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Cyclization of 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles with amines: a mechanistic rationalization

Francisco Carrión, Núria Mont, Xavier Batllori, José I. Borrell and Jordi Teixidó*

Grup d'Enginyeria Molecular, Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta 390, E-08017 Barcelona, Spain

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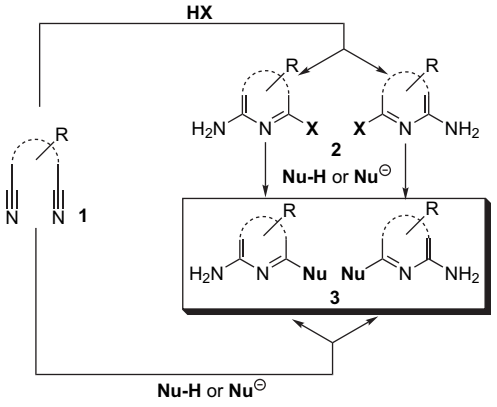
Abstract—A mechanistic rationalization for the cyclization of the 1,5-dinitrile system present in pyridines **4**{1–3} with amines to lead to 1,6-naphthyridines is proposed. Three factors play an important role on the direction of cyclization: (1) the cyclization involves nucleophilic attack of an amidine onto a nitrile or amidine; (2) the attack has to fulfill strict geometrical constraints to allow the cyclization to proceed; (3) the cyclization step should involve the nucleophilic attack combined with a tautomerism to achieve the high levels of regioselectivity observed.

1. Introduction

The cyclization of α,ω-dinitriles has attracted the interest of organic chemists due to the wide possibilities that offer for the synthesis of nitrogen heterocycles. A good knowledge of the mechanism and factors that influence such cyclizations is crucial because two possible regioisomers can be formed both in the presence of acidic or basic reagents.

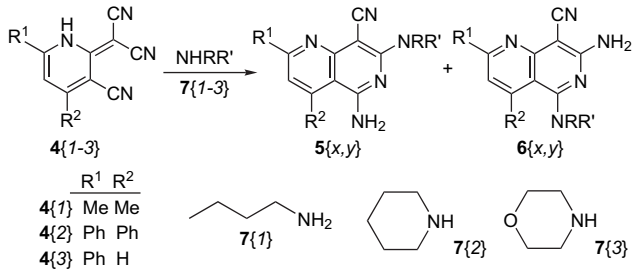
Cyclizations of 1,5-dinitriles **1** in acidic media are usually carried out in the presence of hydrogen halides to afford a mixture of two halogen-substituted regioisomers **2** (Scheme 1). In most cases the halogen atom can be substituted by a nucleophile to yield the corresponding compounds **3**.[1–6] Compounds **3** are, normally, also accessible by direct cyclization of the dinitrile system (**1**) upon treatment with the nucleophilic reagent.



Scheme 1.

As for the mechanistic rationalization of such cyclizations in acidic media, many has been the revisions and updates since the pioneering work of Johnson and Madronero in 1966,[7] the latest ones being contributions of our group.[8,9] As a result of them, we proposed a mechanistic rationalization based on three factors; (1) the relative basicity of the cyano groups involved in the reaction, (2) the planarity of the reactive site, and (3) the tautomeric equilibrium of the starting dinitrile system.

On the contrary, far less attention has been paid to cyclizations in basic media although its synthetic utility is quite obvious as shown above. A better knowledge of the factors involved in such cyclizations would allow a better control of the reaction and, ideally, the synthesis of one or another isomer at will. As a part of our work in the area of α,ω-dinitrile cyclizations, we decided to study the factors affecting the formation of the regioisomeric 1,6-naphthyridines **5** and **6** by cyclization with different amines of the 1,5-dinitrile system present in pyridines **4**{1–3}[10] (Scheme 2). The present paper reports the results of such study.



Scheme 2. Chemset numbering of compounds **5**{*x*,*y*} and **6**{*x*,*y*} is standardized as follows: **5**{building block **4**, building block **7**} and **6**{building block **4**, building block **7**}.

* Corresponding author. Fax: +34932056266; e-mail: j.teixido@iqs.url.edu

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2. Results and discussion

Three amines, butylamine **7**{1}, cyclohexylamine **7**{2}, and morpholine **7**{3}, were selected in order to cover a range of amine class, basicity, and size.

In order to unequivocally assign the structure of the resulting 1,6-naphthyridines **5**{*x*,*y*} and **6**{*x*,*y*}, we obtained the corresponding compounds **5**{*x*,*y*} by nucleophilic substitution on the previously described 5-amino-7-bromo-1,6-naphthyridine-8-carbonitriles **8**{1–3} (Fig. 1).[10] As for the factors studied, we systematically modified the solvent (methanol, dioxane, chloroform or the net amine), the ratio between the substrate and the amine (from 1:10 to 1:2000), and the reaction time (from 24 h to 6 days). All the assays were carried out at reflux and the reaction mixtures were analyzed by HPLC avoiding any manipulation that could alter the results obtained.

Our first observation was that, in all cases, the reactions turned to be very slow, therefore long reaction times being needed. This fact is probably due to the presence of an acidic proton in compounds **4**{1–3}, which underwent deprotonation in the basic media to afford an anion far less reactive with nucleophiles.

The results obtained mainly depend on the nature of the amine employed. Thus, in the case of morpholine **7**{3}, the less basic of the amines, cyclization of pyridines **4**{1} (R^1=R^2=Me) and **4**{2} (R^1=R^2=Ph) gave similar results, the 7-morpholino substituted 1,6-naphthyridines **5**{1,3} and **5**{2,3} being the major compounds obtained nearly independent of the solvent or the reaction time employed. However, in both cases a second compound was isolated whose structure corresponded to the enediamines **9**{1,3} and **9**{2,3}, respectively, which are stabilized by an intramolecular hydrogen bond (Fig. 1).

Compounds **9** are the result of a nucleophilic addition of the amine to one of the nitrile groups of pyridines **4**. Their ratio in the reaction mixture decreases with an increase in the reaction time (in the case of **9**{1,3} from 38% to 1% in dioxane using a 1:10 **4**{1}/morpholine ratio for 24 h and 6 days, respectively) and with an increase in the morpholine amount (being negligible in dioxane or $CHCl_3$ using a 1:1000 ratio or in net morpholine). More important is the effect of the substrate, thus the presence of a phenyl substituent in *ortho* position to the nitrile group of **4**{2} causes an increase in the amount of **9**{2,3} being now the major compound (17%) in dioxane using a 1:10 **4**{2}/morpholine ratio for 24 h or 3 days. Only the use of a 1:1000 ratio, net morpholine or long reaction times reverses the situation allowing **5**{2,3} to be the major compound. Finally, the effect of the solvent is not so clear and good conversions into **5**{1,3} and **5**{2,3} can be achieved in almost any solvent by tuning the substrate/amine ratio or the reaction time.

