HETEROCYCLES, Vol. 89, No. 6, 2014, pp. 1491 - 1501. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 19th March, 2014, Accepted, 16th April, 2014, Published online, 17th April, 2014
DOI: 10.3987/COM-14-12986

AN EFFICIENT METHOD FOR THE PREPARATION OF 4-ALKOXY-SUBSTITUTED THIENO[2,3-*b*]PYRIDINES

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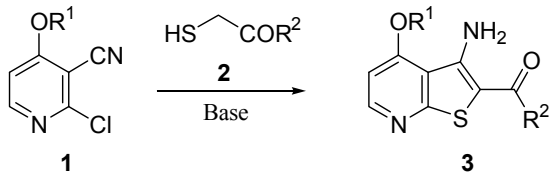
Abstract – An efficient method for the preparation of 4-alkoxy-substituted thieno[2,3-*b*]pyridines is described. The key intermediates, 4-alkoxy-2-chloro-3-cyanopyridines, were synthesized from a variety of alcohols by nucleophilic substitution with 3-cyano-2,4-dichloropyridine or by Mitsunobu reaction with 2-chloro-4-hydroxynicotinonitrile. Subsequent reaction of 4-alkoxy-2-chloro-3-cyanopyridines with 2-(acetylthio)acetamide under basic conditions provided 4-alkoxy-substituted thieno[2,3-*b*]pyridines in fair to good yields.

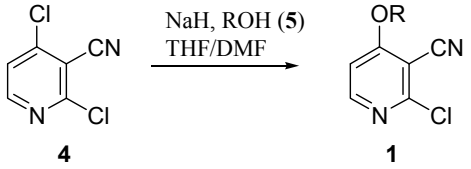
During the course of a project directed at the synthesis of antiosteoporotic compounds,[1] the need arose for a general route for the synthesis of 4-alkoxy-substituted thieno[2,3-*b*]pyridine derivatives **3** (Scheme 1). Since thieno[2,3-*b*]pyridines **3** can be synthesized from chloropyridines **1** and thiols **2** in the presence of a base,[2,3] 4-alkoxy-2-chloro-3-cyanopyridines **1** are thought to be the straightforward precursors. It is known that 4-alkoxy-substituted chloropyridines **1** can be prepared from malononitrile.[4] However, only methoxy and ethoxy groups are introduced as the C4 substituent of chloropyridines **1**. Although there is another precedent exploiting the *O*-alkylation of 3-cyano-2-halo-4-hydroxypyridines with alkylhalides, only a limited number of primary alkyl groups are incorporated with moderate yields.[5] Using our method, a variety of alkoxy groups derived from the corresponding primary and secondary alcohols can be installed efficiently and effectively. Herein, we report a general procedure for the preparation of 4-alkoxy-substituted 2-chloro-3-cyanopyridines **1**, followed by syntheses of 4-alkoxy-substituted thieno[2,3-*b*]pyridines **3**.

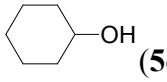
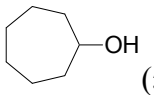
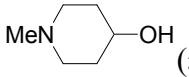


Scheme 1. Preparation of thieno[2,3-*b*]pyridines **3**

Given that nucleophilic substitution of 2,4-dichloropyridine occurs selectively at the 4-position,[6] our initial approach to 4-alkoxy-2-chloro-3-cyanopyridines **1** was nucleophilic substitution of 3-cyano-2,4-dichloropyridines (**4**)[7] with sodium alkoxides, as summarized in Table 1. The regiochemistry of the products **1** was determined by comparison with the ^{1}H NMR spectrum of the authentic sample **1a** (R = Me, Table 1).[4a] Several products precipitated after the addition of water to the reaction mixture, and subsequent filtration, provided the desired products in moderate (**1a**, **1b** and **1c**) to good (**1d**) yields. As cyclohexyl derivative **1e** and cycloheptyl derivative **1f** were oily products, typical workup and purification by column chromatography were performed. As *N*-methylpiperidine derivative **1h** is water-soluble, the reaction mixture was concentrated, and the following purification provided **1h** in an excellent yield of 94%.

