Organic Process Research & Development

Technical Note

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An Improved Synthesis of 4-(1-Piperazinyl)benzo[*b*]thiophene Dihydrochloride

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Supporting Information

ABSTRACT: 2-Chloro-6-fluorobenzaldehyde was converted to 4-(1-piperazinyl)benzo[*b*]thiophene dihydrochloride (**18**), an intermediate in the synthesis of brexpiprazole, via a five-step sequence in 54% overall yield. This procedure requires no expensive catalyst and avoids the side products produced in the coupling step in the reported process. Several kilograms of compound **18** were prepared using this economical and scalable process.

INTRODUCTION

Brexpiprazole (**1**) (Figure 1), a serotonin−dopamine activity modulator, is an investigational new drug currently in phase-III

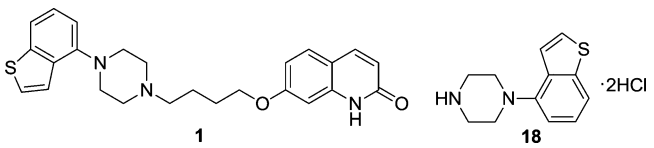


Figure 1. Brexpiprazole (**1**) and intermediate **18**.

clinical trials for the treatment of depression, schizophrenia, and attention deficit hyperactivity disorder.[1] Brexpiprazole is also considered to be a possible successor to the top-selling antipsychotic agent aripiprazole.[2]

The synthesis of 4-(1-piperazinyl)benzo[*b*]thiophene hydrochloride (**8**) was originally accomplished by Yamashita and co-workers (Scheme 1).[3] In the first step, 4-bromobenzo[*b*]-thiophene was coupled with unprotected piperazine using tris(dibenzylideneacetone)dipalladium as the catalyst. However, this process suffered from the formation of impurities **2** and **3** (Figure 2), which are difficult to remove via a crystallization method. An alternative process using protected piperazine and an expensive catalyst in order to minimize the generation of impurities was reported by Shinhama and co-workers (Scheme 1).[4]

Herein we report a new process for producing 4-(1-piperazinyl)benzo[*b*]thiophene hydrochloride. The strategy of replacement rather than coupling was used to construct the arylpiperazine in order to avoid the formation of impurities in the reported coupling step and the use of an expensive catalyst. The improved process has a number of industrial advantages such as economical material cost, convenient operation, and relatively high yield.

RESULTS AND DISCUSSION

Substituted phenylpiperazine was constructed through the S_NAr reaction of 2-chloro-6-fluorobenzaldehyde (**11**) and *tert*-butyl piperazine-1-carboxylate (**9**) in *N*-methyl-2- pyrrolidinone in the presence of *N*,*N*-diisopropylethylamine (DIPEA) (Scheme 2).[5,6] Fluorine atom and chlorine atom are both active at the ortho position of the aldehyde group, so the leaving group ability ($F^- > Cl^-$) decides the regioselectivity of the S_NAr reaction. The amount of compound **9** has an important influence on the reaction. Lower amounts of compound **9** gave incomplete conversion of compound **11**, and higher amounts gave more of impurity **16** (Figure 3). Finally, optimum equivalent of compound **9** was found to be 1.1 equiv, based on compound **11**. HPLC result indicated the reaction mixture contained 93% of compound **12**, approximate 5% of byproduct **15** and 1% of impurity **16**. Fortunately, byproduct **15** was subsequently converted to desired intermediate **13** in the cyclization step, and impurity **16** can be conveniently removed in the following purification.

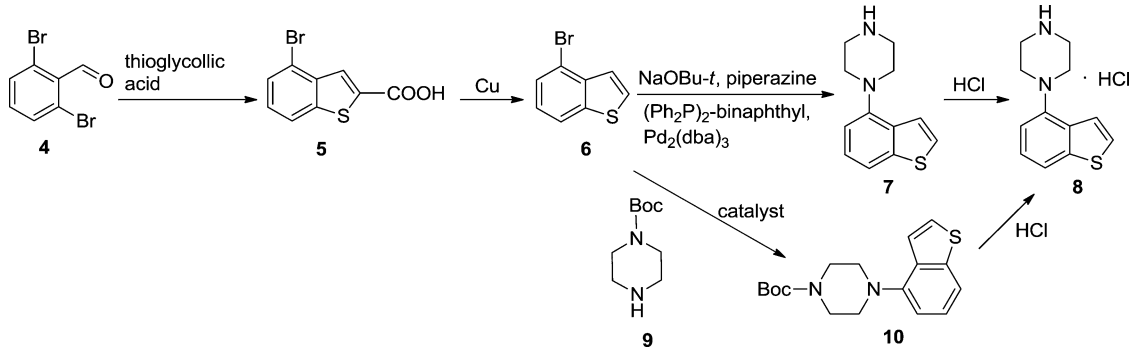
Alternative solvents for the S_NAr reaction were evaluated. The use of acetonitrile was avoided since very low conversion of dihalide **11** to arylpiperazine **12** was observed even at its boiling point (81 °C). *N*-Methyl-2-pyrrolidinone was found to be a good solvent for this step in terms of both product yield and quality. Potassium carbonate, sodium carbonate, and triethylamine also worked as basic reagents giving good yields. After completion of the reaction, the reaction mass was added to a mixture of acetone and water. The ratio of acetone and water was important for the precipitation of compound **12** from the mixture, as a higher ratio of acetone resulted in a yield reduction. The precipitated compound **12** was purified by reslurrying in *n*-heptane, which can be recovered in high yield and reused in the next batch, to give compound **12** as a white solid in excellent yield (94%) containing 4% byproduct **15**.

