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On the Reaction of Thieno[*c*][1,5]naphthyridine 5-Oxides and 9-Oxides with Thionyl Chloride and Thionyl Bromide. Some Selective Nucleophilic Reactions

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Thieno[2,3-*c*][1,5]naphthyridine 5-oxide (**1**), 1-bromothieno[2,3-*c*][1,5]naphthyridine 5-oxide (**4**), thieno[3,4-*c*][1,5]naphthyridine 5-oxide (**6**) and thieno[3,2-*c*][1,5]naphthyridine 5-oxide (**9**) all gave the 4-chloro isomers with loss of the *N*-oxide group in the reaction with thionyl chloride. The reactions were performed at room temperature and gave mostly high yields. Thieno[2,3-*c*][1,5]naphthyridine 9-oxide (**15**), on the other hand, gave a mixture of the 6-,7- and 8-chloro isomers. Thieno[3,2-*c*][1,5]naphthyridine 9-oxide did not react under these conditions. Reaction with thionyl bromide gave no brominated products, instead, thieno[2,3-*c*][1,5]naphthyridine (**3**) was obtained from **1** and **15**. Various nucleophilic substitutions of 4-chlorothieno[2,3-*c*][1,5]naphthyridine (**2**) were carried out and gave 4-thioxo-4,5-dihydrothieno[2,3-*c*][1,5]naphthyridine (**11**), 4-(1-piperidyl)thieno-[2,3-*c*][1,5]naphthyridine (**12**), 4-(4-methylpiperazin-1-yl)thieno[2,3-*c*][1,5]naphthyridine (**13**) and 4-dimethylaminothieno[2,3-*c*][1,5]naphthyridine (**14**) in good yields. 8-Thioxodihydrothieno[2,3-*c*][1,5]naphthyridine (**21**) was prepared from **15** via 8-bromothieno[2,3-*c*][1,5]naphthyridine (**20**) and 8-oxodihydrothieno[2,3-*c*][1,5]naphthyridine (**19**). Attempts to prepare **21** directly from **19** were not successful.

In connection with our work on the effects of the mode of annelation on physical properties and reactivities of tricyclic heterocyclic systems with the phenanthrene annelation pattern (for a review cf. Gronowitz[1]), we have previously described convenient one-pot procedures involving Pd(0)-catalyzed cross couplings for the synthesis of thieno[*b,c*]quinolines and isoquinolines,[2–5] dithieno-[*b,d*]pyridines,[6–8] thieno[*c*]naphthyridines[9–12] and thieno[*b*]naphthyridines.[13–15]

Extensive experimental studies and theoretical calculations of electrophilic substitution of many of the isomeric dithienopyridines,[16,17] thieno[*c*][1,5]naphthyridines,[18,19] and the six thieno analogues of phenanthrene *N*-oxide,[20,21] have been carried out.

In a recent article we described the attempted bromination of thieno[2,3-*c*][1,5]naphthyridine 5-oxide with bromine in refluxing thionyl chloride. Instead of brominated products, we observed the formation of 4-chlorothieno[2,3-*c*][1,5]naphthyridine and 7-bromo-4-chlorothieno[2,3-*c*][1,5]naphthyridine in 44% and 9% yields, respectively.[18] As this reaction might lead to easy access to 4-substituted thieno[*c*][1,5]naphthyridines, via nucleophilic substitutions we wished to examine more closely the reaction of thionyl chloride and thionyl bromide with the isomeric thieno[*c*][1,5]naphthyridine *N*-oxides.

It should be noted that α- and γ-halo heterocycles have been prepared from heterocyclic *N*-oxides by the action of phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride or sulfuryl chloride at elevated temperatures.[22] On the other hand, thionyl chloride has been used for deoxygenation reactions of heterocyclic *N*-oxides.[22,24]

Results and discussion

Thieno[2,3-*c*][1,5]naphthyridine 5-oxide (**1**) and 1-bromothieno[2,3-*c*][1,5]naphthyridine 5-oxide (**4**) reacted with thionyl chloride at room temperature. The products were 4-chlorothieno[2,3-*c*][1,5]naphthyridine (**2**) and 1-bromo-4-chlorothieno[2,3-*c*][1,5]naphthyridine (**5**), in 83% and 79% yields, respectively. It seems most likely that the same general addition–elimination sequence operates in this case as in for example the reaction of pyridine *N*-oxide with phosphorus oxychloride and sulfuryl chloride.[25] It should also be noted that no trace of

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substitution of chlorine in the thiophene ring could be detected in these reactions. Chlorine substitution had previously been observed by us with thieno[2,3-*c*][1,5]naphthyridine in refluxing thionyl chloride and in the presence of bromine.[18]

In contrast with thionyl chloride, thionyl bromide gave no halogenated product in the reaction with **1**, but instead thieno[2,3-*c*][1,5]naphthyridine (**3**) in 75% yield at room temperature. As far as we could find, thionyl bromide has not been used before in the deoxygenation of heterocyclic *N*-oxides and seems to be a particularly mild and efficient reagent for this.

