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Access to Indole-Fused Polyheterocycles via Pd-Catalyzed Base-Free Intramolecular Cross Dehydrogenative Coupling

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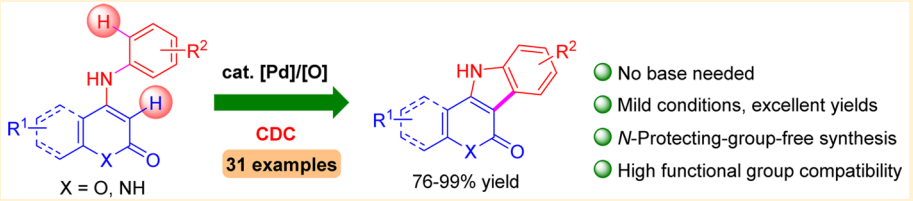
Supporting Information



ABSTRACT: A base-free process to access indole-fused polyheterocycles via a highly efficient and atom-economic palladium-catalyzed intramolecular cross dehydrogenetive coupling (CDC) reaction of 4-aniline substituted coumarins, quinolinones, and pyrones has been developed. A wide range of indolo[3,2-*c*]coumarins, indolo[3,2-*c*]quinolinones, and indolo[3,2-*c*]pyrones can be facilely afforded in good to excellent yields (up to 99%).

Indole and coumarin skeletons are recognized as two important classes of structural motifs distributed in a number of natural products which exhibit a broad range of biological and pharmaceutical activities. Design of new molecules by combination of different pharmacophores is of great interest in medicinal chemistry and drug discovery. Indolo[3,2-*c*]coumarin with a fused cyclic ring system containing both indole and coumarin components belongs to an intriguing family of structurally unique polyheterocycles having an interesting biological profile such as antitumor angiogenesis and estrogenic activity.[1] Accordingly, there have been significant interest in developing useful methodologies for construction of this fused polycyclic skeleton. Among them, the most conventional method is the intramolecular thermal cyclization of 4-azido-3-aryl coumarins to form the indole ring under harsh reaction conditions (150 °C), which inevitably requires the use of highly toxic NaN_3 to synthesize the cyclization precursor (Scheme 1, cutoff a).[2] Alternatively, 3-(2-nitroaryl)coumarins can be employed as substrates for reductive cyclization via microwave-assisted Cadogan reaction at high temperature (200 °C) (Scheme 1, cutoff b).[3] In recent years, several new methods mediated by transition-metal salts or complexes have been successfully developed. For example, Hong reported an intramolecular Heck cyclization approach to construct the indole ring from prebromo-functionalized 4-aniline coumarins utilizing a special cobalt-sandwich diphosphine chelated palladium catalyst (cutoff c).[4] Thasana and co-workers disclosed a Cu(I)-mediated microwave-assisted intramolecular lactonization method capable of producing indolo-[3,2-*c*]coumarins (cutoff d),[5] while Larock et al. developed a Pd-catalyzed lactonization via CO insertion using an acetoxy group as the nucleophile (cutoff e).[6] Most recently, an efficient Pd-catalyzed intramolecular oxidative C−H/C−H coupling protocol was realized by Lan and You with indole-3-carboxylates as reaction substrates (cutoff f).[7] While these methods are useful for synthesis of valuable indolo[3,2-*c*]coumarins, they mainly rely on the manipulation of prefunctionalized substrate and overall require multistep transformations. Moreover, most of them suffer from harsh reaction conditions, limited substrate scope, poor functional-group compatibility and require protection of indole NH. From the perspective of atom economy and step efficiency, an ideal synthesis would involve an efficient ring construction via direct C−H coupling without prefunctionalization and *N*-protection.

In the past few years, the cross dehydrogenative coupling (CDC) protocol has received considerable attention, as it allows C−C bond formation by directly connecting two different C−H bonds.[8] Recently, we reported the development of a Pd-catalyzed efficient intramolecular CDC approach for facile construction of coumestans from readily available 4-aryloxy coumarins.[9] Our preliminary study indicates that this strategy is also applicable for the synthesis of indolo[3,2-*c*]coumarins; however, the reaction yield varies depending on the substitution pattern of substrates. Continuing our interest in the nitrogen-containing polyheterocycles[10] for a drug discovery program, we envisioned developing a more general synthetic approach toward structurally diverse indole-fused polycyclic motifs. Herein we disclose our success on the improvement of this promising intramolecular CDC reaction to construct indolo[3,2-*c*]coumarins with a very broad substrate scope in excellent yields. Notably, this method also provides

