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Glycosyl azides of sugar 2-sulfonic acids

Ferenc Sajtos, László Lázár, Anikó Borbás, István Bajza and András Lipták*

Research Group for Carbohydrates of the Hungarian Academy of Sciences, H-4010 Debrecen, PO Box 55, Hungary

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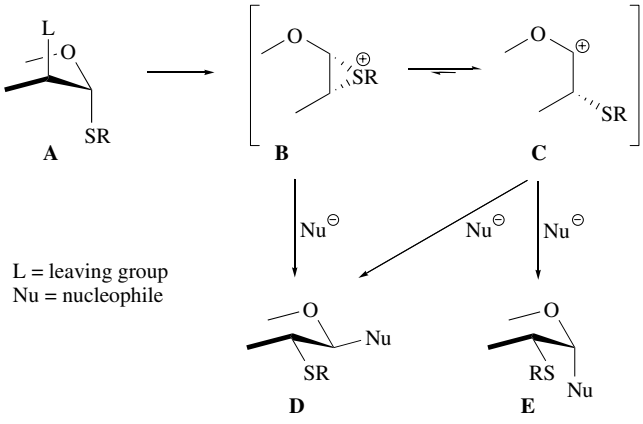
Abstract—Phenyl and trityl 2-*O*-sulfonyl-1-thio-α-D-manno- and β-D-glucopyranosides were reacted with sodium azide to yield 2-*S*-phenyl or 2-*S*-trityl-D-gluco- and D-mannopyranosyl azides, respectively. Usually, both anomers were formed in approximately equal amounts and formation of glycals was also observed in some cases. The product distribution of these reactions depends on the nature of the aglycone, the applied reagent and also on the solvent. These results can be rationalised by the intermediacy of episulfonium as well as oxocarbenium ions. Oxidation of the 2-*S*-trityl-α-D-glucopyranosyl or α-D-mannopyranosyl azides by Oxone®, gave sodium 2-sulfonato-α-D-gluco- and α-D-mannopyranosyl azides, respectively.

It is generally accepted, that the 1,2-thiomigration (the migration of thioalkyl or thioaryl aglycone to C-2) which was first utilised in the synthesis of 2-thio-D-ribose and 2′-thio-adenosine derivatives,[1] proceeds through an episulfonium ion intermediate.[1–3] Preconditions for this reaction are (i) an anomeric *S*-alkyl or *S*-aryl group, (ii) a good leaving group at C-2 (*O*-methanesulfonyl, *O*-toluenesulfonyl, *O*-SF_2NEt_2, etc.), (iii) a trans orientation of the aforementioned substituents. The added nucleophile opens the episulfonium intermediate producing the 'normal' 1,2-*trans* product, however, formation of the 'abnormal' 1,2-*cis* products in these reactions was also reported. Normally, inversion of configuration at C-2 occurs indicating that besides the episulfonium ion mechanism, another, the oxocarbenium-ion mechanism, also operates. On the basis of MNDO semi-empirical[4] and high-level ab initio calculations,[5] it was suggested that the oxocarbenium ion is the more reactive species (Scheme 1).



Scheme 1. Proposed mechanism of the formation of 1,2-*cis* and 1,2-*trans* products during the 1,2-thiomigration reaction.

We have reported[6] 1,2-thiomigration of β-D-glucopyranosides in the presence of NaOMe. From *p*-methoxybenzylthio-, tritylthio- and (2-naphthyl)methylthio-β-D-glucopyranosides, methyl 2-*S*-(*p*-methoxybenzyl), methyl 2-*S*-trityl and methyl 2-*S*-(2-naphthyl)methyl-α-D-mannopyranosides, respectively, were formed in excellent yields (>90%). However, when a trityl 1-thio-mannopyranosyl derivative was used the yield was only 59% but formation of the α-anomer was not observed. These and our earlier observations, together with some sporadic data in the literature suggest that 1,2-thiomigration strongly depends on reaction conditions: the bulkiness of the aglycone, the bulkiness and power of the nucleophile, the nature of the solvent and the temperature.

