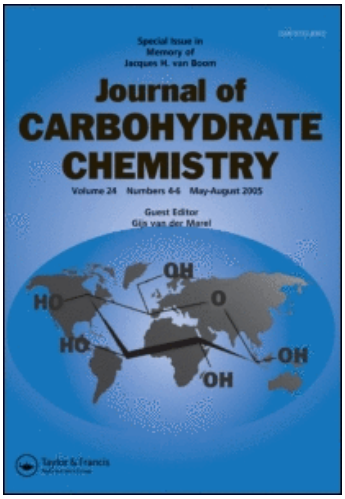

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SYNTHESIS OF 6-SUBSTITUTED 5-AZAURIDINES AND THEIR PYRANOSE-TYPE NUCLEOSIDES BY CYCLODESULFURIZATION OF GLYCOSYL THIOUREAS

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SYNTHESIS OF 6-SUBSTITUTED 5-AZAURIDINES AND THEIR PYRANOSE-TYPE NUCLEOSIDES BY CYCLODESULFURIZATION OF GLYCOSYL THIOUREAS

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ABSTRACT

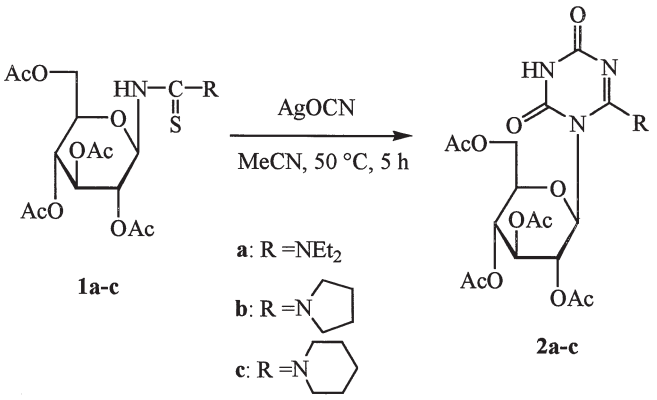
Cyclodesulfurization of *N,N,N′*-trisubstituted glycosyl thioureas with silver cyanate in acetonitrile for 5 h at 50 °C gave 1-glycosyl 5-azauracil derivatives as nucleoside analogues in good yields. The structures were determined by spectroscopic and X-Ray analyses and the reaction mechanism is discussed.

INTRODUCTION

Much attention has been paid to the synthesis of glycosylamino heterocycles as nucleoside analogues, which exhibit biological and pharmaceutical activities.[1,2] Glycosyl thioureas have been widely used as important intermediates in synthetic approaches to nucleoside analogues.[3–6] During our serial study on silver ion mediated desulfurization of thiocarbonyl compounds, we have found that the reaction of glucosyl isothiocyanates with *N*-monosubstituted amino acids[7] or hydroxy acids[8] gives new types of glucosylamino heterocycles in good yields. We report here new efficient routes for the synthesis of 1-glycosyl 5-azauracil derivatives as nucleoside analogues by cyclodesulfurization of *N,N,N′*-trisubstituted glycosyl thioureas with silver cyanate.

RESULTS AND DISCUSSION

We carried out the cyclodesufurization of *N,N*-diethyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**1a**) with silver cyanate (AgOCN). Treatment



Scheme 1.

of **1a** with 2.6 equivalents of AgOCN in dry acetonitrile for 5 h at 50 °C gave 6-diethylamino-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-azauracil (**2a**) in 77% yield (Scheme 1).

The molecular structure of **2a** was unequivocally established by a single crystal X-Ray diffraction structure analysis.[9,10] An ORTEP of **2a** drawing is shown in Figure 1. The 1,3,5-triazine-2,4-dione ring was almost planar, and the angles between it and the glucosyl group were 108.0° (N1-C8-O3) and 113.4° (N1-C8-C9), where the numbering is according to that of Figure 1. Selected bond length (Å) and angles (°): N1-C8; 1.455(5), N1-C1; 1.398(5), C1-N2; 1.407(6), C2-N3; 1.333(6), N1-C3; 1.409(5), C3-N3; 1.310(5), C1-O1; 1.207(5), C2-O2; 1.226(5). C1-N1-C3; 118.6(3), N1-C1-N2; 114.3(4), N2-C2-N3; 116.8(4), N3-C3-N1; 120.9(4), N1-C3-N4; 119.0(4).

