Palladium-Mediated Intramolecular C–O and C–C Coupling Reactions: An Efficient Synthesis of Benzannulated Oxazepino- and Pyranocarbazoles

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Abstract: An efficient route towards the synthesis of benzannulated oxazepino- and pyranocarbazoles has been accomplished via palladium-catalyzed intramolecular C–O and C–C cross-coupling reactions, respectively.

Key words: C–O and C–C coupling, intramolecular arylation, palladium catalysis, oxazepinocarbazoles, pyranocarbazoles.

Palladium-catalyzed reactions are one of the most versatile methods for creation of covalent bonds in organic chemistry. The tremendous impact of reactions such as the Suzuki coupling, Heck reaction, Negishi coupling, Stille reaction, and Sonogashira coupling on synthetic organic chemistry was recognized in 2010 with the Nobel Prize in Chemistry. Palladium-catalyzed reactions have proven to be especially useful for the construction of carbon–carbon, as well as carbon–heteroatom bonds of ring systems,[1] and they offer an extremely efficient entry to complex cyclic compounds from relatively simple precursors.[2] Intramolecular biaryl coupling reactions are of considerable interest due to their utility in the synthesis of many condensed heteroaromatic compounds, such as indoles, quinolines, and carbazoles.[3] Among these, carbazoles[4] and their fused derivatives, such as pyrido,[5] pyrrolo,[6] and pyranocarbazoles[7] have received considerable attention from both medicinal as well as synthetic chemists as these compounds display a wide range of biological activities such as anticancer,[8] anti-HIV,[9] DNA-intercalator,[10] and antimicrobial.[11] Some examples of natural products containing the pyranocarbazole core structure include clauszoline-H (**I**), girinimbine (**II**), and pyrayafoline B (**III**, Figure 1).[12] Over recent years considerable efforts have been made towards the preparation and synthetic manipulation of these compounds.[4c,7,13] A number of compounds with diverse biological activities has been obtained. However, to the best of our knowledge, there are no reports describing the preparation of benzannulated analogues of oxazepinocarbazoles and pyranocarbazoles. This may be due to the lack of a general synthetic route towards these classes of heteroaromatics from easily accessible precursors.

In view of the importance of oxazepines and coumarins, several methods have been developed for the synthesis of oxazepine[14] and coumarin[15] compounds by palladium-catalyzed cyclization reactions. However, many of the synthetic protocols reported so far suffer from disadvantages, such as harsh reaction conditions, multistep reaction, expensive reagents, extended reaction time, need for large quantities of catalyst or low yields. Therefore, a new protocol with reagent economy, minimum of catalyst, and improved yields is desirable.

In continuation of our interest,[16] we herein report a simple and efficient synthetic protocol for the synthesis of benzannelated oxazepino- and pyrano-carbazoles such as benzo[*f*][1,4]oxazepino[4,3,2-*l*,*m*]carbazol-9-ones or isochromeno[3,4-*a*]carbazol-2(13*H*)-one using palladium-catalyzed intramolecular arylation of starting materials based on readily available 1-hydroxycarbazole[17] such as 1-hydroxy-9-(2-halobenzoyl)carbazole or 9*H*-carbazol-1-yl 2-halobenzoate.

The desired benzoylated products were prepared by the reaction of 2-halobenzoyl chloride **2** with 1-hydroxycarbazoles **3** under various reaction conditions (Table 1) as depicted in Scheme 1. In the presence of triethylamine in THF only the N-benzoylated product was obtained[18] (Table 1, entry 1). The identity of **4a** was confirmed by its spectroscopic data as well as single-crystal structural X-ray analysis. The case where **3c** failed to give **4c** and **5c**

