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Cyclization of Isothiosemicarbazones. IV.[1] Synthesis of the [1,2,4]Triazolo[1,5-*c*]pyrimidine Ring System

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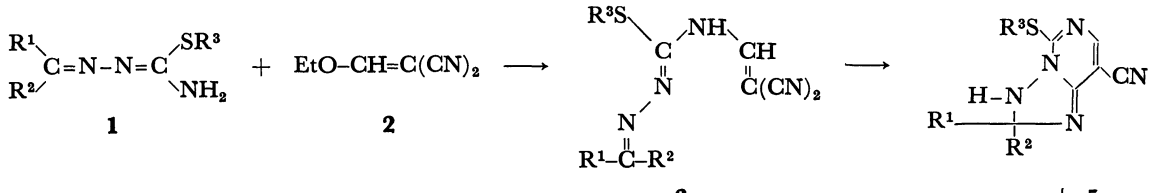
Condensation of isothiosemicarbazones with ethoxymethylenemalononitrile gave 2,3-dihydro[1,2,4]triazolo-[1,5-*c*]pyrimidines in moderate to high yields. The 2,3-dihydro compounds were readily oxidized in dimethyl sulfoxide to give the corresponding [1,2,4]triazolo[1,5-*c*]pyrimidines.

Isothiosemicarbazones (**1**) are polyfunctional nucleophiles for the reaction with α-halo carbonyl compounds leading to the formation of nitrogen-containing heterocycles.[1,2] The internal nitrogen (N-2) of **1** preferentially attacks the halogen-bearing carbon of the halo compound to displace the halide and is considered to be a softer nucleophilic center[3] than the terminal nitrogen (N-4). On the other hand, N-4 invariably becomes attached to the carbonyl carbon whether it is unsubstituted[2] or monosubstituted.[1] In the present work, an attempt was made to initiate the cyclization of **1** at N-4 by the reaction with ethoxymethylenemalononitrile (**2**) and to examine the formation of a six-membered heterocycle. If **1** reacts with **2** at N-4, 3,4-disubstituted isothiosemicarbazone (**3**) might initially be formed, undergoing intramolecular cycloaddition to give a 1-(alkylidene- or benzylideneamino)-5-cyano-6-imino-2-mercapto-1,6-dihydropyrimidine derivative (**4**) in a similar way to that for pyrimidine formation from *S*-alkylisothioureas.[4]

It was found that the reaction of **1** with **2** leads directly to the formation of 2,3-dihydro[1,2,4]triazolo-[1,5-*c*]pyrimidines (**5**) and that, when R^2 is hydrogen, the dihydro compound (**5**) easily undergoes oxidation to [1,2,4]triazolo[1,5-*c*]pyrimidines (**6**) (Scheme 1). Among many condensed pyrimidine derivatives, few examples are known for the preparation of [1,2,4]-triazolo[1,5-*c*]pyrimidines,[5] no reports having been published on a one-step synthesis of the bicyclic pyrimidines from an open-chain, flexible molecule. This paper deals with the preparation and structure of a new series of 2,5-disubstituted and 2,2,5-trisubstituted 8-cyano-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines (**5a**—**n**) and 2,5-disubstituted 8-cyano[1,2,4]triazolo-[1,5-*c*]pyrimidines (**6a**—**i**).

Results and Discussion

The reaction was performed by allowing a solution of **1** and **2** in a 1 : 1.15 molar ratio in benzene to stand at room temperature (Procedure A). Except for **5i** and **5n**, most of **5** crystallized out of the reaction mixture in a substantially pure form, yields depending in part on the reaction period. For example, **5a** was obtained in 97% yield after the reaction mixture had been left to stand for one week, but the yield decreased to 82 and 56% with the elapse of 18 and 3 h, respectively (Table 1). Prolonged periods of time, however, may cause discoloration of the product, analytically pure compounds being obtained within no more than 1 d. The reaction can also be performed by heating a mixture of **1** and **2** (1 : 1.15) at 95—100 °C in the absence of solvent (Procedure B). The melted mixture rapidly solidifies within a few minutes, giving **5** in 55—86% yields after



