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Palladium-mediated intramolecular O-arylation: a simple route for the synthesis of quino[2,3-*c*] and quino[3,2-*b*]carbazoles

Devanga K. Sreenivas, Rajagopal Nagarajan *

School of Chemistry, University of Hyderabad, Hyderabad 500046, India

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ABSTRACT

A simple route for the synthesis of quinocarbazoles in good yields via palladium-mediated intramolecular arylation involving *ortho* C–H activation is reported.

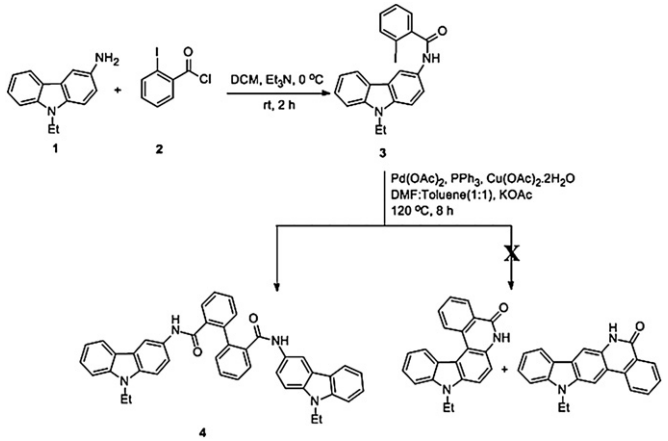
1. Introduction

Aryl–aryl bond plays an important role in the area of transition metal mediated reactions.[1] Among these cross coupling reactions are one of the most important tools. Recently, direct arylation of palladium catalyzed electron rich hetero aromatic rings has begun to replace the above mentioned methods.[2] Intramolecular direct arylation of arenes using palladium catalysts is one of the very useful alternative method for the synthesis of various heterocycles, such as cabazoles, isoquinolines, and indoles.[3] Among these carbazoles[4] and its fused derivatives, such as pyrido,[5] pyrrolo,[6] and quinocarbazoles[7] have attracted considerable attention from medicinal and synthetic chemists mainly because of the wide range of biological applications (antitumor,[8] anticancer,[9] DNA intercalator[10]) displayed by this class of compounds. As a result, immense interest has grown in the development of various methods for the efficient and rapid synthesis of these molecules. Developing new synthetic methodologies for the synthesis of biologically active indole and carbazole skeleton has been our longstanding quest.[11]

In continuation of our interest, herein we report an efficient and simple synthetic protocol for the synthesis of quinocarbazoles from *N*-alkyl-*N*-(9-ethyl-*H*-carbazol-3-yl)-2-iodobenzamides using palladium-catalyzed intramolecular *ortho* arylation. In this paper we described the palladium-catalyzed intramolecular arylation of *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-iodo benzamide derivatives for the synthesis of two isomers of quinocarbazoles. The formation of two isomers is due to the presence of two reactive *ortho* positions. When one of the *ortho* positions has a substituent, only one ring closure product is formed (75–82%). Various reaction conditions were varied, such as catalyst, ligands, additives, bases, and solvents to improve the yield and the regioselectivity of the reaction.

2. Results and discussion

The first attempt of cyclization with *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-iodobenzamide **3** (prepared from 9-ethyl-3-aminocarbazole and 2-iodobenzoyl chloride) using various conditions like changing catalyst, base, and solvent gave unsatisfactory results and starting material was recovered in most of the cases as shown in Scheme 1.



Scheme 1. Attempted synthesis of quinocarbazoles.

* Corresponding author. Tel.: +91 40 66794831; fax: +91 40 23012460; e-mail address: rnsc@uohyd.ernet.in (R. Nagarajan).

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Table 1
Biaryl coupling[a] of *N*-(9-ethyl-*H*-carbazole-3-yl)-2-iodobenzamide (**3**)

Entry	Catalyst	Ligand	Additive	Oxidant	Base	Solvent	Temp (°C)	Time (h)	Yield[e] (%)
1	$Pd(OAc)_2$	PPh_3	TBAB	—	Ag_2CO_3	DMF	140	24	—
2	Pd/C[b]	PPh_3	TBAB	—	KOAc	DMSO	140	24	—
3	$Pd(OAc)_2$	—		—	—	DMF/ACOH[c]	120	36	—
4	$Pd(OAc)_2$	—	TBAB	—	K_2CO_3	DMF/DMSO[c]	150	24	—
5	$Pd(OAc)_2$	PPh_3	—	CuI	KOAc	DMF	120	12	55
6	$Pd(OAc)_2$	PPh_3	—	$Cu(OAc)_2{\cdot}2H_2O$	KOAc	DMF/toluene[d]	120	10	70
7	—	PPh_3	—	$Cu(OAc)_2{\cdot}2H_2O$	KOAc	DMF/toluene[d]	120	24	—
8	$Pd(OAc)_2$	—	—	—	KOAc	DMF/toluene[d]	120	24	—

