TiCl₄/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 TiCl₄ 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-methylbenzenesulfonylamine 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, anti-cancer, and antiviral activities. For example, indirubin (A) from a traditional Chinese herbal medicine is an inhibitor of protein kinases such as glycogen synthase kinase-3b (GSK-3b) 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. 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. (Fig. 1) Furthermore, 3-ylideneoxindoles are the core structure in biologically natural products alkaloids (including neolauergine, costinone A, and costinine B). 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. The palladium-catalyzed Heck–Suzuki–Miyaura domino reactions for the construction of substituted 3-alkylideneoxindoles from ynamides have also been reported.†

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. 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, 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.

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Fig. 1 Illustrative examples of bioactive 3,2′-pyrrolidinyl spirooxindoles.
Due to the high reaction velocities, good yields, low toxicity, and tolerance of basic labile functionalities, the TiCl4/base mediated Knoevenagel, Claisen and Dieckmann 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 TiCl4/Et3N system, allowing access to a variety of (E)-β-alkoxy- and (E)-β-aryloxyacrylates 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 TiCl4 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 TiCl4 and 3.0 equiv. of Et3N at room temperature. The results of the TiCl4/Et3N system were promising, although the stereoselectivity was bad (entry 1). We then employed the organic bases, for instance n-Bu3N, 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 TiCl4 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 ESIF). Thus, the best result could be achieved in the presence of 1.5 equiv. of TiCl4 and 2.0 equiv. of DMAP at room temperature, affording 3a in 90% yield and 9:1 Z/E ratio.

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 TiCl4. The reaction of halogenated isatins proceeded smoothly and gave the desired product in good results (73–95% yields and 16:1 Z/E stereoselectivities, entries 5–9 and 11). However, the strong electron withdrawing group, for instance, 5-NO2 substituted isatin could not provide the desired product at all (entry 13); and isatin with electron-donating 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). The TiCl4/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 electron-
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 1H 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 TiCl₄ and DMAP were used separately, which means that TiCl₄ and DMAP work cooperatively in the condensation reaction (Scheme 4a and b). When the reaction was carried out in 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 Table 2 The exploration of substrate scope

| Entry | R¹ | R² | t (h) | Yield (%) | Z/E |
|-------|----|----|------|-----------|-----|
| 1     | H  | H  | 8    | 90 (3a)   | 9:1 |
| 2     | H  | H  | 8    | 85 (3b)   | 6:1 |
| 3     | H  | H  | 8    | 91 (3c)   | 20:1|
| 4     | H  | H  | 8    | 83 (3a)   | 20:1|
| 5     | H  | H  | 8    | 95 (3d)   | 20:1|
| 6     | H  | H  | 8    | 80 (3e)   | 20:1|
| 7     | H  | H  | 8    | 76 (3f)   | 20:1|
| 8     | H  | H  | 24   | 75 (3g)   | 20:1|
| 9     | H  | H  | 24   | 78 (3h)   | 5:1 |
| 10    | H  | H  | 24   | 61 (3i)   | 4:1 |
| 11    | H  | H  | 24   | 73 (3j)   | 16:1|
| 12    | H  | H  | 24   | 74 (3k)   | 5:1 |
| 13    | H  | H  | 8    | —        | —   |
| 14    | H  | H  | 8    | 54 (3l)   | 20:1|
| 15    | H  | H  | 12   | 82 (3a)   | 10:1|

The reaction was carried out in 10 mmol scale.

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 TiCl₄ and 3.0 equiv. (1.5 mmol) of DMAP at room temperature. b Yields of isolated product after column chromatography. c Determined by 1H NMR analysis. d The reaction was carried out in 10 mmol scale.

![Fig. 2 X-Ray crystal structure of product 3c.](image-url)
in conclusion, we have developed a Z-selective Knoevenagel condensation reaction of isatins with nitroacetates in the presence of TiCl₄ 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 to yield the corresponding products. A representative procedure for TiCl₄/DMAP mediated condensation reaction of isatins with ethyl nitroacetate

A stirred solution of isatin (1a, 0.5 mmol, 1.0 equiv.) and ethyl nitroacetate (2a, 0.5 mmol, 1.0 equiv.) was 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₁N₂O₅ (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 159.5, 146.1, 135.0, 134.3, 130.2, 129.0, 128.1, 127.8, 127.4, 127.3, 123.3, 116.8, 110.1, 63.4, 44.1, 13.7; HRMS (ESI+) calcd for C₁₅H₁₂N₂O₅ (M + H)⁺ = 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, CDCl₃) δ 8.03 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.4 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); ¹³C NMR (125 MHz, CDCl₃) δ 165.4, 159.5, 146.9, 135.1, 129.1, 127.2, 123.6, 123.4, 116.7, 109.0, 63.6, 26.4, 13.7; HRMS (ESI+) calcd for C₁₅H₁₁N₂O₅ (M + H)⁺ = 353.1059, found 353.1078.

