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Three-Component Tandem Reaction Involving Acid Chlorides, Terminal Alkynes, and 2-Aminoindole Hydrochlorides: Synthesis of α-Carboline Derivatives in Aqueous Conditions via Regioselective [3 + 3] Cyclocondensation

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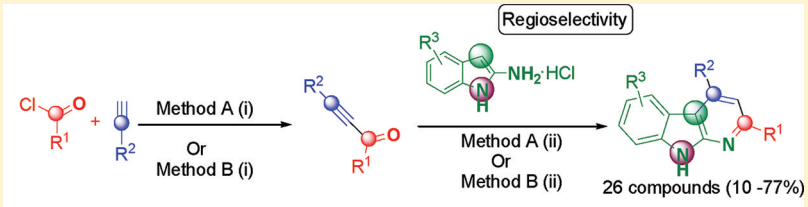
Supporting Information



Method A: (i) $PdCl_2(PPh_3)_2$/CuI, K_2CO_3, SDS, H_2O (1 mL), 3 h, 0-65 °C (ii) KOH (4 equiv.), DMSO (1 mL), 2 h
Method B: (i) $PdCl_2(PPh_3)_2$/CuI, TEA, THF, rt, 1 h (ii) KOH (4 equiv.), DMSO-H_2O, rt; 15 min

ABSTRACT: An efficient synthesis toward highly diversified α-carboline derivatives via a three-component tandem reaction using acid chlorides, terminal alkynes, and 2-aminoindole hydrochlorides has been described. The salient feature of the one-pot strategy involves regioselective [3 + 3]-cyclocondensation and the presence of water in the reaction medium to facilitate cyclization. Nonaqueous conditions furnished products in poor yields.

INTRODUCTION

The search for a one-pot, three-component tandem process[1] with multiple bond-forming abilities to furnish natural product based polyheterocycles has become one of the major challenges for synthetic chemists in both academia and industry. As part of our continuing effort toward the development of new routes involving multistep/one-pot reactions[2] for the synthesis of indole-based natural products[3] as well as polyheterocycles,[4] we embarked with a search for a one-pot, three-component tandem format for the synthesis of naturally occurring α-carboline (9*H*-pyrido[2,3-*b*]indole) derivatives. The α-carbolines are structural templates found in an array of natural products: dendrodoine A, grossularines-1 and -2, metabolites isolated from the tunicate *Dendrodoa grossularia*,[5] indoloquinoline alkaloid cryptotackiene from *Cryptolepis sanguinolenta*,[6] kapakahines from the marine sponge *Cribrochalina olemda*,[7] and mescengricin, isolated from *Streptomyces griseoflavus*.[8] These naturally derived α-carboline derivatives as well as synthetic α-carbolines are associated with pharmacological activities ranging from anticancer[9] to antiviral.[10] Thus, as an attractive naturally occurring synthetic target, several multistep methodologies involving Diels–Alder reaction,[11] annulation of azaindoles,[12] modified Graebe–Ullman reaction of triazoles,[13] annulation of indole ring onto pyridine,[14] generation of the pyrrole ring by annulating appropriately tethered phenyl and pyridine rings,[15] nucleophilic arylfluorine displacement reactions,[16] and more recently,[17] one-pot synthesis involving Pd-catalyzed aryl amination followed by intramolecular arylation have been reported in the literature for this tricyclic template. Retrosynthetic analysis (Figure 1) of the α-carboline, among many possible routes, suggests that the 2-aminoindole (**1**) could be an important component for the straightforward synthesis of α-carboline derivatives in one pot. The reason for its poor exploration to the synthesis of α-carboline may be attributed to its association with extremely poor stability as a free base.[18] Recently, we addressed the stability issues by employing bis-carbamate-protected 2-aminoindole and subjecting it to a three-component tandem format by treatment with disubstituted propargyl alcohols and I_2/ICl.[19] Although by using the protected 2-aminoindoles we were able to prevent degradation of 2-aminoindole, the strategy furnished N^a-derivatized-α-carbolines via iodocycloelimination with an alkyloxy carbonyl group anchored to the N^aH of the indole. Since further attempts to remove the N^a-protecting group were not successful, this prompted us to develop an alternative strategy for the synthesis of 9*H*-pyrido[2,3-*b*]indole derivatives directly from the unprotected 2-aminoindole hydrochloride. In this paper, we report a three-component tandem reaction involving acid chlorides, terminal aromatic/aliphatic alkynes, and 2-aminoindole hydrochlorides that allows direct access to the highly substituted α-carbolines.

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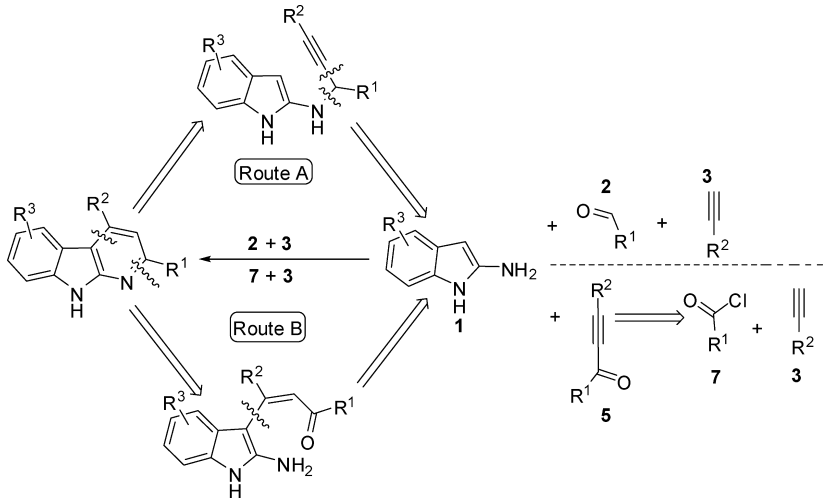
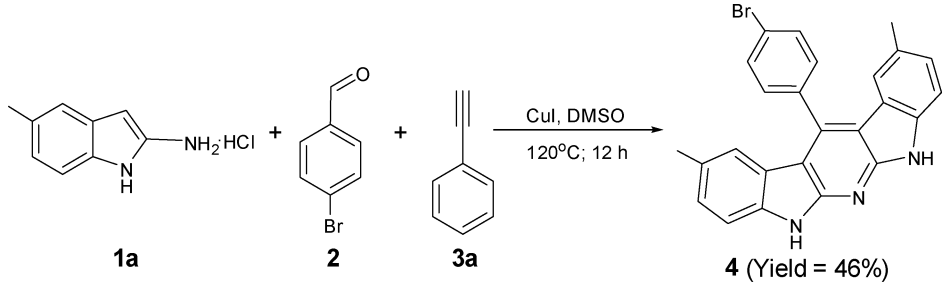


Figure 1. Retrosynthetic strategies for the α-carboline depicting involvement of the 2-aminoindole as one of the common reactants for the synthesis of 9*H*-pyrido[2,3-*b*]indole in two different formats.

