Synthesis of Fused 1,2,4-Triazines: 6- and 7-Azapteridine and 6-Azapurine Ring Systems[1a]

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The reaction of diethyl oxomalonate with *S*-methylisothiosemicarbazide under basic condition was found to give 3-(methylthio)-5-oxo-6-carbethoxy-4,5-dihydro-1,2,4-triazine (**1**) and 3-(methylthio)-5-carbethoxy-6-oxo-1,6-dihydro-1,2,4-triazine (**2**). While via **1** the pyrimido[4,5-*e*]-1,2,4-triazine (6-azapteridine) ring system was formed, **2** gave rise to the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) and imidazo[4,5-*e*]-1,2,4-triazine (6-azapurine) systems. By means of displacement of the cyano group derived in two steps from **2**, the thiazolo-[5,4-*e*]-1,2,4-triazine system was also achieved.

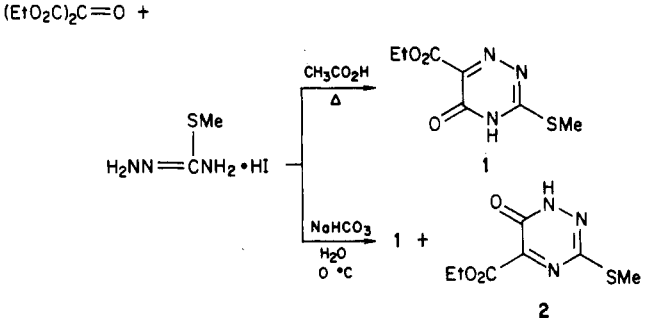
The interest in the chemistry of the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) ring system was initially stimulated by the discovery of the naturally occurring derivatives, potent but highly toxic antibiotics: toxoflavin, fervenulin, and MSD-92 (4-methylfervenulone).[2]

In principle, the synthesis of the pyrimido[5,4-*e*]-1,2,4-triazine system could be approached from a pyrimidine or a triazine followed by the formation of the bicyclic system. Previous work has been directed mainly toward the first method, starting with a pyrimidine. Although there are two preparations involving annulation of the pyrimidine to the preformed triazine ring, the triazines, in both cases, are in fact the ring-cleavaged products of the pyrimido-[5,4-*e*]-1,2,4-triazines which were synthesized starting with pyrimidines.[3] Thus, despite some attempts[4] it remained of interest, methodologically, to investigate a practical preparative route that would involve initial construction of a monocyclic triazine and subsequent formation of the condensed pyrimidine ring. This report describes the preparation of 1,2,4-triazines which lead to the desired bicyclic system and unexpected fused five-membered heterocycles.[5]

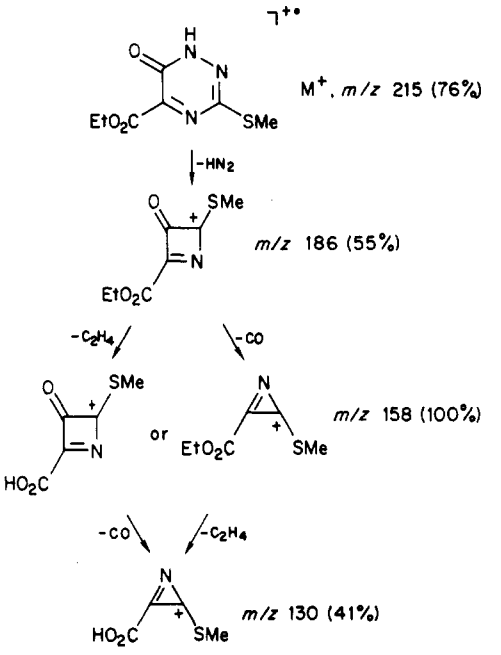
It is well-known that diethyl oxomalonate reacts with thiosemicarbazide to give 3-thio-5-oxo-6-carbethoxy-2,3,4,5-tetrahydro-1,2,4-triazine followed by methylation to give 3-(methylthio)-5-oxo-6-carbethoxy-4,5-dihydro-1,2,4-triazine (**1**).[6] In the present study, thiosemicarbazide was methylated by methyl iodide and the resulting *S*-methylisothiosemicarbazide hydroiodide[7] was reacted with diethyl oxomalonate under different reaction conditions to examine the effect of an alkylthio substituent on the triazine ring formation[8] (Scheme I).

In acetic acid at reflux, the reaction product was found to be **1** as one would expect.[9] When the free *S*-methylisothiosemicarbazide was used in aqueous solution at 0 °C, in addition to white solid **1**, a less polar greenish yellow solid product was also isolated and characterized to be the isomeric 1,2,4-triazine **2** as determined by ^{1}H NMR spectroscopy and acidity measurement coupled with the elemental and mass spectral analyses. The SCH_3 protons in **1** at δ 2.59 are more deshielded than in **2** at δ 2.48 in chloroform solution apparently due to the effect of conjugation of the methylthio group with the electron-withdrawing carbethoxy group in the para position in **1**. The

Scheme I



Scheme II



(1) (a) Presented in part at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 1984; ORGN 95. (b) Mailing address: Burroughs Wellcome Co., Research Triangle Park, NC 27709.

(2) For a review, see: Brown, D. J.; Lynn, R. K. In "Chemistry and Biology of Pteridines"; Pfleiderer, W., Ed.; Walter de Gruyter: New York, 1975; pp 575–601.

(3) (a) Temple, C., Jr.; Kussner, C. L.; Montgomery, J. A. *J. Heterocycl. Chem.* **1968**, *5*, 581; *J. Org. Chem.* **1969**, *34*, 2102. (b) Brown, D. J.; Lynn, R. K. *Aust. J. Chem.* **1974**, *27*, 1781.

(4) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1972**, *37*, 3958.

(5) For comprehensive reviews of the 1,2,4-triazines, see: (a) Neunhoeffer, H. In "Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines"; Neunhoeffer, H., Wiley, P. F., Eds.; Wiley-Interscience: New York, 1978; pp 189–1072. (b) Neunhoeffer, H. In "Comprehensive Heterocyclic Chemistry"; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 3, pp 385–456.

(6) Cristescu, C. *Rev. Roumaine Chim.* **1970**, *15*, 1409. Cristescu, C.; Panaitescu, T. *Pharmazie* **1963**, *18*, 336.

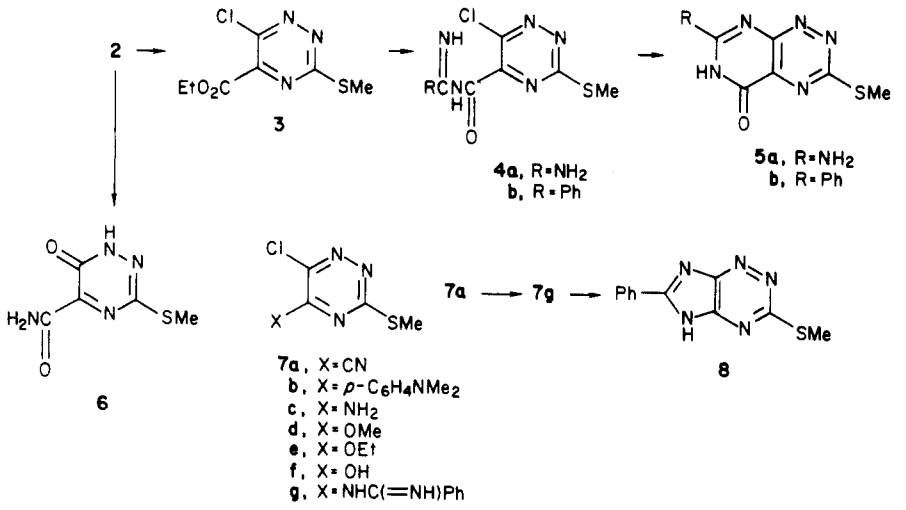
(7) Freund, M.; Paradies, T. *Ber.* **1901**, *34*, 3110.

