Synthesis of 2,4-Diaminopyrrolo[2,3-*d*]pyrimidines *via* Thermal Fischer Indolization. Pyrazole Formation with Ytterbium Triflate Catalysis

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The high-yield synthesis of the 2,4-diaminopyrrolo[2,3-*d*] pyrimidine **4** (PNU-87663) *via* a Bischler-like alkylation-cyclization sequence was reported earlier. We describe herein an alternative synthesis of this potent antioxidant and several analogs based on the thermal Fischer indolization, starting from hydrazino substituted pyrimidines **5** and **13**. In several cases where the thermal Fischer indolization failed, attempts to catalyze the reaction with Lewis acids, especially ytterbium triflate, led to the surprising and unprecedented formation of pyrazolo[3,4-*d*]pyrimidines, *e.g.* 1-methyl-3-phenyl-4,6-di-1-pyrrolidinyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**24**), with the loss of the elements of methane. Mechanistic details of this transformation remain to be investigated.

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Several 6-substituted 2,4-diaminopyrrolo[2,3-*d*]pyrimidines have been synthesized by utilizing a Bischler-like alkylation/cyclization/dehydration protocol outlined in Scheme 1 [1] (**1** → **2** → **3** → **4**). This sequence generally proceeded under very mild conditions and in high yield with a wide variety of α-bromoketones. In many cases, simple filtration of the crude reaction mixtures provided analytically pure products **4**. As a class, the diaminopyrrolopyrimidines have exhibited excellent antioxidant activity [1], and their lipophilic nature has proven advantageous in targeting the compounds to biomembranes, where damaging lipid peroxidation can play an important role in a variety of pathological conditions [2].

During the course of an analog program based on the prototypical pyrrolopyrimidine **4**, it became apparent that the bromoketone alkylation/cyclization sequence did not always work well, especially in cases where the bromoketone component contained an additional nucleophilic heteroatom. We report herein a versatile alternative approach to the pyrrolopyrimidines, which involves as the key step the thermal [3] Fischer indolization [4] of the appropriate hydrazone, outlined in Scheme 1 for the preparation of **4** (**1** → **5** → **6** → **4**). The key intermediate, substituted hydrazine **5** was prepared simply and in virtually quantitative yield by treating chloropyrimidine **1** [5] with excess methylhydrazine at reflux. The observed regiospecificity, *i.e.* attack on **1** by the more nucleophilic, but more hindered, hydrazine nitrogen atom, is fully consistent with literature analogy [6]. When solutions of the crude hydrazone **6** (obtained from the treatment of **5** with acetophenone) in decalin or diphenyl ether were heated under nitrogen at 200-230 °C for 18 hours, in the absence of acidic catalysts, the desired 6-phenyl-2,4-diaminopyrrolo[2,3-*d*]pyrimidine **4** was formed in 44% yield after purification. The reluctance of other heterocyclic hydrazones to undergo acid catalyzed Fischer indolization due to protonation of the heterocyclic ring has been noted [4], and the utility of the thermal variant to synthesize 4-oxopyrrolo[2,3-*d*]pyrimidines has recently been disclosed by Taylor and Hu [7]. Since the bromoketone cyclization route worked very well for the preparation of **4**, little effort was expended at optimization of the thermal Fischer conditions with substrate **6**, except to note that yields were better when the indolization temperature was kept as low as possible, a temperature which varied depending on the substrate. At temperatures above 230 °C, destruction of the products more than offset their more rapid formation.

The versatility of the thermal Fischer route can be appreciated by noting the examples in Table 1. Although these yields would be considered moderate at best, all of these represent cases for which the bromoketone route failed completely. As expected, the analogs **7-11** retained the potent antioxidant activity first noted with **4** (PNU-87663), but in general were more toxic and hence less appropriate for pharmacological use. The details will be reported elsewhere. An extension of the thermal Fischer protocol, for the preparation of analogs bearing water-solubilizing side chains on the indole nitrogen *via* key intermediate **13**, is illustrated in Scheme 2. As in Table 1, the yields of the Fischer products, *e.g.* **16** and **19**, were generally in the moderate, but usable range. In these cases, the reaction proceeded *via* isolable but unstable intermediates **14** and **15** respectively, which are isomeric and interconvertible with the desired hydroxyethyl substituted hydrazones. The further conversion of **14** and **15** to **16** and **19** was best accomplished at lower temperatures (160-190 °C) for longer reaction periods (2-3 days). Transformation of these hydroxyethyl intermediates to morpholinylethyl derivatives **18** and **21** was accomplished routinely in good yield.

