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One-Pot Stereoselective Synthesis of Glycosyl Azides *via* 1,2-Cyclic Sulfite

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Abstract : In a one-pot procedure, treatment of partially protected or unprotected aldoses with *N,N'*-thionyldiimidazole and then, lithium azide leads stereoselectively to glycosyl azides.

Stereoselective glycosylation is usually obtained by an S_N2 mechanism. So, α-glycosyl halides led to β-glycosyl azides in homogeneous[1] or heterogeneous conditions[2]. Although sodium or lithium azides are classical reagents, tetramethylguanidinium azide was preferred for azidation of peracetylated glycosyl bromine[3] to increase the yield of this reaction. With the acetate leaving group, trimethylsilyl azide [4,1c] and Lewis acid were used instead of NaN_3. α-and β-diphenyl phosphate anomeric groups were displaced[5] by Me_3SiN_3-Me_3SiOTf to introduce the azido group in the β-and α-positions respectively.

Recently, our laboratory reported the azidation of some unprotected aldoses by using the PPh_3-*N*-chlorosuccinimide-LiN_3 system[6]. After activation of the anomeric hydroxyl group by transformation into alkoxyphosphonium salt, substitution by N_3^- led to an α/β mixture of glycosyl azide in which mainly the 1,2-*trans* derivative was formed.

Activation of the anomeric hydroxyl group was also obtained by 1,2-cyclic sulfite formation in monosaccharide where the other hydroxyl groups were protected. Thereafter, the key step is a *trans* cycle opening with N_3^- to afford one anomeric derivative solely[7] : *e.g.* ; 3,5-di-O-benzyl-β-D-ribofuranosyl azide may be synthesized by reaction of sodium azide with 3,5-di-O-benzyl-1,2-sulfite-α-D-ribofuranose[7b]. Treatment of the four diastereoisomeric β-L-arabinopyranose 1,2;3,4-disulfites by NaN_3 led to 1,2-*trans*-glycosides. In this structure, a non anomeric cyclic sulfite group acted as a protecting group[8].

We describe herein a stereoselective one-pot synthesis of 1,2-*trans*-glycosylazides from partially protected or unprotected monosaccharides *via* 1,2-cyclic sulfites.

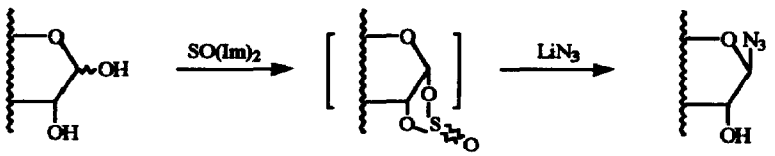
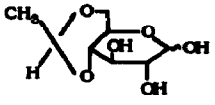
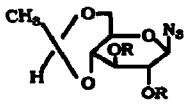
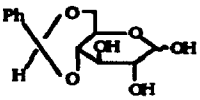
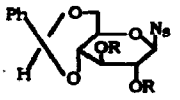
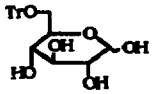
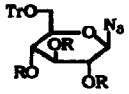
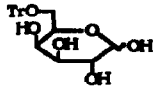
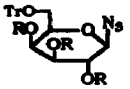
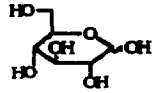
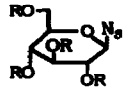
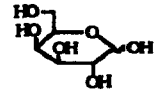
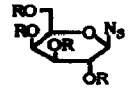
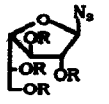
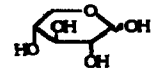
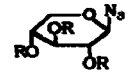


Table 1 : Stereoselective azidation of some monosaccharides

Substrat	Product		Yield %	mp°c	$[\alpha]_D^{25}$ (c, solv.)	ν_{as} (cm^{-1})	Litt.
		R = H	64	162-163	- 64 (1.2, MeOH)	2 124	
		R = Ac		148-150	- 74 (1.0, $CHCl_3$)		
		R = H	55	153	- 76 (1.0, MeOH)	2 119	
		R = Ac		176	- 95 (1.0, $CHCl_3$)	2 117	
		R = H	72	68-70	- 50 (1.3, $CHCl_3$	2 117	
		R = Ac		126-127	16 (1.0, $CHCl_3$)		
		R = H	58		- 32 (1.0, $CHCl_3$)	2 119	
		R = Ac			- 18 (1.8, $CHCl_3$)		
		R = H	53		+100 (1.0, THF)	2 115,5	
		R = Ac			+ 42 (1.8, $CHCl_3$)	2 120	
		$\alpha/\beta = 5$					
		R = Ac	16		+ 94 (0.8, $CHCl_3$)	2 119	5 17 4c
		R = Ac	70	123-124	- 22 (1.8, $CHCl_3$)	2 120	5 4c 2c
		R = Ac	32		- 8 (1.0, $CHCl_3$)	2 119	5 4a,c 2c
		R = H	27		-145 (1.8, MeOH)		4a
		R = Ac			-106 (1.54, $CHCl_3$)	2 115	
		R = H	72	106	- 56 (1.2, MeOH)	2 110	
		R = Ac		87	- 86 (1.0, $CHCl_3$)		4c

