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ARTICLE

Efficient syntheses of substituted (±)-3-oxoisoindoline-1-carbonitriles and carboxamides using OSU-6

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An efficient synthesis of 3-oxoisoindolines is described from 2-carboxybenzaldehyde, TMSCN and benzylic or aliphatic amines using a Strecker approach with OSU-6 as the catalyst. The reaction can be tuned to generate two different products: a substituted (±)-3-oxoisoindoline-1-carbonitrile at 23 °C or the corresponding C1 primary amide at 78 °C. Aromatic amines divert from this reactivity to give isobenzofuranone derivatives. The formation of primary amides in these Strecker cyclizations has not been previously reported. The OSU-6 catalyst is a newly developed MCM-41 type hexagonal mesoporous silica with high Lewis acid strength and robust character, which facilitates recycling.

Introduction

Isoindolinones are recognized as valuable building blocks for various drug intermediates and natural products.[1-3] These systems are extensively used in pharmaceuticals for the treatment of hypertension,[4] inflammation,[5] psychosis,[6, 7] pain,[8] anxiety,[9] cancer,[10, 11] bacterial infections[12] and ulcers.[13] They are also found in powerful inhibitors of tumor necrosis factor production.[14] The commercial drug indoprofen, which was used as an anti-inflammatory agent in the 1970s, contains an isoindolinone ring in its core structure.[15, 16] Apart from their bioactivity, these heterocycles also find utility as molecular switches due to their electrochemical properties.[17] Despite their potential medicinal and electrochemical applications, relatively few approaches exist for the preparation of isoindolinone rings and these generally require multistep syntheses or expensive metal catalysts.

In recent years, multicomponent reactions have emerged as powerful tools in the field of organic syntheses. This is due to their ability to generate diverse and complex targets in fewer steps from readily available starting materials.[18] Multicomponent reactions have unique advantages due to operational simplicity, green protocols and low cost.

The Strecker reaction is regarded as one of the first multicomponent reaction and has been widely employed in the synthesis amino acids and α-aminonitriles.[19, 20] Although Strecker reactions generate specific targets, the presence of neighbouring reactive sites can lead to intramolecular reactions that form nitrogen heterocycles. In this project, we have taken advantage of the neighbouring functionality in 2-carboxybenzaldehyde and extended this multicomponent reaction to the synthesis of 3-oxoisoindoline derivatives.

Earlier work has applied the Strecker protocol to the preparation of isoindolinones rings, but with only modest success. The Opatz group was the first to employ this approach by reacting 2-carboxybenzaldehyde with methylamine hydrochloride and potassium cyanide in methanol containing acetic acid.[21] The single example reported produced (±)-2-methyl-3-oxoisoindoline-1-carbonitrile in moderate yield along with several by-products that made product isolation difficult. Recently, Hu and co-workers reported a similar route using trimethylsilyl cyanide (TMSCN) as the cyanide source in refluxing ethanol with sulfamic acid as the catalyst.[22] Though this procedure afforded acceptable yields, limitations were encountered with respect to the amine reactants allowed in the cyclization.

Over the years, our research group has been involved in synthesizing heterocycles using environmentally benign approaches. Among these targets, benzoxazoles, benzothiazoles, benzimidazoles[23] and oxadiazoles[24] have been prepared using ammonium chloride as the catalyst. The current study has successfully developed a green approach to the formation of (±)-3-oxoisoindoline-1-carbonitriles using OSU-6, and reports a novel cyanide to amide conversion. The method has been further extended to 2-acetylbenzoic acid, which cyclizes with comparable efficiency.

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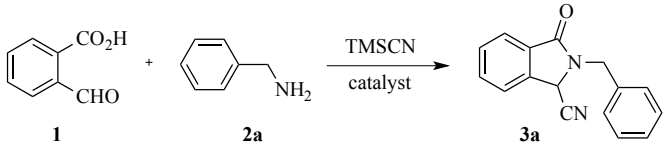
OSU-6, an MCM-41 type hexagonal mesoporous silica developed at Oklahoma State University by AlOthman and Apblett,[25] piqued our interest as a potential catalyst for this process due to its strong Lewis acid properties and high surface area. This material is more robust than traditional MCM-41 due to its greater channel wall thickness, and offers a relatively large pore size (> 8 nm) and volume (> 1.7 cm^3/g). In this study, we have explored the use of OSU-6 for the synthesis of isoindolinones from 2-carboxybenzaldehyde, TMSCN and a series of amines and found that complete conversion can be accomplished in high yields at room temperature. Moreover, this heterogeneous catalyst can be readily regenerated and reused without significant loss of activity. Finally, the current method minimizes waste by avoiding tedious workup procedures as most products were isolated by filtration.

Results and discussion

The reaction of 2-carboxybenzaldehyde (**1**) with benzylamine (**2a**) and TMSCN in anhydrous ethanol was used as a model reaction to evaluate catalysts for the preparation of (±)-3-oxoisoindoline-1-carbonitrile **3a** under various solvent and temperature conditions (**Table I**). In control experiments without catalyst, this transformation gives low conversion to **3a** and a varying number of by-products. The catalysts screened were NH_4Cl, dry amberlyst-15 (A-15), *p*-TsOH, $Bi(OTf)_3$, SiO_2 and OSU-6, while the solvents included methanol, ethanol (95% and 100%), tetrahydrofuran, dioxane and acetonitrile. In each case, the reaction was performed using 10-wt% of the catalyst. These initial trials established that OSU-6 in 100% ethanol at room temperature produced the highest yield of **3a**. Encouraged by this result, we endeavoured to determine the optimum catalyst loading. To this end, comparison of 1, 5, 10, and 20-wt% of OSU-6 indicated that 5-wt% loading consistently afforded the best results.

