

HETEROCYCLES, Vol. 96, No. 10, 2018, pp. 1759 - 1770. © 2018 The Japan Institute of Heterocyclic Chemistry  
Received, 8th August, 2018, Accepted, 10th September, 2018, Published online, 28th September, 2018  
DOI: 10.3987/COM-18-13968

## ONE-POT SYNTHESIS OF ISOINDOLIN-1-ONES FROM NITROARENES AND *o*-PHTHALALDEHYDE VIA INDIUM-MEDIATED REDUCTIVE CONDENSATION REACTIONS

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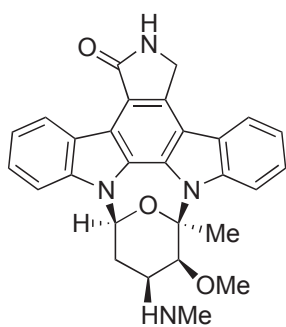
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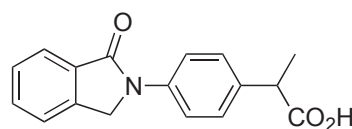
**Abstract** – Indium-mediated reductive condensation reactions of various nitroarenes with *o*-phthalaldehyde toward isoindolin-1-ones were investigated. In the presence of indium/AcOH in toluene at reflux, nitroarenes were coupled and cyclized with *o*-phthalaldehyde to produce corresponding isoindolin-1-ones with reasonable yields.

### INTRODUCTION

Isoindolinone skeleton is an important building block found in many bioactive organic substrates, and it has been investigated continuously.<sup>1</sup> It is not only present in alkaloids, but also present in simple natural and synthetic heterocycles as basic cores. These compounds are known to exhibit versatile and attractive biological activities, including anti-cancer, anti-inflammation, and immunomodulating activities.<sup>2</sup> For example, (+)-staurosporine alkaloid is one of the most potent protein kinase inhibitors up to date<sup>3</sup> while indoprofen possesses anti-inflammatory activity.<sup>4</sup>



(+)-staurosporine



indoprofen

Because of their biological activity and potential pharmacological application, several synthetic methods of isoindolin-1-ones (2,3-dihydro-1*H*-isoindol-1-ones) have been developed recently. Since the

pioneering work of Thiele,<sup>5</sup> many researchers have demonstrated numerous synthetic methodologies.<sup>6-10</sup> One of the most representative method is coupling reaction of *o*-phthalaldehyde with primary amines toward isoindolin-1-ones.<sup>6</sup> In addition, diverse synthetic approaches have been made lately using materials other than *o*-phthalaldehyde, such as 2-carboxybenzaldehyde,<sup>7</sup> benzamide,<sup>8</sup> *N*-tosylarylimine,<sup>9</sup> or *o*-halobenzoyl chloride.<sup>10</sup> Although these modified methods under various conditions or change of starting materials have a large contribution to the development of synthetic applications, none of them has reported the one-pot use of a nitro compound as a source of nitrogen heteroatom in isoindolin-1-one heterocycles.

