

Review of cyclopropyl bromide synthetic process

Kunyao Li

Beijing University of Chemical Technology, No. 15, North Third Ring East Road,
Chaoyang District, Beijing, China

kunyao_li@163.com

Abstract. Cyclopropyl bromide is a significant pharmaceutical intermediate that plays a crucial role in the synthesis of various cyclopropyl drugs and quinolone drugs, including ciprofloxacin, enrofloxacin, and sparfloxacin. This review aims to explore the process of manufacturing cyclopropyl bromide, analyze the merits and drawbacks of some typical synthesis routes, and propose optimization strategies for each. Two synthetic pathways exist for the production of the crucial intermediate compound in the synthesis of the important intermediate of ciprofloxacin. Foreign literature has documented that the second pathway exhibits a high percent yield and it can be co-produced with norfloxacin and pefloxacin. However, the process conditions for the second route are not mature yet of which cyclopropyl bromide is considered one of the most important pharmaceutical intermediates. A mature process would be more suitable for the large-scale volume production of China's pharmaceutical industry. Consequently, the utilization of the second route is now scarcely used in China. The initial phase in the industrialization of the second pathway involves conducting a comprehensive analysis on the pharmaceutical intermediate cyclopropyl bromide. The synthesis of cyclopropyl bromide and the realization of the process can improve the productivity of quinolones.

Keywords: Cyclopropyl Bromide, γ -butylactone, Industry.

1. Introduction

Cyclopropyl bromide is an organobromine compound with the chemical formula C_3H_5Br . The molar mass is $120.977\text{ g}\cdot\text{mol}^{-1}$. It exhibits immiscibility with chloroform, and soluble chloroform (sparingly), methanol (slightly). Due to the special property of the ring structure, the carbon-carbon bond angle in cyclopropyl bromide in its molecule deviates from the ideal valence bond angle of 109.5 degrees. This deviation results in ring tension variation, which will affect the reactivity of the molecule. Specifically, it makes the molecule more prone to undergo ring opening reactions.

Among the quinolones available in the market, ciprofloxacin hydrochloride has a broad antibacterial spectrum, potent bactericidal activity, effective tissue penetration, high blood night concentration, good absorbability, high bioavailability, short treatment duration, and low cost. This issue has generated significant concern within both the domestic and international pharmaceutical industry. The aforementioned characteristics of high efficiency, low toxicity, and low price. Ciprofloxacin is currently undergoing rapid development, and the international market competition is highly intense. There are two routes for the synthesis of the significant intermediate 7-chloro-6-fluoro-1-cyclopropyl-1, 4-dihydro-4-oxy-3-quinoline carboxylic acid. The first method involves the use of cyclopropyl followed

by cyclization. In this method, 2, 4-dichloro-5-fluorophenone is utilized as the starting material and undergoes a series of reactions including β -ketoacid esterification, eschemoser, the Kulinkovich reaction, cyclization, hydrolysis reaction, and piperazine synthesis [1].

The alternative approach involves the process of cyclization, which is subsequently followed by the Kulinkovich Reaction [2]. Currently, the former route is employed for all domestic industrial routes adopt the former one. The first route offers several advantages, including shorter steps and mature process conditions. The substance exhibits a low condensation percent yield, low total percent yield, and high cost, thus necessitating careful consideration of production safety. For Chinese manufacturers of quinolones, the short step and well-established procedure would be better suited for the large-scale volume production of China's pharmaceutical industry. Industrializing the second route has the potential to enhance the percent yield of quinolones. The initial step towards achieving this is to industrialize the synthesis of cyclopropyl bromide.

2. Classic synthesis process

2.1. Synthesis methods of cyclopropyl bromide

According to the existing literature, three synthesis methods for cyclopropyl bromide:

- (1) The synthesis of cyclopropyl bromide from allyl compounds.
- (2) The reaction of 1,1,3-trihaloalkane with a mixed solution of methyl lithium and ether under conditions of -30°C to -20°C results in the formation of the corresponding cyclopropyl halides.
- (3) According to the Hunsdieker reaction, liquid bromine is added to cyclopropanecarboxylic acid in the presence of mercury oxide catalyst.