With regard to the cyclization of **4**{3} (R^1=Ph, R^2=H) with morpholine, this was the only case in which, regardless of the substrate or amine used, the corresponding 5-(substituted amino)-1,6-naphthyridine **6**{3,3} was obtained (Fig. 1) although as a minor compound (less than 10% in all cases). In all the reaction conditions assayed the 7-morpholino substituted derivative **5**{3,3} was the major compound (up to 89% in dioxane using a 1:10 **4**{3}/morpholine ratio for 6 days). It is also interesting to note the formation, in this case, of a byproduct **10**{3,3} (Fig. 1) whose structure shows no relation with the cyclization process. This aspect and others will be discussed later on.

In the case of butylamine **7**{1} (Fig. 2), the overall cyclization yields were lower than those obtained with morpholine and, depending on the substrate employed, more complex reaction mixtures were obtained, which included some compounds whose structures seemed to be alien to the cyclization process. Thus, treatment of pyridine **4**{1} (R^1=R^2=Me) with butylamine gave the 7-butylamino substituted 1,6-naphthyridine **5**{1,1} (Fig. 2) as the major compound (up to 90% in dioxane using a 1:1000 **4**{1}/butylamine ratio for 6 days). When the reaction was carried out in dioxane using a 1:10 ratio, a second compound **11**{1,1} was isolated (less than 5%), which carries two butylamino groups. Structure **11**{3,1} was also formed in similar amount when pyridine **4**{3} (R^1=Ph, R^2=H) was treated with a 1:10 ratio of butylamine in dioxane.

Treatment of **4**{2} (R^1=R^2=Ph) with butylamine also afforded the 7-butylamino substituted 1,6-naphthyridine **5**{2,1} (Fig. 2) as the major compound although conversions were lower than in the preceding case (up to 73% in net butylamine). In all the experiments a third compound was obtained, which corresponds to amide **10**{2,1} (Fig. 2) that reaches up to 35% in dioxane or $CHCl_3$ when a 1:10 **4**{2}/butylamine ratio is used.

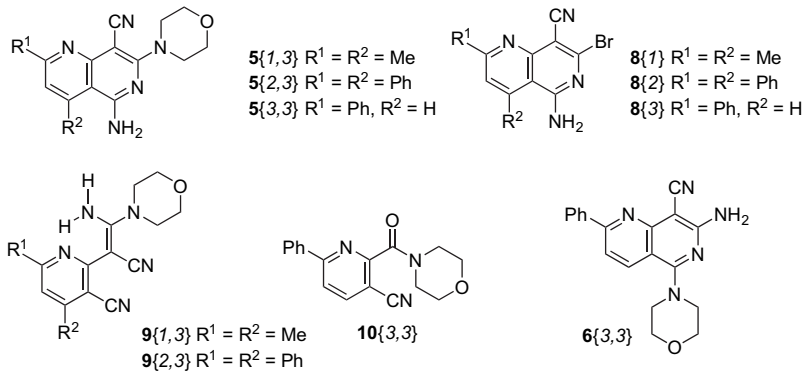


Figure 1.

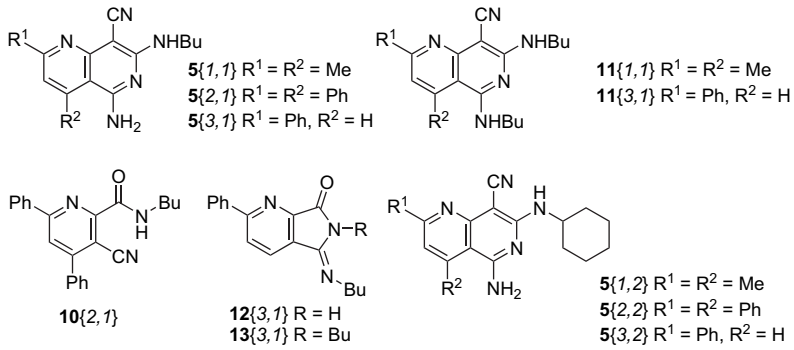


Figure 2.

The behavior in the case of **4**{3} (R^1=Ph, R^2=H) was very peculiar, the 7-butylamino substituted 1,6-naphthyridine **5**{3,1} (Fig. 2) not being the major compound in any case (only 24% in dioxane using a 1:1000 **4**{3}/butylamine ratio for 6 days). On the contrary, two new compounds **12**{3,1} and **13**{3,1} were formed even as the major reaction products (10% and 26% in dioxane using a 1:10 **4**{3}/butylamine ratio for 6 days). The origin of such products will be discussed later on this paper.

Finally, cyclizations with cyclohexylamine **7**{2} only gave good yields of the 7-cyclohexylamino substituted 1,6-naphthyridines **5**{1,2} (97%), **5**{2,2} (39%), and **5**{3,2} (64%) (Fig. 2) using net cyclohexylamine for 6 days at reflux. Again it was also possible to obtain good results in dioxane using a 1:1000 **4**{3}/cyclohexylamine ratio for 6 days. Although some byproducts were formed, the small amounts in which they were isolated did not allow an adequate structural assignment.

The overall experiments for the cyclization of pyridines **4** with amines allowed to extract the following initial conclusions:

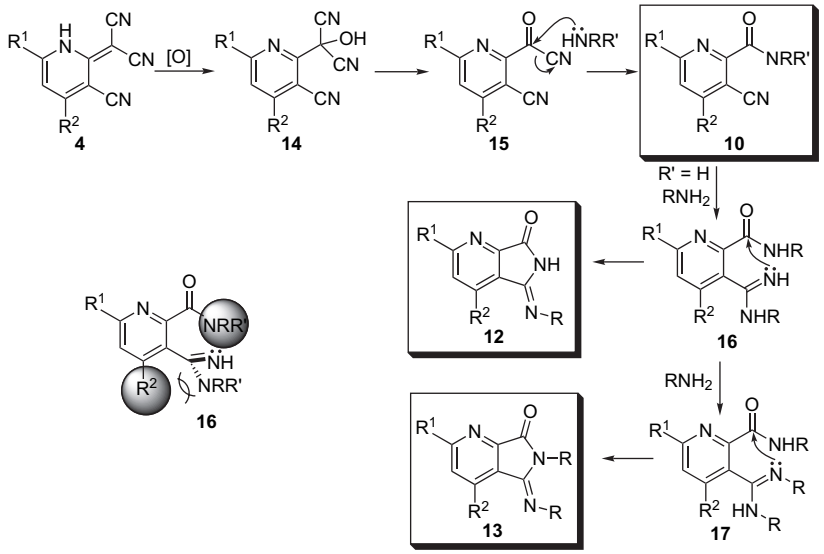
(a) Cyclizations are almost regiospecific, the 7-(substituted amino)-1,6-naphthyridines **5** being obtained independently of the reaction conditions employed. Only in the case of **4**{3} and morpholine was detected the 5-morpholino substituted isomer **6**{3,3} (Fig. 1) whose proportion increased with the amount of amine and polarity of the medium.

(b) The best results were always obtained in dioxane, precisely a solvent that also favored cyclizations of pyridines **4** with hydrogen halides,[8] or in net amines. Morpholine **7**{3} globally afforded the best yields of cyclization. In general, an increase in the concentration of amines does not significantly raise the yields.

(c) Some byproducts are formed during cyclizations whose structures **10**{2,1}, **10**{3,3}, **12**{3,1}, and **13**{3,1} are not related to the cyclization reaction of nitriles, whose amount seems to be favored by low-protic environments (low concentration of amine and dioxane or $CHCl_3$ as solvent). In the case of pyridine **4**{1} no byproducts have been isolated.