Scheme 1

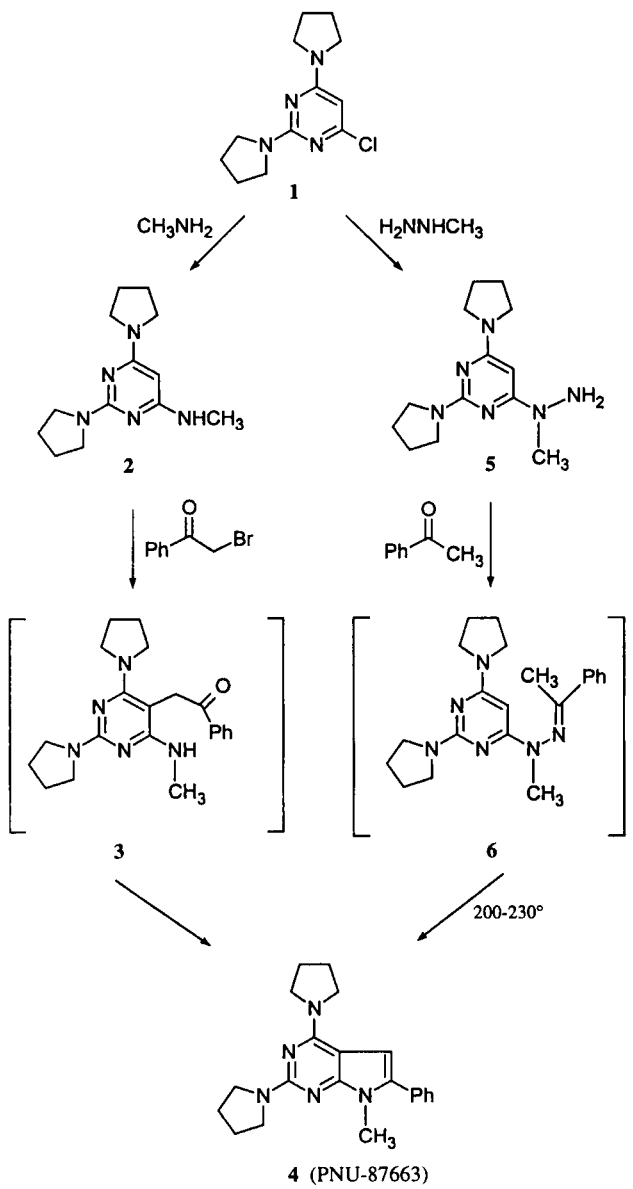
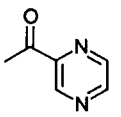
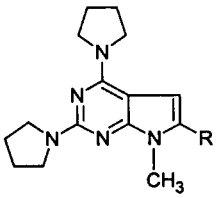
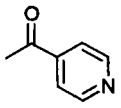
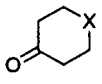
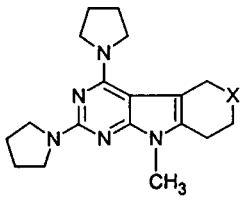
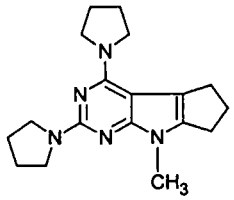
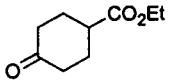
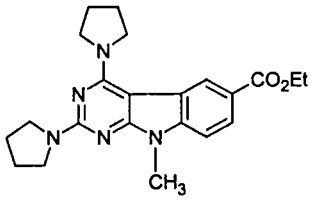


Table 1

Preparation of Pyrrolopyrimidines from Hydrazine **5** *via* Thermal Fischer Indolization

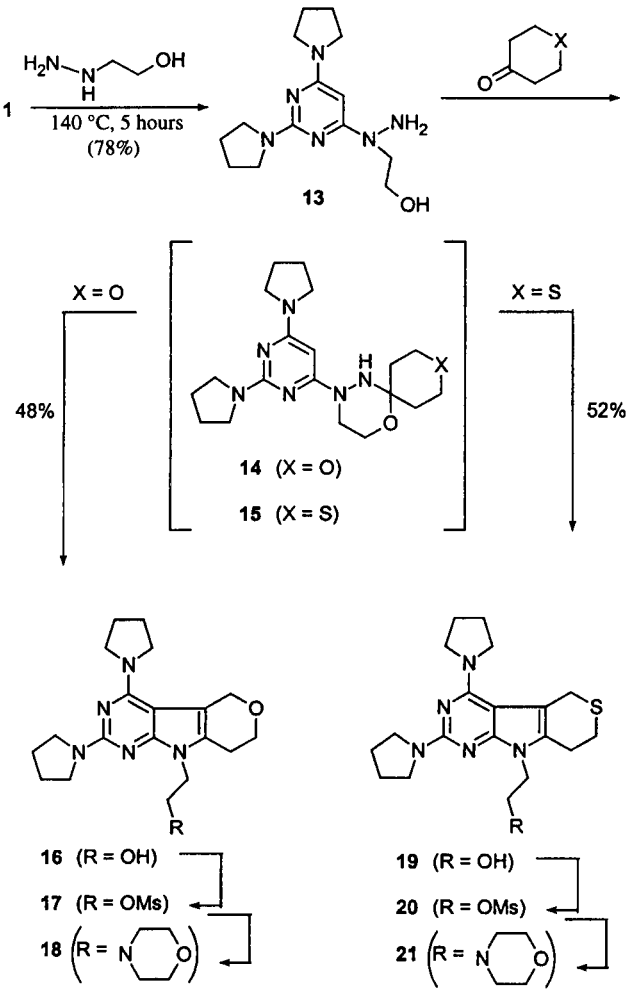
Ketone	Product	Yield [a]
	 **7** (R = 2-pyrazinyl) **8** (R = 4-pyridinyl)	54% 71%
		
 X = O X = NCbz	 **9** (X = O) **10** (X = NH)	47% 37% [b]
	 **11**	44%
	 **12**	28% [c]

[a] Isolated yield of chromatographically pure material; [b] After Cbz removal with TMSI; [c] After dehydrogenation with Pd/C.

