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A one-pot synthesis of novel *N*,*N*-dialkyl-*S*-glycosylsulfenamides

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Abstract

An efficient new entry into *N*,*N*-dialkyl-*S*-glycosylsulfenamides is reported. The reaction of bis-activated alkyl halides in the presence of a secondary amine base with glycosylic *S*-acetyl derivatives (1-*S*-acetyl-1-thioaldoses or 2-*S*-acetyl-2-thioketoses) results in the formation of novel carbohydrate sulfenamides. These new carbohydrate-based sulfenamides may provide useful derivatives with biological activity, as well as provide reactive carbohydrate sulfenylating agents. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Sulfenamides; Anomeric position; Synthesis

1. Introduction

Sulfenamides are a class of compounds containing a trivalent nitrogen bonded to a divalent sulfur. These stable and reactive sulfenylating reagents have found a number of practical applications in both industry and medicinal chemistry [1]. Although sulfenamides are quite a useful functionality, their formation is generally limited to rather harsh methods that may not be compatible with other groups within the molecule. The three most common methods for the synthesis of sulfenamides being the condensation of sulfenyl halides with amines [2], the reaction of thiols and amines in the presence of oxidising reagents [3], or via the reaction of disulfides and amines in the presence of silver or mercuric salts [4]. Previously, a two-step procedure, via a glycosylsulfenyl bromide, has been used to generate glycosylsulfenamides and other thio sugar derivatives [5]. Here we present an alternative one-pot synthesis of novel anomeric carbohydrate sulfenamides. The synthetic method to access these derivatives was shown to tolerate a number of different functionalities and is specific for the anomeric position of carbohydrates.

2. Results and discussion

As part of our ongoing study into the formation of biologically active carbohydrate molecules [6], we were interested in the formation of highly charged 1-thio-galactofuranose type structures such as compound **1**. Access to these derivatives was via compound **2**, which is easily obtained using known literature procedures [7].

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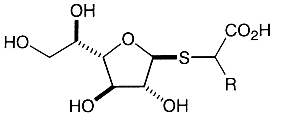
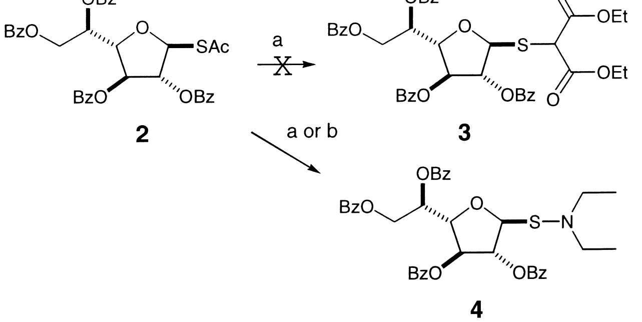


1

R = H, Et, CO_2H, $P(O)OH_2$

During the course of our studies, we were surprised to find that reaction of compound **2** with diethyl bromomalonate under standard conditions, i.e., with a secondary amine base [8], furnished the *N*,*N*-diethylsulfenamide **4** in 74% yield, rather than the expected thioether **3** (Scheme 1). When the reaction was repeated using trimethyl bromophosphonoacetate, once again the *N*,*N*-diethylsulfenamide **4** was isolated in 72% yield. This result seemed to indicate that the reaction was general for bis-activated bromides.

It is not unreasonable to suggest that compound **4** could be formed via one of two reactive intermediates. Thus, attack of the activated bromide by the thiol will result in either the formation of the desired thioether **3** or the formation of a very reactive sulfenyl bromide. Subsequent reaction of either of these activated species with excess amine would furnish the sulfenamide **4**. To investigate the possibility of the involvement of a sulfenyl bromide, we replaced bromomalonate with an excess of *N*-bromosuccinimide. The formation of compound **4** was observed, albeit in a rather poor yield of 33%. This result suggests that the sulfenyl bromide could potentially be an intermediate formed in the reaction and is further supported by the previous report that glycosylsulfenamides can be readily prepared from a glycosylsulfenyl bromide [5].



Reagents and conditions: (a) $BrCH(CO_2Et)_2$, DMF, $HNEt_2$, 25 °C, 14 h, 74%. (b) $BrCH(CO_2Me)[P(O)(OMe)_2]$, DMF, $HNEt_2$, 25 °C, 14 h, 72%.

Scheme 1. Formation of anomeric sulfenamides.

