SYNTHESIS OF 3-ALKYLFUROPYRIDINES *VIA* PALLADIUM-CATALYZED CYCLIZATION OF IODOPYRIDINYL ALLYL ETHERS

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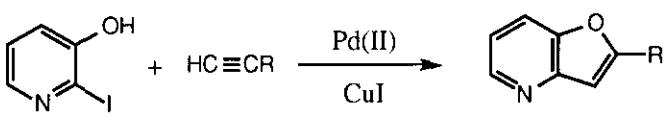
Abstract- The palladium-catalyzed cyclization of iodopyridinyl allyl ethers derived from dihalopyridines and sodium allyl alkoxide provides furo[2,3-*b*]-pyridines, furo[3,2-*c*]pyridines, and furo[2,3-*c*]pyridines.

Furopyridines are chemically interesting molecules because of their structural similarity to quinoline, isoquinoline, and benzofuran which are important nuclei in many biologically active compounds.[1] We are interested in using various furopyridines instead of pyridines to develope new omeprazole analogues,[2] representive a new class of effective gastric acid secretion inhibitors. Several synthetic pathways exist in the literature for the preparation of furopyridine.[3] However, the scope and usefulness of those procedures are often limited by the drastic reaction conditions, multi-steps, and difficulty in preparation of starting materials.

Recently, the progress in the palladium-catalyzed carbon-carbon bond forming reactions in aromatic and heteroaromatic system is removing the restriction of the thermal approaches.[4] It was reported that the reaction of 3-pyridinol with iodine substitution with variety of 1-alkynes in the presence of palladium (II) and copper iodides as co-catalyst provided 2-substituted furopyridines (eq 1).[5]

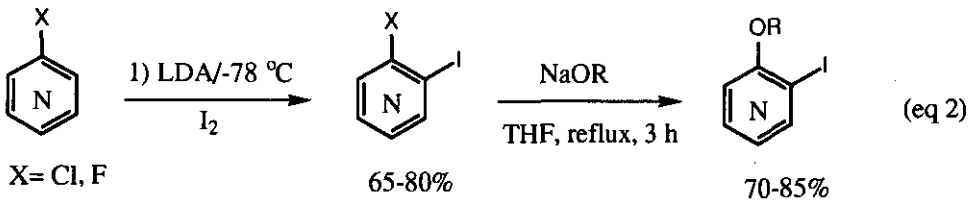


(eq 1)

However, the synthesis of 3-alkylfuropyridine by palladium-catalyzed cyclization has not yet been

reported. Probably, one difficulty is that iodopyridinyl allyl ethers are forming π-allyl palladium complexes with palladium(0) catalyst.[6] Another difficulty may be that 2- and 4-pyridones exist predominantly in the oxo form rather than the hydroxypyridine form. The alkylation of 2- and 4-hydroxypyridine is complicated, as it may occur at either the oxygen or nitrogen, depending on the conditions and reagents employed.[7]

We now report a facile preparation of 3-alkylfuropyridines by palladium-catalyzed cyclization of various iodopyridinyl allyl ethers under mild reaction conditions. For the preparation of iodopyridine allyl ethers, the dihalopyridines were prepared by regioselective lithiation of 3-fluoro-, 2-fluoro-, and 4-chloropyridines with LDA followed by treatment with I_2 as electrophile.[8] The reactions of dihalopyridines with sodium allyl alkoxide afforded variety of iodopyridinyl allyl ethers in 70-85 % isolated yields (eq 2).



X= Cl, F

65-80%

70-85%

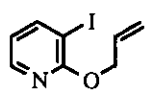
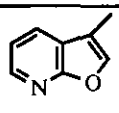
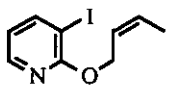
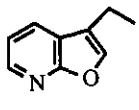
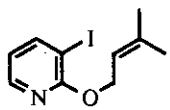
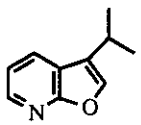
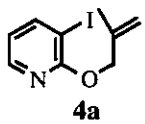
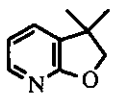
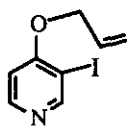
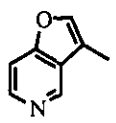
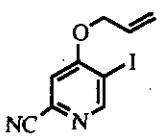
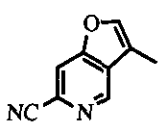
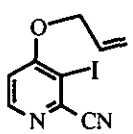
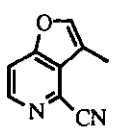
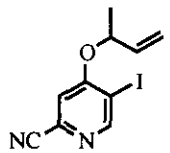
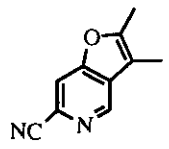
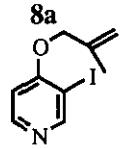
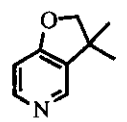
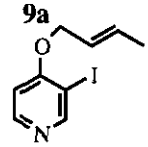
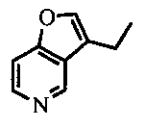
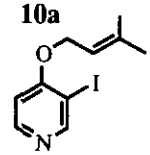
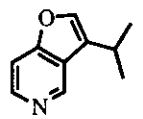
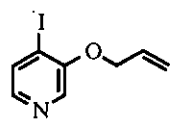
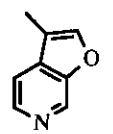
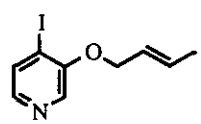
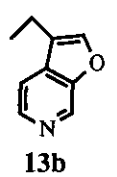
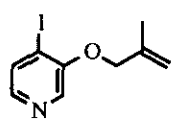
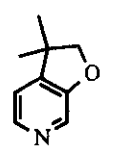
(eq 2)

