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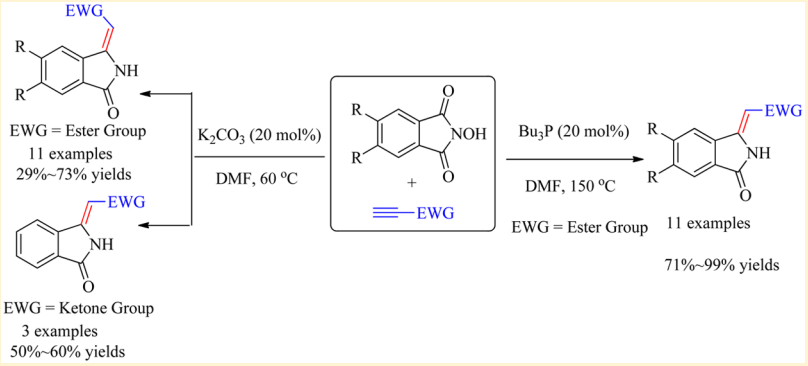
Stereoselective Synthesis of 3-Methyleneisoindolin-1-ones via Base-Catalyzed Intermolecular Reactions of Electron-Deficient Alkynes with *N*-Hydroxyphthalimides

Xin Chen,[†] Fei-Fei Ge,[†] Tao Lu,*[,†] and Qing-Fa Zhou*[,†,‡]

[†]School of Basic Sciences, China Pharmaceutical University, Nanjing, 210009, P. R. China

[‡]State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing, 210009, P. R. China

Supporting Information



ABSTRACT: Highly stereoselective intermolecular reactions of electron-deficient alkynes with *N*-hydroxyphthalimides for efficient construction of N-unprotected 3-methyleneisoindolin-1-ones have been developed through base catalytic strategies. The reaction of alkynoates with *N*-hydroxyphthalimides catalyzed by Bu_3P in DMF at 150 °C gave the corresponding 3-methyleneisoindolin-1-ones with a (Z)-configuration, while the reaction of alkynoates with *N*-hydroxyphthalimides catalyzed by K_2CO_3 in DMF at 60 °C gave the corresponding 3-methyleneisoindolin-1-ones with an (E)-configuration, and (*Z*)-3-methyleneisoindolin-1-ones were obtained when alkyne ketones reacted with *N*-hydroxyphthalimide.

Isoindolinones are important scaffolds in organic chemistry and medicinal chemistry due to their prevalence in numerous synthetic and naturally occurring bioactive molecules. In particular, 3-methyleneisoindolin-1-ones have been recognized as core structures in natural compounds such as enterocarpam II, the secophthalide–isoquinoline ene-lactam fumaridine,[1] magallanesine, an isoindolobenzazocine isolated from the South-American plant Berberis darwinii.[2] 3-Methyleneisoindolin-1-ones have shown a diverse range of bioactivities, such as vasorelaxant property[3] and local anesthetic activity.[4] In addition, 3-methyleneisoindolin-1-ones are also important intermediates for the synthesis of other useful alkaloids.[5] Owing to their great importance, many methods have been developed for the preparation of 3-methyleneisoindolin-1-ones. These methods mainly involved the traditional condensation reaction of phthalimides with stabilized phosphoranes,[6] or addition of organometallic reagents, followed by dehydration of the resulting 3-hydroxyphthalimidines,[7] the Horner condensation of 3-(diphenylphosphinoyl)-isoindolin-1-ones with aldehydes,[8] ortholithiation–anionic cyclization of *N*-acyl-2-bromobenzamides,[9] electrophilic cyclizations of 2-alkynylbenzamides,[10] and recently developed metal-catalyzed cascade reactions.[11] However, most of the present procedures suffer from one or more drawbacks such as the use of expensive metal reagents or poor stereoselectivity of the products; therefore, more efficient and simple protocols to stereoselectively prepare 3-methyleneisoindolin-1-one would be highly desirable.

Over the past 20 years, base-catalyzed annulation has grown significantly and represents one of the most powerful synthetic methodologies for preparing various heterocyclic compounds. Nonetheless, base catalytic, direct syntheses of 3-methyleneisoindolin-1-one derivatives have seen considerably less progress. We have recently developed a convenient phosphine-catalyzed [3 + 2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide (NHPI) for the synthesis of 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones (Scheme 1).[12] In the context of ongoing projects for the diversely functionalized construction of isoindolin-1-ones, we wish to report the novel process for stereoselective synthesis of 3-methyleneisoindolin-1-ones (Scheme 1).

We started our investigation by examining the Bu_3P-catalyzed reaction of 2-hydroxyisoindoline-1,3-dione **1a** and ethyl propiolate **2a** (Table 1). First, the reaction of **1a** with **2a**

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Scheme 1. Phosphine-Catalyzed Reactions of 2-Hydroxyisoindoline-1,3-dione and Ethyl Propiolate

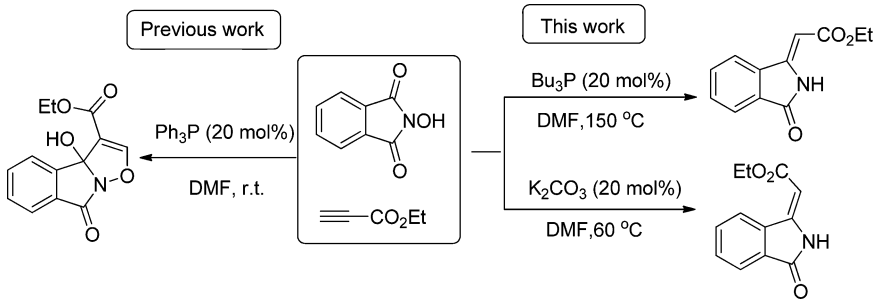
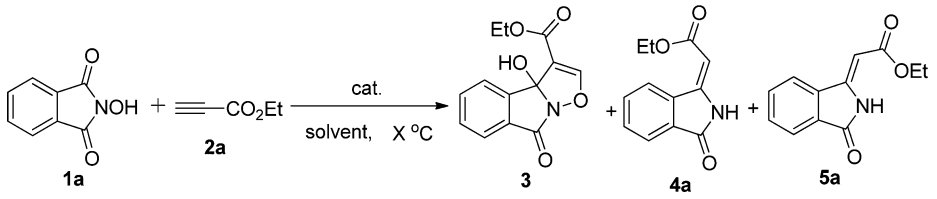


