A Facile and General Synthesis of 2,4-Di- and 2,4,7-trisubstituted Thieno[2,3-*c*]pyridines

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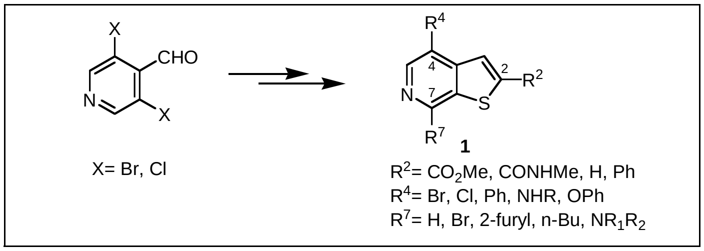

Treatment of 3,5-dibromo- or 3,5-dichloro-pyridine-4-carboxaldehyde **2** with one equivalent of methyl thioglycolate, followed by exposure to base, provided 4-bromo- or 4-chloro-thieno[2,3-*c*]pyridine-2-carboxylate **4** in good yields. Oxidation of the thieno[2,3-*c*]pyridine scaffold such as **7** with mCPBA, followed by treatment with $POBr_3$, introduced a bromine exclusively at the 7-position of the heterocycle. The 4- or 7-bromide of the thienopyridines readily underwent Suzuki, Stille coupling, and Buchwald amination reactions, to afford 4- or 7-substituted analogs **6** or **11**. The 2-carboxylate of **4b** or **12** was smoothly removed through saponification and decarboxylation to furnish **15** or **16**. Deprotonation of the thienopyridine at C-2 position, followed by trapping with trimethyltin chloride, afforded a 2-stannyl analog, which was readily converted to other C-2 derivatives *via* Stille reaction.

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INTRODUCTION

Thieno[2,3-*c*]pyridine, an isostere of isoquinoline [1], has emerged as an attractive structural scaffold in search for small molecule pharmaceutical agents [2]. Thieno-[2,3-*c*]pyridine resembles isoquinoline sterically, but contains a π-rich thiophene and a π-deficient pyridine, leading to an inherently polarized push-pull system with a ground-state dipole moment of 2.85 D [1a]. In case of biological interest, polarization of the thienopyridine scaffold can be further improved by introduction of donors to the thiophene and/or acceptors to the pyridine ring. There are a number of methods available for synthesis of unsubstituted or less substituted thieno[2,3-*c*]–pyridines [3]. However, further functionalization of the heterocycle is challenging with those methodologies. Herein we report a facile and general method to synthesize 2,4-di- and 2,4,7-trisubstituted thieno[2,3-c]-pyridines **1**.

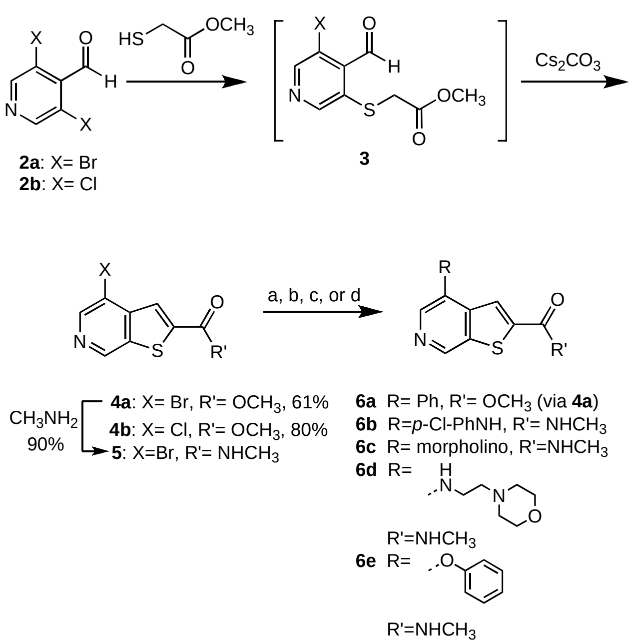
RESULTS AND DISCUSSION

It has been known that methyl 4-bromothieno[2,3-*c*]pyridine carboxylate **4a** [1b] can be prepared in very low yield (10%) from 3,5-dibromopyridine-4-carbox-aldehyde **2a** and methyl thioglycolate in the presence of sodium methoxide. Given the fact that a bromide functionality can be potentially converted to a wide variety of substituents through transition metal-catalyzed coupling reactions, we further explored this methodology. We envisioned that a stronger base (*i.e.* sodium methoxide) employed in the reported procedure could have resulted in many undesired reactions, including displacement of bromide and hydrolysis of the carboxylate. Indeed, after screening a number of bases, we found that the reaction became much cleaner in the presence of cesium carbonate, providing **4a** in >60% yield in several trials (Scheme 1).

Nucleophilic displacement of one bromide of **2a** by methyl thioglycolate gave a mono-substituted product **3**. Because of the electron-donating effect of the sulfide, the bromide in **3** was less reactive, leading to predominant formation of mono-substituted product. Under the same conditions, the reaction of a relatively cheaper 3,5-dichloropyridine-4-carboxaldehyde **2b** with methyl thio-glycolate afforded the 4-chloro analog **4b** in 80% yield.