Scheme 1. Three-Component Reaction Involving 1a, 2, and 3a Furnishing an Unusual Pentacyclic Ring[20] with No Participation of the Alkyne Moiety



RESULTS AND DISCUSSION

As depicted in route A of Figure 1, we envisaged that owing to the activated nature of the indole ring, it may be possible to construct α-carbolines in one pot by treating **1** with an aldehyde (**2**) and a terminal aromatic alkyne (**3**) as this may initiate heteroannulation via 6-*endo* cyclization by involving the *C*-3 nucleophilic carbon of the indole. Our studies thus commenced with a CuI-catalyzed three-component reaction (Scheme 1) involving 5-methyl-2-aminoindole hydrochloride (**1a**), 4-bromobenzaldehyde (**2**), and phenylacetylene (**3a**). However, after completion of the reaction, instead of isolating the desired α-carboline derivative, we obtained a pentacyclic compound (**4**) in 46% yield with no participation of the alkyne moiety. Indeed, a literature survey revealed the synthesis of a compound based on **4** by simply heating 1-methyl-1*H*-indol-2-ylamine hydrochloride and benzaldehyde in ethanol.[20]

This prompted us to examine the second retrosynthetic route B as depicted in Figure 1 for the α-carboline, which suggests its accessibility via [3 + 3]-cyclocondensation of the 2-aminoindole hydrochloride **1** with an alkynone[21] **5** by employing an appropriate base for in situ generation of 2-aminoindole. Accordingly, we screened a variety of bases for developing a rapid [3 + 3]-cyclocondensation protocol in a manner that will prevent degradation of the 2-aminoindole following an autoxidation[22] pathway (Table 1).

The optimization studies were carried out by using 5-methyl-2-aminoindole hydrochloride **1a** and 1-(4-methoxyphenyl)-3-phenylpropynone **5a** as model substrates. Initially, we carried out [3 + 3]-cyclocondensation by treating **1a** with **5a** in the presence of a series of bases such as TEA, DABCO, Cs_2CO_3, Na_2CO_3, *t*-BuOK, and KOH using acetonitrile and DMSO as solvents, and the results are summarized in Table 1 (entries 1−14). Among the bases used, *t*-BuOK (entry 4) and KOH (entry 5) in ACN at 80 °C afforded products in 44% and 65% isolated yield, respectively, whereas others failed to afford the title compound (entries 1−3). Switching solvent from acetonitrile to DMSO under heating at 120 °C for 1 h in the presence of Cs_2CO_3 (2.5 equiv), *t*-BuOK (2.5 equiv), and KOH (2.5 equiv) furnished **6a** in 56% (entry 6), 41% (entry 8), and 16% (entry 10) isolated yields, respectively. Use of DABCO (entry 7) and Na_2CO_3 (entry 9) completely failed to afford the title compounds. It is interesting to note from these findings that although addition of solid KOH promoted cyclization in the acetonitrile (entry 5) in 65% yield, use of DMSO as solvent was found to be detrimental (entries 10 and 11). We attributed this to an incomplete deprotonation of the 2-aminoindole hydrochloride in DMSO in comparison to the acetonitrile. This then prompted us to use 10% aqueous KOH (1.3 equiv) as a base in DMSO with the view to facilitate deprotonation, and pleasingly, we observed formation of the title compound **6a** in 81% isolated yield within 2 min at rt (entry 12). Nonetheless, application of 10% aqueous KOH as a base in acetonitrile or water either reduced the yield of **6a** to 10% (entry 13) or failed to promote cyclocondensation (entry 14).

We were intrigued by these findings because it is apparent that the presence of water/KOH/DMSO in the reaction mixture facilitates the rapid [3 + 3]-cyclocondensation between the alkynone **5a** and 5-methyl-2-aminoindole hydrochloride **1a**

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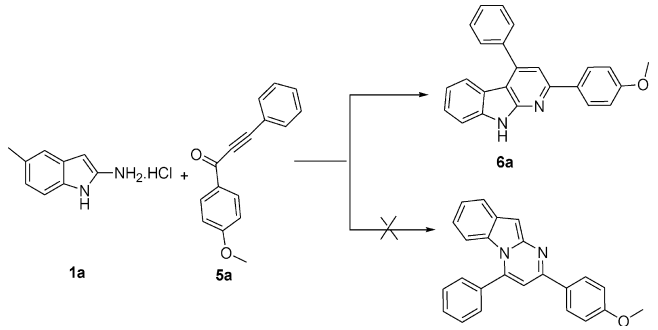
Table 1. Optimization of Reaction Conditions for the Regioselective [3 + 3] Cyclocondensation Involving 1-(4-Methoxyphenyl)-3-phenylpropynone 5a and 5-Methyl-2-aminoindole Hydrochloride 1a To Afford 6a



entry	solvent	T (°C)/time	base	yield (%)
1	ACN	80/5 h	TEA	0
2	ACN	80/12 h	DABCO (2.5 equiv)	0
3	ACN	80/6 h	Na_2CO_3 (2.5 equiv)	0
4	ACN	80/1 h	*t*-BuOK (2.5 equiv)	44
5	ACN	80/1 h	KOH (2.5 equiv)	65
6	DMSO	120/1 h	Cs_2CO_3 (2.5 equiv)	56
7	DMSO	120/1 h	DABCO (2.5 equiv)	0
8	DMSO	120/1 h	*t*-BuOK (2.5 equiv)	41
9	DMSO	120/1 h	Na_2CO_3 (2.5 equiv)	0
10	DMSO	120/1 h	KOH (2.5 equiv)	16
11	DMSO	rt/12 h	KOH (2.5 equiv)	0
12	DMSO	rt/2 min	10% aq KOH (1.3 equiv)	81
13	ACN	rt/1 h	10% aq KOH (1.3 equiv)	10
14	H_2O	rt/16 h	KOH (2.5 equiv)	0

to afford α-carboline derivative **6a**. Nevertheless, it is also interesting to note that during [3 + 3]-cyclocondensation we observed complete regioselectivity despite availability of two nucleophilic centers N^aH and *C*-3 in the indole ring, and indeed, the more nucleophilic *C*-3 was preferred over N^a for the cyclocondensation (Table 1). Recently, we reported involvement of N^aH in the 2-amino-1*H*-indole-3-carboxylic acid ethyl ester during the [3 + 3]-cyclocondensation with an alkynone by keeping the *C*-3 of the indole blocked with a COOEt group to give pyrimido[1,2-*a*]indoles.[23]

Once the conditions for the regioselective [3 + 3]-cyclocondensation between 5-methyl-2-aminoindole hydrochloride **1a** and the alkynone **5a** were optimized, we next proceeded with the development of a one-pot, three-component tandem strategy for the synthesis of α-carboline derivatives by carrying out both reactions in a sequential format. Indeed, the challenging task for us was to combine the two organic reaction conditions involving Sonogashira coupling and [3 + 3]-cyclocondensation in a manner that will lead to the formation of several bonds resulting in α-carboline derivatives without the isolation of the intermediate(s).

