Catalytic and Stereoselective Glycosylation with a Novel and Efficient Disarmed Glycosyl Donor: Glycosyl *p*-Trifluoromethylbenzylthio-*p*-trifluoromethylphenyl Formimidate

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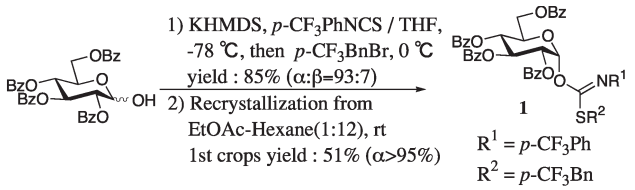
(Received November 26, 2001; CL-011191)

A novel and efficient glycosyl donor having a *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate function as a leaving group is easily prepared by the addition of anomeric hydroxyl group of 2,3,4,6-tetra-*O*-benzoyl-α,β-D-glucopyranose to *p*-trifluoromethylphenyl isothiocyanate, followed by treatment with *p*-trifluoromethylbenzyl bromide. Catalytic and stereoselective glycosylation using this glycosyl donor effectively proceeds by activating its nitorogen atom with various protic and Lewis acids.

In recent years, a great deal of effort has been devoted to developing efficient and stereoselective glycosylation methods[1] due to the biological significance of glycoconjugates.[2] There have been known many useful glycosyl donors which contributed to the advancement of this field; e.g. thioglycosides,[3] glycosyl trichloroacetimidates,[4] glycosyl fluorides,[5] glycals,[6] glycosyl sulfoxides,[7] and *n*-pentenyl glycosides.[8] Now, further exploration of novel and efficient glycosyl donors with a leaving group having two active sites, that is, alkyl or aryl thio and imidate linkages within the same leaving group, was tried. The planned donors were considered to be activated arbitrarily by choosing two different kinds of promoter; e.g. a) imidate linkage by protic and Lewis acids, b) thio linkage by thiophilic reagents. In this communication, we would like to report on catalytic and stereoselctive glycosylation with a newly devised glycosyl donor via effective activation of the nitorogen atom of the leaving group by using various protic and Lewis acids.

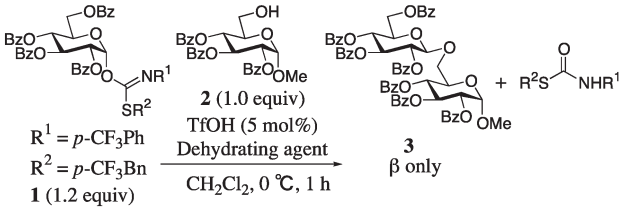
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate (**1**) was easily prepared as a crystalline form in good yields with high α-stereoselectivity by the addition of anomeric hydroxyl group of 2,3,4,6-tetra-*O*-benzoyl-α,β-D-glucopyranose to *p*-trifluoromethylphenyl isothiocyanate, followed by treatment with *p*-trifluoromethylbenzyl bromide (Scheme 1). This compound was stable even when stored at room temperature for a long time.



Scheme 1. Preparation of newly devised glycosyl donor.

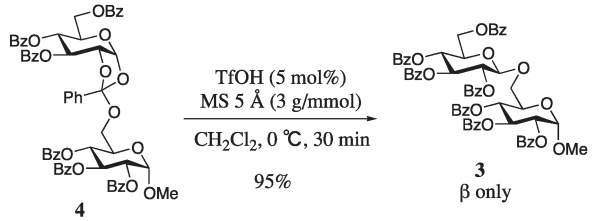
In the first place, the reaction of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate (**1**) with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**2**) was tried in the presence of 5 mol% of TfOH (Table 1). The reaction smoothly proceeded in CH_2Cl_2 at 0 °C to give the corresponding disaccaride **3** in 70% yield, as expected (entry 1). Next, effect of the additives was examined. As a result, MS 5 Å proved to work most effectively among various additives screened (entry 8). It is interesting to note that the amount of orthoester **4**, a precursor of the glycoside, increased when basic MS 3 Å and MS 4 Å or a large amount of neutral Drierite were used (entries 2–7). It was assumed that orthoester **4** was formed initially by adding an acceptor at the cationic benzyl position of the intermediate under the above condition, and the orthoester **4** was in turn converted into the desired disaccaride **3** by using TfOH, MS 5 Å in CH_2Cl_2 at 0 °C (Scheme 2).

Table 1. Effect of dehydrating agents



Entry	Dehydrating agent (g/mmol)		Yield/% 3	4	2
1	None	-	70	-	28
2	Drierite (= $CaSO_4$)	2.5	85	-	12
3	Drierite (= $CaSO_4$)	3.0	89	-	9
4	Drierite (= $CaSO_4$)	3.5	62	19	17
5	Drierite (= $CaSO_4$)	4.0	52	29	19
6[a]	MS 3 Å (= $K_9Na_3[(AlO_2)_{12}(SiO_2)_{12}]$)	3.0	26	36	31
7[a]	MS 4 Å (= $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]$)	3.0	12	33	55
8	MS 5 Å (= $Ca_{4.5}Na_3[(AlO_2)_{12}]$)	3.0	96	-	-

[a]When 20 mol% of TfOH was used, the glycoside **3** was obtained in the presence of MS 3 Å (y. 90%) and of MS 4 Å (y. 99%), respectively.

