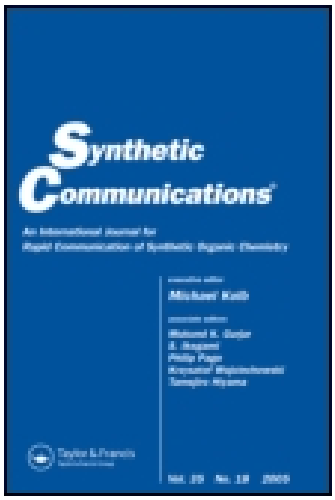

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Jeremy Chmielewski [a], Michelle Haun [a], Krista Topmiller [a], Jacob Ward [a] & Kevin M. Church [a]

[a] Department of Chemistry, University of Dayton, 300 College Park, Dayton, OH, 45469, U.S.A.

Published online: 16 Aug 2006.

To cite this article: Jeremy Chmielewski, Michelle Haun, Krista Topmiller, Jacob Ward & Kevin M. Church (2002) AMINO-THIOCYANATION OF ELECTRON RICH OLEFINS AS AN EFFICIENT PURINE AND PYRIMIDINE N-ALKYLATION PROCESS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:3, 343-353

To link to this article: http://dx.doi.org/10.1081/SCC-120002117

SYNTHETIC COMMUNICATIONS, 32(3), 343–353 (2002)

AMINO-THIOCYANATION OF ELECTRON RICH OLEFINS AS AN EFFICIENT PURINE AND PYRIMIDINE *N*-ALKYLATION PROCESS

Jeremy Chmielewski, Michelle Haun, Krista Topmiller, Jacob Ward, and Kevin M. Church*

Department of Chemistry, University of Dayton,
300 College Park, Dayton, OH 45469

ABSTRACT

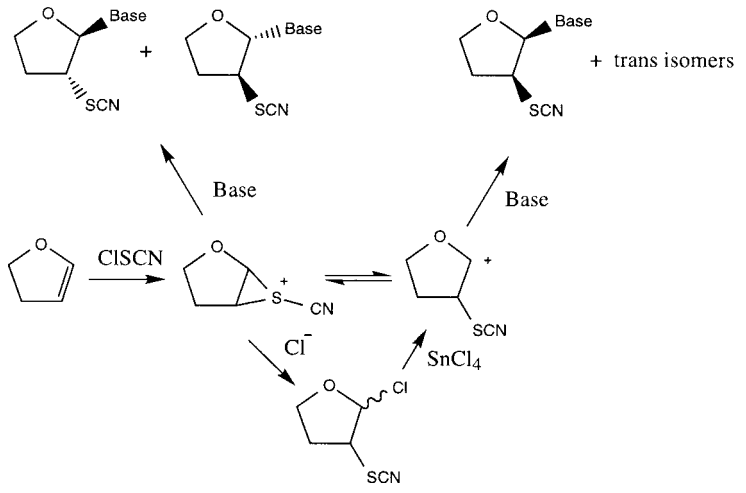
This work describes a relatively simple process to form thiocyanate substituted nucleoside mimics. ClSCN is slowly added to a solution of silylated heterocycle and suitable electron rich alkene. *N*-alkylated heterocycles are isolated in good yields after hydrolytic workup and flash chromatography.

For many years nucleoside mimics have had important uses in the treatment of viral and cancerous disease states.[1] With the development of anti-sense oligonucleotide technology the need for suitably functionalized nucleosides is even greater.[2] Acyclic nucleoside mimics which contain a non cyclic sugar moiety have also shown promise in the treatment of several disease states.[3] Although many synthetic processes have been delineated

*Corresponding author.

to form nucleosides the reaction of most general synthetic use is the *N*-glycosylation process.[4] Here suitably protected reactive sugars are condensed with silylated heterocycles generally giving yields in excess of 80%. Relatively recently several researches have described strategies that utilize protected furals and glycals.[5] In these reactions electrophiles such as RSeCl and RSCl are added across the fural double bond to give β-chloro selenide or sulfide intermediates. These intermediates then undergo *N*-glycosylation with heterocycles in the presence of strong Lewis acid catalysts giving 2′-substituted nucleosides. In many cases good stereo- and regiochemical control can be achieved. In this paper we outline the utility of trapping alkene derived cyclic ion intermediates with silylated heterocycles to give alkylated purines and pyrimidines containing abundant functionality.

