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Preliminary communication

An efficient approach to *O*-glycosides through $CuBr_2$–Bu_4NBr mediated activation of glycosides

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Modification of reactivity of stable 1-thioglycosides to afford reactive glycosyl donors has been performed by use of methyl triflate[1], NBS[2], trimethyldisulfonium triflate[3], and such heavy-metal salts as mercuric sulfate[4], mercuric benzoate[5], mercuric nitrate[6], phenylmercuric triflate[7], and cupric triflate[8]. Even though the methyl triflate and trimethyldisulfonium triflate methods seem the most efficient at present, these approaches still have some drawbacks concerning the choice of protective groups and the enhancement of stereoselectivity.

We now describe a novel method of activation of 1-thioglycosides by the aid of cupric bromide in the presence of a catalytic amount of tetrabutylammonium bromide which constitutes an efficient, mild approach to the synthesis of glycosides, provided that there is further addition of such well established promotors[9] as silver triflate, mercuric bromide, or tetrabutylammonium bromide, together with powdered molecular sieves 4A.

1-Thioglycosides **1** (ref. 10), **6** (ref. 11), and **8** (ref. 12) were chosen as representative glycosyl donors for the synthesis of 1,2-*trans*-glycosides, and 1-thioglycosides **10** (ref. 11) and **13** (ref. 13) for that of 1,2-*cis*-glycosides. As the glycosyl acceptors, two sterically congested alcohols **2** (ref. 14) and **4** (ref. 11), and a sterically easily accessible alcohol **16** (ref. 14) were selected.

A typical experimental procedure was as follows. Into a mixture of $CuBr_2$ (900 μmol), Bu_4NBr (100 μmol), powdered molecular sieves 4A (1 g), and an appropriate promotor (900 μmol, see Table I), in a two-necked flask was injected, in one portion, a solution of a 1-thioglycoside (600 μmol) and a glycosyl acceptor (500 μmol) in a solvent (10 mL, see Table I) at 20° under Ar. The mixture was stirred for a selected time (see Table I) at 20°, and filtered through Celite. The filtrate was successively washed with aq. $NaHCO_3$ and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 C-300 afforded glycosides. The results are summarized in Table I.

As shown in Table I, alkyl 1-thioglycosides **1**, **6**, and **8** with either an *O*-acetyl or an *N,N*-phthaloylamino group at C-2 afforded a high yield of 1,2-*trans*-glycosides by using silver triflate or mercuric bromide as an additional promotor. The use of

