A Novel Smiles Rearrangement Gives Access to the A-Ring Pyridine Isomers of the Nevirapine Ring System†

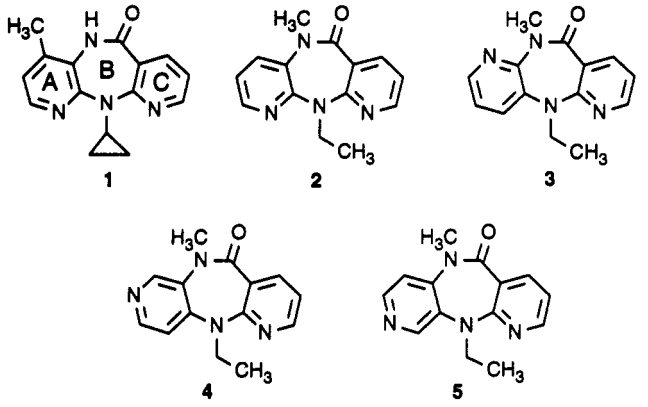
John R. Proudfoot,* Usha R. Patel, and Scot J. Campbell

Research and Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877

Received June 2, 1993•

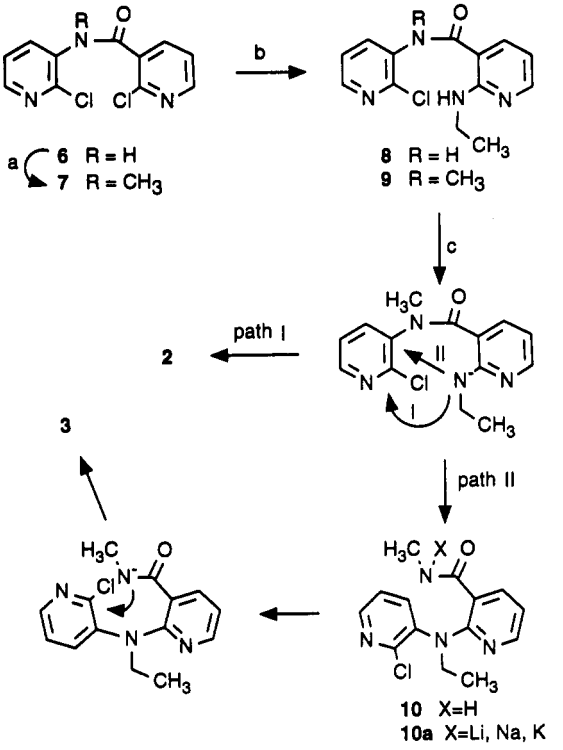
The cyclization of *N*-methylamide **9** gives, along with the expected product **2**, the isomeric diazepinone **3** resulting from a novel Smiles rearrangement in which an *N*-methylcarboxamide functions as a leaving group. The mechanism of the reaction has been proven by isolation of the intermediate **10** and by conducting the rearrangement on the model compound **13**. The relative amounts of **2**, **3**, and **10** formed from **9** are subject to some control by variation of the base and reaction temperature (Table I). This new Smiles rearrangement was applied to the synthesis of the remaining two A-ring isomers **4** and **5** of the nevirapine ring system **1** by cyclization of the thioether **16** and the sulfoxide **17**.

During the course of the synthetic program which led to the discovery and development of the HIV-1 reverse transcriptase (RT) inhibitor nevirapine **1**[1,2] we were interested in obtaining the diazepinones **3–5** in order to define the optimal ring system for anti RT activity. The



diazepinone **2** has been previously described,[2] and it was in examining a modified route to this compound that we made an observation which allowed us to access the isomers **3–5**. Previously, **2** had been obtained by cyclization of the dianion of **8** followed by *N*-methylation of the tricyclic product[2] (Scheme I). Because only monoanion formation is required, we reasoned that the *N*-methylamide **9** should cyclize more readily than **8** and give direct access to **2**. Cyclization of **9** does indeed proceed under milder conditions (rt in THF vs pyridine under reflux for the cyclization of **8**) but an unexpected Smiles rearrangement intervenes giving access to the isomeric diazepinone **3**. Here, we demonstrate the intermediacy of this Smiles rearrangement in the formation of **3**, show how variation of the reaction conditions affects the product distribution,

Scheme I[a]



[a] Key: (a) NaH, DMSO, MeI, rt; (b) $EtNH_2$, xylene, 150 °C (pressure tube), overall a, b, 92%; (c) see Table I.

and apply the reaction to the synthesis of the remaining two A-ring isomers, **4** and **5**, of the nevirapine ring system.

