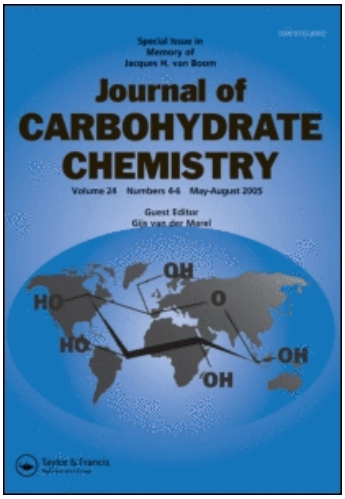

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A NEW APPROACH TO O-GLYCOSYL PHOSPHOROTHIOATES

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ABSTRACT

O-Glycosyl phosphorothioates can be conveniently prepared by treatment of reducing monosaccharides with p-tolylsulfonyl chloride and the triethylammonium salt of phosphorothioic acid under phase-transfer catalysed conditions.

INTRODUCTION

The synthesis of O-glycosyl thiophosphates is of interest both from a biological and practical point of view. Thiophosphates, analogues of naturally occuring phosphates, are potentially valuable as regulators, activators or inhibitors of metabolism.[1]

Esters, derivatives of O-glycosyl and S-glycosyl thiophosphates have been synthesised by reacting phosphorothioate with hexopyranosyl halides.[2,3] The S/O ratio of glycosylated phosphorothioates depends markedly on the reaction conditions. Ammonium salts of protected phosphorothioic acid favour the formation of S-derivatives, when the silver salt is used O-derivatives predominate in the reaction mixture.[2] Chmielewski and BeMiller[3] have pointed out that

di-tert-butyl triethylammonium phosphorothioate with glycosyl halides produce derivatives of S-D-hexopyranosyl thiophosphates.

We have found that the generation of a good leaving group from a hydroxy group can be achieved by treating alcohols with sulfonyl chlorides under phase-transfer (PT) conditions.[4] We have reported the application of this method to the synthesis of glycosyl dithiocarbonates[5], dithiocarbamates[6], and alkyl glucosides[7] in the intermolecular nucleophilic substitution of sulfonates, formed from reducing sugar derivatives under PT conditions. Continuing this study, we now report a novel approach to the synthesis of the O-glycosyl phosphorothioates.

RESULTS AND DISCUSSION

Treatment of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (1a),[8] 2,3,4,6-tetra-O-benzyl-D-mannopyranose (1b),[8] 2,3,4-tri-O-benzyl-D-xylopyranose (1c),[9] and 2,3:5,6-di-O-isopropylidene-D-mannofuranose (1d)[10] with tosyl chloride and the triethylammonium salt of 5,5-dimethyl-2-hydroxy-2-thiono-1,3,2-dioxaphosphorinane (2)[11] in the two-phase system of benzene/aqueous sodium hydroxide solution in the presence of tetrabutylammonium chloride affords almost quantitative yields of O-glycosyl-phosphorothionates (5). The structure of each thionoester formed from the obtained compounds was determined by the presence of a band at 690 cm^{-1} in its IR spectrum; characteristic for the P=S group, and from ^{31}P chemical shift data; δ=60.45 and 60.35 ppm for glucopyranosyl (5a), δ=59.50 and 59.40 ppm for mannopyranosyl (5b), δ=60.40 ppm for xylopyranosyl (5c), and δ=58.10 ppm for mannofuranosyl derivatives (5d).

The configuration of 2-(glycosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinanes (5a-d) was established from NMR data. The ^{1}H-NMR spectrum of 5d showed only one anomeric proton signal, a dublet at δ=5.90 ppm having a large value for $J_{1,P}$(7.2 Hz). The coupling constant between H-1 and H-2