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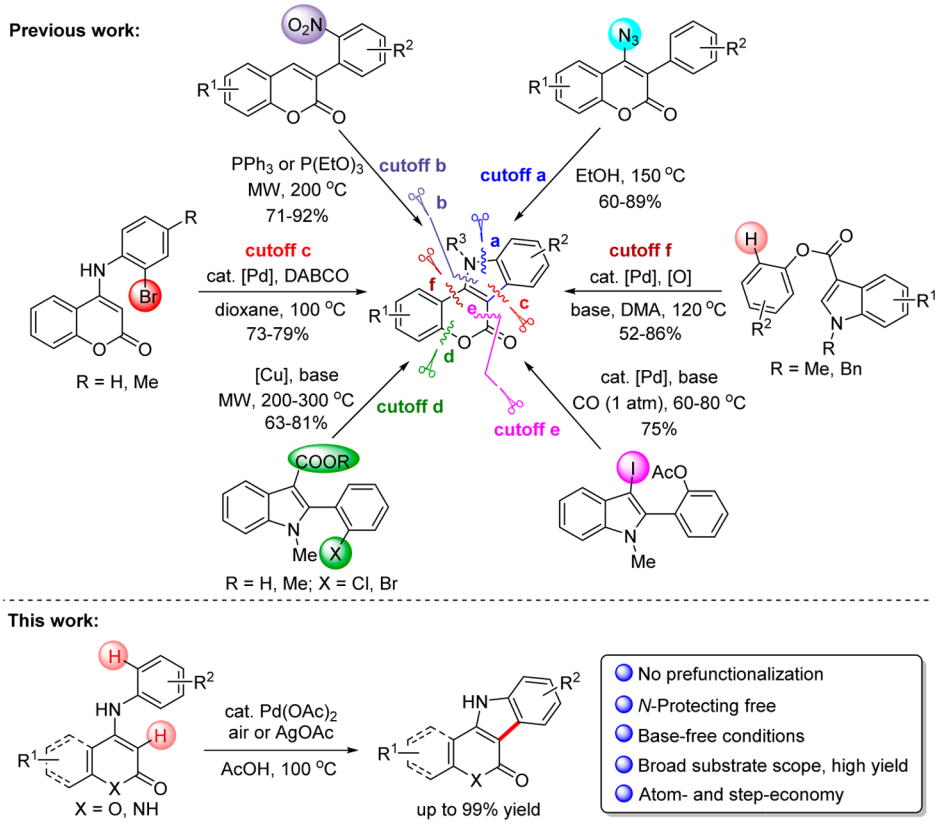
Scheme 1. Synthetic Routes of Indolo[3,2-*c*]coumarins through Different Cutoffs

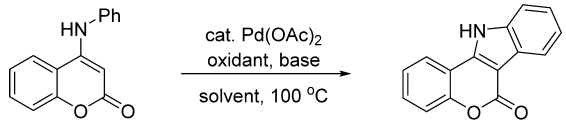


efficient access to other interesting units including indole-quinolinones and indole-pyrones (Scheme 1).

Although the previous standard conditions for synthesis of coumestans, with $Pd(OAc)_2$ as the catalyst, AgOAc as the oxidant, CsOAc as the additive, and PivOH as the solvent, are applicable to the intramolecular dehydrogenative coupling of 4-aniline coumarin **1a** to provide indolo[3,2-*c*]coumarin **2a** (Table 1, entry 1), the yields for other substituted substrates are less satisfactory. To improve the reaction generality, we thus commenced further optimization studies to determine the influence of various reaction parameters. The results are summarized in Table 1. Intriguingly, the reaction proceeded smoothly under similar conditions in the absence of CsOAc, giving indolo[3,2-*c*]coumarin **2a** in a comparable 91% yield (entry 2). To our knowledge, base is typically essential in the CDC reactions,[11] and such avoidable use of a base additive has rarely been reported.[12] To our delight, changing the solvent from PivOH to inexpensive AcOH could lead to a further increase of the reaction yield to 95% (entry 3). Unfortunately, lowering the amount of AgOAc oxidant (1.5 equiv) or the loading of palladium catalyst (5 mol %) resulted in much lower conversions (entries 4 and 5). Replacing AgOAc with other oxidants such as $K_2S_2O_8$ and $Cu(OAc)_2$ failed to furnish better results, only providing moderate yields (entries 6 and 7). Notably, we were very pleased to find that air could be employed as an effective oxidant in promoting the reaction. Under an air balloon with no use of any other oxidant, the desired product **2a** was obtained in 86% yield after 48 h (entry 8). Most gratifyingly, the reaction could be greatly accelerated and the yield could be significantly improved to 95% with an increase of the catalyst loading to 15 mol % (entry 9).

With these optimized conditions in hand, we set out to evaluate the substrate scope of the reaction (Scheme 2). The substituents on the aniline moiety were first investigated. Substrates with electron-donating (Me, OMe) or electron-withdrawing (F) groups at the C2′, C3′, C4′, C5′ positions all underwent efficient intramolecular dehydrogenative coupling under the air conditions (Method A), giving the corresponding indolo[3,2-*c*]coumarin products **2b**–**2n** in mostly excellent yields. Although the presence of a meta-substituent would lead to a mixture of two regioisomers (**2i** and **2j**, **2k** and **2l**, **2m** and

Table 1. Optimization Studies[a]



1a **2a**

entry	oxidant	base	solvent	*T* (h)	yield (%)[b]
1	AgOAc	CsOAc	PivOH	6	92
2	AgOAc	–	PivOH	10	91
3	**AgOAc**	**–**	**AcOH**	**10**	**95**
4[c]	AgOAc	–	AcOH	24	72[d]
5[e]	AgOAc	–	AcOH	24	72[d]
6[f]	$K_2S_2O_8$	–	AcOH	24	86
7[f]	$Cu(OAc)_2$	–	AcOH	24	84
8	air	–	AcOH	48	86
9[g]	**air**	**–**	**AcOH**	**28**	**95**

[a]Reaction conditions: **1a** (0.20 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (2 equiv), and base (2 equiv) in 1.0 mL of solvent at 100 °C unless otherwise noted. [b]Isolated yields. [c]1.5 equiv of AgOAc. [d]NMR yield. [e]5 mol % of $Pd(OAc)_2$. [f]3 equiv of oxidant. [g]15 mol % of $Pd(OAc)_2$.

