Carbohydrate Research 344 (2009) 134–135

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Formation and structure elucidation of *N*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea

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ARTICLE INFO

Article history:
Received 24 July 2008
Accepted 11 August 2008
Available online 15 August 2008

Keywords:
Glucopyranosylthiourea
Deacetylation

ABSTRACT

Treatment with concd HCl/MeOH transformed *N*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea, via selective cleavage of the primary alcoholic ester group, into the title compound.

The chemistry of (thio)urea derivatives of saccharides is extensively elaborated and well documented.[1] These compounds arouse interest as potential biologically active substances and versatile intermediates for preparing various (e.g., heterocyclic) derivatives as well. The biological properties of polyhydroxy compounds have been reported[2,3] to vary in a wide range depending on the number and position of acetyl groups. This phenomenon gave motives for the synthesis of partially ac(et)ylated sugar thiourea derivatives. The enzymic partial deacetylation of carbohydrates[4] may be accompanied[2] by accidental acetyl migration. Although selective 1-deacetylation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(*N*′-phenylureido)-α- or β-D-glucopyranose by treatment with NaOMe/MeOH has been performed,[5,6] a survey of the literature revealed that both acetylation of β-D-glucopyranosylthiourea (**1**) and basic deacetylation of glucosides **2**, **3**, **4** and **5** proceed completely on the sugar moiety. Thus, treatment with NaOMe/MeOH[5,7–9] or NH_3/MeOH,[10–13] $MeNH_2$/MeOH[14] and Me_2NH/MeOH[15] deacetylate not only tetra-*O*-acetyl compound **2** into **1**[8,10,12,13,16] and the *N*′-substituted analogues **3**, **4** and **5** into **6**[11], **7**[14] and **8**,[17] respectively, but also NaOMe/MeOH[8] or even NH_3/MeOH[13] exert O,N-deacetylation on *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea (**9**)[8,13] and give **1**.

Also methods for cleavage of the ester bonds under acid conditions have been developed using $HBF_4{\cdot}Et_2O$ in MeOH[18] or *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in CH_2Cl_2/MeOH.[19] Moreover, the HCl/MeOH couple[20] has been found to be suitable for complete deacetylation of peracetylated aldohexoses and aldobioses,[20a] and successfully applied for cleavage of *O*-fomyl[20b] group or general removal of *O*-acetyl[20c,20d] groups under preservation of benzoate bonds. Also, the above methods under acid conditions, however, have not been applied for partial deacetylation and are not indicated to be chemo- or regio-selective within the acetates themselves.

Although previously HCl/MeOH has been used[20] for general removal of *O*-acetyl groups, now treatment with this agent transformed *O*,*N*-acetyl compound **9** selectively into a tetraacetyl derivative of **1** and not, via complete O-deacetylation, into compound **10**. In addition to the elemental and group analyses, the structure of the product was stated by NMR investigations. A full $^1H/^{13}C$ assignment, carried out using HSQC and COSY measurements, revealed the product to be the title compound *N*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea (**11**) with a free primary hydroxyl group. In the HSQC spectrum the OH signal does not exhibit cross-peak, while its connectivity to both H-6 protons is observable in the COSY spectrum. The selective cleavage of the primary alcoholic ester group is presumably due to a spacial proximity of the protonable β-anomeric thioamide moiety as well.

Adduct ions observed by MALDI-TOF MS measurements supported the structures stated for substrate **9** (*m*/*z* 471.108 $[M+Na]^+$ and *m*/*z* 449.145 $[M+H]^+$) and product **11** (*m*/*z* 429.095 $[M+Na]^+$ and *m*/*z* 407.115 $[M+H]^+$). By using electron-spray technique also fragmentation patterns could be recorded, for example, from substrate **9** adduct ions of tetra-*O*-acetylglucopyranosylium cation with Na (*m*/*z* 353.083) or H (*m*/*z* 331.100) were detected, while from product **11** the adduct ions with Na (*m*/*z* 311.073) or H (*m*/*z* 289.092) revealed the formation of the sugar anhydride triacetyllaevoglucosan, 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucose.

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0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.08.015

The formation of this 1,6-anhydro compound is in conformity with the selective cleavage of the 6-Ac group of **9** spatial near the protonated β-thioureido moiety in the reaction **9**→**11**.

1. Experimental

Melting points are uncorrected, and were determined on a Kofler block. Solutions were concentrated under reduced pressure by using a rotary evaporator. TLC: Kieselgel 60 F_{254} (Alurolle, Merck). Optical rotation: Perkin–Elmer 241 polarimeter, at 23 °C. ^{1}H (500.13 MHz) and ^{13}C NMR (125.76 MHz) spectra were recorded with Bruker DRX-500 spectrometer in DMSO-d_6 at 300 K. Chemical shifts were referenced to internal TMS. Full ^{1}H/^{13}C assignment was carried out using HSQC and COSY methods. Mass spectrometry: micrOTOF—Q 9 instrument, for obtaining fragmentation spectra, electron-spray technique was used.

1.1. ^{1}H and ^{13}C NMR ($CDCl_3$) as well as mass spectral data of precursor 9

^{1}H NMR: δ 10.986 (d, 1H, $J_{1,N}$ = 8.4 Hz, NH), 9.248 (s, 1H, N′*H*Ac), 5.724 (dd, 1H, $J_{1,2}$ = 9.1 Hz, H-1), 5.352 (t, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.146 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 5.104 (t, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 4.277 (dd, 1H, H-6a), 4.131 (dd, 1H, H-6b), 3.844 (m, 1H, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 2.2 Hz, $J_{6a,6b}$ = 12.5 Hz, H-5), 2.152, 2.087, 2.044, 2.034, and 2.024 (5s, each 3H, 5Ac).

