Palladium-Catalyzed Synthesis of 3-(Alkylamino)isoindolin-1-ones by Carbonylative Cyclization of 2-Bromobenzaldehyde with Primary Amines

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Received February 12, 1997

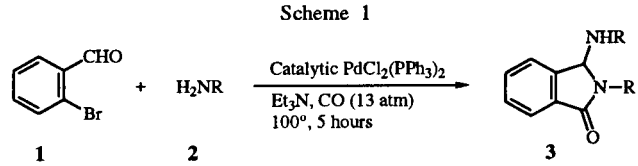
2-Bromobenzaldehyde reacts with an excess of primary amines under a carbon monoxide in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride together with triethylamine to give the corresponding 3-(alkylamino)isoindolin-1-ones in good yields.

J. Heterocyclic Chem., **34**, 1371 (1997).

The palladium-catalyzed carbonylative reaction has proved to be a useful synthetic tool for the formation of a variety of heterocyclic compounds [1]. In the course of our series of studies on the synthesis of heterocyclic compounds catalyzed by transition metals, we have reported recently on the synthesis of several nitrogen heterocycles [2-6]. Among them, it is worth while to note the palladium-catalyzed synthesis of isoindolinones [7] *via* carbonylative cyclization utilizing the substrates which bear C=N double bond, 2-(2-bromophenyl)-2-oxazolines [8] and 2-bromobenzaldimines formed *in situ* from 2-bromobenzaldehyde and primary amines [9]. In the latter reaction, 3-methoxy- and 3-carbomethoxyisoindolin-1-ones could be obtained by the use of an equimolar amount of 2-bromobenzaldehyde and primary amines in methanol. Thus, we attempted the latter reaction using an excess amount of primary amines in the absence of the alcohol for the formation of 3-(alkylamino)isoindolin-1-ones. We now disclose and report the development of a facile method for the synthesis of 3-(alkylamino)isoindolin-1-ones from readily available 2-bromobenzaldehyde and primary amines through the carbonylative cyclization process.

We examined the carbonylative cyclization between 2-bromobenzaldehyde (**1**) and benzylamine (**2a**) to optimize the reaction conditions under similar catalytic systems we reported for the syntheses of 3-methoxy- and 3-carbomethoxyisoindolin-1-ones [9] and 3-alkoxyphthalides [10]. Thus, treatment of 2-bromobenzaldehyde (**1**) with an excess of benzylamine (**2a**) (20 equivalents) under carbon monoxide (13 atm) in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (1.5 mole%) and triphenylphosphine (4 mole%) together with triethylamine (2.5 equivalents) at 100° for 5 hours afforded *N*-benzyl-3-(benzylamino)isoindolin-1-one (**3a**) in 64% yield (Scheme 1). These reaction conditions were shown to be best for obtaining **3a** (Table 1). A variety of bases such as sodium acetate, potassium carbonate and sodium bicarbonate can also be used in place of triethylamine, but the yield of **3a** was generally lower than when triethylamine was used. Both lower and higher pressures of carbon monoxide also resulted in lower yields of **3a**.

Scheme 1



1 **2** **3**

a, R = benzyl
b, R = CH_2CH_3
c, R = $CH_2(CH_2)_2CH_3$
d, R = $CH_2(CH_2)_{10}CH_3$
e, R = 4-methoxybenzyl
f, R = $CH(CH_3)_2$
g, R = $CH(CH_3)(CH_2)_4CH_3$

Table 1

Palladium-Catalyzed Synthesis of 3-(Alkylamino)isoindolin-1-ones **3**

Amine	Base	CO (atm)	Product	Isolated yield
2a	Et_3N	13	**3a**	64
2a	NaOAc	13	**3a**	10
2a	K_2CO_3	13	**3a**	57
2a	$NaHCO_3$	13	**3a**	27
2a	Et_3N	5	**3a**	23
2a	Et_3N	20	**3a**	41
2b	Et_3N	13	**3b**	34
2c	Et_3N	13	**3c**	83
2d	Et_3N	13	**3d**	55
2e	Et_3N	13	**3e**	68
2f	Et_3N	13	**3f**	[a]
2g	Et_3N	13	**3g**	[a]

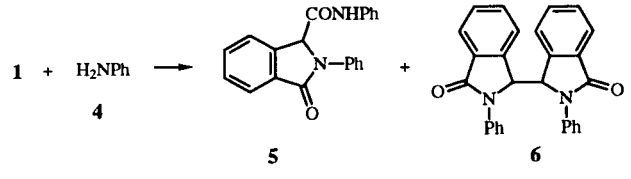
[a] Many unidentified compounds.

