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Synthesis of 2,3-Diaryl Isoindolin-1-one by Copper-Catalyzed Cascade Annulation of 2-Formylbenzonitriles, Arenes and Diaryliodonium Salts

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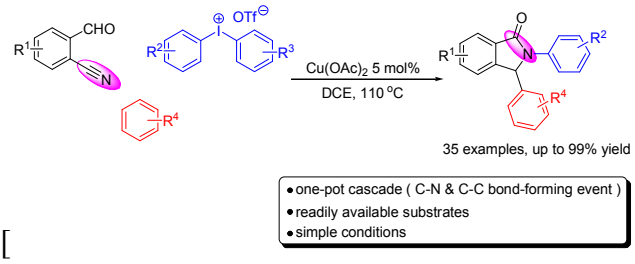
Supporting Information



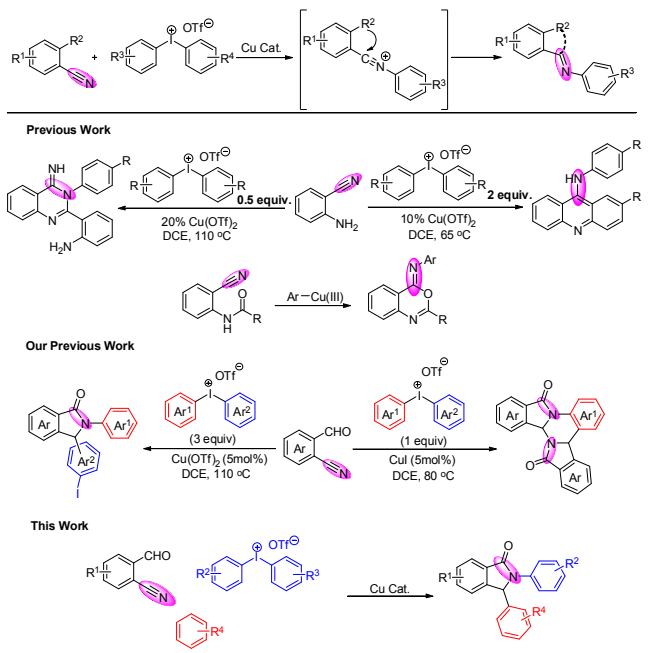
A three-component cascade cyclization was developed to synthesize 2,3-diarylisoindolin-1-one by using 2-formylbenzonitrile, arenes and diaryliodonium salts. The process underwent copper-catalyzed tandem C-N / C-C bonds formation, producing isoindolin-1-one derivatives in good to excellent yields.

■ INTRODUCTION

Aryl nitriles are undoubtedly one of the most valuable structural motifs in organic synthesis,[1] due to the versatility of conversion to other functional groups[2] and nitrogen-containing heterocycles.[3] Chen and co-workers demonstrated convenient protocols for synthesis of nitrogen-containing heterocycles from aryl nitriles and diaryliodonium salts, using the concept of aromatic electrophile generation via the intermediacy of Cu(III) species described by Gaunt et al.[4,5] Very Recently, Novák reported a copper-catalyzed reaction for the synthesis of iminobenzoxazine derivatives from *ortho*-cyanoanilides and diaryliodonium triflates via the formation of the C-N and C-C bonds.[6] All the reactions produced an activation of a nitrile group with a copper catalyst and generated *N*-aryl nitrilium cation in situ, then the *N*-phenylnitrilium intermediate would be attacked by group R followed by tandem ring closure to give final heterocycle product (Scheme 1).[6,7] Inspired by this cyclization concept, we chose aldehyde as the group R in the *ortho* position and the reaction should provide new heterocycle through similar cyclization path.

Isoindolin-1-ones is an important structural scaffolds commonly found in pharmaceuticals and natural products.[8] Furthermore, 2,3-substituted isoindolin-1-ones show great significance in many biologically active molecules,[9] such as Pagoclone,[10] anxiolytic drug, is related to better-known drugs as the sleeping medication zopiclone. Therefore, how to synthesize the isoindolin-1-ones efficiently is an interesting

Scheme 1. Synthesis of nitrogen-containing heterocycles by cyclization of *o*-cyanobenzene and diaryliodonium salts

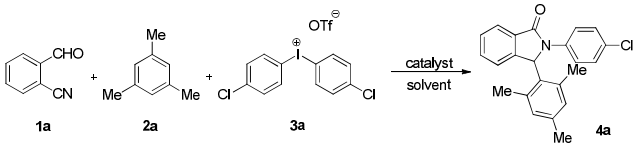


theme in organic chemistry and drug discovery. As a result, numerous methods for the construction of the isoindolin-1-ones have been developed rapidly in recent decades.[11] However, most of these methods suffer from certain limitations with respect to the substrate scope, yield, or apparative requirements, and are not suitable for the preparation of compound libraries. Recently, we reported a cascade cyclization mode for the construction of isoindolin-1-one scaffolds with diaryliodonium salts.[12] As a result of ongoing project, we herein report a three-component cascade cyclization to synthesize 2,3-substituted isoindolin-1-one by using readily available substrates including of 2-formylbenzonitrile, arenes and diaryliodonium salts. The reaction proceeded smoothly with copper catalysts through the formation of the C-N bond and C-C bond in cascade annulation reaction (Scheme 1).

■ RESULTS AND DISCUSSION

At the outset, we selected 2-formylbenzonitrile **1a**, 1,3,5-trimethylbenzene **2a** and di-*p*-chloroliodoniumtriflate **3a** as model substrates to investigate the feasibility for this three-component reaction. Without catalyst the reaction did not work in DCE at 110 °C overnight (Table 1, entry 1). Some proton acids such as TfOH, PTSA and CF_3COOH were employed as the catalysts, negative results were obtained under the same conditions above.