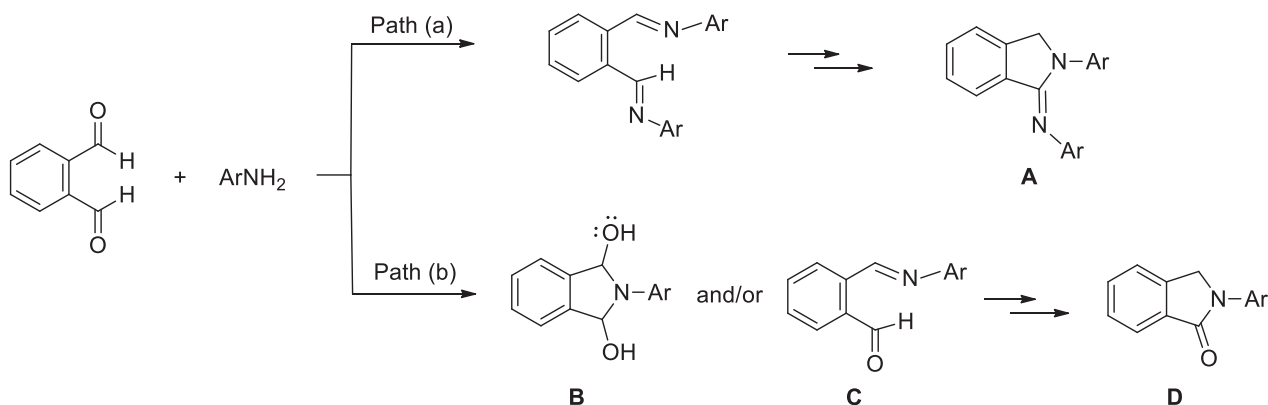
With environmental concerns and green chemistry are becoming hot issues, synthetic indium-mediated organic transformations are gradually increasing in the literature in the past two decades.<sup>11</sup> Our group has been engaged in the development of new synthetic methodologies using indium-mediated reaction conditions including reductive heterocyclizations towards 2,1-benzisoxazoles,<sup>12a,b</sup> benzimidazoles,<sup>12c</sup> quinolines,<sup>12d</sup> indazoles,<sup>12b</sup> indoles,<sup>12e,f</sup> pyrroles,<sup>12g,h</sup> and quinoxalines.<sup>12i</sup> Based on our accumulated knowledge of these reductive heterocyclizations, we attempted to extend our methodologies to another useful heterocycle synthesis. We hypothesized that indium-mediated one-pot synthesis of isoindolin-1-one heterocycles from the coupling reaction of nitroarenes with *o*-phthalaldehyde could be a unique inventive method using nitro compounds as starting substrate. Herein, we report the development of one-pot isoindolin-1-one synthesis from condensation reaction between nitroarenes and *o*-phthalaldehyde *via* indium-promoted reductive heterocyclization reactions.

## RESULTS AND DISCUSSION

In our previous indium-mediated reductive heterocyclization reactions, we have demonstrated that reductively in situ formed aniline intermediate could couple with carbonyl group immediately toward imine intermediate which could go further to form pyrroles<sup>12g,h</sup> or quinoxalines<sup>12i</sup> depending on dicarbonyls used for the reaction. Accordingly, we wondered whether we could develop another kind of reductive heterocyclization with the same concept to synthesize another type of useful heterocyclic compounds.

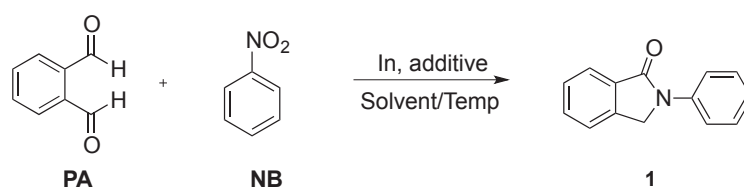
Thus, *o*-phthalaldehyde was elected as a coupling partner of in situ formed aniline intermediate. Since the actual behavior of in situ forming aniline or aniline-like intermediate could possibly be different from the direct use of aniline depending on its timing of formation and coupling, there might be two kinds of possible products (**A** and/or **B**) depending on how fast the reaction intermediates form and convert into the next step. If two individual carbonyl groups in *o*-phthalaldehyde immediately coupled with in situ formed each individual aniline intermediate to form diimine intermediate at the same time, it would transform into product **A** by sequential follow-up steps. However, if in situ formed one aniline coupled

with dicarbonyls to form intermediate **B** and/or imine that formed coupled with an aldehyde to form intermediate **C** to one coupling to the one imine-containing imine intermediate followed by fast cyclization with neighboring aldehyde, it would have transformed into product **D** instead (Scheme 1).



