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PALLADIUM-MEDIATED INTRAMOLECULAR BIARYL COUPLING REACTION: CONVENIENT PREPARATION OF FUROQUINOLINONE DERIVATIVES †

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Abstract – Furo[2,3-*c*] or furo[3,2-*c*]quinolinone derivatives were prepared via intramolecular biaryl coupling reaction of 2-furoylanilides or 3-furoylanilides using a palladium catalyst.

Furoquinoline derivatives are widely distributed in nature, which often exhibit interesting biological properties such as antifungal, antibacterial, antiviral, and antimicrobial activities.[1] Therefore, the development of a synthetic method for furoquinolines is an important subject whereas there have been only limited methods known in the literature.[2,3]

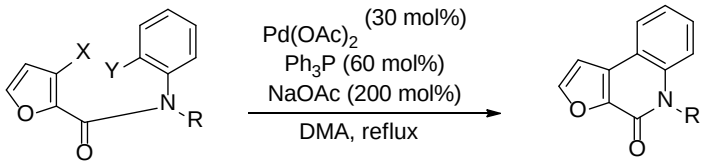
In this context, an intramolecular biaryl coupling reaction using a palladium catalyst[4] must be an efficient technique for the preparation of the furo[2,3-*c*] or furo[3,2-*c*]quinolinone. Although a few examples have been reported for the transformation into these compounds by a palladium-catalyzed reaction,[3] a systematic investigation has never been reported. In this short report, we demonstrate the palladium-mediated biaryl coupling reaction of several types of furoylanilides for the preparation of furoquinolinone derivatives.

We first prepared six furoylanilides (**1a**-**1c** and **2a**-**2c**) as the precursor of the intramolecular coupling reaction. These compounds were easily derived from 2-furancarboxylic acid by the conventional amidation (see experimental section). In Table 1, the coupling reaction was carried out under the conditions of using $Pd(OAc)_2$, Ph_3P, NaOAc, and DMA. Among the employed substrates **1a**-**1c**, which furnish an iodo atom on the side of the anilide moiety, the reaction of the *N*-unsubstituted **1a** did not afford the desired coupling product **3a** (entry 1). On the other hand, *N*-methyl anilide[5] **1b** and *N*-MOM anilide[6] **1c** were transformed into the corresponding furoquinolinones **3b** and **3c**, respectively (entries 2 and 3).

The substrates **2a**-**2c**, which have the iodo atom on the furan ring, were also examined under the same

conditions. Similar to the results of entries 1-3, the unsubstituted compound **2a** did not give the coupling product **3a** (entry 4),[7] whereas the *N*-methyl and *N*-MOM anilides, **2b** and **2c**, were converted into the cyclized products **3b** and **3c**, respectively (entries 5 and 6).

Table 1 Coupling Reaction of 2-Furoylanilides



1a: X = H, Y = I, R = H
1b: X = H, Y = I, R = Me
1c: X = H, Y = I, R = MOM
2a: X = I, Y = H, R = H
2b: X = I, Y = H, R = Me
2c: X = I, Y = H, R = MOM

3a: R = H
3b: R = Me
3c: R = MOM

Entry	Substrate	Time (h)	Product	Yield (%)
1	**1a**	2	**3a**	0
2	**1b**	4	**3b**	51
3	**1c**	1.5	**3c**	59
4	**2a**	2	**3a**	0
5	**2b**	1	**3b**	41
6	**2c**	1	**3c**	62

Next, Table 2 shows the reaction of the other types of substrates, 3-furoylanilides (**4a**-**4c** and **5a**-**5c**). Similar to the results of Table 1, the unsubstituted materials **4a** and **5a** did not produce furoquinolinone **6a** (entries 1 and 4). On the contrary, the *N*-methyl anilides **4b** and **5b**, and *N*-MOM anilides **4c** and **5c** produced the coupling compounds **6b** and **6c**, respectively (entries 2, 3, 5, and 6).

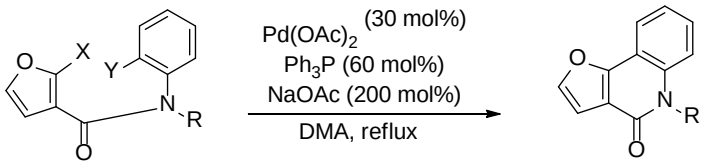
All attempts to obtain the NH products **3a** and **6a** directly from the unsubstituted NH anilides **1a**, **2a**, **4a** and **5a** were unsuccessful. However, when **3c** and **6c** were treated with aqueous acid, the MOM group was smoothly eliminated to afford **3a** and **6a**, respectively (Scheme).

In conclusion, we investigated the Pd-mediated intramolecular coupling reaction of several furoylanilide derivatives. The formation of *N*-substituted furoquinolinones was successful although the NH products were not formed by this procedure. Alternatively, the *N*-MOM derivatives could be transformed into the NH furoquinolinones by treatment with aqueous acid.

