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A FACILE SYNTHESIS OF 6-SUBSTITUTED 7-ARYLTHIENO[2,3-*b*]-PYRAZINES FROM 2-CHLOROPYRAZINE

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Abstract – A series of 6,7-disubstituted thieno[2,3-*b*]pyrazines were prepared by two- or three-pot reaction sequences starting from commercially available 2-chloropyrazine. The reaction of 2-chloro-3-lithiopyrazine with *N*,*N*-dimethylbenzamides gave directly aryl(3-chloropyrazin-2-yl)methanones, which were treated successively with sodium sulfide, $BrCH_2EWG$ (EWG = CN, CO_2t-Bu, COAr), and sodium hydride to give the corresponding 6-substituted 7-arylthieno[2,3-*b*]pyrazines. Similarly, 6-substituted 7-heterarylthieno[2,3-*b*]-pyrazines were prepared from (3-chloropyrazin-2-yl)heterarylmethanones, derived by the reaction of 2-chloro-3-lithiopyrazine with heteraromatic aldehydes followed by the PCC oxidation.

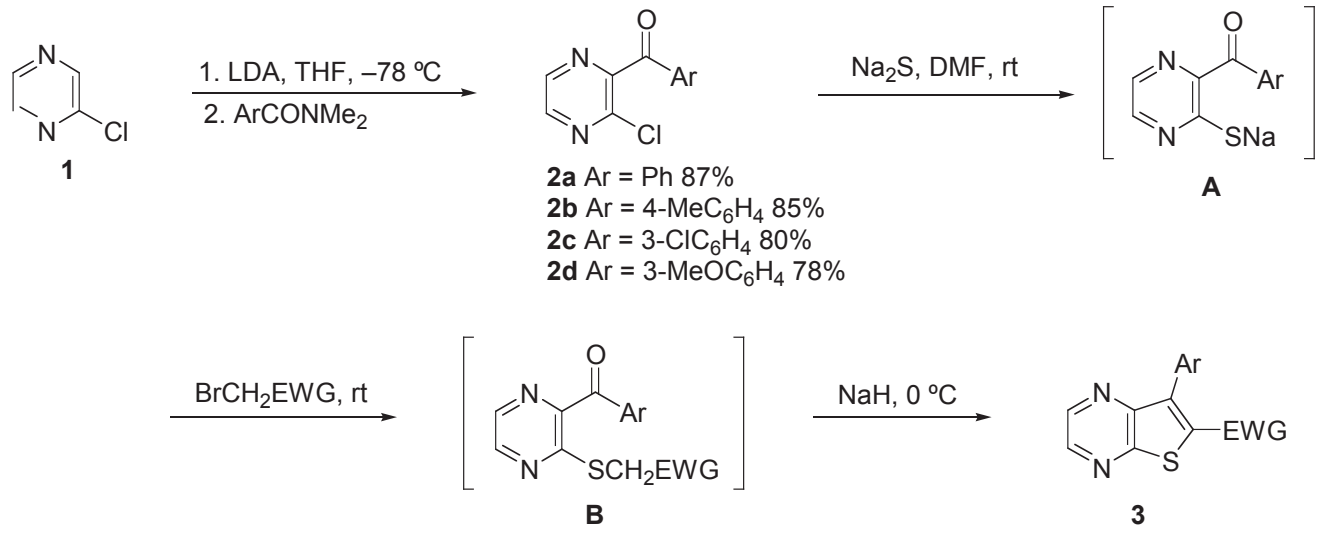
INTRODUCTION

Thieno[2,3-*b*]pyrazines are an important class of heterocycles, because some compounds having this heterocyclic moiety have been reported to exhibit biological activities.[1] Moreover, some thieno[2,3-*b*]pyrazine derivatives have been used for the preparation of more important and structurally complex heterocyclic systems,[2] such as thieno[3,2-*g*]pteridin-4(3*H*)-ones[2b,c] and pyrazino[2',3':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones.[2d-f] However, there have been only a few practical methods for the construction of thieno[2,3-*b*]pyrazines.[2b-d,3] On the other hand, we have previously reported that 2-substituted 3-arylthieno[2,3-*b*]-, [2,3-*c*]- or -[3,2-*c*]pyridines can be synthesized in one-pot from the respective aryl(chloropyridinyl)methanones and $BrCH_2EWG$ (EWG = CN, CO_2t-Bu, COAr).