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CARBOHYDRATE RESEARCH

Note

Access to tetrachlorophthalimide-protected ethyl 2-amino-2-deoxy-1-thio-β-D-glucopyranosides

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Abstract

Ethyl 2-deoxy-2-tetrachlorophthalimido-1-thio-β-D-glucopyranoside (**7**) was prepared from glucosamine hydrochloride in four steps with a 20–25% overall yield. Formation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (**5**) was found to be crucial for this reaction sequence since the corresponding α-1-acetate did not react in Lewis-acid-catalyzed ethylthio glycosidations. Formation of the β-1-acetate (**5**) was achieved by treatment of 3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-D-glucopyranosyl bromide (**4**) with acetic acid under silver zeolite promotion. This was necessary because conditions normally used for β-1-acetate formation were not tolerated by the tetrachlorophthalimido (TCP) group. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Tetrachlorophthalimide; Thioglycosides; 2-Amino-2-deoxy glycosides; Glucosamine

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1. Introduction

Synthesis of natural products containing 2-amino-2-deoxy sugars has received considerable attention through the past decades and has recently been an area of special interest for our research group [1,2]. During these studies the amino protecting group tetrachlorophthalimido (TCP) was introduced [3–5] and utilized [6,7] as an alternative to the well-established phthalimido group [8]. The TCP group has the same properties as the phthalimido group except that it can be removed under very mild basic conditions. The TCP group can therefore serve as an alternative to the phthalimido group, or it can be cleaved off in the presence of the phthalimido group for selective exploration of amino functions [5,6]. Recently, we also reported that TCP-protected amino sugars can serve as convenient precursors to 2-azido-2-deoxyglucopyranosides [9].

Thus far, the TCP group has only been prepared in combination with 4-pentenyl [5] or trichloroacetimidate [4] as anomeric leaving groups. In both cases, introduction of the anomeric group is readily achieved from the α-1-acetate derivative **3**. 1-Thioglycosides, as with 4-pentenyl glycosides, are useful both for protecting and/or activating the anomeric center and hence have widespread appeal [10,11]. In order to extend the use of the TCP group further, we have therefore developed a simple, non-chromatographic access route to ethyl 2-

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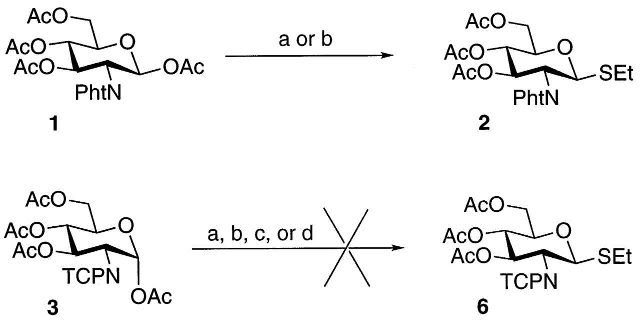
deoxy-2-tetrachlorophthalimido-1-thio-β-D-glucopyranoside (**7**).

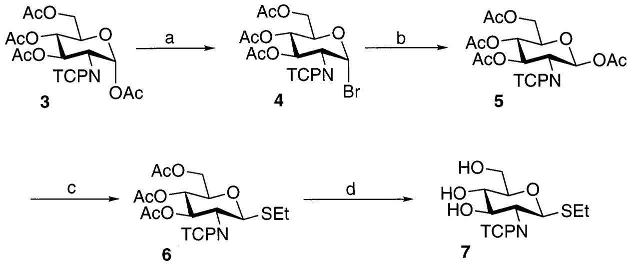
2. Results and discussion

The preferred method for preparation of alkyl thioglycosides during recent years has been Lewis-acid-catalyzed substitution of the anomeric acetate of peracetylated sugars with the desired alkanethiol [10]. In general 1,2-trans-acetates react faster in these reactions than their 1,2-cis counterparts [10]. Lönn [12] and Paulsen et al. [13] have prepared phthalimido-protected ethyl 1-thioglycoside **2** using this approach in reactions catalyzed by $TiCl_4$ or $FeCl_3$, respectively. In both cases the starting material was the β-1-acetate **1**, acting as an equivalent to a 1,2-trans acetate. However, in the case of TCP-protected glucosamine, preparation of the corresponding β-1-acetate derivative was not as straightforward, since the typical conditions used (sodium acetate, acetic anhydride, high temperature [14]) were not tolerated by the TCP group. Therefore, several attempts were made to utilize the readily available α-1-acetate **3** as the starting material for preparation of the desired 1-thioglycoside **6**. Despite the use of different reagent systems, including ethanethiol or the more nucleophilic trimethyl(ethylthio)silane [15,16] combined with various Lewis acids (see Scheme 1), only very minor amounts, if any, of product **6** could be detected.

