Project on Green Chemistry

Process chosen: Production of Ibuprofen

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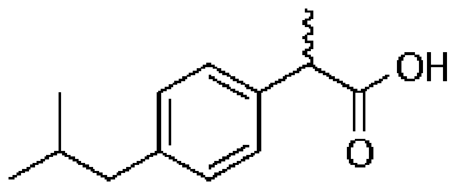
Introduction

Ibuprofen is an anti-inflammatory drug (NSAID) used for relief of symptoms of arthritis, fever, as a pain reliever. It can also act as a vasodilator. It has the following structure:



After the patent of production of ibuprofen ran out, a company successfully used 'green' synthesis, which is presently adopted, to replace the Boot's synthesis, as Boot's synthesis involves processes which can pollute the environment.

What is green chemistry?

It is a design of chemical products and processes that reduce or eliminate the production and use of hazardous substances and reduce energy consumption so that it is cleaner and safer.

What are the benefits of green chemistry?

Green chemistry holds the promise of reducing health and environmental damage. In the past we have focused on cleaning up toxic messes, is a movement to design chemicals that are safer for the environment and human.

The principles of Green Chemistry:

1. It would be better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to increase efficiency and reduce pollutants.

5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible
6. Energy should be minimized. That is the temperature and pressure should be lowered.
7. Renewable resources should be used wherever technically and economically practicable.
8. Reduce derivatives - Unnecessary derivatives should be avoided.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Byproducts should not persist in the environment and break down into innocuous degradation products.
11. We should monitor and control prior to the formation of hazardous substances.
12. Chemical process should be chosen to minimize potential for chemical accidents like fires and explosions.

Prevention

The previous Boot's synthesis is as follow:

