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Reaction of 6-Aminouracils with Ketenethioacetals

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Reaction of ketenethioacetals [methyl 2-cyano-3,3-bis(methylthio)acrylate (**2**), 3,3-bis-(methylthio)-2-phenylsulfonylacrylonitrile (**13**)] with 6-aminouracils (**1a**: $R^1=R^2=Me$, **1b**: $R^1=Ph$, $R^2=H$) in the presence of potassium carbonate followed by cyclization under reflux in diphenyl ether gave the corresponding 5-amino-6-methoxycarbonyl-7-methylthiopyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione derivatives (**4a**, **b**). Reaction of other ketenethioacetals [2-cyano-3,3-bis(methylthio)acrylonitrile (**10**), dimethyl bis(methylthio)methylenemalonate (**18**), α-oxo ketenethioacetals (**21a—e**)] with **1** directly afforded pyrido[2,3-*d*]pyrimidine derivatives (**11a**, **b**, **20a**, **b**, **23a—e**) in good yields. 5-Amino-7-methylthiopyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives (**16a—c**) were also synthesized from 6-aminouracils (**1a**, **b**) and dimethyl cyanoimidodithiocarbonate (**15**) in a manner similar to that used for the preparation of compound **11a**.

Keywords——ketenethioacetal; 6-aminouracil; displacement; cyclization; desulfurization; pyrido[2,3-*d*]pyrimidine; pyrimido[4,5-*d*]pyrimidine

Ketenethioacetals appropriately functionalized (cyano, methoxycarbonyl, sulfonyl, nitro, acyl, aroyl, *etc.*) are reactive toward nucleophiles such as amine or active methylene compounds. These reactions produce useful heterocyclic compounds not otherwise readily available.[1] Recently, we have reported that the reaction of ketenethioacetals with enamines gave the corresponding displacement products of a methylthio group.[2] In our present paper, we wish to report the reaction of 6-aminouracils, which have an enamine structure, with various typical ketenethioacetal derivatives.

Reaction of 6-amino-1,3-dimethyluracil (**1a**) with methyl 2-cyano-3,3-bis(methylthio)-acrylate (**2**) in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 100 °C for 4—5 h gave only a displacement product (**3a**) in 75% yield. The nuclear magnetic resonance (NMR) spectrum (δ in CF_3COOH) showed the proton of the 5-position on the pyrimidine ring at 6.43 ppm. Its infrared (IR) spectrum showed two carbonyl absorption bands at 1710 cm^{-1} ($COOCH_3$) and 1650 cm^{-1} (C=O of pyrimidine) and cyano absorption at 2220 cm^{-1}. Compound **3b** ($R^1=Ph$, $R^2=H$) was also prepared in 72% yield from 6-amino-1-phenyluracil (**1b**) and **2** in a similar manner. These products **3a** and **3b**, when heated in diphenyl ether, gave the corresponding cyclized products, 5-amino-6-methoxycarbonyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives (**4a**, **b**), in 86 and 85% yields, respectively, by cyclization between the 5-position in uracil and a cyano group. Compound **4a** was treated with 40% hydrobromic acid to give the demethoxycarbonylation product, 5-amino-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**5**), in 48% yield. The NMR spectrum (δ CF_3COOH) revealed the signal of the proton at the 6-position at 6.75 ppm as a singlet. Raney-nickel desulfurization of **5** in ethanol afforded 5-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**6**) in 70% yield. Its IR spectrum showed primary amino absorption bands at 3420 and

3300 cm^{-1} and the NMR spectrum (δ DMSO-d_6) showed two doublets due to the hydrogens at the 6- and 7-positions at 6.37 (J=6 Hz) and 7.92 (J=6 Hz). On the other hand, a positional isomer of the amino group, 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9**), was synthesized by desulfurization of 7-amino-6-cyano-5-methylthio-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**8**). Compound **8** was prepared in good yield by the reaction of methyl 6-amino-1,3-dimethyluracil-5-dithiocarboxylate (**7**) with dimethyl sulfate followed by reaction with malononitrile in the presence of potassium carbonate in dimethyl sulfoxide (DMSO). When compounds **1a** and **b** were reacted with 2-cyano-3,3-bis(methylthio)acrylonitrile (**10**) in the presence of potassium carbonate in DMF at 100 °C for 5 h, the corresponding fused pyrimidopyrimidine derivatives, 5-amino-6-cyano-7-methylthiopyrimido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**11a** and **b**), were obtained in 60 and 56% yields, respectively. Determination of the structures, **11a** and **b**, was based on comparison of the IR and NMR spectra with those of the structural isomer **8**. The IR spectrum of **11a** showed primary amino absorption bands at 3360 and 3200 cm^{-1}. The NMR spectrum