In our work on the synthesis of sugar sulfonic acids, one specific goal is the preparation of sugar sulfonic acids of glycosyl azides. Here, we report on some 1,2-thiomigrations in the presence of the azide nucleophile. To the best of our knowledge, synthesis of 2-thioalkyl/aryl

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* Corresponding author. Tel.: +36 52512900; fax: +36 52512913; e-mail: liptaka@puma.unideb.hu

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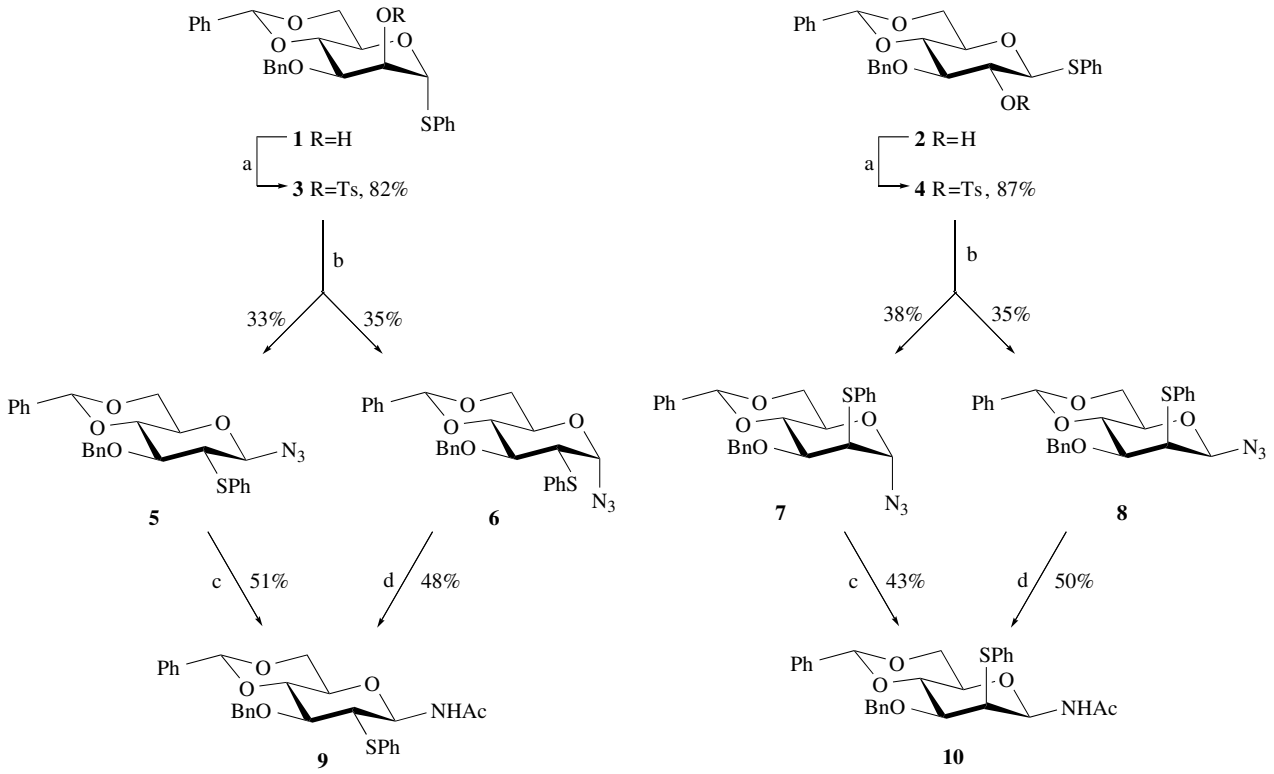


