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The Oxygenation of Thieno[2,3-*b*]thiophenes

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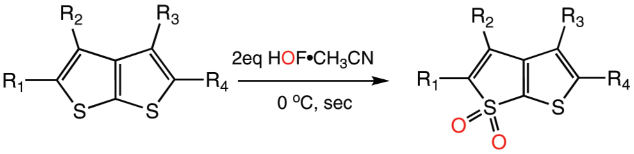

Members of thieno[2,3-*b*]thiophenes were oxidized using the HOF·CH_3CN complex, transforming the sulfur atom to the corresponding sulfonyl group in high yield and under very mild conditions.

Thiophene derivatives represent a class of important and well-studied heterocycles.[1] In the past few years, there has been a resurgence of interest concentrated around oligothiophenes. This family is among the most explored π-systems with favorable electronic and optical properties for a wide range of new technologies.[2]

In our previous works we described the first syntheses and some key properties of conjugated oligothiophene [all]-*S*,*S*-dioxides[3] as well as fused thieno[3,2-*b*]thiophene *S*,*S*-dioxides,[4] both promising classes of organic materials. In general, unlike the thieno[3,2-*b*]thiophenes, thieno[2,3-*b*]thiophenes contain two annulated thiophene rings with the two sulfur atoms facing the same direction. These compounds are planar, rigid, and highly stable heterocycles with a central cross-conjugated double bond. Previous attempts to obtain thieno[2,3-*b*]thiophene *S*,*S*-dioxide by orthodox oxidations either failed or resulted in very low yields even after prolonged reaction times.[5] Such an oxidation is not easy since the harsh conditions, usually required to overcome the aromatic stabilization, could lead to Diels–Alder-type reactions, SO_2 eliminations, and more.[5a]

We report here a general method for the direct oxidation of thieno[2,3-*b*]thiophene derivatives using the HOF·CH_3CN complex. A solution of this reagent is easily prepared by bubbling dilute fluorine through aqueous acetonitrile and is considered today as one of the best oxygen-transfer agents organic chemistry has to offer. The reagent's oxygen atom is a strong electrophile since it is weakly bonded to the most electronegative element, fluorine. This complex is able to serve as an oxygen transfer agent even to very weak nucleophiles[6] under mild conditions. Some of the work with this reagent was described in two reviews,[7] and later we had used it for the preparation of episulfones,[8] various *N*,*N*-diazafluorenes,[9] tetrazole 3*N*-oxide derivatives believed to be inaccessible,[10] and much more.

Compounds 3,4-dimethylthieno[2,3-*b*]thiophene (**1a**) and 3,4-diphenylthieno[2,3-*b*]thiophene (**1b**),[11] both with two indistinguishable sulfur atoms, were reacted with 2 molar equiv of HOF·CH_3CN at 0 °C. Within a few seconds, the previously unknown 3,4-dimethylthieno[2,3-*b*]thiophene-1,1-dioxide (**2a**) and 3,4-diphenylthieno[2,3-*b*]thiophene-1,1-dioxide (**2b**) were formed in quantitative yield. No other byproducts, usually associated with long reaction times and high temperatures, were observed. When only 1 molar equiv of HOF·CH_3CN was applied to **1a**, 50% was converted to the sulfone **2a** while the rest proved to be the starting material with no sulfoxide in sight. Parallel results have been observed and explained previously.[8,12] Attempts to fully oxidize either **1a** or **1b** to their tetraoxide derivatives by adding an excess of HOF·CH_3CN were unsuccessful. At this point, we emphasize that no two adjacent thiophene units in any thieno[2,3-*b*]thiophene we tried could be converted to the tetraoxide. Since both sulfur atoms are attached to the same carbon, it appears that the first SO_2 moiety formed reduces the nucleophilic character of the second sulfur to almost nonexistence, and even the strong electrophilic oxygen of the HOF·CH_3CN could not be attracted to it anymore. Support for this assumption is also provided by DFT calculations (B3LYP/6-311G-(d,p)) carried out on the parent skeletons and focused on the Mulliken charge distribution of each sulfur atom before and after oxidation. Table 1 clearly shows that the partly oxidized fused oligothiophenes considerably reduce the negative charges on the remaining sulfur, compared to the starting materials, rendering the second sulfur oxidation improbable by any known oxygen-transfer agent.[5] This is in contrast to oligothiophenes where although the first sulfur oxidation naturally reduces the electron density of the second sulfur atom, it still leaves enough negative charge for the efficient HOF·CH_3CN to transfer additional oxygen atoms to it as well.[3]

