OXIDATION METHODS FOR AROMATIC DIAZINES: SUBSTITUTED PYRAZINE-*N*-OXIDES, PYRAZINE-*N*,*N*'-DIOXIDES, AND 2,2':6',2"-TERPYRIDINE-1,1"-DIOXIDE

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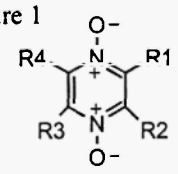
Abstract: In the course of investigations into the intermolecular interactions of azaaromatic *N*-oxides it was necessary to perform oxidations of the pyridine and pyrazine moieties. Generally, it was found that direct oxidation with OXONE® gave efficient preparation of pyrazine dioxides. Oxidation with dimethyldioxirane was used to preclude problems associated with the isolation of particularly hydrophilic pyrazine and pyrazine-*N*-oxides.

In this work we describe the convenient and efficient synthesis of oxygenated pyrazine and pyridine moieties. The use of the reagent OXONE® (potassium peroxomonosulfate) in water or OXONE® / acetone (dimethyldioxirane) mixtures gave the desired *N*-oxide products in good yield. Dimethyldioxirane[1,2,3] proved to be a convenient oxidizing agent for acetone soluble compounds. This procedure compares well to that employed by Landquist[4] to prepare quinoxaline-*N*,*N*'-dioxide using urea-hydrogen peroxide in nonaqueous solutions or rhenium reagents used by Sharpless [5a,5b] to oxidize substituted pyridines to pyridine-*N*-oxides.

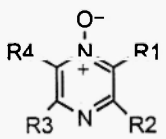
Methylated pyrazine dioxides **1a-g** and monoxides **2a-g** were prepared by oxidation of the parent pyrazines with commercially available OXONE®. The yields were generally good and comparable to previously reported[5-9] methods (see Tables I and II). The yields obtained by this work are in bold font in the tables. The OXONE® method eliminates the need for concentrated peroxides and other explosive reagents or problematic steps associated with oxidation procedures that use hydrogen peroxide[6-8] or sodium perborate.[10] This method logically extends the work done by Mixan[11] with chloropyrazines using Caro's reagent and persulfate modified Caro's reagent. The method described herein has the advantages of utilizing a commercially available oxidizing agent and ambient reaction conditions.

Pyrazine to pyrazinedioxide oxidations were carried out as biphasic (aqueous/organic) reactions with vigorous stirring for 24 hours at 25 °C. Extraction then provided moderately pure dioxides in good yields. In many cases, the dioxide yields were enhanced by continuous extraction into organic solvents, particularly for recovery of the parent pyrazinedioxide **1a** and other especially hydrophilic *N*-oxide products.

Figure 1



1a: R1, R2, R3, R4 = H
1b: R1 = CH_3; R2, R3, R4 = H
1c: R1, R2 = CH_3; R3, R4 = H
1d: R1, R3 = CH_3; R2, R4 = H
1e: R1, R4 = CH_3; R2, R3 = H
1f: R1, R2, R3 = CH_3; R4 = H
1g: R1, R2, R3, R4 = CH_3

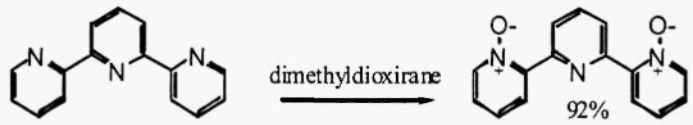


2a: R1, R2, R3, R4 = H
2b: R1 = CH_3; R2, R3, R4 = H
2c: R1, R2 = CH_3; R3, R4 = H
2d: R1, R3 = CH_3; R2, R4 = H
2e: R1, R4 = CH_3; R2, R3 = H
2f: R1, R2, R3, R4 = CH_3
2g: R2, R3 = CH_3; R1, R4 = H

In fact, the hydrophilic mono-*N*-oxides such as **2a-g** were most conveniently prepared using OXONE® / acetone / $NaHCO_3$ (~0.08 M dimethyldioxirane[3a]) mixtures[1] (Table I). The observed *N*-oxide product yields of 82% and 70% for **2d** and **2f**, respectively, are comparable to previously used hydrogen peroxide methods.[6-8] The absence of water facilitates product isolation and makes the dimethyldioxirane method preferred over aqueous peroxide oxidation procedures for hydrophilic compounds.

