

# Optimization and Process Intensification of Ketal Reaction in Industrial Ibuprofen Synthesis

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Ketal reaction is one of the most important reactions in the synthetic of ibuprofen. The reaction mechanism was analyzed to increase the rate and conversion. Mechanical stir, forced external circulation and combination of the above two ways were compared to achieve the best mixing effect and the results show that the combined strategy performs better in mass transfer. Water as the product was removed to improve the efficiency of the reaction by introducing a process coupled reactive distillation and azeotropic distillation. The best conversion rate can be obtained when the boiling-range of petroleum ether is 90 - 120 °C and the feed ratio of petroleum ether and chlorinone is 2:1. After the improvement of the equipment and optimization of operating parameters, the reactive time of the ketal reaction is reduced from more than 22 h to less than 8 h. The improved ketal technology has been industrialized and demonstrated good economic efficiency for two enterprises.

## 1. Introduction

Ibuprofen, also known as 2-(4-isobutylphenyl) propionic acid, which is a traditional nonsteroidal anti-inflammatory drug belongs to arylpropionic acid family. In 1986, Laska et al. (1986) studied the basic pharmacokinetic properties of ibuprofen and they concluded that the proposition increased ibuprofen serum levels lead to increased analgesia. Ibuprofen is widely employed for its analgesic, anti-inflammatory and antipyretic properties. Ibuprofen is available under prescription, primarily for the treatment of inflammatory and painful disorders (Manrique-moreno et al., 2016) including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute gouty arthritis and soft tissue injuries and so on.

In 1964, ibuprofen had been successfully synthesized by Adams et al. (1969). Then various methods of ibuprofen synthesis were developed and put into industrial production. For example, Abbas et al. (2014) concluded that Ibuprofen could be synthesized by using Friedel-Crafts type alkylation of isobutylbenzene with ethyl lactate instead of reaction with lactic acid itself. Gharib et al. (2014) have reported a new catalytic method for the synthesis of ibuprofen using Silica-Supported Preyssler Nanoparticles as catalyst. Kjonaas et al. (2011) reported a method for the synthesis of ibuprofen in introductory organic chemistry laboratory.

The catalytic carbonylation method and ary-1,2-translocation rearrangement (Jiang, 2013) are widely used methods for the synthesis of ibuprofen. The catalytic carbonylation method was cooperatively developed by American company Hoechst-Celanese and British company Boots, which used the isobutyl benzene and acetic anhydride as reactants to generate butyl styrene acrylic aldehyde, then ibuprofen can be synthesized by subsequent hydrogenation and carbonylation. The method of ary-1,2-translocation rearrangement started with the Friedel-Crafts acyl reaction between isobutyl benzene and 2-chloropropionyl chloride, then ketal reaction took place between 2-chloro-1-(4-isobutylphenyl) propan-1-one and neopentyl glycol to protect carbonyl structure in 2-chloro-1-(4-isobutylphenyl) propan-1-one, and the ibuprofen can be obtained after two steps of rearrangement reaction and one step hydrolysis reaction. The detailed synthetic route is shown as following:

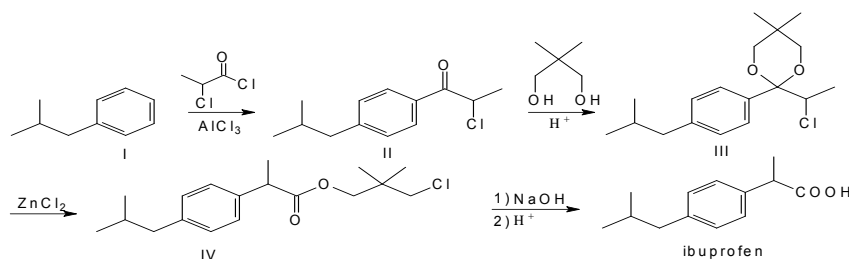


Figure 1: The technology roadmap of ary-1, 2-translocation rearrangement

The goal in catalytic chemistry is to achieve the idea synthesis in terms of catalytic activity, selectivity, atom-efficiency and step-efficiency (Shimizu, 2014). Compared with ary-1, 2-translocation rearrangement, catalytic carbonylation method has the advantages of simple process and high atomic utilization. However, there are still some problems such as high cost of the catalyst and strict operation condition in the method, which make it difficult to promote the application. Most of the pharmaceutical enterprises in India and China apply ary-1,2-translocation rearrangement to produce ibuprofen. The ary-1,2-translocation rearrangement is recognized as an economic and environmental approach because of its lower cost of catalyst and less waste emission.

