Lab 2. What a Pain! Phenacetin Synthesis from Acetaminophen

What reaction conditions converts acetaminophen to phenacetin? Which functional group reacts? What conditions makes this reaction occur in the reverse direction?

Objectives

1. Convert an alcohol to an ether by substitution reaction.
2. Synthesize phenacetin from Acetaminophen.
3. Analyze your sample by HPLC.
4. Propose a reaction mechanism.


Introduction

If you have a headache, you take a pain reliever, such as acetaminophen (Tylenol). In this lab, you will take acetaminophen and convert it into phenacetin, another pain reliever. Phenacetin was banned by the Food and Drug Administration (FDA) in 1983 due to adverse side effects including increased risk of certain cancers and kidney damage. Phenacetin is metabolized to acetaminophen. Interestingly, acetaminophen replaced phenacetin in some over-the-counter medications following the ban.

Once you make phenacetin, you will identify the reaction conditions to convert the phenacetin back to acetaminophen and do your experiment. In other words, reverse the reaction.

Materials

Tylenol tablets
1 M NaOH in ethanol
HPLC
ethyl iodide
1 M HCl (aq)

Procedure

While you are doing this experiment, try to determine the purpose of each step in the procedure, e.g.,

- Is this reagent reacting with one of the acid, base, or neutral? If so, write a chemical equation that represents the reaction. Is this reagent the limiting reactant or excess reactant?
- If the solvent I just added formed two layers, is the solvent extracting something? Which substance is being extracted?
- What is the reason for heating or cooling?

Record the purpose of each step in your notes.

Caution: The acids and bases in this experiment are corrosive. Be careful handling these substances.

Synthesize phenacetin from acetaminophen.

1. Synthesis
   a. Grind 2 tablets of Tylenol (350 mg of acetaminophen per tablet or an equivalent amount) using a mortar and pestle. Place the powder in a 50-mL round bottom flask with a magnetic stir bar.
   b. Add 5.25-mL of 1M ethanolic NaOH solution to the Tylenol.
   What does the ethanol or NaOH do?
   c. Attach a condenser to the RB flask and bring to a vigorous reflux. Maintain reflux for 15 minutes. Then, remove the flask from its heat source.

   While you are refluxing, go to Step 4.

d. To the hot solution, add 0.7 mL of ethyl iodide.
   Is the ethyl iodide the limiting reactant?
Reflex for an additional 15 minutes.

2. Workup
   a. Filter the hot solution under vacuum through a Buchner funnel and into a filter flask containing a mixture of ice and water. The insoluble starches should be collected on the filter paper.
   b. The phenacetin precipitates from the filtrate as a white solid upon contact with the cold water. Wash with cold water. (Why wash with cold water and not hot water?)
   c. While still cold, collect the solid phenacetin by vacuum filtration.
   d. Dry the solid in the oven at 100 °C for 5 to 10 minutes or by place the sample on a watch glass over a heat source not exceeding 100 °C.
   e. The phenacetin prepared by this method is generally pure. If necessary, you can further purify the phenacetin by recrystallization from hot water. Use decolorizing charcoal if the impure phenacetin is ____. (What does decolorizing charcoal do?)

Ethanolic NaOH – neutralize with acid and dispose in sink.
Any solution containing iodide – in halogenated waste.

3. Characterization
   a. Determine the % yield.
   b. Characterize the product by:
      (i) melting point.
      (ii) IR.
      (iii) HPLC.
   c. Summarize your data and results in Table 3.

Table 3. Phenacetin synthesis data and results.

<table>
<thead>
<tr>
<th></th>
<th>Run 1</th>
<th>Run 2</th>
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</thead>
<tbody>
<tr>
<td>Method</td>
<td>reflux</td>
<td>microwave</td>
</tr>
<tr>
<td>Mass of acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moles of acetaminophen</td>
<td></td>
<td></td>
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<tr>
<td>Volume of 1 M NaOH</td>
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<tr>
<td>Moles of NaOH</td>
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<tr>
<td>Limiting reactant</td>
<td></td>
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<tr>
<td>Moles of Phenacetin</td>
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<tr>
<td>Theoretical yield of Phenacetin, g</td>
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<tr>
<td>Actual yield of Phenacetin, g</td>
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<tr>
<td>% yield of Phenacetin</td>
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<tr>
<td>Experimental melting point range, °C</td>
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<tr>
<td>True melting point, °C</td>
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4. Repeat the experiment except this time use the microwave oven to heat your reaction mixture instead of doing a reflux.