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Note

A facile protocol for direct conversion of unprotected sugars into phenyl 4,6-*O*-benzylidene-per-*O*-acetylated-1,2-*trans*-thioglycosides

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Abstract

A short and practical methodology for conversion of unprotected D-glucose, maltose, cellobiose and lactose into the corresponding phenyl 4,6-*O*-benzylidine-per-*O*-acetylated-1,2-*trans*-thioglycosides is described. The protocol is based on the execution of five reaction steps (bromoacetylation, thiophenolysis under phase transfer catalysis conditions, deacetylation, benzylidenation and acetylation) in one continuous procedure and provides a fast access to the title compounds as pure crystalline products without chromatographic purification. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Phenyl 1-thio-β-glycosides; Benzylidenation; Crystallisation; Quick access; Scale up

1. Introduction

Previously, we have reported the chemical synthesis of a set of oligosaccharides[1–4] using a number of building blocks derived from maltotriose,[1] maltose,[2] and glucose[3] or combinations thereof.[4] In addition, we have described[5] the synthesis of a number of phenyl 6,4′-substituted-1-thio-β-maltosides to be used as building blocks for the synthesis of linear and branched maltooligosaccharides. Key intermediates in the synthesis of these building blocks are the phenyl 4, 6-*O*-benzylidene-thioglycoside derivatives **5**[3] (Scheme 1) and **6**[2,5] (Scheme 1). These derivatives were previously obtained *via* a number of distinct reaction steps which each require a separate work-up and chromatographic purification. In the present work, we describe a strategy for direct conversion of unprotected sugars D-glucose (**1**), maltose (**2**), cellobiose (**3**), and lactose (**4**) into the corresponding phenyl 4,6-*O*-benzylidene-per-*O*-acetylated-1,2-*trans*-thioglycosides **5**–**9** (Scheme 1) based on the execution of a number of reaction steps in one continuous procedure providing the end product as a pure one isomer by crystallisation. The reaction sequence was designed as an easy and quick access to these benzylidene derivatives **5**–**9** using direct conversion of the appropriate sugar into the corresponding acetobromo derivative following the procedure developed by Kartha & Jennings.[6] TLC revealed the formation of the acetobromo derivative as the sole product. Subsequent thiophenolysis of the acetobromo derivative formed in situ was carried out under phase-transfer catalysis (PTC) conditions in EtOAc at room temperature using tetrabutylammonium hydrogen sulphate (TBAHS) as catalyst.[7,8] The thiophenolysis proceeded fast with $>90\%$ conversion as revealed by TLC. The product was subjected to deacetylation using sodium methoxide in methanol and the benzylidene group was introduced by employing the *gem*-dihalide α,α-dibromotoluene[9–11] in pyridine and subsequently acetylated. The crude product was then recrystallised from EtOH and/or aq acetone to provide compounds **5**–**9** in 14–45% overall yield from the unprotected sugar with-

