REACTION OF KETENE DITHIOACETALS WITH THIOAMIDES. A SYNTHESIS OF PYRIMIDINE DERIVATIVES

Antonio Lorente*[a] M. Luisa García[a], Misericordia Fernández[a], and José L. Soto[b]

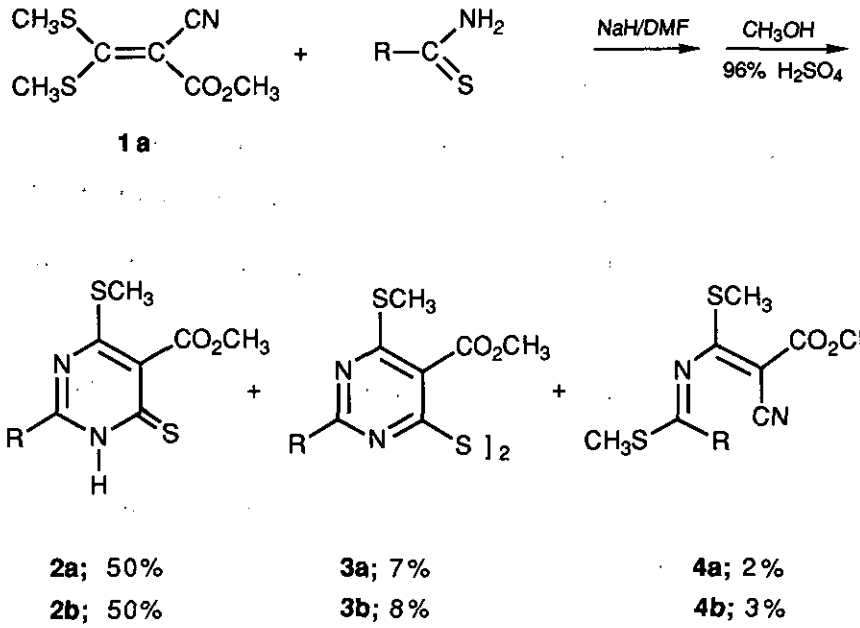
a) Department of Organic Chemistry, University of Alcalá. 28871-Alcalá de Henares (Madrid), Spain

b) Department of Organic Chemistry, Faculty of Chemistry, Complutense University, 28040-Madrid, Spain

Abstract - Reaction of ketene dithioacetals with thioamides gave 5-cyano-2-methyl(or phenyl)-6-methylthio-4-thioxopyrimidines.

Ketene dithioacetals bearing electron-withdrawing groups are versatile reagents for the synthesis of heterocyclic compounds.[1-4] We have previously described [5-7] a convenient method for the preparation of 2- and 4-aryl(or alkyl)substituted 4-thioxopyrimidines by reaction of various methoxymethylene compounds with thioamides. As part of our studies on the synthesis of substituted pyrimidines we now describe the reaction of ketene dithioacetals with thioamides as a procedure for the synthesis of 4-thioxopyrimidines having a methylthio group at the 6-position.

Reaction of methyl 2-cyano-3,3-bis(methylthio)propenoate (**1a**) with thioacetamide or thiobenzamide in the presence of sodium hydride in dimethylformamide at room temperature gave, after acidification with concentrated sulfuric acid (pH 4), a mixture of 2-substituted 5-methoxycarbonyl-6-methylthio-4-thioxo-3,4-dihydropyrimidine (**2a,b**), 2-substituted bis-(5-methoxycarbonyl-6-methylthio-4-pyrimidinyl) disulfide (**3a,b**) and methyl 2-cyano-3-methylthio-3-[α-methylthiobenzylidene(or ethylidene)amino]propenoate (**4a,b**).[8]