The first reaction pathway being considered is the photochemical reaction. However, due to the limited availability of the raw material is not easy to get and the photochemical reaction is difficult to promote in the pharmaceutical industry, this pathway (1) is not deemed feasible. In (2), the raw materials are limited, posing a challenge. Additionally, the process requires the use of refrigeration equipment under demanding industrial conditions. In addition, the presence of significant safety issues renders (2) as not being considered. In (3), with the exception of cyclopropanecarboxylic acid, the remaining raw materials are inexpensive and readily available. The reaction involves a free radical substitution under mild conditions, resulting in a stable percent yield. The third route presents clear advantages in comparison to the first two routes.

2.2. Synthesis of precursor cyclopropanecarboxylic acid

The following four routes are commonly utilized both domestically and internationally [3-6]:

- (1) 1-chloro-bromopropane reacted with sodium cyanide then cyclize with sodium amino to obtain cyclopropylmethyl nitrile, hydrolyze to cyclopropanecarboxylic acid.
- (2) γ -butyrolactone reacts with concentrated hydrochloric acid under pressure to obtain γ -chlorobutyrate, then cyclize in sodium alcohol to obtain methyl cyclopropane carboxylate, then hydrolyze to cyclopropanecarboxylic acid.
- (3) γ -butyrolactone reacts with sulfoxide chloride with the catalyst ZnCl_2 to form γ -methyl chlorobutyrate, then brominate to form γ -chloro-butyrate. Cyclopropyl bromide is synthesized in the presence of sodium alcohol.
- (4) 1, 2-dibromo(chloro)ethane and diethyl didicarboxylic acid are catalyzed by a phase transfer catalyst (PTC) under concentrated base conditions to obtain cyclopropane dicarboxylic acid. After decarboxylation and bromination, obtain cyclopropyl bromide.

The drawback associated with route (1) involves the utilization of serious drugs and hazardous substances that are flammable and explosive, resulting in a low percentage yield. The implementation of route (2) necessitates the utilization of pressurized equipment that is resistant to corrosion, thereby imposing stringent equipment requirements. The route (4) utilizes dibromoethane as a starting material, which is known to be costly. Among the aforementioned four routes, route (3) exhibits several advantages including cost-effectiveness, high percent yield and readily accessible raw materials.

2.3. *Synthesis of cyclopropyl bromide*

Form mercury salts with mercury oxide in 1,1,2,2-tetrachloroethane; Then decarboxylate and brominate to obtain bromocyclopropane [7].

2.4. *Synthesis process of cyclopropyl bromide*

The reaction mixture containing anhydrous ZnCl_2 and sulfoxide chloride was subjected to stirring and subsequent distillation under reduced pressure in order to isolate 4-chloro-butryl chloride. The synthesis of methyl 4-chlorobutyrate involved the suspension of sodium metal in toluene, followed by the addition of a solution containing methyl 4-chlorobutyrate and toluene. The mixture was then refluxed and sodium hydroxide solution was added, which was vigorously stirred throughout the reflux process. The organic layer is separated and subsequently adjusted to a pH of 2~3, the oil layer is precipitated, extracted, and dried. It is then distilled under vacuum to obtain cyclopropane formic acid. Cyclopropyl bromide was synthesized in accordance with the methodology described in the reference [8].

3. Synthesis methods optimization

3.1. *Three steps method*

The classical reaction pathway consists of five steps. In order to enhance the percent yield and streamline the procedure, the original five-step reaction has been modified to a three-step process. The three steps produce the following product [9].

(1) γ -methyl chlorobutyrate, (2) cyclopropanecarboxylic acid, and (3) cyclopropyl bromide.

