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# SYNTHESIS OF THE AZATHIOPURINE ANALOGS

**Alicja Kowalska* and Krystian Pluta**

Department of Organic Chemistry, The Medical University of Silesia, Jagiellońska 4, 41-200 Sosnowiec, Poland

E-mail: kowalska@slam.katowice.pl

**Abstract** – The effective synthesis of the azathioprine analogs - 2-subsituted derivatives of 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)purines **5** has been achieved by the reaction of 2-subsituted 6-purinethiones **4** with 5-chloro-1-methyl-4-nitroimidazole in ethanol. In the case of 7-methyl-2,6-dithioxanthine **4j**, reaction in DMF gave di(imidazolyl) product **5l**. The key step in this synthesis was preparation of the appropriate 2-substituted 6-purinones **2** and 6-chloropurines **3** which were further converted to 6-purinethione **4**.

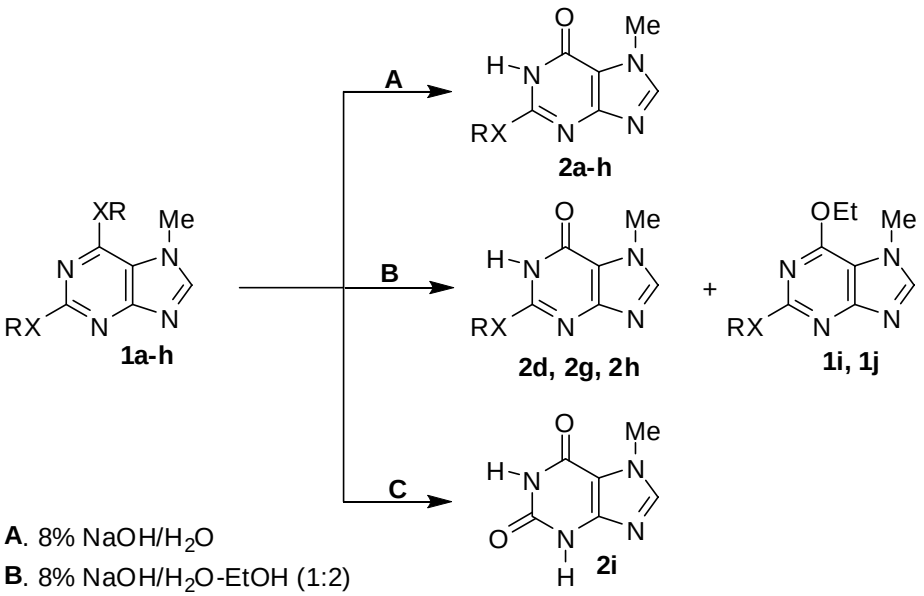
## INTRODUCTION

Azathioprine, 6-(1-methyl-4-nitroimidazol-5-ylthio)purine, is one of the oldest immunosuppressive agents available today.[1,2] Now rarely used for chemotherapy but more for immunosuppresion in solid organ transplantation and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, hematologic malignancies, dermatologic afflictions, ulcerative colitis or Crohn's disease.[1,3-5] Azathioprine is a prodrug that is converted in the liver to imidazole derivatives and 6-mercaptopurine. The metabolites of both substances have independent immunosuppressive properties. The accepted mechanism of its action is at the level of DNA.[4] Azathioprine interferes with DNA and RNA synthesis and has numerous non-specific effects on immune system. The active metabolite of 6-mercaptopurine, thioquanine, is incorporated into ribonucleotides, thereby exerting an antiproliferative effect on mitotically active lymphocyte populations.[1,3,4] Azathioprine also possesses direct antiinflammatory properties by inhibiting cytotoxic T cell and natural killer cell function.[4,6-8] The unique and unexpected role for azathioprine and its metabolites is the control of T cell apoptosis by modulation of GTP-binding protein – Rac 1 upon CD28 costimmulation.[7-9] Searching for prodrugs with potential biological activity, the synthesis of new analogs of azathioprine as 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)purines has been described.

## RESULTS AND DISCUSSION

The key step in the synthesis of the azathioprine analogs **5** was a preparation of appropriate 2-substituted 7-methyl-6-purinethiones **2** and 2-substituted 6-chloro-7-methylpurines **3** which were further transformed into appropriate 6-purinethiones **4**. Problems with the synthesis of the chloro substrates **3** were overcome

exploiting regioselective reactions of identical substituted 2,6-dialkoxy- and 2,6-dialkylthio-7-methylpurines **1** with the hydroxide ion to give the hypoxanthine analogs **2**. This alkaline hydrolysis of compounds **1** proceeded in aqueous sodium hydroxide solution in position 6 and was effective for compounds with the methoxy, ethoxy, allyloxy, methylthio and ethylthio substituents in position 2 (**2a-c**, **2e**, **2f**, 85-98% yield, Scheme 1). The yields of hydrolysis of compounds **1** with other substituents, i.e. benzyloxy, allylthio and benzylthio were unsatisfactory (10-21% yields) in these conditions, probably for




**A**. 8% NaOH/$H_2O$
**B**. 8% NaOH/$H_2O$-EtOH (1:2)
**C**. 5% NaOH/$H_2O$-DMSO (1:2)

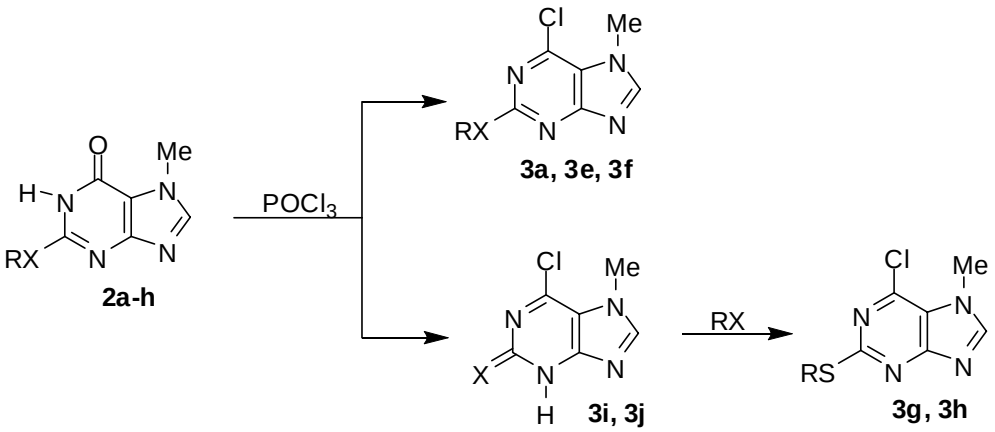
| Substrate **1** | | | Method | Products | | | |
|---|---|---|---|---|---|---|---|
| No | X | R | | No | X | R | Yield (%) |
| **a** | O | Me | A | **2a** | O | Me | 85 |
| **b** | O | Et | A | **2b** | O | Et | 97 |
| **c** | O | allyl | A | **2c** | O | allyl | 95 |
| **d** | O | Bn | A | **2d** | O | Bn | 21 |
| | | | B | **2d** | O | Bn | 94 |
| | | | C | **2i** | | | 92 |
| **e** | S | Me | A | **2e** | S | Me | 98 |
| **f** | S | Et | A | **2f** | S | Et | 90 |
| **g** | S | allyl | A | **2g** | S | allyl | 19 |
| | | | B | **2g** | S | allyl | 88 |
| | | | | **1i** | S | allyl | 8 |
| **h** | S | Bn | A | **2h** | S | Bn | 10 |
| | | | B | **2h** | S | Bn | 87 |
| | | | | **1j** | S | Bn | 12 |
| | | | C | **2i** | | | 90 |

