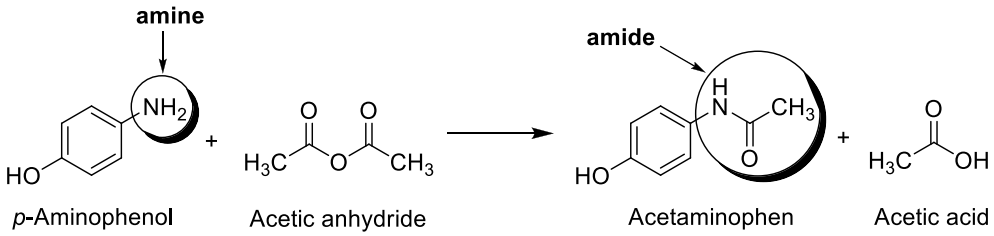
UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE

Synthesis of Acetaminophen (Tylenol®)

Acetaminophen is a widely used over-the-counter medicine because it is a powerful analgesic (relieves pain) and antipyretic (reduces fever). It is commonly used for fever, headaches, and minor aches and pains. It is also relatively inexpensive, has a low toxicity (when used properly) and few side effects.



p-Aminophenol | Acetic anhydride | Acetaminophen | Acetic acid

Acetaminophen is formed when the **amine** group of *p*-aminophenol is acetylated by acetic anhydride to form an **amide** functional group. The by-product of this reaction is acetic acid.

After the reaction, acetaminophen is isolated as a crude solid (not pure). This crude solid will be purified using a recrystallization technique. Recrystallization is a purification method that involves dissolving a solid and then causing it to recrystallize (precipitate as a crystal solid) from the solution.

In a typical recrystallization procedure, the crude solid is dissolved by heating it in a minimal amount of solvent (termed recrystallization solvent). The hot solution is then cooled to room temperature and then in an ice-water bath, whereupon crystals solidify out of the saturated solution. The crystals obtained after recrystallization are purer than the crude solid because most of the impurities remain dissolved in the cold solution.

Material List

Chemicals

- 4-aminophenol (approximately 3.0 g)
- Acetic anhydride (pre-measured, 4 mL)
- Deionized water (in squeeze bottle)

Equipment

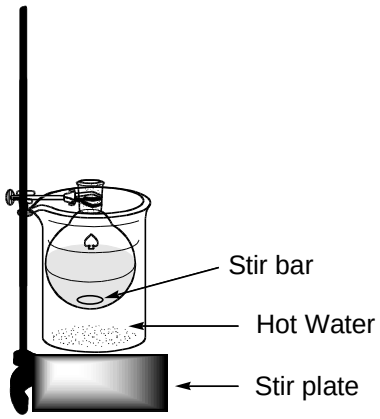
- 100 mL round bottom flask
- 600 mL beaker
- Hot plate
- Stir bar
- 2 three-prong clamps
- 25 mL graduated cylinder
- Scoopula
- Buchner funnel
- 250 mL filter flask
- Filter paper
- 100 mL beaker
- Glass rod

Experimental Procedure

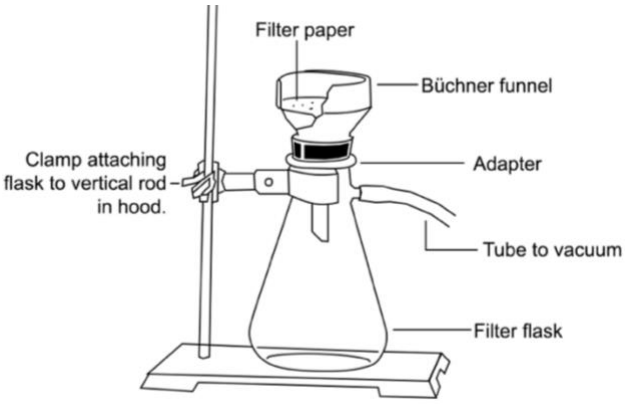
The reaction mixture will be heated in a water bath at ~85 °C. This will already be set up for you when you arrive to the lab.

Partner 1: Obtain 4.0 mL of acetic anhydride from the reagent fumehood at the front of the laboratory and measure the 10.0mL of DI water at your fumehood.
Partner 2: Weigh out 3.0 g of 4-aminophenol using the weigh paper at one of the balances at the front of the laboratory.