The product **2a** shows υ_{max} at 3256 (NH), 1748 (OAc, C═O), 1696 (C═O), and 1588 (C═N) cm^{-1}, characteristic of 6-amino-1,3,5-triazine-2,4-dione.[11] The ^{1}H NMR spectrum of **2a** contains a doublet H-1′ (β-glucoside) at δ 5.00 ppm, the β-configuration being confirmed by the large ($J_{1',2'}$ = 9.3 Hz) vicinal coupling constant. The methylene protons of the diethylamino groups are observed as a quartet at δ 3.49 (2H, J = 7.2 Hz) and 3.61 (2H, J = 7.2 Hz) ppm, respectively. The ^{13}C NMR spectrum of **2a** contains signals at δ 150.46 and 160.97 ppm due to the two carbonyl carbon atoms in the nitrogen heterocycle unit. Their NMR assignments are in good agreement with those of some 6-amino-1,3,5-triazine-2,4-dione derivatives.[11] From glucosyl thioureas **1b–c**, the novel 1-glucosyl 5-azauracil derivatives **2b–c** were obtained in good yields (67–73%) under the same conditions.

We next undertook the cyclodesulfurization of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl thioureas (**3a–c**) with AgOCN in the same manner to afford 6-amino-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-azauracils (**4a–c**) in good yields (61–75%) (Scheme 2).

The ^{1}H NMR spectrum of **4a** (R═NEt_2) shows the anomeric proton (H-1′) at δ 5.33 ppm as a doublet ($J_{1',2'}$ = 3.3 Hz) and the four methylene protons of

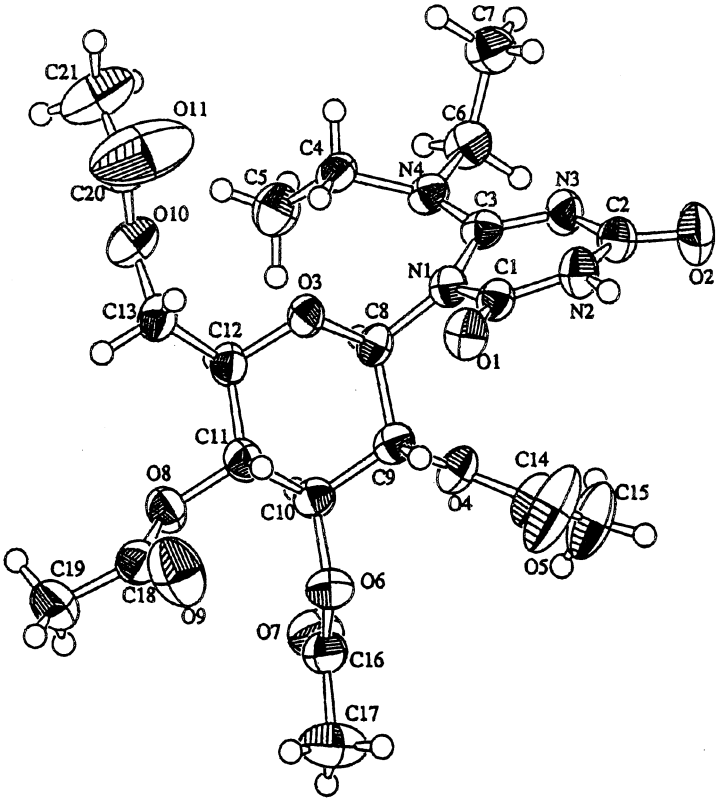
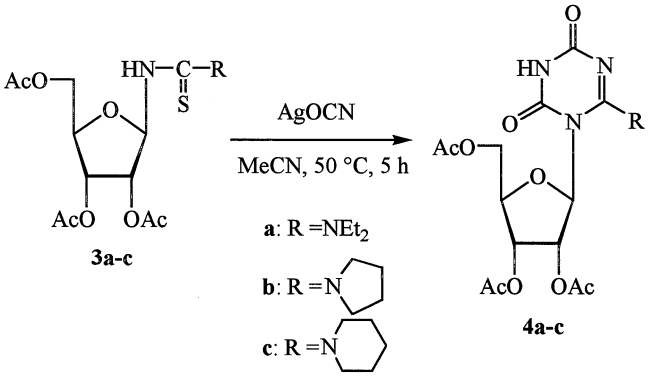


Figure 1. ORTEP drawing of the molecular structure of 2a.

diethylamino groups at δ 3.47 ppm as a quartet (4H, J = 6.9 Hz). The ^{13}C NMR spectrum of **4a** contains two carbonyl carbon signals corresponding to the carbonyl groups in the nitrogen heterocycle at δ 151.02 and 160.74 ppm, respectively.



