Cyclization of Isothiosemicarbazones. 5.[1] [1,2,4]Triazolo[1,5-c]pyrimidines

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The 4-[2-cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazones of aromatic aldehydes underwent cyclization upon being heated in 1-butanol, *N,N*-dimethylformamide, dioxane, or pyridine to give 2,5-disubstituted [1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylates in moderate yields. Competitive formation of ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate occurred in this cyclization with elimination of benzonitriles probably through a nonionic pathway. Treatment of the aromatic ketone analogues with hot acetic acid or pyridine gave 2,2,5-trisubstituted 2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylates by intramolecular cycloaddition. These compounds exist as a chain–ring tautomeric mixture in pyridine at elevated temperatures and gradually lose the substituents at the 2-position to give the same bicyclic pyrimidines as those from aldehyde isothiosemicarbazones. A mechanism was proposed in which the ring closure of the 2,3,5,9-tetraaza-1,3,6-nonatrien-8-yne systems may involve a ten-electron cyclic transition state.

It has previously been reported[1] that treatment of N-(4)-unsubstituted isothiosemicarbazones of both aldehydes and ketones with (ethoxymethylene)malononitrile gave directly bicyclic pyrimidine derivatives and that the reaction may probably proceed through an open-chain condensation product. This work deals with the cyclization and nitrile elimination of *N*(4)-(substituted vinyl)isothiosemicarbazones (**3**) formed from the reaction between *N*(4)-unsubstituted isothiosemicarbazone (**1**) and ethyl (ethoxymethylene)cyanoacetate (**2**; see Scheme I).

Results and Discussion

The *N*(4)-(substituted vinyl)isothiosemicarbazones (**3**) were generally prepared by heating **1** with a slight excess of **2** in benzene. 2-Methoxyethanol was used for the preparation of **3f** in place of benzene because of solubility consideration. The products crystallized out of the reaction mixture and were easily isolated by filtration in up to 95% yields.

A solution of **3a** in pyridine was heated to 130 °C (bath temperature)[2] for 1 h. The reaction mixture was found to contain a dehydrogenated cyclized product, ethyl 5-(methylthio)-2-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (**5a**), ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate (**6**), and benzonitrile (**7a**), the first two compounds being present in a molar ratio of approximately 2:1. Other 3,4-disubstituted isothiosemicarbazones, **3b–f**, were subjected to the same treatment as for **3a**. Except for **3c**, the yields of **6** fell into a relatively narrow range from 15% to 25% independent of whether the substituent on R^1 is electron-donating or -withdrawing. A steric factor may be responsible for the marked tendency of **3c** to lose 2,6-dichlorobenzonitrile (**7c**) and the higher yields of **6** from **3b,d** in which R^1 is ortho substituted.

At lower temperatures (95–100 °C), elimination of **7a** from **3a** in pyridine occurred to the same extent but only in a negligible amount at 55 °C. When the reaction was performed at 55 °C for preparative purpose, the yield of isolated **5a** was only 46% due to undetermined side reactions, although the loss of nitrile could practically be eliminated. However, it was necessary to conduct the reaction of **3c** in pyridine at the lower temperature in order to obtain an analytical sample of **5c** which could not be formed in an isolable amount at higher temperatures. Conversion of **3** to **5** was so slow at room temperature[3] that the preparation of **5** was not practical under such conditions.

When the facts that comparable formation of **7a** from **3a** was observed in *N,N*-dimethylformamide at 130 °C and that the elimination of **7c** from **3c** occurred to the extent of 36% in boiling BuOH are taken into account, the presence of pyridine or a base is not essential to the elimination of nitrile. On the basis of these facts and the substantially equivalent formation of **6** from **3d** and **3f**, the elimination of **7** does not appear to occur through initial abstraction of the aldehydic hydrogen (R^2 = H) by a base as in the case of nitrile-forming elimination of aldoxime ethers.[4]

