

Convenient synthesis of 2-pyridyl thioglycosides

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A reported method for preparation of a new class of pyridine thioglycosides via reaction of pyridine-2(1*H*)-thiones with 2,3,4-tri-*O*-acetyl- α -D-xylo- and - β -D-arabinopyranosyl bromides has been studied.

Keywords: 2-pyridinethioglycosides, pyridinethiones, deazanucleosides

Recently deazanucleoside analogues have been shown to exhibit antitumour activity.¹ During our studies of nucleoside analogues with novel H-bonding patterns a route for the synthesis of *N*- or *S*-nucleosides bearing a substituted pyridine ring as the heterocyclic aglycone was desired.^{2,3} Such a route could provide access to a variety of analogues of pyrimidine nucleosides with novel H-bonding patterns.⁴ Such molecules might serve as components of an expanded genetic “alphabet” or display pharmaceutically useful antimetabolite activity.⁵ We report here the results of an investigation into the utility of the reaction of our previously reported pyridine-2(1*H*)-thiones **4a–d**⁶ with 2,3,4-tri-*O*-acetyl- α -D-xylo- and - β -arabinopyranosyl bromide for the synthesis of *S*-xylopyranosylthio- and *S*-arabinopyranosylthiopyridine glycosides, compounds **4a–d** were prepared by the reaction of α -alkylated β -diketones **3** with cyanothioacetamide in boiling sodium ethoxide for 2 h. Compounds **4a–c** reacted with 2,3,4-tri-*O*-acetyl- α -D-xylo- and - β -arabinopyranosyl bromide in aqueous potassium hydroxide to give the corresponding *S*-xylosides **6a–d** and *S*-arabinosides **6e–h** (Scheme 1). The structure of the reaction products **6a–h** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR, UV, ¹H NMR, ¹³C NMR). Thus, the analytical data for **6d** revealed a molecular formula (C₂₆H₂₈N₂O₇). The ¹H NMR spectrum showed the anomeric proton as a doublet at δ 6.38 ppm. The other five xylose protons resonated at δ 4.10–6.15 ppm and the three acetyl groups appeared as three singlets at δ 2.02–2.12 ppm. The ¹³C NMR spectrum of **6d** contained a signal at δ 81.12 ppm corresponding to the C-1' atom and four signals appearing at δ 64.73–71.62 ppm that were assigned to (C-4', C-2', C-3', C-5') respectively. The formation of *S*-glycosides **6** and not the corresponding *N*-glycosides were proved using ¹³C NMR spectroscopy which revealed the absence of the thione carbon at δ 178 ppm and the appearance of a signal at δ 158 ppm corresponding to the C-S carbon⁷ and also with the same value of the corresponding *S*-methyl derivative.⁶ When compounds **6a–h** were treated with methanolic ammonia at 0°C, the free glycoside derivatives **7a–h** were obtained, the structures of those compounds were established on the basis of elemental analysis and spectral data. Thus, the ¹H NMR spectrum of **7c** showed the anomeric proton as a doublet at δ 5.59 ppm. The other five xylose protons resonated at δ 3.07–3.87 ppm while the three hydroxyl groups of the xylose appeared at δ 5.06–5.48 ppm.

These pyridine thioglycosides can be utilised as an excellent starting material for the synthesis of other carbohydrate derivatives and for further biological evaluation studies.

Experimental

All melting points were uncorrected on a Gallenkamp melting point apparatus. The IR spectra were recorded (KBr disk) on a Perkin Elmer 1650 FT-IR instrument. The ¹H NMR spectra

were measured on a Varian 400 MHz spectrometer for solution (CDCl₃)₂SO using Si(CH₃)₄ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Elemental analyses were obtained from The Microanalytical Data Centre at Cairo University, Egypt.

4-Methyl-2-(2',3',4'-tri-*O*-acetyl- β -D-xylo- and -arabinopyranosylthio)pyridine-3-carbonitriles (**6a–h**): general procedure

To a solution of the pyridine-2(1*H*)-thiones **4a–d** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in 6 ml distilled water], a solution of 2,3,4-tri-*O*-acetyl- α -D-xylo- or - β -D-arabinopyranosyl bromide (0.01 mol) in acetone (30 ml) was added. The reaction mixture was stirred overnight at room temperature, then was poured on ice cold water, the resulting product was filtered, collected, dried and recrystallised from ethanol.

6a: Yellow, m.p. 220°C, yield (30%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2218 (CN); 1761 (CO). ¹H NMR: δ 2.01–2.11 (t, 9H, 3H₃CO); 2.13 (s, 3H, CH₃); 2.22 (s, 3H, CH₃); 2.30 (s, 3H, CH₃); 3.55–5.40 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.11 (d, 1H, H-1'). C₂₀H₂₄N₂O₇S, Calcd: C, 55.03%; H, 5.54%; N, 6.41%. Found: C, 55.09%; H, 5.57%; N, 6.52%.