This carbonylative cyclization could be applied to many aliphatic primary amines. Typical results are summarized in Table 1. The reaction proceeded even with the use of 70% aqueous ethylamine solution, but the yield was lower than that when other aliphatic primary amines were used. On the other hand, the reactions with primary amines such as isopropylamine (**2f**) and 2-aminoheptane

(**2g**) were unsuccessful for the present carbonylative cyclization and resulted in the formation of many unidentified compounds.

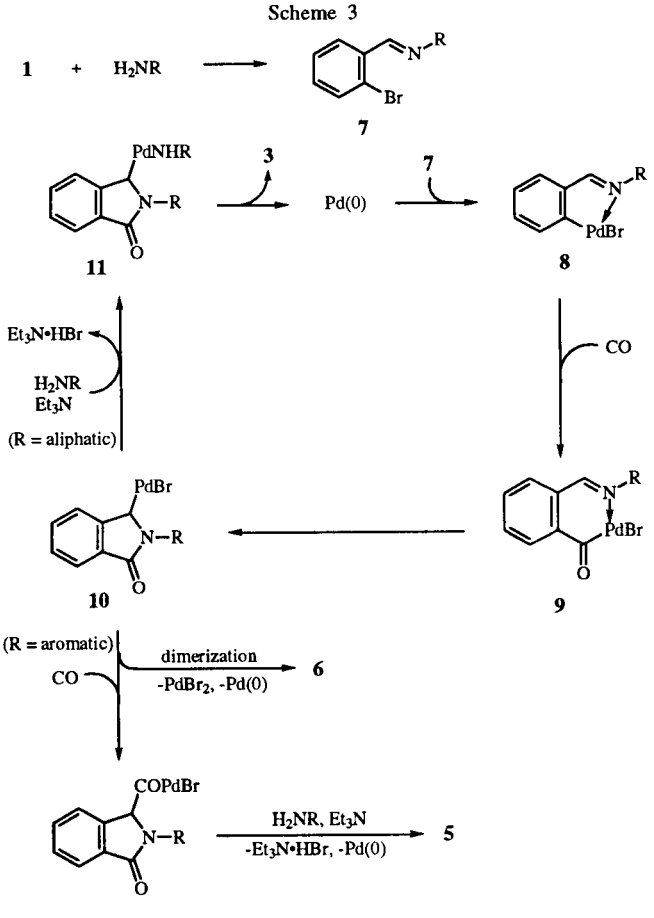
In contrast, in the reaction with aniline (**4**) in place of aliphatic primary amines under the same reaction conditions, *N*-phenyl-3-(phenylcarbamoyl)isoindolin-1-one (**5**) and 3,3'-bis(*N*-phenylisoindolin-1-one) (**6**) were obtained in 37% and 40% [11] yields, respectively (Scheme 2). Performing the reaction under lower carbon monoxide pressure also proved to be unsuccessful in the formation of 3-(alkylamino)isoindolin-1-one. Thus, considering the type of products between aliphatic primary amine and aromatic primary amine, it is reasonable to assume that the basic difference of the reactions stems from the nucleophilicity of amines.

Scheme 2



Although the details of the reaction scheme are not yet clear, a plausible pathway is presented in Scheme 3.

Scheme 3



Oxidative addition of the carbon-bromide bond of imine **7**, initially formed *in situ* between 2-bromobenzaldehyde (**1**) and primary amine, to palladium(0) produces an aroylpalladium(II) complex **8**, where carbon monoxide coordination to palladium and then aryl migration from palladium to the carbon of carbon monoxide occurs to give an acylpalladium(II) intermediate **9**. This is followed by intramolecular addition of the acylpalladium to the carbon-nitrogen double bond (acylpalladation [12]) to give the alkylpalladium(II) species **10**. Intermediate **10** reacts with an excess of aliphatic primary amines to produce alkylamidopalladium(II) intermediate **11** [13] which can reductively eliminate to give the 3-(alkylamino)isoindolin-1-one **3**. However, the reaction of intermediate **10** with a less nucleophilic aromatic primary amine, aniline may retard the formation of 3-(alkylamino)isoindolin-1-one **3** because of its nucleophilicity. Instead, carbamoylisoindolin-1-one **5** and dimer **6** are formed by carbonylation/amine exchange sequence and dimerization of intermediate **10**, respectively. A similar catalytic sequence has already been proposed in the transition metal-catalyzed carbonylative cyclization reactions [9,10,14].