**Scheme 1**

With those two possibilities in mind, a one-pot reductive heterocyclization using *o*-phthalaldehyde and nitrobenzene substrates in the presence of indium metal was examined initially. As a primary control experiment, the same reaction system that was previously developed for the synthesis of pyrroles using nitrobenzenes and 1,4-dicarbonyls was selected.<sup>12g</sup> Reactions of *o*-phthalaldehyde (**PA**) and nitrobenzene (**NB**) in the presence of indium and acetic acid in toluene solvent at 80 °C were examined first (Entries 1-3, Table 1). From incomplete one-hour reaction to elucidate conceivable reaction intermediacy and probable direction of the reaction path, trace amount of aniline intermediate was observed from GC and GC-MS analysis with poor yield of 2-phenylisoindolin-1-one (Entry 1). However, any evidence for the path (a) toward imine **A** compound was not observed. Moreover, it produced 2-phenylisoindolin-1-one in reasonable yield (61%, Entry 2) with extended reaction time to 8 h. Increase of indium amount was helpful for diminishing the reaction time, but not for improving the yield (Entry 3). Without doubt, this trial could serve as a good foundation for developing new synthetic approaches to obtain isoindolin-1-one derivatives since one-pot reductive synthesis for isoindolin-1-one derivatives from nitro substrates are rarely known to date. To find better yielding condition, additional control experiments were conducted as shown in Table 1. The best condition was obtained in toluene at reflux with 74% of the desired product (Entry 4). Changing the solvent from toluene to protic one (Entries 8, 9), the use of indium(III) chloride Lewis acid (Entry 10), or the use of strong acid such as hydrochloric acid (Entry 11) did not work at all. Applying double amount of nitrobenzene was not successful either (Entry 12). Thus, the reaction of *o*-phthalaldehyde (1 mmol)/nitrobenzene (1 mmol)/indium (4 equiv)/acetic acid (10 equiv) in toluene (5 mL) at reflux (Entry 4) was selected as the most practical reaction condition for the synthetic application of isoindolin-1-one derivatives.

**Table 1.** Indium-mediated reductive condensation reaction between *o*-phthalaldehyde and nitrobenzene towards 2-phenylisoindolin-1-one under various conditions

Entry	Molar equiv.				Solvent (mL)/ Temp (°C)	Time (h)	Yield <sup>a</sup> (%)
	PA	NB	In	additive (equiv)			
1	1	1	4	AcOH (10)	toluene (5)/80	1	15 <sup>b</sup>
2	1	1	4	AcOH (10)	toluene (5)/80	8	61
3	1	1	6	AcOH (10)	toluene (5)/80	1	52
4	1	1	4	AcOH (10)	toluene (5)/reflux	4	74 <sup>c</sup>
5	1	1	4	AcOH (10)	toluene (5)/reflux	20	50 <sup>c</sup>
6	1	1	4	AcOH (10)	toluene (10)/reflux	6	58
7	1	1	6	AcOH (10)	toluene (5)/reflux	1.5	64
8	1	1	4	AcOH (10)	MeOH (10)/50	20	trace <sup>b,d,e</sup>
9	1	1	4	AcOH (10)	MeOH (10)/reflux	20	trace <sup>b,d,e</sup>
10	1	1	4	InCl <sub>3</sub> (1~2)	toluene (5)/reflux	4	0 <sup>d,e</sup>
11	1	1	4	HCl (12 N, 1 ml)	toluene (5)/reflux	4	trace <sup>b,d,e</sup>
12	1	2	4	AcOH (10)	toluene (5)/reflux	6	55 <sup>b</sup>

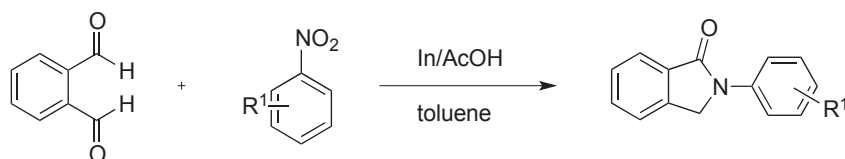
<sup>a</sup>NMR yield with an internal standard (dichloromethane). <sup>b</sup>Aniline intermediate was remained. <sup>c</sup>Isolated yield.

<sup>d</sup>Nitrobenzene was remained. <sup>e</sup>Phthalaldehyde was remained.