The results of the reaction of thionyl chloride with thieno[3,4-*c*][1,5]naphthyridine 5-oxide (**6**) were interesting. A mixture consisting of 4-chlorothieno[3,4-*c*][1,5]-naphthyridine (**7**) and 8-chlorothieno[3,4-*c*][1,5]naphthyridine (**8**) was obtained in 40% and 8% yields, respectively. The substitution in the naphthyridine ring is indeed surprising. Some decomposition of the starting material or of the products might explain the low total yield, as the mixture turned dark upon standing.

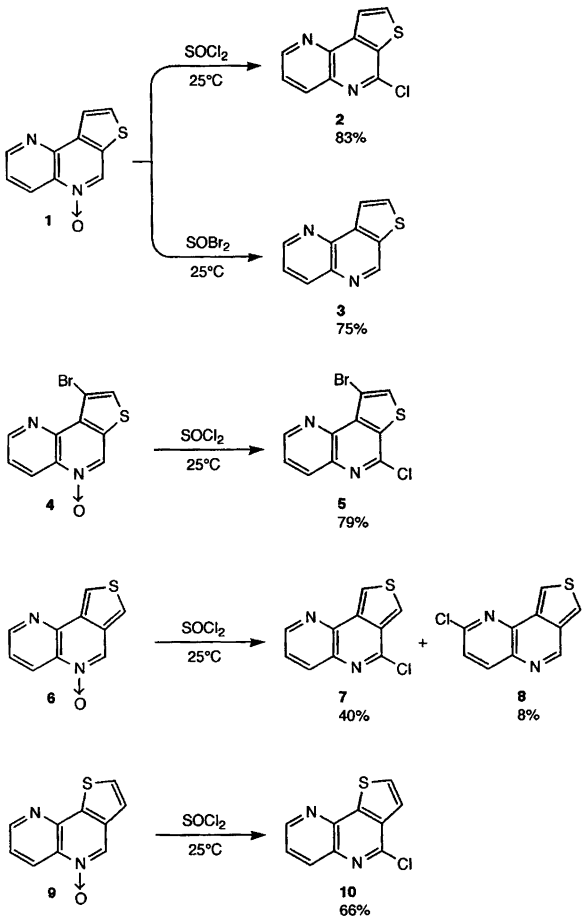
Thieno[3,2-*c*][1,5]naphthyridine 5-oxide (**9**) also underwent reaction with thionyl chloride at room temperature. 4-Chlorothieno[2,3-*c*][1,5]naphthyridine (**10**) was obtained in 66% yield, and again no trace of substitution in the thiophene ring could be detected.

Various nucleophilic substitutions of 4-chlorothieno-[2,3-*c*][1,5]naphthyridine (**2**) were investigated (Scheme 2). 4-Thioxo-4,5-dihydrothieno[2,3-*c*][1,5]naphthyridine (**11**) was prepared in 72% yield by treatment with thiourea in refluxing ethanol. This compound might be interesting as an antitubercular agent, as the corresponding 2-thio-1,2-dihydro-1,5-naphthyridine showed some activity.[26]

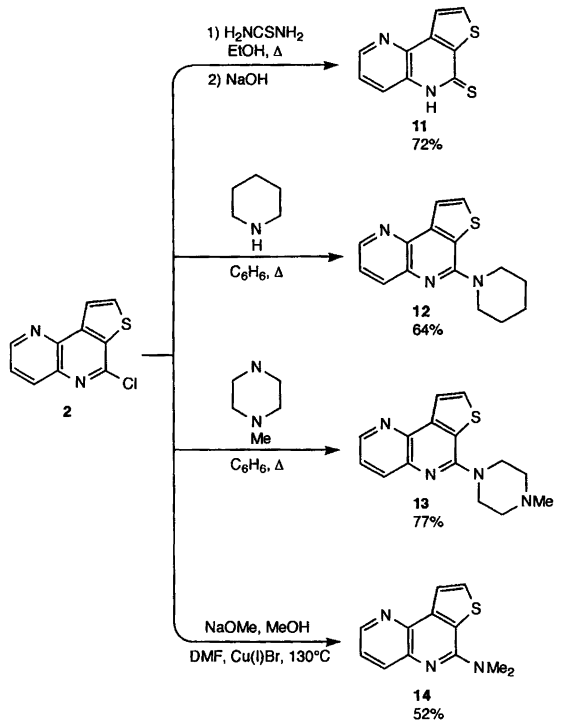
Piperidine and *N*-methylpiperazine both gave the expected products, 4-(1-piperidyl)thieno[2,3-*c*][1,5]naphthyridine (**12**) and 4-(4-methylpiperazin-1-yl)thieno[2,3-*c*][1,5]naphthyridine (**13**) in 64% and 77% yelds, respectively.

