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An efficient method for the preparation of glycosides with a free C-2 hydroxyl group from thioglycosides

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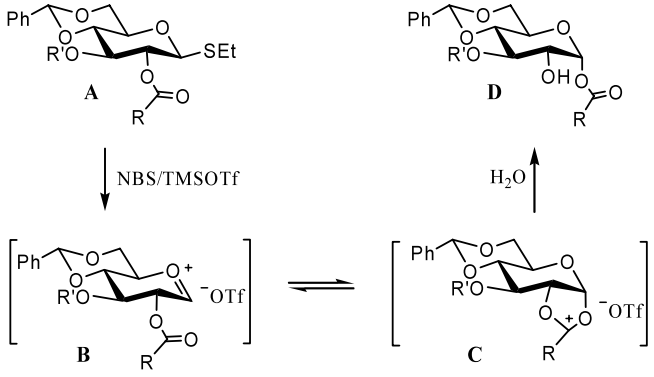
Abstract—A new and efficient method to produce glycosides with a free C-2 hydroxyl group through 1,2-acyl group migration which occurs during the hydrolysis of 4,6-benzylidene protected thioglycosides has been developed. The acyl transfer products allow for further elaboration.

Glycosides with a free hydroxyl group at C-2 are useful synthons for the preparation of naturally occurring oligosaccharides and glycoconjugates containing (1→2)-linked saccharide units.[1] Also, it is well known that to achieve stereochemical control in the formation of β-glycosidic linkages a C-2 ester capable of neighboring group participation must be used.[2] In some cases special C-2 esters are needed[3] and it is very convenient to install these ester groups from glycosides with a free C-2 hydroxyl group. In addition, free C-2 hydroxyl glycosides have been used in the synthesis of glycosylamines.[4]

Several methods have been developed for the preparation of various glycosides with a free C-2 hydroxyl group.[4,5] Here we report a convenient method for the preparation of glycosides with a free C-2 hydroxyl group from 4,6-benzylidene protected thioglycosides.



Scheme 1.

Thioglycosides are now well established as stable and versatile synthons in the field of synthetic carbohydrate chemistry[6] since they are stable under a wide range of reaction conditions and also can be used as efficient glycosyl donors. During the course of our work on oligosaccharide assembly, we required a mild, versatile protocol for the conversion of protected thioglycosides into their corresponding hemiacetals, which could then be converted into the corresponding trichloroacetimidate. Subjecting compound **1a** to the literature procedure for hydrolysis of thioglycosides (NBS/aqueous acetone)[7] gave a complex mixture of products with none corresponding to the hydrolysis product. However, **1a** was smoothly converted into **1b** when treated with 1 equivalent of NBS and a catalytic amount of TMSOTf at 0°C in wet CH_2Cl_2 for 10 min. The process results not only in hydrolysis of the thioglycoside linkage, but also migration of the 2-acyl substituent to the 1-position, presumably via the initially formed oxycarbenium ion C (Scheme 1). Encouraged by the high yield and selectivity of the reaction, we explored the application of this approach for the preparation of glycosides with a free C-2 hydroxyl group from thioglycosides.

Several examples of the hydrolysis of thioglycosides are demonstrated in Table 1. Various 4,6-benzylidene protected thioglycosides, **1a**–**9a**, bearing different ester groups at C-2 were explored. All reactions proceeded smoothly under the standard reaction conditions to provide the corresponding acyl transfer products, **1b**–**9b**, in good yields.

