Synthesis of Tricyclic Aminopyridines by a Cadmium Promoted Cyclization

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A novel cyclocondensation of *o*-amino nitriles with cyclic 1,3-diones has been developed as a synthetic route to assemble fused tricyclic aminopyridine derivatives. The reaction sequence involves the initial formation of an enaminone. The enaminone is then cyclized at 120 °C to 190 °C in the presence of Lewis acids which include zinc, cadmium and copper(I) salts. The cyclization may be promoted under more mild conditions by first deprotonating the enaminone to form the anion followed by exposure to cadmium(II) salts at 60 °C to 90 °C. Alternatively, the enaminones may be reacted with organocadmium reagents such as dibutylcadmium to effect the deprotonation and cyclization directly at room temperature. Synthetic applications of these novel cadmium-mediated cyclizations are presented and mechanistic considerations discussed.

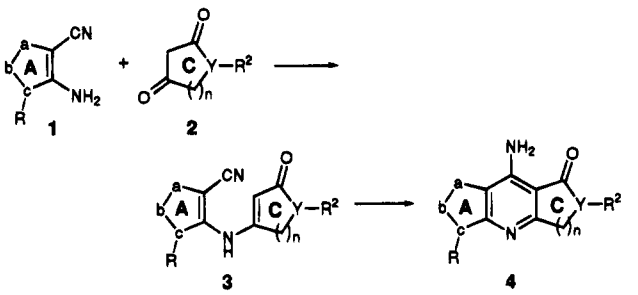
Introduction

We have been interested in evaluating a series of pyrazolopyridines (**4**, a = CH, b = N, c = NR) as possible anxiolytic agents.[1] More recently, we wanted to extend our investigations and to examine other structurally related analogs primarily through variation of the A and C ring moieties of the generic structure **4**. Hence, a general synthesis was required for the preparation of such linearly fused heterocycles with a 4-aminopyridine as the central ring and additional rings A and C fused to the pyridine.

We envisioned a convergent coupling approach to assemble the fused pyridines **4** by the reaction of an *o*-amino nitrile (A ring) **1** with a cyclic 1,3-dione (C ring) **2** to form an intermediate enaminone **3** (Scheme 1). Subsequent cyclization of **3** should form the desired [*b*,*e*]-fused pyridine ring system and should also introduce the amine and carbonyl functionalities in the appropriate positions. Related cyclocondensation approaches to amino-substituted tricyclic rings have been reported. Several procedures have employed base[2a–c] or acid[2d] to induce cyclization of enamino nitriles (nonstabilized enamines) to form bi- and tricyclic ring systems. Other approaches have employed Lewis acids. Moore et al. described a "one pot" synthesis of aminoquinolines via a zinc chloride-catalyzed condensation of anthranilonitrile with cyclohexanone, purportedly through the intermediacy of an enamine.[2e] The synthesis of a series of quinolizidinones was accomplished by a magnesium salt-catalyzed cyclization of enamines which were derived from condensation of aliphatic enamino nitriles with cycloalkanones.[2f]

We report herein our investigation of the cyclization of the related, but less reactive, enaminones derived from condensation of *o*-amino nitriles with a variety of cyclic 1,3-diones. These investigations have resulted in a general and efficient synthesis of [*b*,*e*]-fused aminopyridines **4**. During the course of these investigations cadmium salts were discovered to be especially effective in promoting the cyclization of enaminone anions formed by deprotonation of **3**. Furthermore, the reaction of organocadmium reagents with enaminones directly affords the [*b*,*e*]-fused aminopyridine derivatives without the need for prior anion generation. The remarkable and unique role of cadmium in effecting this cyclization and mechanistic implications for the reaction sequence are also discussed.

Scheme 1



Results and Discussion

A. Initial Investigations. We required a representative substrate to investigate the cyclocondensative approach to assembling the targeted tricyclic pyridine analogs. Accordingly, enaminone **7** was prepared in 93% yield upon heating together 5-amino-4-cyano-1-pentylpyrazole (**5**), 1,3-cyclohexanedione (**6**), and a catalytic amount of *p*-toluenesulfonic acid in toluene with azeotropic removal of water (eq 1).

Our initial efforts to generate the desired tricyclic ring system **8** focused on base-induced cyclization of **7**. However, an extensive survey of several different bases (NaH, NaOEt, LDA, KH, KOt-Bu) under a variety of reaction conditions, resulted in recovery of starting material or the production of very polar unidentified byproducts. Likewise, a preliminary evaluation of acid-catalyzed cyclization of **7** (including CF_3COOH, H_2SO_4, PPA) again gave none of **8**. Very strong Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ resulted in the rapid decomposition of the starting material and produced complex reaction mixtures.

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1995.

(1) (a) Bare, T. M.; Heald, A. F. U.S. Patent 4 511 568, Apr 16, 1985. (b) Campbell, J. B.; Bare, T. M. U.S. Patent 4 546 104, Oct 8, 1985. (c) Campbell, J. B. U.S. Patent 5 118 688, June 2, 1992.

(2) (a) Lalezari, I. *J. Heterocycl. Chem.* **1979**, *16*, 603. (b) Schafer, H.; Sattler, K.; Gewald, K. *J. Prakt. Chem.* **1979**, *321*, 695. (c) Sinsky, M. S.; Bass, R. G. *J. Heterocycl. Chem.* **1984**, *21*, 759. (d) Shramm, N. I.; Konshin, M. E. *Khim. Geterotsikl. Soedin* **1982**, 674. *Chem. Abstr.* 97:92173m. (e) Moore, J. A.; Kornreich, L. D. *Tetrahedron Lett.* **1963**, 1277. (f) Meyers, A. I.; Reine, A. H.; Sircar, J. C.; Rao, K. B.; Singh, S.; Weidmann, H.; Fitzpatrick, J. *J. Heterocycl. Chem.* **1968**, *5*, 151.

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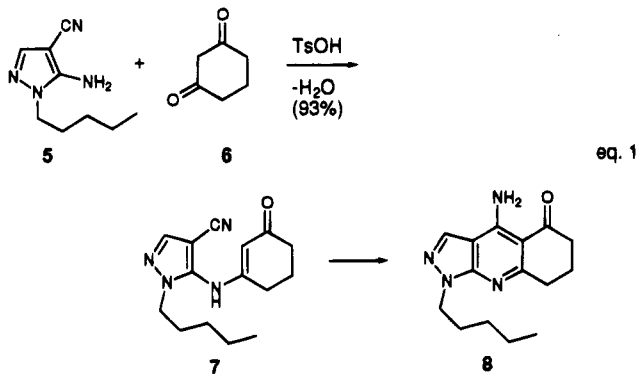


B. Lewis Acid-Promoted Cyclization. A series of selected Lewis acid salts, which included zinc chloride, zinc bromide, cadmium chloride, and copper(I) acetate were found to be capable of promoting the cyclization of **7** to afford the pyrrolopyridine **8** (eq 1). Thus, heating **7** together with either the zinc salts or cadmium chloride to 180–200 °C, or with copper(I) acetate at 120 °C, cleanly gave **8**. The procedure appears to be general for the preparation of a variety of tricyclic pyrazolopyridines **4** (a = CH, b = N, c = NR) from the corresponding enaminones **3** (a = CH, b = N, c = NR). Examples we have investigated include the five-, six-, and seven-membered ring ketones and the five- and six-membered ring lactams as C ring precursors (Table 1). In the absence of added Lewis acid, **3** (a = CH, b = N, c = NR) could be cyclized to **4** (a = CH, b = N, c = NR) in only ~20% yield. This also required a reaction temperature of 220 °C maintained for several hours and was accompanied by the production of several unidentified byproducts.