With the optimum condition obtained from control experiments, indium-acetic acid-promoted intermolecular coupling reaction toward isoindolin-1-one derivatives with *o*-phthalaldehyde and various nitroarenes were tried to establish synthetic utilization. Differently substituted nitroarenes including halo (F, Cl, Br), alkyl, and cyano groups on ortho-, meta-, and para-positions were tested for heterocyclizations via reductive coupling reactions with *o*-phthalaldehyde counterpart. Reactions accomplished are summarized in Table 2.

In most cases, heterocyclization reactions worked well to produce the desired product, 2-phenylisoindolin-1-ones, in reasonable yield within four to seven hours regardless of the position or the nature of substituent. Even though *o*-phthalaldehyde and nitroarenes were disappeared completely during the reaction, yields stayed in the moderate range because the reactions accompanied undesired polymeric product(s) that could be simply removed by the flash column chromatography.

**Table 2.** Indium-mediated reductive cyclizations towards 2-phenylisoindolin-1-one derivatives under optimized conditions (*o*-phthalaldehyde (1 mmol)/nitrobenzenes (1 mmol)/indium (4 mmol)/AcOH (10 mmol) in toluene (5 mL) at reflux

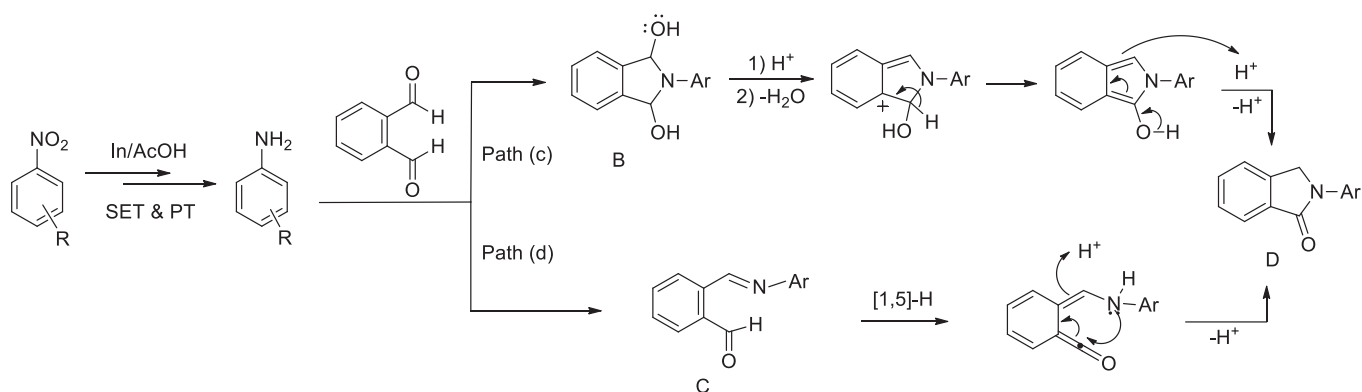


Entry	Substrate	Time/h	Product	Yield (%) <sup>a</sup>
1		4		74%
2		4		63%
3		5		57%
4		5		58%
5		6		62%
6		6		56%
7		4		60%
8		7		58%
9		4		54%
10		4		52%
11		7		67%
12		6		64%
13		6		63%

<sup>a</sup>Isolated yield.

Electron-withdrawing effect by halo-substituents and hyperconjugation donating effect seemed to have little effect on the reaction yield. In addition, in the case of meta-cyano substituted nitrobenzene (Entry 10, Table 2), reasonable yield was also observed with traces of undesired by-products formation that were removable by a conventional separation technique. Overall, this methodology can be utilized to synthesize substituted isoindolin-1-one derivatives with ease and in terms of green chemistry.

