Synthesis of Thienodolin

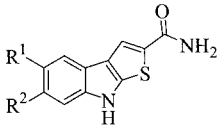
Robert Engqvist,[a,b] Atif Javaid,[b] and Jan Bergman*[a,b]

Keywords: Alkaloid / Total synthesis / Indoles

We report a total synthesis of the alkaloid thienodolin (**1a**), as well as its 5-chloro isomer **1b** and its unsubstituted analogue **1c**, in three steps from the corresponding oxindoles **8a**–**c**. The preparation was achieved through an initial Vilsmeier–Haack–Arnold reaction (chloro-formylation) followed by protection at the indole nitrogen, creation of the fused thiophene ring by nucleophilic substitution at the 2-position and an intramolecular cyclization using mercaptoacetamide. This gave **1a**, **1b** and **1c** in total yields of 42%, 35% and 37%, respectively.

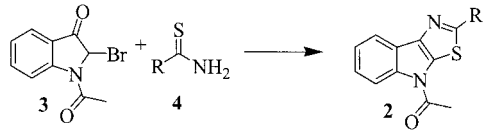
Introduction

Thienodolin (**1a**) was isolated from the culture broth of *Streptomyces albogriseolus* MJ286−76F7 and structurally elucidated in the early 1990's by Nakamura et al.[1−2] The alkaloid **1a** was shown to have both growth promoting and inhibiting activities in rice seedlings.



1a $R^1 = H$, $R^2 = Cl$
1b $R^1 = Cl$, $R^2 = H$
1c $R^1 = R^2 = H$

Despite its relative simplicity, only a few methods are available for the synthesis of the thieno[2,3-*b*]indole ring system[3−6] and no total synthesis of the alkaloid **1a** has been reported until now. Some aza derivatives, i.e. thiazolo[4,5-*b*]indoles (**2**), have been synthesized (Scheme 1) from 1-acetyl-2-bromoindolinone (**3**) and thioacetamides **4**.[7]

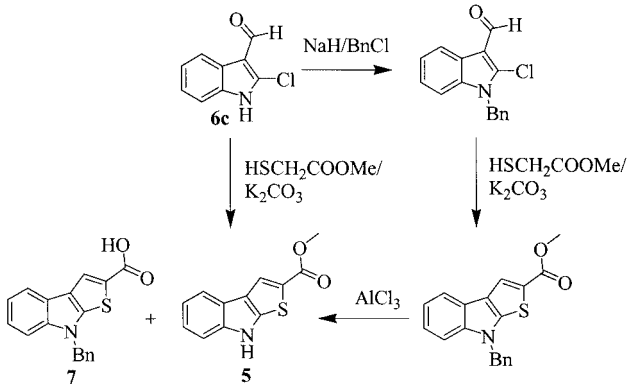


Scheme 1. Synthesis of thiazolo[4,5-*b*]indoles (**2**).[7]

[a] Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute,
Novum Research Park, 141 57 Huddinge, Sweden
[b] Södertörn University College,
141 04 Huddinge, Sweden
Fax: (internat.) +46-8-6081501
E-mail: jabe@cnt.ki.se

Results and Discussion

In 1995, Olesen et al. presented a synthetic pathway to methyl thieno[2,3-*b*]indole-2-carboxylate (**5**) starting from 2-chloroindole-3-carbaldehyde (**6c**) (Scheme 2).[6] The disadvantage of this approach, as a prospective way to **1c**, lies in the deprotection step, which should result in an inconvenient mixture of **5** and the acid **7** in moderate yields.



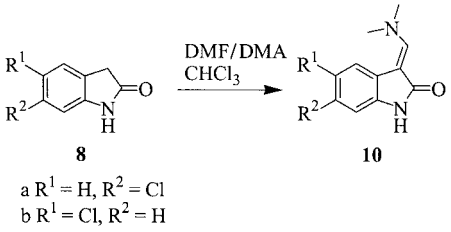
Scheme 2. Olesen's route to thieno[2,3-*b*]indoles[6]

Subsequently, we contemplated the possibility that the easily-removable Boc-protecting group would be more suitable during any synthesis of **1a** since it should activate the indole ring towards nucleophilic attack.

