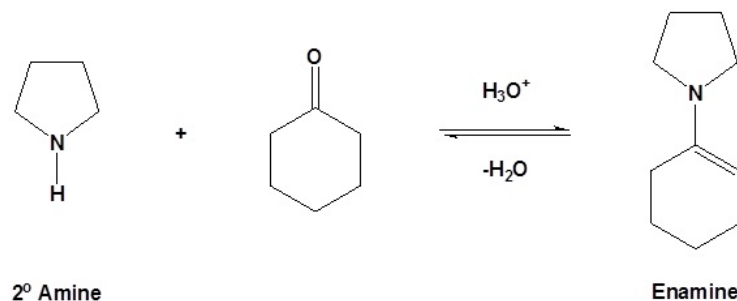


23.7: ALKYLATION OF THE ALPHA-CARBON VIA THE ENAMINE PATHWAY

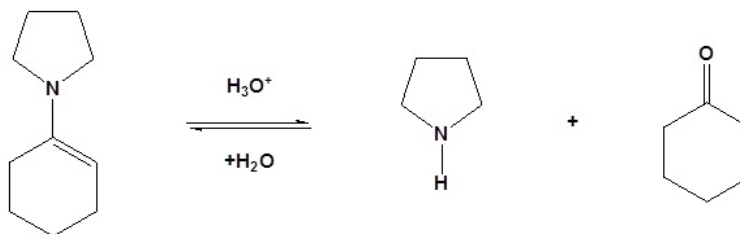
OVERVIEW OF THE STORK ENAMINE REACTION

The reaction conditions for the direct alkylation of the alpha carbon with LDA or other very strong base are quite harsh. Many organic compounds cannot withstand the reaction environment at synthetically useful amounts. Therefore, an alternate synthetic pathway was developed by Gilbert Stork of Columbia University. Some of the advantages of using an enamine over an enolate are that enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. As shown in the example below, the aldehyde or ketone can be recovered from the enamine via a hydrolysis reaction.

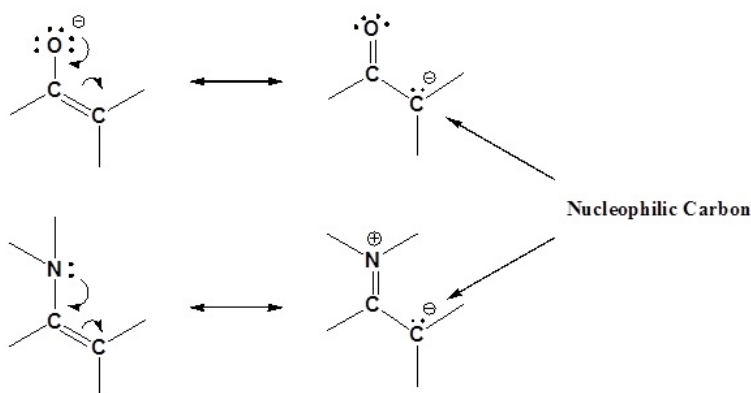
Example



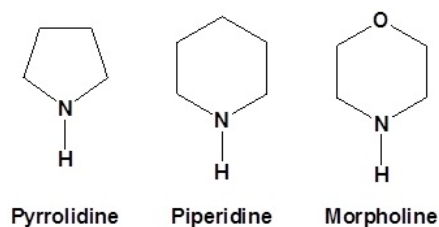
Reversible



Enamines act as nucleophiles in a fashion similar to enolates. Because of this, enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an electrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone.



