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邻甲酰基苯甲酸甲酯还原胺化/内酰胺化一锅法合成 *N*-取代异吲哚-1-酮

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摘要 报道了一种通过邻醛基苯甲酸甲酯的胺化还原/内酰胺化一锅法合成 *N*-取代异吲哚-1-酮的高效方法. 反应包括以 $NaBH_3CN$ 为还原剂, 邻醛基苯甲酸甲酯与伯芳基胺或烷基胺的胺化还原以及 N 原子对羰基碳的分子内亲核进攻过程. 对于 4-取代芳胺、烷基胺和邻甲基苯胺, 该反应可以在室温下的二氯乙烷中顺利完成转化. 而其他的 2-取代芳胺, 则需 K_2CO_3 (2 equiv.)促进下在乙腈中回流 8 h 完成. 该反应的底物适用范围很广, 最高收率可达 99%.

关键词 *N*-取代异吲哚-1-酮; 胺化还原; 内酰胺化; 一锅法合成

One-Pot Synthesis of *N*-Substituted Isoindolin-1-ones via Reductive Amination/Lactamization of Methyl 2-Formylbenzoate

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Abstract An efficient, one-pot synthesis of *N*-substituted isoindolin-1-ones by an aminative reduction/lactamisation sequence of methyl 2-formylbenzoate is introduced. The reaction process includes aminative reduction of *o*-phthalaldehydic acid methylesters with primary aryl or alkyl amines using $NaBH_3CN$ and the following intramolecular nucleophilic *N*-attack on carbonyl carbon atom. For 4-substituted aromatic amines, alkyl amines and *o*-methylaniline, the transformation can be successfully completed in 1,2-dichloroethane at room temperature. For other 2-substituted aromatic amines, reflux in acetonitrile for 8 h in the presence of K_2CO_3 (2 equiv.) is needed. The reaction scopes were quite broad and up to 96% yield of diverse products was achieved.

Keywords *N*-substituted isoindolin-1-ones; aminative reduction; lactamisation; one-pot synthesis

1 Introduction

N-Substituted isoindolin-1-one derivatives are ubiquitous heterocycles exhibiting broad biological activities (Figure 1),[1-2] such as anti-inflammatory,[3] antibacterial,[4] anxiolytic,[5] inhibition of protein-protein interactions[6] and human immunodeficiency virus (HIV)-reverse transcriptase inhibition.[7] Furthermore, some of them have been found to be potent as chemical probes due to their fluorescent properties.[8] Among numerous synthetic approaches to *N*-substituted isoindolin-1-ones,[9] reaction based on *o*-phthalaldehydic acid methylesters as convenient starting points represents one of the simplest methods.[2,10] Mamidyala and Cooper[10] reported that *N*-substituted isoindolin-1-ones could be obtained in generally good to excellent yields through *aza*-Wittig/cyclisation of *o*-phthalaldehydic acid methylesters with benzylic, aromatic and aliphatic azides (Scheme 1a). Ghosh and coauthors[2] developed an efficient method for the synthesis of *N*-substituted isoindolin-1-ones from *o*-phthaldehydic acid methylthiomethyl ester (Scheme 1b). Hererin, We'd like to report a one-pot entry to *N*-substituted isoindolin-1-ones

