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Facile synthesis of glycofuranosyl isothiocyanates

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Abstract

Peracylated glycofuranosyl isothiocyanates are obtained under smooth conditions starting from the corresponding glycosyl chloride by reaction with potassium thiocyanate in anhydrous acetone at room temperature, classical conditions for the synthesis of glycopyranosyl thiocyanates. In the case of furanoses, no glycosyl thiocyanates are obtained, and the procedure leads to the 1,2-*trans* isothiocyanates, stereoselectively, with over 80% yield.

Keywords: Glycofuranosylisothiocyanates; Glycofuranosylthiourethanes

1. Introduction

Isothiocyanates are versatile starting materials in synthesis, as they readily undergo cyclo and nucleophilic additions [1,2]. Particularly, glycosylisothiocyanates have been used for the synthesis of glycosylthiourea derivatives [3], heterocyclic derivatives, such as nucleoside analogues [4], and glycosylamino heterocycles [3,5]. Condensation of sugar isothiocyanates with suitable haptens afforded *N*-linked glycoconjugates of biological interest [6].

The wide use of glycosyl isothiocyanates as convenient synthons has prompted the development of preparation procedures which improved the classical Fischer synthesis from an acylated glycosyl bromide and silver thiocyanate. Depending on the conditions employed, the reaction usually leads to the isothiocyanate or/and the thiocyanate derivatives, which are difficult to separate [2]. Modified procedures for the synthesis of sugar isothiocyanates include the treatment of glycosylamines with thiophosgene [7], the addition of isothiocyanate derivatives to glycals [8], and the reaction of glycosyl halides to isothiocyanate salts under phase-transfer catalysis [9]. Recently, glycopyranosyl isothiocyanates were obtained by melting the acylated glycosyl bromides with potassium thiocyanate [10].

The procedures just described have been applied to pyranose derivatives, affording the corresponding glycopyranosyl thiocyanates from moderate to good yields. We now report the preparation, under smooth conditions, of glycofuranosyl isothiocyanates from acylated glycofuranosyl halides.

2. Results and discussion

Treatment of per-*O*-acylated-glycofuranoses (**1a–c**) with acetyl chloride saturated with hydrogen chloride afforded the corresponding glysosyl chlorides

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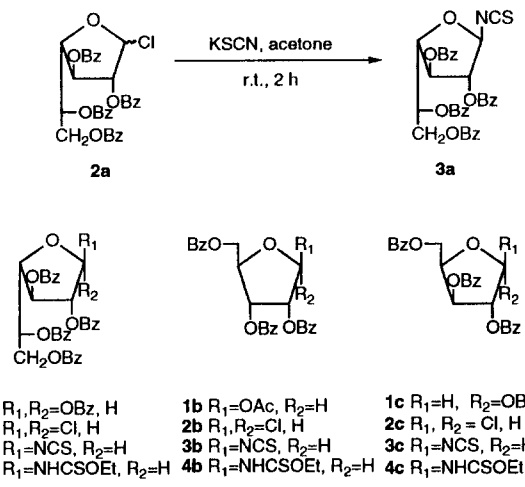
2a–c. These crude compounds were directly used for the next step.



Reaction of **2a–c** with potassium thiocyanate in anhydrous acetone gave the isothiocyanates **3a–c** in high yield (> 80%). Under similar reaction conditions, acetylated glycopyranosyl halides afforded the thiocyanate derivatives as main products (30–40% yield) together with 8–18% of the isothiocyanates [11]. The yield of thiocyanates increased considerably (70–88%) when benzoylated glycosyl bromides were employed.

The fact that glycopyranosyl thiocyanates undergo thermal isomerization to the corresponding isothiocyanates [2], would indicate that the latter are the thermodynamically stable products. Therefore, rather drastic conditions were required [10] to prepare isothiocyanates by SCN^- substitution of glycopyranosyl halides. The ribofuranosyl derivative (**3b**) was previously prepared by heating the peracylated D-ribofuranosyl bromide with silver thiocyanate in benzene for 3–6 h at 80–90 °C [12]. In our case, the isothiocyanate derivatives **3a–c** are readily formed from the furanosyl halides (**2a–c**) under smooth conditions (room temperature and short reaction times). No other products were detected. The reaction is totally diastereoselective affording the 1,2-*trans* isothiocyanates, probably due to the anchimeric participation of the vicinal benzoyloxy group.

