

## 5.9: NUCLEOPHILIC ADDITION OF AMINES - IMINE AND ENAMINE FORMATION

### OBJECTIVES

After completing this section, you should be able to

- write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
- identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
- identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
- explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

### KEY TERMS

Make certain that you can define, and use in context, the key terms below.

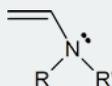
- 2,4-dinitrophenylhydrozone
- enamine
- imine

### STUDY NOTES

An imine is a compound that contains the structural unit



An enamine is a compound that contains the structural unit



Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

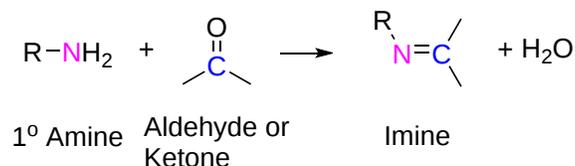
You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrazone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colorful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

The nucleophilic addition of amines involves reacting primary or secondary amines with carbonyl compounds like aldehydes or ketones. This forms imines (with primary amines) or enamines (with secondary amines) along with water as a byproduct. These reactions are crucial in organic synthesis for building carbon-nitrogen bonds and creating various functional groups.

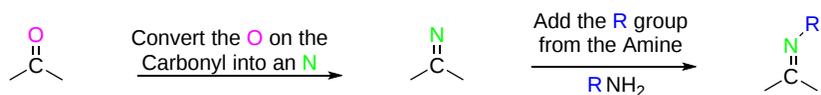
### REACTION WITH PRIMARY AMINES TO FORM IMINES

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

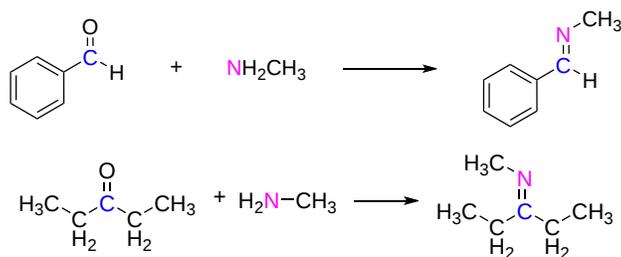


### PREDICTING THE PRODUCTS OF AN IMINE FORMING REACTION

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



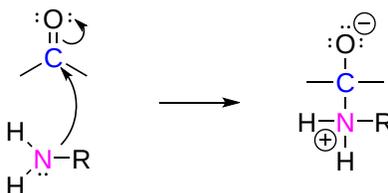
### EXAMPLES OF IMINE FORMING REACTIONS



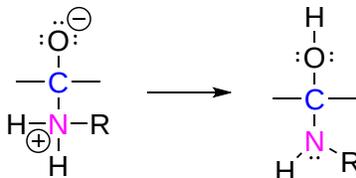
### MECHANISM OF IMINE FORMATION

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

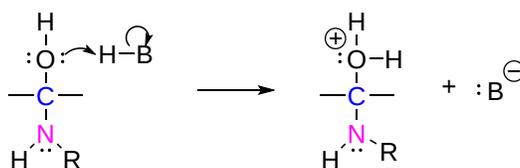
Step 1: Nucleophilic addition



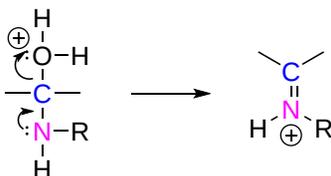
Step 2: Proton transfer



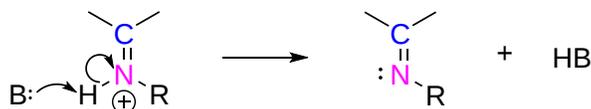
Step 3: Protonation



Step 4: Water is eliminated to form an iminium ion.

