HETEROCYCLES, Vol. 92, No. 3, 2016, pp. -. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 21st December, 2015, Accepted, 21st January, 2016, Published online, .
DOI: 10.3987/COM-15-13398

ROOM-TEMPERATURE ONE-POT PALLADIUM-CATALYZED SYNTHESIS OF 3-HYDROXYISOINDOLIN-1-ONES FROM PHENYLGLYOXYLIC ACIDS

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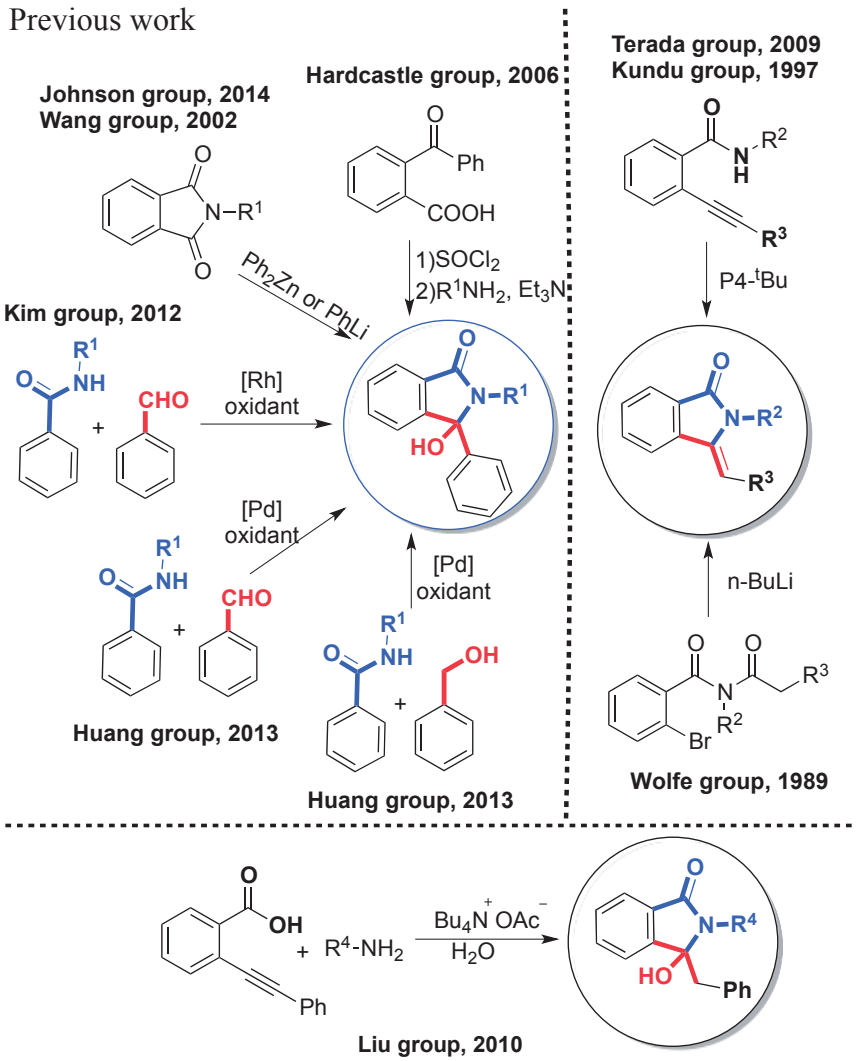
Abstract – A room-temperature and efficient synthesis of 3-hydroxyisoindolin-1-ones by Pd-catalyzed C-H activation has been proposed. Wide ranges of benzamides and phenylglyoxylic acids indicated good functional group tolerance and wide potential application of this approach. Moreover, good yields of products further made it practical and attractive.

3-Hydroxyisoindolin-1-ones are common structures in various bioactive compounds, such as inhibitors of the MDM2-p53 protein-protein interaction, HIV-1 integrase inhibitors, PTP1B inhibitors, antimicrobial corollosporines, PARP-1 inhibitors, and potassium channel inhibitors.[1-7] Additionally, 3-hydroxyisoindolin-1-ones are also important synthetic intermediates of potent C.N.S. agents, TRPM8 antagonists, MAPK pathway signaling inhibitors, and P2Y1 urea antagonists.[8-11]

