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Palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones: a strategy for the construction of Pyrrolo[1,2-*a*]indoles

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Abstract

A palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones has been developed. Three examples of pyrrolo[1,2-*a*]indoline derivatives were readily obtained with good yields up to 82% utilizing this strategy. Importantly, this palladium-catalyzed intramolecular cyclization process represents an important contribution to the application of indole-3-one derivatives.

Keywords

indolin-3-ones; Conia-ene reaction; palladium catalysis; pyrrolo[1,2-*a*]indoline; 1-alkynylindolin-3-ones

Introduction

Pyrrolo[1,2-*a*]indoles are important class of compounds featured with structural motifs that are widely found in a large number of natural products and biologically active molecules (Figure 1) [1-5]. For example, isatisine A (I) is one of the major components of the traditional Chinese medicine plant *Isatis indigotica Fort.* (*Cruciferae*) and its acetonide derivative showed cytotoxicity against C8166 Cells (CC50 = 302 μM) and anti-HIV-1IIIB activity (EC50 = 37.8 μM) [1-2]. Compound (II) is a protein kinase C (PKC) inhibitor and showed the selective inhibition for isozyme β [3]. Mitomycin A (III) and B (IV) are representative pyrrolo[1,2-*a*]indoles of *mitomycin* alkaloids family [4]. The alkaloid yuremamine (V) is isolated from the stem bark of *Mimosa tenuiflora* and has potential inhibitory effects on monoamine oxidase (MAO) [5]. Due to the importance of their structure and biological activity, the scaffold of pyrrolo[1,2-*a*]indoles attracted much attention of synthetic and medicinal chemists. In the last few decades, a number of elegant synthetic methods (such as pallidium-catalyzed intramolecular alkyne insertion protocol [6], chiral phosphoric acids

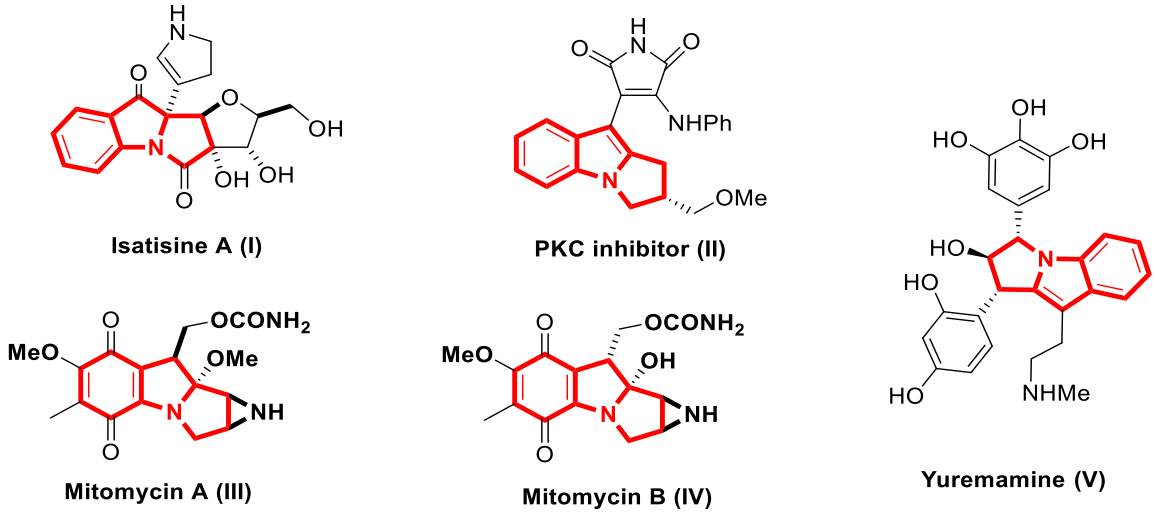
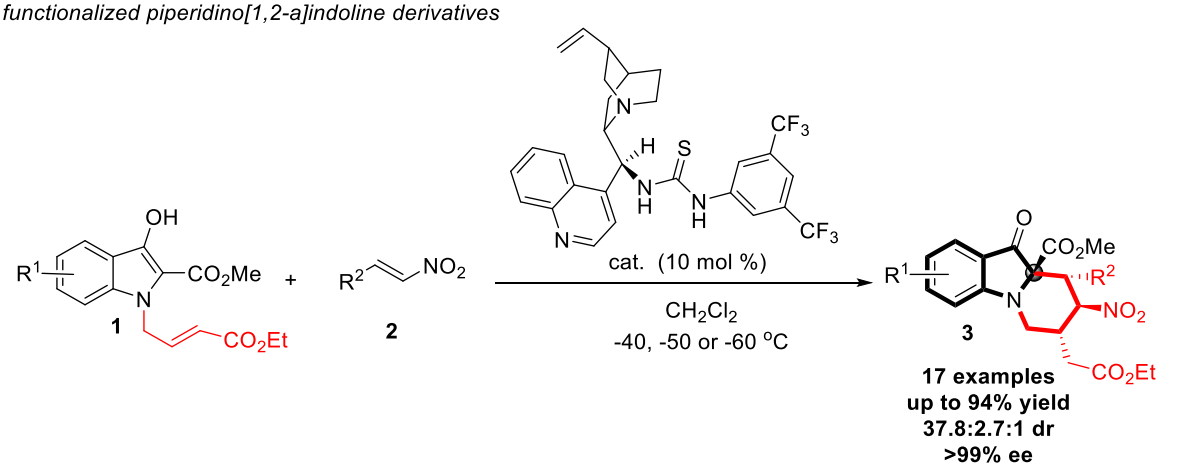


