Palladium-Catalyzed Intramolecular Cyclization of 2-Iodobenzamides: An Efficient Synthesis of 3-Acyl Isoindolin-1-ones and 3-Hydroxy-3-acylisoindolin-1-ones

Wanli Chen,*[a] Lina Jin,[a] Yinghong Zhu,*[b] Xiaoji Cao,[a] Lebin Zheng,[a] Weimin Mo[a]

[a] Center of Analysis & Measurement, Zhejiang University of Technology, Hangzhou 310014, P. R. of China
Fax +86(571)88320961; E-mail: chenwl@zjut.edu.cn

[b] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, P. R. of China
E-mail: yhzhuchem@zjut.edu.cn

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Abstract: Palladium-catalyzed intramolecular cyclization of 2-iodobenzamides with a 2-oxoethyl function group on the nitrogen atom moiety is presented, providing an efficient method for the synthesis of 3-acyl isoindolin-1-ones and 3-hydroxy-3-acylisoindolin-1-ones under mild conditions in moderate yields.

Key words: intramolecular cyclization, palladium-catalyzed, 3-acyl isoindolin-1-ones, 3-hydroxy-3-acylisoindolin-1-ones, 2-iodobenzamides

Isoindolinones with substitution at C-3 is the core structure of a number of biologically active natural products and pharmaceutically interesting compounds.[1,2] For example (Figure 1), pagoclone (**A**) is a commercialized anxiolytic drug,[3] and lennoxamine (**B**) is a typical alkaloid isolated from barberries species.[4] Pestalachloride A (**C**) is a strongly antifungal metabolite isolated from the plant endophytic fungus *Pestalotiopsis adusta*,[5] while isoindolinone **D** is a potent inhibitor of DNA gyrase, which shows promising antibacterial activity against Gram-positive bacterial strains.[6]

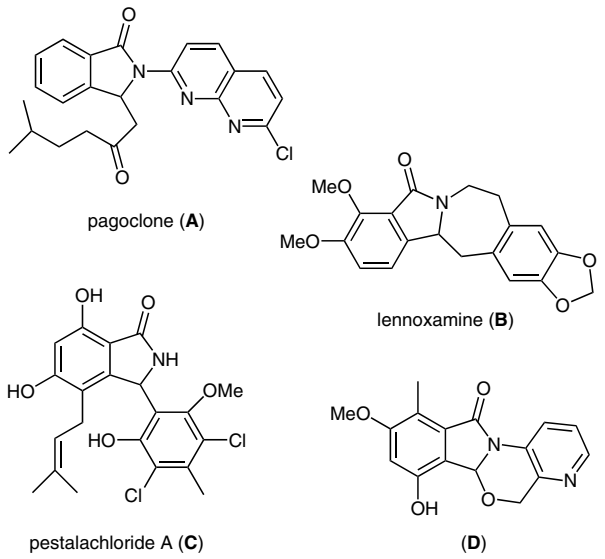

Figure 1

As a consequence, much attention has been paid to the synthesis of 3-substituted isoindolinone derivatives. Traditionally, the preparation of 3-substituted isoindolinones has been carried out by the nucleophilic attack reduction sequence of phthalimide, which usually involves the use of active organometallic nucleophiles.[7] The deprotonation reaction of unsubstituted isoindolinone by strong base represents another conventional strategy in providing different 3-substituted isoindolinones.[8] More modern achievements in the construction of substituted isoindolinones include rhenium-catalyzed reaction of aromatic aldimines with isocyanates,[9] superacid-catalyzed aza-Nazarov reaction of *N*-acyliminium ion salts,[10] palladium-catalyzed aromatic carbonylation of benzylic amines,[11] and iodoamination of R-substituted secondary 2-vinylbenzamides.[12] Recently, substituted isoindolinones could be readily prepared by the means of Pd-,[13] Rh-[14] or Ru-catalyzed[15] C–H activation sequences. Despite these well-established routes in the synthesis of C-3 functionalized isoindolinones, development of new and efficient methodologies for the synthesis of isoindolinones with different substituent groups from simple, readily available starting materials remains an active research area in organic chemistry regarding its broad structural diversity.

Recently, we have succeeded in the construction of isoquinolin-1(2*H*)-ones through DBU-promoted cyclization of *o*-(3-hydroxy-1-alkynyl)benzamides with a 2-oxoethyl function group on the nitrogen atom moiety, which could be obtained conveniently by a Sonogashira coupling between propargyl alcohols and 2-iodobenzamides with a 2-oxoethyl function group on the nitrogen atom moiety.[16] We proposed that this kind of 2-iodobenzamides might be used as efficient substrates in the construction of isoindolinones with an acyl group, which have not been accessible previously (Scheme 1). Retrosynthetically, 3-acyl isoindolin-1-one derivatives could be prepared by intramolecular α-arylation[17] of carbonyl derivatives, which in turn could be obtained conveniently by a reaction between 2-iodobenzoyl chloride and amino ketone. Herein, we report a general and efficient protocol for the preparation of 3-acyl isoindolin-1-ones[18] and 3-hydroxy-3-acylisoindolin-1-ones[19] through the palladium-catalyzed intramolecular cyclization of 2-iodobenzamides.

