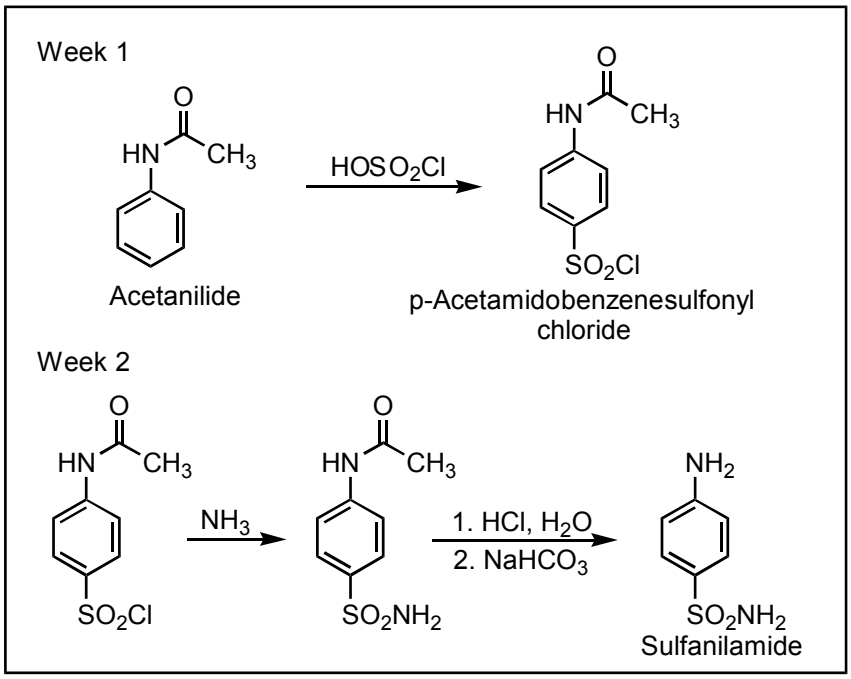
THE SYNTHESIS OF SULFA DRUGS

Introduction

In this experiment, you will use your organic chemistry expertise to synthesize a sulfa drug, then test its effectiveness in inhibiting bacterial growth. Time and availability of instruments permitting, you may also take an IR and a ^{1}H NMR spectrum of your product.

The following experiment has been adapted from experiments in Fieser and Williamson=s **Organic Experiments**, third edition, and **Introduction to Organic Laboratory Techniques**, third edition, by Pavia, Lampman, and Kriz.

This is an example of a two step synthesis. In the first week of the synthesis, you will prepare *para*-acetamidobenzenesulfonyl chloride from acetanilide. During the second week, this product will be converted into the sulfa drug sulfanilamide:



WEEK 1: Preparation of *p*-acetamidobenzenesulfonyl chloride

PRECAUTION: Chlorosulfonic acid is a corrosive liquid; handle it with care. Graduated cylinders for measuring this reagent will be under the hood with the stock bottle. Wear gloves to handle this reagent if you wish. This reaction generates HCl gas so please carry out all procedures in your hood.

Reaction of chlorosulfonic acid with water:

$$HOSO_2Cl + H_2O \text{ ----> } H_2SO_4 + HCl$$

Place 6 g of dry acetanilide into a **dry** 100-mL Erlenmeyer flask. Melt the acetanilide by **gentle** heating on a hot place. Swirl the heavy oil so that it is deposited uniformly on the lower wall and bottom of the flask. This distributes the acetanilide more evenly and increases the surface area for the subsequent reaction to take place. It also allows you to control the rate of reaction better. Cool the flask in an ice bath. When the acetanilide is cool, add 16.5 mL of chlorosulfonic acid, $ClSO_2OH$ (density 1.77 g/mL), in one portion, and then attach the trap.

Remove the flask from the ice bath and swirl it. Hydrogen chloride gas is evolved vigorously, so be certain that the rubber stopper is securely placed in the neck of the flask. The reaction mixture should not have to be cooled, but if the reaction becomes too vigorous, slight cooling may be necessary. After 10 minutes, the reaction should have subsided and only a small amount of acetanilide should remain. Carefully, heat the flask for an additional 10 minutes on the hot plate to complete the reaction (continue to use the trap). After this time, remove the trap assembly and cool the flask in an ice bath in your hood.