[a] Unless otherwise stated, all reactions were carried out by using 0.1 equiv of catalyst, 0.2 equiv of ligand, 1.5 equiv of additive/oxidant, 2 equiv of base.
[b] Pd/C (0.2 equiv) was used.
[c] Mixture of solvents were used in the ratio 1:1.
[d] (DMF/toluene) used in the ratio 1:1.
[e] Isolated yields. (TBAB=Tetrabutyl ammonium bromide).

When we examined the reaction with oxidants like $Cu(OAc)_2$ and CuI, etc., in a mixture of solvents, homo coupled product $N^2,N^{2'}$-bis (9-ethyl-9*H*-carbazol-3-yl)biphenyl-2,2′-dicarboxamide **4** was obtained. Various reaction conditions performed are summarized in Table 1.

The structure of **4** was also confirmed by the single crystal X-ray analysis. The ORTEP diagram is shown in Fig. 1.[12]

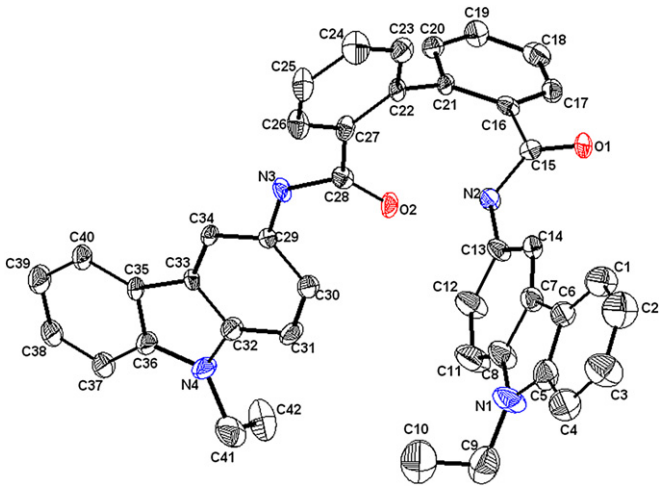
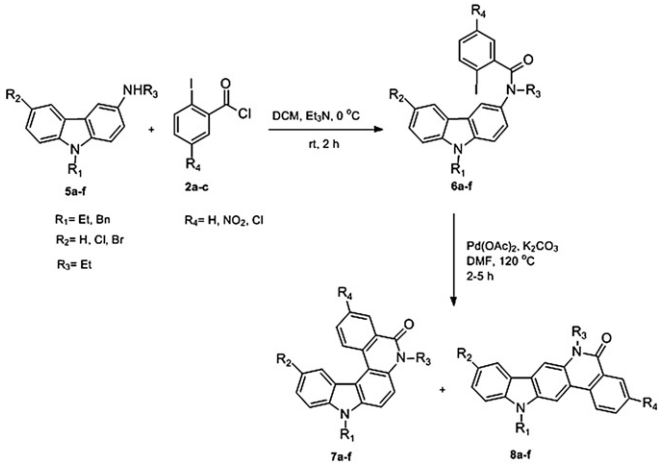


Fig. 1. ORTEP diagram of **4**.

This homo coupling was probably due to the free N–H group of amide that forms the Pd(II) complexes with both *ortho* positions, i.e., C2 and C4 of **3** in the presence of a base to undergo the coupling reaction.[13]

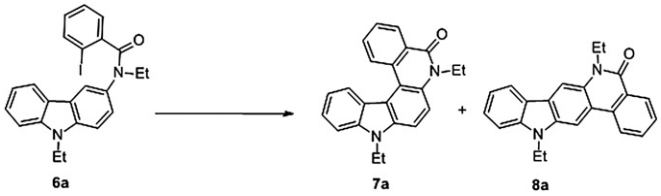


Scheme 2. Synthesis of quinocarbazole derivatives.

