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SYNTHESIS OF 3-HYDROXY-1,3-DIHYDRO-2*H*-PYRROLO[2,3-*b*]-, -[2,3-*c*]-, OR -[3,2-*c*]PYRIDIN-2-ONES FROM THE RESPECTIVE *N*-PYRIDINYLPIVALAMIDES AND α-KETO ESTERS

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Abstract – A convenient synthesis of the title compounds utilizing the reaction of the dilithium compounds, generated *in situ* by the reaction between *N*-(pyridin-2-, -3-, or -4-yl)pivalamides and two equivalents of butyllithium in THF, with α-keto esters is described. Thus, *N*-(3-lithiopyridin-2-yl)pivalamide reacts smoothly leading to the formation of the corresponding α-hydroxy esters. These undergo deprotective cyclization in refluxing hydrochloric acid to afford 3-substituted 3-hydroxy-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones. Similarly, starting from *N*-(pyridin-3- or -4-yl)pivalamides, the corresponding 3-dihydro-2*H*-pyrrolo[2,3-*c*]- or -[3,2-*c*]pyridin-2-one derivatives, respectively, can be prepared.

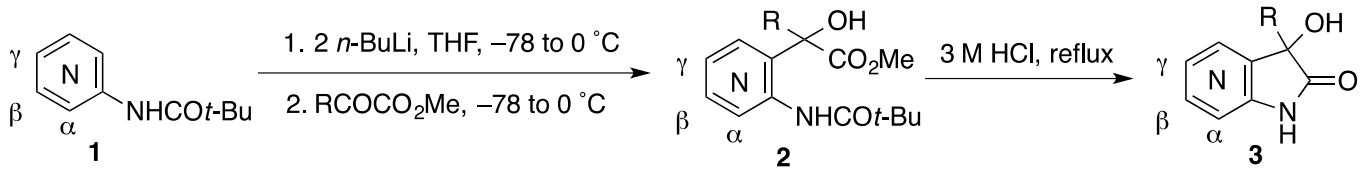
INTRODUCTION

Literature survey has revealed that some compounds having the 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (7-azaoxyindole) skeleton exhibit a variety of biological activities,[1] and that a few efficient method for the general preparation of this class of heterocycles are recorded.[2] In this paper, we wish to report the first method for the general synthesis of 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one derivatives carrying a hydroxyl group at the 3-position. As part of our study[3] aimed at developing the methods for the synthesis of pyridine-fused heterocycles utilizing the dilithium compounds, generated *in situ* from *N*-(pyridinyl)pivalamides and two equivalents of butyllithium,[4] we anticipated that the reaction of *N*-(3-lithiopyridin-2-yl)pivalamide with α-keto esters would afford the corresponding α-hydroxy esters, of which acidic hydrolysis could lead to the formation of 3-hydroxy-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one derivatives. Such 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one derivatives would also be

of biological interest. To date, only a few syntheses of this class of derivatives have been recorded.[5] For example, 3-hydroxy-1-methyl-3-phenyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one has been prepared by reductive cyclization of *N*-(3-bromopyridin-2-yl)-*N*-methyl-2-oxo-2-phenylacetamide.[5c] However, these methods suffer from the lack of generality. A similar synthesis of 3-dihydro-2*H*-pyrrolo[2,3-*c*]-[6] or -[3,2-*c*]pyridin-2-one derivatives starting from *N*-(pyridin-3- or -4-yl)pivalamides, respectively, is also reported.

RESULTS AND DISCUSSION

Our synthesis of these 3-hydroxy-1,3-dihydro-2*H*-pyrrolopyridin-2-one derivatives (**3**) from the respective *N*-(pyridinyl)pivalamides (**1**) was conducted as shown in Scheme 1. These amides are readily prepared by the pivaloylation of the respective pyridinamines according to the published procedures.[7] Treatment of **1** with two equivalents of butyllithium in THF at –78 to 0 ˚C[4] followed by addition of α-keto esters to the solutions of the resulting dilithium intermediates provided, after aqueous workup, the corresponding α-hydroxy esters derivatives (**2**) in generally fair yields as listed in Table 1. Entry 6 shows that the reaction of the dilithium compound, derived from *N*-(pyridin-3-yl)pivalamide (**1b**), with methyl benzoylformate gave the corresponding product in a rather lower yield compared to those using the other two dilithium compounds. However, no products resulting from lithiation at 2-positon were obtained. The lithiation at 4-position is highly selective as described before.[4] The yields of the products with methyl pyruvate were somewhat lower (Entries 1 and 7) than those with methyl aroylformates. We reasoned that it might be arisen from the abstraction of one of the acetyl protons by the dilithium compounds.