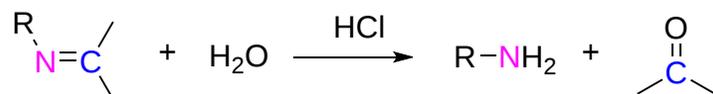


Step 5: Deprotonation



## REVERSIBILITY OF IMINE FORMING REACTIONS

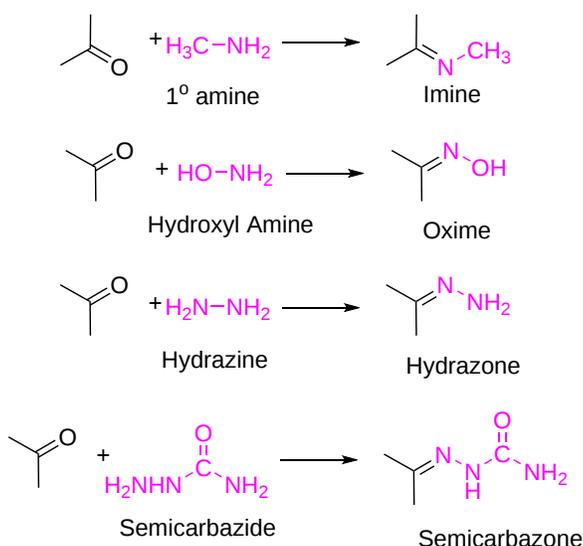
Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.



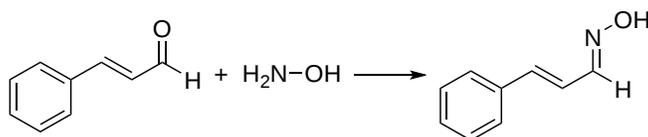
## REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH<sub>2</sub>

A wide variety of substances with -NH<sub>2</sub> groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y-NH<sub>2</sub> have been studied, and found to give stable products (R<sub>2</sub>C=N-Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed below, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in [Section 19.9](#).

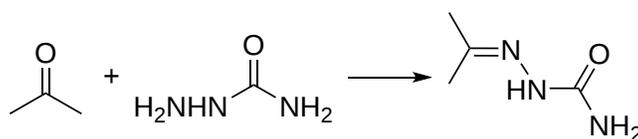
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups (-NH<sub>2</sub>) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.



### EXAMPLE



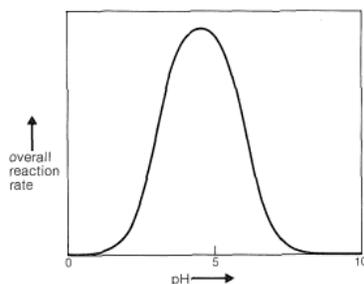
Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime



Acetone reacting with semicarbazide to form acetone semicarbazide

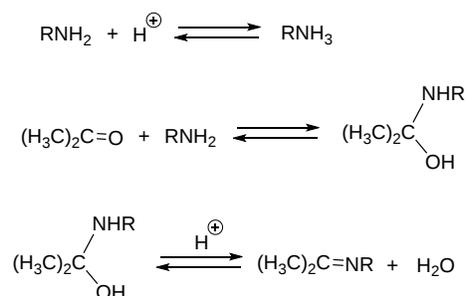
## THE PH DEPENDENCE OF IMINE FORMING REACTIONS

The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H<sub>2</sub>O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Schematic variation of the rate of condensation of  $\text{RNH}_2$  with a carbonyl compound as a function of pH.

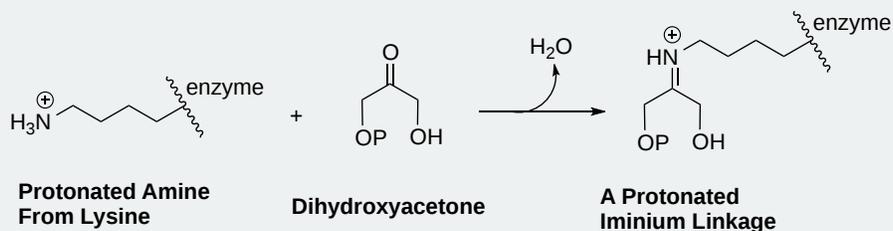
Clearly, if the unshared electron pair on the nitrogen of  $\text{RNH}_2$  is combined with a proton it cannot attack the carbonyl carbon to give the aminoalkanol produced during the mechanism. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable.