Table 1. Optimization of the reaction conditions[a]

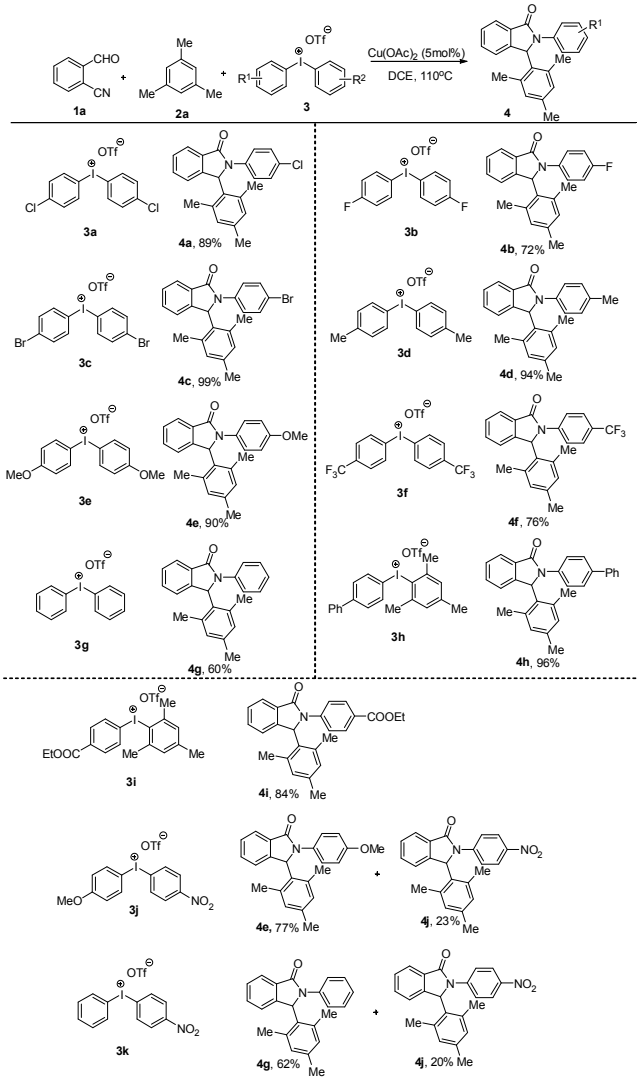


Entry	Catalyst	T (℃)	Solvent	Yield (%) [b]
1	--	110	DCE	--
2	TfOH	110	DCE	--
3	PTSA	110	DCE	--
4	TFA	110	DCE	--
5	CuI	110	DCE	82
6	$FeCl_3$	110	DCE	--
7	$CoCl_2$	110	DCE	--
8	$Cu(OTf)_2$	110	DCE	75
9	CuBr	110	DCE	77
10	$CuBr_2$	110	DCE	82
11	$[Cu(CH_3CN)_4]PF_6$	110	DCE	85
12	**$Cu(OAc)_2$**	**110**	**DCE**	**89**
13	$Cu(OAc)_2$	80	DCE	53
14	$Cu(OAc)_2$	110	MeCN	--
15	$Cu(OAc)_2$	110	DMF	--
16	$Cu(OAc)_2$	110	THF	trace
17	$Cu(OAc)_2$	110	1,4-Dioxane	58
18	$Cu(OAc)_2$	110	Toluene	48

[a] Reaction condition: **1a** (0.5 mmol), **2a** (1.0 mmol), **3a** (0.6 mmol) and catalyst (10 mol%) in DCE (2.0 mL), 110°C, 2 h. [b] Isolated yield.

Delightedly, the desired product **4a** was collected in 82% yield in the presence of 10% CuI (Table 1, entry 5). To our surprise, the reaction finished in only 2 hours. Other Lewis acids such as $FeCl_3$ and $CoCl_2$ were not suitable for this transformation. The screening of copper-catalysts showed that $Cu(OAc)_2$ was the most efficient for this reaction, 89% yield of **4a** was obtained (entry 12). To improve the yield of **4a**, we adjusted the temperature and found that **4a** was obtained in lower yield at 80 °C. Further screening of the solvents, such as MeCN, DMF, THF, 1,4-dioxane and toluene, DCE was found to be the best solvent.

Table 2. Diaryliodonium salts scope[a,b]

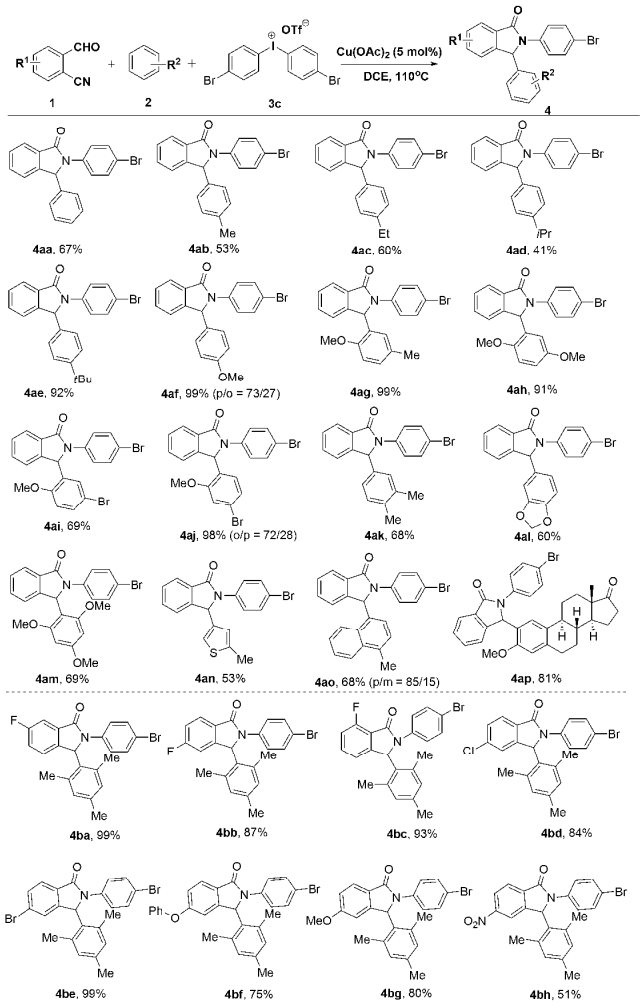


[a] Reaction condition: **1a** (0.5 mmol), **2a** (1.0 mmol), **3** (0.6 mmol) and $Cu(OAc)_2$ (10mol%) in DCE (2.0 mL), 110°C, 2 h. [b] Isolated yield.

