Direct Transformation of *O*-Glycosides into Other *O*-Glycosides Using Trimethylsilyl Bromide and Zinc Bromide

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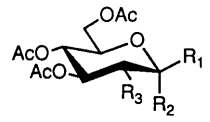
We have succeeded in developing a novel glycosidation catalyzed by a combination of trimethylsilyl bromide (TMSBr) and a Lewis acid using simple *O*-glycosides as glycosyl donors. Treatment of benzyl 2-deoxy-2-trichloroethoxycarbonylamino-D-glucopyranoside with TMSBr and zinc bromide in the presence of glycosyl acceptors gave α-*O*-glycosides in moderate to high yields. Zinc triflate and tin(II)triflate were also found to be effective as the Lewis acid. This new methodology is applicable to methyl D-glucopyranoside.

Keywords glycosidation; direct transformation; trimethylsilyl bromide; zinc bromide; zinc triflate; one-pot reaction; *O*-glycoside; glycosyl donor; activator

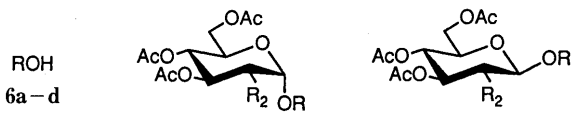
In carbohydrate synthesis, *O*-glycosides have been frequently used as intermediates for preparation of glycosyl donors.[1] *O*-Glycosides are readily prepared and are stable under a variety of conditions commonly encountered in carbohydrate manipulations, so that they fulfill at least some of the requirements for an ideal glycosyl donor.[1,2] If the *O*-glycosides could be used directly as glycosyl donors, many benefits might accrue.[1] So far, however, few glycosidations using *O*-glycosides directly as glycosyl donors have been reported, because of the difficulty in their activation into glycosyl donors. Recently, Fraser-Reid *et al.* have shown that 4-pentenyl glycosides are versatile glycosyl donors that can be activated under mild conditions by halonium ions.[3]

During the course of synthetic studies of the key intermediate (**7a**)[4] for lipid A derivatives, we have found that the combination of trimethylsilyl bromide (TMSBr) and zinc bromide ($ZnBr_2$)[5] was a good catalyst for anomerization of the β-glycoside of a D-glucosamine derivative to the α-glycoside. Based on these studies, we anticipated that if another alcohol were present in the reaction system, the replacement reaction would take place to give the corresponding new *O*-glycoside. We report herein a novel glycosidation using a simple *O*-glycoside as a glycosyl donor, catalyzed by a combination of TMSBr and a Lewis acid.

The *O*-glycosides (**1**—**5**) used here as glycosyl donors for this glycosidation are shown in Chart 1. These compounds were prepared according to published procedures.[5d] When the β-benzyl glycoside (**1**) was treated with TMSBr and $ZnBr_2$ in the presence of benzyl alcohol, anomerization took place to afford the α-benzyl glycoside (**2**) along with the 1-bromo sugar.[5c] When the reaction was carried out using dimethyl 3-hydroxyglutarate (**6a**) instead of benzyl alcohol, glycosidation proceeded, as expected, to afford the corresponding α-glycoside (**7a**) in 57% yield; only a trace amount of β-glycoside was detected by thin layer chromatography in the reaction mixture (Table I run 1). When the α-benzyl glycoside (**2**) was used as a glycosyl donor, a similar reaction took place, giving compound **7a** in 73% yield (run 2). In contrast to these results, when TMSBr alone was used as an activator, no reaction oc-

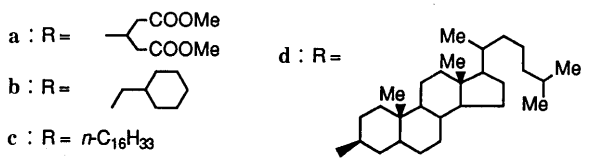


1 : R_1 = OBn, R_2 = H, R_3 = TrocHN
2 : R1 = H, R_2 = OBn, R_3 = TrocHN
3 : R_1 = H, R_2 = OMe, R_3 = TrocHN
4 : R_1 = H, R_2 = O-iso-Pr, R_3 = TrocHN
5 : R_1 = H, R_2 = OMe, R_3 = AcO



7a–d : R_2 = TrocHN
8c : R_2 = AcO
9c : R_2 = HO

10c : R_2 = AcO



Troc: 2,2,2-trichloroethoxycarbonyl
Bn: benzyl

Chart 1

TABLE I. Direct Transformation of *O*-Glycosides (**1**—**5**) into Other *O*-Glycosides (**7a**—**d**, **8**—**10c**) Using TMSBr and a Lewis Acid

