POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS. 46 SYNTHESIS OF THIENO[2,3-*h*][1,6]NAPHTHYRIDINES FROM 2-(3-CYANOPROPYLTHIO)PYRIDINE-3-CARBONITRILE

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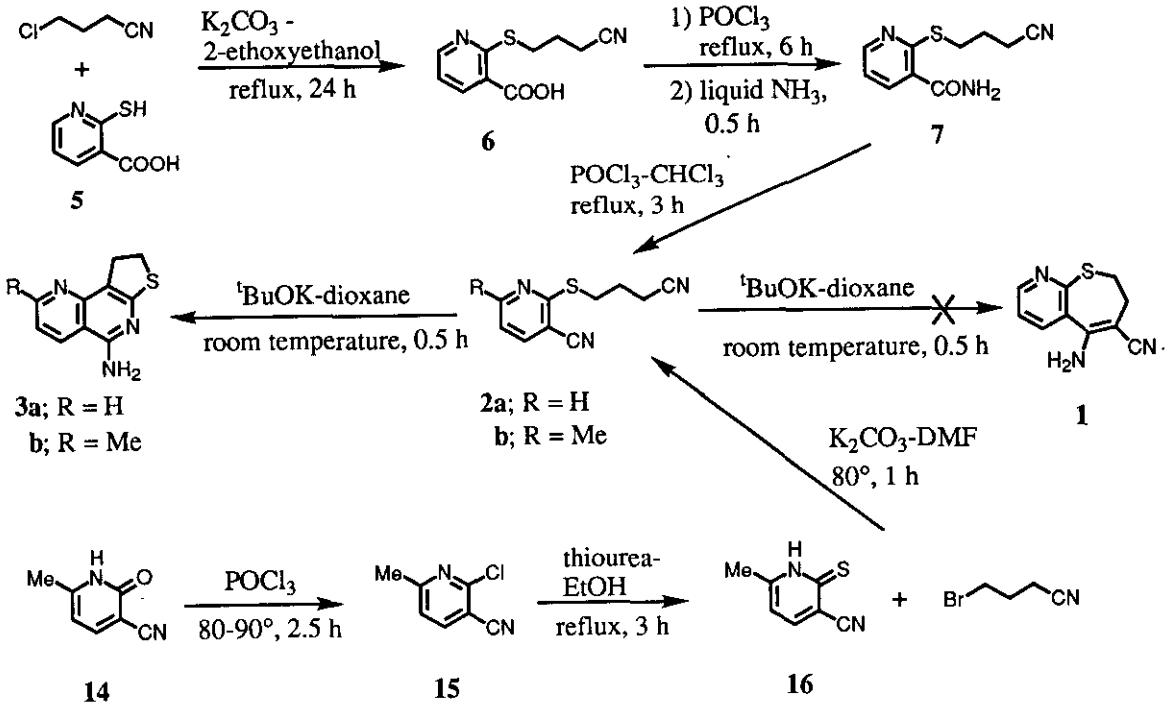
Abstract - An efficient methodology for the synthesis of thieno[2,3-*h*][1,6]-naphthyridine skeleton *via* Smiles type rearrangement reaction followed by cyclization is described. Synthesis of its derivatives is also described.

One of our principal research program is to synthesize new polycyclic heterocyclic ring systems. Especially, since the discovery in our laboratory that 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines had stronger inhibitory activity against collagen-induced aggregation of rabbit blood platelets *in vitro* than that of aspirin,[1] such polycyclic heterocyclic compounds have arisen considerable recent interest for us.[2] As an extension of our synthetic studies, we designed to prepare 5-amino-2,3-dihydro[1]thiepino[2,3-*b*]-pyridine-4-carbonitrile (**1**) from 2-(3-cyanopropylthio)pyridine-3-carbonitrile (**2a**) by a Dieckmann-type dinitrile cyclization, because compound (**1**) is a suitable starting material for pyrimidine cyclization of enamino nitrile moiety. However, the reaction of the dinitrile (**2a**) with potassium *tert*-butoxide did not give the desired **1** but afforded unexpected 5-amino-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (**3a**).[3] Recently, Gronowitz *et al.* have reported the first preparation of thieno[2,3-*h*][1,6]naphthyridine (**4a**).[4] However, their reports described only non-substituted **4a** and did not include the preparation of any substituted compounds of this parent ring system. Furthermore, experimental details and spectroscopic data were not reported except ^{1}H-nmr and high-resolution ms spectra. On the other hand, our method is very simple and applicable for variety of dinitriles. These facts also prompted us to study on this new