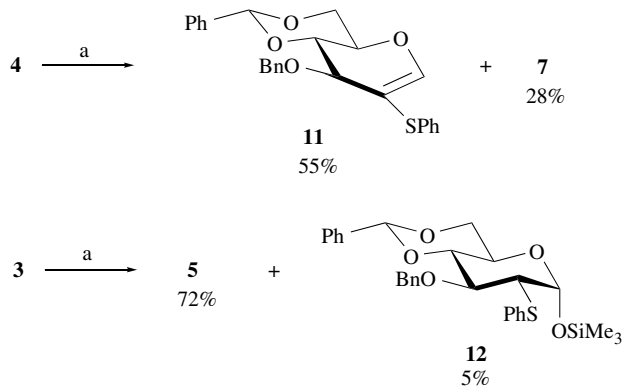
Scheme 2. Reagents and conditions: (a) 1.1 equiv TsCl, 5.7 equiv NaOH, 5.2 equiv K_2CO_3, rt, 4 h; (b) 10 equiv NaN_3, DMF, 80 °C, overnight; (c) H_2/Pd(C), 1.5 equiv TEA, THF, rt, 2 h; Ac_2O, Py, rt, 2 h; (d) 1.2 equiv PPh_3, THF, 35 °C, 5 h; H_2O, 35 °C, overnight; Ac_2O, Py, rt, 2 h.

glycosyl azides is unprecedented. A few 2-deoxy-2-phenylseleno-glycopyranosyl azides[7–9] have been prepared by free radical or polar addition of phenylselenyl azide on glycals, however, 1,2-selenomigration in the presence of azide has not been reported.

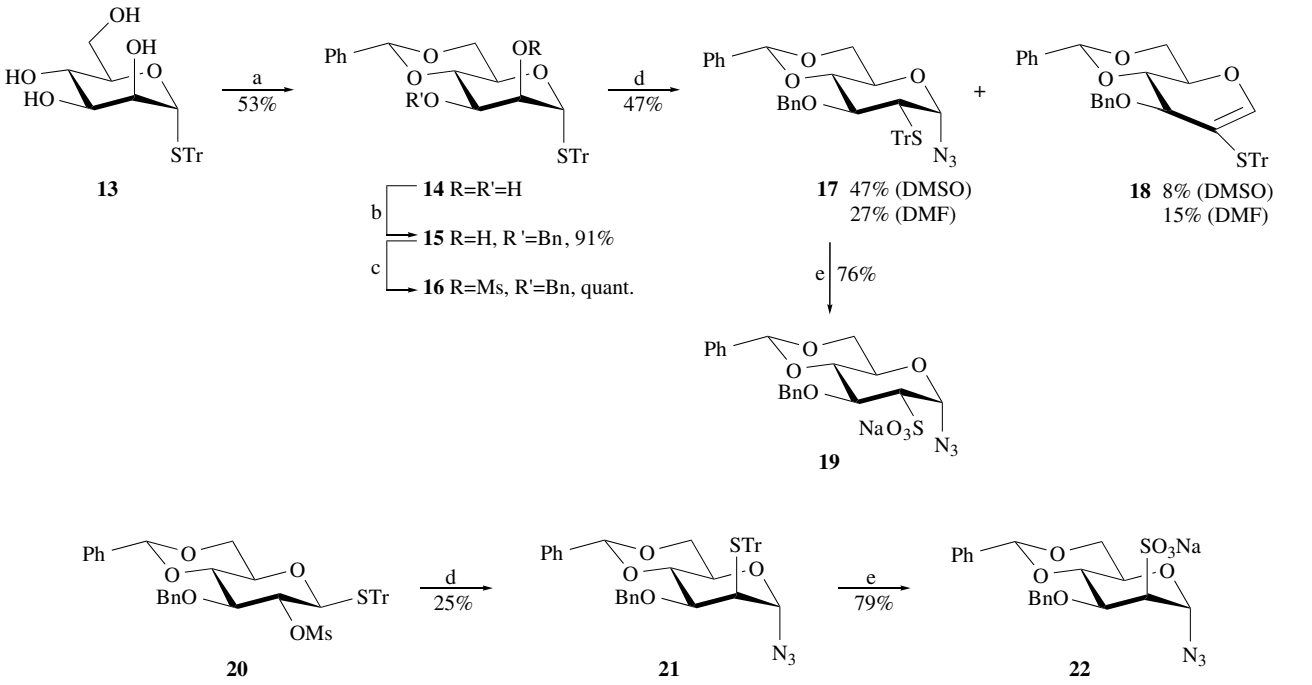
Conventional tosylation of **1**[10,11] and **2**[12,13] gave compounds **3** and **4**, respectively (Scheme 2), which were treated with NaN_3 (10 equiv) in *N*,*N*-dimethylformamide at 80 °C overnight. From the reaction of **3** with sodium azide, compounds **5** and **6** were isolated in yields of 33% and 35%, respectively. Compound **4** also gave two products, **7** (38%) and **8** (35%). The characteristic band in the IR spectra of **5**–**8** at $\upsilon = 2150\ cm^{-1}$ confirmed the presence of the N_3 functionality. In the ^{13}C NMR spectra, there was a substantial upfield shift of the signals corresponding to C-2 and a slight downfield shift of the anomeric signals. Due to signal overlapping, the proton spectra were unsuitable for the determination of the anomeric configurations, and the small difference in the $[\alpha]_D$ values also caused uncertainty in this respect. However, large differences in $^1J_{C1,H1}$ couplings left no doubt about the anomeric configurations: **5** (162.0 Hz) and **8** (158.0 Hz) were the β-, while **6** (170.3 Hz) and **7** (172.7 Hz) were the α-anomers.[14]