Dehydration of the aminoalkanol is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. As the pH is increased above 4, the dehydration step in the mechanism decreases in rate because it requires an acid catalyst. At pH 6 dehydration is the slow step of the mechanism, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction.

#### 📌 BIOLOGICAL IMINE FORMING REACTIONS

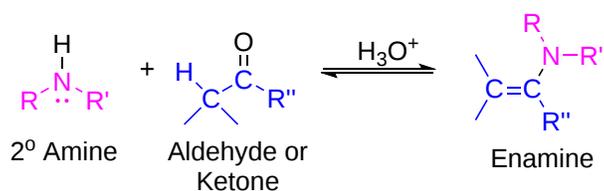
Imine intermediates are common in biological pathways. Carbon-carbon bond forming enzymes called aldolases often form a protonated iminium link between a carbonyl carbon on a substrate and the  $-\text{NH}_3^+$  from a lysine amino acid found in the active site of the enzyme. The reaction below shows an aldolase reaction from the Calvin Cycle where the carbonyl containing substrate is dihydroxyacetone. The Calvin Cycle is involved in the biochemical processes of carbon fixation and the production of sugars in plants.



After the carbon-carbon bond forming part of an aldolase reaction is completed, the iminium linkage is hydrolyzed, freeing the product so that it can diffuse out of the active site and allow another catalytic cycle to begin.

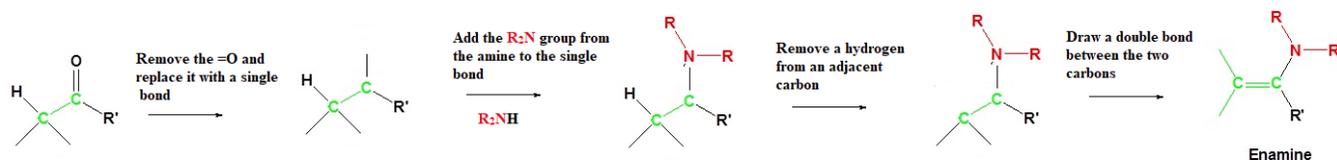
#### REACTION WITH SECONDARY AMINES TO FORM ENAMINES

Most aldehydes and ketones react with 2°-amines to give products known as **enamines** (alkene + amine). It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Secondary amines form a distinctly different functional group after nucleophilic addition because they lack the second hydrogen on nitrogen required for imine formation. During this reaction a hydrogen is removed from an adjacent carbon forming a  $\text{C}=\text{C}$  bond.

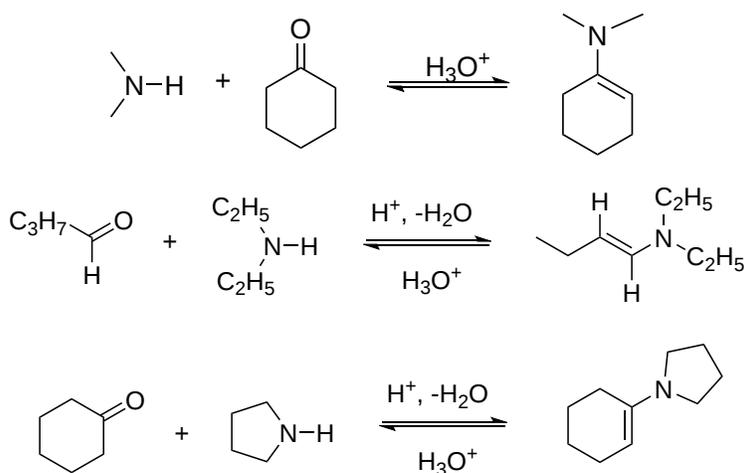


### PREDICTING THE PRODUCTS OF AN ENAMINE FORMING REACTION

During enamine formation the carbonyl oxygen is completely removed. The nitrogen of the amine reactant replaces the oxygen to form a N-C bond. During the process the amine loses its lone hydrogen. A hydrogen is removed from a carbon adjacent to the original carbonyl carbon forming a C=C between them.

