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A Highly Efficient Synthesis of Tri-*O*-Acyl-α-D-Glucopyranose 1,2-(Orthoesters) under High Pressure

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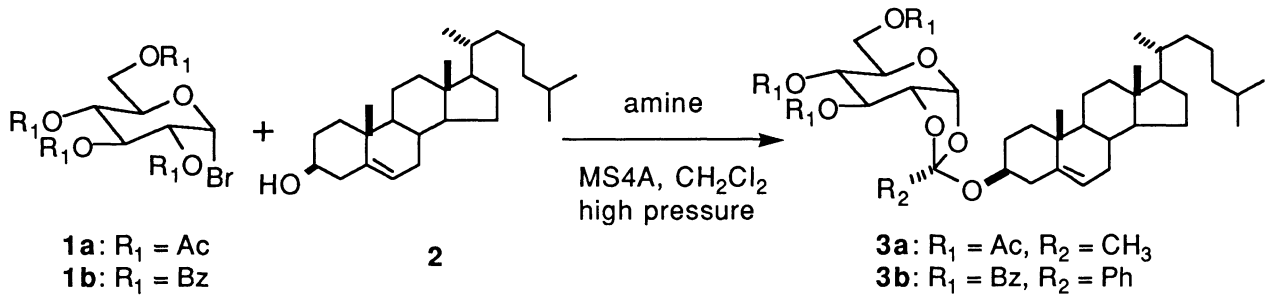
High pressure-assisted condensation reaction of acylated glucosyl bromides with complex alcohols in the presence of diisopropylethylamine and tetrabutylammonium bromide gave the corresponding 1,2-orthoesters in good to excellent yields without using heavy metal salts.

The Königs-Knorr condensation reaction of acylated glycosyl halides with alcohols occasionally leads to the formation of 1,2-orthoesters.[1] The stereospecific transformation of the orthoesters into 1,2-*trans* glycosides has been well established.[2] Therefore, the development of an efficient synthetic procedure for the orthoesters of various alcohols could lead to the synthesis of complex glycosides. In recent years, the application of high pressure has made many reactions possible that do not proceed under normal conditions.[3] Kochetkov *et al.*[4] could show that glycoside bond formation was influenced by high pressure under Helferich conditions using a mercuric salt. On the other hand, Dauben *et al.*[5] recently reported that the formation of orthoesters was increased under high pressure in tetraethylammonium bromide or silver triflate-collidine activated glycosylation between hindered alcohols and glycosyl halides. In this communication, we wish to report a highly efficient synthesis of sugar 1,2-orthoesters under high pressure without using heavy metal salts.

Firstly, we examined the condensation reaction of 2,3,4,6-tetra-*O*-acyl-α-D-glucopyranosyl bromide (**1**) with cholesterol (**2**) as a model reaction (Scheme 1).[6] Treatment of **2** with 1.2 equiv. of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1a**) and 1.2 equiv. of *i*-Pr_2NEt in dichlorometane in the presence of molecular sieve 4A (MS4A) under 8 kbar at 70 °C for 20 h afforded 3,4,6-tri-*O*-acetyl-1,2-*O*-cholesterylorthoacetyl-α-D-glucopyranose (**3a**) in 53% yield (Table 1, Run 6). When a catalytic amount (0.6 equiv.) of Bu_4NBr was added, the condensation reaction was accelerated under 8 kbar for 20 h to afford **3a** in excellent yields (Runs 7, 8, and 9). The same reaction was carried out at room temperature under atmospheric pressure for 50 h to give **3a** in 35% yield (Run 11). When other amines such as Bu_3N, DMAP, and TMU were used instead of *i*-Pr_2NEt, cholesteryl acetate was obtained as a major product. In a similar manner, the condensation reaction of the bromide (**1b**) with **2** afforded 3,4,6-tri-*O*-benzoyl-1,2-*O*-cholesterylorthobenzoyl-α-D-glucopyranose (**3b**) in

quantitative yield (Run 13). Thus, it was shown that the most favorable results with respect to the yield were achieved when the reaction was carried out in the presence of *i*-Pr_2NEt, Bu_4NBr, and MS4A in dichloromethane under the condition of 8 kbar.



