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Note

Environmentally friendly C-glycosylation of phloroacetophenone with unprotected D-glucose using scandium(III) trifluoromethanesulfonate in aqueous media: key compounds for the syntheses of mono- and di-*C*-glucosylflavonoids

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Abstract—The direct C-glycosylation of phloroacetophenone with an unprotected D-glucose in aqueous media using scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) as the catalyst, gave mono- and bis-*C*-β-glycosylic compounds in highest total yield of 81%. The second and third use of the recovered $Sc(OTf)_3$ afforded them in total yields of 56% and 53%, respectively.

Keywords: *C*-Glycosylflavonoid; Direct C-glycosylation; Unprotected glucose; $Sc(OTf)_3$; Aqueous media; Recycling

The availability of a variety of *C*-glycosylflavonoids, which are found in low concentrations in plant tissue such as citrus fruit peels, are attractive because they are nontoxic and have hypotensive activity.[1] A number of *C*-glycosylic aryl compounds ('aryl *C*-glycosides') with antibiotic activity have also been isolated from microorganisms, and some useful synthetic methods for preparing these aryl *C*-glycoside antibiotics have been reported. One such method is Suzuki's C-glycosylation technique, in which the reaction of a selectively hydroxyl-protected polyphenol with per-*O*-benzylglycosyl fluoride proceeds via an *O*→*C* glycoside rearrangement.[2] We also reported on the synthesis of some *C*-glycosylflavonoids, using Suzuki's method.[3] This reaction results in high yields and in high regio- and stereoselectivities, but requires the use of undesirable solvents such as CH_2Cl_2. In addition, the selective protection reaction of hydroxyl groups of the glycosyl donor and the polyphenol derivative such as phloroacetophenone did not proceed in good yield. One reason for this is that *O*-demethylation by acid hydrolysis of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside is low yield,[4] and *C*-alkylation tends to occur between the 1,3-diol groups on the benzene ring under the protection reaction conditions of the phenolic hydroxyl. As a result, the reaction requires considerable operating time, and a number of reagents be used in the protection reaction.

Toshima and co-workers recently reported on the environmentally benign C-glycosylation of selective hydroxyl-protected aryl compounds with unprotected 2-deoxy sugars using a solid acid in aqueous media, that afforded aryl *C*-glycosides in good yields with good β-selectivity.[5] After C-glycosylation of the methyl-protected phenol, however, difficulties are encountered in the deprotecting of the methoxyl group.[6]

To the best of our knowledge, a reliable method for the direct C-glycosylation of unprotected polyphenols with unprotected general sugars such as a D-glucose in aqueous media has not been reported.[7] Since *C*-glycosylflavonoids are typically harmless, we attempted to examine such environmentally friendly glycosylation conditions as a route to their synthesis. The goal was

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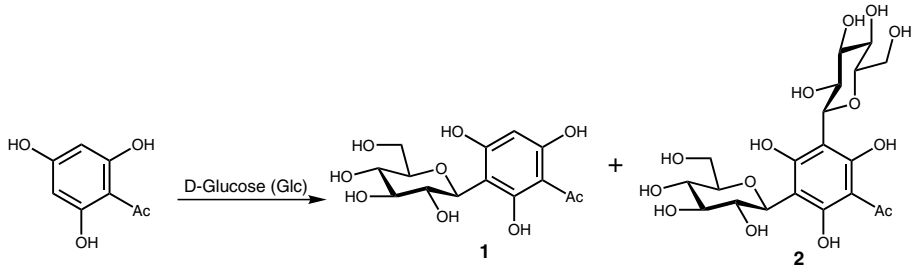
to develop conditions for the glycosylation of an unprotected polyphenol using an unprotected sugar in aqueous media.