Table I. Evaluation of various catalysts for the synthesis of (±)-**3a**

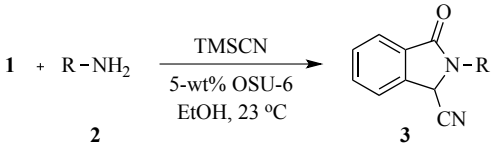


1 2a 3a

Entry	Catalyst (10-wt%)	Solvent	Temp (°C)	Yield (%)
1	NH_4Cl	EtOH	78	< 5
2	NH_4Cl	CH_3CN	30	< 5
3	A-15	EtOH	78	15
4	A-15	MeOH	65	22
5	$Bi(OTf)_3$	THF	25	20
6	$Bi(OTf)_3$	dioxane	80	10
7	*p*-TsOH	THF	67	51
8	*p*-TsOH	CH_3CN	81	46
9	**OSU-6**	**EtOH**	**25**	**94**
10	OSU-6	CH_3CN	25	64
11	SiO_2	EtOH	25	60
12	SiO_2	EtOH	78	70

Once the optimized conditions were established, the method was applied to a broad range of amines to define the substrate scope (**Table II**). Initially, benzylamines **2a-f** were evaluated. The excellent yields obtained with these substrates revealed that isoindolinone cyclizations were unaffected by the presence of electron donating (CH_3, OCH_3, OCF_3) or electron withdrawing (F, Cl, CF_3) substituents at the *meta* or a *para* positions of the aromatic ring. Subsequent examination of a series of aliphatic amines, including 2-phenylethylamine (**2g**), allylamine (**2h**), cyclopropylamine (**2i**) and ethylamine (**2j**), also afforded the cyclized products in excellent yields. Workup was performed via a four-step sequence involving (1) filtration of the crude product containing the catalyst, (2) dissolution of the product in ethyl acetate, (3) filtration to remove the catalyst, and (4) concentration of the filtrate.

Table II. Formation of (±)-2-alkyl-3-oxoisoindoline-1-carbonitriles



2 3

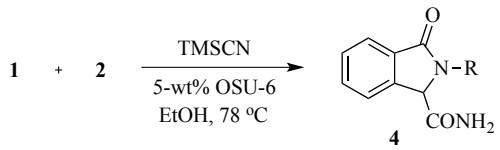
Substrate: R	Pdt	Temp (°C)	Time (min)	Yield (%)
2a: $C_6H_5CH_2$	**3a**	23	60	94
2b: 4-$ClC_6H_5CH_2$	**3b**	23	60	89
2c: 4-$FC_6H_5CH_2$	**3c**	23	90	90
2d: 3-$MeOC_6H_5CH_2$	**3d**	23	20	94
2e: 4-$MeOC_6H_5CH_2$	**3e**	23	30	95
2f: 4-$CF_3C_6H_5CH_2$	**3f**	78[a]	120	86
2g: $C_6H_5CH_2CH_2$	**3g**	23	120	76
2h: CH_2=CH-CH_2	**3h**	23	120	84
2i: cyclopropyl	**3i**	23	180	82
2j: ethyl	**3j**	23	90	78

[a]This reaction required heating, presumably due to the strong electron withdrawing CF_3 substituent.

Although products **3a-j** were generally formed in < 3 hours at room temperature, we decided to explore temperature effects on the rate of reaction. Interestingly, under reflux conditions, reaction of **1** with **2a** and TMSCN produced a white precipitate within 30 minutes. Thin layer chromatography (TLC) indicated this material to be significantly different from isoindolinone **3a**. Isolation of the precipitate and complete spectral analysis identified this product as primary amide **4a**. We repeated the cyclization reactions for a selection of benzyl and aliphatic

amines at reflux and found that all furnished primary amides in excellent yields as shown in **Table III**.

Table III. Formation of (±)-2-alkyl-3-oxoisoindoline-1-carboxamides

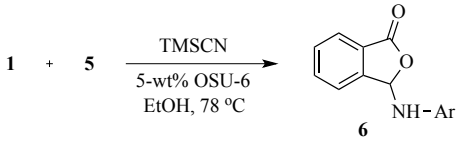


4

Substrate: R	**Pdt**	**Temp** (°C)	**Time** (min)	**Yield** (%)
2a: $C_6H_5CH_2$	**4a**	78	60	92
2b: 4-$ClC_6H_5CH_2$	**4b**	78	60	87
2d: 3-$MeOC_6H_5CH_2$	**4c**	78	30	92
2e: 4-$MeOC_6H_5CH_2$	**4d**	78	120	85
2k: 4-$MeC_6H_5CH_2$	**4e**	78	20	94
2l: cyclohexyl	**4f**	78	120	82
2m: *n*-hexyl	**4g**	78	90	75
2n: isobutyl	**4h**	78	120	78

Once our study with benzyl and aliphatic amines was complete, we further explored the behaviour of aromatic amines. An initial study of **1** with aniline (**5a**), TMSCN and OSU-6 in refluxing anhydrous ethanol failed to give the expected isoindolinone, but instead, gave the isobenzofuranone derivative **6a**. This transformation has been previously reported from **1** by heating with anilines in acetic acid[26] or neat.[27] Subsequent reaction of **1** with anilines **5b-e** in refluxing ethanol demonstrated the generality of this divergent pathway, affording high yields of **6b-e**, respectively, after 30 minutes (**Table IV**).

Table IV. Formation of (±)-3-(arylamino)isobenzofuran-1(3*H*)-ones[a]



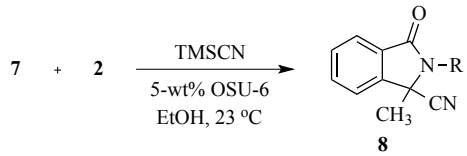
6

Substrate: Ar	**Pdt**	**Temp** (°C)	**Time** (min)	**Yield** (%)
5a: C_6H_5	**6a**	78	30	92
5b: 3-ClC_6H_5	**6b**	78	30	89
5c: 4-$MeOC_6H_5$	**6c**	78	30	92
5d: 4-$CF_3C_6H_5$	**6d**	78	30	95
5e: 4-$NO_2C_6H_5$	**6e**	78	30	90

[a]This reaction proceeds in the presence of OSU-6 without added TMSCN.

The reactivity of 2-acetylbenzoic acid (**7**) was also assessed using the standard room temperature protocol with amines **2**. This process was more difficult to control, and thus, it was important to follow the reaction progress closely by TLC. In general, the conversion proceeded cleanly to give nitriles **8a-f** in nearly quantitative yields with benzylic and aliphatic amines (**Table V**).