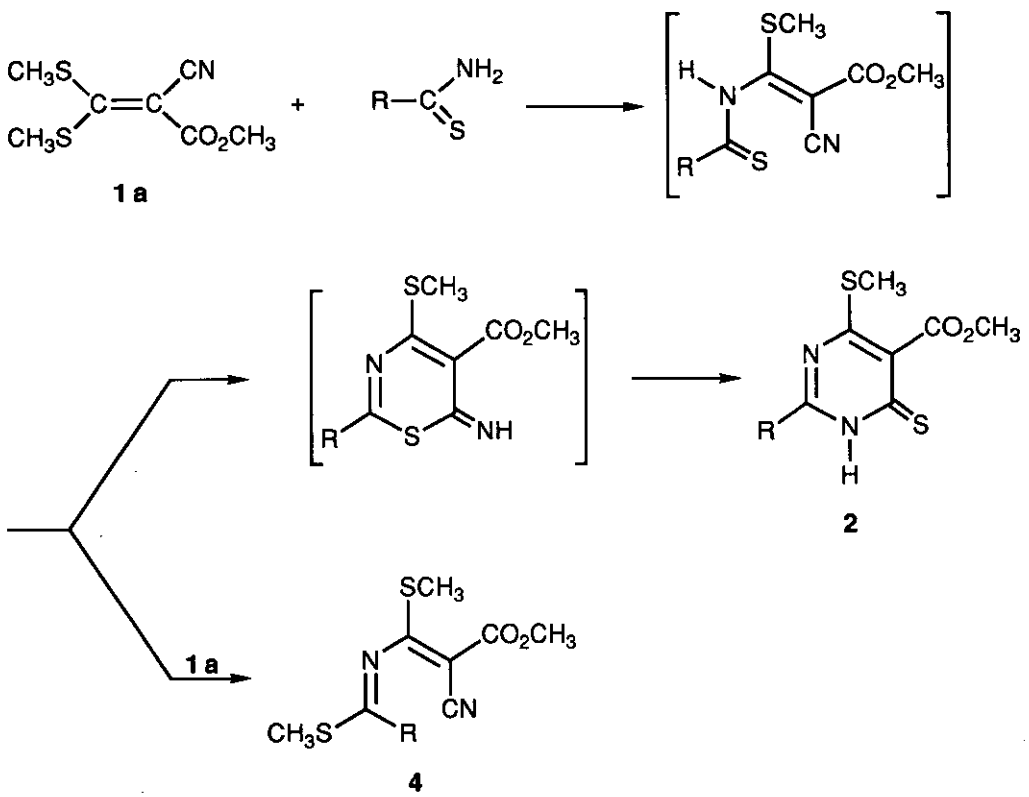


2a; 50% **3a**; 7% **4a**; 2%
2b; 50% **3b**; 8% **4b**; 3%

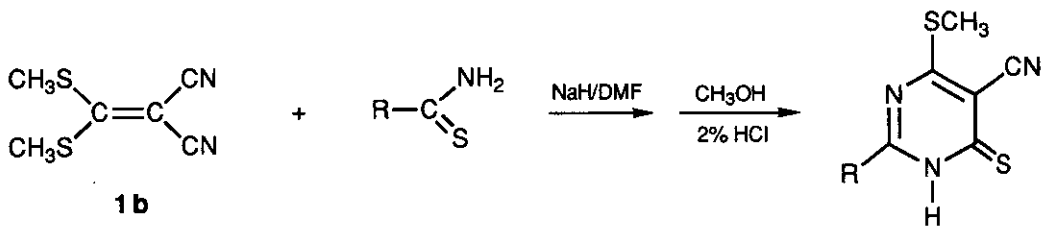
a: R=CH_3; b: R=C_6H_5

Disulfides (**3a**) and (**3b**) were also prepared by oxidation of the corresponding 4-thioxopyrimidine (**2**) with iodine-potassium iodide in methanol in 87 and 92% yields, respectively.