Table 1. Synthesis of 4-alkoxypyridines **1** from **4**[a]



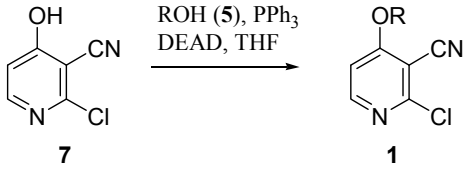
Entry	**1**	ROH (**5**)	Yield/%[b]
1	**1a**	MeOH(**5a**)	69[c]
2	**1b**	EtOH(**5b**)	67
3	**1c**	*i*-PrOH(**5c**)	63
4	**1d**	$PhCH_2OH$(**5d**)	85
5	**1e**	 (**5e**)	94
6	**1f**	 (**5f**)	86
7	**1g**	EtO_2CCH_2OH(**5g**)	0[d]
8	**1h**	 (**5h**)	94

[a]All reactions were carried out on a 1.0-mmol scale. [b]Isolated yield. [c]10-mmol scale. [d]2-Alkoxylpyridine **6** was isolated in 63% yield.[8]

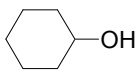
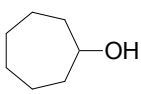
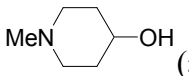
Due to its relatively high water solubility, the isolated yields of **1a**, **1b** and **1c** are not better than the yield of **1e** and **1f**, because compounds **1e** and **1f** were chromatographically purified. When dichloropyridine **4** was reacted with ethyl glycolate **5g**, the precipitate obtained was not desired **1g**, but 2-alkoxyl compound **6**,[8] which was isolated in 63% yield. The reason for the changes in regioselectivity is unclear. However, even in polar solvent, like DMF, sodium mediated interaction between the carbonyl oxygen of ethyl glycolate **5g** and the nitrogen of pyridine **4** seems to affect the regioselectivity greatly.[9]

Next, we envisioned an alternative synthetic approach to 4-alkoxy-2-chloro-3-cyanopyridines **1** because 4-alkoxypyridine **1g** needed to be synthesized. The alternative approach includes Mitsunobu reaction[10] of 4-hydroxypyridine **7** as shown in Table 2. Using this method, compound **1g** was successfully obtained in 59% yield, and the regiochemistry of **1b–1g** was reconfirmed by the comparison of ^{1}H NMR spectra. Simple alcohols such as ethyl, isopropyl, and benzyl alcohol provided 4-alkoxypyridines **1** in excellent yields. Interestingly, the reaction of 4-hydroxypyridine **7** with cyclohexyl alcohol (**5e**) provided 4-alkoxypyridine **1e** in poor yield and a large amount of starting **7** was recovered, whereas the reaction with cycloheptyl alcohol (**5f**) provided 4-alkoxypyridine **1f** in quantitative yield. Since the reaction with alcohol **5h** also provided a trace amount of 4-alkoxypyridine **1h**, saturated six-membered-ring-substituted alcohols are not suitable in these reaction conditions.[11]

Table 2. Synthesis of 4-alkoxypyridines **1** from **7**[a]



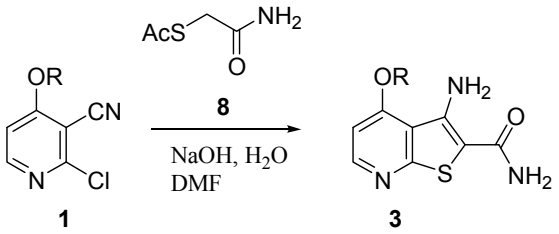
7 **1**

Entry	**1**	ROH (**5**)	Yield/%[b]
1	**1b**	EtOH(**5b**)	83
2	**1c**	*i*-PrOH(**5c**)	96
3	**1d**	$PhCH_2OH$(**5d**)	89
4	**1e**	 (**5e**)	27
5	**1f**	 (**5f**)	99
6	**1g**	EtO_2CCH_2OH(**5g**)	59
7	**1h**	 (**5h**)	trace

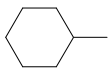
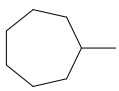
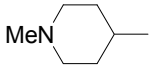
[a]All reactions were carried out on a 1.0-mmol scale. [b]Isolated yield.