For additional structural elucidations, azides **5**–**8** were converted into the acetamides **9** and **10**.[15] In the case of the 1,2-*cis* derivatives (**6** and **8**), PPh_3 was used for the reductions,[16] however, under the same conditions, the 1,2-*trans* compounds (**5** and **7**) gave complex mixtures, therefore, catalytic hydrogenation (Pd–C in the presence of Et_3N) was the method of choice. In both cases, both anomeric azides furnished exclusively the β-products **9** ($^1J_{C1,H1} = 159.7$ Hz) and **10** ($^1J_{C1,H1} = 156.0$ Hz) after acetylation. The appearance of coupling between the NH protons and the anomeric protons in the spectra of compounds **9** and **10** proved unambiguously the position of the azide group in compounds **5**–**8**.

The tosylates **3** and **4** were also reacted with Me_3SiN_3 (Scheme 3) to study the effect of the counter-ion on the reaction. Starting from **4**, the 'normal' product **7** was isolated in a yield of only 28%, and the major product was the glycal **11**. In contrast, compound **3** gave only the 'normal' product **5** in good yield (72%) and no glycal



Scheme 3. Reagents and conditions: (a) 10 equiv Me_3SiN_3, DMF, 80 °C, overnight.



Scheme 4. Reagents and conditions: (a) 1.5 equiv benzaldehyde dimethyl acetal, 0.02 equiv TsOH, DMF, 50 °C, 6 h; (b) 1.3 equiv Bu_2SnO, 2 equiv CsF, toluene, reflux, 3 h; 2 equiv BnBr, DMF, rt, overnight; (c) 2 equiv MsCl, Py, rt, 4 h; (d) 10 equiv NaN_3, DMSO or DMF, 80 °C, 24 h; (e) 2.5 equiv Oxone®, 20 equiv KOAc, AcOH, rt, overnight.

formation was observed. (A small amount of the trimethylsilyl glycoside **12** was isolated from the reaction mixture.)[17]

