Regiocontrolled S_NAr Reaction on 2,3-Dihalopyridines with NaSMe To Obtain Bromo(methylthio)pyridines as Key Precursors of 3-Halo-2-(hetero)arylthieno[2,3-*b*]pyridines and Thieno[3,2-*b*]pyridines

Agathe Begouin, Daniela Peixoto, Maria-João R. P. Queiroz*

Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
Fax +351(253)604382; E-mail: mjrpq@quimica.uminho.pt

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Abstract: The synthesis of 3-halo-2-(hetero)arylthieno[2,3-*b*]pyridines and 3-halo-2-(hetero)arylthieno[3,2-*b*]pyridines has been performed through a three-step methodology from 3-bromo-2-chloropyridine or 2-bromo-3-fluoropyridine, respectively. The key step of this methodology is the formation of the required bromo(methylthio)pyridines by a regiocontrolled nucleophilic aromatic substitution (S_NAr) with sodium methanethiolate (NaSMe). Then, the Sonogashira coupling with (hetero)arylalkynes followed by a halocyclization with bromine or iodine, afforded the expected 3-halo-2-(hetero)arylthienopyridines.

Key words: thienopyridines, nucleophilic aromatic substitution, methanethiolate, Sonogashira coupling, halocyclization

Thienopyridines are of chemical and pharmacological interest, due to their isosterism with quinolines and isoquinolines, two important heterocycles that can be found in various alkaloids.[1] Up to now, the chemistry of the thieno[2,3-*b*]pyridines is better known than the chemistry of the thieno[3,2-*b*]pyridines. However, many thieno[3,2-*b*]pyridines have recently shown to possess a large variety of biological activities. For instance, diheteroarylamine derivatives[2] and *N*[3]-arylmalonamides[3] in the thieno[3,2-*b*]pyridine series as well as substituted thieno[3,2-*b*]pyridine ureas[4] were shown to be inhibitors of the vascular endothelial growth factor receptor (VEGFR2), mediator of the biological function of the vascular endothelial growth factor (VEGF) related to angiogenesis. Other thieno[3,2-*b*]pyridine derivatives are inhibitors of the nonreceptor Src tyrosine kinases[5a,b] that are overexpressed and/or activated in several types of cancer and also play a key role in tumor progression and metastases. This diversity of biological activities gave an impulse to the development of new convenient synthetic routes for the thieno[3,2-*b*]pyridine skeleton.

Most of the methods for the synthesis of thieno[3,2-*b*]pyridines are based on the use of readily accessible 3-aminothiophenes or their N-derivatives[6a–e] and only few syntheses have already been described starting from the pyridine ring.[7a–e] For example, Fort et al.[7d] have reported a three-step process allowing the construction of the thiophene ring from 3-methylthiopyridine that had to be synthesized through the lithiation of 3-bromopyridine using *t*-BuLi at –80 °C, followed by a reaction with dimethyl disulfide at –95 °C in anhydrous THF and by a not completely regioselective lithiation–bromination at the 2-position of 3-methylthiopyridine, induced by the BuLi-LiDMAE superbase [DMAE: 2-(dimethylamino)ethanol]. Then, the 2-bromo-3-methylthiopyridine was submitted to a Sonogashira coupling followed by a halocyclization giving the corresponding 2-substituted (Ph or TMS) 3-halothieno[3,2-*b*]pyridines.

Kawai and co-workers[7e] have also reported the synthesis of thieno[3,2-*b*]pyridine derivatives via the formation of the intermediate 2-bromo-3-(methylthio)pyridine, which was obtained by treatment of 2,3-dibromopyridine with *n*-BuLi and dimethyl disulfide in Et_2O. The Sonogashira coupling of 2-bromo-3-(methylthio)pyridine with trimethyl(prop-1-ynyl)silane, followed by a halocyclization with I_2 gave the 3-iodo-2-methylthieno[3,2-*b*]pyridine.

In the past few years, our research group has been interested in the synthesis of thieno[3,2-*b*]pyridine derivatives. In 2010, the synthesis of the methyl 3-amino-6-bromothieno[3,2-*b*]pyridine-2-carboxylate has been reported by us for the first time from 5-bromo-3-nitropicolinonitrile and methyl thioglycolate in DMF–aqueous KOH.[8] Further functionalizations at the 6-position of the thieno[3,2-*b*]pyridine of this compound by C–C (Suzuki, Sonogashira)[9a–c] or C–N (Buchwald–Hartwig)[9d] couplings have given new derivatives, some of them exhibiting growth inhibitory activity in human tumor cell lines.

More recently, we have reported[10] a simple and efficient method for the synthesis of 2-(hetero)arylthieno[2,3-*b*]pyridines and 2-(hetero)arylthieno[3,2-*b*]pyridines from 3-bromo-2-chloropyridine or 2-bromo-3-chloropyridine, respectively, and (hetero)arylalkynes through a Sonogashira coupling involving selectively the bromine atom, followed by a reaction with sodium sulfide on the chlorine. A bromination of some of the thienopyridines obtained was also performed with Br_2 to obtain the corresponding 3-bromo-2-(hetero)arylthienopyridines.

Herein, we describe the synthesis of 2-substituted (aryl or heteroaryl) 3-halothienopyridines from 2,3-dihalopyridines (3-Br-2-Cl, or 2-Br-3-F) through the formation of bromo(methylthio)pyridines followed by a Sonogashira coupling and a halocyclization with Br_2 or I_2, as depicted in Scheme 1.

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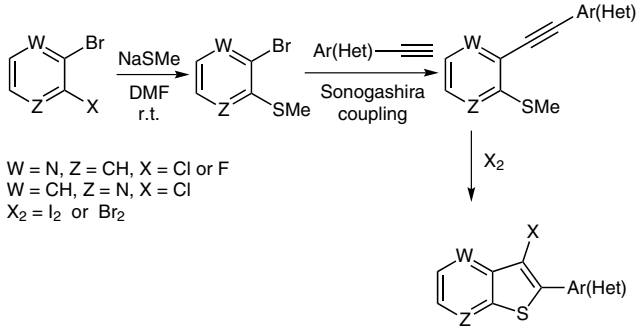
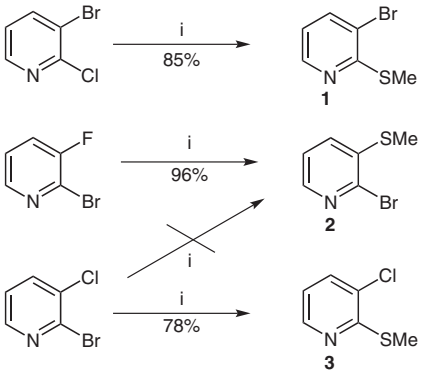


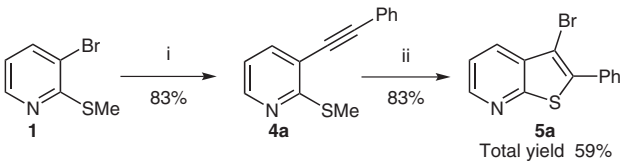
Scheme 1 Strategy envisaged for the three-step synthesis of 3-halothienopyridines from 2,3-dihalopyridines

In the present work, the synthesis of 3-halo-2-(hetero)arylthienopyridines was carried out through an initial nucleophilic aromatic substitution with sodium methanethiolate (NaSMe). Thus, the synthesis of the required bromo(methylthio)pyridines **1** and **2** was achieved in high to excellent yields using 3-bromo-2-chloropyridine and 2-bromo-3-fluoropyridine, respectively. Nevertheless starting from 2-bromo-3-chloropyridine, only the 3-chloro-2-(methylthio)pyridine (**3**) was obtained (Scheme 2). The presence of the fluorine atom in the 3-position allows the regiocontrol of the S_NAr reaction by offsetting the reactivity of the bromine in the 2-position of the pyridine, thus permitting the synthesis of the thieno[3,2-*b*]pyridine derivatives starting from compound **2**.



