Studies on Pyrazines. Part 25.[1] Lewis Acid-promoted Deoxidative Thiation of Pyrazine *N*-Oxides: New Protocol for the Synthesis of 3-Substituted Pyrazinethiols

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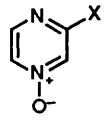
Reaction of 3-substituted pyrazine 1-oxides with *p*-methoxytoluene-α-thiol in the presence of diethylcarbamoyl chloride in refluxing acetonitrile gave the corresponding 3-substituted 2-(methoxybenzylthio)pyrazines. Based on these yields, the ease of substitution is remarkably affected by nucleophilicity of the *N*-oxide oxygen. Addition of zinc bromide to the reaction mixture increased the yields of thiation products of 3-methyl-, 3-phenyl-, 3-(*N*-butylcarbamoyl)-, 3-methoxycarbonyl- and the parent pyrazine 1-oxides, but their regioselectivities were rather low. The Lewis acid-mediated reaction of 3-methoxypyrazine 1-oxide gave a different major product, the 2,6-isomer. Conversion of the sulfides to pyrazinethiols was accomplished by mercuriation and successive reduction. This debenzylation was also found to be dependent on the electron density in the pyrazine ring.

A variety of 3-substituted pyrazinethiols, useful as intermediates for chemotherapeutics,[2] are usually synthesized from the corresponding chloropyrazines by treatment with thiourea or alkali hydrosulfide.[3] The starting halogeno compounds are practically accessible by chlorination of hydroxypyrazines or pyrazine *N*-oxides.[4] Direct thiation of these precursors then should serve as a more convenient method for synthesis of pyrazinethiols. Indeed, reaction of hydroxypyrazines with the Lawesson reagent gave thiols in high yields.[5] On the other hand, immediate formation of pyrazinethiol from the pyrazine *N*-oxide was deemed to be impracticable since there is no precedent for such a conversion to our knowledge. In addition, deoxidative nucleophilic substitution of pyrazine *N*-oxides with alkanethiols led only to low yields of the sulfides.[6] In this paper, we report the synthesis of 3-substituted pyrazinethiols by a two-step sequence of reaction commencing from the corresponding pyrazine *N*-oxides. Thus, the strategy in the transformation consists in thiation with 4-methoxytoluene-α-thiol in the initial stage followed by removal of the 4-methoxybenzyl group.

As an approach to the synthesis of pyrazinethiols, we first attempted a reaction of pyrazine *N*-oxides with potassium thiocyanate or *O*-ethyl xanthate in view of the accessibility of those sulfur nucleophiles and the ease of conversion into a mercapto group. Thiation of pyridine 1-oxide with butanethiol was shown to require the presence of a carboxylic acid anhydride or chloride such as dialkylcarbamoyl chloride or benzenesulfonyl chloride.[7] However, neither of the acid chlorides could stimulate the substitution of pyrazine *N*-oxides, resulting in recovery of only the starting materials. The use of diethyl phosphorochloridate was also problematical and led to complex products. Then we turned our attention to thiation with toluene-α-thiol or its derivatives because the *S*-benzyl group was expected to be easily cleaved under mild conditions to generate the thiol.[8] When 3-methoxypyrazine 1-oxide **1b** was conducted with 2 mol equiv. of 4-methoxytoluene-α-thiol **8** in refluxing acetic anhydride for 2 h, 2-(4-methoxybenzylthio)-3-methoxypyrazine **2b** was obtained in 62% yield. This method, however, suffered from a considerable decrease in the yields of sulfide **2** at the purification work-up stage by fractional distillation from the by-product, *S*-(4-methoxybenzyl) thioacetate. Meanwhile, treatment of 3-aminopyrazine 1-oxide **1a** under the same conditions furnished only a 10% yield of 2-diacetylamino-3-(4-methoxybenzylthio)pyrazine **9**. The extreme reduction of yield is probably attributed to an electronic influence of the diacetylamino moiety formed initially, rather than a steric impediment of the substituent, because compound **9** was quantitatively prepared by acetylation of 2-amino-3-(4-methoxybenzylthio)pyrazine **2a** synthesized afterwards. An attempt to prolong the reaction time to 5 h resulted in no improvement in the yield.



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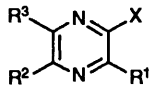
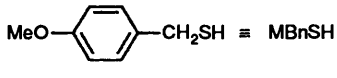
a; X = NH_2
b; X = OMe
c; X = Ph
d; X = Me
e; X = H
f; X = Cl
g; X = CONHBu
h; X = CO_2Me



2 R^1 = MBnS, R^2 = R^3 = H
3 R^1 = R^3 = H, R^2 = MBnS
4 R^1 = R^2 = H, R^3 = MBnS
5 R^1 = SH, R^2 = R^3 = H
6 R^1 = R^3 = H, R^2 = SH
7 R^1 = R^2 = H, R^3 = SH
9 X = NAc_2, R^1 = MBnS, R^2 = R^3 = H
10 X = NH_2, R^1 = Cl, R^2 = R^3 = H
11 X = NHAc, R^1 = SH, R^2 = R^3 = H



