Bridgehead Nitrogen Heterocycles Derived from the Potassium Salt of 2,3,5,6,7,8-Hexahydro-3-amino-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one

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Derivatives of tetraheterocyclic linear system **2**, **4** and **5** were prepared by reacting the potassium salt **1** with the appropriate *alpha*-halocarbonyl compounds. Moreover, through reaction of methyl mercapto **6** with hydrazine the new heterocyclic system 1,4,7,8,9,10-hexahydro-6*H*-[1]benzothieno[2',3':4,5]pyrimido[1,2-*b*]-[1,2,4,5]tetrazin-6-one (**8**) was also obtained.

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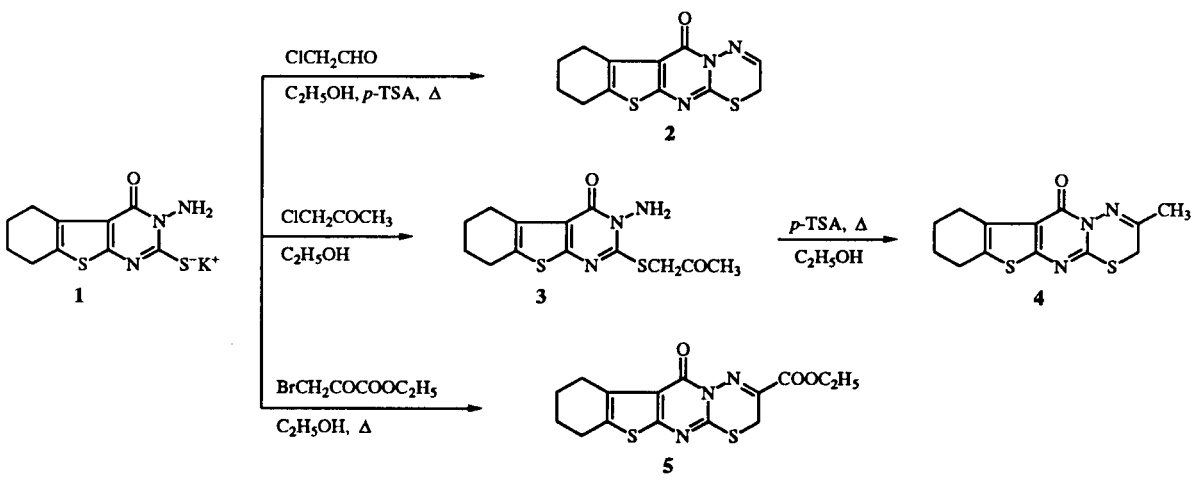
In a recent paper [1] we have described the preparation of 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[1]benzothieno-[2,3-*d*]pyrimidin-4(1*H*)-one and of its potassium salt **1**, which are versatile intermediates for the preparation of bridgehead nitrogen polyheterocycles, due to the presence of two adjacent reactive functional groups.

In this paper we report the syntheses of three new derivatives **2**, **4** and **5** from intermediate **1**, containing the thieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine system, and of a new heterocyclic system **8**, having a 1,2,4,5-tetrazine ring.