For combining the two reactions in a sequential format in one pot, we carried out optimization studies using 4-methoxybenzoyl chloride **7a**, phenylacetylene **3a**, and 5-methyl-2-aminoindole hydrochloride **1a** as model substrates, and results have been summarized in Table 2 (entry 1−15). The progress of the reaction after each step was monitored by TLC/HPLC. We initiated our investigation by treating **7a** and **3a** in the presence of $PdCl_2(PPh_3)_2$/CuI and TEA in THF at rt for 1 h followed by the addition of **1a** in the presence of 10% aq KOH. Under these conditions, although the alkynone formation was complete, its conversion to **6a** was not observed even after the solvent was changed from THF to acetonitrile and DMSO (entries 1−3). Next, we decided to carry out Sonogashira couplings under aqueous conditions and accordingly treated **7a** with **3a** in the presence of $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, and SDS in H_2O using the literature procedure[24] followed by the addition of **1a** in the presence of *t*-BuOK (2.5 equiv) in DMSO at rt. Under these conditions, although formation of the alkynone **5a** occurred in 90% yield (based on HPLC), the title compound was obtained in traces (entry 4); however, increasing the temperature led to a meager enhancement in the yield to 15% (entry 5). Attempts to further improve the yield were then made by replacing *t*-BuOK with Cs_2CO_3 and KOH. Carrying out reaction in the presence of Cs_2CO_3 (2.5 equiv) at rt furnished **6a** in traces (entry 6), whereas increasing the temperature or concentration of the Cs_2CO_3 to 4 equiv raised the yield of the final product to 24% (entry 7) and 56% (entry 8), respectively. Replacing Cs_2CO_3 with 10% aq KOH in DMSO was found to be ineffective when added to the alkynone generated in situ under aqueous conditions (entry 9). This can be attributed to the overall dilution in the concentration of KOH in the reaction mixture following its addition as 10% aqueous solution to the alkynone **5a** synthesized in neat water (used as a medium for Sonogashira coupling). This prompted us to add solid KOH in DMSO and as anticipated, in the initial experiments. Addition of 2 equiv of solid KOH at rt afforded α-carboline derivative **6a** in 57% isolated yield; however, increasing the concentration of solid KOH from 2.0 equiv to 3.0 and 4.0 equiv in DMSO at rt raised the isolated yield of **6a** to 65% (entry 11) and 76% (entry 12), respectively. Notably, under the increased concentrations of KOH, the time taken for the completion of cyclocondensation was significantly reduced from 6 to 2 h. In the next set of experiments, we established the role of water for the three-component tandem reaction by carrying out

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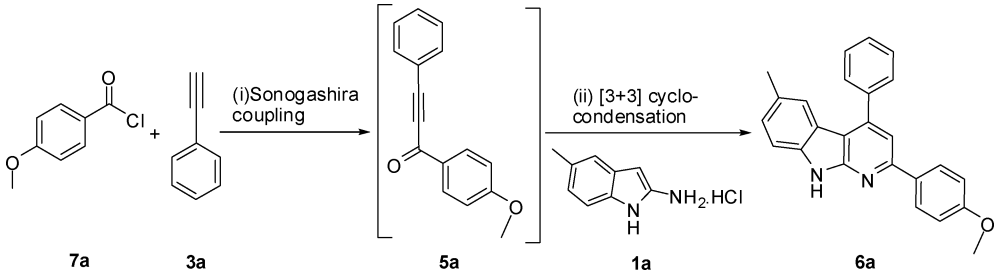
Table 2. Optimization of reaction Conditions for the Three-Component Tandem Protocol in One Pot Involving 4-Methoxy Acid Chloride 7a, Phenylacetylene 3a, and 5-Methyl-2-aminoindole Hydrochloride 1a



entry	tandem reaction conditions in one-pot (i) Sonogashira coupling and (ii) [3 + 3] cyclocondensation	reaction time for steps i/ii	% yields of alkynones[a]/products **5a**/**6a**
1	(i) $PdCl_2(PPh_3)_2$/CuI, TEA, THF, rt (i) 10% aq KOH, THF, rt	1 h/16 h	89/0
2	(ii) $PdCl_2(PPh_3)_2$, CuI, TEA, ACN, rt (ii) 10% aq KOH, ACN, rt	1 h/16 h	83/0
3	(i) Pd/C, $PdCl_2(PPh_3)_2$, CuI, TEA, THF, rt (ii) 10% aq KOH, DMSO, rt	1 h/16 h	90/0
4	(i) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) *t*-BuOK (2.5 equiv), DMSO, rt	3 h/16 h	90/trace[b]
5	(i) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) *t*-BuOK (2.5 equiv), DMSO, 65 °C	3 h/16 h	91/15[b]
6	(i) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) Cs_2CO_3 (2.5 equiv), DMSO, rt	3 h/16 h	92/trace[b]
7	(i) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) Cs_2CO_3 (2.5 equiv), DMSO, 65 °C	3 h/16 h	88/24[b]
8	(i) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) Cs_2CO_3 (4 equiv), DMSO, 65 °C	3 h/16 h	87/56[b]
9	(i) $PdCl_2$ $(PPh_3)_2$/CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) 10% KOH (1.3 equiv), DMSO, rt	3 h/6 h	89/<10[b]
10	(i) $PdCl_2$ $(PPh_3)_2$/CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) KOH (2.0 equiv), DMSO, rt	3 h/16 h	91/57[b]
11	(i) $PdCl_2$ $(PPh_3)_2$/CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) KOH (3.0 equiv), DMSO, rt	3 h/2 h	88/65[b]
12	(i) $PdCl_2$ $(PPh_3)_2$/CuI, K_2CO_3, SDS, H_2O, 0 to 65 °C (ii) KOH (4.0 equiv), DMSO, rt	3 h/2 h	91/76[b]
13	(i) $PdCl_2(PPh_3)_2$/CuI, TEA, THF, rt (ii) KOH (4.0 equiv), DMSO, rt	1 h/12 h	90/0
14	(i) $PdCl_2(PPh_3)_2$/CuI, TEA, THF, rt (ii) KOH (4.0 equiv), DMSO−H_2O, rt	1 h/15 min	90/79[b]
15	(i) $PdCl_2(PPh_3)_2$/CuI, TEA, ACN, rt (ii) KOH (4.0 equiv), DMSO−H_2O, rt	1 h/1 h	90/61[b]

[a]Yield of alkynone is based on HPLC. [b]Isolated yields; SDS = sodium dodecyl sulfate.

formation of the alkynone **5a** via Sonogashira couplings in THF and followed it up by adding solid KOH (4 equiv) and 2-aminoindole hydrochloride either in DMSO or in DMSO−water mixture. As envisaged, use of DMSO alone completely failed to furnish the desired compound (entry 13), whereas use of a DMSO−water mixture afforded the title compound in 79% isolated yield (entry 14) with the time for cyclocondensation being reduced to 15 min. Switching solvent from THF to acetonitrile for the Sonogashira reaction coupled with the use of DMSO−water mixture for cyclocondensation afforded the title compound in reduced yield (entry 15). Thus, nonaqueous conditions in general failed to promote formation of the title compounds, whereas the two optimized aqueous conditions that were found to be suitable included method A, involving water/KOH in DMSO, and method B, involving THF/KOH in DMSO−water.

Following the optimization of reaction conditions in one pot, we next examined the scope and limitation of our strategy by treating a variety of 2-aminoindole hydrochlorides with a range of acid chlorides and terminal alkynes using the optimized conditions. The R^1 in the acid chlorides has been exclusively restricted to aromatic rings, whereas R^2 in the terminal alkynes include both aliphatic and aromatic moieties. The R^3 in the phenyl ring of the indole moiety has been substituted by introducing electron-donating CH_3 at position 5 and electron-withdrawing groups (F, CF_3) at position 6. The 2-aminoindole hydrochloride derivatives (**1a−d**) were obtained using a literature procedure[25] and characterized by NMR in their respective ring-protonated tautomeric forms, 1,3-dihydro-2*H*-indol-2-imine hydrochloride derivatives.[26] The latter in the presence of base gets transformed into 2-aminoindole as a free amine. The reactants **1a−d**, **7a−e**, and **3a−f** were then subjected to three-component tandem reactions to furnish 25

