Cyclohexanone Oxime Synthesis Notes

Application:
Oximes are common chemical intermediates. The oxime we are making today is used commercially in the synthesis of Nylon-6. Nylon-6 is a major industrial chemical which is used to make car tire tread and shoe laces.

Oximes have also shown to have promise as drugs which reduce the harmful impact from deliberate or accidental organophosphate poisoning. Organophosphates are used as chemical warfare agents and pesticides.

Background:
The carbonyl functional group has a large dipole. The carbon of the carbonyl carries a partial positive charge, the oxygen carries a partial negative charge. The carbon of a carbonyl is susceptible to nucleophilic attack which results in breaking the \( \pi \) bond to oxygen and forming a tetrahedral intermediate. This is usually followed by a series of proton exchanges where the oxygen is converted to a better leaving group, then a new bond is formed from the nucleophile to the carbon reforming an \( \text{sp}^3 \) center and the oxygen simultaneously leaves. A wide variety of carbonyl derivatives are made by this same general reaction mechanism.
In this experiment a cyclohexanone oxime will be formed from cyclohexanone and hydroxylamine. Cyclohexanone oxime will be synthesized, isolated, and analyzed by melting point determination. The percent yield and the purity of the product will be assessed.

Reaction:

\[
\text{Cyclohexanone} + \text{H}_2\text{N-OH} \cdot \text{HCl} + \text{NaOH} \rightarrow \text{Cyclohexanone oxime} + 2 \text{H}_2\text{O} + \text{NaCl}
\]
Mechanism:
1. The overall reaction consists as two separate reactions. Hydroxyl amine is packaged and sold as a solid salt, hydroxyl amine hydrochloride. This is commonly written as \( \text{H}_2\text{N-OH} \cdot \text{HCl} \), it means that the HCl separates and associates with the hydroxyl amine molecule forming a quaternary nitrogen salt \( \text{H}_3\text{N-OH}^+ \text{Cl}^- \).

2. The quaternary nitrogen in \( \text{H}_3\text{N-OH} \text{Cl}^- \) has a formal plus one charge and no available non-bonded electrons. This nitrogen is not nucleophilic. The first reaction in this experiment is an acid-base reaction between hydroxylamine hydrochloride salt with sodium hydroxide. The sodium hydroxide removes a proton (deprotonates) the quaternary amine salt and liberates or frees the hydroxyl amine reactant. The nitrogen on the resulting free hydroxyl amine (\( \text{NH}_2\text{-OH} \)) has one pair of non-bonded electrons. This nitrogen is a very good nucleophile.

3. The nitrogen of the hydroxyl amine, \( \text{NH}_2\text{-OH} \) is a stronger nucleophile than the adjacent oxygen because nitrogen is less electronegative and more willing to share electrons to form a covalent bond. Hence nitrogen and not oxygen attacks the carbon of the carbonyl. The next reaction occurs between the hydroxyl amine and cyclohexanone.

4. The full mechanism is depicted below.
5. Neat Cyclohexanone is a clear liquid at room temperature with a density of 0.948 g/mL. Pure cyclohexanone oxide is an opaque white solid at room temperature with a literature melting point of 91°C.

6. The solubility of cyclohexanone oxime in water is lower than the solubility of the parent cyclohexanone. This fact allows the product to be isolated by vacuum filtration.

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**Reaction and Useful Data**

\[
\text{Cyclohexanone} + \text{H}_2\text{N} \cdash \text{OH} \cdot \text{HCl} + \text{NaOH} \rightarrow \text{Cyclohexanone oxime} + \text{NaCl} + 2\text{H}_2\text{O}
\]

<table>
<thead>
<tr>
<th></th>
<th>Cyclohexanone</th>
<th>hydroxylamine hydrochloride (Aq)</th>
<th>Sodium Hydroxide (Aq)</th>
<th>Cyclohexanone oxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>-</td>
<td>2.5 M</td>
<td>2.5 M</td>
<td></td>
</tr>
<tr>
<td>dens</td>
<td>0.9478 g/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m.wt</td>
<td>98.15 g/mol</td>
<td>69.49 g/mol</td>
<td>40.0 g/mol</td>
<td>113.16 g/mol</td>
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<tr>
<td>b.p.</td>
<td>155 °C</td>
<td></td>
<td></td>
<td>206-210°C</td>
</tr>
<tr>
<td>m.p.</td>
<td>-16.4 °C</td>
<td></td>
<td></td>
<td>91 °C</td>
</tr>
</tbody>
</table>

7. **Analogous reactions:**

There are many other similar reactions with carbonyl carbons which proceed by the same general reaction mechanism. In each of these, a nucleophile attacks the carbon of the carbonyl. In many but not all of these the tetrahedral intermediate reacts further and a sp\(^2\) hybridized carbon is reformed.

With water a hydrate is produced.

\[
\text{Cyclohexanone} + \text{H}_2\text{O} \rightleftharpoons \text{Cyclohexanone hydrate}
\]

With an alcohol, in presence of acid, a ketal is produced.

\[
\text{Cyclohexanone} + \text{HO-CH}_2\text{CH}_3 \rightleftharpoons \text{Cyclohexanone ketal} + \text{H}_2\text{O}
\]
With ammonia or a primary amine, an imine is produced.

\[
\text{K} + \text{NH}_2\text{-CH}_3 \rightarrow \text{K} + \text{H}_2\text{O}
\]

With a secondary amine an imine is first formed which tautomerizes into an enamine.

\[
\text{K} + \text{NH-(CH}_3)_2 \rightarrow \text{K} + \text{H}_2\text{O}
\]

With a hydrazine a hydrazone is formed.

\[
\text{K} + \text{H}_2\text{N}-\text{N-} + \text{H}_2\text{O}
\]

With 2,4-Dinitrophenylhydrazine, 2,4-dinitrophenylhydrazone is formed.

\[
\text{K} + \text{H}_2\text{N}-\text{N-} + \text{H}_2\text{O}
\]

With semicarbazide a semicarbaxone is formed

\[
\text{K} + \text{H}_2\text{N}-\text{C} = \text{NH}_2 + \text{H}_2\text{O}
\]

The mechanisms for the above transformations are all very similar to the mechanism for the oxime formation. Be sure you are familiar with these mechanisms.

References:


Revised March 20, 2014, S.L. Weaver