Several factors were proposed to be contributing to the acceleration of the cyclization observed in the presence of the copper and zinc salts. Complexation of the Lewis acidic metal salt to the nitrile should activate the nitrile triple bond toward nucleophilic addition by the enaminone (Scheme 2, **12** → **9** → **10**).[3,4] As the ring closure proceeds, the lone pair formed from rupture of the triple bond should develop *anti* to the incoming nucleophilic carbon of the enaminone.[5] This should progressively orient the coordinating metal atom closer to the carbonyl oxygen of the C ring. This progressive formation of the intramolecular metal chelate **10** should also help to drive the cyclization. Once the cyclization has occurred, rapid tautomerization of the initially formed imine **10** would result in aromatization of the central ring to give the pyridine **11**, which would release product upon exposure to water.

(3) End-on or longitudinal complexation of organonitriles to transition metal salts and complexes has been thoroughly investigated. The possibility of back-donation of filled or partially filled metal d orbital electron density into π^* orbitals of the coordinated nitrile concurrent with σ donation of the nitrile nitrogen lone pair electron density into empty (or partially filled) metal d orbitals of appropriate symmetry might provide a further contribution to the cyclization reaction. Stabilization of the complex by such synergistic back-bonding, in analogy to that observed in metal carbonyl complexes, should decrease the C–N triple bond order (by pushing electron density into the π^* orbitals) and increase σ donation (polarization of the C–N bond) to enhance the nitrile reactivity.

(4) (a) Storhoff, B. N.; Lewis, H. C., Jr. *Coord. Chem. Rev.* **1977**, *23*, 1. (b) Silver, J. L.; Al-Janabi, M. Y.; Johnson, R. M.; Burmeister, J. L. *Inorg. Chem.* **1971**, *10*, 994. (c) Diamond, S. E.; Grant, B.; Tom, G. M.; Taube, H. *Tetrahedron Lett.* **1974**, 4025. (d) Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872. (e) Creaser, I. I.; Harrowfield, J. M.; Keene, F. R.; Sargeson, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 3559. (f) Moore, J. A.; Partain, E. M. *J. Org. Chem.* **1983**, *48*, 1105. (g) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700.

(5) Hegarty, A. F. *Acc. Chem. Res.* **1980**, *13*, 448.

Table 1. Cyclization of Pyrazoloenaminones 3 (a = CH, b = N, c = *N*-pentyl) Using Zinc and Cadmium Halides or Copper (I) Acetate

entry	R^2	Y	*n*	% yield **4**[a]	salt/temperature (°C)
1	H	CH	2	89	$ZnCl_2$/180
				82	CuOAc/120
2	Bu	CH	2	82[b]	$ZnBr_2$/180
3	H	CH	1	43	$ZnCl_2$/180
4	Pr	CH	1	66	$ZnBr_2$/180
5	2-propenyl	CH	1	35[b,c]	$ZnCl_2$/180
				87[b]	CuOAc/120
				73	$CdCl_2$/190
6	H	CH	3	60	CuOAc/120
7	Pr	N	1	80	$ZnCl_2$/180
8	H	N	2	77	$ZnCl_2$/180
				93	CuOAc/120

[a] Yields represent isolated, recrystallized products. [b] Mixture of isomers at enaminone; less hindered isomer predominates ca. 19:1. [c] Product a mixture of isomers, ca. 65% of desired product and 35% of exo-α,β-unsaturated ketone as a mixture of *E* and *Z* isomers.

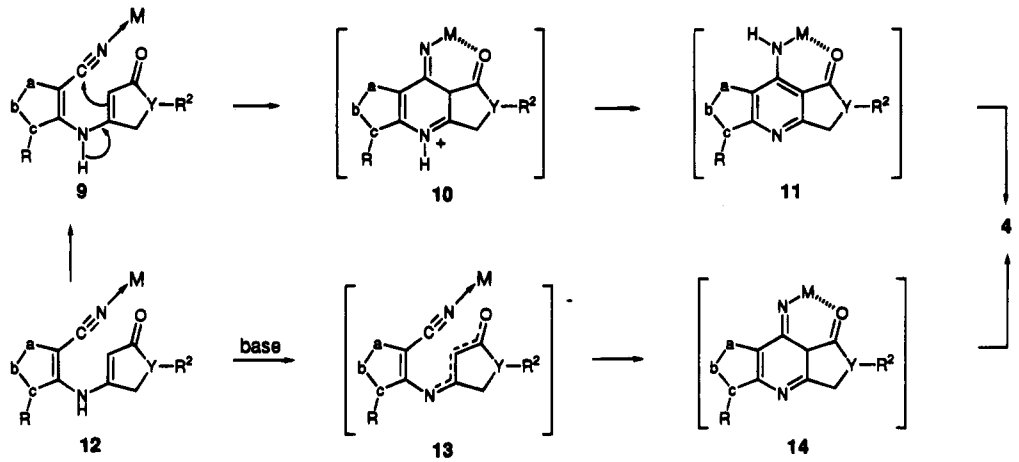
C. Enaminone Anion/Cadmium Salt Activation. Some difficulty was encountered while attempting to effect the cyclization of an 4-allylcyclopentanedione-derived enaminone **3** (a = CH, b = N, c = *N*-pentyl; Y = CH, R^2 = allyl, *n* = 1; see Table 1, entry 5) with $ZnCl_2$. The allyl double bond was isomerized into conjugation with the ketone carbonyl under the harsh reaction conditions. With an increasing need to evaluate the synthesis of related compounds with even more sensitive substituents, we needed to reinvestigate the cyclization to find more mild conditions. On the basis of the simple mechanistic considerations presented above, we reasoned that the cyclization reaction might be improved by enhancing the nucleophilicity[6] of enaminone **3** with simultaneous electrophilic activation of the nitrile. A simple method to accomplish this might be to deprotonate the enaminone with a suitable base in the presence of a Lewis acid to generate a complexed enaminone anion (i.e. **12** → **13**, Scheme 2). Alternatively, the complexed anion **13** might be more conveniently formed by first deprotonating the enaminone and then adding a Lewis acid. The net result of either pathway would potentially lead to double activation of the enaminone substrate thereby promoting a more facile cyclization (Scheme 2). We also hoped to better understand how different metal counterions could influence the cyclization of enaminone anion **13**, in particular the zinc, cadmium, and copper salts described above. For example, a Lewis acid of some optimal size and ligating capacity (metal-based stereoelectronics) could potentially coordinate both the oxygen and nitrile nitrogen of **13** and hence more effectively induce the cyclization.[7]

To investigate this further, a representative enaminone anion was generated by treatment of **3** (a = CH, b = N=, c = *N*-pentyl, R^2 = propyl, Y = N, *n* = 1) with 1 equiv of sodium hydride in THF at 0 °C. After the resulting solution had been warmed to ambient temperature, to ensure complete formation of the anion, the metal salt

(6) (a) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7. (b) Greenhill, J. V.; Moten, M. A. *Tetrahedron* **1983**, *39*, 3405.

