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Solvent-free synthesis of δ-carbolines/carbazoles from 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives using DPPE as a reducing agent

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ABSTRACT

A green and efficient preparation of functionalized δ-carbolines/carbazoles via reductive ring closure by 1,2-bis(dipenylphosphino)ethane under solvent-free conditions is described. The starting materials 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives are readily prepared through Suzuki–Miyaura cross-coupling reaction from commercially available compounds. And the polar by-product ethane-1,2-diylbis(diphenylphosphine oxide) is easily removed from the relatively polar reaction mixture. Various substituted δ-carbolines/carbazoles are obtained in acceptable yields. It is particularly worth mentioning that substrates with electron-withdrawing groups (EWG) also give the desired products in good yield.
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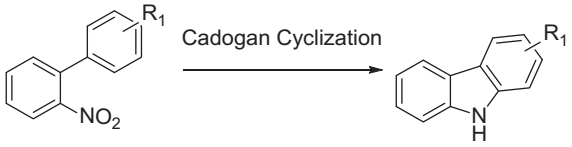
1. Introduction

Carbolines and carbazoles are the key structural units for a variety of biologically important natural alkaloids and pharmaceuticals.[1–6] A number of carbolines/carbazoles display various biological properties including antimalarial, antitumor, anti-plasmodial, and antitrypanosomal activities.[7,8] In addition, carbazoles are important building blocks in materials science.[9] The synthesis of carboline/carbazole derivatives including naturally occurring carbolines/carbazoles has received considerable attention.[10–12] The development of green and efficient approach to both core structures with different functional groups is a major objective in organic synthesis currently.

Few efficient methods are described for preparing functionalized δ-carbolines.[13–24] And most of the syntheses reported in the literature for δ-carbolines are low yielding and require several steps from starting materials. Those materials are usually unstable or not commercially available. One important general method for carbazole synthesis is Cadogan cyclization, while preparation of δ-carbolines by Cadogan cyclization has not been described in the literature. This reaction involves the reductive cyclization of 2-ntitrobiphenyl derivatives in the presence of trivalent organophosphorus reagents (Scheme 1). $P(OEt)_3$ and PPh_3 are usually employed as reductants, and $P(OEt)_3$ is also used as solvent in reactions. The reductive cyclizations with $P(OEt)_3$ suffer from several drawbacks: the first is the strong foul-smelling odor of this toxic solvent; the second is that the side products *N*-hydroxy derivatives and ethylated carbazoles or *N*-ethylindoles are usually formed in those reactions, which are quite difficult to remove from the desired products; Thirdly a large excess of $P(OEt)_3$ was used. The ethylation is probably due to alkylation of the nitrogen by the solvent or generated triethyl phosphate.[25–28] These side reactions could be avoided by using PPh_3 as reductant due to the non-electrophilic property of triphenylphosphine oxide.[29]



Scheme 1. Cadogan cyclization with organo-phosphorus reagents.

Cadogan and co-workers described reductive cyclization of 2-nitrobiphenyl to carbazole with molten PPh_3 in a sealed tube only in modest yield (43%).[30–33] Freeman used high boiling-point *o*-dichlorobenzene (*o*-DCB) as solvent at high temperature (refluxed at 180 °C) for long time[29] and Sanz needed toxic and not-easily obtained molybdenum complex as catalyst.[34] However, in some cases triphenylphosphine oxide could be a stumbling block in purification because it is very difficult to separate from polar products.[29,35,36]

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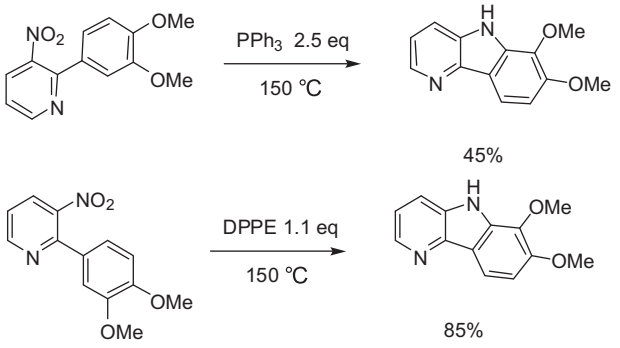
On the other hand, those reported Cadogan reactions are limited in the diversity of functional groups (R_1) on the benzene, in which R_1 represents hydrogen, halogen or electron-donating groups, such as methoxy, alkyl group. Substrates with strong electron-withdrawing groups as R_1 are scarcely explored. Here we describe a concise solvent-free method for the synthesis of novel or useful substituted δ-carbolines/carbazoles from the reductive deoxygenation of the nitro group of the corresponding 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives using a slight excess of 1, 2-bis(dipenylphosphino)-ethane (DPPE). And the starting materials 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives are easily prepared through Suzuki–Miyaura cross-coupling reaction of commercially available 2-chloro-3-nitro-pyridine/chloro-2-nitro-benzene and various boronic acids.