All attempts to obtain the 4-methoxy derivative failed. Finally, a product was obtained with *N*,*N*-dimethylformamide as cosolvent, but instead of the expected product, 4-dimethylaminothieno[2,3-*c*][1,5]naphthyridine (**14**) was obtained in 52% yield. These results are indeed surprising, compared with the easy methoxylation of 2-chloropyridine.[27]

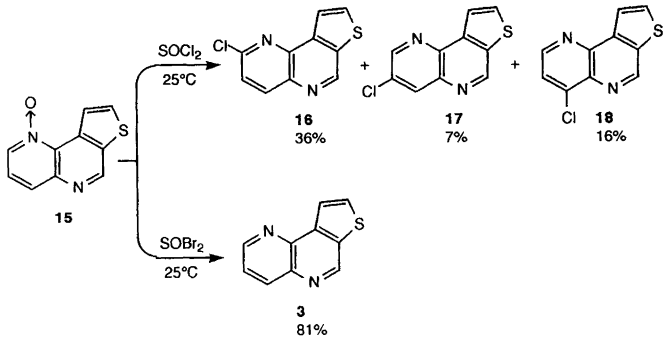
The reaction of thieno[2,3-*c*][1,5]naphthyridine 9-oxide (**15**) with thionyl chloride gave a mixture of 8-chlorothieno[2,3-*c*][1,5]naphthyridine (**16**), 7-chlorothieno-[2,3-*c*][1,5]naphthyridine (**17**) and 6-chlorothieno[2,3-*c*]-[1,5]naphthyridine (**18**) in 36%, 7% and 16% yields, respectively (Scheme 3), analogous to the Meisenheimer reaction of 1,5-naphthyridine *N*-oxide with phosphorus oxychloride, which gave 42% of 2-chloro-, 3% of 3-chloro- and 54% of 4-chloro-1,5-naphthyridine.[28]



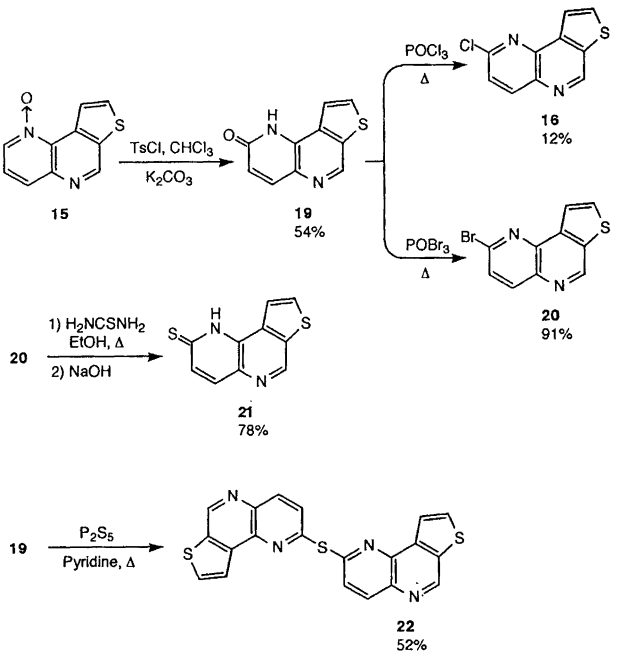
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Again, the use of thionyl bromide resulted in deoxygenation of **15** and gave **3** in 81% yield. Thieno[3,2-*c*][1,5]naphthyridine 9-oxide did not react under these reaction conditions.

We also wished to prepare 8-thioxo-8,9-dihydrothieno-[2,3-*c*][1,5]naphthyridine (**21**), because of its possible pharmacological properties (Scheme 4). 8-Oxo-8,9-dihydrothieno[2,3-*c*][1,5]naphthyridine (**19**) was obtained from **15** in 54% yield by the well known reaction with tosyl chloride. Treatment of **19** with phosphorus oxybromide gave 8-bromothieno[2,3-*c*][1,5]naphthyridine (**20**) in 91% yield. On the other hand, the reaction of **19** with phosphorus oxychloride gave **16** in low yield. The desired product was finally obtained in 78% yield by treatment of **20** with thiourea.

