Simple and Efficient Method for the Oxidation of Sulfides to Sulfoxides: Application to the Preparation of Glycosyl Sulfoxides

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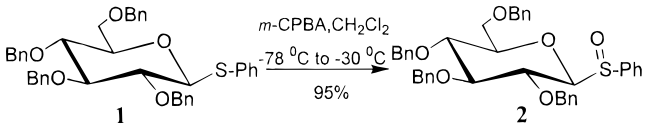
Compounds containing a sulfoxide moiety are useful synthetic intermediates for the construction of various chemically and biologically significant molecules.[1] The discovery by Kahne and co-workers[2] of the anomeric glycosyl sulfoxide as a novel glycosyl donor provided a new and powerful method for chemical glycosylation. Synthesis of a wide range of glycosides[3] and oligosaccharides[4] have been reported using the Kahne sulfoxide glycosylation methodology. Glycosyl sulfoxide donor technology has been applied not only to solution-phase glycosylations[5] but also to the solid-phase synthesis of carbohydrates.[6] High α or β anomeric stereochemical control with a variety of glycosyl acceptors has been reported with this methodology.[2] It was also determined that the stereochemical outcome of the glycosylation is independent of both the anomeric stereochemistry (α or β) and the sulfoxide stereochemistry[2,7] (*R* or *S*) in the glycosyl donor. Consequently, glycosyl sulfoxide glycosylation chemistry avoids the need for separation of anomers and allows for the use of a diastereomeric mixture of glycosyl sulfoxides.

In our efforts to develop glycosylated cholic acid derivatives as drug transport reagents, it was desirable to effect large-scale glycosylations using the glycosyl sulfoxide glycosylation methodology.[8] Consequently, kilogram quantities of various glycosyl sulfoxides were required. The oxidation of sulfides to sulfoxides or sulfones has been studied extensively using various oxidation protocols.[9] However, the oxidation of glycosyl sulfides to sulfoxides has primarily been achieved with *m*-CPBA[2,10] in CH_2Cl_2 (Scheme 1). Our investigation of the large-scale *m*-CPBA oxidation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) to provide the corresponding sulfoxide (**2**) identified several drawbacks to this method. The *m*-CPBA oxidation of glycosyl sulfides to the corresponding sulfoxides is initiated at −78 °C and allowed to warm slowly to −30 °C. The low temperature is required to avoid sulfone formation. However, the reaction does not proceed to completion at −78 °C and, consequently, warming is needed. In addition, *m*-CPBA is only partially soluble in CH_2Cl_2, and complete removal of the byproduct *m*-chlorobenzoic acid from the reaction mixture was difficult and often incomplete. During reaction workup at room temperature, overoxidation of some sulfoxide product to the undesired and unreactive sulfone was also problematic. Attempts to quench the unspent oxidant before workup added procedural complications to the process and introduced concerns about sulfoxide to sulfide reduction. These problems with *m*-CPBA oxidation of glycosyl sulfides prompted us to investigate alternate oxidation protocols that would be simple, mild, and efficient and afford selective oxidation of glycosyl sulfides to sulfoxides at room temperature without overoxidation to the corresponding sulfone.

Scheme 1



1 2

Results and Discussion

We focused our efforts on inexpensive reagent systems (Table 1) for developing a simplified method for the room temperature oxidation of sulfides to sulfoxides. We also chose the glycosyl sulfide **1** as our model substrate. Our initial attempts to oxidize **1** using urea−H_2O_2[11] in AcOH/THF (Table 1, entry 2) or in AcOH/CH_2Cl_2/MeOH (Table 1, entry 3) provided the sulfoxide **2** in 60% and 80% yield, respectively. Replacing AcOH with Ac_2O as the promoter in combination with urea−H_2O_2 (Table 1, entry 4) gave **2** in 85% yield along with 15% of the sulfone. A recent report on the oxidation of various aliphatic and aromatic sulfides by *tert*-butyl hydroperoxide[9g] (TBHP) showed that the reaction was accelerated by adding silica gel (SiO_2) as an adsorbent resulting in the rapid formation