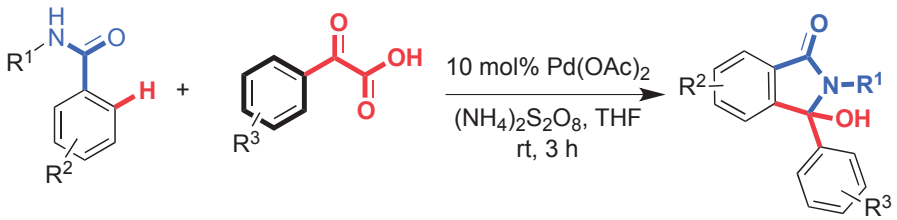
Traditionally, 3-hydroxyisoindolin-1-ones are usually prepared from the reaction of phthalimide derivatives and organometallic reagents.[12,13] Hardcastle group reported a novel approach to 3-hydroxyisoindolin-1-ones with 2-benzoylbenzoic acids in two steps.[2] Kundu and Terada groups provided their synthesis of 3-alkylideneisoindolinones with similar intermediates of *o*-(substituted ethynyl) benzamides.[14,15] Meanwhile, lithiation-cyclization of *N*-acyl-2-bromobenzamides has been reported as an alternative synthetic pathway to obtain 3-alkylideneisoindolinones.[16] With phase transfer catalysts, Liu group also synthesized 3-hydroxyisoindolin-1-ones via a metal-free transformation from 2-(phenylethynyl)benzoic acid and primary amines.[17] These approaches above, however, are more or less limited by rigorous reaction conditions, poor regioselectivity, availability of starting materials and functional group tolerance, all reducing their potential application.

Recently, with the development of transition-metal-catalyzed reactions, it is recognized that metal-catalyzed C-H activation could be a desirable strategy for the synthesis of 3-hydroxyisoindolin-1-ones. It was first reported that Kim group directly synthesized 3-hydroxyisoindolin-1-ones via tandem Rh(III)-catalyzed oxidative acylation of secondary benzamides with aldehydes and intramolecular cyclization.[18] Then Huang group described their synthesis of 3-hydroxyisoindolin-1-ones by Pd-mediated C-H activation/annulation reactions with aldehydes or alcohols.[19,20] Yet, these reactions suffer from expensive Ag oxidant and high reaction temperature, receptively. Herein, inspired by the activation of phenylglyoxylic acids with Pd, we report a room-temperature and efficient synthesis of 3-hydroxyisoindolin-1-ones by Pd-catalyzed C-H activation employing phenylglyoxylic acids as the simple coupling partners.[21,22]



Scheme 1. Conventional approaches and catalyzed C-H activation reactions for the synthesis of 3-hydroxyisoindolin-1-one derivatives

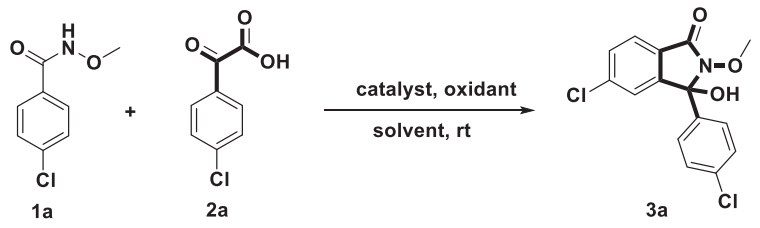
This work



Scheme 2. Room-temperature one-pot palladium-catalyzed synthesis of 3-hydroxyisoindolin-1-ones with phenylglyoxylic acids

Initially, we investigated the reactivity of benzamides with phenylglyoxylic acids by using *p*-chlorobenzamide (**1a**) and *p*-chlorophenylglyoxylic acids (**2a**) as starting substrates. A screening of catalysts showed that $Pd(OAc)_2$ gave the best yield in the presence of $(NH_4)_2S_2O_8$ in diglyme. Meanwhile, $Pd(PPh_3)_2(OAc)_2$ and $Pd(TFA)_2$ also could efficiently catalyze the reaction while $PdCl_2(dppf)$, $FeCl_2$ and CuI failed to facilitate the reaction (Table 1, entries 1–6). The effectiveness of the oxidant was also examined. It was found that $(NH_4)_2S_2O_8$ was an effective oxidant while other oxidants, such as air, H_2O_2, TBHP and *m*-CPBA, were relatively ineffective in the reaction (Table 1, entries 3 and 7-10).[23] Common organic solvents were screened. To our delight, THF was the optimal solvent prior to other solvents, such as diglyme, DMF, dioxane, toluene and DME (Table 1, entries 3 and 11-15). It was also noted that changing the oxidant amount or reaction time could reduce the yield of our desired product (Table 1, entries 14 and 16-20). Finally, when benzamide was treated with 1.2 equivalents of phenylglyoxylic acid in the presence of 10 mol% of $Pd(OAc)_2$ and 8 equivalents of ammonium persulphate in THF at room temperature for 3 h, our desired **3a** was successfully isolated in a good 80% yield (Table 1, entry 14).