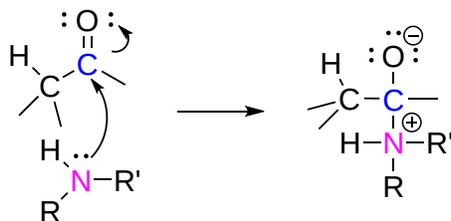


### EXAMPLE

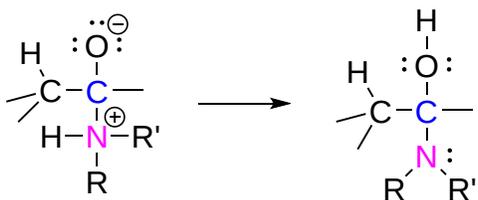


### MECHANISM

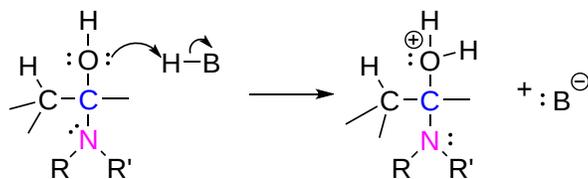
Step 1: The secondary amine undergoes nucleophilic addition to form a neutral tetrahedral intermediate.



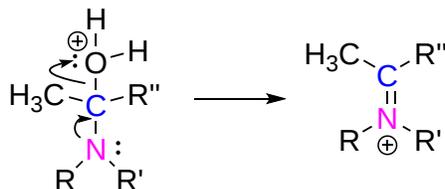
Step 2: A proton is transferred from the ammonium ion moiety of the tetrahedral intermediate to the alkoxide ion moiety. This forms a neutral functional group called a carbinolamine.



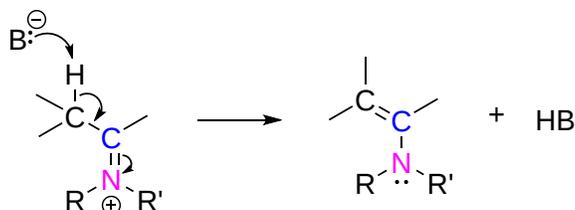
Step 3: The OH group on the carbinolamine is protonated by hydronium turning it into a good leaving group.



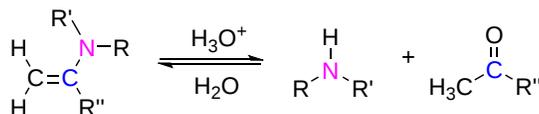
Step 4: The lone pair electrons on the nitrogen form the C=N double bond causing water to be eliminated. This forms an iminium ion



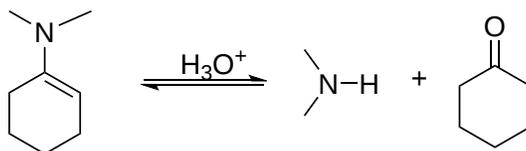
Step 5: Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond. This pushes two electrons from the C=N double bond onto the positively charged nitrogen creating the neutral enamine product and hydronium (or BH).



### REVERSIBILITY OF ENAMINES

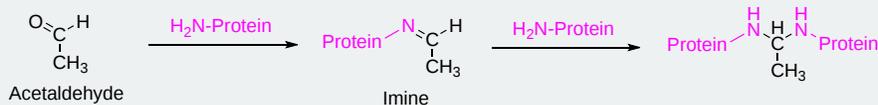


### EXAMPLE



### 📌 SOMETHING EXTRA: HOW DOES ALCOHOL CAUSE CIRRHOSIS AND LIVER CANCER?

One of the most insidious aspects of alcohol abuse is the fact that it will allow a user to continue, sometimes for decades, while it slowly destroys their body. Our bodies are actually designed to handle limited amounts of alcohol. Human metabolism includes enzymes that can convert alcohol into harmless metabolites in three steps. In the first step, an enzyme called alcohol dehydrogenase (ADH) acts as a catalyst for the conversion of alcohol to the toxic intermediate acetaldehyde.

