A degradation reaction of ethyl thiodisaccharides as glycosyl donors during glycosylations

Wei Zou and Walter A. Szarek*

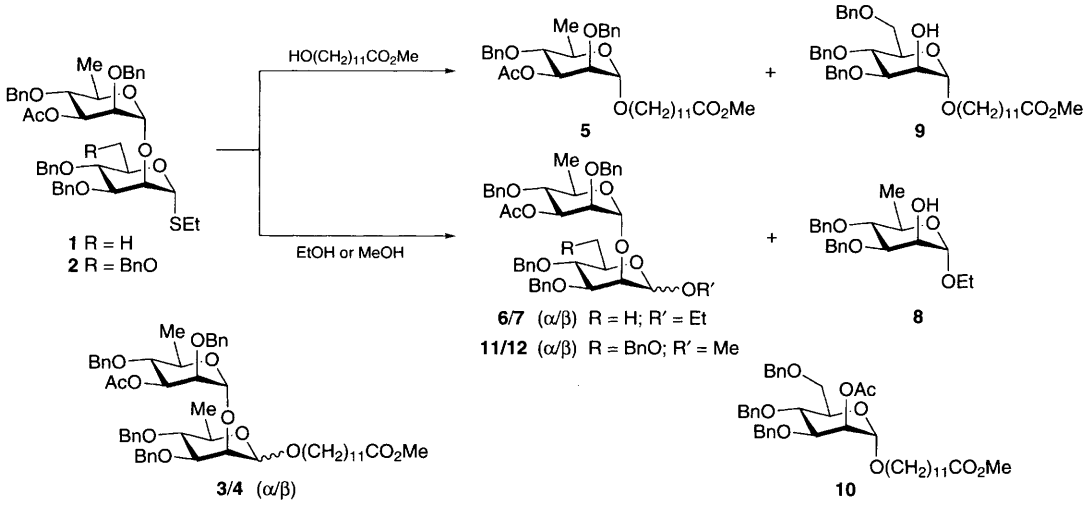
Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

The formation of monosaccharide products during glycosylation of ethyl thioglycosides using the radical-cation reagent, tris(4-bromophenyl)ammoniumyl hexachloroantimonate, as the activator of the thioglycoside is described.

In the recent years the use of thioglycosides as glycosyl donors has been a major focus in the synthesis of oligosaccharides.[1–15] A variety of reagents[1–14] have been used as activators of the thioglycosides in the glycosylation reactions. There are many advantages of thioglycosides over glycosyl halides as glycosyl donors, however, in some cases side reactions, such as glycal formation,[1,14] alkylthio group transfer[16–18] and decomposition,[18] have been observed. Here we report a new observation, namely a degradation reaction involving the ethyl thioglycosides **1** and **2** as glycosyl donors, and tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA$^{+\cdot}$), an one-electron transfer reagent,[13] as the activator of the thioglycoside.

During the course of the synthesis of a conjugate of *O*-α-D-Rha*p*-(1 → 3)-*O*-α-D-Rha*p*-(1 → 2)-*O*-α-D-Rha*p* and bovine serum albumin,[19] we attempted the reaction of ethyl thioglycoside **1** and methyl 12-hydroxydodecanoate in an effort to obtain the disaccharide derivatives **3** and/or **4** (Scheme 1), which possess a spacer for conjugation with proteins. TBPA$^{+\cdot}$ was used as an activator in the glycosylation reaction as reported by Sinaÿ.[13] Thus, to a solution of **1** (200 mg, 0.265 mmol) and methyl 12-hydroxydodecanoate (90 mg, 0.363 mmol) in dry acetonitrile (5 ml) was added TBPA$^{+\cdot}$ (300 mg, 0.368 mmol) and the mixture was stirred at room temperature for 4 h, by which time the dark blue colour had disappeared and the starting material **1** had been completely consumed. Fractionation of the reaction products by chromatography on silica gel [ethyl acetate–hexane, 1 : 3 (*v*/*v*)] did not afford any of the expected compounds **3** or **4**, but rather 11-(methoxycarbonyl)undecyl 3-*O*-acetyl-2,4-di-*O*-benzyl-α-D-rhamnopyranoside **5** in 68% yield and other unidentified compounds. When ethanol was used (in place of methyl 12-hydroxydodecanoate) in a reaction with **1** under the same conditions, the normal glycosylation products, namely the ethyl disaccharides **6** and **7**, were the major products, a mixture (*ca.* 1 : 1) of which was isolated in 70–80% yield, however, the cleavage product **8** was also isolated in low yield (< 10%). The structures of **5** and **8** were established easily by ^{1}H and ^{13}C NMR spectroscopy (the data are summarized in Tables 1 and 2), and by mass spectrometry; for **5**, MS (CI, CH_4) *m*/*z*: 598 (M)$^+$, 597, 567 (M − OMe)$^+$, 549, 491 (M − OBn)$^+$, 459, 370 and 369 [M − O(CH$_2$)$_{11}$CO$_2$Me]$^+$; for **8**, MS (CI, CH_4) *m*/*z*: 371 (M − 1)$^+$, 369, 327 (M − OEt)$^+$, 281 (M − Bn)$^+$. The anomeric configurations were determined by gated ^{13}C NMR measurements ($J_{C1,H1}$ 168.61 Hz for **5**; $J_{C1,H1}$ 167.85 Hz for **8**).

