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SYNTHESIS OF MELATONIN ANALOGUES DERIVED FROM FURO[2,3-*b*]- AND [2,3-*c*]PYRIDINES BY USE OF A PALLADIUM-COPPER CATALYST SYSTEM

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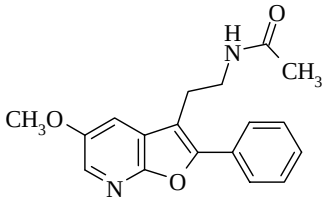
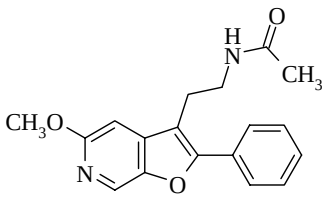
Abstract - 2,3,5-Substituted furo[2,3-*b*]pyridine was synthesised by palladium-catalyzed reaction of 5-bromo-2-hydroxy-3-iodopyridine and phenylacetylene with $(Ph_3P)_2PdCl_2$, CuI in Et_3N. A carbonylative cyclization of 5-hydroxy-2-methoxy-4-(2-phenylethynyl)pyridine with carbon monoxide in methanol with $PdCl_2$, $CuCl_2$ under basic conditions, has been accomplished to prepare methyl 2,5-substituted furo[2,3-*c*]pyridine-3-carboxylate.

In the course of our research on the synthesis of melatonin analogues,[1] our attention has been focused on developing a catalytic approach to the furopyridine derivatives (**1**) and (**2**). Several studies have shown that 2-substituted melatonin analogues can be more potent than melatonin itself.[2] This increase in potency has been ascribed to the presence of a C-2 binding site. Thus, to take advantage of this increase in binding, we envisaged to synthesize furopyridines analogues substituted with a phenyl group at the C-2 position whilst keeping the 5-methoxy group and the 3-ethanamide side chain present in melatonin itself.



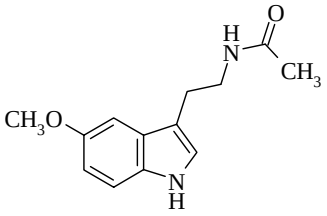
1

Furo[2,3-*b*]pyridine derivative



2

Furo[2,3-*c*]pyridine derivative



Melatonin

It was reported that the reaction of 2-hydroxypyridinyl iodides with variety of 1-alkynes in the presence of palladium (II) and copper iodide as co-catalyst provided 2-substituted furopyridines.[3] The synthesis of two kinds of furopyridines, which were expected to be obtainable by the above-mentioned method, was examined. Initial studies were directed to the preparation of the suitable substrates

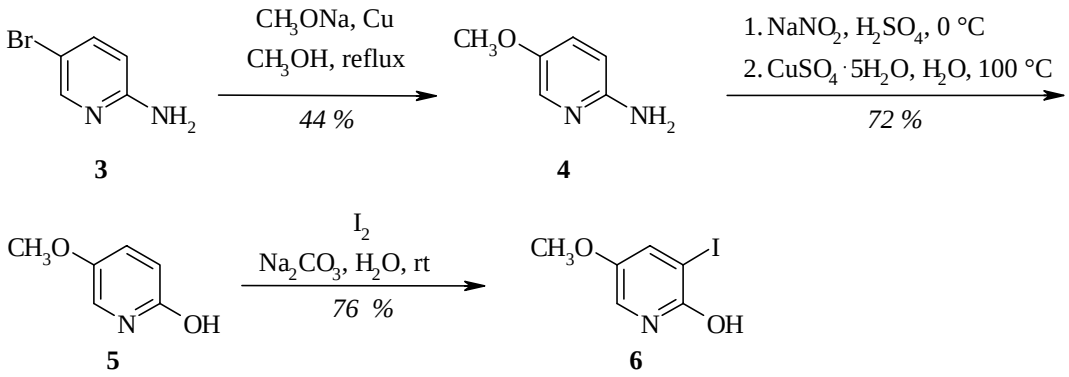
2-hydroxypyridinyl iodides (**6**) and (**12**) for palladium-catalyzed cyclizations.

RESULTS AND DISCUSSION

Synthesis of 2-hydroxy-3-iodo-5-methoxypyridine (6)

The synthesis of the 2-amino-5-methoxypyridine (**4**) was already described in a 2 or 3-step procedure[4] but when 2-amino-5-bromopyridine (**3**) was allowed to react with sodium methoxide in the presence of copper in methanol, (**4**) can be directly obtained in moderate yield.[5] Next, the amino group was converted to the diazonium salt using sodium nitrite in sulfuric acid and then treated with copper sulfate to give the corresponding pyridinol (**5**) in 72 % yield.[6] The iodination of **5** was readily accomplished according the procedure of Koch and Schnatterer[7] for the halogenation of hydroxypyridine using one equivalent of iodine in the presence of sodium carbonate in water (Scheme 1).

Scheme 1

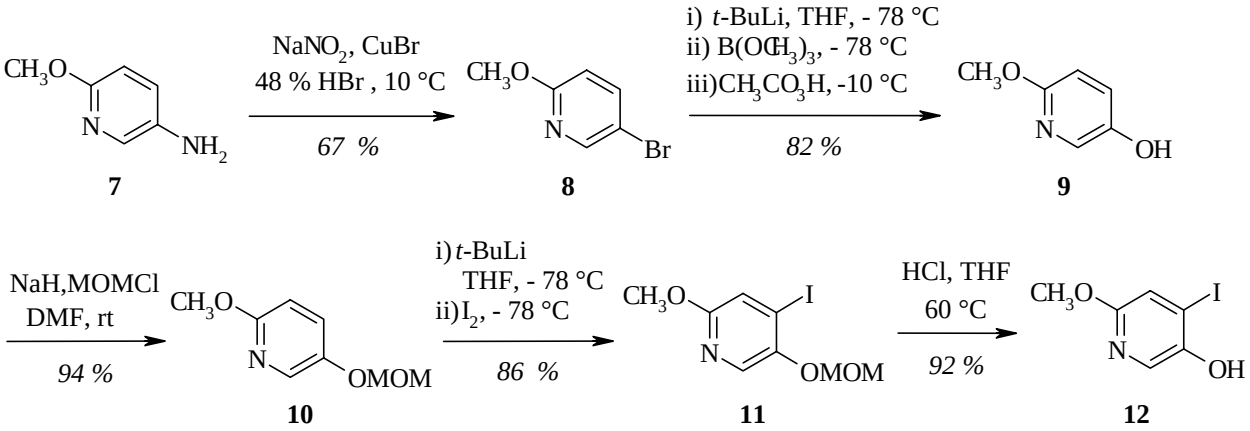


Synthesis of 5-hydroxy-4-iodo-2-methoxypyridine (12)

The required 5-hydroxy-2-methoxypyridine (**9**) was prepared in three steps from 5-amino-2-methoxypyridine (**7**) by Holladay *et al.*[8] For our purposes, a two-step sequence of **9** was carried out in satisfactory yield from **7** by replacement of the amino group with bromine, according to the Sandmeyer reaction,[9] followed successively in one pot by lithiation, reaction of trimethylborate at low temperature, and *in situ* oxidation of the boronic intermediate with peracetic acid[10] in 55 % overall yield (Scheme 2). In an attempt to prepare **9** directly from commercially available 5-amino-2-methoxypyridine (**7**) by a diazotation reaction, a bipyridine product (structure not shown) was obtained as only product.[11]

In order to iodinate the C-4 position of compound (**9**), we used the MOM group to direct *ortho* metallation of the aromatic compound.[12] Thus, the MOM protected compound was prepared using methoxymethyl chloride in the presence of sodium hydride in *N*,*N*-dimethylformamide and then treated with 2 equivalents of *tert*-butyllithium at -78 °C in tetrahydrofuran. The lithio species was trapped with 1.5 equivalent of iodine to give the iodinated compound in 86 %. After the removal of the MOM group by heating in hydrochloric acid and tetrahydrofuran at 60 °C, the 5-hydroxy-4-iodo-2-methoxypyridine (**12**) was obtained in 92 % (Scheme 2).