[4] We therefore decided to apply this thienopyridine synthesis to a one-pot preparation of thieno[2,3-*b*]pyrazines from aryl(3-chloropyrazin-2-yl)methanones and $BrCH_2EWG$. In this paper, we wish to report the results of our study, which provide a convenient method for preparing 6-substituted 7-arylthieno[2,3-*b*]pyrazines or 7-heterarylthieno[2,3-*b*]pyrazines from aryl(3-chloropyrazin-2-yl)-

methanones or (3-chloropyrazin-2-yl)heterarylmethanones, respectively. To the best of our knowledge, these types of thieno[2,3-*b*]pyrazines have not been prepared so far.

RESULTS AND DISCUSSION

Jones and co-workers have synthesized (3-chloropyrazin-2-yl)phenylmethanone (**2a**) by the reaction of 2-chloro-3-lithiopyrazine, generated by the treatment of 2-chloropyrazine with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at –78 ˚C, with benzaldehyde followed by oxidation of the resulting alcohol with manganese(IV) oxide.[5] Initially, we investigated the possibility of preparing **2a**, one of the starting materials for the present one-pot preparation, directly from 2-chloro-3-lithiopyrazine. We were relieved to find that 2-chloro-3-lithiopyrazine could be generated efficiently by the treatment of 2-chloropyrazine with LDA in THF at –78 ˚C and reacted with *N*,*N*-dimethylbenzamide at the same temperature to afford **2a** in 87% yield. This procedure was successfully used for the preparation of other three aryl(3-chloropyrazin-2-yl)methanones (**2b-d**) in good yields as shown in Scheme 1.



Scheme 1

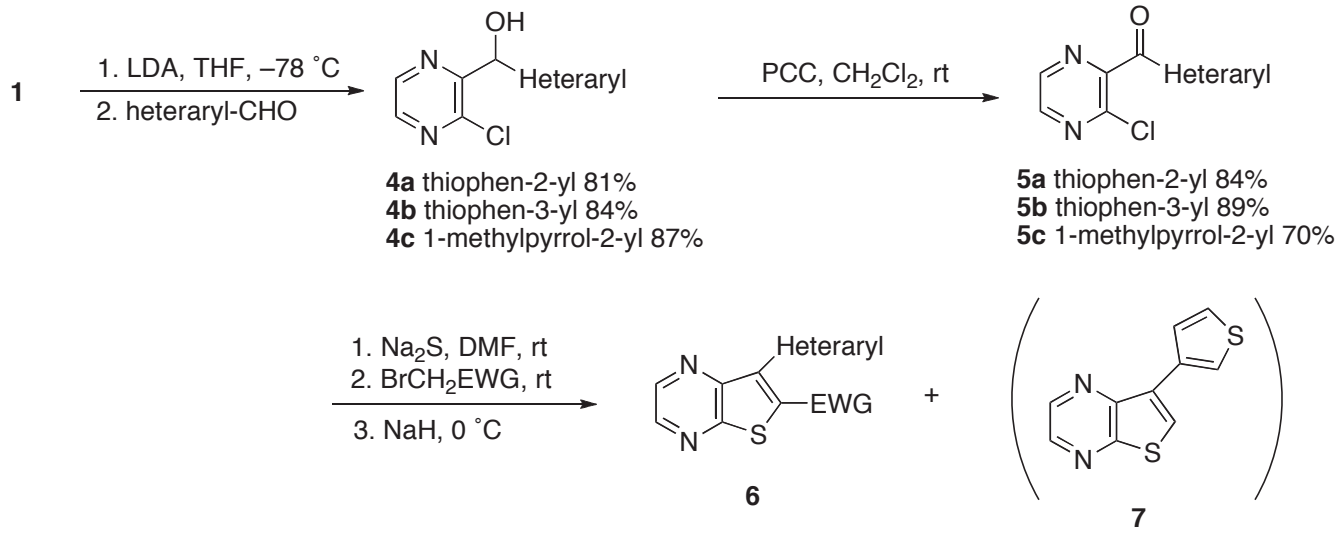
Table 1. Preparation of 6-substituted 7-arylthieno[2,3-*b*]pyrazines (**3**)

