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$TiCl_4$/DMAP mediated *Z*-selective knovenagel condensation of isatins with nitroacetates and related compounds†

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A highly efficient *Z*-selective Knovenagel condensation reaction of isatins with nitroacetates mediated by $TiCl_4$ and DMAP was described. The desired 2-nitro-3-ylideneoxindole acetates were obtained in good to excellent stereoselectivities and yields. Other activated methylene derivatives as well as 4-methylbenzenesulfonamide could provide good results too. This method makes it possible to obtain various unreported 3-ylideneoxindole derivatives under mild reaction conditions.

Introduction

The 3-ylideneoxindole moieties are pharmacologically important structure motifs in many natural indole alkaloids and bioactive molecules, which exhibit potent antifungal,[1] anticancer,[2] and antiviral activities.[3] For example, indirubin (**A**) from a traditional Chinese herbal medicine is an inhibitor of protein kinases such as glycogen synthase kinase-**3b** (GSK-**3b**)[4] and cyclin-dependent kinases (CDKs). Nintedanib (Ofev) (**B**) has been reported as a kinases inhibitor, launched for the treatment of idiopathic pulmonary fibrosis (IPF) and cancer.[5] Oxindole compound **C** and related compounds also exhibited inhibitory effects on CDKs. Recently, 3-ylideneoxindole acetamides (**D**), as antitumor agents, displayed a similar profile to that of roscovitine.[6] (Fig. 1) Furthermore, 3-ylideneoxindoles are the core structure in biologically natural products alkaloids (including neolaugerine,[7] costinone A, and costinine B[8]). Following reports on the medicinal potential and synthetic applicability of 3-ylideneoxindole derivatives, reactions toward the synthesis of such kind of compounds have been intensely explored and several synthetic strategies have been reported. Wittig and Knoevenagel reaction, which are undoubtedly considered as some of the most effective strategies for the preparation of alkenes, have been traditionally applied for the 3-ylideneoxindoles synthesis.[9] The palladium-catalyzed Heck–Suzuki–Miyaura domino reactions for the construction of substituted 3-alkylideneoxindoles from ynamides have also been reported.[10]

The nitro group is one of the most versatile functional groups, not only because it is essentially a masked amine, but also because its chemistry can be exploited in a number of useful ways.[11] The introduction of a nitro group to 3-ylideneoxindole moiety might be of great importance. However, the synthesis of 2-nitro-2-(2-oxoindolin-3-ylidene)acetate derivatives have remained difficult, and to our knowledge, have not been reported to date. Efforts towards the synthesis of such kind of compounds failed when isatins were reacted with ethyl nitroacetate by Alencastro,[12] only ethyl (*Z*)-2-(2-oxoindolin-3-ylidene)-2-(piperidin-1-yl)acetate was obtained (Scheme 1). The outcomes indicated that the nitro group here was unstable and could be easily substituted by the nucleophilic piperidine. Therefore, the development of a highly efficient stereoselective approach for the synthesis of biological and synthetic applicable important 2-nitro-3-ylideneoxindole acetates with regard to stereo-, regio-, and chemoselectivities and substrate generality is in high demand.

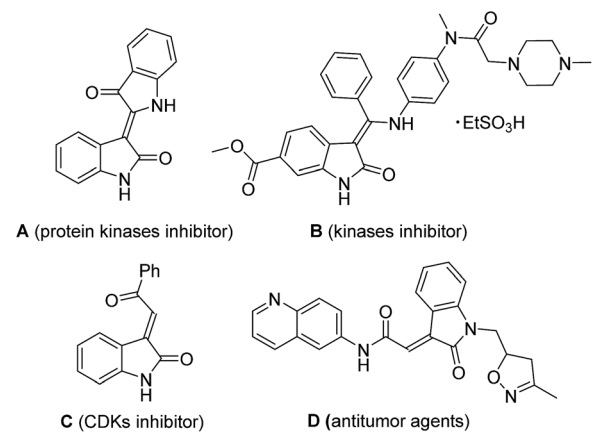

Fig. 1 Illustrative examples of bioactive 3,2′-pyrrolidinyl spirooxindoles.

