Preparation of the Four Regioisomeric 2-(Methylthio)oxazolopyridines: Useful Synthons for Elaboration to 2-(Amino substituted)oxazolopyridines

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Introduction

2-Amino-substituted benzoxazoles **1** have been incorporated in a variety of potential pharmaceutical agents (Figure 1).[1] The related aza analogs, oxazolopyridines **2a-d**, are of interest since incorporation of a nitrogen in the benzenoid portion of the benzoxazole could favorably alter the physicochemical and pharmacokinetic properties of these derivatives. Thus, a practical and general route to compounds such as **2** was desirable wherein the amino substituent at position 2 could be easily varied.

Discussion

The 2-(methylthio)oxazolopyridines **3a-d** were chosen as the precursors to the desired products **2a-d** for their ease of preparation[2ab] from the corresponding aminopyridinols **4a-d** as well as for their physical properties; i.e., these compounds are usually stable solids and easily handled (Scheme 1). Furthermore, the 2-methylthio moiety is reactive enough for displacement by amine nucleophiles but not so reactive as to be unstable and hard to manage, as often is the case for the 2-chloro congeners.[2c]

2-Amino-3-hydroxypyridine (**4a**) is commercially available while 3-amino-4-hydroxypyridine (**4b**) and 3-amino-2-hydroxypyridine (**4d**) are easily obtained via hydrogenation of the corresponding nitro derivatives.[3] 4-Amino-3-hydroxypyridine (**4c**), on the other hand, is not readily available, with three syntheses reported in the literature to date. The first synthesis of **4c** relies on oxidation of 4-aminopyridine to 4-aminopyridine-3-pyridyl hydrogen sulfate followed by base-induced cleavage of the sulfate group to give the target compound in 5% overall yield for the two steps.[4] A second route to **4c** proceeds in four steps from 3-methoxypyridine.[5] However, 3-methoxypyridine is not commercially available and not easily prepared.[6] The third synthesis of **4c** was reported in

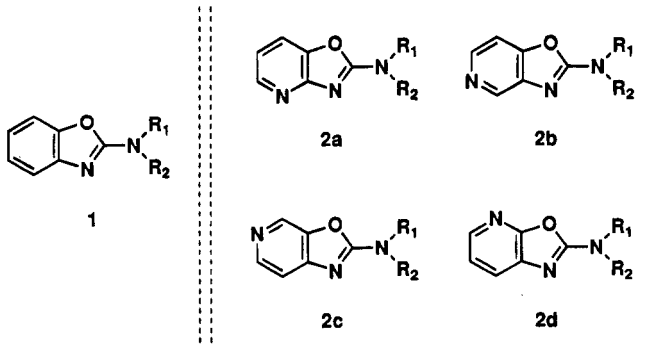
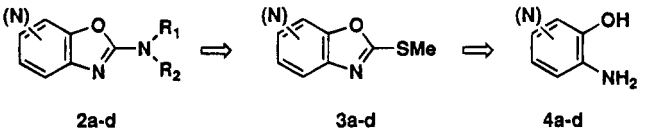
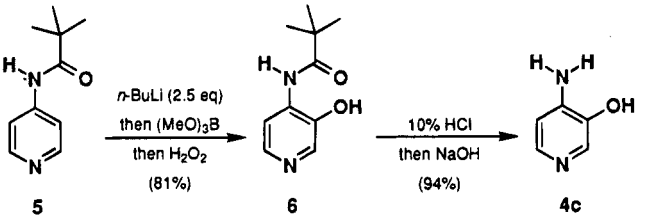


Figure 1.

Scheme 1



Scheme 2



1992 by Shutske *et al.*[7] Thus, 3-pyridyl *N,N*-diethylcarbamate was ortho-aminated with *p*-toluenesulfonyl azide (TsN_3) followed by cleavage of the carbamate with hydrazine to provide the target compound. Although this method is concise and moderate yields are obtained, TsN_3 is not commercially available and potentially shock sensitive, making the reaction difficult to scale up.[7]

Results

A new synthesis of **4c** has been developed which follows an ortho lithiation strategy similar to that of Shutske (Scheme 2).[7] However, starting with pivalamide **5**[8a] and incorporating the hydroxyl group, rather than starting with a carbamate and incorporating an amino group, obviates the use of TsN_3. Ortho lithiation of (pivaloylamino)pyridines has been studied, and several potent electrophiles (cf. D_2O, TMSCl, MeI, etc.) react readily with the derived dianion.[8] Attempted introduction of the hydroxyl group via quenching of the dianion of **5** with molecular oxygen[9] gave only starting material. Use of the more reactive electrophile trimethyl borate ($B(OMe)_3$)[10] produced, after oxidative workup, 3-hydroxy-4-(pivaloylamino)pyridine (**6**) in 81% overall yield. Cleavage of the

(1) Some recent citations include: (a) Monge, A.; del Carmen Peña, M.; Palop, J. A.; Calderó, J. M.; Roca, J.; García, G. R.; del Río, J.; Lasheras, B. *J. Med. Chem.* **1994**, *37*, 1320–1325. (b) Laser, E. S.; Miao, C. K.; Wong, H.-C.; Sorcek, R.; Spero, D. M.; Gilman, A.; Pal, K.; Behnke, M.; Graham, A. G.; Watrous, J. M.; Homon, C. A.; Nagel, J.; Shah, A.; Guindon, Y.; Farina, P. R.; Adams, J. *J. Med. Chem.* **1994**, *37*, 913–923. (c) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kederskey, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719–1728.

