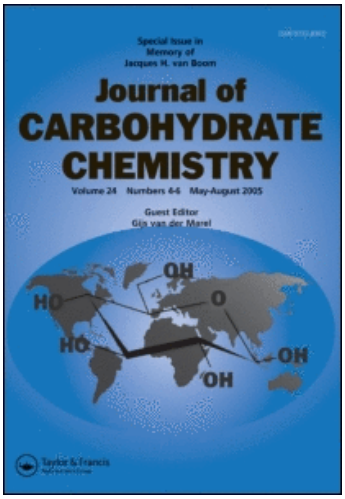

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A Direct Route to a New Class of Acrylamide Thioglycosides

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The preparation of a new class of acrylamide thioglycosides via one-pot reaction of the potassium 2-cyanoethylene-1-thiolate salts with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides has been studied. The *E*-configuration of these thioglycosides was proven by their transformations to the corresponding 5-aminopyrazoles.

Keywords Acrylamide thioglycosides, Potassium 2-cyanoethylene-1-thiolate salts, 5-Aminopyrazoles

Nucleoside analogs have occupied a significant position in the search for effective antiviral agents, owing to the fact that a large number of unnatural nucleoside derivatives have been shown to inhibit infection caused by viruses.[1] Heterocyclic thioglycosides constitute a class of analogs with potential biological activity.[2] As part of our program directed toward the development of new, simple, and efficient procedures for the synthesis of antimetabolites[3,4] we described that pyridine thioglycosides exerted inhibitory effects on both DNA and RNA containing viruses.[5] Based on these findings, it was of interest to prepare modified cyclic and acyclic thioglycosides to search for more effective agents. Here we report novel syntheses of acrylamide thioglycoside derivatives. The potassium 2-cyanoethylene-1-thiolate salts **3a**–**d** were chosen as the key

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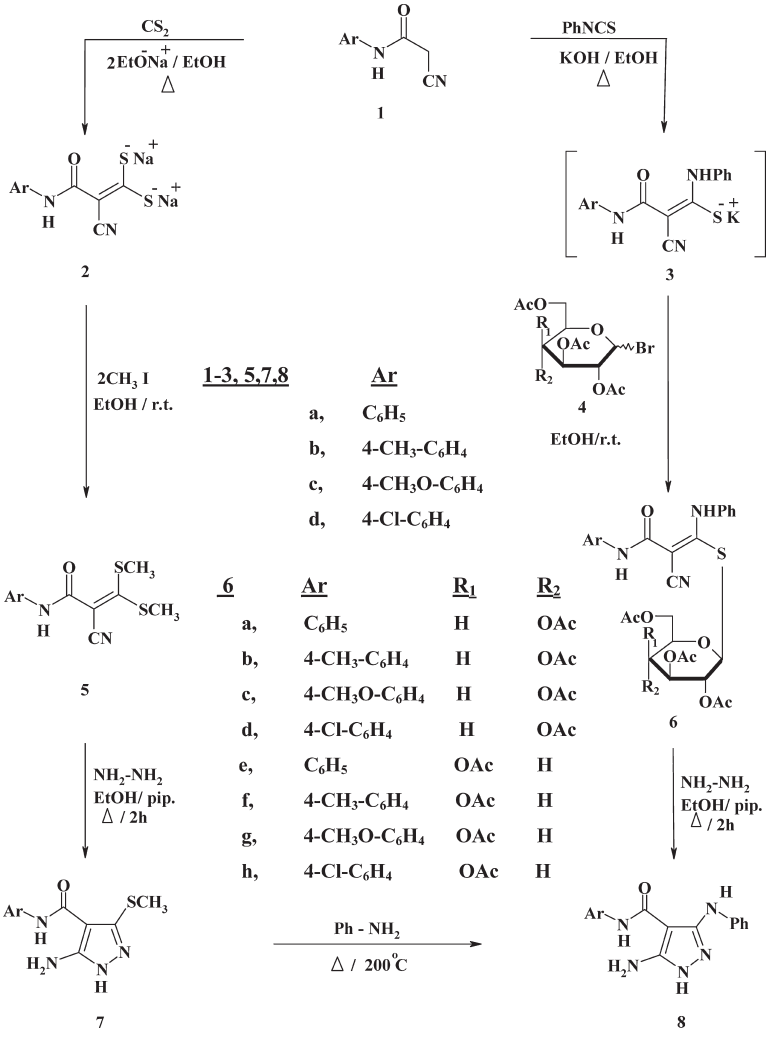
intermediate. The reaction sequence to prepare the compounds is summarized in Scheme 1. Substituted acetanilide derivatives **1a**–**d** reacted with phenyl isothiocyanate in KOH-EtOH with heating to give the corresponding stable potassium 2-cyano-ethylene-1-thiolate salts **3a**–**d**. The latter react with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galacto-pyranosyl bromides **4** in ethanol at rt to give the corresponding *S*-glucosides **6a**–**d** or *S*-galactosides **6e**–**h**, in high yield. Attempted removal of protecting groups in **6a**–**h** by methanolic ammonia did not result in formation of the corresponding free glycosides. We suggested that **6a**–**h** should be present in the *E* and not in the *Z* form. This was shown by reacting **6a**–**h** with hydrazine in refluxing ethanol to give the corresponding