2,6-Dichloroindole-3-carbaldehyde (**6a**) has been prepared previously by Acheson and co-workers[8] using a tedious route. However, the method of choice for the synthesis of a 2-chloro-3-carboxaldehyde-substituted indole involves reacting an oxindole with a Vilsmeier reagent generated in situ from DMF and phosphorus oxychloride ($POCl_3$) i.e. the Vilsmeier−Haack−Arnold reaction.[9] When we applied this reaction to the chlorosubstituted oxindoles **8a**−**b**,

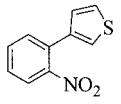
 DOI: 10.1002/ejoc.200400073

we noticed that a higher yield was obtained if the oxindoles were pretreated with $POCl_3$ then treated with a fresh solution of the Vilsmeier reagent at 0 °C, and finally heated at reflux for 20 h. This procedure gave mixtures of the desired dichloroindole-3-carbaldehydes **6a**−**b** and, because of the excess Vilsmeier reagent, the by-product chloro-3-(dimethylaminomethylene)-1-formyloxindoles **9a**−**b**. This kind of transformation has been reported twice previously in the literature.[10] The corresponding des-*N*-formyl enamine amides **10a** and **10b** have been prepared selectively by Sarges et al. by reacting the oxindoles **8a** and **8b** with *N*,*N*-dimethylformamide dimethyl acetal (DMF/DMA) in refluxing chloroform.[11]



Scheme 3. Synthesis of **10a**−**b** from **8a**−**b** according to Sarges et al.[11]

Chloro-3-(dimethylaminomethylene)-1-formyloxindoles **9a**−**b** were easily converted into **6a** and **6b** in good yields by refluxing in neat $POCl_3$. The aldehydes **6a**−**b** were subsequently protected using di-*tert*-butyl dicarbonate (Boc_2O) and 4-(dimethylamino)pyridine (DMAP) in tetrahydrofuran. The protected indole derivative **11c** was heated with methyl thioglycolate and potassium carbonate in methanol yielding the ester **5** in 70% yield. The corresponding Boc-protected methyl thieno[2,3-*b*]indole-2-carboxylate was obtained in a low yield by performing the reaction at lower temperatures for a shorter period of time. When **5** was treated with ammonia in methanol in a sealed tube at 80 °C for 6 days, **1c** was obtained in 27% isolated yield together with 50% of unreacted **5**. If the reaction was performed at 120 °C only small amounts of the unsubstituted thieno[2,3-*b*]indole (**12**) could be isolated. Compound **12** has been prepared previously by Olesen and co-workers by heating **5** in morpholine. This result has been confirmed previously.[6] Additionally, the parent compound **12** has been prepared recently by a palladium promoted reductive cyclization of 3-(2-nitrophenyl)thiophene (**13**) in the presence of CO.[12]

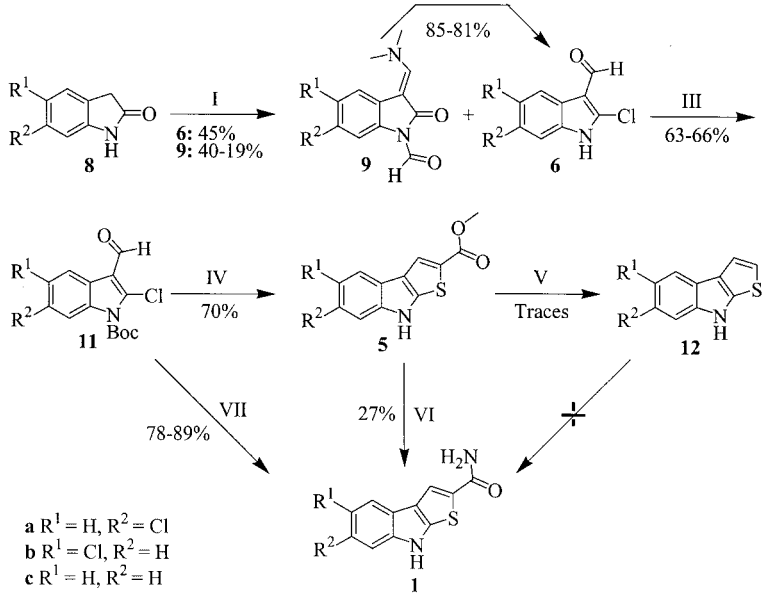


Several attempts to react **12** with hydrogen isocyanate (generated in situ) or chlorosulfonyl isocyanate failed. The desired thienoindoles **1a**−**c**, were prepared instead by treatment of **11a**−**c** with 2-mercaptoacetamide in the presence of K_2CO_3 in methanol at reflux for 16 h.

