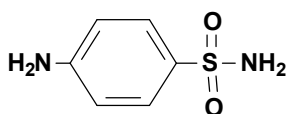


SYNTHESIS OF SULFANILAMIDE FROM ACETANILIDE

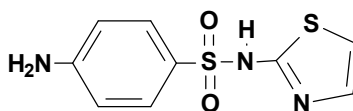


I. Introduction.

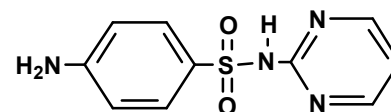
Sulfanilamide is one of a group of chemotherapeutic agents commonly referred to as Sulfa drugs discovered in the 1930's. Sulfa drugs were the first synthetic compounds found to be effective against such grave bacterial infections as meningitis, pneumonia and blood poisoning, and saved thousand of lives in World War II (1939-1945). The following are formulas of sulfanilamide and several related Sulfa drugs.



Sulfanilamide



Sulfathiazole

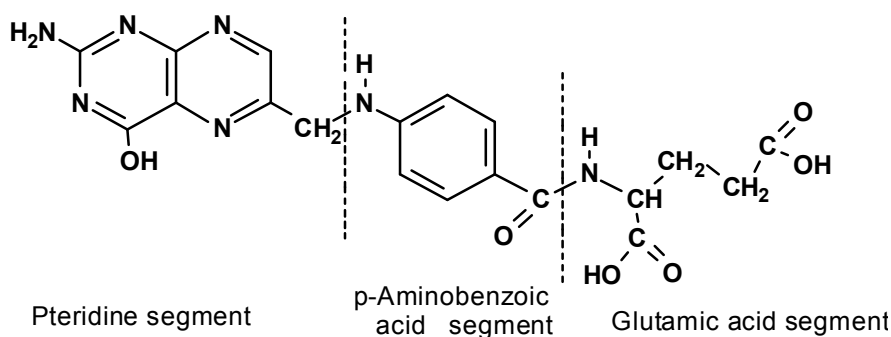


Sulfadiazine

Although Sulfa drugs represented a medical breakthrough at the time, their toxicity and other side-effects have presented difficulties for extended continued usage. Today, safer and more powerful antibiotics such as penicillin and tetracycline are available, but some Sulfa drugs are still being used in the treatment of meningitis and urinary tract infections.

The activity of the sulfa drugs has been extensively studied and can be explained in the following manner. Microorganisms **have** to synthesize folic acid to grow, sulfanilamide inhibits the formation of folic acid and the bacteria ceases to grow and dies. Humans must supply folic acid in their diet because they cannot synthesize it and the Sulfa drugs do not interfere in a specific human metabolic step. One of the steps in the synthesis of folic acid is the incorporation of para-aminobenzoic acid (PABA) into the folic acid molecule by attaching PABA to a pteridine molecule. The following are the formulas for folic acid and PABA.

FOLIC ACID

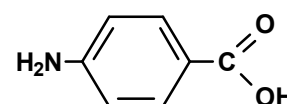


Pteridine segment

p-Aminobenzoic acid segment

Glutamic acid segment

para-Aminobenzoic acid



The structure of sulfanilamide resembles that of PABA in that both have the "amino-phenyl" segment on one end. The enzyme responsible for attaching the PABA to the pteridine recognizes only the "amino-phenyl" group segment of either molecule and mistakenly attaches the sulfanilamide instead of PABA. The next step, involving the formation of an amide linkage (on the opposite end of the phenyl ring) between the carboxyl group of the PABA segment and the amino group of glutamic acid cannot proceed, ergo, no folic acid is formed and bacterial growth is stunted.

