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THE BRΦNSTED ACID-CATALYZED *O*-GLYCOSIDATION OF 1-*C*-ALKYL-D- GLUCOPYRANOSE DERIVATIVES

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Abstract – We found that the *O*-glycosidation between various kinds of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyanoses and alcohols in the presence of 5 mol % of trifluoromethanesulfonic acid or bis(trifluoromethane)sulfonimide stereoselectively produced the corresponding 1-*C*-alkyl-α-D-glucopyranosides in good yields.

INTRODUCTION

The 1-*C*-alkyl-sugars, which have alkyl groups at their anomeric carbon centers, are considered as to be a novel class of artificial ketoses which replace naturally occurring aldoses. Their glycosylated compounds (1-*C*-alkyl-glycosides) are expected to show biological functions different from those of natural compounds.[1] Therefore, considerable attention has been paid to the useful glycosidation methods for synthesizing the 1-*C*-alkyl-*O*-glycosides.[2]

Several kinds of 1-*C*-alkyl-*O*-D-hexopyranosides were synthesized by the glycosidation of the corresponding 1-*C*-alkyl-hexopyranose derivatives with alcohols.[3] However, few successful catalytic glycosidation examples have been reported. Our recent synthetic studies of the 1-*C*-alkyl-D-glucopyranosides have succeeded in the catalytic glycosidation of 1-*C*-alkyl-D-glucopyranosyl acetates with alcohols.[4] The glycosidation reaction was efficiently catalyzed by only 5 mol % scandium (III) trifluoromethanesulfonate to afford 1-*C*-alkyl-D-glucopyranosides. Under the method, the hydroxyl group on the anomeric centers of the 1-*C*-alkyl-D-glucopyranoses was acetylated using butyllithium and acetic anhydride in THF, and the acetyloxy group operated as a good

leaving group for the glycosidation.

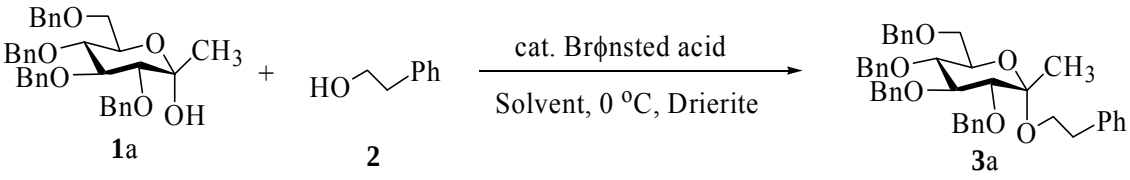
Our next interest focused on a more convenient method for producing 1-*C*-alkyl-D-glucopyranosides by the direct glycosidation of the 1-*C*-alkyl-D-glucopyranoses without introducing leaving groups into the glycosyl donors. We attempted the dehydration-condensation type glycosidation using a catalytic amount of Brϕnsted acids, which were potentially resistant to water. Two glycosidation approaches were investigated using the 1-*C*-alkyl-D-hexopyranoses as the glycosyl donors. The first one is the intramolecular β-glycosidation of 1-*C*-alkyl-D-hexopyranoses using 5 mol% trifluoromethanesulfonic acid (TfOH) to produce the β-anhhydroketopyranoses having 6,8-dioxabicyclo[3.2.1]octane structures.[5] The second one, which we describe in this paper, is the intermolecular glycosidation between the 1-*C*-alkyl-D-glucopyranoses and alcohols using catalytic amounts of Brϕnsted acids.

In order to establish a convenient glycosidation method for producing 1-*C*-alkyl-*O*-hexopyranosides and increase their utilizations in synthetic carbohydrate chemistry, we investigated the Brϕnsted acid-catalyzed glycosidation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses[4] as the glycosyl donors.

RESULTS AND DISCUSSION

We first used 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranose (**1**a) as the glycosyl donor and phenethyl alcohol (**2**) as the glycosyl acceptor. When 5 mol% of the Brϕnsted acids, such as camphorsulfonic acid, trifluoroacetic acid (CF_3CO_2H) and TfOH were used in dichloromethane at 0 °C in the presence of the dry agent, Drierite (anhydrous $CaSO_4$), only TfOH could effectively activate the glycosidation to give the desired phenethyl ketopyranoside (**3**a)[4] in 59% yield with an α-stereoselectivity.[6] The use of acetonitrile as the solvent slightly increased the yield of **3**a up to 73%. Heptadecafluorooctanesulfonic acid ($C_8F_{17}SO_3H$) and bis(trifluoromethane)sulfonimide (Tf_2NH) as the Brϕnsted acid analogs of TfOH, and tetrafluoroboric acid (HBF_4) were similarly effective for the activation of **1**a under similar reaction conditions. Particularly, Tf_2NH gave **3**a in the maximum yield of 77%. Although 10 mol% Tf_2NH hardly increased the yield of **3**a, the reaction using even 1 mol% Tf_2NH gave **3**a in 56% yield. These results are summarized in Table 1.

