Novel and Practical Industrial Process Scale-Up of 5-Bromo-2-chloro-4-(methoxycarbonyl) benzoic acid, a Key Intermediate in the Manufacturing of Therapeutic SGLT2 Inhibitors

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Abstract

5-Bromo-2-chloro-4-(methoxycarbonyl)benzoic acid (1) is a key intermediate for the synthesis of a family of promising SGLT2 inhibitors currently in preclinical and phase I studies for diabetes therapy. In this investigation, cheap, easily available dimethyl terephthalate was used as the raw starting material, and compound 1 was prepared effectively in six steps, including nitration, hydrolysis, hydrogenation, esterification, bromination, and diazotization. The preparation was run successfully on approximately 70 kg/batch with the total yield of 24%. This practical process was demonstrated to be scalable with a great yield and significant cost reduction.

Introduction

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar, or glucose) or when the body cannot effectively use the insulin it produces. Diabetes is an important public health problem, one of four priority noncommunicable diseases targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. Although there are antidiabetic drugs on the market, hyperglycemia is still clinically hard to be controlled. So, it is necessary to develop new antidiabetic drugs with novel targets and mechanisms. Sodium-glucose...
cotransporter-2 (SGLT2) inhibitors are a new class of diabetes treatment drugs. Mechanistically, they remove glucose from the urine by inhibiting the reabsorption of near-curved renal tubular glucose, which reduces blood glucose levels without depending on insulin. Besides, they could also reduce body weight, lower blood pressure, and have broad application prospects.\(^1\)

In recent years, several research teams have devoted to the study of structure–activity relationship of SGLT2 inhibitors, and discovered that bromoaryls are active fragments to synthesize various promising candidate compounds as highly effective SGLT2 inhibitors.\(^2\)–\(^5\) Among these inhibitors, 5-bromo-2-chloro-4-(methoxycarbonyl)benzoic acid (1) is a key intermediate in high demand that is utilized for developing SGLT-2 inhibitors (\(\pm\)Fig. 1).\(^6\) The known synthetic routes of compound 1 are all in small scale, in which the operation is complex and unpractical for industrial scale-up. Therefore, it is necessary to develop a feasible synthetic route and industrialized preparation method with high yield, low cost, and easy scale-up.

The reported synthetic route of compound 1 is shown in Scheme 1.\(^7\)–\(^9\) Route A: 3-amino-4-toluic acid (2) is used as the starting material, the key intermediate 5 is obtained in three steps including aryl bromination, esterification, and Sandmeyer reaction. Route B: 2-bromo-4-methylbenzoic acid (6) goes through aromatic ring chlorination and esterification to prepare intermediate 5. The key intermediate 5 is oxidized with different oxidizing reagents and related conditions to obtain the target 1. These preparation methods have their deficits such as the expensive starting materials and undesirable oxidation efficiency, which is difficult to meet the market demand for industrialized mass production.

To develop an industrial process of intermediate 1, we conducted retro-synthesis analysis based on structural characteristics of the compound. Specifically, compound 1 can be synthesized from compound 12 through compound 11 (\(\pm\)Fig. 2), based on the existing literature.\(^10\)–\(^13\) Herein, a new synthetic route (Scheme 2) of compound 1 was designed and explored. Compound 11 is new compound that has not been reported in the literature.

![Diagram of synthetic routes](image)