2. Results and discussion

We chose δ-carbolines as the synthetic target compound at first because of their high polarity. We compared the efficacy of triphenylphosphine and DPPE during the reductive cyclization of 2-(3,4-dimethoxyphenyl)-3-nitropyridine (Scheme 2). Because DPPE had two reductive groups, we employed 1.1 M equiv of DPPE as reducing agent. The conditions were simple: 2-(3,4-dimethoxyphenyl)-3-nitropyridine and PPh_3 or DPPE were mixed well and heated at 150 °C under N_2 atmosphere, respectively. After 5 h TLC indicated the reaction was complete. When PPh_3 was used, 6,7-dimethoxy-δ-Carboline only could be obtained in moderate yield (45%) by column chromatography. In addition, it is very difficult to separate PPh_3O from the polar product. While DPPE was employed instead of PPh_3 the purification of the δ-carboline was easily achieved by simple column chromatography in excellent yield (85%) as we expected and the product was not contaminated by any side product DPPE dioxide.

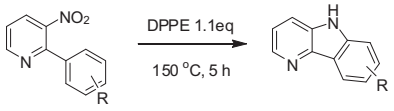


Scheme 2. Reductive cyclization of 2-(3,4-dimethoxyphenyl)-3-nitropyridine to δ-carboline.

Subsequently, we examined the effect of temperature on the reaction. Increasing the temperature to 180 °C made the reaction completed within 30 min, but the yield decreased dramatically (50%). While at 130 °C, the starting material 2-(3,4-dimethoxyphenyl)-3-nitropyridine was not consumed completely after 9 h, afforded the product in 60% yield.

Thus, after establishing the general experimental conditions, we set about to elaborate the substrate scope and functional group tolerance of the method. We prepared a wide variety of 3-nitro-2-phenylpyridines with different functional groups through Suzuki–Miyaura cross-coupling reactions between the appropriately substituted phenyl boronic acids and 2-chloro-3-nitropyridine. The cross-couplings were performed by microwave heating in common conditions: aqueous potassium carbonate (2 equiv), 5% mol $Pd(PPh_3)_4$ and afforded moderate to good yields (50%–92%). Once these intermediates were accessible, they were subjected to reductive cyclization using our previously optimized conditions. The results were summarized in Table 1.

Table 1
δ-Carbolines prepared by reductive cyclization of 3-nitro-2-phenylpyridines[a]



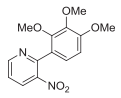
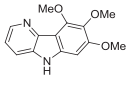
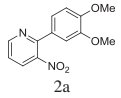
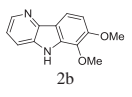
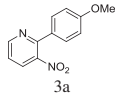
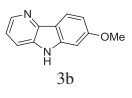
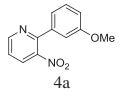
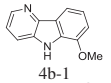
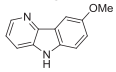
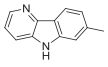
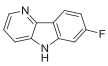
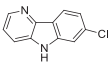
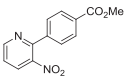
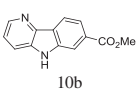
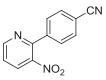
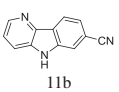
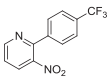
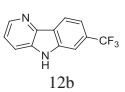
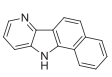
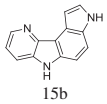
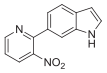
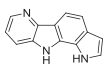
Entry	Substrate	Product	Yield (%)
1	 1a	 1b	70
2	 2a	 2b	85
3	 3a	 3b	75
4	 4a	 4b-1	36
		 4b-2	45
5	 5a	 5b	60
6	 6a	 6b	65
7	 7a	 7b	66
8	 8a	 8b	60
9	 9a	 9b	50
10	 10a	 10b	52
11	 11a	 11b	50
12	 12a	 12b	56
13	 13a	 13b	90

Table 1 (*continued*)

Entry	Substrate	Product	Yield (%)
14	 14a	 14b	89
15	 15a	 15b	50
16	 16a	 16b	68
17	 17a	 17b	60

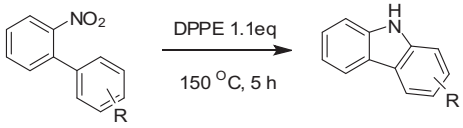
[a] Reactions were run on a 100 mg scale of 3-nitro-2-phenylpyridines and 1.1 equiv DPPE at 150 °C for 5 h. DPPE=1,2-bis(dipenylphosphino)ethane.

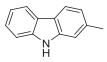
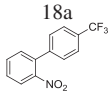
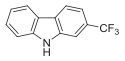
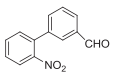
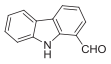
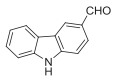
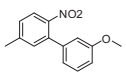
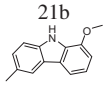
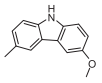
Generally, the reaction could complete within 5 h and gained moderate to good yields. The regioselectivity of this reaction was dependent on the nature of electron density of the carbon and the intermediate nitrene was in favor of insertion into relatively electron-rich carbon-hydrogen bond (entries 2 and 13–17). When there was one methoxy group on the *meta*-position of benzene, the nitrene insertion took place both at *ortho*- and *para*-position, the yield of *para*-product was slightly higher than that of *ortho*-compound (entry 4). When there are two methoxy groups on the benzene ring, the nitrene insertion mainly took place at the relatively electron rich *ortho*-position to the methoxy, and no *para*-product was obtained (entry 2). Similarly the insertion only took place at the α-position of thiophene (entry 17). Moreover, the reaction could tolerate a wide range of functional groups, including not only electron-donating groups (EDG), such as alkoxy, alkyl groups (entries 4–7), but also electron-withdrawing groups (EWG) as carboxylic ester, nitrile, and trifluoromethyl group (entries 8–12). To our delight, carbolines could be easily purified by simple column chromatography and the by-product 1,2-bis(dipenylphosphino) ethane oxide was removed completely.