While some of the halogenated heterocycles are less reactive toward transition-metal catalyzed reactions, the 4-bromide in ester **4a** smoothly underwent a Suzuki coupling with phenylboronic acid to afford 4-phenyl derivative **6a**. The 2-carboxylate in **4a** was not stable in our hands under a typical Buchwald amination protocol ($Pd_2(dba)_3$/(-)-BINAP/$NaOBu^t$) [4], and thus **4a** was converted to methyl amide **5** by heating in a methanolic methylamine solution (90% yield). When **5** was heated with *para*-chloroaniline and sodium t-butoxide in THF, under the catalysis of $Pd_2(dba)_3$ and (-)-BINAP, its 4-amino analog **6b** was obtained in 84% yield. For reasons that are not known, the reactions of **5** with the more nucleophilic morpholine and 1-(3'-aminoethyl)morpholine, under the same conditions, led to **6c** and **6d** in much lower yields (38% and 34% respectively). Attempts to install a 4-phenoxy group on **4a** or **5** by the known copper-mediated coupling methodologies [5] failed to provide diaryl ether **6e** (Scheme 1). Nevertheless, as described in our previous report [2a], a 4-phenoxy derivative **7** can be prepared by a sequential displacement of two chlorides of **2b** with one equivalent of phenoxide and methyl thioglycolate, followed by exposure to base.

Scheme 1

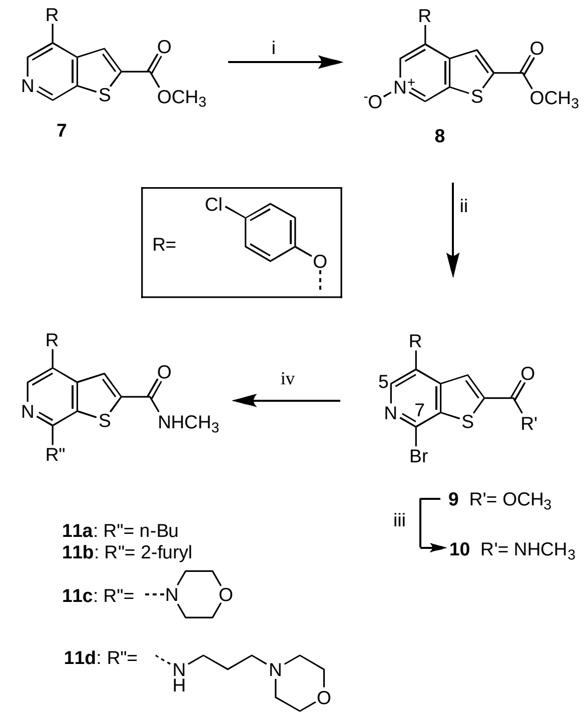


Reagents and conditions: a. $PhB(OH)_2$, $Pd(PPh_3)_4$, CsF, DME, 82%. b. p-Cl-$PhNH_2$, $Pd_2(dba)_3$, (-)-BINAP, $NaOBu^t$, THF, 84%. c. morpholine, $Pd_2(dba)_3$, (-)-BINAP, $NaOBu^t$, THF, 38%. d. 2-morpholinylethylamine, $Pd_2(dba)_3$, (-)-BINAP, $NaOBu^t$, THF, 34%.

The 7-position of the thieno[2,3-*c*]pyridine was functionalized through a two-step sequence as shown in Scheme 2. mCPBA oxidation of **7**, which was synthesized previously in our laboratory [2a], in methylene chloride specifically resulted in N-oxide **8** in almost quantitative yield. Treatment of the N-oxide **8** with $POBr_3$ afforded 7-bromide **9** (62% yield) as assigned by an NOE experiment. No regioisomeric 5-bromide was detected in the reaction mixture.

The 7-bromide was converted to a variety of substituents through Suzuki (**11a**), Stille (**11b**) coupling, or Buchwald amination (**11c** and **11d**) reactions. When bromide **10** was coupled with butylboronic acid, the desired product **11a** was obtained in poor yields (<20%) under a variety of conditions [$Pd(OAc)_2$/DPPF/CsF/DME, $Pd_2(dba)_3$/(*o*-tol)$_3$P/CsF/THF, $Pd(PPh_3)_4$/NaOH/H_2O/dioxane]. Using tri-*t*-butylphosphine as the ligand and cesium carbonate as base, this reaction afforded **11a** in a respectable 70% yield. When **10** was heated with 2-tributylstannylfuran in DMF in the presence of catalytic $Pd(OAc)_2$ and tri-*o*-tolylphosphine, 7-(2-furyl) analog **11b** was isolated in 87% yield. By employing a typical Buchwald amination protocol [$Pd_2(dba)_3$/(-)-BINAP/18-crown-6/$NaOBu^t$/THF] [4], the 7-bromide in **10** was converted to a morpholine (**11c**) and N-(3-aminopropyl)-morpholine (**11d**) derivatives in 86% and 94% yields, respectively.