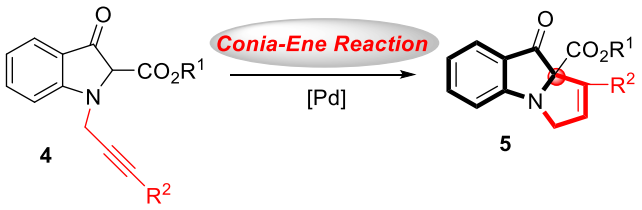
Figure 1: Representative compounds containing pyrrolo[1,2-*a*]indole motifs.

catalyzed intramolecular conjugated addition of C2-substituted indoles [7], virous radical cascade cyclization [8-13], gold-catalyzed reaction between 2-alkynyl arylazides and alkynols [15], and so on) have been developed for the pyrrolo[1,2-*a*]indole scaffolds [6-15]. Despite these significant advances have been made, most of these established methods are need ligands, stoichiometric oxidant and harsh reaction conditions. Therefore, the development of efficient and easy approaches for the construction of pyrrolo[1,2-*a*]indole scaffolds is highly desired.

a) Our previous work: *Organocatalytic asymmetric Michael-Michael cascade for the construction of highly functionalized piperidino[1,2-a]indoline derivatives*



b) This work: *Palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones for the construction of pyrrolo[1,2-a]indoles*



Scheme 1: Organocatalytic Asymmetric Michael−Michael Cascade and Palladium-Catalyzed Conia–Ene Reaction of Indolin-3-ones with Substituents at the N1 Positions.