3.2. *Preparation of γ -methyl chlorobutyrate*

The synthesis of γ -butyrolactone involves the chlorination of sulfone chloride and the esterification of methanol under the catalysis of zinc chloride. The resulting percent yield is 70%~95%. The operational procedure of this process is straightforward, and the raw materials required are readily available, resulting in low costs. However, a significant drawback is the generation of a substantial amount of mixed waste gas containing sulfur dioxide and hydrochloric acid [10, 11]. For instance, the methodology employed in the research has a laboratory yield of 95%. However, it is not deemed appropriate for industrial applications.

3.3. *Preparation of cyclopropanecarboxylic acid*

The prepared γ -chlorobutyrate was closed under the action of quaternary ammonium phase transfer catalyst. Dichloromethane, sodium oxide and quaternary salt phase transfer catalyst were added with γ -methyl chlorobutyrate [12]. This is the method used in the laboratory, the percent yield reached 90.3%, but the experiment needs to use concentrated hydrochloric acid, and the operation is complicated, the reaction equipment requirements are high, not suitable for industrialization.

3.4. *Preparation of cyclopropyl bromide*

Cyclopropane carboxylic acid, mercury oxide and 1,1,2, 2-tetrachloroethane were heated under stirring, bromine was slowly dripped, and the distillate was collected by distillation [7].

3.5. *Advantages and limitations*

As for this particular method, it should be noted that the reaction conditions are relatively gentle, leading to an enhanced percent yield of the product. However, it is important to acknowledge that there are still many factors that limit its applicability to industrial-scale production.

By modifying the process conditions and selecting the phase transfer catalyst, the new process can synthesize cyclopropyl bromide in a concise three-step process. Compared to the original five-step synthesis process, the process flow has been shortened, which is advantageous for facilitating industrial production. Cyclopropane carboxylic acid, obtained through the process of hydrolysis, is subsequently subjected to decarboxylation and bromination reactions, resulting in the formation of cyclopropane

bromide. The overall yield of cyclopropane bromide with a percent yield of 59%. Despite the observed improvement in the percent yield has improved, it still has high cost, low percent yield and dangerous chemicals such as mercury oxide and bromine are used.

4. New synthesis method

4.1. Method using cyclopropyl formic acid as raw material

Cyclopropyl formic acid was initially subjected to a reaction with carbonyl diimidazole, resulting in the synthesis of cyclopropyl imidazole. This compound was then combined with trichloroastromethane, then dropped with an oxidizing agent for free radical deacidification bromination reaction to obtain cyclopropyl bromine crude product, and after simple atmospheric distillation, the purity of the product was more than 99%. Cyclopropyl bromide was synthesized by two steps from cyclopropyl formic acid. This method exploits the inherent instability of the intermediate cyclopropyl dicarboxylic acid peroxide, which undergoes decarboxylation and self-decomposition upon reheating. Subsequently, it can be effectively captured by bromomethane trichloride, resulting in the efficient formation of cyclopropyl bromide [13].

4.2. Advantages and limitations

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The reaction conditions employed in this study are characterized by their mild nature, making them highly favorable for practical applications. Additionally, the reagent used in this process is readily available, eliminating the need for the use of mercury oxide. This particular method is also well-suited for industrial scale-up production. However, it should be noted that if the process were to utilize cyclopropyl formic acid directly, the cost would be high, referring to the 2023 price (CAS: 1759-53-1) 290 yuan per twenty-five milliliters.

5. Another new synthesis method

5.1. Method using cyclopropylamine as raw material

The primary constituent utilized in this procedure is cyclopropylamine, which undergoes diazotization followed by bromination. The addition of aminocyclopropane and acidic substances in a specific ratio, under the protection of the protective agent bromide, is carried out. The temperature is carefully regulated, and subsequently, the catalyst solution is introduced. Under the influence of an acidic substance and a catalyst, the bromide and aminocyclopropane undergo substitution to yield cyclopropyl bromide. Finally, the process of stratification, water washing, vacuum distillation, and rectification is employed to obtain cyclopropyl bromide with a high degree of purity [14].

