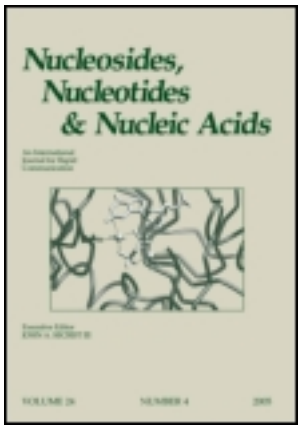


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

Glucopyranosides Derived From 6-Aryl-5-Cyano-2-(Methylthio)Pyrimidin-4(3H)Ones

Ibrahim M. Abdou [a] , Adel M. Attia [a] & Lucjan Strekowski [a a]
[a] Department of Chemistry, Georgia State University, Atlanta, Georgia, 30303, U.S.A.

Version of record first published: 17 Aug 2006

To cite this article: Ibrahim M. Abdou, Adel M. Attia & Lucjan Strekowski (2002): Glucopyranosides Derived From 6-Aryl-5-Cyano-2-(Methylthio)Pyrimidin-4(3H)Ones, Nucleosides, Nucleotides and Nucleic Acids, 21:1, 15-21

To link to this article: http://dx.doi.org/10.1081/NCN-120006527

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 21(1), 15–21 (2002)

GLUCOPYRANOSIDES DERIVED FROM 6-ARYL-5-CYANO-2-(METHYLTHIO)PYRIMIDIN-4(3*H*)ONES

Ibrahim M. Abdou,* Adel M. Attia,† and Lucjan Strekowski‡

Department of Chemistry, Georgia State University,
Atlanta, Georgia 30303, USA

ABSTRACT

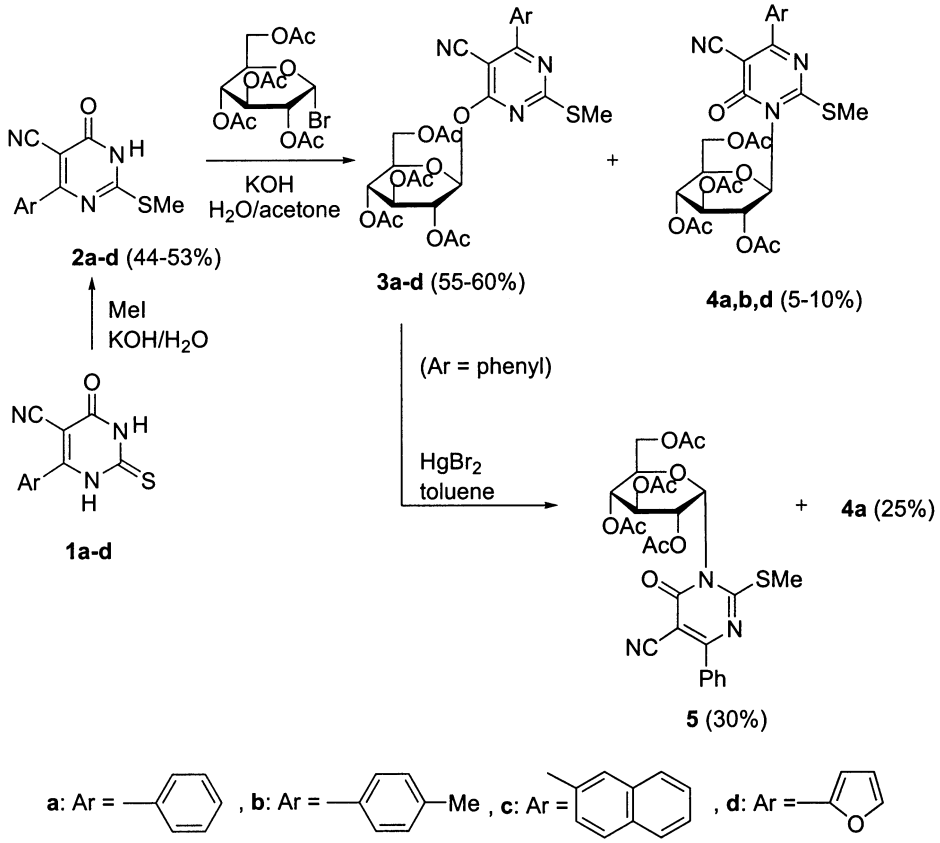
The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with a 6-aryl-5-cyano-2-(methylthio)pyrimidin-4(3*H*)one in aqueous acetone in the presence of KOH furnishes a 4-(β-D-glucopyranosyloxy)pyrimidine and a 3-(β-D-glucopyranosyl)pyrimidine as the major and minor product, respectively.

