Studies on Pyrazines. Part 33.[1] Synthesis of 2,3-Diaminopyrazines *via* [1,2,5]Thiadiazolo-[3,4-*b*]pyrazines†

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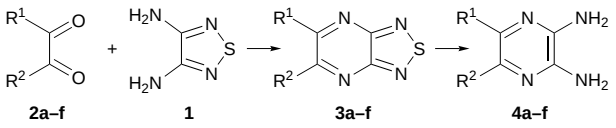
The syntheses of [1,2,5]thiadiazolo[3,4-*b*]pyrazine (**3**) and its methyl and/or phenyl derivatives as well as their reduction to 2,3-diaminopyrazines **4** are described.

The cleavage of fused pyrazines represents a useful method for the synthesis of substituted pyrazines.[2] We have previously reported the synthesis of 2,3-diaminopyrazines *via* hydrogenolysis of furazano[3,4-*b*]pyrazines which were prepared by the condensation of 3,4-diaminofurazan with α-dicarbonyl compounds.[3] Unfortunately, this methodology was limited to the synthesis of diaminopyrazines having at least one phenyl group, namely the diaminofurazan underwent condensation with neither glyoxal, methylglyoxal nor butane-2,3-dione. In contrast, 3,4-diamino-1,2,5-thiadiazole[4] (**1**) was converted into a variety of [1,2,5]thiadiazolo[3,4-*b*]pyrazines **3** including the parent and dimethyl derivatives,[4–6] which would be expected to form similarly 2,3-diaminopyrazines **4** by reductive desulfurization.

We report here the synthesis of the thiadiazolopyrazines **3** and their successful reduction to diaminopyrazines **4**.



2a–f **1** **3a–f** **4a–f**

a $R^1 = R^2 = H$; **b** $R^1 = Me$, $R^2 = H$; **c** $R^1 = R^2 = Me$; **d** $R^1 = Ph$, $R^2 = H$; **e** $R^1 = Ph$, $R^2 = Me$; **f** $R^1 = R^2 = Ph$

Scheme 1

The diaminothiazole **1** was conveniently prepared by the hydrolysis of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole with ammonium hydroxide, in which the bicyclic compound was produced by the cyclization of oxamide dioxime with an excess of sulfur dichloride.[6a] Numerous thiadiazolopyrazines **3** have been synthesized mainly for use as agrochemicals, but since most of them are patented procedures, only a few preparations are available in the literature. Therefore, the synthesis of **3** from **1** and the 1,2-diketones **2** was investigated using a variety of solvents. Condensation of **1** with benzil **2f** easily proceeded in refluxing acetic acid and after 4 h gave the thiadiazolopyrazine **3f** in 85% yield. An almost equal yield of **3f** was obtained using a mixture of acetic acid and ethanol (1:3 *v*/*v*)[3] as the solvent for the same period, but trifluoroacetic acid was found to be less practical (81% yield) than the former acidic media. Treatment of **1** with phenylglyoxal hydrate in refluxing acetic acid for 4 h afforded **3d** in excellent yield but treatment with 1-phenylpropane-1,2-dione generated **3e** in only 66% yield. Under identical conditions, however, the aliphatic diketones **2a–c** gave modest yields (23–39%) of the corresponding products **3**.

When ethanol was used as the solvent instead of acetic acid, a better yield (60%) of **3c** was obtained even after shortening the reaction time to 1 h. An obvious improvement in the yield to 90% was achieved by a dropwise addition of 2 equiv. of **2c** into a boiling mixture of **1** in ethanol followed by refluxing. Similar treatment of **1** with **2e** gave an excellent yield of **3e**, and the synthesis of **3b** was best effected by changing the solvent to methanol. This method, however, was found to be of little value for the preparation of **3f** because of its low yield (24%). In comparison with the earlier synthetic procedure[4] for the parent thiadiazolopyrazine **3a**, the condensation was notably improved by running the reaction in ethanol at 55–60 °C, but a 42% yield of the desired product was barely realized after purification by sublimation. Incidentally, condensation of **1** with glyoxal–sodium bisulfite addition compound did not proceed at all. The results are summarized in Table 1.