Scheme 1

We were able to obtain the desired products (**3**) by simply heating **2** in 3 M hydrochloric acid at reflux temperature. We found that deprotective cyclization proceeded cleanly in general to give **3**. The yields are also compiled in Table 1 and are generally fair-to-good. Somewhat poor yields were obtained with 2-hydroxy-2-(4-methoxyphenyl)-2-pyridinylacetates (**2e**) and (**2j**) (Entries 5 and 10). Somewhat complicated mixtures of products were produced. This might be ascribed to demethylation of the methoxy substituent upon prolonged heating. The reactions with 2-hydroxy-2-pyridinylpropanoates (**2a**) and (**2g**) proceeded very cleanly as judged by TLC analyses of the reaction mixture. However, the isolated yields of the corresponding products (**3a**) and (**3g**) were only moderate (Entries 1 and 7), because

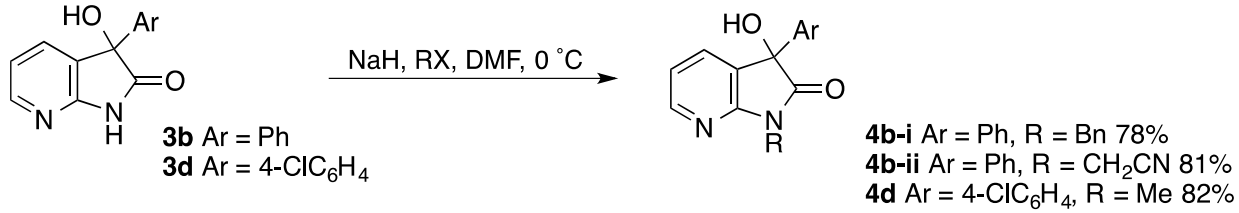
these were considerably hard to extract with usual organic solvents probably due to their high solubility in water.

Table 1. Preparation of 3-hydroxy-1,3-dihydro-2*H*-pyrrolopyridin-2-ones (**3**)

Entry	**1**	R	**2**	Yield/%[a]	**3**	Yield/%[a]
1	**1a** (N at α position)	Me	**2a**	50	**3a**	47
2	**1a**	Ph	**2b**	68	**3b**	68
3	**1a**	4-MeC_6H_4	**2c**	70	**3c**	76
4	**1a**	4-ClC_6H_4	**2d**	61	**3d**	80
5	**1a**	4-$MeOC_6H_4$	**2e**	66	**3e**	52
6	**1b** (N at β position)	Ph	**2f**	41	**3f**	55
7	**1c** (N at γ position)	Me	**2g**	49	**3g**	54
8	**1c**	Ph	**2h**	66	**3h**	80
9	**1c**	4-MeC_6H_4	**2i**	69	**3i**	80
10	**1c**	4-$MeOC_6H_4$	**2j**	69	**3j**	50

[a] Yields of isolated products.

We next became interested in investigating behaviors of compounds (**3**) in *N*- or *O*-alkylation. Sequential treatment of **3b** and **3d** with an equimolar amount of sodium hydride and haloalkanes in DMF at 0 ˚C resulted in highly selective formation of the corresponding 1-alkylated products (**4**) in good yields, as illustrated in Scheme 2.