Table 1. Evaluation of Conditions for the Reaction of 1a with Ethyl Propiolate (2a)[a]



entry	catalyst (mol %)	solvent	temperature (°C)	time (h)	yield of **3** (%)[b]	yield of **4a** (%)[b]	yield of **5a** (%)[b]
1	Bu_3P (10)	DMF	r.t.[c]	48	48	42	0
2	Bu_3P (20)	DMF	r.t.	24	0	69	11
3	Bu_3P (50)	DMF	r.t.	2	0	76	6
4	Bu_3P (20)	DMF	0	48	40	36	14
5	Bu_3P (20)	DMF	−20	6	97	0	0
6	Bu_3P (20)	DMF	60	6	0	74	17
7	Bu_3P (20)	DMF	100	2	0	80	11
8	Bu_3P (20)	DMF	150	2	0	0	95
9	Bu_3P (20)	THF	reflux	48	0	0	0
10	Bu_3P (20)	CH_2Cl_2	r.t.	48	18	28	5
11	Bu_3P (20)	CH_2Cl_2	reflux	48	38	35	11
12	Bu_3P (20)	CH_3CN	r.t.	48	31	49	10
13	Bu_3P (20)	CH_3CN	reflux	12	0	65	13
14	Bu_3P (20)	toluene	r.t.	48	30	19	trace
15	Bu_3P (20)	toluene	reflux	12	0	51	21
17	Ph_3P (20)	DMF	100	18	0	40	31
18	Ph_3P (20)	DMF	150	16	0	0	62
19	Ph_2PEt (20)	DMF	100	18	0	51	42
20	Ph_2PEt (20)	DMF	150	14	0	0	92
21[d]	Et_3N (20)	DMF	60	4	0	0	0
22	K_2CO_3 (20)	DMF	60	4	0	73	trace
23	K_2CO_3 (20)	DMF	100	6	0	0	74

[a]Unless noted otherwise, reaction of *N*-hydroxyphthalimide **1a** (0.3 mmol), ethyl propiolate **2a** (0.36 mmol) was performed in 1 mL of solvent under N_2. [b]Isolated yield based on **1a**. [c]r.t. = room temperature. [d]The Michael addition product was formed in 77% yield.

in the presence of Bu_3P (10 mol %) in DMF at room temperature for 48 h afforded the (*E*)-3-methyleneisoindolin-1-one **4a** in the yield of 42% accompanied by 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivative **3** in the yield of 48% (entry 1, Table 1). It was interesting to note that 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivative **3** was not found and the (*E*)-3-methyleneisoindolin-1-one **4a** was formed in good yield beside a little amount of (*Z*)-3-methyleneisoindolin-1-one **5a** when the loading of the catalyst Bu_3P was increased to 20 or 50 mol % (entries 2 and 3, Table 1). To improve the reaction selectivity, the temperature was then evaluated. To our delight, an excelent yield of **5a** was obtained when the reaction was carried out at 150 °C (entry 8, Table 1). The (*E*)-3-methyleneisoindolin-1-one **4a** was formed in good yield accompanied by a small quantity of its (Z)-isomer **5a** when the reaction was disposed at 60 °C for 6 h or 100 °C for 2 h (entries 6 and 7, Table 1). However, only 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivative **3** was given when the reaction was performed at −20 °C (entry 4, Table 1). When shifting the solvent to THF, CH_2Cl_2, CH_3CN, or toluene, the reaction did not give the better results (entries 9−15, Table 1). Other nucleophilic phosphines was also tested, and both Ph_3P and Ph_2PEt were proved to be useable catalysts for **5a** at 150 °C (entries17−20, Table 1). The base containing nitrogen, such as Et_3N, was also examined in the reaction; only the Michael addition product was observed (entry 21, Table 1). It is highlighted here that only (*E*)-3-methyleneisoindolin-1-one **4a** was given in 73% yield when the reaction was performed in DMF at 60 °C for 4 h using inorganic base K_2CO_3 as catalyst, and the sole product **5a** was formed in 74%

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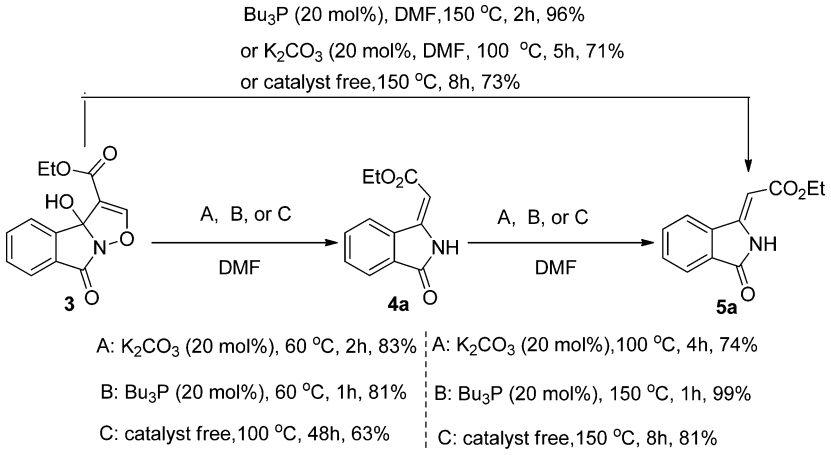
Scheme 2. Transformation of Isoindolinone Derivatives at Different Conditions