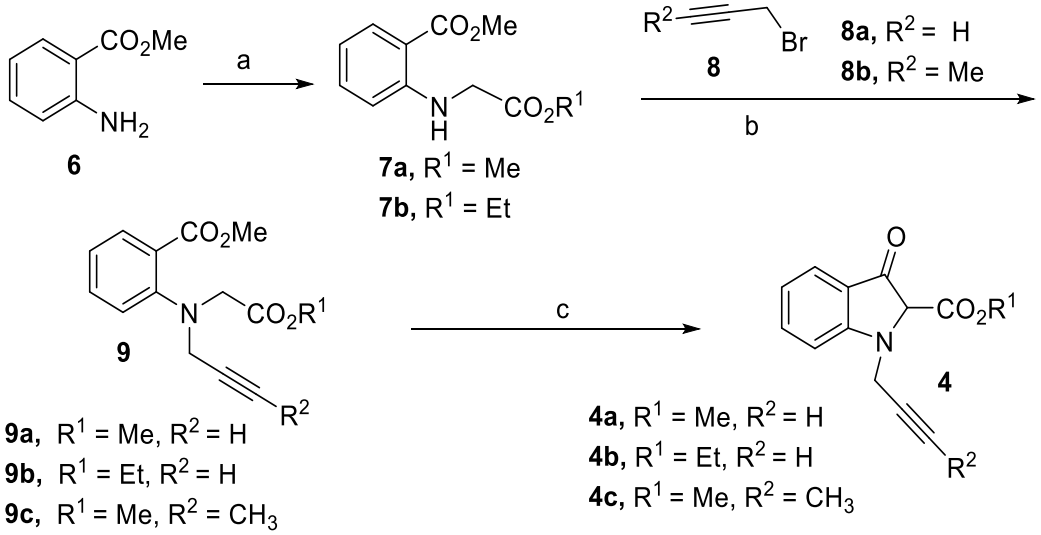
Over the past decade, much efforts was focused on the nucleophilic indole-3-ones for the construction of C2-quaternary indolin-3-one and indole-polycyclic-skeletons (such as indole-fused cyclic at the N1 and C2 positions, 2,2'-spirocyclic indoles and indole-fused cyclic at the C2 and C3 positions) [16-20]. Unlike the significant progress of 2-oxindole chemistry in the synthesis of indole-polycyclic-skeletons,

indolin-3-ones have received very little attention [16-17, 21]. In 2014, we have developed a bifunctional thiourea-catalyzed asymmetric Michael-Micheal cascade reaction for the construction of highly functionalized N-fused piperidinoindoline derivatives via employing less explored indolin-3-ones **1** (Scheme 1a) [20]. With our ongoing interest in the design and development of indolin-3-one chemistry [20, 22-23], we describe herein a palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones **4** for the construction of N-fused pyrrolo[1,2-*a*]indoline skeletons **5** (Scheme 1b).

Results and Discussion

On the basis of the synthesis of indolin-3-ones **1** in our previous works [20], we synthesized 1-alkynylindolin-3-ones **4** by three-step reactions as shown in the Scheme 2. Firstly, compounds **7** were prepared through a substitution reaction of **6** with methyl or ethyl bromoacetate in 50-70% yields (Scheme 2, reaction a). Then, key intermediates **9** were synthesized in 36-70% yields via the substitution reaction of compounds **7** with 3-bromoprop-1-yne **8a** or 1-bromobut-2-yne **8b** under the

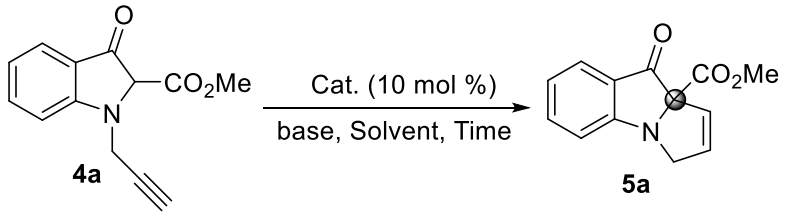
Scheme 2: Synthesis of 1-alkynylindolin-3-ones **4**.[a]



[a]Reactants and conditions: (a) $BrCH_2CO_2R^1$, DMF, reflux, 80 °C; (b) K_2CO_3, NaI, CH_3CN, reflux, 80 °C; (c) t-BuOK, THF, 0 °C.

conditions as shown in Scheme 2, reaction **b**. The obtained key intermediates **9** could be readily converted into the target 1-alkynylindolin-3-ones **4** (50-75% yields) via a intramolecular cyclization reaction promoted by t-BuOK (Scheme 2, reaction c).