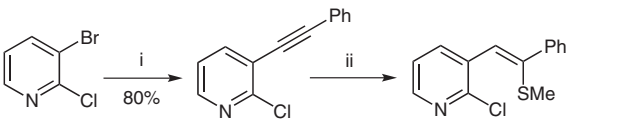
Scheme 2 *Reagents and conditions*: (i) NaSMe (1.5 equiv), DMF, 0 °C to r.t.

The Sonogashira coupling of compound **1** was first performed with phenylacetylene using conditions previously optimized by our research group for the coupling of bromochloropyridines.[10] Using these conditions, the expected 2-(methylthio)-3-(phenylethynyl)pyridine (**4a**) was obtained in 83% yield. Then, a bromocyclization was performed with Br_2, which afforded the 3-bromo-2-phenylthieno[2,3-*b*]pyridine (**5a**) also in 83% yield, with a total yield of 59% (Scheme 3). This yield is far better than the one previously obtained by us in the synthesis of the same thieno[2,3-*b*]pyridine **5a** through a Sonogashira coupling followed by a reaction with Na_2S and at the end a bromination step (only 40% yield).[10]



Scheme 3 *Reagents and conditions*: (i) PhC≡CH (1.1 equiv), $PdCl_2(PPh_3)_2$ (6 mol%), CuI (3 mol%), Et_3N (1–2 mL), 100 °C, overnight; (ii) Br_2 (1.5 equiv), anhyd Et_2O, 0 °C to r.t., 0.5 h, under argon.

Another strategy was also experimented for the synthesis of **5a**: first a Sonogashira coupling was performed followed by a S_NAr reaction with NaSMe and a halocyclization. Using this strategy, the expected 2-chloro-3-(phenylethynyl)pyridine was obtained in 80% yield through the Sonogashira coupling of the 3-bromo-2-chloropyridine with phenylacetylene. However, the reaction with NaSMe did not afford the 2-(methylthio)-3-(phenylethynyl)pyridine (**4a**), but the 2-chloro-3-(2-methylsulfanyl-2-phenylvinyl)pyridine resulting from the addition of SMe to the triple bond of the Sonogashira product instead of the expected nucleophilic substitution of the chlorine atom of the pyridine ring (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) PhC≡CH (1.1 equiv), $PdCl_2(PPh_3)_2$ (6 mol%), CuI (3 mol%), Et_3N (1–2 mL), 100 °C, overnight; (ii) NaSMe (1.5 equiv), DMF, r.t., 1 h.

Having these results in hands, the strategy depicted in Scheme 1 was used to obtain the 3-(hetero)arylethynyl-2-(methylthio)pyridines **4a**–**f** and the 2-(hetero)ethynyl-3-(methylthio)pyridines **6a**–**f**, from compounds **1** and **2**, respectively, in good to excellent yields (70–93%). Sonogashira couplings were also performed with two heteroarylalkynes, the electron-deficient 3-ethynylpyridine and the electron-rich 3-ethynylthiophene, giving compounds **4e**, **f** and **6e**, **f** in high yields (Table 1). After halocyclization of compounds **4** and **6**, the 3-halo-2-(hetero)arylthieno[2,3-*b*]pyridines **5a**–**h** and the 3-halo-2-(hetero)arylthieno[3,2-*b*]pyridines **7a**–**g** were obtained, respectively (Table 1).

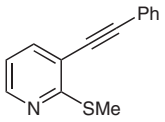
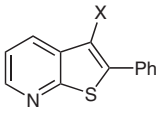
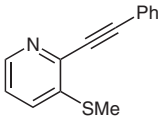
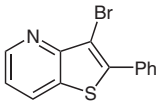
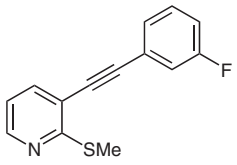
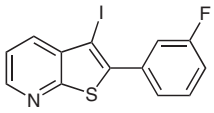
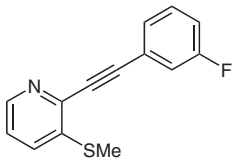
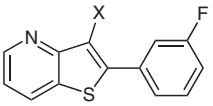
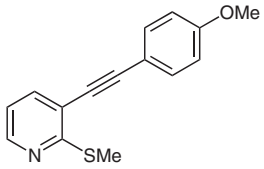
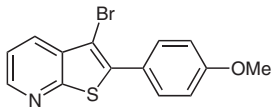
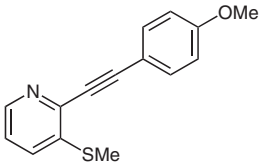
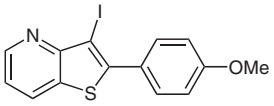
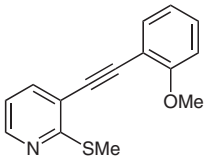
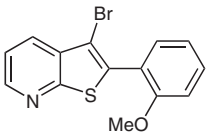
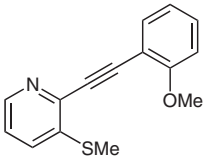
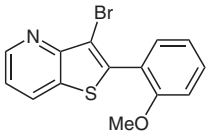
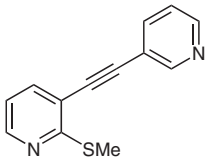
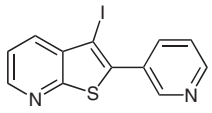
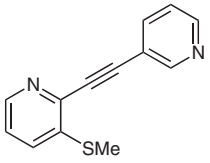
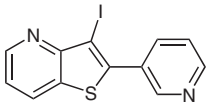
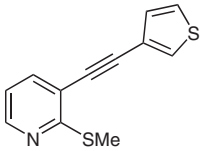
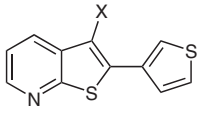
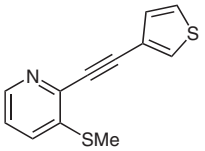
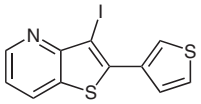
In our previous work, related to the synthesis of 2-(hetero)arylthienopyridines from 2,3-dihalopyridines, (hetero)arylalkynes and Na_2S, hydroxylated thienopyridines were obtained from the *ortho*-methoxylated Sonogashira coupling products, instead of the expected 2-(2-methoxyphenyl)thienopyridines. This result was probably due to the spatial proximity of the sulfide anion intermediate with the methoxy group.[10] This led us to propose the most probable mechanism consisting in the preliminary addition of Na_2S to the triple bond of the alkynylpyridine, followed by a S_NAr/cyclization (Scheme 5).

This is in accordance with the observation made in the present work while following the strategy depicted in Scheme 4: the reaction of NaSMe was carried out after the Sonogashira coupling leading to the addition of SMe to the triple bond, thus avoiding the formation of the cyclized products.

