Easy access to the family of thiazole *N*-oxides using HOF·CH_3CN†

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An efficient procedure for transferring an oxygen atom to thiazole-containing compounds, resulting in the corresponding *N*-oxides, was developed by using HOF·CH_3CN; mild reaction conditions, high yields and easy purification are the main features of this novel route, while X-ray structural analysis reveals a hydrogen bond between the *N*-oxide functionality and a water molecule.

The thiazole ring appears in a wide range of natural and synthetic products, such as epothilones and thiopeptide antibiotics, oligosaccharides, *C*-glycosides, and more.[1] Dynamic interest lay behind the development of many modifications of this heterocycle, but mainly concentrated on the carbon atoms of the ring. Changes around the heteroatoms were relatively rare, with the notable exception of the synthesis of *N*-oxide derivatives, which captured the attention of the chemical and especially pharmaceutical communities.

A few examples underline the reasons for this interest. β-Lactam antibiotics, such as cephalosporins, bearing thiazole *N*-oxide derivatives, display unusual and effective antibacterial properties.[2] Thiazole *N*-oxide analogues of epothilones A and B serve as novel anticancer agents.[3] Recent studies on the design and synthesis of oligonucleotides containing thiazole *N*-oxide disclose that this functionality is unique in the sense of introducing a pronounced directional dipole into molecules that is capable of forming specific and strong hydrogen bonds.[4] Such biologically important findings have triggered intensive efforts aimed at the preparation of the thiazole *N*-oxide moiety, but the built-in limitations of the orthodox routes used did not result in conspicuous success. The synthesis, *via* cyclization of ω-(dialkylamino-oximinomercapto)-acetophenone, involves a multi-step reaction and is restricted to specific starting materials,[5] while direct oxidation using *meta*-CPBA or permaleic acid requires very long reaction times, leading to thiazole *N*-oxides in yields of 15 to 50% only.[3,4,6,7] There is only one example describing the formation of thiazole *N*-oxide *C*-nucleoside in good yield using trifluoroacetic anhydride and hydrogen peroxide–urea complex.[4] Clearly, a general and efficient methodology for the preparation of this important family is needed.

The readily made HOF·CH_3CN complex[8] is considered to be one of the best oxygen transfer agents in chemistry.[9] Unlike all other oxygen transfer reagents, HOF·CH_3CN is a unique source of a permanent electrophilic oxygen species since it is bound to fluorine, the only atom more electronegative than itself. This facilitates the transfer of the oxygen atom to most nucleophilic sites under mild conditions (0 °C or lower, in seconds or minutes). This complex has been instrumental in transforming azides and amines, including vicinal ones, into their corresponding nitro derivatives,[10] in the epoxidation of practically every conceivable olefin,[11] in the unprecedented oxidation of oligothiophenes to their corresponding *S*,*S*-dioxides,[12] and much more.[13] Exploring the possibilities offered by this reagent in transforming thiazole rings directly into their desired corresponding *N*-oxide derivatives was therefore quite attractive, and the results were rewarding.

Treating 2,4-dimethylthiazole (**1a**) with 2 equivalents of HOF·CH_3CN for 20 min at room temperature resulted in the formation of the previously unknown *N*-oxide **2a** in 91% yield. While none of the double bonds of the thiazole moiety were affected by this reaction, a small amount of water soluble *N*,*S*,*S*-trioxide **3a** was also formed and identified. It is worth mentioning that normal MS methods could not detect the molecular ion of the fully oxygenated **3a**, and we had to resort to Amirav's supersonic GC-MS, developed in our department, to detect it.[14]

Steric hindrance is not a compelling factor in this reaction, so replacing the methyl group at the C-2 position with a bulkier isopropyl one, as in **1b**, did not change the outcome, and the new 2-isopropyl-4-methylthiazole *N*-oxide (**2b**) was formed after 30 min in 87% yield. It was important to find out whether an unsubstituted thiazole at C-2 could also be transferred to the corresponding *N*-oxide, since it could open the way for further chemical transformations. 4,5-Dimethylthiazole (**1c**) and 4-methyl-5-thiazolylethyl acetate (**1d**) served as test compounds, and both were converted in excellent yields to their respective *N*-oxides **2c** and **2d**. The latter also demonstrated that protected alcohols will not interfere with the oxygen transfer process. The *N*-oxide moiety did not prevent reactions at C-2, such as bromination with NBS, which formed 2-bromo-4-methyl-5-thiazolylethyl acetate *N*-oxide (**2d–Br**) after 30 min in 91% yield. Obviously, introducing a bromine atom at the 2-position means that a host of other reactions become feasible.