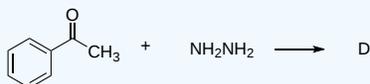
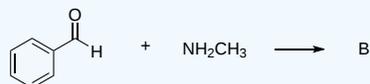
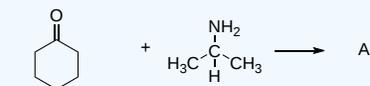


How acetaldehyde forms a protein adduct

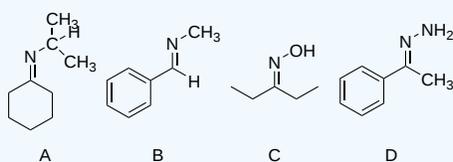
Forming adducts with DNA changes its structure and increases the chances of irregular replication, which is the starting point of cancer. Our bodies have processes that can repair or replace damaged proteins and DNA, but if enough build up they can lead to cirrhosis, liver cancer, liver failure, and death. Alcohol accounts for 28% of all liver-disease-related deaths in the U.S., and is also responsible for a little over 3% of all cancer deaths that occur globally. Hepatocellular carcinoma (liver cancer) is the fifth most common type of cancer, with an estimated 500,000 new cases being diagnosed every year worldwide. Because this type of cancer is usually discovered late, the prognosis is poor, with a median survival time of 1-2 months.

✓ EXAMPLE 5.9.1

Please draw the products of the following reactions.

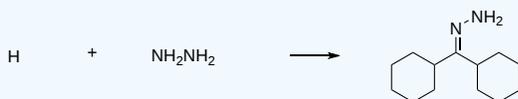
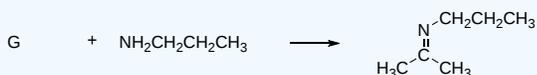


**Solution**

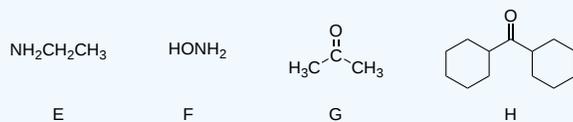


✓ EXAMPLE 5.9.2

Please draw the structure of the reactant needed to produce the indicated product.

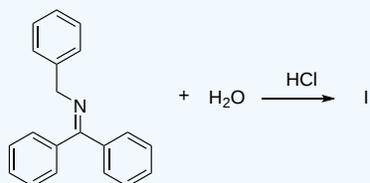


**Solution**

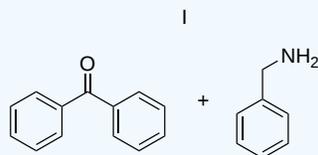


✓ EXAMPLE 5.9.3

Please draw the products of the following reactions.

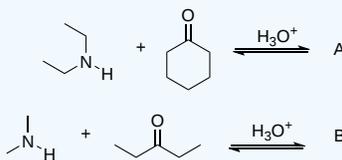


Solution

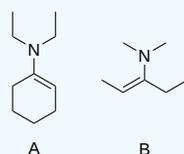


✓ EXAMPLE 5.9.4

Please draw the products for the following reactions.

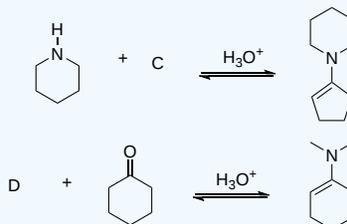


Solution

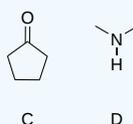


✓ EXAMPLE 5.9.5

Please give the structure of the reactant needed to product the following product



Solution



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