Attempts to prepare **21** directly from **19** were not very successful. Hexamethylphosphoric triamide (HMPT) is the proper choice of solvent for thionation reactions of heterocyclic pyridones with *p*-methoxyphenylthionophosphine sulfide (Lawesson's reagent).[29] However, HMPT has been shown to be highly carcinogenic in animal tests.[30,31] Therefore several other solvents such as benzene, pyridine, 1,2-dimethoxyethane and *N*,*N*-dimethylformamide were tried for the reaction of **19** with Lawesson's reagent. The general problem was the low solubility of the reagent and/or the reactant in the solvents, even at elevated temperatures. Finally, in *N*,*N*-dimethyl-*N*,*N*′-propylene urea (DMPU) at 100°C, using excess of Lawesson's reagent, **21** was isolated in 35% yield after 24 hours, together with a minor amount of 8,8′-thiodithieno[2,3-*c*][1,5]naphthyridine (**22**). The modest yield of **21** can be explained by formation of tarry products during the reaction and the tendency of the reagent to react with the solvent. Obviously, it is more profitable to prepare **21** via **20**, as the total yield of **21** from **19** in this case is 71% (see above).

On the other hand, the reaction of **19** with phosphorus pentasulfide in boiling pyridine gave exclusively **22** in 52% yield.

This anomalous behavior has previously been observed in for example the reaction of 2,6-di-*tert*-butyl-4-pyridone with phosphorus pentasulfide, where the sulfide was obtained, instead of the expected thiol.[32]

^{13}C NMR spectra of the halothieno[c]naphthyridines. Unambiguous assignments of the ^{13}C signals and the carbon coupling constants of the halogenated thieno[*c*]naphthyridines are given in Tables 1 and 2. Correlation between carbon and proton resonances was made by means of ^{1}H–^{13}C HETCOR NMR spectra. The chemical shifts and the magnitudes of the ^{1}H–^{13}C coupling constants were generally of the same magnitude as in the parent thieno[*c*]naphthyridines.[9]

Table 1. ^{13}C NMR chemical shifts (in ppm) of the halothienonaphthyridines **5,7,8,10,16,20**.

Compound	1C	2C	3C	4C	6C	7C	8C
5		131.7			136.5	124.1	149.5
7	121.4		126.4		136.1	123.6	149.2
8	120.7		125.3	148.8	138.8	123.9	
10		129.9	124.1		136.8	124.2	150.2
16	122.9	133.3		145.5	139.8	124.7	
20	122.9	132.6		146.0	139.8	128.1	

Table 2. J_{CH} values (Hz) of the halothienonaphthyridines **5,7,8,10,16,20**.

Compound	1C	2C	3C	4C	6C	7C	8C
5							
$^1J_{CH}$		191.2			166.1	165.2	180.4
$^2J_{CH}$						9.1	3.2
$^3J_{CH}$					6.3		7.8
7							
$^1J_{CH}$	193.3		190.3		164.6	165.0	179.3
$^2J_{CH}$						8.8	3.1
$^3J_{CH}$	3.8		6.3		6.4		7.6
8							
$^1J_{CH}$	191.9		188.5	181.7	165.3	172.0	
$^2J_{CH}$							
$^3J_{CH}$	4.8		5.2;1.2	2.9			
10							
$^1J_{CH}$		187.4	174.9		165.9	167.7	180.1
$^2J_{CH}$		6.7	4.5			9.4	3.3
$^3J_{CH}$					6.2		7.8
16							
$^1J_{CH}$	175.1	183.3		185.6	166.7	172.4	
$^2J_{CH}$	4.8	7.3					
20							
$^1J_{CH}$	175.0	186.2		183.8	166.1	172.8	
$^2J_{CH}$	4.6	8.0					

Experimental

NMR Spectra were recorded on a Varian XL-300 spectrometer. Deuteriochloroform was used as the solvent for ^{13}C NMR and HETCOR spectra. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer (70 eV). The elemental analyses were carried out by H. Kolbe, Mülheim, Germany. All melting points are uncorrected. Chloroform was distilled over phosphorus pentaoxide and ethyl acetate over molecular sieves prior to use. Pyridine and DMPU were distilled over calcium hydride and kept under nitrogen. All other chemicals were purchased from commercial sources in analytical grade and used without further purification. The substances were purified by flash chromatography on silica gel 60 (purchased from Merck) or by chromatography on a silica gel Dynamax HPLC column, 500 × 10 mm.

