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Note

Novel approaches to the syntheses of N-substituted *S*-glycosyl-sulfenamides

Tünde-Zita Illyés,[a] Dóra Molnár-Gábor[b] and László Szilágyi[a,*]

[a]*Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen Pf. 20, Hungary*
[b]*Department of Chemistry, University of Novi Sad, Novi Sad, Trg D. Obradovica 3, YU-21 000, Serbia and Montenegro*

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Abstract—Bis(tetra-*O*-acetyl-β-D-glucopyranosyl)disulfide reacts, under silver ion activation, with primary and secondary aliphatic as well as aromatic amines to furnish the title compounds in moderate to good yields. The same derivatives could also be obtained from (tetra-*O*-acetyl)-β-D-glucopyranosyl methanethiolsulfonate **1** by nucleophilic substitution with amines. It was shown that the polarization of the S–S-bond in **1** is enhanced by Ag^+ so as to allow reaction with sterically hindered amines as well.

Keywords: Disulfide; Silver ion activation; Sulfenamide; Methanethiolsulfonate

Although sulfenamides are synthetically useful and structurally interesting compounds with a number of practical applications,[1] scant references can only be found for carbohydrate derivatives featuring the S–N functionality. The reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide with aniline provided the corresponding *S*-glucosyl-*N*-phenyl derivative[2a,b] whereas the 'reverse' *N*-glucosyl-*S*-phenyl variant was obtained via reaction of the appropriate glucosylamine with phenylsulfenyl chloride.[3] A number of *N*,*N*-dialkyl-*S*-glycosyl-sulfenamides have recently been prepared via a serendipitous route.[4] Also, the transformation of two glycosyl disulfide derivatives into a mixture of glycosyl-thiosulfenanilide and -sulfenanilide (plus some glycosyl-chloride) presumably through thiosulfenyl- and sulfenyl-chlorides, respectively, has been reported.[6]

Here we present more general alternatives for the syntheses of various N-substituted *S*-glycosyl-sulfenamides. These syntheses are based on the nucleophilic attack of amine (the 'aglycon' or receptor) components on suitable glycosylthio donors, or sulfenyl transfer reagents. The latter fall in three general categories: sulfenyl halogenides (A), thiolsulfonate esters (B) and disulfides (C).

$$\mathrm{R{-}S{-}Hlg + R^1{-}NH_2 \rightarrow R{-}S{-}NH{-}R^1 + HHlg} \quad \text{(A)}$$

$$\mathrm{R{-}SSO_2R^2 + R^1{-}NH_2 \rightarrow R{-}S{-}NH{-}R^1 + R^2{-}SO_2H} \quad \text{(B)}$$

$$\mathrm{R{-}SS{-}R^2 + R^1R^3{-}NH \xrightarrow{Ag^+} R{-}S{-}N{-}R^1R^3 + R^2{-}SH} \quad \text{(C)}$$

(A) Sulfenyl halogenides represent the oldest known sulfenyl transfer reagents.[1,5] They are, however, thermally unstable, especially glycosylsulfenyl bromides or chlorides[2a,b,6] that undergo side reactions and are incompatible with several functional groups.[5]

(B) The divalent sulfur in thiolsulfonate esters is readily attacked, due to its electrophilic character, by nucleophiles such as amines. Aliphatic and aromatic sulfenamides have been obtained this way in good yields.[7]

(C) Metal ion-assisted cleavage of disulfides and subsequent reaction with amines in a one-pot procedure was shown to be a convenient and rather general route to sulfenamides.[8,9] The reaction is compatible with a number of functional groups attached to the starting materials. We have investigated the application of the

* Corresponding author. Tel.: +36-52-316666; fax: +36-52-453836; e-mail: lszilagyi@tigris.klte.hu

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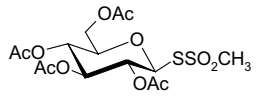
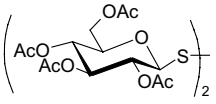
two latter methods for the syntheses of glycosylsulfenamides.

