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Graphical Abstract

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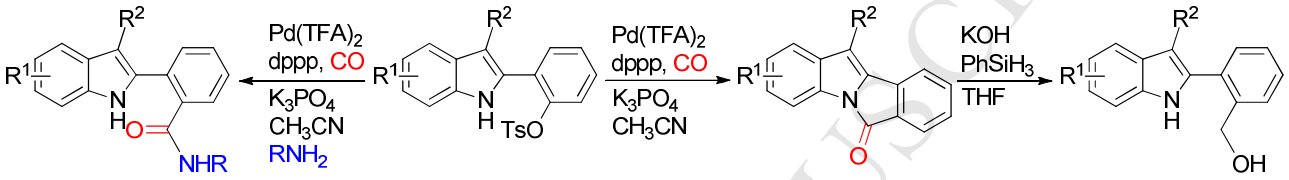

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Synthesis of 6H-Isoindolo[2,1-*a*]indol-6-ones via Pd-Catalyzed Cycloaminocarbonylation of *2*-(1H-Indol-2-yl)phenyl Tosylates with CO

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ABSTRACT

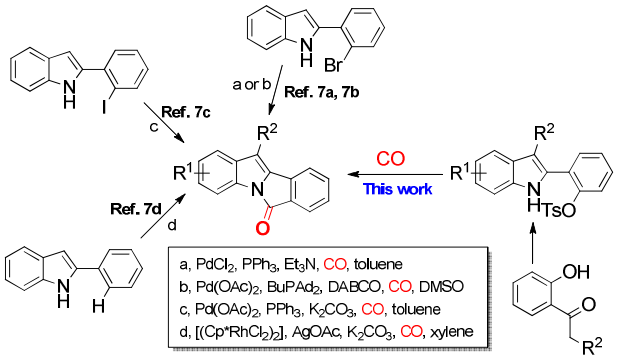
An efficient method for preparation of substituted 6H-isoindolo[2,1-*a*]indol-6-ones (**2**) that are important structural components of a vast array of naturally occurring and pharmacologically active compounds, has been developed by the palladium-catalyzed intramolecular cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylates with CO. Significantly, *2*-(1H-indol-2-yl)benzamides resulting from intermolecular aminocarbonylation are formed when an excess of amine is used in this reaction system. Alternatively, *2*-(1H-indol-2-yl)benzamides can also be synthesized by the in situ aminolysis of **2**. Furthermore, treatment of **2** with hydrosilane in the presence of KOH gave the unprecedented reducing products *2*-(-1H-indol-2-yl)benzyl alcohols in 75-86% yields. These results demonstrate that 6H-isoindolo[2,1-*a*]indol-6-ones are versatile substrates for further synthetic elaboration.

1. Introduction

Substituted 6H-isoindolo[2,1-*a*]indol-6-ones are important structural components of a vast array of naturally occurring and pharmacologically active compounds.[1] Such types of heterocycles are valuable intermediates in organic synthesis,[2] and can also be used as melatonin MT_3 ligands,[3] potential anticancer agents[4] and bacterial N or A efflux pump inhibitors[5]. Therefore, the importance of 6H-isoindolo[2,1-*a*]indol-6-ones justifies a longstanding interest in the development of efficient and versatile approaches to their synthesis and new structures.

Transition metal-catalyzed carbonylative coupling reactions of organic substrates with CO have become a powerful tool in organic synthesis.[6] In 2016, Cho[7a] and Fan[7b] reported the Pd-catalyzed cyclocarbonylation of *2*-(*2*-bromophenyl)-1H-indoles for preparing 6H-isoindolo[2,1-*a*]indol-6-ones (**Scheme 1**, paths a and b). Huang and co-workers[7c] reported the synthesis of substituted 6H-isoindolo[2,1-*a*]indol-6-ones by Pd-catalyzed carbonylation of *2*-(2-iodophenyl)-1H-indoles with CO (**Scheme 1**, path c). The preparation of 6H-isoindolo[2,1-*a*]indol-6-ones via rhodium-catalyzed intramolecular C-H carbonylation of 2-aryindoles with carbon monoxide has also been achieved, but the reaction needs 3 equivalents of AgOAc as oxidant (**Scheme 1**, path d).[7d]

Given the easier synthesis and crystalline isolation of *2*-(1H-indol-2-yl)phenyl tosylates[8] from cheap *2*-hydroxyphenyl alkyl ketone precursors compared with *o*-(*2*-halophenyl)-1H-indoles, we were interested in the synthesis of 6H-isoindolo[2,1-*a*]indol-6-ones from *2*-(1H-indol-2-yl)phenyl tosylates. Herein, we describe a new method for preparation of 6H-isoindolo[2,1-*a*]indol-6-one derivatives by the Pd-catalyzed cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylates with CO.