The reaction mechanism is conceivable as follows. Initially, addition of the thioamide to the ketene dithioacetal (**1a**) affords methyl 2-cyano-3-methylthio-3-thioamidopropenoate intermediate, which cyclizes *in situ* by site-selective nucleophilic attack of the sulphur to the cyano group. Dimroth rearrangement of 6-imino-1,3-thiazine gave the corresponding 4-thioxo-3,4-dihydropyrimidines (**2**). Alternatively, transmethylation of methyl 2-cyano-3-methylthio-3-thioamidopropenoate with **1a** yields the thioimidates (**4**).



Moreover, reaction of 2-cyano-3,3-bis(methylthio)propenenitrile (**1b**) with thioamides, in a similar procedure as described in the preceding case, gave, after acidification with diluted hydrochloric acid, 5-cyano-2-methyl(or phenyl)-6-methylthio-4-thioxo-3,4-dihydropyrimidine (**5a,b**).

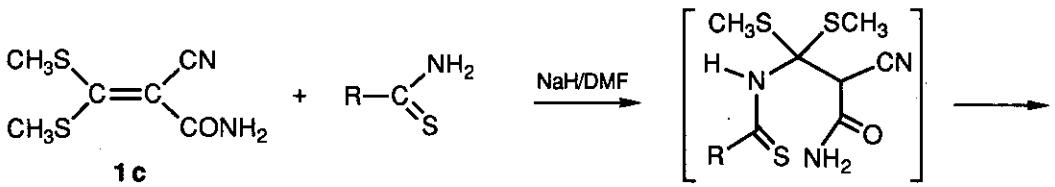


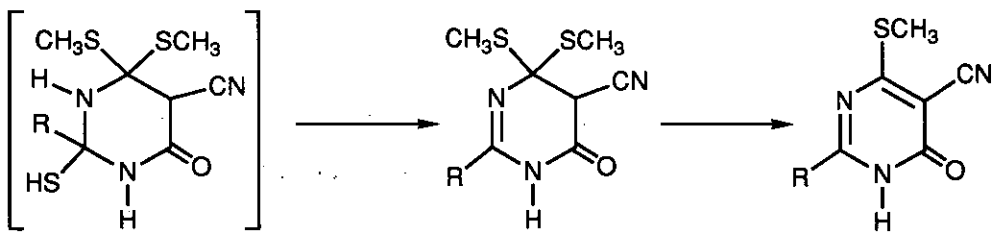
5a; R= CH_3
5b; R= C_6H_5

The reactions of 2-cyano-3,3-bis(methylthio)propenamide (**1c**) with thioamides follow a

different course to the preceding cases yielding 2-substituted 5-cyano-6-methylthio-4-oxo-3,4-dihydropyrimidines (**7a, b**). From the reaction of **1c** with thioacetamide an additional product identified as 5-cyano-2-methyl-4,4-bis(methylthio)-6-oxo-1,4,5,6-tetrahydropyrimidine (**6a**) was isolated.

According with these results the reaction probably proceeds by addition of the thioamide to the ketene dithioacetal followed by cyclization and subsequent loss of hydrogen sulfide. The tetrahydropyrimidine thus formed affords the aromatized compounds by elimination of methanethiol.