Since 4-alkoxy-2-chloro-3-cyanopyridines **1** were on hand, the ring closure reaction was examined. Although thioglycolamide **2** (Scheme 1; $R^2 = NH_2$) is known to react with 2-chloro-3-cyanopyridine **1** to provide thieno[2,3-*b*]pyridine-2-carboxamide **3**,[3] thioglycolamide was found to be unstable and dimerized in several days even under a nitrogen atmosphere. Moreover, thioglycolamide can be purchased only in alcoholic ammonia solution. On the other hand, 2-(acetylthio)acetamide **8** (Table 3) is commercially available and deacetylation of **8** proceeds smoothly to provide thioacetamide **2** quantitatively. Therefore, one-pot reaction was performed as indicated in Table 3. The product **3** precipitated after the addition of water to the reaction mixture. The exception was carboxylic acid **3g**, which precipitated upon the addition of 1 M HCl. 4-Isopropoxythieno[2,3-*b*]pyridine **3c**, 4-(benzyloxy)thieno[2,3-*b*]pyridine **3d**, 4-(cyclohexyloxy)thieno[2,3-*b*]pyridine **3e**, 4-(cycloheptyloxy)thieno[2,3-*b*]pyridine **3f**, and 4-[(1-methylpiperidin-4-yl)oxy]thieno[2,3-*b*]pyridine **3h** were isolated in good to excellent yields. On the other hand, the reaction with 4-methoxythieno[2,3-*b*]pyridine **3a** and 4-ethoxythieno[2,3-*b*]pyridine **3b** showed moderate yields due to its relatively high water solubility. In particular, the yield of acid **3g** was only 42% because of its higher water solubility.

Table 3. Synthesis of thieno[2,3-*b*]pyridine-2-carboxamides **3**



1 **3**

Entry	**3**	R	Yield/%[a]
1	**3a**	Me	60
2	**3b**	Et	73
3	**3c**	*i*-Pr	84
4	**3d**	$PhCH_2$	80
5	**3e**		94
6	**3f**		86
7	**3g**	HO_2CCH_2[b]	42[c]
8	**3h**		91

[a]Isolated yield. [b]Starting **1g** was ethyl ester ($R = EtO_2CCH_2$). [c]Isolated as HCl salt.

In summary, an efficient method for the preparation of 4-alkoxy-substituted thieno[2,3-*b*]pyridines **3** has been established. The regioselective nucleophilic substitution of alkoxide takes place in the 4-position of 3-cyano-2,4-dichloropyridine (**4**) in most cases to provide 4-alkoxy-2-chloro-3-cyanopyridines **1**. Mitsunobu reaction of 2-chloro-3-cyano-4-hydroxypyridines **7** also provides 4-alkoxy-2-chloro-3-cyanopyridines **1** in good yields with the secured regiochemistry. The reaction of 4-alkoxy-2-chloro-3-cyanopyridines **1** with 2-(acetylthio)acetamide **8** under basic conditions affords 4-alkoxy-substituted thieno[2,3-*b*]pyridines **3** in fair to excellent yields.

EXPERIMENTAL

Melting points are uncorrected. IR absorption spectra were recorded on a Jasco FT/IR-830 spectrophotometer. NMR spectra were recorded on a VARIAN Mercury 400 (400 MHz) or VARIAN Inova 500 (500 MHz) instrument using tetramethylsilane as an internal reference. Low-resolution MS and HRMS were recorded on a JEOL JMS-AX505H. Elemental analyses were performed by the Institute of Science and Technology, Inc. TLC analysis was performed on 60 F254 plate (Merck, art. 5715). Separation of the compounds by column chromatography was carried out with silica gel 60 (Merck, 230–400 mesh ASTM).

2-Chloro-4-methoxynicotinonitrile (1a).