Entry	**2**	EWG	**3**	Yield/%[a]
1	**2a** (Ar = Ph)	CN	**3a**	72
2	**2a**	CO_2t-Bu	**3b**	66
3	**2a**	COPh	**3c**	51
4	**2a**	CO(2-ClC_6H_4)	**3d**	71
5	**2b** (Ar = 4-MeC_6H_4)	CO_2t-Bu	**3e**	63
6	**2c** (Ar = 3-ClC_6H_4)	CN	**3f**	55
7	**2d** (Ar = 3-$MeOC_6H_4$)	CN	**3g**	72
8	**2d**	CO_2t-Bu	**3h**	61

[a] Yields of isolated products.

The one-pot procedure previously used for the preparation of three types of thienopyridines from aryl(chrolopyridinyl)methanones[4] was found to be effective for the present one-pot preparation of thieno[2,3-*b*]pyrazines (**3**) from **2** as shown in Scheme 1. Thus, simply treating **2** with sodium sulfide nonahydrate, $BrCH_2EWG$, and then sodium hydride (about equimolar amount each) in DMF allowed the formation of **3** (*via* intermediates **A** and **B**) in moderate to fair yields as summarized in Table 1. An additional equivalent of sodium hydride did not improve the yields. The present procedure proved to be inefficient with bromonitromethane (no data indicated in the Table).

In order to investigate the possibility of obtaining corresponding 3-heteraryl derivatives (**6**), we planed to prepare (3-chloropyrazin-2-yl)heterarylmethanones (**5**) in a similar manner as described for the preparation of **2** from **1**. Unfortunately, however, attempts were made to obtain **5** by using heterocyclic *N*,*N*-dimethylamides, such as *N*,*N*-dimethylthiophene-2-carboxamide, *N*,*N*-dimethylthiophene-3-carboxamide and 1,*N*,*N*-trimethylpyrrole-3-carboxamide, without success. 3-Heteraroylation of 2-chloropyrazine did not occur at all, probably due to the inactivity of these amides toward 2-chloro-3-lithiopyrazine. Accordingly, 2-chloro-3-lithiopyrazine was allowed to react with thiophene-2-carboxaldehyde, thiophene-3-carboxaldehyde, and 1-methylpyrrole-2-carboxaldehyde to afford the corresponding (3-chloropyrazin-2-yl)heterarylmethanols (**4**) in good yields. Subsequent PCC oxidation of these alcohols was successfully accomplished to result in the formation of **5** in good yields as shown in Scheme 2.



Scheme 2

With precursors (**5**) in hand the conversion of these compounds into 6-substituted 7-heterarylthieno[2,3-*b*]pyrazines (**6**) was then carried out. The reaction sequence using these precursors uneventfully proceeded in general under conditions similar to those used for the conversion of **2** into **3** as described above and the desired products (**6**) could be obtained, as depicted in Scheme 2 as well. The

results are summarized in Table 2, which indicates that the yields of **6** are generally fair. However, it should be noted that when **5b** was allowed to react with sodium sulfide, 2-bromo-1-phenylethanone, and then sodium hydride, surprisingly 7-(thiophen-3-yl)thieno[2,3-*b*]pyrazine (**7**) was obtained in a fair 62% yield along with the desired product (**6e**) in a low 28% yield (Entry 5). Unfortunately, however, the reason for the preferential production of **7** is unclear.

Table 2. Preparation of 6-substituted 7-heterarylthieno[2,3-*b*]pyrazines (**6**)

Entry	**5**	Heteraryl	EWG	**6**	Yield/%[a]
1	**5a**	thiophen-2-yl	CN	**6a**	62
2	**5a**	thiophen-2-yl	CO(2-ClC_6H_4)	**6b**	71
3	**5b**	thiophen-3-yl	CN	**6c**	65
4	**5b**	thiophen-3-yl	CO_2t-Bu	**6d**	67
5	**5b**	thiophen-3-yl	COPh	**6e**	28[b]
6	**5c**	1-methylpyrrol-2-yl	CO_2t-Bu	**6f**	66

[a] Yields of isolated products. [b] A 62% yield of **7** was obtained along with **6e**.

