Green Synthesis of 7,8-Difluoro-6,11-Dihydrodibenz[B,E]Thiophene-11-One of Baloxavir Marboxil -- Reducing Environmental Pollution

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Abstract: Baloxavir marboxil is a novel anti-influenza drug with a unique mechanism of action that can effectively treat both type A and type B influenza. Key intermediate compound 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one is not only an important component of the chemical structure of baloxavir marboxil but also an essential intermediate in the synthetic route of the drug. However, conventional synthesis methods for key intermediate 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one usually utilize dangerous and harmful chemicals that can cause significant environmental pollution during large-scale production. This article proposes a new synthesis route for 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one to facilitate large-scale production while integrating the principles of green chemistry. This new route feature mild reaction conditions and simpler steps that result in an overall yield increase to 64.9%. More significantly, the new synthesis route reduces the use of hazardous chemicals, thus limiting the generation of hazardous waste during industrial production. This research offers significant potential for environmental pollution control.

1. Introduction

The new antiviral drug baloxavir marboxil (Figure 1) was approved for market by the U.S. Food and Drug Administration (FDA) on October 25th, 2018. The uniqueness of the small molecule prodrug baloxavir marboxil lies in its brand-new mechanism of action, which sets it apart from any other antiviral drugs for influenza that have come before. Baloxavir marboxil is a polymerase acidic endonuclease inhibitor that enters the human body and is rapidly hydrolyzed by the aromatic ethyamide in the small intestine, blood, and liver into baloxavir acid [1]. Baloxavir acid can bind with the RNA polymerase of the flu virus and inhibit its activity, thereby preventing the replication of flu virus RNA in the human body and the generation of new viral particles. Clinical trials have shown that baloxavir marboxil exhibits broad and effective antiviral activity against both influenza A and B viruses, and has significant advantages, including the ability to cure flu symptoms with a single dose and quick onset, as well as minimal side effects and resistance [2].

![Figure 1. Chemical structure of baloxavir marboxil.](image1)

![Figure 2. Chemical structure of 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one.](image2)

The synthesis of key intermediate compound 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one (Figure 2) is essential to industrial manufacturing of...
baloxavir marboxil. From a chemical structure perspective, baloxavir marboxil is composed of two fragments (Figure 3): key intermediate 1 (7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-ol) and key intermediate 2. Typically, the synthesis of baloxavir marboxil involves the separate synthesis of these two fragments followed by subsequent coupling and additional steps [3]. After discovering the new drug baloxavir marboxil, the Japanese company Shionogi developed three synthesis routes. These three synthesis routes all employ a retrosynthetic strategy: they combine the two fragments in the molecule through substitution reactions, followed by deprotection and etherification to obtain baloxavir marboxil. Considering that the final reduction reaction is well established, thus the synthesis of key intermediate compound 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one is an issue to be addressed in the synthesis of baloxavir marboxil.

In 2017, the Shionogi team synthesized the 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-ol of baloxavir marboxil from 3,4-difluorobenzoic acid (Figure 4). This route employed 3,4-difluorobenzoic acid as the starting material [4]. The synthetic route consists of five reaction steps, including a first step of cyclic reaction that requires low temperature conditions of -40℃ without moisture. This reaction requires strict conditions and the use of hazardous and explosive n-butyl lithium reagent [5]. In the second step, toxic and malodorous thiophenol is used, which poses a significant risk to experimenters. This route has been applied to the industrial synthesis of 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-ol. However, the use of reagents such as n-butyl lithium, thiophenol, and polyphosphoric acid can cause damage to the environment.

In previous study, the synthesis of 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one typically required stringent reaction conditions, and the principles of green chemistry were seldom considered when designing the synthesis route [6]. As a result, reagents with significant environmental impacts were frequently used (as shown in Table 1). Therefore, developing an efficient and easily scalable synthesis route for 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one to meet the industrial synthesis demands of Baloxavir marboxil and to help control the environmental pollution generated during the synthesis process is still very necessary.

<table>
<thead>
<tr>
<th>Chemical reagents</th>
<th>Potential hazards</th>
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<tr>
<td>n-Butyllithium</td>
<td>Containing organic lithium compounds, which have strong corrosiveness, are highly flammable and can trigger fire and explosion incidents, hence highly dangerous.</td>
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<tr>
<td>Thiophenol</td>
<td>With strong irritability and a certain level of toxicity, it also emits an unbearable foul odor.</td>
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<tr>
<td>1,1,3,3-Tetramethyldimethoxysilane</td>
<td>Vapor in the air is highly flammable and poses an explosion risk. Additionally, it has poor biodegradability and can cause pollution in the environment, including water bodies and soil, which can negatively impact ecological safety.</td>
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Green chemistry is a sustainable approach that strives to minimise or eliminate potential hazards to the environment and human health in the synthesis and product design of chemicals [7]. Compared with traditional chemical processes, green chemistry places greater emphasis on the sustainability and environmental friendliness, reducing the environmental damage and threats to human health caused by the chemical industry. The core concept is to reduce or eliminate the use and production of hazardous substances wherever possible. The American Chemical Society proposed the twelve principles of green chemistry at the International Conference on Green Chemistry in 1998. The new route proposed in this study is based on several principles: firstly, the Prevention Principle suggests that preventing pollution is better than treating it. Secondly the Green Synthesis Principle emphasizes the use of methods that have minimal environmental and health risks in synthesizing compounds. Thirdly, the Safer Reagents Principle advocates for the use of mild chemical reaction conditions. Fourthly, the Energy Efficiency Principle emphasizes reducing the energy consumption of chemical processes. Fifthly, the Waste Prevention Principle encourages minimizing chemical residues, waste and waste disposal. Lastly, the Environmentally Friendly Chemistry Principle emphasizes that chemical products and processes should not cause long-term harm to the environment and the biosphere [8].