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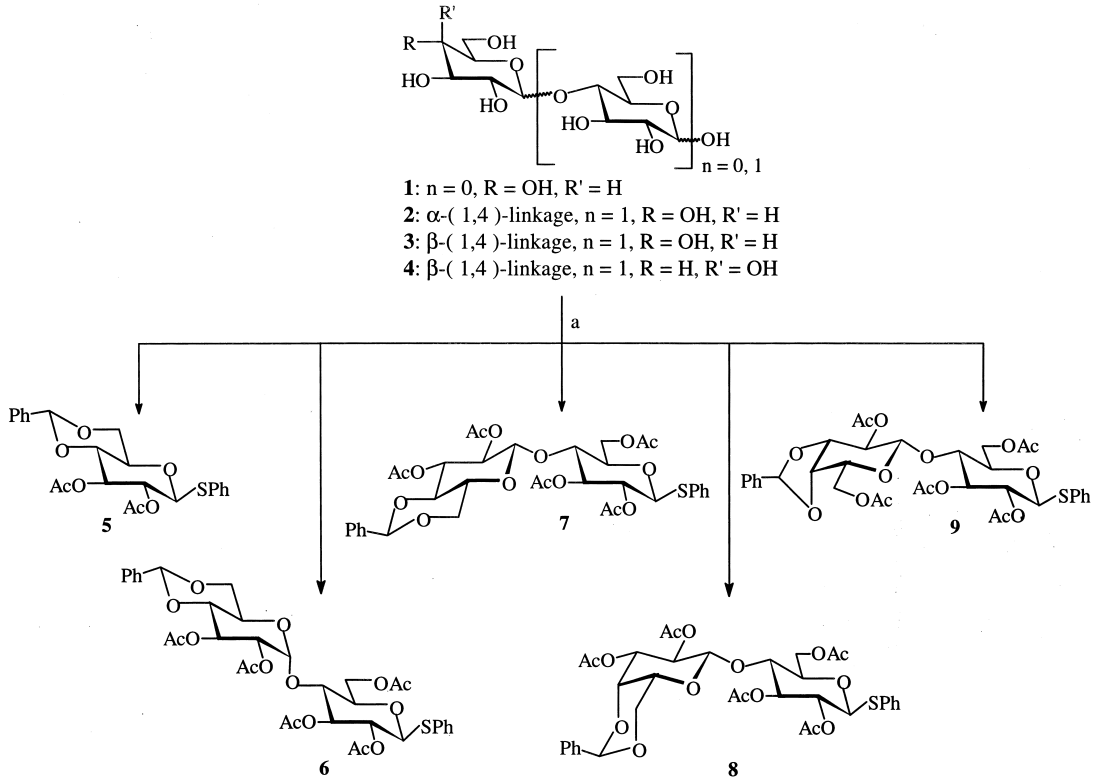
out the use of any chromatographic purification (Table 1, it found that the purifications in between the individual reaction-steps could be eliminated by one final crystallisation in the end of the sequence). The low yield reported from lactose (14%, Table 1) is partly due to the formation of the 3,4-benzylidene analogue derivative **9**. Compound **9** was isolated by chromatography in 10% yield.

In conclusion, we have shown that a number of phenyl 4′, 6′-*O*-benzylidene-1-thio-β-D-saccharides can be prepared from the unprotected sugars. This was accomplished by execution of five reaction steps in one continuous procedure followed by a final crystallisation step. The overall yield obtained is just as good as when the product obtained in each separate reaction was purified. The method significantly reduces the time required to obtain the target compounds. Furthermore, scale-up of the reaction does not result in lower yields. The identity of the synthesised compound was confirmed by NMR-spectroscopy.

2. Experimental

Melting points were determined with a Mettler FP81 MBC Cell connected to a Mettler FP80 Central Proces-



Scheme 1. Reaction conditions: (a) Acetic anhydride, HBr in acetic acid (33% w/v); TBAHS, thiophenol, 1 M Na_2CO_3 (aq), EtOAc; $NaOCH_3$, methanol; α,α-dibromotoluene, pyridine, acetic anhydride.

Table 1
Conversion of sugars **1**–**4** into their benzylidenated derivatives **5**–**9**

Entry	Product	% Yield	Melting point	Optical rotation $[\alpha]_D$	^{1}H NMR $\delta_{(ppm)}$		^{13}C NMR $\delta_{(ppm)}$	
					H-1	PhCH	C-1	PhCH
1	**5**[2]	29	206 ± 0.2 °C Lit.[2] 205–206 °C	−53.4° (*c* 0.67, $CHCl_3$) Lit.:[2] −53.4° (*c* 0.59, $CHCl_3$)	4.80	5.49	86.5	101.4
2	**6**[4]	33	199 ± 0.4 °C Lit.[4] 196–197 °C	+29.2° (*c* 0.75, $CHCl_3$) Lit.:[2] +29.6° (*c* 0.82, $CHCl_3$)	4.71	5.47	85.5	101.5
3	**7**	45	267 ± 0.1 °C	−45.3° (*c* 0.83, $CHCl_3$)	4.66	5.47	85.5	101.3
4	**8**	14	255 ± 0.25 °C	+24.4° (*c* 0.70, $CHCl_3$)	4.69	5.46	85.2	101.5
4	**9**	10	175 ± 0.6 °C	+14.0° (*c* 0.71, $CHCl_3$)	4.69	6.15	85.6	103.9