Scheme 1

the reason of weak solubility of the 2,6-dibenzyloxy-, 2,6-diallylthio- and 2,6-dibenzylthio-7-methylpurines **1d**, **1g**, **1h** in water. When the alkaline hydrolysis was carried out in aqueous ethanol solution (water-ethanol 1:2 v/v) 6-purinones **2d**, **2g** and **2h** were obtained in good yields (87-94%) but 2-allylthio-

and 2-benzylthio-6-ethoxy-7-methylpurines **1i** and **1j** were also obtained (in 8 and 12% yields) as a result of high reactivity of the position 6 in identical substituted purines towards the oxygen nucleophilic agents, as observed previously in other purine derivatives.[10] Hydrolysis in alkaline DMSO solution led to only one product, 7-methylxanthine **2i**, as the result of the double substitution (Scheme 1).

Next we wanted to convert 6-purinones **2** into corresponding 6-purinethiones **4** by the described earlier procedure of chlorination of 2-substituted 7-methyl-6-purinones **2** with phosphorus oxychloride followed by reaction with thiourea in ethanol.[10a] It appeared that only 2-methoxy-, 2-methylthio- and 2-ethylthio-7-methyl-6-purinones **2a**, **2e** and **2f** reacted smoothly with phosphorus oxychloride to give 6-chloroderivatives **3a**, **3e** and **3f**. The other 6-purinones with the ethoxy, benzyloxy, allylthio or benzylthio groups underwent *O*- and *S*-dealkylation in position 2 during reaction with phosphorus oxychloride giving 6-chloro-7- methyl-2- purinone **3i** or 2-purinethione **3j** (Scheme 2). The last compound was used later for the synthesis of the 2-allylthio- and 2-benzylthio derivatives **3g** and **3h** by *S*-alkylation.

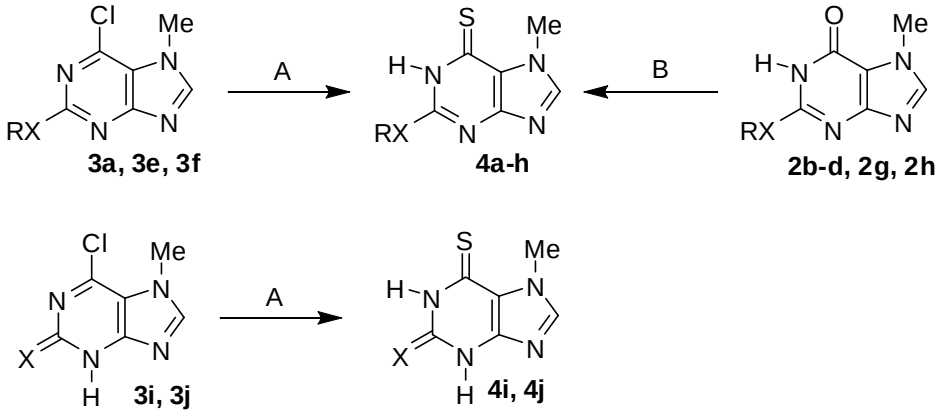



| Substrate | | | Product | | | |
|---|---|---|---|---|---|---|
| No | X | R | No | X | R | Yield (%) |
| **2a** | O | Me | **3a** | O | Me | 75 |
| **2b** | O | Et | **3i** | O | | 82 |
| **2c** | O | allyl | **3i** | O | | 81 |
| **2d** | O | Bn | **3i** | O | | 95 |
| **2e** | S | Me | **3e** | S | Me | 87 |
| **2f** | S | Et | **3f** | S | Et | 89 |
| **2g** | S | allyl | **3j** | S | | 78 |
| **2h** | S | Bn | **3j** | S | | 85 |
| **3j** | S | | **3g** | S | allyl | 91 |
| **3j** | S | | **3h** | S | Bn | 85 |

Scheme 2

In order to obtain 6-purinethiones **4** with the alkoxy and alkylthio groups in position 2 two routes were used. In the first one 6-chloroderivatives **3** were refluxed with thiourea in ethanol and in the second one 6-purinones **2** were heated with phosphorus pentasulfide in pyridine. Treatment of 6-chloro-7-methyl-2-purinone **3i** or 2-purinethione **3j** with thiourea led to 7-methyl-6-thioxanthine **4i** and 7-methyl-2,6-dithio-

xanthine **4j** (Scheme 3).



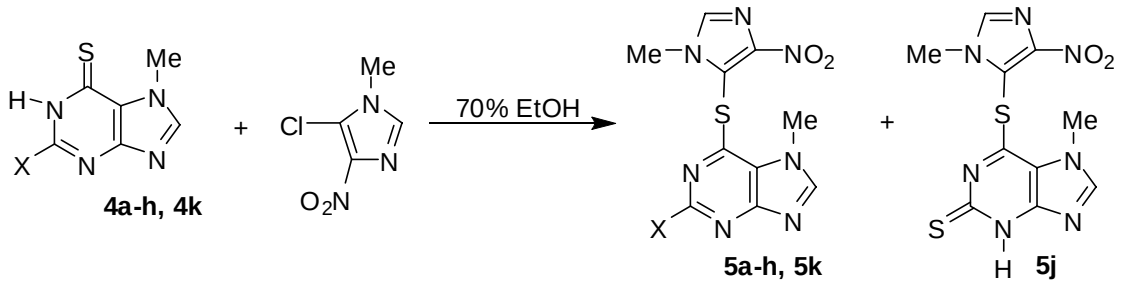

**A.** $NH_2CSNH_2$, EtOH
**B.** $P_2S_5$, pyridine

| Substrate | | | Method | Product | | | |
|---|---|---|---|---|---|---|---|
| No | X | R | | No | X | R | Yield (%) |
| **3a** | O | Me | A | **4a** | O | Me | 73 |
| **2b** | O | Et | B | **4b** | O | Et | 76 |
| **2c** | O | allyl | B | **4c** | O | allyl | 56 |
| **2d** | O | Bn | B | **4d** | O | Bn | 62 |
| **3e** | S | Me | A | **4e** | S | Me | 86 |
| **3f** | S | Et | A | **4f** | S | Et | 84 |
| **3g** | S | allyl | A | **4g** | S | allyl | 73 |
| **3h** | S | Bn | A | **4h** | S | Bn | 78 |
| **2g** | S | allyl | B | **4g** | S | allyl | 63 |
| **2h** | S | Bz | B | **4h** | S | Bn | 66 |
| **3i** | O | | A | **4i** | O | | 95 |
| **3j** | S | | A | **4j** | S | | 98 |