The *N*-methylamide **9** was synthesized from **6**[2] as shown in Scheme I. Cyclization of **9** (KO-*t*-Bu, THF, rt, 5 min) gave two isomeric tricyclic compounds. One was assigned structure **2** on the basis of a strong NOE observed from the amide methyl group to H-4 (Figure 1) and by comparison with authentic material (NMR, TLC) prepared by the dianion route above.[2] The second compound exhibited a strong NOE from the CH_2 group to H-4 and was assigned structure **3**. We rationalized its formation as shown in Scheme I. A Smiles rearrangement,[3] involving attack of the 2′-nitrogen anion on the 3-position of the pyridine A-ring with displacement of the carboxamide

† Dedicated to Professor Carl Djerassi on the occasion of his 70th birthday.

• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

(1) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. *Science* **1990**, *250*, 1411.

(2) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231.

(3) For a review of the Smiles rearrangement, see: Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99.

0022-3263/93/1958-6996$04.00/0

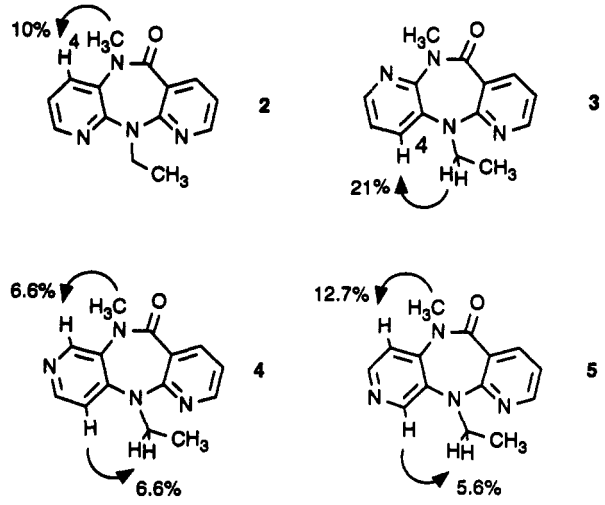
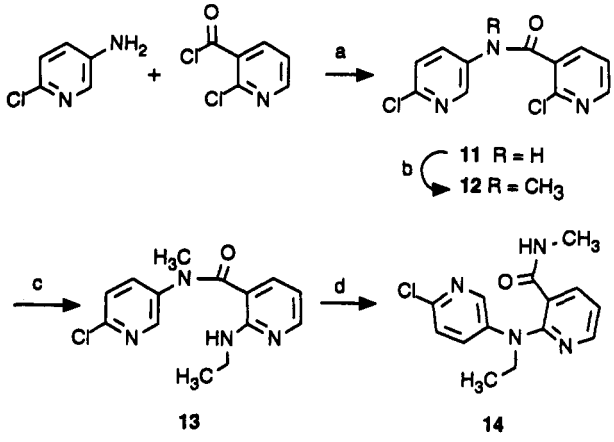


Figure 1. NOE's observed for **2–5**.

Scheme II[a]



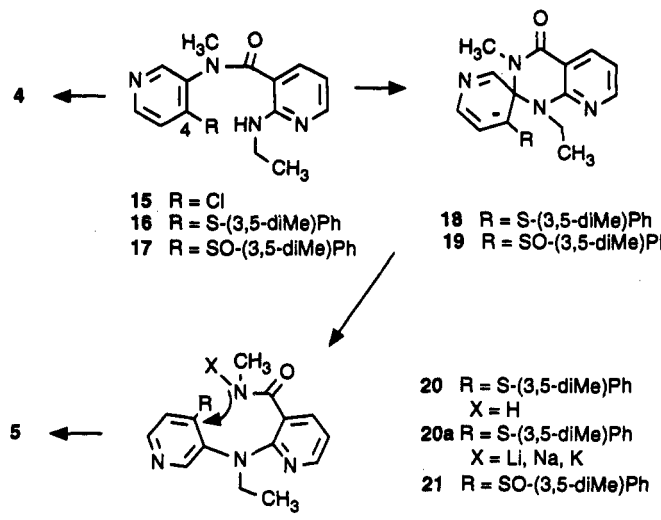
[a] Key: (a) $CHCl_3$/EtOAc, rt, 99%; (b) NaH, DMSO, MeI, rt, 82%; (c) $EtNH_2$, *i*-Pr_2EtN, xylene, 150 °C, pressure tube, 67%; (d) NaHMDS, THF, rt, 5 min, 92%.

anion[4] (path II), competes with direct ring closure (path I) in the first step. Subsequent closure of the carboxamide anion onto the 2-position of ring A gives the tricyclic compound **3**, isomeric with the anticipated product **2**.