3. Mechanistic rationalization

First of all, it is interesting to understand the mechanism, which leads to the byproducts in order to minimize their formation. We postulate that structures **10**, **12**, and **13** are formed through a common pathway involving oxidative decyanation[11–13] of the starting pyridines **4** (Scheme 3), which leads to the α-ketonitrile **15**. The nucleophilic acyl



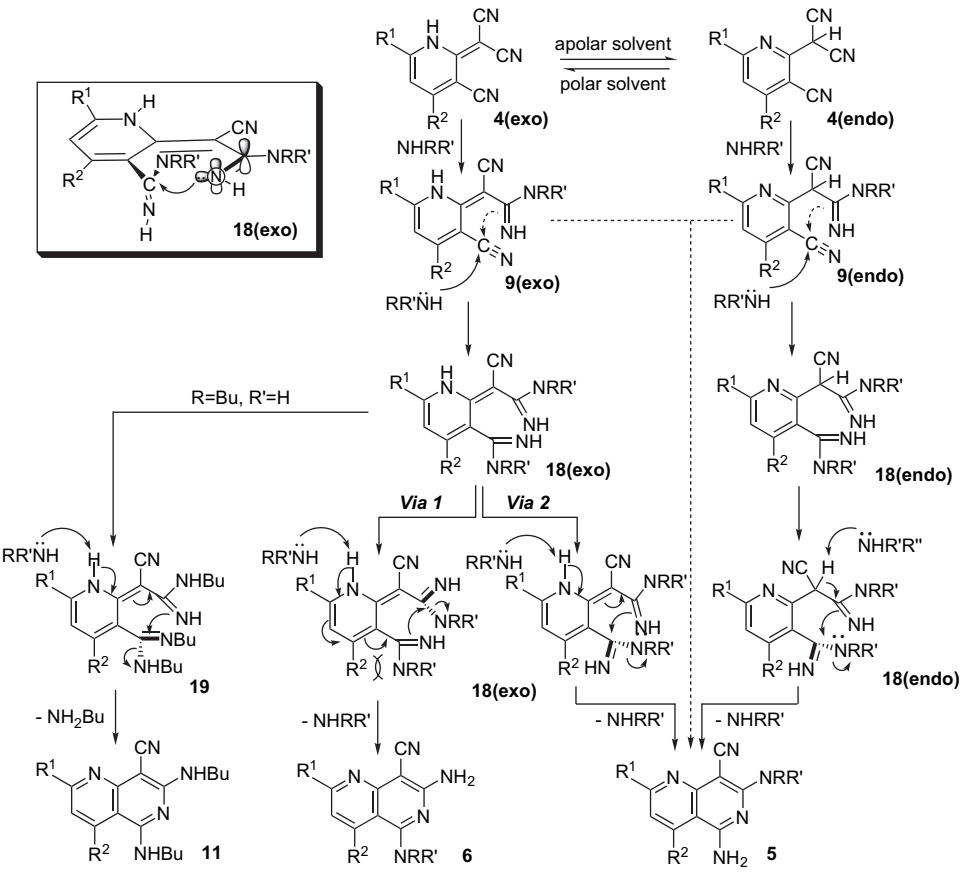
Scheme 3.

substitution of the cyano group of **15** by the amine yields amides **10**. In the case of primary amines, the subsequent reaction of the remaining cyano group with an excess of amine could form either a monosubstituted amidine **16** or a disubstituted amidine **17**. Further cyclization of these amidines onto the amide group would lead to isoindolin-1-ones **12** or **13**, respectively (Scheme 3). An experiment carried out with pyridine **4**{2} and butylamine using a 1:10 **4**{2}/butylamine ratio in an argon atmosphere for 3 days clearly showed a diminution of such oxygen-related byproducts.

The obvious question is, why only the reaction between pyridine **4**{3} (R^1=Ph, R^2=H) and butylamine did not stop at amide **10**, like the other combinations did, but led to bicyclic compounds **12**{3,1} and **13**{3,1}? The most likely explanation to this behavior might lie on the influence that steric hindrance can exert on the formation of isoindolin-1-ones **12** and **13**. Thus, while the conversion of the nitrile group present in amides **10** to the monosubstituted or disubstituted amidines **16** and **17** does not imply any difficulty,[14,15] their further cyclization needs the planarity of the reaction site in order to allow the amidine to attack onto the amide group. The presence of any substituent in R^2 or bulky substituents in R and R′ of the amide is an obstacle to achieve this planarity (Scheme 3). Consequently, the cyclization is only possible in the case of **4**{3}, where R^2=H, in the presence of butylamine, the less bulky amine employed.

Concerning the mechanism that leads to 1,6-naphthyridines **5** and **6**, it is clear that amidine groups play a key role in the cyclization mechanism. The isolation of amidines **9**{1,3} and **9**{2,3}, which evolve to the corresponding cyclization product **5** upon heating, pointed structures **9** as intermediates in such process. Thus, conversion of **4**(*exo*) tautomer (the tautomerism of the starting pyridines **4** will be discussed later) on the **9**(*exo*) amidine followed by the attack of the amidine nitrogen onto the cyano group would easily explain the formation of the 7-(substituted amino)-1,6-naphthyridines **5** (Scheme 4, dotted line). This could be the mechanism involved when very low concentrations of amine are used.

However, such kind of mechanism cannot explain the formation of either 5-(substituted amino)-1,6-naphthyridines **6** or 5,7-di(butylamino)-1,6-naphthyridines **11**{1,1} and **11**{3,1}. Consequently, it is necessary to postulate the addition of a second amine molecule to the nitrile bound to the pyridine ring of **9**(*exo*) leading to diamidines **18**(*exo*) (Scheme 4), a behavior that could be favored with higher amine concentrations. Once the two amidines are formed, the subsequent attack of one amidine onto the other has to fulfill strict geometrical constraints to allow the cyclization to proceed. Thus, the amidine acting as the nucleophile should be coplanar with the pyridine ring of **18**(*exo*) while the attacked amidine should be out of this plane (Scheme 4). Such geometrical restrictions allow to explain the high regioselectivity for the 7-(substituted amino) isomer **5** because the presence of R^2 makes much more difficult to achieve the coplanarity of the amidine bound to the pyridine ring, thus precluding the formation of the 5-(substituted amino)-1,6-naphthyridines **6** (via 1, Scheme 4).



Scheme 4.

Only when R^2=H, as in pyridine **4**{3}, it is possible to detect compound **6**{3,3} upon treatment with morpholine. The fact that the 5-(substituted amino) isomer **6** was only detected using morpholine might be due to the higher yields obtained with this amine. On the contrary, the formation of compounds **5** (via 2, Scheme 4) does not imply any geometrical problem.