Table 2: Optimization of reaction conditions.[a]



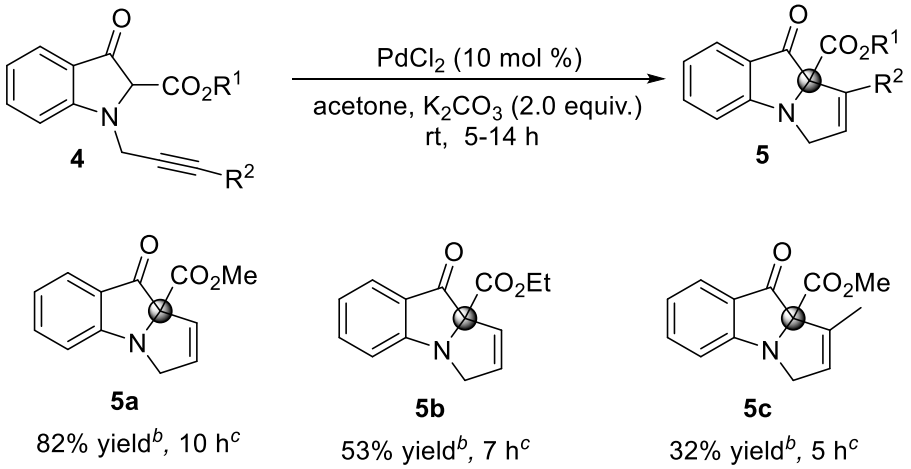
Entry	Base	Cat.	Solvent	Time (h)[b]	Yield %[c]
1	K_2CO_3	$PdCl_2$	THF	23	26
2	K_2CO_3	$PdCl_2$	MTBE	46	n.r.[d]
3	K_2CO_3	$PdCl_2$	DMSO	5	57
4	K_2CO_3	$PdCl_2$	CH_2Cl_2	23	22
5	K_2CO_3	$PdCl_2$	toluene	26	<10
6	K_2CO_3	$PdCl_2$	DMF	5	30
7	K_2CO_3	$PdCl_2$	H_2O	24	n.r.[d]
8	K_2CO_3	$PdCl_2$	acetone	10	82
9	K_2CO_3	$FeCl_2$	acetone	28	n.d.[e]
10	K_2CO_3	$CuCl_2$	acetone	28	<10
11	K_2CO_3	$Pd(OAc)_2$	acetone	24	44
12	K_2CO_3	$Pd(acac)_2$	acetone	8	21
13	K_2CO_3	$Pd_2(dba)_3$	acetone	3	26
14	K_2CO_3	$Pd(OAc)_2$	acetone	24	44
15	t-BuOK	$PdCl_2$	acetone	21	n.d.[e]
16	KOH	$PdCl_2$	acetone	21	n.d.[e]
17	AcONa	$PdCl_2$	acetone	21	13
18	-	$PdCl_2$	acetone	21	n.r.[d]

[a]Unless otherwise specified, all reactions were carried out with **4a** (0.10 mmol), catalyst (10 mol %) and base (2.0 equiv.) in the indicated solvent (1.0 ml) at room temperature. [b]As judged by TLC analysis. [c]All yields are isolated yields after flash chromatography. [d]n.r. = no reaction. [e]n.d. = not determined.

With the indolin-3-one substrates for reactions research in hand, the palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones **4a** was chosen as the model reaction (Table1). To our delight, the target product **5a** was obtained albeit with 26% yield under the conditions of K_2CO_3, THF and $PdCl_2$ (10 mol %) as the catalyst at room temperature (Table 1, entry 1). With this expected result, we next screened