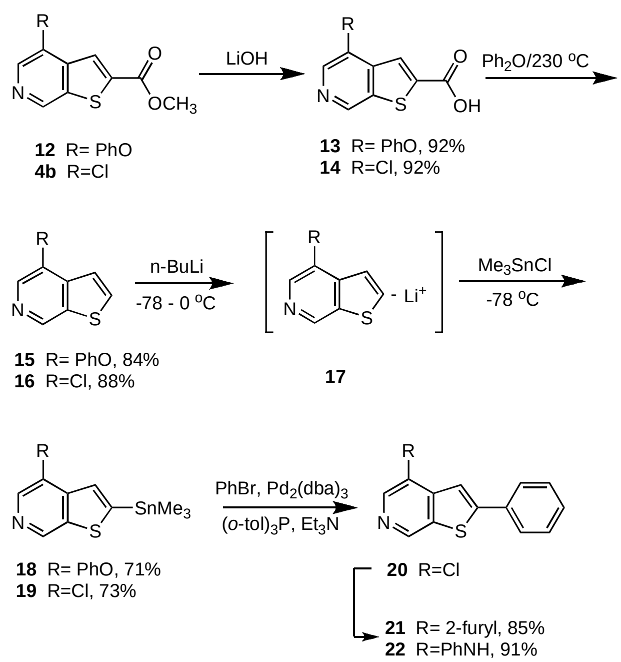
Scheme 2



Reaction conditions: [i] mCPBA, CH_2Cl_2, rt, 95%; [ii] $POBr_3$, CH_2Cl_2, rt, 62%; [iii] $MeNH_2$, MeOH, 45 °C, 93%; [iva] n-butylboronic acid, $Pd_2(dba)_3$, (t-Bu)$_3$P, Cs_2CO_3, dioxane, 70%; [ivb] 2-tributylstannylfuran, $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N, DMF, 87%; [ivc] morpholine, $Pd_2(dba)_3$, (-)-BINAP, 18-crown-6, $NaOBu^t$, THF, 86%; [ivd] 3-(4-morpholino)propylamine, $Pd_2(dba)_3$, (-)-BINAP, 18-crown-6, $NaOBu^t$, THF, 94%.

Scheme 3 demonstrates a typical conversion of 2-carboxylate of the thienopyridine to other substituents. Saponification of **12**, which was again previously synthesized in this laboratory, with lithium hydroxide afforded acid **13**. When a suspension of the acid in diphenyl ether was heated at 230 °C, decarboxylation proceeded smoothly and furnished **15** in 84% yield. Lithiation of **15** with *n*-butyllithium proceeded specifically at the 2-position, giving intermediate **17**. Trapping of the lithio species **17** with trimethyltin chloride afforded **18** in 71% yield. The 2-trimethylstannyl functionality could be further converted to other substituents through Stille reaction. As also shown in Scheme 3, a 4-chloro analog **19** was prepared by a similar protocol. 4-Chloro-2-trimethylstannylthieno-[2,3-*c*]pyridine **19** is a more flexible intermediate, in which both 2- and 4-positions could be further functionalized. For example, Stille coupling of **19** with bromobenzene afforded **20** which underwent another Stille reaction with 2-trimethylstannylfuran to give **21**. Amination of the 4-chloride in **20** proceeded smoothly under Nolan's system [6], providing, for example, **22** in 91% yield.

Scheme 3



In summary, we have developed a facile and general approach to the synthesis of 2-, 4- and 7-substituted thieno[2,3-*c*]pyridines. The bromo and chloro functionalities of the thieno[2,3-*c*]pyridine scaffold proceeded Suzuki, Stille and Buchwald type of reactions smoothly while poor yields were frequently obtained with some of the other heterocycles. $(t\text{-Bu})_3P/Pd_2(dba)_3/Cs_2CO_3$ system was found to be superior in the Suzuki reaction of **10** with butylboronic acid to the other conditions screened. 4-Chloro-2-trimethylstannylthieno[2,3-*c*]pyridine **19** represents a more flexible intermediate, with which both 2- and 4-positions of the thienopyridine scaffold can be readily functionalized.

EXPERIMENTAL

General Spectroscopic and Experimental Data. Infrared spectra were recorded on Nicolet 5SX and Nicolet Magna-IR 750 spectrometer. The NMR spectra were obtained on Varian UP-300, Varian M-300, Bruker AMX-400, and Varian U-400 magnetic resonance spectrometer (300/400MHz for ^{1}H and 75/100MHz for ^{13}C) with deuteriochloroform as solvent and internal standard unless otherwise indicated. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). When peak multiplicities are given the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Mass spectra were performed as follows: ESI (electrospray ionization) was performed on a Finnigan SSQ7000 MS run as a flow injection acquisition; DCI (desorption chemical ionization) was performed on a Finnigan SSQ7000 MS using a direct exposure probe with ammonia gas; APCI (atmospheric pressure chemical ionization) was performed on a Finnigan Navigator MS run as flow injection acquisition. Elemental analysis was performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise mentioned. All solvents and other reagents were purified when necessary using standard procedures. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) using the indicated solvent. For routine aqueous workup, the reaction mixture was partitioned between brine and EtOAc, and the organic layer was washed with brine and dried over $MgSO_4$.