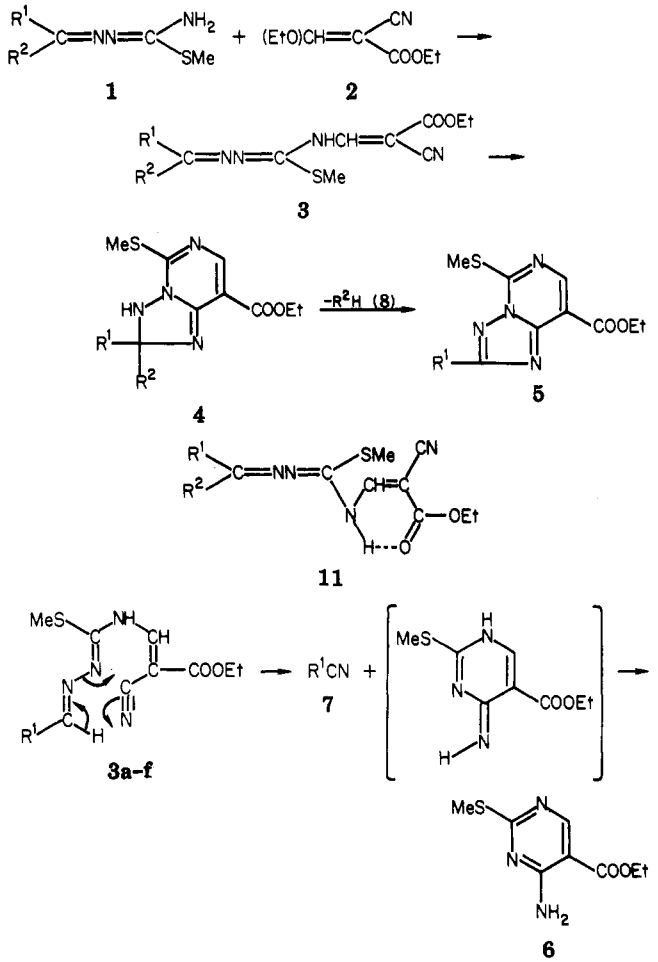
Further support of this idea came from the behavior of a diester analogue (**10**) of **3c** which does not undergo elimination of **7c** in pyridine even at 160 °C over a period of 4 h. Thus the ring closure of **3a-f** to **6** with loss of **7** should be a nonionic process induced by heat probably through a six-centered transition state (Scheme I). Since isothiosemicarbazones[5] tend to exist in a configuration in which the two nitrogen atoms N-1 and N-4 are cis to each other about the N(2)=C bond, isomerization must be involved to obtain the structure favorable to ring closure. The yield of **6** increased to 72% when triethylamine was added to the reaction mixture of **3c** and dioxane from a product in a few percent yield in the absence of the amine within 1 h. This observation might be the result of facilitated isomerization from *E* to *Z* about the N(2)=C bond rather than ionic abstraction of the aldehydic hydrogen of **3c**.

The benzonitriles formed in this reaction were confirmed by actual isolation when formed in large amounts (**7c**) or by the identity of the retention time in high-performance liquid chromatography (HPLC) of the authentic sample with the product formed from the corresponding **3**. Ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate (**6**) was identified by comparison with an authentic compound prepared according to the literature.[6] The structures of **5a–f** were established by the elemental analyses and spectral data, particularly by the characteristic resonance

(1) Part 4: C. Yamazaki, *Bull. Chem. Soc. Jpn.* **54**, 1767 (1981).
(2) Throughout the discussion, the reaction temperatures refer to the bath temperatures.
(3) For example, **3a** was converted to **5a** in only 56% yield after 5 weeks at room temperature.
(4) A. F. Hegarty and P. J. Tuohey, *J. Chem. Soc., Perkin Trans. 2*, **1980**, 1313.
(5) C. Yamazaki, *Can. J. Chem.*, **53**, 610 (1975).
(6) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956).

