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Palladium-Catalyzed Cyclocarbonylation of 2-Halobenzaldehyde and Hydrazines: A Facile Synthesis of 2-Aminoisoindolin-1-ones

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An efficient procedure for the synthesis of 2-aminoisoindolin-1-ones *via* a palladium-catalyzed three-component reaction of 2-halobenzaldehydes, hydrazines and carbon monoxide is reported. This cyclocarbonylation process can be performed smoothly under 1 atmospheric pressure of carbon monoxide to afford 2-aminoisoindolin-1-ones in moderate to excellent yields.

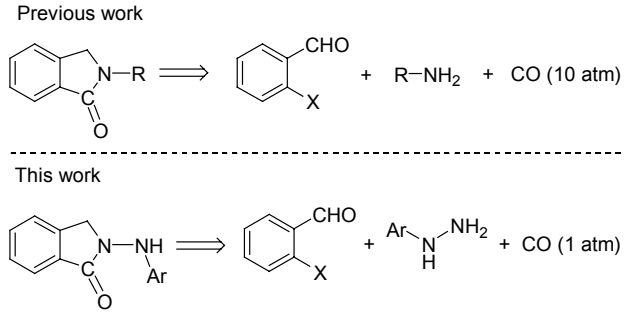
Keywords cyclocarbonylation, 2-aminoisoindolin-1-ones, multicomponent reactions, heterocycles

Introduction

Isoindolinones (phthalimidines) and their derivatives are an important class of compounds in organic and pharmaceutical chemistry, not only as the key structural units in many natural products and pharmaceuticals but also as useful building blocks for various biologically active molecules, such as staurosporine, indoprofen, and DN-2327.[1,2] Multicomponent reactions (MCRs) have emerged as powerful tools in organic, combinatorial, and medicinal chemistry with high bond-forming efficiency.[3] Among them, the transition metal-catalyzed MCRs have been applied for the preparation of isoindolinones.[4] These reactions involved a palladium-catalyzed cyclocarbonylation process using carbon monoxide as the carbonyl resource. A number of 2-aryl/alkyl isoindolin-1-ones were synthesized by this strategy (Scheme 1). Nevertheless, the approaches to 2-amino isoindolin-1-ones, exhibiting excellent effects on modulating mGluR function, have seldom been reported.[5]

As a continuation of our efforts to develop novel MCRs strategies on heterocyclic synthesis,[6,7] herein we reported a three-component reaction for the synthesis of 2-amino isoindolin-1-ones (Scheme 1). This one-pot cascade reaction could run under 1 atmospheric pressure of carbon monoxide in the presence of a catalytic amount of palladium and afforded 2-amino isoindolinones in moderate to excellent yields from readily available 2-halobenzaldehydes, carbon monoxide and hydrazines.

Scheme 1 Approaches to 2-substituted isoindolin-1-ones



Results and Discussion

Primarily, we screened the reaction conditions for the reaction of 2-bromobenzaldehyde (**1a**), phenylhydrazine (**2a**), and CO in the presence of palladium catalyst, which gave 2-amino isoindolin-1-one (**3a**) (Table 1). When the reaction was carried out under palladium acetate and DPPB in DMF at 120 ℃ for 12 h,[4,8] **3a** was obtained in 83% yield (Table 1, Entry 1). Lowering the reaction temperature to 90 ℃, the yield could be reduced down to 16% (Table 1, Entries 1—4). The optimal reaction time was found to be 12 h (Table 1, Entries 5 and 6). DPPP worked well for the reaction, while PPh_3 did not work at all (Table 1, Entries 7 and 8). Changing the base additive from Et_3N to K_2CO_3 or Cs_2CO_3 led to a remarkable reduction in yield (Table 1, Entries 9 and 10). Two equivalent amounts of Et_3N were essential to the reaction (Table 1, Entries 11—13). DMF was selected as the optimal solvent among all of the screened solvents, such as THF, toluene, 1,4-dioxane,

