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Selective Oxidation of Glycosyl Sulfides to Sulfoxides Using Magnesium Monoperoxyphthalate and Microwave Irradiation

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Abstract: A protocol that uses moist magnesium monoperoxyphthalate (MMPP) as an oxidant under microwave irradiation rapidly yields a variety of glycosyl sulfoxides from corresponding sulfides in high yields with high selectivity.

Sulfoxides are an important class of synthetic intermediates used for stereocontrol in the construction of chemically and biologically important molecules.[1−3] In carbohydrate chemistry, glycosyl sulfoxides[4] constitute as a distinct class of donors[5] for glycosylation because of the mild conditions[6] under which they react, their good to excellent anomeric stereocontrol,[4,7] and their adaptabilities in both solution- and solid-phase synthesis.[8] They have been used in preparing oligosaccharides[9] and glycoconjugates.[10] Moreover, the stereochemical outcome of such glycosylation is independent of the configuration at sulfur atom,[4] eliminating the need to prepare diastereomerically pure gycosyl sulfoxide donor for glycosidation. Apart from glycosyl donors, glycosyl carbanions, obtained by sulfinyl−lithium exchange, are useful in the stereospecific construction of an important class of compounds called C-glycosides.[11] The rich chemistry of glycosyl sulfoxides motivates the development of selective and efficient methods for their synthesis.

Although several methods for oxidizing sulfides to sulfoxides or sulfones have been developed,[12] very few are sufficiently selective to terminate oxidation at the sulfoxide stage and prevent overoxidation to sulfones.[13] Even fewer methods of synthesizing glycosyl sulfoxides have been investigated.[4,14] The oxidation of glycosyl sulfides to sulfoxides has most successfully been achieved using *m*-CPBA (*m*-chloroperbenzoic acid).[4] However, this method suffers from a number of shortcomings, including the requirement that a low temperature be maintained to prevent overoxidation to sulfone, the partial solubility of *m*-CPBA in the solvent, and the difficulty of separating the byproduct, *m*-chlorobenzoic acid, from the sulfoxide. Accordingly, a new highly selective method with mild reaction conditions and simple workup is required. A few years ago, one such selective and mild method, using hydrogen peroxide (30%) as an oxidant in the presence of silica gel, was reported.[14g] Very recently, we reported another selective and mild method that involved silica gel-supported oxone or *tert*-butyl hydroperoxide (TBHP) as an oxidant at room temperature, to oxidize glycosyl sulfides to sulfoxides.[15] Herein, a protocol, which rapidly generates various glycosyl sulfoxides and improves upon the selectivity and efficiency of previously reported methods, is presented. This protocol uses magnesium monoperoxyphthalate (MMPP) as an oxidant under microwave irradiation.

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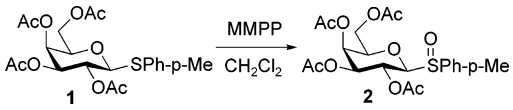
TABLE 1. Oxidation of Glycosyl Sulfide (1) to Sulfoxide (2)[a]



						yield[c] (%)		
entry	oxidant	adsorbent	water (μL)	condition[b]	time (h)	sulfoxide	sulfide	sulfone
1	MMPP			A	10		96	
2	MMPP	Al_2O_3	500	A	6	86	10	trace[d]
3	MMPP		50	A	6	84	8	4
4	MMPP		50	B	0.7	90	6	
5	MMPP		50	C	3	85	11	trace
6	$NaIO_4$[e]		50	A	6		97	
7	$NaIO_4$[e]		50	B	0.5		95	
8	$NaIO_4$[e]	silica gel	400	A	6	83	12	8
9	$NaIO_4$[e]	silica gel	400	B	0.7	80	13	trace
10	OXONE[f]	silica gel	20	A	7	76	15	3
11	OXONE[f]		20	B	0.7	78	16	trace

[a] Mixture of *R* and *S* isomers. [b] Condition A: Stirred at 25 °C. Condition B: Microwave heating. C: conventional heating. [c] Isolated yield. [d] The use of exess MMPP (2 mmol) affords the corresponding glycosyl sulfone **3**. [e] 1.7 mmol. [f] 1.5 mmol of $KOSO_2OOH$.

