Stereoselective Glycosylation of Thioglycosides Promoted by Respective Combinations of *N*-Iodo- or *N*-Bromosuccinimide and Trityl Tetrakis(pentafluorophenyl)borate. Application to One-Pot Sequential Synthesis of Trisaccharide

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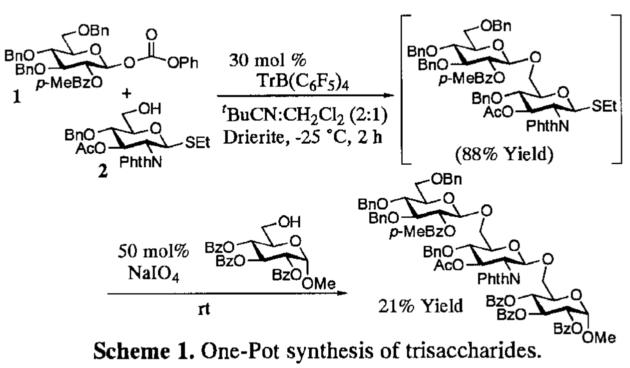
New highly effective promoter system for the glycosylation of thioglycoside, the combined use of stoichiometric amount of either *N*-iodosuccinimide or *N*-bromosuccinimide and a catalytic amount of $TrB(C_6F_5)_4$, was developed and was successfully applied to the one-pot sequential synthesis of trisaccharides. In the first glycosylation step, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-toluoyl-β-D-glucopyranosyl phenylcarbonate was treated with thioglycosides in the presence of a catalytic amount of $TrB(C_6F_5)_4$ alone, and the following glycosylation with methyl α-D-glycosides was carried out by further addition of either *N*-iodosuccinimide or *N*-bromosuccinimide to the initially resulted reaction mixture to afford the corresponding trisaccharides in one-pot manner.

Developments in new strategies and tactics of oligosaccharide synthesis are of growing importance and many examples are reported; for example, armed–disarmed, two-stage activation, active–latent, orthogonal, one-pot multistep and solid-phase glycosylation reactions and so on.[1] A one-pot sequential glycosylation method[2] is among the most promising strategies for the synthesis of polysaccharides because of its simplicity in preparing saccharide blocks.

In our previous paper,[3] a one-pot synthesis of trisaccharides by the combination of two types of $TrB(C_6F_5)_4$–catalyzed glycosylation reactions to form trisaccharide composed of three glucoses, Glcβ1-6Glcβ1-6Glc, was reported. In the preceding communication,[4] detailed conditions for glycosylation reaction using glycosyl phenylcarbonate were presented and now we would like to report the improved one-pot sequential glycosylation reactions of forming various trisaccharides including those containing 2-amino-2-deoxy sugar by promotion of $TrB(C_6F_5)_4$ catalyst.



Scheme 1. One-Pot synthesis of trisaccharides.

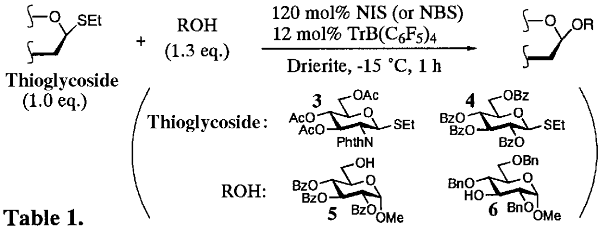


Table 1.

Entry	Donor/Acceptor	Solvent	Yield /%
1	**3** / **5**	^{t}BuCN:CH_2Cl_2 (2:1)	95
2[a]	**3** / **5**	CH_2Cl_2	95
3	**3** / **6**	CH_2Cl_2	85
4[a]	**3** / **6**	CH_2Cl_2	92
5	**4** / **5**	CH_2Cl_2	94
6[a]	**4** / **5**	CH_2Cl_2	93
7	**4** / **6**	CH_2Cl_2	79
8[a]	**4** / **6**	CH_2Cl_2	69

[a] NBS was used instead of NIS.