0022-3263/81/1946-3956$01.25/0

Scheme I

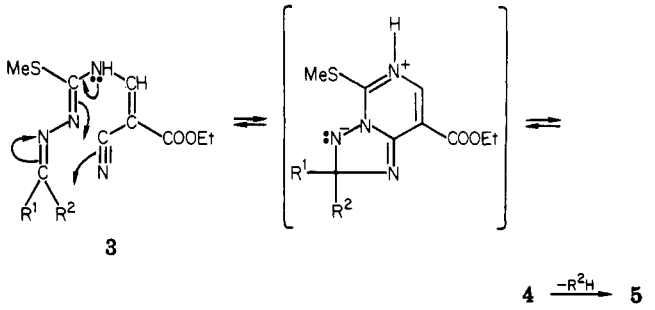


	R^1	R^2
a	C_6H_5	H
b	o-ClC_6H_4	H
c	2,6-$Cl_2C_6H_3$	H
d	o-$MeOC_6H_4$	H
e	p-$MeOC_6H_4$	H
f	m-$O_2NC_6H_4$	H
g	C_6H_5	Me
h	C_6H_5	C_6H_5
i	p-$MeOC_6H_4$	C_6H_5
j	Me	Me

at δ 8.70–8.85 in chloroform-d assignable to the H-7 proton. They were also supported by the irreversible formation of **5a** from a ring–chain tautomeric mixture of **3g** and **4g** or **3h** and **4h** in pyridine at high temperature as will be discussed later.

Although cyclization of **3** gave directly the dehydrogenated bicyclic compounds **5**, the precursor of **5** would be expected to be **4** (R^2 = H). The latter compound was not detected in the reaction mixture even at room temperature where the reaction is extremely slow. The 2,3-dihydro-[1,2,4]triazolo[1,5-c]pyrimidines **4**, however, could be obtained if the aldehydic hydrogen (R^2 = H) in **3** was replaced by a methyl (**3g**) or an aryl group (**3h,i**). Thus, when **3g** was heated in acetic acid at 70 °C for 2 h, **4g** was

Scheme II



obtained in more than 80% yield. Higher temperatures led to the competitive formation of **5a**, which might formally be derived from **4g** by loss of methane (**8**, R^2 = Me). A mixture consisting of **4g** and **5a** in a molar ratio of approximately 1:1 was obtained when the reaction was carried out at 95 °C for 6 h. The formation of **5a** from **3g** was markedly facilitated by hot pyridine, **5a** being the sole cyclized product for the reaction in pyridine at 95 °C for 6 h. Prolonged heating was found to cause an increase in the proportion of **5a**, suggesting that the initially formed **4g** underwent pyrolytic elimination of methane, i.e., **4g** is the precursor of **5a**. Thus treatment of **4g** with hot pyridine provides the best method for preparation of **5a** with respect to the overall yield starting with **3g**. The formation of methane from **4g** is supported in part by the appearance of a sharp singlet at δ 0.12 in the reaction of **4g** in pyridine-d_5 carried out in a sealed tube in which the conversion of **4g** into **5a** proceeded by 88%. Hydrogen, which would be formed from **3a–f**, could not be detected.

At higher temperatures, a small amount of **3g** has been detected in a solution of **4g** in pyridine by the NMR measurement and HPLC, indicating reversible ring-opening of **4g** to **3g**. In order to confirm the possible interconversion between a bicyclic pyrimidine (**4**) and an open-chain 3,4-disubstituted isothiosemicarbazone (**3**), two solutions of **3g** and **4g** in pyridine-d_5 were simultaneously heated, and the changes in composition were followed by means of NMR spectroscopy. Both solutions ultimately exhibited exactly identical spectra and contained three components, **3g**, **4g**, and **5a**. The relative concentration among these components could not be determined because of the absence of isolated resonance corresponding to each component.

Cyclization of **3h** in acetic acid required a higher temperature than did **3g** due to its insolubility in this solvent at 70 °C and was best carried out at 130 °C for 1 h, the yield of isolated **4h** amounting to 80%. In pyridine, however, the starting **3h** remained even after the mixture was heated over a period of 4 h at 130 °C, and **5a**, which was considered to be formed from **4h** with loss of a benzene molecule, was found in the reaction mixture. The behavior of **3h** at high temperatures was further examined by means of NMR spectroscopy at intervals in pyridine-d_5. It was found to produce a mixture consisting **3h**, **4h**, and **5a** in which the ratio of **3h** to **4h** was substantially constant (1:3.17 ± 0.03) for the first 6 h while that of **3h** to **5a** constantly increased from 1:0.48 to 1:3.64. These observations[7] suggest that equilibration establishes between **3h** and **4h** and the latter is irreversibly converted into **5a** which may be the ultimate product under such conditions. When two solutions of **3h** and **4h** in pyridine-d_5 at the same concentration were heated to 130 °C, both solutions

(7) Some variations in ratio were invariably observed in every experiment possibly due to the purity of the starting material and/or a trace of stain on the NMR tubes.

became identical with each other within 1 h, and reversible ring opening of **4h** was thus confirmed (Scheme II).

