Highly Regioselective Synthesis of Indenocarbazolones via Palladium-Catalyzed Intramolecular *ortho* Arylation

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Received 12 December 2011

Abstract: An efficient protocol for the synthesis of indenocarbazolones through palladium-catalyzed intramolecular arylation in good yield with high regioselectivity under ligand-free conditions is reported.

Key words: palladium catalysis, *ortho* arylation, indenocarbazolones, C–H activation

The fluorenone motif has been found in many natural products such as dengibsin, dengibsinin, dendroorin, kinofluorenone, and kinobscurinone showing a range of biological activities[1] (Figure 1). Moreover, carbazole and its fused derivatives have attracted great attention from medicinal and synthetic chemists due to their wide range of biological applications.[2–5] In addition to their use in medicinal chemistry, fused heterocycles, such as heteroarylcarbazoles, have attracted increasing attention from the community of material scientists owing to their potential in photophysical and optoelectronic (OLED, PLED) applications (Figure 1).[6–11] Strohriegl et al. reported liquid crystalline bisindenocarbazole derivatives which exhibit blue fluorescence.[12] A careful survey of the literature disclosed that no reports were available for the synthesis of the indenocarbazolones. Therefore, we explored the synthetic methodology for the synthesis of indenocarbazolones.

The indenocarbazoles are a new class of heteroarylcarbazole analogues of indolocarbazoles, in which the indole nitrogen is replaced with a carbon. These molecules are not fully explored and were reported by the Hudkins group as PKC, VEGFR2, and trkA inhibitors.[13] Underiner and Singh have prepared indenocarbazole analogues of the STP ring system, which show activity against trkA and VEGF-R2 (KDR) but weak activity against PKC and PDGFR.[14] Tripathy et al.[15] have also prepared indenocarbazoles via parallel synthesis. Gingrich et al.[16] have reported an optimized method for the indenocarbazole derivatives CEP-5214 and its prodrug form CEP-7055 as a potent inhibitor of VEGFR3 (Flt-4), VEGFR2 (KDR), VEGFR1 (Flt-1), and Flt-3 (Figure 1).

In view of these important applications, we set out to develop the metal-catalyzed synthesis of indenocarbazolone derivatives. Transition-metal-catalyzed C–C and C–heteroatom bond formations via cleavage of C–H bonds are now becoming increasingly used protocols in organic synthesis due to their potential shortening of synthetic steps.[17] As a result, the increase of C–H activation could act as an attractive alternative to the traditional carbon–carbon couplings and thereby emerge as a fascinating area that is rich in opportunities and challenges.[18] Herein, we wish to report the synthesis of indenocarbazolone derivatives starting with various carbazolyliodophenylmethanone

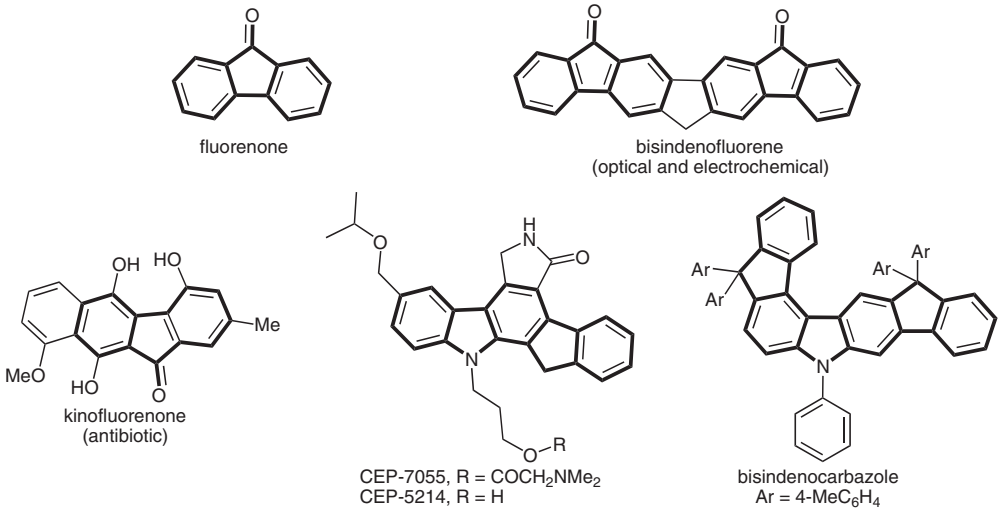
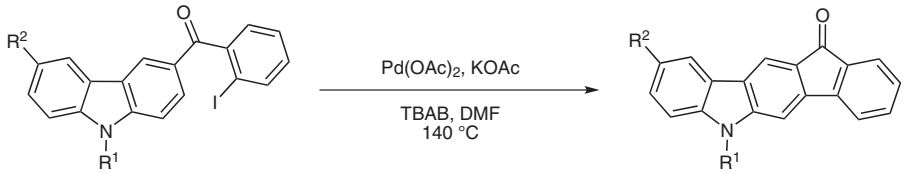