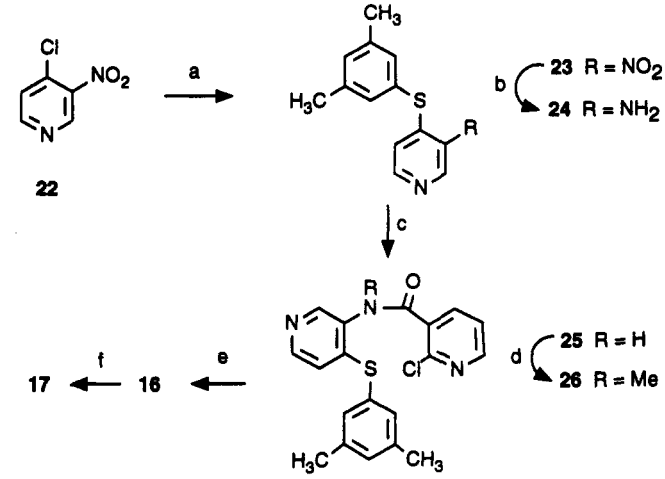
The intermediacy of the Smiles rearrangement was proven in two ways. We synthesized the amide **13** (Scheme II) which can only undergo the rearrangement and not the subsequent cyclization reaction. As expected, the Smiles product **14** was obtained (92% yield) on treatment with NaHMDS in THF at rt. In a separate study aimed at isolating the intermediate **10** we examined various conditions for the rearrangement reaction (Table I). Upon deprotonation of **9** with LHMDS at low temperature the reaction proceeded only through the Smiles rearrangement, and we isolated **10** in 76% yield (Table I, entry 2). Deprotonation of **10** at rt resulted in cyclization to **3** (Table I, entry 6), supporting the sequence shown in Scheme I. Interestingly, compound **2** was also isolated from this reaction indicating that the initial rearrangement is a reversible process. When NaHMDS or potassium *tert*-butoxide was used to deprotonate **9** increasing amounts of the normal cyclization product **2** were seen relative to products resulting from the Smiles process (**3** + **10**).

(4) For an example of a carboxamide acting as a leaving group in a Smiles rearrangement, see: Fukazawa, Y.; Kato, N., Ito, S. *Tetrahedron Lett.* **1982**, *23*, 437.

Scheme III



Scheme IV[a]



[a] Key: (a) 3,5-dimethylthiophenol, *i*-Pr_2EtN, dioxane, rt, 98%; (b) $SnCl_2 \cdot 2H_2O$, acetic acid, (concd HCl, 95%; (c) 2-chloronicotinoyl chloride, *i*-Pr_2EtN, EtOAc, rt, 66%; (d) KO-*t*-Bu, DMSO, MeI, rt, 88%; (e) $EtNH_2$, dioxane 140 °C, 5 h, pressure tube, 94%; (f) $NaIO_4$, $MeOH/H_2O$, rt, 17 days, 43% (recovered **16**, 48%).

Coordination of the counterion to the amide group may play a role in activating it toward displacement since Li > Na > K, the relative coordination abilities, follows the trend of relative amounts of rearrangement product seen.

Having demonstrated the usefulness of the Smiles rearrangement in accessing the isomer **3** we were interested in applying the same strategy to obtain the remaining two A-ring isomers **4** and **5**. By analogy with Scheme I above they should be accessible from an intermediate such as **15** (Scheme III). Direct displacement of the 4-substituent of **15** would give isomer **4** while a Smiles rearrangement followed by ring closure would give isomer **5** (Scheme III).

Rather than the 4-chloro derivative **15**, which would correspond to the precursor **9** used in the synthesis of **2** and **3**, the 4-arylthio compound **16** was chosen as the key intermediate for the following reasons: (1) the greater reactivity of the chloro substituent in the 4-position[5] of the pyridine ring in **15** relative to the 2-position halogen of **9** could result in normal ring closure exclusively, (2) the sulfur atom can stabilize the α-carbanion in the depiction **18** of the transition state and favor the rearrangement,

(5) Kolder, C. R.; Den Hertog, H. J. *Rec. Trav. Chim.* **1953**, *72*, 285.

Table I. Summary of Smiles Rearrangement and Cyclization Reactions

entry	starting material	base/solvent	temp (°C)	time		products[a] (%)		
1	9	LHMDS/THF	rt	30 min		2 (20)	3 (39)	10 (34)
2	9	LHMDS/THF	−10	2 h	9 (5)	2 (17)		10 (76)
3	9	NaHMDS/THF	rt	30 min		2 (41)	3 (48)	10 (8)
4	9	NaH/xylene	155	35 min		2 (51)	3 (32)	
5	9	KO-*t*-Bu/THF	rt	5 min	9 (11)	2 (54)	3 (22)	
6	10	LHMDS/THF	rt	4 h		2 (5)	3 (78)	12 (10)
7	13	NaHMDS/THF	rt	5 min	14 (92)			
8	16	NaH/xylene	155	5 h		4 (50)	5 (21)	
9	16	LHMDS/toluene	rt	24 h		4 (58)		20 (9)
10	16	NaHMDS/THF	−20	48 h		4 (75)		20 (8)
11	16	KHMDS/toluene	−20	120 h		4 (47)		20 (24)
12	16	KHMDS/benzene	rt	1 h		4 (55)		20 (28)
13	17	KHMDS/benzene	rt	3 h		4 (39)[b]	5 (39)[b]	
14	17	LHMDS/THF	5	3 h		4 (<5)	5 (79)	

[a] Isolated yields. [b] 78% yield of a 1:1 mixture of 4 and 5 by NMR. Mixture was not fractionated.

and (3) an examination of the effect of sulfur oxidation state on the rearrangement reaction is possible, i.e., a comparison of the reactivity of 16 vs 17.

