A General Strategy for the Synthesis of Amino-Substituted 2-Pyridones Using a Palladium-Catalyzed Amination Reaction

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Received February 5, 2007

A novel library of amino-substituted 2-pyridones has been constructed through a two-step sequence of microwave-promoted Buchwald-Hartwig amination of 2-benzyloxy halopyridines followed by debenzylation. Microwave-promoted amination of 3- or 4-halopyridine in the presence of a suitable palladium catalyst and ligand system provided amino-substituted 2-benzyloxypyridines in excellent yields. Then, debenzylation of 2-benzyloxypyridines afforded the corresponding 2-pyridones with high efficiency.

Key Words : 2-Pyridone, Aminopyridine, Palladium-catalyzed amination, Microwave, Buchwald-Hartwig amination

Introduction

The 2-pyridone moiety frequently found in a variety of interesting compounds has received remarkable attention due to its promising features as a key scaffold and in privileged building blocks.[1] A wide range of biological activities has been observed in compounds possessing a 2-pyridone motif which includes antitumor,[2] antifungal,[3] antibacterial,[4] anti-inflammatory,[5] antiviral (*e.g.*, **1** and **2**),[6] and antithrombotic (*e.g.*, **3**)[7] properties. In particular, the 3-amino-2-pyridone template has been considered as a peptidomimetic system which mimics the hydrogen-bonding interactions compared with the backbone of peptide inhibitors (Figure 1).[8]

Although many synthetic methods for the preparation of aminopyridine derivatives have been reported, there are few simple methods for the preparation of amino-substituted 2-pyridones from available halopyridines.[5,9,10] In recent studies, we have demonstrated that palladium-catalyzed amination of 5- or 6-bromo-2-benzyloxypyridines under microwave irradiation readily provides the corresponding 5- or 6-amino-substituted 2-benzyloxypyridines, which can be transformed to amino-substituted 2-pyridones *via* hydrogenolysis of the benzyl ether group.[11] This microwave-promoted amination reaction allowed for a rapid and efficient preparation of amino-substituted 2-pyridones in excellent yields.[12,13] In this paper, we wish to expand the scope of our method for the synthesis of a series of 3- or 4-amino-substituted 2-pyridones.

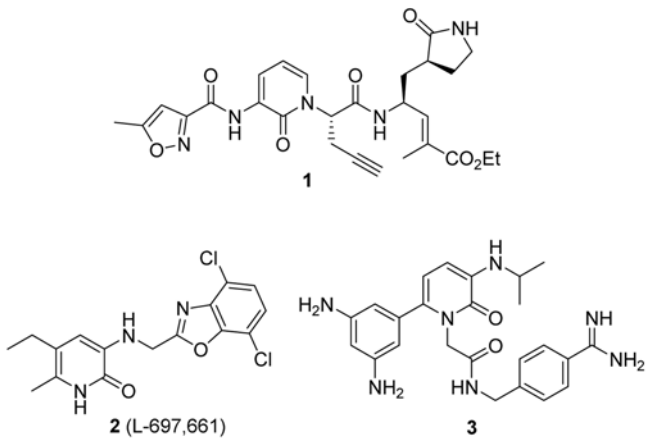
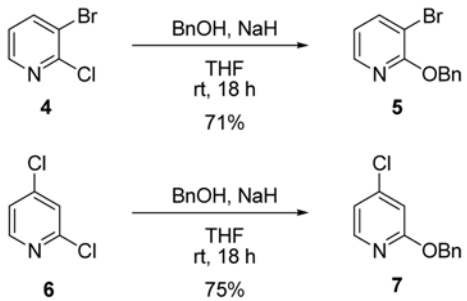


Figure 1. Examples of 2-pyridones with biological activities.

Results and Discussion

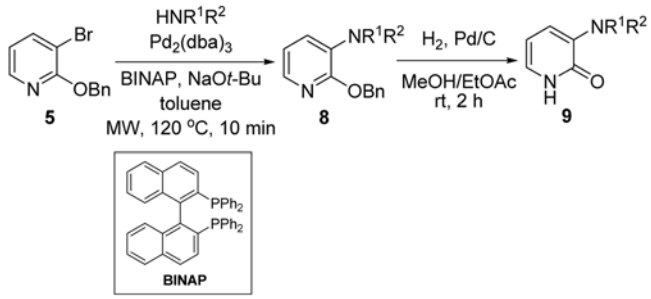
The 2-benzyloxypyridines (**5** and **7**) were easily prepared by nucleophilic aromatic substitution reaction of the corresponding 2-chloropyridines.[14] Thus, treatment of commercially available 3-bromo-2-chloropyridine (**4**) or 2,4-dichloropyridine (**6**) with benzyl alcohol in the presence of sodium hydride provided 2-benzyloxy-3-bromopyridine (**5**) or 2-benzyloxy-4-chloropyridine (**7**), respectively, in high yield (Scheme 1).

