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Article

Synthesis of Acetylsalicylic Acid from Salicylic Acid and Acetic Anhydride, Using Phosphoric Acid as Catalyst

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ABSTRACT

Acetylsalicylic acid (ASA) is known worldwide as the active substance in the ASA drug, with antipyretic, anti-inflammatory, and analgesic activities. For many years, researchers have been improving the formulation of this medicine, craving reduce you effects collateral effects on organisms and remove the characteristic bitter taste. To attend the demand, the aspirin needed to be produced in scale industrial, being necessary to use alternative raw material. Therefore, in this work, we aimed to synthesize the acetylsalicylic acid (aspirin) from salicylic acid and anhydrous acetic acid, using phosphoric acid as a catalyst. As well as purifying the final product using the recrystallization technique. With the methodology carried out, it was possible to obtain, through the acetylation reaction, the synthesis of the acid acetylsalicylic, and an weight in aspirin in 2.5128 g. The same was purified using the technique of recrystallization and it was obtained an income in 48.16%. This result demonstrates loss of product; however, it did not make the formation of the product desired by reaction of acetylation.

Key words: Salicylic acid, Acetylsalicylic acid, Aspirin.

1. INTRODUCTION

Acetylsalicylic acid (ASA), also known as aspirin, is one of the most popular worldwide, which is an active substance in the well-known drug ASA, the same belongs to the group in substances anti-inflammatory no steroids, features properties antipyretic, anti-inflammatory, and analgesics [1]. The origin of this drug is in the bark of the white willow (*Salix alba*), which, per many years old, was used for treatment in pains [2]. At present, although the pharmacological market be extremely competitive, the aspirin continues to be the sales leader in its segment, as it is a in low cost, safe, and easy access [3].

There are many studies on the action of this drug in the human body, and the growing interest in this medicine encourages still most at researches and work on aspirin [4]. For many years, researchers have been improving the formulation of this medicine, craving reduce you effects collateral effects on organisms and remove the characteristic bitter taste. To attend the demand, the aspirin needed to be produced in scale industrial, being necessary to use alternative raw material. In this way, ASA, active principle of aspirin, began to be produced synthetically by the reaction nucleophilic, too known how reaction in esterification [5].

In general, the synthesis organic is very important in obtaining from drugs, the story of ASA highlights such relevance. For Menegatti *et al*. [6], the synthesis makes it possible to obtain molecules at various levels of complexity. The synthesis of aspirin it is an of practices most common us courses in chemistry and drugstore, addressed at discipline in synthesis organic [5,7]. Therefore, in this work, we aimed to synthesize the acetylsalicylic acid (aspirin) from salicylic acid and anhydrous acetic acid, using phosphoric acid as a catalyst. As well as purifying the final product using the recrystallization technique.

2. MATERIALS AND METHODS

2.1. Synthesis of ASA

Initially, 4.0002 g of salicylic acid was weighed in a 100 mL beaker, and with the aid of a spatula, the solute was transferred to a 250 mL round bottom flask. In the hood, 10 mL of acetic anhydride was added to the beaker that was used for weighing, seeking to minimize the loss of the initial mass of salicylic acid. This volume was, then, transferred to the round-bottomed flask. Ten drops of 85% phosphoric acid were added to the flask, which was later connected to the reflux system on the bench and heated to a temperature of 85–90ºC for 15 min, under magnetic stirring [Figure 1a]. At the end of the previously established time, the heating was terminated. And fur top of condenser, added 4 mL in water distilled aiming decompose O excess in anhydride acetic. Withdrew the balloon still hot of system, keeping the manual agitation and slow give mix. So what the reaction ceased, added 25 mL in Water distilled icy, put up the flask in the ice bath for approximately 10 min, until the appearance of crystals [Figure 1b]. The obtained crystals were filtered in a vacuum system with filter paper and a Büchner funnel and washed with small amounts of ice water to avoid mass loss. With the aid of two tweezers, the filter paper was removed from the funnel and placed under a watch glass with a lid, the filtered crystals were stored in the refrigerator for about 24 h.

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2.2. Purification by Recrystallization

The crystals obtained were dissolved with 10 mL of ethyl alcohol (ethanol) in a 100 mL beaker, in then added 35 ml in water distilled at solution. The mixture was heated until the maximum solubilization of the crystals and, later, submitted to an ice bath to cool. After cooling, the crystals obtained were filtered in a vacuum system with filter paper (previously weighed on an analytical balance) and a Büchner funnel, and washed with small amounts of ice water to avoid mass loss. Soon after, with the aid of two tweezers, the filter paper was removed from the funnel and placed under a watch glass, which was then dried in the greenhouse and, later, aiming to reach room temperature, it was directed to the desiccator. After cool down, weighed the filter paper mass with crystals purified [Figure 1c].