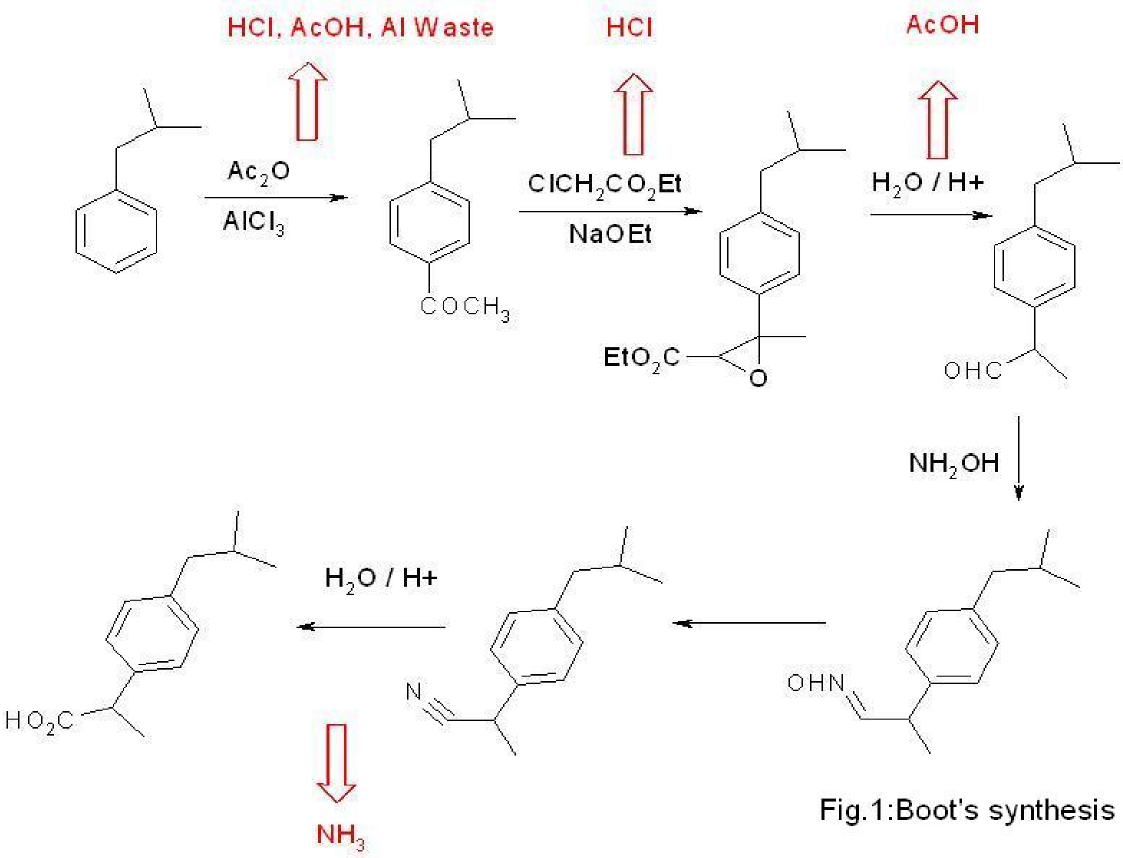


Fig.1:Boot's synthesis

Since the above synthesis gives out lots of unwanted products such as HCl, AcOH, NH_3 and Al waste. According to the principle of green chemistry, it is better to design processes that produce less waste than to produce waste and clean it up. Therefore, 'green' synthesis is developed.

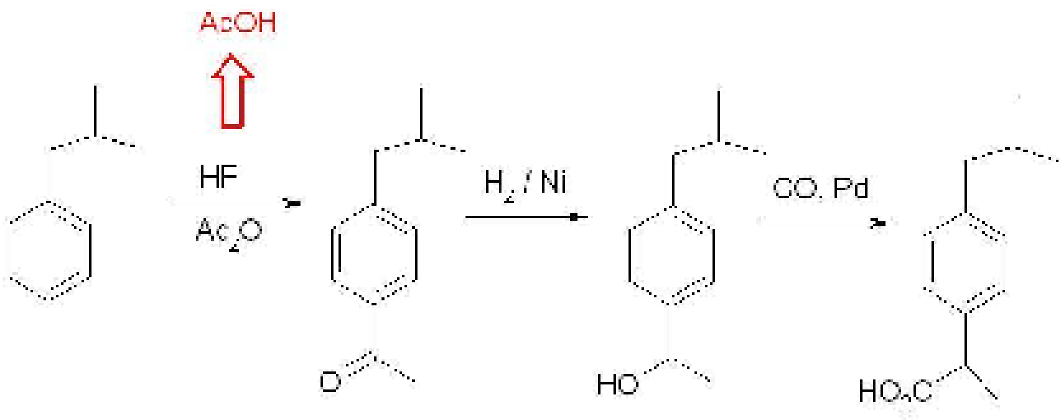


Fig. 2: Green synthesis

After the improvement, only AcOH is produced as the waste. No more HCl, NH_3 and Al waste are produced anymore. Therefore, we can save the process for finding ways to dispose these unwanted products.

<u>Atom economy and Reducing derivatives</u>

To calculate atom economy, the following formula is used:

$$\frac{Molecular\,Weight\,of\,desired\,product}{Molecular\,Weight\,of\,all\,reactants} \times 100$$

In the previous synthetic method, the calculated percentage atom economy is only 40%. The reason for such a low atom economy is due to the production of lots of unwanted materials, such as C_2H_5ONa and $C_3H_6ClO_2$. The tables below show the formula mass of substances produced during the manufacture of Ibuprofen:

Reagent formula	Formula mass
$C_{10}H_{14}$	134
$C_4H_6O_3$	102
$C_4H_7ClO_2$	122.5
C_2H_5ONa	68
H_3O	19

NH_3O	33
H_4O_2	36

Table 1:Reagent used in manufacturing Ibuprofen (Boot's synthesis)

