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POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS. 57 SYNTHESES OF FUSED FURO(OR THIENO)[2,3-*b*]PYRIDINE DERIVATIVES *VIA* SMILES REARRANGEMENT AND CYCLIZATION

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Abstract - An efficient methodology for the synthesis of thieno[2,3-*c*][2,7]-naphthyridine (**6**), thieno[2,3-*c*]isoquinoline (**11**), furo[2,3-*c*]isoquinoline (**14**), [1]benzothieno[3,2-*d*]thieno[2,3-*b*]pyridine (**21**), and [1]benzothieno[3,2-*d*]furo-[2,3-*b*]pyridine (**26**) skeletons from 4-[*o*-cyanoarylthio(or oxy)]butyronitriles with base *via* Smiles type rearrangement reaction followed by the cyclization is described.

We previously reported a new methodology for the syntheses of thieno(or furo)naphthyridine derivatives from 4-[*o*-cyanopyridylthio(or oxy)]butyronitriles with *t*-BuOK *via* Smiles rearrangement reaction followed by the cyclization.[1-5] In those reports new tricyclic heterocycles, 5-substituted 8,9-dihydrothieno[2,3-*h*][1,6]naphthyridines,[1,2,5] 5-substituted and non-substituted 1,2-dihydrofuro[3,2-*f*][1,7]naphthyridines,[3] 2,5-disubstituted 8,9-dihydrofuro[2,3-*h*][1,6]naphthyridines,[4] were prepared efficiently (Figure 1). The bronchodilatory activity of these compounds was also evaluated on the basis of their relaxation activity to tracheal contraction induced by carbamylcholine chloride as a primary *in vitro* assay. Effect of some naphthyridines on carbamylcholine chloride-induced contractions of trachea in the presence or absence of milrinone or 4-(3-butoxy-4-methoxyphenyl)imidazolidin-2-ones, which are

a inhibitor of phosphodiesterase III or IV, was also evaluated.[5] We describe here the successful application of this reaction employing 4-(3-cyanopropylthio)pyridine-3-carbonitrile (**5**), 2-(3-cyanopropylthio)benzonitrile (**10**), 2-(3-cyanopropoxy)benzonitrile (**13**), 3-(3-cyanopropylthio)[1]benzothiophene-2-carbonitrile (**20**), and 3-(3-cyanopropoxy)[1]benzothiophene-2-carbonitrile (**25**) in which cyano and 3-cyanopropylthio (or 3-cyanopropoxy) groups are attached on 1,2 positions of the molecule as a precursor to give fused thieno(or furo)[2,3-*b*]pyridine derivatives (**6**, **11**, **14**, **21**, and **26**).

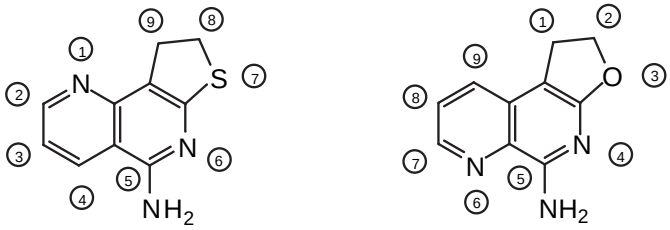
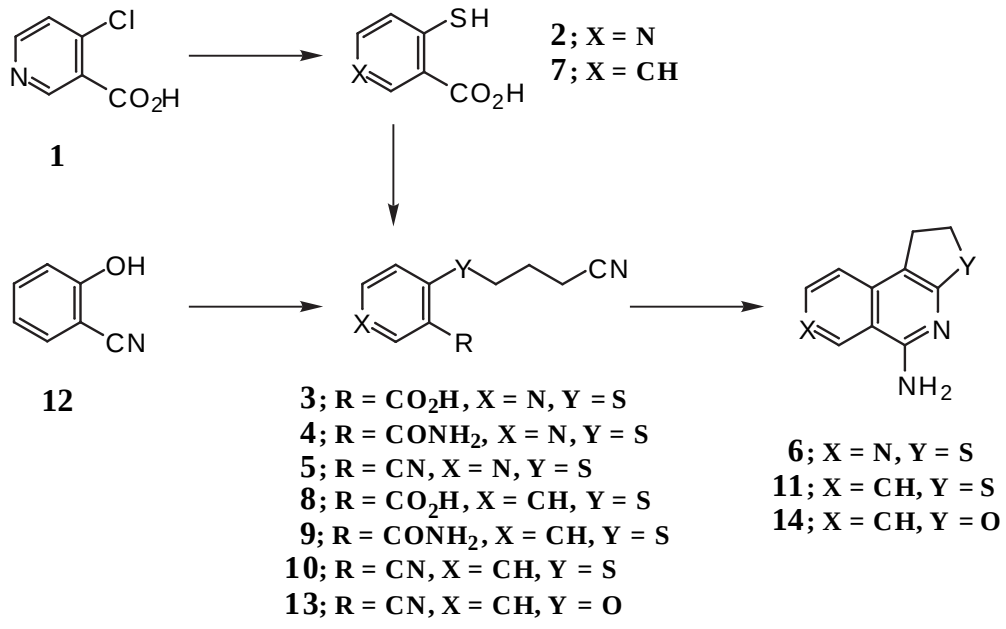


