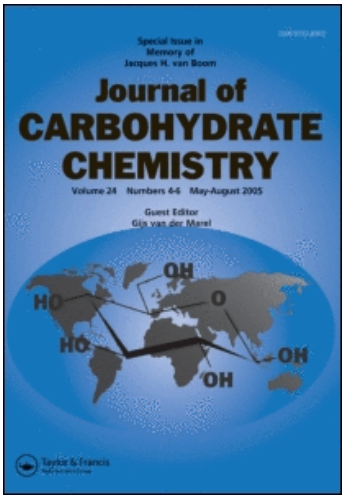

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SYNTHESIS OF (2,3,4,6-TETRA-*O*-ACETYL-α-D-GLYCOPYRANOSYL) THIOPHENE DERIVATIVES AS NEW *C*-NUCLEOSIDE ANALOGUES[1]

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ABSTRACT

Treatment of 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)ethanal (**1a**) and 2-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)ethanal (**1b**), respectively, with malononitrile in the presence of silica gel provided the corresponding 4-[2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl]-2-cyanocrotononitriles (**2a**) and (**2b**). Starting from **2a** and **2b**, respectively, cyclizations with sulfur and triethylamine yielded 5-[2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl]-2-aminothiophene-3-carbonitriles (**3a**) and (**3b**). Further cyclizations could be achieved by utilizing of triethyl orthoformate/ammonia to furnish the 6-(α-D-glycopyranosyl)thieno[2,3-d]pyrimidine-4-amines **4a** and **4b**.

INTRODUCTION

Thiophene derivatives show a wide spectrum of interesting biological properties that include serine protease inhibitions,[2] dihydrofolate reductase inibitions,[3] analgesic,[4,5] and anti-inflammatory[5] properties.

The connection of a thiophene derivative with a carbohydrate moiety should increase its cell membrane permeability and, therefore, it could also enhance the corresponding biological availability. *C*-Glycoside derivatives are of special inter-

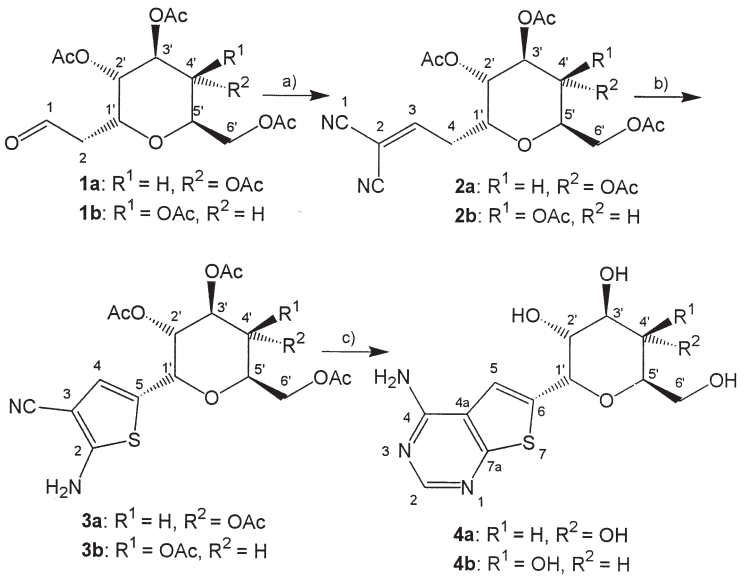
est in this sense because of their hydrolytic stability against acids and enzymes, and these properties would seem to indicate their use as stable pharmacophores.[6] In particular, the synthesis of *C*-nucleoside analogues has received great attention due to their potential antiviral, antibacterial and antitumor activities.[7,8]

Recently we reported a new method for the preparation of acyclo-*C*-nucleosides by ring transformation with branched-chain glycals.[9] In the present paper we describe the synthesis of (2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)thiophene and thienopyrimidine derivatives.