To avoid homocouple product, we perform the reaction using *N*-alkylated amides (Scheme 2). The *N*-ethyl-*N*-(9-ethyl-*H*-carbazol-3-yl)-2-iodobenzamide **6a** successfully underwent cyclization to give the products **7a** and **8a**. The two regioisomeric products **7a** and **8a** are formed due to the availability of two *ortho* C–H positions. Then we made consequential changes to catalyst, ligand, additive, base, and solvent to improve the yield and regioselectivity. Various reaction conditions were checked and the details are listed in Table 2.

We performed the reaction with various catalysts. Among them, $Pd(OAc)_2$ was found to be the best. Even though Pd/C also gave better results, yields were poor when substituents were introduced. When PPh_3, TBAB were used as ligand and additive, respectively, longer reaction times were required. When we performed the reaction without ligand and additive, the reaction proceeded well within 2 h in 88% yield and with good regioselectivity (50:38). All the products were well characterized. The

Table 2
Optimization conditions[a] of palladium mediated cyclization of **6a** to **7a** and **8a**



Entry	Catalyst	Ligand	Additive	Base	Solvent	Time (h)	Yield[g] (%)
1	$Pd(OAc)_2$	PPh_3	TBAB	KOAc	Toluene	20	20
2	$Pd(OAc)_2$	PPh_3	TBAB	Et_3N	DMSO	24	45
3	$Pd(OAc)_2$	PPh_3	TBAB	Et_3N	DMF	18	70
4	$Pd(OAc)_2$	PPh_3	TBAB	Ag_2CO_3	DMF	20	55
5	$Pd(OAc)_2$	PPh_3	TBAB	KOAc	DMF	10	80
6	$Pd(OAc)_2$	PPh_3	TBAB	K_2CO_3	DMF	10	80
7	$Pd(OAc)_2$	PPh_3		KOAc	DMF	10	80
8	$Pd(OAc)_2$		TBAB	KOAc	DMF	10	80
9	$Pd(OAc)_2$			KOAc	DMF	10	88
10	$PdCl_2$			K_2CO_3	DMF	3	85
11	—			K_2CO_3	DMF	24	nr[e]
12	**$Pd(OAc)_2$**			**K_2CO_3**	**DMF**	**2**	**88**[f]
13	Pd/C			K_2CO_3	DMF	3	80
14	—			K_2CO_3	DMF+H_2O[c]	3	80
15	Pd/C[b]			K_2CO_3	DMF+H_2O[c]	3	80
16	Pd/C[b]			K_2CO_3	DMF+H_2O[d]	24	20
17	$PdCl_2(PPh_3)_2$			K_2CO_3	DMF	3	85
18	$Pd(OAc)_2$			K_2CO_3	H_2O	20	nr

[a] Unless otherwise stated, all reactions were carried at 120 °C in a seal tube using 1.5 mL solution, using 0.05 equiv of catalyst, 0.2 equiv of ligand, 1.5 equiv of additive, 2.5 equiv of base.
[b] Pd/C used 10 mol %.
[c] DMF+H_2O in the ratio 1:0.2 mL.
[d] DMF+H_2O in the ratio 1:1.
[e] No reaction.
[f] High regioselectivity and high yield obtained, i.e., (50:38).
[g] Isolated and combined yield of **7a**+**8a**. (TBAB=tetrabutylammonium bromide).

Table 3
Synthesis of quinocarbazole derivatives

Entry	R_1	R_2	R_3	R_4	Amide	Yield (%)	Cyclized product	Time (h)	Yield[a] (%)
1	Et	H	Et	H	**6a**	79	**7a**/**8a**	2	50:38
2	Et	H	Et	NO_2	**6b**	82	**7b**/**8b**	2	78:12
3	Et	H	Et	Cl	**6c**	76	**7c**/**8c**	5	52:18
4	Bn	H	Et	H	**6d**	75	**7d**/**8d**	3	60:25
5	Et	Cl	Et	H	**6e**	70	**7e**/**8e**	5	62:16
6	Et	Br	Et	H	**6f**	68	**7f**/**8f**	5	55:15