EXPERIMENTAL

General Information

Table 2 Coupling Reaction of 3-Furoylanilides



4a: X = H, Y = I, R = H
4b: X = H, Y = I, R = Me
4c: X = H, Y = I, R = MOM
5a: X = I, Y = H, R = H
5b: X = I, Y = H, R = Me
5c: X = I, Y = H, R = MOM

6a: R = H
6b: R = Me
6c: R = MOM

Entry	Substrate	Time (h)	Product	Yield (%)
1	**4a**	2	**6a**	0
2	**4b**	1.5	**6b**	63
3	**4c**	1.5	**6c**	70
4	**5a**	2	**6a**	0
5	**5b**	2	**6b**	66
6	**5c**	1	**6c**	98

Scheme Demethoxymethylation of **3c** and **6c**

Melting points were measured using a Yanagimoto MP-500D micro melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a SHIMADZU FTIR-8400 spectrophotometer. The NMR spectra were obtained using a JEOL α-400 (400 MHz), JNM-ECX500, or JNM-ECP600 instrument. The chemical shifts are given in δ ppm with TMS as the internal standard. The elemental analyses were performed using a Thermo Scientific FlashEA1112 analyzer. The MS were obtained using a JMS-AX505HAD. Silica gel column chromatography was carried out using a Wakogel® C-200.

Preparation of substrates 1a-1c, 2a-2c, 4a-4c, and 5a-5c

***N*-(2-Iodophenyl)-2-furamide (1a)**[8]

A mixture of 2-furancarbonyl chloride (10.4 g, 79.7 mmol), 2-iodoaniline (17.5 g, 79.9 mmol), and CH_2Cl_2 (200 mL) was stirred for 2 h at rt. After extractive work-up with CH_2Cl_2, the organic layer was

washed with brine, dried over $MgSO_4$, and evaporated. The resulting residue was recrystallized from MeOH to give **1a** (16.9 g, 68%). Yellow ocher solid, mp 80.9-83.7˚C (MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.59 (1H, dd, J = 2.0, 3.2 Hz, 4-H), 6.88 (1H, dt, J = 1.2, 7.6 Hz, 4'-H or 5'-H), 7.28 (1H, d, J = 3.2 Hz, 3-H), 7.39 (1H, t, J = 7.6 Hz, 4'-H or 5'-H), 7.58 (1H, d, J = 1.2 Hz, 5-H), 7.82 (1H, dd, J = 1.2, 8.0 Hz, 3'-H or 6'-H), 8.41 (1H, d, J = 6.8 Hz, 3'-H or 6'-H), 8.51 (1H, s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 89.9, 112.8, 115.8, 121.7, 126.1, 129.4, 138.0, 139.0, 144.8, 147.7, 156.1. IR (KBr): ν_{max} 577, 753, 936, 1010, 1163, 1306, 1430, 1531, 1583, 1594, 3113, 3115, 3367 cm^{-1}. *Anal*.Calcd for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 41.99; H, 2.72; N, 4.43.

***N*-(2-Iodophenyl)-*N*-methyl-2-furamide (1b)**

To a suspension of NaH (60%, 7.53 mg, 0.188 mmol) and DMF (1 mL), a solution of **1a** (52.1 mg, 0.166 mmol) in DMF (1 mL) was added, and the mixture was stirred for 1 h. MeI (0.010 ml, 0.161 mmol) was added and the mixture was stirred for 2 h at rt. After quenching the reaction with water and extractive work-up with AcOEt, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The resulting residue was subjected to silica gel column chromatography with AcOEt to produce **1b** (44.6 mg, 82%). Colorless solid, mp 148.3-149.7˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.35 (3H, s, NMe), 5.81 (1H, s, 4-H), 6.20 (1H, s, 3-H), 7.11 (1H, ddd, J = 1.6, 7.2, 7.6 Hz, 4'-H or 5'-H), 7.29 (2H, m, 3'-H or 6'-H, 5-H), 7.42 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, 4'-H or 5'-H), 7.93 (1H, dd, J = 1.6, 7.6 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.1, 99.4, 111.0, 115.9, 129.2, 129.8, 129.9, 140.0, 144.4, 146.0, 146.8, 158.7. IR (KBr): ν_{max} 580, 724, 747, 774, 886, 1007, 1106, 1239, 1304, 1391, 1415, 1472, 1558, 1634, 2860, 2925, 3126 cm^{-1} *Anal*. Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 44.05; H, 3.31; N, 4.08.