RESULTS AND DISCUSSION

The glycopyranosyl ethanals **1a** and **1b** can act as efficient starting materials for the preparation of more complicated *C*-glycoside derivatives. Compounds **1a** and **1b** have been used as precursors for different biologically active molecules in which the presence of a C—C bond at the anomeric center of a carbohydrate moiety is a determining feature.[10]

Starting from the pyranosyl ethanals **1a** and **1b**, respectively, we could carry out Knoevenagel reactions with malononitrile to give the corresponding pyranosyl crotononitrile derivatives **2a** and **2b** (Scheme 1). These reactions were catalyzed by both aluminium oxide [11,12] and silica gel.[13] The former gave several by-products, while high yields were achieved with the latter catalyst (83–85%). It must be



Scheme 1.

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pointed out that an excess of malononitrile was necessary for the complete transformation of the starting materials.

After purification by column chromatography the spectroscopic data of the products clearly verified the formation of compounds **2a** and **2b**. In their IR spectra both cyano groups appeared within the range of 2271–2239 cm^{-1}. The mass spectra of **2a** and **2b** gave peaks corresponding to their molecular masses.

Compounds with a 3,3-dicyanoprop-2-enyl group can be used for the formation of 2-aminothiophene-3-carbonitrile derivatives by treatment with elementary sulfur and triethylamine.[14,15] Use of ethanol as solvent as reported in the original procedures, resulted in the cleavage of the acetyl protective groups. For that reason *N,N*-dimethylformamide was the solvent of choice[16] producing the corresponding pyranosyl thiophene-3-carbonitriles **3a**, **3b** as yellow solids in 55–60 % yields.

In the IR spectra of **3a** and **3b** only one υ(CN) band was found, and as expected, at a lower wave number (2207 and 2208 cm^{-1}, respectively), due to the conjugation of the cyano group with the thiophene ring. In the ^{13}C NMR spectra of **3a** and **3b** the CN signal appears at δ = 114.9 compared to about 110.3 and 111.6 (117.7, respectively) for the both CN groups of **2a** and **2b**.

The enaminonitrile unit located in the thiophene ring of **3a** and **3b** could be used for a further cyclization.[17] **3a** and **3b** reacted with triethyl orthoformate to afford the syrupy formimidic acid esters which underwent cyclization by treatment with a saturated methanolic ammonia solution to furnish the corresponding 6-α-D-glycopyranosyl)thieno[2,3-d]pyrimidine-4-amines **4a** and **4b** in 65 and 49% yield, respectively. The basic conditions of these reactions are responsible for the simultaneous deblocking of the acetyl groups. The spectroscopic data are in accordance with the given structures. Signals corresponding to the CN group were absent in the ^{13}C NMR and IR spectra of **4a** and **4b**.

EXPERIMENTAL

General Procedures. Melting points were determined with a Boëtius apparatus and are corrected. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. Specific optical rotations were measured with a Gyromat HP (Dr. Kernchen). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker instrument ARX 300 and AC 250 with $CDCl_3$ or D_2O as solvent. The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: $\delta^1H = 7.25$; $\delta^{13}C = 77.0$; dioxane: δ^1H ?= 3.71; $\delta^{13}C = 67.6$ for recording in D_2O). The ^{13}C NMR signals were assigned by DEPT and/or two-dimensional $^1H,^{13}C$ correlation experiments. The mass spectra were recorded on an AMD 402/3 spectrometer AMD (Intectra GmbH). For chromatography Merck silica gel 60 (0.063–0.2 mm) was used. TLC was performed on silica gel 60 GF_{254} (Merck) with detection by charring with 5% sulfuric acid in methanol. Elemental analyses were performed on a Leco CHNS-932 instrument. Compounds **1a** and **1b** were prepared according to known procedures.[18,19]

