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REGULAR ARTICLE

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Delineating an alternate convergent synthesis of brexpiprazole: a novel use of commercial 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one as precursor to an efficacious Buchwald–Hartwig amination step

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Abstract. Brexpiprazole – an anti-psychotic drug approved for the treatment of schizophrenia – has been synthesized *via* an extremely concise and convergent route, which involves in essence two key C–N bond formation (amination) steps that serve to link the piperazine core between the constituent benzo[*b*]thiophene and 7-butoxyquinolin-2(1*H*)-one fragments. The highlight of this synthesis is the first amination step, which was effected quite efficaciously by a novel palladium mediated Buchwald–Hartwig coupling between *N*-Boc-piperazine and the triflate ester of benzo[*b*]thiophen-4-ol (conveniently prepared in three steps from commercially available 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one). Indeed, even without an extensive screening of catalysts, ligands and reaction conditions, this amination step could be performed quite efficiently with merely 1 mol% catalyst loading, which cleanly afforded in 87% overall yield 1-(benzo[*b*]thiophen-4-yl)piperazine—the starting material for the second C–N bond formation and the final step in the synthesis of Brexpiprazole.

Keywords. Schizophrenia; anti-psychotic drugs; brexpiprazole; Buchwald–Hartwig amination; heterocycles; benzo[*b*]thiophen-4-ol.

1. Introduction

1.1 *Background*

The USFDA approval of the atypical (or, 'second generation') anti-psychotic drug brexpiprazole **1**(Rexulti®, Otsuka Pharmaceutical Company Ltd.) in 2015 strengthened a new way forward in the treatment of schizophrenia, a severe mental disorder that as of 2016, affects more than 21 million people worldwide.[1,2] Most notably, **1** is a partial agonist of the dopamine receptor D_2 and prior to its approval, the only D_2 partial agonist that had reached the market with the approved indication of schizophrenia was its top-selling predecessor aripiprazole **2**(Abilify®).[1a] Projected as a better tolerated variant, brexpiprazole **1** has been reported to have a lesser tendency than **2** to bring about D_2 partial agonist induced adverse effects such as akathisia, insomnia, restlessness and nausea.[1,3] In fact, the Thomson Reuters 2015 annual report named Rexulti® as one of the predicted blockbuster entrants and slated its annual sales to reach $1.353 billion in 2019.[4]

From a structural perspective (and a viewpoint of retrosynthetic analysis as well), brexpiprazole **1** and aripiprazole **2** are broadly similar, and consist essentially of an *N*-arylpiperazine moiety joined by a *n*-butyl linker to a subunit derived from 7-hydroxyquinolinone **3**. Unsurprisingly, the foregoing structural analysis also defines the two key retrosynthetic disconnections which are common to best known syntheses of **1** and **2** (Scheme 1). Thus, the most widely employed method of aripiprazole synthesis involves *N*-alkylation of 1-(2,3-dichlorophenyl)piperazine **4** with 7-(4-halobutoxy)-3,4-dihydroquinolinone **5**; the latter in turn is obtained *via* etherification of 7-hydroxy-3,4-dihydroquinolinone **6** (Scheme 1).[5] Likewise, a majority of the synthetic

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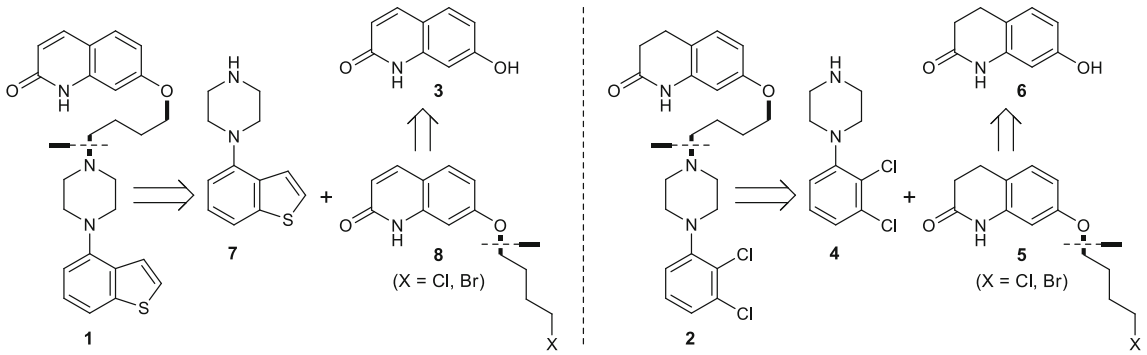
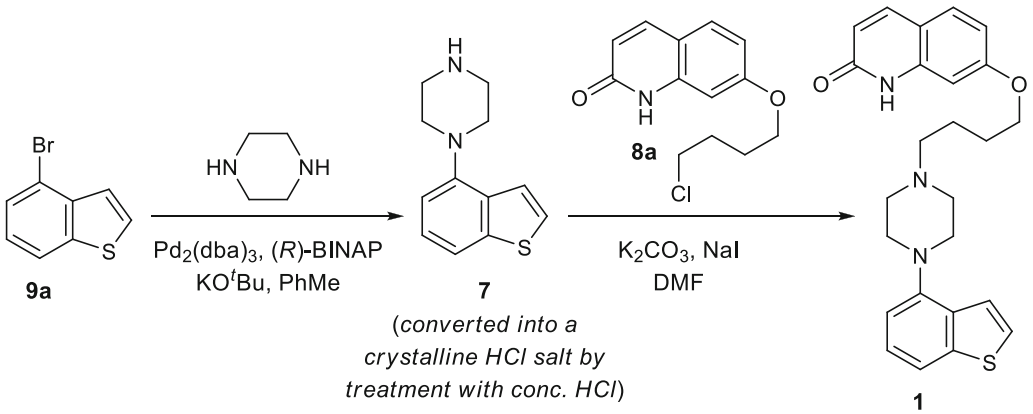


Scheme 1. Commonalities in the retrosynthetic bond disconnection strategies most widely adopted for brexpiprazole **1** and aripiprazole **2**.

