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THERMAL GLYCOSIDATION WITH BENZYLATED GLYCOSYL CHLORIDES: A VERY SIMPLE PROCEDURE FOR *O*-GLYCOSIDATION

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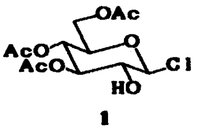
Thermal condensation of benzylated glucosyl chlorides with a variety of alcohols has been achieved efficiently without using any metal salts via a simple operation, and the procedure is used not only for a glucosyl halide, but also for a xylosyl chloride.

KEYWORDS *O*-glycosidation; thermal glycosidation; glucosyl chloride; xylosyl chloride; disaccharide

The paramount importance of *O*-glycosidic linkages in natural product synthesis has been widely pointed out and a large number of efficient glycosidation procedures have been developed.[1,2] We recently described a 2'-discriminated *O*-glucosidation procedure[3] with 3,4,6-tri-*O*-acetyl-*β*-*D*-glucopyranosyl chloride (1)[4] under thermal conditions without using any metal salt, and discussed the efficiency of this novel glycosidation on the basis of higher reactivity of the 2-hydroxyl group of non-protected glucosyl chloride.[5] Now we have found that the efficiency of the thermal condensation between glucosyl halides with alcohols is not limited to only the 2-hydroxyl group of non-protected glucosyl chloride 1, but is also generally applicable to a variety of perbenzylated glycosyl halides such as 2 and 3. The condensation of 2,3,4,6-tetra-*O*-benzyl-*α*-*D*-glucopyranosyl chloride (2)[6] with a variety of alcohols has been achieved smoothly under analogous thermal conditions in the presence or absence of tetramethylurea (TMU). Preliminary azeotropic removal of contaminating water is recommended to get glycosides in better yields. Therefore the glycosidation procedure described herein could be a general way considering its operational simplicity and no need to use any hazardous heavy metal salt.



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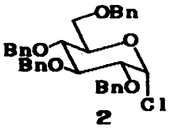

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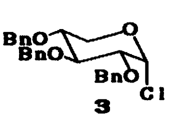

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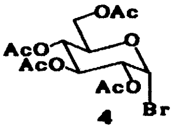

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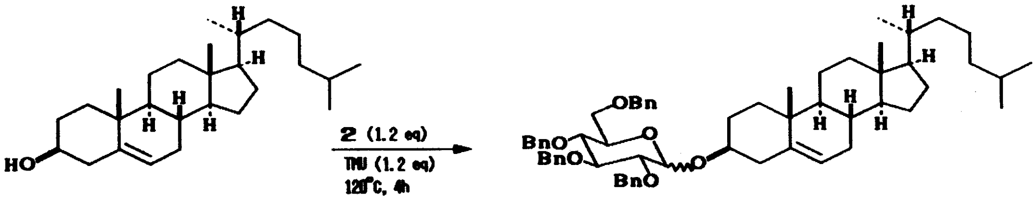


5ab (92% yield, α/β 60:40)

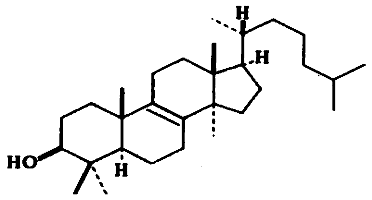
The results are summarized in Table I. In most cases the glycosidations are completed only by heating a neat mixture of an alcohol and a glycosyl chloride around 120 °C for 2 to 4 h with or without TMU after azeotropic removal of contaminating water using dichloromethane. The typical experimental detail follows. A solution of cholesterol (589 mg, 1.5 mmol), glucosyl chloride 2 (1.03 g, 1.8 mmol), and TMU (209 mg, 1.8 mmol) in dichloromethane (20 ml) was heated for 2 h under reflux through a column containing molecular sieves 4A (20 g).[3] The solvent was transferred to the upper column by closing a stopcock, and the resulting residue was heated to 120 °C for 4 h. The diluted solution obtained by opening the stopcock was directly subjected to column chromatography on silica gel (30 g) using hexane and ethyl acetate (15:1) as an eluant affording a mixture of α- and β-glucosides **5ab** (1.26 g, 92% yield). These glucosides were separated by HPLC with a YMC-D-SIL-5 column (20 x 250 mm) using hexane and ethyl acetate (15:1) as an eluant (flow rate 15 ml/min) to give α-glucoside **5a** (Rt 25.6 min) and β-glucoside **5b** (19.5 min) in a ratio of 60:40.