(8) Formation of isomeric 1,2,4-triazinones from the reaction of α-keto esters with benzamidrazones has been reported: Domany, G.; Nyitrai, J.; Simig, G.; Lempert, K. *Tetrahedron Lett.* **1977**, 1393.

(9) A similar reaction has been reported. See ref 16.

0022-3263/85/1950-2293$01.50/0

Scheme III



pK_a values of **1** and **2** were found to be 4.5 and 6.3, respectively. The fact that **1** is more acidic than **2** may be accounted for by more delocalization of the negative charge of the anion of **1** than that of **2**. As expected, the mass spectra of the isomeric **1** and **2** showed different fragmentation patterns upon electron impact. While the base peak of **1** was the parent peak, the base peak of **2** was the fragment resulting from the elimination of HN_2 and CO (or C_2H_4) from the molecular ion (Scheme II). Chemically, the feasibility of conversion of **2** to **3** by $POCl_3$ in the presence of concentrated sulfuric acid, and the disappearance of an NH absorption in the IR spectrum of **3** as is present in **2** further supports the structure of a six-membered ring of **2**.

It is conceivable that the formation of **2** is due to the enhancement of the nucleophilicity of the N(4) atom of the amino/imino group of the amidrazone by the methylthio substituent in the form of free base toward the keto function of diethyl oxomalonate[10] in the initial reaction of the ring formation.

The functionally substituted triazine **3** was then reacted with guanidine and benzamidine in ethanol at room temperature to give the corresponding 5-guanidinocarbonyl and 5-benzamidinocarbonyl derivatives **4a** and **4b**, respectively, which were cyclized in dimethylformamide (DMF) at reflux in the presence of potassium carbonate to yield 7-amino- and 7-phenyl-3-(methylthio)-5-oxo-5,6-dihydropyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines), **5a** and **5b**, respectively (Scheme III). These findings represent the first examples of preparation of this bicyclic system directly from a 1,2,4-triazine.

Treatment of **2** with methanolic ammonia gave the 5-carbamoyl derivative **6**, which was then reacted with phosphorus oxychloride in the presence of a catalytic amount of *N,N*-dimethylaniline to give 3-(methylthio)-5-cyano-6-chloro-1,2,4-triazine (**7a**). (The reaction failed without the catalyst.) In view of the fact that the 5-position of this π-deficient system is the most reactive site toward nucleophilic substitution,[11] an interesting question arises: will the cyano substituent be displaced by a nucleophile and, if at all, preferentially to the chloro and the methylthio substituents? The first indication that the cyano group will behave as a leaving group was noticed when an excessive amount of *N,N*-dimethylaniline was used in the preparation of the cyano compound **7a**. An additional product was isolated and characterized as a 1,2,4-triazine derivative (**7b**) with the 5-cyano group having been displaced by *N,N*-dimethylaniline in the para position based on analytical data and spectral analyses. The ^1H NMR spectrum showed, in addition to the two sharp singlets for SCH_3 and $N(CH_3)_2$ protons at δ 2.67 and 3.08, respectively, an AA'XX' coupling pattern at δ 6.17 and 8.14 and the IR spectrum 1600- and 810-cm^{-1} absorptions characteristic of a para-substituted phenyl.[12] The displacement of a cyano group in heterocyclic compounds by nucleophiles is rare, but a few cases have been reported.[13]

The cyano compound **7a** was subjected to various nitrogen and oxygen nucleophiles to confirm the generality of nucleophilic displacement of the cyano substituent. It reacted smoothly with ammonia, sodium ethoxide, or methanol (slight warming was necessary to complete the reaction with methanol without sodium methoxide) to yield the corresponding 5-substituted compounds **7c–e** without detection of other byproducts. Compound **7a** also was readily hydrolyzed to give the 5-hydroxy derivative (or as the oxo form) **7f**. All of these reaction products consistently retained chlorine at the 6-position. These findings substantiate that the cyano group at the 5-position, as a consequence of being para to a ring nitrogen, is readily displaced by nucleophiles and the chloro substituent at the 6-position is somewhat inert.

In a similar manner, the cyano compound **7a**[14] was then treated with benzamidine to give the 5-benzamidino derivative **7g**, which was cyclized in refluxing DMF in the presence of potassium carbonate to give the imidazo[4,5-*e*]-1,2,4-triazine (6-azapurine) bicyclic system (**8**).[15]

The same method was applied to the isomeric triazine **1**. Treatment of **1** with $SOCl_2$ yielded 3-(methylthio)-5-chloro-6-carbethoxy-1,2,4-triazine (**9**).[16] The condensation

(10) The keto grouping of diethyl oxomalonate is considerably more reactive than the ester groups; for example: (a) Falco, E. A.; Pappas, E.; Hitching, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 1938. (b) Ciganek, E. *J. Org. Chem.* **1965**, *30*, 4366.

(11) (a) Piskala, A.; Gut, J.; Sorm, F. *Chem. Ind. (London)* **1964**, 1752; *Collect. Czech. Chem. Commun.* **1975**, *40*, 2680. (b) Neunhoeffer, H.; Lehmann, B. *Chem. Ber.* **1976**, *109*, 1113.

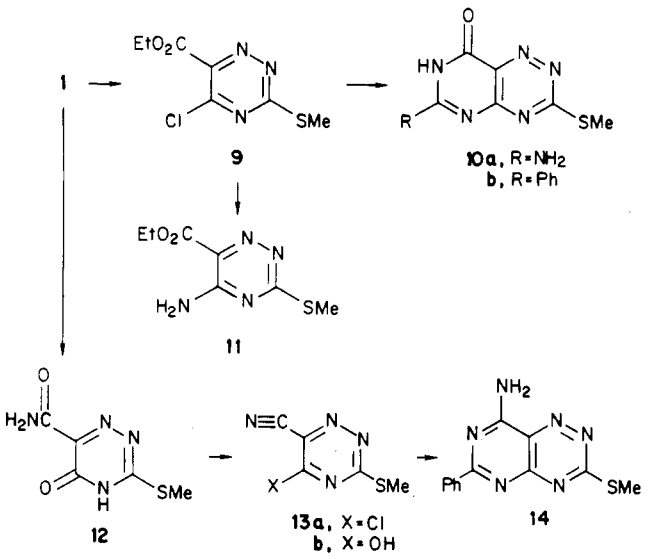
(12) (a) Nakanishi, K.; Soloman, P. H. "Infrared Absorption Spectroscopy", 2nd ed.; Holden-Day: San Francisco, 1977. (b) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981.

