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

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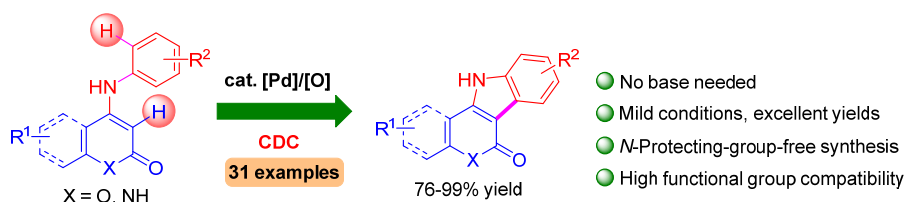
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Abstract

A base-free process to access indole-fused polyheterocycles via a highly efficient and atom-economic palladium-catalyzed intramolecular cross dehydrogenative 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%).

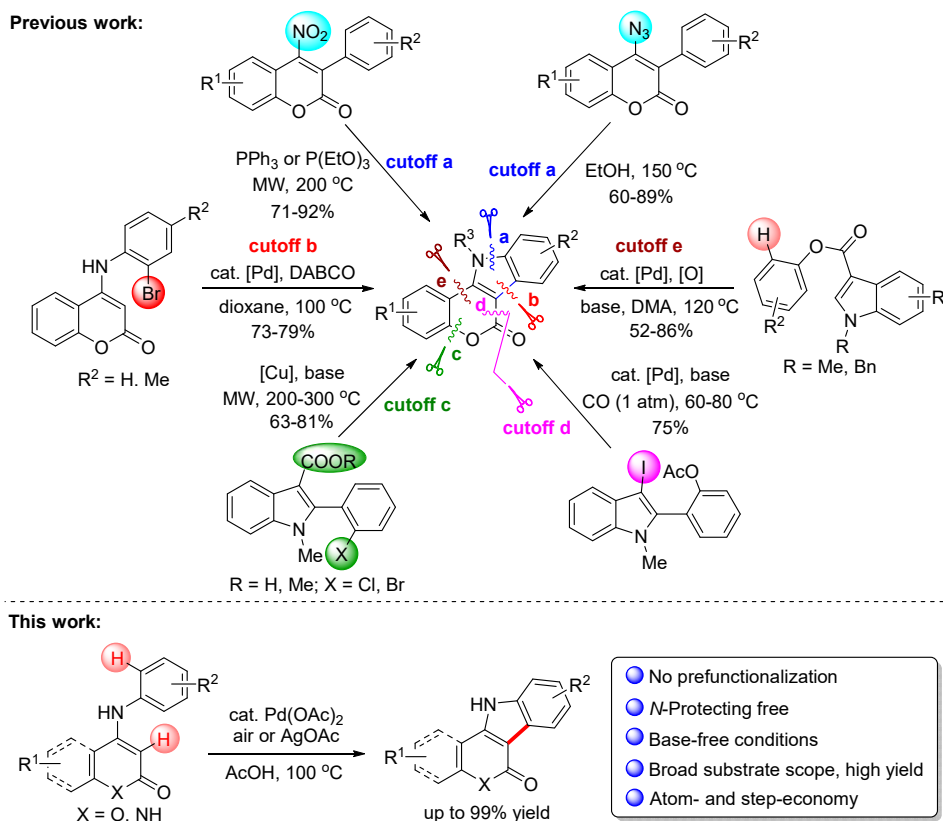
Indole and coumarin skeletons are recognized as two important classes of structural motifs distributed in a number of natural products which exhibit a broad range of biological and pharmaceutical activities. Design of new molecules by combination of