Next, we investigated the glycosidation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-ethyl-α-D-glucopyranose (**1**b),



Scheme 1

Table 1. The investigation of glycosidation conditions between **1**a and **2**.

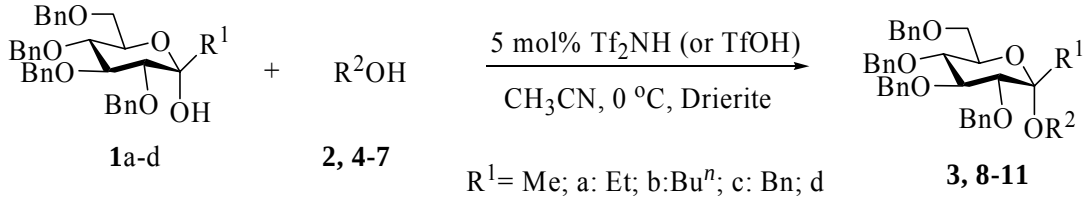
Entry[a]	Brϕnsted acid (Mol%)	Solvent	Yield (%)
1	Camphorsulfonic acid (5)	CH_2Cl_2	No reaction
2	CF_3CO_2H (5)	CH_2Cl_2	No reaction
3	TfOH (5)	CH_2Cl_2	59
4	TfOH (5)	CH_3CN	73
5	$C_8F_{17}SO_3H$ (5)	CH_3CN	56
6	Tf_2NH (5)	CH_3CN	77
7	HBF_4 (5)	CH_3CN	73
8	Tf_2NH (10)	CH_3CN	69
9	Tf_2NH (3)	CH_3CN	65
10	Tf_2NH (1)	CH_3CN	56

[a]Molar ratio; **1**a: **2**= 1:1. Reaction time; 2 h.

2,3,4,6-tetra-*O*-benzyl-1-*C*-*n*-butyl-α-D-glucopyranose (**1**c) and 1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**d) with **2** in acetonitrile at 0 °C using 5 mol% of Tf_2NH in order to investigate how the difference in the alkyl groups at the anomeric carbon centers would influence the reactivity and stereoselectivity of the glycosidation. The corresponding α-ketopyranosides (**3**b-d)[4] were stereoselectively obtained in the yields from 56% to 64%. These results indicated that the difference in the alkyl groups at the anomeric carbon centers of **1**a-d had almost no influence on the glycosidation reactivity and stereoselectivity. This finding was in agreement with our former observation regarding the glycosidation using 1-*C*-alkyl-α-D-glucopyranosyl acetates as the glycosyl donors.[4]

Furthermore, we examined the glycosidation of **1**a (or **1**d) with various alcohols (**4**-**7**) in acetonitrile at 0 °C using 5 mol% Tf_2NH or TfOH. The desired octyl ketopyranoside (**9**a) and disaccharides (**8**a, **10**a and **11**d) were similarly obtained in good yields with single isomers. The anomeric configurations of all the ketopyranosides were determined to be α by the observations of the NOE interactions between H-2 and H-1' of the alkyl groups of the 1-*C*-alkyl-D-glucopyranosyl rings. Interestingly, even when the anomeric mixture of **6** was used, the trehalose analogue (**10**a), the product by the reaction of **1**a with **6**, was obtained as a single isomer by the measurement of the NMR spectrum. In the ^{1}H-NMR spectrum of **10**a, the anomeric proton of the glucopyranosyl residue was observed at 5.34 ppm with a doublet peak (*J* 3.4 Hz) and the value of the coupling constant indicated α. This suggested that the glycosidation strictly recognized the anomeric stereochemistry of the acceptor (**6**) and only the α isomer of **6** operated as the glycosyl acceptor. These results are summarized in Table 2.

In summary, we have successfully developed a convenient Brϕnsted acid-catalyzed glycosidation using 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses, and found that only 5 mol% of Tf_2NH or TfOH efficiently promoted the glycosidation to afford the 1-*C*-alkyl-D-glucopyranosides in good yields with α-stereoselectivities. We are now applying the glycosidation system to the synthesis of natural products and their analogs.