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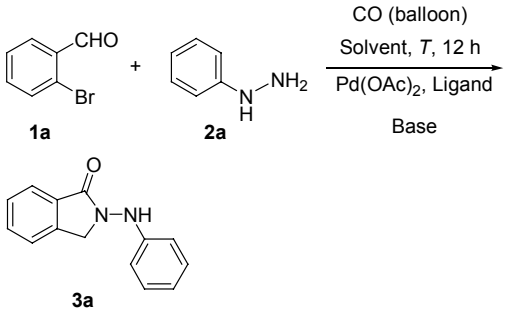
acetonitrile, and DMSO (Table 1, Entries 14—18). We also examined the Pd(0) catalyst $Pd(PPh_3)_4$, but a poor yield was obtained. Structure of **3a** was established by single crystal analysis (Figure 1).[13]

Table 1 Optimization of reaction conditions for the synthesis of **3a**[a]



Entry	Ligand (%)	Base (equiv.)	Solvent	T/℃	Yield[b]/%
1[c]	DPPB (4%)	Et_3N (2.0)	DMF	120	83
2[c]	DPPB (4%)	Et_3N (2.0)	DMF	110	82
3	DPPB (2%)	Et_3N (2.0)	DMF	100	83
4	DPPB (2%)	Et_3N (2.0)	DMF	90	16
5[c]	DPPB (2%)	Et_3N (2.0)	DMF	100	53
6[d]	DPPB (2%)	Et_3N (2.0)	DMF	100	83
7	DPPP (2%)	Et_3N (2.0)	DMF	100	79
8	PPh_3 (4%)	Et_3N (2.0)	DMF	100	trace
9	DPPB (2%)	K_2CO_3 (2.0)	DMF	100	7
10	DPPB (2%)	Cs_2CO_3 (2.0)	DMF	100	26
11	DPPB (2%)	Et_3N (3.0)	DMF	100	83
12	DPPB (2%)	Et_3N (1.0)	DMF	100	65
13	DPPB (2%)	—	DMF	100	N.R.
14[e]	DPPB (4%)	Et_3N (2.0)	THF	reflux	trace
14[e]	DPPB (4%)	Et_3N (2.0)	toluene	100	17
16[e]	DPPB (4%)	Et_3N (2.0)	dioxane	100	trace
17[e]	DPPB (4%)	Et_3N (2.0)	MeCN	reflux	34
18[e]	DPPB (4%)	Et_3N (2.0)	DMSO	100	messy

[a] Reaction conditions: **1a** (1.05 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand, base, solvent (5 mL), CO (1 atm), the indicated temperature, 12 h. [b] Yield of isolated product. [c] Reacted for 4 h. [d] Reacted for 18 h. [e] 4 mol% $Pd(OAc)_2$ was used.

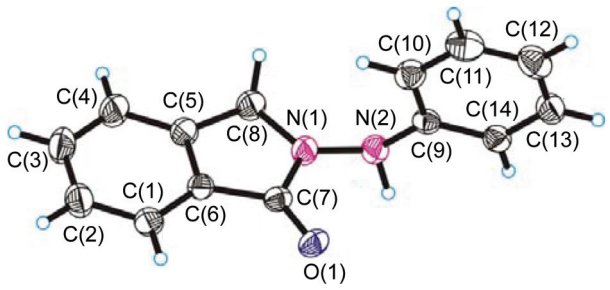
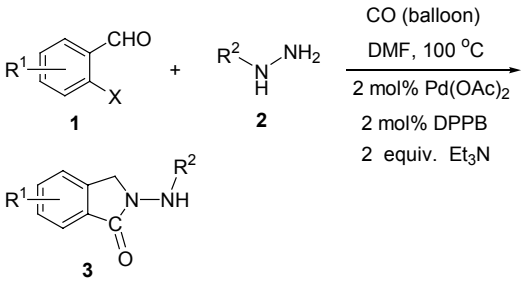


Figure 1 Ellipsoid plot of **3a** with the thermal ellipsoid drawn at the 50% probability level.