Cyclization of compound **12** with thioglycollic acid ethyl ester in *N*,*N*-dimethylformide (DMF) in the presence of potassium carbonate furnished compound **13**, which was hydrolyzed in situ and acidified to give compound **14**.[7−9] Several bases were evaluated for their effect on this cyclization

Received: January 27, 2015

DOI: 10.1021/acs.oprd.5b00027
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Reported synthetic routes for 4-(1-piperazinyl)benzo[*b*]thiophene hydrochloride (8)



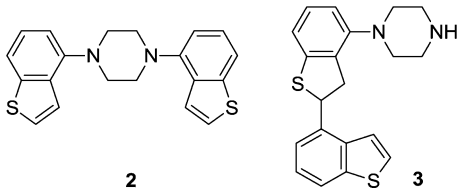


Figure 2. Impurities **2** and **3**.

in DMF, such as DIPEA, potassium carbonate, and triethylamine. When DIPEA was used as the base, the conversion of compound **12** was only around 30%, even with excess thioglycollic acid ethyl ester, as well as triethylamine.

Since it is tedious to recover DMF from mixtures of DMF and water, to make the process greener we tried to use other solvents, such as toluene, dioxane, acetonitrile, and ethanol. However, the reactions in these solvents suffered from low conversion of compound **12** and decreased yield.

Since 1 equiv of water (based on the charge of **12**) was generated in the cyclization, upon heating of the aqueous reaction mixture in the presence of potassium carbonate, the potassium salt of **14** was found in the reaction mass in a ratio of 10−20%. After completion of the cyclization, a solution of potassium hydroxide in water was directly added to the cooled reaction mixture to hydrolyze **13**. Subsequently, the reaction mass was extracted with ethyl acetate to remove some impurities, and then the aqueous layer was acidified to furnish **14** as a white precipitate in satisfying yield (80% over two steps) and purity (99.4%). The precipitate was directly used in the next step without further purification.

Alternatively, a more convenient and efficient cyclization of compound **12** with thioglycollic acid was successful on a several-gram scale in the presence of sodium hydroxide.

In the published process for the decarboxylation of benzothiophene-2-carboxylic acid, quinoline was used as the solvent and catalyst as well.[4] In the present process, the use of quinoline is avoided, since it is a toxic and high-boiling-point (238 °C) solvent, which made the recovery hazardous for the working environment. Replacement of quinoline by DMF led to almost the same yield, and the solvent can be conveniently recovered under reduced pressure in situ.

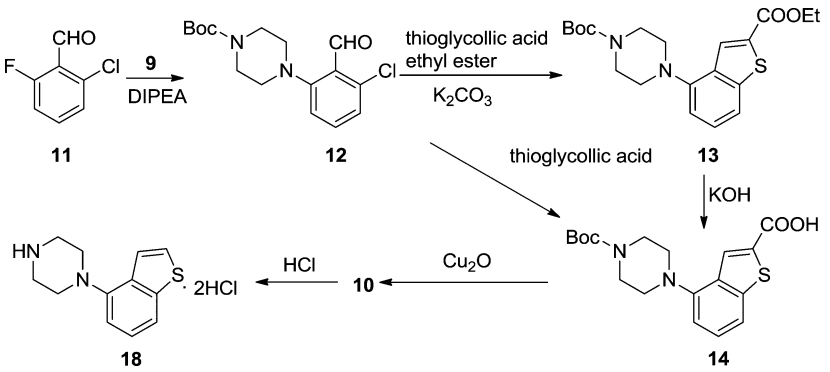
The *tert*-butoxycarbonyl protecting group on piperazine in compound **14** is not stable enough in heated DMF, so that about a 6% yield of impurity **17** was found in the LC−MS spectrum of the reaction mixture. To our delight, most of impurity **17** can be removed simply by purification in ethanol, and the remaining impurity **17** was converted to the desired compound **18** in the deprotection step. After the purification in ethanol, compound **10** was simply obtained in 85% yield with excellent purity (98.7%).[10,11]