At lower temperatures, **4h** did not undergo opening of the ring but gradual elimination of a benzene molecule to give **5a**. Prolonged heating caused extensive loss of benzene, **5a** being produced in more than 80% yield. The benzene liberated from **4h** was detected by means of HPLC on silica gel and identified by NMR and IR measurements of a sample obtained by distilling the reaction mixture of **4h** in pyridine to collect an initial benzene-rich fraction and partitioning the fraction between carbon tetrachloride and aqueous hydrobromic acid.

Assignment of structure **4** was based on the analytical and spectral data as well as on chemical transformations as described above. Characteristic fragmentations occurred on the dihydro-1,2,4-triazole ring and produced two fragment ions, $M^+ - R^1$ and $M^+ - R^2$, one of which represented the base peak. The dihydro-1,2,4-triazole arrangement was further supported by NMR spectroscopy. The characteristic H-7 proton resonance appeared at δ 8.10–8.13, showing an upfield shift by 0.60–0.72 ppm relative to that of **5**. The 2-methyl protons of **4g** resonated at δ 1.79 which is 0.71 ppm higher than that of the corresponding **3g**, reflecting rehybridization of the carbon atom (C-2) from sp^2 in **3g** to sp^3 in **4g**.

Attempts to cyclize **3j** to the corresponding **4** or **5** were unsuccessful. Treatment of **3** (R^2 = H) with acetic acid led to unexpected cleavage of ethyl cyanoacetate even at room temperature in diluted solution and resulted in the formation of undetermined products.

In the previous publication,[1] the author suggested initial formation of an open-chain product such as **3** in the reaction of N(4)-unsubstituted isothiosemicarbazones with (ethoxymethylene)malononitrile. Attempts to isolate such an intermediate were unsuccessful. In the present work, however, stabilization of conformation **11** by intramolecular hydrogen bonding[8] inhibits N-2 to approach the cyano function and thus makes it possible to isolate **3** at the open-chain stage. The one-step synthesis of bicyclic pyrimidines by the reaction of N(4)-unsubstituted isothiosemicarbazones with (ethoxymethylene)malononitrile might be initiated in the same manner as in the formation of **3**. Nucleophilic addition of N-2 to the cyano group in **3** would give 1,6-dihydro-6-iminopyrimidine derivative **9**. From the foregoing discussion, however, an alternative pathway to **4** through such an intermediate **9** is not supported. The interconversion between **3g** and **4g** or **3h** and **4h** is a reversible process associated with hydrogen shift and should be one category of the electrocyclic reactions which probably involves a ten-electron cyclic transition state (Scheme II). The driving force of elimination of R^2H (**8**) may be establishment of an extended conjugation system over two heteroaromatic rings and/or release from steric crowding at C-2.

Experimental Section

General Methods. Melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 or 260-30 spectrophotometer and calibrated by comparison with a standard polystyrene film sample. ^1H NMR spectra were obtained with a Hitachi R-24 spectrometer at 60 MHz. Unless otherwise stated, chemical shifts are reported in parts per million (δ scale) downfield from internal tetramethylsilane in deuteriochloroform. Mass spectra (75 eV) were recorded on a JMS-D100 mass spectrometer. High-performance liquid chromatography (HPLC) was carried out on a Kusano Kagaku KHLC-201 instrument using a 300 × 4 mm glass column packed with silica gel. Ethyl (ethoxymethylene)cyanoacetate (**2**) was purchased from the Aldrich Chemical Co. Inc.