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4 different pharmacophores is of great interest in medicinal chemistry and drug discovery.
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7 Indolo[3,2-*c*]coumarin with fused cyclic ring system containing both indole and
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10 coumarin components belongs to an intriguing family of structurally unique
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12 polyheterocycles having interesting biological profile such as anti-tumor angiogenesis
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14 and estrogenic activity.¹ Accordingly, there have been significant interests in
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16 developing useful methodologies for construction of this fused polycyclic skeleton.
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18 Among them, the most conventional method is the intramolecular thermal cyclization
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20 of 4-azido-3-aryl coumarins to form the indole ring under harsh reaction conditions
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22 (150 °C), which inevitably requires the use of highly toxic NaN₃ to synthesize the
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24 cyclization precursor (Scheme 1, right cutoff a).² Alternatively, 4-nitro-3-aryl
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26 coumarins can be employed as substrates for reductive cyclization *via* microwave-
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28 assisted Cadogan reaction at high temperature (200 °C) (Scheme 1, left cutoff a).³ In
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30 recent years, several new methods mediated by transition-metal salts or complexes have
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32 been successfully developed. For example, Hong reported an intramolecular Heck
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34 cyclization approach to construct the indole ring from pre-bromo-functionalized 4-
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36 aniline coumarins utilizing a special cobalt-sandwich diphosphine chelated palladium
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38 catalyst (cutoff b).⁴ Thasana and co-workers disclosed a Cu(I)-mediated microwave-
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40 assisted intramolecular lactonization method capable of producing indolo[3,2-
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42 *c*]coumarins (cutoff c),⁵ while Larock et al. developed a Pd-catalyzed lactonization via
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44 CO insertion using an acetoxy group as the nucleophile (cutoff d).⁶ Most recently, an
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46 efficient Pd-catalyzed intramolecular oxidative C-H/C-H coupling protocol was
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48 realized by Lan and You with indole-3-carboxylates as reaction substrates (cutoff e).⁷
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4 While these methods are useful for synthesis of valuable indolo[3,2-*c*]coumarins, they
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7 mainly rely on the manipulation of prefunctionalized substrate and overall require
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10 multi-step transformations. Moreover, most of them suffer from harsh reaction
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12 conditions, limited substrate scope, poor functional-group compatibility and require
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14 protection of indole NH. From the perspective of atom-economy and step-efficiency,
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17 an ideal synthesis would involve an efficient ring construction *via* direct C-H coupling
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19
20 without prefunctionalization and *N*-protection.
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23 In the past few years, the cross dehydrogenative coupling (CDC) protocol has
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25 received considerable attention as it allows C-C bond formation by directly connecting
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27 two different C-H bonds.⁸ Recently, we reported the development of a Pd-catalyzed
28
29 efficient intramolecular CDC approach for facile construction of coumestans from
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31 readily available 4-aryloxy coumarins.⁹ Our preliminary study indicates that this
32
33 strategy is also applicable for the synthesis of indolo[3,2-*c*]coumarins, however, the
34
35 reaction yield varies depending on the substitution pattern of substrates. Continuing our
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37 interest in the nitrogen-containing polyheterocycles¹⁰ for a drug discovery program, we
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39 envisioned to develop a more general synthetic approach toward structurally diverse
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41 indole-fused polycyclic motifs. Herein we disclose our success on the improvement of
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43 this promising intramolecular CDC reaction to construct indolo[3,2-*c*]coumarins with
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45 a very broad substrate scope in excellent yields. Notably, this method also provides
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47 efficient access to other interesting units including indole-quinolinones and indole-
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49 pyrones (Scheme 1).
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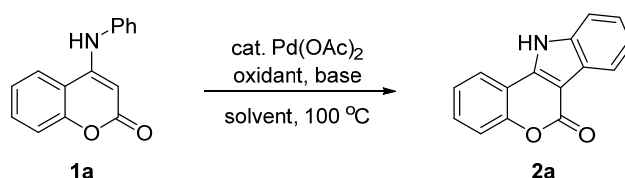
Scheme 1. Synthetic Routes of Indolo[3,2-*c*]coumarins through Different Cutoffs.



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, is 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 our 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 base additive has rarely been reported.¹² To our delight, changing the solvent from PivOH to

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4 inexpensive AcOH could lead to a further increase of the reaction yield to 95% (entry
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6
7 3). Unfortunately, lowering the amount of AgOAc oxidant (1.5 equiv) or the loading of
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9
10 palladium catalyst (5 mol%) resulted in much lower conversions (entries 4 and 5).
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12 Replacing AgOAc with other oxidants such as K₂S₂O₈ and Cu(OAc)₂ failed to furnish
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14 better results, only providing moderate yields (entries 6 and 7). Notably, we were very
15
16 pleased to find that air could be employed as effective oxidant in promoting the reaction.
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18 Under an air balloon with no use of any other oxidant, the desired product **2a** was
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20 obtained in 86% yield after 48 h (entry 8). Most gratifyingly, the reaction could be
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22 greatly accelerated and the yield could be significantly improved to 95% with increase
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28 of the catalyst loading to 15 mol % (entry 9).

33 **Table 1.** Optimization Studies.^a



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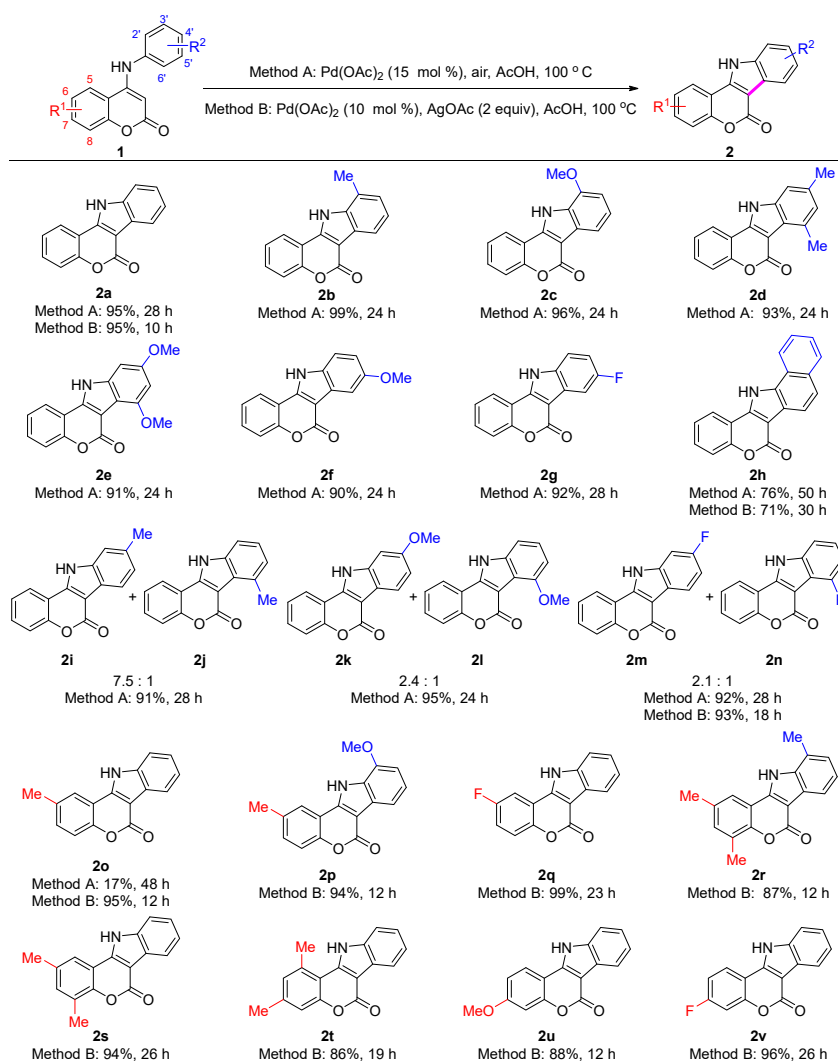
entry	oxidant	base	solvent	<i>T</i> (h)	yield(%) ^b
1	AgOAc	CsOAc	PivOH	6	92
2	AgOAc	--	PivOH	10	91
3	AgOAc	--	AcOH	10	95
4 ^c	AgOAc	--	AcOH	24	72 ^d
5 ^e	AgOAc	--	AcOH	24	72 ^d
6 ^f	K ₂ S ₂ O ₈	--	AcOH	24	86
7 ^f	Cu(OAc) ₂	--	AcOH	24	84
8	air	--	AcOH	48	86
9^g	air	--	AcOH	28	95