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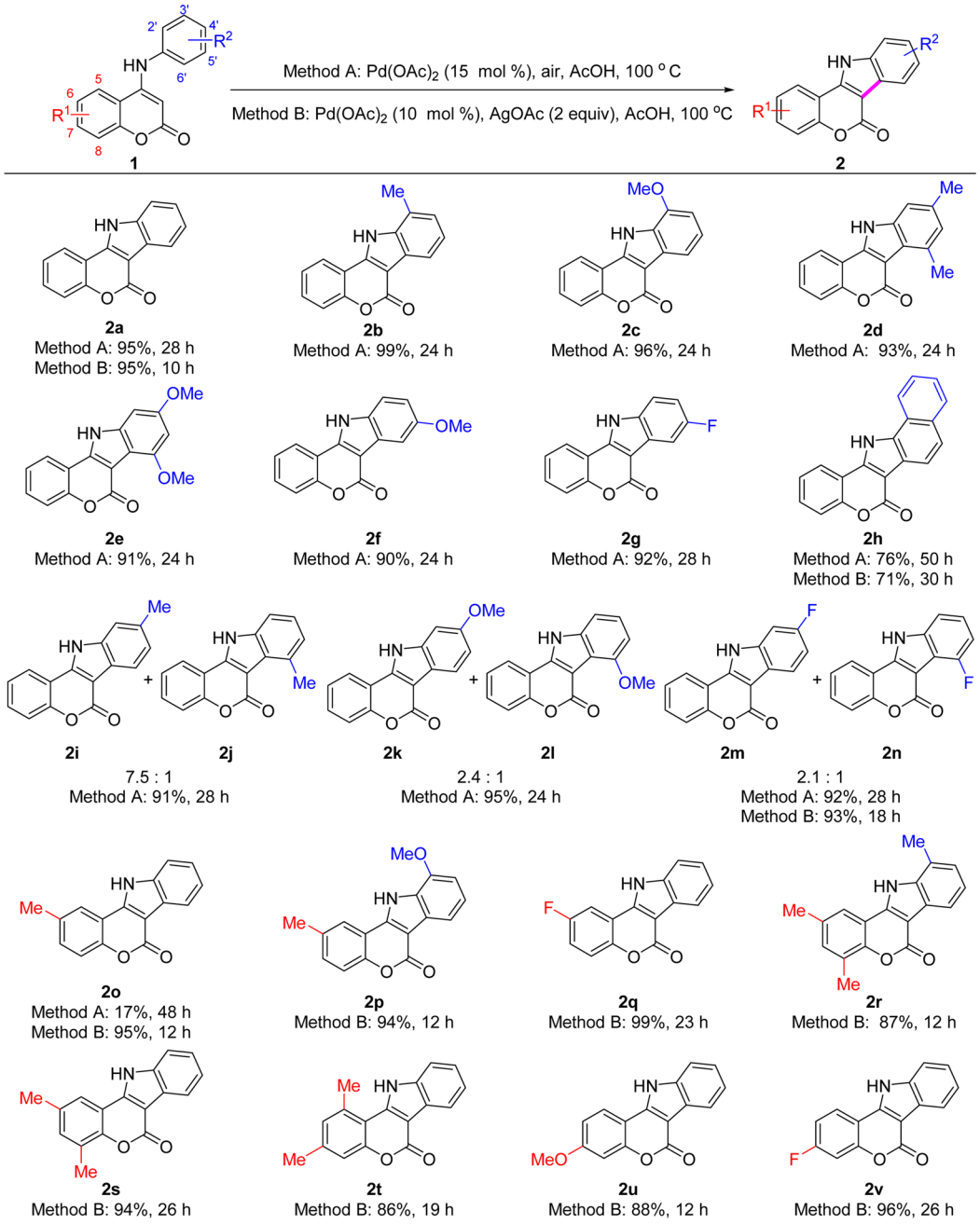
Scheme 2. Substrate Scope of 4-Ayrlamino Coumarins[a]



[a]Reaction conditions for Method A: **1** (0.20 mmol) and $Pd(OAc)_2$ (15 mol %) in 1.0 mL of AcOH at 100 °C; Method B: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol %), and AgOAc (0.40 mmol, 2 equiv) in 1.0 mL of AcOH at 100 °C.

2n) with a preference for the less hindered products (**2i**, **2k**, and **2m**), the total yields remain high (91−95% yield).[13] However, the use of the same conditions for substrate with a methyl group at the C6 position led to a dramatic drop in product yield (**2o**, 17%), suggesting a significant impact of substitution on the coumarin moiety. Fortunately, we found that the transformation proceeded well in the presence of AgOAc under the conditions shown in entry 3 of Table 1 (Method B), giving **2o** in 95% yield. Moreover, the reaction time could be shortened to 12 h. As illustrated in Scheme 2, a variety of substituents were well tolerated, regardless of their position on the phenyl ring of coumarin. The desired products **2p**−**2v** could be easily accessed in satisfactory yields (86−99%). Notably, compounds **1p** and **1r** bearing substituents on both the aniline and coumarin moieties were found to be equally suitable substrates, furnishing products **2p** and **2r** in 94% and 87% yields.