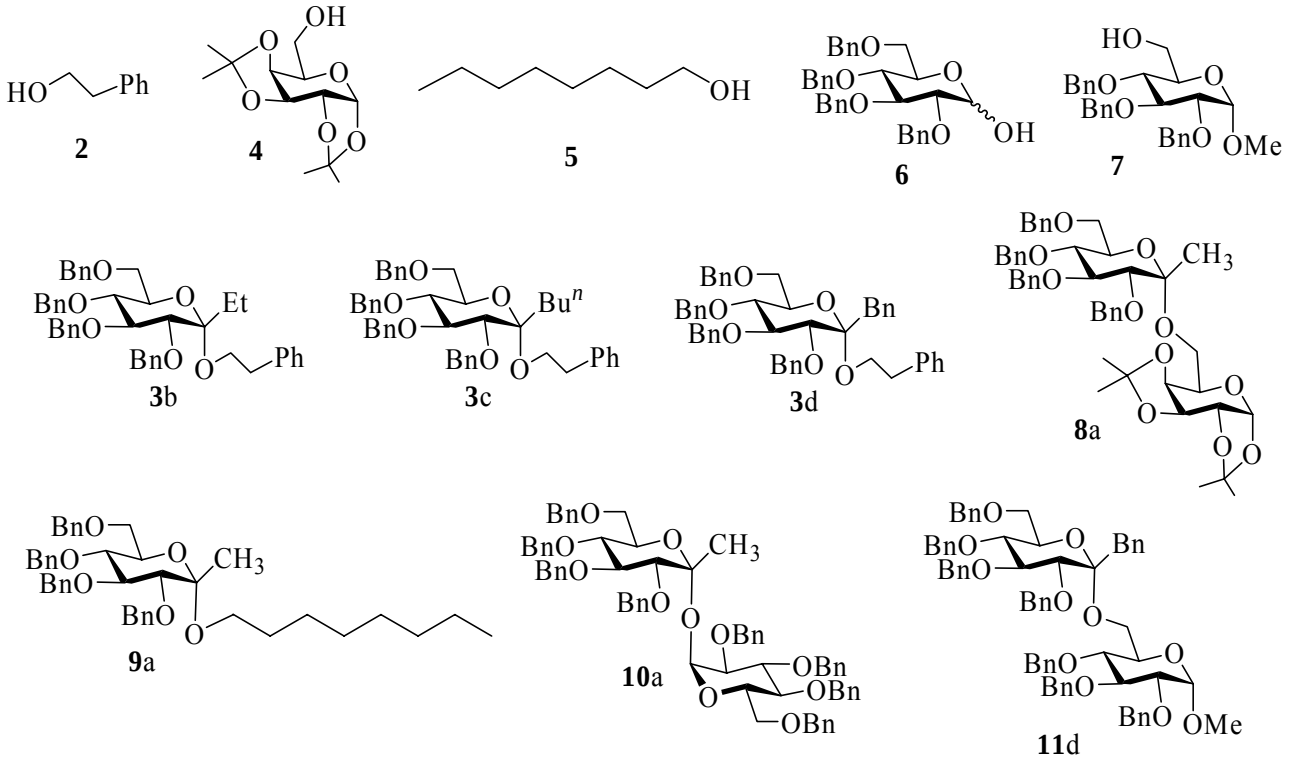
1a-d **2, 4-7** R^1= Me; a: Et; b:Bu^n; c: Bn; d **3, 8-11**

Scheme 2

Table 2. The glycosidation of several 1-*C*-alkyl-glucopyranoses with various alcohols.

Entry[a]	1-C-Alkyl-glucopyranose	Alcohol	Product	Yield (%)
1	**1**a	**2**	**3**a	77
2	**1**b	**2**	**3**b	57
3	**1**c	**2**	**3**c	64
4	**1**d	**2**	**3**d	56
5[b]	**1**a	**4**	**8**a	55
6	**1**a	**5**	**9**a	78
7[b]	**1**a	**6**	**10**a	47
8[b,c]	**1**d	**7**	**11**d	66

[a]Molar ratio; 1-C-alkyl-glucopyranose: alcohol: Tf_2NH= 1:1: 0.05. Reaction time; 2 h. [b]Molar ratio; 1-C-alkyl-glucopyranose: alcohol: Tf_2NH = 1.5:1: 0.075. Reaction time; 3 h. [c]TfOH was used.



REFERENCES AND NOTES

1. For example, a) M. Brockhaus and J. Lehmann, *Carbohydr. Res.*, 1977, **53**, 21; b) P. Schlesselmann, H. Fritz, J. Lehmann, T. Uchiyama, C. F. Brewer, and E. J. Hehre, *Biochemistry*, 1982, **21**, 6606.
2. X. L. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Synlett*, 2001, 1885.

