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SYNTHESIS OF FURO[2,3-*b*]PYRIDINE

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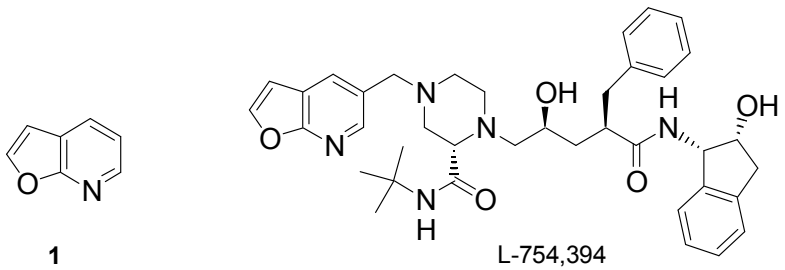
Abstract – Two synthetic routes toward furo[2,3-*b*]pyridine (**1**) starting with the known β,γ-unsaturated ester (**3**) are described.

Furo[2,3-*b*]pyridine (**1**) is a key biologically active moiety in drug discovery libraries.[1] An important example is the furo[2,3-*b*]pyridine (**1**) contained in L-754,394, a derivative reported as a potent HIV protease enzyme inhibitor (Figure 1).[2] There are a number of processes available to generate the core skeleton of furo[2,3-*b*]pyridine with bicyclic fused 5,6-ring system,[3] but generally, two major approaches have been developed. One is the annulation of a furan ring onto a substituted pyridine, and the other is the cyclization of a functionalized pyridine ring from a furan derivative. Some other synthetic routes are described as follows: (1) palladium-catalyzed annulation of 3-alkynyl 2-hydroxypyridine or 2-pyridone,[4] (2) base-induced cyclization of 2-fluoropyridine with α-hydroxyester,[5] (3) one-pot condensation of 2-aminofuran with 1,3-dicarbonyl synthon,[6] and (4) multi-component approach.[7]