is small ($J_{1,2} < 0.2$ Hz)[12] indicating that the compound has an α-D-configuration. The ^{1}H- and ^{13}C-NMR spectra of 5c with H-1α (5.89 ppm, dd with $J_{1,P}$=10.2 Hz and $J_{1,2}$=3.0 Hz) and C-1α (95.60 ppm, d with $J_{C,P}$=5.2 Hz) indicate the formation of one product. In the case of the monosaccharides (1a) and (1b), an α,β-mixture of O-glycosylphosphorothioates (5a-b) was obtained. For 5a the following signals were observed: H-1α (6.04 ppm, dd with $J_{1,P}$=10.2 Hz and $J_{1,2}$= 3.0 Hz); H-1β (5.37 ppm, dd, $J_{1,P}$=10.3 Hz and $J_{1,2}$=7.4 Hz); C-1β (99.1 ppm, d, $J_{C,P}$=5.8 Hz); C-1α (95.8 ppm, d, $J_{C,P}$= 5.2 Hz). ^{1}H-NMR data for 5b are the following: H-1α (5.86 ppm, dd, $J_{1,P}$=9.0 Hz, $J_{1,2}$=2.0 Hz); H-1β in the area (4.97-3.52 ppm) together with other sugar and benzyl proton signals. The proportion of α,β-isomers was established by comparing the intensity of signals in ^{1}H-, ^{13}C- and ^{31}P-NMR spectra.

In order to explain the mechanism of thionophosphorylation of reducing monosaccharides we have investigated the reaction process using 1a. This compound has in its crystalline state an α-D-configuration. With 1a, tosyl chloride and 2, as the thiophosphorylating agent, we have investigated the dependence of the α/β-selectivity of the glycosyl thiophosphate formation on the reaction conditions. Treatment of 1a with tosyl chloride and the triethylammonium salt of 2 under PT conditions favoured the β-anomer. Under these conditions the esterification of the formed sugar alcoholate takes place, followed by substitution of tosylate. It is to be expected that in a nonpolar solvent with a very reactive sulfur containing nucleophile the S_N2 substitution takes place, similarly as in other known reactions leading to thiosugars. Under PT conditions tosyl chloride also reacts with 2. Stirring these reagents, 5,5-dimethyl-2-hydroxy-2-thiono-1,3,2-dioxaphosphorinanyl-4-toluenesulfonic anhydride (4) is obtained, the structure of which was assigned from ^{1}H- and ^{31}P-NMR data. If 4 is treated with sugar alcoholate, formed from 1a with sodium hydride, aqueous sodium hydroxide or solid potassium carbonate, a mixture of thionophosphates is formed (Table). These results suggest that

Table. The influence of bases and catalysts on the proportion of isomers in the reaction of mixed anhydride (4) with 2,3,4,6-tetra-O-benzyl-D-glucopyranose (1a).

Base	Catalyst	Proportion of products α : β
aq NaOH	Bu_4NCl	7 : 3
NaH	Bu_4NCl	2 : 1
K_2CO_3	Bu_4NHSO_4	2 : 1

The high yield of O-glycosyl thionophosphates, the applicability to the protected reducing sugar derivatives containing acid labile acetal groups, the use of cheap and common reagents and the simple work-up make the present procedure useful for the synthesis of thionophosphates from reducing sugar derivatives.

under the proposed conditions the composition of products depends on the configuration of starting sugar, and that the anomerisation of sugar alcoholate is a minor factor influencing the stereoselectivity of the reaction.

EXPERIMENTAL

General Procedures. Melting points were determined with a BOETIUS PHMKO 5 apparatus and are uncorrected. Specific rotations were determined with POLAMAT A polarimeter, and IR spectra were recorded with Zeiss-Jena spectrometer. ^{1}H-NMR spectra were recorded with TESLA (80 MHz) and VARIAN (300 MHz) spectrometers. ^{13}C-NMR spectra were recorded with TESLA (80 MHz), VARIAN (300 MHz) and BRUKER (500 MHz) spectrometers. ^{31}P-NMR spectra were recorded with JEOL FT (60 MHz) and VARIAN (300 MHz) spectrometers with H_3PO_4 as internal standard. TLC was carried out on silica gel plates (Kieselgel