To demonstrate the synthetic generality of this intramolecular dehydrogenative coupling protocol, we next turned our attention to the construction of other indole-fused polycyclic ring systems. Indolo[3,2-*c*]quinolinones[14] and indolo[3,2-*c*]pyrones[15] are important scaffolds that often exhibit interesting bioactivities; they also serve as useful building blocks for natural products syntheses.[16] The key strategies for the synthesis of indolo[3,2-*c*]quinolinones include the use of Fischer indolization[14a] to construct the indole ring,

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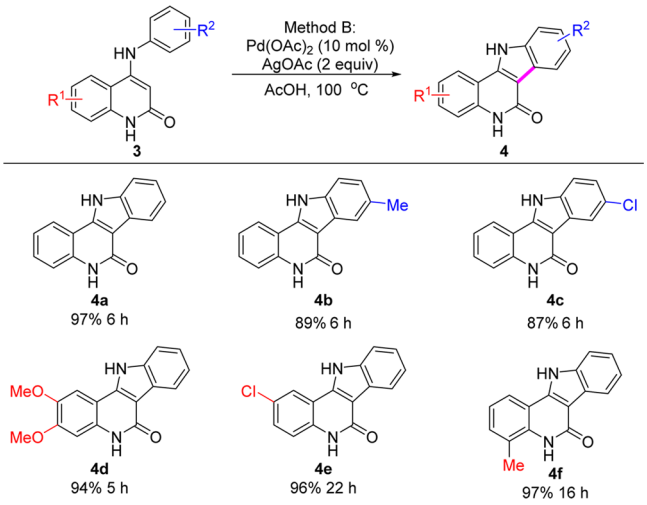
and intramolecular arylation,[17] Heck cyclization,[18] or lactamization[19] to assemble the quinolinone ring. In contrast, the synthetic approaches for indolo[3,2-*c*]pyrones are much less documented and only limited to the pathway of pyrone ring formation.[15,20] Not surprisingly, most of these existing protocols for indolo[3,2-*c*]quinolinones and indolo[3,2-*c*]-pyrones rely on the prefunctionalized substrates and offer limited scope. Inspired by the above success, we anticipated that this CDC strategy may be equally applicable to the synthesis of indolo[3,2-*c*]quinolinones and indolo[3,2-*c*]-pyrones.

To our delight, the reactions of readily available 4-aniline quinolinones **3** in the presence of AgOAc under the above latter conditions led to the formation of indolo[3,2-*c*]-quinolinone products **4a–f** in very good yields (87–97%) (Scheme 3). Substrates with different substitution patterns on

Scheme 3. Synthesis of Indolo[3,2-*c*]quinolinones[a]



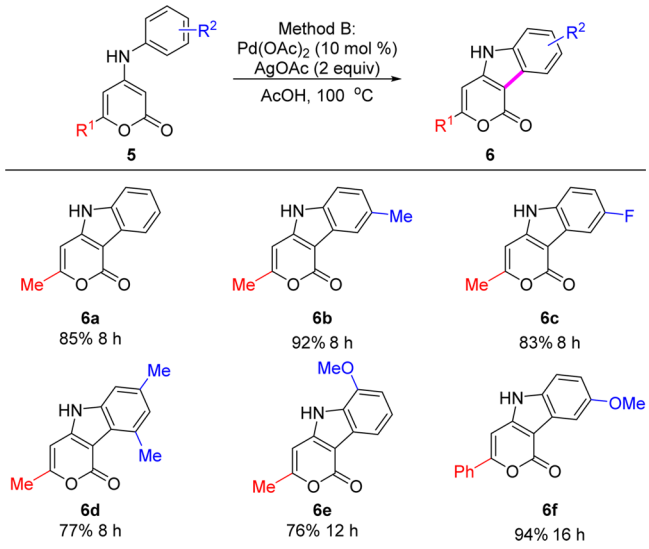
[a]Reaction conditions for Method B: **3** (0.20 mmol), $Pd(OAc)_2$ (10 mol %), and AgOAc (0.40 mmol, 2 equiv) in 1.0 mL of AcOH at 100 °C.

the benzene rings of both the aniline and quinolinone moieties can be efficiently converted into the corresponding products **4b–f**. In particular, the chloro-substituent on either ring was tolerated (**4c** and **4e**), leaving a space for further structural elaboration. It is also worth noting that protecting-group-free synthesis is challenging and direct access to such *N*-unprotected indolo[3,2-*c*]quinolinones is difficult using existing methods.[16b,17,18,21]

Similarly, 4-aniline pyrone can be subjected to efficient intramolecular cross dehydrogenative coupling (**6a**, 85% yield) under the palladium/AgOAc catalytic system (Scheme 4). The variant of substituents such as Me, OMe, F, and Ph on both the aniline and pyrone moieties can tolerate the reaction conditions well. Pleasingly, a range of high value, tricyclic indolo[3,2-*c*]pyrone products (**6b–6f**) can be easily prepared in good yields (76–94%).

