

Acid-Catalyzed Tandem Hydrolysis–Esterification of Acetylsalicylic Acid from Commerical Aspirin Tablets to Form Methyl Salicylate

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Abstract

Methyl salicylate was synthesized from commercial aspirin tablets via an acid-catalyzed tandem hydrolysis–esterification sequence. Acetylsalicylic acid (ASA) was extracted from the tablet matrix into methanol and reacted under reflux with a catalytic volume of H_2SO_4 . This one-pot method facilitates simultaneous deacetylation and Fischer esterification, bypassing the isolation of a salicylic acid intermediate. The resulting methyl salicylate was isolated via aqueous quenching and liquid–liquid extraction. Crude product purification was achieved through neutralization with saturated NaHCO_3 and drying over anhydrous MgSO_4 . This synthesis demonstrates an efficient, high-yield conversion of a common pharmaceutical precursor into a high-value fragrance ester, highlighting fundamental principles of equilibrium-driven organic transformations and multistep one-pot synthesis.

Introduction

Acetylsalicylic acid (ASA), $\text{C}_9\text{H}_8\text{O}_4$, is a synthetic organic derivative of salicylic acid and is commonly known as aspirin [1].

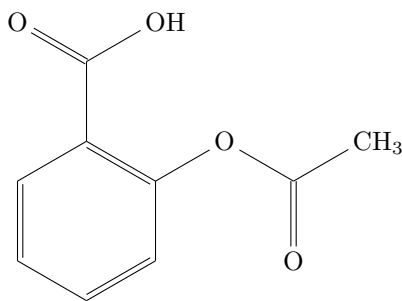


Figure 1: Chemical structure of ASA

Commercial aspirin is commonly synthesized from salicylic acid through Eq 1, and the two molecules differ by an ester group ($-\text{OCOCH}_3$) [2].



Another common derivative product of salicylic acid is methyl salicylate, $\text{C}_8\text{H}_8\text{O}_3$, commonly referred to as

wintergreen oil. Methyl salicylate is commonly used in edibles (e.g. gum, mints), perfumes, and pain-relief ointments (e.g. Icy Hot, BenGay) [3]. Methyl salicylate also differs with salicylic acid by a single ester group and has simply been esterified differently than ASA.

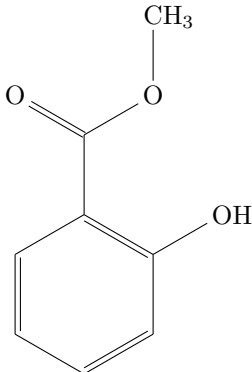


Figure 2: Chemical structure of methyl salicylate

Due to the similarity between the two molecules, ASA can be reacted to synthesize methyl salicylate [4, 5]. The purpose of this experiment was to convert acetylsalicylic acid obtained from commercial aspirin tablets into methyl salicylate through acid-catalyzed esterification in methanol under reflux conditions.

Results and discussion

Extraction and Solvation of ASA

The synthesis began with the mechanical breakdown of commercial aspirin tablets (500 mg ASA/tablet) using a mortar and pestle. The resulting powder was digested in an excess of methanol for one hour with constant stirring.

The heterogeneous mixture was subsequently clarified via filtration through a cellulose-based filter. This step effectively isolated the soluble ASA and miscible plasticizers from the insoluble structural excipients and pigments (Table 1).

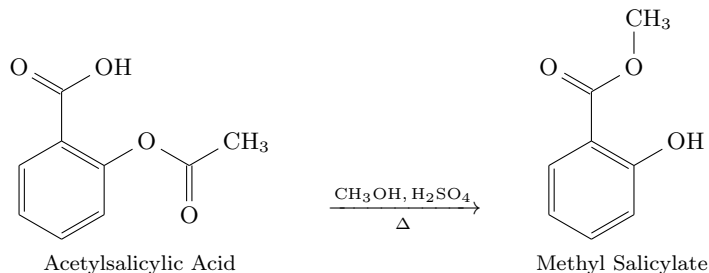
Table 1: Methanol Solubility/Miscibility Profile of Tablet Components

Component Category	Specific Ingredients	Solubility in CH ₃ OH
Active Ingredient	Acetylsalicylic Acid (ASA)	Soluble
Binders / Fillers	Corn Starch, Powdered Cellulose	Insoluble
Coating Agents	Carnauba Wax, Shellac, Hypromellose	Insoluble / Sparingly
Plasticizers	Propylene Glycol, Triacetin	Miscible
Pigments / Lakes	Titanium Dioxide, D&C Red #7, FD&C Blue #2, FD&C Red #40	Insoluble

H₂SO₄ Catalyzed Tandem Hydrolysis–Esterification

The conversion of ASA to methyl salicylate proceeds via a one-pot tandem sequence (Scheme 1). Concentrated H₂SO₄ serves as a Brønsted acid catalyst, activating the carbonyl groups toward nucleophilic attack

by methanol, and as a dehydrating agent to shift the equilibrium.



Scheme 1: Tandem deacetylation and Fischer esterification sequence.

The transformation encompasses two concurrent equilibrium-driven processes:

1. **Acid-Catalyzed Solvolysis:** The acetoxy group undergoes transesterification with methanol to yield salicylic acid and methyl acetate (Eq 2).
2. **Fischer Esterification:** The carboxylic acid is esterified by the methanol solvent (Eq 3).