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4 ^aReaction conditions: **1a** (0.20 mmol), Pd(OAc)₂ (10 mol %), oxidant (2 equiv) and
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6
7 base (2 equiv) in 1.0 mL of solvent at 100 °C unless otherwise noted. ^bIsolated yields.
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10 ^c1.5 equiv of AgOAc. ^dNMR yield. ^e5 mol % of Pd(OAc)₂. ^f3 equiv of oxidant. ^g15 mol %
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12 of Pd(OAc)₂.
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18 With these optimized conditions in hand, we set out to evaluate the substrate scope
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20 of the reaction (Scheme 2). The substituents on the aniline moiety were first
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22 investigated. Substrates with electron-donating (Me, OMe) or electron-withdrawing (F)
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24 groups at the C2', C3', C4', C5' positions all underwent efficient intramolecular
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26 dehydrogenative coupling under the air conditions (Method A), giving the
27
28 corresponding indolo[3,2-*c*]coumarin products **2b-2n** in mostly excellent yields.
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31 Although the presence of a meta-substituent would lead to a mixture of two
32
33 regioisomers (**2i** and **2j**, **2k** and **2l**, **2m** and **2n**) with a preference for the less hindered
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35 products (**2i**, **2k**, and **2m**), the total yields remain high (91-95% yield).¹³ However, the
36
37 use of the same conditions for substrate with a methyl group at the C6 position led to a
38
39 dramatic drop in product yield (**2o**, 17%), suggesting a significant impact of substitution
40
41 on the coumarin moiety. Fortunately, we found that the transformation proceeded well
42
43 in the presence of AgOAc under the conditions shown in entry 3 of Table 1 (Method
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45 B), giving **2o** in 95% yield. Moreover, the reaction time could be shortened to 12 h. As
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47 illustrated in Scheme 2, a variety of substituents were well tolerated, regardless of their
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49 position on the phenyl ring of coumarin. The desired products **2p-2v** could be easily
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51 accessed in satisfactory yields (86-99%). Notably, compounds **1p** and **1r** bearing
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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.

Scheme 2. Substrate Scope of 4-Arylamino Coumarins.^a



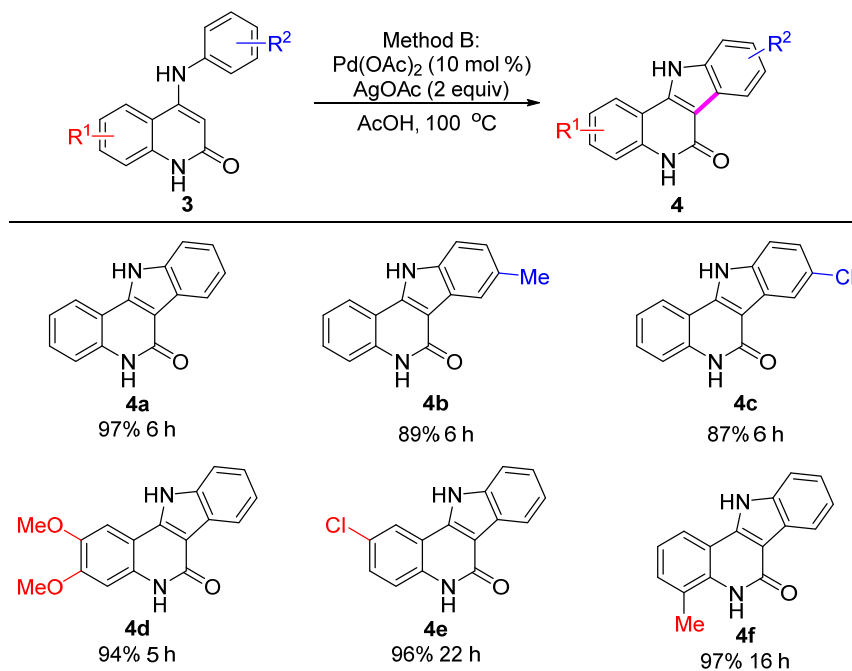
^aReaction conditions for Method A: **1** (0.20 mmol) and Pd(OAc)₂ (15 mol %) in 1.0 mL of AcOH at 100 °C; Method B: **1** (0.20 mmol), Pd(OAc)₂ (10 mol %) and AgOAc (0.40 mmol, 2 equiv) in 1.0 mL of AcOH at 100 °C.