Scheme 1. Comparison of the previous cycloaminocarbonylative work to the current work.

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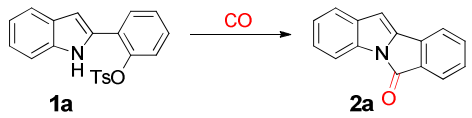
2. Results and discussion

Our initial screening of reaction conditions focused on the cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylate (**1a**) with CO in the presence of *1,3*-bis(diphenyphosphino)propane (dppp) and different Pd catalyst (**Table 1**). In a series of preliminary screening of Pd catalysts (**Table 1**, entries 1-3), it was found that $Pd(TFA)_2$ showed the highest catalytic activity. Screening several different bases such as K_2CO_3, DBU, AcONa, K_3PO_4, Na_3PO_4, K_2HPO_4 and PhONa, 2 equivalents of K_3PO_4 gave the best result with 50% yield (**Table 1**, entries 4-11). Compared with dppp, *1,2*-bis(diphenylphosphino)ethane (dppe), *2*-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (X-phos) and *4,5*-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), were less effective (**Table 1**, entries 12-14). The yield could be improved to 54% by using the more amount of $Pd(TFA)_2$ (**Table 1**, entry 15). Replacement of CH_3CN with *1,4*-dioxane as solvent led to the decrease of the yield (**Table 1**, entry 16). Additionally, increasing the reaction temperature up to 150 °C or 160 °C gave a higher yield, while reducing the reaction temperature or using less amount of $Pd(TFA)_2$ and dppp led to a decrease of yields (**Table 1**, entries 17-22).

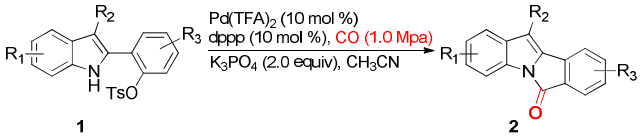
Table 1. Palladium, Ligand, and Base Effects[a]

