Synthesis of Polycyclic Nitrogen-containing Heterocyclic [1]: One Pot Formation of 1,6-Naphthyridine Ring System by Reaction of Amino-cyano-methylthio-heterocycles with Dialkyl Acetyeledicarboxylates

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Reaction of 3-amino-3-methylthio-2-cyanoacrylonitrile (**1**) with excess dimethyl acetylenedicarboxylate(DMAD) in the presence of potassium carbonate in dimethyl sulfoxide gave a novel tricyclic heterocycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5a**). When one equivalent of DMAD was used in this reaction, dimethyl 4-amino-3-cyano-2-methylthiopyridine-5,6-dicarboxylate (**3a**), a key intermediate of **5a**, was obtained.

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The reaction of 5-amino-6-cyano-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione with DMAD in the presence of potassium carbonate in dimethyl sulfoxide gave tetramethyl 8,9,10,11-tetrahydro-8,10-dimethyl-9,10-dioxo-4*H*-pyrimido[4',5':5,6]pyrido-[2,3,4-*cb*][1,6]-naphthyridine-2,3,5,6-tetracarboxylate (**5c**) in good yield. The reaction of other heterocycles bearing amino, cyano, and methylthio groups with DMAD or DEAD (diethyl acetylenedicarboxylate) under the same reaction conditions gave also the corresponding tetracyclic heterocycles containing the fundamental 1,6-naphthyridine ring system in moderate yields.

In connection with our program of preparing new polyheterocyclic compounds which are of interest from both theoretical and practical standpoints and which might also exhibit potential biological activity, we have recently described the synthesis of 4-aminopyrazolo[3,4-*d*]pyridine-5,6-dicarboxylate by the reaction of 5-aminopyrazole-4-carbonitrile in the presence of the base potassium carbonate in moderate yield [2]. This reaction can be conveniently applied to the formation of dimethyl 4-aminopyridine-2,3-dicarboxylate derivatives. We now wish to report the reaction of various pyridine or pyrimidine derivatives bearing amino, cyano, and methylthio groups with dialkyl acetylenedicarboxylates in the presence of a base such as potassium carbonate to obtain the polycyclic nitrogen-containing tri- or tetracyclic heterocycles by one pot formation of the 1,6-naphthyridine ring system, as shown in Scheme 1.

3-Amino-3-methylthio-2-cyanoacrylonitrile (**1**)[3], readily prepared by reaction of bis-(methylthio)methylene-propanedinitrile [3] with ammonium hydroxide in good yield, is one of the simplest compounds in a large number of ketene *N*,*S*-acetals and enaminonitriles [4]. This compound should prove useful for the synthesis of nitrogen-containing heterocyclic compounds.

Reactions of enaminonitriles with DMAD give a variety of compounds [5]. We examined the reaction of **1** with DMAD in the presence of a base to give dimethyl 2-methylthiopyridine-5,6-dicarboxylate, possibly for use as intermediates of biologically active compounds. At the start of the present study, the reaction of **1** with DMAD was studied under various basic conditions. The results are shown in Table 1. This reaction gave a cyclized product, 4-amino-3-cyano-2-methylthiopyridine-5,6-dicarboxylate(**3a**) from basic solution. Michael product, 3-(*N*-1',2'-bis(methoxy-carbonyl)ethenylamino-2-cyano-3-methylthioacrylonitrile (**2a**) was obtained by acidification of the mother liquor. However, the pyrido[4,3-*c*]pyridine derivative (**4a**) of intermediate **5a** could not be detect in any reaction mixture. Most crucial to the formation of **5a** by reaction of **1** with DMAD was that of **3**. Potassium carbonate as a base gave the most effective results in the reaction of **1** with DMAD at room temperature in dimethyl sulfoxide. Other bases such as potassium hydrogen phosphate, potassium phosphate *n*-hydrate and potassium *tert*-butoxide also served efficiently as catalysts to give the

Scheme 1

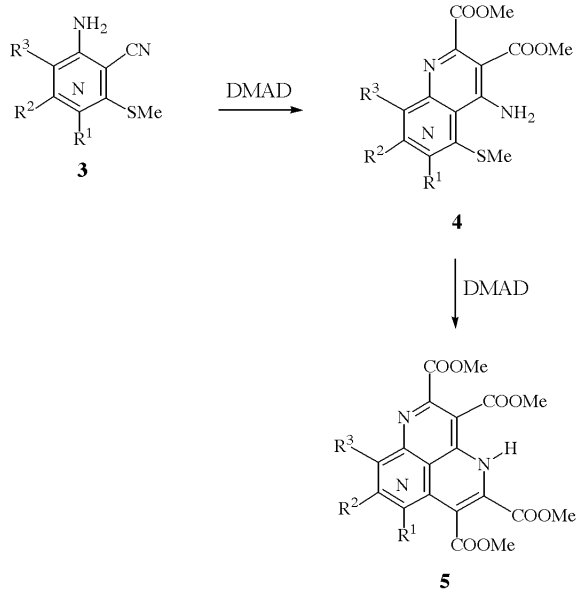
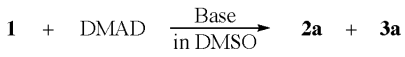


