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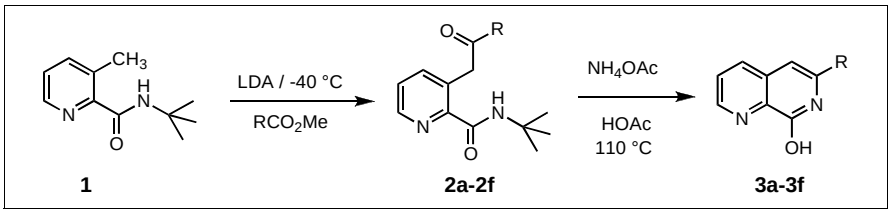

A general method for the synthesis of 8-hydroxy-6-substituted-1,7-naphthyridines is described using acylation of the dianion derived from *tert*-butylamide **1**, followed by cyclization of the resulting intermediate ketones **2** with ammonium acetate.

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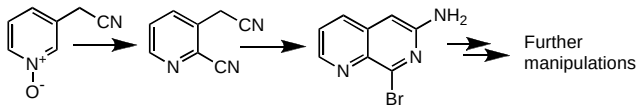
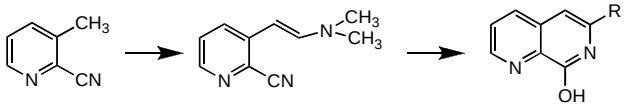
The discovery of 1,7-naphthyridines as a novel class of potent phosphodiesterase type 4 inhibitors [1] created much interest in finding facile methods for preparing these compounds. As the interest in this class of heterocycles is rather new, not many methods are described in the literature. One of the methods [1] started from 3-pyridylacetonitrile-*N*-oxide employing trimethylsilylcyanide and diethylcarbamyl chloride as reagents (Scheme 1) to make the desired compounds. The workup is tedious and the yields are low.

Scheme 1



Another method [2] that was tried starting from the easily available 2-cyano-3-methylpyridine is shown in Scheme 2. Here the 8-hydroxy-1,7-naphthyridine was prepared through the intermediacy of the corresponding enamine, and the yield of the final product was only 5% overall.

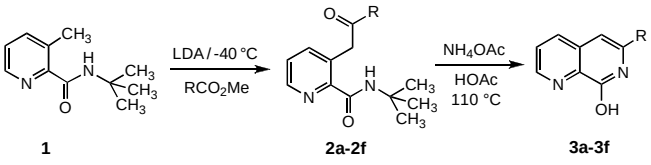
Scheme 2



The ready availability of 2-cyano-3-methylpyridine made us think of different options for transforming this material to the 1,7-naphthyridine system. In this connection, the synthesis used in the production of loratadine (a tricyclic antihistamine) [3] became quite handy to us. Here the 2-cyano-3-methylpyridine was converted initially to *tert*-butylamide **1** *via* a Ritter reaction using *tert*-butyl alcohol and sulfuric acid. The dianion of **1** formed by treating with *n*-butyllithium was effectively alkylated with *m*-chlorobenzyl chloride in very high yield. Taking advantage of this finding we extended the scope of this anion chemistry to acylations, and the results obtained led to a general synthesis of 8-hydroxy-6-substituted-1,7-naphthyridines that are reported in this communication.

Following the literature procedure, 2-cyano-3-methylpyridine was converted to *tert*-butylamide **1** in 92% yield using *tert*-butyl alcohol and sulfuric acid. The dianion of **1** was readily prepared by adding **1** in THF to freshly prepared LDA (prepared by adding *n*-butyllithium to diisopropylamine in THF at −20 °C) at

Scheme 3



−40 to −50 °C. Treatment of dianion of **1** with different methyl esters followed by work up afforded the desired functionalized ketones **2a-2f** in good yields (Scheme 3). Theoretically, 2 equiv of LDA are needed for the formation of dianion of **1**, however, since the acylated products **2a-2f** are more acidic than **1**, 2.3 equiv of LDA were used in the reaction to avoid quenching of the intermediate dianion of **1**. As can be seen in the Table, under these reaction conditions, the acylated products **2a-2f** were obtained in good yield.

