Highly α-Selective Glycosylation with Glycopyranosyl Fluorides Having Diethylthiocarbamoyl Group

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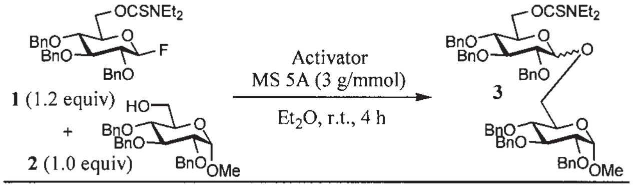
Highly α-selective glycosylation of various glycosyl acceptors with glucopyranosyl fluoride having diethylthiocarbamoyl group at 6-position or galactopyranosyl fluoride having the same group at 4-position proceeded smoothly in the presence of a catalytic amount of protic acid to afford the corresponding disaccharides in high yields.

To develop a new method for stereoselective glycosylation is one of the most important and fundamental topics in carbohydrate chemistry.[1] Especially, general methods for stereoselective syntheses of 1,2-cis-α-glycosides still remain unestablished because so-called neighboring effect participation from C(2)-position can not be utilized. Recently, it was demonstrated from our laboratory that TfOH or $HClO_4$ catalyzed α-selective glycosylation with glycosyl fluoride gave a good result by using Et_2O as a solvent.[2] However, the α-stereoselectivity was not satisfactory enough for the synthesis of complex oligosaccharides. In the meantime, stereoselective syntheses of 2-deoxyribonucleosides by using remote participation of diethylthiocarbamoyl protecting group at 3- or 5-position was reported from our laboratory in 1996.[3] The above result prompted us to study on the stereoselective synthesis of α-glycopyranosides by way of remote participation from β-face by the protecting group. In this communication, we would like to report on a highly α-selective glycosylation with glucopyranosyl fluoride having diethylthiocarbamoyl group at 6-position or galactopyranosyl fluoride having the same group at 4-position in the presence of a catalytic amount of TfOH or $HClO_4$ to afford the corresponding disaccharides in high yields.

In the first place, effects of various catalysts or promoter were examined by taking the reaction of 2,3,4-tri-*O*-benzyl-6-*O*-diethylthiocarbamoyl-β-D-glucopyranosyl fluoride (**1**)[4] with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**) as a model (Table 1). It was made clear that a catalytic amount of TfOH or $HClO_4$ (Table 1, Entries 3 and 4) effectively activated glycosyl fluoride to afford the corresponding disaccharide in high yield with high α-selectivity whereas the results were good to moderate when the other catalysts were used. Then, the glycosylation of several acceptors with various donors was further studied by using TfOH or $HClO_4$ in a catalytic amount each.

Next, effects of various solvents on stereoselectivity were examined (Table 2). In every case, higher α-selectivity was observed when donor **1** was used in comparison to the cases using donor **4**, having benzyl group at 6-position. This result indicated that the remote participation of diethylthiocarbamoyl group from 6-position to anomeric position would expectedly affect the generation of the key intermediate **A** in any solvent. Especially, highest α-selectivity was observed when the reaction was carried out in Et_2O.

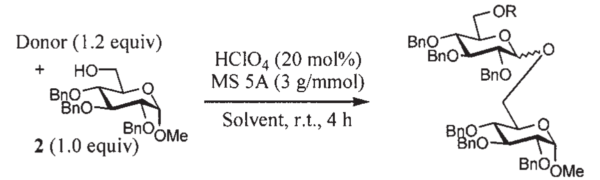
Table 1. Effect of catalyst



Entry	Activator (mol% based on acceptor)	Yield /% (α / β)[a]
1	$SnCl_2 + AgClO_4$ (100)[5]	81 (93 / 7)
2	$TrB(C_6F_5)_4$ (20)[6]	33 (96 / 4)
3	TfOH (20)[2]	quant. (95 / 5)
4	$HClO_4$ (20)[2]	89 (97 / 3)
5	$HNTf_2$ (20)[2]	59 (87 / 13)
6	$HB(C_6F_5)_4$ (20)[2]	77 (91 / 9)

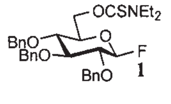
[a]The α / β ratios were determined by HPLC analysis.