The use of a large excess of the amine base was also required for the reaction. Although we found that the thiolacetate moiety could be fully deprotected with two equivalents of diethylamine, experiments utilising three to five equivalents of base provided the sulfenamide only in poor yields (28–35%).

To further investigate the formation of novel sulfenamide products and the general use of this reaction, several other glycosyl thiolacetates, compounds **5** [9], **7** [10], **9** [11] and **11**[1] and amines were tried. As is clearly shown in Table 1, the reaction does appear to be general for a number of compounds, as shown by entries 1, 4, 5 and 6, all of which contain a number of different functionalities. The reaction is, however, quite specific for anomeric thiolacetates, as reaction of the 6-thiolacetate derivative (entry 7) under the standard conditions returned unchanged starting material. Given that diethylamine is ineffective at deprotecting thiolacetates in non-anomeric positions in carbohydrates[1], this outcome is not surprising. A second attempt at this reaction using the more powerful base, hydrazine acetate, was tried. Although the 6-thiolacetate group was deprotected, it did not furnish any of the desired sulfenamide. At this point we have no explanation as to why the 6-thiol does not undergo formation of a sulfenamide derivative.

In trials of different bases, the reaction was shown to be quite general for secondary amines, providing the desired sulfenamides in moderate to good yields. Tertiary amines, as expected, did not undergo reaction, due to their inability to deprotect the thiolacetate moiety, while primary amines, not unexpectedly, resulted in O-deacetylation, making recovery of the desired product virtually impossible.

For all the compounds listed in Table 1, isolation of the desired product from the reaction mixture was easily achieved by removal

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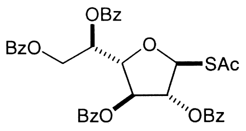
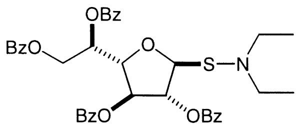
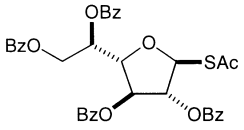
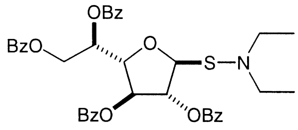
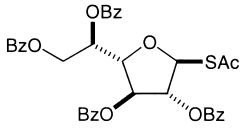
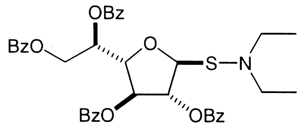
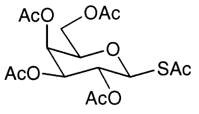
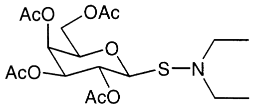
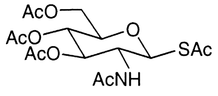
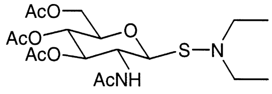
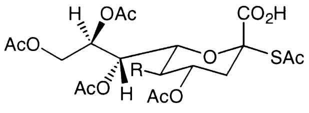
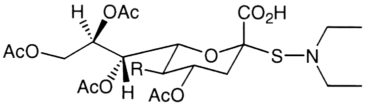
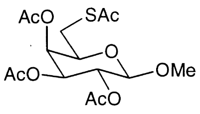
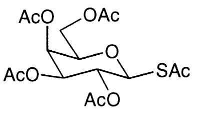
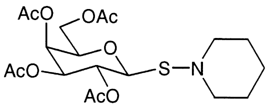
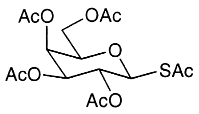
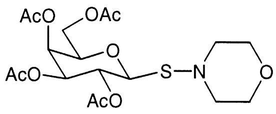
[1] S.J. Bradley, A. Fazli, M.J. Kiefel, M. von Itzstein, manuscript in preparation.

Table 1
Formation of carbohydrate sulfenamide derivatives [a]

Entry	Substrate	Reaction conditions	Product	Yield
1	 **2**	a	 **4**	74%
2	 **2**	b	 **4**	33%
3	 **2**	c	 **4**	28–35%
4	 **5**	a	 **6**	75%
5	 **7**	a	 **8**	78% [b]
6	 **9** R = NHAc	a	 **10** R = NHAc	81%
7	 **11**	a,d	No reaction	–
8	 **5**	e	 **12**	33%
9	 **5**	f	 **13**	67%

[a] Reagents and conditions (a) $BrCH(CO_2Et)_2$, DMF, $HNEt_2$, 25 °C, 14 h; (b) NBS, DMF, $HNEt_2$, 25 °C, 14 h; (c) $BrCH(CO_2Et)_2$, DMF, 2–5 equiv $HNEt_2$, 25 °C, 14 h; (d) $BrCH(CO_2Et)_2$, DMF, $HNEt_2$, hydrazine acetate, 25 °C, 14 h; (e) $BrCH(CO_2Me)_2$, DMF, piperidine, 25 °C, 14 h; (f) $BrCH(CO_2Et)_2$, DMF, morpholine, 25 °C, 14 h.