This procedure gave a total yield of 42% for the synthesis of thienodolin (**1a**) from the known 6-chloroxindole in three

Table 1. Yields for the total synthesis of **1a**−**c**

Entry		Yields (%)				
	R^1, R^2	**6**, **9**	**9** → **6**	**10**	**1**	Total yield (%)
1	H, Cl	45, 40	85	63	84	42
2	Cl, H	45, 19	81	66	89	35
3	H, H	73,[5] 0	–	65[7]	78	37



Scheme 4. I) i. $POCl_3$, 1,2-dichloroethane, ii. Vilsmeier reagent, reflux, 20 h. II) $POCl_3$, 100 °C, 0.5 h. III) Boc_2O, DMAP, THF, 0 °C, 1.5 h. IV) methyl thioglycolate, methanol, reflux, 16 h. V) NH_3, methanol. VI) ammonia, methanol, sealed tube, 80 °C, 6 days. VII) 2-mercaptoacetamide, methanol, reflux, 16 h

steps (Table 1, Scheme 4). The spectroscopic data recorded for **1a** are in accordance with the literature data.[1,2]

Conclusions

Starting from the corresponding oxindoles **8a−c**, we have prepared the alkaloid thienodolin (**1a**) as well as the two analogues **1b−c** in total yields of 35−42% in three steps.

Experimental Section

NMR spectra were recorded from [D_6]DMSO solutions at room temperature, using the signal from residual DMSO (^{1}H: δ = 2.50 ppm; ^{13}C: δ = 39.5) as internal standard, on a Bruker DPX 300 (300 MHz) spectrometer. Coupling constants and chemical shifts are given in Hz and ppm, respectively. IR spectra were recorded on a Perkin−Elmer 1600 FTIR. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. Mass spectra were recorded using an LC/MS system operating in the electron spray ionisation (ESI) mode at 70 eV. Chromatography was performed on Merck silica gel 60. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Solvents were of analytical grade and were used as received. 2-Chloroindole-3-carboxaldehyde,[9] 1-(*tert*-butoxycarbonyl)-2-chloroindole-3-carboxaldehyde,[13] 5-chloroxindole,[14] 6-chloroxindole[15] and 2-mercaptoacetamide[16] were prepared as described in the literature.

Methyl Thieno[2,3-*b*]indole-2-carboxylate (5): A mixture of **11c**[13] (1.12 g; 4.0 mmol), methyl 2-mercaptoacetate (0.50 g; 4.4 mmol), K_2CO_3 (0.61 g; 4.4 mmol) and methanol (16 mL) was refluxed for 16 h. Thereafter, the reaction mixture was allowed to cool to room temperature and poured into water (160 mL). The resulting precipitate was collected by filtration, washed with water and dried. Yield: 0.70 g (70%). M.p. 201−202 °C [ref.[6] m.p. 201−209 °C].

Synthesis of Dichloroindole-3-carbaldehydes 6a−b and Chloro-3-[(dimethylamino)methylene]oxindoles 9a−b. General Procedure: $POCl_3$ (3.83 g; 25 mmol) was added to a solution of the appropriate chloroxindole (2.10 g; 12.5 mmol) and dry 1,2-dichloroethane (100 mL) at room temperature under argon. The reaction mixture was heated at reflux for 30 min and was then stirred at room temperature for 90 min. Simultaneously, a solution of the Vilsmeier's salt in 1,2-dichloroethane was prepared as follows: $POCl_3$ (5.75 g, 37.5 mmol) was added dropwise to a solution of dry 1,2-dichloroethane (20 mL) and dry DMF (2.74 g, 37.5 mmol) over 30 min at 0 °C under argon, followed by stirring for 90 min at room temperature. This solution was then added to the reaction mixture, which was subsequently heated at reflux for 20 h. The solvent was then removed at reduced pressure, ice-water was added, and the mixture was allowed to stand for 3 h. The resulting precipitate was collected by filtration, washed with water, and purified by column chromatography on silica gel eluting with hexane/ethyl acetate, 6:4 then methanol/chloroform, 1:9.