Table 1

Reactions of Ketene N, S-Acetal
with DMAD in the Presence of a Base [a]



No	Base (mmol)	Reaction Time	Yield (%) **2a**	Yield (%) **3a**
1	K_2CO_3 (12)	8 hr	37.3	24.8
2	K_2CO_3 (30)	24 hr, 4 hr (at 60°)	48.6	18.1
3	K_2CO_3 (30)	48 hr	29.3	30.0
4	K_2CO_3 (40)	72 hr	37.5	16.5
5	K_2HPO_4 (12)	48 hr	20.9	14.6
6	$K_3PO_4H_2O$ (15)	48 hr	39.6	25.6
7	KOH (20)	48 hr	22.0	-----
8	*t*-BuOK (12)	48 hr	11.8	6.5
9	AcONa (20)	48 hr	27.7	13.4
10	K_2HPO_4 (10), K_2CO_3 (10)	48 hr	33.0	29.0

[a] Reactions were carried out in a system of **1** (10 mmol) and DMAD (10 mmol) at room temperature in DMSO.

corresponding **2a** and **3a**, but potassium hydroxide and sodium hydroxide were not effective for conversion to **3a** or **5a**. This reaction did not occur without a base and starting material **1** was recovered. When excess DMAD (1.2 equivalents) was used, a third product (**5a**) was obtained in 0.6% yield along with **2a** in 20.7% and **3a** in 19.2% yield. The yield of **5a** *via* triple cyclization was improved by increasing the amount of DMAD in the presence of potassium carbonate in DMSO at room temperature, as shown in Table 2.

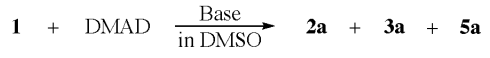
A system of amino-cyano-methylthio-heterocycles containing pyridine or pyrimidine rings is a very important and versatile synthetic starting material for construction of fused pyridine or pyrimidine derivatives. These heterocycles are generally obtained by the reaction of ketene dithioacetals [6] with various nucleophiles. Reaction of **1a** with DMAD in the presence of potassium carbonate as a base in dimethyl sulfoxide (DMSO) gave an expected tricyclic heterocycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5a**), in 68% yield. When potassium phosphate hydrate is employed as the base in this reaction a yield of 70% is obtained. Diethyl acetylenedicarboxylate (DEAD) also reacted with **1a** under a same reaction condition to give **5b** in 63% yield.

This synthesis of tricyclic heterocycles is applicable to the preparation of tetracyclic heterocycles. At first, the reaction of 4-amino-3-cyano-2-methylthioquinoline (**3c**) with DMAD in the presence of potassium carbonate in DMSO gave the corresponding tetramethyl 1*H*-quinolino[2,3,4-*de*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**5c**) in 33% yield. The IR spectrum of this compound clearly shows a broad peak at 3240 cm^{-1} due to an amino group and a peak at 1740 cm^{-1} due to the carbonyl groups. The ^{1}H-NMR spectrum exhibited a four-spin system in the aromatic region at δ 7.42(d), 7.45(t), 7.69(t), and 8.84(d) and four singlet signals due to the methoxy protons at δ 3.98, 3.99, 4.05, and 4.07(each 3H) and a broad singlet signal corresponding to the amino group at δ 12.10. In the nuclear Overhauser effect (NOE) experiment, NOE enhancement between the 11-H doublet (δ 7.42) and the N-H singlet at δ 12.10 was observed.

In a similar manner, the reaction of 5-amino-6-cyanopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3d**), which was prepared by the condensation of 6-aminouracils with ketene dithioacetal, bis(methylthio)methylene-propanedinitrile [7], with DMAD in the presence of potassium carbonate or tripotassium phosphate gave the tetracyclic heterocycle, **5d**, in 53 and 35 % yields, respectively. As shown in Entry 3, the reaction of **3d** with DEAD was also carried out under the same reaction conditions to give the corresponding tetra cyclic compound, **5e**, in 59% yield.

Table 2

Reaction of Ketene N, S-Acetal with DMAD in The Presence of Base [a]

