

HETEROCYCLES, Vol. 85, No. 10, 2012, pp. 2473 - 2483. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 11th July, 2012, Accepted, 2nd August, 2012, Published online, 8th August, 2012
DOI: 10.3987/COM-12-12546

SYNTHESIS OF 2- AND 6-(DIALKYLAMINOALKYLTHIO)- AND 2,6-BIS(DIALKYLAMINOALKYLTHIO)-7-METHYLPURINES

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Abstract – An efficient synthesis of 21 new thiopurines being 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines, 6-substituted 2-(dialkylaminoalkylthio)-7-methylpurines, and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines was reported. 2-Substituted 6-(dialkylaminoalkylthio) and 2,6-bis(dialkylaminoalkylthio) derivatives were obtained *via* direct *S*-dialkylaminoalkylation of the appropriate purinethiones. The different reactivities of the dialkylaminoalkylthio groups in positions 2 and 6 towards sodium alkoxides were the key processes in a few step synthesis of 2-(dialkylaminoalkylthio) derivatives from 2,6-bis(dialkylaminoalkylthio) derivatives.

INTRODUCTION

The purine ring system is a key structural element of substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins, and polymerases.¹ Thiopurine antimetabolites such as 6-mercaptopurine, 6-thioguanine and azathioprine form an important group of cytotoxic drugs used in treating in several diseases including cancer. They have been used as immunosuppressants and anti-inflammatory agents in organ transplantation and chemotherapy, exhibited antineoplastic, antileukemic, antiviral, antibacterial and antifungal activities.²⁻⁸

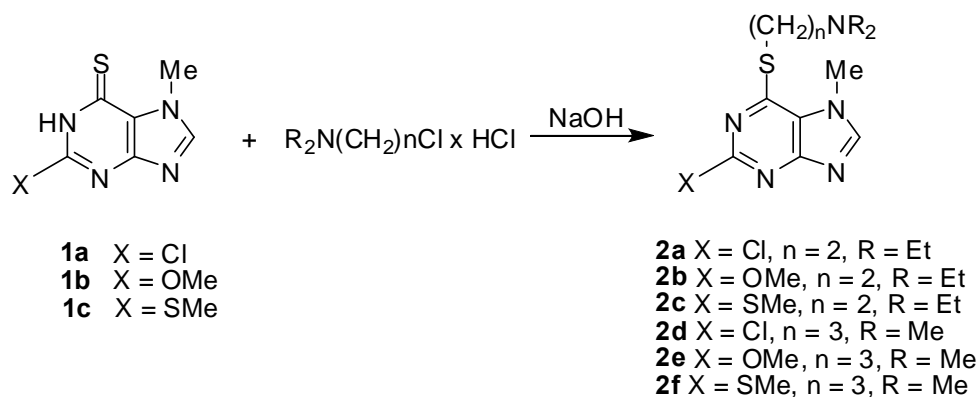
6-Substituted mercaptopurine derivatives possessing the pyrimidyl, imidazolyl, quinolyl¹ or aminoalkyl⁹ groups at the sulfur atom were very effective against *Mycobacterium paratuberculosis*,^{1,10} *Leishmania amazonensis* and *L. chagasi*.⁹ Alkylaminoalkylthiopurines alone¹¹ and with the phenyl or pyridyl substituents¹² showed antibacterial¹² and antithrombotic activities.¹¹ There was also described the synthesis of the thiopurinyl piperazine derivatives useful as cardiogenic and antiarrhythmic agents¹³ and the quinoline,² steroid, and triazole¹⁴ conjugates with 6-mercaptopurine possessing antimalarial and antileishmanial activity.^{1,14}

Recently it has been revealed a new mechanism of action the thiopurine drugs by which they regulate dendritic cells (DC) integrated functions, inducing a functionally less immunogenic phenotype.¹⁵ 6-Thioguanine (6-TG) incorporated into the DNA of macrophages sensitizes them to killing by endogenously produced reactive oxygen species. The findings suggests that the low oxidation potential of DNA 6-TG may influence the immunomodulatory effects of thiopurines and suggests a potential new therapeutic role for this long established class of drugs.¹⁶

In our previous papers,^{17,18} we reported the effective synthesis of the azathioprine analogs containing one or two 1-methyl-4-nitroimidazol-5-yl groups at the sulfur atom in positions 2 or/and 6 of 7-methylpurines. In continuation of our studies on the thiopurine derivatives, we describe in this paper the synthesis of a series of new 7-methylpurines with pharmacophoric dialkylaminoalkyl substituents: diethylaminoethyl, dimethylaminopropyl, pyrrolidinyethyl, piperidinyethyl and morpholinylethyl groups at the sulfur atoms in positions 2 and 6.

