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A Novel Glycosylation Reaction of 2-Amino-2-deoxy-D-glucopyranose Using Dimethylphosphinothioate

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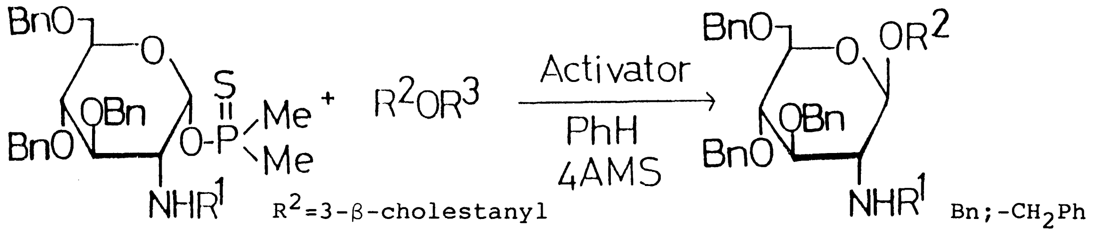
β-Glucosides were stereoselectively obtained in good yields from 3,4,6-tri-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl dimethylphosphinothioate with several alcohols in the presence of iodine and a catalytic amount of trityl or perchlorate salts.

Amino sugars are known to exist as aminoglycosides, oligosaccharides and glycopeptides, which are said to play important roles on cell membrane.(1) For a synthesis of these compounds, the glycosylation reaction is extremely important and several glycosylation reactions using amino sugars have been reported. However, there are some problems such as an instability of the glycosyl donors and the poor glycosylation yields in the reported methods. In addition, in spite of the difficulties of the deprotections phthaloyl, acetyl, p-methoxybenzylidene, and dinitrophenyl groups are usually used as the amino protective groups in these methods.(2) Although benzyloxycarbonyl (Z) group which can be smoothly removed by H_2/Pd is known to be a useful amino protective group, the side reaction of Z group has already been reported.(3) The reaction between 3,4,6-tri-O-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl bromide and alcohol in the presence of mercuric chloride gave only 1,2-cyclocarbonated compound via the cationic intermediate.

We have already reported that 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl dimethylphosphinothioate which is very stable and easy to handle gave the corresponding α-glucosides predominantly in high yields with various alcohols in the presence of silver perchlorate.(4) As one of the application studies of dimethylphosphinothioate method to the other sugars, the corresponding glucosides were obtained stereoselectively in good yields from 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranosyl dimethylphosphinothioate (**1a**) and 3,4,6-tri-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl dimethylphosphinothioate (**1b**). These glycosyl donors are very stable and easily prepared by the reactions between the corresponding D-glucopyranoses[5)] and dimethylphosphinothioyl chloride using butyllithium as described previously.[4)]

We examined the glycosylation reactions between 3-β-cholestanol (**2a**) and **1a** using various trityl salts, perchlorate salts, and iodo compounds. These



R^2=3-β-cholestanyl

Bn;-CH_2Ph

1a;R^1=Ac
1b; =Z

2a;R^3=H
2b; =$Si(CH_3)_3$

3a;R^1=Ac
3b; =Z

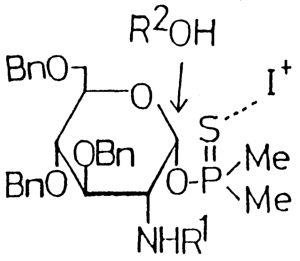
4AMS=molecular sieves 4A

Table 1.[a)] Glycosylation Reactions Using **1a** or **1b**

Entry	Glycosyl donor	Substrate	Activator(equiv.)	Yield of **3a** or **3b** / % [b)]
1	**1a**	**2a**	$AgClO_4(1)$	Complex mixture
2	**1a**	**2a**	$TrtClO_4(1)$	64
3	**1a**	**2a**	$I_2(0.5)$-$TrtClO_4(0.1)$	73
4	**1b**	**2a**	$I_2(0.5)$-$TrtClO_4(0.1)$	57
5	**1b**	**2a**	$I_2(1)$-$TrtClO_4(0.1)$	72
6	**1b**	**2b**	$I_2(1)$-$TrtClO_4(0.1)$	92
7	**1b**	**2b**	$I_2(1)$-$TrtSbCl_6(0.1)$	90
8	**1b**	**2b**	$I_2(1)$-$TrtBF_4(0.1)$	63
9	**1b**	**2b**	$I_2(1)$-$LiClO_4 3H_2O(0.1)$	77
10	**1b**	**2b**	$I_2(1)$-n-$Bu_4NClO_4(0.1)$	64
11	**1b**	**2b**	$TrtClO_4(0.1)$	15
12	**1b**	**2b**	$PhI(1)$-$TrtClO_4(0.1)$	0
13	**1b**	**2b**	$(-CH_2CO)_2NI$-$TrtClO_4(0.1)$	19