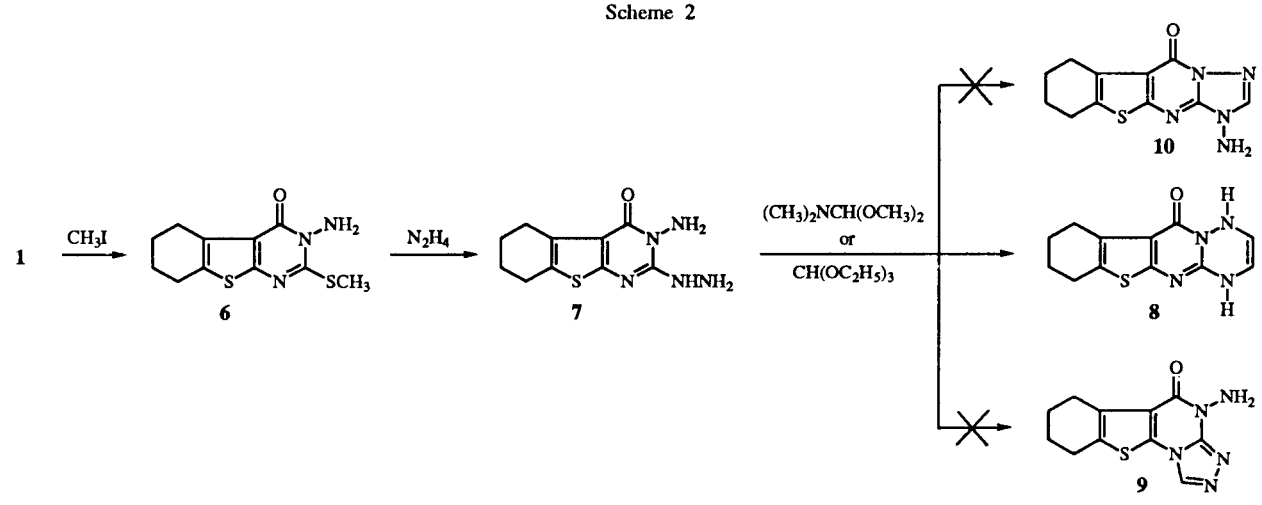
The syntheses of unsubstituted 7,8,9,10-tetrahydro-3*H*, 11*H*-[1]-benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazin-11-one (**2**) and of its 2-methyl **4** and ethyl 2-carboxylate **5** derivatives were achieved by starting from the potassium salt **1** and the appropriate *alpha*-halocarbonyl compounds through different routes (Scheme 1). The unsubstituted heterocycle **2** was obtained by adding *p*-toluensulfonic acid (*p*-TSA) to the refluxing ethanolic solution of the reaction mixture of **1** and chloroacetaldehyde. The methyl derivative **4** was prepared by heating in ethanol in the presence of *p*-toluensulfonic acid the derivative **3**, previously obtained from **1** and chloroacetone. The ethyl ester derivative **5** was obtained by reacting in refluxing ethanol compound **1** with ethyl bromopyruvate. The structures of heterocycles **2**, **4** and **5** were supported by elemental analyses and ir, ^{1}H nmr and mass spectra. Consistently with the proposed structures the ir and ^{1}H nmr spectra of compounds **2**, **4** and **5** did not show signals attributable to NH_2 or NH groups. In the ^{1}H nmr spectra of **2**, **4** and **5** methylene resonances at δ 3.55, 3.44 and 3.93, respectively, attributable to methylene hydrogens adjacent to a sulfur atom, confirmed the formation of a thiadiazine ring. Moreover, the ^{1}H nmr spectrum of compound **2** showed confirmatory resonances at δ 7.85 (t, 1H-2, J = 4.3 Hz) and at δ 3.55 (d, 2H-3, J = 4.3 Hz).

Treatment of the methylmercapto derivative **6** with hydrazine gave the 2-hydrazino derivative **7**, which by cyclocondensation with triethyl orthoformate or *N*,*N*-dimethylformamide dimethyl acetal afforded only one product identified as the new heterocycle **8** (Scheme 2). Efforts to isolate the isomers **9** and **10** were unsuccessful, thus indicating that probably these isomers were not formed under our reaction conditions. Assignment of the structure

Scheme 1



Scheme 2



to compound **8** was obtained by elemental analysis, and ir, ^{1}H nmr and mass spectra. Diagnostically important signals in the ^{1}H nmr spectrum of **8** were a singlet at δ 9.77 attributable to the N-1 proton, a doublet at δ 9.59 (J = 2.5 Hz) attributable to the N-4 proton which, in turn, was coupled with the C-3 proton, whose signal failed at δ 7.00 (d, J = 2.5 Hz). As expected for the proposed structure, in presence of deuterium oxide, the signals due to the NH groups disappeared and the signal attributable to H-3 became a singlet.