For the syntheses of title compounds via routes B and C, appropriate glycosylthio donors, such as 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl methanethiolsulfonate (**1**) and the symmetric disulfide **2**, are required. These starting materials were obtained using known procedures: (**1**)[10a,b] and (**2**)[11]. We have previously established that nucleophilic substitution reactions of **1** with peracetylated glycopyranosyl thiols lead to unsymmetrical diglycosyl disulfides with good to moderate yields.[12] It was expected that similar reactions with amine nucleophiles would yield the desired sulfenamides (route B).



1

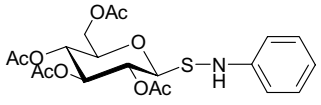
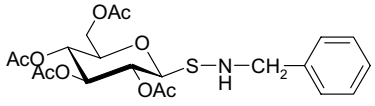
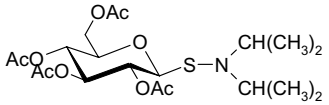
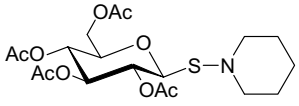
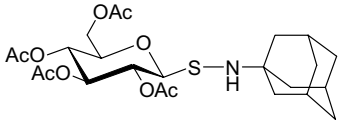


2

First, we have explored the reactivity of **1** towards simple aliphatic and aromatic amines. Benzylamine reacted readily with **1** in methanol or acetonitrile at room temperature and the starting material practically disappeared (TLC) after 1 h when the amine component was used in excess (1:8 mol ratio). TLC indicated the formation of **4** (Table 1) as the major reaction product. The reactions were more sluggish with secondary amines such as diisopropylamine or piperidine or with the aromatic aniline, all showing low conversions according to TLC. No reaction at all occurred, however, with 1-adamantylamine presumably due to significant steric hindrance in the latter.

Next, route C, based on silver ion activation of the S–S-bond in symmetrical disulfides[8] was investigated. In this reaction, the electrophilic Ag^+ ion is thought to act cooperatively with nucleophiles such as amines to result in cleavage of the S–S-bond.[9] We have found that this reaction, described for simple aliphatic and aromatic disulfides,[8,9] could be readily extended to glycosyl disulfides. Indeed, **2** underwent smooth reactions with various amines such as primary- (benzyl-), secondary- (diisopropyl-, piperidine) or aromatic (aniline) ones under mild conditions and furnished the expected sulfenamides with moderate to good yields (Table 1). The reactions were run at room temperature in methanol or acetonitrile solutions using silver nitrate in equimolar ratio with respect to **2**. It is seen from the data in Table 1 that amines, which showed low reactivity towards **1** (entries **3**, **5** and **6**) proved to be more reactive with **2** under silver ion activation. This observation suggests that attachment of the Ag^+ ion to one of the sulfur atoms of the S–S-bond[9] in **2** makes the other one more electrophilic than the divalent sulfur is in **1**. No reaction occurred, however, with the highly hindered 1-adamantylamine under these conditions (route C) either.

Table 1. Structures of carbohydrate sulfenamides and reaction conditions

	Product	Procedure	Reagent ratio[a]	Solvent	Yield (%)[b]
3		B	1:2	MeOH	32
		C	1:8	MeCN	51
4		B	1:4	MeOH	45[c]
		B	1:8	MeCN	57[c]
		C	1:4	MeOH	60
		C	1:8	MeCN	87
5		B	1:4	MeOH	41
		C	1:4	MeCN	43
6		B	1:4	MeOH or MeCN	51
		C	1:4	MeOH	53
7		B	1:4	MeOH	15

[a] Thiol donor/amine; 1 mol/equiv of $AgNO_3$ with respect to the thiol donor was added in all cases.
[b] Data refer to isolated yields of pure products.
[c] Comparable yields were obtained in the absence of $AgNO_3$.