Magnesium monoperoxyphthalate is a commercially available and safe alternative to commonly used peroxy acid oxidants for oxidizing various functional groups.[13g,i,14a,l,16] Its stability and the fact that it need not be assayed before use make it particularly attractive. However, its solubility in only polar solvents has greatly limited its acceptability as a popular oxidant. This limitation has recently been overcome using moist MMPP on a solid support such as silica gel[13i] or bentonite[17] and a relatively nonpolar solvent such as dichloromethane. Moreover, a recent report described the use of no adsorbent in converting sulfides to sulfoxides using MMPP, with the reactions accelerated by microwave heating.[13g] Although microwave heating is extensively used to accelerate reactions in other areas of organic synthesis,[18] its use in carbohydrate chemistry is very limited.[19] This work investigates the micowave protocol for converting glycosyl sulfides to sulfoxides.

Initially, glycosyl sulfide **1** was chosen as the model substrate to study its oxidation to glycosyl sulfoxide **2**. Table 1 summarizes the results. When dry MMPP and dichloromethane was used, glycosyl sulfide **1** was recovered almost quantitatively (entry 1), even with stirring for 10 h, since only moist MMPP is known to generate the desired reaction products.[13f] MMPP adsorbed over moist alumina (entry 2) resulted in 86% conversion to glycosyl sulfoxide **2** with 10% recovery of the starting sulfide after stirring for 6 h at room temperature. Without alumina support, but in the presence of a small amount of water (50 μL), similar results were obtained (entry 3). Conventional heating in an oil bath at 60 °C took 3 h (entry 4) to afford 85% conversion and 11% recovery of the starting sulfide. Dramatic acceleration of the reaction was observed under microwave conditions; only 0.7 h of irradiation was required to give 90% conversion to glycosyl sulfoxide **2**, with 6% recovery of the starting sulfide **1** (entry 5). Notably, the amount of MMPP per mole of glycosyl sulfide should be only slightly above 1 equiv: the use of excess (such as 2 equiv) led to the formation of the corresponding sulfone **3** rather than the sulfoxide. Other oxidants, including sodium periodate and oxone, produced slightly lower yields of glycosyl sulfoxide **2** (entries 8−11) and the recovery of more starting sulfide **1**, both at room temperature and under microwave irradiation, implying the superiority of MMPP as an oxidant for oxidizing glycosyl sulfides to glycosyl sulfoxides. These findings also indicated that the "microwave effect" reduced the required reaction time (entry 8 vs 9 and entry 10 vs 11). It should be noted that no solid support was required when MMPP or oxone is used under microwave irradiation conditions (entries 4 and 11).

Next, the generality of this protocol was examined by subjecting glycosides with various types of protective groups to the established reaction conditions; Table 2 shows the results. Glycosyl sulfides were observed to undergo smooth oxidation to the corresponding sulfoxides within periods from 10 to 45 min, with yields of over 80%. All the protective groups remained intact during the reactions and no overoxidation to sulfone wwas observed on the basis of TLC analysis. The levulinyl group (entry

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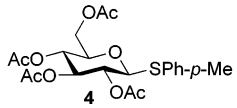
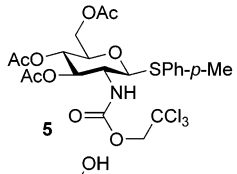
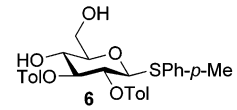
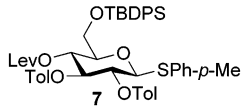
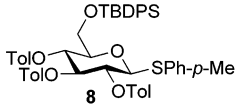
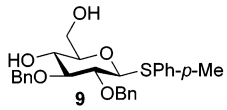
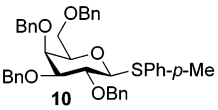
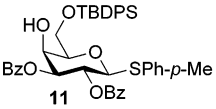
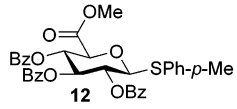
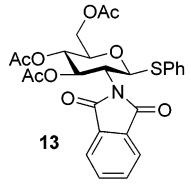
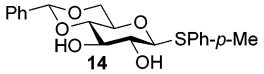
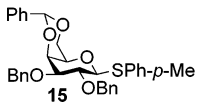
TABLE 2. Oxidation of Glycosyl Sulfides

