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-
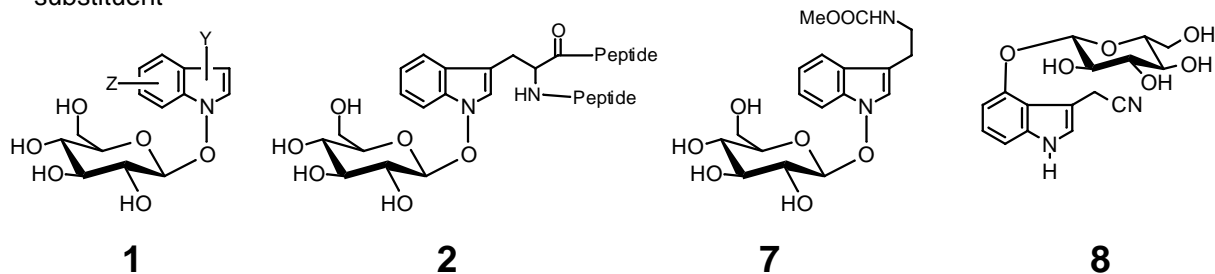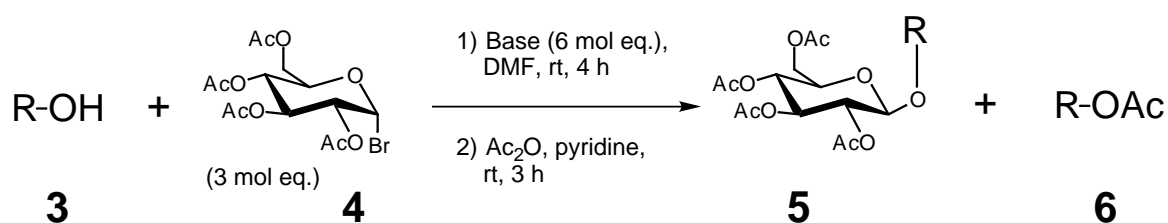
Figure 1

Y, Z = an appropriate substituent

1   **2**   **7**   **8**

Scheme 1

R-OH + (3 mol eq.) → + R-OAc

1) Base (6 mol eq.), DMF, rt, 4 h

2) Ac₂O, pyridine, rt, 3 h

3   **4**   **5**   **6**

Table 1. Reaction of Hydroxy Compound (**3**) with 2,3,4,6-Tetra- *O*-acetyl-α-D-gluco-pyranosyl Bromide (**4**) in the Presence of LiOH, Followed by Acetylation with Ac₂O 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 cappariloside 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

1. This is Part 101 of a series entitled "The Chemistry of Indoles". Part 100: M. Somei, Y. Fukui, M. Hasegawa, N. Oshikiri, and T. Hayashi, *Heterocycles*, 2000, **53**, 1725. All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or oils, respectively. **5a**, colorless oil, $[\alpha]_D^{24}$ –8.4° (c=0.25, MeOH); **5b**, mp 88—89 °C (EtOH), $[\alpha]_D^{28}$ –24.2° (c=0.43, CHCl$_3$); **5c**, mp 138—140 °C (MeOH), $[\alpha]_D^{27}$ –22.2° (c=0.28, CHCl$_3$); **5e**, mp 211—212 °C (MeOH), $[\alpha]_D^{26}$ –38.2° (c=0.34, CHCl$_3$); **5f**, mp 166—168 °C (EtOH), $[\alpha]_D^{26}$ –57.7° (c=0.24, CHCl$_3$); **7**, colorless oil, $[\alpha]_D^{27}$ –42.5° (c=0.21, MeOH).

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3. a) Review: M. Somei, *Heterocycles*, 1999, **50**, 1157 and references cited therein. b) The p*Ka* values of compounds: (±)-*Nb*-acetyl-1-hydroxytryprophan methyl ester, 9.8; **3b**, 8.4; **3d**, 10.2; **3e**, 6.8; **3f**, 4.99, **3g**, 6.9.

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5. Direct heating of **3a-c** with α-D-glucose and usual acid catalyzed acetal exchange reaction[4] of penta-*O*-acetyl-α-D-glucopyranoside[4a] with **3a-c** did not afford the expected glucosides (**5a-c**). Reactions of **3a-c** with **4** using Bu$_4$N$^+$HSO$_4^-$ in aq. NaOH–CHCl$_3$[9b] was not successful. Reactions of **3a-c** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[4b] under acidic conditions resulted in the formations of tars.

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