virous solvent (such as MTBE, DMSO, CH_2Cl_2, toluene, DMF, H_2O and acetone) in the conditions of K_2CO_3 as base and $PdCl_2$ (10 mol %) as the catalyst at room temperature (Table 1, entries 1-8). The results showed that acetone was the optimized choice for this Conia-ene reaction and the yield of product **5a** was increased to 82 % (Table 1, entry 8). For MTBE and H_2O as solvents, no expected product **5a** was obtained. Then, we evaluated the influence of virous metal catalysts on this intramolecular cyclization process (Table 1, entries 8-14). The results revealed that $PdCl_2$ was the most promising metal catalyst for this intramolecular cyclization process. When $FeCl_2$ was used as the catalyst, no expected product **5a** was obtained (Table 1, Entry 9). Others metal catalysts such as $CuCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$,and $Pd_2(dba)_3$ were also used in this intramolecular cyclization process, but the lower yield were obtained for product **5a** (Table 1,entries 10-14). Finally, the effect of virous bases (such as K_2CO_3, $^{t-}$BuOK, KOH, AcONa) were screened to

Scheme 3: Substrate Scopes.[a]

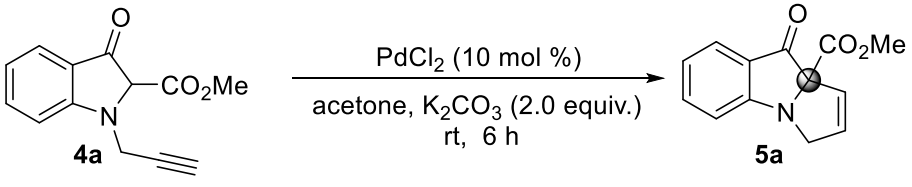


[a]Unless otherwise specified, all reactions were carried out with **4** (0.10 mmol), $PdCl_2$ (10 mol %) and K_2CO_3 (2.0 equiv.) in the acetone (1.0 ml) at room temperature. [b]All yields are isolated yields after flash chromatography. [c]Reaction time was judged by TLC analysis.

further improve the yield of this conia-ene reaction of 1-alkynylindolin-3-ones **4a** (Table 1, Entries 8, 15-18). The resullts showed that using K_2CO_3 as a base was the best choice, however, complex reaction systems or products **4a** with low yields could be obtained under other bases conditions. In addition, in the absence of any bases, the intramolecular cyclization process did not proceed even in the optimal reaction conditions (Table 1, entry 18).

With the established optimal reaction conditions (10 mol % of $PdCl_2$ as the metal catalyst and 2.0 equivalent of K_2CO_3 as the base in 1.0 ml acetone at room temperature), we then investigated the substrate scope of this palladium-catalyzed Conia-ene reaction of 1-alkynylindolin-3-ones **4**. In general, all the synthesized 1-alkynylindolin-3-ones **4a**-**c** could offer the desired cyclic products **5a**-**c** with 32-82% yields (Scheme 3). Pherhaps owing to the steric effect of terminal alkynes and substituents at C2 positions of indolin-ones **4**, compared with indolin-3-ones **4a**, the intramolecular cyclization of **4b**-**c** gave **5b**-**c** with lower yield and the stability of substrates **4b**-**c** was also reduced in reaction conditions.

Scheme 4: The large-scale synthesis of the product **5a**.

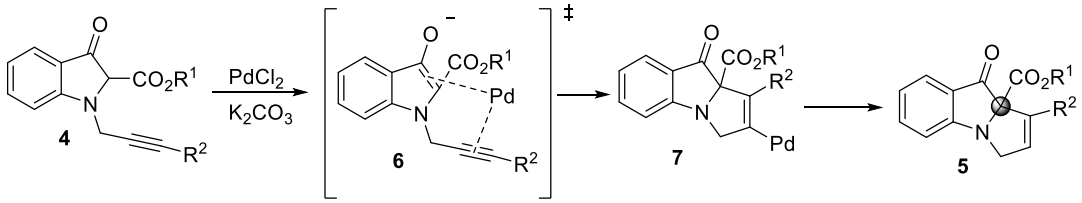


2.18 mmol
0.50 g

0.32 g, 61% yield

Under the optimized conditions, the large-scale synthesis of **5a** was also performed and the corresponding cyclic product **5a** was obtained albeit with the actual yield decreased to 61% (Scheme 4). The structures of product **5** was confirmed by NMR spectra with the reported known compounds **5c** [13]. Based on the previous reported works [24-26], a possible mechanism involving nucleophilic addition of an enol to a

Pd(II) alkyne complex **6** and generate the key carbocyclic intermediate **7** for this Conia-ene reaction of 1-alkynylindolin-3-ones **4** was also depicted in Scheme 5.



