SYNTHESES OF BIPYRIDINE-*N*-OXIDES AND BIPYRIDINE-*N,N'*-DIOXIDES

S.E. McKay *[a], R.W. Lashlee III[a], L.W. Maina[a] K.A. Wheeler[b], A.B. Brown[c]

[a]Department of Biochemistry, Chemistry & Physics, University of Central Missouri, Warrensburg, MO, USA

[b]Department of Chemistry, Eastern Illinois University, Charleston, Illinois, USA

[c]Department of Chemistry, Florida Institute of Technology, Melbourne, FL, USA

Abstract: Dimethyldioxirane (DMD) was used to synthesize heterocyclic aromatic *N*-oxides enabling the product isolation and reaction solutions to be free of potentially dangerous peroxide intermediates. Additionally, this work combines important crystallographic, spectroscopic, and melting point data to shed light on inconsistent literature previously reported for the identity of 2,4'-bipyridine-*N'*-oxide.

Introduction

Oxidations of electron deficient heterocycles have been performed by a variety of oxidizing reagents including H_2O_2 [1], MCPBA[2,3] and other peracids (e.g. monoperphthalic [4] or monopermaleic[5]) and OXONE®.[6] Oxidation methods that use peroxides and peracids often involve the isolation of dangerous intermediates and suffer from tedious and extensive aqueous extractions. Previous work in our group on the oxidation of diazaaromatics with OXONE®[6] and subsequently dimethyldioxirane [7] (DMD) allowed for the preparation of heterocyclic aromatic *N*-oxide compounds in comparable yields to more rigorous oxidation methods. The use of dimethyldioxirane [8] provides the benefit of avoiding cumbersome aqueous extractions and thus offers a facile method for the preparation and isolation of product.

Results and Discussion

Using DMD, 4,4'-bipyridine (**1**, Figure 1) was converted to 4,4'-bipyridine-*N*-oxide (**2a**) in 31% yield, along with the dioxide **2b** (34% yield). Although, this preparation does not result in increased yields for either the *N*-oxide or *N,N'*-dioxide in comparison to the previous preparations, it does have the advantage of ease of isolation and relatively safe conditions.

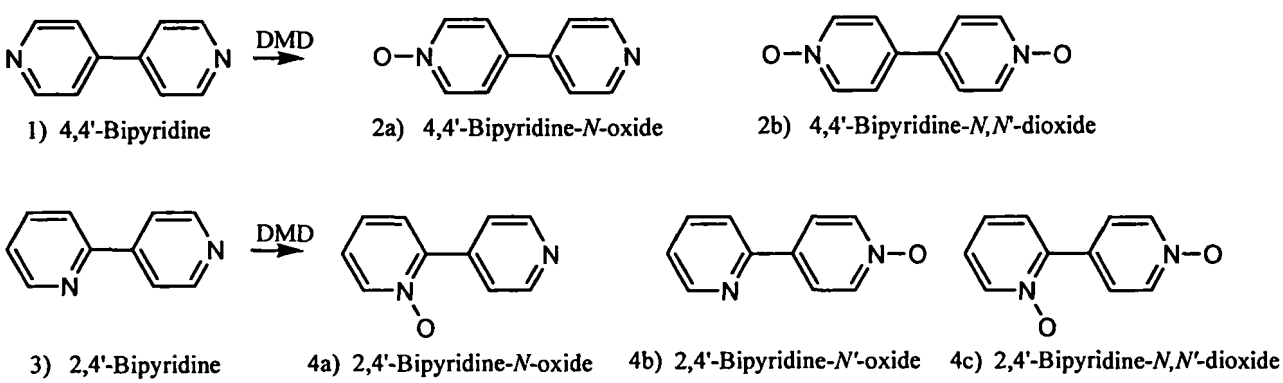
One of the most intriguing aspects of this study centers on the conversion of 2,4'-bipyridine (**3**) to 2,4'-bipyridine-*N*-oxide (**4a**, Figure 1) and its isomer 2,4'-bipyridine-*N'*-oxide (**4b**). Mono-oxide **4b** had mp of 120-121 °C and was prepared in 68% yield . Since the melting point behavior of **4b** prepared in our laboratory differed significantly from previous reports (169-173°C [9] and 168-170°C [10]), we wondered if the origin of this discrepancy was due to incorrect product assignment or the existence of a new polymorphic form of the same compound. The identity of our

sample was confirmed as **4b** by use of X-ray crystallographic methods (Table 1, Figure. 2). Our assessment of a small sample of isolated crystals (mp and NMR) and the crystal used for X-ray diffraction studies (mp) were indistinguishable from data collected on the remainder of the bulk sample (mp and NMR).

