

A lab report of the preparation of ibuprofen —— whether it can be made at home

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Abstract. The present study investigates the process of making ibuprofen and to verify whether this process can be done at home. The 1-(4-isobutylphenyl)ethan-1-ol(97%) is used as the starting reagent which underwent carbonyl reduction, chloride substitution, and Grignard reaction. And is finally evidenced that the assumption of producing the medicine at home by oneself is not feasible since the apparatus required is not commonly presented at home, the environment needed for the reaction to take place is difficult to achieve and some of the reagents the reaction needs is strictly controlled and unable to be purchased. The study also highlights some of the mistakes and problems met during the experiment process and the corresponding solutions and improvements are given. The process of operating paper chromatography and column chromatography are shown and discussed as well. Moreover, some applications of ibuprofen which are being used today are also mentioned such as reducing fever, relieving pain and diminishing inflammation.

Keywords: Lab report, preparation of ibuprofen, applications of ibuprofen

1. Introduction

Ibuprofen is a Non-Steroidal Anti-Inflammatory Drug(NSAID) very commonly used in our daily life [1]. Its discovery was the result of research during the 1950s and 1960s to find a safer alternative to aspirin for long-term use for rheumatoid arthritis. The molecule was discovered and synthesized by a team led by Stewart Adems and John Nicholson. After screening more than 600 candidates, Adems and Nicholson file a patent for the 2-(4-isobutylphenyl) propionic acid in 1961, later to be called ibuprofen and is granted the following year and was approved as an over-the-counter drug in 1984.1 [2,3]. Moreover, in the second outbreak of COVID-19 in the end of 2022, many people bought and took medicines containing ibuprofen to alleviate the pain brought by the virus. According to some of the online rumors, some students whose major was medicine received a homework of producing ibuprofen according to a picture of mechanism. The credibility of this is controversial. So this report will look for some applications of ibuprofen which are now applying in real life, and will mainly focus on its preparing process. Ibuprofen is often took for the effect of reducing fever and relieving minor aches and pain from headaches, muscle aches, arthritis, menstrual periods, the common cold, toothaches, and backaches [4]. It will be synthesized from the starting materials isobutylbenzene and hydrochloric acid through chloride substitution and Grignard reaction as well as requiring an equipment called rotary evaporator. Then, the mistakes made during the preparing process will be took down, and the improving methods leading to a more successful process will be given and included in the text. Moreover, whether ibuprofen can be made at home will be discussed according to the experiment and an answer towards this question will be given.

2. Application

Ibuprofen is now widely used in the world. The main mechanism of action of ibuprofen is the non-selective, reversible inhibition of the cyclooxygenase enzymes COX-1 and COX-2 [5]. This is involved in the reduction of synthesis of prostaglandins, and prostaglandins have an important role in the production of pain, inflammation and fever [6]. Some common over-the-counter uses for ibuprofen are muscle sprains or strains, joint aches, pain from migraine, sore throat, and pain from

cold or cases of flu [7]. This report is going to talk about its effects in relieving pain, diminishing inflammation and reducing fever.

2.1. Relieve Minor Aches and Pain

Ibuprofen is found to have a significant effect in relieving minor pain such as headache, toothache and menstrual periods. But it is not so effective in reducing sharp pain like the pain after surgery. Although it is not so strong a painkiller as morphine or pethidine, it is not as likely to get addicted to as the other two drugs, so ibuprofen is more widely used compared to morphine and pethidine [8].

2.2. Diminish Inflammation

Ibuprofen is a kind of Non-Steroidal Anti-Inflammatory Drug(NSAID), so from its name, it can be seen that it has the effect of diminishing inflammation. It diminishes inflammation by reducing your body's ability to make prostaglandins [9]. However, according to NHS, the painkilling effect of ibuprofen begins soon after a dose is taken, but the anti-inflammatory effect can sometimes take up to 3 weeks to get the best results, so it should not be mainly used as an anti-inflammatory drug [10].

2.3. Reduce Fever

There is study shown that ibuprofen is much more effective in reducing fever compared to acetaminophen [11]. During COVID-19, a wide variety of people take it to reduce the discomfort of fever. It works by interrupting hormones that increase body temperature [12]. Ibuprofen may start working within 30 minutes. But meaningful fever relief may take up to 2 hours [13].