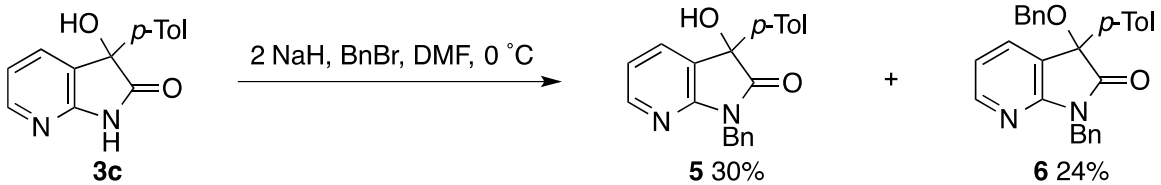


3b Ar = Ph
3d Ar = 4-ClC_6H_4

4b-i Ar = Ph, R = Bn 78%
4b-ii Ar = Ph, R = CH_2CN 81%
4d Ar = 4-ClC_6H_4, R = Me 82%

Scheme 2

However, when an equimolar amount of benzyl bromide was added to the reaction mixture after treatment of compound **3c** with two molar amounts of sodium hydride in DMF at 0 ˚C, *N*-benzylated product (**5**) (30%) and *N,O*-dibenzylated product (**6**) (24%) were obtained, as shown in Scheme 3. In this case, a respectable amount of the starting material was recovered (33%), but no *O*-benzylated product could be isolated.



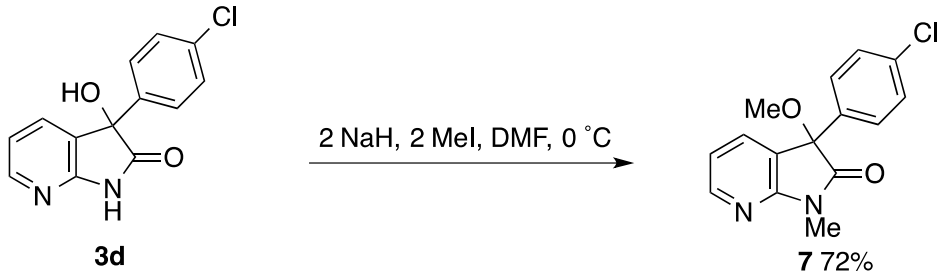
3c

5 30%

6 24%

Scheme 3

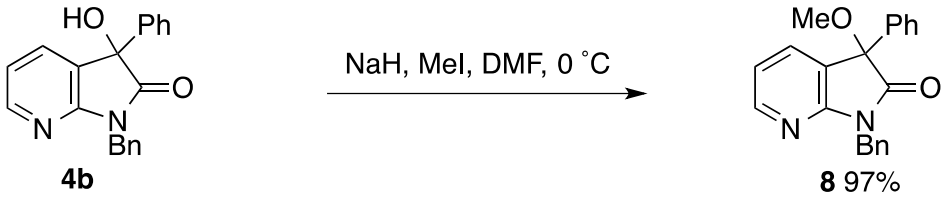
N,O-Dimethylation of **3d** was achieved on treatment with two equivalents each of sodium hydride and iodomethane in DMF at 0 ˚C to afford **7** in relatively good yield, as shown in Scheme 4.



3d **7** 72%

Scheme 4

Treatment of **4b** with an equimolar amount of sodium hydride and subsequent methylation of the resulting sodium alkoxide with iodomethane was done uneventfully to give 1-benzyl-3-methoxy-3-phenyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**8**) in excellent yield, as depicted in Scheme 5. Thus, different alkyl groups could be introduced at *N*- and *O*-atoms of compound **3b**.



4b **8** 97%

Scheme 5

In conclusion, we have developed for the first time a method for the general preparation of three types of 3-hydroxy-1,3-dihydro-2*H*-pyrrolopyridin-2-one derivatives from the respective *N*-(pyridinyl)pivalamides. As the present method starts with readily available materials and involves very simple manipulations, it is efficient and may be of value in organic synthesis.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI, positive) or a JEOL JMS-T100GCV (EI, TOF; 70eV) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and

distilled prior to use.