Ethyl (Z)-2-(2-chloro-2-oxoindolin-3-ylidene)-2-nitroacetate (3d). 93% yield, a yellow solid; mp. = 168–170 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.89 (s, 1H), 7.90 (s, 1H), 7.28 (d, 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); ¹³C NMR (125 MHz, CDCl₃) δ 165.8, 163.0, 140.2,
Ethyl (Z)-2-(4-bromo-2-oxindolin-3-ylidene)-2-nitroacetate (3e).

1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) δ 164.8, 159.0, 142.9, 134.7, 131.2, 129.6, 127.4, 126.0, 122.2, 113.9, 62.3, 13.4; HRMS (ESI) calcd for C₁₂H₉BrNaN₂O₅ [M + Na]⁺, m/z 362.9587, found 362.9592.

Ethyl (Z)-2-(6-bromo-2-oxindolin-3-ylidene)-2-nitroacetate (3f).

1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) δ 164.8, 159.0, 142.9, 134.7, 131.2, 129.6, 127.4, 126.0, 122.2, 113.9, 62.3, 13.4; HRMS (ESI) calcd for C₁₂H₉BrNaN₂O₅ [M + Na]⁺, m/z 362.9587, found 362.9592.

Ethyl (Z)-2-(7-bromo-2-oxindolin-3-ylidene)-2-nitroacetate (3g).

1H NMR (500 MHz, CDCl₃) 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), 1.40 (m, 1H), 1.30–1.06 (m, 1H), 0.96–0.91 (m, 1H); 13C NMR (125 MHz, CDCl₃) δ 164.8, 162.9, 140.6, 136.3, 129.3, 126.2, 124.2, 123.8, 122.0, 103.2, 63.3, 13.8; HRMS (ESI) calcd for C₁₂H₁₀BrNaN₂O₅ [M + Na]⁺, m/z 349.9590, found 349.9592.

Ethyl (Z)-2-(8-bromo-2-oxindolin-3-ylidene)-2-nitroacetate (3h).

1H NMR (500 MHz, CDCl₃) δ 7.10–7.00 (m, 1H), 6.99–6.95 (m, 1H), 4.40 (m, 2H), 2.27 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 167.4, 164.4, 140.8, 132.7, 131.3, 129.9, 124.7, 122.2, 119.9, 62.9, 61.9, 13.8; HRMS (ESI) calcd for C₁₁H₁₂N₂O₅ [M + H]⁺, m/z 297.0744, found 297.0774.

Ethyl (Z)-2-(9-fluoro-2-oxindolin-3-ylidene)-2-nitroacetate (3j).

1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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 = 21.5 Hz), 117.81, 112.99 (d, J = 11.4 Hz), 110.69, 63.19, 13.75; HRMS (ESI) calcd for C₁₁H₁₀FN₃O₂ [M + H]⁺, m/z 281.0568, found 281.0563.

Ethyl (Z)-2-(4,6-dimethyl-2-oxindolin-3-ylidene)-2-nitroacetate (3k).

1H NMR (500 MHz, CDCl₃) δ 8.24 (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); 13C NMR (125 MHz, CDCl₃) 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 C₁₄H₁₄N₂NaO₅ [M + Na]⁺, m/z 313.0795, found 313.0798.

Ethyl (Z)-2-(5-methyl-2-oxindolin-3-ylidene)-2-nitroacetate (3l).

54% yield, a dark red solid; mp. = 154–155 °C; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₃NO₃ [M + H]⁺, m/z 293.0695, found 293.0698.

A representative procedure for TiCl₄/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, TiCl₄ (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-oxindolin-3-ylidene)-1,3-dioxane-4,6-dione (5a).

71% yield, an orange solid; mp. = 146–147 °C; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) δ 165.9, 160.1, 158.7, 145.5, 142.4, 136.4, 130.6, 123.0, 120.0, 111.2, 105.6, 72.7; HRMS (ESI) calcd for C₁₄H₁₂N₂O₄ [M + Na]⁺, m/z 296.0529, found 296.0533.
4-Methyl-N-(2-oxoindolin-3-ylidene)benzenesulfonamide (6). 57% yield, a yellow solid; mp. = 259–260 °C; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) δ 160.4, 150.6, 143.6, 140.1, 139.7, 139.5, 130.9, 125.9, 125.6, 124.0, 117.8, 112.9, 21.1; HRMS (ESI+) calcd for C₁₅H₁₃N₂O₃S (M + H)⁺, m/z 301.1545.

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; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₂N₂O₃ (M + H)⁺, m/z 301.1545, found 301.1545.

Conflicts of interest
There are no conflicts to declare.

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