Tetrahedron Letters, Vol.31, No.45, pp 6549-6552, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

GLYCOSYLATION REACTION UNDER HIGH PRESSURE

Makoto SASAKI,* Yasuo GAMA, Masahiko YASUMOTO, and Yutaka ISHIGAMI

National Chemical Laboratory for Industry, Tsukuba, Ibaraki 305, Japan

Abstract: Glycosylation of various alcohols with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (1) in the presence of hindered amines under conditions of high pressure gave α-glycosides in good yield with high selectivity.

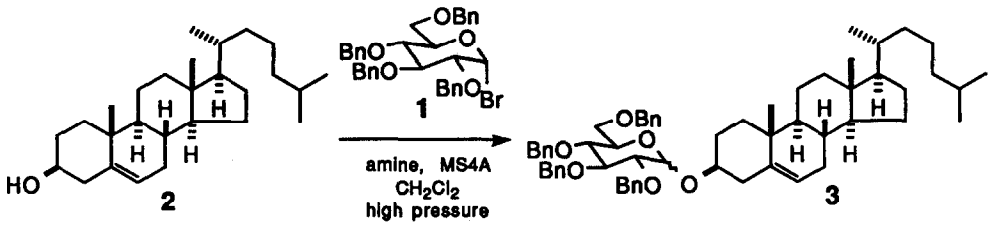
Stereocontrolled glycosylation reactions are one of the most important topics in oligosaccharide synthesis and a large number of methods have been reported.[1] However, there still remains a strong demand to develop simple, mild, and efficient methods for the stereoselective construction of *O*-glycoside bond.[2]

The present study demonstrates that elevated pressures accelerate the condensation reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (1) and various alcohols in the presence of hindered amines to afford α-glycosides in good yield with high selectivity.

The reaction of cholesterol (2) with 1.2 equivalent of the bromide 1 and 1.2 equivalent of triethylamine at 25 °C under a pressure of 8 kbar for 20 h afforded cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (3) in 23 % yield as a mixture of α- and β-anomers (α:β = 93:7). The low yield is ascribed to low reactivity of the intermediate, 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl triethylammonium, readily obtainable from 1 by treating with triethylamine at room temperature under ambient pressure.[3] On the other hand, the replacement of triethylamine to hindered amines accelerated the reaction. Among various amines tested, 2,6-lutidine gave the most favorable results with respect to the yield and stereoselectivity (Table 1). The same reaction was carried out at room temperature under ambient pressure and only a 20 % yield of 3 was obtained. These results are very different from the effect of hindered amine observed under ambient pressure.[4] Incidentally, inorganic bases (potassium carbonate, cesium fluoride, *etc.*) were not effective in the reaction. When the glycosylation was performed with 1.5 equivalent of 1, the yield was increased up to 88 %. Unfortunately, further improvement of the yield and stereoselectivity could not be realized though the pressure was elevated up to 13 kbar.

We next undertook the glycosylation of a variety of alcohols in the presence of 2,6-lutidine under a pressure of 8 kbar. The results are summarized in Table 2. Good yields and high selectivity were obtained when the procedure was applied to primary, unhindered secondary, and even tertiary alcohols. A drawback of the present method, however, was that it was inapplicable to the glycosylation of hindered secondary alcohols. For example, methyl

Table 1 Glycosylation of cholesterol (2) under high pressure.[a]



run	molar ratio[b]	amine	pressure (kbar)	temperature (°C)	% yield[c]	α / β ratio[d]
1	A	Et_3N	8	25	23	93: 7
2	A	*i*-Pr_2NEt	8	25	59	90:10
3	A	TMU[e]	8	25	60	95: 5
4	A	2,6-lutidine	8	25	67	94: 6
5	A	2,6-lutidine	8	40	73	94: 6
6	B	2,6-lutidine	8	40	88	92: 8
7	A	2,6-lutidine	13	40	78	93: 7
8	A	2,6-lutidine	0.001	25	20	94: 6

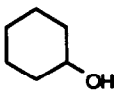
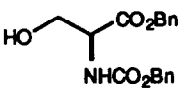
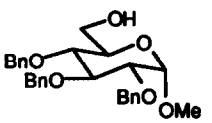
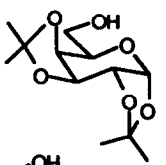
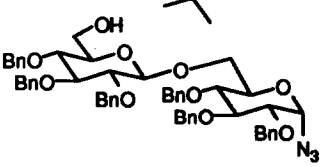
a) All reactions were carried out on 0.25 mmol scale.

b) A: **1** / **2** / base = 1.2 / 1 / 1.2; B: **1** / **2** / base = 1.5 / 1 / 1.5. c) Isolated total yield. d) Determined by HPLC analysis. e) TMU=1,1,3,3-tetramethylurea

2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[5] failed to undergo the high pressure-mediated glycosylation.