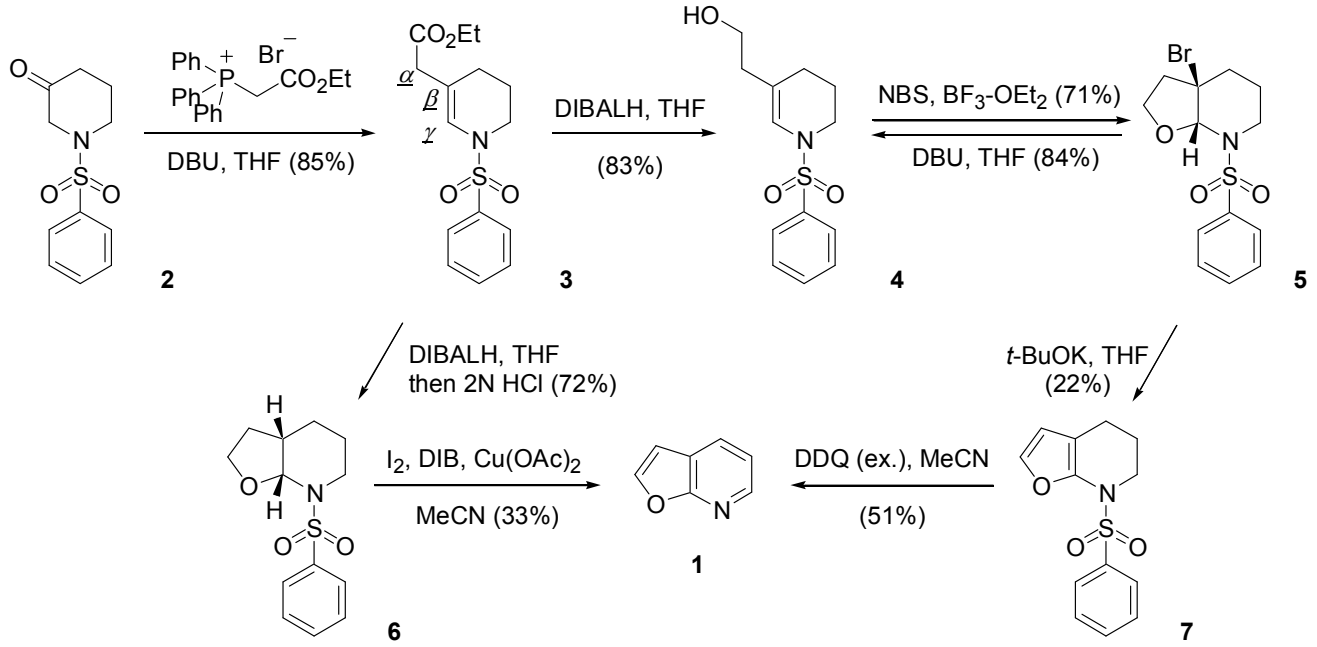


1 L-754,394

Figure 1. Structures of furo[2,3-*b*]pyridine (**1**) and L-754,394

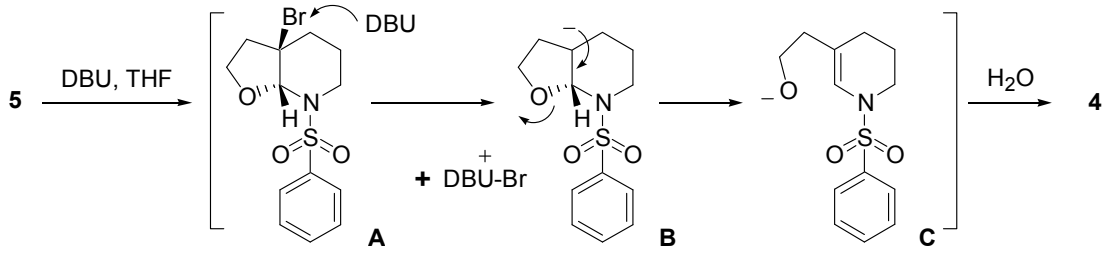
Recently, we described the synthesis of homokainoid from N-benzenesulfonylpiperidin-3-one (**2**).[8a] In previous studies, furo[2,3-*c*]pyridine was discussed as the regioisomer of furo[2,3-*b*]pyridine (**1**); it had been synthesized from N-benzenesulfonylpiperidin-4-one.[8b] To continue our investigation, two synthetic

routes to furo[2,3-*b*]pyridine (**1**) were reported (see Scheme 1). The known compound (**3**) was prepared in two-step protocol via Wittig olefination and deconjugation.[8a] Because 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could be used as the same base in the preparation of Wittig ylide and the deconjugation reaction, the combination of two procedures required further study. DBU-mediated one-pot reaction of ketone (**2**) with Wittig salt in THF under reflux produced β,γ-unsaturated ester (**3**) as the sole product. In comparison with two routes, the one-pot reaction provided a higher yield (85%) than the two-step reaction process did (61%).[8a]



Scheme 1. Synthetic approach toward furo[2,3-*b*]pyridine (**1**)

Furthermore, reduction of compound (**3**) with three equivalents of diisobutylaluminum hydride (DIBALH, 1.0 M in THF) at rt afforded alcohol (**4**) with 83% yield. Compound (**5**) was prepared as a sole isomer in 71% yield by *N*-bromosuccinimide (NBS)-mediated intramolecular addition reaction of compound (**4**) in the presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) at rt for 5 h. With the skeleton of octahydrofuro[2,3-*b*]pyridine obtained, the aromatization reaction was next examined. However, when compound (**5**) was treated with DBU under reflux for 4 h, compound (**4**) was generated in 84% yield without the formation of dehydrobromination products. This is an interesting reversible transformation. We expected DBU to function as a key promoter for the debrominative ring-opening reaction.[9] As shown in Equation 1, DBU should abstract the bromo group to form the intermediate (**A**). Furthermore, compound (**4**) was obtained by the ring-opening of intermediate (**B**) and protonation of intermediate (**C**).



Equation 1. A possible mechanism for DBU-promoted reaction of compound (**5**)

Attempts to perform the reaction with different bases (i.e., sodium hydride, sodium methoxide or lithium diisopropylamide) and under different reaction conditions (rt or reflux) afforded the complex mixture. When compound (**5**) was treated with potassium *t*-butoxide (*t*-BuOK) in THF under reflux for 1 h, tetrahydrofuro[2,3-*b*]pyridine (**7**) was obtained with only 22% yield. Literature reports on aromatization reaction,[10] show that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a good oxidant for the formation of furan and pyridine ring. Under the reported condition, the reaction of compound (**7**) with five equivalents of DDQ in toluene at reflux afforded furo[2,3-*b*]pyridine (**1**) with a 51% yield. This five-step route provided a poor total yield (5.6%) from ketone (**2**).

