Preparation of 1-substituted and 1,4-disubstituted derivatives of 2,6-naphthyridine

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Abstract

Novel 1-substituted and 1,4-disubstituted derivatives of 3-amino-2,6-naphthyridine were prepared by the base-mediated intramolecular cyclization of 3-cyano-methylpyridine-4-carbonitrile and 3-(1-cyano-3-alkenyl)pyridine-4-carbonitriles. The latter nitriles were then converted to pyrrolo[2,3-*c*]-2,6-naphthyridines by palladium catalyzed amination.

Keywords: 3-Amino-2,6-naphthyridines, intramolecular cyclization

Introduction

We[1,2] have reported the synthesis of a variety of nitrogen heterocycles by treating a-cyano-*o*-tolunitrile and a-allyl-a-cyano-*o*-tolunitriles with a variety of lithium amides and alkyllithiums. In the former case, 1-substituted derivatives of 3-aminoisoquinolines were obtained. In the latter case, 1-substituted derivatives of 4-alkenyl-3-aminoisoquinolines were produced that were subsequently converted to 4-alkenyl derivatives gave 3*H*-pyrrolo[2,3-*c*] and dihydropyrido[4,3-*c*] derivatives of 1,7- and 1,8-naphthyridines by Hegedus[3] coupling.

We have extended these reactions to the synthesis of 2,6-naphthyridines. We were motivated by the paucity of synthetic methodology reported for these potentially biologically important heterocyclics, since the other naphthyridine ring systems have been investigated extensively.[4] For example, 2,6-naphthyridines were the last of the six isomeric naphthyridines to be synthesized since none of the usual method of synthesis for these heterocycles[5] lead to the 2,6-isomer. The first synthesis involved a 4-step synthesis of the parent 2,6-naphthyridine from 4-carbethoxynicotinic acid.[6] However, the overall yield was quite low, and the reaction could not be easily extended to substituted 2,6-naphthyridines. Subsequently, a base-mediated cyclization of 3-cyanomethylpyridine-4-carbonitrile and some alkoxides was reported[7] in which 2,6-naphthyridines were obtained directly, however mixtures of 1-amino-3-alkoxy and 3-amino-1-alkoxy derivatives were obtained, and product yields were not reported. The first substituted 3-

cyanomethylpyridine-4-carbonitrile, namely 3-cyanomethyl-5-hydroxy-6-methylpyridine-4-carbonitrile, was reported in 1983.[8] This nitrile was found to cyclize to 1-bromo-3-amino-7-methyl-8-hydroxy-2,6-naphthyridine in the presence of 40% HBr/HOAc. Likewise, 2-(4-cyano-3-pyridinyl)propionitrile cyclized in the presence of anhydrous HBr to give, after a series of reactions, 3-amino-4-methyl-2,6-naphthyridine.[9] There are a few reported synthesis of 2,6-naphthyridines using non-dinitrile cyclization reactions.[10] However, they suffer from providing mixtures of products or require somewhat exotic starting materials.

We report here the synthesis of 1-substituted and 1,4-disubstituted derivatives of 3-amino-2,6-naphthyridine by the base-mediated intramolecular cyclization of 3-cyanomethylpyridine-4-carbonitrile and 3-(1-cyano-3-alkenyl)pyridine-4-carbonitriles. In addition, pyrrolo[2,3-*c*]-2,6-naphthyridines were also obtained by Hegedus coupling some of the 1-cyano-3-alkenyl derivatives.

Results and Discussion

Synthesis of 1-substituted 2,6-naphthyridines (3a-h). 1-Substituted derivatives of 2,6-naphthyridines (**3a-g**) were prepared from the reaction of 3-cyanomethylpyridine-4-carbonitrile (**1**) with various lithium amides (**2a-f**) and methyllithium (**2g**) at -78^{o}C. Nitrile **1** was prepared by treating 3-cyanomethylpyridine with *m*-chloroperbenzoic acid and dimethyl sulfate followed by cyanation at C-4 with KCN.[6] The individual yields are listed in Table 1. As shown, compounds (**3a-c**), all of which possess a 1-nitrogen heterocycle, were formed in highest yields (91-94%) whereas the 1-alkylamino-containing compounds (**3d-f**), were obtained in lower yields ranging from 50-70%. Interestingly among the 1-alkylamino substituted analogs, the 1-*t*-butylamino analog (**3f**) was obtained in highest yield. The 1-methyl derivative (**3g**) was formed in only 35% yield and the 1-(*N*-pyrrolynyl) and 1- (*N*-anilino) analogs (**3h**) and (**3I**) failed to react with **1** even with extended reaction times.

The use of strong THF-soluble bases and the low temperature used in this study led to the complete conversion of **1** to **4** before competing coupling reactions of these two compounds could occur. It is noteworthy that treatment of **1** with excess *n*-butyllithium gave the 1,5-di-*n*-butylated derivative (**3j**).