Scheme 3

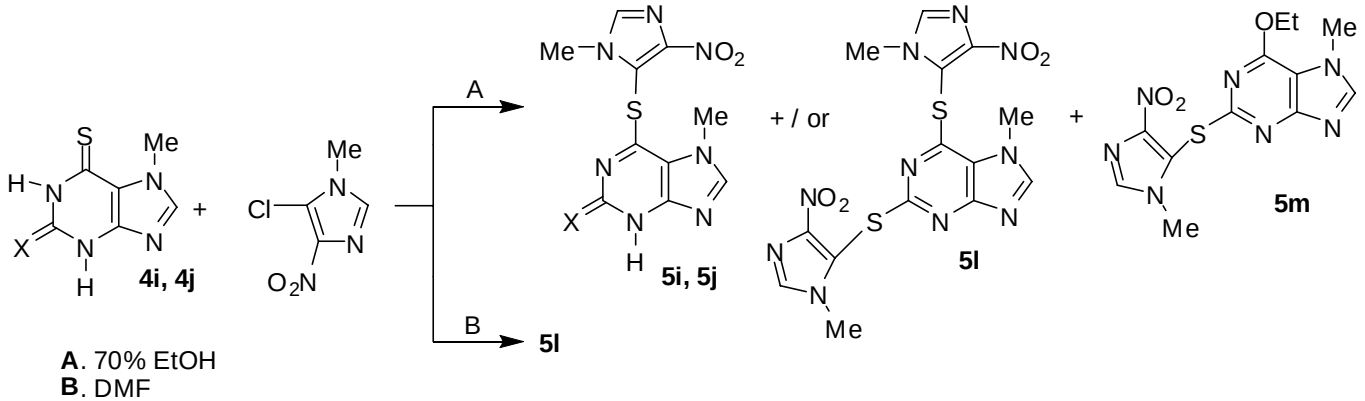
Reactions of 2-substituted (with the alkoxy, alkylthio and chloro groups) 7-methyl-6-purinethiones **4a-4h** and **4k** with 5-chloro-1-methyl-4-nitroimidazole in 70% ethanol gave 2-substituted 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)purines **5a-5h** and **5k** in good yields (71-98%, Scheme 4). In the case of the 2-allylthio and 2-benzylthio compounds **4g** and **4h** a process of *S*-dealkylation was also observed to give derivative **5j** (in 12% and 18% yield). Whereas reaction of 7-methyl-6-thioxanthine **4i** with 5-chloro-1-methyl-4-nitroimidazole in ethanol gave only expected imidazolylthio derivative **5i** (in 68% yield), 7-methyldithioxanthine **4j** gave 3 products: expected imidazolylthio derivative **5j** (in low yield of 9%), di(imidazolylthio) product **5l** (in 62% yield) and a product being the result of an action of ethanol, ethoxy derivative **5m** (in 24%). Only di(imidazolylthio) product **5l** in high yield of 91% was observed when the reaction was carried out in DMF (Scheme 5). Unexpected ethoxy compound **5m** was considered as a result of the subsequent reaction of the formed di(imidazolylthio) product **5l** rather than the substrate **4j** with ethanol. The separate reaction of compound **5l** with boiling ethanol for 2 h showed the

imidazolylthio group in position 6 to be a quite good leaving group to give ethoxy derivative **5m** in 82% yield (Scheme 6).



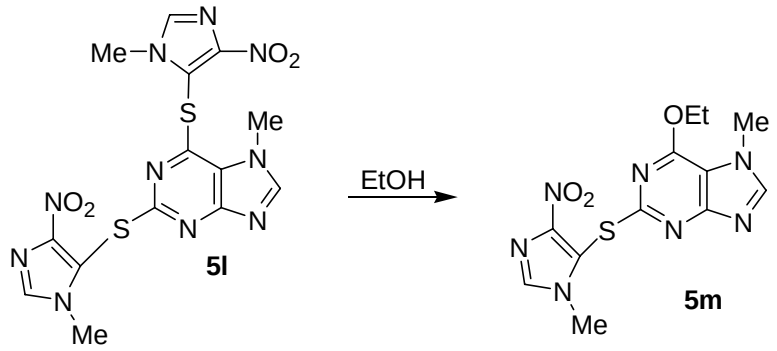

| Substrate | | Products | | |
|---|---|---|---|---|
| No | X | No | X | Yield (%) |
| **4a** | OMe | **5a** | OMe | 94 |
| **4b** | OEt | **5b** | OEt | 78 |
| **4c** | Oallyl | **5c** | Oallyl | 72 |
| **4d** | OBn | **5d** | OBn | 71 |
| **4e** | SMe | **5e** | SMe | 83 |
| **4f** | SEt | **5f** | SEt | 77 |
| **4g** | Sallyl | **5g** | Sallyl | 72 |
| | | **5j** | | 12 |
| **4h** | SBn | **5h** | SBn | 75 |
| | | **5j** | | 18 |
| **4k** | Cl | **5k** | Cl | 98 |

Scheme 4




| Substrate | | | Products | | |
|---|---|---|---|---|---|
| No | X | Method | No | X | Yield (%) |
| **4i** | O | A | **5i** | O | 68 |
| **4j** | S | A | **5j** | S | 9 |
| | | | **5l** | - | 62 |
| | | | **5m** | - | 24 |
| **4j** | S | B | **5l** | - | 91 |

Scheme 5




Scheme 6

## Conclusion

We report here an efficient synthesis of 13 new azathioprine analogs being of 2-subsituted derivatives of 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)purines **5** in the series of transformations starting from 2,6-dialkoxy- and 2-dialkylthio-7-methylpurines **1**.

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The $^1$H NMR spectra were recorded on a Varian Unity-Inova 300 spectrometer at 300 MHz in deuteriochloroform and dimethyl sulphoxide-$d_6$ with tetramethylsilane as the internal standard. Electron impact (EI MS) and chemical ionization mass spectra (CI MS) were run on Finnigan MAT 95 spectrometer at 70eV. Column chromatography was performed on silica gel 60 (Merck) using a mixture of chloroform-methanol (10:1, v/v) as an eluent. 2,6-Dialkoxy-7-methylpurines **1a-d** with identical alkyl groups were prepared from 2,6-dichloro-7-methylpurine and corresponding sodium alkoxide in alcohol solution according to known procedure.[10c,11]

1. 2,6-Dimethoxy-7-methylpurine (**1a**), mp 197-198 $^o$C (EtOH), lit.,[10c] mp 198-199 $^o$C.

2. 2,6-Diethoxy-7-methylpurine (**1b**), mp 147-148 $^o$C (EtOH), lit.,[10c] mp 146-148 $^o$C.

3. 2,6-Diallyloxy-7-methylpurine (**1c**), mp 109-110 $^o$C ($Et_2O$), lit.,[11b] mp 111-112 $^o$C.

4. 2,6-Dibenzyloxy-7-methylpurine (**1d**), (2.57g, 75%), mp 103-105 $^o$C ($Et_2O$).