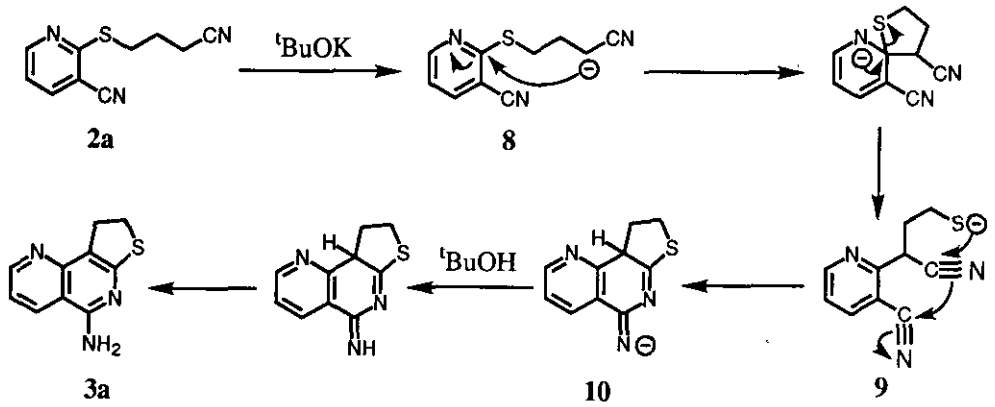
ring-formation reaction. This report presents the synthesis and structural characterization of **3a** and its related compounds including their 8-methyl derivatives.

As shown in Scheme 1, compound (**2a**) was prepared in four steps from commercially available 2-mercaptonicotinic acid (**5**). That is, compound (**5**) was transformed to butyronitrile derivative (**6**), which led to the desired dinitrile (**2a**) *via* amide (**7**). The reaction of **2a** with potassium *tert*-butoxide in dioxane at room temperature gave one major product, that is, **3a** and not **1**. The structure of **3a** was confirmed by



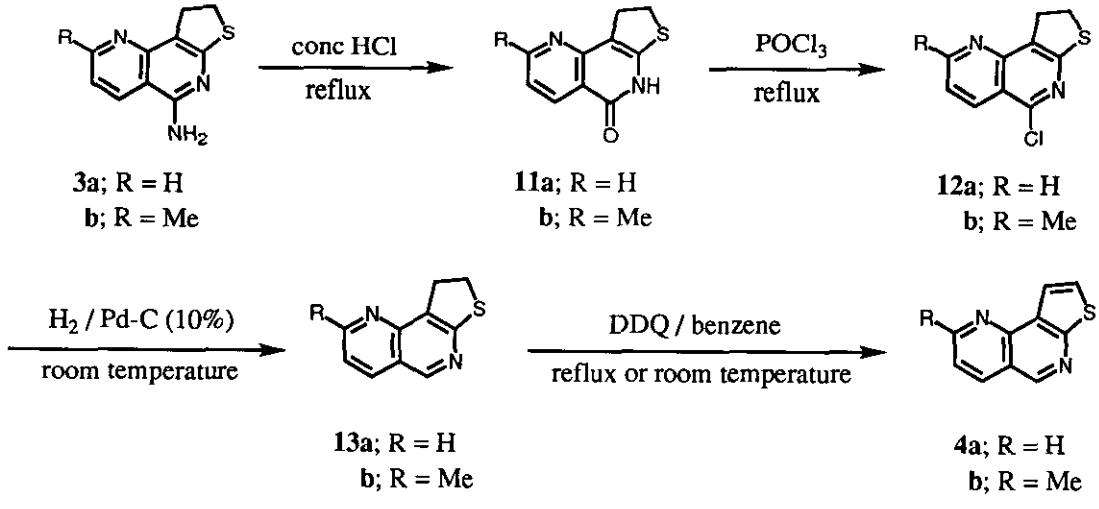
Scheme 1

characteristic spectra and analytical data as well as by X-ray diffraction.[3] As a mechanism of this ring formation, we proposed the Smiles type rearrangement reaction[6] followed by a cyclization as depicted in Scheme 2. The carbanion (**8**) generated from **2a** by potassium *tert*-butoxide causes an intramolecular nucleophilic rearrangement just like Smiles rearrangement. After that, the newly produced anion (**9**) leads to an intramolecular nucleophilic cyclization to afford **10**, which accepts proton from *tert*-butanol and finally transforms to **3a** by prototropy.