[b] Product unstable.

of all the volatile material under high vacuum, followed by quick passage of the resultant orange residue through flash silica gel. Once isolated, all the products except entry 5 appeared to be quite stable at room temperature for a number of months. Unfortunately, compound **8** (entry 5) proved to be rather unstable, decomposing at room temperature over a couple of days.

It is our belief that this mild and selective method for the formation of carbohydrate-based sulfenamides may provide interesting new functionalities to add to the medicinal chemist's armory. Furthermore, it may provide useful intermediates for the formation of carbohydrate sulfenylation reagents for the production of mixed carbohydrate disulfides and carbohydrate thiolphosphates.

3. Experimental

General.—Compounds **5** [9], **7** [10], **9** [11] and **11**[1] were prepared as per known literature methods without modification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker AM 300 spectrometer. Chemical shifts are given in ppm relative to the solvent used [$CDCl_3$: 7.26 for ^{1}H; 77.0 for ^{13}C]. ESI mass spectra were obtained using a Micromass Platform II electrospray-ionizsation spectrometer, and HRMSs were obtained using a Bruker BioApex II FTMS. Reactions were monitored by thin-layer chromatography (TLC) on aluminum plates coated with Silica Gel 60 F_{254} (E. Merck) and visualised with either 10% H_2SO_4 or ninhydrin. All compounds were purified by flash chromatography using E. Merck Silica Gel 60 (0.040–0.063 mm). All new compounds gave the expected spectroscopic data.

*1-*S*-Acetyl-2,3,5,6-tetra-*O*-benzoyl-1-thio-β-*D*-galactofuranose* (**2**).—To a stirred solution of per-*O*-benzoyl-α,β-D-galactofuranose [7] (3.8 g, 5.4 mmol) in 30 mL of dry CH_2Cl_2 at 0 °C under an atmosphere of nitrogen was added tin tetrachloride (0.7 mL, 5.9 mmol). After 10 min thiolacetic acid was added (0.7 mL, excess), and the reaction was left stirring for 1 h. After this time the reaction was diluted with satd aq $NaHCO_3$ and EtOAc. The layers were separated, and the organic phase was washed once with the $NaHCO_3$ soln and once with brine. The organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo to yield 3.2 g of the desired compound as a thick golden syrup (90%). The residue could be used without further purification, but an analytical sample was obtained by chromatography on silica gel using 2:1 hexane–EtOAc as eluent. R_f 0.55 (1:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.26–8.10 (m, 20 H, $4 \times COC_6H_5$), 6.34 (s, 1 H, H-1), 6.08 (m, 1 H, H-5), 5.73 (d, J 4.2 Hz, 1 H, H-3), 5.68 (t, J 1.2 Hz, 1 H, H-2), 4.76 (m, 2 H, H-6 and H-6′), 4.66 (t, J 4.2 Hz, 1 H, H-4), 2.44 (s, 3 H, $SCOCH_3$); ^{13}C NMR ($CDCl_3$): δ 192.0 ($SCOCH_3$), 166.0, 165.7, 165.2 ($4 \times CO_2C_6H_5$), 133.7, 133.5, 133.2, 133.0, 130.0, 129.9, 129.8, 129.6, 129.5, 129.3, 128.7, 128.5, 128.4, 128.3 (aromatic C), 86.5 (C-1), 83.3 (C-4), 82.0 (C-2), 77.8 (C-3), 70.3 (C-5), 63.6 (C-6), 31.1 (SCH_2CO_2); ESIMS m/z (relative intensity, %) 672 [$M^+ + NH_4$, 100]; HRMS: Calcd for $C_{36}H_{34}NO_{10}S$ [$M^+ + NH_4$] 672.1900. Found 672.1898.

General procedure for the sulfenamide reaction.—To a solution of the glycosyl thioacetate (0.5 mmol) in dry DMF (2 mL) under an atmosphere of N_2 was added an excess of the appropriate amine (e.g., 1 mL of dry diethylamine), followed by diethyl bromomalonate (1–2 mmol, 2–4 equiv). The reaction was left to stir at room temperature overnight. The next morning all volatile compounds were carefully removed under high vacuum, the residue was diluted in EtOAc, washed once with brine, dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting orange residue was purified by flash chromatography using 2:1 hexane–EtOAc as eluent.

