Simple syntheses of indol-1-yl glucosides

SIMPLE SYNTHESES OF INDOL-1-YL GLUCOSIDES[1]

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Abstract — A lithium hydroxide promoted glucosidation of 1-hydroxyindoles with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide is newly developed. Applying this method, the first and simple syntheses of novel indol-1-yl glucosides were achieved.

Variety of glycosides and nucleosides are widely distributed in nature and they play important roles in living organisms.[2] In our 1-hydroxyindole hypotheses,[3a] we speculated the existence and roles of a novel type of compounds, indol-1-yl glycosides (**1**, **2**, etc.) as shown in general formulae in Figure 1. Although many glucosidation methods have been reported,[4] we have not been able to obtain satisfactory results in applying them[5] to 1-hydroxyindoles with an hope to produce **1**. Now, we wish to report the success in developing a novel synthetic method well-suited for the preparation of **1**.

Among various 1-hydroxyindoles, 1-hydroxy-*Nb*-methoxycarbonyltryptamine (**3a**), a potent platelet aggregation inhibitor,[6] was selected as a substrate for examining glucosidation with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[7] (**4**) as shown in Scheme 1. Since 1-hydroxyindoles are weak acids,[3b] the reaction was carried out in the presence of base, and the glucosidated products were isolated after acetylation with Ac_2O and pyridine in order to facilitate separation.

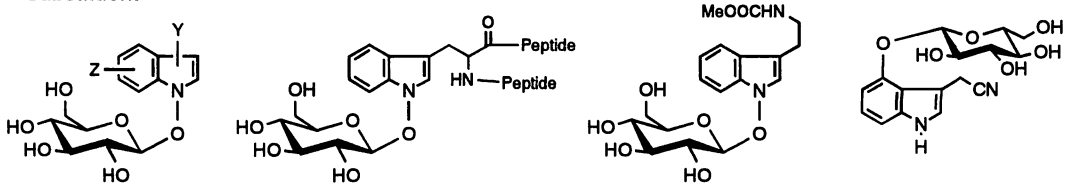
Typical procedure is as follows. Initially, **3a** was dissolved in a methanol solution containing an appropriate base (6 mol eq.) and the solvent was evaporated under reduced pressure to dryness. To the resultant metal salt of **3a** was added a solution of **4** (3 mol eq.) in DMF and allowed to react at room temperature for 4 h. After usual work up, the products were acetylated with Ac_2O and pyridine at room temperature to give **5a** and **6a**.

It was found that DMF is the solvent of choice among the examined MeOH, Et_2O, THF, and DMF, and the yield of **5a** depends on bases. Thus, when Cs_2CO_3 was used, **5a** and **6a** were generated in 15 and 65% yields, respectively. Employing $CsOH \cdot H_2O$, the yield of **5a** was raised to 24% together with 30% yield of **6a**. Slight increase in the yield of **5a** to 28% was observed upon use of KOH in addition to 37% yield of **6a**. In the case of NaOH, **5a** and **6a** were produced in 43 and 52% yields, respectively. Dramatical improvement in the yield of **5a** up to 93% (Table 1, Entry 1) was finally achieved upon employing LiOH as the base though formation of **6a** was observed in 6% yield. The β-configulation of **5a** was proved by the coupling constant of the anomeric proton (J=8.1 Hz) which is readily discernible in the NMR spectrum of indol-1-yl β-D-glucopyranoside (**7**) obtained in 84% yield by hydrolysis of **5a** with NaOMe in MeOH.

Under the same reaction conditions, the LiOH promoted reaction was successfully applied to other biolog-

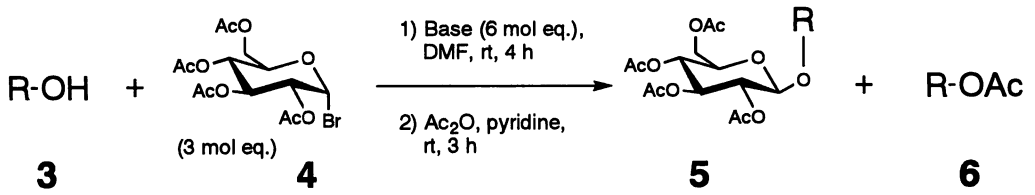
Figure 1

Y, Z = an appropriate substituent



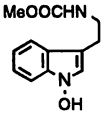
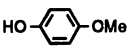
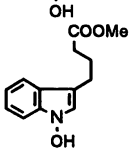
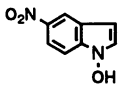
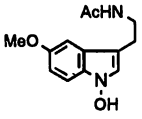
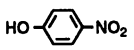
1 2 7 8

Scheme 1



3 4 5 6

Table 1. Reaction of Hydroxy Compound (**3**) with 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Bromide (**4**) in the Presence of LiOH, Followed by Acetylation with Ac_2O and Pyridine

Entry		R-OH **3**	Yield (%) of **5**	Entry		R-OH **3**	Yield (%) of **5**
1	**a**		**93**	4	**d**		**54**
2	**b**		**78**	5	**e**		**42**
3	**c**		**77**	6	**f**		**35**
				7	**g**		**29**

ically active 1-hydroxyindoles. Methyl 1-hydroxyindole-3-butylate[6] (**3b**) and 1-hydroxymelatonin (**3c**) afforded **5b** and **5c** in 78 and 77% yields, respectively (Entries 2,3). When the reaction was applied to

p-methoxyphenol (**3d**), the yield of the expected glucoside (**5d**)[8] was 54% (Entry 4). On the other hand, more acidic 1-hydroxy-5-nitroindole (**3e**), 8-oxyquinoline (**3f**), and *p*-nitrophenol (**3g**) afforded the corresponding glucosides, (**5e**, **5f**, and **5g**[9]), in 42, 35, and 29% yields, respectively (Entries 5—7). Application of these facts to the first synthesis of capparilosides A[10] (**8**) was successfully carried out as reported in the previous paper.[11]

These data clearly suggest that this LiOH promoted reaction is p*Ka* dependent and it seems to give sufficient results for the hydroxy compounds having p*Ka* values of 8—10.[3b]

In conclusion, we have developed a novel method which is suitable for the syntheses of glucosides of 1-hydroxyindoles. A study for investigating their chemical reactivities and biological evaluations, and further extension to various glycosides syntheses are currently in progress.

REFERENCES AND NOTES

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