RESULTS AND DISCUSSION

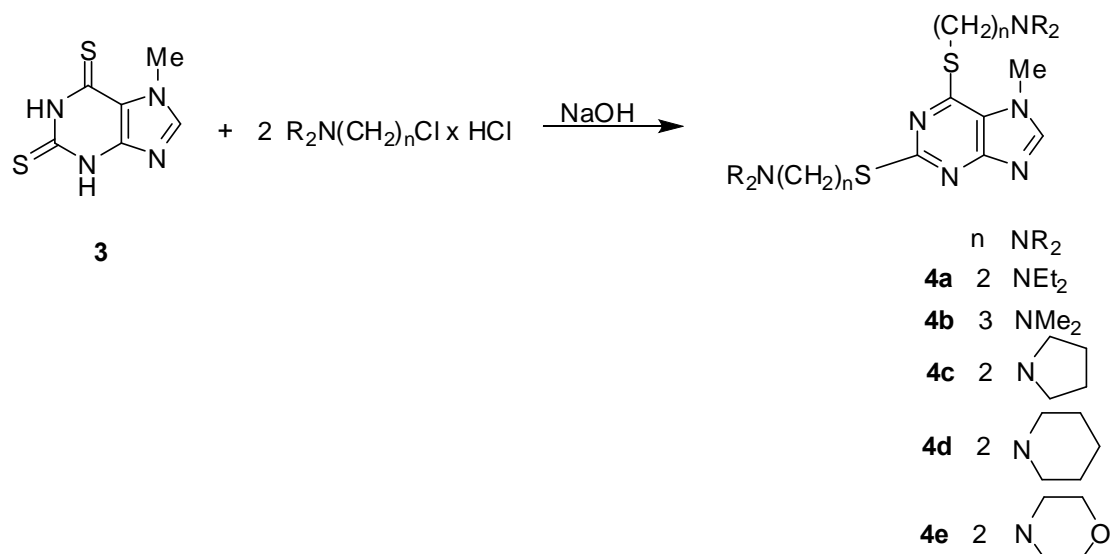
We started our synthesis from the reactions of 2-substituted 7-methyl-6-purinethiones **1a-c**, possessing the chloro, methoxy and methylthio groups, with hydrochlorides of 2-diethylaminoethyl or 3-dimethylaminopropyl chlorides in boiling ethanol in the presence of sodium hydroxide to give 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines **2a-f** in very good yields (77.5-95%, Scheme 1).



Scheme 1

When the similar reactions were carried out using 7-methyl-2,6-dithioxanthine (**3**) and hydrochlorides of dialkylaminoalkyl chlorides in refluxing ethanol, to obtain the double dialkylaminoalkylation products, 7-methyl-2,6-bis(dialkylaminoalkylthio)purines (**4a-e**), the yields were not quite satisfactory (48-56%). Only the reactions carried out in refluxing dioxane in the presence of sodium hydroxide led to the desired products **4** in high yields (80-95%) (Scheme 2). These conditions enabled to introduce the

dialkylaminoalkyl substituent possessing not only acyclic but also cyclic amino groups (pyrrolidine, piperidine and morpholine) at the sulfur atoms in both positions 2 and 6.