Although sterical interactions play a central role in the direction of cyclization, there is a second factor that has to be considered. Somewhere along the reaction a tautomerization process is needed to afford a totally aromatic system. Such process, which could also play an important role according to some authors,[16] has been integrated in our mechanistic proposal in such a way that the cyclization (meaning the nucleophilic attack) and this tautomerism would take place in the same process, running in the same direction and almost simultaneously (Scheme 4). Such process can be favored by a protic assistance of the amine or protic solvent for the required proton transfer to the leaving amine.[17] This kind of single step mechanism is kinetically favored and is also used to explain the regioselectivity found in a dinitrile cyclization in the presence of alkoxides found in literature.[16,18–20]

The diamidine **18**(*exo*) is also capable of explaining the formation of the 5,7-dibutylamino-1,6-naphthyridines **11**{1,1} and **11**{3,1}. Thus, the addition of a third molecule of butylamine to the corresponding diamidine **18**(*exo*) (R=Bu, R′=H) would afford the *N*,*N*′-disubstituted amidine **19**, a reaction favored by the lower sterical hindrance of butylamine.[14,15] The subsequent cyclization and tautomerization would lead to the corresponding 5,7-dibutylamino substituted naphthyridine **11**.

A final aspect to be considered in our mechanistic study is the presence of tautomeric equilibrium in the starting pyridines **4**. This tautomerism (Scheme 4), described in several isoelectronic systems,[21–25] lies in this case totally displaced to the **4**(*exo*) tautomer both in solid state and in polar solvents (such as DMSO in which NMR spectra are registered). It is expected that apolar solvents (such as $CHCl_3$) should favor the **4**(*endo*) but it was not possible to confirm this assumption due to the low solubility of compounds **4** in apolar solvents, which preclude registering the NMR spectrum. In any case, in apolar solvents where **4**(*endo*) should be the major tautomer, the aromatic character of pyridine ring would favor even more the cyclization leading from amidine **18**(*endo*), or directly from nitrile **9**(*endo*), to the 7-(substituted amino)-1,6-naphthyridines **5** (Scheme 4).

In conclusion, an increase in polarity of the medium is expected to shift the population of the starting pyridine to the **4**(*exo*) tautomer that leads to a mixture of the cyclization products **5** and **6** in which **5** always predominates. A decrease in polarity favors the **4**(*endo*) tautomer whose cyclization exclusively affords 1,6-naphthyridines **5**. Such interpretation matches with the variations in the regioselectivity observed during our study.

4. Conclusion

To sum up, we have proposed a mechanistic rationalization for the cyclization of pyridines **4** with amines based on three factors: (1) the cyclization involves an amidine as the nucleophile, which attacks either a nitrile or a second amidine, (2) the attack of one amidine onto the other has to fulfill strict geometrical constraints to allow the cyclization to proceed, and (3) the cyclization step should probably involve the aforementioned nucleophilic attack simultaneously with a tautomerism to achieve, in single step mechanism, the high levels of regioselectivity observed.

5. Experimental

5.1. General

All melting points were determined with a Büchi 530 capillary apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna 560 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Varian Gemini-300 operating in a field strength of 300 and 75.5 MHz, respectively. Chemical shifts are reported in parts per million (δ) and coupling constants (J) in hertz, using in the case of ^{1}H NMR, tetramethylsilane (TMS) as internal standard and setting, in the case of ^{13}C NMR, the references at the signal of the solvent (77.0 ppm for $CDCl_3$ and 39.5 ppm for DMSO-d_6). MS spectra at low and high resolutions (LRMS and HRMS) were registered with a VG AutoSpec (Micromass Instruments) Trisector EBE spectrometer using electronic impact (IE) or FAB. Elemental microanalyses were obtained on a Carlo-Erba CHNS-OR/EA 1108 analyzer and gave results for the elements stated with ±0.4% of the theoretical values. HPLC analyses were carried out on a Gilson NebulaTM HPLC provided with UV detector at 220 and 254 nm. Column used was a Kromasil-100 C18 (15×0.46 mm, 5 μm) supplied by Teknokroma, Ref. TR-011941 (Barcelona, Spain). Column chromatography was carried out on silica gel (70–230 mesh). Compounds **4**{1–3} and **8**{1–3} were synthesized as described before.[10]

5.2. Reactions of 2-(dicyanomethylene)-1,2-dihydro-4,6-dimethylpyridine-3-carbonitrile (4{1})

5.2.1. Cyclization with morpholine.

5.2.1.1. 5-Amino-2,4-dimethyl-7-morpholino-1,6-naphthyridine-8-carbonitrile (5{1,3}). A solution of 2-(dicyanomethylene)-1,2-dihydro-4,6-dimethylpyridine-3-carbonitrile **4**{1} (100 mg, 0.51 mmol) in 10 mL of morpholine was refluxed for 24 h. The resulting mixture was concentrated in vacuo and the residue was treated with pentane (10 mL) at reflux to remove any remaining amine. After cooling, the solid was filtered and washed with pentane to afford 138 mg (96%) of **5**{1,3} as yellow crystals. IR (KBr) ν (cm^{-1}): 3503 and 3376 (N–H), 2951, 2914, 2856, 2203 (C≡N), 1614, 1588, 1541, 1475; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.90 (s, 1H, *H*–C3), 3.73 (m, 4H, CH_2O), 3.72 (m, 4H, CH_2N), 2.69 (s, 3H, CH_3–C2), 2.47 (s, 3H, CH_3–C4), 7.20 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 162.4 (C5), 160.5 (C7), 158.5 (C2), 156.8 (C8a), 145.9 (C4), 121.6 (C3), 119.3 (C≡N), 106.4 (C4a), 75.2 (C8), 66.1 (C–O), 47.7 (C–N), 24.4 (*C*H_3–C2), 22.2 (*C*H_3–C4); MS, *m*/*z* (%): 283 (100) [M^+], 252 (37), 225 (64), 197 (71), 170 (26). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.43; H, 6.14; N, 24.56. 1,6-Naphthyridine **5**{1,3} was also obtained by the treatment

of 220 mg (0.79 mmol) of 5-amino-7-bromo-2,4-dimethyl-1,6-naphthyridine-8-carbonitrile **8**{1} with morpholine (5 mL) in methanol (15 mL) at reflux for 24 h. The solvent was concentrated in vacuo and the residue was suspended in water, filtered, and recrystallized from ethanol to yield 151 mg (83%) of (**5**{1,3}).

5.2.1.2. 2-((*Z*)-2-Amino-1-cyano-2-morpholinovinyl)-4,6-dimethylpyridine-3-carbonitrile (9{1,3}). A solution of pyridine **4**{1} (100 mg, 0.51 mmol) in a mixture of dioxane (10 mL) and morpholine (0.5 mL) was refluxed for 72 h. The mixture was concentrated in vacuo and the residue was column chromatographed using AcOEt/hexane (3:1) as the eluent to yield 30 mg of **9**{1,3} (29%). IR (KBr) ν (cm^{-1}): 3299 (N–H), 2999, 2922, 2858, 2213 and 2172 (C≡N), 1634, 1580, 1554, 1513, 1493; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.85 (s, 1H, H–C3), 3.61 (m, 4H, CH_2OR), 3.33 (m, 4H, CH_2N), 2.39 (s, 3H, CH_3–C2), 2.35 (s, 3H, CH_3–C4), 6.87 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 164.5 (N–C=N), 159.5 (C2), 159.0 (C6), 152.0 (C4), 122.3 (C3), 117.6, 116.3 (C≡N), 100.9 (C5), 65.8 (C–O), 59.7 (=*C*–CN), 48.6 (C–N), 24.4 (*C*H_3–C2), 20.1 (*C*H_3–C4); MS, *m*/*z* (%): 283 (100) [M^+], 252 (55), 226 (63), 198 (69), 170 (32). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.39; H, 5.97; N, 24.72.

