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A CONVENIENT TWO-STEP SYNTHESIS OF 7-ARYL-6,7-DIHYDROTHIENO[2,3-*b*]PYRAZINES FROM ARYL(3-CHLOROPYRAZIN-2-YL)METHANONES

Kazuhiro Kobayashi,* Teruhiko Suzuki, and Naoki Matsumoto

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – An efficient method for the preparation of 7-aryl-6,7-dihydrothieno[2,3-*b*]pyrazines (**3**) under mild conditions has been developed. The reaction of aryl(3-chloropyrazin-2-yl)methanones (**1**), derived from commercially available 2-chloropyrazine, with methylenetriphenylphosphorane in THF at room temperature gave the corresponding 2-(1-arylethenyl)-3-chloropyrazines (**2**), which were treated with $NaSH{\cdot}nH_2O$ in DMF at room temperature to lead to the desired products (**3**) in acceptable yields. These products are dehydrogenated with air in refluxing toluene in the presence of a catalytic amount of Pd/C to yield the corresponding 7-arylthieno[2,3-*b*]pyrazines (**4**).

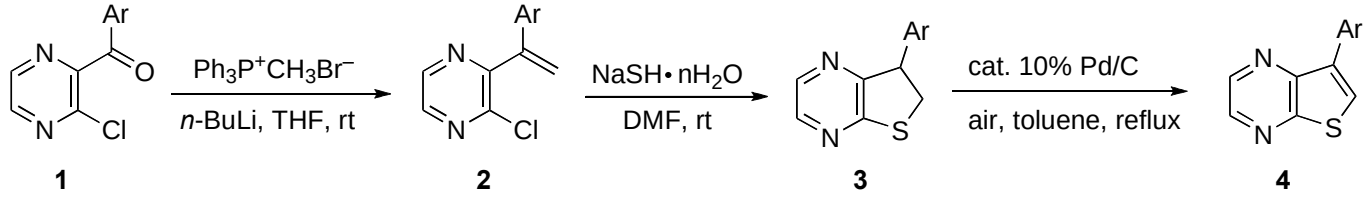
INTRODUCTION

The 6,7-dihydrothieno[2,3-*b*]pyrazine skeleton is found in some biologically active compounds.[1] However, few general methods for the preparation of 6,7-dihydrothieno[2,3-*b*]pyrazine derivatives have been reported so far, while Taylor and Sabb have synthesized 6-substituted 3-amino-6,7-dihydrothieno[2,3-*b*]pyrazine-2-carbonitriles by the treatment of β-substituted 2-amino-6-chloro-5-vinylpyrazine-3-carbonitriles with thiourea.[2] Therefore, we became interested in developing a new and general method for the synthesis of 6,7-dihydrothieno[2,3-*b*]pyrazine derivatives from easily accessible starting materials. In this paper, we wish to describe a facile general procedure for the synthesis of 7-aryl-6,7-dihydrothieno[2,3-*b*]pyrazines (**3**), which is based on cyclization of 2-(1-arylethenyl)-3-chloropyrazines (**2**), derived from Wittig reaction of 2-aroyl-3-chloropyrazines, with $NaSH{\cdot}nH_2O$ under

mild conditions. Conversion of **3** into 7-arylthieno[2,3-*b*]pyrazines (**4**) is also reported. These heterocycles are also of importance not only biologically[3] but also synthetic chemically.[4]

RESULTS AND DISCUSSION

The synthesis of 7-aryl-6,7-dihydrothieno[2,3-*b*]pyrazines (**3**) from aryl(3-chloropyrazin-2-yl)methanones (**1**) was conducted by the process depicted in Scheme 1. Compounds (**1**) could be easily prepared from commercially available 2-chloropyrazine according to the procedures reported previously.[5] Wittig reaction of **1** with methylenetriphenylphosphorane in THF at room temperature afforded 2-(1-arylethenyl)-3-chloropyrazines (**2**) in around 60% yields as summarized in Table 1.



1 **2** **3** **4**

Scheme 1

Table 1. Preparation of 7-arylthieno[2,3-*b*]pyrazines (**3**) and (**4**)

Entry	Ar	**2**	Yield/%[a]	**3**	Yield /%[a]	**4**	Yield/%[a]
1	Ph	**2a**	64	**3a**	59	**4a**	82
2	3-MeC_6H_4	**2b**	56	**3b**	61	**4b**	64
3	4-MeC_6H_4	**2c**	62	**3c**	62	**4c**	68
4	3-ClC_6H_4	**2d**	60	**3d**	57	**4d**	94
5	4-ClC_6H_4	**2e**	57	**3e**	60	**4e**	73
6	3-$MeOC_6H_4$	**2f**	61	**3f**	64	**4f**	90
7	4-$MeOC_6H_4$	**2g**	60	**3g**	56	**4g**	85
8	thiophen-3-yl	**2h**	55	**3h**	56	**4h**	77

[a] Yields of isolated products.