4-[2-Cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazones **3a–j** were prepared and characterized according to the method reported previously.[1] The new compounds are as follows. **3b**: pale yellow fine crystals from benzene–EtOH (1:1 by volume); mp 157 °C; 75% yield; IR (CCl_4) 3195 (NH), 2222 (CN), 1693 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{15}ClN_4O_2S$: C, 51.36; H, 4.31; N, 15.97. Found: C, 51.53; H, 4.29; N, 16.01. **3c**: pale yellow long needles from benzene–EtOH (2:3 by volume); mp 145.5–146.5 °C; 91% yield; IR (CCl_4) 3265 (NH), 2222 (CN), 1725, 1697 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{14}Cl_2N_4O_2S$: C, 46.77; H, 3.66; N, 14.54. Found: C, 46.78; H, 3.62; N, 14.70. **3d**: yellow needles from benzene–EtOH (1:1 by volume); mp 135 °C; 64% yield; IR (CCl_4) 3185 (NH), 2222 (CN), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_4O_3S$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.69; H, 5.12; N, 16.35. **3e**: pale yellow fine needles from benzene–EtOH (1:1 by volume); mp 163–164 °C; 95% yield; IR (CCl_4) 3185 (NH), 2222 (CN), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_4O_3S$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.40; H, 5.21; N, 16.21. **3f**: pale yellow needles from benzene–EtOH (1:1 by volume); mp 179–180 °C; 72% yield; IR[9] (CCl_4) 2220 (CN), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_5O_4S$: C, 49.86; H, 4.18; N, 19.39. Found: C, 49.89; H, 4.07; N, 19.15. **3g**: pale yellow needles from EtOH; mp 139–139.5 °C; 77% yield; IR (CCl_4) 3190 (NH), 2220 (CN), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.19; H, 5.41; N, 17.09. **3h**: yellow prisms from benzene–EtOH (1:1 by volume); mp 174.5–175 °C; 77% yield; IR (CCl_4) 3195 (NH), 2220 (CN), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.37; H, 5.10; N, 14.30. **3i**: yellow tiny prisms from benzene–EtOH (1:1 by volume); mp 142 °C; 37% yield; IR (CCl_4) 3195 (NH), 2220 (CN), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.65; H, 5.29; N, 13.18. **3j**:[10] colorless needles from EtOH; mp 114–114.5 °C; 26% yield; IR (CCl_4) 3200 (NH), 2200 (CN), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_4O_2S$: C, 49.25; H, 6.01; N, 20.89. Found: C, 49.30; H, 5.89; N, 20.94.

Ethyl 5-(Methylthio)-2-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (5a) (a Typical Example of Cyclization of 3a–f). A solution of **3a** (0.5 g) in pyridine (2.5 mL) was heated at 55 °C for 10 h and evaporated under reduced pressure. The residual solid was triturated with EtOH, collected by filtration, washed with EtOH, and then air-dried, giving 0.23 g (46%) of **5a** as colorless crystals, mp 159–160 °C. Recrystallization from EtOH gave pure **5a** as colorless plates: mp 163–164 °C; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.46 (t, J = 7.0 Hz, CH_2CH_3, 3), 2.77 (s, SCH_3, 3), 4.50 (q, J = 7.0 Hz, CH_2CH_3, 2), 7.49 (m, $H^{m,p}$ of phenyl, 3), 8.39 (m, H^o of phenyl, 2), 8.73 (s, H-7, 1); mass spectrum, m/e (relative intensity) 314 (100, M^+), 269 (30, $M^+ - OC_2H_5$), 242 (67, $M^+ - CO_2C_2H_4$), 169 (61), 104 (12, $C_6H_5C{\equiv}NH^+$), 103 (12, C_6H_5CN). Anal. Calcd for $C_{15}H_{14}N_4O_2S$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.20; H, 4.48; N, 17.78.

When a solution of **4g** (0.40 g) in pyridine (4 mL) was heated on a boiling water bath for 6 h and the reaction mixture was worked up as in the procedure described above, 0.30 g (79%) of **5a** (mp 162–163 °C) was obtained.