1a: R_1 = Ac
1b: R_1 = Bz

2

3a: R_1 = Ac, R_2 = CH_3
3b: R_1 = Bz, R_2 = Ph

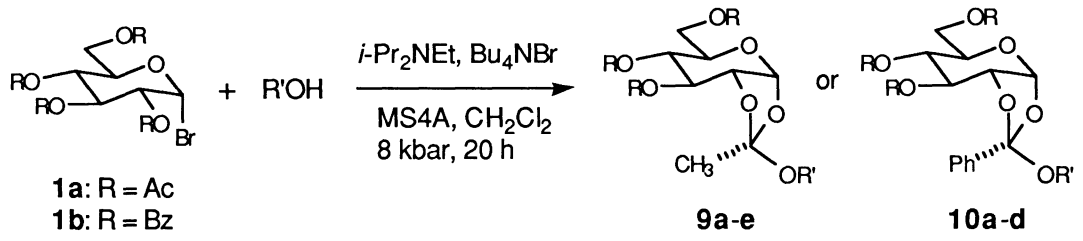
Scheme 1.

Table 1. Condensation reaction of acylated glucosyl bromide (**1**) with cholesterol (**2**) in the presence of various amines under high pressure[a)]

Run	Glucosyl bromide	Amine[b)]	Additive (equiv.)	Pressure kbar	Temp °C	Time h	Yield[c)] %
1	**1a**	DBU	--	6	100	20	30
2	**1a**	Bu_3N	--	6	100	20	trace[d)]
3	**1a**	DMAP	--	6	100	20	trace[d)]
4	**1a**	TMU	--	8	70	20	trace[d)]
5	**1a**	Collidine	--	8	70	20	45
6	**1a**	*i*-Pr_2NEt	--	8	70	20	53
7	**1a**	*i*-Pr_2NEt	Bu_4NBr (0.6)	8	25	20	89
8	**1a**	*i*-Pr_2NEt	Bu_4NBr (0.6)	8	40	20	quant.
9	**1a**	*i*-Pr_2NEt	Bu_4NBr (0.6)	6.5	40	20	96
10	**1a**	Lutidine	Bu_4NBr (0.6)	6.5	40	20	93
11	**1a**	*i*-Pr_2NEt	Bu_4NBr (0.6)	0.001	r.t.	50	35
12	**1a**	*i*-Pr_2NEt	--	0.001	r.t.	50	6
13	**1b**	*i*-Pr_2NEt	Bu_4NBr (0.6)	8	40	20	quant.

a) Molar ratio: cholesterol (**2**) / bromide (**1**) / amine = 1 / 1.2 / 1.2.
b) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-dimethylaminopyridine; TMU = 1,1,3,3-tetramethylurea. c) Isolated yields based on **2**. **3a**: mp 100-101 °C, $[\alpha]_D^{27}$+2.0° (*c* 1.05, $CHCl_3$); **3b:** mp 93-94 °C, $[\alpha]_D^{27}$-11.8° (*c* 1.03, $CHCl_3$). d) Cholesteryl acetate was obtained as a major product in more than 90% yield.

On the basis of the result, we next undertook the condensation of **1** and other complex alcohols by using *i*-Pr_2NEt-Bu_4NBr-MS4A system in dichloromethane under 8 kbar

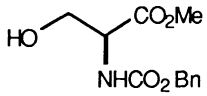
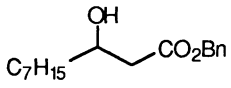
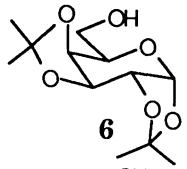
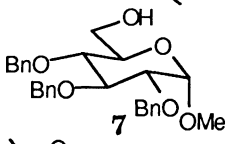
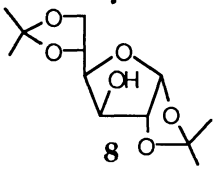


1a: R = Ac
1b: R = Bz

9a-e **10a-d**

Scheme 2.

Table 2. High pressure-assisted orthoesterification[a)]

Run	Glucosyl bromide	Alcohol R'OH	Temp °C	Product 9 / 10	Yield[b)] %
1	**1a**	 **4**	40	**9a**	quant.
2	**1a**	 **5**	40	**9b**	quant.
3	**1a**	 **6**	40	**9c**[6b)]	quant.
4	**1a**	 **7**	40	**9d**	87
5	**1a**	 **8**	40	**9e**[6b)]	56
6	**1b**	**4**	40	**10a**	83
7	**1b**	**6**	40	**10b**	91
8	**1b**	**7**	25	**10c**	82
9	**1b**	**8**	40	**10d**	72

a) Molar ratio: alcohol / bromide / *i*-Pr_2NEt / Bu_4NBr = 1 / 1.2 / 1.2 / 0.6.
b) Isolated yields based on R'OH.