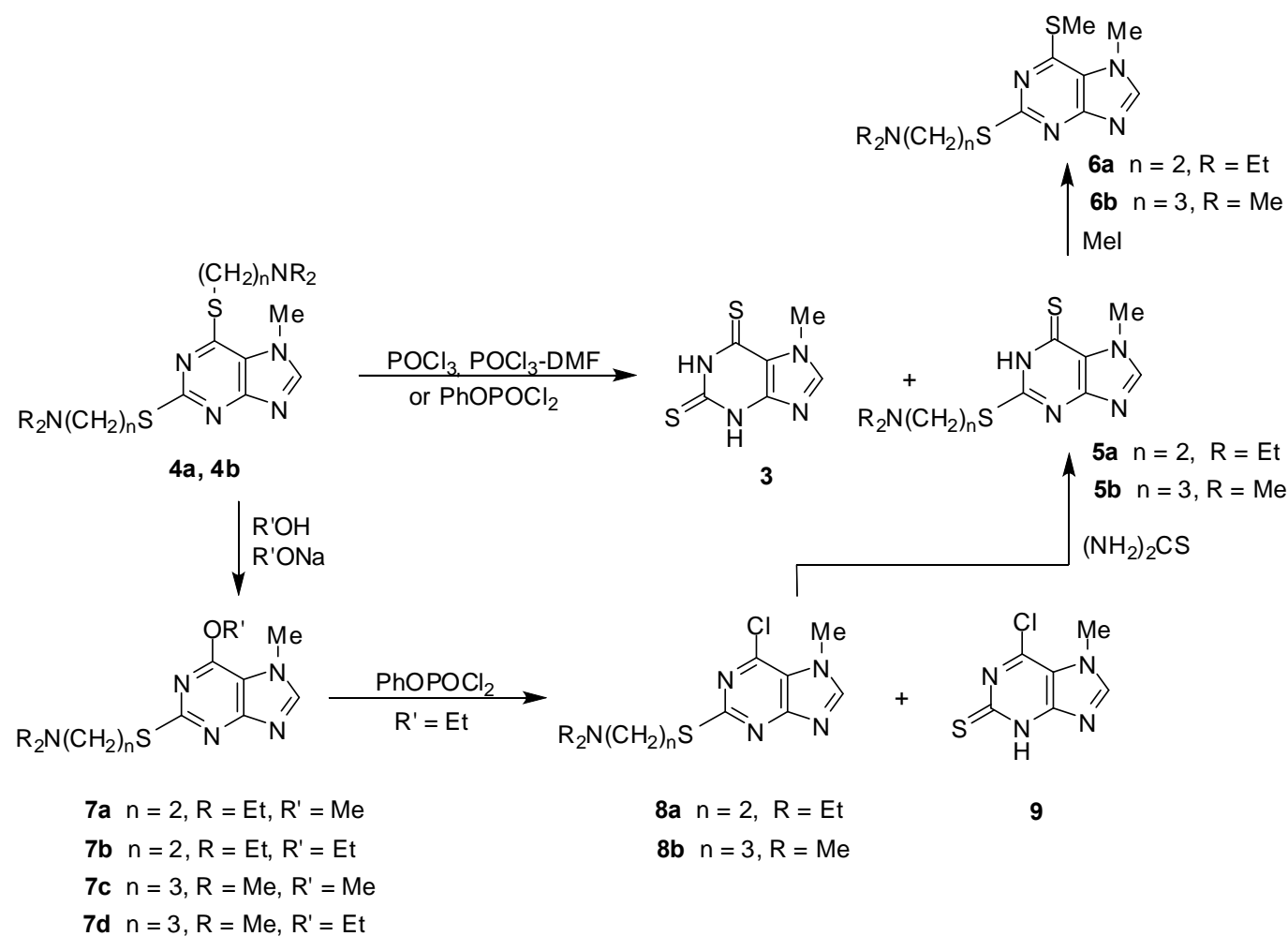


Scheme 2

Next step was synthesis of 2-(dialkylaminoalkylthio)-7-methylpurines, isomeric to compounds **2**. The isomeric substrates, 6-substituted 7-methylpurine-2(3*H*)thiones, are not available in a simple way but in a few step synthesis from 2-chloro-7-methylpurin-6(1*H*)-one.¹⁹ As the substituents in position 6 are much more susceptible for nucleophilic reagents than in position 2,¹⁷⁻¹⁹ 2,6-disubstituted products **4** were used as the substrates. Our previous regioselective results with 2,6-di[(alkyl/aryl)thio]-7-methylpurines with nucleophilic reagents¹⁷⁻¹⁹ prompted us to carried out the reaction with boiling phosphorus oxychloride to obtain the 6-chloro derivatives. Unfortunately, this reaction and the reactions with a mixture POCl₃-DMF or phenyl dichlorophosphate at 105-110 °C led to *S*-de(dialkylaminoalkylation) products, 2,6-dithio compound **3** (in 52–61% yield) and 2-(dialkylaminoalkylthio)-7-methylpurine-6(1*H*)thiones **5a** and **5b** in low yields (5-17%, the details in Experimental) (Scheme 3). Unlike the 1-methyl-4-nitroimidazol-5-ylthio group, the diethylaminoethylthio and dimethylaminopropylthio groups did not undergo the chlorination with phosphorus oxychloride and its derivatives.

Next we carried out the reactions with sodium alkoxides in boiling alcohols (methyl and ethyl). This time the reaction did not run as the dialkylaminoalkyl-sulfur bond cleavage process but as the monoalkoxylation to give 2-(dialkylaminoalkylthio)-6-alkoxy-7-methylpurines (**7a-d**) in very good yields (74-85.5%). The structural problem (which dialkylaminoalkylthio group was substituted by the alkoxy group) was solved comparing the physical (mp), chromatographical (R_f) and spectroscopical (¹H NMR spectra) data of compounds **7a** and **7c** with compounds **2b** and **2e**, which turned out to be different.

Compounds **7b** and **7d** treated with phenyl dichlorophosphate at 105-110 °C gave 2-(dialkylaminoalkylthio)-6-chloro compounds **8a** and **8b** (in 72% and 76% yields), and 6-chloro-2-purinethione **9** (in 15% and 12% yield, respectively) as *S*-de(dialkylaminoalkylation) product. The chloro derivatives **8** in the reaction with thiourea gave the same thio compounds **5a** and **5b** (in 83% and 85.5% yields) directly from compound **4**. *S*-Methylation of compounds **5a** and **5b** with methyl iodide led to methylthio compounds **6a** and **6b** in 82% and 83% yields (being isomeric to compounds **2c** and **2f**). The dialkylaminoalkyl groups in position 6 in thiopurines **4a** and **4b** turned out to be quite good leaving groups in the reactions with sodium alkoxides.