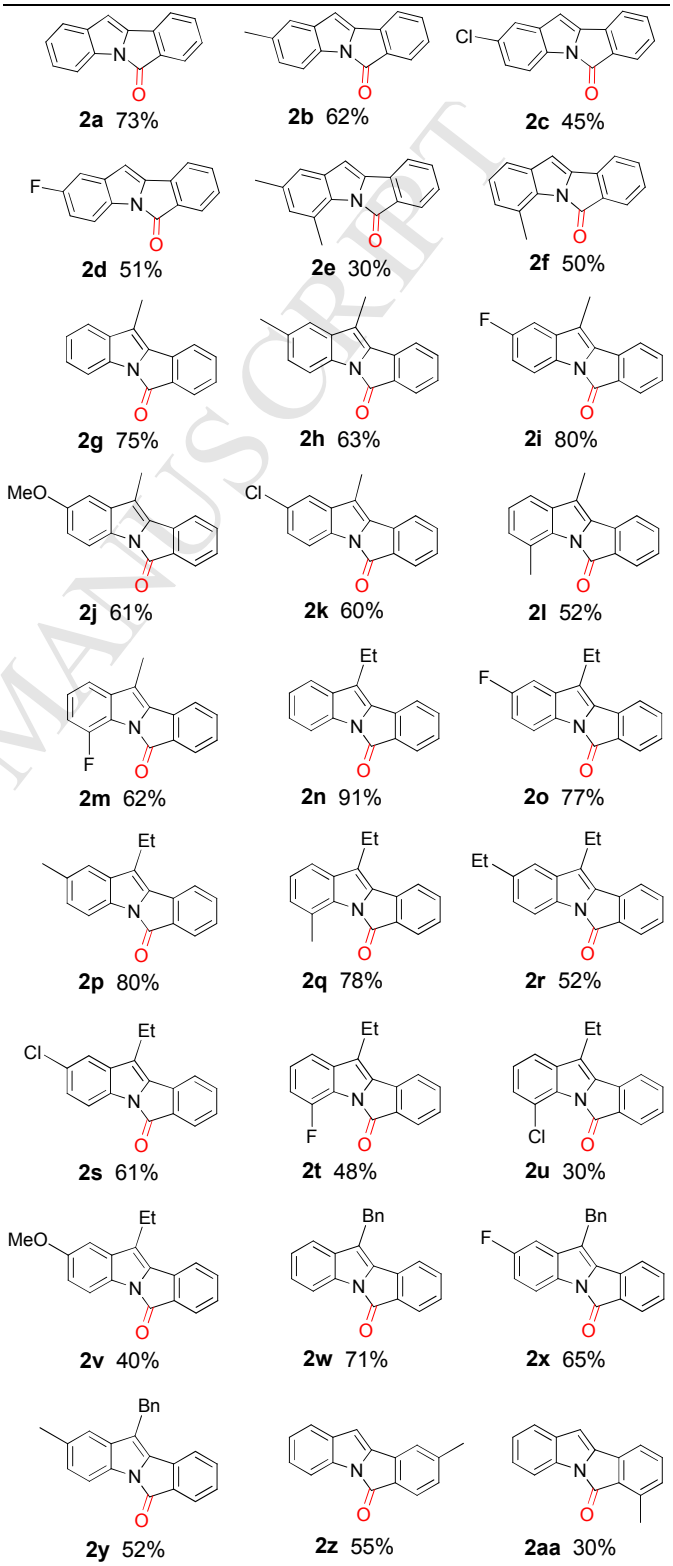


Entry	[Pd] (mol%)	Ligand (mol%)	Base (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	dppp (10)	K_2CO_3(1.2)	19
2	$Pd(TFA)_2$ (5)	dppp (10)	K_2CO_3 (1.2)	21
3	$Pd(PhCN)Cl_2$ (5)	dppp (10)	K_2CO_3 (1.2)	16
4	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	trace
5	$Pd(TFA)_2$ (5)	dppp (10)	AcONa (1.2)	15
6	$Pd(TFA)_2$ (5)	dppp (10)	K_3PO_4 (1.2)	39
7	$Pd(TFA)_2$ (5)	dppp (10)	Na_3PO_4 (1.2)	35
8	$Pd(TFA)_2$ (5)	dppp (10)	K_2HPO_4 (1.2)	25
9	$Pd(TFA)_2$ (5)	dppp (10)	PhONa (1.2)	18
10	$Pd(TFA)_2$ (5)	dppp (10)	K_3PO_4 (2)	50
11	$Pd(TFA)_2$ (5)	dppp (10)	K_3PO_4 (3)	30
12	$Pd(TFA)_2$ (5)	dppe (10)	K_3PO_4 (2)	5
13	$Pd(TFA)_2$ (5)	X-phos (10)	K_3PO_4 (2)	trace
14	$Pd(TFA)_2$ (5)	Xantphos (10)	K_3PO_4 (2)	trace
15	$Pd(TFA)_2$ (10)	dppp (10)	K_3PO_4 (2)	54
16[c]	$Pd(TFA)_2$ (10)	dppp (10)	K_3PO_4 (2)	trace
17[d]	$Pd(TFA)_2$ (10)	dppp (10)	K_3PO_4 (2)	28
18[e]	$Pd(TFA)_2$ (10)	dppp (10)	K_3PO_4 (2)	72
19[f]	**$Pd(TFA)_2$ (10)**	**dppp** (10)	**K_3PO_4 (2)**	**73**
20[f]	$Pd(TFA)_2$ (7.5)	dppp (10)	K_3PO_4 (2)	54
21[f]		dppp (10)	K_3PO_4 (2)	—
22[f]	$Pd(TFA)_2$ (10)		K_3PO_4 (2)	trace

[a] Conditions: substrate (1 mmol), [Pd], Ligand, Base, CO (1 MPa), CH_3CN, 140 °C, 12 h. [b] Isolated yield. [c] *1,4*-Dioxane instead of CH_3CN as solvent. [d] 130 °C. [e] 150 °C. [f] 160 °C.