General procedure for the reaction of thienonaphthyridine N-*oxides* **1** *with thionyl chloride and thionyl bromide.* A solution of thionyl chloride or thionyl bromide (5 ml) and the appropriate thienonaphthyridine *N*-oxide (2.00 mmol)[10] was stirred at room temperature until the starting material was consumed. The thionyl halide was evaporated off and the residue treated with ice, followed by a saturated solution of sodium hydrogen carbonate. The aqueous phase was extracted with chloroform, dried over magnesium sulfate and finally subjected to chromatography.

*4-Chlorothieno[2,3-c][1,5]naphthyridine (***2***).* This compound was purified by flash chromatography using chloroform–methanol (95:5) as the eluent, giving 365 mg (83%) of the title compound, with ^1H NMR spectrum and melting point identical with those described in Ref. 18.

*Thieno[2,3-c][1,5]naphthyridine (***3***).* This compound was purified by flash chromatography using ethyl acetate as the eluent, giving 279 mg (75%) of the title compound in the reaction of thionyl bromide with thieno[2,3-*c*][1,5]naphthyridine 5-oxide and 301 mg (81%) with thieno[2,3-*c*][1,5]naphthyridine 9-oxide. The title compound had ^1H NMR spectrum and melting point identical with those described in Ref. 9.

*1-Bromo-4-chlorothieno[2,3-c][1,5]naphthyridine (***5***).* This compound was purified by flash chromatography using chloroform–methanol (99:1) as the eluent giving 471 mg (79%) of the title compound, m.p. 194–196°C. Anal. Calc. for $C_{10}H_4BrClN_2S$: C, H, N. ^1H NMR: δ 9.10 (dd, 1 H, H8, J = 4.5, 1.7 Hz), 8.44 (dd, 1 H, H6, J = 8.5, 1.7 Hz), 7.93 (s, 1 H, H2), 7.72 (dd, 1 H, H7, J = 8.5, 4.5 Hz). MS: *m/z* (%) 302 (27, $M^+ + 1$), 300 (100, M^+), 298 (74, $M^+ - 1$), 265 (19), 263 (19), 184 (19).

*4-Chlorothieno[3,4-c][1,5]naphthyridine (***7***).* This compound was purified by HPLC using ethyl acetate–heptane–isopropyl alcohol (30:69:1) as the eluent giving 174 mg (40%), m.p. 158–161°C. Peak matching on M^+. Calc. for $C_{10}H_5ClN_2S$: 219.9863. Found: 219.9862. ^1H NMR: δ 8.81 (dd, 1 H, H8), 8.59 (d, 1 H, H1, J = 3.0 Hz), 8.28 (d, 1 H, H3, J = 2.9 Hz), 8.22 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 7.54 (dd, 1 H, H, J = 8.5, 4.5 Hz).

MS: *m/z* (%) 222 (37, $M^+ + 1$), 220 (100, M^+), 185 (46), 158 (12).

8-Chlorothieno[3,4-c][1,5]naphthyridine (**8**). This compound was purified by HPLC using ethyl acetate–heptane–isopropyl alcohol (30:69:1) as the eluent giving 36 mg (8%), m.p. 160–163°C. Peak matching on M^+. Calc. for $C_{10}H_5ClN_2S$: 219.9863. Found: 219.9864. ^1H NMR: δ 9.09 (d, 1 H, H4, J = 1.0 Hz), 8.59 (dd, 1 H, H1, J = 3.0, 1.0 Hz), 8.24 (d, 1 H, H6, J = 8.5 Hz), 8.18 (d, 1 H, H3, J = 3.0 Hz), 7.52 (d, 1 H, H7, J = 8.5 Hz). MS: *m/z* (%) 222 (37, $M^+ + 1$), 220 (100, M^+), 185 (39), 158 (10).

4-Chlorothieno[3,2-c][1,5]naphthyridine (**10**). This compound was purified by HPLC using chloroform–isopropyl alcohol (99.5:0.5) as the eluent giving 290 mg (66%), m.p. 158–161°C. Anal. Calc. for $C_{10}H_5ClN_2S$: C, H, N. ^1H NMR: δ 8.93 (dd, 1 H, H8, J = 4.5, 1.5 Hz), 8.40 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 7.76 (d, 1 H, H2, J = 5.5 Hz), 7.70 (d, 1 H, H3, J = 5.5 Hz), 7.65 (dd, 1 H, H7, J = 8.5, 4.5 Hz). MS: *m/z* (%) 222 (37, $M^+ + 1$), 220 (100, M^+), 185 (51), 158 (12).