The process of ary-1, 2-translocation rearrangement involves four chemical reactions (Wang, 2014): Friedel-Crafts acyl reaction, ketal reaction, catalytic rearrangement reaction and hydrolysis reaction, and the ketal reaction is the key step. Ketal reaction is a heterogeneous reversible catalytic reaction that the conversion and rate of the reaction have serious impact on the production efficiency and yield of ibuprofen.

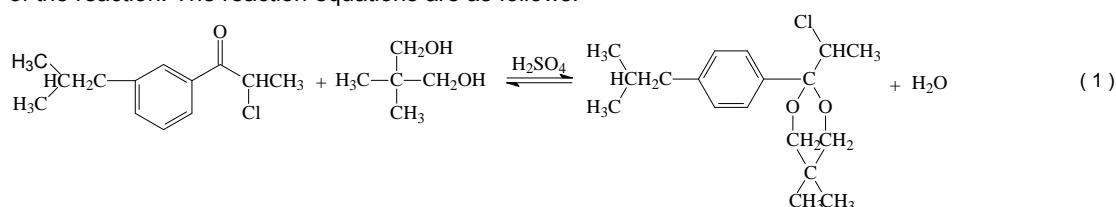
Ketones can react with two molecules of alcohol and produce one molecule of water and ketal is synthesized in the process under acidic conditions. The reaction is reversible, which means that the ketal is produced under acid catalysis, but it can also be catalyzed to the original carbonyl group. Therefore, it is necessary to remove water from the system to promote the reaction move forward. Reactive distillation (Holtbruegge et al., 2013) is an effective way which can combine the reaction and separation to increase the conversion.

In this paper, the reaction mechanism of ketal reaction was analyzed to increase the rate and conversion. Different liquid mixing methods were studied to enhance the mass transfer effect. Water as the product was removed to improve the efficiency of the reaction by introducing a process coupled reactive distillation and azeotropic distillation. Experiments were investigated to select the amount of water carrier and determine the removal rate of free water.

The existing ketal process has long reaction time and high energy consumption, which seriously restricts the synthesis efficient of ibuprofen. In this paper, the reaction mechanism of ketal reaction was analyzed to increase the rate and conversion. Different liquid mixing methods were studied to enhance the mass transfer effect. Water as the product was removed to improve the efficiency of the reaction by introducing a process coupling reactive distillation and azeotropic distillation. Experiments were investigated to select the amount of water carrier and determine the removal rate of free water. After the improvement of the equipment and optimization of operating parameters, the reactive time of the ketal reaction is reduced from 22 h to less than 8 h and the energy cost reduced by 60 %.

## 2. Analysis and solution

The ketal reaction involved in the synthesis of ibuprofen is based on neopentyl glycol and the Friedel-Crafts acyl reaction product 2-chloro-1-(4-isobutylphenyl) propan-1-one (chlorine ketone) as the raw material and sulfuric acid as catalyst to realize the transformation of the carbonyl group, and petroleum ether is the solvent of the reaction. The reaction equations are as follows:



Sulfuric acid as the catalyst of the ketal reaction tends to sink to the bottom of reaction solution due to a large density. It will weaken the condensation reaction between the chlorine ketone and neopentyl glycol in the upper layer of the reaction solution. In addition, the ketal product is astaticism in the acidic environment and

the reversible hydrolysis will occur. The occurrence of reverse reactions has serious effects on the conversion and the time of reaching balance.

The key to solve these problems lies in two points. The mixture of the catalyst and reactant needs to be strengthened to increase the rate of the reaction and water as the byproduct must be spun off from the system to suppress the occurrence of reverse reactions. To remove water, the separation rate and the amount of free water carrier need to be taken into consideration.

### 3. Experiment

#### 3.1 Chemicals

The chemical purities of neopentyl glycol, petroleum ether (purchased from Tianjin Kernel Chemical Reagent Co., Ltd. with a stated purity of >0.990 mass fraction) were checked by gas chromatography, the chlorine ketone was the product of Friedel-Crafts acyl reaction provided by a pharmaceutical company of China. The list of chemicals used in this work with information is presented in Table 1.