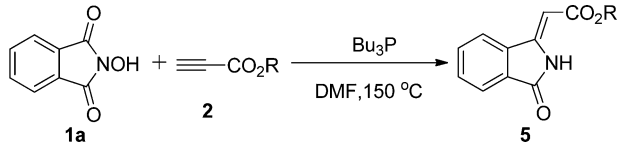


yield when the reaction was performed in DMF at 100 °C for 6 h (entries 22 and 23, Table 1). Herein, we established the optimal reaction conditions for the stereoselective synthesis of N-unprotected 3-methyleneisoindolin-1-one derivatives via the reaction conditions' control.

To understand these novel processes, 3a-hydroxyisoxazolo-[3,2-*a*]isoindol-8(3a*H*)-one derivative **3** and (*E*)-3-methylene-isoindolin-1-one **4a** were treated under different conditions (Scheme 2). We found that compound **3a** could be effectively transformed to (*E*)-3-methyleneisoindolin-1-one **4a** in the presence of a catalytic amount of both K_2CO_3 and Bu_3P at 60 °C, while it was fully transformed to (*Z*)-3-methylene-isoindolin-1-one **5a** at 150 °C in the presence of Bu_3P or at 100 °C in the presence of K_2CO_3. We also found that (*E*)-3-methyleneisoindolin-1-one **4a** could be effectively transformed to (*Z*)-3-methyleneisoindolin-1-one **5a** in the presence of a catalytic amount of both K_2CO_3 and Bu_3P at a higher temperature, which shows a novel example that the (E)-configuration of the carbon−carbon double bond could be transformed to the (Z)-configuration of the carbon−carbon double bond. It is worth mentioning here that compound **3a** could also be transformed to (*E*)-3-methyleneisoindolin-1-one **4a** and (*Z*)-3-methyleneisoindolin-1-one **5a** in the absence of catalyst, and compound **4a** could also be transformed to its isomer **5a**. There is an obvious intramolecular hydrogen bonding of the N−H group of **5a** in its crystal structure, and this could be the cause of the Z-stereoselectivity under higher temperature.[13]

With these results in hand, we first investigated the scope of alkynoates for the synthesis of (*Z*)-3-methyleneisoindolin-1-ones (Table 2). As shown in Table 2, all terminal alkynoates were proved to be applicable to this reaction and selectively gave product (*Z*)-3-methyleneisoindolin-1-ones in good to excellent yields under the optimized reaction conditions. The alkynoates bearing both little alkyl units, namely, ethyl and methyl, and a branched bulky alkyl group, such as *t*-butyl, could give the products in 95, 99, and 99% yields, respectively (entries1−3, Table 2). The nature of the substituent on the benzene ring of the benzyl propiolate did impact the yields. For example, for substrates with a halogen Cl or methoxy group attached on the benzene ring, the yields of the corresponding products were obtained in the yields of 98% and 86%, respectively (entries 5 and 8, Table 2). Gratifyingly, furan-2-ylmethyl propiolate also reacted smoothly with **2a** to give the desired (*Z*)-3-methyleneisoindolin-1-one **5i** in an excellent

Table 2. Bu_3P-Catalyzed Synthesis of *Z*-3-Methyleneisoindolin-1-ones[a]



entry	R	time (h)	product	yield (%)
1	Et	2	**5a**	95
2	Me	2	**5b**	99
3	*t*-Bu	2	**5c**	99
4	$PhCH_2$	2	**5d**	99
5	4−Cl-$C_6H_4CH_2$	2	**5e**	98
6	4−Br-$C_6H_4CH_2$	2	**5f**	94
7	4-Me-$C_6H_4CH_2$	4	**5g**	90
8	4-MeO-$C_6H_4CH_2$	6	**5h**	86
9	2-furyl-CH_2	2	**5i**	99
10	Ph	6	**5j**	71

[a]All the reactions were carried out with **1a** (0.3 mmol) and **2** (0.36 mmol) at 150 °C in 1.0 mL of DMF under N_2, and isolated yields were reported.

yield (entry 9, Table 2). It is worthy to note that phenyl propiolate could also proceed with **2a** to provide the corresponding (*Z*)-3-methyleneisoindolin-1-one **5j** in the yield of 71%. However, only the 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one products were formed, when *β*-substituted alkynoates were applied in the reaction.

We then investigated the scope of alkynoates for the synthesis of (*E*)-3-methyleneisoindolin-1-ones in the presence of K_2CO_3 (Table 3). As exemplified in Table 3, a wide array of alkynoates was suitable for the present strategy despite that some examples need to be careful about the reaction temperature. For example, the (*E*)-3-methyleneisoindolin-1-ones were effectively given at room temperature when methyl propiolate or 4-bromophenyl propiolate was used in this reaction; however, the (*Z*)-3-methyleneisoindolin-1-ones were formed as major products at 60 °C for 2 h (entries 2 and 6, Table 3). Notably, phenyl propiolate was also compatible with the standard reaction conditions but in a decreased yield (entry 10, Table 3).