Keywords: thioglycoside hydrolysis; 1,2-acyl migration.
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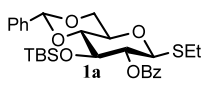
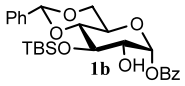
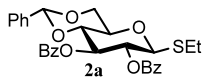
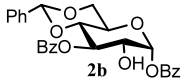
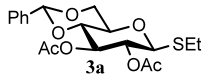
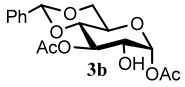
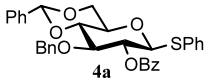
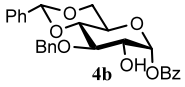
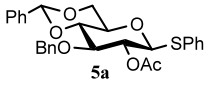
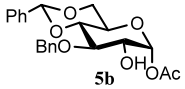
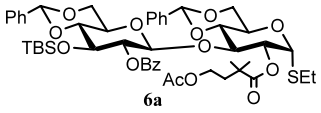
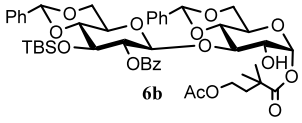
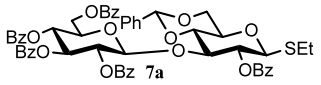
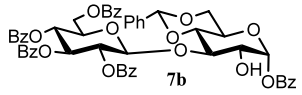
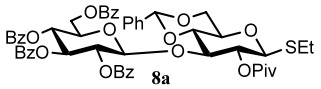
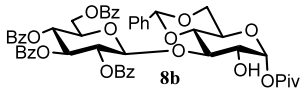
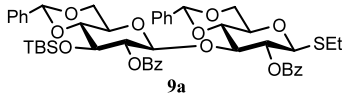
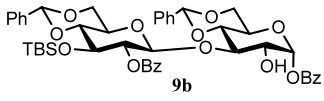
Table 1. Hydrolysis of various 4,6-benzylidene protected thioglycosides

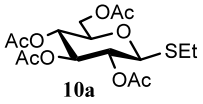
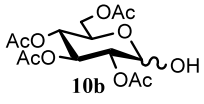
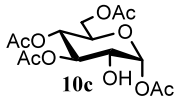
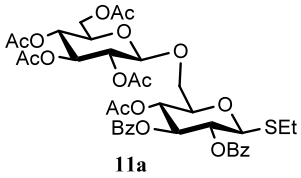
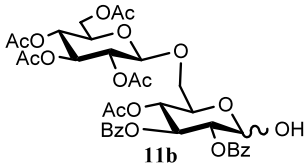
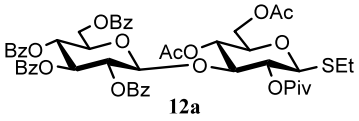
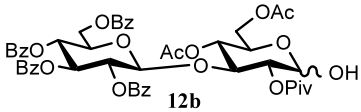
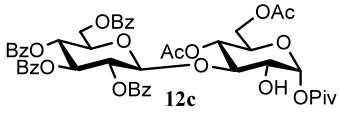
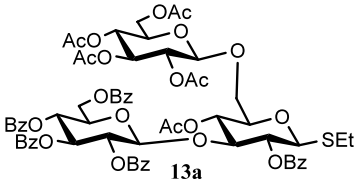
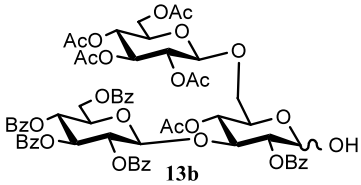
entry	thioglycosides	products	yield(%)
1	 **1a**	 **1b**	90%
2	 **2a**	 **2b**	88%
3	 **3a**	 **3b**	84%
4	 **4a**	 **4b**	88%
5	 **5a**	 **5b**	85%
6	 **6a**	 **6b**	92%
7	 **7a**	 **7b**	88%
8	 **8a**	 **8b**	90%
9	 **9a**	 **9b**	91%

