

# Oxidation with Concurrent Solvolysis of 4-Alkylthio-pyrimidines

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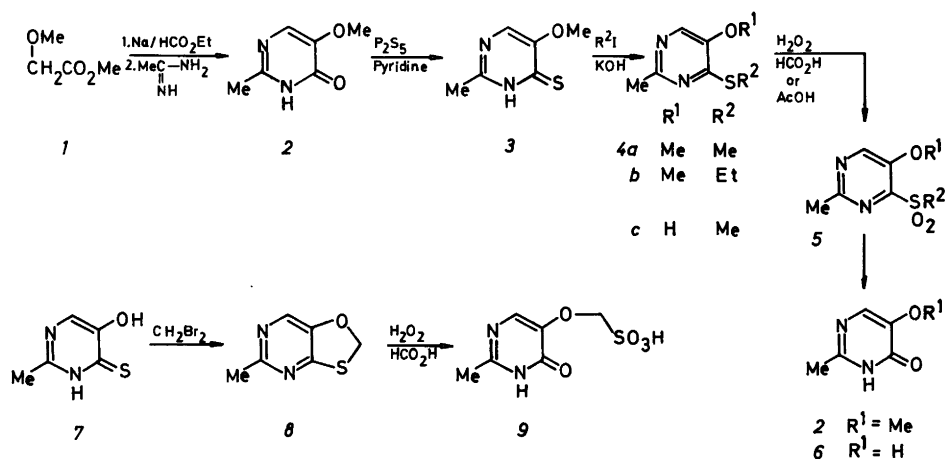
Sulfonyl and sulfinyl substituents in active azine positions are readily displaced by nucleophiles.<sup>1</sup> The oxides of heterocyclic sulfides are generally formed by oxidation reactions of the parent sulfide. Whereas the rate of oxidation of the sulfide is enhanced by high electron availability on the thioether sulfur atom, substitution of the oxidized sulfide is facilitated by electron deficiency in its environment. We herein report on cases where the rate of solvolysis of the oxidized thioether function is faster than its formation under the conditions chosen for the experiments.

The thioethers for the oxidation studies were prepared as shown in Scheme 1. Formylation of methyl methoxyacetate by means of sodium and ethyl formate, and then subsequent condensation of the product with acetamide furnished the 5-methoxy-2-methyl-4-pyrimidinone **2**. The latter was converted into the thiolactam **3** by means of phosphorus pentasulfide, and **3** was subsequently S-alkylated (**4a**, **4b**). The 5-hydroxy analogue **4c** was similarly prepared. In **4**, the electron deficient pyrimidine ring will decrease the rate of oxidation as compared with its benzene analogue. This is to some extent compensated for by the electron donating

properties of the 2-methyl group and the 5-substituent. Even so, the rate of oxidation using peracetic acid, which was generated *in situ* from acetic acid and hydrogen peroxide, was such that at least one week at room temperature was required before all the thioether had reacted. The stronger electron donating power of the hydroxy group over the methoxy group did not markedly affect the rate. With the more powerful performic acid, which was generated *in situ* as above, all the thioether had reacted after 2 days. The product isolated from the reaction has been identified as the lactams **2**<sup>2</sup> and **6**.<sup>3</sup> Oxidized sulfides in the 2-position are less reactive,<sup>4</sup> however, and did not suffer solvolysis when oxidized under the above conditions.<sup>5</sup>

Irrespective of whether the solvolysis occurs at the oxidation level of a sulfoxide or sulfone, the resultant acid is expected to be oxidized further to a sulfonic acid.<sup>6,7</sup> This was confirmed through the preparation of the bicyclic analogue 5-methyl[1,3]-oxathiolo[4,5-*d*]pyrimidine **8** from the 5-hydroxy-4-pyrimidinethione **7** and dibromomethane, and by the subsequent oxidation of **8** as above; the product was the postulated sulfonic acid **9**.

**Experimental.** 5-Methoxy-2-methyl-4-pyrimidinone **2**. Methyl methoxyacetate (104.1 g, 1.0 mol) was added dropwise with stirring at 0 °C to a mixture of sodium (23.0 g, 1.0 mol) and ethyl formate (74.1 g, 1.0 mol) in dry diethyl ether (800 ml). The mixture was stirred at room temperature for 5 h before acetamide hydrochloride (94.5 g, 1.0 mol) in methanol (600 ml) was added, and the ether was subsequently distilled off. The residual mixture was then heated under reflux for 17 h, the solvent distilled off at reduced pressure, water (500 ml) added, and the resultant solution adjusted to pH 5 with concentrated hydrochloric acid which



Scheme 1.

precipitated the product; yield 49.5 g (35%), m.p. 212–215 °C (CHCl<sub>3</sub>).