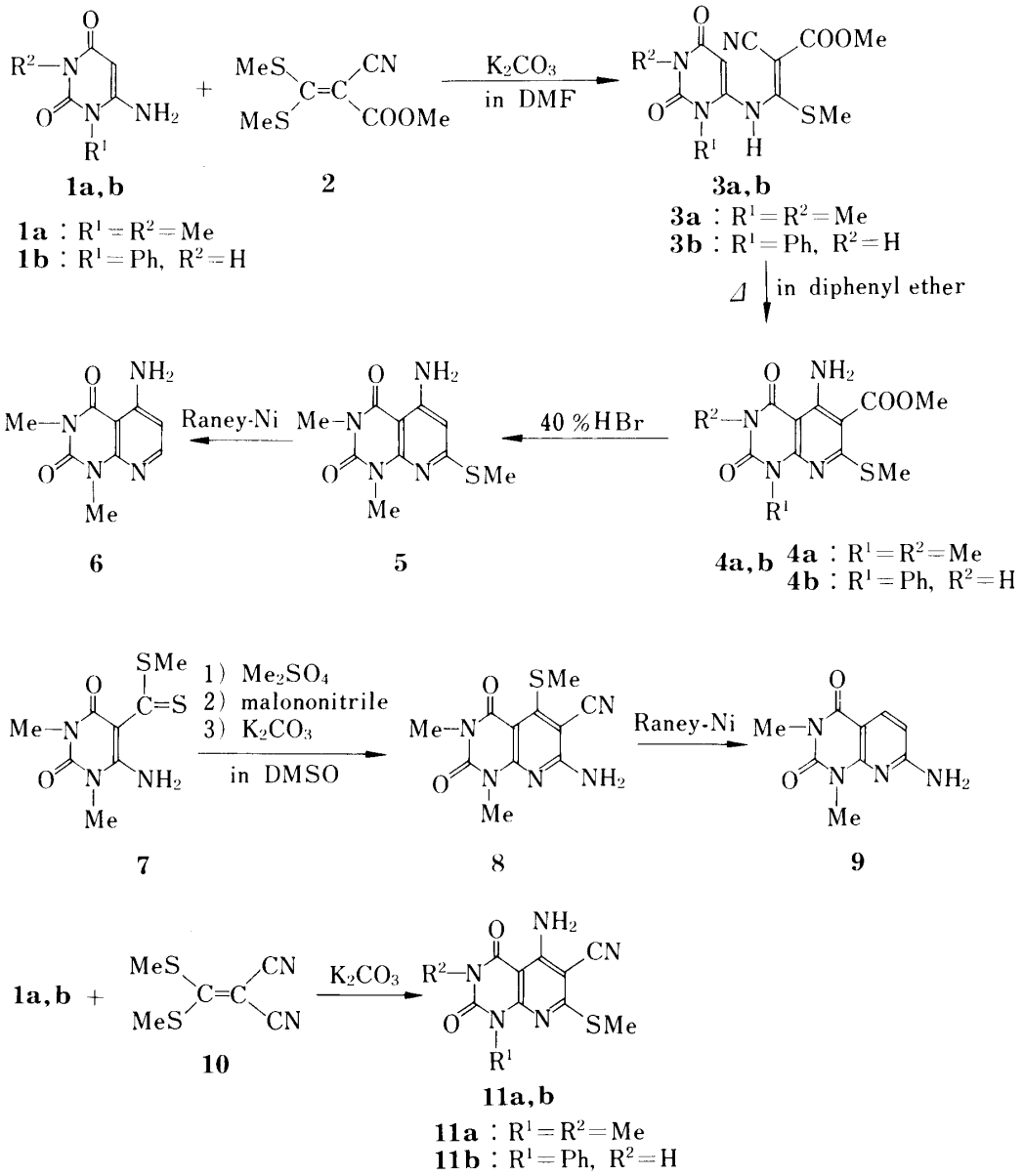
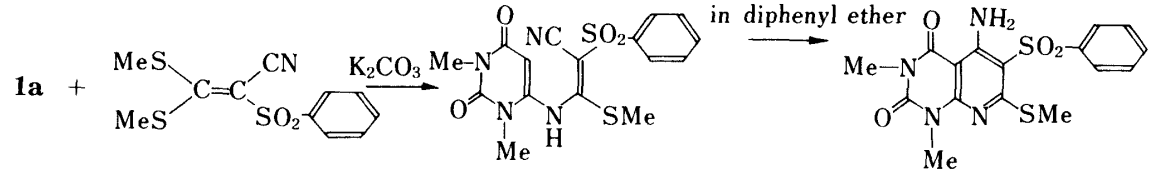


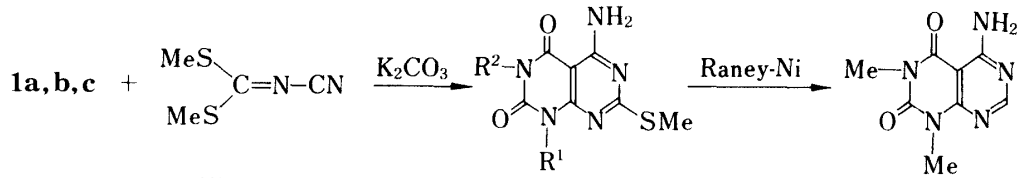
Chart 1

(δ DMSO-d_6) showed two broad singlets due to amino protons at 7.96 and 8.96 ppm and did not show any signal of a proton at the 5-position in uracil.