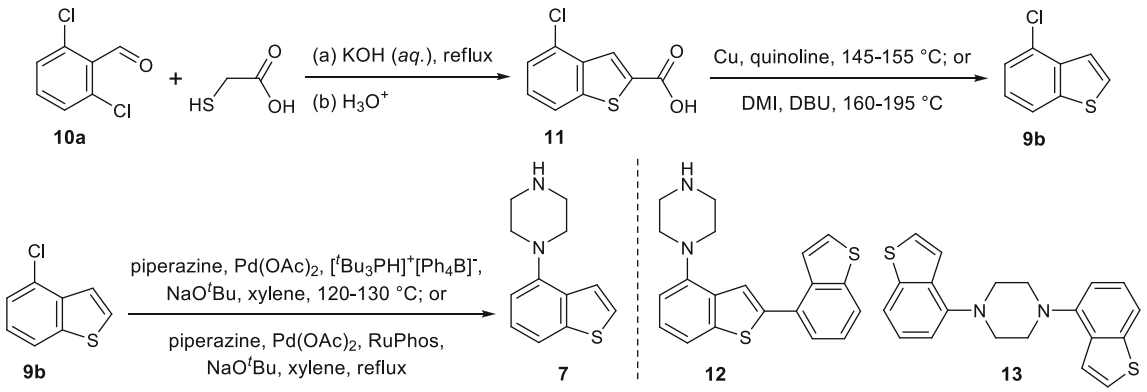


Scheme 2. Synthesis of the key intermediate **7** and its elaboration to **1** (Otsuka; WO 2006/112464 A1).

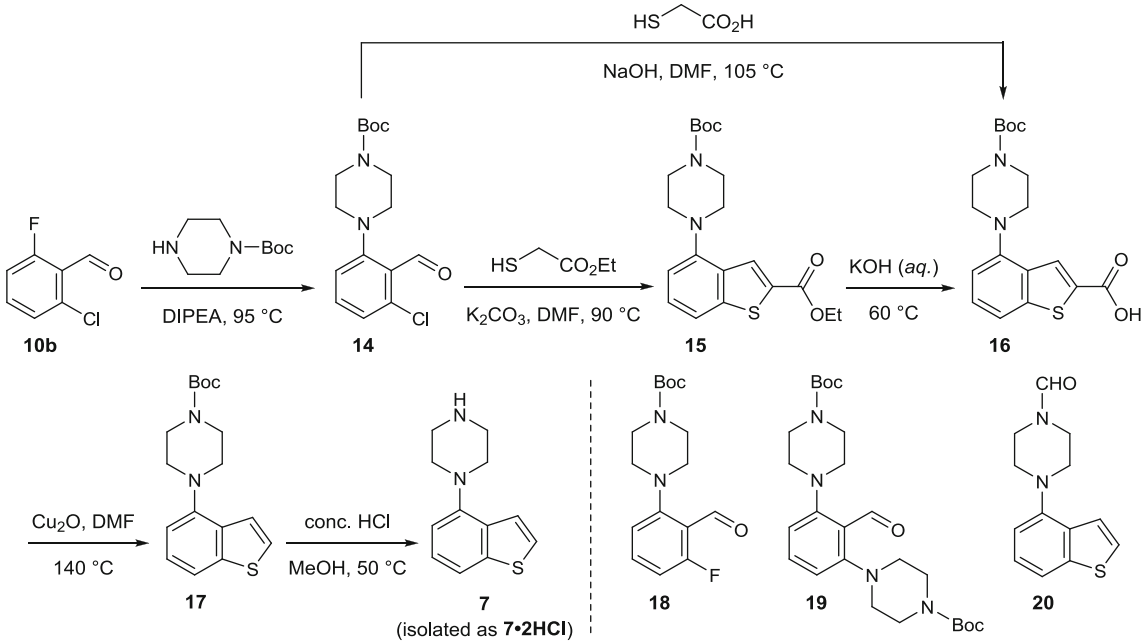
routes to **1** invariably involve reacting 1-(benzo[*b*]thiophen-4-yl)piperazine **7** with 7-(4-halobutoxy)-quinolinone **8** (prepared by etherification of **3**).[6] Given the well demonstrated (and predicted) efficiency of the *N*-alkylation step, advances in commercial manufacturing of **1** have, needless to say, primarily targeted an efficacious acquisition of the tricyclic framework of **7**.[7]