Starting Materials. 2,2-Dimethyl-*N*-(pyridinyl)propanamides (**1**),[7] methyl 2-(4-chlorophenyl)-2-oxoacetate,[8] 2-(4-methoxyphenyl)-2-oxoacetate,[9] and 2-(4-methylphenyl)-2-oxoacetate[10] were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Hydroxy Esters (2). Methyl 2-{2-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxypropanoate (2a). To a stirred solution of **1a** (0.36 g, 2.0 mmol) in THF (5 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 4.0 mmol) dropwise. After 15 min, temperature was raised to 0 ˚C and stirring was continued for 2.5 h. Then, the mixture was cooled to –78 ˚C and $MeCOCO_2Me$ (0.20 g, 2.0 mmol) was added dropwise. The resulting mixture was gradually warmed to 0 ˚C, treated with saturated aqueous NH_4Cl (20 mL), and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:3) to afford **2a** (0.28 g, 50%); a white solid; mp 126–127 ˚C (hexane/CH_2Cl_2); IR (KBr) 3320, 1746, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.85 (s, 3H), 3.71 (s, 3H), 3.95 (s, 1H), 7.12 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.52 (dd, *J* = 5.2, 1.7 Hz, 1H), 8.95 (br s, 1H). HR-MS (EI). Calcd for $C_{14}H_{20}N_2O_4$ (M): 280.1423. Found: *m/z* 280.1416.

Methyl 2-{2-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-phenylacetate (2b): a colorless amorphous powder; R_f 0.37 (AcOEt/hexane 1:3); IR (KBr) 3348, 1744, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 3.84 (s, 3H), 4.57 (s, 1H), 7.02 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.39–7.43 (m, 5H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.81 (br s, 1H). HR-MS (EI). Calcd for $C_{19}H_{22}N_2O_4$ (M): 342.1580. Found: *m/z* 342.1591.

Methyl 2-{2-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-(4-methylphenyl)acetate (2c): a colorless amorphous powder; R_f 0.20 (AcOEt/hexane 1:10); IR (KBr) 3335, 1743, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 9H), 2.37 (s, 3H), 3.83 (s, 3H), 4.48 (s, 1H), 7.01 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.20–7.23 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 2H), 8.52 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.83 (br s, 1H). HR-MS (ESI). Calcd for $C_{20}H_{25}N_2O_4$ (M+H): 357.1814. Found: *m/z* 357.1800.

Methyl 2-(4-Chlorophenyl)-2-{2-[(2,2-dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxyacetate (2d): a colorless amorphous powder; R_f 0.29 (AcOEt/hexane 1:2); IR (KBr) 3347, 1744, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 9H), 3.84 (s, 3H), 4.77 (s, 1H), 7.05 (dd, *J* = 7.4, 4.6 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 8.54 (dd, *J* = 4.6, 1.1 Hz, 1H), 8.68 (br s, 1H). HR-MS (ESI). Calcd for $C_{19}H_{22}ClN_2O_4$ (M+H): 377.1268. Found: *m/z* 377.1254.

Methyl 2-{2-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-(4-methoxyphenyl)-acetate (2e): a colorless amorphous powder; R_f 0.37 (AcOEt/hexane 1:5); IR (KBr) 3348, 1743, 1696

cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 3.82 (s, 6H), 4.62 (br, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.01 (dd, *J* = 7.4, 4.6 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 8.51 (d, *J* = 4.6 Hz, 1H), 8.87 (br s, 1H). HR-MS (ESI). Calcd for $C_{20}H_{25}N_2O_5$ (M+H): 373.1763. Found: *m/z* 373.1748.

Methyl 2-{3-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-4-yl}-2-hydroxy-2-phenylacetate (2f): a white solid; mp 183–185 ˚C (hexane/THF); IR (KBr) 3312, 1748, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.03 (s, 9H), 3.73 (s, 3H), 6.81 (d, *J* = 5.2 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.38–7.43 (m, 3H), 7.98 (br, 1H), 8.25 (d, *J* = 5.2 Hz, 1H), 9.15 (s, 1H), 9.26 (s, 1H). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.43; H, 6.37; N, 8.17.

Methyl 2-{4-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxypropanoate (2g): a white solid; mp 146–148 ˚C (hexane/CH_2Cl_2); IR (KBr) 3291, 1736, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.92 (s, 3H), 3.74 (s, 3H), 4.45 (br, 1H), 8.33 (d, *J* = 5.7 Hz, 1H), 8.456 (d, *J* = 5.7 Hz, 1H), 8.463 (s, 1H), 9.62 (br s, 1H). HR-MS (ESI). Calcd for $C_{14}H_{21}N_2O_4$ (M+H): 281.1501. Found: *m/z* 281.1488.

