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Activated Nitriles in Heterocyclic Synthesis: Facile Synthesis of Heteroarylthymine Analogs and Their Nucleosides

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ABSTRACT: *5-Heteroarylthymine analogs (***5***) were synthesized via binucleophilic attack with bidentate thiols on the cyano group of cyanoacetylurea to form the heteroarylurea derivatives (***2–4***) followed by their cyclization with formamide. Also, their nucleosides* **6a** *and* **6b** *with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose were prepared.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:209–212, 2000

INTRODUCTION

Active nitriles are versatile reagents; in previous reports, these synthons were utilized as precursors for the synthesis of a variety of heterocycles, for example, benzothiazoles, benzimidazoles, coumarins, and pyridines [1–3]. Furthermore, thymines and their substituted derivatives were prepared to investigate their biological behavior (e.g., anticancer and antiviral properties) [4–6]. In the present work, we aimed at preparing heteroaryl analogs of thymines, as well as their nucleosides, starting with *N*-cyanoacetylurea (**1**).

RESULTS AND DISCUSSION

Thioglycolic acid was caused to react with **1** in acetic acid to give the 2-ureaylacetylthiazole derivative (**2**) in good yield. The ^{1}H NMR spectrum of the latter showed the methylene and the thiazole H-5 singlets at δ = 3.7 and 5.8, respectively, in addition to three (D_2O) exchangeable protons at δ = 7.1, 7.8 (NH_2), 9.9 (NH), and 11.6 (OH). Its IR spectrum and elemental analysis are in accord with this structure, as well as its mass spectral data, which gave a molecular formula compatible with $C_6H_7N_3O_3S$ *m/z* (M^+201, 22%).

Then, the reaction was carried out with *o*-aminothiophenol instead of thioglycolic acid, affording the 2-ureaylacetylbenzothiazole derivative (**3**). The methylene protons appeared at δ = 4.25, together with the urea (D_2O) exchangeable protons at δ = 7.2, 7.6, and 10.5, with the absence in the IR spectrum of CN absorption detected in the parent compound (**1**).

Similarly, thiosalicylic acid reacted with **1** to form the 1,3-benzothiazine (**4**). Again, it showed the methylene and the urea residue at their expected locations and gave a peak at *m/z* (M^+ 263, 25%) corresponding to its molecular weight, along with ^{1}H NMR aromatics as multiplets at δ = 7.2, 7.7. These, heterocycles, namely **2–4**, were formed via a binucleophilic ring closure of the bidentate thiol with loss of H_2O or NH_3 [7] (cf. Scheme 1).

To fulfill our objective, each compound (**2–4**) was treated with formamide to give heteroarylthymine analogs (**5**) via condensation involving the formamide carbonyl group and active methylene with subsequent cyclization accompanied by loss of NH_3. The products revealed pyrimidine H-6 in the region of δ = 8.2–8.9 with absence of the characteristic ureayl NH_2 and methylene protons previously detected in their parents (**2–4**) (cf. Experimental). Moreover, their mass spectra showed an ion base

peak at *m/z* (M^+ 59) corresponding to an ureayl fragment along with their corresponding molecular ions.

Furthermore, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was prepared following the reported acetylation/bromination method of α−D-glucopyranose [8]. Then, it was allowed to react with the sodium salts of **5a,b** prepared using NaH in DMF, according to the procedure of Simons et al. [9]. As a result, thymine nucleosides (**6a,b**) were obtained. Their ^{1}H NMR spectra revealed, in addition to the parent heteroaryl signals, the carbohydrate moiety signals at δ = 1.9–2.1, 4.0, 4.2, 4.9, 5.2, 5.5, and 6.0. While at δ = 6.35–6.40 (J = 3–7 Hz) two nearly superimposed doublets were observed after careful inspection of their spectra, exemplified by **6b**, integrated both to 1H attributable to the C-1 glucopyranose H in the α and β-forms, respectively. However, it was found that the α-configuration is the predominant one (95%).

This was also supported by the ^{13}C-NMR spectrum of **6b** where the C-1 glucopyranose appeared at δ = 93.4 confirming the α-configuration, whereas the minor β form C-1 appeared at δ = 99.0. Also, their mass spectra, IR, and microanalytical data confirmed the given structure.