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Instead of acetic anhydride, several acid chlorides and trimethylsilyl chloride were examined for the thiation of *N*-oxide **1a**, and these results are summarized in Table 1. The best yield of 92% for sulfide **2a** was achieved by treatment with diethylcarbamoyl chloride in refluxing acetonitrile. Diethyl phosphorochloridate and trimethylsilyl chloride were also effective in the presence of triethylamine to afford compound **2a** in 78 and 60% yield, respectively. However, reaction of compound **1a** with tosyl chloride led not to the sulfide **2a** but to 2-amino-3-chloropyrazine **10** in low yield. In comparison with diethylcarbamoyl chloride, its methyl homologue decreased the yield of compound **2a** to 57% owing mainly to dispersion of volatile dimethylamine formed along with the cleavage of the nitrogen–oxygen bond as shown in Scheme 1. For entries 3 and 5, the yields of compound **2a** are reduced by triethylamine on treating the oxide **1a** with dialkylcarbamoyl chlorides. This decrease can presumably be ascribed to rapid consumption of the toluenethiol **8** by acylation with the carbamoyl chloride in

Table 1 Reaction of pyrazine *N*-oxide **1a** with 4-methoxytoluene-α-thiol **8** in refluxing acetonitrile[a]

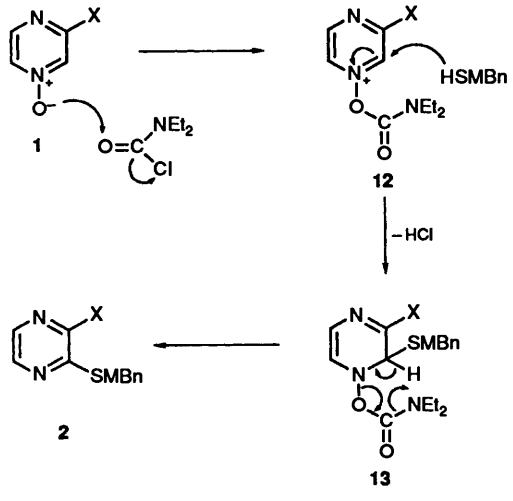
Entry	Reagent system	Time (t/h)	Product	Yield (%)	Recovered (%)
1	Et_2NCOCl	6	**2a**	92	0
2	Et_2NCOCl[b]	6	**2a**[c]	76	0
3	Et_2NCOCl/TEA	6	**2a**	77	*d*
4	Me_2NCOCl	6	**2a**	57	16
5	Me_2NCOCL/TEA	6	**2a**	36	50
6	$(EtO)_2POCl$	20	**2a**	20	*d*
			10	20	
7	$(EtO)_2POCl$/TEA	36	**2a**	78	21
8	TMSCl	20		0	62
9	TMSCl/TEA	24	**2a**	60	16
10	TsCl	20	**10**	34	*d*
11	TsCl/TEA	24	**10**	40	*d*

[a] TEA: triethylamine. [b] Toluene-α-thiol was used instead of thiol **8**. [c] This product is 2-amino-3-(benzylthio)pyrazine. [d] The starting *N*-oxide was detected by TLC but could not be isolated from unidentified materials.

Table 2 Deoxidative thiation of pyrazine *N*-oxides **1b–h**

Substrate	Method[a]	Product and yield (%) 2	3	4	Total yield (%)	Recovered (%)
1b	A	58	0	21	79	20
	A[b]	62	0	23	85	10
	B	*c*	0	60	> 60	0
	B[d]	*c*	0	57	> 57	0
	C	56	0	1	57	38
1c	A	63	24	0	87	12
	B	21[e]	38[f]	41[e]	< 100	0
1d	A	67	6	1	74	29[f]
	B	71	3	11	85	0
1e	A	——67——			67	33
	B	——78——			78	0
1f	A	33	0	0	35[g]	64
	B	≈0	0	0	≈0	0
1g	A	5	40	10	55	32
	B	0	32[e,h]	46[e,h]	78	0
1h	A	9	26	14	49	48
	B	0	49	24	73	0
	C	7	32	3	37	57

[a] A: With 2 mol equiv. each of thiol **8** and Et_2NCOCl in refluxing MeCN for 6 h. B: With 2 mol equiv. each of thiol **8**, Et_2NCOCl and $ZnBr_2$ in refluxing MeCN for 6 h. C: With 1.5 mol equiv. each of thiol **8** and $(EtO)_2POCl$ and 3 mol equiv. of TEA in refluxing MeCN for 36 h. [b] Reaction time: 18 h. [c] Exact yield could not be obtained because of contamination with unidentified materials. [d] With 1 mol equiv. each of thiol **8**, Et_2NCOCl and $ZnBr_2$ in refluxing MeCN for 6 h. [e] The ratio was determined from the ^1H NMR spectrum. [f] A small amount of unidentified material was present as a contaminant. [g] A 2% yield of bis-(4-methoxybenzylthio)pyrazine was also obtained. [h] Purified by Kugelrohr distillation. The ratio of compounds **3g** and **4g** in the crude product was ~1:1.



Scheme 1

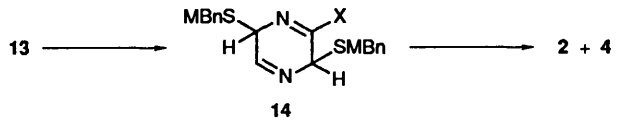
the presence of the base. In a similar fashion, acetylation of adamantane-1-thiol is strongly catalysed by triethylamine.[9] It can be concluded that thiation of pyrazine *N*-oxides proceeds more slowly than that of pyridine *N*-oxides because the latter heterocycles give approximately equal yields of the sulfides in spite of the presence of the base.[7] The sulfur nucleophile 4-methoxytoluene-α-thiol **8** was ascertained to be superior to the parent toluene-α-thiol as shown in entry 2. Accordingly, the reaction conditions exhibited in entry 1 were employed for the thiation reactions.