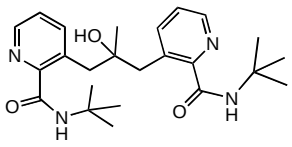
Table

Yields of the Products

Compound No.	R	Yield (%) Product **2**	Product **3**
a	methyl	65	80
b	ethyl	78	86
c	isopropyl	75	85
d	cyclohexyl	78	89
e	phenyl	84	93
f	4-pyridinyl	88	96

It is worth noting that in the case of the condensation of the dianion of **1** with methyl acetate, a byproduct (15% by HPLC) was observed in addition to the desired **2a** (65% isolated yield). Based on LC-MS data this byproduct was assigned the structure shown in the Figure,

Figure

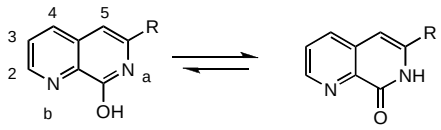


resulting from further condensation of the product with the starting anion of **1**. With other methyl esters the corresponding byproduct was not observed.

The cyclization of **2a-2f** was extensively investigated and several reagents were tried. When **2d** was treated with 85% H_3PO_4 at 100 °C, the desired **3d** was formed in 59% yield along with lactone **4** in 41% yield (Scheme 4). With $POCl_3$ at 105 °C, **5** was the major product (87% yield), and lactone **4** was the minor product. However, with 10 equiv of ammonium acetate in acetic acid at 108 °C for 5 h, **2d** was quantitatively converted to the desired **3d**, and it was isolated by quenching the reaction mixture with water followed by filtration. Compounds **3c**, **3e** and **3f** were also isolated in a similar fashion. In the case of **3a** and **3b** an extractive work up with methylene chloride was found to be necessary. The overall yield of **3** starting from **1** was in the range of 52% to 84%.

For the sake of clarity, the 8-hydroxynaphthyridine structure was proposed for **3a**-**3f**. It is quite possible that they exist in the corresponding lactam form as shown in Scheme 5. For **3c** and **3e** we did study the structure in solution by NMR. However, proton NMR in DMSO did not give any conclusive evidence. By using ^{1}H-^{15}N HMBC, the two forms can be distinguished. For compound **3e** (R = phenyl), the hydroxy proton at 11.8 ppm shows multiple-bond coupling to N-*a* at 156 ppm, which clearly supports the enol form A. Also the H at position 5 shows HMBC correlations to N-*a*. N-*b* was observed at 315 ppm with HMBC correlations from H-3 and H-2. Whereas for compound **3c** (R = isopropyl), ^{1}H-^{15}N HMBC indicated one bond coupling (J = 88 Hz) from N-*a*-H at 11.45 ppm to N-*a* at 160 ppm confirming the lactam form in solution.

Scheme 5



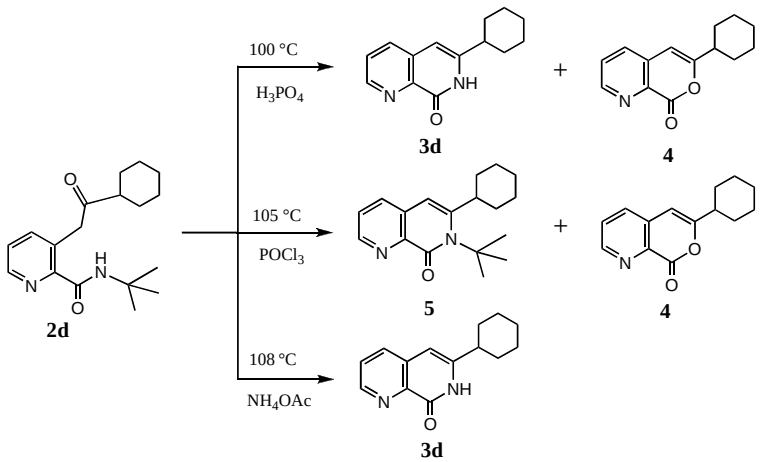
A B

In conclusion, we have developed a simple and practical synthetic route to 8-hydroxy-6-substituted-1,7-naphthyridines starting from inexpensive raw materials.