With the optimized reaction conditions in hand (Table 1, Entry 3), the substrate diversity was tested and the results are summarized in Table 2. Structures of **3a**—**3p** were characterized by ^1H NMR, ^{13}C NMR, IR and HRMS. Copies of spectra were presented in supporting information. Electronic effect of the substituents on phenyl hydrazine was observed. With strong electron-donating group (**2c**) or strong electron-withdrawing group (**2f**) on 4-position of phenyl hydrazine, apparently lower yields were obtained in comparison with those with moderate electron-donating group (**2b**) or electron-withdrawing group (**2d**) (Table 2, Entries 1—7). Remarkably, 2-tolylhydrazine (**2i**) afforded **3i** in 90% yield, while 3-tolylhydrazine (**2h**) gave **3h** in 74% yield only. Similar situation was observed for the pair of **2j** and **2k**, which furnished **3j** and **3k** in 73% and 81% yields, respectively (Table 2, Entries 8—11). Acetohydrazide (**2l**) and benzohydrazide (**2m**) also worked for this transformation and produced **3l** and **3m** in 53% and 65% yields, accordingly (Table 2, Entries 12 and 13). Elec-

Table 2 Scope of the reaction[a]



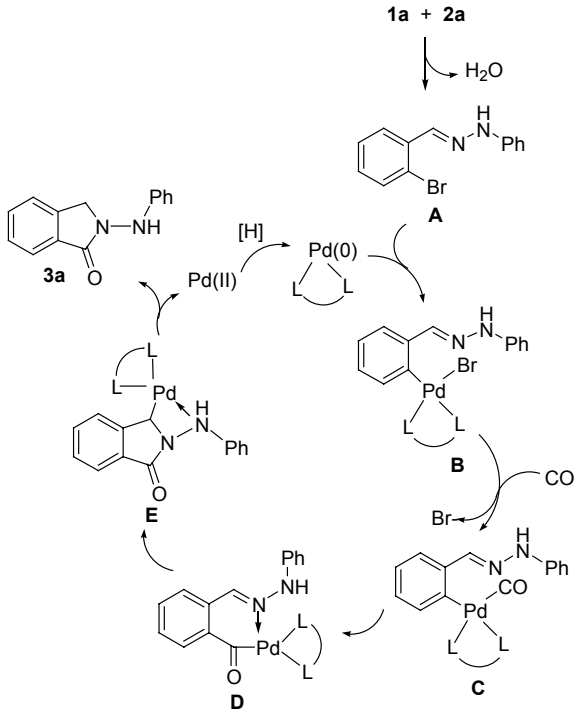
Entry	**1** (R^1, X)	**2** (R^2)[b]	**3**/(Yield[c]/%)
1	**1a** (H, Br)	**2a** (Ph)	**3a**/83
2	**1a**	**2b** (4-MeC_6H_4)	**3b**/55
3	**1a**	**2c** (4-$MeOC_6H_4$)	**3c**/47
4[d]	**1a**	**2d** (4-ClC_6H_4)	**3d**/95
5	**1a**	**2e** (4-FC_6H_4)	**3e**/68
6	**1a**	**2f** (4-$NO_2C_6H_4$)	**3f**/38
7[d]	**1a**	**2g** (4-$CF_3C_6H_4$)	**3g**/84
8	**1a**	**2h** (3-MeC_6H_4)	**3h**/74
9	**1a**	**2i** (2-MeC_6H_4)	**3i**/90
10[d]	**1a**	**2j** (3-$CF_3C_6H_4$)	**3j**/73
11[d]	**1a**	**2k** (2-$CF_3C_6H_4$)	**3k**/81
12	**1a**	**2l** (MeCO)	**3l**/53
13	**1a**	**2m** (PhCO)	**3m**/65
14	**1b** (4-Me, Br)	**2a**	**3n**/85
15	**1c** (5-F, Br)	**2a**	**3o**/90
16	**1d** (5-MeO, Br)	**2a**	**3p**/81
17	**1e** (H, I)	**2a**	**3a**/85
18	**1f** (H, OTf)	**2d**	**3d**/49