Under the optimal conditions, the substrate scope of diaryliodonium salts **3** was investigated in this reaction (Table 2). Diaryliodonium salts could be easily prepared according to the literature.[13] To our delight, the reaction displayed excellent functional group tolerance, symmetric diaryliodonium salts

with a variety of substituents involving fluoro, chloride, bromide, methyl, methoxyl and CF_3 group on the aromatic ring all worked well with 2-formylbenzonitrile **1a** and 1,3,5-trimethylbenzene **2a**, providing the corresponding 2,3-diarylisoindolin-1-one in up to 99% yield (Table 2). The structure of the resulting **4b** was unequivocally confirmed using X-ray diffraction.[14] It is noteworthy that the electron-donating group substrates show higher activity than withdrawing group substrates (**4d**, **4e** vs **4f**). Moreover, unsymmetrical diaryliodonium salts were proven to be suitable substrates, which underwent a similar process toward **4** in good to excellent yields (Table 2, **4h-4j**). Interestingly, the higher the steric hindrance on one of the aryl groups of diaryliodonium salts, the more pronounced chemselectivity favoring is observed, **4h** was the only one product in the reaction, the same phenomenon occurred in **4i**. With the aim to explore the electronic nature of the substituents on the neighboring aryl group of the salts, unsymmetrical diaryliodonium salts **3j** and **3k** were tested. The reaction of **3j** is conducted towards the formation of **4e** and **4j** in 77/23 ratio, showing that Ar_2IOTf bearing electron-donating substituents favor the transformation.

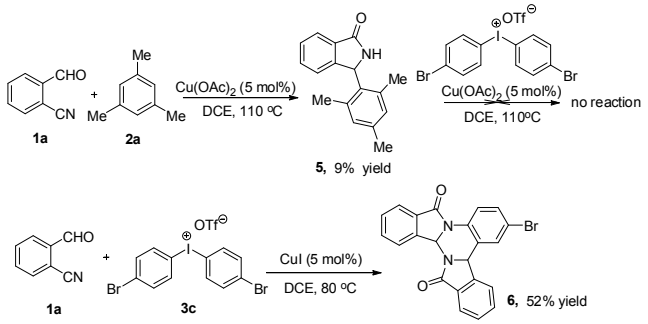
Table 3. Arene and 2-formylbenzonitrile scope[a,b]



[a] Reaction condition: **1** (0.5 mmol), **2** (1.0 mmol), **3c** (0.6 mmol) and $Cu(OAc)_2$ (10 mol%) in DCE (2.0 mL), 110 °C, 2 h. [b] Isolated yield.

After exploring the applicability of diaryliodonium triflates, we surveyed the scope of 2-formylbenzonitrile and arenes in this copper-catalyzed annulation (Table 3). The scope and generality of the reaction were explored by treating different benzene derivatives. Benzene was used to give the corresponding product **4aa** in 67% yield. Various mono-substituted benzene derivatives, including toluene, ethylbenzene, cumene, tert-butylbenzene and anisole were examined in the reaction, giving the desired products in 41-99% yields (**4ab**-**4af**). Notably, when anisole was employed, the final product **4af** was obtained as a mixture of regioisomers (*ortho*/*para* = 26/73). Besides, the disubstituted and trisubstituted benzenes also worked efficiently, affording 2,3-diarylisoindolin-1-one in up to 99% yield (**4ag**-**4am**). Furthermore, 1-methylnaphthalene and 2-methylthiophene were also appropriate partners for this reaction. Interestingly, estrone 3-methyl ether [15] was proven to be a suitable substrate, which underwent a similar three-component cyclization process toward complex steroid compound **4ap** in 81% yield. Disappointingly, arenes with electron-withdrawing group, such as nitrobenzene, (trifluoromethyl)benzene, did not proceed under standard conditions. Next, the scope of 2-formylbenzonitrile was probed. 2-formylbenzonitrile with fluoro, bromide and chloride group on the aromatic ring gave the desired product **4ba**-**4be** in 84-99% yields. The position of substituted groups had less influence on the reaction, such as fluoro group on 5-, 6- and 7-position of 2-formylbenzonitrile (**4ba, 4bb** and **4bc**), which proceeded smoothly to generate the products in good to excellent yields. In addition, electron-donating and electron-withdrawing groups at 5- positions of **1** also afforded products **4bg** and **4bh** in synthetically useful yields (**80%** and **51%**).

Scheme 2. Preliminary mechanistic studies



Preliminary mechanistic experiments were conducted to gain insights into the transformation (Scheme 2). Interestingly, 2-formylbenzonitrile **1a** reacted with mesitylene **2a** under the standard conditions to produce 3-mesitylisoindolin-1-one **5** in only 9% yield;[16, 17] next, treatment **5** with diaryliodonium salts **3c** under standard conditions, the reaction did not afford the final product **4c**. In another parallel reaction, polycycle product **6** was obtained in 52% yield from the reaction of **1a** and diaryliodonium salts **3c**. The results indicated that the reaction was not initiated by the reaction of 2-formylbenzonitrile **1a**

and aromatic ring, 2-formylbenzonitrile **1a** was activated first by diaryliodonium salts in the presence of copper.

