Role of Hexafluoro-2-propanol in Selective Oxidation of Sulfide to Sulfoxide: Efficient Preparation of Glycosyl Sulfoxides

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Aqueous 30% H_2O_2 in hexafluoro-2-propanol (HFIP) is described as a facile, selective and efficient oxidant for the conversion of sulfides to sulfoxides under neutral conditions. The nitrogen center of the pyridine molecule and the carbon–carbon double bond are shown to not be affected by the reagent system used. The oxidation of glycosyl sulfides to glycosyl sulfoxides was achieved in very high yield at room temperature.

Results and Discussion

In our search for new low-cost and environmental friendly oxidizing systems, we have recently reported on the Mn(OAc)3·2H2O catalyzed aerobic oxidation of olefins.[9a] However, this system was not selective in sulfide oxidation, leading to a mixture of sulfoxide and sulfone.[9b] We thus turned to oxidation reactions involving 30% aqueous H_2O_2 as the most readily available inexpensive oxidant. The use of a fluorous phase has recently been proved to present several advantages in organic syntheses,[10] and considering the high efficiency of protic solvents for oxidation of sulfide with aqueous H_2O_2, we chose 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (pK = 9.3)[11] as a fluorous alcoholic solvent. The oxidation of ethyl phenyl sulfide was carried out in HFIP with aqueous 30% H_2O_2 at room temp., and after 30 min afforded the corresponding ethyl phenyl sulfoxide as the only product in an excellent yield (97%). The sulfoxide was recovered in HFIP which was further distilled and reused. The sulfoxide was recovered in the HFIP phase after quenching the reaction with satd. sodium sulfite solution. The fluorous solvent (HFIP) can be recovered by distillation. Prolonging the reaction to 3 h did not give any sulfone. With an excess of aqueous 30% H_2O_2 at room temp., ethyl phenyl sulfoxide was formed within 5 min. When ethyl phenyl sulfoxide was allowed to react with 30% aqueous H_2O_2 in HFIP at 25°C, the starting sulfoxide was recovered unchanged.

The present system was applied to the oxidation of various sulfides (see Table 1)[9b]. Di-*n*-butyl sulfide (**1a**), dibenzyl sulfide (**1b**), di-*tert*-butyl sulfide (**1c**), and the cyclic sulfide **1d** afforded the corresponding sulfoxides in very good yields. Aromatic sulfides such as ethyl phenyl sulfide (**1e**), benzyl phenyl sulfide (**1f**) and the less nucleophilic diphenyl sulfide (**1g**) afforded sulfoxides as the only product in a very short reaction time. The substituents on the phenyl group had no significant effect on the reaction: With electron-donating *p*-methyl, *p*-chloro substituents (**1h** and **1i**) and with a strong electron-withdrawing group like *p*-nitro (**1j**) the reaction occurred smoothly to give the corresponding sulfoxides **2h–j** in excellent yields.

Table 1. Oxidation of sulfides R–S–R* with aqueous 30% H_2O_2 in HFIP[a]

Substrate	R	R′	Time [min]	Product	Yield (%)[b]
1a	*n*Bu	*n*Bu	5	**2a**	92
1b	$PhCH_2$	$PhCH_2$	5	**2b**	98
1c	*t*Bu	*t*Bu	20	**2c**	97
1d	$-C_4H_8-$		5	**2d**	82
1e	Ph	Et	5	**2e**	97
1f	Ph	$PhCH_2$	5	**2f**	97
1g	Ph	Ph	5	**2g**	99
1h	*p*-MeC_6H_4	Me	5	**2h**	98
1i	*p*-ClC_6H_4	Me	5	**2i**	95
1j	*p*-$O_2NC_6H_4$	Me	10	**2j**	92

[a] Sulfide (2 mmol), aqueous 30% H_2O_2 (4 mmol), HFIP (2.5 ml). – [b] Isolated yields.

We then investigated the stability of sensitive functionalities under these oxidation conditions. Cyclopropyl phenyl sulfide (**3**) gave cyclopropyl phenyl sulfoxide (**4**) without affecting the strained cyclopropyl group (see Table 2). Allylic sulfides **5** and **7**, terminal olefinic sulfide **9** and vinylic sulfide **11** afforded the corresponding sulfoxides in high yields without affecting the carbon–carbon double bond. With the thiomethyl-substituted pyridine **13** no oxidation occurred at the nitrogen center.

