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Safe and Efficient Decarboxylation Process: A Practical Synthetic Route to 4-Chlorobenzo[*b*]thiophene

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Supporting Information

ABSTRACT: We established an improved synthetic route to 4-chlorobenzo[*b*]thiophene, a key intermediate in brexpiprazole synthesis, via a practical decarboxylation process in three steps. Thermal analysis demonstrated that the coexistence of the decarboxylated product with DBU should be avoided and that removal of the product outside the reactor was vital. Our process yields the target compound by distillation under reduced pressure and is safe, highly batch efficient, cost-effective, and high yielding. Furthermore, manufacturing on a pilot scale was also accomplished through our approach.

INTRODUCTION

Brexpiprazole **1** is a serotonin−dopamine activity modulator (SDAM) for the treatment of schizophrenia and is used as adjunctive therapy for the treatment of clinical depression.[1] Its new drug application (NDA) has recently been approved by the US Food and Drug Administration (FDA), and clinical trials for its application in attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and agitation associated with dementia of the Alzheimer's type are currently underway.

In the preparation of brexpiprazole **1**, 4-chlorobenzo[*b*]-thiophene **2** is a key intermediate, and therefore, cost reduction for the synthesis of **2** is directly related to the cost of brexpiprazole production.[2] To achieve a more efficient synthetic route to **2**, the selection of an appropriate starting material is particularly important. Several approaches to benzo[*b*]thiophene analogs have been reported, with reactions starting from benzaldehydes and thioglycolic acid (TGA) being regarded as practical and economical because of the wide availability of both materials.[2b,3] Of these approaches, we considered the preparation of **2** from 2,6-dichlorobenzaldehyde **3**, which was considered a desirable starting material in terms of its regioselectivity and low material expenses (Scheme 1, Conventional Method).[4] This route requires two transformations, namely, the formation of benzothiophene carboxylic acid **4** and its subsequent decarboxylation. Given the lower material cost of **3** and fewer number of steps to **2**, this strategy was deemed reasonable.

Generally, in the synthesis of benzothiophene analogues from their corresponding carboxylic acids, decarboxylation using copper/quinoline is widely utilized, due to its ease of handling and the availability of each material.[5] However, this general procedure demands copper metal and quinoline which are unfavorable due to residual amounts in active pharmaceutical ingredients (APIs). In particular, residual quinoline should be strictly controlled because of genotoxic issues, and therefore, alternative strategies are recommended. While there have been several publications reporting decarboxylation by other methods, including the use of copper/phenanthroline,[6] gold,[7] and silver,[6a,8] we focused on decarboxylation using DBU.[2c,9] While this method is advantageous in not requiring metals or genotoxic chemicals, it does have some drawbacks for its application to large-scale production. For example, this method sometimes requires special apparatus, such as microwaves or tube reactors, to boost reaction rates. In addition, solvents with higher boiling points must be used since the reaction normally occurs at higher temperature. Especially, these solvents are difficult to remove from the reaction mixture, leading to the problem of residual solvents in APIs. Thus, these issues result in high costs, batch inefficiency, and a large heat capacity. To resolve these issues, we believed that carrying out this reaction in the absence of solvents would be ideal. We therefore report the successful synthesis of 4-chlorobenzo[*b*]thiophene **2** from 2,6-dichlorobenzaldehyde **3** with a practical decarboxylation via intermediate **5** (Scheme 1, Our Method).

RESULTS AND DISCUSSION

We first examined the chemical transformation of **3** to **4**. Based on a previously reported method,[2b] we attempted the reaction of **3** with 1.3 eq of TGA and 3 eq of aqueous KOH under reflux. After 3 h, the resulting mixture gave the target compound **4** in 62% isolated yield. A similar result was obtained when KOH was replaced with NaOH. Since the air oxidation of TGA and sublimation of **3** during the reaction hindered an improvement in yield, we carried out the reaction under N_2 using a mixture of DME/water as solvent to dissolve sublimed **3**. Following reaction optimization, **4** was obtained in the highest yield (82%) with the use of 1.3 eq of TGA and 3 eq of aqueous NaOH in water/DME (7:3) under reflux.

