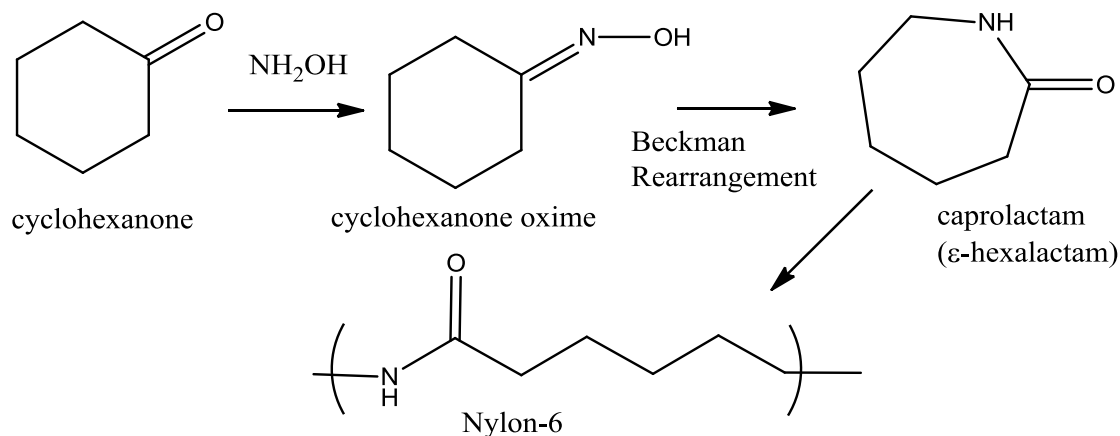


Reminder: These notes are meant to supplement, not replace, the laboratory manual.

Cyclohexanone Oxime Synthesis Notes

Application:

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



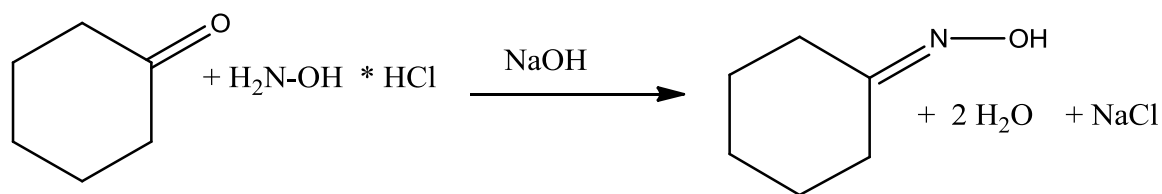
Oximes have also shown to have promise as drugs which reduce the harmful impact from deliberate or accidental organophosphate poisoningⁱⁱ. Organophosphates are used as chemical warfare agents and pesticides.

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 π 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 sp^2 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:



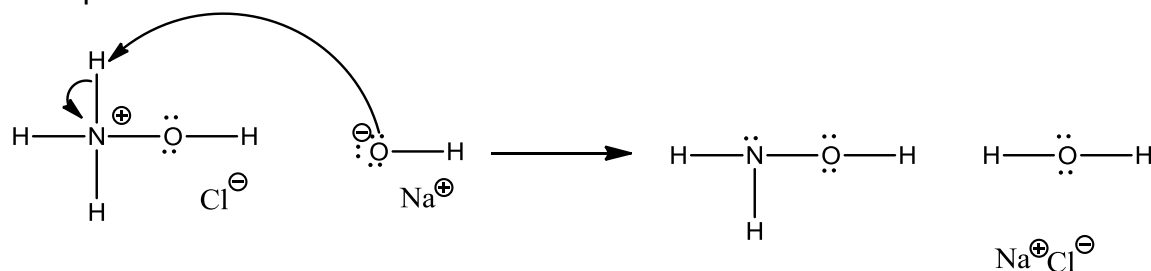
Mechanism:

1. Hydroxyl amine is packaged and sold as a solid salt, hydroxyl amine hydrochloride.

This is commonly written as $\text{H}_2\text{N-OH} \cdot \text{H-Cl}$, it means that the HCl separates and associates with the hydroxyl amine molecule forming a quaternary nitrogen salt