Entry	Substrate[a]	Time (min)	Sulfoxide	Yield(%)[b]
1	 **4**	45	**16**	83 (1:1)
2	 **5**	30	**17**	82 (5:4)
3	 **6**	20	**18**	87 (5:1)
4	 **7**	45	**19**	89 (4:1)
5	 **8**	45	**20**	90 (2:1)
6	 **9**	10	**21**	85 (3:2)
7	 **10**	15	**22**	91 (5:2)
8	 **11**	20	**23**	86 (2:1)
9	 **12**	30	**24**	93 (1:1)
10	 **13**	45	**25**	84 (3:1)
11	 **14**	10	**26**	82 (3:1)
12	 **15**	15	**27**	80 (4:1)

[a] Tol = *p*-methylbenzoyl, Lev = levulinyl ($CH_3COCH_2CH_2COO$). [b] The isolated yield after chromatographic purification. The number in parentheses indicates the ratio of diastereomers on the basis of H-1 chemical shifts (downfield/upfield).

4) which has potential to undergo Baeyer−Villiger oxidation with MMPP[16e] (and under *m*-CPBA oxidation) survived, suggesting the utility of MMPP and its mild oxidative property. Acid-labile protecting groups, such as TBDPS and benzylidene, were stable under the reaction conditions used herein (entries 4, 5, 11, and 12). Interestingly, among the glycosyl sulfides subjected to the oxidation protocol, more polar substances (with the free hydroxyl groups; entries 3, 6, 8, and 11) underwent faster oxidation. The electronic effect of the protecting group on the C-2 of the glcosyl sulfide was also found to influence the reaction rate. Electron-donating groups (e.g., ethers) on C-2 resulted in much higher reaction rates than electron-withdrawing groups (e.g., ester). The diastereomeric ratios of sulfoxides were determined using ^{1}H NMR based on the chemical shifts of the anomeric protons.[20] The chemical shifts of the anomeric protons of the major isomers were further downfield shifted as compared to those of minor isomers. Interestingly, the sulfoxide isomer ratios are not similar to those obtained previously.[15] The differences may have been associated with "microvawe effect" or the oxidant used.

In conclusion, fast generation of various glycosyl sulfoxides from the corresponding sulfides was developed by using moist MMPP as an oxidant and microwave irradiation. This protocol is highly selective and efficient. It involves the use of a cheap, stable, and safe reagent and a simple workup. Moreover, this study demonstrates that this protocol outperforms the other currently available methods for the synthesis of glycosyl sulfoxides.

Experimental Section:

The isolated compounds **17**−**22**, **24**, and **25** have previously been characterized, and the NMR spectral data are in good agreement with the literature data.[15]

Oxidation of Glycosyl Sulfide 1 on Supported Reagent. A round-bottom flask was charged with 0.5 mmol of MMPP, 1.7 mmol of $NaIO_4$, or 1.5 mmol of Oxone adsorbed on the solid support (2.5 g of Fisher A 540 Alumina or NM-Kieselgel 60 (0.04−0.063 mm mesh size) and then moistened with an appropriate quantity of water (Table 1). A solution of glycosyl sulfide (1.0 mmol) in dichloromethane (5.0 mL) was added, and the suspension was stirred at 25 °C or heated in oil bath at room temperature for the time specified in Table 1.

Oxidation of Glycosyl Sulfides by Microwave Irradiation. Solid MMPP (0.52 mmol), moistened with the appropriate quantity of water, was charged into a 10 mL round-bottom flask. A solution of glycosyl sulfide (1.0 mmol) in dichloromethane (5 mL) was added to the flask. This stirred suspension was irradiated for the time specified in Table 2. After completion of the reaction (checked by TLC), the reaction mixture was filtered through Celite pad and the solvent was removed on a rotary evaporator to give crude product. Purification of crude product was carried out by flash chromatography with ethyl acetate/hexane as an eluant.