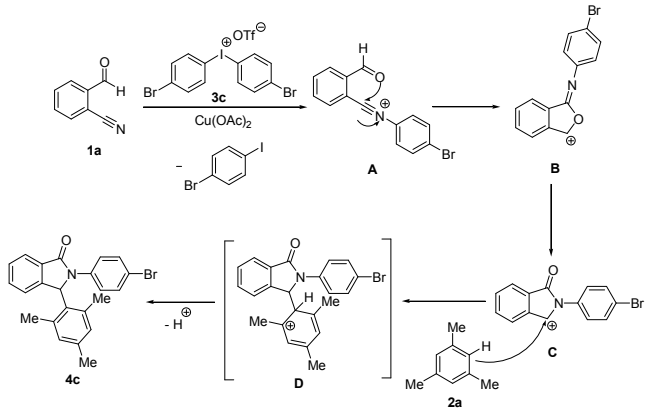


Figure 1. Proposed reaction mechanism

On the basis of the above experimental results, a reasonable mechanism suggested that N-aryl nitrilium cation is involved as shown in Figure 1. First, the reaction of 2-formylbenzonitrile **1a** with diaryliodonium salts **3c** gives the *N*-aryl nitrilium cation **A** in the presence of copper catalyst. Then the phenylnitrilium intermediate **A** is attacked by the aldehyde to afford intermediate **B**, which undergoes an intramolecular rearrangement via *aza*-Michael reaction to give cation intermediate **C**. Finally, the aimed product **4c** is generated through the Friedel-Crafts reaction between **C** and mesitylene **2a**.

■ CONCLUSIONS

In conclusion, we have demonstrated a three-component cascade cyclization for the construction of 2,3-diarylisoindolin-1-one with 2-formylbenzonitriles, arenes and diaryliodonium salts. The transformation proceeds via electrophilic Ar-Cu(III) activation of cyano group, undergoes C-N/C-C tandem cyclization into the 2,3-diaryl isoindolin-1-one core. The developed methodology provides straightforward access to 2,3-diaryl isoindolin-1-one derivatives in up to 99% yields. Further applications of these three-component cascade reactions are ongoing in our laboratory.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out under an airatmosphere condition. Various reagents were purchased from Aldrich, Acros or Alfa. The diaryliodonium salts **2** were prepared according literature. Flash column chromatography was performed using silica gel (200–300 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–300 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were recorded in $CDCl_3$ on Bruker NMR-300 (300MHz), NMR-400 (400MHz and NMR-500 (500MHz) with TMS as an internal reference. The model of HRMS is BrukermaXis UHR-TOF. The preparation of 2-formylbenzonitrile derivatives was described according to the literature.[18]

*General Procedure for preparation of compound **4.*** A solution of 2-formylbenzonitrile **1** (0.5 mmol), arene **2** (1.0 mmol), diaryliodonium salt **3** (0.6 mmol), $Cu(OAc)_2$ (0.025 mmol, 10mol%) in DCE (2 mL) was stirred at 110 ºC for 2 hours. After completion of the reaction (observed on TLC), the solvent was evaporated under reduced pressure to obtain the crude mixture. The residues was purified by silica-gel column chromatography (Ethyl acetate/Petroleum ether = 1/4 - 1/2) to afford the pure product **4**. The obtained product was analyzed by ^{1}H NMR, ^{13}C NMR and HRMS.

■ EXPERIMENTAL DATA OF PRODUCTS

*2-(4-Chlorophenyl)-3-mesitylisoindolin-1-one **(4a)**.* White solid (160.5 mg, 89%). MP: 151-153 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.92 (m, 1H), 7.51-7.48 (m, 4H), 7.24-7.20 (m, 2H), 7.17-7.14 (m, 1H), 6.93 (s, 1H), 6.58 (s, 1H), 6.46 (s, 1H), 2.65 (s, 3H), 2.19 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 143.8, 138.7, 138.0, 137.0, 136.5, 136.4, 132.7, 132.1, 131.8, 130.0, 129.8, 128.9, 123.9, 123.1, 122.4, 61.5, 29.7, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{23}H_{21}ClNO$ ($[M+H]^+$): 362.1306 found 362.1310.

*2-(4-Fluorophenyl)-3-mesitylisoindolin-1-one **(4b)**.* White crystalline solid (123.6 mg, 72%). MP: 164-166 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 1H), 7.51-7.44 (m, 4H), 7.18-7.15 (m, 1H), 6.99-6.91 (m, 3H), 6.60 (s, 1H), 6.47 (s, 1H), 2.62 (s, 3H), 2.19 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 159.9 (d, J = 242.8 Hz), 144.1, 138.0, 136.9 (d, J = 18.7 Hz), 133.8, 132.6, 131.7, 129.8, 128.5, 123.8 (d, J = 7.5 Hz), 122.4, 115.7 (d, J = 22.5 Hz), 61.9, 21.3, 20.8, 18.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.7. HRMS (ESI) calcd for $C_{23}H_{21}FNO$ ($[M+H]^+$): 346.1602 found 346.1600.

*2-(4-Bromophenyl)-3-mesitylisoindolin-1-one **(4c)**.* White solid (199.4 mg, 99%). MP: 150-151 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 1H), 7.48-7.43 (m, 4H), 7.37-7.34 (m, 2H), 7.16-7.13 (m, 1H), 6.93 (s, 1H), 6.57 (s, 1H), 6.44 (s, 1H), 2.66 (s, 3H), 2.18 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 143.8, 138.1, 136.9, 132.8, 131.8, 129.9, 129.1, 128.5, 123.9, 122.9, 122.4, 117.8, 61.4, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{23}H_{21}BrNO$ ($[M+H]^+$): 406.0801 found 406.0803.

*3-Mesityl-2-p-tolylisoindolin-1-one **(4d)**.* White solid (159.5 mg, 94%). MP: 145-147 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.97 (m, 1H), 7.52-7.50 (m, 2H), 7.42 (d, J =8.4 Hz 2H), 7.19-7.17 (m, 1H), 7.11 (d, J =8.4 Hz 2H), 6.93 (s, 1H), 6.61 (s, 1H), 6.52 (s, 1H), 2.66 (s, 3H), 2.12 (s, 3H), 2.27 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 144.2, 137.7, 137.2, 136.7, 135.2, 134.6, 132.4, 131.7, 129.7, 129.4, 128.4, 123.8, 122.4, 121.9, 61.7, 21.3, 20.9, 20.8, 18.9. HRMS (ESI) calcd for $C_{24}H_{24}NO$ ($[M+H]^+$): 342.1852 found 342.1855.