Table V. Formation of (±)-2-alkyl-1-methyl-3-oxoisoindoline-1-carbonitriles



8

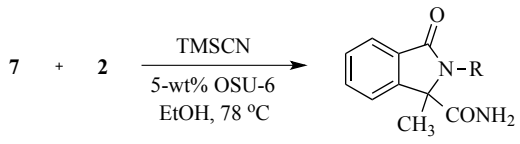
Substrate: R	**Pdt**	**Temp** (°C)	**Time** (min)	**Yield** (%)
2a: $C_6H_5CH_2$	**8a**	23	60	92
2b: 4-$ClC_6H_5CH_2$	**8b**	23	60	89
2c: 4-$FC_6H_5CH_2$	**8c**	23	60	92
2h: CH_2=CH-CH_2	**8d**	23	20	94
2j: cyclopropyl	**8e**	23	30	95
2k: 4-$MeC_6H_5CH_2$	**8f**	23	90	90

Repeating the reactions of **7** with **2** at higher temperature afforded amide products despite the steric hindrance of the nitrile intermediates. An extended series of substrates was studied to generate products **9a-n**. At reflux, the formation of these primary amides was ordinarily complete in less than 2 hours (**Table VI**).

Several details were noted during our study: (1) traces of water in the amines tended to accelerate amide formation, while dry amines slowed this process to give better reaction control and (2) deliberate addition of water to the reaction mixture did not produce clean amide products. Based on these observations, it appears that water adsorbed into the pores of OSU-6 is most important for the nitrile hydrolysis. This water remains in the pores after the initial condensation to form the nitrile or is ushered in by wet reagents or solvents. Water added to the reaction after exposure of the catalyst to anhydrous reactants does not efficiently displace these molecules from the pores and, thus is not immediately available for hydrolysis of the initially formed nitrile.

To reduce the environmental impact of the current transformation, we sought to develop a protocol to permit regeneration of the OSU-6 catalyst. Following the reaction to prepare **3a**, two procedures were evaluated for reactivating the catalyst. Attempts to reuse the catalyst immediately after removal from the crude product and washing with ethyl acetate resulted in a significant loss of activity. On the other hand, when the catalyst was filtered and washed with copious amounts of 1:1 ethanol:water, followed by drying at 200 °C under vacuum for 14 hours, catalytic activity was almost fully restored. **Figure 1** shows a comparison of the catalyst activity following regeneration by washing with ethyl acetate (red) and with 1:1 ethanol:water (blue).

Table VI. Formation of (±)-2-alkyl-1-methyl-3-oxoisoindoline-1-carboxamides



9

Substrate: R	**Pdt**	**Temp** (°C)	**Time** (min)	**Yield** (%)
2a: $C_6H_5CH_2$	**9a**	78	60	92
2b: 4-$ClC_6H_5CH_2$	**9b**	78	60	89
2c: 4-$FC_6H_5CH_2$	**9c**	78	60	85
2d: 3-$MeOC_6H_5CH_2$	**9d**	78	20	94
2e: 4-$MeOC_6H_5CH_2$	**9e**	78	30	95
2f: 4-$CF_3C_6H_5CH_2$	**9f**	78	120	86
2g: $C_6H_5CH_2CH_2$	**9g**	78	120	86
2h: CH_2=CH-CH_2	**9h**	78	120	84
2i: cyclopropyl	**9i**	78	180	83
2j: ethyl	**9j**	78	90	78
2k: 4-$MeC_6H_5CH_2$	**9k**	78	90	90
2l: cyclohexyl	**9l**	78	60	85
2m: *n*-hexyl	**9m**	78	45	92
2n: isobutyl	**9n**	78	120	76

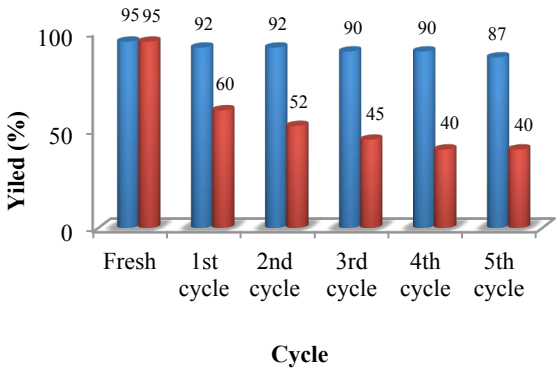


Figure 1. Yields obtained following regeneration of the OSU-6 catalyst by washing with ethyl acetate (red) *vs* washing with 1:1 ethanol:water and drying under high vacuum (blue).

Conclusions

In summary, we have developed a simple and environmentally benign method for the synthesis of 3-oxoisoindoline rings by using OSU-6, an MCM-41 type hexagonal mesoporous silica catalyst. The method does not require tedious workup procedures and the product can be obtained by a simple four-step sequence. The reaction can be tuned to generate (±)-2-alkyl-3-oxoisoindoline-1-carbonitriles at room temperature or the corresponding C1 primary amides under reflux conditions. The clean hydrolysis of nitriles to amides in these substituted 3-oxoisoindolines appears to be the first report of this transformation promoted by Lewis acid sites in a highly structured, heterogeneous, silica catalyst. Fine control of these reactions is contingent on the use of dry reagents as attempts to employ an older samples of hygroscopic amines or solvents lead to acceleration of the nitrile to amide conversion. The method has also been extended to 2-acetylbenzoic acid to prepare (±)-1-methyl-2-alkyl-3-oxoisoindoline-1-carbonitriles or carboxamides, but these reactions must be closely monitored since they are more difficult to control.

Experimental Section

Commercial anhydrous ethanol was stored under dry nitrogen and transferred by syringe into reactions when needed. All other commercial reagents were used as received. Unless otherwise specified, all reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521); band elution was monitored using a hand held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on NaCl disks. Unless otherwise indicated, ^{1}H- and ^{13}C-NMR spectra were measured at 400 MHz and 100 MHz, respectively, in the indicated solvents using $(CH_3)_4Si$ as the internal standard; coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer.

General experimental procedure to prepare 3 and 7.

To a stirred solution of **1** or **6** (1.0 mmol) in 10 mL dry ethanol (10 mL) was added amine **2** (1.05 mmol) and OSU-6 (5-wt%), followed by TMSCN (1.05 mmol) and the solution was stirred at room temperature for a period of 30-120 min. In most cases, the product was observed as a solid. The crude reaction mixture was cooled in an ice bath and filtered. The filtered product was then washed with cold ethanol (10 mL) and hexanes (10 mL). After drying, the OSU-6 was removed by dissolving the product in ethyl acetate (50 mL) and filtering. The organic layer was concentrated under vacuum to afford the 3-oxoisoindoline-1-carbonitrile products as solids. In cases where the product was not a solid, the product was directly concentrated along with 1-2 g of silica gel and purified on a 2.5-cm × 10-cm silica gel column eluted with increasing concentrations of ethyl acetate in hexanes to afford nitriles **3** or **7** in the yields shown in **Tables II** and **V**. (*Note*: The amines used in the reactions must be anhydrous. Traces of water in the amines will lead to amides **4** and **9** as minor products at room temperature).