Finally, we extended our method to the syntheses of functionalized carbazoles in good to excellent yields. Both substrates with EDG or EWG proceeded smoothly (Table 2). Aldehyde group was also tolerated in this reaction, and the result was similar to the substrates with EDG (entry 20 vs entry 4). Noticeably, compound **20b-1**, a key intermediate of popular heart failure drug carvedilol, was obtained in nearly quantitative yield (entry 21). Bautista and co-workers reported a tedious total synthesis procedure of natural antimicrobial product glycozolicine **22b-1**, which was also the natural precursor of mukolidine and mukoline.[37] We prepared glycozolicine in a concise two-step procedure in acceptable yield (entry 22). However, when we tried to synthesize unsubstituted β-carboline from 4-(2-nitrophenyl)pyridine using the same protocol, the reaction only yielded product in 30%, and it was not easy to separate the product from DPPE dioxide due to the significant polarity of the β-carboline.

In order to make such a reaction practical, the solvent-free synthesis of δ-carboline **3b**/**13b** was scaled-up to yield gram quantities. For the compound **3b**, starting from 2.50 g of **3a**, 1.50 g of **3b** was produced (70% yield). In the subsequent preparation of **13b**, 2.30 g of **13a** was utilized to produce 1.83 g (91.5% yield).

Table 2
Carbazoles prepared by DPPE mediated reductive cyclization[a]



Entry	Substrate	Product	Yield (%)
18	 18a	 18b	65
19	 19a	 19b	70
20	 20a	 20b-1	33
		 20b-2	47
21	 21a	 21b	98
22	 22a	 22b-1	46
		 22b-2	37

[a] Reactions were run on a 100 mg scale of 2-nitro-1,1′-biphenyls and 1.1eq DPPE at 150 °C for 5 h. DPPE=1,2-bis(dipenylphosphino)ethane.

3. Conclusion

An efficient and practical solvent-free synthesis of novel or useful δ-carbolines/carbazoles has been developed. A wide variety of functionalized 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives were used to afford the desired aza heterocycles in acceptable to excellent yields and various functional groups are tolerated well. The advantages of this method include its environmentally benign, simple manipulation, short reaction time, and high regioselectivity. It is the first time using DPPE as a reductant in Cadogan cyclization. More importantly, the procedure using DPPE as reductant may provide a better approach to construct more polar nitrogen heterocycles than using PPh_3.

4. Experimental section

4.1. General procedure

Reagents (chemicals) were purchased and used without further purification. Analytical thin layer chromatography (TLC) used was

HSGF 254 (0.15–0.2 mm) thickness. All products were characterized by NMR and MS. Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained.

4.2. Detailed synthetic protocols

4.2.1. General procedures for preparations of ***1a–22a****.* A 30-mL screw-cap culture tube was charged with 2-chloro-3-nitropyridine (3.16 mmol), phenyl boronic acid (3.80 mmol, 1.2 equiv), and DMF (10 mL). $Pd(PPh_3)_4$ (5% eq) and K_2CO_3 (0.3 mL of 2 M aqueous solution, 0.60 mmol, 2 equiv) were added to the tube sparged with N_2 for 5 min. The reaction mixture was stirred and then irradiated for 15 min at 50 W. The resulting mixture was diluted with ethyl acetate and washed with water and brine, and then was dried over anhydrous Na_2SO_4. The residue was concentrated with an evaporator, and purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluent, yielded the desired product.

*4.2.1.1. 3-Nitro-2-(2,3,4-trimethoxyphenyl)pyridine (****1a****).* A yellow powder (92% yield): mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (dd, J=4.8, 1.5 Hz, 1H), 8.24 (dd, J=8.1, 1.5 Hz, 1H), 7.41 (dd, J=8.1, 4.7 Hz, 1H), 7.37 (d, J=8.8 Hz, 1H), 6.82 (d, J=8.8 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.3, 150.9, 150.1, 146.4, 141.2, 131.9, 124.8, 123.6, 121.9, 107.4, 61.0, 60.7, 56.0. HRMS (m/z) calcd for $C_{14}H_{14}N_2O_5$ $[M]^+$ 290.0903, found 290.0900.

4.2.1.2. 2-(3,4-Dimethoxyphenyl)-3-nitropyridine[38] *(****2a****).* A yellow powder (75% yield): mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.82 (dd, J=4.8, 1.4 Hz, 1H), 8.07 (dd, J=8.0, 1.4 Hz, 1H), 7.39 (dd, J=8.0, 4.7 Hz, 1H), 7.26 (s, 1H), 7.19 (d, J=1.8 Hz, 1H), 7.11 (dd, J=8.1, 1.9 Hz, 1H), 6.92 (d, J=8.1 Hz, 1H), 3.93 (s, 6H).

4.2.1.3. 2-(4-Methoxyphenyl)-3-nitropyridine[38] *(****3a****).* A pale yellow powder (80% yield): mp 230–232 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.88 (dd, J=4.7, 1.4 Hz, 1H), 8.40 (dd, J=8.2, 1.4 Hz, 1H), 7.62 (dd, J=8.2, 4.7 Hz, 1H), 7.49 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 3.82 (s, 3H).

