Purpose

To gain a greater understanding of the reactions between aldehydes and amines and of their usefulness in synthesis and biology.

Learning Objectives

Carry out a three-step synthesis, including a solvent-free step.

Write and interpret a reaction mechanism for each step.

Make and explain observations made during the reactions.

Theory and Background

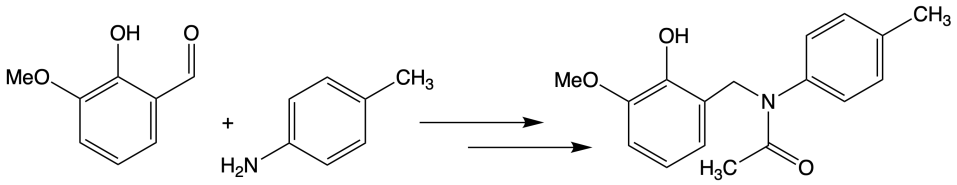

Figure 14B.1: Reaction of aldehyde and amine to form an amide.

During today's experiment we will be looking at the reaction between aldehydes and amines (Figure 14B.1). We have learned in Chem 109B and 109C that when an aldehyde or ketone is treated with a primary or secondary amine an imination reaction occurs to form an imine (Figure 14B.2). If a secondary amine is used, the product is an iminium ion which can quickly tautomerize to an enamine. Imines and enamines play an important role in both synthetic organic chemistry as well as biological chemistry.

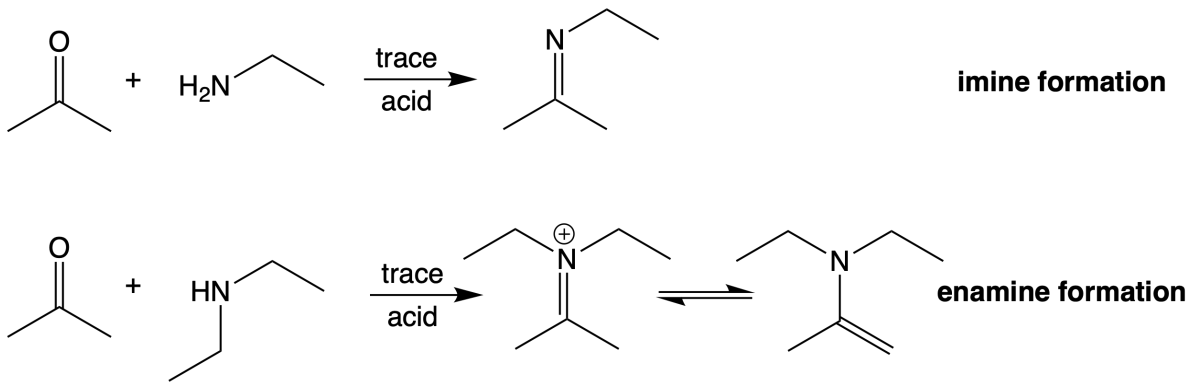

Figure 14B.2: Formaion of imines and enamines.

In a lab setting, imines have multiple uses. For example, imines may be reduced to form amines. When performed in tandem, imine formation and reduction are known overall as reductive amination. This two-step procedure allows for the synthesis of complex amines from relatively simple starting materials. Because of this, reductive amination is a very common procedure in organic synthesis. In today's reaction we'll be using sodium borohydride as the reducing agent but other types of reducing agents are also available for use by the synthetic chemist. Reductive amination has many uses, such as installing a new amine into a molecule or, if the aldehyde or ketone and amine are on the same molecule, forming a new heterocyclic rings(Figure 14B.3). Because enamines are good nucleophiles, they are regularly used in alkylation reactions.

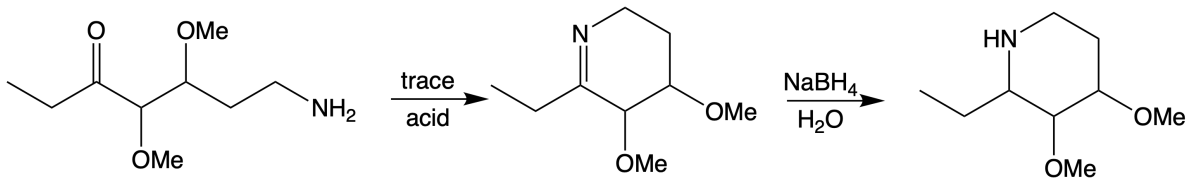

Figure 14B.3: Using reductive amination to form a heterocycle.

