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Palladium-catalyzed carbonylative cyclization of 2-bromobenzaldehyde with primary amines leading to isoindolin-1-ones

Chan Sik Cho *, Wen Xiu Ren

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, South Korea

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ABSTRACT

2-Bromobenzaldehyde is carbonylatively cyclized with primary amines under carbon monoxide pressure in DMF at 100 °C in the presence of a catalytic amount of a palladium catalyst to give the corresponding isoindolin-1-ones in moderate to high yields.

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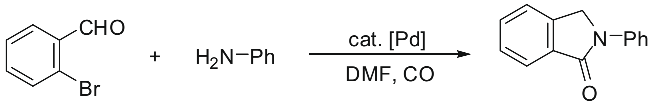
Palladium-catalyzed annulation provides a useful and convenient synthetic tool for the construction of skeletons of carbo- and heterocyclic compounds, which play an important role as a basic unit for the design of many pharmacologically and biologically active compounds.[1,2] Among them, palladium-catalyzed carbonylation with carbon monoxide followed by cyclization (carbonylative cyclization) has been recognized as an easy route for heterocyclic compounds containing carbonyl group such as lactones and lactams.[3] In connection with this report, several synthetic methods for isoindolin-1-ones have also been exemplified with such a palladium-catalyzed carbonylative cyclization.[4] For example, it is reported by us that 2-(2-bromophenyl)-2-oxazolines are carbonylatively cyclized with aliphatic alcohols in the presence of a palladium catalyst to give tricyclic isoindolinones.[5] 2-Bromobenzaldehyde was also found to be coupled and cyclized with ethanolamines and ethylenediamines under carbon monoxide pressure in the presence of a palladium catalyst to afford tricyclic isoindolin-1-ones.[6,7] It is also reported that isoindolin-1-ones can be synthesized by the palladium-catalyzed three-component cyclative carbonylation–amination cascade.[8] It was disclosed by Miura that aryl iodides undergo a novel palladium-catalyzed cross-carbonylation reaction with *N*-benzylideneamines to give isoindolin-1-ones.[9] Under these circumstances, during the course of our ongoing studies on palladium-catalyzed cyclization reactions,[10,11] herein this report describes a palladium-catalyzed carbonylative cyclization of 2-bromobenzaldehyde with primary amines leading to isoindolin-1-ones.[12,13]

The results of several attempted carbonylative cyclizations of 2-bromobenzaldehyde (**1**) with aniline (**2a**) for the optimization of conditions are listed in Table 1. Treatment of **1** with equimolar amount of **2a** under carbon monoxide (10 atm) in DMF in the presence of $PdCl_2(PPh_3)_2$ afforded *N*-phenylisoinolin-1-one (**3a**) in 25%

Table 1
Optimization of conditions for the reaction of **1** with **2a**[a]



1 **2a** **3a**

Run	[**1**]/[**2a**]	Palladium catalyst	Bases	Temp (°C)	Yield (%)
1	1.0	$PdCl_2(PPh_3)_2$	–	100	25
2	1.2	$PdCl_2(PPh_3)_2$	–	100	48
3	1.2	$PdCl_2(PPh_3)_2$	–	130	30
4[b]	1.2	$PdCl_2(PPh_3)_2$	–	100	64
5[b]	1.2	$PdCl_2(PPh_3)_2$	–	80	52
6[b]	1.2	$PdCl_2(PPh_3)_2$	HCO_2Na	100	66
7[b]	1.2	$PdCl_2(PPh_3)_2$	Et_3N	100	6
8[b]	1.2	$PdCl_2(PPh_3)_2$	K_2CO_3	100	46
9[b]	1.2	$PdCl_2(PPh_3)_2$	$NaHCO_3$	100	27
10[b]	1.2	$PdCl_2/2PPh_3$	–	100	73
11[b]	1.2	$Pd(OAc)_2/2PPh_3$	–	100	58
12[b]	1.2	$PdCl_2(PhCN)_2/2PPh_3$	–	100	81

[a] Reaction conditions: **2a** (0.5 mmol), palladium catalyst (0.02 mmol), base (2 mmol), CO (10 atm), DMF (5 mL), for 24 h.
[b] DMF (10 mL).

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* Corresponding author. Tel.: +82 53 950 5586; fax: +82 53 950 6594.
E-mail address: cscho@knu.ac.kr (C.S. Cho).