Our earlier work on cyanation of the pyrazine *N*-oxides with trimethylsilyl cyanide[10] shows that electron-donating groups enhance the nucleophilicity of the *N*-oxide oxygen, resulting in highly regioselective formation of 2-substituted 3-cyanopyrazines. Namely, attack of the *N*-oxide oxygen on trimethylsilyl cyanide is the rate-determining step. This conclusion is firmly supported from the reactivity increase observed upon addition of a zinc halide to the reaction mixture. Conversely, the *N*-oxides carrying an electron-withdrawing methoxycarbonyl or other group underwent the rate-determining attack of cyanide ion prior to trimethylsilylation of the *N*-oxide oxygen. In these cases, therefore, use of the Lewis acid had no effect on the yields and regioselectivities.

Inspection of Table 2 shows the clear substituent effect on reactivity in thiation. Electron-donating groups facilitate the substitution reaction more easily than in the case of the parent

N-oxide **1e**, while an *N*-butylcarbamoyl and a methoxycarbonyl substituents suppress thiation to some degree. Compared with the yields of substitution products and the recovered amount of the starting *N*-oxide, 3-chloropyrazine 1-oxide **1f** seems to be the least reactive of all. Addition of zinc bromide to the thiation mixture prompted complete consumption of the starting *N*-oxides **1** within the given reaction period, to increase the yield of the sulfides except for **1a**, **1b** and **1f**. A noteworthy aspect is that the zinc bromide-mediated reaction encouraged the substitution in substrates **1g** and **1h** bearing a *N*-butylcarbamoyl and a methoxycarbonyl group, respectively, unlike in the above cyanation. Zinc bromide probably co-ordinates with diethylcarbamoyl chloride rather than with the *N*-oxide oxygen, to form a more reactive acylium complex. The observed sequence of reactivity indicates that the thiation depends upon the nucleophilicity of the *N*-oxide oxygen, which proceeds in the same manner as that involved the rate-determining silylation despite either the electron-donating or the electron-withdrawing category of the substituent. On the basis of semiempirical AM1 molecular orbital calculations for 3-substituted pyrazine 1-oxides, the coefficients and charges of the *N*-oxide oxygens as well as the energy levels of HOMO orbitals show their order of nucleophilicity to be **1a** > **1b** > **1h** > **1f**,[11] which is in agreement with the observed reactivities. On the other hand, the addition of the Lewis acid complicated the reaction of substrate **1a**, producing a large amount of unidentified material. Under the above conditions, thiation of compound **1b** was also intricate, but surprisingly the 2,6-isomeric sulfide **4b** was obtained in 60% yield. Another isomer, compound **2b**, could not be isolated after a difficult separation from unidentified by-products, although its formation was established by ^{1}H NMR spectroscopy; its yield is believed to be low. A failure in thiation of substrate **1f** resulted from the probable consumption of reagent **8** by acylation with diethylcarbamoyl chloride–zinc bromide complex prior to reaction with compound **1f** because of the lowered reactivity of the *N*-oxide oxygen.

As in the above cyanation, an electron-donating group leads to a preferred substitution at the C-2 carbon which is the seemingly more hindered α-position with respect to the *N*-oxide function, and an electron-withdrawing *N*-butylcarbamoyl or methoxycarbonyl group favours C-6 α-substitution. Albeit in low yields, substitution on the β-carbon was also observed for the thiation of pyrazine *N*-oxides except for compound **1a**. A mechanism of β-substitution for chlorination[12] or cyanation[10] was proposed, modification of which for the thiation involves a common intermediate **14** for α- and β-substituted products, shown in Scheme 2, or its 5,6-bis(methoxybenzylthio)isomer. In the case of thiation, a different intermediate, the episulfonium ion **16** illustrated in Scheme 3, is additionally feasible. This type of intermediate was first devised for the deoxidative thiation of pyridine *N*-oxides.[13] Apparently, the formation of an episulfonium ring seemed to be much more possible for the pyrazine series because the C-5 carbon of the precursor **15** is perhaps susceptible to attack of the neighbouring sulfide due to an electron-withdrawing effect of the ring nitrogen at N-4. As a matter of course, the annulation to give intermediate **16** from the 3-substituted pyrazine 1-oxides **1** needs an initial nucleophilic substitution at the C-6 carbon. On the thiation of phenylpyrazine *N*-oxide **1c**, however, the β-thiated product **4c** could not be detected at all whereas the isomeric sulfide **3c** as the α-substituted product was obtained in **24**% yield. A more notable finding is the non-formation of the 2,5-disubstituted pyrazine **3b** in the thiation of compound **1b** by diethyl phosphorochloridate in the presence of triethylamine. This reagent system promotes the abstraction of hydrogen from the 1,2-dihydropyrazine intermediates analogous to species **13** and **15** due to the stronger reinforcing effect of the diethyl phosphate group.[10] In other words, those products are kinetically favoured



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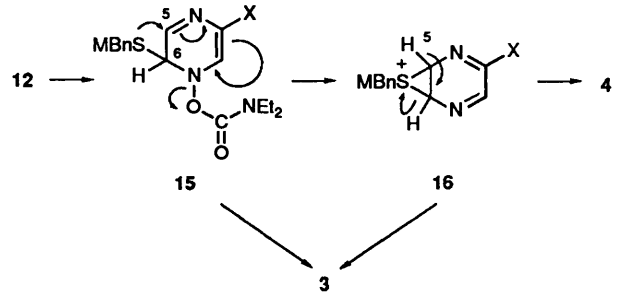
Scheme 2



15 **16**

3

Scheme 3

ones, whose regioselectivity vividly reflects the site where the nucleophilic attack occurs initially.