Initial studies were directed to finding the general reaction conditions for palladium-catalyzed cyclization of iodopyridine allyl ethers. We explored the reaction with various bases and chloride sources which were used by Larock and coworkers in the synthesis of benzofurans[9] and indoles.[10] The reaction using *n*-Bu_4NCl as a chloride source proceeded much faster compared to other chloride sources (LiCl, Me_4NCl, Et_4NCl) (Entry 1). We were able to obtain 3-alkylfuro[2,3-*b*]pyridine in moderate yields under previously reported standard reaction conditions [2.5% $Pd(OAc)_2$, 1 eq *n*-Bu_4NCl, 1 eq HCO_2Na, 1 eq K_2CO_3, DMF, 100 °C, 3-4 h].[9,10]

We proceeded to investigate the substituent effects on the reaction with variety of iodopyridyl allyl ethers. The results are summarized in Table 1.

The substituent effect of allyl ether part was first examined using 3-iodo-2-pyridyl allyl ethers (Entries 1-4). The allyl ethers with longer side chains provided somewhat lower yield of the desired products, although the reaction rate was about same. We also examined substituent effect of nitrile (Entries 5-7). As shown in Table 1, 6-cyanopyridyl allyl ether afforded a higher yield of desired product compared to

Table 1. Synthesis of 3-alkylfuropyridines *via* palladium-catalyzed cyclization.

Entry [a,b]	Starting substrate	Product	Yield(%)
1[c]	 **1a**	 **1b**	80
2	 **2a**	 **2b**	73
3	 **3a**	 **3b**	69
4	 **4a**	 **4b**	80
5	 ***5a***	 ***5b***	40
6	 **6a**	 **6b**	55
7	 **7a**	 **7b**	35
8	 **8a**	 **8b**	50
9	 **9a**	 **9b**	74
10	 **10a**	 **10b**	42
11	 **11a**	 **11a**	41
12	 **12a**	 **12b**	40
13	 **13a**	 **13b**	40
14	 **14a**	 **14b**	55

[a]All reactions were carried out under standard reaction conditions (1.0 mmol starting substrate, 2.5 % Pd $(OAc)_2$, 1 eq *n*-Bu_4NCl, 1 eq K_2CO_3, 1 eq HCO_2Na in 5 ml of DMF at 100 °C for 3-4 h).

[b] All products gave appropriate ^1H-, ^{13}C- nmr, and ms spectral data.

[c] The reactions using other chloride sources (LiCl, Me_4NCl, Et_4NCl) instead of *n*-Bu_4NCl required 24 h for the reaction to be completed (Yield: LiCl = 73% , Me_4NCl = 75%, Et_4NCl = 77%).

2-cyanopyridyl allyl ether. The cyclization of various iodopyridinyl allyl ethers gave the high yields of dihydrofuropyridines (Entries 4, 9, and 14). Presumably, the sodium formate is reducing the initially cyclized organo-palladium intermediates. Finally, we examined 4-iodo-3-pyridyl allyl ethers (Entries 12 and 13). The reaction provided furo[2,3-*c*]pyridines in 40-55 % isolated yields. We suppose that these reactions proceeds by the same mechanism as reported by Larock and coworkers.[9,10] Probably, the low yields of furo[2,3-c]pyridine and furo[3,2-c]pyridine are due to decomposition of starting materials by forming π-allylpalladium complexes during the reaction.

These result shows that the palladium-catalyzed cyclization approach to the furopyridines is a significant improvement over the previously reported thermal procedures. The major advantages are fewer reaction steps, and the mild reaction conditions. Furthermore, 3-alkylfuropyridines can be used as important intermediates in the preparation of biologically active compounds.

EXPERIMENTAL

A. Equipment

The infrared spectra were obtained on a Shimadzu IR - 435 spectrometer. ^{1}H and ^{13}C nmr spectra on a Varian Gemini-200MHz spectrometer, GC-ms spectral data were obtained on a Shimadzu QP 100 GC/Ms and on a JEOL JMS-DX-305 high resolution mass spectrometer. Elemental analysis were carried out by Chemical Analysis Lab at Korea Research Institute of Chemical Technology.