In another approach, compound (**6**) was synthesized as a single stereoisomer with 72% yield via reduction of compound (**3**) with DIBALH under the abovementioned conditions and the subsequent acidic work-up with hydrochloric acid. The structural framework of compound (**6**) with *cis*-fused bicyclic ring was determined by single-crystal X-ray analysis (Figure 2).[11]

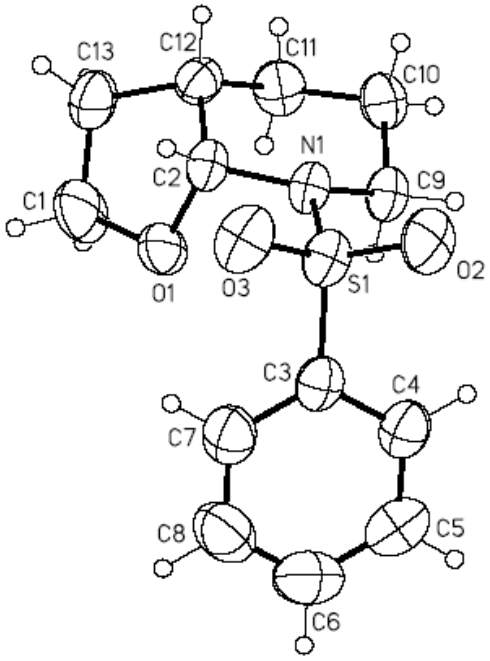
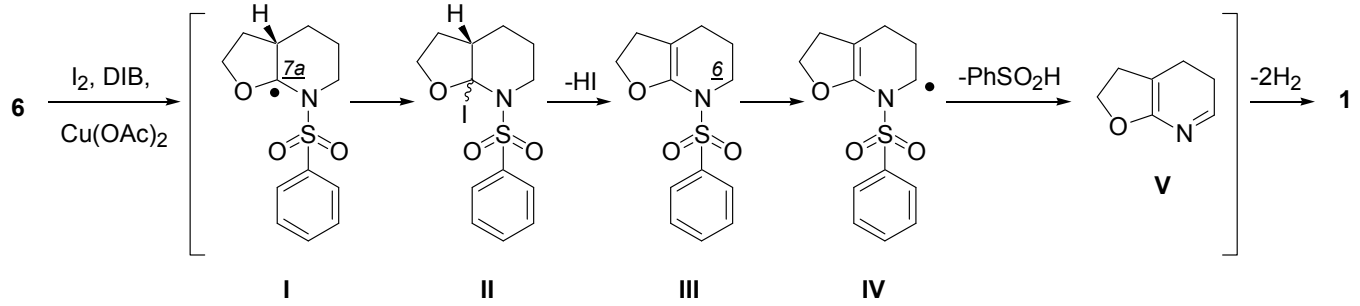


Figure 2. X-Ray structure of compound (**6**)

Finally, furo[2,3-*b*]pyridine (**1**) was produced in a 33% yield by the $Cu(OAc)_2$-mediated aromatization reaction of octahydrofuro[2,3-*b*]pyridine (**6**) with (diacetoxyiodo)benzene (DIB) and I_2 in MeCN under reflux for 42 h.[12,13] Mechanically, it is not clear if the reaction followed the same pathway as shown in Equation 2: (a) the initial event might be considered as the radical formation at C-7a position, (b) the next step should be the iodination reaction of intermediate (**I**), followed by the dehydroiodination reaction of intermediate (**II**); (c) furthermore, intermediate (**IV**) was generated by the radical formation at C-6 position of intermediate (**III**), and (d) furo[2,3-*b*]pyridine (**1**) was afforded via the aromatization reaction with the desulfonation reaction of intermediate (**IV**) and the double dehydrogenative reaction of intermediate (**V**). Notably, the second methodology provided a rapid process to form the ring system of furan and pyridine. The total yield of three-step route was 20% from ketone (**2**).



Equation 2. A possible mechanism for synthesis of furo[2,3-*b*]pyridine (**1**)

In summary, we have successfully presented two new synthetic methodologies for producing the furo[2,3-*b*]pyridine (**1**). Further studies on the synthetic application of β,γ-unsaturated ester (**3**) are actively underway in the laboratory.

EXPERIMENTAL

General. Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 200/400 and at 50/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-OS-Rapid Analyzer or Elementar Vario EL III.