sor unit and are uncorrected. Optical rotations were measured at 21 ± 2 °C with an Optical Activity Ltd. AA-1000 Polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument at 400 and 101 MHz, respectively. δ_H-values are relative to internal TMS and δ_C-values are referenced to the solvent [δ_C ($CDCl_3$) = 77.0] standard. Reactions were monitored by TLC on aluminium sheets coated with silica gel $60F_{254}$ (0.2-mm thickness, E Merck, Darmstadt, Germany) and the spots were detected by charring with 10% H_2SO_4 in MeOH. Column chromatography was carried out using Silica Gel 60 (particle size 0.040–0.063, 230–400 mesh ASTM, E Merck, Darmstadt, Germany). All of the chemicals used in this study were commercially available.

2.1. General procedure for the preparation of phenyl 4,6-*O*-benzylidene-1,2-trans-thioglycosides 5–9

To a stirred suspension of the unprotected sugar (13.9 mmol) in Ac_2O (25 mL) a solution of HBr in HOAc (33% w/v, 6.8 mL) was added at room temperature. Stirring was continued until a clear solution was obtained (approx. 15 min) and the reaction mixture was cooled to 0 °C. An additional amount of HBr solution (34 mL) was slowly added and stirring was continued for 2 h at room temperature. Solvents were removed by rotary evaporation and residual traces of solvent removed by coevaporation with toluene (3 × 50 mL). The resulting solid was dissolved in EtOAc (100 mL) and added to a mixture of Bu_4NHSO_4 (4.7 g, 13.9 mmol), thiophenol (2 mL, 19.5 mmol) in 1M Na_2CO_3 (100 mL) and vigorously stirred at room temperature for 15 min. After addition of EtOAc (50 mL) was added, the organic phase was separated and washed with 1M NaOH (50 mL), water (2 × 50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated to dryness and the residue dissolved in dry methanol (50 mL). The solution was treated with NaOMe (33% v/v, 6.5 mL) for 2 h, neutralised with Dowex 50W-X8 (H^+ form, 200–400 mesh) ion-exchange resin, filtered, passed through a layer of sand and silica gel and the residue obtained by evaporation was dissolved in dry pyridine (75 mL). α,α-Dibromotoluene (3 mL) was added and the mixture was refluxed for 2.5 h at 140 °C and cooled to room temperature. Ac_2O (35 mL) was slowly added and the stirring was continued for 12–24 h at room temperature after which solvents were evaporated and trace amounts of solvents removed by coevaporation with toluene. The residue was dissolved in EtOAc and washed with 1N NaOH (50 mL), H_2O (2 × 50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated and coevaporated with 96% EtOH until a solid was formed. Cold EtOH was added and the precipitate formed was filtered off and recrystallised.

2.2. Phenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucpyranoside (5)

Recrystallised from 96% EtOH to give compound **5** (2.2 g, 29%, colourless needles): R_f 0.61 (EtOAc/CH_2Cl_2 1:9).

2.3. Phenyl 2,3,6,2′,3′-penta-*O*-acetyl-4′,6′-*O*-benzylidene-1-thio-β-maltoside (6)

Recrystallised from 96% EtOH to give compound **6** (3.36 g, 33%, buff-shaped crystals): R_f 0.39 (EtOAc/CH_2Cl_2 1:9).