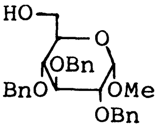
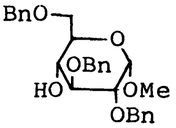
Trt=Triphenylmethyl
a) Molar ratio;**1a**(or**1b**):**2a**(or**2b**)=1:1.
b) Only β-glucoside was detected by ^{13}C NMR.

results are summarized in Table 1. The reaction using silver perchlorate unexpectedly gave only complex mixture (Table 1, Entry 1). But we found the use of 1 equiv. of trityl perchlorate and the combined use of 0.5 equiv. of iodine and 10 mol% amount of trityl perchlorate gave the corresponding glucoside (**3a**) in 64, 73% yield respectively (Table 1, Entries 2, 3). In the similar reaction conditions, the β-glucoside (**3b**) was obtained in 72% yield (Table 1, Entry 5). This is the first case of the successful glycosylation reaction using amino sugar containing 2-benzyloxycarbonylamino group. We assumed that iodo cation would promote this reaction with alcohols to afford the β-glucosides and the derivatives of dimethylphosphinothioic acid by the S_N2 or intimate ion pair mechanism.



In the case of utilizing cholestanyl trimethylsilyl ether (**2b**), the yield was increased to 92% (Table 1, Entry 6). Trityl hexachloroantimonate and trityl fluoroborate were also useful (Table 1, Entries 7, 8). As we found this glycosylation reaction proceeded with even such neutral salts as tetrabutylammonium perchlorate and lithium perchlorate (Table 1, Entries 9, 10), we expect this reaction to be useful for the synthesis of the glycosides containing the acid sensitive groups. Iodo benzene and N-iodosuccinimide were almost ineffective (Table 1, Entries 12, 13), therefore iodine is essential for this glycosylation

Table 2. Glycosylation Between **1b** and Various Alcohols

Entry	Substrate	Yield/%	^{13}C NMR of C-1 δ /ppm
1[a]	MeOH **4**	45	101.6
2[a]	3-β-cholestanol **2a**	72	98.9
3[a]	(ℓ)-Menthol **5**	67	98.0
4[b]	 **6**[6)]	68	100.8
5[b]	 **7**[6)]	33[7)]	100.4

a) Molar ratio;**1b**:**4**(or**2a**or**5**):I_2:$TrtClO_4$=1:1:1:0.1.
b) Molar ratio;**1b**:**6**(or**7**):I_2:$TrtClO_4$=1.3:1:1:0.6.

reaction in the presence of a catalytic amount of trityl perchlorate.

In the similar manner, several β-glucosides were obtained in good yields from **1b** using the representative alcohols (**2a**,**4**-**7**). These results are shown in Table 2.

A typical experimental procedure is as follows: Compound **6** (47 mg, 0.1 mmol) in benzene (1 ml) was added to a mixture of **1b** (90 mg, 0.13 mmol), trityl perchlorate (19 mg, 0.06 mmol) and powdered molecular sieves 4A (ca. 100 mg) to keep the reaction system costantly dry. A 0.1 M (1 M=1 mol·dm^{-3}) iodine/benzene solution (1 ml) was added dropwise to this mixture, and stirred for 16 h at room temperature. A 5% sodium hydrogencarbonate solution (ca. 5 ml) was added to this reaction mixture and filtered. The filtrate was extracted with dichloromethane. The extract was washed with a 5% sodium thiosulfate solution and dried over sodium sulfate. After evaporation the crude product was purified by TLC (developing solvent;CH_2Cl_2:Et_2O=8:1) to give the corresponding glucoside (71 mg, 68%).

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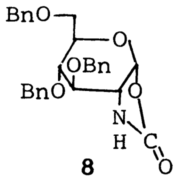
7) Compound **8** as a by-product was obtained in 37% yield, which was supposed to proceed by a similar cyclic reaction mechanism based on Ref. 3.



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