The examples in Table 1 and Scheme 2 illustrate the considerable versatility of the thermal Fischer indolization with respect to both the ketone and hydrazine components for the synthesis of pyrrolopyrimidines bearing heteroatom substituents. However, there were several ketones, including 1-benzyl-3-piperidone, 1-indanone, norcamphor, and 4-(1-imidazolyl)acetophenone, for which this ring forming protocol was completely unsuccessful, despite the facile formation of the requisite hydrazones from hydrazine **5**. Preliminary attempts to facilitate the ring formation with Lewis acids (zinc chloride, boron trifluoride etherate, phosphorous trichloride, *etc.*) [4] afforded only complex, intractable mixtures. Finally, investigations were undertaken with ytterbium triflate [8], a commercially available, strong Lewis acid, but one which is versatile, water-tolerant and usable with amine containing substrates [9] which deactivate most Lewis acids.

When solutions of hydrazone **22** in decalin were heated at 190 °C for 4 hours in the presence of 10 mole % of ytterbium triflate, the substituted pyrazolo[3,4-*d*]pyrimidine **23** was formed cleanly in 25% purified yield. No reaction was found to occur under these conditions in the absence of the Lewis acid. The structure of this surprising

Scheme 2

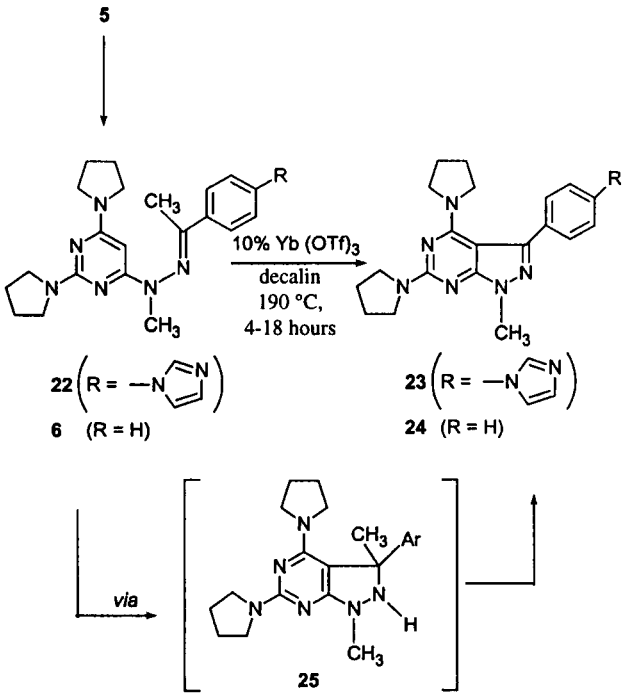


product, tentatively assigned on the basis of nmr and mass spectroscopy, was confirmed by an x-ray structure determination on the unsubstituted and more readily crystallized phenyl derivative **24**, formed in 63% yield under similar conditions, starting from the acetophenone hydrazone **6**. In this case, the ytterbium triflate catalyzed reaction afforded a 4:1 mixture of pyrazole **24** and the 'normal' pyrrolopyrimidine **4**. Only traces of the pyrazole were evident upon careful tlc analysis of the crude product from the uncatalyzed thermal indolization (**5** → **6** → **4**).

At the time this work was done, the formation of pyrazoles *via* Fischer indolization with loss of the elements of CH_4 appeared to be completely unprecedented. Taylor and Hu's [7] recent report of a related finding involved an aldehyde hydrazone, no Lewis acid, and no loss of carbon during the cyclization. Although the mechanism and scope of our pyrazole formation (**6** → **24**) have not been investigated in detail, the following observations were noted. For the pyrazole formation, ytterbium triflate is apparently advantageous, even among the lanthanide triflates, as catalysis by the closely related scandium triflate afforded a 3:2 mixture of indole **4** and pyrazole **24**. However, the use of a full equivalent of ytterbium triflate in the reaction with hydrazone **6** led to the formation of an unpurifiable mixture of at least ten products. At this point, the ytterbium triflate catalyzed Fischer indolization appears not to be a general method for the synthesis of fused pyrazoles, as the substrate tolerance may be somewhat restricted. The structural features required to facilitate pyrazole formation *via* this protocol have not yet been determined. Heating solutions of acetophenone phenylhydrazone in the presence of ytterbium triflate afforded mixtures containing six equally abundant products including the 3-phenylindazole, whose presence was indicated by mass spectroscopy.

In terms of mechanism, standard Fischer indolization steps could conceivably afford intermediates such as **25** (Scheme 3). However, without any experimental evidence for the existence of that or any other intermediate, the details of its further conversion to the observed pyrazole product remain obscure. A single, superficially related and equally unexplained disappearance of a methyl group during a Fischer indolization has been reported [10].

