

HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 1332 - 1342. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 15th July, 2014, Accepted, 4th August, 2014, Published online, 19th August, 2014
DOI: 10.3987/COM-14-S(K)84

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

Hitoshi Abe,* Mayu Kamimura, Yoshinori Komatsu, and Yoshikazu Horino

Graduate School of Science and Engineering, University of Toyama, 930-8555
Japan; E-mail: abeh@eng.u-toyama.ac.jp

Abstract – Furo[2,3-*c*] or furo[3,2-*c*]quinolinone derivatives were prepared via the 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}

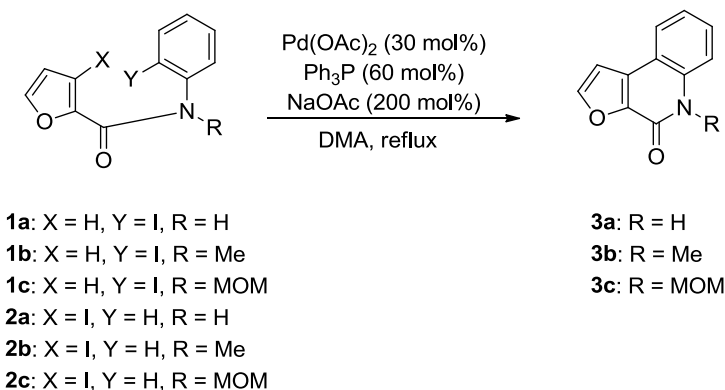
In this context, an intramolecular biaryl coupling reaction using a palladium catalyst⁴ must be an efficient technique for the preparation of the furo[2,3-*c*] or furo[3,2-*c*]quinolinone. Although a few examples have been reported for the transformation into these compounds by a palladium-catalyzed 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, Ph₃P, 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 anilide⁵ **1b** and *N*-MOM anilide⁶ **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

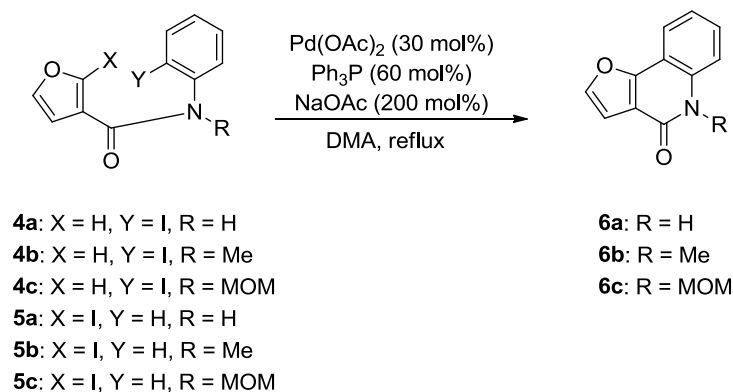


Entry	Substrate	Time (h)	Product	Yield (%)
1	1a	2	3a	0
2	1b	4	3b	51
3	1c	1.5	3c	59
4	2a	2	3a	0
5	2b	1	3b	41
6	2c	1	3c	62

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*-methylanilides **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.

Table 2. Coupling Reaction of 3-Furoylanilides

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****EXPERIMENTAL****General Information**

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-furancarboxyl 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). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $\text{C}_{11}\text{H}_8\text{INO}_2$: 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). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $\text{C}_{12}\text{H}_{10}\text{INO}_2$: 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). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $\text{C}_{13}\text{H}_{12}\text{INO}_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.81;

H, 3.59; N, 3.89.

3-Iodofuran-2-carboxylic acid⁹

A solution of furan-2-carboxylic acid (5.01 g, 44.7 mmol) in THF (90 mL) was dropwise added at $-78\text{ }^{\circ}\text{C}$ 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 5N HCl aqueous solution (10 mL). After extractive work-up with Et₂O, the organic layer was washed with brine, dried over MgSO₄, and evaporated to give a solid material which was recrystallized from CHCl₃. 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 $-78\text{ }^{\circ}\text{C}$. After 1 h, a solution of I₂ (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. NH₄Cl aqueous solution. After extractive work-up with Et₂O, the organic layer was successively washed with a Na₂S₂O₃ aqueous solution and brine, dried over MgSO₄, and evaporated. The resulting residue was subjected to silica gel column chromatography with Et₂O/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 1N H₂SO₄ aqueous solution was added to the mixture. The mixture was extracted with ether, and the organic layer was successively washed with Na₂S₂O₃ aqueous solution and brine, dried over MgSO₄, and evaporated. The crude product was subjected to silica gel column chromatography with CHCl₃/AcOH/hexane (50:5:450) to give a solid which was further recrystallized from CHCl₃. The title compound (4.91 g, 72%) was obtained as colorless crystallines, mp 161.3-163.3 °C (CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ : 6.75 (1H, d, *J* = 2.0 Hz, 4-H), 7.57 (1H, d, *J* = 1.6 Hz, 5-H). ¹H-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). ¹³C-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 C₅H₃IO₃: 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 CH₂Cl₂ (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 MgSO₄, and evaporated. The resulting residue was subjected to silica gel column chromatography with CH₂Cl₂/AcOEt/hexane (1/1/16) to give **2a** (122 mg, 93%), a colorless solid, mp

