STUDY OF THIAZOLO[4,5-*d*]PYRIMIDINES : THE SYNTHESIS OF THIAZOLO[4,5-*d*]PYRIMIDINE-2,7-DIONES AND NOVEL RING OPENING TO 2,4-THIAZOLIDINEDIONE

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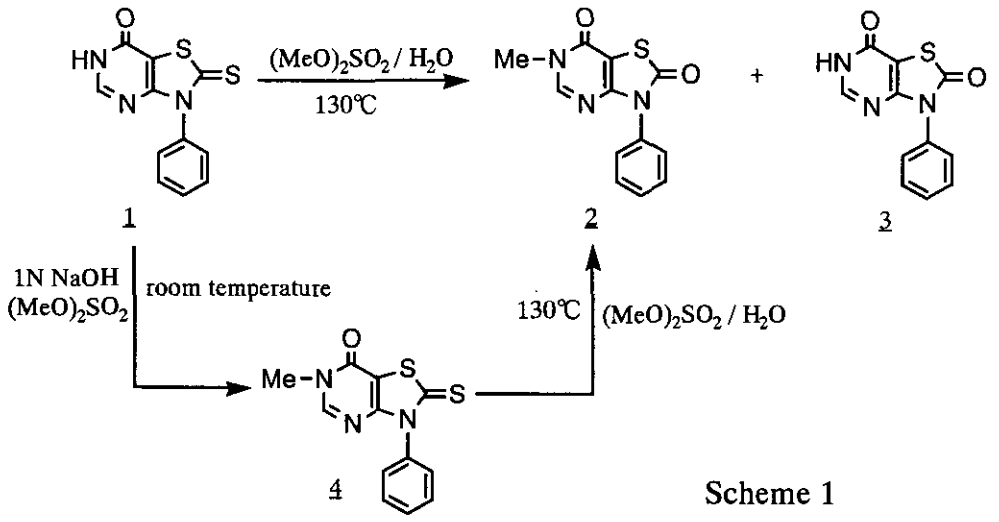
Abstract --- Treatment of 7-oxo-3-phenylthiazolo[4,5-*d*]-pyrimidine-2(6*H*)-thione (**1**) with dimethyl sulfate afforded 6-methyl-3-phenylthiazolo[4,5-*d*]pyrimidine-2,7-dione (**2**), 3-phenylthiazolo[4,5-*d*]pyrimidine-2,7(6*H*)-dione (**3**) and/or 5-*N*-methylcarbamoyl-3-phenyl-2,4-thiazolidinedione (**5**), depending on reaction conditions. Furthermore, reaction of **3** with dimethyl sulfate caused the ring opening to give corresponding **5**. Also, treatment of **5** with phosphorus oxychloride gave 4-chloro-2-oxo-3-phenylthiazolidine-5-*N*-methylcarboxamide (**6**).

We have recently described the synthesis and immunopotentiating properties

of purine nucleoside analogues in the thiazolo[4,5-*d*]pyrimidine ring system.[1,2] We now report the reaction of dimethyl sulfate with a substituted thiazolo-[4,5-*d*]pyrimidine-2-thione. Gewald reported that the reaction of 7-oxo-3-phenyl-thiazolo[4,5-*d*]pyrimidine-2(6*H*)-thione (**1**) with dimethyl sulfate gave only 6-methyl-3-phenylthiazolo[4,5-*d*]pyrimidine-2,7-dione (**2**).[3] However, we found that the treatment of **1** with dimethyl sulfate under the same reaction conditions (at 130°C) afforded **2** and 3-phenylthiazolo[4,5-*d*]pyrimidine-2,7(6*H*)-dione (**3**).[4] Also, heating of **1** with dimethyl sulfate at 110-120°C or 150-160°C gave only **3** or the corresponding **2** and a small amount of a new 2,4-thiazolidinedione (**5**), respectively. Furthermore, the reaction of **3** with aqueous dimethyl sulfate at 150-160°C caused the novel ring cleavage of thiazolo[4,5-*d*]pyrimidine-2,7-dione to give **5**.