Since Kobayashi and co-workers[8] recently developed a number of carbon–carbon bond-forming reactions using rare-earth metal triflates, that function as Lewis acids, even in aqueous media, we attempted the use of ytterbium(III) trifluoromethanesulfonate ($Yb(OTf)_3$) and $Sc(OTf)_3$ to satisfy the above reaction conditions (Table 1). We examined the C-glycosylation of phloroacetophenone, a key compound in *C*-glycosylflavonoid synthesis, with D-glucose in aqueous acetonitrile solution. Detailed structural analyses of the sugar moieties were carried out after acetylation of the products.[7] A structural analysis of the *C*-glucosides obtained indicated that they were, in fact, the desired mono- and bis-*C*-β-D-glucopyranosides (**1**[3a,b], **2**[9,10]). As of this writing, the bis-*C*-glucoside **2** produced here could not be synthesized by repeating the *O*→*C* glycoside rearrangement method from phloroacetophenone.[10] The reaction barely proceeded at room temperature (entry 3). When the temperature was increased to 65 °C, 80 °C, or to reflux, the yield of the *C*-glycosides increased (entries 4, 5 and 8). A higher yield was obtained using $Sc(OTf)_3$, rather than $Yb(OTf)_3$ as a promoter (entry 2). The use of *p*-toluensulfonic acid as a promoter led to no reaction,[7] and the use of a Brønsted acid such as HCl and H_2SO_4 also resulted in no yields of *C*-glucosides (entry 1). When the amount of added $Sc(OTf)_3$ was increased, the yield of bis-*C*-glucoside **2** was also increased (entries 5 and 10). When acetonitrile–water was used as a solvent system, good yield and selectivity of the mono-*C*-glucoside was obtained (entries 6 and 7). An ethanol–water solvent system gave a good yield but no selectivity (entries 9 and 10). The use of 0.2 equiv of $Sc(OTf)_3$ in 2:1 EtOH–H_2O gave the highest yield (81%) of *C*-glucosides (**1**: 43%, **2**: 38%) (entry 9). The best yield of the mono- and bis-*C*-glucosides was 48% and 40%, respectively (entries 6 and 10). In this reaction, the additional formation of small amounts of phloroacetophenone dimers linked via a D-glucose chain was confirmed. The use of more than 0.4 equiv of $Sc(OTf)_3$ and 3 equiv of D-glucose, or an extension of the refluxing time, or the use of water as a solvent (entry 11) did not lead to an improved yield of mono- and bis-*C*-glucosides, and side reaction products made the product separation by silica-gel chromatography difficult. Since phenol or 2,4-*O*-dimethyl-protected phloroacetophenone was unreactive under these reaction conditions, it is suggested that this direct *C*-glycosylation of polyphenols proceeds regioselectively only between the 1,3-diol. Thus, this reaction is a carbon–carbon bond-forming reaction of the 1,3-diketone with an aldehyde. In entry 10, the second use of the recovered glucose and $Sc(OTf)_3$ gave the *C*-glycosides in a total of 56% yield (**1**:**2** = 68:32), and further the third use in a total of 53% yield (**1**:**2** = 81:19). Direct recycling of the $Sc(OTf)_3$ used in the reaction with excess glucose permits excellent yields to be obtained.

Table 1. C-glycosylation of phloroacetophenone with D-glucose in aqueous media



Entry	Glc (equiv)	Promoter (equiv)	Solvent	Temp (°C).	Time (h)	Yield (%)	
						mono-C (**1**)	bis-C (**2**)
1	3.0	*p*-TsOH (−0.4)	CH_3CN:H_2O (1:1)	Reflux	6	No reaction	
2	3.0	$Yb(OTf)_3$ (0.2)	CH_3CN:H_2O (1:1)	Reflux	8	13	3
3	1.5	$Sc(OTf)_3$ (0.1)	CH_3CN:H_2O (1:1)	rt	24	No reaction	
4	3.0	$Sc(OTf)_3$ (0.2)	CH_3CN:H_2O (1:1)	65	20	16	10
5	3.0	$Sc(OTf)_3$ (0.2)	CH_3CN:H_2O (2:1)	Reflux	8	43	29
6	3.0	$Sc(OTf)_3$ (0.1)	CH_3CN:H_2O (2:1)	Reflux	8	48	14
7	3.0	$Sc(OTf)_3$ (0.2)	CH_3CN:H_2O (1:2)	Reflux	8	47	24
8	3.0	$Se(OTf)_3$ (0.2)	THF:H_2O (2:1)	Reflux	8	16	12
9	3.0	$Sc(OTf)_3$ (0.2)	EtOH:H_2O (2:1)	Reflux	9	43	38
10	3.0	$Sc(OTf)_3$ (0.4)	EtOH:H_2O (2:1)	Reflux	6.5	39	40
11	5.0	$Sc(OTf)_3$ (0.2)	H_2O	Reflux	8	8	34
12	3.0	$Sc(OTf)_3$ (0.2)	CH_3CN	Reflux	8	5	22
13	3.0	$Sc(OTf)_3$ (0.2)	1,4-Dioxane	Reflux	3	0	0