(2) Cf. For benzoxazoles, see: (a) Van Allan, J. A.; Deacon, B. D. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 569–570. (b) Yamamoto, M.; Takeuchi, Y.; Hashigaki, K.; Hirota, T. *Chem. Pharm. Bull.* **1983**, *31*, 733–736. (c) Yamamoto, M.; Takeuchi, Y.; Hattori, K.; Hashigaki, K. *Chem. Pharm. Bull.* **1984**, *32*, 3053–3060.

(3) (a) For **4b**, see: Fraser, J.; Tittensor, E. *J. Chem. Soc.* **1956**, 1781–1784. (b) For **4d**, see: Albert, A.; Hampton, A. *J. Chem. Soc.* **1952**, 4985–4993.

(4) Boyland, E.; Sims, P. *J. Chem. Soc.* **1958**, 4198–4199.

(5) (a) Den Hertog, H. J.; Van Ammers, M. *Rec. Trav. Chim.* **1955**, *74*, 1160–1166. (b) Shen, T. Y.; Clark, R. L.; Pessalano, A. A.; Witzel, B. E.; Lanza, T. J. Ger. Patent 2 330 109, 1974; *Chem. Abstr.* **1974**, *80*, 95916s. The overall yield for the first three steps is 53% (ref 5a). No yield is given for the last step (ref 5b).

(6) Finkentey, C.; Langhals, E.; Langhals, H. *Chem. Ber.* **1983**, *116*, 2394–2397 and references therein.

(7) Shutske, G. M.; Tomer, J. D.; Kapples, K. J.; Hrib, N. J.; Jurcak, J. G.; Bores, G. M.; Huger, F. P.; Petko, W.; Smith, C. P. *J. Pharm. Sci.* **1992**, 380–385.

(8) (a) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401–3408. (b) Tamura, Y.; Fujita, M.; Chen, L.-C.; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564–3567. (c) Smith, K.; Lindsay, C. M.; Morris, I. K. *Chem. Ind.* **1988**, 302–303.

(9) Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674–676.

(10) (a) Kidwell, R. L.; Murphy, M.; Darling, S. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 918–921. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34–46.

0022-3263/95/1960-5721$09.00/0

Scheme 3

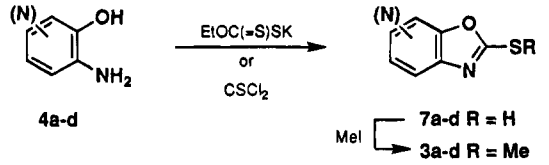
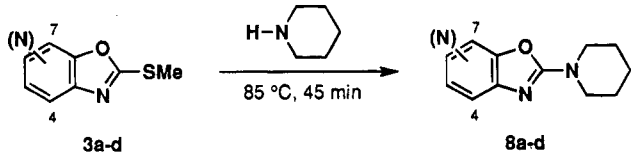


Table 1. Reaction of 2-(Methylthio)oxazolopyridines 3a-d with Piperidine



entry	compd	N position	yield (%)
1	**8a**	4	93
2	**8b**	5	95
3	**8c**	6	93
4	**8d**	7	95

pivaloyl group with 10% HCl was uneventful, providing desired pyridinol **4c** in 94% yield. This novel route to **4c** is of value because of its simplicity and because it is easily executed on larger scales (see Experimental Section).

With all four of the requisite aminopyridinols in hand, conversion to the corresponding 2-(methylthio)oxazolopyridines could be studied (Scheme 3). Reaction of **4a-c** with potassium ethyl xanthate[2a] in refluxing EtOH, or for **4d** with thiophosgene in THF at room temperature,[11] provided 2-mercaptooxazolopyridines **7a-d**. Subsequent treatment with MeI in DMF readily gave 2-(methylthio)-oxazolopyridines **3a-d**. Compounds **7a-d** and **3a-d** are all easily isolated from the reaction and require no further purification. This procedure allows rapid production of ample amounts of material sufficient for the generation of a variety of 2-(amino substituted)oxazolopyridines.