^{13}C NMR: δ 183.08 (C═S), 171.19, 171.10, 170.43, 170.40, and 169.88 (5C═O), 82.81 (C-1), 74.18 (C-5), 73.20 (C-3), 70.69 (C-2), 68.57 (C-4), 62.01 (C-6).

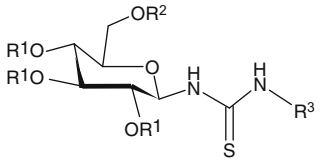
$C_{17}H_{24}N_2O_{10}S$ (448.5); Fragmentation of [M+Na] (*m*/*z* 471.108): *m*/*z* 412.069 $[M+Na-AcNH_2]^+$, 370.111 $[M+Na-AcNCS]^+$, strongest signal 353.083 $[M+Na-AcNH{\cdot}CS{\cdot}NH_2]^+$, 293.063 $[M+Na-AcNH{\cdot}CS{\cdot}NH_2-AcOH]^+$. Fragmentation of $[M+H]^+$ (*m*/*z* 449.145): weak signal *m*/*z* 331.100 $[M+1-AcNH{\cdot}CS{\cdot}NH_2]^+$.

1.2. *N*-(2,3,4-Tri-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea (11)

In a mixture of MeOH (50 mL) and concd HCl (0.25 mL, 3 mmol) was stirred finely powdered *N*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acetylthiourea[13,18] (**9**, 4.95 g, 11 mmol) for 2 h. From the transiently formed clear solution, colourless crystals were separated which after being kept at 3 °C for 7 h were filtered off, washed with MeOH and hexane, dried in a vacuum desiccator over KOH to give crude (2.52 g, 56.4%) or recrystallised **11,** mp 209–210 °C (from EtOAc). The crude product when recrystallised from 1,2-dichloroethane had mp 213 °C, and after being finely powdered and kept at 100 °C/0.5 Torr until constant weight, mp 220–221 °C, $[\alpha]_D$ +14.1 (*c* 0.13, $CHCl_3$).

^{1}H NMR ($(CD_3)_2SO$): δ 11.485(s, 1H, N′HAc), 11.036 (d, 1H, $J_{1,N}$ = 8.9 Hz, NH), 5.895 (dd, 1H, $J_{1,2}$ = 9.2, 8.9 Hz, H-1), 5.387 (t, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 4.982 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.972 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.817 (t, 1H, $J_{6,O}$ = 6.0 Hz, 6-OH), 3.794 (m, 1H, H-5), 3.500 (m, 1H, H-6a), 3.488 (m, 1H, H-6b), 2.090 (s, 3H, NAc), 1.994 (s, 3H, OAc), 1.977 (s, 3H, OAc), 1.961 (s, 3H, OAc). ^{13}C NMR ($(CD_3)_2SO$): δ 182.36 (C═S), 172.57 (NAc), 169.51 (OAc), 169.39 (OAc), 169.16 (OAc), 81.05 (C-l), 75.65 (C-5), 72.51 (C-3), 70.63 (C-2), 68.17 (C-4), 59.74 (C-6), 23.70 (NAc), 20.47 (OAc), 20.29 (OAc), 20.21 (OAc).

Mass spectral fragmentation of $[M+Na]^+$ (*m*/*z* 429.095): *m*/*z* 370.058 $[M+Na-AcNH_2]^+$, 353.095 $[M+Na-AcNH_2-H_2O]^+$, 328.100 $[M+Na-AcNCS]^+$, strongest signal 311.073 $[M+Na-AcNCS-NH_3]^+$, 251.052 $[M+Na-AcNCS-NH_3-AcOH]^+$. Fragmentation of $[M+H]^+$ (*m*/*z* 407.115): strongest signal *m*/*z* 289.092 $[M+Na-AcNH{\cdot}CS{\cdot}NH_2]^+$, 229.072 $[M+Na-AcNH{\cdot}CS{\cdot}NH_2-AcOH]^+$. Anal. Calcd for $C_{15}H_{22}N_2O_9S$ (406.41): C, 44.33; H, 5.46; N, 6.89; Ac, 42.37. Found: C, 44.02; H, 5.43; N, 6.84; Ac, 41.62.



	R^1	R^2	R^3
1	H	H	H
2	Ac	Ac	H
3	Ac	Ac	Ph
4	Ac	Ac	Me
5	Ac	Ac	$CH_2{\cdot}CO_2Et$
6	H	H	Ph
7	H	H	Me
8	H	H	$CH_2{\cdot}CO_2NH_4$
9	Ac	Ac	Ac
10	H	H	Ac
11	Ac	H	Ac

Acknowledgements

The authors thank Dr. Éva R. Dávid for microanalyses and Mrs. Márta Rácz (Department of Biochemistry) for the optical rotation measurement. We are deeply indebted to Drs. Lajos Nagy and Sándor Kéki, Ph.D. (Department of Applied Chemistry, University of Debrecen) for recording the mass spectra. Generous support from the Hungarian Fund OTKA NK 68578 is gratefully acknowledged.

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