2,2′:6′,2″-Terpyridine (**3**, Figure 2) was treated with an approximately 0.08 molar solution of dimethyldioxirane in acetone to afford 2,2′:6′,2″-terpyridine-1,1′-di-*N*-oxide (4) crystals, which fell out of solution in 92% yield. The excellent yields and relative ease of isolation compares very favorably to Thummel's [12] MCPBA synthesis of **4**. Calculated[13a] PM3[13b] Mulliken charges at the nitrogens of –0.069, -0.057, –0.069 for **3** and possible steric contributions may explain the observed regioselectivity of this oxidation.

Figure 2



3 4

Table I: Pyrazine-*N,N'*-dioxides

	Compound	Yields
1a	Pyrazine-*N,N'*-dioxide	90[a,6], **75**[b],
1b	2-methylpyrazine-*N,N'*-dioxide	57[a,6], **85**[b], 76[c,8]
1c	2,3-dimethylpyrazine-*N,N'*-dioxide	**88**[b]
1d	2,5-dimethylpyrazine-*N,N'*-dioxide	60[a,6], **88**[b], 21[d,14], 24[e,9], 90[f,7]
1e	2,6-dimethylpyrazine-*N,N'*-dioxide	86[a,6], **91**[b]
1f	2,3,5-trimethylpyrazine-*N,N'*-dioxide	82[15], **95**[b]
1g	2,3,5,6-tetramethylpyrazine-*N,N'*-dioxide	89[a,7], **69**[b], 73[15]

a) 4 molar equiv. of 30% hydrogen peroxide to 10 molar equiv. CH_3CO_2H 16-24 hr. b) 3-6 equiv. excess of OXONE® stirred at room temperature for 24 hr. c) 35% H_2O_2 in glacial acetic acid heated on steam bath for 16 hr. d) 1.2 molar equiv. of sodium perborate tetrahydrate in acetic acid at 80 °C for 5 hr. e) hydrogen peroxide in acetic acid at 56 °C for 16 hr.

Table II: Pyrazine-*N*-monoxides

	Compound	Yields
2a	pyrazine-*N*-oxide	60[a,6], **53**[b]
2b	2-methylpyrazine-1-oxide	57[a,6]
2c	2,3-dimethylpyrazine-1-oxide	**47**[b]
2d	2,5-dimethylpyrazine-1-oxide	84[a,6], **49**[b], 76[c,14], 62[d,9], **82**[e]
2e	2,6-dimethypyrazine-1-oxide	29[a,6]
2f	2,3,5,6-tetramethylpyrazine-1-oxide	90[a,6], **39**[b], **70**[c]
2g	2,6-dimethylpyrazine-4-oxide	33[a,6]

a) 2 molar equiv. of 30 % H_2O_2 in 5 molar equiv. CH_3CO_2H, 8hr. b) 1.2 molar equiv. of sodium perborate tetrahydrate in acetic acid, 80 °C, 5 hr. c) 1.2 molar equiv. of sodium perborate tetrahydrate in acetic acid, 80 °C, 5 hr. d) H_2O_2 in acetic acid, 56 °C, 16 hr, filtrates from dioxide procedure. e) ~0.08 M dimethyldioxirane in acetone is added dropwise to 2,5-dimethylpyrazine.

Conclusion

Direct oxidation with OXONE® and indirect oxidation with OXONE® via dimethyldioxirane has proven to be efficient for *N*-oxygenation of the pyrazines and pyridine moieties. Generally, OXONE® or dimethyldioxirane can be used as an effective oxidizing agent for a plethora of azaaromatic compounds. These oxidation reactions have the advantages of high yields, experiment simplicity, good reproducibility and are less hazardous than peracid or hydrogen peroxide based procedures.

