Convenient *N*-Oxidation of Pyrazines

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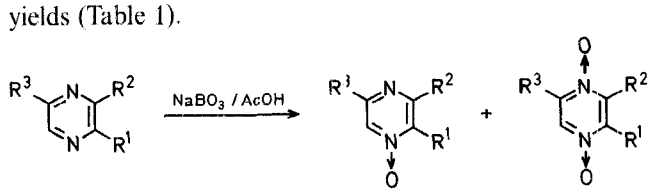
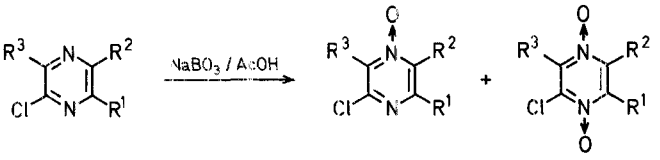
For *N*-oxidation of aromatic tertiary amines, peroxycarboxylic acids such as peracetic, perbenzoic, and permaleic acids have been generally used In the course of an investigation on pyrazines we used either peracetic or permaleic acids, according to the individual case[1]. Peracetic acid in acetic acid is suitable for the preparation of water-soluble *N*-oxides whereas permaleic acid is used for *N*-oxidations in haloalkane solutions when the products are water-insoluble. However, work-up of the reaction mixtures containing peracetic acid is troublesome, because the solvent has to be distilled off in vacuo, the danger of explosion being implied. We report here that sodium perborate can be conveniently used for the *N*-oxidation of pyrazines, especially for the preparation of water-soluble pyrazine *N*-oxides.

Sodium perborate has been used for the oxidation of primary amines to the corresponding azo and nitro compounds, and of sulfides to sulfoxides and sulfones[2]. When pyrazines were heated at 80°C for 5 h with 1.2 molecular equivalents of sodium perborate in glacial acetic acid, sodium borate appeared as crystals as the oxidation proceeded. After removal of the precipitate by suction, the solvent was distilled off in vacuo and the residue triturated with aqueous potassium carbonate. In the case of water-soluble products, the alkaline solutions were concentrated to dryness in vacuo and the residue extracted with chloroform. Water-insoluble products were easily extracted from the alkaline solutions with dichloromethane. The products were obtained in satisfactory yields (Table 1).



1a-f **2a-f** **3a-f**

Some 2-chloropyrazines (**4**) were also submitted to this reaction, however under harsher conditions. The oxidations occurred exclusively at N-4 which is thought to be more basic; only chloropyrazines having small side chains gave a small amount of dioxide. However, the yields of products **5** were not always so good (Table 2) and a considerable amount of starting material was recovered in all cases.



4a-d,f **5a-d,f** **6a-d,f**

It may be concluded that sodium perborate is a convenient reagent for the preparation of pyrazine *N*-oxides, in particular, of water-soluble *N*-oxides mainly because of the easy and undangerous work-up.

Oxidation of Pyrazines (1a–f); General Procedure:

A mixture of the pyrazine (**1a–f**; 10 mmol) and sodium perborate (1.85 g, 12 mmol) in acetic acid (50 ml) is heated at 80°C for 5 h. After cooling, the mixture is filtered by suction and the filtrate is concentrated to dryness in vacuo. The residue is triturated with aqueous 20% potassium carbonate (20 ml). In the case of the oxidations of **1a** and **1e**, these alkaline solutions are concentrated to dryness and the residue is extracted with chloroform (5 × 20 ml) to give a mixture of mono- and dioxides, which are separated by chromatography on a silica gel (35 g) column, eluting with hexane containing an increasing amount of ether. In other cases, the alkaline solutions are extracted with dichloromethane (3 × 20 ml) and the products are purified by column chromatography on silica gel (35 g) as above.

2,5-Diisopropylpyrazine 1-Oxide (**2c**):

$C_{10}H_{16}N_2O$ (180.3) calc. C 66.63 H 8.95 N 15.54 found 66.50 9.03 15.35

M.S.: *m/e* = 180 (M^+), 163 ($M^+ - 17$, 100%).

U.V. (ethanol): λ_{max} = 225.5 (ε = 11900); 268.5 (7300); 293 (2700); 302 nm (2100).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.34 (s, 1H, pyrazine ring proton); 8.00 (s, 1H, pyrazine ring proton); 3.58 [m, 1H, $CH(CH_3)_2$, J = 7.0 Hz]; 2.98 [m, 1H, $CH(CH_3)_2$, J = 7.0 Hz]; 1.32 [d, 6H, $CH(CH_3)_2$, J = 7.0 Hz]; 1.28 ppm [d, 6H, $CH(CH_3)_2$, J = 7.0 Hz].

2,5-Diisobutylpyrazine 1-Oxide (**2d**):

$C_{12}H_{20}N_2O$ (208.3) calc. C 69.19 H 9.68 N 13.45 found 69.19 9.80 13.73

M.S.: *m/e* = 208 (M^+), 191 ($M^+ - 17$, 100%).