Compound **10** was treated with excess concentrated hydrochloric acid in methanol. After the reaction end point, methyl *tert*-butyl ether was added to the reaction mass as an antisolvent to promote the precipitation of crude 4-(1-piperazinyl)benzo[*b*]thiophene dihydrochloride (**18**), which was further purified in methyl *tert*-butyl ether to give compound **18** with 99.8% purity on HPLC.

CONCLUSION

An improved process for 4-(1-piperazinyl)benzo[*b*]thiophene hydrochloride, including the replacement reaction of 2-chloro-6-fluorobenzaldehyde with 1-*tert*-butoxycarbonylpiperazine, has been provided. It affords a total yield of 54% over five steps and a purity of 99.8%. Because of the good leaving ability of fluorine, the synthesis of compound **18** was successfully

Scheme 2. Improved synthetic route for 4-(1-piperazinyl)benzo[*b*]thiophene dihydrochloride (18)



DOI: 10.1021/acs.oprd.5b00027
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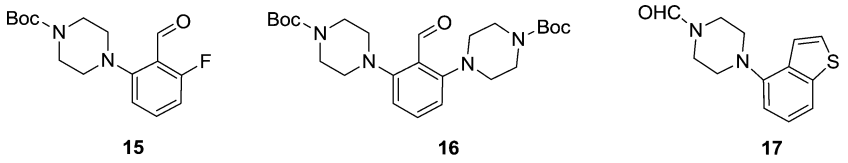

Figure 3. Structures of **15**–**17**.

accomplished by this new process. The resulting new intermediates have some industrially favorable physical properties. For example, compounds **14** and **10** can be simply purified from the reaction mixtures with satisfying purities. The advantages ensure that the efficient, cost-effective, and industrially convenient process will be employed for commercial production.

EXPERIMENTAL SECTION

General Procedures. All commercially available materials and solvents were used without any further purification. TLC analyses were performed on Merck silica gel 60 F_{254} plates. ^{1}H NMR spectra were recorded at room temperature on a Bruker AMX-400 using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT-95/711 spectrometer. Reversed-phase HPLC analyses were performed on an Agilent 1100 HPLC system with a DAD detector (area normalization). HPLC method A: Waters XTerra Phenyl column (5 μm, 4.6 mm × 250 mm); flow rate = 1 mL/min; 30 °C; gradient elution from 30:70 A/B to 80:20 A/B over 20 min, where A = acetonitrile and B = 0.1% H_3PO_4 in water; UV detection at 210 nm. HPLC method B: Waters XTerra MS C18 column (4.6 mm × 150 mm); flow rate = 1 mL/min; 30 °C; gradient elution from 10:90 A/B to 80:20 A/B over 20 min, where A = acetonitrile and B = 0.02 M KH_2PO_4 (pH 6.0); UV detection at 210 nm.

***tert*-Butyl 4-(3-Chloro-2-formylphenyl)piperazine-1-carboxylate (12).** A mixture of 2-chloro-6-fluorobenzaldehyde (5 kg, 31.52 mol), *tert*-butylpiperazine-1-carboxylate (6.46 kg, 34.67 mol), DIPEA (7.80 L, 47.28 mol), and *N*-methyl-2-pyrrolidinone (25 L) was heated at 95 °C overnight under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into a prepared mixture of water (33 L) and acetone (17 L). The resulting suspension was stirred for 15 min and filtered, and the wet cake was washed with water and dried to give a yellow solid, which was slurried in heated *n*-heptane (30 L) to give compound **12** (9.62 kg, 94% yield) as a white solid containing 4% compound **15**. HPLC for compound **12** (t_R = 14.4 min, identical to authentic sample) 94% purity, compound **15** (t_R = 7.6 min); HPLC method A. The ^{1}H NMR data were identical with those in the literature.[5]

12: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 3.49 (s, 4H), 2.96 (s, 4H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.24, 155.69, 153.80, 134.62, 134.34, 125.38, 124.31, 118.70, 79.05, 52.88, 43.77 (br), 42.72 (br), 28.03. MS (ESI, eV): m/z = 325.1 $[M + H]^+$.