Herein the Sonogashira couplings of compounds **1** and **2** were also performed with 2-ethynylanisole, leading to the formation of the corresponding 3-[(2-methoxyphenyl)ethynyl]-2-(methylthio)pyridine (**4d**) and 2-[(2-methoxyphenyl)ethynyl]-3-(methylthio)pyridine (**6d**), and then to the expected 3-bromo-2-(2-methoxyphenyl)thieno[2,3-*b*]pyridine (**5e**) and 3-bromo-2-(2-methoxyphenyl)thieno[3,2-*b*]pyridine (**7e**), respectively, in high yields after halocyclization with Br_2.

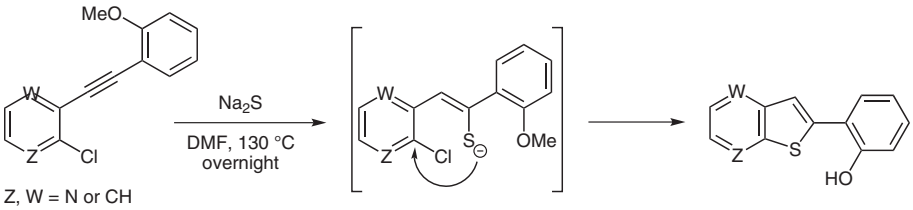
In summary, we have described an efficient three-step methodology for the synthesis of 3-halo-2-(hetero)arylthieno[2,3-*b*]pyridines and 3-halo-2-(hetero)arylthieno[3,2-*b*]pyridines using 3-bromo-2-chloropyridine or 2-bromo-3-fluoropyridine as starting materials, respectively. The

Table 1 Synthesis of (Methylthio)pyridines and 3-Halo-2-(hetero)arylthienopyridines[a]

3-(Hetero)aryl-2-(methylthio)pyridines **4a–f**	3-Halo-2-(hetero)arylthieno[2,3-*b*]pyridines **5a–h**	2-(Hetero)aryl-3-(methylthio)pyridines **6a–f**	3-Halo-2-(hetero)arylthieno[3,2-*b*]pyridines **7a–g**
 **4a**, 83%	 **5a** X = Br, 83% **5b** X = I, 73%	 **6a**, 88%	 **7a**, 89%
 **4b**, 79%	 **5c**, 76%	 **6b**, 81%	 **7b** X = Br, 90% **7c** X = I, 80%
 **4c**, 79%	 **5d**, 99%	 **6c**, 93%	 **7d**, 98%
 **4d**, 87%	 **5e**, 80%	 **6d**, 70%	 **7e**, 87%
 **4e**, 80%	 **5f**, 80%[b]	 **6e**, 81%	 **7f**, 90%[b]
 **4f**, 74%	 **5g** X = Br, 81% **5h** X = I, 77%	 **6f**, 75%	 **7g**, 77%

[a] Sonogashira coupling: $PdCl_2(PPh_3)_2$ (6 mol%), CuI (3 mol%), Et_3N (1–2 mL), 100 °C, overnight (from **1**) or 1 h (from **3**). Halocyclization: Br_2 or I_2 (1.5 equiv), anhyd Et_2O, 0 °C to r.t., 0.5 h.

[b] Halocyclization was performed in anhyd CH_2Cl_2 due to the poor solubility of **4e** and **6e** in Et_2O.



Scheme 5 Formation of 2-(thieno[2,3-*b*] or [3,2-*b*]pyridin-2-yl)phenols by the reaction of chloro(2-methoxyphenylethynyl)pyridines with Na_2S[10]

key step of this methodology consists in the regiocontrolled S_NAr reaction of these 2,3-dihalopyridines with NaSMe, allowing the formation of the bromo(methylthio)pyridines needed for the Sonogashira coupling. From 3-bromo-2-chloropyridine, the 3-chloro-2-(methylthio)pyridine was the only product isolated. However, the change of the halide from chlorine to fluorine allowed the formation of the required 2-bromo-3-(methylthio)pyridine. Finally, the halocyclization step afforded the expected 3-bromo- or 3-iodo-2-(hetero)arylthienopyridines in high yields. It is worth noting that the Sonogashira coupling has to be performed after the S_NAr with NaSMe, otherwise this reaction leads to the addition of SMe to the triple bond, thus preventing the formation of the thienopyridines.

Melting points were determined in a Stuart SMP3 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III at 400 and 100.6 MHz or on a Varian Unity Plus at 300 and 75.4 MHz, respectively. Heteronuclear correlations, ^1H-^{13}C, HMQC or HSQC and HMBC were performed to assign some signals. MS-EI and HRMS on the M^+ data were recorded by the mass spectrometry service of the University of Vigo (C.A.C.T.I.), Spain.

Column chromatography was performed on Macherey-Nagel silica gel 230–400 mesh. Petroleum ether (PE) refers to the fraction with boiling range 40–60 °C. The increase of polarity in solvent gradient was made from neat PE to mixtures of Et_2O–PE, increasing 10% of Et_2O each time, until the isolation of the products. Known compounds were not fully described.

Halo(methylthio)pyridines 1–3; General Procedure
To a solution of 3-bromo-2-chloropyridine, 2-bromo-3-chloropyridine (192 mg, 1.00 mmol), or 2-bromo-3-fluoropyridine (176 mg, 1.00 mmol) in DMF (5 mL/mmol) at 0 °C (ice bath) was added NaSMe (105 mg, 1.5 mmol, 1.5 equiv) and the reaction mixture was allowed to stir for 1 h at 0 °C. EtOAc (15 mL) and H_2O (3 × 10 mL) were added and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and removal of the solvent gave the expected halo(methylthio)pyridines **1**–**3** as depicted in Scheme 2.

3-Bromo-2-(methylthio)pyridine (1)
Yield: 174 mg (85%); pale yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, SCH_3), 6.90 (dd, *J* = 7.8, 4.8 Hz, 1 H, 5-H), 7.71 (dd, *J* = 7.8, 1.6 Hz, 1 H, 4-H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.24 (SCH_3), 119.07 (C), 119.65 (5-CH), 136.90 (4-CH), 147.44 (6-CH), 159.34 (C).

MS-EI: *m*/*z* = 204.94 ([$^{81}BrM^+$], 24), 202.94 ([$^{79}BrM^+$], 25), 124.02 (100).

HRMS: *m*/*z* [M^+] calcd for $C_6H_6{}^{79}BrNS$: 202.9405; found: 202.9404. [M^+] calcd for $C_6H_6{}^{81}BrNS$: 204.9383; found: 204.9384.

2-Bromo-3-(methylthio)pyridine (2)
Yield: 195 mg (96%); pale yellow oil (Lit.[7d] brown gummy solid).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, SCH_3), 7.27 (dd, *J* = 7.8, 4.6 Hz, 1 H, 5-H), 7.40 (dd, *J* = 7.8, 1.8 Hz, 1 H, 4-H), 8.14 (dd, *J* = 4.6, 1.8 Hz, 1 H, 6-H).

MS-EI: *m*/*z* = 204.94 ([$^{81}BrM^+$], 98), 202.94 ([$^{79}BrM^+$], 100), 124.02 (9).

HRMS: *m*/*z* [M^+] calcd for $C_6H_6{}^{79}BrNS$: 202.9404: found 202.9407. [M^+] calcd for $C_6H_6{}^{81}BrNS$: 204.9384; found: 204.9382.