3. Process

3.1. Reagents and Chemicals

The chemicals involved in this experiment includes Petroleum ether(99.9%)(PE) bought from Huzhou Shuanglin Chemical Tech. Co. Ltd; Ethyl Acetate(99.5%)(EA) bought from Wuxi Yatai Chemical Tech. Co. Ltd; hydrochloric acid(12%)(HCl), concentrated hydrochloric acid(37%)(Conc. HCl) Magnesium rod(99.9%) and Silica gel($\geq 60\%$) bought from Sinoreagent Chemical Ltd. The starting reagent, 1-(4-isobutylphenyl)ethan-1-ol(97%) was purchased from Rhawn Ltd.

3.2. Equipments

The apparatus involved in this experiment includes air plump, bureaus, bureau clamp, beakers, condenser, capillary tubes, clamps, claws, pH indicator, rotary evaporator connected with vacuum pump, round bottom flasks(single neck and two necks.), racks, rubber tubes, separating funnel, stands, silica gel plates thin layer, test tubes and water bath.

3.3. The Standard Process

This is the synthesis of ibuprofen in the introductory organic laboratory [14].

Step 1: Take 0.25g of starting material and two test-tubes containing concentrated hydrochloric acid (both are half-filled and shaken for 2 minutes). When the two reagents reacted completely, the mixture will be washed twice with EA (25ml of EA for each wash) and the organic phase will be collected. In order to make EA more concentrated while prevent vaporization of hydrogen chloride, 20ml of water must be added into the collector before starting the rotary evaporator.

Step 2: Add 1g of magnesium ribbon, and add PE to 20ml. The nitrogen gas should be flushed from top to bottom in a condenser for 30s, and the water bath should reflow at 40 degree celsius for 40 minutes. The product after reflowing should be flushed by carbon dioxide for 90s, followed by sealing and left for 5 minutes. Remove the magnesium strip using tweezers, and then wash the product with PE, which should be collected in a beaker after that. Add 20ml of diluted hydrochloric acid.

Step 3: Transfer the mixture to a 100ml separation funnel and extract the organic phase. Concentrate and pass the organic phase through the column once, leaving the inorganic phase aside. If the yield is too low, then do more extraction using the inorganic phase.

3.4. The Actual Process

The actual process we operated in the lab was different from the standard process given by the teacher. Our preparation process of ibuprofen was also divided into 3 parts, but a lot of other steps relating to the common testing methods that will be used when operating a chemical experiment was added.

3.4.1 Step 1

In the first step, 0.25 grams of the starting material alpha-(4-Isobutylphenyl)ethanol was added into the Separatory funnel. Then, the concentrated hydrochloric acid was added into two test-tubes and each of the test-tubes is half filled. Next, the hydrochloric acid was also poured into the separatory funnel to be mixed with the chemical compound that was already there, and 5 minutes was waited to let them fully react with each other. After the 5 minutes, 20 milli liters of petroleum ether was added into the separatory funnel, and the funnel would be shaken for a few times, with each time opening the plunger to leave out the gas to prevent the funnel from bursting. Then, another 10 minutes was waited to let the shaken solution being completely stratified into a layer of non-polar organic compound which was dissolved in the solvent petroleum ether and a layer of a mixture containing water, inorganic salt and some polar organic compound. The upper layer was the non-polar organic part which was clear and the bottom layer was the mixture part and was in a state of cloudy white solution. After viewing the solution being layered, another two test tubes was used to collect the solution in either layer separately and the test-tube containing the organic compound was noted as S1 upper, and the other one was noted as S1 bottom. To ensure the purity of the solution being collected, the liquid in the transition part between two layers was not collected into the test-tube and would be regarded as waste solution. Then, the same process was being operated again with only the solution in the bottom layer and it will again became two layers. The purpose of this operation is to check whether there was any chemical compound in the bottom layer that could dissolve in petroleum ether. Again, the test-tubes were named as S2 upper for the one containing non-polar organic compound and S2 bottom for that containing the mixture. At the end of this step, 3 test-tubes were got and noted as S1 upper, S2 upper and S2 bottom (Figure.1)



Fig. 1 The final solution get from step 1. The left test tube contains S2 upper solution, the middle test tube contains S2 bottom solution, the right test tube contains S1 upper solution.