Reaction of **1a** with 3,3-bis(methylthio)-2-phenylsulfonylacrylonitrile (**12**) afforded a

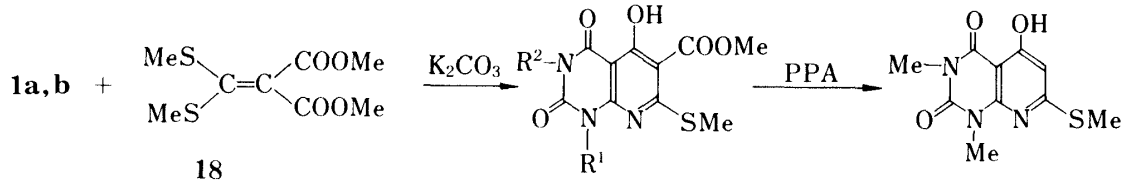


12 **13** **14**



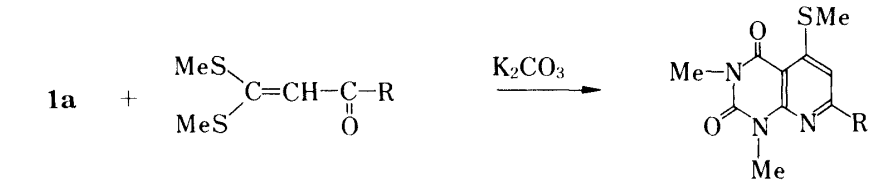
15 **16a,b,c** **17**

16a : $R^1=R^2=Me$
16b : $R^1=Ph$, $R^2=H$
16c : $R^1=Ph$, $R^2=Me$



18 **19a,b** **20**

19a : $R^1=R^2=Me$
19b : $R^1=Ph$, $R^2=H$



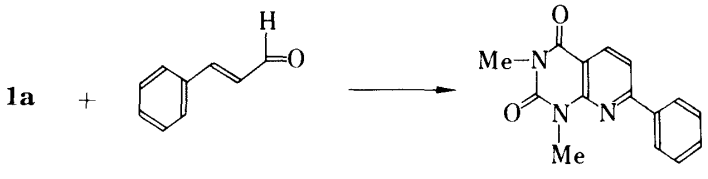
21a,b,c,d,e **22a,b,c,d,e**

R

21a : Ph
21b : p-Cl-Ph
21c : p-Br-Ph
21d : p-Me-Ph
21e : 2-furyl

R

22a : Ph
22b : p-Cl-Ph
22c : p-Br-Ph
22d : p-Me-Ph
22e : 2-furyl



23

Chart 2

displacement product (**13**) in good yield. In a manner similar to that used for the preparation of **4a**, cyclization of **13** in diphenyl ether gave the desired product, 5-amino-1,3-dimethyl-7-methylthio-6-phenylsulfonylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14**), mp 231 °C, in 46% yield.

Condensation of **1a** with dimethyl cyanoimidodithiocarbonate (**15**) in the presence of potassium carbonate in DMF on a boiling water bath for 5 h gave a fused pyrimidine, 5-amino-1,3-dimethyl-7-methylthiopyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**16a**), colorless needles, mp 236 °C, in 72% yield. Raney-nickel desulfurization of **16a** in ethanol afforded 5-amino-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**17**), mp 268 °C, which was also synthesized by treatment of methyl 6-amino-1,3-dimethyluracil-5-dithiocarboxylate (**7**) with formamide at 180 °C for 5 h in 45% yield.[3] By the same method, other 5-aminopyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives (**16b**, **c**) were also obtained by the reaction of **1b** and **c** with **15** in good yields.

Similarly, reaction of **1a** and **b** with dimethyl bis(methylthio)methylenemalonate (**18**) afforded the corresponding desired products (**19a** and **b**), 5-hydroxy-6-methoxycarbonyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**19a**: $R^1=R^2=CH_3$, **19b**: $R^1=Ph$, $R^2=H$), in 48 and 20% yields, respectively. Compound **19a** was treated with polyphosphoric acid (PPA) to give 5-hydroxy-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**20**) in 39% yield.