Having clarified the structure of the products of migration of the SPh aglycone, we used these reaction conditions for the trityl 1-thio-α-D-mannopyranoside derivative **15** (Scheme 4). The advantage of the STr group is that it can be easily and directly oxidised with Oxone® to the corresponding sulfonic acid. Compound **15** was prepared from trityl 1-thio-α-D-mannopyranoside[6] (**13**) in a short synthetic sequence. We note here, that tosylation of **15** was unsuccessful, probably due to steric reasons, so a mesyl group was used instead. The 1,2-thiomigration reaction in this case gave **17** in a yield of 27%, but this could be improved (47%) by changing the solvent to DMSO. No 'normal' product formation was observed. As a by-product, the glycal **18** was isolated in a minor amount (DMF, 15%; DMSO, 8%). By changing the solvent (MeCN, 2-butanone), the glycal was formed exclusively. Spectroscopic (IR, NMR) and X-ray diffraction data were used for the structural elucidation of **17**.[18]

Performing the 1,2-thiomigration with compound **20**,[6] the 'normal' product **21** was isolated, albeit in a poor yield (25%) along with an inseparable mixture of by-products.

Compounds **17** and **21** were then successfully oxidised using Oxone® to yield sulfonates **19** and **22**, respectively.[18]

In conclusion, we have performed 1,2-thiomigration reactions with phenyl and trityl 2-*O*-sulfonyl-1-thio-α-D-manno- and β-D-glucopyranosides. In each case, complete inversion of the configuration was observed at C-2. Using NaOMe, a product with inversion of the anomeric configuration was formed exclusively. The anomeric selectivity nearly disappeared when NaN_3 was used with phenylthio glycosides, however with Me_3SiN_3, formation of the 'normal' product was observed. Exclusive formation of the 'abnormal' product was found in the case of the tritylthio D-mannopyranosyl compound, which is unprecedented in the literature. These observations suggest that with azide as the nucleophile, besides the episulfonium intermediate, the oxocarbenium ion intermediate also plays a substantial role in the determination of the product distribution. Although there are many factors governing this transformation, we have succeeded in developing a new approach for the synthesis of a new class of carbohydrate derivatives, the 2-*C*-sulfonyl-glycosyl amines.