Scheme 2

For the purpose of getting the parent ring system of **3a**, the following efforts were performed as shown in Scheme 3. Hydrolysis of **3a** with concentrated hydrochloric acid afforded the 5-oxo derivative (**11a**) in 89% yield. Chlorination of **11a** by refluxing in phosphorus oxychloride gave the 5-chloro derivative (**12a**) in 76% yield. Catalytic dechlorination of **12a** with 10% Pd/C in benzene-methanol (1:1, v/v) solution containing potassium hydroxide under a hydrogen atmosphere afforded 1,2-dihydrothieno-[2,3-*h*][1,6]naphthyridine (**13a**) in 49% yield. The parent ring system compound, namely, thieno-



Scheme 3

[2,3-*h*][1,6]naphthyridine (**4a**) was obtained in 38% yield by refluxing in benzene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for 3 h. The ^{1}H-nmr spectrum of **4a** showed two doublets (AB quartet) at δ 8.05 and 8.14 ppm with J = 5.8 Hz attributable to H-1 and H-2, respectively, except of *naphthyridine ring proton* [H-5 (9.33 ppm, *s*), H-6 (8.73 ppm, dd, $J_{6,7}$ = 8.2, $J_{6,8}$ = 1.8), H-7 (7.79 ppm, dd, $J_{7,6}$ = 8.2, $J_{7,8}$ = 4.4), H-8 (9.21 ppm, dd, $J_{8,7}$ = 4.4, $J_{8,6}$ = 1.8)]. These coupling constants of **4a** are in fair agreement with the values reported by Gronowitz *et al.* [H-1 (8.18 ppm, d, $J_{1,2}$ = 5.9), H-2 (7.70 ppm, d), H-5 (9.15 ppm, s), H-6 (8.42 ppm, dd, $J_{6,7}$ = 8.2), H-7 (7.60 ppm, dd), H-8 (9.16 ppm, dd, $J_{8,7}$ = 4.4, $J_{8,6}$ = 1.8)].[4]

Further attempt for preparing 8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (**4b**) was performed as shown in Scheme 1. 6-Methyl-2-pyridone-3-carbonitrile (**14**) was converted to 2-chloro derivative (**15**), which led to 2-thioxo derivative (**16**) by refluxing in ethanol with thiourea. Reaction of **16** with 4-bromobutyronitrile in the presence of potassium carbonate gave the key intermediate 2-(3-cyanopropyl-thio)-6-methylpyridine-3-carbonitrile (**2b**). Overall yield from **14** to **2b** was 77%. Likewise as described in the preparation of **3a**, when **2b** was allowed to react with potassium *tert*-butoxide in dioxane, 5-amino-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (**3b**) was obtained in 82% yield. As shown in Scheme 3, 8-methyl-5-oxo-1,2,4,5-tetrahydrothieno[2,3-*h*][1,6]naphthyridine (**11b**) was obtained by hydrolysis of **3b** with concentrated hydrochloric acid. Chlorination of **11b** was accomplished by refluxing in phosphorus oxychloride to afford 5-chloro-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]-naphthyridine (**12b**) in 68% yield. 8-Methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (**13b**) was obtained in 73% yield by catalytic dechlorination of **12b** with 10% Pd/C in benzene-methanol (1:1, v/v) solution containing potassium hydroxide under a hydrogen atmosphere. Compound (**13b**) was dehydrogenated at 1,2-position with DDQ to give 8-methylthieno[2,3-*h*][1,6]naphthyridine (**4b**) in low yield (5%). It showed two doublets (AB quartet) at δ 7.64 and 8.18 ppm with J = 5.9 Hz attributable to H-1 and H-2, respectively, in its ^{1}H-nmr spectrum. A singlet signal attributable to H-5 was also observed at δ 9.08 ppm.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The EI-,

FAB- and high-resolution ms spectra were recorded on a VG 70-SE mass spectrometer, using glycerol or *m*-nitrobenzyl alcohol as a matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. Unless otherwise stated, they were measured as potassium bromide pellets and frequencies are expressed in cm^{-1}. The ^{1}H-nmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90 MHz) or Varian VXR-200 instrument (200 MHz) in the solvent indicated with tetramethylsilane as the internal standard, and unless otherwise stated, they were recorded on the Varian VXR-200 instrument. Chemical shifts are reported in ppm (δ) and *J* values in Hz, and the signals are designated as follows; s, singlet; d, doublet; dd, double doublet; triplet; q, quartet; quin, quintet; br, broad.