(13) (a) Ozaki, K.-I.; Yamada, Y.; Oine, T. *Chem. Pharm. Bull.* **1983**, *31*, 2234 and references therein. (b) Hirano, H.; Lee, R.; Tada, M. *J. Heterocycl. Chem.* **1982**, *19*, 1409 and references therein.

(14) Of biological interest is the finding that among some of the 1,2,4-triazines **7a** has been shown to have an antibacterial activity in a preliminary test. B. Graham is acknowledged for this contribution.

(15) For the chemistry of 6-azapurines, see: Kametani, T.; Higuchi, M.; Noguchi, M.; Hashiguchi, Y.; Yoneda, F. *Heterocycles* **1980**, *14*, 1295 and references therein.

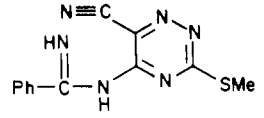
Scheme IV



of **9** with benzamidine or guanidine in ethanol at room temperature went smoothly, giving the corresponding 6-azapteridines **10**, without isolation of the intermediates[17] (Scheme IV). The intermediate of the cyclization reaction is believed to be the 5-substituted derivative on the basis of the observation that the reaction of **9** with ethanolic ammonia afforded 3-(methylthio)-5-amino-6-carbethoxy-1,2,4-triazine (**11**). Although 6-azapteridines have not been found to exist in natural products, some of the synthesized derivatives have been shown to have antiviral and antiinflammatory activities.[18] This has stimulated an interest in the chemistry of this ring system.

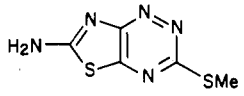
Thus, these results demonstrate that both 6- and 7-azapteridines are feasible from isomeric triazines and can be prepared from the common precursors which had previously been attempted without success.[4]

The isomeric 3-(methylthio)-5-chloro-6-cyano-1,2,4-triazine (**13a**) was also prepared by reaction of the carbamoyl precursor **12**[19] with $POCl_3$. Compound **13a** was found to be readily hydrolyzed to give the 5-hydroxy derivative (or as the 5-oxo form) **13b**. Cyclization of **13a** with benzamidine to give a 6-azapteridine (**14**) was rapidly accomplished at room temperature.[20] The possibility of the isomeric structure **15** was ruled out by the lack of a cyano absorption in both the IR and ^{13}C NMR spectra.



As a summary of the above, the previously unknown yellow 1,2,4-triazine derivative **2** gave rise to the formation of two biologically interesting bicyclic systems of 7-azapteridine and 6-azapurine,[21] while the isomer **1** gave the 6-azapteridine system.

Furthermore, to demonstrate the versatility of the triazine **7a** for the synthesis of fused rings containing other than nitrogen atoms, thiourea was, in a representative example, reacted with **7a** to give a thiazolo[5,4-*e*]-1,2,4-triazine system (**16**).[22] The methylthio substituent, in



addition to its role of directing the triazine formation, may provide a functionality for the preparation of such biologically interesting compounds as 7-azafolic acid derivatives or for simple transformations.

Experimental Section

Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Electron-impact mass spectra were measured on a Hitachi-Perkin-Elmer RMU-6M or a Varian MAT CH5 mass spectrometer at an ionizing voltage of 70 eV. pK_a values were measured spectrophotometrically with a Cary 118 instrument. ^1H NMR spectra were obtained with a Varian HA-100, a Hitachi-Perkin-Elmer R-20B (60 MHz), or a Varian FT-80A spectrometer. All ^{13}C NMR spectra were taken with a Hitachi-Perkin-Elmer R-26 or a Varian FT-80A spectrometer. Chemical shifts are reported as δ (ppm) downfield from tetramethylsilane Me_4Si. Infrared spectra were recorded on a Beckman Acculab 1 instrument. The elemental analyses were performed by the Analytical Services of the University of Alabama Department of Chemistry and by Atlantic Microlab Inc., Atlanta, GA.

3-(Methylthio)-5-oxo-6-carbethoxy-4,5-dihydro-1,2,4-triazine (1) and 3-(Methylthio)-5-carbethoxy-6-oxo-1,6-dihydro-1,2,4-triazine (2). A solution of 25 g (0.14 mol) of diethyl oxomalonate and 13 g (0.16 mol) of sodium bicarbonate in 500 mL of ice water was added to a solution of 36 g (0.16 mol) of *S*-methylisothiosemicarbazide hydroiodide[7] in 150 mL of ice water. A vigorous gas evolution was observed. The resulting solution was kept in a refrigerator overnight and was extracted with chloroform using a continuous extractor. The chloroform extract was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The resulting residue was chromatographed on silica gel with chloroform followed by 95:5 chloroform/methanol to give two major fractions. The first fraction was recrystallized from ethyl acetate to give 10.1 g (33%) of greenish yellow solid **2**: mp 149–150 °C; pK_a 6.3; mass spectrum, *m/z* (relative intensity) 215 (76, M^+), 186 (55, M – N_2H), 170 (7, M – OC_2H_5), 158 (100, M – N_2H – CO), 130 (41, $HO_2CC{=}NCSCH_3$), 73 (18), 47 (26), 29 (36); ^1H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7 Hz, CH_3), 2.48 (s, 3 H, SCH_3), 4.49 (q, 2 H, CO_2CH_2); ^1H NMR (Me_2SO-d_6) δ 1.30 (t, 3 H, J = 7 Hz, CH_3), 2.45 (s, 3 H, SCH_3), 4.37 (q, 2 H, CO_2CH_2); ^{13}C NMR (Me_2SO-d_6) δ 13.8 (CH_3, SCH_3 overlapped), 62.4, 150.7, 151.4, 157.4, 161.6; ^{13}C NMR ($CDCl_3$) δ 14.1, 14.5, 63.6, 152.5, 155.0, 157.0, 161.4.

Anal. Calcd for $C_7H_9N_3O_3S$: C, 39.06; H, 4.22; N, 19.52; S, 14.90. Found: C, 38.96; H, 4.24; N, 19.52; S, 14.80.

The second fraction was recrystallized from ethanol to give 6 g (19%) of white solid **1**: mp 140–142 °C (lit.[6] mp 139–140 °C); pK_a 4.5; mass spectrum, *m/z* (relative intensity) 215 (100, M^+), 200 (54, M – CH_3), 170 (6, M – OC_2H_5), 141 (28), 86 (61), 74 (94), 69 (62), 48 (20), 47 (26), 45 (93), 42 (45), 29 (79), 28 (77), 27 (31); ^1H NMR ($CDCl_3$) δ 1.39 (t, 3 H, J = 7 Hz, CH_3), 2.59 (s, 3 H, SCH_3), 4.45 (q, 2 H, CO_2CH_2); ^1H NMR (Me_2SO-d_6) δ 1.27 (t, 3 H, J = 7 Hz, CH_3), 2.50 (s, 3 H, SCH_3), 4.30 (q, 2 H, CO_2CH_2);

(16) Pesson, M.; Antoine, M.; Benichon. J. L.; De Lajudie, P.; Horvath, E.; Leriche, B.; Patte, S. *Eur. J. Med. Chem.-Chim. Ther.* **1980**, *15*, 269.