The incorporation of an electron-withdrawing group at the 2 and 5 positions,[11,13] as in **1c** and **1d**, naturally decreases the

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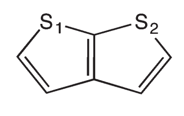
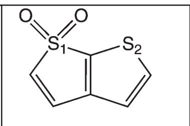
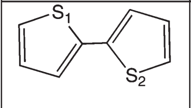
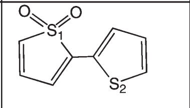
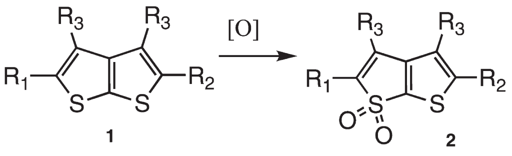
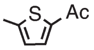
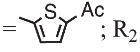
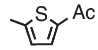
TABLE 1. Mulliken Charge on Sulfur Atoms in Atomic Units

	S_1= S_2= 0.279834		S_1= 1.002491 S_2= 0.368850
	S_1= S_2= 0.283862		S_1= 0.984029 S_2= 0.297319

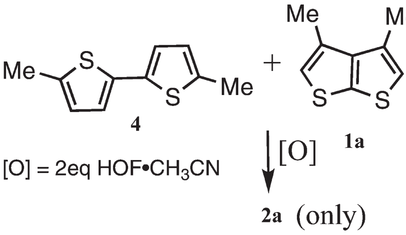
SCHEME 1. Oxygenation of thieno[2,3-*b*]thiophenes



[O] = HOF•CH$_3$CN (2 eq. 0 °C, sec)

a	$R_1 = R_2 = H$	R_3 = Me	98%
b	$R_1 = R_2 = H$	R_3 = Ph	98%
c	$R_1 = R_2$ = COOEt	R_3 = Me	95%
d	$R_1 = R_2$ = COOEt	R_3 = Ph	95%
e	$R_1 = R_2$ = *p*-C_6H_4CN	R_3 = Me	95%
f	R_1 = H; R_2 = 	R_3 = Me	65%
3f	R_1 =  ; R_2 = H	R_3 = Me	35%
g	$R_1 = R_2$ = 	R_3 = Me	95%

SCHEME 2. Oxidation Competition between Bithiophene and Thieno[2,3-*b*]thiophene Derivatives



propensity of the sulfur atom to undergo oxidation, but not to a degree of preventing the hypofluorous acid from accomplishing the oxygen-transfer process. When 2 molar equiv of HOF·CH$_3$CN was used, the unknown diethyl 3,4-dimethylthieno-[2,3-*b*]thiophene-2,5-dicarboxylate 1,1-dioxide (**2c**) and diethyl 3,4-diphenylthieno[2,3-*b*]thiophene-2,5-dicarboxylate 1,1-dioxide (**2d**) were both obtained in 95% yield. Replacing the ester groups with the benzonitrile as in the 2,5-di-*p*-benzonitrile-3,4-dimethylthieno[2,3-*b*]thiophene (**1e**)[14] gave similar results, and 2 molar equiv of HOF·CH$_3$CN complex was enough to form 2,5-di-*p*-benzonitrile-3,4-dimethylthieno[2,3-*b*]thiophene 1,1-dioxide (**2e**) in 95% yield (Scheme 1). As was the case with **1a** and **1b**, addition of excess reagent to each of the starting materials **1** did not change the results.

