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A novel synthesis of *N*-protected carbazoles involving electrocyclization of in situ generated enamines

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Abstract—A new route for the synthesis of carbazoles has been realized through the intermediacy of 2,3-divinylindoles involving an electrocyclization followed by aromatization.
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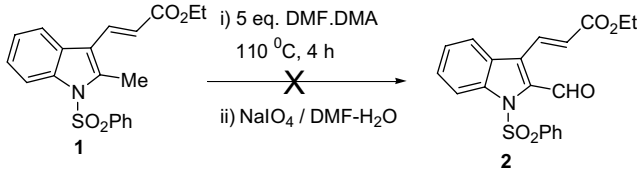
Ever since the first isolation of the carbazole alkaloid, murrayanine[1] organic chemists have been interested in the synthesis of carbazole alkaloids due to their promising biological activities. In particular, many biomimetic oxidation products of 3-methylcarbazole have been isolated and their syntheses have been widely reported.[2] Recently Knölker and Reddy extensively reviewed the synthesis of biologically active carbazole alkaloids.[3]

Thermal electrocyclization methodology has been widely used for the synthesis of carbazole based natural products.[4] Mohanakrishnan and Srinivasan outlined a novel synthesis of phenylsulfonylcarbazoles involving electrocyclization of *N*-phenylsulfonyl 2,3-divinylindoles as the key step.[5] Very recently syntheses of multifunctional carbazoles[6] have been reported involving either cycloaddition or base mediated cyclization.

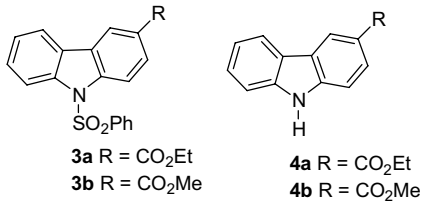
In continuation of our interest in carbazole based alkaloids we wanted to prepare the aldehyde **2**. In this connection, a survey of the literature revealed that Coe's procedure has been widely utilized for the synthesis of benzaldehydes, pyridine aldehydes, naphthaldehydes and quinoline aldehydes.[7–9] The enamine intermediates involved in Coe's protocol have also been utilized for the synthesis of indoles,[10] azaindoles,[11] quinolones[12] etc. Very recently the acetals DMF/DMA, DMA/DMA were used for formylation/acetylation of acetylenic systems.[13]



Scheme 1.

We presumed that the condensation of vinyl ester **1** with DMF/DMA followed by oxidation using $NaIO_4$ might lead to aldehyde **2**. However when **1** was reacted with 5 equiv of DMF/DMA at 110 °C for 4 h followed by treatment with $NaIO_4$, aldehyde **2** was not obtained, Scheme 1.

When **1** was reacted with DMF/DMA and the resulting crude product was analyzed by mass spectrometry, the presence of M^+ ions at *m*/*z* 379, 365, 239 and 225, corresponding to carbazoles **3a**,**b** and **4a**,**b** were observed, Scheme 2.



Scheme 2.

Keywords: Enamine; 2,3-Divinylindole; Electrocyclization; Carbazole.
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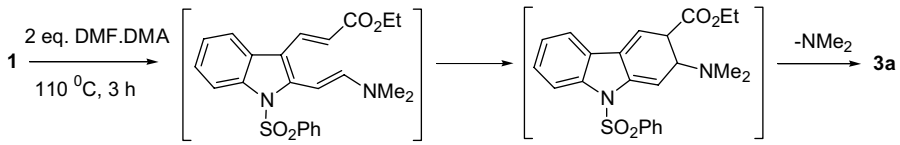


Scheme 3.

The mechanism of formation of carbazole **3a** can be understood as the electrocyclization of an intermediate enamine followed by aromatization, Scheme 3. The formation of the remaining carbazoles **3b**, **4a** and **b** would involve the secondary reaction of **3a** with methoxide ions. This was further confirmed by prolonging the reaction period or by using excess of DMF/DMA, when carbazoles **4a** and **b** were the major products.

When the reaction was carried out using 2 equiv of DMF/DMA for 3 h at 110 °C, the carbazole **3a** was obtained as sole product in 73% yield, Scheme 3.

