Evaluation and Improvement of Synthesis Method for Ibuprofen

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Abstract. Ibuprofen as an alternative to aspirin has notable values on medical fields including antipyretic, anti-inflammatory and analgesic. Firstly, this article evaluates the existing methods of ibuprofen synthesis and analyzes their relative pros and cons. Based on this analysis, this paper then proposes an improved method based on the research of Snead and Jamison (2015). Compared with the previous methods, the proposed method is considered to have higher yield, safer production environment, and more obtainable raw materials.

1. Introduction of Ibuprofen
Considered as a substitute of aspirin, ibuprofen has stronger efficacies on antipyretic, anti-inflammatory and analgesic and shows fewer side effects at the same time (Huskisson et al. 1971; Busson 1986). Therefore, the production of ibuprofen has been developing promptly since it came into market in the late 1970s. Ibuprofen has been applied worldwide and becomes one of the best-selling OTCs. Currently, this medicine is considered as one of the three most important analgesics-antipyretics, together with aspirin and acetaminophen. During the past few years, its sales are increasing in 2-4% per year in Europe and the United States and 10% in South Asia. In the 21\textsuperscript{st} century, the production rate of ibuprofen becomes over ten thousand tons every year worldwide. The medicinal mechanism of ibuprofen is to lower the uterus interior pressure and reduce uterine contraction by restraining the activity of cyclooxygenase and decreasing the production of prostaglandin; ibuprofen is able to restrain the tissue prototype (physiological) epoxidase in the stomach and kidney.

In 1964, Nicholson et al. in Britain first synthesized ibuprofen. Other countries gradually began to study ibuprofen. Laterly, Butts Pharmaceutical Factory in Britain obtained patent and put it into production. In the initial production process, due to the backward production technology, ibuprofen production costs were high, production rate was low, and the scale of enterprises was greatly limited. Until the late 1980s, with the emergence of new processes of ibuprofen such as carboxylation and 1,2-translocation, the production cost of ibuprofen was greatly reduced, and the scale of enterprises was also growing. At present, German BASF, American Albemarle and Ethyl have a large scale of production. They have their own core technology and choose the appropriate process, which leads to economic benefits and scale advantages. In recent 10 years, due to government support, the pharmaceutical industry in India has developed rapidly. Indian companies such as Sumitra and Cheminor also have the same production scale as the large Western companies mentioned above. Because of the low labor prices in India, the production costs are lower and the low price of ibuprofen in India has greatly impacted the global market of ibuprofen (Anderson 1990).

Ibuprofen, a pharmaceutical crystalline product, the quality of the product plays an important role in whether it can occupy a favorable position in the international market competition. At present, there is a gap in quality between domestic ibuprofen and similar products abroad, such as poor crystal shape and uneven particle size. The backward crystallization technology and equipment used by domestic
production enterprises lead to poor product quality and high production costs, making it difficult for domestic ibuprofen products to compete with foreign products. This also leads to the dominant position of domestic market and domestic and foreign ibuprofen products, such as Sino-US Scoop's ibuprofen. Currently, Finnish preparations account for 70% of China's market share. To change this situation, it is necessary to improve the crystallization and equipment to produce high quality ibuprofen crystals.

2. Evaluation of Ibuprofen Synthesis Methods

Ibuprofen was first developed by the research group led by Nicholson in England, 1964. English pharmaceutical factory, Boots, gained the patent and took the lead in producing ibuprofen in industrial. Recently, large amounts of research are done on the synthesis of ibuprofen in many countries. Many useful routes are found out and evaluations are done on them. The dominating methods nowadays are discussed below.