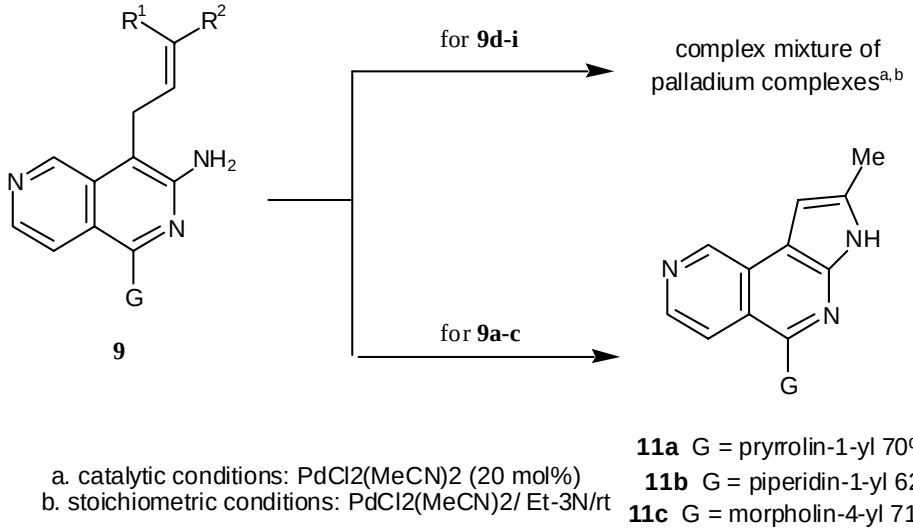
The proposed structures of compounds (**3a-g**) were consistent with their IR, MS, ^{1}H and ^{13}C NMR spectra. For example, each ^{1}H NMR spectrum revealed the presence of two singlets that ranged from 8.76 to 9.02 ppm (HC-5) and from 6.00 to 6.66 ppm (HC-4). Additionally, the IR spectrum of each derivative exhibited typical NH_2 stretching bands around 3350-3300 cm^{-1}.

4-Alkenyl-3-amino 2,6-naphthyridines (**7**) were prepared by a three-step reaction. First, dinitrile **1** was treated with allyl bromides (**4a-c**) to give the corresponding 3-(1-cyano-3-alkenyl)pyridine-4-carbonitriles (**5a-c**) in 70-95% yields. Secondly, compounds (**5a- c**) were converted to 4-alkenyl derivatives (**6**) and/or (**7**) by treatment with appropriate alkyllithium (**2**). As shown in Table 2, 4-allyl-3-amino products (**6a- m**) were, with some exceptions, formed in

yields ranging from 50 to 100%. In the case of G = phenyl, the isomerized product (**7d**) was the sole naphthyridine product; it was obtained in 38% yield. In addition, smaller amounts of the isomerized products (**7a-c**) were also obtained in 6-30% yields. The use of the sterically hindered 2-methoxyphenyllithium resulting in very low yield (12%) of the 1-(2-methoxyphenyl) derivative (**6h**).

With compounds (**6**) on hand, Hegedus coupling reactions were then carried out under catalytic conditions using $PdCl_2(MeCN)_2$ (20 mol%), benzoquinone (1 equiv) and 10 equiv of LiCl in refluxing THF. As shown in Scheme 1 substrates with unsubstituted allyl side-chains (**5a-c)** cyclized to pyrroles (**6a-c**) in 62-71% yield *via* attack at the secondary carbon of the olefin. However substrates with allyl groups possessing one methyl (**6j-m**) or two methyl groups (**6e-i**) gave no cyclized product, but rather complex mixtures. A modest increase in yield of only one pyrrole product (**11b**) was obtained when stoichiometric conditions (*i.e.* $PdCl_2(MeCN)_2$/ Et_3N/rt) were used. The failure of the substituted allyl naphthyrdines to undergo Hedegus cyclization may reflect the decreased stability of the corresponding alkene-palladium[11] as compared to the unsubstituted allyl derivatives. Hence these complexes would be expected to be less firmly bound to palladium. Consequently, undesirable side reactions such as displacement of alkene by triethylamine yielding unreactive bisaminopalladium complexes (stoichiometric), prevail over the desired displacement of the aniline required for the cyclization process. The relative stabilities of the olefin-palladium(II) complexes required for the cyclization process are presumably less than those of the unsubstituted allyl group.[12] Consequently, the alkyl substituted olefins would be less firmly bound to palladium than the unsubstituted olefins. In these cases, displacement of the substituted olefin by palladium by the base, triethylamine occurs exclusively yielding unreactive bisaminopalladium complexes.

In summary, the chemistry presented here offers an attractive method for the synthesis of a wide variety of 2,6-naphthyridines. The palladium-assisted intramolecular cyclization proceeds well with 4-allyl-2,6-naphthyridines yielding pyrrolo[2,3-*c*][2,6]naphthyridines regiospecifically. The cyclization however fails with methyl substituted allyl analogs. This cyclization should find application in the synthesis of natural products containing structural features intolerant of the conditions required for other indole syntheses which are very important in pharmaceutical industry.



Scheme 1

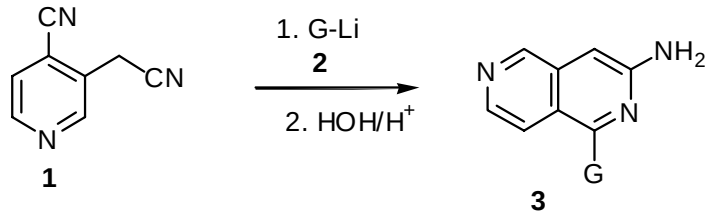
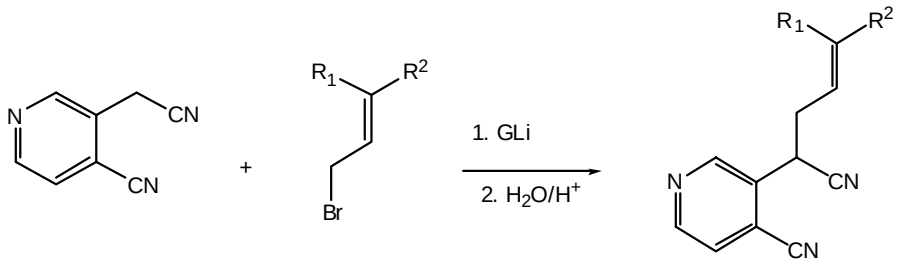