When the reaction was carried out at 120 °C for 2 h without using molecular sieves, the yield of **5ab** was decreased to 79%, but the α-selectivity was increased to 85:15. Without using TMU, glucosides **5ab** were also obtained in 84% yield in an α/β ratio of 46:54.

As seen in Table I, this procedure is applicable to a variety of primary and secondary alcohols and yields are generally quite satisfactory with only a 1.2 equivalent of glycosyl chlorides. Although the glycosidation of the 2' hydroxyl group of glycosides is generally difficult due to their increased steric bulkiness,[2a] both of the α- and β-glycosides **7a** and **7b**, prepared from cholesterol and 1 by our previously described method,[3] were transformed to disaccharides **8ab** and **9ab**, respectively, in moderate yields by using a 1.8 equiv of 2.

2,3,4-Tri-*O*-benzyl-α-*D*-xylopyranosyl chloride (3) was also effectively used for this thermal glycosidation reaction, giving rise to xylosides in high yields under analogous conditions. For example, the reaction of cholesterol with 3 at 140 °C for 2 h afforded xylosides **10ab** in 64% yield.

However 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide (4) was not effective in this thermal glycosidation. The major product of its reaction with cholesterol at 120 °C for 2 h was cholesterol acetate (45% yield), and the glycosides were obtained in only 23% yield. The cholesterol acetate must have been produced by the fragmentation of the ortho ester intermediate 11 indicated below.[7]



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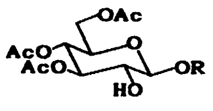
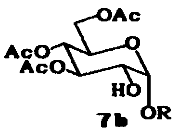
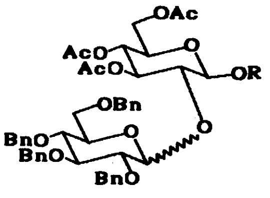


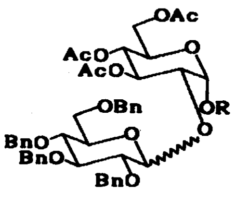
7a



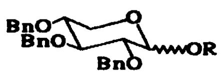
7b



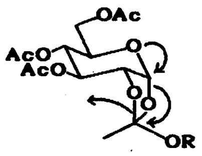
8ab



9ab



10ab



11

7ab–11ab R = cholesteryl

Table I. Thermal Glycosidation of Alcohols

Run	Alcohol	Donor	Temp(°C)	Time(h)	Yield(%)	α/β ratio[a]
1	Cholesterol	2	120	4	92	60:40
2	Cholesterol[b]	2	120	4	84	46:54
3	Cholesterol[c]	2	120	4	79	85:15
4	Cholesterol	3	120	3	64	45:55
5	Cholesterol	4	140	2	23[d]	50:50
6	Decanol	2	120	2	69	74:26
7	Decanol	3	120	2	73	57:43
8	Geraniol	2	120	2	94	71:29
9	Geraniol	3	120	2	54	63:37
10	Dihydrolanosterol (6)	2	120	8	55	59:41
11	Glucoside 7a	2	140	2	39[e]	40:60
12	Glucoside 7b	2	160	5	22[f]	69:31

a) The α/β ratio was established by RI detector (Shimadzu RID-6A) equipped with Shimadzu Chromatopac C-R6A. b) Reaction was carried out without TMU. c) Without prior azeotropic removal of contaminating water. d) Cholesterol acetate was the major product in 45% yield. e) Starting alcohol (48%) was recovered. f) Starting alcohol (61%) was recovered.

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