Honors Cup Synthetic Proposal

Section: 230-II
Group Members: Michael Kheir; David Nguyen; Jesse Song

Title: Three-step Synthesis of Ibuprofen

Introduction: Ibuprofen was developed by a research group from Boots Group during the 1960s. Its discoverer was Stewart Adams, with colleagues John Nicholson and Colin Burrows. Its patent was filed in 1961. The drug was launched as a treatment for rheumatoid arthritis in the United Kingdom in 1969, and in the United States in 1974. Boots was awarded the Queen's Award For Technical Achievement for the development of the drug in 1987. Ibuprofen is currently classified as a non-steroidal anti-inflammatory drug (NSAID). It is used not only for relief of symptoms of arthritis, but also for primary dysmenorrhea, fever, and as an analgesic, especially where there is an inflammatory component. Ibuprofen is known to have an antiplatelet (blood-thinning) effect, though it is relatively mild and short-lived when compared to that of aspirin or other more well-known antiplatelet drugs. It is still available in the United States and used by millions of people.
Step 1

Synthetic transformation 1:

\[
\text{Isobutylbenzene} + \text{Propionyl chloride} \xrightarrow{\text{AlCl}_3, \text{CH}_2\text{Cl}_2} 1-(4\text{-Isobutyl-phenyl})\text{-propan-1-one}
\]

**Experimental 1**
(note: this experiment is based off the first experiment done in class. We had a difficult time finding another source with this step)
Place anhydrous aluminum chloride (0.011 mol, 1.1 equiv) and 15 mL of methylene chloride in a 250-mL three neck round bottom flask. Cap one of the necks and attach a reflux condenser and an addition funnel to the other two necks. Flush the flask system with nitrogen, first through reflux condenser, then through addition funnel. Cool the mixture down to 0ºC in an ice/water bath. Mix propionyl chloride (0.011 mol, 1.1 equiv) with 10 mL of methylene chloride and slowly added to the system through the addition funnel. Next, mix Isobutylbenzene (.01 mol) with 10 mL of methylene chloride and add it in a similar manner. After adding all the solutions, remove the mixture from the ice bath and let it cool down to room temperature. Stir the reaction for an additional 15 minutes and then slowly pour it into another beaker containing 25 g of ice and 15 mL of concentrated HCl. Transfer the mixture to a sep funnel and collect the organic layer. Extract the aqueous layer with 20 mL of methylene chloride. Combine the two organic layers and extract it with two portions of saturated sodium bicarbonate and dry it with anhydrous MgSO\(_4\). Remove the drying agent by gravity filtration. Then, dry the methylene chloride through rotary evaporation. Next, set up a simple distillation to separate the aromatic reactant and product. The product contains hydrogen bonding, meaning it will have a much greater b.p. Collect the product and save it for the next step.

**Expected yield: 60% 1.14 g**

**Safety, disposal and green issues 1:**

Isobutylbenzene is flammable and is an irritant. It is found irritating to eyes, the respiratory system, and skin. Propionyl chloride is corrosive. It reacts violently with water. Regular lab safety guidelines should be followed for 1-(4-isobutyl-phenyl)-propan-1-one and methylene dichloride as well. Aluminum chloride is water sensitive, an irritant, and corrosive. It will react with the moisture on your skin to liberate HCl. Handle it with care, weigh out only what is necessary, and work quickly but safely. Acetyl chloride is also corrosive. Keep it in a hood. Keep all reagent bottles tightly capped. All of these molecules should be disposed of in the proper waste basket. Take care to prevent chemicals from entering the drainage systems.
Step 2

**Synthetic transformation 2:**

\[
\begin{align*}
\text{1-(4-Isobutyl-phenyl)-propan-1-one} & \quad \xrightarrow{I_2} \quad \text{Methyl Ibuprofen} \\
\text{HO(OCH}_3\text{)}_3 &
\end{align*}
\]

**Experimental 2**

(note: the experiment was scaled down, because we do not need as much reactant, so everything was scaled down by 11/19th)

1.14 g (6 mmol, or the amount from previous step) of 1-(4-Isobutyl-phenyl)-propan-1-one is mixed with TMOF [3.2 g of HO(OCH_3)_3] to create a solution. 3.05 g of Iodine (12 mmol, 2 equiv) is added into the solution and mixed at 23°C for 24 hours. Aqueous sodium thiosulfate (10%, 20 mL) is then added and will create a brown solution, which is extracted with CH_2Cl_2 (2 x 30 mL). The extract is dried with MgSO_4 and the solvent was evaporated under reduced pressure. The oily residue left over is then purified by column chromatography on SiO2 [hexane-EtOAc (25:1) as eluent].

**Expected yield:** 80 % 1.06 g

(actually 98% yield in the article, but we doubt we will get that high)

**Safety, disposal and green issues 2:**

Iodine may cause severe eye irritation and skin burns. Methyl Ibuprofen should be kept under a fumehood. TMOF (trimethyl orthoformate) should be handled under regular laboratory safety guidelines. All of these molecules should be disposed of in the proper waste basket. Take care to prevent chemicals from entering the drainage systems.
Step 3

**Synthetic transformation 3:**

![Diagram showing the transformation from Methyl Ibuprofen to Ibuprofen]

**Experimental 3**

(This experiment was scaled up by 4/3 from the original experiment. Additionally, KOH replaces NaOH. The original experiment was used for another kind of ether.)

Make a solution of about 1.06 g potassium hydroxide (1.0 equiv) in a mixture of 4 mL distilled water and 4 mL 95% ethanol in a 10 mL Erlenmeyer flask. We measured out and placed our methyl ibuprofen in a 25 mL Erlenmeyer flask and add the potassium hydroxide solution to it. Heat the mixture in a sand bath at about 120°C. Place an inverted 50 mL beaker over the neck of the flask to help reduce evaporation. Swirl the Erlenmeyer flask every few minutes.

Extraction is done through the separation funnel. Collect the organic layer.

**Expected yield: 80 % 0.79 g**

**Safety, disposal and green issues 3:**

KOH may cause severe burns. Avoid eye contact. Ibuprofen should be handled under regular laboratory safety guidelines. All of these molecules should be disposed of in the proper waste basket. Take care to prevent chemicals from entering the drainage systems.
Overall budget:

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Supplier</th>
<th>Cost (g)</th>
<th>Amt. Needed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isobutylbenzene</td>
<td>Aldrich</td>
<td>$0.290/g</td>
<td>1.90 g</td>
<td>$0.56</td>
</tr>
<tr>
<td>Propionyl Chloride</td>
<td>Aldrich</td>
<td>$0.0712/g</td>
<td>1.012 g</td>
<td>$0.08</td>
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<tr>
<td>AlCl₃</td>
<td>Aldrich</td>
<td>$0.496/g</td>
<td>1.46 g</td>
<td>$0.73</td>
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<tr>
<td>I₂</td>
<td>Aldrich</td>
<td>$0.406/g</td>
<td>3.05 g</td>
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</tr>
<tr>
<td>HC(OCH₃)₃</td>
<td>Aldrich</td>
<td>$0.418/g</td>
<td>3.2 g</td>
<td>$1.34</td>
</tr>
</tbody>
</table>

Total costs per synthesis: $3.95

References:

**Step 1:**
"Experiment 1." Friedel-Crafts Acylation. 216H Winter 2008. 03 Feb. 2008
<http://www.umich.edu/~chem215/CHEM216/Experiment1/experiment%201.pdf>.

**Step 1 + 3:**

**Step 2:**