	R^1	R^2	R^3
a	C_6H_5	H	CH_3
b	*o*-ClC_6H_4	H	CH_3
c	*p*-ClC_6H_4	H	CH_3
d	2,6-$Cl_2C_6H_3$	H	CH_3
e	*o*-$CH_3OC_6H_4$	H	CH_3
f	*p*-$CH_3OC_6H_4$	H	CH_3
g	*p*-$CH_3OC_6H_4$	H	$CH_2CH_2CH_3$
h	*p*-$CH_3OC_6H_4$	H	$CH_2{=}CHCH_2$
i	2,6-$Cl_2C_6H_3$	H	$CH_2{=}CHCH_2$
j	C_6H_5	H	$C_6H_5CH_2$
k	CH_3	CH_3	CH_3
l	C_6H_5	CH_3	CH_3
m	*p*-ClC_6H_4	CH_3	CH_3
n	C_6H_5	C_6H_5	CH_3

Scheme 1. The reaction of isothiosemicarbazones with ethoxymethylenemalononitrile.

TABLE 1. 2,5-DI- AND 2,2,5-TRISUBSTITUTED 8-CYANO-2,3-DIHYDRO[1,2,4]TRIAZOLO[1,5-*c*]PYRIMIDINES

Compd No.	Yield/%	Procedure	Mp/°C	Formula	Found (Calcd) (%) C	H	N
5a	56—97	A	181—182(dec)[a]	$C_{13}H_{11}N_5S$	57.93 (57.98	4.19 4.12	26.33 26.01)
5b	76—82	A	162—175[b,c]	$C_{13}H_{10}ClN_5S$	51.38 (51.40	3.28 3.32	23.26 23.06)
5c	92	A	159—159.5[a]	$C_{13}H_{10}ClN_5S$	51.43 (51.40	3.30 3.32	23.23 23.06)
5d	86	B	191[d]	$C_{13}H_9Cl_2N_5S$	46.18 (46.17	2.65 2.68	20.98 20.71)
5e	86	A	162—163[b]	$C_{14}H_{13}N_5OS$	56.32 (56.18	4.29 4.38	23.58 23.40)
5f	64[e]—87	A	193—194[a,f]	$C_{14}H_{13}N_5OS$	56.16 (56.18	4.35 4.38	23.44 23.40)
5g	63—70	A	141—170[a,c]	$C_{16}H_{17}N_5OS$	58.73 (58.72	5.23 5.20	21.46 21.41)
5h	71—80	A	151[b]	$C_{16}H_{15}N_5OS$	59.04 (59.07	4.62 4.65	21.61 21.53)
5i	80	B	174—175[d]	$C_{15}H_{11}Cl_2N_5S$	49.48 (49.46	3.00 3.04	19.49 19.23)
5j	70	A,B	160.5—161.5[b]	$C_{19}H_{15}N_5S$	65.97 (66.07	4.53 4.38	20.51 20.28)
5k	77	g)	180.5—181.5[h]	$C_9H_{11}N_5S$	48.91 (48.86	4.99 5.01	31.74 31.66)
5l	70	i)	157(dec)[j]	$C_{14}H_{13}N_5S$	59.39 (59.35	4.66 4.63	24.99 24.72)
5m	60	A	176 (dec)[k]	$C_{16}H_{18}ClN_5OS$	52.83 (52.82	4.98 4.99	19.27 19.25)
5n	86	B	200.5—201.5(dec)[h]	$C_{19}H_{15}N_5S$	65.90 (66.07	4.37 4.38	20.39 20.28)

a) An analytically pure compound obtained without recrystallization. b) Light yellow needles from EtOH–MeCN (1 : 1). c) Homogeneous on TLC (Kieselgel 60 F_{254} plate, $CHCl_3$ containing 5% by volume of MeOH), partial oxidation during the course of melting point measurement presumably responsible for the wide melting range. d) Yellow prisms from EtOH–MeCN (1 : 1). e) MeCN used in place of benzene. f) Substantially converted into **6f** on recrystallizing from EtOH–MeCN (1 : 1). g) Refluxed in benzene for 30 min. h) Light yellow needles from 80% aqueous EtOH. i) Refluxed in EtOH for 30 min. j) An analytically pure compound obtained by drying *in vacuo* the initially formed product solvated with one molecule of EtOH. k) Yellow needles solvated with one molecule of EtOH.