EXPERIMENTAL

Melting points are uncorrected and were taken on an Electrothermal 9100 apparatus, and IR spectra were recorded with a Carl Zeiss spectrophotometer, model UR 10 in KBr pellets. ^{1}H NMR spectra were determined with a Jeol 270 MHz instrument (internal TMS). Mass spectra were recorded with a Finigan SSQ 7000 mass spectrometer. Microanalyses were performed by the Central Service Laboratory at Cairo University and the Microanalytical Unit at the National Research Centre.

General procedure for N-(2-heteroarylacetyl) urea (**2–4**)

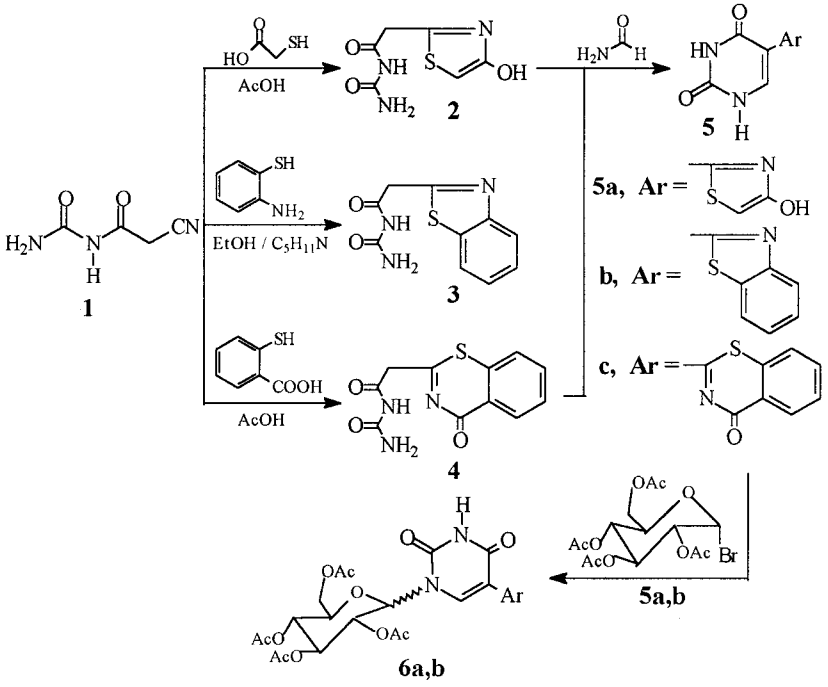
Compound **1** (0.01 mole, 2.1 g) was refluxed with an equimolecular amount of thioglycolic acid or thiosalicylic acid in acetic acid (25 mL) or with *o*-aminothiophenol in ethanol (30 mL) in the presence of piperidine (4 drops) for 6 hours (until the evolution of NH_3 ceased). A precipitate was formed in the hot mixture, and it was filtered off, boiled in water to get rid of excess **1**, filtered again, and finally crystallized from the proper solvent.

N-[2-(4-Hydroxythiazolyl) acetyl] urea (**2**)

m.p. 240°C; yield 80% (acetic acid).

^{1}H NMR (D_2O, DMSO-d_6, TMS), δ, 3.72 (s, 2H, CH_2), 5.80 (s, 1H, H-5, ArH), 7.10, 7.79 (2s, 2H, NH_2), 9.92 (s, 1H, NH), 11.62 (s, 1H, OH).

IR (KBr), *v*, 3400–2900 (br NH_2-NH and CH_2), 1700, 1680 (2CO) MS:*m/z* (M^+ = 201, 22%).



SCHEME 1

Anal. Calcd. for $C_6H_7N_3O_3S$ (201.20): C, 35.82; H, 3.51; N, 20.88; S, 15.94. Found: C, 35.70; H, 3.30; N, 20.55; S, 15.70.

N-(*2-Benzothiazolylacetyl*) *urea* (**3**)

m.p. 210°C, yield 85% (EtOH).

^{1}H NMR (D_2O, DMSO - d_6, TMS), δ, 4.25 (s, 2H, CH_2), 7.25, 7.64 (2 brs, 2H, NH_2), 7.35–7.54 (m, 2H, H-5, H-6, ArH), 7.90, 8.06 (m, 2H, H-4, H-7, ArH), 10.54 (s, 1H, NH).