Scheme 3



In summary, we have demonstrated with the examples in Table 1 and Scheme 2 that the uncatalyzed thermal Fischer indolization constitutes a versatile and reliable protocol for the preparation of heteroatom laden and oxidation sensitive pyrrolopyrimidines. The intervention of fused pyrazole products, sometimes in good yield, when the reaction was catalyzed by ytterbium triflate is also noteworthy. With the single related exception noted above [7], this 'abnormal' pathway has not been previously documented in the extensive Fischer indole literature. Although the versatility of the ytterbium triflate protocol for the preparation of fused pyrazoles may be limited by as-yet-undetermined restrictions on the substrate structure, the mechanistic details of this novel transformation may warrant further investigation.

EXPERIMENTAL

General.

All reagents were obtained from Aldrich Chemical Co. and were used as received. Distilled, purified solvents were obtained from Burdick and Jackson, Inc., and were used without further purification. Except as noted, all reactions were carried out with magnetic stirring in flame-dried glassware in an atmosphere of nitrogen. Column chromatographic purifications were performed on E. Merck 230-400 mesh silica gel 60. The ^1H and ^{13}C nmr spectra were recorded at 300 and 75 MHz, respectively, on deuteriochloroform solutions. Melting points are uncorrected.

7-Methyl-6-phenyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**4**).

(A) *Via* Bromoketone Cyclization.

A solution of triaminopyrimidine intermediate **2** [11] (5.03 g, 20.3 mmol), phenacyl bromide (4.09 g, 20.5 mmol) and diisopropylethylamine (4.3 mL, 24.7 mmol) in acetonitrile (130 mL) was stirred at 25 °C under nitrogen for 18 hours, and heated at reflux for 2 hours. The mixture was then cooled to 0 °C, and the product **4** was isolated by filtration (5.72 g, 81%, a white solid >98% pure by tlc in 9:1 methylene chloride:acetone). Recrystallization of a small portion from methylene chloride:acetone afforded the analytical sample; mp 162-163 °C; ^1H nmr δ 7.48-7.29 (m, 5H), 6.43 (s, 1H), 3.85-3.75 (m, 4H), 3.68 (s, 3H), 3.75-3.60 (m, 4H), 1.98-1.92 (8H); ^{13}C nmr 158.0, 155.5, 155.4, 133.4, 133.2, 128.4, 128.2, 126.7, 100.9, 96.5, 47.5, 46.6, 29.8, 25.7; hrms Calcd. for $C_{21}H_{25}N_5$: 347.2110. Found: 347.2109.

Anal. Calcd. for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.67; H, 7.26; N, 20.36.

(B) *Via* Thermal Fischer Indolization.

A solution of hydrazine intermediate **5** (prepared below; 500 mg, 1.91 mmol) and acetophenone (0.33 mL, 2.83 mmol) in 12 mL of diphenyl ether was heated under nitrogen at 210 °C for 24 hours. The mixture was then cooled to ambient temperature, diluted with 12 mL of heptane and chromatographed (75 g silica; elution with hexane until the diphenyl ether had come off, then 2% acetone/methylene chloride), thereby affording **4** (293 mg, 44%), identical by tlc and nmr to the material from (part A) above.

4-(1-Methylhydrazino)-2,6-di-1-pyrrolidinylpyrimidine (**5**).

A solution of chloropyrimidine **1** [5] (51 g, 202 mmol) in 320 mL of methylhydrazine (Aldrich) was heated at reflux (approx. 90 °C) under nitrogen for 4 hours. (The initial suspension became homogeneous by the time reflux began.) The mixture was then cooled to 0 °C, diluted with 350 mL of water and filtered. The white solids were dried (0.05 mm, 25 °C, 24 hours) and yielded clean **5** (52.5 g, 99%); mp 128-130 °C; ir (Nujol mull) 2954, 2925, 2855, 1573, 1553, 1469, 1452, 1346; ^1H nmr δ 5.30 (s, 1H), 4.19 (s, 2H, NH_2), 3.55-3.51 (m, 4H), 3.49-3.33 (m, 4H), 3.16 (s, 3H), 1.94-1.87 (m, 8H); ^{13}C nmr δ 165.6, 162.1, 159.9, 71.6, 46.1, 45.9, 39.7, 25.5, 25.2; hrms Calcd. for $C_{13}H_{22}N_6$: 262.1906. Found: 262.1915.

General Procedures for Table 1 - Thermal Fischer Indolizations.

(A) A solution of 10 mmol of hydrazine **5** and 15 mmol of the ketone component in 75 mL of decalin was heated under nitrogen at 180 °C for 18 hours. Products which crystallized upon cooling were isolated by filtration and then chromatographed, if necessary. In other cases, removal of the decalin *in vacuo* was followed by chromatography of the resulting residue.