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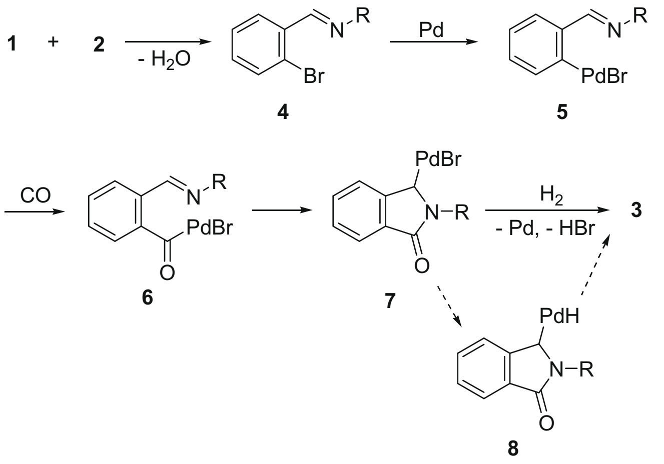
Table 2
Palladium-catalyzed synthesis of isoindolin-1-ones **3**[a]

Run	Primary amines **2**	Isoindolin-1-ones **3**	Isolated yield (%)
1	**2a**	**3a**	81
2	**2b**	**3b**	86
3	**2c**	**3c**	57
4	**2d**	**3d**	80
5	**2e**	**3e**	81
6	**2f**	**3f**	41
7	**2g**	**3g**	77
8	**2h**	**3h**	72
9	**2i**	**3i**	76
10	**2j**	**3j**	30
11	**2k**	**3k**	78
12	**2l**	**3l**	54
13	**2m**	**3m**	61
14	**2n**	**3n**	49
15	**2o**	**3o**	54

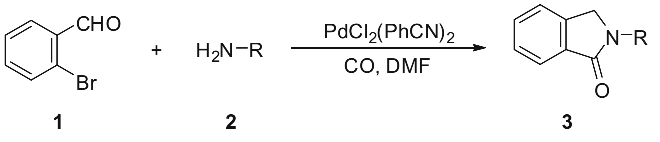
[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $PdCl_2(PhCN)_2$ (0.02 mmol), DMF (10 mL), CO (10 atm), 100 °C, for 24 h.



Scheme 2.

isolated yield (run 1). The yield of **3a** was considerably affected by the molar ratio of **1** to **2a**, a slightly higher molar ratio, [**1**]/[**2a**] = 1.2, resulting in the effective formation of **3a** (run 2). Lower and higher reaction temperatures resulted in lower yields of **3a** (runs 3 and 5). Higher yield of **3a** was observed with dilution of the reaction mixture (run 4). It is known that sodium formate works as a hydride source in palladium-catalyzed hydrogenolysis of organohalides and intramolecular cyclization.[14,15] However, the reaction gave no significant change with further addition of sodium formate (run 6). Further addition of several bases such as Et_3N, K_2CO_3, and $NaHCO_3$ to the reaction system rather resulted in a decreased yield of **3a** (runs 7–9). The catalytic systems using $PdCl_2$ and $Pd(OAc)_2$ combined with PPh_3 were revealed to be as effective as that using $PdCl_2(PPh_3)_2$ (runs 10 and 11). As a result, the best result was accomplished by the catalytic system using $PdCl_2(PhCN)_2$ combined with PPh_3 as shown in run 12 of Table 1.

After the reaction conditions have been established, various aromatic and aliphatic primary amines **2** were subjected to the reaction with **1** in order to investigate the reaction scope, and several representative results are summarized in Table 2 (Scheme 1). With aromatic primary amines (**2a**–**k**), the corresponding isoindolin-1-ones (**3a**–**k**) were formed in the range of 30–86% isolated yields without any identifiable side products (runs 1–11). The product yield was not significantly affected by the electronic nature of the substituent on the aromatic ring of **2a**–**k**, whereas the position of that had a considerable relevance to the product yield. With *meta*-substituted aromatic primary amines (**2c**, **2f**, and **2j**), the product yield is generally lower than those with primary aromatic amines having *ortho*- and *para*-substituents. Lower reaction rates and yields were observed with 1-aminonaphthalene (**2l**) and heteroaromatic primary amine **2m** when compared to those of primary aromatic amines having *ortho*- and *para*-substituents (runs 12 and 13). Aliphatic primary amines such as benzylamine (**2n**) and octylamine (**2o**) were also reacted with **1** to give *N*-benzylisoindolin-1-one (**3n**) and *N*-octylisoindolin-1-one (**3o**) in 49% and 54% yields, respectively (runs 14 and 15).



a R = Ph
b R = 2-MeC_6H_5
c R = 3-MeC_6H_5
d R = 4-MeC_6H_5
e R = 2-$MeOC_6H_5$
f R = 3-$MeOC_6H_5$
g R = 4-$MeOC_6H_5$
h R = 4-*sec*-BuC_6H_5
i R = 4-ClC_6H_5
j R = 3,5-$Me_2C_6H_4$
k R = 2,6-$Me_2C_6H_4$
l R = 1-naphthyl
m R = 3-pyridyl
n R = benzyl
o R = octyl

Scheme 1.