2,6-Dichloro-3-formylindole (6a): Yield: 1.19 g (45%). M.p. 240−241 °C [ref.[8] m.p. 238−239 °C]. IR: $\tilde{\nu}$ = 3085, 3037, 2838, 1630, 1573, 1421, 1371, 1061, 852, 806, 755, 688 cm^{-1}. ^{1}H NMR: δ = 7.26 (dd, *J* = 8.5, 1.8 Hz, 1 H, Ar*H*), 7.45 (d, *J* = 1.8 Hz, 1 H, Ar*H*), 8.02 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 9.97 (s, 1 H, C*H*), 13.23 (br. s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 111.5 (d), 112.0 (s), 121.3 (d), 123.0 (s), 123.1 (d), 128.3 (s), 135.0 (s), 135.5 (s), 183.3 (d) ppm. MS (ESI): *m*/*z* = 212 [M − H]$^-$ $C_9H_5NO^{35}Cl_2$, 214 [M − H]$^-$ $C_9H_5NO^{35}Cl\ ^{37}Cl$, 216 [M − H]$^-$ $C_9H_5NO^{37}Cl_2$.

6-Chloro-3-[(dimethylamino)methylene]-1-formyloxindole (9a): Yield: 1.26 g (40%). M.p. 158−160 °C. IR: $\tilde{\nu}$ = 3120, 3005, 2965, 2799, 1703, 1685, 1589, 1346, 1113, 1089, 950, 836, 806, 773, 641 cm^{-1}. ^{1}H NMR: δ = 9.22 (s, 1 H, C*H*), 7.93 (s, 1 H, C*H*), 7.88 (d, *J* = 1.8Hz, 1 H, C*H*), 7.44 (d, *J* = 8.3 Hz, 1 H, C*H*), 7.16 (dd, *J* = 8.3, 1.8 Hz, 1 H, C*H*), 3.58 (s, 3 H, CH_3), 3.37 (s, 3 H, CH_3) ppm. ^{13}C NMR: δ = 162.8 (s), 160.1 (d), 151.9 (d), 131.2 (s), 128.2 (s), 126.2 (s), 123.7 (d), 116.1 (d), 112.8 (d), 88.9 (s), 47.1 (q), 42.9 (q) ppm. MS (ESI): *m*/*z* = 251 [M + H]$^+$ $C_{12}H_{10}N_2O_2{}^{35}Cl$, 253 [M + H]$^+$ $C_{12}H_{10}N_2O_2{}^{37}Cl$.

2,5-Dichloro-3-formylindole (6b): Yield: 1.20 g (45%). M.p. 266−267 °C. IR: $\tilde{\nu}$ = 3111, 2900, 2831, 1631, 1434, 1369, 1218, 1109, 850, 805, 742, 682 cm^{-1}. ^{1}H NMR: δ = 7.30 (dd, *J* = 8.5, 2.1 Hz, 1 H, Ar*H*), 7.44 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.02 (d, *J* = 2.1 Hz, 1 H, Ar*H*), 9.97 (s, 1 H, C*H*), 13.29 (br. s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 111.6 (s), 113.5 (d), 119.0 (d), 123.9 (d), 125.4 (s), 127.5 (s), 133.1 (s), 135.7 (s), 183.4 (d) ppm. MS (ESI): *m*/*z* = 212 [M − H]$^-$ $C_9H_5NO^{35}Cl_2$, 214 [M − H]$^-$ $C_9H_5NO^{35}Cl\ ^{37}Cl$, 216 [M − H]$^-$ $C_9H_5NO^{37}Cl_2$. $C_9H_5NOCl_2$ (214.1): calcd. C 50.50, H 2.35, N 6.54; found C 50.63, H 2.41, N 6.42.

5-Chloro-3-[(dimethylamino)methylene]-1-formyloxindole (9b): Yield: 0.60 g (19%). M.p. 202−204 °C [ref.[10b] m.p. 194−198 °C]. IR: $\tilde{\nu}$ = 3034, 2927, 2901, 2803, 1697, 1681, 1613, 1589, 1389, 1139, 798, 783, 761, 666 cm^{-1}. ^{1}H NMR: δ = 9.20 (s, 1 H, C*H*), 7.94 (s, 1 H, C*H*), 7.82 (d, *J* = 8.4 Hz, 1 H, C*H*), 7.52 (d, *J* = 1.8 Hz, 1 H, C*H*), 7.00 (dd, *J* = 8.4, 1.8 Hz, 1 H, C*H*), 3.59 (s, 3 H, CH_3), 3.37 (s, 3 H, CH_3) ppm. ^{13}C NMR: δ = 163.0 (s), 159.9 (d), 152.2 (d), 131.5 (s), 129.2 (s), 128.7 (s), 121.6 (d), 114.8 (d), 114.2 (d), 88.8 (s), 47.2 (q), 42.9 (q) ppm.