Methyl 4-bromothieno[2,3-*c*]pyridine-2-carboxylate (4a). A solution of 3,5-dibromopyridinecarboxaldehyde (**2a**) (5 g, 18.9 mmol) in THF (100 mL) was treated with methylthioglycolate (1.69 mL, 18.9 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h before powdered Cs_2CO_3 (6.15 g, 18,9 mmol) was added. The mixture was stirred for 18 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (5% acetone in hexane) to provide **4a**. Yield: 3.1 g (62%). ^{1}H nmr (500 MHz, DMSO-d_6): δ 3.95 (s, 3 H), 7.99 (s, 1 H), 8.67 (s, 1 H), 9.31 (s, 1 H); ms (APCI): m/e 272, 274 $(M+H)^+$. *Anal.* Calcd for $C_9H_6BrNO_2S$: C, 39.72; H, 2.22; N, 5.15. Found: C, 39.70; H, 2.32; N, 5.07.

Methyl 4-chlorothieno[2,3-*c*]pyridine-2-carboxylate (4b). To a solution of 3,5-dichloropyridine-4-carboxaldehyde (**2b**) (5.0 g, 28.4 mmol) in THF (50 mL) was added methyl thioglycolate (2.59 mL, 28.4 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and was warmed up to rt for another hour. Cs_2CO_3 (9.25 g, 28.4 mmol) was then added. The reaction mixture was stirred for 18 h, and was partitioned between ethyl acetate and brine. The organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (20-40% gradient EtOAc in hexane) to provide **4b**. Yield: 5.2 g (80%). ^{1}H nmr (400 MHz, DMSO-d_6): δ 3.96 (s, 3 H), 8.04 (s, 1 H), 8.60 (s, 1 H), 9.32 (s, 1 H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 53.2, 125.6, 125.9, 137.8, 139.7, 141.4, 141.9, 144.6, 161.4; ms (DCI/NH_3): *m/e* 228 $(M+H)^+$. *Anal.* Calcd for $C_9H_6ClNO_2S$: C, 47.48; H, 2.66; N, 6.15. Found: 47.40; H, 2.61; N, 6.18.

Methyl 4-bromothieno[2,3-*c*]pyridine-2-carboxamide (5). A solution of **4a** (5.0 g, 18.4 mmol) in methanol (20 mL) was treated with methylamine (2 *M* solution in methanol, 20 mL) at 60 °C for 6 h, and was concentrated. The residue was recrystallized from acetone, and dried to provide 4.5 g of **5**. Yield: 90%. ^{1}H nmr (400 MHz, DMSO-d_6): δ 3.97 (br s, 3H), 8.11 (s, 1H), 8.33 (br s, 1H), 8.43 (s, 1H), 9.24 (s, 1H); ms (DCI/NH_3): m/e 271, 273 $(M+H)^+$. *Anal.* Calcd for $C_9H_7BrN_2OS$: C, 39.87; H, 2.60; N, 10.33. Found: C, 40.05; H, 2.58; N, 10.21.

Methyl 4-phenylthieno[2,3-*c*]pyridine-2-carboxylate (6a). A 25 mL round bottom flask was charged with **4a** (50 mg, 0.18 mmol), phenylboronic acid (25 mg, 0.20 mmol), cesium fluoride (56 mg, 0.36 mmol) and $Pd(PPh_3)_4$ (21 mg, 0.018 mmol), and was purged with nitrogen. Anhydrous DME (4 mL) was added, and the reaction mixture was stirred under reflux for 12 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. The residual oil was separated by flash chromatography (20% EtOAc in hexane) to give **6a** as a slightly yellow solid. Yield: 40 mg (82%). ^{1}H nmr (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.5–7.6 (m, 5H), 8.18 (s, 1H), 8.59 (s, 1H), 9.18 (s, 1H); ms (DCI): *m/z* 270 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.95; H, 4.10; N, 5.13.

Methyl 4-(4-chloroanilino)thieno[2,3-*c*]pyridine-2-carboxamide (6b). A 25 mL round bottom flask was charged with **5** (68 mg, 0.25 mmol), 4-chloroaniline (96 mg, 0.75 mmol), $Pd_2(dba)_3$ (14 mg, 0.014 mmol), (-)-BINAP (27 mg, 0.044 mmol), 18-crown-6 (196 mg, 0.74 mmol) and sodium *tert*-butoxide (71 mg, 0.74 mmol), and was purged with nitrogen. Anhydrous THF (10 mL) was then added. The formed dark red solution was purged with nitrogen again, and was heated at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (20-100% gradient EtOAc in hexane) to afford **6b**. Yield: 67mg (84%). ^{1}H nmr (400 MHz, DMSO-d$_6$): δ 2.83 (d, *J* =4.0 Hz, 3 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 8.67 (s, 1 H), 8.85 (d, *J* = 4.0 Hz, 1 H), 8.91 (s, 1 H); ^{13}C nmr (100 MHz, DMSO-d$_6$): δ 26.3, 118.1, 121.7, 123.6, 129.1, 133.0, 134.4, 137.1, 137.2, 138.2, 142.6, 143.2, 161.4; ms (APCI): *m/z* 318 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_{12}ClN_3OS$: C, 56.69; H, 3.81; N, 13.22. Found: C, 56.78; H, 3.71; N, 13.10.