Table 2. Cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylates[a,b]



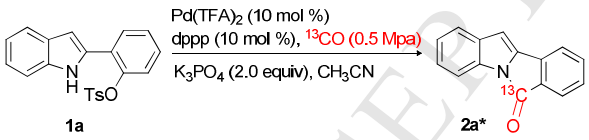


[a] Conditions: substrate (1 mmol), $Pd(TFA)_2$ (10 mol %), dppp (10 mol %), K_3PO_4 (2 mmol), CO (1 MPa), CH_3CN (30 mL), 160 °C, 12 h. [b] Isolated yields.

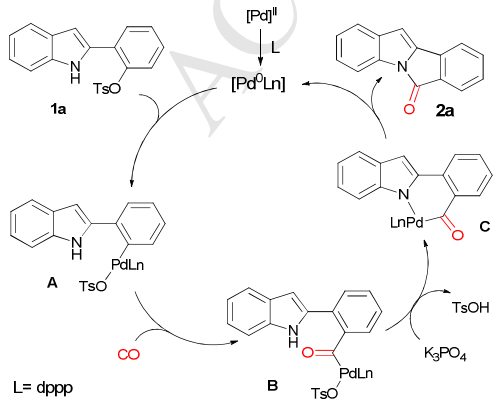
With the optimum reaction conditions in hand, we subsequently investigated the scope of the Pd-catalyzed cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylates (**Table 2**). In general, the presence of substituents such as CH_3, Cl or F at the *5*-position of the indole unit has a slightly negative impact on the catalytic reaction, giving the desirable products in relatively lower yields (**Table 2**, **2b** - **2d**). When the substituent is located at the *7*-position of the indole units, it leads to a more significant decrease of yields due to the sterical effect (**2e**, **2b** vs **2f**, **2h** vs **2l**, **2i** vs **2m**, **2o** vs **2t**, **2s** vs **2u**). Surprisingly, the presence of CH_3 or Et substituent at the *3*-position of the indole ring has promotive impact on the catalytic reaction, giving the corresponding 6H-isoindolo[2,1-*a*]indol-6-one derivatives in satisfactory to excellent yields (**Table 2**, **2g** - **2s**). Significantly, the catalytic system is tolerant to the chlorine substituent (**Table 2**, **2c, 2k, 2s, 2u**). The presence of a benzyl substituent at the 3-position of the indole ring can also give the corresponding 6H-isoindolo[2,1-*a*]indol-6-one derivatives in moderate yields (**Table 2**, **2w** - **2y**). *9*-Methyl-6H-isoindolo[2,1-*a*]indol-6-one and *7*-Methyl-6H-isoindolo[2,1-*a*]indol-6-one were synthesized from the corresponding tosylates in satisfactory yields (**Table 2**, **2z, 2aa**).

In addition, *2,11*-dimethyl-6H-isoindolo[2,1-*a*]indol-6-one, *2*-fluoro-11-methyl-6H-isoindolo[2,1-*a*]indol-6-one and *2*-chloro-11-methyl-6H-isoindolo[2,1-*a*]indol-6-one, which have the pharmacologically activities against hepatocellular liver carcinoma cells as potential anticancer agents,[4] could also be synthesized in 60-80% yields by applying the protocol (**Table 2**, **2h, 2i, 2k**). However, attempts to synthesize the corresponding cyclocarbonylation products at the *3*-position of the indole ring by protecting the -NH moiety with the *t*-butoxycarbonyl or methyl substituent were unsuccessful.

To gain some preliminary understanding of the reaction mechanism, a $^{13}CO_{(g)}$ labeling reaction was carried out. Replacement of CO (1 MPa) with $^{13}CO_{(g)}$ (0.5 MPa), [^{13}C]-6H-isoindolo[2,1-*a*]indol-6-one (**2a***) was successfully obtained from *2*-(1H-indol-2-yl)phenyl tosylate in 50% yield, and the corresponding product (**2a***) was characterized by ^{1}H NMR, ^{13}C NMR and HRMS (**Scheme 2**).