Table 1. Optimization of the reaction conditions[a]



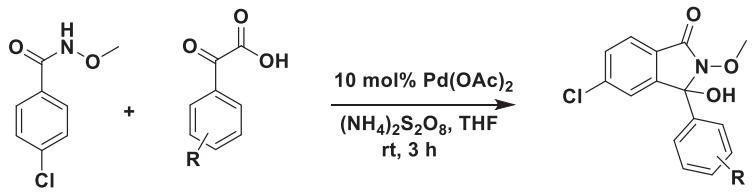
Entry	Catalyst	Oxidant (equiv.)	Solvent	Time	Yield (%)[b]
1	$Pd(TFA)_2$	$(NH_4)_2S_2O_8$(8)	diglyme	3 h	64
2	$Pd(PPh_3)_2(OAc)_2$	$(NH_4)_2S_2O_8$(8)	diglyme	3 h	45
3	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$(8)	diglyme	3 h	77

4	$PdCl_2(dppf)$	$(NH_4)_2S_2O_8(8)$	diglyme	3 h	trace
5	$FeCl_2$	$(NH_4)_2S_2O_8(8)$	diglyme	3 h	0
6	CuI	$(NH_4)_2S_2O_8(8)$	diglyme	3 h	0
7	$Pd(OAc)_2$	air	diglyme	3 h	24
8	$Pd(OAc)_2$	$H_2O_2(8)$	diglyme	3 h	trace
9	$Pd(OAc)_2$	TBHP(8)	diglyme	3 h	27
10	$Pd(OAc)_2$	*m*-CPBA(8)	diglyme	3 h	16
11	$Pd(TFA)_2$	$(NH_4)_2S_2O_8(8)$	DMF	3 h	20
12	$Pd(TFA)_2$	$(NH_4)_2S_2O_8(8)$	dioxane	5 h	72
13	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	toluene	3 h	trace
14	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	THF	3 h	80
15	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	DME	3 h	42
16	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(2)$	THF	3 h	37
17	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(15)$	THF	3 h	42
18	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	THF	7 h	70
19	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	THF	1.5 h	50
20	$Pd(OAc)_2$	$(NH_4)_2S_2O_8(8)$	THF	0.5 h	20
21	_	$(NH_4)_2S_2O_8(8)$	THF	3 h	0

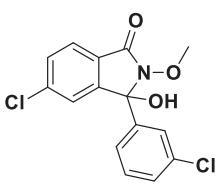
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (10 mol%), oxidant (as indicated), solvent (2 mL), sealed tube, rt. [b]Isolated yields.

Under the optimal condition, various substituted phenylglyoxylic acids were examined as shown in Table 2. In general, electron-deficient and electron-rich phenylglyoxylic acids all provided moderate to high yields. It is worth noting that for phenylglyoxylic acid with chloro-substituent at *para*-position (**3a**) afforded a higher yield than compared with other two positions (**3b** and **3f**), probably due to steric hindrance during the reaction. Similarly, *meta*-Me-phenylglyoxylic acid also provided an excellent yield (**3j**, 87%), which is much higher than *ortho*-Me-phenylglyoxylic acid (**3i**, 53%). In addition, *ortho*-Cl- and *ortho*-Me-phenylglyoxylic acids gave similar yields in the reaction (41% and 53%, respectively). It was found that phenylglyoxylic acids with other halogen groups (F and Br) also had good to excellent yields (65%-88%), providing an approach for further synthesis of bioactive compounds with 3-hydroxyisoindolin-1-one moiety.

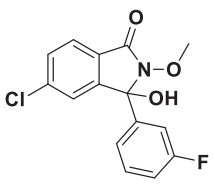
Table 2. Scope of Phenylglyoxylic Acids[a,b]