Methyl 4-(4-morpholinyl)thieno[2,3-*c*]pyridine-2-carboxamide (6c). Compound **6c** was prepared as described for **6b**, substituting morpholine for 4-chloroaniline. Yield: 38%. ^{1}H nmr (400 MHz, DMSO-d$_6$): δ 2.91 (d, *J* = 4.0 Hz, 3 H), 3.23 (m, 4 H), 3.91 (m, 4 H), 8.14 (s, 1 H), 8.18 (s, 1 H), 8.96 (s, 1 H), 8.99 (d, *J* = 4.0 Hz, 1 H); ^{13}C nmr (100 MHz, DMSO-d$_6$): δ 26.1, 51.6, 66.3, 121.2, 131.6, 137.1, 137.9, 139.0, 143.3, 143.9, 161.3; ms (APCI): *m/z* 278 (M+H)$^+$. *Anal.* Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.10; 5.49; N, 15.08.

Methyl 4-(2-morpholin-4-yl-ethylamino)thieno[2,3-*c*]pyridine-2-carboxamide (6d). Compound **6d** was prepared as described for **6b**, substituting 2-morpholinoethylamine for 4-chloroaniline. Yield: 34%. ^{1}H nmr (400 MHz, DMSO-d$_6$): δ 2.39-2.45 (m, 4 H), 2.59 (t, *J* = 6.0 Hz, 2 H), 2.80 (d, *J* = 6 Hz, 3 H), 3.30-3.39 (m, 2 H), 3.57 (t, *J* = 6.0 Hz, 4 H), 6.00 (t, *J* = 5 Hz, 1 H), 7.78 (s, 1 H), 8.16 (s, 1 H), 8.46 (s, 1 H), 8.63 (t, *J* = 6.0 Hz, 1 H); ^{13}C nmr (100 MHz, DMSO-d$_6$): δ 26.3, 39.9, 53.4, 56.8, 66.2, 69.8, 121.7, 124.1, 131.6, 132.4, 136.6, 139.8, 140.6,161.8; ms (APCI): *m/z* 321 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_{20}N_4O_2S$: C, 56.23; H, 6.29; N, 17.49. Found: C, 56.05; H, 6.37; N, 17.36.

Methyl 7-bromo-4-(4-chlorophenoxy)thieno[2,3-*c*]pyridine-2-carboxylate (9). To a solution of **7** (10 g, 31.35 mmol) [2a] in CH_2Cl_2 (200 mL) was added mCPBA (57%, 11.39 g, 37.62 mmol) at 0 °C. The reaction mixture was stirred while gradually warming up to room temperature overnight. After dilution with CH_2Cl_2 (200 mL), the reaction mixture was washed with 1 *N* NaOH (400 mL), brine (400 mL) and H_2O (400 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to provide N-oxide **8** (10.0 g, 95%). This material was directly used in the following step without further purification.

To a solution of **8** (9.53 g, 28.45 mmol) in CH_2Cl_2 (120 mL) was added $POBr_3$ (15.97 g, 56.90 mmol) at 0 °C in one portion. The formed slightly yellow suspension was stirred while gradually warming to room temperature overnight, and was then poured into ice. The mixture was basified to a pH 9, and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic phases were washed with brine (400 mL), dried ($MgSO_4$) and concentrated. The residual solid was purified by flash chromatography (15% EtOAc in hexane) to give **9** as white solid. Yield: 7.1 g (62%). ^{1}H nmr (300 MHz, DMSO-d$_6$): δ 8.10 (s, 1 H), 3.92 (s, 3 H), 7.23 (d, *J* = 9.0 Hz, 2 H), 7.49 (d, *J* = 8.9 Hz, 2 H), 8.09 (s, 1 H); ms (ESI/NH_3): *m/e* 398 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_9BrClNO_3S$: C, 45.19; H, 2.28; N, 3.51. Found: C, 45.10; H, 2.30; N, 3.63.

Methyl 7-bromo-4-(4-chlorophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (10). A solution of **9** (4.0 g, 10 mmol) in a methanolic methylamine solution (2 *M*, 80 mL) was heated at 45 °C in a sealed pressure tube for 4 h. After cooling, the reaction mixture was concentrated, and the residue was triturated with a mixture of ether and hexane. The formed white solid was collected by filtration, and dried to afford **10**. Yield: 3.69 g (93%). ^{1}H nmr (300 MHz, DMSO-d$_6$): δ 2.81 (d, *J* = 4.4 Hz, 3 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.48 (d, *J* = 9.2 Hz, 2 H), 8.05 (s, 1 H), 8.21 (s, 1 H), 9.04 (q, *J* = 4.8 Hz, 1 H); ms (ESI/NH_3): *m/e* 397 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_{10}BrClN_2O_2S$: C, 45.30; H, 2.53; N, 7.04. Found: 45.15; H, 2.63; N, 7.00.