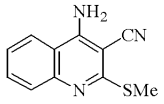
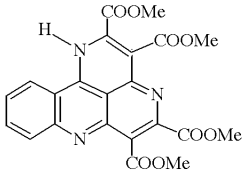
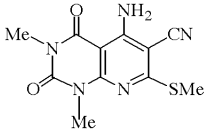
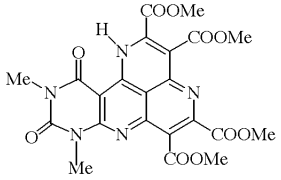
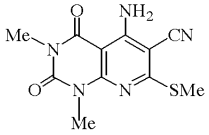
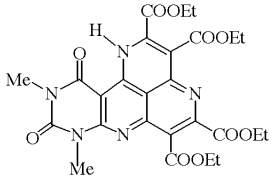
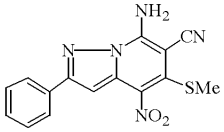
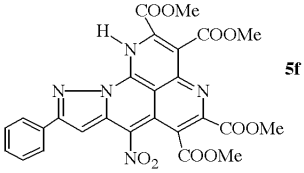
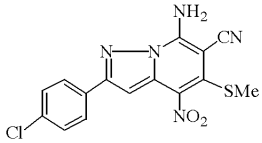
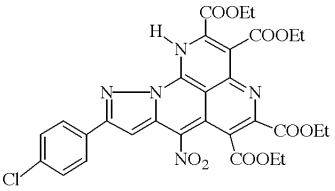
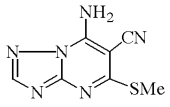
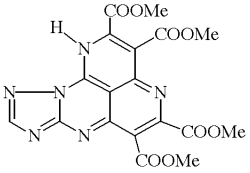
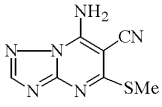
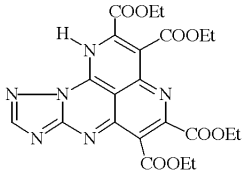
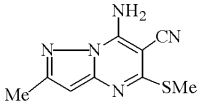
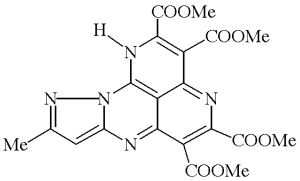


No	DMAD (mmol)	Base (mmol)	Reaction Time	Yield (%) **2a**	**3a**	**5a**
1	12	K_2CO_3 (30)	24 hr	20.7	19.2	0.6
2	22	K_2CO_3 (30)	48 hr	18.0	----	17.1
3	32	K_2CO_3 (60)	48 hr	17.7	----	21.5
4	30	$K_3PO_4H_2O$ (40)	48 hr	16.5	----	21.1

[a] The reactions were carried out at room temperature in DMSO.

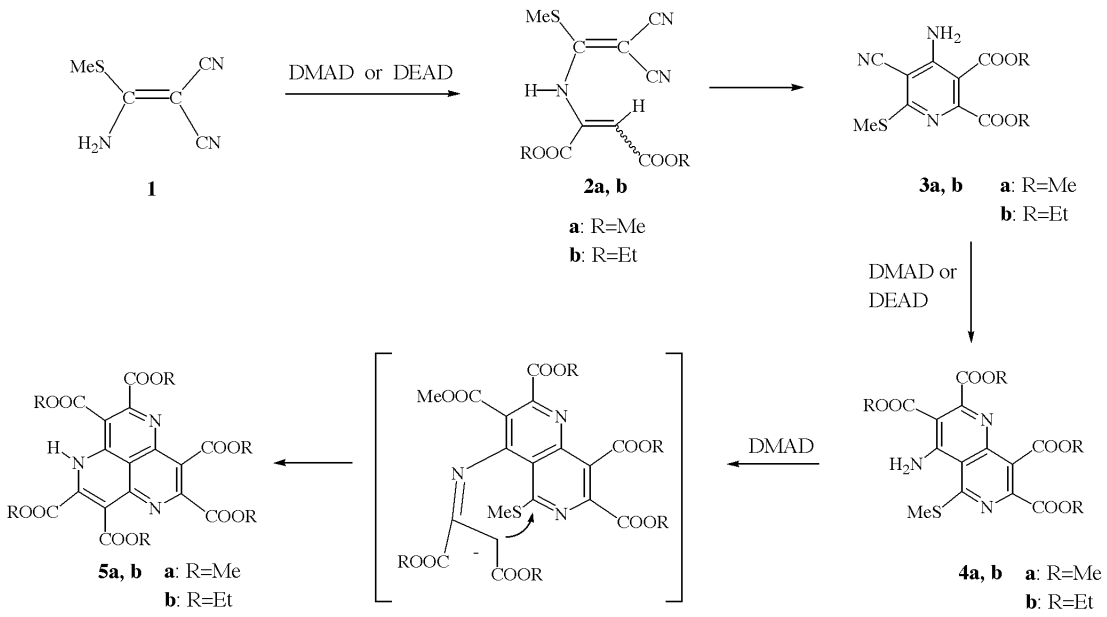
Table 3

Reaction of Amino-cyano-methylthio-heterocycles with Dialkyl Acetylenedicarboxylates in the Presence of Base [a]

Entry	Aminonitrile	Acetylenic comp.	Base	Product	Yield(%)
1	 **3c**	DMAD	K_2CO_3 $K_3PO_4 \cdot H_2O$	 **5c**	33
2	 **3d**	DMAD	K_2CO_3 $K_3PO_4 \cdot H_2O$	 **5d**	53 35
3	 **3d**	DEAD	K_2CO_3	 **5e**	59
4	 **3e**	DMAD	K_2CO_3	 **5f**	75
5	 **3f**	DEAD	K_3PO_4 H_2O	 **5g**	56
6	 **3g**	DMAD	K_2CO_3	 **5h**	43
7	 **3g**	DEAD	K_2CO_3	 **5i**	23
8	 **3h**	DMAD	K_2CO_3	 **5j**	47

a) The reactions were carried out in a system of **1** (20 mmol), DMAD or DEAD (30 mmol), and K_2CO_3 or K_3PO_3 H_2O (50 mmol) at room temperature in DMSO.