We also examined the reaction of **1a** with α-oxo-ketenethioacetals. As recently pointed out by Junjappa *et al.*,[4] these ketenethioacetals are very useful reagents for the preparation of heterocyclic compounds. The reaction of **1a** with bis(methylthio)methyleneacetophenone (**21a**) in the presence of potassium carbonate at 150 °C in DMF or sulfolane gave the cyclized product, 1,3-dimethyl-5-methylthio-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**22a**), in 70% yield. The structure of **22a** was evident from its spectral and chemical data. Its IR spectrum showed carbonyl bands at 1690 and 1650 cm^{-1} and the NMR spectrum showed a broad singlet due to the proton at the 6-position at 7.36 ppm and three singlets corresponding to three methyl groups at 2.52 (SCH_3), 3.44 (NCH_3), and 3.76 ppm (NCH_3). Treatment of **22a** with Raney-nickel gave 1,3-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**23**) in 71% yield. Compound **23** was identical with an authentic sample which was alternatively prepared by the condensation of **1a** with cinnamaldehyde.[5] The above reaction is initiated by condensation of an amino group in uracil with a carbonyl group in ketenethioacetal followed by the displacement between methylthio group and the proton at the 5-position in uracil. The condensation of other α-oxoketenethioacetals (**21b**—**e**) with **1a** was similarly carried out to give the corresponding 7-arylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones (**22b**—**e**) in good yields.

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were recorded in KBr pellets on a JASCO IRA-2 spectrometer, ultraviolet (UV) absorption spectra were determined on a Hitachi EP-S2 spectrometer in 95% EtOH, and NMR spectra were obtained using a JNM-PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-01SG mass spectrometer.

Methyl 2-Cyano-3-methylthio-3-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-pyrimidinyl)aminoacrylate (3a)—A mixture of 6-amino-1,3-dimethyluracil (**1a**) (1.5 g, 10 mmol), methyl 2-cyano-3,3-bis(methylthio)acrylate (**2**) (2.3 g, 10 mmol), K_2CO_3 (2.1 g, 15 mmol), and 30 ml of DMF was heated at 150 °C on an oil bath for 5 h. The reaction mixture was then poured into 200 ml of H_2O and acidified with 10% HCl. The precipitate that appeared was collected by filtration and recrystallized from C_6H_6–MeOH to give 2.25 g (75%) of colorless needles, mp 189 °C. IR ν (KBr) cm^{-1}: 2200 (CN), 1710, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 268 (4.18), 302 (4.13). ^{1}H-NMR (CF_3COOH) δ: 2.63 (3H, s, SCH_3), 3.55 (3H, s, NCH_3), 3.67 (3H, s, NCH_3), 3.95 (3H, s, OCH_3), 6.43 (1H, s, 5-H). *Anal.* Calcd for $C_{12}H_{14}N_4O_4S$: C, 46.45; H, 4.55; N, 18.05; S, 10.33. Found: C, 46.60; H, 4.51; N, 18.10; S, 10.22.

Methyl 2-Cyano-3-methylthio-3-(1,2,3,4-tetrahydro-2,4-dioxo-1-phenyl-6-pyrimidiniyl)aminoacrylate (3b)——This compound was synthesized from 6-amino-1-phenyluracil (**1b**) (2.3 g, 10 mmol) and **2** (2.03 g, 10 mmol) in a manner similar to that described for the preparation of **3a**; **3b** was obtained in 72% yield. An analytical sample was recrystallized from C_6H_6–MeOH to give colorless needles, mp 219 °C. IR ν (KBr) cm^{-1}: 2200 (CN), 1725, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 273 (4.22), 307 (4.17). ^{1}H-NMR (CF_3COOH) δ: 2.68 (3H, s, SCH_3), 3.82 (3H, s, OCH_3), 6.56 (1H, s, 5-H), 7.40—7.80 (5H, m, phenyl protons). MS *m/e*: 358 (M^+, 100). *Anal.* Calcd for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63; S, 8.95. Found: C, 53.52; H, 4.02; N, 15.43; S, 8.99.

5-Amino-6-methoxycarbonyl-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a)——A solution of 1 g (3.2 mmol) of **3a** in 20 ml of diphenyl ether was refluxed for 5 h then cooled and 50 ml of petroleum ether was added. The precipitate was collected by filtration and recrystallized from C_6H_6–MeOH to give 0.86 g (86%) of colorless needles, mp 232 °C. IR ν (KBr) cm^{-1}: 3360, 3240 (NH), 1700, 1675 (C=O). UV λ_{max}^{EtOH} nm (log ε): 267 (4.69), 308 (4.24). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, SCH_3), 3.38 (3H, s, NCH_3), 3.62 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 8.60 (1H, br s, NH), 9.60 (1H, br s, NH). MS *m/e*: 310 (M^+, 100). *Anal.* Calcd for $C_{12}H_{14}N_4O_4S$: C, 46.45; H, 4.55; N, 18.05; S, 10.33. Found: C, 46.39; H, 4.50; N, 18.03; S, 10.21.