A solution of 4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (7.38 g, 49.2 mmol) in $POCl_3$ (50 mL) was refluxed for 1 h. The excess $POCl_3$ was removed under reduced pressure. The residue was diluted with a slurry of ice and water (100 mL). The resulting suspension was made basic with a saturated aqueous solution of $NaHCO_3$ (100 mL). The white crystal was collected to provide **1a** (7.67 g, 93%). Mp 175–176 °C; IR (KBr): 2232, 1580, 1554, 1482, 1432, 1394, 1312, 1039, 843 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (1H, d, J = 4.3 Hz), 7.40 (1H, d, J = 4.3 Hz), 4.05 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 154.0, 152.3, 112.6, 107.9, 98.6, 57.8; MS (EI): m/z = 168 [M^+], 139, 138, 107, 103, 92, 75, 64, 63; HRMS-EI m/z [M^+] calcd for $C_7H_5N_2OCl$: 168.0091; found: 168.0087. Anal. Calcd for $C_7H_5N_2OCl$•$0.11H_2O$: C, 49.29; H, 3.09; N, 16.42; Cl, 20.78. Found: C, 49.40; H, 2.94; N, 16.59, Cl, 20.88.

General Procedure for the Preparation of 1 from 4

To a slurry of sodium hydride (48 mg, 1.1 mmol) in anhydrous THF (1.0 mL) was added alcohol **5** (1.1 mmol). This sodium alkoxide solution was added to a stirred solution of **4** (173 mg, 1.0 mmol) in DMA (1.0 mL) at 0 °C. After stirring for 1 h at 0 °C, water (5 mL) was added to the reaction mixture. In the cases of **1b**,

1c, and **1d**, the precipitate was filtered and washed with water (10 mL) and Et_2O (1 mL) to provide **1b**, **1c**, or **1d**. In the cases of **1e** and **1f**, the mixture was extracted with AcOEt (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography to provide **1e** or **1f**.

2-Chloro-4-methoxynicotinonitrile (1a): Compound **1a** was synthesized in 10-mmol scale, and exhibited an identical ^{1}HNMR spectrum to authentic sample.

2-Chloro-4-ethoxynicotinonitrile (1b): White crystal; Mp 91–93 °C; IR (KBr): 2995, 2925, 1579, 1556, 1468, 1395, 1317, 1257, 1038, 965, 815, 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, d, J = 5.9 Hz), 6.85 (1H, d, J = 5.9 Hz), 4.27 (2H, q, J = 6.8 Hz), 1.53 (3H, t, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 154.4, 153.2, 112.3, 106.5, 100.5, 66.3, 14.2; MS (EI): *m/z* = 182 [M^+], 154, 137, 126, 119, 93, 76, 64; HRMS-EI *m/z* [M^+] calcd for $C_8H_7N_2OCl$ 182.0247; found: 182.0241. Anal. Calcd for $C_8H_7N_2OCl$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.74; H, 3.93; N, 15.19.

2-Chloro-4-isopropoxynicotinonitrile (1c): White powder; Mp 87–88 °C; IR (KBr): 3096, 2985, 2235, 1580, 1550, 1469, 1390, 1316, 1262, 1102, 985, 840 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (1H, d, J = 6.4 Hz), 7.43 (1H, d, J = 6.4 Hz), 4.99 (1H, quint., J = 5.9 Hz), 1.36 (6H, d, J = 5.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.5, 153.8, 152.6, 112.7, 108.7, 99.1, 73.8, 21.2; MS (EI): *m/z* = 196 [M^+], 181, 154, 145, 126, 119, 111, 93, 71, 57, 44; HRMS-EI *m/z* [M^+] calcd for $C_9H_9N_2OCl$ 196.0404; found: 196.0401. Anal. Calcd for $C_9H_9N_2OCl$: C, 54.97; H, 4.61; N, 14.25; Cl, 18.03. Found: C, 54.83; H, 4.48; N, 14.14; Cl, 18.14.