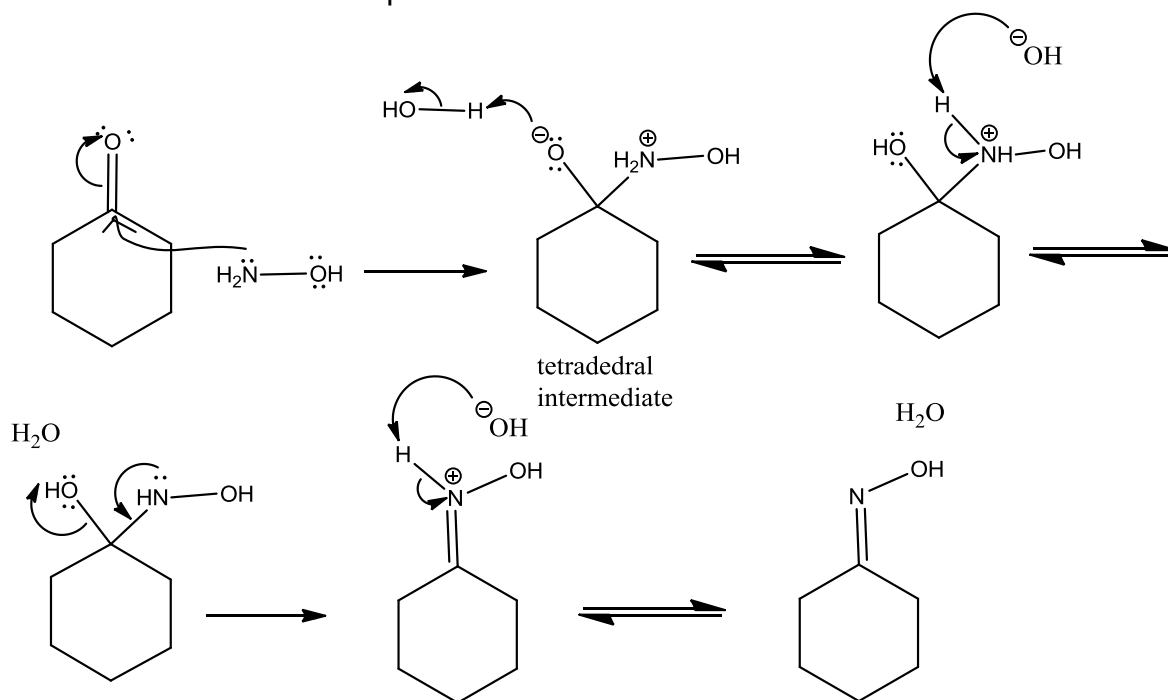


2. The quaternary nitrogen in $\text{H}_3\text{N}^{\oplus}\text{-OH} \text{Cl}^{\ominus}$ has a formal plus one charge and no available non-bonded electrons. This nitrogen is not nucleophilic. The first step in this experiment reacts with the hydroxylamine hydrochloride salt with sodium hydroxide to deprotonate the quaternary amine salt and 'free' the material. The nitrogen on the resulting $\text{NH}_2\text{-OH}$ has one pair of non-bonded electrons. This nitrogen is a good nucleophile.



3. The nitrogen in $\text{NH}_2\text{-OH}$ is a stronger nucleophile than the adjacent oxygen because nitrogen is less electronegative and a stronger base. Hence nitrogen and not oxygen attacks the carbon of the carbonyl.

4. The full mechanism is depicted below.



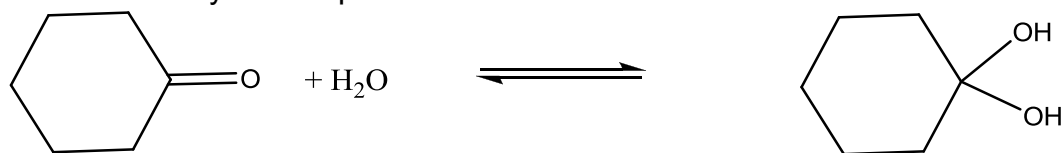
5. Neat Cyclohexanone is a clear liquid at room temperature with a density of 0.948 g/mL. Pure cyclohexanone oxime is an opaque white solid at room temperature with a literature melting point of 91°C.

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.

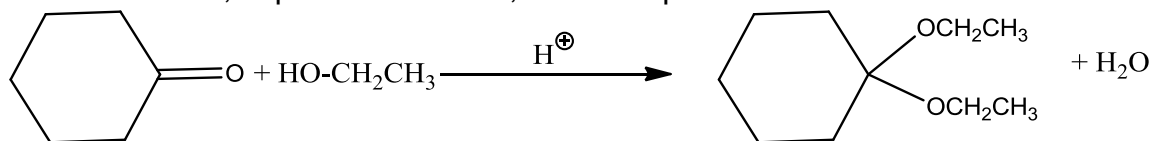
7. Analogous reactions:

There are many other similar reactions with carbonyl carbons which proceed by the same general reaction mechanismⁱⁱⁱ. 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.