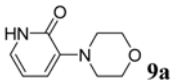
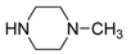
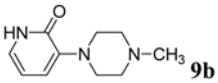
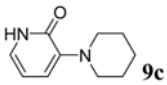
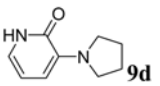
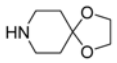
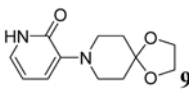
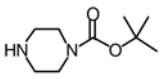
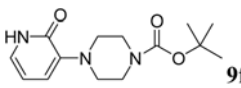
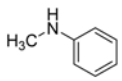
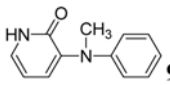
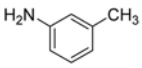
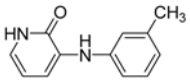
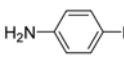
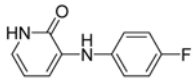
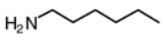
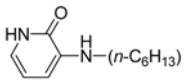
With 2-benzyloxy-3-bromopyridine (**5**) in hand, we first attempted microwave-promoted palladium-catalyzed amination with morpholine employing conditions previously developed in our laboratory ($Pd_2(dba)_3$, (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), NaO*t*-Bu, and toluene).[11] As illustrated in Table 1, reaction of bromopyridine **5** with



Scheme 1

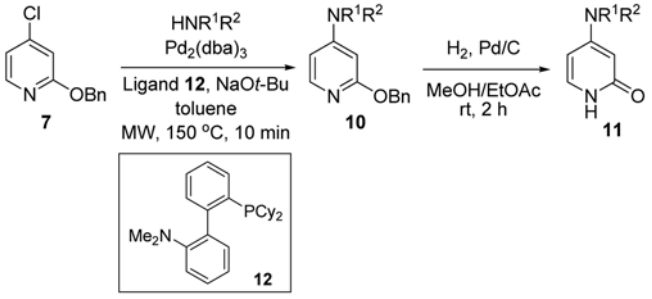
Table 1. Palladium-catalyzed amination of bromopyridine **5**[a] followed by hydrogenation[b]

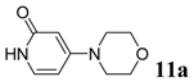
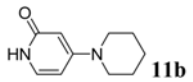
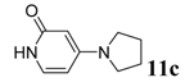
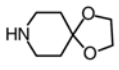
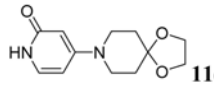
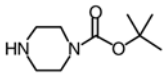
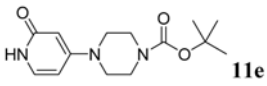
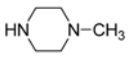
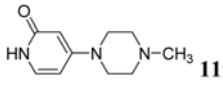
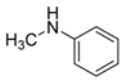
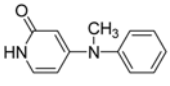
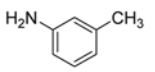
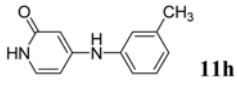
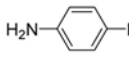
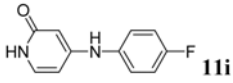


Entry	Amines	Yield of **8** (%)[c]	2-Pyridones	Yield of **9** (%)[c]
1		83 58[d]	 **9a**	89
2		82	 **9b**	97
3		77	 **9c**	95
4		72	 **9d**	96
5		75	 **9e**	83
6		63	 **9f**	78
7		67	 **9g**	80
8		74	 **9h**	89
9		79	 **9i**	91
10		73	 **9j**	95

[a]Reaction conditions: bromopyridine **5** (1 mmol), $Pd_2(dba)_3$ (1 mol% of Pd), BINAP (1.5 mol%), amine (1.2 mmol), NaO*t*-Bu (1.4 mmol), toluene (3 mL), MW, 120 °C, 10 min. [b]Reaction conditions: H_2 (30-40 psi), 10% Pd/C (10 wt%), MeOH/EtOAc (2:1), 2 h. [c]Isolated yield. [d]Oil bath, 120 °C, 22 h.