The intermediate 16 was synthesized as shown in Scheme IV starting from 4-chloro-3-nitropyridine.[6] The results of our experiments on thioether 16 are summarized in Table I (entries 8–12). We obtained 5, the product of a Smiles rearrangement followed by ring closure, in only one instance (Table I, entry 8) and as the minor product. The structures of the isomers 4 and 5 were proven unambiguously by NOE experiments (Figure 1). Various milder reaction conditions (Table I, entries 9–12) gave exclusively 4, the product of normal ring closure. None of the isomer 5 was detected in these experiments. However, we isolated intermediate 20 from these reactions and concluded that the amide anion of 20a is not sufficiently nucleophilic to displace the arylthio group under the milder conditions which favor the Smiles rearrangement. We therefore did not examine the reaction of 16 further.

As the thioether 16 was not a useful precursor of 5, the sulfoxide 17, with a potentially better leaving group, was next examined. This compound, upon deprotonation with LHMDS in THF, underwent a clean rearrangement/cyclization to give 5 in excellent yield (Table I, entry 14). Only a trace (<5%) of 4 was visible in the NMR spectrum of the crude reaction product, and pure material was readily obtained by preparative-layer chromatography. When KHMDS (Table I, entry 13) was used for the deprotonation a 1:1 mixture of the isomers was formed, consistent with the counterion effect we had noted above in the cyclization of 9. In the cyclization of 16 and 17 the product formed depends on the oxidation state of the sulfur atom in the precursor. We had thought that leaving group ability would control the reaction course, but it is clear in comparing the depictions 18 and 19 of the transition state that the sulfoxide is a more effecient stabilizer of the α-carbanion than the sulfide and that this difference is the source of the selectivity seen in the cyclization of 17.

In conclusion, the isomers 3 and 5 of the nevirapine ring system are accessible, via a novel Smiles rearrangement, from precursors which also lead to the expected products 2 and 4. The reaction course is influenced by counterion and, in the case of 16 and 17, by the oxidation state of the leaving group. Additionally, the Smiles rearrangements shown here occur at the 3-position of the pyridine ring system, a position which is relatively unactivated toward nucleophilic attack. We are currently exploring the generality of this chemistry and are applying it to the synthesis of substituted analogs of 3 and 5.

(6) Bishop, R. R.; Cavell, E. A. S.; Chapman, N. B. *J. Chem. Soc.* **1952**, 437.

Experimental Details

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer with tetramethylsilane as an internal standard; *J* values are given in Hz. Mass spectra were recorded on a Finnegan 4023 GC/MS/DS spectrometer. Solutions of LHMDS, NaHMDS, and potassium *tert*-butoxide in tetrahydrofuran were purchased from Aldrich Chemical Co. and used as received. Preparative layer chromatography was performed on Analtech Uniplate precoated plates (silica gel GF, 2000 μm). Elemental analyses were determined by Midwest Laboratories, Indianapolis, IN.

***N*-(2′-Chloro-3′-pyridinyl)-2-(ethylamino)-*N*-methylpyridine-3-carboxamide (9).** To a solution of 2-chloro-*N*-(2′-chloro-3′-pyridinyl)-3-pyridinecarboxamide (6)[2] (5.36 g, 19.0 mmol) in DMSO (15 mL) was added NaH (50 % in oil, 1.05 g, 21.9 mmol), and the mixture was stirred at rt until hydrogen evolution ceased (~20 min). Methyl iodide (3.2 g, 22.6 mmol) was added all at once, and the mixture was stirred for 20 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed, dried, and evaporated to give *N*-methylamide 7[2] which was used directly in the next reaction. The product 7 was dissolved in xylene (5 mL) and ethylamine (2.1 g, 46.7 mmol) added. The mixture was sealed in a pressure tube and heated at 150 °C for 5 h. The reaction mixture was cooled to rt, diluted with ethyl acetate, washed with water, dried, filtered, and evaporated. The residue was fractionated on silica gel (eluent ethyl acetate/hexane) to give 9 (5.1 g, 17.6 mmol, 92%): mp 87–89 °C (isopropyl ether); ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, dd 2, 5), 8.02 (1H, dd 2, 5), 7.43 (1H, dd 2, 8), 7.18 (1H, dd 5, 8), 6.99 (1H, dd 8, 2), 6.33 (1H, br, NH), 6.20 (1H, dd 5, 8), 3.46 (2H, m), 3.38 (3H, s), 1.26 (3H, t 7); MS(EI) 290 ($M^{\cdot+}$, 23), 149 (100). Anal. Calcd for $C_{15}H_{14}N_4OCl$: C, 57.83; H, 5.20; N, 19.27. Found: C, 57.91; H, 5.23; N, 19.25.