*4.2.1.4. 2-(3-Methoxyphenyl)-3-nitropyridine (****4a****).* A white powder (70% yield), mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.86 (dd, J=4.7, 1.5 Hz, 1H), 8.13 (dd, J=8.1, 1.5 Hz, 1H), 7.45 (dd, J=8.1, 4.7 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 7.16–7.12 (m, 1H), 7.10 (ddd, J=7.6, 1.6, 1.0 Hz, 1H), 7.02 (ddd, J=8.3, 2.6, 1.0 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 152.6, 152.0, 146.3, 137.4, 132.0, 129.8, 122.4, 120.2, 115.8, 113.2, 55.3. HRMS (m/z) calcd for $C_{12}H_{10}N_2O_3$ $[M]^+$, 230.0691, found 230.0697.

*4.2.1.5. 2-(2-Methoxyphenyl)-3-nitropyridine (****5a****).* A yellow powder (86% yield), mp 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.87 (d, J=4.7 Hz, 1H), 8.21 (d, J=8.5 Hz, 1H), 7.67 (dd, J=7.7 Hz, 1H), 7.48–7.36 (m, 2H), 7.14 (t, J=7.7 Hz, 1H), 6.91 (d, J=8.5 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 152.4, 150.4, 146.9, 131.6, 131.2, 130.4, 126.1, 122.1, 121.4, 110.5, 54.9. HRMS (m/z) calcd for $C_{12}H_{10}N_2O_3$ $[M]^+$, 230.0691, found 230.0696.

4.2.1.6. 3-Nitro-2-(p-tolyl)pyridine[39] *(****6a****).* A yellow powder (90% yield), mp 88–90 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.84 (dd, J=4.7, 1.5 Hz, 1H), 8.11 (dd, J=8.4, 1.5 Hz, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.40 (dd, J=8.4, 4.7 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 2.41 (s, 3H).

4.2.1.7. 3-Nitro-2-(o-tolyl)pyridine[39] *(****7a****).* A yellow solid (70% yield), mp 58–60 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.88 (d, J=4.8 Hz, 1H), 8.28 (d, J=8.1 Hz, 1H), 7.50–7.45 (m, 1H), 7.40–7.22 (m, 3H), 7.18 (d, J=7.7 Hz, 1H), 2.17 (s, 3H).

4.2.1.8. 2-(4-Fluorophenyl)-3-nitropyridine[40] *(****8a****).* A white powder (65% yield), mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (dd, J=4.7, 1.5 Hz, 1H), 8.15 (dd, J=8.2, 1.5 Hz, 1H), 7.59–7.53 (m, 2H), 7.46 (dd, J=8.2, 4.7 Hz, 1H), 7.22–7.08 (m, 2H).

*4.2.1.9. 2-(4-Chlorophenyl)-3-nitropyridine (****9a****).* A yellow powder (63% yield), mp 134–136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.86 (dd, J=4.7, 1.5 Hz, 1H), 8.1 (dd, J=8.2, 1.5 Hz, 1H), 7.56–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 151.6, 145.9, 136.0, 134.6, 132.3, 129.4, 128.9, 122.7. HRMS (m/z) calcd for $C_{11}H_7ClN_2O_2$ $[M]^+$, 234.0196, found 234.0195.

*4.2.1.10. Methyl 4-(3-nitropyridin-2-yl)benzoate (****10a****).* A white powder (62% yield), mp 118–120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.89 (dd, J=4.7, 1.5 Hz, 1H), 8.21 (dd, J=8.2, 1.45 Hz, 1H), 8.14 (d, J=8.5 Hz, 2H), 7.63 (d, J=8.5 Hz, 2H), 7.50 (dd, J=8.2, 4.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 152.3, 152.0, 146.1, 140.6, 132.4, 131.1, 129.9, 128.1, 123.0, 52.3. HRMS (m/z) calcd for $C_{13}H_{10}N_2O_4$ $[M]^+$, 258.0641, found 258.0649.

*4.2.1.11. 4-(3-Nitropyridin-2-yl)benzonitrile (****11a****).* A white powder (66% yield): mp 192–194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.90 (dd, J=4.7, 1.4 Hz, 1H), 8.26 (dd, J=8.2, 1.4 Hz, 1H), 7.77 (d, J=8.2 Hz, 2H), 7.66 (d, J=8.2 Hz, 2H), 7.55 (dd, J=8.2, 4.7 Hz, 1H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5, 151.1, 145.9, 140.8, 132.6, 132.4, 128.9, 123.5, 118.2, 113.4. HRMS (m/z) calcd for $C_{12}H_7N_3O_2$ $[M]^+$, 225.0538, found 225.0538.

4.2.1.12. 3-Nitro-2-(4-(trifluoromethyl)phenyl)pyridine[41] *(****12a****).* A yellow powder (64% yield), mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.90 (d, J=4.7 Hz, 1H), 8.23 (d, J=8.1 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.52 (dd, J=8.1, 4.7 Hz, 1H).

4.2.1.13. 2-(Naphthalen-2-yl)-3-nitropyridine[42] *(****13a****).* A yellow powder (50% yield), mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (dd, J=4.7, 1.5 Hz, 1H), 8.20 (dd, J=8.2, 1.5 Hz, 1H), 8.11 (s, 1H), 7.9–7.82 (m, 3H), 7.62 (dd, J=8.5, 1.8 Hz, 1H), 7.57–7.52 (m, 2H), 7.48 (dd, J=8.2, 4.7 Hz, 1H).