In this step, petroleum ether was added but ethyl acetate was not since the function for both of the solvent is to separate the organic phase from the inorganic one, so ethyl acetate dose not need to be

added again. Although ethyl acetate was more polar than petroleum ether, the dissolve of the organic compound will not be affected by the change of the solvent since enough solvent was added to wash the reagents.

3.4.2 Step 2

In the second step, firstly, the two-neck round bottom flask was used. One neck of the flask was connected to a condenser, and the nitrogen gas was flushed from top to bottom for 30 seconds in the condenser, and the other neck was connected to a balloon containing nitrogen. The purpose of doing this was to create a nitrogen environment in the beginning and expel the gas which was originally present in the apparatus. Then, the solution of both of the S1 upper and S2 upper were added into the two-neck round bottom flask, followed with a piece of magnesium being added into the solution. And then, Grignard reaction will happen. (Figure.2)

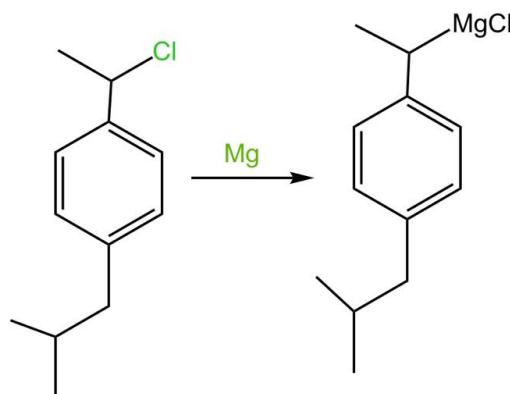


Fig. 2 The reaction happens in step 2. Making Grignard reagent. (Reaction mechanism is drawn by the writer)

To maintain the nitrogen environment, the balloon needed to be changed instantly when all the gas inside the balloon was released into the apparatus. A total of 8 balloons of nitrogen was used in this step. All the nitrogen gas was got from a pot which has the pressure of 150kpa inside, and the flask was put into a water bath reflow at 40 degree Celsius for 30 minutes. The water level inside the water bath should be a little higher than the liquid level inside the flask. After waiting for 30 minutes, the product needed to be flushed by carbon dioxide, so a balloon containing carbon dioxide was connected to the apparatus, substituting the nitrogen balloon. Then, another 5 minutes was waited with the apparatus being sealed. Next, remove the two-neck round bottom flask from the apparatus with the two necks sealed. Then, filter paper was used to remove the magnesium strip from the solution, following with 20ml of dilute hydrochloric acid being added into the solution collected in a test-tube to protonize the product.(Figure.3)

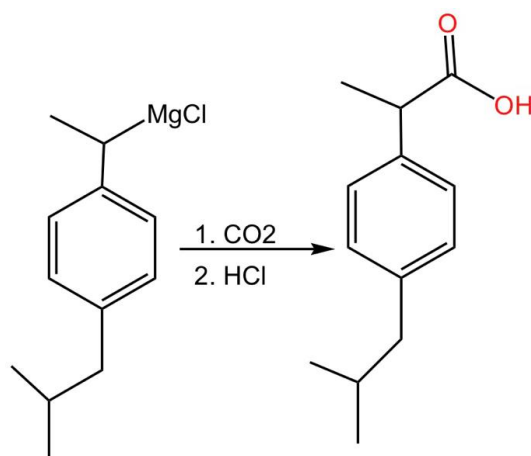


Fig. 3 The reaction happens in step 3. The Grignard reaction. (The reaction mechanism is drawn by the writer)

After adding dilute hydrochloric acid into the solution, the separation of layers would instantly being seen.(Figure.4)



Fig. 4 The final solution get in step. Two layers are clearly seen.

3.4.3 Step 3

In the third step, the solution collected in the test-tube was added into the separating funnel. Then shake the funnel and wait for 10 minutes for stratification. The bottom layer was collected for a further evaporation of the solvent to get the product ibuprofen. The collected solution was then poured into a round bottom flask and connected to the rotary evaporator (Figure.5) to begin the evaporation.

