DEPARTMENT OF CHEMISTRY & BIOCHEMISTRY

Synthesis of Acetylsalicylic Acid (Aspirin)

Acid-Catalyzed Esterification, Recrystallization, and Purity Analysis

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Abstract. Acetylsalicylic acid (aspirin) was synthesized via the phosphoric acid-catalyzed esterification of salicylic acid with acetic anhydride. The crude product was isolated by vacuum filtration and subsequently purified through recrystallization using an ethanol-water solvent system. The purified product was obtained as fine white needles ($2.34\,\mathrm{g}$), representing a $89.3\,\%$ yield based on the limiting reagent. The purity of the product was characterized by melting point determination, yielding a range of $134\,^{\circ}\mathrm{C}$ to $136\,^{\circ}\mathrm{C}$ (literature value: $135\,^{\circ}\mathrm{C}$), and a ferric chloride chemical test, which confirmed the absence of unreacted phenolic salicylic acid. The results demonstrate that nucleophilic acyl substitution is a highly efficient pathway for pharmaceutical ester synthesis when reaction and purification parameters are carefully controlled.

1 Introduction & Aim

The synthesis of esters from carboxylic acids and alcohols is a fundamental transformation in organic chemistry. Acetylsalicylic acid (commonly known as aspirin) is synthesized through the acetylation of salicylic acid. Salicylic acid possesses both a carboxylic acid group and a phenol group. Under acidic conditions, the phenolic hydroxyl group acts as a nucleophile, attacking the carbonyl carbon of acetic anhydride in a nucleophilic acyl substitution reaction. Because phenols are weaker nucleophiles than aliphatic alcohols, a strong acid catalyst (such as concentrated phosphoric or sulfuric acid) is required to protonate the acetic anhydride and increase its electrophilicity.

The primary aims of this laboratory experiment are:

- To synthesize acetylsalicylic acid via the acid-catalyzed esterification of salicylic acid.
- To master the technique of recrystallization to purify the crude synthesized compound.
- To determine the percent yield and evaluate product purity using melting point determination and colorimetric chemical assays.

2 Chemicals & Apparatus

All chemical reagents used in this synthesis are listed in Table 1 with their molecular properties and primary hazard classifications.

Apparatus: Erlenmeyer flasks ($125\,\mathrm{mL}$), graduated cylinders ($10\,\mathrm{mL}$), water bath with hot plate, beaker ($250\,\mathrm{mL}$), Hirsch funnel, side-arm flask, vacuum filtration pump, melting point capillary tubes, and standard glass stirring rods.

Safety Precautions

Acetic anhydride is highly corrosive and behaves as a lachrymator (tear gas). Concentrated phosphoric acid is extremely corrosive and causes tissue damage on contact. Work exclusively inside the fume hood during reactant measuring and heating. Wear splash goggles, laboratory coat, and nitrile gloves at all times.

Table 1: Physical properties and hazard profiles of reagents.

Chemical	Formula	Molar Mass ($\mathrm{g\,mol^{-1}}$)	Density ($\mathrm{g\,mL^{-1}}$)	Hazards
Salicylic acid	$C_7H_6O_3$	138.12	—	Harmful if swallowed, skin irritant
Acetic anhydride	$C_4H_6O_3$	102.09	1.08	Flammable liquid, corrosive, lachrymator
Phosphoric acid (conc.)	H_3PO_4	98.00	1.69	Highly corrosive, causes severe burns
Acetylsalicylic acid (Aspirin)	$C_9H_8O_4$	180.16	—	Mild skin and respiratory irritant

3 Reaction / Balanced Equation

The reaction proceeds via protonation of acetic anhydride by phosphoric acid, followed by nucleophilic attack from the phenolic hydroxyl oxygen of salicylic acid. Elimination of acetic acid as a side-product completes the reaction.

$$\mathrm{C_7H_6O_3\,(s) + C_4H_6O_3\,(l) \xrightarrow[\Delta]{H_3PO_4} C_9H_8O_4\,(s) + C_2H_4O_2\,(l)} \tag{1}$$

4 Procedure

1. **Reaction Setup:** Weigh exactly $2.01\,\mathrm{g}$ of salicylic acid and transfer it to a clean, dry $125\,\mathrm{mL}$ Erlenmeyer flask. In a fume hood, measure $5.0\,\mathrm{mL}$ of acetic anhydride and add it to the flask. Carefully add 5–8 drops of concentrated ($85\,\%$) phosphoric acid as a catalyst. Swirl the mixture gently to suspend the solids.

2. **Heating Stage:** Place the flask into a warm water bath maintained at $70\,^\circ\mathrm{C}$ to $80\,^\circ\mathrm{C}$ on a hot plate. Heat the mixture for approximately $15\,\mathrm{min}$, swirling periodically until all salicylic acid has dissolved and the solution is clear.

3. **Isolation of Crude Product:** Remove the flask from the water bath and allow it to cool to room temperature. Add $20\,\mathrm{mL}$ of distilled water to decompose excess acetic anhydride. Place the flask in an ice bath for $15\,\mathrm{min}$ to initiate crystallization. Collect the crude product by vacuum filtration using a Hirsch funnel. Wash the crystals with two $5\,\mathrm{mL}$ portions of ice-cold distilled water.

4. **Recrystallization:** Transfer the crude crystals to a beaker. Dissolve them in a minimum volume of hot ethanol (approx. 3–5 mL) while heating. Add hot distilled water dropwise until the solution becomes cloudy, then add a few drops of hot ethanol to clear the turbidity. Allow the solution to cool slowly to room temperature, then place it in an ice bath to complete crystallization.