*4.2.1.14. 2-(Naphthalen-1-yl)-3-nitropyridine (****14a****).* A yellow powder (60% yield), mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.38 (s, 1H), 8.97 (dd, J=4.7, 1.5 Hz, 1H), 8.49 (dd, J=8.2, 1.5 Hz, 1H), 7.70 (dd, J=8.2, 4.7 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.43 (t, J=2.8 Hz, 1H), 7.22 (t, J=7.6 Hz, 1H), 7.15 (d, J=7.9 Hz, 1H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.9, 146.6, 135.9, 132.8, 128.0, 126.7, 125.9, 123.0, 120.9, 119.4, 112.9, 99.3. HRMS (m/z) calcd for $C_{13}H_9N_3O_2$ $[M]^+$, 239.0695, found 239.0701.

*4.2.1.15. 4-(3-Nitropyridin-2-yl)-1H-indole (****15a****).* Yellow oil (65% yield); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.97 (dd, J=4.7, 1.4 Hz, 1H), 8.37 (dd, J=8.2, 1.4 Hz, 1H), 8.02–7.88 (m, 2H), 7.62–7.40 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 152.6, 147.0, 134.4, 133.5, 132.2, 130.8, 129.7, 128.5, 126.9, 126.3, 126.2, 125.1, 124.1, 123.0. HRMS (m/z) calcd for $C_{15}H_{10}N_2O_2$ $[M]^+$, 250.0742, found 250.0739.

*4.2.1.16. 6-(3-Nitropyridin-2-yl)-1H-indole (****16a****).* A red power (75% yield), mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, J=4.7 Hz, 1H), 8.35 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.71 (m, 2H), 7.39 (dd, J=8.0, 4.7 Hz, 1H), 7.31 (m, 2H), 6.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 151.8, 146.4, 135.7, 132.1, 129.5, 129.1, 126.3, 121.5, 121.1, 119.7, 111.2, 102.6. HRMS (m/z) calcd for $C_{13}H_9N_3O_2$ $[M]^+$, 239.0695, found 239.0701.

*4.2.1.17. 3-Nitro-2-(thiophen-3-yl)pyridine (**17a**).* Yellow oil (60% yield); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.80 (dd, J=4.7, 1.8 Hz, 1H), 8.03 (dd, J=8.2, 1.8 Hz, 1H), 7.77 (dd, J=3.2, 1.4 Hz, 1H), 7.36 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 151.7, 146.6, 145.2, 136.5, 131.5, 126.7, 126.6, 126.1, 121.9. HRMS (m/z) calcd for $C_9H_6N_2O_2S$ $[M]^+$, 206.0150, found 206.0154.

*4.2.1.18. 4′-Methyl-2-nitrobiphenyl (**18a**)*[43]. Yellow oil (90% yield) ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.90 (dd, J=8.1, 1.0 Hz, 1H), 7.77–7.69 (m, 1H), 7.65–7.58 (m, 1H), 7.54 (dd, J=7.6, 1.1 Hz, 1H), 7.32–7.18 (m, 4H), 2.38 (s, 3H).

*4.2.1.19. 2-Nitro-4′-trifluoromethylbiphenyl (**19a**).* Yellow oil (75% yield); ^{1}H NMR (CD_3OD, 300 MHz): δ 7.98 (dd, J=8.2, 1.1, 1H), 7.78–7.70 (m, 3H), 7.63 (td, J=7.8, 1.5, 1H), 7.55–7.48 (m, 3H).

*4.2.1.20. 2′-Nitrobiphenyl-3-carbaldehyde (**20a**)*[44]. A white powder (86% yield), mp 93–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.00–7.91 (m, 2H), 7.89–7.80 (m, 1H), 7.68 (m, 1H), 7.64–7.52 (m, 3H), 7.46 (dd, J=7.5, 1.3 Hz, 1H).

*4.2.1.21. 2-Methoxy-2′-nitrobiphenyl (**21a**)*[45]. A yellow powder (80% yield), mp 86–87 °C (lit.[46] 83 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (dd, J=8.1, 1.0 Hz, 1H), 7.63 (td, J=7.5, 1.3 Hz, 1H), 7.51–7.35 (m, 3H), 7.32 (dd, J=7.5, 1.5 Hz, 1H), 7.08 (td, J=7.5, 1.1 Hz, 1H), 6.91 (d, J=8.3 Hz, 1H), 3.70 (s, 3H).

*4.2.1.22. 3′-Methoxy-5-methyl-2-nitrobiphenyl (**22a**).* Yellow oil (80% yield), ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, J=8.3 Hz, 1H), 7.46–7.30 (m, 3H), 6.99 (d, J=8.2 Hz, 1H), 6.93–6.80 (m, 2H), 3.79 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.47, 146.76, 143.31, 139.00, 136.12, 132.32, 129.50, 128.63, 124.12, 120.07, 113.45, 113.33, 55.08, 21.20. HRMS (m/z) calcd for $C_{14}H_{13}NO_3$ $[M]^+$, 243.0895, found 243.0890.

4.2.2. General procedures for the preparation of carbolines and carbazoles. 3-Nitro-2-phenylpyridine (0.34 mmol) and DPPE (0.37 mmol, 1.1 equiv) were mixed well in a 10 mL round bottle without solvent, and the bottle was immersed in an oil bath of 150 °C under N_2 atmosphere. The reaction was cooled after 5 h and the residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate as eluants to give the product.