***p*-Methylphenylsulfonyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (3):** R_f 0.24 (1:2 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.93 (s, 3H), 1.94 (s, 3H), 1.95 (s, 3H), 2.14 (s, 3H), 2.44 (s, 3H), 3.67−3.73 (m, 1H), 4.10 (d, 2H, J = 3.6 Hz), 4.47 (d, 1H, J = 9.6 Hz), 4.84 (dd, 1H, J = 9.8, 9.6 Hz), 5.12−5.23 (m, 2H), 7.32 (d, 2H, J = 8.1 Hz), 7.74 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3 (2C), 20.4, 20.5, 21.6, 61.1, 67.0, 67.2, 73.2, 75.9, 88.6, 129.4, 130.4, 131.3, 145.7, 169.1, 169.2, 169.8, 170.0; HRMS (EI) calcd for $C_{21}H_{27}O_{11}S$ [M + H$^+$] 487.1196, found 487.1194.

***p*-Methylphenylsulfenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (16) (mixture):** R_f 0.20 (1:2 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.93 (s, 1.5H), 1.96 (s, 1.5H), 1.98 (s, 1.5H), 1.99 (s, 6H), 2.04 (s, 1.5H), 2.42 (s, 3H), 3.60−3.64 (m, 0.5H), 3.66−3.72 (m, 0.5H), 4.02−4.16 (m, 2H), 4.27 (d, 0.5H, J

(20) (a) Crich, D.; Mataka, J.; Zakharov, L. N.; Rheingold, A. L.; Wink, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 6028. (b) Khiar, N. *Tetrahedron Lett.* **2000**, *41*, 9059.

= 9.2 Hz), 4.41 (d, 0.5H, J = 9.4 Hz), 4.93 (dd, 0.5H, J = 9.4, 9.3 Hz), 4.99 (dd, 0.5H, J = 9.3, 9.2 Hz), 5.18−5.30 (m, 2H), 7.32 (d, 2H, J = 8.1 Hz), 7.51−7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1 (3C), 21.4 (2C), 61.6 (61.2), 67.4 (67.6), 67.5, 73.5 (73.8), 76.1, 89.6 (91.9), 125.8(125.7), 129.5 (2C) (129.4) (2C), 142.2 (142.3), 169.1, 169.2, 170.0, 170.2; HRMS (EI) calcd for $C_{21}H_{27}O_{10}S$ [M + H$^+$] 471.1324, found 471.1321.

***p*-Methylphenylsulfenyl 2,3-di-*O*-benzoyl-6-*tert*-butyldiphenylsilyl-β-D-galactopyranoside (23):** R_f 0.22 (2:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 9H), 2.36 (s, 3H), 2.53 (br s, 1H), 3.61−3.64 (m, 1H), 3.94−4.00 (m, 3H), 4.74 (d, 1H, J = 9.7 Hz), 5.45 (dd, 1H, J = 9.8, 9.7 Hz), 5.66 (dd, 1H, J = 9.8, 9.7 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.36−7.45 (m, 12H), 7.64−7.69 (m, 4H), 7.84 (d, 2H, J = 8.1 Hz). 7.94−7.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 19.1 (3C), 20.9, 62.6, 67.4, 68.7, 77.7, 80.6, 89.6, 125.4, 127.8, 128.2, 128.4, 129.0, 129.6, 129.8, 129.9, 130.0, 132.7, 133.2, 133.4, 133.6, 135.6, 144.2, 145.5, 165.1, 167.1; HRMS (EI) calcd for $C_{43}H_{45}O_8SSi$ [M + H$^+$] 749.2526, found 749.2529. For another isomer: R_f 0.20 (2:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 9H), 2.36 (s, 3H), 2.56 (br s, 1H), 3.63 (m, 1H), 3.99−4.18 (m, 3H), 4.83 (d, 1H, J = 9.7 Hz), 5.61 (dd, 1H, J = 9.8, 9.7 Hz), 5.80 (dd, 1H, J = 9.8, 9.7 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.34−7.47 (m, 12H), 7.63−7.70 (m, 4H), 7.84 (d, 2H, J = 8.1 Hz), 7.93−7.99 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1 (3C), 21.6, 64.0, 70.3, 73.1, 77.8, 82.0, 92.0, 125.4, 127.8, 128.2, 128.4, 129.0, 129.6, 129.8, 129.9, 130.0, 132.7, 133.2, 133.4, 133.6, 135.6, 144.2, 145.5, 165.1, 167.0; MS (EI) 749 (42, [M + H]$^+$), 734 (100).