Scheme 2



The corresponding pyrazolopyridine derivatives, **3e** and **f** [8], was allowed to react with DMAD giving the corresponding tetracyclic compounds, **5f** and **g**, in 75 and 56% yields, respectively. The above reaction could be readily applied to synthesis of fused pyrimido[4,5,6-*d*,*e*]-[1,6]naphthyridine derivatives (**5h, i**), which were prepared by reaction of the corresponding triazolo[1,5-*a*]-pyrimidine derivative (**3g**) with DMAD or DEAD in the presence of potassium carbonate, in 43 and 23% yields, respectively. Similarly, reaction of pyrazolo[1,5-*a*]pyrimidine derivative (**3h**) with DMAD was carried out to give the corresponding tetracyclic compound, **5j**, in 47% yield.

In conclusion, ketene *N*,*S*-acetal, **1**, is a very useful starting material for the preparation of poly functionalized pyridine and derivatives of the novel tricyclic heterocycle, 1*H*-1,4,7-triazaphenalene, which should prove useful for the synthesis of poly fused heterocyclic compounds as starting materials for obtaining biologically active compounds. The tandem addition-cyclization reaction of amino-cyano-methylthio-pyridine or pyrimidine derivatives with dialkyl acetylenedicarboxylates in the presence of appropriate base was found to be a versatile method of forming polycyclic heterocycles containing the 1,6-naphthyridine ring system.

EXPERIMENTAL

All melting points were determined in a capillary tube and are uncollected. Infrared (ir) spectra were recorded in potassium bromide pellets on JASCO 810 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi 323 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JEOL-PS-100(100 MHz), JEOL-FX-90Q(90 MHz), and JEOL-GX-400(400MHz) spectrometers with tetramethylsilane as an internal standard. Mass(ms) spectra were recorded on JEOL-01SG mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University.

Dimethyl 4-Amino-5-cyano-6-methylthiopyridine-1,2-dicarboxylate (**3a**).

To a stirred mixture of 1.39 g (10 mmol) of (amino)-(methylthio)methylene-propanedinitrile (**1**), 4.14 g (30 mmol) of anhydrous potassium carbonate and 20 ml of dimethyl sulfoxide, a solution of 1.6 g (11.3 mmol) of DMAD in 5 ml of dimethyl sulfoxide was added dropwise during 20 minutes with ice-water cooling. Stirring was continued for an additional 48 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 300 ml of ice-water and stirred for 30 minutes. The gray precipitate was collected by filtration. After drying in air the product was recrystallized from methanol to give 0.411 g (1.5 mmol, 15%) of colorless needles, mp 173-175°; ir (potassium bromide): ν 3390, 3290(NH), 2205(CN), 1745, 1705(CO), 1612, 1535, 1265 cm^{-1}; uv (EtOH) λ max nm(log ε): 256(4.56), 310(3.97); ^1H nmr (deuteriochlorofom): δ 2.61(s, 3H, SMe), 3.87(s, 3H, OMe), 3.94(s, 3H, OMe), 6.87(br s, 2H, NH); ms: *m/z*(%) 281(M^+, 95), 249(81), 234(87), 222(36), 189(51), 174(59), 123(100).

Anal. Calcd for $C_{11}H_{11}N_3O_4S$ (281.288): C, 46.97; H, 3.94; N, 14.94; S, 11.40. Found: C, 47.07; H, 3.93; N, 14.91; S, 11.08.

Dimethyl *N*-(2,2-Dicyano-1-methylthio)ethylenaminofumalate (**2a**).

The above filtrate was acidified with 10% hydrochloric acid solution. The resulting precipitate was collected by filtration and recrystallized from methanol to give 0.588 g (2.1 mmol, 21%

yield) of **2a** as colorless needles. An analytical sample was obtained by recrystallized from methanol to give colorless needles, mp 120-121°; ir (potassium bromide): ν 3225(NH), 2210(CN), 1730, 1685(CO), 1630, 1542, 1435, 1280, 1240 cm^{-1}; uv (ethanol) λ nm(log ε): 288(4.12), 340(3.97); ^1H nmr (deuteriochcloroform): δ 2.60 (s, 3H, SMe), 3.83 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.11 (s, 1H, =CH), 10.00 (br s, 1H, NH).

Anal. Calcd for $C_{11}H_{11}N_3O_4S$ (281.288): C, 46.97; H, 3.94; N, 14.94; S, 11.40. Found: C, 47.18; H, 3.90; N, 14.90; S, 11.21.

