THE REACTION OF 5-CHLORO DERIVATIVES OF 3-PYRIDINOL AND 3-METHOXYPYRIDINE WITH VARIOUS AMINES UNDER ARYNE-FORMING CONDITIONS

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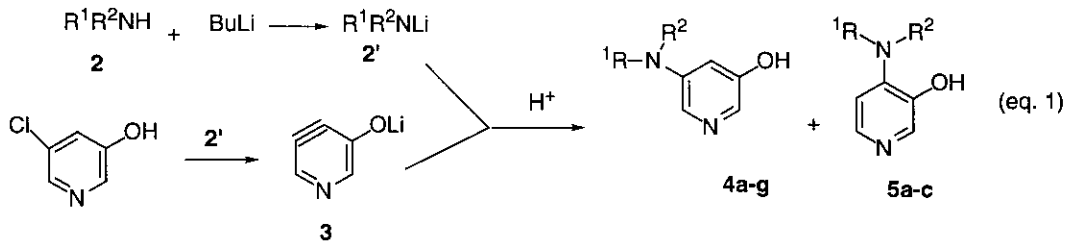
Abstract - The reactions of 5-chloro-3-pyridinol (**1**) and 5-chloro-3-methoxypyridine (**6**) with various lithium amides (**2'**) in THF or free amine solvent (**2**) have been studied and the results reported herein. In most cases, 5-aminated products were exclusively formed; however, in the reaction of **1** with LDA or n-butylamine, 4-aminated products were formed predominantly. Additionally, and without exception, aminated products were obtained in highest yields when the reactions were carried out in the corresponding free amine solvents.

During the course of our investigation of substituent effects on the orientation and reactivity of aryne intermediates, we were led to study the role of charged substituents. In a brief article, we[1] demonstrated that 2-chlorobenzoic acid reacted with various alkanenitriles in the presence of sodium amide in liquid ammonia to give 3-(α-cyanoalkyl)benzoic acids in good yields by the usual aryne arylation mechanism.[2] The exclusive addition of nitrile anions to the 1-position of benzyne-3-carboxylate (each produced *in situ*) was not due to the inductive effect of the carboxylate group (which would been expected to yield both positional isomers),[3] but rather to unfavorable electronic interactions between the carboxylate group and the nitrile anion that would be operative in addition to the 2-position. 5-Bromonicotinic acid[4] was later shown to react with acetonitrile derivatives in similar manner at -70 °C in the presence of LDA in THF to yield 5-(α-aryl-cyano)nicotinic acids. However, 4-substituted 2-halobenzoic acids (R = H, Me, MeO)[5] reacted with acetonitrile derivatives and LDA in THF to give rearranged 4-substituted 2-cyanobenzoic acids (40-61%), presumably by a tandem addition-rearrangement pathway.[6]

Recently we extended this reaction to nucleophilic additions to the 3,4-dehydro-5-pyridineoxide intermediate. In these reactions [7] arylacetonitriles reacted with 5-chloro-3-pyridinol in the presence of excess LDA at –70 °C to give α-aryl-3-hydroxy-5-pyridylacetonitriles. When the 3,4-dehydro-5-pyridinoxide was generated in the presence of pre-formed α-lithio-4-methoxyphenylacetonitriles (the usual method), the expected 3-hydroxy-5-(4'-methoxyphenyl)methylpyridylacetonitriles product was not obtained, but rather 4-(*N*,*N*-diisopropylamino)-3-pyridinol (**5a**) was formed in 15% yield. Although the yield of **5a** was poor, the regioselective addition of LDA to the 4-position of 3-LiO-4,5-dehydropryidine was interesting, and thus a study of the reaction of 5-chloro-3-pyridinol with LDA and other amides was carried out. These reactions are outlined in eq. 1 and the results listed in Table 1.