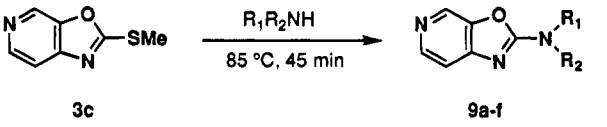
Thus, 2-(methylthio)oxazolopyridines **3a-d** react smoothly with piperidine in the absence of solvent to give the corresponding 2-(1-piperidinyl)oxazolopyridines **8a-d** in excellent yields (Table 1).[12] Reaction of 2-(methylthio)-oxazolo[5,4-*c*]pyridine (**3c**) with other primary and secondary amine nucleophiles is typified by those shown in Table 2, providing 2-(amino substituted)oxazolo[5,4-*c*]-pyridines **9a-f** in yields ranging from 88% to 96%. Of particular note is that incorporation of a piperazine moiety occurs in good yield to provide the desired monoadduct with only trace amounts of the diaddition product (Table 2, entry 6). Finally, although 2 equiv of the amine nucleophile were employed in the above cited cases, it is also possible to use an excess of the 2-(methylthio)oxazolopyridine in those instances where the amine partner is more valuable.[13] Addition of an external base is not required since the liberated methanethiol is nonacidic and does not interfere with the ensuing reaction, providing an advantage over use of the 2-chloro

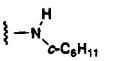
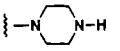
(11) In this case, a more reactive thiocarbonyl source was necessary for reaction to take place. Cf. Kimura, F.; Haga, T.; Sakashita, N.; Maeda, K.; Hayashi, H.; Seki, T.; Yoshida, T. Jpn. Patent 59 10,590, 1984; *Chem. Abstr.* **1984**, *101*, 38448u.

(12) See also: Davidkov, K.; Simov, D.; Kalcheva, V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1988**, 905–906; *Khim. Geterotsikl. Soedin.* **1987**, 1129–1130.

(13) Berger, R. Unpublished results.

Table 2. Reaction of 2-(Methylthio)oxazolo[5,4-*c*]pyridine (3c) with Primary and Secondary Amine Nucleophiles



entry	compd	$-NR_1R_2$	yield (%)
1	**9a**		96
2	**9b**		92
3[a]	**9c**		91
4	**9d**		90
5	**9e**		94
6	**9f**		88

[a] This reaction was run in Et_2NH (0.3 M) at reflux for 60 h.

congeners where neutralization of the generated HCl would be necessary.

Conclusion

In summary, a practical synthesis of 4-amino-3-hydroxypyridine (**4c**) has been achieved. This, in addition to the known aminopyridinols **4a,b,d**, allows the preparation of all four 2-(methylthio)oxazolopyridine isomers **3a-d** via a simple and practical two-step sequence. Finally, 2-(methylthio)oxazolopyridines **3a-d** have been shown to be excellent synthons for the preparation of the corresponding 2-(amino substituted)oxazolopyridines.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550 IR spectrometer. ^1H NMR spectra were obtained on a Bruker AM-250 or a Bruker AM-300 and are reported in parts per million (δ) relative to residual chloroform (7.26 ppm) as an internal reference with coupling constants (J) reported in hertz (Hz). Proton-decoupled ^{13}C NMR were recorded on a Bruker AM-300 and are reported in parts per million (δ) relative to $CDCl_3$ (77 ppm) as an internal reference. Low-resolution mass spectra were obtained on a Fisions Trio 1000 mass spectrometer (thermospray, TS^+) or on a Hewlett-Packard 5989A particle beam mass spectrometer (chemical-ionization, CI). Low-resolution gas chromatography (GC) mass spectra were obtained on a Hewlett-Packard 5890 Series II mass chromatograph. All fast atom bombardment (FAB) high resolution mass spectra were determined on a VG Analytical ZAB high field mass spectrometer by M-Scan Inc., West Chester, PA 19380. Elemental analyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, NJ 11377. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized under UV light as well as with a $KMnO_4$ solution. Liquid column chromatography was performed using forced flow[14] (flash chromatography) of the indicated solvent on EM Science silica gel 60 (230–400 mesh).

3-Hydroxy-4-(pivaloylamino)pyridine (6). To a solution of 4-(pivaloylamino)pyridine (**5**,[8a] 17.4 g, 97.3 mmol) in anhy-

