Fluorous Swern Reaction

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The oxidation of primary and secondary alcohols to aldehydes and ketones is one of the most fundamental and commonly applied transformations in organic chemistry, be it in the research lab or the production plant. It is not surprising therefore that methodology for this functional group interconversion is consistently being refined and improved. Major advances in recent years include Ley and Griffith's introduction of the catalytic tetrapropylammonium perruthenate oxidant[1] and the user-friendly version of the Dess−Martin reagent, namely 2-iodoxybenzoic acid,[2] with its rapidly broadening spectrum of reactivity.[3] Nevertheless, the Swern oxidation and its numerous variants[4,5] remain some of the most widely used methods in fine organic chemistry. Environmental pressure is currently serving to focus interest on cleaner oxidation methods and notable advances in this area have been made by the Marko group with their catalytic processes based on oxygen as overall oxidant.[6] Unfortunately, the Swern reaction, with the stoichiometric generation of dimethyl sulfide, falls down badly on environmental grounds that militate against its use on a large scale. In this laboratory we have been interested for several years in the development of recoverable, environmentally friendly fluorous[7] organoselenium compounds,[8] from where it is but a small step up the periodic table to fluorous organosulfur chemistry and the fluorous Swern reaction as set out here.

The need to modify the Swern reaction so as to eliminate the formation of the volatile, malodorous dimethyl sulfide has been previously addressed by the Vederas group who have introduced polymer-supported and extractable nonvolatile reagents.[9] We reasoned that this task might be more conveniently achieved through the preparation of a simple fluorous sulfoxide, which would be readily recovered and recycled by fluorous extraction. In doing so all the desirable properties of the original Swern reaction would be retained and the problems of adapting conditions to the modified reactivity of a polymer-supported reagent avoided.

In designing the fluorous Swern reagent our primary concern was with the length of the spacer linking the fluorous chain to the sulfoxide. Reagents lacking a spacer, i.e., with the fluorous chain directly bound to the sulfoxide sulfur, were excluded from consideration as it was anticipated that they would reduce the nucleophilicity of the sulfoxide and so reduce activity. Linkers consisting of one methylene were tried and found wanting on the basis of the facile elimination of HF from the sulfoxide. Linkers with three or more methylene groups, while undoubtedly effective, were eliminated from consideration on the grounds that they would require a longer fluorous chain for efficient extraction. We therefore settled on a two methylene group spacer and initially selected perfluorohexyl as the fluorous chain as this would lead to a reagent with 60.2% fluorine, with 60% usually considered the lower cutoff point for efficient fluorous extraction.[10] Reduction of dimethyl disulfide with sodium borohydride in ethanol followed by treatment with commercial 2-perfluorohexylethyl iodide provided, after stirring overnight and standard work up, the fluorous sulfide **1** in 74% yield. This direct synthesis of **1** is a considerable improvement over an earlier multistep protocol, involving reaction of the iodide with sodium thiocyanate, reduction, and methylation.[11] Oxidation with hydrogen peroxide in methanol[7] then provided the sulfoxide **3** in high overall yield with no overoxidation to the sulfone, it having been previously determined that more forcing conditions are required for the exhaustive oxidation of **1**.[11] Sulfoxide **3** was crystalline, white, and odorless but unfortunately insoluble in dichloromethane below ca. −30 °C. We therefore prepared the lower homologous sulfide (**2**) and its sulfoxide (**4**) in the analogous manner in 71% overall yield from commercial perfluorobutylethyl iodide (Scheme 1).

Scheme 1. Preparation of Fluorous DMS and Fluorous DMSO
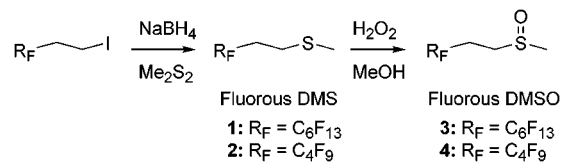
Sulfoxide **4** is also crystalline, white, and odorless but it is soluble in dichloromethane down to −45 °C. It has a fluorine content of 55.1% and is recoverable by continuous fluorous extraction, our preferred protocol,[8] and no doubt, by chromatography over fluorous silica gel.[12] The intermediate sulfide (**2**), however, is relatively volatile and in general we have converted it directly to sulfoxide **4**.[13]

A series of oxidations were conducted in which fluorous DMSO (**4**) was activated with oxalyl chloride in dichloromethane at −30

(1) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(2) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(3) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

(4) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(5) Reviews: (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297. (c) Tidwell, T. T. *Synthesis* **1990**, 857.

(6) (a) Markó, I.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (b) Markó, I. E.; Gautier, A.; Chelle-Regnaut, I.; Giles, P. R.; Tsukazaki, M.; Urch, C. J.; Brown, S. M. *J. Org. Chem.* **1998**, *63*, 7576. (c) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433.

(7) (a) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641. (b) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174.

(8) (a) Crich, D.; Hao, X. *Org. Lett.* **1999**, *1*, 269. (b) Crich, D.; Hao, X.; Lucas, M. *Tetrahedron* **1999**, *55*, 14261. (c) Crich, D.; Barba, G. R. *Org. Lett.* **2000**, *2*, 989. (d) Crich, D.; Neelamkavil, S.; Sartillo-Piscil, F. *Org. Lett.* **2000**, *2*, 4029.

(9) (a) Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407. (b) Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856.

(10) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(11) Dieng, S.; Bertaina, B.; Cambon, A. *J. Fluorine Chem.* **1985**, *28*, 425.

(12) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866.