INTRODUCTION

Synthesis of nucleosides of 6-substituted pyrimidine-4(3*H*)ones including 6-substituted uracils has mostly been conducted under electrophilic conditions.[1] The reactions of multi-centered anions derived from the 6-substituted pyrimidinone substrates with an activated sugar have received relatively little attention, in spite of the fact that such glycosidation reactions can be remarkably regioselective. For example, *O*-peracetyl derivatives of *N*3-(β-D-glucopyranosyl-, *N*3-(β-D-galactopyranosyl-, and *N*3-(β-D-xylopyranosyl-6-methyl-2-(methylthio)pyrimidin-4(3*H*)one have been obtained

*Current address: Chemistry Department, College of Science, UAE University, Al-Ain, United Arab Emirates.
†Current address: Chemistry Department, Faculty of Education, Tanta University, Kafr El-Sheikh, Egypt.
‡Corresponding author. E-mail: Lucjan@gsu.edu

by the reaction of 6-methyl-2-(methylthio)pyrimidin-4(3*H*)one with the corresponding *O*-peracetyl-α-bromo sugar under basic conditions. The analogous reactions of 5-bromo-6-methyl-2-(methylthio)pyrimidin-4(3*H*)one are also N3-regioselective.[2,3] Recently, we have also reported an efficient synthesis of 6-aryl-5-cyano-1-(β-D-pyranosyl or β-D-furanosyl)-2-thiocytosines by glycosidation of 6-aryl-5-cyano-2-thiouracils (structure **1** in Sch.) followed by ammonolysis of the products.[4,5] Regioselectivity of these glycosidation reactions agreed well with the calculated electron density distribution in both of the two monoanions derived by deprotonation of either N1-H or N3-H moiety in 5-cyano-6-phenyl-2-thiouracil **1a**.[4] In the same report, on the basis of the calculated charge density distribution, it was also suggested that the anion derived from 6-aryl-5-cyano-2-(methylthio)pyrimidin-4(3*H*)one (**2**) should undergo preferential glycosidation at the position N1. This work pertains to the experimental testing of the above suggestion. This work was also stimulated by the current interest in unnatural nucleosides as potential biologically active agents. The insecticidal activity of the products will be published in due course.



Scheme.

RESULTS AND DISCUSSION

In absolute disagreement with the theoretical prediction, the treatment of pyrimidinones **2a-d** with *O*-peracetyl-α-D-glucopyranosyl bromide under basic conditions furnished O^4-nucleosides **3a-d** and the corresponding *N*3-nucleosides **4a,b,d** as the major and minor products, respectively. Only the O^4-nucleoside **3c** was obtained in the reaction with a 6-(2-naphthyl)pyrimidin-4(3*H*)one **2c**, and the exclusive O^4-coupling was also observed for the reaction of **2c** with *O*-peracetyl-α-D-galactopyranosyl bromide (not shown). These results are in striking contrast with the N3-regioselectivity of a similar reaction of 6-methyl-2-(methylthio)pyrimidin-4(3*H*)ones (6-Me analogs of **2**) mentioned above. The products **3** and **4** were easily separated by silica gel chromatography and fully characterized by elemental analysis, high resolution mass spectrometry, ^{1}H NMR spectroscopy, and IR spectroscopy.

In particular, in the ^{1}H NMR spectrum of **3a**, the anomeric proton H1′ gives rise to a doublet at δ 6.20 with a coupling constant J(H1′-H2′) of 7.6 Hz. This relatively large coupling constant is characteristic for a β-glucopyranosyl anomer with a diaxial H1′-H2′ interaction.[2, 5] Large coupling constants J(H1′-H2′) of 9.6 ± 2 Hz are obtained in the ^{1}H NMR spectra of the remaining nucleosides **3b-d** as well. The O^4-substitution in **3a** is consistent with the results of proton NOE experiments in which the irradiation at δ 6.20 for H1′ gave strong signals at δ 5.36 for H3′ and δ 5.21 for H5′ (close diaxial interactions) and produced no signals for protons of the phenyl and methylthio groups. In a similar way, the irradiation at either δ 2.63 (SMe) or δ 8.04 (*o*-Ph) gave no NOE enhancements to protons of the sugar moiety, and similar results were obtained for the remaining compounds **3b-d**. All these structural results were confirmed by analysis of NOESY spectra of **3a-d**.