In conclusion, we have developed an efficient method for the preparation of 6,7-disubstituted thieno[2,3-*b*]pyrazines, which relies on a one-pot procedure from aryl(3-chloropyrazin-2-yl)methanones and (3-chloropyrazin-2-yl)heterarylmethanones, obtainable in one- and two-step reaction sequences, respectively, from commercially available 2-chloropyrazine. This method is useful because of the simple operations and the ready availability of the starting materials.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. The ^1H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or JEOL LA400FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. *n*-BuLi was supplied by Asia Lithium Corporation. All chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Aryl(2-chloropyrazin-2yl)methanones 2. (3-Chloropyrazin-2-yl)phenylmethanone (2a).[5] To a stirred solution of LDA (1.2 mmol), generated by the standard method from *n*-BuLi and *i*-Pr_2NH, in THF (5 mL) at –78 ˚C was added 2-chloropyrazine (**1**) (0.11 g, 1.0 mmol) dropwise. After 1 h, *N*,*N*-dimethylbenzamide (0.18 g, 1.2 mmol) was added and the mixture was stirred for an additional 30 min before saturated aqueous NH_4Cl (10 mL) was added. The warmed mixture was extracted with AcOEt (3 × 10 mL) and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:5) to give **2a** (0.20 g, 87%); a yellow solid; mp 71–73 ˚C (hexane–Et_2O); IR (KBr) 1672 cm^{-1}; ^1H NMR (500 MHz) δ 7.52 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.67 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.55 (d, *J* = 2.3 Hz, 1H), 8.61 (d, *J* = 2.3 Hz, 1H).

(3-Chloropyrazin-2-yl)(4-methylphenyl)methanone (2b): a yellow oil; R_f 0.37 (AcOEt–hexane 1:5); IR (neat) 1674, 1605 cm^{-1}; ^1H NMR (400 MHz) δ 2.45 (s, 3H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 8.54 (d, *J* = 2.0 Hz, 1H), 8.90 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.94; H, 3.93; N, 11.90.

(3-Chlorophenyl)(3-chloropyrazin-2-yl)methanone (2c): a yellow oil; R_f 0.31 (AcOEt–hexane 1:10); IR (neat) 1682 cm^{-1}; ^1H NMR (400 MHz) δ 7.46 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.9 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07. Found: C, 52.17; H, 2.58; N, 10.92.

(3-Chloropyrazin-2-yl)(3-methoxyphenyl)methanone (2d): a yellow solid; mp 76–77 ˚C (hexane–Et_2O); IR (KBr) 1676 cm^{-1}; ^1H NMR (500 MHz) δ 3.88 (s, 3H), 7.21 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.27 (d, *J* = 7.4Hz, 1H), 7.40 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.48 (s, 1H), 8.54 (d, *J* = 2.3 Hz, 1H), 8.60 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.94; H, 3.78; N, 11.05.

Typical Procedure for the Preparation of (3-Chloropyrazin-2-yl)heterarylmethanols (4). (3-Chloropyrazin-2-yl)(thiophen-2-yl)methanol (4a). To a stirred solution of 2-chloro-3-lithiopyrazine (3.0 mmol), generated by the procedure described for the preparation of **2a**, was added thiophene-2-carboxaldehyde (0.34 g, 3.0 mmol). After 10 min, the mixture was worked up in a manner similar to that for the preparation of **2a** and the crude product was purified by column chromatography on silica gel to give **4a** (0.55 g, 81%); a yellow oil; R_f 0.31 (THF–hexane 1:3); IR (neat) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 4.56 (d, *J* = 8.8 Hz, 1H), 6.32 (d, *J* = 8.8 Hz, 1H), 6.94–7.00 (m, 2H), 7.28 (d, *J* = 4.9 Hz, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.62; H, 3.15; N, 12.36.