N,N-*Diethyl*-S-*(2,3,5,6-tetra*-O-*benzoyl-β-*D-*galactofuranosyl)sulfenamide* (**4**).—R_f 0.7 (1:2 EtOAc–hexane); ^{1}H NMR ($CDCl_3$): δ 7.26–8.10 (m, 20 H, $4 \times COC_6H_5$), 6.07 (m, 1 H, H-5), 5.75 (d, J 2.1 Hz, 1 H, H-1), 5.69 (dd, J 2.1, J 5.1 Hz, 1 H, H-3), 5.55 (t, J 2.1 Hz, 1 H, H-2), 4.83 (apparent t, J 4.5 Hz, 1 H, H-4), 4.75 (m, 2 H, H-6 and H-6′), 3.03 (q, J 7.0 Hz, 2 H, NCH_2), 3.02 (q, J 7.0 Hz, 2 H, NCH_2'), 1.17 (t, J 7.0 Hz, 6 H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$): δ 166.1, 165.8, 165.7, 165.5, 133.6, 133.5, 133.4, 133.2, 130.1, 129.9, 129.8, 129.7, 129.1, 128.6, 128.5, 128.5, 91.4, 81.3, 80.1, 78.2, 70.7, 63.5, 52.6, 14.0; ESIMS *m/z* (relative intensity, %) 706 [$M^+ + Na$, 5], 684 ($M^+ + H$, 5], 579 [$M^+ - C_4H_{11}SN$, 10]; HRMS: Calcd for $C_{38}H_{37}NO_9SNa$ 706.2081. Found 706.2085.

N,N-*Diethyl*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)sulfenamide* (**6**).—R_f 0.4 (1:2 EtOAc–hexane); ^{1}H NMR ($CDCl_3$): δ 5.41 (d, *J* 3.1 Hz, 1 H, H-4), 5.12 (t, *J* 9.4 Hz, 1 H, H-2), 5.07 (dd, *J* 3.1, *J* 9.4 Hz, 1 H, H-3), 4.60 (dd, *J* 0.9, *J* 9.4 Hz, 1 H, H-1), 4.16 (dd, *J* 6.6, *J* 11.2 Hz, 1 H, H-6), 4.08 (dd, *J* 6.6, *J* 11.2 Hz, 1 H, H-6′), 3.91 (t, *J* 6.6 Hz, 1 H, H-5), 2.95 (q, *J* 7.1 Hz, 2 H, NCH_2), 2.94 (q, *J* 7.0 Hz, 2 H, NCH_2'), 2.14, 2.06, 2.03, 1.98 (4 × s, 12 H, 4 × OAc), 1.14 (t, *J* 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ 170.0, 169.9, 169.7, 169.1, 87.9, 74.0, 72.0, 67.2, 65.3, 61.6, 52.3, 20.5, 20.4, 13.3; ESIMS *m/z* (relative intensity, %) 458 [$M^+ + Na$, 7], 436 [$M^+ + H$, 100]; HRMS: Calcd for $C_{18}H_{30}NO_9S$ 436.1636. Found 436.1637.

N,N-*Diethyl*-S-*(2-Acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl)sulfenamide* (**8**).—R_f 0.4 (EtOAc); ^{1}H NMR ($CDCl_3$): δ 5.76 (br s, 1 H, NHAc), 5.00–5.15 (m, 2 H, H-3 and H-4), 4.21–4.37 (m, 2 H, H-1 and H-2), 4.17 (dd, *J* 5.1, *J* 12.1 Hz, 1 H, H-6), 4.11 (dd, *J* 2.7, *J* 12.1 Hz, 1 H, H-6′), 3.59 (m, 1 H, H-5), 2.83 (m, 4 H, 2 × NCH_2), 2.05, 2.01, 2.00, 1.95 (4 × s, 12, 4 × OAc), 1.07 (t, *J* 6.9 Hz, 6 H, 2 × CH_3); no other data could be obtained before the material decomposed.