IR (KBr), *v*, 3400–2900 (br, NH_2, NH and CH_2), 1705, 1690 (2CO) MS: *m/z* (M^+ = 235, 25%).

Anal. Calcd. for $C_{10}H_9N_3O_2S$ (235.256). C, 51.05; H, 3.86; N, 17.86; S, 13.63. Found: C, 50.82; H, 3.60; N, 17.60; S, 13.43.

2-(*Ureayl acetyl*)*-1,3-benzothiazin-4-one* (**4**)

m.p. 282°C, yield 20% (acetic acid).

^{1}H NMR (D_2O, DMSO - d_6, TMS), δ, 3.52 (s, 2H, CH_2), 7.21–7.73 (m, 6H, NH_2 and H-5 to H-8, ArH), 10.00 (brs, 1H, NH).

IR(KBr), *v*, 3390–2800 (NH_2, NH and CH_2), 1750, 1700, 1660 (3CO). MS: *m/z* (M^+ = 263, 25%).

Anal. Calcd. for $C_{11}H_9N_3O_3S$ (263.277): C, 50.18; H, 3.45; N, 15.96; S, 12.18. Found: C, 50.02; H, 3.20; N, 15.67; S, 12.08.

General Procedure for 5-(*2-Heteroaryl*)*-1,3-H-pyrimidin-2,4-dione* (**5a–c**)

Each compound (**2–4**) (0.01 mole) was refluxed in formamide (20 mL) for 1 hour. After cooling, the precipitate obtained was filtered off and crystallized from acetic acid.

5-(*4-Hydroxythiazol-2-yl*)*-1,3-H-pyrimidin-2,4-dione* (**5a**) *m.p. > 350°C, yield 30%.*

^{1}H-NMR (D_2O, DMSO-d_6, TMS), δ, 6.43 (s, 1H, H-5, thiazole H), 8.91 (s, 1H, H-6, pyrimidine H), 11.20–11.50 (brs, 3H, 2NH, and OH). IR(KBr), *v*, 3100–2800 (NH, OH), 1720, 1700 (2CO). MS: *m/z* (M^+ = 211, 40%).

Anal. Calcd. for $C_7H_5N_3O_3S$ (211.194): C, 39.81; H, 2.39; N, 19.90; S, 15.18. Found: C, 39.65; H, 2.24; N, 19.60; S, 14.90.

5-(*Benzothiazol-2-yl*)*-1,3-H-pyrimidin-2,4-dione* (**5b**)

m.p. > 350°C, yield 55%.

^{1}H NMR (D_2O, DMSO - d_6, TMS), δ, 7.28–7.50 (m, 2H, H-5, H-6, Ar H), 7.88–7.98 (m, 2H, H-4, H-7, Ar H), 8.45 (s, 1H, H-6, pyrimidine H), 11.75, 11.80 (2s, 2H, 2NH).

IR(KBr), *v*, 3200–2800 (2NH), 1720, 1680 (2CO). MS: *m/z* (M^+ = 245, 35%).

Anal. Calcd. for $C_{11}H_7N_3O_2S$ (245.25): C, 53.87; H, 2.88; N, 17.13; S, 13.07. Found: C, 53.60; H, 2.70; N, 16.90; S, 12.80.

5-(*1,3-Benzothiazin-4-one-2-yl*)*-1,3-H-pyrimidin-2,4-dione* (**5c**)

m.p. 187°C, yield 70%.

^{1}H NMR (D_2O, DMSO - d_6, TMS), δ, 7.40–7.72 (m, 4H, H-5 to H-8, Ar H), 8.20 (s, 1H, H-6, pyrimidine H), 11.61, 11.83 (2s, 2H, 2NH).

IR(KBr), *v*, 3400–2800 (2NH), 1710, 1690, 1660 (CO). MS: *m/z* (M^+ = 273, 40%).

Anal. Calcd. for $C_{12}H_7N_3O_3S$ (273.272): C, 52.74; H, 2.58; N, 15.37; S, 11.73. Found: C, 52.60; H, 2.40; N, 15.13; S, 11.50.