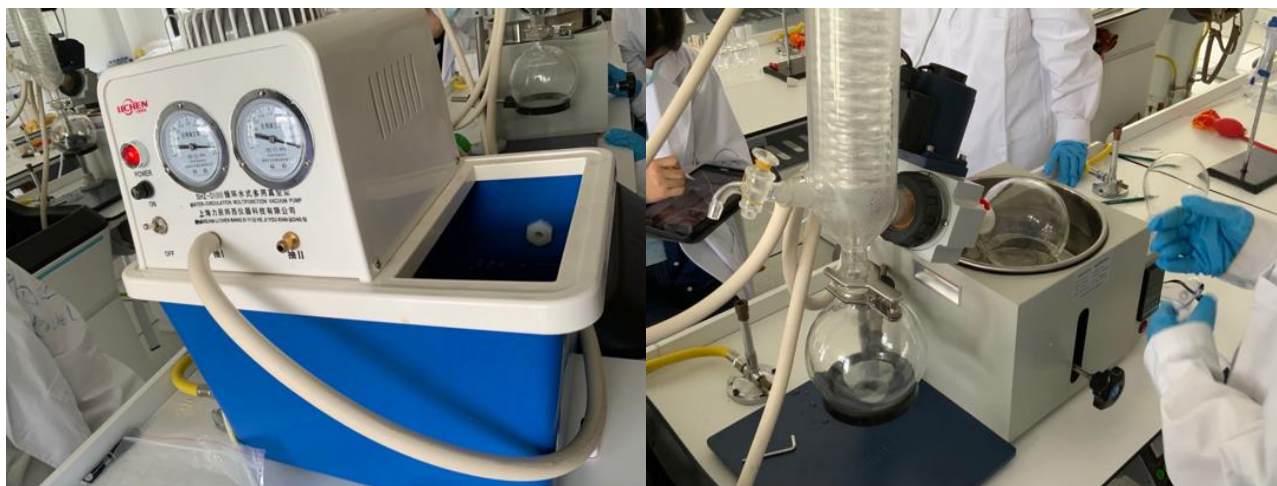


Fig. 5 The two picture adds together shows the rotary evaporator used.

The temperature of the water bath for the solution in the flask was set to be 100 centigrade because the boiling point of the solvent used was lower than 100 centigrade with actually 42 centigrade for petroleum ether and 69 centigrade for ethyl acetate while the boiling point of the solution we expected to get was higher than 100 centigrade at about 140 centigrade. So the solution we wanted to get would stay in the round bottom flask and the solvent being evaporated would go through a condenser and collected by another round bottom flask. After a 40-minute evaporation with the temperature reached 97 centigrade, the experiment was finished and product was got.(Figure.6).



Fig. 6 The final product get after a 40-minute evaporation.

3.5. Chemical Testing Method PaperChromatography and Column Chromatography

After all the separation steps were done, paper chromatography and column chromatography were applied to the experiment.

3.5.1 Paper Chromatography

Paper chromatography, in analytical chemistry, is a technique for separating dissolved chemical substances by taking advantages of their different rates of migration across sheets of paper [15].

Also, paper chromatography may be used to identify the type of the chemical compound, whether it is polar or non-polar. An original reagent was used to compare with the solutions we separated out, so there was one pure reference which is noted as R(stands for reagent) and 3 other samples which were noted as S1 upper, S2 upper and S2 bottom There were also 4 mobile phases, if arranged from non-polar to polar, they were petroleum ether, the 1:1 mixture of petroleum ether and ethyl acetate, the 1:2 mixture of petroleum ether and ethyl acetate, and ethyl acetate. The four silica gel plates thin layer were then put into the four different mobile phases and waited for 5 minutes to let the solute move with the mobile phase. (Figure.7)