General Procedure for the Synthesis of Dichloroindole-3-carbaldehydes 6a−b from Chloro-3-[(dimethylamino)methylene]oxindoles 9a−b: A mixture of the appropriate chloro-3-[(dimethylamino)methylene]-1-formyloxindole (0.445 g; 1.78 mmol) and $POCl_3$ (1.533 g; 10 mmol) was heated at 100 °C for 30 min. Ice-water (50 mL) was added to the reaction mixture, which was then stirred for 1 h then extracted with ethyl acetate. The organic phase was washed with $NaHCO_3$ (sat.), brine, and dried with Na_2SO_4. The solvent was removed at reduced pressure to give a solid, which was purified by column chromatography on silica gel eluting with ethyl acetate/hexane, 1:1.

2,6-Dichloro-3-formylindole (6a): Yield: 0.325 g (85%). M.p. 240−241 °C [ref.[8] m.p. 238−239 °C].

2,5-Dichloro-3-formylindole (6b): Yield: 0.308 g (81%). M.p. 266−267 °C.

Synthesis of 11a−b. General Procedure: DMAP (0.024 g, 0.1 equiv.) was added to a reaction mixture containing Boc_2O (0.655 g, 3.0 mmol) and the appropriate dichloro-3-formylindole (0.428 g; 2.0 mmol) in THF (10 mL) at 0 °C and then stirred at 0 °C for 90 min. The solvent was removed under reduced pressure, and the resulting precipitate was dissolved in ethyl acetate and washed with HCl (1M), $NaHCO_3$ (sat.) and brine. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. White needles were obtained by recrystallisation from 2-propanol.

1-(*tert*-Butoxycarbonyl)-2,6-dichloroindole-3-carboxaldehyde (11a): Yield: 0.395 g (63%). M.p. 127−128 °C. IR: $\tilde{\nu}$ = 3009, 2979, 1759, 1664, 1304, 1139, 1112, 836, 817, 758 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 9 H, CH_3), 7.34 (dd, *J* = 8.5, 1.8 Hz, 1 H, Ar*H*), 8.11

(d, J = 1.8 Hz, 1 H, Ar*H*), 8.20 (d J = 8.5 Hz, 1 H,, Ar*H*), 10.24 (s, 1 H, C*H*) ppm. ^{13}C NMR ($CDCl_3$) δ = 28.0 (q), 87.4 (s), 115.2 (d), 117.2 (s), 121.9 (d), 122.9 (s), 125.6 (d), 131.9 (s), 135.5 (s), 135.7 (s), 147.6 (s), 185.4 (d) ppm. MS (ESI): m/z = 314 $[M + H]^+$, $C_{14}H_{13}NO_3{}^{35}Cl_2$, 316 $[M + H]^+$ $C_{14}H_{13}NO_3{}^{35}Cl\ {}^{37}Cl$, 318 $[M + H]^+$ $C_{14}H_{13}NO_3{}^{37}Cl_2$. $C_{14}H_{13}NO_3Cl_2$ (314.2): calcd. C 53.52, H 4.17, N 4.46; found C 53.61, H 4.23, N 4.32.

1-(*tert*-Butoxycarbonyl)-2,5-dichloroindole-3-carboxaldehyde (11b): Yield: 0.415 g (66%). M.p. 143−144 °C. IR: $\tilde{\nu}$ = 3113, 2973, 1751, 1662, 1441, 1302, 1121, 1068, 1013, 874, 818, 799, 728 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.73 (s, 9 H, CH_3), 7.33 (dd, J = 9.0, 2.0 Hz, 1 H, Ar*H*), 7.97 (d, J = 9.0 Hz, 1 H, Ar*H*), 8.28 (d, J = 2.0 Hz, 1 H, Ar*H*), 10.21 (s, 1 H, C*H*) ppm. ^{13}C NMR ($CDCl_3$) δ = 28.0 (q), 87.3 (s), 115.9 (d), 116.6 (s), 120.5 (d), 125.3 (s), 126.0 (d), 130.8 (s), 133.4 (s), 136.1 (s), 147.5 (s), 185.1 (d) ppm. MS (ESI): m/z = 314 $[M + H]^+$, $C_{14}H_{13}NO_3{}^{35}Cl_2$, 316 $[M + H]^+$ $C_{14}H_{13}NO_3{}^{35}Cl\ {}^{37}Cl$, 318 $[M + H]^+$ $C_{14}H_{13}NO_3{}^{37}Cl_2$. $C_{14}H_{13}NO_3Cl_2$ (314.2): calcd. C 53.52, H 4.17, N 4.46; found C 53.44, H 4.25, N 4.39.

