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A Stereoselective *O*-Aryl Glycosylation Procedure *via* 1,2-Cyclic Sulfite

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Abstract : In a one-pot procedure, treatment of partially protected D-glucose and unprotected D-xylose, with N,N'-thionyldiimidazole and then phenoxide ions gives stereoselectively β-*O*-aryl glycosides.

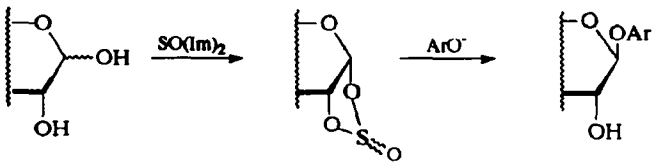
Plant polyphenols are generally isolated in the form of β-glycosides.[1] The synthesis of such molecules requires a stereoselective method of *O*-aryl glycosylation. Substitution reactions on α-glycosyl bromide or chloride lead only to β-glycosides but it is necessary to protect the hydroxyl groups of the glycosyl donor.[2] The *O*-α-glycosyl trichloroacetimidates react with different glycosyl acceptors and the α/β stereoselectivities depend highly on the reaction conditions.[3]

Others methods of *O*-aryl-glycosylation are not stereoselectives.[4] Recently, when 1-azi-2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-glucopyranose is used as glycosyl donor, *C*-glycosides are also obtained.[5]

When the activation of the anomeric hydroxyl group is carried out by a 1,2 cyclic sulfite formation, a nucleo-philic attack gives exclusively the 1,2 *trans* glycoside.

If cyclic sulfite are well known for their high reactivity, only a few nucleophilic reagents are able to react on the *C*-center.[6] Efficient synthesis of β-anomers of glycosyl benzoates, nucleosides and glycosyl azides was reported.[7] Recently, we have shown that the treatment of partially protected or unprotected aldoses, in a one-pot procedure, with N,N'-thionyldiimidazole and then lithium azide led stereoselectively to 1,2-*trans* glycosyl azide.[8]

We describe herein a stereoselective one-pot synthesis of aryl β-D-glycosides *via* 1,2-cyclic sulfite, from partially protected and unprotected sugars. To our knowledge, phenoxide ions were never used as nucleophilic reagents towards a cyclic sulfite derivative of monosaccharides.



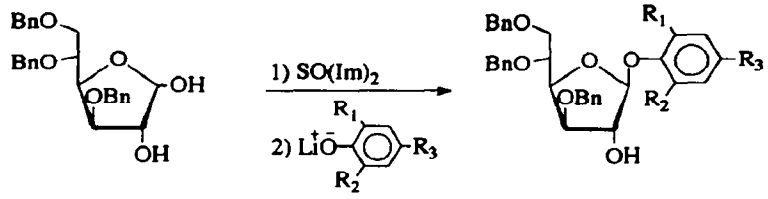
In this procedure, the monosaccharide in DMF was treated, at -30°C, by a solution in THF of N,N'-

thionyldiimidazole[9] ($SO(Im)_2$) in excess. When complete disappearance of the sugar had occured, lithium phenoxide in DMF was added, and the stirring was maintained at room temperature. The *O*-aryl-β-D-glycoside was extracted and without any by-product and identified.

The 3,5,6-tri-*O*-benzyl-D-glucofuranose was chosen as substrat for the optimisation of this reaction.

After addition of $SO(Im)_2$, 3,5,6-tri-*O*-benzyl-1,2-*O*-sulfinyl-α-D-glucofuranose was isolated in 85 % yield[10] and led quickly to phenyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside.

In the one-pot procedure, without isolation of sulfite, better yields were obtained after addition of three equivalents of PhOLi. PhONa gave lower yields and PhOK gave no reaction.

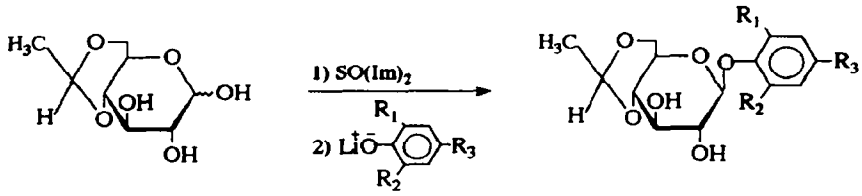


1,2

	Yield %	mp°C	$[\alpha]_D^{20}$ (c, solv.)
1 $R_1 = R_2 = R_3 = H$	58	syrup	- 79 (1.5, $CHCl_3$)
2 $R_1 = R_2 = OMe$; $R_3 = COCH_3$	60	syrup	- 98 (0.5, MeOH)

We could attributed the middle yields to a simultaneous attack of the phenoxide ion at the *C* and *S*-center of the cyclic sulfite derivative, as previously reported in the reaction of methoxide ion with ethylene sulfite.[5]

In the glycosylation of 4,6-*O*-ethylidene-D-glucopyranose, the 1,2-cyclic sulfite intermediate has been previously characterized.[7]