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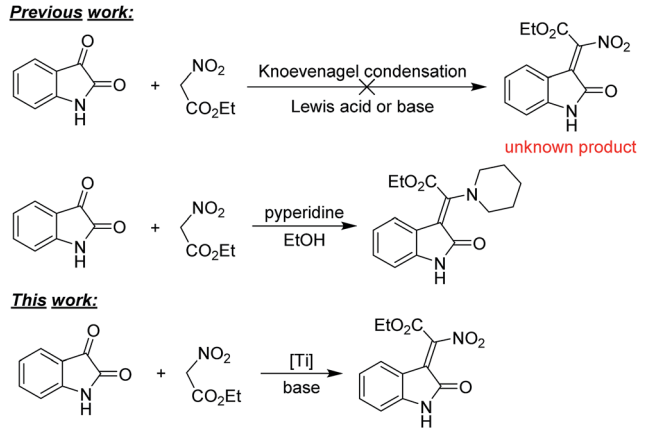


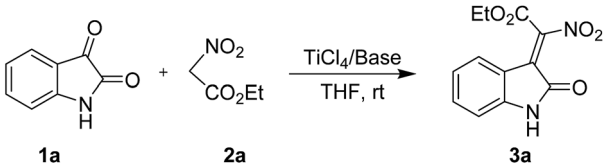
Scheme 1 Condensation reactions between isatin and nitroacetate.

Due to the high reaction velocities, good yields, low toxic and toleration of basic labile functionalities, the $TiCl_4$/base mediated Knoevenagel,[13] Claisen[14] and Dieckmann[15] condensations have gained much attention and great importance over traditional methods. Very recently, Massanet and co-workers reported a condensation of acetates and formate esters employing $TiCl_4/Et_3N$ system, allowing access to a variety of (*E*)-β-alkoxy- and (*E*)-β-aryloxyacrylates in good yields.[16] We envisioned that $TiCl_4$/base system might be good promoter for the condensation reaction and the non-nucleophilic condition could prevent the further transformation of the product. Herein, we report the first Knovenagel condensation reaction of isatins with nitroacetates in the presence of $TiCl_4$/base in good yields and broad substrate scope.

Results and discussion

We initiated this study by choosing isatin (**1a**) and ethyl nitroacetate (**2a**) as model substrates and subjecting to a preliminary condensation condition using $TiCl_4$ and base (Table 1). After some initial screening, we were pleased to find that the desired 2-nitro-3-ylideneoxindole acetates (**3a**) can be obtained in 65% yield and 2 : 1 *Z*/*E* selectivity in the presence of 1.5 equiv. of $TiCl_4$ and 3.0 equiv. of Et_3N at room temperature. The results of the $TiCl_4/Et_3N$ system were promising, although the stereoselectivity was bad (entry 1). We then employed the organic bases, for instance *n*-Bu_3N, DBU, DIPEA, NMM, pyridine and DMAP in the same method (entries 2–7). All organic bases tested could promote the reaction smoothly and the introduction of DMAP improved both the yield and stereoselectivity, and provided the desired **3a** in 88% yield and 8 : 1 *Z*/*E* ratio. Unfortunately, no product could be obtained when inorganic bases were used (entries 8 and 9). After establishment of $TiCl_4$ and DMAP as the optimal reagents in the reaction, different conditions, such as solvents, reaction temperatures, equivalents of metal source and base were subsequently investigated (entries 10–16: for more detailed optimization conditions, see the ESI†). Thus, the best result could be achieved in the presence of 1.5 equiv. of $TiCl_4$ and 2.0 equiv. of DMAP at room temperature, affording **3a** in 90% yield and 9 : 1 *Z*/*E* ratio.

