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Synthesis of 1,10-*N,N′*-Phenanthroline Dioxides Using HOF·CH_3CN Complex

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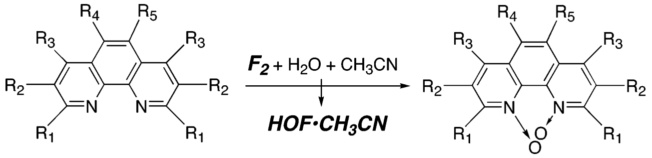

HOF·CH_3CN, a very efficient oxygen-transfer agent, made readily from F_2, H_2O, and CH_3CN, was reacted with various 1,10-phenanthroline derivatives to form the corresponding *N,N′*-dioxides in good yields and short reaction times.

HOF·CH_3CN, considered to be the best oxygen-transfer agent chemistry has to offer, is readily prepared by bubbling dilute fluorine through aqueous acetonitrile. It was previously used to hydroxylate sp^3 tertiary carbon centers, oxidize alcohols, ketones and ethers, as well as transform aliphatic and aromatic amines, including amino acids, into the corresponding nitro derivatives.[1] This agent was also used for other oxygen-transfer reactions such as olefins and aromatic ring epoxidations,[2] transforming azides and vicinal diamines into the corresponding nitro and dinitro derivatives,[3] and much more.[4]

The family of 1,10-phenanthroline *N,N′*-dioxides is of interest as a ligand in organometallic chemistry, as an oxygen-transfer agent, and as a model for preparing of higher heterohalicenes.[5] Despite many attempts, compounds of this family eluded chemists for more than 50 years[6] since it proved to be extremely difficult to take the three rings of the parent 1,10-phenanthroline (**1a**) out of planarity, a prerequisite for accommodating the two oxygen atoms in the bay area of the aromatic **2a**. We report here on the use of this reagent for constructing such *N,N′*-dioxides from the parent 1,10-phenanthrolines as a part of a new family which, not long ago, was considered to be impossible to make.[7]

Result and Discussion

It took less than 2 min for 3 equiv of HOF·CH_3CN to convert 5-chloro-1,10-phenanthroline (**1b**) to the *N,N′*-dioxide (**2b**) in 67% yield (Scheme 1). It should be mentioned that this is the only family member previously synthesized, although the difficult oxidative step of the aromatic phenanthroline system was avoided and the aromatization to **2b** was completed only after the *N,N′*-dioxide moiety was constructed.[8] Although HOF·CH_3CN is known to react with aromatic rings,[2a] the reaction with the nitrogen atoms is much faster and no difficulties were encountered with the disubstituted 4,7-diphenyl-1,10-phenanthroline (**1c**) that was transformed in 2 min using 4 equiv of HOF·CH_3CN to the *N,N′*-dioxide (**2c**) in 74% yield. Increased substitution was also tolerated, and when 3,4,7,8-tetramethyl-1,10-phenanthroline (**1d**) was reacted with 5 equiv of HOF·CH_3CN, the *N,N′*-dioxide (**2d**) was obtained in 3 min and 67% yield.

We were interested to see whether the HOF·CH_3CN could overcome the steric hindrance around the nitrogen atoms. An interesting compound suitable for evaluation

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(1) (a) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325. (b) Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169. (c) Rozen, S.; Dayan, S.; Bareket, Y. *J. Org. Chem.* **1995**, *60*, 8267. (d) Kol, M.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1991**, 567. Rozen, S.; Kol, M. *J. Org. Chem.* **1992**, *57*, 7342. (e) Rozen, S.; Bar-Haim, A.; Mishani, E. *J. Org. Chem.* **1994**, *59*, 1208.

(2) (a) Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, *58*, 1593. (b) Rozen, S.; Golan, E. *Eur. J. Org. Chem.* **2003**, 1915. (c) Golan, E.; Hagooly, A.; Rozen, S. *Tetrahedron Lett.* **2004**, *45*, 3397.

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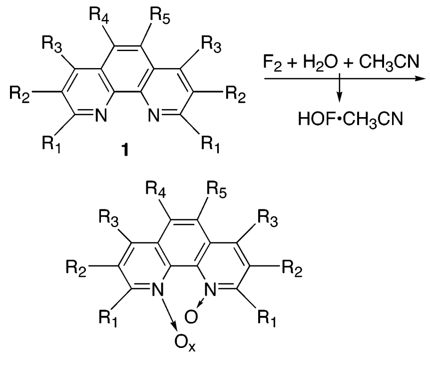
(7) For a preliminary report on the synthesis of the parent *N,N′*-dioxide **2a**, see: Rozen, S.; Dayan, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3471.