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4-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-2-cyanocrotononitrile (2a). Malononitrile (390 mg, 6.0 mmol) and silica gel 60 GF_{254} (100 mg, Merck) were added to a solution of 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)ethanal (**1a**, 800 mg, 2.13 mmol) in dry CH_2Cl_2 (25 mL) at room temperature. The mixture was stirred under reflux for 24 h until the starting material could no longer be detected by TLC (toluene/ethyl acetate 2:1). After filtration and solvent evaporation, a syrup was formed. Column chromatography (toluene/ethyl acetate 2:1) yielded a white powder of **2a** (750 mg, 83%): mp 102°C; $[\alpha]_D^{23.3}$ +57.4 (*c* 1.0, chloroform); IR (KBr) 2271, 2239 (CN); 1630 (C═C); ^{1}H NMR ($CDCl_3$) *(* 2.06 (s, 3H, CH_3); 2.08 (s, 3H, CH_3); 2.10 (s, 6H, 2×CH_3); 2.75 (ddd, 1H, $J_{4a,1'}$ = 3.5 Hz, $J_{3,4a}$ = 6.9 Hz, $J_{4a,4b}$ = 15.9 Hz, H-4a); 3.04 (ddd, 1H, $J_{3,4b}$ = 8.4 Hz, $J_{4b,1'}$ = 8.8 Hz, H-4b); 3.93 (ddd, 1H, $J_{5',6'a}$ = 2.8 Hz, $J_{5',6'b}$ = 7.2 Hz, $J_{4',5'}$ = 7.4 Hz, H-5′); 3.99 (dd, 1H, $J_{6'a,6'b}$ = 12.2 Hz, H-6′a); 4.36–4.44 (m, 2H, H-1′, H-6′b); 4.89 (t, 1H, $J_{3',4'}$ = 7.4 Hz, H-4′); 5.04 (dd, 1H, $J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 7.6 Hz, H-2′); 5.22 (dd, 1H, H-3′); 7.34 (dd, 1H, H-3); ^{13}C NMR ($CDCl_3$) *(* 20.6 (CH_3); 20.7 (3×CH_3); 30.9 (C-4); 61.4 (C-6′); 67.5 (C-4′); 68.9 (C-3′); 68.9 (C-2′); 69.5 (C-1′); 71.2 (C-5′); 92.0 (C-2); 110.3, 111.6 (CN); 164.5 (C-3); 169.5 (3×C═O); 170.5 (C═O). MS (CI, *iso*-butane): *m/z* = 423 $[M+H]^+$.

Anal. Calcd for $C_{19}H_{22}N_2O_9$ (422.39): C, 53.79; H, 5.19; N, 6.89. Found: C, 53.85; H, 5.22; N, 6.62.

4-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-2-cyanocrotononitrile (2b). The reaction of 2-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)ethanal (**1b**, 700 mg, 1.89 mmol) with malononitrile (384 mg, 5.67 mmol) in the presence of silica gel 60 GF_{254} (70 mg, Merck) in CH_2Cl_2 (25 mL) was carried out as described above for **2a**. After column chromatography (toluene/ethyl acetate 2:1) of the crude syrup, **2b** could be separated as a white powder (671 mg, 85%): mp 45°C; $[\alpha]_D^{23.6}$+49.8 (*c* 0.5, chloroform); IR (KBr) 2271, 2239 (CN); 1632 (C═C); ^{1}H NMR ($CDCl_3$) *(* 2.07 (s, 3H, CH_3); 2.09 (s, 6H, 2×CH_3); 2.13 (s, 3H, CH_3); 2.68 (ddd, 1H, $J_{1',4a}$ = 3.5 Hz, $J_{3,4a}$ = 7.0 Hz, $J_{4a,4b}$ = 15.8 Hz, H-4a); 2.89 (ddd, 1H, $J_{3,4b}$ = 8.3 Hz, $J_{1',4b}$ = 10.2 Hz, H-4b); 3.94 (dd, 1H, $J_{5',6'a}$ = 3.8 Hz, $J_{6'a,6'b}$ = 12.0 Hz, H-6′a); 4.13 (m, 1H, H-5′); 4.45 (dt, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′); 4.62 (dd, 1H, $J_{5',6'b}$ = 8.8 Hz, H-6′b); 5.16 (dd, $J_{2',3'}$ = 7.3 Hz, 1H, H-2′); 5.22 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, H-3′); 5.40 (dd, 1H, $J_{4',5'}$ = 4.3 Hz, H-4′); 7.34 (dd, 1H, H-3); ^{13}C NMR ($CDCl_3$) *(* 20.6 (CH_3); 20.7 (CH_3); 20.8 (2×CH_3); 31.5 (C-4); 60.2 (C-6′); 66.3 (C-4′); 67.2 (C-3′); 68.3 (C-1′); 68.3 (C-2′); 70.8 (C-5′); 91.7 (C-2); 110.3, 111.7 (CN); 165.1 (C-3); 169.3 (C═O); 169.6 (2×C═O); 170.9 (C═O). MS (EI): *m/z* = 422 ($M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{22}N_2O_9$ (422. 39): C, 53.79; H, 5.19; N, 6.89. Found: C, 54.03; H, 5.25; N, 6.63.