*3-Mesityl-2-(4-methoxyphenyl) isoindolin-1-one **(4e)**.* White solid (159.8 mg, 90%). MP: 138-140 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.93 (m, 1H), 7.48-7.45 (m, 2H), 7.39-7.37 (m, 2H), 7.15-7.13 (m, 1H), 6.88 (s, 1H), 6.81-6.78 (m, 2H), 6.59 (s, 1H), 6.44 (s, 1H), 3.69 (s, 3H), 2.58 (s, 3H), 2.17(s, 3H), 1.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 156.9, 144.3, 137.8, 136.8, 132.3, 131.6, 130.8, 129.6, 128.3, 123.8, 122.3, 114.1, 62.0, 55.3, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{24}H_{24}NO_2$ ($[M+H]^+$): 358.1802found 358.1803.

*3-Mesityl-2-[(4-trifluoromethyl)phenyl]-isoindolin-1-one **(4f)**.* White crystalline solid (149.1 mg, 76%). MP: 163-164 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 1H), 7.74-7.71

(m, 2H), 7.55-7.52 (m, 4H), 7.19-7.17 (m, 1H), 6.96 (s, 1H), 6.59-6.54 (m, 2H), 2.72 (s, 3H), 2.21 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 143.7, 138.2, 136.8, 136.2, 133.1, 131.9, 129.9, 128.7, 126.0, 124.0, 122.5, 120.6, 61.4, 21.3, 20.8, 18.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.2. HRMS (ESI) calcd for $C_{24}H_{21}F_3NO$ ($[M+H]^+$): 396.1570 found: 396.1569.

*3-Mesityl-2-phenylisoindolin-1-one (**4g**)*. White solid (97.9 mg, 60%). MP: 85-87 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 1H), 7.64-7.61 (m, 2H), 7.52-7.49 (m, 6H), 7.40-7.35 (m, 2H), 7.30-7.28 (m, 1H), 7.18-7.16 (m, 1H), 6.94 (s, 1H), 6.59 (s, 1H), 6.55 (s, 1H), 2.69 (s, 3H), 2.19 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 144.0, 140.4, 137.8, 137.4, 137.2, 137.1, 136.5, 132.5, 131.8, 129.8, 129.5, 128.7, 128.5, 127.4, 127.1, 126.8, 123.9, 122.4, 121.8, 61.6, 21.4, 20.8. HRMS (ESI) calcd for $C_{23}H_{22}NO$ ($[M+H]^+$): 328.1696 found 328.1700.

*2-(Biphenyl-4-yl)3-mesitylisoindolin-1-one (**4h**)*. White solid (193.4 mg, 96%). MP: 163-165 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 1H), 7.64-7.61 (m, 2H), 7.52-7.49 (m, 6H), 7.40-7.35 (m, 2H), 7.30-7.28 (m, 1H), 7.18-7.16 (m, 1H), 6.94 (s, 1H), 6.59 (s, 1H), 6.55 (s, 1H), 2.69 (s, 3H), 2.19 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 144.1, 137.8, 137.2, 136.6, 132.5, 131.8, 129.7, 129.5, 128.8, 128.4, 124.9, 123.8, 122.4, 121.8, 61.6, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{29}H_{26}NO$ ($[M+H]^+$): 404.2009found 404.2015.

*Ethyl 4-(1-mesityl-3-oxoisoindolin-2-yl)benzene (**4i**):* White crystalline solid (167.6 mg, 84%). MP: 175-176 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 3H), 7.69-7.66 (m, 2H), 7.54-7.45 (m, 2H), 7.18-7.16 (m, 1H), 6.95 (s, 1H), 6.55-6.51 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.71 (s, 3H), 2.18 (s, 3H), 1.61 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 166.1, 143.7, 141.8, 138.0, 136.7, 136.2, 132.9, 131.9, 130.3, 129.9, 129.2, 128.6, 126.0, 123.9, 122.4, 120.1, 61.4, 60.8, 21.3, 20.7, 18.9, 14.3. HRMS (ESI) calcd for $C_{26}H_{26}NO_3$ ($[M+H]^+$): 400.1907 found 400.1905.

*3-Mesityl-2-(4-nitrophenyl)isoindolin-1-one (**4j**)*. White solid (42.7 mg, 23%). MP: 261-263 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2H), 7.99-7.97 (m, 1H), 7.82-7.79 (m, 2H), 7.60-7.51 (m, 2H), 7.22-7.19 (m, 1H), 7.00 (s, 1H), 6.59-6.57 (m, 2H), 2.76 (s, 3H), 2.21 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 143.7, 143.5, 143.4, 138.4, 136.5, 136.0, 133.5, 132.1, 131.4, 130.2, 128.8, 124.6, 122.5, 120.0, 61.5, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3$ ($[M+H]^+$): 373.1547 found 373.1547.

*2-(4-Bromophenyl)-3-phenylisoindolin-1-one (**4aa**)*.[19] White solid (120.6 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 1H), 7.55-7.48 (m, 4H), 7.41-7.38 (m, 2H), 7.29-7.22 (m, 4H), 7.18-7.14 (m, 2H), 6.05 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 145.5, 137.2, 136.8, 132.7, 131.9, 130.7, 129.3, 128.7, 128.6, 124.2, 123.6, 117.9, 65.4.

*2-(4-Bromophenyl)-3-p-tolylisoindolin-1-one (**4ab**)*. White solid (99.9 mg, 53%). MP: 166-167 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.92 (m, 1H), 7.54-7.48 (m, 4H), 7.40-7.37 (m, 2H), 7.23-7.21 (m, 1H), 7.07 (s, 4H), 6.00 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 145.7, 138.4, 136.8, 134.1, 132.7, 131.8, 129.9, 128.6, 126.7, 124.1, 123.7, 123.0, 117.8, 65.3, 21.2. HRMS (ESI) calcd for $C_{21}H_{17}BrNO$ ($[M+H]^+$): 378.0488 found 378.0488.