In view of these observations, we have then reasoned that the ground state electrophilicity of the divalent sulfur in **1** might be boosted further by the addition of Ag^+ ion, which would increase the polarization of the S–S-bond through attachment to the nucleophilic SO_2-moiety of the SSO_2-group. Support to this assumption was furnished by the formation of the sterically hindered sulfenamide from **1** with 1-adamantylamine under silver ion activation, albeit in low yield (Table 1).

The β-anomeric configurations of the starting materials **1** and **2** were retained in the reaction products ($J_{H\text{-}1,H\text{-}2}$ values ~9–11 Hz, see Section 1) in all cases, that is, no anomerization occurred during the sulfenamide bond formation. This is to be expected since the presumed reaction mechanism calls for S–S-bond cleavage, as opposed to C–S cleavage, for both routes B and C. Direct evidence for the glycosylsulfenamide structure was provided by ^{15}N-HMBC measurements revealing long-range correlations of the anomeric proton with the sulfenamide nitrogen (Fig. 1).

In summary, we have presented two general approaches for the syntheses of the little known carbohydrate structures, the glycosylsulfenamides. The silver ion-activated cleavage of symmetrical disulfides by amines[9] could be extended in a straightforward manner to the reaction of various amines with the carbohydrate disulfide **2**. Primary and secondary aliphatic as well as aromatic amines react under mild conditions to furnish the target compounds in moderate to good yields. It was shown furthermore that the polarization of the S–S-bond in methanethiolsulfonate **1** gets considerably enhanced by Ag^+ so as to allow reaction with sterically hindered amines as well.

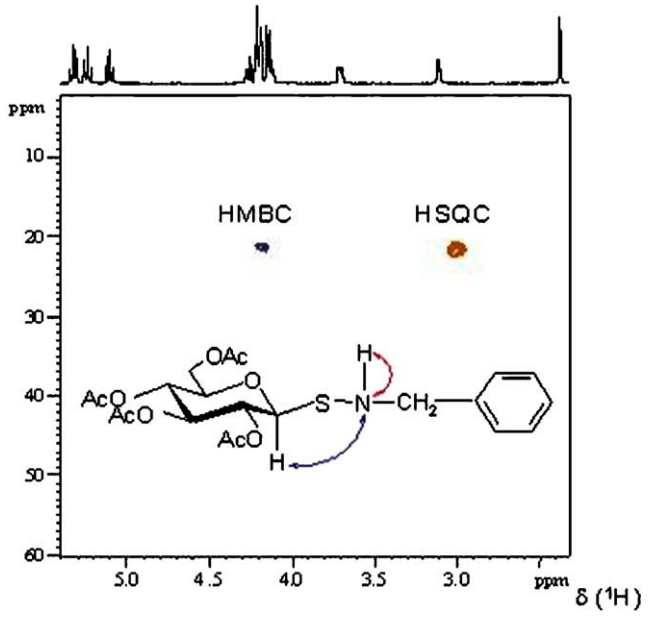


Figure 1. Combined ^{15}N-HSQC and ^{15}N-HMBC spectra of **4**. It is to be noticed that ^{15}N-HSQC correlation could not be detected for **3** and **7** because of exchange-broadened NH resonances in their ^{1}H NMR spectra.

1. Experimental

Melting points were determined with a hot stage microscope. Column chromatography was performed on silica gel (E. Merck, 60–200 mesh). NMR spectra were recorded on a Bruker Avance DRX 500 (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C and 50.69 MHz for ^{15}N) spectrometer. Chemical shifts (δ in ppm) are referenced to internal Me_4Si for ^{1}H NMR, to $^{13}CDCl_3$ (77.0) for ^{13}C NMR and to external nitromethane converted to external liquid ammonia scale (0.0) for ^{15}N NMR.