(B) A solution of 7 mmol of hydrazine **5** and 7 mmol of the ketone component in 10 mL of absolute ethanol was heated at reflux for 24-48 hours until tlc indicated that hydrazone formation was complete. If solids formed when the solution was cooled, the crude hydrazone (syn/anti mixtures) was isolated by filtration. Otherwise evaporation of the ethanol *in vacuo* provided the crude hydrazone in sufficient purity to proceed. A solution of the crude hydrazone in 35 mL of diphenyl ether was heated at 220 °C for 16 hours. The mixture was then cooled to 25 °C and diluted with an equal volume of hexane, and the product was isolated by filtration.

7-Methyl-6-pyrazinyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**7**).

This compound was prepared by Method B on a 63 mmol scale. Filtration and drying (0.05 mm, 40 °C, 2 hours) gave pure **7** (11.9 g, 73%) as a yellow solid; mp 227-228 °C; ^1H nmr δ 8.86 (s, 1H), 8.46-8.45 (m, 1H), 8.27-8.25 (m, 1H), 6.93 (s, 1H), 3.97 (s, 3H), 3.85-3.75 (m, 4H), 3.65-3.61 (m, 4H), 2.02-1.93 (m, 8H); hrms Calcd. for $C_{19}H_{23}N_7$: 349.2015. Found: 349.2015. Analysis was performed on the corresponding HCl salt formed with one equivalent of hydrogen chloride/methanol and recrystallized from methanol/ethyl acetate (yellow solid, 98% yield); mp 248-250 °C.

Anal. Calcd. for $C_{19}H_{24}ClN_7$: C, 59.14; H, 6.27; N, 25.41; Cl, 9.19. Found: C, 57.44; H, 5.95; N, 25.32; Cl, 9.09.

7-Methyl-6-(4-pyridinyl)-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**8**).

This compound was prepared by Method B on a 65 mmol scale. Filtration and drying (0.05 mm, 40 °C, 16 hours) yielded pure **8** (16.2 g, 73%) as a tan solid; mp 261-262 °C; ^1H nmr δ 8.57-8.55 (m, 2H), 7.38-7.36 (m, 2H), 6.63 (s, 1H), 3.80-3.76 (m, 4H), 3.75 (s, 3H), 3.64-3.60 (m, 4H), 1.99-1.92 (m, 8H); hrms Calcd. for $C_{20}H_{24}N_6$: 348.2061. Found: 348.2059. The corresponding di-HCl salt was prepared with two equivalents of hydrogen chloride/methanol (orange solid, 100% yield); mp 275-280 °C.

Anal. Calcd. for $C_{20}H_{26}Cl_2N_6$: C, 57.01; H, 6.22; N, 19.94; Cl, 16.83. Found: C, 55.43; H, 6.22; N, 19.63; Cl, 16.29. Instability of this salt precluded further recrystallization.

5,7,8,9-Tetrahydro-9-methyl-2,4-di-1-pyrrolidinylpyrano-[3',4':4,5]pyrrolo[2,3-*d*]pyrimidine (**9**).

This compound was prepared by Method A on a 38.2 mmol scale; the ketone component tetrahydro-4*H*-pyran-4-one was purchased from Aldrich. Filtration of the cooled reaction mixture afforded **9** (4.04 g, 32%) as a yellow solid. Chromatography of the filtrate (900 g of silica, 2:1 ethyl acetate:hexane) afforded an additional 1.83 g of **9** (total yield 47%). Recrystallization of a small portion from acetonitrile provided the analytical sample; mp 208-210 °C; ^{1}H nmr δ 4.83 (s, 2H), 4.03-4.00 (m, 2H), 3.68-3.55 (m, 8H), 3.52 (s, 3H), 2.80-2.68 (m, 2H), 2.05-1.83 (m, 8H); ^{13}C nmr δ 156.6, 155.6, 154.3, 124.8, 104.6, 92.9, 67.2, 64.2, 48.0, 46.3, 27.2, 25.5, 25.3, 22.8; ir (Nujol mull) 2945, 2926, 2869, 1571, 1544, 1526, 1449, 1442, 1435, 1413, 1401, 1345, 1087; hrms Calcd. for $C_{18}H_{25}N_5O$+H: 327.2059. Found: 327.2065.

Anal. Calcd. for $C_{18}H_{25}N_5O$: C, 66.03; H, 7.70; N, 21.39. Found: C, 65.71; H, 7.68; N, 21.29.

6,7,8,9-Tetrahydro-9-methyl-2,4-di-1-pyrrolidinyl-5*H*-pyrido-[3',4':4,5]pyrrolo[2,3-*d*]pyrimidine (**10**).