*2-(4-Bromophenyl)-3-(4-ethylphenyl)isoindolin-1-one (**4ac**):* white solid (116.5 mg, 60%). MP: 116-117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.93 (m, 1H), 7.58-7.46 (m, 4H), 7.40-7.37 (m, 2H), 7.25-7.21 (m, 1H), 6.01 (s, 1H), 2.57 (q, J = 7.6 Hz, 2H), 1.16 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 145.7, 144.6, 136.8, 134.3, 132.7, 131.8, 130.7, 128.7, 128.6, 126.7, 124.1, 123.6, 123.0, 117.8, 65.3, 28.4, 15.2. HRMS (ESI) calcd for $C_{22}H_{19}BrNO$ ($[M+H]^+$): 392.0645 found 392.0644.

*2-(4-Bromophenyl)-3-(4-isopropylphenyl)isoindolin-1-one (**4ad**)*. white solid (83.0 mg, 41%). MP: 178-180 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.93 (m, 1H), 7.56-7.48 (m, 4H), 7.41-7.38 (m, 2H), 7.24-7.22 (m, 1H), 7.13-7.09 (m, 4H), 6.02 (s, 1H), 2.87-2.78 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 149.2, 145.7, 136.9, 134.3, 132.6, 132.5, 132.3, 131.8, 130.7, 128.6, 127.3, 126.6, 124.1, 123.6, 123.1, 117.8, 65.2, 33.7, 23.8, 23.7. HRMS (ESI) calcd for $C_{23}H_{21}BrNO$ ($[M+H]^+$): 406.0801 found 406.0801.

*2-(4-Bromophenyl)-3-(4-tert-butylphenyl)isoindolin-1-one (**4ae**)*. White solid (192.7 mg, 92%). MP: 210-212 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.93 (m, 1H), 7.57-7.54 (m, 2H), 7.51-7.46 (m, 2H), 7.41-7.38 (m, 2H), 7.29-7.23 (m, 3H), 7.11-7.08 (m, 2H), 6.02 (s, 1H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.4, 145.7, 136.9, 133.9, 132.6, 131.9, 130.7, 128.6, 126.3, 126.2, 124.1, 123.6, 123.1, 117.7, 65.1, 34.6, 31.2. HRMS (ESI) calcd for $C_{24}H_{23}BrNO$ ($[M+H]^+$): 420.0958 found 420.0959.

*2-(4-bromophenyl)-3-(4-methoxyphenyl)isoindolin-1-one (**4af**)*. White solid (195.0 mg, 99%). MP: 154-155 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.93 (m, 1H), 7.52-7.49 (m, 4H), 7.41-7.38 (m, 2h), 7.23-7.20 (m, 1H), 7.10-7.07 (m, 2H), 6.80-6.78 (m, 2H), 5.99 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 159.6, 145.8, 136.7, 132.7, 131.8, 130.7, 128.9, 128.6, 128.1, 124.1, 123.8, 122.9, 117.9, 114.5, 64.9, 55.2. HRMS (ESI) calcd for $C_{21}H_{17}BrNO_2$ ($[M+H]^+$): 394.0437 found 394.0437.

*2-(4-Bromophenyl)-3-(2-methoxy-5-methylphenyl)isoindolin-1-one (**4ag**)***.** White solid (201.4 mg, 99%). MP: 190-191 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.91 (m, 1H), 7.63-7.61 (m, 2H), 7.50-7.45 (m, 2H), 7.40-7.37 (m, 2H), 7.32-7.30 (m, 1H), 6.99-6.95 (m, 1H), 6.85-6.73 (m, 1H), 6.65-6.52 (m, 2H), 3.98 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 154.9, 146.1, 137.2, 136.2, 131.8, 130.6, 129.8, 128.3, 126.7, 124.8, 123.9, 122.9, 122.6, 117.3, 111.0, 55.8, 20.5. HRMS (ESI) calcd for $C_{22}H_{19}BrNO_2$ ($[M+H]^+$): 408.0594 found 408.0598.

*2-(4-Bromophenyl)-3-(2,5-dimethoxyphenyl)isoindolin-1-one (**4ah**)*. White solid (192.4 mg, 91%). MP: 164-165 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.90 (m, 1H), 7.61-7.59 (m, 2H), 7.51-7.45 (m, 2H), 7.40-7.32 (m, 3H), 6.90-6.87 (m, 1H), 6.72-6.65 (m 2H), 6.30 (br, 1H), 3.95 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 153.9, 151.2, 137.1, 132.6, 131.8, 128.5, 124.0, 122.9, 122.8, 117.4, 113.8, 112.1, 56.2, 55.5. HRMS (ESI) calcd for $C_{22}H_{19}BrNO_3$ ($[M+H]^+$): 424.0543 found 424.0548.

*3-(5-Bromo-2-methoxyphenyl)-2-(4-bromophenyl)isoindolin-1-one (**4ai**)*. White solid (162.1 mg, 69%). MP: 140-141 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 1H), 7.58-7.55 (m, 2H), 7.52-7.48 (m, 2H), 7.44-7.41 (m, 2H), 7.31-7.27 (m, 2H), 6.85-6.83 (m, 2H), 6.74 (br, 1H), 4.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 156.1, 136.7, 132.7, 132.2, 131.9,

128.7, 124.2, 122.8, 117.7, 112.9, 56.1. HRMS (ESI) calcd for $C_{21}H_{16}Br_2NO_2$ ($[M+H]^+$) 471.9542 found 471.9545.

3-(4-Bromo-2-methoxyphenyl)-2-(4-bromophenyl)isoindolin-1-one ***(4aj)***. White solid (230.3 mg, 98%). MP: 157-158ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, J = 5.2 Hz, 1H), 7.58-7.56 (m, 2H), 7.50 (q, J = 5.5 Hz, 2H), 7.44-7.42 (m, 3H),7.76 (br, 1H), 6.71-6.66 (m, 2H), 3.80-3.72 (m,3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 159.8, 145.2, 136.5, 132.9, 131.9, 128.8, 128.6, 128.1, 127.8, 124.3, 123.7, 122.9, 118.1, 117.7, 115.1, 62.9, 56.5. HRMS (ESI) calcd for $C_{21}H_{16}Br_2NO_2$ ($[M+H]^+$) 471.9542 found 471.9546.