5.2.2. Cyclization with butylamine.

5.2.2.1. 5-Amino-7-butylamino-2,4-dimethyl-1,6-naphthyridine-8-carbonitrile (5{1,1}). A solution of **4**{1} (100 mg, 0.51 mmol) in a mixture of morpholine (5 mL) and dioxane (5 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue recrystallized from EtOH/H_2O to yield 122 mg (89%) of **5**{1,1}. IR (KBr) ν (cm^{-1}): 3483, 3351, and 3219 (N–H), 2957, 2927, 2859, 2183 (C≡N), 1623, 1587, 1568, 1502, 1476; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.74 (s, 1H, H–C3), 3.43 (m, 2H, CH_2N), 2.67 (s, 3H, CH_3–C2), 2.42 (s, 3H, CH_3–C4), 1.54 (m, 2H, NCH_2CH_2), 1.32 (m, 2H, CH_2CH_3), 0.91 (t, ^3J=7.3 Hz, 3H, –CH_3), 7.04 (s, 2H, NH_2), 6.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 162.3 (C5), 159.9 (C7), 159.4 (C2), 156.3 (C8a), 145.9 (C4), 120.2 (C3), 118.8 (C≡N), 105.2 (C4a), 71.6 (C8), 40.0, 31.8, 19.6, and 13.8 (NBu), 24.4 (*C*H_3–C2), 22.6 (*C*H_3–C4); MS, *m*/*z* (%): 269 (99) [M^+], 240 (28), 225 (100), 213 (37), 197 (39), 170 (38). Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 67.10; H, 7.22; N, 25.68. 1,6-Naphthyridine **5**{1,1} was also obtained by the treatment of 220 mg (0.79 mmol) of 5-amino-7-bromo-2,4-dimethyl-1,6-naphthyridine-8-carbonitrile **8**{1} with butylamine (10 mL) in methanol (10 mL) at reflux for 48 h. The solvent was concentrated in vacuo and the residue was recrystallized from ethanol to yield 163 mg (86%) of **5**{1,1}.

5.2.2.2. 5,7-Bis(butylamino)-2,4-dimethyl-1,6-naphthyridine-8-carbonitrile (11{1,1}). A mixture of **4**{1} (200 mg, 1.02 mmol) in dioxane (20 mL) and butylamine (1 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed using CH_2Cl_2/AcOEt (12:1) as the eluent to afford 16 mg (5%) of **11**{1,1}. IR (KBr) ν (cm^{-1}): 3504 and 3330 (N–H), 2958, 2929, 2859, 2192 (C≡N), 1590, 1524, 1503, 1466; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.75 (s, 1H, H–C3), 3.49 (m, 2H, CH_2N), 3.41 (m, 2H, CH_2N), 2.68 (s, 3H, CH_3–C2), 2.41 (s, 3H, CH_3–C4), 1.64 (m, 2H, NCH_2CH_2), 1.55 (m, 2H, NCH_2CH_2), 1.34 (m, 4H, CH_2CH_3), 0.92 (m, 6H, CH_3), 6.96 (t, ^3J=5.1 Hz, 1H, NH), 6.67 (s, ^3J=5.7 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 161.4 (C5), 158.9 (C7), 157.4 (C2), 155.8 (C8a), 144.7 (C4), 120.1 (C3), 118.7 (C≡N), 105.7 (C4a), 70.6 (C8), 41.4, 40.4, 31.9, 30.5, 19.9, 19.7, 13.8 and 13.8 (NBu), 24.3 (*C*H_3–C2), 22.5 (*C*H_3–C4); MS, *m*/*z* (%): 326 (58) [M^++1], 325 (89) [M^+], 282 (100), 226 (74), 197 (64); HRMS Calcd for $C_{19}H_{27}N_5$: 325.2266. Found: 325.2262.

5.2.3. Cyclization with cyclohexylamine.

5.2.3.1. 5-Amino-7-(cyclohexylamino)-2,4-dimethyl-1,6-naphthyridine-8-carbonitrile (5{1,2}). A solution of **4**{1} (100 mg, 0.51 mmol) in cyclohexylamine (10 mL) was refluxed for 24 h. The solvent was concentrated in vacuo and the residue was recrystallized from EtOH/H_2O to give 129 mg (86%) of **5**{1,2}. IR (KBr) ν (cm^{-1}): 3471, 3350, and 3221 (N–H), 2932, 2852, 2183 (C≡N), 1621, 1584, 1566, 1490, 1475; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.75 (s, 1H, H–C3), 4.07 (m, 1H, CHN), 2.67 (s, 3H, CH_3–C2), 2.42 (s, 3H, CH_3–C4), 1.86–1.82, 1.75–1.71, 1.63–1.59, and 1.41–1.06 (m, 10H, CH_2), 7.07 (s, 2H, NH_2), 6.12 (d, ^3J=8.4 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 162.3 (C5), 159.9 (C7), 158.6 (C2), 156.3 (C8a), 145.9 (C4), 120.3 (C3), 118.7 (C≡N), 105.3 (C4a), 71.8 (C8), 48.9, 32.6, 25.2, and 25.1 (cyclohexane), 24.4 (*C*H_3–C2), 22.5 (CH_3–C4); MS, *m*/*z* (%): 295 (97) [M^+], 252 (95), 238 (40), 213 (100), 196 (20). Anal. Calcd for $C_{17}H_{21}N_5$: C, 69.12; H, 7.17; N, 23.71. Found: C, 69.28; H, 7.34; N, 23.37. 1,6-Naphthyridine **5**{1,2} was also obtained by the treatment of 220 mg (0.79 mmol) of 5-amino-7-bromo-2,4-dimethyl-[1,6]naphthyridine-8-carbonitrile **8**{1} with cyclohexylamine (10 mL) and methanol (10 mL) at reflux for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed using AcOEt/CH_2Cl_2 (1:5) as the eluent to give 153 mg (66%) of **5**{1,2}.