When coupling thieno[2,3-*b*]thiophene units with one thiophene derivative as in 2-(5-acetylthiophene-2-yl)-3,4-dimethylthieno[2,3-*b*]thiophene (**1f**),[13] and then reacting it with 2 molar equivalents of HOF•CH$_3$CN at 0 °C, two products were isolated. The first identified as 2-(5-acetylthiophene-2-yl)-3,4-dimethylthieno[2,3-*b*]thiophene-6,6-dioxide (**2f**), while the second proved to be 2-(5-acetylthiophene-2-yl)-3,4-dimethylthieno[2,3-*b*]thiophene-1,1-dioxide (**3f**) in 65% and 35% yields receptively (scheme 1).

The regiochemistry of the products resulting from the oxidation of **1f** was evident from the respective ^{1}H NMR spectra. The hydrogen at the 5 position of **2f** was up-fielded by 0.6 ppm relative to the starting material, while the same hydrogen in **3f** exhibited a downfield shift of 0.4 ppm, as expected.

The reason for the oxidation of one of the sulfur atoms in the thieno[2,3-*b*]thiophene, rather than a reaction on the sulfur of the isolated thiophene, is understandable since the extent of the aromaticity of the latter is higher. The two fused thiophene rings of the thieno[2,3-*b*]thiophene have similar aromaticity, and the electron-withdrawing substituents seem to be responsible for the somewhat preferred regioselectivity of the oxygenation.

In order to assess the aromaticity difference between bithiophenes and thienothiophenes, we reacted a mixture of **1a** and 5,5′-dimethyl[2,2′]bithiophene (**4**) with 2 molar equiv of HOF·CH$_3$CN at 0 °C. The corresponding *S*,*S*-dioxide **2a** was obtained in about 10 s in quantitative yield, while **4** was recovered unchanged (Scheme 2). It is worth noting, however, that **4** could be fully oxidized if needed.[3]

When bis-aryl thienothiophene (**1g**)[13] was reacted with 2 molar equiv of HOF·CH$_3$CN, once again the attack was on the less aromatic system of the thieno[2,3-*b*]thiophene only, forming 2,5-di(5-acetylthiophene-2-yl)-3,4-dimethylthieno-[2,3-*b*]thiophene 1,1-dioxide (**2g**) in 95% yield (scheme 1).

All attempts to further oxidize the substituted 2-acetylthiophene ring in **2f**, **3f**, and **2g** were unsuccessful because of the two strong electron-withdrawing groups, sulfonyl and acetyl, in positions 2 and 5 of the thiophene skeleton.

The electronic properties of the products discussed were studied by UV–vis. Table 2 lists the maximum wavelength absorption (λ_{max}), the HOMO–LUMO energy gap (ΔE_g), and the lowering of the HOMO–LUMO energy gap following the oxygen-transfer reaction ($\Delta\Delta E_g$).

One can clearly see that the oxidation of one of the sulfur atoms in thieno[2,3-*b*]thiophene (**2a**–**d**) causes a red shift of about 50–72 nm. This indicates that a desirable lowering of the HOMO–LUMO energy gap ($\Delta\Delta E_g$) has taken place. The mono- and diarylthieno[2,3-b]thiophene (**2e**–**g**, **3f**), on the other hand, exhibit a blue shift apparently due to the oxidation of the sulfur atom that causes the molecule to break the π-conjugation.