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

drous THF (280 mL) with mechanical stirring under an atmosphere of N_2 at −78 °C was added *n*-BuLi (2.5 *M* in hexane, 97 mL, 243 mmol) dropwise over 30 min so that the internal temperature did not rise above −60 °C. After 20 mL of the *n*-BuLi was added, a white precipitate formed which eventually dissolved, resulting in a yellow homogeneous solution after the addition was complete. The reaction mixture was then warmed to 0 °C and stirred vigorously for 4 h, whereupon a viscous yellow precipitate formed. After the mixture was recooled again to −78 °C, a soution of trimethyl borate (28 mL, 243 mmol) in anhydrous THF (50 mL) was added dropwise over a 15 min period, maintaining an internal temperature below −60 °C. After the addition was complete, the reaction mixture was slowly warmed to 0 °C and stirred for 2 h (all the solid material dissolved). Glacial AcOH (21 mL, 364 mmol) was then introduced, followed by dropwise addition of aqueous 30% H_2O_2 (28 mL, 268 mmol). This mixture was stirred vigorously for 3 h with gradual warming to room temperature, diluted with H_2O, and evaporated *in vacuo*. The residue was extracted with 10% *i*-PrOH/$CHCl_3$ (3×), and the combined organic extracts were treated with activated charcoal and filtered. The filtrate was washed with H_2O (3×) and brine (1×), dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (3 → 10% MeOH/$CHCl_3$) to afford 15.3 g (81%) of 3-hydroxy-4-(pivaloylamino)-pyridine (**6**) as a white solid: mp 168−169 °C dec; TLC R_f 0.27 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 3420, 2970, 2500 (br), 1692, 1593, 1509, 1480, 1438 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 8.29 (d, J = 5.9 Hz, 1 H), 7.77 (s, 1 H), 7.77 (d, J = 5.3 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 179.8, 151.6, 141.1, 134.1, 131.2, 113.8, 41.4, 27.7; MS (TS^+, NH_3) m/z 195 (M + H^+); HRMS (FAB, *m*-nitrobenzyl alcohol/glycerol/NaCl) exact mass calcd for $C_{10}H_{15}N_2O_2$ (M + H^+) 195.1134, found 195.1145. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.43; H, 7.42; N, 14.29.

4-Amino-3-hydroxypyridine (4c). A suspension of 3-hydroxy-4-(pivaloylamino)pyridine (**6**, 14.5 g, 74.7 mmol) in 3 N HCl (40 mL, 120 mmol) was heated to 90 °C with stirring for 18 h, becoming homogeneous after 1 h. This solution was then cooled to 0 °C, neutralized to pH 7 with 6 N NaOH, and evaporated to dryness. The residue was suspended in MeOH, filtered, and evaporated. The resulting residue was resuspended in EtOH, filtered, and evaporated to give 7.70 g (94%) of 4-amino-3-hydroxypyridine (**4c**) as a light tan solid. An analytical sample was purified by flash column chromatography (15% MeOH/$CHCl_3$ + 4% NH_4OH) to give a white solid: mp 212−215 °C dec; TLC R_f 0.10 (20% MeOH/$CHCl_3$ + 5% NH_4OH); IR (KBr) 3325, 3092 (br), 2946 (br), 2678 (br), 1988 (br), 1631, 1600, 1556, 1528 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.56 (d, J = 6.3 Hz, 1 H), 7.40 (s, 1 H), 6.74 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 154.4, 148.4, 132.4, 123.4, 107.0; MS (GC) m/z 110 (M^+); HRMS (FAB, *m*-nitrobenzyl alcohol/glycerol) exact mass calcd for $C_5H_7N_2O$ (M + H^+) 111.0558, found 111.0557.

2-(Methylthio)oxazolo[4,5-*b*]pyridine (3a). To a solution of 2-amino-3-hydroxypyridine (**4a**, 10.0 g, 90.8 mmol) in EtOH (220 mL) was added potassium ethyl xanthate (29.1 g, 182 mmol) in one portion. This heterogeneous mixture was then heated to reflux with stirring under an atmosphere of N_2 for 18 h, cooled to room temperature, and concentrated *in vacuo*. The residue was dissolved with H_2O and acidified to pH 5 with glacial AcOH. The resulting precipitate was filtered, washed with H_2O (3×), and dried under reduced pressure to give 10.1 g (73%) of 2-mercaptooxazolo[4,5-*b*]pyridine (**7a**) as a brown solid: TLC R_f 0.38 (5% MeOH/$CHCl_3$); ^1H NMR (CD_3OD, 250 MHz) δ 8.18 (dd, J = 5.2, 1.2 Hz, 1 H), 7.69 (dd, J = 8.1, 1.2 Hz, 1 H), 7.22 (dd, J = 8.1, 5.2 Hz, 1 H); MS (GC) m/z 152 (M^+).

To a cooled (0 °C) solution of 2-mercaptooxazolo[4,5-*b*]pyridine (**7a**, 10.0 g, 65.7 mmol) in anhydrous DMF (165 mL) with stirring under N_2 was added potassium carbonate (9.08 g, 65.7 mmol) followed by iodomethane (4.9 mL, 78.9 mmol). The reaction mixture was stirred for 1 h, diluted with H_2O, and extracted with EtOAc (4×). The combined organic extracts were washed with H_2O (3×) and brine (1×), dried (Na_2SO_4), filtered, and evaporated to give 9.98 g (91%) of 2-(methylthio)oxazolo[4,5-*b*]-pyridine (**3a**) as a tan solid. An analytical sample was recrystallized from hot isopropyl ether to give an off-white solid: mp 61−63 °C; TLC R_f 0.56 (5% MeOH/$CHCl_3$); IR ($CHCl_3$) 3006, 1617, 1497, 1406 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.44 (dd, J = 5.0, 1.4 Hz, 1 H), 7.68 (dd, J = 8.1, 1.5 Hz, 1 H), 7.16 (dd, J = 8.0, 5.0 Hz, 1 H), 2.79 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 156.0, 145.7, 144.1, 118.8, 117.0, 14.7; MS (TS^+, NH_3) m/z 167 (M + H^+); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_7H_7N_2OS$ (M + H^+) 167.0279, found 167.0279. Anal. Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.96. Found: C, 50.20; H, 3.60; N, 16.89.