2-(3-Cyanopropylthio)pyridine-3-carboxylic Acid (6)

To a solution of 2-mercaptonicotinic acid (**5**) (15.5 g, 0.10 mol) in dry 2-ethoxyethanol (300 ml) were added 4-chlorobutyronitrile (20.7 g, 0.20 mol) and K_2CO_3 (27.6 g, 0.20 mol) under gentle stirring. After the addition had completed, the reaction mixture was refluxed for 24 h. The reaction mixture was filtered and the precipitate was washed with 2-ethoxyethanol. The filtrate and washing were combined and evaporated, and water (200 ml) was added to the residue. After acidification of the resulting solution with 1*N* HCl (pH 1-2), the precipitated solid was collected by suction. The filtrate was extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to obtain a solid mass, which was combined with the solid obtained by suction described above. Thus combined solid was recrystallized from ethyl acetate to give 19.2 g (87%) of **6** as colorless plates, mp 130-131 °C; ir: 3415 (O-H), 2255 (C≡N), 1602 (C=O); FAB-ms m/z: 223 (MH^+); ^{1}H-nmr (DMSO-d_6, 60 MHz): 1.88 (quin, J = 7, 2H, H-2'), 2.60 (t, J = 7, 2H, H-3'), 3.03 (t, J = 7, 2H, H-1'), 7.00 (dd, $J_{5,4}$ = 7.6, $J_{5,6}$ = 4.7, 1H, H-5), 8.02 (dd, $J_{4,5}$ = 7.6, $J_{4,6}$ = 2.3, 1H, H-4), 8.32 (dd, $J_{6,5}$ = 4.7, $J_{6,4}$ = 2.3, 1H, H-6). High-resolution FAB-ms m/z: Calcd for $C_{10}H_{11}N_2O_2S$: 223.0541. Found: 223.0543 (MH^+).

2-(3-Cyanopropylthio)pyridine-3-carboxamide (7)

A suspension of **6** (11 g, 50 mmol) in $POCl_3$ (91 g, 0.59 mol) was refluxed for 6 h. After complete removal of excess $POCl_3$ *in vacuo*, the residue was treated with liq. NH_3 (56 ml) under gentle stirring at

-5 °C for 0.5 h. After evaporation of excess NH_3 from the reaction mixture, water (50 ml) was added to the mixture and the resulting mixture was filtered *in vacuo* to give a solid. The filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to give a crystalline solid, which was combined with the solid collected by filtration described above. Thus combined solid was recrystallized from a mixture of ethyl acetate and ethanol to give 8.3 g (75%) of **7** as colorless needles, mp 125-126 °C; ir: 3330, 3160 (N-H), 2240 (C≡N), 1664 (C=O); EI-ms m/z: 221 (M^+); ^{1}H-nmr ($CDCl_3$): 2.11 (quin, J = 7, 2H, H-2'), 2.53, 3.37 (each t, J = 7, each 2H, H-3' and -1'), 6.15 (br, exchangeable with D_2O, 2H, NH_2), 7.11 (dd, $J_{5,4}$ = 7.8, $J_{5,6}$ = 4.9, 1H, H-5), 7.88 (dd, $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.9, 1H, H-4), 8.53 (dd, $J_{6,5}$ = 4.9, $J_{6,4}$ = 1.9, 1H, H-6). *Anal*. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.25; H, 4.96; N, 18.97.

