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The Tetrazole 3-*N*-Oxide Synthesis

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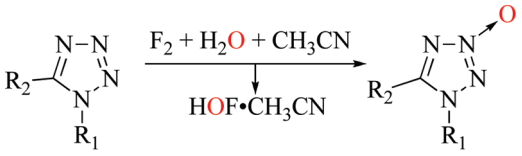

R_1, R_2 = alkyl or aryl

An efficient procedure for transferring an oxygen atom to the 1- or 2-substituted 5-alkyl or aryl tetrazole ring, resulting, for the first time, in the corresponding *N*-oxides, was developed using HOF·CH_3CN. This novel route features mild conditions and high yields. X-ray structure analysis and ^{15}N NMR experiments indicate that the preferred position for the incorporation of the oxygen is on the *N*-3 atom.

Although not found in nature, the tetrazole ring appears in a wide range of important products such as propellants,[1] explosives,[2] and many drugs.[3] In the past decade, due to their extraordinary stability under metabolic conditions, many tetrazole derivatives showed enhanced biological activities when used as antiviral, antibacterial, and antifungal agents,[4] as well as when used as a promoter in the synthesis of oligonucleotides.[5]

It was agreed by most that the tetrazole ring resists oxidation even when very strong oxidizing agents were employed because of its low HOMO.[6] Indeed, we found no reports for the preparation of tetrazole *N*-oxides. The only formation of nitrogen−oxygen bond in this family of compounds led to 1- and 2-hydroxytetrazoles with a limited scope of possible starting materials.[7,8]

We report here that the *N*-selective oxidation of this ring, leading to the *N*-oxide moiety, is possible when using the acetonitrile complex of the hypofluorous acid: HOF·CH_3CN.

This readily made reagent[9] has established itself as one of the best oxygen transfer agents chemistry has in its arsenal. HOF·CH_3CN is a unique source of a strong electrophilic oxygen since it is bonded to fluorine, the only atom more electronegative than itself. Its unusual properties constituted the base of some theoretical studies concerning its geometry and the general mechanism of the oxygen transfer processes.[10] Earlier processes developed with the aid of this reagent are summarized in two reviews describing many first or difficult to achieve transformations.[11,12] Other unique reactions involve synthesis of episulfones,[13] oligothiophenes *S*,*S*′-dioxides,[14,15] quinoxaline *N*,*N*′-dioxides,[16] α-alkylation of natural amino acids,[17] and more. Exploring the new possibilities offered by this reagent in transforming tetrazole rings into their corresponding *N*-oxide derivatives was therefore very attractive.

Treating 1,5-pentamethylenetetrazole (**1a**) with a stochiometric amount or small excess of HOF·CH_3CN did not affect the starting material. However, using a large excess (10 mol equiv) of the reagent at 0 °C changed the outcome and the previously unknown 1,5-pentamethylenetetrazole-3*N*-oxide (**2a**) was formed in 95% yield (50% conversion)[18] in a few minutes (Scheme 1). Electron-withdrawing groups located at the carbon atom of the terazole as in 5-chloro-1-phenyltetrazole (**1b**) did not inhibit the quantitative formation (50% conversion, in minutes) of the new 5-chloro-1-phenyltetrazole-3*N*-oxide (**2b**) (Scheme 1). The sterically hindered 1-cyclohexyl-5-(4-chlorobutyl)tetrazole (**1c**) was also successfully oxidized by the HOF·CH_3CN complex to give the previously unknown 1-cyclohexyl-5-(4-chlorobutyl)tetrazole-3*N*-oxide

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(18) For example, "95% yield (50% conversion)" means that based on the consumed SM the reaction is almost quantitative, while from the mole equivalents perspective the product obtained is only about 50% of the mole equivalents of the SM. The other unchanged 50% of the starting material could be recycled.

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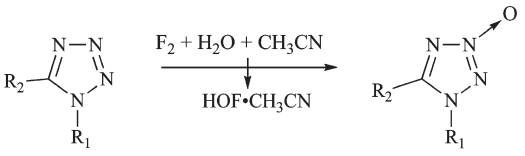
SCHEME 1. Oxygenation of 1,5-Disubstituted Tetrazole



		yield
1a	$R_1, R_2 = cyclo\ (CH_2)_5$	**2a** 95%
1b	R_1 = Ph; R_2 = Cl	**2b** 95%
1c	R_1 = ⬡ ; $R_2 = (CH_2)_4Cl$	**2c** 90%
1f	$R_1 = CH_2COOEt$; R_2 = Ph	**2f** 95%

(**2c**) in 90% yield (90% conversion) and short reaction times (Scheme 1).