In summary, we have developed an efficient Pd-catalyzed intramolecular cross dehydrogenative coupling reaction of readily available anilines for the direct synthesis of indole-fused polyheterocycles. The base-free mild catalytic system is capable of tolerating a broad scope of diversely substituted substrates, allowing facile access to a variety of biologically valuable *N*-unprotected indolo[3,2-*c*]coumarins, indolo[3,2-*c*]quinolinones, and indolo[3,2-*c*]pyrones in good to excellent yields (up to 99%). This protocol is thus practical and attractive; we expect that this work would facilitate biological and drug discovery studies of indole-based polyheterocycles.

Scheme 4. Synthesis of Indolo[3,2-*c*]pyrones[a]



[a]Reaction conditions for Method B: **5** (0.20 mmol), $Pd(OAc)_2$ (10 mol %), and AgOAc (0.40 mmol, 2 equiv) in 1.0 mL of AcOH at 100 °C.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on spectrometers (300 MHz for ^1H and 125 or 150 MHz for ^{13}C) . Chemical shifts are reported in δ ppm referenced to chloroform-*d* (δ 7.26), DMSO-*d* (δ 2.5) for ^1H NMR and chloroform-*d* (δ 77.16), DMSO-*d* (δ 39.52) for ^{13}C NMR. HRMS were recorded on a Q-TOF mass spectrometer with ESI resource or Magnetic Sector for EI. Melting point determinations were performed by the open capillary method. The substrates **1**,[22a] **3**,[22b] and **5**[22c] were prepared following the literature procedure, and copies of their NMR spectra can be found in the Supporting Information (SI).

General Procedures for Intramolecular CDC Reaction To Access Indole-Fused Polyheterocycles 2, 4, and 6. Method A: Compound **1** (0.2 mmol, 1.0 equiv) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 15 mol %) were combined in AcOH (1.0 mL) under air (balloon). Then the reaction mixture was heated to 100 °C for 24–50 h with the progress monitored by TLC (CH_2Cl_2/MeOH = 100/1 as the mobile phase). When completed, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. Then excess $NaHCO_3$(aq.) was added to neutralize AcOH. After stirring the mixture for 10 min, the residue was washed with aqueous $NaHCO_3$. The isolated organic layer was dried over Na_2SO_4. After removal of solvent, the residue was purified by silica gel column chromatography with CH_2Cl_2/MeOH as the eluent (80/1 to 40/1) to give desired product **2**.

Method B: To a 10 mL reaction tube was added compound **1**/**3**/**5** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), AgOAc (66.4 mg, 0.4 mmol, 2 equiv), and AcOH (1.0 mL). Then the reaction mixture was heated to 100 °C for 5–26 h with the progress monitored by TLC (CH_2Cl_2/MeOH = 100/1 as the mobile phase for substrate **1**; CH_2Cl_2/MeOH = 40/1 as the mobile phase for substrates **3** and **5**). The workup procedure is the same as Method A. CH_2Cl_2/MeOH was used as the eluent (80/1 to 40/1) for silica gel column chromatography to give desired products **2**, **4**, and **6**.

*Chromeno[4,3-b]indol-6(11H)-one (**2a**).*[23] Light yellow solid, 43.2 mg, 95%; mp >300 °C; ^1H NMR (300 MHz, DMSO) δ 13.02 (s, 1H),

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8.21 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.69−7.60 (m, 2H), 7.55−7.31 (m, 4H).

10-Methylchromeno[4,3-b]indol-6(11H)-one (**2b**). Light yellow solid, 49.2 mg, 99%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.58 (s, 1H), 8.44 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.66−7.46 (m, 3H), 7.27−7.20 (m, 2H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.9, 152.6, 141.6, 137.3, 130.7, 125.4, 124.2, 124.1, 123.1, 122.5, 122.1, 117.7, 117.2, 113.3, 100.5, 17.0; HRMS (EI): m/z calcd for $C_{16}H_{11}NO_2$ $[M]^+$: 249.0790; found: 249.0794.

10-Methoxychromeno[4,3-b]indol-6(11H)-one (**2c**).[9] Light yellow solid, 51.1 mg, 96%; mp 285−287 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.11 (s, 1H), 8.48 (d, J = 7.6 Hz, 1H), 7.64−7.50 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 7.27 (dd, J = 7.5, 6 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 158.0, 152.6, 146.4, 141.3, 130.7, 127.8, 125.7, 124.3, 123.3, 123.2, 117.1, 113.4, 112.6, 105.5, 100.6, 55.5; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{10}NO_3$: 264.0666; found: 264.0663.

7,9-Dimethylchromeno[4,3-b]indol-6(11H)-one (**2d**).[9] Yellow solid, 48.9 mg, 93%. mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.84 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.62−7.41 (m, 3H), 7.22 (s, 1H), 6.89 (s, 1H), 2.89 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.7, 152.4, 141.6, 138.7, 134.5, 131.3, 130.4, 125.8, 124.0, 122.4, 121.5, 116.7, 113.0, 109.6, 100.6, 21.6, 21.1; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{17}H_{12}NO_2$: 262.0874; found: 262.0868.

