be able to

1. discuss, in detail, the preparation of nitriles:
   a. write an equation to illustrate the formation of a nitrile by the nucleophilic attack of cyanide ion on an alkyl halide.
   b. write an equation to illustrate the formation of a nitrile by the dehydration of a primary amide.
   c. identify the product formed when a primary amide is treated with SOCl₂, P₂O₅, or POCl₃.
   d. identify the primary amide, the reagents, or both, needed to prepare a given nitrile by a dehydration reaction.
   e. write a detailed mechanism for the dehydration of a primary amide by thionyl chloride.

2. discuss, in detail, the reactions of nitriles:
   a. write an equation to describe the (acidic or basic) hydrolysis of a nitrile.
   b. write detailed mechanisms for the acidic and basic hydrolysis of nitriles.
   c. identify the products formed from the (acidic or basic) hydrolysis of a given nitrile.
   d. identify the nitrile, the reagents, or both, needed to obtain a given carboxylic acid from a hydrolysis reaction.
   e. write an equation to describe the reduction of a nitrile to give a primary amine.
   f. identify the product formed from the lithium aluminum hydride reduction of a given nitrile.
   g. identify the nitrile, the reagents, or both, needed to prepare a given amine by direct reduction.
   h. write a detailed mechanism for the reduction of a nitrile to a primary amine using lithium aluminum hydride.
   i. give an example of the reduction of a nitrile with diisobutylaluminum hydride.
   j. write an equation to illustrate the reaction of a nitrile with a Grignard reagent.
   k. identify the product formed from the reaction of a given nitrile with a given Grignard reagent.
   l. identify the nitrile, the Grignard reagent, or both, needed to prepare a given ketone.
   m. write a detailed mechanism for the reaction of a nitrile with a Grignard reagent.

Study Notes

To be able to understand the driving force behind the reactions of nitriles, you must recognize the polarity of this group:

\[
\begin{array}{c}
\delta^+ \\
\text{C≡N} \\
\delta^-
\end{array}
\]

You can therefore expect to see similarities between the behaviour of the nitrile group and the similarly polarized carbonyl group:

\[
\begin{array}{c}
\delta^+ \\
\text{C=O} \\
\delta^-
\end{array}
\]
Properties of Nitriles

The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are $sp$ hybridized which leaves them both with two $p$ orbitals which overlap to form the two $\pi$ bond in the triple bond. The R-C-N bond angle in and nitrile is $180^\circ$ which give a nitrile functional group a linear shape.

The lone pair electrons on the nitrogen are contained in a $sp$ hybrid orbital which makes them much less basic and an amine. The 50% character of an $sp$ hybrid orbital close to the nucleus and therefore less basic compared to other nitrogen containing compounds such as amines.

\[
\text{CH}_3\text{CH}_2\text{C}≡\text{N}: \quad \text{H}_3\text{CH}_2\text{CH}_2\text{C}≡\text{N}: \quad \text{Propanenitrile} \quad \text{Propyl Amine}
\]

\[
pK_b = 24 \quad \text{pK}_b = 3.3
\]

The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.
Interesting Nitriles

One of the most common occurrences of nitriles is in Nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals.

![Nitrile Rubber Structure]

Amygdalin: Found in Bitter Almonds
Preparation of Nitriles

Addition of cyanide (\(^{\sim}\text{C≡N}\)) to an aldehyde or ketone forms a cyanohydrin.
Nitriles are formed by an SN2 reaction between a bromide and sodium cyanide

\[
R-\text{CH}_2\text{Br} + \text{NaCN} \rightarrow R-\text{CH}_2\text{CN} + \text{NaBr}
\]

1° Amides can be converted to nitriles by dehydration with thionyl chloride (or other dehydrating agents like P2O5, or POCl3).

Nitriles are formed by an SN2 reaction between a bromide and sodium cyanide

\[
R-\text{CH}_2\text{Br} + \text{NaCN} \rightarrow R-\text{CH}_2\text{CN} + \text{NaBr}
\]

Mechanism

1) Nucleophilic attack on thionyl chloride

2) Leaving group removal
Reactions of Nitriles

The carbon in a nitrile is electrophilic because a resonance structure can be drawn which places a positive charge on it. Because of this the triple bond of a nitrile accepts a nucleophile in a manner similar to a carbonyl.

Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.
**Example**

$$\text{C} = \text{N}$$

$$\xrightarrow{\text{H}_2\text{SO}_4 \quad \Delta}$$

$$\text{C} = \text{O}$$

---

**Mechanism**

1) Protonation

$$\text{R}-\text{C}=\text{N}^- \xrightarrow{\text{H}^+} \text{R}-\text{C}=\text{N}^+ + \text{H}_2\text{O}$$

2) Nucleophilic attack by water

$$\text{R}-\text{C}=\text{N}^+ \xrightarrow{\text{H}_2\text{O}} \text{R}-\text{C}==\text{N}^- + \text{H}_3\text{O}^+$$

3) Proton Transfer

$$\text{R}-\text{C}==\text{N}^- \xrightarrow{\text{H}_2\text{O}} \text{R}-\text{C}=\text{N}^- + \text{H}_3\text{O}^+$$

4) Resonance

$$\text{R}-\text{C}=\text{N}^- \xrightarrow{\text{H}_2\text{O}} \text{R}-\text{C}==\text{N}^-$$

5) Deprotonation

$$\text{R}-\text{C}==\text{N}^- \xrightarrow{\text{H}_2\text{O}} \text{R}-\text{C}=\text{N}^-$$
6) Further hydrolysis of the amide. This mechanism can be found in Section 21.7

Nitriles can be converted to 1° amines by reaction with LiAlH₄

During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.

General Reaction

Going from reactants to products simplified

Example
Mechanism

1) Nucleophilic Attack by the Hydride

\[
\begin{align*}
\text{R-C≡N} & \quad \xrightarrow{\text{Li}^-} \quad \text{R-CH-N}^- \\
\text{H}_2\text{AlH}_3 & \quad \xrightarrow{\text{R}^-} \quad \text{H}_2\text{AlH}_3\text{N}^- \\
\end{align*}
\]

2) Second nucleophilic attack by the hydride.

\[
\begin{align*}
\text{R-CH-N}^- & \quad \xrightarrow{\text{Li}^-} \quad \text{R-CH-N}^-\text{Li}^- \\
\text{H}_2\text{AlH}_3 & \quad \xrightarrow{\text{R}^-} \quad \text{H}_2\text{AlH}_3\text{N}^-\text{Li}^- \\
\end{align*}
\]

3) Protonation by addition of water to give an amine

\[
\begin{align*}
\text{R-CH-N}^-\text{Li}^- & \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R-CH-N}^- \\
\text{H}_2\text{AlH}_3 & \quad \xrightarrow{\text{R}^-} \quad \text{H}_2\text{AlH}_3\text{N}^- \\
\end{align*}
\]

Reaction of Nitriles with Organometallic Reagents

Grignard reagents can attack the electrophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

General Reaction

\[
\begin{align*}
\text{R-C≡N} & \quad \text{1) R'MgBr} \quad \xrightarrow{\text{2) H}_2\text{O}} \quad \text{R-C}\text{R'} \\
\text{Nitrile} & \quad \text{Ketone} \\
\end{align*}
\]
Example

Mechanism

1) Nucleophilic Attack by the Grignard Reagent

2) Protonation

3) Protonation

4) Nucleophilic attack by water
5) Proton Transfer

6) Leaving group removal

7) Deprotonation

Contributors

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)