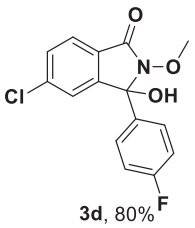
1a 2b-j 3b-j



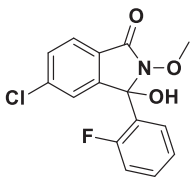
3b, 70%



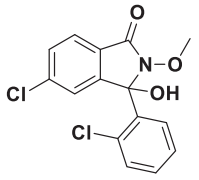
3c, 88%



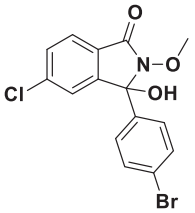
3d, 80%



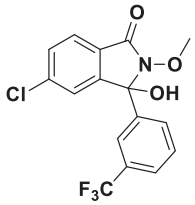
3e, 68%



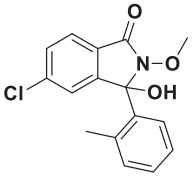
3f, 41%



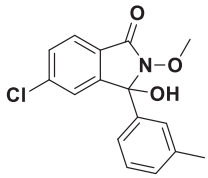
3g, 65%



3h, 61%



3i, 53%

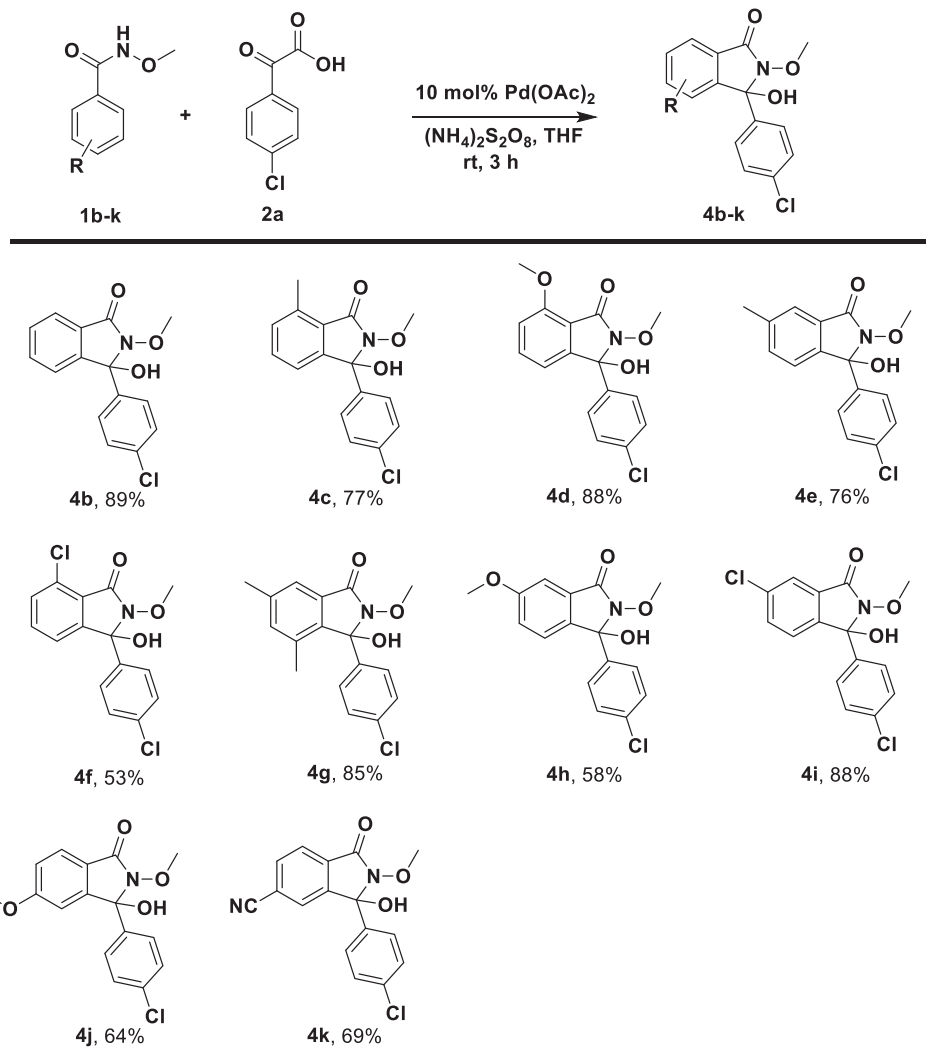


3j, 87%

[a]Reaction conditions: **1a** (0.5 mmol), **2b-j** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (4 mmol), THF (2 mL), sealed tube, rt. [b]Isolated yields.