7,9-Dimethoxychromeno[4,3-b]indol-6(11H)-one (**2e**). Light yellow solid, 53.6 mg, 91%; mp 290−292 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.81 (s, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.57−7.38 (m, 3H), 6.67 (d, J = 1.4 Hz, 1H), 6.41 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.1, 156.0, 154.6, 152.3, 140.4, 140.1, 129.9, 123.9, 122.0, 116.6, 112.9, 108.4, 100.3, 94.3, 87.7, 55.6, 55.4; HRMS (EI): m/z calcd for $C_{17}H_{13}NO_4$ $[M]^+$: 295.0845; found: 295.0844.

8-Methoxychromeno[4,3-b]indol-6(11H)-one (**2f**). Yellow solid, 47.8 mg, 90%; mp 298−299 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.89 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.65−7.39 (m, 5H), 7.08−6.95 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 158.0, 155.6, 152.6, 141.7, 132.4, 130.6, 125.2, 124.3, 122.5, 117.2, 114.6, 113.3, 101.8, 99.8, 55.4; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{10}NO_3$: 264.0666; found: 264.0661.

8-Fluorochromeno[4,3-b]indol-6(11H)-one (**2g**).[9] Light yellow solid, 46.6 mg, 92%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.14 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 11.9, 8.7 Hz, 3H), 7.53−7.44 (m, 2H), 7.25 (dd, J = 9.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 158.5 (d, J_{CF} = 235.0 Hz), 157.7, 152.8, 143.1, 134.3, 131.1, 125.0 (d, J_{CF} = 11.3 Hz), 124.4, 122.8, 117.3, 113.8(d, J_{CF} = 10.0 Hz), 113.0, 112.8 (d, J_{CF} = 25.0 Hz), 105.2 (d, J_{CF} = 25.0 Hz), 100.1 (d, J_{CF} = 3.8 Hz); HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{15}H_7FNO_2$: 252.0466; found: 252.0459.

Benzo[g]chromeno[4,3-b]indol-6(13H)-one (**2h**). Light brown solid, 43.3 mg, 76%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.47 (s, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 7.7 Hz, 1H), 8.12 (dd, J = 16.8, 8.2 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.78−7.73 (m, 1H), 7.67−7.51 (m, 4H); ^{13}C NMR (125 MHz, DMSO) δ 158.1, 152.3, 139.8, 133.2, 131.0, 130.3, 128.8, 126.5, 125.4, 124.4, 123.3, 122.6, 121.5, 121.3, 120.6, 119.1, 117.2, 113.5, 101.7; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{19}H_{10}NO_2$: 284.0717; found: 284.0711.

9-Methylchromeno[4,3-b]indol-6(11H)-one (**2i**). Light yellow solid; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.86 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 11.1, 3.8 Hz, 1H), 7.52−7.44 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 157.9, 152.6, 141.5, 138.2, 134.4, 130.6, 124.3, 124.0, 122.6, 122.1, 119.9, 117.2, 113.3, 112.3, 100.0, 21.5; HRMS (EI): m/z calcd for $C_{16}H_{11}NO_2$ $[M]^+$: 249.0790; found: 249.0785.

7-Methylchromeno[4,3-b]indol-6(11H)-one (**2j**). Light yellow solid; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.01 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.52−7.44 (m, 3H), 7.31−7.26 (m, 1H), 7.06 (d, J = 7.4 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 157.8, 152.6, 142.1, 138.3, 131.8, 130.8, 125.1, 124.2, 124.1, 123.8, 122.6, 116.8, 112.9, 109.9, 100.7, 21.9; HRMS (EI): m/z calcd for $C_{16}H_{11}NO_2$ $[M]^+$: 249.0790; found: 249.0785.

9-Methoxychromeno[4,3-b]indol-6(11H)-one (**2k**). Light yellow solid; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.86 (s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.61−7.56 (m, 1H), 7.52−7.42 (m, 2H), 7.10 (s, 1H), 6.97 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.9, 157.8, 152.4, 141.1, 139.0, 130.3, 124.3, 122.3, 120.9, 118.1, 117.1, 113.3, 111.9, 100.2, 95.8, 55.5; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{10}NO_3$: 264.0666; found: 264.0660.

9-Fluorochromeno[4,3-b]indol-6(11H)-one (**2m**). Light yellow solid; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.25 (s, 1H), 8.22 (d, J = 7.7 Hz, 1H), 8.00 (dd, J = 8.5, 5.6 Hz, 1H), 7.70−7.57 (m, 1H), 7.54−7.47 (m, 3H), 7.23−7.16 (m, 1H); ^{13}C NMR (150 MHz, DMSO) δ 160.4 (d, J_{CF} = 238.5 Hz), 157.7, 152.6, 142.7, 138.2 (d, J_{CF} = 13.5 Hz), 130.9, 124.5, 122.7, 121.4 (d, J_{CF} = 10.5 Hz), 121.0, 117.3, 113.0, 110.8 (d, J_{CF} = 24.0 Hz), 100.0, 99.2 (d, J_{CF} = 25.5 Hz); HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{15}H_7FNO_2$: 252.0466; found: 252.0461.