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* preparative thin-layer chromatography (silica gel 60 HF_{254}, Merck). Commercially available organic and inorganic compounds were used without further purification. Bis(triphenylphosphine)palladium(II) chloride was prepared by the known method [15].

General Procedure for Palladium-Catalyzed Carbonylative Cyclization of 2-Bromobenzaldehyde with Primary Amines.

A mixture of 2-bromobenzaldehyde (**1**) (370 mg, 2 mmoles), primary amine (20 mmoles), bis(triphenylphosphine)-palladium(II) chloride (21 mg, 0.03 mmole), triphenylphosphine (21 mg, 0.08 mmole), and triethylamine (506 mg, 5 mmoles) was placed in a pressure vessel. After the system was flushed and then pressurized with carbon monoxide to 13 atmospheres, the mixture was stirred at 100° for 5 hours. The reaction mixture was filtered and evaporated under reduced pressure to remove excess amine. To the residual oily mixture was added brine (50 ml) and extracted with chloroform (20 ml x 3). The organic phase was washed with water and dried over anhydrous magnesium sulfate. Thin-layer chromatography separation using ethyl acetate-hexane mixture as an eluent leads to the corresponding pure isoindolin-1-ones. The products prepared by the above procedure were fully characterized spectroscopically as shown below.

N-Benzyl-3-(benzylamino)isoindolin-1-one (**3a**).

This compound was obtained as pale yellow oil; ir (neat): ν 3318 (NH), 1686 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.82 (br s, 1H), 3.20 (d, J = 13.2 Hz, 1H), 3.31 (d, J = 13.2 Hz, 1H), 4.34 (d, J = 15.0 Hz, 1H), 5.11 (d, J = 15.0 Hz, 1H), 5.29 (s, 1H), 7.11-7.32 (m, 10H), 7.40-7.49 (m, 3H), 7.84 (d, J = 7.2 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 42.8, 45.2, 72.0, 122.9, 123.1, 126.7, 127.2, 127.8, 127.9, 128.0, 128.4, 128.7, 131.5, 132.5, 137.2, 139.4, 143.1, 167.3; ms: m/z (%) 328 (M^+, 3), 237 (6), 222 (49), 132 (7), 106 (35), 91 (100).

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.33; H, 6.17; N, 8.53.

N-Ethyl-3-(ethylamino)isoindolin-1-one (**3b**).

This compound was obtained as pale yellow oil; ir (neat): ν 3326 (NH), 1675 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.97-1.03 (m, 3H), 1.22-1.27 (m, 3H), 2.09-2.15 (m, 1H), 2.29-2.38 (m, 2H), 3.24-3.36 (m, 1H), 3.83-3.95 (m, 1H), 5.40 (s, 1H), 7.42-7.57 (m, 3H), 7.80 (d, J = 6.9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 13.5, 15.2, 33.4, 35.2, 72.1, 122.7, 122.8, 128.6, 131.2, 132.9, 143.4, 167.1; ms: m/z (%) 204 (M^+, 13), 160 (100), 132 (66), 104 (17), 78 (20).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.67; H, 8.18; N, 13.47.

N-Butyl-3-(butylamino)isoindolin-1-one (**3c**).

This compound was obtained as colorless oil; ir (neat): ν 3320 (NH), ν 1683 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.81 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.23-1.45 (m, 6H), 1.60-1.70 (m, 2H), 2.00-2.08 (m, 1H), 2.25-2.33 (m, 1H), 2.40 (br s, 1H), 3.19-3.28 (m, 1H), 3.84-3.94 (m, 1H), 5.43 (s, 1H), 7.41-7.58 (m, 3H), 7.81 (d, J = 7.2 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 13.9 (x 2), 20.3, 20.4, 30.7, 32.5, 38.6, 40.5, 72.8, 122.9, 123.2, 128.7, 131.4, 133.2, 144.0, 167.5; ms: m/z (%) 260 (M^+, 3), 188 (100), 146 (75), 132 (97), 104 (21).