The IR spectra of starting materials **2a-d** show absorption at $2235 \pm 5\,\text{cm}^{-1}$ and $1685 \pm 5\,\text{cm}^{-1}$ for a cyano group and a carbonyl moiety, respectively. While the former band is retained, the latter absorption is not observed in the spectra of the products **3a-d**, which is fully consistent with the structure of O^4-nucleosides. The IR spectra of **3a-d** are dominated by a strong band centered at $1750\,\text{cm}^{-1}$ for acetyl carbonyls.

By contrast, all three absorption bands for the cyano, pyrimidinone, and acetyl moieties are present in the IR spectra of **4a,b,d**, indicating the *N*-nucleoside structure for these minor products. The substitution at the N3 atom was derived from proton NOE experiments which gave an interaction between the anomeric proton H1′ and the SMe group and the lack of enhancement between the anomeric proton and aromatic protons for all products **4a,b,d**. As with **3,** the coupling constant J(H1′-H2′) of 8.8 ± 0.4 Hz is indicative of the β-configuration of **4**.

Strong structural support for the O^4-nucleosides **3** was obtained by $HgBr_2$-mediated rearrangement of the selected compound **3a**. In addition to

4a which was identical in every respect to the nucleoside obtained as discussed above, this reaction furnished its α-anomer **5**. The α-configuration was assigned on the basis of a small coupling constant (J(H1′-H2′) of 3.0 Hz in the ^{1}H NMR spectrum of **5**. The proton NOE experiments conducted as described above strongly indicated the *N*3-nucleoside. This structural assignment is consistent with the similarity of IR spectra of **4a** and **5** including the absorption band for a pyrimidinone moiety ($1670 \pm 10\,cm^{-1}$).

The order of calculated electron densities[4] for the anion derived from **2a** is N1 (0.55) > O^4(0.27) > N3(0.23). Although the N1 atom contains the greatest charge density, it is also highly sterically hindered by the adjacent aromatic and methylthio groups. Thus, the observed formation of O^4-nucleosides can be explained in terms of this steric hindrance. The expected high polarizability of the ionized molecule **2** may play an additional role for the observed O^4-regioselectivity of the glycosidation.

EXPERIMENTAL SECTION

General. Melting points (pyrex capillary) are not corrected. The ^{1}H NMR including NOESY spectra were recorded and single-irradiation NOE experiments were conducted on a Varian instrument operating at 300 MHz with TMS as an internal standard. Optical rotations were measured in chloroform solutions ($c = 2.0$ mg/mL) at 589 nm on an Autopol polarimeter. FAB mass spectra were recorded by using a thioglycerol matrix. IR spectra were recorded in KBr pellets. Microanalyses were obtained on a Perkin-Elmer elemental analyzer.

2-Thiouracils 1a-d. Compounds **1a-c** were synthesized by condensation of the corresponding aldehyde ArCHO with ethyl cyanoacetate and thiourea in the presence of piperidine in ethanol.[5] In a similar way, the condensation of furfural gave 2-thiouracil **1d**.

5-Cyano-6-(2-furyl)-2-thiouracil (1d): yield 55%; mp > 300°C; ^{1}H NMR (DMSO-d_6) δ 12.70 (bs, exchangeable with D_2O, 2H), 8.15 (m, 1H), 7.85 (m, 1H), 6.85 (m, 1H). Analysis. Calcd for $C_9H_5N_3O_2S$: C, 49.31; H, 2.30; N, 19.17. Found: C, 49.30; H, 2.28; N, 18.96.

Pyrimidinones 2a-d. The synthesis of compounds **2a,b** by methylation of 2-thiouracils **1a,b** with MeI in aqueous KOH has been reported previously.[6,7] This procedure was used for the preparation of **2c,d** starting with **1c,d**. All products **2a-d** were crystallized from ethanol and dried at 70°C/1 mmHg.

5-Cyano-2-methylthio-6-(2-naphthyl)pyrimidin-4(3*H*)one (2c): yield 44%; mp 297–299°C; ^{1}H NMR (DMSO-d_6) δ 12.50 (bs, exchangeable with D_2O, 1H), 8.23 (s, 1H), 7.96 (m, 4H), 7.61 (m, 2H), 2.63 (s, 3H). Analysis. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.42; H, 3.62; N, 14.19.

5-Cyano-6-(2-furyl)-2-(methylthio)pyrimidin-4(3*H*)one (2d): yield 53%; mp 245–247°C; ^{1}H NMR (DMSO-d_6) δ 12.30 (bs, exchangeable with D_2O, 1H), 8.16 (m, 1H), 7.62 (m, 1H), 6.85 (m, 1H), 2.63 (s, 3H). Analysis. Calcd for $C_{10}H_7N_3O_2S$: C, 51.49; H, 3.02; N, 18.02. Found: C, 51.34; H, 2.91; N, 17.96.