Table 2. Effect of the solvent



Entry	Solvent	Yield /% (α / β)[a]	Yield /% (α / β)[b]
1	Et_2O	89 (97 / 3)	98 (92 / 8)
2	CH_2Cl_2	27 (90 / 10)	85 (71 / 29)
3	toluene	91 (87 / 13)	78 (68 / 32)
4	BTF[c]	57 (91 / 9)	82 (67 / 33)
5	^{t}BuCN	50 (88 / 12)	89 (50 / 50)

[a]**1** was used as a glycosyl donor. [b]**4** was used as a glycosyl donor. [c]BTF = trifluoromethylbenzene



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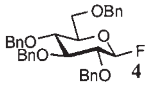

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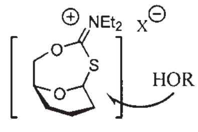
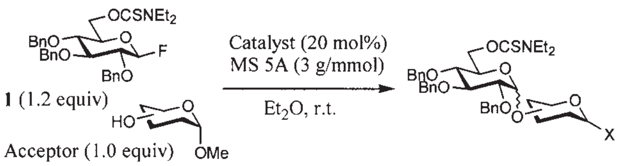


A

Further, the acceptors **5** and **6** having secondary alcohol and the acceptor **7** having ethylthio group at the reducing end were examined (Table 3). In all cases, the corresponding disaccharides were obtained in good to high yields with higher α-selectivities compared to those using donor **4**.[2,7,8] When $HClO_4$ was used as a catalyst in the above glycosylation, the stereoselectivities slightly increased while the yields decreased in comparison with those using TfOH.

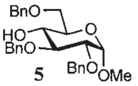
Then, the present glycosylation condition using a catalytic

Table 3. Glycosylation using TfOH or $HClO_4$ as a catalyst



Entry	Acceptor	Catalyst	Time	Yield /% (α / β)[a]
1	**5**	TfOH	8	84 (91 / 9)
2	**5**	$HClO_4$	12	59 (94 / 6)
3	**6**	TfOH	4	95 (88 / 12)
4	**6**	$HClO_4$	4	83 (94 / 6)
5	**7**	TfOH	4	quant. (91 / 9)
6	**7**	$HClO_4$	8	86 (94 / 6)

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



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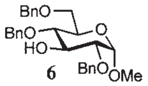

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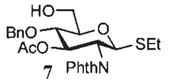

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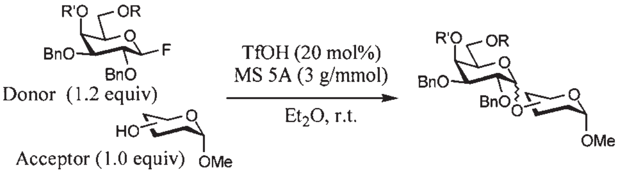
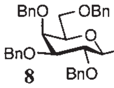
Table 4.



Entry	Donor	Acceptor	Time	Yield /% (α / β)
1	**8**	**2**	1.5	95 (83 / 17)
2	**9**	**2**	1.5	92 (76 / 24)
3	**10**	**2**	1.5	97 (>99 / 1)
4	**8**	**5**	5	87 (90 / 10)
5	**9**	**5**	6	95 (80 / 20)
6	**10**	**5**	4	90 (>99 / 1)



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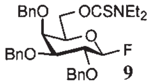

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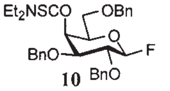

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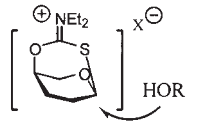