[a] Reaction conditions: **1** (1.05 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), DPPB (0.02 mmol), Et_3N (2.0 mmol), DMF (5 mL), CO (1 atm), 100 ℃, 12 h. [b] If **2** was in its hydrochloride form, Et_3N (3.0 equiv) was added. [c] Yield of isolated products. [d] The reaction completed in 4 h.

tron-withdrawing substituent on 2-halobenzal-dehyde (**1c**) favored the reaction and gave the highest yield among those with electron-donating groups (Table 2, Entries 14—16). Slightly higher yield was observed for 2-iodobenzaldehyde (**1e**) as compared to 2-bromo-benzaldehyde (**1a**) (Table 2, Entries 1 and 17), while lower yield was observed for **1f** that contains C-OTf bond (Table 2, Entries 4 and 18).

Based on these results, we proposed a plausible mechanism for this Pd-catalyzed carbonylation cyclization (Scheme 2). Initially, the condensation of **1a** with **2a** generates **A**. In the presence of the palladium catalyst, an oxidative addition occurs over C—Br bond of **A** and leads to the formation of **B**, which subsequently coordinates with CO under its atmosphere to form **C**. Assisted by the lone-pair electrons of the nitrogen, intermediate **D** is formed via the migratory insertion of CO.[9] Addition of acyl palladium **D** to imine intramolecularly[10] leads to cyclization to form **E**. Then, **E** undergoes a metal-H exchange[12] to produce the final product **3a** and Pd(II), which can be reduced back by either the *in situ* generated H_2[4d,11] or DMF[12] to Pd(0) for catalytic cycle.

Scheme 2 Possible mechanism for the formation of **3**



Conclusions

In summary, we developed an efficient synthesis of 2-aminoisoindolin-1-ones via a palladium-catalyzed carbonylation reaction of 2-halobenzaldehydes, aryl hydrazines and carbon monoxide. The presented three-component reaction can be run smoothly under 1 atmospheric carbon monoxide. Furthermore, the procedure furnishes the desired products in moderate to excellent yields with high atom efficiency, and the substrates are readily available.

Experimental

General information

Infrared spectra were obtained on a FTIR spectrometer. ^{1}H NMR spectra were recorded on 500 or 400 MHz spectrometer unless noted otherwise and the chemical shifts were reported relative to internal standard TMS (δ 0) or DMSO-d_6 (δ 2.50). The following abbreviations are used to describe peak patterns where appropriate: b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants are reported in Hertz (Hz). ^{13}C NMR were recorded on 100 or 125 MHz unless noted otherwise and referenced to the internal solvent signals (central peak is δ 77.0 for $CDCl_3$ or δ 40.0 for DMSO-d_6). MS and HRMS were obtained using EI ionization. Melting points were measured with micro melting point apparatus. Infrared spectra were obtained on an FTIR spectrometer.

DMF was distilled from CaH_2, while THF, dioxane, toluene were distilled from Na/benzophenone respectively.

General procedure for the synthesis of isoindolinones 3

To a solution of $Pd(OAc)_2$ (0.02 mmol), DPPB (0.02 mmol), **1** (1.05 mmol), and **2** (1.0 mmol) in DMF (5 mL) in Schlenk tube was added Et_3N (2.0 mmol) slowly via a syringe under carbon monoxide atmosphere. The reaction mixture was stirred at 100 ℃ for 12 h. After the completion of the reaction, the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate, 2∶1 to 1∶1) to afford pure **3**.

2-(Phenylamino)isoindolin-1-one (3a) White solid; m.p. 186—187 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 4.64 (s, 2H), 6.64 (d, J=8.0 Hz, 2H), 6.77 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 2H), 7.55 (t, J=7.0 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 50.6, 112.1, 119.1, 123.1, 123.8, 128.0, 129.1, 131.0, 131.9, 140.3, 147.5, 166.3; ATR-FTIR v: 3252, 1689, 1600, 1523, 1495, 1468, 1397, 755, 734, 691, 669 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{12}N_2O$ ([M]$^+$) 224.0950, found 224.0948.

