Synthesis of Thieno[2,3-*h*][1,6]naphthyridine from 2-(3-Cyanopropylthio)pyridine-3-carbonitrile: Formation of a Novel Ring System

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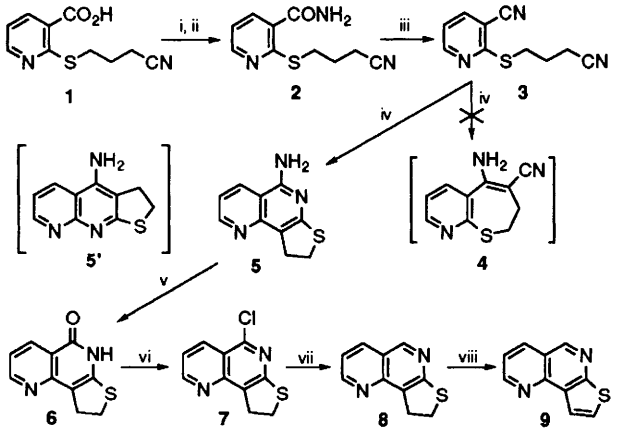
An efficient methodology for the synthesis of novel ring system, thieno[2,3-*h*][1,6]naphthyridine, *via* a Smiles type rearrangement reaction and cyclization is described, its structure is confirmed by an X-ray structure analysis.

As a part of our continuing program on the synthesis of polycyclic *N*-heterocyclic compounds,[1] we have designed the synthesis of 5-amino-2,3-dihydrothiepino[2,3-*b*]pyridine-4-carbonitrile **4** from 2-(3-cyanopropylthio)pyridine-3-carbonitrile **3**† by a Dieckmann type dinitrile cyclization. However, the reaction of the dinitrile **3** with potassium *tert*-butoxide did not give the desired compound **4** but afforded unexpected 5-amino-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine **5**. This report presents the synthesis and structural characterization of **5**‡ and related compounds.§

As shown in Scheme 1, compound **3** was prepared in three steps from compound **1** which was synthesized from commercially available 2-mercaptonicotinic acid. As mentioned above, the reaction of **3** with potassium *tert*-butoxide in dioxane at room temperature gave **5** in 82% yield, and not **4**. The structure assignments of **5** are based upon characteristic spectra and analytical data as well as by X-ray diffraction (Fig. 1). The IR spectrum of the product showed no absorptions due to CN but amino group absorptions occurred at 3310 and 3145 cm^{-1}. In the ^1H NMR spectrum (200 MHz) of the product only a singlet (δ 3.44, 4H) due to ethylene protons was observed besides pyridine-ring protons (δ 7.29, 8.51, 8.82) and the amino proton (δ 7.17). Taking these results into consideration with the mass and the elemental analyses, the product could have structure **5** or **5'** but not **4**. An X-ray structure analysis¶ confirmed structure **5**. We wish to propose the Smiles type reaction mechanism for the first step of this novel ring formation as shown in Scheme 2. As a variation of the Smiles rearrangement of sulfones, many studies have been reported which utilized a methyl or methylene group as the nucleophile.[2] However, only a few reports have been found that utilized an active methylene group of the cyanoacetamide moiety[3] and there are no reports utilizing methylene activated only by a cyano group.



Scheme 1 *Reagents and conditions*: i, phosphorus oxychloride, reflux, 6h; ii, l. NH_3, 0.5 h; iii, phosphorus oxychloride–$CHCl_3$, reflux, 3 h; iv, KBu^{t}O–dioxane, room temp., 0.5 h; v, conc. HCl, reflux, 94 h; vi, phosphorus oxychloride, reflux, 3 h; vii, 10% Pd–C, H_2 gas, KOH, room temp., 14 days; viii, DDQ–benzene, reflux, 3 h

Further attempts to prepare some substituted and non-substituted derivatives of **5** were performed. Compound **5** was hydrolysed with conc. HCl to afford the 5-oxo compound **6** in 89% yield. Chlorination of **6** was performed by refluxing in $POCl_3$ to give the 5-chloro derivative **7** in 76% yield.

Catalytic hydrogenation of **7** with 10% Pd/C under hydrogen gave non-substituted 1,2-dihydrothieno[2,3-*h*]-[1,6]naphthyridine **8** in 49% yield. Compound **8** could be dehydrogenated at the 1,2-position upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing benzene for 3 h to give the mother skeleton, thieno[2,3-*h*]-[1,6]naphthyridine **9**, in 38% yield. The ease of variation of the ring system in preparing analogues of **5** by Scheme 1 is evident indicating the scope and utility of this reaction for obtaining other tricyclic compounds.

