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S–O Acetyl rearrangement in 6-thio-D-glucose derivatives

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Abstract: The solvolytic reaction of 1,2-*O*-isopropylidene-3,6-di-*O*-(*p*-toluenesulphonyl)-*α*-D-glucofuranose (**2**), as well as that of 6-chloro-6-deoxy-1,2-*O*--isopropylidene-3-*O*-(*p*-toluenesulphonyl)-*α*-D-glucofuranose (**3**), in the presence of potassium thioacetate unexpectedly gave the 6-*S*-acetyl-5-*O*-acetyl derivative **5** as the main reaction product. A possible mechanism of these transformations was postulated whereby the main role was ascribed to a neighbouring group participation process, involving hydrogen thio-orthoester formation as an intermediate. The regiospecific monosubstitution of the 6-tosyloxy group in compound **2** was successfully achieved with potassium thioacetate, in presence of 2,3-benzo-15-crown-5 as a catalyst. The corresponding 6-*S*-acetyl derivative **7** was obtained representing a possible intermediate in the mentioned solvolytic reactions. Compound **7** was shown to be very reactive, since it fully transformed into the corresponding mercaptan **8** in the presence of silica gel. This transformation occurred *via* the same thio-orthoester **7a** as in the mentioned solvolytic reactions of furanoses **2** and **3**. The synthesized compounds are key intermediates in the planned synthesis of selected natural products and their analogues.

Keywords: solvolysis; tosyloxy leaving group; thiosugars; neighbouring group participation; thio-orthoester.

INTRODUCTION

Heap and Owen reported[1] in 1970, that 1,2-*O*-isopropylidene-3,6-di-*O*-(*p*--toluenesulphonyl)-α-D-allofuranose (**1a**, Fig. 1) on treatment with potassium thiobenzoate in boiling ethanol (followed by benzoylation of the crude reaction products), gave the expected 6-*S*-benzoyl-5-*O*-benzoyl derivative **1b** accompanied by a 3,6-epithio by-product **1c**. The formation of the side product was attributed to a rearrangement of the benzoyl group from the sulphur at C-6 to the oxygen at C-5, followed by nucleophillic attack on C-3 by the liberated thiol group at C-6. Although a silica gel catalyzed migration of acetyl groups from the

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sulphur atom at C-3 to an oxygen atom at the C-6 position (*via* a six-membered thio-orthoester intermediate) has already been described,[2] no literature example of a similar process including terminal *S*-acetyl group, and a five-membered intermediate, has yet to be reported.

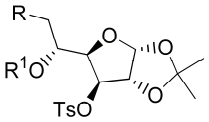
1a R = OTs, R^1 = H
1b R = SBz, R^1 = Bz

1c

Fig. 1. Structures of compounds **1a**–**c**.

The main goal of this work was the synthesis, as well as a study of the chemical behaviour of 6-thio-D-glucofuranose derivative **7** (Fig. 2) in order to obtain additional chemical evidence for the S–O acetyl migration process from sulphur at C-6 to oxygen at C-5. The further goal of this work involves the preparation of some new 6-thio-D-glucose derivatives that could represent convenient intermediates in the future synthesis of some biologically active compounds, such as biotin-like molecules,[3] and nucleoside analogues with modified sugar moieties.[4]

1 R = OH, R^1 = H
2 R = OTs, R^1 = H
3 R = Cl, R^1 = H
4 R = OTs, R^1 = Ac



5 R = SAc, R^1 = Ac
6 R = OH, R^1 = Ac
7 R = SAc, R^1 = H
8 R = SH, R^1 = Ac

Fig. 2. Structures of furanosides **1**–**8**.

EXPERIMENTAL

General methods

Melting points were determined on a Buchi SMP 20 apparatus and are not corrected. Optical rotations were measured on an automatic polarimeter Polamat A (Karl Zeiss, Jena, Germany), at room temperature in chloroform solutions. The IR spectra were recorded on a Perkin Elmer 457 spectrophotometer and the wavenumbers are given in cm^{-1}. The NMR spectra were recorded on a Bruker AC 250 E instrument in deuterochloroform and the chemical shifts (δ) are expressed in ppm values downfield from TMS. Low resolution mass spectra were taken on VG-7035 spectrometer (at 70 eV) and positions of fragments are given in *m*/*e* values. Thin-layer chromatography (TLC) was performed on DC Alufolien Kieselgel 60 F_{254} (Merck, Darmstadt, Germany). Short column chromatography was realised using Kieselgel 60 (0.063–0.200 mm). All extracts were dried over anhydrous Na_2SO_4.

