A facile and efficient method for the synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitrile derivatives catalyzed by sulfamic acid

Ling-Jun Hu,[a] Zha-Jun Zhan,[a] Min Lei,[b]* and Li-Hong Hu [a,b]*

[a] College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, 310014, P. R. China
[b] Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, 501 Haike Road, Shanghai, 201203, PR of China
E-mail: mlei@mail.shcnc.ac.cn, simmhulh@mail.shcnc.ac.cn

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Abstract

A new and efficient method for the synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitrile derivatives by a one-pot, three-component condensation reaction of 2-carboxybenzaldehyde, primary amine, and TMSCN in the presence of 10 mol % sulfamic acid (NH_2SO_3H) as the catalyst in EtOH under reflux temperature is described. The process is simple and environmentally benign and the catalyst is commercially available and inexpensive.

Keywords: multi-component reaction, 2-carboxybenzaldehyde, primary amine, sulfamic acid

Introduction

Isoindolinone derivatives are an important class of compounds because of their therapeutic and pharmacological properties.[1] For examples, indoprofen **I** is shown to have anti-inflammatory activities,[2] while deoxythalidomide **II** is an inhibitor of tumor necrosis factor production,[3] and tricyclic γ-lactam **III** is a non-nucleosidic HIV reverse transcriptase inhibitor (Figure 1).[4] Moreover, isoindolinone compounds **IV** substituted at 3-position have also been shown to be potent inhibitors for DNA gyrase.[5] Hence, there is a need to develop a simple and cost-effective protocol for the synthesis of isoindolinones.

The Strecker reaction between aldehyde, amine, and hydrogen cyanide is widely regarded as the first multi-component reaction (MCR).[6] Its reliability, the ready availability of the starting materials, and the versatility of the resulting products make it a very important process for the diverse synthesis of α-aminoacids and α-aminonitriles. Recently, Strecker reactions have been reported for the multi-component synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitrile

derivatives.[7] These methods used the substrates of aromatic aldehyde with an amine and KCN or NaCN at high temperatures. However, all of these methods suffer from one or more drawbacks, such as unsatisfactory yields, high temperature, long reaction times, and the use of toxic cyanides (KCN or NaCN). Thus, there is a need to develop a safer and more efficient method for the synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitriles.

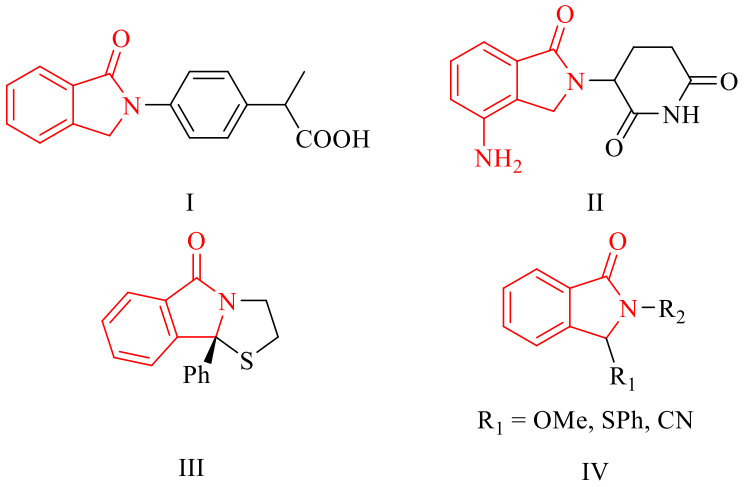
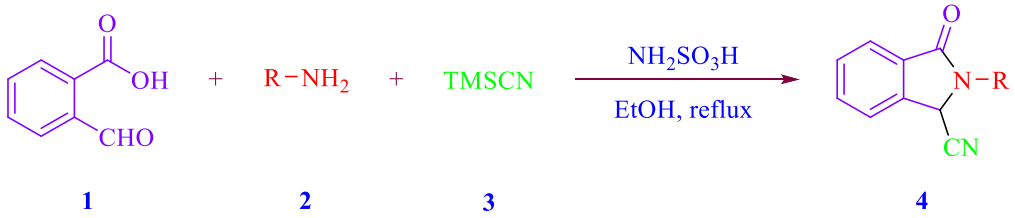


Figure 1. Representative examples of biologically interesting isoindolinones.

