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SYNTHESIS OF 6-ARYL-6,7-DIHYDRO-8*H*-THIOPYRANO[2,3-*b*]-PYRAZIN-8-ONES BY THE REACTION OF 3-ARYL-1-(3-CHLOROPYRAZIN-2-YL)PROP-2-EN-1-ONES WITH SODIUM HYDOGENSULFIDE

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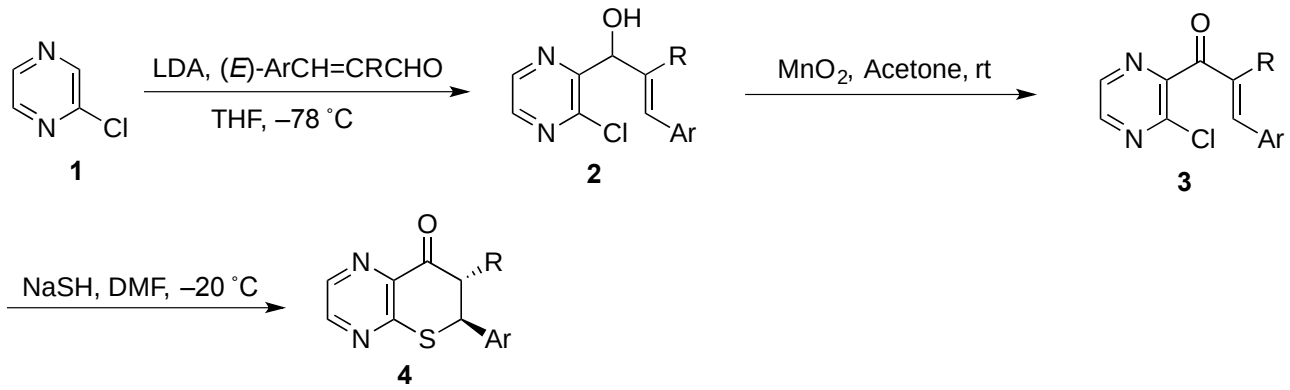
Abstract – A convenient process for the preparation of 6-aryl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones has been developed, which employs the reaction of 3-aryl-1-(3-chloropyrazin-2-yl)prop-2-en-1-ones, derived from 2-chloropyrazine and 3-arylprop-2-enals, with NaSH in DMF at –20 °C.

We previously reported a synthesis of three types of 2,3-dihydro-4*H*-thiopyranopyridin-4-ones by the reaction of respective 1-(chloropyridinyl)alk-2-en-1-ones, derived from chloropyridines and α,β-unsaturated aldehydes, with sodium hydrogensulfide.[1] As an extension of this work, we became interested in exploring the possibility of the preparation of 6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one derivatives by a similar sequence starting from 2-chloropyrazine (**1**). These fused heterocycles are of potentially biological interest, because related systems have been reported to exhibit variety of biological activities.[2] Herein, we wish to demonstrate the first preparation of these thiopyranopyrazinone derivatives. We found that 6-aryl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones (**4**) could be obtained by treating 3-aryl-1-(3-chloropyrazin-2-yl)prop-2-en-1-ones (**3**), easily prepared from **1** and 3-arylprop-2-enals by an easy two-step sequence, with sodium hydrogensulfide in DMF at –20 °C.

Our three-step synthesis of 6-aryl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones (**4**) from 2-chloropyrazine (**1**) and 3-arylprop-2-enals was accomplished according to the sequence illustrated in Scheme 1. Thus, 2-chloro-3-lithiopyrazine was generated by the treatment of **1** with lithium diisopropylamide (LDA) in THF at –78 °C under the conditions reported previously,[3] and was allowed to react with 3-arylprop-2-enals at the same temperature to produce 3-aryl-1-(3-chloropyrazin-2-yl)prop-2-

en-1-ols (**2**) in good yields as listed in Table 1. Oxidation of **2** with excess activated manganese(IV) oxide in acetone at room temperature afforded good yields of 3-aryl-1-(3-chloropyrazin-2-yl)prop-2-en-1-ones (**3**) as shown in Table 1 as well.