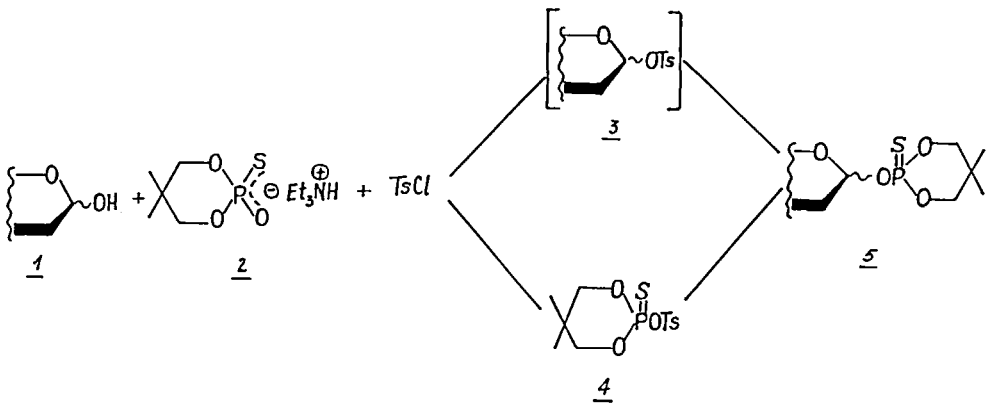

FIGURE 1

$60F_{254}$ Merck) with benzene-ethyl acetate (8:1) and detection by charring with sulfuric acid. Preparative column chromatography was performed on Silica Gel 60 (Merck 0.063-0.2 mm). Evaporations of solvents were conducted in vacuo.

Preparation of O-Glycosyl Phosphorothioates. The solution of sugar (1, 0.5 mmol), p-tolylsulfonyl chloride (143 mg, 0.75 mmol), triethylammonium salt of phosphorothioic acid (2, 142 mg, 0.5 mmol) and tetrabutylammonium chloride (35 mg, 0.125 mmol) in benzene (15 mL) was stirred with 50% aqueous sodium hydroxide solution (5 mL), at room temperature for 2 h. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The product was isolated by column chromatography, eluted with benzene-ethyl ether (25:1 v/v).

2-(2,3,4,6-Tetra-O-benzyl-α,β-D-glucopyranosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (5a): syrup; yield 90%; $[\alpha]_{546}^{20}$ -65.4° (c 0.26, chloroform); IR (tetrachloromethane) 690 (P=S); ^{31}P-NMR ($CDCl_3$) δ 60.45, 60.35; ^{1}H-NMR ($CDCl_3$) δ 0.98, 1.20 (2s, 6H, 5,5-diMe), 3.43-4.93 (m, 18H, H-2,3,4,5,6, $2CH_2O$, $4ArCH_2$), 5.37 (dd, 1H, $J_{1,P}$=10.3 Hz, $J_{1,2}$=7.4 Hz, H-1β), 6.04 (dd, 1H, $J_{1,P}$=10.2 Hz, $J_{1,2}$=3.0 Hz, H-1α), 7.10-7.33 (m, 20H, 4ArH); ^{13}C-NMR ($CDCl_3$) δ 20.8, 20.9

($2Me_e$), 21.8, 22.1 ($2Me_a$), 32.1 (d, $^3J_{P-C}$=6.5 Hz, $C(Me)_2$), 95.8 (d, $^2J_{P-C}$=5.2 Hz, C-1α), 99.1 (d, $^2J_{P-C}$=5.8 Hz, C-1β).

2-(2,3,4,6-Tetra-O-benzyl-α,β-D-mannopyranosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (5b): syrup; yield 82%, $[\alpha]_{546}^{20}$ +7.97° (c 1.4, chloroform); IR (tetrachloromethane) 690 (P=S); ^{31}P-NMR ($CDCl_3$) δ 59.5, 59.4; ^{1}H-NMR ($CDCl_3$) δ 0.66, 1.17 (2s, 6H, 5,5-diMe), 3.52-4.97 (m, 19H, H-1β,2,3,-4,5,6, $2CH_2O$, $4ArCH_2$), 5.86 (dd, 1H, $J_{1,P}$=9.0 Hz, $J_{1,2}$=2.0 Hz, H-1α), 7.18-7.55 (m, 20H, 4ArH).