Acknowledgements

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14. Characteristic ^{13}C NMR (90 MHz, $CDCl_3$) data of compounds **5**–**8**: **5**: δ 91.4 (C-1), 56.1 (C-2). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475.56): C, 65.67; H, 5.30; N, 8.84%. Found: C, 65.90; H, 5.29; N, 8.87%. **6**: δ 90.9 (C-1), 54.7 (C-2). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475.56): C, 65.67; H, 5.30; N, 8.84%. Found: C, 65.62; H, 5.35; N, 8.90%. **7**: δ 90.7 (C-1), 54.3 (C-2). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475.56): C, 65.67; H, 5.30; N, 8.84%. Found: C, 65.81; H, 5.33; N, 8.79%. **8**: δ 88.2 (C-1), 59.0 (C-2). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475.56): C, 65.67; H, 5.30; N, 8.84%. Found: C, 65.74; H, 5.21; N, 8.80%.
15. Physical, selected ^1H and ^{13}C NMR data for compounds **9**–**10**: **9**: $[\alpha]_D$ −15.9 (*c* 0.19, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 5.30 (t, 1H, $^3J_{1,2} = {}^3J_{H1,NH}$ = 10.2 Hz, H-1), 2.97 (t, 1H, $^3J_{1,2} = {}^3J_{2,3}$ = 10.2 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 80.7 (C-1), 56.1 (C-2). Anal. Calcd for $C_{28}H_{29}NO_5S$ (491.60): C, 68.41; H, 5.95; N, 2.85%. Found: C, 68.66; H, 5.81; N, 2.79%. **10**: $[\alpha]_D$ −14.1 (*c* 0.13, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 5.58 (dd, 1H, $^3J_{1,2}$ = 1.9 Hz, $^3J_{H1,NH}$ = 9.8 Hz, H-1), 3.62 (dd, 1H, $^3J_{1,2}$ = 1.9 Hz, $^3J_{2,3}$ = 2.6 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 77.5 (C-1), 58.4 (C-2). Anal. Calcd for $C_{28}H_{29}NO_5S$ (491.60): C, 68.41; H, 5.95; N, 2.85. Found: C, 68.63; H, 5.89; N, 2.87%.
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17. Physical, selected ^1H and ^{13}C NMR data for compounds **11** and **12**: **11**: $[\alpha]_D$ +4.0 (*c* 0.10, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 6.85 (s, 1H, H-1); ^{13}C NMR (90 MHz, $CDCl_3$): δ 152.3 (C-1), 108.0 (C-2). Anal. Calcd for $C_{26}H_{24}O_4S$ (432.53): C, 72.20; H, 5.59%. Found: C, 72.03; H, 5.62%. **12**: $[\alpha]_D$ −55.0 (*c* 0.22, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 5.32 (d, 1H, $^3J_{1,2}$ = 2.5 Hz, H-1), 3.33 (dd, 1H, $^3J_{1,2}$ = 2.5 Hz, $^3J_{2,3}$ = 10.7 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 94.9 (C-1), 56.1 (C-2). Anal. Calcd for $C_{29}H_{34}O_5SSi$ (522.19): C, 66.63; H, 6.56%. Found: C, 66.69; H, 6.52%.
18. Physical, selected ^1H and ^{13}C NMR data for compounds **17**, **19**, **21** and **22**: **17**: $[\alpha]_D$ −43.2 (*c* 0.11, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 2.96 (d, 1H, $^3J_{1,2}$ = 4.0 Hz, H-1), 2.92 (dd, 1H, $^3J_{1,2}$ = 4.0 Hz, $^3J_{2,3}$ = 10.8 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 90.4 (C-1), 50.6 (C-2), $^1J_{C1,H1}$ = 171.3 Hz. Anal. Calcd for $C_{39}H_{35}N_3O_4S$ (641.78): C, 72.99; H, 5.50; N, 6.55%. Found: C, 73.10; H, 5.54; N, 6.52%. **19**: $[\alpha]_D$ +74.1 (*c* 0.10, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 5.71 (d, 1H, $^3J_{1,2}$ = 3.9 Hz, H-1), 3.38 (dd, 1H, $^3J_{1,2}$ = 3.9 Hz, $^3J_{2,3}$ = 10.5 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 88.5 (C-1), 62.8 (C-2). Anal. Calcd for $C_{20}H_{20}N_3NaO_7S$ (469.44): C, 51.17; H, 4.29; N, 8.95%. Found: C, 51.06; H, 4.25; N, 8.91%. **21**: $[\alpha]_D$ +123.9 (*c* 0.73, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 3.47 (d, 1H, $^3J_{1,2}$ = 1.3 Hz, H-1), 3.06 (dd, 1H, $^3J_{1,2}$ = 1.3 Hz, $^3J_{2,3}$ = 4.7 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 91.1 (C-1), 50.2 (C-2), $^1J_{C1,H1}$ = 172.2 Hz. Anal. Calcd for $C_{39}H_{35}N_3O_4S$ (641.78): C, 72.99; H, 5.50; N, 6.55%. Found: C, 73.12; H, 5.44; N, 6.61%. **22**: $[\alpha]_D$ +55.7 (*c* 0.13, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ 6.27 (br s, 1H, H-1), 3.62 (br d, 1H, $^3J_{2,3}$ = 5.3 Hz, H-2); ^{13}C NMR (90 MHz, $CDCl_3$): δ 89.5 (C-1), 61.8 (C-2). Anal. Calcd for $C_{20}H_{20}N_3NaO_7S$ (469.44): C, 51.17; H, 4.29; N, 8.95%. Found: C, 51.09; H, 4.27; N, 8.90%.