Synthesis of 1a−c. General Procedure: A mixture of **11a−c** (4.0 mmol), 2-mercaptoacetamide (0.40 g; 4.4 mmol), K_2CO_3 (0.61 g; 4.4 mmol) and methanol (16 mL) was refluxed for 16 h. Thereafter, the reaction mixture was allowed to cool to room temperature and poured into water (160 mL). The resulting precipitate was collected by filtration, washed with water and dried.

6-Chlorothieno[2,3-*b*]indole-2-carboxamide (Thienodoline, 1a): Yield: 0.210 g [84%, (1/4 scale)]. M.p. 311−312 °C [ref.[2] m.p. 249−250 °C]. IR: $\tilde{\nu}$ = 3457, 3307, 3174, 1644, 1581, 1510, 1490, 1394, 1373, 1244, 1087, 1064, 871, 804 cm^{-1}. ^{1}H NMR: δ = 7.16 (d, J = 8.4 Hz, 1 H, Ar*H*), 7.30 (br. s, 1 H, N*H*), 7.58 (s, 1 H, Ar*H*), 7.76 (d, J = 8.4 Hz, 1 H, Ar*H*), 7.93 (br. s, 1 H, N*H*), 8.12 (s, 1 H, C*H*), 11.93 (br. s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 111.7 (d), 119.7 (d), 119.9(d), 120.0 (d), 120.5 (s), 123.4 (s), 127.1 (s), 132.4 (s), 142.2 (s), 145.0 (s), 164.2 (s) ppm. MS (ESI): m/z = 251 $[M + H]^+$ $C_{11}H_7N_2OS^{35}Cl$, 253 $[M + H]^+$ $C_{11}H_7N_2OS^{37}Cl$.

5-Chlorothieno[2,3-*b*]indole-2-carboxamide (1b): Yield: 0.224 g [89%, (1/4 scale)]. M.p. 289−290 °C. IR: $\tilde{\nu}$ = 3489, 3432, 3372, 3155, 1660, 1598, 1445, 1417, 1387, 1246, 752, 736 cm^{-1}. ^{1}H NMR: δ = 7.23 (d, J = 8.6 Hz, 1 H, Ar*H*), 7.25 (br. s, 1 H, N*H*), 7.51 (d, J = 8.6 Hz, 1 H, Ar*H*), 7.80 (s, 1 H, Ar*H*), 7.94 (br. s, 1 H, N*H*), 8.10 (s, 1 H, C*H*), 11.98 (br. s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 113.3 (d), 118.3 (d), 120.0 (d), 122.4 (d), 122.8 (s), 123.0 (s), 124.1 (s), 132.3 (s), 140.3 (s), 145.5 (s), 164.2 (s) ppm. MS (ESI): m/z = 251 $[M + H]^+$ $C_{11}H_7N_2OS^{35}Cl$, 253 $[M + H]^+$ $C_{11}H_7N_2OS^{37}Cl$. $C_{11}H_7N_2OSCl$ (250.7): calcd. C 52.70, H 2.81, N 11.17; found C 52.61, H 2.88, N 11.03.

Thieno[2,3-*b*]indole-2-carboxamide (1c): Yield: 0.67 g (78%). M.p. 290−291 °C (dec.). IR: $\tilde{\nu}$ = 3366, 3179, 1640, 1595, 1515, 1419, 1400, 1247, 743 cm^{-1}. ^{1}H NMR: δ = 7.14 (t, J = 7.65 Hz, 1 H, Ar*H*), 7.20 (m, 2 H, Ar*H*), 7.49 (d, J = 8.1 Hz, 1 H, Ar*H*), 7.75 (d, J = 7.65 Hz, 1 H, Ar*H*), 7.89 (br. s, 1 H, N*H*), 8.13 (s, 1 H, Ar*H*), 11.83 (s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 111.9 (d), 118.8 (d), 119.6 (d), 120.1 (d), 121.7 (s), 122.6 (d), 123.7 (s), 131.5 (s), 141.9 (s), 144.3 (s), 164.3 (s) ppm. MS (ESI): m/z = 217 $[M + H]^+$. $C_{11}H_8N_2OS$ (216.3): calcd. C 61.09, H 3.73, N 12.95; found C 61.02, H 3.88, N 12.87.

