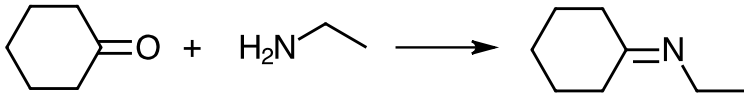
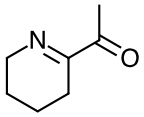
Objective 10. Understand nucleophilic addition reactions of N nucleophiles to C=O compounds.

1. An aldehyde or ketone reacts with a primary amine to form an imine.
a. Ammonia is NH_3. Substitute one H for a R group to make a primary amine. What is the difference between a secondary and tertiary amine?
b. Cyclohexanone reacts with ethyl amine to form an imine.



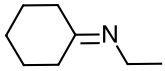
Use curved arrows to show how this imine forms. Steps:
(i) Cyclohexanone reacts with ethyl amine to form a tetrahedral intermediate.
(ii) The tetrahedral intermediate undergoes one or two proton transfers to form a carbinolamine (an alcohol and amine groups bonded to the same carbon).
(iii) The carbinolamine has a –OH group. Make this group into a better leaving group by using ____.
(iv) The leaving group leaves to form a _____. Alternatively, the lone pair on N forms a ____ bond and the leaving group leaves.
(v) Proton transfer occurs to produce the imine.
This reaction is more like a substitution reaction than an addition reaction. Which intermedate has an alpha carbon? Which intermediate has a good leaving group?

c. The Maillard reaction may be the most widely practiced reaction in the world.
The biscuit or cracker-like flavor in bread and popcorn is from 6-acetyl-2,3,4,5-tetrahydropyridine (shown below).

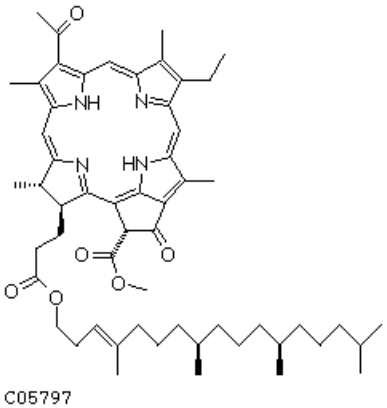


(i) Circle the imine group.
(ii) Draw the structures of the aldehyde or ketone and the amine that is used to make 6-acetyl-2,3,4,5-tetrahydropyridine.

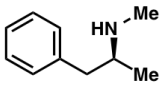
2. An imine undergoes hydrolysis to form a carbonyl compound and amine.
a. See the imine from Question 1b. Use an acid catalyst and curved arrows to show how this imine hydrolyzes to form cyclohexanone and ethyl amine.



b. Show how 6-acetyl-2,3,4,5-tetrahydropyridine undergoes hydrolysis to form the aldehyde or ketone and the amine you drew in Question 1c(ii).
c. Chlorophyll (shown below) is an imine.
(i) Circle the imine group(s).
(ii) The imine group undergoes hydrolysis. Draw the structure of the product.
(iii) How would you synthesize the imine group? Draw the structure of the reactants.



3. Imines can be reduced to amines.
(From LearnBacon.com) Reductive amination is used to make legal and illegal drugs, including methamphetamine. See Breaking Bad.

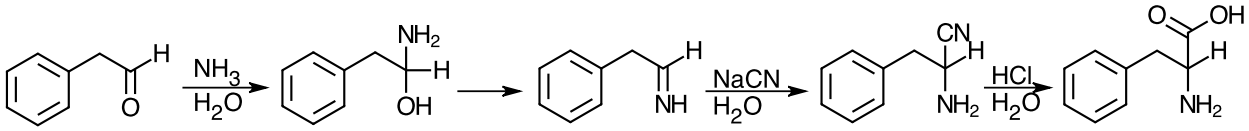


Methamphetamine

Dangerous and Addictive Drug

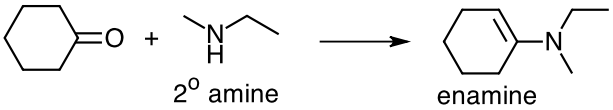
a. Draw the structure of the intermediate that is reduced to the amine in the first reaction.
b. Draw the structure of the carbonyl compound and amine to make the imine that is reduced to methamphetamine. In other words, determine the starting materials to make methamphetamine in a ___ step reaction sequence.

4. Strecker synthesis of phenylalanine is shown below. Use curved arrows to show how bonds break and form in each step.



phenylalanine

5. An aldehyde or ketone reacts with a 1° amine to form an imine. An aldehyde or ketone reacts with a 2° amine to form an enamine.



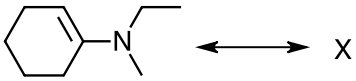
2° amine

enamine

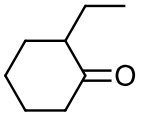
(vs. imine with 1° amine)

a. Use curved arrows to show how this enamine forms. Steps:
(i) Cyclohexanone reacts with ethyl methyl amine to form a tetrahedral intermediate.
(ii) The tetrahedral intermediate undergoes one or two proton transfers to form a carbinolamine (an alcohol and amine groups bonded to the same carbon).
(iii) The carbinolamine has a –OH group. Make this group into a better leaving group by using ____.
(iv) The leaving group leaves to form a carbocation. Draw a resonance structure of this carbocation. Which resonance structure is the major contributor?
(v) (From Chem 12A) A carbocation can undergo elimination to form a pi bond. A base reacts with the proton on the carbon next to the carbocation to form a _____.
(vi) Proton transfer occurs to produce the enamine.
This reaction is more like a substitution reaction than an addition reaction. Which intermedate has an alpha carbon? Which intermediate has a good leaving group?

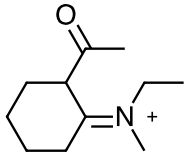
b. An enamine can be used to alkylate and acylate (fancy word to form C-C bonds) aldehydes and ketones in synthesis (https://en.wikipedia.org/wiki/Enamine).
(i) The enamine shown below is from Question 5. Draw resonance structure X. Circle the nucleophilic carbon in X.



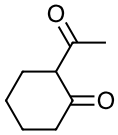
(ii) X reacts with C_2H_5Br. Draw the structure of the product (iminium ion).
(iii) The product from (ii) reacts with HCl/H_2O to form the compound shown below. Use curved arrows to show how this compound forms. Note: this reaction sequence is a way to alkylate cyclohexanone.



c. The enamine from part b(i) reacts with CH_3COCl to form the compound shown below.
(i) Use curved arrows to show how this compound forms.



(ii) This compound reacts with HCl/H_2O to form the compound shown below. Use curved arrows to show how this compound forms.



d. The enamine from part b(i) reacts with Cl_2. Draw the structure of the product.