6b: Yellow, m.p. 206°C, yield (59%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2217 (CN); 1758 (CO). ¹H NMR: δ 1.42 (t, 3H, CH₃); 2.00–2.04 (t, 9H, 3H₃CO); 2.10 (s, 3H, CH₃); 2.34 (s, 3H, CH₃); 2.50 (q, 2H, CH₂); 3.60–5.40 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.13 (d, 1H, H-1'). C₂₁H₂₆N₂O₇S, Calcd: C, 55.98%; H, 5.81%; N, 6.21%. Found: C, 56.20%; H, 5.82%; N, 6.22%.

6c: Yellow, m.p. 156°C, yield (32%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2219 (CN); 1753 (CO). ¹H NMR: δ 2.00–2.03 (t, 9H, 3 H₃CO); 2.27 (s, 3H, CH₃); 2.45 (s, 3H, CH₃); 3.56–5.34 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.03 (d, 1H, H-1'); 7.41–7.64 (m, 5H, C₆H₅). C₂₅H₂₆N₂O₇S, Calcd: C, 60.22%; H, 5.25%; N, 5.62%. Found: C, 60.24%; H, 5.64%; N, 5.62%.

6d: Yellow, m.p. 150°C, yield (35.5%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2218 (CN); 1749 (CO). ¹H NMR: δ 1.25 (t, 3H, 3CH₃); 2.02–2.12 (m, 9H, 3H₃CO); 2.25 (t, 3H, CH₃); 2.35 (s, 3H, CH₃); 2.47 (m, 2H, CH₂); 4.10–6.15 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.38 (d, 1H, H-1'); 7.45–8.25 (m, 5H, C₆H₅). ¹³C NMR: 14.82 (CH₃); 18.37–19.203 (CH₃); 20.52–21.42 (3CH₃CO); 23.28 (CH₂); 64.73–71.62 (C-4', C-2', C-3', C-5'), 81.12 (C-1'); 114.55 (C-3); 117.25 (CN); 122.70–133.74 (C₆H₅); 136.75 (C-5); 153.85 (C-4); 156.65 (C-6); 158.28 (C-S); 169.63–169.94 (3CO). C₂₆H₂₈N₂O₇S, Calcd: C, 60.92%; H, 5.50%; N, 5.46%. Found: C, 60.94%; H, 5.52%; N, 5.48%.

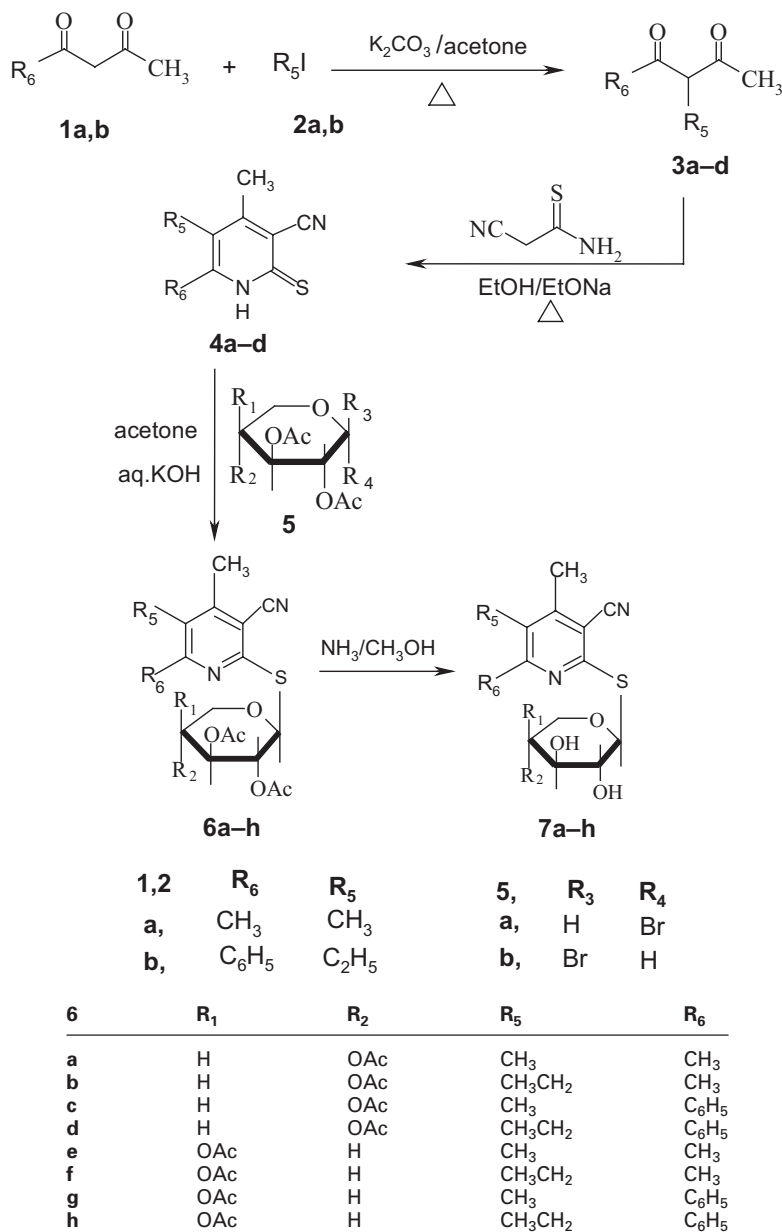
6e: Yellow, m.p. 160°C, yield (78%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2219 (CN); 1744 (CO). ¹H NMR: δ 2.09–2.13 (t, 9H, 3 H₃CO); 2.21(s, 3H, CH₃); 2.45 (s, 3H, CH₃); 2.56 (s, 3H, CH₃); 3.75–6.31 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.87 (s, 1H, H-1'). C₂₀H₂₄N₂O₇S, Calcd: C, 55.03%; H, 5.54%; N, 6.41%. Found: C, 55.05%; H, 5.55%; N, 6.55%.