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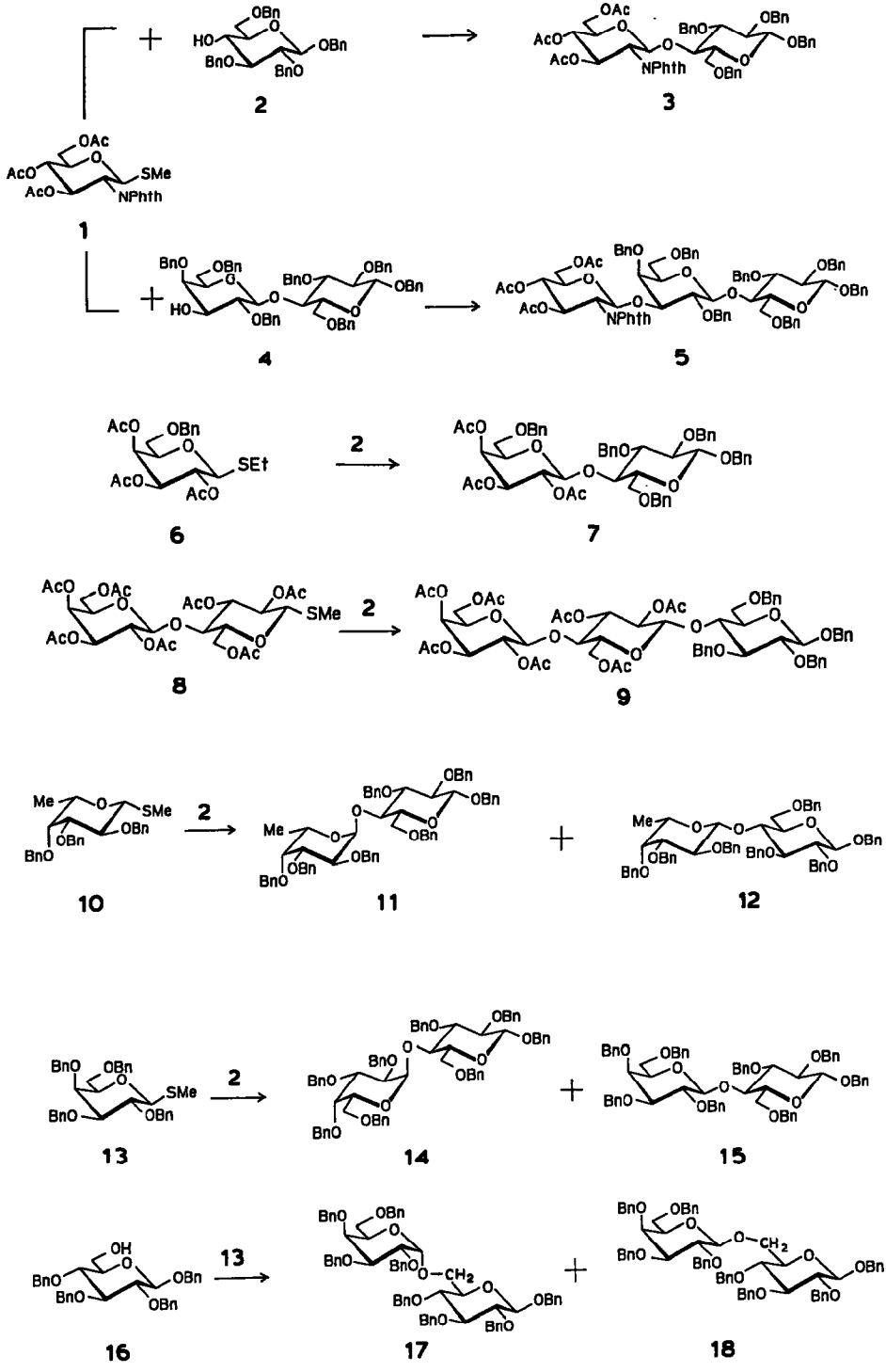
OBn
HO
BnO
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2
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NPhth
1
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OBn
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4
5
AcO
OBn
SEt
AcO
AcO
6
2
7
8
9
Me
SMe
OBn
OBn
BnO
10
11
12
13
14
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OH
16
13
17
18
CH2

TABLE I

REACTIONS AND PRODUCTS[a]

Donor	*Acceptor*	*Promotor*	*Solvent*	*Reaction time (h)*	*Product*	*Yield (%)*	$[\alpha]_D$ ($CHCl_3$) *(degrees)*	R_F	δ_H ($CDCl_3$)[b]	δC[b]
1	2	AgOTF	CH_3NO_2	4	3	84	+8.1 (c 0.9)	0.48 (3:1 toluene–EtOAc)	5.69 (d, *J* 8.6, 1b) 4.37 (d, *J* 7.2, 1a)	102.3 (1a) 97.4 (1b)
		$HgBr_2$	CH_3NO_2	5	3	86				
1	4	AgOTF	CH_3NO_2	3	5	95	−6.7 (c 1.3)	0.50 (3:1 toluene–EtOAc)	5.61 (d, *J* 8.3, 1c)	102.5 (1a) 102.3 (1b) 99.5 (1c)
6	2	AgOTF	CH_3NO_2	4	7	90	−21 (c 0.7)	0.43 (2:1 hexane–EtOAc)	4.59 (d, *J* 7.9, 1b) 4.46 (d, *J* 7.6, 1a)	102.6 (1a) 100.2 (1b)
8	2	AgOTF	CH_3NO_2	4	9	71	−12 (c 1.0)	0.35 (2:1 toluene–EtOAc)	4.62 (d, *J* 7.9, 1c) 4.45 (d, *J* 7.6, 1a) 4.34 (d, *J* 7.9, 1b)	102.5 (1a) 101.1 (1c) 99.7 (1b)
10	2	AgOTF	CH_3NO_2	4	11	86	−39 (c 0.9)	0.44 (9:1 toluene–EtOAc)	5.09 (d, *J* 3.7, 1b) 4.49 (d, *J* 7.3, 1a)	102.5 (1a) 97.7 (1b)
					12	9		0.49 (9:1 toluene–EtOAc)		
		Bu_4NBr	5:1 $Cl(CH_2)_2Cl$–DMF	48	11	72				
13	2	AgOTF	5:1 $Cl(CH_2)_2Cl$–toluene	5	14	76	+15 (c 0.8)	0.67 (7:1 toluene–EtOAc)	5.73 (d, *J* 4.0, 1b)	102.3 (1a) 97.5 (1b)
					15	13	+1.5 (c 1.4)	0.56 (7:1 toluene–EtOAc)	4.48 (d, *J* 7.6, 1a) 4.43 (d, *J* 7.6, 1b)	102.7 (1b) 102.5 (1a)
		Bu_4NBr	5:1 $Cl(CH_2)_2Cl$–DMF	72	14	88				
		Ag zeolite	CH_3NO_2	5	14 15	62 21				
13	16	Ag_2CO_3	$Cl(CH_2)_2Cl$	72	17	41	+21 (c 0.9)	0.61 (3:1 hexane–EtOAc)	5.09 (d, *J* 3.4, 1b) 4.48 (d, *J* 7.9, 1a)	102.5 (1a) 98.0 (1b)
					18	41	−8.2 (c 0.7)	0.57 (3:1 hexane–EtOAc)	4.46 (d, *J* 7.6, 1a) 4.42 (d, *J* 7.9, 1b)	104.3 (1b) 102.6 (1a)