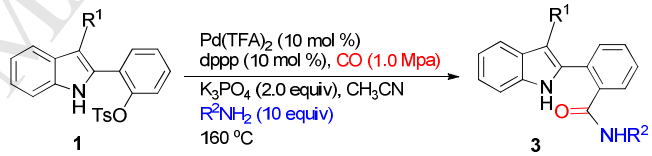
Scheme 2. Preparation of [^{13}C]-6H-isoindolo[2,1-*a*]indol-6-one (**2a***) with ^{13}CO.



Scheme 3. Proposed reaction mechanism for the formation of substituted 6H-isoindolo[2,1-*a*]indol-6-one.

Based on the above observations and previous reports,[7b, 9] a plausible mechanism for the formation of **2a** is shown in **Scheme 3**. The oxidative addition of the in situ generated Pd^0 species with **1a** leads to the formation of the key aryl palladium complex **A**, which undergoes the CO insertion into a Pd-C bond to afford the aroyl complex **B**. Under the promotion of a base, intermediate **B** undergoes the intramolecular ligand exchange to afford intermediate **C**. Finally, the reductive elimination forms the cycloaminocarbonylation product and regenerates the active Pd^0 species for the next catalytic cycle (**Scheme 3**).

To explore the versatility of the methodology, we studied the effect of amine additive on the chemoselectivity. Gratifyingly, it was found that when ten equivalents of primary amine was presented, the intermolecular aminocarbonylation products *2*-(1H-indol-2-yl)-benzamide **(3a - 3d)** were selectively obtained in moderate yields (**Scheme 4**). However, treatment of **1a** with CO in the presence of bulky *t*-$BuNH_2$ instead of *n*-$BuNH_2$, gave only the intra- rather than intermolecular aminocarbonylation product **2a** (60% yield). In order to reveal the mechanism for the formation of **3**, we made an attempt to isolate the intermediates of the reaction of **1n** with CO and *n*-$BuNH_2$ (10 equiv) under standard conditions. When the reaction time was reduced from 12 h to 6 h, a mixture of **3b** (30%) and **2n** (25%) was obtained. However, attempt to prepare the intermolecular aminocarbonylation product from the N-methyl-protected substrate was unsuccessful. Furthermore, **3** could also be synthesized by the in situ aminolysis of 6H-isoindolo[2,1-*a*]indol-6-ones (**2**) (**Scheme 5**). These results demonstrated that the formation of compounds **3** might be from the aminolysis of the newly formed **2**, rather than directly from the competing intermolecular aminocarbonylation of **1** with CO and amine.

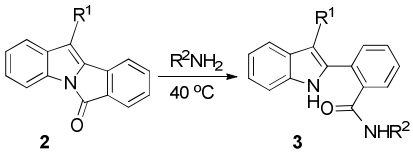


1 3

R^1 = H, R^2 = *n*-Bu, 52% (30%)* yield, **3a**
R^1 = Et, R^2 = *n*-Bu, 50% yield, **3b**
R^1 = H, R^2 = *n*-Pr, 55% yield, **3c**
R^1 = H, R^2 = Bn, 52% yield, **3d**

* *n*-$BuNH_2$ (1 equiv) was used.

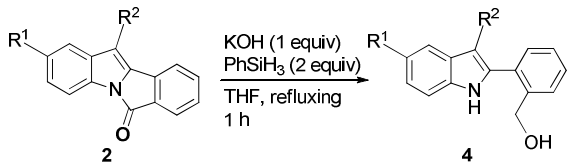
Scheme 4. Preparation of compound **3** from **1** with CO.



2 3

Yield
R^1 = H, R^2 = *n*-Bu, 86%, **3a**
R^1 = Et, R^2 = *n*-Bu, 74%, **3b**
R^1 = H, R^2 = *n*-Pr, 89%, **3c**
R^1 = H, R^2 = Bn, 73%, **3d**
R^1 = Et, R^2 = Bn, 72%, **3e**

Scheme 5. Preparation of compound **3** from **2** via aminolysis.



2 4

R^1= H, R^2= H, 82% yield, **4a**
R^1= Me, R^2= Me, 80% yield, **4b**
R^1= Cl, R^2= Me, 75% yield, **4c**
R^1= Me, R^2= Et, 86% yield, **4d**
R^1= H, R^2= Bn, 76% yield, **4e**

Scheme 6. Preparation of compound **4** from **2**.