In a classical procedure, thionyl chloride[7a] may be used. To avoid chlorination[9] or cleavage of acid labile substituents[10] in structures with more than two hydroxyl groups, triethylamine or pyridine is required. Another way consists in using *N,N'*-thionyldiimidazole[11] instead of $SOCl_2$. 1,3-cyclic sulfites were already synthesized with *N,N'*-thionyldiimidazole.[12]

Treatment with an excess of SO $(Im)_2$ solubilized in THF of monosaccharides (Table 1) in DMF at -30°C, led to the complete disappearance of the latter. After addition of lithium azide[13], we extracted and identified a glycosyl azide without any by-product. Sodium azide gave a lower yield and optimisation of this azidation was realized by addition of three equivalents of lithium azide in DMF. For D-mannose and D-galactose, this addition was followed by a hydrolysis with $NaHCO_3$ to cleave the non anomeric cyclic sulfite.

Due to their instability, most unprotected cyclic sulfites were not isolated. Solely, 6-O-trityl-1,2-sulfite-α-D-glucopyranose and 4,6-O-ethylidene-1,2-sulfite-α-D-glucopyranose, were characterized by IR and NMR spectroscopies[14].

Physical data of all known compounds were in full agreement with literature values. All unknown azides were characterized by elementary analysis and NMR spectroscopy.

In this one-pot reaction, the first step was the stereoselective formation of a cyclic sulfite, followed by stereoselective displacement at the anomeric carbon. Hence, D-glucose, D-galactose and D-xylose derivatives led to β-azides exclusively.

Furthermore, D-galactose involved an initial solubilization in hot DMF and isomerization between pyranic and furanic forms was detected by NMR spectroscopy. We noted that β-D-galactofuranosyl azide is formed in 27 % yield.

As expected, α-D-mannopyranosyl azide was obtained from D-mannopyranose but in a low yield. This result can be attributed to both the competition between the formation of 1,2 and 2,3-cyclic sulfites and to the participation of the OH-6 in another cyclic sulfite (pyranic or furanic form)[15]. With 6-O-trityl-D-mannopyranose, a small amount of β-azide may be attributed to the formation of 1,4-cyclic sulfite intermediate, results already observed with a 1,4-diol[16].

In conclusion, we have shown that partially protected or unprotected monosaccharides can be stereoselectively glycosylated in a one-pot procedure, *via* the activation of anomeric hydroxyl groups by a cyclic sulfite. Others glycosylations are in progress.

General procedure: To sugar in DMF at -30°C (1 g in 10 mL) was slowly added a solution of *N,N'*-thionyldiimidazole (3eq.). The homogeneous solution was stirred until TLC indicated total consumption of sugar. Then LiN_3 (3eq.) was added in solution in DMF and stirring was continued at room temperature for 24 or more hours. Evaporation of solvents gave a yellow sirup which was triturated in methanol. After filtration of salts and concentration of the filtrate, silicagel chromatography (EtOAc-hexane or EtOAc-MeOH) afforded the glycosyl azide in yields indicated in the table.

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14) *Exo* and *endo* derivatives are obtained.

Exo 6-O-Trityl-1,2-sulfite-a-D-glucopyranose : $\nu_{S=O}$ = 1 214 cm^{-1}, ^1H NMR (CDCl3) δppm from TMS : 6.37(d,$J_{1,2}$=4.7Hz,H-1);4.66(t,$J_{2,3}$=5Hz,H-2); 3.72(t,$J_{3,4}$=6.5Hz,H-3);3.68(dd,$J_{4,5}$=9Hz,H-4);3.60(m,H-5);3.40(dd,$J_{5,6}$=3.4Hz, $J_{6,6'}$=10.6Hz,H-6);3.35 (dd,$J_{5,6'}$=4.1Hz,H6');7.3(15H,Ph)
^{13}C NMR (CDCl3) δppm from TMS : 101.4,C-1;77.6,C-2;72.8,C-3;68.6,C-4;64.1, C-6;86.2,CPh3;126.3;127.0;127.6;142.4,Ph

Exo 4,6-O-ethylidene-1,2-sulfite-α-D-glucopyranose : $\nu_{S=O}$ = 1 189 cm^{-1}, ^1HNMR (CDCl3) δppm from TMS : 6.35(d,$J_{1,2}$=4.8Hz,H-1);4.62(dd,$J_{2,3}$=6.4Hz,H-2); 3.84(dd,$J_{3,4}$=9.6Hz,H-3);3.32(t,$J_{4,5}$=9,6Hz,H-4);3.70(m,H-5);3.45(m,H-6);4.17(m, H-6');4.72(q,H-iso);1.33(d,CH_3)
^{13}C NMR (CDCl3) δppm from TMS : 101.4C-1;79.4,C-2;72.0,C-3;76.5,C-4;63.3, C-5;66.5,C-6;98.9,C-iso;19.2,CH_3

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