We chose chlorothiocyanate (ClSCN) as a reactive electrophile based on its known chemistry of addition across carbon–carbon double bonds to give β-chlorothiocyanates.[6] We envisioned (Scheme 1) reaction of ClSCN with a fural to give a cyclic sulfonium ion that could be trapped with silylated heterocycle to give thiocyanate substituted nucleoside mimics. The trapping of this ion would be expected to give rise to *trans* addition stereochemistry in the final product.[7] The use of a Lewis acid such as $SnCl_4$ could drive product formation via the open carbocation giving a mixture of *cis* and *trans* addition products. We sought to eliminate this possibility by not including a Lewis acid and relying on the reactivity of the electrophile for product formation.



Scheme 1.

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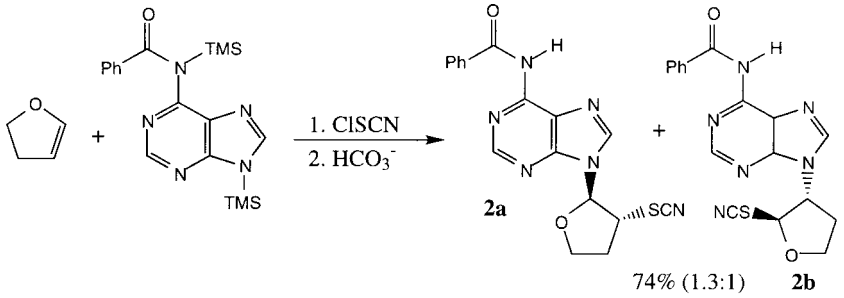

Figure 1.

Our first attempt at this strategy involved *N*-6-benzoyladenine as the heterocyclic partner (See Figure 1). *N*-6-Benzoyladenine was silylated by refluxing in hexamethyldisilizane as before.[8] 2,3-Dihydrofuran was added and ClSCN slowly added to the reagents in 1,2-dichloroethane. Upon hydrolytic workup the alkylated heterocycle was isolated as a mixture of regioisomers **2a** and **2b** in 74% yield. Significantly no *cis* isomer could be isolated in either case.[9] Compounds **2a** and **2b** exhibited identical UV absorption spectra with a λ max of 280 nm. This result allowed us to determine the *N*-9 alkylation pattern rather than reaction at *N*-7 of *N*-6 benzoyladenine.[10] Presumably **2a** and **2b** are formed by attack of the nucleophilic silylated heterocycle at either C-2 or C-3 of the alkene derived cyclic intermediate. The ^{1}H and ^{13}C NMR spectra of **2a** and **2b** are very similar but it was possible to assign the regioisomers by noting the chemical shift of the carbon bearing the heterocycle in each case. In **2a** this carbon is adjacent to two electronegative atoms (N and O) whereas in **2b** the same carbon is adjacent to an O and an S. The ^{13}C NMR shifts of **2a** and **2b** are respectively 91.4 and 86.6 ppm.[11]

Several other electron rich alkenes gave acceptable yields (Table 1) outlining the general synthetic utility of the process. Vinyl ethers and vinyl amines work well in this process presumably due to their high rate of reaction with ClSCN to form reactive intermediates. Less reactive alkenes such as 1-hexene and styrene failed in this reaction. Phenylvinylsulfide and vinyldiphenylphosphine, although electron rich, also failed. We attribute this result to possible side reactions of sulfur and phosphorus with ClSCN rather than addition to the double bond of the alkene. This process was also extended to the formation of pyrimidine analogs. When ClSCN was added to a solution of *N*-vinylcarbazole and silylated thymine in 1,2-dichloroethane the adduct **8** was isolated in 82% yield after hydrolytic workup (Figure 2). No other alkylated products were formed.