B. Reagents

All chemicals were used directly as obtained from commercially unless otherwise noted. All halopyridines and allyl alcohols were purchased from Tokyo Kasei Co. $Pd(OAc)_2$ was purchased from Aldrich Chemical Co. Inc. *n*-Bu_4NCl was purchased from Lancaster Chemical Co.

Preparation of starting substrate for palladium-catalyzed cyclization.

In a round-bottom flask was placed Na (0.23 g, 10 mmol), allyl alcohol (20 mmol) and THF (20 ml). The reaction mixture was stirred until all sodium disappeared. 10 Mmol of dihalopyridine (2-fluoro-3-iodopyridine, 3-fluoro-4-iodopyridine, 4-chloro-3-iodopyridine, 2-cyano-4-chloro-3-iodopyridine, and 6-cyano-4-chloro-3-iodopyridine) was dissolved to the reaction mixture, and refluxing for 3-4 h under nitrogen. After cooling, the reaction mixture was poured into water and extracted with ether. The

extracted ether was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using hexanes / ethylacetate. The following compounds (**1a** - **14a**) were obtained using the above general procedure.

2-Allyloxy-3-iodopyridine (**1a**)

Yield: 80%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (m, 2H, ArH), 6.65 (dd, 1H, J = 5.6 Hz, J = 1.2 Hz, ArH), 5.40 (m, 3H, vinylic), 4.80 (dd, 2H, J = 6.2 Hz, J = 1.2 Hz, OCH_2). Ms (m/z): 261(M^+, 29.4), 244 (30.3), 127(32.1), 93 (92.7), 78 (43.9), 43 (100), 41 (77.1). HRms Calcd for C_8H_8NOI: 260.9651, Found: 260.9647. Anal. Calcd for C_8H_8NOI: C, 36.82; H, 3.09; N, 5.37. Found: C, 36.69; H, 3.06; N, 5.41.

2-(But-2-enyloxy)-3-iodopyridine (**2a**)

Yield: 75%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (m, 2H, ArH), 6.60 (dd, 1H, J = 5.6 Hz, J = 1.2 Hz, ArH), 5.80 (m, 2H, vinylic), 4.60 (d, 2H, J = 4.4 Hz, OCH_2), 1.70 (dd, 3H, J = 2.6 Hz, J = 1.2 Hz, $-CH_3$). Ms (m/z): 275 (M^+, 43.0), 120 (62.0), 57 (100). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9795. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 38.97; H, 3.64; N, 5.10.

3-Iodo-2-(3-methylbut-2-enyloxy)pyridine (**3a**)

Yield: 67%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (m, 2H, ArH), 6.65 (dd, J = 5.6 Hz, J = 1.2 Hz, ArH), 5.15 (s, 1H, vinylic), 4.95 (s, 1H, vinylic), 4.75 (s, 2H, vinylic), 1.85 (s, 3H, $-CH_3$). Ms (m/z): 289 (M^+, 68.0), 220 (79.9), 93 (12.1), 41 (100). HRms Calcd for $C_{10}H_{12}NOI$: 288.9964, Found: 288.9949. Anal. Calcd for $C_{10}H_{12}NOI$: C, 41.56; H, 4.19; N, 4.85. Found: C, 41.38; H, 4.21; N, 4.90.

3-Iodo-2-(2-methyl-allyloxy)pyridine (**4a**)

Yield: 85%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (m, 2H, ArH), 6.65 (dd, J = 5.6 Hz, J = 1.2 Hz, ArH), 5.15 (s, 1H, vinylic), 4.95 (s, 1H, vinylic), 4.75 (s, 2H, vinylic), 1.85 (s, 3H, $-CH_3$). Ms (m/z): 275 (M^+, 33.0), 129 (19.0), 120 (61.0), 57 (100), 41 (67.4). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9813. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 39.23; H, 3.59; N, 5.03.

4-Allyloxy-3-iodopyridine (**5a**)

Yield: 85%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.76 (d, 1H, J = 5.6 Hz, ArH), 8.35 (d, 1H, J = 5.4 Hz, ArH), 6.72 (d, 1H, J = 5.6 Hz, ArH), 6.00 (m, 1H, vinylic), 5.40 (m, 2H, vinylic), 4.65 (d, 2H, J = 6.4 Hz, OCH_2). Ms (m/z): 261 (M^+, 42.5), 134 (23.1), 41 (100). HRms Calcd for C_8H_8NOI: 260.9651, Found: 260.9639. Anal. Calcd for C_8H_8NOI: C, 36.82; H, 3.09; N, 5.37. Found: C, 36.79; H, 3.07; N, 5.33.