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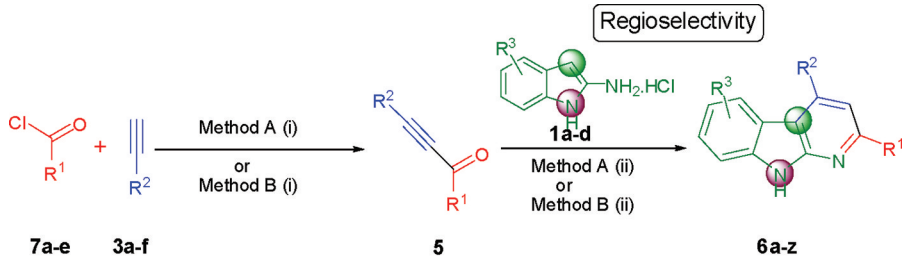
Table 3. Three-Component Tandem Reactions Involving Acid Chlorides 7a−e, Terminal Alkynes 3a−f, and 2-Aminoindole Hydrochlorides 1a−d To Afford α-Carboline Derivatives 6a−z



1a; R^3 = 5-CH_3 | 7a; R^1 = 4-$CH_3OC_6H_4$ | 3a; R^2 = C_6H_5
1b; R^3 = H | 7b; R^1 = C_6H_5 | 3b; R^2 = 4-$CH_3C_6H_4$
1c; R^3 = 6-CF_3 | 7c; R^1 = 4-$CH_3C_6H_4$ | 3c; R^2 = 4-$C(CH_3)_3C_6H_4$
1d; R^3 = 6-F | 7d; R^1 = 4-$(CH_3O)_2C_6H_3$ | 3d; R^2 = C_6H_9
7e; R^1 = $(CH_3)_3C$ | 3e; R^2 = $(CH_2)_5CH_3$
3f; R^2 = $(CH_3)_3Si$

entry	R^1 (7)	R^2 (3)	R^3 (1)	method[a]	compd	yield (%)
1	4-$CH_3OC_6H_4$	C_6H_5	5-CH_3	A	**6a**	76
2	4-$CH_3OC_6H_4$	C_6H_9	H	A	**6b**	58
3	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	6-CF_3	A	**6c**	74
4	4-$CH_3OC_6H_4$	$(CH_2)_5CH_3$	6-CF_3	A	**6d**	46
5	4-$CH_3OC_6H_4$	C_6H_5	6-F	A	**6e**	75
6	C_6H_5	4-$C(CH_3)_3C_6H_4$	H	A	**6f**	71
7	C_6H_5	4-$CH_3C_6H_5$	H	A	**6g**	77
8	C_6H_5	C_6H_5	5-CH_3	A	**6h**	72
9	C_6H_5	4-$C(CH_3)_3C_6H_4$	5-CH_3	A	**6i**	73
10	C_6H_5	C_6H_9	5-CH_3	A	**6j**	56
11	C_6H_5	$(CH_2)_5CH_3$	6-F	A	**6k**	44
12	C_6H_5	4-$C(CH_3)_3C_6H_4$	6-CF_3	A	**6l**	70
13	C_6H_5	C_6H_5	6-CF_3	A	**6m**	75
14	C_6H_5	4-$CH_3C_6H_4$	6-F	A	**6n**	71
15	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	A	**6o**	70
16	4-$CH_3C_6H_4$	4-$C(CH_3)_3C_6H_4$	H	A	**6p**	69
17	4-$CH_3C_6H_4$	C_6H_5	5-CH_3	A	**6q**	74
18	4-$CH_3C_6H_4$	C_6H_5	6-F	A	**6r**	76
19	4-$CH_3C_6H_4$	4-$C(CH_3)_3C_6H_4$	6-F	A	**6s**	69
20	4-$CH_3C_6H_4$	C_6H_9	6-CF_3	A	**6t**	58
21	3,4-di-$CH_3OC_6H_3$	C_6H_5	H	B	**6u**	64
22	3,4-di-$CH_3OC_6H_3$	4-$CH_3C_6H_4$	5-CH_3	B	**6v**	70
23	3,4-di-$CH_3OC_6H_3$	C_6H_5	6-CF_3	B	**6w**	66
24	3,4-di-CH_3O−C_6H_3	C_6H_9	6-F	B	**6x**	52
25	$C(CH_3)_3$	C_6H_5	H	B	**6y**	10
26	C_6H_5	$(CH_3)_3Si$	H	B	**6z**[b]	42

[a]Method A: (i) alkyne (1.0 equiv), acid chloride (2.0 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), CuI (5 mol %), SDS (7 mol %), K_2CO_3 (3 equiv), H_2O, 0−65 °C, 3 h; (ii) KOH (4.0 equiv), 2-amino indole hydrochloride (1.0 equiv) DMSO (1 mL). Method B: (i) alkyne (1.0 equiv), acid chloride (1.0 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), CuI (4 mol %), TEA (1.25 equiv), THF (2 mL), rt, 1 h; (ii) KOH (4.0 equiv), 2-aminoindole hydrochloride (1.0 equiv), DMSO−H_2O (1:1; 4 mL);. [b]The product was obtained with R^2 = H.

new compounds **6a−y** and one known compound **6z**[27] in moderate to good yields (Table 3). As is evident from Table 3, the electronic properties of the substituent on the phenyl ring of the indole moiety had no effect on the yields of the final compounds (entries 1, 5, and 13). Similarly, introducing a substituent on the phenyl ring of the aromatic acid chlorides had a negligible effect on the reactions, offering products with minimal variation in yields (entries 3, 15 and 22). An attempt to employ aliphatic acid chlorides such as propanoyl- and *p*-tolylacetyl chlorides failed to yield the desired compounds except for pivaloyl chloride, which furnished **6y** in poor (∼10%) yield using method B (entry 25). Among terminal alkynes, substitution on the aromatic ring had no effect on the isolated yields of the title compounds (entries 6−8); however, replacement of the aromatic ring with an aliphatic moiety reduced the yields of the final compounds (entries 2, 4, 10, 11, 20, and 24). The use of ethynyltrimethylsilane **3f** afforded final product **6z** (R^2 = H; without the trimethylsilyl group) in 42% isolated yield (entry 26). Thus, among the effects of the three substituents R^1, R^2, and R^3 examined on the reaction yields, substitution on the terminal alkynes represented by R^2 had a major impact. In general, terminal alkynes with R^2 as the aromatic ring furnished products in 10−77% isolated yield, whereas R^2 having an aliphatic moiety furnished products in 42−58% isolated yield.

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CONCLUSION

In conclusion, we have developed an efficient, three-component tandem reaction for the synthesis of highly substituted naturally occurring α-carbolines derivatives. The strategy involves condensation of acid chlorides with terminal alkynes under Sonogashira conditions both in aqueous and nonaqueous medium followed by in situ [3 + 3] cyclocondensation of the resulting alkynones with 2-aminoindole hydrochlorides in the presence of KOH in DMSO/DMSO−H_2O. Further studies with the application of a one-pot, three-component tandem process to other functionalized indoles as one of the reactants is in progress.

EXPERIMENTAL SECTION

I. General Information and Methods. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 200, 300, and 400 MHz spectrometers for ^{1}H NMR and 50, 75, 100, and 150 MHz for ^{13}C NMR. Chemical shifts (δ) are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/DMSO-d_6 for ^{1}H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). High-resolution mass spectra were taken with a mass spectrometer. Column chromatography was performed using silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). The purity and characterization of these compounds were further established using HR/EI mass spectroscopy. Melting points were measured on a capillary melting point apparatus and are uncorrected.