Other ethyl 2-substituted 5-(methylthio)[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylates (5b–f) were similarly prepared from the corresponding **3b–f** as follows. **5b**: colorless needles from benzene–EtOH (1:1 by volume); mp 130–131.5 °C; 50% yield; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.44 (t, J = 7.1 Hz, CH_2CH_3, 3), 2.80 (s, SCH_3, 3), 4.50 (q, J = 7.1 Hz, CH_2CH_3, 2), 7.25–8.22 (m, aromatic, 4), 8.80 (s, H-7, 1); mass spectrum, m/e (relative

(8) Except for **3c**, the N—H and C=O stretching bands of **3** in dilute CCl_4 solutions appeared at 3195–3185 and at 1695–1690 cm^{-1}, respectively. The corresponding diester analogues such as **10**, except for the 2,6-dichlorobenzylidene compound **10**, showed comparable frequencies for the respective band at the same concentration in CCl_4. However, the diester analogues exhibited an additional carbonyl band near 1730 cm^{-1} evidently assignable to the free stretching vibration of the remaining carbonyl band. These infrared measurements support the idea that the intramolecular hydrogen bond should exist between the hydrogen on N-4 and the carbonyl oxygen in **3**.

(9) The N-H band of **3f** was not identified at the usual frequency region.

(10) This compound was obtained by reacting **1j** with **2** in MeCN at room temperature.

intensity) 348 (100, M^+), 303 (35, $M^+ - OC_2H_5$), 276 (78, $M^+ - CO_2C_2H_4$), 138 (25, $ClC_6H_4C{\equiv}NH^+$). Anal. Calcd for $C_{15}H_{13}ClN_4O_2S$: C, 51.65; H, 3.76; N, 16.06. Found: C, 51.66; H, 3.72; N, 16.24. **5c**: colorless plates from benzene–EtOH (2:1 by volume); mp 212 °C; 48% yield; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.45 (t, J = 7.0 Hz, CH_2CH_3, 3), 2.81 (s, SCH_3, 3), 4.52 (q, J = 7.0 Hz, CH_2CH_3, 2), 7.38 (s, aromatic, 3), 8.85 (s, H-7, 1); mass spectrum, m/e (relative intensity) 382 (64, M^+), 337 (29, $M^+ - OC_2H_5$), 310 (100) ($M^+ - CO_2C_2H_4$), 172 (13, $Cl_2C_6H_3 - C{\equiv}NH^+$). Anal. Calcd for $C_{15}H_{12}Cl_2N_4O_2S$: C, 47.01; H, 3.16; N, 14.62. Found: C, 46.86; H, 3.02; N, 14.90. **5d**: colorless needles from benzene–EtOH (1:1 by volume); mp 135–136 °C; 36% yield; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.47 (t, J = 7.0 Hz, CH_2CH_3, 3), 2.79 (s, SCH_3, 3), 3.98 (s, OCH_3, 3), 4.53 (q, J = 7.0 Hz, CH_2CH_3, 2), 6.95–8.30 (m, aromatic, 4), 8.79 (s, H-7, 1); mass spectrum, m/e (relative intensity) 344 (47, M^+), 301 (100), 299 (30, $M^+ - OC_2H_5$), 272 (17, $M^+ - CO_2C_2H_4$), 134 (8, $CH_3O - C_6H_4C{\equiv}NH^+$). Anal. Calcd for $C_{16}H_{16}N_4O_3S$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.86; H, 4.74; N, 16.54. **5e**: colorless needles from benzene–EtOH (1:1 by volume); mp 192–193 °C; 57% yield; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.46 (t, J = 7.1 Hz, CH_2CH_3, 3), 2.78 (s, SCH_3, 3), 3.86 (s, OCH_3, 3), 4.46 (q, J = 7.1 Hz, CH_2CH_3, 2), 6.94 (d, J = 9.2 Hz, aromatic, 2), 8.29 (d, J = 9.2 Hz, aromatic, 2), 8.70 (s, H-7, 1); mass spectrum, m/e (relative intensity) 344 (100 M^+), 299 (15, $M^+ - OC_2H_5$), 272 (42, $M^+ - CO_2C_2H_4$), 134 (11, $CH_3OC_6H_4C{\equiv}NH^+$). Anal. Calcd for $C_{16}H_{16}N_4O_3S$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.96; H, 4.68; N, 16.46. **5f**: yellow plates from benzene–EtOH (1:1 by volume); mp 204 °C; 70% yield; IR (CCl_4) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.50 (t, J = 7.2 Hz, CH_2CH_3, 3), 2.81 (s, SCH_3, 3), 4.56 (q, J = 7.2 Hz, CH_2CH_3, 2), 7.25–8.92 (m, aromatic, 4), 8.82 (s, H-7, 1); mass spectrum, m/e (relative intensity) 359 (62, M^+), 314 (23, $M^+ - OC_2H_5$), 287 (39, $M^+ - CO_2C_2H_4$), 285 (100), 149 (8, $O_2NC_6H_4C{\equiv}NH^+$). Anal. Calcd for $C_{15}H_{13}N_5O_4S$: C, 50.14; H, 3.65; N, 19.49. Found: C, 50.42; H, 3.63; N, 19.30.