2-(Methylthio)oxazolo[4,5-*c*]pyridine (3b). To a suspension of 4-hydroxy-3-nitropyridine (10.0 g, 71.4 mmol) in EtOH (200 mL) was added 10% Pd/C (1.00 g, 10 wt %). This mixture was hydrogenated at 50 psi for 1.5 h and then filtered through Celite to yield a purple solution of 3-amino-4-hydroxypyridine (**4b**)[3a] which was used directly in the next step.

To the above solution of 3-amino-4-hydroxypyridine (**4b**) was added potassium ethyl xanthate (22.9 g, 143 mmol) in one portion. This heterogeneous mixture was then heated to reflux with stirring under an atmosphere of N_2 for 18 h, cooled to room temperature, and concentrated *in vacuo*. The residue was dissolved with H_2O and acidified to pH 5 with glacial AcOH. The resulting precipitate was filtered, washed with H_2O (3×), and dried under reduced pressure to give 5.72 g (52%, two steps) of 2-mercaptooxazolo[4,5-*c*]pyridine (**7b**) as a yellow solid: TLC R_f 0.13 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.49 (s, 1 H), 8.32 (d, J = 6.0 Hz, 1 H), 7.46 (d, J = 5.9 Hz, 1 H); MS (GC) m/z 152 (M^+).

To a cooled (0 °C) solution of 2-mercaptooxazolo[4,5-*c*]pyridine (**7b**, 5.70 g, 57.5 mmol) in anhydrous DMF (90 mL) with stirring under N_2 was added potassium carbonate (5.18 g, 57.5 mmol) followed by iodomethane (2.8 mL, 45.0 mmol). The reaction mixture was stirred for 30 min, diluted with H_2O, and extracted with EtOAc (4×). The combined organic extracts were washed with H_2O (3×) and brine (1×), dried (Na_2SO_4), filtered, and evaporated to give 5.16 g (83%) of analytically pure 2-(methylthio)oxazolo[4,5-*c*]pyridine (**3b**) as a white solid: mp 82−83 °C; TLC R_f 0.40 (5% MeOH/$CHCl_3$); IR ($CHCl_3$) 3000 (br), 1594, 1498, 1462, 1432 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (s, 1 H), 8.47 (d, J = 5.5 Hz, 1 H), 7.39 (dd, J = 5.5, 0.9 Hz, 1 H), 2.77 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 167.2, 156.9, 144.6, 140.7, 139.6, 105.7, 14.6; MS (TS^+, NH_3) m/z 167 (M + H^+); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_7H_7N_2OS$ (M + H^+) 167.0279, found 167.0289. Anal. Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.96. Found: C, 50.46; H, 3.64; N, 17.03.

2-(Methylthio)oxazolo[5,4-*c*]pyridine (3c). To a solution of 4-amino-3-hydroxypyridine (**4c**, 7.67 g, 69.6 mmol) in EtOH (200 mL) was added potassium ethyl xanthate (22.3 g, 139 mmol) in one portion. This heterogeneous mixture was then heated to reflux with stirring under an atmosphere of N_2 for 18 h, cooled to room temperature, and concentrated *in vacuo*. The residue was dissolved with H_2O, and acidified to pH 5 with glacial AcOH. The resulting precipitate was filtered, washed with H_2O (3×), and dried under reduced pressure to give 8.83 g (83%) of 2-mercaptooxazolo[5,4-*c*]pyridine (**7c**) as an off white solid: TLC R_f 0.29 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6, 250 MHz) δ 8.63 (s, 1 H), 8.31 (d, J = 6.1 Hz, 1 H), 7.40 (d, J = 6.1 Hz, 1 H); MS (GC) m/z 152 (M^+).

To a cooled (0 °C) solution of 2-mercaptooxazolo[5,4-*c*]pyridine (**7c**, 8.73 g, 57.4 mmol) in anhydrous DMF (283 mL) with stirring under N_2 was added potassium carbonate (7.93 g, 57.4 mmol) followed by iodomethane (4.3 mL, 68.9 mmol). The reaction mixture was stirred for 1 h, diluted with H_2O, and extracted with EtOAc (4×). The combined organic extracts were washed with H_2O (3×) and brine (1×), dried (Na_2SO_4), filtered, and evaporated to give 7.96 g (83%) of 2-(methylthio)oxazolo[5,4-*c*]-pyridine (**3c**) as a light yellow solid. An analytical sample was recrystallized from hot isopropyl ether to give an off white solid: mp 80−81 °C; TLC R_f 0.45 (5% MeOH/$CHCl_3$); IR ($CHCl_3$) 2999, 1606, 1485, 1463, 1435, 1424 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1 H), 8.49 (d, J = 5.3 Hz, 1 H), 7.53 (dd, J = 5.4, 0.9 Hz, 1 H), 2.78 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.1, 150.0, 148.1, 145.0, 131.8, 113.4, 14.6; MS (CI, NH_3) m/z 167 (M + H^+); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200/PEG MME 350) exact mass calcd for $C_7H_7N_2OS$ (M + H^+) 167.0279, found 167.0279. Anal. Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.96. Found: C, 50.43; H, 3.54; N, 17.02.