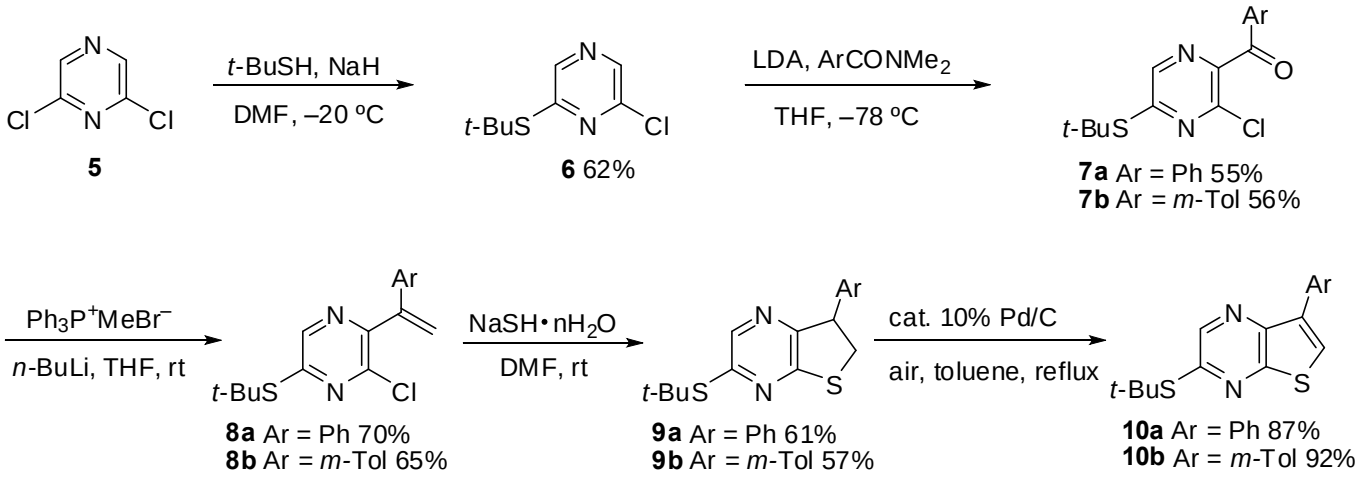
Initially, 2-chloro-3-(1-phenylethenyl)pyrazine (**2a**) was allowed to react with $Na_2S·9H_2O$ in DMF at room temperature. However, monitoring of the reaction by TLC on SiO_2 (AcOEt/hexane 1:5) indicated that it proceeded sluggishly and uncleanly and resulted in the formation of a rather complicated mixture of products. We decided to attempt the use of $NaSH·nH_2O$ in place of $Na_2S·9H_2O$ expecting that the reaction sequence would proceed more smoothly. Indeed, when compound (**2a**) was treated with

$NaSH{\cdot}nH_2O$ in DMF at room temperature, the expected sequence took place cleanly to afford, after usual workup and subsequent purification by column chromatography on SiO_2, the desired 6,7-dihydro-7-phenylthieno[2,3-*b*]pyrazine (**3a**) in 59% yield. Then, the other seven 2-(1-arylethenyl)-3-chloropyrazines (**2b-h**) were treated with $NaSH{\cdot}nH_2O$ under the same conditions as described above, and the corresponding products (**3b-h**) were obtained in yields comparable to that of **3a** as summarized in Table 1. The 7-(thiophen-3-yl) derivative (**3h**) could also be obtained (Entry 8).

The reaction sequence leading to **3** from **2** seems to proceed as follows. The substitution of 2-Cl of **2** with $^{-}$SH gives 2-(1-arylethenyl)-3-sulfanylpyrazines. The addition of the SH group to the alkene moiety gives rise to **3**. A report on the formation of 2-mercaptopyrazine by the reaction of 2-chloropyrazine with $NaSH{\cdot}nH_2O$ in DMF under mild conditions[6] may support this process.

Dehydrogenation of products (**3**) could be achieved by treatment with air in refluxing toluene in the presence of a catalytic amount of 10% Pd/C to provide the corresponding 7-arylthieno[2,3-*b*]pyrazines (**4**) in generally good yields as listed in Table 1 as well.

