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Efficient O-glycosylation of diethyl oxoglutarate via 1,2-*O*-sulfinyl derivatives

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Abstract—1,2-*O*-Sulfinyl derivatives of D- and L-arabinose, D-xylose and D-glucose treated by potassium anion of diethyl oxoglutarate gave, exclusively, the corresponding O-glycosides in 92–97% yields.

Efficient glycosylation methods are of particular interest in the synthesis of biologically important glycomolecules.[1] A number of glycosyl donors have been described as significant alternatives to glycosyl bromides and chlorides classically used, such as thioglycosides, trichloroacetimidates, glycosyl fluorides and iodides, *N*-pentenylglycosides, DISAL glycosides.[2] The formation of the glycosidic bond is often subject to competing S_N1 and S_N2 processes. The advantage of S_N2 displacement reactions is their potential for stereospecificity. Nucleophilic opening of the cyclic sulfite derivatives is regio- and stereospecific at the anomeric centre.

In the previous work, we have shown that 1,2-*O*-sulfinyl monosaccharide derivatives are useful precursors for stereoselective N-glycosylation reactions to form glycosyl azides and 1,2-cyclic carbamates[3,4] for O-glycosylations aimed at obtaining aryl-glycosides[5] and C-glycosylation towards the syntheses of cyanoglycosides.[6]

Given our past successes with these substrates we became interested in studying their reactivity towards the enolate anion derived from diethyl 3-oxoglutarate. Dialkyl 3-oxoglutarates have been studied in metal complexation reactions and their alkylation.[7] They have also been used as starting materials for syntheses of phenolic derivatives.[8] For example, mycophenolic acid, which possesses many biological activities including antifungal, antibacterial and immunosuppressive properties, was prepared from 2-geranyl-dimethyl-3-oxoglutarate (Fig. 1).[9]

1,2-*O*-Sulfinyl-glycofuranoses and pyranoses **4a**–**d** were treated with enolate anion formed in situ from diethyl 3-oxoglutarate **1** (Fig. 2 and Table 2).

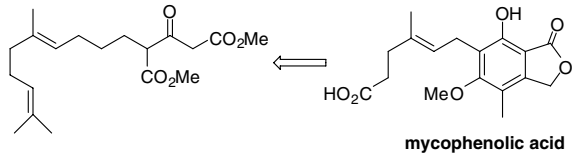

Figure 1.

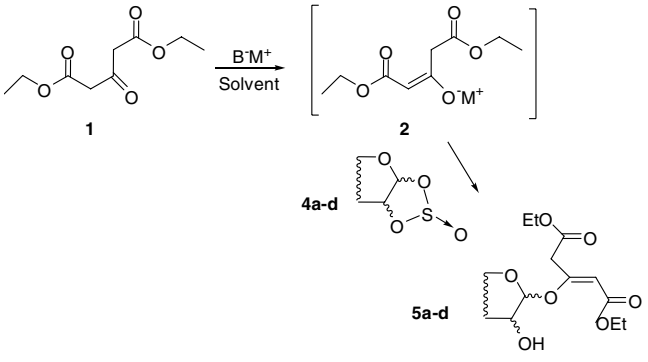

Figure 2.

Keywords: Cyclic sulfite; Carbohydrates, Monosaccharides; Nucleophile substitution; Stereospecific glycosylation.
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3,4-*O*-Isopropylidene-D- and L-arabinopyranoses **3a** and **3b** were selectively synthesized from D- and L-arabinoses, respectively, by treatment with 2,2-dimethoxypropane in dry DMF in the presence of catalytic *p*-TsOH (Table 2).[11]

3,5-Di-*O*-benzyl-D-xylofuranose **3c** was prepared from diisopropylidene-D-xylofuranose in three steps in 57% overall yield.[12] Diisopropylidene D-glucopryranose afforded 3,4,6-tri-*O*-benzyl-D-glucofuranose **3d** in four steps from D-glucose in 36% overall yield (Table 2).[12]

Sulfinylation of 1,2-diols **3a–d** was realized with *N*,*N*′-thionyldiimidazole and gave the corresponding *cis* 1,2-*O*-sulfinyl substrates **4a–d** in 83–97% yields.[3,6] The glycosylation reaction was first studied with 1,2-*O*-sulfinyl-D-arabinopyranose **4a**[6] (Table 1).

The yields obtained by using potassium or sodium carbonate were equivalent.[10] The reaction time was shorter with potassium anion (40 min) (Table 1, entry 2); either DMF and THF gave only O-glycoside compound **5a**. THF was found to be less effective for promoting nucleophilic displacement. The use of DMF enhanced the reaction yield (95%) compared with THF (69%).

Compounds **4b–d** were treated with the potassium form of the diethyl-3-oxoglutarate anion of **1** previously prepared in DMF with potassium carbonate, to give 3-(glycosyloxy)-pent-2-ene dioic acid diethyl ester **5b–d** in 92–97% yields (Table 2).[10]

Compounds **5a–d** were characterized by NMR spectroscopy. Anomeric protons appeared between δ 4.88 and 5.51 ppm and coupling constants $J_{1,2}$ between 6.8 and 7.1 Hz for pyranose sugars and $J_{1,2} = 0$ Hz for furanose derivatives, both of which indicated the 1,2-trans configuration (Table 2). The ^{1}H data were in agreement with the literature, for 1,2-*trans O*-phenyl-α-L-arabinofuranoside, the H-1 signal appeared as a singlet at δ 5.7 ppm.[13]