(±)-2-Benzyl-3-oxoisoindoline-1-carbonitrile (3a). Isolated as a white solid, mp 91-92 °C; IR: 2245, 1707 cm^{-1}; ^{1}H NMR

($CDCl_3$): δ 7.93 (d, *J* = 7.3 Hz, 1H), 7.64 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.35 (m, 5H), 5.50 (d, *J* = 15.0 Hz, 1H), 5.08 (s, 1H), 4.30 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.9, 136.8, 135.2, 133.0, 131.2, 130.5, 129.2, 128.6, 128.4, 124.7, 123.1, 114.5, 48.9, 45.0. HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$: 249.1028, found: 249.1036.

(±)-2-(4-Chlorobenzyl)-3-oxoisoindoline-1-carbonitrile (3b). Isolated as a white solid, mp 139-140 °C; IR: 2242, 1708 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.79 (m, 2H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.96 (s, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.68 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 167.2, 138.4, 135.6, 133.7, 132.8, 130.8, 130.4, 130.3, 129.1, 124.3, 124.2, 116.2, 50.2, 44.8. HRMS (ESI) calcd for $C_{16}H_{12}ClN_2O$ $[M + H]^+$: 283.0638, found: 283.0645.

(±)-2-(4-Fluorobenzyl)-3-oxoisoindoline-1-carbonitrile (3c). Isolated as a white solid, mp 110-111 °C; IR: 2250, 1707 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.79 (m, 2H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.41 (m, 2H), 7.21 (t, *J* = 8.7 Hz, 2H), 5.94 (s, 1H), 4.95 (d, *J* = 15.5 Hz, 1H), 4.66 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 167.1, 162.2 (d, *J* = 244.4 Hz), 138.3, 133.6, 132.8, 130.8 (2C), 130.7 (d, *J* = 8.0 Hz), 124.3, 124.2, 116.2, 116.0 (d, *J* = 21.0 Hz), 50.1, 44.7. HRMS (ESI) calcd for $C_{16}H_{12}FN_2O$ $[M + H]^+$: 267.0934, found: 267.0930.

(±)-2-(3-Methoxybenzyl)-3-oxoisoindoline-1-carbonitrile (3d). Isolated as a white solid, mp 102-103 °C; IR: 2837, 2247, 1706 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.79 (m, 2H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.92 (s, 1H), 6.90 (m, 2H), 5.92 (s, 1H), 5.01 (d, *J* = 15.5 Hz, 1H), 4.57 (d, *J* = 15.5 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.1, 160.0, 138.3, 138.0, 133.6, 130.9, 130.8, 130.3, 124.3, 124.2, 120.5, 116.2, 114.1, 113.7, 55.5, 50.1, 45.3. HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$: 279.1134, found: 279.1141.

(±)-2-(4-Methoxybenzyl)-3-oxoisoindoline-1-carbonitrile (3e). Isolated as a white solid, mp 152-153 °C; IR: 2832, 2248, 1693 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.77 (m, 2H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.85 (s, 1H), 4.96 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 15.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 166.5, 158.9, 137.8, 133.1, 130.5, 130.3, 129.5, 127.8, 123.8, 123.6, 115.7, 114.1, 55.0, 49.4, 44.3. HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$: 279.1134, found: 279.1137.

(±)-2-[(4-Trifluoromethyl)benzyl]-3-oxoisoindoline-1-carbonitrile (3f). Isolated as a white solid, mp 88-89 °C; IR: 2265, 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.81 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 1H), 5.06 (d, *J* = 16.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 167.3, 141.5, 138.4, 133.7, 130.8, 130.7, 129.1, 128.7 (q, *J* = 14.1 Hz), 126.0 (q, *J* = 4.0 Hz), 124.7 (q, *J* = 272.7 Hz), 124.3, 124.2, 116.2, 50.4, 45.1. HRMS (ESI) calcd for $C_{17}H_{12}F_3N_2O$ $[M + H]^+$: 317.0902, found: 317.0911.

(±)-3-Oxo-2-(2-phenylethyl)isoindoline-1-carbonitrile (3g). Isolated as an off-white solid, mp 110-111 °C; IR: 2248, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.89 (d, *J* = 7.4 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.29 (m, 5H), 4.90 (s, 1H), 4.33 (dt, *J* = 14.4, 6.6 Hz, 1H), 3.64 (dt, *J* = 14.4, 7.7 Hz, 1H), 3.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 167.1, 138.0, 136.8, 132.8, 131.3, 130.4, 128.9, 128.7, 127.0, 124.4, 123.0, 114.8, 50.3, 43.0, 34.5. HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M + H]^+$: 263.1184, found: 263.1190.

(±)-2-Allyl-3-oxoisoindoline-1-carbonitrile (3h). Isolated as an off-white solid, mp 83-84 °C; IR: 2244, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.91 (d, *J* = 7.5 Hz, 1H), 7.67 (m, 3H), 5.86 (m, 1H), 5.37 (m, 2H), 5.35 (s, 1H), 4.79 (dd, *J* = 15.4, 4.6 Hz, 1H), 3.91 (dd, *J* = 15.4, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.8, 136.8, 133.0, 131.4, 131.3, 130.5, 124.6, 123.1, 120.3, 114.6, 49.1, 43.8. HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$: 199.0871, found: 199.0877.

(±)-2-Cyclopropyl-3-oxoisoindoline-1-carbonitrile (3i). Isolated as a pale yellow solid, mp 78-79 °C; IR: 2247, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.72-7.63 (m, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 1H), 2.87 (tt, *J* = 7.2, 3.9 Hz, 1H), 1.18 (m, 1H), 1.08 (m, 1H), 1.01 (m, 1H), 0.90 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 168.2, 136.8, 133.0, 131.7, 130.4, 124.4, 123.0, 115.3, 51.1, 24.6, 6.6, 5.4. HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$: 199.0871, found: 199.0880.

(±)-2-Ethyl-3-oxoisoindoline-1-carbonitrile (3j). Isolated as a white solid, mp 98-99 °C; 2285, 1771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.60 (overlapping d and t, *J* = 7.6 Hz, 2H), 6.37 (s, 1H), 4.00 (dq, *J* = 9.4, 7.1 Hz, 1H), 3.87 (dq, *J* = 9.4, 7.1 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 168.7, 145.1, 134.4, 130.8, 127.2, 125.4, 123.4, 102.3, 77.2, 65.9, 15.1. HRMS (ESI) calcd for $C_{11}H_{11}N_2O$ $[M + H]^+$: 187.0871, found: 187.0874.