Figure 1

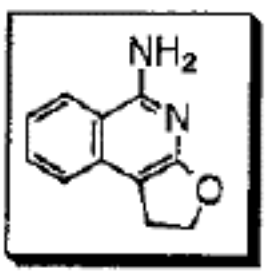
As shown in Scheme 1, dinitrile (**5**) was synthesized in several steps from 4-chloropyridine-3-carboxylic acid (**1**),[6] which was converted to 4-mercaptopyridine-3-carboxylic acid (**2**) with sodium hydrogen-sulfide. Then the reaction of **2** with 4-chlorobutyronitrile in the presence of K_2CO_3 gave nitrile (**3**). This compound was transformed to carboxamide (**4**) *via* carbonyl chloride by the reaction of $SOCl_2$ followed

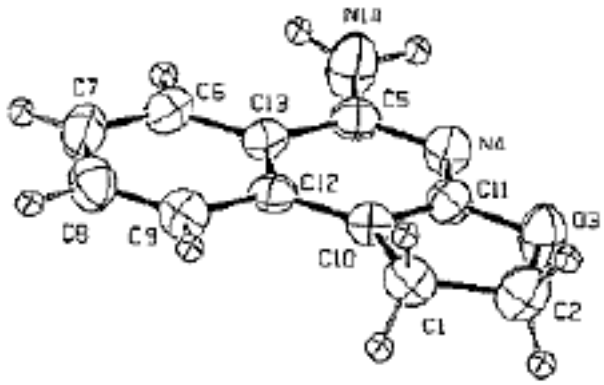


Scheme 1

by ammonolysis with liq. NH_3. Compound (**4**) was dehydrated by $POCl_3$ to give the desired dinitrile (**5**). As described in the previous papers,[1-5] a solution of **5** in dioxane was refluxed in the presence of *t*-BuOK to give the expected 5-amino-1,2-dihydrothieno[2,3-*c*][2,7]naphthyridine (**6**) in 52% yield. The structure assignment of **6** was based upon characteristic spectral and analytical data. That is, the absorption of CN group could not be found and that of amino group was observed at 3349, 3312, and 3127 cm^{-1} in its IR spectrum. In the ^{1}H-NMR spectrum broad singlet protons due to the ethylene moiety were observed at δ 3.41 ppm besides aromatic ring and amino protons.

For further application of this Smiles rearrangement reaction and cyclization, other requisite intermediate (**10**) was prepared as shown in Scheme 1. Thiosalicylic acid (**7**) was employed as a starting material. Acid (**7**) was derived to 2-(3-cyanopropylthio)benzoic acid (**8**) by the reaction with 4-chlorobutyronitrile in dioxane in the presence of K_2CO_3. Compound (**8**) was also transformed to the desired dinitrile (**10**) *via* carboxamide (**9**) similar to the synthesis of **5** from **3**. A solution of **10** in dioxane was refluxed in the presence of *t*-BuOK to afford the rearranged and cyclized product, 5-amino-1,2-dihydrothieno[2,3-*c*]isoquinoline (**11**), in 42% yield. The structure assignment of **11** was also based upon characteristic spectral and analytical data. The IR spectrum of **11** showed no signal due to CN but NH_2 group absorption occurred at 3460 and 3330 cm^{-1}. Broad singlet protons due to ethylene moiety could be also observed in its ^{1}H-NMR spectrum. For trying a similar reaction using another benzonitrile derivative (**13**), the requisite intermediate (**13**) was prepared by the reaction of commercially available 2-cyanophenol (**12**) with 4-chlorobutyronitrile in the presence of K_2CO_3. A solution of **13** in DMF was stirred at room temperature in the presence of *t*-BuOK to give the desired 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline (**14**) in 14% yield. The structure of **14** was consisted by the instrumental (IR, ^{1}H-NMR, and MS spectra) and elemental analytical data. An X-Ray structure analysis also well confirmed the