2-Amino-5-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)thiophene-3-carbonitrile (3a). Sulfur (50 mg, 1.56 mmol) and triethylamine (350 μL, 2.64 mmol) were added to a solution of **2a** (560 mg, 1.32 mmol) in dry DMF (30 mL). The mixture was stirred for 4 h at room temperature and then the resulting brown

solution was poured into water with a pH of 5. After extraction with chloroform (3 × 20 mL) the combined extracts were washed with water until pH 7 (3 × 40 mL), dried with Na_2SO_4, filtered, and concentrated. The syrup obtained was purified by column chromatography (toluene/ethyl acetate 1:1) yielding yellow solid **3a** (361 mg, 60%): mp 174–175°C; $[\alpha]_D^{24.0}$+169.0 (c 1.0, chloroform); IR (KBr) 3433, 3345, 3225 (NH_2); 2208 (CN); 1646 (C═C); ^{1}H NMR ($CDCl_3$) *(* 1.99 (s, 3H, CH_3); 2.03 (s, 3H, CH_3); 2.06 (s, 3H, CH_3); 2.08 (s, 3H, CH_3); 3.83 (ddd, 1H, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 4.8 Hz, $J_{4',5'}$ = 10.0 Hz, H-5′); 4.04 (dd, 1H, $J_{6'a,6'b}$ = 12.2 Hz, H-6′a); 4.24 (dd, 1H, H-6′b); 4.98 (br, 2H, NH_2); 5.05 (dd, 1H, $J_{3',4'}$ = 9.0 Hz, H-4′); 5.22 (dd, 1H, $J_{1',2'}$ = 6.0 Hz, $J_{2',3'}$ = 10.0 Hz, H-2′); 5.32 (dd, 1H, $^4J_{1',4}$ = 1.2 Hz, H-1′); 5.51 (dd, 1H, H-3′); 6.94 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) *(* 20.5 (CH_3); 20.6 (3×CH_3); 61.9 (C-6′); 68.6 (C- 4′); 69.8 (C-5′); 70.1 (C-3′); 70.4 (C-2′); 70.7 (C-1′); 87.4 (C-3); 114.9 (CN); 122.4 (C-5); 126.3 (C-4); 163.3 (C-2); 169.4 (2×C═O); 170.0 (C═O); 170.5 (C═O). MS (EI): *m/z* = 454 ($M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{22}N_2O_9S$ (454.44): C, 50.22; H, 4.88; N, 6.16; S, 7.05. Found: C, 49.91; H, 4.94; N, 6.45; S, 6.98.

2-Amino-5-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)thiophene-3-carbonitrile (3b). **2b** (560 mg, 1.32 mmol), sulfur (50 mg, 1.56 mmol) and triethylamine (350 μL, 2.64 mmol) were allowed to react as described above for the preparation of **3a**. After column chromatography (toluene/ethyl acetate 1:1) a yellow solid was obtained (333 mg, 55.4%): mp 49–50°C; $[\alpha]_D^{24.2}$+65.6 (c 0.8, chloroform); IR (nujol) 3427, 3335, 3221 (NH_2); 2207 (CN); 1646 (C═C); ^{1}H NMR ($CDCl_3$) *(* 2.03 (s, 3H, CH_3); 2.04 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); 2.14 (s, 3H, CH_3); 4.00–4.13 (m, 2H, H-5′, H-6′a); 4.19 (dd, 1H, $J_{5',6'b}$ = 9.0 Hz, $J_{6'a,6'b}$ = 12.8 Hz, H-6′b); 4.86 (br, 2H, NH_2); 5.34–5.49 (m, 4H, H-1′, H-2′, H-3′, H-4′); 6.88 (d, 1H, $^4J_{1',4}$ = 1.4 Hz, H-4); ^{13}C NMR ($CDCl_3$) *(* 20.6 (2×CH_3); 20.7 (CH_3); 20.8 (CH_3); 61.3 (C-6′); 67.5, 67.6, 68.2 (C-2′, C-3′, C-4′); 69.2 (C-5′); 70.8 (C-1′); 87.7 (C-3); 114.9 (CN); 123.0 (C-5); 125.7 (C-4); 162.8 (C-2); 169.5 (C═O); 169.8 (C═O); 170.0 (C═O); 170.4 (C═O). MS (EI): *m/z* = 454 ($M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{22}N_2O_9S$ (454.44): C, 50.22; H, 4.88; N, 6.16; S, 7.05. Found: C, 50.74; H, 5.14; N, 5.83; S, 6.79.