General experimental procedure to prepare 4 and 8.

To a stirred solution of **1** or **7** (1.0 mmol) in 10 mL dry ethanol (10 mL) was added amine **2** (1.05 mmol) and OSU-6 (5-wt%), followed by TMSCN (1.1 mmol) and the solution was refluxed for a period of 1-3 h. In most cases, the product was a solid. The crude reaction mixture was cooled in an ice bath and filtered. The filtered product was washed with cold ethanol (10 mL) and hexanes (10 mL). After drying, the product was re-dissolved in hot ethyl acetate (75 mL) and filtered to remove the catalyst. The organic layer was concentrated under vacuum to afford the 3-oxoisoindoline-1-carboxamide products. In cases where the product was not a solid the product was directly

concentrated along with 1-2 g of silica gel and purified on a 2.5-cm × 10-cm silica gel column eluted with increasing concentrations of ethyl acetate in hexanes to afford the products **4** or **9** in the yields shown in **Tables III** and **VI**.

(±)-2-Benzyl-3-oxoisoindoline-1-carboxamide (4a). Isolated as a white solid, mp 229-230 °C; IR: 3341, 3194, 1671 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.05 (br s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.56 (obscured, 1H), 7.36 (t, J = 7.3 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 7.3 Hz, 2H), 5.25 (d, J = 15.3 Hz, 1H), 4.91 (s, 1H), 4.02 (d, J = 15.3 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 168.8, 168.3, 141.9, 137.4, 132.4, 131.8, 129.3, 129.2, 128.3, 128.0, 123.6, 123.0, 62.6, 44.7. HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$: 267.1134, found: 267.1139.

(±)-2-(4-Chlorobenzyl)-3-oxoisoindoline-1-carboxamide (4b). Isolated as a white solid, mp 248-249 °C; IR: 3333, 3189, 1681 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.03 (br s, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 8.2 Hz, 2H), 7.56 (obscured, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.18 (d, J = 15.5 Hz, 1H), 4.93 (s, 1H), 4.07 (d, J = 15.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 168.7, 168.4, 142.0, 136.5, 132.5, 132.4, 131.7, 130.2, 129.3, 129.1, 123.6, 123.0, 62.7, 44.2. HRMS (ESI) calcd for $C_{16}H_{14}ClN_2O_2$ $[M + H]^+$: 301.0744, found: 301.0760.

(±)-2-(3-Methoxybenzyl)-3-oxoisoindoline-1-carboxamide (4c). Isolated as a pale yellow solid, mp 252-253 °C; IR: 3321, 3133, 1669 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.06 (br s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.55 (obscured, 1H), 7.28 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.78 (obscured, 1H), 5.21 (d, J = 15.2 Hz, 1H), 4.92 (s, 1H), 3.99 (d, J = 15.2 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 168.8, 168.3, 160.0, 141.9, 138.9, 132.4, 131.7, 130.4, 129.3, 123.6, 123.0, 120.4, 114.0, 113.4, 62.6, 55.5, 44.7. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_3$ $[M + H]^+$: 297.1239, found: 279.1244.

(±)-2-(4-Methoxybenzyl)-3-oxoisoindoline-1-carboxamide (4d). Isolated as an off-white solid, mp 210-211 °C; IR: 3350, 3184, 1678 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.03 (br s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.62 (t, J = 7.3 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.54 (obscured, 1H), 7.17 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H), 5.18 (d, J = 15.0 Hz, 1H), 4.85 (s, 1H), 3.95 (d, J = 15.0 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (DMSO) δ 168.8, 168.2, 159.1, 141.9, 132.3, 131.9, 129.8, 129.2, 123.5, 123.0, 114.6, 62.4, 55.6, 44.1 (one aromatic C unresolved). HRMS (ESI) calcd for $C_{17}H_{17}N_2O_3$ $[M + H]^+$: 297.1239, found: 279.1248.

(±)-2-(4-Methylbenzyl)-3-oxoisoindoline-1-carboxamide (4e). Isolated as a white solid, mp 230-231 °C; IR: 3356, 3195, 1667 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.03 (br s, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.54 (obscured, 1H), 7.17 (d, J = 7.7 Hz, 2H), 7.12 (d, J = 7.7 Hz, 2H), 5.21 (d, J = 15.1 Hz, 1H), 4.87 (s, 1H), 3.96 (d, J =15.1 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.8, 168.2, 141.9, 137.2, 134.3, 132.3, 131.8, 129.8, 129.2, 128.4, 123.5, 123.0, 62.5, 44.4, 21.1. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$: 281.1290, found: 281.1292.

(±)-2-Cyclohexyl-3-oxoisoindoline-1-carboxamide (4f). Isolated as a yellow solid, mp 209-210 °C; IR: 3301, 3161, 1674 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.01 (br s, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.43 (br s, 1H), 5.21 (s, 1H), 3.88 (t, J = 12.0 Hz, 1H), 1.91 (d, J = 12.5 Hz, 1H), 1.78 (m, 3H), 1.70-1.45 (complex, 3H), 1.33 (m, 2H), 1.10 (q, J = 12.9 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 170.6, 168.4, 142.7, 132.7, 132.0, 129.0, 123.1, 122.4, 62.2, 53.0, 49.1, 30.8, 30.6, 25.8, 25.7. HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$: 259.1447, found: 259.1462.

(±)-2-Hexyl-3-oxoisoindoline-1-carboxamide (4g). Isolated as off white solid, mp 142-143 °C; IR: 3301, 3161, 1674 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.05 (br s, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.62 (m, 2H), 7.52 (m, 2H), 5.18 (s, 1H), 3.83 (dt, J = 13.9, 7.9 Hz, 1H), 3.00 (m, 1H), 1.56 (m, 2H), 1.27 (m, 6H), 0.86 (distorted t, J = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 169.2, 168.3, 142.1, 132.3, 132.0, 129.1, 123.3, 122.8, 63.1, 41.0, 31.4, 27.8, 26.5, 22.5, 14.4. HRMS (ESI) calcd for $C_{15}H_{21}N_2O_2$ $[M + H]^+$: 261.1603, found: 259.1612.