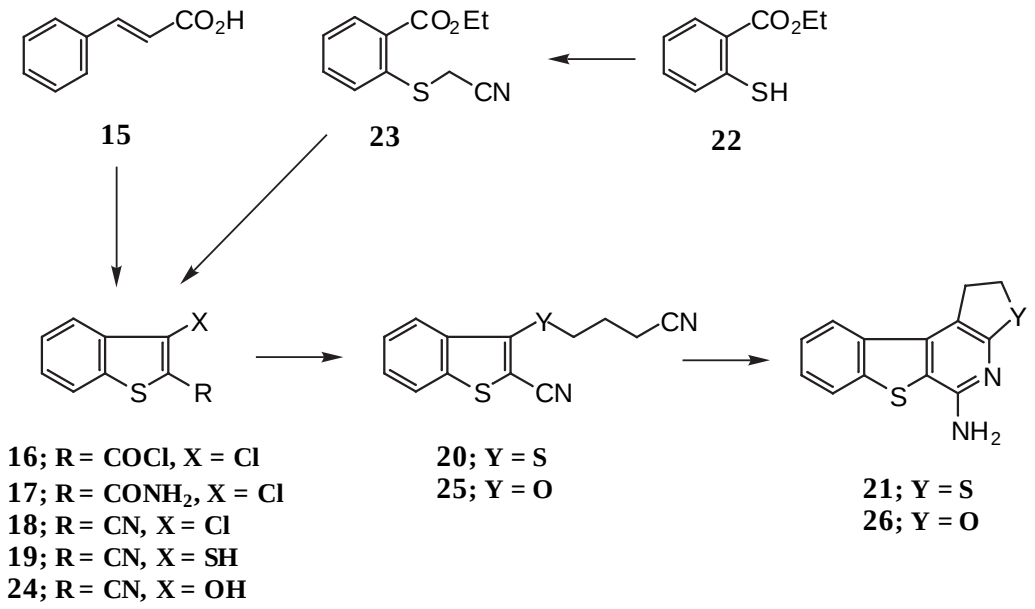




Scheme 2 ORTEP Drawing of Compound (**14**)

structure of **14** as shown in Scheme 2. The cyclized product (**14**) was a new compound, however, some compounds with the same ring system have been already synthesized.[7-10]

For the next application of this Smiles rearrangement and cyclization reaction, we employed compound (**20**) as a key intermediate dinitrile in which cyano and cyanopropoxy groups are attached to the 2,3-positions of the π-sufficient thiophene ring. The requisite precursor (**20**) was prepared from commercially available *trans*-cinnamic acid (**15**) in several steps as shown in Scheme 3. That is, acid (**15**) was cyclized to 3-chloro[1]benzothiophene-2-carbonyl chloride (**16**) by the method of Wright *et*



Scheme 3

al.[11] 3-Chloro[1]benzothiophene-2-carbonitrile (**18**) was obtained by ammonolysis of chloride (**16**) with liq. NH_3 followed by dehydration of carboxamide (**17**) with $POCl_3$. Compound (**18**) reacted with thioacetamide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) by the method of Boschelli *et al.*[12] to give 3-mercapto[1]benzothiophene-2-carbonitrile (**19**). This mercapto derivative (**19**) decomposed during the purification, so that, this compound was used in the next step without further purification. The desired dinitrile (**20**) was prepared by the reaction of unpurified **19** with 4-chlorobutyronitrile in the presence of K_2CO_3. The reaction of the hot benzene solution of compound (**20**) in the presence of *t*-BuONa gave the desired rearranged and cyclized product (**21**) in 8% yield. The IR, ^{1}H-NMR, MS spectra, and elemental analysis of **21** well consisted with its structure. As a further application of this rearranged and cyclized reaction of the [1]benzothiophene derivative, the similar

reaction of dinitrile (**25**) with base was examined. This compound was prepared from ethyl thio-salicylate (**22**) in several steps as shown in Scheme 3. That is, compound (**22**) was derived to ethyl 2-cyanomethylthiobenzoate (**23**) by the reaction with chloroacetonitrile in the presence of K_2CO_3 and KI. Compound (**23**) was cyclized to [1]benzothiophene derivative (**24**) in the presence of NaH, which was transformed to the requisite dinitrile (**25**) by the reaction with 4-chlorobutyronitrile in the presence of K_2CO_3 and KI. The dioxane solution of **25** was refluxed with NaH to give the corresponding rearranged compound, 5-amino-1,2-dihydro[1]benzothieno[3,2-*d*]furo[2,3-*b*]pyridine (**26**) in 26% yield. The structure of **26** was well consisted with its instrumental and elemental analyses.

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 FAB-MS spectra were measured on a VG 70 mass spectrometer and glycerol or *m*-nitrobenzyl alcohol was used as a matrix agent. The IR spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on a Hitachi R-1500 FT-NMR spectrometer at 60 MHz or a Varian VXR-200 instrument working at 200 MHz with TMS as an internal standard. Chemical shifts are given in ppm (δ) and J values in Hz.