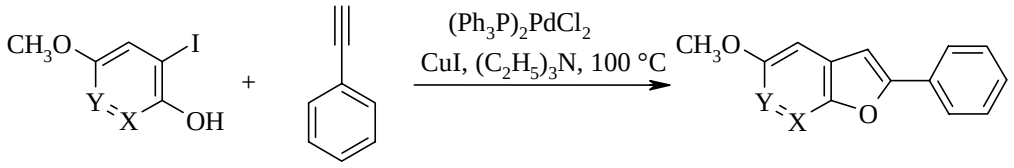
Scheme 2



Synthesis of compounds (13) and (14)

2-Phenyl-5-methoxyfuro[2,3-*b*]pyridine (**13**) and 2-phenyl-5-methoxyfuro[2,3-*c*]pyridine (**14**) were directly obtained in good yield from 2-hydroxy-3-iodo-5-methoxypyridine (**6**) and 5-hydroxy-4-iodo-2-methoxypyridine (**12**), respectively, by heating in a triethylamine solution in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium (5 mol %) and copper iodide (5 mol%) (Scheme 3).

Scheme 3

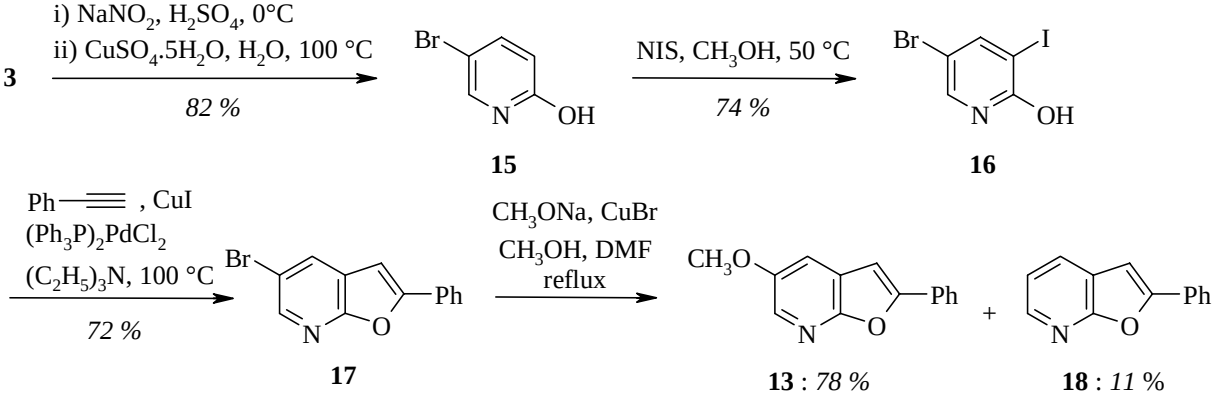


6 : X = N, Y = CH
12 : Y = N, X = CH

13 : X = N, Y = CH ; *65 %*
14 : Y = N, X = CH ; *74 %*

By the method described above, the compound (**13**) was prepared in 4 steps from **3** in 15 % yield. However, a better overall yield (34 %) was obtained by reversing the order of the reactions (Scheme 4). The iodination was performed with *N*-iodosuccinimide as the halogenating agent and the introduction of the methoxy group was achieved in a 78 % yield by a copper-catalyzed reaction of sodium methoxide with the 5-bromofuropyridine (**17**) in a mixture of methanol and *N*,*N*-dimethylformamide (3:1) .[13] The competitive reduction was also observed in 11 % yield.

Scheme 4

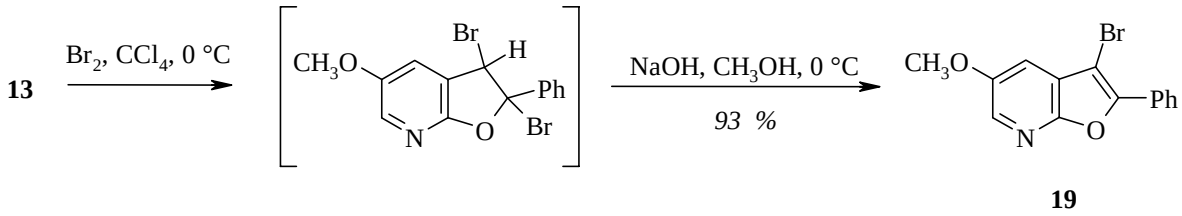


To complete the synthesis of targets (**1**) and (**2**), the introduction of the *N*-ethylacetamido group at the C-3 position of **13** and **14** was now required.

Synthesis of compound (1)

The bromination[14] of **13** with 1.2 mole of bromine in carbon tetrachloride afforded the 2,3-dibromo-2-phenyl-5-methoxy-2,3-dihydrofuro[2,3-*b*]pyridine which was immediately treated with sodium hydroxide in aqueous methanol to give the 3-bromofuropyridine derivative (**19**) in 93 % yield (Scheme 5).

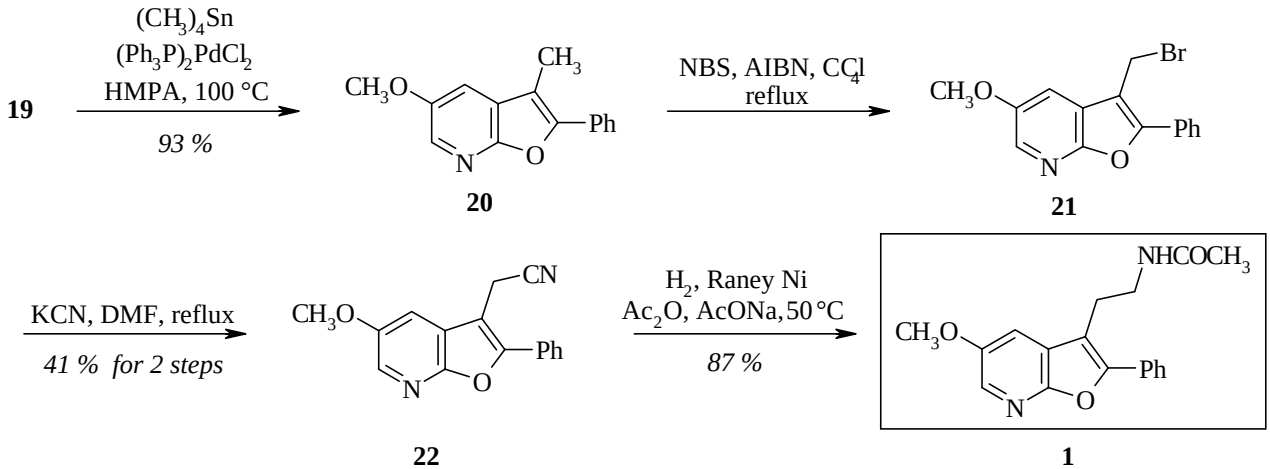
Scheme 5



19

Subsequent chemical modifications converted the bromine atom to the side chain *N*-ethylacetamide. Stille coupling of **19** with tetramethyltin gave the corresponding 3-methylfuropyridine (**20**) in 93 % yield. Treatment of **20** with *N*-bromosuccinimide and 2,2'-azobis(2-methylpropionitrile) in refluxing carbon tetrachloride followed by a nucleophilic substitution with potassium cyanide afforded the nitrile (**22**) which was converted to the final compound (**1**) by an hydrogenation over Raney nickel and a concomitant *N*-acetylation in 87 % overall yield from **22** (Scheme 6).