The efficacy of this methodology under neutral conditions prompted us to extend our reagent system to glycosyl sulfide oxidation. *m*-Chloroperbenzoic acid in CH_2Cl_2 (−78°C to −30°C) was extensively used for the conversion

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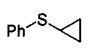
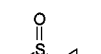
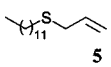
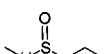
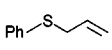
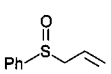
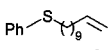
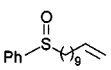
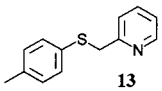
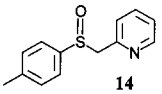
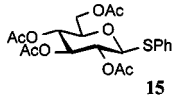
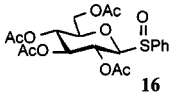
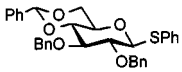
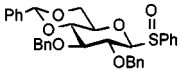
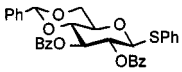
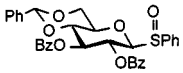
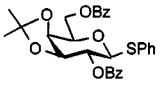
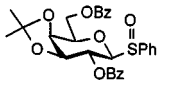
Table 2. Selective oxidation of sulfide with aqueous H_2O_2 in HFIP[a]

entry	Substrate	Time (min)	Product	Yield (%)[b]
1	 **3**	5	 **4**	93
2	 **5**	5	 **6**	95
3	 **7**	5	 **8**	99
4	 **9**	5	 **10**	98
5	 **11**	15	 **12**	94
6	 **13**	10	 **14**	93

[a] Sulfide (2 mmol), aqueous 30% H_2O_2 (4 mmol), HFIP (2.5 ml). – [b] Isolated yields.

Table 3. Oxidation of glycosyl sulfides with aqueous 30% H_2O_2 in HFIP[a]

entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **15**	16	 **16**	86
2	 **17**	3	 **18**	97
3	 **19**	4.5	 **20**	96
4	 **21**	4.5	 **22**	92

[a] Sulfide (0.5 mmol), 30% aqueous H_2O_2 (1 mmol), HFIP (2.5 ml). – [b] Isolated yields.

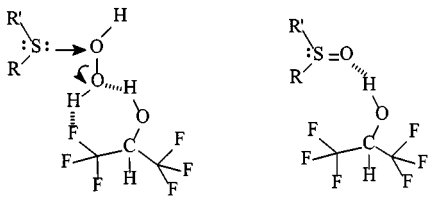
of glycosyl sulfides to sulfoxides.[2][12] However, over-oxidation was observed when the reaction was carried out at room temp. and so further efforts have focussed on more selective conditions.[8d]

At first, we examined the oxidation of the tetraacetate β-D-glucopyranosyl sulfide **15** with aqueous 30% H_2O_2 in HFIP which led to a 50:50 diastereomeric mixture of β-D-glucopyranosyl sulfoxides in 86% yield after 16 h (see Table 3). It is known that glycosyl sulfoxide glycosylation does not require a specific configuration at the sulfur atom.[2][12] The *O*-benzyl and *O*-benzoyl derivatives of the glycosyl sulfides **17**, **19** and **21** afforded (within 3 h) the corresponding sulfoxides **18**, **20** and **22** in very good yield. Benzylidene and acetonide protecting groups, which are sensitive to acidic medium,[13] were stable under the present neutral conditions. COSY- and HMQC-NMR experiments have been performed on **18** for a complete assignment of carbon atoms and protons.

Mechanism: In our oxidation system of sulfide to sulfoxide, it is important to note the following: The oxidation of sulfide to sulfoxide with H_2O_2 in HFIP is faster than in non-fluorous protic solvents,[14] and even faster than in non-fluorous protic solvents in the presence of acid.[7b] Oxidation of sulfide stops at the sulfoxide stage even with excess oxidant at room temp.

In order to understand the reaction better, we have checked that the addition of 30% aqueous H_2O_2 to HFIP [^{19}F NMR: $\delta = -74.6$, (d, $J = 5.8$ Hz)] 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. The efficiency of our oxidizing system can be explained by a specific feature of HFIP. Because of the electron-withdrawing character of the CF_3 group, the hydroxy proton in HFIP forms a strong hydrogen bond with H_2O_2 and activates the hydroxy leaving group from H_2O_2 (see Figure 1, left). When performed in the more basic trifluoroethanol (pK = 12.8)[11] the reaction was very slow. More striking is the fact that HFIP prevents any further oxidation to the sulfone. It is a general feature that sulfoxides are much less nucleophilic at the sulfur atom than sulfides, and that their oxidation is slower than that of the corresponding sulfides. In addition to this, under our reaction conditions, the formation of a strong hydrogen bond between the HFIP solvent and the oxygen atom of the sulfoxide could greatly decrease the nucleophilicity at the sulfur atom (see Figure 1, right). The addition of dimethyl sulfoxide in HFIP/H_2O caused the appearance, in the ^{1}H-NMR spectra, of a coupling constant (7.5 Hz) between the hydroxy proton and the α-proton, indicating a hydrogen bond. Thus, further oxidation of the sulfoxide did not take place.