4- Mercaptopyridine-3-carboxylic Acid (**2**)

Title compound was obtained by the method of Delarge[6] from 4-chloropyridine-3-carboxylic acid (**1**), yield 67%, mp 237-239 °C (from water, lit.,[6] mp 234-237 °C, lit.,[13] mp 236-238 °C, lit.,[14] mp 243-245 °C).

4-(3-Cyanopropylthio)pyridine-3-carboxylic Acid (**3**)

To a solution of acid (**2**) (5.00 g, 32.2 mmol) in 2-ethoxyethanol (100 mL) was added 4-chlorobutyronitrile (3.50 g, 33.8 mmol) and K_2CO_3 (13.8 g, 100 mmol) and the resulting mixture was refluxed for 8 h under N_2 atmosphere. After evaporation of the reaction mixture, ice water (200 mL) was added onto the residue and the resulting mixture was acidified (pH 4) with dil. HCl. The precipitated solid was collected by filtration and the filtrate was extracted with ethyl acetate. The organic layer was treated as usual. The residue was combined to the above collected solid and recrystallized from methanol to give **3** as colorless prisms (5.10 g, 71%), mp 198-200 °C. FAB-MS *m/z*: 223 (MH^+). IR (KBr) cm^{-1}: 3113 (OH), 2243 (CN), 1701 (CO). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.00 (2H, quin, J = 7.2,

$CH_2CH_2CH_2$), 2.69 (2H, t, J = 7.2, CH_2CN), 3.09 (2H, t, J = 7.2, CH_2S), 7.46 (1H, d, J = 5.3, 5-H), 8.54 (1H, d, J = 5.3, 6-H), 8.92 (1H, s, 2-H). *Anal.* Calcd for $C_{10}H_{10}N_2O_2S \cdot 1/10H_2O$: C, 53.61; H, 4.59; N, 12.50. Found: C, 53.66; H, 4.42; N, 12.34.

4-(3-Cyanopropylthio)pyridine-3-carboxamide (**4**)

A solution of **3** (4.50 g, 20.2 mmol) in $POCl_3$ (16.5 g, 108 mmol) was refluxed for 1 h. After evaporation of $POCl_3$, liq. NH_3 (10 mL) was added to the residue under cooling and the mixture was allowed to stand overnight. After evaporation of the mixture the residue was recrystallized from ethyl acetate to give **4** as pale brown needles (3.39 g, 76%), mp 117-119 °C. IR (KBr) cm^{-1}: 3348, 3175 (NH), 2244 (CN), 1654, (CO). This compound was used to the next step without further purification.

4-(3-Cyanopropylthio)pyridine-3-carbonitrile (**5**)

A solution of **4** (2.30 g, 10.4 mmol) in $POCl_3$ (16.5 g, 108 mmol) was refluxed for 4 h. After evaporation of $POCl_3$, ice-water (300 mL) was added to the residue and the mixture was neutralized with $NaHCO_3$. The resulting mixture was extracted with ethyl acetate and the organic layer was treated as usual. The residue was recrystallized from methanol-*n*-hexane to give **5** as colorless needles (1.50 g, 71%), mp 84-86 °C. FAB-MS *m/z*: 204 (MH^+). IR (KBr) cm^{-1}: 2246, 2226 (CN). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.14 (2H, quin, J = 7.0, $CH_2CH_2CH_2$), 2.62 (2H, t, J = 7.0, CH_2CN), 3.26 (2H, t, J = 7.0, CH_2S), 7.25 (1H, d, J = 5.5, 5-H), 8.62 (1H, d, J = 5.5, 6-H), 8.71 (1H, s, 2-H). *Anal.* Calcd for $C_{10}H_9N_3S \cdot 1/5H_2O$: C, 58.06; H, 4.58; N, 20.31. Found: C, 58.11; H, 4.63; N, 20.28.

5-Amino-1,2-dihydrothieno[2,3-*c*][2,7]naphthyridine (**6**)

To a solution of **5** (600 mg, 2.95 mmol) in dioxane (10 mL) was added *t*-BuOK (600 mg, 5.35 mmol) and the resulting mixture was refluxed for 10 min. After evaporation of the solvent, ice water (50 mL) was added onto the residue. The precipitated solid was collected by filtration and the filtrate was extracted with ethyl acetate. The organic layer was treated as usual. The residue was combined to the above collected solid and recrystallized from methanol to give **6** as pale yellow needles (310 mg, 52%), mp > 300 °C. FAB-MS *m/z*: 204 (MH^+). IR (KBr) cm^{-1}: 3349, 3312, 3127 (NH). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 3.41 (4H, br s, 1,2-H), 7.55 (2H, br s, D_2O exchangeable, NH_2), 7.30 (1H, d, J = 6.4, 9-H), 8.47 (1H, d, J = 6.4, 8-H), 9.41 (1H, br s, 6-H). *Anal.* Calcd for $C_{10}H_9N_3S \cdot 1/4H_2O$: C, 57.81; H, 4.61; N, 20.23. Found: C, 57.99; H, 4.57; N, 20.01.