Table 2. Palladium-catalyzed amination of chloropyridine **7**[a] followed by hydrogenation[b]



Entry	Amines	Yield of **10** (%)[c]	2-Pyridones	Yield of **11** (%)[c]
1		18[d], 54[e] 77	 **11a**	90
2		82	 **11b**	96
3		77	 **11c**	98
4		80	 **11d**	95
5		73	 **11e**	90
6		69	 **11f**	93
7		85	 **11g**	97
8		83	 **11h**	98
9		86	 **11i**	96
10		66	**11j**	88

[a]Reaction conditions: chloropyridine **7** (1 mmol), $Pd_2(dba)_3$ (1 mol% of Pd), DavePhos **12** (1.5 mol%), amine (1.2 mmol), NaO*t*-Bu (1.4 mmol), toluene (3 mL), MW, 150 °C, 10 min. [b]Reaction conditions: H_2 (30-40 psi), 10% Pd/C (10 wt%), MeOH/EtOAc (2:1), 2 h. [c]Isolated yield. [d]BINAP was used instead of ligand **12**. [e]Oil bath, 150 °C, 22 h.

morpholine proceeded smoothly to provide the corresponding aminopyridine **8a** in 83% yield (entry 1). In order to figure out thermal effects of microwave heating compared to conventional heating, we ran the identical reaction using conventional oil bath at 120 °C for 22 h and obtained the coupling product **8a** in lower yield. Next, debenzylation of **8a** using Pd-catalyzed hydrogenolysis gave the desired aminopyridone **9a** in excellent yield. Formation of 2-pyridone **9a** was confirmed by ^{1}H NMR analysis based upon the appearance of an amide proton at the far downfield region (δ 11.93 ppm).[10]

We then applied the above protocol to the amination reactions with various other amines. In the case of cyclic secondary amines, amino-substituted pyridines **8a-f** were obtained in excellent isolated yields (entries 1-6). Coupling reactions with aromatic amines as well as aliphatic amine also proceeded quite smoothly to provide aminopyridine **8g-j** in good yields (entries 7-10). Finally, catalytic debenzylations of 2-benzyloxypyridines **8a-j** provided the corresponding 2-pyridones **9a-j** in high yield (Table 1).

We next examined the coupling reactions of less reactive chloropyridine with various amines to probe the reaction

scope (Table 2). However, the amination reactions of 2-benzyloxy-4-chloropyridine **7** using BINAP/$Pd_2(dba)_3$ catalytic system were not effective even at elevated temperature (150 °C). For example, the coupling reaction with morpholine afforded the corresponding aminopyridine only in 18% yield, along with large amounts of recovered starting material (entry 1). The use of DavePhos ligand **12** greatly improved the reaction yields (entry 1).[15] However, the coupling reaction under conventional oil bath heating resulted in lower yield. Under these conditions, the coupling reactions with cyclic amines as well as primary and secondary anilines were rapidly completed within 10 min in good yields (entries 1-9). The reaction with primary alkyl amine resulted in slightly lower yield (entry 10). As expected, catalytic debenzylations of 2-benzyloxypyridines **10a-j** provided the corresponding 2-pyridones **11a-j** in high yields (Table 2).

Conclusion

We have successfully developed a simple and rapid synthetic protocol for amino-substituted 2-pyridones using microwave-promoted palladium-catalyzed amination of 2-benzyloxy halopyridines, followed by debenzylation. Although the more reactive DavePhos ligand **12** and higher reaction temperature are necessary for amination of 4-chloropyridine, amination with a variety of amines was highly effective. This two-step sequence can be further utilized for the efficient construction of amino-substituted 2-pyridone compounds of biological interests.

Experimental Section

Typical procedure for Pd-catalyzed amination. All reactions were conducted by using Biotage Initiator EXP™ microwave reactor. To a thick-well borosilicate glass vial (5 mL) was added bromopyridine (1 mmol), $Pd_2(dba)_3$ (1 mol% of Pd), BINAP (1.5 mol%) or DavePhos **12** (1.5 mol%), amine (1.2 mmol), and NaO*t*-Bu (1.4 mmol) sequentially. The mixture was suspended in toluene (3 mL) and degassed with argon over 5 min. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 120 °C or at 150 °C for 10 min. After being cooled to rt, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by silica gel flash column chromatography with EtOAc/hexanes as eluents.

8a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, 1H, J = 4.9, 1.0 Hz), 7.47-7.30 (m, 5H), 7.10 (dd, 1H, J = 7.5, 1.1 Hz), 6.87 (dd, 1H, J = 7.5, 5.0 Hz), 5.46 (s, 2H), 3.84 (m, 4H), 3.09 (m, 4H); MS (EI) *m/z* M^+ for $C_{16}H_{18}N_2O_2$ calc. 270, found 271 (18), 270 (M^+, 100), 252 (87), 239 (15), 211 (12), 199 (14).

8b: ^{1}H MR (300 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 5.1, 1.5 Hz), 7.47 (d, 2H, J = 7.5 Hz), 7.40-7.30 (m, 3H), 7.12 (dd, 1H, J = 7.8, 1.5 Hz), 6.86 (dd, 1H, J = 7.8, 5.1 Hz), 5.46 (s, 2H), 3.15 (bs, 4H), 2.62-2.60 (m, 4H), 2.35 (s, 3H); MS (EI) *m/z* M^+ for $C_{17}H_{21}N_3O$ calc. 283, found 284 (18), 283 (M^+, 100), 193 (5), 192 (60).