**5-Methoxy-2-methyl-4-pyrimidinethione 3.** A mixture of 5-methoxy-2-methyl-4-pyrimidinone (12.0 g, 0.086 mol) and phosphorus pentasulfide (19.1 g, 0.086 mol) in dry pyridine (330 ml) was heated under reflux and stirring for 3 h. The cold reaction mixture was poured into water (400 ml) and the resultant mixture was concentrated to ca. 50 ml at reduced pressure. Most of the thione crystallized out (10.4 g) during this operation. Another crop was obtained by extracting the filtrate with chloroform (10 × 15 ml); total yield 11.8 g (88%), m.p. 206–208 °C (MeOH). Anal. C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>OS: C, H. <sup>1</sup>H NMR (TFA): δ 2.87 (2-Me), 4.06 (OMe), 7.49 (H-6). MS [70 eV; m/z (% rel. int.)]: 156 (100, M), 155 (22), 123 (28), 122 (22), 93 (22), 87 (21).

**5-Methoxy-2-methyl-4-methylthiopyrimidine 4a.** Methyl iodide (7.1 g, 0.050 mol) was added dropwise to a solution prepared from 5-methoxy-2-methyl-4-pyrimidinethione (6.0 g, 0.038 mol) in 2 M potassium hydroxide (300 ml). The mixture was stirred for 2 h at room temperature before extraction with ether (3 × 100 ml). The ether solution was washed, dried (MgSO<sub>4</sub>), the ether distilled off, and the white solid residue recrystallized from water; yield 5.3 g (82%), m.p. 90 °C. Anal. C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>OS: C, H. <sup>1</sup>H NMR (TFA): δ 2.73 (SMe), 2.85 (2-Me), 4.07 (OMe), 7.73 (H-6). MS [70 eV; m/z (% rel. int.)]: 170 (100, M), 155 (47), 137 (27), 123 (27), 82 (17).

**4-Ethylthio-5-methoxy-2-methylpyrimidine 4b** was prepared as **4a** above. The product was purified by sublimation at 30 °C/0.01 mmHg; yield 80%, m.p. 53–54 °C. Anal. C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>OS: C, H. <sup>1</sup>H NMR (TFA): δ 1.47 and 3.39 (S-Et), 2.83 (2-Me), 4.05 (OMe), 7.69 (H-6). MS [70 eV; m/z (% rel. int.)]: 184 (100, M) 169 (50), 156 (28), 151 (63), 123 (41), 82 (21).

**5-Hydroxy-2-methyl-4-methylthiopyrimidine 8** **4c** was prepared as above.

**5-Methoxy-2-methyl-4-pyrimidinone 2** **2** and **5-hydroxy-2-methyl-4-pyrimidinone 3** **6.** General procedure: The 4-alkylthiopyrimidine **4** (0.015 mol) was added to an ice-cold solution prepared from 35 % hydrogen peroxide (6.3 g, 0.065 mol) and formic acid (60 ml). The mixture was stirred at room temperature for 2 d before most of the solvent was removed at reduced pressure. Water was added to the residue and the solvents again removed at reduced pressure. The residual material was dissolved in water and the pH adjusted to ca. 5 by addition of sodium carbonate; the lactams **2** and **6** were precipitated in 50–75 % yields.

**5-Methyl[1,3]oxathio[4,5-d]pyrimidine 8.** Dibromomethane (1.20 g, 0.007 mol) in DMF (10 ml) was added to a mixture of 5-hydroxy-2-methyl-4-pyrimidinethione<sup>9</sup> (1.00 g, 0.007 mol) and sodium carbonate (0.74 g, 0.007 mol) in DMF (50 ml). The

mixture was stirred at 85 °C for 4 h before the solvent was distilled off at reduced pressure. Water (40 ml) was added to the residue, the mixture extracted with ether (5 × 25 ml), the dried (MgSO<sub>4</sub>) solution evaporated and the residual oil left in the cold where it slowly crystallized and was further purified by sublimation at 20 °C/0.01 mmHg; yield 0.9 g (83%), m.p. 42–43 °C. Anal. C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>OS: C, H. <sup>1</sup>H NMR (TFA): δ 2.82 (5-Me), 6.20 (CH<sub>2</sub>), 7.75 (H-7). MS [70 eV; m/z (% rel. int.)]: 154 (100, M), 153 (20), 113 (22), 109 (58), 108 (52), 82 (23), 80 (63).

**(2-Methyl-4-oxo-5-pyrimidinyloxy)methanesulfonic acid 9.** 35 % hydrogen peroxide solution in formic acid and 5-methyl[1,3]oxathio[4,5-d]pyrimidine were reacted together as described above in the general oxidation procedure for the synthesis of **2** and **6**. After the addition of water to the partially evaporated reaction mixture, and the subsequent evaporation, the semisolid residue was crystallized from ethanol–water (2:1) in large white crystals; yield 45%, m.p. 158 °C (decomp.). <sup>1</sup>H NMR (TFA): 2.93 (2-Me), 5.36 (CH<sub>2</sub>), 8.12 (H-6). MS [70 eV; m/z (% rel. int.)]: 220 (4, M), 139 (33), 138 (33), 126 (92), 108 (19), 64 (100, SO<sub>2</sub>). High resolution MS: Found M: 220.0148. Calc. for C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>S: 220.0152.

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