II. Synthesis of 1*H*-Indol-2-amine Hydrochloride Salt Derivatives 1a−d. These compounds were synthesized using methods reported in the literature.[14d,23]

5-Methyl-1H-indol-2-amine Hydrochloride Salt ***1a.*** Characterized as the tautomeric form 5-methyl-1,3-dihydro-2*H*-indol-2-imine hydrochloride:[24] white solid; yield = 79%; mp 233−235 °C; FT-IR (KBr) ν_{max} 3390, 3253, 3174, 2975, 1488, 1216 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 1H), 10.25 (s, 1H), 9.95 (s, 1H), 7.19 (s, 1H), 7.08 (s, 2H), 4.12 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.7, 140.4, 132.8, 128.2, 126.5, 125.2, 111.5, 35.8, 20.7; HRMS (ESI) calcd for $C_9H_{11}N_2$ [M − Cl] 147.0922, found 147.0922.

1H-Indol-2-amine Hydrochloride Salt ***1b.*** Characterized as the tautomeric form 1,3-dihydro-2*H*-indol-2-imine hydrochloride:[24] white solid; yield = 75%; mp 225−227 °C; FT-IR (KBr) ν_{max} 3473, 3233, 3073, 2947, 1469, 1221 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.49 (s, 1H), 10.31 (s, 1H), 10.03 (s, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.13−7.08 (m, 1H), 4.18 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 142.8, 128.0, 126.5, 124.7, 123.7, 111.8, 36.0; HRMS (ESI) calcd for $C_8H_9N_2$ [M − Cl] 133.0766, found 133.0766.

6-(Trifluoromethyl)-1H-indol-2-amine Hydrochloride Salt ***1c.*** Characterized as the tautomeric form 6-(trifluoromethyl)-1,3-dihydro-2*H*-indol-2-imine hydrochloride:[24] white solid; yield = 77%; mp >250 °C; FT-IR (KBr) ν_{max} 3330, 3222, 3184, 3072, 1451, 1220 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.36 (s, 1H), 10.20 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.51 (s, 2H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.4, 143.8, 131.6, 128.7 (q, J = 32 Hz), 125.5, 122.7, 120.5, 36.2; HRMS (ESI) calcd for $C_9H_8F_3N_2$ [M − Cl] 201.0640, found 201.0640.

6-Fluoro-1H-indol-2-amine Hydrochloride Salt ***1d.*** Characterized as the tautomeric form 6-fluoro-1,3-dihydro-2*H*-indol-2-imine hydrochloride:[24] brown solid; yield = 81%; mp 245−247 °C; FT-IR (KBr) ν_{max} 3466, 3253, 3137, 2945, 1501, 1220 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.46 (s, 1H), 10.27 (s, 1H), 7.43−7.39 (m, 1H), 7.08 (dd, J = 2.0, 9.0 Hz, 1H), 6.96−6.93 (m, 1H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0, 161.9 (d, J = 240 Hz), 144.2 (d, J = 12.75 Hz), 125.8 (d, J = 9.8 Hz), 122.5 (d, J = 2.3 Hz), 110.9 (d, J = 22.5 Hz), 100.2(d, J = 27.8 Hz), 35.4; HRMS (ESI) calcd for $C_8H_8FN_2$ [M − Cl] 151.0672, found 151.0672.

III. Procedure for the synthesis of pentacyclic system 4 via three component reaction following route A (Figure 1). To a stirred solution of 5-methyl-1*H*-indol-2-amine hydrochloride salt **1a** (1.0 mmol), 4-bromobenzaldehyde **2** (1.0 mmol) and phenyl acetylene **3a** (1.0 mmol) in DMSO was added CuI (20 mol %). The resulting solution was heated at 100 °C for 6 h and the crude reaction mixture was filtered through a Celite bed; followed by washing of the Celite bed with EtOAc (2 × 10 mL). The filtrate was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure *in vacuo*. The crude reaction mixture was purified by column chromatography on 60−120 mesh silica using EtOAc/hexane as eluent to afford the title compound (**4**) as white solid; yield =46%; mp >250 °C; FT-IR (KBr) ν_{max} 3150, 3033, 2934, 1594, 1262 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.15−7.08 (m, 6H), 6.75 (s, 2H), 2.34 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 139.1, 136.6, 136.0, 132.2, 130.6, 129.1, 126.2, 122.7, 122.0, 121.2, 110.5, 108.7, 21.8 ppm. HRMS (ESI) calcd for $C_{25}H_{19}BrN_3$ [M + H] 440.0762, found 440.0738.

IV. Procedure for the Synthesis of 2-(4-Methoxyphenyl)-6-methyl-4-phenyl-9*H*-pyrido[2,3-*b*]indole 6a from 1a and 5a. To a stirred solution of 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (100 mg, 0.424 mmol) **5** and 1*H*-indol-2-amine hydrochloride salt (77 mg, 0.424 mmol) **1a** in DMSO (5 mL) was added 10% aqueous KOH (31 mg, 0.551 mmol), and the reaction mixture was stirred at rt for 2 min. The reaction mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in vacuo. The crude reaction mixture was purified by column chromatography on 60−120 mesh silica using EtOAc/hexane as eluent to afford the title compound as white solid (125 mg, 81%).

V. General Procedure for the Synthesis of 9*H*-Pyrido[2,3-*b*]indole Derivatives 6a−z from 1a−d, 3a−f, and 7a−e. *Method A.* Terminal alkynes **3a−e** (1 mmol), acid chlorides **7a−d** (2 mmol), sodium dodecyl sulfate (7 mol %), $PdCl_2(PPh_3)_2$ (2 mol %), and CuI (5 mol %) were added in a small test tube cooled by ice−water bath. To this reaction mixture was added in small portions K_2CO_3 (3 mmol) in 1 mL of water with stirring. After the addition was completed, the vial was capped and heated at 65 °C for 3 h. After the formation of alkynone as monitored by TLC, the reaction mixture was diluted with DMSO (1 mL) at rt followed by addition of 1*H*-indol-2-amine hydrochloride derivatives (1.0 mmol, **1a−d**) and KOH (4.0 mmol). The reaction mixture was stirred for 2 h at rt, and the crude reaction mixture was filtered through a Celite bed followed by washing of the Celite bed with EtOAc (2 × 10 mL). The filtrate was diluted with water (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in vacuo. The crude reaction mixture was purified by column chromatography on 60−120 mesh silica using EtOAc/hexane as eluent to afford the final compounds (**6a−t**).

Method B. To a solution of $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %), and TEA (1.25 mmol) in THF (5.0 mL) were added acid chloride (1.0 mmol, **7a−e**) and terminal alkyne (1.0 mmol, **3a−f**) under N_2 atmosphere. The reaction was stirred at rt for 1 h, the formation of alkynone was monitored by TLC, and the reaction mixture was diluted with DMSO−H_2O (1:1; 10 mL) followed by addition of 1*H*-indol-2-amine hydrochloride derivatives (1.0 mmol, **1a−d**) and KOH (4.0 mmol). The reaction mixture was stirred for 15 min at rt, and the crude reaction mixture was filtered through a Celite bed followed by washing of the Celite bed with EtOAc (2 × 10 mL). The filtrate was diluted with water (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in vacuo. The crude reaction mixture was purified by column chromatography on 60−120 mesh silica using EtOAc/hexane as eluent to afford the final compounds (**6u−z**).

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2-(4-Methoxyphenyl)-6-methyl-4-phenyl-9H-pyrido[2,3-b]indole (**6a**): white solid; yield = 76%; mp 240−242 °C; FT-IR (KBr) ν_{max} 3058, 2939, 1586, 1240 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 7.1 Hz, 2H), 7.65−7.56 (m, 3H), 7.53 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.30 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 3.84 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 152.8, 152.8, 145.0, 138.8, 137.6, 131.8, 128.7, 128.6, 128.2, 127.7, 127.5, 121.5, 120.1, 114.1, 112.0, 111.0, 110.5, 55.2, 21.3; HRMS (ESI) calcd for $C_{25}H_{21}N_2O$ [M + H] 365.1654, found 365.1662.