For example, the first synthetic route to **1**, as disclosed by the innovator in 2006,[8] employed a $Pd_2(dba)_3$/(*R*)-BINAP catalyzed Buchwald–Hartwig coupling between 4-bromobenzo[*b*]-thiophene **9a** and excess piperazine to obtain **7** as a yellow oil in 64% yield after purification by silica gel column chromatography. The free base **7**, thus obtained, was characterized after conversion into its recrystallized hydrochloride salt; the latter was reacted with 7-(4-chlorobutoxy)-1*H*-quinolin-2-one **8a** in presence of K_2CO_3 and NaI to furnish **1** (Scheme 2). As elaborated upon as a prelude to an improved strategy in a subsequent 2013 Otsuka patent,[9] this original process to **1** is inherently inefficient at the *N*-arylation step; it suffers from the formation of a large number of by-products and inevitably requires careful chromatographic separation to obtain **7** in high purity. In Otsuka's second generation approach to brexpiprazole, a $Pd(OAc)_2$ mediated Buchwald–Hartwig coupling between 4-chlorobenzo[*b*]-thiophene **9b** and piperazine was utilized as means to obtain the key intermediate **7** (Scheme 3). Preparation of **9b** involved two key steps: (a) elaboration of 2-carboxy-4-chlorobenzo[b]thiophene **11** from either 2,6-dichlorobenzaldehyde **10a** or 2-chloro-6-fluorobenzaldehyde **10b** by employing either rhodanine or thioglycolic acid as a one carbon synthon and an eventual source of a thiol functionality and (b) protodecarboxylation of **11** to **9b** at temperatures in excess of 140 °C.[9,10] While application of specialized ligands (such as RuPhos and tri-*tert*-butylphosphonium tetraphenylborate) in the $Pd(OAc)_2$ catalyzed *N*-arylation of piperazine with **9b** minimized unwanted reactions, it did not completely eliminate formation of such hard-to-separate diarylated impurities as **12** and **13**.

A workaround solution to deal with the impurities encountered in Otsuka's preparation of **7** was provided in a recent communication by Xiangrui and co-workers (Scheme 4).[11] Herein, the key C–N bond formation *en route* to **7** was achieved at the outset of the synthesis by a controlled S_NAr reaction between **10b** and 1-Boc-piperazine to furnish **14**. Thereafter, the aldehyde **14** was converted into benzo[*b*]thiophene **17** in a down-stream process that closely followed Otsuka's synthesis of **9b**



Scheme 3. An example of Otsuka's synthesis of **9b** and its use in Buchwald–Hartwig coupling with piperazine to obtain **7** (Otsuka; WO 2013/015456 A1).

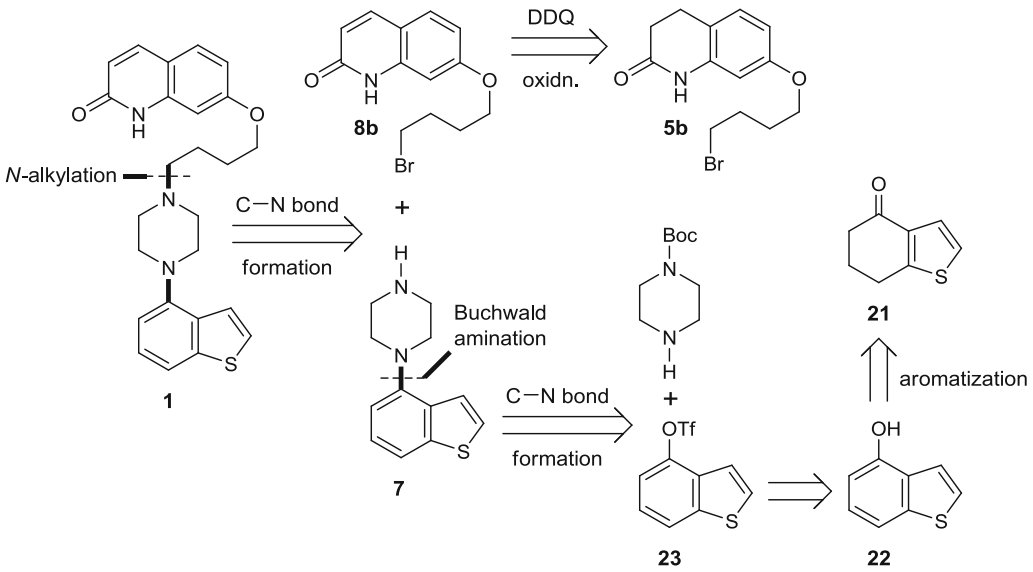


Scheme 4. Synthesis of **7**·**2HCl** from 2-chloro-6-fluorobenzaldehyde **10b** as reported by Xiangrui and co-workers.

from **10b**. Finally, removal of the *N*-Boc protection in **17** with concentrated HCl afforded **7** as a dihydrochloride salt. Despite providing an alternate amination strategy, Xiangrui's synthesis of **7** is nonetheless a linear one, and suffers from formation of impurities such as **18** and **19** [in the step **10b** → **14**] and **20** [in the step **16** → **17**, on account of the instability of the *tert*-butyl-carboxylate moiety at the high temperatures (~140 °C) employed to effect decarboxylation in **16**]. Against this background and in keeping with our on-going interest in investigating applications of transition metal catalysis in the synthesis of contemporary active pharmaceutical ingredients,[12] we decided to re-design Otsuka's convergent synthesis of brexpiprazole **1**, and delineate a highly concise route to the API by employing commercially available 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **21**, 1-Boc-piperazine and the aripiprazole precursor 7-(4-bromobutoxy)-3,4-dihydroquinolinone **5b** as the only building blocks.