Synthesis of crude Tylenol®



1. Add the **4-aminophenol** (**<u>solid</u>**) to the 100 mL round bottom flask containing a stir bar.
2. Measure out 10.0 mL of deionized water (wash bottle) using a 25 mL graduated cylinder and add it to the 100 mL round bottom flask.
3. Heat the mixture in the water bath for 2 minutes with stirring. Press the circular arrow on the hot plate to start the stirring.
4. Add the **acetic anhydride** (quickly) from the vial directly into the round bottom flask.
5. Continue heating and stirring the reaction mixture for **5 more minutes**. Most if not all of the 4-aminophenol should dissolve at this time. **If it doesn't fully dissolve, that is okay!**
   (The only way it <u>won't work</u> is if acetic anhydride is added BEFORE 4-aminophenol.)
6. When 5 minutes have passed, remove the round bottom flask from the water bath by lifting the clamp up the support stand.
7. Remove the larger beaker from the hotplate to cool and dump the water into the sink (it will be used for the ice water bath).
8. Allow the round bottom flask to continue stirring at room temperature for 2-3 minutes so it is cool to touch. You should start your calculations at this point.
9. Prepare your ice water bath by filling the large beaker with ice from the ice machine and water.
10. If your round bottom flask has cooled enough to be safely touched, transfer the flask to an ice-water bath for 5 minutes. The product should precipitate out of the solution at this time. If your product does not precipitate, ask for assistance.



11. Collect the crude Tylenol® by suction filtration. First add a filter paper to the Büchner funnel and turn on the vacuum by turning the yellow dial counter-clockwise until you feel resistance. Wet filter paper with some deionized water (wash bottle) before pouring your solution through the Büchner funnel.
12. Use a small amount of **cold** deionized water to assist in the transfer of the solid to the suction filtration apparatus. You can put some ice in your squeeze bottle to cool the water down.
13. While your product is being filtered, take a **clean, dry 100 mL beaker** to a balance and measure its mass. Record the mass in your Results section.
14. Transfer your crystals of crude Tylenol® to the 100 mL beaker using the scoopula. Determine the mass of your beaker and product. **Do not use water for this step.**
15. Describe the appearance of your crude product in the Results section.
16. Calculate the mass of **crude** Tylenol® you have prepared in the Results section.
17. Dispose of the liquid filtrate in the filter flask in the black aqueous waste container before continuing to the recrystallization.

Recrystallization

18. The crude product will now be purified by recrystallization using deionized water as the solvent.
19. Add 10 mL of deionized water per 1 g of crude product to the beaker.

20. Heat this mixture on a heating plate until all the product dissolves, stir the mixture occasionally using the glass rod. Set the temperature to 190 °C by using the dial on the hot plate. The magnetic stir bar is not used in recrystallization because the crystals would form on it and be of lesser quality. ☺
21. Once the solid has dissolved, remove it from the heat and let the solution cool, undisturbed, to room temperature (~5 minutes).
22. Move your solution to an ice-water bath for 5-10 minutes, **do not disturb** the beaker while it cools.
23. Collect the pure Tylenol® by suction filtration using a small amount of cold deionized water to assist in the transfer.
24. Keep the solid under suction for 5 minutes. **Clean and dry your 100 mL beaker.**
25. The solid crystals are acetaminophen (Tylenol®). Collect the crystals in your **100 mL** beaker and determine the final mass as well as the final percent yield.
26. The liquid filtrate after the recrystallization from the filter flask can be rinsed with tap water and can go down the drain.
27. Ensure all glassware has been properly cleaned/rinsed. Use tap water for cleaning all the glassware then place it back in the fume hood. No need to worry about drying the glassware!
28. If time permits, consult the laboratory instructor about conducting a melting point purity test and fill in the "optional results section".

Waste information

Disposing of waste properly is important for the environment and improper waste disposal can be a potential hazard. **Please look at the waste guide sheet provided at your benches on where things need to go**. If you are ever unsure, please ask for help! ☺

Results Section

Amount of 4-aminophenol used: _____

Mass of 100 mL beaker: _____

Mass of 100 mL beaker + crude product: _____

Mass of crude product: _____

Appearance of crude product:

Amount of deionized water needed for recrystallization: _____

Appearance of purified product:

Mass of pure Tylenol® + 100 mL beaker: _____

Mass of pure Tylenol®: _____

Optional (you can do this if time permits)

Melting points are always recorded in a range! The starting temperature is when the sample is **first seen melting** and the final temperature is when the **entire sample has melted**. The literature melting point of acetaminophen is 168°C-172°C.

Melting point of your pure sample of Tylenol®: _____°C

Calculations

Useful Data:

4-aminophenol (mw = 109.13 g/mol)
Acetic anhydride (mw = 102.09 g/mol, density = 1.08 g/mL)
Acetaminophen (mw = 151.16 g/mol)

Determining the % yield: to determine the % yield we must first determine the theoretical yield (maximum mass) that *could* have been obtained, below are the steps needed to do this:

1. **Determine the limiting reagent:** *(Hint: Calculate the number of moles of each reagent used)*

   Moles of 4-aminophenol: Moles of acetic anhydride:

   Therefore, the limiting reagent is: _____

2. **Determine the theoretical yield in grams:** *(Hint: Your limiting reagent determines how many moles of product you will produce).*

3. **Determine % yield:** *(Hint: % yield = (Experimental Mass/Theoretical Mass) x 100%)*

Optional question:

Literature values list the melting point of acetaminophen as 168°C-172°C. Looking at your experimental melting point, do you think your sample is pure (does it overlap)? If not, what could be a possible impurity present?