(17) This type of reaction has been reported by fusion: Brugger, M.; Wamhoff, H.; Korte, F. *Liebigs Ann. Chem.* **1972**, *758*, 173.

(18) (a) Azev, Yu. A.; Postovskii, I. Ya.; Pidemskii, E. L.; Goleneva, A. F.; Perepechenko, B. P.; Osokin, Yu. A.; Rusinov, V. L. U.S.S.R. Pat. 742 432, 1980; *Chem. Abstr.* **1980**, *93*, 198044d. (b) Küchler, Chr.; Küchler, W.; Heinisch, L. *Arzneimittel-Forsch.* **1966**, *16*, 1122.

(19) Wang, H.; Tsai, M.-S.; Ho, Y.-Y.; Li, C.-H. *Hua Hsueh Hsueh Pao* **1964**, *30*, 183; *Chem. Abstr.* **1964**, *61*, 8311b.

(20) This type of reaction has been reported (see ref 4) except that in the present study, the condensation was found to be rapid even without heating.

(21) For a similar triazine precursor of 6-azapurines, see: Tzeng, C.-C.; Motola, N. C.; Panzica, R. P. *J. Org. Chem.* **1983**, *48*, 1271 and references therein.

(22) For the other two publications on this ring system, see: (a) Kakahashi, M.; Shirahashi, S.; Sugawara, N. *Nippon Kagaku Kaishi* **1973**, 1519; *Chem. Abstr.* **1973**, *79*, 105200z. (b) Neunhoeffer, H.; Hammann, H. *Liebigs Ann. Chem.* **1984**, 283; *Heterocycles* **1984**, *21*, 520.

^{13}C NMR (Me_2SO-d_6) δ 12.2, 13.8, 61.7, 141.4, 156.7, 161.9, 165.5.

Under acidic condition. A mixture of 1 g (5.8 mmol) of diethyl oxomalonate and 1.4 g (6.0 mmol) of *S*-methylisothiosemicarbazide hydroiodide in 20 mL of acetic acid was heated at 90 °C for 1 h. The solution was evaporated under reduced pressure to dryness. The residue was suspended in ethanol and was filtered to give 0.8 g (65%) of solid **1**.

3-(Methylthio)-5-carbethoxy-6-chloro-1,2,4-triazine (3). To a mixture of 15 mL of phosphorus oxychloride and 2 drops of concentrated sulfuric acid was added in portions 1.5 g (7.0 mmol) of **2**. The resulting solution was refluxed for 4 h. The excess of phosphorus oxychloride was evaporated under reduced pressure. The viscous residue was poured into ice. The resulting aqueous mixture was then neutralized with sodium bicarbonate and extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Chromatography of the oily residue in chloroform on silica gel produced 1.5 g (92%) of **3** as a yellow oil. An analytical sample was prepared by distillation at 100 °C (0.1 torr): mass spectrum *m/z* (relative intensity) 235 (15, M^+, ^{37}Cl), 233 (37, M^+), 163 (11), 161 (22), 135 (42), 133 (100); ^1H NMR ($CDCl_3$) δ 1.44 (t, 3 H, *J* = 7 Hz, CH_3), 2.70 (s, 3 H, SCH_3), 4.51 (q, 2 H, CO_2CH_2); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4 (CH_3, SCH_3), 63.7 (CH_2), 148.0, 148.8 (C5, C6), 161.6 (C=O), 172.8 (C3).

Anal. Calcd for $C_7H_8N_3O_2SCl$: C, 35.98; H, 3.45; N, 17.98. Found: C, 35.78; H, 3.43; N, 17.76.

3-(Methylthio)-5-(guanidinocarbonyl)-6-chloro-1,2,4-triazine (4a). To a solution of 450 mg (4.7 mmol) of guanidine hydrochloride in 30 mL of ethanol was added 9.5 mL (4.8 mmol) of 0.5 N ethanolic sodium ethoxide. After stirring at room temperature for $^1/_2$ h and then cooling to 5 °C, the inorganic material was filtered. The cold filtrate was added dropwise to a solution of 1 g (4.3 mmol) of **3** in 10 mL of ethanol, previously cooled in ice water. The resulting solution was allowed to warm up to room temperature and, after 1 h, the ethanol was evaporated to dryness and the residue was dissolved in water. The basic solution was then brought to neutrality with acetic acid. On cooling, a precipitate formed and was filtered to give 0.75 g (71%) of **4a**: mp 216–217 °C; mass spectrum, *m/z* (relative intensity) 248 (9, M^+, ^{37}Cl), 246 (24, M^+), 211 (27, M – Cl), 183 (43, M – Cl – N_2), 176 (15), 138 (49), 128 (100), 117 (26); ^1H NMR (Me_2SO-d_6) δ 2.29 (s, 3 H, SCH_3), 7.8 (b, 2 H, NH_2), 8.66 (s, 1 H, NH), 11.35 (b, 1 H, NH).

Anal. Calcd for $C_6H_7N_6OSCl$: C, 29.21; H, 2.86; N, 34.07; S, 12.99; Cl, 14.37. Found: C, 29.07; H, 3.02; N, 34.01; S, 12.94; Cl, 14.35.

3-(Methylthio)-5-oxo-7-amino-5,6-dihydropyrimido[5,4-*e*]-1,2,4-triazine (5a). Method A. To a solution of 450 mg (4.7 mmol) of guanidine hydrochloride in 30 mL of ethanol was added 9.5 mL of 0.5 N ethanolic sodium ethoxide. The mixture was stirred at room temperature for $^1/_2$ h and cooled in an ice water bath. After filtration, the solution was added to a cooled solution of 1.0 g (4.3 mmo) of **3** in 10 mL of ethanol. The resulting solution was stirred at room temperature for 4 h. After removal of the ethanol, **4a** was obtained. This crude material was dissolved in 20 mL of DMF and 600 mg (4.3 mmol) of anhydrous potassium carbonate was added. The reaction mixture was heated at 160 °C (oil bath) under nitrogen for 5 h. After cooling, the insoluble material was filtered and the filtrate was evaporated to dryness. The residue was suspended in methanol and the insoluble material was filtered. The filtrate was diluted with water and was neutralized by addition of glacial acetic acid. The precipitate was filtered to give 200 mg (21.5%) of reddish brown solid **5a**: mp >300 °C (darkened 240 °C); mass spectrum, *m/z* (relative intensity) 210 (2, M^+), 182 (4, M – N_2), 111 (17), 80 (16), 64 (36), 59 (22), 48 (91), 47 (100, SCH_3), 46 (21), 45 (49), 44 (84), 43 (21, HNCO); ^1H NMR (Me_2SO-d_6) δ 2.63 (s, 3 H, SCH_3), 7.1 (b, 2 H, NH_2), 11.4 (b, 1 H, ring NH).

Anal. Calcd for $C_6H_6N_6OS \cdot {}^2/_5H_2O$: C, 33.15; H, 3.15; N, 38.65. Found: C, 33.16; H, 3.20; N, 38.64.