***N*-(2-Iodophenyl)-*N*-methoxymethyl-2-furamide (1c)**

To a suspension of NaH (60%, 19.6 mg, 0.49 mmol) and DMF (1.5 mL), a solution of **1a** (50.4 mg, 0.161 mmol) in DMF (1 mL) was added, and the mixture was stirred for 30 min. MOMCl (0.018 ml, 0.24 mmol) was added and the mixture was stirred for 1.5 h at rt. After quenching the reaction with water and extractive work-up with AcOEt, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The resulting residue was subjected to silica gel column chromatography with AcOEt/hexane (1/4) to produce **1c** (31.1 mg, 54%). Colorless solid, mp 92.5-94.5˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.53 (3H, s, OMe), 4.57 (1H, d, J = 10 Hz, 4-H), 5.77 (2H, d, J = 10 Hz, CH_2), 6.23 (1H, s, 3-H), 7.14 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, 4'-H or 5'-H), 7.35 (1H, dd, J = 1.6, 7.6 Hz, 3'-H or 6'-H), 7.38 (1H, s, 5-H), 7.44 (1H, dt, J = 1.6, 7.2 Hz, 4'-H or 5'-H), 7.94 (1H, dd, J = 1.6, 7.6 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 57.4, 79.3, 100.6, 111.5, 117.2, 129.6, 130.3, 131.2, 140.1, 143.6, 145.3, 146.6, 159.6. IR (KBr): ν_{max} 596, 652, 729, 785, 910, 997, 1038, 1078, 1099, 1190, 1304, 1400, 1466,

1556, 1649, 2939, 3117 cm^{-1}. *Anal*.Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.81; H, 3.59; N, 3.89.

3-Iodofuran-2-carboxylic acid[9]

A solution of furan-2-carboxylic acid (5.01 g, 44.7 mmol) in THF (90 mL) was dropwise added at -78 ^oC to a solution of LDA (96.3 mmol) in THF (200 mL). After 1 h, TMSCl (6.80 ml, 53.6 mmol) was dropwise added, and then the mixture was allowed to warm to rt. The reaction mixture was stirred for 2.5 h at the same temperature, and quenched with a 5*N* HCl aqueous solution (10 mL). After extractive work-up with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a solid material which was recrystallized from $CHCl_3$. The colorless solid of 5-trimethylsilyl-furan-2-carboxylic acid (7.61 g, 92%) was obtained.

To a solution of the above compound (7.59 g, 41.2 mmol) in THF, *n*BuLi (61.0 ml, 97.0 mmol, 1.59 M in hexane) was dropwise added at -78 ^oC. After 1 h, a solution of I_2 (15.7 g, 61.9 mmol) in THF (160 mL) was dropwise added to the mixture at the same temperature, then the mixture was allowed to warm to rt and left to stand for 7 h. The reaction was quenched with a sat. NH_4Cl aqueous solution. After extractive work-up with Et_2O, the organic layer was successively washed with a $Na_2S_2O_3$ aqueous solution and brine, dried over $MgSO_4$, and evaporated. The resulting residue was subjected to silica gel column chromatography with Et_2O/AcOH/hexane (50:5:400) to give a brown solid of 2-iodo-3-trimethylsilyl-furan-2-carboxylic acid (8.88 g, 69%).

A mixture of the above compound (8.83 g, 28.5 mmol), THF (120 mL), and TBAF (1M in THF, 62.5 mL, 62.5 mmol) was heated for 10 h under reflux. After cooling, a 1*N* H_2SO_4 aqueous solution was added to the mixture. The mixture was extracted with ether, and the organic layer was successively washed with $Na_2S_2O_3$ aqueous solution and brine, dried over $MgSO_4$, and evaporated. The crude product was subjected to silica gel column chromatography with $CHCl_3$/AcOH/hexane (50:5:450) to give a solid which was further recrystallized from $CHCl_3$. The title compound (4.91 g, 72%) was obtained as colorless crystallines, mp 161.3-163.3˚C ($CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.75 (1H, d, J = 2.0 Hz, 4-H), 7.57 (1H, d, J = 1.6 Hz, 5-H). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.87 (1H, d, J = 1.6 Hz, 4-H), 7.89 (1H, d, J = 2.0 Hz, 5-H), 13.3 (1H, s, -COOH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 75.8, 121.4, 144.0, 147.8, 159.1. IR (KBr): ν_{max} 762, 789, 887, 976, 1072, 1202, 1288, 1481, 1560, 1682 cm^{-1}. *Anal*.Calcd for $C_5H_3IO_3$: C, 25.23; H, 1.27. Found: C, 25.31; H, 1.05.

***N*-Phenyl-2-(3-iodo)furamide** (**2a**)

A mixture of 3-iodofuran-2-carboxylic acid (100 mg, 0.420 mmol), aniline (0.0480 mL, 0.526 mmol), EDC (124 mg, 0.646 mmol), DMAP (28.2 mg, 0.231 mmol), and CH_2Cl_2 (4 mL) was stirred for 1 h at rt. The mixture was successively washed with a 10% HCl, a 10% NaOH aqueous solution, and brine, then

