Synthesis of Spiroisoindolinones by Palladium-Catalyzed Heterocyclization of 2-Iodobenzoyl Chloride with Ketimines

Chan Sik Cho, Xue Wu, Li Hong Jiang, Sang Chul Shim* [a] and Hong Rak Kim [b]

[a] Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea
[b] Department of Industrial Chemistry, Andong Institute of Information Technology, Andong 760-830, Korea

Received August 31, 1998

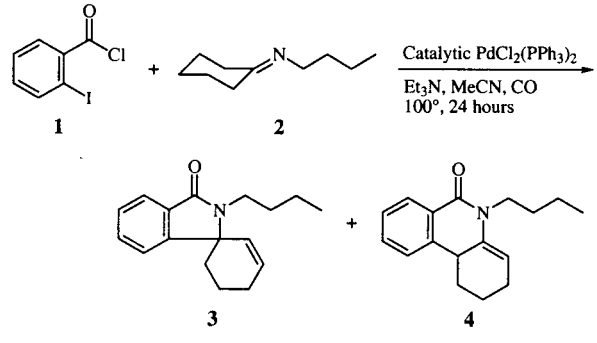
2-Iodobenzoyl chloride reacts with ketimines in acetonitrile at 100° under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst together with triethylamine to afford the corresponding spiroisoindolinones in high yields.

J. Heterocyclic Chem., **36**, 297 (1999).

It is well-known that several isoindolinones (phthalimidines) such as staurosporine, indoprofen, and DN-2327 exert a broad spectrum of physiological activities [1]. Thus, transition metal-catalyzed version through a carbonylative heteroannulation has also been attempted for the formation of the structural core of isoindolinones [2-6]. We have recently developed and reported several palladium-catalyzed synthesis of isoindolinones utilizing the substrates which bear C=N double bond and the precursors which are able to form C=N double bond by simple condensation [7-12]. All reactions proceeded *via* either intramolecular or intermolecular acylpalladation of an acylpalladium moiety of acylpalladium intermediate to C=N double bonds as a mechanistic organometallic key step. As part of our continuing studies on palladium-catalyzed synthesis of isoindolinones [7-12], we now report the palladium-catalyzed synthesis of spiroisoindolinones through coupling and annulation between 2-iodobenzoyl chloride and ketimines.

We examined the coupling and cyclization between 2-iodobenzoyl chloride (**1**) and ketimines under a similar catalytic system which we introduced for the synthesis of 3-alkenylisoindolin-1-ones [12]. Thus, treatment of equimolar amounts of 2-iodobenzoyl chloride (**1**) and *N*-butyl-*N*-cyclohexylidenamine (**2**) in anhydrous acetonitrile in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$, 2 mole%] and triethylamine (10 equivalents) at 100° for 24 hours under 7 atmospheres of carbon monoxide afforded 5-*exo-trig*-cyclized product, spiro[2-cyclohexene-1,1'-(2'-butylisoindolin-3'-one)] (**3**) in 92% isolated yield (Scheme 1). However, 6-*endo-trig*-cyclized product, 5-butyl-1,2,3,5,6,10b-hexahydro-6-phenanthridinone (**4**) was not detected at all on both thin-layer chromatography and spectroscopy [13]. A carbon monoxide atmosphere was necessary for the formation of isoindolinone **3** as has been observed in our recent report for the synthesis of 3-alkenylisoindolin-1-ones [12]. This result may suggest that a carbon monoxide atmosphere hinders decarbonylation of the aroylpalladium(II) complex formed by oxidative addition of the carbon-chloride bond of 2-iodobenzoyl chloride (**1**) to palladium(0) as shown in Scheme 2 [14].

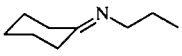
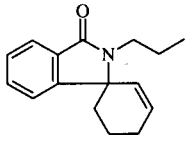
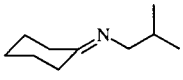
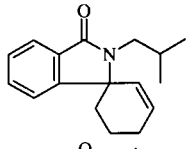
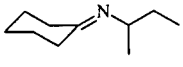
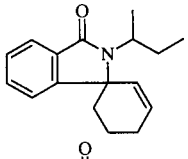
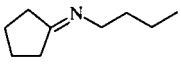
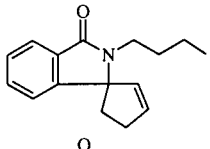
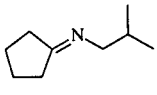
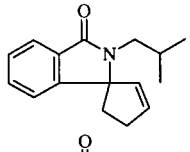
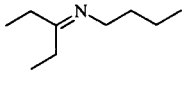
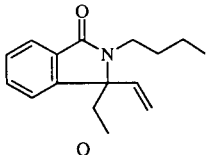
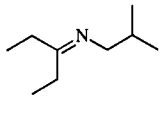
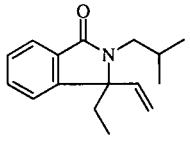
Scheme 1