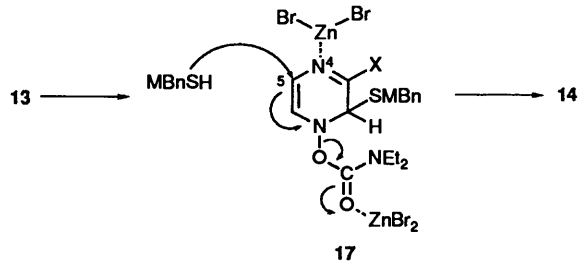
On the other hand, an electron-withdrawing group leads to preferable formation of the 2,5-disubstituted pyrazine **3**. The substituent could conceivably enhance the formation of the episulfonium ring because the resulting electron-deficient intermediate **15** should be susceptible to nucleophilic attack of the adjacent sulfide. In addition, elimination of hydrogen from C-5 of intermediate **16** would be accelerated by the mesomeric electron-withdrawing effect of the *N*-butylcarbamoyl or methoxycarbonyl group, leading to most regiospecific formation of the 2,6-disubstituted pyrazine.[12] The logical deduction, however, is clearly opposite to the regiochemistries observed in thiation of substrates **1g** and **1h**. As a result of the above, formation of the β-substituted pyrazine **4** is likely to proceed *via* the intermediate **14** or its isomer rather than *via* the episulfonium ring **16**. On the thiation of pyridine *N*-oxides with acetic anhydride,[14] the episulfonium intermediate was confirmed by isolation of diacetoxy alkylthio- or acetoxy dialkylthio-substituted tetrahydropyridines as minor products. In the case of pyrazine *N*-oxides, close scrutiny of all chromatographic fractions failed to detect the presence of any such products. Which of the intermediates **14** and **16** is favourable for the β-thiation may be influenced by the reagent–solvent system as well as the substrates; this will be described in a future study.

The zinc bromide-mediated thiation raises the proportion of β-substitution, in particular of substrates **1b** and **1c**, though it lowers the regioselectivity in most cases. Under identical conditions but in the presence of triethylamine, 3-methoxy- and 3-phenyl-pyridine 1-oxides underwent thiation at the α-carbon in ~80% yield. In addition, the former *N*-oxide furnished the β-(4-methoxybenzylthio)pyridine in 4% yield which was suppressed to less than one-fifth of that obtained without the Lewis acid.[15] Consequently, the driving force for the enhanced formation of β-substituted products in the pyrazine series ought to be the co-ordination of zinc bromide to the unoxidized nitrogen atom at N-4, as depicted in structure **17** in Scheme 4. Thus, the resulting electron-deficient nitrogen facilitates the second nucleophilic attack on the adjacent carbon at C-5 by thiol **8** to generate the dihydropyrazine intermediate **14**. In the controlled reaction using 1 mol equiv. each of thiol **8** and zinc bromide, the yield and regioselectivity in thiation of substrate **1b** were nearly equal to those obtained with a two-fold amount of the reagents (see Table 2), implying that the co-ordination is faster than other processes affected by the Lewis acid. Another feature in the zinc bromide-mediated reaction is the decrease in proportion of the 2,3-disubstituted product **2** in contrast to the 2,5-isomer **3** which increases in yield, compared with the

Table 3 Conversion of sulfides into thiols

Sulfide	Method[a]	Product	Yield (%)
2a	B	**5a**	38
9	A	**17**	50
2b	A	**5b**	87
2e	A	**5e**	38
3h	A	**6h**	22

[a] A: With $Hg(OAc)_2$ in TFA containing anisole at 0 °C followed by sodium borohydride reduction. B: With refluxing conc. hydrochloric acid.



Scheme 4

thiation without the Lewis acid. This phenomenon suggests that the β-thiated pyrazines are easily formed from intermediate **13** *via* the intermediate **14** but scarcely from the 5-isomeric intermediate **15**. We have not yet devised a mechanism which could account for this behaviour, but a tentative conclusion is that the relative proportions in the formation of those products are affected by their thermodynamical stabilities.

Debenzylation of the sulfide **2b** was achieved by mercuriation [16] and then by sodium borohydride reduction to give thiol **5b** in 87% yield. Similarly, sulfides **2e** and **3h** were converted into the corresponding thiols, and these results are summarized in Table 3. Identification as 3-substituted pyrazinethiols is conveniently accomplished by their characteristic coupling constants of 3.8–4.1 Hz between the ring protons in the ^1H NMR spectrum, which are larger than those (2.4–2.9 Hz) in almost all other 2,3-isomers.[17] When the sulfide **1a** was debenzylated under the above conditions, only a small amount of bis-(3-aminopyrazinyl) disulfide was obtained. The identical reaction of diacetylamino compound **9** furnished a 50% yield of 2-acetamino-3-mercaptopyrazine **11**. Direct formation of thiol **5a** from substrate **2a** was only successful when the reaction was conducted in refluxing conc. hydrochloric acid,[9] and proceeded in 38% yield. Numerous attempts at debenzylation, *e.g.*, homolytic cleavage or catalytic hydrogenolysis, failed and in most cases the starting sulfides were recovered. Demethylation of the methoxybenzyl moiety is expected to facilitate debenzylation, but reaction with trimethylsilyl bromide or boron trichloride did not occur. As the pyridine series are more easily cleaved, to afford higher yields of pyridinethiols,[15] the observed outcome suggests that debenzylation is enhanced by an electron-donating substituent.