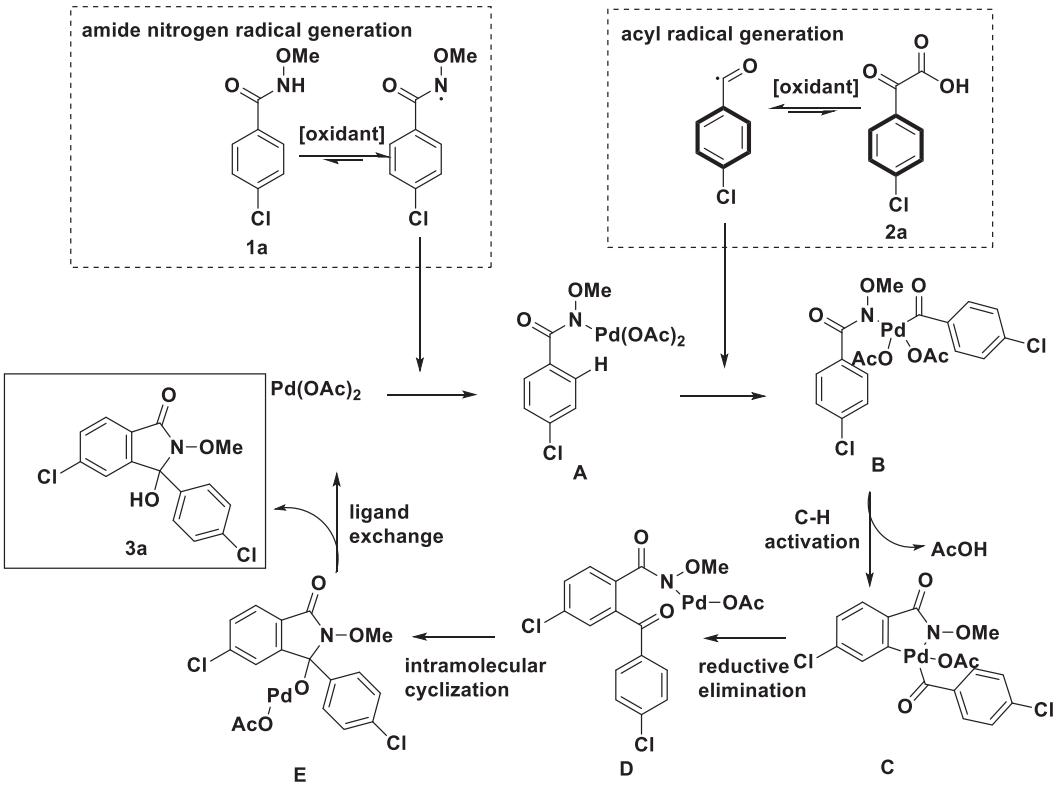
Encouraged by these results, we futher examined the scope of benzamides. Reactions with both electron-withdrawing and electro-donating benzamides all went fluently and gave our desired products in good to high yields. Interestingly, benzamides without any substituent afforded a higher yield (**4b**, 89%) than substituted benzamides. Therefore, subestituents may more or less influence the process of reaction. For substituent groups at meta-position, chloro-substituent gave a better yield (88%) than methyl and methoxy-substituent (76% and 58%, respectively), while for substituent groups at *ortho*-position, methoxy-substituent provided a better yield (88%) than methyl and chloro-substituent (77% and 53%, respectively). However, the yields of the two single methyl-substituted benzamides were both less than that of 3,5-dimethyl-substituted benzamides. Benzamides with methoxy-substituent and cyano-substituent at *para*-position both displayed better reactivity and had similar good yields, 64% and 69% respectively.

Table 3. Scope of Benzamides[a,b]



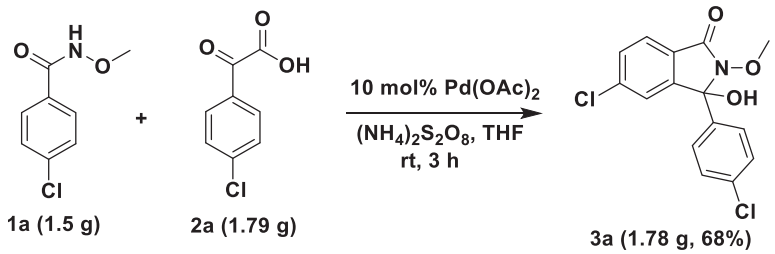
[a]Reaction conditions: **1b-k** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (4 mmol), THF (2 mL), sealed tube, rt. [b]Isolated yields.

Based on the above experiments and results, a possible reaction mechanism was proposed in Scheme 3. In the presence of $Pd(OAc)_2$, intermediate **A** is formed with the assistance of amide nitrogen radical generated by **1a**. Then intermediate **B** is provided after the addition of acyl radical generated by **2a**. The C-H activation of intermediate **B** leads to the formation of intermediate **C**. Then after one step of reductive elimination, intermediate **D** is formed. Intramolecular cyclization of intermediate **D** followed by another reductive elimination provides our desired product **3a**. Meanwhile, [Pd^0] is oxidized into [Pd^{II}] for the next reaction cycle.



Scheme 3. Proposed reaction mechanism

To test the reaction practicability and reliability, a gram-scale synthesis has also been examined. We successfully isolated our desired product **3a** in 68% yield under the optimal condition as shown in Scheme 4.



Scheme 4. Gram-scale synthesis of **3a**

In summary, we have demonstrated a highly efficient approach for the preparation of 3-hydroxyisoindolin-1-ones by Pd-catalyzed C-H activation at room temperature. This fast and environmentally friendly approach has provided good to high yields under mild conditions. Meanwhile, further synthesis of compounds targeting BET-BRD4 with antitumor activity in this approach is under investigation.