Reductive desulfurization is usually accomplished by treatment with Raney nickel or lithium aluminum hydride; use of the former to reduce diphenylthiadiazolopyrazine **3f** only gave a 30% yield of the diaminopyrazine **4f** and use of the latter led to no formation of **4** at all. Recently, treatment with tin powder in a mixture of concentrated hydrochloric acid and dioxane was shown to convert benzobis[1,2,5]thiadiazoles into tetraaminobenzenes.[7] A modified procedure using tin(II) chloride in methanolic hydrochloric acid successfully transformed **3** into **4** in excellent yields. With the exception of **4a**, the cleavage was optimized by treating with 5 equiv. of tin chloride at 60 °C (Table 2). Under the milder conditions of using hydrochloric acid at room temperature, the parent diaminopyrazine **4a** was formed in 83% yield. We have previously[8] carried out the reduction with tin chloride with complete conversion of azidopyrazines to aminopyrazines, in which case some 2,3-diaminopyrazines **3** were obtained from 2-amino-3-azidopyrazines. Compared with the existing synthetic routes *via* 2-amino-3-halopyrazines[9,10] or 1,4-dihydropyrazine-2,3-diones,[11] the current method provides a most

Table 1 Synthesis of [1,2,5]thiadiazolo[3,4-*b*]pyrazines **3**

Product **3**	Solvent	Method[a]	Yield (%)
a	EtOH	A	42
b	MeOH	A	77
c	EtOH	A	90
d	AcOH	B	90
e	EtOH	A	85
f	AcOH	B	85

[a]See Experimental section.

Table 2 Reduction to 2,3-diaminopyrazines **4**

Product **4**	*t*/h	Yield (%)
a	1[a]	83
b	1	89
c	1	87
d	3	83
e	2.5	84
f	3	85

[a]At room temperature (see Experimental section).

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convenient route to 2,3-diaminopyrazines **3** in terms of the accessibility of starting materials and the shorter reaction sequence.

Experimental

Melting points were determined using a Büchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM EX270 instrument at 270 and 67.8 MHz, respectively, with solutions in $CDCl_3$, unless otherwise stated, containing tetramethylsilane as internal standard.

General Procedure for Condensation of 3,4-*Diamino*-1,2,5-*thiadiazole* **1** *with* 1,2-*Diketones* **2**.—*Method A.* Glyoxal (**2a**) and methylglyoxal (**2b**) were used as 40% aqueous solutions. The 1,2-diketone solution (10 mmol for **2a–c**, 6.0 mmol for **2e**) was added *via* syringe to a boiling solution of 3,4-diamino-1,2,5-thiadiazole (**1**) (0.571 g, 5.0 mmol) in alcohol (10 cm^3) over 10 min, and the resulting mixture was refluxed for 1 h. In the synthesis of **3a**, the reaction temperature was kept at 55–60 °C during the reaction. After cooling, the reaction mixture was evaporated under vacuum, and the residue was purified by column chromatography (silica gel, 30 g) using ethyl acetate–hexane (1:7 to 1:1) as eluent, and then sublimed under reduced pressure. Analytical samples were obtained by recrystallization.

Method B. A mixture of 3,4-diamino-1,2,5-thiadiazole (**1**) (0.233 g, 2.0 mmol) and the diketone (2.1 mmol) in acetic acid (4 cm^3) was stirred and refluxed for 4 h. The reaction mixture was cooled and concentrated under vacuum. Water was added to the obtained residue, and the aqueous solution was extracted with chloroform (3×15 cm^3). The extract was washed with water, dried ($MgSO_4$) and evaporated under vacuum. The residue was purified as described above.

The yields of [1,2,5]thiadiazolo[3,4-*b*]pyrazines **3a–f** are summarized in Table 1. The following compounds were obtained. [1,2,5]Thiadiazolo[3,4-*b*]pyrazine (**3a**), Method A, yellow needles, mp 166–168 °C (decomp.) (EtOH) [lit.,[4] 161–162 °C (decomp.)]; δ_H 9.05 (2 H, s); δ_C 149.2, 154.6. 5-*Methyl*[1,2,5]*thiadiazolo*[3,4-b]*pyrazine* (**3b**), Method A, tiny yellow needles, mp 167.5–168 °C (decomp.) (EtOH) (Found: C, 39.7; H, 2.6; N, 37.1. $C_5H_4N_4S$ requires C, 39.5; H, 2.65; N, 36.8%); δ_H 2.90 (3 H, s), 8.92 (1 H, s); δ_C 23.0, 150.9, 152.9, 154.1, 159.8. 5,6-Dimethyl-[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**3c**), Method A, yellow needles, mp 125.5–126 °C (EtOH) (lit.,[4] 124–125 °C); δ_H 2.83 (6 H, s); δ_C 24.0, 153.2, 159.7. 5-Phenyl[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**3d**), Method B, yellow needles, mp 144.5–146 °C (EtOH) (lit.,[5] 115 °C) (Found: C, 56.0; H, 2.7; N, 26.3. $C_{10}H_6N_4S$ requires C, 56.1; 2.8; N, 26.15%); δ_H 7.59–7.65 (3 H, m), 8.28–8.33 (2 H, m), 9.56 (1 H, s); δ_C 128.4 (2 C), 129.5 (2 C), 131.9, 134.9, 148.5, 153.5, 154.5, 156.2. 5-*Methyl*-6-*phenyl*[1,2,5]*thiadiazolo*[3,4-b]*pyrazine (***3e**), Method A, yellow needles, mp 120.5–121 °C (EtOH) (Found: C, 58.0; H, 3.5; N, 24.5. $C_{11}H_8N_4S$ requires C, 57.9; H, 3.5; N, 24.5%); δ_H 2.87 (3 H, s), 7.56–7.69 (5 H, m); δ_C 25.6, 128.7 (2 C), 129.0 (2 C), 130.1, 137.5, 153.15, 153.19, 159.1, 159.9. 5,6-*Diphenyl*[1,2,5]*thiadiazolo*[3,4-b]*pyrazine* (**3f**), Method B, tiny yellow needles, mp 182–182.5 °C (EtOH) (Found: C, 66.2; H, 3.4; N, 19.3. $C_{16}H_{10}N_4S$ requires C, 66.2; H, 3.5; N, 19.3%); δ_H 7.33–7.47 (6 H, m), 7.54–7.57 (4 H, m); δ_C 128.3 (2 C), 130.10, 130.14 (2 C), 137.7, 153.2, 158.7.

