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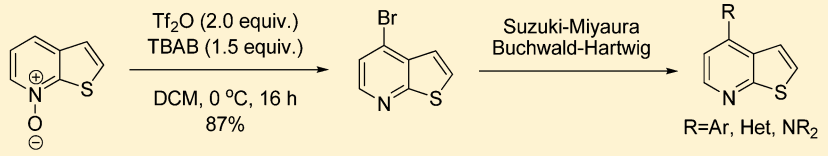
Synthesis of 4-Arylthieno[2,3-*b*]pyridines and 4-Aminothieno[2,3-*b*]pyridines via a Regioselective Bromination of Thieno[2,3-*b*]pyridine

Simon C. C. Lucas,* Jane E. Moore,* Craig S. Donald, and Janet L. Hawkins

†AstraZeneca, Alderley Park, Macclesfield, SK10 4TG, United Kingdom

Supporting Information



ABSTRACT: The first regioselective, mild bromination of thieno[2,3-*b*]pyridine is described herein. The reaction proceeds with selectivity toward the 4-position (87% isolated yield). Subsequent cross-coupling reactions proceed in excellent yields and demonstrate the potential of 4-bromothieno[2,3-*b*]pyridine as a building block for use in drug discovery research.

The thieno[2,3-*b*]pyridine scaffold has recently acquired increasing attention from the medicinal chemistry community. A number of literature reports concerned with this motif as a core in potential small-molecule drugs have been published (Figure 1). For example, work recently published by

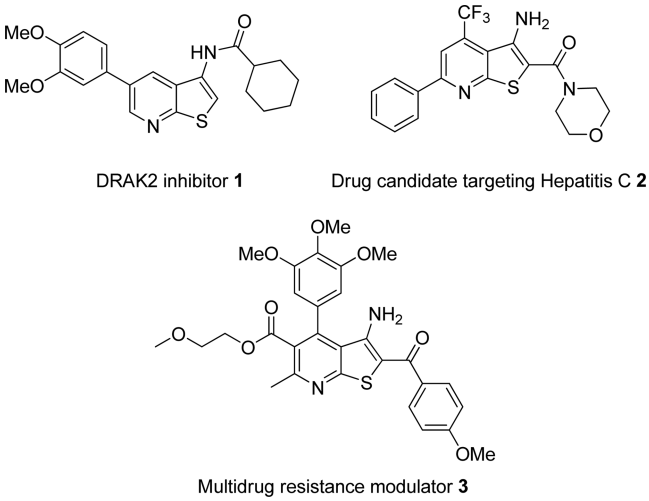


Figure 1. Pharmaceutically active compounds containing the thieno-[2,3-*b*]pyridine structure.[1−3]

Herdewijn et al.[1] explored the use of thieno[2,3-*b*]pyridines (e.g., compound **1**) following a high-throughput screen against DRAK2, i.e., DAPK (death-associated protein kinase) related apoptosis. DRAK2 has emerged as a promising target for the treatment of autoimmune disease and graft-versus-host disease (GvHD). Research by Yu et al. identified the thieno[2,3-*b*]pyridine-based drug candidate **2** for the treatment of hepatitis C.[2] The thieno[2,3-*b*]pyridine core has also been utilized by Krauze et al., who reported a new class of multidrug resistance modulators, such as **3**.[3] Furthermore, inhibition of the c-Src nonreceptor tyrosine kinase by thieno[2,3-*b*]pyridine-based inhibitors has shown promising activity in several in vitro and in vivo models in the oncology research area.[4] There are also reports of thieno[2,3-*b*]pyridines as anti-hepatocellular carcinoma agents,[5] negative allosteric modulators of metabotropic GluR5 receptors,[6] and antibacterial agents against drug-resistant *Staphylococcus epidermidis*.[7]

During the course of one of our drug discovery programs, we became interested in utilizing the thieno[2,3-*b*]pyridine scaffold as a bioisostere for pyrrolo[2,3-*b*]pyridine. However, it became apparent that there was, to the best of our knowledge, no published method of brominating thieno[2,3-*b*]pyridine cores in a highly regioselective manner. We therefore embarked upon a search for facile and robust methodology to affect this transformation.

