Studies on Pyrazines. 15 [1]. A Convenient Synthesis of 2,5-Dihydroxypyrazines

Nobuhiro Sato* and Yukihiro Kato

Department of Chemistry, Yokohama City University,
Yokohama 236, Japan

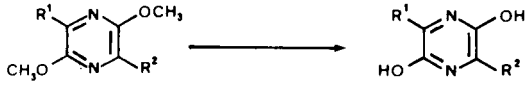
Received May 16, 1986

The reaction of 2,5-dimethoxypyrazines with iodotrimethylsilane followed by hydrolysis was investigated to prepare the title compounds.

J. Heterocyclic Chem., **23**, 1677 (1986).

In a previous publication [1], we described the synthesis of 2,5-dihydroxypyrazines **1** by condensation of α-aminoamides with α-ketoesters and subsequent cyclization of the resulting α-acylaminoamides with refluxing methanolic sodium methoxide. These compounds **1** have been reported to have been also prepared by demethylation of 2,5-dimethoxypyrazines **2** with methanolic sodium methoxide at 170-180°, but the conditions required to hydrolyze **2** was shown to sometimes lead to the decomposition of the products [2]. Recently, ether cleavage of 2,4-dialkoxypyrimidines to uracils was found to be easily accomplished by using iodotrimethylsilane under mild conditions [3]. This paper reports successful application of this method to synthesis of 2,5-dihydroxy-3,6-dimethyl-(**1a**) and -3,6-diphenylpyrazines (**1b**) from the corresponding dimethoxy compounds **2**, as well as some anomalous results obtained during an attempt to prepare 2,5-dihydroxy-3-phenylpyrazine (**1c**) in a similar fashion.

Scheme I

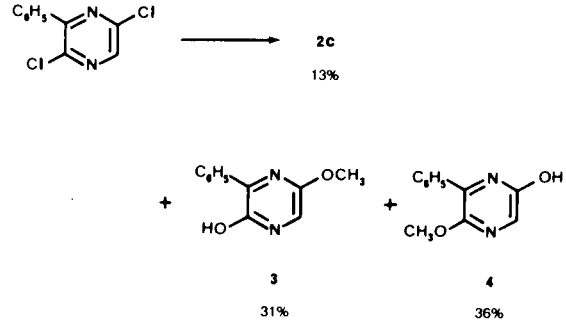


2 **1**

	R^1	R^2
a	CH_3	CH_3
b	C_6H_5	C_6H_5
c	C_6H_5	H

The requisite 2,5-dimethoxypyrazines **2** were readily prepared by treating 2,5-dichloropyrazines with a five-fold excess of 10-20% methanolic sodium methoxide at 120-130° [2]. For the synthesis of 2,5-dimethoxy-3-phenylpyrazine (**2c**), a repetition of the procedure of Karmas and Spoerri [4] was used involving treatment of 2,5-dichloro-3-phenylpyrazine with a three-fold excess of 20% sodium methoxide in methanol at 120°. This currently produced only a 13% yield of the desired compound **2c** (see Scheme II). The major products were revealed by ^{1}H-nmr spectra

Scheme II



2c 13%

3 31% **4** 36%

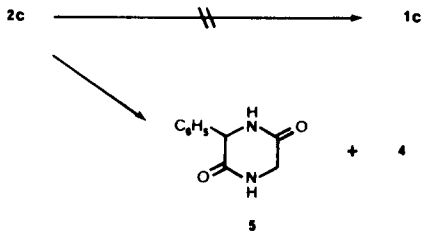
to be 2-hydroxy-5-methoxypyrazines **3** (31%) and **4** (36%), formation which resulted from demethylation of **2c** which was produced initially. In this respect, the same workers showed that the partial demethylation of **2c** was brought about at 150° by treatment with methanolic sodium methoxide to give **4** as a product isolated exclusively whereas direction of the ether cleavage was suggested not to be selective. The ir spectra (potassium bromide) of 2-hydroxy-5-methoxypyrazines **3** and **4** exhibit a broad hydroxy band in the region of 3100-2500 cm^{-1} but do not possess a carbonyl absorption of amide, indicating that these compounds exist in the hydroxy form in the solid phase rather than the amide form. This is unlike most of hydroxypyrazines which favor the tautomeric 2(1*H*)-pyrazinones [5]. Interestingly, acetylation of **4** is not sterically influenced at all, but the reaction required a much longer period of reaction time than that of **3** having the hydroxy group adjacent to the phenyl substituent.