We subsequently investigated the decarboxylation of **4** for the preparation of **2**, beginning with the neat reaction of **4** with DBU under Ar atmosphere at 200 °C. Although the reaction reached completion using 1 eq or even a catalytic amount of DBU, the resulting mixture turned black, and decolorization of **2** was problematic. Since we assumed that oxygen was responsible for causing this color, these reactions were repeated under Ar to exclude oxygen. However, no improvement was

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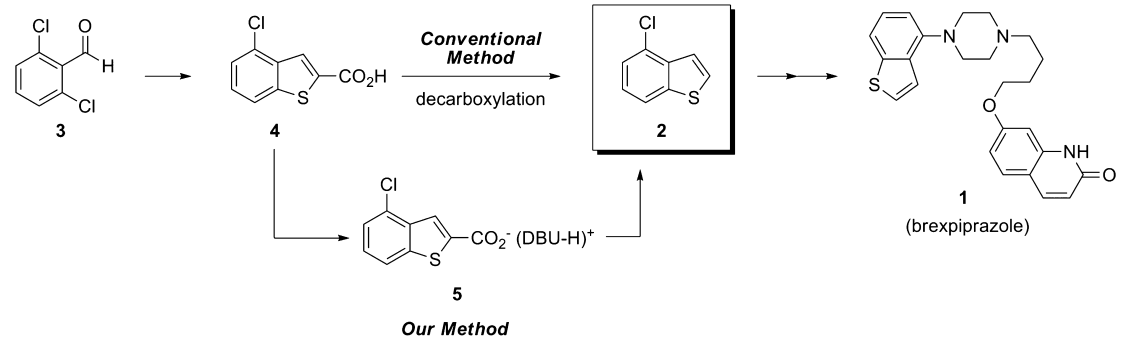
Scheme 1. Proposed Synthetic Route to Thiophene 2 from Aldehyde 3



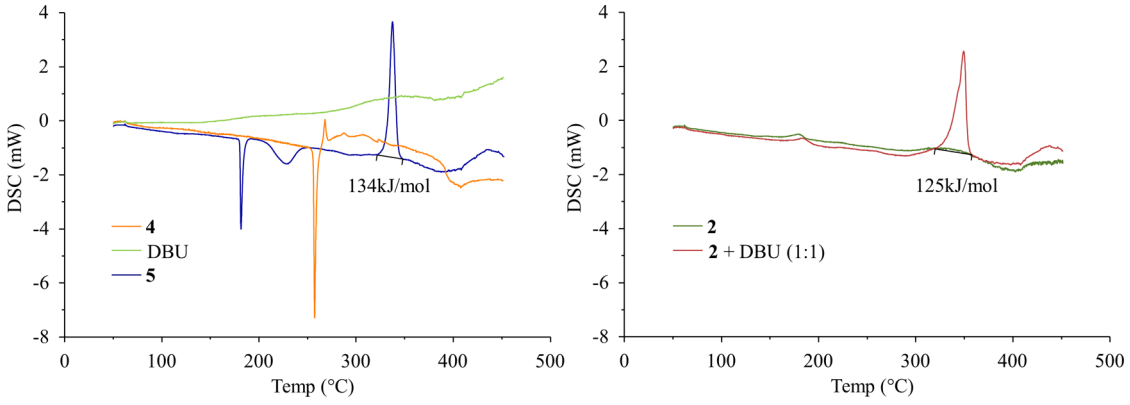


Figure 1. DSC analysis of the relevant compounds.

observed. This result was disappointing, as for APIs, color should generally be avoided.

To understand the characteristics of the decarboxylation reaction, we conducted differential scanning calorimetry (DSC) measurements on 2 mg of sample under Ar. An aluminum pan with a pierced lid was used, along with a linear heating rate of 3 °C/min. When **4** and DBU were analyzed individually, no conspicuous peaks regarding exotherm were observed (Figure 1, left graph). To evaluate the reaction system, a 1:1 molar ratio mixture of **4** and DBU (**5**, DBU salt of **4**) was then prepared. Although two endothermic peaks representing the melting point of **5** and the reaction heat were detected, an exothermic peak was also observed at 320 °C (Figure 1, left graph). From the exothermic onset temperature obtained here, the ADT_{24} (the temperature at which TMR_{ad} is 24 h, as derived from adiabatic measurements) of **5** was calculated to be 162 °C, based on the report by Hungerbühler et al.[10] This indicated that the decarboxylation reaction at 200 °C could not be considered safe.

To investigate this in further detail, additional measurements were carried out. Surprisingly, although the DSC result from **2** did not show a noticeable exothermic peak, a similar exothermic peak to **5** was observed in the mixture of **2** with DBU (Figure 1, right graph). This suggests that decarboxylated product **2** reacted with DBU to generate heat, meaning that the two should not be present in the same reactor at high temperature. As we found that the DBU salt **5** could be isolated as a crystal, we herein proposed a method where **4** was transformed into the DBU salt **5**, followed by heating of intermediate **5** under reduced pressure in the absence of solvents, to give **2** following distillation.

We then focused on optimization for the synthesis of compound **5**. While the formation of **5** proceeded smoothly in methanol, its high solubility to methanol resulted in a drop in yield following crystallization. It was therefore necessary to evaporate methanol at high temperature in combination with solvents of higher boiling point. Butyl acetate was found to be the optimal solvent for this procedure, and methanol was successfully removed to give **5** in high yield (~98%).