Scheme 2.

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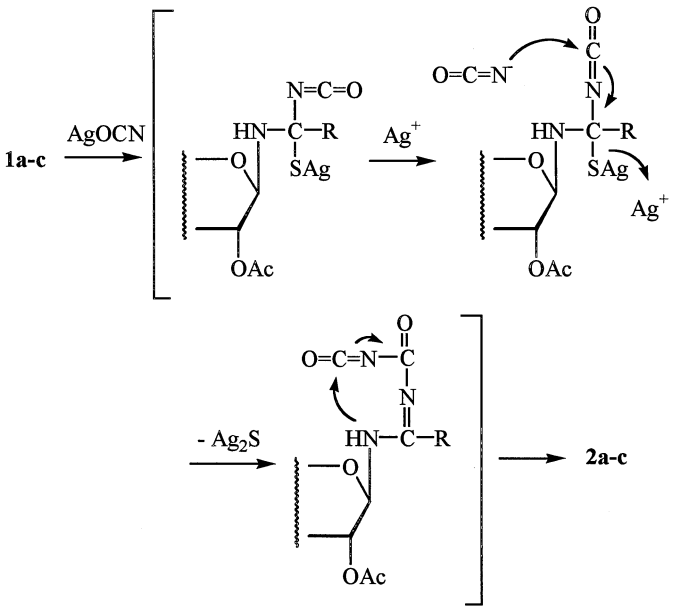

Scheme 3.

This cyclodesulfurization mechanism can be considered to proceed as follows (Scheme 3). Glycosyl thiourea and silver cyanate forms a 1 : 1 adduct, which reacts with a second molecule of silver cyanate followed by cyclization and release of silver sulfide to give **2a–c** or **4a–c**.

In conclusion, we have described the cyclodesulfurization of glycosyl thioureas with silver cyanate under mild conditions affording 5-azauridine analogues as *pseudo*-nucleosides in a facile manner. It is believed that this synthetic method may contribute to research for nucleosides with novel biological functions.

EXPERIMENTAL

General. Melting points were determined on a Mettler FP 90 apparatus and are uncorrected. Optical rotations were measured at 24 °C with a JASCO DIP-370 digital polarimeter for solutions in $CHCl_3$. IR spectra were recorded on a JASCO FT-IR 5300 instrument using KBr disks. NMR spectra were obtained with a Varian Gemini 300 BB spectrometer for solutions in $CDCl_3$. HRMS spectra were obtained with a Hitachi M-80B mass spectrometer. TLC was conducted on plates coated with silica gel F_{254} (Merck), and products were detected by UV light and/or by charring with H_2SO_4. Column chromatography was carried out in columns of silica gel (Wakogel C-200). Starting *N,N,N′*-trisubstituted glycosyl thioureas were prepared from the corresponding glycosyl isothiocyanates and secondary amines according to the literature.[12]

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General procedure for the synthesis of 1-glycosyl 5-azauracils 2a–c and 4a–c: To a solution of **1a–c** or **3a–c** (1 mmol) in dry acetonitrile (10 mL) was added AgOCN (2.6 mmol). The reaction mixture was stirred for 5 h at 50 °C. After evaporation of the solvent under reduced pressure, ethyl acetate and brine were added to the residue, and silver salts were removed by filtration. The organic layer was separated and washed with water and brine. The washed solution was dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on silica gel. The yields, mp, solvents for recrystallization, $[\alpha]_D$, and the characterization data are shown below.

6-Diethylamino-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-azauracil (2a). 77%; mp 190–191 °C (EtOH); $[\alpha]_D$ −47.2° (*c* 1.00); IR 3256, 1748, 1696, 1588 cm^{-1}; ^1H NMR δ 1.27 (t, 6H, J = 7.2 Hz), 1.95, 2.03, 2.06, 2.08 (4s, 12H, OAc), 3.49 (q, 2H, J = 7.2 Hz, NCH_2), 3.61 (q, 2H, J = 7.2 Hz, NCH_2), 3.83 (m, 1H, H-5′), 4.24 (m, 2H, H-6′), 5.00 (d, 1H, J = 9.3 Hz, H-1′), 5.20 (t, 1H, J = 9.6 Hz, H-4′), 5.30 (t, 1H, J = 9.6 Hz, H-3′), 5.82 (t, 1H, J = 9.3 Hz, H-2′), 8.06 (bs, 1H, NH); ^{13}C NMR δ 12.84 (2C), 20.21, 20.59, 20.71 (2C), 44.11 (2C), 62.33 (C-6′), 67.94, 68.50, 73.22, 75.32, 86.82 (C-1′), 150.46 (Het. C═O), 154.20 (Het. C═N), 160.97 (Het. C═O), 169.39, 169.60, 170.76 (2C).