These reactions were carried out in THF (Solvent A) or in the free amine (**2**, Solvent B). In either case, one equiv of **1** was added to a solution at -70 °C (THF) or 0 °C (free amine) containing 3 equiv of lithium amide (**2'**) prepared *in situ* by the reaction of 3 equiv of **2** with n-BuLi. The resulting solutions were allowed to warm to room temperature and stirred an additional 3 h before typical workup. With the exception of diisopropylamine (**2a**), *n*-butylamine (**2b**) and piperidine (**2c**), Entries 1-3, respectively, the products of the reactions run in THF (Entries 4-7) were 5-alkylamino- (**4e,g,h**) and 5-dialkylamino-3-pyridinols (**4d,f**). In the exceptional cases, 4-substituted pyridinols were also obtained, namely, 4-(*N,N*-diisopropylamino)- (**5a**), 4-(*N-n*-butylamino)- (**5b**), and 4-piperidyl-3-pyridinol (**5c**). However, the yields of desired amino alcohols from these reactions were low (trace-39 %) with the major products being water soluble, viscous liquids. NMR spectroscopic analysis of these viscous liquids indicated that they were mixtures of dimeric and trimeric substances containing hydroxypyridyl and *N*-alkylamino groups in a ratio of 2:1, respectively.

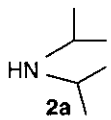
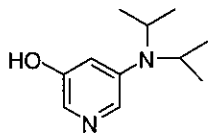
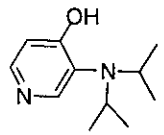
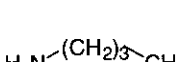
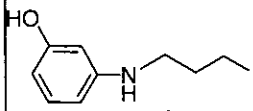
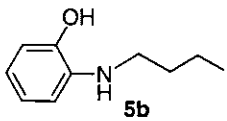
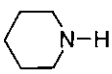
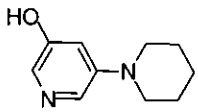
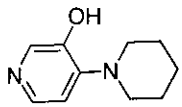
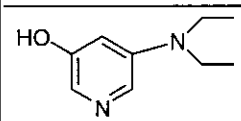
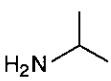
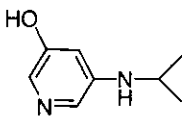
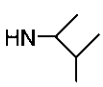
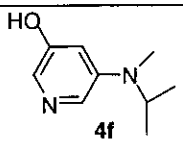
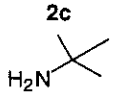
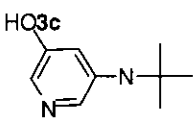
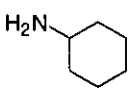
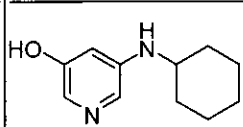
When the reactions of **1** with **2'** were conducted in free amine solvents, the yields of **4** or **5** were substantially increased. For example, the yield of 4-(*N-n*- butylamino)-3-pyridinol (**5b**) increased from 15% to 40% (Entry 2) while the yield of 5-(*N,N*-diethylamino-3-pyridinol (**4d**) increased from 26% to 82% (Entry 4). Interestingly, the reaction of **1** with LDA (Entry 1) in diisopropylamine, which gave both positional isomeric amines (**4a** and **5a**) in THF in about equal amounts, supplied only 4-(*N*-diisopropyl-amino)-3-pyridinol (**5a**). On the other hand, the reaction of **1** with piperidine, which in THF gave the amine products in a 2:1 ratio, **4c**:**5c**, gave only the 5-amino isomer (**4c**).

The structures of **4** and **5** were ascertained by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and HRMS. The pyridine hydrogen's splitting patterns in the ^{1}H NMR spectra were particularly valuable in assigning substitution patterns in the 4- and 5-substituted 3-pyridinols. For example, the three pyridine hydrogens in **4a-c** appear as two doublets with J = 5.2 Hz (*ortho* coupling) and a broad singlet whereas those in **5** appear as two doublets with J = ~ 2 Hz (*meta* coupling) and a broad singlet. A more detailed analysis of the amine products is given later in the text.

The addition of most amination reactions listed in Table 1 occurs regioselectively at the 3-position of the 3,4-dehydropyridine-5-pyridinoxide (**3**). Since the electron-releasing effect *o*-OLi group would be expected to direct nucleophilic addition to the 4-position of **3**, the observed 3-addition most likely reflects the absence of unfavorable electronic interactions that would be operable in addition to the 4-position of **3**. However, the addition of the sterically demanding diisopropylamide (or diisopropylamine) and the non-sterically demanding *n*-butylamine occurs exclusively to the 4-position, indicating that such addition is facilitated by chelation between the OLi and incoming amine nucleophile.