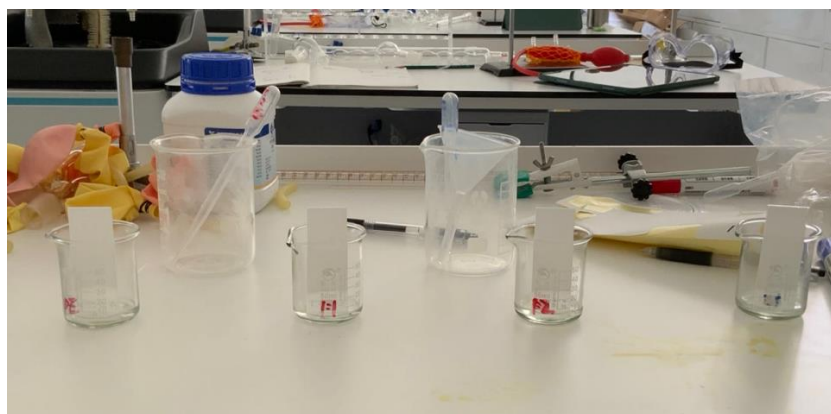


Fig. 7 The paper chromatography process. The left first beaker contains pure petroleum ether. The left middle beaker contains the 1:1 solution of petroleum ether and ethyl acetate. The right middle beaker contains the 1:2 solution of petroleum ether and ethyl acetate. The right first beaker contains pure ethyl acetate.

After the 5 minutes, the thin layer were took away from the solvent by tweezers and put under the hot wind blown out by the hairdryer to volatilize the solvent. At last, ultraviolet light was used to

look for the movement of the organic compound.(Figure. 8) The result is that the chemical compound dissolved in S2 bottom is tend to be more polar since it moved the farthest in ethyl acetate.

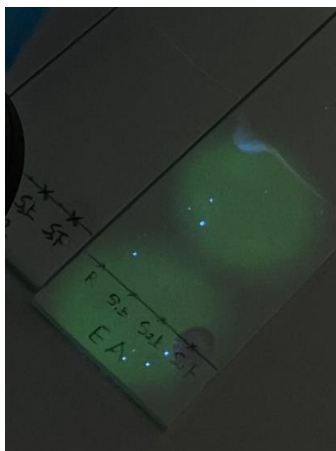


Fig. 8 The chromatography paper thin layer put in the pure ethyl acetate which a movement of the solvent can be observed clearly.

3.5.2 Column Chromatography

After paper chromatography, column chromatography was also operated to separate different solutes from each other using four different solvents. Column chromatography is a preparative technique used to purify compounds depending on their polarity or hydrophobicity [16]. The component of the solvents was the same as those used in operating paper chromatography, but the difference was that when performing the column chromatography, a silica column should be made first. Firstly, adding the silica powder into the column by spatula to near the half, then add petroleum ether to make the powder into a silica gel column. (Figure.9.)



Fig. 9 Column chromatography apparatus with a silica gel column, a pump for increasing the pressure and a test tube holding the solution dropping down.

The column must stay moistened or it may fall into pieces. After that, around 2~3 milli liter of S1 upper solution was added into the plate and to ensure the liquid level to be the same as the surface of the silica gel column, the plunger must be open to discharge the extra solution. Then, the same as the first step, add a little more silica gel powder into the plate and turn it into a column to prevent the S1 upper solution from dissolving into the solvent added later. Finally, take 20 milli liter of each of the solution and pour it into the container, use 4 different test-tubes to collect the solution that flowed out. It can be seen that the solution flowed out was clear after adding petroleum ether and 1:1 mixture of petroleum ether and ethyl acetate while the solution collected was milky after adding the other two solvents.(Figure.10)

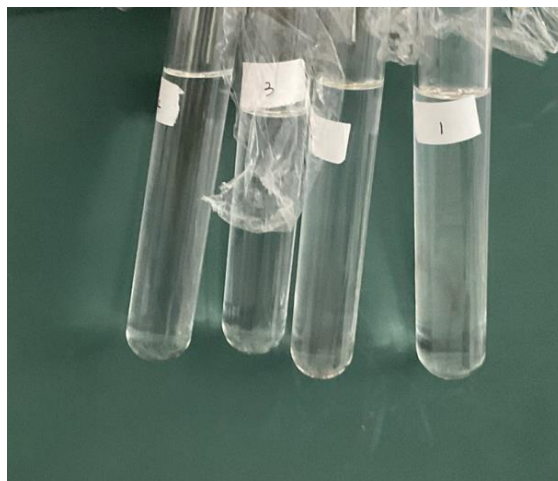


Fig. 10 The solution got after column chromatography. The 4 test tubes contain the same volume of solution and the components do not differ greatly.

4. Problems and Solutions/Improvements

Several small errors in operation or the in the reaction itself can always be found throughout the whole process.