Utilized in Ibuprofen	Formula mass
$C_{10}H_{13}$	133
C_2H_3	27
CH	13
HO_2	33

Table 2:Products utilized in Ibuprofen (Boot’s synthesis)

Unutilized in Ibuprofen	Formula mass
H	1
$C_2H_3O_3$	75
$C_3H_6ClO_2$	109.5
C_2H_5ONa	68
H_3O	19
NH_3O	33
H_3	3

Table 3:Products unutilized in Ibuprofen

(Boot’s synthesis)

Total formula mass in manufacturing Ibuprofen = 514.5
Total formula mass of products utilized in Ibuprofen = 206
Total formula mass of products unutilized in Ibuprofen = 308.5

Therefore, the atom economy in the Boot’s synthesis of Ibuprofen $= {}^{206}/_{514.5}$ = 40% which means that about 60% of reagent atoms are converted into unwanted byproducts, which is a waste of chemicals. Every year, 30 million lb of Ibuprofen are produced. It is estimated that there are 35 million lb of waste generated due to the old synthetic route!

However, with the green synthesis, the atom economy can be increased much up to 77%, as less waste products are produced. The tables below show the formula mass of products in producing Ibuprofen:

Reagent formula	Formula mass
$C_{10}H_{14}$	134
$C_4H_6O_3$	102
CO	28
H_2	2

Table 4: Reagent used in manufacturing Ibuprofen

(Green synthesis)

Utilized in Ibuprofen	Formula mass
$C_{10}H_{13}$	133
C_2H_3O	43
H_2	2
CO	28

Table 5: Products utilized in Ibuprofen

(Green synthesis)

Unutilized in Ibuprofen	Formula mass
H	1
$C_2H_3O_2$	59

Table 6: Products unutilized in Ibuprofen (Green synthesis)

Total formula mass in manufacturing Ibuprofen = 266
Total formula mass of products utilized in Ibuprofen = 206
Total formula mass of products unutilized in Ibuprofen = 60

Percentage atom economy = $^{206}/_{266}$ = 77%

Percentage difference between the two methods = 77-40 = 37%

The three-step green synthesis allows more efficient and environmentally friendly method to produce Ibuprofen. Besides, less unwanted materials are produced which can reduce the use of chemicals. Previously, products of formula mass 308.5 are wasted. However, due to the advent of green synthesis, only products of formula mass 60 are wasted. Those derivates which are unnecessary are eliminated. This helps achieving the objectives of green chemistry.

Less hazardous synthesis and Designing safer chemicals

According to this principle, chemical products should be designed to be fully effective. Yet, it must have little or no toxicity.

In the Boot's synthesis, chemical products include our main product: Ibuprofen and four unwanted by-product: hydrochloric acid, ammonia, acetic acid and aluminium wastes. Certainly, for Ibuprofen, as a kind of medical drug, it has passed many safety test such as pre-clinical testing and human trial to ensure that it is safe to be used. First of all, both acids are corrosive. They can cause skin burn, eye damage and irritation to different parts of our bodies. Besides, when hydrochloric acid is mixed with oxidizing chemicals, a toxic gas chlorine is produced. As for ammonia, its toxicity does not usually cause problems for human. But it is toxic for fish and amphibians. Therefore, the production of these substances should be avoided. Moreover, the production of so many wastes mean that chemical products are not so fully effective.

Therefore, in the later green synthesis, this problem has been improved. No more corrosive hydrochloric acid, toxic ammonia, as well as aluminium waste are produced. The final chemical products only include Ibuprofen and acetic acid. It becomes a lot greener. In addition, the reduction of by-product means that the whole process of synthesis has become more effective. Nearly all the chemical product produced in step 2 and step 3 are fully effective in forming the final product: Ibuprofen. Chemists successfully designed safer chemicals for the synthesis of Ibuprofen.