1.2 *Retrosynthetic analysis*

As shown in Scheme 5, our retrosynthetic analysis of **1** relied on two key C–N bond formation steps, namely: (a) *N*-alkylation of **7** with 7-(4-bromobutoxy)quinolinone **8b**, the latter being obtained by DDQ oxidation of **5b**; and (b) Buchwald–Hartwig coupling of 1-Boc-piperazine with the triflate ester **23** of benzo[*b*]thiophen-4-ol **22**, which in turn can be prepared *via* aromatization of **21**. While commercially available, the bicyclic ketone **21** can also be easily prepared from thiophene in three steps, *viz.,* Friedel-Crafts acylation with succinic



Scheme 5. Retrosynthetic analysis of **1** from 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **21**, 1-Boc-piperazine and the aripiprazole precursor 7-(4-bromobutoxy)-3,4-dihydroquinolinone **5b**.

anhydride, Wolff-Kishner reduction of the γ-ketoacid intermediate and annulation *via* intramolecular Friedel-Crafts acylation in the 4-(thiophen-2-yl)butanoic acid obtained.[13]

2. Experimental

2.1 *General information*

Reactions were carried out in oven-dried glassware under a positive pressure of nitrogen unless otherwise mentioned. Air-sensitive reagents and solutions were transferred *via* syringe and were introduced to the apparatus *via* rubber septa. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. Deuterated solvents for NMR spectroscopic analyses were used as received. Coupling constants are reported in Hz. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded on an Agilent 6430 triple quad LC/MS system. The purity of the compounds were determined by HPLC with a Waters Alliance e2695 separation module, equipped with a Waters 2998 photodiode array detector and analysed by Empower2 software. Reactions were monitored by thin-layer chromatography (TLC) performed on Merck TLC silica gel 60 F254 aluminum plates. Visualization was accomplished with either UV light, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), ninhydrin, or KMnO4, followed by heating with a heat gun for 15 s. Dry toluene and THF were either distilled over sodium benzophenone ketyl, or procured commercially. Yields of **7**·**2HCl** were calculated on the basis of product assay determined by quantitative NMR (qNMR) with 1,3,5-trimethoxybenzene as an internal standard.

2.2 *Experimental procedures and spectral characterization*

2.2a *Benzo[b]thiophen-4-ol (**22**)*: To a 100 mL two-neck round-bottom flask fitted with a magnetic stir bar and nitrogen inlet was charged 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **21** (1.29 g, 8.48 mmol) in 20 mL dry THF and added $PhN^+Me_3Br_3^-$ (3.18 g, 8.48 mmol) portion wise at 0 °C. The resulting solution was stirred at 0 °C for 90 min, warmed slowly to rt, and further stirred at rt for 30 min. Upon consumption of starting material as indicated by TLC (as the ratio of product increases in the reaction mixture, the color of the reaction mixture changed from pale orange to light yellow), the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 70 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a musk colored solid (2.97 g).

The musk color solid obtained in the previous step was taken in DMF (20 mL) without any further purification into a 100 mL round bottom flask. Li_2CO_3 (2.16 g, 29.23 mmol) and LiBr (3.30 g, 38.00 mmol) were charged consecutively and resulting reaction mixture was heated to 150 °C for 5 h. Upon consumption of starting material (as indicated by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine solution, water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude compound as a brownish solid. The crude compound was purified by column chromatography over 60–120 mesh (5% ethyl acetate/ hexane) to afford the title compound **22** as a white solid. Yield: 88% (1.13 g); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.50–7.43 (m, 2H), 7.39–7.35 (m, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.72 (dd, J = 7.7, 0.6 Hz, 1H), 5.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.71, 141.86, 129.23, 125.28, 125.07, 119.69, 115.24, 108.80; ESI (MS): 151 $[M+H]^+$; HPLC purity: 99.18% [RT: 11.930 min; UV detection at 220 nm; Column: X-Terra RP 18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water B) Acetonitrile; T/%B: 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)]. ^{1}H NMR spectral data of **22** was found to be consistent with the values reported in Ref. [14].

2.2b *Benzo[b]thiophen-4-yl trifluoromethanesulfonate (**23**)*: Benzo[*b*]thiophen-4-ol (**22**) (500 mg, 3.33 mmol) was charged in a 100 mL two-neck round-bottom flask fitted with a magnetic stir bar, nitrogen inlet and dry CH_2Cl_2 (10 ml). To this reaction mixture was added triethylamine (1.16 mL, 8.32 mmol) following which the contents were cooled to 0 °C and trifluoromethanesulfonic anhydride (0.61 mL, 3.66 mmol) was added carefully drop wise. The reaction was allowed to stir at 0 °C for 1 h. Upon consumption of starting material (as indicated by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution. The organic layer was washed thoroughly with brine solution, water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude compound was purified by column chromatography over 60–120 mesh (2% ethyl acetate/ hexane) to afford the **23** as colorless oil. Yield: 90% (846 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 5.5 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.04, 142.53, 132.63, 128.91, 124.74, 122.69, 119.25, 118.73 (q, J_{CF} = 319 Hz, CF_3), 116.44; ESI (MS): 281 $[M-H]^-$; HPLC purity: 98.94% [RT: 14.212 min, UV detection at 225 nm; Column: X-Terra RP 18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water B) Acetonitrile; T/%B: 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)]. ^{1}H and ^{13}C NMR spectral data of **23** were found to be consistent with the values reported in Ref. [15].