To examine the scope of 2-hydroxyisoindoline-1,3-dione, 5,6-dichloro-2-hydroxyisoindoline-1,3-dione (**1b**) was investigated. As expected, the (*Z*)-ethyl 2-(5,6-dichloro-3-oxoisoindolin-1-

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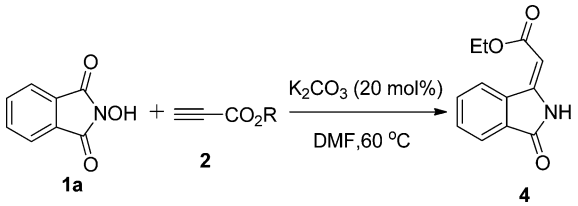
Table 3. K_2CO_3-Catalyzed Synthesis of *E*-3-Methyleneisoindolin-1-ones[a]

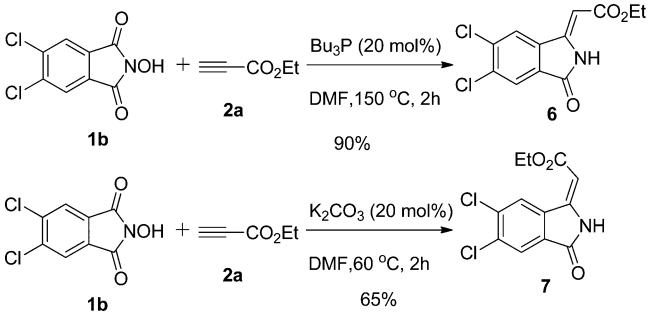


entry	R	time (h)	product	yield (%)
1	Et	4	**4a**	73
2[b]	Me	12	**4b**	66
3	*t*-Bu	4	**4c**	62
4	$PhCH_2$	4	**4d**	60
5	4-Cl-$C_6H_4CH_2$	4	**4e**	62
6[b]	4-Br-$C_6H_4CH_2$	12	**4f**	60
7	4-Me-$C_6H_4CH_2$	6	**4g**	60
8	4-MeO-$C_6H_4CH_2$	6	**4h**	57
9	2-furyl-CH_2	4	**4i**	63
10	Ph	6	**4j**	29

[a]Unless noted otherwise, the reactions were carried out with **1a** (0.3 mmol) and **2** (0.36 mmol) at 60 °C in 1.0 mL of DMF under N_2, and isolated yields were reported. [b]Room temperature.

ylidene)acetate (**6**) was formed in 90% yield when the reaction was performed in DMF at 150 °C for 2 h in the presence of Bu_3P, while the (*E*)-ethyl 2-(5,6-dichloro-3-oxoisoindolin-1-ylidene)acetate (**7**) was formed in 65% yield when K_2CO_3 was used as catalyst in DMF at 60 °C for 2 h (Scheme 3).

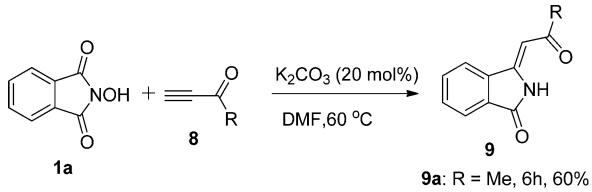
Scheme 3. Reaction of 5,6-Dichloro-2-hydroxyisoindoline-1,3-dione (1b) with Ethyl Propiolate (2a)



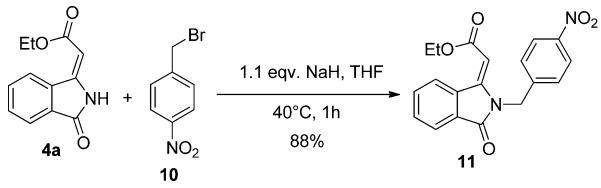
Subsequently, promoted by the successful base-catalyzed direct selective synthesis of 3-methyleneisoindolin-1-ones with alkynoates, a range of alkyne ketones were also examined with respect to 2-hydroxyisoindoline-1,3-dione **1a** to synthesize 3-methyleneisoindolin-1-one compounds. To our surprise, the (*Z*) 3-methyleneisoindolin-1-ones were given when alkyne ketones **8** and **1a** were disposed in DMF at 60 °C in the presence of K_2CO_3, while the reactions were very complicated when the reactions were carried out in the presence of Bu_3P under different temperatures. Both aromatic and aliphatic alkyne ketones could proceed smoothly to give (*Z*)-3-methyleneisoindolin-1-ones in good yields (Scheme 4).

Next, the free N−H group of **4a** was attempted to protect with 1-(bromomethyl)-4-nitrobenzene (**10**) (2.0 equiv) in the presence NaH (2.0 equiv) in THF at 40 °C for 1 h. In the reaction, *N*-benzyl-protected compound **11** was obtained in 88% yield (eq 1).

Scheme 4. Reactions of 2-Hydroxyisoindoline-1,3-dione (1a) with Alkyne Ketones (8)



9a: R = Me, 6h, 60%
9b: R = Ph, 5h, 50%
9c: R = 2-naphthyl, 6h, 51%



(1)

In conclusion, we have developed an efficient and metal-free protocol to synthesize (*E*)-3-methyleneisoindolin-1-ones and (*Z*)-3-methyleneisoindolin-1-ones via base-catalyzed selective reactions of electron-deficient alkynes with *N*-hydroxyphthalimides. The present catalytic process provides a mild and general access to the (*E*)-3-methyleneisoindolin-1-ones and (*Z*)-3-methyleneisoindolin-1-ones, respectively. Especially, the structures of these products are attractive for potential drug discovery.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in anhydrous solvents under a N_2 atmosphere. THF, Et_2O, and toluene were distilled from K and Na metal, respectively. DMF, CH_2Cl_2, and acetone were distilled from CaH_2. CH_3CN was distilled from P_2O_5. PE refers to petroleum ether (boiling range: 60−90 °C). Melting points were obtained on a melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in DMSO-*d6* using a 300 MHz spectrometer: chemical shifts (δ) are given in parts per million, coupling constants (J) in Hz. High-resolution mass spectra were recorded in ESI mode on a QTOF MS spectrometer.