(±)-2-Isobutyl-3-oxoisoindoline-1-carboxamide (4h). Isolated as an off-white solid, mp 191-192 °C; IR: 3337, 3181, 1676 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.08 (br s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.62 (m, 2H), 7.54 (m, 2H), 5.19 (s, 1H), 3.65 (dd, J = 13.8, 9.4 Hz, 1H), 2.83 (dd, J = 13.8, 5.6 Hz, 1H), 1.95 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO) δ 169.1, 168.6, 142.0, 132.2, 132.1, 129.1, 123.3, 122.8, 63.5, 48.5, 27.3, 20.8, 20.4. HRMS (ESI) calcd for $C_{13}H_{17}N_2O_2$ $[M + H]^+$: 233.1290, found: 233.1295.

General experimental procedure to prepare 6.

To a stirred solution of **1** (1.0 mmol) in 10 mL dry ethanol (10 mL) was added aniline **5** (1.05 mmol) and OSU-6 (5-wt%), followed by TMSCN (1.1 mmol) and the solution was refluxed for a period of 2 h. The product precipitated as solid. The crude reaction mixture was cooled in an ice bath and filtered. The filtered product was washed with cold ethanol (10 mL) and hexanes (10 mL). After drying, the product was re-dissolved using hot ethyl acetate (75 mL) and filtered to remove the catalyst. The organic layer was concentrated under vacuum to afford **6** in the yields shown in **Table IV**.

(±)-3-(Phenylamino)isobenzofuran-1(3*H*)-one (6a). Isolated as an off-white solid, mp 200-201 °C; IR: 3457, 3289, 1720 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.92 (d, J = 7.9 Hz, 1H), 7.53 (t, J = 7.6

Hz, 1H), 7.08 (m, 4H), 6.79 (s, 1H), 6.58 (m, 4H); ^{13}C NMR (DMSO) δ 160.8, 148.3, 142.2, 135.3, 129.8, 129.4, 122.6, 120.2, 117.3, 114.5, 113.3, 91.1. HRMS (ESI) calcd for $C_{14}H_{12}NO_2$ $[M + H]^+$: 226.0868, found: 226.0872.

(±)-3-[(3-Chlorophenyl)amino]isobenzofuran-1(3*H*)-one (6b). Isolated as a pale yellow solid, mp 177-178 °C; IR: 3322, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.91 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.74 (m, 2H), 7.56 (d, J = 10.5 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 10.5 Hz, 1H), 7.02 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H); ^{3}C NMR (DMSO-d_6): δ 169.4, 147.4, 146.0, 135.0, 134.2, 131.2, 131.1, 127.7, 125.2, 124.6, 119.3, 114.2, 113.5, 87.6. HRMS (ESI) calcd for $C_{14}H_{11}ClNO_2$ $[M + H]^+$: 260.0478, found: 260.0484.

(±)-3-[(4-Methoxyphenyl)amino]isobenzofuran-1(3*H*)-one (6c). Isolated as a white solid, mp 190-191 °C; IR: 3425, 3280, 1714 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm) 7.92 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.08 (m, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.53 (d, J = 8.6 Hz, 2H), 6.48 (apparent d, J = 9.3 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 160.9, 156.6, 151.9, 142.4, 142.2, 135.3, 129.7, 122.6, 120.3, 115.1, 114.1, 92.0, 55.8. HRMS (ESI) calcd for $C_{15}H_{14}NO_3$ $[M + H]^+$: 256.0974 found: 255.0981.

(±)-3-{[4-(Trifluoromethyl)phenyl]amino}isobenzofuran-1(3*H*)-one (6d). Isolated as a white solid, mp 214-215 °C; IR: 3344, 1736 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.90 (m, 3H), 7.77 (d, J = 7.6 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 10.2 Hz, 1H), 7.11 (d, J = 8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 169.4, 149.2, 145.9, 135.0, 131.1, 127.6, 126.9 (q, J = 4.0 Hz), 125.4 (q, J= 271.7 Hz), 125.3, 124.6, 119.8 (q, J = 31.3 Hz), 114.5, 87.0. HRMS (ESI) calcd for $C_{15}H_{11}F_3NO_2$ $[M + H]^+$: 294.0742, found: 294.0747.

(±)-3-[(4-Nitrophenyl)amino]isobenzofuran-1(3*H*)-one (6e). Isolated as a yellow solid, mp 243-244 °C; IR: 3322, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.42 (d, J = 9.7 Hz, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 9.6 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 169.2, 152.3, 145.6, 139.7, 135.2, 131.3, 127.4, 126.3, 125.4, 124.7, 114.0, 86.0. HRMS (ESI) calcd for $C_{14}H_{11}lN_2O_4$ $[M + H]^+$: 271.0719, found: 271.0725.

(±)-2-Benzyl-1-methyl-3-oxoisoindoline-1-carbonitrile (8a). Isolated as a white solid, mp 150-151 °C; IR: 2336, 1707 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.99 (d, J = 7.9 Hz, 1H), 7.84 (m, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.45-7.23 (complex, 5H), 4.85 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 166.8, 144.0, 137.3, 134.0, 131.0, 129.7, 128.9, 128.3, 127.9, 124.2, 123.2, 118.4, 58.4, 43.6, 24.4. HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M + H]^+$: 263.1184, found: 263.1151.

(±)-2-(4-Chlorobenzyl)-1-methyl-3-oxoisoindoline-1-carbonitrile (8b). Isolated as a white solid, mp 122-123 °C; IR: 2337, 1708 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.99 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 4.89 (d, J = 16.1 Hz, 1H), 4.81 (d, J = 16.1 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (DMSO) δ 166.8, 144.0, 136.4, 134.1, 132.5, 131.0, 130.2, 129.6, 128.9, 124.2, 123.2, 118.4, 58.3, 42.8, 24.3. HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O$ $[M + H]^+$: 297.0795, found: 297.0818.

(±)-2-(4-Fluorobenzyl)-1-methyl-3-oxoisoindoline-1-carbonitrile (8c). Isolated as a yellow solid, mp 123-125 °C; IR: 2238, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.93 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.62 (m, 2H), 7.40 (m, 2H), 7.04 (t, J = 8.6 Hz, 2H), 5.07 (d, J = 15.7 Hz, 1H), 4.66 (d, J = 15.7 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.2, 162.5 (d, J = 247.5 Hz), 143.3, 133.3, 132.4, 130.5, 130.0 (d, J = 8.0 Hz), 129.8, 124.6, 121.8, 117.5, 115.7 (d, J = 23.2 Hz), 58.5, 43.7, 25.9. HRMS (ESI) calcd for $C_{17}H_{14}FN_2O$ $[M + H]^+$: 281.1090, found: 281.1131.