(3-Chloropyrazin-2-yl)(thiophen-3-yl)methanol (4b): a yellow oil; R_f 0.29 (AcOEt–hexane 1:2); IR (neat) 3404 cm^{-1}; ^1H NMR (500 MHz) δ 4.46 (d, *J* = 8.6 Hz, 1H), 6.16 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 7.24 (s, 1H), 7.28 (dd, *J* = 5.1, 2.9 Hz, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 8.55 (d, *J* = 2.3 Hz, 1H).

Anal. Calcd for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.70; H, 3.10; N, 12.18.

(3-Chloropyrazin-2-yl)(1-methylpyrrol-2-yl)methanol (4c): a yellow oil; R_f 0.21 (AcOEt–hexane 1:2); IR (neat) 3391 cm^{-1}; ^1H NMR (400 MHz) δ 3.85 (s, 3H), 4.03 (d, J = 9.2 Hz, 1H), 5.33 (dd, J = 3.4, 1.1 Hz, 1H), 5.97 (dd, J = 3.4, 2.9 Hz, 1H), 6.08 (d, J = 9.2 Hz, 1H), 6.67 (dd, J = 2.9, 1.1 Hz, 1H), 8.41 (d, J = 2.9 Hz, 1H), 8.56 (d, J = 2.9 Hz, 1H). Anal. Calcd for $C_{10}H_{10}ClN_3O$: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.42; H, 4.72; N, 18.81.

Typical Procedure for the Preparation of (3-Chloropyrazin-2-yl)heterarylmethanones 5. (3-Chloropyrazin-2-yl)(thiophen-2-yl)methanone (5a). To a stirred solution of **4a** (0.55 g, 2.4 mmol) in CH_2Cl_2 (20 mL) containing Celite 545 (2 g) at rt was added PCC (1.0 g, 4.9 mmol) in several portions. After 30 min, the mixture was filtered under reduced pressure and the filtrate was concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **5a** (0.46 g, 84%); a yellow oil; R_f 0.35 (THF–hexane 1:3); IR (neat) 1658 cm^{-1}; ^1H NMR (400 MHz) δ 7.19 (dd, J = 4.9, 3.9 Hz, 1H), 7.66 (d, J = 3.9 Hz, 1H), 7.84 (d, J = 4.9 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_9H_5ClN_2OS$: C, 48.11; H, 2.24; N, 12.47. Found: C, 48.07; H, 2.30; N, 12.18.

(3-Chloropyrazin-2-yl)(thiophen-3-yl)methanone (5b): a yellow oil; R_f 0.45 (AcOEt–hexane, 1:2); IR (neat) 1666 cm^{-1}; ^1H NMR (400 MHz) δ 7.41 (dd, J = 5.1, 2.9 Hz, 1H), 7.65 (dd, J = 5.1, 1.1 Hz, 1H), 8.03 (2.9, 1.1 Hz, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_9H_5ClN_2OS$: C, 48.11; H, 2.24; N, 12.47. Found: C, 48.06; H, 2.28; N, 12.17.

(3-Chloropyrazin-2-yl)(1-methylpyrrol-2-yl)methanone (5c): a white solid; mp 80–82 °C (hexane–Et_2O); IR (KBr) 1639 cm^{-1}; ^1H NMR (500 MHz) δ 4.12 (s, 3H), 6.18 (dd, J = 3.9, 2.0 Hz, 1H), 6.52 (br s, 1H), 7.01 (s, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.14; H, 3.65; N, 18.95.