As a part of our program aiming at developing efficient and environmentally friendly methodologies for MCRs,[8] and in continuation of our interest in the organic synthesis of heterocyclic compounds, we report herein an improved Strecker reaction for one-pot synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitrile derivatives from 2-carboxybenzaldehyde, primary amine, and TMSCN catalyzed by sulfamic acid (Scheme 1).



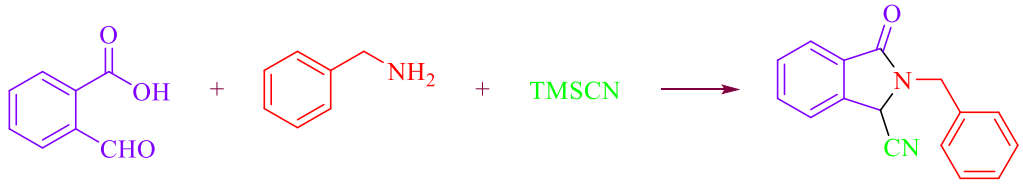
Scheme 1. NH_2SO_3H-catalyzed synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitriles **4**.

Results and Discussion

Initially, we investigated the three-component condensation reaction of 2-carboxybenzaldehyde **1**, benzylamine **2a**, and TMSCN **3** in different reaction conditions (Table 1). As shown in table 1,

only 30% yield of the desired product **4a** was obtained when the reaction was carried out under solvent- and catalyst-free conditions (Table 1, entry 1). However, the yield of product **4a** could be increased to 60% in the presence of 20 mol% of NH_2SO_3H at 90 ºC for 2 h under solvent-free (Table 1, entry 2). This result highlighted the role of NH_2SO_3H as a promoter for this three-component reaction. Further studies revealed that the reactions conducted in EtOH gave relatively higher yields than MeOH, THF, MeCN or DMF (Table1, entries 3-11). Moreover, we also found that 10 mol % of NH_2SO_3H was sufficient and more than this did not increase the yields (Table 1, entries 3-6).

Table 1. Optimization of the reaction conditions[a]



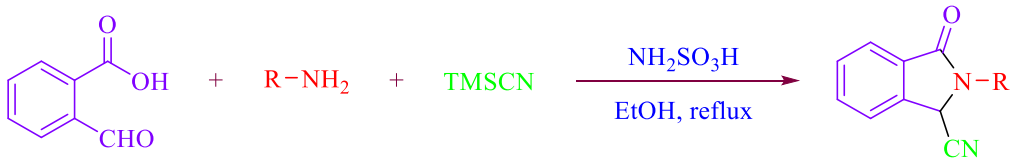
1 **2a** **3** **4a**

Entry	Solvent (mL)	NH_2SO_3H (mol %)	Temp. (ºC)	Time (h)	Yield of **4a** (%)[b]
1	None	None	90	4	30
2	None	20	90	2	60
3	EtOH (2)	20	reflux	1	78
4	EtOH (2)	5	reflux	2	65
5	**EtOH (2)**	**10**	**reflux**	**1**	**87**
6	EtOH (2)	15	reflux	1	82
7	EtOH (5)	10	reflux	1	75
8	MeOH (2)	10	reflux	1	65
9	THF (2)	10	reflux	1	74
10	MeCN (2)	10	reflux	1	80
11	DMF (2)	10	90	1	50

[a] Conditions: 2-carboxybenzaldehyde **1** (3 mmol), benzylamine **2a** (3.6 mmol), TMSCN **3** (4.5 mmol). [b] Isolated yields.