U.V. (ethanol): λ_{max} = 227 (ε = 23100); 269 (13600); 292 (4900); 304 nm (3800).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.27 (s, 1H, pyrazine ring proton); 7.97 (s, 1H, pyrazine ring proton); 2.72 [d, 2H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 2.56 [d, 2H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 2.15 [m, 2H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 0.94 [d, 6H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 0.93 ppm [d, 6H CH_2—$CH(CH_3)_2$, J = 6.5 Hz].

2,5-Diisopropylpyrazine 1,4-Dioxide (**3c**):

$C_{10}H_{16}N_2O_2$ (196.3) calc. C 61.20 H 8.22 N 14.28 found 61.25 8.19 14.47

M.S.: *m/e* = 196 (M^+), 162 ($M^+ - 34$, 100%).

U.V. (ethanol): λ_{max} = 236 (ε = 18200); 308 (14600); 340 nm (4600)

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.00 (s, 2H, pyrazine ring proton); 3.51 [m, 2H, $CH(CH_3)_2$, J = 6.5 Hz]; 1.29 ppm [d, 12H $CH(CH_3)_2$, J = 6.5 Hz].

2,5-Diisobutylpyrazine 1,4-Dioxide (**3d**):

$C_{12}H_{20}N_2O$ (224.3) calc. C 64.26 H 8.99 N 12.49 found 64.09 9.04 12.68

Table 1. Oxidation of Pyridazines **1**

1	R^1	R^2	R^3	1-Oxide **2**		1,4-Dioxide **3**		Recovery of **1** [%]
				Yield [%]	m.p. or b.p./torr [°C] (Lit. Data)	Yield [%]	m.p. [°C] (Lit. Data)	
a[3]	CH_3	H	CH_3	76	m.p. 106–107° (m.p. 105–108°)[6]	21	289° dec. (280° dec.)[6]	–
b[3]	C_2H_5	H	C_2H_5	51	b.p. 130–135°/10 (b.p. 135–140°/10)[3]	19	207–209° (208–209°)[3]	6
c[4]	i-C_3H_7	H	i-C_3H_7	79	b.p. 134–136°/10 (b.p. 113–114°/9)[7]	15	210–212°[a]	4
d[4]	i-C_4H_9	H	i-C_4H_9	83	m.p. 51–52° (m.p. 51°)[7]	8	221–222°[a]	4
e[5]	CH_3	CH_3	H	67	m.p. 86–87° (m.p. 83–83.5°)[5]	25	214–216° (211°)[5]	–
f[5]	C_6H_5	C_6H_5	H	70	m.p. 170–171° (m.p. 171–172°)[5]	3	259–261° dec. (258–259°)[5]	23

[a] Recrystallized from benzene.

Table 2. Oxidation of 2-Chloropyrazines **4a–d,f**

4	R^1	R^2	R^3	4-Oxide **5**		1,4-Dioxide **6**		Recovery of **4** [%]
				Yield [%]	m.p. [°C] (Lit. Data)	Yield [%]	m.p. [°C] (Lit. Data)	
a[3]	CH_3	H	CH_3	56	112–113° (113–115°)[3]	1	196–199° (193–193.5)[3]	8
b[3]	C_2H_5	H	C_2H_5	49	36–38° (38–39°)[3]	6	125–126° (127–129°)[3]	34
c[8]	i-C_3H_7	H	i-C_3H_7	17	76–77°[a]			64
d[9]	i-C_4H_9	H	i-C_4H_9	59	57–58° (56.5–57°)[9]			36
f[5]	C_6H_5	C_6H_5	H	5	122–124° (123–124°)[5]			94

[a] Recrystallized from hexane.

M.S.: m/e = 224 (M^+), 175 ($M^+ - 49$, 100%).

U.V. (ethanol): λ_{max} = 238.5 (ε = 29600); 308.5 (23000); 345 nm (5300).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.01 (s, 2H, pyrazine ring proton); 2.64 [d, 4H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 2.21 [m, 2H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz]; 0.98 ppm [d, 12H, CH_2—$CH(CH_3)_2$, J = 6.5 Hz].

Oxidation of 2-Chloropyrazines (4a–d, f); General Procedure:
A mixture of the 2-chloropyrazine (**4a–d, f**; 10 mmol) and sodium perborate (2.31 g, 15 mmol) in acetic acid (50 ml) is heated at 80°C for 24 h, and worked up as described for products **2a–d, f**. The products are purified by chromatography on a silica gel (35 g) column with hexane containing an increasing amount of ether.

2-Chloro-3,6-diisopropylpyrazine 4-Oxide (**5c**):

$C_{10}H_{15}ClN_2O$ (214.7) calc. C 55.94 H 7.04 N 13.05
found 55.68 7.03 13.15

M.S.: m/e = 214 (M^+), 197 ($M^+ - 17$, 100%).

U.V. (ethanol): λ_{max} = 234 (ε = 17400); 280 (9800); 302 (3600); 311 nm (3200).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 7.97 (s, 1H, pyrazine ring proton); 3.97 [m, 1H, $CH(CH_3)_2$, J = 7.5 Hz]; 2.94 [m, 1H, $CH(CH_3)_2$, J = 7.0 Hz]; 1.43 [d, 6H, $CH(CH_3)_2$, J = 7.5 Hz]; 1.28 ppm [d, 6H, $CH(CH_3)_2$, J = 7.0 Hz].

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