Diethyl 4-Amino-5-cyano-6-methylthiopyridine-2,3-dicarboxylate (**3b**).

This compound (1.24 g, 12.4 mol) was prepared in 20% from amino-methylthio-methylenepropanedinitrile (**1**) (2.78 g, 20 mmol) and DEAD (3.40 g, 20 mmol) in a manner similar to that described for the preparation of **2a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 130-132°; ir (potassium bromide): ν 3450, 3320(NH), 2210(CN), 1740, 1690(CO), 1610, 1545, 1270 cm^{-1}; uv (ethanol) λ max nm(log ε): 256(4.62), 310(4.02); ^1H nmr (deuteriochlorom): δ 1.35(t, 3H, *J*=7.2 Hz, O-CH_2-*CH_3*), 1.39(q, 3H, *J*=7.2 Hz, O-*CH_2*-CH_3), 2.61(s, 3H, SMe), 4.33(q, 2H, *J*=7.2 Hz, O-CH_2-), 4.39(q, 2H, *J*=7.2 Hz, O-CH_2-), 7.24(br s, 2H, NH); ms: *m/z*(%) 309(M^+, 100), 264(17), 234(69), 207(11), 191(37), 163(94).

Anal. Calcd for CHNOS (309.342): C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found: C, 50.51; H, 4.84; N, 13.54; S, 10.26.

Diethyl *N*-(2,2-Dicyano-1-methylthio)ethylenaminofumalate (**2b**).

The above filtate was acidified with 10% hydrochloric acid solution. The resulting precipitate was collected by filtration and recrystallized from methanol to give 1.30 g (4.21 mmol, 21% yield) of **3b** as colorless needles. An analytical sample was obtained by recrystallized from methanol to give colorless needles, mp 106-108°; ir (potassium bromide): ν 3250(NH), 2205(CN), 1720, 1680(CO), 1615, 1540, 1265, 1235 cm^{-1}; uv (ethanol) λ max nm(log ε): 289(4.16), 337(3.99); ^1H nmr (deuteriochclorofom): δ 1.33(t, 3H, *J*=7.1 Hz, O-CH_2-*CH_3*), 1.38(t, 3H, *J*=7.1 Hz, O-CH_2-*CH_3*), 2.59(s, 3H, SMe), 4.27(q, 2H, *J*=7.1 Hz, O-CH_2-), 4.36(q, 2H, *J*=7.1 Hz, O-CH_2-), 6.10(s, 1H, =CH).

Anal. Calcd for $C_{13}H_{15}N_3O_4S$ (309.342): C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found: C, 50.44; H, 4.83; N, 13.56; S, 10.43.

Hexamethyl 1*H*-1,4,7-Triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5a**).

Method a.

To a stirred mixture of 1.39 g (10 mmol) of (amino)-(methylthio)-methylenepropanedinitrile (**1**), 8.28g (60 mmol) of anhydrous potassium carbonate and 20 ml of dimethyl sulfoxide, a solution of 5.11 g (36 mmol) of DMAD in 5 ml of dimethyl sulfoxide was added dropwise during 5 minutes with ice-water cooling. Stirring was continued for an additional 48 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 300 ml of ice-water and stirred for 30 minutes. The mixture was acidified with 10% hydrochloric acid solution. The resulting brown solid was collected by filtration. After drying in air the product was recrystallized from methanol to give 1.112 g (2.15 mmol, 22%) of yellow prisms, mp 231-241°. After evaporation of the solvent of the above filtrate, the residue was chromatographed on a silica gel column using Hexane:ethyl acetate (3:1) as the eluent affording as the first fraction in 18% (0.50 g, 1.77 mmol) yield pure **2a**.

Method b.

To a stirred mixture of 1.39 g (10 mmol) of dimethyl 4-amino-5-cyano-6-methylthiopyridine-2,3-dicarboxylate (**3a**), 6.90 g (50 mmol) of anhydrous potassium carbonate and 20 ml of dimethyl sulfoxide, a solution of 1.6 g (11.3 mmol) of DMAD in 5 ml of dimethyl sulfoxide was added dropwise during -20 minutes with ice-water cooling. Stirring was continued for an additional 48 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 300 ml of ice-water and acidified with 10% hydrochloric acid solution. The gray precipitate was collected by filtration. After drying in air the product was recrystallized from methanol to give 3.52 g (6.8 mmol, 68%) of yellow prisms, mp 231-241°; ir (potassium bromide): ν 3195(NH), 2955(Me), 1750, 1740(CO), 1610, 1435, 1280, 1260, 1220 cm^{-1}; uv (ethanol) λ max nm(log ε): 214(4.62), 367(4.31); ^1H nmr (deuteriochloroform): δ 3.97 (s, 6H, OMe), 3.98 (s, 3H, OMe), 4.00 (s, 3H, OMe), 4.05 (s, 3H, OMe), 4.09 (s, 3H, OMe), 12.45 (br s, 1H, NH); fab ms: m/z 518(M^++1).