In terms of yields and reaction time, we achieved the best conditions to synthesis *N*-benzyl-3-oxoisoindoline-1-carbonitrile **4a** by using 10 mol % of NH_2SO_3H under refluxed temperature in EtOH (Table 1, entry 5). Having established the optimized reaction conditions, we then successfully synthesized a variety of *N*-substituted 3-oxoisoindoline-1-carbonitriles **4**, and the results are summarized in Table 2.

Table 2. Synthesis of 3-oxoisoindoline-1-carbonitrile **4** catalyzed by NH_2SO_3H[a]



1 **2** **3** **4**

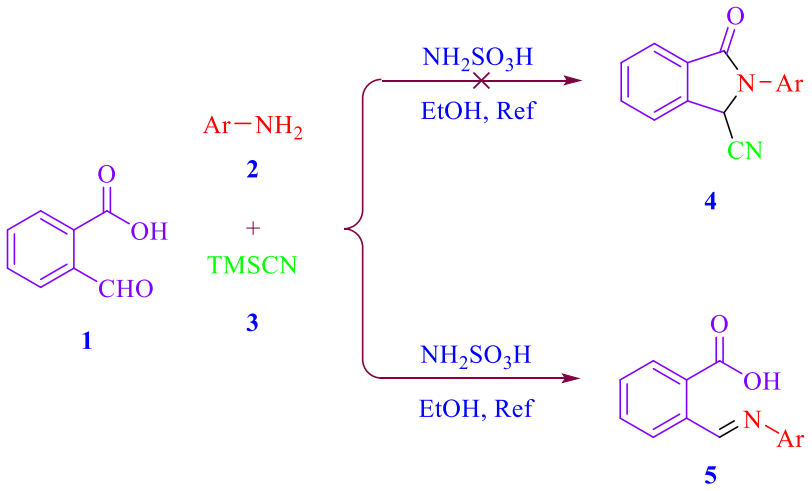
Entry	R in R-NH_2 (**2**)	Time (h)	Product **4**	Yield of **4** (%)[b]
1	$PhCH_2$ **2a**	1	**4a**	87
2	4-$MeOC_6H_4CH_2$ **2b**	0.5	**4b**	90
3	3,4-$(MeO)_2C_6H_3CH_2$ **2c**	1	**4c**	68
4	4-$FC_6H_4CH_2$ **2d**	1	**4d**	85
5	4-$ClC_6H_4CH_2$ **2e**	1	**4e**	76
6	2-FurylCH_2 **2f**	1	**4f**	76
7	3-PyridylCH_2 **2g**	1	**4g**	73
8	3,4-$(MeO)_2C_6H_3(CH_2)_2$ **2h**	1.5	**4h**	60
9	4-$FC_6H_4(CH_2)_2$ **2i**	1.5	**4i**	53
10	$CH_3(CH_2)_2$ **2j**	1.5	**4j**	50
11	$CH_3(CH_2)_3$ **2k**	2	**4k**	50
12	Cyclopropyl **2l**	2	**4l**	59
13	Cyclopentyl **2m**	2.5	**4m**	56
14	$(CH_3)_2CH$ **2n**	2.5	**4n**	< 15
15	$(CH_3)_3C$ **2o**	2.5	**4o**	< 15

[a] Conditions: 2-carboxybenzaldehyde **1** (3 mmol), primary amine **2** (3.6 mmol), TMSCN **3** (4.5 mmol), NH_2SO_3H (0.3 mmol, 10 mol %), and EtOH (2 mL), reflux.[b] Isolated yields.

In all of the studied examples, the benzylamines and aryl-alkylamines could react smoothly to give the corresponding *N*-substituted 3-oxoisoindoline-1-carbonitrile **4** in good to excellent yields (68-90%). Benzylamines carrying either electron-donating or electro-withdrawing groups could react efficiently to give corresponding product **4** in good yields (Table 2, entries 1-5). Furthermore, phenethylamines and alkylamines were also examined for the synthesis of N-substituted-3-oxoisoindoline-1-carbonitrile **4**. The results revealed that both phenethylamines and most of the alkylamines could work well to afford the desired products **4** in moderate yields (50-60%) under same conditions (Table 2, entries 8-13). Moreover, we also examined the condensation reaction using *iso*-propylamine and *tert*-butylamine as the starting materials in the presence of 10 mol % NH_2SO_3H as the catalyst in EtOH at reflux temperature for 2.5 h.