In conclusion, we have demonstrated that the HOF·CH$_3$CN electrophilic oxygen atom could be transferred to a wide range of thieno[2,3-*b*]thiophenes forming the corresponding *S*,*S*-dioxides in unparalleled high yields and under very mild conditions. While the reaction requires working with fluorine, it is much less complicated than what many may think. One can dilute the commercial fluorine on the spot or purchase premixed fluorine/nitrogen mixtures. In both cases, the technical ease of the reaction producing solutions of the reagent (no special equipment is needed) offers an easy way for transferring

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TABLE 2. Absorption λ_{max} (in nm) and HOMO−LUMO Energy Gap (ΔE_g,[a] in eV) in Solution[b]

compd	λ_{max} (ΔE_g)	$\Delta\Delta E_g$[c]
1a	224 (5.54)[11]	
2a	296 (4.19)	(1.35)
1b	230 (5.39)[11]	
2b	282 (4.40)	(0.99)
1c	270 (4.59)	
2c	319 (3.89)	(0.70)
1d	271 (4.58)	
2d	321 (3.86)	(0.72)
1e	318 (3.90)	
2e	295 (4.20)	(−0.30)
1f	364 (3.41)	
2f	316 (3.92)	(−0.51)
3f	301, 369 (3.36)	(0.05)
1g	370 (3.35)	
2g	334 (3.71)	(−0.36)

[a] $\Delta E_g = hc/\lambda$. [b] CH_2Cl_2 solution [c] $\Delta\Delta E_g = \Delta E_g(SM) - \Delta E_g(product)$

oxygen atoms to desirable sites. We hope that this oxygen transfer reaction may become the method of choice in many cases where the alternatives are not potent enough.

Experimental Section

General Experimental Procedures. ^1H NMR spectra were recorded using a 400 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. Here too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. IR spectra were recorded in KBr on an FTIR spectrometer. MS spectra were measured under EI conditions. UV spectra were recorded in CH_2Cl_2.

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and a corrosive material. It should be used only with an appropriate vacuum line.[15] 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 base such as soda lime located at the outlet of the glass reactor. If elementary precautions are taken, the work with fluorine is simple, and we have never experienced difficulties working with it.

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[15] 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 mol/L.

General Procedure for Working with HOF·CH_3CN. A fused thiophene derivative was dissolved in CH_2Cl_2, and the mixture was cooled to 0 °C. The oxidizing agent was then added in one portion to the reaction vessel. The reaction was stopped after a few seconds, and the excess of HOF·CH_3CN was quenched with saturated sodium bicarbonate. The mixture was then poured into water and extracted with CH_2Cl_2, the organic layer dried over $MgSO_4$, and the solvent evaporated. The crude product was usually purified either by vacuum flash chromatography using silica gel 60-H (Merck) with increasing portions of EtOAc in PE as an eluent or by recrystallization.

3,4-Dimethylthieno[2,3-*b*]thiophene 1,1-Dioxide (2a). Compound **2a** was prepared from **1a**[11] (0.4 g, 2.38 mmol) as described above, using 2 equiv of the oxidizing agent and chromatographed on silica gel using PE/ EtOAc 70:30 as eluent. A pale yellow product (0.47 g, 98% yield) was obtained: mp 155 °C (from 2-propanol); λ_{max} 296 nm; IR 1292, 1164 cm^{-1}; ^1H NMR 7.22 (q, ^4J = 0.8 Hz, 1H), 6.26 (q, ^4J = 1.6 Hz, ^4J = 1.6 Hz, 1H), 2.34 (d, ^4J = 0.8 Hz, 3H), 2.27 ppm (d, ^4J = 1.6 Hz, 3H); ^{13}C NMR 15.2, 16.1, 130.0, 131.8, 132.5, 136.9, 140.9, 142.3 ppm; HRMS (EI) *m*/*z* calcd for $C_8H_8O_2S_2$ 199.9966 (M)$^+$, found 199.9966. Anal. Calcd for $C_8H_8O_2S_2$: C, 47.98; H, 4.03; S, 32.02. Found: C, 48.31; H, 4.00; S, 32.29.

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Supporting Information Available: ^1H and ^{13}C NMR data of all new compounds and theoretical calculations details (including **z**-matrix). This material is available free of charge via the Internet at http://pubs.acs.org.

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