Nucleosides 3a-d and 4a,b,d. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.5 g, 11 mmol) in acetone (30 mL) was added to a solution of **2a-d** (10 mmol) in aqueous KOH (1.5 M, 7 mL, 10.5 mmol). The mixture was stirred at 23°C for 6–12 h until a TLC analysis (silica gel, ether/chloroform, 1:1) showed the absence of **2a-d**. Concentration on a rotary evaporator followed by silica gel chromatography of the residue eluting with hexanes/ether/chloroform (1:2:2) gave **3a-d**, which was eluted first, and **4a,b,d**. Compounds **3** and **4** were crystallized from 95% ethanol and dried at 50°C/1 mmHg.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-cyano-2-methylthio-6-phenylpyrimidine (3a): yield 60%; mp 145–147°C; $[\alpha]_D^{25}$ 46.2; ^{1}H NMR ($CDCl_3$) (8.04 (m, 2H), 7.50 (m, 3H), 6.20 (d, J = 7.6 Hz, 1H), 5.36 (m, 2H), 5.21 (m, 1H), 4.24 (m, 2H), 3.99 (m, 1H), 2.63 (s, 3H), 2.04–2.08 (4s, 12H). High resolution FAB-MS. Calcd for $C_{26}H_{28}N_3O_{10}S$ ($M^+ + 1$) m/z 574.1495, observed m/z 574.1500. Analysis. Calcd for $C_{26}H_{27}N_3O_{10}S{\cdot}H_2O$: C, 52.74; H, 4.90; N, 7.09. Found: C, 52.89; H, 4.72; N, 7.07.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-cyano-2-methylthio-6-p-tolyl)pyrimidine (3b): yield 55%; mp 138–140°C; $[\alpha]_D^{25}$ 32.2; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 9.6 Hz, 1H), 5.60 (m, 1H), 5.48 (m, 1H), 5.19 (m, 1H), 4.17 (m, 3H), 2.63 (s, 3*H*), 2.29 (s, 3H), 2.04–2.08 (4s, 12H). Analysis. Calcd for $C_{27}H_{29}N_3O_{10}S$: C, 55.19; H, 4.97; N, 7.15. Found: C, 55.06; H, 4.85; N, 7.11.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-cyano-2-methylthio-6-(2-naphthyl)pyrimidine (3c): yield 55%; mp 135–137°C; $[\alpha]_D^{25}$ 28.6; ^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H), 8.08 (m, 4H), 7.65 (m, 2H), 6.61 (d, J = 11.6 Hz, 1H), 5.65 (m, 1H), 5.23 (m, 1H), 5.08 (m, 1H), 4.41 (m, 1H), 4.24 (m, 1H), 4.08 (m, 1H), 2.70 (s, 3*H*), 2.04–2.08 (4s, 12H). Analysis. Calcd for $C_{30}H_{29}N_3O_{10}S$: C, 57.78; H, 4.69; N, 6.74. Found: C, 57.70; H, 4.56; N, 6.74.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-cyano-6-(2-furyl)-2-methylthio)pyrimidine (3d): yield 60%; mp 142–144°C; $[\alpha]_D^{25}$ 35.9; ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 1H), 7.63 (m, 1H), 6.62 (m, 1H), 6.17 (d, J = 7.6 Hz, 1H), 5.36 (m, 2H), 5.20 (m, 1H), 4.25 (m, 1H), 4.17 (m, 1H), 3.95 (m, 1H), 2.60 (s, 3*H*), 2.04–2.08 (4s, 12H). High resolution FAB-MS. Calcd for $C_{24}H_{26}N_3O_{11}S$ ($M^+ + 1$) m/z 564.1288, observed m/z 564.1302. Analysis. Calcd for $C_{24}H_{25}N_3O_{11}S$: C, 51.15; H, 4.47; N, 7.46. Found: C, 51.08; H, 4.29; N, 7.47.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-2-methylthio-6-phenylpyrimidine (4a): yield 10%; mp 230–232 °C; $[\alpha]_D^{25}$ 51.2; ^{1}H NMR ($CDCl_3$) δ 8.11 (m, 2H), 7.55 (m, 3*H*), 6.57 (d, J = 9.2 Hz, 1H), 6.18 (m, 1H), 5.42 (m, 1H), 5.26 (m, 1H), 4.25 (m, 2H), 3.97 (m, 1H), 2.73 (s, 3H), 1.96–2.10