In the first place, the one-pot sequential glycosylation was attempted according to the reactions shown in Scheme 1. 2-*O*-*p*-Toluoyl protected glucosyl phenylcarbonate (**1**) reacted with thioglycoside (**2**) to afford the corresponding disaccharide in high yield as was shown in the preceding paper.[4] Then the second glycosylation was carried out by adding $NaIO_4$ and glycosyl acceptor to the reaction mixture. However, the desired trisaccharide was obtained in only 21% yield since cleavege of the initially formed glycosidic bond occurred during the second glycosylation step at room temperature. In order to overcome these problems, the development of more effective method for glycosylation of thioglycosides was studied and the combined use of *N*-iodosuccinimide (NIS) and $TrB(C_6F_5)_4$ gave satisfactory results. The NIS–triflic acid system[5] was well known to activate thioglycosides effectively. After that, several Lewis acids such as Et_3SiOTf or AgOTf were used[6] together with NIS as promoters. It was assumed that I^+-$B(C_6F_5)_4^-$, highly thiophilic iodonium cation, was generated in situ by combined use of NIS and $TrB(C_6F_5)_4$. In the present experiment, it was shown that the glycosylation proceeded very rapidly even at -15 °C by using a combination of NIS and $TrB(C_6F_5)_4$ to give the desired glycoside in high yield as shown in Table 1 (Entry 1,3,5,7). In addition, it was observed that the above reaction was also promoted by using *N*-bromosuccinimide (NBS), a cheaper and stabler compound than NIS. Actually, the NBS-$TrB(C_6F_5)_4$ system turned out quite effective to afford several disaccharides in good to high yields as shown in Table 1 (Entry 2,4,6,8).[7]

Finally, the improved one-pot sequential glycosylation was tried based on the above experiments. In the first step, **1** was treated with ethyl thioglycosides (**2**, **7**, **8**) in the presence of a catalytic amount of $TrB(C_6F_5)_4$ alone, and almost complete consumption of thioglycosides was confirmed by TLC

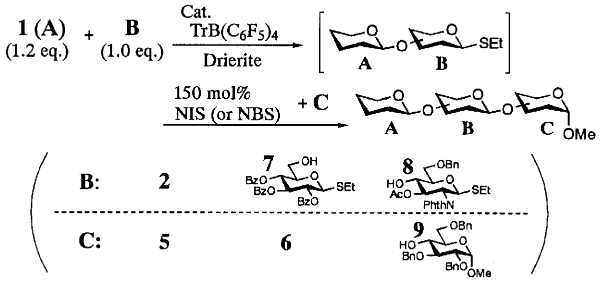
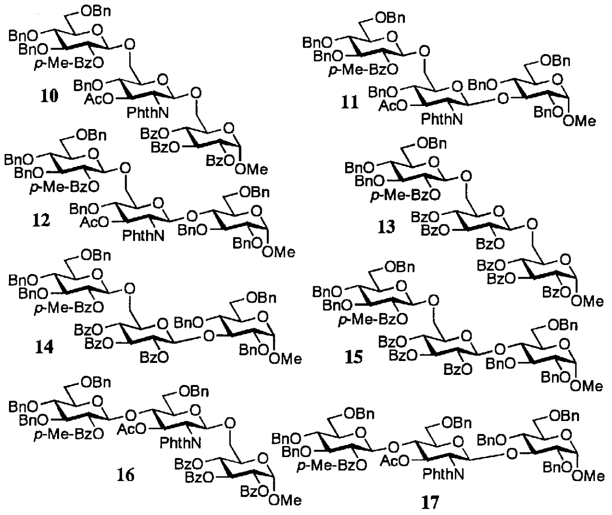


Table 2. One-Pot synthesis of trisaccharides

Entry	Method	B	C (eq.)	product	Yield /%
1	A	2	5 (1.68)	10	83
2	A	2	6 (1.68)	11	47 (68)[a]
3	A	2	9 (1.68)	12	44 (58)[a]
4	B	2	5 (1.68)	10	79
5	B	2	6 (5.0)	11	(66)[a]
6	B	2	9 (5.0)	12	(54)[a]
7	A	7	5 (1.72)	13	88
8	A	7	6 (1.72)	14	51 (71)[a]
9	A	7	9 (1.72)	15	40 (54)[a]
10	C	8	5 (1.77)	16	69
11	C	8	6 (1.77)	17	49 (65)[a]

[a] 5.0 eq. of **C** was used.