Typically we use the following 2° amines for enamine reactions

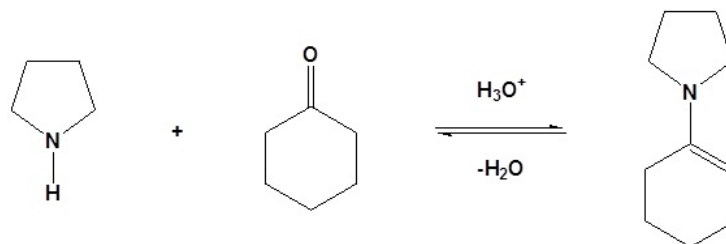


ALKYLATION OF AN ENAMINE

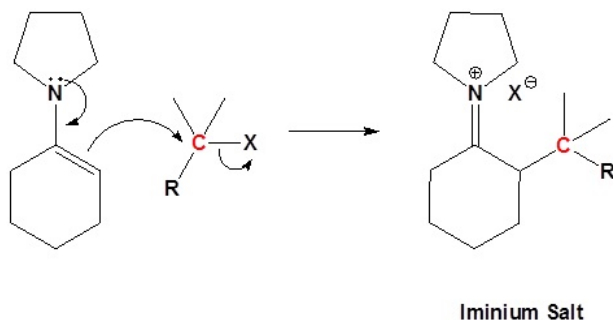
Enamines undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

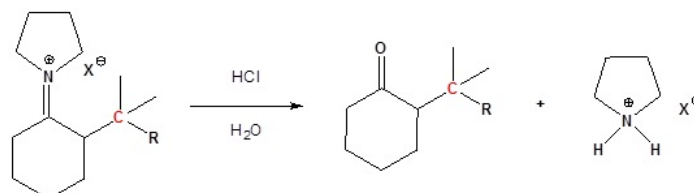
1) Formation of an enamine



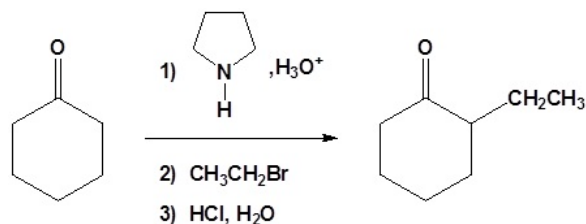
2) S_N2 Alkylation



3) Reform the carbonyl by hydrolysis

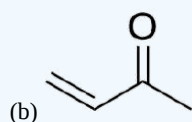
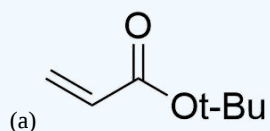


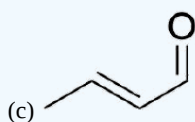
All three steps together:



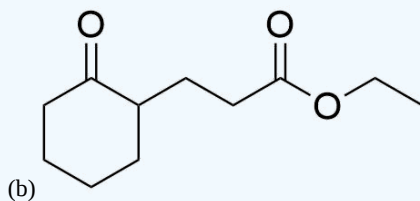
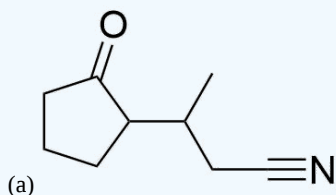
Exercises

10. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.



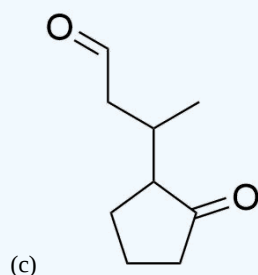
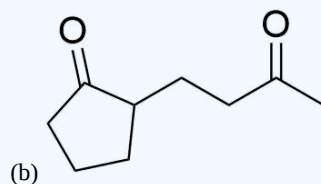
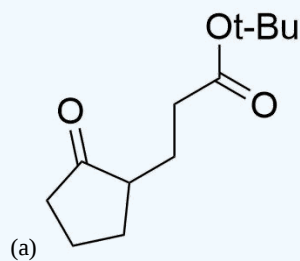


11. Propose a synthesis for the following compounds via an enamine.



Answers

10.



11.

(a) cyclopentanone enamine + 2-cyanopropene

(b) cyclohexanone enamine + ethyl acrylate

CONTRIBUTORS AND ATTRIBUTIONS

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

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