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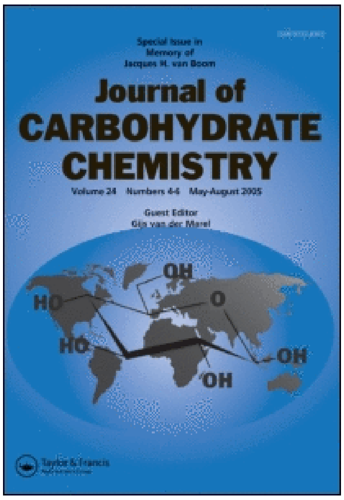

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Communication

ANOMERIC XANTHATES: A NEW ACTIVATION OF THE ANOMERIC CENTER FOR RAPID GLYCOSYLATION

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In recent years, glycosides, especially di- and oligosaccharides, have become substances of interest owing to their biochemical and pharmacological importance as antibiotics and antigens and many reports have appeared concerning the synthesis of these complex molecules[1]. Synthesis generally involved the preparation of two poly - functional partners; the hydroxyl component, prepared by selective blocking of a monosaccharide unit and the electrophilic partner, generated from an activated species. Various methods of activation of the anomeric center have been devised giving generally very good results. Oligosaccharides have been obtained from halogenoses, orthoesters[2], imidates[3], acetates[4] in the presence of acidic catalysts or heavy metal salts[5], as well as from thiomethyl glycosides as a glycosyl donor and methyl triflate or dimethyl-(methylthio)-sulfonium triflate as a promoter[6]. More complex heteroatomic activating groups have been developed such as *N,N*-dialkyldithiocarbamates[7], phosphorodithioates[8] and 2-benzothiazolyl[9] derivatives, the latter providing an efficient glucosylation method.

Sugar xanthate derivatives have found important applications in organic synthesis[10], due to reductive[11], thermal[12] and photolytic reactions[13]. Only one anomeric xanthate, namely 2,3:5,6-di-*O*-isopro-

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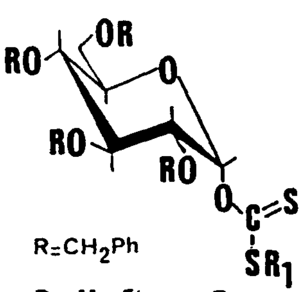
pylidene-1-*O*-{(methylthio)thiocarbonyl}-D-mannofuranose, has been reported[14], but without a study of its chemical properties.

Anomeric xanthates were prepared in a one-pot procedure according to the following methodology: treatment of commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with 2 equivalents of sodium hydride in the presence of a catalytic amount of imidazole, carbon disulfide, and an alkyl halide, provided very stable anomeric xanthates **1** to **3** after purification[15]. The configuration at the anomeric center was proved to be exclusively α (1,2-cis relationship). Physical properties of anomeric xanthates **1** to **3** are summarized in Table I.

Treatment of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose[16] under the same conditions as above gave the α-xanthate **4** in 86% yield; $\{\alpha\}_D = +56°$ (c, 2.09, CCl_4), $\delta H_1 = 6.95$ ppm, $J_{1,2} = 3.3$ Hz.

Thermal isomerization of 1,2:5,6-di-*O*-isopropylidene- 3-*O*-{(methylthio)thiocarbonyl}-D-glucofuranose was first described by K. Freudenberg[14] and formulated without definite evidence as having proceeded without inversion. The resulting more stable 1,2:5,6-di-*O*-isopropylidene-3-*S*-{(methylthio)carbonyl}-3-thio-D-glucofuranose was postulated to be the isomeric substance. A similar rearrangement did not,however, occur with the corresponding derivatives of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose and 1,2:3,4-di-*O*-isopropylidene -D-galactopyranose[10]. However, Wolfrom and Foster[17] found that the D- and L-enantiomorphs of methyl-3,4-*O*-isopropylidene -2-*O*-{(methylthio)thiocarbonyl}-β-arabinopyranoside rearrange , on pyrolysis, to the appropriate 2-*S*-{(methylthio)carbonyl} esters.

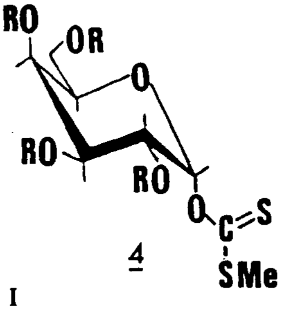
Anomeric xanthates **1** to **3** underwent a thermal or acid-catalysed rearrangement without any evidence for elimination[12] (Chugaev reaction). This reaction is currently thought to be a β-cis elimination which involves a cyclic transition state complex in which the thionosulfur bonds to the β-hydrogen. It is possible that the hydrogen β to the *O*-(*S*-alkyldithiocarbonate) group is inactivated by the oxygen function attached to the same carbon atom. the observed rearrangement occurred without inversion and presumably took place by an intramolecular 1,3 shift involving a 4-membered ring