2-(3-Cyanopropylthio)benzoic Acid (**8**)

To a solution of thiosalicylic acid (**7**) (20.1 g, 0.130 mol) in dioxane (100 mL) was added 4-chlorobutyronitrile (20.2 g, 0.195 mol) and K_2CO_3 (27.0 g, 0.195 mol) and the resulting mixture was heated at 80 °C for 20 h. After evaporation of the reaction mixture, ice water (300 mL) was added to the residue and the resulting mixture was extracted with ethyl acetate. The organic layer was treated as usual and the residue was recrystallized from ethanol to give **8** as colorless needles (21.3 g, 74%), mp 121-122 °C. FAB-MS *m/z*: 222 (MH^+). IR (KBr) cm^{-1}: 3025 (OH), 2255 (CN), 1650 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.10 (2H, quin, J = 7.0, $CH_2CH_2CH_2$), 2.59 (2H, t, J = 7.0, CH_2CN), 3.11 (2H, t, J = 7.0, CH_2S), 7.25-7.85 (4H, m, Ar-H), 13.00 (1H, br s, D_2O exchangeable, OH). *Anal*. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.94; H, 4.80; N, 6.26.

2-(3-Cyanopropylthio)benzamide (**9**)

A solution of **8** (5.00 g, 22.6 mmol) in $SOCl_2$ (26.9 g, 226 mmol) was refluxed for 9 h. After evaporation of $SOCl_2$, liq. NH_3 (100 mL) was added to the residue under cooling and the mixture was allowed to stand overnight. Saturated NaCl aq. solution was added into the mixture, and the precipitated solid was collected and recrystallized from acetone to give **9** as pale brown powder (3.89 g, 78%), mp 112-114 °C. FAB-MS *m/z*: 221 (MH^+). IR (KBr) cm^{-1}: 3450, 3370 (NH), 2225 (CN), 1660 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.97 (2H, br quin, J = 7.0, $CH_2CH_2CH_2$), 2.55 (2H, t, J = 7.0, CH_2CN), 3.12 (2H, t, J = 3.4, CH_2S), 6.46 (2H, br s, D_2O exchangeable, NH_2), 7.23-7.76 (4H, m, Ar-H). *Anal*. Calcd for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72. Found: C, 59.88; H, 5.59; N, 12.63.

2-(3-Cyanopropylthio)benzonitrile (**10**)

A solution of **9** (7.91 g, 35.9 mmol) in $POCl_3$ (55.1 g, 359 mmol) was refluxed for 10 h. After evaporation of $POCl_3$, ice-water (300 mL) was added to the residue and the mixture was neutralized with $NaHCO_3$. The resulting mixture was extracted with ethyl acetate and the organic layer was treated as usual. The residue was recrystallized from ethanol to give **10** as pale brown prisms (4.39 g, 61%), mp 61-62 °C. FAB-MS *m/z*: 203 (MH^+). IR (KBr) cm^{-1}: 2245, 2230 (CN). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.99 (2H, quin, J = 7.0, $CH_2CH_2CH_2$), 2.58 (2H, t, J = 7.0, CH_2CN), 3.17 (2H, t, J = 7.0, CH_2S), 7.24-7.73 (4H, m, Ar-H). *Anal*. Calcd for $C_{11}H_{10}N_2S \cdot 1/10H_2O$: C, 64.74; H, 5.04; N, 13.73. Found: C, 64.88; H, 5.15; N, 13.51.

5-Amino-1,2-dihydrothieno[2,3-*c*]isoquinoline (**11**)

To a solution of **10** (500 mg, 2.47 mmol) in dioxane (15 mL) was added *t*-BuOK (832 mg, 7.42 mmol) and the resulting mixture was refluxed for 5 min. After evaporation of the solvent, ice water (30 mL) was

added to the residue and the mixture was extracted with ethyl acetate. The organic layer was treated as usual to give an oily residue that was subjected to a column-chromatography on silica gel. The eluate with *n*-hexane-ethyl acetate (4 : 1, v/v) afforded **11** which was recrystallized from ethyl acetate to give pale yellow needles (205 mg, 42%), mp 121-122 °C. FAB-MS *m/z*: 203 (MH^+). IR (KBr) cm^{-1}: 3460, 3330 (NH). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.40 (4H, br s, 1,2-H), 5.20 (2H, br s, D_2O exchangeable, NH_2), 7.28 (1H, td, J_t = 8.0, J_d = 1.0, 8-H), 7.46 (1H, d, J = 8.0, 6-H), 7.59 (1H, td, J_t = 8.0, J_d = 1.0, 7-H), 7.73 (1H, d, J = 8.0, 9-H). *Anal.* Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.36; H, 4.76; N, 13.77.