To widen the scope of the present reaction sequence, 2-chloro-6-[(1,1-dimethylethyl)sulfanyl]pyrazine (**6**) was prepared by treating commercially available 2,6-dichloropyrazine (**5**) with *t*-BuSNa. This compound proved to be usable to give 2-[(1,1-dimethylethyl)sulfanyl]-6-arylthieno[2,3-*b*]pyrazine derivatives (**9**) and (**10**) in a similar way. As illustrated in Scheme 2, 2-(1-arylethenyl)-3-chloro-5-[(1,1-dimethylethyl)sulfanyl]pyrazines **8** were formed through aroylation of **6** followed by Wittig reaction of the resulting aroylated products (**7**), and afforded **9** in reasonable yields upon treatment with $NaSH{\cdot}nH_2O$. Dehydrogenation of **9** could also be achieved out uneventfully under the same conditions as described for the conversion of **3** into **4** to give **10** in good yields.



In conclusion, we have demonstrated that 2-(1-arylethenyl)-3-chloropyrazines (**2**) and (**8**) undergo a substitution/cyclization sequence on treatment with $NaSH{\cdot}nH_2O$ under mild conditions to give 7-aryl-6,7-dihydrothieno[2,3-*b*]pyrazines (**3**) and (**9**). The present method, which allows a facile approach

to these heterocycles without using any precious reagents, may be of value in organic synthesis because of simplicity of the procedure, ready availability of the starting materials, and mild reaction conditions.

EXPERIMENTAL

All 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. ^{1}H 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 a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{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 or a JEOL LA400FT NMR spectrometer operating at 100 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. Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Aryl(3-chloropyrazin-2-yl)methanones **1** were prepared by the reaction of 2-chloro-3-lithiopyrazines with the appropriate *N,N*-dimethylbenzamides under the conditions reported previously.[5] The physical, spectral, and analytical data for new compounds follow.

(3-Chloropyrazin-2-yl)(3-methylphenyl)methanone (1b): yield: 60%; a yellow oil; R_f 0.41 (THF–hexane 1:4); IR (neat) 1677, 1602 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.41 (s, 3H), 7.39 (d, J = 7.4 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.67 (s, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H). Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.94; H, 4.04; N, 11.74.

(4-Chlorophenyl)(3-chloropyrazin-2-yl)methanone (1e): yield: 65%; a yellow solid; mp 61–63 °C (hexane); IR (KBr) 1672 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.48 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.56 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07. Found: C, 51.87; H, 2.56; N, 11.02.

(3-Chloropyrazin-2-yl)(4-methoxyphenyl)methanone (1g): yield: 70%; a yellow oil; R_f 0.29 (THF–hexane 1:3); IR (KBr) 1667 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.90 (s, 3H), 6.98 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 8.52 (d, J = 2.3 Hz, 1H), 8.59 (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, 57.74; H, 3.70; N, 11.22.

2-Chloro-6-[(1,1-dimethylethyl)sulfanyl]pyrazine (6). To a stirred suspension of NaH (60% in mineral oil; 0.16 g, 4.0 mmol) in DMF (6 mL) at –20 °C was added *t*-BuSH (0.36 g, 4.0 mmol) dropwise. After

15 min, a solution of 2,6-dichloropyrazine (**5**) (0.60 g, 4.0 mmol) in DMF (4 mL) was added and stirring was continued for an additional 10 min before H_2O (20 mL) was added. The mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 to give **6** (0.50 g, 62%); a colorless liquid; R_f 0.50 (Et_2O–hexane 1:20); IR (neat) 1496, 1156 cm^{-1}; ^1H NMR (400 MHz) δ 1.58 (s, 9H), 8.23 (s, 1H), 8.32 (s, 1H). Anal. Calcd for $C_8H_{11}ClN_2S$: C, 47.40; H, 5.47; N, 13.82. Found: C, 47.24; H, 5.72; N, 13.74.

Aryl{2-chloro-6-[(1,1-dimethylethyl)sulfanyl]pyrazin-3-yl}methanones (7): prepared form **6** by the same procedure for the preparation of **1**.

{2-Chloro-6-[(1,1-dimethylethyl)sulfanyl]pyrazin-3-yl}phenylmethanone (7a): a yellow oil; R_f 0.41 (THF–hexane 1:20); IR (KBr) 1675 cm^{-1}; ^1H NMR (400 MHz) δ 1.66 (s, 9H), 7.50 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 8.33 (s, 1H). Anal. Calcd for $C_{15}H_{15}ClN_2OS$: C, 58.72; H, 4.93; N, 9.13. Found: C, 58.66; H, 5.08; N, 9.04.