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 system. Indolo[3,2-*c*]quinolinones¹⁴ and indolo[3,2-*c*]pyrones¹⁵ 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

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4 indolo[3,2-*c*]quinolinones include the use of Fischer indolization^{14a} to construct the
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6 indole ring, and intramolecular arylation,¹⁷ Heck cyclization¹⁸ or lactamization¹⁹ to
7
8 assemble the quinolinone ring. In contrast, the synthetic approaches for indolo[3,2-
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10 *c*]pyrones are much less documented and only limited to the way of pyrone ring
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12 formation.^{15,20} Not surprisingly, most of these existing protocols for indolo[3,2-
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14 *c*]quinolinones and indolo[3,2-*c*]pyrones rely on the prefunctionalized substrates and
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16 offer limited scope. Inspired by the above success, we anticipated that this CDC strategy
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18 may be equally applicable to the synthesis of indolo[3,2-*c*]quinolinones and indolo[3,2-
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20 *c*]pyrones.
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28 To our delight, the reactions of readily available 4-aniline quinolinones **3** in the
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30 presence of AgOAc under the above latter conditions led to the formation of indolo[3,2-
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32 *c*]quinolinone products **4a-f** in very good yields (87-97%) (Scheme 3). Substrates with
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34 different substitution patterns on the benzene rings of both the aniline and quinolinone
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36 moieties can be efficiently converted into the corresponding products **4b-f**. In particular,
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38 the chloro-substituent on either ring was tolerated (**4c** and **4e**), leaving a space for
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40 further structural elaboration. It is also worth noting that protecting-group-free
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42 synthesis is challenging and direct access to such *N*-unprotected indolo[3,2-
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44 *c*]quinolinones are difficult using existing methods.^{16b,17,18,21}
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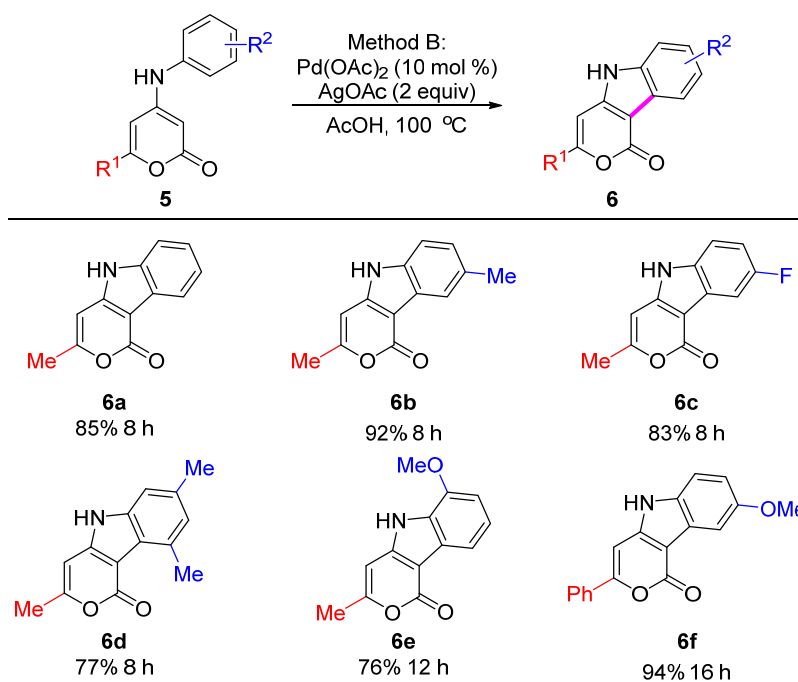
55 **Scheme 3.** Synthesis of Indolo[3,2-*c*]quinolinones.^a
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^aReaction conditions for Method B: **1** (0.20 mmol), Pd(OAc)₂ (10 mol %) and AgOAc (0.40 mmol, 2 equiv) in 1.0 mL of AcOH at 100 °C.

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

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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 substrate, 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.

56 Experimental section

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General Information. NMR spectra were recorded on spectrometers (300 MHz for ¹H and 125 MHz or 150 MHz for ¹³C). Chemical shifts are reported in δ ppm referenced