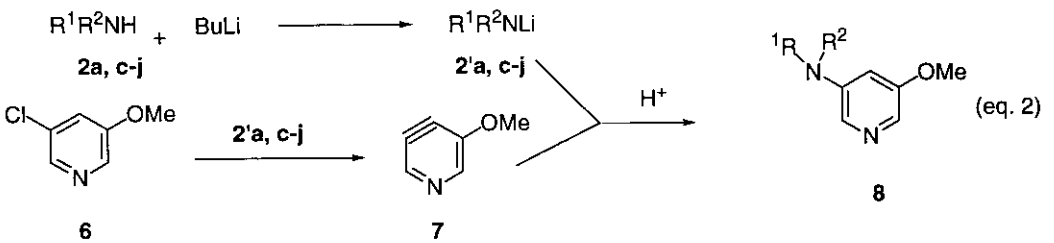
We then turned our attention to the reaction of 5-chloro-3-methoxypyridine (**6**) with lithium amides (**2'**). These reactions were expected to yield 5-amino-3-methoxypyridines (**8**) since addition of the amides (**2'**)

Table 1. Synthesis of 5-Amino-3-pyridinols

Entry	Amine 2	5-Amino-3-pyridinol 4	yield, % A[a]	yield, % B[b]	4-Amino-3-pyridinol 5	yield, % A[a]	yield, % B[n]
1	 **2a**	 4a	17		 **5a**	20	47
2	 **2b**	 **4b**	tr	tr	 **5b**	15	40
3	 **2c**	 **4c**	12	62	 **5c**	5	—
4	 **2d**	 **4d**	26	82			
5	 **2e**	 **4e**	16	45			
6		 **4f**	22	c			
7	**2c**  **2g**	HO **3c**  **4g**	21	46			
8	 **2h**	 **3h**	39	d			

a. THF as solvent b. Free amine as solvent c. High cost prevents its use as solvent d. Solvent difficult to remove from product.

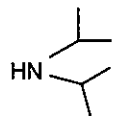
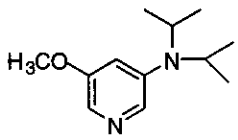
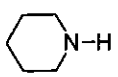
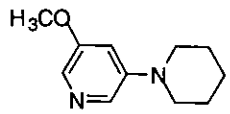
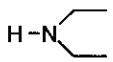
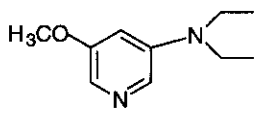
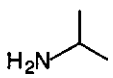
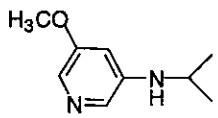
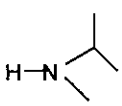
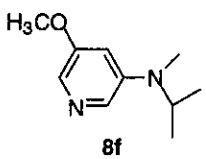
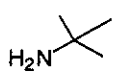
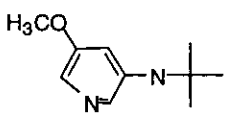
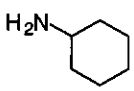
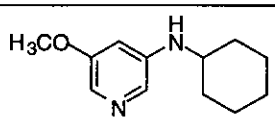
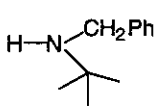
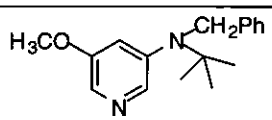
should add to the 3-position of the 5-methoxy-3,4-dehydropyridine intermediate (**7**) owing to the well-established meta directing effect of the methoxy group.[3] Furthermore, a comparison of the influence of the OLi and OMe groups on the mode of the addition to 3,4-dehydropyridine would be obtained. 5-Chloro-3-methoxypyridine (**6**) was easily prepared by the reaction of the commercially available 5-chloro-3-pyridinol (**1**) with diazomethane.5-Chloro-3-methoxypyridine (**6**) was easily prepared by the reaction of the commercially available 5-chloro-3-pyridinol (**1**) with diazomethane. As shown in eq. 2, the reaction of **6** with lithiated amines (**2a, c-j**) in THF (A) gave the corresponding 5-amino-3-methoxypyridines (**8a,c-i**) in yields (shown in Table 2) ranging from 18% for the most sterically demanding amine adduct, benzyl-t-