EXPERIMENTAL

General

All the solvents and commercially available reagents were purchased from commercial sources and used directly. All the reactions mentioned in this article were monitored by thin layer chromatography (TLC) at 254 nm under a UV lamp with the following eluent system: petroleum ether/ethyl acetate. Column chromatography separations were obtained on silica gel (200–300 mesh, purchased from Qing Dao Hai Yang Chemical Industry) eluting with petroleum ether/ethyl acetate (5/1 to 3/1). %Purity of the procudts (> 97%) were determined by HPLC analysis (UV detector, wavelength: 289 nm). ^{1}H NMR and ^{13}C NMR spectra on a Bruker AV 300 MHz spectrometer were recorded in $CDCl_3$ and DMSO-d_6, respectively. Chemical shifts were recorded in δ (ppm) units relative to TMS. High-resolution mass spectra (HRMS) were recorded on a HewlettePackard 1100 LC/MSD spectrometer.

Starting Materials

1g and **1k** were prepared following the procedure reported by Guimond et al.[24] **2a** was prepared from oxidation of the corresponding methyl ketone with SeO_2 according to the reported procedure.[25] Other *N*-methoxybenzamides and α-oxocarboxylic acids were purchased from Sigma-Aldrich, TCI, Alfa Aesar or Acros.

***N*-Methoxy-3,5-dimethylbenzamide (1g).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.63 (s, 1H), 7.35 (s, 2H), 7.17 (s, 1H), 3.68 (s, 3H), 2.30 (s, 6H).

4-Cyano-*N*-methoxybenzamide (1k). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 3.73 (s, 3H).

2-(4-Chlorophenyl)-2-oxoacetic acid (2a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H).

Synthesis of 3-Hydroxyisoindolin-1-ones

A solution of benzamides (0.5 mmol), α-oxocarboxylic acids (0.6 mmol), $Pd(OAc)_2$ (10 mol%) and $(NH_4)_2S_2O_8$ (4 mmol) in THF (3 mL) was stirred in a sealed tube under air at room temperature for 3 h. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was washed with saturated aqueous Na_2CO_3 to remove the acid. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum or in vacuo to provide the crude product. The purification was performed by flash column chromatography on silica gel (eluent: petroleum ether/EtOAc = 4/1, v/v) to give 3-hydroxyisoindolin-1-ones.

5-Chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3a). Following the general procedure, **3a** was isolated as a white solid (140 mg, 80%): Mp 192-194 °C;^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.1 Hz, 1H), 7.46 (dd, J = 8.1, 1.9 Hz, 1H), 7.44–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.25 (d, J = 1.9 Hz, 1H), 3.89 (s, 3H), 3.87–3.79 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.72, 148.05,

138.20, 137.42, 133.32, 130.18, 128.63, 128.18, 126.58, 124.97, 123.02, 89.66, 65.19; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_3$ $[M+Na]^+$ 346.0116; found 346.0119.

5-Chloro-3-(3-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3b). Following the general procedure, **3b** was isolated as a white solid (122 mg, 70%): Mp 196-198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.42 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.33–7.27 (m, 1H), 7.25–7.18 (m, 3H), 3.85 (s, 3H), 3.82 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 161.69, 147.79, 140.87, 138.20, 133.28, 130.56, 130.21, 128.59, 126.52, 126.07, 124.95, 124.84, 123.06, 89.48, 65.18; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_3$ $[M+Na]^+$ 346.0116; found 346.0114.

5-Chloro-3-(3-fluorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3c). Following the general procedure, **3c** was isolated as a white solid (146mg, 88%): Mp 158-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 13.9, 7.9 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 3.90 (s, 3H), 3.70 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 163.82, 160.58, 147.88, 141.31, 138.12, 130.61 (d, *J* = 8.2 Hz), 130.13, 126.55, 124.90, 123.01, 122.05, 115.41 (d, *J* = 20.4 Hz), 113.34 (d, *J* = 23.4 Hz), 89.45, 65.10; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}ClFNO_3$ $[M+Na]^+$ 330.0411; found 330.0410.

5-Chloro-3-(4-fluorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3d). Following the general procedure, **3d** was isolated as a white solid (132 mg, 80%): Mp 151-154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.51–7.40 (m, 3H), 7.27–7.26 (m, 1H), 7.07 (t, *J* = 8.6 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 163.71, 161.60, 160.46, 148.24, 138.09, 134.56 (d, *J* = 2.9 Hz), 130.04, 128.41 (d, *J* = 8.6 Hz), 126.56, 124.88, 122.96, 115.51, 115.23, 89.65, 65.08; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}ClFNO_3$ $[M+Na]^+$ 330.0411; found 330.0407.