3-Chloro-2-(methylthio)pyridine (3)
Yield: 124 mg (78%); pale yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, SCH_3), 6.98 (dd, *J* = 7.8, 4.8 Hz, 1 H, 5-H), 7.56 (dd, *J* = 7.8, 1.6 Hz, 1 H, 4-H), 8.39 (dd, *J* = 4.8, 1.6 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.51 (SCH_3), 119.46 (5-CH), 129.36 (C), 135.90 (4-CH), 146.63 (6-CH), 158.01 (C).

MS-EI: *m*/*z* = 160.99 ([$^{37}ClM^+$], 36), 158.99 ([$^{35}ClM^+$], 100), 149.03 (46), 124.02 (85).

(Hetero)aryl-2 and 3-(Methylthio)pyridines 4a–f and 6a–f; General Procedure
In a dry Schlenk tube, bromo(methylthio)pyridine **1** or **2** (1 equiv), CuI (10 mol%), and $PdCl_2(PPh_3)_2$ (5 mol%) were added under argon in Et_3N (1–2 mL) and the mixture was stirred for 5–10 min at r.t. Then, the (hetero)arylalkyne (1.1 equiv) was added dropwise under argon and the mixture was heated at 100 °C overnight for 3-bromo-2-(methylthio)pyridine (**1**) or 1 h for 2-bromo-3-(methylthio)pyridine (**2**). After cooling, the solution was diluted with $CHCl_3$ (10 mL) and the solvent was evaporated to give a brown oil that was submitted to column chromatography (Table 1).

2-(Methylthio)-3-(phenylethynyl)pyridine (4a)
From **1** (204.0 mg) and phenylacetylene (112.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 1:9); yield: 187 mg (83%); yellow solid; mp 53–55 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, SCH_3), 7.01 (dd, *J* = 7.2, 5.0 Hz, 1 H, 5-H), 7.37–7.39 (m, 3 H), 7.59–7.61 (m, 2 H), 7.67 (br d, 1 H, 4-H), 8.43 (br s, 1 H, 6-H).

^{13}C NMR (100.6 MHz, MHz, $CDCl_3$): δ = 13.43 (SCH_3), 84.32 (C≡C), 98.59 (C≡C), 118.08 (C), 118.40 (5-CH), 128.40 (2 × CH), 128.90 (CH), 131.60 (2 × CH), 138.73 (4-CH), 147.46 (6-CH), 161.74 (*C*SMe).

MS-EI: *m*/*z* = 226.06 ([M^+ + 1], 8), 225.06 ([M^+], 62), 224.06 ([M^+ – 1], 100), 223.05 ([M^+ – 2], 37).

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{11}NS$: 225.0612; found: 225.0612.

3-[(3-Fluorophenyl)ethynyl]-2-(methylthio)pyridine (4b)
From **1** (70.0 mg) and 1-ethynyl-3-fluorobenzene (45.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 1:9); yield: 66.0 mg (79%); yellow solid; mp 77–79 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, SCH_3), 7.01 (dd, *J* = 7.6, 4.8 Hz, 1 H, 5-H), 7.06–7.11 (m, 1 H,), 7.27–7.30 (m, 1 H),

7.33–7.38 (m, 2 H), 7.66 (dd, *J* = 7.6, 1.2 Hz, 1 H, 4-H), 8.43 (dd, *J* = 4.8, 1.2 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.18 (SCH_3), 85.38 (C≡C), 96.87 (d, *J* = 3.0 Hz, C≡C), 116.16 (d, *J* = 21.0 Hz, CH), 117.34 (3-C), 118.18 (5-CH), 118.25 (d, *J* = 22.0 Hz, CH), 124.39 (d, *J* = 10.0 Hz, 1′-C), 127.40 (d, *J* = 3.0 Hz, 6′-CH), 129.92 (d, *J* = 8.0 Hz, 5′-CH), 138.56 (4-CH), 148.12 (6-CH), 161.97 (*C*SMe), 162.36 (d, *J* = 245.0 Hz, CF).

MS-EI: *m*/*z* (%) = 244.05 ([M^+ + 1], 11), 243.05 ([M^+], 56), 242.05 ([M^+ – 1], 100).

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{10}FNS$: 243.0518; found: 243.0523.

3-[(4-Methoxyphenyl)ethynyl]-2-(methylthio)pyridine (4c)
From **1** (60.0 mg) and 4-ethynylanisole (43.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 1:9); yield: 60.0 mg (79%); yellow gummy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, SCH_3), 3.85 (s, 3 H, OCH_3), 6.90 (d, *J* = 8.8 Hz, 2 H, 3′- and 5′-H), 6.99 (dd, *J* = 7.6, 5.2 Hz, 1 H, 5-H), 7.53 (d, *J* = 8.8 Hz, 2 H, 2′- and 6′-H), 7.64 (dd, *J* = 7.6, 2.0 Hz, 1 H, 4-H), 8.40 (br d, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.26 (SCH_3), 55.33 (OCH_3), 83.33 (C≡C), 98.58 (C≡C), 114.07 (3′- and 5′-CH), 114.67 (C), 118.30 (5-CH), 133.13 (2′- and 6′-CH), 134.02 (C), 138.21 (4-CH), 147.42 (6-CH), 160.10 (*C*OMe), 161.54 (*C*SMe).

MS-EI: *m*/*z* (%) = 256.07 ([M^+ + 1], 9), 255.07 ([M^+], 78), 254.06 ([M^+ – 1], 100).

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{13}NOS$: 255.0718; found 255.0721.

3-[(2-Methoxyphenyl)ethynyl]-2-(methylthio)pyridine (4d)
From **1** (45.0 mg) and 2-ethynylanisole (32.0 mg), and after purification by column chromatography using a solvent gradient from (Et_2O–PE, 0:1 to 1:4); yield: 49.0 mg (87%); pale yellow solid; mp 105–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (s, 3 H, SCH_3), 3.94 (s, 3 H, OCH_3), 6.92–6.99 (m, 2 H, 3′- and 5′-H), 7.03 (dd, *J* = 7.8, 4.8 Hz, 1 H, 5-H), 7.33–7.38 (m, 1 H, 4′-H), 7.56 (dd, *J* = 7.8, 1.8 Hz, 1 H, 4-H), 7.73 (dd, *J* = 7.8, 1.6 Hz, 1 H, 6′-H), 8.44 (dd, *J* = 4.8, 18 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.47 (SCH_3), 55.88 (OCH_3), 88.22 (C≡C), 95.25 (C≡C), 110.79 (3′-CH), 111.76 (C), 118.30 (5-CH), 118.43 (C), 120.51 (CH), 130.44 (CH), 133.57 (CH), 138.77 (4-CH), 147.21 (6-CH), 160.07 (*C*SMe), 161.67 (*C*OMe).

2-(Methylthio)-3-[(pyridin-3-yl)ethynyl]pyridine (4e)
From **1** (80.0 mg) and 3-ethynylpyridine (45.0 mg), and after purification by column chromatography (Et_2O–PE, 1:4 to 2:3); yield: 54.0 mg (80%); yellow solid; mp 73–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, SCH_3), 6.99 (dd, *J* = 7.6, 4.8 Hz, 1 H, 5-H), 7.36 (br s, 1 H, 5′-H), 7.66 (dd, *J* = 7.6, 1.6 Hz, 1 H, 4-H), 7.88 (br d, 1 H, 4′-H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1 H, 6-H), 8.69 (br s, 1 H, 6′-H), 7.93 (br s, 1 H, 2′-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.09 (SCH_3), 88.02 (C≡C), 94.45 (C≡C), 116.89 (C), 118.24 (5-CH), 120.17 (C), 123.28 (5′-CH), 138.53 (CH), 138.62 (CH), 148.51 (CH), 148.65 (CH), 151.78 (CH), 161.99 (*C*SMe).