$^1$H NMR ($CDCl_3$) δ: 3.94 (s, 3H, NMe), 5.52 (s, 2H, $O_2CH_2$), 5.58 (s, 2H, $O_6CH_2$), 7.36 (m, 6H, 2 m-$C_6H_5$, 2 p-$C_6H_5$), 7.45 (d, $J$ = 7.5 Hz, 2H, o-$C_6H_5$), 7.54 (d, $J$ = 7.5Hz, 2H, o-$C_6H_5$), 7.83 (s, 1H, H8), EI MS m/z: 346 ($M^+$, 23), 255 (M-$CH_2C_6H_5$, 33), $C_6H_5^+$ (100). Anal. Calcd for $C_{20}H_{18}N_4O_2$: C 69.35, H 5.24, N 16.17. Found C 69.07, H 5.29, N 15.96.

2,6-Dialkylthio-7-methylpurines **1e-h** with identical alkyl groups were prepared from 2,6-dichloro-7-methylpurine and thiourea in EtOH followed *S*-alkylation with 2 equivalents of alkyl halides (methyl iodide, ethyl iodide, allyl bromide and benzyl chloride) in 4% KOH solution at room temperature.[12]

1. 2,6-Dimethylthio-7-methylpurine (**1e**), mp 176-177 $^o$C (EtOH), lit.,[12] mp 176-178 $^o$C.

2. 2,6-Diethylthio-7-methylpurine (**1f**), (2.18g, 85%), mp 132-133 °C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 1.41 (t, *J* = 7.3 Hz, 3H, Me), 1.45 (t, *J* = 7.3 Hz, 3H, Me), 3.24 (q, *J* = 7.3 Hz , 2H, $S_2CH_2$), 3.38 (q, *J* = 7.3 Hz, 2H, $CH_2$), 4.06 (s, 3H, NMe), 7.86 (s, 1H, H-8), EI MS m/z: 254 ($M^+$, 100), 225 (M-$C_2H_5$, 89). Anal. Calcd for $C_{10}H_{14}N_4S_2$: C 47.22, H 5.55, N 22.03. Found C 47.06, H 5.59, N 21.76.

3. 2,6-Diallylthio-7-methylpurine (**1g**) (2.81g, 78%); mp 94-95 °C ($Et_2O$).

$^1$H NMR ($CDCl_3$) δ: 3.91 (d, *J* = 6.9 Hz, 2H, $S_2CH_2$), 4.04 (d, *J* = 6.9 Hz, 2H, $S_6CH_2$), 4.08 (s, 3H, NMe), 5.12 (d, *J* = 10.1 Hz, 1H, =$CH_2$), 5.20 (d, *J* = 10.1 Hz, 1H, =$CH_2$), 5.33 (d, *J* = 13.5 Hz, 1H, =$CH_2$), 5.39 (d, *J* = 13.5 Hz, 1H, =$CH_2$), 6.01 (m, 2H, =CH), 8.00 (s, 1H, H8), EI MS m/z: 278 ($M^+$, 27), 237 (M-$C_3H_5$, 100). Anal. Calcd for $C_{12}H_{14}N_4S_2$: C 51.77, H 5.07, N 20.13. Found C 51.55, H 5.17, N 19.88.

4. 2,6-Dibenzylthio-7-methylpurine (**1h**) (3.48g, 91%); mp 131-132 °C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 4.01 (s, 3H, NMe), 4.52 (s, 2H, $S_2CH_2$), 4.57 (s, 2H, $S_6CH_2$), 7.27 (m, 6H, 2 m-$C_6H_5$, 2 p-$C_6H_5$), 7.41 (d, *J* = 6.9Hz, 2H, o-$C_6H_5$), 7.47 (d, *J* = 6.9Hz, 2H, o-$C_6H_5$), 7.88 (s, 1H, H8), EI MS m/z: 378 ($M^+$, 86), 287 (M-$CH_2C_6H_5$, 100). Anal. Calcd for $C_{20}H_{18}N_4S_2$: C 63.46, H 4.79, N 14.80. Found C 63.21, H 4.86, N 14.51.

**Hydrolysis of dialkoxy- and dialkylthio-7-methylpurines 1 to 2-substituted 7-methyl-6-purinones 2 - general procedure.**

To the substrates **1** (10 mmol) in 8-10% aqueous NaOH solution (100 mL, method A) or a mixture of 8% NaOH-EtOH solution (1:2 v/v, 120 mL, method B) or 5% NaOH-DMSO solution (1:2 v/v, 40 mL, method C) was added. The mixture was boiled (until all the material had gone into solution) for 1-4 h up to full clarification of a suspension. In 5% NaOH-DMSO solution, the suspension of the substrates **1d** or **1h** was stirred on an oil bath at 100 °C for 1.5 h. After cooling the clear solution was brought to pH = 6 by addition of glacial acetic acid. The resulting solid was filtered off, air-dried and crystallized from EtOH to give 6-purinones **2a-h**. When the reaction was carried out in NaOH-EtOH solution, a mixture of two products was obtained. After cooling, EtOH was evaporated *in vaccuo* and the residue was neutralized with diluted hydrochloric acid. The resulting solid was filtered off to give crude products which were purified by column chromatography (silica gel, $CHCl_3$) to give 6-purinones **2d**, **2g** and **2h**. The filtrate was extracted with $CHCl_3$ (3 x 10 mL), the extracts were dried with anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The residue was purified by column chromatography (silica gel, $CHCl_3$) to give 2-allylthio- 6-ethoxy-7-methylpurine **1i** or 2-benzylthio-6-ethoxy-7-methylpurine **1j**.

1. 2-Methoxy-7-methyl-6-oxo-1,6-dihydropurine (**2a**) (1.53g, 85%); mp 219-220 °C (EtOH-water), lit.,[13] mp 220 °C.

2. 2-Ethoxy-7-methyl-6-oxo-1,6-dihydropurine (**2b**) (1.89g, 97%); mp 214-215 °C (EtOH-water).

$^1$H NMR (DMSO-$d_6$) δ: 1.29 (t, $J$ = 6.9 Hz, 3H, Me), 3.88 (s, 3H, NMe), 4.30 (q, $J$ = 6.9 Hz, 2H, $OCH_2$), 7.92 (s, 1H, C8), 10.02 (s, 1H, NH), EI MS m/z: 194 ($M^+$, 76), 166 (M-$C_2H_4$, 100). Anal. Calcd for $C_8H_{10}N_4O_2$: C 49.48, H 5.19, N 28.85. Found C 49.18, H 5.25, N 28.54.

3. 2-Allyloxy-7-methyl-6-oxo-1,6-dihydropurine (**2c**) (1.95g, 95%); mp 199-200 °C (EtOH-water).

$^1$H NMR (DMSO-$d_6$) δ: 3.89 (s, 3H, NMe), 4.80 (d, $J$ = 6.4 Hz, 2H, $OCH_2$), 5.25 (d, $J$ = 11.1 Hz, 1H, $=CH_2$), 5.40 (d, $J$ = 18.0 Hz, 1H, $=CH_2$), 6.04 (m, 1H, =CH), 7.94 (s, 1H, H8), 10.04 (s, 1H, NH), EI MS m/z: 206 ($M^+$, 23), 165 (M-$C_3H_5$, 100). Anal. Calcd for $C_9H_{10}N_4O_2$: C 52.42, H 4.89, N 27.17. Found C 52.18, H 4.96, N 26.88.