Methyl 7-*n*-butyl-4-(4-chlorophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (11a). A 25 mL round bottom flask was charged with **10** (100 mg, 0.25 mmol), $Pd_2(dba)_3$ (22 mg, 0.025 mmol), n-butylboronic acid (51 mg, 0.5 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol), and was purged with nitrogen. Anhydrous dioxane (5 mL) and tri-*t*-butylphosphine (16 μL, 0.0625 mmol) were added. The suspension was purged with nitrogen again, and was stirred at 80 °C for 8 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was separated by HPLC (Zorbax, C-18, CH_3CN/H_2O/0.1% TFA as mobile phase) to provide **11a** as TFA salt. Yield: 86.1 mg (70%). ^{1}H nmr (300 MHz, DMSO-d$_6$): δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.40 (m, 2 H), 1.79 (m, 2 H), 2.79 (d, *J* = 4.4 Hz, 3 H), 3.03 (t, *J* = 7.6 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 9.2 Hz, 2 H), 8.06 (s, 1 H), 8.19 (s, 1 H), 8.98 (q, *J* = 4.5 Hz, 1 H); ms (ESI/NH_3): *m/e* 375 (M+H)$^+$. *Anal.* Calcd for $C_{19}H_{19}ClN_2O_2S$•TFA: C, 51.59; H, 4.12; N, 5.73. Found: C, 51.70; H, 4.08; N, 5.65.

Methyl 4-(4-chlorophenoxy)-7-furan-2-yl-thieno[2,3-*c*]pyridine-2-carboxamide (11b). A 25 mL round bottom flask was charged with **10** (100 mg, 0.25 mmol), $Pd(OAc)_2$ (10.8 mg, 0.048 mmol) and (*o*-tol)$_3$P (44 mg, 0.14 mmol), and was purged with nitrogen. Anhydrous DMF (6 mL), 2-tributylstannylfuran (178 mg, 0.5 mmol) and triethylamine (167 μL, 1.2 mmol) were added. The suspension was purged with nitrogen again, and was stirred at 80 °C for 15 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residual material was purified by HPLC (Zorbax, C-18, CH_3CN/H_2O/0.1% TFA as mobile phase) to provide **11b** as TFA salt. Yield: 108.9 mg (87%). m.p. 145-147 °C. ^{1}H nmr (300 MHz, DMSO-d$_6$): δ 2.81 (d, *J* = 4.4 Hz, 3 H), 6.79 (dd, *J* = 3.3, 1.8 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 3.7 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 8.07 (d, *J* = 1.7 Hz, 1 H), 8.11 (s, 1 H), 8.26 (s, 1 H), 9.00 (d, *J* = 4.8 Hz, 1 H); ms (ESI/NH_3): *m/e* 385 (M+H)$^+$. *Anal.* Calcd for $C_{19}H_{13}ClN_2O_3S$•TFA: C, 50.56; H, 2.83; N, 5.62. Found: C, 50.50; H, 2.87; N, 5.54.

Methyl 4-(4-chlorophenoxy)-7-morpholin-4-ylthieno[2,3-*c*]-pyridine-2-carboxamide (11c). A 25 mL round bottom flask was charged with **10** (100 mg, 0.25 mmol), $Pd_2(dba)_3$ (14 mg, 0.014 mmol), (-)-BINAP (27 mg, 0.044 mmol), 18-crown-6 (196 mg, 0.74 mmol) and sodium *tert*-butoxide (71 mg, 0.74 mmol), and was purged with nitrogen. Anhydrous THF (10 mL) and morpholine (64 mg, 0.75 mmol) were added. The dark solution was purged with nitrogen again, and was stirred at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was separated by HPLC (Zorbax, C-18, CH_3CN/H_2O/0.1% TFA as mobile phase) to provide **11c** as TFA salt. Yield: 112.2 mg (86%). m.p. 170-173 °C. ^{1}H nmr (300 MHz, DMSO-d_6): δ 2.77 (d, *J* = 4.8 Hz, 3 H), 3.52 (t, *J* = 4.6 Hz, 4 H), 3.81 (t, *J* = 4.6 Hz, 4 H), 7.01 (d, *J* = 9.2 Hz, 2 H), 7.40 (d, *J* = 9.2 Hz, 2 H), 7.93 (s, 1 H), 7.96 (s, 1 H), 8.93 (q, *J* = 4.8 Hz, 1 H); ms (ESI/NH_3): *m/e* 404 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{18}ClN_3O_3S$□TFA: C, 48.70; H, 3.70; N, 8.11. Found: C, 48.79; H, 3.76; N, 8.05.

Methyl 4-(4-chlorophenoxy)-7-(3-morpholin-4-ylpropyl-amino)thieno[2,3-*c*]pyridine-2-carbox-amide (11d). Compound **11d** was prepared by the same protocol as described for **11c**, substituting 4-(3-aminopropyl)-morpholine for morpholine. Yield: 94%. ^{1}H nmr (300 MHz, DMSO-d_6): δ 2.03 (m, 2 H), 2.78 (d, *J* = 4.7 Hz, 3 H), 3.22 (m, 2 H), 3.30 (m, 4 H), 3.52 (m, 2 H), 3.85 (m, 4 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 7.40 (d, *J* = 9.0 Hz, 2 H), 7.82 (s, 1 H), 7.83 (s, 1 H), 8.90 (q, *J* = 4.7 Hz, 1 H); ms (ESI/NH_3): *m/e* 461 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{25}ClN_4O_3S$•TFA: C, 50.13; H, 4.56; N, 9.74. Found: C, 50.23; H, 4.48; N, 9.87.