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4 to chloroform-*d* (δ 7.26) DMSO-*d* (δ 2.5) for ^1H NMR and chloroform-*d* (δ 77.16)
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6 DMSO-*d* (δ 39.52) for ^{13}C NMR. HRMS were recorded on a Q-TOF mass spectrometer
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8 with ESI resource or Magnetic Sector for EI. Melting point determinations were
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10 performed by the open capillary method. The substrates **1**,^{22a} **3**^{22b} and **5**^{22c} were prepared
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12 following the literature procedure, and their NMR spectra copies can be found in the
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14 supporting information.
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20 **General Procedures for intramolecular CDC reaction to access indole-fused**
21 **polyheterocycles 2, 4 and 6.**
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24
25 Method A: Compound **1** (0.2 mmol, 1.0 equiv) and Pd(OAc)₂ (6.7 mg, 0.03 mmol, 15
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27 mol %) were combined in AcOH (1.0 mL) under air (balloon). Then the reaction
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29 mixture was heated to 100 °C for 24-50 h with the progress monitored by TLC
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31 (CH₂Cl₂/MeOH = 100/1 as the mobile phase). When completed, the reaction mixture
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33 was cooled to room temperature and diluted with CH₂Cl₂. Then excess NaHCO₃(aq.)
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35 was added to neutralize AcOH. After stirring the mixture for 10 min, the residue was
36
37 washed with aqueous NaHCO₃. The isolated organic layer was dried over Na₂SO₄.
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39 After removal of solvent, the residue was purified by silica gel column chromatography
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41 with CH₂Cl₂/MeOH as the eluent (80/1 to 40/1) to give desired product **2**.
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49 Method B: To a 10 mL reaction tube was added compound **1/3/5** (0.2 mmol, 1.0 equiv),
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51 Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol %), AgOAc (66.4 mg, 0.4 mmol, 2 equiv) and
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53 AcOH (1.0 mL). Then the reaction mixture was heated to 100 °C for 5-26 h with the
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55 progress monitored by TLC (CH₂Cl₂/MeOH = 100/1 as the mobile phase for substrate
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57 **1**; CH₂Cl₂/MeOH = 40/1 as the mobile phase for substrates **3** and **5**). The work-up
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4 procedure is the same as Method A. CH₂Cl₂/MeOH was used as the eluent (80/1 to 40/1)
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6
7 for silica gel column chromatography to give desired products **2**, **4** and **6**.

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9 **Chromeno[4,3-*b*]indol-6(11*H*)-one (2a).**²³ Light yellow solid, 43.2 mg, 95%;
10
11 mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 13.02 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H),
12
13 8.05 (d, *J* = 7.8 Hz, 1H), 7.69-7.60 (m, 2H), 7.55-7.31 (m, 4H).
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16

17 **10-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (2b).** Light yellow solid, 49.2 mg, 99%;
18
19 mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.58 (s, 1H), 8.44 (d, *J* = 7.8 Hz, 1H),
20
21 7.88 (d, *J* = 7.9 Hz, 1H), 7.66-7.46 (m, 3H), 7.27-7.20 (m, 2H), 2.64 (s, 3H); ¹³C NMR
22
23 (125 MHz, DMSO) δ 157.9, 152.6, 141.6, 137.3, 130.7, 125.4, 124.2, 124.1, 123.1,
24
25 122.5, 122.1, 117.7, 117.2, 113.3, 100.5, 17.0; HRMS (EI): *m/z* calcd for C₁₆H₁₁NO₂
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27 [M]⁺: 249.0790; found: 249.0794.
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33 **10-Methoxychromeno[4,3-*b*]indol-6(11*H*)-one (2c).**⁹ Light yellow solid, 51.1 mg,
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35 96%; mp 285-287 °C; ¹H NMR (300 MHz, DMSO) δ 13.11 (s, 1H), 8.48 (d, *J* = 7.6 Hz,
36
37 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,
38
39 *J* = 7.9 Hz, 1H), 4.04 (s, 3H); ¹³C NMR (125 MHz, DMSO) δ 158.0, 152.6, 146.4, 141.3,
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41 130.7, 127.8, 125.7, 124.3, 123.3, 123.2, 117.1, 113.4, 112.6, 105.5, 100.6, 55.5;
42
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47 HRMS (ESI): *m/z* [M-H]⁻ calcd for C₁₆H₁₀NO₃: 264.0666; found: 264.0663.
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50 **7,9-Dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (2d).**⁹ Yellow solid, 48.9 mg, 93%.
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52 mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.84 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H),
53
54 7.62-7.41 (m, 3H), 7.22 (s, 1H), 6.89 (s, 1H), 2.89 (s, 3H), 2.42 (s, 3H); ¹³C NMR (125
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60 MHz, DMSO) δ 157.7, 152.4, 141.6, 138.7, 134.5, 131.3, 130.4, 125.8, 124.0, 122.4,

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4 121.5, 116.7, 113.0, 109.6, 100.6, 21.6, 21.1; HRMS (ESI): m/z $[M-H]^-$ calcd for
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6 $C_{17}H_{12}NO_2$: 262.0874; found: 262.0868.

7
8
9 **7,9-Dimethoxychromeno[4,3-*b*]indol-6(11*H*)-one (2e)**. Light yellow solid, 53.6 mg,
10
11 91%; mp 290-292 °C; 1H NMR (300 MHz, DMSO) δ 12.81 (s, 1H), 8.11 (d, $J = 7.5$ Hz,
12
13 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,
14
15 3H); ^{13}C NMR (125 MHz, DMSO) δ 159.1, 156.0, 154.6, 152.3, 140.4, 140.1, 129.9,
16
17 123.9, 122.0, 116.6, 112.9, 108.4, 100.3, 94.3, 87.7, 55.6, 55.4; HRMS (EI): m/z calcd
18
19 for $C_{17}H_{13}NO_4$ $[M]^+$: 295.0845; found: 295.0844.

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24
25 **8-Methoxychromeno[4,3-*b*]indol-6(11*H*)-one (2f)**. Yellow solid, 47.8 mg, 90%; mp
26
27 298-299 °C; 1H NMR (300 MHz, DMSO) δ 12.89 (s, 1H), 8.16 (d, $J = 7.8$ Hz, 1H),
28
29 7.65-7.39 (m, 5H), 7.08-6.95 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ
30
31 158.0, 155.6, 152.6, 141.7, 132.4, 130.6, 125.2, 124.3, 122.5, 117.2, 114.6, 113.3, 101.8,
32
33 99.8, 55.4; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{16}H_{10}NO_3$: 264.0666; found: 264.0661.