8c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 1H, J = 4.8 Hz), 7.49 (d, 2H, J = 7.5 Hz), 7.39-7.27 (m, 3H), 7.10 (d, 1H, J = 7.2 Hz), 6.84 (dd, 1H, J = 7.7, 5.0 Hz), 5.46 (s, 2H), 3.05-3.02 (m, 4H), 1.77-1.70 (m, 4H), 1.61-1.57 (m, 2H); MS (EI) *m/z* M^+ for $C_{17}H_{20}N_2O$ calc. 268, found 269 (14), 268 (M^+, 60), 178 (26), 177 (74), 176 (100), 149 (23).

8d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.58 (m, 1H), 7.46 (d, 2H, J = 7.5 Hz), 7.38-7.28 (m, 3H), 6.83-6.76 (m, 2H), 5.41 (s, 2H), 3.30 (t, 4H, J = 6.6 Hz), 1.93-1.84 (m, 4H); MS (EI) *m/z* M^+ for $C_{16}H_{18}N_2O$ calc. 254, found 255 (14), 254 (M^+, 72), 185 (60), 184 (5), 164 (10), 163 (100).

8e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, 1H, J = 4.9, 1.5 Hz), 7.47 (d, 2H, J = 7.2 Hz), 7.39-7.30 (m, 3H), 7.11 (dd, 1H, J = 7.6, 1.5 Hz), 6.83 (dd, 1H, J = 7.6, 5.0 Hz), 5.45 (s, 2H), 3.96 (s, 4H), 3.20 (t, 4H, J = 5.6 Hz), 1.89 (t, 4H, J = 5.6 Hz); MS (EI) *m/z* M^+ for $C_{19}H_{22}N_2O_3$ calc. 326, found 327 (78), 326 (M^+, 100), 149 (32).

8f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, 1H, J = 5.0, 1.6 Hz), 7.46 (d, 2H, J = 7.2 Hz), 7.40-7.30 (m, 3H), 7.08 (dd, 1H, J = 7.6, 1.5 Hz), 6.86 (dd, 1H, J = 7.6, 4.9 Hz), 5.46 (s, 2H), 3.57 (t, 4H, J = 5.0 Hz), 3.04 (t, 4H, J = 5.1 Hz), 1.48 (s, 9H); MS (EI) *m/z* M^+ for $C_{21}H_{27}N_3O_3$ calc. 369, found 370 (41), 369 (M^+, 100), 296 (3), 184 (5), 178 (25), 161 (6).

8g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, 1H, J = 3.2, 1.8 Hz), 7.52 (dd, 1H, J = 7.6, 1.8 Hz), 7.23-7.12 (m, 8H), 6.91-6.79 (m, 1H), 6.71 (t, 1H, J = 5.4 Hz), 6.69 (d, 1H, J = 2.3 Hz), 5.37 (s, 2H), 3.24 (s, 3H); MS (EI) *m/z* M^+ for $C_{19}H_{18}N_2O$ calc. 290, found 291 (32), 290 (M^+, 100), 199 (54), 184 (22).

8h: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 1.7 Hz), 7.53-7.37 (m, 6H), 7.21 (t, 1H, J = 7.6 Hz), 6.98 (m, 2H), 6.84 (dd, 2H, J = 7.6, 5.0 Hz), 6.11 (s, 1H), 5.51 (s, 2H), 2.36 (s, 3H); MS (EI) *m/z* M^+ for $C_{19}H_{18}N_2O$ calc. 290, found 291 (35), 290 (M^+, 100), 199 (35), 184 (45), 156 (9).

8i: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, 1H, J = 5.0, 1.5 Hz), 7.47 (d, 2H, J = 7.4 Hz) 7.39-7.35 (m, 3H), 7.26 (dd, 1H, J = 7.6, 1.4 Hz), 7.09-6.90 (m, 4H), 6.78 (dd, 1H, J = 7.6, 5.0 Hz), 5.99 (bs, 1H), 5.46 (s, 2H); MS (EI) *m/z* M^+ for $C_{13}H_{15}FN_2O$ calc. 294, found 295 (92), 294 (M^+, 92), 293 (100), 275 (7), 204 (8), 203 (86), 174 (39).

8j: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.43 (m, 3H), 7.38-7.30 (m, 3H), 6.80-6.71 (m, 2H), 5.41 (s, 2H), 4.18 (bs, 1H), 3.07 (t, 2H, J = 6.9 Hz), 1.60 (quintet, 2H, J = 7.2 Hz) 1.40-1.24 (m, 6H), 0.88 (t, 3H, J = 6.9 Hz); MS (EI) *m/z* M^+ for $C_{18}H_{24}N_2O$ calc. 284, found 285 (31), 284 (M^+, 100), 213 (27), 199 (17), 193 (10).