2-(-1H-Indol-2-yl)benzyl alcohols are valuable intermediates in organic synthesis.[2b,3,5,10] To our delight, treatment of **2** with $PhSiH_3$ in the presence of 1 equivalent of KOH in dry THF at refluxing temperature for 1 h allowed the formation of the desirable reduced products **4** in 75-86% yields (**Scheme 6**), providing a new method for synthesis of *2*-(-1H-Indol-2-yl)benzyl alcohols.

In summary, we have developed an efficient method for the synthesis of 6H-isoindolo[2,1-*a*]indol-6-one derivatives from the corresponding *2*-(1H-indol-2-yl)phenyl tosylates via the Pd-catalyzed intramolecular cycloaminocarbonylation with carbon monoxide in moderate to good yields. Furthermore, it is found that the presence of an excess of primary amines can switch the chemoselectivity of the aminocarbonylation from intramolecular to intermolecular reaction, affording substituted *2*-(1H-indol-2-yl)benzamides. In addition, the direct transformation of isoindolo[2,1-*a*]indol-6-ones into *2*-(-1H-indol-2-yl)benzyl alcohols is also achieved. The easy synthesis and crystalline isolation of *2*-(1H-indol-2-yl)phenyl tosylates from cheap *2*-hydroxyphenyl alkyl ketone precursors makes the present method an attractive and practical alternative to those commonly used *o*-(*2*-halophenyl)-1H-indoles as counterparts in cycloaminocarbonylation protocols. Further investigations on the synthetic applications of this method are underway in our laboratory.

3. Experimental Section

3.1 General procedure for the intramolecular cycloaminocarbonylation of *2*-(1H-indol-2-yl)phenyl tosylates

2-(1H-Indol-2-yl)phenyl tosylate (1 mmol), $Pd(TFA)_2$ (10 mol%), dppp (10 mol%), anhydrous K_3PO_4 (2 mmol) and CH_3CN (30 mL) were charged in a 200 ml-autoclave. The autoclave was flushed and then pressurized with carbon monoxide to 1 MPa, the mixture was stirred at 160 ^oC for 12 h. The mixture was cooled to room temperature and vented to discharge the excess CO. After filtration, solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel with petroleum ether-ethyl acetate as the eluent to afford the desired product.

*3.1.1. [^{13}C]-6H-Isoindolo[2,1-a]indol-6-one (**2a***)*

Yellow solid; 168.6 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.72 (dd, *J* = 7.4, 3.3 Hz, 1H), 7.47 (d, *J* = 4.0 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.33-7.28 (m, 1H), 7.25 (d, *J* = 3.7 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.56 (s, 1H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.6 (^{13}C-enriched), 138.8 (d, *J* = 8.3 Hz), 134.6 (d, *J* = 4.1 Hz), 134.4 (d, *J* = 2.6 Hz), 134.1, 133.6, 133.5, 128.7 (d, *J* = 4.6 Hz), 126.3, 125.2 (d, *J* = 2.8 Hz), 123.8, 122.2, 121.2 (d, *J* = 3.2 Hz), 113.3, 103.4 (d, *J* = 1.8 Hz). HRMS (ESI) Calcd for $C_{14}{}^{13}CH_{10}NO$ $[M+H]^+$: 221.0796; Found: 221.0807.

*3.1.2. 2,4-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2e**)*

Yellow solid; 121.8 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.49-7.44 (m, 2H), 7.32-7.28 (m, 1H), 7.00 (s, 1H), 6.84 (s, 1H), 6.52 (s, 1H), 2.83 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.2, 140.0, 135.5, 134.3, 133.7, 133.6, 133.5, 132.5, 130.0, 128.5, 125.1, 124.4, 120.5, 119.5, 103.7, 21.0, 21.0. HRMS (ESI) Calcd for $C_{17}H_{14}NO$ $[M+H]^+$: 248.1075; Found: 248.1089.