119.9-121.6 °C (AcOEt). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₁H₈INO₂: 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). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₀INO₂: 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. ¹H-NMR (400 MHz, CDCl₃) δ: 3.50 (3H, s, OMe), 5.24 (2H, s, CH₂), 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₁₂INO₃: 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), SOCl₂ (11.5 mL, 159 mmol), DMF (0.28 mL, 3.62 mmol), and CH₂Cl₂ (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), Et₃N (6.76 mL, 48.5 mmol) in CH₂Cl₂ (95 mL) was dropwise added at 0 °C. The mixture was allowed to warm to rt and stirred for 2 h. After cooling to 0 °C, the mixture was acidified by a 10% HCl aqueous solution and extracted with CH₂Cl₂. The organic layer was successively washed with water, a 10% NaOH aqueous solution, and brine. The solution was dried over MgSO₄ 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]. ¹H-NMR (400 MHz, CDCl₃) 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 $\text{C}_{11}\text{H}_8\text{INO}_2$: 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]. ^1H -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 $\text{C}_{12}\text{H}_{10}\text{INO}_2$: 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. ^1H -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 $\text{C}_{13}\text{H}_{12}\text{INO}_3$: 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 °C. The mixture was allowed to warm to rt and stirred for 30 min. After cooling to -78 °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 $\text{Na}_2\text{S}_2\text{O}_3$ 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]. ^1H -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 $\text{C}_5\text{H}_3\text{IO}_3$: 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 CH₂Cl₂ (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 MgSO₄, and evaporated. The resulting residue was subjected to silica gel column chromatography with CH₂Cl₂/ hexane (1/8) to give **5a** (1.25 g, 94%), a colorless solid, mp 140.8-142.0 °C (CH₂Cl₂). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₁H₈INO₂: 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). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₀INO₂: 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. ¹H-NMR (400 MHz, CDCl₃) (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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₁₂INO₃: 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), Ph₃P (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 °C. After an extractive work-up with CH₂Cl₂, the organic layer was washed with brine, dried over MgSO₄, 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 (CHCl₃). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₉NO₂: 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). ¹H-NMR (400 MHz, CDCl₃) δ: 3.46 (3H, s, OMe), 5.87 (2H, s, CH₂), 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₁₁NO₃: 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-CH₂Cl₂) [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]. ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₉NO₂: 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). ¹H-NMR (400 MHz, CDCl₃) δ: 3.45 (3H, s, OMe), 5.84 (2H, s, CH₂), 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₁₁NO₃: 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 °C. After neutralization with a 10% NaOH aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, 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]. ¹H-NMR (400 MHz, CDCl₃) 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). ¹H-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). ¹³C-NMR (150 MHz, CDCl₃) δ: 106.4, 116.2, 117.0, 123.2, 124.0, 128.9, 131.8, 136.4, 142.4, 148.7, 155.0. ¹³C-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 C₁₁H₇NO₂: 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 °C. After neutralization with a 10% NaOH aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, 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]. ¹H-NMR (600 MHz, CDCl₃) 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). ¹H-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). ¹³C-NMR (100 MHz, CDCl₃) δ: 108.0, 112.5, 115.7, 116.5, 120.9, 123.1, 129.7, 136.7, 144.4, 157.0, 161.0. ¹³C-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 C₁₁H₇NO₂ [M]⁺: 185.0477. Found: 185.0480.

REFERENCES AND NOTES

† Dedicated to Professor Isao Kuwajima for the celebration of his 77th birthday

- (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.
- (a) F. Piozzi, P. Venturella, and A. Bellino, *Org. Prep. Proced. Int.*, **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. Brogini, 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.