2-(3-Cyanopropylthio)pyridine-3-carbonitrile (2a)

To a suspension of **7** (8.20 g, 37.1 mmol) in dry $CHCl_3$ (50 ml) was added $POCl_3$ (28.4 g, 186 mmol) dropwise and the resulting mixture was refluxed for 3 h. The reaction mixture was evaporated *in vacuo* for removal of excess $POCl_3$ to give an oily residue. Water (80 ml) was cautiously added to the residue. The resulting mixture was basified with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. Thus obtained oily residue was crystallized to give a solid, which was recrystallized from ethanol to afford 7.5 g (99%) of **2a** as colorless plates, mp 60-61 °C; ir: 2197, 2187 (C≡N); EI-ms m/z: 203 (M^+); ^{1}H-nmr ($CDCl_3$): 2.13 (quin, J = 7, 2H, H-2'), 2.54 (t, J = 7, 2H, H-3'), 3.41 (t, J = 7, 2H, H-1'), 7.10 (dd, $J_{5,4}$ = 8, $J_{5,6}$ = 5, 1H, H-5), 7.83 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2, 1H, H-4), 8.60 (dd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, 1H, H-6). *Anal*. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.06; H, 4.40; N, 20.40.

5-Amino-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (3a)

To a stirred solution of **2a** (9.52 g, 46.9 mmol) in dry dioxane (190 ml) was gradually added potassium *tert*-butoxide (13.1 g, 117 mmol). Thus obtained mixture was stirred at room temperature for 30 min and poured into water (1900 ml). The resulting mixture was kept standing for 6 h under ice-cooling. The precipitated solid in the mixture was collected by filtration. Thus obtained solid was recrystallized from

DMSO to afford 7.82 g (82%) of **3a** as yellow needles, mp 270-273 °C; ir: 3310, 3145 (N-H); FAB-ms m/z: 204 (MH^+); ^{1}H-nmr (DMSO-d_6): 3.44 (s, 4H, H-1 and -2), 7.17 (br s, exchangeable with D_2O, 2H, NH_2), 7.29 (dd, $J_{7,6}$ = 8, $J_{7,8}$ = 4, 1H, H-7), 8.51 (dd, $J_{6,7}$ = 8, $J_{6,8}$ = 2, 1H, H-6), 8.82 (dd, $J_{8,7}$ = 4, $J_{8,6}$ = 2, 1H, H-8). High-resolution FAB-ms m/z: Calcd for $C_{10}H_9N_3S$: 204.0595. Found: 204.0594 (MH^+).

5-Oxo-1,2,4,5-tetrahydrothieno[2,3-*h*][1,6]naphthyridine (11a)

A solution of **3a** (2.00 g, 9.85 mmol) in concentrated HCl (100 ml) was refluxed for 94 h. After removal of excess acid under reduced pressure, water (30 ml) was added to the residue, and the resulting mixture was basified with saturated aqueous $NaHCO_3$ solution. The precipitated solid was collected by filtration *in vacuo*. The filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a crystalline residue. This residue was combined with the solid collected by filtration described above. Thus combined solid was recrystallized from ethanol to afford 1.78 g (89%) of **11a** as pale yellow needles, mp 285-287 °C (decomp.); ir: 3435 (N-H), 1643 (C=O); EI-ms m/z: 204 (M^+); ^{1}H-nmr (DMSO-d_6): 3.29, 3.51 (each t, J = 8, each 2H, H-1 and -2), 7.31 (dd, $J_{7,6}$ = 8.0, $J_{7,8}$ = 4.5, 1H, H-7), 8.36 (dd, $J_{6,7}$ = 8.0, $J_{6,8}$ = 1.9, 1H, H-6), 8.76 (dd, $J_{8,7}$ = 4.5, $J_{8,6}$ = 1.9, 1H, H-8), 12.20 (br s, exchangeable with D_2O, 1H, NH). *Anal*. Calcd for $C_{10}H_8N_2OS$: C, 58.81; H, 3.95; N, 13.72. Found: C, 58.72; H, 3.75; N, 13.32.

5-Chloro-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (12a)

A suspension of **11a** (0.92 g, 4.5 mmol) in $POCl_3$ (8.2 g, 54 mmol) was refluxed for 3 h. After removal of excess $POCl_3$ under reduced pressure, water (10 ml) was gradually added to the residue. The precipitated solid was collected by filtration *in vacuo*. The filtrate was extracted with benzene. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a crystalline residue. This residue was combined with the solid collected by filtration described above. Thus combined solid was recrystallized from benzene to afford 766 mg (76%) of **12a** as pale yellow scales, mp 148-151 °C; EI-ms m/z: 222 (M^+), intensity ratio of the peak at m/z 222 to that at m/z 224 was 3 to 1; ^{1}H-nmr ($CDCl_3$): 3.61, 3.79 (each td, J = 8, 2, each 2H, H-1 and -2), 7.43 (dd, $J_{7,6}$ = 8, $J_{7,8}$ = 4,

1H, H-7), 8.51 (dd, $J_{6,7}$ = 8, $J_{6,8}$ = 2, 1H, H-6), 9.02 (dd, $J_{8,7}$ = 4, $J_{8,6}$ = 2, 1H, H-8). High-resolution EI-ms m/z: Calcd for $C_{10}H_7ClN_2S$: 222.0018. Found: 222.0052 (M^+).