2-(*p*-Tolylamino)isoindolin-1-one (3b) White solid; m.p. 184—185 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.23 (s, 3H), 4.57 (s, 2H), 6.54 (s, 1H), 6.65 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 1H), 7.48 (t, J=7.5 Hz, 1H), 7.58 (t, J=7.5 Hz, 1H), 7.88 (d, J=7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.7, 51.3, 113.9, 123.2, 124.2, 128.4, 129.9, 130.8, 131.4, 132.2, 140.0, 144.3, 167.8; ATR-FTIR v: 3245, 1686, 1610, 1509, 1471, 1395, 738, 711 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O$ ([M]$^+$) 238.1106, found 238.1107.

2-((4-Methoxyphenyl)amino)isoindolin-1-one (3c) White solid; m.p. 162－163 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.71 (s, 3H), 4.55 (s, 2H), 6.60－6.62 (m, 1H), 6.71－6.75 (m, 4H), 7.42 (d, J=7.5 Hz, 1H), 7.47 (t, J=7.5 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 7.87 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 51.0, 55.6, 114.7, 115.5, 123.0, 124.0, 128.2, 131.2, 131.9, 139.8, 140.1, 154.7, 167.7; ATR-FTIR v: 3236, 1684, 1504, 1451, 1396, 1289, 1245, 1167, 1034, 782, 739, 710 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ ($[M]^+$) 254.1055, found 254.1058.

2-((4-Chlorophenyl)amino)isoindolin-1-one (3d) White solid; m.p. 184－185 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.56 (s, 2H), 6.62 (d, J=8.5 Hz, 2H), 7.08 (t, J=8.0 Hz, 3H), 7.44 (d, J=7.5 Hz, 1H), 7.49 (t, J=7.0 Hz, 1H), 7.60 (t, J=7.5 Hz), 7.86 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 5.2, 114.5, 123.1, 124.1, 125.7, 128.4, 129.1, 130.9, 132.3, 139.8, 145.3, 167.9; ATR-FTIR v: 3252, 1682, 1592, 1486, 1442, 1389, 831, 773, 731 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}ClN_2O$ 258.0560 ($[M]^+$) and 260.0530 ($[M+2]^+$), found 258.0563 and 260.0532, respectively.

2-((4-Fluorophenyl)amino)isoindolin-1-one (3e) White solid; m.p. 173－174 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.60 (s, 2H), 6.68－6.71 (m, 3H), 6.86－6.90 (m, 2H), 7.45－7.52 (m, 2H), 7.58－7.61 (m, 1H), 7.88 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 51.4, 115.0 (d, J=7.8 Hz), 116.0 (d, J=23 Hz), 123.2, 124.3, 128.5, 131.1, 132.3, 139.9, 142.8, 158.1 (d, J=238 Hz), 167.9; ATR-FTIR v: 3260, 1684, 1612, 1502, 1444, 1388, 1210, 977, 865, 731, 708 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}FN_2O$ ($[M]^+$) 242.0855, found 242.0857.

2-((4-Nitrophenyl)amino)isoindolin-1-one (3f) Yellow solid; m.p. 241－242 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.71 (s, 2H), 6.78 (d, J=8.5 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 7.65 (d, J=7.5 Hz, 1H), 7.71 (t, J=8.0 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 51.1, 111.4, 123.7, 124.2, 126.4, 128.6, 130.6, 132.8, 139.2, 140.9, 153.9, 166.6; ATR-FTIR v: 3273, 1692, 1594, 1500, 1472, 1383, 1329,1278, 835, 773, 737 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}N_3O_3$ ($[M]^+$) 269.0800, found 269.0802.