Table 1. Preparation of of 2,6-Naphthyridines (**3**)

3	G	Yield, %[a]
A	Pyrrolidin-1-yl	94
B	Piperidin-1-yl	92
C	Morpholin-4-yl	91
D	*iso*-PrNH-	60
E	*n*-BuNH-	50[c]
F	*tert*-BuNH-	70
G	Me-	35
H	1-Pyrrolidinyl	b
I	PhNH-	b

[a.] Yields are for products isolated by (flash) chromatography; [b.]Not detected. [c.]3-Amino-1,5-di-*n*-butyl-2,6-naphthyridine (3j) also obtained in 20% yield.

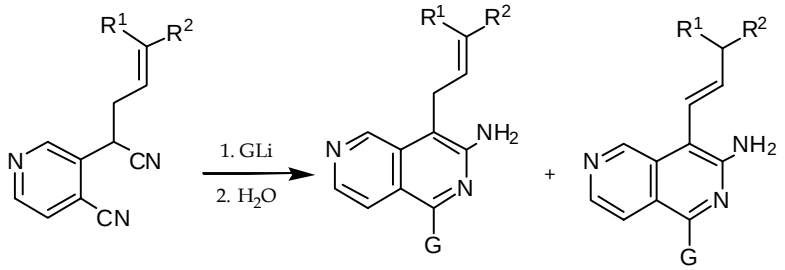
Table 2. Preparation of 3-(1-Cyano-3-alkenyl)pyridine-4-carbonitriles (**5a-c**)



1 4a-c 5a-c

5	R^1	R^2	Yield, %
a	H	H	62
b	Me	H	71
c	Me	Me	95

Table 3. Preparation of 4-Alkenyl Naphthyridines Derivatives (**6,7**)



5 **6** **7**

				Yield, %[a]	Yield, %[a]
	R^1	**R^2**	**G**	**6**	**7**
a	H	H	Pyrrolidin-1-yl	90	6
b	H	H	Piperidin-1-yl	48	30
c	H	H	Morpholin-4-yl	81	16
d	H	H	Phenyl	0	38
e	Me	Me	Pyrrolidin-1-yl	85	b
f	Me	Me	Morpholin-4-yl	100	b

g	Me	Me	Phenyl	54	b
h	Me	Me	*o*-Methoxyphenyl	12	b
i	Me	Me	*p*-Methoxyphenyl	90	b
j	H	Me	Pyrrolidin-1-yl	95	b
k	H	Me	Morpholin-4-yl	100	b
l	H	Me	*p*-Methylphenyl	50	b
m	H	Me	Phenyl	53	b

[a.] Yields are for products purified by (flash) chromatography b. not detected.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR^{TM} 550 FTIR spectrometer and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. The MS were run on a HP G1800C, GCD SeriesII. The amines were distilled before use. The alkyllithiums and phenyllithium were purchased from Aldrich Chemical Company and used as received. The glassware was heated at 125 ^{o}C in an oven overnight prior to use. The reactions carried out in glassware, which had been heated at 125 ^{o}C overnight prior to use, under an atmosphere of dry O_2-free N_2 *via* balloon.

General procedure for the preparation of 3-(1-cyano-3-alkenyl)pyridine-4-carbonitriles (5a-c)
To the solution of **1** (20 mmol) in THF (50 ml) was added n-BuLi (20 mmol, 1.6 M in hexane) at -70 °C. After stirring for 10 min, a solution of the appropriate 2-propenylbromide (30 mmol) in THF (25 ml) was added slowly at -70 °C. A vigorous reaction ensued and the reaction mixture turned dark. The reaction mixture was allowed to warm to rt where it was stirred for 4h, then quenched with water. The resulting mixture was diluted with ethyl acetate, washed twice with water, followed by brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography using hexane-ethyl acetate as the eluent. IR, ^{1}H NMR spectral data of isolated compounds **5a-c** are given below.
3-(1-Cyanobut-3-enyl)pyridine-4-carbonitrile (5a). Viscous oil, 62%. IR (neat) 3080, 2918, 2235, 2265, 1568, 1430, 967, 815, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, *J*=7.0 Hz, 2H), 4.25 (t, *J*=7.0 Hz, 1H), 5.14-5.25 (m, 2H), 5.74-5.85 (m, 1H), 7.55 (d, *J*=4.9Hz, 1H), 8.78 (d, *J*=5.9 Hz, 1H), 8.95 (s, 1H). ^{13} C NMR ($CDCl_3$) 33.8, 38.6, 114.3, 117.5, 119.6, 121.1, 125.5, 130.6, 132.1, 149.9, 150.3. HRMS Calcd for $C_{11}H_9N_3$: 183.0796. Found: 183.0799.

3-(1-Cyanopent-3-enyl)pyridine-4-carbonitrile (5b). Viscous oil, 71%. IR (neat) 3057, 2920, 2244, 1567, 1432, 969, 810, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (d, *J*= 6.3Hz, 3H), 2.66 (t, *J*=7.0 Hz, 2H), 4.22 (m, 1H), 5.39-5.46 (m, 1H), 5.55-5.61 (m, 1H), 7.56 (d, *J*=5.0 Hz, 1H), 8.78 (d, *J*=5.0 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR ($CDCl_3$) 17.4, 34.0, 37.4, 114.1, 117.6, 119.3, 123.1, 25.3, 131.7, 132.1, 149.6, 149.8. HRMS Calcd for $C_{12}H_{11}N_3$: 197.0953. Found: 197.0955.