{2-Chloro-6-[(1,1-dimethylethyl)sulfanyl]pyrazin-3-yl}(3-methylphenyl)methanone (7b): a yellow solid; mp 60–62 °C (hexane–Et_2O); IR (KBr) 1675, 1603 cm^{-1}; ^1H NMR (400 MHz) δ 1.66 (s, 9H), 2.42 (s, 3H), 7.38 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.69 (s, 1H), 8.33 (s, 1H). Anal. Calcd for $C_{16}H_{17}ClN_2OS$: C, 59.90; H, 5.34; N, 8.73. Found: C, 60.02; H, 5.42; N, 8.62.

2-(1-Arylethenyl)-3-chloropyrazines (2) and (8): prepared by treating **2** and **7** with 2 equivalents of $Ph_3P{=}CH_2$ in THF under the conditions reported previously.[7]

2-Chloro-3-(1-phenylethenyl)pyrazine (2a): a yellow oil; R_f 0.41 (AcOEt–hexane 1:5); IR (neat) 1617, 1058 cm^{-1}; ^1H NMR (500 MHz) δ 5.61 (d, J = 4.6 Hz, 1H), 5.99 (d, J = 4.6 Hz, 1H), 7.25 (dd, J = 7.8 Hz, 2H), 7.32–7.34 (m, 3H), 8.38 (d, J = 2.3 Hz, 1H), 8.57 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_{12}H_9ClN_2$: C, 66.52; H, 4.19; N, 12.93. Found: C, 66.43; H, 4.26; N, 12.75.

2-Chloro-3-[1-(3-methylphenyl)ethenyl]pyrazine (2b): a yellow oil; R_f 0.31 (THF–hexane 1:10); IR (neat) 1602, 1058 cm^{-1}; ^1H NMR (400 MHz) δ 2.33 (s, 3H), 5.59 (s, 1H), 5.98 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.06 (m, 1H), 7.14 (d, J = 6.9 Hz, 1H), 7.23 (dd, J = 7.8, 6.9 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; N, 12.14: Found: C, 67.70; H, 4.91; N, 12.00.

2-Chloro-3-[1-(4-methylphenyl)ethenyl]pyrazine (2c): a yellow oil; R_f 0.22 (AcOEt–hexane 1:8); IR (neat) 1608, 1061 cm^{-1}; ^1H NMR (500 MHz) δ 2.35 (s, 3H), 5.55 (s, 1H), 5.96 (s, 1H), 7.14 (s, 4H), 8.37 (d, J = 2.3 Hz, 1H), 8.56 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.53; H, 5.05; N, 12.03.

2-Chloro-3-[1-(3-chlorophenyl)ethenyl]pyrazine (2d): a yellow oil; R_f 0.37 (AcOEt–hexane 1:5); IR (neat) 1623, 1058 cm^{-1}; ^1H NMR (400 MHz) δ 5.68 (s, 1H), 6.01 (s, 1H), 7.11 (d, J = 6.8 Hz, 1H),

7.26–7.32 (m, 3H), 8.40 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{12}H_8Cl_2N_2$: C, 57.40; H, 3.21; N, 11.16. Found: C, 57.34; H, 3.26; N, 11.17.

2-Chloro-3-[1-(4-chlorophenyl)ethenyl]pyrazine (2e): a yellow oil; R_f 0.43 (THF–hexane 1:7); IR (neat) 1621, 1061 cm^{-1}; ^1H NMR (400 MHz) δ 5.65 (s, 1H), 5.99 (s, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 8.39 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{12}H_8Cl_2N_2$: C, 57.40; H, 3.21; N, 11.16. Found: C, 57.09; H, 3.48; N, 11.05.

2-Chloro-3-[1-(3-methoxyphenyl)ethenyl]pyrazine (2f): a yellow oil; R_f 0.41 (AcOEt–hexane 1:4); IR (neat) 1597, 1242, 1057 cm^{-1}; ^1H NMR (500 MHz) δ 3.80 (s, 3H), 5.61 (s, 1H), 6.00 (s, 1H), 6.80–6.81 (m, 2H), 6.87 (dd, J = 8.0, 2.3 Hz, 1H), 7.24 (dd, J = 8.7, 8.0 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 8.56 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.29; H, 4.56; N, 11.31.

2-Chloro-3-[1-(4-methoxyphenyl)ethenyl]pyrazine (2g): a yellow oil; R_f 0.43 (AcOEt–hexane 1:3); IR (neat) 1606, 1252, 1056 cm^{-1}; ^1H NMR (500 MHz) δ 3.81 (s, 3H), 5.49 (s, 1H), 5.91 (s, 1H), 6.87 (d, J = 9.2 Hz, 2H), 7.17 (d, J = 9.2 Hz, 2H), 8.37 (d, J = 2.9 Hz, 1H), 8.57 (d, J = 2.9 Hz, 1H). Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.20; H, 4.71; N, 11.30.

