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A SIMPLE METAL FREE 2'-DISCRIMINATED GLUCOSIDATION PROCEDURE†

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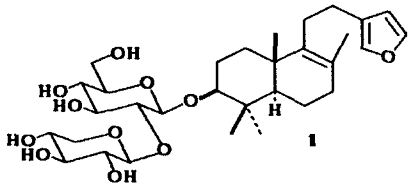
Abstract: A simple and practical glucosidation procedure is reported. A variety of 2'-discriminated glucosides have been prepared in 50-80% yield under thermal conditions without using metal catalysis.

During our synthetic program of the sweet tasting glycosides, baiyunoside (1) and its analogs,[1,2] we have observed that the C-2 hydroxyl group of a non-protected glucosyl halide such as 2[3] is highly reactive[4] in comparison with the corresponding tetraacetate under modified Koenigs-Knorr conditions using silver triflate[5] or mercury(II) triflate[6] with 1,1,3,3-tetramethylurea (hereafter TMU). We also noticed that the removal of trace water from the reaction mixture is of paramount importance in order to insure high yields of glucosidation. Thus we employed an apparatus I containing molecular sieves which continuously azeotropically removes water from the reaction vessel.[7] Here we disclose our observation that the glucosidation occurs smoothly simply by mixing an alcohol, a glucosyl chloride such as 2, and TMU under an essentially neutral conditions at 110-120 °C without using any metal salt. A modest solvent effect was observed.[8] This is the first practical glucosidation via a simple operation—without using a metal catalyst—after more than 85 years history of Koenigs-Knorr type glucosidation.[9,10]

Our results are summarized in Table I. The glucosidation of cholesterol which follows is a typical experimental example. A mixture of cholesterol (200 mg, 0.51 mmol), 3,4,6-tri-*O*-acetyl-*ß*-*D*-glucopyranosyl chloride (2)[11] (331 mg, 1.02 mmol), and TMU (118 mg, 1.02 mmol) in dichlomthane (10 mL) was heated at reflux using apparatus I containing molecular sieves 4A (5 g) under argon atmosphere. After the reflux for 3 h the stopcock A was closed in order to evacuate the solvent, and the concentrated mixture was heated to 110 °C for an additional 2 h. The crude residue was chromatographed on silica gel (30 g) with hexane and ethyl acetate as an eluant to give a mixture of α- and *ß*-glucosides (256 mg, 73% yield), along with small amount of oligosaccharides (73mg, 15%). The mixture of α- and *ß*-glucosides was further subjected to HPLC using Develosil ODS-7 column (10 x 250 mm) with methanol as an eluant (flow rate 6 mL/



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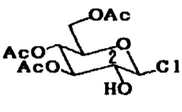

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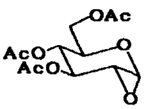

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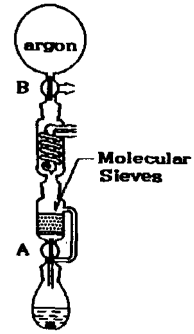
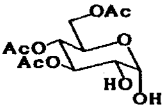


apparatus I



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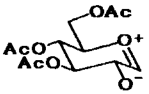

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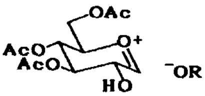

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min) to give the α-glucoside (Rt 12.7 min, 129 mg) and the β-glucoside (Rt 11.1 min, 115 mg). Although 1,2-anhydro sugar 3 was not detected in the reaction mixture by the direct comparison on TLC with an authentic sample, 3,4,6-tri-*O*-acetyl-*D*-glucose (4) (6.4 mg, 2%) was obtained.

We propose a zwitter ionic intermediate 5 as the reacting species under our anhydrous conditions produced by the reaction of 2 and TMU. The negative charge of 5 attracts an alcohol, thus promoting proton transfer (cf. 6) and subsequent glucosidation.

Generally high yields were obtained when this procedure was applied to primary and secondary alcohols, however tertiary alcohols were converted to glucosides in poor yields. Even in a case of primary alcohol, small amount of oligosaccharide formation was detected despite of the increased steric bulkiness around the resulted 2' alcohol group. Stereoselectivity was not observed in each case, and almost equal amounts of α- and β-glucosides were obtained.

Table I. 2'-Discriminated glucosidation of alcohols with 2 (2 equiv) and TMU (2 equiv) at 110-120 ℃ for 2 h after removal of contaminating water using apparatus I.

run	alcohol	yield[a]	α/β ratio[b]
1	cholesterol	73%	52:48
2	decanol	84%	61:39
3	geraniol	56%	39:61
4	cyclohexanol	76%	56:44
5	(±)-baiyunol[c]	53%[d]	49:51

[a] Combined isolation yield of α- and β-glucosides. [b] Determined by HPLC analysis.

[c] See ref 2. [d] 30% of starting (±)-baiyunol was recovered.

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7. When the reaction was carried out in the presence of molecular sieves in the reaction vessel, yield of glucosides became lower.
8. Glucosidation occurs more readily in nitromethane, acetonitrile, or dioxane, and slowly in benzene, dichloromethane, or chloroform.
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11. Although crystals of 2 are rather stable, those turn to 4 very smoothly when the crystals are dissolved in any wet solvents.

†Dedicated to Professor Ryoji Noyori of Nagoya University on the occasion of his 50th birthday.

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