2-(3-Cyanopropoxy)benzonitrile (**13**)

To a solution of *o*-cyanophenol (**12**, 25 g, 0.21 mol) in DMF (400 mL) was added 4-chlorobutyronitrile (33 g, 0.33 mol) and K_2CO_3 (32 g, 0.23 mol) and the resulting mixture was refluxed for 4 h. Ice water (4 L) was added into the reaction mixture. The precipitated solid was collected and recrystallized from ethanol to give **13** as colorless plates (37 g, 95%), mp 48-49 °C. FAB-MS *m/z*: 187 (MH^+). IR (KBr) cm^{-1}: 2230, 2180 (CN). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.23 (2H, quin, J = 5.8, $CH_2C\mathit{H}_2CH_2$), 2.70 (2H, t, J = 5.8, CH_2CN), 4.23 (2H, t, J = 5.8, CH_2O), 6.91-7.68 (4H, m, Ar-H). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.89; H, 5.43; N, 14.88.

5-Amino-1,2-dihydrofuro[2,3-*c*]isoquinoline (**14**)

To a solution of **13** (3.7 g, 20 mmol) in DMF (100 mL) was added *t*-BuOK (4.5 g, 40 mmol) and the resulting mixture was stirred at rt for 4 h. Ice water (1 L) was added into the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was worked up as usual to give an oily residue that was subjected to a column-chromatography on silica gel. The eluate with benzene-ethyl acetate (4 : 1 - 0 : 1, v/v) afforded **14** which was recrystallized from ethyl acetate to give pale brown prisms (0.52 g, 14%), mp 192-194 °C. FAB-MS *m/z*: 187 (MH^+). IR (KBr) cm^{-1}: 3490, 3330 (NH). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.33 (2H, t, J = 8.7, 1-H), 4.70 (2H, t, J = 8.7, 2-H), 5.24 (2H, br s, D_2O exchangeable, NH_2), 7.21 (1H, td, J_t = 8.2, J_d = 1.4, 7-H), 7.41 (1H, d, J = 8.2, 6-H), 7.54 (1H, td, J_t = 8.2, J_d = 1.4, 8-H), 7.71 (1H, d, J = 8.2, 9-H). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.12; H, 5.49; N, 15.17.

This analytical sample was dried around 100 °C under vaccum.

Crystal structure analysis of **14**. Crystal data: $C_{11}H_{10}N_2O$; *Mr* = 372.43; orthorhombic, space group $P2_12_12_1$, *a* = 13.479(2), *b* = 14.321(4), *c* = 9.118(2) Å, *V* = 1760(1) $Å^3$; *Z* = 8; *D*c = 1.405 g cm^{-3}. The

crystals were grown from an ethyl acetate solution by slow evaporation. A crystal of size 0.600 x 0.600 x 0.600 mm was examined by using graphite-monochromated Mo K_α radiation (λ = 0.71073 Å). Cell dimensions were obtained from 25 reflections ($21 < 2\theta < 23°$). In total 2582 reflections were measured by the ω-2θ scan method, and 2309 of these were unique (R_{int} = 0.010). Refinements were carried out including all the hydrogen atoms by using 1790 reflections with $I > 3\sigma(I)$ within $2\theta_{max}$ of 55°. R = 0.035, R_w = 0.034, S = 1.38. Asymmetric unit is composed of two molecules with similar conformations.

3-Chloro[1]benzothiophene-2-carbonyl Chloride (**16**)

Title compound was obtained by the method of Wright *et al.*[11] from *trans*-cinnamic acid (**15**), yield 85%, mp 109-112 °C (from *n*-hexane, lit.,[11] mp 114-116 °C, lit.,[15] mp 113.5-115 °C).