(7) We have speculated that closer approach of the two chelating atoms (nitrile nitrogen and carbonyl oxygen), as expected for the cycloheptenyl enaminone relative to smaller ring-containing enaminones, would increase the potential for intramolecular chelation and increase the rate of cyclization. Qualitative differences in the rate of cyclization which are in accord with this hypothesis have been observed using zinc bromide, cuprous acetate, and cadmium chloride at elevated temperatures with enaminones **3**.

Scheme 2



of interest was added (1.2 equiv), and the reaction mixture immediately placed in a bath preheated to 60 °C. Aliquots were removed at selected time intervals and analyzed.[8] A control reaction revealed that only a trace of the cyclized product **4** (a = CH, b = N=, c = *N*-pentyl, R^2 = propyl, Y = N, n = 1) was formed in 8 h at 60 °C with sodium as the counterion. Several Lewis acid salts were surveyed initially. Gratifyingly, a select few of these salts were able to effectively promote the cyclization under the reaction conditions employed, thereby providing support to the double-activation hypothesis. Cadmium chloride proved to be the most effective salt for inducing the cyclization, giving >95% conversion of starting enaminone to product within 6 h. The use of copper(I) acetate as the added Lewis acid, while able to promote a rapid rate of cyclization, gave indications of competing decomposition of starting material during the course of the reaction, thereby limiting the overall efficiency.[9] Zinc chloride was clearly less effective in promoting the cyclization of the enaminone anion compared to cadmium chloride. Further evaluation of other Lewis acids revealed only a few which were able to promote the cyclization.[10] However, none approached the rate and efficiency provided by $CdCl_2$. Both $SnCl_4$ and $InCl_3$ induced rapid cyclization of enaminone **3** (a = CH, b = N=, c = *N*-pentyl, R^2 = propyl, Y = N, n = 1). However, again competing decomposition during the course of the reactions gave a much poorer recovery of product. All attempts to control the reactivity of these Lewis acids, for example by conducting the reactions at lower temperatures, failed to improve the results.

Thus, $CdCl_2$ emerged as the Lewis acid of choice. The polarizability of cadmium suggested that soft metal atoms may favorably coordinate and activate the enaminones toward cyclization.[11] This might also be a contributing factor for copper(I) acetate, a soft Lewis acid, which appeared capable of promoting rapid enaminone anion cyclization, but unfortunately also caused some competing decomposition. Other Lewis acidic metal salts of varying ionic radius, but with a similar degree of polarizability compared to cadmium(II),[12] failed to promote cyclization effectively. For example, Hg(II) ($HgCl_2$), with a larger ionic radius compared to Cd(II), destroyed the starting material and gave no trace of the desired product. Soft Lewis acids containing metals with smaller ionic radii such as $GaCl_3$, Pd(II) salts, and $Ag(O_2CCF_3)$ proved to be ineffective in promoting the cyclization.

A dramatic example of the utility of the NaH/$CdCl_2$ cyclization method was encountered during the investigation of a related series in which the pyrazole **1** (a = CH, b = N, c = NR) was replaced with a pyrrole. Thus, condensation of 3-amino-2-cyano-4-pentylpyrrole (**1**) (a = NH, b = CH, c = *C*-pentyl) with dione **2** (Y = N, R^2 = propyl, n = 1) gave an excellent yield of the corresponding enaminone **3**. Attempts to cyclize the enaminone using either literature-based reaction conditions (e.g. sodium ethoxide)[2c] gave none of the desired product. Likewise, heating the enaminone in the presence of either the $ZnCl_2$ or CuOAc under the conditions described above in section B afforded only traces of the targeted dipyrrolopyridine derivative **4** (a = NH, b = CH, c = *C*-pentyl; Y = N, R^2 = propyl, n = 1). However, a 78% isolated, recrystallized yield of the dipyrrolopyridine could be obtained by deprotonating the enaminone with sodium hydride followed by heating the resulting anion together with cadmium chloride using the improved cyclization procedure.

The reaction conditions employing the $CdCl_2$ promoted cyclization of enaminone anions proved to be quite general. Cyclization of a variety of different enaminones **3**, prepared from condensation of the corresponding *o*-amino nitriles **1** with cyclic 1,3-diones **2**, gave excellent overall conversions to a variety of linear fused tricyclic [*b*,*e*]-fused aminopyridine rings **4** (Table 2).

D. Further Investigation of Cd(II) Salts. The exact role of cadmium salts in promoting the cyclization of enaminones **3** is unclear. There is an effect on the rate

(8) See Experimental Section describing rate investigations.

(9) During the course of our work on the cyclization of enaminones **3** promoted by Lewis acids in the presence of base, another group reported their results on an analogous reaction. Cyclizations of enaminones were induced with K_2CO_3 in the presence of CuCl to prepare 9-amino-3,4-dihydroacridin-1-ones. Yields were, however, typically less than 30%–40%. See Eur. Patent Appl. 0-179-383 and Shutske, G. M.; Pierrat, F. A.; Cornfeld, M. L.; Szewczak, M. R.; Huger, F. P.; Bores, G. M.; Haroutunian, V.; Davis, K. L. *J. Med. Chem.* **1988**, *31*, 1278–1279.

(10) A number of other Lewis acids were evaluated. Standard reaction conditions involved the addition of the Lewis acid to a solution of the enaminone anion in THF, followed by warming to 60 °C for 6 h. The Lewis acids may be categorized according to their relative reactivity for inducing the model enaminone to undergo the desired cyclization. Those able to promote fast cyclization (>70% formation of product within 6 h) were limited to $CdCl_2$ and CuOAc salts; moderate rate of cyclization (20–70% in 6 h): CuCl, $ZnCl_2$; slow cyclization (<20% in 6 h): $NiCl_2$ and $Tl(O_2CCF_3)_3$. A number of other Lewis acids either were ineffective in promoting the cyclization, decomposed the starting enaminone, or caused extensive formation of byproducts. These included: $BF_3{\cdot}OEt_2$, $AlMe_3$, $GaCl_3$, $SbCl_5$, $Pt(acac)_2$, $TiCl_4$, $RhCl_3$, $CuCl_2$, $SbCl_3$, $ZrCl_4$, $Cu(BF_4)_2$, $PdCl_2$, $Pd(OAc)_2$, $Ag(O_2CCF_3)$, NaH, $CaCl_2$, $LaCl_3$, $CeCl_3$, $HgCl_2$.

