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LETTERS

A Selective Conversion of Sulfide to Sulfoxide in Hexafluoro-2-propanol

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Abstract:

A facile, selective and efficient method for the oxidation of sulfides to sulfoxides by aqueous 30% H_2O_2 in hexafluoro-2-propanol at room temperature is described. Specific role of the solvent in the selectivity is exhibited.

Keywords: *Fluorine and compounds; oxidation; solvents and solvent effects; sulfoxides*

1. Introduction

Organic sulfoxides are useful synthetic intermediates for the construction of various chemically and biologically significant molecules.[1,2] The oxidation of sulfides is still the most common method for preparing sulfoxides. There are several reagents available for this conversion.[3,4] Many of these have the problem of over oxidation of sulfoxides to sulfones. The reaction temperature and the relative amount of oxidants have to be controlled to avoid such over oxidation. Therefore, a need for the development of an easy and efficient reagent for the conversion of sulfide to sulfoxide still exists.

Earlier, we have reported that perfluoro-*cis*-2,3-dialkyloxaziridines could oxidize 1-tri fluoromethylvinylsulfides to the corresponding sulfoxides at -50°C in the solvent mixture $CHCl_3/CFCl_3$ whereas mCPBA oxidation yielded sulfones directly.[5]

The use of "fluorous phase" has recently been proved to present several advantages in traditional organic syntheses.[6-9] We have ourselves reported a metal-catalyzed regio- and stereoselective aerobic epoxidation of unfunctionalized olefins in a fluorous solvent.[7] In continuation of this work, we envisaged to check the dioxygen oxidation of sulfide to sulfoxide [9,8]. Ethyl phenylsulfide (2 mmol) was allowed to react with oxygen/pivalaldehyde (1 eq) in perfluoro-2-butyltetrahydrofuran (FC-75, 2.5 mL, 25°C) in the presence of $Mn(OAc)_3.2H_2O$ (2 mol%) and led to a mixture of ethylphenylsulfoxide and

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ethylphenylsulfone (67:33) in 1 h. The reaction was then carried out in different solvent systems and conditions as shown in Table 1.

It is very clear that i) with a quantitative amount of oxidizing agent, there is no influence of the solvent (CH_2Cl_2, $PhCF_3$, FC-75), the only product is the sulfoxide but the reaction is incomplete even after a prolonged reaction time. ii) an excess of oxidant accelerates the reaction but favors partial formation of sulfone iii) the starting sulfide is completely recovered when the reaction is carried out in hexafluoro-2-propanol (HFIP). This lack of reaction in HFIP has not been elucidated.

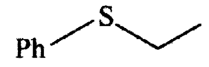
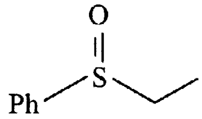
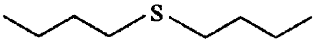
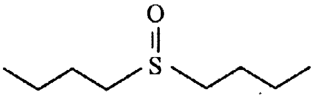
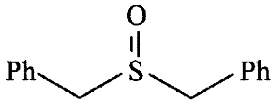
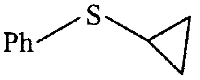
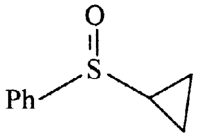
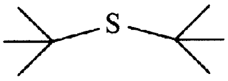
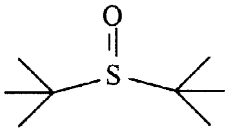
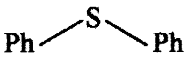
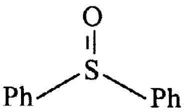
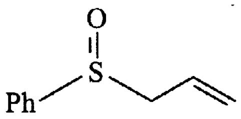
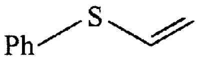
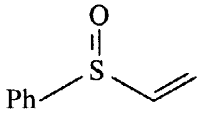
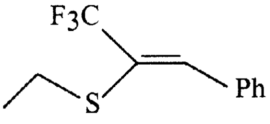
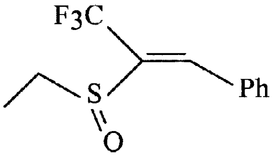
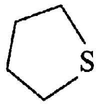
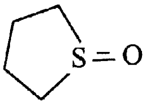
Table 1. $Mn(OAc)_3.2H_2O$ Catalyzed oxidation of ethylphenylsulfide with O_2/Pivalaldehyde[a]

entry	Solvent (5 mL)	Pivalaldehyde (eq)	Time (h)	GC Ratio % sulfide	 sulfoxide	 sulfone
1.	CH_2Cl_2	1	4.5	21	79	-
2.	CH_2Cl_2	1.5	2.0	36	59	5
3.	CH_2Cl_2	3	1.0	--	73	27
4.	$PhCF_3$	1	4.5	36	64	--
5.	Perfluoro-2-butyltetrahydrofuran (FC-75)	1	2.5[b]	37	63	--
6.	Perfluoro-2-butyltetrahydrofuran (FC-75)	2	1.0	--	67	33
7.	Hexafluoro-2-propanol (HFIP)	2	3.0	No Reaction		

a. Ethylphenyl sulfide (1 mmol), $Mn(OAc)_3.2H_2O$ (2 mol%), solvent (2.5 mL), O_2 bubbling, 25°C.
b. No change in GC ratio when the reaction was prolonged to 4.5 h.