4-Phenoxythieno[2,3-c]pyridine-2-carboxylic acid (13). To a solution of **12** (2.11 g) [2a] in THF (40 mL) was added a solution of LiOH•H_2O (621 mg) in H_2O (40 mL) at rt. Methanol was added until a transparent solution formed (5 mL). This solution was aged at rt for 2 h, and was acidified with 10% aq. HCl to a pH 4. The mixture was concentrated at reduced pressure to ~40 mL. The formed white solid was collected by filtration, washed with water and dried to give **13**. Yield: 1.84 g (92%). ^{1}H nmr (300 MHz, DMSO-d_6): δ 7.13 (dd, *J* = 8.5, 1.0 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.44 (dd, *J* = 8.8, 7.5 Hz, 2 H), 7.82 (s, 1 H), 8.18 (s, 1 H), 9.17 (s, 1 H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 118.1, 124.2, 130.3, 132.9, 136.3, 138.9, 140.6, 141.2, 147.9, 156.5, 162.7; ms (DCI/NH_3): *m/e* 272 $(M+H)^+$. *Anal.* Calcd for $C_{14}H_9NO_3S$: C, 61.98; H, 3.34; N, 5.16. Found: 62.06; H, 3.42; N, 5.02.

4-Phenoxythieno[2,3-*c*]pyridine (15). A suspension of acid **13** (1.80 g, 6.6 mmol) in diphenyl ether (12 mL) was purged with nitrogen, and was heated at 228-230 °C (oil bath) for 20 h. After cooling, the formed brown solution was diluted with methylene chloride, and was directly purified by flash chromatography (8-40% gradient EtOAc in hexane) to give **15**. Yield: 1.27 g (84%). ^{1}H nmr (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.6, 0.9 Hz, 2 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 7.35 (m, 3 H), 7.62 (d, *J* = 5.5 Hz, 1 H), 8.15 (s, 1 H), 8.94 (s, 1 H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 118.1, 120.0, 123.7, 129.9, 131.4, 132.9, 137.7, 138.0, 140.0, 148.0, 157.0; ms (DCI/NH_3): *m/e* 228 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.51; H, 3.96; N, 6.11.

4-Phenoxy-2-trimethylstannanylthieno[2,3-*c*]pyridine (18). To a solution of thienopyridine **15** (0.77 g, 3.38 mmol) in THF (10 mL) was slowly added *n*-butyllithium (2.5 *M* solution in hexane, 1.36 mL, 3.38 mmol) at –78 °C. After addition, the solution was warmed up to 0 °C, stirred at 0 °C for 10 min and then cooled to – 78 °C. A solution of trimethyltin chloride (0.808 g) in THF (5 mL) was then added slowly. The solution was stirred at –78 °C for 1 h and at rt for 15 min before being partitioned between EtOAc and brine. The organic phase was washed with water, and concentrated. The residue was purified by flash chromatography (10-35% gradient EtOAc in hexane) to give **18**. Yield: 0.936 g (71%). ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.44 (s, 9 H), 7.06 (dd, *J* = 8.6, 0.9 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.34 (dd, *J* = 8.7, 7.5 Hz, 2 H), 7.47 (s, 1 H), 8.08 (s, 1 H), 8.93 (s, 1 H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 118.2, 123.6, 127.2, 129.8, 132.2, 138.7, 139.2, 142.6, 147.4, 147.9, 157.1; ms (DCI/NH_3): *m/e* 392 $(M+H)^+$. Anal. Calcd for $C_{16}H_{17}NOSSn$: C, 49.26; H, 4.39; N, 3.59. Found: C, 49.50; H, 4.43; N, 3.56.

4-Chlorothieno[2,3-*c*]pyridine-2-carboxylic acid (14). Ester **4b** (5.80 g, 25.5 mmol) was saponified with LiOH (2.2 g, 51 mmol) under the same conditions as described for **13** to provide **14**. Yield: 5.01 g (92%). ir (KBr): ν_{max} 1709 (s) cm^{-1}; ^{1}H nmr (300 MHz, DMSO-d_6): δ 8.06 (s, 1 H), 8.62 (s, 1 H), 9.34 (s, 1 H), 14.21 (s, 1 H); ms (ESI/NH_3): *m/e* 214 $(M+H)^+$. *Anal.* Calcd for $C_8H_4ClNO_2S$: C, 44.98; H, 1.89; N, 6.56. Found: 45.10; H, 1.81; N, 6.48.

4-Chlorothieno[2,3-*c*]pyridine (16). Acid **14** (4.98 g, 23.3 mmol) was decarboxylated in phenyl ether (30 mL) under the same conditions as described for **15** to provide **16**. Yield: 3.5 g (88%). ir (KBr): ν_{max} 1229 (s) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 5.4 Hz, 1 H), 7.80 (d, *J* = 5.4 Hz, 1 H), 8.48 (s, 1 H), 9.04 (s, 1 H); ms (DCI/NH_3) *m/e* 170 $(M+H)^+$. *Anal.* Calcd for C_7H_4ClNS: C, 49.56; H, 2.38; N, 8.26. Found: 49.70; H, 2.25; N, 8.10.