(11) Ho, T.-L. *Tetrahedron* **1985**, *41*, 1.

(12) Values for ionic radii were taken as crystal ionic radii from the *CRC Handbook of Chemistry and Physics*, 53rd ed., 1972–1973.

Table 2. NaH/$CdCl_2$ Promoted Cyclization of Enaminones (3 → 4)[a]

A Ring a	A Ring b	A Ring c	entry	R^1	R^2	Y	n	% yield[b]
C	N	NR^1	1	pentyl	2-propenyl	CH	1	92
			2	pentyl	propyl	N	1	88
			3	pentyl	H	N	2	84
CH=CH	CH	CR^1	4	3-methoxy-phenyl	propyl	N	1	76
			5	2-furyl	propyl	N	1	63
			6	2-methyl-propyl	cyclopropyl-methyl	N	1	77
			7	Br	propyl	N	1	82
NH	CH	CR^1	8	pentyl	2-propenyl	CH	2	78
CH	CH	NR^1	9	butyl	propyl	N	1	69
CH_2	CH_2	CHR^1	10	pentyl	propyl	N	1	80
N	CH	NR^1	11	pentyl	2-methoxy-ethyl	N	1	80

[a] Enaminones were prepared by condensing the *o*-amino nitriles **1** with 1,3-diones **2** in toluene with azeotropic removal of water. Yields of the enaminones were routinely 83–95%. Details are given in the Experimental Section. [b] Yields represent isolated, recrystallized products.

of cyclization depending on which cadmium salt is used. Thus, after first deprotonating **3** (a = CH, b = N, c = *N*-pentyl; Y = N, R^2 = propyl, *n* = 1) with sodium hydride, both $Cd(OAc)_2$ and the highly electrophilic $Cd(OTf)_2$ proved to be superior to $CdCl_2$ in accelerating the rate of the cyclization to produce **4** (a = CH, b = N, c = *N*-pentyl; Y = N, R^2 = propyl, *n* = 1) [$t_{1/2}$ = 55 min for $CdCl_2$ versus $t_{1/2}$ = 12 min for $Cd(OAc)_2$ and $t_{1/2}$ = 9 min for $Cd(OTf)_2$ at 60 °C)].[13] The remarkable reactivity of $Cd(OTf)_2$ may be further exemplified by its ability to promote the cyclization of **3** (a = CH, b = N, c = *N*-pentyl;Y = N, R^2 = propyl, *n* = 1), again after first deprotonating with NaH, at room temperature [$t_{1/2}$ = ~2 h]. The greater solubility of the acetate and triflate salts in tetrahydrofuran compared to $CdCl_2$ might be a major factor contributing to the rate enhancement.

There is also a clear effect of solvent polarity on the rate of cyclization. Conducting the cyclization reactions in THF:DMF (9:1) resulted in a faster reaction [$t_{1/2}$ = 12 min at 60 °C] than conducting the reaction in the more polar mixture THF:DMF (1:9) [$t_{1/2}$ = 130 min at 60 °C] when using NaH/$Cd(OAc)_2$ as the reagents. These results suggest that solvation of cadmium by DMF might be hindering formation of a key coordinating interaction with the substrate. Clearly there appears to be no apparent stabilization of any polar intermediates that would facilitate cyclization.

We later found that organocadmium reagents could directly induce the cyclization of enaminones. The organocadmium reagents are sufficiently basic to deprotonate the enaminones to form the corresponding anions and provide a means to introduce the cadmium counterion. Thus, reaction of enaminone **3** (a = CH, b = N, c = *N*-pentyl; Y = N, R^2 = propyl, *n* = 1) with freshly prepared dibutylcadmium proceeds as a clear, homogeneous solution at 60 °C to give **4** (a = CH, b = N, c = *N*-pentyl; Y = N, R^2 = propyl, *n* = 1) in 87% yield [$t_{1/2}$ = ~8 min]. In fact, the reaction proceeds to completion at room temperature in 3–4 h! Reaction of *n*-butyllithium with $Cd(OTf)_2$ forms the related reagent, nBuCdOTf,[14] which was also capable of inducing a very facile cyclization, again without the need to pregenerate the enaminone anion [$t_{1/2}$ = ~7–8 min at 60 °C]. Thus, the reaction of the enaminone with either of the two organocadmium reagents provides an exceptionally mild and direct method to effect the enaminone cyclization.

E. Mechanism. Our current thoughts regarding likely mechanisms by which the cyclization proceeds are summarized in Scheme 3. Addition of a cadmium salt to an enaminone anion should give a modified enaminone anion **15** or cadmium enolate **16**. Electrophilic activation of the nitrile would be possible if oxygen-bound cadmium could bridge intramolecularly (i.e. **18**) to coordinate the nitrile.[7] This might also help to orient the enaminone in a conformation which would facilitate the rate of ring closure. There would be an additional driving force for the cyclization by the formation of the intramolecular chelated cadmium complex **20**. Subsequent aromatization of the central ring would then complete the reaction. Alternatively, an added cadmium salt could function as simple Lewis acid to activate the nitrile in the presence of a cadmium (or sodium) enolate **19**. This intermediate may then rapidly cyclize to again form the stabilized cadmium coordinated chelate **20**. Another alternative might involve the migration of cadmium over the enaminone π system from oxygen to nitrogen (**16** → **17**) or from the enaminone nitrogen to cyano nitrogen (**15** → **17**) depending upon the tautomeric position of cadmium.[15] Related metallotropic rearrangements have been described for mercury(II) (nondegenerate oxygen to nitrogen migration).[16] The resulting *o*-imino ketenimine[17] **17** would then be poised to undergo a 6-π electron electrocyclization, resulting again in formation of the cadmium-bridged intermediate **20**. This tandem sigmatropic rearrangement/electrocyclization is somewhat appealing since it accommodates a more favorable orbital alignment between the reacting centers to form the new carbon–carbon bond.

Certainly, any of these postulated mechanisms may be operative and are likely to be highly dependent on the nature of the substrates and metal salt additives. Thus, there may be a continuum of mechanisms acting in concert to promote the reaction depending on the particular procedure employed.

Summary

A series of two-step procedures to synthesize [*b*,*e*]-fused aminopyridines have been developed. An enaminone is formed in the first step by condensation of an *o*-amino nitrile with a cyclic 1,3-dione. Cyclization of the enaminone in the second step can then be promoted by one of several procedures. Lewis acids such as copper(I) acetate or zinc halides can promote cyclization of simple enami-

(13) The $t_{1/2}$'s were taken as the time for the reaction to produce 50% of the product **4** (a = CH, b = N, c = *N*-pentyl; Y = N, R^2 = propyl, *n* = 1) in THF at 60 °C. Since yields (isolated) determined from independent reactions were generally >85%, this represents a reasonable approximation of the rate.