General Procedure for Reaction of Electron-Deficient Alkynes with *N*-Hydroxyphthalimide. To the solution of electron-deficient alkyne (0.36 mmol) and *N*-hydroxyphthalimide (0.3 mmol) in dry DMF (1 mL) was added Ph_3P (15.7 mg, 0.06 mmol). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for the required period of time. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with CH_2Cl_2 (15 mL), which was washed with water and brine successively, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2; ethyl acetate/PE, 1:10−1:3) yielded the desired products.

*(E)-Ethyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4a**).* 47.54 mg, 73% isolated yield; white solid. mp: 95−97 °C. IR (KBr) 3744, 3722, 3651, 2360, 2345, 1770, 1750, 1734, 1717, 1700, 1683, 1657, 1562, 1504, 1458, 794 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.34 (s, 1H), 8.11 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.72 (dt, J = 18.5, 7.2 Hz, 2H), 6.11 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.9, 166.2, 146.6, 136.5, 133.1, 131.7, 128.7, 123.1, 122.0, 92.0, 59.9, 14.1. ESIHRMS: Calcd for $C_{12}H_{12}NO_3$: $(M + H)^+$ 218.0812. Found: m/z 218.0815.

*(E)-Methyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4b**).* 40.20 mg, 66% isolated yield; white solid. mp: 197−199 °C; IR (KBr) 3167, 3113, 3086, 1744, 1715, 1643, 1694, 1632, 1607, 1454, 1373, 1302, 1273, 1157, 1115, 845, 773, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.92 (s, 1H), 8.95 (d, J = 7.6 Hz, 1H), 7.83−7.66 (m, 3H), 5.80 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 169.3,

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167.8, 150.0, 135.5, 134.9, 133.7, 133.1, 129.5, 124.7, 99.7, 53.2. ESIHRMS: Calcd for $C_{11}H_9NNaO_3$: $(M + Na)^+$ 226.0475. Found: *m/z* 226.0479.

*(E)-tert-Butyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4c**).* 45.59 mg, 62% isolated yield; white solid. mp: 162−164 °C. IR (KBr) 3318, 2963, 2928, 1713, 1694, 1634, 1614, 1271, 1146, 1136, 1098, 1076, 856, 812, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.88 (s, 1H), 8.95 (d, *J* = 8.6 Hz, 1H), 7.79 (t, *J* = 6.8 Hz, 2H), 7.74−7.65 (m, 1H), 5.73 (s, 1H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.0, 147.2, 133.6, 132.9, 131.6, 131.2, 127.7, 122.7, 100.2, 79.9, 27.8. ESIHRMS: Calcd for $C_{14}H_{16}NO_3$: $(M + H)^+$ 246.1125. Found: *m/z* 246.1129.

*(E)-Benzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4d**).* 50.24 mg, 60% isolated yield; white solid. mp:185−187 °C. IR (KBr) 3181, 3080, 3071, 3030, 2994, 2843, 1721, 1701, 1643, 1634, 1468, 1454, 1155, 1140, 1117, 851, 741, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.41 (s, 1H), 9.09 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.66 (dt, *J* = 25.0, 7.4 Hz, 2H), 7.39 (dd, *J* = 14.6, 7.0 Hz, 5H), 5.97 (s, 1H), 5.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 168.3, 150.1, 138.5, 136.7, 136.0, 134.1, 133.7, 131.2, 131.1, 130.8, 130.8, 125.8, 102.5, 69.0. ESIHRMS: Calcd for $C_{17}H_{14}NO_3$: $(M + H)^+$ 280.0968. Found: *m/z* 280.0972.

*(E)-4-Chlorobenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4e**).* 58.23 mg, 62% isolated yield; white solid. mp: 194−196 °C. IR (KBr) 3204, 3192, 3115, 1753, 1715, 1651, 1454, 1265, 1223, 1153, 1107, 837, 808, 768 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.98 (s, 1H), 8.94 (d, *J* = 7.5 Hz, 1H), 7.75 (ddd, *J* = 13.0, 11.4, 7.1 Hz, 3H), 7.53−7.35 (m, 4H), 5.83 (s, 1H), 5.21 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.2, 148.6, 135.2, 133.5, 133.0, 132.6, 131.8, 131.1, 129.8, 128.3, 127.6, 122.8, 97.4, 64.6. ESIHRMS: Calcd for $C_{17}H_{12}ClNNaO_3$: $(M + Na)^+$ 336.0398. Found: *m/z* 336.0402.

*(E)-4-Bromobenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4f**).* 64.26 mg, 60% isolated yield; white solid. mp: 215−217 °C. IR (KBr) 3306, 3275, 1722, 1682, 1667, 1651, 1470, 1416, 1294, 1280, 1200, 1125, 1063, 824, 770, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.98 (s, 1H), 8.94 (d, *J* = 7.6 Hz, 1H), 7.81 (s, 1H), 7.72 (ddd, *J* = 18.0, 10.5, 4.2 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 5.83 (s, 1H), 5.19 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.2, 148.7, 135.6, 134.2, 133.5, 133.0, 131.9, 131.3, 131.1, 130.1, 127.6, 122.8, 97.4, 64.6. ESIHRMS: Calcd for $C_{17}H_{13}BrNO_3$: $(M + H)^+$ 358.0073. Found: *m/z* 358.0078.