2.4. Phenyl 2,3,6,2′,3′-penta-*O*-acetyl-4′,6′-*O*-benzylidene-1-thio-β-cellobioside (7)

Recrystallised from aqueous acetone to give compound **7** (4.6 g, 45%) as colourless needles: R_f 0.45 (1:9 EtOAc–CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00, 2.02, 2.04, 2.08, 2.10 (5 × s, 15 H, CO*CH*$_3$), 3.46 (m, 1 H, H-5′), 3.61 (ddd, 1 H, $J_{4,5}$ 10.0 Hz, $J_{5,6a}$ 1.8 Hz, $J_{5,6b}$ 5.2 Hz, H-5), 3.67 (dd, 1 H, $J_{5',6'e}$ 9.5 Hz, H-6′e), 3.71 (dd, 1 H, $J_{4',5'}$ 10.1 Hz, H-4′), 3.74 (dd, 1 H, H-4), 4.08 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.34 (dd, 1 H, $J_{5',6'a}$ 5.0 Hz, $J_{6'a,6'b}$ 10.6 Hz, H-6′a), 4.55 (dd, 1 H, H-6a), 4.58 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.66 (d, 1 H, $J_{1,2}$ 10.2 Hz, H-1), 4.88 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 4.91 (dd, 1 H, H-2′), 5.19 (dd, 1 H, $J_{2,3}$ 9.1 Hz, H-3), 5.25 (dd, 1 H, $J_{2',3'}$ 9.3 Hz, H-3′), 5.47 (s, 1 H, Ph*CH*), 7.27–7.48 (m, 10 H, ArH, S*Ph* & *Ph*CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.6, 20.6, 20.6, 20.8, 20.8 (5 × CO*CH*$_3$), 62.1 (C-6), 66.4, 68.4, 68.9, 70.0, 72.0 (C-5′, C-6′, C-2′, C-2, C-3′), 73.1, 73.5, 75.8, 76.9 (C-4′, C-3, C-4, C-5), 85.5 (C-1), 101.0, 101.3 (C-1′, Ph*CH*), 126.4, 128.2, 128.8, 129.2, 131.8, 132.9, 137.4 (ArC, S*Ph* & *Ph*CH), 168.8, 169.5, 170.1, 170.2, 170.7 (5 × *CO*CH$_3$). Anal. Calcd for $C_{35}H_{40}O_{15}S$: C, 57.37; H, 5.50; S, 4.38. Found: C, 57.10; H, 5.48; S, 4.36.

2.5. Phenyl 2,3,6,2′,3′-penta-*O*-acetyl-4′,6′-*O*-benzylidene-1-thio-β-lactoside (8)

Recrystallised from 96% EtOH to give compound **8** (1.4 g, 14%) as colourless needles: R_f 0.26 (EtOAc–CH_2Cl_2 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02, 2.03, 2.03, 2.08, 2.10 (5 × s, 15 H, CO*CH*$_3$), 3.45 (m, 1 H, H-5′), 3.65 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, $J_{5,6a}$ 1.8 Hz, $J_{5,6b}$ 5.6 Hz, H-5), 3.74 (dd, 1 H, $J_{3,4}$ 9.1 Hz, H-4), 4.03 (dd, 1 H, $J_{5',6'e}$ 1.5 Hz, $J_{6'a,6'e}$ 12.4 Hz, H-6′e), 4.11 (dd, 1 H, $J_{6a,6b}$ 12.1 Hz, H-6b), 4.28 (dd, 1 H, $J_{5',6'a}$ 1.0 Hz, H-6′a), 4.32 (brdd, 1 H, H-4′), 4.46 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1′), 4.56 (dd, 1 H, H-6a), 4.69 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 4.88 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, $J_{3',4'}$ 3.7 Hz, H-3′), 4.93 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 5.23 (dd, 1 H, H-3), 5.25 (dd, 1 H, H-2′), 5.46 (s, 1 H, Ph*CH*), 7.27–7.49 (m, 10