Run	Donor	Acceptor (eq)	Activator	Time[a] (h)	Products (% yield)[b]
1	**1**	**6a** (2.0)	TMSBr–$ZnBr_2$	19	**7a** (57)
2	**2**	**6a** (2.0)	TMSBr–$ZnBr_2$	20	**7a** (73)
3	**3**	**6a** (2.0)	TMSBr–$ZnBr_2$	27	**7a** (28), **3** (25)[c]
4	**4**	**6a** (2.0)	TMSBr–$ZnBr_2$	27	**7a** (59)
5	**2**	**6b** (2.0)	TMSBr–$ZnBr_2$	5	**7b** (78)
6	**4**	**6b** (2.0)	TMSBr–$ZnBr_2$	5	**7b** (70)
7	**4**	**6b** (4.0)	TMSBr–$ZnBr_2$	5	**7b** (85)
8	**4**	**6b** (2.0)	TMSBr–$Zn(OTf)_2$	5	**7b** (70)
9	**4**	**6b** (2.0)	TMSBr–$Sn(OTf)_2$	23	**7b** (46), **4** (9)[c]
10	**2**	**6c** (2.0)	TMSBr–$ZnBr_2$	14	**7c** (60)
11	**2**	**6d** (2.0)	TMSBr–$ZnBr_2$	26	**7d** (56), **2** (32)[c]
12	**5**	**6c** (2.0)	TMSBr–$ZnBr_2$	4	**8c** (11), **9c** (8), **10c** (1)

a) All reactions were carried out in dichloromethane at reflux temperature using the combination of TMSBr (3.0 eq) and a Lewis acid (2.0 eq) as the activator. *b*) Isolated yield. *c*) The starting material was recovered.

curred and the starting material was recovered, suggesting that the presence of both TMSBr and $ZnBr_2$ is necessary for the glycosidation to proceed. When the α-methyl and α-isopropyl glycosides (**3** and **4**) were used as starting materials, similar reactions occurred to give **7a** in 28 and 59% yields, respectively, although these yields were low compared to that of the α-benzyl glycoside (runs 3 and 4).

We have succeeded in developing a direct glycosidation of dimethyl 3-hydroxyglutarate (**6a**) with simple *O*-glycosides (**1**—**4**) by using the combination of TMSBr and $ZnBr_2$ as a promoter. To ascertain the limits of this method, we then investigated the reactions with one of the other alcohols (**6b**—**d**) as a glycosyl acceptor. The results are summarized in Table I. All reactions resulted in the formation of α-glycosides (**7b**—**d**)[4] in moderate to high yields (runs 5—11). As the amount of the glycosyl acceptor (**6b**) was increased, the yield of the glycosyl product (**7b**) improved from 70 to 85% (runs 6 and 7). Zinc triflate and tin(II) triflate was also found to be effective as the Lewis acid (runs 8 and 9).

We then investigated the glycosidation using D-glucopyranoside (**5**) as a glycosyl donor in order to ascertain whether this methodology was limited to glucosamine derivatives having the nitrogen atom at position 2 or not. When the α-methyl glycoside (**5**) was treated with TMSBr (3.0 eq) and $ZnBr_2$ (2.0 eq) in the presence of hexadecyl alcohol (**6c**), **8c**, **9c** and **10c** were obtained in 11, 8 and 1% yields, respectively, along with several unidentified polar products (run 12).

In summary, a direct glycosidation of alcohols with simple *O*-glycosides such as methyl, isopropyl and benzyl glycosides has been accomplished using the combination of TMSBr and a Lewis acid as a promoter.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in deuteriochloroform on a JEOL GSX 500 spectrometer (500 MHz). Chemical shifts are reported in parts per million relative to tetramethylsilane (δ units) as an internal standard. Optical rotations were measured with a Horiba SEDA 200 polarimeter at 25 °C. Column chromatography was performed with Merck Silica gel 60 (70—230 mesh).

Typical Procedure for the Reaction between Glucosamine Derivatives (1—4) and Alcohols (6a—d) $ZnBr_2$ (214 mg, 0.95 mmol) was added to a solution of **2** (271 mg, 0.47 mmol), **6c** (230 mg, 0.95 mmol) and TMSBr (218 mg, 1.42 mmol) in dichloromethane (10 ml). The reaction mixture was heated under reflux for 14 h. After being cooled, the reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated at reduced pressure. The residue was chromatographed on silica gel (25 g) with hexane–AcOEt (5 : 1) to give **7c** (200 mg, 60%) as a powder. mp 54—55 °C, $[\alpha]_D$ +65.6° (c=1.06, $CHCl_3$). *Anal.* Calcd for $C_{31}H_{52}Cl_3NO_{10}$: C, 52.80; H, 7.43; N, 1.99. Found: C, 52.69; H, 7.24; N, 2.17. IR (KBr): 3400, 2955, 2850, 1730, 1522, 1464, 1389 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t, J=6.84 Hz, CH_3), 1.22—1.36 (26H, m, $CH_2\times13$), 1.62 (2H, m, CH_2), 2.00 (3H, s, CH_3COO), 2.03 (3H, s, CH_3COO), 2.10 (3H, s, CH_3COO), 3.42—3.48 (1H, m, OCH_2), 3.66—3.72 (1H, m, OCH_2), 3.97 (1H, ddd, J=2.20, 4.64, 10.26 Hz, H-5), 4.05 (1H, ddd, J=3.67, 9.77, 10.26 Hz, H-2), 4.10 (1H, dd, J=2.20, 12.21 Hz, H-6), 4.26 (dd, J=4.64, 12.21 Hz, H-6′), 4.65 (1H, d, J=11.97 Hz, CH_2CCl_3), 4.80 (1H, d, J=11.97 Hz, CH_2CCl_3), 4.87 (1H, d, J=3.67 Hz, H-1), 5.10 (1H, t, J=10.26 Hz, H-4), 5.20 (1H, d, J=9.77 Hz, NH), 5.25 (1H, t, J=10.26 Hz, H-3).

