# Studies on pyrazines, Part 39.[1] Synthesis and acidic hydrolysis of 2-hydroxy-5-methoxypyrazine

**Nobuhiro Sato* and Akio Mizuno**

*Graduate School of Integrated Science, Yokohama City University, Yokohama 236-0027, Japan*

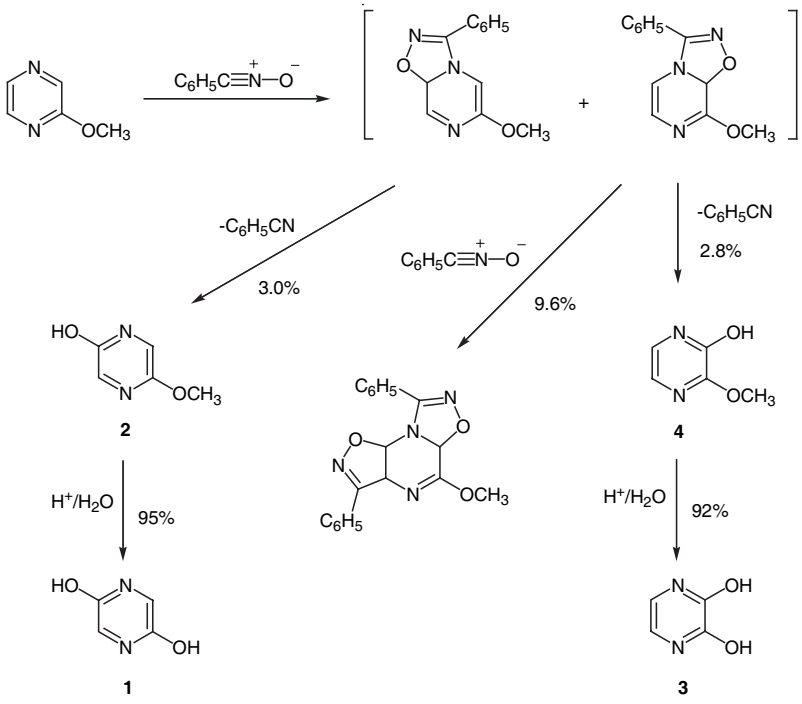
2-Hydroxy-5-methoxypyrazine was synthesised in a three-step reaction sequence starting from aminopyrazine. The product was extensively destroyed on acidic workup without forming 2,5-dihydroxypyrazine.

**Keywords:** hydroxypyrazines, aminopyrazines

One of our continuous interests in pyrazine chemistry is the synthesis of 2,5-dihydroxypyrazines,[2, 3] which may exist predominantly in their 5-hydroxy-2(1*H*)-pyrazinone tautomeric forms. To the best of our knowledge, only four derivatives[2-5] have been characterised, of which two were prepared by ether cleavage of 2,5-dimethoxypyrazines with methanolic sodium methoxide[4] or iodotrimethylsilane.[3] The stability of this class of heteroaromatic has been shown to be affected by the substituents:[4] the dihydroxypyrazines possessing two substituents such as phenyl or methyl groups are stable under basic conditions, although they are sensitive to mineral acids, resulting in hydrolytic fission of the pyrazine nucleus. In particular, the 3,6-dimethyl derivative is destroyed even by bubbling carbon dioxide into its aqueous suspension. Some failed attempts have been made to convert monoalkyl- or monoaryl-substituted 2,5-dimethoxypyrazines into the corresponding 2,5-dihydroxypyrazines.[3, 4] Therefore, it has been assumed that the synthesis of the parent 2,5-dihydroxypyrazine (**1**) is practically impossible. However, during our recent survey of synthetic methods for pyrazines,[6] we found a report that 2,5-dihydroxypyrazine bearing no other substituents was produced by cycloaddition of methoxypyrazine with benzonitrile oxide and subsequent acidic hydrolysis of the resultant 2-hydroxy-5-methoxypyrazine (**2**), and that the 2,3-isomer **4** was also isolated (Scheme 1).[7] In order to ascertain these facts, we undertook an independent synthesis of 2-hydroxy-5-methoxypyrazine (**2**) (Scheme 2). Our conclusion, that the proposed[7] hydroxypyrazines **2** and **4** are not identified as such by comparison of their NMR spectra, is presented here.