1,2 -Dihydrothieno[2,3-*h*][1,6]naphthyridine (13a)

To a stirred mixture of **12a** (300 mg, 1.35 mmol) and KOH (75.6 mg, 1.35 mmol) in a mixture of benzene (75 ml) and methanol (75 ml) was added portionwise 10% Pd-C (143 mg). The reaction mixture was stirred under hydrogen atmosphere at room temperature for 14 days. An equivalent amount of Pd-C was added on the 7th day of the reaction period. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (9:1, v/v) to afford a solid, which was recrystallized from benzene to give 125 mg (49%) of **13a** as colorless needles, mp 99-101 °C; EI-ms m/z: 188 (M^+); ^{1}H-nmr ($CDCl_3$): 3.61, 3.85 (each td, J = 8, 2, each 2H, H-1 and -2), 7.38 (dd, $J_{7,6}$ = 8.3, $J_{7,8}$ = 4.3, 1H, H-7), 8.21 (dd, $J_{6,7}$ = 8.3, $J_{6,8}$ = 1.8, 1H, H-6), 8.98 (s, 1H, H-5), 9.01 (dd, $J_{8,7}$ = 4.3, $J_{8,6}$ = 1.8, 1H, H-8). High-resolution EI-ms m/z: Calcd for $C_{10}H_8N_2S$: 188.0408. Found: 188.0392 (M^+).

Thieno[2,3-*h*][1,6]naphthyridine (4a)

To a solution of **13a** (109 mg, 0.580 mmol) in benzene (3 ml) was added DDQ (329 mg, 1.45 mmol), and the reaction mixture was refluxed for 3 h. After removal of the solid in the reaction mixture by filtration, the filtrate was evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (9:1, v/v) to afford a solid, which was recrystallized from benzene to give 41 mg (38%) of **4a** as colorless granules, mp 113-115 °C; EI-ms m/z: 186 (M^+); ^{1}H-nmr (DMSO-d_6): 7.79 (dd, $J_{7,6}$ = 8.2, $J_{7,8}$ = 4.4, 1H, H-7), 8.05, 8.14 (AB q, J = 5.8, each 1H, H-1 and -2), 8.73 (dd, $J_{6,7}$ = 8.2, $J_{6,8}$ = 1.8, 1H, H-6), 9.21 (dd, $J_{8,7}$ = 4.4, $J_{8,6}$ = 1.8, 1H, H-8), 9.33 (s, 1H, H-5). High-resolution EI-ms m/z: Calcd for $C_{10}H_6N_2S$: 186.0252. Found: 186.0238 (M^+).

2-Chloro-6-methylpyridine-3-carbonitrile (15)

A solution of 6-methyl-1,2-dihydro-2-pyridone-3-carbonitrile (**14**) (20.0 g, 149 mmol) in $POCl_3$ (224 g, 1.46 mol) was heated at 80-90 °C for 2.5 h. After removal of excess $POCl_3$ under reduced pressure, water (100 ml) was cautiously added to the residue. The resulting mixture was made alkaline with saturated aqueous $NaHCO_3$ solution and extracted with benzene. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a solid mass upon standing at room temperature, which was recrystallized from a mixture of *n*-hexane and benzene to afford 21.3 g (94%) of **15** as colorless plates, mp 105-107 °C; ir: 2237 (C≡N); ^{1}H-nmr ($CDCl_3$): 2.64 (s, 3H, CH_3), 7.23 (d, $J_{5,4}$ = 7.9, 1H, H-5), 7.88 (d, $J_{4,5}$ = 7.9, 1H, H-4). *Anal*. Calcd for $C_7H_5N_2Cl$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.29; H, 3.51; N, 18.23.