TABLE 2. 2,5-DISUBSTITUTED 8-CYANO[1,2,4]TRIAZOLO[1,5-*c*]PYRIMIDINES

Compd No.	Yield/%	Method	Mp/°C	Formula	Found (Calcd) (%) C	H	N
6a	57	A	256[a]	$C_{13}H_9N_5S$	58.44 (58.42	3.42 3.39	26.46 26.21)
6b	50	B	226—226.5[a]	$C_{13}H_8ClN_5S$	51.70 (51.74	2.61 2.67	23.32 23.21)
6c	61	A	213—214[b]	$C_{13}H_8ClN_5S$	51.72 (51.74	2.71 2.67	23.31 23.21)
6d	82	B	261—262[c]	$C_{13}H_7Cl_2N_5S$	46.35 (46.49	2.13 2.10	21.03 20.83)
6e	50	A	192—193[b]	$C_{14}H_{11}N_5OS$	56.62 (56.55	3.60 3.73	23.72 23.56)
6f	53	A	238—239[d]	$C_{14}H_{11}N_5OS$	56.32 (56.55	3.64 3.73	23.88 23.56)
6g	50	B	191.5—192[e]	$C_{16}H_{15}N_5OS$	58.82 (59.07	4.62 4.65	21.42 21.53)
6i	56	C	140.5—142.5[f]	$C_{15}H_9Cl_2N_5S$	49.65 (49.73	2.58 2.50	19.19 19.34)

a) Colorless needles from EtOH–pyridine (1 : 1). b) Colorless needles from benzene–EtOH (1 : 1). c) Pale yellow needles from EtOH–pyridine (1 : 1). d) Pale yellow needles from EtOH–MeCN (1 : 1). e) Colorless needles from 80% EtOH. f) Colorless prisms from benzene–EtOH (1 : 1).

Table 3. Partial spectral data on 2,5-disubstituted and 2,2,5-trisubstituted 8-cyano-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines

Compd No.	IR (KBr) $\tilde{\nu}_{CN}/cm^{-1}$	Mass spectra, *m/e* (rel int)			^1H NMR spectra δ/ppm (from TMS in DMSO-d_6)				
		M^+	M^+-R^2	M^+-R^1	SCH_2	SCH_3	H-2(J/Hz)	H-3(J/Hz)	H-7
5b	2220	303(17)	302(28)	192(100)	—	2.50	6.52(9.3)	7.49(9.3)	8.05
5c	2220	303(30)	302(56)	192(100)	—	2.53	6.28(9.7)	7.30(9.7)	8.04
5e	2230	299(35)	298(100)	192(88)	—	2.53	6.42(9.1)	7.20(9.1)	8.06
5f	2225	299(55)	298(100)	192(69)	—	2.51	6.20(10.0)	7.08(10.0)	8.04
5g	2215	327(66)	326(100)	220(50)	3.13[a]	—	6.19(9.5)	7.07(9.5)	8.01
5h	2230	325(15)	324(37)[b]	218(34)	3.85[c]	—	6.20(9.8)	7.10(9.8)	8.04
5i	2220	263(9)	362(7)	218(100)	3.90[c]	—	7.15(9.4)	7.85(9.4)	8.13
5j	2215	345(15)	344(11)[d]	268(11)	4.49	—	6.27(9.5)	7.23(9.5)	8.10
5k	2225	221(10)	206(100)	—	—	2.50	—	6.47	8.00
5k-d_6[e]		227(6)	209(100)	—	—	2.50	—	6.46	7.97
5l	2210	283(5)	268(100)	206(41)	—	2.50	—	6.90	8.02
5l-d_3[f]		286(2)	268(100)	209(16)	—	2.51	—	6.90	8.02
5m	2220	317(4)	302(100)	206(42)	—	2.52	—	7.22	7.71
5n	2210	345(5)	268(100)	—	—	2.55	—	7.18	8.07

a) Triplet, J=6.9 Hz. b) Base peak allyl cation(*m/e* 41). c) Doublet, J=6.2 Hz. d) Base peak tropylium ion (*m/e* 91). e) $R^1=R^2=CD_3$. f) $R^2=CD_3$.

