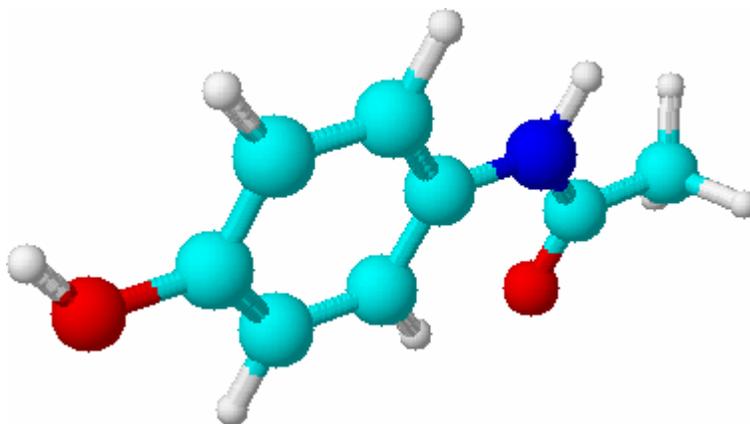
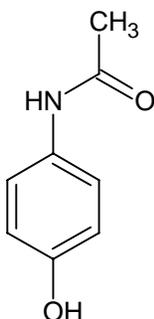


Synthesis of Acetaminophen

Techniques:

Decolorization, Filtration, Crystallization, Craig tube use, Preparation of an Amide

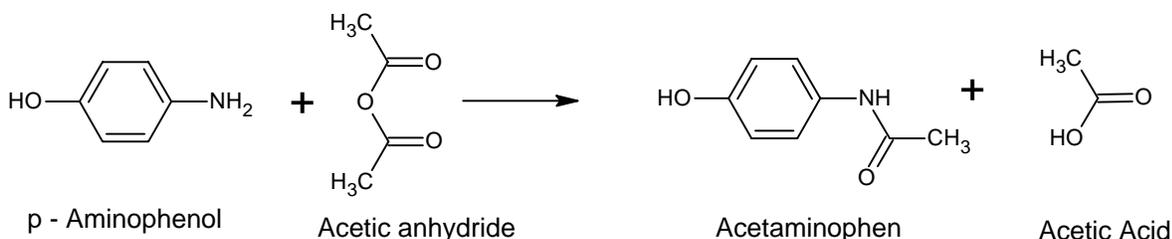
Preparation of acetaminophen involves treating an amine with an acid anhydride to form an amide. In this case, p-aminophenol, the amine, is treated with acetic anhydride to form acetaminophen (p-acetamidophenol), the amide.



Acetaminophen (paracetamol) an analgesic and fever-reducing medicine similar in effect to aspirin. It is an active ingredient in many over-the-counter medicines, including Tylenol and Midol. Introduced in the early 1900s, acetaminophen is a coal tar derivative that acts by interfering with the synthesis of prostaglandins and other substances necessary for the transmission of pain impulses.

Although its action is similar to that of aspirin, it lacks aspirin's anti-inflammatory and blood-thinning effects, is less irritating to the stomach, and can be used by people who are allergic to aspirin. Heavy use, however, has been linked to an increased incidence of liver failure, especially in heavy drinkers of alcoholic beverages and in those who are not eating enough, and overdose, especially in children, can be fatal.

Synthesis



The crude solid acetaminophen contains dark impurities carried along the p-aminophenol starting material. These impurities, which are dyes of unknown structure, are formed from oxidation of the starting phenol. While the amount of the dye impurity is small, it is intense enough to impart color to the crude acetaminophen. Most of the colored impurity is destroyed by heating the crude product with sodium dithionite (sodium hydrosulfite $\text{Na}_2\text{S}_2\text{O}_3$). The dithionite reduces double bonds in the colored dye to produce colorless substances. The decolorized acetaminophen is collected on a

Hirsch funnel. It is further purified by a microscale crystallization technique utilizing a Craig tube.

Caution:

- Acetic anhydride can cause irritation of tissue, especially in nasal passages. Avoid breathing the vapor and avoid contact with skin and eyes. p-Aminophenol is a skin irritant and is toxic.
- Aqueous solutions obtained from filtration operations may be diluted with water and flushed down the drain.

Procedure***Reaction Mixture***

Weigh about 0.150 g of p-aminophenol (MW = 109.1) and place this in a 5-mL conical vial. Using an automatic pipet (or a dispensing pump or a graduated pipet), add 0.450 mL of water and 0.165 mL of acetic anhydride (MW= 102.1, d = 1.08 g/mL). Place a spin vane in the conical vial and attach an air condenser.