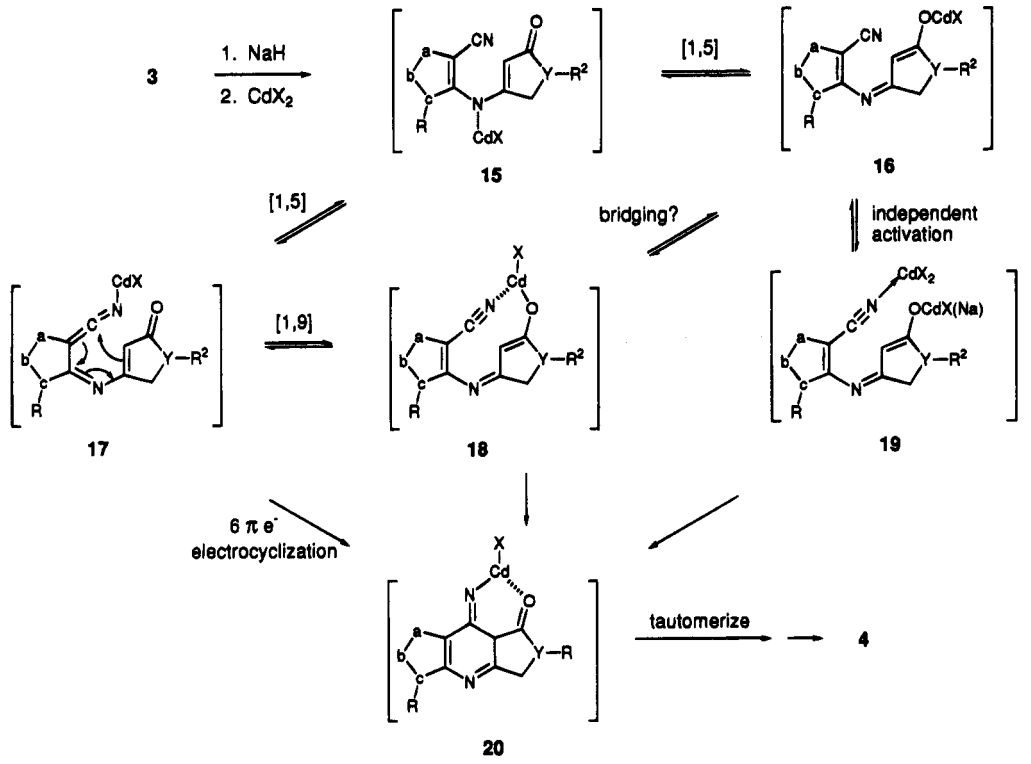
(14) The designation of "BuCdOTf" formed by reaction of BuLi with $Cd(OTf)_2$ only conveys stoichiometry used in the reaction and does not represent any defined structural information.

(15) Formally this could be viewed as a [1,9]-metallotropic rearrangement, in which the cadmium would migrate suprafacially over the enaminone π system.

(16) Fedorov, L. A.; Kravtsov, D. N.; Peregudov, A. S. *Russ. Chem. Rev.* **1981**, *50*, 682, and references cited therein.

(17) (a) Bowen, R. D.; Davies, D. E.; Fishwick, C. W. G.; Glasbey, T. O.; Noyce, S. J.; Storr, R. C. *Tetrahedron Lett.* **1982**, *23*, 4501–4504. (b) Ito, Y.; Nakajo, E.; Saegusa, T. *Tetrahedron Lett.* **1984**, *25*, 5139–5142. (c) Shivanyuk, A. F.; Dashkovskaya, E. V.; Lozinskii, M. O.; Kalinin, V. N. *Acad. Sci. USSR* **1986**, *22*, 1084–1089. (d) Reinecke, M. G.; Brown, E. S. *J. Org. Chem.* **1988**, *53*, 208.

Scheme 3



nones **3** at 120 °C to 200 °C. In an even more effective, mild and general procedure, cadmium(II) salts can promote the cyclization of enaminone anions prepared by deprotonation of enaminones with sodium hydride. This has resulted in the preparation of several otherwise synthetically inaccessible tricyclic fused aminopyridines **4**. The remarkable reactivity of cadmium itself, without the need for added base, in promoting the cyclization reaction, is most notably exemplified by the more direct and even more facile reaction of the enaminones **3** at ambient temperature with dibutylcadmium or butylcadmium triflate to form the targeted ring system **4**. The apparent scope of the cyclization for the preparation of [*b*,*e*]-fused aminopyridines appears only limited by the accessibility of different A and C rings as starting materials (Scheme 1).

Mechanisms proposed for the enaminone cyclization all would involve coordination of cadmium to the nitrile as a critical step. Activation of the nitrile toward nucleophilic addition by the enaminone anion then becomes facilitated. A variation of the mechanism may involve migration of cadmium(II) from oxygen or the enaminone nitrogen to nitrogen of the nitrile. A subsequent symmetry allowed 6-π electron electrocyclization would then complete the central ring closure. Further evaluation of this novel cadmium(II) promoted cyclization might reveal a preferred mechanism. Identification of a more defined mechanistic role for cadmium(II) may then permit further its exploitation in other intramolecular and possibly intermolecular additions to nitriles or other suitable electrophiles.

Experimental Section

General Information. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl immediately prior to use. TLC analyses were performed on silica gel GHLF. Flash chromatography refers to the method reported by Still.[18] All reactions were performed under a nitrogen or argon atmosphere. Ambient temperature refers to 23 °C (±3 °C). Melting points were taken on a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at either 250 or 300 MHz. Chemical ionization (methane or isobutane ionization gas) and electron impact mass spectra were obtained on a mass spectrometer operating at a source pressure of >1 Torr. Elemental analyses were performed by the departmental analytical laboratory at Zeneca Pharmaceuticals, Inc.

Synthesis of Enaminone 7. General Procedure.[19] Condensation of pyrazole **5**[1b] with 1,3-cyclohexanedione (**6**) serves as a representative example: **6** (0.83 g, 7.42 mM) was mixed with pyrazole **5** (1.18 g, 6.64 mM) and 0.070 g *p*-TsOH·H_2O in 30 mL of toluene. The mixture was heated to reflux and the toluene/water azeotrope collected in a Dean–Stark trap. The reaction mixture was heated for 3 h and then cooled to ambient temperature followed by dilution with 20 mL of diethyl ether:THF (1:1). An equal volume of saturated aqueous Na_2CO_3 was added and the mixture shaken vigorously in a separatory funnel. The layers were separated, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to leave a brown gum. Rapid elution through a small plug of silica gel using ethyl acetate:hexanes (2:1) as the eluent afforded 1.67 g (93%) of a light yellow solid: mp 117–118 °C; TLC, R_f = 0.22 methanol:chloroform (1:19); ^{1}H NMR ($CDCl_3$) 0.87 (t, J = 6.9 Hz, 3H), 1.26 (m, 4H), 1.81 (m, 2H), 2.06 (m, 2H), 2.35 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 6.0 Hz, 2H), 3.95 (t, J = 7.3 Hz, 2H), 5.00 (s, 1H), 7.32 (s, 1H), 7.78 (s, 1H); mass spectrum (CI), *m*/*z* 273 (M + 1).