2-(4-Bromophenyl)-3-(3,4-dimethylphenyl)isoindolin-1-one ***(4ak)***. White solid (132.9 mg, 68%). MP: 180-182 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.93 (m, 1H), 7.57-7.54 (m, 2H), 7.49-7.45 (m, 2H), 7.41-7.38 (m, 2H), 7.24-7.21 (m, 1H), 7.05-7.02 (m, 1H), 6.94-6.91 (m, 2H), 5.97 (s, 1H), 2.17 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 145.8, 137.6, 137.1, 136.9, 134.5, 132.7, 131.8, 130.7, 130.4, 128.5, 127.7, 124.3, 124.1, 123.6, 123.2, 117.7, 65.3, 19.8, 19.5. HRMS (ESI) calcd for $C_{22}H_{19}BrNO$ ($[M+H]^+$): 392.0645 found 392.0644.

3-{Benzo[d][1,3]dioxol-5-yl}-2-(4-bromophenyl)isoindolin-1-one ***(4al)***. White solid (122.1 mg, 60%). MP: 188-189 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 1H), 7.53-7.50 (m, 4H), 7.42-7.39 (m, 2H), 7.24-7.22 (m, 1H), 6.80-6.70 (m, 2H), 6.47 (d, J = 1.8 Hz, 1H), 5.94 (s, 1H), 5.87 (q, J = 1.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 148.5, 147.9, 145.5, 136.7, 136.2, 132.7, 131.9, 130.8, 130.7, 128.7, 124.1, 123.8, 123.3, 122.9, 122.4, 120.9, 117.9, 108.6, 106.5, 101.4, 65.2. HRMS (ESI) calcd for $C_{21}H_{15}BrNO_3$ ($[M+H]^+$): 408.0230 found 408.0231.

2-(4-Bromophenyl)-3-(2,4,6-trimethoxyphenyl) isoindolin-1-one ***(4am)***. White solid (156.3 mg, 69%). MP: 180-182 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.89 (M, 1H), 7.58-7.54 (m, 2H), 7.46-7.44 (m, 2H), 7.37-7.34 (m, 2H), 7.19-7.16 (m, 1H), 6.68 (s, 1H), 6.15 (d, J = 2.3 Hz, 1H), 5.83 (d, J = 2.3 Hz, 1H), 3.97 (s, 3H), 3.72 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 161.5, 159.9, 159.5, 145.7, 137.3, 132.7, 131.8, 131.1, 127.9, 127.3, 123.5, 123.0, 122.9, 122.3, 117.0, 104.6, 91.8, 91.4, 90.6, 56.6, 56.2, 55.5, 54.9. HRMS (ESI) calcd for $C_{23}H_{21}BrNO_4$ ($[M+H]^+$): 454.0648 found 454.0651.

2-(4-Bromophenyl)-3-(5-methylthiophen-3-yl)isoindolin-1-one ***(4an)***. White solid (101.5 mg, 53%). MP: 165-167 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.94 (m, 1H), 7.60-7.47 (m, 6H), 7.38-7.37 (m, 1H), 6.85 (d, J = 3.4 Hz, 1H), 6.54-6.53 (m, 1H), 6.26 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 144.9, 141.2, 137.7, 136.4, 132.7, 131.9, 130.6, 129.0, 127.1, 124.8, 124.6, 124.2, 123.1, 118.5, 61.4, 15.4. HRMS (ESI) calcd for $C_{19}H_{15}BrNOS$ ($[M+H]^+$): 384.0052 found 384.0049.

2-(4-Bromophenyl)-3-(4-methylnaphthalen-1-yl) isoindolin-1-one ***(4ao)***. White solid (145.2 mg, 68%). MP: 235-236 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.79 (t, J = 7.0 Hz, 1H), 7.69-7.59 (m, 3H), 7.48-7.45 (m, 2H),7.35-7.32 (m, 3H), 7.10-7.08 (m, 1H), 7.03 (s, 1H), 6.98-6.95 (m, 1H), 2.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 145.8, 137.1,134.9, 133.4,132.6, 131.8, 131.7,131.1, 130.7, 130.6, 130.5, 128.6, 126.9, 126.7, 125.9, 125.7, 125.2, 124.4, 122.7, 122.4, 117.3, 60.1, 19.6. HRMS (ESI) calcd for $C_{25}H_{19}BrNO$ ($[M+H]^+$): 428.0645 found 428.0650.

2-(4-Bromophenyl)-3-((8R,9S,13S,14S)-3-methoxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)isoindolin-1-one ***(4ap)***. White solid (230.8 mg, 81%). MP: 118-120 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.91 (m, 1H), 7.59 (t, J = 8.7 Hz, 2H), 7.50-7.45 (m, 2H), 7.42-7.31 (m, 3H), 6.65 (br, 2H), 3.97 (s, 3H), 2.84-2.82 (m, 2H), 2.49-2.41 (m, 1H), 2.02-1.96 (m, 6H), 1.42-1.33 (m, 6H), 0.81-0.78 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 155.1, 137.2, 132.6, 131.8, 128.3, 124.0, 123.3, 122.9, 117.4, 111.3, 55.7, 50.3, 47.9, 43.7, 38.0, 35.8, 31.3, 29.6, 26.3, 25.6, 21.5, 13.8. HRMS (ESI) calcd for $C_{33}H_{33}BrNO_3$ ($[M+H]^+$): 570.1638 found 570.1627.

2-(4-Bromophenyl)-6-fluoro-3-mesitylisoindolin-1-one ***(4ba)***. White solid (209.3 mg, 99%). MP: 170-172 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 1H), 7.43-7.35 (m, 4H), 7.24-7.18 (m, 1H), 7.14-7.09 (m, 1H), 6.93 (s, 1H), 6.59 (s, 1H), 6.43 (s, 1H), 2.65 (s, 3H), 2.19 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 162.9 (d, J = 246.6 Hz), 139.3, 138.3, 136.9, 136.6, 136.4, 134.0 (d, J = 8.6 Hz), 133.4, 131.9, 129.9, 128.6, 124.0 (d, J = 8.3 Hz), 123.1, 120.4 (d, J = 23.5 Hz),118.2, 110.4 (d, J = 23.4 Hz), 61.2, 21.3, 20.8, 18.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.0. HRMS (ESI) calcd for $C_{23}H_{20}BrFNO$ ($[M+H]^+$): 424.0707 found 424.0709.