Scheme 3

All 2- and 6-(dialkylaminoalkylthio)-7-methylpurines (**2**, **5-8**) and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines (**4**) exhibit promising potential antitumoral, antiaggregation, anti-inflammatory, cardioprotective, antiviral and nootropic activity, and could be useful as anticancer, and in particular as cardioprotective agents.²⁰

CONCLUSION

Here, we report an efficient synthesis of 21 new thiopurines being 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines, 6-substituted 2-(dialkylaminoalkylthio)-7-methylpurines, and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines. 2-Substituted 6-(dialkylaminoalkylthio) and 2,6-bis(dialkylaminoalkylthio) derivatives were obtained *via* the direct *S*-dialkylaminoalkylation of the appropriate purine-thiones. The different reactivities of the dialkylaminoalkylthio groups in positions 2 and 6 towards sodium alkoxides were the key processes in a few step synthesis of 2-(dialkylaminoalkylthio) derivatives from 2,6-bis(dialkylaminoalkylthio) derivatives.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and were uncorrected. The ^1H NMR spectra were recorded on a Varian Unity-Inova 300 spectrometer (300 MHz) in CDCl_3 and $\text{DMSO}-d_6$ with TMS as an internal standard. EI MS and FAB MS (in the *m*-nitrobenzyl alcohol and glycerol matrix) were run on a Finnigan MAT 95 spectrometer at 70eV.

General synthesis of 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines (2)

A mixture of 6-purinethione **1a-c**¹⁹ (1 mmol), 2-diethylaminoethyl or 3-dimethylaminopropyl chloride hydrochloride (1.5 mmol), 10% aqueous NaOH solution (0.25 mL) and absolute EtOH (20 mL) was refluxed for 2 h. After cooling the small amount of resulting solid was filtered off, and the ethanolic filtrate was evaporated *in vacuo*. The residue was extracted with CHCl_3 (3 x 10 mL), dried with anhydrous Na_2SO_4 and evaporated *in vacuo*. Crude products were purified by crystallization from EtOH and column chromatography (aluminium oxide, CHCl_3 -EtOH, 9:1 v/v) to give the 6-(dialkylaminoalkylthio) derivatives **2a-f**:

2-Chloro-6-(2-diethylaminoethylthio)-7-methylpurine (**2a**) (0.284 g, 95%); mp 158-159 °C (EtOH). ^1H NMR (CDCl_3), δ : 1.08 (t, $J = 7.1$ Hz, 6H, 2CCH_3), 2.67 (q, $J = 7.1$ Hz, 4H, 2NCH_2), 2.85 (t, $J = 7.2$ Hz, 2H, SCH_2), 3.48 (t, $J = 7.2$ Hz, 2H, NCH_2), 4.05 (s, 3H, NCH_3), 7.94 (s, 1H, H-8), FAB MS m/z : 300 ($\text{M}+1$, 55), 201 ($\text{M}+1-\text{C}_2\text{H}_3\text{N}(\text{C}_2\text{H}_5)_2$, 18), 100 ($\text{C}_2\text{H}_4\text{N}(\text{C}_2\text{H}_5)_2$, 100). Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{ClN}_5\text{S}$: C 48.07, H 6.05, N 23.36. Found C 48.33, H 5.98, N 23.58.

6-(2-Diethylaminoethylthio)-2-methoxy-7-methylpurine (**2b**) (0.255 g, 86.5%); mp 165-166 °C (EtOH). ^1H NMR (CDCl_3), δ : 1.04 (t, $J = 7.1$ Hz, 6H, 2CCH_3), 2.57 (q, $J = 7.1$ Hz, 4H, 2NCH_2), 2.75 (t, $J = 7.2$ Hz, 2H, SCH_2), 3.14 (t, $J = 7.1$ Hz, 2H, NCH_2), 4.05 (s, 3H, NCH_3), 4.12 (s, 3H, OCH_3), 7.87 (s, 1H, H-8), FAB MS m/z : 296 ($\text{M}+1$, 100), 197 ($\text{M}+1-\text{C}_2\text{H}_3\text{N}(\text{C}_2\text{H}_5)_2$, 16). Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{N}_5\text{OS}$: C 52.86, H 7.17, N 23.71. Found C 52.62, H 7.12, N 23.98.

6-(2-Diethylaminoethylthio)-7-methyl-2-methylthiopurine (**2c**) (0.270 g, 87%); mp 143-144 °C (EtOH). ^1H NMR (CDCl_3), δ : 1.08 (t, $J = 7.1$ Hz, 6H, 2CCH_3), 2.63 (s, 3H, SCH_3), 2.67 (q, $J = 7.1$ Hz, 4H, 2NCH_2), 2.83 (t, $J = 7.2$ Hz, 2H, SCH_2), 3.31 (t, $J = 7.1$ Hz, 2H, NCH_2), 4.07 (s, 3H, NCH_3), 7.88 (s, 1H,

H-8), FAB MS m/z : 312 (M+1, 100), 213 (M+1-C₂H₃N(C₂H₅)₂, 12). Anal. Calcd for C₁₃H₂₁N₅S₂: C 50.13, H 6.80, N 22.48. Found C 50.44, H 6.74, N 22.29.

2-Chloro-6-(3-dimethylaminopropylthio)-7-methylpurine (**2d**) (0.238 g, 83%); mp 186-187 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.11 (m, 2H, CH₂), 2.71 (s, 6H, 2NCH₃), 3.40 (t, $J = 7.1$ Hz, 2H, SCH₂), 3.70 (t, $J = 7.1$ Hz, 2H, NCH₂), 4.03 (s, 3H, NCH₃), 8.11 (s, 1H, H-8), FAB MS m/z : 286 (M+1, 100), 201 (M+1-C₃H₅N(CH₃)₂, 9). Anal. Calcd for C₁₁H₁₆ClN₅S: C 46.23, H 5.64, N 24.50. Found C 46.48, H 5.78, N 24.31.

