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Synthesis of 2,3-Disubstituted Carbazoles, Benzo[*c*]carbazoles, and Phenanthrenes Through $FeCl_3$-Mediated Cyclization of Triene Frameworks

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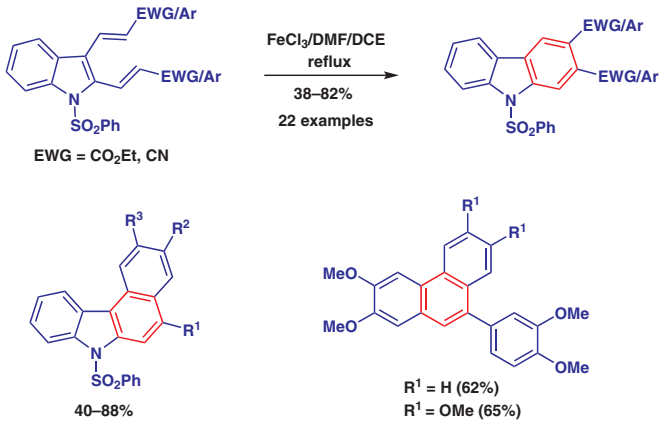

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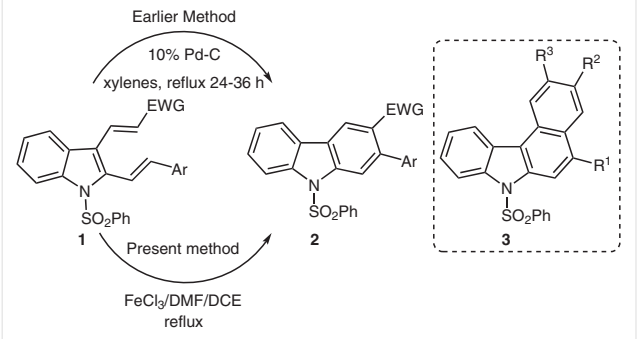
Abstract A facile synthesis of 2,3-disubstituted carbazoles through electrocyclization of 2,3-divinylindoles using $FeCl_3$ in DMF at reflux is reported. The methodology was found to be applicable for smooth transformation of 3-aryl-2-vinylindole as well as 2-styrylbiphenyl into the respective benzo[*c*]carbazole and phenanthrene.

Key words carbazoles, electrocyclization, Iron(III) chloride, 2,3-divinylindole, benzocarbazole, phenanthrene

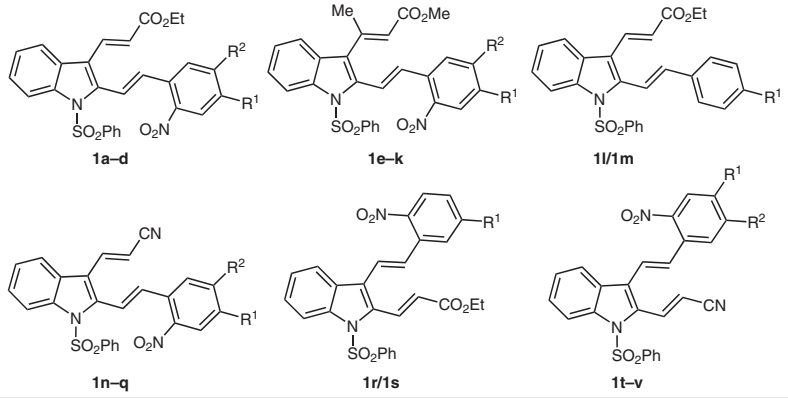
Over the years, our research group has exploited electrocyclization of 1-phenylsulfonyl-2,3-divinylindoles as a key step for the syntheses of quinocarbazoles,[1a] staurosporine aglycone,[1b,1c] and also for accessing a wide variety of substituted carbazoles.[2] We have also accomplished a Lewis acid mediated electrocyclization strategy for accessing calothrixin B and its derivatives.[3] In all these reports, the thermal electrocyclization followed by aromatization of 2,3-divinylindoles could be performed using 10% Pd/C in xylenes at reflux to give the respective carbazoles in good yields. However, the inconsistent quality of 10% Pd-C, difficulty in the aromatization of intermediate dihydrocarbazole, coupled with prolonged reaction time at elevated temperature, makes this protocol unsuitable for performing the reaction on a multi-gram scale. We sought to develop an alternative procedure that avoids the use Pd/C and also overcomes the disadvantages noted above. Hence, in a further continuation of our work on the synthesis of carbazoles,[1–3] we report herein the synthesis of a wide variety of carbazole derivatives **2** through $FeCl_3$-mediated[4,5] electrocyclization as a key step.The synthesis of benzo[*c*]carbazoles **3** could also be achieved from the respective 2-vinyl-3-arylindoles (Scheme 1).