4-(Benzyloxy)-2-chloronicotinonitrile (1d): White needle; Mp 140–142 °C; IR (KBr): 3092, 2231, 1578, 1459, 1387, 1307, 1003, 824, 757, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (1H, d, J = 5.9 Hz), 7.43–7.38 (5H, m), 6.91 (1H, d, J = 5.9 Hz), 5.31 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 154.5, 153.2, 133.7, 129.0, 129.0, 127.2, 112.2, 107.1, 100.9, 71.8; MS (EI): *m/z* = 244 [M^+], 91, 65; HRMS-EI *m/z* [M^+] calcd for $C_{13}H_9N_2OCl$ 244.0404; found: 244.0405. Anal. Calcd for $C_{13}H_9N_2OCl$: C, 63.81; H, 3.71; N, 11.45; Cl, 14.49. Found: C, 63.99; H, 3.64; N, 11.35; Cl, 14.26.

2-Chloro-4-(cyclohexyloxy)nicotinonitrile (1e): Colorless oil; IR (film): 2941, 2862, 2233, 1578, 1465, 1305, 1016, 987, 824 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (1H, d, J = 6.4 Hz), 6.84 (1H, d, J = 6.4 Hz), 4.56–4.50 (1H, m), 1.96–1.42 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 154.6, 152.8, 112.5, 107.2, 101.1, 78.5, 30.9, 25.1, 23.0; MS (EI): *m/z* = 236 [M^+], 207, 195, 181, 155, 119, 83, 67, 55, 42; HRMS-EI

m/z [M^+] calcd for $C_{12}H_{13}N_2OCl$ 236.0717; found: 236.0721. Anal. Calcd for $C_{12}H_{13}N_2OCl$•0.12H_2O: C, 60.34; H, 5.59; N, 11.73; Cl, 14.84. Found: C, 60.06; H, 5.85; N, 11.50; Cl, 15.24.

2-Chloro-4-(cycloheptyloxy)nicotinonitrile (1f): Colorless oil; IR (film): 2933, 2233, 1575, 1464, 1307, 998, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (1H, d, *J* = 6.3 Hz), 6.79 (1H, d, *J* = 6.3 Hz), 4.69–4.64 (1H, m), 2.05–1.47 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 154.6, 152.9, 112.5, 107.3, 101.1, 81.4, 33.2, 28.1, 22.6; MS (EI): *m/z* = 250 [M^+], 215, 172, 155, 137, 119, 97, 81, 55, 42; HRMS-EI *m/z* [M^+] calcd for $C_{13}H_{15}N_2OCl$ 250.0873; found: 250.0880. Anal. Calcd for $C_{13}H_{15}N_2OCl$•0.36H_2O: C, 60.71; H, 6.16; N, 10.89. Found: C, 61.03; H, 6.51; N, 10.93.

2-Chloro-4-[(1-methylpiperidin-4-yl)oxy]nicotinonitrile (1h): White needle; Mp 119–122 °C; IR (KBr): 2943, 2804, 2229, 1578, 1550, 1465, 1314, 1138, 1041, 989, 847, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (1H, d, *J* = 5.9 Hz); 6.84 (1H, d, *J* = 5.9 Hz), 4.63–4.60 (1H, m), 2.67–2.62 (2H, m), 2.45–2.39 (2H, m), 2.33 (3H, s), 2.08–1.93 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 154.7, 152.9, 112.3, 107.1, 101.2, 75.0, 51.6, 46.1, 30.2; MS (EI): *m/z* = 251 [M^+], 216, 209, 154, 119, 98, 70, 55, 42; HRMS-EI *m/z* [M^+] calcd for $C_{12}H_{14}N_3OCl$ 251.0786; found: 251.0839. Anal. Calcd for $C_{12}H_{14}N_3OCl$•0.14H_2O: C, 56.69; H, 5.66; N, 16.53; Cl, 13.94. Found: C, 56.63; H, 5.68; N, 16.46; Cl, 13.84.