Table 1: Crystallography Data* for 2,4'-Bipyridine-*N'*-oxide (4b)

Chemical Formula	$C_{10}H_8N_2O$
Formula Weight	172.18
Crystal Size	0.92 x 0.41 x 0.16 mm
Temperature	298(2) K
Crystal System	Orthorhombic
Space Group, Z	$P2_12_12_1$, 4
Unit Cell Parameters	a = 7.3009(7) Å α= 90.00° b = 10.046(1) Å β = 90.00° c = 11.4606(11) Å γ= 90.00°
Volume, D_{calc}	840.57(14) Å^3, 1.319 g/cm^3
Observed Reflections	1442
Parameters	118
R1, $_wR_2$, GOF	0.047, 0.062, 1.03

*The molecular structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 636622



1) 4,4'-Bipyridine 2a) 4,4'-Bipyridine-*N*-oxide 2b) 4,4'-Bipyridine-*N,N'*-dioxide

3) 2,4'-Bipyridine 4a) 2,4'-Bipyridine-*N*-oxide 4b) 2,4'-Bipyridine-*N'*-oxide 4c) 2,4'-Bipyridine-*N,N'*-dioxide

Figure 1. Synthesis schemes for **2a,b** and **4a-c**

Although our assessment unambiguously identified **4b**, some ambiguity with the structural assignment of compound **4b** still remains partially due to a previous report of the compound.[1] The previously reported proton NMR data[9] and proton and carbon NMR[10] were consistent with our spectral data for **4b** (Table 2); even so, the previous

report cites melting point data that is significantly higher than what we observe (Table 3). A small amount of 2,4'-bipyridine-*N,N'*-dioxide (**4c**) was prepared using dimethyldioxirane as well (18%).

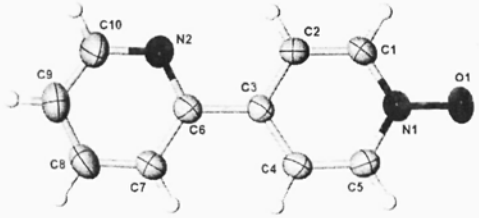


Figure 2. The molecular structure of compound **4b**.

Table 2: Nuclear Magnetic Resonance Chemical Shifts (ppm) Relative to TMS

Compound	^{1}H NMR δ (this study)	^{1}H NMR δ (literature)	^{13}C NMR δ (this study)	^{13}C NMR δ (literature)
4a	-	7.26-7.55; 7.76; 8.26-8.39; 8.71[a]	-	-
4b	7.33; 7.75; 7.82; 7.97; 8.28; 8.72	7.25-7.41; 7.75-8.19; 7.93, 8.38; 8.67-8.74 [9] 7.2-7.32 ; 7.65-7.8; 7.9; 8.22; 8.6-8.67[b]	120.00; 123.37; 123.55; 136.56; 137.17; 139.38; 150.16; 152.45	119.9; 123.3; 123.5; 137.0; 137.1; 139.2; 150.0; 152.2[b]
4c	7.52; 7.70; 7.96; 8.27; 8.70	-	-	-
2a	7.47; 7.56; 8.29; 8.73	7.61-7.84; 8.34; 8.70[a] 7.36-7.5; 8.24; 8.65[b]	-	120.4; 123.7; 134.9; 139.6; 143.1; 150.7[b]
2b	7.53; 8.74	7.84; 8.30 D_2O	-	-

a: reference [9] b: reference [10]

Table 3: Reported Melting Points and Percent Yields

Compound	mp (°C)	Yield (%)	Method used
4a	115-117[a]	65	x-coupling
4b	169-173[a]	57	x-coupling
	168-170[b]	76	MCPBA
	119-121[c]	48	H_2O_2
	118-119	**68**	**DMD**
4c	240-242[c]	15	H_2O_2
	>200[e]	54	MCPBA
	237-238	**18**	**DMD**
2a	170[d]	55	MCPBA
	180[f]	-	H_2O_2
	174-176[c]	40	H_2O_2
	162-164[b]	53	MCPBA
	177-178	**31**	**DMD**
2b	>250[d]	95	H_2O_2/urea
	305[g]	80	H_2O_2/urea
	305-306[h]	-	-
	335[f]	-	-
	298-299	**34**	**DMD**