8-Chlorothieno[2,3-c][1,5]naphthyridine(**16**)*,7-chlorothieno[2,3-c][1,5]naphthyridine* (**17**) *and 6-chlorothieno[2,3-c][1,5]naphthyridine* (**18**). These compounds were purified by HPLC using chloroform–isopropyl alcohol (99:1) as the eluent, giving 260 mg of the three isomers in a mixture. They could, unfortunately, not be separated by any methods available to us. The yields were estimated by using a Varian 3700 gas chromatograph, equipped with a 20 m OV-1701 capillary glass column. Peak areas were determined electronically with a Varian 4270 integrator. **16**: ^1H NMR: δ 9.35 (s, 1 H, H4), 8.44 (d, 1 H, H6, J = 8.5 Hz), 8.29 (d, 1 H, H1, J = 5.5 Hz), 7.92 (d, 1 H, H2, J = 5.5 Hz), 7.62 (d, 1 H, H7, J = 8.5 Hz). MS: *m/z* (%) 222 (37, $M^+ + 1$), 220 (100), 185 (22). **17**: ^1H NMR: δ 9.35(s, 1 H, H4), 8.90 (d, 1 H, H8, J = 2.0 Hz), 8.49 (d, 1 H, H6, J = 2.0 Hz), 8.27 (d, 1 H, H1, J = 5.5 Hz), 7.95 (d, 1 H, H2, J = 5.5 Hz). MS: *m/z* (%) 222 (39, $M^+ + 1$), 220 (100), 185 (12). **18**: ^1H NMR: δ 9.44 (s, 1 H, H4), 8.85 (d, 1 H, H8, J = 4.5 Hz), 8.31 (d, 1 H, H1, J = 5.5 Hz), 7.95 (d, 1 H, H2, J = 5.5 Hz), 7.76 (d, 1 H, H7, J = 4.5 Hz). MS: *m/z* (%) 222 (39, $M^+ + 1$), 220 (100), 185 (12).

4-Thioxo-4,5-dihydrothieno[2,3-c][1,5]naphthyridine (**11**). A stirred mixture consisting of **2** (220 mg, 1.00 mmol) and thiourea (114 mg, 1.50 mmol) in 99.5% ethanol (5 ml) was refluxed for 30 min. After evaporation, the residue was treated with 200 ml of 2 M sodium hydroxide and left to stand at room temperature for 30 min. The aqueous phase was neutralized with 2 M hydrogen chloride. The resulting precipitate was separated by filtration, washed with water and thoroughly dried. This compound was finally purified by flash chromatography using chloroform–methanol (95:5) as the eluent and gave 158 mg (72%), m.p. 303–306°C. Anal. Calc. for $C_{10}H_6N_2S_2$: C, H. ^1H NMR (DMSO-d_6): δ 13.79 (br s, 1 H, NH), 8.69 (dd, 1 H, H8, J = 4.5, 1.5 Hz), 8.31 (d, 1 H, H1, J = 1.5 Hz), 8.09 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 8.08 (d, 1 H, H2, J = 5.5 Hz), 7.64 (dd, 1 H, H7, J = 8.5 Hz). MS: *m/z* (%) 219 (13), 218 (100, M^+), 185 (38), 158 (10).

4-(1-Piperidyl)thieno[2,3-c][1,5]naphthyridine (**12**). A stirred solution consisting of **2** (220 mg, 1.00 mmol) and piperidine (340 mg, 4.00 mmol) in benzene (5 ml) was refluxed for 48 h. After evaporation, the residue was purified by HPLC using chloroform–isopropyl alcohol (99.5:0.5) as the eluent giving 172 mg (64%) of the title compound, m.p. 96–99°C. Anal. Calc. for $C_{15}H_{15}N_3S$: C, H. ^1H NMR: δ 8.69 (dd, 1 H, H8, J = 4.5, 1.5 Hz), 8.24 (d, 1 H, H1, J = 5.5 Hz), 8.14 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 7.73 (d, 1 H, H2, J = 5.5 Hz), 7.48 (dd, 1 H, H7, J = 8.5, 4.5 Hz), 3.7–3.9 (m, 4 H, NCH_2), 1.6–1.9 (m, 6 H, CH_2). MS: *m/z* (%) 269 (100, M^+), 240 (88), 220 (45), 214 (34), 186 (82), 185 (52).