4.1. Step 1

In the first step, the error may come from the incompletely separated solutions. This may lead to a lower yield than expected, and the solution may contain the chemicals other than we need which may interfere the rest experiment. Towards this situation, two conditions were being separated into. The first is due to the unclear boundary between the two layers. This can be improved in two methods, the first is to wait for longer time to let them separate more, and the second is to shake more violently before waiting to make the dissolution more even. However, in the second condition of not being able to collect all the solutions is unavoidable since this error may present in every part of the process.

4.2. Step 2

The main possible problem that would take place in step 2 is the impurity of the nitrogen environment. Any oxygen entering the reaction may lead to an oxidation to the chemical compound dissolved in the solvent, which may lead to a failure in the experiment since the product may be changed from what we expected to get. To avoid this problem, it is suggested to connect a rubber tube directly between the apparatus and the decompressed nitrogen gas. This can effectively reduce the problem caused by other gases.

4.3. Step 3

In this step, since it required the separating funnel, the problems happened in step 1 may also appear here like the incomplete separation of the solution. Another major problem is that the connecting points between the round bottom flask in the water bath and the rotary evaporator is a little loose. So the round bottom flask may fall into the water bath and the chemicals in the flask will be polluted. This indicate that all efforts made before are in vain. So a clamp must be needed to connect the two parts together to prevent it from falling apart.

4.4. Analytical Process

While operating the paper chromatography, several problems was discovered. First of all, the object used for marking can not be black pen since the oil in the pen is also an organic compound and may dissolve in the organic solvent. So, instead of the black pen, pencil is used for marking on the paper. This lead to the second problem that the sharp pencil may slice through the paper, preventing

the solute from moving up. Luckily, this problem can be easily avoided by just simply draw the line more gently. The third problem is that, sometimes, the chemical compound does not have fluorophores, so it can not be seen under the ultraviolet light, and thus, the compound can not be identified. To solve this problem, more equipments like the coloring reagent and infrared spectrum are required for further indicating.

In the step of column chromatography, some mistakes were also made. First, when increasing the pressure to let the liquid drop faster, the plug was blown out due to the higher pressure in the column compared to the standard atmospheric pressure. To prevent this from happening again, a rubber band can be used to fasten the plug and the column. Second, when pouring the solvent into the column, the silica gel powder may be dispersed, leading to cracks in the silica gel column. So, next time, when doing the same test, the solution should be poured slowly and gently. Our group had also made a small mistake, it is mentioned here because it may lead to serious consequences. There was a balloon connected to the plug on the column, when taking off the plug to add another solution, the balloon hung down and hit the beaker, the solution in the beaker then spilt out and spread over the table. It may be very dangerous because the liquid in the beaker is waste solution, and may be extremely harmful if is not dealt in the right way. So, when performing the experiment, be careful to notice all the components connected to the equipment to avoid possible danger.

5. Discussion

The topic is now back to the question mentioned in the introduction— whether making ibuprofen at home is reliable. After performing the whole experiment, the answer given is absolutely no.

Why not?

Despite of the law of banning making medicine at home, there are also many other factors that make this process impossible to be operated at home.

5.1. Reagents

First of all, many of the starting reagents are controlled drugs such as the p-isobutylacetophenone, sodium borohydride and diethyl ether which can not be bought easily. So from this aspect, the plan is impossible from the very beginning, the reagents choosing part.

5.2. Nitrogen environment

Also, another difficulty is that there will not be a pure nitrogen environment at home. But nitrogen environment is very important to this step since if the compound is oxidized a little bit, the whole experiment may fail to produce ibuprofen. Even there is a gas jar at home, its high pressure is also very dangerous and may lead to explosion if there is any improper operation.

5.3. Equipments

Moreover, the equipments that are required in this experiment is commonly not able to appear at home. The rotary evaporator used in the last step is normally not equipped at home. Other evaporation methods can be used but it may lead to a lot of impurities to dissolve in the solution which make the final compound to be impure. In addition, the analytical equipments like the silica gel plates thin layer, the silica gel column or even the infrared spectrum are also not equipped at home. So the product cannot be analyzed for what it is, and the final product we get may even not be ibuprofen, but a mixture of other chemical compounds which are useless for this experiment.