dried over $MgSO_4$, and evaporated. The resulting residue was subjected to silica gel column chromatography with CH_2Cl_2/ AcOEt /hexane (1/1/16) to give **2a** (122 mg, 93%), a colorless solid, mp 119.9-121.6˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.73 (1H, d, J = 2.0 Hz, 4-H), 7.15 (1H, t, J = 7.2 Hz, 4'-H), 7.36 (2H, t, J = 8.4, 3', 5'-H), 7.48 (1H, d, J = 1.6 Hz, 5-H), 7.66 (2H, dd, J = 0.8, 8.4 Hz, 2', 6'-H), 8.12 (1H, s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 70.5, 120.0, 122.0, 124.8, 129.2, 137.3, 145.0, 155.7. IR (KBr): ν_{max} 505, 691, 745, 1061, 1184, 1321, 1483, 1572, 1601, 1653, 2332, 3123, 3244 cm^{-1}. *Anal*.Calcd for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 42.33; H, 2.26; N, 4.37.

***N*-Methyl-*N*-phenyl-2-(3-iodo)furamide** (**2b**)

By the same procedure used for the preparation of **1b**, **2b** (44.6 mg, 82%) was obtained from **2a** (52.1 mg, 0.166 mmol), a colorless solid, mp 148.3-149.7˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.35 (3H, s, NMe), 5.81 (1H, s, 4-H), 6.20 (1H, s, 3-H), 7.11 (1H, ddd, J = 1.6, 7.2, 7.6 Hz, 4'-H or 5'-H), 7.29 (2H, m, 3'-H or 6'-H, 5-H), 7.42 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, 4'-H or 5'-H), 7.93 (1H, dd, J = 1.6, 7.6 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.1, 99.4, 111.0, 115.9, 129.2, 129.8, 129.9, 140.0, 144.4, 146.0, 146.8, 158.7. IR (KBr): ν_{max} 580, 724, 747, 774, 886, 1007, 1106, 1239, 1304, 1391, 1415, 1472, 1558, 1634, 2860, 2925, 3126 cm^{-1}. *Anal*.Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 44.05; H, 3.31; N, 4.08.

***N*-Methoxymethyl-*N*-phenyl-2-(3-iodo)furamide** (**2c**)

By the same procedure used for the preparation of **1c**, **2c** (80.8 mg, 73%) was obtained from **2a** (96.9 mg, 0.310 mmol), yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.50 (3H, s, OMe), 5.24 (2H, s, CH_2), 6.48 (1H, d, J = 1.6 Hz, 4-H), 7.03 (1H, d, J = 2.0 Hz, 5-H), 7.15-7.17 (2H, m, 2', 6'-H), 7.23-7.27 (1H, m, 4'-H), 7.28-7.33 (2H, m, 3', 5'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.7, 71.5, 79.8, 120.1, 126.5, 127.1, 129.0, 141.9, 144.4, 146.4, 160.3. IR (neat): ν_{max} 598, 700, 749, 887, 912, 957, 1069, 1097, 1194, 1296, 1379, 1495, 1595, 1651, 2937 cm^{-1}. *Anal*.Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 44.03; H, 3.21; N, 3.75.

***N*-(2-Iodophenyl)-3-furamide** (**4a**)[3c,5a]

A mixture of furan-3-carboxylic acid (4.01 g, 35.8 mmol), $SOCl_2$ (11.5 ml, 159 mmol), DMF (0.28 ml, 3.62 mmol), and CH_2Cl_2 (35 ml) was heated for 1 h under reflux. After the volatile materials were removed in vacuo, a solution of 2-iodoaniline (10.4 g, 47.5 mmol), Et_3N (6.76 ml, 48.5 mmol) in CH_2Cl_2 (95 ml) was dropwise added at 0 ^{o}C. The mixture was allowed to warm to rt and stirred for 2 h. After cooling to 0 ^{o}C, the mixture was acidified by a 10% HCl aqueous solution and extracted with CH_2Cl_2. The organic layer was successively washed with water, a 10% NaOH aqueous solution, and brine. The solution was dried over $MgSO_4$ and evaporated to give a residue which was recrystallized from MeOH. A yellow ocher solid of **4a** (10.8 g, 96%) was obtained, mp 94.5-95.5˚C (MeOH) [lit.[5a] mp 93-94˚C

(diisopropyl ether), lit.[3c] mp 95-97˚C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.80 (1H, dd, J = 1.2, 2.0 Hz, 4-H), 6.88 (1H, ddd, J = 1.2, 7.6, 8.0 Hz, 4'-H or 5'-H), 7.39 (1H, ddd, J = 1.2, 7.6, 8.0 Hz, 4'-H or 5'-H), 7.52 (1H, t, J = 1.6 Hz, 5-H), 7.80 (1H, dd, J = 1.6, 8.0 Hz, 3'-H or 6'-H), 7.89 (1H, s, NH), 8.10 (1H, dd, J = 1.2, 1.6 Hz, 2-H), 8.39 (1H, dd, J = 1.2, 8.4 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 90.2, 108.4, 121.9, 123.1, 126.1, 129.6, 138.1, 138.9, 144.4, 145.5, 160.5. IR (KBr) ν_{max} 748, 860, 1015, 1070, 1161, 1323, 1433, 1516, 1578, 1659, 2300, 3150, 3317 cm^{-1}. *Anal*.Calcd for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 42.47; H, 2.80; N, 4.41.