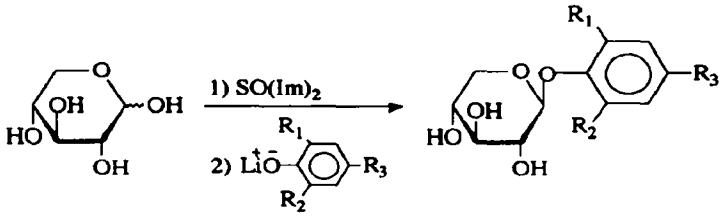


3-10

	Yield %	mp°C	$[\alpha]_D^{20}$ (c, solv.)
3 $R_1 = R_2 = R_3 = H$	34	150-151	-32 (1, MeOH)
4 $R_1 = R_2 = H$; $R_3 = COCH_3$	45	166-168	-64 (0.6, MeOH)
5 $R_1 = H$; $R_2 = OMe$; $R_3 = COCH_3$	57	172-173	-74 (1, MeOH)
6 $R_1 = R_2 = OMe$; $R_3 = COCH_3$	60	168-169	-28 (1, MeOH)
7 $R_1 = H$; $R_2 = OMe$; $R_3 = CHO$	55	186-188	-82 (1, MeOH)
8 $R_1 = R_2 = OMe$; $R_3 = CHO$	55	193-195	-29 (1,MeOH)
9 $R_1 = H$; $R_2 = OMe$; R_3 = CO-CH=CH-Ph-4-OH	35	135-136	-25 (0.3 MeOH)
10 $R_1 = R_2 = OMe$; R_3 = CO-CH=CH-Ph-4-OH	40	96-97	1 (0.5 MeOH)

With the *ortho*-methoxyphenols **5-8**, yields in 1,2-*trans* glycosides were enhanced. When the phenolic derivative bore two phenoxide groups, e.g., 4,4'-dihydroxy-3',5'-dimethoxy-chalcone,[11] and 4,4'-dihydroxy-3'-methoxy-chalcone,[11] we have observed that only one of them reacts with the cyclic sulfite leading to **10** and **9** respectively. This selectivity can be attributed to the complexation of one phenoxide ion by the *ortho*-methoxy group.

This direct *O*-aryl glycosylation does not require any protection of other hydroxyl groups and can be used with free sugars. D-xylose was chosen as an exemple, due to its biological importance in plants.



11-16

		Yield %	mp°C	$[\alpha]_D^{20}$ (c, solv.)
11	$R_1 = R_2 = H$; $R_3 = NO_2$	42	syrup	45 (1, MeOH)
12	$R_1 = R_2 = H$; $R_3 = COCH_3$	38	206-208	-43 (0.5, DMF)
13	$R_1 = H$; $R_2 = OMe$; $R_3 = COCH_3$	42	144-145	-21 (1, DMF)
14	$R_1 = R_2 = OMe$; $R_3 = COCH_3$	45	171-172	-52 (1, MeOH)
15	$R_1 = H$; $R_2 = OMe$; $R_3 = CHO$	48	110-111	-19 (1, DMF)
16	$R_1 = R_2 = OMe$; $R_3 = CHO$	50	152-153	-51 (1,DMF)

To our knowledge this is the first stereoselective *O*-aryl glycosylation of D-xylose without any former protection.

Formation of the sulfite intermediate was followed by thin layer chromatography but its instability did not allow its isolation. The use of the classical four steps Michael strategy for synthesis of *O*-aryl glycoside **12** gave only 30 % yield.

All compounds were characterized by elemental analysis and NMR spectroscopy.

In conclusion, we have shown a first one-pot synthesis of *O*-aryl glycosides *via* 1,2 cyclic sulfite. This stereoselective *O*-glycosylation was applied to D-xylose.

General procedure :

To the sugar solution in DMF at -30°C (0.5 g in 10 ml), a solution of N,N'-thionyldiimidazole (3 eq. in THF) was slowly added. When total consumption of sugar was observed in tlc, a solution in DMF of phenol (4 eq.) and LiH (4 eq.) was added. The solution was stirred for 24 hours while the temperature increased from - 30°C to 20°C. Evaporation of solvents gave a yellow syrup which was triturated in methanol. After concentration of the filtrate, silicagel chromatography (EtOAc-hexane or EtOAc-MeOH) gave the O-aryl-β-D-glycoside.

Acknowledgment :

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10. *endo and exo compounds are obtained.*
endo 3,5,6-tri-*O*-benzyl-1,2-*O*-sulfinyl-α-D-glucofuranose $[\alpha]^{20}_D$: -50 (c = 0.3, $CHCl_3$) ^{1}HNMR ($CDCl_3$) δppm from TMS : 6.46 (d, $J_{1,2}$ = 3.9 Hz, H-1); 5.09 (d, $J_{2,3}$ = OHz, H-2); 4.12 (m, H-3, H-4) ; 3.95 (m, H-5); 3.75 (dd, $J_{5,6}$ = 1.9 Hz, $J_{6,6'}$ = 10.7 Hz, H-6) ; 3.53 (dd, $J_{5,6'}$ = 4.88 Hz, H-6'; 4.70-4.35 (m, 6H, CH_2-Ph); 7.10-7.20 (Ph).
^{13}CNMR ($CDCl_3$) δppm from TMS : 108.1, C-1; 82.4, C-2; 79.8, 78.8, C-3, C-4; 73.7, C-5; 86.9, C-6; 72.4, 71.5, 71.3, CH_2-Ph; 137.3-126.5, Ph.
11. Hydroxy chalcones were synthesized by aldolic condensation, catalyzed by boron trifluoride etherate, between 4-hydroxy benzaldehyde and a substituted acetophenone in dichloromethane. This method was described by Breslow, D.S.; Hauser, C.R. *J. Am. Chem. Soc.* **1940**, *62*, 2385-2388.

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