The reaction system could also be applied to many ketimines, several representative results being summarized in Table 1. Table 1 indicates that the structural nature of the ketone counterpart of the ketimines showed no considerable influence on the formation of the corresponding spiroisoindolinones. With other easily available ketimines synthesized from cyclic ketones and aliphatic primary amines such as *N*-cyclohexyliden-*N*-propylamine, *N*-cyclohexyliden-*N*-isobutylamine, *N*-(*sec*-butyl)-*N*-cyclohexylidenamine, *N*-butyl-*N*-cyclopentylidenamine and *N*-cyclopentyliden-*N*-isobutylamine the corresponding spiroisoindolinones were formed in high yields. In the reaction with *N*-(*sec*-butyl)-*N*-cyclohexylidenamine, the corresponding isoindolinone was obtained as a diastereoisomeric mixture and the yield of the isoindolinone was lower than that when other ketimines were used. On the other hand, in the reactions with ketimines synthesized from 3-pentanone and butylamine as well as isobutylamine the corresponding 3,3-disubstituted isoindolinones were also formed in good yields.

The present coupling and annulation toward spiroisoindolinones seems to proceed similarly to that which has been observed in our previous report as shown in Scheme 2. Subsequent organometallic actions such as oxidative addition, acylpalladation [coupling between aroylpalladium(II) intermediate **5** and ketimine **2**], and β-hydrogen elimination between 2-iodobenzoyl chloride (**1**) and *N*-butyl-*N*-cyclohexylidenamine (**2**) mediated by palladium(0) affords

Table 1
Palladium-Catalyzed Synthesis of Spiroisoindolinones

Ketimine	Product	Isolated yield
		80
		75
		55 [a]
		85
		80
		78
		57

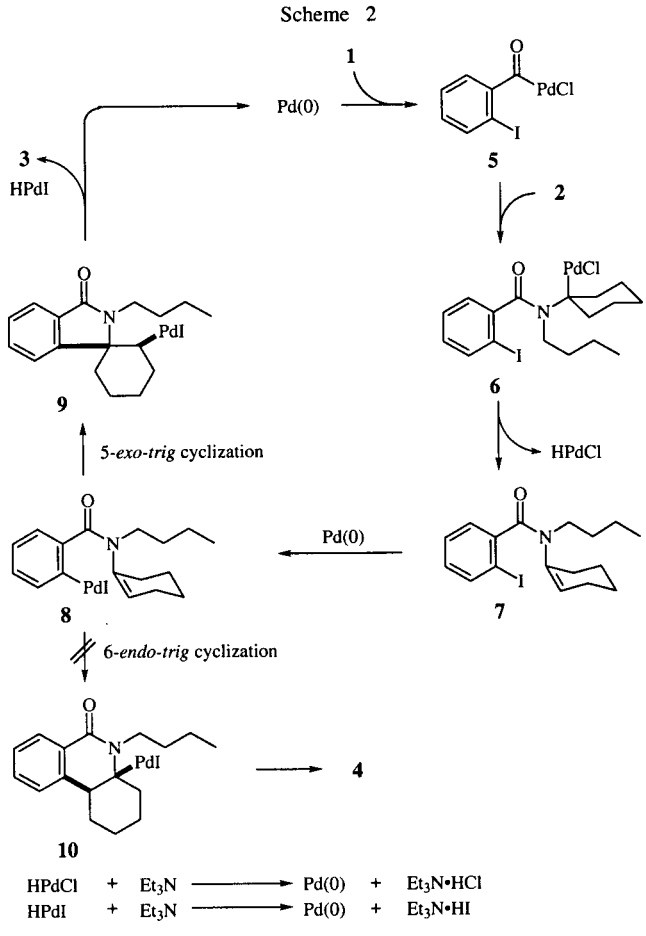
[a] Diastereoisomeric mixture.

arylpalladium(II) species **8** which is followed by intramolecular 5-*exo-trig* carbopalladation to the adjacent cyclohexene carbon-carbon double bond to give alkylpalladium(II) intermediate **9** [13]. This is followed by β-hydrogen elimination to afford spiro[2-cyclohexene-1,1'-(2'-butylisoindolin-3'-one)] (**3**).