4-Allyloxy-6-cyano- 3-iodopyridine (**6a**)

Yield: 75%, mp: 115-117 °C. ^{1}H Nmr ($CDCl_3$): δ 8.85 (s, 1H, ArH), 7.08 (s, 1H, ArH), 6.10 (m, 1H, vinylic), 5.50 (m, 2H, vinylic), 4.75 (d, 2H, J = 4.8 Hz, -OCH_2). Ms (m/e): 286 (M^+, 85.8), 255 (30.3), 159 (48.2), 128 (15.7), 41 (100). HRms Calcd for $C_9H_7N_2OI$: 285.9604, Found: 285.9597. Anal. Calcd for $C_9H_7N_2OI$: C, 37.80; H, 2.47; N, 9.79. Found: C, 36.95 ; H, 2.39; N, 9.87.

4-Allyloxy-2-cyano- 3-iodopyridine **(7a)**

Yield: 71%, mp: 93-95 °C. ^{1}H Nmr ($CDCl_3$): δ 8.43 (d, 1H, J = 5.6 Hz, ArH), 6.82 (d, 1H, J = 5.6 Hz, ArH), 6.10 (m, 1H, vinylic), 5.50 (m, 2H, vinylic), 4.72 (d, 2H, J = 4.8 Hz, -OCH_2). Ms (m/z): 286 (M^+, 42.4), 159 (21.5), 41 (100). HRms Calcd for $C_9H_7N_2OI$: 285.9604, Found: 285.9601. Anal. Calcd for $C_9H_7N_2OI$: C, 37.80; H, 2.47; N, 9.79. Found: C, 37.24 ; H, 2.46; N, 9.75.

6-Cyano-3-iodo-(3-methylallyloxy)pyridine **(8a)**

Yield: 75%, mp: 134-136 °C. ^{1}H Nmr ($CDCl_3$): δ 8.76 (s, 1H, ArH), 7.03 (s, 1H, ArH), 5.85 (m, 1H, vinylic), 5.30 (m, 2H, vinylic), 4.96 (m, 1H, J = 6.2 Hz, -OCH-), 1.54 (d, 1H, J = 6.4 Hz, -CH_3). Ms (m/z): 300 (M^+, 100), 247 (90.4), 55 (87.7), 43 (3.3). HRm Calcd for $C_{10}H_9N_2OI$: 299.9760, Found: 299.9752. Anal. Calcd for $C_{10}H_9N_2OI$: C, 40.04; H, 3.02; N, 9.34. Found: C, 39.78 ; H, 2.97; N, 9.28.

3-Iodo-4-(2-methylallyloxy)pyridine **(9a)**

Yield: 83%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.65 (s, 1H, ArH), 8.24 (d, 1H, J = 5.6 Hz, ArH), 6.64 (d, 1H, J = 5.6 Hz, ArH) , 5.15 (s, 1H, vinylic), 4.95 (s, 1H, vinylic), 4.75 (s, 2H, vinylic), 1.85 (s, 3H, -CH_3). Ms (m/z): 275 (M^+, 5.3), 204 (25.4), 69 (100), 41 (24.2). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9803. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 39.41; H, 3.58; N, 5.05.

4-(But-2-enyloxy)-3-iodopyridine **(10a)**

Yield: 80%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.75 (s, 1H, J = 5.6 Hz, ArH), 8.35 (d, 1H, J = 5.6 Hz, ArH), 6.75 (d, 1H, J = 5.6 Hz, ArH), 5.80 (m, 2H, vinylic), 4.60 (d, 1H, J = 4.4 Hz, -OCH_2), 1.70 (dd, 3H, J = 2.6 Hz, J = 1.2 Hz, -CH_3). Ms (m/z): 275 (M^+, 32.3), 148 (23.6), 41 (100). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9798. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 38.81; H, 3.53; N, 5.03.

3-Iodo-4-(3-methylbut-2-enyloxy)pyridine **(11a)**

Yield: 80%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.65 (s, 1H, ArH), 8.24 (d, 1H, J = 5.6 Hz, ArH), 6.64 (d, 1H, J = 5.6 Hz, ArH), 5.35 (m, 1H, vinylic), 4.55 (d, 2H, J = 6.4 Hz, -OCH_2), 1.75 (s, 2H, -CH_3). Ms (m/z): 289 (M^+, 10.5), 204 (20.5), 77 (10.5), 41 (100). HRms Calcd for $C_{10}H_{12}NOI$: 288.9964, Found: 288.9957.

Anal. Calcd for $C_{10}H_{12}NOI$: C, 41.56; H, 4.18; N, 4.85. Found: C, 40.97; H, 4.15; N, 4.89.