4-Chloro-2-trimethylstannanylthieno[2,3-*c*]pyridine (19). **19** was prepared from **16** (1.83 g, 10.82 mmol) under the same conditions as described for **18**. Yield: 73%. ir (KBr): ν_{max} 1564 (s) cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.49 (s, 9 H), 7.56 (s, 1 H), 8.40 (s, 1 H), 9.00 (s, 1 H); ^{13}C nmr (100 MHz, $CDCl_3$): δ 124.9, 128.7, 141.1, 141.6, 141.9, 144.0, 150.1; ms (ESI/NH_3): *m/e* 334 $(M+H)^+$. *Anal.* Calcd for $C_{10}H_{12}ClNSSn$: C, 36.13; H, 3.64; N, 4.21. Found: 36.22; H, 3.64; N, 4.21.

4-Chloro-2-phenylthieno[2,3-*c*]pyridine (20). A 100 mL round bottom flask was charged with **18** (1.0 g, 3.0 mmol), $Pd_2(dba)_3$ (274 mg, 0.3 mmol), tri-*o*-tolylphosphine (274 mg, 0.9 mmol), and was purged with N_2. Anhydrous DMF (30 mL), bromobenzene (316 *μ*L, 3.0 mmol) and Et_3N (1.25 mL, 9.0 mmol) were added via syringe. The solution was purged with N_2 again, and was heated at 70 °C for 5 h. After cooling, ethyl acetate (150 mL) was added. The mixture was washed with brine (150 mL) and water (150 mL). The ethyl acetate solution was concentrated, and the residual oil was separated by flash chromatography (8-20% gradient EtOAc/hexane) to give **20**. Yield: 530 mg (72%). ^{1}H nmr (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.0 Hz, 2 H), 7.45 (m, 1 H), 7.61 (s, 1 H), 7.71 (dd, *J* = 7.8, 1.7 Hz, 2 H), 8.42 (s, 1 H), 8.90 (s, 1 H); ms (DCI/NH_3) *m/e* 246 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: 63.33; H, 3.21; N, 5.75.

4-Furan-2-yl-2-phenylthieno[2,3-*c*]pyridine (21). A 25 mL round bottom flask was charged with **20** (100 mg, 0.41 mmol), $Pd_2(dba)_3$ (38 mg, 0.04 mmol), and 1,3-bis(2,6-di-i-propyl-phenyl)imidazolium chloride (33 mg, 0.08 mmol), and was purged with N_2. Anhydrous DMF (7 mL), 2-tributylstannylfuran (258 μL, 0.82 mmol) and Et_3N (172 μL, 1.23 mmol) were added *via* syringe. The solution was purged with N_2 again, and was heated at 75 °C for 6 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with water, and concentrated. The residue was separated by flash chromatography (15-50% gradient EtOAc in hexane) to give **21**. Yield: 96 mg (85%). ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.61 (dd, *J* = 3.6, 1.9 Hz, 1 H), 6.91 (d, *J* = 3.4 Hz, 1 H), 7.47 (m, 3 H), 7.68 (d, *J* = 1.7 Hz, 1 H), 7.81 (dd, *J* = 8.0, 1.5 Hz, 2 H), 8.14 (s, 1 H), 8.79 (s, 1 H), 8.99 (s, 1 H); ms (DCI/NH_3): *m/e* 278 $(M+H)^+$. *Anal*. Calcd for $C_{17}H_{11}NOS$: C, 73.62; H, 4.00; N, 5.05. Found: 73.41; H, 3.94; N, 5.18.

4-Phenylamino-2-phenylthieno[2,3-*c*]pyridine (22). A 25 mL RBF was charged with **20** (100 mg, 0.4 mmol)), $Pd_2(dba)_3$ (36 mg, 0.04 mmol), and 1,3-bis(2,6-di-*i*-propylphenyl)-imidazolium chloride (34 mg, 0.08 mmol), and was purged with N_2. Anhydrous dioxane (4 mL), aniline (56 mg, 0.62 mmol) and potassium tert-butoxide (1.0 *M* solution in THF, 0.62 mL, 0.62 mmol) were added *via* syringe. The solution was purged with N_2 again, and was heated at 100 °C for 20 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine, and concentrated. The residue was separated by flash chromatography (30-70% gradient EtOAc in hexane) to provide **22**. Yield: 112 mg (91%). ^{1}H nmr (300 MHz, $CDCl_3$): δ 5.92 (br s, 1 H), 6.98 (t, *J* = 7.5 Hz, 1 H), 7.04 (dd, *J* = 8.0, 1.0 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.30 (dd, *J* = 8.2, 7.4 Hz, 1 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 7.46 (s, 1 H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 2 H), 8.39 (s, 1 H), 8.78 (s, 1 H); ms (DCI/NH_3): *m/e* 303 $(M+H)^+$. *Anal*. Calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26. Found: 75.38; H, 4.77; N, 9.18.

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