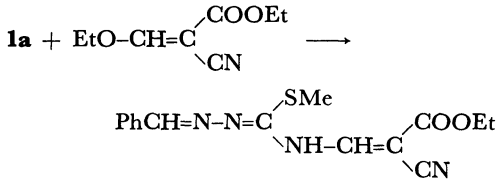
Table 4. Partial spectral data on 2,5-disubstituted 8-cyano[1,2,4]triazolo[1,5-*c*]pyrimidines

Compd No.	IR (KBr) $\tilde{\nu}_{CN}/cm^{-1}$	Mass spectra, *m/e* (rel int)			^1H NMR spectra δ/ppm (from TMS in CF_3COOD)		
		M^+	M^+-R^1CN	$R^1C\equiv\overset{+}{N}H(D)$	SCH_2	SCH_3	H-7
6c	2225	301(24)	164(69)	138(9)	—	3.01	9.00
6d	2240	335(83)	164(100)	172(24)	—	3.00	8.98
6e	2240	297(85)	164(49)	134(6)	—	3.01	9.07
6e-d_3[a]		300(61)	167(56)	135(9)	—	—	9.06
6f	2230	297(100)	164(21)	134(29)	—	3.01	9.03
6f-d_3[a]		300(100)	167(27)	135(27)	—	—	9.03
6g	2240	325(100)	192(6)	134(31)	3.64[b]	—	9.00

a) $R^3=CD_3$. b) Triplet, J=7.1 Hz.

washing with appropriate solvents. Procedure B was satisfactory for **1i** and **1n** from which no **5** was obtained by Procedure A. With ketone isothiosemicarbazones **1k** and **1l**, refluxing in benzene or EtOH gave good results. The reaction of aliphatic aldehyde isothiosemicarbazones (**1**: R^1=Et or *n*-Pr, R^2=H, R^3=Me or *p*-$ClC_6H_4CH_2$) with **2** under these conditions gave a complex mixture from which no expected product was isolated. Attempts to cyclize benzaldehyde 4-methyl- or 4-phenylthiosemicarbazone were unsuccessful with total recovery of the starting thiosemicarbazone.

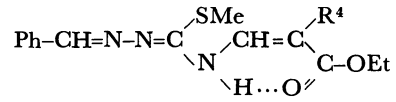
In view of the high yields of hindered compounds (**5d**, **5i** and **5n**), no steric factor may be involved in the 2,3-dihydro-1,2,4-triazole ring formation. Although no intermediate has been detected on the NMR time-scale in the reaction carried out in C_6D_6, C_5D_5N or dimethyl-d_6 sulfoxide (DMSO-d_6), the reaction should proceed through a 3,4-disubstituted isothiosemicarbazone (**3**). In line with the proposed intermediacy, the reaction of **1a** with ethyl ethoxymethylenecyanoacetate gave the open-chain product **7**, the structure of which was established by elemental analysis and spectral data, particularly by the large coupling constant between N^4H and the methine proton (J=13.2 Hz).[6] If a



7

nucleophilic attack of N-2 in **3** on the cyano carbon had occurred, **4** would have been formed which might consecutively undergo intramolecular addition of the 6-imino group to the azomethine double bond at the 1-position giving **5**, although the ring closure of **4** to **5** is disfavored according to the rules proposed by Baldwin.[7] A mechanistic study on the ring formation is now being continued with related compounds including **7**.

Intramolecular hydrogen bonding between the N^4H and the carbonyl oxygen in **7** might stabilize the



8: R^4=CN
9: R^4=COOEt

conformation **8** and prevent N-2 from approaching the cyano group. The resulting insusceptibility to cyclization makes it possible to isolate **7** at the open chain stage. In the infrared spectrum of **7**, N^4–H and the carbonyl stretching frequencies (νNH 3195 and νC=O 1690 cm^{-1}) observed at 4×10^{-3} mol dm^{-3} in carbon tetrachloride were comparable with those of **9** (νNH 3195 and νC=O 1697 cm^{-1}) obtained at the same concentration in carbon tetrachloride. The diester **9**, however, exhibited an additional carbonyl band at a higher frequency (νC=O 1730 cm^{-1}). This band can unambiguously be assigned to the free stretching vibration of the remaining ethoxycarbonyl group which is not involved in the internal bonding. The anomalously downfield resonance (lower than δ 12 ppm) of the N^4H protons of **7** and **9** in chloroform-*d* might also account for the hydrogen bond.[8]