II. Nomenclature.

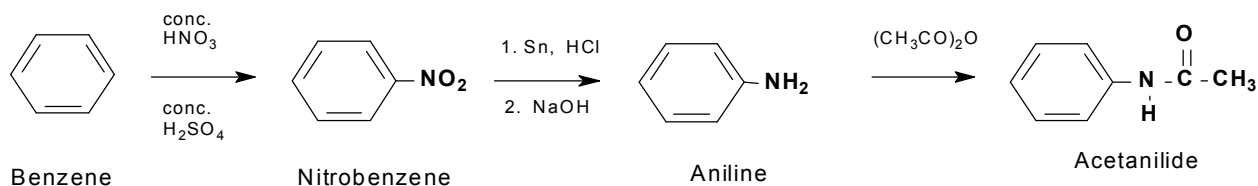
Sulfanilamide is the common name for *para*-aminobenzenesulfonamide (a.k.a., 4-

aminobenzenesulfonamide. A more detailed description of the naming of the compounds involved in the synthesis of sulfanilamide is given as a separate handout. The term sulfanilamide indicates that it is an amide of sulfanilic acid. As is often the case with many common names, they are derived from synthetic precursors that also have well known common names. In this case **aniline** is the precursor. Sulfanilic acid can be prepared from aniline and sulfuric acid, and the name essentially indicates an aniline unit to which has been attached a sulfonic acid group. The names of the intermediates involved in the synthesis starting with the chlorosulfonation of acetanilide onward can be based on sulfanilic acid as being the parent compound. The systematic names will be used in this presentation, but the corresponding common names will also be given in a separate handout.

III. Multi-Step Synthesis.

The synthesis of sulfanilamide from acetanilide is an exercise in multi-step type syntheses that organic chemists will often encounter. The question is how far back does a chemist have to go to begin the synthesis of any desired compound? The answer depends to a great extent on the availability of a convenient "starting material". In the "old days" only the simplest compounds were commercially available as starting materials. For the synthesis of aromatic compounds benzene was the usual starting point. Today there is a plethora of compounds available from a variety of suppliers, and a chemist can eliminate many steps that he would have to do in earlier times. This exercise uses acetanilide as the "starting material". If you took Organic I at UWF in the last few years you did a one-step synthesis of acetanilide by the interaction of aniline with acetic anhydride. You may well say that you actually used aniline as the starting material for the preparation of sulfanilamide, but you are being supplied with commercially purchased acetanilide.

In some schools the synthetic sequence is started with benzene by nitrating it with a mixture of concentrated nitric acid and concentrated sulfuric acid to form nitrobenzene which is then reduced to aniline by using tin and concentrated hydrochloric acid. Aniline is then acylated with acetic anhydride as shown in abbreviated form by the following equations.



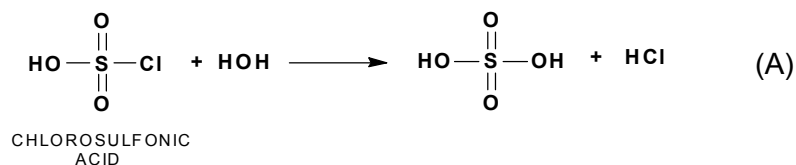
It should be noted that nitrobenzene and aniline are produced commercially in large volumes. The commercial nitration of benzene is similar to the laboratory type reaction. However, the commercial production of aniline involves the reduction of nitrobenzene with iron and hydrochloric acid or by catalytic hydrogenation.

The question should be asked, why not use aniline directly instead of going through the intermediate acetanilide? Sulfanilamide has two groups on the benzene ring in *para*- positions to each other. The amino group is a highly activating *ortho*-directing group and the sulfonamide group is a *meta*-directing group. Consequently, the amino group must be introduced first followed by the introduction of the sulfonamide group. To introduce the sulfonamide group one must first use chlorosulfonic acid then ammonium hydroxide. Unfortunately, amino groups react with chlorosulfonic acid leading to undesired products and the direct chlorosulfonation of aniline would not lead to the desired intermediate product. However, if the amino group is converted to an amide, the undesired side reaction with chlorosulfonic acid is avoided. The acetyl group in this case serves as a "protecting group" for the amine that allows a smooth chlorosulfonation of the benzene ring. The amide nitrogen does not activate the ring towards substitution as much as the free amino group, but it can still exert its *ortho/para*- directing influence. In this case the steric hindrance provided by the acetyl group results in the substitution occurring predominantly at the *para*- substitution. The protecting acetyl group is removed later to give the desired "free" amino group. The protection of groups that would interfere with a given step in a synthesis is not uncommon, but it is necessary for the "protecting group" to be introduced and removed readily