Since *p*-acetamidobenzenesulfonyl chloride reacts with water, the next steps should be performed as efficiently as possible to minimize contact with water. **Slowly** pour the cooled mixture with vigorous stirring (it will splatter somewhat) into a beaker containing 100 mL of ice. Rinse the flask with some cold water and transfer the contents to the beaker containing the ice. Stir the precipitate to break up the lumps and then vacuum-filter

the mixture. Wash the crude *p*-acetamidobenzenesulfonyl chloride with a small amount of cold water. Dissolve the solids in 75 mL of boiling dichloromethane under your hood. The solid may dissolve slowly. *Replace the dichloromethane solvent as it evaporates.* Transfer the mixture to a **warm** separatory funnel. Drain the lower dichloromethane layer rapidly, but carefully, from the funnel and away from the upper water layer.

Cool the mixture in an ice bath and collect the crystalline *p*-acetamidobenzenesulfonyl chloride by vacuum filtration. Draw air through the funnel to dry the product. Weigh the material and calculate the percentage yield. Determine the melting point of the product. The anhydrous compound melts at 140^{o}C. The *p*-acetamidobenzenesulfonyl chloride should be stored in a tightly stoppered bottle or flask.

WEEK 2: Conversion of *p*-acetamidobenzenesulfonyl chloride into a sulfa drug

A. Sulfanilamide

Step 1. Formation of the sulfanamide: Place 2.5 g of *p*-acetamidobenzenesulfonyl chloride into a 100-mL Erlenmeyer flask and add (under your hood) 7.5 mL of concentrated ammonium hydroxide. Stir the mixture well with a stirring rod. A reaction usually begins immediately and the mixture becomes warm. Heat the mixture on a hot plate in the hood for 15 minutes, stirring frequently. During this time the material becomes a pasty suspension. Remove the flask and place it in an ice bath. When the mixture is well cooled, add 6 M hydrochloric acid until the mixture is acidic to pH paper. Continue cooling the mixture in the ice bath until it is thoroughly cold, then collect the product by vacuum filtration. Wash the product with 25 mL of cold water.

Step 2. Hydrolysis of the acetamide group. Transfer the crude product to a small round-bottomed flask and add 1.5 mL of concentrated hydrochloric acid, 3 mL of water, and a boiling stone. Attach a *reflux condenser to the flask*. Allow the mixture to reflux until the solid has dissolved (about 10 minutes) and then reflux for an additional 10 minutes. Cool the mixture to room temperature. If a solid (unreacted starting material) appears, bring the mixture to a boil again for several minutes. When it is cooled to room temperature, no further solids should appear. To this cooled solution, add 2.5 mL of water and a small amount of decolorizing carbon. Shake the mixture and then filter it by gravity into a 100-mL or larger beaker. Rinse the flask with 5 mL of water and pour this through the filter. To the filtrate, cautiously add a solution of 10% sodium bicarbonate with stirring, until the solution is neutral to pH paper. Foaming will occur after each addition of the bicarbonate solution because of carbon dioxide evolution. The sulfanilamide will precipitate during the neutralization. Cool the mixture thoroughly in an ice bath and collect the product by vacuum filtration. Dry the sulfanilamide as much as possible by drawing air through the filter. Recrystallize the solid from water, using about 10 to 12 mL of water per gram of crude product. Allow the material to dry until the next laboratory period. Save your product for possible IR and NMR analysis.

Post Lab Questions:

1. In the synthesis of p-acetamidobenzenesulfonyl chloride, which reagent, chlorosulfonic acid or acetanilide, is the limiting reagent? Show every step of your calculation.
2. Based on your answer to question 1, what is the theoretical yield, in grams, of sulfanilamide (assume that all of the product from one step is used in each subsequent step)?
3. What is meant by ‘heat under reflux? Why is this done?
4. What does it mean to ‘wash a solid’? What does it mean to ‘wash a liquid’?