Glycosyl 6-Nitro-2-benzothiazoate. A Highly Efficient Donor for β-Stereoselective Glycosylation

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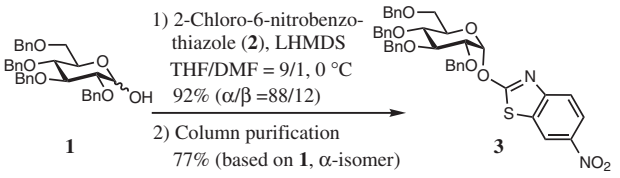
Highly β-stereoselective glycosylations of glycosyl acceptors having a primary hydroxyl group by using a novel glycosyl donor, α-glycosyl 6-nitro-2-benzothiazoate (**3**), proceeded smoothly in the presence of a catalytic amount of trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 at −78 °C to afford the corresponding glycosides in high yields. The donor **3** gave β-saccharides more dominantly compared with those using other α-glycosyl donors such as thioform- and trichloroacet-imidates or fluoride under the same conditions.

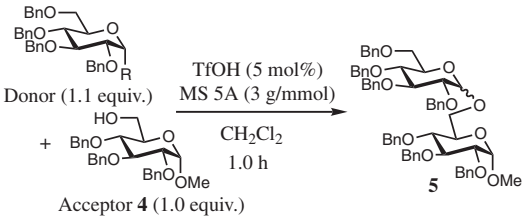
To develop a new method for stereoselective glycosylation is one of the most important and fundamental topics in carbohydrate chemistry.[1] Various combinations of glycosyl donors and activators have been studied during past two decades, which were successfully applied to the syntheses of various saccharides. Recently, glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate was newly reported from our laboratory.[2–4] The above donor, purified easily by recrystallization, led catalytic and highly stereoselective glycosylation to proceed quite smoothly to give either α- or β-saccharides in high yields by choosing suitable solvents and counter anions of the catalysts. Continuously, development of a newer donor having a characteristically similar leaving group, glycosyl 6-nitro-2-benzothiazoate (**3**), was planned. Since a readily available glycosyl benzothiazoate contains a moiety [–O–C(=NR^1)–SR^2] which is activated easily by Lewis or protic acids, **3** was expected to behave as a useful donor in the glycosylation. In this communication, we would like to report on an efficient β-stereoselective glycosylation[5] with the glycopyranosyl donor **3** using trifluoromethanesulfonic acid (TfOH) catalyst.[1–4,6]

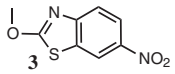
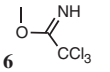
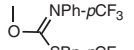


Scheme 1. Synthesis of the glycosyl benzothiazoate.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl 6-nitro-2-benzothiazoate(**3**) was easily prepared by a direct condensation reaction between anomeric hydroxyl group of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside(**1**) and 2-chloro-6-nitrobenzothiazole(**2**).[7] The reaction smoothly proceeded at 0 °C to give a mixture of glycosyl 6-nitro-2-benzothiazoates in 92% chemical yield ($\alpha/\beta = 88/12$). Each isomer of α- or β-one was separated and purified by silica gel chromatography and α-**3** was obtained in 77% and β-one in 7% based on **1** (Scheme 1). It was noted that a glycosyl donor having nonsubstituted benzothiazole was too labile and was partly hydrolyzed during the work-up procedure. This result indicated that it was the nitro group, an electron-withdrawing substituent, that contributed to the increase in stability of **3**.

Table 1. Glycosylation using various donors using TfOH as a catalyst



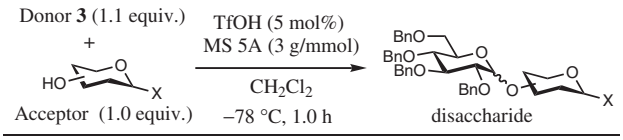
Entry	Donor (R)	Temp. / °C	Yield /% (α/β)[a]
1		0	97 (31/69)
2	**3**	–78	91 (4/96)
3		0	99 (56/44)
4	**6**	–78	98 (8/92)
5[b]		0	98 (66/34)
6[b]	**7**	–78	97 (43/57)
7		0	96 (57/43)
8	**8**	–78	Not detected

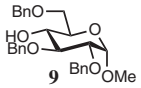
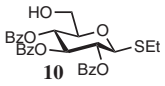
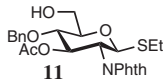
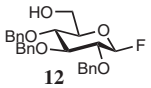
[a]The α/β ratios were determined by HPLC analysis.
[b]These results were previously reported in reference 3.

