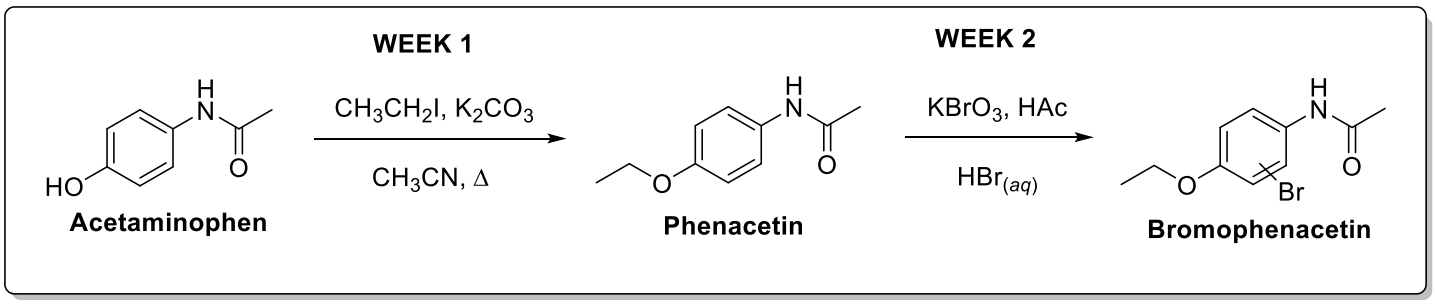
**Experiment 3 – Synthesis and Bromination of Phenacetin:**
**A Substitution Puzzle**




**Scheme 1.** Overview of two-step synthesis of bromophenacetin from acetaminophen.

In this experiment, students will convert the acetaminophen (the active ingredient in Tylenol) into phenacetin to exemplify a Williamson ether synthesis. The product will be analyzed by melting point, chemical tests, TLC, and IR and $^1$H NMR spectroscopy. Phenacetin will then be subjected to an electrophilic aromatic substitution (EArS) reaction to introduce a bromine into the ring at a yet to be determined position. Melting point and $^1$H NMR and IR spectroscopy will be used to analyze the brominated product. $^1$H NMR and melting points will be used to determine the substitution pattern of the bromophenacetin.

Students will work individually to carry out each step of the experiment and collect all data, with the exception of shared NMR spectra to be posted online. Students will be assessed on their lab technique throughout the experiment, including following instructions, handling chemicals and equipment, as well as product yields to a reasonable extent. Technical writing will be emphasized throughout the experiment. Students will write the abstract and/or experimental methods sections in the second week of lab and bring a respectable draft of each to the third week of lab. Lab-mates will proofread each other's work using the writing guidelines online as well as the specific notes for this report on p. E5-6 of this document.

## Notebook Preparation

- *Purpose:* Reaction scheme if performed, or structure (starting material, reagent, solvent, all possible products)
- *Reagent table*: List the amounts (mg or mL and mmol), molar equivalents ("equiv."), and physical properties (MW, bp or mp, density, one-word hazard) of each chemical in the reaction scheme or process.
- *Hand-written procedure:* self-explanatory
- *Safety & Clean*-up*:* copy the pertinent information from **Table 1** at the end of each part

## EXPERIMENTAL PROCEDURE

### Exp 3A – Synthesis of Phenacetin

*Reaction Set Up.* Obtain 360 mg of acetaminophen and transfer into a dry 25-mL round-bottom flask (RBF). Add a stir bar, 560 mg of $K_2CO_3$ (ground if necessary), 6.0 mL of acetonitrile ($CH_3CN$), and lastly 0.56 mL of ethyl iodide. Attach a water-cooled condenser and, after cold water is circulating, heat to reflux directly on a hot plate (medium setting) for 1 hour. Obtain the IR of acetaminophen and work on the abstract or experimental methods during this time. Each student must make an IR sample (nujol mull) and obtain a fresh spectrum of acetaminophen this week (no sharing, there is ample time!).