10a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 6.0 Hz), 7.46-7.27 (m, 5H), 6.40 (dd, 1H, J = 6.0, 2.4 Hz), 6.13 (d, 1H, J = 2.1 Hz), 5.35 (s, 2H), 3.80 (t, 4H, J = 4.9 Hz), 3.23 (t, 4H, J = 4.9 Hz); MS (EI) *m/z* M^+ for $C_{16}H_{18}N_2O_2$ calc. 270, found 271 (42), 270 (M^+, 100), 269 (20), 193 (24), 164 (36).

10b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 1H, J = 6.2 Hz), 7.47-7.29 (m, 5H), 6.40 (dd, 1H, J = 6.2, 2.3 Hz), 6.12 (d, 1H, J = 2.3 Hz), 5.34 (s, 2H), 3.31-3.29 (bs, 4H), 1.69-

1.63 (m, 6H); MS (EI) *m/z* M^+ for $C_{17}H_{20}N_2O$ calc. 268, found 269 (19), 268 (M^+, 100), 267 (31), 191 (15), 162 (22), 91 (7).

10c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 6.0 Hz), 7.47 (d, 1H, J = 1.5 Hz), 7.44-7.29 (m, 4H), 6.15 (dd, 1H, J = 6.0, 2.1 Hz), 5.85 (d, 1H, J = 2.1 Hz), 5.34 (s, 2H), 3.30-3.26 (m, 4H), 2.02-1.97 (m, 4H); MS (EI) *m/z* M^+ for $C_{16}H_{18}N_2O$ calc. 254, found 254 (M^+, 49), 253 (19), 177 (41), 148 (100).

10d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 6.0 Hz), 7.47-7.29 (m, 5H), 6.42 (dd, 1H, J = 6.3, 2.4 Hz), 6.15 (d, 1H, J = 2.4 Hz), 5.34 (s, 2H), 3.99 (s, 4H), 3.45 (t, 4H, J = 5.7 Hz), 1.75 (t, 4H, J = 5.8 Hz); MS (EI) *m/z* M^+ for $C_{19}H_{22}N_2O_3$ calc. 326, found 327 (20), 326 (M^+, 100), 325 (26), 249 (75), 221 (15), 220 (90).

10e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, 1H, J = 6.1 Hz), 7.46-7.30 (m, 5H), 6.40 (dd, 1H, J = 6.3, 2.4 Hz), 6.12 (d, 1H, J = 2.2 Hz), 5.34 (s, 2H), 3.54 (t, 4H, J = 5.3 Hz), 3.28 (t, 4H, J = 5.2 Hz), 1.48 (s, 9H); MS (EI) *m/z* M^+ for $C_{21}H_{27}N_3O_3$ calc. 369, found 371 (11), 370 (56), 369 (M^+, 100), 313 (10), 236 (9), 207 (9).

10f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 6.0 Hz), 7.46-7.30 (m, 5H), 6.41 (dd, 1H, J = 6.3, 2.4 Hz), 6.14 (d, 1H, J = 2.4 Hz), 5.34 (s, 2H), 3.31 (t, 4H, J = 5.1 Hz), 2.50 (t, 4H, J = 5.1 Hz), 2.33 (s, 3H); MS (EI) *m/z* M^+ for $C_{17}H_{21}N_3O$ calc. 283, found 284 (61), 283 (M^+, 100), 206 (26), 177 (20).

10g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 6.1 Hz), 7.46-7.19 (m, 10H), 6.25 (dd, 1H, J = 6.1, 2.3 Hz), 6.05 (d, 1H, J = 2.2 Hz), 5.33 (s, 2H), 3.29 (s, 3H); MS (EI) *m/z* M^+ for $C_{19}H_{18}N_2O$ calc. 290, found 291 (17), 290 (M^+, 100), 289 (14), 213 (11), 184 (14).

10h: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 6.0 Hz), 7.44-7.18 (m, 6H), 6.98-6.90 (m, 3H), 6.44 (dd, 1H, J = 5.8, 1.9 Hz), 6.32 (d, 1H, J = 2.1 Hz), 5.97 (bs, 1H), 5.34 (s, 2H), 2.33 (s, 3H); MS (EI) *m/z* M^+ for $C_{19}H_{18}N_2O$ calc. 290, found 291 (47), 290 (M^+, 100), 289 (51), 214 (13), 213 (63), 184 (62), 183 (36), 169 (11).