2-((4-(Trifluoromethyl)phenyl)amino)isoindolin-1-one (3g) White solid; m.p. 195－196 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.63 (s, 2H), 6.74－6.78 (m, 2H), 6.97 (t, J=8.0 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.52－7.55 (m, 3H), 7.61－7.64 (m, 1H), 7.92 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 51.3, 112.3, 122.5 (q, J=32.4 Hz), 123.2, 124.2, 124.5 (q, J=271 Hz), 126.6 (q, J=3.4 Hz), 128.5, 130.7, 132.5, 139.8, 149.5, 168.1; ATR-FTIR v: 3257, 1690, 1613, 1525, 1471, 1397, 1321, 1153, 1103, 1058, 823, 767, 735 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{11}F_3N_2O$ ($[M]^+$) 292.0823, found 292.0820.

2-(*m*-Tolylamino)isoindolin-1-one (3h) White solid; m.p. 177－178 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.23 (s, 3H), 4.60 (s, 2H), 6.44 (s, 1H), 6.52－6.54 (m, 2H), 6.60 (s, 1H), 6.69 (d, J=7.5 Hz, 1H), 7.07 (t, J=7.5 Hz, 1H), 7.45 (d, J=7.0 Hz, 1H), 7.49 (t, J=7.0 Hz), 7.59 (t, J=7.0 Hz, 1H), 7.90 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.5, 51.2, 110.5, 114.1, 122.1, 123.1, 124.1, 128.2, 129.1, 131.1, 132.1, 139.2, 139.8, 146.6, 167.7; ATR-FTIR v: 3241, 1684, 1595, 1448, 985, 772, 735 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O$ ($[M]^+$) 238.1106, found 238.1108.

2-(*o*-Tolylamino)isoindolin-1-one (3i) White solid; m.p. 167－168 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.24 (s, 3H), 4.61 (s, 2H), 6.44 (s, 1H), 6.54 (d, J=8.0 Hz, 1H), 6.83 (t, J=7.5 Hz, 2H), 7.09 (d, J=7.5 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.49 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.2, 51.5, 111.9, 121.2, 123.2, 123.5, 124.3, 127.1, 128.4, 131.0, 131.3, 132.2, 140.0, 167.8; ATR-FTIR v: 3240, 1684, 1605, 1506, 1478, 1447, 1397, 753, 732 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O$ ($[M]^+$) 238.1106, found 238.1103.

2-((3-(Trifluoromethyl)phenyl)amino)isoindolin-1-one (3j) White solid; m.p. 189－190 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.62 (s, 2H), 6.83－6.84 (m, 1H), 6.92 (s, 1H), 7.06－7.07 (m, 1H), 7.20－7.27 (m, 2H), 7.46－7.53 (m, 2H), 7.62 (t, J=7.0 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 51.6, 109.8, 109.9, 116.3, 117.7, 123.4, 124.2 (q, J=271 Hz), 128.7, 130.0, 130.9, 131.9 (q, J=32.5 Hz), 132.7, 140.1, 147.5, 168.3; ATR-FTIR v: 3255, 1679, 1617, 1393, 1334, 1174, 1126, 797, 734 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{11}F_3N_2O$ ($[M]^+$) 292.0823, found 292.0821.

2-((2-(Trifluoromethyl)phenyl)amino)isoindolin-1-one (3k) White solid; m.p. 138－139 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.60 (s, 2H), 6.68 (d, J=8.5 Hz, 2H), 7.33 (d, J=8.5 Hz, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H), 7.54 (s, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.88 (d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 51.2, 113.6, 115.2 (q, J=30 Hz), 120.6, 123.2, 124.4, 124.5 (q, J=270 Hz), 126.8 (q, J=5.0 Hz), 128.5, 130.7, 132.4, 133.3, 139.7, 144.3, 167.5; ATR-FTIR v: 3297, 1693, 1613, 1584, 1508, 1451, 1100, 758, 728 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{11}F_3N_2O$ ($[M]^+$) 292.0823, found 292.0824.