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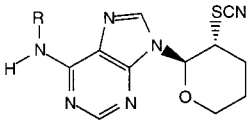
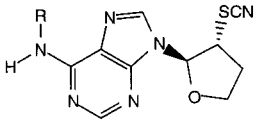
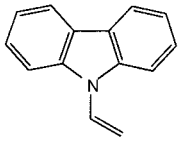
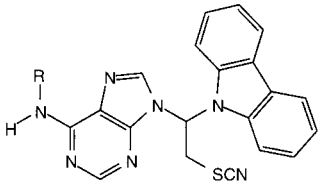
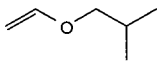
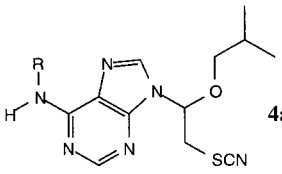
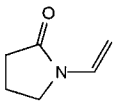
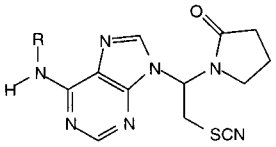
Table 1. Formation of Adenosine Analogs via Amino-Thiocyanation of Electron Rich Alkenes

Entry	Alkene[a]	Major Product[b]	Yield %[c]
1		 **1a**	57 (2.2:1)
2		 **2a**	74 (1.3:1)
3		 **3a**	79 (4.1:1)
4		 **4a**	47 (1.6:1)
5		 **5a**	67 (9.1:1)

a. 2 equiv. of both alkene and ClSCN used. b. Structure of major product N9 regioisomer shown c. Isolated yields after flash chromatography, ratio indicates the major/minor regioisomer ratio.

Alkylation at the *N*-1 position of Thymine rather than *N*-3 was made apparent by the presence of a broad singlet in the ^{1}H NMR spectrum at 11.52 ppm indicating a free succinimide proton. Again the synthetic utility is evident from the outcome of reactions with other olefins (Table 2). In the pyrimidine case again only the *trans* addition products **6** and **7** are formed. This result would tend to argue against the intermediacy of a carbocationic

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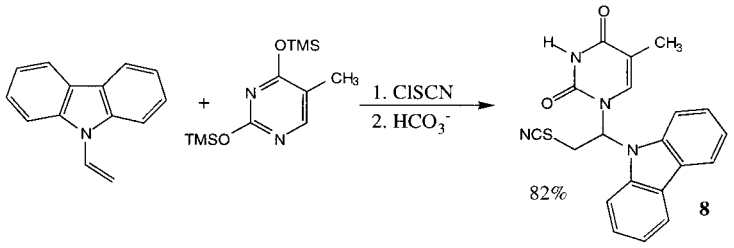


Figure 2.

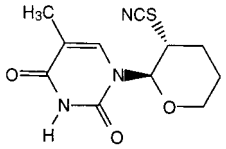
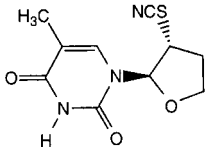
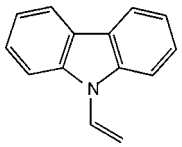
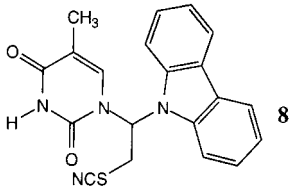
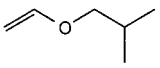
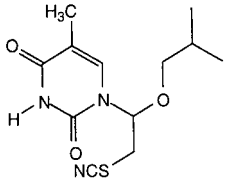
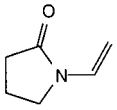
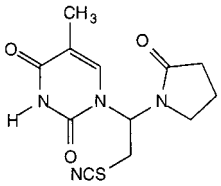
intermediate as in Scheme 1. Compounds **3**, **5**, **8** and **10** all being formed from stable vinyl amines indicate the possibility of generating pyrrolidino based nucleoside analogs via this chemistry.