10i: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 5.7 Hz), 7.89-7.32 (m, 5H), 7.17-7.01 (m, 4H), 6.40 (dd, 1H, J = 6.0, 2.1 Hz), 6.21 (d, 1H, J = 2.1 Hz), 5.86 (bs, 1H), 5.33 (s, 2H); MS (EI) *m/z* M^+ for $C_{13}H_{15}FN_2O$ calc. 294, found 294 (M^+, 29), 293 (9), 217 (7), 188 (21).

10j: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 6.0 Hz), 7.46-7.27 (m, 5H), 6.13 (dd, 1H, J = 6.0, 2.1 Hz), 5.90 (d, 1H, J = 2.1 Hz), 5.33 (s, 2H), 4.09 (bs, 1H), 3.12-3.05 (m, 2H), 1.63-1.53 (m, 2H), 1.41-1.26 (m, 6H), 0.89 (t, 3H, J = 6.8 Hz); MS (EI) *m/z* M^+ for $C_{18}H_{24}N_2O$ calc. 284, found 286 (33), 285 (61), 284 (M^+, 92), 283 (28), 213 (12), 207 (63), 135 (53), 123 (11), 122 (18), 121 (89), 108 (81).

Typical procedure for hydrogenolysis. A solution of 2-benzyloxypyridine in MeOH/EtOAc (2 mL/1 mL) was treated with 10% Pd/C (10 wt%) and hydrogenolysis was carried out on a Parr apparatus at 30-40 psi of hydrogen for 2 h. The reaction mixture was filtered through a short Celite pad, rinsed with EtOAc, and then concentrated *in vacuo* to provide 2-pyridone.

9a: mp 192-194 °C (lit.[10] 195 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.93 (bs, 1H), 7.05 (d, 1H, J = 5.7 Hz), 6.76 (dd, 1H, J = 7.2, 1.2 Hz), 6.24 (t, 1H, J = 6.9 Hz), 3.91 (t, 4H, J = 4.6 Hz), 3.17 (t, 4H, J = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 142.2, 127.1, 122.5, 106.8, 66.8, 49.5; MS (EI) *m/z* M^+ for $C_9H_{12}N_2O_2$ calc. 180, found 180 (M^+, 57), 162 (40), 149 (23), 123 (19), 121 (27), 109 (36).

9b: mp 142-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.90 (bs, 1H), 7.09 (dd, 1H, J = 6.6, 1.5 Hz), 6.81 (dd, 1H, J = 7.4, 1.2 Hz), 6.22 (t, 1H, J = 7.0 Hz), 3.19 (bs, 4H), 2.65-2.64 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 142.4, 127.0, 122.7, 106.9, 55.0, 49.0, 46.2; MS (EI) *m/z* M^+ for $C_{10}H_{15}N_3O$ calc. 193, found 194 (14), 193 (M^+, 91), 179 (8), 178 (100).

9c: mp 130-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.33 (bs, 1H), 7.04 (dd, 1H, J = 6.6, 1.5 Hz), 6.77 (dd, 1H, J = 7.2, 1.5 Hz), 6.20 (dd, 1H, J = 7.2, 6.6 Hz), 3.09-3.05 (m, 4H), 1.80-1.73 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 143.7, 126.7, 122.7, 106.9, 50.7, 25.9, 24.5; MS (EI) *m/z* M^+ for $C_{10}H_{14}N_2O$ calc. 178, found 179 (11), 178 (M^+, 100), 149 (67), 136 (9), 123 (17), 122 (19), 110 (34).

9d: mp 139-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (bs, 1H), 6.75 (d, 1H, J = 6.3 Hz), 6.35 (d, 1H, J = 7.2 Hz), 5.92 (dd, 1H, J = 7.2, 6.6 Hz), 3.44 (t, 4H, J = 6.6 Hz), 1.95-1.90 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 140.6, 123.1, 116.6, 107.6, 49.8, 24.9; MS (EI) *m/z* M^+ for $C_9H_{12}N_2O$ calc. 164, found 164 (M^+, 100), 163 (49), 149 (7), 136 (62), 122 (27), 121 (39), 109 (17), 108 (11), 107 (11), 95 (97).

9e: mp 162-166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.4 (bs, 1H), 7.07 (dd, 1H, J = 6.6, 1.5 Hz), 6.81 (dd, 1H, J = 7.2, 1.5 Hz), 6.24 (t, 1H, J = 6.6 Hz), 4.00 (s, 4H), 3.24 (t, 4H, J = 5.4 Hz), 1.92 (t, 4H, J = 5.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 142.4, 127.2, 123.5, 107.1, 107.0, 64.4, 47.6, 34.8; MS (EI) *m/z* M^+ for $C_{12}H_{16}N_2O_3$ calc. 236, found 236 (M^+, 100), 191 (43), 175 (23), 149 (29), 137 (26), 122 (29), 121 (28), 110 (16), 99 (50), 95 (85).