Cyclization of Enaminone 7 with Zinc Chloride. General Procedure. Cyclization of enaminone **7** with zinc chloride serves as a representative example to prepare 4-amino-1-pentyl-5*H*-1,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolin-5-one **8** (Table 1, entry 1). $ZnCl_2$ (12.0 g, 88 mM) was dried by heating for 1 h at 150 °C under high vacuum. The dried $ZnCl_2$ was cooled to ambient temperature under a stream of N_2, and then enaminone **7** (1.65 g, 6.10 mM) was added as a solid. The

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(19) Full experimental details which describe the preparation and characterization of all of the noncommercially available starting materials and all of the intermediates are disclosed in references 1b and 1c.

mixture was heated to 180 °C using a silicon oil bath and stirred vigorously using a mechanical stirrer. After stirring 2 h at 180 °C, the mixture was cooled to ambient temperature and poured into water. A mixture of THF:methylene chloride (1:1) was then added. The layers were separated with the aqueous phase further extracted with an additional portion of THF:methylene chloride. The combined organic phase was washed twice with water, shaken with 10% aqueous NaOH, and then washed once with saturated aqueous citric acid. The organic layer was washed one additional time with brine and then was dried over anhydrous $MgSO_4$. After removing the volatiles, the resulting light brown solid was chromatographed over silica gel using ethyl acetate:hexanes (1:3) as the eluent. The solid was recrystallized from *tert*-butyl methyl ether/hexanes to leave 1.47 g (89%) of a white crystalline solid: mp 153–154 °C; TLC, R_f = 0.41 methanol:chloroform (1:19); ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 8.0 Hz, 3H), 1.34 (m, 4H), 1.94 (m, 4H), 2.12 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 3.09 (t, J = 7.5 Hz, 2H), 4.38 (t, J = 8.0 Hz, 2H), 5.68 (broad s, 1H), 7.94 (s, 1H), 9.82 (broad s, 1H); mass spectrum (EI), *m/e* 272. Anal. Found: C, 65.73; H, 7.39; N, 20.77. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.39; N, 20.56.

Cyclization of Enaminones with Copper(I) Acetate. General Procedure. Preparation of 4-amino-6,7-dihydro-1-pentyl-6-(2-propenyl)cyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (Table 1, entry 5) serves as a representative example. Copper(I) acetate (1.20 g, 9.78 mM) was added to a solution of 1.47 g (4.90 mM) of enaminone **3** (a = CH, b = N, c = *N*-pentyl; R^2 = 2-propenyl, Y = CH, n = 1) at ambient temperature in 10 mL of butyl acetate. The mixture was plunged into a preheated 120 °C silicon oil bath. The mixture was stirred vigorously for 10 min, removed from the oil bath, and allowed to slowly cool to ambient temperature. Water (5 mL) was added to the mixture followed by adding 5 mL of concentrated ammonium hydroxide. This mixture was stirred for 30 min and then extracted twice with diethyl ether:THF (1:1). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated to leave a brown solid. The crude material was passed through a small pad of silica gel using ethyl acetate:hexanes (1:1) as the eluent. Recrystallization of the solid from *tert*-butyl methyl ether/hexanes gave 1.28 g (87%) of fine white crystals: mp 141.5–142.5 °C; TLC, R_f = 0.31 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 0.87 (t, J = 8.0 Hz, 3H), 1.34 (m, 4H), 1.92 (m, 2H), 2.32 (m, 1H), 2.70 (m, 1H), 2.78–2.92 (m, 4H), 3.27 (dd, J = 9.0 Hz, J = 16.0 Hz, 1H), 4.42 (t, J = 6.5 Hz, 2H), 5.05–5.17 (m, 2H), 5.73 (broad s, 1H), 5.80 (m, 1H), 7.90 (broad s, 1H), 7.96 (s, 1H); mass spectrum (EI), *m/e* 298; IR ($CBrCl_3$) 3430, 3335, 2925, 1639, 1599, 1560, 1465, 1385 cm^{-1}. Anal. Found: C, 68.58; H, 7.71; N, 18.65. Calcd for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78.

4-Amino-6-butyl-1-pentyl-5*H*-1,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolin-5-one (Table 1, entry 2). The title compound was prepared using $ZnBr_2$ giving, after recrystallization, a white solid in 83% yield: mp 58.5–60 °C; TLC, R_f = 0.24 ethyl acetate:hexanes (1:3); ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 8.0 Hz, 3H), 0.94 (t, J = 6.5 Hz, 3H), 1.38 (m, 4H), 1.53 (m, 1H), 1.92 (m, 4H), 2.21 (m, 1H), 2.50 (m, 1H), 3.09 (m, 2H), 4.38 (t, J = 7.5 Hz, 2H), 5.58 (broad s, 1H), 7.92 (s, 1H), 8.84 (broad s, 1H); mass spectrum (EI), *m/e* 328; IR ($CBrCl_3$) 3490, 3275, 2950, 2868, 1615, 1582 cm^{-1}. Anal. Found: C, 69.47; H, 8.60; N, 17.13. Calcd for $C_{19}H_{28}N_4O$: C, 69.45; H, 8.59; N, 17.06.

4-Amino-6,7-dihydro-1-pentylcyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (Table 1, entry 3): white crystalline solid, mp 172–173 °C; TLC, R_f = 0.30 methanol:chloroform (1:19); ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 8.9 Hz, 3H), 1.35 (m, 4H), 1.94 (m, 2H), 2.78 (m, 2H), 3.16 (m, 2H), 4.42 (t, J = 8.0 Hz, 2H), 5.77 (broad s, 1H), 7.94 (broad s, 1H), 7.98 (s, 1H); mass spectrum (EI), *m/e* 258; IR ($CBrCl_3$) 3420, 3310, 2925, 1662, 1619, 1588, 1559, 1466, 1390 cm^{-1}. Anal. Found: C, 64.46; H, 6.97; N, 21.39. Calcd for $C_{14}H_{18}N_4O$: C, 65.07; H, 7.02; N, 21.68.

4-Amino-6,7-dihydro-1-pentyl-6-propylcyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (Table 1, entry 4): white crystals, mp 138–139 °C; TLC, R_f = 0.21 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 0.87 (t, J = 8.0 Hz, 3H), 0.96 (t, J = 6.5 Hz, 3H), 1.34 (m, 4H), 1.48 (m, 4H), 1.94 (m, 2H), 2.79 (m, 1H), 2.87 (m, 1H), 3.30 (dd, J = 9.0 Hz, J = 12 Hz, 1H), 4.43 (t, J = 7.5 Hz, 2H), 5.69 (broad s, 1H), 7.91 (broad s, 1H), 7.96 (s, 1H); mass spectrum (EI), *m/e* 300; IR ($CBrCl_3$) 3430, 3335, 2955, 2930, 1641, 1605, 1565, 1470, 1385 cm^{-1}. Anal. Found: C, 67.95; H, 8.24; N, 18.29. Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65.

