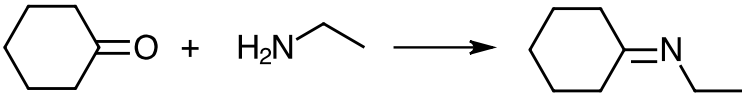
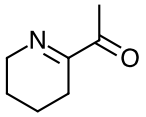
Objective 10. Understand nucleophilic addition reactions of N nucleophiles to C=O compounds.
to form imines and eneamines (imines are common in bio – Maillard reaction)
Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu^- and E^+, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.
Key ideas: C=O bond has pi bond but bond is polarized. See resonance. Carbonyl C = E^+. Reacts with Nu^- to form Td intermediate. ID N Nu^- to form imines and eneamines.

Practice problems solutions:
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.



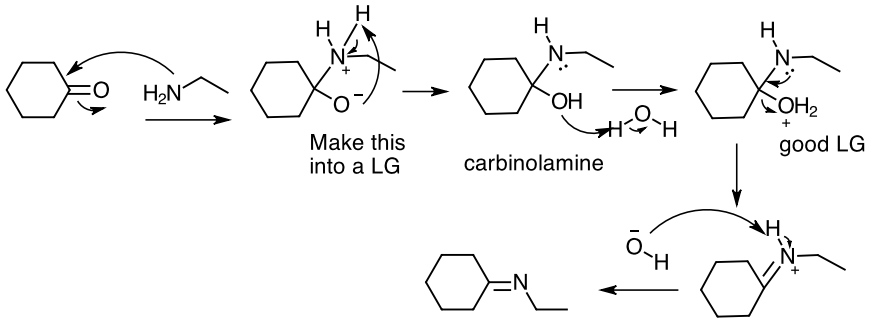
Use curved arrows to show how this imine forms. Steps:
(i) Cyclohexanone reacts with ethyl amine to form a tetrahedral intermediate.
(ii) The tetrahedral intermediate undergoes one or two proton transfers to form a carbinolamine (an alcohol and amine groups bonded to the same carbon).
(iii) The carbinolamine 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).

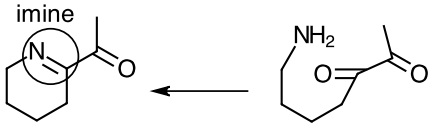


(i) Circle the imine group.
(ii) Draw the structures of the aldehyde or ketone and the amine that is used to make 6-acetyl-2,3,4,5-tetrahydropyridine.

Answers:
a. 2° amine has two carbons bonded to N. 3° amine has three carbons bonded to N.
b. The first intermediate is a tetrahedral intermediate. Make one of the groups into a good LG.

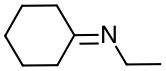


This reaction is more like a substitution reaction than an addition reaction - the N group substitutes for the O.
The carbinolamine intermedate has an alpha carbon.
The intermediate after the carbinolamine has a good leaving group.
c. The C in the C=N bond comes from a carbonyl carbon in the reactant.

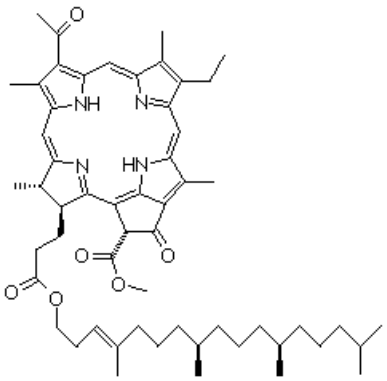


2. An imine undergoes hydrolysis to form a carbonyl compound and amine.

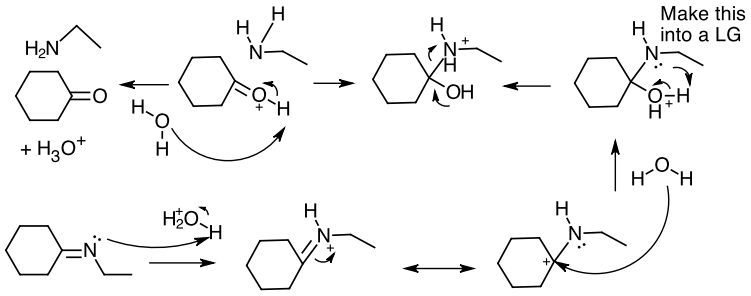
a. See the imine from Question 1b. Use an acid catalyst and curved arrows to show how this imine hydrolyzes to form cyclohexanone and ethyl amine.