Methyl 2-{4-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-phenylacetate (2h): a white solid; mp 186–188 ˚C (hexane/CH_2Cl_2); IR (KBr) 3340, 1740, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H), 3.86 (s, 3H), 4.91 (br s, 1H), 7.37 (s, 5H), 8.12 (s, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 9.03 (br s, 1H). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.49; H, 6.28; N, 8.12.

Methyl 2-{4-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-(4-methylphenyl)acetate (2i): a white solid; mp 202–204 ˚C (decomp) (hexane/CH_2Cl_2); IR (KBr) 3258, 1747, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 2.35 (s, 3H), 3.87 (s, 3H), 4.49 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 8.12 (s, 1H), 8.32 (d, *J* = 5.7 Hz, 1H), 8.51 (d, *J* = 5.7 Hz, 1H), 9.01 (br s, 1H). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.53; H, 6.69; N, 8.02.

Methyl 2-{4-[(2,2-Dimethyl-1-oxopropyl)amino]pyridin-3-yl}-2-hydroxy-2-(4-methoxyphenyl)-acetate (2j): a white solid; mp 203–205 ˚C (hexane/CH_2Cl_2); IR (KBr) 3311, 1741, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 3.80 (s, 3H), 3.86 (s, 3H), 4.71 (br s, 1H), 6.88 (d, *J* = 9.2 Hz, 2H), 7.28 (d, *J* = 9.2 Hz, 2H), 8.11 (s, 1H), 8.33 (d, *J* = 5.7 Hz, 1H), 8.49 (d, *J* = 5.7 Hz, 1H), 9.08 (br s, 1H). HR-MS (ESI). Calcd for $C_{20}H_{25}N_2O_5$ (M+H): 373.1763. Found: *m/z* 373.1747.

Typical Procedure for the Preparation of Hydroxypyrrolopyridinones (3). 3-Hydroxy-3-methyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3a). A mixture of **2a** (0.28 g, 1.0 mmol) and 3 M HCl (6 mL) was heated at reflux temperature for 11 h. After cooling to 0 ˚C, pH of the solution was adjust to 8, and the mixture was saturated with NaCl and extracted with AcOEt (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated by evaporation. The residual solid was recrystallized from hexane/THF to afford **3a** (77 mg, 47%); a white solid; mp 187–189 ˚C; IR (KBr) 3325, 3168, 1725, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 3H), 6.03 (s, 1H), 6.94 (dd, *J* = 6.9, 5.2 Hz, 1H), 7.60 (dd, *J* = 6.9, 1.1 Hz,

1H), 8.04 (dd, *J* = 5.2, 1.1 Hz, 1H), 10.83 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.79, 72.55, 117.84, 127.58, 131.00, 147.35, 156.08, 179.33. HR-MS (ESI). Calcd for $C_8H_9N_2O_2$ (M+H): 165.0664. Found: *m/z* 165.0659. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.42; H, 5.06; N, 16.77.

3-Hydroxy-3-phenyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3b): a pale-yellow solid; mp 235–237 ˚C (hexane/THF); IR (KBr) 3206, 3163, 1748, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.82 (s, 1H), 6.97 (dd, *J* = 6.9, 5.2 Hz, 1H), 7.26–7.34 (m, 5H), 7.46 (dd, *J* = 6.9, 1.7 Hz, 1H), 8.13 (dd, *J* = 5.2, 1.7 Hz, 1H), 11.06 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 77.16, 118.30, 125.39, 127.76, 127.78, 128.26, 132.48, 140.44, 147.96, 156.92, 178.10. HR-MS (EI). Calcd for $C_{13}H_{10}N_2O_2$ (M): 226.0742. Found: *m/z* 226.0745. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.96; H, 4.56; N, 12.40.

3-Hydroxy-3-(4-methylphenyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3c): a pale-yellow solid; mp 229–231 ˚C (hexane/THF); IR (KBr) 3242, 1747, 1608 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 6.75 (s, 1H), 6.97 (dd, *J* = 5.7, 5.2 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 5.2, 1.1 Hz, 1H), 11.03 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.65, 77.03, 118.29, 125.35, 127.88, 128.81, 132.44, 137.02, 137.50, 147.50, 156.88, 178.21. HR-MS (EI). Calcd for $C_{14}H_{12}N_2O_2$ (M): 240.0899. Found: *m/z* 240.0903. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.74; H, 5.05; N, 11.40.