To drive the reaction toward the methyl salicylate product, a substantial stoichiometric excess of methanol was employed, utilizing Le Chatelier’s principle to overcome the reversible nature of the esterification.

Kinetic and Thermodynamic Analysis

The transformation efficiency of the tandem hydrolysis–esterification is determined by the interplay between reaction rate and equilibrium position.

Thermal Activation and Collision Theory

The reflux duration is required to provide the activation energy (E_a) necessary for the nucleophilic attack on the sterically hindered aryl ester. According to the Arrhenius relationship, the rate constant k increases exponentially with temperature:

$$k = Ae^{-E_a/RT} \quad (4)$$

Operating at the boiling point of the solvent increases the frequency of effective collisions and facilitates the formation of the required carbocation intermediates.

Furthermore, by employing a vast molar excess of methanol, the system effectively follows pseudo-first-order kinetics. Under these conditions, the concentration of the alcohol remains negligible in its variation, and the rate depends solely on the concentration of the limiting aspirin precursor:

$$-\frac{d[\text{ASA}]}{dt} = k'[\text{ASA}] \implies [\text{ASA}]_t = [\text{ASA}]_0 e^{-k't} \quad (5)$$

Equilibrium Shifts and Chemical Potential

As a reversible process, the yield is limited by the equilibrium constant (K). Because the esterification step is endothermic ($\Delta H^\circ > 0$), the application of heat shifts the equilibrium toward the products. This temperature dependence is quantified by the Van’t Hoff equation:

$$\frac{d \ln K}{dT} = \frac{\Delta H^\circ}{RT^2} \quad (6)$$

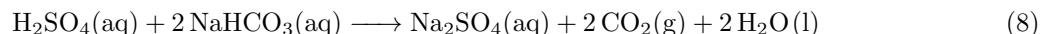
The high reactant-to-substrate ratio further ensures that the reaction quotient (Q) remains lower than K throughout the process. This maintains a negative Gibbs free energy (ΔG), driving the reaction toward the formation of methyl salicylate:

$$\Delta G = \Delta G^\circ + RT \ln Q \quad (7)$$

The combination of thermal input and stoichiometric bias effectively overcomes the reversible nature of the Fischer esterification.

Work-up and Purification

Following reflux, the reaction was quenched in ice-cold distilled water. Methyl salicylate ($\rho \approx 1.17$ g/mL) was isolated as the organic phase via liquid-liquid extraction. Residual acidic species (H_2SO_4 , CH_3COOH) were neutralized using saturated NaHCO_3 :



The organic extract was dried over anhydrous MgSO_4 and filtered to yield the pure essential oil.

Experimental

Materials and Reagents

The starting material consisted of 50 Bayer Extra Strength aspirin tablets (500 mg ASA per tablet). The reaction used ACS-grade methanol and 96% H_2SO_4 . A saturated solution of commercial iodized salt was used for the salting-out step.

Extraction and Filtration

The 50 tablets had a total initial mass of 30.148 g. These were crushed using a mortar and pestle into a fine powder. After grinding, 28.114 g of the powder was recovered, meaning some material was lost in the mortar. Based on the ratio of the original 25.000 g of ASA in the 30.148 g bulk, the actual amount of ASA moved into the beaker was 23.313 g (0.129 mol).

This powder was stirred in 190 mL of methanol for an hour. The mixture was then poured through a coffee filter to strain out the starch and cellulose binders. The resulting liquid had a faint pink tint, likely from the dyes used in the tablet coating.

Tandem Reaction and Reflux

The filtered liquid was poured into a 250 mL round-bottom flask. When the 5 mL of 96% H_2SO_4 was added dropwise, the flask became hot to the touch and the liquid boiled locally where the acid hit. The flask was set up with a water-cooled condenser and boiled at a steady reflux for 60 min. During this time, the liquid lost its clarity and became slightly murky.

Isolation and Salting-Out

After boiling, the liquid was evaporated down to about 100 mL and then poured into 100 mL of ice-cold water. To help the oil separate from the water, 10 mL of saturated salt water was added. Because the total volume was too high for a single small container, the mixture was split into two 125 mL separatory funnels. In both funnels, the wintergreen oil sank to the bottom as a dense layer. These two layers were drained and combined.

Purification and Neutralization

The crude oil was washed twice with 50 mL of saturated NaHCO_3 and separated through gravity separation. Both times, the mixture fizzed a lot as the acid was neutralized, so the funnel had to be vented constantly while shaking. This process removed the leftover sulfuric acid and the acetic acid byproduct, and the fizzy gas was the CO_2 resulting from the neutralization reaction.

Theoretical Yield Analysis

The final oil was dried with anhydrous MgSO_4 until it looked clear and then filtered through a cotton plug. Based on the starting amount of 23.313 g of ASA, the theoretical yield of methyl salicylate is:

$$\text{Mass}_{\text{theoretical}} = 0.129 \text{ mol} \times 152.15 \text{ g/mol} = 19.627 \text{ g} \quad (9)$$

The final product was a clear oil with a very strong wintergreen scent. While the final yield was not recorded, the mass of final product was much lower than 19.627 g, and the researchers estimate the percent yield to be near 10%. This low yield is likely attributed to the equilibrium nature of the reaction. Additionally, substantial oil was lost in separation to prevent accidental passage of the aqueous layer.

References

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