(±)-2-Allyl-1-methyl-3-oxoisoindoline-1-carbonitrile (8d). Isolated as a white solid, mp 71-73 °C; IR: 2336, 1709 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.99 (d, J = 7.8 Hz, 1H), 7.81 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 5.93 (ddt, J = 17.1, 10.2, 5.7 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 4.26 (d, J = 5.7 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7, 143.4, 133.1, 132.6, 130.4, 130.0, 124.4, 121.8, 118.8, 117.9, 58.2, 43.4, 25.6. HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M + H]^+$: 213.1028, found: 213.1058.

(±)-2-Cyclopropyl-1-methyl-3-oxoisoindoline-1-carbonitrile (8e). Isolated as a white solid, mp 159-160 °C; IR: 2360, 1707 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.95 (d, J = 7.6 Hz, 1H), 7.78 (m, 2H), 7.66 (t, J = 7.3 Hz, 1H), 2.68 (s, 1H), 2.01 (s, 3H), 1.15 (m, 1H), 1.02 (m, 2H), 0.88 (m 1H); ^{13}C NMR (DMSO-d_6): δ 167.3, 143.6, 134.0, 130.9, 130.3, 124.0, 123.1, 119.7, 59.1, 24.3, 23.2, 6.4, 3.9. HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M + H]^+$: 213.1028, found: 213.1039.

(±)-1-Methyl-2-(4-methylbenzyl)-3-oxoisoindoline-1-carbonitrile (8f). Isolated as an off-white solid, mp 120-122 °C; IR: 2335, 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.97 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 4.79 (s, 2H), 2.28 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.8, 144.2, 137.0, 134.3, 134.0, 131.0, 129.7, 129.5, 128.3, 124.1, 123.2, 118.4, 58.3, 43.3, 24.5, 21.2. HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M + H]^+$: 277.1341, found: 277.1311.

(±)-2-Benzyl-1-methyl-3-oxoisoindoline-1-carboxamide (9a). Isolated as a white solid, mp 222-224 °C; IR: 3302, 3157, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.76 (d, J = 7.5 Hz, 1H), 7.63 (m,

2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.49 (br s, 1H), 7.39-7.26 (complex, 5H), 7.23 (t, *J* = 7.0 Hz, 1H), 5.14 (d, *J* = 16.0 Hz, 1H), 4.19 (d, *J* = 16.0 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (DMSO) δ 171.5, 168.4, 147.8, 139.0, 132.6, 130.9, 129.2, 128.7, 127.9, 127.3, 123.5, 122.1, 70.1, 44.6, 22.4. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$: 281.1290, found: 281.1242.

(±)-2-(4-Chlorobenzyl)-1-methyl-3-oxoisoindoline-1-carboxamide (9b). Isolated as an off-white solid, mp 193-195 °C; IR: 3381, 3321, 1673 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.64 (m, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.49 (br s, 1H), 7.40-7.32 (complex, 5H), 5.06 (d, *J* = 16.3 Hz, 1H), 4.25 (d, *J* = 16.3 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (DMSO) δ 171.4, 168.4, 147.8, 138.0, 132.7, 131.9, 130.8, 129.9, 129.2, 128.7, 123.5, 122.1, 70.0, 43.9, 22.3. HRMS (ESI) calcd for $C_{17}H_{16}ClN_2O_2$ $[M + H]^+$: 315.0900, found: 315.0962.

(±)-2-(4-Fluorobenzyl)-1-methyl-3-oxoisoindoline-1-carboxamide (9c). Isolated as a white solid, mp 201-203 °C; IR: 3342, 3181, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.63 (q, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.48 (br s, 1H), 7.45-7.37 (m, 2H), 7.34 (br s, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 5.06 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 16.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 168.4, 161.6 (d, *J* = 243.4 Hz), 147.8, 135.2, 132.6, 130.8, 130.0, (d, *J* = 8.1 Hz) 129.2, 123.5, 122.1, 115.4 (d, *J* = 21.2 Hz), 70.0, 43.9, 22.4. HRMS (ESI) calcd for $C_{17}H_{16}FN_2O_2$ $[M + H]^+$: 299.1196, found: 299.1128.

(±)-2-(3-Methoxybenzyl)-1-methyl-3-oxoisoindoline-1-carboxamide (9d). Isolated as off a white solid, mp 213-215 °C; IR: 3311, 3169, 1676 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.76 (d, *J* = 7.4 Hz, 1H), 7.63 (m, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.48 (br s, 1H), 7.34 (br s, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.92 (s, 1H), 6.91 (obscured, 1H), 6.80 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.09 (d, *J* = 16.1 Hz, 1H), 4.16 (d, *J* = 16.1 Hz, 1H), 3.71 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.4, 168.4, 159.7, 147.8, 140.6, 132.6, 130.9, 129.8, 129.2, 123.5, 122.1, 120.1, 113.7, 112.7, 70.1, 55.4, 44.6, 22.4. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: 311.1396, found: 311.1333.

(±)-2-(4-Methoxybenzyl)-1-methyl-3-oxoisoindoline-1-carboxamide (9e). Isolated as a white solid, mp 168-170 °C; IR: 3291, 3157, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.61 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.44 (br s, 1H), 7.32 (br s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 5.06 (d, *J* = 15.8 Hz, 1H), 4.12 (d, *J* = 15.8 Hz, 1H), 3.72 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.5, 168.3, 158.7, 147.8, 132.6, 130.9, 129.4, 129.2, 123.5, 122.0, 114.1, 70.0, 55.5, 44.0, 22.6 (1 aromatic C unresolved). HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: 311.1396, found: 311.1425.

(±)-1-Methyl-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (9f). Isolated as a white solid, mp 214-215 °C; IR: 3321, 3207, 1674 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.68-7.62 (complex, 4H), 7.59-7.53 (m, 3H), 7.52 (br s, 1H), 7.37 (br s, 1H), 5.11 (d, *J* = 16.6 Hz, 1H), 4.38 (d, *J* = 16.6 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 170.8, 168.0, 147.3, 143.3, 132.2, 130.2, 128.8, 128.1, 127.5 (q, *J* = 31.3 Hz), 125.3 (q, *J* = 3.0 Hz), 124.3 (q, *J* = 273.7 Hz), 123.0, 121.7, 69.6, 43.8, 21.7. HRMS (ESI) calcd for $C_{18}H_{16}F_3N_2O_2$ $[M + H]^+$: 349.1164, found: 349.1196.