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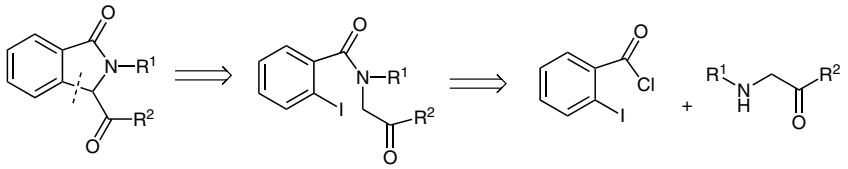
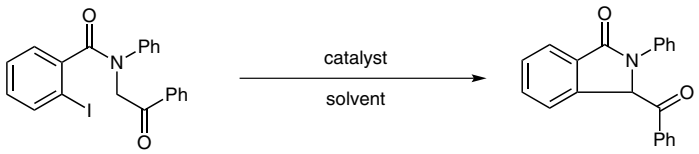


Scheme 1

In our primary investigations, we selected the intramolecular cyclization of 2-iodo-*N*-(2-oxo-2-phenylethyl)-*N*-phenylbenzamide (**1a**) as the model reaction (Table 1). After workup and isolation, the desired product **2a** was obtained in 54% yield using $PdCl_2(PPh_3)_2$ as the catalyst (Table 1, entry 1). In order to optimize the reaction conditions, several solvents and bases were examined. A lower yield was obtained when *i*-Pr_2NH was used as the base (Table 1, entry 4). *i*-PrOH was found to be the suitable solvent for this transformation in comparison with others, such as MeCN, dioxane, $ClCH_2CH_2Cl$, DMF and EtOH (Table 1, entries 3–9). Then, we further examined the effect of Pd catalyst and ligand choice on this reaction. Using $Pd_2(dba)_3$ as the catalyst and Xantphos as the ligand, a much better yield could be obtained (Table 1, entry 14), while others gave a lower yield (Table 1, entries 10–13).

With the optimized reaction conditions in hand (Table 1, entry 14), we further examined the scope of the reaction[20] and the results are summarized in Table 2. From the results in Table 2, we can see that the reaction proceeded smoothly to afford 3-acyl isoindolin-1-ones in moderate to good yields. Lower yields were obtained when R^2 was a methyl group relative to the aryl group (Table 2, entries 10 and 11), and the reactions also needed more time to complete.

Table 1 Optimization of Reaction Conditions for the Pd-Catalyzed Cyclization of **1a**[a]

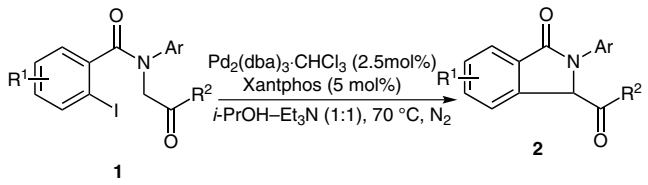


1a **2a**

Entry	Catalyst	Temp (°C)	Solvent	Base	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$	70	MeCN	Et_3N[c]	54[d]
2	$PdCl_2(PPh_3)_2$	100	DMF	Et_3N[c]	68
3	$PdCl_2(PPh_3)_2$	70	MeCN	Et_3N	81
4	$PdCl_2(PPh_3)_2$	70	MeCN	*i*-Pr_2NH	52
5	$PdCl_2(PPh_3)_2$	70	dioxane	Et_3N	67
6	$PdCl_2(PPh_3)_2$	70	DCE	Et_3N	64
7	$PdCl_2(PPh_3)_2$	70	DMF	Et_3N	68
8	$PdCl_2(PPh_3)_2$	70	EtOH	Et_3N	85
9	$PdCl_2(PPh_3)_2$	70	*i*-PrOH	Et_3N	88
10	$PdCl_2$(dppe)	70	*i*-PrOH	Et_3N	11
11	$PdCl_2$(dppf)	70	*i*-PrOH	Et_3N	65
12	$Pd_2(dba)_3$–P(*o*-$MeC_6H_4)_3$	70	*i*-PrOH	Et_3N	54
13	$Pd_2(dba)_3$–BINAP	70	*i*-PrOH	Et_3N	0
14	**$Pd_2(dba)_3$–Xantphos**	**70**	***i*-PrOH**	**Et_3N**	**96**

[a] The reaction was carried out using **1a** (0.3 mmol) in solvent (1 mL) and amine (1 mL) with Pd catalyst (5 mol%).
[b] Isolated yields.
[c] Et_3N (1.5 equiv) was added.
[d] Amide **1a** (34%) was recovered.