In biology, imines are a common way for enzymes to bind to substrates and coenzymes. For example, Vitamin B6 (commonly found in fish, liver, starchy vegetables, and non-citrus fruits) is converted in the body to the coenzyme pyridoxal pyrophosphate (PLP). PLP is kept in the active site of PLP-dependent enzymes (Figure 14B.5) through the formation of an imine with the aldehyde on PLP and the nitrogen on the side chain of a lysine residue. Histidine decarboxylase is one example of a PLP-dependent enzyme. Upon entering the active size of this enzyme, histidine forms an imine with PLP through a trans-imination reaction (a reaction in which one imine is converted into a different imine). This new imine allows the pyridine ring to act as an electron sink for a decarboxylation event, forming histamine, a molecule associated with allergies.

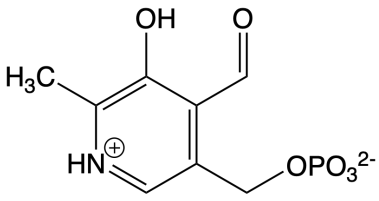

Figure 14B.4: Pyridoxal pyrophosphate (PLP)

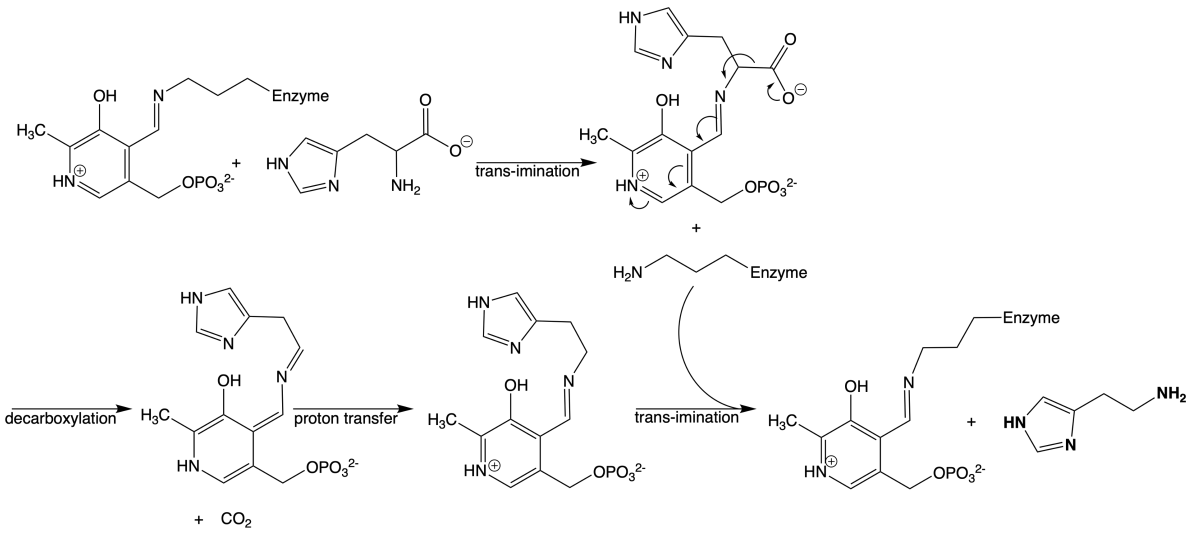

Figure 14B.5: Synthesis of histamine in histidine decarboxylase.

In today's lab, we will synthesize an imine from an aldehyde (ortho-vanillin) and a primary amine (para-toluidine) (Figure 14B.6). This reductive amination will give us access to a new secondary amine which we will convert to the more stable amide through use of acetic anhydride. The formation of the imine in today's reaction occurs in the absence of a solvent.

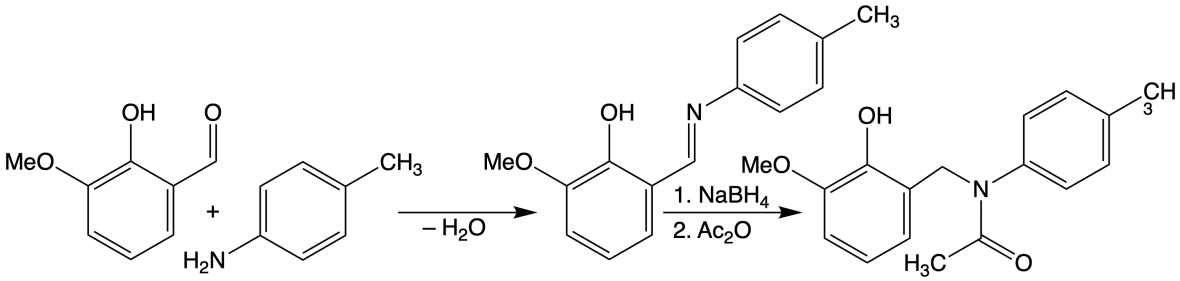

Figure 14B.6: Synthesis of an imine from an aldehyde and a primary amine.