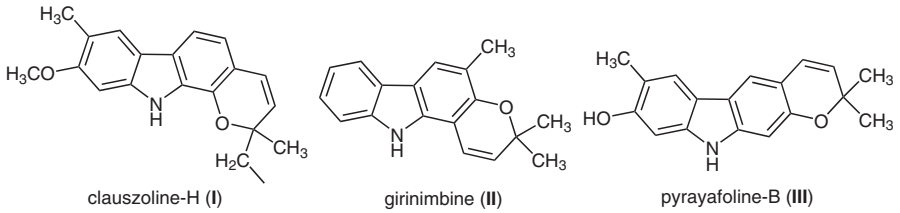

Figure 1

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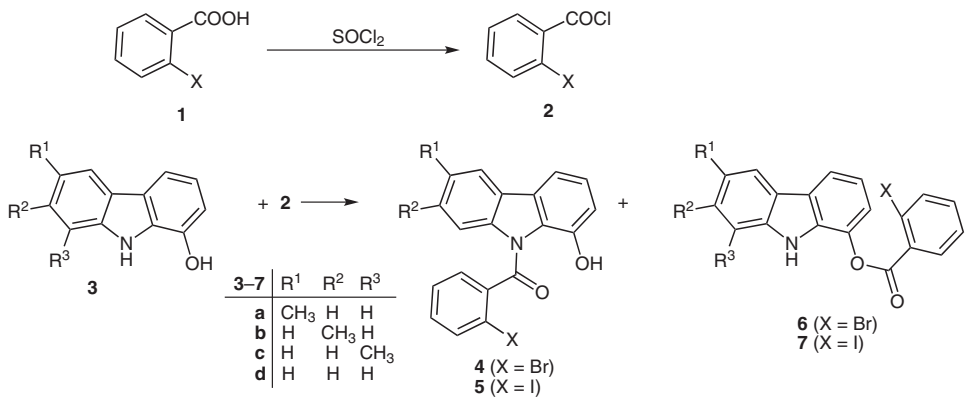


Scheme 1 Benzoylation of 1-hydroxy carbazole **3**

Table 1 Reaction of **3** with 2-Halobenzoyl Chloride under Various Experimental Conditions

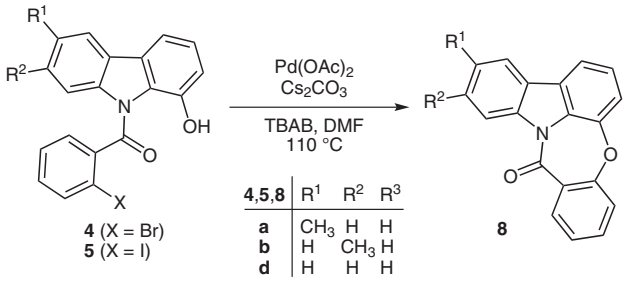
Entry	Reactant	Conditions	Temp (°C)	Product	Yield (%)[a]
1	**3a**, **2** X = Br	Et_3N–THF	r.t.	**4a/6a**	72:0
2	**3a**, **2** X = Br	piperidine–CH_2Cl_2	100	**4a/6a**	24:20
3	**3a**, **2** X = Br	pyridine– CH_2Cl_2	100	**4a/6a**	41:25
4	**3a**, **2** X = Br	K_2CO_3, acetone	100	**4a/6a**	32:38
5	**3a**, **2** X = Br	CH_2Cl_2	100	**4a/6a**	0:72
6	**3a**, **2** X = I	Et_3N–THF	r.t.	**5a/7a**	55:0
7	**3b**, **2** X = Br	Et_3N–THF	r.t.	**4b/6b**	70:0
8	**3b**, **2** X = I	Et_3N–THF	r.t.	**5b/7b**	52:0
9	**3c**, **2** X = Br	Et_3N–THF	r.t.	**4c/6c**	n.r.
10	**3c**, **2** X = I	Et_3N–THF	r.t.	**5c/7c**	n.r.
11	**3d**, **2** X = Br	Et_3N–THF	r.t.	**4d/6d**	72:0
12	**3d**, **2** X = I	Et_3N–THF	r.t.	**5d/7d**	58:0
13	**3a**, **2** X = I	CH_2Cl_2	100	**5a/7a**	0:52
14	**3b**, **2** X = Br	CH_2Cl_2	100	**4b/6b**	0:70
15	**3b**, **2** X = I	CH_2Cl_2	100	**5b/7b**	0:41
16	**3c**, **2** X = Br	CH_2Cl_2	100	**4c/6c**	0:72
17	**3c**, **2** X = I	CH_2Cl_2	100	**5c/7c**	0:45
18	**3d**, **2** X = Br	CH_2Cl_2	100	**4d/6d**	0:76
19	**3d**, **2** X = I	CH_2Cl_2	100	**5d/7d**	0:41

[a] n.r. = no reaction.

can be readily explained by the steric effect of the methyl substituent at C8, which prevents reaction at the N-9 position. However, piperidine, pyridine, and potassium carbonate yielded a mixture of both N- and O-benzoylated products (Table 1, entries 2–4). In the absence of base, the reaction afforded only O-benzoylated product[19] (Table 1, entry 5).