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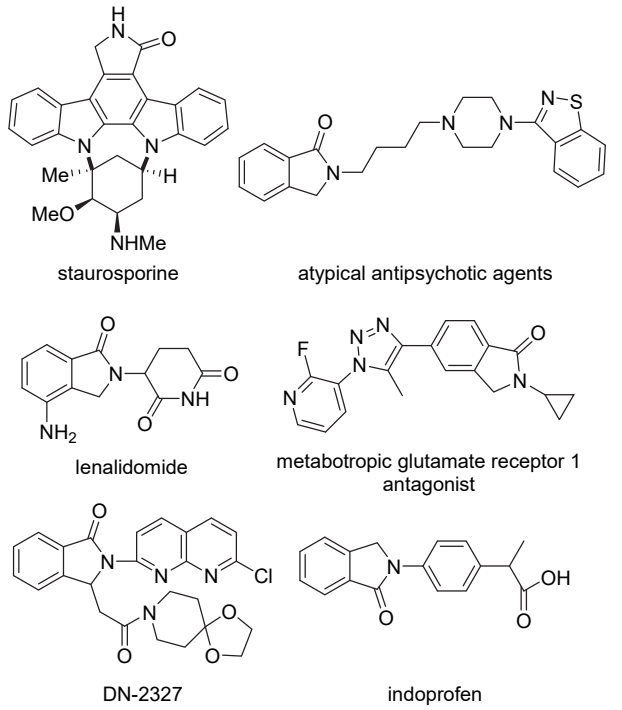
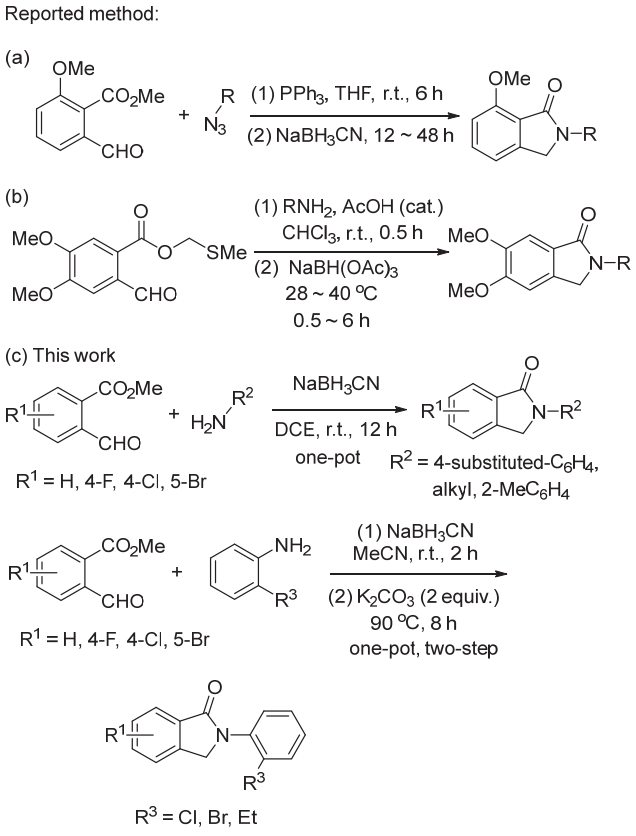


Figure 1 Representative biologically active *N*-substituted isoindolin-1-ones



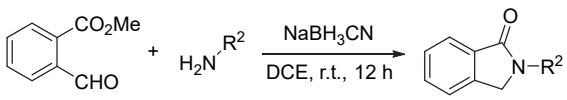
Scheme 1 Synthesis of *N*-substituted isoindolin-1-ones *via* reductive amination/lactamization of methyl 2-formylbenzoate

which involves reductive amination of *o*-phthalaldehydic acid methylesters with diversely substituted aryl and alkyl amines and subsequent lactamization of the corresponding intermediates (Scheme 1c). The present method has advantages of mild reaction conditions, high efficiency and satisfactory yields for most substrates, broad substrate scope and operational simplicity. Furthermore, some *N*-(2-substituted phenyl)isoindolin-1-one products were also furnished via a revised one-pot, two-step reductive amination/lactamization sequence.

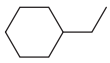
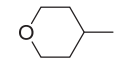
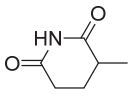
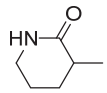
2 Results and discussion

Sodium cyanoborohydride (1.5 equiv.) was added to a solution of methyl 2-formylbenzoate **1a** (1 equiv.) and aniline **2a** (1.05 equiv.) in 1,2-dichloroethane (DCE, 5 mL). The reaction mixture was stirred at ambient temperature for 12 h and 2-phenylisoindolin-1-one **3a** was obtained in a satisfactory yield of 91% (Table 1, Entry 1). Other solvents such as MePh, MeCN and dichloromethane (DCM) were

Table 1 Synthesis of *N*-4-substituted phenyl, *N*-2-methylphenyl and *N*-alkyl isoindolin-1-ones[a]



1a **2a ~ 2o** **3a ~ 3o**

Entry	R^2	Product **3**	Yield[a]/%
1	C_6H_5	**3a**	91
2	4-MeC_6H_4	**3b**	96
3	4-MeOC_6H_4	**3c**	86
4	4-ClC_6H_4	**3d**	90
5	4-BrC_6H_4	**3e**	94
6	4-CNC_6H_4	**3f**	70
7	2-MeC_6H_4	**3g**	93
8	*n*-Bu	**3h**	88
9	*t*-Bu	**3i**	84
10	*i*-Pr	**3j**	85
11	Bn	**3k**	95
12		**3l**	95
13		**3m**	91
14		**3n**	61
15		**3o**	70