(1-Benzenesulfonyl-1,4,5,6-tetrahydropyridin-3-yl)acetic acid ethyl ester (3). A solution of DBU (760 mg, 5.0 mmol) in THF (10 mL) was added to a rapidly stirred solution of ethoxycarbonylmethyl-triphenylphosphonium bromide (2.15 g, 5.0 mmol) in THF (30 mL) at rt. The reaction mixture was stirred at reflux for 30 min and cooled to rt. A solution of **2** (1.0 g, 4.18 mmol) in THF (10 mL) was added to the resulting reaction mixture at rt. The reaction mixture was reflux for 4 h and cooled to rt. A solution of DBU (3.1 g, 20.4 mmol) in THF (10 mL) was added to the reaction mixture at rt. The reaction mixture was reflux for 4 h and cooled to rt again. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1) afforded **3** (1.1 g, 85%). Compound (**3**) is a known compound and the analytical data are consistent with those in the literature.[8a] Colorless oil; HRMS (ESI, M^++1) calcd for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1112; ^{1}H NMR (200 MHz): δ 7.80-7.74 (m, 2H), 7.68-7.49 (m, 3H), 6.61 (s, 1H), 4.10 (q, *J* = 6.8 Hz, 2H), 3.33 (t, *J* = 5.8 Hz, 2H), 2.94 (s, 2H), 1.94 (t, *J* = 5.8 Hz, 2H), 1.67-1.60 (m, 2H), 1.22 (t, *J* = 6.8 Hz, 3H).

2-(1-Benzenesulfonyl-1,4,5,6-tetrahydropyridin-3-yl)ethanol (4). A solution of DIBALH (1.0 M in THF, 3.0 mL, 3.0 mmol) was added to a stirred solution of **3** (310 mg, 1.0 mmol) in THF (20 mL) at 0 ^{o}C. The reaction mixture was stirred for 5 h at rt. The reaction was quenched with water (1 mL) at 0 ^{o}C and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 4/1~2/1) afforded **4** (222 mg, 83%). Colorless oil; HRMS (ESI, M^++1) calcd for $C_{13}H_{18}NO_3S$ 268.1007, found 268.1008; ^{1}H NMR (400 MHz): δ 7.80-7.76 (m, 2H), 7.60-7.55 (m, 1H), 7.54-7.49 (m, 2H), 6.54 (s, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 2H), 2.21 (dt, *J* = 0.8, 6.4 Hz, 2H), 2.15 (br s, 1H), 1.87 (t, *J* = 6.0 Hz, 2H), 1.68-1.61 (m, 2H); ^{13}C NMR (100 MHz): δ 137.75, 132.76, 129.10 (2x), 126.95 (2x), 121.63, 117.35, 60.36, 43.50, 38.38, 24.40, 20.76; Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.72; H, 6.74; N, 5.43.

7-Benzenesulfonyl-3a-bromo-2,3,3a,4,5,6,7,7a-octahydrofuro[2,3-*b*]pyridine (5). NBS (180 mg, 1.0 mmol) was added to a solution of **4** (200 mg, 0.75 mmol) in DCM (10 mL) at rt. The reaction mixture was stirred at rt for 10 min. A solution of BF_3-OEt_2 (0.2 mL) in DCM (1 mL) was added to a stirred solution of the reaction mixture at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on

silica gel (hexanes/EtOAc = 8/1~4/1) afforded **5** (185 mg, 71%). Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{13}H_{16}BrNO_3SNa$ 367.9932, found 367.9930; ^{1}H NMR (400 MHz): δ 7.93-7.90 (m, 2H), 7.59-7.54 (m, 1H), 7.51-7.47 (m, 2H), 5.64 (s, 1H), 3.97-3.85 (m, 2H), 3.54-3.50 (m, 1H), 2.79 (dt, *J* = 2.8, 12.0 Hz, 1H), 2.64 (dt, *J* = 9.6, 12.8 Hz, 1H), 2.34 (ddd, *J* = 3.2, 7.6, 12.8 Hz, 1H), 2.08-2.03 (m, 1H), 1.96-1.88 (m, 1H), 1.86-1.78 (m, 1H), 1.60-1.58 (m, 1H); ^{13}C NMR (100 MHz): δ 138.99, 132.74, 128.74 (2x), 127.94 (2x), 89.39, 63.73, 57.97, 40.98, 39.63, 33.99, 20.97.

A representative procedure for synthesis of compound (4) via the DBU-mediated debrominative ring-opening of compound (5) is as follows: A solution of DBU (150 mg, 1.0 mmol) in THF (5 mL) was added to a rapidly stirred solution of **5** (110 mg, 0.32 mmol) in THF (10 mL) at rt. The reaction mixture was stirred at reflux for 30 min and cooled to rt. The resulting mixture was concentrated under reduced pressure. Water (5 mL) was added to the residue and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1) afforded **4** (72 mg, 84%).