***p*-Methylphenylsulfenyl-β-D-glucopyranoside (26):** R_f 0.30 (1:1 EtOAc/hexane); ^{1}H NMR (CH_3OH-d_6, 300 MHz) δ 2.49 (s, 3H), 3.26 (dd, 1H, J = 9.7, 9.3 Hz), 3.38 (dd, 1H, J = 9.3, 9.0 Hz), 3.56−3.64 (m, 1H), 3.68−3.78 (m, 2H), 4.35 (dd, 1H, J = 9.0, 4.6 Hz), 4.66 (d, 1H, J = 9.7 Hz), 5.54 (s, 1H), 7.36−7.38 (m, 3H), 7.44−7.51 (m, 4H), 7.66−7.68 (m, 2H); ^{13}C NMR (CH_3-OH-d_6, 75 MHz) δ 22.3, 70.0, 72.8, 73.2, 76.8, 82.3, 96.3, 103.8, 128.4, 128.5, 129.9 (2C), 130.8, 131.6, 139.6, 145.0; HRMS (EI) calcd for $C_{20}H_{23}O_6S$ [M + H$^+$] 391.1137, found 391.1134. For another isomer: R_f 0.26 (1:1 EtOAc/hexane); ^{1}H NMR (CH_3OH-d_6, 300 MHz) δ 2.41 (s, 3H), 3.38 (dd, 1H, J = 9.3, 5.0 Hz), 3.49 (dd, 1H, J = 9.3, 9.3 Hz), 3.67−3.76 (m, 2H), 3.89 (dd, 1H, J = 9.8, 9.3 Hz), 3.98 (dd, 1H, J = 9.3, 5.2 Hz), 4.16 (d, 1H, J = 9.8 Hz), 5.53 (s, 1H), 7.29−7.31 (m, 3H), 7.36−7.46 (m, 4H), 7.52−7.55 (m, 2H); ^{13}C NMR (CH_3OH-d_6, 75 MHz) δ 22.3, 69.6, 71.5, 73.0, 76.9, 82.4, 96.0, 103.8, 127.4, 128.4, 129.8 (2C), 130.8, 131.7, 139.8, 145.0; HRMS (EI) calcd for $C_{20}H_{23}O_6S$ [M + H$^+$] 391.1134, found 391.1136.

***p*-Methylphenylsulfenyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (27) (mixture):** R_f 0.25 (2:3 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 3.43−3.46 (m, 1H), 3.68−3.71 (m, 1H), 3.89−4.30 (m, 2.4H), 4.00 (d, 0.8H, J = 12.0 Hz), 4.38 (d, 0.8H, J = 12.0 Hz), 4.63−4.78 (m, 4H), 4.92 (d, 0.2H, J = 11.0 Hz), 4.95 (d, 0.8H, J = 11.0 Hz), 5.31 (s, 0.8H), 5.42 (s, 0.2H), 7.19−7.39 (m, 18H), 7.86 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 68.8 (67.9), 70.0, 71.4 (71.1), 72.6, 73.4 (74.0), 74.6, 81.7 (80.9), 93.6 (92.8), 101.3 (101.9), 126.2, 126.5, 126.6 (2C), 127.5, 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.0 (2C), 128.3, 128.4, 128.6 (2C), 128.8, 128.9, 129.0, 129.1, 129.3, 135.4 (2C), 137.6 (2C), 137.7 (2C), 137.9 (2C), 142.0, 142.2; HRMS (EI) calcd for $C_{34}H_{35}O_6S$ [M + H$^+$] 571.2076, found 571.2078.

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Supporting Information Available: General experimental considerations and ^{1}H and ^{13}C spectra of compounds **3**, **16**, **23**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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