4-Amino-6,7-dihydro-1-pentylcyclohepta[*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (Table 1, entry 6): white crystals, mp 124–125 °C; TLC, R_f = 0.27 ethyl acetate:hexanes (1:1); ^{1}H NMR (DMSO-d_6) 0.81 (t, J = 8.0 Hz, 3H), 1.25 (m, 4H), 1.61–1.88 (m, 6H), 2.69 (m, 2H), 3.05 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 7.5 Hz, 2H), 8.05 (broad s, 1H), 8.22 (s, 1H), 8.67 (broad s, 1H); mass spectrum (EI), *m/e* 286. Anal. Found: C, 67.13; H, 7.72; N, 19.67. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56.

4-Amino-6,7-dihydro-1-pentyl-6-propylpyrazolo[3,4-*b*]-pyrrolo[3,4-*e*]pyridin-5(1*H*)-one (Table 1, entry 7): white crystals, mp 146–146.5 °C; TLC, R_f = 0.30 ethyl acetate:hexanes (2:1); ^{1}H NMR 0.88 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H), 1.32 (m, 2H), 1.69 (m, 2H), 1.93 (m, 2H), 3.54 (t, J = 6.5 Hz, 2H), 4.34 (s, 2H), 4.43 (t, J = 8.0 Hz, 2H), 6.50 (broad s, 2H), 8.0 (s, 1H); mass spectrum (EI), *m/e* 301; IR (Nujol) 3320, 2950, 2915, 1660, 1610, 1595 cm^{-1}. Anal. Found: C, 63.77; H, 7.76; N, 23.22. Calcd for $C_{16}H_{23}N_5O$: C, 63.76; H, 7.69; N, 23.24.

4-Amino-7,8-dihydro-1-pentyl-1*H*-pyrazolo[3,4-*b*][1,6]-naphthyridin-5(6*H*)-one (Table 1, entry 8): white crystalline solid, mp 161–162.5 °C; TLC, R_f = 0.19 methanol:chloroform (1:19); ^{1}H NMR (DMSO-d_6) 0.83 (t, J = 8.0 Hz, 3H), 1.24 (m, 4H), 1.79 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.34 (m, 2H), 4.25 (t, J = 6.5 Hz, 2H), 7.65 (s, 1H), 7.84 (broad s, 1H), 8.18 (s, 1H), 9.06 (broad s, 1H); IR ($CBrCl_3$) 3340, 2925, 1620, 1593, 1403, 1335 cm^{-1}. Anal. Found: C, 61.45; H, 6.94; N, 25.32. Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62.

Rate Investigations. Cyclization of Enaminone 3 (a = CH, b = N, c = *N*-pentyl; R^2 = propyl, Y = N, n = 1) with Sodium Hydride and Various Metal Salt Additives. The cyclization using cadmium chloride serves as a representative example for monitoring the rate of enaminone anion cyclization in the presence of metal salt additives. A suspension of NaH (0.08 g, 1.82 mM, 55% in oil) was washed twice with THF and then suspended in 2 mL of fresh THF. The suspension was cooled in an ice bath and enaminone **10** (R^1 = propyl, Y = N, n = 1, 0.50 g, 1.66 mM) was added as a solution in THF (1.32 mL). The reaction mixture was stirred several minutes at 0 °C and then warmed to ambient temperature and stirred 30 min. Cyclohexylbenzene (0.0912 g, 0.569 mM) was then added as an internal standard for ^{1}H NMR analysis. Cadmium chloride (0.37 g, 1.99 mM) was added all at once and the mixture stirred vigorously. After stirring about 2 min the mixture was plunged into a 60 °C (±3 °C) silicon oil bath. Small aliquots were removed from the reaction mixture at selected time intervals and quenched immediately in excess aqueous Na_2EDTA. The samples were stirred for several minutes and then extracted several times with ethyl acetate. The organic extracts were monitored by TLC at this point to estimate the extent of reaction. The combined extracts were dried ($MgSO_4$) and concentrated. The concentrated samples were placed under high vacuum (ca. 0.05 mmHg) for 10 min and then ^{1}H NMR spectra recorded using $CDCl_3$ as the solvent. The integrals for internal standard absorptions (7.21 ppm, m, 5H) were compared with integrals for enaminone (4.94 ppm, s, 1H and 3.31 ppm, t, 2H) and product (4.41 ppm, t, 2H and 4.03 ppm, s, 2H). The amount of unreacted enaminone and product formed were then quantified for each time interval (estimated error for each time point ca. ±15%).

Cyclization of Enaminone 3 with Sodium Hydride/Cadmium Chloride. General Procedure. The procedure for the preparation of 9-amino-2,3-dihydro-5-(3-methoxyphenyl)-2-propylpyrrolo[3,4-*b*]quinolin-1-one (Table 2, entry 4) serves as a representative example. A suspension of NaH (0.12 g, 2.72 mM, 55% in oil) was washed twice with dry THF and then suspended in 10 mL of fresh THF. The suspension was cooled in an ice–water bath and to this was added slowly a solution containing 0.86 g (2.48 mM) of the enaminone

dissolved in 2 mL of dry DMF. (Note: the DMF may be omitted where the enaminone anion is soluble in THF.) The mixture was stirred for 20 min during which time gas evolution ceased and a clear solution formed. The solution was warmed to ambient temperature and stirred an additional 20 min. Dry $CdCl_2$ (0.55 g, 2.98 mM) was added all at once to the vigorously stirred solution. The mixture was slowly heated to 80 °C whereupon 8 mL of dry toluene was added. The mixture was then heated to ca. 100 °C and refluxed 1 h. The mixture was cooled to ambient temperature and water was added followed by the addition of solid Na_2EDTA. The mixture was stirred 30 min with the pH checked to ensure being >8. Methylene chloride was added, and the layers separated. The organic phase was washed sequentially with saturated aqueous Na_2-EDTA, water, and brine and then dried over anhydrous $MgSO_4$. After removing the volatiles, the crude product was purified by flash chromatography using ethyl acetate:hexanes (1:1) as the eluent. The resulting solid was recrystallized from *tert*-butyl methyl ether to afford 0.65 g (76%) of a white stringy solid: mp 189–190 °C; TLC, R_f = 0.18 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 0.96 (t, J = 7.2 Hz, 3H), 1.67 (m, 2H), 3.55 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 4.37 (s, 2H), 6.41 (broad s, 2H), 6.95 (m, 1H), 7.24–7.86 (m, 6H); mass spectrum (CI) m/z 348 (M^+ + 1); IR ($CBrCl_3$) 3387, 3200, 1685, 1635, 1525, 1457 cm^{-1}. Anal. Found: C, 72.75; H, 6.30; N, 12.13. Calcd for $C_{21}H_{21}N_2O_2$: C, 72.60; H, 6.09; N, 12.10.