Scheme 5: Proposed mechanism for the Palladium-catalyzed Conia–ene reaction of 1-alkynylindolin-3-ones **4**.

Conclusion

In conclusion, we have developed the first strategy of palladium-catalyzed Conia–ene reaction of 1-alkynylindolin-3-ones to construct the scaffold of pyrrolo[1,2-*a*]indoles. This transformation utilized $PdCl_2$ as the catalyst and K_2CO_3 as the base under mild reaction conditions. The three examples of N-fused pyrrolo[1,2-*a*]indole derivatives were obtained in moderate to good yields (up to 82% yield) utilizing this strategy. This work not only provides a strategy for the construction of pyrrolo[1,2-*a*]indoles but also further highlights the potential of indole-3-one derivatives to serve as a very important substrate for the construction of indole-polycyclic skeletons. Further application of activated indol-3-ones in the synthesis of chiral complex indole-polycyclic skeletons is ongoing in our laboratories.

Experimental

Materials and methods

Unless otherwise noted, all chemical reagents and solvents were either purchased from commercial suppliers (such as Energy-chemical, Alfa, Aladdin) or purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th ed. All experiments were monitored by analytical thin-layer chromatography (TLC). TLC was performed on silica gel plates with an F-254 indicator and compounds were

visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography was carried out utilizing silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JNM-ECS400 (400M) spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C). The spectra were recorded in $CDCl_3$ as the solvent at room temperature otherwise stated, ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak as an internal standard: $CDCl_3$ (^{1}H NMR: δ 7.26, singlet; ^{13}C NMR: δ 77.0, triplet). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported as chemical shift. High-resolution mass spectrometry (HRMS) were performed on a Thermofisher (Vanquish (UPLC)-Q-Exactive Plus) mass instrument (Orbitrap-ESI), and methanol was used to dissolve the sample. The substrate of nucleophilic indole-3-ones **4a**-**c** were prepared by following the publish procedures.

Synthetic procedures

General procedure for the synthesis of compounds 7a-b:

Under nitrogen atmosphere, methyl bromoacetate or ethyl bromoacetate (1.2 equiv) was added to a stirred solution of compounds **6** (3.00 g, 19.87 mmol) in dry DMF (20 mL) at room temperature for 5 min. The resulting solution was stirred for 6 h at 80 ^{o}C (as judged by TLC analysis). Then the reaction mixture was allowed to rt and poured into ice water. The resulting solution was extracted with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2$\times$100 mL), H_2O (3 $\times$100 mL) followed by brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The purification of the crude product by flash column

chromatography on silica gel (200-300 mesh) using (PE:EA/15:1) to afford the pure product 7a-b as a white solid with 50% - 70% yields.

General procedure for the synthesis of compounds 9a-c:

To a solution of compounds **7a**-**b** (13.32 mmol,), K_2CO_3 (2.0 equiv), NaI (2.0 equiv) and dry CH_3CN (30 ml) was slowly added 3-bromoprop-1-yne **8a** or 1-bromobut-2-yne **8b** (2.50 equiv) under stirring at room temperature. The reaction mixture was refluxed at 80 ^oC for 2 days. After the reaction time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate and saturated sodium chloride solution, the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The purification of the crude product by flash column chromatography on silica gel (200-300 mesh) using (PE:EA/15:1) to afford the pure products **9a**-**c** as a yellow oil with 36% - 70% yields.