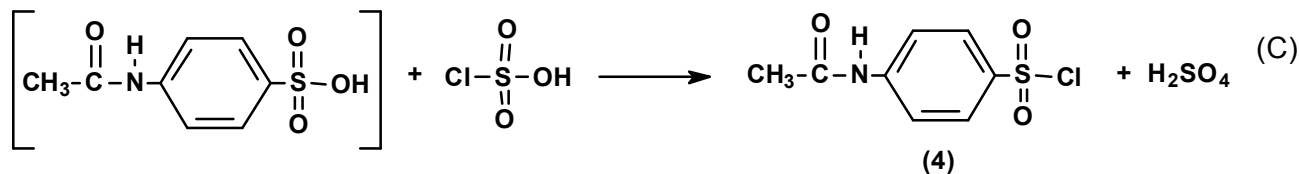
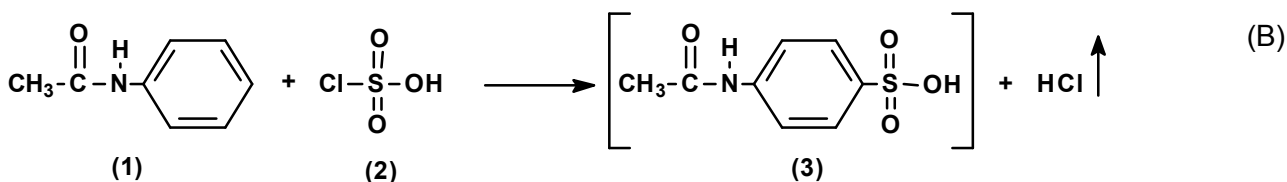
by reactions that will not adversely affect other groups in the molecule.

IV. Chlorosulfonation of Acetanilide. Preparation of *para*-Acetylamino benzenesulfonyl chloride.

The first step in the synthesis you are doing is the chlorosulfonation of acetanilide using chlorosulfonic acid. It is extremely important to be aware of the highly reactive and corrosive nature of chlorosulfonic acid. It will cause severe burns to the skin and other organs. Gloves should be worn and the reaction should be conducted in the hood. Chlorosulfonic acid will react violently with water to produce sulfuric acid and hydrogen chloride gas as shown in equation (A). When a bottle of chloro-sulfonic acid is opened the fumes observed are HCl gas formed by the hydrolysis that occurs due to the moisture in the air.

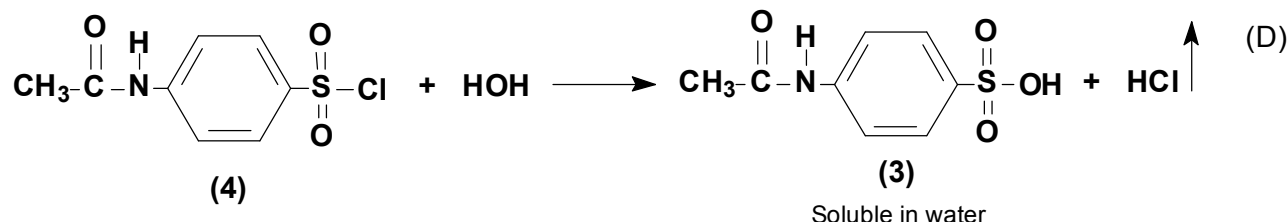


The chlorosulfonation is an electrophilic substitution reaction that will occur predominantly in the *para*-position because of steric hindrance by the acetylamino group, i.e., the size of the protecting group prevents substantial attack at the two *ortho*-positions. The chlorosulfonation occurs in two stages and requires two moles of chlorosulfonic acid per mole of acetanilide as shown in equations (B) and (C). The names of the numbered reactants and products are given in the appendix.



