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Studies on Heterocyclic Enaminonitriles. VIII.[1] Reactions of 2-Benzamido(and 2-Acetamido)-3-cyano-4,5-dihydrothiophenes with Cyanomethylene Compounds

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The reactions of 2-benzamido(and acetamido)-3-cyano-4,5-dihydrothiophenes (Ia and Id) with ethyl cyanoacetate or malononitrile gave ethyl α-cyano-4-[2-phenyl(and methyl)-5,6-dihydrothieno-[2,3-*d*]pyrimidine]acetates (IIa-1 and IId-1) or 4-[2-phenyl(and methyl)-5,6-dihydrothieno[2,3-*d*]pyrimidine]malononitriles (IIa-2 and IId-2). Similarly, 2-benzamido(and acetamido)-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophenes (Ib, e or Ic, f) reacted with ethyl cyanoacetate or malononitrile to form the corresponding ethyl cyanoacetate derivatives (IIb, c-1, IIe, f-1) or malononitrile derivatives (IIb, c-2, IIe, f-2). Compounds IIa—f-1 and IIa—f-2 were prepared by the reactions of the corresponding 4-chloro-5,6-dihydrothieno[2,3-*d*]pyrimidines and ethyl cyanoacetate or malononitrile.

Keywords——2-benzamido-3-cyano-4,5-dihydrothiophene; 4-(5,6-dihydrothieno[2,3-*d*]pyrimidine)malononitrile; cyclization; ethyl cyanoacetate; malononitrile; ethyl α-cyano-4-(5,6-dihydrothieno[2,3-*d*]pyrimidine)acetate; 4-chloro-5,6-dihydrothieno[2,3-*d*]pyrimidine

In a previous paper, we showed that 2-benzamido-3-cyano-4,5-dihydrothiophenes[2] react with an amine to give the corresponding 4-amino-2-phenyl-5,6-dihydrothieno[2,3-*d*]-pyrimidines (**1**).[3] The reaction occurs *via* addition to form the amidine (**2**), which undergoes intramolecular dehydration to yield **1**. This reaction raised the possibility that when an active methylene compound is used in place of an amine, an intermediate (**3**) initially formed may undergo intramolecular dehydration to give (**4**).

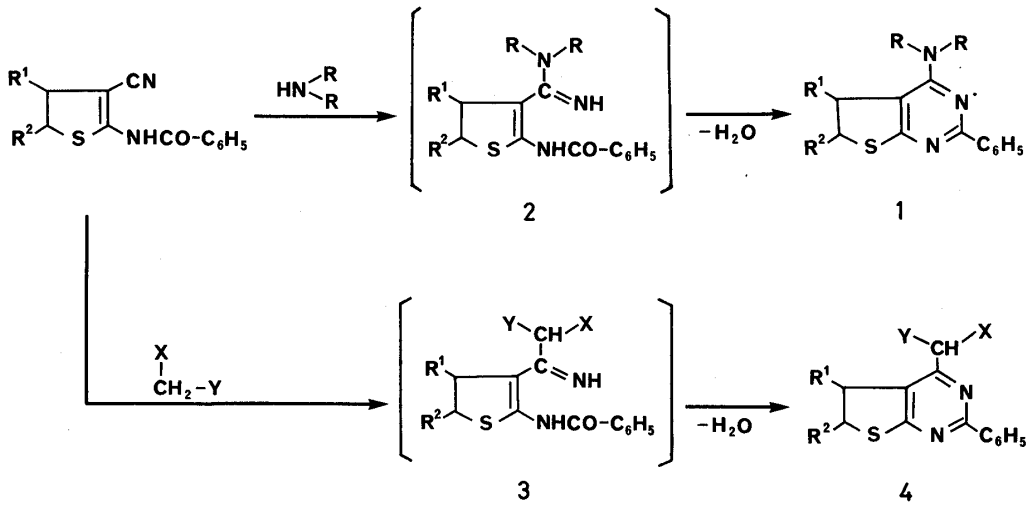
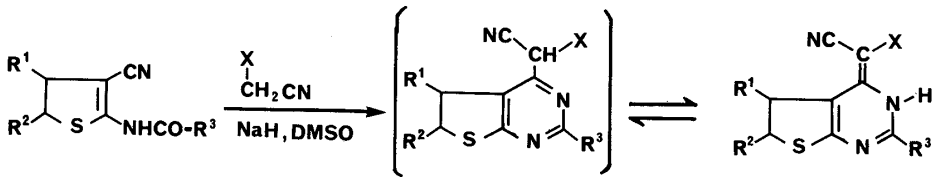


Chart 1

The present paper deals with the reactions of 2-benzamido (and 2-acetamido)-3-cyano-4,5-dihydrothiophenes (Ia—c and Id—f) with active methylene compounds.

