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Silica Gel-Catalyzed β-*O*-Glucosylation of Alcohols with 1,2-Anhydro-3,4,6-tri-*O*-pivaloyl-α-D-glucopyranose

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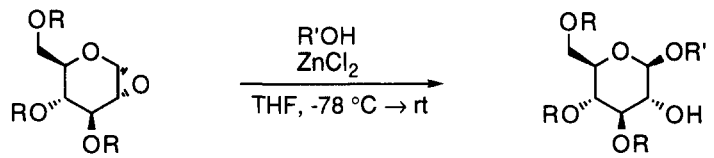
Abstract: 1,2-Anhydro-3,4,6-tri-*O*-pivaloyl-α-D-glucopyranose (**1a**) was allowed to react with alcohols in the presence of solid acids such as silica gel and zeolite HY, to afford β-*O*-glucosides stereoselectively. Several natural glucosides were synthesized by the application of the present reaction. © 1997 Elsevier Science Ltd.

Many approaches to selective *O*-glycosylation have been developed because of the importance of *O*-glycosides in natural product chemistry. Recently, Danishefsky *et al.* reported an excellent method for preparation of β-*O*-glycosides from alcohols and 1,2-α-anhydro sugars as glycosyl donors in the presence of $ZnCl_2$ at -78℃ (Scheme 1),[1] and thereafter the 1,2-α-anhydro sugars have been used on various types of glycosylation.[2] On the other hand, ring-opening reactions of epoxyalkanes with various nucleophiles on solid acids and bases were reported.[3] Since the 1,2-α-anhydro sugars are very reactive, we expected that the solid acids such as silica gel (SiO_2) and zeolite are sufficient to activate the reaction of the 1,2-α-anhydro sugars with alcohols even though their acidity is lower than that of $ZnCl_2$. We would herein report a method for preparation of β-*O*-glucosides from the 1,2-anhydro-α-D-glucopyranose derivatives in the presence of SiO_2 at room temperature and its application to the synthesis of natural glucosides.



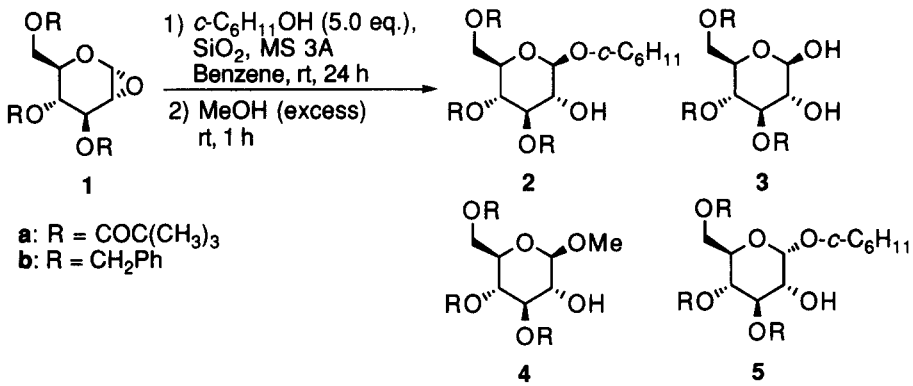
R = CH_2Ph, $SiMe_2$-*t*-Bu R'OH = Methanol, Cholesterol etc.

Scheme 1.

1,2-Anhydro-3,4,6-tri-*O*-pivaloyl-α-D-glucopyranose (**1a**),[4] prepared from D-glucal by the acylation with pivaloyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine followed by the epoxidation with 2,2-dimethyldioxirane,[1,5] was mainly used as the glucosyl donor, since the pivaloyl group was easily removable under basic conditons.

