

Synthesis of Aspirin

In this experiment, Aspirin will be made by the esterification of salicylic acid. The product will be isolated and a Thin Layer Chromatography (TLC) will be used to analyze the success of the reaction. Procedure for two different reactions scales; microscale and mini-scale are provided. Your instructor may have students work in pairs, each students carrying out one scale and compare the efficiency of the two scales.

PRE-EXPERIMENT ASSIGNMENT

Study this chapter of the manual, section 21.9 of Klein and the notes on the Chemistry Department web site. Do the first parts of your notebook writeup. Reread the on-line notes relating to TLC analyses.

A student who has prepared for the Synthesis of Aspirin experiment should be able to:

1. Give a balanced equation for the synthesis of aspirin from salicylic acid and acetic anhydride, identify the functional groups involved, and give the mechanism of the reaction.
2. Calculate the theoretical yield and the percent yield for this and similar experiments given the necessary data, and perform any of the intermediate calculations required by this process.
3. Draw the structure given the name, or give the name from the structure, of the compounds used in the day's experiment, and give the role of each (reactant, solvent, catalyst, etc.).
4. Identify and explain safety considerations for this experiment.
5. Perform the day's experiments safely and successfully.

Safety Precautions

Acetic Anhydride is corrosive, reacts violently with water, is toxic by inhalation, harmful by ingestion and a lachrymator (makes eyes hurt and water severely). Keep reaction in the hood until quench water has been added. Salicylic Acid causes mild skin irritation. Causes severe eye damage. Ethyl acetate and hexanes are flammable organic solvents. Phosphoric Acid is a strong acid. It will cause immediate destruction of tissue upon contact. Avoid all direct contact. Wash with copious amounts of water if accidental contact is made.

Microscale Procedure (~0.15g SA)

Turn on your hot plate and begin heating a 100 mL beaker containing about an inch of water and a boiling stone. The water should be heated to about 90°C- or just until small bubbles form and rise to the surface. Obtain approximately 0.15 g of salicylic acid and place it in a reaction tube. (Again do not waste time weighing out exactly 0.1500 g but do record all digits obtained.) To a clean and **dry** reaction tube add one boiling chip and one drop of 85% phosphoric acid (be careful, it's corrosive) to the reaction tube. Finally add 0.3 mL of acetic anhydride (caution!), using it to wash the other materials to the bottom of the tube. A syringe is an easy way to measure this volume. Record volume used precisely in notebook. Shake to mix the reactants thoroughly. Place in hot water bath and stir or shake until all of the salicylic acid has dissolved. After all of the salicylic acid has dissolved continue to heat the reaction tube in the hot water bath for five additional minutes.

Remove reaction tube from hot water but remain in hood. Cautiously add 0.2 mL of water to the reaction mixture to decompose all excess acetic anhydride. Stir or shake the tube. This will be an exothermic reaction, so allow the reaction to finish before adding another 0.3 mL of water and allowing the tube to cool slowly to room temperature. The product should crystallize during this time. If it doesn't, remember the options you learned in the recrystallization lab, and then ask your instructor for advice.

Once the tube reaches room temperature, cool it in an ice bath for an additional ten minutes. Remove the solvent with a Pasteur pipette. Transfer the crystals onto a piece of clean, dry filter paper. Fold the paper in half and squeeze the crystals between the halves to absorb excess water. Next, spread the crystals out on another piece of clean, dry filter paper and allow them to dry in the air. *If you are also doing the macroscale experiment, begin that part while these crystals are drying.* After the crystals have dried, remove boiling stone, weigh them and analyze via TLC.