Anal. Calcd for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89. Found: C, 49.05; H, 5.99; N, 10.72.

6-Pyrrolidino-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-azauracil (2b). 67%; mp 131–132 °C (hexane-EtOAc); $[\alpha]_D$ +14.6° (*c* 1.10); IR 3366, 1745, 1700, 1562 cm^{-1}; ^1H NMR δ 2.08, 2.06, 2.02, 1.97 (4s, 12H, OAc), 1.99 (bs, 4H), 3.59–3.79 (m, 4H), 3.8 (m, 1H, H-5′), 4.25 (m, 2H, H-6′), 5.03 (d, 1H, J = 9.6 Hz, H-1′), 5.22 (t, 1H, J = 9.6 Hz, H-4′), 5.29 (t, 1H, J = 9.3 Hz, H-3′), 5.94 (t, 1H, J = 9.6 Hz, H-2′), 8.45 (bs, 1H, NH); ^{13}C NMR δ 20.31, 20.60 (2C), 20.72, 25.54(2C), 50.68 (2C), 60.54 (C-6′), 62.15, 67.83, 73.43, 75.41, 84.93 (C-1′), 150.02 (Het. C═O), 153.85 (Het. C═N), 159.9 (Het. C═O), 169.39, 169.62, 170.64, 170.75.

Anal. Calcd for $C_{21}H_{28}N_4O_{11}$: C, 49.22; H, 5.51; N, 10.93. Found: C, 49.35; H, 5.44; N, 10.86.

6-Piperidino-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-azauracil (2c). 73%; 120–121 °C (hexane-EtOAc); $[\alpha]_D$ −19.0° (*c* 1.02); IR 3272, 1755, 1705, 1572 cm^{-1}; ^1H NMR δ 1.71 (bs, 6H), 1.95, 2.02, 2.06, 2.08 (4s, 12H, OAc), 3.5–3.7 (m, 4H), 3.79 (m, 1H, H-5′), 4.23 (m, 2H, H-6′), 5.02 (d, 1H, J = 9.3 Hz, H-1′), 5.20 (t, 1H, J = 9.6 Hz, H-4′), 5.29 (t, 1H, J = 9.6 Hz, H-2′), 5.80 (t, 1H, J = 9.3 Hz, H-3′), 8.17 (bs, 1H, NH); ^{13}C NMR δ 20.25, 20.59 (2C), 20.72, 22.69, 24.69 (2C), 49.78 (2C), 62.21 (C-6′), 67.92, 68.45, 73.41, 75.51, 87.50 (C-1′), 150.50 (Het. C═O), 154.27 (Het. C═N), 160.80 (Het. C═O), 169.45, 169.60, 170.64, 170.73.

Anal. Calcd for $C_{22}H_{30}N_4O_{11}$: C, 50.19; H, 5.74; N, 10.64. Found: C,50.34; H, 5.91; N, 10.53.

6-Diethylamino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-azauracil (4a). 61%; syrup; $[\alpha]_D$ −2.3° (*c* 1.05); IR 3206, 1701, 1562 cm^{-1}; ^1H NMR δ 1.24 (t, 6H, J = 6. 9 Hz), 2.09, 2.10, 2.11 (3s, 9H, OAc), 3.47 (q, 4H, J = 6.9 Hz, NCH_2), 4.24 (m, 2H, H-5′), 4.46 (dd, 1H, J = 6.0, 14.4 Hz, H-4′), 5.33 (d, 1H, J = 3.3 Hz, H-1′), 5.59 (t, 1H, J = 6.6 Hz, H-3′), 5.79 (dd, 1H, J = 3.0, 6.5 Hz, H-2′), 8.42 (bs, 1H, NH). ^{13}C NMR δ 12.55 (2C), 20.43 (2C), 20.82, 44.32 (2C), 63.03 (C-5′), 70.21, 73.61, 79.92, 93.22 (C-1′), 151.02 (Het. C═O), 154.59 (Het. C═N), 160.74 (Het. C═O), 169.52, 169.70, 171.08. HRMS Calcd for $C_{18}H_{26}N_4O_9$: 442.1700. Found: 442.1733.