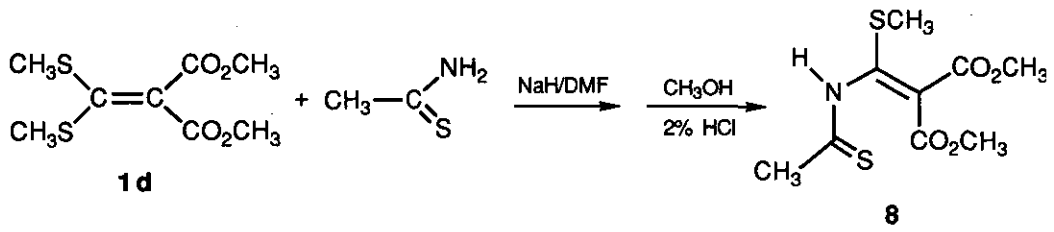




6a
R= CH_3

7a; R= CH_3
7b; R= C_6H_5

We have also investigated the reaction of methyl 3,3-bis(methylthio)-2-methoxycarbonylpropenoate (**1d**) with thioacetamide in a similar conditions as described in the preceding cases. After acidification with 2% hydrochloric acid methyl 2-methoxycarbonyl-3-methylthio-3-thiocetamidopropenoate (**8**) was isolated. When methanolic solution of **8** was acidified with 96% sulfuric acid and stirred at room temperature for 72 h starting product was recovered.



1d **8**

EXPERIMENTAL

All melting points were determined in open capillary and are uncorrected. Ir spectra were performed on a Perkin Elmer 883. Reported values are the more characteristic peaks. Nmr spectra were recorded on a Varian FT-80 A or FT-300 with TMS as an internal standard. Mass spectra were registered on a Hewlett Packard HP-5988. Flash column chromatographies were carried out on silica gel SDS 230-400 mesh.

Ketene dithioacetals (**1a-d**) were prepared according to the procedure described by R. Gompper and W. Töpfl.[9]

Reaction of methyl 2-cyano-3,3-bis(methylthio)propenoate with thioacetamide. To a suspension of 80% sodium hydride (135 mg, 4.5 mmol) in dry dimethylformamide (30 ml), thioacetamide (225 mg, 3 mmol) and methyl 2-cyano-3,3-bis(methylthio)propenoate (609 mg, 3 mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed *in vacuo*. The resulting residue was dissolved in dry methanol and acidified (pH 4) with 96% sulfuric acid. After 48 h with stirring at room temperature the residue obtained by evaporation of the methanol was dissolved in dichloromethane and washed several times with water. The dried organic layer was evaporated and the crude product was purified by flash colum (diameter : 3 cm) chromatography on silica gel with hexane-ethyl acetate (3:1) as eluent to afford **3a** (50 mg, 7%), **4a** (15 mg, 2%), and **2a** (351 mg , 50%).

Bis-(5-methoxycarbonyl-2-methyl-6-methylthio-4-pyrimidinyl) disulfide (3a): mp 202-203 °C (acetone); ir (KBr) υ 1692 (C=O) cm^{-1}; ^1H nmr (300 MHz, TFA-d_1) δ: 2.85 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 4.24 (s, 3H, CO_2CH_3); ms m/z : 458 (M^+, 16), 229 (100), 156 (13), 142 (26), 114 (14), 112 (20), 110 (29), 103 (14), 99 (15), 97 (55). *Anal.* Calcd for $C_{16}H_{18}N_4O_4S_4$: C, 41.90; H, 3.96; N, 12.28. Found: C, 42.14; H, 3.81; N, 12.41.

Methyl 2-cyano-3-methylthio-3-(α-methylthioethylideneamino)propenoate (4a): mp 92-93 °C (2-propanol); ir (KBr) υ 2190 (C≡N), 1695 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6) δ: 2.14 and 2.19 (s, 3H, SCH_3), 2.25 and 2.27 (s, 3H, SCH_3), 2.42 and 2.45 (s, 3H, SCH_3), 3.62 and 3.71 (s, 3H, CO_2CH_3); ms m/z: 244 (M^+, 7), 213 (5), 187 (70), 156 (68), 112 (35), 97 (45), 91 (16), 82 (13), 75 (32), 71 (19), 70 (11), 59 (100). *Anal.* Calcd for $C_9H_{12}N_2O_2S_2$: C, 44.57; H, 4.95; N, 11.47. Found: C, 44.21; H, 4.80; N, 11.89.