The reaction of **1** with cyclohexanol (5.0 eq.) was first examined in the presence of SiO_2 as the catalyst

and/or molecular sieves 3A (MS 3A) as the dehydrating agent in benzene at room temperature (Scheme 2). The reaction mixture was treated with a large excess of methanol in order to convert the remaining **1** into methyl glucosides **4** and then isolated by silica gel column chromatography. The results are summarized in Table 1. The reaction of **1a** scarcely occurred in the absence of SiO_2, and MS 3A had no catalytic activity (Entries 1 and 2). When using 1 wt eq. of SiO_2, the desired β-glucoside **2a** was obtained in 40% yield along with diol **3a** (51%) as shown in Entry 3: Nucleophilic attack of a residual water to **1a** in the reaction mixture seemed to produce **3a**. The addition of MS 3A certainly decreased the yield of **3a**, but the yield of **4a** derived from **1a** increased (Entry 4). Increasing the amounts of both SiO_2 and MS 3A afforded **2a** in increased yield (Entry 5). Tri-*O*-benzyl derivative **1b**, as well as **1a**, underwent the reaction in similar yields (Entry 6). No production of α-glucosides **5** was observed in all cases.



Scheme 2.

Table 1. The reaction of **1** with cyclohexanol in the presence of SiO_2 and molecular sieves 3A.

Entry	Glucosyl donor	SiO_2	MS 3A	Yield / %[a]			
		wt eq.	wt eq.	**2**	**3**	**4**	**5**
1	**1a**	0	0	0	29	43	0
2	**1a**	0	3.0	0	12	76	0
3	**1a**	1.0	0	40	51	5	0
4	**1a**	1.0	3.0	45	21	21	0
5	**1a**	3.0	9.0	72	14	5	0
6	**1b**	3.0	9.0	71	13	7	0

a) Isolated yield.

Next, the effect of solid acid on the reaction was examined. Maximum acid strength (Ho) of the solid acids was determined with Hammett indicators in benzene.[6] The reaction of **1a** with cyclohexanol in the presence of the solid acids was carried out under the similar conditions described in Entry 5 of Table 1. The results are depicted in Table 2. Increasing acid strength tended to increase the total yields of the glucosides **2a** and **5a**. When using zeolite HM and TiO_2-SiO_2, the α-glucoside **5a** was obtained as a by-product in 8% and 11% yields, respectively (Entries 1 and 2): The reaction probably occurs *via* the formation of carbocation

intermediate because of their strong acidity. Zeolite NaY having the weakest acidity among the solid acids slightly promoted the reaction (Entry 5). Since the undesired isomer **5a** was not produced as shown in Entries 3 and 4, SiO_2 or zeolite HY was considered to be the most suitable catalyst on the β-*O*-glucosylation. It is notable that SiO_2 has enough ability to promote the reaction in spite of the weak acidity ($+3.3 < Ho \leq +4.0$).

Table 2. The effect of solid acid on the reaction of **1a** with cyclohexanol in benzene.

Entry	Solid acid [a]	Maximum acid strength of solid acid [b]	Yield / % [c]			
			2a	**3a**	**4a**	**5a**
1	Zeolite HM	$-8.2 < Ho \leq -5.6$	68	11	11	8
2	TiO_2-SiO_2	$-5.6 < Ho \leq -3.0$	71	18	0	11
3	Zeolite HY	$-5.6 < Ho \leq -3.0$	79	14	3	0
4	SiO_2 [d]	$+3.3 < Ho \leq +4.0$	72	14	5	0
5	Zeolite NaY	$+4.0 < Ho \leq +4.8$	19	22	57	0

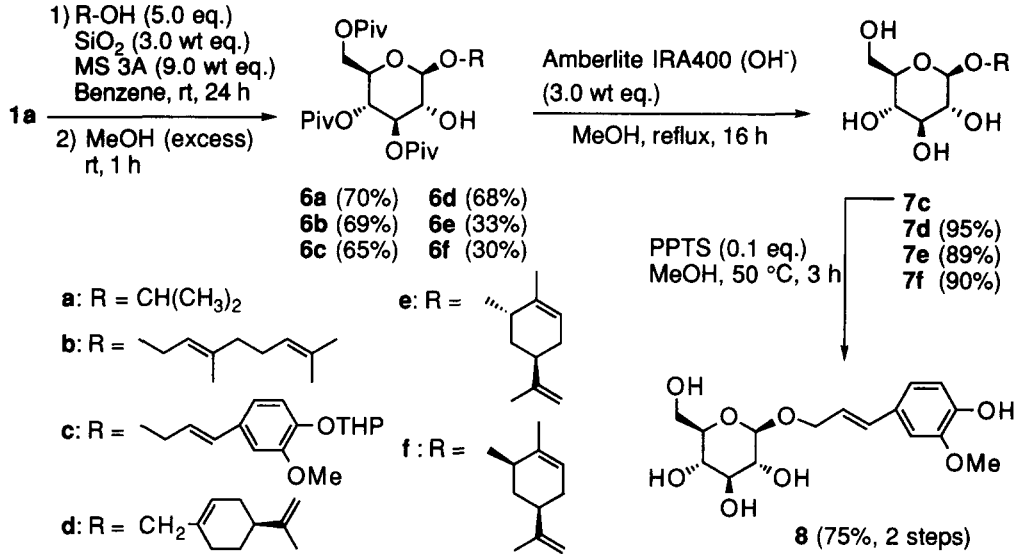
a) Solid acids and MS 3A were dried at 400 ℃ for 6 h *in vacuo*. b) Maximum acid strength was determined with Hammett indicators. c) Isolated yield. d) The acid strength of the mixture of SiO_2 and MS 3A (1/3 wt/wt) was the same value as that of SiO_2, and the acid strength of MS 3A was $+4.8 < Ho \leq +6.8$.