6f: Yellow, m.p. 110°C, yield (37.5%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2181 (CN); 1751 (CO). ¹H NMR: δ 1.21 (t, 3H, CH₃); 1.97–2.08 (m, 12H, 3H₃CO, CH₃); 2.48 (q, 2H, CH₂); 3.93–5.22 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.97 (s, 1H, H-1'). C₂₁H₂₆N₂O₇S, Calcd: C, 55.98%; H, 5.81%; N, 6.21%. Found: C, 56.16%; H, 5.82%; N, 6.21%.

6g: Yellow, m.p. 198°C, yield (36%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2221 (CN); 1752 (CO). ¹H NMR: δ 2.07–2.13 (t, 9H, 3H₃CO); 2.27 (s, 3H, CH₃); 2.53 (s, 3H, CH₃); 3.61–5.38 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.21 (d, 1H, H-1'); 7.26–7.48 (m, 5H, C₆H₅). C₂₅H₂₆N₂O₇S, Calcd: C, 60.22%; H, 5.25%; N, 5.62%. Found: C, 60.25%; H, 5.26%; N, 5.62%.

6h: Yellow, m.p. 174°C, yield (42.67%). IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 2221.3 (CN); 1745 (CO). ¹H NMR: δ 1.77 (t, 3H, CH₃); 2.00–2.10 (t, 9H, 3H₃CO); 2.38 (s, 3H, CH₃); 3.66 (q, 2H, CH₂); 3.89–5.56 (m, 5H, 2H-5', H-4', H-3', H-2'); 6.10 (d, 1H, H-1'); 7.12–7.54 (m, 5H, C₆H₅). C₂₆H₂₈N₂O₇S, Calcd: C, 60.92%; H, 5.50%; N, 5.46%. Found: C, 60.93%; H, 5.52%; N, 5.47%.

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Scheme 1

7	R ₁	R ₂	R ₅	R ₆
a	H	OH	CH ₃	CH ₃
b	H	OH	CH ₃ CH ₂	CH ₃
c	H	OH	CH ₃	C ₆ H ₅
d	H	OH	CH ₃ CH ₂	C ₆ H ₅
e	OH	H	CH ₃	CH ₃
f	OH	H	CH ₃ CH ₂	CH ₃
g	OH	H	CH ₃	C ₆ H ₅
h	OH	H	CH ₃ CH ₂	C ₆ H ₅

Scheme 2

4-Methyl-2-(β-D-xylo- and arabinopyranosylthio)pyridine-3-carbonitriles (7a-h): general procedures

Dry gaseous ammonia was passed through a solution of protected glycosides **6** (0.5 g) in dry methanol (20 ml) at room temperature for 10 min. The reaction mixture was stirred 24 h (Followed by TLC). The resulting mixture was then evaporated under reduced pressure to afford a solid residue that was crystallised from ether.

7a: Yellow, m.p. 130°C, yield (60%). IR, ν_{max}/cm^{-1} (KBr) 3384–3470 (OH); 2220 (CN). 1H NMR: δ 2.00 (s, 3H, CH₃); 2.22 (s, 3H, CH₃); 2.50 (s, 3H, CH₃); 3.12–3.79 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.00–5.55 (m, 3H, 3OH); 5.60 (d, 1H, H-1'). C₁₄H₁₈ N₂O₄S, Calcd: C, 54.17%; H, 5.84%; N, 9.02%. Found: C, 54.18%; H, 5.84%; N, 9.31%.

