One-Pot Synthesis of 1,4-Oxathiino[2,3-*b*]quinoxalines or -pyrazines from 2,3-Dichloroquinoxaline or -pyrazine and 1-Aryl-2-bromoalkan-1-ones

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An efficient one-pot synthesis of novel heterocyclic derivatives, 2-aryl-1,4-oxathiino[2,3-*b*]quinoxalines or -pyrazines **5**, *via* the reaction of 2,3-dichloroquinoxaline or -pyrazine with $Na_2S \cdot 9\,H_2O$, and subsequent treatment of the resulting 2-chloro-3-sodiosulfanylquinoxaline or -pyrazine **2** with 1-aryl-2-bromo-1-alkanones and then NaH under mild conditions is described.

Introduction. – Herein, we wish to present the first synthesis of 1,4-oxathiino[2,3-*b*]quinoxalines or -pyrazines **5**. We were interested in the preparation of these heterocycles, because their preparation has not been reported so far, though related systems, such as pyrido[2′,3′:5,6][1,4]oxathiino[2,3-*b*]quinoxaline [1a], pyrido-[2′,3′:5,6][1,4]oxathiino[2,3-*b*]pyrazine [1b], and [1,4]benzoxathiino[2,3-*b*]quinoxaline [1c], have been synthesized and a theoretical study on these systems has been reported [1d]. As part of our study on the synthesis of fused heterocycles based on the reaction of halogenated heterocycles with $Na_2S \cdot 9\,H_2O$, followed by nucleophilic substitution and cyclization [2], we found that 1,4-oxathiino[2,3-*b*]quinoxalines or -pyrazines **5** could be prepared by a one-pot reaction starting from commercially available 2,3-dichloroquinoxaline or -pyrazine **1** *via* the reaction with $Na_2S \cdot 9\,H_2O$, followed by treatment of the resulting 2-chloro-3-sodiosulfanylquinoxaline or -pyrazine intermediate **2** with 1-aryl-2-bromoalkan-1-ones, and then with NaH in DMF or DMSO at room temperature.

Results and Discussion. – Our one-pot synthesis of 2-aryl-1,4-oxathiino[2,3-*b*]quinoxalines or -pyrazines **5** from 2,3-dichloroquinoxaline (**1a**; R^1_2 = benzo) or -pyrazine (**1b**; R^1 = H), respectively, was conducted according to the procedure illustrated in the *Scheme*. First, we employed **1a** in order to investigate the possibility of the preparation of the desired products **5**. 2-Chloro-3-sodiosulfanylquinoxaline (**2a**; R^1_2 = benzo) was formed by the reaction of **1a** with $Na_2S \cdot 9\,H_2O$ in DMF at room temperature. The mixture was then treated with 1-aryl-2-bromoalkan-1-ones at the same temperature to afford 1-aryl-2-[(3-chloroquinoxalin-3-yl)sulfanyl]alkanone intermediates **3** (R^1_2 = benzo). By adding NaH at the same temperature, deprotonation in α-position to the C=O function generated the sodium enolate intermediates **4** (R^1_2 = benzo), which underwent cyclization to provide the desired 2-aryl-1,4-oxathiino[2,3-*b*]quinoxalines **5a**–**5e**. The yields of these products are fair-to-good as compiled in the

Table, *Entries 1–5*. An attempt to obtain 3-methyl-2-phenyl-1,4-oxathiino[2,3-*b*]quinoxaline (**5f**) using 2-bromo-1-phenylpropan-1-one under the same conditions was successfully carried out (*Entry 6*), and the yield was comparable to those using 2-bromo-1-phenylethanones. The versatility of the present procedure was demonstrated by its applicability to the preparation of a 2-hetaryl-1,4-oxathiino[2,3-*b*]quinoxaline, such as 2-(thiophen-2-yl)-1,4-oxathiino[2,3-*b*]quinoxaline (**5g**), by using 2-bromo-1-(thiophen-2-yl)ethanone (*Entry 7*).