5-Chloro-3-hydroxy-2-methoxy-3-(naphthalen-1-yl)isoindolin-1-one (3e). Following the general procedure, **3e** was isolated as a white solid (116 mg, 91%): Mp 162-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (td, *J* = 8.0, 1.8 Hz, 1H), 7.77–7.71 (m, 1H), 7.47 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.44–7.35 (m, 1H), 7.30 (dd, *J* = 3.5, 1.3 Hz, 1H), 7.26–7.23 (m, 1H), 7.03–6.92 (m, 1H), 3.88 (s, 3H), 3.74 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 161.97, 160.44, 157.15, 147.34, 137.85, 131.30, 131.18, 130.04, 129.58 (d, *J* = 1.7 Hz), 127.40 (d, *J* = 2.1 Hz), 125.03, 124.90, 124.64, 124.57, 122.62, 116.01, 115.72, 87.15, 65.01; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}ClFNO_3$ $[M+Na]^+$ 330.0411; found 330.0410.

5-Chloro-3-(2-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3f). Following the general procedure, **3f** was isolated as a white solid (71 mg, 41%): Mp 205-207 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.7 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.48–7.28 (m, 4H), 7.17 (s, 1H), 4.10 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 162.04, 146.81, 137.72, 133.97, 130.96, 130.90, 130.84, 130.71, 130.03, 128.72, 127.44, 124.57, 122.47, 87.91, 64.57; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_3$ $[M+Na]^+$ 346.0116; found 346.0113.

3-(4-Bromophenyl)-5-chloro-3-hydroxy-2-methoxyisoindolin-1-one (3g). Following the general procedure, **3g** was isolated as a white solid (128 mg, 65%): Mp 190-193 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.52–7.49 (m, 1H), 7.47 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38–7.35 (m, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.25 (s, 1H), 3.90 (s, 3H), 3.68 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 161.66, 147.96, 138.15, 137.82, 131.50, 130.13, 128.45, 126.55, 124.91, 122.99, 121.90, 89.65, 65.13; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}BrClNO_3$ $[M+Na]^+$ 389.9611; found 389.9614.

5-Chloro-3-hydroxy-2-methoxy-3-(3-(trifluoromethyl)phenyl)isoindolin-1-one (3h). Following the general procedure, **3h** was isolated as a white solid (117 mg, 61%): Mp 171-173 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.68–7.60 (m, 1H), 7.55–7.46 (m, 3H), 7.26 (s, 1H), 3.93 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 161.73, 147.66, 139.87, 138.28, 130.32, 129.91, 129.53, 129.47, 126.56, 125.54, 125.50, 125.01, 123.11, 122.63, 89.50, 65.22; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}ClF_3NO_3$ $[M+Na]^+$ 380.0380; found 380.0384.

5-Chloro-3-hydroxy-2-methoxy-3-(*o*-tolyl)isoindolin-1-one (3i). Following the general procedure, **3i** was isolated as a white solid (86 mg, 53%): Mp 166-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.38–7.32 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 1H), 3.68 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 160.48, 147.83, 139.51, 138.11, 135.67, 134.83, 132.76, 132.31, 132.05, 129.06, 128.33, 127.78, 125.65, 123.60, 64.53, 21.34; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_3$ $[M+Na]^+$ 326.0662; found 326.0661.

5-Chloro-3-hydroxy-2-methoxy-3-(*m*-tolyl)isoindolin-1-one (3j). Following the general procedure, **3j** was isolated as a white solid (141 mg, 87%): Mp 154-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.26 (s, 4H), 7.19 (d, *J* = 6.1 Hz, 1H), 3.91 (s, 3H), 3.60 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 161.51, 148.43, 138.15, 137.79, 137.60, 129.72, 128.99, 128.31, 126.46, 126.34, 124.67, 123.09, 122.75, 89.91, 64.84, 20.99; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_3$ $[M+Na]^+$ 326.0662; found 326.0665.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4b). Following the general procedure, **4b** was isolated as a white solid (138 mg, 89%): Mp 180-182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.1 Hz, 1H), 7.50 (dt, *J* = 19.9, 7.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.24 (s, 1H), 3.87 (s, 3H), 3.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 162.65, 146.26, 138.16, 133.45, 132.98, 129.75, 128.48, 128.06, 127.78, 122.83, 122.81, 89.92, 65.04; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}ClNO_3$ $[M+Na]^+$ 312.0506; found 312.0511.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxy-7-methylisoindolin-1-one (4c). Following the general procedure, **4c** was isolated as a white solid (126 mg, 77%): Mp 174-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.39 (m, 1H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 3.86 (s, 3H), 3.35 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 163.87, 146.90, 138.47,

136.50, 132.86, 131.38, 128.38, 128.12, 128.04, 124.52, 120.26, 89.14, 64.90, 16.88; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_3$ $[M+Na]^+$ 326.0662; found 326.0659.