2-(Methylthio)oxazolo[5,4-*b*]pyridine (3d). To a suspension of 2-hydroxy-3-nitropyridine (10.0 g, 71.4 mmol) in EtOH (200 mL) was added 10% Pd/C (1.00 g, 10 wt %). This mixture was hydrogenated at 50 psi for 1.5 h and then filtered through

Celite. The filtrate was evaporated to give 7.86 g (100%) of 3-amino-2-hydroxypyridine (**4d**)[3b] as a purple solid.

To a solution of 3-amino-2-hydroxypyridine (**4d**, 7.86g, 71.4 mmol) in anhydrous THF (220 mL) with stirring under N_2 was added thiophosgene (6.5 mL, 85.7 mmol). This homogeneous mixture was stirred at room temperature for 1 h, adjusted to pH 5 with 10 N NaOH, and evaporated *in vacuo*. The residue was diluted with H_2O, and the precipitate was filtered, washed with H_2O (3×), and dried under high vacuum to give 7.50 g (70%, two steps) of 2-mercaptooxazolo[5,4-*b*]pyridine (**7d**) as an orange-yellow solid: TLC R_f 0.56 (5% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.43 (dd, J = 6.5, 1.9 Hz, 1 H), 7.30 (dd, J = 7.3, 1.9 Hz, 1 H), 6.31 (dd, J = 7.2, 6.6 Hz, 1 H); MS (GC) m/z 152 (M^+).

To a cooled (0 °C) solution of 2-mercaptooxazolo[5,4-*b*]pyridine (**7d**, 7.00 g, 46.0 mmol) in anhydrous DMF (110 mL) with stirring under N_2 was added potassium carbonate (6.36 g, 46.0 mmol) followed by iodomethane (3.5 mL, 55.2 mmol). The reaction mixture was stirred for 30 min, diluted with H_2O, and extracted with EtOAc (4×). The combined organic extracts were washed with H_2O (3×) and brine (1×), dried (Na_2SO_4), filtered, and evaporated to give 7.11 g (93%) of 2-(methylthio)oxazolo[5,4-*b*]-pyridine (**3d**) as a light yellow solid. An analytical sample was recrystallized from hot isopropyl ether to give a light tan solid: mp 80–81 °C; TLC R_f 0.65 (5% MeOH/$CHCl_3$); IR ($CHCl_3$) 3002, 1611, 1490, 1468, 1402 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (dd, J = 5.0, 1.5 Hz, 1 H), 7.85 (dd, J = 7.8, 1.5 Hz, 1 H), 7.25 (dd, J = 7.8, 5.0 Hz, 1 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.9, 160.8, 142.9, 133.8, 126.2, 120.8, 14.1; MS (TS^+, NH_3) m/z 167 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_7H_6N_2OS$ ($M + H^+$) 167.0279, found 167.0271. Anal. Calcd for $C_7H_7N_2OS$: C, 50.59; H, 3.64; N, 16.96. Found: C, 50.65; H, 3.61; N, 17.15.

General Procedure for Reaction of 2-(Methylthio)-oxazolopyridines (3a-d) with Piperidine (Table 1). A mixture of 2-(methylthio)oxazolopyridine **3** (1.00 g, 6.0 mmol) and piperidine (1.2 mL, 12.0 mmol) was heated to 85 °C for 45 min and cooled to room temperature. The residue was purified as specified below.

2-(1-Piperidinyl)oxazolo[4,5-*b*]pyridine (8a).[12] The residue was purified by flash column chromatography (3:1 EtOAc/hexanes) to give 1.13 g (93%) of 2-(1-piperidinyl)oxazolo[4,5-*b*]pyridine (**8a**) as a white solid: mp 103–104 °C; TLC R_f 0.63 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2998, 2946, 2861, 1648, 1562, 1415 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (dd, J = 5.2, 1.4 Hz, 1 H), 7.36 (dd, J = 7.7, 1.4 Hz, 1 H), 6.84 (dd, J = 7.8, 5.2 Hz, 1 H), 3.66–3.58 (c, 4 H) 1.71–1.53 (c, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.6, 158.5, 144.5, 141.2, 115.2, 114.4, 46.4, 25.3, 24.0; MS (TS^+, NH_3) m/z 204 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{11}H_{14}N_3O$ ($M + H^+$) 204.1137, found 204.1147. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.49; H, 6.45; N, 20.73.

