Highly Efficient β-Glucosylation of the Acidic Hydroxyl Groups, Phenol and Carboxylic Acid, with an Peracetylated Glucosyl Fluoride Using a Combination of BF_3·Et_2O and DTBMP as a Promoter

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Received 22 July 1999

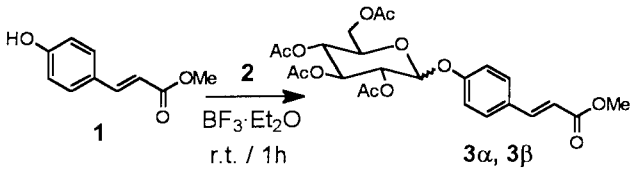
Abstract: A combination of BF_3·Et_2O and DTBMP was established to be an efficient promoter of β-glucosylation of both phenols and carboxylic acids with a peracetylated glucosyl fluoride (**2**). This new method achieved remarkably high yields and β-selectivity.

Key word: phenyl glucoside, 1-acylglucose, BF_3·Et_2O, 2,6-di-*tert*-butyl-4-methylpyridine, peracetylated glucosyl fluoride

Aryl β-glucosides and acyl β-glucosides are widely found in natural products such as anthocyanin, flavonoids, polyphenols and antibiotics and play key roles in the expression of important biological functions.[1,2,3] However, in spite of a number of methods reported in the literature,[4] glucosylation methods for hindered or low-nucleophilic phenols, substituted with electron-withdrawing groups, are not always satisfactory in terms of yield, stereoselectivity or convenience.[3,4a] For example, in the case of low-nucleophilic phenols, the Koenigs-Knorr reaction using a glucosyl bromide or chloride predominantly gives an orthoester or its transformed 1-hydroxy sugar, but only a small amount of glucosides.[4e] Though peracetylglucosyl fluoride (**2**) is very stable and effective for 1,2-*trans*-β-glucosides,[4b,c] it is not suitable as a sugar donor because of its low reactivity.[5] Yamaguchi have approached the problem of glucosylation of phenols using BF_3·Et_2O / 1,1,3,3-tetramethylguanidine (TMG) as a promoter.[6] A Lewis acid-and-base promotion system has been the subject of our attention.

We have thereby developed a very efficient β-glucosylation methodology for phenols and carboxylic acids by peracetylated glucosyl fluoride (**2**), using a combination of a Lewis acid and highly hindered base, BF_3·Et_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Initially, methyl *p*-coumarate (**1**), a low-nucleophilic phenol, was selected as a glucosyl acceptor for the screening of the *O*-glucosylation promoters (Table 1).[7] BF_3·Et_2O specifically enhanced its reaction to give the glycoside (in 37% yield, **3α** predominated over **3β**)[6] in spite of being base-free, whereas other Lewis acids, such as $TiCl_4$, TMSOTf, and $SnCl_4$, afforded no glucosyl-products. Using CH_3CN as the solvent and BF_3·Et_2O as the Lewis acid in the presence of DTBMP, the reaction gave **3** in 80% yield. However, the glucosylation with TMG and 2,6-lutidine gave **3** in 68% and 32%, respectively. With the addition of the base, β-glucosides predominated. The changing of the solvent from CH_3CN to CH_2Cl_2 improved the yield of the glucoside from 80% to 92% (Table 1). However, this reaction is not applicable to the glucosylation of simple alcohols.[8]

Table 1 Glucosylation of methyl *p*-coumarate



Base	Solvent	Yield (%)[a]	α / β[b]
TMG	CH_3CN	68	5 / 95
none	CH_3CN	37	79 / 21
2,6-lutidine	CH_3CN	32	7 / 93
DTBMP	CH_3CN	80	4 / 96
DTBMP	CH_2Cl_2	92	6 / 94

[a] Isolated yield.

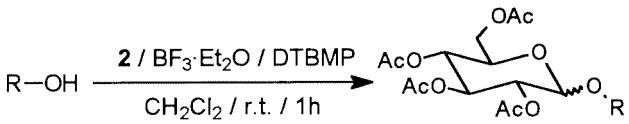
[b] α/β Ratio was determined by ^1H NMR spectra or isolation.

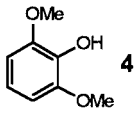
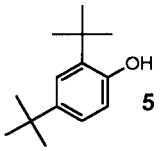
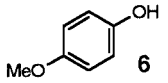
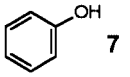
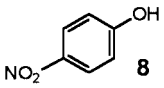
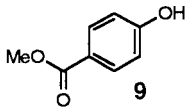
It was reported that phenols with electron-donating groups showed high β-selectivity[6] and electron-withdrawing group retard the reaction.[4a] Thus, the high yield and high β-selectivity might be realized by the increasing the nucleophilicity of the phenols by formation of the naked phenolic hydroxyl anion with the hindered base (DTBMP). Also, high β-selectivity might be realized by the SN2-type process or the neighboring group participation of the carbonyl oxygen at the C2. Less hindered pyridines such as 2,6-lutidine may directly coordinate Lewis acid, so that the reactivity is reduced.