Scheme 1

Table 1. Preparation of 6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones (**4**)

Entry	Ar	R	**2**	Yield/%[a]	**3**	Yield/%[a]	**4**	Yield/%[a]
1	Ph	H	**2a**	95	**3a**	98	**4a**	68
2	4-MeC_6H_4	H	**2b**	80	**3b**	84	**4b**	64
3	4-ClC_6H_4	H	**2c**	83	**3c**	70	**4c**	53
4	4-$MeOC_6H_4$	H	**2d**	84	**3d**	80	**4d**	65
5	3,4-$(MeO)_2C_6H_3$	H	**2e**	84	**3e**	82	**4e**	70
6	3,4-$(OCH_2O)C_6H_3$	H	**2f**	72	**3f**	86	**4f**	79
7	Ph	Me	**2g**	91	**3g**	78	**4g**	69
8	thiophen-2-yl	H	**2h**	70	**3h**	69	**4h**	65

[a] Yields of isolated products.

Initially, 1-(3-chloropyrazin-2-yl)-3-phenylprop-2-en-1-ol (**3a**) was treated with an equivalent of sodium hydrogensulfide in DMF at 0 °C to obtain 6-phenyl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones (**4a**). The starting material was consumed within 30 min, but aqueous workup followed by purification by column chromatography on silica gel gave a rather complicated mixture of products, from which the desired product was isolated only in 36% yield. Next, the reaction was carried out in varied solvents, such as ethanol, acetonitrile, or DMSO–THF (3:1, v/v) in order to improve the yield. Unfortunately, however, the use of these solvents gave disappointing results; on the basis of ^{1}H NMR spectral analyses only about 5% yield of **4a** was included in more complicated reaction mixtures. When the reaction was carried out with two equivalents of sodium hydrogensulfide in DMF, the reaction proceeded more rapidly but the yield was scarcely improved. Therefore, we conducted the reaction at –20 °C with an equivalent of sodium hydrogensulfide in DMF. The ring formation reaction proceeded slowly but much more cleanly and the desired product (**4a**) was obtained in 68% yield (Table 1, Entry 1). The other seven precursors

3b–h were then subjected to the reaction with sodium hydrogensulfide under the optimized conditions described above to afford the corresponding products (**4b–h**) in the yields listed in Table 1 as well. While the results in Table 1 show that the yields of **4** are generally fair, that of the product from the substrate derived from 3-(4-chlorophenyl)prop-2-enal (**4c**) was somewhat lower than those of the others (Entry 3). *trans*-7-Methyl-6-phenyl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (**4g**) was produced almost exclusively; only a trace amount of its diastereomer (*cis* isomer) was detected by ^{1}H NMR spectrum of the crude product (Entry 7). Although no unambiguous evidences for the stereochemistry of **4g** could be obtained, we tentatively determined it to be *trans,* considering the lower encumbrance of the *trans*-form. The substrate derived from 3-(thiophen-2-yl)prop-2-enal (**3h**) yielded the 6-(thiophen-2-yl) derivative (**4h**) (Entry 8).

Subsequently, to investigate the scope of the present process, the substrate derived from **1** and but-2-enal (crotonaldehyde), 1-(3-chloropyrazin-2-yl)but-2-en-1-ones, was subjected to the reaction with sodium hydrogensulfide under the same condition described above. Unfortunately, however, it resulted in the formation of a considerably complex mixture of products, from which no more than a trace amount of the desired product, 6-methyl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one could not be obtained.

In conclusion, we have demonstrate that the reaction of 3-(het)aryl-1-(3-chloropyrazin-2-yl)prop-2-en-1-ones, derived from 2-chloropyrazine and 3-(het)arylprop-2-enals by an easy two step sequence, with sodium hydrogensulfide gives 6-(het)aryl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones, which had not been prepared previously. The present method may be of use in organic synthesis because of the ready availability of starting materials and the simplicity of manipulations, and may provide interesting pharmacophores.