4-Cyclohex-1-en-1-yl-2-(4-methoxyphenyl)-9H-pyrido[2,3-b]-indole (**6b**): white solid; yield = 58%; mp 248−250 °C; FT-IR (KBr) ν_{max} 3150, 2949, 1457, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.13 (s, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.0 (d, J = 7.8 Hz, 1H), 7.36 (s, 1H), 7.28−7.23 (m, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 7.8 Hz, 1H), 6.1 (s, 1H), 3.88 (s, 3H), 2.53−2.34 (m, 4H), 1.96−1.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 152.8, 152.6, 147.7, 139.2, 136.1, 131.9, 128.1, 127.0, 125.8, 121.9, 120.2, 119.3, 114.0, 111.1, 110.4, 55.2, 28.1, 24.9, 22.5, 21.7; HRMS (ESI) calcd for $C_{24}H_{23}N_2O$ [M + H] 355.1811, found 355.1825.

2-(4-Methoxyphenyl)-4-(4-methylphenyl)-7-(trifluoromethyl)-9H-pyrido[2,3-b]indole (**6c**): white solid; yield = 74%; mp >250 °C; FT-IR (KBr) ν_{max} 3245, 1522, 1249 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 7.77−7.65 (m, 5H), 7.45 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 154.5, 153.4, 146.2, 138.4, 135.3, 131.3, 129.4, 128.4, 128.4, 126.1 (t, J = 32.3 Hz), 123.1,123.1, 122.9, 122.2, 115.5, 114.1, 112.9, 109.8, 108.0, 55.2, 20.9; HRMS (ESI) calcd for $C_{26}H_{20}F_3N_2O$ [M + H] 433.1527, found 433.1531.

4-Hexyl-2-(4-methoxyphenyl)-7-(trifluoromethyl)-9H-pyrido[2,3-b]indole (**6d**): white solid; yield = 46%; mp 177−178 °C; FT-IR (KBr) ν_{max} 3051, 2948, 1574, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 12.80 (s, 1H), 8.12 (d, J = 8.6 Hz, 2H), 8.04 (d, J = 8.1 Hz, 1H), 7.43−7.40 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.59 (s, 1H), 3.90 (s, 3H), 3.25 (t, J = 7.5 Hz, 2H), 1.90−1.83 (m, 2H), 1.56−1.54 (m, 2H), 1.37−1.36 (m, 4H), 0.93−0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 155.7, 154.0, 149.5, 138.3, 132.6, 129.5, 127.0 (t, J = 33 Hz), 123.5, 122.9, 122.4, 116.2, 114.8, 114.2, 112.6, 109.0, 55.4, 34.3, 31.9, 29.6, 29.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{25}H_{26}F_3N_2O$ [M + H] 427.1998, found 427.1975.

7-Fluoro-2-(4-methoxyphenyl)-4-phenyl-9H-pyrido[2,3-b]indole (**6e**): white solid; yield = 75%; mp >250 °C; FT-IR (KBr) ν_{max} 3061, 2941, 1112 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.18 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 6.5 Hz, 2H), 7.66−7.58 (m, 4H), 7.49−7.44 (m, 1H), 7.25 (dd, J = 2.1, 9.6 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.92−6.85 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.4, 160.8, 160.5, 153.4 (d, J = 53 Hz), 145.1, 140.6 (d, J = 13 Hz), 138.9, 131.9, 129.3, 129.2, 128.9, 128.6, 123.3 (d, J = 10 Hz), 117.2, 114.5, 112.9, 110.9, 107.7 (d, J = 24 Hz), 98.2 (d, J = 26 Hz), 55.6; HRMS (ESI) calcd for $C_{24}H_{18}FN_2O$ [M + H] 369.1404, found 369.1415.

4-(4-tert-Butylphenyl)-2-phenyl-9H-pyrido[2,3-b]indole (**6f**): white solid; yield = 71%; mp 248−250 °C; FT-IR (KBr) ν_{max} 3073, 2965, 1591, 1293 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.22 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 8.25 Hz, 2H), 7.66−7.62 (m, 4H), 7.53−7.49 (m, 3H), 7.46−7.39 (m, 2H), 7.04 (t, J = 7.2 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 153.5, 152.0, 146.4, 140.4, 139.5, 136.4, 129.2, 128.9, 128.6, 127.9, 126.4, 125.8, 122.6, 120.9, 119.6, 114.7, 113.0, 111.4, 34.9, 31.6; HRMS (ESI) calcd for $C_{27}H_{25}N_2$ [M + H] 377.2017, found 377.2024.

4-(4-Methylphenyl)-2-phenyl-9H-pyrido[2,3-b]indole (**6g**): white solid; yield = 77%; mp 221−223 °C; FT-IR (KBr) ν_{max} 3087, 2953, 1458, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.19 (d, J = 6.8 Hz, 2H), 7.70−7.64 (m, 3H), 7.56−7.45 (m, 4H), 7.39 (d, J = 7.7 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 6.99 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0, 152.7, 145.1, 139.5, 139.3, 138.2, 135.7, 129.3, 128.7, 128.5, 126.9, 126.4, 121.8, 119.9, 119.2, 112.9, 111.4, 111.3, 111.3, 20.9; HRMS (ESI) calcd for $C_{24}H_{19}N_2$ [M + H] 335.1548, found 335.1564.

6-Methyl-2,4-diphenyl-9H-pyrido[2,3-b]indole (**6h**): white solid; yield = 72%; mp 248−249 °C; FT-IR (KBr) ν_{max} 3064, 1584, 1219 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.21 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 6.5 Hz, 2H), 7.67−7.59 (m, 4H), 7.54−7.49 (m, 2H), 7.46−7.40 (m, 2H), 7.33 (s, 1H), 7.24 (d, J = 7.3 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 152.8, 145.0, 139.3, 138.7, 137.8, 129.1, 128.8, 128.7, 127.8, 126.9, 126.8, 121.7, 121.6, 120.0, 112.8, 112.7, 111.2, 111.1, 21.3; HRMS (ESI) calcd for $C_{24}H_{19}N_2$ [M + H] 335.1548, found 335.1557.

4-(4-tert-Butylphenyl)-6-methyl-2-phenyl-9H-pyrido[2,3-b]indole (**6i**): white solid; yield = 73%; mp 229−231 °C; FT-IR (KBr) ν_{max} 3128, 2944, 1464, 1217 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.21 (d, J = 7.2 Hz, 2H), 7.72−7.62 (m, 5H), 7.53−7.37 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 2.28 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.3, 153.2, 151.8, 145.4, 139.8, 138.2, 136.3, 129.1, 129.1, 128.8, 128.2, 128.1, 127.3, 125.9, 122.2, 120.5, 113.2, 111.7, 111.5, 34.9, 31.6, 21.8; HRMS (ESI) calcd for $C_{28}H_{27}N_2$ [M + H] 391.2174, found 391.2187.