*Attempted partial tosylation[4] of compound **1**. Preparation of 6-chloro-6-deoxy-1,2-*O*-isopropylidene-3-*O*-(*p*-toluenesulphonyl)-α-D-glucofuranose (**3**)*

A solution of compound **1**[3] (3.87 g, 10.11 mmol) and *p*-toluenesulphonyl chloride (4.33 g, 22.79 mmol) in a mixture of dry pyridine (40 mL) and chloroform (40 mL) was

stirred at 40 °C for 96 h. The reaction mixture was then diluted with dichloromethane (30 mL) and poured onto ice (50 g) and l:1 aqueous HCl (50 mL). The organic phase was separated and the aqueous solution was extracted with dichloromethane (30 mL). The combined organic solutions were washed with water (to pH 6–7), dried and evaporated, to give a mixture of two main products.

After chromatographic separation on a silica gel column (4:1 cyclohexane/Me_2CO) ditosylate **2** (0.57 g, 11 %) was first isolated as an amorphous solid, $[\alpha]_D^{23} = -10.9$ (*c* 2.2, $CHCl_3$; Lit.[5] $[\alpha]_D = -4.9$, lit.[6] $[\alpha]_D = -24.2$). The characterization data for this fraction are given in the Supplementary material to this paper

The less mobile fraction containing 6-chloro-6-deoxy derivative **3** (0.49 g, 12 %) was isolated as a colourless syrup, $[\alpha]_D^{23} = -13.4$ (*c* 1.9; lit.[7] $[\alpha]_D = -14.1$, *c* 1.9). Spectral (IR, NMR and LRMS) and analytical data of the thus obtained sample **3** were in good agreement with those reported previously.[7]

Unreacted starting compound **1** was recovered in 20 % yield.

1,2-O-*Isopropylidene-3,6-di*-O-*(*p-*toluenesulphonyl)*-α-*D*-*glucofuranose (2)*

A solution of compound **1**[3] (0.77 g, 2.06 mmol) and *p*-toluenesulphonyl chloride (0.78 g, 4.09 mmol) in dry pyridine (15 mL) was left at −18 °C for 48 h. The reaction mixture was then poured onto ice (30 g) acidified with 1:1 aqueous HCl (50 mL) and the resulting suspension extracted with dichloromethane (3×20 mL). The extract was washed with water (to pH 6–7) dried and evaporated whereupon crude compound **2** remained as a colourless syrup. After chromatographic purification on a column of silica gel (49:1 CH_2Cl_2/Me_2CO) pure product **2** was obtained (1.03 g, 95 %) as an amorphous solid, $[\alpha]_D^{23} = -11.1$ (*c* 2.4, $CHCl_3$). The spectral data (IR, NMR and LRMS) of this product were identical to those recorded for fraction 1 obtained in the previous procedure for the preparation of compound **2**.

5-O-*Acetyl-1,2*-O-*isopropylidene-3,6-di*-O-*(*p-*toluenesulphonyl)*-α-*D*-*glucofuranose (4)*

A solution of compound **2** (0.54 g, 1.02 mmol) and acetic anhydride (1 mL, 10.58 mmol) in dry pyridine (5 mL) was left at room temperature for 24 h. The reaction mixture was poured into 4:1 aqueous HCl (30 mL) and the resulting emulsion was extracted with dichloromethane (3×10 mL). The extract was washed with water (to pH 6–7), dried and evaporated, to leave crude **4** as a pale yellow oil. After chromatographic purification on a column of silica gel (19:1 toluene/EtOAc) pure product **4** was obtained (0.42 g, 72 %) as a colourless oil, $[\alpha]_D^{23} = -26.03$ (*c* 0.9, $CHCl_3$). The characterization data for **4** are given in the Supplementary material.