Scheme 6

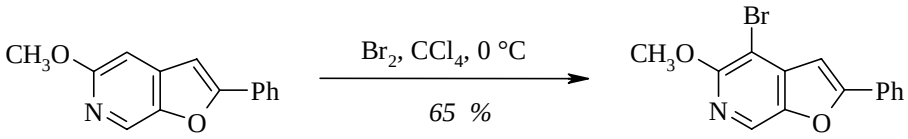


20 **21** **22** **1**

Synthesis of compound (2)

Initial attempts for the synthesis of melatonin analogue (**2**) looked at the selective bromination of **14** in the C-3 position. Unfortunately, the bromination of **14** provided the 4-bromo-substituted compound (**23**) in 65 % yield. The β-free position of the nitrogen atom allowed the regioselective introduction of a bromine atom to the C-4 position (Scheme 7).

Scheme 7



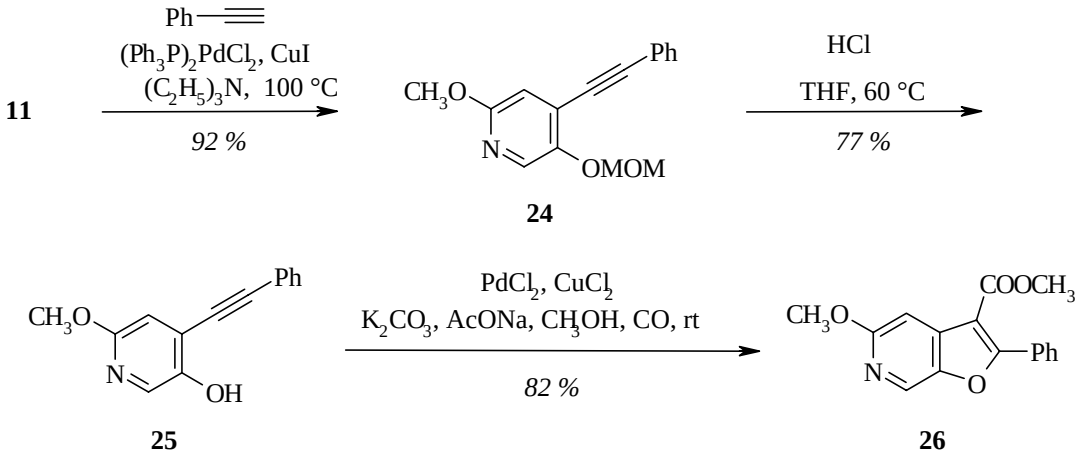
14 **23**

According the C-3 formylation of the benzofuran ring described in literature,[15] we have also tried without success to introduce a formyl group regioselectively at the C-3 position of the compound (**14**) under the Gattermann-Adams conditions.

Finally, the synthesis of **2** was achieved using a closely related strategy which utilised the Sonogashira coupling conditions described above. However, in this case the intermediate 2-(2-phenylethynyl)pyridinol (**25**) was isolated prior to cyclisation and a palladium catalysed carbonylative cyclisation reaction was used to form the furopyridine ring system with concomitant alkoxycarbonylation of the C-3 position. The conditions used for this reaction were based on those developed in literature for the preparation of 2-substituted benzofuran-3-carboxylate.[15]

The palladium-catalyzed cross-coupling reaction of **11** with the phenylacetylene followed by the removal of the MOM protecting group using hydrochloric acid in methanol gave the 2-(2-phenylethynyl)pyridinol (**25**) in 71 % overall yield. When **25** was allowed to react with carbon monoxide in methanol in the presence of palladium chloride, potassium carbonate and sodium acetate, the 5-methoxy-2-phenylfuro[2,3-*c*]pyridine-3-carboxylate (**26**) was obtained in 82 % (Scheme 8).

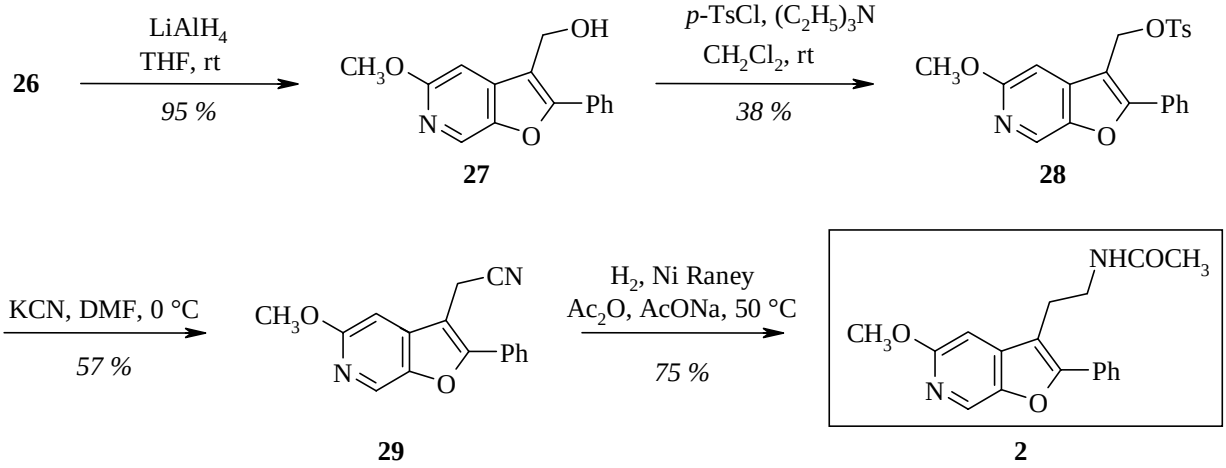
Scheme 8



25 **26**

Thus, an ester function introduced into the C-3 position of the furopyridine ring allowed us to elaborate the side chain. The compound (**26**) was reduced into the corresponding alcohol using lithium aluminum hydride in tetrahydrofuran in good yield. The formation of tosylate from alcohol (**27**) followed by the potassium cyanide displacement afforded the nitrile (**29**) in 22 % in two steps. This low yield was probably due to the instability of the sulfonate. The desired melatonin analogue (**2**) was then obtained by hydrogenation over Raney nickel and a concomitant *N*-acetylation in 75 % yield (Scheme 9).

Scheme 9



In summary, the palladium-catalyzed cross-coupling reactions provide a convenient route to synthesize functionalized furopyridine derivatives. The procedure described herein offer much possibility for design of 2-substituted furopyridines as melatonin analogues by the coupling of **10** or **11** with various of terminal acetylenes.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX250 (250.131 Hz). The coupling constants are recorded in Hz and the chemical shifts are reported in ppm (δ, ppm) downfield from TMS which was used a internal standard. IR spectra were obtained with a Perkin-Elmer FT Paragon 1000 PC. MS spectra were registered on a Perkin-Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230-400 mesh). Analytical thin-layer chromatography was carried out on silica gel F_{254} plates. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred *via* syringe.

2-Amino-5-methoxypyridine (4)

A solution of 2-amino-5-bromopyridine (**3**) (0.50 g, 2.90 mmol) in 5 mL of methanol was heated in a sealed tube for 12 h at 100 °C in the presence of sodium methoxide (0.47 g, 8.70 mmol) and copper powder (0.185 g, 2.90 mmol). After cooling, dilution with dichloromethane, filtration under celite and evaporation of solvent, water was added and the mixture was extracted with dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : ethyl acetate/petroleum ether, 6/4) to provide compound (**4**) (0.158 g, 44 %) as a brown oil : IR (NaCl) ν : 3202, 2925, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.77 (s, 3 H, OC**H$_3$**), 4.13 (s, 2 H, N**H$_2$**), 6.48 (d, J = 9.0 Hz, 1 H, **H$_3$**), 7.08 (dd, J = 9.0 Hz, J = 3.0 Hz, 1 H, **H$_4$**), 7.77 (d, J = 3.0 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 56.2 (O**C**H$_3$), 109.3 (**C$_3$**), 125.5

(**C_4**), 133.3 (**C_6**), 149.5, 153.1. MS (IS) *m/z*: 125 (M+1). *Anal.* Calcd for $C_6H_8N_2O$: C, 58.05 ; H, 6.50 ; N, 22.57. Found : C,58.00 ; H, 6.30 ; N, 22.20.