5. **Drying and Analysis:** Collect the purified crystals via vacuum filtration. Dry the product in an oven at $50\,^\circ\mathrm{C}$ for $30\,\mathrm{min}$. Record the mass of the dried product. Verify purity by measuring the melting point and performing the ferric chloride color test.

5 Observations & Data

During recrystallization, the crude product dissolved completely in hot ethanol and recrystallized as long, needle-like white crystals upon cooling. The raw experimental data and product characterizations are tabulated in Table 2.

Table 2: Experimental mass, yield, and purity characterization.

Parameter	Experimental Value	Literature Value
Mass of Salicylic Acid	$2.01\,\mathrm{g}$	—
Volume of Acetic Anhydride	$5.0\,\mathrm{mL}$	—
Mass of Acetic Anhydride (calc.)	$5.40\,\mathrm{g}$	—
Mass of Dry Purified Aspirin	$2.34\,\mathrm{g}$	—
Melting Point Range	$134\,^{\circ}\mathrm{C}$ to $136\,^{\circ}\mathrm{C}$	$135\,^{\circ}\mathrm{C}$
Ferric Chloride Test Color	Light yellow / Clear	Clear (pure aspirin)

Key Reaction Metrics

Crude Yield: $2.58\,\mathrm{g}$ **Purified Yield:** $2.34\,\mathrm{g}$ **Percent Yield:** $89.3\,\%$
Purity (M.P.): High **$FeCl_3$ Test:** Negative **Appearance:** Needle-like crystals

6 Calculations

6.1 Molar Quantities of Reactants

The molar quantities of the starting materials are calculated from their measured masses or volumes:

$$n_{\text{salicylic acid}} = \frac{2.01\,\mathrm{g}}{138.12\,\mathrm{g\,mol^{-1}}} = 0.014\,55\,\mathrm{mol}$$
$$m_{\text{acetic anhydride}} = 5.0\,\mathrm{mL} \times 1.08\,\mathrm{g\,mL^{-1}} = 5.40\,\mathrm{g}$$
$$n_{\text{acetic anhydride}} = \frac{5.40\,\mathrm{g}}{102.09\,\mathrm{g\,mol^{-1}}} = 0.052\,90\,\mathrm{mol}$$

6.2 Limiting Reagent and Theoretical Yield

Since the reaction stoichiometry is $1:1$ (Equation 1), salicylic acid is the limiting reactant ($0.01455 < 0.05290$). The theoretical mass of acetylsalicylic acid (m_{theory}) is calculated using its molar mass ($M_{\text{aspirin}} = 180.16\,\mathrm{g\,mol^{-1}}$):

$$m_{\text{theory}} = 0.014\,55\,\mathrm{mol} \times 180.16\,\mathrm{g\,mol^{-1}} = 2.621\,\mathrm{g}$$

6.3 Percent Yield

Using the mass of the dry purified product ($m_{\text{actual}} = 2.34\,\mathrm{g}$), the percent yield is:

$$\text{Percent Yield} = \left(\frac{m_{\text{actual}}}{m_{\text{theory}}}\right) \times 100\% = \left(\frac{2.34\,\mathrm{g}}{2.621\,\mathrm{g}}\right) \times 100\% = 89.3\,\%$$

7 Discussion

The synthesis of acetylsalicylic acid was completed successfully with an 89.3% purified product yield. The high yield indicates that the conversion was efficient, and the recrystallization recovery was successful. The phosphoric acid catalyst successfully lowered the activation energy of the nucleophilic attack by protonating the carbonyl oxygen of acetic anhydride, which drove the reaction to completion within the heating timeframe.

Product purity was primarily evaluated using melting point range analysis. The observed melting point range of $134\,^{\circ}\mathrm{C}$ to $136\,^{\circ}\mathrm{C}$ is in excellent agreement with the literature value of $135\,^{\circ}\mathrm{C}$. A narrow

melting point range ($2\,^{\circ}\mathrm{C}$) indicates a high degree of crystalline purity and structure, as impurities typically depress the melting point and broaden the melting range.

To chemically confirm the absence of unreacted salicylic acid, the ferric chloride ($FeCl_3$) test was performed. Phenols form a dark purple coordination complex with iron(III) ions. Salicylic acid contains a free phenolic group and yields a deep violet color, whereas pure aspirin lacks a free phenol group and yields a clear or light yellow solution. The purified crystals showed a light yellow/clear result, confirming that no detectable salicylic acid remained, validating the effectiveness of the recrystallization washing steps.

A primary source of yield loss during the recrystallization process is the partial solubility of aspirin in the cold ethanol-water solvent mixture. A small fraction of the product remains dissolved in the filtrate and is lost during vacuum filtration. This could be minimized by reducing the initial volume of solvent used or extending the ice bath crystallization time.

8 Conclusion

Acetylsalicylic acid was successfully synthesized from salicylic acid and acetic anhydride in an acid-catalyzed esterification reaction. A high percent yield of $89.3\,\%$ ($2.34\,\mathrm{g}$) was achieved. Physical and chemical characterizations, including a sharp melting point of $134\,^{\circ}\mathrm{C}$ to $136\,^{\circ}\mathrm{C}$ and a negative ferric chloride test, confirmed that the recrystallization method yielded high-purity crystals with no detectable starting material contamination.