Figure 1 Some of fluorenone- and carbazole-fused derivatives

SYNLETT 2012, 23, 1007–1012
Advanced online publication: 28.03.2012
DOI: 10.1055/s-0031-1290660; Art ID: B76311ST

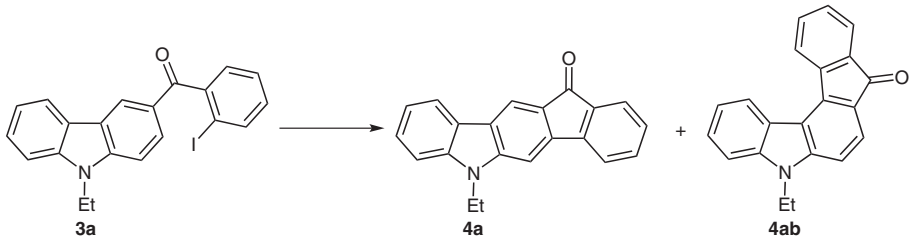


Scheme 1 Schematic representation of our work

derivatives through a palladium-catalyzed *ortho* arylation as shown in Scheme 1.

(9-Ethyl-9*H*-carbazol-3-yl)(2-iodophenyl)methanone, which was synthesized from *N*-ethylcarbazole and 2-iodobenzoyl chloride by Friedel–Crafts acylation, was used as model substrate for optimizing the reaction conditions. The influence of catalyst, ligand, additive, solvent, and temperature in the reaction outcome were examined as shown in Table 1. We performed the reaction with $Pd(OAc)_2$ as catalyst, and Ph_3P, TBAB, KOAc in toluene was unsuccessful (Table 1, entry 1). By changing different ligands, solvents, and bases using various catalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $PdCl_2$ two regioisomers **4a** and **4ab** were obtained (Table 1, entries 3–7). Of the various solvents which were tested for the reaction, DMF was found to be the most effective. Furthermore, different bases such as KOAc, Ag_2CO_3, and K_2CO_3 were tested in the reaction; it was found that KOAc was superior to the other bases. The ligand had no

Table 1 Optimization of the Reaction Conditions for the Conversion of **3a** into **4a** and **4ab**[a]



Entry	Catalyst	Ligand	Additive	Base	Solvent	Temp (°C)	Time (h)	Yield of **4a** (%)[d]	Yield of **4ab** (%)[d]
1	$Pd(OAc)_2$	Ph_3P	TBAB	KOAc	toluene	140	12	n.r.[c]	n.r.[c]
2	$Pd(OAc)_2$	Ph_3P	TBAI	K_2CO_3	DMA	130	8	25	3
3	$Pd(OAc)_2$	Ph_3P	TBAB	K_2CO_3	DMSO	130	12	20	3
4	$Pd(OAc)_2$	Ph_3P	TBAB	Ag_2CO_3	DMF	140	24	n.r.[c]	n.r.[c]
5	$Pd(PPh_3)_4$	Cy_3P	TBAB	KOAc	DMF	110	12	15	4
6	$Pd(PPh_3)_2Cl_2$	Cy_3P	TBAB	KOAc	DMF	120	12	15	5
7	$PdCl_2$	Cy_3P	TBAB	KOAc	DMF	120	18	15	5
8	$Pd(OAc)_2$	–	TBAB	KOAc	DMF	120	8	62	3
9	$Pd(OAc)_2$	–	TBAB	KOAc	DMF	140	3	68	0
10	–	Ph_3P	TBAB	KOAc	DMF	140	24	n.r.[c]	n.r.[c]
11	$Pd(OAc)_2$	–	–	KOAc	DMF	140	12	60	5
12	$Pd(OAc)_2$	–	TBAB	KOAc	NMP	130	5	55	8
13	$Pd(OAc)_2$	–	LiCl	KOAc	DMF	140	4	50	10
14	Pd/C[b]	–	TBAB	KOAc	TEG	150	24	n.r.[c]	n.r.[c]
15	$Pd(OAc)_2$	–	TBAB	K_2CO_3	DMF	130	6	58	8
16	$Pd(OAc)_2$	–	SDS	K_2CO_3	DMF	140	5	50	8

[a] Unless otherwise stated all reactions were carried out using 5 mol% catalyst, 15 mol% ligand, 1.0 equiv additive, and 2.0 equiv of base.
[b] 10% Pd/C.
[c] No reaction.
[d] Isolated yield.

effect on the reaction, without ligand the reaction proceeded well within three hours (Table 1, entry 9).