2-Chloro-3-[1-(thiophen-3-yl)ethenyl]pyrazine (2h): an orange oil; R_f 0.38 (AcOEt–hexane 1:5); IR (neat) 1666, 1617, 1365, 1056 cm^{-1}; ^1H NMR (400 MHz) δ 5.52 (s, 1H), 5.98 (s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 4.9 Hz, 1H), 7.33 (dd, J = 4.9, 2.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{10}H_7ClN_2S$: C, 53.93; H, 3.17; N, 12.58: Found: C, 53.83; H, 3.27; N, 12.56.

2-Chloro-6-(1,1-dimethylethyl)sulfanyl-3-(1-phenylethenyl)pyrazine (8a): a yellow oil; R_f 0.17 (Et_2O–hexane 1:30); IR (neat) 1597, 1277, 1123 cm^{-1}; ^1H NMR (400 MHz) δ 1.61 (s, 9H), 5.61 (s, 1H), 5.95 (s, 1H), 7.27 (dd, J = 7.8, 1.7 Hz, 2H), 7.31–7.36 (m, 3H), 8.38 (s, 1H). Anal. Calcd for $C_{16}H_{17}ClN_2S$: C, 63.04; H, 5.62; N, 9.19. Found: C, 62.76; H, 5.61; N, 9.10.

2-Chloro-6-(1,1-dimethylethyl)sulfanyl-3-[1-(3-methylphenyl)ethenyl]pyrazine (8b): a yellow oil; R_f 0.34 (Et_2O–hexane 1:20); IR (neat) 1603, 1277, 1158 cm^{-1}; ^1H NMR (400 MHz) δ 1.61 (s, 9H), 2.34 (s, 3H), 5.59 (s, 1H), 5.94 (s, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 8.38 (s, 1H). Anal. Calcd for $C_{17}H_{19}ClN_2S$: C, 64.03; H, 6.01; N, 8.79. Found: C, 63.72; H, 6.12; N, 8.64.

Typical Procedure for the Preparation of 6,7-Dihydrothieno[2,3-*b*]pyrazines (3) and (9). 7-Phenyl-6,7-dihydrothieno[2,3-*b*]pyrazine (3a). A mixture of **2a** (0.20 g, 0.92 mmol) and $NaSH{\cdot}nH_2O$ (70% as NaSH; 89 mg, 1.1 mmol) in DMF (4 mL) was stirred at rt until disappearance of **2a** had been confirmed by TLC analyses (SiO_2, AcOEt–hexane 1:3) (ca. 7 h). Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). After evaporation of the solvent, the residue

was purified by column chromatography on SiO_2 to give **3a** (0.12 g, 59%); a pale-yellow oil; R_f 0.32 (AcOEt–hexane 1:5); IR (neat) 1602, 1356 cm^{-1}; ^1H NMR (500 MHz) δ 3.52 (dd, J = 10.9, 8.6 Hz, 1H), 3.82 (dd, J = 10.9, 9.2 Hz, 1H), 4.72 (dd, J = 9.2, 8.6 Hz, 1H), 7.26–7.33 (m, 3H), 7.38 (dd, J = 8.0, 7.4 Hz, 2H), 8.09 (d, J = 2.9 Hz, 1H), 8.14 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 36.52, 51.08, 127.77, 128.02, 129.04, 139.05, 140.80, 142.27, 157.41, 161.84; MS *m/z* 214 (100, M^+). Anal. Calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07. Found: C, 67.18; H, 4.73; N, 13.05.

7-(3-Methylphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3b): a colorless oil; R_f 0.34 (AcOEt–hexane 1:7); IR (neat) 1607, 1354 cm^{-1}; ^1H NMR (400 MHz) δ 2.35 (s, 3H), 3.51 (dd, J = 11.7, 8.8 Hz, 1H), 3.80 (dd, J = 11.7, 8.8 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 7.08–7.13 (m, 3H), 7.27 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 2.9 Hz, 1H), 8.13 (d, J = 2.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.45, 36.55, 51.12, 125.03, 128.58, 128.76, 128.94, 138.74, 139.05, 140.80, 142.21, 157.56, 161.84; MS *m/z* 228 (100, M^+). Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27. Found: C, 68.36; H, 5.58; N, 12.26.

7-(4-Methylphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3c): a colorless oil; R_f 0.35 (AcOEt–hexane 1:5); IR (neat) 1602, 1354 cm^{-1}; ^1H NMR (500 MHz) δ 2.34 (s, 3H), 3.50 (dd, J = 10.7, 8.8 Hz, 1H), 3.78 (dd, J = 10.7, 8.8 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 7.18 (s, 4H), 8.07 (d, J = 2.9 Hz, 1H), 8.12 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 21.08, 36.61, 50.83, 127.91, 129.72, 137.50, 137.75, 139.05, 142.17, 157.60, 161.78; MS *m/z* 228 (100, M^+). Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27. Found: C, 68.26; H, 5.48; N, 12.07.