Previous functionalization focused on chlorination of thieno-[2,3-*b*]pyridine via an N-oxide intermediate. Klemm et al. reported a chlorination method using $POCl_3$. However, the reaction only produced a mixture of 4- and 6-chlorothieno[2,3-*b*]pyridine (1.7:1.0) in a 20% yield.[8] The synthesis and bromination of the analogous pyrrolo[2,3-*b*]pyridine has long been known.[9] Regioselective bromination occurs via formation of a stable N-oxide intermediate, which then coordinates to an activating agent such as methanesulfonic anhydride (Ms_2O). Attack of a bromide ion onto this activated intermediate and subsequent deprotonation/aromatization result in an expedient route to the desired product **6**. Following the work of Thibault, the bromination reaction in Scheme 1 was carried out in a 48% yield (cf. literature 54%).[10] Work by Baran et al. has developed similar methodology for quinolines and isoquinolines using tosic anhydride (Ts_2O) as the activating agent.[11]

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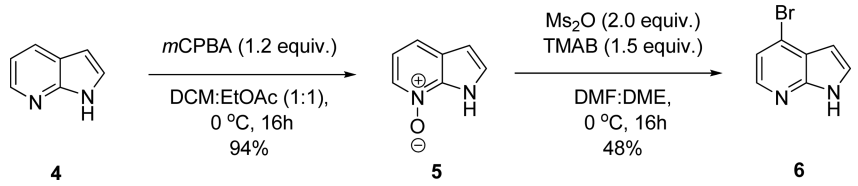
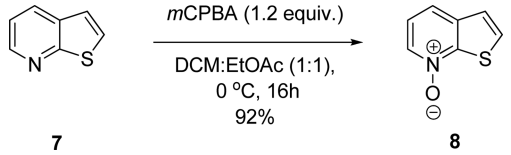
Scheme 1. Synthesis of 4-Bromopyrrolo[2,3-*b*]pyridine



We began our studies by assessing the scope of bromination conditions previously reported for the pyrrolo[2,3-*b*]pyridine scaffold. The sulfur containing N-oxide intermediate **8** was prepared from commercially available thienopyridine **7**, using the same conditions as those for pyrrolo[2,3-*b*]pyridine **4**. The reaction worked well, and the stable N-oxide **8** was isolated in 92% yield (Scheme 2).[8] Formation of the desired product was

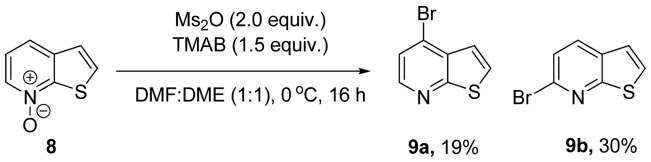
Scheme 2. Synthesis of Thieno[2,3-*b*]pyridine N-Oxide[8]



confirmed by ^{1}H NMR spectroscopy, and the reaction was successfully scaled up to 4.0 g. With the N-oxide in hand, we then investigated the bromination conditions.

When N-oxide **8** was exposed to the conditions used to synthesize bromide **6** (Ms_2O, TMAB, and DMF/DME), two products were isolated from the reaction mixture (Scheme 3).

Scheme 3. Application of Bromination Conditions to Thieno[2,3-*b*]pyridine N-Oxide



The major product, 6-bromothieno[2,3-*b*]pyridine **9b**, was isolated in a 30% yield, and the minor product, 4-bromothieno-[2,3-*b*]pyridine **9a**, in a 19% yield (the mass balance of the reaction was decomposed starting material, **7**). The identity of each compound was confirmed by NMR spectroscopy (^{1}H, HMBC, NOESY). The outcome of this reaction was unexpected and presented a major obstacle to the synthesis of the target compound. It is worthy of note that preference for reaction at the position ortho to the N-oxide is common in many heterocycles.[11] However, in the case of the pyrrolo[2,3-*b*]pyridine, no bromination at the 6-position was observed.