The presence of an isothiocyanate group in compounds **3a–c** was shown by IR spectroscopy. The medium-strong band at 2020–2040 cm^{-1} observed in the IR spectra of compounds **3a–c** indicated that we were dealing with isothiocyanates instead of thiocyanates, which show a strong double band at ~ 2150 cm^{-1} [2]. The structures of **3a–c** were also confirmed

Table 1
^{13}C NMR (50.3 MHz) Chemical shifts for compounds **3a–c** and **4a–c**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C=S
3a[a]	89.3	82.4	76.8	84.1	70.1	63.2	142.7
3b[a]	88.4	75.9	71.3	79.8	63.4	–	144.1
3c[a]	88.6	81.0	74.4	80.6	62.2	–	142.3
4a[b]	88.8	80.0	78.8	81.9	71.6	63.2	191.7
4b[b]	87.1	73.9	71.2	78.0	64.2	–	191.7
4c[b]	88.5	76.4	76.4	79.6	62.5	–	191.4

[a]Recorded in $CDCl_3$.
[b]Recorded in Me_2SO-d_6.

by their ^{13}C NMR spectra (Table 1), which showed the signal of the isothiocyano group at ~ 142–144 ppm. In contrast, the thiocyanate carbon is shown at ~ 108 ppm [11]. The anomeric configuration of **3a–c** was established by means of $J_{1,2}$ coupling constant values (Table 2), which being smaller than 1 Hz indicate a 1,2-*trans* relationship for H-1 and H-2 [13,14].

Isothiocyanate derivatives readily undergo nucleophilic additions [1,2]. Thus, compounds **3a–c** reacted with ethanol to give the corresponding thiourethanes **4a–c**. The replacement of the isothiocyano group by the ethyl thiourethane causes a downfield shift for the H-1 signal, as reported for the thioureides and thiourethanes of pyranosides [3]. Also, larger values for $J_{1,2}$ are observed, which suggest that addition of EtOH to the isothiocyanate group is accompanied by considerable conformational changes in the furanoid ring.

3. Experimental

General methods.—Melting points were determined with a Thomas–Hoover apparatus. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. NMR Spectra were recorded with a Bruker AC 200 spectrometer. FTIR spectra were recorded with a Nicolet 510-P. The EI mass spectrum was recorded with a S QP-5000 instrument. Column chromatography was performed on Silica Gel 60, 200–400 mesh (Merck). Thin layer chromatography (TLC) was carried out on precoated aluminium plates of Silica Gel $60F_{254}$ (Merck), using 9:1 toluene–EtOAc as solvent. The spots were visualized by exposure to UV light and by spraying the plates with 10% (v/v) H_2SO_4 in EtOH, followed by heating.

1,2,3,5,6-Penta-*O*-benzoyl-D-galactofuranose (**1a**) was prepared [14] by benzoylation of D-galactose at 100 °C. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1b**) and 1,2,3,5-tetra-*O*-benzoyl-α-D-xylofuranose (**1c**) were purchased from Sigma. Compounds **1a–c** (10 mmol) were added to a solution of acetyl chloride saturated with HCl. The mixture was kept at room temperature overnight. The solution was evaporated and the excess of reagents were removed by repeated evaporations with toluene. The crude glycofuranosyl chlorides were employed for the next step without further purification.

Glycofuranosyl isothiocyanates (**3a – c**). *General procedure.*—To a solution of per-*O*-benzoylated glycofuranosyl chloride (1 mmol) in anhydrous acetone (5 mL), potassium thiocyanate (3 mmol) was added. The suspension was stirred at room temperature for 2 h, and then concentrated in vacuo. Dichloromethane was added and the excess of potassium thiocyanate was filtered off. TLC examination of the resulting syrup showed a main spot which was faster moving than the starting material (**1a–c**). The crude isothiocyanate was purified as indicated next for each individual compound. No thiocyanates were detected.

2,3,5,6-Tetra-O-benzoyl-β-D-galactofuranosyl isothiocyanate (**3a**). The crude isothiocyanate was macerated with EtOH at room temperature for a few min, affording a crystalline product, which was filtered off, washed with EtOH and dried (0.57 g, 89%), R_f 0.74. Following rapid recrystallization from EtOH **3a** had mp 138–140 °C; $[\alpha]_D$ −98° (*c* 1, $CHCl_3$); ν_{max} (KBr): 2040 (NCS), 1724 (C=O), 1271 (C–O–C) and 707 cm^{-1} (C–H aromatic); MS: *m/z* 595 (30%, M^+–NCS). Anal. Calcd for $C_{35}H_{27}O_9SN$: C, 65.93; H, 4.27; N, 2.19; S, 5.02. Found: C, 65.76; H, 4.55; N, 2.23; S, 5.28.