When a solution of 2-benzamido(or 2-acetamido)-3-cyano-4,5-dihydrothiophene (Ia or Id), ethyl cyanoacetate (2 eq), and sodium hydride (2 eq) in dimethyl sulfoxide (DMSO) was heated at 140 °C for 5 h, the expected ethyl α-cyano-4-(2-phenyl(or 2-methyl)-5,6-dihydrothieno[2,3-*d*]pyrimidine)acetate (IIa-1 or IId-1) was obtained. In a similar fashion, 2-benzamido(and 2-acetamido)-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophenes (Ib, c or Ie, f) provided the corresponding ethyl α-cyano-4-(2-phenyl(or 2-methyl)-5,6-dihydro-



A B

Ia—f

a: $R^1=R^2=H$, $R^3=C_6H_5$
b: $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$
c: $R^1=R^3=C_6H_5$, $R^2=H$

IIa—f-1, IIa—f-2

d: $R^1=R^2=H$, $R^3=CH_3$
e: $R^1=H$, $R^2=R^3=CH_3$
f: $R^1=C_6H_5$, $R^2=H$, $R^3=CH_3$

1: $X=COOC_2H_5$, 2: $X=CN$

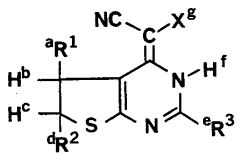
Chart 2

TABLE I. Yields, Melting Points, and Elemental Analyses of IIa—f-1 and IIa—f-2

Compd. No.	Yield (%)	( )[a]	mp (°C) (Recrystn. solvent)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N
IIa-1	36	(69)	215—216 (Acetone)	Yellow needles	$C_{17}H_{15}N_3O_2S$	62.76 (62.42)	4.65 4.47	12.92 12.67)
IIb-1	41	(55)	181—182 (Acetone–petr. ether)	Yellow needles	$C_{18}H_{17}N_3O_2S$	63.70 (63.56)	5.05 4.95	12.38 12.34)
IIc-1	49	(77)	209—210 (Acetone–petr. ether)	Yellow columns	$C_{23}H_{19}N_3O_2S$	68.81 (68.87)	4.77 4.95	10.47 10.17)
IIa-2	60	(78)	301—302 (dec.) (DMF–H_2O)	Pale yellow needles	$C_{15}H_{10}N_4S$	64.73 (64.51)	3.62 3.54	20.13 19.66)
IIb-2	51	(84)	291 (dec.) (MeOH)	Pale yellow needles	$C_{16}H_{12}N_4S$	65.73 (65.41)	4.14 4.01	19.16 19.07)
IIc-2	44	(73)	270—271 (dec.) ($CHCl_3$–MeOH)	Yellow prisms	$C_{21}H_{14}N_4S$	71.17 (70.97)	3.98 3.96	15.81 15.71)
IId-1	40	(61)	182—184 (Acetone)	Pale yellow columns	$C_{12}H_{13}N_3O_2S$	54.74 (54.84)	4.98 4.88	15.96 16.10)
IIe-1	48	(70)	118—120 (Acetone–petr. ether)	Pale yellow needles	$C_{13}H_{15}N_3O_2S$	56.30 (56.49)	5.45 5.36	15.15 15.15)
IIf-1	54	(55)	184—185 (Acetone–petr. ether)	Pale yellow columns	$C_{18}H_{17}N_3O_2S$	63.70 (63.67)	5.05 5.12	12.38 12.20)
IId-2	73	(72)	315—317 (dec.) (DMF–H_2O)	Pale yellow needles	$C_{10}H_8N_4S$	55.54 (55.28)	3.73 3.69	25.91 25.62)
IIe-2	73	(70)	258 (dec.) (DMF–H_2O)	Pale yellow needles	$C_{11}H_{10}N_4S$	57.37 (57.35)	4.38 4.27	24.33 24.13)
IIf-2	51	(60)	258 (dec.) ($CHCl_3$–MeOH)	Yellow prisms	$C_{16}H_{12}N_4S$	65.73 (65.66)	4.14 4.31	19.16 18.88)

a) Yields from the reactions of IIIa—f with ethyl cyanoacetate or malononitrile.