3-Allyloxy-4-iodopyridine (**12a**)

Yield: 70%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (s, 1H, ArH), 7.80 (d, 1H , J = 5.6 Hz, ArH), 7.75 (d, 1H, J = 5.6 Hz, ArH), 5.40 (m, 3H, vinylic), 4.80 (dd, 2H, J = 6.2 Hz, J = 1.2 Hz, -OCH_2). Ms (m/z): 261 (M^+, 22.1), 192 (20.9), 127 (17.0), 86 (100), 41(80.7). HRms Calcd for C_8H_8NOI: 260.9651, Found: 260.9645. Anal. Calcd for C_8H_8NOI: C, 36.82; H, 3.09; N, 5.37. Found: C, 36.70; H, 3.05; N, 5.29.

3-(But-2-enyloxy)-4-iodopyridine (**13a**)

Yield: 70%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (s, 1H, ArH), 7.80 (d, 1H , J = 5.6 Hz, ArH), 7.75 (d, 1H, J = 5.6 Hz, ArH), 5.80 (m, 2H, vinylic), 4.60 (d, 2H, J = 4.4 Hz, OCH_2), 1.70 (dd, 3H, J = 2.6 Hz, J = 1.2 Hz, -CH_3). Ms (m/z): 275 (M^+, 21.0), 148 (10.8), 41(100). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9802. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 39.18; H, 3.72; N, 5.11.

3-Iodo-2-(2-methyl-allyloxy)-pyridine (**14a**)

Yield: 70%, oil. ^{1}H Nmr ($CDCl_3$): δ 8.10 (s, 1H, ArH), 7.80 (d,1H, J = 5.6 Hz, ArH), 7.70 (d, 1H, J = 5.6 Hz, ArH) , 5.15 (s, 1H, vinylic), 4.95 (s, 1H, vinylic), 4.75 (s, 2H, OCH_2), 1.85 (s, 3H, -CH_3). Ms (m/z): 275 (M^+, 1.3), 243 (4.3), 182 (36.8), 148 (100), 85 (98.0), 73 (61.3), 41 (88.9). HRms Calcd for $C_9H_{10}NOI$: 274.9808, Found: 274.9804. Anal. Calcd for $C_9H_{10}NOI$: C, 39.31; H, 3.67; N, 5.09. Found: C, 38.56; H, 3.49; N, 5.01.

General procedure for the synthesis of 3-alkylfuropyridine via palladium-catalyzed cyclization.

To a 10-ml vial containing a magnetic stirring bar was added the following reagents: $Pd(OAc)_2$ (0.025 mmol, 7 mg), K_2CO_3 (1.0 mmol, 138 mg), HCO_2Na (1.0 mmol, 67 mg), *n*-Bu_4NCl (1.0 mmol, 273 mg), 3-iodo-2-pyridyl allyl ether (1.0 mmol, 261 mg), and 5 ml of DMF. The reaction mixture was stirred at 100 °C for 4 h. The reaction mixture was diluted with ether (30 ml) and washed with saturated aqueous NH_4Cl (2x20 ml) and the combined aqueous layer was extracted with ether (20 ml). The combined ether was dried over anhydrous $MgSO_4$. The reaction mixture was filtered, concentrated, and purified *via* flash column chromatography with hexane-ethyl acetate as an eluent. 3-Methylfuro[2,3- *b*]pyridine(**1b**) (106 mg, 80 %) was obtained as a yellow oil: ^{1}H Nmr ($CDCl_3$): δ 8.56 (d, 1H, J = 5.6 Hz, ArH), 7.61 (s, 1H, ArH), 7.59 (m, 2H, ArH), 250 (s, 3H, -CH_3). ^{13}C Nmr ($CDCl_3$): δ 162.0, 143.7, 140.8, 128.3, 120.7, 118.5, 114.9, 7.9. Ms(m/z): 133 (M^+, 100), 104 (20.9). HRms Calcd for C_8H_7NO: 133.0528,

Found: 133.0521. Anal. Calcd for C_8H_7NO: C, 72.22; H, 5.30; N, 10.53. Found: C, 72.15; H, 5.28; N, 10.48.

The following compounds (2b - 14b) were obtained using the above general procedure.

2-Ethylfuro[2,3-b]pyridine (2b)

Yield:73%, oil. Ir (neat): 3030, 2980, 1650, 1590, 1560, 1460, 1410, 1240, 1100, 930, 790 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 8.30 (dd, 1H, J = 5.6 Hz, J = 1.2 Hz, ArH), 7.90 (dd, 1H, J = 5.6 Hz, J = 1.2 Hz, ArH), 7.46 (s, 1H, ArH), 7.15 (m, 1H, ArH), 2.65 (q, 2H, J = 7.4 Hz, $-CH_2$), 1.35 (d, 3H, J = 7.4 Hz, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 160.04, 147.20, 140.71, 130.73, 118.84, 117.18, 117.03, 30.16, 16.56. Ms(m/e): 147 (M^+, 16.9), 121 (42.7), 120 (45.6), 104 (33.7), 84 (52.8), 55 (100). HRms Calcd for C_9H_9NO: 147.0684, Found: 147.0680. Anal. Calcd for C_9H_9NO: C, 73.50; H, 6.16; N, 9.52. Found: C, 73.30; H, 6.09; N, 9.49.

