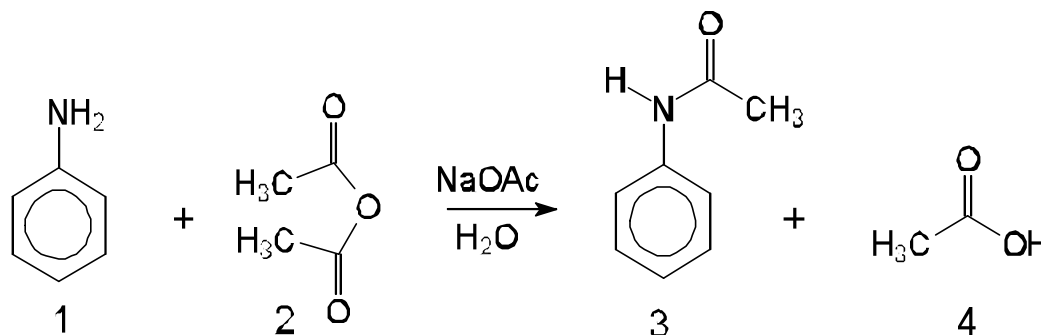


# PREPARATION OF AN INTERMEDIATE FOR A SULFA DRUG AND A HEADACHE REMEDY-- ACETANILIDE



**Introduction:** This experiment involves four functional groups common in organic chemistry. The substrates (**reactants**) are both liquids and one of the **products** is a solid. The reaction of **1** (aniline) with **2** (acetic anhydride) is a **transformation** in which products **3** (acetanilide) and **4** (acetic acid) are obtained. A solid product is often desirable since it may be **recrystallized** and a **melting point** determined. Solids prepared in this manner serve as a **derivative**, whose **mp** may be correlated with known values and thus is a means of **identification** and serves as a test for **homogeneity** or **purity**.



**Methodology:** The procedures illustrated in this experiment involve **recrystallization**, **gravity filtration**, **suction filtration**, **melting** and **mixture melting points**, as well as calculations of **theoretical** and **percentage yields**.

**Note:** Your instructor will lecture on and demonstrate the operations required for this experiment. You may also want to consult reference or complete laboratory texts. Observe caution in handling chemicals. *In any synthetic experiment*, the **theoretical** yield of the product should be calculated prior to performing the experiment.

## Preparation of acetanilide in aqueous solution.

Place 3.0 mL aniline in a 125 mL Erlenmeyer flask by using the 50 mL buret setup at the reagent station. Add with stirring 60 mL of tap water followed by 4.0 mL of concentrated hydrochloric acid and a graduated cylinder from the concentrated HCl bottle provided in your hood. The solution is highly colored, add *ca.* 0.5 teaspoon of Norite (decolorizing charcoal) and *ca.* 0.5 teaspoon celite filter aid, swirl the flask and gravity-filter the solution into a 250 mL beaker. (**Caution:** to avoid spills, be sure the filter paper is above the lip of the filter funnel.)

**Caution:** Aniline has been implicated in the formation of bladder cancer in animals. Use caution in dispensing the reagent.

Prepare a solution of 7.0 g of sodium acetate trihydrate in 50 mL of water and obtain 5.0 mL acetic anhydride from the 50 mL buret at the reagent station. To the (filtered) solution of aniline hydrochloride, add the acetic anhydride with stirring, and at once add the sodium acetate solution and stir 2-3 minutes. Place the beaker in an ice water bath, stir, and then

collect the resultant product by suction filtration using a Büchner funnel. Pour slowly about 20 mL of cold ice water over the crystals to remove traces of acetic acid. By allowing air to pass through the compacted crystals under suction, most of the water will be removed.

At this point, the partially air-dried product is still moist. Spread the moist product onto a tared paper weigh boat, weigh the moist product (with the tared paper boat), and allow the crystals to dry until the next lab period. Reweigh the sample, determine the melting point, and calculate the **percent yield** of the product. Your sample must be recrystallized if your melting point range is more than 5 degrees away from the expected value. Consult your instructor if this is the case.