Access to the β-1-acetate **5** appeared to be crucial for preparation of 1-thioglycoside **6**. Fortunately this could be achieved in a two-step procedure from the α-1-acetate **3** (see Scheme 2). Thus, the material was first transformed into the glycosyl bromide **4**, which was then acetolyzed, under promotion by silver zeolite, to produce the β-1-acetate **5**. The yield for these two steps was 50%, but it is nevertheless attractive because of the simplicity of the procedure and that **5** is collected as crystals thereby avoiding chromatography. As desired, the β-1-acetate **5** then smoothly produced the 1-thioglycoside **6** (68%) when treated with $TiCl_4$ and ethanethiol overnight. Recent studies by Ellervik and Magnusson [17] have included an alternative and useful preparation of the β-1-acetate **5**. By use of temporary *N*-anisylidene protection [18], later smoothly exchanged to TCP, acetylation giving β-1-acetate formation was straightforward (Scheme 2).



Scheme 1. Conditions tested: (a) $FeCl_3$, EtSH, CH_2Cl_2; (b) $TiCl_4$, EtSH, CH_2Cl_2; (c) $TiCl_4$, $EtSSiMe_3$, CH_2Cl_2; (d) $BF_3 \cdot Et_2O$, $EtSSiMe_3$, CH_2Cl_2.



Scheme 2. (a) HBr, HOAc; (b) HOAc, Ag zeolite, CH_2Cl_2, 50% from **3**; (c) $TiCl_4$, EtSH, CH_2Cl_2, 68%; (d) HCl, H_2O, acetone.

Finally, the *O*-acetyl groups were quantitatively removed by acid hydrolysis [5] to give ethyl 2-deoxy-2-tetrachlorophthalimido-1-thio-β-D-glucopyranoside **7**. Purification of all intermediates can be effected by crystallization only, suggesting that this route might serve for simple and large-scale access to TCP-protected 2-amino-2-deoxy thioglycosides, despite a modest overall yield of 20–25% over four steps from glucosamine hydrochloride.

3. Experimental

General methods.—Melting points are uncorrected. Solvents of commercial anhydrous grade were used without further purification. TLC plates (Riedel-de Haen, coated with Silica Gel 60 F 254) were detected by charring with 8% H_2SO_4. Silica Gel (Spectrum SIL 58, 230–400 mesh, grade 60) was used for column chromatography. All NMR spectra were recorded at 25 °C at 400 MHz (^{1}H) or 100 MHz (^{13}C) using a Varian Inova-400 spectrometer, and chemical shifts are reported relative to internal Me_4Si. Elemental analysis were conducted by Atlantic Microlab, Norcross, GA.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (**5**).—Enough HBr (30% solution in HOAc) was added to a round bottomed flask containing 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-D-glucopyranoside (**3**) (9.03 g, 14.6 mmol) [5] to cover the crystals completely. The suspension was stirred at room temperature and the starting material dissolved gradually. After stirring overnight, the mixture was diluted with $CHCl_3$ and then poured into ice-cold water. The layers were separated and the organic phase was washed with water (twice), $NaHCO_3$ (satd), dried ($MgSO_4$), and evaporated. The isolated syrup was dried in vacuum for 5 h and then dissolved in CH_2Cl_2 (50 mL). Silver zeolite (11.8 g, Aldrich, catalog no. 36,660-9.) and HOAc (4.2 mL, 73.2 mmol) were added to the solution and the mixture was stirred in darkness overnight at room temperature. After filtration, the clear yellow solution was evaporated and the remaining residue crystallized from hot MeOH to give the product **5** in 50% yield (4.54 g, 7.36 mmol): mp 192–196 °C, ^{1}H NMR ($CDCl_3$): δ 1.91, 2.04, 2.05, 2.12 (4 s, each 3 H, $COCH_3$)) 3.99 (m, 1 H, H-5), 4.14 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.37 (dd, 1 H, $J_{5,6b}$ 4.5 Hz, H-6b), 4.46 (dd, 1 H, J 8.9, J 10.4 Hz), 5.23 (dd, 1 H, J 9.1, J 10.2 Hz), 5.80 (dd, 1 H, J 9.1, J 10.3 Hz), 6.47 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), ^{13}C NMR ($CDCl_3$): δ 20.5, 20.6, 20.7, 20.8 (4 s, $COCH_3$), 54.3, 61.4, 67.9, 70.7, 72.6, 89.6 (C-1–C-6), 168.6, 169.3, 170.5, 170.6 (4 s, $COCH_3$). Anal. Calcd. for $C_{22}H_{19}NO_{11}Cl_4$: C, 42.95; H, 3.17; N, 2.28. Found: C, 42.72; H, 3.09; N, 2.30.

Ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-tetrachlorophthalimido-1-thio-β-D-glucopyranoside (**6**).—To an ice-cooled solution of **5** (6.00 g, 9.74 mmol) in CH_2Cl_2 (60 mL) was added EtSH (2.64 mL, 35.6 mmol) and $TiCl_4$ (1.39 mL, 12.6 mmol). The mixture was allowed to attain room temperature and stirred overnight. After complete reaction the mixture was diluted with CH_2Cl_2 to double volume and washed with 1 M H_2SO_4, $NaHCO_3$ (satd), and water. The organic phase was then dried ($MgSO_4$) and evaporated to give a syrup. Crystallization from MeOH gave the product **6** in 68% yield (4.04 g, 6.53 mmol): mp 135–138 °C, ^{1}H NMR ($CDCl_3$): δ 1.20–1.30 (m, 3 H, S–CH_2–CH_3), 1.91, 2.05, 2.11 (3 s, each 3 H, $COCH_3$)), 2.60–2.80 (m, 2 H, S–CH_2–CH_3), 3.86 (m, 1 H, H-5), 4.17 (dd, 1 H, $J_{5,6a}$ 2.3, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.31 (dd, 1 H, $J_{5,6b}$ 5.0 Hz, H-6b), 4.37 (t, 1 H, J 10.2 Hz), 5.19 (dd, 1 H, J 10.0, J 10.2 Hz), 5.45 (d, 1 H, $J_{1,2}$ 10.6 Hz, H-1), 5.75 (dd, 1 H, J 9.2, J 10.2 Hz), ^{13}C NMR ($CDCl_3$): δ 14.9 (S–CH_2–CH_3), 20.5, 20.6, 20.8 (3 s, $COCH_3$), 24.5 (S–CH_2–CH_3), 54.4, 62.2, 68.5, 71.6, 76.0, 80.8 (C-1–C-6), 169.4, 170.5, 170.6 (3 s, $COCH_3$). Anal. Calcd. for $C_{22}H_{21}NO_9SCl_4$: C, 42.81; H, 3.43; N, 2.27. Found: C, 42.73; H, 3.45; N, 2.27.

Ethyl 2-deoxy-2-tetrachlorophthalimido-1-thio-β-D-glucopyranoside (**7**).—Compound **6** (1.03 g, 1.67 mmol) was dissolved in acetone (22 mL) and HCl was added (2.0 mL concd HCl in 7.1 mL H_2O). The mixture was stirred at 70 °C and after 1 h additional water (4.0 mL) was added. Continued stirring overnight completed the reaction. Acetone was removed by evaporation and the remaining water phase was extracted four times with EtOAc. The combined organic extract was washed with $NaHCO_3$ (satd), dried ($MgSO_4$), and evaporated. The product **7** was collected as a light yellow foam (quantitative yield, 819 mg, 1.97 mmol) of sufficient purity for further transformations. However, the crude product could be crystallized from MeOH to give pure **7** (62%, 510 mg, 1.04 mmol): mp 202–204 °C, ^{1}H NMR (CD_3OD): δ 1.15–1.30 (m, 3 H, S–CH_2–CH_3), 2.60–2.80 (m, 2 H, S–CH_2–CH_3), 3.44 (m, 2 H), 3.73 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.92 (dd, 1 H, $J_{5,6b}$ 2.0 Hz, H-6b), 4.05 (t, 1 H, J 10.2 Hz), 4.23 (dd, 1 H, J 8.2, J 10.2 Hz), 5.28 (d, 1 H, $J_{1,2}$ 10.2 Hz, H-1), ^{13}C NMR (CD_3OD): δ 15.3 (S–CH_2–CH_3), 24.9 (S–CH_2–CH_3), 58.4, 62.9, 72.2, 73.5, 82.1, 82.6 (C-1–C-6). Anal. Calcd. for $C_{16}H_{15}NO_6SCl_4$: C, 39.13; H, 3.08; N, 2.85. Found: C, 38.89; H, 3.09; N, 2.86.

Acknowledgements

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