Energy efficiency

In the Boot's synthesis, six steps of reactions are involved. As most of the reactions require heating, much energy is used. However, for green synthesis, only three steps of reactions are needed. This reduces the energy required for the synthesis of Ibuprofen, as a faster way can be adopted with fewer steps and less energy needed. The capital expenditure on electricity and resources can be saved. The environment can also be protected by giving out less pollutants.

Furthermore, as hydrogen fluoride, Raney nickel and palladium are used repeatedly as catalysts throughout the production, the energy spent on producing the catalyst can also be reduced. The previous synthesis requires the use of aluminium trichloride, which cannot be converted back after reaction, as aluminium trichloride hydrate is produced.

Use of renewable resources:

Hydrogen fluoride,raney nickel and the Cs of the green synthesis are catalysts that can be recovered and reused repeatedly.

1.Hydrofluoric acid is produced by treatment of the mineral fluorite (CaF_2) with concentrated sulfuric acid. When combined at 265 °C, these two substances react to produce hydrogen fluoride and calcium sulfate according to the following chemical equation:

$$CaF_2 + H_2SO_4 \rightarrow 2\ HF + CaSO_4$$

It serves as a catalyst in alkylation processes in oil refineries.

2. Raney nickel is a solid catalyst of a nickel-aluminium alloy. The porous structure of the catalyst arises from the selective removal of aluminium from alloy particles using concentrated sodium hydroxide solution by the following

chemical equation:

$$2\ Al + 2\ NaOH + 6\ H_2O \rightarrow 2\ Na[Al(OH)_4] + 3\ H_2$$

3. Palladium is a silvery-white metal. It is commonly used in catalytic converters. Palladium is also used in electronics, dentistry, medicine, hydrogen purification, chemical applications and groundwater treatment.It can be recycled from scrapped catalytic converters.

Catalysis and Safer auxiliary substances

In Boot's synthesis, we have to make use of some catalysts or auxiliary substances such as aluminium trichloride, hydroxylamine, 2-chlorobutyl ester ($ClCH_2CO_2Et$) and sodium ethoxide (NaOEt). They are not safe enough.

A. **Hydroxylamine**
   It is a chemical which may explode on heating. In history, there were at least two factories dealing in hydroxylamine had been destroyed with loss of life. It is also an irritant to respiratory tract, skin, eyes and other mucous mutagen.
B. **Sodium ethoxide**
   It is a strong base which reacts with water to give ethanol, which is flammable and sodium hydroxide, which is corrosive. When mixing with other electrophillic substances, it oxidizes quite easily to form a harmful substance.
C. **Aluminium trichloride**
   It reacts vigorously with water and base. Irritation can be caused to the eyes, skin and respiratory system if it is inhaled or in contact.

Because of this, in the improved green synthesis, the use of these catalysts and auxiliary substances are abandoned. Instead, some greener substances such as hydrogen fluoride, Raney nickel and the palladium catalysts are used.

In the previous synthesis, Friedel-Crafts acetylation of isobutylbenzene using aluminium trichloride as the catalyst is the first step. However, aluminium trichloride is in fact not a true catalyst. In that process, it is only hydrated into a substance that has to be disposed. It will actually become a waste by-product which has to be landfilled. In the contrary, hydrogen fluoride in the green synthesis is a true catalyst which can be recovered and reused with over

99.9% efficiency and generates no waste. Apart from this, it is also used as the solvent.

In step 2 and step 3, other catalysts such as Raney nickel and palladium catalysts are also used. They can also be recycled and reused. They are used in the step of hydrogenation and carbonylation without the production of any waste.

Design for degradation

It has been reported that Ibuprofen is a photosensitising agent. It has a half life between 1.9 and 2.2 hours. But this only rarely occurs with ibuprofen and it is considered to be a very weak photosensitising agent. This is because the ibuprofen molecule contains only one single phenyl moiety. Also, there is no bond conjugation in it, resulting in a very weak chromophore system and a very weak absorption spectrum, which does not reach into the solar spectrum. Therefore, there is a photolytic degradation of ibuprofen.