The synthesis of isoindolin-1-ones from the condensation between *o*-phthalaldehyde and primary amine is one of the most widely used method. Mechanistic proposals for those reactions explained in the literature could be applicable for our one-pot reductive heterocyclization between *o*-phthalaldehyde and nitroarenes.<sup>13</sup> One is classical mechanistic proposal that involves 1*H*-2,3-dihydroisoindole-1,3-diols (**B**) intermediate which can be formed by double addition of primary amine to adjacent two carbonyl groups of *o*-phthalaldehyde. Then it can be transformed into isoindolin-1-one by dehydration followed by tautomerization (path (c), Scheme 2).<sup>13a</sup> Regarding other probable mechanistic consideration, Alajarín and co-workers have proposed a [1,5]-H sigmatropic rearrangement based on computational study as depicted in path (d) in Scheme 2.<sup>13b</sup> Both mechanistic proposal are quite convincing. They might be applicable to our reductive one-pot reaction mechanistic consideration. We believe that in situ formed aniline via single electron transfer and proton transfer reactions during the first stage of our one-pot reductive reactions could go to the next steps, similar to the condensation between *o*-phthalaldehyde and primary amine via either path (c) or path (d) as described in Scheme 2.



**Scheme 2**

In conclusion, a new, environmentally friendly, and concise one-pot reductive heterocyclization was developed to obtain variously substituted isoindolin-1-one derivatives directly from condensation between *o*-phthalaldehyde and nitroarenes using indium/acetic acid under toluene reflux conditions. This one-pot cyclization method could be applied to synthesize biologically useful isoindolin-1-one derivatives using *o*-phthalaldehyde and a proper nitro compound.

## EXPERIMENTAL

### 1. General consideration

Most of the chemical reagents were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA) and were used without further purification in most cases. Solvents were purchased and dried using standard methods.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 400 MHz and 100 MHz, respectively (JEOL, Tokyo, Japan). Chemical shifts are reported in parts per million relative to the residual solvent as an internal standard or tetramethylsilane (TMS). GC–MS spectra were recorded on an Agilent 6890N GC connected to an Agilent 5975 mass selective detector (Hewlett-Packard Co., Palo Alto, CA, USA). HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer (JEOL, Tokyo, Japan). Infrared (IR) spectra were recorded using an MB104 FTIR (ABB Bomem, Inc., Zurich, Switzerland). Melting points were determined on a M3000 (Krüss Optronic, Hamburg, Germany) and uncorrected. All major products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, purchased from Merck & Co., Inc., Whitehouse Station, NJ, USA) using a mixed solvent eluent (EtOAc/hexane). Analytical thin layer chromatography (TLC) was performed using a 0.25 mm silica gel 60 F<sub>254</sub> precoated-glass plate.

### 2. General procedure for the indium-mediated reductive reaction of nitrobenzenes with *o*-phthalaldehyde to obtain isoindolin-1-ones

*o*-Phthalaldehyde (1.0 mmol) was added to a mixture of indium powder (460 mg, 4.0 mmol) and acetic acid (0.57 mL, 10 mmol) in toluene (2 mL), and nitrobenzene derivative (1.0 mmol) in toluene (3 mL) was added subsequently. The reaction mixture was stirred at reflux under nitrogen. After the reaction was complete, the reaction mixture was diluted with EtOAc (30 mL), filtered through Celite, and then poured into 10% aqueous NaHCO<sub>3</sub> solution (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was eluted with EtOAc/hexane (v/v = 3/97) through a neutral silica gel column to give the corresponding isoindolin-1-ones. Structures of isoindolin-1-ones were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, FTIR, and GC–MS, which were mostly known compounds. For unknown compounds, HRMS data were reported additionally.

**2-Phenylisoindolin-1-one**<sup>8a</sup> (**1**). White solid; mp 168.0–168.4 °C; TLC (30% EtOAc/hexane) *R*<sub>f</sub> 0.30;  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (d, 1H, *J* = 7.3 Hz), 7.87 (d, 2H, *J* = 7.8 Hz), 7.59 (t, 1H, *J* = 7.3 Hz), 7.53–7.47 (m, 2H), 7.43 (t, 2H, *J* = 7.8 Hz), 7.18 (t, 1H, *J* = 7.8 Hz), 4.85 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.44, 140.05, 139.41, 133.14, 132.01, 129.08, 128.30, 124.38, 124.04, 122.57, 119.35, 50.63; IR (neat) 3040, 2932, 2854, 1682, 1597, 1497, 1381, 1149, 733 cm<sup>-1</sup>; GC–MS *m/z* (rel. intensity) 209 (M<sup>+</sup>, 100), 180 (44), 104 (18), 77 (34).