Typical Procedure for the Cyclization of 9. To a solution of 9 (81.3 mg, 0.28 mmol) in THF (1 mL) at rt under N_2 was added LHMDS (1.0 M in THF, 0.45 mL). The mixture was stirred at rt for 30 min. The reaction was quenched with ethanol, the solvents were evaporated and the residue was fractionated directly by preparative layer chromatography (developer ethyl acetate/hexane (1/3), six developments) to give, in order of increasing polarity, 3 (27.9 mg, 39%) [mp 159–161 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, dd, *J* = 2, 5), 8.22 (1H, dd, *J* = 2, 5), 8.11 (1H, dd, *J* = 2, 8), 7.47 (1H, dd, *J* = 2, 8), 7.12 (1H, dd, *J* = 5, 8), 7.02 (1H, dd, *J*, 5, 8), 3.4–4.2 (2H, br, CH_2), 3.62 (3H, s), 1.24 (3H, t, *J* = 7); MS(CI) 255 (M + H^+). Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.99; H, 5.40; N, 21.92], 2[2] (14.5 mg, 20%) [mp 130–132 °C (lit.[2] mp 130–132 °C) (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, dd, *J* = 2, 5), 8.21 (1H, dd, *J* = 2, 5), 8.10 (1H, dd, *J* = 2, 8), 7.49 (1H, dd, *J*

= 2, 8), 7.09 (1H, dd, J = 5, 8), 7.00 (1H, dd, J = 5, 8), 4.2 (2H, q, J = 7), 3.51 (3H, s), 1.26 (3H, t, J = 7)], and **10** (28.2 mg, 34%). Characterization of **10** is described below.

2-[*N*-(2′-Chloro-3′-pyridinyl)-*N*-ethylamino]-*N*-methylpyridine-3-carboxamide (10). To a solution of the amide **9** (0.151 g, 0.52 mmol) in THF (2 mL) cooled under nitrogen to −30 °C (external temperature) was added dropwise LHMDS (1.0 M in THF, 0.8 mL). The mixture was allowed to warm to −10 °C (external temperature) and maintained there for 2 h. The reaction was quenched by the addition of water (1 mL), diluted with ethyl acetate (30 mL), and washed with water (5 mL). The aqueous phase was separated and extracted with a further quantity of ethyl acetate (30 mL), and the combined organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was triturated with isopropyl ether to give **10** as a solid which was recrystallized from isopropyl ether (83 mg): mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, dd, J = 2, 5), 8.20 (1H, dd, J = 2, 5), 7.91 (1H, dd, J = 2, 7), 7.31 (1H, dd, J = 2, 8), 7.19 (1H, dd, J = 5, 8), 7.02 (1H, dd, J = 5, 7), 6.66 (1H, br, NH), 3.92 (2H, q, J = 7), 2.67 (3H, d, J = 5), 1.25 (3H, t, J = 7); MS(CI) 291 (M + H$^+$). Anal. Calcd for $C_{14}H_{15}N_4OCl$: C, 57.83; H, 5.20; N, 19.27; Cl, 12.19. Found: C, 57.91; H, 5.10; N, 19.21; Cl, 12.44. Fractionation of the combined supernatent from the solid and the crystals by preparative-layer chromatography (developer ethyl acetate/hexane) gave a further 32 mg of **10**, 7 mg of starting material **9**, and 23 mg of **2**. Total yield of **10**, 115 mg, 76%.

2-Chloro-*N*-(2′-chloro-5′-pyridinyl)pyridine-3-carboxamide (11). To a solution of 5-amino-2-chloropyridine (1.4 g, 10.9 mmol) in chloroform/ethyl acetate (1:2, 30 mL) was added 2-chloronicotinoyl chloride (2.2 g, 12.6 mmol). The mixture was stirred at rt overnight, diluted with chloroform, washed with saturated, $NaHCO_3$, dried, filtered, and evaporated to give **11** (2.9 g, 10.8 mmol, 99%): mp 165–167 °C (EtOAC/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 11.05 (1H, s, NH), 8.71 (1H, d, J = 2.7), 8.57 (1H, dd, J = 2.0, 4.8), 8.19 (1H, dd, J = 2.7, 8.6), 8.14 (1H, dd, J = −2.0, 7.7), 7.60 (1H, dd, J = 4.8, 7.7), 7.56 (1H, d, J = 8.6); MS(CI) 268 (M + H$^+$). Anal. Calcd for $C_{11}H_7N_3OCl_2$: C, 49.28; H, 2.63; N, 15.67; Cl, 26.45. Found: C, 49.37; H, 2.51; N, 15.53; Cl, 26.23.