Method A: 0.1 eq. $TrB(C_6F_5)_4$ / -20 °C / ${}^tBuCN:CH_2Cl_2$ (2:1) / 6 h then 1.5 eq. NIS / -20 °C / 1h. Method B: 0.1 eq. $TrB(C_6F_5)_4$ / -20 °C / ${}^tBuCN:CH_2Cl_2$ (2:1) / 6 h then 1.5 eq. NBS / -20 °C / 1h. Method C: 0.3 eq. $TrB(C_6F_5)_4$ / -15 °C / CH_2Cl_2 / 21.5 h then 1.5 eq. NIS / -15 °C / 1 h.



monitoring. Next, the second glycosylations of thus formed disaccharides with several methyl α-glucosides (**5**, **6**, **9**) afforded the corresponding trisaccharides in good to high yields by further addition of 150 mol% of NIS to the reaction mixture. In a similar manner, the desired trisaccharides were also obtained when the same amount of NBS instead of NIS was used in the above experiments (Table 2. Entry 4,5,6). In the case of using glucosides having a C-3 or C-4 hydroxy group as acceptors, the yields of trisaccharides decreased and the 1-hydroxy disaccharides were isolated after quenching. When 5.0 eq. of glycosyl acceptor (**C**) was used in the above experiments, total yields of trisaccharides were much improved. (Table 2. Entry 2,3,5,6,8,9,11).

Thus, an improved one-pot sequential glycosylation reaction was successfully carried out by using a catalytic amount of $TrB(C_6F_5)_4$ and a variety of trisaccharides including those containing 2-amino-2-deoxy sugars were stereoselectively synthesized.[8]

The typical experimental procedure of the one-pot sequential glycosylation is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (4.6 mg, 0.005 mmol) and Drierite (250 mg) in a mixed solvent (pivalonitrile: dichloromethane=2:1, 0.45 ml) was successively added the solution (pivalonitrile:dichloromethane=2:1, 0.8 ml) of **1** (41.3 mg, 0.06 mmol) and **2** (24.3 mg, 0.05 mmol) at -20 °C. After the reaction mixture was stirred for 6 h at -20 °C, **5** (42.5 mg, 0.075 mmol) in dichloromethane (0.75 ml) and NIS (16.9 mg, 0.075 mmol) were successively added at -20 °C. The reaction mixture was stirred for additional 1 h at -20 °C and then it was quenched by adding saturated aqueous $NaHCO_3$ (10 ml). The mixture was filtered through Celite and extracted with dichloromethane (3 times, each of 20 ml). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ (5 ml), water (5 ml) and brine (5 ml). Then, the organic layer was dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **10** (61.5 mg, 83%).

Further study on preparation of naturally occurring oligosaccharides by this glycosylation method is now in progress.

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References and Notes

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8 The structures of trisaccharides (**10**~**17**) are supported by ^1H and ^{13}C NMR (500 MHz) and FAB-MS spectrum. Selected NMR data of **13**: ^1H NMR (500 MHz, $CDCl_3$) 4.68 (d, 1H, H-1'', $J_{1'',2''}$ = 7.94 Hz), 4.70 (d, 1H, H-1', $J_{1',2'}$ = 7.94 Hz), 5.00 (d, 1H, H-1, $J_{1,2}$ = 3.36 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) 96.5 (C-1), 101.1 (C-1'), 101.1 (C-1'').