Since the C-glycosylation method developed here is very simple and environmentally friendly and proceeds with high regio- and β-stereoselectively, we conclude that this reaction has considerable potential for use in the synthesis of nontoxic naturally occurring *C*-glycosylflavonoids, especially di-*C*-glycosylflavonoids in which most of the *C*-β-glycosyl residues are bonded between the 1,3-diol of the polyphenol molecule.[1]

1. Experimental

1.1. General

The solvents used in this reaction were prepared by distillation. For separation and purification, at first, column chromatography was performed on MCI gel CHP20P® (high porous polymer, 75–150 μm, Mitsubishi Chemical Corp.), and then, flash column chromatography was performed on silica gel (230–400 mesh, Fuji-Silysia Co., Ltd., BW-300). Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Mass spectral data were obtained by fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA) as a matrix on a JEOL JMS-AX505HA instrument. IR spectra were recorded on a Horiba FT-720 IR spectrometer. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as an internal standard. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument.

1.2. C-Glycosylation procedure

After the mixture of phloroacetophenone (200 mg, 1.19 mmol), D-glucose (643 mg, 3.57 mmol), and $Sc(OTf)_3$ (117 mg, 0.238 mmol) were dissolved in EtOH (3 mL)/H_2O (1.5 mL) refluxed for 9 h. Water (100 mL) was added to the reaction mixture, and the suspension was passed through a column of MCI GEL CHP20P® (75–150 μm, Mitsubishi Chemical Corp., 2.5 × 10 cm) loaded with water, and the gel was then washed with 200 mL of water, to remove nonabsorbed glucose and $Sc(OTf)_3$. The nonabsorbed components, which include the unreactive glucose and $Sc(OTf)_3$, was evaporated in vacuo to give a colorless solid (550 mg). The absorbed products were eluted from the gel column with 100 mL of 50% aqueous acetone, and the eluate was evaporated in vacuo to give a pale-brown solid (442 mg) that was then separated by silica-gel column chromatography (15:30:2:1 Me_2CO–EtOAc–H_2O–AcOH) to give **1** (168 mg, 42.8%) and **2** (225 mg, 38.3%).

The recovered glucose and $Sc(OTf)_3$ (550 mg), and 200 mg of phloroacetophenone and 300 mg of additional glucose were subjected to the same reaction to give the *C*-glucosides in 56% yield (**1**:**2** = 68:32). The same glycosylation reaction in the third cycle also gave the *C*-glucosides in 53% yield (**1**:**2** = 81:19).

1.3. 3,5-di-*C*-β-D-Glucopyranosylphloroacetophenone (2)

White powder (from EtOH); mp 171–173 °C; $[\alpha]_D^{22}$ +105 (*c* 1.12, MeOH); R_f 0.13 (30:30:5:1 Me_2CO–EtOAc–H_2O–AcOH); IR (KBr) *v* 3346, 2931, 2881, 1621, 1367, 1274, 1082, and 1026 cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O) δ 2.61 (3H, s, Ar*Ac*), 3.27 (4H, m, H-3′, 3″), 3.34 (2H, t, *J* 9.5 Hz, H-4′, 4″), 3.41 (2H, br s, 2′,2″-OH), 3.48 (2H, t, *J* 9.5 Hz, H-2′, 2″), 3.62 (4H, m, H-6′a,b, 6″a,b), 4.72 (2H, d, *J* 9.5 Hz, H-1′, 1″), 4.75 (2H, br s, 6′,6″-OH), 5.01 (2H, br. s, 3′,3″-OH), 5.05 (2H, br s, 4′,4″-OH), 9.17 (1H, br s, 4-OH), 11.77 (2H, br s, 2,6-OH); ^{13}C NMR (DMSO-d_6) δ 32.8 (Ar*Ac*), 59.8 (C-6′, 6″), 69.1 (C-4′, 4″), 71.9 (C-2′, 2″), 74.5 (C-1′, 1″), 77.7 (C-3′, 3″), 81.0 (C-5′, 5″), 103.8 (C-3, 5), 104.7 (C-1), 161.15 and 161.19 (C-2, 6), 172.0 (C-4), 203.4 (Ar*Ac*); FABMS (positive, glycerol, *m*/*z*) 493 $(M+H)^+$; Anal. Calcd for $C_{20}H_{28}O_{14}$: C, 48.78; H, 5.73. Found: C, 48.52; H, 5.86.

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