Mini-scale Procedure (~1g SA)

Turn on your hot plate and begin heating a 250 mL beaker containing about an inch and a half of water and a boiling stone. The water should be heated to about 90°C- or just until small bubbles form and rise to the surface. Weigh out approximately 1 g of salicylic acid. Add this and a boiling stone to a clean and **dry** test tube. Add approximately 2 mL of acetic anhydride. Remember to record all digits from balance and to read graduated cylinder to proper decimal places. Add 5 drops of phosphoric acid to the tube while stirring constantly. The reaction will be exothermic. Shake to mix the reactants thoroughly. Place in hot water bath and stir or shake until all of the salicylic acid has dissolved. After all salicylic acid has dissolved continue to heat the test tube in the hot water bath for an additional five minutes.

Remove test tube from hot water but remain in hood. Transfer the reaction mixture to a 50 mL Erlenmeyer flask containing 10 mL of deionized

water. This will be an exothermic reaction. Rinse the test tube with an additional 1-2 mL of water and add that to the Erlenmeyer flask as well. Swirl the flask. Allow to slowly cool to room temperature by sitting on bench. Do not disturb while crystals are forming. Once solution has cooled to RT, place in beaker containing a slush of ice and water. Allow to cool a minimum of 5 minutes. If no crystals form, scratch the inside of the flask with a glass stirring rod to induce crystallization.

Collect the solid by suction filtration, running the vacuum for a few extra minutes to help dry the crystals. Complete drying in air. Remove boiling stone and weigh the product. Analyze the product via TLC.

TLC

Obtain a TLC plate. Using a pencil mark a line approximately one cm from bottom. Remember to **not** touch the rough side of the TLC plate with fingers. Handle by edges only. Solutions of salicylic acid in acetone are available for comparison. To make a solution of your product place a spatula tip full of product in small beaker or shell vial. Add acetone dropwise and with stirring until solid dissolves. Mark and spot TLC with both “authentic salicylic acid” and “product”. Make a TLC chamber. Two or more students may sequentially (not simultaneously) use the same chamber. Develop TLC using a mobile phase of 50% Ethyl Acetate 50% Hexanes. Mark solvent stop as soon as remove from chamber. Using UV light examine plate. Circle all spots and place a small dot at center of each. Draw a representative copy of your TLC plate in your notebook. Attach TLC to lab report that you will turn in at the beginning of class next week. In lab report be sure to calculate the R_f value for each spot observed. Also discuss reaction success based on the obtained TLC results.

Comparison of Methods

Obtain data from the other reaction scale from one of your classmates. Look at their TLC plate. A Xerox copy of their TLC may be helpful.

CLEANUP

Place used Pasteur pipettes in the broken glass box. Leftover solvents and are placed in the non-halogenated organic liquid waste bottle in the hood, and acetylsalicylic acid product goes in the non-halogenated solid waste jar. Wipe down work area with sponge. Wash hands.

POST-EXPERIMENT ASSIGNMENT

Write the lab report and have it ready to turn in by the beginning of the next lab. Your writeup of this experiment should include a calculation of the percentage yields for both the semi-micro and microscale experiments. An R_f calculation for every spot on the TLC plate should be made. Your conclusions section should include a comparison of the microscale and the macroscale experiments in terms of percent yield and TLC results. Finally conclude which

method was better from the standpoint of both purity and yield (if possible). If your percent yields were not 100%, you should explain where the missing material might have gone (or where extra material might have come from). Prepare for the aspirin synthesis portion of the next quiz.

REFERNCES

Sigma-Aldrich MSDS of Acetic Anhydride

<http://www.sigmaaldrich.com/catalog/DisplayMSDSContent.do> (March 19, 2011)

Sigma Aldrich MSDS of Salicylic Acid.

<http://www.sigmaaldrich.com/catalog/DisplayMSDSContent.do> (March 19, 2011)

Crago, K., DiMaggio, S., Foroozesh, M., Giannamore, V., Goloverda, G., Jordan, Tl, Morgan, K., Polito, M., Politzer, I., Ross, T., Sevenair, J., Organic Chemistry Laboratroy Manual, 6th Ed; Wiley Custom: Hoboken NJ, 2006, p 94-96