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35
36
37
38 **8-Fluorochromeno[4,3-*b*]indol-6(11*H*)-one (2g)**.⁹ Light yellow solid, 46.6 mg, 92%;
39
40 mp >300 °C; 1H NMR (300 MHz, DMSO) δ 13.14 (s, 1H), 8.18 (d, $J = 7.6$ Hz, 1H),
41
42 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
43
44 NMR (125 MHz, DMSO) δ 158.5 (d, $J_{CF} = 235.0$ Hz), 157.7, 152.8, 143.1, 134.3, 131.1,
45
46 125.0 (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,
47
48 $J_{CF} = 25.0$ Hz), 105.2 (d, $J_{CF} = 25.0$ Hz), 100.1 (d, $J_{CF} = 3.8$ Hz); HRMS (ESI): m/z $[M-$
49
50 $H]^-$ calcd for $C_{15}H_7FNO_2$: 252.0466; found: 252.0459.

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57 **Benzo[*g*]chromeno[4,3-*b*]indol-6(13*H*)-one (2h)**. Light brown solid, 43.3 mg, 76%;
58
59 mp >300 °C; 1H NMR (300 MHz, DMSO) δ 13.47 (s, 1H), 8.62 (d, $J = 8.3$ Hz, 1H),
60

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4 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-
5
6 7.73 (m, 1H), 7.67-7.51 (m, 4H); ^{13}C NMR (125 MHz, DMSO) δ 158.1, 152.3, 139.8,
7
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,
9
10 117.2, 113.5, 101.7; HRMS (ESI): m/z $[\text{M}-\text{H}]^-$ calcd for $\text{C}_{19}\text{H}_{10}\text{NO}_2$: 284.0717; found:
11
12 284.0711.
13
14
15
16

17 **9-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (2i).** Light yellow solid; mp >300 °C; ^1H
18
19 NMR (300 MHz, DMSO) δ 12.86 (s, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz,
20
21 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
22
23 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 157.9, 152.6, 141.5, 138.2, 134.4, 130.6, 124.3,
24
25 124.0, 122.6, 122.1, 119.9, 117.2, 113.3, 112.3, 100.0, 21.5; HRMS (EI): m/z calcd for
26
27 $\text{C}_{16}\text{H}_{11}\text{NO}_2$ $[\text{M}]^+$: 249.0790; found: 249.0785.
28
29
30
31
32

33 **7-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (2j).** Light yellow solid; mp >300 °C; ^1H
34
35 NMR (300 MHz, DMSO) δ 13.01 (s, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 7.60 (d, $J = 7.9$ Hz,
36
37 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
38
39 NMR (150 MHz, DMSO) δ 157.8, 152.6, 142.1, 138.3, 131.8, 130.8, 125.1, 124.2,
40
41 124.1, 123.8, 122.6, 116.8, 112.9, 109.9, 100.7, 21.9; HRMS (EI): m/z calcd for
42
43 $\text{C}_{16}\text{H}_{11}\text{NO}_2$ $[\text{M}]^+$: 249.0790; found: 249.0785.
44
45
46
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48

49 **9-Methoxychromeno[4,3-*b*]indol-6(11*H*)-one (2k).** Light yellow solid; mp >300 °C;
50
51 ^1H NMR (300 MHz, DMSO) δ 12.86 (s, 1H), 8.16 (d, $J = 7.6$ Hz, 1H), 7.89 (d, $J = 8.6$
52
53 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),
54
55 3.86 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.9, 157.8, 152.4, 141.1, 139.0, 130.3,
56
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4 124.3, 122.3, 120.9, 118.1, 117.1, 113.3, 111.9, 100.2, 95.8, 55.5; HRMS (ESI): m/z
5
6
7 $[M-H]^-$ calcd for $C_{16}H_{10}NO_3$: 264.0666; found: 264.0660.

8
9 **9-Fluorochromeno[4,3-*b*]indol-6(11*H*)-one (2m).** Light yellow solid; mp >300 °C; 1H
10
11 NMR (300 MHz, DMSO) δ 13.25 (s, 1H), 8.22 (d, $J = 7.7$ Hz, 1H), 8.00 (dd, $J = 8.5$,
12
13 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
14
15 MHz, DMSO) δ 160.4 (d, $J_{CF} = 238.5$ Hz), 157.7, 152.6, 142.7, 138.2 (d, $J_{CF} = 13.5$
16
17 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}
18
19 = 24.0 Hz), 100.0, 99.2 (d, $J_{CF} = 25.5$ Hz); HRMS (ESI): m/z $[M-H]^-$ calcd for
20
21 $C_{15}H_7FNO_2$: 252.0466; found: 252.0461.

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25
26
27 **2-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (2o).** Yellow solid, 47.3 mg, 95%;
28
29 mp >300 °C; 1H NMR (300 MHz, DMSO) δ 12.94 (s, 1H), 8.02 (d, $J = 7.7$ Hz, 1H),
30
31 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,
32
33 3H); ^{13}C NMR (150 MHz, DMSO) δ 158.0, 150.9, 141.8, 137.8, 133.5, 131.6, 124.7,
34
35 124.4, 122.4, 122.3, 120.2, 116.9, 112.8, 112.4, 100.0, 20.6; HRMS (ESI): m/z $[M-H]^-$
36
37 calcd for $C_{16}H_{10}NO_2$: 248.0717; found: 248.0710.