Experimental

Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a FTS-40 Biorad spectrophotometer equipped with a nitrogen purged sample cell. ^{1}H NMR spectra were determined with NT-200 Nicolet, AM-360 Bruker, AM-500 Bruker or Jeol-270 instruments.

Materials. All oxidations were carried out on commercially available pyrazines which were used without purification. Solvents (ACS reagent grade) were obtained from Fisher. Potassium peroxymonosulfate (commercially available from Aldrich as OXONE®) was used without further purification. $CDCl_3$ (CIL or Aldrich) was stored over 3-Å sieves and used without further purification. Chemical shifts (δ -values) are reported relative to TMS in ppm.

Typical dioxygenation using OXONE®. Pyrazine-*N,N'*-dioxide 1a. 1.60 g (19.0 mmol) pyrazine in 60 mL CH_2Cl_2 was stirred with 24.0 g (39.1 mmol) of OXONE® in 140 mL of H_2O for 24 hr at 25 °C. The resulting solution was continuously extracted with CH_2Cl_2 for 2-4 d, and the organic layer dried with anhyd. K_2CO_3. Removal of solvent *in vacuo* afforded 1.65 g (14.2 mmol) of **1a** as a beige powder (74.7%), mp 268-276 °C (dec.). Recrystallization (ethanol) afforded colorless crystals: mp 300 °C (dec) [lit.[8] mp 285-295 °C, lit.[10] mp 300 °C (dec.), lit.[6] mp 300 °C (dec.), lit.[16] mp 300-302 °C (melting with partial decomposition]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.99 (s); IR (cm^{-1}) 3125.9(m), 3106.9(m), 3059.6(m), 3063.0(s), 2965.3(m), 1485.1(s), 1453.1(vs), 1381.8(m), 1302.0(m), 1262.3(vs), 1036.3(vs), 872.6(s), 805.9(vs).

2-Methylpyrazine-*N,N'*-dioxide 1b. 1.00 g (10.65 mmol) 2-methylpyrazine in 60 mL CH_2Cl_2 was stirred with 14.20 g (23.1 mmol) of OXONE® in 70 mL H_2O for 24 hr at 25 °C. Continuous extraction (CH_2Cl_2) gave 0.99 g (9.0 mmol) **1b** as a white powder (85 %), mp 240-244 °C. Recrystallization (CH_3CN) gave colorless crystals: mp 242-243 °C [lit.[6] mp 242-244 °C, lit.[8] mp 230-231 °C, lit.[10] mp 242-244 °C]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.47 (s, 3H), δ 7.97 (m, 1H,); δ 8.06 (m, 2H); IR (cm^{-1}) 3152.7(wk), 3080.8(m), 3020.9(s), 1519.5(m), 1451.9(vs), 1410.0(s), 1380.2(m), 1326.7(s), 1269.0(vs), 1195.2(m), 1172.9(s), 1113.8(m), 1006.1(s), 979.3(s), 909.6(m),858.5(m), 814.4(vs).

2,3-Dimethylpyrazine-*N,N'*-dioxide 1c. 2.02 g (18.7 mmol) 2,3-dimethylpyrazine in 60 mL CH_2Cl_2 was stirred with 24.8 g (40.3 mmol) of OXONE® in 140 mL H_2O for 24 hr at 25 °C. Continuous extraction (CH_2Cl_2) gave 2.30 g (16.4 mmol) of **1c** as a white powder (87.7 %), mp 198-203 °C. Recrystallization (1:1 CH_3CN/EtOH) afforded colorless

crystals: mp 208-210 °C, [lit.[10] mp 209-210 °C]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.55 (s, 6H), δ 8.01 (s, 2H); IR (cm^{-1}) 3124.2(wk), 3089.6(m), 3059.9(s), 1508.0(s), 1441.3(vs), 1404.3(vs), 1288.4(vs), 1223.5(s), 1104.5(s), 845.6(s), 786.3(vs).