Ethyl [(4-chloro-3-cyanopyridin-2-yl)oxy]acetate (6): Pale brown powder; Mp 167–169 °C; IR (KBr): 3500, 3395, 3081, 1721, 1626, 1418, 1386, 1282, 1263, 1142, 965, 840, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (1H, d, *J* = 5.9 Hz); 7.34 (1H, d, *J* = 5.9 Hz), 5.54 (2H, brs), 4.45 (2H, q, *J* = 7.3 Hz), 1.44 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 159.3, 147.1, 144.7, 117.0, 107.9, 60.9, 29.8, 14.6; MS (EI): *m/z* = 240 [M^+], 212, 194, 168, 138, 131, 103, 76, 51, 44; HRMS-EI *m/z* [M^+] calcd for $C_{10}H_9N_2O_3Cl$ 240.0302; found: 240.0302.

Ethyl [(2-chloro-3-cyanopyridin-4-yl)oxy]acetate (1g).

To a stirred solution of **7** (155 mg, 1 mmol), PPh_3 (340 mg, 1.3 mmol), and ethyl glycolate (123 μL, 1.3 mmol) in THF (5.0 mL) was added the solution of DEAD in toluene (0.62 mL, 1.3 mmol) dropwise at 0 °C. After stirring at 0 °C for 20 h, *i*-Pr_2O (5 mL) was added and the precipitate was removed. The residue was concentrated and purified by column chromatography (toluene/MeCN = 10:1) to provide **1g** (142 mg, 59%) as a white needle. Mp 70–72 °C; IR (KBr): 2990, 2232, 1751, 1576, 1470, 1386, 1223, 1085, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 5.9 Hz), 6.73 (1H, d, *J* = 5.9 Hz), 4.85 (2H, s), 4.30 (2H, q, *J* = 7.3 Hz), 1.31 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.9, 153.8, 152.5, 112.4, 108.6,

98.9, 66.0, 61.2, 13.9; MS (EI): *m/z* = 240 [M^+], 195, 181, 167, 139, 103, 76; HRMS-EI *m/z* [M^+] calcd for $C_{10}H_9N_2O_3Cl$ 240.0309; found: 240.0299. Anal. Calcd for $C_{10}H_9N_2O_3Cl$•0.12H_2O: C, 49.47; H, 3.84; N, 11.54. Found: C, 49.09; H, 3.92; N, 11.90.

General Procedure for the Preparation of 3

To a solution of 2-(acetylthio)acetamide **8** (112 mg, 0.84 mmol) in DMF (0.7 mL) was added 8 M aqueous solution of NaOH (0.42 mL, 3.4 mmol). After 5 min, a solution of **1** (0.70 mmol) in DMF (0.7 mL) was added. After stirring for 1 h, water (2 mL) was added. The precipitate was filtered and washed with water (10 mL) and EtOH (1 mL) to provide **3**.

3-Amino-4-methoxythieno[2,3-*b*]pyridine-2-carboxamide (3a): Yellow powder; Mp 238–241 °C; IR (KBr): 3482, 3325, 3149, 1667, 1613, 1583, 1504, 1375, 1289, 1044 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (1H, d, *J* = 5.9 Hz); 7.05 (2H, brs), 6.98 (1H, d, *J* = 5.9 Hz), 6.95 (2H, brs), 4.01 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 163.0, 159.7, 151.6, 146.1, 115.2, 101.9, 94.0, 56.1; MS (EI): *m/z* = 223 [M^+], 205, 178, 150, 137, 122, 104, 77, 66, 45; HRMS-EI *m/z* [M^+] calcd for $C_9H_9N_3O_2S$ 223.0415; found: 223.0416. Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found: C, 48.11; H, 4.32; N, 18.76, S, 14.18.

3-Amino-4-ethoxythieno[2,3-*b*]pyridine-2-carboxamide (3b): Pale yellow powder; Mp 241–243 °C; IR (KBr): 3446, 3331, 1645, 1584, 1506, 1375, 1294, 1046 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (1H, d, *J* = 5.9 Hz), 7.03 (2H, brs), 6.95 (1H, d, *J* = 5.9 Hz), 6.84 (2H, brs), 4.30 (2H, q, *J* = 7.1 Hz), 1.44 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 162.2, 159.9, 151.5, 146.1, 115.1, 102.5, 94.2, 64.6, 14.0; MS (EI): *m/z* = 237 [M^+], 219, 205, 192, 176, 164, 148, 137, 120, 104; HRMS-EI *m/z* [M^+] calcd for $C_{10}H_{11}N_3O_2S$ 237.0572; found: 237.0574. Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.62; H, 4.69; N, 17.97, S, 13.52.