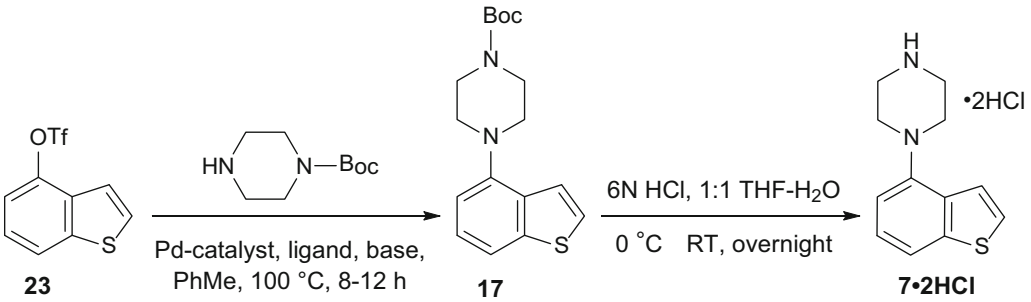
2.2c *1-(Benzo[b]thiophen-4-yl)piperazinedihydrochloride (**7·2HCl**) [Table 1, Entry 10]*: Benzo[*b*]thiophen-4-yl trifluoromethanesulfonate **23** (2.0 g, 7.08 mmol) was charged in dry toluene (20 mL) into a 100 mL two-neck round-bottom flask fitted with a magnetic stir bar and argon inlet. To this reaction mixture, 1-Boc-piperazine (1.97 g, 10.62 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.73 g, 0.708 mmol; 10 mol%), XPhos (0.50 g, 1.062 mmol; 15 mol%) and Cs_2CO_3(6.92 g, 21.24 mmol) were added consecutively under argon atmosphere. The reddish brown solution obtained was degassed with vacuum pump. The reaction was then heated to 100 °C for 8 h under argon atmosphere. Upon completion of the starting material (as indicated by mass and TLC analysis) the reaction mixture was filtered over a short pad of Celite and the filtrate was evaporated under reduced pressure. The residue obtained was passed through a short pad of silica gel (60–120 mesh) using 4% ethyl acetate/hexane to remove metal salts, inorganic matter and excess 1-Boc piperazine.

The partially purified product **17,** (NOTE: Analytical data obtained for a sample of **17** purified by column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.9 Hz, 1H), 7.41 (brs, 2H), 7.28 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 3.66 (brs, 4H), 3.10 (brs, 4H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.83, 148.22, 141.17, 134.17, 125.29, 124.96, 121.61, 117.40, 112.40, 79.84, 52.11, 28.46; ESI (MS): 319.1 $[M+H]^+$, ^{1}H and ^{13}C NMR spectral data of **17** were found to be consistent with the values reported in Ref. [11]), thus obtained was dissolved in 25 mL THF and taken in a 100 mL round bottom flask. 25 mL of 6N HCl was charged at 0 °C and the reaction mixture was stirred overnight at rt. Upon completion of the starting material (as indicated by TLC), THF was evaporated under reduced pressure. The reaction mixture was diluted with 30 mL 6N HCl, and washed with dichloromethane (3 × 20 mL). The washed aqueous layer was evaporated under reduced pressure at 55 °C to furnish the required product 1-(benzo[*b*]thiophen-4-yl) piperazine dihydrochloride (**7·2HCl**) as an off-white solid. 61% over two steps by q-NMR (1.37 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (brs, 2H), 8.68 (brs, 1H), 7.71 (brs, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.49 (brs, 1H), 7.27 (brs, 1H), 6.92 (d, J = 5.9 Hz, 1H), 3.27 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.41, 141.04, 133.84, 126.96, 125.52, 122.36, 118.15, 112.98, 49.00, 43.53; ESI (MS): 219 $[M+H]^+$; HPLC purity: 99.20% [RT: 8.623 min; UV detection at 220 nm; Column: X Bridge C-18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water, B) Acetonitrile; T/%B: 0/10, 3/10, 12/95, 23/95, 25/10, 30/10; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)]. ^{1}H and ^{13}C NMR spectral data of **7·2HCl** were found to be consistent with the values reported in Ref. [11].

2.2d *1-(Benzo[b]thiophen-4-yl)piperazinedihydrochloride (**7·2HCl**) [Table 1, Entry 13]*: To a 50 mL two-neck round-bottom flask fitted with a magnetic stir bar and argon inlet, benzo[*b*]thiophen-4-yl trifluoromethanesulfonate **23** (1.0 g, 3.54 mmol) was charged in dry toluene (10 mL). 1-Boc-piperazine (0.98 g, 5.31 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.036 g, 0.035 mmol; 1 mol%), XPhos (0.05 g, 0.106 mmol; 3 mol%) and Cs_2CO_3(3.45 g, 10.62 mmol) were added consecutively to the reaction mixture under argon atmosphere. The reaction mixture was degassed with vacuum pump and then heated to 100 °C for 8 h under argon atmosphere. Upon completion of the starting material (as indicated by mass and TLC analysis) the reaction mixture was filtered over a short pad of Celite and the filtrate was evaporated under reduced pressure. The residue obtained was passed through a short pad of silica gel (60–120 mesh) using 4% ethyl acetate/hexane as solvent system to remove metal salts, inorganic matter and excess 1-Boc-piperazine.

The partially purified product **17** thus obtained was dissolved in 15 mL of THF and taken in a 100 mL round bottom flask. 15 mL of 6N HCl was charged at 0 °C and

Table 1. Buchwald–Hartwig coupling of the triflate **23** and 1-Boc-piperazine.