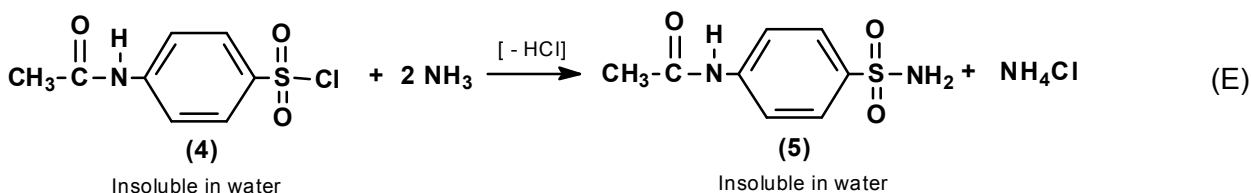
Soluble in H₂SO₄; Insoluble in Water

The reaction solution is then slowly poured onto cracked ice (or an ice-water mixture) to destroy (hydrolyze) the excess chlorosulfonic acid and to precipitate the water insoluble *p*-acetylamino-benzenesulfonyl chloride. It is important to keep the mixture very cold because the sulfonyl chloride will also undergo hydrolysis. The hydrolysis of the sulfonyl chloride is very slow in the cold, but is accelerated in warm water as shown by equation (D).

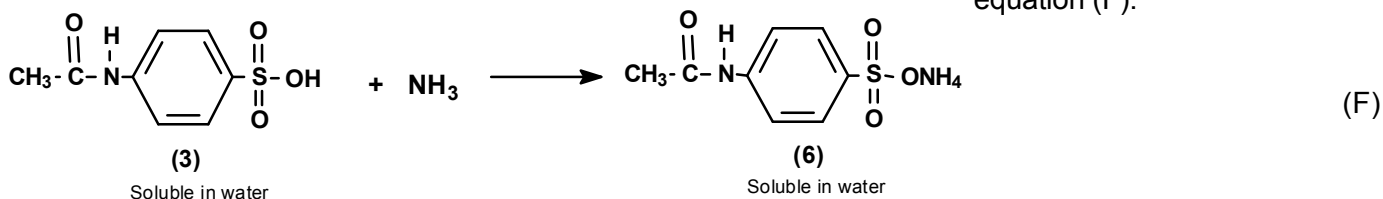


V. Preparation of p-acetylaminobenzenesulfonamide. Amidation (ammonolysis) of 4-acetylaminobenzenesulfonyl chloride.

The second step in the synthesis is the conversion of the “sulfonyl chloride group” to the “sulfonamide group” by treating with an excess of aqueous ammonia (a.k.a. ammonium hydroxide). The “Cl” atom is replaced by the “-NH₂” group resulting in the formation of “HCl” which is “neutralized by some of the excess ammonia to form ammonium chloride. The stoichiometry requires two moles of ammonia per mole of the sulfonyl chloride as shown by equation (E).

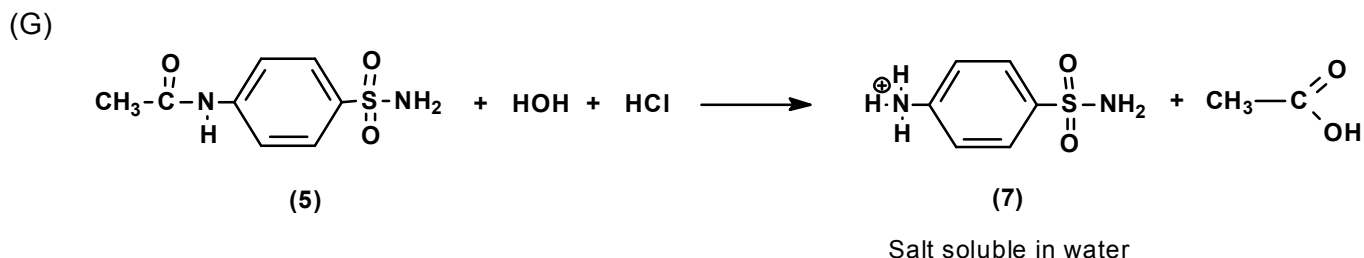


Both, the organic reactant and the organic product, are insoluble in water and it is difficult to determine if the reaction is occurring and when it is completed. There is a slight exotherm and there is a change in the texture of the reaction mixture as it is being stirred. It turns quite “mushy” at one point and then tends to thin out. The hydrolysis of the “sulfonyl chloride” is still possible as shown in equation (D) because of the aqueous medium. However, NH₃ is a better nucleophile than H₂O and the ammonolysis prevails over hydrolysis. Any of the “sulfonic acid” formed by hydrolysis will be converted to the water soluble ammonium salt as shown by equation (F).