Treatment of **1** (1.9 mmol) with 10-fold molar amount of dimethyl sulfate under heat for 1 h at 130°C afforded the corresponding **2** (25%) and **3** (27%), respectively. Next, stirring of **1** with an equivalent amount of dimethyl sulfate in an aqueous solution of 1N NaOH at room temperature for 20 min gave a

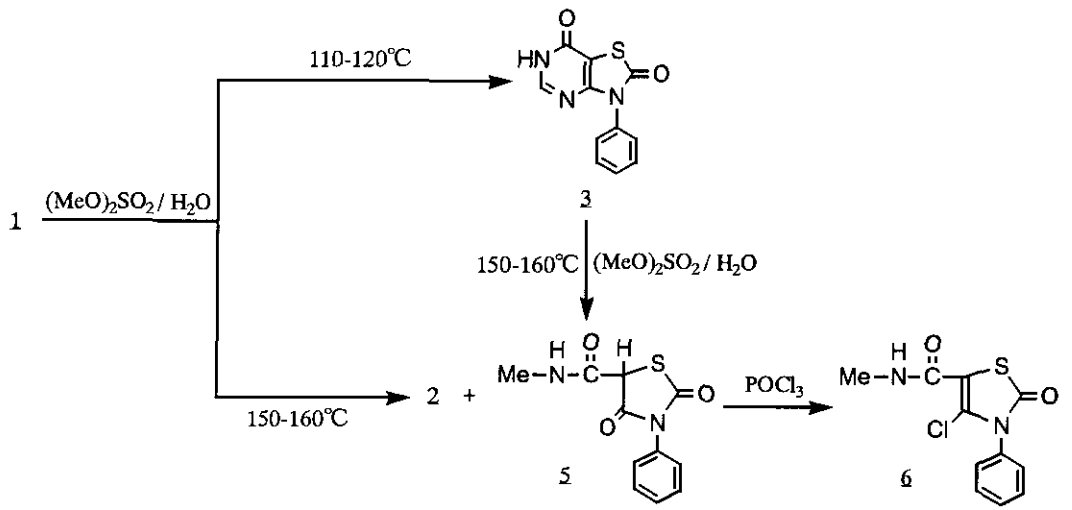


Scheme 1

75% yield of 6-methyl-2-thioxo-3-phenylthiazolo[4,5-*d*]pyrimidin-7-one (**4**).[5] The 6-methyl-2,7-dione type compound (**2**) was identical to the product of the reaction of **4** with dimethyl sulfate under heating for 1 h at 130°C (Scheme 1).

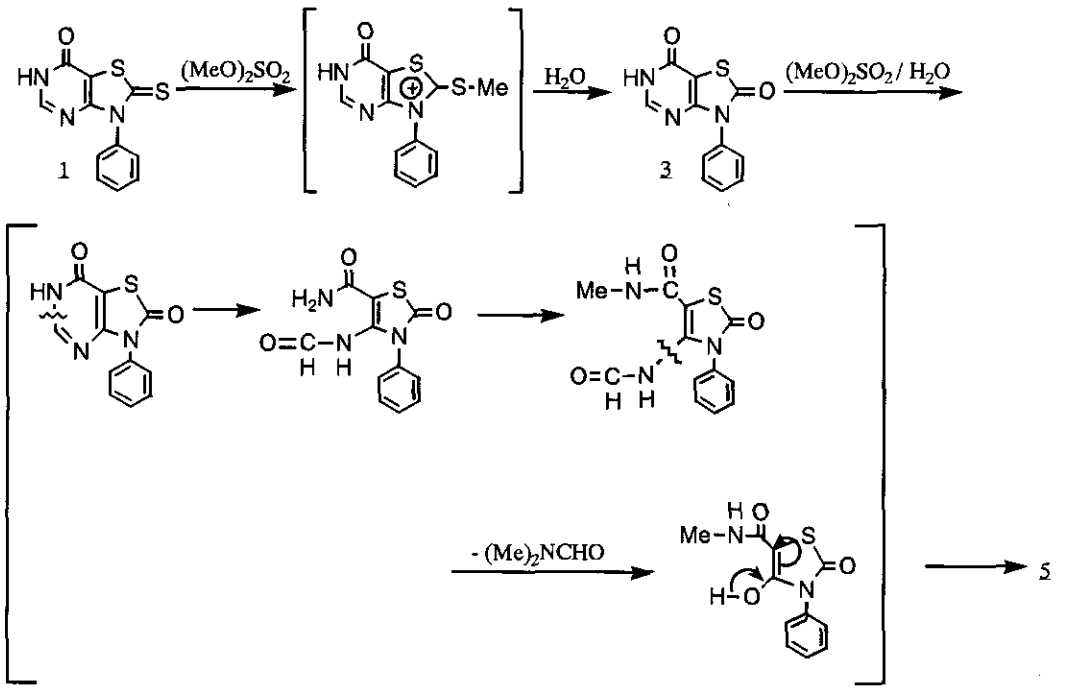
Interestingly, the reaction of **1** with dimethyl sulfate under heating at 110-120°C gave only **3** in high yield (93%). Also, heating of **1** with dimethyl sulfate at 150-160°C afforded **2** (43%) and 5-*N*-methylcarbamoyl-3-phenyl-2,4-thiazolidinedione (**5**) (8%),[6] respectively. Moreover, the reaction of **3** with dimethyl sulfate at 150-160°C for 1 h caused the ring opening to **5** (56%). Heating of **2** with dimethyl sulfate at 150-160°C, however, under the similar reaction conditions resulted in **2** being recovered unchanged.