3-(1-Cyano-4-methylpent-3-enyl)pyridine-4-carbonitrile (5c). Red oil, 95%. IR (neat) 3058, 2973, 2918, 2244, 1672, 1568, 1431, 1095, 808, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 3H), 1.74 (s, 3H), 2.72 (m, 2H), 4.20 (t, *J*=7.0 Hz, 1H0, 5.20 (m, 1H), 7.57 (d, *J*=4.9 Hz, 1H), 8.80 (d, *J*=4.9 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR ($CDCl_3$) 17.2, 25.2, 33.0, 33.7, 114.1, 116.4, 117.8, 119.2, 125.2, 132.2, 138.2, 149.5, 149.7. HRMS Calcd for $C_{13}H_{13}N_3$: 211.1109 Found: 211.1112.

General procedure for the preparation of 1-substituted derivatives of 3-amino-2,6-naphthyrdines (3a-g) and 1-substituted 4-alkenyl-3-amino-2,6-naphthyrdines (9a-c,e-m)

In a flame-dried flask flushed with argon, the lithium amides was prepared by adding 6.4 ml of n-BuLi (10 mmol, 1.6 M in hexane) to a solution of an appropriate amine (10 mmol) in THF (30 ml) at -70 °C. The alkyllithiums and phenyllithium (10 mmol) were added directly to THF (30 ml). The 4-methyl- and 4-methoxyphenyllithium were prepared by adding 6.4 ml of n-BuLi (10 mmol, 1.6 M in hexane) to a solution of an appropriate bromobenzene (10 mmol) in THF (30 ml) at -70 °C. After stirring for 10 min, the dinitrile (**1**) or alkenyldinitriles (1 mmol) in THF (10 ml) was added dropwise over 5 min. The stirring was continued for 30 min at -70 °C, then the reaction mixture was allowed to warm to -30 °C to -20 °C, where it was stirred for an additional 2 h. The reaction mixture was then quenched with water, and the THF evaporated under reduced pressure to give a residue which was extracted with dichloromethane (2 x 20 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated by a rotary evaporator. The remaining mixture was subjected to flash column chromatography (silica gel) using hexane/ethyl acetate as an eluent to give a liquid or solid product.

3-Amino-1-(1-pyrrolidin-1-yl)-2,6-naphthyridine (3a). Yellow solid, mp 189-190°C, 94%. IR (CH_2Cl_2) 3500, 3399, 3296, 3182, 3054, 2985, 2872, 1610, 1553, 1451, 1266, 896 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (m, 4H), 3.79 (t, *J*=6.5 Hz, 4H), 4.29 (s, 2H), 6.07 (s, 1H), 7.74 (d, *J*=6.0 Hz, 1H), 8.07 (d, *J*= 6.0 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 50.9, 87.2, 116.8, 118.7, 137.0, 138.0, 150.0, 154.0, 155.9. HRMS Calcd for $C_{12}H_{14}N_4$: 214.1219. Found: 214.1222.

3-Amino-1-(1-Piperidin-1-yl)-2,6-naphthyridin-3-ylamine (3b). Yellow solid, mp 123-124°C, 92%. IR (CH_2Cl_2) 3479, 3447, 3399, 3293, 3053, 2933, 2854, 1614, 1557, 1483, 1470, 1442, 1265, 1122, 1032, 903 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (m, 2H), 1.80 (m, 4H), 3.37 (t, *J*=5.2 Hz, 4H), 4.36 (br s, 2H), 6.29 (s, 1H), 7.55 (d, *J*=5.8 Hz, 1H), 8.20 (d, *J*=5.8 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.8, 51.8, 90.3, 117.8, 118.1, 135.9, 138.8, 150.2, 153.4, 160.7. HRMS Calcd for $C_{13}H_{16}N_4$: 228.1375. Found: 228.1376.

3-Amino-1-(1-morpholin-4-yl)-2,6-naphthyridine (3c). Yellow solid, mp 191-192°C, 91%. IR (CH_2Cl_2) 3500, 3399, 3346, 3054, 2986, 2918, 2857, 1619, 1561, 1421, 1266 cm^{-1}; ^1H NMR

($CDCl_3$) δ 3.41 (t, *J*=4.6 Hz, 4H), 3.91 (t, *J*=4.6 Hz, 4H), 4.46 (br s, 2H), 6.34 (s, 1H), 7.54 (d, *J*= 5.8 Hz, 1H), 8.20 (d, *J*= 5.8 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 51.0, 66.6, 91.2, 117.3, 117.6, 135.9, 139.00, 150.4, 153.5, 159.6. HRMS Calcd for $C_{12}H_{14}N_4O$: 230.1168. Found: 230.1171.

3-Amino-1-(isopropylamino)-2,6-naphthyridine (3d). Yellow oil, 60%. IR (neat) 3501, 3398, 3300, 3150, 2985, 2920, 2870, 1615, 1560, 1420, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J*=6.5 Hz, 6H), 4.35 (br s, 2H), 4.43 (hept, *J*=6.5 Hz, 1H), 5.07 (d, *J*= 6.7 Hz, 1H), 6.00 (s, 1H), 7.26 (d, *J*=5.8 Hz, 1H), 8.14 (d, *J*=5.8 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 42.6, 85.7, 114.45, 115.4, 135.4, 139.1, 149.9, 153.7, 154.8. HRMS Calcd for $C_{11}H_{14}N_4$: 202.1219. Found: 202.1223.