MS-EI: *m*/*z* (%) = 227.06 ([M^+ + 1], 4), 226.05 ([M^+], 13), 225.05 ([M^+ – 1], 100), 224.04 ([M^+ – 2], 19).

HRMS: *m*/*z* [M^+] calcd for $C_{13}H_{10}N_2S$: 226.0565; found: 226.0565.

2-(Methylthio)-3-[(thien-3-yl)ethynyl]pyridine (4f)
From **1** (60.0 mg) and 3-ethynylthiophene (35.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 1:9); yield: 50.0 mg (74%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, SCH_3), 6.98 (dd, *J* = 7.4, 5.0 Hz, 1 H, 5-H), 7.25 (dd, 5.0, 1.2 Hz, 1 H, 4′-H), 7.33 (dd, *J* = 5.0, 3.0 Hz, 1 H, 5′-H), 7.60 (dd, *J* = 3.0, 1.2 Hz, 1 H, 2′-H), 7.63 (dd, *J* = 7.4, 1.8 Hz, 1 H, 4-H), 8.40 (dd, *J* = 5.0, 1.8 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.16 (SCH_3), 84.08 (C≡C), 93.45 (C≡C), 117.75 (C), 118.23 (5-CH), 121.63 (C), 125.53 (5′-CH), 129.33 (2′-CH), 129.71 (4′-CH), 138.33 (4-CH), 147.81 (6-CH), 161.99 (*C*SMe).

MS-EI: *m*/*z* (%) = 232.01 ([M^+ + 1], 20), 231.02 ([M^+], 72), 230.01 ([M^+ – 1], 100), 229.00 ([M^+ – 2], 29).

HRMS: *m*/*z* [M^+] calcd for $C_{12}H_9N_2S$: 231.0176; found: 231.0175.

3-(Methylthio)-2-(phenylethynyl)pyridine (6a)
From **2** (68.0 mg) and phenylacetylene (37.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 2:3); yield: 66.0 mg (88%); brown solid; mp 78–80 °C (Lit.[7d] mp 75–77 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, SCH_3), 7.23 (dd, *J* = 8.0, 4.8 Hz, 1 H, 5-H), 7.37–7.40 (m, 3 H), 7.50 (dd, *J* = 8.0, 1.6 Hz, 1 H, 4-H), 7.65–7.67 (m, 2 H), 8.38 (dd, *J* = 4.8, 1.6 Hz, 1 H, 6-H).

2-[(3-Fluorophenyl)ethynyl]-3-(methylthio)pyridine (6b)
From **2** (60.0 mg) and 1-ethynyl-3-fluorobenzene (39.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 2:3); yield: 57.0 mg (81%); yellow solid; mp 82–84 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.60 (s, 3 H, SCH_3), 7.27–7.32 (m, 1 H), 7.40–7.43 (m, 1 H), 7.48–7.59 (m, 3 H), 7.76 (br d, 1 H, 4-H), 8.53 (br s, 1 H, 6-H).

^{13}C NMR (100.6 MHz, acetone-d_6): δ = 14.29 (SCH_3), 89.10 (C≡C), 93.80 (d, *J* = 4.0 Hz, C≡C), 117.34 (d, *J* = 21.1 Hz, CH), 118.89 (d, *J* = 22.0 Hz, CH), 125.08 (d, *J* = 10.0 Hz, 1′-C), 128.71 (d, *J* = 3.0 Hz, 6′-CH), 129.37 (5-CH), 131.67 (d, *J* = 9.1 Hz, 5′-CH), 132.08 (4-CH), 132.67 (6-CH), 140.24 (C), 145.84 (C), 163.30 (d, *J* = 244.5 Hz, CF).

MS-EI: *m*/*z* (%) = 244.05 ([M^+ + 1], 12), 243.05 ([M^+], 78), 242.04 ([M^+ – 1], 100).

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{10}FNS$: 243.0518; found: 243.0519.

2-[(4-Methoxyphenyl)ethynyl]-3-(methylthio)pyridine (6c)
From **2** (60.0 mg) and 4-ethynylanisole (43.0 mg), and after purification by column chromatography (Et_2O–PE, 0:1 to 2:3); yield: 70.0 mg (93%); yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.59 (s, 3 H, SCH_3), 3.90 (s, 3 H, OCH_3), 7.05 (d, *J* = 8.8 Hz, 2 H, 3′- and 5′-H), 7.42 (dd, *J* = 8.2, 4.6 Hz, 1 H, 5-H), 7.62 (d, *J* = 8.8 Hz, 2 H, 2′- and 6′-H), 7.76 (br d, 1 H, 4-H), 8.41 (br d, 1 H, 6-H).

^{13}C NMR (100.6 MHz, acetone-d_6): δ = 14.29 (SCH_3), 55.77 (OCH_3), 86.37 (C≡C), 96.95 (C≡C), 114.82 (C), 115.23 (3′- and 5′-CH), 124.22 (5-CH), 132.69 (4-CH), 134.25 (2′- and 6′-CH), 140.55 (C), 140.92 (C), 144.69 (6-CH), 161.63 (*C*OMe).

MS-EI: *m*/*z* (%) = 256.07 ([M^+ + 1], 18), 255.07 ([M^+], 100), 254.07 ([M^+ – 1], 90).

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{13}NOS$: 255.0718; found: 255.0721.

2-[(2-Methoxyphenyl)ethynyl]-3-(methylthio)pyridine (6d)
From **2** (90.0 mg) and 2-ethynylanisole (64.0 mg), compound **24** and after purification by column chromatography (Et_2O–PE, 0:1 to 3:2); yield: 80.0 mg (70%); yellow solid; mp 151–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, SCH_3), 3.93 (s, 3 H, OCH_3), 6.91–6.95 (m, 2 H, 3′- and 5′-H), 7.21 (dd, *J* = 8.0, 4.8 Hz, 1 H, 5-H), 7.33–7.37 (m, 1 H, 4′-H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 1 H, 4-H), 7.62 (dd, *J* = 7.6, 1.6 Hz, 1 H, 6′-H), 8.37 (dd, *J* = 4.8, 1.6 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.27 (SCH_3), 55.81 (OCH_3), 90.15 (C≡C), 92.94 (C≡C), 110.73 (3′-CH), 111.42 (C), 120.41 (5′-CH), 120.65 (5-CH), 130.71 (4′-CH), 131.80 (4-CH), 133.98 (6′-CH), 139.18 (*C*SMe), 140.62 (C), 145.09 (6-CH), 160.54 (*C*OMe).

MS-EI: *m/z* (%) = 256.05 ([M$^+$ + 1], 20), 255.05 ([M$^+$], 100), 254.04 ([M$^+$ – 1], 88).

HRMS: *m/z* [M$^+$] calcd for $C_{15}H_{13}NOS$: 255.0718; found: 255.0720.