**2-(4-Fluorophenyl)isoindolin-1-one<sup>8a</sup> (2).** White solid; mp 179.6–180.4 °C; TLC (30% EtOAc/hexane)  $R_f$  0.46;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (d, 1H,  $J = 8.2$  Hz), 7.84–7.81 (m, 2H), 7.63–7.59 (m, 1H), 7.53–7.50 (m, 2H), 7.16–7.10 (m, 2H), 4.83 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.48, 160.69, 158.26, 139.94, 135.54, 135.51, 132.91, 132.17, 128.45, 124.12, 122.64, 121.21, 121.13, 115.93, 115.71, 50.84; IR (neat) 3113, 3047, 2928, 2866, 1682, 1612, 1493, 1385, 1146, 729  $\text{cm}^{-1}$ ; GC–MS  $m/z$  (rel. intensity) 227 ( $\text{M}^+$ , 100), 198 (51), 122 (13), 95 (21), 75 (11).

**2-(4-Chlorophenyl)isoindolin-1-one<sup>14</sup> (3).** White solid; mp 189.6–180.4 °C; TLC (30% EtOAc/hexane)  $R_f$  0.50;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95–7.92 (m, 1H, including d,  $J = 7.3$  Hz), 7.88–7.82 (m, 2H), 7.65–7.60 (m, 1H), 7.55–7.50 (m, 2H), 7.41–7.37 (m, 2H), 4.85 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.57, 139.85, 138.04, 132.82, 132.32, 129.42, 129.11, 128.49, 124.13, 122.65, 120.28, 50.49; IR (neat) 3051, 2928, 1678, 1623, 1443, 1381, 1153, 733  $\text{cm}^{-1}$ ; GC–MS  $m/z$  (rel. intensity) 243 ( $\text{M}^+$ , 100), 215 (35), 138 (10), 111 (16), 75 (13).

0% EtOAc/hexane)  $R_f$  0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (d, 1H,  $J = 7.3$  Hz), 7.78–7.75 (m, 2H), 7.60–7.57 (m, 1H), 7.51–7.49 (m, 4H), 4.81 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.61, 139.90, 138.66, 132.96, 132.39, 132.15, 128.57, 124.26, 122.68, 120.72, 117.22, 50.50; IR (neat) 3020, 2924, 2862, 1678, 1385, 1157, 729  $\text{cm}^{-1}$ ; GC–MS  $m/z$  (rel. intensity) 288 ( $(\text{M}+2)^+$ , 100), 286 ( $\text{M}^+$ , 100), 261 (28), 259 (28), 180 (10), 104 (17), 76(12).

**2-(4-Methylphenyl)isoindolin-1-one<sup>14</sup> (5).** White solid; mp 136.2–137.4 °C; TLC (30% EtOAc/hexane)  $R_f$  0.42;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (dd, 1H,  $J = 6.8, 1.3$  Hz), 7.74 (d, 2H,  $J = 8.2$  Hz), 7.60 (td, 1H,  $J = 7.3, 1.6$  Hz), 7.53–7.49 (m, 2H), 7.24 (d, 2H,  $J = 8.2$  Hz), 4.85 (s, 2H), 2.37 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.44, 140.14, 136.94, 134.18, 133.31, 131.93, 129.68, 128.32, 124.04, 122.59, 119.53, 50.74, 20.76; IR (neat) 3020, 2924, 2858, 1678, 1443, 1389, 1157, 725  $\text{cm}^{-1}$ ; GC–MS  $m/z$  (rel. intensity) 223 ( $\text{M}^+$ , 100), 194 (36), 118 (9), 91 (20).