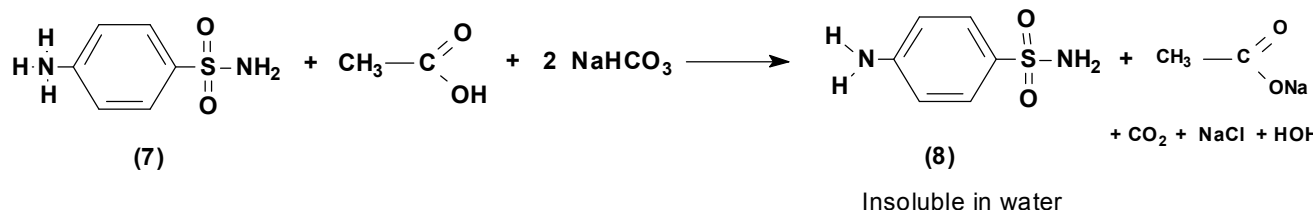
VI. Controlled hydrolysis (deblocking of protective acetyl group). Formation of sulfanilamide.

The protecting acetyl group is now removed by a controlled or selective hydrolysis reaction by boiling with dilute hydrochloric acid (ca. 6M). There are two “amide” groups in the molecule: the ‘acetamido’ group (or acetylamino group) and the ‘sulfonamide’ group. The objective is to bring about hydrolysis of the ‘acetamido’ group without affecting the ‘sulfonamide’ group. Heating with dilute hydrochloric acid affords this result. The acetamido group is more resistant to acid catalyzed hydrolysis than is the sulfonamide group. The sulfonamide group has a tetrahedral geometry compared to the trigonal planar geometry of the acetamido group, and the nucleophilic attack is easier on the trigonal planar structure than on the tetrahedral configuration. The hydrolysis is given by equation (G). The removal of the protecting acetyl group results in the “free” basic amino group that immediately reacts with the excess hydrochloric acid to give the water-soluble hydrochloride salt of sulfanilamide.

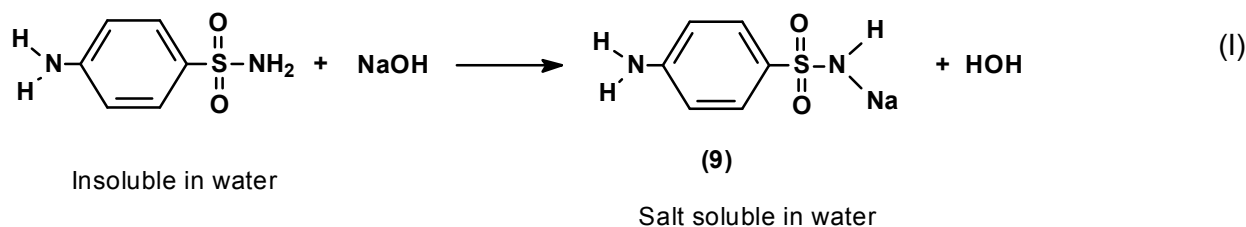


The hydrolysis mixture may be treated with charcoal (Norit or Darco) and Celite to remove colored impurities. If this is the case the resultant mixture is filtered. In either case, the last step is the neutralization of the reaction solution with sodium bicarbonate (a weak base) as shown in equation (H). The "free" sulfanilamide will precipitate from the solution and the sodium acetate formed from the by-product acetic acid will remain in solution.

(H)