2-Chloro-*N*-(2′-chloro-5′-pyridinyl)-*N*-methylpyridine-3-carboxamide (12). To a solution of the amide **11** (2.55 g, 9.6 mmol) in DMSO (20 mL) was added NaH (50% in oil, 0.46 g, 9.6 mmol). The mixture was stirred at rt for 30 min, and methyl iodide (0.7 mL, 11.2 mmol) was added all at once. After 1 h the mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed, dried, filtered, and evaporated. Fractionation of the residue on silica gel (eluent ethyl acetate/hexane) gave **12** (2.2 g, 82%): mp 110–112 °C; ^{1}H NMR (DMSO-d_6) (mixture of conformers, data given for the major one) δ 8.33 (2H, m), 8.02 (1H, dd, J = 3, 8), 7.86 (1H, dd, J = 3, 9), 7.48 (1H, d, J = 9), 7.41 (1H, dd, J = 5, 8), 3.41 (3H, s); MS(CI) 282 (M + H$^+$). Anal. Calcd for $C_{12}H_9N_3OCl_2$: C, 51.09; H, 3.22; N, 14.89; Cl, 25.13. Found: C, 51.00; H, 2.99; N, 14.83; Cl, 25.28.

***N*-(2′-Chloro-5′-pyridinyl)-*N*-methyl-2-(ethylamino)pyridine-3-carboxamide (13).** A mixture of **12** (1.0 g, 3.6 mmol), ethylamine (0.24 g, 5.3 mmol), and diisopropylethylamine (0.46 g, 3.6 mmol) in xylene (10 mL) was heated at 150 °C in a pressure tube for 4 h. The mixture was cooled, diluted with ethyl acetate, washed with water, dried, filtered, and evaporated. Fractionation of the residue over silica gel (eluent ethyl acetate/hexane) gave **13** (0.70 g, 2.4 mmol, 67%) as an oil: ^{1}H NMR (DMSO-d_6) δ 8.24 (1H, d, J = 3), 7.94 (1H, dd, J = 2, 5), 7.76 (1H, dd, J = 3, 8), 7.46 (1H, d, J = 7), 7.27 (1H, dd, J = 2, 7), 6.37 (2H, m), 3.34 (3H, s), 3.27 (2H, m), 1.18 (3H, t, J = 7); MS(CI) 291 (M + H$^+$). Anal. Calcd for $C_{14}H_{15}N_4OCl$: C, 57.83; H, 5.16; N, 19.27. Found: C, 57.69; H, 5.18; N, 19.00.

2-[*N*-(2′-Chloro-5′-pyridinyl)-*N*-ethylamino]-*N*-methylpyridine-3-carboxamide (14). To a solution of **13** (39 mg, 0.13 mmol) in THF (2 mL) at rt under nitrogen was added NaHMDS (1 M in THF, 0.25 mL). The mixture was stirred at rt for 5 min, and the reaction was then quenched with ethanol and evaporated to dryness. The residue was fractionated directly by preparative-layer chromatography (developer, ethyl acetate) to give **14** (36 mg, 92%): mp 146–148 °C; ^{1}H NMR (DMSO-d_6) δ 8.36 (1H, dd, J = 2, 5), 8.06 (1H, m, NH), 7.96 (1H, d, J = 3), 7.59 (1H, dd, J = 2, 7), 7.41 (1H, dd, J = 3, 8), 7.33 (1H, d, J = 8), 7.02 (1H, dd, J = 5, 7), 3.93 (2H, q, J = 7), 2.29 (3H, d, J = 5), 1.12 (3H, t, J = 7); MS(CI) 291 (M + H$^+$). Anal. Calcd for $C_{14}H_{15}N_4OCl$: C, 57.83; H, 5.16; N, 19.27; Cl, 12.19. Found: C, 57.89; H, 5.06; N, 19.32; N, 12.21.

4-[(3′,5′-Dimethylphenyl)thio]-3-nitropyridine (23). To a solution of 4-chloro-3-nitropyridine (**22**) (1.6 g, 10 mmol) in dioxane (10 mL) was added 3,5-dimethylthiophenol (1.0 mL, 7.4 mmol) followed by diisopropylethylamine (2.0 mL). The mixture was stirred under a drying tube for 2 h and then diluted with ethyl acetate, washed with water, and 2 N sodium hydroxide, dried over sodium sulfate, filtered, and evaporated. Fractionation of the residue over silica gel gave **15** (2.10 g, 7.2 mmol, 98%): mp 86–87 °C; ^{1}H NMR (DMSO-d_6) δ 9.29 (1H, s), 8.52 (1H, d, J = 6), 7.29 (3H, m), 6.76 (1H, d, J = 6), 2.34 (6H, s); MS(CI) 261 (M + H$^+$). Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 60.00; H, 4.65; N, 10.73. Found: C, 59.99; H, 4.79; N, 10.64.