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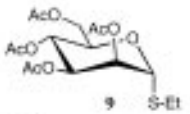
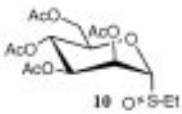
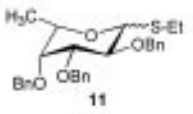
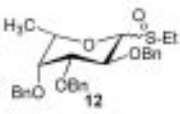
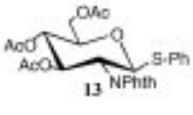
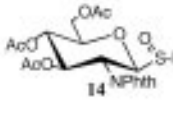
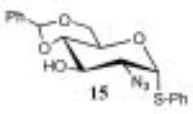
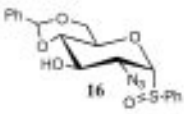
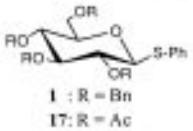
Table 1. Oxidation of Sulfide[a] (1) to Sulfoxide[b] (2) at Room Temperature with Various Oxidizing Reagents and Conditions

exp no.	reagent (mmol)	solvent (10 mL)	time(h)	% yield[c] sulfoxide	sulfone	sulfide
1[d]	*m*-CPBA (1.1)	CH_2Cl_2	2	95	trace	trace
2	urea−H_2O_2 (1.5)	AcOH, THF (2:1)	72	60		40
3	urea−H_2O_2 (1.5)/AcOH (2)	CH_2Cl_2, MeOH (2:1)	24	80	trace	20
4	urea−H_2O_2 (1.5)/Ac_2O (2)	CH_2Cl_2, MeOH (2:1)	8	85	15	
5[e]	urea−H_2O_2 (1.5)/AcOH (2)	CH_2Cl_2, MeOH (4:1)	96	40		60
6	$(CH_3)_3CO_2H$ (2)/AcOH (1)	CH_2Cl_2	48	20		80
7[e]	$(CH_3)_3CO_2H$ (2)/AcOH (1)	CH_2Cl_2	48	30	trace	70
8[e]	H_2O_2 (2)	AcOH, THF (2:1)	120	90		10
9[f]	H_2O_2 (4.4)/CF_3CO_2H (1)	THF	12	50	10	30
10	H_2O_2 (4.4)/Ac_2O (1)	acetone	60	90	trace	10
11	H_2O_2 (4.4)/Ac_2O (2)	acetone	24	85	5	10
12[e]	H_2O_2 (2.2)/AcOH (2)	CH_2Cl_2	96	40		60
13[e]	H_2O_2 (1.2)/Ac_2O (1.1)	CH_2Cl_2	4	95	trace	

[a] 1 mmol of sulfide was used. [b] Mixture of *R* and *S* isomers. [c] Isolated yield. [d] Reaction was done at −78 °C to −30 °C. [e] 200 mg of silica gel (230−400 mesh) was used as an adsorbent. [f] 10% of unknown compound was also isolated and not characterized.

Table 2. Oxidation of Sulfides to Sulfoxides Using H_2O_2, Ac_2O, and SiO_2 in CH_2Cl_2[a]

Sulfide	Time (h)	Sulfoxide[b]	Yield[c] (%)
$(i\text{-}C_3H_7)_2S$ **3**	4	$(i\text{-}C_3H_7)_2S{=}O$ **4**	95[d]
$(n\text{-}C_4H_9)_2S$ **5**	6	$(n\text{-}C_4H_9)_2S{=}O$ **6**	95[d]
$PhCH_2SPh$ **7**	16	$PhCH_2\text{-}SO\text{-}Ph$ **8**	95[d]
 **9**	12	 **10**	95
 **11**	8	 **12**	95
 **13**	24	 **14**	82[e]
 **15**	24	 **16**	60[f]
 **1**: R = Bn **17**: R = Ac **19**: R = Piv	4 20 16	 **2**: R = Bn **18**: R = Ac **20**: R = Piv	95 95 95

[a] Reaction conditions: sulfide (1 mmol), 30% H_2O_2 (1.2 mmol), Ac_2O (1.1 mmol), SiO_2 (200 mg, 230−400 mesh) in CH_2Cl_2 (5 mL) at rt. [b] Mixture of *R* and *S* isomers. [c] Isolated yield. [d] Contains trace quantities of sulfone. [e] 15% starting sulfide was recovered. [f] 35% starting sulfide was recovered.

of sulfoxides or sulfones. This prompted us to investigate the addition of SiO_2 to urea−H_2O_2 and sulfide **1** (Table 1, entry 5), however, resulted in no improvement in the yield of sulfoxide **2**. Furthermore, oxidation of sulfide **1** using the TBHP/AcOH method[9g] without SiO_2 (Table 1, entry 6) and with SiO_2 (Table 2, entry 7) gave sulfoxide **2** in 20% and 30% yield, respectively. On the basis of these results, evidently both the urea−H_2O_2 and TBHP oxidation methods did not meet our criteria for an effective glycosyl sulfide to sulfoxide oxidation procedure.