5-O-*Acetyl-6*-S-*acetyl-1,2*-O-*isopropylidene-3*-O-*(*p-*toluenesulphonyl)-6-thio-α-D-glucofuranose (5)*

Procedure A. A suspension containing compound **2** (0.88 g, 1.67 mmol), potassium thioacetate (0.47 g, 4.12 mmol) and ethyl methyl ketone (20 mL) was stirred at reflux temperature, under a nitrogen atmosphere, for 1 h. The reaction mixture was poured into water (100 mL) and the resulting emulsion was extracted with dichloromethane (3×20 mL). The extract was dried and evaporated, to give crude **5** as a brown oil. After chromatographic purification on a silica gel column (4:1 cyclohexane/Me_2CO), pure product **5** was obtained (0.6 g, 76 %) as a bright yellow solid. On recrystallization from dichloromethane/hexane, an analytical sample of **5** was obtained as transparent needles, m.p.: 106–108 °C, $[\alpha]_D^{23} = -48.9$ (*c* 0.65, $CHCl_3$). The characterization data for **5** are given in the Supplementary material.

Procedure B. By using an analogous procedure as described above, compound **3** (0.36 g, 0.92 mmol) and potassium thioacetate (0.21 g, 1.84 mmol), after stirring in boiling ethyl methyl ketone (10 mL) for 1.5 h, afforded the same thioacetate **5** in a yield of 44 %.

Procedure C. A suspension of compound **3** (0.24 g, 0.62 mmol) and potassium thioacetate (0.2 g; 1.75 mmol) in ethyl methyl ketone (5 mL) was refluxed under a nitrogen atmosphere for 2 h. Reaction mixture was diluted with dichloromethane (5 mL) and filtered. The precipitate was washed with dichloromethane (3×3 mL) and the combined extracts were dried and evaporated. The remaining brown oil was chromatographed on a silica gel column (4:1 cyclohexane/Me_2CO) to give pure product **5** in a yield of 85 %. Compound **5** thus prepared was identical with products obtained according to procedures A and B.

*Solvolysis of compound **2** in 95 % aqueous ethyl methyl ketone*

A suspension containing compound **2** (0.4 g; 0.76 mmol) and potassium thioacetate (0.17 g, 1.5 mmol) in 95 % aqueous ethyl methyl ketone (12.5 mL) was refluxed under a nitrogen atmosphere for 2 h. The reaction mixture was poured into cold water and the resulting suspension was extracted with chloroform (5×10 mL). The extract was dried and evaporated to give a mixture of two products. After chromatographic separation on a silica gel column (4:1 cyclohexane/ Me_2CO), a less polar component (R_f = 0.48) was isolated in a yield of 50 %. The physical constants as well as the spectral data of this material were in excellent agreement with those obtained for compound **5**. The less mobile fraction (R_f = 0.19) containing the alcohol **6** was isolated in a form of colourless syrup (0.11 g, 35 %). The characterization data for **6** are given in the Supplementary material.

5-O-*Acetyl-1,2*-O-*isopropylidene-6-thio-3*-O-*(*p-*toluenesulphonyl)*-α-*D*-*glucofuranose (**8**)*

A solution of compound **2** (0.57 g, 1.08 mmol), 2,3-benzo-15-crown-5 (0.3 g, 1.16 mmol) and potassium thioacetate (0.13 g, 1.14 mmol) in dry *N*,*N*-dimethylformamide (12 mL) was left at room temperature for 24 h. The reaction mixture was then poured into 5 % aqueous NaCl (20 mL) and extracted with chloroform. The extract was washed successively with saturated NaCl (4×25 mL) and water (4×25 mL), dried and evaporated. The crude intermediate **7** was obtained in the form of a pale yellow oil (0.38 g, 82 %). IR (film): 3300 (OH), 1680 (C=O, SAc), 1370 (as. S=O, Ts), 1200–1180 (sym. S=O, Ts). Due to its instability, compound **7** was used in the next step without any further purification. A suspension containing compound **7** (0.12 g, 0.28 mmol) and silica gel (1.2 g, particle size 0.2–0.5 mm) in dry benzene (12 mL) was stirred at room temperature for 7 h. Reaction mixture was evaporated and remaining solid was chromatographed on a column of silica gel (toluene). Pure product **8** was isolated as a colourless crystalline solid (0.088 g, 74 %). An analytical sample of **8** obtained after recrystallization from ethanol showed a m.p. of 109–110 °C.