3-Isopropylfuro[2,3-b]pyridine (3b)

Yield: 69%, oil. Ir (neat): 3030, 2960, 1590, 1570, 1470, 1410, 1200, 1110, 1050, 810, 780, 650 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 8.32 (dd, 1H, J = 4.8 Hz, J = 1.6 Hz, ArH), 7.95 (dd, 1H, J = 4.8 Hz, J = 1.6 Hz, ArH), 7.45 (s, 1H, ArH), 7.20 (m, 1H, ArH), 3.10 (m, 1H, -CH-), 1.30 (d, 6H, J = 6.8 Hz, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 162.05, 143.35, 138.82, 128.01, 126.23, 119.13, 118.19, 24.51, 21.81 (overlap). Ms (m/z): 161 (M^+, 33.4), 146 (100), 117 (32.4), 91 (31.0), 84 (21.6), 41 (19.9). HRms Calcd for $C_{10}H_{11}NO$: 161.0841, Found: 161.0841. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.57; H, 6.88; N, 8.70. Found: C, 74.38; H, 6.79; N, 8.65.

3,3-Dimethyl-2,3-dihydrofuro[2,3-b]pyridine (4b)

Yield: 80% , mp:33-35 °C (hexane). Ir (KBr) 2960, 1600, 1480, 1460, 1220, 1090, 1050, 990, 850, 780 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 7.70 (dd, 1H, J = 5.2 Hz, J = 0.8 Hz, ArH), 7.20 (dd, 1H, J = 5.2 Hz, J = 0.8 Hz, ArH), 6.60 (dd, 1H, J = 5.2 Hz, J = 0.8 Hz, ArH), 3.92 (s, 2H, ArH), 1.20 (s, 6H, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 166.86, 146.00, 130.65, 128.68, 116.22 , 81.71, 40.09, 27.10(overlap). Ms (m/z):149 (35.0), 134 (100.0), 106 (18.5), 91 (10.0), 79 (12.3), 73 (20.1), 55 (10.0), 39 (7.5). HRms Calcd for $C_9H_{11}NO$: 149.1125, Found: 149.1141. Anal. Calcd for $C_9H_{11}NO$: C, 72.49; H, 7.44; N, 9.39. Found: C, 72.29; H, 7.38; N, 9.28.

3-Methylfuro[3,2-c]pyridine (5b)

Yield: 40%, oil. Ir (neat): 3080, 2960, 1720, 1620, 1580, 1460, 1300, 1160, 1080, 870, 820, 620 cm^{-1}.

^{1}H Nmr ($CDCl_3$): δ 8.85 (s, 1H, ArH), 8.47 (d, 1H, J = 5.6 Hz, ArH), 7.39 (s, 1H, ArH), 7.37 (d, 1H, J = 5.6 Hz, ArH), 2.30 (s, 3H, -CH_3). ^{13}C Nmr ($CDCl_3$): δ 159.14, 143.94, 142.36, 141.41, 125.60, 114.15, 106.53, 7.31. Ms (m/z): 133 (M^+, 100), 121 (19.0), 104 (21.0), 94 (15.0), 73 (25.0) , 57 (18.0), 41 (22.0). HRms Calcd for C_8H_7ON: 133.0528, Found: 133.0526. Anal. Calcd for C_8H_7NO: C, 72.22; H, 5.30; N, 10.53. Found: C, 72.03; H, 5.17; N, 10.39.

6 -Cyano-3-methylfuro[3,2-c]pyridine (**6b**)

Yield: 55%, mp 138-140 °C (hexane) . Ir (KBr): 2980, 2260, 1570, 1480, 1340, 1280, 1060, 940, 880, 830 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 8.93 (s, 1H, ArH), 7.93 (s, 1H, ArH), 7.63 (s, 1H, ArH), 2.45 (s, 1H, -CH_3). ^{13}C Nmr ($CDCl_3$): δ 158.31, 145.17, 144.02, 128.77, 127.45, 117.79, 115.36, 112.65, 7.01. Ms (m/z): 158 (M^+, 100), 131 (20.0), 103 (21.0), 79 (5.0), 63 (5.0), 51 (7.5). HRms Calcd for $C_9H_6N_2O$:158.2358, Found : 158.2351. Anal. Calcd for $C_9H_6N_2O$: C, 68.32; H, 3.82; N, 17.70. Found: C, 68.05; H, 3.75; N, 17.48.