*Reaction Work Up.* Turn off the heat, lift the clamped apparatus, allow the mixture to cool, then add 8 mL of water to the flask. **Perform the remainder of this procedure in the fume hood**. Transfer the reaction mixture to a screw-cap test tube and use 2 x 2 mL of BME to complete the transfer. Cap, invert, and vent several times before removing the aqueous layer and placing it into a different screw-cap test tube. Extract the aqueous layer with 2 x 5 mL of BME. Remove the aqueous layer into a separate container, discarding at the end of the experiment. Combine the organic layers and extract with 2 x 5 mL of 5% NaOH followed by 5 mL of sat. NaCl. Save the aqueous layers and dispose at the end of the experiment (can combine with aqueous from previous step). Dry the organic layer with minimal $MgSO_4$ for 5 minutes and filter with a pipet loosely packed with cotton into a dry, pre-weighed 25-mL RBF (or larger if appropriate). Concentrate using a rota-vap and obtain the crude mass of product (mg and % yield).

Eight students in the lab will prepare a sample for $^1$H NMR analysis. Before making $^1$H NMR samples, TLC should be used to test the product for purity relative to standards (conversion to product and absence of acetaminophen). TLC analysis can be performed in week 2 for the remainder of the class not making NMR samples. Weigh approximately 10 mg of product into a dram vial. Add 800 μL of $CDCl_3$, dissolve, then transfer into a labeled NMR tube (initials; section info – day, time, TA; “Phenacetin”), cap, and leave in the designated space per TA instructions. Do not invert the capped NMR tubes! Students will be notified when spectra are available on the course website.

Time permitting, obtain the IR of phenacetin and the melting points of both acetaminophen and phenacetin. This can also be completed next week. All students will save the product in the RBF in a vial for next week.

### Exp 3B – Analysis of Phenacetin

*Ferric Chloride Test for Phenols.* Place 1 mL of an aqueous ferric chloride solution (0.1%) in each of three small, labeled test tubes (acetaminophen, phenacetin product, and water). Add a microspatula-ful of the two solids to two of the test tubes and a drop of water to the third. Observe the change in color. Colors ranging from green to red are considered a positive test; yellow is negative.

*Analysis.* Determine the melting points of acetaminophen and phenacetin. Obtain the IR spectrum of phenacetin. Assess purity of the product by TLC (if not completed the week before) and compare to standards of acetaminophen and/or phenacetin. TLC solutions should be made in test tubes using a few crystals of solid in 1 mL acetone.

Students are strongly encouraged to work on a draft of the abstract and experimental methods sections before leaving lab this week.

**Exp 3C – Substitution Puzzle: Bromination of Phenacetin**

Transfer 200 mg of phenacetin and 63 mg of potassium bromate into a 25-mL Erlenmeyer flask equipped with magnetic stir bar. If you have less than 200 mg of pure phenacetin, scale reagents accordingly. Add 2.5 mL of glacial acetic acid and stir to dissolve phenacetin (potassium bromate will not dissolve at this point). *Slowly* add 0.225 mL of aqueous HBr (1.49 g/mL, 48% w/w) *drop-wise* and stir well during the addition. Continue to stir for 30 minutes at room temperature. The solution should turn orange, indicating the formation of bromine. Proofread your neighbor's abstract and experimental section during the reaction time.

Use a pipet to transfer the reaction mixture to a small beaker containing 20 mL of cold water. Cool the system in an ice-water bath to crystallize the solid. If the solution is still orange, add a few drops of sodium thiosulfate (1 M) to destroy the unreacted bromine. You may need to induce crystallization by briefly scratching the bottom of the beaker with a stir rod. Vacuum filter the suspension using a small Buchner funnel. Let the solid dry on the filter with the vacuum on for 10 minutes then determine the crude yield.

Set aside a small amount of crude solid, dry on a porous plate, then pack a crystal or two into a melting point capillary. Transfer the remaining solid to a 50-mL Erlenmeyer flask and recrystallize from 25-30 mL water (minimal volume necessary to dissolve in hot solvent). Isolate the crystals *via* vacuum filtration, drying the crystals for at least 10 minutes before determining the recrystallized yield. Determine the melting temperature range with a MeltTemp (dry on porous plate first) and obtain the IR spectrum of the product.