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43
44 **10-Methoxy-2-methylchromeno[4,3-*b*]indol-6(11*H*)-one (2p).** Light yellow solid,
45
46 52.5 mg, 94%; mp >300 °C; 1H NMR (300 MHz, DMSO) δ 12.98 (s, 1H), 8.28 (s, 1H),
47
48 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, $J = 7.9$
49
50 Hz, 1H), 4.02 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 158.1, 150.8, 146.4,
51
52 141.3, 133.4, 131.4, 127.7, 125.8, 123.2, 123.0, 116.8, 113.0, 112.5, 105.5, 100.5, 55.5,
53
54 20.6; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{17}H_{12}NO_3$: 278.0823; found: 278.0824.
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3
4 **2-Fluorochromeno[4,3-*b*]indol-6(11*H*)-one (2q).** Light yellow solid, 50.4 mg, 99%;
5
6 mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 13.01 (s, 1H), 8.03 (dd, *J* = 11.3, 5.3 Hz,
7
8 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-
9
10 7.33 (m, 1H); ¹³C NMR (125 MHz, DMSO) δ 158.0 (d, *J*_{CF} = 238.8 Hz), 157.6, 149.0,
11
12 140.9, 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
13
14 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*
15
16 [M-H]⁻ calcd for C₁₅H₇FNO₂: 252.0466; found: 252.0462.
17
18
19
20
21
22

23 **2,4,10-Trimethylchromeno[4,3-*b*]indol-6(11*H*)-one (2r).** Light yellow solid, 48.4 mg,
24
25 87%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.43 (s, 1H), 8.08 (s, 1H), 7.86 (d,
26
27 *J* = 6.3 Hz, 1H), 7.29 (s, 1H), 7.25-7.20(m, 2H), 2.63 (s, 3H), 2.41 (s, 6H); ¹³C NMR
28
29 (125 MHz, DMSO) δ 158.0, 149.1, 142.0, 137.3, 132.7, 125.6, 125.3, 124.1, 122.4,
30
31 122.0, 120.4, 117.7, 112.6, 100.3, 20.5, 17.0, 15.7; HRMS (ESI): *m/z* [M-H]⁻ calcd for
32
33 C₁₈H₁₄NO₂: 276.1030; found: 276.1025.
34
35
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37
38

39 **2,4-Dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (2s).** Light yellow solid, 49.4 mg,
40
41 94%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.90 (s, 1H), 8.03 (d, *J* = 7.6 Hz,
42
43 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
44
45 (s, 3H), 2.40 (s, 3H); ¹³C NMR (125 MHz, DMSO) δ 157.9, 149.2, 142.2, 137.8, 132.8,
46
47 125.7, 124.6, 124.4, 122.2, 120.2, 112.0, 112.5, 112.3, 99.9, 20.5, 15.7; HRMS (ESI):
48
49 *m/z* [M-H]⁻ calcd for C₁₇H₁₂NO₂: 262.0874; found: 262.0868.
50
51
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54

55 **1,3-Dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (2t).** Light yellow solid, 45.3 mg,
56
57 86%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 11.79 (s, 1H), 8.06 (d, *J* = 7.5 Hz,
58
59 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,
60

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4 3H), 2.36 (s, 3H); ¹³C NMR (150 MHz, DMSO) δ 157.9, 153.5, 141.4, 140.4, 138.1,
5
6 133.9, 127.5, 124.3, 123.7, 122.4, 119.8, 115.4, 113.2, 110.1, 100.0, 22.0, 20.9; HRMS
7
8 (ESI): *m/z* [M-H]⁻ calcd for C₁₇H₁₂NO₂: 262.0874; found: 262.0866.

9
10
11 **3-Methoxychromeno[4,3-*b*]indol-6(11*H*)-one (2u).**^{2a} Light yellow solid, 46.8 mg,
12
13 88%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.84 (s, 1H), 8.10 (d, *J* = 8.6 Hz,
14
15 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.40-7.28 (m, 2H), 7.11-7.07
16
17 (m, 2H), 3.88 (s, 3H); ¹³C NMR (125 MHz, DMSO) δ 161.6, 158.0, 154.5, 142.6, 137.6,
18
19 124.5, 124.3, 123.7, 122.2, 119.9, 112.24, 112.20, 106.2, 101.6, 98.1, 55.8.

20
21
22 **3-Fluorochromeno[4,3-*b*]indol-6(11*H*)-one (2v).** Light yellow solid, 49.4 mg, 96%;
23
24 mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 13.04 (s, 1H), 8.28-8.23 (m, 1H), 8.03 (d,
25
26 *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);
27
28 ¹³C NMR (125 MHz, DMSO) δ 163.0 (d, *J*_{CF} = 246.3 Hz), 157.5, 153.8 (d, *J*_{CF} = 13.8
29
30 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,
31
32 *J*_{CF} = 22.5 Hz), 110.2, 104.8 (d, *J*_{CF} = 26.3 Hz), 99.0; HRMS (EI): *m/z* calcd for
33
34 C₁₅H₈NFO₂ [M]⁺: 253.0539; found: 253.0535.

35
36
37 **5,11-Dihydro-6*H*-indolo[3,2-*c*]quinolin-6-one (4a).**²⁴ Light yellow solid, 45.2 mg,
38
39 97%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.55 (s, 1H), 11.42 (s, 1H), 8.20 (d,
40
41 *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,
42
43 1H), 7.28 (q, *J* = 7.9 Hz, 2H).