5-Methoxycarbonyl-2-methyl-6-methylthio-4-thioxo-3,4-dihydropyrimidine (2a): mp 214-216 °C (2-propanol) (lit.,[10] mp 210-212 °C); ir (KBr) υ 3167 (NH), 1727 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6) δ : 2.39 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3); ms m/z : 230 (M^+, 57), 215 (6), 199 (28), 198 (100), 172 (13), 171 (14), 157 (15), 139 (10), 138 (17), 129 (13), 126 (25), 110 (17), 98 (10), 97 (15), 85 (26), 84 (20), 83 (20), 82 (18). *Anal.* Calcd for $C_8H_{10}N_2O_2S_2$: C, 41.72; H, 4.38; N, 12.17. Found: C, 41.82; H, 4.20; N, 12.60.

Reaction of methyl 2-cyano-3,3-bis(methylthio)propenoate with thiobenzamide

To a stirred suspension of 80% sodium hydride (90 mg, 3 mmol) in 25 ml of dry dimethylformamide, thiobenzamide (274 mg, 2 mmol) and methyl 2-cyano-3,3-bis(methylthio)propenoate (406 mg, 2 mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed *in vacuo*. The oily residue was dissolved in dry methanol (30 ml) and acidified (pH 4) with 96% sulfuric acid. After 48 h with stirring at room temperature the reaction mixture was worked up as in the preceding case. The crude product thus obtained was purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (4/1, v/v) to afford **3b** (47 mg, 8%), **4b** (19 mg, 3%), and **2b** (289 mg, 50%).

Bis-(5-methoxycarbonyl-6-methylthio-2-phenyl-4-pyrimidinyl) disulfide (3b): mp 278-280 °C (DMF); ir (KBr) υ 1696 (C=O) cm^{-1}; ^1H nmr (80 MHz, TFA-d_1): δ 2.89 (s, 6H, SCH_3), 4.26 (s, 6H, CO_2CH_3), 7.14-7.61 (m, 6H arom), 7.83-8.15 (m, 4H arom); ms m/z : 582 (M^+, 35), 293 (29), 292 (67), 291 (100), 260 (58), 180 (39), 104 (33), 77 (39). *Anal.* Calcd for $C_{26}H_{22}N_4O_4S_4$: C, 53.59; H, 3.81; N, 9.62. Found: C, 52.91; H, 3.71; N, 9.91.

Methyl 2-cyano-3-methylthio-3-(α-methylthiobenzylideneamino)propenoate (4b): mp 176-177 °C (2-propanol); ir (KBr) υ 2190 (C≡N), 1680 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.37 (s, 3H, SCH_3), 2.53 and 3.38 (s, 3H, SCH_3), 3.58 and 3.64 (s, 3H, CO_2CH_3), 7.56 (s, 5H arom); ms m/z : 306 (M^+, 7), 291 (2), 275 (10), 259 (80), 247 (48), 156 (100), 121 (22), 112 (39), 97 (33), 77 (32). *Anal.* Calcd for $C_{14}H_{14}N_2O_2S_2$: C, 54.88; H, 4.61; N, 9.14. Found: C, 55.11; H, 4.71; N, 9.25.

5-Methoxycarbonyl-6-methylthio-2-phenyl-4-thioxo-3,4-dihydropyrimidine (2b): mp 200-201 °C (2-propanol) ; ir (KBr) υ 3162 (NH), 1736 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.60 (s, 3H, SCH_3), 3.79 (s, 3H, CO_2CH_3), 7.28-7.80 (m, 3H arom), 7.97-8.35 (m, 2H arom), 14.15 (br s, 1H, NH); ms m/z : 292 (M^+, 62), 260 (100), 233 (15), 188 (13), 110 (17), 104 (46), 103 (24), 77 (22). *Anal.* Calcd for $C_{13}H_{12}N_2O_2S_2$: C, 53.40; N, 4.14; N, 9.58. Found: C, 53.61; H, 4.20; N, 9.40.