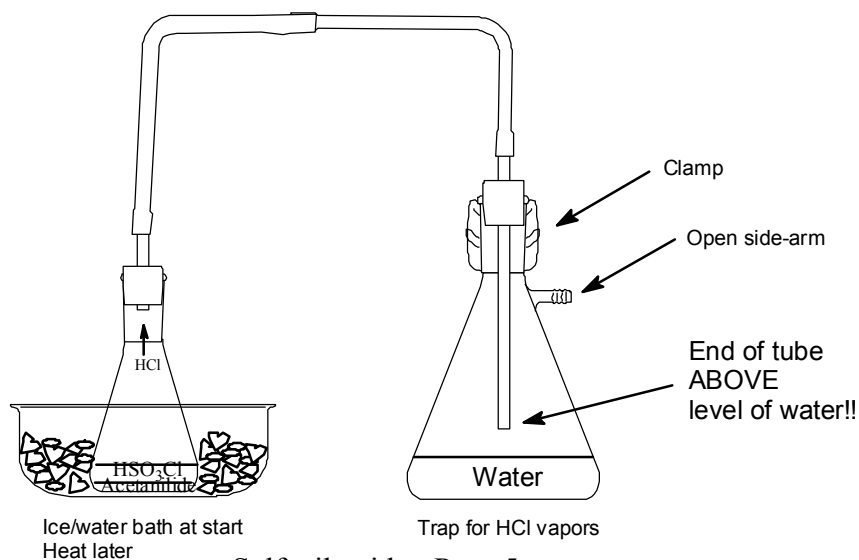
It is important to use a weak base in the neutralization step. The sulfonamide group is weakly acidic and would react with a strong base such as NaOH to form a water soluble salt as shown in equation (I).



PROCEDURE:

Chlorosulfonation of Acetanilide to *para*-Acetylaminobenzenesulfonyl Chloride.

Setting up Equipment. In the **HOOD** set up the apparatus shown in the diagram. It consists of a DRY 125 mL Erlenmeyer flask connected to a 500 mL filter (suction) flask. The connection is made by means of a stopper fitted with glass tube attached to the Erlenmeyer flask. Another rubber stopper with a glass tube passing through it is attached to the filter flask. The two adapters are then connected with rubber tubing. Place about 100-150 mL of water in the filter flask. **Be certain** that the glass tube extending into the filter flask is **well above the level of the water** in the flask. If the tube extends into the water, the



water will be sucked back into the reaction flask with disastrous consequences on the reaction and your grade. The filter flask has to be clamped to a ring stand. The Erlenmeyer flask cannot be clamped because it has to be swirled during the reaction. Care must be exercised that it does not tip over! The hydrogen chloride gas evolved will be “trapped” by letting it diffuse into the filter flask over the water. The first step requires provisions for cooling in a ice-water bath and heating on a hot plate.

CAUTION: Chlorosulfonic acid is a strong, corrosive acid that reacts violently with water and will cause severe burns to skin and other organs. Wear gloves and eye protection. **THE REACTION MUST BE PERFORMED IN THE HOOD.** Destroy any excess acid by pouring it on crushed ice. Leave the graduated cylinder standing in the back of the hood until the experiment is completed to let the acid be partially hydrolyzed by the moisture in the air, then slowly add chips of ice to react with any of the acid that may still be left.

Chlorosulfonation. Weigh **8.0 g of acetanilide** and place it in the **dry** Erlenmeyer flask. The acetanilide provided may be student-prepared, commercial material or a mixture of the two. Be sure to record and report the source of the material. Heat the flask gently on a hot plate just enough to melt the acetanilide. Rotate the flask as it cools so that the acetanilide re-solidifies to coat the bottom and the lower sides of the flask. **Do not splash it over the whole flask.** The purpose is to have the acetanilide as a cake at the bottom instead of as a powder to moderate the rate of the reaction.

In the HOOD cool the flask containing the acetanilide in an ice water bath for at least 5 minutes. Measure **22 mL of chlorosulfonic acid** in a 25 mL graduated cylinder (provided as community equipment) and add approximately one-half of it (about 11 mL) to the flask with the acetanilide by quickly disconnecting and reconnecting the stopper from the flask. Remove the flask from the ice-water bath and **swirl it gently** for about 5 minutes. You **do not** want the reaction mixture to come in contact with the rubber stopper any more than necessary. The acid will attack the rubber and the mixture will turn black. You will observe “fizzing” as the hydrogen chloride gas is evolved. If the evolution of gas starts to go too fast, cool the flask briefly to slow down the reaction. When the rate of the reaction has slowed down (slow gas evolution) add the rest of the chlorosulfonic acid in one portion as before and continue swirling at room temperature. After about 10-15 minutes the rate of gas formation will become much slower and most of the acetanilide should have dissolved. At this point warm the flask gently for about 10 minutes on a hot plate set on **low** to complete the reaction. The conventional statement at this point is that if no more gas is evolved when the warm solution is swirled, one can assume that the reaction is essentially complete. It is important that the mixture not be heated too hot because a lower yield will result. Carefully touch the flask and if it feels uncomfortable it is getting too hot. It should be not higher than 60 °C. We do not have a satisfactory explanation for the poor yields resulting from overheated reactions. **Chill the flask** again in an ice-water bath before proceeding to the next step.