6-Methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (16)

To a solution of **15** (21 g, 0.14 mol) in ethanol (250 ml) was gradually added thiourea (42 g, 0.55 mol) and the resulting mixture was refluxed for 3 h. After removal of the solvent *in vacuo*, water (200 ml) was added to the residue. Thus obtained mixture was basified with 10% aqueous NaOH solution and filtered. The filtrate was acidified with 2*N* aqueous HCl solution to pH 1-2. The resulting yellow crystalline precipitate was collected by suction, washed repeatedly with water, and recrystallized from ethanol to give 20 g (93%) of **16** as yellow granules, mp 278-280 °C; ir: 2927 (N-H), 2227 (C≡N); FAB-ms m/z: 151 (MH^+); ^{1}H-nmr (DMSO-d_6): 2.39 (s, 3H, CH_3), 6.73 (d, $J_{5,4}$ = 8, 1H, H-5), 8.00 (d, $J_{4,5}$ = 8, 1H, H-4), 14.1 (br s, exchangeable with D_2O, 1H, NH). *Anal*. Calcd for $C_7H_6N_2S$: C, 55.98; H, 4.03; N, 18.65. Found: C, 55.86; H, 4.21; N, 18.49.

2-(3-Cyanopropylthio)-6-methylpyridine-3-carbonitrile (2b)

To a stirred suspension of **16** (26 g, 0.17 mol) in DMF (250 ml) were added portionwise K_2CO_3 (38 g, 0.28 mol) and 4-bromobutyronitrile (36 g, 0.24 mol), and the resulting mixture was heated at 80 °C for 1 h. After cooling of the reaction mixture, water (2500 ml) was added to the reaction mixture and the resulting mixture was kept standing for 12 h. The precipitated crystalline solid was collected by filtration and recrystallized from a mixture of *n*-hexane and ethanol to give 33 g (88%) of **2b** as colorless needles, mp 59-60 °C; ir: 2242, 2217 (C≡N); FAB-ms m/z: 218 (MH^+); ^{1}H-nmr ($CDCl_3$): 2.12 (quin, J = 7, 2H,

H-2'), 2.53 (t, J = 7, 2H, H-3'), 2.59 (s, 3H, CH_3), 3.42 (t, J = 7, 2H, H-1'), 6.96 (d, $J_{5,4}$ = 7.9, 1H, H-5), 7.70 (d, $J_{4,5}$ = 7.9, 1H, H-4). *Anal.* Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34. Found: C, 60.72; H, 5.11; N, 19.28.

5-Amino-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (3b)

To a stirred solution of **2b** (6.32 g, 29.1 mmol) in dry dioxane (80 ml) was gradually added potassium *tert*-butoxide (8.17 g, 72.9 mmol). Thus obtained mixture was stirred at room temperature for 30 min. This reaction mixture was then poured into water (500 ml) and the resulting mixture was kept standing for 6 h. The compound deposited as yellow precipitate was collected by filtration and recrystallized from ethanol to give 5.20 g (82%) of **3b** as yellow plates, mp 269-270 °C; ir: 3327, 3277 (N-H); EI-ms m/z: 217 (M^+); ^{1}H-nmr (DMSO-d_6): 2.56 (s, 3H, CH_3), 3.41 (br s, 4H, H-1 and -2), 7.04 (br s, exchangeable with D_2O, 2H, NH_2), 7.17 (d, $J_{7,6}$ = 8.5, 1H, H-7), 8.39 (d, $J_{6,7}$ = 8.5, 1H, H-6). *Anal.* Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34. Found: C, 60.74; H, 5.23; N, 19.17.

8-Methyl-5-oxo-1,2,4,5-tetrahydrothieno[2,3-*h*][1,6]naphthyridine (11b)

To a stirred solution of **3b** (2.92 g, 13.5 mmol) in acetic acid (50 ml) was added concentrated HCl (100 ml) and the resulting mixture was refluxed for 12 days. After evaporation of the reaction mixture *in vacuo*, water (20 ml) was added to the residue. The obtained mixture was made alkaline with saturated aqueous $NaHCO_3$ solution, and precipitated solid mass in the mixture was collected by suction. The filtrate was extracted with ethyl acetate (100 ml) and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. Thus obtained residue was combined with the solid collected by filtration described above. The combined solid was recrystallized from ethanol to give 2.50 g (85%) of **11b** as pale yellow needles, mp >300 °C; ir: 3437 (N-H), 1659 (C=O); FAB-ms m/z: 219 (MH^+); ^{1}H-nmr (DMSO-d_6): 2.57 (s, 3H, CH_3), 3.32 and 3.54 (each t, J = 7.4, each 2H, H-1 and -2), 7.22 (d, $J_{7,6}$ = 8.2, 1H, H-7), 8.29 (d, $J_{6,7}$ = 8.2, 1H, H-6), 12.15 (br s, exchangeable with D_2O, 1H, NH). *Anal.* Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.37; H, 4.56; N, 12.60.