B

amount of TfOH in Et_2O was applied to the galactopyranosyl fluorides **9**[4] and **10**[4] having diethylthiocarbamoyl group at 6- or 4-position (Table 4).[9] Glycosylation with donor **9** having diethylthiocarbamoyl group at 6-position took place to give disaccharides in high yields but with poorer α-selectivities compared to those using donor **8** having perbenzyl protecting groups (Entries 1, 2, 4 and 5). This result indicates that the remote participation by diethylthiocarbamoyl group at 6-position might not work well because it was hard to form the key intermediate **A** due to axial oriented C(4)-subsituent. On the other hand, a perfect α-stereoselectivity was observed when the donor **10** was used in the present glycosylation where the remote participation of diethylthiocarbamoyl group from 4-position to anomeric position would take place effectively to form the key intermediate **B**, which afforded the corresponding disaccharides with almost perfect stereoselectivities (Entries 3 and 6). Similar result has been shown by G.-J. Boons *et al.* that the glycosylation with galactosyl thioglycoside having *p*-methoxybenzoyl group at 4-position was effectively carried out by using IDCP or the combination of NIS and a catalytic amount of TMSOTf to afford the corresponding disaccharide in a good yield with almost perfect α-stereoselectivity.[10]

Thus, highly α-selective glycosylation with gluco- and galactopyranosyl fluorides is established by introducing diethylthiocarbamoyl protecting group to hydroxy group at an appropriate position. Further, it was previously reported from our laboratory[3] that the diethylthiocarbamoyl group could be removed selectively by successive treatments with *m*CPBA and with aqueous NH_3 to afford the corresponding alcohols in high yields even when TBS, Bn protecting groups and ester function were contained in the same molecule.

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References and Notes

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4 Glycosyl fluorides **1**, **9** and **10** were synthesized by 3 steps procedure from the corresponding methyl 2,3,4- or 2,3,6-tri-*O*-benzyl glycopyranosides as follows; 1) diethylthiocarbamoyl chloride, NaH / THF, 2) 2M-H_2SO_4 / AcOH, 130 °C, 3) DAST / THF, $-35\,^{\circ}C \sim$ r.t.

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6 K. Takeuchi and T. Mukaiyama, *Chem. Lett.*, **1998**, 555.

7 Similar effect was reported on α-preferential glycosylation with glucopyranosyl fluoride having 2,2,2-trichloroethoxycarbonyl group at 6-position: K. Fukase, T. Yoshimura, S. Kotani, and S. Kusumoto, *Bull. Chem. Soc. Jpn.*, **67**, 473 (1994).

8 There are some reports describing that highly α-selective glycosylations were carried out by using other glucosyl donors having the following protecting groups at 6-position; that is, trityl, *t*-butyldiphenylsilyl, 2,2,2-trichloroethoxycarbonyl and phenylcarbamoyl groups: S. Houdier and P. J. A. Vottero, *Carbohydr. Res.*, **232**, 349 (1992) (thioglycoside); G.-J. Boons, S. Bowers, and D. M. Coe, *Tetrahedron Lett.*, **38**, 3773 (1997) (thioglycoside); K. Fukase, Y. Nakai, T. Kanoh, and S. Kusumoto, *Synlett*, **1998**, 84 (thioglycoside); H. Tanaka, H. Sakamoto, A. Sano, S. Nakamura, M. Nakajima, and S. Hashimoto, *Chem. Commun.*, **1999**, 1259 (glycosyl phosphite); T. Nakagawa, K. Ueno, M. Kashiwa, and J. Watanabe, *Tetrahedron Lett.*, **35**, 1921 (1994) (thioglycoside).

9 When $HClO_4$ was used as a catalyst, the desired disaccharides were obtained in lower yields compared with those using TfOH.

10 A. V. Demchenko, E. Rousson, and G.-J. Boons, *Tetrahedron Lett.*, **40**, 6523 (1999).