*4.2.2.1. 7,8,9-Trimethoxy-5H-pyrido[3,2-b]indole (**1b**).* A white powder: mp180–182 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.30 (br s, 1H), 8.41 (d, J=4.7 Hz, 1H), 7.77 (d, J=7.9 Hz, 1H), 7.26 (dd, J=8.0, 4.7 Hz, 1H), 6.84 (s, 1H), 4.16 (s, 3H), 3.90 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) : δ 154.3, 148.2, 140.9, 140.7, 138.1, 135.4, 132.5, 118.3, 116.9, 107.7, 90.0, 61.1, 61.0, 55.9; HRMS (m/z) calcd for $C_{14}H_{14}N_2O_3$ $[M]^+$ 258.1004, found 258.0996.

*4.2.2.2. 6,7-Dimethoxy-5H-pyrido[3,2-b]indole (**2b**).* A white powder, mp 186–188 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.36 (br s, 1H), 8.37 (d, J=4.7 Hz, 1H), 7.85 (d, J=8.5 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.30 (dd, J=8.2, 5.0 Hz, 1H), 7.03 (d, J=8.5 Hz, 1H), 3.92 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.7, 142.1, 140.0, 139.6, 134.4, 128.0, 125.0, 121.5, 120.0, 119.8, 118.8, 113.1, 52.1; HRMS (m/z) calcd for $C_{13}H_{12}N_2O_2$ $[M]^+$, 228.0899, found 228.0896.

*4.2.2.3. 7-Methoxy-5H-pyrido[3,2-b]indole (**3b**).* A white powder, mp 228–230 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.29 (br s, 1H), 8.38 (dd, J=4.7, 1.1 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.80 (dd, J=8.2, 1.1 Hz, 1H), 7.29 (dd, J=8.2, 4.7 Hz, 1H), 7.03 (d, J=2.1 Hz, 1H), 6.86 (dd, J=8.5, 2.1 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.9, 142.1, 141.5, 140.9, 132.8, 120.9, 118.8, 117.3, 115.2, 109.0, 94.7, 55.3; HRMS (m/z) calcd for $C_{12}H_{10}N_2O$ $[M+H]^+$, 198.0793, found 198.0801.

*4.2.2.4. 6-Methoxy-5H-pyrido[3,2-b]indole (**4b-1**).* A white powder, mp 242–244 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.48 (br s, 1H), 8.07 (dd, J=4.7, 1.2 Hz, 1H), 7.82 (dd, J=8.2, 1.2 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.36 (dd, J=8.2, 4.7 Hz, 1H), 7.17 (t, J=7.9 Hz, 1H), 7.09 (d, J=7.9 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz,): δ 145.9, 141.3, 141.2, 132.7, 130.6, 122.7, 120.0, 119.8, 118.3, 112.3, 107.6, 55.5; HRMS (m/z) calcd for $C_{12}H_{10}N_2O$ $[M]^+$, 198.0793, found 198.0794.

*4.2.2.5. 8-Methoxy-5H-pyrido[3,2-b]indole (**4b-2**).* A white powder, mp 158–160 °C (lit.[47] 155 °C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.23 (br, 1H), 8.40 (d, J=4.7 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.66 (d, J=2.3 Hz, 1H), 7.48 (d, J=8.8 Hz, 1H), 7.35 (dd, J=8.3, 4.6 Hz, 1H), 7.14 (dd, J=8.8 Hz, 1H), 3.86 (s, 3H).

*4.2.2.6. 9-Methoxy-5H-pyrido[3,2-b]indole (**5b**).* A white powder, mp 288–290 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.44 (br s, 1H), 8.42 (d, J=4.4 Hz, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.41 (t, J=8.2 Hz, 1H), 7.31 (dd, J=7.9, 4.7 Hz, 1H), 7.12 (d, J=8.2 Hz, 1H), 6.74 (d, J=7.9 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.7, 142.1, 141.1, 140.9, 132.1, 128.4, 119.1, 117.2, 110.5, 104.3, 100.7, 55.3. HRMS (m/z) calcd for $C_{14}H_{14}N_2O$ $[M]^+$ 198.0793, found 198.0785.

*4.2.2.7. 7-Methyl-5H-pyrido[3,2-b]indole (**6b**).* A pale yellow powder, mp 212–214 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.78 (br s, 1H), 8.89 (d, J=5.4 Hz, 1H), 8.57 (d, J=8.2 Hz, 1H), 8.26 (d, J=8.2 Hz, 1H), 7.82 (s, 1H), 7.75 (dd, J=8.0, 4.7 Hz, 1H), 7.55 (d, J=7.9 Hz, 1H), 2.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 141.3, 141.0, 140.9, 137.2, 132.8, 120.9, 119.7, 119.6, 119.3, 117.6, 111.5, 21.4. HRMS (m/z) calcd for $C_{12}H_{10}N_2$ $[M]^+$ 182.0844, found 182.0835.

*4.2.2.8. 9-Methyl-5H-pyrido[3,2-b]indole (**7b**).* A white powder, mp 190–192 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.36 (br s, 1H), 8.47 (dd, J=4.7, 1.4 Hz, 1H), 7.85 (dd, J=8.2, 1.4 Hz, 1H), 7.35 (m, 3H), 6.70 (t, J=4.4 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 142.4, 141.0, 140.6, 133.4, 132.8, 127.0, 120.4, 119.7, 119.3, 117.4, 108.9, 19.31; HRMS (m/z) calcd for $C_{12}H_{10}N_2$ $[M]^+$, 82.0844, found 182.0838.