6-(3-Dimethylaminopropylthio)-2-methoxy-7-methylpurine (**2e**) (0.223 g, 79%); mp 169-170 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.01 (m, 2H, CH₂), 2.36 (s, 6H, 2NCH₃), 2.55 (t, $J = 7.1$ Hz, 2H, SCH₂), 3.29 (t, $J = 7.1$ Hz, 2H, NCH₂), 3.92 (s, 3H, OCH₃), 4.01 (s, 3H, NCH₃), 7.86 (s, 1H, H-8), FAB MS m/z : 282 (M+1, 100), 197 (M+1-C₃H₅N(CH₃)₂, 8). Anal. Calcd for C₁₂H₁₉N₅OS: C 51.22, H 6.81, N 24.89. Found C 51.53, H 6.73, N 25.12.

6-(3-Dimethylaminopropylthio)-7-methyl-2-methylthiopurine (**2f**) (0.230 g, 77.5%); mp 147-148 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.10 (m, 2H, CH₂), 2.61 (s, 3H, SCH₃), 2.68 (s, 6H, 2NCH₃), 2.93 (t, $J = 7.1$ Hz, 2H, SCH₂), 3.55 (t, $J = 7.1$ Hz, 2H, NCH₂), 4.06 (s, 3H, NCH₃), 7.98 (s, 1H, H-8), FAB MS m/z : 298 (M+1, 100), 213 (M+1-C₃H₅N(CH₃)₂, 19). Anal. Calcd for C₁₂H₁₉N₅S₂: C 48.46, H 6.44, N 23.55. Found C 48.22, H 6.52, N 23.86.

General synthesis of 2,6-bis(dialkylaminoalkyl or 2-pyrrolidinyethyl, piperidinyethyl and morpholinylethyl)thio-7-methylpurines (**4**)

To a mixture of 7-methylpurine-2(3*H*),6(1*H*)-dithione (**3**) (0.198 g, 1 mmol) and NaOH (0.4 g, 10 mmol) in stirred (10 mL) dry dioxane at rt for 1 h, 2.5 mmol of 2-diethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidinyethyl, 2-piperidinyethyl or 2-morpholinylethyl chloride hydrochloride was added and the mixture was refluxed for 2 h. After cooling the solid was filtered off and the solvent removed *in vacuo*. The residue was extracted with CHCl₃ (3 x 10 mL), dried with anhydrous Na₂SO₄ and evaporated *in vacuo*. Crude products were crystallized from EtOH and purified by column chromatography (aluminium oxide, CHCl₃-EtOH, 9:1 v/v) to give the bis(dialkylaminoalkylthio) derivatives **4a-e**.

2,6-Bis(2-diethylaminoethylthio)-7-methylpurine (**4a**) (0.343 g, 86.5%); an oil. ¹H NMR (CDCl₃), δ: 1.07 (t, $J = 7.2$ Hz, 6H, 2CCH₃), 1.12 (t, $J = 7.2$ Hz, 6H, 2CCH₃), 2.63 (q, $J = 7.2$ Hz, 4H, 2NCH₂), 2.70 (q, $J = 7.2$ Hz, 4H, 2NCH₂), 2.82 (t, $J = 7.2$ Hz, 2H, SCH₂), 2.91 (t, $J = 7.2$ Hz, 2H, SCH₂), 3.34 (t, $J = 7.2$ Hz, 2H, NCH₂), 3.45 (t, $J = 7.2$ Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.84 (s, 1H, H-8), FAB MS m/z : 397 (M+1, 100), 298 (M+1-C₂H₃N(C₂H₅)₂, 19). Anal. Calcd for C₁₈H₃₂N₆S₂: C 54.51, H 8.13, N 21.19. Found C 54.81, H 8.04, N 20.96.

2,6-Bis(3-dimethylaminopropylthio)-7-methylpurine (**4b**) (0.296 g, 80.5%); mp 127-128 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.03 (m, 4H, 2CH₂), 2.32 (s, 6H, 2NCH₃), 2.37 (s, 6H, 2NCH₃), 2.52 (t, $J = 7.2$ Hz, 2H, SCH₂), 2.67 (t, $J = 7.2$ Hz, 2H, SCH₂), 3.27 (t, $J = 7.2$ Hz, 2H, NCH₂), 3.39 (t, $J = 7.2$ Hz, 2H, NCH₂),

4.05 (s, 3H, NCH₃), 7.86 (s, 1H, H-8), FAB MS *m/z*: 369 (M+1, 100), 284 (M+1-C₃H₅N(CH₃)₂, 15). Anal. Calcd for C₁₆H₂₈N₆S₂: C 52.14, H 7.66, N 22.80. Found C 52.40, H 7.56, N 22.53.