Table 1: The information of the chemicals used in this work

Chemical	Boiling point (°C)	Density (g/cm <sup>3</sup> )	CAS number
Neopentyl glycol	210	1.06	126-30-7
Petroleum ether	90-120	0.66	8,032-32-4
Sulfuric acid	290	1.84	7,664-93-9
Chlorine ketone	319.1	1.04	80,336-66-9
Ibuprofen	157 (4 mmHg)	1.03	15,687-27-1

#### 3.2 Apparatus and procedure

The experimental schematic diagram is shown in Figure 2. The reaction is mainly carried out in a reaction kettle. The reactor is equipped with internal mixing device and a pump is connected to the bottom of the kettle to form external circulation structure. A distillation column with reflux and condensing equipment is installed on the top of the reaction kettle. Gas chromatography was used to measure chlorine content in different reaction conditions. Single variable method was adopted in the experiment, because only one factor is different at a time, so that the effect of the single factor can be determined.

The detailed experimental process named "basic conditions" is as follows. The ratio of the neopentyl glycol and chlorine ketone was 0.65:1, which neopentyl glycol was excessive to improve the conversion of chlorine ketone. Petroleum ether was added in amount of 2,000 g as solvent and the reactants containing neopentyl glycol of about 650 g and chlorine ketone amount of 1000g were added to the reactor. The reflux ratio is 0.2. The reaction started with adding mass fraction of 28 % sulfuric acid 45 mL. (The concentration of sulfuric acid is based on the experience with industry.) It can be considered to meet industrial production requirements when the conversion of chlorine ketone is not less than 95 %.

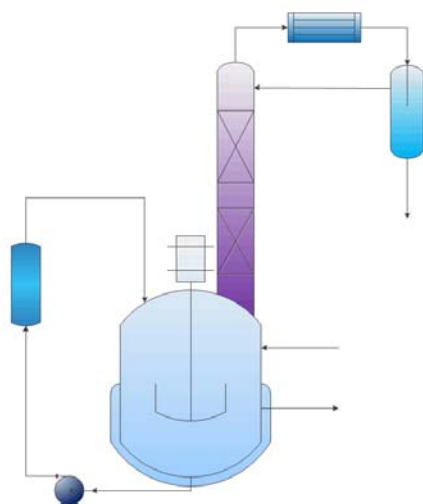


Figure 2: The experimental schematic diagram

## 4. Results and discussion

### 4.1 Effect of mixing mode on ketal reaction

Mechanical stir, forced external circulation and combination of the above two ways were studied to determine the best mixed mode. Forced external circulation means that the reactants are recycled from the bottom of the reactor to the top of that via the external pipes with the help of the pump. Sample once every 2 h in the experiments and the chlorine ketone content is measured by gas chromatography until the content of the chlorine ketone in the system is less than 1.37 %. The experimental results are shown in Figure 3.

On the basis of the data presented in Figure 3, the reaction time is less than 8 h when mechanical stir and forced external circulation are used simultaneously, it decreases more than a half compared with the two methods used alone. It demonstrates that using the combination of mechanical stir and forced external circulation could achieve better mixing effect and shorten the reaction time significantly.

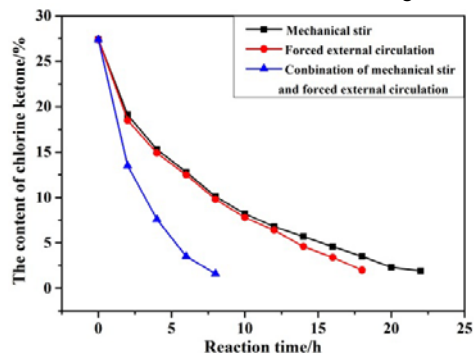


Figure 3: Effect of mixing mode on ketal reaction

### 4.2 Effect of the amount of solvent on ketal reaction

Petroleum ether is not only the solvent of ketal reaction, but also the carrier of free water. The distillation was achieved effectively based on the azeotropic phenomenon between petroleum ether and water. Therefore, the amount of petroleum ether added to the reactor plays an important role on the removal of water. The best amount of petroleum ether was obtained by changing the ratio of petroleum ether (a) and chlorine ketone (b) from 1:1 to 4:1. The conditions of the experiments are the same as “basic conditions” except for the amount of petroleum ether. And the combination of mechanical stir and forced external circulation was used to achieve better mixing effect. The reaction was sampled once per hour and lasted 8 hours. The experimental results and conversion of the reactions are shown in Table 2 and Figure 4.