Scheme

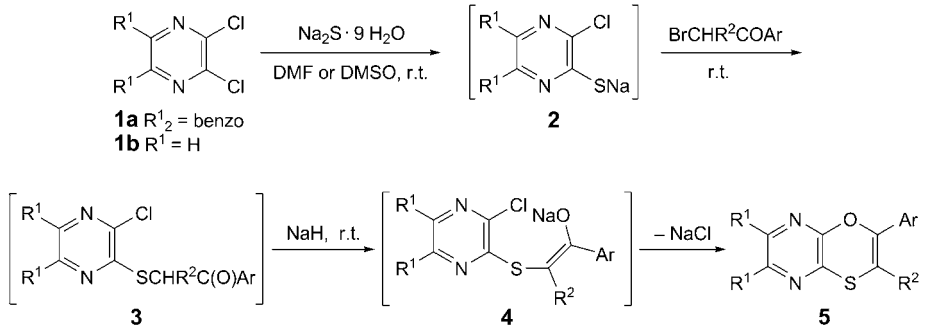

Table. *Preparation of 1,4-Oxathiino[2,3-*b*]quinoxalines and -pyrazines* **5**

Entry	**1**	Ar	R^2	**5**	Yield[a]) [%]
1	**1a** (R^1_2 = benzo)	Ph	H	**5a**	65
2	**1a**	4-Me–C_6H_4	H	**5b**	65
3	**1a**	4-Cl–C_6H_4	H	**5c**	62
4	**1a**	3-MeO–C_6H_4	H	**5d**	68
5	**1a**	4-MeO–C_6H_4	H	**5e**	70
6	**1a**	Ph	Me	**5f**	70
7	**1a**	Thiophen-2-yl	H	**5g**	70
8	**1b** (R^1 = H)	Ph	H	**5h**	57
9	**1b**	4-Cl–C_6H_4	H	**5i**	61
10	**1b**	3-MeO–C_6H_4	H	**5j**	54
11	**1b**	Ph	Me	**5k**	57
12	**1b**	Thiophen-2-yl	H	**5l**	51

[a]) Yields of isolated products.

The initial study on the preparation of 2-phenyl-1,4-oxathiino[2,3-*b*]pyrazine (**5h**) from 2,3-dichloropyrazine (**1b**; R^1 = H) and 2-bromo-1-phenylethanone (phenacyl bromide) was performed in DMF under the same conditions as described for the preparation of **5a**–**5g**. Although the clean formation of intermediate 2-[(3-chloropyrazin-3-yl)sulfanyl]-1-phenylethanone (**3h**) was confirmed by TLC analysis, the cyclization reaction proved to be very sluggish. Later, DMSO was found to be a suitable solvent for the cyclization. Thus, when **1b** was successively treated with $Na_2S \cdot 9\ H_2O$, 2-bromo-1-phenylethanone, and NaH in DMSO at room temperature, the cyclization took place satisfactorily to afford a reasonable yield (57%) of **5h** (*Table*,

Entry 8). Subsequently, 2-chloro-3-sodiosulfanylpyrazine intermediate (**2b**; $R^1 = H$) was similarly treated with four other 2-bromo-1-(het)arylalkan-1-ones, followed by NaH to give the corresponding desired products **5i**–**5l** in the yields compiled in the *Table*, *Entries 9–12*. The yields of these products are moderate-to-fair and slightly lower than those of 1,4-oxathiino[2,3-*b*]quinoxaline derivatives **5a**–**5g**.

In conclusion, we have succeeded in the preparation of novel heterocyclic systems, 1,4-oxathiino[2,3-*b*]quinoxaline and -pyrazine **5**, starting with commercially available 2,3-dichloroquinoxaline and -pyrazine **1**, respectively, under mild conditions by a one-pot reaction. The present method may be of use in organic synthesis, particularly due to its simplicity in operations, and may provide interesting pharmacophores. Further work on the preparation of related heterocycles by applying this method is currently ongoing.

Experimental Part

General. All of the org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako Gel C-200E.* M.p.: *Laboratory Devices MEL-TEMP II* apparatus; uncorrected. IR Spectra: as KBr disks with *Perkin–Elmer Spectrum65 FTIR* spectrophotometer. NMR Spectra: in $CDCl_3$ with TMS as an internal reference with *JEOL ECP500* FT NMR spectrometer; at 500 (^{1}H) and 125 MHz (^{13}C). HR-MS (DART, positive-ion mode): *Thermo Scientific Exactive* spectrometer.

1-(Thiophen-2-yl)-2-bromoethanone was prepared as described in [3]. All other chemicals used in this study were commercially available.

*1,4-Oxathiino[2,3-*b*]pyrazines and -quinoxalines* **5**: *General Procedure.* A mixture of $Na_2S \cdot 9\,H_2O$ (0.24 g, 1.0 mmol) and 2,3-dichloroquinoxaline (**1a**; 0.20 g, 1.0 mmol) or *2,3-dichloropyrazine* (**1b**; 0.15 g, 1.0 mmol) in DMF (4 ml, for **1a**) or DMSO (4 ml, for **1b**) was stirred for 15 min at r.t. One of the 1-aryl-2-bromoethanones (1.0 mmol) and, after 10 min, NaH (60% in mineral oil; 40 mg, 1.0 mmol) were added, and stirring was continued overnight at the same temp. Then, H_2O (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), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized to afford **5**.