4-(4-Methylpiperazin-1-yl)thieno[2,3-c][1,5]naphthyridine (**13**). A stirred solution consisting of **2** (176 mg, 0.80 mmol) and *N*-methylpiperazine (321 mg, 3.20 mmol) in benzene (4 ml) was refluxed for 96 h. After evaporation, the residue was purified by HPLC using chloroform–isopropyl alcohol (95:5) as the eluent giving 175 mg (77%) of the title compound as a heavy, pale oil, which turned dark on standing at room temperature. Peak matching on M^+. Calc. for $C_{15}H_{16}N_4S$: 284.1095. Found: 284.1096. ^1H NMR: δ 8.72 (dd, 1 H, H8, J = 4.5, 1.5 Hz), 8.26 (d, 1 H, H1, J = 5.5 Hz), 8.16 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 7.75 (d, 1 H, H2, J = 5.5 Hz), 7.50 (dd, 1 H, H7, J = 8.5, 4.5 Hz), 3.95 (t, 4 H, NCH_2), 2.71 (t, 4 H, CH_3NCH_2), 2.43 (s, 3 H, NCH_3). MS: *m/z* (%) 284 (11, M^+), 226 (11), 215 (22), 214 (100), 202 (25), 186 (20), 185 (23), 83 (30).

4-Dimethylaminothieno[2,3-c][1,5]naphthyridine (**14**). A mixture consisting of **2** (110 mg, 0.50 mmol), sodium methoxide (136 mg, 2.50 mmol), methanol (0.5 ml), *N,N*-dimethylformamide (0.5 ml) and copper(I) bromide (28 mg, 0.20 mmol) was heated in a sealed tube at 130°C for 48 h. The crude product was treated with 10% sodium cyanide, extracted with chloroform and dried over magnesium sulfate. After evaporation, the residue was purified by HPLC using ethyl acetate–heptane–isopropyl alcohol (14:85:1) as the eluent giving 56 mg (52%) of the title compound, m.p. 101–103°C. Anal. Calc. for $C_{12}H_{11}N_3$: C, H. ^1H NMR: δ 8.63 (dd, 1 H, H8, J = 4.5, 1.5 Hz), 8.23 (d, 1 H, H1, J = 5.5 Hz), 8.08 (dd, 1 H, H6, J = 8.5, 1.5 Hz), 7.74 (d, 1 H, H2, J = 5.5 Hz), 7.45 (dd, 1 H, H7, J = 8.5, 4.5 Hz), 3.47 (s, 6 H, NCH_3). MS: *m/z* (%) 229 (95, M^+), 214 (79), 200 (100), 186 (60), 185 (48).

8-Oxo-8,9-dihydrothieno[2,3-c][1,5]naphthyridine (**19**). A mixture consisting of **15** (1.01 g, 5.00 mmol) and tosyl chloride (1.15 g, 6.00 mmol) in chloroform (25 ml) and

10% potassium carbonate solution (25 ml) was shaken at room temperature for 8 h. The resulting precipitate was separated by filtration, washed with water, dried and finally washed with 25 ml of diethyl ether followed by 5 ml of chloroform. This gave 543 mg of the title compound as white crystals, which according to spectral and analytical data were completely pure. The analytical sample could be recrystallized in low yield from dimethyl sulfoxide–water, m.p. 325–329°C. Anal. Calc. for $C_{10}H_6N_2OS$: C, H. ^{1}H NMR (DMSO-d_6): δ 12.4 (br s, 1 H, NH), 9.12 (s, 1 H, H4), 8.32 (dd, 1 H, H1, J = 5.5, 1.0 Hz), 8.22 (d, 1 H, H2, J = 0 5.5 Hz), 8.08 (d, 1 H, H6, J = 9.5 Hz), 6.72 (d, 1 H, H7, J = 9.5 Hz). MS: m/z (%) 202 (100, M^+), 174 (52), 147 (16), 121 (14).

*Preparation of 8-chlorothieno[2,3-c][1,5]naphthyridine (**16**) from **19***. A mixture consisting of **19** (101 mg, 0.50 mmol), phosphorus pentachloride (250 mg, 2.50 mmol) and phosphorus oxychloride (2.5 ml) was refluxed for 48 h. The crude product was treated with sodium carbonate, extracted with chloroform and dried over magnesium sulfate. After evaporation, the residue was purified by HPLC using chloroform–isopropyl alcohol (99.75:0.25) as the eluent giving 13 mg (12%) of the title compound, m.p. 154–157°C. Peak matching on M^+. Calc. for $C_{10}H_5ClN_2S$: 219.9863. Found: 219.9870. ^{1}H NMR: δ 9.47 (s, 1 H, H4), 8.50 (d, 1 H, H6, J = 8.5 Hz), 8.32 (dd, 1 H, H1, 5.5, 0.5 Hz), 7.97 (d, 1 H, H7, J = 8.5 Hz). MS: m/z (%) 221 (36), 220 (100, M^+), 185 (46).