3-(4-Chlorophenyl)-3-hydroxy-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3d): a white solid; mp 227–229 ˚C (hexane/THF); IR (KBr) 3323, 3169, 1729, 1611 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.94 (s, 1H), 7.00 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.48 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.15 (dd, *J* = 5.2, 1.7 Hz, 1H), 11.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 76.79, 118.47, 127.27, 127.43, 128.34, 132.55, 132.61, 139.38, 148.24, 156.91, 177.72. HR-MS (EI). Calcd for $C_{13}H_9ClN_2O_2$ (M): 260.0353. Found: *m/z* 260.0348. Anal. Calcd for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.63; H, 3.45; N, 10.62.

3-Hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3e): a white solid; mp 199–201 ˚C (hexane/THF); IR (KBr) 3392, 3342, 1762, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H), 6.70 (s, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.98 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 5.2 Hz, 1H), 10.98 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.13, 76.79, 113.67, 118.29, 126.84, 127.80, 132.34, 132.50, 147.90, 156.84, 158.92, 178.31. HR-MS (EI). Calcd for $C_{14}H_{12}N_2O_3$ (M): 256.0848. Found: *m/z* 256.0839. Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.41; H, 4.72; N, 10.79.

3-Hydroxy-3-phenyl-1,3-dihydro-2*H*-pyrrolo[2,3-*c*]pyridin-2-one (3f): a white solid; mp 232–234 ˚C (hexane/THF); IR (KBr) 3327, 1731, 1614 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H), 7.16 (d, *J* = 4.0 Hz, 1H), 7.27–7.38 (m, 5H), 8.22 (s, 1H), 8.26 (d, *J* = 4.0 Hz, 1H), 10.65 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ

76.98, 119.48, 125.28, 127.92, 128.35, 131.17, 138.85, 139.97, 141.73, 144.36, 177.83. HR-MS (EI). Calcd for $C_{13}H_{10}N_2O_2$ (M): 226.0742. Found: *m/z* 226.0743. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.98; H, 4.70; N, 12.10.

3-Hydroxy-3-methyl-1,3-dihydro-2*H*-pyrrolo[3,2-*c*]pyridin-2-one (3g): a white solid; mp 257–259 ˚C (decomp) (hexane/THF); IR (KBr) 3312, 1721, 1619 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 3H), 6.08 (s, 1H), 6.84 (d, *J* = 5.2 Hz, 1H), 8.30 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 10.64 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.99, 71.61, 105.62, 129.21, 143.66, 148.46, 150.22, 179.37. HR-MS (EI). Calcd for $C_8H_8N_2O_2$ (M): 164.0586. Found: *m/z* 164.0591. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.45; H, 4.91; N, 16.79.

3-Hydroxy-3-phenyl-1,3-dihydro-2*H*-pyrrolo[3,2-*c*]pyridin-2-one (3h): a white solid; mp 200–202 ˚C (hexane/THF); IR (KBr) 3234, 1737, 1617 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.87 (s, 1H), 6.95 (d, *J* = 5.2 Hz, 1H), 7.27–7.35 (m, 5H), 8.16 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 10.85 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 76.14, 105.88, 125.35, 127.82, 128.31, 129.49, 140.43, 144.83, 149.35, 150.61, 178.13. HR-MS (EI). Calcd for $C_{13}H_{10}N_2O_2$ (M): 226.0742. Found: *m/z* 226.0747. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.01; H, 4.60; N, 12.37.

3-Hydroxy-3-(4-methylphenyl)-1,3-dihydro-2*H*-pyrrolo[3,2-*c*]pyridin-2-one (3i): a white solid; mp 265–267 ˚C (decomp) (hexane/THF); IR (KBr) 3202, 1752, 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 6.79 (s, 1H), 6.93 (d, *J* = 4.6 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 7.16 (d, *J* = 7.4 Hz, 2H), 8.14 (s, 1H), 8.36 (d, *J* = 4.6 Hz, 1H), 10.81 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.67, 75.99, 105.84, 125.32, 128.85, 129.57, 137.08, 137.50, 144.80, 149.32, 150.55, 178.24. HR-MS (ESI). Calcd for $C_{14}H_{13}N_2O_2$ (M+H): 241.0977. Found: *m/z* 241.0970. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.71; H, 5.17; N, 11.39.