5.3. Reactions of 2-(dicyanomethylene)-1,2-dihydro-4,6-diphenylpyridine-3-carbonitrile (4{2})

5.3.1. Cyclization with morpholine.

5.3.1.1. 5-Amino-7-morpholino-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile (5{2,3}). A solution of 2-(dicyanomethylene)-1,2-dihydro-4,6-diphenylpyridine-3-carbonitrile **4**{2} (300 mg, 0.93 mmol) in dioxane (15 mL) and morpholine (15 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/hexane, 1:1) to yield 292 mg (77%) of **5**{2,3}. IR (KBr) ν (cm^{-1}): 3501, 3391, and 3342 (N–H), 3058, 2999, 2914, 2853, 2199 (C≡N), 1653, 1603, 1593, 1556, 1499; ^{1}H NMR (DMSO-d_6) δ (ppm): 7.43 (s, 1H, H–C3), 8.30–8.27 (m, 2H, H–Ph), 7.57–7.55 (m, 3H, H–Ph), 7.50–7.44 (m, 5H, H–Ph), 3.93 (m, 4H, CH_2O), 3.84 (m, 4H, CH_2N), 4.99 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 160.5 (C5), 159.7 (C7), 157.4 (C2), 156.6 (C8a), 148.7 (C4), 138.9–127.7 (Ph), 118.9 (C≡N), 117.8 (C3), 104.2 (C4a), 78.0 (C8), 67.0 (CH_2O), 48.0 (CH_2N); MS, *m*/*z* (%): 407 (100) [M^+], 376 (50), 362 (51), 350 (81), 321 (73), 188 (62); HRMS Calcd for $C_{25}H_{21}N_5O$: 407.1746. Found: 407.1747. Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19. Found: C, 73.51; H, 5.09; N, 17.30. 1,6-Naphthyridine **5**{2,3} was also obtained by the treatment

of 200 mg (0.50 mmol) of 5-amino-7-bromo-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile **8**{2} with morpholine (1 mL) and dioxane (10 mL). The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/hexane, 1:1) to give 115 mg (56%) of **5**{2,3}.

5.3.1.2. 2-((*Z*)-2-Amino-1-cyano-2-morpholinovinyl)-4,6-diphenylpyridine-3-carbonitrile (9{2,3}). A solution of **4**{2} (300 mg, 0.93 mmol) and morpholine (0.5 mL) in dioxane (20 mL) was refluxed for 72 h. The solvent was removed in vacuo and the residue was column chromatographed (AcOEt/hexane, 1:1) to yield 65 mg (17%) of **9**{2,3}. IR (KBr) ν (cm^{-1}): 3291 and 3148 (N–H), 3060, 2967, 2912, 2857, 2211 and 2177 (C≡N), 1624, 1568, 1526, 1493; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22–8.20 (m, 2H, H–Ph), 7.70–7.67 (m, 3H, H–Ph), 7.60 (s, 1H, H–C3), 7.58–7.52 (m, 5H, H–Ph), 3.66 (m, 4H, CH_2O), 3.48 (m, 4H, CH_2N), 7.88 (br, 2H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 164.1 (N–C═N), 160.9 (C2), 157.0 (C6), 154.5 (C4), 137.3–127.0 (Ph), 122.5 (C3), 117.7 and 113.1 (C≡N), 99.7 (C5), 65.9 (C–O), 60.9 (═*C*–CN), 48.6 (C–N). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19. Found: C, 73.45; H, 4.99; N, 17.12.

5.3.2. Cyclization with butylamine.

5.3.2.1. 5-Amino-7-(butylamino)-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile (5{2,1}). A solution of **4**{2} (100 mg, 0.31 mmol) and morpholine (5 mL) in dioxane (5 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/hexane, 1:4) to afford 35 mg (29%) of **5**{2,1}. IR (KBr) ν (cm^{-1}): 3514, 3404, and 3340 (N–H), 3053, 2954, 2927, 2868, 2193 (C≡N), 1673, 1654, 1610, 1578, 1555, 1457; ^{1}H NMR (DMSO-d_6) δ (ppm): 8.27 (m, 2H, H–P), 7.72 (br, 2H, NH_2), 7.61–7.52 (m, 8H, H–Ph), 7.42 (s, 1H, C3–H), 7.00 (t, ^3J=5.4 Hz, 1H, NH), 3.44 (m, 2H, CH_2N), 1.56 (m, 2H, NCH_2CH_2), 1.34 (m, 2H, CH_2CH_3), 0.91 (t, ^3J=7.2 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 159.6 (C5), 158.3 (C7), 158.1 (C2), 155.8 (C8a), 149.3 (C4), 138.7–127.2 (Ph), 118.2 (C≡N), 115.9 (C3), 102.9 (C4a), 72.0 (C8), 40.1, 31.7, 19.6, and 13.9 (NBu); MS, *m*/*z* (%): 393 (78) [M^+], 350 (100), 336 (22), 321 (18). Anal. Calcd for $C_{25}H_{23}N_5$: C, 76.31; H, 5.89; N, 17.80. Found: C, 76.20; H, 5.78; N, 17.92. 1,6-Naphthyridine **5**{2,1} was also obtained by the treatment of 120 mg (0.30 mmol) of 5-amino-7-bromo-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile **8**{2} with butylamine (2 mL) in ethanol (10 mL) at reflux for 24 h. The solvent was concentrated in vacuo and the residue was suspended in water. The resulting solid was filtered and recrystallized from $CHCl_3$/Et_2O to yield 92 mg (78%) of **5**{2,1} as a yellow powder.

5.3.2.2. *N*-Butyl-3-cyano-4,6-diphenylpyridine-2-carboxamide (10{2,1}). A solution of **4**{2} (100 mg, 0.31 mmol) and butylamine (0.5 mL) in dioxane (10 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (hexane/AcOEt, 10:1) to give 17 mg (15%) of **10**{2,1}. IR (KBr) ν (cm^{-1}): 3310 (N–H), 3061, 2960, 2932, 2872, 2221 (C≡N), 1651 (C═O), 1584, 1549, 1529; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.06 (m, 2H, H–Ph), 7.96 (s, 1H, H–C5), 7.64 (m, 3H, H–Ph), 7.55 (m, 5H, H–Ph), 3.56 (m, 2H, CH_2N), 1.70 (m, 2H, NCH_2CH_2), 1.47 (m, 2H, CH_2CH_3), 0.99 (t, ^3J=7.2 Hz, 3H, CH_3), 8.12 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.9 (C═O), 157.6 (C2), 156.7 (C2), 152.4 (C4), 136.6, 135.8, 130.8, 130.0, 129.1, 128.9, 128.7, and 127.4 (Ph), 122.7 (C5), 115.5 (C≡N), 114.9 (C3), 39.6, 31.8, 20.3, and 13.9 (Bu); HRMS Calcd for $C_{23}H_{21}N_3O$: 355.1684. Found: 355.1673. Anal. Calcd for $C_{23}H_{21}N_3O$: C, 68.87; H, 5.17; N, 21.03. Found: C, 68.80; H, 5.23; N, 20.98.

5.3.3. Cyclization with cyclohexylamine.

5.3.3.1. 5-Amino-7-(cyclohexylamino)-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile (5{2,2}). A solution of **4**{2} (100 mg, 0.31 mmol) and of cyclohexylamine (0.5 mL) in dioxane (10 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (hexane/AcOEt, 5:1) to afford 32 mg (25%) of **5**{2,2}. IR (KBr) ν (cm^{-1}): 3507, 3390, and 3304 (N–H), 3063, 2920, 2850, 2203 (C≡N), 1610, 1581, 1557, 1493; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.26–8.24 (m, 2H, H–Ph), 7.54 (m, 3H, H–Ph), 7.46 (m, 5H, H–Ph), 4.02 (m, 1H, CHN), 2.04–2.00, 1.80–1.75, 1.65–1.62, and 1.41–1.24 (m, 10H, cyclohexane), 5.20 (d, ^3J=8.1 Hz, 1H, NH), 5.05 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.7 (C5), 159.2 (C7), 158.3 (C2), 156.2 (C8a), 148.9 (C4), 139.4–127.6 (Ph), 118.6 (C≡N), 116.7 (C3), 103.2 (C4a), 74.9 (C8), 49.7, 33.6, 25.7, and 25.1 (cyclohexane). Anal. Calcd for $C_{27}H_{23}N_5$: C, 77.30; H, 6.01; N, 16.69. Found: C, 77.11; H, 5.88; N, 16.99. 1,6-Naphthyridine **5**{2,2} was also obtained by the treatment of 150 mg (0.37 mmol) of 5-amino-7-bromo-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile **8**{2} with cyclohexylamine (3 mL) in ethanol (30 mL) at reflux for 48 h. The solvent was concentrated in vacuo, the residue was suspended in water (30 mL), and extracted with $CHCl_3$ (2×20 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 95 mg (62%) of **5**{2,2}.