**Fig. 1** SGLT-2 inhibitor drugs under investigation.

**Fig. 2** Retrosynthetic analysis of compound 1 through a nonoxidative route.

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**Scheme 1** The reported synthetic route of 1. Reagents and conditions: (a) NBS, DMF; (b) SOCl\(_2\), MeOH; (c) NaNO\(_2\), CuCl, HCl, dioxane; (d) NCS, CCl\(_4\); (e) SOCl\(_2\), MeOH; (f) NBS, AIBN, CCl\(_4\); (g) AcONa, DMF; (h) LiOH·H\(_2\)O, THF, MeOH, H\(_2\)O; (i) PDC, DMF; (j) KMnO\(_4\), 18-crown-6, t-BuOH, H\(_2\)O or 10% NaClO, TBAB, RuCl\(_3\)-3H\(_2\)O, DCE, pH = 9.
Utilizing cheap and commercially available dimethyl terephthalate (13) as a raw material, compound 14 was obtained by nitrification in the mixture of HNO₃ and H₂SO₄. Then, 14 was hydrolyzed with NaOH and the product 16 is a solution of disodium salt. Direct catalytic hydrogenation of 15 without separation could easily provide 16, which reacted with TMSCI in MeOH to yield monoesterified intermediate 12. Compound 12 was brominated to obtain intermediate 11, which formed salt 17 (11·HCl) with hydrogen chloride gas. The target compound 1 was synthesized by the Sandmeyer reaction from compound 17.

After the optimization of the above synthetic route, 70 kg of compound 1 was prepared with high yield and purity, and this large-scale production is a feasible and low-cost new route.

**Results and Discussion**

In this new synthetic route of compound 1, compound 11 and its hydrochloride salt 17 are new compounds that have not been reported in the literature; it is the focus of this work. Compound 12 can be prepared by bromination of 12, but it also produces dibromo by-product 18 (Scheme 3), which is difficult to separate from compound 11 and unavoidably decreases the purity of final product. In this article, excess amount of N-bromosuccinimide (NBS) was used to react with compound 12 to prepare the main by-product 18, which was used as a reference substance for screening reaction conditions (Scheme 4). Both Br₂ and NBS were used as brominating agents in tetrahydrofuran, respectively, and reaction conditions were investigated and optimized regarding the amounts of bromination reagents and reaction temperature (Table 1).

The results showed that: (1) the proportion of dibromo impurity increased significantly as the reaction temperature increased (Table 1, entries 1–7); (2) under the same equiv., NBS was a preferable brominating agent due to less formation of dibromo impurities 18 (Table 1, entries 2 and 7); (3) using 1.22 equiv. of NBS gave the target compound 11 with the highest yield and purity (Table 1, entries 7–10).

In summary, it was found that 1.22 equiv. of NBS was used as the brominating agent to carry out the reaction at 0–10°C and provided the best result. After the reaction, the solvent was removed by concentration under reduced pressure to obtain a mixed solid of product 11 and succinimide. The purification of 11 was achieved by refluxing the mixture in acetonitrile because of its high solubility in acetonitrile.

Based on our knowledge, product 1 prepared from compound 11 by diazotization has not been reported in the literature. Theoretically, 1 could be prepared by diazotization, followed by Sandmeyer reaction. For the Sandmeyer reaction, the corresponding diazonium salt needed to be prepared first, and then the reaction was performed under the catalysis of cuprous salt to obtain the product (Scheme 5). Several commonly available industrial systems for the preparation of diazonium salts to generate compound 1 by Sandmeyer reaction were investigated. The results showed that the yield of the reaction was relatively low (25–46%), which could not meet the requirement of the practical application of scale-up (Table 2).

After carefully studying and analyzing the reaction process of diazonium–Sandmeyer, we found that the yield of the reaction was limited by the diazonium salt formation. The more of the diazonium salts was produced in the solvent, the higher yield would be obtained after work-up. Otherwise,
the reaction would be mess if there were not sufficient diazonium salts formed in the process. As compound 11 was an electron-withdrawing group-substituted aniline, it was difficult to perform salinization thoroughly under the reaction conditions. Therefore, we need to design a route to fully salify 11 to improve the yield of the subsequent diazotization reaction. Considering that 11 was easily soluble in a certain volume of THF, we prepared 11 in THF and introduced hydrogen chloride gas to generate the hydrochloride 17. Intermediate 17 was poorly soluble in THF and could be collected by centrifugation from the solvent THF without further purification. Intermediate 17 was an ideal intermediate in the manufacturing process because it was chemical stable, free of moisture, and less hygroscopic.