5-Amino-6-methoxycarbonyl-7-methylthio-1-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b)——This compound was synthesized from **3b** in a manner similar to that described for the preparation **4a**; **4b** was obtained in 85% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 281 °C. IR ν (KBr) cm^{-1}: 3380, 3240 (NH), 1730, 1700 (C=O). UV EtOH (poorly soluble) nm: λ_{max}: 266, 309, λ_{min}: 285. ^{1}H-NMR (DMSO-d_6) δ: 2.46 (3H, s, SCH_3), 3.76 (3H, s, OCH_3), 7.24—7.52 (5H, m, phenyl protons), 8.32 (1H, br s, NH), 9.44 (1H, br s, NH), 11.36 (1H, br s, NH). MS *m/e*: 358 (M^+, 100). *Anal.* Calcd for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63; S, 8.95. Found: C, 53.56; H, 3.75; N, 15.69; S, 8.78.

5-Amino-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5)——A mixture of 3.1 g (10 mmol) of **4a**, 50 ml of AcOH and 20 ml of 40% HBr was refluxed for 10 h on an oil bath. After evaporation of the solvent, the residue was recrystallized from C_6H_6–MeOH to give 1.2 g (48%) of colorless needles, mp 268 °C. IR ν (KBr) cm^{-1}: 3420, 3310 (NH), 1680—1690 (br), 1637 (C=O). UV λ_{max}^{EtOH} nm (log ε): 250 (4.47), 295 (4.27). ^{1}H-NMR (CF_3COOH) δ: 2.68 (3H, s, SCH_3), 3.57 (3H, s, NCH_3), 3.85 (3H, s, NCH_3), 6.57 (1H, s, 6-H). *Anal.* Calcd for $C_{10}H_{12}N_4O_2S$: C, 47.62; H, 4.80; N, 22.22; S, 12.70. Found: C, 47.52; H, 4.80; N, 22.04; S, 12.85.

5-Amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6)——A mixture of 2.5 g (10 mmol) of **5**, 20 ml of EtOH suspension of Raney-Ni, and 50 ml of EtOH was refluxed for 24 h and filtered to remove Raney-Ni. The filtrate was concentrated and the residue was recrystallized from EtOH to give 1.4 g (70%) of colorless needles, mp 223 °C. IR ν (KBr) cm^{-1}: 3420, 3300 (NH), 1690, 1675 (C=O). UV λ_{max}^{EtOH} nm (log ε): 235 (4.54), 316 (3.83). ^{1}H-NMR (DMSO-d_6) δ: 3.21 (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 6.37 (1H, d, J=6 Hz, 6-H), 7.60 (1H, br s, NH), 7.92 (1H, d, J=6 Hz, 7-H), 8.10 (1H, br s, NH). *Anal.* Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.26; H, 4.82; N, 27.00.

7-Amino-6-cyano-1,3-dimethyl-5-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8)——A mixture of 2.45 g (10 mmol) of methyl 6-amino-1,3-dimethyluracil-5-dithiocarboxylate (**7**) and 3.78 g (30 mmol) of Me_2SO_4 was heated on a boiling water bath for 10 min. After cooling, malononitrile (1.3 g, 30 mmol) was added to the above methyl sulfate salt. This mixture was stirring for 20 min then added to a mixture of 50 ml of dimethyl sulfoxide and 4 g (30 mmol) of K_2CO_3 and whole was stirred at room temperature for 1 h then heated on a boiling water bath. The reaction mixture was poured into 300 ml of ice-water. The precipitate was collected by filtration and recrystallized from MeOH to give 1.45 g (53%) of colorless needles, mp 267 °C. IR ν (KBr) cm^{-1}: 3300, 3200 (NH), 2200 (CN), 1710 (C=O). UV λ_{max}^{EtOH} nm (log ε): 226 (4.42), 268 (4.38), 277 (4.40), 337 (4.16). ^{1}H-NMR (CF_3COOH) δ: 3.08 (3H, s, SCH_3), 3.60 (3H, s, NCH_3), 3.88 (3H, s, NCH_3). *Anal.* Calcd for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.26; S, 11.56. Found: C, 47.86; H, 3.97; N, 25.51; S, 11.58.

7-Amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9)——This compound was synthesized from **8** by treatment with Raney-Ni in a manner similar to that described for the preparation of **6**; **9** was obtained in 97% yield. An analytical sample was recrystallized from EtOH to give colorless needles, mp 309 °C. IR ν (KBr) cm^{-1}: 3320, 3220 (NH), 1690, 1600 (C=O). UV λ_{max}^{EtOH} nm (log ε): 223 (4.43), 277 (3.93), 316 (4.28), 321 (4.28), 328 (4.24). ^{1}H-NMR ($CDCl_3$) δ: 3.52 (3H, s, NCH_3), 3.84 (3H, s, NCH_3), 7.81 (1H, d, J=8 Hz, 6-H), 8.60 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.50; H, 4.94; N, 26.98.