2.1. Translocation Rearrangement

Aryl-1, 2- translocation rearrangement is commonly used by the factories in China now. This method applies isobutyl benzene as the raw material. Isobutyl benzene reacts with 2-chloropropionyl chloride in Friedel-crafts acylation patterns. Next, the product after the previous step catalytically ketonize with neopentyl glycol. Rearrange the product with catalyst and hydrolyze in order to gain ibuprofen at last. The reaction equations are listed below:

The advantages of this craft are: (1) avoid the side products caused by acylation with aromatic impurities if petroleum ether is used as solvent, (2) avoid the poison and solvent residue in reactors if dichloroethane is used as solvent, (3) lower the requirements of chilling brine, (4) lower the energy cost and equipment corrosion and so on.

2.2. Alcohol Carbonylation

Alcohol carbonylation is also called as BHC method. This method uses isobutyl benzene as well. The raw material experiences acylation with acetyl chloride, catalytic hydrogenation, and carbonylation so as to produce ibuprofen. This is the most advanced route applied in China now and applied by factories all over the world.
The central metal atoms of the catalyst adopted in carbonylation are palladium or platinum. Although this craft is advanced in many ways, improvements should be done on the separation and recycle of palladium, which is a precious metal. Meanwhile, it is also important to find a cheaper and more convenient substitute.

2.3. Olefin Carbonylation
Aryl substituted olefin reacts with carbon monoxide and alcohol or water catalyzed by palladium in acidic environment to produce aromatic alkyl carboxylic acid or carboxylate ester (Michael et al. 1997). The catalytic activity of palladium can be strengthened by the combination of some ligands. For example, under the same circumstances, 1:1 n (Ph P): n (Ph PO) combined with palladium chloride has rapid reaction rate and the highest conversion with very few isomers. The reactions are shown below:

2.4. Halogenated Hydrocarbons Carbonylation
Raw material of halogenated hydrocarbons carbonylation is 1-P-isobutyl phenyl-1-chloroethane. The cycloethane experiences catalytic carbonylation with CO in basic environment to generate ibuprofen and the reactions are listed below:

The catalysts of the reaction are often the compounds of palladium and the solvents are alcohols. Since the products are created under basic environment, acidification is needed to transform the salt to ibuprofen. In addition, halogenated hydrocarbon will produce side products with two carbonyl groups and thus, the conditions like temperature and pressure need to be controlled strictly.

2.5. Olefin Hydrogenation Law
Catalyzed by Ruthenium complex with chiral ligands, 2-(6-methoxyl-2-napthyl) propenoic acid is hydrogenated to Naproxen, with 96% enantiomeric excess. The reactions are listed below:
The raw material of catalytic hydrogenation can also be 2-(4-isobutyl phenyl) propenoic acid. Conditions including the composition and recycle of the catalysts, pressure, solvent and temperature will affect the optical purity of product (Kevin et al. 2006).

When it comes to the reaction between isobutyl benzene and pyruvic esters catalyzed by Lewis acids, the catalysts used, input of raw materials, solvents and reaction temperature also affects significantly. For example, some of the reactions need to occur under -30 degrees Celsius.

2.6. Rearrangement of Propylene Oxide Method
In the process of rearrangement of propylene oxide, isobutyl acetophenone is produced with Darzens Condensation method. Then, the ketone reacts with sulfur ylide to get 2-(isobutyl phenyl)-1,2-epoxypropane. The product from the previous step can be rearranged to 2-(isobutyl phenyl) propanal. The reactions are below:
To transform from 2-(isobutyl phenyl) propanal to ibuprofen, tetrabutyl ammonium bromide and 30% hydrogen peroxide are used as catalysts and the yield is nearly 90%.
3. Improved Ibuprofen Synthesis Method

Based on the ideas provided in Snead and Jamison’s article (2015), this paper has proposed a new ibuprofen synthesis method and its flow diagram is shown below:

3.1. Flow Diagram

The explanations of the equations and chemical products are listed below:

Table 1 Equation Meanings

| No | Materials       | No   | Materials                              |
|----|-----------------|------|----------------------------------------|
| (1 ) | Pc ibb a        | (17 ) | four five TMOF DMF Icl NP AC           |
| (2 ) | Pc ibb a ci four| (18 ) | four five                              |
| (3 ) | hcl w           | (19 ) | four five Icl DMF TMOF AC NP           |
| (4 ) | a Pc ibb hcl w four | (20 ) | TMOF DMF Icl NP four five AC          |
| (5 ) | a four w hcl    | (21 ) | four five                              |
| (6 ) | a four w hcl    | (22 ) | five                                   |
| (7 ) | a               | (23 ) | MeoH Mer w NaoH                       |
| (8 ) | ibb Pc four     | (24 ) | five six NaoH Mer w MeoH               |
| (9 ) | pcq four ibb    | (25 ) | H                                     |
| (10) | four            | (26 ) | H five six NaoH Mer w MeoH             |
3.2. Process of the New Method

Based on the analysis above, the improved method includes three main reactions (John et al. 2017). The first reaction involves isobutyl benzene and propionyl chloride. The two substances are combined to produce the aryl ketone, product 4. This reaction is designed based mainly on the ideas given by Snead and Jamison (2015). However, the input amounts of raw materials are increased so as to provide with higher yield. One reactor, one mixer and three separators are involved here. Below are the detailed procedures:

First, the two reactants together with catalyst, AlCl3, are imported as stream 1 into the reactor 1 on a scale of 1:1:1. The temperature and pressure in the reactor are set to be 90 degrees Celsius and about 17 atm. Propionyl chloride can work as the solvent of AlCl3 as well. It is necessary to recycle aluminum chloride since its price is relatively high. The ratio  of 1:1:1 of input materials lead to a 95% yield, according to Snead and Jamison (2015).

Next, the stream 2 leaving reactor 1 contains the product four an d the left reactants. Mixer 1 is used to mix stream 2 thoroughly with hydrochloride solution with concentration of 1 mole per liter and flowrate of 50 kilogram-moles per hour. Layers will separate since water can hardly dissolve nonpolar organic matters. The side products with aluminum enter the inorganic layer so as to be removed in the separator. 90% of impurities are eliminated in this separation step. Some of the solid aluminum chloride can be recycled by filters to reactor 1.

Finally, other impurities are removed by a distilling separator. Since product 4 has a boiling point of 286 degrees Celsius while those of the two reactants are 170 and 77 degrees, separately, about 99% isobutyl benzene and propionyl chloride is going to be removed. The nearly pure aryl ketone will enter the next reacting device and the steam with impurities is collected. Whether the impurities should be recycled needs more tests.

The second reaction is that the product 4 reacts with trimethyl orthoformate (dissolved in dimethyl formamide, or DMF for short) to produce one methyl ester, product 5 catalyzed by iodine chloride (dissolved in propanol). Trimethyl orthoformate is also called as TMOF for short. To avoid solid iodine chloride from blocking the tubes, acetone is added and mixed thoroughly with the mixer 2. The stream 14 flowing outside reactor 2 contains acetone, product 5 and the remaining reactants.
Both product 4 and 5 have comparatively high boiling points. Thus a cooler is used to control the temperature at 35 degrees Celsius and a drum filter is used to separate the two materials from the others. 99% of the two products will be separated in solids.

Then, keep cooling the rest liquids. When the temperature of the liquid approaches 20 degrees Celsius, 99% of iodine chloride dissolved is separated from the organic solvent since the solubility decreases significantly. The solids are going to be separated out by filtration and recycle to the reactor 2. Because propanol shares similar boiling point, 100 degrees, with TMOF, they can also be obtained by distillation. Acetone, with a boiling point of 56 degrees, will be separated out first and recycled to the mixer.

When the distillation temperature approaches 100 degrees, about 90% of propanol and TMOF will be recycled to the reactor 2. Also, since the boiling point of product 5 is higher than that of product 4, after distillation, 99% of product 5 will enter reactor 3. Meanwhile, as acetone is benign to the reaction, it can also be recycled to the reactor 2. 