4-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)benzo[*b*]thiophene-2-carboxylic Acid (14). *Method A.* A three-neck bottle was charged with compound **12** (3 kg, 9.24 mol), potassium carbonate (5.11 kg, 36.96 mol), and DMF (15 L). The mixture was stirred for 20 min at room temperature, and thioglycollic acid ethyl ester (1.21 L, 11.04 mol) was added. The reaction mixture was stirred at 90 °C overnight to give the reaction mass containing compound **13**. Potassium hydroxide aqueous solution (8.28 L, 16.56 mol) was added, and the reaction mixture was stirred at 60 °C for 5 h, cooled to room temperature, and extracted with ethyl acetate. Then the pH of the aqueous phase was adjusted to 5 using 4 N HCl, and the precipitate was collected by filtration, washed with water, and dried to give compound **14** (2.68 kg, 80% yield over two steps). HPLC for compound **14** (t_R = 12.5 min, identical to authentic sample) 99.4% purity; HPLC method A.

Method B. A three-neck bottle was charged with compound **12** (3 g, 9.24 mmol), sodium hydroxide (1.48 g, 36.92 mmol) and DMF (15 mL). Then the mixture was stirred for 20 min at room temperature. Thioglycollic acid (0.77 mL, 11.08 mmol) was added, and the reaction mixture was stirred at 105 °C overnight, cooled to room temperature, and extracted with ethyl acetate. Then the pH of the aqueous phase was adjusted to 5, and the precipitate was collected by filtration, washed with water, and dried to give compound **14** (2.61 g, 78% yield).

13: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 0.6 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.58 (s, 4H), 3.09–2.97 (m, 4H), 1.43 (s, 9H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.89, 153.84, 149.64, 142.74, 132.66, 131.57, 128.35, 127.93, 117.28, 113.49, 78.97, 61.44, 51.89, 28.03, 14.12. MS (ESI, eV): m/z = 391.2 $[M + H]^+$.

14: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 7.99 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 3.57 (s, 4H), 3.10–2.96 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.42, 153.83, 149.48, 142.79, 133.38, 132.85, 128.00, 127.47, 117.25, 113.28, 78.97, 51.87, 28.04. MS (ESI, eV): m/z = 363.1 $[M + H]^+$, m/z = 361.1 $[M - H]^-$.

***tert*-Butyl 4-(Benzo[*b*]thiophen-4-yl)piperazine-1-carboxylate (10).** A reactor was charged with compound **14** (2.5 kg, 6.90 mol), cuprous oxide (250 g, 1.75 mol), and DMF (10 L). The mixture was purged with nitrogen three times and stirred at 140 °C for 15 h. The reaction mass was cooled to 70–80 °C, and DMF was recovered under reduced pressure to give a residue, which was cooled to ambient temperature and dispersed in ethyl acetate (10 L). The resulting suspension was stirred under reflux for 2 h after the addition of active carbon (75 g) and then hot-filtered. The filtrate was concentrated to obtain crude **10**, which was further purified by reslurrying in ethanol and dried to give compound **10** (1.87 kg, 85% yield). HPLC for compound **10** (t_R = 15.1 min, identical to authentic sample) 98.7% purity; HPLC method A. The ^{1}H NMR data were identical with those in the literature.[4]

10: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 5.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.56 (s, 4H), 3.07–2.93 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.87, 147.94, 140.41, 133.51, 126.03, 125.02, 121.82, 117.03, 112.40, 78.92, 51.60, 28.04. MS (ESI, eV): m/z = 319.1 $[M + H]^+$.

1-(Benzo[*b*]thiophen-4-yl)piperazine Dihydrochloride (18). Compound **10** (1.5 kg, 4.71 mol) was dissolved in

DOI: 10.1021/acs.oprd.5b00027
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methanol (6.8 L), and concentrated hydrochloric acid (2.27 L, 27.27 mol) was added. The reaction mixture was stirred at 50 °C for 1 h. After completion of the reaction, methyl *tert*-butyl ether (10 L) was added to the reaction mixture, which was then stirred 30 min. The precipitates were collected by filtration, washed with methyl *tert*-butyl ether, and then dried to give compound **18** (1.17 kg, 85% yield). HPLC for compound **18** (t_R = 6.3 min, identical to authentic sample) 99.8% purity; HPLC method B.

18: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.65 (s, 2H), 7.75 (d, J = 5.5 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 5.5 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 3.30 (s, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.92, 140.62, 133.40, 126.50, 125.06, 121.91, 117.73, 112.56, 48.52, 43.00. MS (ESI, eV): m/z = 219.1 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for compounds **7**, **8**, **10**, and **12**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Science and Technology Commission of Shanghai Municipality (14431905500) and the National Natural Science Foundation of China (81273366).

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DOI: 10.1021/acs.oprd.5b00027
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