Although the two different heterocycle alkylations were performed under the same conditions the lack of isomer formation in the Thymine case indicates a somewhat different mechanism. In the *N*-6-Benoyladenine case it appears that product formation arises from attack on a cyclic intermediate as in Scheme 1 to give two regioisomers whereas in the Thymine case product formation may be completely via the open resonance stabilized cation. Differences in mechanism could also be due to differences in the nucleophilicity of the silylated heterocycle.

EXPERIMENTAL

All chemicals and solvents were of reagent grade purity and used without further purification. *N*-6-Benzoyladenine was purchased from Aldrich and used directly in the silylation reaction. All flash chromatographic purifications were performed utilizing Merck 60 silica gel. Whatman glass backed UV indicator impregnated 0.25 μ analytical tlc plates were used exclusively. Analytical HPLC determinations were carried out on a Waters Baseline 810 chromatography workstation utilizing a 100 angstrom Deltapak C-18 column. Elution was carried out at a 2 mL/min flow rate with isocratic water/methanol solvent mixtures and UV detection at 254 nm. NMR determinations were carried out on a JEOL-FX270 instrument operating at 269.65 MHz for ^{1}H and 67.8 MHz for ^{13}C. Frequencies are reported in parts per million (ppm) downfield from the internal reference tetramethylsilane. NMR solvent utilized unless otherwise noted was deuterochloroform. Coupling constants are in hertz. High resolution mass spectra were determined in either the Electron

Table 2. Formation of Thymidine Analogs via Amino-Thiocyanation of Electron Rich Alkenes

Entry	Alkene[a]	Product	Yield %[b]
1		 **6**	62
2		 **7**	75
3		 **8**	82
4		 **9**	71
5		 **10**	50

a. 2 equiv. of both alkene and ClSCN used. b. Isolated yields after flash chromatography.

Impact or Fast Atom Bombardment mode. Representative synthetic procedures for the amino thiocyanation process follow. Full spectral data for major isomers shown.

6-*N*-Benzoyl-9-[(3-thiocyanato)-2-pyranyl]adenine: 1a *N*-6-Benzoyladenine (0.6 g, 2.51 mmol) was silylated by refluxing in 30 mL of HMDS

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containing 30 mg of $(NH_4)_2SO_4$ for 5 h. Excess HMDS was removed *in vacuo* and co-evaporated once with toluene to give a yellow syrup. In a separate reaction vessel chlorothiocyanate was generated by the addition of 5.2 mL of 1 M SO_2Cl_2 (5 mmol) in dichloromethane to a suspension of 0.84 g (2.5 mmol) of $Pb(SCN)_2$ in 10 mL of dichloromethane at 25°C. This solution was stirred for one hour under nitrogen gas atmosphere. The resulting thiocyanate solution was filtered into an addition funnel and slowly added to a solution of the silylated base and 0.69 mL (7.5 mmol) of 2,3-dihydropyran in 5 mL of dichloromethane. The subsequent mixture was allowed to react at 25°C for 18 h under a nitrogen gas atmosphere. The reaction was poured into 150 mL of cold aqueous bicarbonate and stirred for 15 min. This solution was extracted 3X with EtOAc and the combined extracts dried with $MgSO_4$. Subsequent reduction of solvent and flash chromatography on silica gel with 5% acetone in dichloromethane gave the product as a mixture of regioisomers (0.54 g) in 57% yield. HPLC and ^{1}H-NMR analysis showed the isomers were present in a 2.2 to 1 ratio. MP; 83–84°C. HPLC retention times (50% MeOH/50% water); major isomer = 5.88 min, minor isomer = 7.87 min. UV (EtOH); 234 and 281 nm. IR (KBr); 3247, 3090, 2949, 2861, 2155, 1699, 1612, 1582, 1453, 1334, 1249, 1073, 945, 797, 710 cm^{-1}. ^{1}H-NMR; 9.25 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 8.03 (d, 2H, J = 7.7), 7.61 (t, 1H, J = 6.9), 7.52 (t, 2H, J = 7.6), 5.65 (d, 1H, J = 9.9), 4.29 (m, 2H), 3.82 (t, 1H, J = 10.6), 2.63 (m, 1H), 2.22–1.83 (m, 3H). ^{13}C-NMR; 164.7, 153.0, 151.7, 150.0, 142.1, 133.6, 132.9, 128.9, 127.9, 123.3, 108.6, 85.9, 68.7, 45.8, 31.2, 26.1. EI-HRMS; $C_{18}H_{16}N_6O_2S$ calcd. for 380.1055 (obs. 380.1056). Anal. Calcd. for $C_{18}H_{16}N_6O_2S$: C, 56.83; H, 4.24; N, 22.09. Found: C, 56.97; H, 4.17; N, 22.13.