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 JEOL LA400 FT 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. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive 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. (*E*)-3-(1,3-Benzodioxol-5-yl)propen-2-enal,[4] (*E*)-3-(3,4-dimethoxyphenyl)prop-2-enal,[5] and (*E*)-3-(thiophen-2-yl)prop-2-enal,[6] were prepared according to the appropriate reported

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

Typical Procedure for the Preparation of (*E*)-3-Aryl-1-(2-chloropyrazin-3-yl)prop-2-en-1-ols (2). (*E*)-1-(2-Chloropyrazin-3-yl)-3-phenylprop-2-en-1-ol (2a). To a stirred solution of LDA (2.4 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**) (0.23 g, 2.0 mmol) dropwise. After 1 h, (*E*)-3-phenylprop-2-enal (0.25 g, 1.0 mmol) was added and stirring was continued for 5 min at the same temperature before saturated aqueous NH_4Cl (15 mL) was added. The mixture was warmed to rt and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford **2a** (0.47 g, 95%); a yellow oil; R_f 0.18 (AcOEt/hexane 1:3); IR (neat) 3413, 1641 cm^{-1}; ^1H NMR (500 MHz) δ 4.19 (d, *J* = 8.0 Hz, 1H), 5.69 (dd, *J* = 8.0, 6.9 Hz, 1H), 6.27 (dd, *J* = 15.5, 6.9 Hz, 1H), 6.84 (d, *J* = 15.5 Hz, 1H), 7.23–7.39 (m, 5H), 8.38 (s, 1H), 8.52 (s, 1H). Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.10; H, 4.54; N, 11.18.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(4-methylphenyl)prop-2-en-1-ol (2b): a yellow oil; R_f 0.16 (AcOEt/hexane 1:3); IR (neat) 3417, 1653 cm^{-1}; ^1H NMR (500 MHz) δ 2.32 (s, 3H), 4.14 (d, *J* = 8.0 Hz, 1H), 5.67 (dd, *J* = 8.0, 6.9 Hz, 1H), 6.21 (dd, *J* = 16.0, 6.9 Hz, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.51 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.03; N, 10.74. Found: C, 64.32; H, 5.03; N, 10.81.

(*E*)-3-(4-Chlorophenyl)-1-(2-chloropyrazin-3-yl)prop-2-en-1-ol (2c): a yellow oil; R_f 0.26 (AcOEt/hexane 1:2); IR (neat) 3397 cm^{-1}; ^1H NMR (500 MHz) δ 4.20 (d, *J* = 8.0 Hz, 1H), 5.67 (dd, *J* = 8.0, 6.3 Hz, 1H), 6.26 (dd, *J* = 15.5, 6.3 Hz, 1H), 6.80 (d, *J* = 15.5 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 8.39 (d, *J* = 2.9 Hz, 1H), 8.52 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.47; H, 3.78; N, 9.90.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-ol (2d): a yellow oil; R_f 0.26 (AcOEt/hexane 1:2); IR (neat) 3425, 1649, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 3.80 (s, 3H), 4.14 (d, *J* = 8.0 Hz, 1H), 5.66 (dd, *J* = 8.0, 6.9 Hz, 1H), 6.12 (dd, *J* = 16.0, 6.9 Hz, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 8.37 (d, *J* = 2.9 Hz, 1H), 8.51 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12. Found: C, 60.74; H, 4.94; N, 10.04.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (2e): a beige oil; R_f 0.16 (AcOEt/hexane 1:2); IR (neat) 3456, 1651, 1601 cm^{-1}; ^1H NMR (400 MHz) δ 3.87 (s, 3H), 3.88 (s, 3H), 4.15 (d, *J* = 6.8 Hz, 1H), 5.67 (t, *J* = 6.8 Hz, 1H), 6.11 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.76 (d, *J* = 15.6 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 8.38 (d, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.52; H, 5.04; N, 8.84.

(*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2-chloropyrazin-3-yl)prop-2-en-1-ol (2f): an orange solid; mp 109–110 °C (hexane/CH_2Cl_2); IR (KBr) 3414, 1651, 1605 cm^{-1}; ^1H NMR (500 MHz) δ 4.17 (d, *J* = 8.0 Hz, 1H), 5.65 (d, *J* = 8.0, 6.9 Hz, 1H), 5.94 (s, 2H), 6.08 (dd, *J* = 16.0, 6.9 Hz, 1H), 6.736 (d, *J* = 8.0 Hz, 1H), 6.738 (d, *J* = 16.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.52 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; N, 9.64. Found: C, 57.60; H, 3.91; N, 9.44.