EXPERIMENTAL

The ^1H (300 MHz) and ^{13}C (75.5 MHz) nmr spectra were recorded on a Varian Unity Plus 300 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported in δ units downfield from tetramethylsilane. Infrared spectra were recorded on a Galaxy Series FT-IR 7000M spectrophotometer. Electron impact mass spectra were obtained on a shimadzu QP-1000 spectrometer. The isolation of pure products was carried out *via* column chromatography (silica gel 60 HF_{254}, Merck). Commercially available organic and inorganic compounds were used without further purification.

Scheme 2



General Procedure for Palladium-Catalyzed Synthesis of Spiroisoindolinones.

A mixture of 2-iodobenzoyl chloride (533 mg, 2 mmoles), ketimine (2 mmoles), bis(triphenyphosphine)palladium(II) chloride (28 mg, 0.04 mmole), triphenylphosphine (42 mg, 0.16 mmole), triethylamine (2.8 ml, 20 mmoles), and anhydrous acetonitrile (10 ml) was placed in a 50 ml stainless steel autoclave. After the system was flushed and then pressurized with carbon monoxide to 7 atmospheres, the mixture was stirred at 100° for 24 hours. The reaction mixture was poured into water (about 50 ml) and extracted with dichloromethane (30 ml x 2). The combined organic layer was washed with brine (30 ml) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left an oil which was separated by column chromatography using ethyl acetate-hexane mixture as an eluent to give the corresponding spiroisoindolinones. The products obtained by the above procedure were fully characterized spectroscopically as shown below.

Spiro[2-cyclohexene-1,1'-(2'-butylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3025, 2955, 1690, 1468, 1397, 1085, 764 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95 (t, J = 7.8 Hz, 3H), 1.33-1.46 (m, 2H), 1.59-1.96 (m, 4H), 2.03-2.10 (m, 2H), 2.21-2.23 (m, 2H), 3.40 (t, J = 8.1 Hz, 2H), 5.21 (d, J = 10.2 Hz, 1H), 6.16 (dt, J = 10.2 and 3.6 Hz, 1H), 7.39-7.52 (m, 3H), 7.80 (d, J = 7.8 Hz, 1H); ^{13}C nmr

(deuteriochloroform): δ 13.7, 19.8, 20.5, 23.9, 31.5, 32.8, 40.3, 64.9, 122.5, 123.1, 127.9, 128.1, 131.1, 131.4, 132.6, 150.4, 167.9; ms: m/z (%) 255 (M^+, 66), 227 (20), 212 (100), 198 (17), 183 (52), 129 (9), 78 (7).

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.64; H, 7.95; N, 5.44.

Spiro[2-cyclohexene-1,1'-(2'-propylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3023, 2941, 1683, 1468, 1081, 764 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 (t, J = 7.2 Hz, 3H), 1.63-1.93 (m, 4H), 2.02-2.12 (m, 2H), 2.23-2.25 (m, 2H), 3.37 (t, J = 8.1 Hz, 2H), 5.21 (d, J = 9.6 Hz, 1H), 6.15 (dt, J = 9.6 and 3.8 Hz, 1H), 7.38-7.51 (m, 3H), 7.79-7.82 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 11.5, 19.6, 22.4, 23.7, 32.6, 42.0, 64.7, 122.4, 123.0, 127.7, 127.8, 131.0, 131.2, 132.5, 150.3, 167.8; ms: m/z (%) 241 (M^+, 44), 225 (8), 212 (100), 197 (42), 182 (82), 155 (18), 141 (8), 128 (25), 115 (25), 102 (15), 91 (11), 77 (24).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.33; H, 7.75; N, 5.74.

