Tetrahedron Letters No. 41, pp 3681 - 3684, 1977. Pergamon Press. Printed in Great Britain.

SUGAR THIO ORTHOESTERS AS GLYCOSYLATING AGENTS

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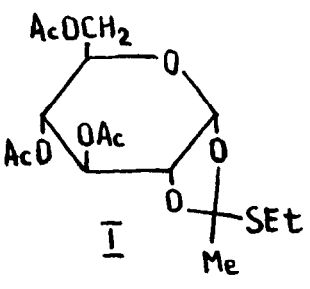
(Received in UK 4 August 1977; accepted for publication 25 August 1977)

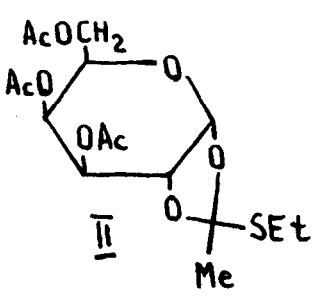
The existing methods of synthesis of O-glycosides are based, as a rule, on the use of acylglycosyl halides and sugar orthoesters as glycosylating agents.[1] The proton-catalyzed glycosylation by sugar 1,2-orthoesters is known to be accompanied by formation of glycosides with free hydroxyl group at $C_{(2)}$ as side products [2]. It is obviously connected with the protonation of both exocyclic and cyclic oxygen atoms of the orthoester grouping [3].

The recent approach to glycosylation by sugar pyruvonitrile ketals in the presence of triphenylcarbonium salts as catalysts [4] is devoid of this drawback due to selectivity of attack by carbocation on the exocyclic (nitrile) group.

The same selectivity could be anticipated in the case of analogues of bicyclic sugar orthoesters containing alkylthio- instead of exocyclic alkoxy-group. Here we report on the glycosylating properties of thio orthoesters of D-glucose, D-galactose and D-mannose exemplified by the synthesis of D-glycosyl-(1→6)-D-glucoses.



I



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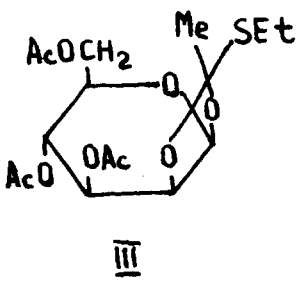


III

Thio orthoesters I - III were obtained by the reaction of the corresponding 2,3,4,6-tetra-O-acetyl-α-D-glycopyranosyl bromides with ethanethiol in dry nitromethane in the presence of 2,6-lutidine. Column chromatography on silica gel afforded thio orthoesters I (syrup, $[\alpha]_D^{20}$ + 32.1° (c 1, $CHCl_3$)), II (syrup, $[\alpha]_D^{20}$ +70° (c 1, $CHCl_3$)) and III, m.p. 63-65° (ether-pentane), $[\alpha]_D^{20}$ -29° (c 1.9, $CHCl_3$) in 70, 33 and 24% yield; correct elemental analysis data were obtained for these products. Their characteristic PMR data are listed in the Table 1.