2-(1-Piperidinyl)oxazolo[4,5-*c*]pyridine (8b). The residue was purified by flash column chromatography (3:1 EtOAc/hexanes) to give 1.17 g (95%) of 2-(1-piperidinyl)oxazolo[4,5-*c*]-pyridine (**8b**) as a white solid: mp 117–118 °C; TLC R_f 0.55 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2983, 2946, 2860, 1647, 1572, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.62 (s, 1 H), 8.27 (d, J = 5.3 Hz, 1 H), 7.19 (dd, J = 5.3, 0.5 Hz, 1 H), 3.70–3.62 (c, 4 H) 1.71–1.61 (c, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.2, 154.0, 141.9, 141.1, 138.0, 104.6, 46.7, 25.2, 23.9; MS (TS^+, NH_3) m/z 204 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{11}H_{14}N_3O$ ($M + H^+$) 204.1137, found 204.1151. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.83; H, 6.53; N, 20.77.

2-(1-Piperidinyl)oxazolo[5,4-*c*]pyridine (8c). The residue was purified by flash column chromatography (5% MeOH/EtOAc) to give 1.13 g (93%) of 2-(1-piperidinyl)oxazolo[5,4-*c*]-pyridine (**8c**) as a white solid: mp 117–119 °C; TLC R_f 0.54 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2947, 2862, 1646, 1573, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.47 (s, 1 H), 8.30 (d, J = 5.2 Hz, 1 H), 7.22 (d, J = 5.2 Hz, 1 H), 3.72–3.61 (c, 4 H) 1.75–1.60 (c, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.4, 150.6, 147.1, 145.2, 129.5, 111.3, 46.6, 25.2, 23.8; MS (TS^+, NH_3) m/z 204 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{11}H_{14}N_3O$ ($M + H^+$) 204.1137, found 204.1130. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.82; H, 6.60; N, 20.79.

2-(1-Piperidinyl)oxazolo[5,4-*b*]pyridine (8d). The residue was purified by flash column chromatography (2:3 EtOAc/hexanes) to give 1.16 g (95%) of 2-(1-piperidinyl)oxazolo[5,4-*b*]-pyridine (**8d**) as a white solid: mp 103–104 °C; TLC R_f 0.71 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2989, 2946, 2860, 1648, 1609, 1578, 1452, 1414 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (dd, J = 5.1, 1.5, 1 H), 7.49 (dd, J = 7.7, 1.5 Hz, 1 H), 7.06 (dd, J = 7.7, 5.1 Hz, 1 H), 3.75–3.60 (c, 4 H) 1.76–1.59 (c, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.3, 158.5, 138.5, 136.1, 122.5, 120.4, 46.3, 25.2, 24.0; MS (CI, NH_3) m/z 204 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{11}H_{14}N_3O$ ($M + H^+$) 204.1137, found 204.1125. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.92 H, 6.43; N, 20.89.

General Procedure for Reaction of 2-(Methylthio)-oxazolo[5,4-*c*]pyridine (3c) with Amine Nucleophiles (Table 2, 9a,b,d-f). A mixture of 2-(methylthio)oxazolo[5,4-*c*]pyridine (**3c**, 0.50 g, 3.0 mmol) and the corresponding amine nucleophile (2.0 equiv, 6.0 mmol) was heated to 85 °C for 45 min and cooled to room temperature. The residue was purified as specified below.

2-(Benzylamino)oxazolo[5,4-*c*]pyridine (9a). The residue was purified by flash column chromatography (1.5% MeOH/$CHCl_3$) to give 651 mg (96%) of 2-(benzylamino)oxazolo[5,4-*c*]-pyridine (**9a**) as a white solid: mp 174–176 °C; TLC R_f 0.54 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 3435, 2980 (br), 1649, 1614, 1577, 1467, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (d, J = 0.5 Hz, 1 H), 8.26 (d, J = 5.3 Hz, 1 H), 7.47 (br s, 1 H), 7.41–7.28 (c, 5 H), 7.08 (d, J = 5.3 Hz, 1 H), 4.70 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.9, 150.2, 147.1, 145.2, 137.0, 129.8, 128.9, 128.1, 127.7, 111.7, 47.1; MS (TS^+, NH_3) m/z 226 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{13}H_{12}N_3O$ ($M + H^+$) 226.0980, found 226.0990. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 68.95; H, 5.10; N, 18.90.

2-(Cyclohexylamino)oxazolo[5,4-*c*]pyridine (9b). The residue was purified by flash column chromatography (2% MeOH/$CHCl_3$) to give 653 mg (92%) of 2-(cyclohexylamino)-oxazolo[5,4-*c*]pyridine (**9b**) as a white solid: mp 145–147 °C; TLC R_f 0.45 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 3430, 2939, 2859, 1645, 1613, 1575, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J = 0.6 Hz, 1 H), 8.33 (d, J = 5.2 Hz, 1 H), 7.25 (dd, J = 5.2, 0.7 Hz, 1 H), 6.41 (br s, 1 H), 3.79 (m, 1 H), 2.14–2.10 (c, 2 H), 1.82-1.76 (c, 2 H), 1.65 (m, 1 H), 1.49–1.14 (c, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.2, 150.5, 147.0, 145.1, 129.6, 111.5, 52.4, 33.3, 25.4, 24.7; MS (TS^+, NH_3) m/z 218 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol) exact mass calcd for $C_{12}H_{16}N_3O$ ($M + H^+$) 218.1293, found 218.1280. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.08; H, 7.08; N, 19.48.