butylamine (**8i**) to 90 % for the isopropylamine adduct (**8e**). These yields generally were higher than those for similar reactions of 5-chloro-3-pyridinol (**1**), *e.g.* 60% (Entry 1, Table 2) vs. 17% (Entry 1, Table 1) for the diisopropylamine products (**8a** and **5a**), respectively. Furthermore the yields of **8a,c,d,g,h** were substantially increased to 78-94% (entries 1-3,6,7, respectively) while those of the benzyl-t-butyl product (**8i**) was increased to 38% when the free amine was used as solvent (B 5-amino-3-methoxypyridines (**8a,c-i**) in yields (shown in Table 2) ranging from 18% for the most sterically demanding amine adduct, benzyl-t-butylamine (**8i**) to 90 % for the isopropylamine adduct (**8e**). These yields generally were higher than those for similar reactions of 5-chloro-3-pyridinol (**1**), *e.g.* 60% (Entry 1, Table 2) vs. 17% (Entry 1, Table 1) for the diisopropylamine products (**8a**) and (**5a**), respectively. Furthermore the yields of **8a,c,d,g,h** were substantially increased to 78-94% (Entries 1-3,6,7, respectively) while those of the benzyl-t-butyl product (**8i**) was increased to 38% when the free amine was used as solvent (B).

The ^{1}H NMR spectra of these amines confirmed the structural assignments. For example, each amine exhibited three signals in the aromatic region due to 2-H (δ 7.60-7.67 ppm), 4-H (δ ~6.3 - 6.5 ppm) and 6-H (δ ~7.65-7.88 ppm). The most deshielded proton 6-H was assigned on the basis of its presence adjacent to the more electronegative methoxy oxygen atom as compared to the location of 2-H adjacent to a less electronegative amino nitrogen atom. Furthermore, the coupling constants $J_{(2\text{-}H)4\text{-}H)}$ and $J_{(4\text{-}H)(6\text{-}H)}$ were similar which resulted in the signal of 4-H being split into an apparent triplet and those of 2-H and 6-H being split into doublets. Interestingly, the difference in the chemical shifts of 2-H and 6-H was greater for the disubstituted amines (R = R' = isopropyl, ethyl) as compared to the monosubstituted ones (R = isopropyl, t-butyl, and cyclohexyl). This difference was mostly due to the greater deshielding of the chemical shift of 6-H by the more substituted amino substituent as compared to 2-H, e.g. compare the

Table 2. Synthesis of 5-Amino-3-pyridinols

entry	amine **2**	5-Amino-3-methoxypyridine **8**	yield, % A[a]	B
1	 **2a**	 **8a**	60	88
2	 **2c**	 **8c**	61	94
3	 **2d**	 **8d**	52	94
4	 **2e**	 **8e**	90	-
5	 **2f**	 **8f**	46	c
6	 **2g**	 **8g**	34	78
7	 **2h**	 **8h**	53	90
8	 **2i**	 **8i**	18	38

a. THF as solvent b. Free amine as solvent c. High cost prevents its use as solvent

chemical shifts of the diisopropyl (δ = 7.88 ppm) vs. isopropyl (δ= 7.70 ppm) substituted amino-pyridines. This most likely is the result of steric inhibition of resonance between the amino group and pyridine ring.

In conclusion, this study has shown that, in general, 5-*N*-alkylamino- and 5,5-*N*,*N*-dialkylamino derivatives of 3-pyridinol and 3-methoxypyridine can be prepared in good to excellent yields by the aryne reaction. In a few cases, 4-*N*-alkylamino-3-pyridinol can be obtained indicating that the 5-OLi appears to direct the orientation of the amide (or amine) nucleophile to 3-position of 3,4- dehydropyridine by chelation. These reactions are of particular significance in that they provide ready access to 3,5-disubstituted pyridines, which are difficult to obtain by the usual electrophilic substitution or nucleophilic addition methodologies. Furthermore, pure *N*-alkylamino analogs can be prepared uncontaminated with pesky *N*,*N*-dialkyl side products which are generally obtained in typical alkylation reactions.