2-(Acetylamino)isoindoline-1-one (3l) White solid; m.p. 196－197 ℃; ^{1}HNMR (DMSO-d_6, 500 MHz) δ: 1.97 (s, 3H), 4.56 (s, 2H), 7.53 (t, J=7.5 Hz, 1H), 7.59 (d, J=7.5 Hz, 1H), 7.66 (t, J=7.5 Hz, 1H), 7.75 (t, J=7.5 Hz, 1H), 10.38 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 20.5, 51.0, 123.3, 123.7, 128.1, 130.4, 132.2, 140.7, 166.1, 168.8; ATR-FTIR v: 3199, 3012, 1710, 1666, 1523, 1452, 1290, 729 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}N_2O_2$ ($[M]^+$) 190.0742, found 190.0746.

2-(Benzamido)isoindoline-1-one (3m) White solid; m.p. 247－248 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 4.69 (s, 2H), 7.54－7.58 (m, 3H), 7.63－7.65 (m, 2H), 7.71 (t, J=7.5 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H), 7.97 (t, J=8.0 Hz, 2H); ^{13}CNMR (DMSO-d_6, 125 MHz) δ: 51.2, 123.3, 123.8, 127.6, 128.2, 128.7, 130.4,

131.7, 132.4, 140.8, 165.6, 166.5; ATR-FTIR *v*: 3244, 2921, 2852, 1694, 1670, 1520, 1469, 1286, 1255, 887, 770, 722, 686 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{12}N_2O_2$ ($[M]^+$) 252.0899, found 252.0895.

6-Methyl-2-(phenylamino)isoindolin-1-one (3n) Yellow solid; m.p. 230—231 ℃; ^{1}HNMR (DMSO-d_6, 500 MHz) δ: 2.42 (s, 3H), 4.57 (s, 2H), 6.61—6.62 (m, 2H), 6.76—6.77 (m, 1H), 7.15—7.16 (m, 2H), 7.48 (s, 2H), 7.57 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 20.9, 50.4, 112.1, 119.1, 123.2, 123.5, 129.0, 131.1, 132.8, 137.4, 137.6, 147.6, 166.4; ATR-FTIR *v*: 3248, 1690, 1618, 1512, 1452, 1325, 1282, 831, 752 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O$ ($[M]^+$) 238.1106, found 238.1105.

5-Fluoro-2-(phenylamino)isoindolin-1-one (3o) White solid; m.p. 175—176 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.56 (s, 2H), 6.67—6.71 (m, 3H), 6.87 (t, J=7.5 Hz, 1H), 7.13—7.20 (m, 4H), 7.85—7.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 50.9 (d, J=1.6 Hz), 110.6 (d, J=24 Hz), 113.4, 116.2 (d, J=23 Hz), 121.3, 126.3 (d, J=10 Hz), 127.2 (d, J=2 Hz), 129.4, 142.2 (d, J=10.6 Hz), 146.4, 165.5 (d, J=250.1 Hz), 166.9; ATR-FTIR *v*: 3262, 1685, 1626, 1598, 1478, 1443, 1391, 1249, 749 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}FN_2O$ ($[M]^+$) 242.0855, found 242.0848.

5-Methoxy-2-(phenylamino)isoindolin-1-one (3p) White solid; m.p. 199—200 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.85 (s, 3H), 4.57 (s, 2H), 6.61 (d, J=8.0 Hz, 2H), 6.75 (t, J=7.5 Hz, 1H), 7.08—7.09 (m, 1H), 7.15—7.18 (m, 3H), 7.67 (d, J=8.5 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 50.4, 55.6, 108.3, 112.0, 115.1, 119.0, 123.3, 124.6, 129.0, 142.6, 147.6, 162.6, 166.2; ATR-FTIR *v*: 3271, 1683, 1607, 1488, 1452, 1393, 1303, 1263, 1090, 1021, 756, 735, 702 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ ($[M]^+$) 254.1055, found 254.1054.

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[13] CCDC 832672 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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