*(E)-4-Methylbenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4g**).* 52.76 mg, 60% isolated yield; white solid. mp:166−168 °C. IR (KBr) 3418, 3410, 3404, 1748, 1712, 1703, 1694, 1651, 1643, 1634, 1267, 1152, 1146, 1107, 847, 808 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.96 (s, 1H), 8.95 (d, *J* = 7.6 Hz, 1H), 7.92−7.55 (m, 3H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 5.81 (s, 1H), 5.16 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.3, 148.4, 137.3, 133.5, 133.1, 133.0, 131.8, 131.1, 128.9, 128.1, 127.6, 122.8, 97.7, 65.3, 20.6. ESIHRMS: Calcd for $C_{18}H_{16}NO_3$: $(M + H)^+$ 294.1125. Found: *m/z* 294.1131.

*(E)-4-Methoxybenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4h**).* 52.86 mg, 57% isolated yield; white solid. mp:203−205 °C. IR (KBr) 3418, 3400, 2359, 2342, 1732, 1713, 1645, 1634, 1614, 1520, 1277, 1256, 1117, 843 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.95 (s, 1H), 8.95 (d, *J* = 7.5 Hz, 1H), 7.8−7.64 (m, 3H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.79 (s, 1H), 5.14 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.3, 159.1, 148.3, 133.5, 133.0, 131.8, 131.1, 130.0, 128.0, 127.6, 122.8, 113.7, 97.8, 65.2, 55.0. ESIHRMS: Calcd for $C_{18}H_{16}NO_4$: $(M + H)^+$ 310.1074. Found: *m/z* 310.1081.

*(E)-Furan-2-ylmethyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4i**).* 50.86 mg, 63% isolated yield; white solid. mp: 154−155 °C. IR (KBr) 3192, 3183, 3136, 3112, 1728, 1705, 1636, 1613, 1267, 1157, 1142, 1105, 1076, 1001, 841, 752, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (s, 1H), 9.05 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.65 (dt, *J* = 24.5, 7.4 Hz, 2H), 7.45 (s, 1H), 6.47 (d, *J* = 2.9 Hz, 1H), 6.39 (d, *J* = 1.7 Hz, 1H), 5.90 (s, 1H), 5.20 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.0, 165.5, 149.9, 149.2, 144.2, 134.0, 133.6, 132.4, 131.7, 128.1, 123.4, 113.3, 113.2, 97.8, 57.9. ESIHRMS: Calcd for $C_{15}H_{12}NO_4$: $(M + H)^+$ 270.0761. Found: *m/z* 270.0764.

*(E)-Phenyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**4j**).* 23.06 mg, 29% isolated yield; white solid. mp: 196−198 °C. IR (KBr) 3161, 3088, 3071, 1713, 1643, 1634, 1611, 1591, 1493, 1271, 1204, 1136, 1096, 1072, 839, 775, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.10 (d, *J* = 6.7 Hz, 1H), 8.68 (s, 1H), 7.92 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.73−7.62 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 153.2, 151.6, 136.5, 136.2, 135.6, 134.5, 133.5, 132.1, 131.5, 128.5, 126.0, 124.3, 101.2. ESIHRMS: Calcd for $C_{16}H_{12}NO_3$: $(M + H)^+$ 266.0812. Found: *m/z* 266.0813.

*(Z)-Ethyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5a**).* 61.87 mg, 95% isolated yield; white solid. mp167−169 °C. IR (KBr) 3187, 1728, 1682, 1634, 1607, 1470, 1296, 1271, 1153, 1138, 1100, 1076, 854, 779, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.95 (s, 1H), 8.98 (d, *J* = 7.6 Hz, 1H), 7.91−7.60 (m, 3H), 5.80 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.4, 165.5, 148.0, 133.6, 133.0, 131.7, 131.2, 127.6, 122.7, 98.2, 59.8, 14.1. ESIHRMS: Calcd for $C_{12}H_{12}NO_3$: $(M + H)^+$ 218.0812. Found: *m/z* 218.0815.

*(Z)-Methyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5b**).* 60.31 mg, 99% isolated yield; white solid. mp: 122−124 °C. IR (KBr) 3404, 1732, 1667, 1651, 1645, 1634, 1614, 1441, 1283, 1209, 1128, 1097, 764, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.88 (d, *J* = 4.2 Hz, 1H), 7.70 (d, *J* = 4.2 Hz, 1H), 7.64 (dd, *J* = 11, 4.2 Hz, 2H), 5.78 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 167.9, 147.5, 136.4, 132.8, 131.6, 129.6, 124.0, 121.01, 91.2, 51.7. ESIHRMS: Calcd for $C_{11}H_{10}NO_3$: $(M + H)^+$ 204.0655. Found: *m/z* 204.0657.

*(Z)-tert-Butyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5c**).* 72.80 mg, Yield: 99% isolated yield; white solid. mp: 140−142 °C. IR (KBr) 3188, 3175, 3078, 1720, 1699, 1707, 1682, 1643, 1368, 1279, 1258, 1153, 1138, 1115, 775, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.88 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 4.4 Hz, 1H), 7.61 (dt, *J* = 8.8, 4.2 Hz, 2H), 5.72 (s, 1H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 167.0, 146.6, 136.7, 132.6, 131.3, 129.6, 123.9, 120.8, 93.6, 81.3, 28.2. ESIHRMS: Calcd for $C_{14}H_{16}NO_3$: $(M + H)^+$ 246.1125. Found: *m/z* 246.1128.