General Procedure for the Reduction of [1,2,5]*Thiadiazolo*[3,4-b]*pyrazines* **3**.—A mixture of [1,2,5]thiadiazolo[3,4-*b*]pyrazines **3** (1.0 mmol) and tin(II) chloride (1.13 g, 5.0 mmol) in 12 mol dm^{-3} hydrochloric acid (6 cm^3) and methanol (6 cm^3) was stirred and heated at 60 °C (internal temperature). In the case of **3a**, 1.5 mol dm^{-3} hydrochloric acid was used instead of the concentrated acid, and the mixture was stirred at room temperature. The extent of the reaction was monitored by TLC and the reaction was completed in the time shown in Table 2. After being cooled to room temperature, the solution was basified with sodium carbonate at pH 8–9 and then evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl acetate (4×15 cm^3), and the combined extracts were evaporated to dryness. Recrystallization of the residue gave the following 2,3-diaminopyrazines **4a–f** (Table 2). 2,3-Diaminopyrazine (**4a**), light tan microprisms, mp 200 °C (MeOH) (lit.,[8] 207–209 °C); δ_H 4.23 (4 H, brs), 7.53 (2 H, s); δ_C [$(CD_3)_2SO$] 129.0, 143.9. 2,3-Diamino-5-methylpyrazine (**4b**), light tan needles, mp 176.5–177 °C (EtOAc) (lit.,[8] 176.5–178 °C); δ_H 2.29 (3 H, s), 4.05 and 4.21 (each 2 H, brs), 7.39 (1 H, s); δ_C 20.1, 130.8, 141.3, 141.5, 143.4. 2,3-Diamino-5,6-dimethylpyrazine (**4c**), yellow needles, mp 214–215 °C (C_6H_6) (lit.,[10] 212–216 °C); δ_H 2.26 (6 H, s), 4.05 (4 H, brs); δ_C 20.2, 138.3, 141.1. 2,3-Diamino-5-phenylpyrazine (**4d**), light tan needles, mp 172–173 °C (C_6H_6) (lit.,[3] 173 °C); δ_H 4.31 (4 H, brs), 7.34–7.46 (3 H, m), 7.84–7.86 (2 H, m), 7.99 (1 H, s); δ_C 125.8 (2 C), 127.9, 128.3, 128.7 (2 C), 129.5, 137.4, 142.8, 143.3. 2,3-Diamino-5-methyl-6-phenylpyrazine (**4e**), microcrystals, mp 168.5–169 °C (C_6H_6) (lit.,[3] 167–168 °C); δ_H 2.38 (3 H, s), 4.16 and 4.26 (each 2 H, brs), 7.34–7.50 (5 H, m); δ_C 21.2, 127.4, 128.1 (2 C), 129.0 (2 C), 138.2, 139.4, 140.9, 141.1, 142.2. 2,3-Diamino-5,6-diphenylpyrazine (**4f**), light tan needles, mp 276–278 °C (MeOH) (lit.,[8] 288.5–290 °C); δ_H 4.35 (4 H, brs) and 7.22–7.33 (10 H, m); δ_C 127.3, 128.0 (2 C), 129.6 (2 C), 132.7, 139.3, 142.0.

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