Reaction of Methyl Glucopyranoside (5) with Hexadecyl Alcohol (6c) $ZnBr_2$ (333 mg, 1.48 mmol) was added to a solution of **5** (268 mg, 0.74 mmol), **6c** (359 mg, 1.48 mmol) and TMSBr (340 mg, 2.22 mmol) in dichloromethane (20 ml). The reaction mixture was heated under reflux for 4 h. After being cooled, the reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated at reduced pressure. The residue was chromatographed on silica gel (30 g) with hexane–AcOEt (3 : 1) to give **8c** (47 mg, 11%), **10c** (6 mg, 1%) and **9c** (33 mg, 8%), in order of elution.

8c: mp 37—38 °C, $[\alpha]_D$ +93.7° (c=1.14, $CHCl_3$). *Anal.* Calcd for $C_{30}H_{52}O_{10}$: C, 62.91; H, 9.15. Found: C, 62.35; H, 9.52. IR (KBr): 3408, 2924, 2856, 1732, 1522, 1470, 1392 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t, J=6.84 Hz, CH_3), 1.20—1.40 (26H, m, $CH_2\times13$), 1.54—1.62 (2H, m, CH_2), 2.01 (3H, s, CH_3COO), 2.03 (3H, s, CH_3COO), 2.06 (3H, s, CH_3COO), 2.09 (3H, s, CH_3COO), 3.39—3.45 (1H, m, OCH_2), 3.65—3.71 (1H, m, OCH_2), 4.01 (1H, ddd, J=2.44, 4.64, 9.77 Hz, H-5), 4.09 (1H, dd, J=2.44, 12.21 Hz, H-6), 4.25 (dd, J=4.64, 12.21 Hz, H-6′), 4.85 (1H, dd, J=3.66, 9.77 Hz, H-2), 5.02 (1H, t, J=9.77 Hz, H-4), 5.06 (1H, d, J=3.66 Hz, H-1), 5.48 (1H, t, J=9.77 Hz, H-3).

10c: mp 71—73 °C, $[\alpha]_D$ −14.6° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{30}H_{52}O_{10}$: C, 62.91; H, 9.15. Found: C, 62.31; H, 9.47. IR (KBr): 3492, 2924, 2856, 1746, 1472, 1434 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t, J=6.84 Hz, CH_3), 1.20—1.40 (26H, m, $CH_2\times13$), 1.54—1.62 (2H, m, CH_2), 2.01 (3H, s, CH_3COO), 2.03 (3H, s, CH_3COO), 2.04 (3H, s, CH_3COO), 2.09 (3H, s, CH_3COO), 3.44—3.50 (1H, m, OCH_2), 3.69 (1H, ddd, J=2.44, 4.64, 9.53 Hz, H-5), 3.84—3.90 (1H, m, OCH_2), 4.13 (1H, dd, J=2.44, 12.21 Hz, H-6), 4.26 (1H, dd, J=4.64, 12.21 Hz, H-6′), 4.49 (1H, d, J=7.82 Hz, H-1), 4.99 (1H, dd, J=7.82, 9.53 Hz, H-2), 5.09 (1H, t, J=9.53 Hz, H-4), 5.21 (1H, t, J=9.53 Hz, H-3).

9c: mp 38—39 °C, $[\alpha]_D$ +100.9° (c=0.98, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{50}O_9\cdot1/2H_2O$: C, 62.31; H, 9.53. Found: C, 62.52; H, 9.62. IR (KBr): 3436, 2924, 2856, 1746, 1470, 1370 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t, J=6.84 Hz, CH_3), 1.20—1.40 (26H, m, $CH_2\times13$), 1.60—1.67 (2H, m, CH_2), 2.04 (3H, s, CH_3COO), 2.08 (3H, s, CH_3COO), 2.09 (3H, s, CH_3COO), 3.47—3.52 (1H, m, OCH_2), 3.67 (1H, dt, J=3.91, 9.77 Hz, H-2), 3.71—3.76 (1H, m, OCH_2), 3.96 (1H, ddd, J=2.20, 4.64, 9.77 Hz, H-5), 4.07 (1H, dd, J=2.20, 12.21 Hz, H-6), 4.27 (dd, J=4.64, 12.21 Hz, H-6′), 4.91 (1H, d, J=3.91 Hz, H-1), 5.01 (1H, t, J=9.77 Hz, H-4), 5.48 (1H, t, J=9.77 Hz, H-3).

References and Notes

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