1.1. General method for the preparation of sulfenamides from bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)disulfide (2)

To a stirred soln of **2** (100 mg, 0.138 mmol) in a minimal amount of MeOH or MeCN was added the amine (4 or 8 equiv, see Table 1) and $AgNO_3$ (1 equiv). After 24 h at room temperature, the reaction mixture was filtered and evaporated under diminished pressure, the residue separated by column chromatography using 4:1 hexane–EtOAc as eluent or crystallized (**3**, **4**, **5**) from the solvent indicated.

1.2. General method for the preparation of sulfenamides from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-methanethiolsulfonate (1)

To a stirred soln of **1** (100 mg, 0.226 mmol) in a minimal amount of MeOH or MeCN was added the amine (2, 4 or 8 equiv, see Table 1) and $AgNO_3$ (1 equiv). After 24 h at room temperature, the reaction mixture was filtered and evaporated under diminished pressure and the residue purified by column chromatography using 4:1 hexane–EtOAc.

1.3. *N*-Phenyl-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfenamide (3)

Colourless, fine needles (from *tert*-butylmethylether), mp 114–116 °C, lit.[2b] 116–117 °C; $[\alpha]_D^{20}$ −327 (*c* 2.3, $CHCl_3$), lit.[2b] −330. ^{1}H NMR ($CDCl_3$): δ 7.20 (t, 2H, H-2′); 7.10 (d, 2H, H-3′); 6.87 (t, 1H, H-4′); 5.30 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3); 5.16 (t, 1H, $J_{2,3}$ 9.4 Hz, H-2); 5.04 (s, 1H, NH); 4.99 (t, 1H, $J_{4,5}$ 9.8 Hz, H-4); 4.28 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1); 4.24 (dd, 1H, $J_{5,6a}$ 4.3 Hz, $J_{6a,6b}$ 12.2 Hz, H-6a); 4.05 (dd, 1H, $J_{5,6b}$ 2.1 Hz, H-6b); 3.68 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 147.11 (C-1′); 128.81 (C-2′); 120.44

(C-4′); 115.52 (C-3′); 88.08 (C-1); 75.70 (C-5); 73.68 (C-3); 68.13 (C-4); 67.76 (C-2); 61.70 (C-6). ^{15}N NMR ($CDCl_3$): δ 43.35.

1.4. *N*-Benzyl-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfenamide (4)

White crystals (from *tert*-butylmethylether), mp 66–68 °C, $[\alpha]_D^{20}$ −63.1 (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.35–7.15 (5H, H-2′, H-3′, H-4′); 5.30 (dd, 1H, $J_{4,5}$ 9.6 Hz, H-4); 5.22 (t, 1H, $J_{2,3}$ 9.9 Hz, H-2); 5.08 (t, 1H, $J_{3,4}$ 9.9 Hz, H-3); 4.24 (dd, 1H, $J_{5,6a}$ 4.4 Hz, $J_{6a,6b}$ 12.4 Hz, H-6a); 4.18 (overlapping signals, 2H, H-6b, H-1, $J_{1,2}$ 9.9 Hz); 4.11 (2H, CH_2a, CH_2b); 3.68 (m, 1H, H-5); 3.08 (t, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 139.73 (C-1′); 128.45 (C-2′); 128.12 (C-3′); 127.41 (C-4′); 88.30 (C-1); 75.93 (C-5); 73.85 (C-3); 68.29 (C-4); 67.54 (C-2); 62.11 (C-6); 57.90 (CH_2). ^{15}N NMR ($CDCl_3$): δ 21.36. Anal. Calcd for $C_{21}H_{27}NO_9S$: C, 53.72; H, 5.80; N, 2.98; S, 6.82. Found: C, 52.53; H, 5.80; N, 3.09; S, 6.87.