Treatment of dimethoxypyrazines **1a,b** with iodotrimethylsilane in sulfolane at 40-45° followed by hydrolysis afforded excellent yields of the expected 2,5-dihydroxypyrazines **1a,b**, respectively. Similarly, compound **1a** was obtained by the use of chloroform instead of sulfolane as the solvent in 59% yield [6].

A program that we primarily aimed at in this work was the synthesis of 2,5-dihydroxy-3-phenylpyrazine (**1c**) because our previous method [1] involving cyclization of aliphatic compound was not efficient for the construction of **1c**. Demethylation of **2c** with methanolic sodium

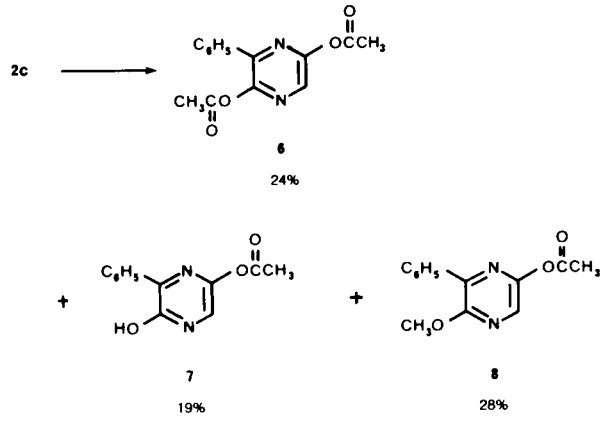
methoxide at 170-180° [2] was also unsuccessful and resulted in extensive decomposition. Therefore, iodotrimethylsilane dealkylation performed under essentially neutral conditions near room temperatures would be expected to achieve conversion of **2c** into **1c**. However, when **2c** was treated with 4.5 equivalents of iodotrimethylsilane in chloroform [7], surprisingly 3-phenyl-2,5-piperazinedione **5** was isolated in 69% yield together with a 11% yield of 2-hydroxy-5-methoxy-6-phenylpyrazine (**4**) as outlined in Scheme III. In this reaction, no formation of 2-hydroxy-5-methoxy-3-phenylpyrazine (**3**) was caused by probable steric hindrance by the phenyl group, in contrast to the nonregioselective demethylation of **2c** with methanolic sodium methoxide at elevated temperatures as described

Scheme III



above. On the other hand, trimethylsilylation of **2c** and successive acetylation with acetic anhydride in the presence of 4-dimethylaminopyridine instead of hydrolysis gave 2,5-diacetoxy-3-phenylpyrazine (**6**), 2-acetoxy-5-hydroxy-6-phenylpyrazine (**7**), and 2-acetoxy-5-methoxy-6-phenylpyrazine (**8**) [8], as illustrated in Scheme IV. This fact indicates that a fragile 2,5-bis(trimethylsilyloxy)pyrazine **9** forms initially and undergoes replacement of labile trimethylsilyloxy substituents by the acetate ion leading to

Scheme IV



acetoxypyrazines **6** and **7**. Similarly, the intermediate **9** is speculated to proceed by hydrolysis to 2,5-dihydroxypyrazine **1c**, where it further transforms into **5** without being isolated due to the extraordinary instability of **1c**. To our disappointment, however, the mechanism for the conversion of **2c** to **5** has yet been unexplained and is still under investigation.

Finally note that attempts to prepare 2,6-dihydroxypyrazines by debenzylation [9] in a similar fashion were unsuccessful and resulted in the recovery of unchanged starting materials upon workup.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. The infrared spectra were recorded on a Hitachi 260-10 spectrometer, and the ^{1}H-nmr spectra on a JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard and deuteriochloroform was used as the solvent unless otherwise mentioned.

2,5-Dimethoxy-3,6-dimethylpyrazine (**2a**).

A mixture of 2,5-dichloro-3,6-dimethylpyrazine (5.00 g, 0.028 mole) and methanolic sodium methoxide prepared from sodium (6.55 g, 0.028 mole) and methanol (80 ml) was heated at 120° in a stainless steel autoclave for 14 hours and then evaporated *in vacuo*. Water was added to the residue, and the resulting solution was extracted with ether (3 x 20 ml). The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give **2a** (3.37 g, 73%), mp 60-61° (from pentane), lit [2] mp 63-65°.

2,5-Dimethoxy-3,6-diphenylpyrazine (**2b**).

This compound was similarly obtained from 2,5-dichloro-3,6-diphenylpyrazine in 71% yield, mp 147-148° (from 1-butanol), lit [2] mp 146-147°.

2,5-Dimethoxy-3-phenylpyrazine (**2c**).

