

General, fast, and high yield oxidation of thiols and disulfides to sulfonic and sulfinic acids using HOF·CH₃CN

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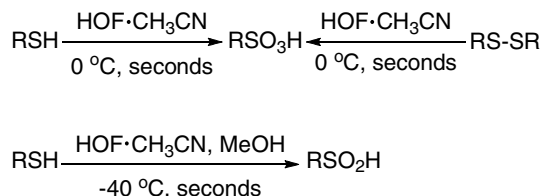
Abstract—Thiols and disulfides are oxidized to the corresponding sulfonic and sulfinic acids using HOF·CH₃CN. This oxidation is suitable for a variety of thiols and disulfides and proceeds under mild conditions, in short reaction times and with high yields.

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Sulfonic acids serve as important molecules in organic chemistry. For example, the sulfonic group, in either its acidic or salt form, is capable of solubilizing substances in water thus increasing their usefulness especially in the organic dye industry.¹ These acids are also frequently used as catalysts in organic chemistry, for instance, in esterification of amino acids and peptides.^{2,3} Most aliphatic sulfonic acids are made by oxidation of thiols,⁴ while aromatic sulfonic acids are usually obtained through sulfonation of the ring with sulfuric acid.⁵ Still, among the hundreds of aromatic sulfonic acids known in the literature, only a few contain electron-withdrawing groups and none of those were made by direct oxidation of thiols or disulfides.

We present here a general method for direct oxidation of various thiols or disulfides to sulfonic acids using HOF·CH₃CN complex. Although some of the acids described had been previously prepared, the present combination of very mild conditions and short reaction times gave better results than those reported in the literature. What is more, at low temperatures (around –40 °C) in the presence of methanol, it is possible to stop the reaction at the sulfinic acid stage (Scheme 1).

The HOF·CH₃CN complex, easily prepared by bubbling dilute fluorine through aqueous acetonitrile,⁶ is considered today as one of the best oxygen-transfer agents available to organic chemists. The oxygen atom is strongly electrophilic because it is weakly bonded to



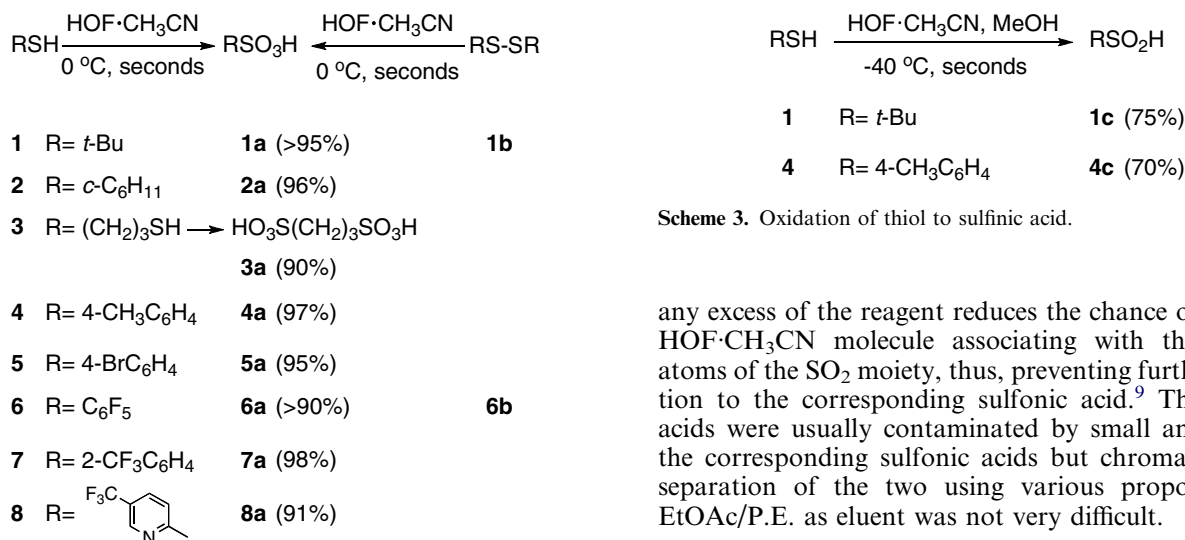
Scheme 1. Oxidation of thiols and disulfides into sulfonic and sulfinic acids.