***N*-(2-Iodophenyl)-*N*-methyl-3-furamide (4b)** [3c,5a]

By the same procedure used for the preparation of **1b**, **4b** (223 mg, 74%) was obtained from **4a** (287 mg, 0.917 mmol), a brown solid, mp 90.1-90.5˚C (AcOEt) [lit.[5a] mp 81-83˚C (diisopropyl ether), lit.[3c] mp 80-82˚C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.32 (3H, s, NMe), 6.20 (1H, s, 4-H), 6.79 (1H, s, 5-H), 7.12 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, 4'-H or 5'-H), 7.16 (1H, s, 2-H), 7.30 (1H, dd, J = 1.2, 8.0 Hz, 3'-H or 6'-H), 7.42 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, 4'-H or 5'-H), 7.93 (1H, dd, J = 1.6, 7.6 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.1, 100.0, 111.0, 121.9, 129.8, 130.0, 130.3, 140.4, 142.3, 145.3, 146.3, 163.1. IR (KBr): ν_{max} 572, 598, 750, 739, 842, 876, 1009, 1153, 1359, 1391, 1426, 1469, 1509, 1565, 2921, 3137 cm^{-1}. *Anal*.Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 43.98; H, 3.29; N, 4.15.

***N*-(2-Iodophenyl)-*N*-methoxymethyl-3-furamide (4c)**

By the same procedure used for the preparation of **1c**, **4c** (1.14 g, 87%) was obtained from **4a** (1.11 g, 3.54 mmol), brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.51 (3H, s, OMe), 4.53 (1H, d, J = 10.0 Hz), 5.76 (1H, d, J = 9.6 Hz), 6.28 (1H,s), 6.72 (1H, s), 7.15 (1H, t, J = 7.6 Hz), 7.20 (1H, s), 7.35-7.37 (1H, m), 7.45 (1H, dt, J = 1.2, 8.0, 7.6 Hz, 4'-H or 5'-H), 7.95 (1H, dd, J = 1.2 Hz, 8.0 Hz, 3'-H or 6'-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 57.2, 79.1, 100.9, 111.2, 121.6, 129.7, 130.6, 131.6, 140.2, 142.4, 143.5, 145.7, 163.7. IR (neat) ν_{max} 598, 729,750, 876, 1020, 1076, 1107, 1205, 1315, 1381, 1470, 1508, 1651, 2937 cm^{-1}. *Anal*.Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.47; H, 3.69; N, 3.94.

2-Iodofuran-3-carboxylic acid[10]

A solution of furan-3-carboxylic acid (4.41 g, 39.3 mmol) in THF (40 mL) was dropwise added to a solution of *n*BuLi (55.0 ml, 9.07 mol, 1.65 M in hexane) in THF at -78 ^{o}C. The mixture was allowed to warm to rt and stirred for 30 min. After cooling to -78 ^{o}C, a solution of I_2 (11.0 g, 43.3 mmol) in THF (60 mL) was dropwise added to the mixture, then the mixture was warmed to rt and allowed to stand for 2 h. After a 10% HCl aqueous solution was added to acidify the mixture, an extractive work-up with Et_2O was carried out. The organic layer was successively washed with $Na_2S_2O_3$ and brine, then dried over $MgSO_4$. After evaporation, the resulting residue was subjected to silica gel column chromatography with

AcOH/1,1,2,2-tetrachloroethane (1/100) to give a colorless solid of the title compound (5.77 g, 62%), mp 168.2-170.0˚C ($CHCl_3$) [lit.[10] mp 148-150˚C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.79 (1H, d, J = 2.0 Hz, 4-H), 7.61 (1H, d, J = 2.0 Hz, 5-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 99.9, 112.9, 123.6, 148.7, 167.9. IR (KBr): ν_{max} 741, 889, 1180, 1312, 1501, 1564, 1690 cm^{-1}. *Anal*.Calcd for $C_5H_3IO_3$: C, 25.23; H, 1.27. Found: C, 25.32; H, 1.45.