Table 1 Reaction condition optimization[a]



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

Entry	$TiCl_4$ (equiv.)	Base (equiv.)	*t* (h)	Yield[b] (%)	*Z*/*E*[c]
1	1.5	Et_3N (3.0)	8	65	2 : 1
2	1.5	*n*-Bu_3N (3.0)	8	55	2 : 1
3	1.5	DBU (3.0)	8	67	1.5 : 1
4	1.5	DIEPA (3.0)	8	88	1.5 : 1
5	1.5	NMM[d] (3.0)	8	85	2 : 1
6	1.5	Pyridine (3.0)	8	68	6 : 1
7	1.5	DMAP (3.0)	8	88	8 : 1
8	1.5	$CsCO_3$ (3.0)	24	—[e]	—
9	1.5	Na_2CO_3 (3.0)	24	—	—
10[f]	1.5	DMAP (3.0)	24	Trace	—
11[g]	1.5	DMAP (3.0)	24	32	2 : 1
12[h]	1.5	DMAP (3.0)	24	Trace	—
13	1.0	DMAP (3.0)	8	43	9 : 1
14	1.5	DMAP (2.0)	8	90	9 : 1
15	1.5	DMAP (1.5)	12	72	9 : 1
16	2.0	DMAP (3.0)	12	90	9 : 1

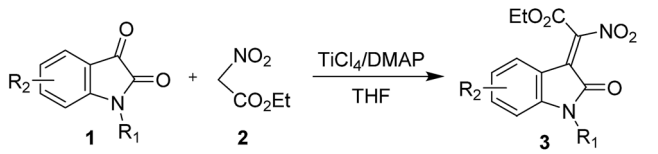
[a] All reactions were carried out with 1.0 equiv. (0.5 mmol) of **1a**, 1.0 equiv. (0.5 mmol) of **2a**, $TiCl_4$ and base at room temperature. [b] Yields of isolated product after column chromatography. [c] Determined by ^{1}HNMR analysis. [d] NMM = *N*-methylmorpholine. [e] No reaction. [f] CH_2Cl_2 was used as reaction solvent. [g] Diethyl ether was used as reaction solvent. [h] Toluene was used as reaction solvent.

With the optimized reaction conditions in hand, we continued with evaluation of the reaction scope. We first used the ethyl nitroacetate in a variety of combinations with isatins, the corresponding products **3** were isolated in 54–95% yields (Table 2). When we use *N*-benzyl, *N*-methyl protected isatins in the reaction, we obtained **3b** and **3c**, respectively, in 85% and 91% yields and good *Z*/*E* ratio (entries 2 and 3); while the *N*-Boc protected **2d** only provided the deprotected **3a** in 83% yield with excellent stereoselectivity (entry 4), probably due to the strong acidity of $TiCl_4$. The reaction of halogenated isatins proceeded smoothly and gave the desired product in good results (73–95% yields and 16 : 1 → 20 : 1 stereoselectivities, entries 5–9 and 11). However, the strong electron withdrawing group, for instance, 5-NO_2 substituted isatin could not provide the desired product at all (entry 13); and isatin with electrondonating groups resulted in lower yields (entries 10, 12 and 14). Importantly, the reaction is amenable to upscaling, and we were able to prepare 1.41 g of **3a** in 82% yield with 10 : 1 *Z*/*E* ratio (entry 15).

To determine the stereochemistry of the 2-nitro-3-ylideneoxindole acetates, the structure of **3c** was confirmed by X-ray crystallographic analysis (Fig. 2, CCDC 1571225).[17] The $TiCl_4$/DMAP mediated condensation reaction provided the desired products in *Z* conformations (Fig. 2).

It is noteworthy that this method is equally successful with activated methylene derivatives that carry different electro-

Table 2 The exploration of substrate scope[a]



Entry	R^1	R^2	t (h)	Yield[b] (%)	Z/E[c]
1	H	H	8	90 (**3a**)	9 : 1
2	Bn	H	8	85 (**3b**)	6 : 1
3	CH_3	H	8	91 (**3c**)	>20 : 1
4	Boc	H	8	83 (**3a**)	>20 : 1
5	H	5-Cl	8	95 (**3d**)	>20 : 1
6	H	4-Br	8	80 (**3e**)	>20 : 1
7	H	5-Br	8	76 (**3f**)	>20 : 1
8	H	6-Br	24	75 (**3g**)	>20 : 1
9	H	7-Br	24	78 (**3h**)	5 : 1
10	H	7-Me	24	61 (**3i**)	4 : 1
11	H	5-F	24	73 (**3j**)	16 : 1
12	H	5,7-CH_3	24	74 (**3k**)	5 : 1
13	H	5-NO_2	8	—	—
14	H	5-OCH_3	8	54 (**3l**)	>20 : 1
15[d]	H	H	12	82 (**3a**)	10 : 1

[a] All reactions were carried out with 1.0 equiv. (0.5 mmol) of **1**, 1.0 equiv. (0.5 mmol) of **2**, 2.0 equiv. (1.0 mmol) of $TiCl_4$ and 3.0 equiv. (1.5 mmol) of DMAP at room temperature. [b] Yields of isolated product after column chromatography. [c] Determined by ^{1}HNMR analysis. [d] The reaction was carried out in 10 mmol scale.