5.4. Reactions of 2-(dicyanomethylene)-1,2-dihydro-6-phenylpyridine-3-carbonitrile (4{3})

5.4.1. Cyclization with morpholine.

5.4.1.1. 5-Amino-7-morpholino-2-phenyl-1,6-naphthyridine-8-carbonitrile (5{3,3}). A solution of **4**{3} (124 mg, 0.51 mmol) and morpholine (0.46 mL) in dioxane (10 mL) was refluxed for 24 h. The solvent was concentrated in vacuo and the residue was recrystallized from acetone/pentane to afford 145 mg (86%) of **5**{3,3}. IR (KBr) ν (cm^{-1}): 3450, 3330, 3225, and 3202 (N–H), 3037, 2973, 2888, 2855, 2193 (C≡N), 1628, 1596, 1582, 1535, 1447; ^{1}H NMR (DMSO-d_6) δ (ppm): 8.55 (d, ^3J=8.4 Hz, 1H, C4–H), 8.29–8.26 (m, 2H, H–Ph), 7.88 (d, ^3J=8.4 Hz, 1H, C3–H), 7.56–7.50 (m, 3H, H–Ph), 3.80 (m, 4H, CH_2O), 3.71 (m, 4H, CH_2N), 7.88 (br, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.6 (C5), 159.4 (C7), 158.0 (C2), 155.0 (C8a), 133.8 (C4), 137.5, 130.1, 128.7, and 127.1 (Ph), 118.9 (C≡N), 114.9 (C3), 106.6 (C4a), 74.3 (C8), 66.1 (C–O), 47.8 (C–N); MS, *m*/*z* (%): 331 (100) [M^+], 300 (48), 274 (54), 246 (56), 150 (40). Anal. Calcd for $C_{19}H_{17}N_5O$; C, 68.87; H, 5.17; N, 21.03. Found C, 68.80; H, 5.23; N, 20.98.

5.4.1.2. 7-Amino-5-morpholino-2-phenyl-1,6-naphthyridine-8-carbonitrile (6{3,3}). A solution of **4**{3}

(220 mg, 0.91 mmol) and morpholine (1 mL) in MeOH (20 mL) was refluxed for 5 days. The solvent was concentrated in vacuo, the residue was heated in 40 mL of CH_2Cl_2, and the resulting precipitate was filtered. The solid was purified by column chromatography (CH_2Cl_2/AcOEt, 10:1) to give 22 mg (7%) of **6**{3,3}. IR (KBr) ν (cm^{-1}): 3487, 3424, 3385, 3329, and 3229 (N–H), 3061, 2972, 2953, 2852, 2202, and 2190 (C≡N), 1640, 1592, 1575, 1549; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.24 (m, 2H, H–Ph), 8.07 (d, ^3J=8.7 Hz, 1H, C4–H), 7.57 (d, ^3J=8.7 Hz, 1H, C3–H), 7.51–7.48 (m, 3H, H–Ph), 3.87 (m, 4H, CH_2O), 3.64 (m, 4H, CH_2N), 5.26 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 162.0 (C5), 160.1 (C7), 159.5 (C2), 155.2 (C8a), 137.7 (C4), 134.7, 130.4, 128.8, and 127.7 (Ph), 117.3 (C≡N), 114.4 (C3), 108.2 (C4a), 74.3 (C8), 66.7 (C–O), 50.1 (C–N); MS, *m/z* (%): 331 (100) [M^+], 286 (74), 274 (65), 246 (52). Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.03. Found: C, 68.95; H, 5.17; N, 21.33.

5.4.1.3. 2-(Morpholino-4-carbonyl)-6-phenyl-nicotinonitrile (10{3,3}). A solution of **4**{3} (300 mg, 1.24 mmol) and morpholine (1.5 mL) in dioxane (30 mL) was refluxed for 3 days. The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/CH_2Cl_2, 1:10) to yield 11 mg (3%) of **10**{3,3}. IR (KBr) ν (cm^{-1}): 3070, 2963, 2861, 2225 (C≡N), 1647 (C═O), 1582; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.12 (d, ^3J=8.4 Hz, 1H, C4–H), 8.05 (m, 2H, H–Ph), 7.89 (d, ^3J=8.4 Hz, 1H, C3–H), 7.51–7.54 (m, 3H, H–Ph), 3.89 (m, 4H, CH_2O), 3.75 (m, 2H, CH_2N), 3.50 (m, 2H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 164.1 (C═O), 159.1 (C2), 156.3 (C6), 141.6 (C4), 136.4, 131.0, 129.1, and 127.4 (Ph), 119.9 (C5), 115.6 (C≡N), 106.5 (C3), 66.8, and 66.7 (C–O), 47.5 and 42.7 (C–N); HRMS Calcd for $C_{17}H_{15}N_3O_2$: 293.1164. Found: 293.1160.

5.4.2. Cyclization with butylamine.

5.4.2.1. 5-Amino-7-(butylamino)-2-phenyl-1,6-naphthyridine-8-carbonitrile (5{3,1}). A solution of **4**{3} (300 mg, 1.23 mmol) and butylamine (1.5 mL) in dioxane (30 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (CH_2Cl_2/hexane, 10:1) to give 166 mg (43%) of **5**{3,1}. IR (KBr) ν (cm^{-1}): 3322 and 3163 (N–H), 2956, 2926, 2868, 2192 (C≡N), 1659, 1594, 1577, 1505; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.29–8.25 (m, 2H, H–Ph), 7.92 (d, ^3J=8.7 Hz, 1H, C4–H), 7.56 (d, ^3J=8.7 Hz, 1H, C3–H), 7.54–7.51 (m, 3H, H–Ph), 3.59 (m, 2H, CH_2N), 1.60 (m, 2H, NCH_2CH_2), 1.47 (m, 2H, CH_2CH_3), 1.00 (t, ^3J=7.2 Hz, 3H, CH_3), 5.50 (s, 2H, NH_2), 5.39 (t, ^3J=7.4 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.4 (C5), 160.5 (C7), 158.0 (C2), 154.6 (C8a), 131.8 (C4), 138.0, 130.3, 128.7, and 127.6 (Ph), 118.3 (C≡N), 114.1 (C3), 104.9 (C4a), 74.5 (C8), 41.3, 32.1, 20.1, and 14.0 (NBu); MS, *m/z* (%): 317 (13) [M^+], 274 (89), 245 (242), 218 (29), 191 (30), 164 (25), 41 (100). Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 71.76; H, 5.89; N, 22.25. 1,6-Naphthyridine **5**{3,1} was also obtained by the treatment of 100 mg (0.30 mmol) of 5-amino-7-bromo-2-phenyl-1,6-naphthyridine-8-carbonitrile **8**{3} with butylamine (10 mL) in dioxane (10 mL) at reflux for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/CH_2Cl_2, 1:5) to yield 61 mg (63%) of **5**{3,1}.