***N*-Phenyl-3-(2-iodo)furamide** (**5a**)

A mixture of 2-iodofuran-3-carboxylic acid (1.01 g, 4.24 mmol), aniline (0.460 mL, 5.04 mmol), EDC (1.22 g, 6.36 mmol), DMAP (258 mg, 2.11 mmol), and CH_2Cl_2 (20 mL) was stirred for 30 min at rt. The mixture was successively washed with a 10% HCl, a 10% NaOH aqueous solution, and brine, then dried over $MgSO_4$, and evaporated. The resulting residue was subjected to silica gel column chromatography with CH_2Cl_2/ hexane (1/8) to give **5a** (1.25 g, 94%), a colorless solid, mp 140.8-142.0˚C (CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.82 (1H, d, J = 2.4 Hz, 4-H), 7.16 (1H, dt, J = 0.8, 7.0 Hz, 4'-H), 7.37 (2H, t, J = 7.0 Hz, 3', 5'-H), 7.62-7.64 (2H, m, 2', 6'-H), 7.65 (1H, d, J = 2.4 Hz, 5-H), 7.82 (1H, s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 92.8, 112.1, 120.2, 124.9, 127.6, 129.2, 137.5, 148.6, 159.6. IR (KBr): ν_{max} 583, 598, 687, 752, 804, 889, 1051, 1161, 1325, 1441, 1479, 1520, 1560, 1595, 1651, 2359, 3101, 3323 cm^{-1}. *Anal*.Calcd for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 42.28; H, 2.44; N, 4.56.

***N*-Methyl-*N*-phenyl-3-(2-iodo)furamide** (**5b**)

By the same procedure used for the preparation of **1b**, **5b** (107 mg, 98%) was obtained from **5a** (104 mg, 0.332 mmol), a colorless solid, mp 130.8-132.7˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.45 (3H, s, NMe), 5.63 (1H, s), 7.13 (2H, dd, J = 1.2, 8.2 Hz), 7.24-7.27 (2H, m), 7.30-7.34 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 38.0, 95.0, 112.1, 127.1, 127.3, 127.4, 129.4, 143.9, 147.0, 163.6. IR (KBr): ν_{max} 557, 600, 700, 746, 766, 847, 887, 970, 1040, 1146, 1304, 1371, 1493, 1568, 1597, 1638, 2934, 3146 cm^{-1}. *Anal*.Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 44.37; H, 2.89; N, 4.16.

***N*-Methoxymethyl-*N*-phenyl-3-(2-iodo)furamide** (**5c**)

By the same procedure used for the preparation of **1c**, **5c** (2.00 g, 88%) was obtained from **5a** (2.00 g, 6.39 mmol), yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomers based on the amide bond) δ: 3.49 (3H, s, OMe), 5.22 (s), 5.66 (brs), 7.17 (2H, m), 7.24-7.33 (4H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.8, 79.7, 96.1, 112.0, 126.9, 127.7, 127.8, 129.4, 141.9, 147.1, 164.5. IR (neat): ν_{max} 610, 702, 749, 887, 912, 1043, 1072, 1113, 1209, 1304, 1379, 1485, 1595, 1651 cm^{-1}. *Anal*.Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.93; H, 3.46; N, 3.70.

Typical procedure of the Pd-mediated coupling reaction (Table 1, Entry 2)

5-Methylfuro[2,3-*c*]quinolin-4(5*H*)-one (**3b**)[3b]

A mixture of **1b** (50.2 mg, 0.153 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0486 mmol), Ph_3P (24.5 mg, 0.0934 mmol), NaOAc (25.1 mg, 0.306 mmol), and DMF (2.5 mL) was heated for 4 h at 170 ^oC. After an extractive work-up with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to silica gel column chromatography with hexane/AcOEt (2/1). A reddish brown solid of **3b** (15.7 mg, 51%) was obtained, mp 124.8-126.4˚C [lit.[3b] mp 140-142˚C ($CHCl_3$)]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.85 (3H, s, NMe), 7.08 (1H, d, J = 2.0 Hz, 1-H), 7.35 (1H, t, J = 7.2 Hz, 7-H or 8-H), 7.48 (1H, d, J = 8.4 Hz, 6-H or 9-H), 7.57 (1H, ddd, J = 2.0, 8.8, 8.0 Hz, 7-H or 8-H), 7.84 (1H, d, J = 1.6 Hz, 2-H), 7.87 (1H, dd, J = 1.6, 7.6 Hz, 6-H or 9-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.4, 105.9, 115.3, 116.5, 122.6, 124.5, 128.8, 129.4, 138.0, 142.4, 148.1, 153.8. IR (KBr): ν_{max} 427, 597, 621, 744, 806, 1013, 1093, 1147, 1235, 1326, 1434, 1490, 1586, 1665, 2971, 2890, 3095 cm^{-1}. *Anal.*Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.40; H, 4.66; N, 7.02.

5-(Methoxymethyl)furo[2,3-*c*]quinolin-4(5*H*)-one (**3c**)

A colorless solid, mp 128.4-130.0˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.46 (3H, s, OMe), 5.87 (2H, s, CH_2), 7.08 (1H, d, J = 2.0 Hz, 1-H), 7.35 (1H, t, J = 7.2 Hz, 7-H or 8-H), 7.54 (1H, ddd, J = 1.6, 8.0, 8.0 Hz, 7-H or 8-H), 7.68 (1H, d, J = 8.4 Hz, 6-H or 9-H), 7.84-7.87 (2H, m, 6-H or 9-H, 2-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.6, 73.1, 106.1, 116.5, 116.8, 123.2, 124.5, 129.1, 130.7, 137.3, 141.8, 148.8, 154.5. IR (KBr): ν_{max} 598, 683, 752, 797, 897, 961, 1030, 1084, 1219, 1437, 1456, 1491, 1589, 1668, 2814, 3105 cm^{-1}. *Anal.*Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.90; H, 4.94; N, 6.10.