4. 2-Benzyloxy-7-methyl-6-oxo-1,6-dihydropurine (**2d**) (method A: 0.54g, 21%, method B: 2.41g, 94%); mp 191-192 °C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 3.87 (s, 3H, NMe), 5.32 (s, 2H, $CH_2$) 7.32 (t, $J$ = 7.4 Hz, 1H, p-$C_6H_5$), 7.38 (t, $J$ = 7.4 Hz, 2H, m-$C_6H_5$), 7.44 (d, $J$ = 7.4 Hz, 2H, o-$C_6H_5$), 7.89 (s, 1H, H8), 10.12 (s, 1H, NH), EI MS m/z: 256 ($M^+$, 30), 165 (M-$CH_2C_6H_5$, 13), $C_6H_5CH_2^+$ (100). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C 60.93, H 4.72, N 21.86. Found C 60.81, H 4.77, N 21.49.

5. 2-Methylthio-7-methyl-6-oxo-1,6-dihydropurine (**2e**) (1.92g, 98%); mp 303-305 °C (water), lit.,[10b] mp > 300 °C.

6. 2-Ethylthio-7-methyl-6-oxo-1,6-dihydropurine (**2f**) (1.89g, 90%); mp 275-276 °C (EtOH-water).

$^1$H NMR (DMSO-$d_6$) δ: 1.27 (t, $J$ = 7.2 Hz, 3H, Me), 3.03 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 3.88 (s, 3H, NMe), 7.82 (s, 1H, H8), 10.19 (s, 1H, NH), EI MS m/z: 210 ($M^+$, 100), 182 (M-$C_2H_4$, 43). Anal. Calcd for $C_8H_{10}N_4OS$: C 45.70, H 4.79, N 26.65. Found C 45.49, H 4.69, N 26.39.

7. 2-Allylthio-7-methyl-6-oxo-1,6-dihydropurine (**2g**) (method A: 0.42 g, 19%, method B: 1.05g, 88%); mp 216-218 °C (EtOH-water).

$^1$H NMR (DMSO-$d_6$) δ: 3.83 (d, $J$ = 6.9 Hz, 2H, $SCH_2$), 3.91 (s, 3H, NMe), 5.12 (d, $J$ = 10.5 Hz, 1H, $=CH_2$), 5.31 (d, $J$ = 17.4 Hz, 1H, $=CH_2$), 5.95 (m, 1H, =CH), 8.07 (s, 1H, H8), 10.38 (s, 1H, NH), EI MS m/z: 222 ($M^+$, 100), 181 (M-$C_3H_5$, 55). Anal. Calcd for $C_9H_{10}N_4OS$: C 48.64, H 4.53, N 25.21. Found C 48.41, H 4.55, N 24.92.

In the case of method B an additional product was isolated: 2-allylthio-6-ethoxy-7-methylpurine (**1i**) (0,20g, 8%); mp 165-166 °C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 1.47 (t, $J$ = 7.2 Hz, 3H, Me), 3.90 (d, $J$ = 6.9 Hz, 2H, $SCH_2$), 4.02 (s, 3H, NMe), 4.60 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 5.11 (d, $J$ = 10.2 Hz, 1H, $=CH_2$), 5.34 (d, $J$ = 17.3 Hz, 1H, $=CH_2$), 6.04 (m, 1H, =CH), 8.03 (s, 1H, H8), EI MS m/z: 250 ($M^+$, 39), 209 (M-$C_3H_5$, 65), 222 (M-$C_2H_4$, 100). Anal. Calcd for $C_{11}H_{14}N_4OS$: C 52.78, H 5.64, N 22.38. Found C 52.52, H 5.74, N 22.09.

8. 2-Benzylthio-7-methyl-6-oxo-1,6-dihydropurine (**2h**) (method A: 0.27 g, 10%, 2.37g, 87%); mp 246-248 °C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 3.91 (s, 3H, NMe), 4.44 (s, 2H, $CH_2$), 7.32 (m, 3H, m-$C_6H_5$, p-$C_6H_5$), 7.43 (d, $J$ = 6.9 Hz, 2H, o-$C_6H_5$), 8.10 (s, 1H, H8), 12.28 (s, 1H, NH), EI MS m/z: 272 ($M^+$, 100), 181 (M-$CH_2C_6H_5$, 22), $C_6H_5CH_2^+$ (78). Anal. Calcd for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57. Found C 57.07, H 4.49, N 20.28.

In the case of method B an additional product was isolated: 2-benzylthio-6-ethoxy-7-methylpurine (**1j**) (0.36g, 12%), mp 142-143 °C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 1.39 (t, $J$ = 6.9 Hz, 3H, Me), 3.96 (s, 3H, NMe), 4.51 (s, 2H, $SCH_2$), 4.53 (q, $J$ = 6.9 Hz, 2H, $OCH_2$), 7.25 (m, 3H, m-$C_6H_5$, p-$C_6H_5$), 7.42 (d, $J$ = 6.9 Hz, 2H, o-$C_6H_5$), 8.04 (s, 1H, H8), EI MS m/z: 300 ($M^+$, 32), 209 (M-$CH_2C_6H_5$, 19), 272 (M-$C_2H_4$, 100). Anal. Calcd for $C_{15}H_{16}N_4OS$: C 59.98, H 5.37, N 18.65. Found C 59.66, H 5.41, N 18.39.

9. 7-Methylxanthine (**2i**) (1.53 g, 92% from **1d**, 1.49 g, 90% from **1h**), mp > 300 °C (EtOH), lit.,[14] mp > 300 °C.

**Synthesis of 2-subsituted 6-chloro-7-methylpurines 3**

2-Subsituted 6-chloro-7-methylpurines **3a**, **3b** and **3f** were obtained by boiling appropriate 6-purinones **2** with phosphorus oxychloride, as described previously.[10a] When in position 2 in derivatives **2** the ethoxy, allyloxy, benzyloxy **2b-d** or allythio **2g** and benzylthio **2h** groups were present, *O*- or *S*-dealkylation took place and the products were identified as 6-chloro-7-methyl-2-purinone **3i** or 2-purinethione **3j**. 6-Chloroderivatives **3g** and **3h** were prepared by *S*-alkylation with allyl bromide or benzyl chloride of 2-purinethione **3j** according to earlier described procedure.[12]

1. 2-Methoxy-6-chloro-7-methylpurine (**3a**) (1.49g, 75%); mp 156-157 °C (EtOH), lit.,[15] mp 156-158 °C.

2. 2-Methylthio-6-chloro-7-methylpurine (**3e**) (1.86g, 87%); mp 178-179 °C (EtOH), lit.,[10a] mp 176-177 °C.