TABLE II. Spectral Data for IIa—f-1 and IIa—f-2



IIa—f-1, IIa—f-2

IIa-1: $R^1=R^2=H$, $R^3=C_6H_5$, $X=COOC_2H_5$
IIb-1: $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$, $X=COOC_2H_5$
IIc-1: $R^1=R^3=C_6H_5$, $R^2=H$, $X=COOC_2H_5$
IIa-2: $R^1=R^2=H$, $R^3=C_6H_5$, $X=CN$
IIb-2: $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$, $X=CN$
IIc-2: $R^1=R^3=C_6H_5$, $R^2=H$, $X=CN$
IId-1: $R^1=R^2=H$, $R^3=CH_3$, $X=COOC_2H_5$
IIe-1: $R^1=H$, $R^2=R^3=CH_3$, $X=COOC_2H_5$
IIf-1: $R^1=C_6H_5$, $R^2=H$, $R^3=CH_3$, $X=COOC_2H_5$
IId-2: $R^1=R^2=H$, $R^3=CH_3$, $X=CN$
IIe-2: $R^1=H$, $R^2=R^3=CH_3$, $X=CN$
IIf-2: $R^1=C_6H_5$, $R^2=H$, $R^3=CH_3$, $X=CN$

Compd. No.	IR ν_{max}^{KBr} cm^{-1}			^{1}H-NMR spectra (ppm) (J in Hz)							UV $\lambda_{max}^{CHCl_3}$ nm (log ε)			MS m/z (M^+)
	NH	CN	CO	H^a	H^b	H^c	H^d	H^e	H^f	H^g				
IIa-1		2200	1630	[a] 3.34—3.60 (m)		3.72—3.96 (m)		7.47—7.64 (3H, m) 8.00—8.18 (2H, m)	14.98 (br s)	1.35 (3H, t) 4.32 (2H, q)	270 (4.32)	343 (4.26)	376[d] (3.99)	325
IIb-1		2200	1635	[a] 3.29—4.18 (m) ($J_{c,d}=6$)			1.53 (d)	7.40—7.65 (3H, m) 7.94—8.18 (2H, m)	14.94 (br s)	1.36 (3H, t) 4.31 (2H, q)	270 (4.43)	342 (4.34)	375[d] (4.07)	339
IIc-1		2205	1630	[a] 7.30 (s)	5.59 (dd)	3.24 (dd)	4.07 (dd) ($J_{b,c}=1$, $J_{b,d}=9$, $J_{c,d}=11.5$)	7.49—7.67 (3H, m) 8.09—8.28 (2H, m)	15.11 (br s)	1.28 (3H, t) 4.24 (2H, q)	277 (4.36)	343 (4.28)	377[d] (3.95)	401
IIa-2	3190	2205 2195		[b] 3.00—3.24 (m)		3.55—3.78 (m)		7.27—7.41 (3H, m) 8.66—8.82[c] (m)	14.53 (br s)		267 (4.40)	342 (4.29)	388 (4.01)	278

IIb-2	3190	2203 2190		[b] 3.22—4.02 (m) ($J_{c,d}=6.5$)			1.25 (d)	7.29—7.43 (3H, m) 8.65—8.84[c] (m)	13.81 (br s)			267 (4.18)	341 (4.09)	388 (3.82)	292
IIc-2	3180	2200 2180		[b] 7.13[c] —7.62 (m)	5.66 (dd)	3.05 (dd)	3.79 (dd) ($J_{b,c}=1$, $J_{b,d}=8.5$, $J_{c,d}=11$)	7.13—7.62[c] (m) 8.78—8.98 (2H, m)	15.02 (s)			268 (4.12)	341 (4.03)	386 (3.70)	354
IId-1		2200	1635	[a] 3.35—3.56 (m)		3.67—3.91 (m)		2.52 (s)	14.25 (br s)	1.33 (3H, t) 4.27 (2H, q)		279 (4.07)	315 (3.99)	371 (4.32)	263
IIe-1		2200	1630	[a] 3.23—4.01 (m) ($J_{c,d}=6.5$)			1.50 (d)	2.50 (s)	14.18 (br s)	1.33 (3H, t) 4.26 (2H, q)		279 (4.05)	315 (3.98)	370 (4.30)	277
IIf-1		2200	1638	[a] 7.28 (s)	5.51 (dd)	3.20 (dd)	4.01 (dd) ($J_{b,c}=1$, $J_{b,d}=9$, $J_{c,d}=11.5$)	2.55 (s)	14.29 (br s)	1.26 (3H, t) 4.19 (2H, q)		283 (4.01)	317 (4.01)	370 (4.29)	339
IId-2	3205	2215 2195		[b] 3.13—3.37 (m)		3.43—3.67 (m)		2.39 (s)	10.53 (br s)			284 (3.96)	317 (3.93)	377 (4.11)	216
IIe-2	3220	2220 2195		[b] 3.12—4.14 (m) ($J_{c,d}=7$)			1.28 (d)	2.41 (s)	12.88 (s)			284 (4.15)	317 (4.11)	377 (4.30)	230
IIf-2	3230	2205 2195		[b] 7.22 —7.48 (m)	5.52 (dd)	3.16 (dd)	3.96 (dd) ($J_{b,c}=1$, $J_{b,d}=8.5$, $J_{c,d}=11$)	2.50 (s)	12.82 (s)			285 (4.04)	317 (4.05)	375 (4.15)	292