The β-*O*-glucosylation on SiO_2 was applied to the synthesis of various glucosides containing natural products (Scheme 3). From 2-propanol, geraniol, tetrahydropyranyl (THP) ether of coniferyl alcohol, and (-)-perillyl alcohol, the corresponding glucosides **6a-d** were obtained in good yields. The acid-labile THP group of **6c** was entirely retained under the present conditions: When $ZnCl_2$ was used on the reaction in the place of SiO_2 according to the procedure of Danishefsky,[1] the inseparable mixture of several glucosides was produced. The low yields of **6e** and **6f** are apparently due to the steric hindrance of *trans*- and *cis*-carveol. Hydrolysis of **6c** with Amberlite IRA400 (OH^-) in refluxing methanol for 16 h followed by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol gave citrucin D (**8**)[7] in 75% yield. **6d-f** were hydrolyzed under the same conditions as described above, to afford perilloside A (**7d**),[8] *trans*-carveol 6-β-D-glucopyranoside (**7e**),[9] and *cis*-carveol 6-β-D-glucopyranoside (**7f**), respectively. The spectral data of the synthetic glucosides were coincident with those of natural products.

Thus, the silica gel-catalyzed reaction of **1** with alcohols provides a facile method for β-*O*-glucosylation under mild conditions. The present glucosylation with carbohydrates is now under investigation.

A typical procedure is described for the reaction of **1a** with cyclohexanol: SiO_2 (Silica gel BW300, Fuji Syricia, Japan) and MS 3A were dried at 400 ℃ for 6 h *in vacuo* and stored over P_2O_5. After stirring a mixture of **1a** (100 mg, 0.24 mmol), cyclohexanol (120 mg, 1.20 mmol), and MS 3A (900 mg) in benzene (5 ml) at room temperature for 1 h, SiO_2 (300 mg) was added and the mixture was stirred for 24 h. The reaction mixture was treated with methanol (20 ml) at room temperature for 2 h, and then SiO_2 and MS 3A were removed by filtration. The filtrate was evaporated to dryness under reduced pressure to afford the crude product, which was chromatographed on silica gel using hexane-EtOAc (15/1-2/1) as the eluent to give **2a** as a colorless solid (mp. 43-45 ℃) in 72% yield along with **3a** (14%) and **4a** (5%).

We thank Dr. T. Fujita (College of Agriculture, University of Osaka Prefecture, Japan) for providing the authentic samples and the spectral data of **7d-f** for purposes of comparison.



Scheme 3.

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4. Preparation of **1a:** Treatment of D-Glucal (2.03 g, 13.9 mmol) with pivaloyl chloride (9.76 g, 81.0 mmol) in the presence of DMAP (0.17 g, 1.39 mmol) and Et_3N (22.9 ml, 165 mmol) in THF (80 ml) at room temperature for 72 h gave tri-*O*-pivaloyl-D-glucal (3.45 g, 62%) as a colorless solid (mp. 110-111 ℃ / MeOH), which was allowed to react with 2,2-dimethyldioxirane (11.3 mmol) in acetone[1], to afford **1a** (2.36 g, 66%) as colorless crystals (mp. 98.0-99.0 ℃) after recrystalization with hexane.
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