Evidently, the reaction required optimization. When the solvent was changed to DCM, we observed a change in the regioselectivity of the reaction. The major isomer was the desired 4-bromothieno[2,3-*b*]pyridine **9a**, and the minor product was 6-bromo[2,3-*b*]pyridine **9b**, which were isolated in yields of 26 and 20%, respectively (Table 1, entry 2). The reaction was repeated using tetrabutylammonium bromide (TBAB) (entry 3) as a source of bromide (instead of TMAB), and an increase in yield was observed (52%, 57:43 ratio **9a**/**9b**). All further reactions used TBAB as the bromide source.

Table 1. Optimization of Solvent on the Synthesis of 4-Bromothieno[2,3-*b*]pyridine[a]

entry	solvent	bromide	yield [%][b] (ratio **9a**/**9b**)[c]
1	DMF/DME (1:1)*	TMAB	49 (42:58)
2	DCM	TMAB	46 (56:44)
3	DCM	TBAB	52 (57:43)
4	2-MeTHF	TBAB	66 (37:63)
5	trifluorotoluene/DCM (1:1)	TBAB	65 (50:50)
6	DCE	TBAB	58 (55:45)
7	toluene	TBAB	50 (34:66)
8	EtOH	TBAB	0 (nd)
9	MTBE	TBAB	48 (38:62)
10	MeCN	TBAB	48 (54:46)
11	DCM (MS[d])	TBAB	27 (56:44)

[a]Reaction conditions: Thieno[2,3-*b*]pyridine *N*-oxide (1.0 equiv), bromide (1.5 equiv), Ms_2O (2.0 equiv), 0 °C, 16 h. [b]Isolated yield. [c]Ratio determined using ^{1}H NMR of crude product. [d]4 Å molecular sieves; nr = no data; ratio error ±1.

A solvent screen was conducted in order to explore this parameter further (Table 1). A range of solvents was utilized, and the major product observed in the crude reaction mixture varied between the two isomers (this was consistent with the isolated ratio). While the reaction worked well in polar aprotic solvents, the use of ethanol failed to produce the brominated products (entry 8). Rigorously anhydrous solvents did not aid the reaction, as demonstrated by the use of molecular sieves in (entry 11). The solvent clearly plays a small yet important role in the regioselectivity of the reaction. DCM was identified as the optimal solvent from those screened due to the ease of workup and the improved regioselectivity. All further reactions were performed using this solvent.

Next, we turned our attention to the activating reagent by testing a range of other N-oxide activating groups.[12] The reactions were run in DCM with 1.5 equiv of TBAB as the source of bromide (Table 2). While Ts_2O afforded no real improvement over Ms_2O, benzenesulfonic anhydride increased selectivity for the desired bromide (entry 3). The major and minor products were isolated in a total yield of 49% with a major to minor isomer ratio of 90:10. Next, trifluoromethane-sulfonic anhydride (Tf_2O) and nonafluorobutanesulfonic anhydride were used as activating agents (entries 4 and 5). Both activating groups selectively gave the desired bromide **9a** in a much higher yield than Ms_2O. In the case of Tf_2O, bromide **9a** was isolated in an 87% yield and none of the undesired bromide **9b** was isolated from the reaction. None of the other activating groups afforded any improvement over Tf_2O. The amount of Tf_2O used was then reduced (entries 10 and 11). The best results were achieved when 2.0 equiv of activating agent was employed. Increasing the equivalents further was not investigated in order to keep the reaction atom economical.