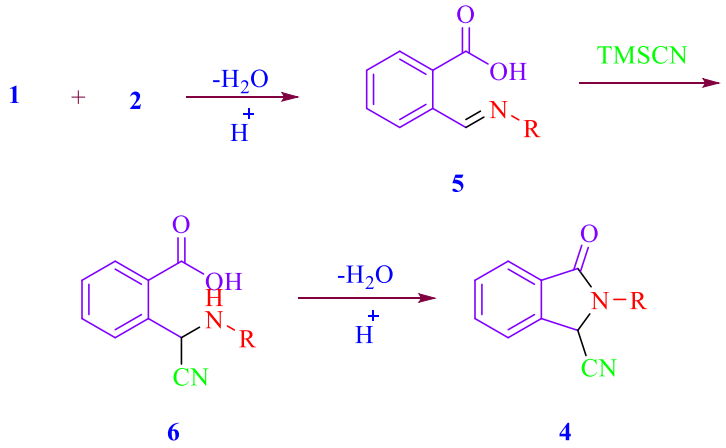
Unfortunately, in these cases, several side reactions were observed; the yields of the desired products were less than 15% as indicated by LC-MS and we failed to isolate the target products (Table 2, entries 14 and 15).

Furthermore, aromatic amines such as aniline, 4-toluidine, and 4-chloroaniline were also subjected to the conditions of this multi-component condensation (Scheme 2). Unfortunately, the products **5**, shown in Scheme 2 and confirmed by LC-MS, were obtained in 85% yield, and the desired products **4** were not obtained.



Scheme 2. Reaction of 2-carboxybenzaldehyde, aniline and TMSCN in EtOH.

We propose a mechanism of the condensation as shown in Scheme 3. Initially, the condensation between 2-carboxybenzaldehyde **1** and primary amine **2** gave imine **5** in the presence of NH_2SO_3H. Then the Strecker reaction between TMSCN and **5** furnished **6** which dehydrated to give product **4**. We have mentioned previously that the three-component condensation reaction could not proceed smoothly when using aromatic amines as the starting materials. The probable reason was that in these cases, the intermediates **5** were difficult to form the intermediate **6**, which meant that the reaction could not proceed smoothly to afford the corresponding products.



Scheme 3. A possible mechanism for the formation of compound **4**.

Conclusions

In summary, we describe a simple and efficient method for the one-pot three-component synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitriles **4** from 2-carboxybenzaldehyde **1**, primary amines **2**, and TMSCN **3** in the presence of 10 mol % NH_2SO_3H as catalyst. This procedure not only affords the products in good yields but also avoids the problems associated with handling safety and pollution. The reactions are conducted in a green solvent (EtOH), and the toxic substrates NaCN and KCN are replaced by TMSCN which is relatively safer. Hence, it is a green and useful procedure for the synthesis of *N*-substituted 3-oxoisoindoline-1-carbonitriles **4**.

Experimental Section

General. Melting points were measured by a WRS-1B micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 400 instrument using solvent peaks as DMSO-d_6 solutions. HRESIMS were determined on a Micromass Q-Tof Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China).

General procedure for the synthesis of 3-oxoisoindoline-1-carbonitrile derivatives 4. a mixture of 2-carboxybenzaldehyde **1** (3 mmol), primary amine **2** (3.6 mmol), TMSCN **3** (4.5 mmol), and NH_2SO_3H (10 mol %) in EtOH (2 mL) was heated to reflux under stirring for the given time (Table 2). After completion (by TLC), the reaction mixture was cooled to room temperature, then 20 mL of EtOAc was added and washed with aq. Na_2CO_3 (conc. 5%), brine, and concentrated in vacuum to give a course product, which was chromatographed on silica gel and eluted with petroleum ether–acetone (8:1-4:1) to give the pure product **4**.