5-Chloro-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (12b)

To a mixture of **11b** (5.90 g, 27.1 mmol) in dry toluene (50 ml) was added $POCl_3$ (122 g, 797 mmol) and the mixture was heated at 80-90 °C for 24 h. After removal of excess $POCl_3$ under reduced pressure, water (50 ml) was cautiously added to the residue. The resulting mixture was basified with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to obtain an oily residue. This residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (9:1-8:2, v/v) to afford a solid, which was recrystallized from ethyl acetate to give 4.35 g (68%) of **12b** as yellow prisms, mp 184-185 °C; FAB-ms m/z: 237 (MH^+), intensity ratio of the peak at m/z 237 to that at m/z 239 was 3 to 1; ^{1}H-nmr ($CDCl_3$): 2.74 (s, 3H, CH_3), 3.57, 3.77 (each td, J = 7.7, 2.4, each 2H, H-1 and -2), 7.29 (d, $J_{7,6}$ = 8.6, 1H, H-7), 8.35 (d, $J_{6,7}$ = 8.6, 1H, H-6). *Anal.* Calcd for $C_{11}H_9N_2ClS$: C, 55.81; H, 3.83; N, 11.83. Found: C, 55.72; H, 3.96; N, 11.79.

8-Methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine (13b)

To a stirred solution of **12b** (200 mg, 0.846 mmol) in a mixture of benzene (100 ml) and methanol (100 ml) were added a solution of KOH (47.5 mg, 0.848 mmol) in methanol (10 ml) and 10% Pd-C (90 mg). Then the reaction mixture was vigorously stirred under hydrogen atmosphere at room temperature for 64 h. Afterward, the catalyst was discarded through filtration and the filtrate was evaporated to dryness. Thus obtained residue was chromatographed on silica gel with cyclohexane-ethyl acetate (9:1, v/v) to give a solid, which was recrystallized from a mixture of cyclohexane and ethanol to afford 125 mg (73%) of **13b** as colorless prisms, mp 117-119 °C; EI-ms m/z: 202 (M^+); ^{1}H-nmr ($CDCl_3$): 2.74 (s, 3H, CH_3), 3.57 (td, J_t = 8, J_d = 2, 2H, H-1 or -2), 3.82 (br t, J = 8, 2H, H-1 or -2), 7.23 (d, $J_{7,6}$ = 8.4, 1H, H-7), 8.06 (d, $J_{6,7}$ = 8.4, 1H, H-6), 8.89 (s, 1H, H-5). High-resolution EI-ms m/z: Calcd for $C_{11}H_{10}N_2S$: 202.0564. Found: 202.0577 (M^+).

8-Methylthieno[2,3-*h*][1,6]naphthyridine (4b)

To a solution of **13b** (100 mg, 0.495 mmol) in benzene (5 ml) was added DDQ (123 mg, 0.542 mmol), and the reaction mixture was stirred at room temperature for 18 h. After removal of the solid in the reaction mixture, the filtrate was evaporated *in vacuo*. Hot methylene chloride soluble fraction of the

residual solid mass was subjected to preparative tlc (solvent system; cyclohexane-ethyl acetate, 1:1, v/v) and the zone of R*f* value 0.36 gave 5 mg (5%) of **4b** as colorless crystalline solid, which behaved as a single spot on tlc, mp 110-112 °C; EI-ms m/z: 200 (M^+); ^{1}H-nmr ($CDCl_3$): 2.86 (s, 3H, CH_3), 7.45 (d, $J_{7,6}$ = 8.3, 1H, H-7), 7.64 (d, $J_{1,2}$ = 5.9, 1H, H-1), 8.18 (d, $J_{2,1}$ = 5.9, 1H, H-2), 8.27 (d, $J_{6,7}$ = 8.3, 1H, H-6), 9.08 (s, 1H, H-5). High-resolution EI-ms m/z: Calcd for $C_{11}H_8N_2S$: 200.0408. Found: 200.0433 (M^+).

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