As shown in Table 2, the results obtained from different activating agents were variable, ranging from no reaction to a

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Table 2. Optimization of the Activating Agent for the Synthesis of 4-Bromothieno[2,3-*b*]pyridine[a]

entry	activating agent	equiv	yield [%][b] (ratio **9a**/**9b**)[c]
1	Ms_2O	2.0	52 (56:44)
2	Ts_2O	2.0	66 (58:42)
3	benzenesulfonic anhydride	2.0	49 (90:10)[d]
4	Tf_2O	2.0	87 (>98:2)
5	nonafluorobutanesulfonic anhydride	2.0	76 (>98:2)
6	Ac_2O	2.0	0 (nd)
7	trifluoroacetic anhydride	2.0	40 (39:61)
8	pivalic anhydride	2.0	0 (nd)
9	PyBroP	2.0	0 (nd)
10	Tf_2O	1.5	66 (>98:2)
11	Tf_2O	1.0	61 (>98:2)

[a]Reaction conditions: Thieno[2,3-*b*]pyridine *N*-oxide (1.0 equiv), TBAB (1.5 equiv), activating agent, DCM, 0 °C, 16 h. [b]Isolated yield. [c]Ratio determined using ^{1}H NMR of crude product. [d]Ratio of isolated products; nd = no data; ratio error ±1.

regioselective, high-yielding reaction. The cause of this trend was not apparent at first. Our early theory was that the size of the activating group was directing the regioselectivity. In that, bulkier groups would effectively block the 6-position to nucleophilic attack via the intermediate shown in Figure 2.

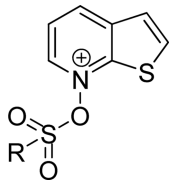


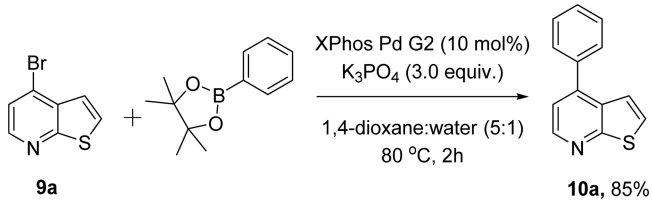
Figure 2. Proposed intermediate in the bromination reaction.

This theory was quickly discounted because with more sterically hindered groups such as Ts_2O and benzenesulfonic anhydride (entries 2 and 3) the reaction produced both isomers. However, with the smaller Tf_2O (entry 4), the reaction is selective. We hypothesize that the observed outcome is not merely due to steric size but as a result of the electronic nature of the activating group. Both fluorinated activating agents selectively produce the 4-bromothieno[2,3-*b*]pyridine isomer **9a**. Therefore, it is plausible that the electronegative fluorine atoms of the activating groups repel the incoming negatively charged (electron-rich) bromide ion. This blocks attack at the 6-position adjacent to the activating group and hence the 4-bromothieno[2,3-*b*]pyridine **9a** is formed. Furthermore, the inductive effects on the intermediate resonance forms also contribute to the observed regioselectivity; the favored 4-bromothieno[2,3-*b*]pyridine **9a** forms via the more stabilized intermediate.

Having established optimal conditions, the reaction was scaled up for two reasons: first, to prove that this was a facile route to the desired building block on a more synthetically useful scale; second, to synthesize a larger quantity of material and hence demonstrate the potential of this compound as a building block for drug discovery. An 80% yield was achieved on a 1.00 g scale synthesis. With this in hand, we investigated the Suzuki–Miyaura coupling of our novel substrate.

Bromide **9a** was reacted with phenyl boronic ester in an 85% yield (Scheme 4) using second-generation XPhos precatalyst.[13]

Scheme 4. Suzuki–Miyaura Coupling of 4-Bromothieno[2,3-*b*]pyridine



As the initial conditions used afforded the desired product **10a** in high yield, no further optimization of the conditions was conducted. Instead, a range of boronates was screened in order to demonstrate a wider functional group tolerance. The reaction was successful with both electron-rich and -poor aromatics as well as heteroaromatic halides (Figure 3). The desired biaryl compounds **10a–f** were synthesized in isolated yields of up to 93%.