4-Cyano-3-methylfuro[3,2-c]pyridine (**7b**)

Yield: 35%, mp: 120-122 °C (hexane). Ir (KBr): 2980, 2260, 1570, 1450, 1290, 1080, 1050, 830, 620 cm^{-1}. ^{1}H Nmr ($CDCl_3$) δ 8.60 (d, 1H, J = 5.6 Hz, ArH), 7.60 (d, 1H, J = 5.6 Hz, ArH), 7.55 (s, 1H, ArH), 2.50 (s, 3H, -CH_3). ^{13}C N mr ($CDCl_3$): δ 159.85, 145.10, 144.84, 128.61, 125.66, 116.10, 114.12, 110.20, 7.85. Ms(m/z) :158 (M^+, 100), 130 (23.7), 129 (16.0), 103 (33.7), 76 (15.9). HRms Calcd for $C_9H_6N_2O$: 158.0480, Found : 158.0475. Anal. Calcd for $C_9H_6N_2O$: C, 68.32; H, 3.82; N, 17.70. Found: C, 67.95; H, 3.69; N, 17.52.

6-Cyano-2,3-dimethylfuro[3,2-c]pyridine (**8b**)

Yield: 50%, oil. Ir (neat): 2980, 2250, 1600, 1500, 1470, 1260, 1010, 880, 840 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 8.80 (s, 1H, ArH), 7.75 (s, 1H, ArH), 2.50 (s, 3H, -CH_3), 2.25 (s, 3H, -CH_3). ^{13}C Nmr ($CDCl_3$): δ 158.61, 144.34, 142.24, 126.41, 126.01, 115.36, 109.30, 108.67, 21.49, 7.98. Ms (m/z): 172 (44.6), 157 (25.1), 86 (61.5), 84 (100.0). HRms Calcd for $C_{10}H_8N_2O$: 172.0916, Found: 172.0926. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.79; H, 4.69; N, 16.28. Found: C, 69.48; H, 4.57; N, 16.03.

3,3-Dimethyl-2,3-dihydrofuro[3,2-c]pyridine (**9b**)

Yield: 74%, oil. Ir (neat): 2980, 1620, 1590, 1480, 1260, 1030, 890 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 8.31 (d, 1H, J = 5.4 Hz, ArH), 8.27 (s, 1H, ArH), 6.73 (d, 1H, J = 5.4 Hz, ArH), 4.29 (s, 2H, -OCH_2), 1.39 (s, 6H, -CH_3). ^{13}C Nmr ($CDCl_3$): δ 165.33, 149.30, 143.68, 132.61, 105.44, 84.90, 40.25, 27.32, 27.31. Ms (m/

e):149 (13.5), 134.0 (44.0), 84,0 (100), 50 (18.0), 49 (16.7). HRms Calcd for $C_9H_{11}NO$: 149.1125, Found:149.1132. Anal. Calcd for $C_9H_{11}NO$: C, 72.49; H, 7.44; N, 9.39. Found: C, 71.95; H, 7.25; N, 9.43.

3-Ethylfuro[3,2-c]pyridine (10b)

Yield: 42%, oil. Ir (neat): 3020, 2980, 1620, 1580, 1460, 1440, 1300, 1170, 1080, 870, 810 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 8.87 (s, 1H, ArH), 8.46 (d, 1H, J = 5.6 Hz, ArH), 7.40 (s, 1H, ArH), 7.38 (d, 1H, J = 5.6 Hz, ArH), 2.76 (q, 2H, J = 7.4 Hz, $-CH_2$), 1.34 (t, 3H, J = 7.4 Hz, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 159.50, 144.06, 142.68, 140.73, 125.08, 121.03, 106.83, 16.60, 13.28. Ms (m/z): 147 (33.0), 137 (87.0), 117 (15.0), 105 (100), 91 (14.0), 77 (15.0), 55 (25.5), 41 (10.1). HRms Calcd for C_9H_9NO: 147.0684, Found: 147.0679. Anal. Calcd for C_9H_9NO: C, 73.50; H, 6.16; N, 9.52. Found: C, 72.80; H, 6.05; N, 9.47.

3-Isopropylfuro[3,2-c]pyridine (11b)

Yield: 41%, oil. Ir (neat): 3050, 2990, 1610, 1470, 1370, 1260, 1160, 1080, 1060, 870, 820, 660 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 8.92 (s, 1H, ArH), 8.45 (d, 1H, J = 5.6 Hz, ArH), 7.32 (d, 1H, J = 5.6 Hz, ArH), 7.30 (s, 1H, ArH), 3.21 (m, 1H, $-CH_2$), 1.34 (d, 6H, J = 6.8 Hz, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 159.62, 143.80, 142.95, 139.81, 125.99, 124.45, 106.90, 24.33, 22.20(overlap). Ms (m/z): 161 (110, M^+), 147 (36.1), 120 (14.4), 117 (16.7), 94 (10.6), 89 (20.7), 85 (18.0), 71 (25.8), 69 (38.5), 64 (12.4), 55 (12.5). HRms Calcd for $C_{10}H_{11}NO$: 161.0841, Found: 161.0823. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.57; H, 6.88; N, 8.70. Found: C, 74.38; H, 6.79; N, 8.65.