This compound was prepared by Method A on a 0.38 mmol scale; the ketone component, 1-Cbz-4-piperidone, was prepared as described by Shoji, *et al.* [12]. Chromatographic purification of the residue following evaporation of the decalin (80 g silica, 2:1 ethyl acetate/hexane) afforded pure **10**-Cbz (92 mg, 53%) as a yellow solid; mp 162-164 °C; ^{1}H nmr 7.42-7.27 (m, 5H), 5.17 (s, 2H), 4.70 (s, 2H), 3.88-3.79 (m, 2H), 3.70-3.54 (m, 8H), 3.42 (s, 3H), 2.80-2.64 (m, 2H), 1.99-1.86 (m, 8H); hrms Calcd. for $C_{26}H_{32}N_6O_2$+H: 461.2665. Found: 461.2654. For Cbz removal, a solution of **10**-Cbz (1.06 g, 2.30 mmol; from a larger scale but lower yield preparation) in 20 mL of chloroform was treated with trimethylsilyl iodide (0.77 mL, 5.4 mmol), and the solution was stirred 30 minutes at 25 °C. Additional trimethylsilyl iodide (0.39 mL, 2.7 mmol) was added, and the mixture was stirred 3 hours longer at 25 °C, then treated with 1.3 mL of methanol. Following removal of the solvents *in vacuo*, the residue was partitioned between ether and 5% aqueous hydrochloric acid. Basification of the aqueous layer (sodium hydroxide) and extraction with chloroform, followed by evaporation of the dried extracts yielded crude **10**, a white solid. Recrystallization of this material from methanol (as rapidly as possible to minimize oxidative degradation) yielded pure **10** (517 mg, 69% this step, 37% over the two steps from **5**) as an off-white solid; mp 210-212 °C; ^{1}H nmr δ 4.01 (s, 2H), 3.64-3.57 (m, 8H), 3.50 (s, 3H), 3.19-3.16 (m, 2H), 2.70-2.60 (m, 2H), 1.94-1.90 (m, 8H); ^{13}C nmr δ 156.6, 156.0, 154.2, 126.2, 106.1, 93.8, 48.6, 46.7, 46.5, 42.9, 27.1, 25.5, 25.4, 23.2; hrms Calcd. for $C_{18}H_{26}N_6$+H: 327.2297. Found: 327.2312. Satisfactory CHN analyses could not be obtained for this material or the corresponding di-HCl salt; mp 225-227 °C, and further recrystallization of **10** was precluded by its oxidative instability.

5,6,7,8-Tetrahydro-8-methyl-2,4-di-1-pyrrolidinylcyclo-penta[4,5]pyrrolo[2,3-*d*]pyrimidine (**11**).

This compound was prepared by Method B on a 38.2 mmol scale. Evaporation of the diphenyl ether afforded a residue, chromatography of which (40 g silica, 10% ethyl acetate/hexane) yielded pure **11** (3.31 g, 44%) as a light brown solid; mp 156-158 °C; ^{1}H nmr δ 3.65 (m, 4H), 3.59 (m, 4H), 3.55 (s, 3H), 2.80 (m, 4H), 2.38 (m, 2H), 1.93 (m, 8H); hrms Calcd. for $C_{18}H_{25}N_5$: 311.2110. Found: 311.2090. The HCl salt was prepared (hydrogen chloride/methanol; recrystallized from methanol/ethyl acetate) for analysis; mp 225-230 °C.

Anal. Calcd. for $C_{18}H_{25}N_5$•HCl: C, 62.15; H, 7.53; N, 20.13; Cl, 10.19. Found: C, 61.82; H, 7.51; N, 20.15; Cl, 10.02.

Ethyl 9-methyl-2,4-di-1-pyrrolidinyl-9*H*-pyrimido[4,5-*b*]indole-6-carboxylate (**12**).

A solution of hydrazine **5** (8.39 g, 32.02 mmol) and ethyl 4-oxocyclohexanecarboxylate (5.44 g, 32.02 mmol, Aldrich) in 50 mL of absolute ethanol was heated at reflux under nitrogen for 36 hours. Cooling to 25 °C and filtration yielded the crude hydrazone (11.49 g, 87%) as a tan solid. A suspension of the hydrazone in 500 mL of decalin was heated at reflux under nitrogen for 18 hours. The mixture was cooled to 25 °C, treated with 3.45 g of 10% palladium/carbon, and reflux was continued for 24 hours. Following cooling and removal of the palladium/carbon by filtration through Celite, evaporation of the decalin *in vacuo* gave crude **12**. Chromatography (400 g silica, 5% methanol/methylene chloride) then yielded pure **12** (3.5 g, 28%) as a white solid; mp 164-167 °C; ir (Nujol mull) 1701, 1611, 1585, 1553, 1525, 1243; ^{1}H nmr δ 8.63 (s, 1H), 7.93 (dd, J = 1.6, 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 4.39 (m, 2H), 3.95 (m, 4H), 3.76 (s, 3H), 3.65 (m, 4H), 1.97 (m, 8H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C nmr δ 167.9, 160.4, 158.6, 157.9, 140.8, 123.4, 122.3, 121.7, 89.9, 60.5, 49.6, 46.6, 27.6, 25.7, 25.6, 14.5; hrms Calcd. for $C_{22}H_{27}N_5O_2$: 393.2165. Found: 393.2170.

Anal. Calcd. for $C_{22}H_{27}N_5O_2$: C, 67.15; H, 6.92; N, 17.80. Found: C, 67.05; H, 7.02; N, 17.72.

2-[1-(2,6-Di-1-pyrrolidinyl-4-pyrimidinyl)hydrazino]ethanol (**13**).