(*E*)-1-(2-Chloropyrazin-3-yl)-2-methyl-3-phenylprop-2-en-1-ol (2g): a yellow oil; R_f 0.18 (AcOEt/hexane 1:1); IR (neat) 3440 cm^{-1}; ^1H NMR (500 MHz) δ 1.71 (d, *J* = 1.1 Hz, 3H), 4.47 (d, *J* = 8.0 Hz, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 8.39 (d, *J* = 2.3 Hz, 1H), 8.55 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.03; N, 10.74. Found: C, 64.30; H, 5.05; N, 10.66.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-ol (2h): a beige oil; R_f 0.35 (AcOEt/hexane 1:2); IR (neat) 3401, 1643, 1609 cm^{-1}; ^1H NMR (500 MHz) δ 4.19 (d, *J* = 8.0 Hz, 1H), 5.64 (dd, *J* = 8.0, 6.3 Hz, 1H), 6.10 (dd, *J* = 15.5, 6.3 Hz, 1H), 6.94–6.97 (m, 2H), 7.00 (d, *J* = 3.4 Hz, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 8.38 (d, *J* = 2.9 Hz, 1H), 8.52 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.08. Found: C, 51.99; H, 3.83; N, 11.08.

Typical Procedure for the Preparation of (*E*)-3-Aryl-1-(2-chloropyrazin-3-yl)prop-2-en-1-ones (3).

(*E*)-1-(2-Chloropyrazin-3-yl)-3-phenylprop-2-en-1-one (3a). A mixture of **2a** (0.25 g, 1.0 mmol) and activated MnO_2 (0.88 g, 10 mmol) in acetone (5 mL) was stirred at rt for 1 h. Then, the mixture was filtered through a Celite pad and filtrate was concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt/hexane 1:3) to afford **3a** (0.24 g, 98%); a yellow solid; mp 69–70 °C (hexane); IR (KBr) 1681, 1655, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 7.42–7.44 (m, 3H), 7.54 (d, *J* =16.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.3 Hz, 2H), 7.73 (d, *J* = 16.0 Hz, 1H), 8.54 (d, *J* = 2.3 Hz, 1H), 8.62 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.66; H, 3.99; N, 11.41.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(4-methylphenyl)prop-2-en-1-one (3b): a yellow solid; mp 88–89 °C (hexane); IR (KBr) 1675, 1651, 1597 cm^{-1}; ^1H NMR (400 MHz) δ 2.40 (s, 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 15.6 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.61 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 64.90; H, 4.41; N, 10.70.

(*E*)-3-(4-Chlorophenyl)-1-(2-chloropyrazin-3-yl)prop-2-en-1-one (3c): a yellow solid; mp 118–120 °C (hexane); IR (KBr) 1680, 1604 cm^{-1}; ^1H NMR (500 MHz) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 16.0 Hz, 1H), 8.55 (d, *J* = 2.3 Hz, 1H), 8.61 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{13}H_8Cl_2N_2O$: C, 55.94; H, 2.89; N, 10.04. Found: C, 55.85; H, 3.07; N, 9.85.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (3d): a yellow solid; mp 113–114 °C (hexane); IR (KBr) 1674, 1651, 1593 cm^{-1}; ^1H NMR (500 MHz) δ 3.86 (s, 3H), 6.94 (d, *J* = 9.2 Hz, 2H), 7.37 (d, *J* = 16.0 Hz, 1H), 7.59 (d, *J* = 9.2 Hz, 2H), 7.66 (d, *J* = 16.0 Hz, 1H), 8.52 (d, *J* = 2.3 Hz, 1H), 8.60 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20. Found: C, 61.35; H, 3.87; N, 9.97.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (3e): a yellow solid; mp 114–115 °C (hexane/CH_2Cl_2); IR (KBr) 1674, 1652, 1592 cm^{-1}; ^1H NMR (500 MHz) δ 3.94 (s, 6H), 6.90 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.36 (d, *J* = 16.0 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.62 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.19. Found: C, 59.02; H, 4.49; N, 9.17.

(*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2-chloropyrazin-3-yl)prop-2-en-1-one (3f): a yellow solid; mp 138–140 °C (hexane/CH_2Cl_2); IR (KBr) 1668, 1607, 1589 cm^{-1}; ^1H NMR (400 MHz) δ 6.04 (s, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 15.6 Hz, 1H), 8.53 (d, *J* = 2.9 Hz, 1H), 8.60 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{14}H_9ClN_2O_3$: C, 58.25; H, 3.14; N, 9.70. Found: C, 58.03; H, 3.18; N, 9.67.