the most electronegative element—fluorine. The complex is able to transfer an oxygen atom even to very weak nucleophiles under mild conditions. In the past, we have demonstrated this ability by converting a variety of sulfur-containing compounds such as sulfides, including very deactivated examples,⁷ thiophenes,⁸ episulfides,⁹ and even polythiophenes¹⁰ into the corresponding SO₂ derivatives. This reagent was also used to oxidize azides and vicinal diamines into the corresponding nitro¹¹ and dinitro¹² derivatives, to form a variety of N-oxides,¹³ including the 1,10-phenanthroline *N,N'*-dioxide derivatives, which had eluded chemists for many decades,¹⁴ and much more.¹⁵

The oxidation with HOF·CH₃CN complex was applied to a number of aliphatic and aromatic thiols and disulfides and the corresponding sulfonic acids were formed after a few seconds in almost quantitative yields.¹⁶ Scheme 2 summarizes these results. When compared to the parallel reactions reported in the literature, it becomes clear that this method results in higher, or in a few cases, equal yields to those obtained with other reagents. It should be noted that all the high yield

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**Scheme 3.** Oxidation of thiol to sulfinic acid.**Scheme 2.** Conversion of thiols and disulfides into sulfonic acids.

procedures mentioned in the literature involved the use of a catalyst and much longer reaction times.

Reacting *t*-butylthiol (**1**) or bis(*tert*-butyl) disulfide (**1b**), with HOF·CH₃CN at 0 °C produced the corresponding *t*-butylsulfonic acid (**1a**)¹⁷ in a few seconds in 96%, and 98% yields, respectively. For comparison, when dimethyl sulfoxide was used as an oxidant, the oxidation led to decomposition and only sodium sulfate was identified after neutralization.¹⁸

Reacting straight chain or cyclic thiols such as **2** and **3** with HOF·CH₃CN produced, in a few seconds, the corresponding cyclohexanesulfonic acid (**2a**)¹⁹ and 1,3-propanedisulfonic acid (**3a**) in 96% and 90% yields. It should be noted that compound **3a** has been known since the 1930s,²⁰ but it had never been prepared by direct oxidation. Many base-catalyzed oxidations of aliphatic thiols containing acidic α-hydrogen atoms such as **2** and **3** lead to β-eliminations and/or other side reactions,²¹ however, these were not observed when HOF·CH₃CN was used.

Potential complications might occur with aromatic thiols, since HOF·CH₃CN is also capable of oxidizing aromatic rings.²² However, the initial attack of the reagent on the sulfur atom is much faster preventing any attack on the aromatic ring. This was demonstrated by the formation of *p*-toluenesulfonic acid **4a** from **4** in a few seconds in 97% yield.

Several methods are available for the synthesis of sulfinic acids.²³ Most of these are carried out through indirect and multi-step routes. HOF·CH₃CN offers a new procedure for the one-step preparation of sulfinic acids by lowering the reaction temperature to -40 °C and diluting the reagent with methanol. Thus, the aliphatic *t*-butylsulfonic acid (**1c**)²⁴ as well as the aromatic *p*-toluenesulfonic acid (**4c**) were obtained in 75% and 70% yields from the respective thiols **1** and **4** (Scheme 3). The low temperature and the methanol which solvates

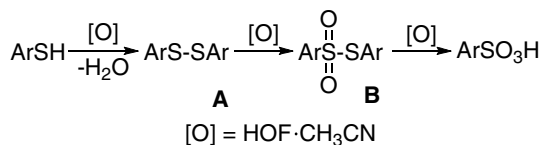
any excess of the reagent reduces the chance of another HOF·CH₃CN molecule associating with the oxygen atoms of the SO₂ moiety, thus, preventing further oxidation to the corresponding sulfonic acid.⁹ The sulfinic acids were usually contaminated by small amounts of the corresponding sulfonic acids but chromatographic separation of the two using various proportions of EtOAc/P.E. as eluent was not very difficult.

Electron-donating or -withdrawing groups on the aromatic ring did not affect the efficiency of the reaction. 4-Bromobenzenesulfonic acid (**5a**), pentafluorobenzenesulfonic acid (**6a**) and 2-(trifluoromethyl)-benzenesulfonic acid (**7a**)²⁵ were obtained from the corresponding thiols **5**, **6** and **7** in a few seconds in 95%, >90% and 98% yields, respectively. Nor did we encounter any problem in forming **6a** from bis(pentafluorobenzene) disulfide (**6b**).²⁶ It should be noted that this is the first time these electron-deficient thiols have been directly oxidized to the sulfonic acids.