6-*N*-Benzoyl-9-{[1-(N-carbazoyl)-2-thiocyanato]ethyl}adenine: 3a MP; 117–118°C. HPLC retention time; major 6.3 min and minor 4.46 min (75% MeOH/25% water). UV (EtOH); 231, 248, 283, 289, and 328 nm. IR (KBr); 3251, 3060, 2157, 1702, 1608, 1581, 1484, 1448, 1324, 1246, 1209, 1158, 797, 751, 722 cm^{-1}. ^{1}H-NMR; 9.30 (s, 1H), 8.83 (s, 1H), 8.08 (d, 2H, J = 7.7), 7.95 (s, 1H), 7.91 (d, 2H, J = 7.3), 7.59 (d, 2H, J = 8.0), 7.55–7.20 (m, 8H), 5.07 (dd, 1H), 4.31 (dd, 1H). ^{13}C-NMR; 164.9, 153.0, 152.0, 150.0, 142.0, 135.5, 133.4, 132.9, 128.8, 127.9, 126.9, 124.3, 122.9, 121.5, 121.0, 110.6, 109.7, 66.1, 34.2. FAB-HRMS; $C_{27}H_{20}N_7OS$ calcd. for 490.1450 (obs. 490.1467). Anal. Calcd. for $C_{27}H_{19}N_7OS$: C, 66.24; H, 3.91; N, 20.03. Found: C, 66.35; H, 4.06; N, 20.14.

6-*N*-Benzoyl-9-{[1-(N-pyrrolidinonyl)-2-thiocyanato]ethyl}adenine: 5a HPLC retention time major 5.01 min and minor 3.60 min (50% MeOH/50% water). MP; 126–127°C. UV (EtOH); 231 nm and 280 nm. IR (KBr); 3170, 3087, 2976, 2160, 1680, 1665, 1578, 1513, 1456, 1411, 1250, 896, 736, 707 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$); 11.26 (s, 1H), 8.79 (s, 1H), 8.69

(s, 1H), 8.05 (d, 2H, J = 6.8), 7.58 (mult, 3H), 6.66 (t, 1H, J = 7.7), 4.65 (dd, 1H), 4.55 (dd, 1H), 3.68 (q, 1H, J = 6.0), 3.53 (q, 1H, J = 6.8), 2.30 (m, 2H), 1.95 (m, 2H). ^{13}C-NMR ($DMSO_{d_6}$); 175.1, 165.6, 152.0, 151.7, 150.4, 143.4, 133.2, 132.4, 128.4, 125.1, 62.1, 43.5, 40.9, 29.9, 17.6. FAB-HRMS; $C_{19}H_{18}N_7O_2S$ calcd. for 408.1243 (obs. 408.1219). Anal. Calcd. for $C_{19}H_{18}N_7O_2S$: C, 56.01; H, 4.21; N, 24.06. Found: C, 55.87; H, 4.37; N, 23.94.