2-Hydroxy-5-methoxypyridine (5)

The compound (**4**) (5 g, 40.27 mmol) was dissolved in a mixture of concentrated sulfuric acid (8 mL) and water (115 mL). The solution was cooled to 0 °C and treated dropwise with good stirring with a solution of sodium nitrite (3 g, 44.88 mmol) in water (20 mL), keeping the temperature below 5 °C. After the addition, the stirring was continued for 0.5 h at the temperature of diazotation. The solution was then poured into a solution at 100 °C of copper sulfate (40.4 g, 161.08 mmol) in water (70 mL) and the heating continued until the evolution of nitrogen ceased. The reaction solution was allowed to cool to rt, dichloromethane and a saturated aqueous solution of sodium bicarbonate were added to the mixture. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent : ethyl acetate) to afford **5** (3.63 g, 72 %) as a yellow solid : mp 94-95 °C (pentane). IR (KBr) ν : 3058 cm^{-1}. ^{1}H-NMR ($CDCl_3$+D_2O) δ : 3.65 (s, 3 H, OC**H_3**), 6.55 (d, J = 9.7 Hz, 1 H, **H_3**), 6.95 (d, J = 3.0 Hz, 1 H, **H_6**), 7.30 (dd, J = 9.7 Hz, J = 3.0 Hz, 1 H, **H_4**). ^{13}C-NMR ($CDCl_3$) δ : 56.4 (O**C**H_3), 115.5 (**C_6**), 120.7 (**C_3**), 135.4 (**C_4**), 144.3, 163.2. MS (IS) *m/z*: 126 (M+1). *Anal.* Calcd for $C_6H_7NO_2$: C, 57.59 ; H, 5.64 ; N, 11.19. Found : C, 57.40 ; H, 5.55 ; N, 11.10.

2-Hydroxy-3-iodo-5-methoxypyridine (6)

To a solution of **5** (0.20 g, 1.60 mmol) and sodium carbonate (0.34 g, 3.20 mmol) in water (5 mL) was added iodine (0.407 g, 1.60 mmol) with stirring at 20 °C. After stirring for 45 min, the pH was adjusted to 3 with a solution of 5% hydrochloric acid and the reaction was extracted with ethyl acetate. The combined organic extracts were washed with a saturated aqueous solution of sodium thiosulfate and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel (eluent : ethyl acetate) to afford (**6**) (0.305 g, 76 %) as a white solid : mp 104-105 °C (pentane). IR (KBr) ν : 3110, 2932, 1611 cm^{-1}. ^{1}H-NMR ($CDCl_3$+D_2O) δ : 3.70 (s, 3 H, OC**H_3**), 7.08 (d, J = 3.0 Hz, 1 H, **H_4**), 7.95 (d, J = 3.0 Hz, 1 H, **H_6**). ^{13}C-NMR ($CDCl_3$) δ : 56.8 (O**C**H_3), 91.8 (**C_3**), 116.5 (**C_4**), 144.2 (**C_6**), 144.4, 160.6. MS (IS) *m/z*: 252 (M+1). *Anal.* Calcd for $C_6H_6NO_2I$: C, 28.71 ; H, 2.41 ; N, 5.58. Found : C, 28.65 ; H, 2.35 ; N, 5.42.

5-Bromo-2-methoxypyridine (8)

Copper(I) bromide (17.0 g, 120.96 mmol) was dissolved in 48 % hydrobromic acid (25 mL).

To this solution, 5-amino-2-methoxypyridine (**7)** (6.0 g, 48.40 mmol) was added with stirring. The mixture was cooled to 10 °C and sodium nitrite (4.35 g, 63.04 mmol), dissolved in water (30 mL) , was added dropwise maintaining the temperature between 10 and 15 °C. After the addition was completed, the

mixture was allowed to stand for 1 h at 10-15 °C and was then heated on a steam bath for 10 min. It was finally made basic by the addition of 50 % potassium hydroxide solution. The solution was filtered under celite and washed with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to provide compound (**8**) (6.09 g, 67 %) as a colorless oil : IR (NaCl) ν : 2945, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.82 (s, 3 H, OC**H$_3$**), 6.77 (d, J = 8.6 Hz, 1 H, **H$_3$**), 7.81 (dd, J = 8,6 Hz, J = 2,6 Hz, 1 H, **H$_4$**), 8.21 (d, J = 2,6 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 53.4 (O**C**H_3), 111.5, 112.4 (**C$_3$**), 140.7 (**C$_4$**), 147.3 (**C$_6$**), 162.7. MS (IS) *m/z*: 188 (M) 190 (M+1). *Anal.* Calcd for C_6H_6NOBr : C, 38.33 ; H, 3.22 ; N, 7.45. Found : C, 38.20 ; H, 3.15 ; N, 7.40.

5-Hydroxy-2-methoxypyridine (9)

To a solution of **8** (2.60 g, 13.83 mmol) in dry tetrahydrofuran (100 mL) at - 78 °C under argon was added a solution of *n*-butyllithium in hexane (13.1 mL of a 1.6 M solution, 20.90 mmol) and the mixture was stirred for 20 min before addition at - 78 °C of trimethyl borate (2.37 mL, 20.90 mmol). After 2 h of stirring, a solution of peracetic acid (32 wt % in dilute acetic acid) (4.4 mL, 20.90 mmol) was then added, and the mixture was warmed to 0 °C under stirring for 1 h and then cooled to - 10 °C, whereupon an aqueous solution of sodium hydrogenosulfite (10 mL) was poured dropwise. The mixture was warmed to rt and then extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 7/3) to provide **9** (1.41g, 82 %) as a yellow solid : mp 77-78 °C (ethyl acetate). IR (KBr) ν : 3180, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.84 (s, 3 H, OC**H$_3$**), 6.65 (d, J = 8.9 Hz, 1 H, **H$_3$**), 7.26 (dd, J = 8.9 Hz, J = 2.9 Hz, 1 H, **H$_4$**), 7.75 (d, J = 2.9 Hz, 1 H, **H$_6$**), 9.38 (sl, 1 H, O**H**). ^{13}C-NMR ($CDCl_3$) δ : 54.1 (O**C**H_3), 110.6 (**C$_3$**), 128.6 (**C$_4$**), 132.2 (**C$_6$**), 148.3, 158.1. MS (IS) *m/z*: 126 (M+1). *Anal.* Calcd for $C_6H_7NO_2$: C, 57.59 ; H, 5.64 ; N, 11.19. Found : C, 57.62 ; H, 5.70 ; N, 11.30.

2-Methoxy-5-(methoxymethoxy)pyridine (10)

A mixture of compound (**9**) (1.80 g, 14.40 mmol) and sodium hydride (60 % ,0.69 g, 17.28 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred at rt for 45 min. To the mixture, methoxymethyl chloride (1.25 mL, 16.56 mmol) was added and the solution was stirred at rt for 2 h. After dilution with water, the reaction mixture was extracted with ethyl acetate. The organic layer was separated, washed with water (4 times) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to afford **10** (2.31 g, 94 %) as a colorless oil. IR (NaCl) ν : 2946, 1280, 1233 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.42 (s, 3 H, OC**H$_3$**), 3.83 (s, 3 H, OC**H$_3$**), 5.03 (s, 2 H, C**H$_2$**), 6.62 (d, J = 8.2 Hz, 1H, **H$_3$**), 7.27 (dd, J = 8.2 Hz, J = 2.7 Hz, **H$_4$**), 7.89 (d, J = 2.7 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 53.1 (O**C**H_3), 55.6 (O**C**H_3), 95.4 (**C**H_2), 110,6 (**C$_3$**), 128.4 (**C$_4$**), 134.7 (**C$_6$**), 148.5, 159.3. MS (IS) *m/z*: 170 (M+1). *Anal.* Calcd for $C_8H_{11}NO_3$: C, 56.80 ; H, 6.55 ; N, 8.28. Found :

C, 56.60 ; H, 6.50 ; N, 8.19.