Experimental

M.p.s were determined using a Büchi 535 apparatus and are uncorrected. B.p.s are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrometer. NMR spectra were obtained with a JEOL JNM EX270 (270 MHz ^1H, 67.8 MHz ^{13}C) instrument with solutions in $CDCl_3$, unless otherwise noted, containing Me_4Si as internal standard. *J* Values are given in Hz.

General Procedure of Thiation of Pyrazine N-*Oxides* **1** *with* 4-*Methoxytoluene-α-thiol* **8**.—An *N*-oxide **1** (1 mmol) or the mixture with $ZnBr_2$ (2 mmol) was purged by passage of argon after evacuation of air, and then MeCN (7 cm^3), 4-methoxytoluene-α-thiol **8** (0.28 cm^3, 2 mmol), and finally diethylcarbamoyl chloride (0.25 cm^3, 2 mmol) were added *via* a syringe. The mixture was refluxed and stirred for 6 h and then evaporated under reduced pressure. The residue was subjected to flash chromatography on SiO_2 (20 g) or to HPLC on a pre-packed column (2.2 × 30 cm; 10 μm SiO_2), and eluted with hexane–ethyl acetate (5:1 to 3:1).

The following compounds were obtained by the above procedure.

2-*Amino*-3-(4-*methoxybenzylthio*)*pyrazine* **2a**. As needles, m.p. 82–83 °C (from hexane) (Found: C, 58.3; H, 5.2; N, 17.1. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.3; N, 17.0%); ν_{max}(KBr)/cm^{-1} 3440, 1620, 1510, 1420 and 1100; δ_H 3.76 (3 H, s), 4.41 (2 H, s), 4.80 (2 H, br s), 6.82 (2 H, d, *J* 8.7), 7.26 (2 H, d), 7.72 (1 H, d, *J* 2.6) and 7.83 (1 H, d); δ_C 33.8, 55.1, 113.9, 129.1, 130.1, 133.6, 137.2, 140.9, 151.6 and 158.8.

2-*Methoxy*-3-(4-*methoxybenzylthio*)*pyrazine* **2b**. As plates; m.p. 67 °C (from hexane) (Found: C, 59.5; H, 5.4; N, 10.8. $C_{13}H_{14}N_2O_2S$ requires C, 59.5; H, 5.4; N, 10.7%); ν_{max}(KBr)/cm^{-1} 2930, 1605, 1505, 1360 and 1100; δ_H 3.78 (3 H, s), 4.00 (3 H, s), 4.36 (2 H, s), 6.83 (2 H, d, *J* 8.6), 7.34 (2 H, d), 7.76 (1 H, d, *J* 3.0) and 7.97 (1 H, d); δ_C 32.6, 53.9, 55.3, 113.9, 129.2, 130.3, 134.9, 135.5, 146.5, 156.4 and 158.8.

2-*Methoxy*-6-(4-*methoxybenzylthio*)*pyrazine* **4b**. As an oil; b.p. 165 °C/3 mmHg (Kugelrohr) (Found: C, 59.5; H, 5.6; N, 10.2%); ν_{max}(neat)/cm^{-1} 2950, 1610, 1510, 1390 and 1300; δ_H 3.76 (3 H, s), 3.96 (3 H, s), 4.34 (2 H, s), 6.82 (2 H, d, *J* 8.7), 7.29 (2 H, d), 7.86 (1 H, s) and 7.99 (1 H, s); δ_C 33.5, 53.5, 55.1, 113.8, 129.0, 129.6, 129.7, 134.1, 152.5, 158.7 and 159.6.

2-(4-*Methoxybenzylthio*)-3-*phenylpyrazine* **2c**. As pale yellow needles; m.p. 98–99.5 °C (from hexane) (Found: C, 70.0; H, 5.2; N, 9.1. $C_{18}H_{16}N_2OS$ requires C, 70.1; H, 5.2; N, 9.1%); ν_{max}(KBr)/cm^{-1} 1600, 1440, 1340, 1230, 1100 and 1030; δ_H 3.77 (3 H, s), 4.34 (2 H, s), 6.81 (2 H, dd, *J* 8.6 and 3.0), 7.30 (2 H, dd), 7.42–7.49 (3 H, m), 7.67–7.72 (2 H, m), 8.31 (1 H, d, *J* 2.6) and 8.36 (1 H, d); δ_C 34.5, 55.2, 113.9, 128.4, 128.8, 128.9, 129.4, 130.4, 137.2, 138.7, 141.7, 152.5, 155.2 and 158.8.

2-(4-*Methoxybenzylthio*)-5-*phenylpyrazine* **3c**. As needles; m.p. 146.5–147.5 °C (from hexane) (Found: C, 69.8; H, 5.2; N, 8.8%); ν_{max}(KBr)/cm^{-1} 1600, 1460, 1300, 1230, 1120, 1020 and 1000; δ_H 3.78 (3 H, s), 4.42 (2 H, s), 6.84 (2 H, d, *J* 8.6), 7.34 (2 H, d), 7.46–7.49 (3 H, m), 7.94–7.98 (2 H, s), 8.47 (1 H, d, *J* 1.7) and 8.84 (1 H, d); δ_C 33.8, 55.3, 114.0, 126.4, 129.0, 129.2, 129.3, 130.1, 136.2, 140.8, 142.8, 148.0, 154.5 and 158.9.