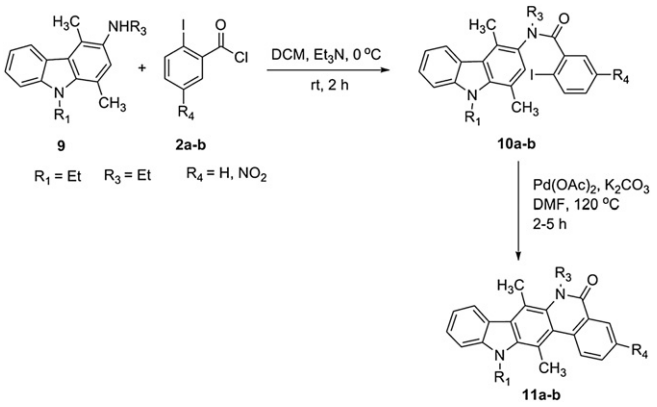
[a] Isolated yield and regioisomeric ratio of **7a**–**f** and **8a**–**f**.

effect of the base on the reaction was also investigated. KOAc and K_2CO_3 were more effective than the other bases while DMF is better solvent than DMSO and toluene. No reaction was found to occur at or below 80 °C.

To examine the versatility of this intramolecular palladium catalyzed *ortho* arylation, a number of quinocarbazole annulated cyclic amide derivatives were synthesized by employing the optimized reaction condition, $Pd(OAc)_2$, K_2CO_3, and DMF. When the products **6a**–**f** were subjected to cyclization under optimized conditions, they underwent facile cyclization to give isomeric products **7a**–**f** and **8a**–**f**. These results are summarized in Scheme 2 and Table 3.

The two regioisomers were characterized by ^1H NMR. In the ^1H NMR spectrum of **7a**, two doublets were observed at δ 9.01 and 8.61 ppm, whereas for **8a** two singlets were observed at δ 8.12 and 8.29 ppm. Structure of **7a** was further confirmed by the single crystal X-ray analysis.[12] When nitro group is present, the reaction was proceeded within 2 h with high yield due to its high electron withdrawing nature. ORTEP diagram of **8b** was shown in Fig. 2.[14] The ORTEP diagrams of chloro substituted derivatives **7c** and **8c** were shown in Fig. 3.[14]

The same methodology is also extended to various substituted 1,4-dimethylcarbazoloiodobenzamides **10a**–**b** under optimized conditions to give the products **11a**–**b** in good yields as shown in Scheme 3 and Table 4.



Scheme 3. Synthesis of indolo[2,3-*b*]phenanthridinone derivatives.

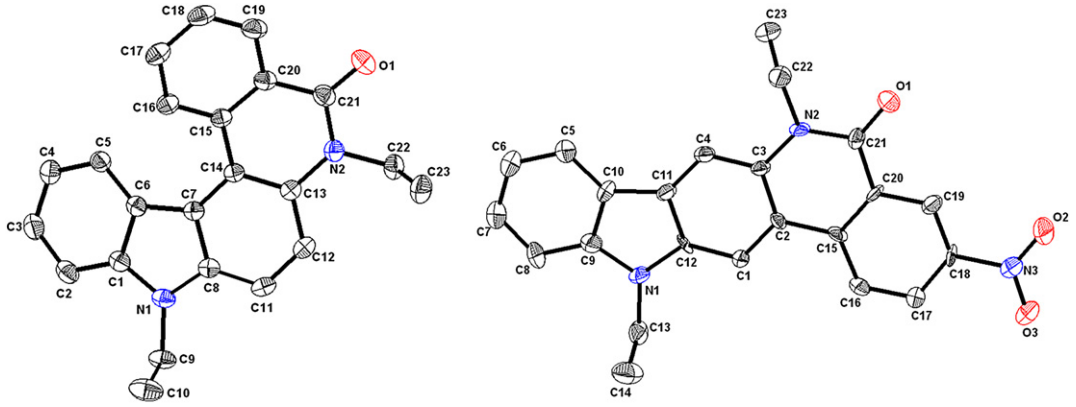


Fig. 2. ORTEP diagram of **7a** and **8b**.