2-Methylchromeno[4,3-b]indol-6(11H)-one (**2o**). Yellow solid, 47.3 mg, 95%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.94 (s, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.98 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.42−7.38 (m, 3H), 7.34−7.27 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 158.0, 150.9, 141.8, 137.8, 133.5, 131.6, 124.7, 124.4, 122.4, 122.3, 120.2, 116.9, 112.8, 112.4, 100.0, 20.6; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{10}NO_2$: 248.0717; found: 248.0710.

10-Methoxy-2-methylchromeno[4,3-b]indol-6(11H)-one (**2p**). Light yellow solid, 52.5 mg, 94%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.98 (s, 1H), 8.28 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.36 (s, 2H), 7.24 (dd, J = 7.5, 7.5 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 4.02 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 158.1, 150.8, 146.4, 141.3, 133.4, 131.4, 127.7, 125.8, 123.2, 123.0, 116.8, 113.0, 112.5, 105.5, 100.5, 55.5, 20.6; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{17}H_{12}NO_3$: 278.0823; found: 278.0824.

2-Fluorochromeno[4,3-b]indol-6(11H)-one (**2q**). Light yellow solid, 50.4 mg, 99%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.01 (s, 1H), 8.03 (dd, J = 11.3, 5.3 Hz, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.59 (dd, J = 9.1, 4.6 Hz, 1H), 7.52−7.41 (m, 2H), 7.38−7.33 (m, 1H); ^{13}C NMR (125 MHz, DMSO) δ 158.0 (d, J_{CF} = 238.8 Hz), 157.6, 149.0, 140.9, 137.7, 125.0, 124.1, 122.5, 120.3, 119.2 (d, J_{CF} = 8.8 Hz), 117.8 (d, J_{CF} = 23.8 Hz), 114.0 (d, J_{CF} = 10.0 Hz), 112.5, 108.3 (d, J_{CF} = 26.3 Hz), 100.4; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{15}H_7FNO_2$: 252.0466; found: 252.0462.

2,4,10-Trimethylchromeno[4,3-b]indol-6(11H)-one (**2r**). Light yellow solid, 48.4 mg, 87%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.43 (s, 1H), 8.08 (s, 1H), 7.86 (d, J = 6.3 Hz, 1H), 7.29 (s, 1H), 7.25−7.20(m, 2H), 2.63 (s, 3H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 158.0, 149.1, 142.0, 137.3, 132.7, 125.6, 125.3, 124.1, 122.4, 122.0, 120.4, 117.7, 112.6, 100.3, 20.5, 17.0, 15.7; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{18}H_{14}NO_2$: 276.1030; found: 276.1025.

2,4-Dimethylchromeno[4,3-b]indol-6(11H)-one (**2s**). Light yellow solid, 49.4 mg, 94%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.90 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.43−7.38 (m, 1H), 7.35−7.29 (m, 2H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.9, 149.2, 142.2, 137.8, 132.8, 125.7, 124.6, 124.4, 122.2, 120.2, 112.0, 112.5, 112.3, 99.9, 20.5, 15.7; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{17}H_{12}NO_2$: 262.0874; found: 262.0868.

1,3-Dimethylchromeno[4,3-b]indol-6(11H)-one (**2t**). Light yellow solid, 45.3 mg, 86%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.79 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.41−7.30 (m, 2H), 7.16 (s, 1H), 7.04 (s, 1H), 2.84 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 157.9, 153.5, 141.4, 140.4, 138.1, 133.9, 127.5, 124.3, 123.7, 122.4, 119.8, 115.4, 113.2, 110.1, 100.0, 22.0, 20.9; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{17}H_{12}NO_2$: 262.0874; found: 262.0866.

3-Methoxychromeno[4,3-b]indol-6(11H)-one (**2u**).[2a] Light yellow solid, 46.8 mg, 88%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.84 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.62

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J. Org. Chem. 2016, 81, 11501−11507

(d, J = 7.9 Hz, 1H), 7.40−7.28 (m, 2H), 7.11−7.07 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.6, 158.0, 154.5, 142.6, 137.6, 124.5, 124.3, 123.7, 122.2, 119.9, 112.24, 112.20, 106.2, 101.6, 98.1, 55.8.

3-Fluorochromeno[4,3-b]indol-6(11H)-one (**2v**). Light yellow solid, 49.4 mg, 96%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.04 (s, 1H), 8.28−8.23 (m, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 9.9 Hz, 1H), 7.45−7.32 (m, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.0 (d, J_{CF} = 246.3 Hz), 157.5, 153.8 (d, J_{CF} = 13.8 Hz), 141.5, 137.6, 124.7, 124.5 (d, J_{CF} = 11.3 Hz), 124.2, 122.4, 120.1, 112.4, 112.2 (d, J_{CF} = 22.5 Hz), 110.2, 104.8 (d, J_{CF} = 26.3 Hz), 99.0; HRMS (EI): m/z calcd for $C_{15}H_8NFO_2$ $[M]^+$: 253.0539; found: 253.0535.

5,11-Dihydro-6H-indolo[3,2-c]quinolin-6-one (**4a**).[24] Light yellow solid, 45.2 mg, 97%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.55 (s, 1H), 11.42 (s, 1H), 8.20 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.54−7.45 (m, 2H), 7.37 (dd, J = 7.7, 7.5 Hz, 1H), 7.28 (q, J = 7.9 Hz, 2H).