Anal. Calcd for $C_{22}H_{19}N_3O_{12}$ (517.409): C, 51.07; H, 3.70; N, 8.12. Found: C, 50.93; H, 3.69; N, 14.91.

Hexaethyl 1*H*-1,4,7-Triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5b**).

This compound was prepared from **3b** and DEAD in a manner similar to that described for the synthesis of **5a** and yellow needles were obtained in 63% yield, mp 153-154°; ir (potassium bromide): ν 3330(NH), 2955(Me), 1740, 1720(CO), 1605, 1280, 1260, 1250 cm^{-1}; uv (ethanol) λ max nm(log ε): 212(4.65), 367(4.36); ^1H nmr (deuteriochlorofom): δ 1.15-1.56 (18H, m, 6xOCH_2-*CH_3*), 4.31-4.65 (12H, m, 6x*OCH_2*-CH_3), 12.43 (1H, br s, NH); fab ms: m/z 602(M^++1).

Anal. Calcd for $C_{28}H_{31}N_3O_{12}$ (601.572): C, 55.91; H, 5.19; N, 6.99. Found: C, 55.81; H, 5.18; N, 7.00.

4-Amino-3-cyano-2-methylthioquinoline (**3c**).

A mixture of 0.46 g (2.0 mmol) of 4-chloro-3-cyano-2-methylthioquinoline [10] and 20 ml of 28% ammonium hydroxide was heated at 180° for 1 hour in mini-autoclave (nichidenn rika garasu). After cooling, the precipitate that appeared was collected by filtration to give 0.40 g (1.86 mmol) colorless needles in 93% yield. An analytical sample was recrystallized from methanol to give colorless needles, mp 189-190°; ir (potassium bromide): ν 3440, 3350(NH), 2920(Me), 2200(CN), 1655, 1505, 750 cm^{-1}; uv (ethanol) λ max nm(log ε): 214(4.33), 265(4.65), 298(3.99); ^1H nmr (deuteriochloroform): δ 2.70 (s, 3H, SMe), 5.60 (br s, 2H, NH_2), 7.43 (m, 1H, 6-H), 7.68 (m, 1H, 8-H), 7.71 (m, 1H, 7-H), 7.86 (m, 1H, 5-H).

Anal. Calcd for $C_{11}H_9N_3S$ (215.2725): C, 61.37; H, 4.21; N, 19.52; S, 14.89. Found: C, 61.55; H, 4.26; N, 19.49; S, 14.81.

Tetramethyl 1*H*-Quinolino[2,3,4-*de*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**5c**).

This compound was prepared from **3c** and DEAD in a manner similar to that described for the synthesis of **5a** and yellow needles were obtained in 33% yield, mp 282-285°; ir (potassium bromide): ν 3240(NH), 2950(Me), 1740(CO), 1610, 1440, 1245

cm^{-1}; uv (ethanol) λ max nm: 233, 321, 386: λmin nm: 315, 340; ^{1}H nmr (deuteriochloroform) δ: 3.98 (s, 3H, OMe), 3.99 (s, 3H, OMe), 4.04 (s, 3H, OMe), 4.06 (s, 3H, OMe), 7.42 (d, 1H, *J*=7.5 Hz, 8-H), 7.46 (dd, 1H, J=7.0. 7.3 Hz, 10-H), 7.69 (dd, 1H. J=7.5, 7.3 Hz, 9-H), 8.84 (d, 1H, *J*=7.0 Hz, 11-H), 12.10 (br s, 1H, NH): Compound **5c** was differentiated using an noe-difference experiment. For **5c** irradiation of the singlet at δ=12.10 transferred only one nOe was observed at the singlet at δ=8.84, verifying the structure of **5c**; ms: m/z 452(M$^+$+1, 23), 451(M$^+$, 100), 420(27), 419(40), 303(30), 194(13), 105(22), 43(89).

Anal. Calcd for $C_{22}H_{17}N_3O_8$ (451.3923): C, 58.54; H, 3.80; N, 9.31. Found: C, 55.52; H, 3.81; N, 9.22.

Tetramethyl 8,9,10,11-Tetrahydro-8,10-dimethyl-9,10-dioxo-4*H*-pyrimido[5',4':5,6]pyrido[2,3,4-*cb*][1,6]naphthyridine-2,3,5,6-tetrcarboxylate (**5d**).

This compound was prepared from **3d** and DMAD in a manner similar to that described for synthesis of **5a** and yellow needles were obtained in 53% yield, mp 290-293°; ir (potassium bromide): ν 3130(NH), 1750, 1725, 1710, 1650, 1630(CO), 1615, 1440, 1280 cm^{-1}; uv (ethanol) λ max nm: 237, 291, 334, 368: λ min 220, 255, 285, 340; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.33 (s, 3x1/3H, 1/3NMe), 3.34 (s, 3x2/3H, 3x2/3NMe), 3.54 (s, 3x1/3H, 1/3NMe), 3.55 (s, 3x2/3H, 3x2/3NMe), 3.86 (s, 3x1/3, 1/3NMe), 3.89 (s, 3x1/6, OMe), 3.90 (s, 3x1/6H, OMe), 3.92 (s, 3x2/3H, 2/3OMe), 4.03 (s, 3x2/3H, 2/3OMe), 8.42 (s, 1/3x1/2, NH), 8.49 (s, 1/3x1/2, NH), 12.91 (br s, 2/3H, NH); fab ms: m/z 514(M$^+$+1).

