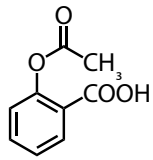
School of Engineering
Institute of Materials
Laboratory of Macromolecular
and Organic Materials

Organic Chemistry (MSE 211)

Synthesis and Purification of Aspirin

1. Introduction



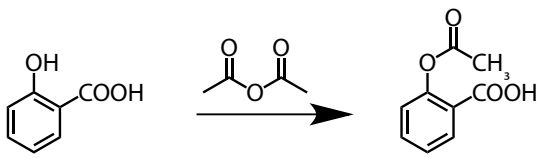
Aspirin, or acetylsalicylic acid, is a widely consumed anti-inflammatory drug. Its successful impact on reducing inflammation and pain is due to the inhibition of enzymes (cyclooxygenase) that catalyse the synthesis of prostaglandin, a class of compounds responsible for pain, blood coagulation and inflammation.

Aspirin is synthesized via an acetylation of salicylic acid. This reaction is a nucleophilic substitution at a carbonyl atom. While this reaction can be industrially performed on a tonne scale, the scope of this laboratory experiment is to synthesize and purify aspirin on a gram scale.

See also: *Chapter 4.3* of the class.
Reading Recommendation: *McMurry,* 7th ed., chapters 21.2-21.5; *Clayden*, Chapter 12

2. General Principle of the Synthesis

The preparation of acetylsalicylic acid is an esterification of salicylic acid with acetic anhydride and a catalytic amount of sulfuric acid. The reaction takes place without an additional solvent.
The crude aspirin is separated from the catalyst and acetic acid by washing with water (in which aspirin is poorly soluble) and purified by recrystallization from ethanol/water.



salicylic acid acetylsalicylic acid

3. Required Equipment

- A 100 mL three-necked round-bottom flask
- A DrySin© with heating plate and magnetic stirrer
- Thermometer
- Reflux condenser
- Büchner funnel
- Spatula

4. Experimental Procedure

Salicylic acid (72 mmol) is put into a 100 mL three-necked, round-bottom flask. Acetic anhydride (14 mL) is added under vigorous stirring. Five drops of concentrated sulfuric acid are

Learning Objective: **Construction of a Simple Reaction Apparatus**

The construction of an apparatus for a chemical reaction always starts with the round bottomed flask. It is mounted in a height that provides sufficient space between the flask and the desk for the placement of laboratory jack and heating plate. Heating or cooling baths must be immediately removable, if necessary.

The simplest apparatus for a chemical reaction, which requires heating (or even boiling) of a solvent, starting material or product, consists of a round-bottomed flask equipped with a reflux condenser. To avoid strains leading to breakage of the glassware the reflux condenser is fixed only loosely. The apparatus must not be closed in order to avoid potential high pressures occurring during a reaction.

More sophisticated reactions require the dropwise addition of a solution or liquid reactant to an already stirred solution, which is met by using a three-necked-bottom flask equipped with reflux condenser and a dropping funnel. In case of largely exothermic reactions the temperature of the reaction mixture is controlled by adjusting the dropping rate.

added, and the mixture is stirred at 60 °C for 15 min. The mixture is cooled to room temperature and then, 70 mL of water is added. A colorless solid forms that is collected over a Büchner funnel. The solid is washed with 150 mL water.

Learning Objective: **Recrystallization – Principle and Practical Realization**

Aspirin is purified by recrystallization. This technique is very practical on an industrial scale, typically resulting in compounds in a very pure form.

A product obtained by a chemical reaction always contains "impurities", such as solvents, traces of starting materials, decomposition products, or side products. Several techniques have been developed to remove these impurities, among which recrystallization is of utmost importance for the purification of *solid products.*

Recrystallization is based on the different solubility of a compound at different temperatures. The solubility increases with increasing temperature and becomes disproportionately high towards the boiling point. Accordingly, a compound is typically recrystallized from a solvent referred to as "bad solvent" at room temperature, whereas it provides sufficient solubility close to its boiling point.