EXPERIMENTAL

The amines were dried over calcium hydride and distilled prior to use; n-butyllithium was used as received. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrophotometer and chemical shifts were related to TMS as an internal standard. HRMS analyses were performed by the Washington University Mass Spectrometry Resource, an *NIH Research Resource (Grant No. P41RR0954)*. *All benzyne reactions were done under* an atmosphere of dry O_2-free N_2. 5-Chloro-3-methoxypyridine (**6**) was prepared by treating 5-chloro-3-pyridinol with diazomethane: ^1H NMR ($CDCl_3$) δ 3.87 (s, 3 H), 7.22 (t, *J* = 2.0 Hz, 1 H), 8.20 (d, *J* = 2.0 Hz, 1 H), 8.22 (d, *J* = 2.0 Hz, 1 H). *Anal.* Calcd for C_6H_6NOCl: C, 50.19; H, 4.21; N, 9.76. Found: C, 50.25; H. 4.26; N, 9.83.

General Procedure for the Reaction of 5-Chloro-3-pyridinol (1) or 5-Chloro-3-methoxypyridine (6) with Amines (2) in the Presence of n-BuLi. In an oven dried flask, 3 mmol of the lithium amide (**2'**) was prepared by the addition of 3.0 mmol of BuLi to the appropriate amine (**2**) in THF (A) at -70 °C or at O°C when free amine is used as solvent (B). After stirring 10 min, **1** (120 mg, 1 mmol) or **6** (143 mg, 1 mmol) was added dropwise, and the resulting solution allowed to warm to rt where it was stirred an additional 3 h. The resulting dark-red solution was quenched by the addition of 2 mL of ethanol, the excess THF was removed by rotatory evaporation, and the residue dissolved in methylene chloride. The resulting solution was washed with water, dried, and evaporated to yield a brownish residue. In the case of solvent system A, the residue was subjected to column chromatography (silica gel) using methylene chloride followed by 95:5 mixture of methylene chloride and ethyl acetate to yield the amines (**4, 5** or **8**). In the case of solvent system B, the amine solvent and products were separated by Kugelrohr distillation. The physical properties of the amines are listed below.

5-(*N*, *N* –Diisopropylamino)-3-pyridinol (4a): viscous liquid; ^1H NMR ($CDCl_3$) δ 1.24 (d, *J* = 7.8 Hz, 12 H), 3.79 (sept ,*J* = 7.8 Hz, 2 H), 6.77 (s, 1 H), 7.69 (S, 1 H), 7.70 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 21.22, 47.58, 112.75, 124.76, 130.20, 146.22, 155.92. HRMS: Calcd for $C_{11}H_{18}N_2O$:

194.1419. Found: 194.1419. *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 68.10; H, 9.47; N, 14.28.

5-Piperidyl-3-pyridinol (4c): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 1.73 (m, 4 H), 3.21 (t, *J* = 5.2 Hz, 4 H), 6.77 (t, *J* = 2.4 Hz, 1 H), 7.73 (d, *J* = 2.4 Hz, 1 H), 8.09 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 24.18, 25.53, 49.90, 55.62, 108.46, 126.53, 131.63, 149.01, 157.85. HRMS: Calcd for $C_{10}H_{14}N_2O$: 178.1106. Found: 178.1103. *Anal.* Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: 67.46; H, 8.04; N, 15.93.

5-(*N*, *N* -Diethylamino)-3-pyridinol (4d): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.54 (t, *J* = 8.9 Hz, 6 H), 3.32 (q, *J* = 8.9 Hz, 4 H), 6.58 (t, *J* = 2.5 Hz, 1 H), 7.55 (d, *J* = 2.5 Hz, 1 H), 7.64 (d, *J* = 2.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 42.46, 44.33, 106.92, 123.6, 124.1, 145.72. HRMS: Calcd for $C_9H_{14}N_2O$: 166.1106. Found: 166.1113). *Anal.* Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.18; H, 8.55; N, 17.02.

5-(*N* -Isopropyl-N-methylamino)-3-pyridinol (4e): viscous liquid. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, *j* = 6.4 Hz, 6 H), 2.73 (s, 3 H), 4.02 (sept, *J* = 6.4 Hz, 2 H), 6.67 (t, *J* = 2.4 Hz, 1 H), 7.67 (d, *J* = 2.4 Hz, 1 H), 7.68 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 19.36, 29.58, 48.68, 108.20, 124.20, 125.26, 147.91, 155.95. HRMS: Calcd for $C_9H_{14}N_2O$: 166.1106. Found: 166.1113. *Anal.* Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.88; H, 8.67; N, 17.01.