**Solubility Tests:** (This test may be done with the acetanilide product provided at the reagent station.)

In separate and small dry test tubes, test the solubility of aniline (2 drops for each test) and acetanilide (ca. 10 mg for each test) and benzoic acid. For the latter, use a small spatula and take a portion of the solid - an amount to cover the tip of the spatula. Tests for solubilities are conducted with ca. 1 mL aqueous solutions of

- (a) 5% hydrochloric acid
- (b) 5% sodium hydroxide
- (c) an organic solvent (*t*-butyl methyl ether)

In each test, cork the test tube, shake, and record your observations. Rationalize the observed results and include this in the **Discussion** section Use equations, where appropriate (See table on last page).

**Melting points and Mixture melting points** (optional):

Determine the melting point ranges of samples **A** and **B** and mixtures (approximately 1:1) of your product with sample **A** in one experiment and sample **B** in another. Record and note the melting points ranges of both samples **A** and **B**. Report your findings for both melting point determinations. In the **Discussion** section, comment on your observed results.

**Helpful Hints - ACETANILIDE:**

\* **Calculation of theoretical and percentage yields** must be included in your laboratory report. The calculation must be shown in the **DATA ENTRY** section (even-numbered pages) of your lab book, but the results of the calculation should be included at the end of the laboratory report in a summary along with the expected and experimentally determined melting points (or boiling points, as appropriate). The **limiting reagent** will govern your theoretical yield. Note in cases where quantities are expressed in volume (mL, *etc.*), these must be converted to weights (mg or g) using the relationship,  $D = W/V$ , since **molar quantities are required** in the calculations of **theoretical** yield. The theoretical yield is determined based on the **limiting reagent**. Your instructor will provide further details and examples.

\* **Gravity-filtration** utilizes a "fluted" filter paper in the decolorizing or recrystallization step. In gravity filtration, generally the **filtrate** is the desired material which is used further in the experiment.

\* In **suction-filtration**, a **Büchner funnel** is employed to collect the desired **crystals** resulting from a reaction or recrystallization attempt. Be sure to "wet the filter paper" with the solvent/solid mixture to be filtered. When performing a suction filtration, it is advisable to install a trap between the aspirator and the suction flask. In any case **always** break the vacuum before turning the water off. In this operation, the filtrate or "mother liquor" may be concentrated to obtain a **second crop**, *etc.* (or, it may be disposed - consult with your instructor).

\* (Optional) **Recrystallization** is a purification procedure which requires solubility of the impure solid in a heated solution and crystallization of the solid upon cooling. Clearly, this operation depends upon solute-solvent interaction involving a number of parameters including concentration, polarity of solute and solvent, *etc.* Choice of a solvent or solvent pair for recrystallization experiments generally involves preliminary tests using a small sample and various solvent systems. To determine the proper solvent or solvent system, the steps listed below are performed. Be certain to retain a small sample of crude crystals as "**seed crystals**".

Use Erlenmeyer flasks and be sure the liquid volume does not exceed 50% of the flask's capacity. One or two boiling chips are always added (at room temperature) to prevent "bumping".

- i) The crude crystals should be pretty insoluble in the chosen solvent system at room temperature.
- ii) The crude crystals should be quite soluble in the chosen solvent system when heated to boiling.
- iii) The solution is filtered by gravity filtration.
- iv) The filtrate is allowed to cool *s l o w l y* to permit crystallization. Adding the **seed crystals** after the solution has cooled to room temperature may be helpful.
- v) Collect the crystals by suction filtration saving the filtrate for a second crop of crystals.

Failure in recrystallization attempts may be caused by several factors; chief among these are the choice of solvent system, solutions which are too dilute (solvent may have to be removed by distillation), solutions which may be too concentrated (very viscous) and too rapid cooling (microcrystalline material incorporating the reprecipitated impurities), *etc.*

Choice of solvents requires experimentation since the solubilities vary from compound to compound. Generally, polar compounds will dissolve in polar solvents such as alcohols, and nonpolar compounds in hexane. A **mixed solvent system** such as methanol-water or hexane-ether is often used in the respective cases. Your instructor should be consulted when in doubt.

If alcohol (MeOH or EtOH) is used, add a minimal amount of **alcohol** to just cover the crude crystals in an Erlenmeyer flask to effect a saturated solution. Heat to dissolution and, after cooling, add **water** dropwise with swirling until the solution becomes "cloudy". Add a few more drops of water; at this point the solid may "oil out" or precipitate. Heat to dissolve the solution until it is homogeneous. Norite (decolorizing carbon) may be added [**Caution: Never add the Norite** while the solution is near the boiling point of the solvent system - or, you're regret it!!]. Gravity filter the hot solution and again (hopefully) permit the crystals to precipitate.