2-Benzyl-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4a**). White solid; mp: 93.6–94.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.58 (d, *J* 13.7 Hz, 1H), 5.00 (d, *J* 13.7 Hz, 1H), 5.89 (s, 1H), 7.29–7.37 (m, 5H), 7.66 (t, *J* 7.6 Hz, 1H), 7.72–7.79 (m, 2H), 7.83 (d, *J* 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.85, 49.59, 115.66, 123.68, 123.83, 127.72, 127.90, 128.70, 130.27, 130.35, 133.11, 135.95, 137.79, 166.60.; MS (ESI): *m/z* 249 ([M+H]$^+$); HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ [M+H]$^+$ 249.1022, found 249.1030.

2-(4-Methoxybenzyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4b**). White solid; mp: 153.5–155.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H), 4.52 (d, *J* 15.2 Hz, 1H), 4.96 (d, *J* 15.2 Hz, 1H), 5.85 (s, 1H), 6.84 (d, *J* 8.7 Hz, 2H), 7.28 (d, *J* 8.7 Hz, 2H), 7.67 (t, *J* 7.5 Hz, 1H), 7.76 (t, *J* 7.5 Hz, 1H), 7.79 (d, *J* 7.5 Hz, 1H), 7.84 (t, *J* 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.30, 49.38, 55.08, 114.13, 115.73, 123.69, 123.86, 127.80, 129.53, 130.29, 130.50, 133.09, 137.78, 158.90, 166.52; MS (ESI): *m/z* 301 ([M+Na]$^+$); HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ [M+H]$^+$ 279.1128, found 279.1126.

2-(3,4-Dimethoxybenzyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4c**). White solid; mp: 136.8–137.1 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 3.74 (s, 3H), 3.74 (s, 3H), 4.51 (d, *J* 15.1 Hz, 1H), 4.98 (d, *J* 15.1 Hz, 1H), 5.86 (s, 1H), 6.89 (dd, *J* 8.2, 1.8 Hz, 1H), 6.94 (d, *J* 8.2 Hz, 1H), 6.97 (d, *J* 1.8 Hz, 1H), 7.66 (d, *J* 7.2 Hz, 1H), 7.75 (d, *J* 7.2 Hz, 1H), 7.79 (d, *J* 7.2 Hz, 1H), 7.84 (d, *J* 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 44.75, 49.45, 55.41, 55.46, 111.77, 111.93, 115.82, 120.59, 123.70, 123.85, 128.07, 130.26, 130.55, 133.06, 137.85, 148.52, 148.88, 166.55.; MS (ESI): *m/z* 309 ([M+H]$^+$); HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3$ [M+H]$^+$ 309.1234, found 309.1234.

2-(4-Fluorobenzyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4d**). White solid; mp: 111.8–112.9 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.66 (d, *J* 15.5 Hz, 1H), 4.96 (d, *J* 15.5 Hz, 1H), 5.94 (s, 1H), 7.20 (t, *J* 8.8 Hz, 2H), 7.41 (dd, *J* 8.8, 5.5 Hz, 2H), 7.67 (t, *J* 7.1 Hz, 1H), 7.76 (t, *J* 7.1 Hz, 1H), 7.80 (d, *J* 7.1 Hz, 1H), 7.84 (d, *J* 7.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 44.24, 49.61, 115.39 and 115.60 ($^2J_{CF}$ = 21.4 Hz), 115.72, 123.73, 123.83, 130.15 and 130.23 ($^3J_{CF}$ = 8.3 Hz), 130.29, 130.38, 132.29 and 132.31 ($^4J_{CF}$ = 2.9 Hz), 133.16, 137.86, 160.52 and 162.94 ($^1J_{CF}$ = 242 Hz), 166.68; MS (ESI): *m/z* 267 ([M+H]$^+$); HRMS (ESI) calcd for $C_{16}H_{12}FN_2O$ [M+H]$^+$ 267.0928, found 267.0928.