In addition, environmental impact factor (E-factor) is also an important aspect of green chemistry, as it can be used to evaluate the level of impact that chemical production processes have on the environment. The definition of E-factor is the ratio between the total of waste produced and the total of target product generated in a chemical reaction (1). Calculating environmental impact factor can help the chemical industry design new chemical reactions that reduce waste generation and promote environmentally friendly production methods [9]. Chemical reactions with relatively low E-factor are typically more sustainable and environmentally friendly in green synthesis, making greater contributions to environmental protection and pollution control.

\[
E \text{ factor} = \frac{\text{mass of reactants} - \text{mass of products}}{\text{mass of products}}
\]

This study designed a green synthesis route (Scheme 1) for 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one based on previous research. The new route conforms to the green chemistry principles mentioned earlier in this paper, with high yield and mild reaction conditions, reducing the use of harmful chemicals and the generation of waste. As the final reduction reaction has been well reported, we have carried out synthetic experiments on a 10 g scale for the green synthetic route to support its industrial application. The E-factor calculation confirms that the new route has a smaller impact on the environment and is more conducive to pollution control.

![Scheme 1. Green synthetic route of 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one](image)

### 2. Experimental

#### 2.1 Step 1 of green synthesis route

Compound I, 3,4-difluoro-2-methylbenzoic acid (10.32 g, 60 mmol), was dissolved in 240 mL of 1,2-dichloroethane solvent, giving a molar concentration of 0.25 mmol/mL. 240 mmol (4 equivalents) of sodium bromate was dissolved in approximately 200 mL of water and added to the above solution while stirring. 120 mmol (2 equivalents) of sodium bisulfite was dissolved in 60 mL of water and slowly added to the solution to avoid local overheating. After the addition was completed, the reaction mixture was heated to reflux, and the actual reaction temperature was maintained at 78°C. The reaction progress was monitored every hour using thin-layer chromatography (developing agent: petroleum ether: ethyl acetate = 5:1, with two drops of acetic acid added). After completion of the reaction, the post-treatment was carried out as follows: the organic phase in the lower layer was collected, the aqueous phase was extracted three times with 100 mL of dichloromethane, and the organic phases were combined, washed with 100 mL of saturated NaCl solution, and dried over anhydrous magnesium sulfate. The dried organic phase was filtered and the anhydrous magnesium sulfate were removed. The remaining bromine and organic phase were removed by rotary evaporation to obtain a white solid, which was crude product compound II. The crude product was further purified by crystallization using 100 mL of petroleum ether, to obtain the pure product of compound II and weighed to be 12.39 g, with a yield of 82.2%.

#### 2.2 Step 2 of green synthesis route

Compound II, at a quantity of 40 mmol (10.04 g) was added to 100 mL of water. Slowly add 60 mmol (1.5 eq) of potassium carbonate in batches and stir at room temperature until dissolved. Then, add 48 mmol (1.2 eq) of sodium phenylthiolate and stir the reaction mixture continuously while monitoring the temperature. Heat the
and product purity than traditional bromination reactions. After the reaction, the remaining bromine in the reaction system can be easily removed in post-processing, saving post-processing steps, effectively avoiding the generation of hazardous waste, and being environmentally friendly, which is more in line with the principle of pollution prevention.

Based on the sustainability principles and waste prevention principles in green chemistry, water is used as the reaction solvent in the second reaction. Water is a green and harmless solvent; when it is used as a solvent in chemical reactions, it does not harm human health or cause environmental pollution. It is cost-effective and much easier to handle than organic solvents [10]. Water replaces the organic solvent N, N-dimethylformamide commonly used in previous routes for the reaction in this step. The extraction, separation, and purification of the target product will be much simpler, and the post-treatment of laboratory synthesis and industrial production will be more convenient, which complies with the energy-saving principle of green chemistry and reduces the energy consumption of the chemical process.