RESULTS AND DISCUSSION

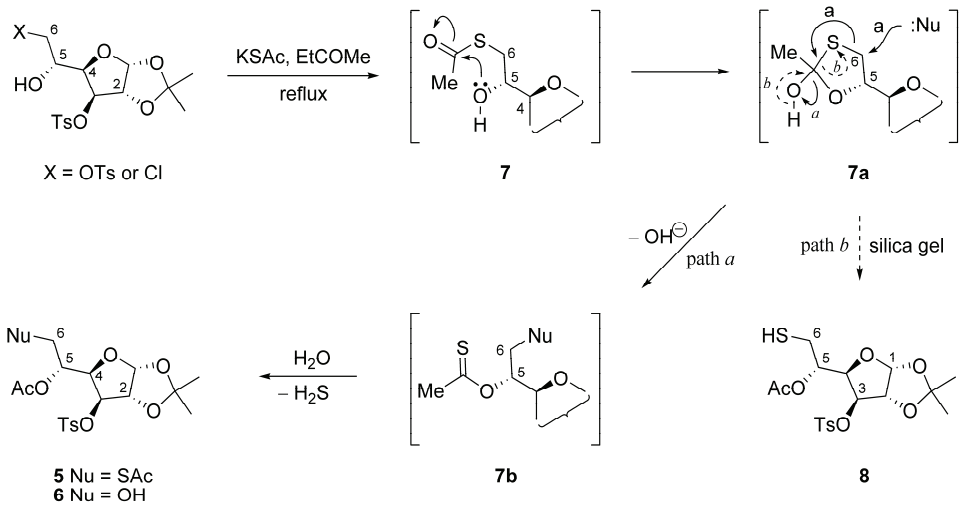
An attempted synthesis of compound **2** (Fig. 1) according to a literature procedure[5] resulted in obtaining a complex reaction mixture of several products, whereby 3,6-ditosylate **2** was obtained in a small yield (11 %). The unexpected 6-chloro-6-deoxy derivative **3** was also isolated in a yield of 12 %, while unreacted starting material **1** was recovered in 20 % yield.

In order to achieve a better yield of **2**, a partial tosylation of **1** was studied under carefully controlled reaction conditions. Thus a reaction of diol **1** with tosyl chloride in dry pyridine at −18 °C, for 48 h, afforded compound **2** in a yield

of 95 %. However, the most efficient method for the preparation of **3** remains the procedure previously developed in our laboratory.[7]

Evidence that the acetyl group from the sulphur at C-6 might migrate to the oxygen at C-5 unexpectedly came from initial experiments directed towards the preparation of compound **7**. Namely, in attempting to perform a regiospecific **8** monosubstitution of ditosylate **2** with thioacetate anion (KSAc, EtCOMe, reflux, 1 h), the corresponding 5,6-di-*O*-acetyl derivative **5** was unexpectedly obtained as the main reaction product in a yield of 76 %. Under analogous reaction conditions, 6-chloro-6-deoxy derivative **3** reacted after 1.5 h to give the same diacetate **5** in a yield of 44 %. However, in the reaction of compound **2** with potassium thioacetate in aqueous ethyl methyl ketone (5 % of water, reflux, 2 h), in addition to 6-thioacetate **5** (50 %), alcohol **6** was unexpectedly obtained in a yield of 35 %.

A possible mechanism of the mentioned transformations was postulated, whereupon the main role was ascribed to a neighbouring group participation process, involving the formation of the hydrogen thio-orthoester **7a** in the first step (Scheme 1).



Scheme 1. Possible mechanism for the formation of compounds **5**, **6** and **8**.