3-Hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-pyrrolo[3,2-*c*]pyridin-2-one (3j): a white solid; mp 109–111 ˚C (hexane/THF); IR (KBr) 3264, 1737, 1618 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.71 (s, 3H), 6.74 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 5.2 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 8.16 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 10.76 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.07, 75.70, 105.74, 113.60, 126.75, 129.46, 132.28, 144.81, 149.24, 150.46, 158.90, 178.26. HR-MS (EI). Calcd for $C_{14}H_{12}N_2O_3$ (M): 256.0848. Found: *m/z* 256.0836. Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.62; H, 4.72; N, 10.72.

Typical Procedure for the 1-Alkylation of 3-Hydroxy-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one Derivatives (3). 3-Hydroxy-3-phenyl-1-(phenylmethyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (4b-i). To a stirred suspension of NaH (60% in mineral oil; 19 mg, 0.47 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **3b** (0.11 g, 0.47 mmol) in DMF (1 mL) dropwise. After evolution of H_2 gas had ceased, BnBr (80 mg, 0.47 mmol) was added. After 10 min, the mixture was worked up as described for

the preparation of **2a**. The crude solid product was purified by recrystallization from hexane/THF to afford **4b-i** (97 mg, 65%); a white solid; mp 149–151 ˚C (hexane/CH_2Cl_2); IR (KBr) 3353, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 1H), 5.01 (d, *J* = 14.9 Hz, 1H), 5.03 (d, *J* = 14.9 Hz, 1H), 7.03 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.27–7.33 (m, 8H), 7.45 (d, *J* = 6.9 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 8.21 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 42.83, 77.55, 119.08, 125.09, 126.09, 127.67, 128.28, 128.58 (2 overlapped Cs), 128.76, 132.47, 136.13, 139.29, 148.57, 156.32, 177.21. HR-MS (EI). Calcd for $C_{20}H_{16}N_2O_2$ (M): 316.1212. Found: *m/z* 316.1206. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.64; H, 5.20; N, 8.77.

2-(3-Hydroxy-2-oxo-3-phenyl-1,3-dihydropyrrolo[2,3-*b*]pyridin-1-yl)acetonitrile (4b-ii): a beige solid; mp 185–187 ˚C (hexane/CH_2Cl_2); IR (KBr) 3338, 2223, 1722, 1607 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.89 (d, *J* = 13.7 Hz, 1H), 4.91 (d, *J* = 13.7 Hz, 1H), 7.13 (s, 1H), 7.17 (dd, *J* = 7.4, 5.7 Hz, 1H), 7.29–7.37 (m, 5H), 7.64 (dd, *J* = 5.7, 1.7 Hz, 1H), 8.32 (dd, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 26.71, 76.89, 115.57, 120.09, 125.48, 127.20, 128.25, 128.49, 133.11, 139.45, 148.16, 154.11, 175.75. HR-MS (EI). Calcd for $C_{15}H_{11}N_3O_2$ (M): 265.0851. Found: *m/z* 265.0849. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.91; H, 4.18; N, 15.69.

3-(4-Chlorophenyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (4d): a yellow solid; mp 178–180 ˚C (hexane/CH_2Cl_2); IR (KBr) 3282, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (s, 3H), 6.99 (s, 1H), 7.07 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 1H), 8.25 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.19, 76.32, 119.01, 127.00, 127.55, 128.35, 132.33, 132.69, 139.05, 148.17, 156.62, 176.23. HR-MS (EI). Calcd for $C_{14}H_{11}ClN_2O_2$ (M): 274.0509. Found: *m/z* 274.0518. Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20. Found: C, 60.83; H, 4.08; N, 10.11.

Treatment of 3b with Two Equivalents of NaH and then an Equivalent of Benzyl Bromide. To a stirred suspension of NaH (60% in mineral oil; 39 mg, 0.98 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **3b** (0.12 g, 0.49 mmol) in DMF (1 mL) dropwise. After evolution of H_2 gas had ceased, BnBr (84 mg, 0.49 mmol) was added. After 10 min, the mixture was worked up as described for the preparation of **2a**. The crude product was purified by column chromatography on SiO_2 to afford **5** (49 mg, 30%) and **6** (50 mg, 24%).