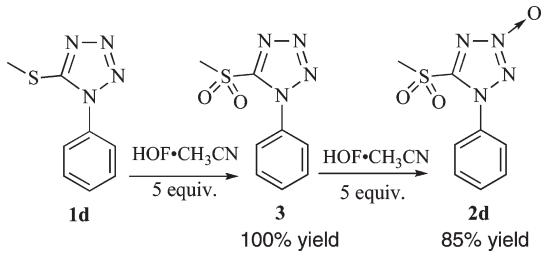
To find out if the formation of tetrazole *N*-oxide derivatives is unique to HOF·CH_3CN we have reacted **1a** and **1b** with a large excess of either *m*-CPBA or dimethyldioxirane (DMDO), but even after prolonged reaction times no traces of the desired **2a** or **2b** could be detected.

In the past we had found that the electrophilic oxygen of the HOF·CH_3CN has no significant preference between nitrogen or sulfur atoms.[19] This fact prompted us to investigate the oxidation of 5-methylsulfide-1-phenyltetrazole (**1d**). When using 5 equiv of the reagent 5-methylsulfone-1-phenyltetrazole (**3**) was obtained in quantitative yield emphasizing the resistance of the tetrazole ring toward oxidation. The same result was obtained by using 35% H_2O_2 with AcOH in MW(30W) leading to the corresponding sulfone without affecting any of the nitrogens.[20] However, by adding an additional 5 equiv of HOF·CH_3CN to **1d**, we were able to affect the ring as well as the sulfur atom forming eventually the desired new 5-methylsulfonyl-1-phenyltetrazole-3-oxide (**2d**) in 85% yield (Scheme 2).

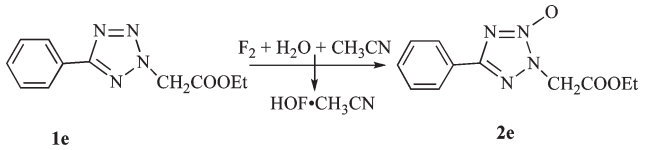
To investigate the scope of the reaction we have also tested tetrazoles substituted at *N*-2. The reaction of 2-carboethoxymethyl-5-phenyltetrazole (**1e**) with 3 equiv of acetonitrile–hypofluorous acid complex yielded 2-carboethoxymethyl-5-phenyltetrazole-3*N*-oxide (**2e**) in almost quantitative yield, but in only 20% conversion, a result which did not change even after 20 equiv of the reagent were used (Scheme 3). Obviously the proximity, and not the chemical character of the functional group (an ester) to the reacting *N*-3 center, is the major factor for the sluggish reaction since a 10 min reaction of 1-carboethoxymethyl-5-phenyltetrazole (**1f**) with the reagent resulted in 1-carboethoxymethyl-5-phenyltetrazole-3*N*-oxide (**2f**) in 95% yield and in almost full conversion (Scheme 1).

To determine the location of the oxygen in the four-nitrogen containing ring, we performed X-ray structural

SCHEME 2. Oxygenation of 5-Methylsulfide-1-phenyltetrazole (1d)



SCHEME 3. Oxygenation of 2-Carboxyethoxymethyl-5-phenyltetrazole (1e)



analysis on both **2a** and **2b** (X-ray structures can be found in the SI).[21] The conclusion is that no matter which group is attached to the carbon of the tetrazole ring the oxygen's position is exclusively on the *N*-3 atom.

Additional evidence for the *N*-oxide position was made possible by using $^1H-^{15}N$ heteronuclear 2D NMR shift correlation experiments combined with ^{15}N 1D NMR. Thus, a strong long-range correlation from the methylene hydrogens of the starting material **1a** to the *N*-1, *N*-2, and *N*-4 nitrogens helped us attribute their shifts at 240, 371, and 327 ppm, respectively. After the oxidation, the same nitrogen atoms were found at 210, 320, and 295 ppm (see SI). Since the *N*-3 of the starting **1a** does not correlate with any of the hydrogens in the molecule, we used ^{15}N 1D NMR and found its chemical shift to be at 387 ppm. After the oxidation, the *N*-3 signal, which again could be observed only by ^{15}N 1D NMR, was shifted upfield by almost 50 ppm and found at 339 ppm. The same pattern was found for **1f** and its corresponding oxidized derivative **2f**. Again the *N*-3 oxide nitrogen atom was shifted upfield by 47 ppm (388 ppm for the starting material). These results helped us characterize the structure of *N*-2 substituted tetrazole-*N*-3 oxide **2e**, where the long-range correlations placed the *N*-1, *N*-2, and *N*-3 atoms at 302, 230, and 347 ppm, respectively, while the 1D experiment revealed the *N*-4 atom at 305 ppm. Thus *N*-3, which at the starting material **1e** appeared at 384 ppm, was once again shifted upfield by almost 40 ppm consistent with all previous cases.

In conclusion, tetrazole *N*-oxides were synthesized for the first time using the powerful oxygen transfer reagent HOF·CH_3CN in fast and high yield reactions. Considering the commercial availability of premixed gases of fluorine and nitrogen, this method of transferring oxygen may become a method of choice for many cases were the alternatives are not potent enough.