3-Chloro[1]benzothiophene-2-carboxamide (**17**)

To compound (**16**) (1.01 g, 4.37 mmol) was added liq. NH_3 (30 mL) under cooling and the mixture was allowed to stand for 1 d. Thus obtained solid was recrystallized from ethyl acetate to give **17** as pale brownish powder (757 mg, 82%), mp 227-228 °C. FAB-MS *m/z*: 214 ($[M+2]H^+$), 212 (MH^+). IR (KBr) cm^{-1}: 3450, 3120 (NH), 1650 (CO). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 7.52-7.74 (2H, m, 5- and 6-H), 7.87-8.11 (4H, changed to 2H after D_2O addition, m, 4- and 7-H and NH_2). *Anal.* Calcd for C_9H_6NOClS: C, 51.07; H, 2.86; N, 6.62. Found: C, 50.71; H, 3.00; N, 6.38.

3-Chloro[1]benzothiophene-2-carbonitrile (**18**)

A solution of **17** (2.12 g, 10.0 mmol) in $POCl_3$ (15.3 g, 100 mmol) was refluxed for 3 h. After evaporation of $POCl_3$, the residue was recrystallized from *n*-hexane to give **18** as colorless needles (1.77 g, 92%), mp 120-121 °C. FAB-MS *m/z*: 194 (MH^+). IR (KBr) cm^{-1}: 2210 (CN). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 7.50-7.66 (2H, m, 5- and 6-H), 7.70-8.02 (2H, m, 4- and 7-H). *Anal.* Calcd for $C_9H_4NClS \cdot 1/10H_2O$: C, 55.30; H, 2.17; N, 7.17. Found: C, 55.39; H, 2.34; N, 6.97.

3-Mercapt[1]benzothiophene-2-carbonitrile (**19**)

To a solution of **18** (5.06 g, 26.2 mmol) and thioacetamide (6.21 g, 82.8 mmol) in DMF (70 mL) was added DBU (11.8 g, 77.6 mmol) and the mixture was heated at 80 °C for 3 h under N_2 atmosphere. After evaporation of the solvent, the residue was triturated with ethyl acetate. The organic layer was washed with successive 1*N* HCl aq. solution and sat. NaCl aq. solution, and then extracted with 1*N* NaOH aq. solution. The alkaline aq. layer was acidified with 2*N* HCl aq. solution. The precipitated solid was collected to give **19** which was used for the next step without further purification.

3-(3-Cyanopropylthio)[1]benzothiophene-2-carbonitrile (**20**)

A mixture of **19**, K_2CO_3 (10.8 g, 78.3 mmol) and 4-chlorobutyronitrile (4.01 g, 38.7 mmol) in DMF (70 mL) was heated at 60 °C for 6 h. After filtration of the mixture, the filtrate was evaporated and ice water (200 mL) was added onto the residue. The resulting mixture was extracted with ethyl acetate. The organic layer was treated as usual and an oily residue was subjected to a column-chromatography on silica gel. The eluate with *n*-hexane-ethyl acetate (9 : 1, v/v) afforded **20** which was recrystallized from cyclohexane to give pale yellow needles (4.27 g, 64% as overall yield from **18**), mp 67-68 °C. FAB-MS *m/z*: 259 (MH^+). IR (KBr) cm^{-1}: 2260, 2220 (CN). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.95 (2H, quin, J = 7.0, $CH_2CH_2CH_2$), 2.61 (2H, t, J = 7.0, CH_2CN), 3.18 (2H, t, J = 7.0, SCH_2), 7.54-7.65 (2H, m, 5- and 6-H), 7.89 (1H, m, 4-H), 8.05 (1H, m, 7-H). *Anal.* Calcd for $C_{13}H_{10}N_2S_2 \cdot 1/10H_2O$: C, 60.02; H, 3.95; N, 10.77. Found: C, 59.97; H, 3.88; N, 10.72.

5-Amino-1,2-dihydro[1]benzothieno[3,2-*d*]thieno[2,3-*b*]pyridine (**21**)

To a hot solution of **20** (1.00 g, 3.88 mmol) in benzene (200 mL) was added *t*-BuONa (1.86 g, 19.4 mmol) and the resulting mixture was refluxed for 1 h. After evaporation of the solvent, ice water (30 mL) was added onto the residue and the mixture was extracted with ethyl acetate. The organic layer was treated as usual to give an oily residue which was subjected to a column-chromatography on silica gel. The eluate with *n*-hexane-ethyl acetate (9 : 1, v/v) afforded **21** which was recrystallized from benzene to give pale yellow needles (80 mg, 8%), mp 207-208 °C. FAB-MS *m/z*: 259 (MH^+). IR (KBr) cm^{-1}: 3450, 3280 (NH). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.59 (2H, t, J = 7.8, 2-H), 3.79 (2H, t, J = 7.8, 1-H), 4.61 (2H, br s, D_2O exchangeable, NH_2), 7.42-7.62 (2H, m, 8- and 9-H), 7.87 (1H, dd, J = 8.9 and 1.5, 10-H), 8.12 (1H, dd, J = 8.5 and 1.8, 7-H). *Anal.* Calcd for $C_{13}H_{10}N_2S_2$: C, 60.44; H, 3.90; N, 10.84. Found: C, 60.48; H, 4.01; N, 10.74.