2-Methoxy-4-iodo-5-methoxymethoxypyridine (11)

To a solution of **10** (0.20 g, 1.18 mmol) in dry tetrahydrofuran (6 mL) at - 78 °C under argon was added a solution of *tert*-butyllithium in pentane (1.4 mL of a 1.7 M solution, 2.37 mmol). The mixture was stirred for 35 min before addition at - 78 °C of a solution of iodine (0.45 g, 1.77 mmol) in tetrahydrofuran (3 mL). After 1 h of stirring, water was added, and the mixture was warmed to rt and then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium thiosulfate and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to afford **11** (0.30 g, 86 %) as a brown solid : mp 46-47 °C (pentane). IR (KBr) ν : 2947, 1582 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.50 (s, 3 H, OC**H$_3$**), 3.84 (s, 3 H, OC**H$_3$**), 5.12 (s, 2 H, C**H$_2$**), 7.19 (s, 1 H, **H$_3$**), 7.83 (s, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) : δ = 53.8 (O**C**H_3), 56.5 (**C**H_3), 96.3 (**C**H_2), 102.0, 120.9 (**C$_3$**), 133.1 (**C$_6$**), 148.3, 159.5. MS (IS) *m/z*: 296 (M+1). *Anal.* Calcd for $C_8H_{10}NO_3I$: C, 32.56 ; H, 3.42 ; N, 4.75. Found : C, 32.43 ; H, 3.33 ; N, 4.68.

5-Hydroxy-4-iodo-2-methoxypyridine (12)

A solution of compound (**11**) (2.10 g, 7.12 mmol) in 3 N hydrochloric acid (15 mL) and tetrahydrofuran (10 mL) was heated at 60°C for 3 h, cooled to rt and then extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 7/3) to provide compound **12** (1.64 g, 92 %) as a yellow solid : mp 122-123 °C (pentane). IR (KBr) ν : 3330 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.88 (s, 3 H, OC**H$_3$**), 5.28 (s, 1 H, O**H**), 7.14 (s, 1 H, **H$_3$**), 7.81 (s, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 54.3 (O**C**H_3), 100.4, 119.9 (**C$_3$**), 131.9 (**C$_6$**), 149.3, 157.6. MS (IS) *m/z*: 252 (M+1). *Anal.* Calcd for $C_6H_6NO_2I$: C, 28.71 ; H, 2.41 ; N, 5.58. Found : C, 28.82 ; H, 2.52 ; N, 5.54.

5-Methoxy-2-phenylfuro[2,3-*b*]pyridine (13)

Method A : A mixture of 2-hydroxy-3-iodo-5-methoxypyridine (**6**) (0.22 g, 0.88 mmol), phenylacetylene (0.116 mL, 1.05 mmol), *bis*(triphenylphosphine)palladium chloride (0.031 g, 0.04 mmol) and copper iodide (0.008 g, 0.04 mmol) in triethylamine (5 mL) was heated under argon at 100 °C for 10 h. After cooling at rt and evaporating of the solvent, the residue was diluted with water and extracted with dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to give compound (**13**) (0.143 g, 65 %) as a white solid.

Method B : A mixture of compound (**17**) (2.40 g, 8.76 mmol), sodium methoxide (23.60 g, 436.90 mmol) and copper(I) bromide (2.50 g, 17.42 mmol) in methanol (75 mL) was heated under argon at reflux for 1 h before addition of *N*,*N*-dimethylformamide (25 mL). The mixture was heated at reflux for 12 h. After cooling at rt and evaporation of solvents, the residue was diluted with water and ethyl acetate and filtered

under celite. The organic layer was separated, washed with water (4 times) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to afford **13** (1.54 g, 78 %) as a white solid and **18** (19 mg, 11 %) as a white solid.

5-Methoxy-2-phenylfuro[2,3-*b*]pyridine (**13**) : mp 90-91 °C (pentane). IR (KBr) ν : 2942, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.90 (s, 3 H, OC**H$_3$**), 6.94 (s, 1 H, **H$_3$**), 7.38 (d, J = 2.6 Hz, 1 H, **H$_4$**), 7.38-7.50 (m, 3 H, **H$_{arom}$**), 7.87-7.91 (m, 2 H, **H$_{arom}$**), 8.01 (d, J = 2.6 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 56.4 (O**C**H_3), 100.1 (**C$_3$**), 113.1 (**C$_4$**), 121.5, 125.1 (2 **C$_{arom}$**), 128.9 (2 **C$_{arom}$**), 129.2 (**C$_{arom}$**), 129.7, 132.5 (**C$_6$**), 153.6, 156.8, 156.9. MS (IS) *m/z*: 226 (M+1). *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65 ; H, 4.92 ; N, 6.22. Found : C, 74.00 ; H, 4.85 ; N, 6.42.

2-Phenylfuro[2,3-*b*]pyridine (**18**): mp 89-90 °C (pentane). IR (KBr) ν : 1596 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ : 6.98 (s, 1 H, **H$_3$**), 7.20 (dd, J = 7.6 Hz, J= 4.8 Hz, 1 H, **H$_5$**), 7.37-7.49 (m, 3 H, **H$_{arom}$**), 7.85-7.91 (m, 3 H, **H$_{arom}$**, **H$_4$**), 8.28 (dd, J = 4.8 Hz, J= 1.5 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 100.1 (**C$_3$**), 113.1 (**C$_4$**), 121.5, 125.1 (2 **C$_{arom}$**), 128.9 (2 **C$_{arom}$**), 129.2 (**C$_{arom}$**), 129.7, 132.5 (**C$_6$**), 153.6, 156.8, 156.9. MS (IS) *m/z*: 196 (M+1). *Anal.* Calcd for $C_{13}H_9NO$: C, 79.98 ; H, 4.65 ; N, 7.17. Found : C, 79.82 ; H, 4.85 ; N, 7.07.

5-Methoxy-2-phenylfuro[2,3-*c*]pyridine (14)

Compound (**14**) was prepared from **12** (0.22 g, 0.88 mmol) according to the procedure used for **13**, purification by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) gave compound (**14**) (0.146 g, 74 %) as a yellow solid. mp 104-105 °C (pentane). IR (KBr) ν : 2949, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.98 (s, 3 H, OC**H$_3$**), 6.90 (s, 1 H, **H$_3$**), 7.34-7.39 (m, 3 H, **H$_{arom}$**), 7.55-7.60 (m, 3 H, **H$_{arom}$**, **H$_4$**), 8.38 (s, 1 H, **H$_7$**). ^{13}C-NMR ($CDCl_3$) δ : 54.4 (O**C**H_3), 99.8 (**C$_4$**), 101.1 (**C$_3$**), 128.1 (2 **C$_{arom}$**), 129.3 (**C$_7$**), 129.4 (2 **C$_{arom}$**), 130.1 (**C$_{arom}$**), 132.4, 133.9, 148.7, 151.3, 159.9. MS (IS) *m/z*: 226 (M+1). *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65 ; H, 4.92 ; N, 6.22. Found : C, 74.35 ; H, 4.85 ; N, 5.98.

5-Bromo-2-hydroxypyridine (15)

Prepared in 82 % yield following the procedure used for the preparation of **5**.

mp 180-182 °C (ethyl acetate). IR (KBr) ν : 3052 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ : 6.33 (d, J = 9.5 Hz, 1 H, **H$_3$**), 7.52 (dd, J = 9.5 Hz, J= 2.7 Hz, 1 H, **H$_4$**), 7.66 (d, J= 2.7 Hz, 1 H, **H$_6$**), 11.7 (s, 1 H, O**H**). ^{13}C-NMR (DMSO-d_6) δ : 99.9, 121.1 (**C$_3$**), 138.5 (**C$_4$**), 144.1 (**C$_6$**), 162.1. MS (IS) *m/z*: 174 (M) 176 (M+1). *Anal.* Calcd for C_5H_4NOBr : C, 34.52 ; H, 2.32 ; N, 8.05. Found : C, 34.45 ; H, 2.23 ; N, 7.91.

