Experiment 5 – Synthesis of Aspirin

Learning Objectives

- Perform and understand esterification reactions
- Purification – acidification & recrystallization
- Observe and interpret iron (III) chloride tests for phenols
- Interpret infrared (IR) spectra of starting materials and product to determine reaction success
- Predict and interpret ^{1}H and ^{13}C NMR spectra of aspirin

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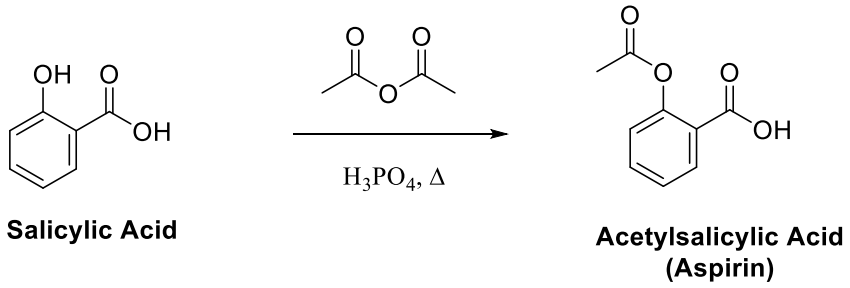
* Please find "How to Prepare for Lab & Assignments" after the procedure in this doc.

Lab Overview

In this experiment, students carry out the acid-catalyzed esterification of salicylic acid with acetic anhydride and isolate aspirin as a white solid (**Scheme 1**). The mechanism is similar to Fischer esterification (Exp 4). The difference is the use of an acid anhydride instead of an alcohol. Acetic anhydride loses its acetate group, which is removed in the reaction workup with a weak base extraction. Conversion to product is confirmed with iron (III) chloride chemical tests in comparison to standards. IR spectra of starting material and product as well as ^{1}H and ^{13}C NMR spectra of aspirin will be interpreted.



Scheme 1. Aspirin synthesis *via* acid-catalyzed esterification with acetic anhydride.

PROCEDURE

Procedure Diagrams must be complete in your notebook before you can start the lab (see worksheet).

1. Reaction Setup: Fill a small crystallizing dish half way with water. Place on a hotplate (medium setting) and bring to a gentle boil. You may do this when you enter the lab, before the TA's pre-lab talk. *The water bath must be pre-heating before obtaining reagents.* In the meantime, in a clean and **dry** 15-mL round-bottom flask add a small stir bar and approximately 200 mg of salicylic acid. Add 2 mL of acetic anhydride using the pluringe provided (keep this and all reagent bottles in the fume hood). Finally, add 2 drops of H_3PO_4 to catalyze the reaction.

Attach a microscale condenser using a small amount of grease and Keck clip. Place the apparatus half-way in the *boiling* water bath and let the system react for about 5 minutes. The reaction will not proceed if the water bath is not at a boil for the full 5 minutes. *Carefully* move the apparatus out of the water bath and allow the system to cool to room temperature. Add 1 mL of water through the top of the condenser to quench excess acetic anhydride. Place the system back in the water bath and allow this to react for an additional 5 minutes. There is no need to continue heating the water bath during this time - just the warm water bath is sufficient.

2. Reaction Workup: Carefully remove the water bath from the hot plate using a hot mitt and let the reaction apparatus cool to room temperature. Use a pipet to transfer the liquid to a labeled 50-mL beaker. Wash the walls of the RBF with 2 mL of water to facilitate transfer of any reaction mixture still in the flask. Add 3 mL of water to the beaker then cool the system in an ice-water bath for a few minutes. Once the solution has cooled, *scratch the bottom of the beaker with a glass stir rod to release small crystals attached to the glass* and promote further crystal growth. If crystals do not form within a few minutes after scratching, raise your hand to obtain a seed crystal from your TA. Allow crystals to form undisturbed in the ice-water bath for an additional 5 minutes (Pro-tip: crystals tend to form when you're not watching them!).