In the synthesis route of previous researchers, polyphosphoric acid is usually used as a condensing reagent to catalyze the condensation reaction that generates compound IV. However, when this synthesis scheme is applied to industrial production, it results in a significant amount of phosphate waste and may generate other harmful gases such as ammonia, nitrogen oxide, and phosphine. Therefore, it is necessary to thoroughly remove polyphosphoric acid after the reaction is completed. Improper handling can cause serious environmental pollution problems and significantly increase the difficulty of post-reaction processing. This study proposes a new solution to the waste management problem in large-scale industrial production by using oxalyl chloride to react with compound III to generate acyl chloride, followed by the Friedel-Crafts acylation reaction catalyzed by anhydrous aluminum chloride to form compound IV. This approach minimizes the potential environmental pollution problem and demonstrates the principles of prevention and waste reduction in green chemistry.

After completing the 10-gram-scale synthesis experiment, this article calculates the E-factor of each reaction step of green synthesis route, so as to make the impact of the reaction process on the environment more intuitive and quantifiable. The calculation results of each step are shown in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Calculation of E-factor</th>
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<tbody>
<tr>
<td>Step</td>
<td>E-factor</td>
<td>Yield</td>
</tr>
<tr>
<td>Step1</td>
<td>1.28</td>
<td>82.2%</td>
</tr>
<tr>
<td>Step2</td>
<td>1.21</td>
<td>90.7%</td>
</tr>
<tr>
<td>Step3</td>
<td>2.11</td>
<td>87.1%</td>
</tr>
<tr>
<td>Average</td>
<td>1.53</td>
<td>86.7%</td>
</tr>
</tbody>
</table>

The average of E-factor for new route has an average E-factor of 1.53, with a total sum of 4.6, as shown in the calculation results. It is clear that the new green synthesis route achieves a lower E-factor value. This means that if it is applied to industrial production, it has a lower potential environmental impact.

### 3. Result and discussion

The overall yield of the 10-gram-scale experiment for the green synthesis route of 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiophene-11-one was 64.9%. The reaction conditions in each step were mild, and the generated waste was minimal and easy to handle, making it suitable for large-scale industrial production. In the bromination reaction, sodium bromate was chosen as the bromine source instead of the commonly used NBS reagent. As an inorganic salt, sodium bromate is cheaper and has better controllability, achieving higher selectivity and reduction in green chemistry.

### 2.3 Step 3 of green synthesis route

Compound III (40 mmol, 11.2 g) was dissolved in 400 mL of 1,2-dichloroethane, and a catalytic amount of N, N-dimethylformamide was added dropwise as a catalyst. While stirring, 72 mmol (1.8 eq) of oxalyl chloride was slowly added at 60°C for 5 hours. After the reaction was completed, the reaction system was cooled to room temperature under reduced pressure, and the remaining small amount of oxalyl chloride and 1,2-dichloroethane solvent were removed. Then, 200 mL of 1,2-dichloroethane solution was added to the reaction system, and after stirring thoroughly at room temperature, 60 mmol (1.5 eq) of anhydrous aluminum chloride was slowly added in batches. The mixture was heated to reflux (78°C) and reacted for 2 hours, and the reaction progress was monitored every hour with thin-layer chromatography (petroleum ether: ethyl acetate = 5:1). After the reaction, 80 mL of water was added to quench the reaction. The organic phase was extracted three times with 80 mL of dichloromethane, and the combined organic phases were washed with 50 mL of saturated sodium bicarbonate solution. The organic phase was collected, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain light yellow solid, which was compound III. Recrystallize the crude product using 80 mL of petroleum ether, filter to collect the precipitate, with a weight of 10.16 g and a yield of 90.7%.

The mixture to reflux at 100°C for 2 hours. The reaction progress was monitored every hour using thin-layer chromatography with a developing solvent of petroleum ether:ethyl acetate=5:1, with two drops of acetic acid added. After the completion of the reaction, the reaction mixture was allowed to cool to room temperature and 1N hydrochloric acid was added dropwise to adjust the pH of the reaction mixture to 4-5. During the dropwise addition, white solid precipitated, which was compound III. Filter the precipitate to obtain the crude product of compound III. Extract the filtrate three times with 50 mL of dichloromethane. Collect the organic phase and dry with anhydrous magnesium sulfate. Remove the remaining organic phase by vacuum distillation to obtain a white solid product total of 10.65g, which is the crude product of compound III. Recrystallize the crude product using 80 mL of petroleum ether, filter to collect the precipitate, with a weight of 10.16 g and a yield of 90.7%.
environmental impact and is more conducive to pollution management and control.

4. Conclusion

Based on the principles of green chemistry, a new green synthesis route for the 7,8-difluoro-6,11-dihydrodibenz[b,e]thiophene-11-one of baloxavir marboxil has been designed in this article. The new route avoids the use of hazardous and polluting reagents as much as possible, and the reaction conditions are also milder. A synthesis experiment at a scale of 10 grams was carried out, and the overall yield reached 64.9%. Through the calculation of E-factor, it was verified that the new green synthesis route has significant advantages in environmental pollution control, which better conforms to the principles of green chemistry and pollution control. Therefore, the application of the new green synthesis route in industrial production of baloxavir marboxil will effectively reduce the environmental pollution risk in the production process and help with pollution control.

References