EXPERIMENTAL

All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 300 ND at 125 and 75 MHz respectively. Proton and carbon chemical shifts are expressed in ppm relative

Scheme 4



to internal tetramethylsilane; coupling constants (*J*) are expressed in Hertz. Melting points were measured on a Büchi 535 melting point apparatus.

Representative Procedure for **2**.

A 100-mL flask was charged with 69 mmol of triethylamine in 48 mL of anhydrous THF. The resulting solution was cooled to –20 to –30 °C, and 34.5 mL of 2 *M n*-BuLi in hexanes was slowly added while maintaining the temperature. Stirring was continued for 30 min followed by cooling to –40 to –55 °C. A solution containing 30 mmol of **1** in 30 mL of anhydrous THF was slowly added while keeping the temperature below –40 °C. After 30 min at this temperature, a solution containing 31.5 mmol of methyl ester substrate in 10 mL of anhydrous THF was added fast. The reaction mixture was stirred for 30 min followed by quenching with 10 mL of saturated ammonium chloride and 30 mL of water. The crude mixture was extracted with 60 mL of ethyl acetate, and the organic layer was dried over $MgSO_4$. The evaporation of organic solvent afforded the desired **2**, which can be further purified by either by recrystallization or column chromatography on silica gel as needed.

N-(1,1-Dimethylethyl)-3-(2-oxopropyl)-2-pyridine-carboxamide (**2a**).

^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9 H), 2.32 (s, 3 H), 4.28 (s, 2 H), 7.32 (m, 1 H), 7.47 (m, 1 H), 8.03 (s, 1 H), 8.42 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.08, 30.58, 48.38, 51.12, 125.77, 131.68, 141.78, 142.88, 146.78, 148.39, 165.30; MP: 78-79 °C; MS ($M+H^+$): *m/z* 235.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.47; H, 7.76; N, 11.76.

N-(1,1-Dimethylethyl)-3-(2-oxobutyl)-2-pyridine-carboxamide (**2b**).

^{1}H NMR ($CDCl_3$): δ 1.09 (t, J = 3.54 Hz, 3 H), 1.44 (s, 9 H), 2.66 (q, J = 7.35 Hz, 2 H), 4.26 (s, 2 H), 7.32 (dd, J = 5.3 Hz, 6.21 Hz, 1 H), 7.48 (dd, J = 6.21 Hz, 1.5 Hz, 1 H), 7.99 (brs, 1 H), 8.24 (dd, J = 5.3 Hz, 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.10, 29.03, 36.36, 47.24, 51.08, 125.7, 131.8, 141.8, 146.6, 149.0, 165.4, 208.4; MP: 62-63 °C; MS ($M+H^+$): *m/z* 249.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.50; H, 8.40; N, 11.03.

N-(1,1-Dimethylethyl)-3-(2-oxo-3-methylbutyl)-2-pyridinecarboxamide (**2c**).

^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 6.96 Hz, 6 H), 1.43 (s, 9 H), 2.90 (p, J = 6.96 Hz, 1 H), 4.36 (s, 2 H), 7.32 (dd, J = 4.7 Hz, 6.2 Hz, 1 H), 7.48 (dd, J = 6.21 Hz, 1.50 Hz, 1 H), 7.93 (s, 1 H), 8.42 (dd, J = 4.7 Hz, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.24, 28.66, 40.86, 45.20, 50.75, 125.2, 131.6, 141.4, 146.1, 148.8, 165.0, 211.5; MP: 90-91 °C; MS ($M+H^+$): *m/z* 263.

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.84; H, 8.31; N, 10.71.

N-(1,1-Dimethylethyl)-3-[2-oxo-2-cyclohexylethyl]-2-pyridine-carboxamide (**2d**).