(*E*)-1-(2-Chloropyrazin-3-yl)-2-methyl-3-phenylprop-2-en-1-one (3g): a pale-yellow solid; mp 103–104 °C (hexane); IR (KBr) 1660, 1618 cm^{-1}; ^1H NMR (400 MHz) δ 2.30 (s, 3H), 7.05 (s, 1H), 7.38–7.42 (m, 5H), 8.50 (d, *J* = 2.0 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 64.91; H, 4.56; N, 10.70.

(*E*)-1-(2-Chloropyrazin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one (3h): a yellow solid; mp 83–85 °C (hexane/CH_2Cl_2); IR (KBr) 1674, 1589 cm^{-1}; ^1H NMR (400 MHz) δ 7.11 (dd, *J* = 4.9, 3.9 Hz, 1H), 7.33 (d, *J* = 15.6 Hz, 1H), 7.39 (d, *J* = 3.9 Hz, 1H), 7.49 (d, *J* = 4.9 Hz, 1H), 7.86 (d, *J* = 15.6 Hz, 1H), 8.53 (d, *J* = 2.9 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H). Anal. Calcd for $C_{11}H_7ClN_2OS$: C, 52.70; H, 2.81; N, 11.17. Found: C, 52.61; H, 2.91; N, 11.11.

Typical Procedure for the Preparation of 5-Aryl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-ones (4). 6-Phenyl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4a). To a stirred solution of $NaSH{\cdot}nH_2O$ (70% as NaSH; 77 mg, 0.95 mmol) in DMF (1.5 mL) at –20 °C was added a solution of **3a** (0.23 g, 0.95 mmol) in DMF (1.5 mL), and the mixture was stirred until complete consumption of the starting materials had been confirmed by TLC analyses (silica gel, AcOEt/hexane 1:1) (about 2 h) at the same temperature. The mixture was worked up as described for the preparation of **2a** to give a residue, of which purification by column chromatography on silica gel (AcOEt/hexane 1:1) afforded **4a** (0.15 g, 68%); a yellow solid; mp 129–131 °C (hexane/CH_2Cl_2); IR (KBr) 1703 cm^{-1}; ^1H NMR (400 MHz) δ 3.40 (dd, *J* = 15.6, 2.9 Hz, 1H), 3.53 (dd, *J* = 15.6, 12.7 Hz, 1H), 4.87 (dd, *J* = 12.7, 2.9 Hz, 1H), 7.36–7.47 (m, 5H), 8.53 (d, *J* = 2.9 Hz, 1H), 8.54 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR δ 43.77, 46.88, 127.40, 128.95, 129.25,

138.88, 141.36, 141.43, 147.14, 161.83, 192.27. HR MS. Calcd for $C_{13}H_{11}N_2OS$ (M+H): 243.0592. Found: *m/z* 243.0581. Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.16; H, 4.19; N, 11.28.

6-(4-Methylphenyl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4b): a yellow solid; mp 184–185 °C (hexane/CH_2Cl_2); IR (KBr) 1695 cm^{-1}; ^1H NMR (500 MHz) δ 2.37 (s, 3H), 3.38 (dd, *J* = 16.0, 2.3 Hz, 1H), 3.51 (dd, *J* = 16.0, 13.1 Hz, 1H), 4.83 (dd, *J* = 13.1, 2.3 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 2H), 8.52 (s, 1H), 8.53 (s, 1H); ^{13}C NMR δ 21.12, 43.54, 46.96, 127.26, 129.88, 133.86, 138.90, 141.36, 141.37, 147.10, 161.95, 192.40. HR MS. Calcd for $C_{14}H_{13}N_2OS$ (M+H): 257.0748. Found: *m/z* 257.0739. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.51; H, 4.72; N, 10.85.

6-(4-Chlorophenyl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4c): a yellow solid; mp 141–143 °C (hexane/CH_2Cl_2); IR (KBr) 1702 cm^{-1}; ^1H NMR (500 MHz) δ 3.39 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.49 (dd, *J* = 16.6, 12.6 Hz, 1H), 4.83 (dd, *J* = 12.6, 2.9 Hz, 1H), 7.40 (s, 4H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.55 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 43.07, 46.72, 128.77, 129.46, 134.88, 135.40, 141.33, 141.58, 147.20, 161.43, 191.84. HR MS. Calcd for $C_{13}H_{10}ClN_2OS$ (M+H): 276.0202. Found: *m/z* 276.0187. Anal. Calcd for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.28; H, 3.39; N, 10.07.