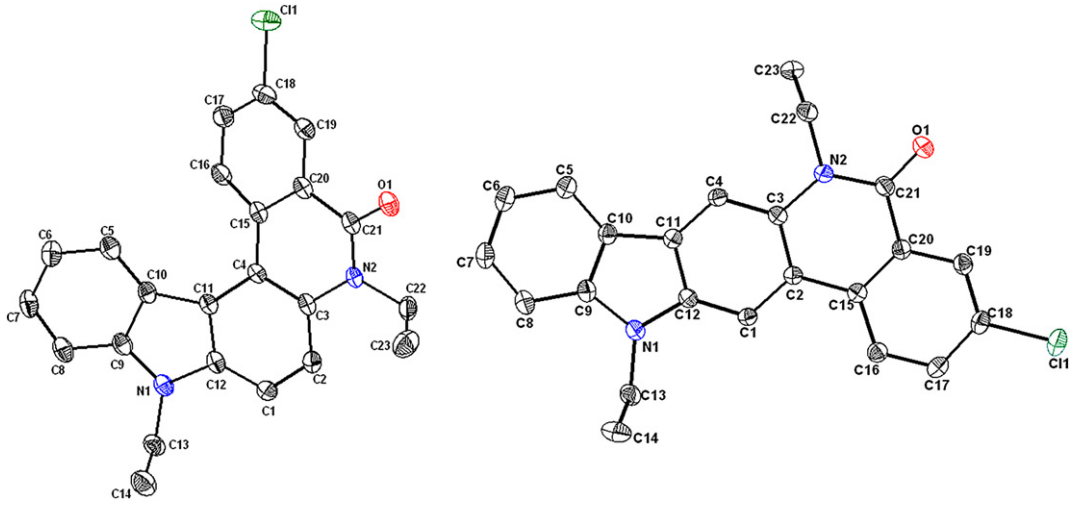


Fig. 3. ORTEP diagrams of **7c** and **8c**.

Table 4
Synthesis of indolo[2,3-*b*]phenanthridinone derivatives

Entry	R_1	R_3	R_4	Amide	Yield (%)	Cyclized product	Time (h)	Yield (%)
1	Et	Et	H	**10a**	79	**11a**	5	75
2	Et	Et	NO_2	**10b**	82	**11b**	4	82

3. Conclusion

In summary, we have developed a simple and an efficient route for the synthesis of quinocarbazoles in good yields (70–90%). Our method is superior to the earlier methods[15] in terms of avoiding the use of toxic, air sensitive phosphine ligands, additives, inert atmosphere, and benefits from shorter reaction times. Because of its generality and simplicity, we believe this method can contribute further in the area of C–H activation.

4. Experimental

4.1. General procedure

The procedure does not require inert atmosphere. All the products obtained were purified by column chromatography using silica-gel (100–200 mesh). Hexane was used as a co-eluent. ^{1}H and ^{13}C NMR were recorded in Bruker 400 and 100 MHz spectrometer, respectively. The chemical shifts are reported in parts per million downfield to TMS (δ=0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer in School of Chemistry at University of Hyderabad. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010A mass spectrometer. Melting points were measured in open capillary tubes and are uncorrected.

4.2. General procedure for the preparation of carbazoleiodobenzamide precursors

To the compound **5a** (0.5 g, 2.1 mmol) in 10 mL DCM was added Et_3N (0.42 mL, 4.3 mmol), stirred at room temperature for 15 min. Then the reaction mixture was cooled in an ice bath and added freshly prepared **2a** (0.7 mL, 2.6 mmol) (prepared from *o*-iodobenzoic acid and thionyl chloride) was added drop wise. After stirring for 15 min the reaction mixture was brought to room temperature and stirring continued up to 2 h. Water was added to the reaction mixture and extracted with DCM, washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude material was purified by column chromatography (25% EtOAc/hexane) to obtain the pure product **6a**. Similarly compounds **6b**–**f** and **10a**–**b** were obtained by the same procedure.

*4.2.1. N-(9-Ethyl-9H-carbazol-3-yl)-2-iodobenzamide (**6a**).* White solid (0.82 g, 79%); mp 139 °C; IR (KBr): 3047, 2976, 2928, 2866, 1633, 1485, 1116, 1008, 808, 744 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ=8.05 (1H, d, J=7.6 Hz), 7.9 (1H, s), 7.5 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.36 (1H, d, J=8.0 Hz), 7.31 (1H, d, J=8.4 Hz), 7.25 (1H, d, J=7.6 Hz), 7.19 (1H, d, J=8.4 Hz), 7.07 (1H, d, J=6.0 Hz), 6.99 (1H, t, J=6.0 Hz), 6.69 (1H, t, J=7.2 Hz), 4.26 (2H, q, J=7.2 Hz, N–CH_2CH$_3$), 4.09 (2H, q, J=7.2 Hz, NCH_2CH$_3$), 1.47 (3H, t, J=6.8 Hz, N–CH$_2$CH_3), 1.39 (3H, t, J=7.2 Hz, N–CH$_2$CH_3); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ=170.2, 143.0, 140.3, 139.2, 139, 138.6, 133.1, 129.2, 128.2, 127.2, 126.2, 125.9, 120.5, 120.1, 119.6, 119.1, 109.1, 108.7, 108.5, 93.9, 44.9, 37.6, 13.8, 12.9; LC–MS: m/z=469 (M+H$^+$), positive mode. Anal. Calcd for molecular formula $C_{23}H_{21}IN_2O$: C, 58.99; H, 4.52; N, 5.98%; found: C, 58.89; H, 4.56; N, 5.89%.