3-Amino-1-(butylamino)-2,6-naphthyridine (3e). Yellow oil, 50%. IR (neat) 3329, 3053, 2959, 2930, 2872, 1615, 1580, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J*=7.4 Hz, 3H), 1.48 (m, 2H), 1.67 (m, 2H), 3.56 (m, 2H), 4.39 (br s, 2H), 5.32 (s,1H), 6.03 (s, 1H), 7.31 (d, *J*= 5.8 Hz, 1H), 8.17 (d, *J*= 5.8 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.3, 31.7, 41.2, 85.7, 114.4, 115.4, 135.3, 139.1, 149.9, 154.5, 154.7. HRMS Calcd for $C_{12}H_{16}N_4$: 216.3751. Found: 216.3752.

3-Amino-(1-*tert*-butylamino-2,6-naphthyridine (3f). Yellow oil, 70%. IR (neat) 3376, 2960, 2924, 2850, 1708, 1615, 1455, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 4.36 (br s, 2H), 5.14 (s, 1H), 6.00 (s, 1H), 7.22 (d, *J*= 5.7 Hz, 1H), 8.15 (d, *J*=5.7 Hz, 1H), 8.76; ^{13}C NMR ($CDCl_3$) δ 28.9, 52.0, 85.3, 114.4, 115.9, 135.2, 139.1, 150.0, 153.7, 154.2. HRMS Calcd for $C_{12}H_{16}N_4$: Calcd: 216.1375. Found: 216.1377

3-Amino-1-(methylamino)-2,6-naphthyridine (3g). Yellow solid, mp 167-168°C, 35%. IR (CH_2Cl_2) 3326, 3169, 3065, 2924, 2854, 1650, 1616, 1573, 1277 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 3H), 4.59 (br s, 2H), 6.66 (s, 1H), 7.66 (d, *J*=5.7 Hz, 1H), 8.34 (d, *J*=5.7 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 95.9, 117.7, 123.8, 133.7, 140.2, 151.0, 154.5, 158.5. HRMS Calcd for $C_9H_9N_4$: 159.0797. Found: 159.0799.

3-Amino-1,5-di-butyl-2,6-naphthyridine (3j). yellow oil, 20%. IR (neat) 3319, 3190, 3066, 2956, 2929, 2871, 1621, 1570, 1482, 1465, 1422, 1392 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6H), 1.44 (m, 4H), 1.76 (m, 4H), 3.10 (m, 4H), 4.53 (br s, 2H), 6.75 (s, 1H), 7.51 (d, *J*= 5.9 Hz, 1H), 8.21 (d, *J*= 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 22.9, 23.0, 31.7, 31.9, 34.8, 35.1, 94.5, 115.7, 123.5, 132.5, 138.8, 154.3, 160.8, 163.0. HRMS Calcd for $C_{16}H_{23}N_3$: 257.1892. Found: 257.1888.

4-Allyl-3-amino-(1-pyrrolidin-1-yl)-2,6-naphthyridine (9a). Yellow solid, mp 103-104°C, 90%. IR (CH_2Cl_2) 3493, 3396, 3052, 2975, 2870, 1602, 1572, 1549, 1455, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 4H), 3.55 (dd, *J*=3.8 Hz, 1.7 Hz, 2H), 3.82 (m, 4H), 4.31 (br s, 2H), 5.02-5.11 (m, 2H), 5.94-6.02 (m, 1H), 7.81 (d, *J*=5.9 Hz, 1H), 8.18 (d, *J*=5.9 Hz, 1H), 9.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 29.3, 51.1, 94.4, 115.6, 117.7, 118.6, 134.2, 135.1, 137.6, 147.0, 155.2. HRMS Calcd for $C_{15}H_{18}N_4$: 254.1532. Found: 254.1533

4-Allyl-3-amino-(1-piperidin-1-yl)-2,6-naphthyridine (9b). Yellow solid, mp 118-119°C, 48%. IR (CH_2Cl_2) 3483, 3395, 3190, 3050, 2925, 2863, 1605, 1580, 1480, 1265 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 1.69 (m, 2H), 1.81 (m, 4H), 3.34 (t, *J*=5.2 Hz, 4H), 3.60 (dd, *J*=3.8 Hz, 1.7 Hz, 2H), 4.39 (br s, 2H), 5.01-5.14 (m, 2H), 5.94-6.01 (m, 1H), 7.65 (d, *J*= 6.1 Hz, 1H), 8.29 (d, *J*= 6.1 Hz, 1H), 9.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.8, 29.0, 52.0, 98.1, 115.7, 117.9, 118.9, 133.4, 134.3, 138.5, 147.3, 151.3, 159.6. HRMS Calcd for $C_{16}H_{20}N_4$: 268.1689. Found: 268.1686.