6-(4-Methoxyphenyl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4d): a yellow solid; mp 169–171 °C (hexane/CH_2Cl_2); IR (KBr) 1700 cm^{-1}; ^1H NMR (500 MHz) δ 3.37 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.50 (dd, *J* = 16.5, 13.2 Hz, 1H), 3.83 (s, 3H), 4.83 (dd, *J* = 13.1, 2.9 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 8.52 (d, *J* = 1.7 Hz, 1H), 8.53 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR δ 43.28, 47.10, 55.35, 114.55, 128.61, 128.74, 141.36 (2C), 147.12, 159.91, 161.96, 192.46. HR MS. Calcd for $C_{14}H_{13}N_2O_2S$ (M+H): 272.0687. Found: *m/z* 272.0672. Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.70; H, 4.60; N, 10.23.

6-(3,4-Dimethoxyphenyl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4e): a pale-yellow solid; mp 179–181 °C (hexane/CH_2Cl_2); IR (KBr) 1703 cm^{-1}; ^1H NMR (500 MHz) δ 3.40 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.52 (dd, *J* = 16.6, 13.2 Hz, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 4.83 (dd, *J* = 13.2, 2.9 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.6, 2.3 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.54 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 43.61, 47.09, 55.93, 55.95, 110.35, 111.34, 119.68, 129.13, 141.33, 141.38, 147.14, 149.32, 149.42, 161.81, 192.39. HR MS. Calcd for $C_{15}H_{15}N_2O_3S$ (M+H): 302.0803. Found: *m/z* 302.0797. Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.41; H, 4.86; N, 9.22.

6-(1,3-Benzodioxol-5-yl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4f): a yellow viscous oil; R_f 0.27 (AcOEt/hexane 1:1); IR (neat) 1704, 1610 cm^{-1}; ^1H NMR (500 MHz) δ 3.37 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.47 (dd, *J* = 16.6, 13.2 Hz, 1H), 4.79 (dd, *J* = 13.2, 2.9 Hz, 1H), 6.01 (s, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.54 (d, *J* = 2.3 Hz,

1H); ^{13}C NMR δ 43.69, 47.15, 101.52, 107.64, 108.71, 121.10, 130.43, 141.29, 141.42, 147.15, 148.08, 148.25, 161.81, 192.29. HR MS. Calcd for $C_{14}H_{11}N_2O_3S$ (M+H): 286.0490. Found: *m/z* 286.0485. Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78. Found: C, 58.64; H, 3.59; N, 9.70.

***trans*-7-Methyl-6-phenyl-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4g):** a yellow amorphous; R_f 0.15 (AcOEt/hexane 1:2); IR (neat) 1699 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.16 (d, *J* = 6.8 Hz, 3H), 3.41–3.49 (m, 1H), 4.49 (d, *J* = 12.7 Hz, 1H), 7.38–7.45 (m, 5H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 12.98, 48.96, 49.93, 128.24, 128.88, 129.20, 136.43, 141.23, 141.33, 147.03, 160.85, 194.65. HR MS. Calcd for $C_{14}H_{13}N_2OS$ (M+H): 256.0748. Found: *m/z* 256.0743. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.42; H, 4.72; N, 10.70.

6-(Thiophen-2-yl)-6,7-dihydro-8*H*-thiopyrano[2,3-*b*]pyrazin-8-one (4h): a orange viscous oil; R_f 0.24 (AcOEt/hexane 1:1); IR (neat) 1700 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.52–3.60 (m, 2H), 5.11 (dd, *J* = 9.7, 4.6 Hz, 1H), 6.98 (dd, *J* = 4.6, 4.0 Hz, 1H), 7.11 (d, *J* = 4.0 Hz, 1H), 7.30 (d, *J* = 4.6 Hz, 1H), 8.53 (s, 2H); ^{13}C NMR δ 39.07, 47.54, 126.14, 126.53, 127.19, 140.54, 141.37, 141.62, 147.24, 160.93, 191.53. HR MS. Calcd for $C_{11}H_9N_2OS_2$ (M+H): 248.0156. Found: *m/z* 248.0147. Anal. Calcd for $C_{11}H_8N_2OS_2$: C, 53.20; H, 3.25; N, 11.28. Found: C, 53.16; H, 3.36; N, 11.00.

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