Method B. To a solution of 540 mg (2.3 mmol) of **3** in 7 mL of DMF was added 210 mg (1.2 mmol) of guanidine carbonate. The resulting mixture was protected by a $CaCl_2$ drying tube and refluxed for 24 h. The DMF was evaporated to dryness and the brick-red residue was recrystallized from DMF/H_2O to afford 205 mg (42%) of **5a**.

3-(Methylthio)-5-(benzamidinocarbonyl)-6-chloro-1,2,4-triazine (4b). The free base of benzamidine was prepared by dissolving 250 mg (1.4 mmol) of the dry hydrochloride salt in 10 mL of ethanol. To this solution was added 2.8 mL (1.4 mmol) of 0.5 N ethanolic sodium ethoxide. The resulting mixture was stirred at room temperature for $^1/_2$ h and then filtered to remove inorganic material. The filtrate was cooled in an ice water bath and then added to a cooled solution of 300 mg (1.28 mmol) of **3** in 5 mL of ethanol. The resulting solution was allowed to warm to room temperature. After the reaction was complete as indicated by TLC analysis, the solution was evaporated to dryness. The gummy residue was recrystallized from ethyl acetate–chloroform to give 220 mg (56%) of off-white solid **4b**: mp 218–219 °C; mass spectrum, *m/z* (relative intensity) 309 (10, M^+, ^{37}Cl), 307 (25, M^+), 272 (14, M – Cl), 266 (18), 264 (39), 199 (62), 176 (29), 163 (24), 161 (58), 147 (25), 141 (37), 104 (100, $C_6H_5C{=}NH$), 103 (28); ^1H NMR (Me_2SO-d_6) δ 2.31 (s, 3 H, SCH_3), 7.5–7.7 (m, 4 H, NH and 3 aromatic protons), 7.9–8.1 (m, 2 H, aromatic), 11.7 (b, 1 H, NH).

Anal. Calcd for $C_{12}H_{10}N_5OSCl$: C, 46.83; H, 3.27; N, 22.76. Found: C, 46.70; H, 3.37; N, 22.63.

3-(Methylthio)-5-oxo-7-phenyl-5,6-dihydropyrimido[5,4-*e*]-1,2,4-triazine (5b). To a solution of 1.0 g (6.4 mmol) of benzamidine hydrochloride in 40 mL of ethanol was added 9.5 mL (4.6 mmol) of 0.5 N ethanolic sodium ethoxide. The mixture was stirred at room temperature for $^1/_2$ h and at 5 °C for another $^1/_2$ h. The inorganic material was filtered and the cold filtrate was added dropwise to a solution of 1.0 g (4.3 mmol) of **3** in 10 mL of ethanol cooled in an ice-water bath. The reaction mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was extracted with an ethanol/ethyl acetate mixture. After evaporation **4b** was obtained. This crude material was dissolved in 40 mL of DMF, and 500 mg (3.6 mmol) of anhydrous potassium carbonate was added. The mixture was heated at 150 °C (oil bath) for 6 h. The inorganic material was filtered, and the filtrate was evaporated under reduced pressure to dryness. The residue was dissolved in water and the insoluble material was filtered. Neutralization of the filtrate with glacial acetic acid gave 400 mg of precipitate. Recrystallization from methanol/water gave 270 mg (28%) of **5b**: mp 281–283 °C; mass spectrum, *m/z* (relative intensity) 271 (3, M^+), 243 (61, M – N_2), 104 (100, $C_6H_5C{=}NH$), 77 (40, C_6H_5); ^1H NMR (Me_2SO-d_6) δ 2.73 (s, 3 H, SCH_3), 7.5–7.7 (m, 3 H, aromatic), 8.2–8.4 (m, 2 H, aromatic), 13.1 (b, 1 H, ring NH).

Anal. Calcd for $C_{12}H_9N_5OS$: C, 53.13; H, 3.34; N, 25.81. Found: C, 53.20; H, 3.38; N, 25.82.

3-(Methylthio)-5-carbamoyl-6-oxo-1,6-dihydro-1,2,4-triazine (6). Three grams (14 mmol) of **2** were dissolved in 50 mL of anhydrous methanol and the solution was saturated with ammonia gas. The resulting mixture was stirred at room temperature for 10 h and evaporated under reduced pressure to dryness. The residue was recrystallized from isopropyl alcohol to give 2.4 g (92%) of bright yellow solid **6**: mp 198–199 °C; mass spectrum, *m/z* (relative intensity) 186 (87, M^+), 169 (44, M – OH), 157 (31, M – HN_2), 130 (23), 85 (100, $HOC{\equiv}CCONH_2$); ^1H NMR (Me_2SO-d_6) δ 2.43 (s, 3 H, SCH_3), 8.06 (b, 1 H, NH), 8.35 (b, 1 H, NH), 13.7 (b, 1 H, ring NH); ^{13}C NMR (Me_2SO-d_6) δ 13.8, 152.1, 152.8, 158.5, 162.9.

Anal. Calcd for $C_5H_6N_4O_2S$: C, 32.25; H, 3.25; N, 30.10; S, 17.22. Found: C, 32.22; H, 3.29; N, 30.01; S, 17.23.

3-(Methylthio)-5-cyano-6-chloro-1,2,4-triazine (7a) and 3-(Methylthio)-5-(*p*-*N*,*N*-dimethylanilino)-6-chloro-1,2,4-triazine (7b). To a cooled solution of 20 mL of phosphorus oxychloride and 10 drops of *N*,*N*-dimethylaniline was added in portions, with stirring, 2 g (10.8 mmol) of **6**. The resulting mixture was refluxed under protection of a drying tube until the starting material disappeared (4 h) as established by TLC. Evaporation of the resulting dark solution under reduced pressure afforded an oily residue. The residue was poured into ice water and the aqueous solution was neutralized with sodium bicarbonate. The neutral solution was extracted with chloroform and the combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The resulting brown liquid residue was chromatographed on silica gel and eluted with chloroform. Evaporation of the chloroform eluants afforded 1.7 g (85%) of greenish yellow solid **7a**: mp 57–58 °C; mass spectrum, *m/z* (relative intensity) 188 (12, M^+, ^{37}Cl), 186 (31, M^+), 158 (8, M –

N_2), 73 (100, $CH_3SC{\equiv}N$); IR (Nujol) 2230 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H, SCH_3); ^{13}C NMR ($CDCl_3$)[23] δ 14.5 (SCH_3), 111.8 (C≡N), 134.5 (C5), 151.4 (C6), 173.8 (C3); ^{13}C NMR (Me_2SO-d_6) δ 13.8, 112.8, 136.1, 151.4, 171.6.

Anal. Calcd for $C_5H_3N_4SCl$: C, 32.18; H, 1.62; N, 30.02; S, 17.18; Cl, 19.00. Found: C, 32.18; H, 1.63; N, 30.03; S, 17.07; Cl, 19.07.