3-(4-Chlorophenyl)-3-hydroxy-2,7-dimethoxyisoindolin-1-one (4d). Following the general procedure, **4d** was isolated as a white solid (152 mg, 88%): Mp 158-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.45 (m, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.08 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 162.21, 156.43, 148.63, 138.51, 135.26, 132.82, 128.38, 128.03, 114.58, 112.58, 88.91, 64.87, 55.85; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_4$ $[M+Na]^+$ 342.0611; found 342.0611.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxy-6-methylisoindolin-1-one (4e). Following the general procedure, **4e** was isolated as a white solid (124 mg, 76%): Mp 165-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.44–7.38 (m, 2H), 7.38–7.30 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 162.83, 143.58, 139.58, 138.40, 134.01, 132.87, 128.39, 128.02, 127.89, 122.91, 122.60, 89.84, 64.98, 20.92; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_3$ $[M+Na]^+$ 326.0662; found 326.0666.

7-Chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4f). Following the general procedure, **4f** was isolated as a white solid (92 mg, 53%): Mp 200-202 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.32 (m, 6H), 7.17 (d, *J* = 6.3 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 160.69, 148.80, 137.56, 134.84, 133.21, 131.02, 129.37, 128.55, 128.14, 123.74, 121.89, 88.72, 65.02; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_3$ $[M+Na]^+$ 346.0116; found 346.0114.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxy-4,6-dimethylisoindolin-1-one (4g). Following the general procedure, **4g** was isolated as a white solid (146 mg, 85%): Mp 177-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.29 (s, 1H), 7.25–7.15 (m, 3H), 7.04 (s, 1H), 3.72 (s, 3H), 3.40 (s, 1H), 2.29 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 162.46, 140.30, 139.62, 137.27, 135.63, 133.23, 132.68, 128.56, 128.19, 120.40, 89.61, 64.90, 20.73, 16.59; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}ClNO_3$ $[M+Na]^+$ 340.0819; found 340.0820.

3-(4-Chlorophenyl)-3-hydroxy-2,6-dimethoxyisoindolin-1-one (4h). Following the general procedure, **4h** was isolated as a white solid (100 mg, 58%): Mp 147-149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 162.62, 160.48, 138.49, 138.35, 132.84, 129.34, 128.39, 128.01, 124.11, 120.10, 106.67, 89.79, 64.97, 55.77; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_4$ $[M+Na]^+$ 342.0611; found 342.0617.

6-Chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4i). Following the general procedure, **4i** was isolated as a white solid (154 mg, 88%): Mp 195-197 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 1.9 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.7 Hz,

2H), 7.22 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.54 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.25, 144.74, 137.51, 134.58, 133.40, 133.25, 129.89, 128.59, 128.13, 124.91, 122.74, 89.76, 65.15; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_3$ $[M+Na]^+$ 346.0116; found 346.0115.

3-(4-Chlorophenyl)-3-hydroxy-2,5-dimethoxyisoindolin-1-one (4j). Following the general procedure, **4j** was isolated as a white solid (110 mg, 64%): Mp 142-145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 1H), 7.38–7.27 (m, 3H), 7.20 (s, 1H), 6.98–6.80 (m, 1H), 6.66 (d, J = 2.2 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.56 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.63, 163.07, 148.69, 138.32, 132.93, 128.43, 128.09, 124.72, 119.89, 115.98, 107.67, 89.72, 65.06, 55.88; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClNO_4$ $[M+Na]^+$ 342.0611; found 342.0611.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxy-1-oxoisoindoline-5-carbonitrile (4k). Following the general procedure, **4k** was isolated as a white solid (117 mg, 69%): Mp 172-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.57 (s, 1H), 7.47–7.33 (m, 4H), 4.10 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 160.70, 146.63, 136.86, 134.21, 133.43, 131.84, 128.60, 128.22, 126.87, 124.01, 117.85, 115.56, 89.75, 65.16; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}ClN_2O_3$ $[M+Na]^+$ 337.0458; found 337.0455.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Natural Science Foundation (No. BK 20141349) and the China National Key Hi-Tech Innovation Project for the R&D of Novel Drugs (No. 2013ZX09301303-002) for their financial support.

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