(8) Antkowiak, R.; Antkowiak, W. Z. *Heterocycles* **1998**, *47*, 893.

10.1021/jo047960e CCC: $30.25

SCHEME 1. Synthesis of 1,10-Phenanthroline *N,N'*-Dioxides



2: x = 1 **3**: x = 0

	yields of **2**
a: $R_1 = R_2 = R_3 = R_4 = R_5 = H$	(60%)
b: $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = Cl$	(67%)
c: $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = Ph$	(74%)
d: $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = Me$	(67%)
e: $R_2 = R_4 = R_5 = H$; $R_1 = Me$; $R_3 = Ph$	(66%)
f: $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NO_2$	(47%)

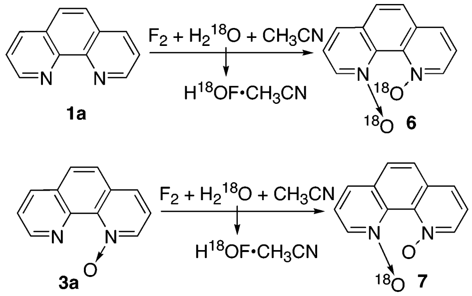
of such a question seems to be the tetrasubstituted 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (**1e**).[9] The outcome of the reaction provided a positive answer, but an excess of 12 equiv was needed for forming the *N,N'*-dioxide (**2e**) in 2 min and 66% yield. It should be mentioned that using only 1.2 equivalent of HOF•CH_3CN resulted in the mono *N*-oxide of 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (**3e**) in 93% yield after a few seconds.

A less reactive, electron-deficient 4-nitro-1,10-phenanthroline (**1f**) was also reacted. Although the yield was somewhat lower, the *N,N'*-dioxide (**2f**) was still obtained in 47% yield after 3 min using 6-equiv of HOF•CH_3CN.

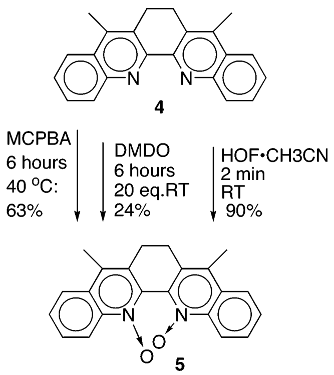
Compared to the parent phenanthrolines, the UV spectra of all *N,N'*-dioxides exhibit a red shift of up to 75 nm and with somewhat lower ϵ. The main reason for these phenomena seems to be the electrostatic repulsion between the nonbonding electron pairs of the oxygen atoms which are in close proximity.[7] Such a repulsion increases the electron density of the core and enables an easier n → π^* transition with characteristic lower ϵ.

Upon heating these dioxides to their melting or decomposition point, the two oxygen atoms were expelled and the parent phenanthrolines were obtained in yields of up to 30%. It was of interest to find out whether the two oxygen atoms released from **2a** for example, combined to form molecular oxygen. We heated this compound to its melting point (210 °C) in nitrogen atmosphere containing an inner capillary tube, loaded with Et_2Zn. After a few seconds, the Et_2Zn lost its clarity and started to smoke, indicating that molecular oxygen was indeed evolved. In a control experiment where the parent phenanthroline **1a** was melted, no gases were evolved and the Et_2Zn remained clear.

SCHEME 2. Synthesis of 1,10-Phenanthroline *N,N'*-Dioxides with [18]O Isotope



SCHEME 3. Oxidation of Dihidrophenanthrolines



One of the advantages of the HOF•CH_3CN complex is that its electrophilic oxygen comes from water, which is the best source for all oxygen isotopes. We have passed fluorine through a solution of acetonitrile and $H_2{}^{18}O$ and obtained $H^{18}OF$•CH_3CN, which was reacted with either **1a** or **3a** (Scheme 2). In the first case, the MS (FAB) [*m/z* = 217 $(M + 1)^+$] clearly shows that **6**, with both oxygen atoms being [18]O isotopes, is obtained. In the case of **3a**, compound **7** with only one [18]O was formed without any scrambling of the oxygen atoms (MS (CI) [*m/z* = 215 $(M + 1)^+$]). Coupled with the previous results we can conclude that 1,10 phenanthroline *N,N'*-dioxides has a potential of serving as a source for molecular oxygen with any isotope variation (Scheme 2).

