

The Synthesis of a Common Analgesic

Principles of Chemistry (CH114)

Prepared by Guillermo Moyna

Introduction

Almost all the materials that we are exposed to daily are the product of chemical modifications of compounds or materials occurring naturally. In particular, all the drugs that we employ in the treatment of diseases are prepared synthetically, either from scratch or by modification of naturally occurring compounds. Therefore, knowledge of the process of making new molecules (i.e., synthesis) is crucial to anyone involved in one way or another with a career in chemical and pharmaceutical sciences.

A Brief History of Aspirin

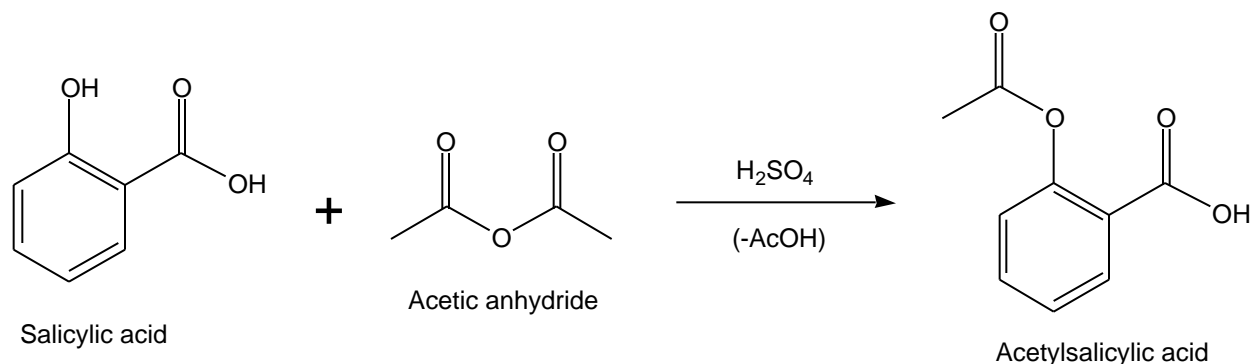
Aspirin, or acetylsalicylic acid, is a synthetic compound known virtually to everyone. As an example, 1 in 5 Americans take aspirin at least once a day. It is extensively used for the relief of headaches, inflammations, arthritic pain, and lately it has been used for the prevention of heart attacks and strokes.¹ It was developed by German scientists around 1895, and first put to good use by Felix Hoffman, an employee of Bayer AG who gave it to his father to treat arthritic pain, because it was much better tolerated than other salicylic acid derivatives used at the time.

Its mode of action, whose discovery gave the Nobel Prize to Sir John Vane in 1970,² involves the inhibition of the synthesis of prostaglandins, molecules that cause inflammation, blood clotting, and trigger pain.

Although drug industries have developed thousands of far more complicated compounds for the treatment of numerous diseases, aspirin is still called the most successful drug in history, and it is to this day one of the products that generates the largest revenues for pharmaceutical companies.¹

The Experiment

In today's experiment you will prepare aspirin from salicylic acid and acetic anhydride. The area of chemistry that deals with these type of molecules and reactions is called **Organic Chemistry**, because these molecules contain carbon, oxygen, hydrogen, and nitrogen, which are the constituents of living (or organic) systems. The reaction is shown below:



In these **stick diagrams** organic chemists are very succinct: The lines mean that there is a bond, and the vertices represent carbon atoms. Note that the hydrogens are not drawn, but are present, so that all carbons that have less than 4 bonds have hydrogens on them.

The reaction is called an **acetylation**, because an **acetyl group** is being added to one of the reagents, in this case salicylic acid. This reaction belongs to a larger class of organic transformations called **esterifications**,³ because an **ester** of the **acid** (in this case acetic acid) is made by combination with an **alcohol** or **phenol** (in this case salicylic acid). The reaction is catalyzed (that means, speeded up) by an acid, which will be phosphoric acid in this case. The lab instructor will tell you about the mechanism of this reaction while the reaction is running.

Experimental Procedure

*Safety Precautions: Avoid coming in contact with acetic anhydride or phosphoric acid. Both compounds will produce burns. Avoid inhaling acetic anhydride vapors. Wear your safety goggles **AT ALL TIMES**.*

1. Weigh out 3.0 g of salicylic acid and place it in a 250 mL Erlenmeyer flask.
2. Measure 6.0 mL of acetic anhydride with a graduated cylinder, and add them carefully to the Erlenmeyer.
3. Take the Erlenmeyer to the hood, and carefully add 5 to 10 drops of 85% phosphoric acid, the catalyst. Swirl the flask carefully so that the contents mix thoroughly.
4. Place the flask on top of a heating plate at a setting of approximately **2**. The plate should be at ~ 70 °C. To measure this, you can place a thermometer in a beaker next to the Erlenmeyer flask. Heat the mixture gently for 15 to 20 minutes swirling the contents from time to time.
5. After heating the mixture, let it cool to room temperature and CAREFULLY add 25 to 30 mL of distilled water. Let the mixture sit undisturbed. Crystals of aspirin should start appearing as the mixture cools. If no crystals appear after 10 minutes, scratch the sides of the Erlenmeyer CAREFULLY to induce crystallization.
6. After 10 minutes, place the flask in an ice-water bath, and leave it there for 10 minutes. This will maximize the recovery from the crystallization.
7. While your flask is in the ice-bath, set up a filter flask with a Büchner funnel and a piece of moist filter paper. Make sure that there is good suction on the water aspirator.
8. Transfer the contents of the Erlenmeyer flask to the Büchner funnel and apply suction. You have to do your best to transfer as much of the material as possible with a spatula.
9. Wash the Erlenmeyer flask with 2 to 5 mL portions of chilled water, and pour these washes through the Büchner funnel. Wash the product in the Büchner funnel with two additional 2 to 5 mL portions of chilled distilled water.
10. Draw air through the Büchner funnel for 10 minutes. After that, carefully take out the filter paper and your product and put it in a watch-glass. Put this watch-glass in an oven at 100°C for 10 additional minutes to dry your product.
11. Take the product out of the oven and let it cool, and then carefully weigh it. Calculate your yield as explained below.

12. In order to test the purity of the aspirin you just prepared you will use thin layer chromatography (TLC). Your instructor will discuss with you the solvent system to use and how to prepare the samples for this part of the experiment.

The Lab Report

For this laboratory you will prepare a formal lab. Thus, you will need to type it up with a word processor and use the appropriate format. You should also attempt to draw the reactions that you did using a structure drawing program (ChemSketch or ChemDraw). If you cannot make it work, draw them carefully by hand.

In your report, you should include the **yield** of the acetylation reaction. The yield is calculated as:

$$\text{Yield (\%)} = 100 \times \frac{\text{(Moles of compounds obtained)}}{\text{(Moles of compound that you should obtain theoretically)}}$$

Alternatively, you can use grams instead of moles:

$$\text{Yield (\%)} = 100 \times \frac{\text{(Grams of compounds obtained)}}{\text{(Grams of compound that you should obtain theoretically)}}$$

In either case, you should calculate the theoretical amount of compound from the reaction from the moles that you used from your limiting reagent, which in this case is salicylic acid.

References

1. Mann, C. C.; Plummer, M. L. *The aspirin wars: Money, medicine, and 100 years of rampant competition*. Knopf, New York, NY; 1991.
2. Feinman, S. E. (Ed.). *Beneficial and toxic effects of aspirin*. CRC Press, Boca Raton, FL; 1993.
3. March, J. *Advanced Organic Chemistry, Fourth Edition*. John Wiley & Sons, New York, NY; 1992.