Experimental Section

General Experimental Procedures. ^1H NMR spectra were recorded on a 400 MHz spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. $CDCl_3$ (Me_4Si as an internal standard) served as solvent. ^{15}N NMR was calibrated with ^{15}N-enriched formamide. IR spectra were recorded in $CHCl_3$ solutions on an FTIR spectrometer.

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(21) X-ray structures: **2a** ($C_6H_{10}N_4O$) (CCDC 756152) and **2b** ($C_7H_5ClN_4O$) (CCDC 756153). The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 756152 and 756153. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via http://www.ccdc.cam.ac.uk/deposit.

MS were measured under CI, EI, FAB, ESI-QqTOF, and MALDI-TOF conditions. UV spectra were recorded in $CHCl_3$.

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and a corrosive material. It should be used with an appropriate vacuum line. For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, thereby simplifying the process. Unreacted fluorine should be captured by a simple trap containing a solid base such as sodalime located at the outlet of the glass reactor. A detailed setup for working with F_2 could be found in the literature.[22] If elementary precautions are taken, work with fluorine is relatively simple and we have never experienced any difficulties or unpleasant situations.

General Procedure for Producing HOF·CH_3CN. A mixture of 10−20% F_2 in nitrogen was used throughout this work. The gas mixture was prepared in a secondary container prior to the reaction and passed at a rate of about 400 mL per minute through a cold (−15 °C) mixture of 100 mL of CH_3CN and 10 mL of H_2O in a regular glass reactor. 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 molar.

General Procedure for Working with HOF·CH_3CN. A tetrazole derivative was dissolved in CH_2Cl_2, and the mixture was cooled to 0 °C. The solution containing the oxidizing agent was than added in one portion to the reaction vessel. The reaction was stopped after a few minutes. Adding $NaHCO_3$ destroys all excess of the reagent and neutralizes the HF present in the reaction mixture. The aqueous layer was then extracted three times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography yielded the desired tetrazole *N*-oxide compounds. The crude product was usually purified by vacuum flash chromatography, using 60-H silica gel with increasing portions of EtOAc in petroleum ether followed by recrystallization with hexane−benzene mixtures.

1,5-Pentamethylenetetrazole-3-oxide (**2a**) was prepared from the commercially available **1a** (0.5 g, 3.62 mmol), using 10 equiv of the oxidizing agent as described above. It was purified by flash chromatography with 70:30 EtOAc:PE as eluent and then recrystallized from 1:1 hexane:benzene. A crystalline white solid (0.24 g, 1.54 mmol, 95% yield, 50% conversion) was obtained: Mp 124−125 °C. IR 1210, 1505 cm^{-1}. ^1H NMR 4.31(2H, t, J = 5 Hz), 2.99 (2H, t, J = 5.8 Hz), 1.91−1.99 (4H, m), 1.83 (2H, quin, J = 2.5 Hz) ppm. ^{13}C NMR 156.3, 50.2, 29.4, 26.9, 24.6, 24.3 ppm. ^{15}N NMR (1D + 2D) 210, 295, 320, 339 ppm, for *N*-1, *N*-4, *N*-2, and *N*-3 correspondingly. Respective values for the starting material 1,5-pentamethylenetetrazole (**1a**): ^{15}N NMR (1D + 2D) 240, 327, 371, 387 ppm. HRMS (CI) (*m*/*z*) calcd for $C_6H_{10}N_4O$ 155.0933 $(MH)^+$, found 155.0931. Anal. Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.69; H, 6.45; N, 36.44.

5-Chloro-1-phenyltetrazole-3-oxide (**2b**) was prepared from commercially available **1b** (0.5 g, 2.77 mmol) as described above, using 10 equiv of the oxidizing agent. The product was purified by flash chromatography with 30:70 EtOAc:PE as eluent and then recrystallized from 1:1 hexane:benzene. A crystalline cream solid (0.26 g, 1.32 mmol, 95% yield, 50% conversion) was obtained: Mp 156−157 °C. λ_{max} 265 nm. IR 1273, 1401, 1510 cm^{-1}. ^1H NMR 7.57−7.63 (5H, m) ppm. ^{13}C NMR 141.5, 131.9, 131.6, 130.4, 125.0 ppm. HRMS (CI) (*m*/*z*) calcd for $C_7H_5ClN_4O$ 197.0230 $(MH)^+$, found 197.0229. Anal. Calcd for $C_7H_5ClN_4O$: C, 42.77; H, 2.56; N, 28.50; Cl, 18.03. Found: C, 43.01; H, 2.36; N, 28.33; Cl, 18.48.

Acknowledgment. This work was supported by the Israel Science Foundation.

Supporting Information Available: Complete experimental procedures, as well as ^1H NMR, ^{13}C NMR, and ^{15}N NMR spectra for all new compounds and crystallographic data for compounds **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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