Scheme 1

5-aminopyrazole derivatives **8a–d**. Alternatively, **8a–d** could be prepared by reaction of the 3-methylthiopyrazoles **7a–d** with aniline. Compounds **7a–d** were prepared by the reaction of substituted acetanilide derivatives **1** with carbon disulfide in the presence of sodium ethoxide followed by the alkylation with methyl iodide to give the ketene *S*,*S*-acetals **5**; the latter reacts with hydrazine to give compounds **7a–d**.[6]

In summary, we have achieved the synthesis of acrylamide thioglycosides by the reaction of the potassium 2-cyanoethylene-1-thiolate salts with α-glycosyl halides. These acyclic glycosides can be utilized as starting materials for the synthesis of other carbohydrate derivatives.

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 ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer in $(CD_3)_2SO$ using $Si(CH_3)_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Elemental analyses were obtained from the Microanalytical Data Center at Cairo University, Egypt.

Progress of the reactions was monitored by TLC using aluminum sheets coated with silica gel F254 (Merck). Viewing under a short-wavelength UV lamp effected detection. All evaporations were carried out under reduced pressure at 40°C.

Compounds **5** and **7** were prepared following reported procedures.[6]

(*2e*)-3-Anilino-*N*-Aryl-2-Cyano-3-(2′,3′,4′,6′-Tetra-*O*-Acetyl-β-D-Gluco- and Galactopyranosylthio)acrylamides (6a–h)

General Procedure

A mixture of *N*-substituted cyanoacetamide derivatives **1a–d** (0.01 mol) and phenyl isothiocyanate (0.01 mol) was heated for 10 to 20 min in ethanol (25 mL) containing potassium hydroxide (0.01 mol). After cooling, a solution of 2,3,4,6-tetra-*O*-acetyl-(-D-gluco- or galacto-pyranosyl bromide **4a**,**b** (0.01 mol) in ethanol (20 mL) was added. The reaction mixture was stirred at rt until completion (TLC) and then evaporated under reduced pressure, and the residue was washed with distilled water to remove the formed potassium bromide. The resulting solid product was dried and crystallized from a mixture of EtOH/DMF.