3. References were cited in Ref. 4.
4. T. Yamanoi, Y. Oda, I. Yamazaki, M. Shinbara, K. Morimoto, and S. Matsuda, *Lett. Org. Chem*., 2005, **2**, 242.
5. T. Yamanoi, K. Matsumura, S. Matsuda, and Y. Oda, *Synlett*, 2005, 2973.
6. A typical glycosidation procedure is as follows: To a stirred solution of Tf_2NH (2.8 mg, 0.01 mmol) and **2** (24 mg, 0.2 mmol) in acetonitrile was added **1**a (111 mg, 0.2 mmol) at 0 °C in the presence of Drierite (ca. 100 mg). The resulting mixture was stirred for 2 h. The reaction was then quenched by the addition of a sat. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a sat. NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **3**a as a colorless oil (102 mg, 77%). **9**a, **10**a, and **11**d were new compounds and their spectral data are described as follows. Compound (**9**a): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.9 Hz, H-8'), 1.27~1.30 (13H, m, CH_3, H-3', H-4', H-5', H-6', and H-7'), 1.55~1.63 (2H, m, H-2'), 3.32 (1H, d, *J*=9.6 Hz, H-2), 3.41 (2H, dd, *J*=6.9 Hz, *J*=7.6 Hz, H-1'), 3.62 (1H, dd, *J*=9.6 Hz, *J*=8.6 Hz, H-4), 3.63~3.72 (3H, m, H-5, H-6a and H-6b), 4.08 (1H, dd, *J*=9.6 Hz, *J*=8.9 Hz, H-3): ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-8'), 21.0 (CH_3), 22.7, 26.3, 29.3, 29.4, 29.7 (C-2'), 31.8, 60.8 (C-1'), 68.9 (C-6), 71.4 (C-5), 78.8 (C-4), 83.2 (C-3), 84.1 (C-2), 100.2 (C-1). Compound (**10**a): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.49 (3H, s, CH_3), 3.29 (1H, d, *J*=9.6 Hz, H-2'), 3.33~3.39 (3H, m, H-6a, H-6b and H-6'a), 3.55~3.58 (1H, m, H-6'b), 3.56 (1H, dd, *J*=10.3 Hz, *J*=3.4 Hz, H-2'), 3.64 (1H, dd, *J*=9.6 Hz, *J*=10.3 Hz, H-4), 3.68 (1H, t, *J*=9.6 Hz, H-4'), 4.03 (1H, t, *J*=10.3 Hz, H-3), 4.05 (1H, t, *J*=9.6 Hz, H-3'), 4.17~4.19 (1H, m, H-5'), 4.29~4.28 (1H, m, H-5), 5.34 (1H, d, *J*=3.4 Hz, H-1'): ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.7 (CH_3), 68.3 (C-6'), 68.5 (C-6), 70.0 (C-5'), 71.0 (C-5), 78.0 (C-4'), 78.6 (C-4), 80.1 (C-2'), 81.8 (C-3), 82.7 (C-3'), 85.1 (C-2'), 90.2 (C-1'), 101.0 (C-1). Compound (**11**d): ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.95 (1H, d, *J*=14.4 Hz, $CC\underline{H}_a H_bPh$), 3.14 (1H, d, *J*= 13.7 Hz, $CCH_a\underline{H}_bPh$), 3.19 (1H, d, *J*=9.6 Hz, H-2'), 3.33 (1H, dd, *J*=8.9 Hz, *J*=9.6 Hz, H-3), 3.36 (3H, s, OMe), 3.47 (1H, t, *J*=9.6 Hz, H-4'), 3.46~3.52 (2H, m, H-2 and H-6a), 3.63 (1H, d, *J*=11.0 Hz, H-6'a), 3.69 (1H, dd, *J*=3.4 Hz, *J*=11.0 Hz, H-6'b), 3.86~3.90 (3H, m, H-5, H-5' and H-6b), 3.98 (1H, t, *J*=8.9 Hz, H-4), 4.05 (1H, dd, *J*=8.9 Hz, *J*=9.6 Hz, H-3'), 4.56~4.59 (2H, m, H-1 and $OC\underline{H}_aH_bPh$): ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.7($C\underline{C}H_2Ph$), 55.0 (OMe), 60.6 (C-6), 69.1 (C-6'), 70.3, 71.8, 78.6 (C-4'), 78.7 (C-3), 79.8 (C-2'), 80.2 (C-2), 82.3 (C-4), 83.4 (C-3'), 97.6 (C-1), 102.4 (C-1').