*2-Phenyl[1,4]oxathiino[2,3-*b*]quinoxaline* (**5a**). Yellow solid. M.p. 142–144° (hexane/CH_2Cl_2). IR: 3063, 1624, 1388, 1321. ^{1}H-NMR: 5.82 (*s*, 1 H); 7.36–7.41 (*m*, 3 H); 7.52–7.57 (*m*, 2 H); 7.65 (*d*, $J = 8.0$, 2 H); 7.75–7.78 (*m*, 2 H). ^{13}C-NMR: 91.6; 124.3; 127.3; 127.7; 128.57; 128.8; 129.2; 129.8; 131.9; 139.8; 141.4; 143.1; 147.6; 150.4. HR-MS: 279.0580 ($[M+H]^+$, $C_{16}H_{11}N_2OS^+$; calc. 279.0592). Anal. calc. for $C_{16}H_{10}N_2OS$ (278.33): C 69.04, H 3.62, N 10.06, S 11.52; found: C 68.83, H 3.74, N 9.87, S 11.61.

*2-(4-Methylphenyl)[1,4]oxathiino[2,3-*b*]quinoxaline* (**5b**). Yellow solid. M.p. 200–201° (hexane/CH_2Cl_2). IR: 3081, 1635, 1390, 1323. ^{1}H-NMR: 2.38 (*s*, 3 H); 5.77 (*s*, 1 H); 7.21 (*d*, $J = 7.6$, 2 H); 7.54–7.58 (*m*, 4 H); 7.76–7.79 (*m*, 2 H). ^{13}C-NMR: 21.3; 90.4; 124.2; 127.3; 127.6; 128.7; 129.2; 129.3; 129.7; 139.4; 139.8; 141.4; 143.3; 147.8; 150.5. HR-MS: 293.0735 ($[M+H]^+$, $C_{17}H_{13}N_2OS^+$; calc. 293.0749). Anal. calc. for $C_{17}H_{12}N_2OS$ (292.36): C 69.84, H 4.14, N 9.58, S 10.97; found: C 69.78, H 3.95, N 9.66, S 10.98.

*2-(4-Chlorophenyl)[1,4]oxathiino[2,3-*b*]quinoxaline* (**5c**). Yellow solid. M.p. 204–206° (hexane/CH_2Cl_2). IR: 3092, 1623, 1393, 1326. ^{1}H-NMR: 5.83 (*s*, 1 H); 7.37 (*d*, $J = 8.6$, 2 H); 7.54–7.60 (*m*, 4 H); 7.76 (*d*, $J = 9.2$, 1 H); 7.78 (*d*, $J = 9.2$, 1 H). ^{13}C-NMR: 92.3; 125.5; 127.3; 127.7; 128.8; 128.9; 129.9; 130.4; 135.1; 139.8; 141.8; 142.7; 146.6; 150.2. HR-MS: 313.0197 ($[M+H]^+$, $C_{16}H_{10}ClN_2OS^+$; calc. 313.0202). Anal. calc. for $C_{16}H_9ClN_2OS$ (312.77): C 61.44, H 2.90, N 8.96, S 10.25; found: C 61.24, H 2.64, N 9.01, S 10.48.

*2-(3-Methoxyphenyl)[1,4]oxathiino[2,3-*b*]quinoxaline* (**5d**). Yellow solid. M.p. 140–141° (hexane/CH_2Cl_2). IR: 3069, 1603, 1390, 1313, 1292. ^{1}H-NMR: 3.86 (*s*, 3 H); 5.83 (*s*, 1 H); 6.93 (*ddd*, $J = 8.0$, 2.3, 1.1, 1 H); 7.19 (*dd*, $J = 2.3$, 1.7, 1 H); 7.25 (*dd*, $J = 8.0$, 1.7, 1 H); 7.32 (*t*, $J = 8.0$, 1 H); 7.53–7.59 (*m*, 2 H); 7.76–7.80 (*m*, 2 H). ^{13}C-NMR: 55.4; 92.0; 110.1; 115.0; 116.9; 127.3; 127.7; 128.8; 129.7; 129.8; 133.5;

139.8; 141.5; 143.2; 147.6; 150.5; 159.8. HR-MS: 308.0686 ($[M+H]^+$, $C_{17}H_{13}N_2O_2S^+$; calc. 308.0698). Anal. calc. for $C_{17}H_{12}N_2O_2S$ (308.35): C 66.22, H 3.92, N 9.08, S 10.40; found: C 66.18, H 3.97, N 9.07, S 10.22.