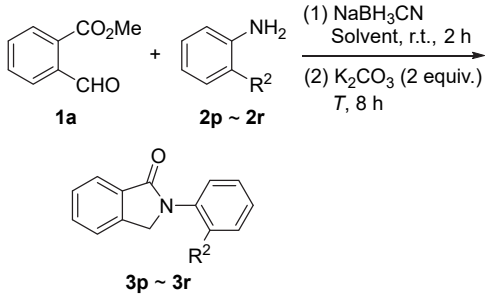
[a] Reaction condition: methyl 2-formylbenzoate **1a** (1 mmol), amine **2a**~**2o** (1.05 mmol), DCE (5 mL), $NaBH_3CN$ (1.5 mmol), r.t., 12 h. [b] Isolated yield.

tested, leading to relatively reduced yield of product **3a** (80%, 86% and 87%, respectively). Thus, DCM was chosen as the optimal solvent.

The scope of amine **2** was further examined. Electron-rich and electron-deficient substituted aryl amines as well as alkyl amines were evaluated. A variety of expected products were generated under the abovementioned mild reaction conditions and the results were outlined in Table 1. Firstly, the reactions of electron-rich substituted aryl amines **2b** and **2c** with substrates **1** were examined. The desired cyclization products **3b** and **3c** were obtained in high to excellent yields (Table 1, Entries 2, 3). Electron-deficient substituted aryl amines **2d**～**2f** were also tested, giving rise to moderate to high yields of products (Entries 4～6). Substrate **2g** bearing *o*-methyl group on benzene ring could also react with substrate **1**, giving 93% yield of **3g** (Entry 7). Alkyl amines were then screened, satisfactory yields of products were isolated. For instance, the reactions of **2h**～**2m** with substrates **1** afforded the corresponding products **3h**～**3m** in yields range from 84% to 94% (Table 1, Entries 8～13), Additionally, when **2n** and **2o** were used as substrates, biologically active lenalidomide analogs (Figure 1) **3b** and **3c** were formed in moderate yields of 61% and 70% (Table 1, Entries 14, 15).

When R^2 was an *ortho*-substituted phenyl group (except for 2-methyl phenyl group, Entry 7 of Table 1), however, the intramolecular cyclization couldn't occur at ambient temperature to furnish the expected products due to steric reasons. For instance, use of *o*-chloroaniline as substrate produced no expected product **3p** (Table 2, Entry 1). The yield of **3p** was increased to 66% when the reaction was carried out at room temperature (r.t.) for 2 h and then 90 ℃ for 8 h in the presence of 2 equiv. of K_2CO_3 (Entry 2). Investigation of solvents, such as THF, toluene and MeCN (Entries 3～5), proved that MeCN was more suitable for the lactamization process and the yield of **3p** was promoted to 90% (Entry 5). Products **3q** and **3r** were also obtained in good yields of 84% and 87% respectively under the same conditions (Entries 6, 7).

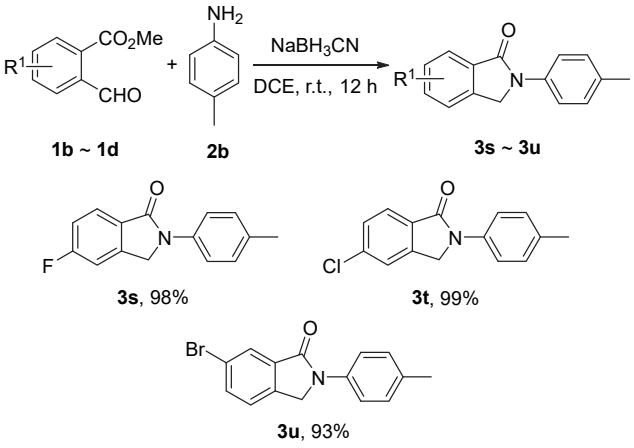
Table 2 Synthesis of *N*-2-substituted phenyl isoindolin-1-ones[a]



Entry	R^2	Solvent	*T*/℃	Product **3**	Yield[b]/%
1	Cl	DCE	r.t.	**3p**	0
2	Cl	DCE	90	**3p**	66
3	Cl	MePh	90	**3p**	71
4	Cl	THF	90	**3p**	70
5	Cl	MeCN	90	**3p**	90
6	Br	MeCN	90	**3q**	84
7	Et	MeCN	90	**3r**	87

[a] Reaction condition: methyl 2-formylbenzoate **1a** (1 mmol), amine **2p**～**2r** (1.05 mmol), DCE (5 mL), $NaBH_3CN$ (1.5 mmol), r.t., 2 h, and then 80 ℃, 8 h. [b] Isolated yield.