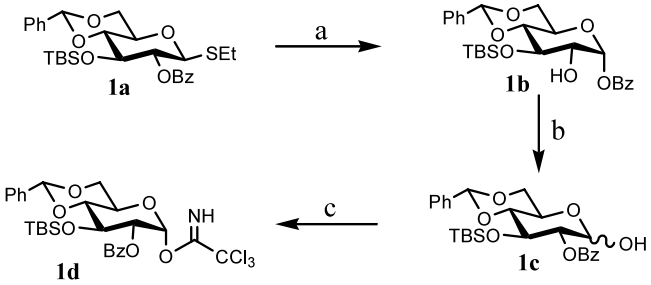
When the reaction was applied to thioglycosides which lacked the 4,6-benzylidene protecting group, the acyl migration from the 2-position to the 1-position was partially or completely retarded and mixtures of hydrolysis products were sometimes obtained. For example, when peracetate **10a** was hydrolyzed under the standard conditions the hydrolysis product **10b** was obtained in 56% yield along with a 42% yield of the hydrolysis product which had undergone the 1,2-acyl migration, **10c**. Other examples are shown in Table 2. These results indicate that the regioselective acyl transfer depends critically on the presence of the cyclic 4,6-benzylidene protecting group. Crich and coworkers[8] have observed similar effects of 4,6-benzylidene protecting groups increasing the stability of α-glycopyranosyl triflates. As in the case of α-glycopyranosyl triflates, we propose that the 4,6-benzylidene moiety stabilizes the intermediate oxycarbenium ion C.

Interestingly, we found that the 1,2-acyl group migration which accompanies NBS mediated hydrolysis of the 4,6-benzylidene protected thioglycosides can be easily reversed, in high yield, by treatment with Et_3N in CH_2Cl_2. For example, compound **1b** was converted into hemiacetal **1c**, which can then be converted into glycosyl trichloroacetimidate **1d**, a widely used glycosyl donor,[2,11] for the next glycosylation (Scheme 2). The migration reversal procedure is particularly useful in those cases in Table 2 which initially result in a mixture of products. Treatment with Et_3N in CH_2Cl_2 affords a single product in high yield.[12–14]

In conclusion, we have developed a simple and efficient method for the hydrolysis of thioglycosides which provides glycosides with a free C-2 hydroxyl group through 1,2 migration. The resulting free alcohol can be manipulated to form 1,2-linked saccharides or glycosylamines or install different groups, if desired. The acyl migration can readily be reversed to afford the 2-acylhemiacetal. We believe this method should find wide application in carbohydrate chemistry.

Table 2. Hydrolysis of various thioglycosides without benzylidene protecting groups

entry	thioglycosides	products	yield(%)
1	 **10a**	 **10b**	56%[9]
		 **10c**	42%[10]
2	 **11a**	 **11b**	90%
3	 **12a**	 **12b**	48%
		 **12c**	50%
4	 **13a**	 **13b**	93%



Scheme 2. *Reagents and conditions*: (a) *N*-bromosuccinimide (1.0 equiv.), TMSOTf (0.1 equiv.), CH_2Cl_2–H_2O (100:1), 0°C, 10 min, 90%; (b) Et_3N/CH_2Cl_2 (1:4), rt, 24 h, 92%; (c) Cl_3CCN, DBU, CH_2Cl_2, rt, 95%.