3. RESULTS AND DISCUSSION

The synthesis of acid acetylsalicylic, commercially known how aspirin, it's classified with an reaction in esterification, what occurs per quite gives reaction in between the acid salicylic and the anhydride acetic, under heating, and converting the group hydroxyl acid of salicylic acid on an ester group. The result is ASA and acetic acid. Figure 1 represents the synthesis of acetylsalicylic acid and Figure 2 represents the esterification reaction of ASA with their respective weights and molecular formulas.

Table 1 provides you dice obtained during the experimental work in synthesis of acid ASA. Weighing was performed before and at the end of the process, this record is important for the calculation of theoretical and real yield.

Table 1: Data obtained during practice acetylsalicylic acid synthesis

Material/reagent	The amount	Unit
Weight in acid salicylic	4.0002	g
Volume of anhydride acetic	10	mL
Weight in ASA + paper filter + glass in clock	90.5570	g
Weight of paper filter	0.9117	g
Glass mass _ in clock	87.1325	g
Weight in ASS purified	2.5128	g

Source: Authors (2022)

3.1. Calculation of Income Theoretical

- Mole of salicylic acid ($C_7H_6O_3$)

$$n = \frac{m}{MM}$$

n = 0, 0 2896 mole of salicylic acid

Where:

n = number of moles of salicylic acid;
m = mass of salicylic acid (g) = 4.002 g;
MM = molear mass of salicylic acid = 138.12 g.

- Mole of Acetic Anhydride ($C_4H_6O_3$)

$$d = \frac{m}{V}$$

n = 10.8 g of _ acetic anhydride

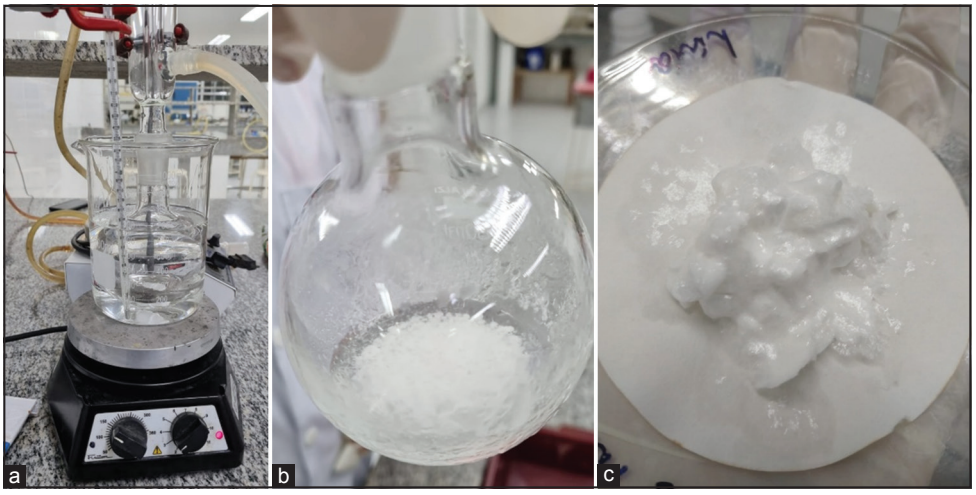

Figure 1: Synthesis of acetylsalicylic acid: reflux system on the bench and heated and under magnetic stirring (a); appearance of crystals after ice bath of the flask, and (b); crystals purified, and (c); Source: authors (2022).

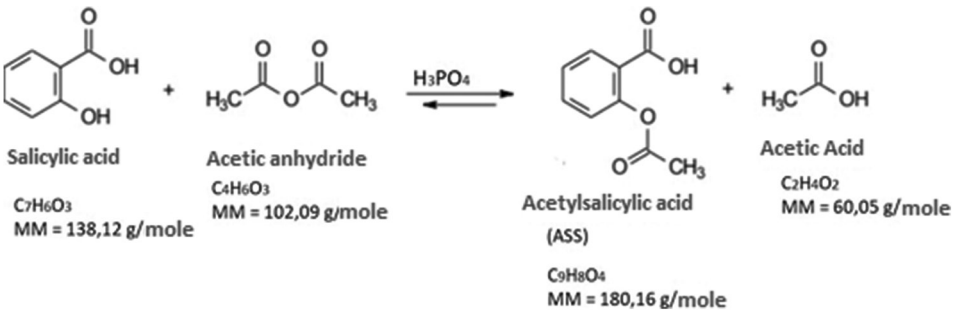

Figure 2: Reaction of acetylsalicylic acid synthesis. Source: Authors (2022).

Where:

d = theoretical density of acetic anhydride (g. L^{-1}) = 1.08 g. L^{-1};
m = mass of acetic anhydride (g);
V = volume of acetic anhydride (mL) = 10 mL.

$$n = \frac{m}{MM}$$

n = 0.10579 mole of acetic anhydride

Where:

n = number of moles of salicylic acid;
m = mass of salicylic acid (g) = 10.8;
MM = molear mass of acetic anhydride = 102.09 g.