Table 2 Synthesis of 3-Acyl Isoindolin-1-ones **2**

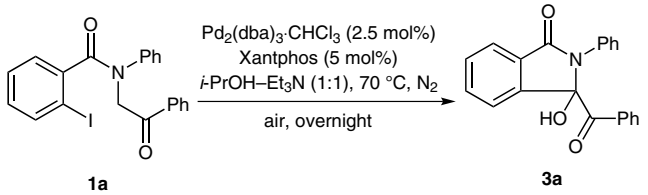


1 **2**

Entry	R^1, R^2, Ar	Time (h)	Product	Yield (%)[a]
1	H, Ph, Ph; **1a**	2	**2a**	96
2	H, Ph, *p*-MeC_6H_4; **1b**	2	**2b**	95
3	H, Ph, *p*-ClC_6H_4; **1c**	2	**2c**	95
4	H, *p*-FC_6H_4, Ph; **1d**	2	**2d**	87
5	H, *p*-MeC_6H_4, Ph; **1e**	5	**2e**	94
6	H, *p*-ClC_6H_4, *p*-MeC_6H_4; **1f**	5	**2f**	87
7	5-Cl, Ph, Ph; **1g**	2	**2g**	96
8	5-Me, Ph, Ph; **1h**	2	**2h**	66
9	4-Cl, Ph, Ph; **1i**	2	**2i**	82
10	H, Me, Ph; **1j**	5	**2j**	72
11	H, Me, *p*-ClC_6H_4; **1k**	5	**2k**	58
12	H, OEt, Ph; **1l**	24	**2l**	0[b]

[a] Isolated yields based on **1**.
[b] Compound **1l** was recovered.

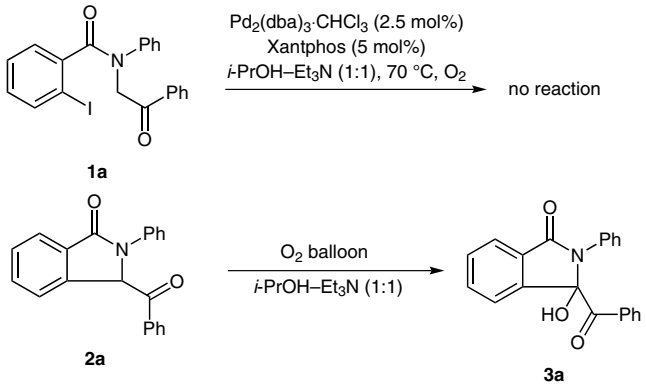
Interestingly, it was surprising to find the formation of the hydroxy product **3a** took place if the reaction mixture was left overnight under air without any precautions taken after the cyclization reaction (Scheme 2).



1a **3a**

Scheme 2

Where did the oxygen atom come from? The first reaction step was run under nitrogen, thus the possibility of the oxygen introduced at the cyclization stage was excluded. So we thought that the hydroxy isoindolin-1-one product **3a** may come from the reaction between isoindolin-1-one and oxygen in the air.[21] Therefore we conducted the control experiments which might be helpful for supporting the above points (Scheme 3).

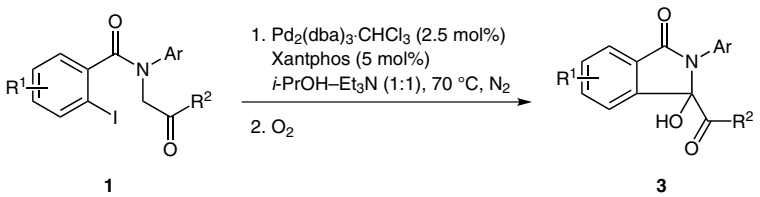


Scheme 3

When we ran the cyclization reaction under bubbled O_2, only the starting material **1a** was recovered due to the precipitation of palladium black. When isoindolin-1-one **2a** was stirred under O_2 at 70 °C, it was completely transformed into the hydroxy product **3a**. Further screening demonstrated that the reaction could be run in a one-pot, sequential procedure. Using N_2 for the first cyclization step and O_2 for the second step, we obtained **3a** in 80% yield. Then, a variety of similar compounds (**1b**–**k**) were also reacted under the same conditions[22] and the corresponding 3-hydroxy-3-acylisoindolin-1-ones (**3b**–**k**) were obtained in moderate yields (Table 3, entries 2–11).