In the next step the precursors were subjected to palladium coupling conditions. When a C–O coupling reaction was carried out with precursor **4a** in the presence of 10 mol% of $Pd(OAc)_2$ as the catalyst, Cs_2CO_3 as the base, and tetrabutylammonium bromide (TBAB) as an additive in anhydrous DMF as the solvent, reaction at 110 °C for 2 hours gave 13-methyl-benzo[*f*][1,4]oxazepino[4,3,2-*l*,*m*]carbazol-9-one (**8a**) as the only product in 90% isolated yield (Scheme 2).[20] In the ^1H NMR spectrum of the reaction product the absence of a peak at δ = 12.76 ppm for the OH proton indicated that the compound had undergone reaction involving a C–O coupling reaction and not coupling with C8 of the carbazole ring. All other spectroscopic and analytical data confirmed the formation of the C–O coupling product **8**. The optimum conditions for the palladium-catalyzed cyclization were found through a series of experiments where various changes were made to the catalyst, base, additives, and the solvent used in the reaction (Table 2). All of these variables showed to have a profound effect on the reaction efficiency, specificity, and yield. Without the catalyst, no reaction was observed (Table 2, entry 1). The use of $PdCl_2$, which is most commonly used in Heck-type reactions, led only to moderate yields of cyclized product **8** (Table 2, entry 2). Without an additive under different basic conditions with $Pd(OAc)_2$, the reaction afforded a moderate yield (Table 2, entries 3–5). Use of $Pd(OAc)_2$ as the catalyst precursor gave moderate to high yields, with the exception of the system $Pd(OAc)_2/Et_3N$/TBAB in DMF, which also did not yield any of the desired products (Table 2, entry 6). The effect of base on the reaction showed that use of Cs_2CO_3 as the base gave high yields of **8** when the reactions were conducted in DMF (Table 2, entries 7–12). Details of all reaction conditions that were examined are given in Table 2.

We next turned our attention towards the palladium-catalyzed intramolecular C–C coupling of compounds **6a–d** and **7a–d** (Scheme 3). In our initial attempt to initiate cyclization of **6a** in the absence of Pd catalyst, no reaction was observed (Table 3, entry 1). Reactions using a $PdCl_2$ catalyst system, which is generally employed in such cyclization reactions, provided a mixture of 10-methyl-isochromeno[3,4-*a*]carbazol-2(13*H*)-one (**9a**) and debrominated product (Table 3, entry 2). The structure of **9a**



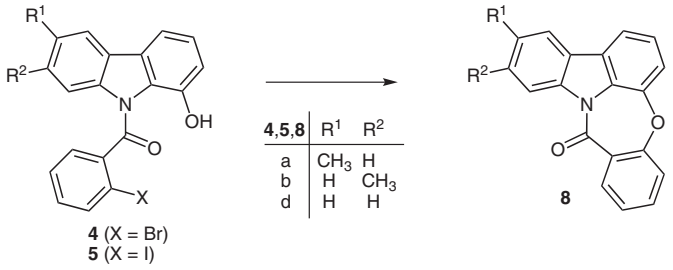
Scheme 2 Synthesis of benzo[*f*][1,4]oxazepino[4,3,2-*l*,*m*]carbazol-9-one

was confirmed by its spectroscopic and analytical data as well as single-crystal X-ray analysis.[21] Without addition of triphenylphosphine as an additional ligand with Ag_2CO_3 as the base only debrominated product was obtained (Table 3, entry 3). In the presence of KOAc as the base, triphenylphosphine as an additional ligand in DMF as the solvent, the cyclized product **9a** was isolated in 70% yield along with a small amount (8%) of the debrominated side product (Table 3, entry 4). Use of other bases such as K_2CO_3, KOAc, or Ag_2CO_3 gave decreased yields of **9a** with more of the side product. All attempts to optimize the reaction conditions using $PdCl_2$ and different bases gave similar mixtures of the two compounds. Therefore, we decided to focus the optimization attempts on the $Pd(OAc)_2/Ph_3P$ system.

A study of the influence of various solvents (DMF and DMSO) suggested that DMF is the best choice. No reaction was found to occur below 90 °C. Switching to the mild base Cs_2CO_3 under these conditions gave the desired cyclized product **9a** without any debrominated byproduct. The best results were achieved using Cs_2CO_3 as the base, $Pd(OAc)_2$ as the catalyst, along with Ph_3P as ligand and DMF as a solvent at 110 °C. After four hours reaction time this procedure provided a 85% yield of the cyclized product **9a** (Table 3, entry 5).[22] The results are summarized in Table 3.

