Synthesis of 3-Alkenylisoindolin-1-ones *via* Palladium(0)-Catalyzed Coupling and Cyclization between 2-Iodobenzoyl Chloride and Aldimines

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2-Iodobenzoyl chloride reacts with aldimines in acetonitrile at 100° under carbon monoxide in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride together with triethylamine to give the corresponding 3-alkenylisoindolin-1-ones in good yields.

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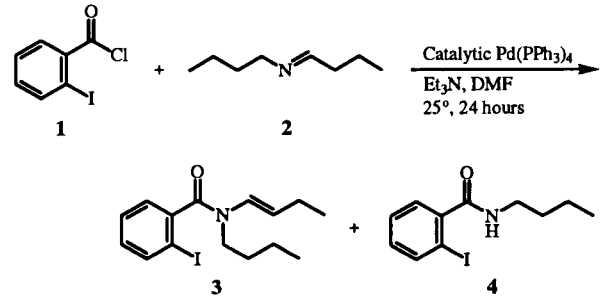
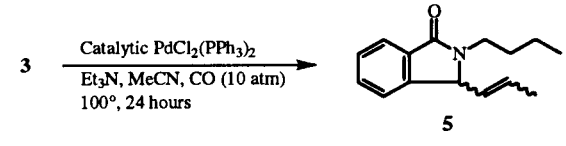
The palladium-catalyzed cyclization reaction provides a useful and convenient method for the construction of skeletons of heterocyclic compounds [1]. Thus, the formation of structural core of isoindolinones also has been applied by the aid of palladium catalysts [2] since several isoindolinones exert broad biological activities [3]. Recently, we developed and reported several synthetic methods for the formation of isoindolinones using the substrates which bear C=N double bond, 2-(2-bromophenyl)-2-oxazolines [4] and 2-bromobenzaldimines formed *in situ* from condensation between 2-bromobenzaldehyde and chiral alkanolamines [5] as well as primary amines [6-8], all catalyzed by palladium(0). All reactions proceeded *via* an intramolecular acylpalladation of an acylpalladium moiety of acylpalladium intermediate to C=N double bonds as a mechanistic organometallic key step. Thus, we here report another approach for the synthesis of isoindolinones from 2-iodobenzoyl chloride and aldimines *via* palladium(0)-catalyzed cascade intermolecular acylpalladation-cyclization sequence.

Treatment of equimolar amounts of 2-iodobenzoyl chloride (**1**) and *N*-[(*E*)-butylidene]-1-butanamine (**2**) in *N*,*N*-dimethylformamide in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$, 3 mole%] and triethylamine (2 equivalents) at 25° for 24 hours afforded *N*-[(*E*)-1-butenyl]-*N*-butyl-2-iodobenzamide (**3**) and *N*-butyl-2-iodobenzamide (**4**) in 60% and 19% yields, respectively (Scheme 1). The use of bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$] together with triphenylphosphine in place of $Pd(PPh_3)_4$ and higher reaction temperature resulted in similar yields of **3** and **4**. Therefore, the above reaction conditions were not useful for the formation of isoindolinone skeleton. Thus, several attempts were carried out with **1** and **2** to achieve cyclization reaction toward isoindolinones. Among them, the following two facts led us to attempt the direct and effective synthesis of 3-alkenylisoindolin-1-ones from 2-iodobenzoyl chloride (**1**) and aldimines. First, when acetonitrile was used as solvent in place of *N*,*N*-dimethylformamide under similar reaction conditions, *N*-butyl-3-(1-propenyl)-1-isoindolinone (**5**) was formed in 30% yield as an isomeric mixture. Secondly, when *N*-[(*E*)-1-butenyl]-*N*-butyl-2-iodobenzamide (**3**) thus obtained was reacted at 10 atmospheres of carbon monoxide under similar reaction conditions, isoindolinone **5** was formed in 75% yield (Scheme 2). These results indicate that performing the reaction under conditions of acetonitrile as the solvent and in a carbon monoxide atmosphere was necessary for the effective formation of isoindolinone **5**. Eventually, it was disclosed that our newly developed reaction conditions were applicable to the direct synthesis of isoindolinones from **1** and aldimines, resulting in formation of isoindolinone **5** in 70% yield from **1** and **2**.