Spiro[2-cyclohexene-1,1'-(2'-isobutylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3024, 2936, 1692, 1468, 1393, 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95 (t, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.73-2.29 (m, 7H), 3.19 (dd, J = 13.5 and 7.8 Hz, 1H), 3.37 (dd, J = 13.5 and 8.5 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 6.13 (dt, J = 10.2 and 3.6 Hz, 1H), 7.40-7.53 (m, 3H), 7.81 (d, J = 6.9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 19.9, 20.3, 20.6, 23.9, 27.9, 32.8, 47.8, 65.0, 122.5, 123.4, 128.0, 128.5, 131.2, 132.2, 150.5, 168.5; ms: m/z (%) 255 (M^+, 25), 212 (100), 184 (60), 166 (26), 155 (12), 129 (10), 77 (8).

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.61; H, 8.01; N, 5.49.

Spiro[2-cyclohexene-1,1'-(2'-*sec*-butylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3024, 2967, 1687, 1467, 1356, 1082, 794, 694 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.89 (t, J = 7.7 Hz, 3/2H), 0.95 (t, J = 7.7 Hz, 3/2H), 1.46 (d, J = 6.6 Hz, 3/2H), 1.52 (d, J = 6.6 Hz, 3/2H), 1.67-1.72 (m, 2H), 1.87-2.18 (m, 6H), 3.18-3.32 (m, 1H), 5.31 (d, J = 9.6 Hz, 1H), 6.14-6.20 (m, 1H), 7.38-7.51 (m, 3H), 7.76-7.79 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 51.37 (methine), 51.44 (methine), 65.82 (quaternary), 65.90 (quaternary), 167.50 (carbonyl), 167.60 (carbonyl); ms: m/z (%) 255 (M^+, 30), 239 (7), 225 (100), 198 (40), 182 (95), 152 (16), 142 (7), 127 (18), 115 (18), 77 (16).

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.75; H, 8.01; N, 5.39.

Spiro[2-cyclopentene-1,1'-(2'-butylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3054, 2958, 1689, 1469, 1393, 1078, 759, 696 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, J = 7.8 Hz, 3H), 1.31-1.43 (m, 2H), 1.61-1.71 (m, 2H), 2.25-2.31 (m, 2H), 2.68-2.74 (m, 2H), 3.16-3.26 (m, 1H), 3.40-3.50 (m, 1H), 5.40 (dt, J = 5.4 and 2.4 Hz, 1H), 6.24 (dt, J = 5.1 and 2.4 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.39-7.53 (m, 2H), 7.79 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 13.8, 20.5, 31.7, 32.3, 33.9, 39.9, 43.7, 121.5, 123.0, 128.0, 131.3, 131.6, 132.6, 136.3, 150.2, 167.6; ms: m/z (%) 241 (M^+, 54), 198 (45), 184 (12), 169 (100), 158 (7), 142 (17), 116 (16), 77 (2).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.35; H, 7.58; N, 5.79.

Spiro[2-cyclopentene-1,1'-(2'-isobutylisoindolin-3'-one)].

This compound was obtained as colorless oil; ir (neat): ν 3054, 2961, 1692, 1468, 1385, 1089, 796 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.93 (d, J = 6.9 Hz, 6H), 2.05-2.25 (m, 1H), 2.25-2.29 (m, 2H), 2.66-2.74 (m, 2H), 3.05 (dd, J = 14.4 and 7.3 Hz, 1H), 3.35 (dd, J = 14.4 and 7.7 Hz, 1H), 5.41 (dt, J = 5.1 and 1.8 Hz, 1H), 6.22 (dt, J = 6.0 and 1.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.41-7.55 (m, 2H), 7.80 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 20.2, 20.4, 20.5, 28.0, 32.2, 33.8, 47.4, 121.5, 123.0, 127.9, 131.0, 131.6, 132.6, 136.2, 150.2, 168.1; ms: m/z (%) 241 (M^+, 26), 199 (46), 184 (6), 170 (100), 142 (17), 128 (4), 115 (16), 77 (3).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.37; H, 7.68; N, 5.83.

2-Butyl-3-ethyl-3-vinyl-1-isoindolinone.