Prepare a sample for $^{1}$H NMR analysis. Weigh approximately 10 mg of product into a vial. Add 800 μL of $CDCl_3$, dissolve, then transfer into a labeled NMR tube (initials; section info – day, time, TA; "Phenacetin-Br"), cap, and leave in the designated space per TA instructions.

**Table 1.** Clean up and safety notes

| Clean up | Safety |
|---|---|
| *Liquid waste:* aqueous washes, BME from rota-vap trap, unused solvents | **Ethyl iodide** is a severe irritant. Wear gloves and dispense in fume hood. Change gloves immediately after using. |
| *Solid waste:* contaminated pipets, $MgSO_4$, capillary tubes, melting point capillaries | **Phenacetin** is a probable carcinogen and a mutagen. Harmful if ingested. Avoid skin contact. |
| Save phenacetin products (week 1, crude and week 2, pure) in a labeled vial in your drawer. | **BME** is flammable and volatile. Handle in fume hood. |
| Turn in the bromated product (week 3) in a labeled vial in the designated space in the fume hood. | **Acetone, hexane, and ethyl acetate** are flammable. |
| IR kits should remain intact when not directly in use. Desiccators must stay closed. | **Hydrobromic acid** is highly toxic and corrosive |
| Clean all countertops and balances. | **Potassium bromate** is an oxidizer and possible carcinogen |
| Put away all shared equipment to its original location. | **$CDCl_3$** is a cancer suspect agent. Dispense in the fume hood. |
| Lockers should be clean and organized at the end of each week. This will be checked for credit at the end of Exp 5, including proper disposal of products. | **NMR tubes** are very fragile. Handle with care. |
| | **Dilute sodium thiosulfate and ferric chloride** solutions are irritants. |

## References


Palleros, D. R. *Experimental Organic Chemistry*; Wiley: New York, **2000**; pp. 329-333, 350-353.

Schatz, P. F. *J. Chem. Ed.* **1996**, *73*, 267.

Volker, E. J.; Pride, E.; Hough, C. *J. Chem. Ed.* **1979**, *56*, 831.

**Pre-Lab Questions** – *assignment descriptions & due dates in Canvas*

### *Exp 3A&B Pre-Lab Qs*

1. Calculate the mmols of each reagent used in the synthesis of phenacetin (excluding the solvent). Determine the limiting reagent. Show your work.

2. Calculate the theoretical yield of phenacetin. Show your work.

3. Draw the mechanism for the synthesis of phenacetin from acetaminophen, potassium carbonate, and ethyl iodide.

4. Why is the reaction mixture extracted with the aqueous NaOH solution?

5. What are the expected *distinguishing* IR signals in phenacetin and how do they differ from acetaminophen? Include the functional groups, bonds, and expected ranges.

### *Exp 3C Pre-Lab Qs*

*In addition to pre-lab questions, prepare a draft of the Exp 5 abstract and experimental methods with characterization for both reactions (leave xx's for data yet to be obtained).*

6. Draw the mechanism for the bromination of phenacetin with molecular bromine, including an explanation for the formation of isomeric products.

7. How will you tell the difference between the two possible bromination products by $^1$H NMR? Estimate/calculate chemical shifts of as many or as few H's as you feel necessary. Also give the expected splitting patterns, including long-range (4-bond) coupling. It will be useful to label the protons on both possible products and refer to those signals in your answer.

8. What is the molar ratio of HBr and $KBrO_3$ you will be adding to this reaction? What molar ratio of HBr and $KBrO_3$ should be used to generate $Br_2$? Consider equation 1 below and answer assuming HBr is the only source of protons.

$$6\ HBr + KBrO_3 \rightarrow 3\ Br_2 + KBr + 3\ H_2O \qquad \text{(eq. 1)}$$

Answer the same question considering equation 2, where there is an additional acid catalyst.

$$5\ Br^- + BrO_3^- + 6\ H_3O^+ \rightarrow 3\ Br_2 + 9\ H_2O \qquad \text{(eq. 2)}$$

Determine whether HBr or $KBrO_3$ is the limiting reactant in the formation of $Br_2$ in the reaction you will be performing and report how many mmol of $Br_2$ will be theoretically formed.