We thus investigated the oxidation with the classical oxidizing reagent H_2O_2, in a fluorous medium. Considering the best efficiency of protic solvents for oxidation with H_2O_2, we chose HFIP as solvent, although this had not allowed any dioxygen oxidation. Oxidation of ethylphenylsulfide (2 mmol) was carried out in HFIP (2.5 mL) with 30% aqueous H_2O_2 (1 eq) at room temperature and yielded after 30 min the corresponding ethylphenyl sulfoxide as the only product in excellent yield (97%). Prolonging the reaction to 3 h did not give any sulfone. When ethylphenyl sulfoxide (2 mmol) was allowed to react (8 h) with 30% aqueous H_2O_2 (2 eq) in HFIP at 25°C, the starting sulfoxide was recovered unchanged. A wide range of sulfides, dibutylsulfide, dibenzylsulfide, di-*tert*-butylsulfide and a cyclic sulfide yielded corresponding sulfoxides in very good yield (Table 2). Cyclopropylphenyl sulfide gave cyclopropylphenyl sulfoxide without affecting the strained cyclopropyl group. The less nucleophilic diphenylsulfide underwent clean oxidation to the corresponding sulfoxide in a very short reaction time. Allylic and vinylic sulfides yielded the corresponding sulfoxide without affecting the carbon-carbon double bond. It is worth noting that the trifluoromethyl substituted vinyl sulfide yielded the corresponding sulfoxide as the only product in a very short reaction time at room temperature. The solvent (HFIP) can be easily recovered back by distillation (bp 59°C).

Table 2. Oxidation of Sulfides with 30% aqueous H_2O_2 in Hexafluoro-2-propanol.[a]

entry	Substrate	Time (min)	Product	Yield (%)[b]
1.		5		97
2.		5		92
3.		5		98
4.		5		93
5.		20		97
6.		5		99
7.		5		99
8.		15		94
9.		5		98
10.		5		82

a. sulfide (2 mmol), 30% aqueous H_2O_2 (4 mmol), hexafluoro-2-propanol (2.5 mL)
b. Isolated yields

The rate of oxidation of sulfides by H_2O_2 depends on the nucleophilicity of sulfur. In order to understand the reaction better, we have checked that the addition of 30% aqueous H_2O_2 to HFIP (^{19}F NMR -74.57, d, J = 2.8 Hz ppm) in D_2O did not give any change in the ^{19}F NMR signal. This indicates that HFIP acts as a solvent and does not give any peroxide intermediate. Reactions in HFIP are faster than in a non-fluorous solvent.[12, 13] This can be easily explained by a specific feature of HFIP. Because of the electron-withdrawing character of the CF_3 group, the hydroxyl proton in HFIP forms a strong hydrogen bond with H_2O_2 and activates the hydroxyl leaving group. More striking is that HFIP prevents from any further oxidation into sulfone. This may be due to the formation of a strong hydrogen bond between the solvent and the oxygen of the sulfoxide, which highly decreases the nucleophilicity of sulfur atom.

In conclusion, we have found a new and selective oxidation reaction of sulfide to sulfoxide with H_2O_2 in hexafluoro-2-propanol (HFIP) at room temperature. No strict conditions are required to allow selectivity towards formation of sulfoxide. Carbon-carbon double bond are not affected under the present reaction conditions. This novel oxidation methodology should find widespread use in organic synthesis.

Typical Procedure for the oxidation of ethylphenyl sulfide in hexafluoro-2-propanaol.

To a stirred solution of ethylphenyl sulfide (0.28 g, 2 mmol) in HFIP (2.5 mL) at 25°C was added 30% aqueous H_2O_2 (0.45 mL, 4 mmol). The reaction was followed by GC. After complete disappearance of sulfide (5 min), the excess H_2O_2 was quenched with 10% Na_2SO_3 solution in brine (2.0 mL), extracted with toluene (10 mL) and the organic phase was dried (anhydrous $MgSO_4$). After distillation and separation of solvents, the ethylphenylsulfoxide was obtained as an oil (0.30 g, 97%, purity 99.4% by GC).

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