For a further investigation, compound **2**, a more easily obtained ethyl thiodisaccharide, that was synthesized by the reaction of ethyl 3,4,6-tri-*O*-benzyl-l-thio-α-D-mannopyranoside and 3-*O*-acetyl-2,4-di-*O*-benzyl-α-D-rhamnopyranosyl chloride in the presence of silver triflate, was used as the glycosyl donor, instead of **1**, in the glycosylation reaction involving TBPA$^{+\cdot}$ and methyl 12-hydroxydodecanoate in acetonitrile. Compound **5** was isolated again; in addition, compound **9**, derived from the other half of **2**, was obtained. The structure of **9** was confirmed by ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2); the spectra were identical to those of a synthetic sample, that was prepared by the reaction of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride and methyl 12-hydroxydodecanoate to give **10**, followed by *O*-deacetylation with sodium methoxide in methanol. When methanol was used (in place of methyl 12-hydroxydodecanoate) in the reaction with **2**, results analogous to those obtained in the



Scheme 1

Table 1 Partial ^{1}H NMR data[a] for **5**, **8**, **9** and **10**

Compound	Chemical shifts (δ) and coupling constants J (in Hz)					
	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}$	H-6
5	4.72(d) 1.6	3.83(dd) 3.3	5.20(dd) 9.5	3.62(t) 9.5	3.77(dq) 6.1	1.40(d) 6.1[b]
8	4.81(d) 1.7	4.03(dd) 3.4	3.86(dd) 9.5	3.45	3.72	1.31(d) 6.1[b]
9	4.91(d) 1.5	4.04(br)	3.81———		———3.90	3.71–3.76
10	4.87(d) 1.5	5.39(dd) 3.0	3.80———		———4.05	3.71–3.76

[a] The spectra were recorded with a Bruker AC-F200 (200.13 MHz) spectrometer at room temp. in $CDCl_3$; the signal of solvent at 7.25 ppm was used as a reference. Chemical shifts (δ) are relative to Me_4Si. The additional signals of OAc, OBn and $O(CH_2)_{11}CO_2Me$ are not listed. [b] The coupling constant $J_{6,5}$.

Table 2 Partial ^{13}C NMR data[a] for **5**, **8**, **9** and **10**

Compound	Chemical shifts (δ)					
	C-1	C-2	C-3	C-4	C-5	C-6
5	97.73	76.51	73.89	79.33	67.63	18.05
8	98.62	68.66	80.23	80.09	67.15	17.90
9	99.09	68.39	80.29	74.33	70.92	68.90
10	97.66	68.83	78.25	74.33	71.24	67.92

[a] The spectra were recorded with a Bruker AC-F200 (50.32 MHz) spectrometer at room temp. in $CDCl_3$; the signal of solvent at 77.0 ppm was used as a reference. Chemical shifts (δ) are relative to Me_4Si. The additional signals of OAc, OBn and $O(CH_2)_{11}CO_2Me$ are not listed.

reaction of **1** with ethanol were observed; the normal glycosylation products **11** and **12** were obtained in good yield. The presence of the cleavage product, methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside, was also observed as a minor component in TLC by comparison with an authentic sample.

Significantly, when the reaction of the thiodisaccharide **1** and methyl 12-hydroxydodecanoate was conducted in the presence of both TBPA$^{+\cdot}$ and 4 Å molecular sieves a mixture (*ca.* 1 : 1) of the (normal) disaccharides **3** and **4** was obtained in 54% yield; compound **5** was not isolated. Moreover, the same reaction in dichloromethane using *N*-iodosuccinimide–trifluoromethanesulfonic acid[8,11] as an activator and in the presence of 4 Å molecular sieves afforded only a mixture (*ca.* 1 : 1) of **3** and **4**, which was isolated by chromatography in 70–80% yield.

The mechanism of the degradation is still unclear, but the role of the molecular sieves in the reactions is clearly important.

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