As in many biologically important compounds the thiazole ring is often fully substituted, it was of interest to find out if such trisubstituted heterocycles would undergo an oxygen transfer process. Compounds **1e**, **1f** and **1g** served as model molecules and were subjected to the HOF·CH_3CN complex. In all these cases, a three-fold excess of the oxidant was required, but the new major products 2,4,5-trimethylthiazole *N*-oxide (**2e**), 2-ethyl-4,5-dimethylthiazole *N*-oxide (**2f**) and 2,4-dimethyl-5-acetylthiazole *N*-oxide (**2g**) were obtained in high yield. It should be noted that in all of these reactions, small amounts (5–10%) of the *N*,*S*,*S*-trioxo derivatives (**3e–3g**) were also formed, but their separation was straightforward since they are all soluble in water. While

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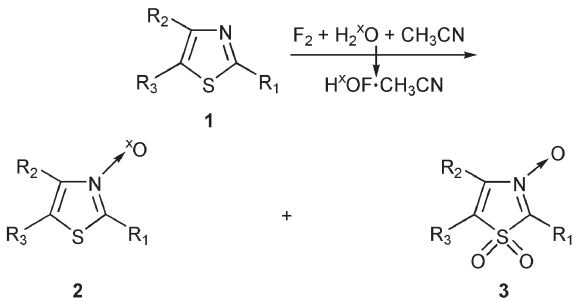
HOF·CH_3CN is known to react with the π-electrons of aromatic rings, such as benzene or phenanthrene derivatives, resulting in the corresponding epoxides,[15] it reacts much faster with the nitrogen atom of thiazole rings. This is demonstrated by the reaction of 2-methylnaphtho[1,2-*d*]thiazole (**1h**) with HOF·CH_3CN, which produced the corresponding *N*-oxide **2h** in 78% yield without affecting the naphthalene core.

One of the advantages of HOF·CH_3CN is that the origin of its electrophilic oxygen atom is water, which is the most convenient source of all oxygen isotopes. $H^{18}OF{\cdot}CH_3CN$, prepared by passing diluted fluorine through $H_2{}^{18}O$ and acetonitrile, was reacted with **1a**, leading to thiazole **2a** with a N–^{18}O functionality. This functionality is difficult to introduce by other routes, and can serve as a probe in degradation and other studies. The heavy oxygen in the N–^{18}O moiety is not interchangeable with the common ^{16}O isotope when treated with regular water or exposed to air, as evident from its HRMS (CI) (*m*/*z*): calc. for $C_5H_8N^{18}OS$ 132.036906 $(MH)^+$, found 132.036609.



91%	**a:**	$R_1 = R_2 = Me$; $R_3 = H$; x = 16,18	5%
87%	**b:**	R_1 = i-Pr; $R_2 = Me$; $R_3 = H$; x = 16	6%
95%	**c:**	$R_1 = H$; $R_2 = R_3 = Me$; x = 16	3%
91%	**d:**	$R_1 = H$; $R_2 = Me$; $R_3 = CH_2CH_2OAc$; x = 16	5%
90%	**e:**	$R_1 = R_2 = R_3 = Me$; x = 16	5%
87%	**f:**	$R_1 = Et$; $R_2 = R_3 = Me$; x = 16	6%
85%	**g:**	$R_1 = R_2 = Me$; $R_3 = Ac$; x = 16	10%
78%	**h:**	$R_1 = Me$; $R_2 = R_3$ =  ; x = 16	10%

91% **2d** —NBS→ **2d-Br**: $R_1 = Br$; $R_2 = Me$; $R_3 = CH_2CH_2OAc$

In the past we had found that there was no distinct preference by the electrophilic oxygen in HOF·CH_3CN towards nitrogen or sulfur atoms.[16] Despite the aromaticity of the ring, which should encourage attack at the nitrogen, there is always the remote possibility of the oxygen reacting with the sulfur atom to form a sulfoxide. However, X-ray structural analysis performed on **2g** (Fig. 1) clearly shows that an *N*-oxide moiety is obtained.[17] The thiazole ring remains planar and there is a hydrogen bond between the oxygens of two thiazole *N*-oxide molecules and the hydrogens of water, an important feature of thiazole *N*-oxide-containing nucleosides when forming strong contacts with DNA polymerases.[18]

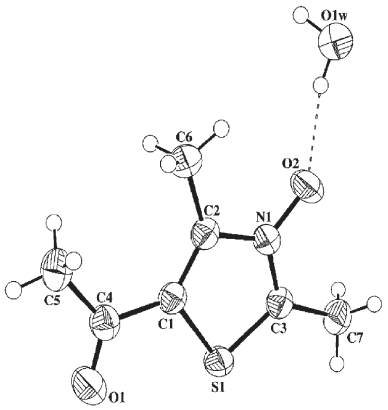


Fig. 1 X-Ray crystal structure of **2g**.

Additional evidence for *N*-oxide *vs.* *S*-oxide formation can be extracted from the ^{1}H–^{15}N heteronuclear NMR shift correlation experiment we performed on **2f** and its starting material **1f**. The results reveal a strong long-range correlation from the methyl hydrogens at the C-4 carbon, as well as from the methylene hydrogens of the ethyl moiety at the C-2 position, to the N-3 nitrogen. While the $^3J_{NH}$ correlation for **1f** is observed at 318.7 ppm,[19] the corresponding value for the product **2f** is at 276.6 ppm (liquid ammonia was used as a chemical shift reference standard). A similar shift to higher field of about 40 ppm for the thiazole *N*-oxide **2g** relative to its non-oxygenated precursor **1g** (from 321.8 to 283.4 ppm, respectively) was also recorded.