Figure 1. Role of HFIP in sulfide oxidation



Conclusion

We have found a new and selective oxidation reaction of sulfides to sulfoxides with H_2O_2 in hexafluoro-2-propanol (HFIP) under neutral conditions and at room temp. This method can be applied to the oxidation of many sulfides without sulfone formation, even with excess aqueous 30% H_2O_2. No strict conditions are required for this selectivity. Carbon–carbon double bonds and nitrogen atoms are not

affected under these reaction conditions. The oxidation of glycosyl sulfides to the corresponding sulfoxides was achieved in high yield without affecting the *O*-protecting groups. The reaction is fast, the experimental procedure is simple, and the solvent (HFIP) is recovered and can be reused as such without any further purification.

K. S. R. thanks the *CNRS* and the *CEFIPRA* for a position as associate researcher.

Experimental Section

General: 1,1,1,3,3,3-hexafluoro-2-propanol was obtained from Aldrich. − ^{1}H NMR: 200 MHz in $CDCl_3$. − TLC: 0.25 mm Merck precoated silica plates (60F-254). Unless otherwise stated, sulfides were used as purchased from Lancaster. Sulfide **13**[15] was prepared according to the literature procedure. The sulfoxides **2a**[8d], **2b**[16], **2c**[14], **2d**[17], **2e−j**[16], **4**[18], **8**[19], **12**[20] and **14**[15] are known compounds and were identified by comparing physical and spectroscopic data with the values reported in the literature.

11-(Phenylthio)-1-undecene (**9**): 11-Bromo-1-undecene (1.17 g, 5 × 10^{-3} mol) was added to a stirred solution of thiophenol (0.55 g, 5 × 10^{-3} mol), sodium hydroxide (0.4 g, 10^{-2} mol) and a catalytic amount of tributyl(hexadecyl)phosphonium bromide (0.1 g) in a solvent mixture (water/benzene = 1 mL:5 ml). After stirring for 24 h, the organic layer was separated, washed with aqueous 10% sodium hydroxide (2 × 10 ml) and then with water, and dried with calcium chloride. Evaporation of the solvent afforded the sulfide **9**[21] as a colorless oil (1.26 g, 96%). − IR (neat): $\tilde{\nu}$ = 1636 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.8 (m, 14 H), 2.05 (m, 2 H), 2.9 (t, *J* = 7.3 Hz, 2 H), 4.8−5.1 (m, 2 H), 5.7−5.9 (m, 1 H) 7.1−7.4 (m, 5 H).

General Procedure for the Oxidation of Sulfides in HFIP: 30% aqueous H_2O_2 (0.45 ml, 4 × 10^{-3} mol) was added to a stirred solution of allyl dodecyl sulfide (**5)** (0.484 g, 2 × 10^{-3} mol) in HFIP (2.5 ml) at 25°C. The reaction was monitored by GC. After the complete disappearance of the sulfide (5 min), the excess H_2O_2 was quenched with a saturated Na_2SO_3 solution (2.0 ml). The two phases (aqueous and HFIP) were separated and the HFIP phase was dried (molecular sieve 3Å). After distillation of the solvent, 3-(dodecylsulfinyl)-1-propene (**6**) was obtained as a white solid (0.49 g, 95%, purity 99% by GC), m.p. 56°C. − IR (thin film): $\tilde{\nu}$ = 1640 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.26 (br. s, 18 H), 1.6−1.9 (m, 2 H), 2.6−2.8 (dt, *J* = 1.0, 6.9 Hz, 2 H), 3.3−3.6 (m, 2 H), 5.3−5.5 (m, 2 H), 5.7−6.0 (m, 1 H). − $C_{15}H_{30}OS$ (258.47): calcd. C 69.69, H 11.72, S 12.4; found C 69.60, H 11.08, S 12.23.

11-(Phenylsulfenyl)-1-undecene (**10**): Colourless oil (0.545 g, 98%). − IR (thin film): $\tilde{\nu}$ = 1635 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3−1.8 (m, 14 H), 2.05 (m, 2 H), 2.7−2.9 (m, 2 H), 4.8−5.1 (m, 2 H), 5.7−5.9 (m, 1 H), 7.4−7.7 (m, 5 H). − $C_{17}H_{26}OS$ (278.46): calcd. C 73.31, H 9.43, S 11.51; found C 73.25, H 9.37, S 11.48.