Typical Procedure for the Preparation of Thienopyrazines (3) and (6). 7-Phenylthieno[2,3-*b*]-pyrazine-6-carbonitrile (3a). After a solution of **2a** (0.10 g, 0.46 mmol) in DMF (2.5 mL) containing Na_2S nonahydrate (0.13 g, 0.55 mmol) was stirred at rt for 1.5 h, $BrCH_2CN$ (49 mg, 0.41 mmol) was added. Ten min later, the mixture was cooled to 0 °C and NaH (60 % in mineral oil; 20 mg, 0.50 mmol) was added, and stirring was continued for 10 min at the same temperature. Saturated aqueous NH_4Cl (10 ml) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:2) to give **3a** (85 mg, 72%); an orange solid; mp 172–174 °C (hexane–CH_2Cl_2); IR (KBr) 2224 cm^{-1}; ^1H NMR (400 MHz) δ 7.52–7.63 (m, 3H), 7.89 (dd, J = 7.8, 0.9 Hz, 2H), 8.73 (d, J = 2.4 Hz, 1H), 8.86 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 109.55, 113.94, 128.97, 129.54, 130.13, 130.38, 143.51, 143.54, 145.13, 146.63, 156.51; MS m/z 237 (M^+, 100). Anal. Calcd for $C_{13}H_7N_3S$: C, 65.80; H, 2.97; N, 17.71. Found: C, 65.62; H, 2.99; N, 17.64.

1,1-Dimethylethyl 7-Phenylthieno[2,3-*b*]pyrazine-6-carboxylate (3b): an orange solid; mp 114–116 °C

(hexane–Et_2O); IR (KBr) 1697 cm^{-1}; ^1H NMR (500 MHz) δ 1.40 (s, 9H), 7.45–7.52 (m, 5H), 8.61 (d, *J* = 2.3 Hz, 1H), 8.71 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 27.78, 83.39, 127.96, 128.46, 130.01, 132.90, 135.20, 140.08, 142.69, 142.86, 148.79, 155.99, 161.40; MS *m/z* 312 (M^+, 27), 256 (100). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.33; H, 5.21; N, 9.01.

Phenyl(7-phenylthieno[2,3-*b*]pyrazin-6-yl)methanone (3c): a yellow solid; mp 139–141 ˚C (hexane–CH_2Cl_2); IR (KBr) 1631 cm^{-1}; ^1H NMR (400 MHz) δ 7.19–7.29 (m, 5H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 8.67 (d, *J* = 2.0 Hz, 1H), 8.80 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 128.12, 128.21, 128.61, 129.80, 130.67, 132.20, 133.23, 136.21, 137.94, 140.95, 142.48, 142.87, 147.77, 156.39, 191.23; MS *m/z* 316 (M^+, 100). Anal. Calcd for $C_{19}H_{12}N_2OS$: C, 72.13; H, 3.82; N, 8.85. Found: C, 72.01; H, 3.72; N, 8.87.

(2-Chlorophenyl)(7-phenylthieno[2,3-*b*]pyrazin-6-yl)methanone (3d): a yellow solid; mp 145–146 ˚C (hexane–CH_2Cl_2); IR (KBr) 1638 cm^{-1}; ^1H NMR (400 MHz) δ 7.03–7.27 (m, 9H), 8.67 (d, *J* = 2.0 Hz, 1H), 8.76 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 126.29, 127.76 (2C), 128.62, 129.90, 130.35, 131.44, 131.59, 131.83, 137.55, 140.97, 141.85, 143.19, 143.27, 148.46, 157.08, 189.86; MS *m/z* 350 (M^+, 100). Anal. Calcd for $C_{19}H_{11}ClN_2OS$: C, 65.05; H, 3.16; N, 7.99. Found: C, 65.04; H, 3.15; N, 7.97.

1,1-Dimethylethyl 7-(4-Methylphenyl)thieno[2,3-*b*]pyrazine-6-carboxylate (3e): a yellow solid; mp 120–122 ˚C (hexane–CH_2Cl_2); IR (KBr) 1697 cm^{-1}; ^1H NMR (500 MHz) δ 1.55 (s, 9H), 2.43 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 8.60 (d, *J* = 1.1 Hz, 1H), 8.70 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR δ 21.43, 27.85, 83.32, 128.72, 129.77, 129.93, 134.52, 138.34, 140.37, 142.67, 142.80, 148.89, 156.00, 161.32; MS *m/z* 326 (M^+, 44), 270 (100). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.12; H, 5.77; N, 8.41.