Different additives such as TBAB, LiCl, SDS, and TBAI were tested in the reaction; 1.0 equivalent of TBAB was suitable for the reaction (Table 1, entry 9). Amongst the various catalysts that were tested $Pd(OAc)_2$ produced the best yields. No reaction occurred below a reaction temperature of 110 °C. After careful screening, the best reaction conditions[22] were found by involving 5 mol% of $Pd(OAc)_2$, 1.0 equivalent of TBAB, and 2.0 equivalents of KOAc in DMF at 140 °C furnishing **4a** in good yield with high regioselectivity (Table 1, entry 9).

The two regioisomers **4a** and **4ab** were characterized by their ^{1}H NMR spectra.[19] In the ^{1}H NMR spectrum of **4a**, two singlets were observed at δ = 8.39 and 7.42 ppm whereas for **4ab** clearly two doublets at δ = 8.81 and 8.71 ppm were observed. The two regioisomers were further confirmed by the single-crystal X-ray analysis. The ORTEP diagrams are shown in Figure 2 and Figure 3.[20]

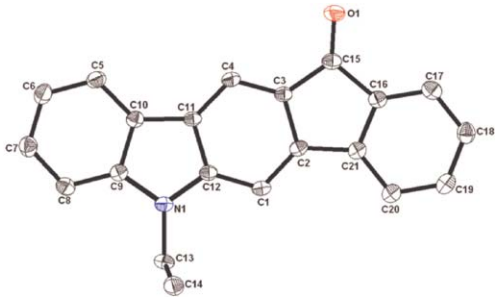


Figure 2 ORTEP diagram of **4a**

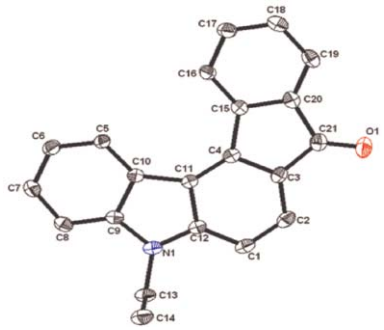


Figure 3 ORTEP diagram of **4ab**

By utilizing the above optimized conditions various indenocarbazolone derivatives were synthesized by subjecting **3a**–**g** to provide the cyclized products **4a**–**g** in good yields as shown in Table 2.

The methoxy derivative **4d** was also confirmed by the single-crystal X-ray analysis. The ORTEP diagram is shown in Figure 4.[20]

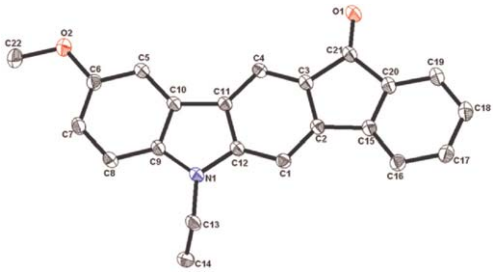


Figure 4 ORTEP diagram of **4d**

Wong et al. reported an interesting bisindenocarbazole derivative cyclization at the C2 and C7 position of the carbazole unit used in hole transporting materials and in OLED.[21] This approach led us to prepare bisindenocarbazolone derivatives. When **5a** was subjected to the above optimized conditions, **6a** was expected to be the major product. But from the ^{1}H NMR spectra only two singlets were observed at δ = 8.59 and 7.37 ppm (integration of one for each proton) which confirmed that **6b** was the product shown in Scheme 2.