3. 2-Ethylthio-6-chloro-7-methylpurine (**3f**) (2.03g, 89%); mp 174-175 °C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 1.43 (t, $J$ = 7.2Hz, 3H, Me), 3.32 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 4.06 (s, 3H, NMe), 7.75 (s, 1H, C8), EI MS m/z: 228 ($M^+$, 100), 200 (M-$C_2H_4$, 23). Anal. Calcd for $C_8H_9ClN_4S$: C 42.02, H 3.97, N 24.50. Found C 41.84, H 3.91, N 24.18.

4. 2-Allylthio-6-chloro-7-methylpurine (**3g**) (2.18g, 91%); mp 206-207° C (EtOH).

$^1$H NMR ($CDCl_3$) δ: 3.97 (d, $J$ = 6.9 Hz, 2H, $SCH_2$), 4.06 (s, 3H, NMe), 5.17 (d, $J$ = 10.3 Hz, 1H, =$CH_2$), 5.36 (d, $J$ = 17.2 Hz, 1H, =$CH_2$), 5.97 (m, 2H, =CH), 7.75 (s, 1H, H8), EI MS m/z: 240 ($M^+$, 100), 199 (M-$C_3H_5$, 83). Anal. Calcd for $C_9H_9ClN_4S$: C 44.91, H 3.77, N 23.28. Found C 44.63, H 3.79, N 23.01.

5. 2-Benzylthio-6-chloro-7-methylpurine (**3h**) (2.47g, 85%); mp 163-164 $^{o}$C (EtOH).

$^{1}$H NMR ($CDCl_3$) δ: 4.02 (s, 3H, NMe), 4.45 (s, 2H, $CH_2$), 7.31 (m, 3H, m-$C_6H_5$, p-$C_6H_5$), 7.45 (d, *J* = 6.9 Hz, 2H, o-$C_6H_5$), 8.66 (s, 1H, H8), EI MS m/z: 290 ($M^+$, 100), 199 (M-$CH_2C_6H_5$, 28), $C_6H_5CH_2^+$ (96). Anal. Calcd for $C_{13}H_{11}ClN_4S$: C 53.70, H 3.81, N 19.27. Found C 53.49, H 3.86, N 19.02.

6. 6-Chloro-7-methyl-2-oxo-2,3-dihydropurine (**3i**); mp 290-292 $^{o}$C (water).

$^{1}$H NMR (DMSO-$d_6$) δ: 3.82 (s, 3H, NMe), 7.90 (s, 1H, H8), 11.52 (s, 1H, NH), EI MS m/z: 184 ($M^+$, 100). Anal. Calcd for $C_6H_5ClN_4O$: C 39.04, H 2.73, N 30.35. Found C 38.82, H 2.79, N 30.03.

7. 6-Chloro-7-methyl-2-tioxo-2,3-dihydropurine (**3j**); mp > 300$^{o}$C (water), lit.,[10a] mp > 300 $^{o}$C.

**Synthesis of 6-purinethiones 4a-h**

A. Reaction with thiourea.

A solution of 6-chloroderivative **3a** and **3e-h** (5 mmol) and thiourea (0.76 g, 10 mmol) in absolute EtOH (75 mL) was refluxed for 1-2 h. The solvent was removed *in vaccuo* and the residue was dissolved in 5% NaOH solution. The reaction product was precipitated with 15% hydrochloric acid and the process was repeated twice to give 6-purinethiones **4a** and **4e-h** in 73-86% yields, and **4i**, **4j** in 95% and 98% yields, respectively.

1. 2-Methoxy-7-methyl-6-thioxo-1,6-dihydropurine (**4a**) (0.72g, 73%); mp 238-240 $^{o}$C (EtOH), lit.,[10a] mp. 239-240 $^{o}$C.

2. 2-Methylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4e**) (0.91g, 86%); mp 176-177 $^{o}$C (EtOH), lit.,[10a] mp 176-177 $^{o}$C.

3. 2-Ethylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4f**) (0.95g, 84%); mp 194-196 $^{o}$C (EtOH).

$^{1}$H NMR (DMSO-$d_6$) δ: 1.29 (t, *J* = 7.1 Hz, 3H, Me), 3.06 (q, *J* = 7.1Hz, 2H, $CH_2$), 3.91 (s, 3H, NMe), 7.97 (s, 1H, H8), 13.82 (s, 1H, N1), EI MS m/z: 226 ($M^+$, 100), 198 (M-$C_2H_4$, 12). Anal. Calcd for $C_8H_{10}N_4S_2$: C 42.46, H 4.45, N 24.76. Found C 42.16, H 4.49, N 24.49.

4. 2-Allylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4g**) (0.87 g, 73%); mp 186-188 $^{o}$C (EtOH).

$^{1}$H NMR (DMSO-$d_6$) δ: 3.85 (d, *J* = 6.9 Hz, 2H, $SCH_2$), 3.93 (s, 3H, NMe), 5.13 (d, *J* =10.2 Hz, 1H, =$CH_2$), 5.32 (d, *J* = 17.1 Hz, 1H, =$CH_2$), 5.96 (m, 1H, =CH), 8.10 (s, 1H, H8), 13.92 (s, 1H, N1), EI MS m/z: 238 ($M^+$, 100), 197 (M-$C_3H_5$, 42). Anal. Calcd for $C_9H_{10}N_4S_2$: C 45.36, H 4.23, N 23.51. Found C 45.23, H 4.29, N 23.32.

5. 2-Benzylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4h**) (1.12g, 78%); mp 201-203 $^{o}$C (EtOH).

$^{1}$H NMR (DMSO-$d_6$) δ: 4.15 (s, 3H, NMe), 4.41 (s, 2H, $CH_2$), 7.29 (m, 3H, m-$C_6H_5$, p-$C_6H_5$), 7.44 (d, *J* = 6.9 Hz, 2H, o-$C_6H_5$), 8.18 (s, 1H, H8), 13.59 (s, 1H, N1), EI MS m/z: 288 ($M^+$, 100), 197 (M-$CH_2C_6H_5$, 87). Anal. Calcd for $C_{13}H_{12}N_4S_2$: C 54.14, H 4.19, N 19.43. Found C 53.91, H 4.11, N 19.21.

5. 7-Methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydropurine (**4i**) (0.87g, 95%); mp 342-344 °C (water), lit.,[12] mp 343-344 °C.

6. 7-Methyl-2,6-dithioxo-1,2,3,6-tetrahydropurine (**4j**) (0.97g, 98%); mp >300 °C (EtOH), lit.,[12], mp >300 °C.

B. Reaction with phosphorus pentasulfide

A mixture of 2-alkoxy- or 2-alkylthio-7-methyl-6-purinone **2b-d**, **2g** and **2h** (1 mmol) and phosphorus pentasulfide (0.67g, 3 mmol) in dry pyridine (30 mL) was stirred on oil bath at boiling temperature for 3.5 h. After cooling, the pyridine was removed *in vaccuo* and the residue was treated with boiling water (15 mL) for 15 min. The insoluble portion was dissolved in 25% $NH_4OH$ solution and the products were precipitated by acidification with glacial acetic acid to pH = 5. The resulting solid was filtered off and air-dried to give 6-purinethiones **4b-d, 4g** and **4h** in 56-76% yields.