3-Amino-4-[(3′,5′-dimethylphenyl)thio]pyridine (24). To a solution of **23** (1.99 g, 7.65 mmol) in acetic acid (11 mL) was added a solution of stannous chloride dihydrate (11.25 g, 50 mmol) in concd HCl. The mixture was stirred at rt for 4 h. The reaction mixture was poured cautiously into 10% sodium hydroxide (200 mL) which was extracted with chloroform (2 × 100 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated to give **24** (1.67 g, 7.26 mmol, 94.9%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, s), 7.91 (1H, d, J = 5), 7.02 (1H, d J = 5), 6.93 (3H, s), 4.10 (2H, br s), 2.28 (6H, s); MS(CI) 231 (M + H$^+$). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.50; H, 6.15; N, 12.00.

2-Chloro-*N*-[4′-[(3″,5″-dimethylphenyl)thio]-3′-pyridinyl]-pyridine-3-carboxamide (25). To a solution of **24** (1.302 g, 5.66 mmol) in ethyl acetate (30 mL) was added 2-chloronicotinoyl chloride (2.100 g, 12 mmol) and diisopropylethylamine (4 mL). The mixture was stirred overnight at rt. The reaction mixture was diluted with ethyl acetate, washed with water and saturated sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated. The residue was taken up in methanol (30 mL), and hydrazine hydrate (1 mL) was added.[7] After 30 min the product was separated by filtration to give **25** (1.203 g). The supernatent was evaporated and fractionated over silica gel (eluent, chloroform/ethyl acetate gradient) to give a further 0.169 g of product, total yield 1.372 g (3.72 mmol, 66%): mp 128–141 °C (from ethyl acetate as the monohydrate); ^{1}H NMR (DMSO-d_6) δ 10.60 (1H, br s), 8.57 (1H, dd, J = 2, 5), 8.49 (1H, s), 8.26 (1H, d, J = 5), 8.09 (1H, dd, J = 2, 8), 7.60 (1H, dd, J = 5, 8), 7.20 (3H, m), 6.74 (1H, d, J = 5), 2.31 (6H , s); MS(CI) 370 (M + H$^+$). Anal. Calcd for $C_{19}H_{16}N_3OSCl{\cdot}H_2O$: C, 58.84; H, 4.67; N, 10.83; Cl, 9.14; S, 8.25. Found: C, 58.47; H, 4.75; N, 10.98; Cl, 9.57; S, 8.66.

2-Chloro-*N*-[4′-[(3″,5″-dimethylphenyl)thio]-3′-pyridinyl]-*N*-methylpyridine-3-carboxamide (26). To a solution of **25** (1.196 g, 3.33 mmol) in DMSO (10 mL) stirred under N_2 was added potassium *tert*-butoxide (1 M in THF, 3.4 mL). After 3 min, methyl iodide (0.25 mL, 4 mmol) was added. After 15 min the reaction was diluted with ethyl acetate (100 mL), washed with water (5 × 25 mL), dried over sodium sulfate, filtered, and evaporated to give the product as an oil (1.121 g, 2.92 mmol, 88%) which solidified on standing: mp 173–174 °C (ethyl acetate/isopropyl ether); ^{1}H NMR ($CDCl_3$) δ 8.43 (1H, s), 8.30 (1H, dd, J = 2, 5), 8.09 (1H, d, J = 5), 7.91 (1H, dd, J = 2, 8), 7.14–7.09 (4H, complex), 6.49 (1H, d, J = 5), 3.49 (3H, s), 2.37 (6H, s); MS(CI) 384 (M + H$^+$). Anal. Calcd for $C_{20}H_{18}N_3OS$: C, 62.58; H, 4.73; N, 10.95; Cl; 9.24; S, 8.34. Found: C, 62.52; H, 4.74; N, 10.96; Cl, 9.49; S, 8.20.

2-(Ethylamino)-*N*-[4′-[(3″,5″-dimethylphenyl)thio]-3′-pyridinyl]-*N*-methylpyridine-3-carboxamide (16). A mixture of **26** (1.066 g, 2.78 mmol) and ethylamine (0.73 g, 16.6 mmol) in dioxane (10 mL) was sealed in a pressure tube and heated at 140 °C for 5 h. The reaction mixture was cooled, diluted with ethyl acetate, washed with water, dried over sodium sulfate, filtered, and evaporated to give crystalline product (1.126 g, 2.62 mmol, 94%): mp 165–167 °C (from Et_2O as the hemihydrate); ^{1}H NMR δ ($CDCl_3$) 8.16 (1H, s), 8.12 (1H, d, J = 5), 8.05 (1H, dd, J = 2, 5), 7.20 (1H, m), 7.12 (1H, br s), 7.05 (2H, br s), 6.58 (1H, d, J = 5), 6.49 (1H, br), 6.22 (1H, dd, J = 5, 8), 3.48 (2H, m) , 3.43

(7) Treatment of the reaction mixture with hydrazine hydrate converts any bis-acylated amine to the desired product **25**.