When an excess of *N,N*-dimethylaniline was used in the above reaction, evaporation of the chloroform eluants afforded an orange red solid which was recrystallized from hexane to yield 1.4 g (46%) of reddish brown solid **7b**: mp 144–145 °C; mass spectrum, *m/z* (relative intensity) 282 (17, M^+, ^{37}Cl), 280 (51, M^+), 245 (4, M – Cl), 181 (28), 180 (29), 179 (100, $ClC{\equiv}CC_6H_4N(CH_3)_2$), 178 (53); IR (Nujol) 1600 cm^{-1} (C=C), 810 (C–H bending of two adjacent aromatic hydrogens, para-substituted phenyl); ^1H NMR ($CDCl_3$) δ 2.67 (s, 3 H, SCH_3), 3.08 (s, 6 H, $N(CH_3)_2$), 6.74 (AA'XX' system, 2 H, $J_{A,X}$ = 9.3 Hz, aromatic), 8.14 (AA'XX' system, 2 H, aromatic).

Anal. Calcd for $C_{12}H_{13}N_4SCl$: C, 51.33; H, 4.67; N, 19.95; Cl, 12.63. Found: C, 51.35; H, 4.69; N, 19.94; Cl, 12.62.

Heating **7a** in *N,N*-dimethylaniline also gave **7b** as determined by TLC analysis.

3-(Methylthio)-5-amino-6-chloro-1,2,4-triazine (7c). Into a solution of 70 mg (0.38 mmol) of **7a** in 10 mL of ethyl acetate[24] was bubbled ammonia gas. The yellow solution turned colorless rapidly. The resulting solution was evaporated to dryness. The residue was recrystallized from water to give 42 mg (63%) of white solid **7c**: mp 133–134 °C; mass spectrum, *m/z* (relative intensity) 178 (14, M^+, ^{37}Cl), 176 (41, M^+), 141 (6, M – Cl), 95 (10), 77 (30), 75 (100, $ClC{\equiv}CNH_2$), 45 (17); ^1H NMR ($CDCl_3$) δ 2.58 (s, 3 H, SCH_3), 5.5 (b, 2 H, NH_2).

Anal. Calcd for $C_4H_5N_4SCl$: C, 27.20; H, 2.85; N, 31.72; Cl, 20.07. Found: C, 27.31; H, 2.88; N, 31.70; Cl, 20.11.

3-(Methylthio)-5-methoxy-6-chloro-1,2,4-triazine (7d). A solution of 80 mg (0.54 mmol) of **7a** in 10 mL of methanol was heated at reflux under the protection of a drying tube for 24 h. The solution was evaporated to dryness and the residue was extracted with hexane. The hexane solution was condensed to afford 50 mg (61%) of off-white solid **7d**: mp 153–154 °C; mass spectrum, *m/z* (relative intensity) 193 (35, M^+, ^{37}Cl), 191 (92, M^+), 176 (22, M – CH_3), 148 (14, M – CH_3 – N_2), 92 (31), 90 (96, $ClC{\equiv}COCH_3$), 69 (20), 43 (20), 28 (100, N_2); ^1H NMR ($CDCl_3$) δ 2.64 (s, 3 H, SCH_3), 4.10 (s, 3 H, OCH_3).

Anal. Calcd for $C_5H_6N_3OSCl$: C, 31.34; H, 3.16; N, 21.93; S, 16.73; Cl, 18.50. Found: C, 31.40; H, 3.19; N, 21.90; S, 16.67; Cl, 18.44.

When the above reaction was carried out at room temperature in the presence of sodium methoxide, the reaction was completed rapidly.

3-(Methylthio)-5-ethoxy-6-chloro-1,2,4-triazine (7e). To a solution of 100 mg (0.54 mmol) of **7a** in 5 mL of ethanol was added 1.1 mL of 0.5 N ethanolic sodium ethoxide (0.55 mmol). The yellow solution turned colorless rapidly. The solution was evaporated to dryness, and the residue was extracted with hexane. The hexane solution was evaporated to give 75 mg (67.5%) of off-white solid **7e**: mp 150–152 °C; mass spectrum, *m/z* (relative intensity) 207 (29, M^+, ^{37}Cl), 205 (80, M^+), 179 (16), 177 (45, M – N_2), 106 (5), 104 (15, $ClC{\equiv}COC_2H_5$), 78 (19), 76 (60, $ClC{\equiv}COH$), 74 (97), 69 (20), 47 (21, SCH_3), 45 (19, C_2H_5O), 29 (76, C_2H_5), 28 (100, N_2), 27 (38); ^1H NMR ($CDCl_3$) δ 1.47 (t, 3 H, *J* = 7 Hz, CH_3), 2.63 (s, 3 H, SCH_3), 4.55 (q, 2 H, OCH_2).

Anal. Calcd for $C_6H_8N_3OSCl$: C, 35.04; H, 3.92; N, 20.43; S, 15.59; Cl, 17.24. Found: C, 35.12; H, 3.95; N, 20.33; S, 15.49; Cl, 17.18.

3-(Methylthio)-5-oxo-6-chloro-4,5-dihydro-1,2,4-triazine (7f). To 4 mL of 0.1 N aqueous sodium hydroxide solution was added 60 mg (0.34 mmol) of **7a**. The mixture was stirred at room temperature for 20 min. To this resulting solution was added 1 N HCl until the pH was 2. The precipitate that formed was filtered to give 25 mg (43%) of **7f**: mp 197–198 °C; mass spectrum, *m/z* (relative intensity) 179 (16, M^+, ^{37}Cl), 177 (48, M^+), 116 (18), 74 (24), 69 (100), 48 (46), 47 (27), 45 (22), 43 (23), 28 (20); ^1H NMR (Me_2SO-d_6) δ 2.51 (s, 3 H, SCH_3).

Anal. Calcd for $C_4H_4N_3OSCl$: C, 27.05; H, 2.27; N, 23.66; S, 19.96. Found: C, 27.14; H, 2.32; N, 23.62; S, 20.00.

When this reaction was conducted in acidic medium, the reaction was slower than that in basic solution.

3-(Methylthio)-5-benzamidino-6-chloro-1,2,4-triazine (7g). To a solution of 1.0 g (6.4 mmol) of benzamidine hydrochloride in 10 mL of dry DMF[24] was added 250 mg (5.9 mmol) of a 57% oil dispersion of sodium hydride. After being stirred at room temperature for $^1/_2$ h, the mixture appeared uniform. The resulting mixture was cooled in an ice-water bath and 1.0 g (5.36 mmol) of **7a** was added. The mixture was then stirred at 0 °C for an additional 5 h. Water was added to form a precipitate, which was filtered and recrystallized from chloroform to yield 866 mg (58%) of light brown solid **7g**: mp 217–218 °C; mass spectrum, *m/z* (relative intensity) 281 (8, M^+, ^{37}Cl), 279 (26, M^+), 198 (14), 104 (100, $C_6H_5C{=}NH$), 77 (53, C_6H_5), 51 (23); ^1H NMR (Me_2SO-d_6) δ 2.52 (s, 3 H, SCH_3), 7.50–7.65 (m, 3 H, aromatic), 7.95–8.15 (m, 2 H, aromatic), 9.40 (b, 2 H, NH_2).

Anal. Calcd for $C_{11}H_{10}N_5SCl$: C, 47.23; H, 3.60; N, 25.03. Found: C, 47.20; H, 3.61; N, 25.00.