Abbreviations: br s, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; t, triplet. *a*) In $CDCl_3$. *b*) In pyridine-d_5. *c*) Overlapping with the solvent signal. *d*) Shoulder.

thieno[2,3-*d*]pyrimidine)acetates (IIb, c-1 or IIe, f-1) (Chart 2).

Subsequently, the reactions of Ia—f with malononitrile resulted in the formation of the corresponding 4-[2-phenyl(or methyl)-5,6-dihydrothieno[2,3-*d*]pyrimidine]malononitriles (IIa—f-2) in moderate yields. The structures of IIa—f-1 and IIa—f-2 were confirmed by direct comparison with the corresponding authentic specimens prepared by the method described later in this paper.

These structures were also supported by the analytical (Table I) and spectral data (Table II). On the other hand, when Ia was treated with diethyl malonate or ethyl acetoacetate under the same conditions, no reaction occurred, and the starting material was recovered.

In order to confirm the structures of IIa—f-1 and IIa—f-2, we synthesized them by an alternative route (Chart 3). When a solution of the corresponding 4-chloro-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidines (IIIa—c),[3] ethyl cyanoacetate (or malononitrile), and sodium hydride in DMSO was heated at 120 °C for 7 h, IIa—c-1 (or IIa—c-2) were obtained. A solution of Id—f and dimethylamine hydrochloride[3] in pyridine was refluxed for 7 h, providing the corresponding 2-methyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (IV—VI) in good yields. On chlorination with phosphoryl chloride, IV—VI were converted to the corresponding 4-chloro derivatives (IIId—f). The reactions of IIId—f with ethyl cyanoacetate (or malononitrile) in the presence of sodium hydride gave IId—f-1 (or IId—f-2).