7-(3-Chlorophenyl)thieno[2,3-*b*]pyrazine-6-carbonitrile (3f): an orange solid; mp 189–191 ˚C (hexane–CH_2Cl_2); IR (KBr) 2221 cm^{-1}; ^1H NMR (400 MHz) δ 7.53–7.54 (m, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.91 (s, 1H), 8.74 (d, *J* = 2.0 Hz, 1H), 8.87 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 110.36, 113.55, 127.66, 129.68, 130.22, 130.26, 131.96, 134.95, 143.38, 143.66, 143.76, 145.37, 156.43; MS *m/z* 271 (M^+, 100). Anal. Calcd for $C_{13}H_6ClN_3S$: C, 57.46; H, 2.23; N, 15.46. Found: C, 57.39; H, 2.50; N, 15.48.

7-(3-Methoxyphenyl)thieno[2,3-*b*]pyrazine-6-carbonitrile (3g): a pale-yellow solid; mp 147–149 ˚C (hexane–CH_2Cl_2); IR (KBr) 2222, 1607 cm^{-1}; ^1H NMR (400 MHz) δ 3.90 (s, 3H), 7.08–7.10 (m, 1H), 7.43 (dd, *J* = 2.3, 1.7 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.51 (dd, 8.0, 7.4 Hz, 1H), 8.72 (d, *J* = 2.3 Hz, 1H), 8.85 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 55.42, 109.72, 115.91, 115.01, 115.94, 121.88, 130.05, 131.50, 143.52, 143.54, 144.94, 145.65, 156.47, 159.79; MS *m/z* 267 (M^+, 100). Anal. Calcd for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72. Found: C, 62.87; H, 3.48; N, 15.49.

1,1-Dimethylethyl 7-(3-Methoxyphenyl)thieno[2,3-*b*]pyrazine-6-carboxylate (3h): a yellow solid; mp 127–129 ˚C (hexane–CH_2Cl_2); IR (KBr) 1720, 1600 cm^{-1}; ^1H NMR (500 MHz) δ 1.41 (s, 9H), 3.84 (s, 3H), 6.99 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 8.0, 7.4 Hz, 1H), 8.61

(d, J = 2.3 Hz, 1H), 8.71 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 27.79, 55.24, 83.36, 114.00, 115.78, 122.38, 129.00, 134.16, 135.36, 139.86, 142.69, 142.90, 148.77, 155.92, 159.11, 161.34; MS *m/z* 342 (M^+, 28), 288 (100). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.86; H, 5.32; N, 8.07.

7-(Thiophen-2-yl)thieno[2,3-*b*]pyrazine-6-carbonitrile (6a): a yellow solid; mp 168–170 °C (hexane–CH_2Cl_2); IR (KBr) 2220 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.27 (dd, J = 5.1, 3.9 Hz, 1H), 7.64 (dd, J = 5.1, 1.1 Hz, 1H), 8.30 (dd, J = 3.9, 1.1 Hz, 1H), 8.73 (d, J = 2.3 Hz, 1H), 8.89 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 105.76, 114.59, 127.60, 129.63, 129.79, 131.56, 137.35, 142.99, 143.69, 144.94, 155.98; MS *m/z* 243 (M^+, 100). Anal. Calcd for $C_{11}H_5N_3S_2$: C, 54.30; H, 2.07; N, 17.27. Found: C, 54.06; H, 2.28; N, 17.17.

(2-Chlorophenyl)[7-(thiophen-2-yl)thieno[2,3-*b*]pyrazin-6-yl]methanone (6b): a yellow solid; mp 109–111 °C (hexane–CH_2Cl_2); IR (KBr) 1637 cm^{-1}; ^{1}H NMR (500 MHz$_3$) δ 6.82 (dd, J = 5.2, 3.4 Hz, 1H), 7.09–7.14 (m, 2H), 7.25–7.27 (m, 2H), 7.32–7.35 (m, 2H), 8.68 (d, J = 2.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 126.35, 126.77, 128.95, 130.07, 130.23, 131.04, 131.14, 132.11, 132.16, 132.98, 137.21, 141.94, 143.13, 143.32, 147.99, 156.58, 189.48; MS *m/z* 355 (M^+, 100). Anal. Calcd for $C_{17}H_9ClN_2OS_2$: C, 57.22; H, 2.54; N, 7.85. Found: C, 57.13; H, 2.62; N, 7.83.