5-Bromo-2-hydroxy-3-iodopyridine (16)

N-Iodosuccinimide (846 mg, 3.75 mmol) was added under inert atmosphere to a stirred solution of 5-bromo-2-hydroxypyridine (**15**) (500 mg, 2.88 mmol) in methanol (12 mL), and stirring was continued

for 10 h at 50 °C. After cooling at rt and evaporating of the solvent, the residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with aqueous 10% $Na_2S_2O_3$ solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : ethyl acetate/petroleum ether, 6/4) to give compound (**16**) (638 mg, 74 %) as a white solid. mp 253-254 °C (ethyl acetate). IR (KBr) ν : 3051 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ : 7.72 (d, J= 2.5 Hz, 1 H, **H$_4$**), 8.19 (d, J= 2.5 Hz, 1 H, **H$_6$**), 12.21 (s, 1 H, O**H**). ^{13}C-NMR (DMSO-d_6) δ : 94.5, 97.9, 137.6 (**C$_4$**), 151.5 (**C$_6$**), 159.8. MS (IS) *m/z*: 300/302 (M+1). *Anal.* Calcd for C_5H_3NOBrI : C, 20.03 ; H, 1.01 ; N, 4.67. Found : C, 19.93 ; H, 1.01 ; N, 4.63.

5-Bromo-2-phenylfuro[2,3-*b*]pyridine (17)

This compound was prepared in 72 % yield following the general procedure used for the preparation of **13** and **14**. mp 204-205 °C (pentane). IR (KBr) cm^{-1} : ν = 1596 (C=C, Ar). ^{1}H-NMR ($CDCl_3$) δ : 6.93 (s, 1 H, **H$_3$**), 7.40-7.49 (m, 3 H, **H$_{arom}$**), 7.86-7.89 (m, 2 H, **H$_{arom}$**), 7.98 (d, J = 3.0 Hz, 1 H, **H$_4$**), 8.31 (d, J = 3.0 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 99.4 (**C$_3$**), 115.3, 123.3, 125.3 (2 **C$_{arom}$**), 128.9 (2 **C$_{arom}$**), 129.1, 129.8 (**C$_{arom}$**), 131.6 (**C$_4$**), 144.3 (**C$_6$**), 157.2, 160.4. MS (IS) *m/z*: 274 (M), 276 (M+1). *Anal.* Calcd for $C_{13}H_8NOBr$: C, 56.96 ; H, 2.94 ; N, 5.11. Found : C, 56.89 ; H, 2.87 ; N, 5.00.

3-Bromo-2-methoxyfuro[2,3-*b*]pyridine (19)

To a solution of compound (**13**) (1.50 g, 6.67 mmol) in carbon tetrachloride (30 mL) at - 15 °C was added a solution of bromine (0.5 mL, 9.62 mmol) in carbon tetrachloride (5 mL). The mixture was stirred for 10 min at this temperature. The solvent was then removed under reduced pressure at rt. The residue was taken up in methanol (30 mL) and a 20 % sodium hydroxide solution (20 mL) was added. After being stirred for 10 min at rt, the solution was evaporated and the residue was taken up in dichloromethane and washed with water. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to afford **19** (1.88 g, 93 %) as a white solid : mp 126-127 °C (pentane). IR (KBr) ν : 2945, 1592 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.96 (s, 3 H, OC**H$_3$**), 7.35 (d, J = 2.8 Hz, 1 H, **H$_4$**), 7.47-7.56 (m, 3 H, **H$_{arom}$**), 8.07 (d, J = 2.8 Hz, 1 H, **H$_6$**), 8.20-8.24 (m, 2 H, **H$_{arom}$**). ^{13}C-NMR ($CDCl_3$) δ : 56.4 (O**C**H$_3$), 111.4 (**C$_4$**), 122.1, 125.8, 126.9 (2 **C$_{arom}$**), 128.6 (2 **C$_{arom}$**), 128.9, 129.6 (**C$_{arom}$**), 134.6 (**C$_6$**), 151.1, 154.1, 154.5. MS (IS) *m/z*: 304 (M), 306 (M+1). *Anal.* Calcd for $C_{14}H_{10}NO_2Br$: C, 55.29 ; H, 3.31 ; N, 4.61. Found : C, 55.10 ; H, 3.07 ; N, 4.49.

5-Methoxy-3-methyl-2-phenylfuro[2,3-*b*]pyridine (20)

Bis(triphenylphosphine)palladium chloride (0.135 g, 0.19 mmol) and tetramethyltin (0.530 mL, 3.79 mmol) were respectively added to a solution of compound (**19**) (0.960 g, 3.16 mmol) in hexamethylphosphoramide (5 mL). The mixture was stirred at 110 °C for 3 h. After cooling to rt, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated,

washed with water (4 times) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) and further purified by recrystallization (petroleum ether/ ether, 2/1) to afford **20** (0.700 g, 93 %) as a white solid. mp 178-179 °C . IR (KBr) ν : 2939, 1583 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 2.47 (s, 3 H, C**H$_3$**), 3.92 (s, 3 H, OC**H$_3$**), 7.33 (d, J = 2.9 Hz, 1 H, **H$_4$**), 7.35-7.52 (m, 3 H, **H$_{arom}$**), 7.82-7.85 (m, 2 H, **H$_{arom}$**), 8.01 (d, J = 2.9 Hz, 1 H, **H$_6$**), ^{13}C-NMR ($CDCl_3$) δ : 10.0 (**C**H_3), 56.8 (O**C**H_3), 110.8, 112.1 (**C$_4$**), 123.7, 127.3 (2 **C$_{arom}$**), 128.8 (2 **C$_{arom}$**), 129.1 (**C$_{arom}$**), 131.7, 132.9 (**C$_6$**), 151.9, 153.7, 156.4. MS (IS) *m/z*: 240 (M+1). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30 ; H, 5.48 ; N, 5.85. Found : C, 75.12 ; H, 5.39 ; N, 5.78.

2-(5-Methoxy-2-phenylfuro[2,3-*b*]pyridin-3-yl)acetonitrile (22)

A solution of **20** (0.240 g, 1.0 mmol) in carbon tetrachloride (10 mL) was heated to reflux after which the *N*-bromosuccinimide (0.186 g, 1.06 mmol) and a catalytic amount of AIBN were added. The heating was continued during 3 h. The mixture was then cooled to rt. The succinimide produced as a byproduct was filtered off and washed with cold carbon tetrachloride. The filtrates were combined, and the solvent was removed under reduced pressure. The residue was taken up in *N*,*N*-dimethylformamide (10 mL) and potassium cyanide (0.105 g, 1.61 mmol) was added at 0 °C. The solution which resulted was stirred at this temperature for 2 h. After dilution with water, the reaction mixture was extracted with ethyl acetate. The organic layer was separated, washed with water (4 times) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 8/2) to afford **22** (0.110 g, 41 %) as a white solid. mp 169-170 °C (pentane). IR (KBr) ν : 2945, 2248, 1583 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.94 (s, 3 H, OC**H$_3$**), 3.95 (s, 2 H, C**H$_2$**), 7.48-7.58 (m, 4 H, **H$_{arom}$**, **H$_4$**), 7.70-7.73 (m, 2 H, **H$_{arom}$**), 8.08 (d, J = 2.8 Hz, 1 H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 13.7 (**C**H_2), 56.3 (O**C**H_3), 103.6, 111.2 (**C$_4$**), 116.3, 120.4, 127.4 (2 **C$_{arom}$**), 128.5, 129.0 (2 **C$_{arom}$**), 129.8 (**C$_{arom}$**), 133.8 (**C$_6$**), 153.4, 153.6, 155.5. MS (IS) *m/z*: 265 (M+1). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72 ; H, 4.58 ; N, 10.60. Found : C, 72.69 ; H, 4.50 ; N, 10.51.