In the subsequent decarboxylation, compound **5** was placed in the reactor and heated to 190−200 °C under reduced pressure. When the external temperature reached 180 °C, **5** began to melt, changing from a solid to a viscous liquid. Distillation of this viscous liquid gave a colorless distillate, which contained compound **2**. As the distillate was a mixture of **2** with DBU, it was acidified using HCl to remove DBU.[11] Following extraction with ethyl acetate, the solution was concentrated to afford **2** as a pure colorless oil in high yield. Our strategy therefore appeared to be the only successful approach for preventing the coexistence of decarboxylated **2** and DBU within the reaction system, by expelling the mixture by distillation. In addition, our method is superior as it allows simultaneous purification and decarboxylation. Our results also confirmed that the coloring was not caused by oxygen but by an intermolecular reaction between **2** and DBU.[12]

To acquire safety information for our process, we investigated the relationship between temperature and pressure. When the reaction was carried out at 7.2 kPa, the vapor temperature of **2** during the distillation was 152 °C, which was less than the calculated ADT_{24} value. Actually, 7.2 kPa is feasible pressure also on large scale; therefore, it was found that this decarboxylation could be performed safely. As a result, no colored material was observed in the reactor or in the distillate, and we established a safer pyrogenic reaction that allowed simultaneous distillation and decarboxylation. Furthermore, this

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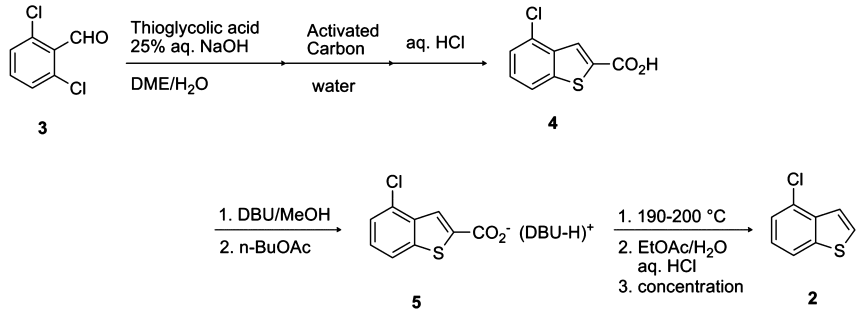
Scheme 2. Established Synthetic Route to 2



was also a highly batch efficient process, which did not require additional reagents or solvents.

With the optimized reaction conditions in hand, we manufactured **2** on a pilot scale starting from ~20 kg of **3** (Scheme 2). Compound **3** was heated at reflux in the presence of TGA and 25% aqueous NaOH under N_2 in a mixed solvent (water/DME) to afford **4** as its sodium salt. Treatment with HCl afforded **4** in good yield (82%). The reaction of **4** with DBU was then achieved, followed by concentration of the reaction mixture using butyl acetate, allowing the elimination of methanol. Cooling of the resulting slurry afforded **5** in excellent yield (~98%). Finally, **5** was heated under reduced pressure, and the distillate was washed and concentrated to give pure **2** as a colorless oil in excellent yield (18.69 kg, ~ 93%). This gave an overall yield of approximately 75% over three steps.

CONCLUSION

A practical route to the preparation of 4-chlorobenzo[*b*]-thiophene **2**, a key intermediate in the synthesis of brexpiprazole, was developed. Our synthetic route began from 2,6-dichlorobenzaldehyde, a low cost material, to give target compound **2** in good yield over three steps. Thermal analysis by DSC offered crucial information regarding the decarboxylation step to allow the reaction to proceed safely. In addition, our decarboxylation process allowed the distillation of the decarboxylated compound under reduced pressure to give the colorless and pure **2**. Our method fulfills a number of key process requirements, including safety, high batch efficiency, high yield, and low cost. Finally, using this method, we succeeded in manufacturing **2** on a pilot scale. Following further optimization, this procedure should be applicable on a commercial scale. Studies into the scale up of this process for commercial production are currently underway.

EXPERIMENTAL SECTION

All commercially available materials and solvents were used as received without any further purification. The conversion of **3** to **4** was monitored by high performance liquid chromatography (HPLC) analysis using a Shimadzu SLC 10A*vp* System. NMR spectra were recorded on a Bruker-Spectrospin 300 with TMS (tetramethylsilane) as an internal standard in DMSO-d_6/$CDCl_3$. Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS. The purity of **2** was measured by gas chromatography using an Agilent technology GC 6890 System. Differential scanning calorimetry (DSC) was performed using a Shimadzu DSC-60A system.