3-Amino-4-isopropoxythieno[2,3-*b*]pyridine-2-carboxamide (3c): White powder; Mp 238–240 °C (Dec.); IR (KBr): 3485, 3322, 3137, 1672, 1616, 1582, 1506, 1378, 1287, 1107, 995 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (1H, d, *J* = 5.9 Hz), 7.02 (2H, brs), 6.98 (1H, d, *J* = 5.9 Hz), 6.83 (2H, brs), 4.94 (1H, quint, *J* = 6.3 Hz), 1.40 (6H, d, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 161.4, 160.2, 151.4, 146.2, 115.5, 103.1, 94.1, 71.6, 21.3, 21.2; MS (EI): *m/z* = 251 [M^+], 209, 192, 180, 164, 137, 120, 103, 92, 66, 52, 42; HRMS *m/z* [M^+] calcd for $C_{10}H_{13}N_3O_2S$ 251.0728; found: 251.0742. Anal. Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.20; H, 5.20; N, 16.71; S, 12.41.

3-Amino-4-(benzyloxy)thieno[2,3-*b*]pyridine-2-carboxamide (3d): White powder; Mp 216–221 °C; IR (KBr): 3490, 3324, 3151, 1651, 1580, 1502, 1370, 1290, 1039, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (1H, d, *J* = 5.5 Hz), 7.55–7.36 (5H, m), 7.07 (2H, brs), 7.04 (1H, d, *J* = 5.5 Hz), 6.89 (2H, brs), 5.44 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 161.9, 159.9, 151.4, 145.9, 135.6, 129.0, 128.6, 128.2, 127.7, 126.0, 115.4, 103.2, 94.5, 69.9; MS (FAB): *m/z* = 299 [M^+], 283, 273, 257, 200, 193, 165, 91, 65; HRMS-FAB *m/z* [M^+] calcd for $C_{15}H_{13}N_3O_2S$ 299.0728; found: 299.0730. Anal. Calcd for $C_{15}H_{13}N_3O_2S$•0.12H_2O: C, 59.75; H, 4.43; N, 13.94; S, 10.63. Found: C, 60.09; H, 4.36; N, 13.63; S, 10.26.

3-Amino-4-(cyclohexyloxy)thieno[2,3-*b*]pyridine-2-carboxamide (3e): White powder; Mp 206–208 °C; IR (KBr): 3492, 3330, 3159, 2935, 1654, 1580, 1504, 1368, 1286, 1041, 1020, 992 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (1H, d, *J* = 5.9 Hz), 7.04 (2H, brs), 7.02 (1H, d, *J* = 5.9 Hz), 6.81 (2H, brs), 4.76–4.70 (1H, m), 2.03–1.94 (2H, m), 1.77–1.28 (8H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 161.2, 160.2, 151.4, 146.1, 115.6, 103.2, 94.2, 76.0, 30.5, 24.7, 22.9; MS (EI): *m/z* = 291 [M^+], 209, 192, 164, 137, 120, 55, 41; HRMS-EI *m/z* [M^+] calcd for $C_{14}H_{17}N_3O_2S$ 291.1041; found: 291.1040. Anal. Calcd for $C_{14}H_{17}N_3O_2S$•0.36H_2O: C, 56.45; H, 6.00; N, 14.11; S, 10.76. Found: C, 56.75; H, 5.74; N, 14.07; S, 10.46.