7-(3-Chlorophenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3d): a pale-yellow oil; R_f 0.36 (THF–hexane 1:5); IR (neat) 1596, 1356 cm^{-1}; ^1H NMR (500 MHz) δ 3.48 (dd, J = 11.4, 8.6 Hz, 1H), 3.81 (dd, J = 11.4, 9.2 Hz, 1H), 4.69 (dd, J = 9.2, 8.6 Hz, 1H), 7.19 (dd, J = 6.3, 1.7 Hz, 1H), 7.28–7.32 (m, 3H), 8.10 (*d*, J = 2.9 Hz, 1H), 8.16 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 36.27, 50.62, 126.23, 128.01, 128.20, 130.28, 134.82, 139.12, 142.55, 142.65, 156.62, 161.76; MS *m/z* 248 (100, M^+). Anal. Calcd for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26. Found: C, 57.91; H, 3.67; N, 11.20.

7-(4-Chlorophenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3e): a yellow oil; R_f 0.23 (AcOEt–hexane 1:9); IR (neat) 1597, 1355 cm^{-1}; ^1H NMR (400 MHz) δ 3.47 (dd, J = 11.7, 8.8 Hz, 1H); 3.81 (dd, J = 11.7, 8.8 Hz, 1H), 4.70 (t, J = 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 2.9 Hz, 1H), 8.15 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 36.39, 50.46, 129.23, 129.38, 133.73, 139.11, 139.18, 142.51, 157.66, 161.76; MS *m/z* 248 (100, M^+). Anal. Calcd for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26. Found: C, 57.90; H, 3.66; N, 11.20.

7-(3-Methoxyphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3f): a pale-yellow oil; R_f 0.33 (AcOEt–hexane 1:3); IR (neat) 1599, 1355 cm^{-1}; ^1H NMR (500 MHz) δ 3.52 (dd, J = 11.5, 8.6 Hz, 1H), 3.78 (dd, J = 11.5, 8.6 Hz, 1H), 3.79 (s, 3H), 4.68 (t, J = 8.6 Hz, 1H), 6.83–6.89 (m, 3H), 7.29 (dd, J = 8.0, 7.4 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 8.14 (d, J = 2.3 Hz, 1H); ^{13}C NMR (125 MHz) δ 36.43, 51.10, 55.21, 112.95, 113.96,

120.30, 130.06, 139.06, 142.29, 142.32, 157.28, 159.99, 161.82; MS *m/z* 244 (100, M^+). Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.87; H, 5.09; N, 11.41.

7-(4-Methoxyphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3g): a pale-yellow oil; R_f 0.36 (AcOEt–hexane 1:2); IR (neat) 1611, 1353 cm^{-1}; ^1H NMR (400 MHz) δ 3.48 (dd, *J* = 10.8, 8.8 Hz, 1H), 3.78 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.80 (s, 3H), 4.67 (t, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 2.9 Hz, 1H), 8.13 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 36.72, 50.46, 55.26, 114.45, 129.10, 132.80, 139.04, 142.18, 157.80, 159.09, 161.73; MS *m/z* 244 (100, M^+). Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.89; H, 5.07; N, 11.40.

7-(Thiophen-3-yl)-6,7-dihydrothieno[2,3-*b*]pyrazine (3h): a yellow oil; R_f 0.27 (AcOEt–hexane 1:4); IR (neat) 1353 cm^{-1}; ^1H NMR (400 MHz) δ 3.50 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.80 (dd, *J* = 11.7, 8.7 Hz, 1H), 4.83 (t, *J* = 8.7 Hz, 1H), 7.07 (dd, *J* = 5.8, 2.0 Hz, 1H), 7.23 (br d, *J* = 2.9 Hz, 1H), 7.37 (dd, *J* = 5.8, 2.9 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 35.87, 46.21, 122.28, 126.65, 126.68, 138.96, 140.23, 142.37, 156.81, 161.43; MS *m/z* 220 (100, M^+). Anal. Calcd for $C_{10}H_8N_2S_2$: C, 54.52; H, 3.66; N, 12.72. Found: C, 54.49; H, 3.82; N, 12.48.

