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A Highly Stereoselective Synthesis of α-Glucosides from 1-Thioglucoside Derivative under High Pressure

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High pressure-assisted glycosylation reaction of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with various alcohols by using methyl iodide as an activator gave α-glucosides in good yield with high selectivity without any use of heavy metal salts.

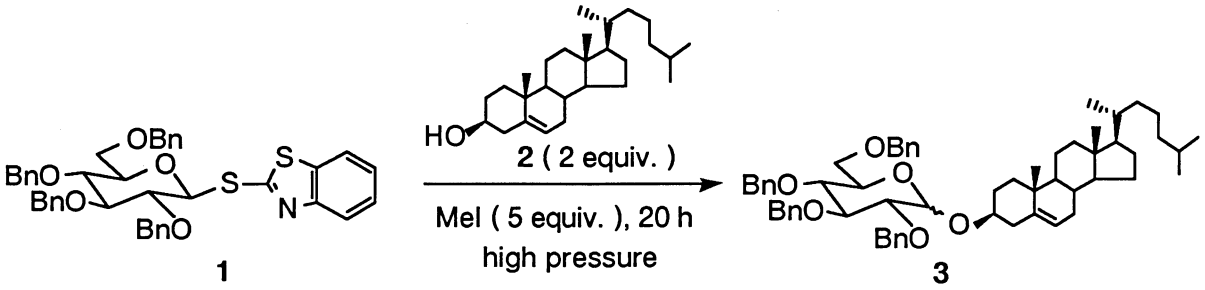
Stereocontrolled construction of *O*-glycoside bond is one of the most challenging problem in carbohydrate chemistry and a large number of methods have been reported.[1] However, there still remains a strong demand to develop simple, mild, and efficient methods for the stereoselective glycosylation. In recent years, it has been reported that several glycosylation reactions under high pressure proceed stereoselectively.[2] We have recently disclosed that the condensation reaction of glycosyl bromide with various alcohols was accelerated under high pressure in the presence of amines to afford α-glucosides in good yield with high selectivity.[3] In this communication, we wish to report the high pressure-assisted glycosylation of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) [4] and various alcohols by using methyl iodide as an activator to give the corresponding glucosides in good yield with high α-selectivity.

We first examined the glycosylation reaction of **1** with cholesterol (**2**) under high pressure by using methyl iodide as an activator in several solvents (Table 1). Treatment of **1** with 2 equivalent of **2** and 5 equivalent of methyl iodide in dichloromethane under 0.8 GPa for 20 h at 50 °C afforded cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**3**) in 51% yield as a mixture of α- and β-anomers (α / β = 89 / 11) along with 3-methylbenzothiazole-2-thione and its salt. When the same reaction was performed under 1.3 GPa for 20 h at 30 °C, the yield increased up to 80% (α / β = 90 / 10). Among several solvents such as dichloromethane, ether, tetrahydrofuran, toluene, and dichlorometane / acetonitrile screened, dichloromethane gave the most favorable results with respect to the yield, but the selectivities were not quite different. The glycosylation

was carried out under atmospheric pressure for 20 h at 30 °C to give a trace amount of **3**.

On the basis of the results, we next undertook the glycosylation of **1** with other alcohols having different reactivities in dichloromethane in the presence of methyl iodide under 1.3 GPa for 20 h at 30 °C. The results are summarized in Table 2. In every case including sterically hindered alcohols, α-glucosides are obtained in good yield with high selectivity. It is assumed that **1** first reacts with methyl iodide under high pressure to afford *N*-methyl quaternary benzothiazolium glucoside.[5] Then, the formed salt reacts with an alcohol to give the corresponding glucoside in a manner similar to 2-pyridyl 1-thioglycosides.[6] A typical procedure is described as follows: A solution of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) (150.4 mg, 0.22 mmol), cholesterol (**2**) (170 mg, 0.44 mmol), and methyl iodide (68 μl, 1.1 mmol) in dry dichloromethane (2 ml) was placed in a sealed Teflon tube. The tube was pressurized at 1.3 GPa in a high pressure equipment[7] and allowed to stand for 20 h at 30 °C. The reaction mixture was depressurized and then purified with column chromatography on silica gel to afford cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-

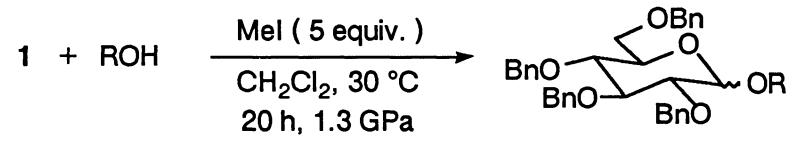
Table 1. Glycosylation reaction of **1** with cholesterol (**2**) under high pressure

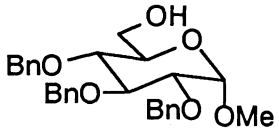
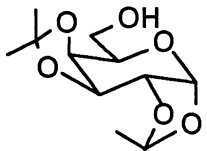
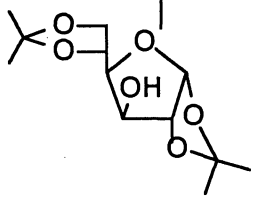


Entry	Solvent	Pressure / GPa	Temp / °C	Yield / % [a]	α / β [b]
1	Et_2O	0.8	50	35	90 / 10
2	THF	0.8	50	30	90 / 10
3	$PhCH_3$	0.8	50	25	89 / 11
4	CH_2Cl_2 / MeCN (3 / 2)	0.8	50	37	89 / 11
5	CH_2Cl_2	0.8	50	51	89 / 11
6	CH_2Cl_2 / MeCN (3 / 2)	1.3	30	49	90 / 10
7	CH_2Cl_2	1.3	30	80	90 / 10
8	CH_2Cl_2	1×10^{-4}	30	trace	—

a) Isolated yield based on **1**. b) The ratio was determined by HPLC analysis.

Table 2. Glycosylation reaction of **1** with various alcohols under 1.3 GPa



Entry	ROH	Yield / % [a]	α / β [b]	δ ^{13}C [c]	
				α-anomer	β-anomer
1	$CH_3(CH_2)_6CH_2OH$	85	89 / 11	96.89	103.68
2	$(CH_3)_3COH$	65	89 / 11	91.50	97.88
3		71	88 / 12	97.25	103.81
4		77	90 / 10	97.05	104.38
5		40	90 / 10	97.99	105.12

a) Isolated yield based on **1**. b) The ratio was determined by HPLC analysis.
c) Chemical shift (δ ppm) in ^{13}C (125 MHz, $CDCl_3$) for the anomeric centers newly formed.

glucopyranoside (**3**) (159 mg, 80% yield). The anomer ratio was determined to be α / β = 90 / 10 by HPLC analysis (Wakosil 5SIL column, 4.0 mm x 300 mm; eluent 10 % ethyl acetate in hexane; UV 254 nm; flow rate 1 ml / min).

In conclusion, we have described the high pressure-assisted glycosylation reaction of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) with various alcohols by using methyl iodide as an activator affording 1,2-*cis*-glucosides in good yield with high selectivity without any use of heavy metal salts. Further application of this procedure to the synthesis of complex oligosaccharides is now in progress.

References

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