***N*-[2-(5-Methoxy-2-phenylfuro[2,3-*b*]pyridin-3-yl)ethyl]acetamide (1)**

A solution of compound (**22**) (0.20 g, 0.75 mmol) in acetic anhydride (10 mL) was hydrogenated over Raney nickel (0.03 g) in the presence of sodium acetate (0.092 g, 1.12 mmol) for 12 h at 50 °C. The reaction was cooled to rt and the catalyst was filtered on Celite and the filtrate concentrated *in vacuo*. The residue was taken up in dichloromethane, washed with water and dried over $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent : ethyl acetate) and purified by recrystallization (pentane/ether, 2/1) to afford **1** (0.202 g, 87 %) as a white solid : mp 134-135 °C. IR (KBr) ν : 3283, 2934, 1669, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.92 (s, 3 H, COC**H$_3$**), 3.20 (t, J = 7 Hz, 2 H, C**H$_2$**-CH_2-N), 3.61 (td, J = 7 Hz, J = 5 Hz, 2 H, CH_2-C**H$_2$**-N), 3.95 (s, 3 H, OC**H$_3$**), 6.61-6.63 (m, 1 H, N**H**), 7.41-7.61 (m, 4 H, H$_{arom}$, **H$_4$**), 7.84-7.87 (m, 2 H, **H$_{arom}$**), 8.01 (d, J = 2.8 Hz, 1 H, **H$_6$**).

^{13}C-NMR ($CDCl_3$) δ : 23.1 (CO**C**H_3), 24.3 (**C**H_2-CH_2-N), 38.9 (CH_2-**C**H_2-N), 56.3 (O**C**H_3), 111.7 (**C_4**), 112.2, 122.6, 126.7 (2 **C_{arom}**), 128.7 (2 **C_{arom}**), 128.8 (**C_{arom}**), 130.0, 132.7 (**C_6**), 152.4, 153.5, 155.8, 170.6 (**C**O). MS (IS) *m/z*: 311 (M+1). *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found : C, 69.27; H, 5.87; N, 8.80.

4-Bromo-5-methoxy-2-phenylfuro[2,3-*c*]pyridine (23)

This compound was prepared according the same methodology described for derivative (**19**). The crude mixture was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 99/1) to afford **23** in 65 % yield as a white solid : mp 127-128 °C (pentane). IR (KBr) ν : 2942, 1588 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 4.11 (s, 3 H, OC**H_3**), 7.12 (s, 1 H, **H_3**), 7.42-7.49 (m, 3 H, **H_{arom}**), 7.79-7.84 (m, 2 H, **H_{arom}**), 8.01 (s, 1 H, **H_7**). ^{13}C-NMR ($CDCl_3$) δ : 54.7 (O**C**H_3), 101.4 (**C_3**), 101.7, 125.1 (**C_7**), 125.8 (2 **C_{arom}**), 128.8 (2 **C_{arom}**), 129.1 (**C_{arom}**), 129.4, 144.3, 145.6, 157.1, 159.9. MS (IS) *m/z*: 304 (M), 306 (M+1). *Anal.* Calcd for $C_{14}H_{10}NO_2Br$: C, 55.29 ; H, 3.31 ; N, 4.61. Found : C, 55.00 ; H, 3.28 ; N, 4.58.

2-Methoxy-5-methoxymethoxy-4-(2-phenylethynyl)pyridine (24)

A mixture of compound (**11**) (3.16 g, 10.71 mmol), phenylacetylene (1.41 mL, 12.86 mmol), *bis*(triphenylphosphine)palladium chloride (0.376 g, 0.54 mmol) and copper iodide (0.102 g, 0.54 mmol) in triethylamine (50 mL) was heated under argon at 100 °C for 4 h. After cooling at rt and evaporating of the solvent, the residue was diluted with water and extracted with dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 95/5) to afford **24** (2.64 g, 92 %) as a brown solid : mp 35-36 °C (ether). IR (KBr) ν : 2946, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.55 (s, 3 H, CH_2-O-C**H_3**), 3.89 (s, 3 H, O**C**H_3), 5.20 (s, 2 H, C**H_2**), 6.84 (s, 1 H, **H_3**), 7.33-7.36 (m, 3 H, **H_{arom}**), 7.52-7.56 (m, 2 H, **H_{arom}**), 8.02 (s, 1 H, **H_6**). ^{13}C-NMR ($CDCl_3$) δ : 54.2 (O**C**H_3), 55.8 (CH_2-O-**C**H_3), 83.4, 96.8 (**C**H_2), 113.5 (**C_3**), 122.4, 126.2, 128.7 (2 **C_{arom}**), 129.5 (**C_{arom}**), 132.2 (2 **C_{arom}**), 135.3 (**C_6**), 135.8, 148.4, 159.6. MS (IS) *m/z*: 270 (M+1). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36 ; H, 5.61 ; N, 5.20. Found : C, 71.12 ; H, 5.49 ; N, 5.08.

5-Hydroxy-2-methoxy-4-(2-phenylethynyl)pyridine (25)

A solution of compound (**24**) (2.60 g, 9.66 mmol) in 3 N hydrochloric acid (20 mL) and tetrahydrofuran (15 mL) was heated at 60 °C for 3 h, cooled to rt and then extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 7/3) to provide compound (**25**) (2.11 g, 77 %) as a brown solid : mp 118-119 °C (ether). IR (KBr) ν : 3100, 2965, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + D_2O) δ : 3.88 (s, 3 H, OC**H_3**), 6.78 (s, 1 H, **H_3**), 7.33-7.40 (m, 3 H, **H_{arom}**), 7.51-7.55 (m, 2 H, **H_{arom}**), 7.92 (s, 1 H, **H_6**). ^{13}C-NMR ($CDCl_3$) δ : 54.1 (O**C**H_3), 81.4, 98.8, 111.6 (**C_3**),

121.4, 121.9, 128.4 (2 $\mathbf{C_{arom}}$), 129.4 ($\mathbf{C_{arom}}$), 131.8 (2 $\mathbf{C_{arom}}$), 132.8 ($\mathbf{C_6}$), 147.3, 158.0. MS (IS) *m/z*: 226 (M+1). *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65 ; H, 4.92 ; N, 6.22. Found : C, 74.49 ; H, 4.81 ; N, 6.08.

Methyl 5-methoxy-2-phenylfuro[2,3-*c*]pyridine-3-carboxylate (26)

A mixture of compound (**25**) (0.165 g, 0.74 mmol), sodium acetate (0.121 g, 1.47 mmol), potassium carbonate (0.203 g, 1.47 mmol), copper(II) dichloride (0.375 g, 2.22 mmol) and palladium chloride (0.010 g, 0.05 mmol) in methanol (10 mL) was vigorously stirred under carbon monoxide atmosphere at rt for 3 h. After removal of the solvent, the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 9/1) to afford compound (**26**) (0.170 g, 82 %) as a yellow solid : mp 96-97 °C (pentane). IR (KBr) ν : 2953, 1726, 1586 cm^{-1}. 1H-NMR ($CDCl_3$) δ : 3.92 (s, 3 H, OC$\mathbf{H_3}$), 3.99 (s, 3 H, COOC$\mathbf{H_3}$), 7.29 (s, 1 H, $\mathbf{H_4}$), 7.49-7.52 (m, 3 H, $\mathbf{H_{arom}}$), 8.03-8.07 (m, 2 H, $\mathbf{H_{arom}}$), 8.44 (s, 1 H, $\mathbf{H_7}$). ^{13}C-NMR ($CDCl_3$) δ : 51.8 (COO$\mathbf{C}H_3$), 54.2 (O$\mathbf{C}H_3$), 101.6 ($\mathbf{C_4}$), 108.0, 128.3 (2 $\mathbf{C_{arom}}$), 128.7, 129.1 ($\mathbf{C_{arom}}$), 129.8 (2 $\mathbf{C_{arom}}$), 131.3 ($\mathbf{C_7}$), 137.6, 147.6, 160.7, 163.7, 165.2. MS (IS) *m/z*: 284 (M+1). *Anal.* Calcd for $C_{16}H_{13}NO_4$: C, 67.84 ; H, 4.63 ; N, 4.94. Found : C, 67.78 ; H, 4.50 ; N, 4.79.