\* **Melting** and **mixture melting points** are indications of a phase change from solid to liquid. Impurities will depress your melting point while a mixture melting point with an identical compound should have the same melting point. In determining a melting point, be sure to report the range (first indication of melting and final liquidification of solid). Note that the mp reading is affected by the rate of heating. Use an initial heat-setting of 4 or 5 on your melting point apparatus.

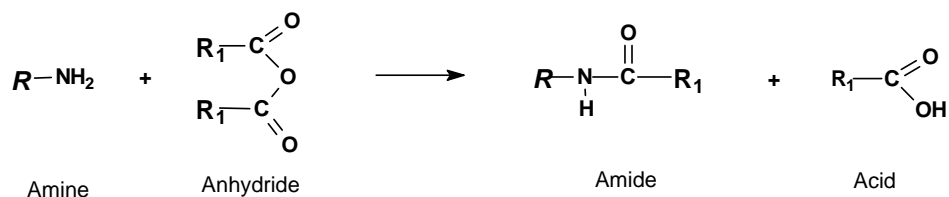
\* Students are expected to check, cite, and incorporate **reference sources** for data in future laboratory reports. For example, the following specific gravities from the *Handbook of Chemistry and Physics* are listed below:

<u>Compound</u>	<u>Specific Gravity</u>
aniline	1.0217
acetic anhydride	1.0820

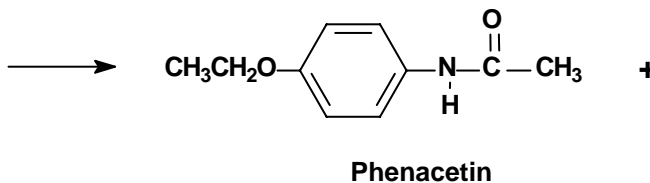
## Synthesis of Acetanilide - Homework Questions

- For the reaction, which substrate is considered to be the **nucleophile** and which is the **electrophile**? Why?
- Show by means of the appropriate equation the function of sodium acetate in the synthesis of acetanilide as it was carried out in the lab.

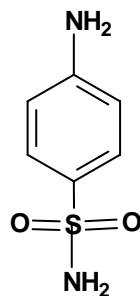
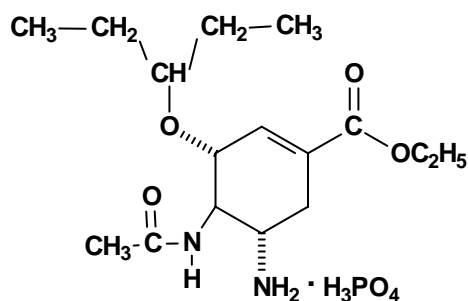
3. The preparation of acetanilide from aniline and acetic anhydride is a specific reaction that can be applied to the preparation of any amide from the corresponding amine and anhydride as shown by the following generic equation.



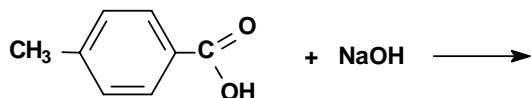
Based on the above equation, complete the following equation for the preparation of phenacetin, a compound once used as an analgesic, but discontinued because of its toxic side effects.



4. **Circle and name** the FUNCTIONAL groups in the structures of the following compounds


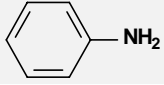
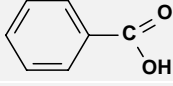


5. Complete and balance the following equation



## SOLUBILITY OF REPRESENTATIVE BASIC, ACIDIC AND NEUTRAL COMPOUNDS

(Set up a table such as given below in your notebook to record the data. Neatly transfer the data to the table on this sheet and turn it in with your report)

 <b>SOLVENT</b>	<b>WATER</b> (H <sub>2</sub> O)	<b>5% HCl</b>	<b>5% NaOH</b>	<b>Methyl tert-butyl ether (MTBE)</b>
<b>SOLUTE</b>				
<b>ANILINE</b> 				
<b>BENZOIC ACID</b> 				
<b>ACETANILIDE</b> 