6a: White, m.p. 198°C (from EtOH/DMF), yield (87%). IR (KBr) ν_{max}/cm^{-1} 3340 (NH), 2206 (CN), 1751 (CO). ^{1}H NMR (DMSO) δ 1.94–2.02 (4s, 12H, 4 × CH_3CO), 3.66 (m, 2H, H_2-6′), 4.08 (m, 1H, H-5′), 4.84 (m, 2H, H-4′, H-3′),

5.20 (d, $J_{1'\text{-}2'}$ 9.62 Hz, 1H, H-1′), 5.25 (t, 1H, H-2′), 7.22–7.50 (m, 9H, C_6H_5, C_6H_4), 9.88 (s, 1H, NH). ^{13}C NMR (DMSO) δ 20.13–20.37 (4 × CH_3), 61.34 (CH_2, C-6′), 67.38 (C-4′), 69.65 (C-2′), 72.62 (C-3′), 74.54 (C-5′), 83.84 (C-1′), 117.85 (CN), 121.17–138.44 (2C_6H_5), 154.00 (C-2), 160.18 (C-3), 163.70 (C-1), 169.00–169.80 (4 × CO). $C_{30}H_{31}N_3O_{10}S$, Calcd: C, 57.58; H, 5.00; N, 6.71, Found: C, 57.24; H, 5.25; N, 6.37%.

6b: White, m.p. 205°C (from EtOH/DMF), yield (86%). IR (KBr) ν_{max}/cm^{-1} 3402 (NH), 2198 (CN), 1743 (CO). ^{1}H NMR (DMSO) (1.90–2.00 (4s, 12H, 4 × CH_3CO), 2.25 (s, 3H, CH_3), 3.65 (m, 2H, H_2-6′), 4.00 (m, 1H, H-5′), 4.85 (m, 2H, H-4′, H-3′), 5.15 (m, 1H, H-2′) 5.25 (d, $J_{1'\text{-}2'}$ 9.9, 1H, H-1′), 7.10–7.50 (m, 9H, C_6H_5, C_6H_4), 9.55 (s, 1H, NH).^{13}C NMR (DMSO) (20.13–20.37 (5 × CH_3), 61.34 (CH_2, C-6′), 67.38 (C-4′), 69.60 (C-2′), 72.62 (C-3′), 74.52 (C5′), 83.47 (C-2′), 83.87 (C-1′), 117.85 (CN), 121.24–138.42 (C_6H_4 and C_6H_5), 160.04 (C-3), 163.63(C-1), 169.00–169.79 (4 × CO). $C_{31}H_{33}N_3O_{10}S$, Calcd: C, 58.19; H, 5.20; N, 6.56, Found: C, 58.10; H, 5.35; N, 6.55%.

6c: White, m.p. 215°C (from EtOH/DMF), yield (77%). IR (KBr) ν_{max}/cm^{-1} 3402 (NH), 2206 (CN), 1743 (CO). ^{1}H NMR (DMSO) δ 1.90–2.00 (4s, 12H, 4 × CH_3CO), 3.70 (m, 2H, 6′-H_2), 3.75 (s, 3H, OCH_3), 4.00 (m, 1H, H-5′), 4.85 (m, 2H, H-4′, H-3′), 5.15 (d, $J_{1'\text{-}2'}$ 9.75, 1H, H-1′), 5.25 (t, 1H, H-2′), 6.80–7.50 (m, 9H, C_6H_5, C_6H_4), 9.50 (s, 1H, NH). ^{13}C NMR (DMSO) (20.14–20.37 (4 × CH_3), 55.07 (OCH_3), 61.35 (CH_2, C-6′), 67.40 (C-4′), 69.67 (C-2′), 72.63 (C-3′), 74.51 (C-5′), 83.90 (C-1′), 113.51 (CN), 117.85–138.41 (C_6H_4 and C_6H_5), 155.88(C-2), 159.94(C-3), 163.64(C-1), 169.01–169.80 (4 × CO). $C_{31}H_{33}N_3O_{11}S$, Calcd: C, 56.77; H, 5.08; N, 6.40, Found: C, 57.04; H, 5.20; N, 6.35%.