*2-(4-Methoxyphenyl)[1,4]oxathiino[2,3-*b*]quinoxaline* (**5e**). Yellow solid. M.p. 200–201° (hexane/CH_2Cl_2). IR: 3079, 1602, 1389, 1313. ^{1}H-NMR: 3.85 (*s*, 3 H); 5.68 (*s*, 1 H); 6.92 (*d*, *J* = 9.2, 2 H); 7.54–7.57 (*m*, 2 H); 7.61 (*d*, *J* = 9.2, 2 H); 7.77 (*d*, *J* = 9.2, 1 H); 7.79 (*d*, *J* = 9.2, 1 H). ^{13}C-NMR: 55.4; 89.2; 113.9; 124.7; 125.9; 127.3; 127.6; 128.7; 129.7; 140.0; 141.4; 143.5; 147.6; 150.6; 160.4. HR-MS: 309.0681 ($[M+H]^+$, $C_{17}H_{13}N_2O_2S^+$; calc. 309.0697). Anal. calc. for $C_{17}H_{12}N_2O_2S$ (308.35): C 66.22, H 3.92, N 9.08, S 10.40; found: C 66.11, H 3.95, N 9.05, S 10.32.

*3-Methyl-2-phenyl[1,4]oxathiino[2,3-*b*]quinoxaline* (**5f**). Yellow solid. M.p. 135–136° (hexane/CH_2Cl_2). IR: 1391, 1324. ^{1}H-NMR: 2.10 (*s*, 3 H); 7.39–7.44 (*m*, 3 H); 7.52–7.56 (*m*, 4 H); 7.74 (*dd*, *J* = 7.4, 1.7, 1 H); 7.81 (*dd*, *J* = 7.4, 2.3, 1 H). ^{13}C-NMR: 18.3; 103.8; 127.3; 127.7; 128.3; 128.5; 128.7; 129.1; 129.6; 132.7; 139.9; 141.3; 143.6; 144.5; 151.1. HR-MS: 293.0732 ($[M+H]^+$, $C_{17}H_{13}N_2OS^+$; calc. 293.0748). Anal. calc. for $C_{17}H_{12}N_2OS$ (292.36): C 69.84, H 4.14, N 9.58, S 10.97; found: C 69.76, H 4.14, N 9.40, S 10.82.

*2-(Thiophen-2-yl)[1,4]oxathiino[2,3-*b*]quinoxaline* (**5g**). Yellow solid. M.p. 148–150° (hexane/CH_2Cl_2). IR: 1387, 1315. ^{1}H-NMR: 5.75 (*s*, 1 H); 7.05 (*dd*, *J* = 5.2, 3.4, 1 H); 7.30 (*d*, *J* = 5.2, 1 H); 7.39 (*d*, *J* = 3.4, 1 H); 7.55–7.60 (*m*, 2 H); 7.78–7.80 (*m*, 2 H). ^{13}C-NMR: 90.4; 124.5; 125.9; 127.3; 127.6; 127.7; 128.9; 129.9; 135.5; 139.7; 141.4; 143.4; 148.6; 150.1. HR-MS: 285.0142 ($[M+H]^+$, $C_{14}H_9N_2OS_2^+$; calc. 285.0156). Anal. calc. for $C_{14}H_8N_2OS_2$ (284.36): C 59.13, H 2.84, N 9.85, S 22.55; found: C 59.07, H 2.85, N 9.72, S 22.21.

*2-Phenyl[1,4]oxathiino[2,3-*b*]pyrazine* (**5h**). Yellow solid. M.p. 81–83° (hexane/CH_2Cl_2). IR: 3069, 1644, 1380. ^{1}H-NMR: 5.72 (*s*, 1 H); 7.34–7.40 (*m*, 3 H); 7.60 (*dd*, *J* = 7.8, 2.0, 2 H); 7.86 (*d*, *J* = 2.0, 1 H); 8.02 (*d*, *J* = 2.0, 1 H). ^{13}C-NMR: 92.4; 124.3; 128.6; 129.2; 131.9; 139.4; 140.6; 141.7; 148.5; 154.1. HR-MS: 229.0420 ($[M+H]^+$, $C_{12}H_9N_2OS^+$; calc. 229.0436). Anal. calc. for $C_{12}H_8N_2OS$ (228.27): C 63.14, H 3.53, N 12.27, S 14.05; found: C 63.87, H 3.62, N 12.23, S 14.02.