6-(α-D-Glucopyranosyl)thieno[2,3-d]pyrimidine-4-amine (4a). **3a** (200 mg, 0.44 mmol) was stirred for 6 h in triethyl orthoformate (15 mL) under reflux. After evaporation of the excess triethyl orthoformate, a syrup was obtained which was purified by column chromatography (toluene/ethyl acetate 2:1). The syrup (150 mg) was dissolved in a saturated methanolic solution of ammonia (20 mL) and stirred for 5 h at room temperature. Then, the mixture was concentrated under reduced pressure and, after treatment with acetone (15 mL), **4a** was precipitated as a white solid (89 mg, 65%): mp 158–160°C; $[\alpha]_D^{24.0}$+80.0 (c 1.0, water); IR (nujol) 3334, 3206 (NH_2); 1646 (C═C); 1575 (C═C); ^{1}H NMR (D_2O) *(* 3.44 (t, 1H, $J_{4',5'}$ = $J_{5',6'a}$ = 9.0 Hz, H-5′); 3.57–3.88 (m, 4H, H-3′, H-4′, H-6′); 3.91 (dd, 1H, $J_{1',2'}$ = 6.2 Hz, $J_{2',3'}$ = 9.9 Hz, H-2′); 5.38 (dd, 1H, $J_{1',5}$ = 1.0 Hz, H-1′); 7.42 (d, 1H,

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H-5); 8.10 (s, 1H, H-2); ^{13}C NMR (D_2O) (61.9 (C-6′); 71.1 (C-5′); 72.4 (C-2′); 74.2 (C-3′); 75.0 (C-1′); 75.6 (C-4′); 116.8, 137.6 (C-4a, C-6); 120.1 (C-5); 154.0 (C-2); 158.7, 166.6 (C-4, C-7a). MS (EI): *m/z* = 313 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{15}N_3O_5S$ (313.33): C, 46.0; H, 4.83; N, 13.41; S, 10.23. Found: C, 45.72; H, 5.01; N, 13.05; S, 9.87.

6-(α-D-Galactopyranosyl)thieno[2,3-d]pyrimidine-4-amine (4b). **3b** (200 mg, 0.44 mmol) was treated with triethyl orthoformate (15 mL) and a saturated methanolic solution of ammonia (20 mL) as described above for preparation of **4a**. Compound **4b** was isolated as a white solid (67 mg, 49.1%): mp 170°C (dec.); $[\alpha]_D^{24.0}$+98.0 (*c* 1.0, water); IR (nujol) 3334, 3206 (NH_2); 1646 (C═C); 1575 (C═C); ^{1}H NMR (D_2O) (3.65–3.90 (m, 4H, H-3′, H-5′, H-6′); 3.96 (d, 1H, $J_{4',5'}$ = 3.1 Hz, H-4′); 4.28 (dd, 1H, $J_{1',2'}$ = 6.0 Hz, $J_{2',3'}$ = 10.0 Hz, H-2′); 5.42 (dd, 1H, $^4J_{1',5}$ = 1.0 Hz, H-1′); 7.46 (d, 1H, H-5); 8.17 (s, 1H, H-2); ^{13}C NMR (D_2O) (62.1 (C-6′); 69.6 (C-2′); 69.9 (C-4′); 70.7 (C-5′); 74.6 (C-1′); 75.1 (C-3′); 116.7, 138.9 (C-4a, C-6); 119.7 (C-5); 152.1 (C-2); 157.7, 166.0 (C-4, C-7a). MS (EI): *m/z* = 313 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{15}N_3O_5S$ (313.33): C, 46.0; H, 4.83; N, 13.41; S, 10.23. Found: C, 45.87; H, 4.99; N, 13.36; S, 10.15.

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