3-(Methylthio)-2-[(pyridin-3-yl)ethynyl]pyridine (6e)
From **2** (65.0 mg) and 3-ethynylpyridine (37.0 mg), and after purification by column chromatography (Et_2O–PE, 2:3 to 4:1); yield: 59.0 mg (81%); yellow gummy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, SCH_3), 7.22 (dd, *J* = 8.0, 4.8 Hz, 1 H, 5-H), 7.27–7.31 (m, 1 H, 5′-H), 7.48 (dd, *J* = 8.0, 1.2 Hz, 1 H, 4-H), 7.88–7.91 (m, 1 H, 4′-H), 8.35 (dd, *J* = 4.8, 1.2 Hz, 1 H, 6-H), 8.57 (dd, *J* = 5.2, 1.6 Hz, 1 H, 6′-H), 8.85 (d, *J* = 1.2 Hz, 1 H, 2′-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.55 (SCH_3), 89.41 (C≡C), 91.81 (C≡C), 119.44 (C), 123.05 (5′-CH), 123.31 (5-CH), 131.43 (4-CH), 138.87 (4′-CH), 139.61 (*C*SMe), 145.43 (6-CH), 149.11 (6′-CH), 152.33 (2′-CH).

MS-EI: *m/z* (%) = 227.06 ([M$^+$ + 1], 10), 226.05 ([M$^+$], 76), 225.05 ([M$^+$ – 1], 100), 224.04 ([M$^+$ – 2], 25).

HRMS: *m/z* [M$^+$] calcd for $C_{13}H_{10}N_2S$: 226.0565; found: 226.0566.

3-(Methylthio)-2-[(thien-3-yl)ethynyl]pyridine (6f)
From **2** (60.0 mg) and 3-ethynylthiophene (35.0 mg), and after purification by column chromatography (Et_2O–PE, 1:4 to 1:1); yield: 51.0 mg (75%); brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, SCH_3), 7.29–7.33 (m, 3 H), 7.51 (br d, 1 H, 4-H), 7.69 (br d, 1 H), 8.37 (br s, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.68 (SCH_3), 85.84 (C≡C), 91.44 (C≡C), 121.22 (C), 122.84 (5-CH), 125.50 (CH), 129.93 (CH), 130.40 (CH), 131.53 (4-CH), 139.23 (*C*SMe), 140.19 (C), 145.08 (6-CH).

MS-EI: *m/z* (%) = 232.01 ([M$^+$ + 1], 20), 231.02 ([M$^+$], 91), 230.01 ([M$^+$ – 1], 100), 229.00 ([M$^+$ – 2], 25).

HRMS: *m/z* [M$^+$] calcd for $C_{12}H_9N_2S$: 231.0176; found: 231.0173.

3-Halo-2-[(hetero)aryl]thieno[2,3-*b*]pyridines 5a–h and 3-Halo-2-[(hetero)aryl]thieno[3,2-*b*]pyridines 7a–g; General Procedure
To a stirred solution of 2,3-(hetero)arylethynyl(methylthio)pyridine **4** or **6** (1 equiv) in anhyd Et_2O (3–5 mL) or anhyd CH_2Cl_2 (3–5 mL) at 0 °C was added I_2 or Br_2 (1.1 equiv) gradually. The reaction was performed under argon and the mixture stirred at r.t. for 30 min. When a precipitate was formed during the reaction, the 3-halo-2-[(hetero)aryl]thienopyridines were directly obtained as pure products after filtration. Otherwise, the mixture was diluted with Et_2O (15 mL) or CH_2Cl_2 (15 mL) and washed with 10% aq $Na_2S_2O_3$ (3 × 10 mL) and H_2O (3 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and the removal of the solvent under reduced pressure gave either the pure product, or a crude that was submitted to column chromatography (Table 1).

3-Bromo-2-phenylthieno[2,3-*b*]pyridine (5a)
From **4a** (90.0 mg) in anhyd Et_2O, compound **5a** was obtained after purification by column chromatography (Et_2O–PE: 0:1 to 2:3); yield: 96.0 mg (83%); yellow solid; mp 56–57 °C (Lit.[10] mp 54–55 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.52 (m, 4 H), 7.78–7.80 (m, 2 H), 8.14 (br d, 1 H, 4-H), 8.06 (br s, 1 H, 6-H).

3-Iodo-2-phenylthieno[2,3-*b*]pyridine (5b)
From **4a** (90.0 mg) in anhyd Et_2O, compound **5b** was obtained as a pure product after extraction; yield: 98.0 mg (73%); yellow solid; mp 136–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.4, 5.0 Hz, 1 H, 5-H), 7.46–7.53 (m, 3 H), 7.71 (m, 2 H), 8.06 (br d, 1 H, 4-H), 8.57 (br d, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 76.29 (CI), 120.78 (5-CH), 128.61 (2 × CH), 129.28 (4′-CH), 129.90 (2 × CH), 133.73 (4-CH), 134.04 (C), 136.36 (C), 142.92 (C), 147.27 (6-CH), 160.29 (C).

MS-EI: *m/z* (%) = 336.94 ([M$^+$], 100), 210.04 ([M$^+$ – I], 24).

HRMS: *m/z* [M$^+$] calcd for $C_{13}H_8INS$: 336.9422; found: 336.9417.

2-(3-Fluorophenyl)-3-iodothieno[2,3-*b*]pyridine (5c)
From **4b** (45.0 mg) in anhyd Et_2O, compound **5c** was obtained as a pure product after extraction; yield: 50.0 mg (76%); yellow solid; mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.21 (m, 1 H), 7.43–7.49 (m, 4 H), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1 H, 4-H), 8.59 (br d, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 76.94 (CI), 116.27 (d, *J* = 20.1 Hz, 4′- or 2′-CH), 116.95 (d, *J* = 23.1 Hz, 2′- or 4′-CH), 120.95 (5-CH), 125.75 (d, *J* = 3.0 Hz, 6′-CH), 130.31 (d, *J* = 9.1 Hz, 5′-CH), 134.07 (4-CH), 135.99 (d, *J* = 8.0 Hz, 1′-C), 136.34 (C), 141.39 (d, *J* = 2.01 Hz, 2-C), 147.46 (6-CH), 160.05 (C), 165.52 (d, *J* = 247.5 Hz, CF).

MS-EI: *m/z* (%) = 354.92 ([M$^+$], 100), 228.03 ([M$^+$ – I], 19), 184.05 (16), 157.04 (10).

HRMS: *m/z* [M$^+$] calcd for $C_{13}H_7FINS$: 354.9328; found: 354.9316.

2-(4-Methoxyphenyl)-3-bromothieno[2,3-*b*]pyridine (5d)
From **4c** (29.0 mg) in anhyd Et_2O, compound **5d** was obtained as a pure product after extraction; yield: 35.0 mg (99%); brown solid; mp 190–192 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, OCH_3), 7.12 (d, *J* = 8.8 Hz, 2 H, 3′- and 5′-H), 7.59 (dd, *J* = 8.0, 4.6 Hz, 1 H, 5-H), 7.72 (d, *J* = 8.8 Hz, 2 H, 2′- and 6′-H), 8.14 (br d, 1 H, 4-H), 8.66 (br s, 1 H, 6-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 55.37 (OCH_3), 101.39 (CBr), 114.49 (3′- and 5′-CH), 121.36 (C), 123.79 (5-CH), 130.70 (2′- and 6′-CH), 130.88 (4-CH), 132.76 (C), 137.91 (C), 147.79 (6-CH), 157.69 (C), 160.15 (*C*OMe).