(3H, s), 2.35 (6H, s), 1.25 (3H, t, J = 7); MS(CI) 393 (M + H$^+$). Anal. Calcd for $C_{22}H_{24}N_4OS$·0.5H_2O: C, 65.82; H, 6.28; N, 13.96. Found: C, 66.22; H, 6.28; N, 13.63.

2-(Ethylamino)-*N*-[4′-[(3″,5″-dimethylphenyl)thio]-3′-pyridinyl]-*N*-methylpyridine-3-carboxamide *S*-Oxide (17). To a solution of **16** (0.197 g, 0.50 mol) in methanol (10 mL) was added a solution of sodium periodate (0.136 g, 0.64 mmol) in water (2 mL). The mixture was stirred at rt for 4 days. A further quantity of periodate (0.153 g, 0.72 mmol) in water (2 mL) was added, and stirring was continued for 13 days. The mixture was diluted with ethyl acetate, washed with water, dried over sodium sulfate, filtered, and evaporated. The residue was fractionated over silica gel (eluent, ethyl acetate/hexane gradient) to give recovered starting material (0.095 g, 0.24 mmol, 48%) followed by **17** (0.089 g, 0.22 mmol, 43%): mp 148–149 °C (ethyl acetate/isopropyl ether); MS(CI) 409 (M + H$^+$). Anal. Calcd for $C_{22}H_{24}N_4O_2S$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.51; H, 5.95; N, 13.56.

Typical Cyclization of the Thioether 16. To a solution of **16** (34.2 mg, 0.087 mmol) stirred in benzene (2 mL) under nitrogen at rt was added KHMDS (0.5 M in toluene, 0.20 mL, 0.10 mmol). The mixture was stirred at rt for 1 h, the reaction was then quenched with ethanol, and the solvents were evaporated. The residue was fractionated by preparative-layer chromatography (developer, ethyl acetate/hexane (9/1)) to give two compounds. The less polar (12.3 mg, 0.048 mmol, 55%) was identified as **4** (see NOE data, Figure 1): mp 159–161 °C (EtOAc/hex); ^{1}H NMR δ $CDCl_3$ 8.47 (1H, s), 8.37–8.32 (2H, overlapping d and dd), 8.12 (1H, dd, J = 2, 8), 7.08–7.03 (2H, overlapping d and dd), 4.25 (1H, br), 3.65 (1H, br), 3.60 (3H, s), 1.28 (3H, t, J = 7); MS(CI) 255 (M + H$^+$). Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.95; H, 5.48; N, 21.60. The more polar compound **20** was isolated as a glass which retained solvent on drying from ethyl acetate (9.7 mg, 0.025 mmol, 28%): ^{1}H NMR δ ($CDCl_3$) 8.38 (1H, dd, J = 2, 5), 8.04 (1H, d, J = 5), 7.99 (1H, s), 7.87 (1H, dd, J = 2, 7), 7.18 (2H, br s), 7.11 (1H, br s), 6.97 (1H, dd, J = 5, 7), 6.7 (1H, br, NH), 6.66 (1H, d, J = 5), 3.95 (2H, q, J = 7), 2.70 (3H, d, J = 5), 2.36 (6H, s), 1.30 (3H, t, J = 7); MS(CI) 393 (M + H$^+$). Anal. Calcd for $C_{22}H_{24}OS$·0.5$C_4H_8O_2$: C, 66.04; H, 6.47; N, 12.84. Found; C, 65.68; H, 6.33; N, 13.21.

Cyclization of the Sulfoxide 17. To a solution of **17** (22.5 mg, 0.055 mmol) in dry THF stirred under nitrogen and cooled on an ice bath was added LHMDS (1M in THF, 0.10 mL, 0.10 mmol). The mixture was left at 5 °C for 3 h. TLC showed complete consumption of starting material. Ethanol (0.25 mL) was added, and solvents were evaporated. The residue was filtered through a short silica plug (eluent, chloroform/ethyl acetate gradient) to give the product (>95:5 5:4 by NMR) (13.4 mg). Fractionation by preparative-layer chromatography (developer, ethyl acetate/hexane/ethanol (1/2/0.02) gave pure **5** (11.1 mg, 0.044 mmol, 79%): mp 141–144 °C (ethyl acetate/hexane); ^{1}H NMR δ ($CDCl_3$) 8.43 (1H, s), 8.37 (1H, dd, J = 2, 5), 8.35 (1H, d, J = 5), 8.09 (1H, dd, J = 2, 8), 7.09 (1H, d, J = 5), 7.02 (1H, dd, J = 5, 8), 4.35 (1H, br s), 3.75 (1H, br s), 3.56 (3H, s), 1.27 (3H, t, J = 7); MS(CI) 255 (M + H$^+$). Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.89; H, 5.54; N, 21.87.

Acknowledgment. We thank Roger Dinallo for recording mass spectra and Dr. Julian Adams, Dr. Karl Hargrave, and Professor W. D. Ollis for helpful discussions.