3-Methylfuro[2,3-c]pyridine (12b)

Yield: 40%, oil. Ir (neat): 3030, 2970, 1620, 1590, 1470, 1300, 1190, 1090, 830 cm^{-1}.

^1H Nmr ($CDCl_3$) δ 8.75 (s, 1H, ArH), 8.30 (d, 1H, J = 5.4 Hz, ArH), 7.45 (s, 1H, ArH), 7.40 (d, 1H, J = 5.4 Hz, ArH), 2.15 (s, 3H, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 144.43, 144.21, 141.81, 141.59, 133.40, 115.02, 114.22, 7.53. HRms Calcd for $C_9H_{11}ON$: 149.1125, Found: 149.1098. Anal .Calcd for $C_9H_{11}NO$: C, 72.49; H, 7.44; N, 9.39. Found: C, 72.04; H, 7.32; N, 9.28.

3-Methylfuro[2,3-c]pyridine (13b)

Yield: 40%, oil. Ir (neat): 3030, 2970, 1600, 1500, 1260, 1230, 1080, 840 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 8.80 (s, 1H, ArH), 8.35 (d, 1H, J = 5.4 Hz, ArH), 7.52 (s, 1H, ArH), 7.42 (d, 1H, J = 5.4 Hz, ArH), 2.55 (q, 2H, J = 7.4 Hz, $-CH_2$), 1.35 (t, 3H, J = 7.4 Hz, $-CH_3$). ^{13}C Nmr ($CDCl_3$): δ 142.98, 141.40, 137.97,

137.80, 123.00, 117.49, 116.86, 30.56, 17.10. HRms Calcd for C_9H_9NO: 147.1167, Found: 147.1153. Anal. Calcd for C_9H_9NO: C, 73.50; H, 6.16; N, 9.52. Found: C, 72.50; H, 6..18; N, 9.41.

3,3-Dimethyl-2,3-dihydrofuro[2,3-c]pyridine **(14b)**

Yield: 55%, oil. Ir (neat): 2980, 1600, 1440, 1210, 1080, 800 cm^{-1}. ^1H Nmr ($CDCl_3$) δ 8.21 (d, 1H, J = 4.8 Hz, ArH), 8.20 (s, 1H, ArH), 7.04 (d, 1H, J = 4.8 Hz, ArH), 4.21(s, 2H, $-OCH_3$). Ms (m/z): 149 (M^+, 17.2), 134 (100), 84 (33.7). HRms Calcd for $C_9H_{11}NO$: 149.1125, Found: 149.1103. Anal. Calcd for $C_9H_{11}NO$: C, 72.49; H, 7.44; N, 9.39. Found: C, 72.06; H, 7.28; N, 9.19.

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REFERENCES

1. P. G. Sammes and J. B. Taylor, *Comprehensive Medicinal Chemistry*, C. J. Drayton, Vol. 6, Pergmon Press Ltd, 1990.
2. J. Prous, N. Mealy, and J. Castaner, *Drugs . Fut*, 1994, **19**, 1018.
3. (a) S. Gronowits, C. Wasterlund, and A. B. Hornfeldt, *Acta Chem. Scand. Ser. B*, 1975, **29**, 233; (b) C. H. McNab, *J. Chem. Soc., Perkin Trans. I*, 1980, 2200; (c) C. L. Hickson and H. McNab, *Synthesis*, **1981**, 464; (d) C. D. Weis, *J. Heterocycl. Chem.*, 1978, ***15***, 1529: (e) S. Shiotani and H. Morit, *J. Heterocycl. Chem.*, 1986, ***23***, 665: (f) H. Morita and S. Shiotani, *J. Heterocycl. Chem*, 1986, ***23***, 1465: (g) H. Moria and S. Shiotani, *J. Heterocycl. Chem.*, 1986, ***23***, 549.
4. (a) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, London, 1985: (b) L. S. Hegedus, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1113: (c) A. Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379: (d) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **1988**, *27*, 2225.
5. (a) T. Sakamoto, Y. Kondo, R. Watanabe, and Y. Yamanaka, *Chem. Pharm. Bull.*, **1986**, *34*, 2719; (b) A. Arcadi, F. Marinelli, and S. Cacchi, *Synthesis*, **1986**, 749.
6. J. Tsuji, Y. Kobayashi, H. Kataoka, and J. Takahashi, *Tetrahedron Lett.*, **1980**, *21*, 1475.
7. A. R. Kataritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Vol. 2, Pergmon Press Ltd. 1984, pp. 346-350.

8. G. Gribble and M. G. Saulnier, *Heterocycles*, **1993**, *35*, 151.

9. R. C. Larock and D. E. Stinn, *Tetrahedron Lett.*, **1988**, *29*, 4687.

10. R. C. Larock and S. Babu, *Tetrahedron Lett.*, **1987**, *28*, 5291.

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