Next, treatment of **5** (3.3 mmol) with 10-fold molar amount of phosphorus oxychloride and an equivalent amount of *N,N*-dimethylaniline under reflux at 130°C for 3 h afforded 4-chloro-2-oxo-3-phenylthiazolidine-5-*N*-methylcarboxamide (**6**) (49%)[7] (Scheme 2).



Scheme 2

The novel ring cleavage of **1** to **5** probably proceeds through initial hydrolysis of the thione moiety on the compound (**1**), followed by the ring opening of the pyrimidine ring and methylation, and loss of *N,N*-dimethylformamide by hydrolysis (Scheme 3).



Scheme 3

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2. G. D. Kini, J. D. Anderson, Y. S. Sanghvi, A. F. Lewis, D. F. Smee, G. R. Revankar, R. K. Robins, and H. B. Cottam, *ibid.*, 1991, 34, 3006.

3. K. Gewald, J. Prakt. Chem., 1966, 32, 26.

4. **3** : mp > 300°C; EI-ms : m/z 245 (M^+); ir : ν cm^{-1} 3420 (NH), 1700,

1640 (C=O); ^{1}H-nmr (DMSO-d_6) δ : 8.16 (1H, s, C-H), 13.01 (1H, s, N-H, exchangeable with D_2O).

5. **4** : mp 250-251°C; EI-ms : m/z 275 (M^+); ir : ν cm^{-1} 1670 (C=O).

6. **5** : mp 218-219°C; EI-ms : m/z 250 (M^+); ir : ν cm^{-1} 3320 (NH), 1740, 1700, 1670 (C=O); ^{1}H-nmr (DMSO-d_6) δ : 2.69 (3H, d, J= 4.5 Hz, Me), 5.24 (1H, s, C-H, exchangeable with D_2O), 7.26-7.56 (5H, m, Ph), 8.58 (1H, d, J= 4.5 Hz, NH, exchangeable with D_2O); ^{13}C-nmr (DMSO-d_6) δ : 26.4 (Me), 52.2 (C-5, exchangeable with D_2O), 127.8, 129.2, 129.3, 133.1 (Ph), 164.6 (-NHCO-), 169.6 (C-2), 170.9 (C-4).

7. **6** : mp 178-180°C; EI-ms : m/z 268 (M^+), 270 (M + 2); ir : ν cm^{-1} 3420, 3400 (NH), 1690, 1660, 1630 (C=O); ^{1}H-nmr (DMSO-d_6) δ : 2.76 (3H,d, J=4.0 Hz, Me), 7.24-7.57 (5H, m, Ph), 8.03 (1H, d, J= 4.5 Hz, NH, exchangeable with D_2O); ^{13}C-nmr (DMSO-d_6) δ : 26.6 (Me), 108.1 (C-5), 120.8 (C-4), 129.0, 129.1, 129.9, 134.0 (Ph), 158.9 (-NHCO-), 166.7 (C-2).

The compounds (3, 4, 5, 6) were confirmed by the elemental analyses.

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