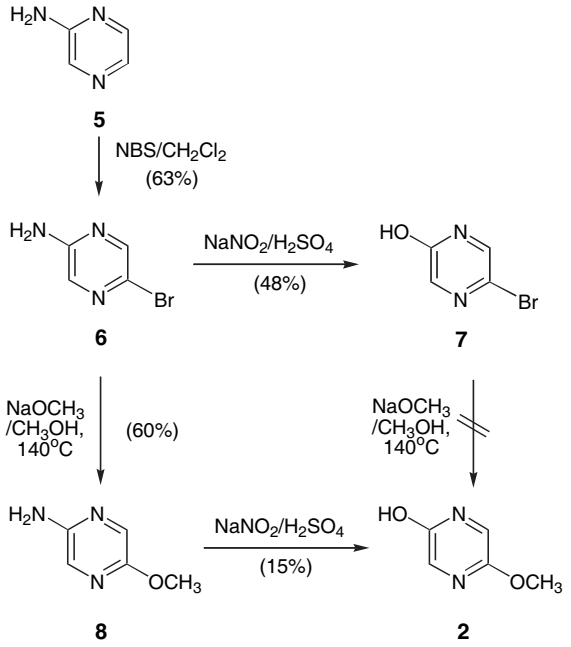
Bromination of aminopyrazines is the method of choice for synthesizing 2,5-difunctional pyrazines.[8, 9] Thus, aminopyrazine (**5**) was brominated with NBS to afford selectively 2-amino-5-bromopyrazine (**6**) in 63% yield (Scheme 2). Diazotisation of **6** followed by hydrolysis gave a 48% yield of 2-hydroxy-5-bromopyrazine (**7**), which was found to be unreactive towards sodium methoxide in refluxing methanol, while it decomposed with the same reagent-solvent system in a sealed vessel at 140 °C for 3 h. In contrast, the nucleophilic methoxylation of **6** smoothly proceeded under the latter reaction conditions, providing a 60% yield of 2-amino-5-methoxypyrazine (**8**). Conversion of **8** into 2-hydroxy-5-methoxypyrazine (**2**) was achieved through diazotisation in sulfuric acid and subsequent warming, albeit in low yield, perhaps because of its instability to mineral acid like the 2,5-dihydroxypyrazines described above.

A convenient indication for the structural determination of isomeric disubstituted pyrazines should be the coupling constants of ring protons in $^1$H NMR spectra.[10] All compounds synthesised here exhibit the coupling constants of 1.3–1.5 Hz, which are typical in 2,5-disubstutued isomers. However,




**Scheme 1** Reaction sequence claimed to yield hydroxypyrazines.[7]

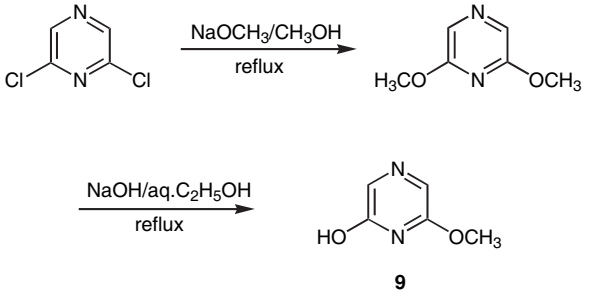
* Correspondent. E-mail: nbsato@yokohama-cu.ac.jp




**Scheme 2** Synthesis of 2-hydroxy-5-methoxypyrazine (2).

the substance claimed to be 2-hydroxy-5-methoxypyrazine showed no coupling between two protons in aromatic region, and the chemical shifts in $^{1}H$ and $^{13}C$ NMR spectra are inconsistent with those of our synthetic sample of **2** (Table 1).