Ethyl 2-Cyanomethylthiobenzoate (**23**)

A mixture of ethyl thiosalicylate (**22**) (10.2 g, 56.0 mmol), K_2CO_3 (15.0 g, 109 mmol), KI (503 mg, 3.03 mmol) and chloroacetonitrile (5.10 g, 67.5 mmol) in acetone (200 mL) was stirred at rt for 3 h under nitrogen atmosphere. After filtration of the mixture, the filtrate was evaporated and ice water (200 mL) was added onto the residue. The resulting mixture was extracted with benzene. The organic layer was treated as usual and the residue was recrystallized from cyclohexane to give **23** as colorless needles (10.8 g, 87%), mp 79-81 °C. FAB-MS *m/z*: 222 (MH^+). IR (KBr) cm^{-1}: 2250 (CN), 1680 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.41 (3H, t, J = 7.0, Me), 3.72 (2H, s, SCH_2), 4.40 (2H, q, J = 7.0, OCH_2), 7.25-7.68

(3H, m, 3-, 4- and 5-H), 7.91-8.20 (1H, m, 6-H). *Anal.* Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.96; H, 5.09; N, 6.27.

3-Hydroxy[1]benzothiophene-2-carbonitrile (**24**)

A mixture of **23** (9.97 g, 45.1mmol) and NaH (60% oil dispersion, 2.20 g, 55.0 mmol) in ethanol (200 mL) was stirred at rt for 1 h. After filtration of the mixture, the filtrate was evaporated and ice water (200 mL) was added onto the residue. The resulting mixture was extracted with ethyl acetate. The organic layer was treated as usual a the residue was recrystallized from acetonitrile to give **24** as pale yellow needles (6.72 g, 85%), mp 160-162 °C. FAB-MS *m/z*: 176 (MH^+). IR (KBr) cm^{-1}: 3170 (OH), 2220 (CN). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 7.42-7.80 (2H, m, 5- and 6-H), 7.80-8.19 (2H, m, 4- and 7-H), 12.25 (1H, br s, D_2O exchangeable, OH). *Anal.* Calcd for C_9H_5NOS: C, 61.70; H, 2.88; N, 7.99. Found: C, 61.85; H, 3.11; N, 8.10.

3-(3-Cyanopropoxy)[1]benzothiophene-2-carbonitrile (**25**)

A mixture of **24** (10.0 g, 57.1 mmol), K_2CO_3 (15.8 g, 114 mmol), KI (497 mg, 2.99 mmol) and 4-chlorobutyronitrile (7.08 g, 68.4 mmol) in acetone (200 mL) was refluxed for 24 h. After filtration of the mixture, the filtrate was evaporated and ice water (200 mL) was added onto the residue. The resulting mixture was extracted with benzene. The organic layer was treated as usual and the residue was recrystallized from benzene to give **25** to give colorless needles (10.4 g, 75%), mp 112-114 °C. FAB-MS m/z: 243 (MH^+). IR (KBr) cm^{-1}: 2260, 2220 (CN). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.12-2.86 (4H, m, CH_2CH_2CN), 4.80 (2H, t, J = 5.0, OCH_2), 7.36-7.98 (4H, m, Ar-H). *Anal.* Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.36; H, 4.26; N, 11.58.

5-Amino-1,2-dihydro[1]benzothieno[3,2-*d*]furo[2,3-*b*]pyridine (**26**)

To a solution of **25** (9.95 g, 41.1 mmol) in dioxane (200 mL) were added NaH (60% oil dispersion, 2.05 g, 51.3 mmol) and 3 drops of *t*-BuOH, and the resulting mixture was refluxed for 5 h. After filtration of the reaction mixture, the filtrate was evaporated and ice water (200 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate. The organic layer was treated as usual to give an oily residue that was subjected to a column-chromatography on silica gel. The eluate with benzene-ethyl acetate (4 : 1, v/v) afforded **26** which was recrystallized from acetonitrile as pale brown prisms (2.53 g, 26%), mp 269-271 °C. FAB-MS m/z: 243 (MH^+). IR (KBr) cm^{-1}: 3450, 3280, 3170 (NH). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 3.54 (2H, t, J = 8.0, 1-H), 4.67 (2H, t, J = 8.0, 2-H), 6.35 (2H, br s, D_2O

exchangeable, NH_2), 7.37-7.74 (2H, m, 8- and 9-H), 7.90-8.18 (2H, m, 7- and 10-H). *Anal.* Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.64; H, 4.29; N, 11.56.

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