Further, **6b** was confirmed by single-crystal X-ray analysis. The ORTEP diagram is shown in Figure 5.[20]

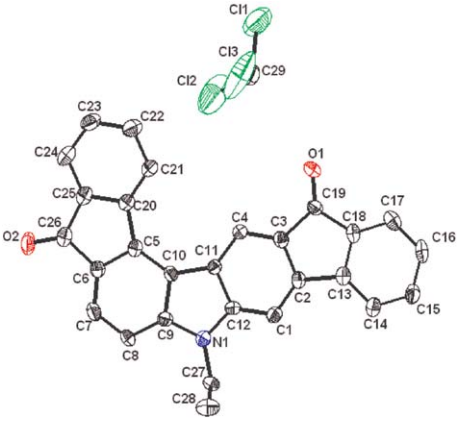
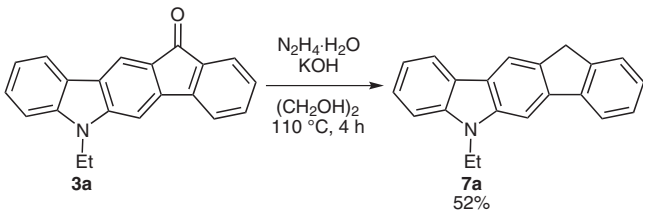
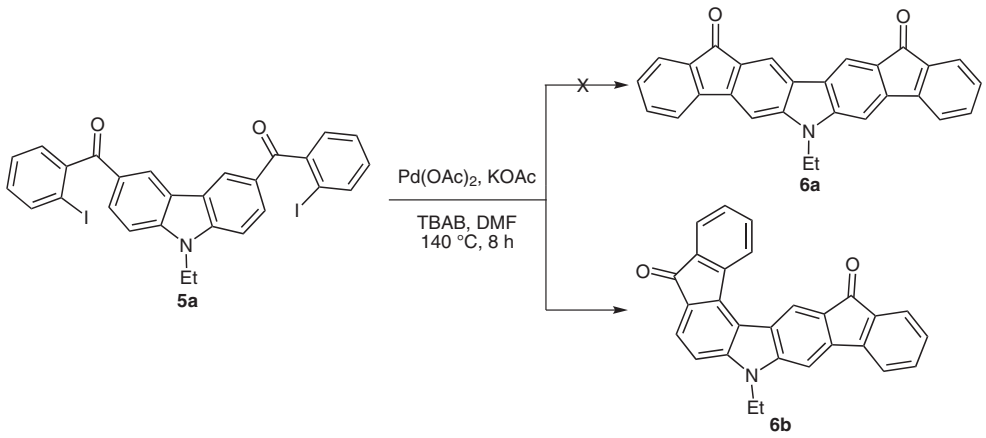


Figure 5 ORTEP diagram of **6b**

The reduction of the indenocarbazolone **3a** with hydrazine hydrate, KOH in ethylene glycol furnished the indenocarbazole 5-ethyl-5,11-dihydroindeno[1,2-*b*]carbazole (**7a**) in 52% yield (Scheme 3).