3-Amino-4-(cycloheptyloxy)thieno[2,3-*b*]pyridine-2-carboxamide (3f): White powder; Mp 179–180 °C; IR (KBr): 3491, 3329, 3163, 2927, 1654, 1582, 1504, 1371, 1288, 1012 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ 8.38 (1H, d, *J* = 5.5 Hz), 7.03 (2H, brs), 6.94 (1H, d, *J* = 5.5 Hz), 6.81 (2H, brs), 4.89-4.83 (1H, m), 2.08–2.01 (2H, m), 1.90–1.81 (2H, m), 1.70–1.46 (8H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 161.2, 160.2, 151.4, 146.1, 115.6, 103.3, 94.1, 78.8, 32.6, 27.7, 22.1; MS (EI): *m/z* = 305 [M^+], 209, 192, 164, 120, 97, 55, 41; HRMS-EI *m/z* [M^+] calcd for $C_{15}H_{19}N_3O_2S$ 305.1198; found: 305.1197. Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.81; H, 6.33; N, 13.60; S, 10.30.

{[3-Amino-2-(aminocarbonyl)thieno[2,3-*b*]pyridin-4-yl]oxy}acetic acid 0.67 HCl (3g): Yellow powder; Mp 180–182 °C (Dec.); IR (KBr): 3462, 3336, 3195, 1735, 1649, 1613, 1518, 1474, 1380, 1263, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (1H, d, *J* = 5.4 Hz), 7.09 (2H, brs), 6.95 (1H, d, *J* = 5.4 Hz), 4.99 (2H, s), 3.91 (2H, brs); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 166.5, 162.6, 157.6, 149.7, 145.6, 116.1, 103.3, 94.8, 65.2; MS (FAB): *m/z* = 267 [M^+], 251, 205, 187, 69, 55; HRMS-FAB *m/z* [M^+] calcd for $C_{10}H_9N_3O_4S$ 267.0314; found: 267.0325. Anal. Calcd for $C_{10}H_9N_3O_4S$•0.67HCl•3H_2O: C, 34.75; H, 4.57; N, 12.16; Cl, 6.84; S, 9.28. Found: C, 35.06; H, 4.76; N, 12.04; Cl, 6.85; S, 9.46.

3-Amino-4-[(1-methylpiperidin-4-yl)oxy]thieno[2,3-*b*]pyridine-2-carboxamide (3h): White powder;

Mp 204–206 °C; IR (KBr): 3479, 3331, 3165, 2935, 2790, 1662, 1582, 1504, 1371, 1287, 1040, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 5.9 Hz), 6.86 (2H, brs), 6.65 (1H, d, *J* = 5.9 Hz), 5.22 (2H, brs), 4.68–4.63 (1H, m), 2.66–2.60 (2H, m), 2.45–2.39 (2H, m), 2.33 (3H, s), 2.16–2.09 (2H, m), 2.03–1.96 (2H. m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 161.6, 161.2, 151.6, 147.6, 116.5, 102.5, 94.0, 73.4, 52.2, 46.2, 30.4; MS (ESI): *m/z* = 307 $[M+H]^+$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{14}H_{19}N_4O_2S$ 307.1229; found: 307.1240. Anal. Calcd for $C_{14}H_{18}N_4O_2S•0.1H_2O$: C, 54.56; H, 5.95; N, 18.18. Found: C, 54.35; H, 5.98; N, 18.36.

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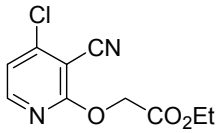

6

8. The structure of **6**.
9. The addition of crown ether is known to be effective for the control of 4-regioselectivity in 2,4-dihaloaromatic compounds by reducing the directing effect of transition state coordination. See: (a) M. D. Wendt and A. R. Kunzer, *Tetrahedron Lett.,* 2010, **51**, 3041; (b) R. L. Jarvest, S. A. Armstrong, J. M. Berge, P. Brown, J. S. Elder, M. J. Brown, R. C. B. Copley, A. K. Forrest, D. W. Hamprecht, P. J. O'Hanlon, D. J. Mitchell, S. Rittenhouse, and D. R. Witty, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3937.
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11. Heaney and co-workers reported Mitsunobu reaction of cyclohexanol in poor yield. Unlike their report, the yield in Mitsunobu reaction of **5e** and **7** was not changed (32%), when carried out in toluene. See: J. Y. Boxhall, P. C. Bulman Page, Y. Chan, C. M. Hayman, H. Heaney, and M. J. McGrath, *Synlett,* 2003, 997.