Anal. Calcd for $C_{22}H_{19}N_5O_{10}$ (513.420): C, 51.47; H, 3.73; N,13.64. Found: C, 51.60; H, 3.77; N, 13.90.

Tetraethyl 8,9,10,11-Tetrahydro-8,10-dimethyl-9,10-dioxo-4*H*-pyrimido[5',4':5,6]pyrido[2,3,4-*cb*][1,6]naphthyridine-2,3,5,6-tetrcarboxylate (**5e**).

This compound was prepared from **3e** and DMAD in a manner similar to that described for synthesis of **5a** and yellow needles were obtained in 59% yield, mp 225-231°; ir (potassium bromide): ν 3520, 3425, 3190(NH), 1730, 1710, 1650, 1630(CO), 1610 cm^{-1}; uv (ethanol) λ max nm(log ε): 237(4.67), 290(4.26), 366(4.18); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.23-1.45 (m, 12H, OCH_2CH_3), 3.33 (s, 3H, NMe), 3.56 (s, 3H, NMe), 4.30-4.52 (m, 8H, OCH_2CH_3), 8.44 (br s, 1/5H, NH), 12.89 (s, 4/5H, NH); ms: m/z 569(M$^+$, 4), 496(3), 425(5), 354(5), 277(5), 44(100).

Anal. Calcd for $C_{26}H_{27}N_5O_{10}$ (569.533): C, 54.83; H, 4.78; N,12.30. Found: C, 54.30; H, 4.72; N, 12.40.

Tetramethyl 7-Nitro-9-phenyl-1*H*-pyrazolo[5',1':5,1]pyrido-[2,3,4-*bc*][1,6]naphthyridine-2,3,5,6-tetrcarboxylate (**5f**).

This compound was prepared from **3f** and DMAD in a manner similar to that described for synthesis of **5a** and orange yellow needles were obtained in 75% yield, mp 282-287°; ir (potassium bromide): ν 3290, 3180 (NH), 1740, 1690(CO), 1630, 1605, 11580, 11440, 1300 cm^{-1}; uv (ethanol) λ max nm: 268, 331, 514: λ min 200, 300, 410; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.87 (s, 9H, OMe), 3.91 (s, 3H, OMe), 7.22-7.52 (m, 3H, phenyl-H), 7.61 (s, 1H, 7-H), 8.03-8.13 (m, 2H, phenyl-H); ms: *m/z*(%) 561(M$^+$, 3), 529(100), 515(36), 498(41), 483(57), 419(26), 413(54), 45(40).

Anal. Calcd for $C_{26}H_{27}N_5O_{10}$ (561.469): C, 55.62; H, 3.41; N,12.47. Found: C, 55.61; H, 3.39; N, 12.38.

Tetraethyl 9-(4-Chlorophenyl)-7-nitro-1*H*-pyrazolo[5',1':5,1]-pyrido[2,3,4-*bc*][1,6]naphthyridine-2,3,5,6-tetrcarboxylate (**5g**).

This compound was prepared from **3f** and DEAD in a manner similar to that described for synthesis of **5a** and yellow needles were obtained in 56% yield, mp 270° (dec.); ir (potassium bromide): ν 3130, 2960(NH), 1735, 1690(CO), 1582, 1445, 1220 cm^{-1}; uv (ethanol) λ max nm: 270, 330, 509: λ min 225, 320, 420; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.24-1.40 (m, 8H, OCH_2-Me), 4.18-4.45 (m, 12H, OCH_2-Me_3), 7.55 (d, 2H, *J*=8.5 Hz, phenyl-H), 7.70 (s, 1H, 8-H), 8.15 (d, 2H, *J*=8.5 Hz, phenyl-H); ms: *m/z*(%) 651(M$^+$-1, 7), 632(19), 623(18), 620(51), 606(25), 547(18), 502(14), 476(36), 474(15), 473(26), 58(20), 45(100).

Anal. Calcd for $C_{30}H_{21}ClN_5O_{10}$ (652.022): C, 55.26; H, 4.02; N,10.74. Found: C, 55.11; H, 4.12; N, 10.57.

Tetramethyl 4*H*-*s*-Triazolo[5',1':2,3]pyrimido[4,5,6-*bc*][1,6]-naphthyridine-2,3,5,6-tetrcarboxylate (**5h**).