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12. A typical experimental procedure, as applied to ethyl 4,6-*O*-benzylidene-2-*O*-benzoyl-3-*O*-*t*-butyldimethylsilyl-1-thio-β-D-glucopyranoside **1a**, is as follows: Compound **1a** (500 mg, 0.94 mmol) was dissolved in 5 mL of CH_2Cl_2–H_2O (100:1) and cooled to 0°C. The solution was treated with 1.0 equiv. of *N*-bromosuccinimide (167 mg, 0.94 mmol) and 0.1 equiv. of TMSOTf. The resulting mixture was stirred at 0°C, and the reaction was monitored by TLC. After the reaction was complete, aqueous $NaHCO_3$ was added, and the reaction mixture was extracted with CH_2Cl_2 three times. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The resulting oil was purified by flash column chromatography (hexane/EtOAc 8:1) to yield of **1b** (412 mg, 90%) as a white amorphous solid. Compound **1b** (400 mg, 0.82 mmol) was dissolved in a mixture of CH_2Cl_2–Et_3N (4:1, v/v, 5 mL). The solution was stirred at room temperature for 24 h. After the reaction was complete, the solution was concentrated and purified by flash column chromatography to give **1c** (380 mg, 95%). To a solution of compound **1c** (350 mg, 0.72 mmol) in anhydrous CH_2Cl_2 (8 mL) was added trichloroacetonitrile (Cl_3CCN, 0.43 mL, 6.0 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 50 μL) at 0°C. After stirring the resulting mixture for 4 h, the solvent was evaporated under reduced pressure and the resulting oil was purified by flash column chromatography to give pure **1d** (431 mg, 95%) as a white amorphous solid.
13. All compounds gave satisfactory ^1H, COSY and ^{13}C NMR spectra. The ^1H NMR signals (400 MHz, $CDCl_3$) for H-1 and H-2 of the corresponding thioglycosides and products are given: **1a** 5.42 (dd, $J=10.0$ Hz and 8.4 Hz, 1H, H-2), 4.76 (d, $J=10.0$ Hz, 1H, H-1); **1b** 6.41 (d, $J=4.0$ Hz, 1H, H-1), 3.80 (dd, $J=9.2$ Hz and 4.0 Hz, 1H, H-2); **2a** 5.52 (t, $J=9.2$ Hz, 1H, H-2), 4.82 (d, $J=10.0$ Hz, 1H, H-1); **2b** 6.52 (d, $J=4.0$ Hz, 1H, H-1), 4.16–4.10 (m, 2H, H-2, H-5); **3a** 5.03 (dd, $J=10.0$ Hz and 9.2 Hz, 1H, H-2), 4.57 (d, $J=10.0$ Hz, 1H, H-1); **3b** 6.19 (d, $J=4.0$ Hz, 1H, H-1), 3.84 (dd, $J=10.0$ Hz and 4.0 Hz, 1H, H-2); **4a** 5.28 (dd, $J=10.0$ Hz and 8.8 Hz, 1H, H-2), 4.83 (d, $J=10.0$ Hz, 1H, H-1); **4b** 6.48 (d, $J=3.6$ Hz, 1H, H-1), 3.97 (dd, $J=9.2$ Hz and 3.6 Hz, 1H, H-2); **5a** 5.82 (dd, $J=10.0$ Hz and 8.8 Hz, 1H, H-2), 4.69 (d, $J=10.0$ Hz, 1H, H-1); **5b** 6.21 (d, $J=3.2$ Hz, 1H, H-1), 3.94–3.84 (m, 3H, H-2, H-3, H-5); **6a** 5.76 (d, $J=5.6$ Hz, 1H, H-1), 5.03 (dd, $J=9.6$ Hz and 6.0 Hz, 1H, H-2); **6b** 6.25 (d, $J=4.0$ Hz, 1H, H-1), 3.96–3.89 (m, 3H, H-2, H-5, H-6b); **7a** 5.34 (t, $J=10.0$ Hz, 1H, H-2), 4.55 (d, $J=10.4$ Hz, 1H, H-1); **7b** 6.36 (d, $J=4.0$ Hz, 1H, H-1), 4.00–3.91 (m, 3H, H-2, H-5, H-5′); **8a** 5.07 (t, $J=9.6$ Hz, 1H, H-2), 4.40 (d, $J=9.6$ Hz, 1H, H-1); **8b** 6.11 (d, $J=4.0$ Hz, 1H, H-1), 3.82–3.68 (m, 3H, H-2, H-4, H-6b); **9a** 5.58 (dd, $J=10.0$ Hz and 8.0 Hz, 1H, H-2), 4.86 (d, $J=10.0$ Hz, 1H, H-1); **9b** 6.46 (d, $J=3.6$ Hz, 1H, H-1), 4.02 (dd, $J=9.2$ Hz and 4.0 Hz, 1H, H-2); **10a** 4.99 (t, $J=10.0$ Hz, 1H, H-2), 4.48 (d, $J=10.0$ Hz, 1H, H-1); **10b** 5.40 (d, $J=3.2$ Hz, 1H, H-1), 4.84 (dd, $J=10.0$ Hz and 3.2 Hz, 1H, H-2); **10c** 6.21 (d, $J=4.0$ Hz, 1H, H-1), 3.87 (dd, $J=10.0$ Hz and 4.0 Hz, 1H, H-2); **11a** 5.39 (t, $J=9.6$ Hz, 1H, H-2), 4.68 (d, $J=10.0$ Hz, 1H, H-1); **11b** 5.65 (d, $J=3.6$ Hz, 1H, H-1), 5.24–5.15 (m, 4H, H-3′, H-4, H-4′, H-2); **12a** 4.99 (t, $J=10.0$ Hz, 1H, H-2), 4.25 (d, $J=10.0$ Hz, 1H, H-1); **12b** 5.40 (d, $J=3.2$ Hz, 1H, H-1), 4.69–4.62 (m, 2H, H-6a, H-2); **12c** 6.07 (d, $J=3.6$ Hz, 1H, H-1), 3.77 (dd, $J=9.6$ Hz and 4.0 Hz, 1H, H-2); **13a** 5.33 (dd, $J=9.2$ Hz and 8.0 Hz, 1H, H-2), 4.84 (d, $J=8.0$ Hz, 1H, H-1); **13b** 5.41 (d, $J=3.6$ Hz, 1H, H-1); 4.79 (dd, $J=10.0$ Hz and 3.6 Hz, 1H, H-2).
14. Complete spectral data for selected compounds: **6a** ^1H NMR δ 8.01–7.40 (m, 15H), 5.76 (d, $J=5.6$ Hz, 1H, H-1), 5.69 (s, 1H), 5.34 (s, 1H), 5.33 (t, $J=7.2$ Hz, 1H, H-2′), 5.16 (d, $J=7.2$ Hz, 1H, H-1′), 5.03 (dd, $J=9.6$ Hz and 6.0 Hz, 1H, H-2), 4.46–4.36 (m, 4H), 4.25–4.20 (m, 2H), 4.03 (dd, $J=8.3$ Hz and 7.4 Hz, 1H, H-3′), 3.93 (t, $J=9.6$ Hz, 1H), 3.87–3.81 (m, 3H), 3.56 (m, 1H), 2.63 (m, 2H, CH_2), 2.16 (s, 3H), 2.02–1.98 (m, 2H), 1.34 (t, $J=7.6$ Hz, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 176.3, 171.2, 165.2, 137.4, 137.4, 133.3, 130.1, 130.0, 129.5, 129.1, 128.6, 128.5, 128.3, 126.5, 126.4, 102.0, 101.6, 99.5, 82.3, 81.3, 79.8, 75.7, 74.1, 73.8, 73.3, 68.9, 66.3, 62.9, 61.6, 40.9, 38.1, 25.8, 25.2, 25.2, 24.4, 21.3, 18.1, 15.0, –4.05, –4.76; **6b** ^1H NMR δ 8.21–7.41 (m, 15H), 6.25 (d, $J=4.0$ Hz, 1H, H-1), 5.72 (s, 1H), 5.67 (s, 1H), 5.43 (dd, $J=8.8$ Hz and 8.0 Hz, 1H, H-2′), 5.12 (d, $J=8.0$ Hz, 1H, H-1′), 4.44–4.36 (m, 2H), 4.24–4.01 (m, 4H), 3.96–3.89 (m, 3H, H-2, H-5, H-6b), 3.88–3.77 (m, 3H), 3.58 (m, 1H), 2.12 (s, 3H), 1.98–1.84 (m, 2H), 1.18 (s, 3H), 1.13 (s, 3H), 0.81 (s, 9H), 0.09 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 180.3, 176.1, 171.2, 142.0, 138.3, 134.8, 134.7, 134.2, 134.1, 133.5, 133.3, 133.2, 131.3, 130.8, 107.5, 106.8, 106.2, 96.3, 86.2, 85.4, 84.9, 81.2, 77.8, 75.5, 73.7, 73.6, 71.5, 69.9, 66.1, 45.9, 43.1, 30.5, 30.3, 29.7, 25.9, 22.9, 0.82, 0.00; **13a** ^1H NMR δ 7.96–7.15 (m, 25H), 5.58 (t, $J=9.2$ Hz, 1H, H-3′), 5.53 (t, $J=9.2$ Hz, 1H, H-4′), 5.33 (dd, $J=9.2$ Hz and 8.0 Hz, 1H, H-2′), 5.12 (t, $J=9.6$ Hz, 2H, H-2, H-3″), 5.00 (t, $J=9.6$ Hz, 1H, H-4″), 4.92 (dd, $J=9.2$ Hz and 8.0 Hz, 1H, H-2″), 4.84 (d, $J=8.0$ Hz, 1H, H-1′), 4.83 (t, $J=9.6$ Hz, 1H, H-4), 4.56 (dd, $J=12.4$ Hz and 3.2 Hz, 1H), 4.59 (d, $J=8.0$ Hz, 1H, H-1″), 4.43 (dd, $J=12.4$ Hz and 5.2 Hz, 1H), 4.33 (d, $J=10.0$ Hz, 1H, H-1), 4.21 (dd, $J=12.4$ Hz and 4.4 Hz, 1H), 4.13–3.99 (m, 3H), 3.83–3.47 (m, 3H), 2.58–2.46 (m, 2H), 2.00 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 1.92 (s, 3H), 1.06 (t, $J=7.6$ Hz, 3H); ^{13}C NMR δ 170.9, 170.4, 169.9, 169.7, 169.7, 166.3, 165.9, 165.3, 165.2, 164.6, 133.7, 133.5, 133.1, 130.0, 129.9, 129.8, 129.6, 129.4, 129.3, 128.8, 128.7, 128.6, 128.5, 128.3, 101.3, 101.0, 83.5, 80.0, 77.9, 73.1, 73.0, 72.1, 72.0, 72.0, 71.9, 71.3, 69.8, 69.2, 69.0, 68.5, 63.3, 62.0, 24.0, 21.0, 20.9, 20.9, 20.8, 15.0; **13b** ^1H NMR δ 7.99–6.94 (m, 25H), 5.70 (t, $J=9.6$ Hz, 1H, H-3′), 5.61 (t, $J=9.6$ Hz, 1H, H-4′), 5.49–5.38 (m, 2H, H-1, H-2′), 5.14 (t, $J=9.6$ Hz, 1H, H-3″), 5.05 (d, $J=8.0$ Hz, 1H, H-1′), 5.01 (t, $J=9.6$ Hz, 1H, H-4″), 4.91–4.78 (m, 3H, H-2″, H-4, H-2), 4.59 (dd, $J=12.0$ Hz and 2.8 Hz, 1H), 4.48 (d, $J=8.0$ Hz, 1H, H-1″), 4.45–4.38 (m, 2H), 4.18–4.03 (m, 4H), 3.81–3.78 (m, 1H), 3.64–3.60 (m, 1H), 3.51–3.47 (m, 1H), 2.00 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 1.90 (s, 3H); ^{13}C NMR δ 171.1, 170.5, 170.3, 170.0, 169.7, 166.4, 165.9, 165.3, 165.3, 165.1, 133.8, 133.7, 133.6, 133.4, 133.0, 130.0, 130.0, 129.9, 129.8, 129.6, 129.5, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 101.8, 101.5, 89.9, 76.3, 74.2, 73.2, 72.7, 72.2, 72.1, 71.9, 71.5, 69.7, 69.7, 68.8, 68.6, 68.3, 63.3, 61.8, 29.8, 21.0, 20.9, 20.9, 20.8.