3-(Methylthio)-6-phenyl-5*H*-imidazo[4,5-*e*]-1,2,4-triazine (8). A mixture of 100 mg (0.35 mmol) of **7g** and 65 mg (0.47 mmol) of anhydrous potassium carbonate in 10 mL of DMF was, under nitrogen, heated at reflux for 5 h. The inorganic material was filtered and the solution was evaporated to dryness. The residue was dissolved in methanol and 1 drop of acetic acid was added (neutralization). The solution was evaporated to dryness and recrystallized from ethanol/water to yield 14 mg (16%) of **8**: mp > 280 °C; mass spectrum, *m/z* (relative intensity) 243 (100, M^+), 215 (28, M – N_2), 168 (23, M – N_2 – SCH_3), 142 (20, M – N_2 – SCH_3 – CN), 129 (18), 115 (21), 112 (45), 104 (47, $C_6H_5C{=}NH$), 103 (19, C_6H_5CN), 97 (19), 85 (18), 77 (39, C_6H_5), 70 (36), 51 (23); ^1H NMR (Me_2SO-d_6) δ 2.54 (s, 3 H, SCH_3), 7.40–7.50 (m, 3 H, aromatic), 8.30–8.45 (m, 2 H, aromatic).

Anal. Calcd for $C_{11}H_9N_5S{\cdot}^3/_{10}H_2O$: C, 53.13; H, 3.89; N, 28.16. Found: C, 53.30; H, 4.03; N, 27.77.

3-(Methylthio)-5-chloro-6-carbethoxy-1,2,4-triazine (9). Prepared according to the literature:[16] mp 60–62 °C (lit.[16] mp 65 °C); mass spectrum, *m/z* (relative intensity) 235 (6, M^+, ^{37}Cl), 233 (12, M^+), 188 (5, M – OC_2H_5), 148 (8), 146 (22), 132 (14), 130 (44), 89 (12), 87 (36, $ClC{\equiv}CC{=}O$), 38 (35), 36 (100, HCl); ^1H NMR ($CDCl_3$) δ 1.45 (t, 3 H, *J* = 7 Hz, CH_3), 2.71 (s, 3 H, SCH_3), 4.53 (q, 2 H, CO_2CH_2).

3-(Methylthio)-6-amino-8-oxo-7,8-dihydropyrimido[4,5-*e*]-1,2,4-triazine (10a). To a solution of 900 mg (9.4 mmol) of guanidine hydrochloride in 50 mL of dry ethanol was added 19 mL of 0.5 N ethanolic sodium ethoxide. The resulting mixture was filtered and cooled to 5–10 °C and 1.0 g (4.3 mmol) of **9** in 30 mL of ethanol was added. The reaction mixture was stirred at room temperature for 10 h. The ethanol was evaporated under reduced pressure and the residue was dissolved in water. Neutralization of the aqueous solution with glacial acetic acid yielded 450 mg (48%) of light yellow solid **10a**: mp >280 °C; mass spectrum, *m/z* (relative intensity) 210 (32, M^+), 195 (22, M – CH_3), 182 (39, M – N_2), 167 (43, M – HNCO), 45 (17), 44 (78), 43 (100, HNCO), 28 (56, N_2); ^1H NMR (Me_2SO-d_6) δ 2.55 (s, 3 H, SCH_3), 7.5 (b, 2 H, NH), 12.5 (b, 1 H, ring NH).

Anal. Calcd for $C_6H_6N_6OS{\cdot}^1/_2H_2O$: C, 32.87; H, 3.22; N, 38.34. Found: C, 32.95; H, 3.24; N, 38.34.

3-(Methylthio)-6-phenyl-8-oxo-7,8-dihydropyrimido[4,5-*e*]-1,2,4-triazine (10b). To a solution of 2.0 g (12.8 mmol) of benzamidine hydrochloride in 80 mL of dry ethanol was added 19 mL (9.6 mmol) of 0.5 N ethanolic sodium ethoxide. The insoluble inorganic material was filtered, and the filtrate was cooled and added dropwise to a solution of 1.0 g (4.3 mmol) of **9** in 30 mL of ethanol cooled in an ice water bath. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The ethanol was evaporated under reduced pressure to dryness. The residue was triturated with water, and the resulting precipitate was collected by filtration. The solid was dissolved in methanol and acetic acid was added until slightly acidic. Water was added and the precipitate was filtered. Recrystallization from methanol/water gave 350 mg (30%) of bright

(23) Assignments were based on the parent 1,2,4-triazine (Braun, S.; Frey, G. *Org. Magn. Reson.* **1975**, *7*, 194) and substituent effects (ref 12b, p 265).

(24) Alcoholic medium was avoided due to the undesired preferable formation of the 5-alkoxy derivative.

yellow solid **10b**: mp >300 °C; mass spectrum, *m/z* (relative intensity) 271 (28, M^+), 256 (11, M – CH_3), 243 (77, M – N_2), 228 (100, M – N_2 – CH_3), 185 (17, M – N_2 – CH_3 – HNCO), 104 (96, $C_6H_5C{=}NH$), 103 (15, $C_6H_5C{\equiv}N$), 97 (16), 77 (71), 51 (25); ^1H NMR (Me_2SO-d_6) δ 2.69 (s, 3 H, SCH_3), 7.50–7.80 (m, 3 H, aromatic), 8.20–8.35 (m, 2 H, aromatic), 13.2 (b, 1 H, ring NH).

Anal. Calcd for $C_{12}H_9N_5OS$: C, 53.13; H, 3.34; N, 25.81. Found: C, 53.13; H, 3.37; N, 25.78.

3-(Methylthio)-5-amino-6-carbethoxy-1,2,4-triazine (11). An ice-water-cooled solution of 400 mg (1.7 mmol) of **9** in 20 mL of ethanol was saturated with ammonia gas. After $^1/_2$ h the precipitate was filtered and recrystallized from ethanol/water to give 260 mg (71%) of off-white solid **11**: mp 166–167 °C; mass spectrum, *m/z* (relative intensity) 214 (100, M^+), 199 (66, M – CH_3), 127 (17), 85 (11, $H_2NC{=}CCO_2H$), 74 (37), 69 (27), 68 (97, $H_2NC{=}CC{=}O$), 45 (20, C_2H_5O), 41 (43), 31 (34), 29 (22, C_2H_5), 28 (25, N_2); ^1H NMR ($CDCl_3$) δ 1.44 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.60 (s, 3 H, SCH_3), 4.47 (q, 2 H, CO_2CH_2), 5.65 (b, 1 H, NH), 7.85 (b, 1 H, NH).

Anal. Calcd for $C_7H_{10}N_4O_2S$: C, 39.24; H, 4.70; N, 26.15. Found: C, 39.33; H, 4.73; N, 26.12.