While compounds **2** could not be obtained by reacting the corresponding **1** with *m*-CPBA or dimethyl dioxirane (DMDO), this was not the case with partially reduced phenanthrolines that are not strictly planar. 5,8-Dimethyl-6,7-dihydro-dibenzo[*b,j*][1,10]phenanthroline (**4**) can serve as an example. Although quite sterically hindered around the nitrogen atoms, treating it for more than 6 h with an excess of *m*-CPBA in boiling methylene chloride produced the *N,N'*-dioxide **(5)** in 63% yield. Similarly, **5** was obtained in 24% yield by reacting **4** with 20 equiv of dimethyldioxirane (DMDO) for 6 h. Reacting **4**, however, with 9 equivalents of HOF•CH_3CN furnished **5** in higher than 90% yield in only 2 min reaction carried at room temperature (Scheme 3).

One of the main reasons for the persisting 50 years search for ways to make the family of the 1,10-phenanthroline *N,N'*-dioxides was to examine their complexation ability to metals and potential role as ligands in organometallic chemistry. As a test case we chose to react **2d** with europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]−Eu(tfc)$_3$ since it is easy to follow the complexation by ^1H NMR (Scheme 4). The shift of H-2 and H-9 (+1 ppm: from 8.42 to 9.42 ppm) as well as the shift of the two hydrogens at 5 and 6 (+ 0.71 ppm:

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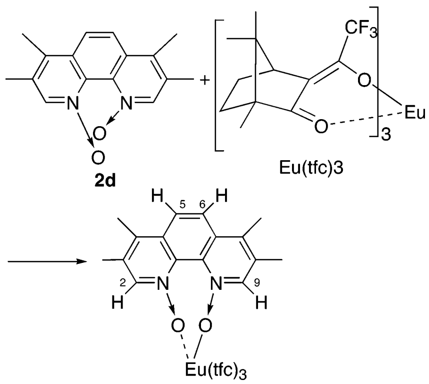
[9] Ono, K.; Yanase, T.; Ohkita, M.; Saito, K.; Matsushita, Y.; Naka, S.; Okada, H.; Onnagawa, H. *Chem. Lett.* **2004**, *33*, 276.

SCHEME 4. Complexation of Phenanthroline Dioxide Derivative with a Metal



from 7.77 to 8.48 ppm) reached a plateau after the addition of 1.2 equiv of the Eu agent. The identical shift of the symmetrical hydrogens as well as the fact that adding an excess of $Eu(tfc)_3$ did not change the outcome mean that the metal complexed itself with the two oxygen atoms of the same molecule, a feature which did not change even after 5 h. An additional reason for working with $Eu(tfc)_3$ was to see if we could observe a separate set of peaks for each enantiomer of the helical **2d**. We were not able to see such diastereoisomeric separation by either ^1H or ^{19}F NMR. It is possible that there is a rapid inversion of the two N−O groups, but it should be emphasized that even at low temperatures of about −60 °C only one set of signals in both ^1H and ^{19}F spectra was observed.

In conclusion, $HOF\cdot CH_3CN$, is unique in its ability to construct a whole new family of 1,10-phenanthroline *N,N′*-dioxides from the corresponding 1,10-phenanthrolines. Among other features these compounds have a potential of becoming a new family of ligands in organometallic chemistry.

We hope that this work will encourage chemists not to shy away from F_2 because of some unjustified fears and prejudice. Reactions with $HOF\cdot CH_3CN$ can provide a good example. Today, prediluted fluorine is commercially available and the work with it is relatively easy. All reaction vessels are standard glassware, and a simple basic trap takes care of small amounts of F_2 which had not reacted with water.

Experimental Section

^1H NMR and ^{13}C NMR were obtained at 400 MHz, with $CDCl_3$ as the solvent and Me_4Si as an internal standard. IR spectra were recorded in a $CHCl_3$ solution on an FTIR spectrophotometer. MS spectra were measured under CI, EI, or FAB conditions. In extreme cases where no conventional instrument was able to detect the molecular ions, they were successfully detected by Amirav's supersonic GC−MS, developed in our department.[10] UV spectra were recorded in $CHCl_3$ and EtOH serving as solvents.