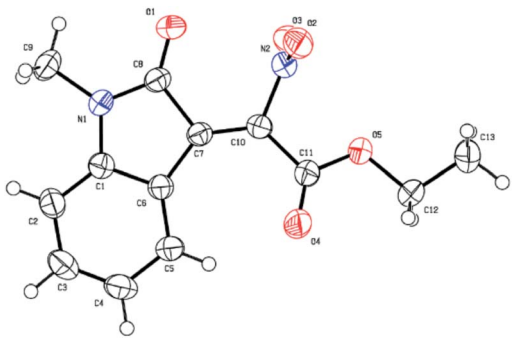
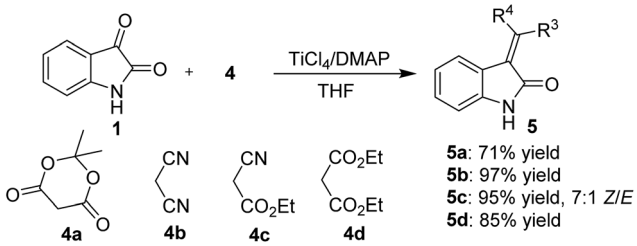


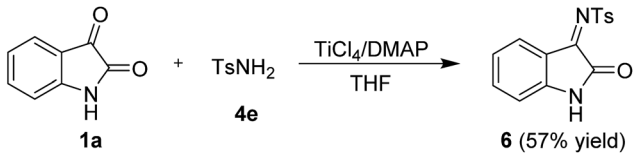
Fig. 2 X-Ray crystal structure of product **3c**.

withdrawing groups, such as 2,2-dimethyl-1,3-dioxane-4,6-dione (**4a**), malononitrile (**4b**), ethyl 2-cyanoacetate (**4c**), and diethyl malonate (**4d**) (Scheme 2). The corresponding products (**5a–d**) were obtained in 71–97% yield and with a 7 : 1 Z/E ratio of **4c** as determined by ^{1}H NMR analysis. Furthermore, the reaction of isatin with 4-methylbenzenesulfonamide (**4e**) also proceeded smoothly and gave the desired imine **6** in 57% yield, which was not reported before (Scheme 3).

To gain insight into the reaction mechanism, we carried out several control experiments. The reaction could not proceed when $TiCl_4$ and DMAP were used separately, which means that $TiCl_4$ and DMAP work cooperatively in the condensation reaction (Scheme 4a and b). When the reaction was carried out in



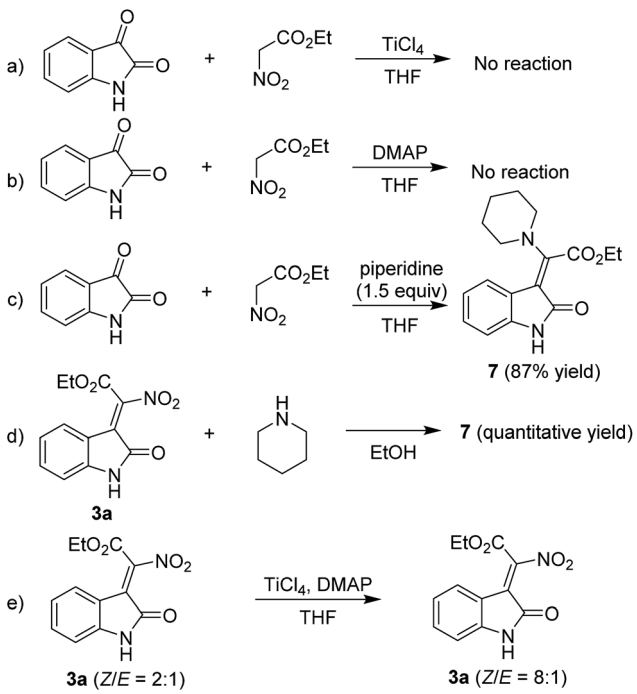
Scheme 2 Condensation reaction of isatins with activated methylenes.