5-Amino-6-cyano-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11a)——A mixture of 1.5 g (10 mmol) of **1a**, 1.7 g (10 mmol) of 2-cyano-3,3-bis(methylthio)acrylonitrile (**10**), 2.1 g (15 mmol) of K_2CO_3, and 30 ml of DMF was heated on a boiling bath for 5 h, then poured into 300 ml of ice-water and acidified with 10% HCl. The precipitate was recrystallized from C_6H_6–MeOH to give 1.64 g (60%) of colorless needles, mp 232 °C. IR ν (KBr) cm^{-1}: 3360, 3200 (NH), 2200 (CN), 1700 (C=O). UV λ_{max}^{EtOH} nm (log ε): 264 (4.71), 304 (4.19). ^{1}H-NMR (DMSO-d_6) δ: 2.56 (3H, s, SCH_3), 3.20 (3H, s, NCH_3), 3.48 (3H, s, NCH_3), 7.98 (1H, br s, NH), 8.96 (1H, br s, NH). *Anal.* Calcd for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.26; S, 11.56. Found: C, 47.79; H, 3.97; N, 25.22; S, 11.29.

5-Amino-6-cyano-7-methylthio-1-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11b)——This compound was synthesized from **1b** (2.3 g, 10 mmol) and 10 (1.7 g, 10 mmol) in a manner similar to that described for the preparation of **11a** and was obtained as colorless needles, mp 335 °C, which were recrystallized from C_6H_6–MeOH, in 56% yield.

IR ν (KBr) cm^{-1}: 3340, 3160 (NH), 2200 (CN), 1710 (C=O). UV λ_{max}^{EtOH} nm (log ε): 264 (4.68), 304 (4.20). ^{1}H-NMR (CF_3COOH) δ: 2.04 (3H, s, SCH_3), 7.28—7.72 (5H, m, phenyl protons). *Anal.* Calcd for $C_{15}H_{11}N_5O_2S$: C, 55.38; H, 3.41; N, 21.53; S, 9.86. Found: C, 55.38; H, 3.35; N, 21.47; S, 9.75.

3-Methylthio-2-phenylsulfonyl-3-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-pyrimidinyl)aminoacrylonitrile (13)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and 3,3-bis(methylthio)-2-phenylsulfonylacrylonitrile (**12**) (2.85 g, 10 mmol) in a manner similar to that described for the preparation of **3a** and was obtained in 70% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 232 °C. IR ν (KBr) cm^{-1}: 3395 (NH), 2180 (CN), 1738, 1684 (C=O). UV λ_{max}^{EtOH} nm (log ε): 264 (4.21), 306 (4.13), 357 (4.26). ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s, SCH_3), 3.10 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 5.90 (1H, br s, 5-H), 7.40—7.92 (5H, m, phenyl protons). *Anal.* Calcd for $C_{16}H_{16}N_4O_4S_2$: C, 48.98; H, 4.11; N, 14.28; S, 16.34. Found: C, 49.04; H, 4.08; N, 14.25; S, 16.10.

5-Amino-1,3-dimethyl-7-methylthio-6-phenylsulfonylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (14)——This compound was synthesized from **13** in a manner similar to that described for the preparation of **4a** and was obtained in 46% yield. An analytical samples was recrystallized from MeOH to give colorless needles, mp 231 °C. IR ν (KBr) cm^{-1}: 3410, 3270 (NH), 1705, 1650 (C=O), 1321, 1137 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 224 (4.25), 268 (4.61), 307 (4.22). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, SCH_3), 3.38 (3H, s, NCH_3), 3.58 (3H, s, NCH_3), 7.40—7.68 (3H, 3′, 4′, 5′-H), 8.00—8.16 (2H, m, 2′, 6′-H), 8.50 (1H, br s, NH). *Anal.* Calcd for $C_{16}H_{16}N_4O_4S_2$: C, 48.97; H, 4.11; N, 14.28; S, 16.34. Found: C, 48.87; H, 4.01; N, 14.33; S, 16.41.

5-Amino-1,3-dimethyl-7-methylthiopyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (16a)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and dimethyl cyanoimidodithiocarbonate (**15**) (1.5 g, 10 mmol) in a manner similar to that described for the preparation of **11a** and was obtained in 70% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 236 °C. IR ν (KBr) cm^{-1}: 3360 (NH), 1710, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 239 (4.56), 281 (4.22), 292 (4.21). ^{1}H-NMR [$CDCl_3$: CF_3COOH (1 : 1)] δ: 2.72 (3H, s, SCH_3), 3.44 (3H, s, NCH_3), 3.66 (3H, s, NCH_3). *Anal.* Calcd for $C_9H_{11}N_5O_2S$: C, 42.68; H, 4.38; N, 27.65; S, 12.66. Found: C, 42.89; H, 4.39; N, 28.03; S, 12.83.