7b: Yellow, m.p. 109°C, yield (56%). IR, ν_{max}/cm^{-1} (KBr) 3404–3480 (OH); 2220 (CN). 1H NMR: δ 1.89 (t, 3H, CH₃); 2.20 (s, 3H, CH₃); 2.44 (s, 3H, CH₃); 2.58 (q, 2H, CH₂); 3.41–3.90 (m, 5H, 2H-

5', H-4', H-3', H-2'); 4.78–5.60 (m, 3H, 3OH); 5.72 (d, 1H, H-1'). $C_{15}H_{20}N_2O_4S$, Calcd: C, 55.53%; H, 6.21%; N, 8.63%. Found: C, 55.54%; H, 6.22%; N, 8.64%.

7c: Yellow, m.p. 119 °C, yield (50%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3411–3480 (OH); 2218 (CN). ^1H NMR: δ 2.24 (s, 3H, CH_3); 2.54 (s, 3H, CH_3); 3.07–3.87 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.06–5.48 (m, 3H, 3OH); 5.59 (d, 1H, H-1'); 7.41–7.54 (m, 5H, C_6H_5). $C_{19}H_{20}N_2O_4S$, Calcd: C, 61.27%; H, 5.41%; N, 7.52%. Found: C, 61.30%; H, 5.44%; N, 7.54%.

7d: Yellow, m.p. 155 °C, yield (75%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3380–3470 (OH); 2214 (CN). ^1H NMR: δ 1.76 (t, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.84 (q, 2H, CH_2); 3.07–3.87 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.11–5.78 (m, 3H, 3OH); 5.99 (d, 1H, H-1'); 7.20–7.76 (m, 5H, C_6H_5). $C_{20}H_{22}N_2O_4S$, Calcd: C, 62.15%; H, 5.73%; N, 7.25%. Found: C, 62.15%; H, 5.74%; N, 7.27%.

7e: Brown, m.p. 82 °C, yield (78%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3368–3440 (OH); 2220 (CN). ^1H NMR: δ 2.02 (t, 3H, CH_3); 2.11 (s, 3H, CH_3), 2.33 (s, 3H, CH_3); 3.45–3.79 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.20–5.84 (m, 3H, 3OH); 6.00 (d, 1H, H-1'). $C_{14}H_{18}N_2O_4S$, Calcd: C, 54.17%; H, 5.84%; N, 9.02%. Found: C, 54.19%; H, 5.85%; N, 9.30%.

7f: Yellow, m.p. 90 °C, yield (67%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3344–3400 (OH); 2179 (CN). ^1H NMR: δ 1.48 (t, 3H, CH_3); 2.09 (s, 3H, CH_3); 2.56 (s, 3H, CH_3); 2.99 (q, 2H, CH_2); 3.51–3.97 (m, 5H, 2H-5', H-4', H-3', H-2'); 4.88–5.67 (m, 3H, 3OH); 5.92 (d, 1H, H-1'). $C_{15}H_{20}N_2O_4S$, Calcd: C, 55.53%; H, 6.21%; N, 8.63%. Found: C, 55.50%; H, 6.25%; N, 8.66%.

7g: Yellow, m.p. 84 °C, yield (78%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3362–3400 (OH); 2217 (CN). ^1H NMR: δ 2.25 (s, 3H, CH_3); 2.50 (s, 3H,

CH_3); 3.39–3.83 (m, 5H, 2H-5', H-4', H-3', H-2'); 4.71–5.57 (3 s, 3H, 2'-OH, 3'-OH, 4'-OH); 6.19 (s, 1H, H-1'); 7.36–7.55 (m, 5H, C_6H_5). $C_{19}H_{20}N_2O_4S$, Calcd: C, 61.26%; H, 5.41%; N, 7.52%. Found: C, 61.29%; H, 5.43%; N, 7.61%.

7h: Yellow, m.p. 99 °C, yield (70%). IR, $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3360–3420 (OH); 2220 (CN). ^1H NMR: δ 1.56 (t, 3H, CH_3); 2.11 (s, 3H, CH_3); 2.76 (q, 2H, CH_2); 3.23–3.89 (m, 5H, 2H-5', H-4', H-3', H-2'); 5.09–5.76 (m, 3H, 3OH); 5.90 (d, 1H, H-1'); 7.12–7.87 (m, 5H, C_6H_5). $C_{20}H_{22}N_2O_4S$, Calcd: C, 62.15%; H, 5.73%; N, 7.25%. Found: C, 62.15%; H, 5.74%; N, 7.29%.

Received 24 March 2008; accepted 8 July 2008

Paper 08/5179 doi: 10.3184/030823408X340816

Published online: 21 August 2008

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