Scheme 3 Condensation reaction of isatins with 4-methylbenzene sulfonamide.

the presence of 1.5 equiv. of piperidine, a piperidine substituted product **7** was afforded in high yield, which was indicated to E configuration through NOE spectrum (see the ESI†) (Scheme 4c). We then used **3a** to react with piperidine, it was found that **7** could be obtained in quantitative yield, indicating that the piperidine mediated reaction went through a Knovenagel condensation first, followed by a nucleophilic substitution reaction to yield **7** (Scheme 4d).

Based on the above results and previous literature reports, a plausible reaction mechanism is proposed and shown in



Scheme 4 Control experiments.

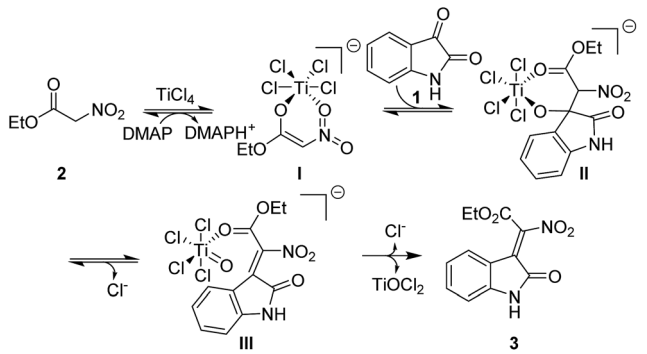


Fig. 3 Proposed reaction mechanism.

Fig. 3. Firstly, the ethyl nitroacetate is activated by $TiCl_4$ to form an anionic titanium enolate; then an aldol reaction will happen between the enolate and isatin, leading to the formation of a six membered metallacycles; next, an elimination will occur to form the new C=C double bond; further elimination of a $TiOCl_2$ yields the desired product. The organic bases play a major role in the stereoselectivity of the condensation reaction. We found that the *Z*/*E* ratio of **3a** could be changed from 2 : 1 to 8 : 1 under the $TiCl_4$/DMAP condition, which indicated that highly nucleophilic DMAP would undergo repetitive addition–elimination onto the double bond formed to isomerize the initially formed *E* isomers into the *Z* isomers (Scheme 4e).

Conclusions

In conclusion, we have developed a *Z*-selective Knovenagel condensation reaction of isatins with nitroacetates in the presence of $TiCl_4$ and an organic base. Wild substrate scope was explored, and provided the corresponding 2-nitro-3-ylideneoxindole acetates in good stereoselectivities and yields. In addition, other activated methylene derivatives such as 2,2-dimethyl-1,3-dioxane-4,6-dione, malononitrile, ethyl 2-cyanoacetate, and diethyl malonate reacted under identical conditions in the same way, yielded the condensation product in good results. As an extension, condensation between isatin with 4-methylbenzenesulfonamide was also promoted by $TiCl_4$/DMAP, gave the unreported imine in moderate yield.

Experimental section

General

All starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. THF was dried and distilled from sodium benzophenone prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (d-chloroform δ 7.26), carbon (d-chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on an Agilent 5975 spectrometer. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash column chromatography was performed using Merck aluminium oxide 90 active neutral with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

A representative procedure for $TiCl_4$/DMAP mediated condensation reaction of isatins with ethyl nitroacetate

A stirred solution of isatin (**1a**, 0.5 mmol, 1.0 equiv.) in anhydrous THF was cooled to 0 °C, $TiCl_4$ (1.0 mmol, 2.0 equiv.) and ethyl nitroacetate (**2a**, 0.5 mmol, 1.0 equiv.) were added slowly, then DMAP (1.5 mmol, 3.0 equiv.) was added, the resulting mixture was stirred at rt. After the reaction was complete (monitored by TLC), DCM (10 mL) was added and the mixture was filtered through a pad of celite; the celite pad was then washed by DCM (5.0 mL each) for two times; the combined organic layers were dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **3a**.