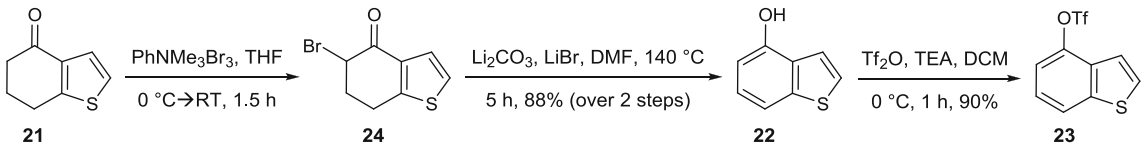
Entry	Catalyst (loading)	Ligand (loading)	Base	Yield (%) of 7·2HCl (over two steps from 23)[a]
1	$Pd(OAc)_2$(20 mol%)	CyJohnPhos (20 mol%)	NaO^tBu	–
2	$Pd(OAc)_2$(10 mol%)	tri(*o*-tolyl)phosphine (15 mol%)	NaO^tBu	Trace
3	$Pd(OAc)_2$(10 mol%)	tri(*o*-tolyl)phosphine (15 mol%)	Cs_2CO_3	–
4	$Pd(OAc)_2$(10 mol%)	XPhos (15 mol%)	Cs_2CO_3	70
5	$Pd(PPh_3)_4$(10 mol%)	XPhos (15 mol%)	Cs_2CO_3	10
6	$Pd(PPh_3)_2Cl_2$(10 mol%)	XPhos (15 mol%)	Cs_2CO_3	64
7	$Pd_2(dba)_3·CHCl_3$(10 mol%)	XPhos (15 mol%)	Cs_2CO_3	78
8	$Pd_2(dba)_3·CHCl_3$ (10 mol%)	tri(*o*-tolyl)phosphine (15 mol%)	Cs_2CO_3	68
9	$Pd_2(dba)_3·CHCl_3$ (10 mol%)	CyJohnPhos (15 mol%)	Cs_2CO_3	25
10	$Pd_2(dba)_3·CHCl_3$ (10 mol%)	XPhos (15 mol%)	Cs_2CO_3	61
11	$Pd_2(dba)_3·CHCl_3$ (3 mol%)	XPhos (6 mol%)	Cs_2CO_3	66
12	$Pd_2(dba)_3·CHCl_3$ (1 mol%)	XPhos (3 mol%)	Cs_2CO_3	96
13	$Pd_2(dba)_3·CHCl_3$ (1 mol%)	XPhos (3 mol%)	Cs_2CO_3	87

Reaction Conditions: All reactions were performed at 100 °C in dry toluene (4 mL for Entries 1–9, 11 and 12) with 1.0 mole equiv. of triflate **23**, 1.5 mole equiv. of 1-Boc-piperazine and 3.0 mole equiv. of the base. Entries 1–9, 11 and 12 were performed with ~200 mg of **23**. Entries 10 and 13 were performed with 2 g and 1 g of **23**, respectively (*cf*. Sections 2.2c and 2.2d for details).

[a]For Entries 1–9, yields were calculated based simply on the weight of the product isolated, assuming the sample to be entirely 7·2HCl. For Entries 10–13, yields of **7·2HCl** were calculated on basis of the assay of the isolated product as determined by quantitative NMR (qNMR) with 1,3,5-trimethoxybenzene as an internal standard (*cf*. Sections 2.2c and 2.2d for details).

the contents were stirred overnight at rt. Upon completion of the starting material (indicated by TLC), THF was evaporated under reduced pressure. The reaction mixture was diluted with 15 mL 6N HCl and washed with dichloromethane (3 × 20 mL). The washed aqueous layer was evaporated under reduced pressure at 55 °C to furnish an off-white solid which was subsequently washed with diethyl ether to afford required product 1-(benzo[*b*]thiophen-4-yl) piperazine dihydrochloride (**7·2HCl**) as an off white solid. Yield: 87% over two steps by q-NMR (919 mg,); HPLC purity: 98.73% [RT: 8.645 min; UV detection at 220 nm; matches with the RT of Table 1, Entry 10 obtained under the given HPLC conditions; Column: X-Terra RP 18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water B) Acetonitrile; T/%B: 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)].

2.2e *7-(4-Bromobutoxy)quinolin-2-(1H)-one (**8b**)*: To a 500 mL two-neck round-bottom flask fitted with a magnetic stir bar and argon inlet was charged 7-[4-bromobutoxy]-3,4-dihydro-2(1*H*)-quinolinone **5b** (10 g, 0.033 mol) in THF (200 mL). To the aforementioned mixture 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (30.4 g, 0.13 mol) was added and the contents were stirred at rt until the completion of the reaction. Upon the consumption of starting material (as indicated by TLC), THF was evaporated under reduced pressure. The residual product obtained was washed with water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish the crude product. The crude product was purified by column chromatography using Ethyl acetate and *n*-Hexane as solvent system to afford the title compound **8b**. Yield: 98.99% (9.8 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.77 (d, J = 9.4 Hz, 1H), 7.53 (d, J = 9.4 Hz, 1H), 6.83–6.69 (m, 2H), 6.27 (d, J = 9.6 Hz, 1H), 4.02 (t, J = 6.1 Hz, 2H), 3.59 (t, J = 6.6 Hz, 2H), 2.03–1.89 (m, 2H), 1.89–1.74 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.67, 160.72, 141.05, 140.44, 129.69, 118.97, 113.77, 111.19, 99.05, 67.28, 35.26, 29.46, 27.74; ESI (MS): 296 $[M+H]^+$; HPLC purity: 99.26% [RT: 11.545 min; UV detection at 210 nm; Column: X Bridge C-18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water, B) Acetonitrile; T/%B: 0/10, 3/10, 15/95, 23/95, 25/10, 30/10; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)]. ^{1}H NMR spectral data of **8b** was found to be consistent with the values reported in Ref. [16].



Scheme 6. Synthesis of the Buchwald–Hartwig arylation partner **23**.