^{1}H NMR ($CDCl_3$): δ 1.30 (m, 5 H), 1.4 (s, 9 H), 1.68 (m, 1 H), 1.80 (m, 2 H), 1.98 (m, 2 H),2.61 (m, 1 H), 4.36 (s, 2H), 7.31 (m, 1 H), 7.46 (dd, J = 1.5 Hz, 7.3 Hz, 1 H), 7.93 (brs, 1 H), 8.41 (dd, J = 1.7 Hz, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.07, 26.32, 28.82, 29.05, 45.74, 51.00, 51.12, 125.59, 131.97, 141.79, 146.51, 149.30, 165.47, 210.82. MP: 99-100 °C; MS ($M+H^+$): *m/z* 303.

Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.63; H, 8.72; N, 9.36.

N-(1,1-Dimethylethyl)-3-[2-oxo-2-phenylethyl]-2-pyridinecarboxamide (**2e**).

^{1}H NMR ($CDCl_3$): δ 1.410 (s, 9 H), 4.97 (s, 2 H), 7.36 (dd, J = 4.7 Hz, 7.7 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.99 (b, 1 H), 8.05 (m, 2 H), 8.47 (dd, J = 4.6 Hz, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.05, 43.56, 51.17, 125.68. 128.70, 128.93, 131.86, 133.34, 137.58, 141.48, 146.70, 149.47, 165.50, 197.44; MP: 106-107 °C; MS ($M+H^+$): *m/z* 297.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.13; H, 7.09; N, 9.40.

N-(1,1-Dimethylethyl)-3-[2-oxo-(4-pyridinyl)-ethyl]-2-pyridine-carboxamide (**2f**).

^{1}H NMR ($CDCl_3$): δ 1.39 (s, 9 H), 4.86 (s, 2 H),), 7.39 (dd, J = 4.7 Hz, 7.7 Hz, 1 H), 7.58 (dd, J = 1.7 Hz, 7.7 Hz, 1 H), 7.84 (dd, J = 1.5 Hz, 4.4 Hz, 2 H), 8.06 (brs, 1 H), 8.49 (dd, J = 1.7 Hz, 4.7 Hz, 1 H), 8.82 (dd, J = 1.5 Hz, 4.5 Hz, 2 H), 11.97 (brs,1 H); ^{13}C NMR ($CDCl_3$) δ 29.01, 44.21, 51.17, 121.71, 125.87, 130.92, 141.82, 143.86, 147.11, 148.96, 151.19, 165.17, 197.02; mp: 133.5-134.6 °C; MS ($M+ H^+$): *m/z* 298.

Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.64; H, 6.25; N, 14.12.

Representative Procedure for **3**.

A 100-mL flask was charged with 10 mmol of **2**, 7.7 g of ammonium acetate and 10 mL of acetic acid. The resulting suspension was heated to 108 °C and stirred at this temperature for 8 h. The reaction was monitored by HPLC, and after the reaction was completed, 10 mL of water was added, and the pH of the reaction mixture was adjusted to 6-7 by adding 1 *N* NaOH solution. If solids precipitated out, the desired product **3** was collected by filtration, washed and dried in the oven. If the desired product **3** was not precipitated, the reaction mixture was extracted with CH_2Cl_2, followed by drying of the organic phase and evaporation to dryness to afford **3**, which can be further purified by recrystallization.

8-Hydroxy-6-methyl-1,7-naphthyridine (**3a**).

^{1}H NMR ($CDCl_3$): δ 2.240 (s, 3 H), 6.308 (s, 1 H), 7.672 (m, 1 H), 7.979 (m, 1 H), 8.694 (m. 1 H), 11.561 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.8, 103.58, 127.18, 134.33, 135.36, 140.33, 140.48, 149.21, 164.43; MP: 233-234 °C; MS ($M+H^+$): *m/z* 161.

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.21; H, 5.14; N, 17.29.

8-Hydroxy-6-ethyl-1,7-naphthyridine (**3b**).