5-Methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**6b**)[2e, 2f, 2g, 2h, 3c, 5a]

A reddish brown solid, mp 126.5-128.5˚C (AcOEt-CH_2Cl_2) [lit.[3c] mp 126-128˚C, lit.[2h] mp 132-133˚C, lit.[5a] mp 132-134˚C (diisopropyl ether), lit.[2g] mp 134-135˚C, lit.[2f] mp 129-130˚C, lit.[2e] mp 132-134˚C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.77 (3H, s, NMe), 7.06 (1H, d, J = 2.4 Hz, 3-H), 7.29 (1H, t, J = 6.8 Hz, 7-H or 8-H), 7.42 (1H, d, J = 8.8 Hz, 6-H or 9-H), 7.53 (1H, ddd, J = 1.2, 8.0, 8.0 Hz, 7-H or 8-H), 7.61 (1H, d, J = 2.4 Hz, 2-H), 7.98 (1H, d, J = 8.0 Hz, 6-H or 9-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.6, 108.5, 113.3, 115.1, 115.5, 121.3, 122.4, 129.6, 138.2, 144.1, 155.2, 159.6. IR (KBr): ν_{max} 669, 743, 964, 1022, 1105, 1124, 1231, 1319, 1360, 1439, 1504, 1585, 1649, 2926, 3121 cm^{-1}. *Anal.*Calcd for $C_{12}H_9NO_2$: C, 72.35; H,4.55; N, 7.03. Found: C, 72.09; H, 4.71; N, 6.98.

5-(Methoxymethyl)furo[3,2-*c*]quinolin-4(5*H*)-one (**6c**)

A colorless solid, mp 107.2-108.8˚C (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.45 (3H, s, OMe), 5.84 (2H, s, CH_2), 7.07 (1H, d, J = 2.4 Hz, 3-H), 7.34 (1H, dt, J = 1.2, 7.6 Hz, 7-H or 8-H), 7.55 (1H, ddd, J = 1.6, 8.0, 8.0 Hz, 7-H or 8-H), 7.64-7.68 (2H, m, 2-H, 6-H or 9-H), 8.01 (1H, dd, J = 1.2, 8.0 Hz, 6-H or

9-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.5, 73.1, 108.5, 113.5, 114.8, 116.3, 121.2, 123.1, 129.8, 137.5, 144.3, 155.9, 160.2. IR (KBr): ν_{max} 756, 910, 1074, 1099, 1123, 1171, 1207, 1308, 1443, 1504, 1585, 1688, 2950, 3150 cm^{-1}. *Anal*.Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.89; H, 4.95; N, 6.10.

Removal of methoxymethyl group

Furo[2,3-*c*]quinolin-4(5*H*)-one (**3a**)[2d]

A mixture of **3c** (51.4 mg, 0.224 mmol), conc.HCl (10 mL), and DME (10 mL) was stirred for 2 h at 85 ^{o}C. After neutralization with a 10% NaOH aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a solid which was recrystallized from AcOEt. The colorless solid of **3a** (28.2 mg, 68%) was obtained, mp 261.0-262.2˚C (EtOAc) [lit.[2d] mp 282.5-283˚C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.13 (1H, d, J = 2.0 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.51 (1H, t, J = 8.0 Hz), 7.58 (1H, d, J = 8.4 Hz), 7.85 (1H, d, J = 7.6 Hz), 7.90 (1H, d, J = 1.6 Hz), 11.5 (1H, s, NH). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.26 (1H, t, J = 6.8 Hz), 7.42-7.47 (3H, m), 7.99 (1H, d, J = 7.6 Hz), 8.23 (1H, s), 11.9 (1H, s, NH). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 106.4, 116.2, 117.0, 123.2, 124.0, 128.9, 131.8, 136.4, 142.4, 148.7, 155.0. ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 106.8, 115.5, 116.2, 122.3, 124.3, 128.7, 130.7, 136.9, 142.2, 149.3, 153.2. IR (KBr): ν_{max} 449, 592, 654, 692, 750, 791, 887, 1059, 1213, 1337, 1435, 1489, 1558, 1670, 2363, 2883 cm^{-1}. *Anal*.Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 70.97; H, 4.00; N, 7.46.