5.4.2.2. 5,7-Bis(butylamino)-2-phenyl-1,6-naphthyridine-8-carbonitrile (11{3,1}). A solution of **4**{3} (200 mg, 0.82 mmol) and butylamine (2 mL) in dioxane (20 mL) was refluxed for 4 days. The solvent was concentrated in vacuo and the residue was column chromatographed (CH_2Cl_2/hexane, 9:1) to afford 19 mg (6%) of **11**{3,1}. IR (KBr) ν (cm^{-1}): 3440 and 3342 (N–H), 3061, 2956, 2925, 2855, 2186 (C≡N), 1602, 1583; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.21–8.19 (m, 2H, H–Ph), 7.81 (d, ^3J=8.7 Hz, 1H, C4–H), 7.47–7.43 (m, 4H, H–Ph and C5–H), 3.59 (m, 4H, CH_2N), 1.64 (m, 4H, NCH_2CH_2), 1.42 (m, 4H, CH_2CH_3), 0.95 (m, 6H, CH_3), 5.63 (t, ^3J=4.8 Hz, 1H, NH), 5.38 (t, ^3J=5.4 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.7 (C5), 160.6 (C7), 156.5 (C2), 154.5 (C8a), 130.0 (C4), 138.1, 130.5, 128.6, and 127.5 (Ph), 118.9 (C≡N), 113.6 (C3), 105.7 (C4a), 72.4 (C8), 41.6, 41.3, 32.3, 31.5, 20.4, 20.2, and 14.0 (NBu); HRMS Calcd for $C_{23}H_{27}N_5$: 373.2266. Found: 373.2270.

5.4.2.3. 5-(Butylimino)-5,6-dihydro-2-phenylpyrrolo[3,4-*b*]pyridin-7-one (12{3,1}) and 6-butyl-5-(butylimino)-5,6-dihydro-2-phenylpyrrolo[3,4-*b*]pyridin-7-one (13{3,1}). Prepared as above for **11**{3,1} to give 9 mg (4%) of **12**{3,1} and 13 mg of **13**{3,1}. **12**{3,1}: IR (KBr) ν (cm^{-1}): 3269 (N–H), 3055, 2959, 2931, 2873, 2858, 1729 (C═O), 1652; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.19–8.16 (m, 3H, H–Ph and C4–H), 8.03 (d, ^3J=8.1 Hz, 1H, C3–H), 7.54–7.52 (m, 3H, H–Ph), 3.92 (t, ^3J=7.2 Hz, 2H, CH_2N), 1.76 (m, 2H, NCH_2CH_2), 1.44 (m, 2H, CH_2CH_3), 0.99 (t, ^3J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8 (C═O), 161.9 (C2), 150.4 (C7a), 137.4, 130.3, 128.8, and 127.5 (Ph), 129.6 (C4), 123.8 (C3), 38.4, 30.5, 20.3, and 13.9 (NBu); HRMS Calcd for $C_{19}H_{19}N_5$: 279.1372. Found: 279.1381. Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 71.76; H, 5.89; N, 22.25. **13**{3,1}: IR (KBr) ν (cm^{-1}): 2956, 2932, 2868, 1732 (C═O), 1666; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, ^3J=8.4 Hz, 1H, C4–H), 8.18–8.15 (m, 2H, H–Ph), 7.94 (d, ^3J=8.4 Hz, 1H, C3–H), 7.51–7.49 (m, 3H, H–Ph), 3.99 (t, ^3J=6.9 Hz, 2H, CH_2N), 3.87 (t, ^3J=7.2 Hz, 2H, CH_2N), 1.80 (m, 2H, NCH_2CH_2), 1.69 (m, 2H, NCH_2CH_2), 1.53 (m, 2H, CH_2CH_3), 1.38 (m, 2H, CH_2CH_3), 1.01 (t, ^3J=7.2 Hz, 3H, CH_3), 0.94 (t, ^3J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.4 (C═O), 160.4 (C2), 152.0 (C7a), 147.9 (C═N), 133.6 (C4), 137.4, 130.1, 128.8, and 127.5 (Ph), 122.4 (C4a), 122.3 (C3), 50.2, 38.6, 33.9, 30.5, 20.7, 20.2, 14.0, and 13.9 (NBu); MS, *m/z* (%): 335 (63) [M^+], 278 (48), 237 (66), 179 (100), 149 (52); HRMS Calcd for $C_{21}H_{25}N_3O$: 335.1998. Found: 335.1995.

5.4.3. Cyclization with cyclohexylamine.

5.4.3.1. 5-Amino-7-(cyclohexylamino)-2-phenyl-1,6-naphthyridine-8-carbonitrile (5{3,2}). A solution of **4**{3} (200 mg, 0.82 mmol) and cyclohexylamine (2 mL) in dioxane (20 mL) was refluxed for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (CH_2Cl_2:MeOH, 98:2) to yield 63 mg (22%) of **5**{3,2}. IR (KBr) ν (cm^{-1}): 3489, 3335, and 3190 (N–H), 3059, 2943, 2924, 2845, 2198 (C≡N), 1646, 1617, 1595, 1576, 1504, 1484; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.24–8.21 (m, 2H,

H–Ph), 7.88 (d, ^3J=8.4 Hz, 1H, C4–H), 7.50 (d, ^3J=8.4 Hz, 1H, C3–H), 7.51–7.47 (m, 3H, H–Ph), 4.07 (m, 1H, CHN), 2.05–2.01, 1.82–1.77,1.68–1.62, and 1.47–1.20 (m, 10H, cyclohexyl), 5.49 (s, 2H, NH_2), 5.23 (^3J=7.8 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.3 (C5), 159.8 (C7), 158.1 (C2), 154.7 (C8a), 131.8 (C4), 138.0, 130.2, 128.7, and 127.6 (Ph), 118.4 (C≡N), 114.0 (C3), 104.9 (C4a), 74.3 (C8), 41.9, 33.6, 25.7, and 25.1 (–cyclohexyl); MS, *m*/*z* (%): 343 (93) [M^+], 300 (89), 286 (63), 261 (100). Anal. Calcd for $C_{21}H_{21}N_5$: C, 73.44; H, 6.16; N, 20.39. Found: C, 73.32; H, 6.11; N, 20.33. 1,6-Naphthyridine **5**{3,2} was also obtained by the treatment of 80 mg (0.25 mmol) of 5-amino-7-bromo-2-phenyl-1,6-naphthyridine-8-carbonitrile **8**{3} with cyclohexylamine (1 mL) in dioxane (5 mL) at reflux for 72 h. The solvent was concentrated in vacuo and the residue was column chromatographed (AcOEt/CH_2Cl_2, 1:4) to yield 44 mg (52%) of **5**{3,2}.

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