Another possibility is that the substance proposed as **2** is 2-hydroxy-6-methoxypyrazine (**9**), because 2,6-disubstituted pyrazines normally show ring proton coupling constants of 0–0.5 Hz. Fortunately, this compound **9** is a known material which has been prepared by methoxylation of commercially available 2,6-dichloropyrazine and successive hydrolysis of the resulting dimethoxypyrazine (Scheme 3).[11] Compound **9** has also been obtained by hydrolysis of 2-acetoxy-6-methoxypyrazine.[12] Comparison of NMR spectral data (Table 1) revealed that the substance[7] under consideration was not identical with compound **9**. On the other hand, 2-hydroxy-3-methoxypyrazine (**4**) was claimed to be another product of the cycloaddition (see Scheme 1), and to be transformed into 2,3-dihydroxypyrazine (**3**). Those materials were still not identical with the compounds as proposed by comparison of their NMR spectral data with those of authentic samples which were previously synthesised in our laboratory[12,13] (Table 2). We were therefore prompted to reexamine the cycloaddition of methoxypyrazine with benzonitrile oxide according to the literature.[7] However, we were able neither to isolate nor detect hydroxy-methoxypyrazines **2** or **4**, although the formation of some products was recognised by TLC.




**Scheme 3** Synthesis of 2-hydroxy-6-methoxypyrazine (9).

**Table 1** NMR spectra of hydroxypyrazines **2** and **9** in DMSO-$d_6$

| | | **2**,[a] δ | **2**,[b] δ | **9**, δ |
|---|---|---|---|---|
| $^{1}H$ | $CH_3O$ | 3.98 | 3.81 | 3.85 |
| | H-3 | 8.14 | 7.76 | 7.73 |
| | H-5 | – | – | 7.65 |
| | H-6 | 7.97 | 7.68 | – |
| | (*J* value) | (0 Hz) | (1.4 Hz) | (0 Hz) |
| | OH | 11.23 | 10.79 | 11.44 |
| $^{13}C$ | $CH_3O$ | 54.90 | 53.6 | 53.3 |
| | C-2 | 153.23 | 155.4 | 158.3 |
| | C-3 | 142.36 | 128.4 | 123.2 |
| | C-5 | 148.50 | 154.5 | 123.4 |
| | C-6 | 140.60 | 127.6 | 158.6 |

[a]Reported.[7] [b]Present work.

**Table 2** NMR spectra of hydroxypyrazines **3** and **4** in DMSO-$d_6$

| | | **3**,[a] δ | **3**[b] δ | **4**[a] δ | **4**[b] δ |
|---|---|---|---|---|---|
| $^{1}H$ | $CH_3O$ | – | – | 4.01 | 3.81 |
| | H-5 | 6.64 | 6.25 | 7.00 | 6.79 |
| | H-6 | 6.64 | 6.25 | 6.91 | 6.95 |
| | (*J* value) | 0 Hz | 0 Hz | 4.2 Hz | 4.3 Hz |
| | OH | 11.42 | 11.13 | 12.64 | 11.84 |
| $^{13}C$ | $CH_3O$ | – | – | 53.50 | 53.4 |
| | C-2 | 153.86 | 156.8 | 152.54 | 150.8 |
| | C-3 | 153.86 | 156.8 | 158.28 | 156.3 |
| | C-5 | 119.34 | 109.2 | 112.36 | 118.1 |
| | C-6 | 119.34 | 109.2 | 119.72 | 119.8 |

[a]Reported.[7] [b]Present work.

An additional program that we undertook in this research was to verify the report[7] of the hydrolysis of methoxypyrazinol **2** to dihydroxypyrazine **1**. Since the conversion was asserted to be realised by treatment with 20% hydrochloric acid in refluxing ethanol for 6 h, our synthetic compound **2** was exposed to such acidic media. As expected, the hydroxypyrazine underwent extensive destruction to give no aromatic compounds. Indeed, 2,5-dihydroxypyrazine **1** has been reported in the literature,[14] but it was an unstable species in aqueous solution, and actually not isolated.

Finally, we find that the hydroxy-methoxypyrazines **2** and **4** cannot be identified as proposed,[7] but the compounds reported as possessing these structures could belong to a different class of heteroaromatic, because methoxypyrazines behave as efficient dienes in normal electron demand Diels–Alder reactions.[15,16]

## Experimental

All melting points were determined using a Büchi capillary apparatus. IR spectra were recorded on a Perkin Elmer Spectrum One. NMR spectra were obtained with a Bruker Avance 600 spectrometer and were referenced to TMS or residual proton signals in solvents. FAB MS spectra were determined on a Jeol JMS-700 instrument.