We have extended this study to heterocyclic thiols where two potentially reactive sites are present. The preparation of 5-(trifluoromethyl)-2-pyridinesulfonic acid (**8a**)²⁷ serves as an example. Despite the fact that HOF·CH₃CN can react with tertiary amines to produce the corresponding N-oxides,¹³ the sulfur atom of the thiol reacted faster than the nitrogen, and **8a** was formed in a few seconds in 91% yield. Even when a large excess of the reagent was used, only a small amount (<5%) of the N-oxide was formed.

It was of interest to compare the present reaction with other oxygen transfer agents, such as *m*-chloroperbenzoic acid. *m*-CPBA was not able to transform **7** and **8** into the acids **7a** and **8a** even when a large excess and 8 hours reflux were employed. The only identifiable products in the resulting mixtures were the corresponding sulfinic acids. Apparently *m*-chloroperbenzoic acid is too mild to force completion of the reaction to the sulfonic acid.²⁸ It seems that HOF·CH₃CN is indeed a stand-alone oxygen transfer agent when the transformation of thiols containing electron-withdrawing groups is the issue.

One of the advantages of HOF·CH₃CN is that the origin of its electrophilic oxygen is water, which of course, is the most convenient source of all oxygen isotopes. H¹⁸O·CH₃CN, prepared by passing diluted fluorine through H₂¹⁸O and acetonitrile, was reacted with **4**, leading to sulfonic acid **4a** with three ¹⁸O isotopes. Similarly sulfonic acid **4c** with two ¹⁸O isotopes was prepared. These compounds are very difficult to be made by any other route, and can be useful as probes and



Scheme 4. The mechanism for the oxidation of thiols or disulfides with HOF·CH₃CN.

for studies of the ultimate degradation fate of these acids.²⁹ The heavy oxygen atoms are not interchangeable with the common ¹⁶O isotope found in air or regular water as evident from mass spectra taken after the acids had been in prolonged contact with air and water. The HRMS of **4a** (CI) (*m/z*): calcd from C₇H₈O₃S, 179.039975 (MH)⁺, found: 179.040067 and for **4c** calcd from C₇H₈O₂S, 161.040816 (MH)⁺, found: 161.040981 clearly demonstrate this point.

The mechanism for this oxidation reaction, portrayed in **Scheme 4**, involves the formation of the respective disulfides (**A**), which are then converted into thiosulfonates (**B**), both of which were observed when only 2.5 mol equiv of HOF·CH₃CN were used. It should be mentioned, however, that other pathways, especially for aliphatic thiols have also been proposed.²⁴

In conclusion, the efficiency of this method, its simplicity, short reaction times, high yield and the purity of the products are excellent features. Considering the commercial availability of premixed fluorine/nitrogen mixtures and the technical ease of the reaction (no special equipment is needed),⁶ this method may become a method of choice for many cases where the alternatives are not good enough.