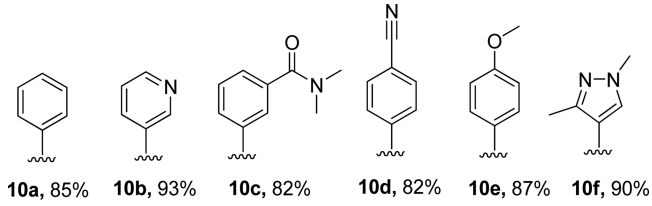
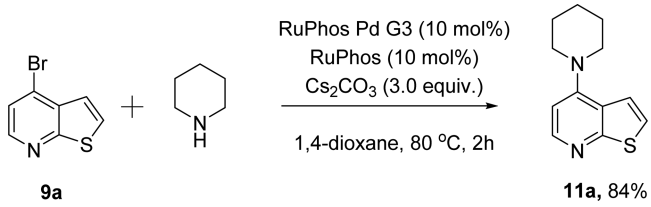


Figure 3. Products: Suzuki–Miyaura coupling.

Next, we turned our attention to Buchwald–Hartwig amination. Cyclic amines are common motifs in pharmaceutical compounds; therefore, the coupling of piperidine to bromide **9a** was explored. Buchwald–Hartwig conditions were used, with both the third-generation RuPhos precatalyst and the RuPhos ligands in the reaction mix alongside a mild base.[14] The reaction in Scheme 5 was carried out, and, pleasingly, the

Scheme 5. Buchwald–Hartwig Amination of 4-Bromothieno[2,3-*b*]pyridine



desired product was synthesized in an 84% yield. Therefore, a short investigation into the scope of the reaction was undertaken. Morpholine and 1-methylpiperazine were reacted under the same conditions, and the results are presented in Figure 4.

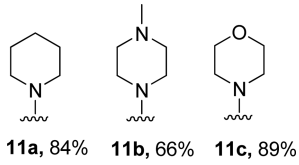


Figure 4. Products: Buchwald–Hartwig amination.

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In conclusion, a highly regioselective route to 4-bromothieno[2,3-*b*]pyridine has been described. The utility of this synthetic intermediate has been evidenced by successful palladium cross-coupling reactions. We believe this motif has the potential for use in drug discovery programs as a valuable synthetic building block, which is now readily available via this methodology. We are currently extending the Tf_2O "activated bromination" methodology to other heteroaromatic substrates, which will be reported in due course.

EXPERIMENTAL SECTION

General Experimental. Reactions were conducted at rt unless indicated otherwise, and this specifies a temperature range from 18−25 °C. Reactions were monitored using TLC or LCMS. All solvents used in this investigation were commercial. Commercially available reagents and solvents were not purified further prior to use. Thieno[2,3-*b*]pyridine was sourced from Fluorochem, and palladium catalysts were obtained from Sigma-Aldrich. Water is deionized water, and brine refers to a saturated solution of sodium chloride in water. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 101 MHz. Chemical shifts (δ) are quoted in ppm relative to $CDCl_3$ (δ_H = 7.26, δ_C = 77.0 ppm), and coupling constants are quoted in Hz. The details of the solvent used are recorded separately in the experimental procedures. IR spectra were recorded using concentrated solutions in CH_2Cl_2/KBr disc method and reported in terms of frequency absorption (cm^{-1}). For HRMS, the mass analyzer type was TOF. The samples were analyzed in ESI positive ion mode on an Orbitrap analyzer with resolution set to 7500. Data was collected from 100 to 2000 amu, and the output was converted using Fourier transform. Collision induced dissociation (CID) was carried out on the most intense ion at 35 eV.

General Procedure A: Bromination. Anhydride (1.0−2.0 equiv) was added dropwise to a stirred suspension of 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide and bromide (1.15 g, 6.61 mmol, 1.5 equiv) in solvent cooled to 0 °C over a period of 10 min under nitrogen. The resulting solution was stirred at 0 °C, slowly warming to rt overnight. The reaction was diluted with water and adjusted to pH 7 by careful addition of 2 M NaOH. The solution was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford crude product. The crude product was purified by silica column chromatography (DCM) to afford bromination products.