EXPERIMENTAL

All melting points were taken in open capillaries using a Gallemkamp melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 281 spectrometer in potassium bromide disks. Elemental analyses for C, H, N and S were obtained on an EA1108 Elemental Analyzer Fisons-Carlo Erba instruments. The low resolution mass spectra were recorded by direct insertion into the ion source on a VG-2AB2SE mass spectrometer under the following conditions: ionization energy, 70 eV; source temperature 250-300°; trap current 60 μA. The sample temperature ranged from room temperature to 300°. The ^{1}H-nmr spectra were recorded on a Bruker AC 250 spectrometer operating at 250 MHz Chemical shifts are reported in δ ppm from TMS as the internal standard. The purity of the compounds was checked by tlc (pre-coated Silica Gel plates Merck kiesegel 60 F_{254}).

7,8,9,10-Tetrahydro-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido-[2,1-*b*][1,3,4]thiadiazin-11-one (**2**).

A mixture of potassium salt **1** [1] (0.30 g, 1.02 mmoles) and of chloroacetaldehyde (0.2 ml, 50%, d = 1.236) in ethanol (50 ml) was refluxed under stirring for 1 hour. The mixture was filtered while hot and the filtrate, after addition of *p*-TSA (50 mg), was then refluxed for 1 hour. After cooling, the resulting solid was collected, washed with a little amount of warm ethanol, dried and crystallized from dioxane to give **2** as white solid (90 mg, 32%), mp 240-242° dec. After concentration of the filtrate and crystallization of the resulting crude product, other 60 mg were obtained; ir: ν 1680 (C=O) cm^{-1}; ms: m/z 277 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 7.85 (t, 1H-2, J = 4.3 Hz), 3.55 (d, 2H-3, J = 4.3 Hz), 3.00 (m, 2H-10), 2.74 (m, 2H-7), 1.86 (m, 2H-8 and 2H-9).

Anal. Calcd. for $C_{12}H_{11}N_3OS_2$: C, 51.98; H, 3.97; N, 15.16; S, 23.10. Found: C, 51.55; H, 3.95; N, 14.70; S, 22.80.

5,6,7,8-Tetrahydro-3-amino-2[(2-oxopropyl)thio]-[1]benzothieno-[2,3-*d*]pyrimidin-4(3*H*)-one (**3**).

A mixture of **1** (0.55 g, 1.8 mmoles) and chloroacetone (0.2 ml, 96%, d = 1.16) in ethanol (25 ml) was gently warmed under stirring for 2 hours. The mixture was then poured into water (100 ml) and the resulting solid was collected, dried and crystallized from ethanol/water to give **3** as white solid (0.3 g, 51%), mp 145-147° dec; ir: ν 3320 and 3220 (NH$_2$), 1725 and 1680 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}N_3O_2S_2$: C, 50.48; H, 4.85; N, 13.59; S, 20.71. Found: C, 50.90; H, 4.60; N, 13.75; S, 21.05.

7,8,9,10-Tetrahydro-2-methyl-3*H*,11*H*-[1]benzothieno[2',3':4,5]-pyrimido[2,1-*b*][1,3,4]thiadiazin-11-one (**4**).

A mixture of **3** (0.3 g, 0.97 mmole) and of *p*-TSA (20 mg) in ethanol (25 ml) was refluxed for 2 hours. The solution was then cooled to room temperature. The resulting precipitate was collected, dried and recrystallized from ethanol to give **4** as bright yellow needles (150 mg, 53%), mp 220-222°; ir: ν 1680 (C=O) cm^{-1}; ms: m/z 291 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 3.44 (s, 2H-3), 2.94 (m, 2H-10), 2.72 (m, 2H-7), 2.44 (s, 3H, CH$_3$), 1.83 (m, 2H-8 and 2H-9).

Anal. Calcd. for $C_{13}H_{13}N_3OS_2$: C, 53.61; H, 4.47; N, 14.43; S, 21.99. Found: C, 53.20; H, 4.45; N, 14.15; S, 21.60.

Ethyl Ester of 7,8,9,10-Tetrahydro-3*H*-11-oxo[1]benzothieno-[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine-2-carboxylic Acid (**5**).