2-*Methyl*-3-(4-*methoxybenzylthio*)*pyrazine* **2d**. As needles; m.p. 44–45 °C (from hexane) (Found: C, 63.4; H, 5.5; N, 11.4. $C_{13}H_{14}N_2OS$ requires C, 63.4; H, 5.7; N, 11.4%); ν_{max}(KBr)/cm^{-1} 1610, 1510, 1380, 1250 and 1100; δ_H 2.47 (3 H, s), 3.79 (3 H, s), 4.39 (2 H, s), 6.84 (2 H, d, *J* 8.6), 7.34 (2 H, d), 8.12 (1 H, d, *J* 2.7) and 8.24 (1 H, d); δ_C 21.5, 33.4, 55.3, 114.0, 129.2, 130.2, 138.3, 140.9, 151.3, 155.6 and 158.9.

2-(4-*Methoxybenzylthio*)*pyrazine* **2e** (≡ **3e** ≡ **4e**). As pale yellow plates; m.p. 67–68 °C (from hexane) (Found: C, 62.1; H, 4.9; N, 12.0. $C_{12}H_{12}N_2OS$ requires C, 62.1; H, 5.2; N, 12.1%); ν_{max}(KBr)/cm^{-1} 1610, 1510, 1260, 1130 and 1000; δ_H 3.78 (3 H, s), 4.38 (2 H, s), 6.84 (2 H, d, *J* 8.8), 7.32 (2 H, d), 8.21 (1 H, d, *J* 0.3), 8.38 (1 H, dd, *J* 1.4 and 0.3) and 8.42 (1 H, d, *J* 1.4); δ_C 33.6, 55.3, 114.0, 129.1, 130.2 (2 C), 139.6, 143.8, 156.9 and 159.0.

N-*Butyl*-5-(4-*methoxybenzylthio*)*pyrazinecarboxamide* **3g**. As needles; m.p. 106–109 °C (from hexane) (Found: C, 61.5; H, 6.4; N, 12.6. $C_{17}H_{21}N_3O_2S$ requires C, 61.6; H, 6.4; N, 12.7%); ν_{max}(KBr)/cm^{-1} 3350, 2900, 1640, 1600, 1490 and 1230; δ_H 0.95 (3 H, t), 1.41 (2 H, sextet), 1.61 (2 H, quintet), 3.46 (2 H, q), 3.78 (3 H, s), 4.43 (2 H, s), 6.83 (2 H, d, *J* 8.9), 7.32 (2 H, d), 7.66 (1 H, br s), 8.28 (1 H, d, *J* 1.7) and 9.16 (1 H, d); δ_C 13.7, 20.1, 31.6, 33.5, 39.0, 55.2, 114.0 (2 C), 128.6, 130.2 (2 C), 139.7, 140.8, 143.2, 159.0, 160.0 and 163.2.

Methyl 5-(4-*methoxybenzylthio*)*pyrazinecarboxylate* **3h**. As pale yellow crystals; m.p. 105–106 °C (from hexane) (Found: C, 57.9; H, 4.6; N, 9.5. $C_{14}H_{14}N_2O_3S$ requires C, 57.9; H, 4.9; N, 9.7%); ν_{max}(KBr)/cm^{-1} 1730, 1610, 1520, 1510, 1300 and 1150; δ_H 3.79 (3 H, s), 4.01 (3 H, s), 4.44 (2 H, s), 6.84 (2 H, d, *J* 8.7), 7.33 (2 H, d), 8.48 (1 H, d, *J* 1.4) and 9.08 (1 H, d); δ_C 33.6, 52.8, 55.2, 114.1, 128.3, 130.2, 137.8, 142.7, 145.3, 159.1, 161.6 and 164.8.

The following materials could not be isolated or obtained in sufficient quantity for analysis so that only their NMR spectral data are given.

2-(4-Methoxybenzylthio)-6-phenylpyrazine **4c**. δ_H 3.77 (3 H, s), 4.34 (2 H, s), 6.81 (2 H, dd, *J* 8.6 and 3.0), 7.30 (2 H, dd), 7.42–7.49 (3 H, m), 7.67–7.72 (2 H, m), 8.34 (1 H, s) and 8.66 (1 H, s).

2-(4-Methoxybenzylthio)-5-methylpyrazine **3d**. δ_H 2.47 (3 H, s), 3.79 (3 H, s), 4.39 (2 H, s), 6.84 (2 H, d, *J* 8.7), 7.34 (2 H, d), 8.28 (1 H, d, *J* 1.7) and 8.32 (1 H, d).

2-(4-Methoxybenzylthio)-6-methylpyrazine **4d**. δ_H 2.47 (3 H, s), 3.79 (3 H, s), 4.39 (2 H, s), 6.84 (2 H, d, *J* 8.8), 7.34 (2 H, d), 8.07 (1 H, s) and 8.22 (1 H, s).

2-Chloro-3-(4-methoxybenzylthio)pyrazine **2f**. δ_H 3.78 (3 H, s), 4.35 (2 H, s), 6.84 (2 H, d, *J* 8.4), 7.33 (2 H, d), 8.01 (1 H, d, *J* 2.7) and 8.30 (1 H, d).

Bis-(4-methoxybenzylthio)pyrazine. δ_H 3.78 (6 H, s), 4.39 (4 H, s), 6.82 (4 H, d, *J* 8.9), 7.31 (4 H, d) and 8.08 (2 H, s).