1.5. *N*,*N*-Diisopropyl-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfenamide (5)

Pale yellow powder (from *tert*-butylmethylether), mp 117–119 °C, $[\alpha]_D^{20}$ −26.8 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.22 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3); 4.99 (t, 1H, $J_{4,5}$ 10.0 Hz, H-4); 4.85 (t, 1H, $J_{2,3}$ 9.5 Hz, H-2); 4.27 (d, 1H, $J_{1,2}$ 10.6 Hz, H-1); 4.19 (dd, 1H, $J_{5,6a}$ 5.8 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a); 4.13 (dd, 1H, $J_{5,6b}$ 2.0 Hz, H-6b); 3.66 (m, 1H, H-5); 3.23 (m, 2H, CH); 1.12 (d, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 93.5 (Glc-C1); 75.8 (Glc-C5); 74.5 (Glc-C3); 68.8 (Glc-C4); 68.4 (Glc-C2); 62.6 (Glc-C6); 57.0 (2×CH); 20.5 (4×CH3). ^{15}N NMR ($CDCl_3$): δ 61.76. Anal. Calcd for $C_{20}H_{33}NO_9S$: C, 51.82; H, 7.18; N, 3.02; S, 6.91. Found: C, 51.91; H, 7.31; N, 3.15; S, 6.97.

1.6. 1-Piperidyl-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfenamide (6)

Syrup, $[\alpha]_D^{20}$ −45.1 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.25 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3); 5.10 (t, 1H, $J_{2,3}$ 9.7 Hz, H-2); 5.08 (t, 1H, $J_{4,5}$ 9.7 Hz, H-4); 4.65 (d, 1H, $J_{1,2}$ 10.1 Hz, H-1); 4.21 (dd, 1H, $J_{5,6a}$ 5.1 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a); 4.15 (dd, 1H, $J_{5,6b}$ 2.4 Hz, H-6b); 3.71 (m, 1H, H-5); 2.95 (m, 4H, H-2′); 1.58 (m, 4H, H-3′); 1.40 (m, 2H, H-4′). ^{13}C NMR ($CDCl_3$): δ 84.2 (C-1); 75.0 (C-5); 73.8 (C-3); 67.8 (C-2, C-4); 62.5 (C-6); 59.0 (C-2′); 26.5 (C-3′); 22.9 (C-4′). ^{15}N NMR ($CDCl_3$): δ 38.07. Anal. Calcd for $C_{19}H_{29}NO_9S$: C, 51.00; H, 6.53; N, 3.13; S, 7.16. Found: C, 51.06; H, 6.64; N, 3.17; S, 7.19.

1.7. *N*-1-Adamantyl-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfenamide (7)

1-Adamantylamine was liberated from 1-adamantylamine-hydrochloride by addition of an equimolar amount of NaOMe in MeOH and this soln was used for the reaction with **1**. Syrup, $[\alpha]_D^{20}$ +7.4 (*c* 0.2, MeOH). ^{1}H NMR ($CDCl_3$): δ 5.40 (t, 1H, $J_{2,3}$ 9.5 Hz, H-2); 5.24 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3); 5.11 (t, 1H, $J_{4,5}$ 9.7 Hz, H-4); 4.72 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1); 4.21 (m, 2H, H-6a,b); 3.74 (m, 1H, H-5); 3.48 (s, 1H, NH); 2.05 (m, 3H, H-3′, H-5′, H-7′); 1.68 (m, 6H, H-2′, H-8′, H-9′); 1.61 and 1.58 (m, 6H, H-4′, H-6′, H-10′). ^{13}C NMR ($CDCl_3$): δ 86.82 (C-1); 76.05 (C-5); 73.77 (C-3); 69.64 (C-2); 68.12 (C-4); 61.81 (C-6); 43.00 (Ad-CH, C-2′, C-8′, C-9′); 36.26 (Ad-CH, C-4′, C-6′, C-10′); 29.41 (Ad-CH_2, C-3′, C-5′, C-7′). ^{15}N NMR ($CDCl_3$): δ 37.83. Anal. Calcd for $C_{24}H_{35}NO_9S$: C, 56.14; H, 6.82; N, 2.73; S, 6.24. Found: C, 56.19; H, 6.89; N, 2.76; S, 6.28.

Acknowledgements

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