After 17 was obtained, the conditions for the diazotization–Sandmeyer reaction with 17 were further screened and optimized (→ Table 3). It was found that when the 1.3 equiv.

### Table 1 Screening conditions of brominating reaction

| Entry | Brominating agent | Brominating agent (equiv.) | Temp (°C) | 11 (%)<sup>a</sup> | 18 (%)<sup>a</sup> | 12 (%)<sup>a</sup> |
|-------|-------------------|---------------------------|----------|-------------------|-------------------|-------------------|
| 1     | Br<sub>2</sub>     | 1                         | −20 to −10 | 92                | 1.1               | 5.5               |
| 2     | Br<sub>2</sub>     | 1                         | −10 to 0  | 93                | 2.8               | 2.5               |
| 3     | Br<sub>2</sub>     | 1                         | 0–10      | 90                | 3.5               | 1.8               |
| 4     | Br<sub>2</sub>     | 1.1                       | −20 to −10 | 95                | 3.2               | 1.1               |
| 5     | NBS               | 1                         | 20–30     | 92                | 3.4               | 1.5               |
| 6     | NBS               | 1                         | 10–20     | 91                | 3.0               | 2.6               |
| 7     | NBS               | 1                         | 0–10      | 92                | 1.5               | 3                 |
| 8     | NBS               | 1.1                       | 0–10      | 93                | 1.7               | 1.5               |
| 9     | NBS               | 1.2                       | 0–10      | 95                | 1.8               | 1.1               |
| 10    | NBS               | 1.22                      | 0–10      | 96                | 1.8               | 0.8               |

<sup>a</sup>HPLC analysis. The conditions for HPLC method were: Thermo scientific C18 column, C18 (5 μm, 150 mm × 4.6 mm); mobile phase A (0.1% H<sub>3</sub>PO<sub>4</sub> in water) and B (CH<sub>3</sub>OH): 35:65 A/B—10:90 A/B, 25 minutes, 10:90 A/B, 10 minutes, 10:90 A/B—35:65 A/B, 1 minute, 35:65 A/B, 9 minutes; detection at 210 nm; flow rate = 1.0 mL/min.

### Scheme 5 The preparation of diazonium salt and the final desired product 1.

![Scheme 5](image)

### Table 2 Screening acid system of diazotization<sup>a</sup> and Sandmeyer reaction<sup>b</sup>

| Entry | Acid system         | Yield (%) |
|-------|---------------------|-----------|
| 1     | Conc. HCl           | 30        |
| 2     | Conc. H<sub>3</sub>PO<sub>4</sub> | 25        |
| 3     | Conc. H<sub>2</sub>SO<sub>4</sub> | 40        |
| 4     | Conc. HCl/AcOH      | 35        |
| 5     | Conc. H<sub>2</sub>SO<sub>4</sub>/AcOH | 46        |

<sup>a</sup>1.15 equiv. of NaNO<sub>2</sub> was used, and the reaction performed at −5 to 5°C, unless otherwise stated.

<sup>b</sup>CuCl/conc. HCl was used.

### Table 3 Screening of diazotization<sup>a</sup> and Sandmeyer reaction<sup>b</sup> using 17

| Entry | NaNO<sub>2</sub> (equiv.) | Yield (%) |
|-------|---------------------------|-----------|
| 1     | 1.1                       | 85        |
| 2     | 1.2                       | 88        |
| 3     | 1.3                       | 92        |

<sup>a</sup>The reaction was performed at −5 to 5°C, using conc. HCl as an acid system.

<sup>b</sup>CuCl/conc. HCl was used.

of NaNO<sub>2</sub> was used, and the reaction temperature was −5 to 5°C, the final desired product 1 was obtained with the highest yield (92%).