6d: White, m.p. 215°C (from EtOH/DMF), yield (77%). IR (KBr) ν_{max}/cm^{-1} 3402 (NH), 2198 (CN), 1743 (CO). ^{1}H NMR (DMSO) δ 1.90–2.05 (4s, 12H, 4 × CH_3CO), 3.70 (m, 2H, H_2-6′), 4.00 (m, 1H, H-5′), 4.90 (m, 2H, H-4′, H-3′), 5.20 (d, $J_{1'\text{-}2'}$ 9.80, 1H, H-1′), 5.25 (t, 1H, H-2′), 7.20–7.55 (m, 9H, C_6H_5, C_6H_4), 9.80 (s, 1H, NH). ^{13}C NMR (DMSO) δ 20.13–20.37 (4 × CH_3), 61.34 (CH_2, C-6′), 67.37 (C-4′), 69.63 (C-2′), 72.59 (C-3′), 74.56 (C-5′), 83.75 (C-1′), 117.78 (CN), 122.60–138.47 (C_6H_4 and C_6H_5), 160.31 (C-2), 163.58 (C-3), 168.99 (C-1), 169.35–169.79 (4 × CO). $C_{30}H_{30}ClN_3O_{10}S$, Calcd: C, 54.54; H, 4.54; N, 6.36, Found: C, 54.44; H, 4.80; N, 6.34%.

6e: White, m.p. 179°C (from EtOH/DMF), yield (85%). IR (KBr) ν_{max}/cm^{-1} 3397 (NH), 2201 (CN), 1745 (CO). ^{1}H NMR (DMSO) δ 1.85–2.00 (4s, 12H, 4 × CH_3CO), 3.85 (m, 2H, H_2-6′), 4.10 (m, 1H, H-5′), 5.00 (t, 1H, H-4′), 5.10 (m, 2H, H-3′, 2′-H), 5.25 (d, $J_{1'\text{-}2'}$ 9.8, 1H, H-1′), 7.05–7.70 (m, 10H, 2C_6H_5), 9.60 (s, 1H, NH). ^{13}C NMR (DMSO) δ 20.01–20.40 (4 × CH_3), 60.83 (CH_2, C-6′), 66.77 (C-4′), 67.06 (C-2′), 70.64 (C-3′), 73. 81 (C-5′), 84.03 (C-1′), 118.03 (CN), 120.98–138.75 (2C_6H_5), 155.70 (C-2), 159.61 (C-3), 163.10 (C-1),

169.24–169.70 (4 × CO). $C_{30}H_{31}N_3O_{10}S$, Calcd: C, 57.58; H, 5.00; N, 6.71, Found: C, 57.53; H, 5.00; N, 7.06%.

6f: White, m.p. 210°C (from EtOH/DMF), yield (86%). IR (KBr) ν_{max}/cm^{-1} 3402 (NH), 2198 (CN), 1743 (CO). ^{1}H NMR (DMSO) δ 1.85–2.05 (4s, 12H, 4 × CH_3CO), 2.25 (s, 3H, CH_3), 3.85 (m, 2H, H_2-6′), 4.10 (m, 1H, H-5′), 5.00 (t, 1H, H-4′), 5.10 (m, 3H, H-3′, H-2′) 5.30 (d, $J_{1'-2'}$ 9.6, 1H, H-1′), 7.10–7.50 (m, 9H, C_6H_5, C_6H_4), 9.55 (s, 1H, NH). ^{13}C NMR (DMSO) δ 20.04–20.47 (5 × CH_3), 60.82 (CH_2, C-6′), 66.80 (C-4′), 67.06 (C-2′), 70.65 (C-3′), 73.78 (C-5′), 84.11 (C-1′), 118.03 (CN), 119.66–138.71 (C_6H_4 and C_6H_5), 155.60 (C-2), 159.51 (C-3), 163.09 (C-1), 169.24–169.72 (4 × CO). $C_{31}H_{33}N_3O_{10}S$, Calcd: C, 58.19; H, 5.20; N, 6.56, Found: C, 57.90; H, 4.90; N, 6.64%.