4-Chlorobenzo[*b*]thiophene-2-carboxylic Acid (4). Purified water (95.9 L), 1,2-dimethoxyethane (20.9 kg), and 25% NaOH aq. (54.9 kg, 341.29 mol) were added to the reactor, and the mixture was degassed over three vacuum/nitrogen cycles. TGA (13.7 kg, 147.89 mol) was then added, and the resulting mixture stirred under a flow of N_2. After 15 min, 2,6-dichlorobenzaldehyde **3** (19.91 kg, 113.76 mol) was added and heated at reflux for 9 h (N_2 flow continued until just before reflux). The mixture was then cooled and stirred at <5 °C for 1 h. The resulting precipitate was filtered and washed with purified water (60 L) to give a white solid, which was dissolved in purified water (200 L) and heated to 80 °C. Activated carbon (0.4 kg) was then added and the mixture stirred at 90 °C for 30 min. The resulting suspension was filtered at 80−90 °C, following the addition of purified water (20 L). Following filtration, the filtrate was heated to >70 °C, conc. HCl (11.7 kg, 113.76 mol) and purified water (11.7 L) were added, and stirring was carried out at 75 °C for 15 min. The slurry was then cooled <30 °C, filtered, and washed with purified water (200 L). The obtained wet cake was dried at 80 °C to give the desired product **4** as a white solid (19.85 kg, 82.06%). mp 260 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (d, 1H, J = 11.6, 7.7 Hz), 7.56 (dd, 1H, J = 17.8, 7.7 Hz), 8.03 (d, 1H, J = 0.7 Hz), 8.07 (td, 1H, J = 7.6, 0.9 Hz), 13.19 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 122.21, 125.01, 126.84, 127.99, 128.96, 136.50, 136.57, 142.55, 163.10. Elemental analysis calcd for C: 50.83%, H: 2.37%, found C: 50.84%, H: 2.21%.

2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-*a*]azepin-1-ium 4-Chlorobenzo[*b*]thiophene-2-carboxylate 5. A mixture of **4** (19.81 kg, 93.16 mol), methanol (40 L), and DBU (14.18 kg, 93.16 mol) was stirred to give a homogeneous solution. Butyl acetate (99 L) was then added, and the mixture was heated to 110 °C to remove methanol by evaporation. The mixture was cooled to <25 °C, butyl acetate was added (19.8 L), and stirring continued at <25 °C for 3 h. The resulting slurry was filtered and washed with butyl acetate (29.6 L) to give a wet cake, which was dried at 80 °C to give **5** as a white solid (33.31 kg, 97.97%). Mp 182.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (m, 6H), 1.80−1.75 (m, 2H), 2.98−2.94 (m, 2H), 3.45−3.39 (m, 4H), 3.55−3.51 (m, 2H), 7.31−7.20 (m, 2H), 7.69 (dd, 1H, J = 3.9, 0.6 Hz), 7.97 (s, 1H), 13.19 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.51, 24.03, 26.70, 28.88, 31.99, 38.01, 48.36, 53.94, 121.04, 123.00, 125.17, 126.61, 128.98, 138.21, 142.43, 146.85, 165.91, 167.20. Elemental analysis calcd for C: 59.25%, H: 5.80%, N: 7.68%, found C: 59.10%, H: 5.44%, N: 7.53%.

4-Chlorobenzo[*b*]thiophene (2). **5** (43.58 kg, 119.43 mol) was placed in the reactor, heated to 190−200 °C, and distilled under reduced pressure. Ethyl acetate (131 L) and purified water (44 L) were added to the obtained distillate. The aqueous layer was removed, and a further portion of purified water (22 L) and conc. HCl (1.31 kg, 0.03 wt %) were added to the organic layer. After washed with purified water (33 L), the

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residual ethyl acetate solution was evaporated at atmospheric pressure then reduced pressure to give a **2** as a colorless oil (18.69 kg, 92.78%) in >99.9% purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, 1H, J = 7.8 Hz), 7.36 (dd, 1H, J = 7.8, 0.9 Hz), 7.50 (d, 1H, J = 5.7 Hz), 7.52 (d, 1H, J = 5.7 Hz), 7.76 (d, 1H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.12, 122.40, 125.02, 127.43, 128.93, 138.06, 141.07. Elemental analysis calcd for C: 56.98%, H: 2.99%, found C: 56.76%, H: 2.94%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00340.

Characterization spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

SDAM, serotonin-dopamine activity modulator; NDA, new drug application; FDA, Food and Drug Administration; ADHD, attention-deficit hyperactivity disorder; PTSD, post-traumatic stress disorder; TGA, thioglycolic acid; DME, dimethoxyethane; API, Active Pharmaceutical Ingredients; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DSC, differential scanning calorimetry; ADT_{24}, temperature at which TMR_{ad} is 24 h derived from adiabatic measurements; TMR_{ad}, time to maximum rate under adiabatic conditions

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