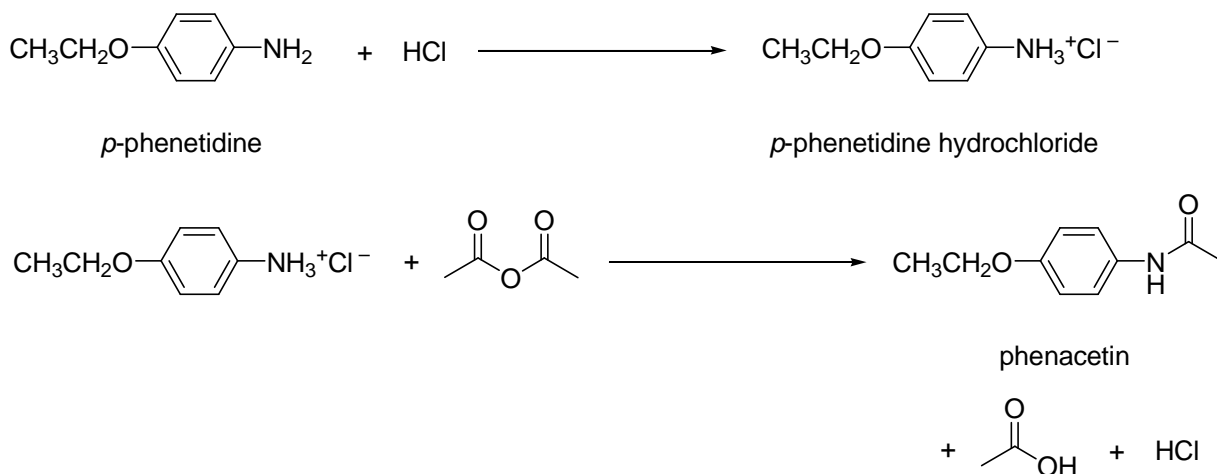


Title: Synthesis of Phenacetin*New tricks:* B2 and D2*New principles:* using pipets to transfer liquids, pipet filtration*Instrument Operation:* Fisher-Johns Melting Point Apparatus*Introduction:*

The preparation of phenacetin is a straightforward, two-step “one-pot” organic synthesis. It introduces the classic reaction of an amine with an anhydride to form an amide, and it also reinforces the principles of recrystallization and the determination of melting points.



Amines such as *p*-phenetidine are generally sensitive to air. Over time, sitting in a bottle, amines slowly decompose to produce disgusting dark-colored polymeric “tars.” The wise chemist always purifies amines prior to use. The first step above, involving protonation of the amine, allows a simple way to purify the *p*-phenetidine, because the tars that are present, though very polar, won’t protonate fully. These tars then can be absorbed onto activated carbon (a very polar weakly acidic substance) and separated by filtration. At the same time, the protonated amine provides a weak acid, which catalyzes the next step.

Green aspects:

Although *p*-phenetidine is toxic, the reaction conditions are mild, using water and dilute acid as the reaction medium. Water is used as the recrystallizing solvent.

PRE-LAB QUESTIONS:

1. Calculate the atom economy of each of the two steps of this transformation. In each case, what is the desired product? Identify the *coproducts* in each case. Determine registry numbers and make safety notes for reactants and products.
2. Why is concentrated HCl added to the solution of *p*-phenetidine in the first step of this preparation?
3. Why is suction filtration used instead of gravity filtration to collect the crude and pure crystals?
4. Why is slow cooling of the solution necessary in order to achieve the best results in recrystallization? What would you expect for the melting point – too high or too low – if the recrystallization was carried out too quickly? What would you expect for the *yield* – too high or too low – in that case?

Time-saving Tip: Create a Green Process Analysis Report using the Green Chemistry Assistant (<http://fusion.stolaf.edu/gca>) for this reaction. (This reaction is one of the samples.) When your report is complete, use the “Preview Report” link to pull up a new window, and paste *the entire contents* of that window into a Word document. Then you can add the answers to these questions and send that document to your lab assistant.

In Your Laboratory Notebook:

Observations Make careful observations relating to each step of the procedure as you carry it out. What volumes are involved? What color changes do you see? How would you describe the product crystals (*needles, flakes, cubes, fluffy, chunky, etc.*)?

Analysis Recalculate the theoretical yield of recrystallized product based on how much compound you actually used. Compare your actual yield of purified phenacetin to the theoretical yield you calculate. Report your melting point (RANGE!) and compare that to what is reported in the chemical literature. (Be sure to indicate your source.)

Conclusions What are the steps where material was lost in your procedure, which thereby contributed to your percent yield being less than 100%? Discuss the green aspects of this experiment. How could the reaction conditions be made greener?

Procedure:

In a 10-mL Erlenmeyer flask place 0.20 g (1.46 mmol) of *p*-phenetidine (MW 137) and 3.50 mL of water.

Add 4 drops only (about 1.0 mmol) of concentrated (12 *M*) hydrochloric acid, which should dissolve the amine completely. Do not be concerned if some undissolved material remains. Add a spatula-tip of activated carbon (decolorizing charcoal) to the solution, swirl the solution on a **hot plate** for a few minutes, and remove the charcoal by **pipette filtration** into a clean 10-mL flask.

Note: If a very slight color persists in the *p*-phenetidine hydrochloride solution, do not repeat the decolorizing procedure but continue with the remainder of the experiment. If the solution is fairly dark, however, a second decolorizing charcoal treatment may be necessary.

Prepare a weakly basic solution by dissolving 0.24 g (2.92 mmol) of sodium acetate (MW 82) in 0.80 mL of water in a 10-mL flask. Set this solution aside for later use.

Warm the *p*-phenetidine hydrochloride solution on a hot plate. Add 0.20 mL (0.22 g, 2.20 mmol) of acetic anhydride (MW 102) while swirling the solution. Add the sodium acetate solution *all at once*, and swirl the solution vigorously to insure mixing. Allow the solution to stand at room temperature for 5 minutes. If no crystals form, add 1 or 2 drops of acetic anhydride.

Cool the reaction mixture by immersing the flask in an ice-water bath, and swirl the mixture vigorously until the crude phenacetin crystallizes. Collect the crystals by **suction filtration**. Wash the crystals with a portion of cold water.

Purify the crystals by **recrystallization** from water. Collect the crystals by **suction filtration** and air dry the crystals.

At the beginning of the next laboratory period:

Record the weight of the phenacetin obtained in the experiment, calculate the **percentage yield**, and finally determine the **melting point** of the recrystallized sample. Submit the sample of the recrystallized material to the instructor in a properly labeled vial.

p-Phenetidine is toxic and harmful on skin contact. “Water” in this manual always means deionized water. “Cold” always means ice-cold. “Hot” always means almost-boiling or boiling.

Concentrated hydrochloric acid is corrosive; avoid skin contact or breathing of fumes.

Norit and Darco are trade names for brands of activated carbon.

NOTE: NEVER leave ANYTHING on a hot plate. Before you put anything on a hot plate have a plan for how you are going to get it off if it starts to overheat. SIMPLY TURNING OFF THE HOT PLATE WILL NOT WORK. Perhaps use a clamp; perhaps have a wooden test tube clamp nearby. Think about this BEFORE you start heating.

Sodium acetate is an innocuous chemical.

Acetic anhydride is irritating to mucous membranes; avoid skin contact or breathing of vapors.

Allow the crystals to dry open to the air

Use only one or two crystals for the melting point. The NMR spectrum of phenacetin is very pretty. Consider taking one just for fun!