4-Allyl-3-amino-(1-morpholin-4-yl)-2,6-naphthyridine (9c). Yellow solid, mp 149-150°C, 81%. IR (CH_2Cl_2) 3457, 3356, 3208, 3072, 2961, 2919, 2852, 1607, 1562, 1487, 1435, 1269, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.39 (t, *J*=4.6 Hz, 4H), 3.61 (dd, *J*=3.9 Hz, 1.8Hz, 2H), 3.94 (t, *J*=4.3 Hz, 4H), 4.47 (br s, 2H), 5.01-5.06 (dd, *J*=17 Hz, 1.6 Hz, 1H), 5.12 (dd, *J*=10.0 Hz, 1.5 Hz, 1H), 5.94-6.00 (m, 1H), 7.65 (d, *J*=5.7 Hz, 1H), 8.30 (d, *J*=5.7 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 51.9, 67.3, 99.8, 116.6, 118.0, 119.1, 134.1, 134.8, 139.4, 148.2, 152.0, 159.0. HRMS Calcd for $C_{15}H_{18}N_4O$: 270.1481. Found: 270.1483.

3-Amino-4-(3-methylbut-2-enyl)-1-(pyrrolidin-1-yl)-2,6-naphthyridine (9e). Yellow solid, mp 117-118°C, 85%. IR (CH_2Cl_2) 3490, 3395, 3194, 3052, 2974, 2932, 2871, 1602, 1574, 1549, 1453, 1265, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.88 (s, 3H), 1.99 (m, 4H), 3.48 (d, *J*=6.5 Hz, 2H), 3.78 (t, *J*=6.6 Hz, 4H), 4.30 (s, 2H), 5.10 (m, 1H), 7.80 (d, *J*=6.0 Hz, 1H), 8.17(d, *J*=6.0 Hz, 1H), 9.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.0, 24.0, 25.7, 25.9, 51.1, 97.2, 117.7, 118.7, 122.2, 133.0, 134.0, 137.5, 147.1, 151.4, 155.0. HRMS Calcd for $C_{17}H_{22}N_4$: 282.1844. Found: 282.1844.

3-Amino-1-(morpholin-4-yl)-4-(3-methylbut-2-enyl)-2,6-naphthyridine (9f). Yellow viscous liquid, 100%. IR (neat) 3469, 3364, 3208, 3064, 2964, 2915, 2853, 1732, 1607, 1558, 1268, 1115, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3H), 1.77 (s, 3H), 3.26 (t, *J*= 4.4Hz, 4H), 3.43 (d, *J*= 6.3Hz, 2H), 3.82 (t, *J*=5.3 Hz, 4H), 4.54 (br s, 2H), 5.01 (t, *J*=5.3 Hz, 1H), 7.54 (d, *J*=5.7 Hz, 1H), 8.19 (d, *J*=5.7 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.7, 23.7, 25.3, 51.2, 66.5, 101.5, 117.3, 118.1, 121.1, 133.1, 138.4, 147.5, 151.1, 157.9. HRMS Calcd for $C_{17}H_{22}N_4O$: 298.1794. Found: 298.1799.

1-Amino-4-(3-methylbut-2-enyl)-1-phenyl-2,6-naphthyridin-3-ylamine (9g). Yellow solid, mp 153-154°C, 54%. IR (CH_2Cl_2) 3472, 3382, 3311, 3177, 3056, 2973, 2856, 1621, 1557, 1266, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.91 (s, 3H), 3.68 (d, *J*=6.4 Hz, 2H), 4.72 (br s, 2H), 5.15 (m, 1H), 7.53 (m, 3H), 7.65 (m, 3H), 8.29 (d, *J*=5.8 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 24.4, 25.7, 108.0, 119.5, 120.5, 123.4, 128.5, 128.9, 129.7, 131.9, 134.63, 138.3, 139.6, 148.1, 152.8, 157.6. HRMS Calcd for $C_{19}H_{19}N_3$: 289.1579. Found: 289.1581.

3-Amino-1-(2methoxyphenyl)-4-(3-methylbut-2-enyl)-2,6-naphthyridine (9h). Yellow oil, 12%. IR (neat) 3472, 3383, 3170, 3051, 1968, 2931, 2860, 1673, 1601, 1556, 1247, 982 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.77 (s, 3H), 3.71 (s, 3H), 4.26 (m, 2H), 4.82 (br s, 2H), 5.67 (m, 1H), 7.10 (m, 1H), 7.26 (m, 1H), 7.34 (m, 1H), 7.45 (m, 1H), 7.74 (d, *J* =5.8 Hz, 1 H), 8.21 (d, *J*= 5.8 Hz, 1H), 9.57 (s, 1H). HRMS Calcd for $C_{20}H_{21}N_3O$: 319.1685. Found: 319.1685.

3-Amino-1-(4-methoxyphenyl)-4-(3-methylbut-2-enyl)-2,6-naphthyridine (9i). Yellow solid, mp 147-148°C, 90%. IR (CH_2Cl_2) 3432, 3399, 3283, 3162, 3054, 2974, 2856, 1609, 1553, 1265, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.91 (s, 3H), 3.67 (d, *J*=6.5 Hz, 2H), 3.89 (s, 3H),

4.69 (br s, 2H), 5.14 (t, *J*=1.4 Hz, 1H), 7.05 (dd, *J*=6.7 Hz, 2.0 Hz, 2H), 7.61 (dd, *J*=6.7 Hz, 2.0 Hz, 2H), 7.71 (d, *J*=5.8 Hz, 1H), 8.29 (d, *J*=5.8 Hz, 1H), 9.36 (s,1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 24.4, 25.7, 55.4, 107.5, 114.0, 119.6, 120.6, 123.5, 130.9, 131.1, 132.0, 134.5, 139.6, 148.1, 152.7, 157.3, 160.2. HRMS Calcd for $C_{15}H_{18}N_4$: 319.1685. Found: 319.1688.