General procedure for oxidation of 4-thioxo-3,4-dihydropyrimidines (2a,b)

To a dry methanol solution (50 ml) of iodine (140 mg, 0.55 mmol) and potassium iodide (61mg, 0.37 mmol), 4-thioxo-3,4-dihydropyrimidine (**2**)(0.5 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then poured into water (200 ml). The precipitate formed was collected and recrystallized from the appropriate solvent.

5-Cyano-2-methyl-6-methylthio-4-thioxo-3,4-dihydropyrimidine (5a)

To a suspension of 80% sodium hydride (120 mg, 4 mmol) in dry dimethylformamide (20 ml) thioacetamide (300 mg, 4 mmol) and 2-cyano-3,3-bis(methylthio)propenenitrile (682 mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed up to dryness. The resulting residue was dissolved in the minimal volume of

ethanol, cooled at 0 °C and acidified with 2% hydrochloric acid. The solid thus obtained was purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (1/1, v/v) as eluent to afford 514 mg (65 %) of product, which was recrystallized from 2-propanol; mp 278-280 °C; ir υ 3158 (NH), 2222 (C≡N) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 2.58 (s, 3H, CH_3); ^{13}C nmr (20 MHz, DMSO-d_6): δ 12.90 (SCH_3), 21.71 (CH_3), 105.43 (C-5), 160.43 (C-4), 173.32 and 179.42 (C-2 and C-6); ms m/z : 197 (M^+, 100), 164 (25), 156 (54), 123 (18), 109 (18), 108 (21), 97 (14), 83 (22), 82 (35), 80 (16), 70 (14). *Anal.* Calcd for $C_7H_7N_3S_2$: C, 42.62; H, 3.58; N, 21.30. Found: C, 42.34; H, 3.50; N, 21.71.

5-Cyano-6-methylthio-2-phenyl-4-thioxo-3,4-dihydropyrimidine (5b)

To a stirred suspension of 80 % sodium hydride (120 mg, 4 mmol) in dry dimethylformamide (20 ml) thiobenzamide (548 mg, 4 mmol) and 2-cyano-3,3-bis(methylthio)propenenitrile (682 mg, 4 mmol) were added. After stirring for 72 h at room temperature the solvent was removed at reduced pressure and the oily residue was dissolved in the minimal volume of ethanol. The solution was acidified with 2 % hydrochloric acid and the precipitate thus obtained was filtered, washed with water and recrystallized from 2-propanol to yield 550 mg (53 %) of **5b**; mp 241-243 °C; ir (KBr): υ 3134 (NH), 2216 (C≡N) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.69 (s, 3H, SCH_3), 7.21-7.76 (m, 3H arom), 7.88-8.32 (m, 2H arom); ms m/z : 259 (M^+, 100), 226 (29), 156 (60), 123 (11), 109 (13), 104 (67), 103 (21), 97 (10), 83 (11), 82 (16), 77 (37), 76 (22). *Anal.* Calcd for $C_{12}H_9N_3S_2$: C, 55.57; H, 3.50; N, 16.20. Found: C, 55.70; H, 3.12; N, 16.40.

Reaction of 2-cyano-3,3-bis(methylthio)propenamide with thioacetamide

Thioacetamide (225 mg, 3mmol) and 2-cyano-3,3-bis(methylthio)propenamide (566 mg, 3 mmol) were added to a suspension of 80% sodium hydride (135 mg, 4.5 mmol) in dry dimethylformamide (15 ml). After 96 h with stirring at room temperature the reaction mixture was poured into water (200 ml) and extracted with ether. The dried combined organic layers were evaporated and the crude product obtained was purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (1/2, v/v) as eluent to afford 186 mg (27 %) of **5-cyano-2-methyl-4,4-bis(methylthio)-6-oxo-1,4,5,6-tetrahydropyrimidine (6a)**, which was recrystallized from 2-propanol; mp 199-200 °C; ir (KBr) υ 3164 (NH), 2216 (C≡N), 1657 (C=O)

cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 1.64 (s, 6H, 2 SCH_3), 2.62 (s, 3H, CH_3), 4.12 (br, 1H, C_5-H), 8.68 (s, 1H, NH); GC ms m/z: 229 (100), 211 (14), 193 (29), 181 (20), 149 (21), 126 (18), 109 (20), 100 (20), 91 (37). *Anal.* Calcd for $C_8H_{11}N_3OS_2$: C, 41.90; H, 4.84; N, 18.32. Found: C, 42.27; H, 4.74; N, 18.21.