A mixture of **1** (0.5 g, 1.7 mmoles) and of ethyl bromopyruvate (0.2 ml, 90%, d = 1.554) in ethanol (50 ml) was refluxed for 3 hours. The mixture was filtered while hot and the filtrate cooled to room temperature. The resulting precipitate was collected, dried and recrystallized from ethanol to give **5** as a yellow powder (180 mg, 30%), mp 178-179° dec; ir: ν 1730 and 1700 (C=O) cm^{-1}; ms: m/z 349 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 4.43 (q, 2H, OCH$_2$), 3.94 (s, 2H-3), 2.95 (m, 2H-10), 2.73 (m, 2H-7), 1.84 (m, 2H-8 and 2H-9), 1.41 (t, 3H, CH$_3$).

Anal. Calcd. for $C_{15}H_{15}N_3O_3S_2$: C, 51.58; H, 4.30; N, 12.03; S, 18.34. Found: C, 51.15; H, 4.35; N, 11.80; S, 17.90.

5,6,7,8-Tetrahydro-3-amino-2-(methylthio)-[1]benzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (**6**).

A mixture of **1** (2.2 g, 7.6 mmoles), and methyl iodide (1.5 ml, 99%, d = 2.27) in water (100 ml) was stirred at room temperature for 1.5 hours. The resulting solid was collected, washed with petroleum ether, dried and crystallized from 2-propanol to give **6** as white needles (1.5 g, 74%), mp 156-157°; ir: ν 3330 and 3210 (NH_2), 1680 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}N_3OS_2$: C, 49.44; H, 4.87; N, 15.73; S, 23.97. Found: C, 49.40; H, 4.80; N, 15.40; S, 23.50.

5,6,7,8-Tetrahydro-3-amino-2-hydrazino-[1]benzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (**7**).

A mixture of **6** (0.33 g, 1.2 mmoles), hydrazine hydrate (5 ml, 98%, d = 1.032) and 2-propanol (5 ml) was refluxed for 8 hours. After cooling, the resulting solid was collected, dried and crystallized from ethanol/dioxane to give **7** as colorless needles (0.15 g, 48%) mp 244-245°; ir: ν 3330 and 3150 (NH_2 or NH), 1670 (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_5OS$: C, 47.81; H, 5.18; N, 27.89; S, 12.75. Found: C, 47.50; H, 5.40; N, 27.55; S, 12.45.

1,4,7,8,9,10-Hexahydro-6*H*-[1]benzothieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one (**8**).

A mixture of **7** (0.3 g, 1.1 mmoles), ethyl orthoformate (0.2 ml, 98%, d = 0.89) and acetic acid (5 ml) was refluxed for 30 minutes. The solution was then cooled to room temperature and the resulting solid was collected, washed with diethyl ether, dried and recrystallized from ethanol/dioxane to give **8** as white powder (100 mg, 32%), mp 261-263°; ir: ν 3320 (NH), 1675 (C=O), 1655 (C=N) cm^{-1}; ms: m/z 261 (M^+); ^1H nmr (DMSO-d_6): δ 9.77 (s, 1H-1, deuterium oxide exchangeable), 9.59 (d, 1H-4, J = 2.5 Hz, deuterium oxide exchangeable), 7.00 (d, 1H-3, J = 2.5 Hz), 2.75 (m, 2H-7), 2.61 (m, 2H-10), 1.72 (m, 2H-8 and 2H-9).

Anal. Calcd. for $C_{11}H_{11}N_5OS$: C, 50.57; H, 4.21; N, 26.82; S, 12.26. Found: C, 50.40; H, 4.30; N, 26.45; S, 12.00.

A mixture of **7** (0.65 g, 2.5 mmoles), *N,N*-dimethylformamide dimethyl acetal (0.35 ml, 94%, d = 0.87) and acetic acid (4.5 ml) was stirred at room temperature for 3 hours. The suspended product was then collected, washed with ethanol, dried and crystallized from ethanol/dioxane to give **8** as white powder (150 mg, 22%).

REFERENCES AND NOTES

[1] A. Santagati, M. Santagati and M. Modica, *Heterocycles*, **36**, 1315 (1993).