(13) Preparation of **2** and **4**: NaBH₄ (1.4 g, 37.0 mmol) was added under Ar to a stirred solution of Me₂S₂ (3.3 g, 35.0 mmol) in EtOH (25 mL). After being stirred for 30 min the reaction mixture was cooled to 0 °C and a solution of perfluorobutylethyl iodide (10 g, 26.7 mmol) in anhydrous THF (15 mL) was added dropwise over 1 h. The reaction mixture was then stirred overnight at room temperature before further Me₂S₂ (1.0 g, 10.6 mmol) reduced with NaBH₄ (0.45 g, 11.9 mmol) in EtOH (10 mL) was added. After the reaction mixture was stirred for 6 h more, it was diluted with hexanes (20 mL) and washed with H₂O and brine. The hexane layer was diluted with MeOH (10 mL) and H₂O₂ (3.1 mL of 30%, 27 mmol) and stirred for 1 h before it was diluted with CH₂Cl₂ (25 mL), washed with H₂O, dried (Na₂SO₄), and concentrated in vacuo to give **4** (5.9 g, 19.0 mmol, 71%) as a white, crystalline solid with mp 46 °C.

Table 1. Fluorous Swern Oxidations

Entry	Substrate (X = H, OH)	% Product (X = O)	% Recd **4**
1		92	87
2		77	84
3		91	88
4		91	86
5		90	89
6[a]		94	90
7[b]		83	86
8[c]		81	86
9[d]		81	84
10[e]		80	88
11[f]		79	85
12[f]		86	87

[a] Isoborneol. [b] Diacetone glucofuranose. [c] *myo*-Inositol. [d] (*R*)-Alcohol, DAM = dianisylmethyl. [e] 17β-Alcohol. [f] A mixture of anomers was used.

°C and subsequently treated with the substrate and then diisopropylethylamine almost as in the standard Swern oxidation. The practicality of the classical Swern protocol is therefore retained. Workup involved brief partitioning of the reaction mixture with water, concentration of the dichloromethane solution, and partitioning of the residue between toluene and FC72 (a commercial fluorous hydrocarbon) in the continuous extractor for ~4 h.[8] The oxidized product (aldehyde or ketone) was then recovered from the toluene phase, while treatment of the FC72 phase with hydrogen peroxide returned the sulfoxide ready for reuse.[14] The results of these oxidations, together with the yields of recovered sulfoxide, are presented in Table 1.[15]

An important practical consideration in these oxidations is the exchange of dichloromethane, the reaction solvent, for toluene before the fluorous extraction. At this stage most of the sulfoxide (**4**) has been reduced to the sulfide **2**, which, itself, is very nonpolar and readily recovered in the extraction protocol. However, any residual sulfoxide is not readily extracted from dichloromethane solution, presumably because of its somewhat polar nature. Replacing dichloromethane by the apolar toluene reduces the affinity of **4** for the organic phase and enables the efficient recoveries recorded in Table 1.

As is apparent from Table 1, the fluorous Swern reaction retains the mildness of conditions and applicability in the presence of a wide range of functional groups that have contributed to the popularity of the original reaction. In addition to the typical oxidations of primary and secondary alcohols we note the compatibility with Lipshutz's new triisopropylsiloxycarbonyl protecting group (entry 2),[16] the absence of β-elimination of a *tert*-butyldimethylsiloxy group (entry 3), and the oxidation of lactols to lactones (entries 11 and 12), again without β-elimination.

The Swern oxidation is but one variant on oxidation with activated DMSO or other oxidized forms of dimethyl sulfide. All suffer the same problem of release of the malodorous volatile dimethyl sulfide. We anticipate that the fluorous DMS and DMSO reagents described herein may be successfully employed in several of these protocols. Toward this end we have simply investigated the oxidation of 1-octanol to octanal using the fluorous DMS and *N*-chlorosuccinimide, i.e., the fluorous version of the Corey Kim reaction.[17] This reaction employs the sulfide and not the sulfoxide and hence it was possible to work with the higher homologue (**2**), taking advantage of its convenient, less volatile nature. In the event the yield of aldehyde was 96% with 81% of the fluorous DMS recovered clean and ready for reuse.

(14) Recovered **4**, as expected for a well-defined chemical entity, performed analogously to freshly synthesized **4**. Indeed, samples of **4** were routinely recovered and recycled with no attempt to discriminate from the virgin material.

(15) Typical protocol for oxidation with **4** and its recovery: To a well-stirred solution of anhydrous CH₂Cl₂ (5 mL) under Ar at −30 °C was added oxalyl chloride (0.14 mL, 1.6 mmol). **4** (1.0 g, 3.2 mmol) was then added dropwise and the reaction mixture stirred for an additional 20 min. Isoborneol (0.153 g, 1.0 mmol) dissolved in CH₂Cl₂ (5 mL) was then added to this solution followed, after an additional 0.5 to 1 h, by EtN(*i*−Pr)₂ (0.88 mL, 5.0 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for a period of 30 min before it was quenched with H₂O, washed with ammonium chloride (5 mL), extracted with CH₂Cl₂ (10 mL), and carefully concentrated under aspirator vacuum in a cold water bath. The reaction mixture was then dissolved in toluene (6 mL) and extracted continuously with FC 72 (15 mL) in a cooled continuous extractor[8] for 4 h. After decantation, concentration of the toluene layer and chromatography on silica gel yielded camphor (0.142 g, 94%). The FC-72 phase, containing a mixture of **3** and **4**, was then stirred with MeOH (3 mL) and H₂O₂ (0.23 mL of 30%, 2 mmol) for 1 h after which it was diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (10 mL) in a three-phase system. Concentration of the CH₂Cl₂ layer then gave recovered **4** (0.9 g, 90%).

(16) Lipshutz, B. H.; Papa, P.; Keith, J. M. *J. Org. Chem.* **1999**, *64*, 3792.

(17) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.