2,5-Dimethylpyrazine-*N,N'*-dioxide 1d. 1.01 g (9.35 mmol) 2,5-dimethylpyrazine in 30 mL CH_2Cl_2 was stirred with 12.2 g (19.8 mmol) of OXONE® in 70 mL H_2O for 24 hr at 25 °C. Continuous extraction (CH_2Cl_2) gave 1.13 g (8.19 mmol) of **1d** as a white powder (87.6 %), mp 270-275 °C (dec.). Recrystallization (1:1 CH_3CN/EtOH) afforded colorless crystals: mp 290 °C (dec) [lit.[10] mp 360 °C (dec.), lit.[6] mp >300 °C (dec.), lit.[9] mp 360 °C (dec.)]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.41 (s, 6H, CH_3), δ 8.07 (s, 2H); IR (cm^{-1}) 3163.4(wk), 3093.0(wk), 3054.6(s), 1524.4(s), 1449.3(vs), 1401.3(m), 1354.1(vs), 1330.1(vs), 1273.4(s), 1195.8(vs), 1183.7(vs), 1141.1(vs), 1013.0(vs), 905.6(s), 870.7(m), 709.5(vs).

2,6-Dimethylpyrazine-*N,N'*-dioxide 1e. 2.01 g (18.6 mmol) 2,6-dimethylpyrazine in 60 mL CH_2Cl_2 was stirred with 24.8 g (40.3 mmol) of OXONE® in 140 mL of H_2O for 24 hr at 25 °C. Continuous extraction (CH_2Cl_2) gave 2.37 g (16.9 mmol) of **1e** as a white powder (91.0 %), mp 221-224 °C. Recrystallization (1:1 CH_3CN/EtOH) afforded colorless crystals: mp 222-224 °C [lit.[6] mp 227 °C, lit.[10] mp 227 °C]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.46 (s,6H), δ 7.97 (s, 2H); IR (cm^{-1}) 3167.9(wk), 3041.1(s), 2971.9(m), 1650.2(m), 1533.6(m), 1450.7(vs), 1376.4(s), 1367.4(s), 1271.5(vs), 1186.2(vs), 1052.2(m), 988.0(s), 894.5(s), 815.4(vs).

2,3,5-Trimethylpyrazine-*N,N'*-dioxide 1f. 1.01 g (8.26 mmol) 2,3,5-trimethylpyrazine in 30 mL CH_2Cl_2 was stirred with 24.0 g (39.1 mmol) of OXONE® in 75 mL of H_2O for 24 hr at 25 °C. Continuous extraction (CH_2Cl_2) gave 1.21 g (7.86 mmol) of **1f** as a white powder (95.1 %), mp 117-123 °C. Recrystallization (ethyl acetate) afforded colorless crystals: mp 130-132 °C [lit.[10] mp 136-137 °C, lit.[15] mp 136-137 °C]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.43 (s, 3H), δ 2.53 (s, 3H), δ 2.56 (s, 3H), δ 8.05 (s, 1H); IR (cm^{-1}) 3150.4(wk), 3087.5(m) 3044.7(m), 1625.9(m), 1521.5(s), 1456.7(vs), 1437.8(vs), 1398.2(m), 1354.6(vs), 1291.4(s), 1223.4(s), 1157.8(m), 1141.1(m), 1105.8(vs), 1029.0(m), 1003.5(m), 941.4(m), 879.8(s), 723.5(s).

2,3,5,6-Tetramethylpyrazine-*N,N'*-dioxide 1g. 2.95 g (22.0 mmol) 2,3,5,6-tetramethylpyrazine in 50 mL CH_2Cl_2 was stirred with 66.6 g (108 mmol) of OXONE® in 400 mL of H_2O for 24 hr at 25 °C. Extraction (CH_2Cl_2, 10 x 75 mL gave **1g** as a white solid (2.58 g, 69%). Recrystallization (ether) afforded colorless crystals: mp 225 °C [lit.[10] mp 227 °C]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56 (s): IR (cm^{-1}) 1460.7(s), 1377.2(m), 1335.4(wk), 1306.4(m), 1118.0(m), 1035.5(wk), 872.2(wk), 718.8(wk).