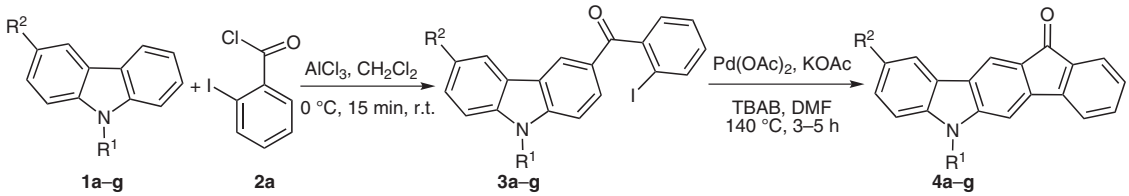


Scheme 3 Synthesis of indenocarbazole derivatives



Scheme 2 Synthesis of bisindenocarbazolone derivatives

Table 2 Synthesis of Indenocarbazolone Derivatives



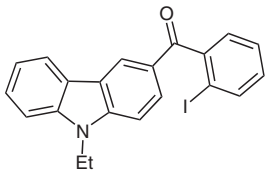
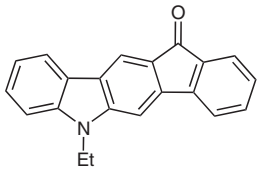
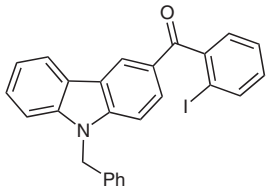
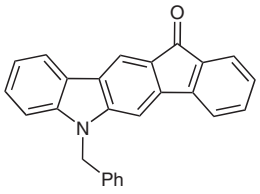
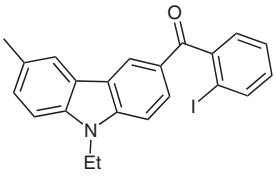
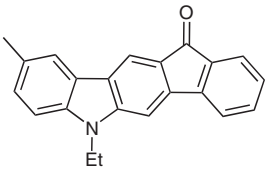
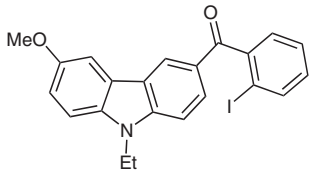
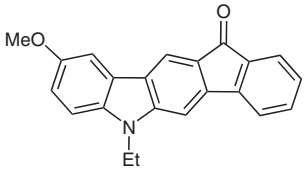
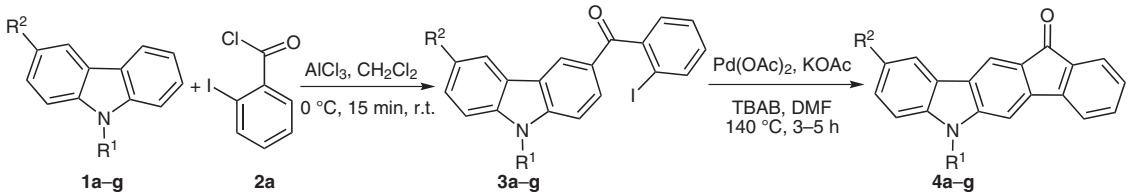
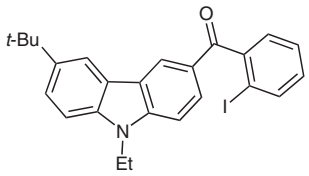
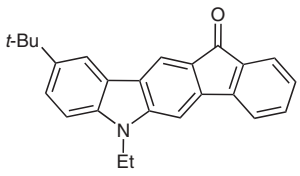
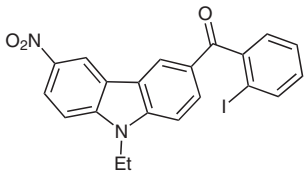
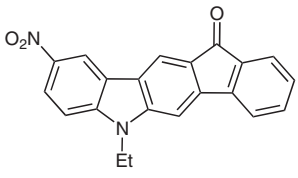
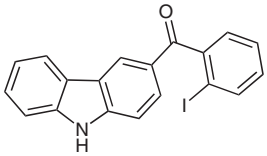
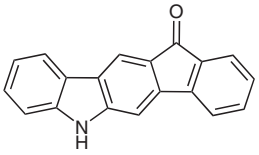
Entry	R^1	R^2	Substrate	Yield (%)[b]	Product	Time (h)	Yield (%)[b]
1	Et	H	 **3a**	80	 **4a**	3	68
2	Bn	H	 **3b**	86	 **4b**	3	72
3	Et	CH_3	 **3c**	82	 **4c**	4	68
4	Et	OCH_3	 **3d**	85	 **4d**	4	68

Table 2 Synthesis of Indenocarbazolone Derivatives (continued)



Entry	R^1	R^2	Substrate	Yield (%)[b]	Product	Time (h)	Yield (%)[b]
5	Et	*t*-Bu	 **3e**	82	 **4e**	4	70
6	Et	NO_2	 **3f**	72	 **4f**	5	72
7	H	H	 **3g**	94	 **4g**	6	55

[a] Reaction conditions: **3a**–**g** (0.02 mmol), TBAB (0.02 mmol), KOAc (0.04 mmol), $Pd(OAc)_2$ (5 mol%) in DMF 3.0 mL.
[b] Isolateed yield.

We also studied spectral properties of the compounds **4a**–**f** and **6b**. The electronic absorption spectrum of the compound **4a** shows an absorption (in CH_2Cl_2) at λ = 395 nm in the visible region, and the corresponding emission band was observed at λ = 571 nm as shown in Figure 6 (a).

The emission spectrum of compound **4a** is dependent on the polarity of the solvents. The emission band maximum shifts to the low-energy region with increasing the polarity of the solvents as shown in Figure 6 (b).[19] It varies from λ = 517–573 nm from hexane to DMF.