9f: mp 158-162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.45 (bs, 1H), 7.09 (d, 1H, J = 6.6 Hz), 6.78 (dd, 1H, J = 7.4, 1.2 Hz), 6.24 (t, 1H, J = 6.9 Hz), 3.65 (t, 4H, J = 5.1 Hz), 3.10 (t, 4H, J = 5.1 Hz), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 154.8, 142.2, 127.5, 123.3, 107.0, 79.9, 49.1, 28.5; MS (EI) *m/z* M^+ for $C_{14}H_{21}N_3O_3$ calc. 279, found 279 (M^+, 24), 222 (9), 162 (33), 161 (13), 149 (55), 137 (20), 136 (28), 123 (63), 109 (20), 95 (33).

9g: mp 160-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.71 (bs, 1H), 7.32 (dd, 1H, J = 7.2, 1.5 Hz), 7.25-7.19 (m, 3H), 6.87-6.81 (m, 3H), 6.24 (t, 1H, J = 6.9 Hz), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 148.7, 139.3, 135.5, 131.2, 129.0, 119.5, 116.2, 101.2, 38.7; MS (EI) *m/z* M^+ for $C_{12}H_{12}N_2O$ calc. 200, found 201 (26), 200 (M^+, 100), 199 (33), 183 (9), 157 (10), 156 (10), 130 (25), 123 (57), 108 (50), 106 (27).

9h: mp 136-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.96 (bs, 1H), 7.22-7.15 (m, 2H), 7.02-7.01 (m, 2H), 6.90-6.83 (m, 3H), 6.25 (t, 1H, J = 7.2 Hz), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.9, 139.5, 134.7, 129.4,

123.5, 121.7, 120.6, 116.9, 113.1, 108.6, 21.7; MS (EI) *m/z* M^+ for $C_{12}H_{12}N_2O$ calc. 200, found 200 (M^+, 100), 181 (7), 171 (22), 154 (6), 142 (4), 130 (10), 103 (7).

9i: mp 154-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.92 (bs, 1H), 7.19-7.14 (m, 2H), 7.07-6.98 (m, 3H), 6.85 (dd, 1H, *J* = 6.6, 1.2 Hz), 6.80 (s, 1H), 6.23 (t, 1H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.8, 155.9, 138.0, 134.3, 122.4, 120.6, 115.7, 111.1, 105.6; MS (EI) *m/z* M^+ for $C_{11}H_9FN_2O$ calc. 204, found 205 (79), 204 (M^+, 72), 203 (91), 185 (22), 176 (77), 175 (100), 147 (94), 122 (48).

9j: mp 54-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.58 (bs, 1H), 6.68 (dd, 1H, *J* = 6.3, 1.5 Hz), 6.28-6.14 (m, 2H), 4.83 (bs, 1H), 3.07 (dd, 2H, *J* = 12.9, 6.6 Hz), 1.69-1.61 (m, 2H), 1.44-1.24 (m, 6H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 139.1, 119.1, 108.4, 108.3, 43.3, 31.7, 28.9, 27.0, 22.7, 14.1; MS (EI) *m/z* M^+ for $C_{11}H_{18}N_2O$ calc. 194, found 196 (28), 195 (73), 194 (M^+, 92) 177 (62), 165 (47), 151 (75), 148 (53), 137 (44), 136 (81), 123 (88), 122 (95).

11a: mp 220-222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.01 (bs, 1H), 7.20 (s, 1H), 5.96 (s, 1H), 5.70 (s, 1H), 3.80 (t, 4H, *J* = 4.7 Hz), 3.28 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.2, 134.8, 97.5, 96.1, 66.5, 46.5; MS (EI) *m/z* M^+ for $C_9H_{12}N_2O_2$ calc. 180, found 181 (10), 180 (M^+, 86), 165 (30), 122 (58), 121 (100).

11b: mp 204-210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.92 (bs, 1H), 7.13 (d, 1H, *J* = 7.2 Hz), 5.96 (d, 1H, *J* = 4.8 Hz), 5.68 (d, 1H, *J* = 2.4 Hz), 3.36-3.22 (m, 4H), 2.07-1.64 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 158.7, 134.5, 97.9, 95.2, 47.7, 25.3, 24.5; MS (EI) *m/z* M^+ for $C_{10}H_{14}N_2O$ calc. 178, found 179 (14), 178 (M^+, 100), 177 (62), 163 (17), 149 (19), 137 (14), 123 (13), 122 (19), 121 (72).