*3.1.3. 2-Methoxy-11-methyl-6H-isoindolo[2,1-a]indol-6-one (**2j**)*

Yellow solid; 178.4 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.65 (t, *J* = 7.2 Hz, 2H), 7.45-7.38 (m, 2H), 7.24-7.21 (m, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.76 (s, 1H), 3.82 (d, *J* = 1.5 Hz, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 161.8, 156.6, 136.7, 135.3, 134.8, 133.9, 133.1, 128.0, 127.8, 124.9, 120.9, 115.1, 113.7, 113.6, 104.0, 55.6, 9.4. HRMS (ESI) Calcd for $C_{17}H_{14}NO_2$ $[M+H]^+$: 264.1025; Found: 264.1026.

*3.1.4. 4,11-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2l**)*

Yellow solid; 174.4 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.47-7.42 (m, 2H), 7.25-7.22 (m, 1H), 7.11 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.04-6.99 (m, 2H), 2.84 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 161.7, 136.4, 135.5, 134.4, 134.1, 133.5, 133.3, 128.9, 127.8, 125.1, 124.7, 123.8, 120.5, 117.1, 115.2, 21.2, 9.3. HRMS (ESI) Calcd for $C_{17}H_{14}NO$ $[M+H]^+$: 248.1075; Found: 248.1089.

*3.1.5. 4-Fluoro-11-methyl-6H-isoindolo[2,1-a]indol-6-one (**2m**)*

Yellow solid; 223.6 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.50-7.46 (m, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.11-7.03 (m, 2H), 6.99-6.94 (m, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 160.5, 149.9 (d, J_{CF} = 250 Hz), 139.1, 135.7, 134.4, 133.5, 133.1, 128.3, 125.4, 124.3 (d, J_{CF} = 5.7 Hz), 121.0, 120.6 (d, J_{CF} = 13.6 Hz), 115.7 (d, J_{CF} = 2.4 Hz), 114.9 (d, J_{CF} = 3.7 Hz), 113.2 (d, J_{CF} = 18.5 Hz), 9.4. HRMS (ESI) Calcd for $C_{16}H_{11}FNO$ $[M+H]^+$: 252.0825; Found: 252.0839.

*3.1.6. 11-Ethyl-2-fluoro-6H-isoindolo[2,1-a]indol-6-one (**2o**)*

Yellow solid; 136.6 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.80-7.68 (m, 2H), 7.53-7.45 (m, 2H), 7.29 (t, *J* = 6.9 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 6.96 (t, *J* = 8.9 Hz, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.0, 159.8 (d, J_{CF} = 238 Hz), 135.9 (d, J_{CF} = 9.0 Hz), 135.5, 134.6, 133.7, 133.5, 130.0, 128.3, 125.3, 121.4 (d, J_{CF} = 3.9 Hz), 121.3, 113.9 (d, J_{CF} = 9.3 Hz), 113.6 (d, J_{CF} = 25 Hz), 106.6 (d, J_{CF} = 25 Hz), 18.0, 14.3. HRMS (ESI) Calcd for $C_{17}H_{13}FNO$ $[M+H]^+$: 266.0981; Found: 266.0985.

*3.1.7. 11-Ethyl-4-methyl-6H-isoindolo[2,1-a]indol-6-one (**2q**)*

Yellow solid; 132.4 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.56-7.45 (m, 2H), 7.30-7.27 (m, 1H), 7.21 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.08-7.03 (m, 2H), 2.88-2.83 (m, 5H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 161.9, 135.5, 135.0, 134.5, 134.4, 133.6, 133.4, 128.9, 127.9, 125.2, 125.0, 123.8, 121.9, 120.7, 117.3, 21.3, 17.8, 14.3. HRMS (ESI) Calcd for $C_{18}H_{16}NO$ $[M+H]^+$: 262.1232; Found: 262.1233.

*3.1.8. 2,11-Diethyl-6H-isoindolo[2,1-a]indol-6-one (**2r**)*

Yellow solid; 125.0 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.49-7.42 (m, 2H), 7.24-7.21 (m, 1H), 7.19 (s, 1H), 7.09 (dd, *J* = 8.1, 0.9 Hz, 1H), 2.83 (q, *J* = 7.6 Hz, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H), 1.26 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.1, 139.7, 135.0, 134.9, 134.1, 133.9, 133.3, 132.0, 127.8, 126.4, 125.1, 122.0, 121.0, 119.3, 113.1, 29.0, 18.0, 16.1, 14.4. HRMS (ESI) Calcd for $C_{19}H_{18}NO$ $[M+H]^+$: 276.1388; Found: 276.1394.