It was generally known that the reactivities and stereoselectivies of glycosylations using conventional donors were influenced considerably by the properties of donors, catalysts and solvents. In the first place, glycosylation of a glycosyl acceptor **4** with **3** in the presence of 5 mol% of TfOH in CH_2Cl_2, nonpolar solvent, was tried under the conditions previously reported[3] (Table 1). The glycosylation proceeded smoothly to afford the corresponding disaccharides **5** in high yield with β-stereoselectivity (Entry 1, $\alpha/\beta = 31/69$) at 0 °C. Interestingly, the β-stereoselectivity of the present glycosylation was higher compared with that of using a donor **7** which afforded the disaccharide in moderate α-stereoselectivity ($\alpha/\beta = 66/34$) under the same conditions (Entry 5) shown in our previous report.[3] Though the similar moieties [–O–C(=NR^1)–SR^2] were involved in the above two donors, **3** and **7**, it was noteworthy that the above two

glycosylations afforded the saccharides with reversed stereoselectivities (Entries 1 and 5). The donor **3** also gave the saccharides in a more highly β-stereoselective manner than α-glycosyl trichloroacetimidate[8] (**6**) did at 0 °C (Entries 1 and 3). The α-glycosyl fluoride (**8**), a less reactive donor compared with the above imidate donors, reacted with acceptor **4** to afford the glycosides in moderate α-stereoselectivity (Entry 7). These results evidently showed that the glycosylation reaction of α-**3** gave β-anomer more predominantly than those using **6**, **7** and **8** under the above mentioned conditions. On the other hand, the highest β-stereoselectivity ($\alpha/\beta = 4/96$) was also performed (Entry 2) when the donor **3** was allowed to react at −78 °C.

Table 2. Glycosylation of various acceptors



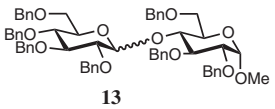
Entry	Acceptor	Product	Yield /% (α/β)[a]
1	 **9**	**13**	80 (27/73)[b, c]
2	 **10**	**14**	98 (9/91)
3	 **11**	**15**	90 (9/91)
4	 **12**	**16**	89 (7/93)[d]

[a]The α/β ratios were determined by HPLC analysis.

[b]The reaction was carried out for 4 h.

[c]**13** was obtained in 56% yield (α/β = 50/50) when **6** was used instead of **3**.

[d]The α/β ratio was determined by isolated yields of both isomers.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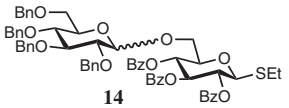
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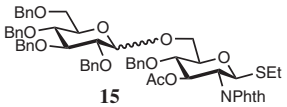
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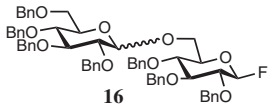
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Next, in order to extend the scope of the present reaction, β-stereoselective glycosylation of various glycosyl acceptors **9** containing a hindered secondary hydroxyl group, thioglycoside **10**, **11** and glycosyl fluoride **12** with **3** were tried (Table 2). In all cases that used glycosyl acceptors having primary hydroxyl group, the desired disaccharides were obtained in high yields with high β-stereoselectivities; however, a moderate β-stereoselectivity was observed ($\alpha/\beta = 27/73$) (Entry 1) in the case of glycosylation using **9**. The donor **3**, α-glycosyl 6-nitro-2-benzothiazoate, gave the β-saccharide more dominantly compared with α-glycosyl trichloroacetimidate **6** even when the hindered acceptor **9** was used (56%, $\alpha/\beta = 50/50$). Furthermore, chemoselective glycosylations using ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**10**), ethyl 3-*O*-acetyl-*O*-4-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**11**) or 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl fluoride (**12**) as acceptors gave good results also without giving any damage to thio- or fluoro-linkage, respectively (Entries 2, 3 and 4).

The typical experimental procedure is as follows: to a stirred suspension of MS 5A (150 mg), **3** (39.5 mg, 0.055 mmol) and **4** (23.2 mg, 0.050 mmol) in CH_2Cl_2 (1.25 mL) was added TfOH (0.38 mg, 2.5 µmol) in toluene (0.05 mL) at −78 °C. After the reaction mixture was stirred for 1 h at the same temperature, it was quenched by adding saturated $NaHCO_3$. The mixture was filtered through Celite and extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over Na_2SO_4. After being filtered and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **5** (44.9 mg, 91%, $\alpha/\beta = 4/96$).

The donor **3** enabled the glycosylation to achieve higher β-stereoselectivity in CH_2Cl_2 than donors **6**, **7** or **8** when a catalytic amount of TfOH was used. These results imply that glycosyl benzothiazoate has a potent feature of constructing the stereoselective β-saccharide linkage without using the neighboring effect of *O*-2-acyl protecting group. Further application of this glycosyl benzothiazoate donor to other sugars, such as β-mannoside and β-2-deoxy-glycoside,[1] is now in progress.

It should be noted, on the other hand, that the highly α-stereoselective glycosylation of **4** with **3** at 0 °C can be successfully carried out to afford **5** in high yield (88%, $\alpha/\beta = 88/12$) using a properly selected combination of catalyst and solvent[9] (20 mol% of $HClO_4$ in ^{t}BuOMe).

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References and Notes

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7 2-Chloro-6-nitrobenzothiazole (**2**) was prepared by the nitration (*conc.* HNO_3 and *conc.* H_2SO_4) of 2-chlorobenzothiazole according to the literature method. K. Akasaka, A. Kajiwara, S. Nagato, Y. Iimura, I. Yoshida, A. Sasaki, M. Mizuno, A. Kubota, T. Kagaya, and M. Komatsu, W. O. Patent 9308179 (1993).
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9 H. Jona, H. Mandai, W. Chavasiri, K. Takeuchi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **75**, 291 (2002), and related references are also herein.