4-Cyclohex-1-en-1-yl-6-methyl-2-phenyl-9H-pyrido[2,3-b]indole (**6j**): white solid; yield = 56%; mp 206−208 °C; FT-IR (KBr) ν_{max} 2931, 1634, 1218 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.10 (d, J = 7.2 Hz, 2H), 7.68 (s, 1H), 7.47−7.32 (m, 5H), 7.19 (d, J = 7.4 Hz, 1H), 5.98 (s, 1H), 2.45−2.44 (m, 2H), 2.39 (s, 3H), 2.25 (s, 2H), 1.85−1.75 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 152.8, 147.8, 139.5, 137.6, 136.2, 128.7, 128.6, 128.0, 127.4, 127.2, 126.8, 122.1, 120.3, 111.1, 111.0, 28.2, 24.9, 22.6, 21.8, 21.4; HRMS (ESI) calcd for $C_{24}H_{23}N_2$ [M + H] 339.1861, found 339.1873.

7-Fluoro-4-hexyl-2-phenyl-9H-pyrido[2,3-b]indole (**6k**): white solid; yield = 44%; mp 150−152 °C; FT-IR (KBr) ν_{max} 3157, 2946, 1450, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.30 (s, 1H), 8.13 (d, J = 5.1 Hz, 2H), 7.86−7.88 (m, 1H), 7.55 (s, 3H), 7.42 (s, 1H), 6.92−6.90 (m, 1H), 5.95 (d, J = 8.9 Hz, 1H), 3.20 (s, 2H), 1.87−1.81 (m, 3H), 1.52−1.26 (s, 5H), 0.90 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.1, 153.9 (d, J = 15 Hz), 147.8, 140.6, 140.2 (d, J = 13 Hz), 129.4, 128.9, 128.1, 123.3 (d, J = 10 Hz), 117.3, 114.4, 113.7, 107.9 (d, J = 24 Hz), 98.4 (d, J = 27 Hz), 34.1, 31.8, 29.6, 29.2, 22.7, 14.2; HRMS (ESI) calcd for $C_{23}H_{24}FN_2$ [M + H] 347.1923, found 347.1928.

4-(4-tert-Butylphenyl)-7-(trifluoromethyl)-2-phenyl-9H-pyrido-[2,3-b]indole (**6l**): white solid; yield = 70%; mp 243−244 °C; FT-IR (KBr) ν_{max} 3044, 2957, 1522, 1249 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.25 (d, J = 7.0 Hz, 2H), 7.80−7.72 (m, 5H), 7.65 (d, J = 8.3 Hz, 2H), 7.55−7.44 (m, 3H), 7.39 (d, J = 8.6 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.6, 153.4, 151.7, 146.2, 138.9, 138.7, 135.2, 129.1, 128.8, 128.3, 127.1, 126.5, 126.0, 125.7, 122.9, 122.5, 115.6, 113.7, 110.5, 108.1, 34.5, 31.1; HRMS (ESI) calcd for $C_{28}H_{24}F_3N_2$ [M + H] 445.1891, found 445.1890.

2,4-Diphenyl-7-(trifluoromethyl)-9H-pyrido[2,3-b]indole (**6m**): white solid; yield = 75%; mp 238−240 °C; FT-IR (KBr) ν_{max} 3034, 2868, 1593, 1232 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.46 (s, 1H), 8.26 (d, J = 7.0 Hz, 2H), 7.80−7.76 (m, 4H), 7.71−7.45 (m, 7H), 7.38 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.7, 153.4, 146.3, 138.9, 138.7, 138.1, 129.2, 129.1, 129.0, 128.8, 128.6, 127.1, 126.5, 126.1, 122.9, 122.4, 115.6, 113.6, 110.5, 108.2; HRMS (ESI) calcd for $C_{24}H_{16}F_3N_2$ [M + H] 389.1265, found 389.1265.

7-Fluoro-4-(4-methylphenyl)-2-phenyl-9H-pyrido[2,3-b]indole (**6n**): white solid; yield = 71%; mp >250 °C; FT-IR (KBr) ν_{max} 3092, 2940, 1509, 1212 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.20 (d, J = 7.2 Hz, 2H), 7.65 (d, J = 8.0 Hz, 3H), 7.58−7.49 (m, 3H), 7.46−7.43 (m, 3H), 7.25 (dd, J = 2.3, 9.6 Hz, 1H), 6.90 (td, J = 2.3, 9.6 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 163.7, 158.9, 153.2, 152.8, 144.8, 140.4 (d, J = 13 Hz), 139.2, 138.4, 135.5, 129.5, 128.8, 128.5, 126.9, 123.2 (d, J = 10 Hz), 116.7, 113.3, 111.2, 107.3 (d, J = 24 Hz), 97.9 (d, J = 32 Hz), 20.9; HRMS (ESI) calcd for $C_{24}H_{18}FN_2$ [M + H] 353.1454, found 353.1442.

2,4-Bis(4-methylphenyl)-9H-pyrido[2,3-b]indole (**6o**): white solid; yield = 70%; mp 245−247 °C; FT-IR (KBr) ν_{max} 3057, 2973, 1588, 1298 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.1 (d, J =

8.0 Hz, 2H), 7.69−7.63 (m, 3H), 7.53 (s, 1H), 7.41−7.32 (m, 4H), 7.25−7.22 (m, 1H), 7.03−6.98 (m, 1H), 6.84 (d, J = 8.1 Hz, 1H), 2.51 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.6, 153.1, 145.6, 139.9, 138.7, 138.6, 136.9, 136.2, 129.8, 129.7, 128.9, 127.2, 126.8, 122.1, 120.4, 119.6, 113.0, 111.8, 111.6, 21.4, 21.3; HRMS (ESI) calcd for $C_{25}H_{21}N_2$ [M + H] 349.1704, found 349.1690.

*4-(4-tert-Butylphenyl)-2-(4-methylphenyl)-9H-pyrido[2,3-b]indole (**6p**):* white solid; yield = 69%; mp >250 °C; FT-IR (KBr) ν_{max} 3047, 2955, 1450, 1025 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (s, 1H), 8.13 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.66−7.61 (m, 4H), 7.50 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 2.38 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 153.1, 152.7, 151.4, 145.0, 139.5, 138.3, 136.5, 135.8, 129.4, 128.4, 126.8, 126.3, 125.6, 121.7, 120.0, 119.2, 112.7, 111.3, 111.1, 34.6, 31.2, 20.8; HRMS (ESI) calcd for $C_{28}H_{27}N_2$ [M + H] 391.2174, found 391.2161.

*6-Methyl-2-(4-methylphenyl)-4-phenyl-9H-pyrido[2,3-b]indole (**6q**):* white solid; yield = 74%; mp 224−226 °C; FT-IR (KBr) ν_{max} 3063, 2995, 1587, 1217 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.77−7.74 (m, 2H), 7.66−7.58 (m, 4H), 7.40 (d, J = 8.2 Hz, 1H), 7.32−7.30 (m, 3H), 7.22 (d, J = 8.2 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 152.8, 144.9, 138.8, 138.2, 137.7, 136.6, 129.3, 128.7, 128.6, 127.7, 127.6, 126.7, 121.5, 120.0, 112.4, 112.4, 111.1, 110.9, 21.2, 20.8; HRMS (ESI) calcd for $C_{25}H_{21}N_2$ [M + H] 349.1704, found 349.1704.

*7-Fluoro-2-(4-methylphenyl)-4-phenyl-9H-pyrido[2,3-b]indole (**6r**):* white solid; yield = 76%; mp >250 °C; FT-IR (KBr) ν_{max} 3088, 2922, 1590, 1210 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.12 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 6.4 Hz, 2H), 7.64−7.59 (m, 4H), 7.51−7.46 (m, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.27−7.24 (m, 1H), 6.92−6.87 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 153.1, 153.0, 144.7, 140.5, 138.5, 136.4, 129.4, 128.9, 128.6, 126.8, 123.1, 123.0, 116.7, 112.9, 110.9, 107.5, 107.1, 98.1, 97.6, 20.8 ppm; HRMS (ESI) calcd for $C_{24}H_{18}FN_2$ [M + H] 353.1454, found 353.1459.