N-Butyl-3-(4-methoxybenzylthio)pyrazinecarboxamide **2g**. δ_H 0.95 (3 H, t), 1.41 (2 H, sextet), 1.61 (2 H, quintet), 3.46 (2 H, q), 3.78 (3 H, s), 4.43 (2 H, s), 6.83 (2 H, d, *J* 8.9), 7.32 (2 H, d), 7.66 (1 H, br s), 8.15 (1 H, d, *J* 2.3) and 8.52 (1 H, d).

N-Butyl-6-(4-methoxybenzylthio)pyrazinecarboxamide **4g**. δ_H 0.96 (3 H, s), 1.40 (2 H, sextet), 1.60 (2 H, quintet), 3.45 (2 H, q), 3.79 (3 H, s), 4.36 (2 H, s), 6.86 (2 H, d, *J* 8.9), 7.32 (2 H, d), 7.52 (1 H, br s), 8.57 (1 H, s) and 9.00 (1 H, s).

Methyl 3-(4-methoxybenzylthio)pyrazinecarboxylate **2h**. δ_H 3.78 (3 H, s), 4.00 (3 H, s), 4.36 (2 H, s), 6.83 (2 H, d, *J* 8.9), 7.34 (2 H, d), 8.35 (1 H, d, *J* 2.3) and 8.56 (1 H, d).

Methyl 6-(4-methoxybenzylthio)pyrazinecarboxylate **4h**. δ_H 3.79 (3 H, s), 4.04 (3 H, s), 4.43 (2 H, s), 6.83 (2 H, d, *J* 8.5), 7.41 (2 H, d), 8.53 (1 H, s) and 8.88 (1 H, s).

2-*Diacetylamino*-3-(4-*methoxybenzylthio*)*pyrazine* **9**.—A mixture of sulfide **2a** (1.343 g, 5.4 mmol) in acetic anhydride (6 cm^3) containing 4-(dimethylamino)pyridine (8 mg) was stirred and heated at 70 °C for 3 h. After cooling to room temperature, the solution was evaporated under reduced pressure and the residue was chromatographed on SiO_2 (15 g) and eluted with hexane–ethyl acetate (1:1) to give the *title compound* **9** (1.726 g, 96%) as light tan oil, b.p. 180 °C/3 mmHg (Kugelrohr) (Found: C, 57.8; H, 5.1; N, 12.7. $C_{16}H_{17}N_3O_3S$ requires C, 58.0; H, 5.2; N, 12.7%); ν_{max}(neat)/cm^{-1} 1720, 1510, 1360, 1240 and 1220; δ_H 2.23 (6 H, s), 3.78 (3 H, s), 4.38 (2 H, s), 6.83 (2 H, d, *J* 8.9), 7.28 (2 H, d), 8.26 (1 H, d, *J* 2.4) and 8.47 (1 H, d); δ_C 26.1, 33.7, 55.2, 114.0, 128.1, 130.2, 138.5, 144.0, 146.0, 156.6, 159.1 and 171.5.

General Procedure of Debenzylation of Pyrazinyl Sulfides **2**, **3** *and* **11**.—A mixture of sulfide (0.5 mmol) in trifluoroacetic acid (TFA) (6 cm^3) containing anisole (0.13 cm^3) was cooled at 0 °C and stirred, and mercury(II) acetate (0.159 g, 0.5 mmol) was added in small portions. The resulting mixture was stirred at 0 °C for 15 min and then evaporated at room temperature under reduced pressure. The residue was dissolved in 0.2 mol dm^{-3} aq. sodium hydroxide and then $NaBH_4$ (0.095 g, 2.5 mmol) was added. After the mixture had been stirred at room temperature for 1.5 h, insoluble matter was removed by filtration. The filtrate was acidified to pH 5 (Merck Universal indicator sticks) with acetic acid, and the precipitate was collected by filtration and washed with a small amount of chloroform. For compound **5b**, the acidified solution was extracted with chloroform (20 cm^3 × 3), and the crude product obtained after evaporation was purified by chromatography on SiO_2. In the case of compound **11**, the filtrate was evaporated under reduced pressure after the acidification. The residue was extracted with hot ethyl acetate (250 cm^3 × 2) and the extract was evaporated. The resulting tarry material was washed successively with a small amount of ethyl acetate and then with chloroform to give the pyrazinethiol **11**.

The following compounds were obtained by the above procedure.

3-(*Acetylamino*)*pyrazinethiol* **11**. As pale yellow needles, m.p. 205 °C (decomp.) (from ethyl acetate) (Found: C, 42.5; H, 3.7; N, 24.5. $C_6H_7N_3OS$ requires C, 42.6; H, 4.2; N, 24.8%); ν_{max}(KBr)/cm^{-1} 1700, 1610, 1560, 1520 and 1270; δ_H[$(CD_3)_2SO$] 2.36 (3 H, s), 7.46 (1 H, d, *J* 4.1), 7.61 (1 H, d), 9.70 (1 H, s) and 14.53 (1 H, br s); δ_C[$(CD_3)_2SO$] 39.5, 138.7, 143.2, 166.1, 178.4 and 183.7.

3-*Methoxypyrazinethiol* **5b**. As yellow tiny needles, m.p. 186–187 °C (from cyclohexane) (Found: C, 42.5; H, 4.2; N, 19.5. $C_5H_6N_2OS$ requires C, 42.2; H, 4.25; N, 19.7%); ν_{max}(KBr)/cm^{-1} 1590, 1480, 1310, 1110, 1000 and 780; δ_H[$(CD_3)_2SO$] 3.86 (3 H, s), 7.28 (1 H, d, *J* 4.0), 7.37 (1 H, d) and 14.05 (1 H, br s); δ_C[$(CD_3)_2SO$] 54.4, 122.7, 126.3, 161.4 and 165.7.