^{1}H NMR (DMSO): δ 1.21 (t, J = 7.53 Hz, 3 H), 2.52 (q, J = 7.53 Hz, 2 H), 6.33 (s, 1 H), 7.62 (dd, J = 4.32 Hz, 6.42 Hz, 1 H), 8.01 (dd, J = 1.68 Hz, 4.32 Hz, 1 H), 11.52 (brs, 1 H); ^{13}C NMR (DMSO) δ 12.98, 25.79, 100.08, 127.07, 134.52, 134.89, 140.81, 145.51, 148.41, 161.58; MP: 188-189 °C; MS ($M+H^+$): *m/z* 175.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.87; H, 5.72; N, 16.11.

8-Hydroxy-6-isopropyl-1,7-naphthyridine (**3c**).

^{1}H NMR (DMSO): δ 1.24 (d, J = 6.96 Hz, 6 H), 2.81 (p, J = 6.96 Hz, 1 H), 6.36 (s, 1 H), 7.62 (dd, J = 4.32 Hz, 8.10 Hz, 1

H), 8.04 (dd, J = 8.10 Hz, 1.5 Hz, 1 H), 8.69 (dd, J = 4.32 Hz, 1.5 Hz, 1 H), 11.50 (s, 1 H); ^{13}C NMR (DMSO) δ 21.59, 31.37, 98.38, 127.27, 134.74, 134.85, 140.87, 148.49, 149.58, 161.69; MP: 245-246 °C; MS (M+H$^+$): *m/z* 189.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.31; H, 6.53; N, 15.00.

8-Hydroxy-6-cyclohexyl-1,7-naphthyridine (**3d**).

^{1}H NMR (DMSO): δ 1.22 (m, 1 H), 1.38 (m. 5 H), 1.69 (m, 1 H), 1.78 (m, 2 H), 1.99 (m, 2 H), 2.54 (m, 1 H), 6.18 (s, 1 H), 6.44 (dd, J = 4.3 Hz, 8.1 Hz, 1 H), 7.77 (dd, J = 1.5 Hz, 7.2 Hz, 1 H), 8.74 (dd, J = 1.7 Hz, 4.3 Hz, 1 H), 10.156 (brs, 1 H); ^{13}C NMR(DMSO) δ 25.01, 27.66, 31.07, 40.62, 99.10, 125.68, 133.24, 133.83, 139.76, 147.00, 147.49, 162.00; MP: >250 °C; MS (M+ H$^+$): *m/z* 229.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.49; H, 7.29; N, 12.17.

8-Hydroxy-6-phenyl-1,7-naphthyridine **3e**.

^{1}H NMR (DMSO): δ 6.64 (s, 1 H), 7.46 (m, 4 H), 7.65 (m, 2H), 7.88 (dd, J = 1.5 Hz, 8.2 Hz, 1 H), 8.78 (dd, J = 1.5 Hz, 5.4 Hz, 1 H), 1.15 (brs, 1 H); ^{13}C NMR (DMSO) δ 101.50, 125.09, 126.02, 128.45, 129.06, 132.60, 133.49, 133.78, 139.72, 140.17, 148.44, 161.44; MP: 238-240 °C; MS (M+ H$^+$): *m/z* 223.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.52; H, 4.51; N, 12.57.

8-Hydroxy-6-(4-pyridinyl)-1,7-naphthyridine **3f**.

^{1}H NMR (DMSO): δ 7.16 (s, 1 H), 7.75 (dd, J = 4.3 Hz, 7.9 Hz, 1 H), 7.84 (d, J = 5.8 Hz, 2 H), 8.20 (d, J = 8.1Hz, 1 H), 8.72 (d, J = 5.8 Hz, 2 H), 8.83 (d, J = 3.0 Hz, 1 H), 11.96 (brs, 1 H); ^{13}C NMR (DMSO) δ 103.93, 121.21, 127.54, 134.07, 135.81, 138.47, 140.69, 141.96, 150.01, 150.54, 161.60; MP: >250 °C; MS (M+H$^+$): *m/z* 224.

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.78; H, 4.09; N, 18.93.

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