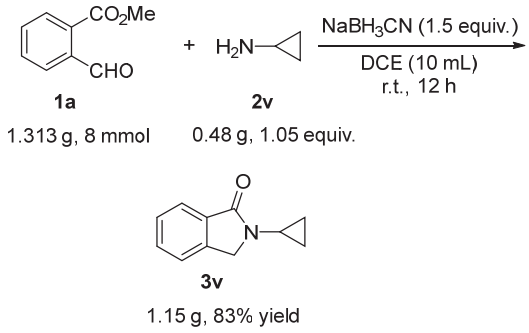
The reaction generality of methyl 2-formylbenzoate was then evaluated under the optimized conditions with **2b** as the partner reactant and the results were summarized in Scheme 2. Methyl 2-formylbenzoates with 4-F, 4-Cl and 5-Br groups on the benzene ring (**1b**, **1c** and **1d**) reacted with **2b** smoothly to generate products **3s**, **3u** and **3v** up to quantitative yields.



Reaction condition: methyl 2-formylbenzoate **1b**～**1d** (0.5 mmol), amine **2b** (0.525 mmol), DCE (5 mL), $NaBH_3CN$ (0.75 mmol), r.t., 12 h

Scheme 2 Scope of methyl 2-formylbenzoates

The reaction was also proven effectively and conveniently to prepare *N*-substituted isoindolin-1-one **3v** on a gram-scale with satisfactory reactivity (Scheme 3). When 8 mmol of **1a** was stirred with cyclopropylamine **2v** (1.05 equiv.) and $NaBH_3CN$ (1.5 equiv.) in 10 mL of DCE at r.t. for 12 h, 83% yield of **3v** was isolated.



Reaction condition: methyl 2-formylbenzoate **1a** (8 mmol), amine **2v** (1.05 equiv.), DCE (10 mL), $NaBH_3CN$ (1.5 equiv.), r.t., 12 h

Scheme 3 Gram-scale of reaction of **1a**

3 Conclusions

In summary, one-pot synthesis of *N*-substituted isoindolin-1-ones through aminative reduction/lactamization of

methyl 2-formylbenzoate with amines was reported. The developed methodology offers facile access to diverse substituted *N*-substituted isoindolin-1-ones in moderate to excellent yields. The choice of reaction temperature and solvents depends on the structure of amine. *N*-Alkyl-, *N*-(4-sustituted phenyl)- and *N*-(2-methyl phenyl)isoindolin-1-ones could be obtained in DCE at ambient temperature, whereas other *N*-(2-sustituted phenyl)isoindolin-1-ones need a reflux condition using MeCN as solvent to complete the lactamisation process.

4 Experimental section

4.1 General methods

Chemicals and solvents were purchased from commercial suppliers and used without further purification. Flash chromatography separations were performed on a CHEETAH II medium pressure purification preparative chromatography system with Agela silica gel columns (230～400 μm mesh). Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F254 plates, which were visualized by exposure to ultraviolet light. Melting points were measured using WRS-2 digital melting point meter (uncorrected). NMR spectra were recorded on a Bruker AV-400 NMR spectrometers with TMS as internal standard (Bruker, Switzerland). HRESIMS data were collected on a Thermo LTQ Orbitrap XL hybrid FTMS or an Agilent 6210 ESI-TOF mass spectrometer.

4.2 Preparation of products **3a**～**3o**, **3s**～**3u**

To a solution of methyl 2-formylbenzoate **1** (1 mmol) and aryl amine **2** (1.05 mmol) in DCE (5 mL) was added $NaBH_3CN$ (1.5 mmol). The reaction mixture was stirred at r.t. for 12 h. Upon completion of the reaction monitored by TLC, the reaction mixture was concentrated and purified by column chromatography [*V*(petroleum ether)∶*V*(ethyl acetate)=4∶1] to afford products **3a**～**3o** and **3s**～**3u**.