(Scheme 2).[7] The results are summarized in Table 2. In every case, 1,2-orthoesters were obtained in good to excellent yields.

A typical procedure is as follows: A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1a**) (153.1 mg, 0.37 mmol), cholesterol (**2**) (120 mg, 0.31 mmol), Bu_4NBr (61.3 mg, 0.19 mmol), *i*-Pr_2NEt (48 mg, 0.37 mmol), molecular sieve 4A (activated powder, 100 mg) in dry dichloromethane (2 ml) was placed in a sealed Teflon tube. The tube was compressed to 8 kbar in a high-pressure equipment,[8] and maintained for 20 h at 40 °C. After being cooled to room temperature, the reaction mixture was depressurized, filtrated through Celite, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford 1,2-orthoester **3a** in quantitative yield.

In conclusion, the reaction described herein provides a convenient method for the synthesis of sugar 1,2-orthoesters, which are difficult to prepare by other methods. Further applications of the procedure to the synthesis of more hindered orthoesters are now in progress.

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2) For the acid-catalyzed rearrangement of orthoestes to 1,2-*trans* glycosides, see: a) N. K. Kochetkov, A. J. Khorlin, and A. F. Bochkov, *Tetrahedron*, **23**, 693 (1967); b) T. Ogawa, K. Beppu, and S. Nakabayashi, *Carbohydr. Res.*, **93**, C6 (1981); c) T. Ogawa and T. Nukada, *ibid.*, **136**, 135 (1988); d) D. M. Mootoo, P. Konradsson, and B. Fraser-Reid, *J. Am. Chem. Soc.*, **111**, 8540 (1989).

3) a) K. Matsumoto, A. Sera, and T. Uchida, *Synthesis*, **1985**, 1; b) K. Matsumoto and A. Sera, *ibid.*, **1985**, 999.

4) N. K. Kochetkov, V. M. Zhulin, N. M. Malysheva, E. M. Klimov, and Z. G. Makarova, *Carbohydr. Res.*, **167**, C8 (1987).

5) W. G. Dauben and P. Kohler, *Carbohydr. Res.*, **203**, 47 (1990).

6) The physical data for **3a** and **3b** are identical with those of the authentic sample, see: a) Ref. 2a; b) T. Ogawa and M. Matsui, *Carbohydr. Res.*, **51**, C13 (1976); c) H. Kunz and A. Harreus, *Liebigs Ann. Chem.*, **1982**, 41; d) A. Harreus and H. Kunz, *ibid.*, **1986**, 717.

7) All the new compounds reported gave satisfactory elemental analyses. Selected physical data for new compounds are described below. $[\alpha]_D^{27}$ and ^{13}C NMR were measured in $CHCl_3$ and $CDCl_3$ solutions, respectively. **9a**: syrup, $[\alpha]_D$ +31.5° (*c* 1.53); δ = 170.6, 170.3, 169.5, 169.0, 155.8, 121.1, 96.8, 53.9, 52.5, 20.5. **9b**: A mixture of diastereomers was obtained. syrup, $[\alpha]_D$ +23.0° (*c* 1.99); δ = 121.83, 121.80, 97.10, 97.05, 68.13, 68.09, 22.00, 22.08. **9d**: syrup, $[\alpha]_D$ +36.5° (*c* 1.79); δ = 170.7, 169.6, 169.0, 121.5, 98.1,97.0, 55.1. **10a**: syrup, $[\alpha]_D$ +2.8° (*c* 1.42); δ = 170.3, 165.9, 165.1, 164.5, 155.8, 121.1, 97.6. **10b**: syrup, $[\alpha]_D$ -25.4° (*c* 1.21); δ = 166.0, 165.1, 164.5, 121.1, 109.2, 108.5, 97.6,96.2. **10c**: syrup, $[\alpha]_D$+15.2 ° (*c* 1.88); δ = 166.0, 165.2, 164.5, 121.4, 97.9, 97.6, 55.1. **10d**: syrup, $[\alpha]_D$ -8.8° (*c* 1.44); δ = 165.9, 165.1, 164.5, 121.0, 111.7, 109.1, 105.0, 97.7.

8) M. Kurabayashi, K. Yanagiya, and M. Yasumoto, *Bull. Chem. Soc. Jpn.*, **44**, 3413 (1971).

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