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and very corrosive material. It should be used only with an appropriate vacuum line.[11] For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying the process. If elementary precautions are taken, work with fluorine is relatively simple, and we had no bad experiences working with it.

General Procedure for Producing $HOF\cdot CH_3CN$. Mixtures of 10−20% F_2 with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. It was then passed at a rate of about 400 mL/min through a cold (−15 °C) mixture of 100 mL of CH_3CN and 10 mL of H_2O. The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4−0.6 M.

General Procedure for Working with $HOF\cdot CH_3CN$. 1,10-Phenanthroline derivative was dissolved in $CHCl_3$, and the mixture was cooled to 0 °C. The oxidizing agent was then added in one portion to the reaction vessel. The excess of $HOF\cdot CH_3CN$ was quenched with saturated sodium bicarbonate and extracted with $CHCl_3$, and the organic layer dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization gave the corresponding 1,10-phenanthroline *N,N′*-dioxide.

4,7-Diphenyl-1,10-phenanthroline *N,N′*-dioxide (2c) was prepared from **1c** (1gr, 3 mmol) as describe above resulting in a 74% yield of an orange solid recrystallized from EtOH/CH_2Cl_2 (2/1): mp = 230−231 °C; IR 663, 702, 780, 820, 1183, 1295, 1373, 1433, 2989 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 254 ($\epsilon = 4.5 \times 10^4$), 270 ($\epsilon = 3.6 \times 10^4$), 300 ($\epsilon = 2.6 \times 10^4$), 376 nm ($\epsilon = 0.8 \times 10^4$); ^1H NMR 7.42−7.53 (2 H, m), 7.61 (2 H, s), 8.62 ppm (2 H, d, $J = 6.6$ Hz); ^{13}C NMR 123.9, 125.7, 128.7, 128.9, 129.7, 130.5, 134.2, 135.5, 136.6, 138.4 ppm; GC/MS $m/z = 364$ $(M)^+$.[10] Anal. Calcd for $C_{24}H_{16}N_2O_2$: C, 79.11; H, 4.43; N, 7.69. Found: C, 78.95; H, 4.56; N, 7.71.

3,4,7,8-Tetramethyl-1,10-phenanthroline *N,N′*-dioxide (2d) was prepared from **1d** (1.1 gr, 4.7 mmol) as described above resulting in a 67% yield of a yellow solid decomposing at 300 °C: IR 666, 734, 761, 782, 1303, 3020 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 245 ($\epsilon = 2.1 \times 10^4$), 281 ($\epsilon = 2.1 \times 10^4$), 398 nm ($\epsilon = 0.12 \times 10^4$); ^1H NMR 2.42 (6 H, s), 2.57 (6 H, s), 7.81 (2 H, s), 8.44 ppm (2 H, s); ^{13}C NMR 14, 17.3, 123.7, 129.5, 130.8, 132.6, 133.3, 139.2 ppm; HRMS (CI) m/z = calcd 269.129114, found 269.29114 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_2\cdot {}^1/_2H_2O$: C, 69.31; H, 6.13; N, 10.10. Found: C, 68.92; H, 5.92; N; 9.96.

2,9-Dimethyl-4,7-diphenyl-1,10-phenanthroline *N,N′*-dioxide (2e) was prepared from **1e** (0.9 gr, 2.5 mmol) as described above resulting in a 66% yield of an orange solid recrystallized from EtOH and decomposing at 215 °C: IR 704, 735, 765, 778, 790, 1301, 3018 cm^{-1}; UV−vis (CHCl3) λ_{max} 253 ($\epsilon = 2.8 \times 10^4$), 298 ($\epsilon = 1.4 \times 10^4$), 349 ($\epsilon = 0.9 \times 10^4$), 392 nm ($\epsilon = 0.4 \times 10^4$); ^1H NMR 2.82 (6 H, s), 7.44−7.55 ppm (14 H, m); ^{13}C NMR 18.2, 124.6, 128.4, 128.7, 129.1, 129.8, 133.2, 135.4, 137, 148 ppm. Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 78.97; H, 5.40; N, 7.23.