2-(4-Chlorobenzyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4e**). White solid; mp: 142.1–143.1 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.71 (d, *J* 15.7 Hz, 1H), 4.96 (d, *J* 15.7 Hz, 1H), 5.96 (s, 1H), 7.38 (d, *J* 8.7 Hz, 2H), 7.43 (d, *J* 8.7 Hz, 2H), 7.68 (d, *J* 7.6 Hz, 1H), 7.78 (d, *J* 7.6 Hz, 1H), 7.81 (d, *J* 7.6 Hz, 1H), 7.85 (d, *J* 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 44.77, 50.17, 116.18, 124.22, 124.31, 129.13, 130.36, 130.78, 130.79, 132.85, 133.69, 135.63, 138.35, 167.21; MS (ESI): *m/z* 283 ([M+H]$^+$); HRMS (ESI) calcd for $C_{16}H_{12}ClN_2O$ [M+H]$^+$ 283.0633, found 283.0639.

2-(2-Furylmethyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4f**). White solid; mp: 141.1–141.2 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.73 (d, *J* 15.9 Hz, 1H), 4.93 (d, *J* 15.9 Hz, 1H), 5.91 (s, 1H), 6.46 (dd, *J* 3.2, 1.9 Hz, 1H), 6.52 (d, *J* 3.2 Hz, 1H), 7.63–7.68 (m, 2H), 7.76 (t, *J* 7.5 Hz, 1H), 7.82 (d, *J* 7.5 Hz, 1H), 7.83 (d, *J* 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 39.69, 51.37, 111.47, 112.54, 117.39, 125.55, 125.71, 132.11, 132.12, 135.06, 139.73, 145.19, 150.68, 168.18; MS (ESI): *m/z* 239 ([M+H]$^+$); HRMS (ESI) calcd for $C_{14}H_{11}N_2O_2$ [M+H]$^+$ 239.0815, found 239.0817.

2-(3-Pyridylmethyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4g**). White solid; mp: 160.2–162.0 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.78 (d, *J* 15.7 Hz, 1H), 4.97 (d, *J* 15.7 Hz, 1H), 6.04 (s, 1H), 7.41 (ddd, *J* 7.8, 4.8, 0.6 Hz, 1H), 7.68 (td, *J* 7.2, 0.8 Hz, 1H), 7.75–7.86 (m, 4H), 8.54 (dd, *J* 4.8, 1.6 Hz, 1H), 8.63 (d, *J* 1.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 42.76, 49.87, 115.80, 123.73, 123.76, 123.79, 130.25, 130.29, 131.96, 133.21, 136.01, 137.92, 148.83, 149.15, 166.84; MS (ESI): *m/z* 250 ([M+H]$^+$); HRMS (ESI) calcd for $C_{15}H_{12}N_3O$ [M+H]$^+$ 250.0975, found 250.0976.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4h**). **4h**: White solid; mp: 125.6–126.5 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 2.87–3.00 (m, 2H), 3.55–3.64 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.05–4.12 (m, 1H), 6.00 (s, 1H), 6.77 (dd, *J* 8.2, 1.9 Hz,

1H), 6.85 (d, *J* 8.2 Hz, 1H), 6.88 (d, *J* 1.9 Hz, 1H), 7.65 (t, *J* 7.6 Hz, 1H), 7.73–7.78 (m, 2H), 7.84 (d, *J* 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.91, 42.54, 49.78, 55.29, 55.38, 111.81, 112.29, 116.17, 120.49, 123.53, 123.71, 130.26, 130.58, 130.68, 133.00, 137.58, 147.39, 148.63, 166.37; MS (ESI): *m/z* 323 ([M+H]$^+$); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ [M+H]$^+$ 323.1390, found 323.1391.