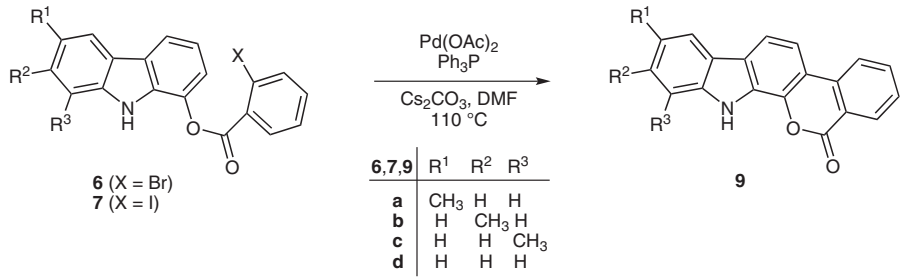
To examine the versatility and scope of this intramolecular palladium-catalyzed cyclization, isochromeno-annulated carbazole derivatives **9b–d** were synthesized by employing the optimized reaction conditions $Pd(OAc)_2/Ph_3P/Cs_2CO_3$/DMF (Table 3, entries 5–12). It was observed that the use of *o*-iodobenzoyl derivatives dramatically improves the yield of the desired products.

Table 2 Synthesis of Benzo[*f*][1,4]oxazepino[4,3,2-*l*,*m*]carbazol-9-ones **8** under Various Experimental Conditions



Entry	Reactant	Catalyst (10 mol%)	Ligand (15 mol%)	Base (1.5 equiv)	Additive (1.5 equiv)	Solvent	Yield (%)[a]
1	**4a**	–	Ph_3P	Cs_2CO_3	TBAB	DMF	n.r.
2	**4a**	$PdCl_2$	Ph_3P	Cs_2CO_3	TBAB	DMF	45
3	**4a**	$Pd(OAc)_2$	–	NaOAc	–	DMF	46
4	**4a**	$Pd(OAc)_2$	–	KOAc	–	DMF	52
5	**4a**	$Pd(OAc)_2$	–	Cs_2CO_3	–	DMF	66
6	**4a**	$Pd(OAc)_2$	–	Et_3N	TBAB	DMF	n.r.
7	**4a**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	90
8	**4b**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	88
9	**4d**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	92
10	**5a**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	93
11	**5b**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	90
12	**5d**	$Pd(OAc)_2$	–	Cs_2CO_3	TBAB	DMF	94

[a] n.r. = no reaction.



Scheme 3 Synthesis of isochromeno[3,4-*a*]carbazol-2(13*H*)-one

In conclusion, we have developed a convenient and high-yielding route for the construction of a new class of benz-annelated oxazepinocarbazoles as well as isochromeno-carbazoles via palladium-catalyzed intramolecular arylation. Use of mild base reaction conditions for these C–O and C–C bond-forming process proved to result in effective transformations.

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

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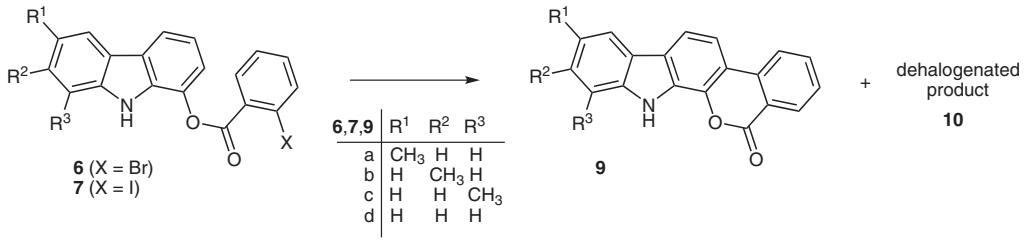
Table 3 Synthesis of Isochromeno[3,4-*a*]carbazol-2(13*H*)-ones **9** under Various Experimental Conditions



Entry	Reactant	Catalyst (10 mol%)	Ligand (20 mol%)	Base (2 equiv)	Additive (2 equiv)	Solvent	Yield of **9**/**10** (%)
1	**6a**	–	Ph_3P	Cs_2CO_3	–	DMF	n.r.[a]
2	**6a**	$PdCl_2$	Ph_3P	KOAc	TBAB	DMF	40:35
3	**6a**	$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	TBAB	DMSO	0:80
4	**6a**	$Pd(OAc)_2$	Ph_3P	K_2CO_3	–	DMF	70:8
5	**6a**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	85:0
6	**6b**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	78:0
7	**6c**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	76:0
8	**6d**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	82:0
9	**7a**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	89:0
10	**7b**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	85:0
11	**7c**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	84:0
12	**7d**	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	–	DMF	87:0

[a] n.r. = no reaction.