First step of postulated mechanism involves an S_N2 replacement of the leaving group from C-6 by thioacetate anion, whereupon the corresponding 6 thioacetate **7** is formed as a key intermediate. The next steps involve successive hydrogen thio-orthoester **7a** formation (by a nucleophilic addition of the C 5 hydroxyl group across the 6-thioacetate carbonyl function), followed by a subsequent attack of an external nucleophile (AcS^- or water) at the C-6 position of intermediate **7a** affording thioacetate **7b**, readily hydrolyzable[8,9] into the final products **5** or **6**.

In order to provide additional proof for the proposed mechanism, the next stage of the work was directed towards an independent synthesis of the postulated intermediate **7**. Namely, the main goal of such a study was to test the possibility of using thioacetate **7** as a substrate in other reactions occurring *via* a thio-orthoester intermediate of the type **7a**.

Regiospecific monosubstitution of the 6-tosyloxy group in compound **2** was successfully achieved with potassium thioacetate in *N*,*N*-dimethylformamide, at room temperature, in the presence of 2,3-benzo-15-crown-5 ether as a catalyst. The corresponding 6-*S*-acetyl derivative **7** was obtained as a possible intermediate in the mentioned S–O acetyl migration reaction. Compound **7** was shown to be rather reactive since it transforms into the corresponding mercaptan **8** in presence of silica gel.[2] This smooth transformation represents additional proof that both S–O acetyl migration reactions occur *via* the same hydrogen thio-orthoester intermediate **7a**.

To the best of our knowledge, a process involving S–O acetyl migration from C-6 to C-5 *via* a five-membered thio-orthoester of the type **7a** has not hitherto been described in the literature.

The synthesized 6-thio-D-glucofuranose derivatives represent possible intermediates in a planned synthesis of (+)-biotin-like compounds[3] and novel nucleoside analogues with modified sugar segments.[4]

CONCLUSIONS

Solvolytic reaction of 1,2-*O*-isopropylidene-3,6-di-*O*-(*p*-toluenesulphonyl)-*α*-D-glucofuranose (**2**), in the presence of potassium thioacetate, and/or 2,3-benzo-15-crown-5 as a catalyst, was studied in order to obtain 6-thio derivatives **5**, **7** and **8**, as possible intermediates in the synthesis of biologically active compounds. A possible mechanism of these transformations has been postulated whereby the main role was ascribed to a neighbouring group participation process, involving hydrogen thio-orthoester formation.

SUPPLEMENTARY MATERIAL

Analytical and spectral data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

S–O АЦЕТИЛ ПРЕМЕШТАЊЕ КОД ДЕРИВАТА 6-ТИО-D-ГЛУКОЗЕ

ВЕЛИМИР ПОПСАВИН[1,2], МИРЈАНА ПОПСАВИН[1] и ДУШАН МИЉКОВИЋ[1]

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При солволизи 1,2-*O*-изопропилиден-3,6-ди-*O*-(*p*-толуенсулфонил)-*α*-D-глукофуранозе (**2**), односно 6-хлоро-6-деокси-3-*O*-(*p*-толуенсулфонил)-*α*-D-глукофуранозе (**3**) у присуству калијум-тиоацетата, неочекивано је добијен 6-*S*-ацетил-5-*O*-ацетил дериват **5** као главни реакциони производ. Постулиран је механизам поменутих трансформација, при чему је одлучујућа улога приписана партиципацији суседне C-5 хидроксилне групе, уз формирање тио-ортоестарског интермедијера **7a**. Региоселективна супституција 6-тозилокси групе једињења **2** успешно је остварена реакцијом са калијум-тиоацетатом у присуству 2,3-бензо-15-круне-5 као катализатора. При томе је добијен 6-*S*-ацетил дериват **7** који представља могући интермедијер у поменутим реакцијама солволизе **2** и **3**. Једињење **7** се показало веома реактивним, јер се у присуству силика-гела потпуно трансформише у оговарајући 6-меркапто-дериват **8**. Ова реакција такође тече преко тио-ортоестра **7a**, који је постулирани интермедијер и у поменутим солволитичким реакцијама фураноза **2** и **3**. Синтетизована једињења представљају важне интермедијере у планираним синтезама одабраних природних производа и њихових аналога.

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