H, ArH, S*Ph* & *Ph*CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.5, 20.7, 20.7, 20.8, 20.9 ($5 \times CO\mathit{CH_3}$), 61.9, 66.3, 68.4 (C-6, C-5′, C-6′), 70.1, 71.9, 72.5, 74.2, 76.5, 76.8, 77.9 (C-2, C-3′, C-2′, C-3, C-5, C-4, C-4′), 85.2 (C-1), 101.5, 101.5 (C-1′, Ph*CH*), 126.1, 128.2, 128.3, 128.8, 129.2, 131.4, 133.2, 136.5 (ArC, S*Ph* & *Ph*CH), 169.3, 169.4, 169.5, 170.1, 170.2 ($5 \times \mathit{CO}CH_3$). Anal. Calcd for $C_{35}H_{40}O_{15}S$: C, 57.37; H, 5.50; S, 4.38. Found: C, 57.66; H, 5.77; S, 4.08.

2.6. Phenyl 2,3,6,2′,6′-penta-*O*-acetyl-3′,4′-*O*-benzylidene-1-thio-β-D-lactoside (9)

The mother liquor of compound **8** was evaporated until dryness. Chromatography of the residue on silica gel (90 g) with CH_2Cl_2–EtOAc (9:1) gave **9** (1 g, 10%) as colourless fibres: R_f 0.34 (EtOAc–CH_2Cl_2 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06, 2.07, 2.09, 2.10, 2.11 ($5 \times$ s, 15 H, $CO\mathit{CH_3}$), 3.68 (ddd, 1 H, $J_{4,5}$ 10.0 Hz, $J_{5,}$ 6a 2.0 Hz, $J_{5,6b}$ 5.5 Hz, H-5), 3.74 (dd, 1H, H-4), 3.93 (ddd, 1 H, $J_{4',5'}$ 2.0 Hz, $J_{5',6'a}$ 5.1 Hz, $J_{5',6'b}$ 7.2 Hz, H-5′), 4.19 (m, 2 H, H-6b, H-4′), 4.31 (dd, 1 H, $J_{6'a,6'b}$ 11.7 Hz, H-6′b), 4.37 (dd, 1 H, H-6′a), 4.43 (d, 1 H, $J_{1',2'}$ 7.0 Hz, H-1′), 4.45 (dd, 1 H, H-3′), 4.53 (dd, 1 H, $J_{6a,6b}$ 11.8 Hz, H-6a), 4.69 (d, 1 H, $J_{1,2}$ 10.4 Hz, H-1), 4.94 (dd, 1 H, H-2), 5.00 (dd, 1 H, $J_{2',3'}$ 7.0 Hz, H-2′), 5.25 (dd, 1 H, $J_{2,3}$ 9.1 Hz, $J_{3,4}$ 9.1 Hz, H-3), 6.15 (s, 1 H, Ph*CH*), 7.27–7.50 (m, 10 H, ArH, S*Ph* & *Ph*CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.8, 20.8, 20.8, 20.8, 20.8 ($5 \times CO\mathit{CH_3}$), 62.3, 63.1 (C-6, C-6′), 70.2, 70.3, 71.1, 73.1, 73.4, 76.2, 76.9, 77.6 (C-2, C-2′, C-5′, C-4′, C-3, C-4, C-5, C-3′), 85.6 (C-1), 100.4 (C-1′), 103.9 (Ph*CH*), 126.2, 128.2, 128.4, 128.9, 129.3, 132.0, 132.8, 137.7 (ArC, S*Ph* & *Ph*CH), 169.2, 169.4, 169.5, 170.1, 170.2 ($5 \times \mathit{CO}CH_3$). Anal. Calcd for $C_{35}H_{40}O_{15}S$: C, 57.37; H, 5.50; S, 4.38. Found: C, 57.06; H, 5.73; S, 4.53.

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