N,N-*Diethyl*-S-*(methyl 5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy*-D-glycero-*α*-D-galacto-*2-nonulopyranos-2-yl-onate)sulfenamide* (**10**).—R_f 0.3 (1:2 EtOAc–hexane); ^{1}H NMR ($CDCl_3$): δ 5.32 (m, 2 H, H-8 and H-7), 5.14 (d, *J* 9.9 Hz, 1 H, NH), 4.88 (ddd, *J* 4.8, *J* 10.8, *J* 11.1 Hz, 1 H, H-4), 4.41 (br d, *J* 11.4 Hz, 1 H, H-6), 4.16 (dd, *J* 4.6, *J* 12.4 Hz, 1 H, H-9), 3.99 (apparent q, *J* 10.3 Hz, 1 H, H-5), 3.80 (dd, *J* 3.6, *J* 12.4 Hz, 1 H, H-9′), 3.78 (s, 3 H, OMe), 3.03 (br s, 4 H, 2 × NCH_2), 2.58 (dd, *J* 4.8, *J* 12.9 Hz, 1 H, H-3_{eq}), 2.13, 2.12, 2.03, 2.02 (4 s, 12 H, 4 × OAc), 1.87 (s, 4 H, H-3_{ax} and $NHCOCH_3$), 1.10 (t, *J* 7.0 Hz, 6 H, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ 171.1, 170.7, 170.3, 170.2, 169.5, 90.9, 74.9, 70.2, 70.2, 67.9, 62.3, 52.8, 52.5, 49.5, 34.9, 23.2, 21.2, 21.0, 20.9, 14.0; ESIMS *m/z* (relative intensity, %) 579 [$M^+ + H$, 100]; HRMS: Calcd for $C_{24}H_{39}N_2O_{12}S$ 579.2218. Found 579.2227.

1-[(2,3,4,6-Tetra-O-*acetyl-β*-D-*galactopyranosyl)sulfenyl]piperidine* (**12**).—R_f 0.39 (1:2 EtOAc–hexane); ^{1}H NMR ($CDCl_3$): δ 5.42 (d, *J* 3.3 Hz, 1 H, H-4), 5.25 (t, *J* 9.9 Hz, 1 H, H-2), 5.09 (dd, *J* 3.3, *J* 9.9 Hz, 1 H, H-3), 4.73 (d, *J* 9.9 Hz, 1 H, H-1), 4.17 (dd, *J* 6.7, *J* 11.2 Hz, 1 H, H-6), 4.09 (dd, *J* 6.4, *J* 11.2 Hz, 1 H, H-6′), 3.95 (t, *J* 6.7 Hz, 1 H, H-5), 2.99 (m, 4 H, 2 × NCH_2), 2.15, 2.06, 2.04, 1.99 (4 s, 12 H, 4 × OAc), 1.55–1.63 (m, 6 H, 3 × CH_2); ^{13}C NMR ($CDCl_3$): δ 170.1, 170.0, 169.9, 169.2, 85.7, 73.9, 72.1, 67.2, 65.1, 61.5, 58.6, 27.1, 23.1, 20.7, 20.5; ESIMS *m/z* (relative intensity, %) 470 [$M^+ + Na$, 15], 448 [$M^+ + H$, 100]; HRMS: Calcd for $C_{19}H_{30}NO_9S$ 448.1636. Found 448.1640.

4-[(2,3,4,6-Tetra-O-*acetyl-β*-D-*galactopyranosyl)sulfenyl]morpholine* (**13**).—R_f 0.2 (1:2 EtOAc–hexane); ^{1}H NMR ($CDCl_3$): δ 5.44 (d, *J* 3.3 Hz, 1 H, H-4), 5.34 (t, *J* 9.9 Hz, 1 H, H-2), 5.09 (dd, *J* 3.4, *J* 10.0 Hz, 1 H, H-3), 4.68 (d, *J* 10.2 Hz, 1 H, H-1), 4.16 (dd, *J* 6.6, *J* 11.1 Hz, 1 H, H-6), 4.09 (dd, *J* 6.6, *J* 11.1 Hz, 1 H, H-6′), 3.95 (t, *J* 6.6 Hz, 1 H, H-5), 3.69 (t, *J* 4.5 Hz, 4 H, OCH_2), 3.03 (m, 4 H, NCH_2), 2.16, 2.06, 1.99 (4 s, 12 H, 4 × OAc); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.3, 170.2, 169.5, 86.3, 74.8, 72.3, 67.9, 67.5, 65.3, 61.8, 57.5, 20.9, 20.8, 20.7; ESIMS *m/z* (relative intensity, %) 472 [$M^+ + Na$, 38], 450 [$M^+ + H$, 100], 331 [$M^+ - C_4H_8NOS$, 20]; HRMS: Calcd for $C_{18}H_{28}NO_{10}S$ 450.1428. Found 450.1433.

Acknowledgements

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