2-Phenylisoindolin-1-one (**3a**): White solid, yield 91%. m.p. 155.9～157.9 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.84～7.91 (m, 3H), 7.39～7.59 (m, 5H), 7.14～7.18 (m, 1H), 4.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.5, 140.2, 139.5, 133.2, 132.1, 129.2 (2C), 128.4, 124.4, 124.1, 122.6, 119.4 (2C), 50.7; HRMS (ESI) calcd for $C_{14}H_{12}NO$ $(M+H)^+$ 210.0913, found 210.0912.

2-(*p*-Tolyl)isoindolin-1-one (**3b**): White solid, yield 96%. m.p. 139.7～141.0 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.93 (d, *J*=6.4 Hz, 1H), 7.75 (d, *J*=6.8 Hz, 2H), 7.50～7.61 (m, 3H), 7.24 (d, *J*=6.4 Hz, 2H), 4.82 (s, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.4, 140.2, 137.0, 134.2, 133.3, 131.9, 129.7 (2C), 128.3, 124.1, 122.6, 119.6 (2C), 50.9, 20.9; HRMS (ESI) calcd for $C_{15}H_{13}NNaO$ $(M+Na)^+$ 246.0899, found 246.0908.

2-(4-Methoxyphenyl)isoindolin-1-one (**3c**): White solid, yield 86%. m.p. 135.2～137.1 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 7.52～7.81 (m, 6H), 7.01 (d, *J*=9.2 Hz, 2H), 4.97 (2H, s), 3.77 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 166.7, 156.5, 141.5, 133.1, 133.1, 132.4, 128.6, 123.7, 123.6, 121.8 (2C), 114.6 (2C), 55.8, 51.2; HRMS (ESI) calcd for $C_{15}H_{13}NNaO_2$ $(M+Na)^+$ 262.0838, found 262.0836.

2-(4-Chlorophenyl)isoindolin-1-one (**3d**): White solid, yield 90%. m.p. 175.9～177.2 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.92 (d, *J*=6.0 Hz, 1H), 7.85 (d, *J*=7.2 Hz, 2H), 7.62 (t, *J*=6.0 Hz, 2H), 7.52 (t, *J*=6.0 Hz, 1H), 7.39 (d, *J*=6.8 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.5, 139.9, 136.1, 132.9, 132.3, 129.5 (2C), 129.2, 128.5, 124.2, 122.7, 120.4 (2C), 50.6; HRMS (ESI) calcd for $C_{14}H_{10}ClNNaO$ $(M+Na)^+$ 266.0303, found 266.0347.

2-(4-Bromophenyl)isoindolin-1-one (**3e**): White solid, yield 94%. m.p. 179.7～180.8 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.12 (d, *J*=8.0 Hz, 1H), 7.77 (d, *J*=8.8 Hz, 2H), 7.48～7.61 (m, 5H), 4.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.5, 139.9, 138.6, 132.9, 132.4, 132.1 (2C), 128.5, 124.2, 122.7, 120.7 (2C), 117.2, 50.6; HRMS (ESI) calcd for $C_{14}H_{11}BrNO$ $(M+H)^+$ 288.0019, found 288.0016.

4-(1-Oxoisoindolin-2-yl)benzonitrile (**3f**): White solid, yield 70%. m.p. 179.7～180.8 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.12 (d, *J*=8.8 Hz, 1H), 7.54～7.90 (m, 6H), 5.05 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 167.8, 143.8, 141.5, 133.8 (2C), 133.4, 132.2, 128.8, 124.0, 123.9, 119.3 (2C), 106.1, 50.7; HRMS (ESI) calcd for $C_{15}H_{11}N_2O$ $(M+H)^+$ 235.0866, found 235.0863.

2-(*o*-Tolyl)isoindolin-1-one (**3g**): Colorless waxy solid, yield 93%. m.p. 48.0～50.0 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.95 (d, *J*=7.2 Hz, 1H), 7.50～7.62 (m, 3H), 4.72 (s, 2H), 7.24～7.33 (m, 4H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.8, 141.6, 137.0, 136.4, 132.5, 131.7, 131.2, 128.3, 128.2, 127.5, 126.9, 124.3, 122.8, 53.1, 18.2; HRMS (ESI) calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 274.1070, found 274.1068.