2,6-Bis(2-pyrrolidinyethylthio)-7-methylpurine (**4c**) (0.364 g, 93%); mp 116-117 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.29 (m, 8H, 4CH₂), 2.67 (m, 8H, 4CH₂), 2.82 (t, *J* = 7.5 Hz, 2H, SCH₂), 2.87 (t, *J* = 7.5 Hz, 2H, SCH₂), 3.38 (t, *J* = 7.5 Hz, 2H, NCH₂), 3.50 (t, *J* = 7.5 Hz, 2H, NCH₂), 4.04 (s, 3H, NCH₃), 7.84 (s, 1H, H-8), FAB MS *m/z*: 393 (M+1, 100), 296 (M+1-C₂H₃NC₄H₈, 18). Anal. Calcd for C₁₈H₂₈N₆S₂: C 55.07, H 7.19, N 21.41. Found C 55.35, H 7.14, N 21.65.

2,6-Bis(2-piperidinyethylthio)-7-methylpurine (**4d**) (0.400 g, 95%); an oil. ¹H NMR (CDCl₃), δ: 1.45 (m, 4H, 2CH₂), 1.61 (m, 8H, 4 CH₂), 2.55 (m, 8H, 4CH₂), 2.69 (t, *J* = 7.5 Hz, 2H, SCH₂), 2.78 (t, *J* = 7.5 Hz, 2H, SCH₂), 3.39 (t, *J* = 7.5 Hz, 2H, NCH₂), 3.51 (t, *J* = 7.5 Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.84 (s, 1H, H-8), FAB MS *m/z*: 421 (M+1, 19), 308 (M+1-C₂H₅NC₅H₁₀, 7), 112 (C₂H₄NC₅H₁₀, 100). Anal. Calc for C₂₀H₃₂N₆S₂: C 57.11, H 7.67, N 19.98. Found C 56.82, H 7.60, N 20.21.

2,6-Bis(2-morpholinylethylthio)-7-methylpurine (**4e**) (0.385 g, 90.5%); an oil. ¹H NMR (CDCl₃), δ: 2.58 (m, 8H, 4CH₂), 2.67 (m, 8H, 4CH₂), 2.73 (t, *J* = 7.5 Hz, 2H, SCH₂), 2.78 (t, *J* = 7.5 Hz, 2H, SCH₂), 3.39 (t, *J* = 7.5 Hz, 2H, NCH₂), 3.51 (t, *J* = 7.5 Hz, 2H, NCH₂), 4.06 (s, 3H, NCH₃), 7.86 (s, 1H, H-8), FAB MS *m/z*: 425 (M+1, 44), 312 (M+1-C₂H₃NOC₄H₈, 14), 114 (C₂H₄NOC₄H₈, 100). Anal. Calcd for C₁₈H₂₈N₆O₂S₂: C 50.92, H 6.65, N 19.79. Found C 51.19, H 6.71, N 19.51.

Synthesis of 7-methyl-6-purinethiones (**5a**, **5b**)

A. From **8a,b**

A solution of the 6-chloro derivative **8a** or **8b** (1 mmol) and thiourea (0.152 g, 2 mmol) in absolute EtOH (10 mL) was refluxed for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in 5% aqueous NaOH solution. The reaction product was precipitated with 15% hydrochloric acid and the process was repeated twice to give pure 6-purinethiones **5a** or **5b** in 83% and 85.5% yields, respectively.

B. From **4a,b**

A solution of anhydrous substrates **4a** (or **4b**) (1 mmol) in POCl₃ (5 mL) or in a mixture of POCl₃-DMF (1:2 v/v, 10 mL) or in phenyl dichlorophosphate (5 mL) was stirred on oil bath at 105-110 °C for 4 h. After cooling the reaction mixture was poured into crushed ice (10 g), neutralized with concentrated NH₄OH solution at 0-5 °C up to pH = 4-5 and the resulted solid was filtered off to give the mixture of products **3** and **5a** (or **5b**). The resulting mixture was separated by extraction with absolute EtOH (3 x 15 mL). The solvent was removed *in vacuo* and the residue was dissolved in 5% aqueous NaOH solution. The product **5a** (or **5b**) was precipitated with 15% aqueous HCl. The residue after extraction with EtOH was also dissolved in 5% aqueous NaOH solution and the product **3** was precipitated by acidification with 15% aqueous HCl to pH = 3.

Substrate	Reagent/solvent	Products (yield, %)
4a	POCl ₃	3 (56), 5a (7)
4a	POCl ₃ -DMF	3 (54), 5a (10)
4a	PhOPOCl ₂	3 (52), 5a (17)
4b	POCl ₃	3 (61), 5b (6)
4b	POCl ₃ -DMF	3 (53), 5b (12)
4b	PhOPOCl ₂	3 (57), 5b (17)

2-(2-Diethylaminoethylthio)-7-methylpurine-6(1*H*)-thione (**5a**) (0.246 g, 83%); mp 177-178 °C (EtOH). ¹H NMR (DMSO-*d*₆), δ: 1.38 (t, *J* = 7.2 Hz, 6H, 2CCH₃), 2.68 (t, *J* = 7.2 Hz, 2H, SCH₂), 2.98 (q, *J* = 7.2 Hz, 4H, 2NCH₂), 3.23 (t, *J* = 7.2 Hz, 2H, NCH₂), 4.07 (s, 3H, NCH₃), 8.05 (s, 1H, H-8), 9.44 (s, 1H, NH), FAB MS *m/z*: 298 (M+1, 100), 255 (M+1-(C₂H₅)₂NH, 6). Anal. Calcd for C₁₂H₁₉N₅S₂: C 48.46, H 6.44, N 23.55. Found C 48.73, H 6.35, N 23.38.