Scheme 1



Scheme 2



From other easily available aldimines the corresponding isoindolinones were also formed in good yields. Several representative results are summarized in Table 1. Table 1 indicates that the structural nature of aldehyde counterpart of the aldimines showed no considerable influence on the

formation of the corresponding 3-alkenylisoindolin-1-ones. However, the reactions with aldimines such as *N*-*t*-butyl-*N*-[(*E*)-2-methylpropylidene]amine (**6a**) and *N*-phenyl-*N*-[(*E*)-2-methylpropylidene]amine (**6b**) did not proceed toward the present cyclization and resulted in the formation of many unidentified compounds (Scheme 3). This result shows that the present cyclization seems to be dependent on the structural nature of the amino counterpart of the aldimines.

Scheme 3

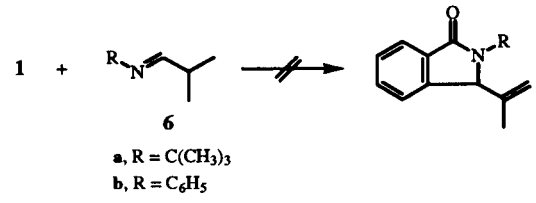
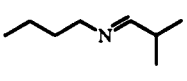
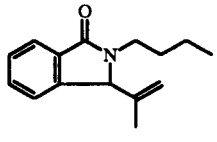
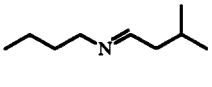
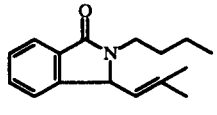
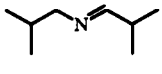
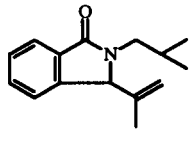
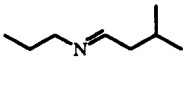
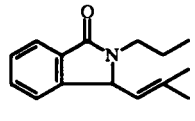
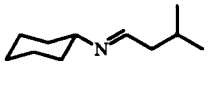
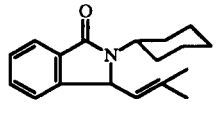
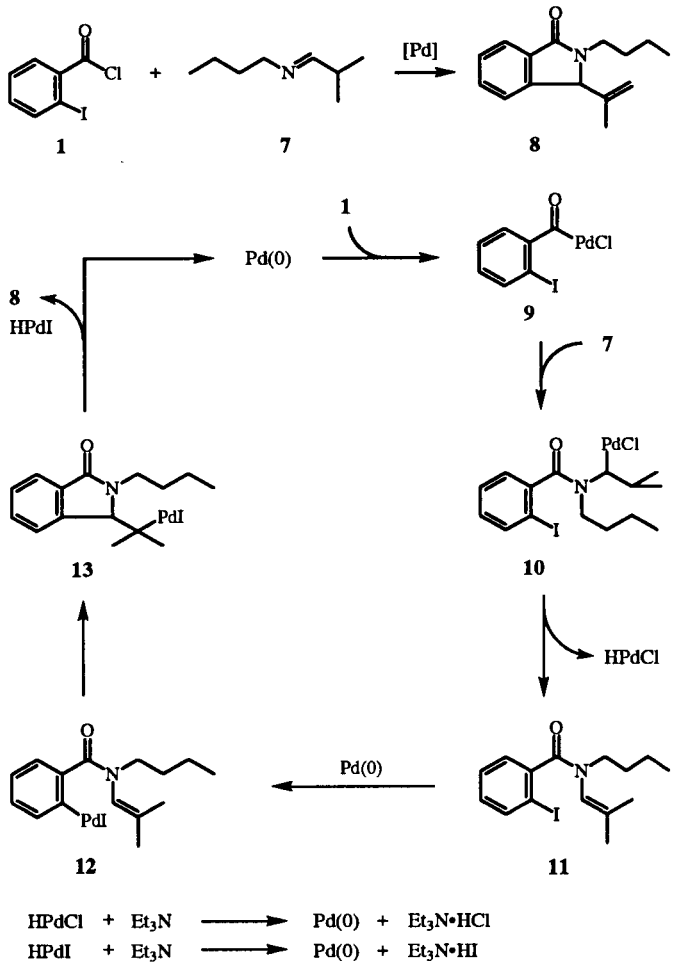