R=CH$_2$Ph

R$_1$= Me, Et or n-Bu

Table I



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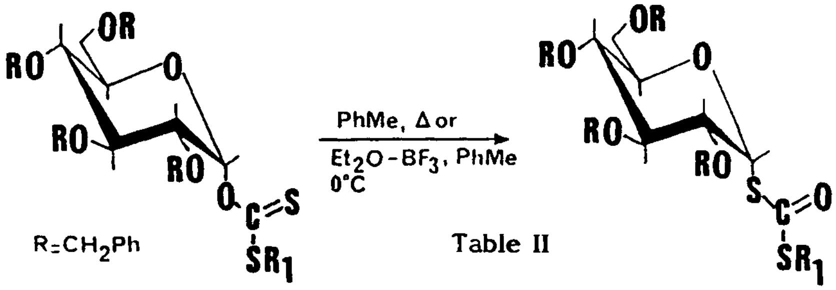
R_1	Yield %	$[\alpha]_D$ CCl_4 (c, 1.0.)	NMR δH_1 ppm $J_{1,2}$ Hz	m/e [M+18]
Me 1	95	+43°	6,95 3.0	648
Et 2	65	+34°	6.96 3.0	662
n-Bu 3	75	+31°	6.96 3.0	690



R=CH$_2$Ph

Table II

R_1	Yield % BF_3-Et_2O	Yield % Δ	$[\alpha]_D$ CCl_4 (c, 1.0.)	NMR δH_1 ppm $J_{1,2}$ Hz	m/e M+18
Me 5	70 (5mn)	50	+96°	6.35 5.0	648
Et 6	70 (60mn)	62	+92°	6.35 5.0	662
n-Bu 7	50 (90 mn)	65	+78°	6.35 5.0	690

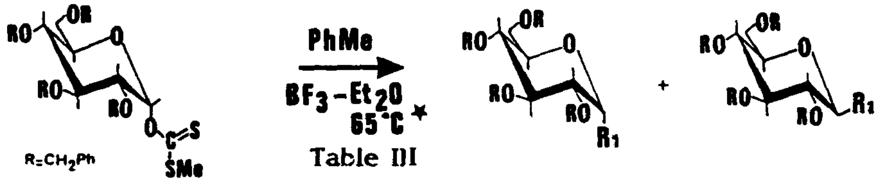
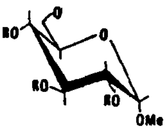
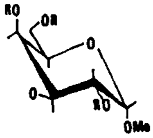
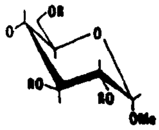


Table III

R$_1$	Yield %	8α/8β	8α (c, 1.0, CH_2Cl_2)	8β (c, 1.0, CH_2Cl_2)
OMe	89	3:7[a]	$[\alpha]_D$ = +17°	$[\alpha]_D$ = +10° m.p. 70°C
	86	1:1[b]	$[\alpha]_D$ = +59° m.p. 103°C	
	92	1:0[c]	$[\alpha]_D$ = +42°	
	94	Mainly α[d]	$[\alpha]_D$ = +31°	

a. Ratio determined after chromatographic separation and characterization of isomers 8α and 8β[18a,b].

b. Ratio determined by integration of OMe signals of the 300 MHz ^{1}H sprectrum and by polarimetry. Pure sample of compound 8α was isolated by flash chromatography. Pure compounds 8α and 8β have been previously described[19].

c. Disaccharide isolated as the pure 8α isomer. 300 MHz ^{1}H-n.m.r. spectrum exhibited a single OMe resonance and the interglycosidic proton $H_{1'}$ at δ 5.60 ppm showed a $J_{1',2'}$ value = 3.4 Hz in agreement with an equatorial-axial relationship.

d. 300 MHz ^{1}H-n.m.r. spectrum exhibited a single OMe resonance and the interglycosidic proton $H_{1'}$ at δ 5.69 ppm showed a $J_{1',2'}$ value = 3.4 Hz. This compound was previously reported[19] with $[\alpha]_D$ = +48°.

★ When these reactions were conducted at room temperature, glycosylation occurred slowly (24 to 30 h) but gave exactly the same results.

intermediate with front side attack. Physical properties of the rearranged derivatives **5** to **7** are summarized in Table II.

It was interesting to discover that in the presence of an alcohol and a catalytic amount of a Lewis acid (BF_3-Et_2O), spontaneous glycosylation of **1** took place, affording either a mixture of α and β glucosides (with reactive primary alcohols) or mainly α disaccharides (with less reactive alcohols). Results are summarized in Table III.

Every condensation was carried out in dry toluene at 65°C using xanthate **1** and an alcohol in a 1.5 to 1.0 ratio. In a typical experiment, a mixture of syrupy xanthate **1** (246 mg, 0.39 mM, 1.5 eq) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (119.7 mg, 0.26 mM, 1.0 eq) was dried under vacuum and the flask was filled with argon. Dry toluene (5 ml) was added and the solution was heated at 65°C. BF_3-Et_2O (5 μl) was injected and after 1 min, the reaction mixture was quenched with an excess of anhydrous sodium carbonate. Filtration followed by concentration of the solution, gave a residue which was purified by flash chromatography (hexane-ether 1:1, v/v) to give first a mixture of the methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α- and β-D-glucopyranosides (60 mg) then the disaccharide **8** as a syrup (238 mg, 94%).

In every case, glucosylation occurred in less than 1 min with evolution of a gas: carbon oxysulfide. This leaving group, an inactive species, cannot interact with the oxonium ion and this could be an explanation of the efficiency of the procedure. However, the formation of methyl 1-thio-α- and β-D-glucopyranosides due to the remaining nucleophile MeS^- could not be totally avoided; but this competitive reaction occurred only to a small extent.

Rearranged derivatives **5** - **7** did not undergo glycosylation when submitted to this reaction. We are now extending this reaction to other biologically important monosaccharides.

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