*2-Amino-5-bromopyrazine* (**6**): A solution of aminopyrazine **5** (3.00 g, 31.6 mmol) in dry dichloromethane (150 ml) was stirred and cooled to 0 °C, and NBS (5.62 g, 31 mmol) was portionwise added. The mixture was stirred at 0 °C for 24 h, and then saturated aqueous $Na_2CO_3$ (50 ml) was added to quench the reaction. The organic layer was washed with saturated aqueous $Na_2CO_3$ and then water. The solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50 g), using 4 : 1 hexane/EtOAc, to afford the bromopyrazinamine **6** (3.46 g, 63%) as needles, m.p. 112–113 °C (lit.[8] m.p. 113–114 °C) from cyclohexane. IR (KBr): $\nu_{max}$ 3183, 1631, 1568, 1463, 1379, 1103, 1012 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$) δ 4.64 (2H, s, $NH_2$), 7.77 (1H, d, *J* = 1.3 Hz, H-3), 8.09 (1H, d, *J* = 1.3 Hz, H-6); $^{13}C$ NMR ($CDCl_3$): δ 127.2 (C-5), 131.7 (C-3), 144.3 (C-6), 153.4 (C-2).

*5-Bromo-2-hydroxypyrazine* (**7**): Sodium nitrite (0.17 g, 2.5 mmol) was portionwise added with stirring to conc. sulfuric acid (0.9 ml) at 0 °C, and the mixture was warmed to dissolve the solid. The mixture was again cooled to 5 °C, and a solution of **6**

(0.360 g, 2.1 mol) in conc. sulfuric acid (1.6 ml) was added slowly. The mixture was stirred below 5 °C for 20 min, warmed to 40 °C, stirred at that temperature for 15 min, and then poured into ice-water (20 ml). The aqueous solution was extracted with ether (3 × 10 ml), and the extract was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g), using 4 : 1 hexane/EtOAc to give **7** (0.175 g, 48%) as needles, m.p. 115–116 °C, from cyclohexane. IR (KBr): $\nu_{max}$ 1645, 1585, 1230, 988, 886, 658, 615 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 1.3 Hz, H-3), 8.09 (1H, d, *J* = 1.3 Hz, H-6). $^{13}C$ NMR ($CDCl_3$): δ 120.6 (C-5), 131.6 (C-3), 144.8 (C-6), 158.0 (C-2). Anal. Calcd for $C_4H_3BrN_2O$: C, 27.46; H, 1.73; N, 16.01. Found: C, 27.89; H, 1.52; N, 15.76 %.

*2-Amino-5-methoxypyrazine* (**8**): A mixture of **6** (0.302 g, 1.74 mmol) in methanolic sodium methoxide, prepared from sodium (0.7 g, 30 mmol) and dry MeOH (35 ml), in a stainless steel sealed vessel was heated at 140 °C for 3 h. After cooling to r.t. the mixture was diluted with water (30 ml) and extracted with EtOAc (4 × 20 ml). The extract was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30 g), using 5:1 hexane/EtOAc, followed by HPLC (10 μm silica gel 3 × 30 cm), using 4:1 hexane/EtOAc, to give **8** (0.131 g, 60%), m.p. 106–107 °C (hexane) as pale yellow tiny needles (lit.[17] m.p. 111 °C). IR (KBr): $\nu_{max}$ 3294, 1623, 1493, 1387, 1281, 1031 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 3.88 (3H, s, $OCH_3$), 4.20 (2H, br s, $NH_2$), 7.56 (1H, d, *J* = 1.5 Hz, H-3), 7.77 (1H, d, *J* = 1.5 Hz, H-6). $^{13}C$ NMR ($CDCl_3$): δ 53.7 ($CH_3$), 126.2 (C-3), 130.9 (C-6), 149.4 (C-2), 154.9 (C-5). Anal. Calcd for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.24; H, 5.61; N, 33.70 %.