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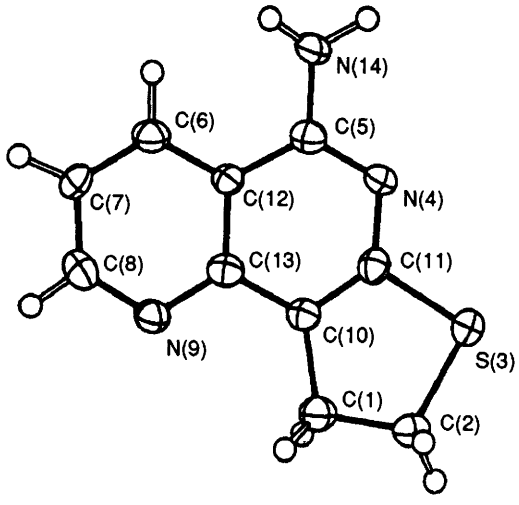
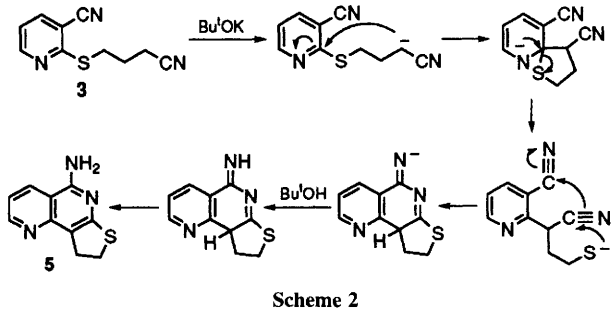


Fig. 1 ORTEP drawing of compound 5



Scheme 2

Footnotes

† *Spectral data for* 3: IR(KBr) cm^{-1} 2197 and 2187 (C≡N); ^1H NMR ($CHCl_3$, 200 MHz) δ 2.13 (qnt. J = 7 Hz, 2H, SCH_2CH_2), 2.54 (t, J = 7 Hz, 2H, CH_2CN), 3.40 (t, J = 7 Hz, 2H, SCH_2), 7.10 (dd, J_{ortho} = 8 and 5 Hz, 1H, H-5), 7.83 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-4), 8.60 (dd, J_{ortho} = 5, J_{meta} = 2 Hz, 1H, H-6); EI-MS m/z 203 (M^+).

‡ *Spectral data for* **5**: IR(KBr) cm^{-1} 3310 and 3145 (N–H); ^1H NMR [$(CD_3)_2SO$, 200 MHz] δ 3.44 (s, 4H, CH_2CH_2), 7.17 (br s, exchangeable with D_2O, 2H, NH_2), 7.29 (dd, J_{ortho} = 8 and 4 Hz, H-7), 8.51 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-6), 8.82 (dd, J_{ortho} = 4, J_{meta} = 2 Hz, 1H, H-8); EI-MS m/z 203 (M^+).

§ *Spectral data* for **6**: IR(KBr) cm^{-1} 3435 (N–H) and 1643 (C=O); ^1H NMR [$(CD_3)_2SO$, 200 MHz) δ 3.29 and 3.51 (each br t, J = 8 Hz, each 2H, CH_2CH_2), 7.31 (dd, J_{ortho} = 8 and 4.5 Hz, 1H, H-7), 8.36 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-6), 8.76 (dd, J_{ortho} = 4.5, J_{meta} = 2 Hz, 1H, H-8), 12.20 (br s, exchangeable with D_2O, 1H, NH); EI-MS m/z 204 (M^+). For **7**; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.61 and 3.79 (each br t, J = 8 Hz, each 2H, CH_2CH_2), 7.43 (dd, J_{ortho} = 8 and 4 Hz, 1H, H-7), 8.51 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-6), 9.02 (dd, J_{ortho} = 4, J_{meta} = 2 Hz, 1H-8), EI-MS m/z 222 (M^+). For **8**; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.61 and 3.85 (each br t, J = 8 Hz, each 2H, CH_2CH_2), 7.38 (dd, J_{ortho} = 8 and 4 Hz, 1H, H-7), 8.21 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-6), 8.98 (s, 1H, H-5), 9.01 (dd, J_{ortho} = 4, J_{meta} = 2Hz, 1H, H-8); EI-MS m/z 188 (M^+). For **9**; ^1H NMR [$(CD_3)_2SO$, 200 MHz) δ 7.79 (dd, J_{ortho} = 8 and 4 Hz, 1H, H-7), 8.05 and 8.14 (ABq, J = 5.8 Hz, each 1H, H-1 and H-2), 8.73 (dd, J_{ortho} = 8, J_{meta} = 2 Hz, 1H, H-6), 9.21 (dd, J_{ortho} = 4, J_{meta} = 2 Hz, 1H, H-8), 9.33 (s, 1H, H-5); EI-MS m/z 186 (M^+).

¶ *Crystal data for* **5**: $C_{10}H_9N_3S$; M = 203.26; monoclinic, space group $P2_1/c$, a = 5.016(2), b = 14.522(2), c = 12.452(2) Å, β = 95.98(2)°, V = 902.0(4) $Å^3$; Z = 4; D_c = 1.497 g cm^{-3}. A crystal of size 0.10 × 0.08 × 0.35 mm was examined by the ω–2θ scan technique using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Cell dimensions were obtained from 25 reflections ($21 < 2\theta < 23°$). 2080 unique data were obtained and 961 of these with $I \geqslant 3\sigma(I)$ were used in the refinement; R = 0.046, R_w = 0.030, S = 1.19.

An N–H···N hydrogen bond is formed between molecules related by an inversion centre [N···N(4) 3.051(5) Å]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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