Ethyl 2-Methyl-5-(methylthio)-2-phenyl-2,3-dihydro-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (4g). A solution of **3g** (0.50 g) in acetic acid (4 mL) was heated at 70 °C for 2 h and evaporated under reduced pressure. The amorphous residue was triturated with a 10% aqueous sodium carbonate solution (2.5 mL) to neutralize the acid and then with a few drops of EtOH to induce crystallization of the desired product, giving **4g** (0.45 g, 90%) as yellow fine crystals, mp 126–143.5 °C dec. Recrystallization from MeOH gave pure **4g** as lustrous yellow needles: mp 143–144 °C dec; IR (CCl_4) 1710 (C=O) cm^{-1}; ^1H NMR δ 1.39 (t, J = 6.9 Hz, CH_2CH_3, 3), 1.79 (s, 2-CH_3, 3), 2.50 (s, SCH_3, 3), 4.31 (q, J = 6.9 Hz, CH_2CH_3, 2), 4.50 (s, H-3, 1) 7.25–7.80 (m, phenyl, 5), 8.11 (s, H-7, 1); mass spectrum, m/e (relative intensity) 330 (3, M^+), 315 (100, $M^+ - CH_3$), 268 (21), 170 (19), 77 (16). Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.40; H, 5.48; N, 16.91.

Similarly, **4h** and **4i** were prepared except for refluxing in acetic acid for 1 h. **4h**: yellow fine needles from benzene; mp 166.5–168 °C; 75% yield; IR (CCl_4) 1710 (C=O) cm^{-1}; ^1H NMR δ 1.38 (t, J = 7.0 Hz, CH_2CH_3, 3), 2.54 (s, SCH_3, 3), 4.34 (q, J = 7.0 Hz, CH_2CH_3, 2), 4.70 (s, H-3, 1), 7.23–7.73 (m, phenyls, 10), 8.13 (s, H-7, 1); mass spectrum, m/e (relative intensity) 392 (9, M^+), 315 (100, $M^+ - C_6H_5$), 77 (17). Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.22; H, 5.22; N, 14.24. **4i**: pale yellow fine needles from EtOH; mp 145–147.5 °C; 30% yield; IR (CCl_4) 1710 (C=O) cm^{-1}; ^1H NMR δ 1.34 (t, J = 6.9 Hz, CH_2CH_3, 3), 2.50 (s, SCH_3, 3), 3.72 (s, OCH_3, 3), 4.30 (q, J = 6.9 Hz, CH_2CH_3, 2), 4.59 (s, H-3, 1), 6.80 (d, J = 8.8 Hz, *p*-methoxyphenyl, 2), 7.18–7.67 (m, phenyl, 5), 7.47 (d, J = 8.8 Hz, *p*-methoxyphenyl, 2), 8.10 (s, H-7, 1); mass spectrum, m/e (relative intensity) 422 (39, M^+), 345 (100, $M^+ - C_6H_5$), 315 (39, $M^+ - CH_3OC_6H_4$), 210 (96). Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.49; H, 5.22; N, 13.46.