Since our initial attempts with urea−H_2O_2 and TBHP reagent systems failed to give acceptable yields of pure sulfide oxidation product **2**, we turned our efforts toward other H_2O_2-mediated oxidation protocols. Oxidation of **1** with 30% aqueous H_2O_2 in AcOH/THF (Table 1, entry 8) after 120 h gave **2** in 90% yield. Addition of TFA accelerated the H_2O_2 oxidation of **1** (Table 1, entry 9), but also resulted in the formation of sulfone (10%) and an unidentified side product (10%). Addition of Ac_2O (Table 1, entry 10) to H_2O_2 provided **2** in 90% yield, and 10% of unreacted starting material **1** was recovered. Increasing the amount of Ac_2O (Table 1, entry 11) accelerated the reaction, but the formation of sulfone was also observed. The combination of H_2O_2, AcOH, and SiO_2 in CH_2Cl_2 (Table 1, entry 12) resulted in 40% yield of **2**. However, a considerable acceleration in the reaction rate was observed when SiO_2 was added (Table 1, entry 13) to the reaction mixture containing **1**, H_2O_2, and Ac_2O in CH_2Cl_2. Under these conditions, the reaction was complete within 4 h, and the desired sulfoxide (**2**) was obtained in 95% yield.

The scope of the $H_2O_2/Ac_2O/SiO_2$-mediated sulfide to sulfoxide oxidation was surveyed using additional glycosyl, aliphatic, and aromatic sulfides (Table 2). As shown in Table 2, good yields (82−95%) of sulfoxides **4**, **6**, **8**, **10**, **12**, **14**, **18**, and **20** were obtained from the corresponding sulfides. The benzylidene protecting group in sulfide **15** is stable under the acidic reaction conditions and gave 60% yield of sulfoxide **16** along with 35% of unreacted starting material. Oxidation of **3**, **5**, and **7** (Table 2) illustrated that this method was effective for the oxidation of non-carbohydrate substrates with excellent yields. However, the time required to complete the oxidation of aromatic sulfide (**7**) was longer than the aliphatic sulfides **3** and **5**. In contrast, the time required for oxidation of compound **11** and **1** was far less than that required for the oxidation of compounds **9**, **13**, **17**, and **19**. This rate difference indicates that the protecting group at C-2 of the thioglycoside (ether vs ester) greatly affected the rate of the sulfide oxidation. Clearly, the more electron rich the sulfur of the thioglycoside the more easily it is oxidized.

We found that only 200 g of SiO_2 adsorbent per mole (632 g) of substrate (**1**) was needed to oxidize it to the sulfoxide **2**. This large-scale oxidation gave **2** in 90% isolated yield at 100% purity producing no detectable amounts of sulfide or sulfone as determined by HPLC.

In conclusion, this oxidation method ($H_2O_2/Ac_2O/SiO_2$ in CH_2Cl_2) represents a simple, inexpensive, and highly efficient approach for both small- and large-scale preparation of glycosyl and noncarbohydrate sulfoxides from their corresponding sulfides. The sulfoxides **2**, **4**, **6**, **8**, **10**, **12**, **18**, and **20** were obtained in pure form by simply filtering the reaction mixture and washing successively with aqueous $NaHSO_3$, $NaHCO_3$, and brine followed by solvent removal. This procedure provides a convenient and efficient alternative to the standard *m*-CPBA oxidation of glycosyl sulfides, thus avoiding difficult experimental and workup procedures. We are currently exploiting this method for the scaleup of other glycosyl sulfoxides, which will be used in our solution and solid phase generation of combinatorial libraries. We are also evaluating the use of our newly developed reagent system ($H_2O_2/Ac_2O/SiO_2$) in a variety of other oxidations and will report the results in due course.

Experimental Section

ACS-grade solvents were used for the reactions. Silica gel 60 (230−400 mesh) was used for flash chromatography. TLC was performed with 0.2 mm coated commercial silica gel plates (Kieselgel $60F_{254}$). Melting points were determined in open capillary tubes and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$. Mass spectra (FAB) analyses were performed by Mid-Atlantic spectrometry services, Frederick, MD. Benzyl phenyl sulfide (**7**), diisopropyl sulfide (**3**), and di-*n*-butyl sulfide (**5**) were purchased from Aldrich Chemical Co. Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**9**) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-α,β-L-fucopyranoside (**11**) were purchased from Toronto Research Chemicals. All other sulfides (**1**, **13**, **15**, **17**, and **19**) were synthesized according to the modified literature procedures.[12]