Ethyl (*Z*)-2-nitro-2-(2-oxoindolin-3-ylidene)acetate (3a). 90% yield, a dark red solid; mp. = 131–132 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 4.47–4.40 (m, 2H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.4, 141.7, 131.4, 130.3, 125.4, 122.7, 120.8, 117.7, 110.5, 63.1, 29.7; HRMS (ESI^+) calcd for $C_{12}H_{10}N_2NaO_5$ $(M + Na)^+$ = 285.0482, found = 285.0481.

Ethyl (*Z*)-2-(1-benzyl-2-oxoindolin-3-ylidene)-2-nitroacetate (3b). 85% yield, a dark red solid; mp. = 98–99 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.39–7.27 (m, 6H), 7.04 (t, J = 7.9 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 4.88–4.90 (m, 2H), 4.51 (q, 2H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 159.5, 146.1, 135.0, 134.5, 130.2, 129.0, 128.1, 127.8, 127.4, 127.3, 123.5, 116.8, 110.1, 63.6, 44.1, 13.7; HRMS (ESI+) calcd for $C_{19}H_{17}N_2O_5$ $(M + H)^+$, *m*/*z* 353.1059, found 353.1060.

Ethyl (*Z*)-2-(1-methyl-2-oxoindolin-3-ylidene)-2-nitroacetate (3c). 91% yield, a dark red solid; mp. = 104–106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 4.54 (q, 2H), 3.21 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 159.5, 146.9, 135.1, 129.1, 127.2, 123.5, 123.4, 116.7, 109.0, 63.6, 26.4, 13.7; HRMS (ESI+) calcd for $C_{13}H_{13}N_2O_5$ $(M + H)^+$, *m*/*z* 277.0819, found 277.0817.

Ethyl (*Z*)-2-(5-chloro-2-oxoindolin-3-ylidene)-2-nitroacetate (3d). 95% yield, a yellow solid; mp. = 168–170 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.90 (s, 1H), 7.28 (dd, J = 8.3, 2.0 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 4.43 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 163.0, 140.2,

132.9, 131.1, 128.0, 125.6, 125.4, 122.0, 111.3, 63.2, 13.8; HRMS (ESI+) calcd for $C_{12}H_{10}ClN_2O_5$ (M + H)$^+$, *m*/*z* 297.0273, found 297.0274.

Ethyl (*Z*)-2-(4-bromo-2-oxoindolin-3-ylidene)-2-nitroacetate (3e). 80% yield, a yellow solid; mp. = 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.26–7.12 (m, 2H), 6.87 (dd, J = 8.8, 1.5 Hz, 1H), 4.42 (m, 2H), 1.35 (t, J = 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 164.5, 143.8, 133.7, 132.3, 129.0, 126.3, 120.9, 118.4, 109.2, 63.0, 13.8; HRMS (ESI+) calcd for $C_{12}H_{10}BrN_2O_5$ (M + H)$^+$, *m*/*z* 340.9590, found 340.9599.

Ethyl (*Z*)-2-(5-bromo-2-oxoindolin-3-ylidene)-2-nitroacetate (3f). 76% yield, a yellow solid; mp. = 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86 (s, 1H), 7.44 (dd, J = 8.3, 1.9 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 4.44 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.0, 142.9, 134.7, 131.2, 129.6, 127.4, 126.0, 122.2, 113.9, 63.2, 13.4; HRMS (ESI+) calcd for $C_{12}H_9BrNaN_2O_5$ (M + Na)$^+$, *m*/*z* 362.9587, found 362.9590.

Ethyl (*Z*)-2-(6-bromo-2-oxoindolin-3-ylidene)-2-nitroacetate (3g). 75% yield, a dark red solid, mp. = 151–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.82 (d, J = 6.5 Hz, 1H), 7.23–7.21 (m, 1H), 7.05 (d, J = 2.0 Hz, 1H), 4.44 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 163.1, 142.5, 132.2, 126.4, 125.7, 125.4, 125.3, 119.7, 113.7, 63.2, 13.8; HRMS (ESI+) calcd for $C_{12}H_{10}BrN_2O_5$ (M + H)$^+$, *m*/*z* 340.9590, found 340.9592.