With the same eluent 164 mg (30 %) of **5-cyano-2-methyl-6-methylthio-4-oxo-3,4-dihydropyrimidine (7a)** was obtained and recrystallized from 2-propanol; mp 309 °C (lit.,[10] 307 °C) ; ir (KBr) υ 3302 (NH), 2221 (C≡N), 1656 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 13.15 (br s, 1H, NH); ms m/z : 181 (M^+, 22), 140 (100), 112 (16), 93 (7), 85 (10). *Anal.* Calcd for $C_7H_7N_3OS$: C, 46.39; H, 3.89; N, 23.19. Found: C, 46.50; H, 3.72; N, 23.40.

5-Cyano-6-methylthio-4-oxo-2-phenyl-3,4-dihydropyrimidine (7b)

To a stirred suspension of 80 % sodium hydride (225 mg, 7.5 mmol) in 20 ml of dry dimethylformamide, thiobenzamide (685 mg, 5 mmol) and 2-cyano-3,3-bis(methylthio)-propenamide (943 mg, 5mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then concentrated up to dryness. The oily residue was dissolved in the minimal volume of ethanol and acidified with 2% hydrochloric acid. The precipitate thus obtained was purified by column chromatography using toluene-ethyl acetate (6/4, v/v) as eluent to afford 500 mg (41%) of **7b**, which was recrystallized from 2-propanol; mp 339-341 °C (lit.,[10] 341 °C); ir (KBr) υ 2223 (C≡N), 1664 (C=O) cm^{-1}; ^1H nmr (80 MHz, TFA-d_1): δ 2.86 (s, 3H, SCH_3), 7.30-7.80 (m, 3H arom), 7.90-8.40 (m, 2H arom); ms m/z : 243 (M^+, 24), 140 (100), 104 (65), 77 (44). *Anal.* Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27. Found: C, 58.75; H, 3.60; N, 16.94.

Methyl 2-methoxycarbonyl-3-methylthio-3-thioacetamidopropenoate (8)

To a suspension of 80 % sodium hydride (180 mg, 6 mmol) in dry dimethylformamide (30 ml), thioacetamide (300 mg, 4 mmol) and methyl 3,3-bis(methylthio)-2-methoxycarbonylpropenoate (945 mg, 4 mmol) were added. After 72 h with stirring at room temperature the reaction mixture was concentrated up to dryness. The residue thus obtained was dissolved in water (40 ml), cooled at 0 °C, acidified with 2 % hydrochloric acid and extracted with dichloromethane. The crude product obtained by evaporation of the solvent was purified by flash column (diameter: 3 cm)

chromatography using hexane-ethyl acetate (2/1, v/v) as eluent to afford 317 mg (30 %) of product, which was recrystallized from ethyl acetate; mp 129-130 °C; ir (KBr) υ 3192 (NH), 1708 (C=O) cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 2.22 (s, 3H, SCH_3), 2.49 (s, 3H, CH_3), 3.67 (s, 6H, CO_2CH_3), 11.47 (br s, 1H, NH); CI ms m/z : 264 (M^++ 1, 96), 248 (17), 232 (100), 218 (15), 216 (17), 206 (14), 200 (20), 89 (92). *Anal.* Calcd for $C_9H_{13}NO_4S_2$: C, 41.05; H, 4.97; N, 5.32. Found: C, 40.97; H, 4.71; N, 5.70.

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