1. 2-Ethoxy-7-methyl-6-thioxo-1,6-dihydropurine (**4b**) (0.16g, 76%); mp 206-208 °C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 1.29 (t, $J$ = 7.1 Hz, 3H, Me), 3.68 (s, 3H, NMe), 4.33 (q, $J$ = 7.1 Hz, 2H, $OCH_2$), 7.98 (s, 1H, C8), 12.05 (s, 1H, NH), EI MS m/z: 210 ($M^+$, 83), 182 (M-$C_2H_4$, 100). Anal. Calcd for $C_8H_{10}N_4OS$: C 45.70, H 4.79, N 26.65. Found C 45.41, H 4.69, N 26.37.

2. 2-Allyloxy-7-methyl-6-thioxo-1,6-dihydropurine (**4c**) (0.12g, 56%); mp 187-189 °C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 3.77 (s, 3H, NMe), 4.81 (d, $J$ = 6.9 Hz, 2H, $OCH_2$), 5.25 (d, $J$ = 10.1 Hz, 1H, =$CH_2$), 5.42 (d, $J$ = 17.4 Hz, 1H, =$CH_2$), 6.02 (m, 1H, =CH), 8.05 (s, 1H, H8), 12.15 (s, 1H, NH), EI MS m/z: 222 ($M^+$, 19), 181 (M-$C_3H_5$, 100). Anal. Calcd for $C_9H_{10}N_4OS$: C 48.64, H 4.53, N 25.21. Found C 48.39, H 4.56, N 24.92.

3. 2-Benzyloxy-7-methyl-6-thioxo-1,6-dihydropurine (**4d**) (0.17g, 62%); mp 228-230 °C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 4.01 (s, 3H, NMe), 5.80 (s, 2H, $CH_2$), 7.24 (t, $J$ = 7.2 Hz, 1H, p-$C_6H_5$), 7.44 (t, $J$ = 7.2 Hz, 2H, m-$C_6H_5$), 7.56 (d, $J$ = 7.2 Hz, 2H, o-$C_6H_5$), 8.10 (s, 1H, H8), 12.27 (s, 1H, NH), EI MS m/z: 272 ($M^+$, 26), 181 (M-$CH_2C_6H_5$, 18), $C_6H_5CH_2^+$ (100). Anal. Calcd for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57. Found C 57.38, H 4.48, N 20.32.

4. 2-Allylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4g**) (0.15g, 63%); mp 186-188 °C (EtOH).

5. 2-Benzylthio-7-methyl-6-thioxo-1,6-dihydropurine (**4h**) (0.19g, 66%); mp 201-203 °C (EtOH).

**Synthesis of 2-substituted 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)purines 5 - general procedure**

A. A mixture of 6-purinethione **4a-k** (1 mmol), 5-chloro-1-methyl-4-nitroimidazole (0.16g, 1 mmol), 10% NaOH (0.4 mL) and 70% EtOH (10 mL) was refluxed for 2 h. After cooling the resulting solid was filtered off, washed with water, air dried and recrystallized or purified by column chromatography (silica

gel, $CHCl_3$-EtOH, 10:1) to give **5a-k**. The ethanolic filtrate was concentrated *in vaccuo* to 5 mL to give an additional amount of products **5a-h** and **5k** or 7-methyl-6-(1-methyl-4-nitroimidazol-5-ylthio)-2-purinone **5i** and 2-purinethione **5j**. Compounds **5l** and **5m** were separated by column chromatography (silica gel, $CHCl_3$).

1. 2-Methoxy-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5a**) (0.3g, 94%); mp 218-219 $^oC$ (EtOH).

$^1H$ NMR (DMSO-$d_6$) δ: 3.68 (s, 3H, OMe), 3.74 (s, 3H, $N_7Me$), 4.14 (s, 3H, NMe), 8.27 (s, 1H, C8), 8.53 (s, 1H, CH), CI MS m/z: 322 (M+1, 100). Anal. Calcd for $C_{11}H_{11}N_7O_3S$: C 41.12, H 3.45, N 30.51. Found C 41.01, H 3.40, N 30.22.

2. 2-Ethoxy-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5b**) (0.26g, 78%); mp 182-183 $^oC$ (EtOH).

$^1H$ NMR (DMSO-$d_6$) δ: 1.15 (t, $J$ = 7.1 Hz, 3H, Me), 3.72 (s, 3H, N7Me), 4.06 (q, $J$ = 7.1 Hz, 2H, $OCH_2$), 4.12 (s, 3H, NMe), 8.26 (s, 1H, C8), 8.50 (s, 1H, CH), CI MS m/z: 336 (M+1, 60), 307 (M-$C_2H_5$ +1, 100). Anal. Calcd for $C_{12}H_{13}N_7O_3S$: C 42.98, H 3.91, N 29.24. Found C 42.69, H 3.95, N 29.01.

3. 2-Allyloxy-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5c**) (0.25g, 72%); mp 177-178 $^o$C (EtOH).

$^1H$ NMR (DMSO-$d_6$) δ: 3.70 (s, 3H, $N_7Me$), 4.11 (s, 3H, NMe), 4.85 (d, $J$ = 6.9 Hz, 2H, $OCH_2$), 5.18 (d, $J$ = 11.2 Hz, 1H, =$CH_2$), 5.32 (d, $J$ = 18.2 Hz, 1H, =$CH_2$), 5.93 (m, 1H, =CH), 8.23 (s, 1H, H8), 8.45 (s, 1H, CH), CI MS m/z: 348 (M+1, 16), 307 M-$C_3H_5$ +1, 100). Anal. Calcd for $C_{13}H_{13}N_7O_3S$: C 44.95, H 3.77, N 28.23. Found C 44.66, H 3.79, N 27.94.

4. 2-Benzyloxy-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5d**) (0.28g, 71%); mp 192-193 $^o$C (EtOH).

$^1H$ NMR (DMSO-$d_6$) δ: 3.74 (s, 3H, $N_7Me$), 3.85 (s, 3H, NMe), 5.15 (s, 2H, $CH_2$), 7.26 (m, 3H, m-$C_6H_5$, p-$C_6H_5$), 7.41 (d, $J$ = 7.2Hz, 2H, o-$C_6H_5$), 7.46 (s, 1H, H8), 7.88 (s, 1H, CH), CI MS m/z: 398 (M+1, 14), 307 (M-$CH_2C_6H_5$+1, 100). Anal. Calcd for $C_{17}H_{15}N_7O_3S$: C 51.38, H 3.80, N 24.67. Found C 51.19, H 3.89, N 24.38.

5. 2-Methylthio-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5e**) (0.28g, 83%); mp 224-225 $^o$C (DMF/water).

$^1H$ NMR (DMSO-$d_6$) δ: 2.17 (s, 3H, SMe), 3.73 (s, 3H, $N_7Me$), 4.15 (s, 3H, NMe), 8.28 (s, 1H, H8), 8.58 (s, 1H, NH), CI MS m/z: 338 (M+1, 100). Anal. Calcd for $C_{11}H_{11}N_7O_2S_2$: C 39.16, H 3.29, N 29.06. Found C 38.87, H 3.35, N 28.82.