A solution of chloropyrimidine **1** [5] (8.0 g, 32 mmol) in 2-hydroxyethylhydrazine (46 g, 600 mmol, Aldrich) was heated at 140 °C for 5 hours under nitrogen, then cooled to room temperature. The reaction mixture was diluted with 200 mL of 2*N* aqueous sodium hydroxide and extracted with methylene chloride. The combined extracts were washed with brine, dried (anhydrous sodium sulfate), and evaporated *in vacuo*, thereby affording crude **13** (9.11 g) as a viscous oil which solidified on standing. Recrystallization from ether afforded **13** (7.18 g, 78% yield) as a white solid; mp 92-95 °C; ^{1}H nmr δ 5.75 (br s, 1H), 5.11 (s, 1H), 4.00 (s, 2H), 3.83 (m, 4H), 3.50 (m, 8H), 1.91 (m, 8H).

Anal. Calcd. for $C_{14}H_{24}N_6O$: C, 57.51; H, 8.27; N, 28.74. Found: C, 57.54; H, 8.16; N, 28.70.

7,8-Dihydro-2,4-di-1-pyrrolidinylpyrano[3',4':4,5]pyrrolo[2,3-*d*]-pyrimidine-9(5*H*)ethanol (**16**).

A solution of hydroxyethylhydrazine intermediate **13** (6.0 g, 20.6 mmol) and tetrahydro-4*H*-pyran-4-one (2.24 g, 22.4 mmol) in absolute ethanol (20 mL) was stirred at 25 °C for 50 minutes. The reaction mixture was concentrated *in vacuo*, the residue was reconstituted in 90 mL of decalin, and the resulting suspension was heated under nitrogen at 160 °C for 64 hours. The mixture was cooled to 30 °C and concentrated *in vacuo*. Crystallization of the residue from acetone/hexane yielded pure **16** (3.53 g, 48%) as a light tan solid; mp 161-162 °C; ^{1}H nmr δ 7.5 (s, 1H), 4.82 (m, 2H), 4.04-4.00 (m, 4H), 3.93-3.90 (m, 2H), 3.62-3.50 (m, 8H), 2.72-2.68 (m, 2H), 1.98-1.90 (m, 8H); ir (Nujol mull) 3391, 1569, 1549, 1521; ms: ei 357 (M^+), 326, 314, 313, 285, 255, 84.

Anal. Calcd. for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.81; H, 7.66; N, 19.47.

5,7,8,9-Tetrahydro-9-[2-(4-morpholinyl)ethyl]-2,4-di-1-pyrrolidinylpyrano[3',4':4,5]pyrrolo[2,3-*d*]pyrimidine (**18**).

A solution of hydroxyethyl intermediate **16** (270 mg, 0.756 mmol) and triethylamine (0.14 mL, 1.00 mmol) in 25 mL of methylene chloride was cooled to 0 °C and treated with methanesulfonyl chloride (95 mg, 0.83 mmol). After 10 minutes longer at 0 °C, the mixture was diluted with ice/water, and the mesylate was extracted with methylene chloride. The crude mesylate **17** was dissolved in 6 mL of morpholine, and the solution was heated at reflux under nitrogen for 30 hours. Following removal of the excess morpholine *in vacuo* from the cooled reaction mixture, the residue was partitioned between aqueous potassium carbonate and methylene chloride. Concentration of the dried combined extracts afforded crude **18** (0.33 g). Trituration with ether then gave pure **18** (120 mg, 38%) as a off-white solid; mp 145-146 °C; ^{1}H nmr δ 4.85 (m, 2H), 4.18-4.10 (m, 2H), 4.08-4.00 (m, 2H), 3.75-3.70 (m, 4H), 3.65-3.55 (m, 8H), 2.81-2.78 (m, 2H), 2.70-2.65 (m, 2H), 2.58-2.55 (m, 4H), 1.97-1.95 (m, 8H); ir (Nujol mull) 1559, 1549, 1516, 1497, 1433, 1422, 1397, 1353, 1346, 1328, 1292, 1151, 1114, 1095, 864; ms: ei 426 (M^+), 314, 313, 312, 286, 100.

Anal. Calcd. for $C_{23}H_{34}N_6O_2$: C, 64.76; H, 8.03; N, 19.70. Found: C, 64.39; H, 8.15; N, 19.61.

7,8-Dihydro-2,4-di-1-pyrrolidinylthiopyrano[3',4':4,5]pyrrolo-[2,3-*d*]pyrimidine-9(5*H*)ethanol (**19**).

This transformation was performed according to general procedure A above (50 mmol scale) utilizing tetrahydrothiopyran-4-one (10.0 g, 86 mmol, Aldrich) as the carbonyl component. Chromatography of the crude product (400 g silica gel, 10% ethyl acetate/hexane) gave product **19** as a foam; trituration with methanol then yielded pure **19** (9.8 g, 52%) as a light tan solid; mp 164-165 °C; ^{1}H nmr δ 7.33 (s, 1H), 4.07 (m, 2H), 3.92 (m, 4H), 3.68 (m, 4H), 3.55 (m, 4H), 2.99 (m, 2H), 2.87 (m, 2H), 1.91 (m, 8H); ms: ei 373 (M^+), 340, 328, 327, 284, 255.

Anal. Calcd. for $C_{19}H_{27}N_5OS$: C, 61.10; H, 7.29; N, 18.75. Found: C, 60.84; H, 7.36; N, 18.41.