44
45
46 **8-Methyl-5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-one (4b).**²⁵ Yellow solid, 43.9
47
48 mg, 89%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.41 (s, 1H), 11.38 (s, 1H),
49
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4 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),
5
6
7 7.18 (d, $J = 8.0$ Hz, 1H), 2.47 (s, 3H).

8
9 **8-Chloro-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (4c).**²⁵ Yellow solid, 46.7
10
11 mg, 87%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.74 (s, 1H), 11.50 (s, 1H),
12
13 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
14
15 (d, $J = 8.6$ Hz, 1H), 7.31 (dd, $J = 7.4, 7.4$ Hz, 1H).

16
17
18
19 **2,3-Dimethoxy-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (4d).** Light gray solid,
20
21 55.8 mg, 94%; mp 282-285 °C; ¹H NMR (300 MHz, DMSO) δ 11.19 (s, 1H), 8.15 (d,
22
23 $J = 7.5$ Hz, 1H), 7.77 (s, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.34-7.20 (m, 2H), 7.04 (s, 1H),
24
25 3.88 (s, 3H), 3.83 (s, 3H); ¹³C NMR (125 MHz, DMSO) δ 159.7, 150.8, 144.7, 141.4,
26
27 137.6, 133.3, 124.7, 123.4, 120.8, 120.4, 111.4, 105.0, 104.4, 103.9, 98.9, 55.8, 55.5;
28
29 HRMS (ESI): m/z [M+Na]⁺ calcd for C₁₇H₁₄N₂NaO₃: 317.0897; found: 317.0890.

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31
32
33
34 **2-Chloro-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (4e).**²⁶ Light yellow solid,
35
36 52.0 mg, 96%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.58 (s, 1H), 11.55 (s,
37
38 1H), 8.32 (s, 1H), 8.20 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.55 (dd, $J = 8.8,$
39
40 1.9 Hz, 1H), 7.48-7.37 (m, 2H), 7.28 (dd, $J = 7.5, 7.5$ Hz, 1H).

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45
46 **4-Methyl-5,11-dihydro-6H-indolo[3,2-c]quinolin-6-one (4f).** Light green solid, 48.6
47
48 mg, 97%; mp >300 °C; ¹H NMR (300 MHz, DMSO) δ 12.52 (s, 1H), 10.43 (s, 1H), 8.21
49
50 (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, $J = 8.7,$
51
52 2.8 Hz, 2H), 7.25 (dd, $J = 15.9, 7.8$ Hz, 2H), 2.52 (s, 3H); ¹³C NMR (125 MHz, DMSO)
53
54
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56
57
58
59
60 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,

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3
4 112.0, 111.7, 106.2, 17.9; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{16}H_{11}N_2O$: 247.0877;
5
6
7 found: 247.0875.
8

9
10 **3-Methylpyrano[4,3-*b*]indol-1(5*H*)-one (6a).** Yellow solid, 34.0 mg, 85%; mp 252-
11
12 253 °C; 1H NMR (300 MHz, DMSO) δ 12.13 (s, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.52 (d,
13
14 $J = 7.7$ Hz, 1H), 7.34-7.23 (m, 2H), 6.66 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz,
15
16 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;
17
18 HRMS (EI): m/z calcd for $C_{12}H_9NO_2$ $[M]^+$: 199.0633; found: 199.0632.
19
20
21
22

23 **3,8-Dimethylpyrano[4,3-*b*]indol-1(5*H*)-one (6b).** Yellow solid, 34.2 mg, 92%; mp
24
25 280-282 °C; 1H NMR (300 MHz, DMSO) δ 12.01 (s, 1H), 7.71 (s, 1H), 7.40 (d, $J = 8.3$
26
27 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
28
29 (125 MHz, DMSO) δ 159.6, 159.2, 146.0, 135.5, 130.8, 125.3, 124.0, 119.5, 111.7,
30
31 97.7, 95.3, 21.1, 19.7; HRMS (EI): m/z calcd for $C_{13}H_{11}NO_2$ $[M]^+$: 213.0790; found:
32
33 213.0789.
34
35
36
37
38

39 **8-Fluoro-3-methylpyrano[4,3-*b*]indol-1(5*H*)-one (6c).** Yellow solid, 36.0 mg, 83%;
40
41 mp 279-280 °C; 1H NMR (300 MHz, DMSO) δ 12.21 (s, 1H), 7.56-7.50 (m, 2H), 7.19-
42
43 7.12 (m, 1H), 6.65 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 160.4, 158.3
44
45 (d, $J_{CF} = 234.3$ Hz), 158.9, 147.2, 133.9, 124.5 (d, $J_{CF} = 11.0$ Hz), 113.3 (d, $J_{CF} = 9.5$
46
47 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;
48
49
50
51
52 HRMS (EI): m/z calcd for $C_{12}H_8FNO_2$ $[M]^+$: 217.0539; found: 217.0538.
53
54

55 **3,7,9-Trimethylpyrano[4,3-*b*]indol-1(5*H*)-one (6d).** Yellow solid, 34.8 mg, 77%;
56
57 mp >300 °C; 1H NMR (300 MHz, DMSO) δ 11.97 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H),
58
59 6.56 (s, 1H), 2.84 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ
60

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(5*H*)-one (6e). Yellow solid, 34.8 mg, 76%;

mp 263-265 °C; 1H 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(5*H*)-one (6f).^{20a} Light brown solid, 54.9

mg, 94%; mp >300 °C; 1H 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).

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

at DOI: 10.1021/acs.joc.xxxxxxx.

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

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