3-Amino-4-(but-2-enyl)-1-(pyrrolidin-1-yl)-2,6-naphthyridine (9j). Yellow solid, mp 96-97°C, 95%. IR (CH_2Cl_2) 3477, 3392, 3200, 3049, 2870, 1602, 1454, 1265, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (dd, *J*=5.6 Hz, 1.2 Hz, 3H), 1.96 (m, 4H), 3.45 (m, 2H), 3.78 (m, 4H), 4.34 (br s, 2H), 5.44-5.49 (m, 1H), 7.78 (d, *J*=5.9 Hz, 1H), 8.17 (d, *J*=5.9 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 25.6, 27.8, 50.8, 95.3, 117.3, 118.4, 125.7, 128.4, 133.9, 137.1, 146.8, 151.4, 154.8. HRMS Calcd for $C_{16}H_{20}N_4$: 268.1688. Found: 268.1685.

3-Amino-4-(but-2-enyl)-1-(morpholin-4-yl)-2,6-naphthyridine (9k). Viscous liquid, 100%. IR (neat) 3489, 3352, 3190, 2960, 2920, 1608, 1435, 1261, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (dd, *J*=6.1 Hz, 1.4 Hz, 3H), 3.32 (t, *J*=4.7 Hz, 4H), 3.46 (m, 2H), 3.87 (t, *J*=4.7 Hz, 4H), 4.53 (br s, 2H), 5.40-5.44 (m, 1H), 5.47-5.52 (m, 1H), 7.59 (d, *J*=5.7 Hz, 1H), 8.24 (d, *J*=5.7 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 27.8, 51.3, 66.7, 100.3, 117.4, 118.3, 126.4, 126.9, 133.4, 138.6, 147.7, 151.4, 158.3. HRMS Calcd for $C_{16}H_{20}N_4O$: 284.1637. Found: 284.1639.

3-Amino-4-(but-2-enyl)-1-(4-methylphenyl)-2,6-naphthyridine (9l). Yellow solid, mp 119-120°C, 50%. IR (CH_2Cl_2) 3483, 3396, 3308, 3198, 3052, 2964, 2858, 1610, 1265, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (dd, *J*= 6.9Hz, 1.5 Hz, 3H), 2.46 (s, 3H), 3.66 (m, 2H), 4.80 (br s, 2H), 5.56 (m, 1H), 5.58-5.61 (m, 1H), 7.34 (d, *J*=7.8 Hz, 2H), 7.56 (d, *J*=7,8 Hz, 2H), 7,71 (d, *J*=5.3 Hz, 1H), 8.30 (d, *J*=5.8 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.7, 21.2, 28.3, 106.1, 119.4, 123.3, 126.4, 127.3, 129.1, 129.6, 132.0, 135.3, 138.7, 139.4, 147.8, 152.8, 157.8. HRMS Calcd for $C_{19}H_{19}N_3$: 289.1579. Found: 289.1579.

3-Amino-4-(but-2-enyl)-1-phenyl-2,6-naphthyridine (9m). Yellow solid, mp 117-118°C, 53%. IR (CH_2Cl_2) 3500, 3397, 3308, 2986, 2857, 1609, 1266, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (d, *J*=5.1 Hz, 3H), 3.64 (d, *J*=5.2 Hz, 2H), 4.88 (br s, 2H), 5.38-5.74 (m, 2H), 7.46-7.54 (m, 3H), 7.64-7.67 (m, 3H), 8.29 (d, *J*=5.9 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.7, 28.2, 106.3, 119.2, 123.1, 126.3, 127.2, 128.3, 128.7, 129.6, 131.9, 138.1, 139.4, 147.9, 152.8, 157.6. HRMS Calcd for $C_{18}H_{17}N_3$: 275.1423. Found: 275.1424.

3-Amino-4-propenyl-1-(pyrrolidin-1-yl)-2,6-naphthyridine (10a). Red oil, 6%. ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 3H), 1.99 (m, 4H), 3.80 (m, 4H), 4.37 (br s, 2H), 6.05-6.10 (m, 1H), 6.37 (dd, *J*=10.8 Hz, 1.6 Hz, 1H), 7.79 (d, *J*=5.8 Hz, 1H), 8.16 (d, *J*= 5.8 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 25.9, 51.1, 95.0, 116.9, 118.5, 122.8, 131.5, 134.0, 137.8, 148.6, 150.6, 155.4. HRMS Calcd for $C_{15}H_{18}N_4$: 254.1532. Found: 254.1533

3-Amino-1-(piperidin-1-yl)-4-propenyl-2,6-naphthyridine (10b). Orange solid, mp 89-90°C, 30%. ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 3H), 1.68-1.72 (m, 2H), 1.78-1.84 (m, 4H), 3.37 (t, *J*=5.1 Hz, 4H), 4.45 (br s, 2H), 6.11-6.15 (m, 1H), 6.41 (dd, *J*=10.9 Hz, 1.4 Hz, 1H), 7.61 (d, *J*= 5.9 Hz, 1H), 8.26 (d, *J*=5.9 Hz, 1H), 8.99(s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.8, 24.5, 25.8, 52.0, 98.3, 117.7, 118.1, 121.9, 131.9, 133.0, 138.5, 148.8, 150.1, 159.9. HRMS Calcd for $C_{16}H_{20}N_4$: 268.1689. Found: 268.1686.