2-(3-Dimethylaminopropylthio)-7-methylpurine-6(1*H*)-thione (**5b**) (0.242 g, 85.5%); mp 193-194 °C (EtOH). ¹H NMR (DMSO-*d*₆), δ: 2.12 (m, 2H, CH₂), 2.83 (s, 6H, 2NCH₃), 3.47 (t, *J* = 7.2 Hz, 2H, SCH₂), 3.75 (t, *J* = 7.2 Hz, 2H, NCH₂), 4.08 (s, 3H, NCH₃), 8.10 (s, 1H, H-8), 10.81 (s, 1H, NH), FAB MS *m/z*: 284 (M+1, 100), 239 (M+1-(CH₃)₂NH, 9). Anal. Calcd for C₁₁H₁₇N₅S₂: C 46.62, H 6.05, N 24.71. Found C 46.89, H 6.08, N 24.52.

Synthesis of 2-(dialkylaminoalkylthio)-7-methyl-6-methylthiopurines (**6a, b**)

To a stirred solution of 6-purinethione **5a** (or **5b**) (1 mmol) in 4% aqueous KOH solution at rt, methyl iodide (0.28 g, 2 mmol) was added. After 20 min the resulting solid was filtered off and washed with water. The crude products were purified by column chromatography (aluminium oxide, CHCl₃, and CHCl₃-EtOH, 9:1, v/v) to give compound **6a** (or **6b**).

2-(2-Diethylaminoethylthio)-7-methyl-6-methylthiopurine (**6a**) (0.256 g, 82%); mp 134-135 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.10 (t, *J* = 7.1 Hz, 6H, 2CCH₃), 2.68 (q, *J* = 7.1 Hz, 4H, 2NCH₂), 2.72 (s, 3H, SCH₃), 2.91 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.41 (t, *J* = 7.1 Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.90 (s, 1H, H-8), FAB MS *m/z*: 312 (M+1, 100), 239 (M+1-(C₂H₅)₂NH, 16). Anal. Calcd for C₁₃H₂₁N₅S₂: C 50.13, H 6.80, N 22.48. Found C 49.89, H 6.73, N 22.74.

2-(3-Dimethylaminopropylthio)-7-methyl-6-methylthiopurine (**6b**) (0.246 g, 83%); mp 139-140 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.08 (m, 2H, CH₂), 2.45 (s, 6H, 2NCH₃), 2.74 (s, 3H, SCH₃), 3.03 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.81 (t, *J* = 7.1 Hz, 2H, NCH₂), 4.07 (s, 3H, NCH₃), 7.96 (s, 1H, H-8), FAB MS *m/z*: 298 (M+1, 100), 253 (M+1-(CH₃)₂NH, 12). Anal. Calcd for C₁₂H₁₉N₅S₂: C 48.46, H 6.44, N 23.55. Found C 48.74, H 6.36, N 23.24.

Reaction of 2,6-bis(dialkylaminoalkylthio)-7-methylpurines (**4a,b**) with alcohols

A solution of **4a** or **4b** (1 mmol) and sodium methoxide or ethoxide (1 mmol) in respective dry alcohol (methanol or ethanol, 10 mL) was refluxed for 2 h. After cooling small amount of resulting solid was filtered off and the alcoholic filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from EtOH and purified by column chromatography (aluminium oxide, CHCl₃-EtOH, 9:1 v/v) to give compounds **7a-d**.

2-(2-Diethylaminoethylthio)-6-methoxy-7-methylpurine (**7a**) (0.220 g, 74.5%); mp 155-156 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.11 (t, *J* = 7.2 Hz, 6H, 2CCH₃), 2.68 (q, *J* = 7.2 Hz, 4H, 2NCH₂), 2.90 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.44 (t, *J* = 7.1 Hz, 2H, NCH₂), 3.67 (s, 3H, OCH₃), 4.05 (s, 3H, NCH₃), 7.85 (s, 1H, H-8), FAB MS *m/z*: 296 (M+1, 100), 223 (M+1-(C₂H₅)₂NH, 6). Anal. Calcd for C₁₃H₂₁N₅OS: C 52.86, H 7.17, N 23.71. Found C 52.59, H 7.23, N 23.89.

2-(2-Diethylaminoethylthio)-6-ethoxy-7-methylpurine (**7b**) (0.242 g, 78%); mp 124-125 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.13 (t, *J* = 7.1 Hz, 6H, 2CCH₃), 1.45 (t, *J* = 7.2 Hz, 3H, CCH₃), 2.69 (q, *J* = 7.1 Hz, 4H, 2NCH₂), 2.98 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.51 (t, *J* = 7.1 Hz, 2H, NCH₂), 3.99 (s, 3H, NCH₃), 4.58 (q, *J* = 7.2 Hz, 2H, OCH₂), 7.84 (s, 1H, H-8), FAB MS *m/z*: 310 (M+1, 100), 237 (M+1-(C₂H₅)₂NH, 20). Anal. Calcd for C₁₄H₂₃N₅OS: C 54.34, H 7.49, N 22.63. Found C 54.61, H 7.54, N 22.32.