6. Conclusion

Ibuprofen is widely used in clinical practice and has a broad market. People have already made a lot of research progress on its various levels, but there are not many studies on the improvement of its derivatives and production process apis. In this study, ibuprofen was successfully synthesised from

the starting material 1-(4-isobutylphenyl)ethan-1-ol(97%) and hydrochloric acid through chloride substitution and Grignard reaction. The type of the product was analyzed by paper chromatography and column chromatography. During the synthesis process, some mistakes were made and improvements were found and made. After all the studies, the results indicate that it is impossible to make ibuprofen at home since the reagents are hard to get, the environment is not suitable for the reaction and some of the apparatus may not present at home. So, the hearsay online is not feasible.

References

- [1] Poutoglidou F, Saitis A, Kouvelas D. Ibuprofen and COVID-19 disease: separating the myths from facts. *Expert Rev Respir Med*. 2021 Aug;15(8):979-983. doi: 10.1080/17476348.2021.1951239. Epub 2021 Jul 8. PMID: 34196258.
- [2] Dawn Connelly. A brief history of ibuprofen. 27 July 2017. Retrieved on 30 July 2023. <https://pharmaceutical-journal.com/article/infographics/a-brief-history-of-ibuprofen>
- [3] Ibuprofen synthesis. Central college. <https://central.edu/writing-anthology/2019/04/11/ibuprofen-synthesis/>
- [4] Natural Medicines Comprehensive Database Consumer Version [Internet]. Stockton (CA): Therapeutic Research Faculty; c1995-2018. Clove; [updated 2020 Jun 4; reviewed 2020 May 21; cited 2020 Jul 1]; [about 4 p.]. Available from: <https://medlineplus.gov/druginfo/natural/251.html>
- [5] Mazaleuskaya LL, Theken KN, Gong L, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: ibuprofen pathways. *Pharmacogenet Genomics*. 2015 Feb;25(2):96-106. doi: 10.1097/FPC.000000000000113. PMID: 25502615; PMCID: PMC4355401.
- [6] Bushra R, Aslam N. An overview of clinical pharmacology of Ibuprofen. *Oman Med J*. 2010 Jul;25(3):155-1661. doi: 10.5001/omj.2010.49. PMID: 22043330; PMCID: PMC3191627.
- [7] Ngo VTH, Bajaj T. Ibuprofen. [Updated 2023 May29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK542299/>
- [8] Zhang Xiaopeng, Xv Zhi. Advances in synthesis and application of ibuprofe[J]. *Foreign medicine (antibiotic fascicle)*. 2020,41(5):404-410.
- [9] Ibuprofen. Healthdirect. Last reviewed: April 2022. Retrieved on 14 September 2023. <https://www.healthdirect.gov.au/ibuprofen>
- [10] Ibuprofen. NHS 24. Last updated: 03 March 2023. Retrieved on 15 September 2023. <https://www.nhsinform.scot/tests-and-treatments/medicines-and-medical-aids/types-of-medicine/ibuprofen>
- [11] Jamerson BD, Haryadi TH. The use of ibuprofen to treat fever in COVID-19: A possible indirect association with worse outcome? *Med Hypotheses*. 2020 Nov;144:109880. doi: 10.1016/j.mehy.2020.109880. Epub 2020 May 25. PMID: 32505846; PMCID: PMC7247463.
- [12] Ibuprofen: frequently asked questions answered. Retrieved on 15 September 2023 <https://www.yashodahospitals.com/medicine-faqs/ibuprofen/>
- [13] Arthritis Foundation. (n.d.). NSAIDs. Lawati, H. L., et al. (2016). Onset action and efficacy of ibuprofen liqigel as compared to solid tablets: A systematic review and meta-analysis. *Journal of Pharmacy and Pharmaceutical Sciences*.
- [14] Synthesis of Ibuprofen in the Introductory Organic Laboratory Richard A. Kjonaas, Peggy E. Williams, David A. Counce, and Lindsey R. Crawley. *Journal of Chemical Education* 2011 88 (6), 825-828. DOI: 10.1021/ed100892p
- [15] Britannica, The Editors of Encyclopaedia. "paper chromatography". *Encyclopedia Britannica*, 9 Aug. 2023, <https://www.britannica.com/science/paper-chromatography>. Accessed 12 August 2023.
- [16] Column chromatography theory. University of Toronto. <https://www.utoronto.ca/webapps/chemistryonline/production/column.php>