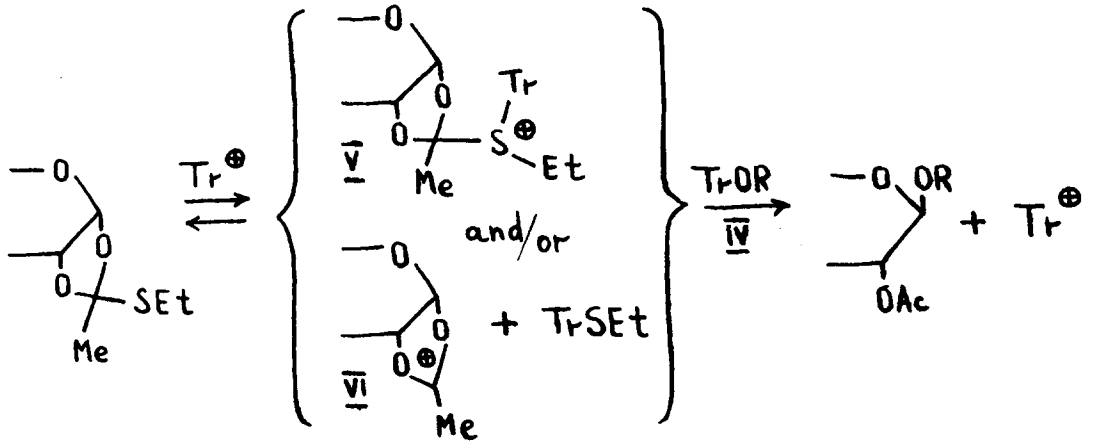
Table 1

Chemical shifts of protons (δ, ppm, Me_4Si, CCl_4, Varian DA-60-IL)

Thio orthoesters	C-CH_3(s)	S-$CH_2$$CH_3$(q) (J,Hz)	S-$CH_2$$CH_3$(t) (J,Hz)	H-1(d) (J,Hz)
I	1.90	2.56(8)	1.24(8)	5.55(5)
II	1.87	2.59(7.5)	1.25(7.5)	5.78(5)
III	1.92	2.58(7)	1.22(7)	5.35(2.5)

Analogous thio orthoesters containing p-methylthiophenyl group were recently described by Magnusson [5].

Thio orthoesters I-III were treated with equimolar amount of 1,2,3,4-tetra-O-acetyl-6-O-trityl-β-D-glucopyranose (IV) in dichloromethane in the presence of trityl perchlorate (0.1 - 1.0 mole) using high-vacuum technique [4]. Soon after mixing of the reagents the yellow colour of the solution (conditioned by the presence of trityl ion) disappears and then appears again. Such a change of colour can be possibly explained by the following sequence of transformations connected with consumption and liberation of the trityl cation:



The reaction mixture is kept for 1 hour at room temperature, treated with methanol-pyridine (1:1 v/v) mixture and after 10 minutes the colourless solution taken to dryness. Thin-layer chromatography of the reaction mixture revealed the complete disappearance of the starting thio orthoester. Alongside with the main product, peracetylated disaccharide, small amounts of unreacted IV, ethyl thioglycoside and thio orthoester decomposition products were detected. The formation of ethyl thioglycoside, isomeric to the original thio orthoester, is the main side process of this reaction and is probably conditioned by interaction of intermediate sulfonium salt (V) or acyloxonium ion (VI) with trityl ethyl sulfide or with the starting thio orthoester.

Column chromatography on silica gel affords disaccharide derivatives. Their yields and properties are listed in the Table 2.

Table 2

Yields and properties of hexopyranosyl-(1→6)-D-glucopyranoses β-octaacetates

β-octaacetate of	yield, %	m.p.°C (ethanol)	$[\alpha]_D^{20}$ ($c, CHCl_3$)	literature data		
				m.p.°C	$[\alpha]_D^{20}$	reference
β-D-Glc-D-Glc	55	193-195	-4° (2.5)	191-193	-5.5°	6
β-D-Gal-D-Glc	49	159-160	+1.8° (1.9)	166	0°	7
α-D-Man-D-Glc	69	amorph.	+38° (1.2)	soft. at 90°	+38.9°	8

The disaccharide fraction obtained after column chromatography from the reaction of thio orthoester I with IV was subjected to saponification with sodium methoxide in absolute methanol. Ion-exchange chromatography of the deacetylated disaccharide obtained (Technicon SC-2 analyzer, 13x0.5 cm column with Durrum DAx4 resin, 0.7 M sodium borate pH 7.7 buffer, elution rate 20 ml/h at 80°) revealed the absence of the isomeric, α-linked, disaccharide isomaltose, authentic gentiobiose and isomaltose serving as standards. This indicates the stereospecificity of glycosylation by sugar thio orthoesters.

Acknowledgement. We are indebted to Drs. V.I.Betanely and Ya.V.Wozney for fruitful discussions.

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