This compound was obtained as colorless oil; ir (neat): ν 3052, 2964, 1690, 1466, 1393, 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.42 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.8 Hz, 3H), 1.32-1.45 (m, 2H), 1.63-1.73 (m, 2H), 2.07-2.20 (m, 2H), 3.20 (dt, J = 13.5 and 7.5 Hz, 1H), 3.44 (dt, J = 13.5 and 8.7 Hz, 1H), 5.29 (d, J = 10.2 Hz, 1H), 5.38 (d, J = 17.6 Hz, 1H), 5.72 (dd, J = 17.6 and 10.2 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 6.8, 13.7, 20.6, 25.7, 30.9, 40.0, 69.7, 115.9, 121.7, 123.2, 128.0, 131.5, 132.4, 139.9, 147.3, 168.7; ms: m/z (%) 243 (M^+, 21), 226 (13), 213 (100), 171 (89), 158 (88), 143 (41), 128 (52), 115 (57), 103 (34), 91 (13), 77 (27).

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.73; H, 8.61; N, 5.75.

3-Ethyl-2-isobutyl-3-vinyl-1-isoindolinone.

This compound was obtained as colorless oil; ir (neat): ν 3052, 2964, 1690, 1385, 926, 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.40 (t, J = 7.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 2.05-2.18 (m, 3H), 2.95 (dd, J = 13.5 and 6.9 Hz, 1H), 3.42 (dd, J = 13.5 and 6.9 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 5.38 (d, J = 17.1 Hz, 1H), 5.73 (dd, J = 17.1 and 10.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 6.7, 20.4, 20.8, 25.6, 27.9, 47.4, 69.7, 115.8, 121.8, 123.4, 128.1, 131.6, 132.4, 140.4, 147.2, 169.3; ms: m/z (%) 243 (M^+, 3), 227 (7), 214 (100), 200 (77), 186 (3), 171 (31), 158 (35), 143 (34), 128 (28), 115 (26), 102 (14), 91 (6), 77 (14).

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.81; H, 8.42; N, 5.52.

Acknowledgment.

This work was supported by Korea Science & Engineering Foundation (98-05-01-05-01-3) and by grant of Post-Doc. (C.S.C.) Program from Kyungpook National University (1998). The authors are grateful to Korean Federation of Science and Technology Societies for Brain Pool Program-KOSEF-1996 (X.W.).

REFERENCES AND NOTES

[1] I. Takahashi, T. Kawakami, E. Hirano, H. Yokota and H. Kitajima, *Synlett*, 353 (1996) and references cited therein.

[2] C. W. Bird, *J. Organomet. Chem.*, **47**, 296 (1973).

[3] J. M. Thompson and R. F. Heck, *J. Org. Chem.*, **40**, 2667 (1975).

[4] M. Mori, K. Chiba and Y. Ban, *J. Org. Chem.*, **43**, 1684 (1978).

[5] J. J. Brunet, C. Sidot and P. Caubere, *J. Org. Chem.*, **48**, 1166 (1983).

[6] S. C. Shim, L. H. Jiang, D. Y. Lee and C. S. Cho, *Bull. Korean Chem. Soc.*, **16**, 1064 (1995).

[7] C. S. Cho, J. W. Lee, D. Y. Lee, S. C. Shim and T. J. Kim, *Chem. Commun.*, 2115 (1996).

[8] C. S. Cho, L. H. Jiang, D. Y. Lee and S. C. Shim, *Bull. Korean Chem. Soc.*, **17**, 1095 (1996).

[9] C. S. Cho, L. H. Jiang, D. Y. Lee, S. C. Shim, H. S. Lee and S.-D. Cho, *J. Heterocyclic Chem.*, **34**, 1371 (1997).

[10] C. S. Cho, D. Y. Chu, D. Y. Lee, S. C. Shim, T. J. Kim, W. T. Lim and N. H. Heo, *Synth. Commun.*, **27**, 4141 (1997).

[11] C. S. Cho, L. H. Jiang and S. C. Shim, *Synth. Commun.*, **28**, 849 (1998).

[12] C. S. Cho, X. Wu, L. H. Jiang and S. C. Shim, *J. Heterocyclic Chem.*, **35**, 265 (1998).

[13] For the transition metal-catalyzed *exo* and *endo* cyclizations, see: C. Thebtaranonth and Y. Thebtaranonth, Cyclization Reactions, CRC Press, London, 1994, pp 255-330.

[14] H. M. Colquhoun, H. M. Tompson and M. V. Twigg, Carbonylation: Direct Synthesis of Carbonyl Compounds, Plenum Press, New York, 1991, pp 205-225.