Oxidation of **5** (R^2=H) to the corresponding [1,2,4]-triazolo[1,5-*c*]pyrimidines (**6**) was performed simply by leaving a solution of **5** in DMSO in an open vessel to stand at ambient temperature (Method A), a relatively insoluble **6** crystallizing out of the solution. In another procedure, the reaction between **1** and **2** was conducted in the absence of solvent, and the crude **5**, without isolation, was dissolved in DMSO to give **6** in moderate overall yields (Method B). The oxidation was also carried out with iron(III) chloride in aqueous acetic acid with poor yields of **6** (Method C), although **6i** was obtained only by this procedure in satisfactory purity. Some of **5** in which R^1 is unsubstituted or para-substituted phenyl group were particularly susceptible to oxidation and could not be recrystallized without contamination with the oxidized product.

The structures of the compounds **5** and **6** have been established on the basis of spectral measurements and elemental analyses. Partial spectral data are given in Tables 3 and 4 together with those for certain deuterated compounds. In mass spectrometry, molecular ions were obtained for all the compounds **5a**—**n**, with the intensity depending upon steric crowding at the 2-position (2—65%). Abundant ions M^+–R^1 and M^+–R^2 observed in the spectra of **5** characterized the 2,3-dihydro-1,2,4-triazole structure. The fragmentation pathways were confirmed by the mass spectra of deuterated compounds of **5a**, **5k**, and **5l**, in which R^2 is D, CD_3, and CD_3, respectively. The dehydrogenated compounds **6** showed a much more intense peak for M^+ ion than that of **5**, indicating their extended conjugation systems (24—100%). A characteristic fragment ion $R^1C{\equiv}\overset{+}{N}H$ (6—31%) observed in the spectra of **6** should be formed by hydrogen transfer from R^3 group to N-3 probably through a six-membered transition state as evidenced by the spectra of trideuterated compounds of **6b**, **6e**, and **6f** ($R^3=CD_3$), confirming the proposed arrangements of **5** and **6**. In NMR spectroscopy, two protons H-2 and H-3 on the dihydro-1,2,4-triazole ring of **5** (R^2=H) appear as two AB-type doublets with coupling constants of 9.1—10.0 Hz. The peak assignment is based on the observation that the upfield resonance collapses to a singlet while the downfield one disappears on addition of methanol-d_1. The spectrum of 2-deuterated **5a** (R^2=D) lacks the upfield resonance, exhibiting the H-3 proton as a singlet. The chemical shift values of the H-2 proton in **5** are *ca.* 2.0 ppm higher than those of the azomethine proton in the corresponding isothiosemicarbazones, reflecting rehybridization of the carbon atom (C-2) from sp^2 in **1** to sp^3 in **5**. The 2-methyl protons of **5k**—**m** (R^2=Me) resonate at 0.6—0.7 ppm higher than those of the corresponding **1k**—**m**, also indicating the rehybridization of C-2. In line with the rehybridization of C-2, the anisotropic deshielding (0.43 ppm in DMSO-d_6) of phenyl protons ortho to the azomethine double bond in **1a** disappears in **5a** which exhibits only a single signal for the phenyl protons at δ 7.36. The effect recommences in **6a** in which the ortho protons (H^o) of 2-phenyl group are deshielded by 0.49 ppm (trifluoroacetic acid-*d*) relative to the remaining aromatic protons ($H^{m,p}$) due to the resonance interaction with the heteroaromatic ring system.[9] Substantially constant values of the chemical shifts of H-7 proton in **5** or **6** when R^1–R^3 were widely changed in structure are in line with the assigned structures.

Experimental

General. Melting points were taken in open glass capillaries and are uncorrected. Infrared spectra were recorded on a Hitachi EPI-G2 or 260-30 spectrophotometer, and calibrated by comparison with a standard polystyrene film sample. Proton nuclear magnetic resonance spectra were obtained with a Hitachi R-24 spectrometer at 60 MHz. Unless otherwise stated, chemical shifts are given in parts per million (δ scale) downfield from internal tetramethylsilane (TMS). Solvents used are DMSO-d_6 for 2,3-dihydro-1,2,4-triazolo compounds (**5**) and trifluoroacetic acid-*d* for 1,2,4-triazolo compounds (**6**). The mass spectra (75 eV) were recorded on a JMS-D100 mass spectrometer. Ethoxymethylenemalononitrile (**2**) (Aldrich Chemical Co. Inc.) was used after removal of insoluble substances in benzene at room temperature.