Acknowledgement

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References and notes

- Weberndoerfer, V.; Brunnmüller, F.; Eisert, M.; Bermes, R. U.S. Patent 4,560,745, 1985; *Chem. Abstr.* (for the appl.) **1982**, 96, 574.
- Tian, S. H.; Shu, D.; Wang, S. J.; Xiao, M.; Meng, Y. Z. *Fuel Cells* **2007**, 7, 232–237.
- Boesten, W. H. J.; Quaedflieg, P. J. L. M. PCT Int. Appl. WO 9849133, 1998; *Chem. Abstr.* **1998**, 129, 739.
- (a) Levene, P. A.; Mikeska, L. A. *J. Biol. Chem.* **1927**, 75, 587–605; (b) Levene, P. A.; Mikeska, L. A. *J. Biol. Chem.* **1925**, 65, 515–518; (c) Vivian, D. L.; Reid, E. E. *J. Am. Chem. Soc.* **1935**, 57, 2559–2560.
- Cerfontain, H.; Lambrechts, H. J. A.; Schaasberg, Z. R. H.; Coombes, R. G.; Hadjigeorgion, P.; Tucker, G. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 659–667.
- 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.¹³ For the occasional user, however, various premixed mixtures of F₂ 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, work with fluorine is simple and we have never experienced difficulties.
- General procedure for producing HOF·CH₃CN:* A mixture of 10–20% F₂ in nitrogen was used throughout this work. The gas mixture was prepared in a secondary container prior to the reaction¹³ and passed at a rate of about 400 mL per minute through a cold (–15 °C) mixture of 100 mL CH₃CN and 10 mL H₂O 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. The typical concentrations of the oxidizing reagent were around 0.4–0.6 mol/L.
- Rozen, S.; Bareket, Y. *J. Org. Chem.* **1997**, 62, 1457–1462.
- Rozen, S.; Bareket, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1959.
- Harel, T.; Amir, E.; Rozen, S. *Org. Lett.* **2006**, 8, 1213–1216.
- Amir, E.; Rozen, S. *Angew. Chem., Int. Ed.* **2005**, 44, 7374–7378.
- (a) Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* **2003**, 125, 8118–8119; (b) Carmeli, M.; Rozen, S. *J. Org. Chem.* **2006**, 71, 4585–4589.
- Golan, E.; Rozen, S. *J. Org. Chem.* **2003**, 68, 9170–9172.
- Dayan, S.; Kol, M.; Rozen, S. *Synthesis* **1999**, 1427–1430.
- (a) Rozen, S.; Dayan, S. *Angew. Chem., Int. Ed.* **1999**, 38, 3471–3473; (b) Rozen, S.; Carmeli, M. *J. Org. Chem.* **2005**, 70, 2131–2134.
- (a) Rozen, S. *Eur. J. Org. Chem.* **2005**, 2433–2447; (b) Rozen, S. *Acc. Chem. Res.* **1996**, 29, 243–248.
- General procedure for sulfonic acid preparation:* The requisite mercaptan (0.01 mol) was dissolved in methylene dichloride (20 ml) and cooled to 0 °C. HOF·CH₃CN (0.07 mol) was then added slowly to the stirred mercaptan solution. After a few seconds the solvent was removed under reduced pressure. Because the compounds are hygroscopic the products were kept in an evacuated desiccator in the presence of P₂O₅ for an hour before ¹H NMR spectra were recorded at 200 and 400 MHz and ¹³C NMR at 50 and 100 MHz. The IR spectra were recorded in KBr on an FTIR spectrophotometer. The MS were measured under CI or EI conditions. The spectral and physical properties of known products were compared with those reported in the literature. In every case excellent agreement was obtained.
- (a) Smith, K.; Hou, D. *J. Org. Chem.* **1996**, 61, 1530–1532; (b) Freeman, F.; Angeletakis, C. N. *Org. Magn. Reson.* **1983**, 21, 86–93.
- Loew, O. G. *J. Org. Chem.* **1976**, 41, 2061–2064.
- (a) Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* **2000**, 122, 7390–7391; (b) Ferguson, R. R.; Crabtree, R. H. *J. Org. Chem.* **1991**, 56, 5503–5510.
- Stone, G. C. H. *J. Am. Chem. Soc.* **1936**, 58, 488–489.
- Wallace, T. J.; Schriesheim, A. *Tetrahedron* **1965**, 21, 2271–2280.
- Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, 58, 1593–1595.
- Zoller, U. *In The Chemistry of Sulphinic Acids, Esters and their Derivatives.* Patai, S., Ed.; 1990; pp 185–215.
- Gu, D.; Harpp, D. N. *Tetrahedron Lett.* **1993**, 34, 67–70.
- Spectroscopic data of 7a:* ¹H NMR (400 MHz, MeOD) 8.23 (d, *J* = 7.5, 1H), 7.78 (d, *J* = 7.5, 1H), 7.64 (t, *J* = 7.5, 1H), 7.58 (t, *J* = 7.5, 1H); ¹³C NMR (100 MHz, MeOH) 144.2, 133.1, 131.8, 131.0, 128.3 (q, *J* = 6.4), 128.1 (q, *J* = 32.4), 124.8 (q, *J* = 273.2); ¹⁹F NMR (376 MHz, MeOD) –59.5 (s, 3F); IR (KBr) 3500 (br) (OH), 1271

- (SO₃) cm⁻¹; HRMS (CI): calcd for C₇H₅O₃F₃S [(M+H)⁺] 226.9990. Found: 226.9993; Microanalysis and mp of the sulfonic acid were not meaningful because of the very hygroscopic nature of the compound.^{19b}
26. Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2005**, *11*, 719–727.
27. Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563–6570.
28. Filby, W. G.; Gunther, K.; Penzhorn, R. D. *J. Org. Chem.* **1973**, *38*, 4070–4071.
29. Caschili, S.; Delogu, F.; Cao, G. *Annal. Chim.* **2005**, *95*, 813–821.