Another important feature of the thiazole *N*-oxide family can be revealed from their UV-vis spectra. There are two well-defined differences between the starting materials **1** and the respective products **2**. While the spectra of the thiazoles present a single absorption maximum around 250 nm (see the ESI†), the corresponding *N*-oxides display two major peaks. The first has a value close to the one of the starting material, while the second maximum is red-shifted by 24–76 nm. These shifts and the consequent narrowing of the HOMO–LUMO energy gap, derived from the absorption maxima, point to the greater electron delocalization and electron affinity of the thiazole *N*-oxides, a very important feature for organoelectronic devices.[12]

In conclusion, it is clear that the HOF·CH_3CN complex is a powerful reagent for the preparation of almost any thiazole *N*-oxide in fast and high yielding reactions. Despite the superstitious reluctance of some chemists to use F_2 (needed for the reagent preparation), working with this halogen is no more complicated than working with chlorine. Moreover, the commercial availability of pre-diluted fluorine makes this procedure very simple indeed.

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Notes and references

1 K. C. Nicolaou, A. Ritzen and K. Namoto, *Chem. Commun.*, 2001, **17**, 1523–1535; A. Dondoni and A. Marra, *Chem. Rev.*, 2004, **104**, 2557–2599; M. C. Bagley, J. W. Dale, E. A. Merritt and X. Xiong, *Chem. Rev.*, 2005, **105**, 685–714; K. C. Nicolaou, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zecri and S. Bulat, *J. Am. Chem. Soc.*, 2005, **127**, 11159–11175.

2 E. Perrone, M. Alpegiani, F. Giudici, F. Buzzetti, G. Nannini, G. Meinardi, S. Grasso, A. Bianchi and I. De Carneri, *J. Antibiot.*, 1984, **37**, 1423–1440.

3 G. Hofle, N. Glaser, T. Leibold and M. Sefkow, *Pure Appl. Chem.*, 1999, **71**, 2019–2024.
4 T. J. Miller, H. D. Farquar, A. Sheybani, C. E. Tallini, A. S. Saurage, F. R. Fronczek and R. P. Hammer, *Org. Lett.*, 2002, **4**, 877–880.
5 K. Hirai and T. Ishiba, *Heterocycles*, 1978, **9**, 1223–1231.
6 N. Honjo, T. Niiya and Y. Goto, *Chem. Pharm. Bull.*, 1982, **30**, 1722–1730.
7 E. Perrone, M. Alpegiani, F. Giudici, A. Bedeschi, R. Pellizzato and G. Nannini, *J. Heterocycl. Chem.*, 1984, **21**, 1097–1111.
8 A detailed procedure for the preparation of HOF·CH_3CN from either commercially pre-diluted or pure (95%) fluorine can be found in: S. Dayan, Y. Bareket and S. Rozen, *Tetrahedron*, 1999, **55**, 3657–3664.
9 S. Rozen and S. Dayan, *Angew. Chem., Int. Ed.*, 1999, **38**, 3471–3473.
10 E. Golan and S. Rozen, *J. Org. Chem.*, 2003, **68**, 9170–9172; S. Rozen and M. Carmeli, *J. Am. Chem. Soc.*, 2003, **125**, 8118–8119; G. K. S. Prakash and M. Etzkorn, *Angew. Chem., Int. Ed.*, 2004, **43**, 26–28.
11 S. Rozen and E. Golan, *Eur. J. Org. Chem.*, 2003, 1915–1917; E. Golan, A. Hagooly and S. Rozen, *Tetrahedron Lett.*, 2004, **45**, 3397–3399.
12 E. Amir and S. Rozen, *Angew. Chem., Int. Ed.*, 2005, **44**, 7374–7378.
13 For the latest review on HOF·CH_3CN, see: S. Rozen, *Eur. J. Org. Chem.*, 2005, **12**, 2433.
14 A. B. Fialkov and A. Amirav, *J. Chromatogr., A*, 2004, **1058**, 233–242.
15 M. Kol and S. Rozen, *J. Org. Chem.*, 1993, **58**, 1593–1595; S. Rozen, Y. Bareket and J. Blum, *Tetrahedron Lett.*, 1997, **38**, 2333–2334.
16 S. Rozen and Y. Bareket, *J. Org. Chem.*, 1997, **62**, 1457–1462.
17 $C_{14}H_{20}N_2O_5S_2$, M = 360.45, monoclinic, space group $C2/c$, a = 25.7986(15), b = 6.0590(3), c = 10.8001(6) Å, β = 99.7930 (10)°, U = 1663.60(16) Å^3, T = 293 K, Z = 4, μ(Mo-Kα) = 0.346 mm^{-1}, 8836 reflections measured, 1807 independent (R_{int} = 0.0176) which were used in all calculations. The final R_1 was 0.0419 and w$R(F_2)$ was 0.1065 (all data). CCDC 289613. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602594c.
18 J. R. Kiefer, C. Mao, J. C. Braman and L. S. Beese, *Nature*, 1998, **391**, 304–307.
19 G. E. Martin and C. E. Hadden, *J. Nat. Prod.*, 2000, **63**, 543–585.