3-Amino-1-(morpholin-4-yl)-4-propenyl-2,6-naphthyridine (10c). Orange oil, 16%. ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 3H), 3.42 (t, *J*=4.5 Hz, 4H), 3.94 (t, *J*=4.3 Hz, 4H), 4.51 (br s, 2H), 6.16 (m, 1H), 6.40 (dd, *J*=10.9 Hz, 1.6 Hz, 1H), 7.61 (d, *J*=5.8 Hz, 1H), 8.29 (d, *J*=5.8 Hz, 1H), 9.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5, 51.9, 67.3, 100.0, 117.9, 118.3, 122.3, 133.0, 133.7, 139.5, 149.8, 150.8, 159.5. HRMS Calcd for $C_{15}H_{18}N_4O$: 270.3296. Found: 270.3295.

3-Amino-1-phenyl-4-propenyl-2,6-naphthyridine (10d). Yellow solid, mp 102-103°C, 38%. ^{1}H NMR ($CDCl_3$) δ 2.09 (dd, *J*=6.5 Hz, 1.8 Hz, 3H), 4.88 (br s, 2H), 6.24-6.28 (1H), 6.57 (dd, *J*=15 Hz, 1.8 Hz, 1H), 7.53 (m, 3H), 7.65-7.68 (m, 3H), 8.28 (d, *J*= 6.0 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 107.7, 119.5, 122.9, 123.4, 128.9, 129.3, 130.1, 132.2, 135.4, 138.6, 140.2, 129.7, 152.4, 158.3. HRMS Calcd for $C_{17}H_{15}N_3$: 261.3211. Found: 261.3212.

General procedure for the preparation of 5-substituted derivatives of 2-methyl-3*H*-pyrrolo[2,3-*c*]-2,6-naphthyridines (8a-c).

a) Under catalytic conditions Into a flame-dried flask flushed with argon were placed $PdCl_2(MeCN)_2$ (20 mol%), benzoquinone (1 equiv), LiCl (10 equiv.) and 20 ml of THF, the resulting mixture was stirred at rt for 5 min. The substrates (**6**) (1 equiv.) in 5 ml of THF was then added to the flask, and the resulting solution was refluxed for 15 h. The mixture was then filtered through Celite® and concentrated on a rotary evaporator. Products were isolated by silica gel column chromatography using hexane-ethyl acetate as the eluent.

b) Under stoichiometric conditions. Into a flame-dried flask flushed with argon were placed $PdCl_2(MeCN)_2$ (1 equiv.) and 10 ml THF and allowed to stir for 5 min. The substrate (**6**) (1 equiv) in 5 ml of THF was then added to slurry of the palladium complex. After the mixture was stirred for 1.5 h at rt, triethylamine (1 equiv.) was added and the resulting mixture stirred for 3 h. A second equiv. of triethylamine was added. Finally a third equiv of triethylamine was added after an additional 1 h of stirring. The mixture was then allowed to stir for a further 2 h, and was then worked up in a similar procedure described above. The physical and spectral properties of products (**8**) are listed below.

2-Methyl-5-(pyrrolidin-1-yl)-3*H*-pyrrolo[2,3-*c*][2,6]-naphthyridine (8a). Yellow solid, mp 141-142°C. IR (CH_2Cl_2) 3233, 2970, 2873, 1610, 1540, 1432, 1330 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01-2.05 (m, 4H), 2.49 (s, 3H), 3.79 (t, *J*=6.6 Hz, 4H), 6.56 (s, 1H), 8.01 (d, *J*=5.8 Hz, 1H), 8.41 (d, *J*=5.8 Hz, 1H), 8.45 (br s, 1H), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 25.9, 51.6, 97.2, 105.9, 119.8, 120.3, 127.8, 130.0, 139.4, 147.8, 149.8, 153.5. HRMS Calcd for $C_{15}H_{16}N_4$: 252.1375. Found: 252.1380.

2-Methyl-5-(piperidin-1-yl)-3*H*-pyrrolo[2,3-*c*][2,6]-naphthyridine (8b). Brown solid, mp 125-126°C. IR (CH_2Cl_2) 3230, 2950, 2860, 1600, 1548, 1430, 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2H), 1.83 (m, 4H), 2.53 (s, 3H), 3.26 (t, *J*=5.3 Hz, 4H), 6.67 (s, 1H), 7.85 (d, *J*=6.5 Hz, 1H), 8.55 (d, *J*=6.5 Hz, 1H), 8.60 (br s, 1H), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 24.6, 26.1, 53.8, 98.2, 108.2, 120.8, 121.4, 127.4, 132.7, 142.2, 143.1, 152.4, 156.2. HRMS Calcd for $C_{16}H_{18}N_4$: 266.1532. Found: 268.1533.

2-Methyl-5-(morpholin-4-yl)-3*H*-pyrrolo[2,3-*c*][2,6]-naphthyridine (8c). Orange solid, mp 280-281°C. IR (CH_2Cl_2) 3223, 2938, 2865, 1606, 1550, 1428, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.30 (t, *J*= 4.5Hz, 4H), 3.97 (t, *J*=4.5 Hz, 4H), 6.61 (s, 1H), 7.83 (d, *J*= 6.6 Hz, 1H), 8.54 (d, *J*= 6.6Hz, 1H), 8.82 (br s, 1H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 52.1, 66.9, 98.2, 108.8, 120.2, 120.7, 127.1, 133.5, 142.3, 142.9, 152.6, 154.6. HRMS Calcd for $C_{15}H_{16}N_4O$: 268.1324. Found: 270.1325.

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