The third reaction is the reaction to synthesize ibuprofen. This step involves two chemical reactions and four separations. The product 5 will react with sodium hydroxide to synthesize sodium ibuprofen in reactor 3 and ibuprofen is reduced from sodium ibuprofen by hydrochloric acid in reactor 4. In order to separate sodium ibuprofen from the stream 24, before adding acid, liquid hexane is added and mixed. The sodium ibuprofen and others with high water solubility remain in the water layer and product 5 is drawn to the hexane layer. To separate the hexane layer from the water layer, a decanter centrifuge is applied. This centrifuge works under 60 degrees and 1 atm. After separation, sodium ibuprofen solution is obtained and 95% of sodium ibuprofen is in this solution. After hydrochloric acid is added, ibuprofen is produces and it has a worse water solubility than its sodium salt. Ibuprofen then leaves the water layer and can easily be separated out by 99%. To keep the reactions running fluently, it is important to keep the ratio between molar flowrates of sodium hydroxide and product 5 1:3, that of hexane and water 8:1 and that of hydrochloric acid and sodium ibuprofen 1:4.

To make the process more effectively, 2-mercapto ethanol, methanol, sodium hydroxide and water are added to reactor 3 as well. Methanol works as a catalyst here while 2-mercaptoethanol is utilized to clear the clogs in the pipes. The reaction temperature and pressure for the reaction between sodium hydroxide and product 5 is 90 degrees Celsius and 13.6 atm. The yield of sodium ibuprofen is estimated to be 83%.

In reactor 4, two reactions are happening under the ratio 4:1 at the same time. The dominating one is that hydrochloric acid reacts with sodium ibuprofen to produce ibuprofen and sodium chloride. The other one is the neutralization reaction between the acid and the excess base. The former reaction has a yield of 95% while the latter one is complete. Only ibuprofen will be obtained and the solutions of other materials are likely to be dumped.

4. Implications and discussions

Ibuprofen is considered as a key medicine by WHO and produced under a rate of more than 20000 tons per year. Despite the high production rate, the demands have still been not fully met yet. The target production rate of the method provided in the passage is 200 tons per year. Based on the designing, the devices should produce 45.65 kilograms per hour. The ibuprofen produced per hour is worth 2737 dollars (if a kilo is worth 60 dollars) and a profit of about 700 dollars is made per hour. After taking the energy cost into consideration, the profit is still 300 dollars. Most of the separators used work under a pressure of 1 atm and then cost less energy. The routes with a production of 200 tons per year are limited in the world now.

Meanwhile, compared with other methods, the method in this passage is also convenient and safe. Most of the raw materials listed are cheap and available. The usage of expensive materials, like 2-mercaptoethanol, is also limited based on the design. Also, the working conditions of the devices are not harsh, which lowers the requirements for costly devices and the danger of manufacture at the same time. The hazards involved are actually not difficult to deal with. The 2-mercaptoethanol needs to be
recollect from the waste streams before discharging and the acids will be neutralized by weak base like sodium bicarbonate.

5. Conclusions
Firstly, the synthetic methods of ibuprofen were reviewed, and their advantages, disadvantages and applicable conditions were analyzed. On this basis, an improved method for ibuprofen synthesis is proposed. Improvements have been made in terms of economic efficiency and safety. The results showed that the production of ibuprofen increased in terms of economic efficiency and safety. In the future design, the following synthetic processes can be further improved. First, the hexane solution of methyl ester III and a small amount of ibuprofen sodium are currently removed as waste. However, the cost of recovering and reusing hexane can still reduce the cost of the reaction. Similarly, the aqueous solution of other substances separated by Bloven cannot be directly discharged into the outside world. Some substances such as 2-mercaptoethanol, hydrochloric acid and so on have a lot of damage to the environment. Therefore, it is necessary to consider the recovery of 2-mercaptoethanol and the neutralization of hydrochloric acid before discharging.

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