3-Hydroxy-3-(4-methylphenyl)-1-(phenylmethyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (5): a pale-yellow oil; R_f 0.37 (AcOEt/hexane 1:2); IR (neat) 3393, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.69 (s, 1H), 5.00 (d, *J* = 14.9 Hz, 1H), 5.02 (d, *J* = 14.9 Hz, 1H), 6.94 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.26–7.31 (m, 3H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 8.20 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.09, 42.81, 77.44, 119.04, 125.04, 126.14, 127.63, 128.26, 128.56, 129.45, 132.39, 136.21, 136.34, 138.50, 148.50, 156.36, 177.28. HR-MS (ESI). Calcd for

$C_{21}H_{19}N_2O_2$ (M+H): 331.1446. Found: *m/z* 331.1439. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.20; H, 5.59; N, 8.31.

3-(4-Methylphenyl)-3-(phenylmethoxy)-1-(phenylmethyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (6): a pale-yellow oil; R_f 0.60 (AcOEt/hexane 1:2); IR (neat) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H). 4.29 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 5.03 (d, *J* = 14.3 Hz, 1H), 5.04 (d, *J* =14.3 Hz, 1H), 7.00 (dd, *J* = 7.4, 5.2 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.23–7.31 (m, 10 H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 1H), 8.27 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.12, 42.78, 67.64, 82.88, 118.88, 123.37, 126.19, 127.62, 127.74, 127.79, 128.27, 128.29, 128.55, 129.31, 133.21, 134.70, 136.45, 137.42, 138.59, 148.92, 157.05, 174.85. HR-MS (ESI). Calcd for $C_{28}H_{25}N_2O_2$ (M+H): 421.1916. Found: *m/z* 421.1912. Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.94; H, 5.84; N, 6.59.

3-(4-Chlorophenyl)-3-methoxy-1-methyl-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (7). Compound **3d** (0.12 g, 0.46 mmol) was treated successively with NaH (60% in mineral oil, 37 mg, 0.92 mmol) and MeI (0.13 g, 0.92 mmol) as described for the preparation of **4**. The same workup, followed by purification of the crude product by recrystallization, gave **7** (95 mg, 72%); a white solid; mp 95–97 ˚C (hexane/CH_2Cl_2); IR (KBr) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (s, 3H), 3.32 (s, 3H), 7.07 (dd, *J* = 7.4, 5.7 Hz, 1H), 7.31 (s, 4H), 7.52 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.32 (d, *J* = 5.7, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.46, 53.29, 83.00, 118.89, 122.21, 127.42, 127.72, 128.75, 133.21, 134.79, 136.04, 149.25, 174.48. HR-MS (EI). Calcd for $C_{15}H_{13}ClN_2O_2$ (M): 288.0666. Found: *m/z* 288.0675. Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.37; H, 4.54; N, 9.65.

3-Methoxy-3-phenyl-1-(phenylmethyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (8). Compound **4b** (0.19 g, 0.60 mmol) was treated successively with NaH (60% in mineral oil, 24 mg, 0.60 mmol) and MeI (85 mg, 0.60 mmol) as described for the preparation of **4b**. The same workup, followed by purification of the crude product by column chromatography on SiO_2, gave **8** (0.19 g, 97%); a pale-yellow oil; R_f 0.38 (AcOEt/hexane 1:4); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (s, 3H), 5.02 (d, *J* = 14.3 Hz, 1H), 5.03 (d, *J* = 14.3 Hz, 1H), 7.03 (dd, *J* = 6.9, 5.2 Hz, 1H), 7.23–7.36 (m, 8H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.52 (dd, *J* = 6.9, 1.7 Hz, 1H), 8.29 (dd, *J* = 5.2, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 42.75, 53.23, 83.32, 118.87, 122.72, 126.10, 127.61, 128.26, 128.52, 128.58, 128.67, 133.27, 136.38, 137.55, 149.03, 157.26, 174.76. HR-MS (EI). Calcd for $C_{21}H_{18}N_2O_2$ (M): 330.1368. Found: *m/z* 330.1377. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.20; H, 5.68; N, 8.39.

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