Typical mono-oxidation of pyrazines using sodium perborate tetrahydrate. Pyrazine-*N*-oxide 2a. 1.04 g (13.0 mmol) pyrazine was stirred with 2.40 g (15.6 mmol) of sodium perborate tetrahydrate in 50 mL acetic acid for 5 hr at 80 °C. The mixture was filtered to remove excess sodium borate crystals, neutralized with 5% K_2CO_3, extracted (3 X 50

mL, CH_2Cl_2) and dried with anhyd K_2CO_3. Purification on alumina (neutral) columns in 100% CH_2Cl_2 provided **2a** as a white solid (0.66 g, 52.8%): mp 110-112 °C [lit.[10] 113-114 °C].

2,3-Dimethylpyrazine-*N*-oxide 2c. 1.07 g (9.89 mmol) of 2,3-dimethylpyrazine was stirred with 1.84 g (12.0 mmol) of sodium perborate tetrahydrate in 50 mL acetic acid for 5 hr at 80 °C. Chromatography provided **2c** as a white solid (0.57 g, 47%): mp 82-84 °C [lit.[10] 85-86 °C].

2,5-Dimethylpyrazine-*N*-oxide 2d. 0.540 g (4.99 mmol) of 2,5-dimethylpyrazine was stirred with 0.921 g (5.99 mmol) of sodium perborate tetrahydrate in 50 mL acetic acid for 5 hr at 80 °C. Chromatography provided **2d** as a white solid (0.300 g, 48.5 %): mp 103-104 °C [lit.[10] 108 °C]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (s, 1H), δ 8.03 (s, 1H), 2.49 (s, 3H), 2.41 (s, 3H).

2,3,5,6-Tetramethylpyrazine-*N*-oxide 2f. 1.36 g (10.0 mmol) of 2,3,5,6-tetramethylpyrazine was stirred with 1.85 g (12.0 mmol) of sodium perborate tetrahydrate in 50 mL acetic acid for 5 hr at 80 °C. Removal of solvent *in vacuo* provided 1.63 grams of a yellow solid. Chromatography provided **2f** as a white solid (0.60 g, 39%): mp 83-84 °C [lit.[10] 83 °C]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54 (s, 6H), δ 2.47 (s, 6H).

Dimethyldioxirane. The oxidizing agent was prepared[3a] with 0.039 mol OXONE®, 0.138 mol $NaHCO_3$ in 38.4 mL of acetone and 50 mL of water with vigorous stirring at -10 °C followed by distillation (40-100 torr) at ambient temperature to obtain a ~ 0.06 – 0.08 M dimethyldioxirane (concentration verified by titration against thioanisole).

2,5-Dimethylpyrazine-*N*-oxide 2d. 8.50 mL (~0.08 M) dimethyldioxirane in acetone was stirred with 60.0 mg (0.555 mmol) of 2,5-dimethylpyrazine in acetone for 20 min. at 25 °C. The resulting solution was dried with anhyd K_2CO_3 and the solvent removed *in vacuo* providing **2d** as a white solid (0.0568 g, 82%): mp 106.8-107.6 °C [lit.[6] 108 °C].

2,3,5,6-Tetramethylpyrazine-*N*-oxide 2f. 13.61 mL (~0.08 M) dimethyldioxirane in acetone was stirred with 99.1 mg (0.728 mmol) of 2,3,5,6-tetramethylpyrazine in acetone for 20 min. at 25 °C. Removal of the solvent in *vacuo* provided **2f** as a white solid (0.077 g, 70%): mp 81.9-83.6 °C [lit.[6] 83 °C].

2,2′:6′,2″-Terpyridine-1,1″-dioxide 4. 17.71 mL (~ 0.08 M) dimethyldioxirane in acetone was stirred with 150.4 mg (0.64 mmol) **3** (Aldrich 98%) in 2 mL of acetone (Fischer reagent grade) for 5 d at 25 °C. Filtration of the mixture provided **4** as a white solid (92.2%, 157.6 mg): mp 229-234 °C [lit.[12] 232-233 °C].

Acknowledgements

We are grateful to the donors of the Petroleum Research Fund administered by the ACS, Central Missouri State University (College of Arts and Science), and the NSF-HAMP for financial support of this work.

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Received on July 17, 2001