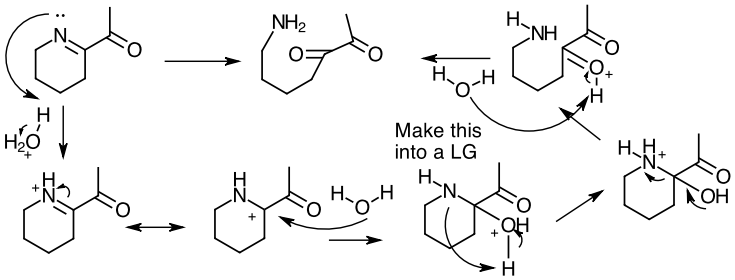
b. Show how 6-acetyl-2,3,4,5-tetrahydropyridine undergoes hydrolysis to form the aldehyde or ketone and the amine you drew in Question 1c(ii).
c. Chlorophyll (shown below) is an imine.
(i) Circle the imine group(s).
(ii) The imine group undergoes hydrolysis. Draw the structure of the product.
(iii) How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



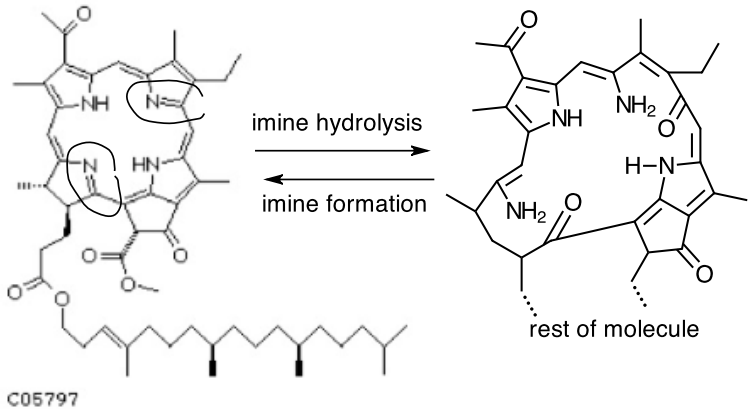
Answers:
a. Most organic reactions are equilibrium reactions.
The imine hydrolysis is the reverse of imine formation. Note: the C in the C=N bond is an electrophile like a carbonyl carbon.
Note tetrahedral intermediate. Make one of the groups into a good LG.



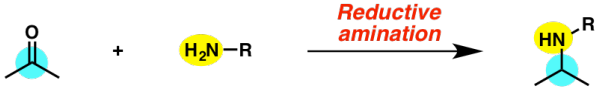
b. Which one is the tetrahedral intermediate? Make one of the groups into a good LG.



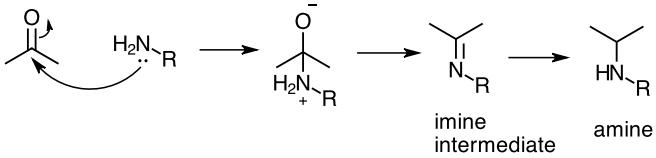
c. The C in the C=N bond comes from a carbonyl carbon in the reactant.



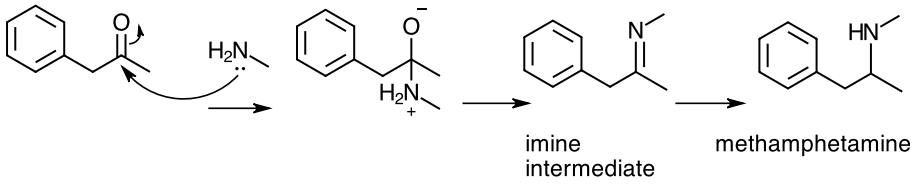
3. Imines can be reduced to amines.
(From LearnBacon.com) Reductive amination is used to make legal and illegal drugs, including methamphetamine. See Breaking Bad.



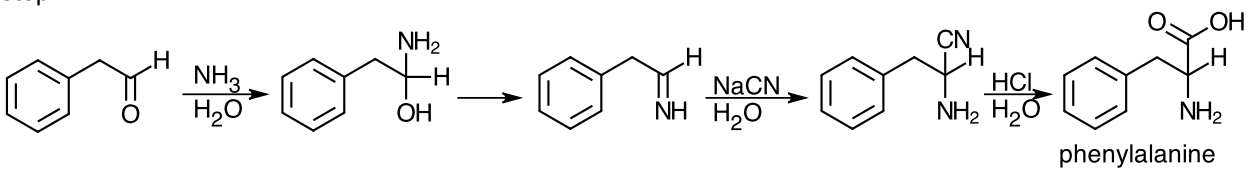
a. Draw the structure of the intermediate that is reduced to the amine in the first reaction.
b. Draw the structure of the carbonyl compound and amine to make the imine that is reduced to methamphetamine. In other words, determine the starting materials to make methamphetamine in a ___ step reaction sequence.
Answers:
Remember, reduction is gain of H or loss of O or both.
a. Acetone reacts with amine to form a tetrahedral intermediate. Make one of the groups into a good LG.