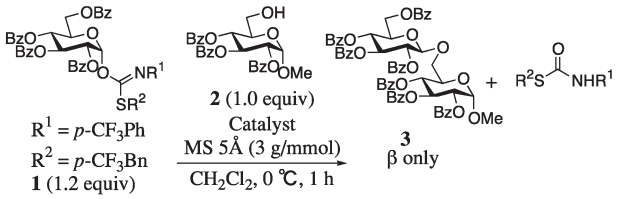


Scheme 2. Conversion to β-disaccharide **3** from orthoester **4**.

Next, glycosylation using various protic and Lewis acids was examined (Table 2). While MsOH did not promote the reaction even at room temperature, a catalytic amount of TfOH and Nafion® (NR50) accelerated it at −78 °C and at room tempera-

ture, respectively (entries 1–4). In situ generated strong protic acids[9] such as $HClO_4$ and $HB(C_6F_5)_4$ were further examined and $HB(C_6F_5)_4$ proved to be an effective catalyst (entries 5, 6). Various Lewis acids such as $[TrB(C_6F_5)_4$,[10] TMSOTf] and combinations of $SnCl_2$ and $AgClO_4$,[11] or $AgB(C_6F_5)_4$[12] also promoted the reaction smoothly. (entries 7–10).

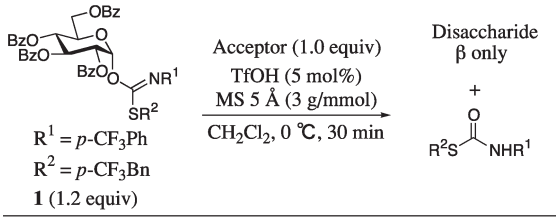
Table 2. Glycosylation using various catalysts



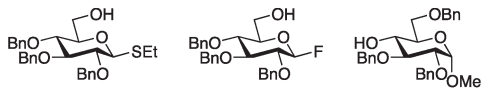
Entry	Catalysts (mol%)		Yield/% 3	4	2
1	MsOH	(5)	-	-	N.R.
2	TfOH	(5)	96	-	-
3[a]	TfOH	(20)	70	-	28
4[b]	Nafion® (NR50)	-	52	8	40
5[c]	$HClO_4$	(5)	56	28	15
6[d]	$HB(C_6F_5)_4$	(5)	99	-	-
7	$TrB(C_6F_5)_4$	(5)	88	-	10
8	$SnCl_2$-$AgClO_4$	(20)	72	-	24
9	$SnCl_2$-$AgB(C_6F_5)_4$	(20)	92	-	8
10	TMSOTf	(5)	96	-	-

[a]The reaction was carried out at -78 ℃ for 1 h. [b]The reaction was carried out at rt for 18 h using 3 beads (7-9 mesh) of Nafion® (NR50). [c]The protic acid was generated from $AgClO_4$ and *t*-BuCl in toluene, and supernatant was used. [d]The protic acid was generated from $AgB(C_6F_5)_4$ and *t*-BuBr in toluene-Et_2O, and supernatant was used.

Table 3. Glycosylation using various acceptors



Entry	Acceptor	Yield/% Disaccharide
1	**5**	60
2	**6**	90
3	**7**	96



5 **6** **7**

Finally, glycosylation of various glycosyl acceptors including **7** having secondary alcohol with the present donor proceeded smoothly within 30 min in CH_2Cl_2 at 0 °C to give the corresponding disaccharides in high yields without activating the armed glycosyl fluoride **6** (Table 3, entries 2, 3). When thioglycoside **5** was used, on the other hand, the same glycosylation gave the corresponding disaccharide in moderate yield along with the transglycosylated compound, ethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl thioglycoside, in 20% yield (entry 1).

The typical experimental procedure is as follows: to a stirred suspension of MS 5 Å (178 mg), **1** (56.7 mg, 0.059 mmol) and **2** (25.0 mg, 0.049 mmol) in CH_2Cl_2 (2.0 mL) was added TfOH (0.44 mg, 3.0 μmmol) in toluene solution (*ca.* 0.1 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and was quenched by adding saturated aqueous $NaHCO_3$. The mixture was filtered through the pad of celite, and aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over Na_2SO_4. After filtration and evaporation, the resulted residue was purified by preparative TLC (toluene/MeCN 9 : 1) to give the desired product **3** (51.4 mg, 96%, β-only).

Thus, catalytic and stereoselective glycosylation of several glycosyl acceptors with a novel glycosyl donor was efficiently performed in the presence of 5 mol% TfOH and MS 5 Å in CH_2Cl_2. Further study on the alternative activation method of thio group involved in the leaving group of the present glycosyl donor with thiophilic reagents is now in progress.

The present research is partially supported by Grant-in-Aids for Scientific Research from Ministry of Education, Science, Sports and Culture.

References and Notes

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12 T. Mukaiyama, H. Maeshima, and H. Jona, *Chem. Lett.*, **2001**, 388; Silver tetrakis(pentafluorophenyl)borate $[AgB(C_6F_5)_4]$ was prepared by adding an ethereal solution of $LiB(C_6F_5)_4$ (purchased from Tokyo Chemical Industry Co., Ltd.) to an aqueous solution of $AgNO_3$. After azeotropic removal of water and diethyl ether with toluene, $AgB(C_6F_5)_4$ was obtained as a brown solid containing 1–3 mol of toluene.