*Results from this work in bold; a: reference [9]; b: reference [10]; c: reference [1]; d: reference [2] e: reference [14]; f: reference [15]; g: reference [16]; h: reference [17]

Thus, we have found that the oxidation of 2,4'-bipyridine with dimethyldioxirane affords **4b** rather than **4a**. From the Mulliken charge partitioning [11], the 2N atom is slightly more electronegative than the 4N position in the parent 2,4'-bypyridine with Mulliken values of -0.579 and -0.536, respectively (Table 4). Since the oxidation with DMD is ostensibly an S_N2 reaction [12] preferential attack by the more nucleophilic nitrogen should follow. In contrast, we observed that the *N'*-oxide product prevails, presumably due to steric interactions with the incoming DMD reagent although the *N'*-oxide is slightly favored thermodynamically (Table 4).

Due to putative CH ··O intramolecular hydrogen bonding between the adjacent rings,[13] it was predicted that the *N*-oxide product would be thermodynamically favored but in both thermodynamic calculations (Table 4) and the synthetic product, this did not prove to be the case. In both instances the kinetic product was preferred.

Table 4: Computational Data for Various Bipyridines and their N-oxide Derivatives (SCF HF 6-31G)**

Compound	Atom	Mulliken Charge	Energy (a.u)	Intermolecular Distance (Å)	Dihedral Angle (|°|)
2,4'-bipyridine	4'-N 2-N	-0.536 -0.579	492.257	2.558	26.35
2,4'-bipyridine-*N*-oxide	4'-N 2-N	-0.531 -0.149	-567.029	2.418	44.39
2,4'-bipyridine-*N'*-oxide	4'-N 2-N	-0.096 -0.593	-567.036	2.514	21.17
4,4'-bipyridine	4-N	-0.535	-492.254	-	43.68
4,4'-bipyridine-*N*-oxide	4-N 4'-N	-0.534 -0.096	-567.031	-	41.62
2,2'-bipyridine	2-N	-0.603	-429.263	2.468	0.14

Conclusion

We have prepared several bipyridine *N*-oxides and *N,N'*-dioxides using dimethyldioxirane as an oxidizing agent, thus avoiding possible hazardous peroxide isolations or the need for exhaustive or continuous extractions from aqueous mixtures. The preference for the less sterically hindered isomer in the oxidation of 2,4'-bipyridine was confirmed via X-ray crystallography.

Experimental

X-ray Diffraction Analysis

Crystallographic details for **4b** are summarized in Table 1. The X-ray data was collected at 25°C on a Siemens P4 diffractometer using a graphite monochromatic Mo Kα radiation (λ = 0.71073Å) and XSCANS software package.[18] Data were corrected for Lorentz and polarization effects. No absorption correction was applied since the absorption coefficient, μ, was low and crystal geometry was favorable. Crystal stability was monitored by measuring three standard reflections every 97 reflections with no significant variations (<±3%). The X-SEED software platform,[19] equipped with SHELX modules[20] on a PC computer, was used for all structure solution and refinement calculations and molecular graphics. The structure was solved by direct methods, and refined by anisotropic full-matrix least-squares for all non-hydrogen atoms. Several parameters were taken from ref. [21].

Computational Details

Ab initio calculations at the level RHF/6-31G(d,p) were performed using Spartan '04 Windows.[22] All structures were determined to be energetic minima via frequency calculations. HF/6-31G(d,p) single point energy

calculations were done on the optimized geometries and are reported in atomic units (au). Atomic charges were estimated via Mulliken population analysis. [11]

General Experimental

Melting points were obtained with a Mel-Temp capillary apparatus and are uncorrected. NMR spectra were collected on a Bruker Avance FT-NMR instrument, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, and a JEOL-270 instrument, operating at 270 MHz for ^{1}H NMR.

Solvents (Fischer and Mallinckrodt HPLC grade) were commercially available and were used without further purification. 2,4'-Bipyridine was available from ACROS and was used without further purification. $CDCl_3$ (Aldrich) was stored over 3 Å sieves and used without further purification. Thin-layer chromatography (TLC) was performed on Selecto Scientific 60 F_{254} silica gel plates and were visualized by irradiation with UV light.