General Procedure for the Oxidation of Glycosyl Sulfides in HFIP: Aqueous 30% H_2O_2 (0.11 ml, 10^{-3} mol) was added to a stirred solution of glycosyl sulfide **17** (0.27 g, 0.5 × 10^{-3} mol) in HFIP (2.5 ml) at 25°C. The reaction was monitored by TLC. After the complete disappearance of the sulfide (3 h), the excess H_2O_2 was quenched with saturated Na_2SO_3 solution (2.0 ml) and the fluorous phase containing the sulfoxide was separated. After distillation of HFIP, sulfoxide **18** was obtained as a white solid (0.27 g, 97%), m.p. 144°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (td, *J* = 9.7 Hz, *J* = 5 Hz, 0.5 H, 5-H), 3.58 (m, 1 H, 0.5 H, 5-H, 0.5 H, 4-H), 3.70 (m, 0.5 H, 6-H), 3.75 (t, *J* = 10.5 Hz, 0.5 H, 6-H), 3.79 (t, *J* = 9.3 Hz, 0.5 H, 4-H), 3.85 (dd, *J* = 9.1 Hz, *J* = 7.7 Hz, 0.5 H, 2-H), 3.92 (m, 1 H, 3-H), 4.0 (dd, *J* = 10.5 Hz, *J* = 5 Hz, 0.5 H, 6-H), 4.02 (d, *J* = 9.8 Hz, 0.5 H, 1-H), 4.16 (dd, *J* = 9.8 Hz, *J* = 8.5 Hz, 0.5 H, 2-H), 4.42 (m, 0.5 H, 6-H), 4.6 (d, *J* = 9.1 Hz, 0.5 H, 1-H), 5.53 (s, 1 H, 7-H), 7.0−7.7 (m, 20 H). − ^{13}C NMR: δ = 68 (C-6), 70.2/71 (C-5),75/76.5 (C-2), 81 (C-4), 83 (C-3), 94/96 (C-1), 101.5 (C-7) 122−132 (aromatic). − $C_{33}H_{32}O_6S$ (558.70): calcd. C 71.19, , 5.81, S 5.76; found C 71.16, H 5.92, S 5.66

Phenylsulfenyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (**16**): White crystalline solid (0.19 g, 86%). M.p. 46°C. − IR (thin film): $\tilde{\nu}$ = 1757 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.9−2.2 (m, 12 H), 3.52−3.72 (m, 1 H), 4.0−4.16 (m, 2 H), 4.26 (d, *J* = 9.7 Hz, 0.5 H), 4.44 (d, *J* = 9.5 Hz, 0.5 H), 4.88−5.04 (m, 1 H), 5.16−5.38 (m, 2H), 7.48−7.56 (m, 3 H), 7.60−7.72 (m, 2H). − $C_{20}H_{24}O_{10}S$ (458.49): calcd. C 52.62, H 5.31, S 7.02; found C 52.55, H 5.49, S 6.85.

Phenylsulfenyl 2,3-Di-O-benzoyl-4,6-O-benzylidene-β-D-glucopyranoside (**20**): White solid (0.28 g, 96%), m.p. 176°C. − IR (thin film): $\tilde{\nu}$ = 1733 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.5−3.7 (m, 0.6 H), 3.7−4.1 (m, 3 H), 4.17−4.25 (dd, *J* = 4.9, 10.4 Hz, 0.4 H), 4.46 (d, *J* = 9.2 Hz, 1 H), 5.51 (s, 1 H), 5.79−5.99 (m, 2 H), 7.24−8.02 (m, 20 H). − $C_{33}H_{28}O_8S$ (584.65): calcd. C 67.79, H 4.84, S 5.48; found C 67.37, H 5.01, S 5.67.

Phenylsulfenyl 2,6-Di-O-benzoyl-3,4-O-isopropylidene-β-D-galactopyranoside (**22**): White solid (0.242 g, 92%); m.p. 172°C. − IR (thin film): $\tilde{\nu}$ = 1730, 1716 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.64 (s, 3 H), 4.2−4.3 (m, 1 H), 4.32−4.74 (m, 5 H), 5.36 (dd, *J* = 5.3, 6.8 Hz, 0.3 H), 5.97 (t, *J* = 3.7 Hz, 0.6 H), 7.3−8.1 (m, 15 H). − $C_{29}H_{28}O_8S$ (536.61): calcd. C 64.90 H 5.27, S 5.97; found C 64.23, H 5.32, S 6.19.

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