2-(4-Bromophenyl)-5-fluoro-3-mesitylisoindolin-1-one ***(4bb)***. White solid (184.0 mg, 87%). MP:165-166 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 1H), 7.43 (s, 4H), 7.22 (t, J = 8.1 Hz, 1H), 6.96 (s, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 6.48 (s, 1H), 2.66 (s, 3H), 2.24 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8 (d, J =243.9 Hz), 146.3, 138.4, 137.0, 136.4, 131.9, 129.9, 128.5, 128.2, 126.2, 123.0, 118.0, 116.5 (d, J = 8.1 Hz), 109.8 (d, J = 24.1 Hz), 61.2, 21.2, 20.8, 18.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.1. HRMS (ESI) calcd for $C_{23}H_{20}BrFNO$ ($[M+H]^+$): 424.0707 found 424.0708.

2-(4-Bromophenyl)-7-fluoro-3-mesitylisoindolin-1-one ***(4bc)***. White solid (196.6 mg, 93%). MP: 186-187 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 1H), 7.42-7.35 (m, 4H), 7.10 (q, J = 8.9 Hz, 1H), 6.95-6.94 (m, 2H), 6.61 (s, 1H), 6.46 (s, 1H), 2.67 (s, 3H), 2.21 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 158.9 (d, J = 256.3 Hz), 146.6, 138.3, 136.9, 136.6, 136.4 (d, J = 15.3 Hz), 134.6, 131.8 (d, J = 5.5 Hz), 129.9, 128.7, 123.1, 119.4, 118.5, 118.0, 115.7 (d, J = 18.6 Hz), 61.2, 21.3, 20.8, 18.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -156.9. HRMS (ESI) calcd for $C_{23}H_{20}BrFNO$ ($[M+H]^+$): 424.0707 found 424.0710.

2-(4-Bromophenyl)-5-chloro-3-mesitylisoindolin-1-one ***(4bd)***. White solid (184.3 mg, 84%). MP: 92-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 1H), 7.46-7.34 (m, 5H), 7.13-7.12 (m, 1H), 6.94 (s, 1H), 6.60 (s, 1H), 6.42 (s, 1H), 2.64 (s, 3H), 2.19 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 145.4, 139.1, 138.4, 136.9, 136.5, 136.4, 133.4, 131.9, 130.5, 130.0, 129.3, 128.3, 125.2, 122.9, 118.1, 61.1, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{23}H_{20}BrClNO$ ($[M+H]^+$): 440.0411 found 440.0413.

2-(4-Bromophenyl)-5-bromo-3-mesitylisoindolin-1-one ***(4be)***. White solid (238.5 mg, 99%). MP: 125-126 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 1H), 7.66-7.63 (m, 1H), 7.41 (s, 4H), 7.31 (s, 1H), 6.95 (s, 1H), 6.63 (s, 1H), 6.46 (s, 1H), 2.65 (s, 3H), 2.22 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 145.6, 138.5, 137.0, 136.6, 136.4, 132.1, 132.0, 131.9, 131.1, 130.0, 128.3, 127.5, 125.7, 123.1,

118.2, 61.1, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{23}H_{20}Br_2NO$ ($[M+H]^+$): 483.9906 found 483.9908.

2-(4-Bromophenyl)-3-mesityl-5-phenoxyisoindolin-1-one ***(4bf)***. White solid (186.7 mg, 75%). MP: 194-195 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 1H), 7.35-7.24 (m, 6H), 7.06 (t, J = 7.2 Hz, 1H), 6.92-6.90 (m, 3H), 6.81-6.73 (m, 2H), 6.52 (s, 1H), 6.34 (s, 1H), 2.51 (s, 3H), 2.10 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 161.8, 155.8, 146.3, 138.1, 137.0, 136.4, 131.8, 130.0, 129.9, 128.9, 126.7, 125.6, 124.4, 122.9, 119.6, 118.2, 117.7, 112.1, 61.2, 21.2, 20.8, 18.9. HRMS (ESI) calcd for $C_{29}H_{25}BrNO_2$ ($[M+H]^+$): 498.1063 found 498.1057.

2-(4-Bromophenyl)-3-mesityl-5-methoxyisoindolin-1-one ***(4bg)***. Liquid (170.0 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 1H), 7.37 (m, 4H), 6.98 (dd, J = 8.4, 1.9 Hz, 1H), 6.91 (s, 1H), 6.58 (s, 2H), 6.36 (s, 1H), 3.77 (s, 3H), 2.64 (s, 3H), 2.19 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 163.8, 146.2, 137.9, 137.1, 136.4, 131.8, 129.8, 1239.3, 125.4, 124.7, 122.8, 117.5, 115.1, 107.2, 61.2, 55.7, 21.3, 20.8, 18.9. HRMS (ESI) calcd for $C_{24}H_{23}BrNO_2$ ($[M+H]^+$): 436.0907 found 436.0901.

2-(4-Bromophenyl)-3-mesityl-5-nitroisoindolin-1-one ***(4bh)***. White solid (114.7 mg, 51%). MP: 213-214 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 1.6 Hz, 1H), 8.42 (dd, J = 8.3, 2.0 Hz, 1H), 7.46-7.42 (m, 4H), 7.36 (d, J = 8.3 Hz, 1H), 6.98 (s, 1H), 6.65 (s, 1H), 6.59 (s, 1H), 2.68 (s, 3H), 2.24 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 149.7, 148.7, 138.9, 136.9, 136.6, 136.1, 133.7, 132.1, 130.2, 127.6, 123.2, 119.6, 118.8, 61.7, 21.4, 20.8, 19.0. HRMS (ESI) calcd for $C_{23}H_{20}BrN_2O_3$ ($[M+H]^+$): 451.0652 found 451.0648.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Characterization of products (copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF).
X-ray data for **4b, 4i, 4ah, 4al** and **4ao.** (**CIF**)

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Notes

The authors declare no competing financial interest.

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