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 74.04; H, 9.52; N, 10.72.

N-Dodecyl-3(dodecylamino)isoindolin-1-one (**3d**).

This compound was obtained as colorless oil; ir (neat): ν 3326 (NH), 1686 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.87 (t, J = 6.8 Hz, 6H), 1.08-1.62 (m, 41H), 1.99-2.07 (m, 1H), 2.25-2.32 (m, 1H), 3.11-3.20 (m, 1H), 3.81-3.91 (m, 1H), 5.37 (s, 1H), 7.43-7.53 (m, 3H), 7.80 (d, J = 6.9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 14.0, 22.5, 27.0, 28.5, 29.2, 29.3, 29.4, 29.5, 30.2, 31.8, 38.8, 40.8, 72.5, 122.8, 123.0, 128.7, 131.2, 133.0, 143.5, 167.4; ms: m/z (%) 484 (M^+, 5), 315 (3), 300 (100), 184 (14), 146 (35).

Anal. Calcd. for $C_{32}H_{56}N_2O$: C, 79.28; H, 11.64; N, 5.78. Found: C, 79.50; H, 11.73; N, 5.87.

N-(4-Methoxybenzyl)-3-(4-methoxybenzylamino)isoindolin-1-one (**3e**).

This compound was obtained as pale yellow oil; ir (neat): ν 3330 (NH), 1686 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.16 (br s, 1H), 3.18 (d, J = 12.6 Hz, 1H), 3.29 (d, J = 12.6 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 4.28 (d, J = 15.3 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 5.29 (s, 1H), 6.77-6.86 (m, 4H), 7.05-7.08 (m, 2H), 7.24-7.28 (m, 2H), 7.45-7.53 (m, 3H), 7.84-7.87 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 42.6, 44.9, 55.2 (x 2), 72.2, 113.8, 114.1, 123.1, 123.4, 129.0, 129.2, 129.5, 129.6, 131.8, 132.8, 141.2, 143.4, 158.7, 159.1, 167.6; ms: m/z (%) 388 (M^+, 1), 251 (58), 250 (57), 136 (44), 121 (100), 77 (10).

Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.23; H, 6.53; N, 7.18.

N-Phenyl-3-(phenylcarbamoyl)isoindolin-1-one (**5**).

This compound was obtained as white solid, mp 252-253°; ir (potassium bromide): ν 3296 (NH), 1693 (C=O), 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 6.09 (s, 1H), 6.95-7.86 (m, 14H), 10.73 (s, 1H); ^{13}C nmr (deuteriochloroform/DMSO-d_6): δ 62.9, 117.9, 118.6, 120.4, 121.8, 122.3, 122.8, 126.9, 127.1, 127.3, 130.2, 130.7, 136.5, 136.6, 138.8, 163.6, 165.5; ms: m/z (%) 328 (M^+, 9), 208 (100), 180 (9), 152 (5), 130 (3), 78 (14).

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.85; H, 4.86; N, 8.47.

3,3'-Bis(*N*-phenylisoindolin-1-one) (**6**).

This compound was obtained as white solid, mp 267-269°; ir (potassium bromide): ν 1687 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.72 (s, 2H), 6.85 (br s, 6H), 7.15-7.29 (m, 6H), 7.43-7.54 (m, 4H), 7.78 (d, J = 7.8 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 61.4, 122.0, 123.8, 124.1, 125.9, 128.7, 129.3, 132.1, 132.8, 135.9, 139.9, 166.4; ms: m/z (%) 416 (M^+, 2), 208 (100), 180 (5), 152 (3), 130 (2), 78 (7).

Anal. Calcd. for $C_{28}H_{20}N_2O_2$: C, 80.75; H, 4.84; N, 6.73. Found: C, 80.68; H, 5.15; N, 6.43.

Acknowledgment.

The authors are grateful to the Organic Chemistry Research Center of Korea Science & Engineering Foundation (KOSEF-OCRC) and the Basic Science Research Institute Programe of the Ministry of Education of Korea (BSRI-96-3408) for financial support and KOSEF for postdoctoral fellowship to C.S.C.

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