*2-(4-Chlorophenyl)[1,4]oxathiino[2,3-*b*]pyrazine* (**5i**). Yellow solid. M.p. 159–160° (hexane/CH_2Cl_2). IR: 3069, 1641, 1380. ^{1}H-NMR: 5.71 (*s*, 1 H); 7.36 (*d*, *J* = 8.6, 2 H); 7.53 (*d*, *J* = 8.6, 2 H); 7.86 (*d*, *J* = 2.9, 1 H); 8.03 (*d*, *J* = 2.9, 1 H). ^{13}C-NMR: 93.1; 125.5; 127.8; 128.8; 128.9; 139.5, 140.8; 141.4; 147.5; 153.9. HR-MS: 263.0032 ($[M+H]^+$, $C_{12}H_8ClN_2OS^+$; calc. 263.0047). Anal. calc. for $C_{12}H_7ClN_2OS$ (262.71): C 54.86, H 2.69, N 10.66, S 12.21; found: C 54.71, H 2.77, N 10.50, S 12.12.

*2-(3-Methoxyphenyl)[1,4]oxathiino[2,3-*b*]pyrazine* (**5j**). Yellow solid. M.p. 70–72° (hexane/CH_2Cl_2). IR: 3083, 1643, 1381. ^{1}H-NMR: 3.83 (*s*, 3 H); 5.71 (*s*, 1 H); 6.90 (*ddd*, *J* = 8.0, 2.3, 1.1, 1 H); 7.13 (*dd*, *J* = 2.3, 1.7, 1 H); 7.17 (*ddd*, *J* = 8.6, 1.7, 1.1, 1 H); 7.28 (*dd*, *J* = 8.6, 8.0, 1 H); 7.85 (*d*, *J* = 2.8, 1 H); 8.01 (*d*, *J* = 2.8, 1 H). ^{13}C-NMR: 55.4; 92.8; 109.8; 115.0; 116.8; 129.6; 133.3; 139.4; 140.6; 141.6; 148.3; 154.0; 159.8. HR-MS: 259.0537 ($[M+H]^+$, $C_{13}H_{11}N_2O_2S^+$; calc. 259.0542). Anal. calc. for $C_{13}H_{10}N_2O_2S$ (258.30): C 60.45, H 3.90, N 10.85, S 12.41; found: C 60.26, H 3.91, N 10.65, S 12.26.

*3-Methyl-2-phenyl[1,4]oxathiino[2,3-*b*]pyrazine* (**5k**). Yellow solid. M.p. 86–87° (hexane/CH_2Cl_2). IR: 1654, 1375. ^{1}H-NMR: 1.97 (*s*, 3 H); 7.37–7.42 (*m*, 3 H); 7.48 (*d*, *J* = 7.4, 2 H); 7.86 (*d*, *J* = 2.3, 1 H); 8.04 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR: 18.4; 104.8; 128.3; 128.7; 129.0; 132.7; 139.3; 140.3; 142.7; 144.2; 154.5. HR-MS: 243.1285 ($[M+H]^+$, $C_{13}H_{11}N_2OS^+$; calc. 243.1304). Anal. calc. for $C_{13}H_{10}N_2OS$ (242.30): C 64.44, H 4.16, N 11.56, S 13.23; found: C 64.33, H 4.15, N 11.62, S 13.34.

*2-(Thiophen-2-yl)[1,4]oxathiino[2,3-*b*]pyrazine* (**5l**). Yellow solid. M.p. 79–80° (hexane/CH_2Cl_2). IR: 3105, 1377. ^{1}H-NMR: 5.62 (*s*, 1 H); 7.03 (*ddd*, *J* = 5.2, 3.4, 1.1, 1 H); 7.28 (*dd*, *J* = 5.2, 1.1, 1 H); 7.32 (*dd*, *J* = 3.4, 1.1, 1 H); 7.86 (*d*, *J* = 2.9, 1 H); 8.03 (*d*, *J* = 2.9, 1 H). ^{13}C-NMR: 91.1; 124.5; 125.8; 127.6; 135.4; 139.4; 140.7; 141.4; 144.1; 153.8. HR-MS: 234.9996 ($[M+H]^+$, $C_{10}H_7N_2OS_2^+$; calc. 234.9999). Anal. calc. for $C_{10}H_6N_2OS_2$ (234.30): C 51.26, H 2.58, N 11.96, S 27.37; found: C 51.21, H 2.60, N 11.80, S 27.37.

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