2,9-Dimethyl-4,7-diphenyl-1,10-phenanthroline monoxide (3e) was prepared from **1e** (0.7 gr, 1.9 mmol) as described above resulting in a 93% yield of a yellow solid: mp = 236−240 °C; IR 700, 704, 734, 759, 780, 1292, 3020 cm^{-1}; UV−vis λ_{max} ($CHCl_3$) 259 ($\epsilon = 2.9 \times 10^4$), 285 ($\epsilon = 3.3 \times 10^4$), 344 ($\epsilon = 1.05 \times 10^4$), 402 nm ($\epsilon = 0.2 \times 10^4$); ^1H NMR 2.84 (3 H, s), 2.99 (3 H, s), 7.55−7.48 (12 H, m), 7.67 (1 H, d, $J = 5$ Hz), 7.71 ppm (1 H, d, $J = 5$ Hz); ^{13}C NMR 19.5, 25.9, 123.3, 123.9, 124.6, 125.1, 125.3, 128.3, 128.4, 128.5, 128.6, 129.3, 129.7, 129.8, 135.9, 137.7, 137.9, 138, 142.7, 148.2, 149.4, 157.4 ppm; MS (FAB) $m/z = 377.1$ $(M + 1)^+$. Anal. Calcd for $C_{26}H_{20}N_2O\cdot H_2O$: C, 78.79; H, 5.48; N, 7.19. Found: C, 79.41; H, 5.61; N, 7.25.

5-Nitro-1,10-phenanthroline *N,N′*-dioxide (2f) was prepared from **1f** (1 gr, 4.5 mmol) as described above resulting in a 47% yield of a brown solid, recrystallized from H_2O and decomposing at 200 °C: IR 670, 726, 748, 765, 794, 1215, 1541, 1603, 3029 cm^{-1}; UV−vis (MeOH) λ_{max} 233 ($\epsilon = 1.5 \times 10^4$),

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[10] (a) Dagan, S.; Amirav, A. *J. Am. Soc. Mass. Spectrom.* **1996**, *7*, 550. (b) Fialkov, A. B.; Amirav, A. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1326.

[11] Dayan, S.; Kol, M.; Rozen, S. *Synthesis* **1999**, 1427.

258 ($\epsilon = 1.0 \times 10^4$), 343 ($\epsilon = 0.3 \times 10^4$); ^{1}H NMR 7.59 (1 H, dd, $J_1 = 4$ Hz, $J_2 = 3$ Hz), 7.61 (1 H, dd, $J_1 = 4$ Hz, $J_2 = 3$ Hz), 7.82 (1 H, d, $J = 4$ Hz), 8.21 (1 H, d, $J = 4$ Hz), 8.46 (1 H, s), 8.56 (1 H, d, $J = 3$ Hz), 8.58 ppm (1 H, d, $J = 3$ Hz); ^{13}C NMR 122, 127.5, 127.8, 128.2, 128.4, 128.6, 129.5, 132.6, 132.9, 142.9, 144.7 ppm; MS (CI) $m/z = 258$ (M + 1)$^+$.

6,7-Dihydro-5,8-dimethyldibenzo[*b*,*j*][1,10]phenanthroline *N*,*N′*-dioxide (5) was prepared from **4** (1.2gr, 3.9 mmol) as described above resulting in an 90% yield of yellow solid, recrystallized from $CHCl_3$ and decomposing at 200−201 °C: IR 669, 726, 748, 779, 1231, 1357, 3026 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 247 ($\epsilon = 2.5 \times 10^4$), 344 ($\epsilon = 1.0 \times 10^4$), 377 nm ($\epsilon = 0.9 \times 10^4$); ^{1}H NMR 2.66 (6 H, s), 2.72 (2 H, d, $J = 5$ Hz), 3.39 (2 H, d, $J = 5.5$ Hz) 7.67−7.76 (4 H, m), 8.04 (2 H, d, $J = 4$ Hz), 8.92 ppm (2 H, d, $J = 4$ Hz); ^{13}C NMR δ 15.9, 28.1, 122.3, 126.3, 128.6, 130.7, 131.1, 131.2, 134.5, 138.4, 143 ppm; MS (FAB) $m/z = 343$ (M + 1)$^+$. Anal. Calcd for $C_{22}H_{18}N_2O_2 \cdot {}^1/_2H_2O$: C, 76.18; H, 5.90; N, 8.10. Found: C, 75.99; H, 6.07; N, 7.39.

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