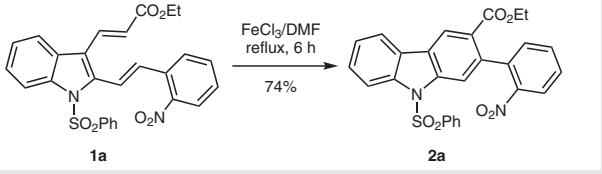
Scheme 1 Synthesis of carbazoles **2** and **3** using $FeCl_3$-mediated cyclization

To realize this objective, the required 2,3-divinylindoles **1a–v** were prepared (Scheme 2) from the respective phosphonate esters.[6] As a representative case, thermal electrocyclization of **1a** in the presence of anhydrous $FeCl_3$ in anhydrous DMF at reflux for 6h afforded 2-nitrophenyl carbazole **2a**[7] in 74% yield (Scheme 3).

To our delight, $FeCl_3$-mediated electrocyclization of a wide variety of 2,3-divinylindoles could be smoothly performed to afford the respective carbazoles.



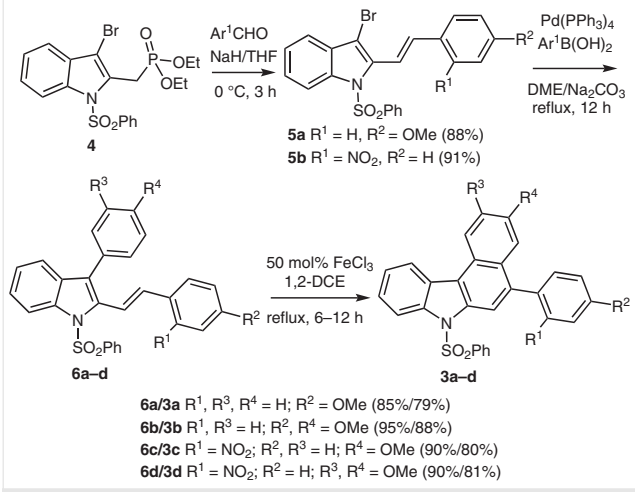
Scheme 2 List of 2,3-divinylindoles **1a–v**



Scheme 3 $FeCl_3$-mediated electrocyclization of divinylindole **1a**

The structures of various types of divinylindoles employed and the resulting carbazoles obtained are presented in Table1. The reaction of 1-phenylsulfonyl-2,3-divinylindoles **1b–d** with $FeCl_3$ in anhydrous DMF at reflux afforded carbazoles **2b–d** in 71–78% yields, respectively (entry 1). The $FeCl_3$-mediated elctrocyclization could be smoothly performed with 2,3-divinylindoles **1e–k** to afford the expected 4-methylcarbazoles **2e–k** in good yields (entry 2). However, the reaction was found to proceed slowly with 2,3-divinylindole **1l/1m**, containing a phenyl or *p*-anisyl unit, yielding the respective carbazole **2l** and **2m** in 43% and 38% yields (entry 3). The isolation of compounds **2l** and **2m** in low yields confirms that the electron-donating nature of the aryl unit present in 2,3-divinylindole **1l** or **1m** is not conducive for the $FeCl_3$-mediated electrocyclization reaction. As expected, the 2,3-divinylindoles **1n–q**, containing a cyanovinyl unit, upon reaction with 50mol% $FeCl_3$ in DMF at reflux furnished the respective 3-cyano-2-(2′-nitrophenyl)carbazoles **2n–q** in 78–82% yields (entry 4). Under identical conditions, the isomeric 3-(2′-nitrophenyl)-vinylindoles **1r–v**, containing 2-vinyl ester as well as a 2-vinyl cyanide unit, could be smoothly transformed into the appropriate carbazoles **2r–v** (entries 5 and 6).