4.3. General procedure for the preparation of quinocarbazoles

A mixture of compound **6a** (0.15 g, 0.3 mmol), anhydrous K_2CO_3 (0.096 g, 7.5 mmol), and $Pd(OAc)_2$ (0.004 mg, 5 mol %) in DMF was taken in a seal tube and heated at 120 °C for 2 h with continuous stirring. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and water was added (10 mL). A solid precipitate was formed, extracted with $CHCl_3$ or DCM (3×20 mL), and washed with water (3×20 mL) followed by brine (20 mL) and dried over Na_2SO_4. Evaporation of solvent and the crude material was purified by column chromatography over silica-gel (100–200 mesh), using EtOAc/hexane (15:85%) as an eluent to give mixture of the products **7a** and **8a**. Similarly compounds **7b**–**f**, **8b**–**f**, and **11a**–**b** were obtained in the same manner.

*4.3.1. 7,12-Diethyl-7H-indolo[2,3-c]phenanthridin-13 (12H)-one (**7a**).* Yellow solid (0.047 g, 50%); mp 176 °C; IR (KBr): 3051, 2972, 1637, 1483, 1419, 1332, 1302, 1224, 1180, 1072, 798 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ=9.01 (1H, d, J=8.0 Hz), 8.61 (1H, d, J=2.8 Hz), 8.38 (1H, d, J=4.0 Hz), 7.78 (1H, t, J=8.0 Hz), 7.66 (1H, d, J=8.0 Hz), 7.63 (1H, s), 7.58 (1H, d, J=8.0 Hz), 7.51 (2H, d, J=4.0 Hz), 7.19 (1H, m), 4.58 (2H, q, J=8.0 Hz, N–CH_2CH$_3$), 4.49 (2H, q, J=8.0 Hz, N–CH_2CH$_3$), 1.32–1.50 (6H, m); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ=160.8, 141.6, 136.1, 134.0, 132.1, 130.6, 129, 127.5, 126.9, 125.4, 124.8, 122.3, 121.5, 120.8, 118.9, 118.6, 108.7, 105.7, 101.8, 38, 37.6, 13.8, 12.7; LC–MS: m/z=341 (M+H$^+$), positive mode. Anal. Calcd for molecular formula $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23%; found: C, 81.36, H, 5.85; N, 8.32%.

*4.3.2. 6,12-Diethyl-6,12-dihydro-5H-indolo[2,3-b]phenanth-ridin-5-one (**8a**).* Yellow solid (0.036 g, 38%); mp 172 °C; IR (KBr): 2974, 2926, 1651, 1440, 1323, 846, 771, 740, 696 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ=8.64 (1H, d, J=8.0 Hz), 8.48 (1H, d, J=7.6 Hz), 8.29 (1H, s, ArH), 8.22 (1H, d, J=7.6 Hz), 8.12 (1H, s, ArH), 7.82 (1H, t, J=7.2 Hz), 7.63 (1H, d, J=7.2 Hz), 7.56 (1H, d, J=7.6 Hz), 7.47 (1H, d, J=8.4 Hz), 7.16 (1H, d, J=7.6 Hz), 4.65 (2H, q, J=6.8 Hz, N–CH_2CH$_3$), 4.49 (2H, q, J=7.6 Hz, N–CH_2CH$_3$), 1.52 (6H, m); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ=160.9, 140.5, 136.8, 133.3, 131.6, 130.5, 128.2, 127.8, 126.7, 126.3, 126.0, 123.4, 122.6, 118.1, 118.0, 116.1, 113.2, 110.4, 109.0, 38.3, 37.6, 13.8, 13.2; LC–MS: m/z=341 (M+H$^+$), positive mode. Anal. Calcd for molecular formula $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23%; found: C, 81.10, H, 5.98; N, 8.28%.

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Supplementary data

Characterization data, ^{1}H, ^{13}C, LC–MS, and elemental analysis spectra of all compounds are included in the supplementary data. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.073.

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