6-*N*-Benzoyl-9-[(1-isobutyloxy-2-thiocyanato)ethyl]adenine: 4a HPLC retention time; major 4.33 min and minor 5.02 min (65% MeOH/35% water). MP; 49–50°C. UV (EtOH); 233 nm and 280 nm. IR (KBr); 3246, 3067, 2959, 2158, 1700, 1610, 1580, 1510, 1458, 1251, 1208, 1111, 895, 798, 709 cm^{-1}. ^{1}H-NMR; 9.09 (s, 1H), 8.81 (s, 1H), 8.22 (s, 1H), 8.04 (d, 2H, J = 7.0), 7.55 (m, 3H), 6.00 (t, 1H, J = 5.7), 4.00 (m, 2H), 3.37 (dd, 1H), 3.21 (dd, 1H), 1.91 (m, 1H), 0.90 (dd, 6H). ^{13}C-NMR; 164.8, 152.9, 152.1, 149.7, 140.8, 133.6, 132.8, 128.9, 127.9, 123.1, 84.3, 44.7, 28.3, 19.0. EI-HRMS; $C_{19}H_{20}N_6O_2S$ calcd. for 396.1368 (obs. 396.1346). Anal. Calcd. for $C_{19}H_{20}N_6O_2S$: C, 57.56; H, 5.08; N, 21.20. Found: C, 57.52; H, 5.05; N, 21.26.

6-*N*-Benzoyl-9-[(3-thiocyanato)-2-furanyl]adenine: 2a HPLC retention time; major 4.15 min and minor 4.88 min (50% MeOH/50% water). MP; 70–72°C. UV (EtOH); 233 and 281 nm. IR (KBr); 3100, 2967, 2899, 2156, 1699, 1612, 1579, 1453, 1250, 1068, 797, 710 cm^{-1}. ^{1}H-NMR; 9.27 (s, 1H), 8.79 (s, 1H), 8.18 (s, 1H), 8.06–8.02 (m, 2H), 7.61–7.50 (m, 3H), 6.48 (d, 1H, J = 5.6), 4.59 (m, 1H), 4.36 (m, 1H), 4.20 (m, 1H), 2.79 (m, 2H). ^{13}C-NMR; 164.8, 152.9, 151.3, 149.9, 141.2, 133.6, 132.8, 128.9, 127.9, 123.2, 109.3, 86.6, 68.3, 49.2, 31.5. EI-HRMS; $C_{17}H_{14}N_6O_2S$ calcd. for 366.0898 (obs. 366.0895). Anal. Calcd. for $C_{17}H_{14}N_6O_2S$: C, 55.73; H, 3.85; N, 22.92. Found: C, 55.57; H, 4.00; N, 22.87.

1-[(3-Thiocyanato)-2-pyranyl]thymine: 6 HPLC retention time; 3.71 min (35% MeOH/65% water). MP; 169–170°C. IR (KBr); 3020, 2842, 2157, 1704, 1665, 1479, 1431, 1300, 1258, 1211, 1134, 1076, 1042, 952, 758 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$); 11.48 (s, 1H), 7.56 (s, 1H), 5.62 (d, 1H, J = 10.1), 3.99 (t, 2H), 3.67 (t, 1H), 2.29 (d, 1H), 1.92 (m, 1H), 1.79 (s, 3H), 1.73 (m, 2H). ^{13}C-NMR ($DMSO_{d_6}$); 163.4, 150.5, 135.9, 110.1, 108.7, 83.0, 67.6, 45.6, 29.9, 25.6, 11.9. EI-HRMS; $C_{11}H_{13}N_3O_3S$ calcd. for 267.0677 (obs. 267.0674). Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72. Found: C, 49.36; H, 4.94; N, 15.85.

1-{[1-(*N*-Carbazoyl)-2-thiocyanato]ethyl}thymine: 8 HPLC retention time; 4.43 min (60% MeOH/35% water). MP; 211–212°C. IR(KBr); 3160, 3039, 2831, 2150, 1690, 1448, 1426, 1274, 1213, 1196, 1126, 751 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$, $CDCl_3$); 11.52 (s, 1H), 8.09 (d, 2H, J = 7.4), 7.88 (d, 2H, J = 8.3), 7.81 (s, 1H), 7.47 (t, 2H, J = 7.4), 7.36 (t, 1H, J = 7.4), 7.28 (t, 2H, J = 7.4),

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4.67 (dd, 1H), 4.35 (dd, 1H), 1.79 (s, 3H), ^{13}C-NMR ($DMSO_{d_6}$, $CDCl_3$); 163.5, 151.1, 139.2, 136.2, 126.3, 123.5, 120.5, 120.2, 111.1, 110.8, 110.7, 65.4, 34.1, 12.4. EI-HRMS; $C_{20}H_{16}N_4O_2S$ calcd. for 376.0993 (obs. 376.0986). Anal. Calcd. for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.82; H, 4.40; N, 14.77.