**2-(4-Isopropylphenyl)isoindolin-1-one (6).** White solid; mp 155.8–156.6 °C; TLC (30% EtOAc/hexane)  $R_f$  0.57;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (dd, 1H,  $J = 7.3, 1.3$  Hz), 7.80–7.75 (m, 2H), 7.60 (td, 1H,  $J = 7.3, 1.6$  Hz), 7.52–7.48 (m, 2H), 7.32–7.27 (m, 2H), 4.86 (s, 1H), 2.93 (quin, 1H, 6.9 Hz), 1.27 (d, 6H, 6.9 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.47, 145.30, 140.18, 137.18, 133.33, 131.97, 128.37, 127.13, 124.13, 122.63, 119.75, 50.79, 33.53, 30.92, 23.94; IR (neat) 3040, 2962, 2878, 1682, 1389, 1157, 771  $\text{cm}^{-1}$ ; GC–MS  $m/z$  (rel. intensity) 251 ( $\text{M}^+$ , 50), 236 (100), 77 (9). HRMS  $m/z$  calc. for  $\text{C}_{17}\text{H}_{17}\text{NO}$  351.1311, found 351.1305.



**2-(3-Fluorophenyl)isoindolin-1-one<sup>15</sup> (7).** White solid; mp 182.6–183.2 °C; TLC (30% EtOAc/hexane)  $R_f$  0.52; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.93 (d, 1H,  $J$  = 7.3 Hz), 7.81 (dd, 1H,  $J$  = 11.4, 1.8 Hz), 7.64–7.58 (m, 2H), 7.55–7.49 (m, 2H), 7.41–7.35 (m, 1H), 6.88 (td, 1H,  $J$  = 7.6, 1.5 Hz), 4.85 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.59, 164.35, 161.92, 141.07, 140.97, 139.86, 132.92, 132.39, 130.28, 130.19, 128.52, 124.26, 122.63, 114.15, 114.12, 111.12, 110.90, 106.76, 106.50, 99.89, 50.64; IR (neat) 3109, 3040, 2939, 1682, 1381, 1149, 771 cm<sup>-1</sup>; GC–MS  $m/z$  (rel. intensity) 227 (M<sup>+</sup>, 100), 198 (55), 122 (11), 95 (20), 75 (11).

**2-(3-Chlorophenyl)isoindolin-1-one<sup>14</sup> (8).** White solid; mp 187.6–188.4 °C; TLC (30% EtOAc/hexane)  $R_f$  0.52; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.93–7.91 (m, 2H), 7.82 (ddd, 1H,  $J$  = 7.4, 1.9, 0.8 Hz), 7.61 (t, 1H,  $J$  = 7.4 Hz), 7.52 (td, 2H,  $J$  = 7.3, 1.2 Hz), 7.34 (broad t, 1H,  $J$  = 8.0 Hz), 7.15 (ddd, 1H,  $J$  = 7.4, 1.9, 0.8 Hz), 4.84 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.66, 140.73, 139.95, 134.93, 132.90, 132.47, 130.20, 128.59, 124.36, 122.70, 119.25, 117.11, 50.54; IR (neat) 3047, 2962, 2870, 1682, 1597, 1450, 1389, 733 cm<sup>-1</sup>; GC–MS  $m/z$  (rel. intensity) 243 (M<sup>+</sup>, 100), 215 (39), 138 (10), 111 (17), 90 (17).

**2-(3-methylphenyl)isoindolin-1-one<sup>14</sup> (9).** White solid; mp 147.3–148.2 °C; TLC (30% EtOAc/hexane)  $R_f$  0.42; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.92 (d, 1H,  $J$  = 7.2 Hz), 7.72 (s, 1H), 7.66–7.56 (m, 2H), 7.52–7.48 (m, 2H), 7.29 (t, 1H,  $J$  = 7.9 Hz), 6.98 (d, 1H,  $J$  = 7.9 Hz), 4.82 (s, 2H), 2.39 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.43, 140.11, 139.39, 138.97, 133.26, 131.95, 128.91, 128.29, 125.28, 124.05, 122.54, 120.23, 116.57, 50.8, 21.65; IR (neat) 3086, 3040, 2955, 2916, 1682, 1381, 1157, 733 cm<sup>-1</sup>; GC–MS  $m/z$  (rel. intensity) 223 (M<sup>+</sup>, 100), 194 (36), 118 (9), 91 (24).