*3.1.9. 2-Chloro-11-ethyl-6H-isoindolo[2,1-a]indol-6-one (**2s**)*

Yellow solid; 142.0 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.75-7.70 (m, 2H), 7.50-7.47 (m, 2H), 7.34-7.28 (m, 2H), 7.21-7.18 (m, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.0, 136.0, 135.2, 134.5, 133.6, 131.9, 129.1, 128.4, 126.2, 125.4, 121.4, 121.0, 120.1, 114.1, 99.9, 17.9, 14.3. HRMS (ESI) Calcd for $C_{17}H_{13}ClNO$ $[M+H]^+$: 282.0686; Found: 282.0683.

*3.1.10. 11-Ethyl-4-fluoro-6H-isoindolo[2,1-a]indol-6-one (**2t**)*

Yellow solid; 190.2 ^oC; ^1H NMR ($CDCl_3$, 400MHz): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.53-7.47 (m, 2H), 7.30 (t, *J* = 7.3 Hz, 1H),

7.16 (d, *J* = 7.7 Hz, 1H), 7.09-7.04 (m, 1H), 7.00-6.95 (m, 1H), 2.86 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 160.6, 150.1 (d, J_{CF} = 251 Hz), 138.2 (d, J_{CF} = 4.9 Hz), 135.2, 134.4, 133.6, 133.1, 128.4, 125.5, 124.3 (d, J_{CF} = 6.1 Hz), 121.5, 121.1, 120.8, 115.8 (d, J_{CF} = 3.3 Hz), 113.1 (d, J_{CF} = 18.5 Hz), 17.9, 14.3. HRMS (ESI) Calcd for $C_{17}H_{13}FNO$ $[M+H]^+$: 266.0981; Found: 266.0989.

*3.1.11. 4-Chloro-11-ethyl-6H-isoindolo[2,1-a]indol-6-one (**2u**)*

Yellow solid; 159.6 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.51 (q, *J* = 7.6 Hz, 2H), 7.33-7.27 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.04 (td, *J* = 7.8, 1.6 Hz, 1H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 160.7, 137.5, 135.9, 134.0, 133.7, 133.3, 132.3, 128.4, 127.8, 125.5, 124.3, 120.9, 120.9, 119.4, 118.2, 17.7, 14.2. HRMS (ESI) Calcd for $C_{17}H_{13}ClNO$ $[M+H]^+$: 282.0686; Found: 282.0683.

*3.1.12. 11-Ethyl-2-methoxy-6H-isoindolo[2,1-a]indol-6-one (**2v**)*

Yellow solid; 158.0 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.46-7.41 (m, 2H), 7.25-7.22 (m, 1H), 6.87-6.78 (m, 2H), 3.83 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 161.9, 156.5, 135.8, 134.8, 134.7, 133.9, 133.2, 128.2, 127.9, 125.0, 121.7, 121.0, 113.8, 113.4, 104.4, 55.7, 17.9, 14.3. HRMS (ESI) Calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1181; Found: 278.1179.

*3.1.13. 11-Benzyl-2-fluoro-6H-isoindolo[2,1-a]indol-6-one (**2x**)*

Yellow solid; 174.2 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.80-7.77 (m, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.45-7.41 (m, 1H), 7.34-7.27 (m, 6H), 7.25-7.21 (m, 1H), 6.99-6.91 (m, 2H), 4.17 (s, 2H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 162.0, 159.8 (d, J_{CF} = 239 Hz), 138.2, 136.8, 136.0 (d, J_{CF} = 9.4 Hz), 134.5, 133.8, 133.7, 129.9, 128.8, 128.6, 128.4, 126.8, 125.4, 121.4, 117.7 (d, J_{CF} = 3.9 Hz), 113.9, 113.8 (d, J_{CF} = 17.7 Hz), 107.0 (d, J_{CF} = 24.5 Hz), 30.7. HRMS (ESI) Calcd for $C_{22}H_{15}FNO$ $[M+H]^+$: 328.1138; Found: 328.1136.

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