The formation of carbazole **3a** also supported our earlier observation[5] that *N*-protection is essential for smooth electrocyclization of 2,3-divinylindoles. Thus the presence of the phenylsulfonyl group on the indole nitrogen conveys typical triene character to the 2,3-divinylindole system and thereby electrocyclization is facilitated.

The enamine-based electrocyclization methodology was then tested with a variety of 2-methyl-3-vinylindoles and 3-methyl-2-vinylindoles **1**–**1h**, and the results are detailed in Table 1. Comparatively the reaction with

Table 1. Preparation of carbazoles using vinylindoles and *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide dimethyl acetals

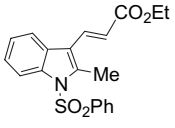
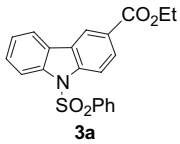
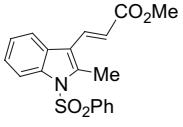
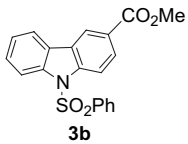
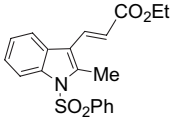
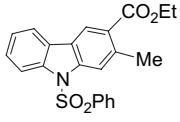
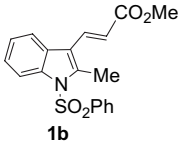
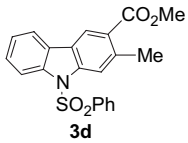
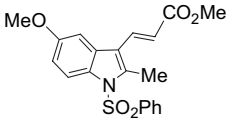
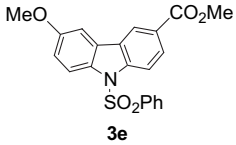
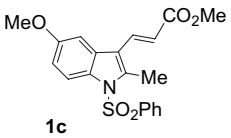
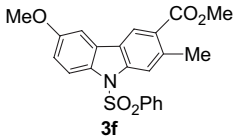
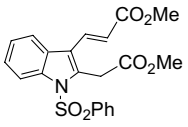
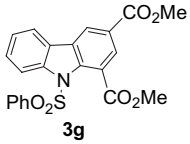
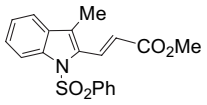
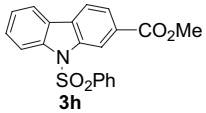
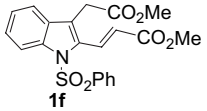
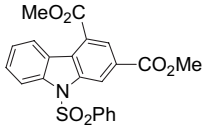
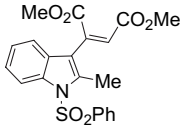
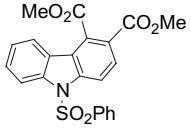
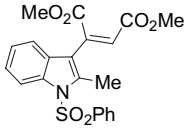
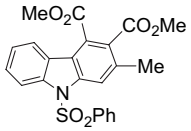
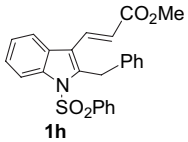
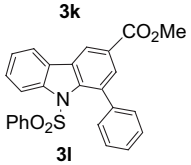
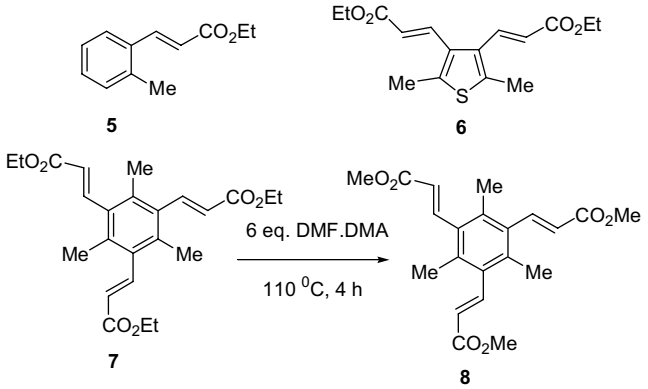
Entry	Vinylindoles[14]	Acetal	Carbazole[15]	Yield, % & (mp)
1	 **1**	DMF/DMA	 **3a**	73 (180)
2	 **1b**	DMF/DMA	 **3b**	70 (188)
3	 **1**	DMA/DMA	 **3c**	67 (174)
4	 **1b**	DMA/DMA	 **3d**	68 (171)
5	 **1c**	DMF/DMA	 **3e**	68 (183)
6	 **1c**	DMA/DMA	 **3f**	55 (175)
7	 **1d**	DMF/DMA	 **3g**	65 (102)