General Procedure for Sulfoxide Synthesis from Sulfides. To a stirred mixture of appropriate sulfide (1 mmol), Ac_2O (1.1 mmol), and silica gel (200 mg, 230−400 mesh) in CH_2Cl_2 (5 mL) was added aqueous 30% H_2O_2 solution (1.2 mmol). After being stirred at rt between 2 and 24 h (reaction progress is monitored by TLC), the reaction mixture was filtered through a fine frit (sintered) funnel and the filtrate washed with saturated aqueous $NaHSO_3$ (50 mL), $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was separated, dried (anhydrous Na_2SO_4), and concentrated to furnish a mixture of *R* and *S* sulfoxides.

Phenylsulfenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (2): white solid (95% yield); mp 120−122 °C; R_f 0.3 (1:3 EtOAc/hexane); ^{1}H NMR δ 7.72−7.14 (m, 25H), 5.04−4.45 (m, 8H), 4.27 (ABq, 1H, J_{AB} = 12.0 Hz, Δν = 28.1 Hz), 4.14 (d, 0.5H, *J* = 9.9 Hz), 3.98 (d, 0.5H, *J* = 9.9 Hz), 3.83−3.72 (m, 2H), 3.62−3.42 (m, 2H), 3.40−3.28 (m,1H); MS (Fab) 671 (M + Na)$^+$. Anal. Calcd for $C_{40}H_{40}O_6S$: C, 74.04; H, 6.22; S, 4.93. Found: C, 73.96; H, 6.30; S, 4.83.

Diisopropyl sulfoxide (4): colorless oil[13] (95% yield); R_f 0.1 (1:9 EtOAc/hexane); ^{1}H NMR δ 2.81−2.63 (m, 2H), 1.25−1.19 (m, 12H); MS (Fab) 157 (M + Na)$^+$. Anal. Calcd for $C_6H_{14}OS$: C, 53.70; H, 10.52; S, 23.85. Found: C, 53.67; H, 10.46; S, 23.51.

Di-*n*-butyl sulfoxide (6): colorless oil[13] (95% yield); R_f 0.1 (1:4 EtOAc/hexane); ^{1}H NMR δ 2.67−2.48 (m, 4H), 1.80−1.68 (m, 4H), 1.58−1.38 (m, 4H), 0.95 (t, 6H, *J* = 7.2 Hz); MS (Fab) 185 (M + Na)$^+$. Anal. Calcd for $C_8H_{18}OS$: C, 59.22; H, 11.19; S, 19.72. Found: C, 58.99; H, 11.16; S, 19.34.

Benzyl phenyl sulfoxide (8): white solid[13] (95% yield); mp 123−125 °C; R_f 0.1 (1:4 EtOAc/hexane); ^{1}H NMR δ 7.46−7.32 (m, 5H), 7.30−7.20 (m, 3H), 7.00−6.80 (m, 2H), 4.03 (ABq, 2H, *J* = 12.6 Hz, Δν = 27.0 Hz); MS (Fab) 239 (M + Na)$^+$. Anal. Calcd for $C_{13}H_{12}OS$: C, 72.20; H, 5.60; S, 14.80. Found: C, 72.41; H, 5.62; S, 14.66.

Ethylsulfenyl 2,3,4,6-tetra-*O*-acetyl-α-D-Mannopyranoside (10): white solid (95% yield); mp 134−136 °C; R_f 0.2 (1:2, EtOAc/hexane); IR (KBr) 1746 (br) cm^{-1}; ^{1}H NMR δ 5.82−5.50 (m, 2H), 5.35−5.20 (m, 1H), 4.63 (s, 1H), 4.40−4.02 (m, 3H), 3.10−2.76 (m, 2H), 2.20−1.94 (m, 12H), 1.42−1.32 (m, 3H); MS (Fab) 431 (M + Na)$^+$. Anal. Calcd for $C_{16}H_{24}O_9S$: C, 47.05; H, 5.93; S, 7.83. Found: C, 47.16; H, 5.97; S, 7.73.

Ethylsulfenyl 2,3,4-tri-*O*-benzyl-α,β-L-fucopyranoside (12): colorless oil (95% yield); R_f 0.2 (1:2 EtOAc/hexane); ^{1}H NMR δ 7.45−7.10 (m, 15H), 5.28−4.60 (m, 7H), 4.12−3.47 (m, 5H), 3.24−3.00 (m, 1H), 1.50−1.00 (m, 6H); MS (Fab) 517 (M + Na)$^+$. Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93; S, 6.47. Found: C, 70.15; H, 6.87; S, 6.30.