A mixture of 2,5-dichloro-3-phenylpyrazine (2.83 g, 12.6 mmoles) and methanolic sodium methoxide prepared from methanol (85 ml) and sodium (3.00 g, 0.13 mole) was worked up in a predescribed manner to give **2c** as a yellow oil (1.33 g, 49%), bp 160° (7 mm Hg), lit [4] bp 107-108° (0.1 mm Hg).

2-Hydroxy-5-methoxy-3-phenylpyrazine (**3**) and 2-Hydroxy-5-methoxy-6-phenylpyrazine (**4**).

A mixture of 2,5-dichloro-3-phenylpyrazine (13.04 g, 0.058 mole) and methanol (95 ml) containing sodium methoxide (18.8 g, 0.35 mole) was heated at 120° in a stainless steel autoclave and then evaporated *in vacuo*. Water was added to the residue, and the resulting solution was extracted with hexane. The extract was worked up in predescribed manner to provide **2c** (1.67 g, 13%). The aqueous layer was neutralized with 6*N* hydrochloric acid and extracted with several portions of chloroform. The extract was evaporated to dryness *in vacuo*, and the residue was recrystallized several times from acetone to give **4** (1.93 g) as tiny yellow plates, mp 206-207°, lit [2] mp 208-209°; ir (potassium bromide): 3100-2500 cm^{-1} (O-H); ^{1}H-nmr: δ 4.00 (s, CH_3O, 3H), 7.46 (s, H-3, 1H), 7.4-7.55 (m, phenyl, 3H), 8.3-8.4 (m, phenyl, 2H). The mother liquor was evaporated to dryness *in vacuo*, and the residue was chromatographed over silica gel (300 g). The first elution with benzene-ethyl acetate (9:1) gave **3** (3.58 g, 31%), mp 153-154° (from ethanol); ir (potassium bromide): 3100-2500 cm^{-1} (O-H); ^{1}H-nmr: δ 3.93 (s, CH_3O, 3H), 7.34-7.5 (m, phenyl, 3H), 7.74 (s, H-6, 1H), 7.7-7.9 (m, phenyl, 2H).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.28; H, 4.99; N, 13.84.

Further elution with benzene-ethyl acetate (9:1 to 4:1) provided compound **4** (2.30 g, total yield 36%).

2-Acetoxy-5-methoxy-3-phenylpyrazine.

A mixture of **3** (0.236 g, 1.17 mmoles) in acetic anhydride (5 ml) was stirred under reflux for 2 hours and then evaporated *in vacuo*. The residual oil was dissolved in chloroform, and the solution was washed

with water, dried over magnesium sulfate and evaporated to give the title compound (0.226 g, 79%), bp 150-152° (2 mm Hg); ir (neat): 1770 cm^{-1} (C=O); ^{1}H-nmr: δ 2.30 (s, $CH_3C=O$, 3H), 3.97 (s, CH_3O, 3H), 7.3-7.5 (m, phenyl, 3H), 7.91 (s, H-6, 1H), 8.0-8.15 (m, phenyl, 2H).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.77; H, 4.97; N, 11.34.

2-Acetoxy-5-methoxy-6-phenylpyrazine (**8**).

A mixture of **4** (0.404 g, 2.0 mmoles) and 4-dimethylaminopyridine (36 mg) in acetic anhydride (10 ml) was stirred and refluxed for 18 hours and then evaporated *in vacuo*. The residue was dissolved in benzene, and the solution was passed through a column of Florisil. The elution was evaporated *in vacuo* and Kugelrohr-distilled at 138-140° (bath temperature)/2 mm Hg to afford **8** (0.390 g, 80%); ir (neat): 1765 cm^{-1} (C=O); ^{1}H-nmr: δ 2.24 (s, $CH_3C=O$, 3H), 4.03 (s, CH_3O, 3H), 7.4-7.5 (m, phenyl, 3H), 7.8-7.9 (m, phenyl, 2H), 7.96 (s, H-3, 1H).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.70; H, 4.95; N, 11.46.

2,5-Dihydroxy-3,6-dimethylpyrazine (**1a**).

Iodotrimethylsilane (315 μl, 2.0 mmoles) was added under nitrogen to a stirred solution of **2a** (0.168 g, 1.0 mmole) in dry sulfolane (2.0 ml), and then the mixture was heated at 40-45° for 2 hours. After cooling to room temperature, water (36 μl, 2.0 mmoles) was added to the solution, and the resulting mixture was heated at 70° for 30 minutes and stirred at room temperature overnight. The precipitate which formed was collected by filtration, washed with a small amount of dichloromethane and extracted with methanol by a Soxlet extractor to give **1a** (0.118 g, 84%), mp 320° dec, lit [2] mp 320° dec.