2-*n*-Butylisoindolin-1-one (**3h**): Slightly yellow oily liquid, yield 88%. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.83 (d, *J*=7.2 Hz, 1H), 7.43～7.52 (m, 3H), 4.37 (s, 2H), 3.62 (d, *J*=7.2 Hz, 2H), 1.61～1.69 (m, 2H), 1.35～1.43 (m, 2H), 0.96 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 168.5, 141.1, 133.1, 131.1, 127.9, 123.6, 122.6, 49.9, 42.1, 30.5, 20.1, 13.8; HRMS (ESI) calcd for $C_{12}H_{15}NNaO$ $(M+Na)^+$ 212.1046, found 212.1047.

2-(*t*-Butyl)isoindolin-1-one (**3i**): Colorless waxy solid, yield 84%. m.p. 55.5～57.0 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.78 (d, *J*=7.6 Hz, 1H), 7.39～7.51 (m, 3H), 4.45 (s, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 168.9, 140.7, 134.4, 130.9, 127.8, 123.1, 122.3, 54.3, 48.5, 28.0 (3C); HRMS (ESI) calcd for $C_{12}H_{16}NO$ $(M+H)^+$ 190.1226, found 190.1224.

2-*i*-Propylisoindolin-1-one (**3j**). Colorless waxy solid, yield 85%. m.p. 52.0～54.5 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.84 (d, *J*=6.8 Hz, 1H), 7.43～7.53 (m, 3H), 4.63～4.73 (m, 1H), 4.34 (s, 2H), 1.29 (d, *J*=6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 167.8, 141.2, 133.4, 131.0, 127.9, 123.5, 122.7, 45.0, 42.6, 20.8 (2C); HRMS (ESI) calcd for $C_{11}H_{14}NO$ $(M+H)^+$ 176.1070, found 176.1070.

2-Benzylisoindolin-1-one (**3k**): White solid, yield 95%. m.p. 85.3～87.2 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.89

(d, J=7.2 Hz, 1H), 7.45～7.50 (m, 2H), 4.80 (s, 2H), 7.27～7.38 (m, 6H), 4.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 141.3, 137.1, 132.7, 131.4, 128.8 (2C), 128.2 (2C), 128.0, 127.7, 123.9, 122.8, 49.5, 46.4; HRMS (ESI) calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1070, found 224.1068.

2-(Cyclohexylmethyl)isoindolin-1-one (**3l**): White solid, yield 95%. m.p. 87.5～89.4 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (d, J=7.2 Hz, 1H), 7.42～7.52 (m, 3H), 4.38 (s, 2H), 3.45 (d, J=8.8 Hz, 2H), 1.67～1.77 (m, 6H), 1.02～1.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 141.2, 133.0, 131.1, 127.9, 123.7, 122.6, 50.7, 48.8, 37.1, 30.8 (2C), 26.4, 25.8 (2C); HRMS (ESI) calcd for $C_{15}H_{20}NO$ $(M+H)^+$ 230.1539, found 230.1534.

2-(Tetrahydro-2*H*-pyran-4-yl)isoindolin-1-one (**3m**): White solid, yield 91%. m.p. 125.0～126.7 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.85 (d, J=7.2 Hz, 1H), 7.30～7.56 (m, 3H), 4.48～4.56 (m, 1H), 4.37 (s, 2H), 4.08 (dd, J=8.0, 4.2 Hz, 2H), 3.54～3.60 (m, 2H), 1.77～1.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.0, 141.2, 133.0, 131.3, 128.1, 123.6, 122.8, 67.3, 47.8, 46.0, 31.2. HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ $(M+H)^+$ 218.1176, found 218.1174.

3-(1-Oxoisoindolin-2-yl)piperidine-2,6-dione (**3n**): White solid, yield 61%. m.p. 234.4～236.0 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.00 (s, 1H), 7.53～7.75 (m, 4H), 5.13 (dd, J=8.0, 5.2 Hz, 1H), 4.45 (s, 1H), 4.36 (s, 1H), 2.88～2.94 (m, 1H), 2.39～2.64 (m, 2H), 1.99～2.03 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 173.4, 171.5, 168.6, 142.6, 132.2, 128.4, 124.0, 132.1, 123.4, 52.1, 47.7, 31.7, 23.0; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_3$ $(M+H)^+$ 243.0764, found 243.0767.