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(18) **General Procedure for the Preparation of 4 and 5**
To 2-halobenzoic acid (2.5 mmol) was added $SOCl_2$ (2 mL). The solution was refluxed for 2 h, after which the excess of $SOCl_2$ was removed under reduced pressure, and the residual traces were then removed by coevaporation with dry toluene. The acid chloride was then added to a solution of 1-hydroxycarbazole (2.5 mmol) and Et_3N (2 mL) in dry THF (10 mL) at 0 °C. After the addition of the acid chloride, the mixture

was allowed to warm up to r.t. while stirring under a nitrogen atmosphere. After stirring overnight, the mixture was diluted with H_2O and neutralized with 4% HCl to pH 7. The precipitated amide was then filtered off and washed with 4% HCl and copious amounts of H_2O. The crude product was purified by chromatography using 1% EtOAc and afforded **4** and **5**.

1-Hydroxy-9-(2-bromobenzoyl)-6-methylcarbazole (4a)

White solid; mp 126 °C; yield 0.682 g, 72%. IR (KBr): ν = 3432 (OH), 1646 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 6.86 (t, 1 H, *J* = 8.0 Hz, H-3), 7.13 (dd, 1 H, J_m = 2.0 Hz, J_o = 8.0 Hz, H-7), 7.21 (dd, 1 H, J_m = 2.0 Hz, J_o = 8.0 Hz, H-2), 7.58–7.62 (m, 2 H, H_{arom}), 7.67–7.71 (m, 2 H, H_{arom}), 7.75 (d, 1 H, *J* = 8.0 Hz, H-8), 7.85 (s, 1 H, H-5), 7.94 (dd, 1 H, J_m = 2.0 Hz, J_o = 7.5 Hz, H-3′), 12.76 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 111.0, 111.6, 116.8, 119.1, 120.2, 122.3, 122.9, 126.1, 126.5, 127.5, 128.3, 129.9, 131.8, 132.2, 132.8, 138.4, 139.3, 148.5, 165.7 (CO). LC-MS: *m/z* = 380 [M + H^+]. Anal. Calcd (%) for $C_{20}H_{14}BrNO_2$: C, 63.32; H, 3.69; N, 3.69. Found: C, 63.34; H, 3.67; N, 3.72.

(19) **General Procedure for the Preparation of 6 and 7**

To a solution of 1-hydroxycarbazole (**3a**–**d**, 2.5 mmol) in dry CH_2Cl_2, 2-bromobenzoyl chloride, or 2-iodobenzoyl chloride (prepared as before) in dry CH_2Cl_2 solution (10 mL) was added, and the reaction mixture was heated to reflux for 12 h. The mixture was then washed with H_2O and brine solution and dried (Na_2SO_4). Evaporation of the CH_2Cl_2 gave a crude product which was purified by chromatography with PE–EtOAc (98:2) to afford **6** and **7**.

6-Methyl-9*H*-carbazol-1-yl 2-Bromobenzoate (6a)

White solid; mp 147 °C; yield 0.682 g, 72%. IR (KBr): ν = 3389 (NH), 1741 (OC=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 7.24–7.28 (m, 2 H, H_{arom}), 7.35 (d, 1 H, *J* = 8.0 Hz, H-8), 7.39 (dd, 1 H, J_m = 1.0 Hz, J_o = 8.0 Hz, H-4), 7.46–7.53 (m, 2 H, H_{arom}), 7.81 (dd, 1 H, J_m = 1.5 Hz, J_o = 7.7 Hz, H-2), 7.89 (s, 1 H, H-5), 7.97 (d, 1 H, *J* = 7.5 Hz, H-3′), 8.13 [dd, 2 H, J_m = 2.0 Hz, J_o = 7.5 Hz, H-6′ (overlapped with NH)]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.29 (CH_3), 110.66, 117.57, 117.98, 119.24, 120.29, 122.04, 123.52, 126.27, 127.38, 127.66, 129.18, 131.28, 131.68, 131.96, 133.25, 134.54, 135.59, 137.88, 163.93 (C=O). LC-MS: *m/z* = 380 [M + H^+]. Anal. Calcd (%) for $C_{20}H_{14}BrNO_2$: C, 63.32; H, 3.69; N, 3.69. Found: C, 63.36; H, 3.70; N, 3.72.