3-(1,1-Dimethylethyl)sulfanyl-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyrazine (9a): a yellow oil; R_f 0.33 (AcOEt–hexane 1:10); IR (neat) 1307, 1149 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (s, 9H), 3.51 (dd, *J* = 10.8, 8.8 Hz, 1H), 3.81 (dd, *J* = 10.8, 8.8 Hz, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 7.26–7.32 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 2H), 8.06 (s, 1H); ^{13}C NMR (100 MHz) δ 31.03, 36.85, 48.38, 50.58, 127.75, 127.99, 129.05, 140.94, 141.54, 153.46, 153.53, 160.95; MS *m/z* 302 (100, M^+). Anal. Calcd for $C_{16}H_{18}N_2S_2$: C, 63.54; H, 6.00; N, 9.26. Found: C, 63.51; H, 6.01; N, 9.26.

3-(1,1-Dimethylethyl)sulfanyl-7-(3-methylphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (9b): a yellow oil; R_f 0.31 (AcOEt–hexane 1:10); IR (neat) 1607, 1297, 1148 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (s, 9H), 2.35 (s, 3H), 3.50 (dd, *J* = 11.7, 8.8 Hz, 1H), 3.79 (dd, *J* = 11.7, 8.8 Hz, 1H), 4.62 (t, *J* = 8.8 Hz, 1H), 7.08–7.13 (m, 3H), 7.25 (t, *J* = 7.8 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz) δ 21.46, 31.03, 36.84, 48.35, 50.60, 125.04, 128.55, 128.73, 128.93, 138.72, 140.90, 141.57, 153.41, 153.64, 160.93; MS *m/z* 316 (100, M^+). Anal. Calcd for $C_{17}H_{20}N_2S_2$: C, 64.52; H, 6.37; N, 8.85. Found: C, 64.32; H, 6.50; N, 8.76.

Typical Procedure for the Preparation of Thieno[2,3-*b*]pyrazines (4) and (10). 7-Phenylthieno[2,3-*b*]pyrazine (4a): A solution of **3a** (33 mg, 0.15 mmol) in toluene (2 mL) containing 10% Pd/C (37 mg) was refluxed until disappearance of **3a** had been confirmed by TLC analyses (SiO_2, AcOEt–hexane 1:5) (*ca*. 7 h). After filtration of Pd/C, the filtrate was concentrated by evaporation and purified by column chromatography on SiO_2 to give **4a** (26 mg, 82%); a white solid; mp 68–70 °C (hexane–Et_2O); IR (KBr) 1600, 1334, 1179 cm^{-1}; ^1H NMR (500 MHz) δ 7.42 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.51 (dd, *J* = 8.0, 7.4 Hz, 2H), 9.94 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.97 (s, 1H), 8.56 (d, *J* = 2.9 Hz, 1H), 8.74 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 127.44, 128.14, 128.74, 133.73, 134.87, 140.31, 141.49,

144.84, 147.42, 156.62; MS *m/z* 212 (100, M^+). Anal. Calcd for $C_{12}H_8N_2S$: C, 67.90; H, 3.80; N, 13.20. Found: C, 67.83; H, 3.87; N, 13.16.

7-(3-Methylphenyl)thieno[2,3-*b*]pyrazine (4b): a pale-yellow oil; R_f 0.49 (AcOEt–hexane 1:5); IR (neat) 1606, 1328, 1162 cm^{-1}; ^1H NMR (400 MHz) δ 2.46 (s, 3H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.73 (br s, 2H), 7.94 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.73 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.57, 125.29, 127.35, 128.62, 128.82, 128.97, 133.67, 135.07, 138.33, 140.24, 141.47, 147.50, 156.58; MS *m/z* 226 (100, M^+). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C 68.86, H 4.50, N 12.36.

7-(4-Methylphenyl)thieno[2,3-*b*]pyrazine (4c): a white solid; mp 70–72 °C (hexane–Et_2O); IR (KBr) 1331, 1176 cm^{-1}; ^1H NMR (400 MHz) δ 2.42 (s, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.92 (s, 1H), 8.54 (d, *J* = 2.9 Hz, 1H), 8.73 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 21.29, 126.77, 128.01, 129.43, 130.90, 134.89, 138.05, 140.22, 141.44, 147.55, 156.62; MS *m/z* 226 (100, M^+). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.80; H, 4.62; N, 12.31.

7-(3-Chlorophenyl)thieno[2,3-*b*]pyrazine (4d): a white solid; mp 118–120 °C (hexane–Et_2O); IR (KBr) 1331, 1184 cm^{-1}; ^1HNMR (400 MHz) δ 7.39 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 2H), 8.57 (d, *J* = 2.0 Hz, 1H), 8.75 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 126.15, 128.12, 128.17, 128.20, 129.93, 133.27, 134.62, 135.34, 140.55, 141.59, 147.10, 156.51; MS *m/z* 246 (100, M^+). Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.42; H, 2.86; N, 11.35. Found: C, 58.18; H, 3.08; N, 11.47.