1-{[1-(*N*-Pyrrolidinonyl)-2-thiocyanato]ethyl}thymine: 10 HPLC retention time; 5.78 min (20% MeOH/80% water). MP; 204–205°C. IR (KBr); 3173, 3027, 2836, 2154, 1724, 1700, 1427, 1364, 1291, 1270, 1221, 1115, 762 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$); 11.41 (s, 1H), 7.58 (s, 1H), 6.15 (t, 1H, J = 7.4), 3.89 (m, 2H), 3.49 (hex., 2H, J = 8.8), 2.29 (t, 2H, J = 9.9), 1.95 (t, 2H, J = 6.9), 1.78 (s, 3H). ^{13}C-NMR ($DMSO_{d_6}$); 175.4, 163.6, 150.6, 138.4, 112.2, 109.1, 64.3, 44.7, 32.4, 30.2, 17.9, 12.0. FAB-HRMS; $C_{12}H_{15}N_4O_3S$ calcd. for 295.0864 (obs. 295.0876). Anal. Calcd. for $C_{12}H_{14}N_4O_3S$: C, 48.97; H, 4.79; N, 19.04. Found: C, 48.90; H, 4.75; N, 19.11.

1-[(3-Thiocyanato)-2-furanyl]thymine: 7 HPLC retention time; 7.58 min (25% MeOH/75% water). MP; 209–210°C. IR (KBr); 3084, 3016, 2830, 2158, 1708, 1666, 1477, 1272, 1102, 899 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$); 11.42 (s, 1H), 7.52 (s, 1H), 5.94 (d, 1H, J = 5.2), 4.28 (m, 2H), 4.05 (quart, 1H, J = 5.2), 2.58 (hex, 1H, J = 6.1), 2.21 (hex, 1H, J = 7.5), 1.80 (s, 3H). ^{13}C-NMR ($DMSO_{d_6}$); 163.8, 150.5, 136.1, 111.1, 109.8, 89.8, 68.0, 47.8, 31.4, 12.1. EI-HRMS; $C_{10}H_{11}N_3O_3S$ calcd. for 253.0521 (obs. 253.0521). Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.59. Found: C, 47.51; H, 4.42; N, 16.66.

1-[(1-Isobutyloxy-2-thiocyanato)ethyl]thymine: 9 HPLC retention time; 7.49 min (50% MeOH/50% water). MP; 175–176°C. IR (KBr); 3170, 3042, 2958, 2158, 1711, 1678, 1474, 1279, 1216, 1127, 1091 cm^{-1}. ^{1}H-NMR ($DMSO_{d_6}$); 11.33 (brd. s, 1H), 7.55 (s, 1H), 5.79 (t, 1H, J = 6.2), 3.55 (dd, 2H, J = 2.2, 6.1), 3.23 (dd, 2H, J = 1.8, 6.2), 1.83 (hept., 1H, J = 6.6), 1.79 (s, 3H), 0.87 (dd, 6H, J = 1.8, 6.6). ^{13}C-NMR ($DMSO_{d_6}$); 163.6, 150.9, 135.0, 112.4, 110.1, 82.7, 75.07, 35.2, 27.6, 18.9, 12.1. EI-HRMS; $C_{12}H_{17}N_3O_3S$ calcd. for 283.0990 (obs. 283.0992). Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83. Found: C, 50.77; H, 6.07; N, 14.64.

ACKNOWLEDGMENTS

We would like to thank the Department of Chemistry and the Honors Program at the University of Dayton for funding this project. Mass spectral determinations were carried out at the Chemical Instrumentation Center of

the Ohio State University. Elemental analysis determinations were carried out by Onieda Research Services.