**Conclusion**

In this article, a novel process for the large-scale production of 1, a key intermediate of SGLT2 inhibitors, was developed. Using cheap and easily available dimethyl terephthalate (13) as the raw starting material, 1 was prepared in six steps, including nitration, hydrolysis, hydrogenation, esterification, bromination, and diazotization. The preparation scale was approximately 70 kg with the total yield of 24%. Compound 11 and its hydrochloride salt 17 are new compounds and chemically stable. Through process screening and optimization, the amount of dibromo impurity 18 produced in the bromination reaction of compound 11 was reduced significantly. The salt-forming reaction of intermediate 11 not only increased the stability of the corresponding compound, but also improved the yield of the subsequent diazotization reaction and Sandmeyer.
reaction (from 40 to 92%). This synthetic process is appealing in industry because it starts from cheap and easily available materials, avoids unfriendly oxidative procedure, and harvests high yield and purity of products.

Experimental Section

General

Unless otherwise specified, nuclear magnetic resonance (1H NMR) spectra were recorded on a Bruker Biospin 400 MHz instrument using tetramethylsilane as the internal standard. All chemical shifts were reported in ppm. Mass spectrometry (MS) spectra were obtained on an Agilent 6460 QQQ mass spectrometer (Agilent, United States) analysis system. All materials were obtained from commercial suppliers and were used without further purification. Reactions' time and purity of the products were monitored by thin-layer chromatography (TLC) on FLUKA silica gel aluminum cards (0.2 mm thickness) with fluorescent indicator 254 nm. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Reaction progress and compound purity were determined by high-performance liquid chromatography (HPLC).

The conditions of HPLC method were: Thermo scientific-C18 column, C18 (5 μm, 150 mm × 4.6 mm); mobile phase A (0.1% H3PO4 in water) and B (CH3OH), from 35:65 A/B to 10:90 A/B over 25 minutes, and keep 10:90 A/B over 10 minutes, from 10:90 A/B to 35:65 A/B over 1 minutes, and keep 35:65 A/B over 25 minutes, and keep 10:90 A/B over 10 minutes, from material temperature not more than 30°C. After the addition, starting (1,200 kg) at temperature not more than 30°C in another after the completion of the reaction con...
bubbled from the bottom of the reactor at temperature below 30°C and stirred for 1 hour. The resulting slurry was filtered with a centrifuge. The filter cake was washed with THF (50 kg), and air-dried to give 17 as a brown solid (96.9 kg, 70%). ESI-MS (m/z): calcd. for C₉H₆Br₂NO₄ [M – H]⁻ 271.9637, found: 271.95, 273.95. ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (s, 1H, ArH), 7.17 (s, 1H, ArH), 3.84 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 168.15, 166.44, 150.50, 136.98, 135.91, 119.14, 113.43, 102.20, 53.08.

5-Bromo-2-chloro-4-(methoxycarbonyl)benzoic Acid (1)
A clean 1,000 L glass-lined reactor was charged with 31% HCl (368 kg), and then 17 (80.00 kg, 257.6 mol) and water (140 kg) were added thereto. Then, the reaction was cooled to –5 to 0°C, and then NBS (3.56 g, 0.02 mol) was added. The reaction mixture was stirred for 3 hours at room temperature. The reaction solution was concentrated. The residue was purified by column chromatography. ESI-MS (m/z): calcd. for C₉H₆Br₂NO₄ [M – H]⁻ 290.9138, found: 290.91, 292.91. ¹H NMR (400 MHz, DMSO-d₆) δ 14.00 (s, 1H, COOH), 8.09 (s, 1H, COOH), 7.97 (s, 1H, ArH), 7.88 (s, 1H, ArH), 7.17 (s, 1H, ArH), 3.84 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 118.79 (C₂), 53.54.

Supporting Information
Copies of NMR spectra and MS of compounds 12, 16, 17, 1, and 18 are included in the Supporting Information (~ Figs. S1–S14 [online only]).

Conflict of Interest
We declared no conflict of interest.

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