6. 2-Ethylthio-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5f**) (0.27g, 77%); mp 238-239 $^o$C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 1.24 (t, $J$ = 7.5 Hz, 3H, Me), 2.95 (q, $J$ = 7.5 Hz, 2H, $SCH_2$), 3.06 (s, 3H, $N_7$Me), 3.85 (s, 3H, NMe), 6.99 (s, 1H, H8), 7.64 (s, 1H, CH), CI MS m/z: 352 (M+1, 100), 323 (M-$C_2H_5$ +1, 66). Anal. Calcd for $C_{12}H_{13}N_7O_2S_2$: C 41.02, H 3.73, N 27.90. Found C 40.82, H 3.77, N 27.57.

7. 2-Allylthio-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5g**) (0.26g, 72%); mp 174-175 $^o$C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 3.54 (s, 3H, $N_7$Me), 3.88 (d, $J$ = 6.9 Hz, 2H, $SCH_2$), 3.96 (s, 3H, NMe), 5.05 (d, $J$ = 10.1 Hz, 1H, =$CH_2$), 5.22 (d, $J$ = 16.9 Hz, 1H, =$CH_2$), 5.82 (m, 1H, =CH), 7.11 (s, 1H, C8), 7.83 (s, 1H, CH), CI MS m/z: 364 (M+1, 100), 323 (M-$C_3H_5$ +1, 83). Anal. Calcd for $C_{13}H_{13}N_7O_2S_2$: C 42.97, H 3.61, N 26.98. Found C 42.71, H 3.51, N 26.66.

8. 2-Benzylthio-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5h**) (0.31g, 75%); mp 234-235 $^o$C (EtOH).

$^1$H NMR (DMSO-$d_6$) δ: 3.77 (s, 3H, $N_7$Me), 3.87 (s, 3H, NMe), 4.27 (s, 2H, $CH_2$), 7.19 (t, $J$ = 7.2 Hz, 1H, p-$C_6H_5$), 7.27 (t, $J$ = 7.2Hz, 2H, m-$C_6H_5$), 7.39 (d, $J$ = 7.2Hz, 2H, o-$C_6H_5$), 7.65 (s, 1H, H8), 8.09 (s, 1H, CH), CI MS m/z: 414 (M+1, 100), 323 (M-$CH_2C_6H_5$ +1, 88). Anal. Calcd for $C_{17}H_{15}N_7O_2S_2$: C 49.38, H 3.66, N 23.71. Found C 49.21, H 3.56, N 23.48.

9. 7-Methyl-2-oxo-2,3-dihydro-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5i**) (0.21g, 68%); mp 216-218 $^o$C (EtOH-water).

$^1$H NMR (DMSO-$d_6$): δ: 3.77 (s, 3H, $N_7$Me), 3.99 (s, 3H, NMe), 7.99 (s, 1H, H8), 8.09 (s, 1H, CH), 12.24 (s, 1H, $N_3$H), CI MS m/z: 308 (M+1, 100). Anal. Calcd for $C_{10}H_9N_7O_3S$: C 39.09, H 2.95, N 31.91. Found C 39.01, H 2.90, N 31.66.

10. 7-Methyl-2-thioxo-2,3-dihydro-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5j**) (0.04g, 12% from **4g**, 0.06g, 18% from **4h**, 0.03g, 9% from **4j**); mp 223-225 $^o$C (EtOH-water).

$^1$H NMR (DMSO-$d_6$): δ: 3.78 (s, 3H, N7Me), 4.12 (s, 3H, NMe), 8.12 (s, 1H, H8), 8.66 (s, 1H, CH), 12.35 (s, 1H, N1H), CI MS m/z: 324 (M+1, 100). Anal. Calcd for $C_{10}H_9N_7O_2S_2$: C 37.15, H 2.81, N 30.32. Found C 36.91, H 2.88, N 30.02.

11. 2-Chloro-7-methyl-6-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5k**) (0.32g, 98%); mp 257-258 $^o$C (EtOH), lit.,[16] mp 254-255 $^o$C.

$^1$H NMR (DMSO-$d_6$) δ: 3.76 (s, 3H, $N_7$Me), 4.19 (s, 3H, NMe), 8.74 (s, 1H, H8), 8.29 (s, 1H, CH), CI MS m/z: 326 (M+1, 100).

12. 7-Methyl-2,6-bis(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5l**) (0.28g, 62%); mp 165-166 $^o$C (EtOH).

$^1$H NMR (DMSO-$d_6$): δ: 3.68 (s, 3H, $N_7$Me), 3.76 (s, 3H, NMe), 3.89 (s, 3H, NMe), 8.07 (s, 1H, H8), 8.21 (s, 1H, CH), 8.36 (s, 1H, CH), CI MS m/z: 449 (M+1, 100). Anal. Calcd for $C_{14}H_{12}N_{10}O_4S_2$: C 37.50,

H 2.70, N 31.23. Found C 37.23, H 2.77, N 30.99.

13. 6-Ethoxy-7-methyl-2-(1-methyl-4-nitroimidazolyl-5-ylthio)purine (**5m**) (0.08g, 24%); mp 154-156 $^{o}$C (EtOH).

$^{1}$H NMR (DMSO-$d_6$) δ: 1.28 (t, $J$ = 6.9 Hz, 3H, Me), 3.69 (s, 3H, $N_7$Me), 3.90 (s, 3H, NMe), 4.31 (q, $J$ = 6.9 Hz, 2H, $CH_2$), 8.03 (s, 1H, H8), 8.35 (s, 1H, CH), CI MS m/z: 336 (M+1, 12), 307 (M-$C_2H_5$+1, 100). Anal. Calcd for $C_{12}H_{13}N_7O_3S$: C 42.98, H 3.91, N 29.24. Found C 42.71, H 3.81, N 29.01.

B. A mixture of 7-methyl-2,6-thioxanthine **4j** (0.20 g, 1 mmol) and NaH (0.072 g, 3 mmol, washed out with hexane from mineral oil) in dry DMF (6 mL) was stirred at rt for 1 h. 5-Chloro-1-methyl-4-nitroimidazole (0.48 g, 3 mmol) was added and the stirring was continued for 24 h. The reaction mixture was poured into water (15 mL) and extracted with $CHCl_3$ (3 x 5 mL). The extracts were dried with anhydrous $Na_2SO_4$, and evaporated *in vaccuo*. The residue was recrystallized from EtOH to give compound **5l** (0.41g, 91%);

**Reaction of di(imidazolylthio) compound 5l with boiling ethanol**

A solution of di(imidazolylthio) compound **5l** (0.224 g, 0.5 mmol) in dry EtOH (5 mL) was refluxed for 2 h. After cooling a resulted small amount of solid was filtered off and the ethanolic filtrate was was evaporated to dryness *in vaccuo*. The residue was crystallized from 70% EtOH to give compound **5m** (0.14 g, 82%), mp 154-156 $^{o}$C.

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