Isothiosemicarbazones. The compounds **1a**—**n** were prepared by the method reported.[8] *S*-(Methyl-d_3)isothiosemicarbazones were obtained by using methyl-d_3 iodide in place of methyl iodide in the usual procedure. Other deuterated isothiosemicarbazones were similarly prepared from the corresponding deuterated carbonyl compounds, acetone-d_6 (CD_3COCD_3), acetophenone-α,α,α-d_3 ($C_6H_5COCD_3$), and benzaldehyde-*formyl-d* (C_6H_5CDO). New compounds are: 2,6-dichlorobenzaldehyde *S*-allylisothiosemicarbazone (**1i**): pale yellow prisms (from *i*-Pr_2O), mp 99—101 °C; NMR ($CDCl_3$) δ=3.76 (2H, dt, *J*=6.5 and 0.8 Hz, SCH_2), 5.5—6.3 (5H, m, CH_2=CH and NH_2), 7.06—7.45 (3H, m, aromatic), 8.62 (1H, s, CH=N). Found: C, 45.54; H, 3.79; N, 14.83%. Calcd for $C_{11}H_{11}Cl_2N_3S$: C, 45.84; H, 3.85; N, 14.58%. *p*-Chloroacetophenone *S*-methylisothiosemicarbazone (**1m**): colorless needles (from aqueous EtOH), mp 231 °C (HBr salt); NMR ($CDCl_3$) (free base): δ=2.38 (3H, s, CCH_3), 2.47 (3H, s, SCH_3), 5.41 (2H, bs, NH_2), 7.30 (2H, d, *J*=8.3 Hz, aromatic), 7.75 (2H, d, *J*=8.3 Hz, aromatic). Found: C, 37.30; H, 3.96; N, 13.30%. Calcd for $C_{10}H_{13}BrClN_3S$: C, 37.22; H, 4.06; N, 13.02%. Benzophenone *S*-methylisothiosemicarbazone (**1n**): colorless fine needles (from EtOH), mp 135.5—136 °C; NMR ($CDCl_3$) δ=2.20 (3H, s, SCH_3), 5.35 (2H, bs, NH_2), 7.35 (5H, s, aromatic), 7.21—7.73 (5H, m, aromatic). Found: C, 66.95; H, 5.57; N, 15.91%. Calcd for $C_{15}H_{15}N_3S$: C, 66.90; H, 5.61; N, 15.61%.

8-Cyano-2,3-dihydro-5-methylthio-2-phenyl[1,2,4]triazolo[1,5-c]-pyrimidine (5a) (A Typical Example of Procedure A). A solution

of **1a** (0.19 g, 1 mmol) and **2** (0.14 g, 1.15 mmol) in benzene (1 ml) was allowed to stand at room temperature. After *ca.* 30 min, yellow prisms began to separate and the reaction was allowed to proceed for 18 h. The crystals were collected by filtration, washed with benzene, and air-dried, giving 0.22 g (82%) of analytically pure **5a**; mp 181—182 °C (dec); IR (KBr) 2220 (CN) cm^{-1}; NMR δ=2.53 (3H, s, SCH_3), 6.26 (1H, d, J=9.7 Hz, H-2), 7.24 (1H, d, J=9.7 Hz, H-3), 7.36 (5H, s, aromatic), 8.04 (1H, s, H-7); MS, *m/e* (rel intensity), 269 (29) (M^+), 268 (56) (M^+-H), 192 (100) ($M^+-C_6H_5$).

The 2-deuterio compound of **5a** was similarly obtained from benzaldehyde-*formyl-d* *S*-methylisothiosemicarbazone [Ph-CD=N-N=C(SMe)NH_2] as yellow prisms, mp 181 °C (dec); NMR δ=2.51 (3H, s, SCH_3), 7.20 (1H, s, H-3), 7.34 (5H, s, aromatic), 8.03 (1H, s, H-7); MS, *m/e* (rel intensity), 270 (25) (M^+), 268 (40) (M^+-D), 193 (100) ($M^+-C_6H_5$).