Set up the vacuum filtration apparatus while crystals continue to form and pre-weigh the filter paper. Vacuum-filter the product using a Buchner funnel. It is common for more crystals to form in the filtrate after filtration. If that is the case, transfer the funnel onto a different filter flask and filter again. Carefully collect a small amount of aspirin off the filter paper for the chemical test (microspatula tip). The effect on product yield is negligible. Let the solid dry on the filter paper with the vacuum on for 10 minutes while performing the chemical tests. Weigh the product and calculate the yield by subtracting the mass of filter paper. Calculate the % yield using the theoretical yield from the pre-lab.

4. Analysis: Iron (III) Chloride tests, IR, ^{1}H NMR, and ^{13}C NMR

Start early with the standards while the reaction is running, aspirin crystals are forming, or any other down time. Obtain reagents in the fume hood then bring the samples back to your workspace. Prepare 3 labeled test tubes each with 1 mL of a 0.1% aqueous ferric chloride solution in each. To one test tube, add a small amount of salicylic acid (microspatula tip). Add the aspirin product to another test tube. Add a drop of water to the third test tube. Observe any change in color. A red-purple color is a positive test for phenols; yellow is considered negative. Have your TA initial your exam to confirm that you have completed the chemical tests.

Analyze the IR spectrum of the alcohol (provided in lab, posted on Canvas). Obtain the IR spectrum of your product and identify ester peaks. Is there an OH peak in the product?

Interpret the ^{1}H and ^{13}C NMR of aspirin on Canvas. Assign every H on the structure to a signal on the spectrum. This is all covered in lab lecture ☺

Table 1. Clean up and safety instructions

Clean-up	*Safety*
Keep all reagents in the fume hood and clean up spills with spill mats, NOT the sponges from the sink.	**Label** all glassware (except for reflux setup). **Phosphoric acid is corrosive** – change gloves after use
Return all shared glassware, cleaned, to its original location.	**Acetic anhydride is a lachrymator** (induces tears) – wear goggles
Unplug hotplates. Disassemble the reflux and filtration apparatus – leave materials as you found them.	**Wear gloves, goggles, and lab coat at all times.**
Solid waste: Used pipets, filter paper, product *Liquid waste:* filtrates	*** Allow reaction to cool (raise out of water bath) before quenching with water.**

Adapted from Palleros, D. R. “Transforming Bengay into Aspirin” in *Experimental Organic Chemistry.* Wiley: New York, **2000**.

How to Prepare for Lab + Assignments

Follow Canvas Exp 5 Module…

Before Lab

- Read this PDF – background, procedure, safety, pre-lab and in-lab questions
- Attend and/or watch **lab lecture** – we go over everything you need for your assignments!
- Practice the lab online *via* **Slugs@home platform** - sites.google.com/ucsc.edu/slugshome/home
- Complete the **pre-lab questions** at the end of this doc - incorporated into Canvas quiz ☺
    - **Quiz** due before your enrolled section – check Canvas for due date
- Download the **Exp 5 worksheet** and prepare your **lab notebook**…

Lab Notebook Preparation – *worksheet = template / outline to copy by hand into lab notebook*

- **Purpose:** one-sentence summary of the main lab goals plus the reaction scheme
- **Reagent Table** – add chemical properties; Wikipedia is a reliable source for chemical properties!
- **Procedure with Diagrams** – complete before starting lab; sample on Canvas
    - Use the procedure on the previous pages to create your hand-drawn experimental instructions
        - Simple sketches & labels for all **equipment, chemical names** with **amounts**, & **transfers**
    - Format: Break it up with flow charts, bullet-points, comic strip, and/or whatever works for you!
        - Avoid copying the procedure word-for-word.
        - Make it easy for anyone to follow your procedure without referring to this document.
    - **Slugs@home Exp 5 website** - Equipment & Safety pages; pictures & videos of the whole lab
    - The **class notes** include useful diagrams as well

During Lab

- Check the **safety rules** to dress for lab and arrive a few minutes early to **Thimann Labs**
- **Pre-lab talk:** tips for success and open Q&A
- Show your **lab notebook pages** to your TA
- Perform the experiment with a partner, fill out data & observations in **lab notebook**

After Lab – each partner submits separate, individual assignments

- Upload **Notebook Pages** to Canvas by midnight on lab day – graded on completeness / participation
- Complete & upload the **Lab Report** on GradeScope (GS) – due date on Canvas
    - In-lab questions & experimental methods – see last page of this document

Pre-lab Questions / Quiz – see your class notes!