5,7,8,9-Tetrahydro-9-[2-(4-morpholinyl)ethyl]-2,4-di-1-pyrrolidinylthiopyrano[3',4':4,5]pyrrolo[2,3-*d*]pyrimidine (**21**).

Compound **21** was prepared by using a procedure analogous to that described above for the **16** → **18** conversion (starting with 1.07 g, 2.85 mmol of **19**). Crystallization of the crude product (1.27 g) from acetone/hexane afforded pure **21** (820 mg, 65% from **19**) as a light tan solid; mp 143-145 °C; ^{1}H nmr δ 4.11 (m, 2H), 3.88 (s, 2H), 3.68 (m, 8H), 3.56 (m, 4H), 2.97 (m, 4H), 2.63 (m, 2H), 2.55 (m, 4H), 1.91 (m, 8H); ms: ei 442 (M^+), 330, 329, 328, 296, 283.

Anal. Calcd. for $C_{23}H_{34}N_6OS$: C, 62.41; H, 7.74; N, 18.99. Found: C, 62.51; H, 7.73; N, 18.70.

3-[4-(1*H*-Imidazol-1-yl)phenyl]-1-methyl-4,6-di-1-pyrrolidinyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**23**).

A solution of hydrazine **5** (502 mg, 1.91 mmol), 4'-(imidazol-1-yl)acetophenone (1.04 g, 5.59 mmol, Aldrich) and ytterbium (III) trifluoromethanesulfonate hydrate (120 mg, 0.19 mmol, Aldrich) in decalin (50 mL) was heated at reflux (190 °C) under nitrogen for 18 hours. Removal of the solvent (0.05 mm, 50 °C) gave a brown oil, chromatography of which (180 g silica, 5:1 ethyl acetate/chloroform to 10% methanol/methylene chloride) yielded pure **23** (198 mg, 25%) as a light yellow solid. Recrystallization from tetrahydrofuran afforded analytically pure material; mp 253-256 °C; ^{1}H nmr δ 7.92 (s, 1H), 7.68-7.66 (m, 2H), 7.45-7.42 (m, 2H), 7.35-7.33 (m, 1H), 7.24-7.23 (m, 1H), 3.90 (s, 3H), 3.67-3.62 (m, 4H), 3.38-3.22 (m, 4H), 1.99-1.95 (m, 4H), 1.74-1.70 (m, 4H); ^{13}C nmr δ 158.8, 157.9, 143.6, 136.9, 135.5, 130.8, 130.6, 120.8, 118.1, 94.4, 49.9, 46.7, 33.3, 25.6, 25.4; ir (Nujol mull) 2961, 2946, 2925, 2868, 2856, 1584, 1552, 1532, 1477, 1457; ms: ei 414 (M^+), 386, 372, 358, 344, 331, 316, 302, 290, 275, 247, 207, 186, 172, 70.

Anal. Calcd. for $C_{23}H_{26}N_8$: C, 66.65; H, 6.32; N, 27.03. Found: C, 66.49; H, 6.36; N, 26.95.

1-Methyl-3-phenyl-4,6-di-1-pyrrolidinyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (**24**).

A stirred suspension of hydrazine **5** (1.02 g, 3.89 mmol) and acetophenone (0.49 mL, 4.2 mmol) in 6 mL of absolute ethanol was heated at reflux under nitrogen for 24 hours, then cooled to 0 °C. Filtration afforded 637 mg (26%) of hydrazone intermediate **6** (mp 113-115 °C) as a light tan solid. (An additional 680 mg of hydrazone **6** could be obtained by chromatographic purification of the mother liquors.) A mixture of hydrazone **6** (50 mg, 0.137 mmol) and ytterbium triflate (15.9 mg, 0.026 mmol) in 5 mL of decalin was heated at reflux for 18 hours. The decalin was removed *in vacuo*, and the crude product (a 4:1 mixture of **24** and **4** by nmr) was chromatographed (25 g silica; 25% ethyl acetate/hexane), thereby yielding pure indole **4** (7 mg, 15%) and pure pyrazole **24** (30.5 mg, 63%) as a pale yellow solid. For **24**: mp 124-127 °C; ^{1}H nmr δ 7.54-7.51 (m, 2H), 7.41-7.26 (m, 3H), 3.89 (s, 3H), 3.66-3.62 (m, 4H), 3.25 (br s, 4H), 1.98-1.94 (m, 4H), 1.70-1.65 (m, 4H); ^{13}C nmr δ 158.8, 158.1, 157.8, 145.0, 136.3, 129.3, 128.0, 127.9, 94.5, 53.4, 49.6, 46.6, 33.2, 25.6, 25.3; hrms Calcd. for $C_{20}H_{24}N_6$: 348.2062. Found: 348.2074.

Anal. Calcd. for $C_{20}H_{24}N_6$ (corrected for observed 0.27% acetone and 0.07% H_2O): C, 68.87; H, 7.02; N, 24.04. Found: C, 69.11; H, 7.04; N, 24.21. The structure of **24** was confirmed by x-ray crystallography.

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