5-Amino-7-methylthio-1-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (16b)——This compound was synthesized from **1b** (2.03 g, 10 mmol) and **15** (1.5 g, 10 mmol) in a manner similar to that described for the preparation of **11a** and was obtained in 67% yield. An analytical sample was recrystallized from MeOH to give colorless crystals, mp 329 °C. IR ν (KBr) cm^{-1}: 3360 (NH), 1700 (C=O). UV EtOH (poorly soluble) nm λ_{max}: 240, 282; λ_{min}: 218, 264. *Anal.* Calcd for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24; S, 10.64. Found: C, 51.92; H, 3.31; N, 23.10; S, 10.55.

5-Amino-3-methyl-7-methylthio-1-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (16c)——This compound was synthesized from **1c** (2.17 g, 10 mmol) and **15** (1.5 g, 10 mmol) in a manner similar to that described for the preparation of **11a** and was obtained in 38% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 257 °C. IR ν (KBr) cm^{-1}: 3380, 3280 (NH), 1700, 1645 (C=O). UV λ_{max}^{EtOH} nm (log ε): 240 (4.54), 283 (4.23). *Anal.* Calcd for $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.16; N, 22.21; S, 10.26. Found: C, 53.18; H, 4.20; N, 22.20; S, 10.32.

5-Amino-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (17)——This compound was synthesized from **16** by treatment with Raney-Ni in a manner similar to that described for the preparation of **6** and was obtained in 45% yield. This product was obtained colorless needles, mp 268 °C.[3]

5-Hydroxy-6-methoxycarbonyl-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (19a)——A mixture of 1.5 g (10 mmol) of **1a**, 2.36 g (10 mmol) of dimethyl bis(methylthio)methylenemalonate (**18**), 2.1 g (15 mmol) of K_2CO_3, and 50 ml of sulfolane was heated at 150 °C on an oil bath for 8 h. The reaction mixture was poured into 300 ml of ice-water and then acidified with 10% HCl. The precipitate was recrystallized from C_6H_6–MeOH to give 1.5 g (48%) of colorless needles, mp 222 °C. IR ν (KBr) cm^{-1}: 1700, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 262 (4.50), 319 (4.10). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, SCH_3), 3.44 (3H, s, NCH_3), 3.68 (3H, s, NCH_3), 3.92 (3H, s, OCH_3), 12.80 (1H, s, OH). *Anal.* Calcd for $C_{12}H_{13}N_3O_5S$: C, 46.30; H, 4.21; N, 13.50; S, 10.30. Found: C, 46.27; H, 4.30; N, 13.65; S, 9.91.

5-Hydroxy-6-methoxycarbonyl-7-methylthio-1-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (19b)——This compound was synthesized from **1b** (2.03 g, 10 mmol) and **18** (2.36 g, 10 mmol) in a manner similar to that described for the preparation of **19a** and was obtained in 20% yield. An analytical sample was recrystallized from C_6H_6–MeOH to give colorless needles, mp 312 °C. IR ν (KBr) cm^{-1}: 1730, 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 261 (4.50), 317 (4.10). ^{1}H-NMR (DMSO-d_6) δ: 1.80 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 7.32—7.48 (5H, m, phenyl protons), 12.00 (1H, s, OH or NH), 12.60 (1H, s, NH or OH). *Anal.* Calcd for $C_{16}H_{13}N_3O_5S$: C, 53.48; H, 3.65; N, 11.70; S, 8.90. Found: C, 53.82; H, 3.58; N, 11.42; S, 8.84.

5-Hydroxy-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (20)——A mixture of **19a** (0.62 g, 2 mmol) and 10 ml of polyphosphoric acid was heated at 100 °C for 5 h. The reaction mixture was poured into 100 ml of ice-water. The precipitate was collected by filtration and recrystallized from C_6H_6–MeOH to give 0.4 g (39%) of colorless needles, mp 162 °C. IR ν (KBr) cm^{-1}: 1708, 1645—1655 (C=O). UV λ_{max}^{EtOH} nm (log ε): 232 (4.27), 250 (4.39), 283 (4.04), 318 (4.25). ^{1}H-NMR (DMSO-d_6) δ: 2.52 (3H, s, SCH_3), 3.22 (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 6.58 (1H, s, 6-H), 12.38 (1H, s, OH). *Anal.* Calcd for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.59; S, 12.66.

Found: C, 47.34; H, 4.42; N, 16.67; S, 12.34.

1,3-Dimethyl-5-methylthio-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22a)——A mixture of **1a** (1.5 g, 10 mmol), bis(methylthio)methyleneacetophenone (**21a**) (2.24 g, 10 mmol), K_2CO_3 (2.1 g, 15 mmol), and 50 ml of DMF was heated at 150 °C for 5 h, then poured into 200 ml of ice-water and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from MeOH to give 2.2 g (70%) of colorless needles, mp 249 °C. IR ν (KBr) cm^{-1}: 1690, 1650 (C=O). UV EtOH (poorly soluble) nm: λ_{max}: 228, 256, 314; λ_{min}: 226, 287. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, SCH_3), 3.44 (3H, s, NCH_3), 3.76 (3H, s, NCH_3), 7.36 (1H, s, 6-H), 7.52—7.60 (3H, m, 3′,4′,5′-H), 8.08—8.40 (2H, m, 2′,6′-H). *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.83; N, 13.41; S, 10.23. Found: C, 61.28; H, 4.75; N, 13.44; S, 9.86.