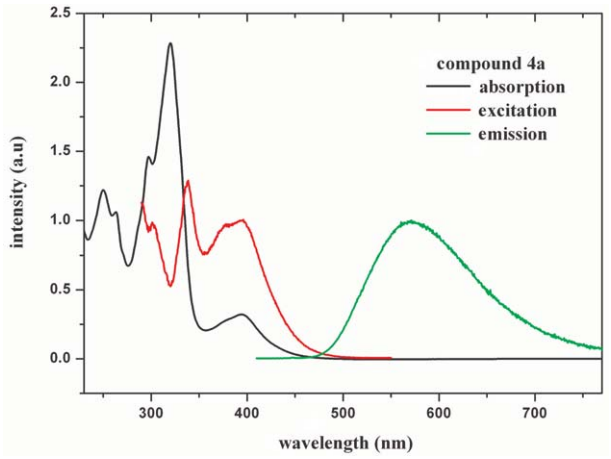


Figure 6 (a) Electronic spectra of compound **4a**, [4×10^{-5} M]. Absorption spectra, black line; excitation spectra (λ_{em} = 571 nm), red line; emission spectra (λ_{ex} = 395 nm), green line.

In conclusion, we developed a new class of indenocarbazolones[22] with high regioselectivity in good yield by palladium-catalyzed intramolecular *ortho* arylation. Further studies on biological and photochemical properties of the corresponding compounds are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We gratefully acknowledge DST for financial assistance (Project number: SR/S1/OC-70/2008) and for providing single-crystal X-ray diffractometer facility in our school. D.K.S. thanks CSIR for Senior Research Fellowship. D.K.S. also thanks Rambabu for helping with the crystal studies.

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(19) See Supporting Information.

(20) **Analytical Data**
Compound **4a**: CCDC deposition number 854724. Formula: $C_{21}H_{15}N_1O_1$. Unit cell parameters: a = 18.8910 (15), b = 14.7317 (11), c = 5.3252 (3), space group $P2_12_12$.
Compound **4ab**: CCDC deposition number 854725. Formula: $C_{21}H_{15}N_1O_1$. Unit cell parameters: a = 15.9003 (8), b = 5.4237 (3), c = 17.1149 (8), space group $Pna2_1$.
Compound **4d**: CCDC deposition number 854726. Formula: $C_{22}H_{17}N_1O_2$. Unit cell parameters: a = 8.3015 (8), b = 9.1172 (9), c = 10.6868 (10), α = 83.461 (2), β = 79.759 (2), γ = 81.777 (2), space group $P\bar{1}$.
Compound **6b**: CCDC deposition number 854727. Formula: $C_{29}H_{18}Cl_3N_1O_2$. Unit cell parameters: a = 9.0516 (13), b = 10.4572 (20), c = 13.2939 (17), α = 100.684 (14), β = 101.200(12), γ = 101.784 (15), space group $P\bar{1}$.

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(22) **General Procedure**
A mixture of compound **3a** (0.10 g, 0.02 mmol), anhyd KOAc (0.04 g, 0.04 mmol), TBAB (0.06 g, 0.02 mmol), and $Pd(OAc)_2$ (0.003 g, 5 mol%) in DMF (3.0 mL) was taken in a Schlenk tube and heated at 140 °C for 3 h with continuous stirring. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and poured into cold H_2O (10 mL). A solid precipitate was formed, extracted with $CHCl_3$ (3 × 20 mL), and washed with H_2O (3 × 20 mL) followed by brine (20 mL) and dried over anhyd Na_2SO_4. Evaporation of solvent, and the crude material was purified by column chromatography over silica gel (100–200 mesh), using 12% EtOAc in hexanes as eluent to give product **4a** in 68% yield. Compounds **4b**–**g** and **6b** were obtained using same procedure.
5-Ethylindeno[1,2-*b*]carbazol-11 (5*H*)-one (4a)
Yellow solid; mp 181–182 °C; yield 68%. IR (KBr): 2986, 1697, 1570, 1446, 1331, 1111, 931, 742 cm^{-1}. ^1H NMR (400 MHz, TMS, $CDCl_3$): δ = 8.39 (s, 1 H), 8.05 (d, 1 H, J = 7.6 Hz), 7.66 (d, 1 H, J = 7.2 Hz), 7.59 (d, 1 H, J = 7.2 Hz), 7.50–7.46 (ddd, 2H, J_1 = 1.2 Hz, J_2 = 7.6 Hz, J_3 = 15.2 Hz), 7.42 (s, 1 H), 7.33–7.27 (m, 3 H), 4.41 (q, 2 H, J = 7.2 Hz), 1.51 (t, 3 H, J = 7.2 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ = 193.2, 144.6, 144.1, 142.6, 140.7, 136.3, 134.1, 128.8, 126.4, 126.2, 123.8, 123.1, 120.6, 120.5, 119.9, 118.0, 109.1, 100.7, 37.9, 14.0. LC–MS (positive mode): m/z = 298 $[M + H]^+$. Anal. Calcd (%) for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.65; H, 5.12; N, 4.68.