1. Convert the amounts of salicylic acid and acetic anhydride provided in the procedure into **mmoles**. Calculate the mmol of salicylic acid and acetic anhydride used in the reaction. Calculate the **theoretical yield** for the esterification reaction (synthesis of aspirin from salicylic acid). Show your work.

2. What would happen if the glassware were not **dry** during the esterification reaction? How is water used to **quench the reaction** after it is complete?

3. What differences would you expect to see in the IR and ^{1}H NMR spectra of salicylic acid and aspirin?

4. There are several periods of down time during this experiment. What / when are these periods and what can you do in your down-time to be efficient with your time?

Take the **Canvas Exp 5 pre-lab quiz by midnight Monday** *before* your enrolled section.

- The quiz incorporates the questions below - the questions may be reworded.
- **Be prepared with your responses to the pre-lab questions *before* starting the quiz.**
- There is a 20-minute time limit on the quiz and you get two attempts.
    - Make sure you have enough time to complete the quiz - you can't save and come back later.
    - If you choose to re-take the quiz, your grade will be the highest of the two attempts.

Though we encourage collaboration in this class, this is an individual quiz.

- The responses should be a product of your original work so that you are assessed on *your* understanding of the material.

Sharing your quiz or your responses in any format (screenshots, email, CHEGG, social media, text, carrier pigeon, etc.) is in violation of the UCSC academic integrity policy.

LAB REPORT

Upload to GradeScope (GS) – see due date on Canvas

- **Select Pages** to correlate your responses to the GS outline ☺
- OPTION to work with a partner – one person uploads the PDF then **"Add Group Member"** – gives both of you the same grade

A. In-Lab Questions – see your class notes!

1. Draw the arrow-pushing **mechanism** for the synthesis of aspirin from salicylic acid. You may abbreviate the aromatic ring ("Ar") in the intermediates; draw full structures of starting materials and products.

2. What are the two **roles of water** in the reaction work-up? Show the **chemical reaction** for the water-sensitive reagent.

3. Report the **mass of salicylic acid** given and the re-calculated **theoretical yield of aspirin** (mmol and mg). Report the **mass of product** and calculate the **% yield** of aspirin. Show your work.

Use the table format provided in the **Exp 5 Worksheet** to report data in addition to the prompts below.

4. Report the observations and interpretation of the **ferric chloride tests**. Was the reaction successful? Briefly explain.

5. Interpret the **IR** spectra of starting material and product in table format. Which peaks in each IR spectra be used to tell whether the reaction is complete?

6. Interpret the **^{1}H NMR** of aspirin on Canvas. Report integration, chemical shift (expected and observed), and splitting patterns for each signal in table format. Clearly assign each signal to the structure. You may list a range of expected chemical shifts where appropriate but you are graded on proper assignments of all signals to observed shifts.

7. Interpret the **^{13}C NMR** of aspirin on Canvas. Assign as many signals as possible on the spectrum to the structure (you're not expected to definitively assign each carbon, but you can get close!). Report the appropriate expected chemical shift range of each carbon using the NMR table of values.

B. Experimental Methods

Writing guidelines and sample experimental methods are available on Canvas. Remember the sample experimental contains way more information than is pertinent to CHEM 8M students! Apply the format used in previous reports:

Analysis: Report whether the absence of a phenol was confirmed by the **iron (III) chloride test** (no procedural details). **IR** is the only form of characterization to report, as you are not directly analyzing your sample by NMR.