*4-Bromothieno[2,3-b]pyridine (**9a**).* Isolated yield, 246 mg (87%); cream solid; mp 58−60 °C; IR (cm^{-1}) 1647, 1531, 1452, 1342, 1116, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.0 Hz), 7.60 (d, J = 6.0 Hz), 7.50 (d, J = 5.0 Hz), 7.39 (d, J = 6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 146.6, 133.5, 127.9, 122.1, 121.7; HRMS (EI+) m/z: $[M+]^+$ calcd for C_7H_4NSBr, 212.9248; found, 212.9249.

*6-Bromothieno[2,3-b]pyridine (**9b**).* Cream solid; mp 65−67 °C; IR (cm^{-1}) 1538, 1464, 1363, 1097, 819, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.5 Hz), 7.51 (d, J = 5.0 Hz), 7.45 (d, J = 8.5 Hz), 7.24 (d, J = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 138.2, 132.8, 131.5, 127.5, 123.6, 121.1; HRMS (ESI+) m/z: $[M + H]^+$ calcd for C_7H_5NSBr 213.9321; found, 213.9322.

General Procedure B: Suzuki−Miyaura Coupling. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (1.2 equiv) was added to 4-bromothieno[2,3-*b*]pyridine (50 mg, 0.23 mmol, 1.0 equiv), XPhos Pd G2 precatalyst (10 mol %), and potassium phosphate (3.0 equiv) in 1,4-dioxane (2.0 mL) and water (0.2 mL) at rt degassed under nitrogen. The resulting solution was stirred at 80 °C for 2 h. Reaction was cooled to rt, concentrated under vacuum, diluted with water (20 mL), and extracted with DCM (3 × 20 mL). The combined organics were dried using $MgSO_4$ and concentrated under vacuum to afford crude product. The crude product was purified by silica column chromatography (EtOAc/heptane) to afford 4-arylthieno[2,3-*b*]-pyridine products.

*4-Phenylthieno[2,3-b]pyridine (**10a**).* Isolated yield, 42 mg (85%); orange gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 5.0 Hz, 1H), 7.63−7.57 (m, 2H), 7.55−7.44 (m, 4H), 7.41 (d, J = 6.0 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.72, 146.7, 145.1, 138.5, 130.8, 128.9, 128.7, 128.7, 126.8, 120.9, 119.1; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{13}H_{10}NS$, 212.0529; found, 212.0533.

*4-(Pyridin-3-yl)thieno[2,3-b]pyridine (**10b**).* Isolated yield, 46 mg (93%); white solid; mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 1.5, 2.0 Hz, 1H), 8.73 (dd, J = 1.5, 5.0 Hz, 1H), 8.66 (d, J = 5.0 Hz, 1H), 7.92 (dd, J = 2.0, 8.0 Hz, 1H), 7.60 (d, J = 6.0 Hz, 1H), 7.47 (dd, J = 5.0, 8.0 Hz, 1H), 7.37 (d, J = 6.0 Hz, 1H), 7.30 (d, J = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 149.9, 149.4, 146.8, 141.4, 135.9, 134.2, 130.6, 127.8, 123.6, 120.1, 119.1; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{12}H_9N_2S$, 213.04810; found, 213.04822.

*N,N-Dimethyl-3-(thieno[2,3-b]pyridin-4-yl)benzamide (**10c**).* Isolated yield, 42 mg 82%; yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 5.0 Hz, 1H), 7.66−7.64 (m, 2H), 7.60−7.50 (m, 3H), 7.39 (d, J = 6.0 Hz, 1H),), 7.30 (d, J = 5.0 Hz, 1H), 2.90−3.20 (m, broad, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 162.8, 146.7, 144.1, 138.7, 137.3, 130.6, 129.8, 129.8, 129.0, 127.4, 127.2, 120.6, 119.1, 100.0, 37.5; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{16}H_{15}N_2OS$, 283.0900; found, 283.0899.

*4-(Thieno[2,3-b]pyridin-4-yl)benzonitrile (**10d**).* Isolated yield, 48 mg (87%); white solid; mp 220−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.0 Hz, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 6.1 Hz, 1H), 7.33 (d, J = 6.0 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.99, 146.8, 143.0, 142.8, 132.7, 130.2, 129.5, 128.1, 120.0, 118.9, 118.4, 112.7; ESI + m/z: $[M + H]^+$ calcd for $C_{14}H_9N_2S$, 237.0481; found, 237.0483.