*8-Bromothieno[2,3-c][1,5]naphthyridine (**20**)*. A mixture consisting of **19** (202 mg, 1.00 mmol) and phosphorus oxybromide (1.4 g) was heated in a sealed tube at 120°C for 5 h. The crude product was treated with sodium carbonate, extracted with chloroform and dried over magnesium sulfate. After evaporation, the residue was purified by flash chromatography using chloroform–methanol (98:2) as the eluent giving 238 mg (90%) of the title compound, m.p. 170–173°C. Anal. Calc. for $C_{10}H_5BrN_2S$: C, H, N. ^{1}H NMR: δ 9.06 (s, 1 H, H4), 8.02 (d, 1 H, H6, J = 8.5 Hz), 7.95 (dd, 1 H, H1, J = 5.0, 1.0 Hz), 7.70 (d, 1 H, H2, J = 5.0 Hz), 7.47 (d, 1 H, H7, J = 8.5 Hz). MS: m/z (%) 266 (95, $M^+ + 1$), 264 (95, $M^+ - 1$), 186 (55), 185 (100), 159 (51), 114 (39).

*8-Thioxo-8,9-dihydrothieno[2,3-c][1,5]naphthyridine (**21**)*. A stirred mixture consisting of **20** (264 mg, 1.00 mmol) and thiourea (114 mg, 1.50 mmol) in 99.5% ethanol (5 ml) was refluxed for 24 h. After evaporation, the residue was treated with 200 ml of 2 M sodium hydroxide and left to stand overnight. The aqueous phase was neutralized with 2 M hydrogen chloride. The resulting precipitate was separated by filtration, washed with water and thoroughly dried. This compound was finally purified by flash chromatography using chloroform–methanol (95:5) as the eluent giving 170 mg (78%) of the title compound, m.p. 321–324°C. Anal. Calc. for $C_{10}H_6N_2OS$: C, H. ^{1}H NMR (DMSO-d_6): δ 14.0 (br s, 1 H, NH), 9.25 (s, 1 H, H4), 8.62 (d, 1 H, H1, J = 5.5 Hz), 8.30 (d, 1 H, H2, J = 5.5 Hz), 7.96 (d, 1 H, H6, J = 9.0 Hz), 7.48 (d, 1 H, H7, J = 9.0 Hz). MS: m/z (%) 219 (18), 218 (100, M^+), 185 (36), 174 (27).

*Synthesis of **21** from **19**, using* p-*methoxyphenylthionophosphine sulfide (Lawesson's reagent)*. A stirred mixture consisting of **19** (101 mg, 0.50 mmol) and Lawesson's reagent (102 mg, 0.50 mmol) in *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU) (2.5 ml) was heated at 100°C for 24 h. After cooling the reaction mixture to room temperature, it was treated with ice-cooled sodium chloride solution and kept in the refrigerator overnight. The resulting precipitate was separated by filtration, washed with water, thoroughly dried and finally subjected to chromatography as above. The first fraction consisted of minor amounts of 8,8'-thiodithieno[2,3-*c*][1,5]naphthyridine (**22**), together with unknown materials, and the second fraction of 38 mg (35%) of **21**.

*8,8'-Thiodithieno[2,3-c][1,5]naphthyridine (**22**)*. A stirred mixture consisting of **19** (101 mg, 0.50 mmol) and phosphorus pentasulfide (111 mg, 0.50 mmol) in pyridine (2.5 ml) was refluxed for 24 h. After evaporation, the residue was treated with saturated sodium hydrogen carbonate. The aqueous phase was extracted with chloroform and dried over magnesium sulfate. This compound was finally purified by flash chromatography using chloroform–methanol (98:2) as the eluent giving 52 mg (52%) of the title compound, m.p. 219–222°C. Peak matching on $M^+ - 1$. Calc. for $C_{20}H_9N_4S_3$: 400.9989. Found: 400.9994. ^{1}H NMR (DMSO-d_6): δ 8.32 (s, 1 H, H4), 8.29 (d, 1 H, H1, J = 5.5 Hz), 8.07 (d, 1 H, H2, J = 5.5 Hz), 8.53 (d, 1 H, H6, J = 8.5 Hz), 8.12 (d, 1 H, H7, J = 8.5 Hz). MS: m/z (%) 402 (88, M^+), 401 (100), 185 (18).

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