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GLUCOSYLATION USING GLUCOPYRANOSYL DIMETHYLPHOSPHINOTHIOATE

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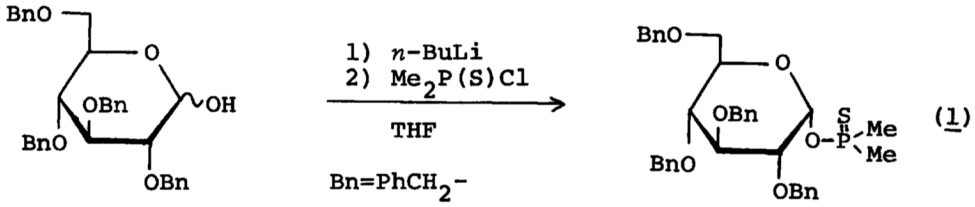
Several glucosides were prepared in good yields from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl dimethylphosphinothioate and alcohols in the presence of silver perchlorate. By this method α-glucosides were predominantly obtained.

Glycosylation reaction is one of the most important problems in carbohydrate chemistry. The classical Königs-Knorr reaction or its modifications are most widely used and recently many methods for the synthesis of glucosides were reported.[1-6] However, it seems that the starting materials in these methods are not so stable to be stored for a long time.

Recently we have shown that dimethylphosphinothioyl chloride (Mpt-Cl) was useful in peptide chemistry for the protection of hydroxy function of tyrosine[7] and for the activation of carboxyl group as stable mixed anhydride.[8] When this Mpt group is introduced into the hydroxy function of carbohydrate, it can be expected to become a protecting and activating group. As the first example of this line of investigation, a new glucosylation reaction using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl dimethylphosphinothioate (1) derived from the corresponding glucopyranose and Mpt-Cl was studied.

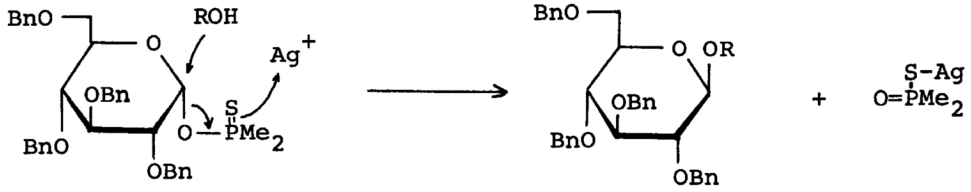


(1)

Compound 1 was prepared by the following procedure: to a stirred dry tetrahydrofuran (THF) solution (20 cm^3) of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (5 mmol) was added a 1.6 M (1 M=1 mol dm^{-3}) hexane solution of butyllithium (1.08 equiv.) at -30 °C under nitrogen. After stirring for 30 min, a THF solution (5 cm^3) of Mpt-Cl (5.4 mmol) was added to it and the resulting mixture was

stirred for 1 h at the same temperature. The solution was poured into water and extracted with ether two times. The combined organic layers were washed with water and dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The oily residue was purified by the silica-gel column chromatography to give colorless crystals 1 in 76% yield.[9] This material was stable at room temperature without any special care.

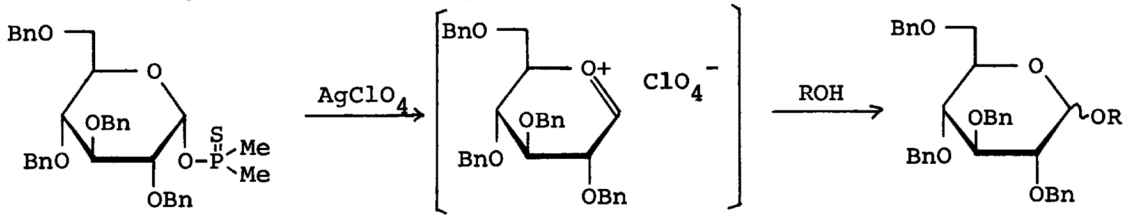
We expected that silver cation would promote the reaction of 1 with alcohols to afford the β-glucosides in the following equation.



Based on this hypothesis, we tried the reaction of 1 and 3β-cholestanol in THF at room temperature in the presence of several metal salts, such as silver perchlorate, silver triflate (AgOTf), silver oxide, stannous chloride, mercuric acetate and so on. The glucosylation reaction was promoted with only silver perchlorate. In the cases of the other salts, the glucoside could not be obtained, and the reaction with an excess of mercuric acetate afforded β-1-*O*-acetate in 32% yield.

Next, the effect of solvents on the reaction was investigated by using several solvents, such as THF, ether, benzene, dimethylformamide (DMF) and acetonitrile. It was made clear that THF, ether and benzene were good as solvent, benzene, *inter alia*, being superior in yields and anomer ratios to the other solvents. These results were summarized in Table 1.

Unexpectedly these results suggested that 1 might react with alcohols *via* glucosyl perchlorate, which was known as the intermediate of Königs-Knorr reaction,[10] to give α-glucosides predominantly.



A typical procedure for the glucosylation described is as follows: to a stirred suspension of 1 (0.2 mmol), 3β-cholestanol (0.2 mmol) and 4A molecular sieves in benzene (0.5 cm^3) was added a mixture of benzene (1.5 cm^3) and silver

Table 1. Glucosylation of 3β-Cholestanol with 1

Metal Salt	Solvent	Temp.	Yield/%[a]	α/β
$AgClO_4$	THF	R.T.	63	72/28
$Hg(OAc)_2$(excess)	THF	R.T.	--(32)[b]	--
$AgClO_4$	Benzene	R.T.	89	81/19
$AgClO_4$	Ether	R.T.	52	81/19

a) Isolated yield. b) Yield of β-1-*O*-acetate.

perchlorate (0.2 mmol) at room temperature. After stirring for 24 h, a 5% sodium sulfide solution was added to the mixture and insoluble materials were removed by filtration. The filtrate was extracted with ether and the organic layer was washed with a 5% sodium sulfide solution, and water, then dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated *in vacuo*. The oily residue was purified by silica-gel thin-layer chromatography (TLC) to give 3β-cholestanyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (71%) and the corresponding β-anomer (17%).

In a similar manner, several glucosides were prepared in good yields as shown in Table 2. In the case of sterically hindered secondary alcohol excess use of silver perchlorate and 1 could improve the yield.

According to the present procedure, α-glucosides were obtained predominantly from 1 and various hydroxy compounds in the presence of silver perchlorate without operational difficulties. It should be noted that 1 was very stable compound compared to the conventional glucosyl doners.

Table 2. Glucosylation of Alcohols with 1

ROH	Yield/%	α/β[a]
MeOH	90	69/31[4]
Cyclohexanol	91	75/25[4]
3β-Cholestanol	89	81/19[5]
Z-L-Ser-OMe	86	87/13[b]
Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside	69	89/11[3]
Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside	82[c]	90/10[3]

a) These compounds were purified by TLC and were identified by ^1H NMR or comparison with the reported physical constants. b) Authentic samples were synthesized from glucosyl fluoride.[5] c) Compound 1 and $AgClO_4$ were used in 2 equiv. portions.

Further applications of the present procedure for the syntheses of complex carbohydrates are now in progress.

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9) Compound 1: Mp 62-64 °C; $[\alpha]_D^{25}$+37.4° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.86 (6H, d, *J*=13 Hz, P-CH_3), 6.18 (1H, dd, *J*=13 and 3 Hz, H-1), 7.03-7.45 (20H, m, Ph).
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