Pyrazinethiol **5e** (≡ **6e** ≡ **7e**). As yellow prisms, m.p. 220 °C (decomp.) (from ethanol) [lit.,[18] 229 °C (decomp.)]; ν_{max}(KBr)/cm^{-1} 1660, 1200, 1180, 840 and 720; δ_H[$(CD_3)_2SO$] 7.61 (1 H, d, *J* 3.0), 7.79 (1 H, d, *J* 4.1), 8.52 (1 H, s) and 11.0 (1 H, br s).

Methyl 5-*mercaptopyrazinecarboxylate* **6h**. As tan flakes, m.p. 165–173 °C (decomp.) (from ethanol) (Found: C, 41.9; H, 3.3; N, 16.2. $C_6H_6N_2O_2S$ requires C, 42.35; H, 3.55; N, 16.5%); ν_{max}(KBr)/cm^{-1} 1720, 1560, 1320, 1200, 1160 and 960; δ_H[$(CD_3)_2SO$] 3.82 (3 H, s), 8.07 (1 H, s), 8.49 (1 H, s) and 14.61 (1 H, br s); δ_C[$(CD_3)_2SO$] 52.1, 129.5, 133.4, 156.0, 163.4 and 175.9.

3-*Aminopyrazinethiol* **5a**.—A mixture of sulfide **2a** (0.123 g, 0.5 mmol) in conc. hydrochloric acid (7 cm^3) was stirred and refluxed for 1 h. After being cooled to room temperature, the mixture was filtered to remove insoluble matter and was then evaporated under reduced pressure. The residue was dissolved in water and the solution was basified with 6 mol dm^{-3} aq. sodium hydroxide. Insoluble material was removed by filtration and the filtrate was acidified to pH 6 with acetic acid. The filtrate was evaporated under reduced pressure and the residue was extracted with hot chloroform. The crude product was purified by chromatography on SiO_2 (20 g) and eluted with hexane–ethyl acetate (1:4), m.p. 235–245 °C (decomp.) (from ethanol) [lit.,[19] 260–261 °C (decomp.)]; ν_{max}(KBr)/cm^{-1} 3400, 1600, 1340, 1130 and 760; δ_H[$(CD_3)_2SO$] 6.94 (1 H, d, *J* 4.1), 7.27 (1 H, d, *J* 3.8 + 2 H, br s) and 13.76 (1 H, br s); δ_C[$(CD_3)_2SO$] 117.1, 129.6, 158.0 and 161.8.

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References

1 Part 24, N. Sato and N. Matsui, *J. Heterocycl. Chem.*, in the press.

2 J. H. Jones, W. J. Holtz and E. J. Cragoe, Jr., *J. Med. Chem.*, 1969, **12**, 285; E. J. Cragoe, Jr. and J. H. Jones, *US Pat.*, 3 472 848, 1969 (*Chem. Abstr.*, 1970, **72**, 21708); A. Klausener and D. Haebich, *Ger. Pat.*, DE 3 641 869, 1988 (*Chem. Abstr.*, 1988, **109**, 190447); D. Haebich, W. Hartwig, A. Klausener, K. G. Metzger and H. J. Zeiler, *Ger. Pat.*, DE 3 641 872, 1988 (*Chem. Abstr.*, 1988, **109**, 210793).

3 G. B. Barlin, *The Pyrazines* in *The Chemistry of Heterocyclic*

Compounds, eds. A. Weissberger and E. C. Taylor, Interscience, New York, 1982, vol. 41, p. 196.
4 G. B. Barlin, *The Pyrazines* in *The Chemistry of Heterocyclic Compounds*, eds. A. Weissberger and E. C. Taylor, Interscience, New York, 1982, vol. 41, pp. 99 and 105.
5 A. Ohta, M. Shimazaki, N. Tanekura and S. Hayashi, *Heterocycles*, 1983, **20**, 797.
6 L. Bauer and A. L. Hirsch, *J. Org. Chem.*, 1966, **31**, 1210.
7 L. Bauer, T. E. Dickerhofe and K.-Y. Tserng, *J. Heterocycl. Chem.*, 1975, **12**, 797.
8 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991, p. 277.
9 S. Prachayasittikul and L. Bauer, *J. Heterocycl. Chem.*, 1985, **22**, 771.
10 N. Sato, Y. Shimomura, Y. Ohwaki and R. Takeuchi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2877.
11 T. Sakakibara, Y. Ohwaki and N. Sato, unpublished data.
12 N. Sato, *J. Chem. Res.*, 1984, (*S*) 318; (*M*) 2860.
13 A. Albini and S. Pietra, *Heterocyclic N-Oxides*, CRC Press, Boca Raton, Florida, 1991, p. 178.
14 L. Bauer and S. Prachayasittikul, *Heterocycles*, 1986, **24**, 161; S. Prachayasittikul, G. Doss and L. Bauer, *J. Heterocycl. Chem.*, 1991, **28**, 1051.
15 N. Sato and E. Nagano, unpublished data.
16 O. Nishimura, C. Kitada and M. Fujino, *Chem. Pharm. Bull.*, 1978, **26**, 1576.
17 G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocycl. Chem.*, 1972, **14**, 99.
18 A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.
19 T. S. Safonova and L. A. Myshkina, *Chem. Heterocycl. Compd.*, 1970, **6**, 1019.

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