2,5-Dihydroxy-3,6-diphenylpyrazine (**1b**).

This compound was similarly prepared by trimethylsilylation-hydrolysis of **2b** in 88% yield, mp 296-300° dec, lit [2] mp 295-300° dec.

Reaction of 2,5-dimethoxy-3-phenylpyrazine (**2c**) with Iodotrimethylsilane.

(a) Trimethylsilylation-Hydrolysis.

Iodotrimethylsilane (0.65 ml, 4.5 mmoles) was added under nitrogen to a stirred solution of **2c** (0.217 g, 1.0 mmole) in dry chloroform (10 ml), and the resulting solution was heated to 40-45° for 2 hours. After cooling to room temperature, water (83 μl, 4.5 mmoles) was added to it, and the mixture was stirred at room temperature overnight. The solution was washed with water (2 x 5 ml), dried over magnesium sulfate and evaporated *in vacuo* to give **4** (23 mg, 11%). The aqueous washings were evaporated to dryness *in vacuo*, and the residual oil was crystallized with a small amount of methanol under refrigeration to provide **5** (0.132 g, 69%), mp 242-243° (from water), lit [10] mp 241-243°; ir (potassium bromide): 1670 cm^{-1} (C=O); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 3.80 (d, H-6, 1H, $J_{6,6'}$ = 3.0 Hz), 3.89 (s, H-3, 1H), 4.90 (d, H-6', 1H), 7.38 (s, phenyl, 5H), 8.14 (br s, NH, 1H), 8.63 (br s, NH, 1H). This compound obtained was identical in all respects with an authentic sample of **5** prepared according to the procedure of Koppel and Ohnishi [10].

(b) Trimethylsilylation-Acetoxylation.

Trimethylsilylation of **2c** was carried out in the same manner as (a) above. After cooling to room temperature, freshly distilled acetic anhydride (10 ml) and 4-dimethylaminopyridine (22 mg) were added to the solution, and the chloroform was distilled away. The resulting solution was refluxed with stirring for 14 hours and then evaporated *in vacuo*. The residue in benzene was passed through a column of silica gel (40 g). The chromatogram was first eluted with benzene to give **8** (63 mg, 28%) and successively with benzene-ethyl acetate (4:1) to provide **6** (64 mg, 24%), mp 74-76° (from ethanol), lit [1] mp 76-78°. Further elution with benzene-ethyl acetate (4:1) afforded **7** (44 mg, 19%), mp 176-178° (from methanol), lit [1] mp 175-178°. These compounds obtained were identical in every respect with the corresponding authentic samples of **6** and **7** in hand [1].

N,N'-Diacetyl-3-phenyl-2,5-piperazinedione.

A mixture of **5** in acetic anhydride (5 ml) was stirred and refluxed for 3 hours and then evaporated *in vacuo*. The residue was Kugelrohr-distilled at 165° (bath temperature)/2 mm Hg to give the title compound (0.484 g, 67%); ir (neat): 1700 cm^{-1} (C=O); ^{1}H-nmr: δ 2.63 (s, CH_3, 3H), 2.69 (s, CH_3, 3H), 3.66 (d, H-6, 1H, $J_{6,6'}$ = 19 Hz), 5.10 (d, H-6', 1H), 6.48 (s, H-3, 1H), 7.2-7.4 (m, phenyl, 5H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.34; H, 5.16; N, 10.18.

REFERENCES AND NOTES

[1] Part **14**: J. Adachi and N. Sato, *J. Heterocyclic Chem.*, **23**, 871 (1986).

[2] G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **79**, 680 (1957).

[3] R. B. Silverman, R. E. Radak, and N. P. Hacker, *J. Org. Chem.*, **44**, 4970 (1979).

[4] G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 4071 (1956).

[5] G. B. Barlin, "The Pyrazines" in the series of "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor, eds, Interscience Publishers, New York, 1982, p 172.

[6] Similarly, demethylation of **2a** to **1a** was achieved by treatment with boron tribromide in dichloromethane (yield 54%).

[7] An attempted trimethylsilylation of **2c** in sulfolane was frustrated by the high-solubility of the products in solvent.

[8] Compound **2c** was resistant to acetoxylation under the same conditions, which was quantitatively recovered upon workup.

[9] The debenzylation was shown to be much more facile than demethylation in pyrimidine series [3].

[10] K. D. Koppel and M. Ohnishi, *J. Am. Chem. Soc.*, **91**, 962 (1969).