2-(2-Oxopiperidin-3-yl)isoindolin-1-one (**3o**): White solid, yield 70%. m.p. 181.4～183.0 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.47～7.80 (m, 5H), 4.69 (dd, J=11.6, 6.4 Hz, 1H), 4.46 (d, J=17.2 Hz, 1H), 4.27 (d, J=17.2 Hz, 1H), 3.19～3.26 (m, 2H), 1.88～2.00 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 173.5, 173.0, 147.2, 137.3, 136.1, 133.1, 128.6, 128.0, 56.7, 52.5, 31.2, 26.8; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ $(M+H)^+$ 231.1128, found 231.1128.

5-Fluoro-2-(*p*-tolyl)isoindolin-1-one (**3s**): White solid, yield 98%. m.p. 193.3～194.2 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (dd, J=9.2, 5.2 Hz, 1H), 7.80 (d, J=8.4 Hz, 2H), 7.16～7.21 (m, 4H), 4.77 (s, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 166.3, 164.1, 142.6, 142.4, 136.8, 134.3, 129.7 (2C), 129.4, 126.2, 126.1, 119.5 (2C), 116.3, 116.1, 110.1, 109.9, 50.5, 20.9; HRMS (ESI) calcd for $C_{15}H_{13}FNO$ $(M+H)^+$ 242.0976, found 242.0974.

5-Chloro-2-(*p*-tolyl)isoindolin-1-one (**3t**): Light yellow solid, yield 99%. m.p. 223.6～224.2 ℃; ^{1}H NMR (Pyridine-d_5, 400 MHz) δ: 8.02 (d, J=8.4 Hz, 2H), 7.91 (d, J=8.0 Hz, 2H), 7.47～7.51 (m, 2H), 7.25 (d, J=8.4 Hz, 2H), 4.74 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.0, 142.6, 137.7, 137.5, 133.8, 132.2, 129.7 (2C), 128.7, 125.1, 123.4, 119.5 (2C), 50.2, 20.5; HRMS (ESI) calcd for $C_{15}H_{13}ClNO$ $(M+H)^+$ 258.0678, found 258.0680.

6-Bromo-2-(*p*-tolyl)isoindolin-1-one (**3u**): Light yellow solid, yield 93%. m.p. 231.1～231.6 ℃; ^{1}H NMR (Pyridine-d_5, 400 MHz) δ: 8.19 (s, 1H), 8.01 (d, J=8.2 Hz, 2H), 7.70 (d, J=8.2 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.25 (d, J=8.2 Hz, 2H), 4.67 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 139.7, 137.4, 135.7, 134.7, 133.9, 129.7 (2C), 126.8, 124.9, 122.0, 119.5 (2C), 50.4, 20.5; HRMS (ESI) calcd for $C_{15}H_{13}BrNO$ $(M+H)^+$ 302.0174, found 302.0175.

4.3 Preparation of products 3p～3r

To a solution of methyl 2-formylbenzoate **1** (0.5 mmol) and aryl amine **2** (0.525 mmol) in MeCN (5 mL) was added $NaBH_3CN$ (0.75 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, K_2CO_3 (1 mmol) was added to the reaction system and heated under 90 ℃ for 8 h. Upon completion of the reaction monitored by TLC, the reaction mixture was concentrated and purified by column chromatography [V(petroleum ether)∶V(ethyl acetate)=4∶1] to afford products **3p**～**3r**.

2-(2-Chlorophenyl)isoindolin-1-one (**3p**): White solid, yield 84%. m.p. 102.3～103.9 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95 (d, J=7.2 Hz, 1H), 7.59～7.63 (m, 1H), 7.51～7.54 (m, 3H), 7.31～7.44 (m, 3H), 4.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1, 141.7, 135.9, 132.7, 132.0, 132.0, 130.6, 130.1, 129.4, 128.3, 127.8, 124.4, 122.9, 52.3; HRMS (ESI) calcd for $C_{14}H_{11}ClNO$ $(M+H)^+$ 244.0522, found 244.0522.

2-(2-Bromophenyl)isoindolin-1-one (**3q**): Light yellow solid, yield 80%. m.p. 125.7～127.5 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (d, J=7.6 Hz, 1H), 7.40～7.71 (m, 6H), 7.25～7.29 (m, 1H), 4.80 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.0, 141.6, 137.6, 133.7, 132.0, 130.3, 129.8, 128.6, 128.3, 124.5, 123.0, 122.9, 52.4; HRMS (ESI) calcd for $C_{14}H_{11}BrNO$ $(M+H)^+$ 288.0919, found 288.0919.