In practice, recrystallization is performed as follows:

a) Dissolving of the impure solid in the minimum volume of an appropriate solvent at the solvent boiling temperature (ideally forming a saturated solution at boiling temperature). In some cases, binary solvent mixtures can be applied instead of a single solvent.

b) A slow cooling of this solution is required for the success of recrystallization, particularly at temperatures close to the boiling point when nucleation of the crystals is initiated. Along with a further temperature decrease, the decrease of solubility promotes the separation of the product crystals that contain less impurities than the crude product.

Although the purity of the crystalline product is improved by means of recrystallization, exclusion of the impurities is not complete. Some impurities still co-crystallize with the target compound, their concentration being a function of their initial amount, their chemical nature, the cooling rate, and the solvent. If the degree of purity achieved by recrystallization is not considered as sufficient, it can be improved by a second (or even third) recrystallization. In current practice, a purity of 98-99% is acceptable for most applications.

5. Purification

The crude aspirin is recrystallized from ethanol/water (2:5). Use 10 mL of this solvent mixture. The crystals are collected over a Büchner funnel and dried in an oven. The dry crystals are weighed to determine the yield of the reaction.

6. Control of the Purity

The melting point (MP) of the dry sample is measured and compared with the literature-known value (135 °C).

7. End of the Manipulation

1.) Aspirin is stored in a glass vial that is labelled with the compound name, student name, and date.

2.) All starting materials and chemicals are put back into the retention trays.

Learning Objective: **Melting Point**

The melting point (MP) is the temperature at which a solid substance changes to the liquid state.

For a pure and crystalline substance, the melting point is a characteristic physical property of the substance. It is therefore used as a first check of the identity of a substance, but more importantly as a qualitative measure of purity, since all impurities reduce the melting point.

In the most common method for melting point determination, a small amount of the solid is collected in a glass capillary tube, which is slowly heated within a "melting point apparatus" until the solid melts.

In practice, two temperatures are observed: the temperature at which the liquid state begins to appear (starting temperature of melting) and the disappearance of the last solid trace (end temperature of melting). Both temperatures define the melting range.

In organic chemistry, the melting range is always reported, and not a single temperature, e.g. MP = 122-124 °C indicates that melting began at 122 °C and ended at 124 °C.

Recording the two temperatures is important because impurities increase the melting range, which therefore is another indicator for the purity of a solid.

EPFL STI IMX LMOM
Dr. Daniel Görl
MXG 037, Station 12
CH-1015 Lausanne

+41 21 693 78 65
daniel.gorl@epfl.ch
lmom.epfl.ch

3.) The glassware is cleaned from any contaminant and put into the dishwasher. Remaining trances of chemical compounds are removed by rinsing the flask with a minimum of solvent (for example acetone), which is subsequently disposed as non-halogenated organic solvent waste. Clean glass ware from the dishwasher is placed pack into its original location.

4.) The fume hood is tidied up. All electrical appliances are unplugged. Ventilation and lighting of the hood are switched off.

5.) The sink (if used) is cleaned.

6.) All waste contaminated with chemicals (absorbent paper, etc.) is collected in specific recovery cans, according to the indications of the assistants.

8. To be Addressed in the Protocol

1.) Give a detailed reaction mechanism including the elementary steps.

2.) What is the reactivity of acetic anhydride compared to other carbonyl functions (carboxylic acids, acyl chlorides, esters, ketones, aldehydes).

3.) What is the purpose of the catalytic amount of sulfuric acid? Would it make sense to use a base for the activation of the nucleophile?

4.) Calculate the yield of the reaction. What is the relevance of this value?

5.) Why is acetylsalicylic acid less soluble in water than salicylic acid?

Be sure you have also completed the prelab protocol with the relevant safety information (**BEFORE** the lab course).

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lmom.epfl.ch