The excess chlorosulfonic acid must now be destroyed (hydrolyzed) to isolate the solid *p*-acetylamino benzenesulfonyl chloride. Place crushed ice in a 400 mL beaker up to the 300 mL mark, i.e., about 3/4 full. Still in the HOOD add the oily reaction solution very slowly to the ice in small portions while stirring vigorously with a glass rod as the solid precipitates out. The operative words are **very slow addition** to keep the mixture cold. If the acid chloride gets too warm it will hydrolyze with a resultant lower yield and lower grade. The heat released may cause all of the ice to melt. If this happens before all of the reaction mixture has been added to the beaker, add more ice to the beaker before you continue the addition of the reaction solution. After the addition has been completed add some crushed ice and some water to the Erlenmeyer flask and transfer the solid to the beaker. Collect the product by suction filtration in a medium size (5.5 cm) Büchner funnel and rinse the Erlenmeyer flask and the beaker freely with ice-water to transfer the remaining solids into the funnel. Press down the solids with an inverted cork wrapped

in GladWrap (or other polyethylene wrap) to squeeze out the water. Leave the suction on for about 5 minutes, then transfer the solid into a clean 125 mL Erlenmeyer flask. **Discard the aqueous filtrate down the drain and flush with plenty of water.**

Preparation of *para*-Acetylamino benzenesulfonamide (ammonolysis of the sulfonyl chloride). Under the hood add 25 mL of concentrated ammonium hydroxide (15 M NH_3) to the moist *p*-acetamidobenzenesulfonyl chloride in the 125 mL Erlenmeyer flask and stir well with a flat spatula for about 5 minutes. As the sulfonamide forms, the mixture warms up slightly and thickens to a paste that may be difficult to stir. Add 25 mL of water and continue stirring for a few minutes, then warm the mixture on a hot plate at a low setting for about 10 minutes at about 60 - 70 °C. The mixture should **not** boil vigorously. Chill the mixture in ice-water and collect the solid in a Büchner funnel (suction filtration) and wash with cold water and press down to squeeze out water as in the previous step. Save the solid in a paper boat for the next step. **Discard the aqueous filtrate down the drain and flush with water.**

Preparation of *para*-Amino benzenesulfonamide (Deblocking reaction). The hydrolysis will be carried out in a 100 mL round-bottomed flask equipped with a condenser for refluxing (ChemKit). Clamp the flask to a ring stand and transfer the solid *p*-Acetylamino benzenesulfonamide into the flask and add a couple of boiling chips. Add 10 mL of conc. hydrochloric acid and 20 mL of water and attach the condenser to the flask. Connect the water to the condenser in the usual manner. Use a ceramic heater supported on an iron ring to heat the mixture to boiling at reflux for 20-25 minutes. The solid will dissolve at some point during the heating as it is being hydrolyzed. After the heating period allow the solution to cool a few minutes, then add 40 mL of water and allow to cool further to room temperature. There should not be any solid present at this time. If there is any solid consult with the instructor. It may be necessary to heat again for some time to complete the hydrolysis.

If there is no solid present after the cooling, add a 1/8 teaspoon of decolorizing charcoal and swirl the flask for several minutes, then add about 1/8 teaspoon of Celite, swirl for a few minutes and gravity filter using a stemless funnel holding a fluted filter prepared from 15 cm filter paper. Use a 250 mL beaker to collect the filtrate (use the FilterVac ring to support the funnel). Weigh out 10 g of sodium bicarbonate and mix it with about 50 mL of water. Not all of it will dissolve. Place the beaker in a bowl to collect any mixture that may overflow. **Slowly** add the bicarbonate solution and any undissolved solid to neutralize the hydrochloric acid (care, frothing! What is the gas evolved?). Check the solution with indicator paper. It must be neutral. If it is still acidic, add more bicarbonate solid until it is neutral. Chill the mixture in ice-water and collect the solid (Büchner funnel, suction filtration) and use small portions of cold water to transfer solid remaining in the beaker to the Büchner funnel.