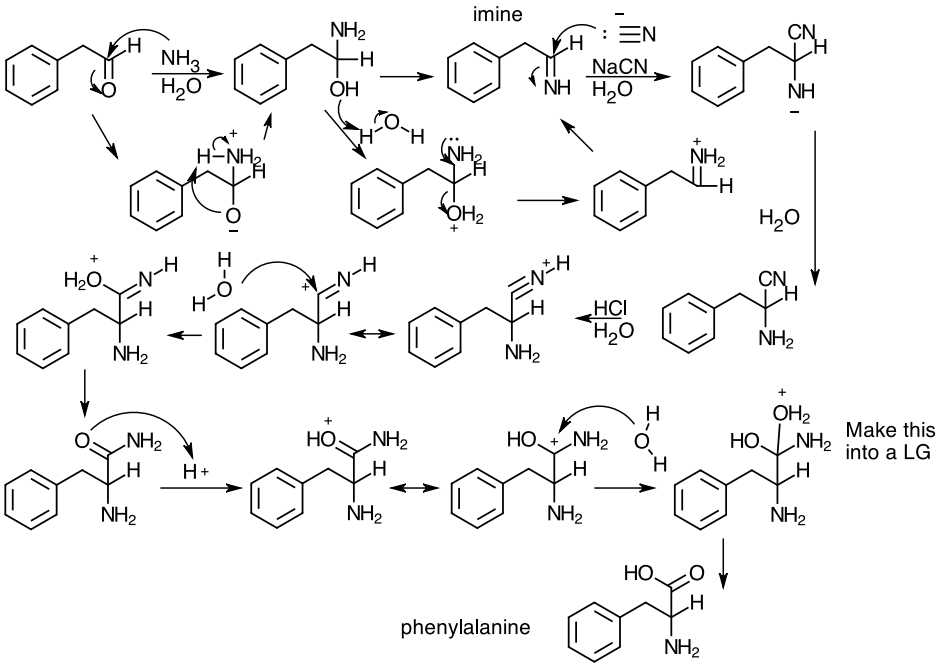
b. methamphetamine in a 2 step reaction sequence. Note tetrahedral intermediate. Make one of the groups into a good LG.



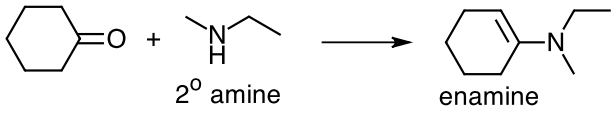
4. Strecker synthesis of phenylalanine is shown below. Use curved arrows to show how bonds break and form in each step.



Answers: imine C is an electrophile like carbonyl C.
N in CN (nitrile) is a nucleophile like carbonyl O is a nucleophile.



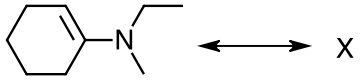
5. An aldehyde or ketone reacts with a 1° amine to form an imine. An aldehyde or ketone reacts with a 2° amine to form an enamine.



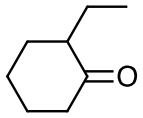
(vs. imine with 1° amine)

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?

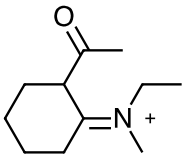
b. An enamine can be used to alkylate and acylate (fancy word to form C-C bonds) aldehydes and ketones in synthesis (https://en.wikipedia.org/wiki/Enamine).
(i) The enamine shown below is from Question 5. Draw resonance structure X. Circle the nucleophilic carbon in X.



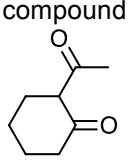
(ii) X reacts with C_2H_5Br. Draw the structure of the product (iminium ion).
(iii) The product from (ii) reacts with HCl/H_2O to form the compound shown below. Use curved arrows to show how this compound forms. Note: this reaction sequence is a way to alkylate cyclohexanone.



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.