Table 2: Content of chlorine ketone with different amount of petroleum ether

a:b=1:1		a:b=2:1		a:b=3:1		a:b=4:1	
Time (h)	Chlorine ketone (%)	Time (h)	Chlorine ketone (%)	Time (h)	Chlorine ketone (%)	Time (h)	Chlorine ketone (%)
0	37.7	0	27.4	0	21.5	0	17.7
1	30.1	1	21.7	1	16.3	1	14.3
2	24.3	2	13.5	2	11.4	2	11.2
3	19.5	3	10.1	3	8.3	3	9.5
4	14.7	4	7.6	4	6.1	4	8.2
5	10.5	5	5.2	5	5.7	5	6.4
6	7.3	6	3.5	6	4.2	6	5.2
7	4.8	7	2.3	7	2.6	7	4.3
8	2.4	8	1.3	8	1.1	8	1.5

The amount of petroleum ether added to the reactor has serious effect on the conversion of ketal reaction. If the amount of petroleum ether is small, water cannot be removed in time and the reverse reaction will occur. While if petroleum ether is excessive, the concentration of reactants will decrease and the reaction rate will be

reduced. As shown in Figure 4, the industrial production requirements could be achieved when the ratio of petroleum ether (a) and chlorine ketone (b) is 2:1 and 3:1. The optimal ratio of a and b is 2:1 in terms of economic efficiency.

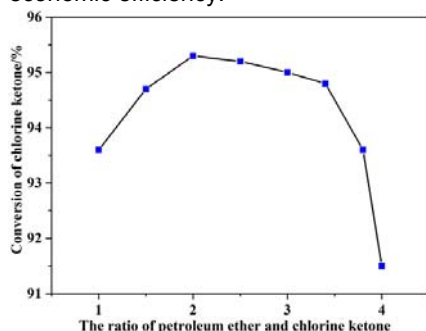


Figure 4: Conversion of chlorine ketone with different amount of petroleum ether

#### 4.3 Effect of reflux ratio on ketal reaction

The removal rate of free water can be controlled by adjusting the reflux ratio. In theory, a high free water removal rate is beneficial to the reaction. For distillation, the smaller the reflux ratio, the lower the energy consumption is. Experiments were carried out under different reflux ratios. The conditions of the experiments are the same as “basic conditions” except for the reflux ratio, and the combination of mechanical stir and forced external circulation was used to achieve better mixing effect. The results are shown in Table 3. The results show that a smaller the reflux ratio can promote the reaction.

Table 3: Content of chlorine ketone with different reflux ratio

RR=0.2		RR=0.5		RR=1	
Time (h)	Chlorine ketone (%)	Time (h)	Chlorine ketone (%)	Time (h)	Chlorine ketone (%)
0	27.4	0	27.4	0	27.4
1	21.7	1	20.2	1	22.5
2	13.5	2	12.4	2	15.7
3	10.1	3	8.5	3	11.2
4	7.6	4	7.2	4	9.1
5	5.2	5	6.4	5	7.3
6	3.5	6	5.1	6	5.8
7	2.3	7	4.3	7	3.6
8	1.3	8	3.2	8	2.8

#### 4.4 Energy consumption

Through the optimization and process intensification for ketal reaction, the rate and conversion of the reaction is increased, and the unit energy consumption is reduced. The energy consumption contains electricity and steam consumption, and the energy cost reduced by 60 %. Table 4 shows the unit energy consumption of original technology and improved technology.

Table 4: Unit energy consumption of original technology and improved technology

Energy consumption	Original technology	Improved technology
Electricity / (kW·h/kg)	2.3	0.9
Steam consumption/ (kg/kg)	28.2	11.3
Energy cost/ (¥/kg)	7.5	3.0

## 5. Conclusion

In this paper, the ketal reaction process in the 1,2-transposition rearrangement of ibuprofen synthesis was optimized. After the improvement of the equipment and optimization of operating parameters, the reactive time of the ketal reaction is reduced from 22 h to less than 8 h and the conversion of chlorine ketone is more than 95 %, and the energy costs reduce by 60 %. The improved ketal technology has been industrialized and demonstrated good economic efficiency for two enterprises. However, the level of automation is low, which limits the development of production capacity to some extent. For further study, reactive distillation technology should be combined with automatic control technology to realize automatic and programmed production of ketal reaction process.

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