*4-(4-Methoxyphenyl)thieno[2,3-b]pyridine (**10e**).* Isolated yield, 46 mg (82%); colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.26 (d, J = 5.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 162.8, 160.2, 146.7, 144.8, 130.9, 130.7, 130.0, 126.5, 121.0, 118.9, 114.4, 55.4; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NOS$, 242.0634; found, 242.0640.

*4-(1,3-Dimethyl-1H-pyrazol-4-yl)thieno[2,3-b]pyridine (**10f**).* Isolated yield, 48 mg (90%); white solid; mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.55 (d, J = 5.0 Hz, 1H), 7.55 (s, 1H), 7.50 (d, J = 6.0 Hz, 1H), 7.28 (d, J = 6.0 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 3.94 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 162.4, 146.6, 146.5, 137.0, 131.2, 130.2, 126.3, 121.0, 119.3, 117.6, 38.9, 12.7; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{12}H_{12}N_3S$, 230.07464; found, 230.07468.

General Procedure C: Buchwald−Hartwig Amination. Cesium carbonate (3.0 equiv), amine (1.2 equiv), and 4-bromothieno [2, 3-b] pyridine **26** (50 mg, 0.23 mmol, 1.0 equiv) in 1,4-dioxane (2.0 mL) were degassed under nitrogen. RuPhos Pd G3 precatalyst (5 mol %) and RuPhos (5 mol %) were added, and the resulting solution was stirred at 100 °C for 2 h. The reaction mixture was evaporated to dryness, redissolved in water (20 mL), and washed sequentially with DCM (3 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to afford crude product. The crude product was purified by silica column chromatography (EtOAc/heptane) to afford 4-aminothieno[2,3-*b*]pyridine products.

*4-(Piperidin-1-yl)thieno[2,3-b]pyridine (**11a**).* Isolated yield, 43 mg (84%); white solid; mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 5.5 Hz, 1H), 7.34 (d, J = 6.0 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 6.65 (d, J = 5.5 Hz, 1H), 3.33−3.27 (m, 4H), 1.82−1.76 (m, 4H), 1.73−1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 155.0, 147.7, 123.3, 120.3, 106.6, 100.0, 51.9, 26.0, 24.5; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{12}H_{15}N_2S$, 219.0505; found, 219.0496.

*4-(4-Methylpiperazin-1-yl)thieno[2,3-b]pyridine (**11b**).* Isolated yield, 36 mg (66%); yellow solid; mp 98−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.36 (d, J = 5.5 Hz, 1H), 7.37 (d, J = 6.0 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 6.68 (d, J = 5.5 Hz, 1H), 3.43−3.31 (m, 4H), 2.58−2.7 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 163.5, 160.7, 147.8, 124.8, 123.9, 120.0, 106.7, 54.9, 50.6, 46.1; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{12}H_{16}N_3S$, 234.1059; found, 234.1061.

*4-(Thieno[2,3-b]pyridin-4-yl)morpholine (**11c**).* Isolated yield, 46 mg (89%); white solid; mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.39 (d, J = 5.0 Hz, 1H), 7.40 (d, J = 6.0 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 6.68 (d, J = 5.0 Hz, 1H), 3.97−3.89 (m, 4H), 3.36−3.28 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) 163.6, 154.1, 147.8, 124.8,

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124.3, 119.7, 106.5, 66.8, 51.1; HRMS ESI+ m/z: $[M + H]^+$ calcd for $C_{11}H_{13}N_2OS$, 221.0743; found, 221.0743

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01735.

^1H and $^{13}C\{1H\}$ NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*(S.C.C.L.) E-mail: simon.lucas@astrazeneca.com. Fax: +4401625513019

*(J.E.M.) E-mail: jane.moore2@astrazeneca.com.

Notes

The authors declare no competing financial interest.

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