5-(*N* -Isopropylamino)-3-pyridinol (4f): viscous liquid; ^{1}H NMR ($CDCl_3$) δ1.18 (d, *J* = 7.25 Hz, 6 H), 3.57 (sept, *J* = 7.25 Hz, 1 H), 6.67 (t, J = 2.5 Hz, 1 H), 7.66 (d, *J* = 2.5 Hz, 1 H), 7.68 (d, J = 2.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 21.24, 47.36, 110.20, 124.76, 128.81, 145.55, 156.25. HRMS: Calcd for $C_8H_{12}N_2O$: 152.0950. Found: 152.0954. *Anal.* Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.98; H, 8.05; N, 18.59.

5-(*N*-*t*-Butylamino)-3-pyridinol (4g): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 6.68 (br s, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 29.55, 109.15, 126.51, 129.80, 144.33, 154.20. HRMS: Calcd for $C_9H_{14}N_2O$: 166.1106. Found: 166.1109. *Anal.* Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.89; H, 8.60; N, 16.89.

5-Cyclohexylamino-3-pyridinol (4h): viscous liquid: ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 4 H), 1.28 (m, 2 H), 1.64 (m, 2 H), 1.98 (m, 2 H), 3.1 (br s, 1 H), 6.45 (t, *J* = 2.0 Hz, 1 H), 7.44 (d, *J* = 2.0 Hz, 1 H), 7.58 (d, *J* = 2.0 Hz, 1 H). HRMS: Calcd for $C_{11}H_{16}N_2O$: 192.1262. Found: M, 192.1280. *Anal.* Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.93; H, 8.45; N, 14.71.

4-(*N*, *N* -Diisopropylamino-3-pyridinol (5a): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz, 12 H), 3.50 (sept, *J* = 6.4 Hz, 2 H), 7.05 (d, *J* = 5.2 Hz, 1 H), 8.11 (d, *J* = 5.2 Hz, 1 H), 8.33 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.50, 49.81, 106.04, 122.03, 136.21, 142.23, 155.02. HRMS: calcd

for $C_{11}H_{18}N_2O$: 194.1419. Found: M, 194.1421). *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 69.21; H, 9.45; N, 14.38.

4-(*N*-*n*-Butylamino)-3-pyridinol (5b): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H), 1.42 (m, 2 H), 1.64 (m, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 7.13 (d, *J* = 4.8 Hz, 1 H), 7.90 (d, *J* = 4.8 Hz, 1 H), 8.25 (d, *J* = 2.2 Hz, 1 H). HRMS: Calcd for $C_9H_{14}N_2O$: 166.1106. Found: 166.1111.

4- Piperidyl-3-pyridinol (5c): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 1.73 (m, 4 H), 3.21 (m, 4 H), 6.76 (d, *J* = 5.2 Hz, 1 H), 7.90 (d, *J* = 5.2 Hz, 1 H), 8.09 (t, *J*= 2.1 Hz, 1 H). HRMS: Calcd for $C_{10}H_{14}N_2O$: 178.1106. Found: 178.1103). *Anal.* Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.51; H, 8.01; N, 15.82.

3-(*N, N* -Diisopropylamino)-5-methoxypyridine (8a): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, *J* = 8.4 Hz, 12 H), 3.76 (m, 2 H), 3.78 (s, 3 H), 6.62 (t, *J* = 2.5 Hz) 7.66 (d, *J*= 2.5 Hz, 1 H), 7.88 (d, *J*= 2.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 21.91, 47.61, 55.52, 109.95, 124.74, 133.19, 145.19, 155.92. HRMS: Calcd for $C_{12}H_{20}N_2O$: 208.1575. Found: 208.1578).