*4-(4-tert-Butylphenyl)-7-fluoro-2-(4-methylphenyl)-9H-pyrido-[2,3-b]indole (**6s**):* white solid; yield = 69%; mp >250 °C; FT-IR (KBr) ν_{max} 3004, 2965, 1599, 1216 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.09 (d, J = 8.1 Hz, 2H), 7.79−7.53 (m, 6H), 7.30−7.21 (m, 3H), 6.93−6.86 (m, 1H), 2.35 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 160.0, 153.1 (d, J = 30 Hz), 151.5, 144.7, 140.3 (d, J = 13 Hz), 138.3, 136.4, 135.6, 129.4, 128.3, 126.8, 125.7, 123.1 (d, J = 10 Hz), 116.8, 113.1, 110.8, 107.3 (d, J = 24 Hz), 97.8 (d, J = 26 Hz), 34.6, 31.2, 20.8; HRMS (ESI) calcd for $C_{28}H_{26}FN_2$ [M + H] 409.2080, found 409.2084.

*4-Cyclohex-1-en-1-yl-7-(trifluoromethyl)-2-(4-methylphenyl)-9H-pyrido[2,3-b]indole (**6t**):* white solid; yield = 58%; mp >250 °C; FT-IR (KBr) ν_{max} 3099, 2917, 1595, 1232 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.17−8.10 (m, 3H), 7.77 (s,1H), 7.59 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 6.09 (s, 1H), 2.50 (s, 2H), 2.38 (s, 3H), 2.32 (s, 2H), 1.91−1.82 (m, 4H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 154.6, 153.4, 149.0, 138.6, 135.9 (d, J = 27 Hz), 129.4, 128.6 (d, J = 22 Hz), 127.8, 127.1, 126.9, 125.7, 123.2, 122.8, 122.5, 115.7, 111.5, 109.9, 108.0, 28.1, 24.9, 22.5, 21.6, 20.8; HRMS (ESI) calcd for $C_{25}H_{22}F_3N_2$ [M + H] 407.1735, found 407.1740.

*2-(3,4-Dimethoxyphenyl)-4-phenyl-9H-pyrido[2,3-b]indole (**6u**):* pale yellow solid; yield = 64%; mp 211−213 °C; FT-IR (KBr) ν_{max} 2953, 1452, 1261 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.83−7.75 (m, 4H), 7.66−7.58 (m, 4H), 7.49 (d, J = 5.7 Hz, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.09−6.99 (m, 2H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.1, 152.6, 149.7, 149.0, 145.1, 139.5, 138.8, 132.0, 128.8, 128.7, 128.7, 126.3, 121.6, 120.0, 119.7, 119.2, 112.4, 111.8, 111.4, 110.9, 110.2, 55.6; HRMS (ESI) calcd for $C_{25}H_{21}N_2O_2$ [M + H] 381.1603, found 381.1602.

*2-(3,4-Dimethoxyphenyl)-6-methyl-4-(4-methylphenyl)-9H-pyrido[2,3-b]indole (**6v**):* orange solid; yield = 70%; mp 211−212 °C; FT-IR (KBr) ν_{max} 3194, 2952, 1514, 1259 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.79−7.75 (m, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.55 (s, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.39−7.37 (m, 2H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 152.9, 149.7, 149.0, 145.1, 138.3, 137.7, 136.0, 132.2, 129.4, 128.6, 127.7, 127.6, 121.6, 120.2, 119.6, 112.4, 111.8, 111.1, 110.7, 110.2, 55.6, 21.4, 21.0; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_2$ [M + H] 409.1916, found 409.1898.

*2-(3,4-Dimethoxyphenyl)-4-phenyl-7-(trifluoromethyl)-9H-pyrido[2,3-b]indole (**6w**):* white solid; yield = 66%; mp 158−160 °C; FT-IR (KBr) ν_{max} 2946, 2836, 1449, 1221 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.45 (s, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.79−7.74 (m, 4H), 7.66−7.64 (m, 4H), 7.36 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.6, 153.3, 150.1, 149.0, 146.2, 138.5, 138.3, 131.6, 129.0, 128.6, 126.6, 126.2, 125.8, 123.0, 122.2, 119.9, 115.6, 113.1, 111.7, 110.3, 110.0, 108.1, 55.6; HRMS (ESI) calcd for $C_{26}H_{20}F_3N_2O_2$ [M + H] 449.1477, found 449.1477.

*4-Cyclohex-1-en-1-yl-7-fluoro-2-(3,4-dimethoxyphenyl)-9H-pyrido[2,3-b]indole (**6x**):* pale yellow solid; yield = 52%; mp 222−224 °C; FT-IR (KBr) ν_{max} 3097, 2958, 1509, 1259 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.96−7.91 (m, 1H), 7.75 (d, J = 9.0 Hz, 2H), 7.50 (s, 1H), 7.22 (dd, J = 2.1, 9.6 Hz, 1H), 7.08−7.00 (m, 2H), 6.04 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.50 (s, 2H), 2.30 (s, 2H), 1.90−1.81 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.0 (d, J = 239 Hz), 152.4 (d, J = 32 Hz), 149.7, 148.9, 147.4, 140.1 (d, J = 12 Hz), 135.9, 132.0, 127.3, 123.4 (d, J = 11 Hz), 119.5, 117.0, 111.7, 110.9, 110.2, 110.1, 107.3 (d, J = 24 Hz), 97.7 (d, J = 27 Hz), 55.6, 28.1, 24.9, 22.6, 21.7; HRMS (ESI) calcd for $C_{25}H_{24}FN_2O_2$ [M + H] 403.1822, found 403.1819.

*2-tert-Butyl-4-phenyl-9H-pyrido[2,3-b]indole (**6y**):* pale yellow solid; yield = 10%; mp 202−204 °C; FT-IR (KBr) ν_{max} 3154, 2942, 1513, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.69 (d, J = 6.5 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.56−7.46 (m, 3H), 7.37−7.29 (m, 2H), 7.18 (s, 1H), 7.02−6.97 (m, 1H), 1.50 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.3, 145.6, 139.8, 138.8, 128.9, 128.8, 128.6, 126.2, 122.5, 121.2, 119.6, 112.8, 111.4, 111.0, 37.9, 30.8; HRMS (ESI) calcd for $C_{21}H_{21}N_2$ [M + H] 301.1705, found 301.1706.

*2-Phenyl-9H-pyrido[2,3-b]indole (**6z**):* pale yellow solid; yield = 42%; mp 242−244 °C (lit.[27] mp 245−246); FT-IR (KBr) ν_{max} 3134, 2931, 1601, 1449 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.53 (d, J = 8.1 Hz, 1H), 8.18−8.14 (m, 3H), 7.77 (d, J = 8.1 Hz, 1H), 7.53−7.40 (m, 5H), 7.22 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 152.1, 139.5, 139.4, 129.2, 128.7, 128.6, 126.7, 126.6, 121.1, 120.4, 119.5, 114.3, 111.9, 111.3; HRMS (ESI) calcd for $C_{17}H_{13}N_2$ [M + H] 245.1079, found 245.1065.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR, HRMS spectra of all obtained compounds, and 2D spectra of **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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