2-(2,3,4-Tri-O-benzyl-α-D-xylopyranosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (5c): syrup; yield 95%; $[\alpha]_{546}^{20}$ +47.4° (c 0.46, chloroform); IR (tetrachloromethane) 690 (P=S); ^{31}P-NMR ($CDCl_3$) δ 60.4; ^{1}H-NMR ($CDCl_3$) δ 0.84, 1.19 (2s, 6H, 5,5-diMe), 3.50-4.86 (m, 15H, H-2,3,4,5, $2CH_2O$, $3ArCH_2$), 5.89 (dd, 1H, $J_{1,P}$=10.2 Hz, $J_{1,2}$=3.0 Hz, H-1), 7.19-7.46 (m, 15H, 3ArH); ^{13}C-NMR ($CDCl_3$) δ 20.9 (Me_e), 21.0 (Me_a), 32.2 (d, $^3J_{P-C}$=6.6 Hz, $C(Me)_2$), 95.6 (d, $^2J_{P-C}$= 5.2 Hz, C-1).

2-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (5d): mp 58-60°C; yield 93%; $[\alpha]_{546}^{20}$ +50.0° (c 0.5 chloroform); IR (tetrachloromethane) 690 (P=S); ^{31}P-NMR ($CDCl_3$) δ 58.1; ^{1}H-NMR ($CDCl_3$) δ 0.88, 1.10 (2s, 6H, 5,5-diMe), 1.39, 1.48, 1.50, 1.55 (4s, 12H, $2C(Me)_2$), 3.80-4.90 (m, 10H, H-2,3,4,5,6, $2CH_2O$), 5.90 (d, 1H, $J_{1,P}$=7.2 Hz, H-1).

5,5-Dimethyl-2-hydroxy-2-thiono-1,3,2-dioxaphosphorinanyl-4-toluenesulfonic Anhydride (4). The mixture of p-tolylsulfonyl chloride (76.2 mg, 0.4 mmol), triethylammonium salt of 5,5-dimethyl-2-hydroxy-2-thiono-1,3,2-dioxaphosphorinane (2, 113 mg, 0.4 mmol), tetrabutylammonium chloride (12 mg, 0.04 mmol) and potassium carbonate (138 mg, 1 mmol) in benzene (10 mL) was stirred at room temperature for 3 h, while the course of the reaction was monitored by TLC. The precipitate was filtered off, the filtrate was washed with water and dried over sodium sulfate. After evaporation the

syrupy residue was crystallised from ether-heptane to give 124 mg (93%) of crystalline product (colourless needles) mp 69-71°C, ^{31}P-NMR ($CDCl_3$) δ 43.4; ^{1}H-NMR ($CDCl_3$) δ 0.83, 1.20 (2s, 6H, 5,5-diMe), 2.80 (s, 3H, Me), 2.97-4.47 (m, 4H, $2CH_2O$), 7.20-7.90 (m, 4H, ArH).

The Reaction of Mixed Anhydride (4) with 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (1a). The mixture of p-tolylsulfonyl chloride (95 mg, 0.5 mmol), triethylammonium salt of 5,5-dimethyl-2-hydroxy-2-thiono-1,3,2-dioxaphosphorinane (2, 142 mg, 0.5 mmol), tetrabutylammonium chloride (37.5 mg, 0.125 mmol) and potassium carbonate (172 mg, 1.25 mmol) in benzene (10 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC and after 3 h, all tosyl chloride was converted into the anhydride (4). To this stirred mixture a solution of compound 1a (90 mg, 0.165 mmol) in benzene (5 mL) and 50% aqueous sodium hydroxide solution (5 mL) was added. The stirring was continued for 1.5 h at room temperature. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The product, isolated by column chromatography, was shown to be an α,β-mixture of 2-(2,3,4,6-tetra-O-benzyl-α,β-D-glucopyranosyl)-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (5a). Proportion of isomers: α,β=7:3; yield 94%; $[\alpha]_{546}^{20}$ +8.64° (c 1.1, chloroform).

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