*(Z)-Benzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5d**).* 82.89 mg, 99% isolated yield; white solid. mp: 146−148 °C. IR (KBr) 3322, 1742, 1692, 1668, 1645, 1424, 1298, 1277, 1211, 1198, 1177, 1161, 1128, 1065, 770, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.89 (d, *J* = 4.2 Hz, 1H), 7.75−7.57 (m, 3H), 7.40 (dt, *J* = 8.6, 4 Hz, 5H), 5.85 (s, 1H), 5.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 167.3, 147.9, 136.4, 135.7, 132.8, 131.6, 129.6, 128.6, 128.4, 128.3, 124.1, 121.0, 91.2, 66.4. ESIHRMS: Calcd for $C_{17}H_{14}NO_3$: $(M + H)^+$ 280.0968. Found: *m/z* 280.0975.

*(Z)-4-Chlorobenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5e**).* 92.04 mg, 98% isolated yield; white solid. mp 180−182 °C. IR (KBr) 3325, 1740, 1688, 1667, 1422, 1296, 1275, 1196, 1171, 1126, 1094, 1063, 812, 768, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.43 (s, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 6.7 Hz, 1H), 7.72 (dd, *J* = 18.0, 7.3 Hz, 2H), 7.45 (s, 4H), 6.15 (s, 1H), 5.23 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.0, 165.8, 147.1, 136.4, 135.3, 133.1, 132.5, 131.7, 129.8, 128.7, 128.3, 123.1, 122.0, 91.5, 64.5. ESIHRMS: Calcd for $C_{17}H_{13}ClNO_3$: $(M + H)^+$ 314.0578. Found: *m/z* 314.0585.

*(Z)-4-Bromobenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5f**).* 100.68 mg, 94% isolated yield; white solid. mp: 191−193 °C. IR (KBr) 3327, 1738, 1688, 1682, 1667, 1422, 1294, 1275, 1196, 1171, 1126, 1063, 808, 768, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.44 (s, 1H), 8.10 (d, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.70 (dt, *J* = 18.5, 7.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.15 (s, 1H), 5.22 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.0, 165.8, 147.1, 136.4, 135.7, 133.1, 131.7, 131.2, 130.1, 128.7, 123.1, 122.0, 121.1, 91.5, 64.5. ESIHRMS: Calcd for $C_{17}H_{12}BrNO_3$: $(M + H)^+$ 358.0073. Found: *m/z* 358.0077.

*(Z)-4-Methylbenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5g**).* 79.14 mg, 90% isolated yield; white solid. mp: 154−156 °C. IR

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(KBr) 3327, 1744, 1682, 1667, 1422, 1273, 1294, 1273, 1196, 1179, 1125, 1063, 814, 768, 691 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.39 (s, 1H), 8.09 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.70 (dd, J = 10.7, 7.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 6.13 (s, 1H), 5.19 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.9, 166.0, 146.9, 137.2, 136.4, 133.1, 133.1, 131.7, 128.8, 128.7, 128.1, 123.1, 122.0, 91.7, 65.2, 20.6. ESIHRMS: Calcd for $C_{18}H_{16}NO_3$: $(M + H)^+$ 294.1125. Found: m/z 294.1131.

*(Z)-4-Methoxybenzyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5h**).* 79.75 mg, 86% isolated yield; white solid. mp: 173−175 °C. IR (KBr) 3339, 1742, 1682, 1667, 1660, 1651, 1645, 1634, 1514, 1470, 1120, 1173, 1060, 822, 168, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.39 (s, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.70 (dd, J = 10.6, 7.4 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.13 (s, 1H), 5.17 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.5, 166.6, 159.7, 147.4, 137.0, 133.6, 132.3, 130.6, 129.2, 128.6, 123.7, 122.5, 114.3, 92.3, 65.8, 55.6. ESIHRMS: Calcd for $C_{18}H_{15}NNaO_4$: $(M + Na)^+$ 332.0893. Found: m/z 332.0896.

*(Z)-Furan-2-ylmethyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5i**).* 79.92 mg, 99% isolated yield; white solid. mp: 119−121 °C. IR (KBr) 3426, 3333, 1746, 1732, 1688, 1665, 1645, 1422, 1198, 1177, 1126, 1062, 780, 687 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.98 (s, 1H), 8.95 (d, J = 7.6 Hz, 1H), 7.84−7.66 (m, 4H), 6.58 (d, J = 3.0 Hz, 1H), 6.48 (s, 1H), 5.77 (s, 1H), 5.19(s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.5, 166.3, 149.9, 147.8, 144.1, 136.9, 133.6, 132.3, 129.2, 123.7, 122.6, 111.3, 111.2, 91.8, 57.8. ESIHRMS: Calcd for $C_{15}H_{12}NO_4$: $(M + H)^+$ 270.0761. Found: m/z 270.0764.

*(Z)-Phenyl 2-(3-Oxoisoindolin-1-ylidene)acetate (**5j**).* 56.46 mg, 71% isolated yield; white solid. mp: 134−136 °C. IR (KBr) 3242, 1713, 1694, 1643, 1634, 1275, 1202, 1153, 1117, 1096, 1057, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 4.8 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 4.4 Hz, 1H), 7.68 (dt, J = 12.1, 4.4 Hz, 2H), 7.44 (t, J = 4.6 Hz, 2H), 7.28 (dd, J = 5.4, 3.1 Hz, 1H), 7.19 (d, J = 4.9 Hz, 2H), 6.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 166.1, 150.4, 149.2, 136.3, 133.0, 131.9, 129.4, 126.0, 124.2, 121.5, 121.2, 114.9, 90.4. ESIHRMS: Calcd for $C_{16}H_{12}NO_3$: $(M + H)^+$ 266.0812. Found: m/z 266.0816.