Table 1
Palladium-Catalyzed Synthesis of Isoindolinones

Aldimine	Product	Isolated yield
		54
		62
		59
		56
		40

The present cyclization pathway is presented in Scheme 4 by choosing aldimine **7** as a cyclization counterpart. Oxidative addition of the carbon-chloride bond of 2-iodobenzoyl chloride (**1**) to palladium(0) affords aroylpalladium(II) complex **9**. Intermolecular addition of the acylpalladium moiety of the intermediate **9** to carbon-nitrogen double bond of **7** (acylpalladation) gives alkylpalladium(II) intermediate **10** which is followed by β-hydrogen elimination to give the vinyl amide **11**. The formation of the vinyl amide was confirmed separately in the similar reaction between **1** and **2** (Scheme 1). Subsequent oxidative addition of the carbon-iodide bond of the vinyl amide **11** to palladium(0) affords an arylpalladium(II) species **12** which is followed by intramolecular carbopalladation to the adjacent carbon-carbon double bond to give alkylpalladium(II) intermediate **13**. This is followed by β-hydrogen elimination to give 3-alkenylisoindolin-1-one **8**. A similar catalytic cycle has already been proposed in palladium-catalyzed cyclization reactions [4-10].

Scheme 4



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 Mattson Galaxy 6030E FT-IR spectrophotometer. Electron impact

mass spectra were obtained on a shimadzu QP-1000 spectrometer. Melting points were determined on a Yamato Model MP-21 apparatus and were uncorrected. 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. Aldimines were prepared by condensation of aldehydes with primary amines.

General Procedure for Palladium(0)-Catalyzed Synthesis of Isoindolinones from 2-Iodobenzoyl Chloride and Aldimines.

A mixture of 2-iodobenzoyl chloride (533 mg, 2 mmoles), aldimine (2 mmoles), bis(triphenylphosphine)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 pressure vessel. After the system was flushed and then pressurized with carbon monoxide to 10 atmospheres, the mixture was stirred at 100° for 24 hours. The reaction mixture was poured into water (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 isoindolinones. The products obtained by the above procedure were fully characterized spectroscopically as shown below.

2-Butyl-3-(1-propenyl)-1-isoindolinone.

This compound was obtained as pale yellow oil and isomeric mixture; ir (neat): ν 3026, 2934, 1690 (C=O), 1405, 749, 695 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, J = 7.0 Hz, 6/3H), 0.95 (t, J = 7.5 Hz, 3/3H), 1.28-1.44 (m, 2H), 1.50-1.70 (m, 2H), 1.84 (d, J = 7.0 Hz, 6/3H), 1.97 (dd, J = 7.0 and 1.5 Hz, 3/3H), 3.08-3.23 (m, 1H), 3.80-3.95 (m, 1H), 4.84 (d, J = 8.0 Hz, 2/3H), 5.09 (dd, J = 14.4 and 8.0 Hz, 1H), 5.35 (d, J = 9.6 Hz, 1/3H), 6.04 (dq, J = 14.4 and 7.0 Hz, 1H), 7.33 (d, J = 7.0 Hz, 1H), 7.42 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H); ms: m/z (%) 229 (M^+, 71), 186 (100), 158 (13), 146 (35), 132 (38), 115 (19), 77 (20).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.27; H, 8.10; N, 5.99.

2-Butyl-3-isopropenyl-1-isoindolinone.

This compound was obtained as pale yellow oil; ir (neat): ν 2960, 2932, 2873, 1694 (C=O), 1651, 1403, 746 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, J = 6.9 Hz, 3H), 1.22 (s, 3H), 1.30-1.42 (m, 2H), 1.49-1.65 (m, 2H), 2.97 (dt, J = 13.5 and 6.9 Hz, 1H), 3.96 (dt, J = 13.5 and 6.9 Hz, 1H), 4.97 (s, 1H), 5.21 (s, 1H), 5.36 (s, 1H), 7.33 (d, J = 6.9 Hz, 1H), 7.43-7.55 (m, 2H), 7.84 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 13.5, 15.0, 19.9, 30.2, 39.5, 66.5, 117.5, 122.1, 123.1, 128.1, 131.2, 132.4, 141.2, 143.5, 168.2; ms: m/z (%) 229 (M^+, 63), 214 (70), 200 (10), 186 (100), 172 (17), 158 (13), 145 (56), 132 (63), 115 (29), 104 (18), 90 (15), 77 (31).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.11; N, 6.09.