7-(4-Chlorophenyl)thieno[2,3-*b*]pyrazine (4e): a white solid; mp 139–141 °C (hexane–Et_2O); IR (KBr) 1331, 1180 cm^{-1}; ^1H NMR (400 MHz) δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.99 (s, 1H), 8.57 (d, *J* = 2.9 Hz, 1H), 8.73 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 127.61, 128.93, 129.32, 132.11, 133.53, 134.15, 140.48, 141.52, 147.17, 156.56; MS *m/z* 246 (100, M^+). Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.42; H, 2.86; N, 11.35. Found: C, 58.27; H, 2.97; N, 11.16.

7-(3-Methoxyphenyl)thieno[2,3-*b*]pyrazine (4f): a colorless oil; R_f 0.42 (AcOEt–hexane 1:5); IR (neat) 1600, 1366, 1160 cm^{-1}; ^1H NMR (500 MHz) δ 3.89 (s, 3H), 6.97 (dd, *J* = 7.8, 2.9 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 2.9, 2.0 Hz, 1H), 7.97 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.73 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ: 55.31, 113.54, 114.00, 120.51, 127.64, 129.71, 134.61, 134.96, 140.31, 141.50, 147.40, 156.56, 159.78; MS *m/z* 242 (100, M^+). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.30; H, 4.27; N, 11.44.

7-(4-Methoxyphenyl)thieno[2,3-*b*]pyrazine (4g): a white solid; mp 98–99 °C (hexane–Et_2O); IR (KBr) 1609, 1333, 1176 cm^{-1}; ^1H NMR (400 MHz) δ 3.87 (s, 3H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.87 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 8.54 (d, *J* = 2.0 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 55.36, 114.20, 126.04, 126.40, 129.31, 134.48, 140.19, 141.38, 147.51, 156.62, 159.61; MS *m/z* 242 (100, M^+). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.36; H, 4.08; N, 11.46.

7-(Thiophen-3-yl)thieno[2,3-*b*]pyrazine (4h): a white solid; mp 89–91 °C (hexane–Et_2O); IR (KBr) 1347, 1159 cm^{-1}; ^1H NMR (400 MHz) δ 7.44 (dd, J = 4.9, 2.0 Hz, 1H), 7.65 (d, J = 4.9 Hz, 1H), 8.00 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 123.11, 125.71, 126.04, 126.29, 129.76, 133.93, 140.36, 141.42, 147.30, 156.38; MS *m/z* 218 (100, M^+). Anal. Calcd for $C_{10}H_6N_2S_2$: C, 55.02; H, 2.77; N, 12.83. Found: C, 54.92; H, 2.82; N, 12.82.

3-(1,1-Dimethylethyl)sulfanyl-7-phenylthieno[2,3-*b*]pyrazine (10a): a yellow oil. R_f 0.46 (AcOEt–hexane 1:15); IR (neat) 1601, 1287, 1134 cm^{-1}; ^1H NMR (500 MHz) δ 1.59 (s, 9H), 7.40 (tt, J = 7.4, 1.1 Hz, 1H), 7.49 (dd, J = 8.0, 7.4 Hz, 2H), 7.81 (s, 1H), 7.91 (dd, J = 8.0, 1.1 Hz, 2H), 8.63 (s, 1H); ^{13}C NMR (100 MHz) δ 30.91, 48.94, 125.50, 128.05 (2 C), 128.73, 133.80, 134.74, 143.92, 144.07, 151.81, 155.95; MS *m/z* 300 (100, M^+). Anal. Calcd for $C_{16}H_{16}N_2S_2$: C, 63.96; H, 5.37; N, 9.32: Found: C, 63.80; H, 5.56; N, 9.06.

3-(1,1-Dimethylethyl)sulfanyl-7-(3-methylphenyl)thieno[2,3-*b*]pyrazine (10b): a yellow oil; R_f 0.42 (AcOEt–hexane 1:15); IR (neat) 1607, 1287, 1133 cm^{-1}; ^1H NMR (500 MHz) δ 1.59 (s, 9H), 2.45 (s, 3H), 7.22 (d, J = 7.4 Hz, 1H), 7.38 (dd, J = 8.0, 7.4 Hz, 1H), 7.69–7.01 (m, 2H), 7.79 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (100 MHz) δ 21.58, 30.93, 48.90, 125.20, 125.46, 128.61, 128.73, 128.90, 133.72, 134.92, 138.30, 144.03, 144.11, 151.64, 155.92; MS *m/z* 314 (100, M^+). Anal. Calcd for $C_{17}H_{18}N_2S_2$: C, 64.93; H, 5.77; N, 8.91. Found: C, 64.72; H, 5.74; N, 8.84.

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