

Experiment 4

Solid-Solid reaction of reductive amination

prepared by **Kim M. Touchette**, Bard College

modified by **EunJin Ahn**, KAIST

Kim M. Touchette, *J. Chem. Edu.*, **2006**, Vol.83 No.6, 929-930

PURPOSE OF THE EXPERIMENT

3 step one-spot reductive amination reaction for undergraduate organic chemistry experiment. Learn concepts as green chemistry, solid-solid reaction, reductive amination of carbonyl compounds.

BACKGROUND INFORMATION

The purpose of 'solid-solid reaction of reductive amination' is to proceed 3 step organic synthesis of amination including dehydration. Amination the most basic and applicable reaction because lots of biological materials and drugs are composed of amine group. The most well-known reaction is the reductive amination of carbonyl compounds. These reactions include the immediate interaction of aldehyde (or ketone) with ammonia to form imine. This experiment also includes imine formation which minimized formation of byproduct and amount of solvent.

Organic Chemistry 1 and 2 explains aldehyde, amine reaction and boron hydride reduction reactions. This experiment will be the chance to perform these concepts in the laboratory. It will also provide opportunity to learn unfamiliar concepts as solid-solid reaction, green chemistry.

In the first step, the reaction of solid ortho-vanillin and solid para-toluidine is considered as solid-solid reaction. Previously, most of these reactions were treated in inorganic chemistry part and explained by ion displacement of crystalline compounds, and crystal deformation mechanism. Gradually, solid state reaction meant high yield, short reaction time, moderate condition in organic chemistry. Most of solid reactions are not a strict solid reaction-they generates liquid(ex)water) during the reaction which affords high mobility place. Nevertheless, solid-solid reaction is still a conceptual group of reactions that starts without solvent: The only solvent used in this reaction is ethanol!

We expect this experiment to be appropriate for students to learn green chemistry, solid-solid reaction, amination and the purpose and meaning of organic synthesis.

EXPERIMENT

Reductive Amination : A Remarkable Experiment for the Organic Laboratory

Materials Used

100 mL beakers	water bath
250 mL beakers	support ring
boiling chips	2 support stands
glass-stirring rod	2 utility clamp
Buchner funnel	gloves

Filter paper	50 mL graduated cylinder
pasteur pipettes	spatula
NMR tube	Stirring bar

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (<i>g/mol</i>)	<i>mmol</i> [†]	<i>mp</i> (<i>°C</i>)	<i>bp</i> (<i>°C</i>)	<i>density</i> (<i>g/mL</i>)
Ortho-vanillin	0.76 g					
Para-toluidine	0.535 g					
95% ethanol	15 mL					
NaBH ₄	0.1 g					
Acetic acid	2 mL					
Acetic anhydride	2 mL					
H ₂ O	75 mL					
ice						

PROCEDURE

Caution: Wear lab coats and safety goggles at all times while in the lab. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Wearing contact lens is strictly prohibited.

1. Imine formation

Prepare weighed 100 mL beaker. Add 0.76 g of ortho-vanillin in one side of the beaker. Then add 0.535 g of para-toluidine to the other side of the beaker. Mix two solid compounds with glass-stirring rod and record observation. Mix them until they become homogeneous dry powder. You may weigh the mass to determine the yield. Take a little amount of solid for NMR sample.

2. Reduction of imine

Add 15 mL of 95% ethanol to the 100 mL beaker (methanol is also appropriate for the reaction) and dissolve imine powder. Notice that powder will dissolve only partly. Add about 0.1 g of NaBH₄ to the solution slowly. Record what happens to the mixture.

Note 1.

Imine will be formed in this step, and can be separated by recrystallization but we will not separate it here.

3. Acetylation of the amine

Heat water bath to 80 °C before addition of acetic acid and acetic anhydride. Also prepare ice bath.

Add 2 mL of acetic acid to the amine solution. Then add 2 mL of acetic anhydride. Put the beaker inside the water bath for about 10 minutes. After 10 minutes, place the beaker on the stirring plate. While stirring strongly, add 75 mL of H₂O slowly. After addition, put beaker in the ice bath for precipitation of product. Wait for precipitation, and collect them by using Buchner funnel. Use water for washing beaker. If possible, take dry sample of final product for NMR spectrum. Dry the product in the oven or air-dry overnight for calculating yield.

4. Characterizing the Product

Using NMR Spectroscopy to characterize the starting material, imine and final amine solids.

Caution: CDCl₃ is toxic and a suspected carcinogen. Dispense it in a fume hood. Wear protective gloves.

Product was dissolved in CDCl₃. Obtain a NMR spectrum of your product as directed by your laboratory instructor.

3. Cleaning up

Clean glass wears and all the instruments. Instructor should check each student's hood.

Post-Laboratory Questions

1. Explain the whole mechanism of the experiment (imine formation, reduction of imine, amide formation).
2. Why does the color change occur during imine formation reaction?
3. Why we proceeded the reaction even though imine dissolved partly? How could the reaction go forward?
4. What is the purpose of adding acetic acid and water at final step?
5. Characterize NMR spectrum.

**Pre-Laboratory
Questions**

1. Summarize MSDS of all chemicals used in this experiment?
2. Explain the concept of lowering in the melting temperature of solids.
3. Search few ways to synthesize imine compound.