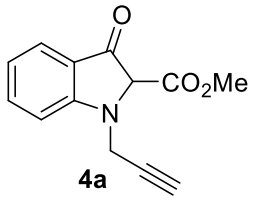
General procedure for the synthesis of compounds 4a-c:

$^{t-}$BuOK (3.0 equiv, 1.65 g) was dissolved in freshly distilled THF (15 ml), and the resulting solution was stirred for 5 minutes at 0 ^oC. At this temperature, the solution of compound **9a** - **c** (5.2 mmol) in freshly distilled THF (5.0 ml) was slowly added dropwise to the solution. After about 30 minutes at 0 ^oC, the resulting solution was concentrated under reduced pressure and extracted with EtOAc. The combined organic phases were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered and concentrated in vacuo. The purification of the crude product by flash column chromatography on silica gel (200-300 mesh) using (PE:EA/15:1) to afford the pure product **4a**-**c** as a white solid with 50% - 75% yields.

General procedure for the synthesis of compounds 5a-c:

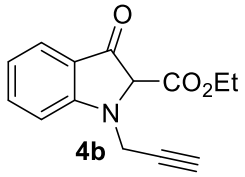
Under nitrogen atmosphere, 1-alkynylindolin-3-ones **4a**-**c** (0.1 mmol), $PdCl_2$ (0.01 mmol), K_2CO_3 (0.2 mmol, 2.0 equiv) were dissolved in freshly distilled acetone (1.0

ml), and the resulting solution was stirred at rt. After completion of the reaction (as judged by TLC analysis). The reaction mixture was directly purified by flash column chromatography (eluted with petroleum ether/EtOAc = 5:1) to afford the desired cyclic products **5a**-**c** with 32 - 82% yields.



4a

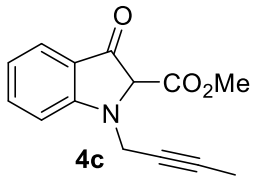
Methyl 3-oxo-1-(prop-2-yn-1-yl) indoline-2-carboxylate (**4a**, 0.63 g, 2.76 mmol, 53% yield) was obtained from compound **9a** (1.36 g, 5.2 mmol, 1.00 equiv) as a white solid; mp 114–115 °C; 1H NMR (400 MHz, CDCl3) δ 8.59 (s, 1H), 7.80 - 7.75 (m, 1H), 7.46 - 7.39 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.17 - 7.09 (m, 1H), 5.13 (d, *J* = 2.4 Hz, 2H), 4.01 (s, 3H), 2.21 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 164.1, 149.7, 137.6, 127.7, 120.5, 119.9, 117.6, 110.2, 108.3, 78.7, 71.8, 60.3, 51.7, 34.1. HRMS (Orbitrap-ESI) m/z: calculated calculated $[M+H]^+$ for $C_{13}H_{12}NO_3$: 230.08117, found $[M+H]^+$: 230.08104.



4b

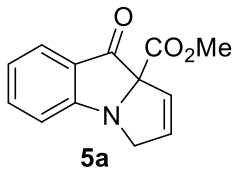
Ethyl 3-oxo-1-(prop-2-yn-1-yl)indoline-2-carboxylate (**4b**, 0.91 g, 3.74 mmol, 72% yield) was obtained from compound **9b** (1.43 g, 5.2 mmol, 1.00 equiv) as a white solid; mp 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.80 - 7.75 (m, 1H), 7.46 - 7.38 (m, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.16 - 7.08 (m, 1H), 5.13 (d, *J* = 2.4 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 2.4 Hz, 1H), 1.47 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 163.8, 149.6, 137.3, 127.6, 120.4, 119.8, 117.4, 110.1,

108.3, 78.8, 71.7, 60.9, 53.4, 34.1, 14.3. HRMS (Orbitrap-ESI) m/z: calculated $[M+H]^+$ for $C_{14}H_{14}NO_3$: 244.09682, found $[M+H]^+$: 244.09663.