(±)-1-Methyl-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide (9g). Isolated as a white solid, mp 201-202 °C; IR: 3371, 3206, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.61 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.38 (br s, 1H), 7.35 - 7.25 (complex, 5H), 7.22 (m, 1H), 3.84 (ddd, *J* = 13.9, 9.9, 5.1 Hz, 1H), 3.31 (m, 1H), 2.99 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.8, 168.1, 147.7, 139.8, 132.4, 131.3, 129.2, 129.1, 128.9, 126.7, 123.2, 122.1, 69.7, 43.7, 34.6, 21.8. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M + H]^+$: 295.1447, found: 295.1480.

(±)-2-Allyl-1-methyl-3-oxoisoindoline-1-carboxamide (9h). Isolated as a white solid, mp 223-225 °C; IR: 3350, 3174, 1673 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.61 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.41 (br s, 1H), 7.26 (br s, 1H), 5.91 (ddt, *J* = 16.7, 10.2, 5.2 Hz, 1H), 5.23 (d, *J* = 16.7 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.33 (dd, *J* = 16.3, 5.3 Hz, 1H), 3.81 (dd, *J* = 16.2, 6.3 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (DMSO): δ 171.7, 167.7, 147.8, 134.9, 132.5, 131.0, 129.1, 123.3, 122.0, 117.2, 69.6, 43.7, 22.2. HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ $[M + H]^+$: 231.1134, found: 231.1195.

(±)-2-Cyclopropyl-1-methyl-3-oxoisoindoline-1-carboxamide (9i). Isolated as a white solid, mp 238-240 °C; IR: 3369, 3205, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (overlapping d and t, *J* = 7.7 Hz, 2H), 7.29 (br s, 1H), 7.14 (br s, 1H), 2.55 (m, 1H), 1.72 (s, 3H), 0.96 (m, 2H), 0.85 (m, 1H), 0.67 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 172.7, 169.6, 148.1, 132.6, 131.4, 129.1, 123.4, 121.6, 69.8, 23.8, 21.6, 6.4, 3.3. HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ $[M + H]^+$: 231.1134, found: 231.1102.

(±)-2-Ethyl-1-methyl-3-oxoisoindoline-1-carboxamide (9j). Isolated as a white solid, mp 228-230 °C; IR: 3336, 3166, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.59 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.34 (br s, 1H), 7.23 (br s, 1H), 3.67 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.23 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.69 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 171.9, 167.7, 147.8, 132.3, 131.4, 129.1, 123.1, 122.0, 69.5, 36.0, 22.0, 14.4. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$: 219.1134, found: 219.1189.

(±)-1-Methyl-2-(4-methylbenzyl)-3-oxoisoindoline-1-carboxamide (9k). Isolated as a white solid, mp 190-191 °C; IR: 3294, 3192, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.75 (d, *J* =

7.4 Hz, 1H), 7.62 (m, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.45 (br s, 1H), 7.33 (br s, 1H), 7.22 (d, J = 7.7 Hz, 2H), 7.10 (d, J = 7.7 Hz, 2H), 5.09 (d, J = 16.0 Hz, 1H), 4.12 (d, J = 16.0 Hz, 1H), 2.26 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.5, 168.3, 147.8, 136.4, 135.9, 132.6, 130.9, 129.3, 129.2, 127.9, 123.5, 122.1, 70.0, 44.3, 22.5, 21.1. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ [M + H]$^+$: 295.1447, found: 295.1482.

(±)-2-Cyclohexyl-1-methyl-3-oxoisoindoline-1-carboxamide (9l). Isolated as a white solid, mp 256-257 °C; IR: 3316, 3186, 1668 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.60 (m, 2H), 7.49 (m, 2H), 7.28 (br s, 1H), 7.24 (br s, 1H), 3.21 (m, 1H), 2.33 (m, 1H), 2.12 (m, 1H), 1.94 (m, 1H), 1.72 (m, 4H), 1.67 (s, 3H), 1.30 (m, 1H), 1.17 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 171.9, 167.5, 147.7, 132.4, 132.1, 128.9, 123.1, 121.7, 70.2, 54.6, 30.4, 29.6, 26.4, 26.1, 25.7, 22.3. HRMS (ESI) calcd for $C_{16}H_{21}N_2O_2$ [M + H]$^+$: 273.1603, found: 273.1576.

(±)-2-Hexyl-1-methyl-3-oxoisoindoline-1-carboxamide (9m). Isolated as a white solid, mp 163-165 °C; IR: 3357, 3185, 1673 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.66 (d, J = 7.5 Hz, 1H), 7.59 (m, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.33 (br s, 1H), 7.25 (br s, 1H), 3.58 (m, 1H), 3.12 (m, 1H), 1.73 (m, 1H), 1.68 (s, 3H), 1.55 (m, 1H), 1.29 (m, 6H), 0.88 (distorted t, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 171.9, 167.9, 147.7, 132.3, 131.4, 129.0, 123.2, 122.0, 69.5, 41.5, 31.5, 28.6, 26.9, 22.5, 22.0, 14.4. HRMS (ESI) calcd for $C_{16}H_{23}N_2O_2$ [M + H]$^+$: 275.1760, found: 275.1739.

(±)-2-Isobutyl-1-methyl-3-oxoisoindoline-1-carboxamide (9n). Isolated as a white solid, mp 193-194 °C; IR: 3349, 3189, 1678 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.67 (d, J = 7.5 Hz, 1H), 7.59 (m, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.33 (br s, 1H), 7.29 (br s, 1H), 3.46 (dd, J = 14.1, 7.8 Hz, 1H), 2.92 (dd, J = 14.1, 7.6 Hz, 1H), 2.14 (nonet, J = 6.9 Hz, 1H), 1.70 (s, 3H), 0.89 (d, J = 6.7 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 171.7, 168.6, 147.7, 132.3, 131.4, 129.0, 123.3, 122.0, 69.8, 49.0, 27.7, 22.1, 21.1, 20.9. HRMS (ESI) calcd for $C_{14}H_{19}N_2O_2$ [M + H]$^+$: 247.1447, found: 247.1481.

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Graphical Abstract

Efficient syntheses of substituted (±)-3-oxoisoindoline-1-carbonitriles and carboxamides using OSU-6

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A tunable synthesis of substituted oxoisoindolines is reported using OSU-6, a modified MCM-41 type hexagonal mesoporous silica catalyst.