11c: mp 264-268 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (bs, 1H), 7.13 (s, 1H), 5.76 (s, 1H), 5.40 (s, 1H), 3.49-3.31 (m, 4H), 2.04-1.98 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 155.7, 134.5, 97.4, 92.7, 47.5, 25.4; MS (EI) *m/z* M^+ for $C_9H_{12}N_2O$ calc. 164, found 165 (11), 164 (M^+, 100), 163 (58).

11d: mp 138-144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.54 (s, 1H), 7.08 (d, 1H, *J* = 7.0 Hz), 6.04 (d, 1H, *J* = 6.0 Hz), 5.40 (s, 1H), 3.33 (s, 4H), 2.48 (s, 4H), 1.59 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 158.2, 134.8, 107.0, 98.1, 95.6, 64.6, 44.9, 34.4; MS (EI) *m/z* M^+ for $C_{12}H_{16}N_2O_3$ calc. 236, found 237 (10), 236 (M^+, 80), 191 (21), 175 (17), 121 (84), 111 (14).

11e: mp 210-214 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.00 (bs, 1H), 7.19 (s, 1H), 5.95 (s, 1H), 5.68 (s, 1H), 3.56 (t, 4H, *J* = 5.1 Hz), 3.32 (t, 4H, *J* = 5.1 Hz), 1.48 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4, 157.7, 153.8, 134.6, 96.4, 95.3, 79.1, 45.4, 28.0; MS (EI) *m/z* M^+ for $C_{14}H_{21}N_3O_3$ calc. 279, found 280 (29), 279 (M^+, 100), 223 (53), 222 (17), 208 (29), 206 (20), 178 (11), 137 (12), 136 (11).

11f: mp 176-178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (bs, 1H), 7.20 (d, 1H, *J* = 7.5 Hz), 6.08 (d, 1H, *J* = 6.6 Hz), 5.56 (s, 1H), 3.80 (s, 3H), 2.77 (bs, 4H), 2.51 (bs, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 158.0, 134.4, 96.5, 95.2, 54.1, 45.7; MS (EI) *m/z* M^+ for $C_{10}H_{15}N_3O$ calc. 193, found 194 (19), 193 (M^+, 100), 178 (27), 122 (16), 121 (41), 94 (15), 71 (26), 70 (95).

11g: mp 204-208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.30 (bs, 1H), 7.41 (t, 2H, *J* = 7.7 Hz), 7.30-7.18 (m, 3H), 7.03 (s, 1H), 5.68 (s, 2H), 3.28 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.8, 157.8, 146, 1, 134.1, 130.0, 127.3, 127.0, 98.7, 95.2, 40.2; MS (EI) *m/z* M^+ for $C_{12}H_{12}N_2O$ calc. 200, found 201 (27), 200 (M^+, 100), 199 (80).

11h: mp 124-128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (bs, 1H), 8.96 (s, 1H), 7.28-7.22 (m, 2H), 7.09-6.86 (m, 3H), 6.04 (d, 1H, *J* = 7.2 Hz), 5.80 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.1, 154.6, 139.5, 138.7, 135.3, 129.1, 124.4, 122.1, 118.8, 99.7, 92.9, 21.0; MS (EI) *m/z* M^+ for $C_{12}H_{12}N_2O$ calc. 200, found 201 (46), 200 (M^+, 100), 199 (95), 181 (16), 144 (33), 130 (22), 117 (12), 115 (21), 106 (11), 104 (12), 103 (12).

11i: mp 218-220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (bs, 1H), 8.59 (s, 1H), 7.27-7.12 (m, 5H), 5.83 (d, 1H, *J* = 7.2 Hz), 5.51 (s, 1H, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 158.3 (d, *J* = 239 Hz), 154.1, 136.3, 135.0, 123.8 (d, *J* = 3.8 Hz), 115.9 (d, *J* = 22.5 Hz), 98.2, 93.4; MS (EI) *m/z* M^+ for $C_{11}H_9FN_2O$ calc. 204, found 204 (M^+, 82), 203 (44), 176 (29), 148 (100), 136 (37), 135 (22), 101 (21).

11j: mp 121-128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (bs, 1H), 7.05 (d, 1H, *J* = 6.0 Hz), 6.73 (s, 1H), 5.76 (d, 1H, *J* = 5.1 Hz), 5.16 (s, 1H), 2.95 (d, 2H, *J* = 5.4 Hz), 1.50-1.48 (m, 2H), 1.28 (bs, 6H), 0.87-0.85 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.1, 157.2, 134.2, 99.0, 89.4, 41.8, 31.0, 28.0, 26.2, 22.1, 13.9; MS (EI) *m/z* M^+ for $C_{11}H_{18}N_2O$ calc. 194, found 194 (M^+, 29), 137 (11), 124 (43), 123 (100).

Acknowledgements. We thank the Korea Research Institute of Chemical Technology (KK-0601-A2) for the support of this work.

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