Dimethyldioxirane [8]. This oxidizing agent was prepared by reacting potassium peroxomonosulfate (0.0390 mol) and $NaHCO_3$ (0.138 mol) in acetone (38.4 ml) and water (50 ml). Vigorous stirring of the mixture at 263 K followed by distillation (40–100 Torr) at ambient temperature resulted in 0.06–0.08 M dimethyldioxirane, as verified by titration against thioanisole.

4,4'-Bipyridine-*N,N'*-dioxide (2b) and 4,4'-Bipyridine-*N*-oxide (2a). To a solution of 4,4'-bipyridine (0.1027 g, 0.658 mmol) in dichloromethane (30 mL) was added 39 mL of dimethyldioxirane in four equivalent aliquots over 1 hour at 25 °C. Fibrous colorless crystals of **2b** fell out of solution and were filtered (0.035 g, 34%) [lit.[2] 95%, lit.[16] 80%], mp 298-299°C, [lit.[2] > 250°C, lit.[16] 305°C, lit.[17] 305-306 °C, lit.[15] 335 °C]. R_f (80:20 dichloromethane/methanol) 0.12. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.74 (d, 4 H, J = 5.8 Hz), 7.53 (d, 4 H, J = 5.8 Hz) ppm. The NMR spectrum was consistent with literature.[2]

The resulting filtrate was transparent and slightly yellow in color. Dichloromethane was removed in vacuo affording a yellow, powdery solid. Preparative TLC on silica gel (mobile phase: 90:10 dichloromethane /methanol) afforded crude **2a** as a brown solid (0.055 g, 54%). Recrystallization from toluene afforded colorless crystals (0.032 g, 31%) [lit.[10] 53%, lit.[1] 40%, lit.[2] 55%], mp 177-178°C, [lit.[10] 162-164°C, lit.[1] 174-176°C, lit.[15] 180°C, lit.[2] 170°C]. R_f (90:10 dichloromethane/methanol) 0.58. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.73 (d, 2 H, J = 6.2 Hz), 8.28 (d, 2 H, J = 7.2 Hz), 7.55 (d, 2 H, J = 7.2 Hz), 7.47 (d, 2 H, J = 6.2 Hz) . The NMR spectrum was consistent with literature.[2,9,10]

2,4'-Bipyridine-*N,N'*-dioxide (4c). To a solution of 2,4'-bipyridine (0.102 g, 0.65 mmol) in dichloromethane (20 mL) was added 15 mL of dimethyldioxirane in three equivalent aliquots over 35 minutes at 25 °C. Dichloromethane was removed in vacuo affording an-off-white, powdery solid. The solid was redissolved in acetone for two days with vigorous stirring at room temp. The undissolved solid afforded **4c** as a brown solid (0.022g, 18%) [lit.[1] 15%, lit.[14] 54%], mp. 237-238 °C [lit.[1] 240-242 °C, lit.[14] 200 °C]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.70 (d, 1H, J = 4.4 Hz), 8.27 (d, 2H, J = 6.4 Hz), δ 7.96 (d, 2H, J = 6.4 Hz), 7.70 (m, 1H), 7.52 (m, 2H,).

2,4'-Bipyridine-*N'*-oxide (4b). To a solution of 2,4'-bipyridine (0.1018 g, 0.652 mmol) in dichloromethane (20 mL) was added 15 mL of dimethyldioxirane in three equivalent aliquots over 35 minutes at 25 °C. Dichloromethane was removed in vacuo affording an off-white, powdery solid. Preparative TLC on silica gel (mobile phase: 95:5 dichloromethane/methanol) afforded crude **4b** as a colorless solid (0.076g, 68%) [lit.[9] 57%, lit.[10] 76%, lit.[1] 48%], mp 118-119 °C [lit.[9] 169-173 °C, lit.[10] 168-170 °C, lit.[1] 119-121 °C]. R_f (95:5 dichloromethane /methanol) 0.30. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.72 (m, 1H), 8.28 (d, 2H, J = 7.3 Hz), 7.97 (d, 2H, J = 7.3 Hz), 7.82 (m, 1H,, 7.75 (m, 1H), 7.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.0, 123.4, 123.5, 136.6, 137.2, 139.4, 150.2, 152.5 . The NMR spectra were consistent with literature.[9,10]

Crystallization of 2,4'-Bipyridine-*N'*-oxide. A sample of **4b** was dissolved in dichloromethane and allowed to crystallize at room temperature via slow evaporation. After several days, transparent colorless block-shaped crystals were collected, assessed for quality using polarizing microscopy, and mounted on a glass fiber for subsequent crystallographic investigation, mp 120-121 °C (dec).