Synthesis of Thieno[2,3-*b*]indole-2-carboxamide (1c) from 5: Compound **5** (0.120 g, 0.52 mmol) and methanol saturated with ammonia (at 0 °C) were heated in a sealed tube at 80 °C for 6 days. The solvent was removed under reduced pressure and the solid was purified by chromatography on silica gel eluting with ethyl acetate/hexane, 1:1 then ethyl acetate, 100%. Yield: 30 mg (27%); M.p. 291−292 °C (dec.).

[1] K. Kanbe, H. Naganawa, M. Okamura, Y. Okami, T. Takeuchi, S. Hattori, M. Hamada, *Biosci. Biotech. Biochem.* **1993**, *57*, 632−635.

[2] K. Kanbe, H. Naganawa, T. Nakamura, Y. Okami, T. Takeuchi, *Biosci. Biotech. Biochem.* **1993**, *57*, 636−637.

[3] J. Levy, D. Royer, J. Guilhem, M. Cesario, C. Pascard, *Bull. Soc. Chim. France* **1987**, 193−198.

[4] G. Kobayashi, Y. Matsuda, Japanese Patent 47036757 B4, 1972, *Chem. Abstr.* **1972**, *77*, 140005.

[5] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, *Yakuguku Zasshi* **1969**, *89*, 58−63.

[6] [6a] P. Olesen, J. Hansen, M. Engelstoft, *J. Heterocycl. Chem.* **1995**, *32*, 1641−1642. [6b] P. Jakobsen, A. Kanstrup, P. Faarup, P. Olesen, J. Lundbech, (Novo Nordisk A/S, Den.), US. Pat. 5536721, **1998** [*Chem. Abstr.* **1998**, *129*, 148909]. [6c] P. Jakobsen, A. Kanstrup, P. Faarup, P. Olesen, (Novo Nordisk A/S, Den.), WO. Pat. 9525110, **1995** [*Chem. Abstr.* **1995**, *124*, 117290].

[7] V. Velezheva, A. Lepeshkin, O. Fedotova, V. Shvedov, K. Turchin, A. Sedov, O. Anisimova, *Pharm. Chem. J. (Engl. Transl.)* **1996**, *30*, 643−647.

[8] M. Acheson, P. Hunt, D. Littlewood, B. Murrer, H. Rosenberg, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1117−1125.

[9] [9a] U. Stoess, PhD thesis, Münster, **1967**. [9b]K. Shulze, J. Reisch, U. Stoess, *Arch. Pharm. (Weinheim, Ger.)* **1972**, *305*, 523−533. [9c] H. Showalter, A. Sercel, B. Leja, C. Wolfangel, L. Ambroso, W. Elliott, D. Fry, A. Kraker, C. Howard, G. Lu, C. Moore, J. Nelson, B. Roberts, P. Vincent, W. Denny, A. Thompson, *J. Med. Chem.* **1993**, *40*, 413−426.

[10] [10a] S. Seshadri, M. Sardessai, A. Betrabet, *Indian J. Chem.* **1969**, *7*, 662−666. [10b] G. Hardtmann (Sandoz AG), Ger. Pat. 2338668, **1974** [*Chem. Abstr.* **1974**, *80*, 133063].

[11] R. Sarges, H. Howard, K. Koe, A. Weissman, *J. Med. Chem.* **1989**, *32*, 437−444.

[12] J. Smitrovich, I. Davies, *Org. Lett.* **2004**, *6*, 533−535.

[13] P. Kutschy, M. Suchy, A. Andreani, M. Dzurilla, V. Kovacik, J. Alfoeldi, M. Rossi, M. Gramatova, *Tetrahedron* **2002**, *58*, 9029−9040.

[14] S. Kadin (Pfizer Inc.), US. Pat. 4569942, **1986** [*Chem. Abstr.* **1986**, *105*, 42644].

[15] E. Kraynack, J. Dalgard, F. Gaeta, *Tetrahedron Lett.* **1998**, *39*, 7679−7682.

[16] W. Ried, D. Kuhnt, *Liebigs Ann. Chem.* **1986**, 780−784.

Received February 4, 2004