5.2. Advantages and limitations

This method offers ease in obtaining raw materials, simplicity in operation, and high product yield, with a yield of over 80% and a high purity level of more than 98%. The protective agent exhibits reusability, does not impact the yield, and greatly reduces the production cost. As a result, the production is favorable for large-scale industrial production. This method effectively circumvents the utilization of hazardous or detrimental substances, such as sulfoxide chloride and mercury oxide. If the process utilizes cyclopropylamine directly, the cost would be significantly high, based on the 2023 price (CAS: 765-30-0) 260 yuan per five milliliters. The production technology for cyclopropylamine has reached a mature stage; however, butyrolactone continues to be utilized as the primary starting material. If the synthesis of cyclopropylamine and cyclopropyl bromide is integrated into a unified procedure, it becomes inevitable to encounter the utilization of hazardous substances, such as sulfoxide chloride and mercury oxide. However, despite this approach, the fundamental problem that this method seeks to circumvent remains unresolved.

6. Uniform Design Experimentation in Cyclopropyl bromide synthesis process

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In addition to enhancing the synthesis process, there exist various factors that influence the reaction percent yield, raw material ratio and the control of the reaction. In order to increase the percent yield, uniform design experimentation can be employed. Uniform design is a test design methodology that solely takes into account the uniform distribution of test points within the designated test range. By adjusting the ratio of cyclopropyl carboxylic acid and bromine, the quantity of mercury oxide, and the duration of the dropping process, the optimal conditions for achieving the highest percent yield were determined. According to the existing literature, this method not only achieves the purpose of improving the percent yield, but also solves some environmental pollution resulting from the use of mercury salt [15].

7. Discussion

Tables should be centred unless they occupy the full width of the text.

For the three-step method, we can optimize the steps by referring to the literature.

(1) It has also been reported that γ -butyrolactone can react with sulfoxide chloride at atmospheric pressure to obtain γ -chloroprene chloride and then react with methanol and pyridine to obtain γ -methyl chlorobutyrate, with a total percent yield of 60.78%. The reaction condition of this method is mild, but it requires a lot of pyridine and ether, which is not conducive to industrial production [16].

The chemical name of solid phosgene is double (trichloromethyl) carbonate (BTC), which is a rapidly developing green chemical product. It has high melting boiling point, low volatility and low toxicity. Using solid phosgene as raw material instead of sulfoxide chloride as chlorination reagent, γ -chloroprene chloride was synthesized from γ -butyrolactone, and 4-methyl chlorobutyrate was synthesized by esterification. The reaction conditions are optimized, the operation is simple, the percent yield is increased, and it is suitable for industrial production [17, 18].

(2) According to the production process of cyclopropanecarboxylic acid, the three-step method can be changed to two steps. cyclopropanecarboxylic acid is produced from butyrolactone and then decarboxylated to obtain the product cyclopropyl bromide. The ring-opening esterification of γ -butyrolactone and isopropyl alcohol was carried out with HBr instead of sulfoxide chloride at atmospheric pressure. In one step, isopropyl gamma-bromobutyrate is formed, then cyclized to isopropyl cyclopropane carboxylic acid, and finally hydrolyzed to cyclopropane carboxylic acid [19].

According to the two new methods with high percent yield, but the starting materials of this two methods are expensive. We can consider combining the synthesis process of the starting material with the new method.

8. Conclusion

This review provides a summary of the synthesis process of cyclopropyl bromide and discusses its optimization. Currently, the synthesis process of cyclopropyl bromide is not sufficiently developed and requires improvement, particularly in terms of environmental considerations. While certain novel techniques have demonstrated the ability to achieve high percent yields, it is crucial to take into account the associated industrial costs. In order to increase the percent yield of quinolones, such as ciprofloxacin, it is imperative to persist in the investigation and optimization of the synthesis process for cyclopropyl bromide.

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