As to the reaction pathway, although it is not yet fully understood, this seems to proceed via an initial formation of imine **4** by the condensation between **1** and **2** (Scheme 2). Oxidative addition of a carbon–bromide bond of **4** to palladium(0) produces an arylpalladium(II) complex **5**, where carbon monoxide coordination to palladium and then aryl migration from palladium to the carbon of carbon monoxide occurs to give an aroylpalladium(II) intermediate **6**. This is followed by an intramolecular acylpalladation to carbon–nitrogen double bond to give an alkylpalladium(II) intermediate **7**. Subsequent hydrogenolysis of **7** with molecular hydrogen gives isoindolin-1-one **3**. Molecular hydrogen seems to be produced by the reaction of DMF and/or CO with H_2O generated in the initial condensation stage (Scheme 3). It is known that several transition metals catalyze hydrogen evolution from aqueous DMF solutions under relatively mild conditions.[16,17] The conversion of CO and H_2O into CO_2 and H_2 is well known as water gas shift reaction.[18] We confirmed in a separate experiment that treatment of **1** with **2a** and further addition of D_2O (0.5 mL) under the employed conditions afforded ca. 78% deuterated **3a** in 69% yield.[19] This result clearly indicates that H_2O works as a hydrogen source in the hydrogenolysis of **7**.[20,21]

General experimental procedure: To a 50 mL stainless steel autoclave were added 2-bromobenzaldehyde **1** (0.6 mmol), primary amine **2** (0.5 mmol), $PdCl_2(PhCN)_2$ (0.02 mmol), PPh_3 (0.04 mmol), and DMF (10 mL). After the system was flushed and then pressurized with carbon monoxide to 10 atm, the mixture was stirred at 100 °C for 24 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–hexane) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was

$$\mathrm{DMF} + H_2O \xrightarrow{\mathrm{Pd}} CO_2 + H_2 + HNMe_2$$

$$CO + H_2O \xrightarrow{\mathrm{Pd}} CO_2 + H_2$$

Scheme 3.

separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give isoindolin-1-ones **3**.[22]

In summary, we have shown that 2-bromobenzaldehyde undergoes carbonylative cyclization with aromatic and aliphatic primary amines under carbon monoxide pressure in the presence of a palladium catalyst to give isoindolin-1-ones in good yields. The present reaction is a straightforward methodology for the synthesis of isoindolin-1-ones from readily available starting compounds. The mechanistic rationale and further elaborated synthetic application for N-heterocycles using this protocol are currently under investigation.

Acknowledgment

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19. Deuterated **3a** was characterized with ^{13}C NMR spectrum [δ 50.58 (t, $^{1}J_{\mathrm{C\text{–}D}}$ = 21.8 Hz)] and the distribution was determined from the comparision of the peak area of a clearly separated signal with benzylic signal in ^{1}H NMR spectrum. An excess H_2O seems to reduce the product yield by imine hydrolysis.
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21. A reviewer suggested that the transformation of **7** to **3** may also involve a hydridopalladium(II) **8** formation by the action of CO (on coordination sphere) and H_2O without forming H_2.
22. Selected spectroscopic data. Compound **3a**: Solid (hexane–chloroform); mp 162–163 °C; (lit.[23] 163–163.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 2H), 7.17 (t, J = 7.3 Hz, 1H), 7.40–7.44 (m, 2H), 7.48–7.52 (m, 2H), 7.57–7.61 (m, 1H), 7.85–7.88 (m, 2H), 7.92 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.15, 119.89, 123.04, 124.56, 124.90, 128.80, 129.58, 132.49, 133.64, 139.90, 140.54, 167.94. Compound **3b**: Solid (hexane–chloroform); mp 98 °C; (lit.[23] 98–98.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.72 (s, 2H), 7.22–7.34 (m, 4H), 7.51 (t, J = 7.6 Hz, 2H), 7.58–7.62 (m, 1H), 7.94 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.34, 53.15, 122.95, 124.33, 126.96, 127.55, 128.30, 128.38, 131.32, 131.80, 132.51, 136.48, 137.09, 141.69, 167.75. Compound **3n**: Solid (hexane–chloroform); mp 88–89 °C; (lit.[24] 87–89 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H), 4.79 (s, 2H), 7.26–7.38 (m, 6H), 7.43–7.52 (m, 2H), 7.89 (d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.48, 49.55, 122.89, 123.96, 127.79, 128.15, 128.26, 128.91, 131.49, 132.69, 137.11, 141.34, 168.62.
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