MS-EI: *m/z* (%) = 320.97 ([^{81}BrM$^+$], 100), 318.97 ([^{79}BrM$^+$], 96), 305.95 (54), 303.94 (53), 277.95 (29), 275.95 (30).

HRMS: *m/z* [M$^+$] calcd for $C_{14}H_{10}{}^{79}BrNOS$: 318.9666; found: 318.9678. [M$^+$] calcd for $C_{14}H_{10}{}^{81}BrNOS$: 320.9646; found: 320.9656.

2-(2-Methoxyphenyl)-3-bromothieno[2,3-*b*]pyridine (5e)
From **4d** (10.0 mg) in anhyd Et_2O, compound **5e** was obtained as a pure product after extraction; yield: 10.0 mg (80%); yellow solid; mp 147–148 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 3.93 (s, 3 H, OCH_3), 7.16–7.20 (m, 1 H, 5′-H), 7.26–7.29 (m, 1 H, 3′-H), 7.57–7.62 (m, 2 H, 4′ and 6′-H), 7.98 (dd, *J* = 8.4, 5.2 Hz, 1 H, 5-H), 8.61 (dd, *J* = 8.4, 1.2 Hz, 1 H, 4-H), 8.91 (br d, *J* = 5.2 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, acetone-d_6): δ = 56.16 (OCH_3), 105.64 (C), 112.71 (3′-CH), 114.90 (C), 120.56 (C), 121.59 (5′-CH), 122.45 (5-CH), 132.78 (4′ or 6′-CH), 132.82 (4′ or 6′-CH), 139.51 (C), 143.64 (6-CH), 155.01 (C), 158.07 (C).

3-Iodo-2-(pyridin-3-yl)thieno[2,3-*b*]pyridine (5f)
From **4e** (44.0 mg) in anhyd CH_2Cl_2, compound **5f** was obtained as a pure product after extraction; yield: 48.0 mg (80%); yellow solid; mp 73–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, *J* = 8.0, 4.4 Hz, 1 H, 5-H), 7.48 (br s, 1 H, 5′-H), 8.03 (br d, 1 H, 4′-H), 8.06 (dd, *J* = 8.0, 1.6 Hz, 1 H, 4-H), 8.61 (dd, *J* = 4.4, 1.6 Hz, 1 H, 6-H), 8.77 (br s, 1 H, 6′-H), 9.01 (br s, 1 H, 2′-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 78.00 (CI), 121.03 (5-CH), 123.52 (5′-CH), 130.91 (C), 133.86 (4-CH), 136.02 (C), 137.22 (4′-CH), 138.94 (C), 148.06 (6-CH), 149.96 (CH), 150.16 (CH), 160.66 (C).

MS-EI: *m/z* (%) = 337.93 ([M$^+$], 100), 225.05 (38), 211.03 ([M$^+$ – I], 30).

HRMS: *m/z* [M$^+$] calcd for $C_{12}H_7IN_2S$: 337.9375; found: 337.9367.

3-Bromo-2-(thien-3-yl)thieno[2,3-*b*]pyridine (5g)
From **4f** (50.0 mg) in anhyd Et_2O, compound **5g** was obtained as a pure product after extraction; yield: 52.0 mg (81%); brown gummy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 5.0, 3.0 Hz, 1 H, 5′-H), 7.55 (br s, 1 H, 5-H), 7.64 (dd, *J* = 5.0, 1.2 Hz, 1 H, 4′-H), 8.01 (dd, *J* = 2.8, 1.2 Hz, 1 H, 2′-H), 8.23 (br d, 1 H, 4-H), 8.63 (br s, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 101.59 (CBr), 120.83 (5-CH), 126.32 (2′-CH), 126.58 (5′-CH), 127.69 (4′-CH), 132.15 (4-CH), 132.78 (C), 135.10 (C), 135.44 (C), 144.66 (6-CH), 155.90 (C).

MS-EI: *m/z* (%) = 296.91 ([^{81}BrM$^+$], 100), 294.91 ([^{79}BrM$^+$], 98), 215.99 (M$^+$ – Br], 18), 172.02 (43).

HRMS: *m/z* [M$^+$] calcd for $C_{11}H_6{}^{79}BrNS_2$: 294.9125; found: 294.9134. [M$^+$] calcd for $C_{11}H_6{}^{81}BrNS_2$: 296.9105; found: 296.9113.

3-Iodo-2-(thien-3-yl)thieno[2,3-*b*]pyridine (5h)
From **4f** (35.0 mg) in anhyd Et_2O, compound **5h** was obtained as a pure product after extraction; yield: 40.0 mg (77%); yellow solid; mp 93–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 8.0, 4.8 Hz, 1 H, 5-H), 7.48 (dd, *J* = 5.2, 2.8 Hz, 1 H, 5′-H), 7.59 (dd, *J* = 5.2, 1.4 Hz, 1 H, 4′-H), 7.91 (dd, *J* = 2.8, 1.4 Hz, 1 H, 2′-H), 8.02 (dd, *J* = 8.0, 1.4 Hz, 1 H, 4-H), 8.55 (dd, *J* = 4.8, 1.4 Hz, 1 H, 6-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 75.35 (CI), 120.81 (5-CH), 125.92 (2′-CH), 126.20 (5′-CH), 128.14 (4′-CH), 133.47 (4-CH), 134.16 (C), 136.54 (C), 137.87 (C), 147.32 (6-CH), 159.57 (C).

MS-EI: *m/z* (%) = 342.90 ([M$^+$], 100), 215.19 ([M$^+$ – I], 11), 172.02 (24).

HRMS: *m/z* [M$^+$] calcd for $C_{11}H_6INS_2$: 342.8986; found: 342.8989.

3-Bromo-2-phenylthieno[3,2-*b*]pyridine (7a)
From **6a** (20.0 mg) in anhyd Et_2O, and after purification by column chromatography (Et_2O–PE, 0:1 to 2:3); yield: 23.0 mg (89%); yellow solid; mp 111–112 °C (Lit.[7d] mp 110–112 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 7.8, 4.5 Hz, 1 H, 6-H), 7.49–7.57 (m, 3 H), 7.81–7.84 (m, 2 H), 8.22 (dd, *J* = 7.8, 1.1 Hz, 1 H, 7-H), 8.87 (br s, 1 H, 5-H).

3-Bromo-2-(3-fluorophenyl)thieno[3,2-*b*]pyridine (7b)
From **6b** (70.0 mg) in anhyd Et_2O, compound **7b** was obtained as a solid, which was filtered from the reaction mixture; yield: 80.0 mg (90%); yellow solid; mp 113–114 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19–7.24 (m, 1 H, 4′- or 2′-H), 7.54 (dd, *J* = 8.2, 4.8 Hz, 1 H, 6-H), 7.58–7.66 (m, 3 H), 8.60 (dd, *J* = 8.2, 1.2 Hz, 1 H, 7-H), 8.80 (dd, *J* = 4.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 107.84 (CBr), 115.94 (d, *J* = 23.1 Hz, 4′- or 2′-CH), 116.52 (d, *J* = 21.1 Hz, 2′ or 4′-CH), 120.82 (6-CH), 125.48 (d, *J* = 3.0 Hz, 6′-CH), 131.22 (d, *J* = 9.0 Hz, 5′-CH), 131.70 (7-CH), 132.13 (C), 133.15 (C), 134.17 (d, *J* = 9.0 Hz, 1′-C), 148.38 (5-CH), 151.81 (C), 161.96 (d, *J* = 245.5 Hz, CF).

