Studies on Pyrazines. 12 [1].
N-Oxidation of Aminopyrazines with *m*-Chloroperbenzoic Acid

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Received December 11, 1984

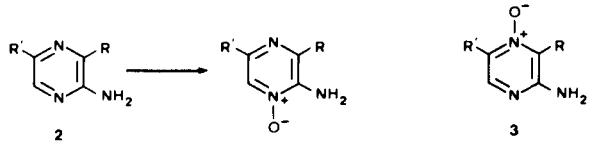
N-Oxidation reactions of 2-aminopyrazines, substituted by methyl or phenyl groups at C-3 or C-5, with *m*-chloroperbenzoic acid were undertaken to obtain the 2-aminopyrazine 1-oxides.

J. Heterocyclic Chem., **22**, 1145 (1985).

Because of its structural similarity to antibiotic aspergillic acid, several alkyl substituted 2-aminopyrazine 1-oxides were first prepared by condensation of α-aminonitriles with α-oximinocarbonyl compounds [2,3]. After seventeen years, the parent 2-aminopyrazine 1-oxide (**1a**) was produced together with the isomeric 4-oxide by *N*-oxidation of acetamidopyrazine with peracetic acid, followed by hydrolysis [4]. Recently, the *N*-oxide **1a** was conveniently produced by direct oxidation of 2-aminopyrazine (**2a**) with *m*-chloroperbenzoic acid [5]. In this paper, we focus on the development of this oxidation method to methyl or phenyl substituted 2-aminopyrazine 1-oxides **1b-e** because of the low yields by the condensation reaction of aminoacetonitriles with oximinoketones [6,7].

The oxidation of **2a** with *m*-chloroperbenzoic acid in acetone gave the 1-oxide **1a** in 63% yield, which was comparable to that of the literature [5]. In a similar manner, substituted aminopyrazines **2b-e** were oxidized, and the results are summarized in Table 1. Although oxidation of phenyl aminopyrazines resulted in exclusive formation of 2-aminopyrazine 1-oxides **1**, methyl aminopyrazines gave a mixture of both the 1- and 4-oxides. Determination of the position of the N-O group in these *N*-oxides was unfeasible by comparison of ir or ^{1}H nmr spectra of each pair of isomers. However, 2-aminopyrazine 1-oxides **1** were easily distinguished from the 4-oxides by their characteristic deep-blue coloration in the ferric chloride test [2].

Scheme I



2 1 3

	R	R'
a	H	H
b	CH_3	H
c	H	CH_3
d	C_6H_5	H
e	H	C_6H_5

Table 1

N-Oxidation of Aminopyrazines with *m*-Chloroperbenzoic Acid in Acetone

Aminopyrazine	Product	Yield %	Mp °C	Lit Mp °C
2a	1-oxide (**1a**)	63	187-188 [c]	186-187 [4]
2b	1-oxide (**1b**) [a]	43	205-207 [d]	
	4-oxide (**3b**)		175-177 [f]	
2c	1-oxide (**1c**) [b]	62	221-223 [c]	221-223 [6]
	4-oxide (**3c**)		213-214 [c]	
2d	1-oxide (**1d**)	87	154 [e]	
2e	1-oxide (**1e**)	51	224-245 [d]	235 [7]

Product	Formula	Analyses % Calcd./Found C	H	N
1b	$C_5H_7N_3O$	47.99	5.64	33.58
		47.94	5.65	33.46
3b	$C_5H_7N_3O$ [g]	47.99	5.64	33.58
		47.48	5.51	33.57
1c				
3c	$C_5H_7N_3O$ [h]	47.99	5.64	33.58
		47.92	5.65	33.46
1d	$C_{10}H_9N_3O$	64.16	4.85	22.45
		63.98	4.83	22.42

[a] Relative ratio, 1-oxide:4-oxide 19:1. [b] 17:3. [c] Recrystallized from ethanol and ethyl acetate (1:1). [d] methanol. [e] ethanol. [f] Purified by sublimation *in vacuo*. [g] Exact ms: Calcd: 125.0588. Found: 125.0622. [h] Found: 125.0576.