Ethyl (*Z*)-2-(7-bromo-2-oxoindolin-3-ylidene)-2-nitroacetate (3h). 78% yield, a dark red solid; mp. = 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.92 (m, 1H), 7.75 (s, 1H), 7.46–7.44 (m, 1H), 7.00–6.97 (m, 1H), 4.44 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 162.9, 140.6, 133.6, 129.3, 126.2, 124.2, 123.8, 122.0, 103.2, 63.3, 13.8; HRMS (ESI+) calcd for $C_{12}H_9BrNaN_2O_5$ (M + Na)$^+$, *m*/*z* 362.9587, found 362.9579.

Ethyl (*Z*)-2-(7-methyl-2-oxoindolin-3-ylidene)-2-nitroacetate (3i). 61% yield, a dark red solid; mp. = 124–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.13–7.11 (m, 1H), 6.99–6.95 (m, 1H), 4.40 (m, 2H), 2.27 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 164.4, 140.8, 132.7, 131.3, 126.9, 122.9, 122.6, 120.3, 119.9, 62.9, 16.1, 13.8; HRMS (ESI+) calcd for $C_{13}H_{13}N_2O_5$ (M + H)$^+$, *m*/*z* 277.0746, found 277.0744.

Ethyl (*Z*)-2-(5-fluoro-2-oxoindolin-3-ylidene)-2-nitroacetate (3j). 73% yield, a yellow solid; mp. = 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.71 (dd, J = 8.6, 2.5 Hz, 1H), 7.04 (td, J = 8.7, 2.5 Hz, 1H), 6.79 (dd, J = 8.5, 4.2 Hz, 1H), 4.44 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 163.0, 159.6 (d, J_{C-F} = 225.5 Hz), 137.63 (d, J = 21.5 Hz), 132.90, 125.93 (d, J = 23.7 Hz), 121.74 (d, J = 12.5 Hz), 117.81, 112.99 (d, J = 11.4 Hz), 110.69, 63.19, 13.75; HRMS (ESI+) calcd for $C_{12}H_{10}FN_2O_5$ (M + H)$^+$, *m*/*z* 281.0568, found 281.0563.

Ethyl (*Z*)-2-(4,6-dimethyl-2-oxoindolin-3-ylidene)-2-nitroacetate (3k). 74% yield, a dark red solid; mp. = 184–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.63 (s, 1H), 7.07 (s, 1H), 4.46 (m, 2H), 2.29 (s, 3H), 2.20 (s, 3H), 1.40 (t, J = 8.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 159.0, 143.3, 142.2, 137.7, 131.5, 129.5, 127.5, 120.5, 117.1, 62.4, 21.0, 16.6, 14.1; HRMS (ESI+) calcd for $C_{14}H_{14}N_2NaO_5$ (M + Na)$^+$, *m*/*z* 313.0795, found 313.0798.

Ethyl (*Z*)-2-(5-methoxy-2-oxoindolin-3-ylidene)-2-nitroacetate (3l). 54% yield, a dark red solid; mp. = 154–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.57 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.5, 2.5 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 4.44 (m, 2H), 3.81 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 163.3, 155.6, 135.4, 131.5, 126.5, 121.7, 116.6, 112.1, 110.5, 63.0, 55.9, 13.8; HRMS (ESI+) calcd for $C_{13}H_{13}N_2O_6$ (M + H)$^+$, *m*/*z* 293.0695, found 293.0698.

A representative procedure for $TiCl_4$/DMAP mediated condensation reaction of isatins with activated methylenes (4a–4d) and 4-methylbenzenesulfonamide (4e)

A stirred solution of isatin (**1a**, 0.5 mmol, 1.0 equiv.) in anhydrous THF was cooled to 0 °C, $TiCl_4$ (1.0 mmol, 2.0 equiv.) and 2,2-dimethyl-1,3-dioxane-4,6-dione (**4a**, 0.5 mmol, 1.0 equiv.) were added slowly, then DMAP (1.5 mmol, 3.0 equiv.) was added, the resulting mixture was stirred at rt. After the reaction was complete (monitored by TLC), DCM (10 mL) was added and the mixture was filtered through a pad of celite; the celite pad was then washed by DCM (5.0 mL each) for two times; the combined organic layers were dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **5a**.