[a] All new compounds afforded reasonable elemental analysis data.

[b] The numbers 1a, 1b, 1c designate the successive anomeric protons or carbons, beginning with the reducing residue.

$CuCl_2$–Bu_4NCl instead of the bromides, in the presence of added promotor (silver triflate), for the reaction of **1** with **2** resulted in a clean but slower reaction, and, after 2 d at 20°, only a 51% yield of **3** was isolated. When 1-thioglycoside **1** was treated with cupric bromide, tetrabutylammonium bromide, and molecular sieves 4A, but in the absence of silver triflate, in nitromethane for 5 h at 20°, **1** was recovered quantitatively, and no glycosyl bromide was detected. Therefore, 1-thioglycoside **1** may be activated by the cupric bromide–tetrabutylammonium bromide complex[15] $[(Bu_4N^+)_2CuBr_4^{2-}]$ through ligand exchange.

It may be note that such 1-thioglycosides as **6** and **8**, having an acetyl group at O-2, were reported[1] to give only a low yield of glycosylation products under the previously established conditions[1]. Considering the frequent use of the acetyl group as a temporary protective group, this new method of activation of 1-thioglycosides should complement the methods already available.

In the presence of Bu_4NBr as the promotor, in 5:1 dichloroethane–DMF, thioglycosyl donors **10** and **13**, having a nonparticipating benzyl group at O-2, afforded at room temperature a good to high yield of 1,2-*cis*-glycosylation products with complete stereoselectivity. It is to be noted that, in contrast to the halide ion-catalyzed glycosylation using glycosyl halide[16] with sterically hindered alcohols, the glycosylation product, for example **14**, obtained by the $CuBr_2$–Bu_4NBr–1-thioglycoside approach was not accompanied by the elimination product, a glycal. Use of the $CuBr_2$–Bu_4NBr–$AgOSO_2CF_3$ system, however, afforded a good yield of a mixture of the 1,2-*cis* and 1,2-*trans* products, in which the 1,2-*cis* products preponderate in the ratio of 6:1 to 10:1. Use of silver zeolite[17], instead of silver triflate also gave a good yield of the products, but lower stereoselectivity, and a mixture of **14** and **15** (3:1 ratio) was obtained. The glycosylation of primary alcohol **16** with 1-thioglycoside **13** in the presence of the additional promotor Ag_2CO_3, afforded an 82% yield of a mixture of 1,2-*cis* (**17**) and 1,2-*trans* (**18**) products in the ratio of 1:1. Therefore, in the case of glycosyl donor **13**, enhancement of stereoselectivity in favor of a 1,2-*trans* product could not be achieved.

In conclusion, this mild approach to glycosides from 1-thioglycosides by use of $CuBr_2$–Bu_4NBr complex and an additional promotor gives a good to high yield of products with high stereocontrol, when appropriate glycosyl donors are employed.

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