Mechanisms

There are three mechanisms for today. The first, imine formation, is the longest. For a review of imine formation, see the video posted on Labflow. When writing mechanisms, the term "Ar" is an acceptable abbreviation for aromatic rings.

Procedure

Procedure adapted from Touchette, K. M. J. Chem. Edu. 2006, 83, 929.

Safety Precautions

All chemistry should be performed in the fume hood.

Acetic acid and acetic anhydride are corrosive.

Acetic anhydride is a lachrymator.

Amines are potential carcinogens.

Toluidine is highly toxic.

Step 1: Synthesis of 2-methoxy-6-(p-tolyliminomethyl)-phenol: Imine Formation

1. Weigh a 50-mL beaker and then add 213 mg (1.4 mmol) of *ortho*-vanillin. Record the total mass of the beaker plus the *ortho*-vanillin.

2. Using weighing paper, accurately weigh one equivalent of *para*-toluidine (150 mg, 1.4 mmol) and add this to the beaker. Observe this mixture for a few minutes and record what is happening.

3. Using a heavy glass stirring rod or metal spatula, mix and grind the solids *until they become a homogeneous dry powder*.

> As the solids mix, they should melt and start reacting. Using the liquid formed you should be able to mix everything rather easily. After a few minutes, the liquid starts to "dry out" as the reaction goes to completion, forming an orange powder. You should make sure it is thoroughly dry before continuing.

4. Weigh the beaker and record the mass. Determine the percent yield. Remove a small sample of this material for an IR and melting point analysis (literature value: 102 °C-103 °C).

5. Compare the features of your spectrum with those of the starting materials. Recrystallize the product from a minimal amount of warm hexane, then filter and dry the crystals.

Step 2: Synthesis of N-(2-hydroxy-3-methoxybenzyl)-p-methylaniline:Reduction of the Imine

1. Add about 5 mL of 95% ethanol to the beaker containing your imine product. Add a stir bar and stir the mixture. The solid will dissolve as the reaction stirs.

2. Weigh out approximately 28 mg of sodium borohydride and slowly add this to the beaker with continued stirring.

3. Record all observations and explain what is occurring in the reaction.

> A colorless solution is an indication that the reaction is complete. However, there may be a slight yellow that persists even with the addition of more reducing agent.

4. The reaction should be complete within 10 minutes.

Step 3: Synthesis of N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide: Acetylation of the Amine

1. Add 0.6 mL of acetic acid to the beaker containing the amine solution to quench the excess borohydride and to neutralize the phenoxide ion.

2. Slowly add 0.6 mL of acetic anhydride and warm the solution in a hot water bath for 5–10 minutes. Move this beaker to a stir plate, and stir the solution fairly rapidly while slowly adding 21 mL of water over the course of 2 minutes.

> Slow addition with rapid stirring is needed. Quick addition can cause the product to oil out and stick to the glassware, making recovery much more difficult.

3. After allowing the mixture to stir for a few minutes, cool the mixture in an ice bath and collect the solid with a Büchner funnel. Dry the product on the Büchner funnel by maintaining vacuum for 5–10 minutes.

4. Weigh the product and calculate the percent yield. Take an IR and melting point of your product (literature value: 127 °C-128 °C. If necessary, a small sample may be recrystallized from hexanes.

Discussion

Make sure to include the following points as your write your lab report:

1. Explain what was observed during Step 1 of the procedure.
2. Explain what you observed during the reduction of the imine.
3. Why is it necessary to wait until the imine is fully formed before adding $NaBH_4$?

Step 1: Synthesis of 2-methoxy-6-(p-tolyliminomethyl)-phenol: Imine Formation

Mass of beaker (g) _____

Mass of beaker + *ortho*-vanillin (g) _____

Mass of *para*-toluidine added (g) _____

Observations of mixture:

Melting point of Step 1 product (°C) _____

Step 2: Synthesis of N-(2-hydroxy-3-methoxybenzyl)-p-methylaniline:Reduction of the Imine

Observations of reaction:

Step 3: Synthesis of N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide: Acetylation of the Amine

Mass of product (g) _____

Melting point of Step 3 product (°C) _____