Phenylsulfenyl 2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (14). Flash column chromatography of the crude product over silica gel using gradient eluent (25% to 60% EtOAc in hexane) gave **14** as a white solid (82% yield): mp 78−80 °C; R_f 0.3 (2:1 EtOAc/hexane); IR (KBr) 1749, 1720 cm^{-1}; ^{1}H NMR δ 7.90−7.47 (m, 7H), 7.24−7.06 (m, 2H), 5.85−5.70 (m, 1H), 5.46 & 5.41 (2d, 1H, *J* = 8.4 Hz), 5.16 (t, 0.6H, *J* = 10.2 Hz), 5.08 (t, 0.4H, *J* = 10.2 Hz), 4.90 (t, 0.6H, *J* = 10.2 Hz), 4.67 (t, 0.4H, *J* = 10.2 Hz), 4.30−4.05 (m, 2H and solvent $-OCH_2-CH_3$ signal), 3.95 (m, 0.6H), 3.65 (m, 0.4H), 2.20−1.80 (m, 9H); MS (Fab) 566 (M + Na)$^+$. Anal. Calcd for $C_{26}H_{25}NO_{10}S$: C, 57.45; H, 4.64; N, 2.58; S, 5.89. Found: C, 57.73; H, 4.55; N, 2.53; S, 5.68.

Phenylsulfenyl 2-Deoxy-2-azido-4,6-*O*-benzylidene-α-D-glucopyranoside (16). Flash column chromatography of the crude product over silica gel using gradient eluent (25%−40% EtOAc in hexane) gave **16** as white solid (60% yield): mp 151−153 °C; R_f 0.3 (2:3 EtOAc/hexane). IR (KBr) 3364, 2114 cm^{-1}; ^{1}H NMR δ 7.76−7.35 (m, 10H), 5.51 (s, 1H), 4.69 (d, 1H, *J* = 5.7 Hz), 4.60 (td, 1H, *J* = 9.0, 3.3 Hz), 4.16−4.00 (m, 2H), 3.98−3.88 (m, 1H), 3.64−3.50 (m, 2H), 3.43 (brs, 1H); MS (Fab) 424 (M + Na)$^+$. Anal. Calcd for $C_{19}H_{19}N_3O_5S$: C, 56.84; H, 4.77; N, 10.47; S, 7.97. Found: C, 56.54; H, 4.89; N, 10.31; S, 7.87.

Phenylsulfenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (18): white solid (95% yield); mp 54−56 °C; R_f 0.2 (1:1 EtOAc/hexane); IR (KBr) 1755, 1746 cm^{-1}; ^{1}H NMR δ 7.65 (m, 2H), 7.54 (m, 3H), 5.38−5.18 (m, 2H), 5.04−4.92 (m, 1H), 4.46 (d, 0.6H, *J* = 9.6 Hz), 4.28 (d, 0.4H, *J* = 9.6 Hz), 4.20−4.00 (m, 2H), 3.76 & 3.60 (m, 1H), 2.10−1.90 (m, 12H); MS (Fab) 479 (M + Na)$^+$. Anal. Calcd for $C_{20}H_{24}O_{10}S$: C, 52.62; H, 5.30; S, 7.01. Found: C, 52.43; H, 5.29; S, 6.98.

Phenylsulfenyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside (20): white solid (95% yield); mp 63−65 °C; R_f 0.5 (1:3 EtOAc/hexane); IR (KBr) 1744 (br) cm^{-1}; ^{1}H NMR δ 7.69−7.43 (m, 5H), 5.35 (t, 1H, *J* = 9.0 Hz), 5.06 & 5.01 (2t, 1H, *J* = 9.0 Hz), 4.88 (t, 1H, *J* = 9.0 Hz), 4.52 (d, 0.65H, *J* = 9.9 Hz), 4.26 (d, 0.35H, *J* = 9.9 Hz), 4.22−4.11 (m, 1H), 3.99 and 3.89 (m, 1H), 3.74 and 3.60 (m, 1H), 1.25−1.05 (m, 36H); MS (Fab) 647 (M + Na)$^+$. Anal. Calcd for $C_{32}H_{48}O_{10}S$: C, 61.51; H, 7.75; S, 5.12. Found: C, 61.53; H, 7.79; S, 5.04.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2**, **8**, **10**, **12**, **14**, **16**, **18**, and **20** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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