8-Cyano-2-(2,6-dichlorophenyl)-2,3-dihydro-5-methylthio[1,2,4]triazolo[1,5-c]pyrimidine(5d) (A Typical Example of Procedure B). A mixture of **1d** [hydriodide, mp 200—200.5 °C (dec)(lit,[10] mp 209—211 °C (dec)); Found: C, 27.88; H, 2.60; N, 11.00%. Calcd for $C_9H_{10}Cl_2IN_3S$: C, 27.71; H, 2.58; N, 10.77%] (0.26 g, 1 mmol) and **2** (0.14 g, 1.15 mmol) was heated on a boiling water bath to melt the solids. The liquid formed, still of low viscosity, was thoroughly agitated in order to confirm complete homogeneity. The mixture rapidly solidified within 30 s and heating was continued for 5 min to allow the by-product EtOH to evaporate. After cooling, the solid was triturated with acetone, collected by filtration, washed with acetone, and air-dried to give 0.29 g (86%) of **5d** as yellow crystalline powder, mp 175—178 °C. This was recrystallized from an EtOH–MeCN mixture (1 : 1 by volume) giving sparkling yellow prisms, mp 191 °C; IR (KBr) 2220 (CN) cm^{-1}; NMR δ=2.55 (3H, s, SCH_3), 7.14 (1H, d, J=9.7 Hz, H-2), 7.43 (3H, s, aromatic), 7.79 (1H, d, J=9.7 Hz, H-3), 8.09 (1H, s, H-7); MS *m/e* (rel intensity), 337 (8) (M^+), 336 (7) (M^+-H), 192 (100) ($M^+-C_6H_3Cl_2$).

When Procedure A was applied to the preparation of **5d**, a product, mp 189—190 °C, was obtained in 65% yield after standing for 6 h.

8-Cyano-5-methylthio-2-phenyl[1,2,4]triazolo[1,5-c]pyrimidine (6a) (A Typical Example of Method A; One-step Synthesis from Isothiosemicarbazones). A mixture of **1a** (0.1 g, 0.52 mmol) and **2** (0.07 g, 0.58 mmol) was heated in an open vessel on a boiling water bath with constant shaking, the ethanol formed being allowed to evaporate for 5 min. The resulting crystalline mass was dissolved still hot in DMSO (1 ml) and the solution was allowed to stand at room temperature for 1 d. The separated crystals were collected by filtration, washed with DMSO and water and then air-dried, giving analytically pure **6a** in 57% overall yield as colorless needles, mp 255.5—256 °C. Recrystallization from an EtOH–pyridine mixture (1 : 1 by volume) gave colorless needles, mp 256 °C; IR (KBr) 2220 (CN) cm^{-1}; NMR δ=3.00 (3H, s, SCH_3), 7.73 (3H, m, $H^{m,p}$ of phenyl), 8.22 (2H, m, H^o of phenyl), 9.02 (1H, s, H-7); MS, *m/e* (rel intensity), 267 (100) (M^+), 164 (85) ($M^+-C_6H_5CN$), 104 (31) ($C_6H_5C{\equiv}\overset{+}{N}H$), 103 (27).

2-(o-Chlorophenyl)-8-cyano-5-methylthio[1,2,4]triazolo[1,5-c]pyrimidine (6b) (A Typical Example of Method B). A solution of **5b** (0.1 g) in DMSO (1 ml) was allowed to stand at room temperature for 1 d and separated crystals were collected by filtration, washed with DMSO and water and then air-dried, giving **6b** in 50% yield as colorless needles, mp 226—226.5 °C. Recrystallization from an EtOH–pyridine mixture (1 : 1 by volume) did not change the mp or appearance. IR (KBr) 2230 (CN) cm^{-1}; NMR δ=3.00 (3H, s, SCH_3), 7.50—8.07 (4H, m, aromatic), 9.04 (1H, s, H-7); MS, *m/e* (rel intensity), 301 (66) (M^+), 266 (53) (M^+-Cl), 164 (24) ($M^+-ClC_6H_4CN$), 138 (29) ($ClC_6H_4C{\equiv}\overset{+}{N}H$), 137 (100).