Nitrile-Forming Cleavage of 2,6-Dichlorobenzaldehyde 4-[2-Cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazone 4-[2-Cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazone (3c) in Hot Pyridine. A solution of **3c** (0.24 g) in pyridine (2 mL) was heated under reflux in an oil bath at 130 °C for 1 h, and the solvent was evaporated under reduced pressure, giving a crystalline residue. The solid, after being dissolved in a benzene-EtOH mixture (49:1 by volume), was charged onto a silica gel column (15 g) which was then eluted with the same solvent to give three fractions, I (0.08 g), II (0.085 g), and III (0.06 g) in the order of elution. The major component of I was found to be **7c**, being contaminated with a small amount of **5c**. Recrystallization of I from benzene gave **7c** as colorless needles, mp 143–145 °C, not depressed on admixture with commercial 2,6-dichlorobenzonitrile. The ^1H NMR and IR spectra of this product were in accord with those of the authentic compound. Fraction III was spectroscopically pure ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate (**6**) and, after being recrystallized from benzene, afforded lustrous colorless prisms, mp 131–132 °C, not depressed on being mixed with an authentic sample (mp 130–131.5 °C) prepared by the method described in the literature.[6] The ^1H NMR and IR (CCl_4) spectra of III were well in accord with those of the authentic sample. (Found: C, 45.10; H, 5.17; N, 19.67; M^+, m/e 213). Fraction II consisted of **5c** (35%) and **6** (65%), and thus the yields of **5c**, **6**, and **7c** were estimated to be 13%, 86%, and 75%, respectively.

In another experiment, a solution of **3c** (0.100 g) in pyridine (1 mL) was similarly heated and the pyridine was removed by evaporation in vacuo. The residue was dissolved in EtOH (1 mL) and the solution was subjected to evaporation in vacuo, this procedure being repeated to ensure complete removal of pyridine. The residue was dissolved in carbon tetrachloride to make 40 mL of the total volume. Absorbance of the asymmetric vibration of the amino bands at 3500 cm^{-1} was measured in 5-mm KRS-5 cells. Calculation of the concentration of **6** was made by using a molar extinction coefficient of 231.58 obtained from the authentic compound under similar conditions. The solution was found to contain 5.61×10^{-3} mol/L of **6** corresponding to an 84.8% yield.

The yields of **6** from **3a,b,d–f** were similarly determined with appropriate dilutions: **3a**, 17.2%; **3b**, 21.7%; **3d**, 25.6%; **3e**, 15.6%; **3f**, 24.9%. At the same time, the yields of **5a–f**, estimated on the basis of integrated intensities of the *S*-methyl proton peaks, were 32.2%, 27.0%, 10.0%, 35.6%, 32.5% and 55.6%, respectively.

When a solution of 0.050 g of **3c** in 0.5 mL of 1-butanol was refluxed for 2.5 h and worked up similarly, **6** was found to be produced in 36.5% yield. Refluxing of **3c** (0.050 g) in dioxane (0.5 mL) or a mixture of dioxane (0.5 mL) and triethlyamine (0.05 g) at a bath temperature of 130 °C for 1 h gave **6** in 3.3% and 71.8% yields, respectively.

2,6-Dichlorobenzaldehyde 4-[2,2-bis(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazone (**10**) was obtained according to the method for preparing benzaldehyde 4-[2,2-bis(ethoxycarbonyl)-vinyl]-3-methylisothiosemicarbazone as reported previously[1] in 73% yield as yellow fine needles (from EtOH): mp 99–101 °C; IR (CCl_4) 3223 (NH), 1733, 1705 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{19}Cl_2N_3O_4S$: C, 47.23; H, 4.43; N, 9.72. Found: C, 47.18; H, 4.38; N, 9.57.

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Registry No. 1a, 7410-58-4; **1b**, 67280-19-7; **1c**, 35600-32-9; **1d**, 67280-20-0; **1e**, 67280-21-1; **1f**, 78514-81-5; **1g**, 7575-81-7; **1h**, 78514-82-6; **1i**, 78514-83-7; **1j**, 41208-11-1; **2**, 94-05-3; **3a**, 78514-84-8; **3b**, 78514-85-9; **3c**, 78514-86-0; **3d**, 78514-87-1; **3e**, 78514-88-2; **3f**, 78514-89-3; **3g**, 78514-90-6; **3h**, 78514-91-7; **3i**, 78514-92-8; **3j**, 78514-93-9; **4g**, 78514-94-0; **4h**, 78514-95-1; **4i**, 78514-96-2; **5a**, 78514-97-3; **5b**, 78514-98-4; **5c**, 78514-99-5; **5d**, 78515-00-1; **5e**, 78515-01-2; **5f**, 78515-02-3; **6**, 776-53-4; **7c**, 1194-65-6; **10**, 78515-03-4.