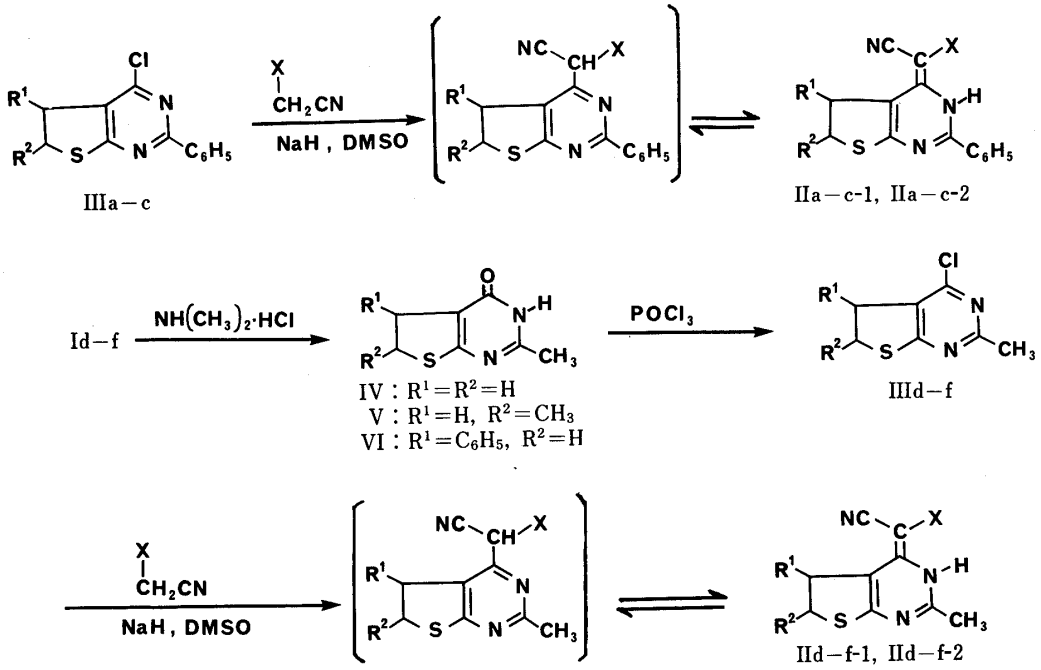


Chart 3

The infrared (IR) spectra of IIa—f-1 displayed bands indicative of a conjugated cyano group at near 2200 cm^{-1} and a carbonyl group at near 1630 cm^{-1}. The proton nuclear magnetic resonance (^{1}H-NMR) spectra showed a broad one-proton singlet at near δ 14.5 due to the N^3-proton. These spectral data suggested the presence of hydrogen bonding between the ester carbonyl and the N^3-proton. The IR spectra of IIa—f-2 exhibited an NH band at near 3200 cm^{-1} and two strong bands at near 2200 cm^{-1} attributable to conjugated cyano groups. In the ^{1}H-NMR spectra, the N^3-proton signal appeared downfield (δ 10.53—15.02).

As shown in Fig. 1, the ultraviolet (UV) spectrum of IIa-1 was similar to that of IIa-2 and

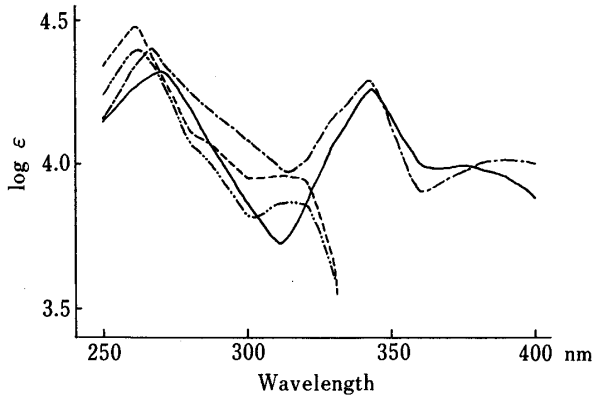
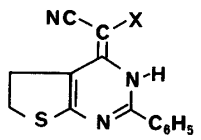
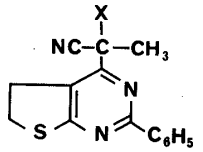


Fig. 1. Ultraviolet Spectra of IIa-1, IIa-2, VII and VIII in $CHCl_3$

——, IIa-1; —·—, IIa-2; ----, VII; — — —, VIII.



IIa-1, IIa-2



VII, VIII

IIa-1, VII: $X=COOC_2H_5$
IIa-2, VIII: $X=CN$

Chart 4

it showed absorption different from those of ethyl α-cyano-α-methyl-4-(2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine)acetate (VII) and α-methyl-4-(2-phenyl-5,6-dihydrothieno-[2,3-*d*]pyrimidine)malononitrile (VIII). These observations are consistent with the 3,4,5,6-tetrahydrothieno[2,3-*d*]pyrimidine structures (**B**) rather than 5,6-dihydrothieno[2,3-*d*]-pyrimidine structures (**A**) in regard to the structures of IIa—f-1 and IIa—f-2. Compounds VII and VIII were prepared by the reactions of IIa-1 and IIa-2 with iodomethane (Chart 4). The structural assignments of VII and VIII were made on the basis of elemental analysis and the spectral data.

Experimental

DMSO was distilled under reduced pressure and stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or a JASCO A-302 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi R-22 (90 MHz) or a JNM-MH-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-01SG spectrometer. UV spectra were determined on a Hitachi 340 spectrophotometer.

Reactions of Ia, b and Id, e with Ethyl Cyanoacetate——Sodium hydride (60%) (10 mmol) was added in small portions to a solution of ethyl cyanoacetate (10 mmol) in DMSO (10 ml), and Ia, b or Id, e (5 mmol) was added. The mixture was stirred for 5 h at 140 °C. After removal of the DMSO *in vacuo*, the residue was poured into ice water, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent, and recrystallized from the solvent indicated in Table I.