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate (**3b**). The crude syrup obtained was purified by column chromatography employing 100:1 toluene–EtOAc as solvent. Evaporation of the fractions having R_f 0.61 afforded syrupy **3b** (0.40 g, 80%), which gave $[\alpha]_D$ −91° (*c* 1, $CHCl_3$); ν_{max} (KBr): 2020 (NCS), 1727 (C=O), 1273 (C–O–C) and 715 cm^{-1} (C–H aromatic). The signals for C-1 and for NCS in the ^{13}C NMR spectrum (Table 1), as well as the NCS in the IR spectrum, are in good agreement with those reported in the literature [12]. Anal. Calcd for $C_{27}H_{20}O_7SN$: C, 64.53; H, 4.01; N, 2.79; S, 6.38. Found: C, 64.48; H, 3.95; N, 2.84; S, 6.41.

2,3,5-Tri-O-benzoyl-β-D-xylofuranosyl isothiocyanate (3c). The crude oil containing compound **3c** was subjected to column chromatography in 100:1 toluene EtOAc. From the fractions having R_f 0.63, syrupy compound **3c** (0.41 g, 82%) was obtained. It gave $[\alpha]_D$ −36° (*c* 1, $CHCl_3$); ν_{max} (KBr): 2024 (NCS), 1737 (C=O), 1260 (C–O–C) and 707 cm^{-1} (C–H aromatic). Anal. Calcd for $C_{27}H_{20}O_7SN$: C, 64.53; H, 4.01; N, 2.79; S, 6.38. Found: C, 64.75; H, 3.91; N, 2.68; S, 6.54.

N-(per-O-benzoyl-β-D-glycofuranosyl)-O-ethyl thiourethanes. General procedure.—Isothiocyanates **3a–c** (0.7 mmol) were suspended in EtOH and stirred at 60 °C for 3 h, or alternatively at room temperature for 12 h. TLC examination showed complete conver-

Table 2
^1H NMR (200 MHz) chemical shifts and coupling constants for compounds **3a–c** and **4a–c**

Compound	δ (ppm), *J* (Hz)									
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-5′ ($J_{4,5'}$)($J_{5,5'}$)	H-6 ($J_{5,6'}$)	H-6′ ($J_{6,6'}$)	NH ($J_{1,NH}$)	OEt (*J*)
3a[a]	5.59 (< 1)	5.72 (< 1)	5.75 (4.2)	4.86 (4.2)	6.10 (3.4)		4.80 (6.5)	4.72 (11.9)		
3b[a]	5.82–5.77 (< 1)	(4.7)	5.90 (6.5)	4.82–4.74		4.61 (5.4)(13.0)				
3c[a]	5.68 (< 1)	5.60 (1.0)	5.96 (4.7)	5.00	4.75–4.72					
4a[b]	6.46 (4.4)	5.82 (3.3)	5.60 (3.6)	4.85	5.93		4.74–4.61		10.23 (8.1)	4.45, 1.26 (6.9)
4b[b]	6.24 (4.7)	5.68 (5.3)	5.82 (5.3)	4.63	4.59–4.51				10.20 (8.8)	4.43, 1.27 (7.0)
4c[b]	6.06 (3.9)	5.72 (2.3)	5.79 (4.8)	4.84	4.64–4.57				10.18 (8.1)	4.43, 1.27 (7.0)

[a]Recorded in $CDCl_3$.
[b]Recorded in DMSO-*d*6.

sion into the slower-migrating thiourethanes **4a–c**. Evaporation of the EtOH afforded a syrup which was purified by column chromatography with 100:1 toluene EtOAc as solvent. The following syrupy thiourethanes were obtained.

N-*(2,3,5,6-tetra*-O-*benzoyl-β*-D-*galactofuranosyl)*-O-*ethyl thiourethane* (**4a**). Yield 0.43 g (90%); $[\alpha]_D$ +2° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{37}H_{33}O_{10}SN$: C, 65.00; H, 4.86; N, 2.05; S, 4.69. Found: C, 64.91; H, 4.69; N, 2.20; S, 4.88.

N-*(2,3,5-tri*-O-*benzoyl-β*-D-*ribofuranosyl)*-O-*ethyl thiourethane* (**4b**). Yield 0.35 g (91%); $[\alpha]_D$ −17° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{29}H_{27}O_8SN$: C, 63.38; H, 4.95; N, 2.55; S, 5.83. Found: C, 63.61; H, 5.01; N, 2.35; S, 5.84.

N-*(2,3,5-tri*-O-*benzoyl-β*-D-*xylofuranosyl)*-O-*ethyl thiourethane* (**4c**).—Yield 0.33 g (85%); $[\alpha]_D$ +22° (*c* 1, $CHCl_3$). Anal. calcd for $C_{29}H_{27}O_8SN$: C, 63.38; H, 4.95; N, 2.55; S, 5.83. Found: C, 63.53; H, 4.99; N, 2.73; S, 5.71.

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