*4.2.2.9. 7-Fluoro-5H-pyrido[3,2-b]indole (**8b**).* A yellowish brown powder, mp 290–292 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.27 (br s, 1H), 8.38 (d, J=4.7 Hz, 1H), 8.02 (d, J=7.9 Hz, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.34–7.28 (m, 2H), 7.05 (d, J=7.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1 (d, J=240 Hz), 141.5, 141.1 (d, J=13 Hz), 140.8, 133.4, 121.6 (d, J=15 Hz), 119.9, 118.3, 118.0, 107.7 (d, J=26 Hz), 98.1 (d, J=26 Hz). HRMS (m/z) calcd for $C_{11}H_7FN_2$ $[M]^+$, 186.0593, found 186.0589.

*4.2.2.10. 7-Chloro-5H-pyrido[3,2-b]indole (**9b**).* A white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.57 (br s, 1H), 8.46 (dd, J=4.7, 1.2 Hz, 1H), 8.15 (d, J=8.8 Hz, 1H), 7.90 (dd, J=8.2, 1.2 Hz, 1H), 7.60 (d, J=1.7 Hz, 1H), 7.40 (dd, J=8.5, 4.7 Hz, 1H), 7.24 (dd, J=8.5, 1.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 141.7, 140.8, 140.4, 133.2, 131.6, 121.3, 120.5, 120.5, 119.6, 118.3, 111.3. HRMS (m/z) calcd for $C_{11}H_7ClN_2$ $[M]^+$, 202.0298, found 202.0296.

*4.2.2.11. Methyl 5H-pyrido[3,2-b]indole-7-carboxylate (**10b**).* A white powder, mp 274–276 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.74 (br s, 1H), 8.54 (d, J=4.1 Hz, 1H), 8.29 (d, J=8.2 Hz, 1H), 8.19 (s, 1H), 7.99 (d, J=9.1 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.48 (dd, J=8.2,

4.7 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.2, 141.8, 140.9, 135.0, 133.5, 133.4, 119.3, 117.6, 117.4, 115.4, 106.8, 60.4, 56.5. HRMS (m/z) calcd for $C_{13}H_{10}N_2O_2$ $[M]^+$, 226.0742, found 226.0736.

*4.2.2.12. 5H-Pyrido[3,2-b]indole-7-carbonitrile (**11b**).* A white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.93 (br s, 1H), 8.57 (d, J=4.6 Hz, 1H), 8.35 (d, J=8.2 Hz, 1H), 8.10 (s, 1H), 8.00 (d, J=8.2 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.52 (dd, J=8.2, 4.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 142.6, 139.6, 139.0, 134.4, 124.8, 122.1, 121.9, 121.0, 119.7, 119.1, 116.3, 108.6. HRMS (m/z) calcd for $C_{12}H_7N_3$ $[M]^+$, 193.0640, found 193.0653.

*4.2.2.13. 7-(Trifluoromethyl)-5H-pyrido[3,2-b]indole[48] (**12b**).* A white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.80 (br s, 1H), 8.55 (d, J=4.7 Hz, 1H), 8.39 (d, J=8.2 Hz, 1H), 8.02 (d, J=8.5 Hz, 1H), 7.92 (s, 1H), 7.54 (d, J=8.2 Hz, 1H), 7.50 (dd, J=8.2, 4.7 Hz, 1H).

*4.2.2.14. 11H-Benzo[g]pyrido[3,2-b]indole (**13b**).* A yellow powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.40 (br s, 1H), 8.53 (m, 2H), 8.23 (d, J=8.2 Hz, 1H), 8.09 (d, J=8.4 Hz, 1H), 8.02 (dd, J=8.5, 1.2 Hz, 1H), 7.66 (m, 3H), 7.41 (dd, J=8.3, 4.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz,): δ 142.0, 141.5, 136.7, 132.8, 131.8, 128.7, 126.1, 125.9, 121.8, 121.3, 120.1, 119.3, 118.7, 118.4, 116.5. HRMS (m/z) calcd for $C_{15}H_{10}N_2$ $[M]^+$, 218.0844, found 218.0841.

*4.2.2.15. 7H-Benzo[e]pyrido[3,2-b]indole (**14b**).* A yellow powder, mp 244–246 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.91 (br s, 1H), 9.44 (d, J=8.2 Hz, 1H), 8.63 (d, J=4.6 Hz, 1H), 8.02 (m, 3H), 7.80 (d, J=8.8 Hz, 1H), 7.73 (t, J=8.2 Hz, 1H), 7.50 (t, J=8.2 Hz, 1H), 7.45 (dd, J=8.2, 4.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz,) δ 142.3, 142.1, 138.4, 131.6, 128.9, 128.5, 128.4, 128.3, 126.9, 123.9, 123.3, 118.6, 118.4, 113.6, 113.1. HRMS (m/z) calcd for $C_{15}H_{10}N_2$ $[M]^+$, 218.0844, found 218.0845.