8-Methyl-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (**4b**).[25] Yellow solid, 43.9 mg, 89%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.41 (s, 1H), 11.38 (s, 1H), 8.17 (d, J = 7.9 Hz, 1H), 8.01 (s, 1H), 7.51−7.43 (m, 3H), 7.27 (dd, J = 6.9, 6.9 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 2.47 (s, 3H).

8-Chloro-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (**4c**).[25] Yellow solid, 46.7 mg, 87%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.74 (s, 1H), 11.50 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.14 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.56−7.46 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.31 (dd, J = 7.4, 7.4 Hz, 1H).

2,3-Dimethoxy-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (**4d**). Light gray solid, 55.8 mg, 94%; mp 282−285 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.19 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.34−7.20 (m, 2H), 7.04 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.7, 150.8, 144.7, 141.4, 137.6, 133.3, 124.7, 123.4, 120.8, 120.4, 111.4, 105.0, 104.4, 103.9, 98.9, 55.8, 55.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{14}N_2NaO_3$: 317.0897; found: 317.0890.

2-Chloro-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (**4e**).[26] Light yellow solid, 52.0 mg, 96%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.58 (s, 1H), 11.55 (s, 1H), 8.32 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 8.8, 1.9 Hz, 1H), 7.48−7.37 (m, 2H), 7.28 (dd, J = 7.5, 7.5 Hz, 1H).

4-Methyl-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (**4f**). Light green solid, 48.6 mg, 97%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.52 (s, 1H), 10.43 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.7, 2.8 Hz, 2H), 7.25 (dd, J = 15.9, 7.8 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 160.0, 141.2, 137.8, 136.3, 130.6, 124.4, 124.3, 124.0, 121.3, 121.0, 120.8, 120.1, 112.0, 111.7, 106.2, 17.9; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{16}H_{11}N_2O$: 247.0877; found: 247.0875.

3-Methylpyrano[4,3-b]indol-1(5H)-one (**6a**). Yellow solid, 34.0 mg, 85%; mp 252−253 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.13 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.34−7.23 (m, 2H), 6.66 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.9, 159.2, 146.1, 137.3, 124.0, 123.7, 121.9, 119.7, 112.1, 98.0, 95.3, 19.8; HRMS (EI): m/z calcd for $C_{12}H_9NO_2$ $[M]^+$: 199.0633; found: 199.0632.

3,8-Dimethylpyrano[4,3-b]indol-1(5H)-one (**6b**). Yellow solid, 34.2 mg, 92%; mp 280−282 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.01 (s, 1H), 7.71 (s, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.62 (s, 1H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.6, 159.2, 146.0, 135.5, 130.8, 125.3, 124.0, 119.5, 111.7, 97.7, 95.3, 21.1, 19.7; HRMS (EI): m/z calcd for $C_{13}H_{11}NO_2$ $[M]^+$: 213.0790; found: 213.0789.

8-Fluoro-3-methylpyrano[4,3-b]indol-1(5H)-one (**6c**). Yellow solid, 36.0 mg, 83%; mp 279−280 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.21 (s, 1H), 7.56−7.50 (m, 2H), 7.19−7.12 (m, 1H), 6.65 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 160.4, 158.3 (d, J_{CF} = 234.3 Hz), 158.9, 147.2, 133.9, 124.5 (d, J_{CF} = 11.0 Hz), 113.3 (d, J_{CF} = 9.5 Hz), 111.8 (d, J_{CF} = 25.4 Hz), 104.8 (d, J_{CF} = 24.6 Hz), 98.2 (d, J_{CF} = 4.1 Hz), 95.3, 19.8; HRMS (EI): m/z calcd for $C_{12}H_8FNO_2$ $[M]^+$: 217.0539; found: 217.0538.

3,7,9-Trimethylpyrano[4,3-b]indol-1(5H)-one (**6d**). Yellow solid, 34.8 mg, 77%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.97 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H), 6.56 (s, 1H), 2.84 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.7, 146.6, 138.6, 134.1, 131.2, 125.6, 121.3, 109.8, 99.0, 95.5, 21.7, 21.5, 20.0; HRMS (EI): m/z calcd for $C_{14}H_{13}NO_2$ $[M]^+$: 227.0946; found: 227.0948.

6-Methoxy-3-methylpyrano[4,3-b]indol-1(5H)-one (**6e**). Yellow solid, 34.8 mg, 76%; mp 263−265 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.27 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.19 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.56 (s, 1H), 3.97 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.6, 159.3, 146.1, 145.6, 127.0, 125.1, 122.7, 112.2, 105.0, 98.5, 95.3, 55.4, 19.7; HRMS (EI): m/z calcd for $C_{13}H_{11}NO_3$ $[M]^+$: 229.0739; found: 229.0738.

8-Methoxy-3-phenylpyrano[4,3-b]indol-1(5H)-one (**6f**).[20a] Light brown solid, 54.9 mg, 94%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.20 (s, 1H), 7.97 (d, J = 7.0 Hz, 2H), 7.57−7.48 (m, 4H), 7.44−7.41 (m, 2H), 6.99 (dd, J = 8.9, 1.9 Hz, 1H), 3.84 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02160.

^{1}H and ^{13}C NMR spectra of the substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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