3-Hydroxymethyl-5-methoxy-2-phenylfuro[2,3-*c*]pyridine (27)

To a suspension of lithium aluminum hydride (0.102 g, 2.67 mmol) in tetrahydrofuran (10 mL) cooled at 0 °C, was added a solution of compound (**26**) (0.630 g, 2.23 mmol) in tetrahydrofuran (10 mL). The reaction was stirred at rt for 1 h before being quenched with ethyl acetate (5 mL) and water (5 mL). The reaction was filtered and washed with water. The organic layer was then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 7/3) to afford compound (**27**) (0.540 g, 95 %) as a white solid : mp 145-146 °C (pentane). IR (KBr) ν : 3300 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.93 (s, 3 H, O$\mathbf{C}H_3$), 4.89 (s, 2 H, C$\mathbf{H_2}$), 6.92 (s, 1 H, $\mathbf{H_4}$), 7.45-7.53 (m, 3 H, $\mathbf{H_{arom}}$), 7.84-7.88 (m, 2 H, $\mathbf{H_{arom}}$), 8.35 (s, 1 H, $\mathbf{H_7}$). ^{13}C-NMR ($CDCl_3$) δ : 54.2 (O$\mathbf{C}H_3$), 55.2 ($\mathbf{C}H_2$), 98.1 ($\mathbf{C_4}$), 113.9, 127.9 (2 $\mathbf{C}_{arom}$), 128.8 ($\mathbf{C_{arom}}$), 128.9 (2 $\mathbf{C_{arom}}$), 129.4, 130.1 ($\mathbf{C_7}$), 139.9, 147.8, 158.1, 159.9. MS (IS) *m/z*: 256 (M+1). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58 ; H, 5.13 ; N, 5.13. Found : C, 70.18 ; H, 4.95 ; N, 4.98.

5-Methoxy-2-phenylfuro[3,2-c]pyridin-3-ylmethyl 4-toluenesulfonate (28)

A solution of *p*-toluenesulfonyl chloride (0.560 g, 2.93 mmol) in dichloromethane (6 mL) was added dropwise to an ice cold solution of **27** (0.500 g, 1.96 mmol) and triethylamine (0.82 mL, 5.88 mmol) in dichloromethane (12 mL). The solution was stirred for 24 h at rt, then the solvents were evaporated. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 9/1) to afford compound (**28**) (0.305 g, 38 %) as a white solid : mp 55-56 °C (ether). IR (KBr) cm^{-1} ν : 1358, 1177 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ : 2.42 (s, 3 H, C$\mathbf{H_3}$), 3.67 (s, 3 H, OC$\mathbf{H_3}$), 4.82 (s, 2 H, C$\mathbf{H_2}$), 6.96 (s,

1 H, **H$_4$**), 7.40 (d, J = 8.3 Hz, 2 H, **H$_{tosyl}$**), 7.53-7.56 (m, 3 H, **H$_{arom}$**), 7.77-7.80 (m, 2 H, **H$_{arom}$**), 7.89 (d, J = 8,3 Hz, 2 H, **H$_{tosyl}$**), 8.42 (s, 1 H, **H$_7$**). MS (IS) *m/z*: 410 (M+1). *Anal.* Calcd for $C_{22}H_{19}NO_5S$: C, 64.53 ; H, 4.68 ; N, 3.42. Found : C, 64.37 ; H, 4.55 ; N, 3.18.

2-(5-Methoxy-2-phenylfuro[2,3-*c*]pyridin-3-yl)acetonitrile (29)

To a solution of tosylate (**28**) (0.112 g, 0.24 mmol) in *N*,*N*-dimethylformamide (5 mL) at 0°C was added potassium cyanide (0.029 g, 0.44 mmol). The solution which resulted was stirred at this temperature for 5 h. After dilution with water, the reaction mixture was extracted with ethyl acetate. The organic layer was separated, washed with water (4 times) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent : petroleum ether/ethyl acetate, 9/1) to afford **29** (0.041 g, 57 %) as a white solid : mp 164-165 °C (ether). IR (KBr) ν : 2946, 2249, 1618 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.86 (s, 2 H, C**H$_2$**), 3.98 (s, 3 H, O**C**H$_3$), 6.96 (s, 1 H, **H$_4$**), 7.52-7.55 (m, 3 H, **H$_{arom}$**), 7.70-7.73 (m, 2 H, **H$_{arom}$**), 8.44 (s, 1 H, **H$_7$**). ^{13}C-NMR ($CDCl_3$) δ : 13.7 (**C**H$_2$), 54.2 (O**C**H$_3$), 98.1 (**C$_4$**), 103.5, 116.3, 120.4, 127.8 (2 **C$_{arom}$**), 128.6, 129.2 (3 **C$_{arom}$**), 130.5 (**C$_7$**), 147.6, 160.1, 178.1. MS (IS) *m/z*: 265 (M+1). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72 ; H, 4.58 ; N, 10.60. Found : C, 72.60 ; H, 4.48 ; N, 10.49

***N*-[2-(5-Methoxy-2-phenylfuro[2,3-*c*]pyridin-3-yl)ethyl]acetamide (2)**

A solution of compound (**29**) (0.08 g, 0.30 mmol) in acetic anhydride (4 mL) was hydrogenated over Raney nickel (0.012 g) in the presence of sodium acetate (0.037 g, 0.45 mmol) for 12 h at 50 °C. The reaction was cooled to rt and the catalyst was filtered on Celite and the filtrate concentrated *in vacuo*. The residue was taken up in dichloromethane, washed with water and dried over $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent : ethyl acetate) and purified by recrystallization (pentane/ ether, 2/1) to afford **2** (0.070 g, 74 %) as a white solid : mp 157 - 158 °C. IR (KBr) ν : 3295, 2949, 1644, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.84 (s, 3 H, COC**H$_3$**), 3.08 (t, J = 7.1 Hz, 2 H, C**H$_2$**-CH_2-N), 3.54 (td, J = 7.1 Hz, J = 5.4 Hz, 2 H, CH_2-C**H$_2$**-N), 3.93 (s, 3 H, OC**H$_3$**), 6.16-6.19 (m, 1 H, N**H**), 6.83 (s, 1 H, **H$_4$**), 7.41-7.52 (m, 3 H, **H$_{arom}$**), 7.81-7.84 (m, 2 H, **H$_{arom}$**), 8.34 (s, 1 H, **H$_7$**). ^{13}C-NMR ($CDCl_3$) δ : 23.1 (CO**C**H$_3$), 24.3 (**C**H$_2$-CH_2-N), 38.9 (CH_2-**C**H$_2$-N), 54.1 (O**C**H$_3$), 98.4 (**C$_4$**), 111.9, 127.3 (2 **C$_{arom}$**), 129.1 (**C$_7$**), 129.3 (2 **C$_{arom}$**), 129.9 (**C$_{arom}$**), 130.0, 140.7, 147.6, 156.3, 159.7, 170.5 (**C**O). MS (IS) *m/z*: 311 (M+1). *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found : C, 69.37; H, 5.82; N, 8.92.

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