General procedure for 5-Aryl-1-(*2′,3′,4′,6′-tetra-O-acetyl-α-D-glucopyranosyl*)*-3H-pyrimidin-2,4-dione* (**6a,b**)

Each of compounds **5a,b** (0.01 mole) was stirred with an equimolecular amount of NaH in dry DMF (25 mL) for 2 hours at 70°C. To the formed salt, a solution of 2, 3, 4, 6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (prepared as reported) [8] (0.01 mole) in DMF (20 mL) was added dropwise, and stirring was continued for an additional 3 hours at room temperature. The reaction mixture was acidified with HCl (50%), then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered, then evaporated under vacuum. The remaining solid was collected and crystallized from methanol.

5-(*4-Hydroxythiazol-2-yl*)*-1-*(*2′,3′,4′,6′-tetra-O-acetyl-α-D-glucopyranosyl*)*-3H-pyrimidin-2,4-dione* (**6a**)

m.p. 84°C, yield 20%.

^{1}H NMR (D_2O, DMSO-d_6, TMS), δ, 1.90–2.05 (4s, 12H, 4xAc), 4.00–4.05 (m, 2H, H-6′, 6″), 4.14–4.20 (m, 2H, H-5′ and H-5, thiazole H), 4.75 (t, $J_{3',4'} = J_{4',5'}$ = 7.0 Hz, 1H, H-4′), 4.95 (t, $J_{1',2'} = J_{2',3'}$ = 7.0 Hz, 1H, H-2′), 5.00 (t, $J_{3',4'} = J_{2',3'}$ = 7.0 Hz, 1H, H-3′), 5.35 (s, 1H, NH), 5.50 (d, $J_{1',2'}$ = 7.0 Hz, 1H, H-1′), 7.85 (s, 1H, H-6, pyrimidine H), 11.00 (s, 1H, OH).

IR(KBr), *v*, 3300 (OH), 3150–2800 (NH and Ac), 1740 (Ac), 1710, 1670 (2CO).

MS: *m/z* (M^+ = 541, 8%).

Anal. Calcd. for $C_{21}H_{23}N_3O_{12}S$ (541.494): C, 46.58;

H, 4.28; N, 7.76; S, 5.92. Found: C, 46.30; H, 4.10; N, 7.35; S, 5.70.

5-(Benzothiazol-2-yl)-1-(2′,3′,4′,6′-tetra-O-acetyl-α-D-glucopyranosyl)-3H-pyrimidin-2,4-dione (**6b**)

m.p. 197–199°C, yield 25%.

^{1}H NMR (D_2O, DMSO-d_6, TMS), δ, 1.90–2.10 (4s, 12H, 4xAc), 4.05–4.10 (m, 2H, H-6′, 6″), 4.20–4.30 (m, 1H, H-5′), 5.00 (t, $J_{3',4'} = J_{4',5'} = 7.0$ Hz, 1H, H-4′), 5.55 (t, $J_{1',2'} = J_{2',3'} = 7.0$ Hz, 1H, H-2′), 6.00 (t, $J_{2',3'} = J_{3',4'} = 7.0$ Hz, 1H, H-3′), 6.30 (s, 1H, NH), 6.35 (d, $J_{1',2'} = 3.0$ Hz, 1H, H-1′ β), 6.40 (d, $J_{1',2'} = 7.0$ Hz, 1H, H-1′ α), 7.40–7.50 (m, 3H, H-5 to H-7, ArH), 7.90 (m, 1H, H-4, ArH), 8.50 (s, 1H, H-6, pyrimidine H).

^{13}C NMR (DMSO-d_6, TMS), δ, 20.22, 20.33, 20.42, 20.56 (CH_3 acetyl), 61.72, 67.87, 72.53, 72.87, 78.33, 93.42, (C-6, C-4, C-5, C-2, C-3, C-1 glucopyranose), 112.54, 122.86, 124.52, 126.42, 127.14, 136.53, 146.99, 155.85, 158.98, 159.93, (benzothiazole and uracil), 169.44, 169.49, 169.63, 170.03 (CO acetyl) [10].

IR(KBr), ν 3150–2800 (NH and Ac), 1740 (Ac), 1710, 1680 (2CO).

MS: m/z ($M^+ = 575$, 10%).

Anal. Calcd. for $C_{25}H_{25}N_3O_{11}S$ (575.555): C, 52.17; H, 4.38; N, 7.30; S, 5.57. Found: C, 52.00; H, 4.20; N, 7.15; S, 5.32.

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