*4.2.2.16. 3,6-Dihydropyrido[3,2-b]pyrrolo[3,2-e]indole (**15b**).* An earth yellow powder, mp 280–282 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.30 (br s, 1H), 11.26 (br s, 1H), 8.47 (dd, J=4.4, 1.1 Hz, 1H), 7.83 (d, J=6.8 Hz, 1H), 7.58 (d, J=8.5 Hz, 1H), 7.46 (t, J=2.6 Hz, 1H), 7.29 (m, 2H), 7.06 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 142.0, 140.8, 135.7, 131.8, 130.5, 124.9, 120.3, 118.1, 117.1, 112.6, 112.3, 106.1, 100.4. HRMS (m/z) calcd for $C_{13}H_9N_3$ $[M]^+$, 207.0796, found 207.0792.

*4.2.2.17. 1,10-Dihydropyrido[3,2-b]pyrrolo[3,2-g]indole (**16b**).* An earth yellow powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.75 (br s, 1H), 8.88 (dd, J=4.7, 1.5 Hz, 1H), 8.28 (dd, J=8.2, 1.4 Hz, 1H), 7.75 (br s, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.58 (dd, J=8.2, 4.7 Hz, 1H), 7.45 (d, J=3.3 Hz, 1H), 7.24 (dd, J=8.2, 1.5 Hz, 1H), 6.52 (d, J=3.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 142.6, 140.9, 131.2, 127.9, 127.5, 124.4, 121.5, 118.1, 117.9, 115.3, 113.0, 111.6, 103.1. HRMS (m/z) calcd for $C_{13}H_9N_3$ $[M]^+$, 207.0796, found 207.0799.

*4.2.2.18. 8H-Thieno[3′,2′:4,5]pyrrolo[3,2-b]pyridine (**17b**).* A yellow powder, mp 294–296 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.80 (br s, 1H), 8.33 (d, J=4.7 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.43 (dd, J=5.3, 0.9 Hz, 1H), 7.18 (dd, J=8.2, 4.7 Hz, 1H), 7.14 (dd, J=5.2, 0.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 144.8, 141.3, 139.4, 134.8, 123.6, 118.6, 118.4, 117.2, 116.8. HRMS (m/z) calcd for $C_9H_6N_2S$ $[M]^+$, 174.0252, found 174.0250.

*4.2.2.19. 2-Methyl-9H-carbazole[49] (**18b**).* A white solid, mp 249–251 °C (lit.[50] 251–260 °C); ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 10.20 (br s, 1H), 8.05 (d, J=7.6 Hz, 1H), 7.97 (d, J=7.9 Hz, 1H), 7.46 (d, J=7.4 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.31 (s, 1H), 7.16–7.11 (m, 1H), 7.01 (d, J=8.2 Hz, 1H), 2.48 (s, 3H).

*4.2.2.20. 2-(Trifluoromethyl)-9H-carbazole (**19b**).* A white powder, mp 209–211 °C (lit.[51] 210–211 °C); ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 10.77 (br s, 1H), 8.34 (d, J=8.8 Hz, 1H), 8.24 (d, J=8.2 Hz, 1H), 7.88 (s, 1H), 7.62 (d, J=7.4 Hz, 1H), 7.50 (m, 2H), 7.27 (t, J=7.6 Hz, 1H).

*4.2.2.21. 9H-Carbazole-1-carbaldehyde[52] (**20b-1**).* A yellow powder, mp 143–145 °C (143 °C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.86 (br s, 1H), 10.23 (br s, 1H), 8.50 (d, J=7.9 Hz, 1H), 8.20 (d, J=7.9 Hz, 1H), 8.00 (d, J=7.3 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.49–7.42 (m, 1H), 7.41–7.35 (m, 1H), 7.28–7.21 (m, 1H).

*4.2.2.22. 9H-Carbazole-3-carbaldehyde[53] (**20b-2**).* An earth yellow powder, mp 157–159 °C (lit.[54] 158–159 °C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.85 (br s, 1H), 10.03 (br s, 1H), 8.72 (s, 1H), 8.24 (d, J=8.2 Hz, 1H), 7.91 (d, J=8.2 Hz, 1H), 7.61 (d, J=8.5 Hz, 1H), 7.55 (d, J=7.6 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H), 7.25 (t, J=8.1 Hz, 1H).

*4.2.2.23. 4-Methoxy-9H-carbazole (**21b**).* A yellow powder, mp 138–139 °C (lit.[55] 135–136 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.14 (d, J=7.8 Hz, 1H), 7.46 (d, J=8.1 Hz, 1H), 7.28–7.37 (m, 2H), 7.14 (m, 1H), 7.09 (d, J=8.1 Hz, 1H), 6.71 (d, J=7.9 Hz, 1H), 4.02 (s, 3H).

*4.2.2.24. 1-Methoxy-6-methyl-9H-carbazole (**22b-1**).* A white powder, mp 137–139 °C (lit.[56] 137–138 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 1H), 7.84 (s, 1H), 7.63 (d, J=7.7 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.17 (d, J=8.2 Hz, 1H), 7.05 (t, J=7.7 Hz, 1H), 6.94 (d, J=7.6 Hz, 1H), 3.96 (s, 3H), 2.44 (s, 3H).

*4.2.2.25. 3-Methoxy-6-methyl-9H-carbazole (**22b-2**).* A white powder, mp 181–182 °C (lit.[57] 180 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.87 (s, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.34 (d, J=8.3 Hz, 1H), 7.31 (d, J=8.9 Hz, 1H), 7.17 (d, J=8.2 Hz, 1H), 6.98 (dd, J=8.2, 1.9 Hz, 1H), 3.82 (s, 3H), 2.44 (s, 3H).

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