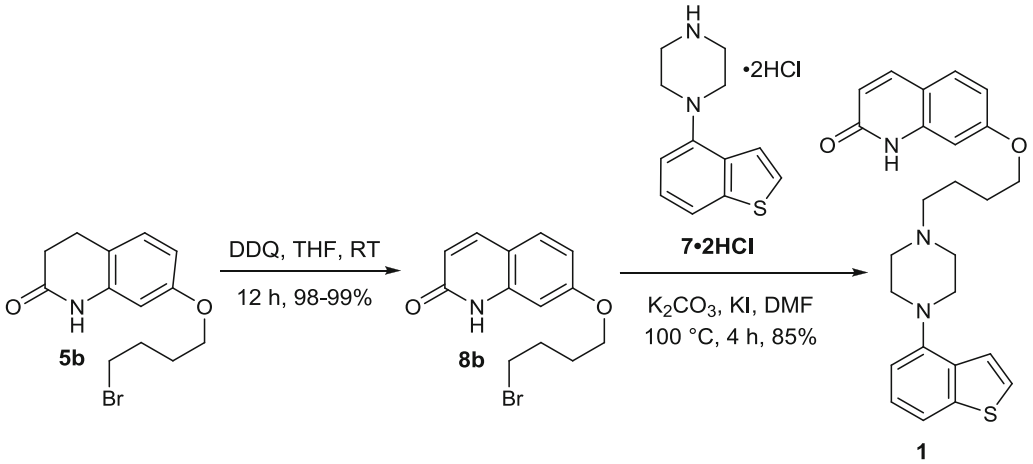
2.2f *Brexpiprazole (**1**)*: 1-(Benzo[*b*]thiophen-4-yl) piperazinedihydrochloride (**7·2HCl**) (282 mg, 0.97 mmol) in dry DMF was taken in a 100 mL two-neck round-bottom flask fitted with a magnetic stir bar and argon inlet. To this reaction mixture, K_2CO_3 (488 mg, 3.53 mmol) was added and the reaction was allowed to stir at rt for 30 min. One mole equivalent of KI (167 mg, 1.01 mmol) and 7-(4-bromobutoxy)quinolin-2(1*H*)-one **8b** (300 mg, 1.01 mmol) were added consecutively. The contents were heated at 100 °C for 4 h. Upon complete consumption of starting material (as indicated by TLC), the reaction mixture was cooled to 0 °C, then 5 mL of water was added and stirred for 30 min. The resultant precipitate (off-white solid) observed was filtered using sintered funnel, redissolved in a mixture of MeOH and CH_2Cl_2 and subjected to column chromatography (100–200 mesh) using 3% MeOH in CH_2Cl_2 as solvent system to furnish the pure product Brexpiprazole **1** as a white solid. Yield: 85% (357 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.67 (d, J = 5.5 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 5.7 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.82–6.73 (m, 2H), 6.28 (d, J = 9.4 Hz, 1H), 4.03 (t, J = 6.4 Hz, 2H), 3.04 (brs, 4H), 2.62 (brs, 4H), 2.44 (t, J = 6.9 Hz, 2H), 1.84–1.70 (m, 2H), 1.70–1.53 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.73, 160.89, 148.62, 141.09, 140.85, 140.49, 133.80, 129.69, 126.28, 125.53, 122.33, 118.89, 117.11, 113.72, 112.47, 111.32, 99.03, 68.04, 57.74, 53.36, 52.05, 26.98, 23.06; ESI (MS): 434 $[M+H]^+$; HPLC purity: 97.97% [RT: 10.504 min; UV detection at 215 nm; Column: X-Terra RP 18, 150 × 4.6 mm, 5 µm particle size; Mobile phase: A) 0.1% TFA in water B) Acetonitrile; T/%B: 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; Flow rate: 1.0 mL/min; Diluent: Acetonitrile:Water (80:20)]. ^{1}H NMR spectral data of **1** was found to be consistent with the values reported in Ref.[9].

3. Results and Discussion

As already alluded to, the Buchwald–Hartwig arylation partner **23** was conveniently prepared from **21** in three steps *via* the intermediacy of the phenol **22** (Scheme 6). Thus, following a known procedure,[14] the ketone **21** was treated with trimethylphenylammonium tribromide in order to mono-brominate selectively the C-5 position and obtain **24**, which was carried forward after work-up to the next step without any further purification. While the α-bromo derivative **24** could also be obtained with molecular bromine in CCl_4,[17] the product obtained was invariably contaminated with a significant amount of 2,5-dibromo-6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **25**.[18] Indeed, even on a 500 mg scale, bromination of **21** with Br_2 would at times result in the formation of nearly an equal amount of **25** as the desired product **24**.

When heated at 150 °C in DMF with a mixture of Li_2CO_3 and LiBr, the crude α-bromoketone **24** underwent a tandem dehydrobromination-aromatization and cleanly furnished the phenol **22** in nearly 88% yield.[14] Esterification of **22** with triflic anhydride under basic conditions[15] afforded the triflate **23** that was then subjected to a palladium catalyzed Buchwald–Hartwig amination with 1-Boc-piperazine. Since the use of **23** as an *N*-arylation partner was found to be unprecedented in literature, a series of catalyst, ligand and base screening experiments were performed to arrive at the best possible reaction conditions for effecting the coupling of 1-Boc-piperazine and **23** (Table 1).