7-(Thiophen-3-yl)thieno[2,3-*b*]pyrazine-6-carbonitrile (6c): a yellow solid; mp 134–136 °C (hexane–CH_2Cl_2); IR (KBr) 2222 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.54 (dd, J = 5.1, 2.9 Hz, 1H), 8.03 (d, J = 5.1 Hz, 1H), 8.50 (dd, J = 2.9, 1.1 Hz, 1H), 8.72 (d, J = 2.3 Hz, 1H), 8.87 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 107.28, 114.57, 126.30, 127.07, 128.02, 130.92, 138.90, 143.20, 143.52, 145.55, 156.26; MS *m/z* 242 (M^+, 100). Anal. Calcd for $C_{11}H_5N_3S_2$: C, 54.30; H, 2.07; N, 17.27. Found: C, 54.00; H, 2.16; N, 17.25.

1,1-Dimethylethyl 7-(Thiophen-3-yl)thieno[2,3-*b*]pyrazine-6-carboxylate (6d): a yellow solid; mp 101–103 °C (hexane–Et_2O); IR (KBr) 1690 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.52 (s, 9H), 7.37 (d, J = 4.6 Hz, 1H), 7.44 (dd, J = 4.6, 2.9 Hz, 1H), 7.69 (d, J = 2.9 Hz, 1H), 8.62 (d, J = 1.7 Hz, 1H), 8.73 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 27.93, 83.52, 124.35, 126.63, 129.51, 131.68, 134.37, 134.72, 142.72, 142.78, 148.54, 155.82, 161.30; MS *m/z* 318 (M^+, 29), 262 (100). Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80. Found: C, 56.50; H, 4.40; N, 8.63.

Phenyl[7-(thiophen-3-yl)thieno[2,3-*b*]pyrazin-6-yl]methanone (6e): a pale-yellow solid; mp 130–132 °C (hexane–CH_2Cl_2); IR (KBr) 1630 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.18–7.22 (m, 2H), 7.30 (t, J = 8.0, 7.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.57 (d, J = 1.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 8.67 (d, J = 2.3 Hz, 1H), 8.81 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 125.45, 127.04, 128.28, 128.73, 129.80, 132.14, 132.28, 133.51, 136.09, 140.08, 142.42, 142.76, 147.66, 156.15, 191.26; MS *m/z* 322 (M^+, 100). Anal. Calcd for $C_{17}H_{10}N_2OS_2$: C, 63.33; H, 3.13; N, 8.69. Found: C, 53.27; H, 3.30; N, 8.67.

7-(Thiophen-3-yl)thieno[2,3-*b*]pyrazine (7): a yellow solid; mp 89–91 °C (hexane–Et_2O); IR (KBr) 3094, 1347, 1324 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.44 (dd, J = 5.1, 3.4 Hz, 1H), 7.66 (dd, J = 5.1, 1.7 Hz, 1H), 7.96 (s, 1H), 8.36 (dd, J = 3.4, 1.7 Hz, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H); ^{13}C

NMR δ 123.06, 125.68, 126.03, 126.25, 129.66, 133.87, 140.32, 141.38, 147.23, 156.30; MS *m/z* 218 (M^+, 100). Anal. Calcd for $C_{10}H_6N_2S_2$: C, 55.02; H, 2.77; N, 12.83. Found: C, 54.93; H, 2.74; N, 12.62.

1,1-Dimethylethyl 7-(1-Methylpyrrol-2-yl)thieno[2,3-*b*]pyrazine-6-carboxylate (6f): an orange solid; mp 80–82 °C (hexane–Et_2O); IR (KBr) 1701 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (s, 9H), 3.48 (s, 3H), 6.30–6.32 (m, 2H), 6,83 (s, 1H), 8.61 (d, *J* = 2.3 Hz, 1H), 8.74 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 27.94, 34.60, 83.26, 108.20, 111.52, 123.67, 123.73, 131.91, 136.41, 142.78, 143.10, 149.20, 155.67, 161.03; MS *m/z* 315 (M^+, 77), 259 (100). Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 60.87; H, 5.42; N, 13.20.

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