The phenols substituted with electron-donating groups selectively gave β-glycosides (Table 2). Furthermore, in spite of hindered phenols, both **4** and **5** gave high yields and complete β-selectivity. The phenols substituted with

electron-withdrawing groups, **8** and **9**, also predominantly gave β-glucosides (Table 2).

Table 2 Glucosylation of phenols using $BF_3{\cdot}Et_2O$ / DTBMP as a promotor



Substrate	Product	Yield (%)[a]	α / β[b]
 **4**	**10**	98	β
 **5**	**11**	91	β
 **6**	**12**	93	β
 **7**	**13**	98	β
 **8**	**14α, 14β**	96	17 / 83
 **9**	**15α, 15β**	96	7 / 93

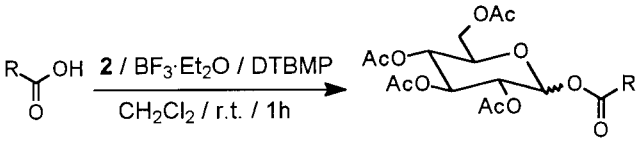
[a] Isolated yield.

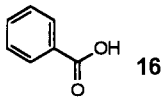
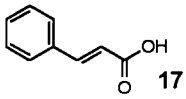
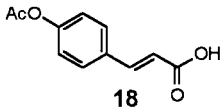
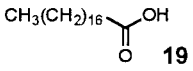
[b] α/β Ratio was determined by ^{1}H NMR spectra.

This new method also proved applicable for β-selective acylation of the anomeric position of glucose (Table 3). Some 1- β-acylglucopyranoses are well-known to be very important in the biosynthetic pathway.[2] For instance, it is well-known that ellagitannin[2a] is a secondary plant metabolite and all the hydroxyl groups of the sugar moiety are acylated. The peracetylated glucosyl fluoride (**2**) reacted with aromatic or aliphatic carboxylic acids in the presence of the combination of $BF_3{\cdot}Et_2O$ and DTBMP to afford 1-acylglucopyranose, with the β isomer predominating.

Finally, our attention was directed to estimation of the difference of the reactivity of phenolic hydroxyl group and carboxylic acid. In order to examine the rates of *O*-glucosylation and 1-acylation, a 1 : 1 mixture of **1** and **18** was

Table 3 Glucosylation of carboxylic acid using $BF_3{\cdot}Et_2O$ / DTBMP as a promotor



Substrate	Product	Yield (%)[a]	α / β[b]
 **16**	**20α, 20β**	73	6 / 94
 **17**	**21**	71	β
 **18**	**22**	67	β
 **19**	**23**	62	β

[a] Isolated yield.

[b] α/β Ratio was determined by ^{1}H NMR spectra.

treated with **2**, $BF_3{\cdot}Et_2O$ and DTBMP. This reaction gave **3** and **22**, 73% and 10%, respectively.[9] Therefore, phenyl glucoside was formed in preference to the glucosyl ester with this new method.

In conclusion, a combination of $BF_3{\cdot}Et_2O$ and DTBMP have proved to be a highly effective promoter for the β-glucosylation of phenols and carboxylic acids.

Acknowledgement

This work was supported by the Grants-in-Aid for Scientific Research (COE) No. 07CE2004 and Scientific Research on Priority Area No. 10169224 from the Ministry of Education, Science, Sports, and Culture of Japan, as well as a Grant-in-Aid from the Ministry of Agriculture, Forestry, and Fisheries of Japan.

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(7) All reactions were carried out by use of the following equivalency: **1** / **2** / $BF_3{\cdot}Et_2O$ / base = 1 / 1.5 / 4 / 4.

(8) Using cyclohexanol, a β-phenethyl alcohol, as a glucosyl acceptor, the corresponding glucosyl products were not afforded.

(9) This reaction was carried out with the following equivalency: **1** / **18** / **2** / $BF_3{\cdot}Et_2O$ / DTBMP = 1 / 1 / 1 / 4 / 4.

(10) **Typical experimental procedure**: To a mixture of phenol (0.1 mmol, 9 mg), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (0.15 mmol, 52 mg) and 2,6-di-*tert*-butyl-4-methylpyridine (0.4 mmol, 82 mg) in CH_2Cl_2 (2 ml) was added $BF_3{\cdot}Et_2O$ (0.4 mmol, 0.05 ml) at room temperature. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 and the organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (Hexane-AcOEt 1 : 1) to afford phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (41 mg, 98 %).

Article Identifier:
1437-2096,E;1999,0,10,1627,1629,ftx,en;Y15199ST.pdf