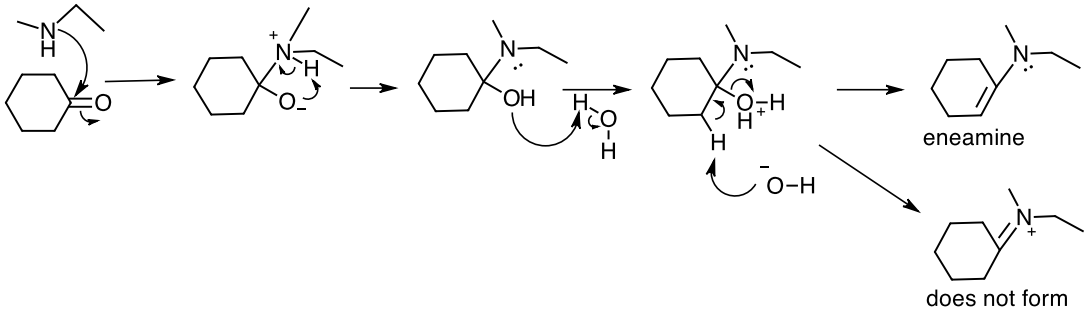
d. The enamine from part b(i) reacts with Cl_2. Draw the structure of the product.

Answers:

a. The 1st intermediate is a tetrahedral intermediate. Make one of the groups into a good LG.

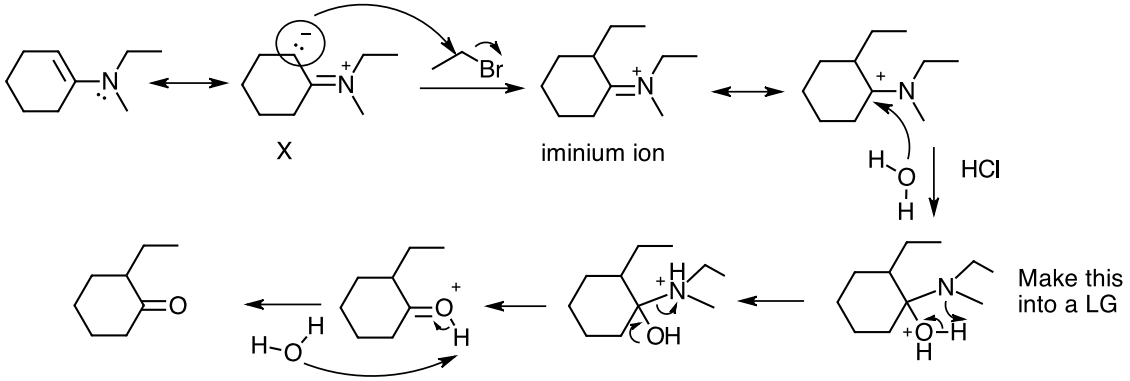
In 3rd intermediate, OH_2 is a good LG. The C bonded to OH_2 is an alpha C. OH^- (nucleophile) reacts with H on beta C to form C=C bond in an elimination reaction.

The lone pair on N does not form a C=N pi bond because the N would have a (+) charge – this is less stable than the eneamine.

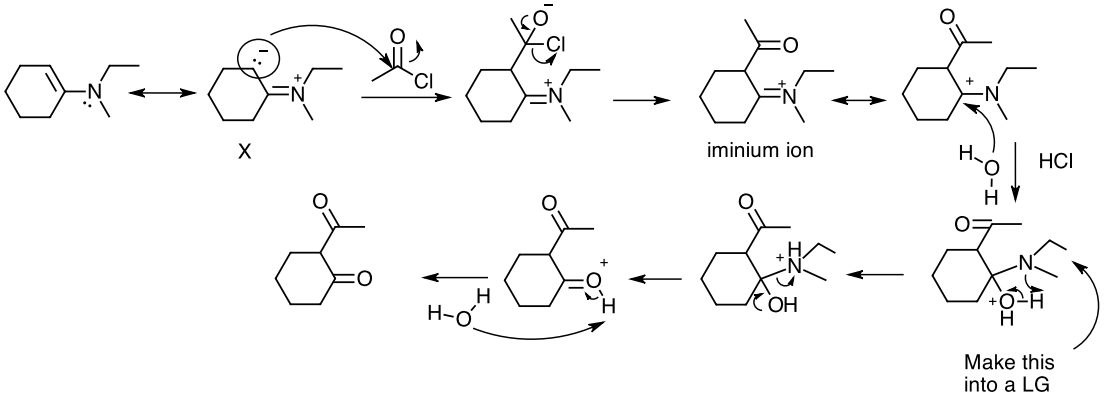


b. X reacts with RBr in a substitution reaction to form the iminium ion.

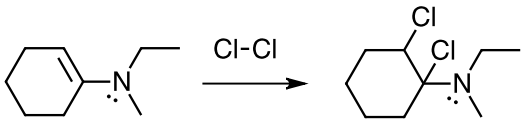
The iminium ion reacts with water to form a tetrahedral intermediate. Make one of the groups into a good LG.



c. X reacts with CH_3COCl to form a tetrahedral intermediate. Make one of the groups into a good LG.



d. Alkene + halogen is an electrophilic addition reaction from CHM 12A.


Cl-Cl
Cl
Cl
N
N