2-(2-Ethylphenyl)isoindolin-1-one (**3r**): Yellow waxy solid, yield 87%. m.p. 61.0～62.0 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93 (d, J=8.4 Hz, 1H), 7.49～7.60 (m, 3H), 7.19～7.37 (m, 4H), 4.70 (s, 2H), 2.60 (q, J=7.6 Hz, 2H), 1.19 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.0, 142.3, 141.6, 136.6, 132.4, 131.7, 129.3, 128.5, 128.3, 127.9, 126.9, 124.2, 122.9, 53.7, 24.3, 14.4; HRMS (ESI) calcd for $C_{16}H_{16}NO$ $(M+H)^+$ 238.1266, found 238.1264.

4.4 Preparation of 3v

To a solution of methyl 2-formylbenzoate **1a** (8 mmol) and aryl amine **2v** (1.05 equiv.) in DCE (10 mL) was added $NaBH_3CN$ (1.5 equiv.). The reaction mixture was stirred at r.t. for 12 h. Upon completion of the reaction monitored by TLC, the reaction mixture was concentrated and purified by column chromatography [V(petroleum ether)∶V(ethyl acetate)=4∶1] to afford products 2- cyclopropyl-isoindolin-1-one (**3v**): Colorless solid, yield 83%. m.p. 55.8～56.9 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.80 (d, J=8.4 Hz, 1H), 7.39～7.50 (m, 3H), 4.30 (s, 2H), 2.93 (s, 1H), 0.86～0.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ: 169.6, 141.1, 133.2, 131.2, 127.9, 123.4, 122.6, 50.3, 25.1, 5.5 (2C); HRMS (ESI) calcd for $C_{11}H_{12}NO$ $(M+H)^+$ 174.0193, found 174.0193.

Supporting Information ^{1}H NMR, ^{13}C NMR spectra of products **3a**～**3v**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] Uno, M.; Ban, H. S.; Nakamura, H. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3166.

[2] Ghosh, U.; Bhattacharyya, R.; Keche, A. *Tetrahedron* **2010**, *66*, 2148.

[3] Ruchelman, A. L.; Man, H. W.; Zhang, W.; Chen, R.; Capone, L.; Kang, J.; Parton, A.; Corral, L.; Schafer, P. H.; Babusis, D.; Moghaddam, M. F.; Tang, Y.; Shirley, M. A.; Muller, G. W. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 360.

[4] Breytenbach, J. C.; van Dyk, S.; van den Heever, I.; Allin, S. M.; Hodkinson, C. C.; North, C. J.; Page, M. I. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1629.

[5] Mark, D. J. M.; Norman, H.; Rigdon, G. C. *J. Med. Chem*. **1996**, *39*, 149.

[6] Hardcastle, I. R.; Ahmed, S. U.; Atkins, H.; Calvert, A. H.; Curtin, N. J.; Farnie, G.; Golding, B. T.; Griffin, R. J.; Guyenne, S.; Hutton, C.; Kallblad, P.; Kemp, S. J.; Kitching, M. S.; Newell, D. R.; Norbedo, S.; Northen, J. S.; Reid, R. J.; Saravanan, K.; Willems, H. M.; Lunec, J. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1515.

[7] Zhao, X.-Z.; Semenova, E. A.; Vu, B. C.; Maddali, K.; Marchand, C.; Hughes, S. H.; Pommier, Y.; Burke, T. R. *J. Med. Chem*. **2008**, *51*, 251.

[8] Suven Das, R. F.; Pramanik, A. *Org. Lett*. **2006**, *8*, 4263.

[9] (a) Pathare, R. S.; Sharma, S.; Elagandhula, S.; Saini, V.; Sawant, D. M.; Yadav, M.; Sharon, A.; Khan, S.; Pardasani, R. T. *Eur. J. Org. Chem*. **2016**, 5579.
(b) Zhu, C.-L.; Zhang, J.-T.; Hoye, T. R. *Org. Lett*. **2021**, *23*, 7550.
(c) Hu, X.-Q.; Liu, Z.-K.; Hou, Y.-X.; Xu, J.-H.; Gao, Y. *Org. Lett*. **2021**, *23*, 6332.
(d) Wan, J.-P.; Wu, B.; Pan, Y.-J. *Tetrahedron* **2007**, *63*, 9338.

[10] Mamidyala, S. K.; Cooper, M. A. *Chem. Commun*. **2013**, *49*, 8407.

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