9. Calculate and report the theoretical yield of the brominated product.

## LAB REPORT

See Technical Writing Guidelines for general format and content of the abstract & experimental methods. For best results, work on the report many times over the course of this two-week lab: ***Draft, revise, repeat.*** Start with adding the bulk content then eliminate excess information and make the finishing touches. Do not wait too long to ask questions or to show your work to your peers for feedback. Be receptive to feedback; try not to take it personally!

**Abstract** one paragraph for the entire experiment in the following order

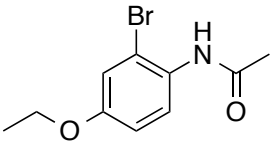
- 1-2 sentences on the **purpose** of the entire experiment
- 2-3 sentences describing the **methods** for each part
    - Include reagents used for each reaction set up, not for workup
- 2-3 **results** sentences
    - Brief description of products, purified yields (not crude), "confirmation *via*…" without listing the data itself (no numbers aside from yields)
- 1-2 conclusion sentences
    - Briefly comment on **success of reactions** and **identification of final product** without lengthy discussion of how you came to that conclusion (that's what the results section is for!)

**Post-Lab Questions**

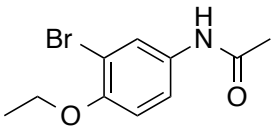
1. Report the ferric chloride test results (observations and positive/negative test) as well as TLC results ($R_f$ values for acetaminophen and phenacetin). Comment on these results in terms of the success of the Williamson ether synthesis. This is in reference to disappearance of starting material and presence of product, not yield.

2. Report and briefly comment the % yield or % recovery for each step (reaction 1, reaction 2, and recrystallization of bromophenacetin).

3. Report the melting temperature ranges of each sample (acetaminophen, phenacetin, and crude or recrystallized bromophenacetin). Compare these to literature values, presenting the data in table format. The literature melting points are of pure samples, not crude. Comment on the purity of samples. Which bromination product was formed, based on MelTemp analysis alone (see below)? Is this reliable? Explain why or why not.




**N-acetyl-2-bromo-4-ethoxyaniline**
mp 96-97 °C




**N-acetyl-3-bromo-4-ethoxyaniline**
mp 112-114 °C

**Post-Lab Questions** (cont'd)

4. Step 1 NMR - Include screenshots of the NMR spectra that you analyzed. Assign each signal in the $^1$H NMR to the protons in acetaminophen and phenacetin using table format (2 separate, labeled tables please). Include the structures with labels for each set of protons (A, B, C, etc.). Compare to the predicted values and to the starting material. Briefly comment on whether each of the products clean / complete based on the NMR spectra.

5. Step 2 NMR - Include screenshots of the NMR spectrum of bromophenacetin that you analyzed. Assign each signal in the $^1$H NMR to the protons in bromophenacetin using table format, include the structure with labels for each set of protons (A, B, C, etc.). Compare to the predicted values and to the starting material (is there any phenacetin remaining?). Based on your interpretation of the bromophenacetin $^1$H NMR, which product was formed? Briefly explain your reasoning. Refer to one or two specific peaks to support your answer ("signal A" or "the 1H doublet at 7.0 ppm" for example).

6. Interpret the IR spectrum of each sample. Present your data in table format (3 separate tables) and use one-to-two sentences to comment on the success of your reactions.

7. Carefully read through the *J. Chem. Ed.* papers used to develop the procedures for this experiment (in the References section, p. E3-4). List the changes in procedure of phenacetin synthesis and comment on expected results of the bromination based on these articles. Explain the possible reasons for the procedural changes and rationalize the expected bromination results given your knowledge of trends in electrophilic aromatic substitution (EArS) reactions.

8. Search the *Journal of the American Chemical Society* (pubs.acs.org) for an article with "phenacetin" in the title. Draw the structure of a phenacetin derivative and provide the citation.

**Experimental Methods**

**** Please see technical writing guidelines on Canvas**

1st Paragraph – General Methods

2nd Paragraph – Phenacetin synthesis and characterization ($^1$H NMR, mp, IR)

3rd Paragraph – Bromophenacetin synthesis, purification, and characterization ($^1$H NMR, mp, IR)