*(Z)-Ethyl 2-(5,6-Dichloro-3-oxoisoindolin-1-ylidene)acetate (**6**).* 76.95 mg, 90% isolated yield; yellow solid. mp: 194−196 °C. IR (KBr) 3390, 3381, 3242, 1737, 1732, 1694, 1682, 1651, 1645, 1634, 1614, 1557, 1537, 1505, 1271, 1067, 906, 854 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.53 (s, 1H), 8.49 (s, 1H), 8.01 (s, 1H), 6.20 (s, 1H), 4.21 (q, J = 6.9 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.9, 167.7, 146.4, 138.3, 137.9, 136.3, 130.8, 127.0, 126.3, 95.9, 62.0, 16.0. ESIHRMS: Calcd for $C_{12}H_9Cl_2N_1NaO_3$: $(M + Na)^+$ 307.9852. Found: m/z 307.9857.

*(E)-Ethyl 2-(5,6-Dichloro-3-oxoisoindolin-1-ylidene)acetate (**7**).* 55.58 mg, 65% isolated yield; white solid. mp: 215−217 °C. IR (KBr) 3200, 3109, 1743, 1732, 1713, 1694, 1643, 1634, 1607, 1393, 1280, 1145, 1105, 1036, 910, 850. ^1H NMR (300 MHz, DMSO-*d6*): δ 11.18 (s, 1H), 9.10 (s, 1H), 7.95 (s, 1H), 5.77 (s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167.3, 167.2, 147.9, 137.5, 136.6, 135.0, 133.3, 131.2, 126.5, 101.5, 62.1, 15.9. ESIHRMS: Calcd for $C_{12}H_{10}Cl_2N_1O_3$: $(M + H)^+$ 286.0032. Found: m/z 286.0037.

*(Z)-3-(2-Oxopropylidene) Isoindolin-1-one (**9a**).* 33.67 mg, 60% isolated yield; white solid. mp: 116−118 °C. IR (KBr) 3443, 3426, 3347, 3333, 1728, 1694, 1682, 1674, 1614, 1607, 1360, 1227, 1098, 760, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.55 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.80 (m, 2H), 7.75−7.68 (m, 1H), 6.52 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 200.2, 170.4, 146.4, 138.8, 136.1, 135.0, 133.8, 125.3, 124.7, 123.7, 101.4, 32.8. ESIHRMS: Calcd for $C_{11}H_{10}NO_2$: $(M + H)^+$ 188.0707. Found: m/z 188.0706.

*(Z)-3-(2-Oxo-2-phenylethylidene) Isoindolin-1-one (**9b**).* 37.36 mg, 50% isolated yield; yellow solid. mp: 165−167 °C. IR (KBr) 3333, 1720, 1651, 1599, 1300, 1227, 1018, 760, 710 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.89 (s, 1H), 8.34 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 7.4 Hz, 2H), 7.81 (dd, J = 14.9, 7.4 Hz, 2H), 7.75−7.62 (m, 2H), 7.58 (t, J = 7.3 Hz, 2H), 7.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 191.7, 170.6, 149.4, 139.7, 139.0, 135.1, 134.9, 133.9, 130.6, 130.3, 130.0, 125.2, 124.4, 97.5. ESIHRMS: Calcd for $C_{16}H_{12}NO_2$: $(M + H)^+$ 250.0867. Found: m/z 250.0863.

*(Z)-3-(2-(Naphthalen-2-yl)-2-oxoethylidene) Isoindolin-1-one (**9c**).* 45.76 mg, 51% isolated yield; white solid. mp: 211−213 °C. IR (KBr) 3426, 3412, 3381, 3352, 1715, 1694, 1645, 1593, 810, 768 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 10.95 (s, 1H), 8. 96 (s, 1H), 8.41 (d, J = 7.5 Hz, 1H), 8.18 (t, J = 8.6 Hz, 2H), 8.06 (dd, J = 15.2, 8.0 Hz, 2H), 7.86 (t, J = 8.4 Hz, 2H), 7.81−7.63 (m, 3H), 7.58 (s, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 191.5, 170.7, 149.3, 139.1, 137.1, 136.9, 135.1, 134.1, 133.9, 131.8, 131.4, 130.5, 130.4, 130.3, 129.6, 128.8, 125.7, 125.3, 124.4, 97.7. ESIHRMS: Calcd for $C_{20}H_{14}NO_2$: $(M + H)^+$ 300.1019. Found: m/z 300.1026.

*(E)-Ethyl 2-(2-(4-Nitrobenzyl)-3-oxoisoindolin-1-ylidene)acetate (**11**).* 98.76 mg, 88% isolated yield; white solid. mp: 138−140 °C. IR (KBr) 3389, 3381, 1720, 1709, 1694, 1634, 1610, 1520, 1342, 1323, 1188, 1155, 1101, 829, 772, 708 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*): δ 8.94 (d, J = 7.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 7.2 Hz, 1H), 7.86−7.66 (m, 2H), 7.51 (d, J = 8.4 Hz, 2H), 5.78 (s, 1H), 5.22 (s, 2H), 4.17 (dd, J = 13.8, 6.9 Hz, 2H), 1.22 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*): δ 168.3, 167.0, 148.6, 145.9, 136.4, 135.5, 134.9, 133.7, 129.6, 129.3, 125.7, 125.1, 124.7, 101.3, 62.1, 43.6, 15.9. ESIHRMS: Calcd for $C_{19}H_{16}N_2NaO_5$: $(M + H)^+$ 375.0951. Found: m/z 375.0955.

■ ASSOCIATED CONTENT

Supporting Information

The ORTEP diagrams of **4a** and **5a**, ^1H and ^{13}C NMR spectra of the products as well as the X-ray crystallographic data (CIF files) of **4a** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: +86-025-86285179. Tel: +86-025-86185160. E-mail: zhouqingfa@cpu.edu.cn (Q.-F.Z.).

*E-mail: lut163@163.com (T.L.).

Notes

The authors declare no competing financial interest.

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