Heating

Heat the reaction mixture with an aluminum block or sand bath at about 115°C and stir gently. If you are using a sand bath, the conical vial should be partially buried in the sand so that the vial is nearly at the bottom of the sand bath. After the solid has dissolved (it may dissolve, precipitate, and re-dissolve), heat the mixture for an additional 10 minutes to complete the reaction.

Isolation of Crude Acetaminophen

Remove the vial from the heat and allow it to cool. When the vial has cooled to the touch, detach the air condenser, and remove the spin vane with clean forceps or a magnet. Rinse the spin vane with two or three drops of warm water, allowing the water to drop into the conical vial. Place the conical vial in a small beaker and allow it to cool to room temperature. If crystallization has not occurred, scratch the inside of the vial with a glass stirring rod to initiate crystallization. Cool the mixture thoroughly in an ice bath for 15-20 minutes and collect the crystals by vacuum filtration on a Hirsch funnel. Rinse the vial with about 0.5 mL of ice water and transfer this mixture to the Hirsch funnel. Wash the crystals on the funnel with two additional 0.5-mL portions of ice water. Dry the crystals for 5-10 minutes by allowing air to be drawn through them while they remain on the Hirsch funnel. Transfer the product to a watch glass or clay plate and allow the crystals to dry in air. It may take several hours for the crystals to dry completely, but you may go on to the next step before they are totally dry. Weigh the crude product and set aside a small sample for a melting point determination and a color comparison after the next step. Calculate the percentage yield of crude acetaminophen (MW = 151.2). Record the appearance of the crystals in your notebook.

Decolorization of Crude Acetaminophen

Dissolve 0.2 g of sodium dithionite (sodium hydrosulfite) in 1.5 mL of water in a 5-mL conical vial. Add your crude acetaminophen to the vial. Heat the mixture at about 100°C for 15 minutes, with occasional stirring with a micro-spatula. Some of the acetaminophen will dissolve during the decolorization process: Cool the mixture thoroughly in an ice bath for about 10 minutes to reprecipitate the decolorized acetaminophen (scratch the inside of the vial, if necessary, to induce crystallization). Collect the purified material by vacuum filtration on a Hirsch funnel using small portions (about 0.5 mL total) of ice water to aid the transfer. Dry the crystals for 5-10 minutes by allowing air to be drawn through them while they remain on the Hirsch funnel. You may go on to the next step before the material is totally dry. Weigh the purified acetaminophen and compare the color of the purified material to that obtained above.

Crystallization of Acetaminophen

Place the purified acetaminophen in a Craig tube. Crystallize the material from a solvent mixture composed of 50% water and 50% methanol by volume. The solubility of acetaminophen in this hot (nearly boiling) solvent is about 0.2 g/mL. Although you can use this as a rough indication of how much solvent is required to dissolve the solid, you should still use the technique determine how much solvent to add. Add small portions (several drops) of hot solvent until the solid dissolves. When the solid has dissolved, place the Craig tube in a 10-mL Erlenmeyer flask, insert the inner plug of the Craig tube, and allow the solution to cool.

When the mixture has cooled to room temperature, place the Craig tube in an ice-water bath for several minutes. If necessary, induce crystallization by gently scratching the inside of the Craig tube with your micro-spatula. Because acetaminophen may crystallize slowly from the solvent, continue to cool the Craig tube in an ice bath for at least 10 minutes. Place the assembly in a centrifuge (be sure it is balanced by a centrifuge tube filled with water so that both tubes contain the same weight) and turn on the centrifuge for several minutes. Collect the crystals on a watch glass or piece of smooth paper. Set the crystals aside to air-dry. Very little additional time should be required to complete the drying.

Yield Calculation and Melting Point Determination

Weigh the crystallized acetaminophen (MW = 151.2) and calculate the percentage yield. This calculation should be based on the original amount of p-aminophenol used at the beginning of this procedure. Determine the melting point of the product. Compare the melting point of the final product with that of the crude acetaminophen. Also compare the colors of the crude, decolorized, and pure acetaminophen. Pure acetaminophen melts at 169.5 -171°C. Place your product in a properly labeled vial and submit it to your instructor.

Questions:

1. During the crystallization of acetaminophen, why was the mixture cooled in an ice bath?
2. In the reaction between p-aminophenol and acetic anhydride to form acetaminophen, 0.450 mL of water was added. What was the purpose of the water?
3. Why should you use a minimum amount of water to rinse the conical vial while transferring the purified acetaminophen to the Hirsch funnel?
4. If 0.130 g of p-aminophenol is allowed to react with excess acetic anhydride, what is the theoretical yield of acetaminophen in moles? in grams?
5. Give two reasons why the crude product in most reactions is not pure.
6. Phenacetin has the structure shown below. Write an equation for its preparation starting from 4-ethoxyaniline.