6-Pyrrolidino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-azauracil (4b). 73%; syrup; $[\alpha]_D$ +25.8° (*c* 1.06); IR 3237, 1748, 1699, 1561 cm^{-1}; ^1H NMR δ 1.92 (m, 4H), 2.08, 2.10 (2s, 9H, OAc), 3.57–3.81 (m, 4H), 4.23 (m, 2H, H-5′), 4.48 (dd, 1H, J = 6.0, 14.1 Hz, H-4′), 5.47 (d, 1H, J = 3.3 Hz, H-1′), 5.64 (t, 1H, J = 6.6 Hz, H-3′), 5.81 (dd, 1H, J = 3.3, 6.5 Hz, H-2′), 8.42 (bs, 1H, NH). ^{13}C NMR δ 20.47, 20.56, 20.82, 25.59 (2C), 51.24 (2C), 63.04 (C-5′), 70.24, 73.59, 80.01, 91.24 (C-1′), 150.63 (Het. C═O), 154.63 (Het. C═N), 157.98 (Het. C═O), 169.51, 169.75, 171.11. HRMS Calcd for $C_{18}H_{24}N_4O_9$: 440.1543. Found: 440.1595.

6-Piperidino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-azauracil (4c). 75%; syrup; $[\alpha]_D$ +6.9° (*c* 1.09); IR 3217, 1750, 1709, 1568 cm^{-1}; ^1H NMR δ 1.68 (bs, 6H), 2.08, 2.10, 2.11 (3s, 9H, OAc), 3.38–3.60 (m, 4H), 4.22 (dd, 2H, J = 6.3, 13.2 Hz, H-5′), 4.47 (dd, 1H, J = 6.0, 14.4 Hz, H-4′), 5.42 (d, 1H, J = 3.0 Hz, H-1′), 5.64 (t, 1H, J = 6.6 Hz, H-3′), 5.82 (dd, 1H, J = 2.7, 6.5 Hz, H-2′), 8.88 (bs, 1H, NH). ^{13}C NMR δ 20.45, 20.82 (2C), 24.05, 25.47 (2C), 50.33 (2C), 63.17 (C-5′), 69.95, 73.86, 79.86, 93.49 (C-1′), 150.89 (Het. C═O), 154.61 (Het. C═N), 160.86 (Het. C═O), 169.49, 169.62, 171.06. HRMS Calcd for $C_{19}H_{26}N_4O_9$: 454.1700. Found: 454.1711.

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9. X-Ray crystallographic analysis of compound (**2a**). A needle-like crystal of approximate dimension of 0.80 × 0.06 × 0.06 mm was used. X-Ray data were collected on an Enraf-Nonius CAD4 diffractometer with graphic monochromate CuKα radiation (λ = 1.54178 Å). Crystal data: $C_{21}H_{30}N_4O_{11}$, orthorhombic, space group $P2_12_12_1$, a = 7.9965 (3)Å, b = 14.1718(5)Å, c = 22.3881(8)Å, V=2537.1(1)Å^3, Z = 4, ρ= 1.347 g/cm^3, μ= 9.40 cm^{-1}. Data were collected $4° < 2\theta < 120°$, with ω scan, ω= (1.00 + 0.15 tanθ)°, empirical absorption (ψ scan) corrections (transmission factors; Tmin = 0.9507, Tmax = 0.9989), no decay. 2411 reflections were collected and 1937 ($I > 2\sigma(I)$) reflections were used. The structure was solved by SIR 92 and difference Fourier synthesis. All hydrogen atoms were found in the difference Fourier map. After refining the coordinates and temperature factors of the hydrogen atoms for two cycles, they were fixed. The refinement was carried out by full matrix least squares with anisotropic temperature factors for the non H-atoms (R = 0.048, Rw = 0.055, w = $1/\sigma^2(F_0)$, S = 2.17). All calculations were performed using the teXsan (Version 1.9).
10. Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Center. These tables may be obtained on request from the Director, Cambridge Data Center, 12 Union Road, Cambridge CB2 IEZ, UK.
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