Reaction of Ic or If with Ethyl Cyanoacetate——A mixture of Ic or If (5 mmol), 60% NaH (15 mmol) and ethyl cyanoacetate (15 mmol) in DMSO (10 ml) was heated for 10 h at 150 °C with stirring. The DMSO was removed *in vacuo*, and the residue was added to ice water, and extracted with $CHCl_3$.

i) For Ic: The $CHCl_3$ extract was chromatographed on silica gel with $CHCl_3$ as the eluent. The first fraction was Ic (250 mg, 16%). The second product to appear was IIc-1 (980 mg, 49%).

ii) For If: The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIf-1 (910 mg, 54%).

Reactions of Ia—f with Malononitrile——A mixture of Ia—f (5 mmol), malononitrile (10 mmol), and 60% NaH (10 mmol) in DMSO (10 ml) was heated at 100 °C (in the case of Ia, b and Id, e) or at 120 °C (in the case of Ic and If) for 5 h with stirring. The solvent was distilled off *in vacuo*, then the residue was poured into ice water, and acidified with 5% HCl. The precipitate was collected, washed with water and petr. benzin, dried, and recrystallized from an appropriate solvent (Table I).

Preparation of 2-Methyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (IV—VI)——A mixture of Id, Ie or If (10 mmol) and dimethylamine hydrochloride (20 mmol) in pyridine (20 ml) was refluxed for 7 h. The pyridine was removed under reduced pressure, and the residue was poured into ice water. The precipitate was collected, washed with water, and dried. Yields were 88% (IV), 93% (V) and 93% (VI), respectively.

i) 2-Methyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (IV) was recrystallized from MeOH to give colorless needles, mp 236—238 °C. *Anal.* Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.80; N, 16.65. Found: C, 49.80; H, 4.80; N, 16.48. MS *m/z*: 168 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 2.22 (3H, s, CH_3), 2.90—3.16 (2H, m, C_5-H), 3.22—3.46 (2H, m, C_6-H), 11.9—12.3 (1H, br s, >NH).

ii) 2,6-Dimethyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (V) was recrystallized from MeOH to provide colorless needles, mp 251—253 °C. *Anal.* Calcd for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.93; H, 5.53; N, 15.35. MS *m/z*: 182 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 1.38 (3H, d, J=7 Hz, C_6-CH$_3$), 2.24 (3H, s, C_2-CH$_3$), 2.70 (1H, dd, J=16, 5 Hz, C_5-H), 3.22 (1H, dd, J=16, 8 Hz, C_5-H), 3.82—4.13 (1H, m, C_6-H), 12.2—12.6 (1H, br s, >NH).

iii) 2-Methyl-5-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4-(3*H*)-one (VI) was recrystallized from CH_2Cl_2 to give colorless needles, mp 230—233 °C. *Anal.* Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.75; H, 5.13; N, 11.36. MS *m/z*: 244 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1645 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 2.28 (3H, s, CH$_3$), 3.15 (1H, dd, J=12, 4 Hz, C_6-H), 3.94 (1H, dd, J=12, 9 Hz, C_6-H), 4.66 (1H, dd, J=9, 4 Hz, C_5-H), 7.35 (5H, s, aromatic H), 12.3—12.6 (1H, br s, >NH).

Reactions of IV—VI with Phosphoryl Chloride——A solution of IV, V or VI (5 mmol) in $POCl_3$ (10 ml) was refluxed for 2 h (in the case of IV, V) or 9 h (in the case of VI). After removal of the $POCl_3$ under reduced pressure, the residue was poured into ice water.

i) For IV and VI: The precipitate was collected, washed with water, and air-dried.

(a) 4-Chloro-2-methyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (IIId) was recrystallized from acetone–petr. ether to give colorless prisms (0.81 g, 87%), mp 85—87 °C. *Anal.* Calcd for $C_7H_7ClN_2S$: C, 45.04; H, 3.78; N, 15.01. Found: C, 45.22; H, 3.85; N, 14.83. MS *m/z*: 186 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 2.62 (3H, s, CH$_3$), 3.43 (4H, s, C_5-H and C_6-H).