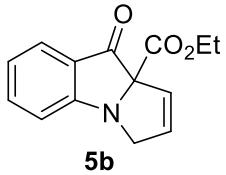
4c

Methyl 1-(but-2-yn-1-yl)-3-oxoindoline-2-carboxylate (**4c**, 0.92 g, 3.80 mmol, 73% yield) was obtained from compound **9c** (1.26 g, 5.2 mmol, 1.00 equiv) as a white solid; mp 102–103 °C; ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.64 (s, 1H), 7.80 - 7.73 (m, 1H), 7.45 - 7.33 (m, 2H), 7.15 - 7.08 (m, 1H), 5.08 (q, *J* = 2.4 Hz, 2H), 4.01 (s, 3H), 1.73 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.4, 137.4, 127.5, 120.3, 119.6, 117.2, 110.4, 108.2, 79.5, 74.1, 53.4, 51.7, 34.4, 3.5. HRMS (Orbitrap-ESI) m/z: calculated $[M+H]^+$ for $C_{14}H_{14}NO_3$: 244.09682, found $[M+H]^+$: 244.09669.



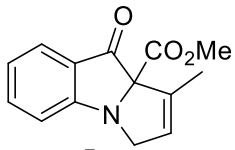
5a

Methyl 9-oxo-3H-pyrrolo[1,2-a]indole-9a (9H)-carboxylate (**5a**, 18.9 mg, 0.082 mmol, 82% yield) was obtained from compound **4a** (22.9 mg, 0.1 mmol, 1.00 equiv) as a light green liquid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.65 - 7.50 (m, 2H), 7.10 - 6.95 (m, 2H), 6.10 - 6.05 (m, 1H), 5.98 - 5.90 (m, 1H), 4.39 (dq, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 3.99 (dt, *J* = 15.6 Hz, *J* = 2.0 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (101MHz,$CDCl_3$) δ 196.6, 168.3, 166.2, 137.6, 130.9, 125.8, 125.1, 122.4, 115.7, 87.0, 59.9, 53.8. HRMS (Orbitrap-ESI) m/z: calculated $[M+Na]^+$ for $C_{13}H_{11}NNaO_3$: 252.0631, found $[M+H]^+$: 252.0642.



5b

Ethyl 9-oxo-3H-pyrrolo[1,2-a]indole-9a(9H)-carboxylate (**5b**, 12.6 mg, 0.052 mmol, 52% yield) was obtained from compound **4b** (24.3 mg, 0.1 mmol, 1.00 equiv) as a light green liquid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.65 - 7.55 (m, 2H), 7.13 - 7.03 (m, 2H), 6.15 - 6.05 (m, 1H), 6.00 - 5.90 (m, 1H), 4.20 (dq, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 4.32 - 4.16 (m, 2H), 4.01 (dt, *J* = 15.6 Hz, *J* = 2.0 Hz, 1H), 1.27 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 196.8, 167.9, 166.3, 137.6, 130.7, 125.2, 122.4, 115.7, 87.3, 62.3, 59.9, 14.1. HRMS (Orbitrap-ESI) m/z: calculated $[M+H]^+$ for $C_{14}H_{14}NO_3$: 244.09682, found $[M+H]^+$: 244.09668.



5c

Methyl 1-methyl-9-oxo-3H-pyrrolo[1,2-a]indole-9a(9H)-carboxylate (**5c**, 7.8 mg, 0.032 mmol, 32% yield) was obtained from compound **4c** (24.3 mg, 0.1 mmol, 1.00 equiv) as a light green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.55 (m, 2H), 7.10 - 7.00 (m, 2H), 5.58 - 5.54 (m, 1H), 4.42 - 4.30 (m, 1H), 3.98 - 3.90 (m, 1H), 3.76 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 196.2, 168.4, 166.2 , 137.4, 135.4, 125.5, 124.9, 123.1, 122.3, 115.5, 86.4, 59.2, 53.0, 12.2. HRMS (Orbitrap-ESI) m/z: $[M+H]^+$ for $C_{14}H_{14}NO_3$: 244.09682, found $[M+H]^+$: 244.09663. The analytical data are in agreement with those reported before [13].

Supporting Information

Supporting Information File 1:

NMR Spectra and HRMS Spectra.

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