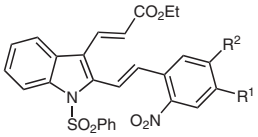
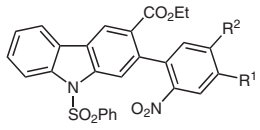
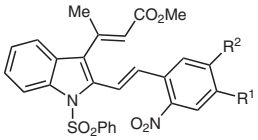
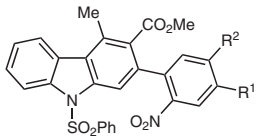
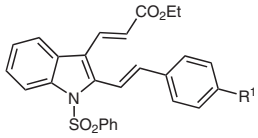
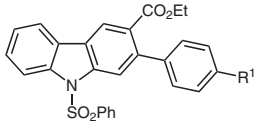
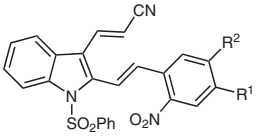
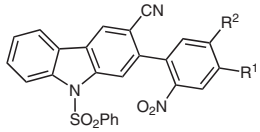
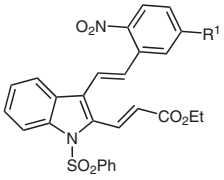
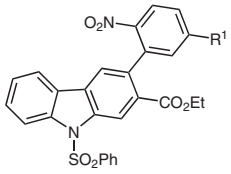
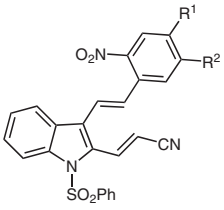
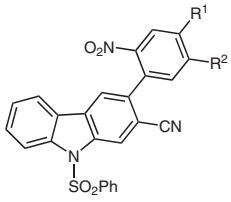
The synthesis of benzo[*c*]carbazole analogues employing the $FeCl_3$-mediated cyclization was then initiated. Accordingly, Wittig–Horner reaction of phosphonate ester **4**[6] with substituted benzaldehydes in the presence of NaH in tetrahydrofuran (THF) at 0°C for 3h afforded 3-bromo-2-arylindoles **5a** and **5b**. As expected, the Suzuki coupling of bromo compound **5a**/**5b** with aryl boronic acid using $Pd(PPh_3)_4$ and Na_2CO_3 in 1,2-dimethoxyethane (DME) at reflux furnished 3-aryl-2-strylindoles **6a–d** as colorless solids in good yields. As expected, the reaction of **6a–d** with 50 mol% $FeCl_3$ in anhydrous 1,2-dichloroethane (DCE) at room temperature or at reflux furnished 2-aryl benzo[*c*]carbazoles **3a–d**[7] in good yields (Scheme 4).



Scheme 4 $FeCl_3$-mediated cyclization of 3-aryl-2-vinylindoles **6a–d**

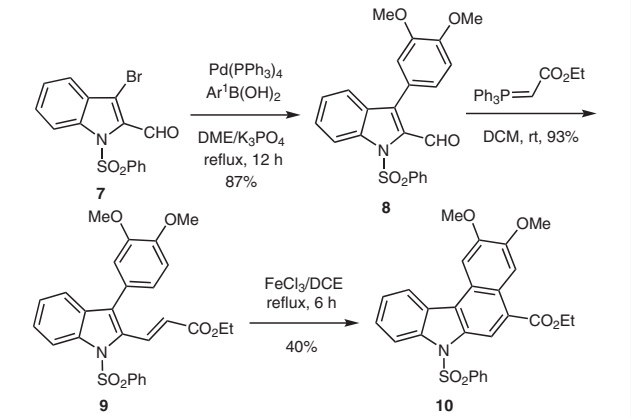
Subsequently, 3-bromo-2-methylindole, upon benzylic bromination followed by hydrolysis and MnO_2 oxidation of corresponding alcohol, led to 3-bromoindole-2-aldehyde **7**. The Suzuki coupling of bromo compound **7** with veratryl boronic acid using $Pd(PPh_3)_4$ in the presence of K_3PO_4 in DME reflux afforded 2-formyl-3-arylindole **8** as a colorless solid in 87% yield. Indole aldehyde **8**, upon Wittig reaction with (carbethoxymethylene)triphenylphosphorane in

Table 1 $FeCl_3$-Mediated Electrocyclization of 1-Phenylsulfonyl-2,3-divinylindoles **1b–v**

