Reductive Amination

Adapted from: K.M. Touchette. *J. Chem Ed.* **2006**, *83(6)*, 929

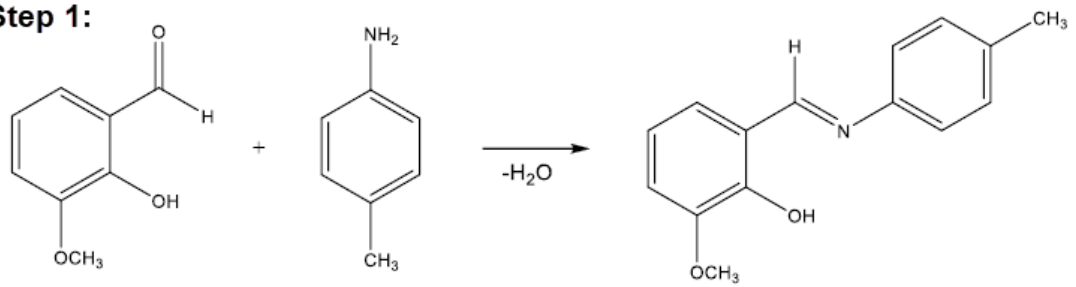
Background

There are 12 Principles of Green Chemistry, which can be used as a guide when designing experiments that maximize the efficiency and minimize hazardous effects on human health and the environment. Many organic chemistry experiments utilize solvents in the chemical reaction and/or during product isolation, so it can be advantageous to implement one of the 12 principles of using "Safer Solvents and Auxiliaries". When it is determined that solvents are not necessary for the success of a reaction, it is better to conduct the reaction in solvent-free conditions. Some chemical reactions can be solvent-free even when the starting materials are solids, this called a "solid-solid" reaction. Often the interaction between the solids when mixed, results in melting, allowing for a liquid reaction.

Experiment Overview

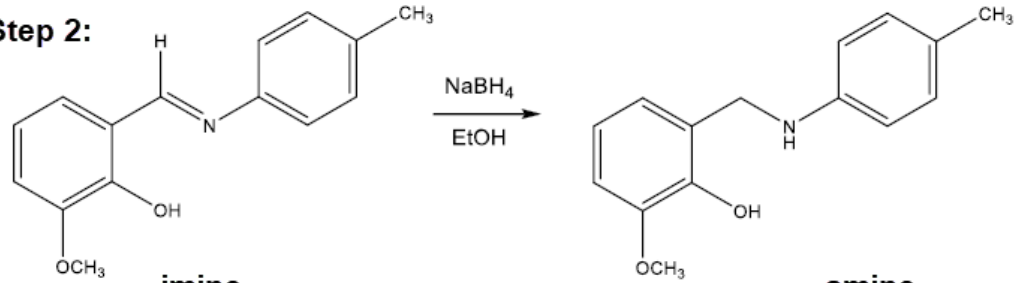
Amine synthesis is an extremely important reaction for synthetic organic chemists and has enormous applicability for biological molecules and drug discovery. One of the most versatile methods used in the synthesis of structurally diverse primary, secondary, and tertiary amines is reductive amination of carbonyl compounds, in which an aldehyde or ketone reacts with an amine to form an imine, which is then reduced by hydrogenation or by treatment with a hydride reagent. In this experiment, we will react ortho-vanillin with para-toluidine to generate an imine. The reaction occurs between two solids in a solvent-free reaction. The imine is then reduced with sodium borohydride to the amine, and then it is acetylated to produce a solid amide derivative. The entire reaction sequence can be performed in one hour in an open beaker.

Step 1:



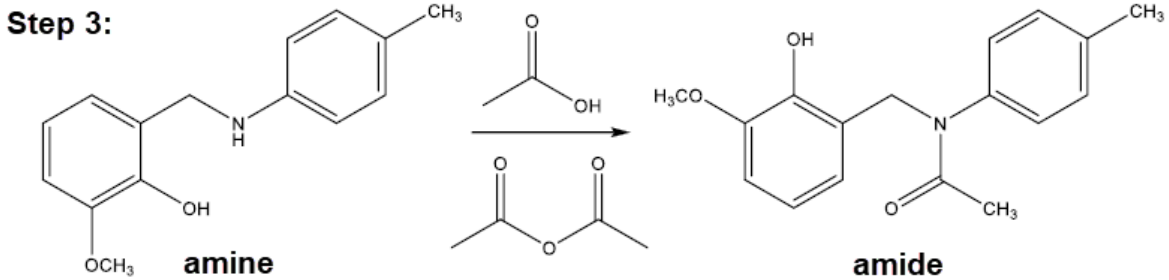
o-vanillin **p-toluidine** **imine**

Step 2:



imine **amine**

Step 3:



amine **amide**

CAUTION

Wear gloves and conduct all aspects of this procedure in a hood.

Acetic acid and acetic anhydride are corrosive**. Acetic anhydride** is a lachrymator. Wear gloves while handling, and dispense only in a hood.

Toluidine is highly toxic and **organic amines** are potential carcinogens. Wear gloves, avoid all contact with skin, eyes, and clothing, and dispense in a fume hood.

Ethanol is flammable. Keep it away from flames and hot electrical heating devices.

Procedure:

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

Weigh a 250 mL beaker and then add 0.76 grams (5 mmol) of *ortho*-vanillin to one side of the beaker. Record the total mass of the beaker plus the *ortho*-vanillin. Using weighing paper, accurately weigh an equivalent amount of *para*-toluidine (0.535 grams, 5 mmol) and add this to the opposite side of the beaker. Using a heavy glass stirring rod, mix and grind the solids together until they become a homogeneous ***dry*** powder (If the starting materials are pre-crushed, the powder forms in about three minutes – If not pre-crushed, it takes about 15 minutes). Record all observations and explain what is occurring in the reaction. Weigh the beaker and record the mass. Determine the percent yield. Remove a small sample of this material for IR analysis. Compare the features of your spectrum with those of the starting materials. Identify the absorption peak for the C=N stretch, and suggest a reason why the frequency is lower than expected.

Step 2: Synthesis of N-(2-hydroxy-3-methyoxybenzyl)-*p*-methylaniline: Reduction of the imine

Add about 15 mL of 95% ethanol to the beaker containing your imine product and stir the mixture to partially dissolve the amine. Weigh out about 0.1 g sodium borohydride and slowly add this to the beaker in small increments with continued stirring. Record all observations and explain what is occurring in the reaction.

Step 3: Synthesis of N-(2-hydroxy-3-methyoxybenzyl)-N-*p*-tolylacetamide: Acetylation of the amine

Add 2 mL of acetic acid to the amine to destroy the excess borohydride and to neutralize the phenoxide ion. Add 2 mL of acetic anhydride and a boiling chip and warm the solution in a beaker of boiling water for 5-10 minutes. Move this beaker to a stir plate, and stir the solution fairly rapidly while slowly adding 75 mL water. Continued stirring should leach out the alcohol and acetic acid causing the amide product to precipitate. Cool the mixture in an ice bath and collect the white solid by vacuum filtration, pulling air through for several minutes to evaporate most of the water. Analyze your product by IR spectroscopy.