Thus, based on reaction conditions reported for Buchwald–Hartwig amination of various aryl triflates with *N*-protected piperazines, our first attempt at arylating 1-Boc-piperazine with **23** was carried out by employing $Pd(OAc)_2$ as the catalyst, CyJohnPhos as the ligand and NaO^{t}Bu as the base. However, even upon increasing the catalyst and ligand loading to 20 mol%, no evidence for formation of the desired product could be discerned (Table 1, Entry 1); rather, the only observable reaction in most of these attempts was a gradual hydrolysis of **23** over time. By replacing CyJohnPhos with tri(*o*-tolyl)phosphine, we were able to detect traces of the desired product **17** in the crude reaction mixture by mass analysis (Table 1, Entry 2). However, hydrolysis of **23** still prevailed, prompting us to replace with Na^{t}OBu with Cs_2CO_3as a base for subsequent screening experiments. Indeed, while a milieu of $Pd(OAc)_2$, $(o\text{-tol})_3P$ and Cs_2CO_3failed to promote the desired Buchwald–Hartwig coupling, no evidence for triflate hydrolysis was observed even after allowing the reaction mixture to be heated at 100 °C for 12 h (Table 1, Entry 3). Much to our delight, we were eventually successful in realizing the coveted *N*-arylation by employing XPhos as the ligand, and the key intermediate **7·2HCl** could be isolated in 70% yield (over two steps) after *N*-Boc deprotection in the Buchwald product **17** (Table 1, Entry 4).



Scheme 7. Preparation of **8b** and the end-game C–N bond formation to afford **1**.

With XPhos as the ligand, other well-known palladium catalysts, namely $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$, were screened (Table 1, Entries 5–7) to evaluate their efficiency vis-à-vis $Pd(OAc)_2$ (Table 1, Entry 4) in promoting the Buchwald–Hartwig coupling between 1-Boc-piperazine and **23**. Thus, a combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and X-Phos (Table 1, Entry 7) was found to perform best and furnished **7·2HCl** in 78% isolated yield. Indeed, when employed with other phosphine ligands [*viz.,* (*o*-tol)$_3$P (Table 1, Entry 8) and CyJohnPhos (Table 1, Entry 9)], $Pd_2(dba)_3{\cdot}CHCl_3$ fared worse in comparison so that $Pd_2(dba)_3{\cdot}CHCl_3$ and X-Phos were eventually chosen as the catalyst/ligand combination in our first attempt to effect the desired Buchwald–Hartwig amination of **23** on a gram scale. Gratifyingly, coupling of the triflate **23** with 1-Boc-piperazine in presence of 10 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 15 mol% XPhos was uneventful even on a 2 g scale (Table 1, Entry 10), and the reaction went to near completion within 8 h at 100 °C to cleanly afford **17**. In fact, absence of any major side reactions in this coupling step rendered a complete purification of the *N*-Boc derivative **17** prior to its conversion into **7·2HCl** entirely unnecessary. The crude reaction mixture, obtained from the Buchwald–Hartwig amination of **23**, needed to be passed through a short silica gel column merely to remove inorganic matter and unreacted 1-Boc-piperazine. The partially purified product **17** was thereafter subjected to *N*-Boc deprotection with dilute HCl, and the desired intermediate **7·2HCl** isolated with >99% purity simply by extracting out the non-basic impurities from the acidic milieu with dichloromethane.

Having established the proof-of-concept for a novel synthesis of **7·2HCl** from **23**, we were goaded to investigate if the Buchwald–Hartwig coupling could be made more economical by lowering the required loading of $Pd_2(dba)_3{\cdot}CHCl_3$ and XPhos. After a few trials, the desired conversion of **23** into **17** could indeed be achieved with not only 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 6 mol% XPhos (Table 1, Entry 11), but also 1 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 3 mol% XPhos (Table 1, Entry 12). It was also possible to employ the latter catalyst/ligand loading to effect a complete consumption of **23** even on a 1 g scale, and obtain **7·2HCl** in 87% yield and ~99% purity (Table 1, Entry 13). Thus, having accessed one of the two building blocks necessary for the construction of **1**, the stage was set for us to usher in the second fragment **8b** and converge on the well-known end-game C–N bond formation step.

As already alluded to in Section 1.2, it is known that 7-(4-bromobutoxy)quinolinone **8b** can be prepared by DDQ oxidation of the commercially available Aripiprazole precursor **5b**.[19] With minor modifications to the reported procedure, it was possible for us to carry out this transformation on a 10 g scale, and conveniently obtain **8b** in near quantitative yield and with HPLC purity >99%. Thus, with both **7·2HCl** and **8b** in hand, the final *N*-alkylation step was effected in the presence of K_2CO_3 and KI to furnish brexpiprazole **1** (purity ~98%) in 85% yield (Scheme 7).

4. Conclusions

To summarize, we have demonstrated a convergent and highly concise synthesis of brexpiprazole **1**, wherein the entire framework of the API has been assembled in a few simple steps from three readily available building blocks, *viz.,* 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **21**, 1-Boc-piperazine and the aripiprazole precursor 7-(4-bromobutoxy)-3,4-dihydroquinolinone **5b**. Of the two efficacious C–N bond formations that constitute

the crux of our synthetic strategy, the one eventuated by Buchwald–Hartwig coupling between 1-Boc-piperazine and **23** is particularly noteworthy. Indeed, while the chemistry of benzo[*b*]thiophen-4-ol **22** is well documented,[20] any report on the use of its triflate ester **23** to arylate amines is hitherto unknown. Our present endeavor should therefore stimulate further investigations into potential application of **23** as a source of benzo[*b*]thiophen-4-yl fragment in Buchwald–Hartwig aminations.

Supplementary Information (SI)

Scanned copies of ^{1}H and ^{13}C NMR spectra of **1**, **7**·**2HCl**, **8b**, **17**, **22** and **23** are available at www.ias.ac.in/chemsci.

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