Entry	2,3-divinylindole[a]		Carbazole	Yield (%)[b]
1	 **1b–d**	**1b**/**2b** R^1=Cl, R^2=H **1c**/**2c** R^1=F, R^2=H **1d**/**2d** R^1=H, R^2=F	 **2b–d**	71 73 78
2	 **1e–k**	**1e**/**2e** R^1, R^2=H **1f**/**2f** R^1=Cl, R^2=H **1g**/**2g** R^1=H, R^2=Cl **1h**/**2h** R^1=F, R^2=H **1i**/**2i** R^1=H, R^2=F **1j**/**2j** R^1=F, R^2=Cl **1k**/**2k**[1] R^1=Cl, R^2=F	 **2e–k**	78 75 76 78 73 71 70
3	 **1l/1m**	**1l**/**2l** R^1=H **1m**/**2m** R^1=OMe	 **2l/2m**	43 38
4	 **1n–q**	**1n**/**2n** R^1, R^2=H **1o**/**2o** R^1=Cl, R^2=H **1p**/**2p** R^1=F, R^2=H **1q**/**2q** R^1=H, R^2=F	 **2n–q**	79 82 81 78
5	 **1r/1s**	**1r**/**2r** R^1=H **1s**/**2s** R^1=F	 **2r/2s**	78 72
6	 **1t–v**	**1t**/**2t** R^1, R^2=H **1u**/**2u** R^1=Cl, R^2=H **1v**/**2v** R^1=F, R^2=H	 **2t–v**	80 72 74

[a] Reactions were carried out using **1a–v** (1 equiv), $FeCl_3$ (0.5–2 equiv) in DMF (10mL) at reflux for 3–12h.
[b] Isolated yield by column chromatography.

anhydrous CH_2Cl_2 at room temperature, led to 3-veratryl-2-vinylindole **9** in 93% yield. The 2-vinyl ester **9**, upon cyclization using 50mol% $FeCl_3$ in anhydrous 1,2-DCE reflux, furnished benzo[*c*]carbazole **10** in a moderate yield (Scheme 5). Attempts to improve the yield of the benzo[*c*]carbazole **10** either by increasing the number of equivalents of $FeCl_3$ or by prolonging the reaction time was not found to be useful.



Scheme 5 $FeCl_3$-mediated cyclization of 2-vinyl-3-veratrylindole **9**

Next, the Wittig–Horner reaction of phosphonate ester **11**[8] with 2-bromo-veratraldehyde **12** in the presence of *t*-BuOK in toluene at reflux afforded vinyl compound **13**. As expected, the Suzuki coupling of **13** with boronic acids furnished the required triene compounds **14a** and **14b** in 85% and 91% yields. The triene frame work of **14a** and **14b** underwent cyclization upon interaction with 50mol% $FeCl_3$ in anhydrous 1,2-DCE at reflux to give 9-arylphenanthrenes **15a**[7] and **15b** in 62% and 65% yields, respectively (Scheme 6).

In summary, we have achieved the syntheses of 2,3-disubstituted carbazoles, benzo[*c*]carbazoles, and phenanthrene derivatives by employing $FeCl_3$-mediated cyclization of the corresponding triene frameworks. For the first time, the $FeCl_3$-mediated cyclization of two vinylic carbons as well as phenyl and vinylic carbons could be achieved in acceptable yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037–1609936.

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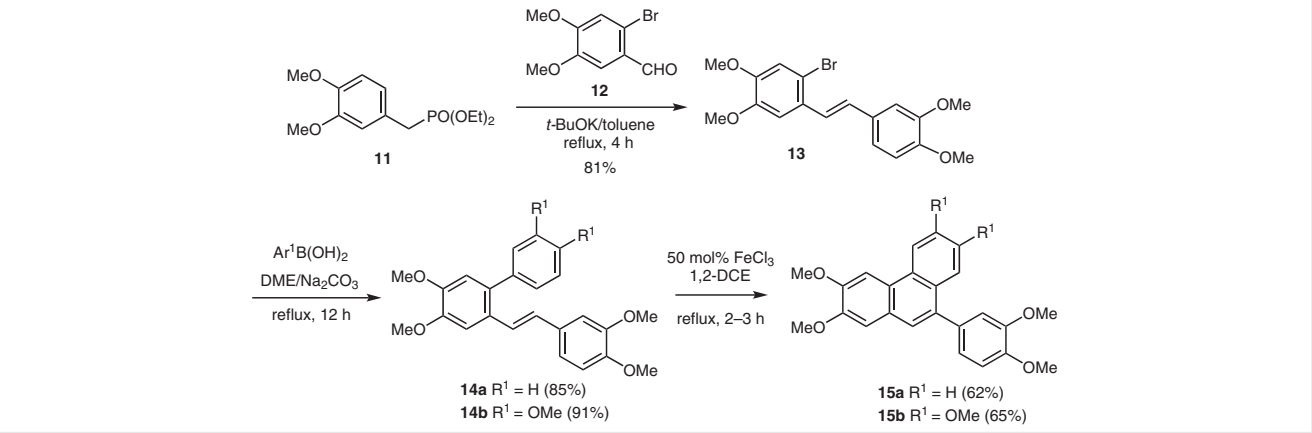