In summary, we have developed an efficient method for the synthesis of 3-acyl isoindolin-1-ones and 3-hydroxy-3-acylisoindolin-1-ones in moderate to good yields under mild conditions. Further studies on the scope, mechanism, and synthetic applications of this transformation are being carried out in our laboratory.

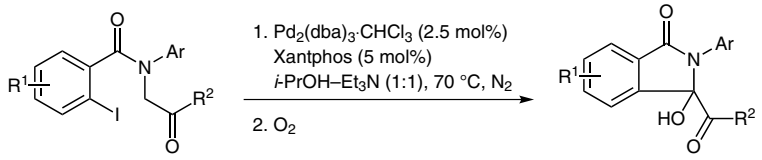
Table 3 Synthesis of 3-Hydroxy-3-acylisoindolin-1-ones **3**



1 **3**

Entry	R^1, R^2, Ar	Time (h)	Product	Yield (%)[a]
1	H, Ph, Ph; **1a**	24	**3a**	80
2	H, Ph, *p*-MeC_6H_4; **1b**	24	**3b**	75
3	H, Ph, *p*-ClC_6H_4; **1c**	24	**3c**	71

Table 3 Synthesis of 3-Hydroxy-3-acylisoindolin-1-ones **3** (continued)



1 **3**

Entry	R^1, R^2, Ar	Time (h)	Product	Yield (%)[a]
4	H, *p*-FC_6H_4, Ph; **1d**	24	**3d**	77
5	H, *p*-MeC_6H_4, Ph; **1e**	24	**3e**	79
6	H, *p*-ClC_6H_4, *p*-MeC_6H_4; **1f**	24	**3f**	68
7	5-Cl, Ph, Ph; **1g**	24	**3g**	72
8	5-Me, Ph, Ph; **1h**	24	**3h**	62
9	4-Cl, Ph, Ph; **1i**	24	**3i**	60
10	H, Me, Ph; **1j**	24	**3j**	67
11	H, Me, *p*-ClC_6H_4; **1k**	24	**3k**	51

[a] Isolated yields based on **1**.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) **General Procedure for the Synthesis of 2**:
2-Iodobenzamide **1** (0.3 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0075 mmol), Xantphos (0.015 mmol), and *i*-PrOH (1 mL) were added into a Schlenk tube at r.t. under N_2. After stirring for 5 min, Et_3N (1 mL) was added. The reaction mixture was stirred at 70 °C until the reaction was complete, as monitored by TLC (usually 2–5 h). Then the reaction mixture was cooled and the solvent was removed under reduced pressure. Dilute HCl (15 mL) was added, the aqueous layer was extracted with EtOAc (3 × 15 mL) and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the residues were purified by flash chromatography (silica gel; PE–EtOAc, 5:1 → 4:1) to afford **2**.
3-Benzoyl-2-phenylisoindolin-1-one (2a): solid (mp 178–180 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.4 Hz, 1 H), 7.95 (d, *J* = 7.5 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.47–7.54 (m, 4 H), 7.33 (t, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 7.13 (d, *J* = 7.4 Hz, 1 H), 6.65 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.3, 167.7, 138.8, 138.1, 135.1, 134.2, 132.4, 132.3, 129.4, 129.2, 129.1, 128.7, 125.1, 124.8, 122.5, 121.0, 67.0. IR: 3056, 1687, 1372, 752 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}NO_2$: 314.1181; found: 314.1177.

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(22) **General Procedure for the Synthesis of 3**:
2-Iodobenzamides **1** (0.3 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0075 mmol), Xantphos (0.015 mmol), and *i*-PrOH (1 mL) were added into a Schlenk tube at r.t. under N_2. After stirring for 5 min, Et_3N (1 mL) was added. The reaction mixture was stirred at 70 °C until the reaction was complete, as monitored by TLC (usually 2–5 h). Then the reaction mixture was stirred continuously under O_2 for 24 h. The reaction mixture was cooled and the solvent was removed under reduced pressure. Saturated NaCl (15 mL) was added, the aqueous layer was extracted with EtOAc (3 × 15 mL) and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the residues were purified by flash chromatography (silica gel; PE–EtOAc, 5:1 → 4:1) to afford **3**.
3-Benzoyl-3-hydroxy-2-phenylisoindolin-1-one (3a): solid (mp 124–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05–8.07 (m, 1 H), 7.61–7.67 (m, 2 H), 7.47–7.51 (m, 3 H), 7.40–7.41 (m, 1 H), 7.24–7.29 (m, 5 H), 7.19–7.21 (m, 2 H), 6.02 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.7, 167.8, 144.1, 134.7, 134.2, 133.6, 132.4, 131.4, 130.8, 129.3, 129.0, 128.8, 127.6, 126.8, 124.8, 122.7, 91.8. IR: 3254, 1684, 1386, 741 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}NO_3$: 330.1130; found: 330.1142.