2-[2-(4-Fluorophenyl)ethyl]-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4i**). White solid; mp: 111.7–112.6 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95–3.07 (m, 2H), 3.59-3.66 (m, 1H), 4.02–4.10 (m, 1H), 6.07 (s, 1H), 7.09 (tt, *J* 8.9, 2.1 Hz, 2H), 7.28–7.33 (m, 2H), 7.63 (t, *J* 7.5 Hz, 1H), 7.73–7.78 (m, 2H), 7.84 (d, *J* 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.51, 42.62, 49.80, 115.07 and 115.28 ($^2J_{CF}$ = 21.0 Hz), 116.13, 123.55, 123.68, 130.21, 130.41 and 130.49 ($^3J_{CF}$ = 8.0 Hz), 130.63, 132.98, 134.46 and 134.49 ($^4J_{CF}$ = 2.9 Hz), 137.62, 159.79 and 162.20 ($^1J_{CF}$ = 241 Hz), 166.43; MS (ESI): *m/z* 281 ([M+H]$^+$); HRMS (ESI) calcd for $C_{17}H_{14}FN_2O$ [M+H]$^+$ 281.1085, found 281.1088.

2-*n*-Propyl-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4j**). Orange oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, *J* 7.4 Hz, 3H), 1.62–1.77 (m, 2H), 3.35–3.42 (m, 1H), 3.70–3.77 (m, 1H), 6.11 (s, 1H), 7.66 (t, *J* 7.4 Hz, 1H), 7.73–7.81 (m, 2H), 7.84 (dd, *J* 7.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.58, 21.21, 43.32, 50.10, 116.71, 123.98, 124.08, 130.65, 131.28, 133.37, 138.18, 167.05; MS (ESI): *m/z* 201 ([M+H]$^+$); HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ [M+H]$^+$ 201.1022, found 201.1026.

2-*n*-Butyl-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4k**). Orange oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (t, *J* 7.3 Hz, 3H), 1.26–1.36 (m, 2H), 1.60–1.71 (m, 2H), 3.36–3.44 (m, 1H), 3.74–3.82 (m, 1H), 6.11 (s, 1H), 7.65 (t, *J* 7.4 Hz, 1H), 7.73–7.80 (m, 2H), 7.83 (dd, *J* 7.5, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.46, 19.42, 29.35, 40.80, 49.56, 116.20, 123.47, 123.58, 130.15, 130.78, 132.86, 137.68, 166.48; MS (ESI): *m/z* 215 ([M+H]$^+$); HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ [M+H]$^+$ 215.1179, found 215.1188.

2-Cyclopropyl-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4l**). White solid; mp: 102.4–103.9 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85–1.04 (m, 4H), 2.81–2.87 (m, 1H), 6.01 (s, 1H), 7.64 (t, *J* 7.8 Hz, 1H), 7.73–7.78 (m, 2H), 7.81 (d, *J* 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 5.06, 6.75, 24.63, 51.13, 117.00, 123.89, 123.99, 130.67, 131.67, 133.51, 138.09, 167.86; MS (ESI): *m/z* 199 ([M+H]$^+$); HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ [M+H]$^+$ 199.0866, found 199.0873.

2-Cyclopentyl-2,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**4m**). White solid; mp: 81.8–83.7 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.58–1.66 (m, 2H), 1.77–1.86 (m, 3H), 1.90–1.99 (m, 2H), 1.99–2.06 (m, 1H), 4.40–4.48 (m, 1H), 6.16 (s, 1H), 7.65 (t, *J* 7.4 Hz, 1H), 7.74–7.78 (m, 2H), 7.82 (d, *J* 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.38, 23.51, 28.96, 29.48, 47.89, 54.15, 117.24, 123.30, 123.47, 130.16, 131.12, 132.90, 138.03, 166.75; MS (ESI): *m/z* 227 ([M+H]$^+$); HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ [M+H]$^+$ 227.1179, found 227.1186.

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