5-Methoxy-3-piperidylpyridine (8c): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 2 H), 1.69 (m, 4 H), 3.17 (t, *J* = 5.6 Hz, 4H), 3.82 (s, 3 H), 6.68 (t, *J* = 2.4 Hz) 7.76 (d, *J*= 2.4 Hz, 1 H),), 7.95 (d, *J*= 2.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 24.90, 25.10, 33.26, 52.00, 56.00, 104.66, 124.86, 129.68, 145.0, 155.0. HRMS: Calcd for $C_{11}H_{16}N_2O$: 192.1262. Found: 192.1267. *Anal.* Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68,79; H, 8.45; N, 14.70.

3-(*N, N* -Diethylamino)-5-methoxypyridine (8d): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 6 H), 3.35 (q, *J* = 7.2 Hz, 4 H), 3.83 (s, 3 H), 6.46 (t, *J* = 2.4 Hz, 1 H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.76 (d, *J* = 2.4 Hz, 1 H). HRMS: Calcd for $C_{10}H_{16}N_2O$: 180.1262. Found: 180.1266). *Anal.* Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.34. Found: C, 66.78; H, 9.03; N, 15.68.

3-(*N*-Isopropylamino)-5-methoxypyridine (8e): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, *J* = 6.0 Hz, 6H), 3.50 (m, 1 H), 3.85 (s, 3 H), 6.42 (t, *J* =1.0 Hz, 1 H), 7.67 (br s, 2 H), 7.59. HRMS: Calcd for $C_9H_{14}N_2O$: 166.1106. Found: 166.1103.

3-(*N*-Isopropyl-*N*-methylamino-5-methoxypyridine (8f): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.4 Hz, 6 H), 2.66 (s, 3 H), 3.75 (s, 3 H), 3.98 (sept, *J* = 6.4 Hz, 1H), 6.46 (t, *J* = 2.2 Hz, 1 H), 7.59 (d, *J* = 2.2 Hz, 1 H), 7.77 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.14, 30.44, 49.66, 56.37, 106.12, 125.11, 130.05, 147.49. 157.223. HRMS: Calcd for $C_{10}H_{16}N_2O$: 180.1262. Found: 180.1264. *Anal.* Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95, N, 15.54. Found: C, 66.75; H, 9.04; N, 15.71.

3-(*N*-t-Butylamino)-5-methoxypyridine (8g): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.80 (s, 3 H), 6.57 (t, *J* = 2.4 Hz, 1 H), 7.67 (t, *J* = 2.4 Hz, 1 H), 7.70 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 29.78, 51.43, 55.42, 107.99, 125.59, 132.21, 143.97, 156.09. HRMS: Calcd for $C_{10}H_{16}N_2O$: 180.1263. Found: 180.1258.**3-(*N*-Cyclohexylamino)-5-methoxypyridine (8h)**:

viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 4 H), 1.32 (m, 2 H), 1.68 (m, 2 H), 1.99 (m, 2 H), 3.1 (br s, 1 H), 3.5 (br s, 1 H), 3.74 (s, 3 H), 6.31 (t, *J* = 2.4 Hz, 1 H), 7.60 (d, *J* = 2.4 Hz, 1 H), 7.66 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 24.91, 25.83, 33.24, 35.47, 52.00, 107.00, 126.50, 126.7, 147.10, 155.80. HRMS: Calcd for $C_{12}H_{18}N_2O$: 206.1419. Found: 206.1417.

3-(*N*-Benzyl-*N*-t-butylamino)-5-methoxypyridine (8i): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9 H), 3.71 (s, 3 H), 3.81 (s, 2 H), 7.15-7.33 (m, 5 H), 7.68-8.22 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 28.47, 52.93, 55.60, 55.07, 120.51, 121.60, 128.08, 132.15, 140.52, 143.80, 145.86, 155.36. HRMS: Calcd for $C_{17}H_{22}N_2O$: 270.1732. Found: 270.1717.

5-Methoxy-3-*N*-pyrrolidylpyridine (8j): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 4 H), 3.26 (t, *J* = 6.4 Hz, 4 H), 3.82 (s, 3 H), 6.31 (t, J = 1.5 Hz) 7.62 (d, *J*= 1.5 Hz, 1 H), 7.65 (d, *J*= 1.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 25.37, 47.47, 55.48, 103.57, 123.79, 127.52, 144.76, 156.44. HRMS: Calcd for $C_{10}H_{14}N_2O$: 178.1106. Found: 178.1099. *Anal.* Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.45; H, 8.01; N, 15.78.

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