7-Benzenesulfonyl-4,5,6,7-tetrahydrofuro[2,3-*b*]pyridine (7). *t*-BuOK (560 mg, 5.0 mmol) was added to a solution of **5** (178 mg, 0.52 mmol) in THF (5 mL) at rt. The reaction mixture was stirred at reflux for 1 h and cooled to rt. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 3/1~2/1) afforded **7** (30 mg, 22%). Pale yellow oil; HRMS (ESI, M^++1) calcd for $C_{13}H_{14}NO_3S$ 264.0694, found 264.0696; ^{1}H NMR (400 MHz): δ 7.86-7.84 (m, 2H), 7.72-7.70 (m, 1H), 7.69-7.60 (m, 2H), 7.25 (br t, *J* = 1.2 Hz, 1H), 6.20 (d, *J* = 1.2 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.44-1.40 (m, 2H); ^{13}C NMR (100 MHz): δ 144.40, 140.19, 136.20, 134.50, 129.95 (2x), 127.28 (2x), 116.46, 107.62, 44.06, 22.08, 19.94; Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.51; H, 5.23; N, 5.50.

Furo[2,3-*b*]pyridine (1). A solution of DDQ (206 mg, 0.9 mmol) was added to a stirred solution of **7** (48 mg, 0.18 mmol) in toluene (3 mL) at rt. The reaction mixture was stirred at reflux for 20 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 4/1~1/1) afforded **1** (11 mg, 51%). Compound (**1**) is a known compound and the ^{1}H NMR data is consistent with those in the literature.[1d] Yellowish oil; ^{1}H NMR (400 MHz): δ 8.29

(dd, *J* = 1.2, 7.2 Hz, 1H), 7.23 (d, *J* = 1.2, 7.2 Hz, 1H), 7.75 (d, *J* = 2.0, 7.6 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 160.45, 158.69, 142.26, 128.73, 121.98, 116.89, 101.33.

7-Benzenesulfonyl-2,3,3a,4,5,6,7,7a-octahydrofuro[2,3-*b*]pyridine (6). A solution of DIBALH (1.0 M in THF, 3.0 mL, 3.0 mmol) was added to a stirred solution of **3** (310 mg, 1.0 mmol) in THF (30 mL) at ice bath. The mixture was further stirred for 5 h at rt. The reaction mixtre was quenched with $HCl_{(aq)}$ (2N, 5 mL) at rt and stirred for 30 min. The reaction mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~6/1) afforded **6** (193 mg, 72%). White solid; Mp = 105-106 ^{o}C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{18}NO_3S$ 268.1007, found 268.1011; ^{1}H NMR (400 MHz): δ 7.94-7.91 (m, 2H), 7.57-7.46 (m, 3H), 5.58 (d, *J* = 4.0 Hz, 1H), 3.89 (dd, *J* = 8.4, 16.0 Hz, 1H), 3.82 (dt, *J* = 2.8, 8.4 Hz, 1H), 3.53 (dt, *J* = 4.0, 12.0 Hz, 1H), 2.67 (dt, *J* = 2.8, 12.0 Hz, 1H), 2.16-2.06 (m, 2H), 1.71-1.54 (m, 4H), 1.26-1.18 (m, 1H); ^{13}C NMR (100 MHz): δ 139.33, 132.46, 128.61 (2x), 128.02 (2x), 84.97, 64.74, 40.18, 35.55, 30.40, 24.75, 23.58. Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.68; H, 6.59, N, 5.46. Single-crystal X-ray diagram: crystal of **6** was grown by slow diffusion of EtOAc into a solution of **6** in DCM to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, *a* = 13.6992(7) Å, *b* = 8.8534(4) Å, *c* = 11.0552(6) Å, *V* = 1304.23(11) Å^3, *Z* = 4, d_{calcd} = 1.361 g/cm^3, *F*(000) = 568, 2*θ* range 1.53~26.60^{o}, R indices (all data) R1 = 0.0601, wR2 = 0.0935.

Furo[2,3-*b*]pyridine (1). $Cu(OAc)_2$ (182 mg, 1.0 mmol), DIB (322 mg, 1.0 mmol) and iodine (254 mg, 1.0 mmol) were added to a solution of **6** (106 mg, 0.4 mmol) in MeCN (8 mL) at rt. The reaction mixture was stirred at reflux for 42 h. $Na_2S_2O_{3(aq)}$ solution (10%, 2 x 5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 4/1~1/1) afforded **1** (16 mg, 33%).

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11. CCDC 833294 (**6**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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