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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.

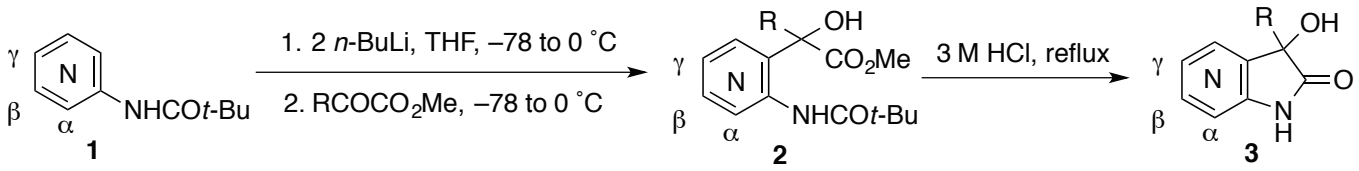
## INTRODUCTION

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

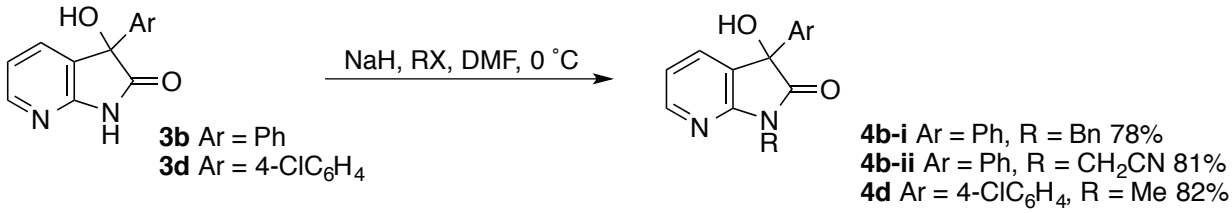
these were considerably hard to extract with usual organic solvents probably due to their high solubility in water.

**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.

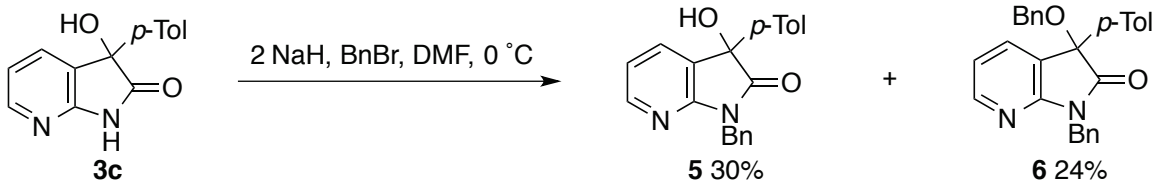



**3b** Ar = Ph
**3d** Ar = 4-$ClC_6H_4$

**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.



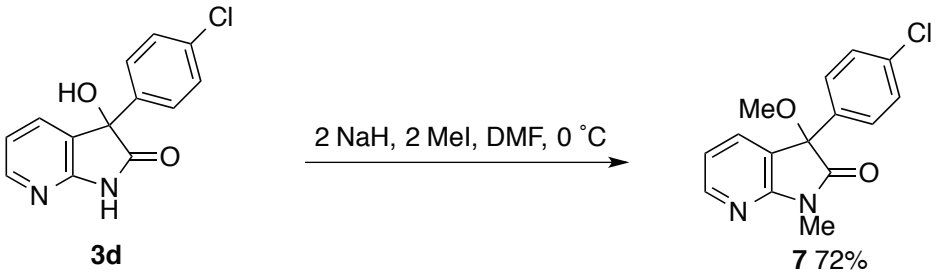

**3c**

**5** 30%

**6** 24%

**Scheme 3**

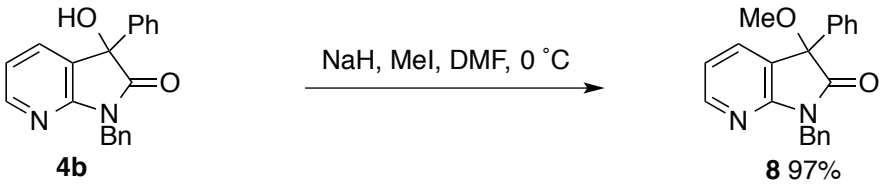
*N,O*-Dimethylation of **3d** was achieved on treatment with two equivalents each of sodium hydride and iodomethane in DMF at 0 ˚C to afford **7** in relatively good yield, as shown in Scheme 4.




**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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