MS-EI: *m/z* (%) = 308.95 ([^{81}BrM$^+$], 96), 306.95 ([^{79}BrM$^+$], 100).

HRMS: *m/z* [M$^+$] calcd for $C_{13}H_7{}^{79}BrFNS$: 306.9470; found: 306.9467. [M$^+$] calcd for $C_{13}H_7{}^{81}BrFNS$: 308.9458; found: 308.9446.

2-(3-Fluorophenyl)-3-iodothieno[3,2-*b*]pyridine (7c)
From **6b** (45.0 mg) in anhyd Et_2O, compound **7c** was obtained as a pure product after extraction; yield: 53.0 mg (80%); yellow solid; mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.24 (m, 1 H, 4′- or 2′-H), 7.44 (dd, *J* = 7.0, 4.2 Hz, 1 H, 6-H), 7.47–7.55 (m, 3 H), 8.25 (br d, 1 H, 7-H), 8.91 (br s, 1 H, 5-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 82.39 (CI), 116.64 (d, *J* = 21.1 Hz, 4′- or 2′-CH), 116.88 (d, *J* = 23.1 Hz, 2′ or 4′-CH), 120.26 (6-CH), 125.63 (d, *J* = 3.0 Hz, 6′-CH), 130.44 (d, *J* = 8.0 Hz, 5′-CH), 131.60 (7-CH), 133.35 (C), 135.82 (d, *J* = 8.0 Hz, 1′-C), 145.42 (C), 147.63 (5-CH), 154.55 (C), 162.59 (d, *J* = 248.5 Hz, CF).

MS-EI: *m/z* (%) = 354.93 ([M$^+$], 100), 228.03 ([M$^+$ – I], 32).

HRMS: *m/z* [M$^+$] calcd for $C_{13}H_7FINS$: 354.9328; found: 354.9331.

2-(4-Methoxyphenyl)-3-iodothieno[3,2-*b*]pyridine (7d)
From **6c** (40.0 mg) in anhyd Et_2O, compound **7d** was obtained as a pure product after extraction;

yield: 55.0 mg (98%); yellow solid; mp 148–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 7.04 (d, *J* = 8.8 Hz, 2 H, 3′- and 5′-H), 7.33 (dd, *J* = 7.8, 4.6 Hz, 1 H, 6-H), 7.70 (d, *J* = 8.8 Hz, 2 H, 2′- and 6′-H), 8.14 (br d, 1 H, 7-H), 8.82 (br s, 1 H, 5-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.38 (OCH_3), 81.72 (C-I), 114.11 (3′- and 5′-CH), 119.69 (6-CH), 126.25 (C), 130.61 (7-CH), 131.09 (2′- and 6′-CH), 132.79 (C), 146.27 (C), 147.76 (5-CH), 155.37 (C), 160.59 (*C*OMe).

MS-EI: *m/z* (%) = 366.95 ([M$^+$], 100), 351.93 ([M$^+$ – Me], 27), 323.94 (9), 241.06 ([M$^+$ – I], 32).

HRMS: *m/z* [M$^+$] calcd for $C_{14}H_{10}INOS$: 366.9528; found: 366.9529.

3-Bromo-2-(2-methoxyphenyl)thieno[3,2-*b*]pyridine (7e)
From **6d** (70.0 mg) compound **7e** was obtained as a pure product after filtration from the reaction mixture; yield: 75.0 mg (87%); yellow solid; mp 151–152 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.80 (s, 3 H, OCH_3), 7.09–7.13 (m, 1 H, 5′-H), 7.21 (dd, *J* = 8.4, 1.2 Hz, 1 H, 3′-H), 7.48 (dd, *J* = 7.4, 2.0 Hz, 1 H, 6′-H), 7.49–7.54 (m, 2 H, 6- and 4′-H), 8.54 (dd, *J* = 8.2, 1.6 Hz, 1 H, 7-H), 8.76 (dd, *J* = 4.8, 1.6 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 55.67 (OCH_3), 109.34 (CBr), 112.02 (3′-CH), 120.30 (6-CH), 120.51 (C), 120.53 (5′-CH), 131.49 (4′-CH), 131.52 (6′-CH), 131.59 (7-CH), 132.12 (C), 139.67 (C), 147.89 (5-CH), 151.35 (C), 156.64 (*C*OMe).

MS-EI: *m/z* (%) = 320.97 ([^{81}BrM$^+$], 47), 318.97 ([^{79}BrM$^+$], 45), 240.05 ([M$^+$ – Br], 49), 225.03 ([M$^+$ – Br – Me], 100).

HRMS: *m/z* [M$^+$] calcd for $C_{14}H_{10}{}^{79}BrNOS$: 318.9666; found: 318.9673. [M$^+$] calcd for $C_{14}H_{10}{}^{81}BrNOS$: 320.9655; found: 320.9646.

3-Iodo-2-(pyridin-3-yl)thieno[3,2-*b*]pyridine (7f)
From **6e** (20.0 mg) in anhyd CH_2Cl_2, compound **7f** was obtained as a pure product after extraction; yield: 27.0 mg (90%); yellow solid; mp 89–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 8.2, 4.6 Hz, 1 H, 6-H), 7.55–7.58 (m, 1 H, 5′-H), 8.18–8.20 (m, 2 H, 7-H and 4′-H), 8.77 (br s, 1 H, 6′-H), 8.86 (dd, *J* = 4.6, 1.6 Hz, 1 H, 5-H), 9.02 (br s, 1 H, 2′-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 85.56 (CI), 120.52 (6-CH), 123.85 (5′-CH), 130.49 (7-CH), 131.23 (C), 132.93 (C), 138.32 (4′-CH), 140.93 (C), 148.79 (2 × CH), 148.89 (CH), 155.40 (C).

MS-EI: *m/z* (%) = 337.93 ([M$^+$], 100), 212.04 (68), 211.03 ([M$^+$ – I], 47).

HRMS: *m/z* [M$^+$] calcd for $C_{12}H_7IN_2S$: 337.9375; found: 337.9387.

3-Iodo-2-(thien-3-yl)thieno[3,2-*b*]pyridine (7g)
From **6f** (50.0 mg) in anhyd Et_2O, compound **7g** was obtained as a pure product after extraction; yield: 57.0 mg (77%); yellow solid; mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 7.6, 4.4 Hz, 1 H, 6-H), 7.48 (dd, *J* = 4.8, 2.8 Hz, 1 H, 5′-H), 7.64 (dd, *J* = 4.8, 1.2 Hz, 1 H, 4′-H), 8.01 (dd, *J* = 2.8, 1.2 Hz, 1 H, 2′-H), 8.14 (br d, 1 H, 7-H), 8.82 (br s, 1 H, 5-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 81.39 (CI), 114.09 (C), 119.88 (6-CH), 126.14 (2′-CH), 126.31 (5′-CH), 127.92 (4′-CH), 130.68 (7-CH), 134.13 (C), 141.22 (C), 147.82 (5-CH), 155.38 (C).

MS-EI: *m*/*z* (%) = 342.90 ([M^+], 100), 215.99 ([M^+ – I], 20), 172.02 (15).

HRMS: *m*/*z* [M^+] calcd for $C_{11}H_6INS_2$: 342.8986; found: 342.8986.

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