Through these calculations, a greater amount of moles of anhydride is observed acetic acid, thus being the excess reactant of the reaction. In this way, to calculate the yield theoretical, one must use the reagent limiting (in this If acid salicylic).

1 mole ASA – 180.16 g

0.02896 moles – C

Ç = 5.2174 g in ASA (theoretical yield).

- Performance theoretical = (Weight of salicylic acid)/(Mass of ASA) × 100
  Performance theoretical = (4.0002 g)/(5.2174g) × 100 = 76.67%
- Performance real = (Weight of ASA real)/(Mass of ASA theoretical) × 100

Performance real = (2.5128)/(5.2174) × 100 = 48.16%

Santiago *et al*. [8], in your work "Synthesis and determination of Score in Fusion of aspirin," used the same calculations to find the theoretical and actual yield, but found an income real of 71.2%. Already at the work developed by Neto [9], the yield found was 61.35%. Then, as expected, even performing the work of aspirin synthesis, the yield tends to vary in each experiment, because there are many factors what they can influence him.

The real yield of ASA synthesis was 48.16%, compared to the yield theoretical; it is observed that the value of the experimental yield was below the value expected. They exist some factors what they can to influence at the yield of that reaction. Normally, there are losses in filtration, as some residues from the mixture are found in the container when the still-wet solids are removed from the funnel, and so get stuck to the paper in filter or up until at the own funnel, reducing the final income. It may also be associated with other factors such as the materials used. During the process, at room temperature; degree of purity of the reagents; at losses during synthesis; and also to the low extent of the chemical reaction itself in synthesis, where he can to have happened an reaction incomplete, because so much the acid salicylic acid and ASA are poorly soluble in water, which limits the your reactivity.

During the experimental work, a whitish solution was obtained when salicylic acid, anhydride acetic, and acid phosphoric (catalyst) were mixed. In this synthesis, the acid phosphoric acid works as a catalyst for this esterification reaction [7]. Because it is a strong acid, it has many available protons, donating one of them to protonate the carbonyl oxygen of acetic anhydride [8], forming the carbocation (electron deficient). The acid salicylic (nucleophile, rich in electrons) react attacking the electrophile, taunting the migration of proton, and forming acetic acid. The tetrahedral intermediate receives a pair of electrons, they are donated, forming the ASA (product), and the acid acetic (by-product) [10].

Heating was used to ensure solubilization of salicylic acid along with anhydride acetic and acid phosphoric, facilitating at reactions. Already the water was added after heating to prevent acetic anhydride reaction with water at the beginning of the experiment, because if that happened, the ASA would not be formed. In this way, acetic anhydride was decomposed after the formation of aspirin, because the excess unreacted anhydride was destroyed with the addition of water, turning it in acid acetic, what was proven fur smell characteristic in vinegar. How the smell characteristic in vinegar, it is due the formation of acetic acid as a by-product of aspirin synthesis. Cooling in an ice bath to obtain ASA crystals, which are white in color. The product was washed with cold water in order to avoid its solubilization.

Organic compounds generally have a percentage of impurity when isolated from organic reactions, thus being contaminated by other compounds (same in small quantities). Aiming get a product most pure, it is important to use purification methods. In aspirin synthesis, the major impurity in the final product is likely to be salicylic acid itself, which can still be present due to an incomplete acetylation reaction, or even by hydrolysis of product to the long of process in isolation. Acetylsalicylic acid is soluble in hot water and ethanol, but poorly soluble in cold water. In this way, by difference of solubility, you can purify acid acetylsalicylic using the technique in recrystallization [11,12]. This addition of cold water is very important in purification and isolation of crystals from the liquid, as aspirin is insoluble in water cold. Purification is necessary to remove any traces of salicylic acid and anhydride acetic that not reacted.

4. CONCLUSION

The proposed work used an methodology simple and effective for the synthesis of aspirin, which is a drug used worldwide by society. Furthermore, this experiment involves fundamental concepts of chemistry that the chemists need to have knowledge and domain. It is concluded that through the acetylation reaction, the synthesis of the acid acetylsalicylic, and it was obtained a weight in aspirin in 2.5128 g. It was purified using the technique of recrystallization and it was obtained an income in 48.16%. This result demonstrates loss of product; however, it did not make the formation of the product desired by reaction of acetylation. This work made it possible to highlight the importance of knowing and respecting the stages and processes during the organic synthesis of a drug. Because, generally, the degree of actual yield is lower than expected (theoretical), in addition, the final product is not totally pure (shows degree of impurity). Therefore, the chemist must always be attentive in its activities, always seeking to minimize errors and losses, as well as how get a product purest possible.

5. INTEREST CONFLICTS

The authors declare that there are no conflicts of interest in relation to the publication of this article.

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