This compound was prepared from **3g** and DMAD in a manner similar to that described for synthesis of **5a** and yellow leaflets were obtained in 43% yield, mp 217-219°; ir (potassium bromide): ν 3200(NH), 1730, 1690(CO), 1625, 1580, 1290 cm$^{-1;}$ uv (ethanol) λ max nm(log ε): 222(4.61), 326(4.00), 382(4.11); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.18(s, 3H, *Me*OH), 3.90(s, 3H, OMe), 3.92(s, 3H, OMe), 3.93(s, 3H, OMe), 3.96(s, 3H, OMe), 8.80(s, 1H, 9-H); ms: *m/z*(%) 442(M$^+$, 16), 411(4), 385(4), 384(18), 321(8), 268(17), 45(100).

Anal. Calcd for $C_{18}H_{14}N_6O_8 \cdot CH_3OH$: C, 48.10; H, 3.82; N,17.72. Found: C, 48.13; H, 3.75; N, 17.72.

Tetraethyl 4*H*-*s*-Triazolo[5',1':2,3]pyrimido[2,3,4-*bc*][1,6]naph-thyridine-2,3,5,6-tetrcarboxylate (**5i**).

This compound was prepared from **3g** and DMAD in a manner similar to that described for the synthesis of **5a** and yellow leaflets were obtained in 23% yield, mp 197-199°; ir (potassium bromide): ν 2975(NH), 1735, 1682(CO), 1625, 160, 1592, 1300 cm^{-1}; uv (ethanol) λ max nm(log ε): 221(4.64), 326(4.03), 383(4.19); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.46 (m, 8H, OCH_2CH_3), 4.55 (m, 12H, OCH_2CH_3), 8.58 (s, 1/2H, 9-H), 8.59 (s, 1/2H, 9-H), 12.70 (br s, 1H, NH); ms: *m/z*(%) 499(M$^+$+1, 9), 498(M$^+$, 30), 354(21), 353(14), 282(24), 69(23), 45(100).

Anal. Calcd for $C_{22}H_{22}N_6O_8 \cdot 0.5H_2O$: C, 52.83; H, 4.43; N,17.60. Found: C, 52.51; H, 4.37; N, 17.45.

5-Amino-6-cyano-2-methyl-7-methylthiopyrazolo[1,5-*a*]pyrimi-dine (**3h**).

A mixture of 9.71 g (0.1 mol) of 3-amino-5-methylpyrazole and 17.0 g (0.1 mol) of bis(methylthio)methylenemalononitrile was heated at 15-180° for 1 hour. After cooling, the reaction mixture was washed methanol. The product was recrystallized from a mixture of methanol and ethyl acetate (2:1) to give 14.23 g (64.98 mmol) of colorless needles, mp 277-279°; ir (potassium bromide): ν 3510, 3180(NH), 2210(CN), 1660, 1600 cm^{-1}; uv (ethanol) λ max nm(log ε): 222(4.2), 258(4.75), 305(4.05). ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.37 (s, 3H, SMe), 2.53 (s, 3H, 2-Me), 6.22 (s, 1H, 3-H), 8.56 (br s, 2H, NH_2).

Anal. Calcd for $C_9H_9N_5S$ (219.266): C, 49.30; H, 4.14; N, 31.94; S, 14.62. Found: C, 49.61; H, 4.14; N, 31.87; S, 14.83.

Tetramethyl 9-Methyl-4*H*-pyrazolo[5',1':2,3]pyrimido[4,5,6-*bc*]-[1,6]naphthyridine-2,3,5,6-tetrcarboxylate (**5j**).

This compound was prepared from **3h** and DMAD in a manner similar to that described for synthesis of **5a** and yellow needles were obtained in 47% yield, mp 245-247°; ir (potassium bromide): ν 3350 (NH), 1745, 1722, 1662 (CO), 1620, 1590, 1440, 1335, 1340, 1250 cm^{-1}; uv (ethanol) λ max nm(log ε): 239(4.56), 286(4.00), 311(4.09), 396(3.94). ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.42(s, 3H, 9-Me), 3.18(s, 3H, *Me*OH), 3.90(s, 3H, OMe), 3.95(s, 3H, OMe), 3.96(s, 6H, 2xOMe), 6.45(s, 1H, 8-H); ms: *m/z*(%) 456(M^++1, 18), 455(M^+, 73), 425(M^+-1, 6), 424(32), 423(100), 307(32), 279(21), 45(12).

Anal. Calcd for $C_{20}H_{17}N_5O_8$•MeOH: C, 51.74; H, 4.34; N,14.37. Found: C, 51.69; H, 4.27; N, 14.30.

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[8] Compounds **3f** and **g** were prepared by reaction of 5-nitromethyl-3-phenylpyrazoles with bis(methylthio)methylene-malononitrile in the presence of potassium carbonate in DMSO in 87and 91% yields, respectively. Details will be published in a forthcoming paper.

[9] A proton of N-H in **5a**, **b**, and **c** is clearly shown in IR and NMR spectra, while N-H protons in compounds **5c-i** are not fixed by a particular nitrogen atom. In the present paper, we are drawing by tentative assignment of configuration to N-H group in Table 3.

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