7-(*p*-Chlorophenyl)-1,3-dimethyl-5-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22b)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and bis(methylthio)methylene-*p*-chloroacetophenone (**21b**) (2.6 g, 10 mmol) in a manner similar to that described for the preparation of **22a** and was obtained in 85% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 283 °C. IR ν (KBr) cm^{-1}: 1690, 1650 (C=O). UV EtOH (poorly soluble) nm: λ_{max}: 220, 256, 327; λ_{min}: 238, 293. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, SCH_3), 3.48 (3H, s, NCH_3), 3.80 (3H, s, NCH_3), 7.30 (1H, s, 6-H), 7.40 (2H, d, J=8 Hz, 3′,5′-H), 8.08 (2H, d, J=8 Hz, 2′,6′-H). *Anal.* Calcd for $C_{16}H_{14}ClN_3O_2S$: C, 55.25; H, 4.06; N, 12.08; S, 9.21. Found: C, 55.33; H, 4.06; N, 11.94; S, 9.52.

7-(*p*-Bromophenyl)-1,3-dimethyl-5-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22c)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and bis(methylthio)methylene-*p*-bromoacetophenone (**21c**) (3 g, 10 mmol) in manner similar to that described for the preparation of **22a** and was obtained in 85% yield. An analytical sample was recrystallized from MeOH to give colorless needles, mp 282 °C. IR ν (KBr) cm^{-1}: 1690, 1650 (C=O). UV EtOH (poorly soluble) nm: λ_{max}: 231, 256, 327; λ_{min}: 222, 239, 294. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, SCH_3), 3.48 (3H, s, NCH_3), 3.80 (3H, s, NCH_3), 8.08 (2H, d, J=8 Hz, 3′,5′-H), 7.40 (2H, d, J=8 Hz, 2′,6′-H), *Anal.* Calcd for $C_{16}H_{14}BrN_3O_2S$: C, 48.99; H, 3.59; N, 10.71; S, 8.17. Found: C, 49.29; H, 3.76; N, 10.92; S, 8.21.

1,3-Dimethyl-7-(*p*-methylphenyl)-5-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22d)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and bis(methylthio)methylene-*p*-methylacetophenone (**21d**) (2.36 g, 10 mmol) in a manner similar to that described for the preparation of **22a** and was obtained in 40% yield. An analytical sample was recrystallized from C_6H_6–MeOH to give colorless needles, mp 284 °C. IR ν (KBr) cm^{-1}: 1690, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 212 (4.28), 254 (4.39), 323 (4.24), 340 (4.17), 353 (4.12). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, *p*-CH_3), 2.52 (3H, s, SCH_3), 3.44 (3H, s, NCH_3), 3.76 (3H, s, NCH_3), 7.32(1H, s, 6-H), 7.32 (2H, d, J=8 Hz, 3′,5′-H), 8.00 (2H, d, J=8 Hz, 2′,6′-H). *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.24; N, 12.83; S, 9.79. Found: C, 62.16; H, 5.16; N, 12.74; S, 9.67.

7-(2-Furyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22e)——This compound was synthesized from **1a** (1.5 g, 10 mmol) and bis(methylthio)methylene-2-acetylfuran (**22e**) (2.14 g, 10 mmol) in a manner similar to that described for the preparation of **22a** and was obtained in 42% yield. An analytical sample was recrystallized from C_6H_6–MeOH to give colorless needles, mp 230 °C. IR ν (KBr) cm^{-1}: 1690, 1640 (C=O). UV EtOH (poorly soluble) nm: λ_{max}: 228, 254, 284, 296, 329; λ_{min}: 240, 277, 289, 301. ^{1}H-NMR (CF_3COOH) δ: 2.76 (3H, s, SCH_3), 3.56 (3H, s, SCH_3), 3.56 (3H, s, NCH_3), 3.96 (3H, s, NCH_3), 6.80 (1H, s, 6-H), 7.57—7.68 (2H, m, 3′,5′-H), 7.80 (1H, m, 4′-H). *Anal.* Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85; S, 10.57. Found: C, 55.22; H, 4.52; N, 13.88; S, 10.35.

1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (23)——This compound was synthesized from **22a** by treatment with Raney-Ni in manner similar to that described for the preparation of **6** and was obtained in 71% yield. Compound **23** was identical with an authentic sample synthesized by the condensation of **1a** with cinnamaldehyde.[5] The product was recrystallized from MeOH to give colorless needles, mp 183 °C.

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