6g: White, m.p. 191°C (from EtOH/DMF), yield (76%). IR (KBr) ν_{max}/cm^{-1} 3409 (NH), 2198 (CN), 1743 (CO). ^{1}H NMR (DMSO) δ 1.85–2.05 (4s, 12H, 4 × CH_3CO), 2.25 (s, 3H, CH_3), 3.85 (m, 2H, H_2-6′), 4.10 (m, 1H, H-5′), 5.00 (t, 1H, H-4′), 5.10 (m, 3H, H-3′, H-2′), 5.30 (d, $J_{1'-2'}$ 9.88, 1H, H-1′), 7.10–7.50 (m, 9H, C_6H_5, C_6H_4), 9.55 (s, 1H, NH). ^{13}C NMR (DMSO) δ 20.05–20.40 (4 × CH_3), 55.06 (OCH_3), 60.80 (CH_2, C-6′), 66.81 (C-4′), 67.05 (C-2′), 70.66 (C-3′), 73.76 (C-5′), 84.14 (C-1′), 113.73 (CN), 118.02–138.69 (C_6H_4 and C_6H_5), 155.81 (C-2), 159.40 (C-3), 163.10 (C-1), 169.25–169.73 (4 × CO). $C_{31}H_{33}N_3O_{11}S$, Calcd: C, 56.77; H, 5.08; N, 6.40, Found: C, 57.07; H, 5.20; N, 6.40%.

6h: White, m.p. 197°C (from EtOH/DMF), yield (87%). IR (KBr) ν_{max}/cm^{-1} 3394 (NH), 2198 (CN), 1743 (CO). ^{1}H NMR (DMSO) δ 1.90–2.05 (4s, 12H, 4 × CH_3CO), 3.85 (m, 2H, H_2-6′), 4.10 (m, 1H, H-5′), 5.05 (t, 1H, H-4′), 5.10 (m, 3H, H-3′, H-2′), 5.25 (d, $J_{1'-2'}$ 9.77, 1H, H-1′), 7.10–7.70 (m, 9H, C_6H_5, C_6H_4), 9.75 (s, 1H, NH), 11.00 (s, 1H, CONH). ^{13}C NMR (DMSO) δ 19.95–20.40 (4 × CH_3), 60.90 (CH_2, C-6′), 66.73 (C-4′), 67.09 (C-2′), 70.64 (C-3′), 73.88 (C-5′), 83.90 (C-1′), 117.98 (CN), 122.34–138.82 (C_6H_4 and C_6H_5), 155.70 (C-2), 159.74 (C-3), 162.92 (C-1), 169.25–169.69 (4 × CO). $C_{30}H_{30}ClN_3O_{10}S$, Calcd: C, 54.59; H, 4.54; N, 6.36, Found: C, 54.70; H, 4.40; N, 6.65%.

5-Amino-3-(Methylthio)-1*H*-Pyrazole-4-Carboxanilides (7a-D)[6]

General Procedure

A mixture of compounds **5a–d** (0.01 mol) and hydrazine (0.01 mol) in ethanol (30 mL) was heated at reflux for 2 h. After cooling, the reaction mixture was diluted with cooled water and the resulting solid product was filtered off and recrystallized from ethanol.

5-Amino-3-Anilino-1*H*-Pyrazole-4-Carboxanilides (8a–D)

General Procedures

Method (a)

A mixture of compounds **6a–d** (0.01 mol) and hydrazine (0.01 mol) in ethanol (30 mL) was heated at reflux for 2 h. The resulting solid product was collected by filtration and recrystallized from ethanol.

Method (b)[7]

A mixture of compounds **7a–d** (0.01 mol) and aniline (0.01 mol) was heated for 2 to 3 h at 200°C in an oil bath. The reaction mixture was dissolved in ethanol and the resulting solid product was filtered off and recrystallized from ethanol.

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