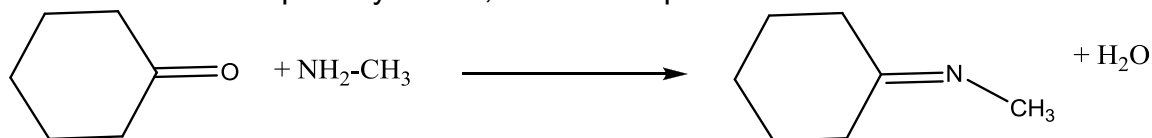
With water a hydrate is produced.



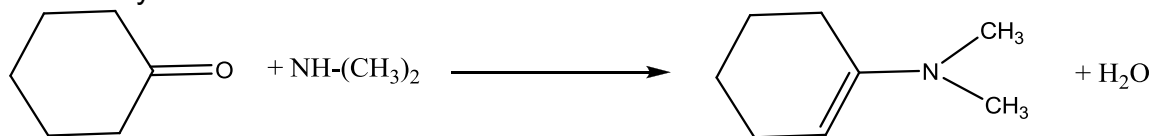
With an alcohol, in presence of acid, a ketal is produced.



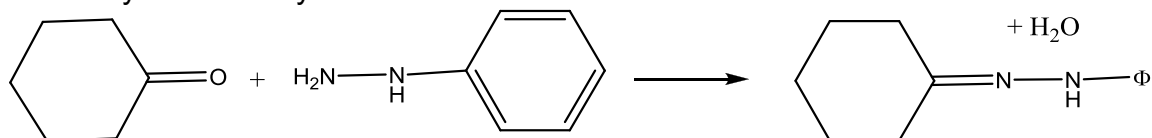
With ammonia or a primary amine, an imine is produced.



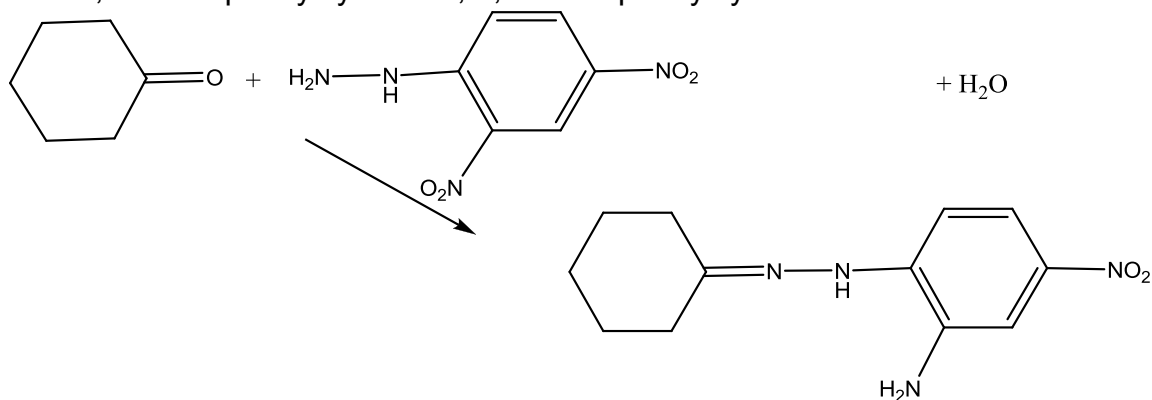
With a secondary amine an imine is first formed which tautomerizes into an enamine.



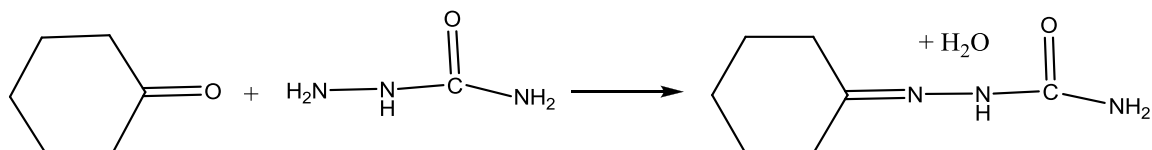
With a hydrazine a hydrazone is formed.



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



With semicarbazide a semicarbazone is formed



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

ⁱ Weissermel, K., Arpe. H. R. *Industrial Organic Chemistry*, 3rd, Wiley, 1997, pp252-262

ⁱⁱ Shrot, S. Markel, G., Dushnitsky, T., Krivoy, *The possible use of oximes as antidotal therapy in organophosphate-induced brain damage*, *Neurotoxicology*, A. 2009, 30(2), 167-173 or <http://www.ncbi.nlm.nih.gov/pubmed?term=19150463>

ⁱⁱⁱ Klein, D., *Organic Chemistry*, Wiley, 2012, pp 915-950