Acknowledgements

The authors would like to thank the College of Arts and Sciences (Creative Research Grant) and the Petroleum Research Foundation administered by the American Chemical Society.

References

(1) Moran, D.B.; Morton, G.O.; Albright, J.D. *J. Heterocycl. Chem.*, **1986**, 23, 1074

(2) Brunner, H.; Störiko, F.; Rominger, F. Eur. *J. Inorg. Chem.*, **1998**, 771

(3) Edwards, O.E.; Gillespie, D.C. *Tet. Lett.*, **1966**, 4867

(4) Bobranski, B.; Kochanska, L.; Kowalewska, A. *Ber. Dtsch. Chem. Ges.*, **1938**, 71, 2385

(5) Weiner, M.A. *J. Organomet. Chem.* **1970**, 23, C20

(6) McKay, S.E.; Sooter, J.A.; Blackstock, S.C.; Bodige, S.G. *Heterocycl. Commun.*, **2001**, 7, 307

(7) McKay, S.E.; Sooter, J.A.; Marshall, T.P. *Heterocycl. Commun.*, **2003**, 9, 221

(8a) Murray, R.W.; Ramasubbu, J. *J. Org. Chem.*, **1985**, 50, 2847. (b) Winkeljohn, W.R.; Vasquez, P.C.; Strekowski, L.; Baumstark, A.L. *Tet. Lett.*, **2004**, 45, 8295-829.

(9) Yamamoto, Y.; Tanaka, T.; Yagi, M.; Inamoto, M. *Heterocycles,* **1996**, 42, 189

(10) Plaquevent, J.-C.; Chichaoui, I. *Bull. Soc. Chim. Fr.*, **1996**, 133, 369

(11) Mulliken, R.S. J. *Chem. Phys.*, **1955**, 23, 1833, 1841, 2338, 2343

(12) Adam, W.; Golsch, D. *Angew. Chem. Int. Ed. Engl.*, **1993**, 32, 737

(13) (a) Bodige, S.G.; Selby, T.D.; McKay, S.E.; Blackstock, S.C. *Trans. Am. Crystallogr. Assoc.*, **1998**, 33, 135.

(b) Bodige, S.G.; Zottola, M.A.; McKay, S.E.; Blackstock, S.C. *Crystal Eng.*, **1998**, 1, 243. (c) Wheeler, K.A; McKay, S.E.; Lashlee, R.W. III, *Acta Crystallogr.*, **2005**, E61, 645. (d) McKay, S.E.; Wheeler, K.A; Blackstock, S.C. *Acta Crystallogr.*, **2004**, E60, 2258

(14) Zoltewicz, J.A.; Cruskie, M.P. Jr.; Dill, C. D. *Tetrahedron*, **1996**, 52, 4239

(15) Fielden, R.; Summers, L. *J. Heterocycl. Chem.*, **1974**, 11, 299

(16) Kaczmarek, L.; Balicki, R.; Nantka-Mamirski, P. *Chem. Ber.*, **1992**, 125, 1965

(17) Tolstikov, G.A.; Emileev, U.M.; Yur'ev, V.P.; Gershanov, F.B.; Rafikov, S.R. *Tet. Lett.*, **1971**, 2807

(18) XSCANS. Diffractometer Controller Software. Bruker AXS, Inc.: Madison, Wisconsin, USA

(19) Barbour, L.J. *J. Supramol. Chem.*, **2001**, 1, 189

(20) Sheldrick, G.M. SHELXS-97; program for structure solution, SHELXL-97: program for structure refinement, University of Göttingen, Germany, **1997**

(21) Prince E. (ed). International Tables for X-Ray Crystallography Vol. C; Springer: **1995**

(22) Spartan '04 Windows, version 1.0.1, Wavefunction, Inc.: Irvine, California, **2004**

Received on June17, 2008