*2-Hydroxy-5-methoxypyrazine* (**2**): Sodium nitrite (0.053 g, 0.77 mmol) was portionwise added with stirring to conc. sulfuric acid (0.3 ml) at 0 °C, and the mixture was warmed to be dissolved. The mixture was again cooled to 5 °C, and a solution of **8** (0.073 g, 0.58 mmol) in conc. sulfuric acid (0.5 ml) was added slowly. The mixture was stirred below 5 °C for 20 min, warmed to 40 °C, stirred at that temperature for 10 min and poured into ice-water (100 ml). The aqueous solution was extracted with ether (3 × 10 ml), and the extract was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g), using 4:1 hexane/EtOAc, to give **2** (0.011 g, 15%), m.p. 155–159 °C, IR (KBr) $\nu_{max}$ 3018, 1496, 1316, 1151, 1038, 777 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.92 (3H, s, $CH_3$), 7.55 (1H, d, *J* = 1.3 Hz, H-6), 7.87 (1H, d, *J* = 1.3 Hz, H-3); $^{13}C$ NMR ($CDCl_3$) δ 54.3 ($CH_3$), 125.5 (C-6), 131.0 (C-3), 155.3 (C-5), 155.4 (C-2); MS (FAB) $[M-H]^-$ 125.1. Anal. Calcd for $C_5H_6N_2O_2$; C, 47.62; H, 4.80; N, 22.21. Found: C, 47.76; H, 4.86; N, 21.77%.

*2-Hydroxy-6-methoxypyrazine* (**9**): This compound was prepared by the literature procedure from 2,6-dimethoxypyrazine,[11] and also obtained by hydrolysis of 2-acetoxy-6-methoxypyrazine. A mixture of 2-acetoxy-6-methoxypyrazine[12] (0.038 g, 0.23 mmol) in MeOH (5 ml) containing 10% aqueous $K_2CO_3$ (2.5 ml) was stirred and refluxed for 1 h and then concentrated under reduced pressure. Water (2 ml) was added to the residue and the solution was adjusted to pH 5 with 6M hydrochloric acid. The mixture was cooled and the precipitate was collected by filtration to give the title product (0.018 g, 63%), m.p. 190 °C. IR (KBr): $\nu_{max}$ 1534, 1449, 1311, 1280, 1149, 845, 761 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 3.91 (3H, s, $CH_3$), 7.798 (1H, s), 7.805 (1H, s).

*Received 27 January 2005; accepted 13 June 2005*
*Paper 05/3037*

## References

1 Part 38: N. Sato and N. Narita, *Synthesis*, 2001, 1551.
2 J. Adachi and N. Sato, *J. Heterocycl. Chem.*, 1986, **23**, 871.
3 N. Sato and Y. Kato, *J. Heterocycl. Chem.*, 1986, **23**, 1677.
4 G. Karmas and P.E. Spoerri, *J. Am. Chem. Soc.*, 1957, **79**, 680.
5 K.W. Blake and P.G. Sammes, *J. Chem. Soc. (C)*, 1970, 980.
6 N. Sato, *Science of Synthesis: Pyrazines*, Vol. 16, ed. Y. Yamamoto, Thieme, Stuttgart, 2003, pp. 751–844.
7 A. Corsaro, U. Chiacchio, V. Pistarà and G. Perrini, *Heterocycles*, 2000, **53**, 69.
8 N. Sato, *J. Heterocycl. Chem.*, 1982, **19**, 673.
9 D.A. de Bie, A. Ostrowicz, G. Geurtsen and H.C. van der Plas, *Tetrahedron*, 1988, **44**, 2977.
10 R.H. Cox and A.A. Bothner-by, *J. Phys. Chem.*, 1968, **72**, 1646.
11 G.W.H. Cheeseman and E.S.G. Törzs, *J. Chem. Soc.*, 1965, 6681.
12 N. Sato, N. Miwa, H. Suzuki and T. Sakakibara, *J. Heterocycl. Chem.*, 1994, **31**, 1229.
13 J. Adachi and N. Sato, *J. Org. Chem.*, 1972, **37**, 221.
14 O.J. Mieden and C. von Sonntag, *Z. Naturforsch.*, 1989, **44B**, 959.
15 A.E.A. Porter and P.G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1970, 1103.
16 I.M. Dawson, A.J. Pappin, C.J. Peck and P.G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1989, 453.
17 G. Palamidessi, A. Vigevani and F. Zarini, *J. Heterocycl. Chem.*, 1974, **11**, 607.