A typical procedure is described for the glycosylation of cholesterol (**2**): A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**1**) (229.4 mg, 0.380 mmol), cholesterol (**2**) (97.4 mg, 0.252 mmol), 2,6-lutidine (45 ml, 0.386 mmol), and molecular sieves 4A (activated powder, *ca.* 100 mg) in dry dichloromethane (2 ml) was placed in a sealed teflon tube. The tube was pressurized at 8 kbar in a high pressure equipment,[6] and allowed to stand for 20 h at 40 °C. After being cooled to room temperature, the reaction mixture was depressurized, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified with column chromatography on silica gel to afford cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**3**) (202.1 mg, 88% yield). The anomer ratio was determined to be α:β = 92:8 by HPLC analysis (Wakosil 5SIL column, 4.0 x 300 mm; eluent 8 %

Table 2 Glycosylations under a pressure of 8 kbar.[a]

run	alcohol	molar ratio[b]	temperature (°C)	% yield[c]	α / β ratio
1		A	25	79	92: 8[d]
2	*tert*-BuOH	A	25	59	93: 7[d]
3		B	40	85	93: 7[e]
4		B	40	95	90:10[d]
5		B	40	94	93: 7[d]
6		B	40	69	91: 9[d]

a) All reactions were carried out on 0.25 mmol scale in the presence of MS4A in dichloromethane.

b) A: alcohol / 1 / 2,6-lutidine = 1 / 1.2 / 1.2; B: alcohol / 1 / 2,6-lutidine = 1 / 1.5 / 1.5.

c) Isolated total yield. d) Determined by HPLC analysis using Walosil 5SIL column.

e) Determined by ^{13}C NMR spectroscopic analysis.

ethyl acetate in hexane; UV 254 nm; flow rate 1 mL/min).

In conclusion, we have described a simple glycosylation of less hindered alcohols with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (1) in the presence of hindered amines under high pressure affording 1,2-*cis*-glycosides in good yield with high selectivity without any use of heavy metal salts. Further application of this procedure to the synthesis of complex oligosaccharides are in progress.

Acknowledgement: The authors thank Dr. Hiroshi Nakanishi, National Chemical Laboratory for Industry, for a measurement of NMR spectra.

REFERENCES AND NOTES

1. For recent reviews, see: a) Gigg, R. *Chem. Phys. Lipids* **1980**, *26*, 287; b) Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155; *Chem. Soc. Rev.* **1984**, *13*, 15; c) Schmitd, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212; d) Kunz, H. *ibid.* **1987**, *26*, 294.
2. For recent papers, see: a) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685; b) Suzuki, K.; Maeta, H.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4853; c) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881; d) Reddy, G. V.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.* **1989**, *30*, 4283; e) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.*Tetrahedron Lett.* **1989**, *30*, 5459; f) Nishizawa, M.; Kan, Y.; Yamada, H. *Chem. Pharm. Bull.* **1989**, *37*, 565; g) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270; h) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275; i) Schmidt, R. R.; Gaden, H.; Jatzke, H. *Tetrahedron Lett.* **1990**, *31*, 327; j) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331; k) Kobayashi, S.; Koide, K.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 2435; l) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinäy, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718; m) Nishizawa, M.; Kan, Y.; Shimomoto, W.; Yamada, H. *Tetrahedron Lett.* **1990**, *31*, 2431; n) Yamanoi, T.; Inazu, T. *Chem. Lett.* **1990**, 849; o) Mukaiyama, T.; Suda, S. *Chem. Lett.* **1990**, 1143.
3. a) West, A. C.; Scheurch, C. *J. Am. Chem. Soc.* **1973**, *95*, 1333; b) Scheurch, C.; Kronzer, F. J. *Carbohydr. Res.* **1974**, *33*, 273.
4. A hindered amine such as diisopropylethylamine was reported not to form 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl ammonium salts at room temperature under ambient pressure, see; Lemieux, R. U.; Hendriks, K. B.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056, 4069.
5. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside is known to resist halide ion catalyzed glycosylations, see: Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056; Pougny, J.-R.; Jacquinet, J.-C.; Nassr, M.; Duchet, D.; Milat, M-L.; Sinäy, P. *J. Am. Chem. Soc.* **1977**, *99*, 6762.
6. A description of the high pressure equipment employed in this study has been given previously, see: Kurabayashi, M.; Yanagiya, K.; Yasumoto, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3413.

(Received in Japan 30 July 1990)