Furo[3,2-*c*]quinolin-4(5*H*)-one (**6a**)[1a,2a,2b,2c,2f,2h]

A mixture of **6c** (25.9 mg, 0.113 mmol), conc.HCl (3 mL), and DME (3 mL) was stirred for 1.5 h at 85 ^{o}C. After neutralization with a 10% NaOH aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a solid which was subjected to silica gel column chromatography with AcOEt /hexane (1/1). The colorless solid of **6a** (17.8 mg, 85%) was obtained, mp (decomp.) 186.0-189.0˚C (AcOEt) [lit.[2f,2h] mp 249-250˚C (EtOH), lit.[2c] mp 245-247˚C, lit.[2b] mp 232-233˚C, lit.[2a] mp 247-249˚C. lit.[1a] mp 243-245˚C]. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.13 (1H, d, J = 1.8 Hz), 7.31 (1H, ddd, J = 1.2, 6.0, 6.0 Hz,), 7.48-7.53 (2H, m), 7.68 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 7.8 Hz), 11.0 (1H, s, NH). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.06 (1H, d, J = 2.0 Hz, 3-H), 7.27 (1H, dt, J = 1.2, 7.6 Hz, 7-H or 8-H), 7.44 (1H, d, J = 8.0 Hz, 6-H or 9-H), 7.50 (1H, ddd, J = 1.2, 8.0, 7.6 Hz, 7-H or 8-H), 7.90 (1H, d, J = 7.6 Hz, 6-H or 9-H), 8.08 (1H, d, J = 2.0 Hz, 2-H), 11.7 (1H, s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 108.0, 112.5, 115.7, 116.5, 120.9, 123.1, 129.7, 136.7, 144.4, 157.0, 161.0. ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 107.9, 111.4, 115.7, 116.2, 120.3, 122.5, 129.6,

137.2, 145.6, 155.5, 159.0. IR (KBr): ν_{max} 461, 669, 752, 889, 1022, 1196, 1265, 1362, 1437, 1674, 2361, 2891, 3115 cm^{-1}. HRMS (EI) Calcd for $C_{11}H_7NO_2$ $[M]^+$: 185.0477. Found: 185.0480.

REFERENCES AND NOTES

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1. (a) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp, and M. F. Tymoschenko, *Org. Lett*., 2003, **5**, 301; (b) M. F. Grundon, *Nat. Prod. Rep.*, 1990, **7**, 131; (c) J. P. Michael, *Nat. Prod. Rep.*, 1997, **14**, 605.
2. (a) F. Piozzi, P. Venturella, and A. Bellino, *Org. Prep. Proc.*, 1971, **3**, 223; (b) S. Gronowitz and G. Timari, *J. Heterocycl. Chem*., 1990, **27**, 1159; (c) B. B. Sinder and X. Wu, *Heterocycles*, 2006, **70**, 279; (d) Y. Kanaoka and K. Itoh, *Synthesis*, 1971, 36. (e) H. Tuppy and F. Böhm, *Monatsh. Chem*., 1956, **87**, 735; (f) M. F. Grundon, N. J. McCorkindale, and M. N. Rodger, *J. Chem. Soc*., 1955, 4284; (g) Y. R. Lee, B. S. Kim, and H. I. Kweon, *Tetrahedron*, 2000, **56,** 3867; (h) T. Ohta and Y. Mori, *Pharm. Bull*., 1956, **4**, 415.
3. (a) K.-F. Lindahl, A. Carroll, R. J. Quinn, and J. A. Ripper, *J. Heterocycl. Chem*., 2010, **47**, 998; (b) L.-C. Campeau., M. Parisien, A. Jean, and K. Fagnou, *J. Am. Chem. Soc*., 2006, **128**, 581; (c) K.-F. Lindahl, A. Carroll, R. J. Quinn, and J. A. Ripper, *Tetrahedron. Lett.*, 2006, **47**, 7493.
4. H. Abe and T. Harayama, *Heterocycles*, 2008, **75**, 1305.
5. (a) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, and C. Zoni, *Eur. J. Org. Chem*. 2005, 2091; (b) H. Iwasaki, T. Eguchi, N. Tsutsui, H. Ohno, and T. Tanaka, *J. Org. Chem*., 2008, **73**, 7145.
6. (a) T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, and Y. Takeuchi, *J. Chem. Soc., Perkin Trans. 1*, 2001, 523; (b) H. Abe, N. Kobayashi, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2010, **80**, 873; (c) T. Harayama, T. Sato, Y. Nakano, H. Abe, and Y. Takeuchi, *Heterocycles*, 2003, **59**, 293.
7. D. E. Ames and A. Opalko, *Tetrahedron*, 1984, **40**, 1919.
8. X. Diao, Y. Wang, Y. Jiang, and D. Ma, *J. Org. Chem*., 2009, **74**, 7974.
9. (a) T. Dey, D. Navarathne, M. A. Invernale, I. D. Berghorn, and G. A. Sotzing, *Tetrahedron Lett*., 2010, **51**, 2089; (b) J.-M. Duffault and F. Tellier, *Synth. Commun.*, 1998, **28**, 2467.
10. K. Kolodziejczyk, G. D. Roiban, M. Schnürch, M. D. Mihovilovic, and P. Stanetty, *Monatsh. Chem*., 2009, **140**, 1349.