(4s, 12H). High resolution FAB-MS. Calcd for $C_{26}H_{28}N_3O_{10}S$ ($M^+ + 1$) m/z 574.1495, observed m/z 574.1469. Analysis. Calcd for $C_{26}H_{27}N_3O_{10}S$: C, 54.44; H, 4.74; N, 7.33. Found: C, 54.15; H, 4.64; N, 7.02.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-2-methylthio-6-(*p*-tolyl)pyrimidin-4(3*H*)one (4b): yield 10%; mp 200–202 °C; $[\alpha]_D^{25}$ 32.2; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 9.2 Hz, 1H), 6.20 (m, 1H), 5.42 (m, 1H), 5.25 (m, 1H), 4.24 (m, 2H), 3.99 (m, 1H), 2.73 (s, 3*H*), 2.42 (s, 3*H*), 1.96–2.10 (4s, 12H). High resolution FAB-MS. Calcd for $C_{27}H_{30}N_3O_{10}S$ ($M^+ + 1$) m/z 588.1652, observed m/z 588.1665. Analysis. Calcd for $C_{27}H_{29}N_3O_{10}S{\cdot}H_2O$: C, 53.55; H, 5.16; N, 6.94. Found: C, 53.59; H, 4.91; N, 6.85.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-6-(2-furyl)-2-(methylthio)pyrimidin-4(3*H*)one (4d): yield 5%; mp 205–206 °C; $[\alpha]_D^{25}$ 18.6; ^{1}H NMR (CDCl3) δ 7.76 (m, 1H), 7.53 (m, 1H), 6.64 (m, 1H), 6.54 (d, Jδ8.4 Hz, 1H), 6.17 (m, 1H), 5.41 (m, 1H), 5.24 (m, 1H), 4.24 (m, 2H), 3.95 (m, 1H), 2.72 (s, 3*H*), 1.95–2.15 (4s, 12H). Analysis. Calcd for $C_{24}H_{25}N_3O_{11}S$: C, 51.15; H, 4.47; N, 7.46. Found: C, 50.98; H, 4.30; N, 7.44.

Rearrangement of *O*-Glucoside 3a. A mixture of **3a** (0.59 g, 1 mmol), anhydrous $HgBr_2$ (0.36 g, 1 mmol), and anhydrous toluene (20 mL) was heated under reflux for 1 h. After cooling, the solvent was removed on a rotary evaporator and the residue was extracted with chloroform (2 × 25 mL). The extract was washed with an aqueous solution of KI, dried over Na_2SO_4, and concentrated. Chromatography on silica gel eluting with hexanes/ether/chloroform (1:1:1) gave, in order of elution, **4a** (0.14 g, 25%) and **5**. Compounds **4a** and **5** were crystallized from 95% ethanol.

3-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-5-cyano-2-methylthio-6-phenylpyrimidin-4(3*H*)one (5): yield 0.17 g (30%); $[\alpha]_D^{25}$ 23.2; ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.56 (m, 3H), 6.98 (d, J = 3.0 Hz, 1H), 5.65 (m, 1H), 5.24 (m, 2H), 4.36 (m, 2H), 4.17 (m, 1H), 2.60 (s, 3H), 1.98–2.11 (4s, 12H). High resolution FAB-MS. Calcd for $C_{26}H_{28}N_3O_{10}S$ ($M^+ + 1$) m/z 574.1495, observed m/z 574.1510. Analysis. Calcd for $C_{26}H_{27}N_3O_{10}S{\cdot}1/2\ H_2O$: C, 53.56; H, 4.80; N, 7.20. Found: C, 53.44; H, 5.08; N, 7.05.

REFERENCES

1. Townsend, L.B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1994.
2. Attia, A.M.; Sallam, M.A.; Almehdi, A.A.; Abbasi, M.M. Nucleosides Nucleotides **1999**, *26* (10), 2307–2315.
3. Hassanein, M.; Abbasi, M.M.; Anwar, M.; Sallam, M. Delta J. Sci. **1993**, *17* (2), 78–90. Chem. Abstr. **1997**, *126*, 305735d.
4. Strekowski, L.; Abdou, I.M.; Attia, A.M.E.; Patterson, S.E. Tetrahedron Lett. **2000**, *41*, 4757–4761.

5. Abdou, I.M.; Strekowski, L. Tetrahedron **2000**, *56*, 8631–8636.
6. Khodair, A.I.; Ibrahim, E.E.; Al Ashry, E.S.H. Nucleosides Nucleotides **1997**, *16* (4), 433–444.
7. Hussain, S.M.; El-Reedy, A.M.; Rezk, A.M.H.; El-Dien, K.A.S. J. Heterocycl. Chem. **1987**, *24* (6), 1605–1610.

Received September 5, 2001
Accepted November 1, 2001