REFERENCES

1. Mitsuya, H.; Yarchoan, R.; Broder, S. Science **1990**, *249*, 1533–1543.
2. Cook, P. Dan. Anti-Cancer Drug Design **1991**, *6*, 585–607.
3. Abu, S.; Tramontano, E.; Loi, G.; Franchetti, P.; Grifantini, M.; La Colla, P. Nucleosides & Nucleotides **1999**, *18*(4 & 5), 849–851. Smeijsters, L.; Franssen, F.; Naesens, L.; De Vries, E.; Holy, A.; Balzarini, J.; De Clerq, E.; Overdulve, J. Int. J. Antimicrob. Agents **1999**, *12*(1), 53–61. Meier, C.; Habel, L.; Haller-Meier, F.; Lomp, A.; Herderich, M.; Klocking, R.; Meerbach, A.; Wutzler, P. Antiviral Chem. Chemother. **1998**, *9*(5), 389–402.
4. Wilson, L.; Hager, M.; El-Kattan, A.; Liotta, D. Synthesis **1995**, 1465–1479.
5. Diaz, Y.; El-Laghdach, A.; Castillon, S.; Tetrahedron **1997**, *53*(31), 10921–10938. Kawakami, H.; Ebata, T.; Koseski, K.; Okano, K.; Katsuya, M.; Matsushita, H. Heterocycles **1993**, *36*(4), 665–669. El-Laghdach, A.; Matheu, M.; Castillon, S. Tetrahedron **1994**, *50*(42), 12219–12234. Wang, J.; Wurster, J.; Wilson, L.; Liotta, D. Tet. Lett. **1993**, *34*(31), 4881–4884. Stewart, D.; Trauth, J.; Windholtz, J.; Church, K. Synth. Commun. **1996**, *26*(22), 4279–4288. El-Laghdach, A.; Diaz, Y.; Castillon, S. Tet. Lett. **1993**, *34*(17), 2821–2822.
6. Vasileva, M.; Bychkova, T.; Ivanova, N.; Dobrynina, L.; Kalabina, A. Zh. Org. Khim. **1986**, *22*(6), 1165–1168.
7. Guy, R.; Pearson, I. J. Chem. Soc. Perkin. Trans. I **1973**, 281–284.
8. Niedballa, U.; Vorbruggen, H. J. Org. Chem. **1974**, *39*(25), 3654–3660. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Chem. Ber. **1981**, *114*, 1234–1255.
9. Proton coupling constants of the protons on C2 and C3 of compounds **1a**, **2a**, **6** and **7** were used to assign their relative stereochemistry. **1a** ($J_{2,3} = 9.9$ Hz), **2a** ($J_{2,3} = 5.6$ Hz), **6** ($J_{2,3} = 10.1$), **7** ($J_{2,3} = 5.2$ Hz). For examples of coupling constants in these types of systems see Fuertes, M.; Garcia-Munoz, G.; Madronero, R.; Stud, M. Tetrahedron **1972**, *28*, 623–635. Leutzinger, E.; Bowles, W.; Robins, R.; Townsend, L. J. Amer. Chem. Soc. **1968**, *90*(1), 150.
10. Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. J. Org. Chem. **1993**, *58*, 2977–2982. Baud, M.; Chavis, C.; Lucas, M.; Imbach, J. Tetrahedron **1991**, *47*(48), 9993–10002.

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Bessodes, M.; Lakaf, R.; Antonakis, K. Carbohydrate Res. **1986**, *148*, 148–152.

11. UV and ^{13}C-NMR (carbon bearing the heterocycle) chemical shift data of the major and minor isomers; **1a** and **1b** through **5a** and **5b**.

Compounds	UV (EtOH, nm)	^{13}C NMR (ppm, $DMSO_{d_6}$)
1a	234, 281	85.9
1b	234, 281	84.3
2a	233, 281	91.4
2b	233, 281	86.6
3a	231, 282, 329	66.8
3b	231, 282, 329	66.1
4a	233, 280	84.3
4b	232, 279	81.7
5a	231, 280	73.6
5b	231, 280	62.1

Received in the USA March 19, 2001

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