(20) **General Procedure for the Preparation of 8**

To a mixture of **4** or **5** (1 mmol), Bu_4NBr (1.5 equiv), and Cs_2CO_3 (1.5 equiv) in anhyd DMF (8 mL) was added $Pd(OAc)_2$ (10 mol%) and the flask placed in a pre-heated oil bath at 110 °C for 2 h. After completion of the reaction, the mixture was cooled and diluted with H_2O. This was extracted with EtOAc. The combined organic extracts were washed with 1 M HCl, H_2O, brine and dried (Na_2SO_4). The solvent was removed by distillation, and the crude product was purified by column chromatography over silica gel using PE as the eluent to give the final compound **8**.

13-Methylbenzo[*f*][1,4]oxazepino[4,3,2-*l*,*m*]carbazol-9-one (8a)

White solid; mp 141 °C; yield 0.269 g, 90%. IR (KBr): ν = 1666 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.12 (d, 1 H, *J* = 8.0 Hz, H-3), 7.18 (t, 1 H, *J* = 8.0 Hz, H-2), 7.19 (t, 1 H, *J* = 7.5 Hz, H-7), 7.23 (d, 1 H, *J* = 8.0 Hz, H-5), 7.28 (d, 1 H, *J* = 8.0 Hz, H-12), 7.48 (t, 1 H, *J* = 7.5 Hz, H-6), 7.60 (d, 1 H, *J* = 7.0 Hz, H-1), 7.67 (s, 1 H, H-14), 8.05 (dd, 1 H, J_m = 1.5 Hz, J_o = 8.0 Hz, H-8), 8.55 (d, 1 H, *J* = 8.5 Hz, H-11). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.42 (CH_3), 115.84, 116.94, 117.69, 120.07, 121.34, 124.73, 125.06, 125.52, 126.59, 128.89, 129.27, 129.79, 133.36, 134.51, 134.89, 137.66, 145.62, 156.51, 164.73 (C=O). LC-MS: *m/z* = 300 [M + H^+]. Anal. Calcd (%) for $C_{20}H_{13}NO_2$: C, 80.27; H, 4.35; N, 4.68. Found: C, 80.21; H, 4.37; N, 4.73.

(21) Complete cif files for compounds **4a** and **9a** were deposited with the Cambridge Crystallographic Data Centre, CCDC Deposit numbers 796527 and 796520. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

(22) **General Procedure for the Preparation of 9**

To a mixture of **6** or **7** (1 mmol), Ph_3P (20 mol%), and Cs_2CO_3 (2 equiv) in anhyd DMF (8 mL) was added $Pd(OAc)_2$ (10 mol%), and the mixture was placed in a pre-heated oil bath at 110 °C for 4 h. After completion of the reaction, the mixture was cooled and diluted with H_2O. This was extracted with EtOAc. The combined organic extracts were washed with 1 M HCl, H_2O, brine and dried (Na_2SO_4). The solvent was removed by distillation, and the crude was purified by column chromatography over silica gel using PE as eluent to give compound **9** as white solid.

10-Methylisochromeno[3,4-*a*]carbazol-2(13*H*)-one (9a)

Mp >300 °C; yield 0.254 g, 85%. IR (KBr): ν = 3305 (NH), 1719 (OC=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 7.25 (d, 1 H, *J* = 8.0 Hz, H-11), 7.37 (d, 1 H, *J* = 8.0 Hz, H-12), 7.50 (t, 1 H, *J* = 8.0 Hz, H-4), 7.54 (d, 1 H, *J* = 8.0 Hz, H-7), 7.78 (d t, 1 H, J_m = 2.0 Hz, J_o = 8.0 Hz, H-5), 7.89 (s, 1 H, H-9), 7.93 (d, 1 H, *J* = 8.5 Hz, H-3), 8.16 (d, 1 H, *J* = 8.0 Hz, H-8), 8.38 (dd, 1 H, J_m = 1.5 Hz, J_o = 8.0 Hz, H-6), 8.56 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.34 (CH_3), 102.32, 111.02, 116.10, 118.38, 118.66, 119.20, 120.46, 121.09, 124.52, 125.52, 126.92, 127.15, 128.00, 128.41, 132.07, 132.45, 133.05, 136.76, 158.12 (C=O). LC-MS: *m/z* = 300 [M + H^+]. Anal. Calcd (%) for $C_{20}H_{13}NO_2$: C, 80.27; H, 4.35; N, 4.68. Found: C, 80.17; H, 4.33; N, 4.61.