Scheme 6 $FeCl_3$-mediated cyclization of 2-styrylbiphenyl compounds **14a** and **14b**

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(7) *Representative procedure for **2a***: To a stirred solution of 2,3-divinyl compound **1a** (0.2 mmol) in anhydrous DMF (10 mL) at r.t., anhydrous $FeCl_3$ (0.4 mmol) was added and the reaction mixture was heated at reflux for 6 h. After completion of the reaction (monitored by TLC), the mixture was poured over crushed ice (50 g) containing conc. HCl (3 mL). The crude product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layer was dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (1% EtOAc/hexane) afforded carbazole **2a** (74 mg, 74%) as a colorless solid. Mp 220–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.23 (d, *J* = 7.2 Hz, 1 H), 8.15 (s, 1 H), 8.07 (d, *J* = 8.1 Hz, 1 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 2 H), 7.61 (m, 8 H), 4.05 (q, *J* = 6.5 Hz, 2 H), 1.01 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 148.4, 140.1, 139.1, 138.9, 137.6, 137.1, 134.2, 132.6, 131.5, 129.2, 128.4, 128.3, 126.4, 126.1, 125.7, 125.1, 124.7, 124.0, 123.1, 120.5, 116.5, 115.3, 61.1, 13.8 ppm.

*Representative procedure for **3a***: To a stirred solution of 3-aryl-2-vinylindole **6a** (0.1 g, 0.21 mmol) in anhydrous 1,2-DCE (8 mL) at r.t., anhydrous $FeCl_3$ (18 mg, 0.10 mmol) was added and the reaction mixture was stirred at reflux for 3 h. After completion of the reaction (monitored by TLC), the mixture was poured over ice water (20 mL) and acidified with conc. HCl (2 mL). It was then extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (Silica gel; EtOAc–hexane, 2:8) gave benzo[*c*]carbazole **3a** as a colorless solid (79 mg, 79%). Mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 8.4 Hz, 1 H), 8.46–8.40 (m, 2 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 7.8 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.42–7.32 (m, 7 H), 7.24–7.17 (m, 2 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 140.7, 138.2, 137.9, 136.1, 133.8, 133.0, 131.3, 129.8, 129.1, 129.0, 127.6, 127.1, 127.0, 126.3, 126.1, 124.8, 124.4, 123.7, 122.1, 119.0, 115.6, 115.3, 113.8, 55.4 ppm. Dept-135 (75 MHz, $CDCl_3$): δ = 133.8, 131.3, 129.0, 127.5, 127.1, 126.3, 126.0, 124.8, 124.4, 123.7, 122.0, 115.6, 115.3, 113.7, 55.3 ppm. HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{29}H_{21}NO_3S$: 463.1242; found: 463.1220.

*Representative procedure for **15a***: To a stirred solution of 2-styrylbiphenyl compound biphenyl vinylene **14a** (0.1 g, 0.26 mmol) in anhydrous 1,2-DCE (10 mL) at r.t., anhydrous $FeCl_3$ (21 mg, 0.13 mmol) was added and the reaction mixture was stirred at reflux for 3 h. Following a similar work up procedure to that for **6a** afforded 2,3-dimethoxyphenanthrene **15a** (62 mg, 62%) as a colorless solid. Mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.4 Hz, 1 H), 8.06 (s, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.27 (d, *J* = 3.3 Hz, 1 H), 7.12–7.02 (m, 3 H), 4.17 (s, 3 H), 4.06 (s, 3 H), 4.00 (s, 3 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 149.3, 148.6, 148.3, 136.9, 133.7, 130.5, 130.0, 127.0, 126.7, 126.5, 126.0, 125.5, 124.4, 122.4, 122.3, 113.5, 111.0, 108.2, 103.2, 56.1, 56.0, 55.9, 55.8 ppm. HRMS (EI): *m*/*z* [M$^+$] cacld for $C_{24}H_{22}O_4$: 374.1518; found: 374.1515.

(8) Koufaki, M.; Theodorou, E.; Galaris, D.; Nousis, L.; Katsanou, E. S.; Alexis, M. N. *J. Med. Chem.* **2006**, *49*, 300.