2,2-Dimethyl-5-(2-oxoindolin-3-ylidene)-1,3-dioxane-4,6-dione (5a). 71 yield, an orange solid; mp. = 146–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.51 (d, J = 7.9 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 1.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 160.1, 158.7, 145.5, 142.4, 136.4, 130.6, 123.3, 121.0, 120.0, 111.2, 105.6, 27.2; HRMS (ESI+) calcd for $C_{14}H_{11}NNaO_5$ (M + Na)$^+$, *m*/*z* 296.0529, found 296.0533.

2-(2-Oxoindolin-3-ylidene)malononitrile (5b). 97% yield, a dark red solid; mp. = 234–235 °C (lit.[18] mp. 232–233 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.54 (d, 7.9 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 5.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 164.2, 159.8, 138.3, 126.3, 125.1, 123.4, 123.2, 119.1, 112.7, 112.1, 81.1; HRMS (ESI+) calcd for $C_{11}H_5N_3NaO$ (M + Na)$^+$, *m*/*z* 218.0325, found 218.0326.

Ethyl (*E*)-2-cyano-2-(2-oxoindolin-3-ylidene)acetate (5c). 95% yield, a dark red solid; mp. = 204–205 °C, (lit.[10a] mp. 208–209 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.39–7.41 (m, 1H), 7.08–7.10 (m, 1H), 6.90 (d, J = 7.9 Hz, 1H), 4.41–4.44 (m, 2H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 160.6, 143.6, 140.4, 134.8, 125.5, 123.4, 119.2, 114.0, 111.1, 106.5, 63.6, 13.7; HRMS (ESI+) calcd for $C_{13}H_{11}N_2O_3$ (M + H)$^+$, *m*/*z* 243.0764, found 243.0757.

Diethyl 2-(2-oxoindolin-3-ylidene)malonate (5d). 85% yield, a dark red solid; mp. = 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.32 (d, J = 7.9 Hz, 1H), 7.31 (td, J = 7.7, 1.1 Hz, 1H), 7.03 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.39–4.44 (m, 4H), 1.35–1.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 165.3, 162.9, 143.6, 134.7, 133.1, 129.6, 129.0, 122.8, 119.8, 110.3, 62.3, 62.1, 13.9, 13.8; HRMS (ESI+) calcd for $C_{15}H_{16}NO_5$ (M + H)$^+$, *m*/*z* 290.1023, found 290.1016.

4-Methyl-*N*-(2-oxoindolin-3-ylidene)benzenesulfonamide (6). 57% yield, a yellow solid; mp. = 259–260 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.4 Hz, 1H), 7.57–7.60 (m, 1H), 7.30–7.33 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.08–7.00 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 150.6, 143.6, 140.1, 139.7, 139.5, 130.0, 125.9, 125.6, 124.0, 117.8, 112.9, 21.1; HRMS (ESI+) calcd for $C_{15}H_{13}N_2O_3S$ (M + H)$^+$, m/z 301.0641, found 301.0644.

Procedure for the substitution reaction of piperidine with 3a

To a stirred solution of **3a** (0.2 mmol, 1.0 equiv.) in EtOH at room temperature, piperidine (0.6 mmol, 3.0 equiv.) was added. The result mixture was stirred at room temperature until the disappearance of the starting material (monitored by TLC). EtOH was removed by rotavapor under reduced pressure; the resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **6**.

(*Z*)-Ethyl 2-(2-oxoindolin-3-ylidene)-2-(piperidin-1-yl)acetate (7). 95% yield, brown solid; mp. = 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 6.88–7.04 (m, 4H), 4.45 (q, 2H), 3.43–3.46 (m, 4H), 1.70–1.75 (m, 6H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 165.8, 150.6, 138.6, 124.7, 123.0, 121.4, 120.5, 117.6, 109.5, 62.5, 52.3, 26.6, 23.7, 13.9; HRMS (ESI+) calcd for $C_{17}H_{21}N_2O_3$ (M + H)$^+$, m/z 301.1547, found 301.1545.

Conflicts of interest

There are no conflicts to declare.

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