The 5-methylthio-d_3 compound of **6b** was obtained from the corresponding trideuterated **5b** by Method B as colorless needles, mp 225—226 °C; NMR δ=7.48—8.07 (4H, m, aromatic), 9.04 (1H, s, H-7); MS, *m/e* (rel intensity), 304 (100) (M^+), 269 (84) (M^+-Cl), 167 (95) ($M^+-ClC_6H_4CN$), 139 (33) ($ClC_6H_4C{\equiv}\overset{+}{N}D$).

5-Allylthio-8-cyano-2-(2,6-dichlorophenyl)[1,2,4]triazolo[1,5-c]pyrimidine (6i) (Method C). To a solution of **5i** (0.09 g, 0.25 mmol) in AcOH (2 ml) was added 0.5 ml of a solution containing 1 mmol/ml of iron(III) chloride in 60% aqueous AcOH and the mixture was allowed to stand at room temperature with occasional agitation for 10 d. After being diluted with water, separated crystals (0.07 g), mp 127—140 °C, were recrystallized from a benzene–EtOH mixture (1 : 1 by volume) to give 0.05 g (56%) of **6i** as colorless prisms, mp 140.5—142.5 °C; IR (KBr) 2230 (CN) cm^{-1}; NMR δ=4.26 (2H, d, J=6.6 Hz, SCH_2), 5.26—6.34 (3H, m, $CH{=}CH_2$), 7.55 (3H, s, aromatic), 8.95 (1H, s, H-7); MS, *m/e* (rel intensity), 361 (61) (M^+), 190 (80) ($M^+-Cl_2C_6H_3CN$), 172 (25) ($Cl_2C_6H_3C{\equiv}\overset{+}{N}H$), 121 (100), 41 (77) (allyl cation).

Benzaldehyde 3-Methyl-4-[2-cyano-2-(ethoxycarbonyl)vinyl]isothiosemicarbazone (7). A mixture of **1a** (0.19 g, 1 mmol), ethyl ethoxymethylenecyanoacetate (0.19 g, 1.15 mmol), and benzene (0.5 ml) was heated at 70 °C for 1 h. On cooling, the separated solid was collected by filtration, washed with EtOH and air-dried, giving 0.27 g (84%) of **7** as pale yellow crystalline powder, mp 140—143 °C. Recrystallization twice from EtOH provided pale yellow needles, mp 145 °C; IR (CCl_4) 3195 (NH), 2220 (CN), 1690 (C=O) cm^{-1}; NMR ($CDCl_3$) δ=1.39 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.60 (3H, s, SCH_3), 4.34 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 7.43 (3H, m, $H^{m,p}$ of phenyl), 7.69 (1H, d, J=13.2 Hz, NH=C$\underline{H}$), 7.90 (2H, m, H^o of phenyl), 8.47 (1H, s, CH=N), 12.40 (1H, d, J=*ca.* 13 Hz, N$\underline{H}$-CH).

Found: C, 56.97; H, 5.09; N, 17.52%; M^+, 316. Calcd for $C_{15}H_{16}N_4O_2S$: C, 56.96; H, 5.10; N, 17.71%; M, 316.

Benzaldehyde 3-Methyl-4-[2,2-bis(ethoxycarbonyl)vinyl]isothiosemicarbazone (9). A mixture of **1a** (0.19 g, 1 mmol) and diethyl ethoxymethylenemalonate (0.22 g, 1 mmol) in benzene (0.5 ml) was refluxed for 4 h, the solvent being evaporated. Recrystallization of the crystalline residue from EtOH gave **9** as pale yellow prisms (0.27 g, 74%), mp 99—100 °C; NMR ($CDCl_3$) δ=1.31 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.36 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.60 (3H, s, SCH_3), 4.18 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 4.29 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 7.41 (3H,m, $H^{m,p}$ of phenyl), 7.88 (2H, m, H^o of phenyl), 8.22 (1H, d, J=13.3 Hz, C$\underline{H}$-NH), 8.42 (1H, s, CH=N), 12.28 (1H, d, J=13.3 Hz, CH-N$\underline{H}$).

Found: C, 56.11; H, 5.83; N, 11.67%; M^+, 363. Calcd for $C_{17}H_{21}N_3O_4S$: C, 56.19; H, 5.83; N, 11.57%; M, 363.

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