9-Amino-2,3-dihydro-5-(2-furyl)-2-propylpyrrolo[3,4-*b*]-quinolin-1-one (Table 2, entry 5): off-white solid, mp 195–196 °C dec; TLC, R_f = 0.40 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 7.5 Hz, 3H), 1.72 (m, 2H), 3.60 (t, J = 7.0 Hz, 2H), 4.47 (s, 2H), 6.39 (broad s, 2H), 6.59 (m, 1H), 7.48–7.56 (m, 2H), 7.72–7.81 (m, 2H), 8.26 (d, J = 7.5 Hz, 1H); mass spectrum (CI), m/z 308 (M^+ + 1); IR ($CBrCl_3$) 3410, 3200, 1670, 1643, 1613, 1463 cm^{-1}. Anal. Found: C, 70.50; H, 5.90; N, 13.25. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.66.

9-Amino-2-(cyclopropylmethyl)-2,3-dihydro-5-(2-methylpropyl)pyrrolo[3,4-*b*]quinolin-1-one (Table 2, entry 6): white solid, mp 157–158 °C; ^{1}H NMR ($CDCl_3$) 0.36 (m, 2H), 0.61 (m, 2H), 0.94 (d, J = 6.5 Hz, 6H), 1.13 (m, 1H), 2.18 (m, 1H), 3.08 (d, J = 7.2 Hz, 2H), 3.48 (d, J = 7.1 Hz, 2H), 4.56 (s, 2H), 6.32 (broad s, 2H), 7.39 (dd, J = 6.0 Hz, J = 8.4 Hz, 1H), 7.53 (d, J = 6.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H); mass spectrum (CI), m/z 310 (M^+ + 1); IR (KBr) 3445, 3358, 2920, 1682, 1635, 1603 cm^{-1}. Anal. Found: C, 73.73; H, 7.54; N, 13.58. Calcd for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58.

9-Amino-5-bromo-2,3-dihydro-2-propylpyrrolo[3,4-*b*]-quinolin-1-one (Table 2, entry 7): white solid, mp 221–226 °C; TLC, R_f = 0.24 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 0.98 (t, J = 7.3 Hz, 3H), 1.70 (m, 2H), 3.59 (t, J = 7.3 Hz, 2H), 4.59 (s, 2H), 6.51 (broad s, 2H), 7.32 (dd, J = 9.0 Hz, J = 7.6 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H); mass spectrum (CI), m/z 320 (M^+ + 1, ^{79}Br), 322 (M^+ + 1, ^{81}Br); IR ($CBrCl_3$) 3325, 3180, 1685, 1633, 1608, 1458 cm^{-1}. Anal. Found: C, 52.46; H, 4.42; N, 13.10. Calcd for $C_{14}H_{14}N_3$-OBr: C, 52.21; H, 4.41; N, 13.12.

8-Amino-3-pentyl-6-(2-propenyl)-4,5,6,7-tetrahydropyrrolo[3,2-*b*]quinolin-7(1*H*)-one (Table 2, entry 8): white solid, mp 195 °C dec; TLC, R_f = 0.29 ethyl acetate:hexanes (1:1); ^{1}H NMR (DMSO-d_6) 0.86 (t, J = 6.5 Hz, 3H), 1.29 (m, 4H), 1.52–1.78 (m, 4H), 2.05 (m, 1H), 2.22 (m, 1H), 2.51–2.67 (m, 5H), 2.94 (m, 2H), 5.06 (m, 2H), 5.82 (M, 1H), 7.24 (broad s, 1H), 7.31 (s, 1H), 8.90 (broad s, 1H), 10.88 (s, 1H); mass spectrum (CI), m/z 312 (M^+ + 1); IR ($CBrCl_3$) 3370, 3275, 2910, 1640, 1585, 1547, 1420 cm^{-1}. Anal. Found: C, 72.58; H, 8.04; N, 13.21. Calcd for $C_{19}H_{25}N_3O$: C, 73.19; H, 8.09; N, 13.49.

4-Amino-1-butyl-6,7-dihydro-6-propyldipyrrolo[2,3-*b*:3,4-*e*]pyridin-5(1*H*)-one (Table 2, entry 9): white solid, mp 169–171 °C; TLC, R_f = 0.24 ethyl acetate:hexanes (1:1); ^{1}H NMR ($CDCl_3$) 0.94 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.33 (m, 2H), 1.67 (m, 2H), 1.82 (m, 2H), 3.54 (t, J = 7.1 Hz, 2H), 4.22 (t, J = 7.1 Hz, 2H), 4.33 (s, 2H), 5.85 (broad s, 2H), 6.41 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H); mass spectrum (CI), m/z 287 (M^+ + 1); IR ($CBrCl_3$) 3197, 2970, 2940, 1690, 1630, 1545, 1405 cm^{-1}. Anal. Found: C, 66.96; H, 8.00; N, 19.06. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56.

4-Amino-7-pentyl-2-propyl-1,3,5,6-tetrahydrocyclopenta[2,3-*b*]pyrrolo[3,4-*c*]pyridin-3(1*H*)-one (Table 2, entry 10): white solid, mp 108–109 °C; TLC, R_f = 0.31 methanol:chloroform (3:97); ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 6.7 Hz, 3H), 0.98 (t, J = 7.9 Hz, 3H), 1.34 (m, 4H), 1.68 (m, 2H), 1.89 (m, 2H), 3.54 (t, J = 7.2 Hz, 2H), 4.21 (t, J = 7.1 Hz, 2H), 4.33 (s, 2H), 6.35 (broad s, 2H), 7.80 (s, 1H); mass spectrum (EI), m/e 301; IR (Nujol) 3340, 3160, 2940, 2905, 1649, 1585, 1410, 1380, 1225 cm^{-1}. Anal. Found: C, 63.33; H, 7.65; N, 23.11. Calcd for $C_{16}H_{25}N_5O{\cdot}0.1H_2O$: C, 63.38; H, 7.71; N, 23.10.

4-Amino-5,7-dihydro-6-(2-methoxyethyl)-1-pentylpyrrolo[3,4-*b*]imidazo[4,5-*c*]pyridin-5(1*H*)-one (Table 2, entry 11): white needles, mp 173.5–174.5 °C; TLC, R_f = 0.30 methanol:chloroform (7:93); ^{1}H NMR ($CDCl_3$) 0.98 (t, J = 7.4 Hz, 3H), 1.68 (m, 2H), 3.34 (s, 3H), 3.54 (t, J = 7.1 Hz, 2H), 3.73 (t, J = 5.0 Hz, 2H), 4.32 (s, 2H), 4.40 (t, J = 5.0 Hz, 2H), 6.28 (broad s, 2H), 7.91 (s, 1H); mass spectrum (EI), m/e 289; IR (Nujol) 3390, 3135, 2895, 2845, 1673, 1635, 1400, 1375, 1318, 1225 cm^{-1}. Anal. Found: C, 58.14; H, 6.65; N, 24.11. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.20.

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