2-(*N*-Benzyl-*N*-methylamino)oxazolo[5,4-*c*]pyridine (9d). The residue was purified by flash column chromatography (1.5% MeOH/$CHCl_3$) to give 647 mg (90%) of 2-(*N*-benzyl-*N*-methylamino)oxazolo[5,4-*c*]pyridine (**9d**) as a white solid: mp 82–83 °C; TLC R_f 0.51 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2984 (br), 1648, 1612, 1575, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 7.38–7.25 (c, 6 H), 4.78 (s, 2 H), 3.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.4, 150.7, 147.6, 145.4, 135.6, 129.8, 128.9, 128.1, 127.7, 111.6, 54.1, 35.3; MS (TS^+, NH_3) m/z 240 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG MME 350) exact mass calcd for $C_{14}H_{14}N_3O$ ($M + H^+$) 240.1137, found 240.1154. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.91; H, 5.64; N, 17.70.

2-(4-Morpholinyl)oxazolo[5,4-*c*]pyridine (9e). The residue was purified by flash column chromatography (2% MeOH/$CHCl_3$) to give 583 mg (94%) of 2-(4-morpholinyl)oxazolo[5,4-*c*]pyridine (**9e**) as a white solid: mp 113–114 °C; TLC R_f 0.54 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2977, 2865, 1641, 1574, 1467, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.53 (s, 1 H), 8.36 (d, J = 5.3 Hz, 1 H), 7.27 (d, J = 5.0 Hz, 1 H), 3.84–3.80 (c, 4 H) 3.77–3.73 (c, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.2, 150.1, 147.2, 145.4, 129.9, 111.8, 66.0, 45.6; MS (TS^+, NH_3) m/z 206 ($M + H^+$); HRMS (FAB, *m*-nitrobenzyl alcohol/PEG 200/PEG MME 350) exact mass calcd for $C_{10}H_{12}N_3O_2$ ($M + H^+$) 206.0930, found 206.0921. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.45; H, 5.52; N, 20.64.

2-(1-Piperazinyl)oxazolo[5,4-*c*]pyridine (9f). The residue was purified by flash column chromatography (5% MeOH/$CHCl_3$ + 1% NH_4OH) to give 540 mg (88%) of 2-(1-piperazinyl)oxazolo-[5,4-*c*]pyridine (**9f**) as a white solid: mp 136–137 °C; TLC R_f

0.15 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2961, 2923, 2865, 2840, 1641, 1574, 1467, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1 H), 8.30 (d, J = 5.2 Hz, 1 H), 7.22 (d, J = 5.1 Hz, 1 H), 3.69 (t, J = 5.1 Hz, 4 H), 2.95 (t, J = 5.1 Hz, 4 H), 1.81 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.4, 150.3, 147.2, 145.4, 129.8, 111.6, 46.6, 45.4; MS (CI, NH_3) m/z 205 ($M + H^+$); HRMS (FAB, m-nitrobenzyl alcohol/PEG 200) exact mass calcd for $C_{10}H_{13}N_4O$ ($M + H^+$) 205.1089, found 205.1105. Anal. Calcd for $C_{10}H_{12}N_4O \cdot 1/2H_2O$: C, 56.33; H, 6.04; N, 26.27. Found: C, 56.09; H, 5.67; N, 26.33.

2-(Diethylamino)oxazolo[5,4-*c*]pyridine (9c). A solution of 2-(methylthio)oxazolo[5,4-*c*]pyridine (**3c**, 0.50g, 3.0 mmol) in diethylamine (10 mL) was refluxed with stirring under N_2 for 60 h, cooled to room temperature, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1.5% MeOH/$CHCl_3$) to give 525 mg (91%) of 2-(diethylamino)oxazolo-[5,4-*c*]pyridine (**9c**) as a white solid: mp 57–58 °C; TLC R_f 0.65 (10% MeOH/$CHCl_3$); IR ($CHCl_3$) 2981, 2940, 1645, 1574, 1467, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.49 (s, 1 H), 8.31 (d, J = 5.3 Hz, 1 H), 7.24 (dd, J = 5.3, 0.6 Hz, 1 H), 3.61 (q, J = 7.2 Hz, 4 H), 1.29 (t, J = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.6, 150.8, 147.4, 145.2, 129.5, 111.3, 43.3, 13.4; MS (TS^+, NH_3) m/z 192 ($M + H^+$); HRMS (FAB, glycerol/NaCl) exact mass calcd for $C_{10}H_{14}N_3O$ ($M + H^+$) 192.1137, found 192.1126. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.95. Found: C, 62.63; H, 7.08; N, 22.17.

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