The mechanism of *N*-oxidation involves a nucleophilic attack of the lone pair of electrons on nitrogen on the outermost oxygen of the peracid. The orientation of the substituted pyrazines is governed by the relative basicities of the ring nitrogen [8,9]. The electron-donating amino group increases basicity of the nitrogen adjacent to the substituent resulting in formation of 2-aminopyrazine 1-oxide (**1a**). Similar electronic effects by the methyl group bring about *N*-oxidation on the nitrogen furthest removed from the amino group resulting in a competitive formation of both the 1- and 4-oxides. The electron-donating effect of methyl group on *N*-oxidation is well demonstrated by our earlier findings that the oxidation of 2-methylpyrazine with peracetic acid gave a mixture of the corresponding 1- and 4-oxides in the ratio of about 3:2 [9]. On the other

hand, *m*-chloroperbenzoic acid oxidation of 2-phenylpyrazine (chloroform, reflux 3 hours) provided only the 4-oxide in 74% yield. Accordingly, amino and phenyl groups progress oxidation on only nitrogen N-1 to lead the exclusive formation of the corresponding 1-oxides.

Table 2

^{1}H-NMR Spectra of Aminopyrazine *N*-Oxides in Dimethylsulfoxide-d_6

Compound	Chemical Shift, δ (coupling constant, Hz)				
	H-3	H-5	H-6		Others
1a	8.15	7.72	8.13	$J_{5,6}$ = 4.1 $J_{3,6}$ = 0.7	6.97 (NH_2)
1b		7.62	8.00	$J_{5,6}$ = 4.4 J_{6,CH_3} = 0.5	2.38 (CH_3) 6.48 (NH_2)
3b		7.52	7.71	$J_{5,6}$ = 4.1	2.22 (CH_3) 6.43 (NH_2)
1c	8.02		8.02	$J_{3,6}$ = 0.8 J_{6,CH_3} = 0.7	2.24 (CH_3) 6.65 (NH_2)
3c	7.90		7.53	$J_{3,6}$ = 0.8 J_{6,CH_3} = 0.7	2.13 (CH_3) 6.20 (NH_2)
1d		7.89	8.19	$J_{5,6}$ = 4.0	6.79 (NH_2) 7.4-7.6, 7.65-7.8 (C_6H_5)
1e	8.75		8.23	$J_{3,6}$ = 0.7	7.03 (NH_2) 7.3-7.65 7.85-8.0 (C_6H_5)

EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected. The ^{1}H-nmr spectra were recorded on a JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard, and ms spectra on a JEOL JMS-DX-300 instrument.

N-Oxidation of Aminopyrazine with *m*-Chloroperbenzoic Acid.

To a stirred solution of aminopyrazine (5.0 mmoles) in acetone (10 ml) was added a solution of *m*-chloroperbenzoic acid (0.950 g, 5.5 mmoles), and the mixture was stirred at room temperature for 24 hours. The reaction was monitored by tlc (ethyl acetate). The starting material had not yet been consumed at the end of the reaction time. The mixture was evaporated to dryness *in vacuo*, and the residue was treated with sodium carbonate (0.60 g, 5.6 mmoles) and water (3 ml). The resulting mixture was again evaporated to dryness, and the residue was extracted with chloroform by a Soxhlet extractor overnight. Evaporation gave a mixture of the starting aminopyrazine and its *N*-oxide(s). The former compound was removed by silica gel or Florisil chromatography eluted with benzene or benzene-ethyl acetate. The desired *N*-oxides were obtained by further elution with benzene-ethyl acetate or ethyl acetate. Separation of 1- and 4-oxides was accomplished by preparative layer chromatography eluted with ethyl acetate. The yields and product ratios were summarized in Table 1. The *N*-oxides **1c** and **1e** were identified by comparison with ir and ^{1}H-nmr spectra of the corresponding authentic samples which were prepared by the condensation reaction [6,7]. The ^{1}H-nmr spectral data of *N*-oxides obtained are summarized in Table 2.

Acknowledgments.

The authors are grateful to Dr. N. Kamigata for recording the exact mass spectra.

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