(b) 4-Chloro-2-methyl-5-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (IIIf) was recrystallized from ether–petr. ether to yield colorless columns (1.1 g, 84%), mp 56—58 °C. *Anal.* Calcd for $C_{13}H_{11}ClN_2S$: C, 59.42; H, 4.22; N, 10.66. Found: C, 59.34; H, 4.22; N, 10.59. MS *m/z*: 262 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 2.66 (3H, s, CH$_3$), 3.32 (1H, dd, J=12, 4 Hz, C_6-H), 3.98 (1H, dd, J=12, 8 Hz, C_6-H), 4.81 (1H, dd, J=8, 4 Hz, C_5-H), 7.20—7.54 (5H, m, aromatic H).

ii) For V: The aqueous solution was basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated. The residue was distilled to give 4-chloro-2,6-dimethyl-5,6-dihydrothieno-[2,3-*d*]pyrimidine (IIIe) (0.73 g, 73%) as a colorless oil, bp 131—133 °C (bath temp.)/2 mmHg. *Anal.* Calcd for $C_8H_9ClN_2S$: C, 47.88; H, 4.52; N, 13.96. Found: C, 47.85; H, 4.58; N, 13.72. MS *m/z*: 200 (M^+). ^{1}H-NMR (in $CDCl_3$) δ: 1.50 (3H, d, J=6 Hz, C_6-CH$_3$), 2.58 (3H, s, C_2-CH$_3$), 2.82—3.52 (2H, m, C_5-H), 3.65—4.17 (1H, m, C_6-H).

Reactions of IIIa—f with Ethyl Cyanoacetate or Malononitrile——A mixture of IIIa—f (2 mmol), ethyl cyanoacetate or malononitrile (3 mmol), and 60% NaH (3 mmol) in DMSO (5 ml) was heated for 7 h at 120 °C with stirring. After removal of the DMSO *in vacuo*, the residue was acidified with 5% HCl. The precipitate was collected, washed with water and petr. benzin, dried, and recrystallized from the solvent listed in Table I to give IIa—f-1 and IIa—f-2.

Preparation of Ethyl α-Methyl-4-(2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine)cyanoacetate (VII)——Sodium hydride (60%) (110 mg, 2.8 mmol) was added to a solution of IIa-1 (810 mg, 2.5 mmol) in DMSO (10 ml), and then CH_3I (710 mg, 5 mmol) was added. The reaction mixture was stirred for 3 h at room temperature and poured into ice water. The precipitate was collected, washed with water, dried, purified by column chromatography on silica gel with $CHCl_3$ as the eluent, and recrystallized from ether to give VII as colorless needles (660 mg, 78%), mp 99—100 °C. *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.82; H, 5.07; N, 12.41. MS *m/z*: 339 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2245 (CN), 1748 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, –OCH$_2$–CH$_3$), 2.06 (3H, s, CH$_3$), 3.36—3.62 (4H, m, C_5-H and C_6-H), 4.36 (2H, q, J=7 Hz, –OCH$_2$–CH$_3$), 7.35—7.53 (3H, m, aromatic H), 8.30—8.47 (2H, m, aromatic H).

Preparation of α-Methyl-4-(2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine)malononitrile (VIII)——A mixture of IIa-2 (700 mg, 2.5 mmol), 60% NaH (110 mg, 2.8 mmol), and CH_3I (710 mg, 5 mmol) in DMF (10 ml) was stirred for 5 h at 60 °C. The DMF was removed *in vacuo*, the residue was poured into ice water, and the deposited crystals were collected, washed with water, dried, and purified by column chromatography on silica gel with $CHCl_3$ as the eluent. Recrystallization from acetone–petr. ether gave VIII (540 mg, 74%) as colorless needles, mp 158—159 °C. *Anal.* Calcd for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.84; H, 4.08; N, 19.55. MS *m/z*: 292 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2245 (CN). ^{1}H-NMR (in $CDCl_3$) δ: 2.22 (3H, s, CH_3), 3.34—3.78 (4H, m, C_5-H and C_6-H), 7.36—7.55 (3H, m, aromatic H), 8.32—8.50 (2H, m, aromatic H).

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References

1) Part VII: H. Matsunaga, M. Sonoda, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, **34**, 396 (1986).
2) K. Yamagata, Y. Tomioka, M. Yamazaki, T. Matsuda, and K. Noda, *Chem. Pharm. Bull.*, **30**, 4396 (1982).
3) K. Yamagata, Y. Tomioka, M. Yamazaki, and K. Noda, *Chem. Pharm. Bull.*, **31**, 401 (1983).