2-(3-Dimethylaminopropylthio)-6-methoxy-7-methylpurine (**7c**) (0.223 g, 79%); mp 159-160 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.97 (m, 2H, CH₂), 2.29 (s, 6H, 2NCH₃), 2.65 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.42 (t, *J* = 7.1 Hz, 2H, NCH₂), 3.69 (s, 3H, OCH₃), 4.04 (s, 3H, NCH₃), 7.85 (s, 1H, H-8), FAB MS *m/z*: 282 (M+1, 100), 237 (M+1-(CH₃)₂NH, 10). Anal. Calcd for C₁₂H₁₉N₅OS: C 51.22, H 6.81, N 24.89. Found C 50.94, H 6.88, N 24.63.

2-(3-Dimethylaminopropylthio)-6-ethoxy-7-methylpurine (**7d**) (0.252 g, 85.5%); mp 130-131 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.45 (t, *J* = 7.2 Hz, 3H, CCH₃), 2.07 (m, 2H, CH₂), 2.40 (s, 6H, 2NCH₃), 2.67 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.26 (t, *J* = 7.1 Hz, 2H, NCH₂), 3.97 (s, 3H, NCH₃), 4.57 (q, *J* = 7.2 Hz, 2H, OCH₂), 7.83 (s, 1H, H-8), FAB MS *m/z*: 296 (M+1, 100), 251 (M+1-(CH₃)₂NH, 19). Anal. Calcd for C₁₃H₂₁N₅OS: C 52.86, H 7.17, N 23.71. Found C 52.59, H 7.17, N 23.94.

Synthesis of 2-(dialkylaminoalkylthio)-6-chloro-7-methylpurines (**8a,b**)

A solution of 6-ethoxy derivatives **7b** or **7d** (1 mmol) in phenyl dichlorophosphate (5 mL) was stirred on oil bath at 105-110 °C for 2 h. After cooling the reaction mixture was poured into crushed ice (20 g), neutralized with concentrated NH₄OH solution at 0-5 °C up to pH = 7 and extracted with CHCl₃ (3 x 15 mL). The combined extracts were dried over anhydrous Na₂SO₄. The solvent was evaporated *in vacuo* and the residue was purified by column (Al₂O₃, CHCl₃-EtOH, 9:1 v/v) and preparative thin layer (aluminium oxide, CHCl₃) chromatographies to give compounds **8a** (0.216 g, 72%) or **8b** (0.217 g 76%).

6-Chloro-2-(2-diethylaminoethylthio)-7-methylpurine (**8a**) (0.216 g, 72%); mp 146-147 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.45 (t, *J* = 7.1 Hz, 6H, 2CCH₃), 3.12 (q, *J* = 7.1 Hz, 4H, 2NCH₂), 3.22 (t, *J* = 7.1 Hz,

2H, SCH₂), 3.85 (t, *J* = 7.1 Hz, 2H, NCH₂), 4.10 (s, 3H, NCH₃), 8.05 (s, 1H, H-8), FAB MS *m/z*: 300 (*M*+1, 100), 227 (*M*+1-(C₂H₅)₂NH, 9). Anal. Calcd for C₁₂H₁₈ClN₅S: C 48.07, H 6.05, N 23.36. Found C 48.35, H 5.97, N 23.17.

6-Chloro-2-(3-dimethylaminopropylthio)-7-methylpurine (**8b**) (0.217 g, 76%); mp 173-174 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.14 (m, 2H, CH₂), 2.62 (s, 6H, 2NCH₃), 3.46 (t, *J* = 7.1 Hz, 2H, SCH₂), 3.85 (t, *J* = 7.1 Hz, 2H, NCH₂), 4.09 (s, 3H, NCH₃), 8.15 (s, 1H, H-8), FAB MS *m/z*: 286 (*M*+1, 100), 241 (*M*+1-(CH₃)₂NH, 7). Anal. Calcd for C₁₁H₁₆ClN₅S: C 46.23, H 5.64, N 24.50. Found C 46.44, H 5.70, N 24.26.

The aqueous solution (after extraction with CHCl₃) was acidified with 15% aqueous HCl up to pH = 4-5 and the resulting solid was filtered off and crystallized from EtOH to give 6-chloro-7-methylpurine-2(3*H*)-thione¹⁹ (**9**) (0.030 and 0.025 g, 15% and 12%); mp > 300 °C (EtOH). ¹H NMR (DMSO-*d*₆), δ: 4.15 (s, 3H, NCH₃), 8.28 (s, 1H, H-8), 12.18 (s, 1H, NH).

ACKNOWLEDGEMENTS

This work was supported by The Medical University of Silesia (grant KNW-1-073/P/1/0).

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