**3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)benzotrile (10).** White solid; mp 222.4–223.2 °C; TLC (30% EtOAc/hexane)  $R_f$  0.33; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23–8.20 (m, 2H), 7.95 (d, 1H,  $J$  = 7.3 Hz), 7.65 (td, 1H,  $J$  = 7.3, 1.1 Hz), 7.56–7.52 (m, 3H), 7.43 (dt, 1H,  $J$  = 7.8, 1.4 Hz), 4.88 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.87, 140.44, 139.79, 132.84, 132.55, 130.14, 128.8, 127.56, 124.52, 122.99, 122.82, 121.95, 118.61, 113.3, 50.31; IR (neat) 3086, 3040, 2947, 2916, 2238, 1690, 1381, 1157, 733 cm<sup>-1</sup>; GC–MS  $m/z$  (rel. intensity) 234 (M<sup>+</sup>, 100), 206 (55), 102 (18). HRMS  $m/z$  calc. for C<sub>15</sub>H<sub>10</sub>N<sub>2</sub>O 234.0794, found 234.0790.

**2-(2-Fluorophenyl)isoindolin-1-one (11).** White solid; mp 172.8–173.4 °C; TLC (30% EtOAc/hexane)  $R_f$  0.43; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95 (d, 1H,  $J$  = 7.3 Hz), 7.67–7.58 (m, 2H), 7.54–7.49 (m, 2H), 7.33–7.17 (m, 3H), 4.87 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.49, 160.82, 158.39, 140.02, 135.65, 135.63, 133.04, 132.19, 128.5, 124.22, 122.65, 121.32, 121.24, 115.97, 115.74, 50.92; IR (neat) 3057,

2939, 1682, 1458, 1389, 1157, 1057, 756, 733  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (rel. intensity) 227 ( $\text{M}^+$ , 100), 199 (52), 122 (18), 95 (17), 75 (17). HRMS  $m/z$  calc. for  $\text{C}_{14}\text{H}_{10}\text{FNO}$  227.0747, found 227.0743.

**2-(2-Methylphenyl)isoindolin-1-one<sup>15</sup> (12).** Brown solid; mp 114.2–115.8 °C; TLC (30% EtOAc/hexane)  $R_f$  0.38;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (d, 1H,  $J = 7.7$  Hz), 7.64–7.59 (td, 1H,  $J = 7.3, 1.0$  Hz), 7.56–7.51 (m, 2H), 7.36–7.24 (m, 4H), 4.74 (s, 2H), 2.27 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 141.46, 136.87, 136.23, 132.27, 131.56, 131.09, 128.14, 128.05, 127.31, 126.72, 124.08, 122.71, 52.91, 18.1; IR (neat) 3048, 2908, 2859, 1690, 1497, 1389, 1165, 741  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (rel. intensity) 223 ( $\text{M}^+$ , 100), 206 (40), 132 (30), 91 (33).

**2-(2-Bromophenyl)isoindolin-1-one (13).** Pale yellow solid; mp 131.6–132.2 °C; TLC (30% EtOAc/hexane)  $R_f$  0.63;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (d, 1H,  $J = 7.3$  Hz), 7.71 (d, 1H,  $J = 7.9$  Hz), 7.65–7.60 (m, 1H), 7.56–7.51 (m, 2H), 7.43–7.40 (m, 2H), 7.30–7.26 (m, 1H), 4.81 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.75, 141.4, 137.27, 133.4, 131.8, 131.69, 130.07, 129.57, 128.34, 128.01, 124.08, 122.78, 122.62, 52.11; IR (neat) 3040, 2939, 1674, 1481, 1396, 1165, 733  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (rel. intensity) 288 ( $(\text{M}+2)^+$ , 100), 286 ( $\text{M}^+$ , 100), 179 (19), 76 (24). HRMS  $m/z$  calc. for  $\text{C}_{14}\text{H}_{10}\text{BrNO}$  286.9946, found 286.9916.

## ACKNOWLEDGEMENT

This work was supported by Kwangwoon University in 2016-2017.

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