^{13}C NMR spectra showed the signal of anomeric carbon at δ 100.4 ppm for D- and L-arabinopyranosides compounds **5a** and **5b**. For furanic derivatives **5c** and **5d** δ of C-1 were between δ 106.2 and 106.4 ppm, which agreed with our previous work: 1,2-*trans* phenyl O-glycopyranosides had similar data.[14] Two signals appeared

Table 1. Optimization of the reaction of **4a** with anion of **1**

Entry	Solvent	Base (2 equiv)	Reaction time	Yield % **5a**
1	DMF	Na_2CO_3	1 h	93
2	DMF	K_2CO_3	40 min	95
3	THF	K_2CO_3	1 h	69

Table 2. Synthesis of diethyl oxoglutarate O-glycosides derivatives

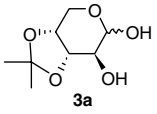
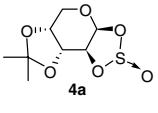
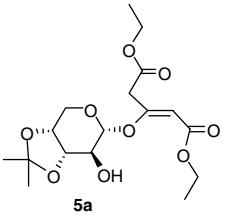
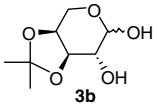
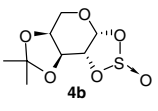
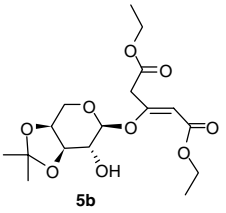
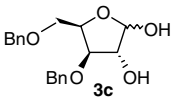
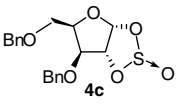
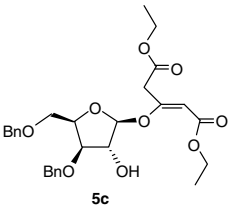
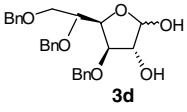
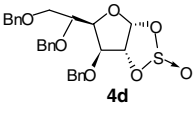
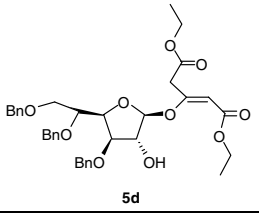
Starting material	Cyclic sulfite	% Yield	Product	Reaction time	% Yield	δ Anomeric proton	$J_{1,2}$ (Hz)	δ Anomeric carbon
 **3a**	 **4a**	82	 **5a**	50 min	95	4.91	7.10	100.4
 **3b**	 **4b**	88	 **5b**	1 h	97	4.88	6.86	100.4
 **3c**	 **4c**	97	 **5c**	30 min	94	5.50	0	106.4
 **3d**	 **4d**	96	 **5d**	40 min	92	5.51	0	106.2

Table 3. ^{13}C NMR data of diethyl 3-oxoglutarate moiety of **5a–d**

Products	C-1′	C-2′	C-3′	C-4′	C-5′
5a	170.0	98.7	165.3	37.7	167.2
5b	170.0	98.7	165.3	37.7	167.2
5c	170.1	97.7	165.0	38.6	167.8
5d	169.9	97.5	165.1	38.7	167.8

between δ 169.9–170.1 ppm and δ 167.2–167.8 ppm assigned to the carbonyl groups C-5′ and C-1′, respectively, quaternary C-3′ had a signal between δ 165.0 and 165.3 and methylene C-4′ between δ 37.7 and 38.7 ppm (Table 3). These data agreed with that reported in the literature for O-alkylated 3-oxoglutarates.[15]

We have observed that reactions of cyclic sulfites with alcohols did not produce the desired O-glycosides. Alkoxides led to hydrolysis of the sulfite via addition at the sulfur atom and gave starting material. D-Glucopyranoside compounds have already been prepared from 1,2-*O*-sulfinyl derivatives by reaction with allyl, benzyl and cyclohexyl alcohol in the presence of lanthanide (III) triflates. Tri-acetylated or benzoylated protected 1,2-cyclic sulfite of D-glucose provided an α/β mixture of anomers, and only benzyl-protected sulfite gave β stereospecificity.[16]

As we observed with our previous results, reactions proceeded efficiently with the stabilized anions such as phenolate; the mechanism of the reaction was an S_N2 displacement at the anomeric atom and only gave 1,2-trans compounds.[3–6]

In the case of diethyl 3-oxoglutarate, the corresponding stabilized enolate led only to the O-glycosides compounds without hydrolysis reaction.

In summary, we have described an easy access to O-glycosides derived from diethyl 3-oxoglutarate in good yields, with free 2-hydroxyl. This method is suitable for the synthesis of complex glycosides in which the C-2 position is glycosylated.[17] The affinity of complexation of these glycosides is evaluated with uric acid and will be reported in due course.

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10. *Typical procedure of O-glycosylation of diethyl oxoglutarate*. To a solution of diethyl oxoglutarate (2 equiv) and anhydrous potassium carbonate (2.05 equiv) in anhydrous DMF previously stirred for 1 h, was added dropwise a solution of 1,2-*O*-sulfinyl-glycose derivative (1 equiv) in anhydrous DMF. The mixture was heated at 70 °C until disappearance of the cyclic sulfite, as checked by thin layer chromatography (hexane–EtOAc 1:1). Then after addition of methanol, the solvents were evaporated under reduced pressure and the residue extracted with CH_2Cl_2–H_2O (70:30). The organic layers were dried on Na_2SO_4 then concentrated. The flash chromatography of the residue afforded the corresponding O-glycoside derivatives.
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