Recrystallize the crude product from water in the usual manner. Be sure to record the volume of water used in the recrystallization. Leave the recrystallized product in a paper boat to dry until the next session. Determine the weight of the dried sulfanilamide and determine the melting point (range). Do the solubility tests described in the next section and turn in the remaining product in a properly labeled snap-cap vial in the box provided.

Solubility Tests:

In each of three test tubes place a small pinch of sulfanilamide. To one tube add 25 drops of 5% HCl, to the second tube add 25 drops of 5% NaOH and to the third test tube add 25 drops of 5% NaHCO_3 . Shake the tubes and record the observations. Report these results in a separate table in your report.

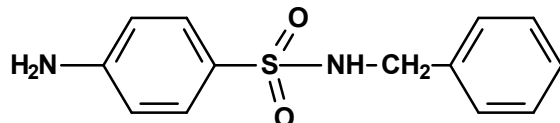
In the report, compare the melting point of your product with that reported in the literature for sulfanilamide and comment on the purity of your compound based on this evidence. Calculate the theoretical and percent yields of your product based on the weight of acetanilide.

Answer the Questions on the following page.

SYNTHESIS OF SULFANILAMIDE - POST-LAB QUESTIONS

(Answer these questions on separate sheets)

1. Starting with **benzene** as the only "aromatic" compound available and any other organic and inorganic reagents give detailed equations for the preparation of the following sulfanilamide derivative.

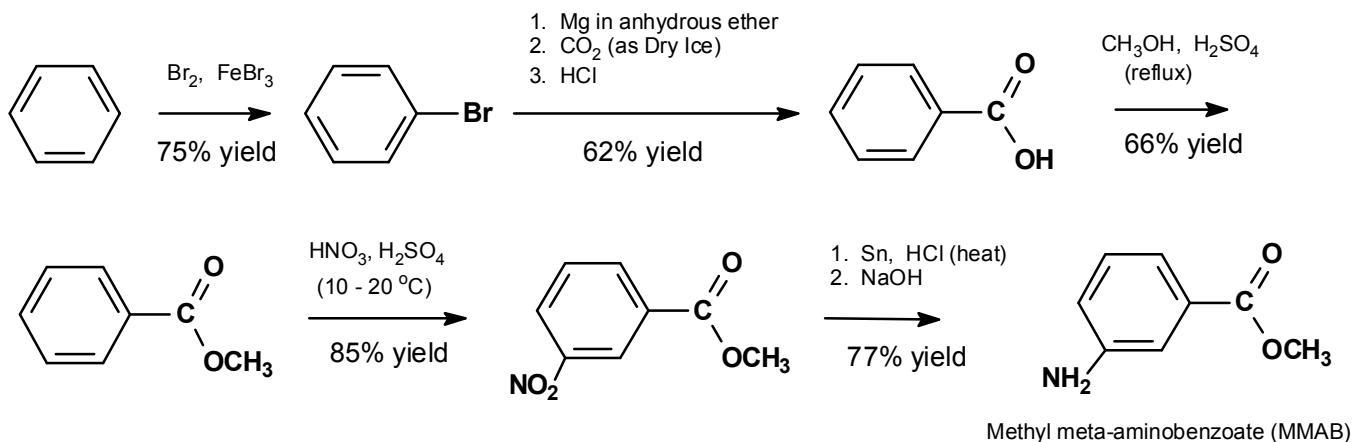


Give the systematic name for this compound.

2. Explain why sodium bicarbonate instead of sodium hydroxide was employed to neutralize the hydrochloric acid used in the controlled hydrolysis to remove the protecting acetyl group.

3. Based on the percent yield you obtained in your experiment, calculate how much acetanilide (in grams) you would have needed at the start of the synthesis to produce 100 grams of sulfanilamide. Show the set-up and calculations.

4. Consider the multi step synthesis of methyl meta-aminobenzoate (MMAB) from benzene shown by the following sequence of steps. What is the "over-all" percent yield of MMAB. What weight in grams of



MMAB would be obtained by this sequence starting with 200 milliliters of benzene. Show the set-up and calculations.