2-Butyl-3-(2-methyl-1-propenyl)-1-isoindolinone.

This compound was obtained as pale yellow oil; ir (neat): ν 3049, 2959, 2931, 2872, 1694 (C=O), 1404, 749, 693 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, J = 6.9 Hz, 3H), 1.30-1.42 (m, 2H), 1.54-1.64 (m, 2H), 1.83 (s, 3H), 1.96 (s, 3H), 3.12 (dt, J = 13.5 and 6.9 Hz, 1H), 3.85 (dt, J = 13.5 and 7.8 Hz, 1H), 4.80 (dd, J = 9.3 and 1.8 Hz, 1H), 5.23 (d, J = 9.3 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.39-7.52 (m, 2H), 7.81 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 13.5, 18.0, 19.8, 25.6, 30.4, 39.5, 58.2, 121.1, 122.4, 122.9, 127.7, 130.9, 132.0, 138.6, 145.2, 167.6; ms: m/z (%) 243 (M^+, 55), 200 (100), 186 (10), 171 (25), 146 (44), 128 (30), 77 (14).

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.63; H, 8.48; N, 5.68.

2-Isobutyl-3-isopropenyl-1-isoindolinone.

This compound was obtained as pale yellow oil; ir (neat): ν 3079, 2960, 1690 (C=O), 1655, 1405, 745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.89 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 1.20 (s, 3H), 1.92-2.08 (m, 1H), 2.77 (dd, J = 13.5 and 6.0 Hz, 1H), 3.78 (dd, J = 13.8 and 9.6 Hz, 1H), 4.98 (s, 1H), 5.21 (s, 1H), 5.34 (s, 1H), 7.34 (d, J = 6.9 Hz, 1H), 7.43-7.55 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 15.1, 19.8, 20.3, 27.6, 47.2, 67.0, 117.7, 122.2, 123.4, 128.3, 131.4, 132.5, 141.2, 143.7, 168.6; ms: m/z (%) 229 (M^+, 18), 214 (14), 186 (100), 157 (6), 144 (16), 128 (17), 115 (11), 77 (6).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.18; N, 5.83.

2-Propyl-3-(2-methyl-1-propenyl)-1-isoindolinone.

This compound was obtained as pale yellow oil; ir (neat): ν 3046, 2962, 1682 (C=O), 1401, 754 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, J = 7.8 Hz, 3H), 1.52-1.75 (m, 2H), 1.83 (s, 3H), 1.96 (s, 3H), 3.05-3.15 (m, 1H), 3.80 (dt, J = 13.5 and 8.7 Hz, 1H), 5.24 (d, J = 9.3 Hz, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.39-7.52 (m, 2H), 7.81 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 11.4, 18.2, 21.8, 25.8, 41.7, 58.5, 121.3, 122.6, 123.2, 127.9, 131.1, 132.3, 138.8, 145.4, 168.0; ms: m/z (%) 229 (M^+, 46), 214 (7), 199 (100), 171 (35), 157 (10), 145 (50), 128 (50), 115 (15), 77 (20).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.53; H, 8.06; N, 5.99.

2-Cyclohexyl-3-(2-methyl-1-propenyl)-1-isoindolinone.

This compound was obtained as white solid, mp 57-58°; ir (potassium bromide): ν 2933, 2850, 1680 (C=O), 1396, 749, 691 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.07-1.21 (m, 2H), 1.30-1.44 (m, 3H), 1.48-1.89 (m, 6H), 1.81 (s, 3H), 1.97 (s, 3H), 4.00 (tt, J = 11.6 and 3.3 Hz, 1H), 4.88 (d, J = 9.3 Hz, 1H), 5.29 (d, J = 9.3 Hz, 1H), 7.23 (d, J = 6.6 Hz, 1H), 7.36-7.48 (m, 2H), 7.78 (d, J = 6.9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 18.0, 25.3, 25.5, 25.7, 25.8, 30.7, 31.8, 52.2, 57.8, 122.3, 122.7, 123.2, 127.6, 130.8, 132.1, 135.5, 145.3, 167.6; ms: m/z (%) 269 (M^+, 100), 227 (61), 189 (15), 173 (17), 147 (25), 135 (40).

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 79.99; H, 8.95; N, 5.22.

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