3-(Methylthio)-5-oxo-6-carbamoyl-4,5-dihydro-1,2,4-triazine (12). Prepared according to the literature:[19] mp >280 °C (lit.[19] mp >300 °C); mass spectrum, *m/z* (relative intensity) 186 (58, M^+), 85 (100, $HOC{\equiv}CCONH_2$), 74 (16), 69 (24, $HOC{\equiv}CC{=}O$), 44 (18), 42 (34, SCH_3), 28 (25); ^1H NMR (Me_2SO-d_6) δ 2.50 (s, 3 H, SCH_3), 7.86 (b, 1 H, NH), 8.39 (b, 1 H, NH), 14.3 (b, 1 H, ring NH); ^{13}C NMR (Me_2SO-d_6) δ 12.2, 142.1, 159.3, 162.3, 165.3.

3-(Methylthio)-5-chloro-6-cyano-1,2,4-triazine (13a). A mixture of 1.0 g (5.37 mmol) of **12** in 10 mL of phosphorus oxychloride was heated to dissolve at reflux for 1 h. The excess of phosphorus oxychloride was evaporated under reduced pressure. The residue was poured onto ice water and was neutralized with sodium bicarbonate. The aqueous solution was extracted with chloroform. The chloroform solution was washed with saturated aqueous sodium bicarbonate and water and was dried over maganesium sulfate. The chloroform was evaporated and the residue was recrystallized from petroleum ether (30–60 °C) to give 480 mg (48%) of light brown solid **13a**: mp 71–72 °C; mass spectrum, *m/z* (relative intensity) 188 (20, M^+, ^{37}Cl), 186 (62, M^+), 160 (8, M – CN), 158 (21, M – N_2), 123 (15, M – N_2 – Cl), 73 (100, $CH_3SC{\equiv}N$), 31 (22); IR (KBr) 2250 cm^{-1} ($C{\equiv}N$); ^1H NMR ($CDCl_3$) δ 2.73 (s, 3 H, SCH_3).

Anal. Calcd for $C_5H_3N_4SCl$: C, 32.18; H, 1.62; N, 30.02. Found: C, 32.20; H, 1.66; N, 30.00.

On prolonged exposure to moisture, this compound was readily hydrolyzed to give 3-(methylthio)-5-oxo-6-cyano-4,5-dihydro-1,2,4-triazine (**13b**): mp 214–216 °C (recrystallized from ethyl acetate); mass spectrum, *m/z* (relative intensity) 168 (26, M^+), 116 (21), 74 (34), 73 (12, CH_3SCN), 69 (100), 48 (42), 47 (20, SCH_3), 45 (21), 43 (32, HNCO); IR (KBr) 2260 cm^{-1} ($C{\equiv}N$); ^1H NMR (Me_2SO-d_6) δ 2.51 (s, 3 H, SCH_3).

Anal. Calcd for $C_5H_4N_4OS$: C, 35.71; H, 2.40; N, 33.32; S, 19.06. Found: C, 35.63; H, 2.47; N, 33.26; S, 18.99.

3-(Methylthio)-6-phenyl-8-aminopyrimido[4,5-*e*]-1,2,4-triazine (14). To a solution of 300 mg (1.92 mmol) of benzamidine hydrochloride in 5 mL of methanol was added 4.0 mL of 0.43 N methanolic methoxide (1.72 mmol). To this solution was added 150 mg (0.8 mmol) of **13a**. The reaction solution rapidly turned yellow and then green. After 15 min the resulting green precipitate was filtered and washed with water to give 130 mg (60%) of **14**: mp 279–280 °C (darkened 270 °C); mass spectrum, *m/z* (relative intensity) 270 (6, M^+), 254 (8, M – NH_2), 242 (37, M – N_2), 104 (100, $C_6H_5C{=}NH$), 77 (18, C_6H_5), 66 (17); IR (KBr) 3440, 3350, 3240 (NH_2 stretching), 1630 (NH_2 bending) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.68 (s, 3 H, SCH_3), 7.45–7.65 (m, 3 H, aromatic), 8.40–8.60 (m, 2 H, aromatic), 8.8 (b, 1 H, NH), 9.4 (b, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) δ 13.3 (CH_3), 128.4 (unsubstituted phenyl carbon by parity technique[25]), 129.0 (unsubstituted phenyl carbon), 130.5, 132.0 (unsubstituted phenyl carbon), 136.9, 153.4, 163.0, 168.4, 176.3.

Anal. Calcd for $C_{12}H_{10}N_6S$: C, 53.32; H, 3.73; N, 31.09. Found: C, 53.43; H, 3.76; N, 31.06.

3-(Methylthio)-6-aminothiazolo[5,4-*e*]-1,2,4-triazine (16). Sixty milligrams (0.3 mmol) of **7a** and 50 mg (0.6 mmol) of thiourea were ground together and placed into a glass tube sealed under vacuum and immersed in an oil bath at 100 °C for 1 h. After being cooled to room temperature, the mixture was washed with ethanol and chloroform. The residue was sublimed to yield a mixture of intermediate 3-(methylthio)-5-(2-thiopseudoureido)-6-chloro-1,2,4-triazine and the cyclization product each showing a molecular ion at 235, 237 (^{37}Cl) and 199, respectively. Prolonged heating of the reaction mixture showed increased formation of the desired compound as determined by mass spectral analysis. The cyclization product was obtained by the following method.

A solution of 60 mg (0.32 mmol) of **7a** and 50 mg (0.6 mmol) of thiourea in 5 mL of DMF was heated at reflux for 3 h. The reaction solution was evaporated to dryness and the residue was triturated with water. The precipitate was filtered and recrystallized from ethanol to give 17 mg (27%) of the product **16**. An analytical sample was prepared by further recrystallization from methanol: mp 267–268 °C; mass spectrum, *m/z* (relative intensity) 199 (100, M^+), 171 (27, M – N_2), 140 (12, M – HNCS), 138 (22), 129 (89, M – N_2 – H_2NCN), 114 (84), 98 (74), 82 (14), 73 (11, CH_3SCN), 71 (32), 70 (91), 47 (20), 45 (37), 43 (21), 28 (45); ^1H NMR (Me_2SO-d_6) δ 2.54 (s, 3 H, SCH_3), 9.43 (b, 2 H, NH_2).

Anal. Calcd for $C_5H_5N_5S_2$: C, 30.14; H, 2.53. Found: C, 30.06; H, 2.69.

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Registry No. **1**, 31143-85-8; **2**, 96259-27-7; **3**, 96259-28-8; **4a**, 96259-29-9; **4b**, 96259-30-2; **5a**, 96259-31-3; **5b**, 96259-32-4; **6**, 96259-33-5; **7a**, 96259-34-6; **7b**, 96259-35-7; **7c**, 96259-36-8; **7d**, 96259-37-9; **7e**, 96259-38-0; **7f**, 96259-39-1; **7g**, 96259-40-4; **8**, 96259-41-5; **9**, 75824-03-2; **10a**, 96259-42-6; **10b**, 96259-43-7; **11**, 96259-44-8; **12**, 89323-15-9; **13a**, 96259-45-9; **13b**, 96259-46-0; **14**, 96259-47-1; **16**, 96292-58-9; diethyl oxomalonate, 609-09-6; *S*-methylisothiosemicarbazide, 44387-06-6; *S*-methylisothiosemicarbazide hydriodide, 35600-34-1; guanidine, 113-00-8; guanidine carbonate, 593-85-1; benzamidine, 618-39-3.

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