Table 1 (*continued*)

Entry	Vinylindoles[14]	Acetal	Carbazole[15]	Yield, % & (mp)
8	 **1e**	DMF/DMA	 **3h**	0
9	 **1f**	DMF/DMA	 **3i**	65 (210)
10	 **1g**	DMF/DMA	 **3j**	62 (128)
11	 **1g**	DMA/DMA	 **3k**	53
12	 **1h**	DMF/DMA	 **3l**	40 (182)

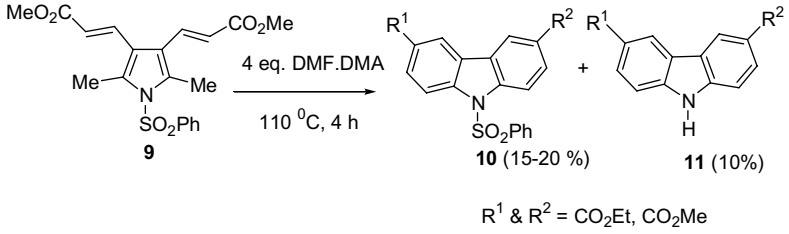
2-methyl-3-vinylesters afforded the corresponding carbazoles in better yields (entries 1–7). The expected annulation failed with 3-methyl-2-vinylindole **1e** even under forcing conditions (entry 8). However the annulation was successful with 3-carbomethoxymethyl-2-vinylindole **1f** (entry 9). Hence the failure in the case of **1e** can be attributed to the relatively less acidic nature of 3-methyl group. The use of DMA/DMA instead of DMF/DMA also led to the respective carbazoles in almost comparable yields (entries 3 and 4). But in two cases, the yields of the carbazoles were relatively less when DMA/DMA was employed (entries 6 and 11). The annulation of 2-benzyl-3-vinylindole **1h** led to the isolation of 1-phenylcarbazole **3l** in 40% yield (entry 12).



Scheme 4.

Attempted annulations with substrates **5** and **6** were unsuccessful even under vigorous conditions and the starting materials were recovered unchanged. Similarly, the attempted tris-annulation of **7** led only to the transesterification product **8** in 30% yield, Scheme 4.

It is noteworthy that in the case of 3-vinyl-2-methylpyrrole **9**, the expected bis-annulation was achieved but the secondary reactions, namely cleavage of the phenylsulfonyl group and transesterification, could not be



Scheme 5.

controlled; a mixture of products **10** and **11** was obtained in low yields, Scheme 5. Use of less than 4 equiv of DMF/DMA led to the formation of vinylindoles as mono annulated products.

In conclusion, we have developed a convenient procedure for the synthesis of functionalized carbazoles involving electrocyclization methodology based on in situ generated enamine intermediates. The further application of this methodology to the synthesis of carbazole-containing natural products is in progress.

Acknowledgements

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14. The starting vinylesters are prepared via the Wittig reaction of the corresponding aldehydes.
15. All the carbazoles **3a–l** gave satisfactory spectral and analytical data. *Typical experimental procedure for* **3a**: to a stirred solution of vinyl ester (0.5 g, 1.35 mmol) in dry DMF (1.5 mL), DMF/DMA (322 mg, 2.71 mmol) was added. The reaction mixture was heated at 110 °C under N_2 for 3 h. It was then poured into 2% aq HCl (15 mL) and extracted with $CHCl_3$ (2×20 mL). The combined extracts were washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (silica gel, EtOAc–hexane 1:5) afforded carbazole **3** as a colourless solid (0.38 g, 73%).
Spectral data of selected carbazoles for **3a**: mp 180 °C; IR (KBr) ν_{max}: 1709, 1369, 1176 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.45 (t, $J = 7.08$ Hz, 3H), 4.40–4.45 (q, $J = 7.32$ Hz, 2H), 7.36–7.55 (m, 5H), 7.82–7.84 (d, $J = 7.32$ Hz, 2H), 7.97–7.99 (d, $J = 7.32$ Hz, 1H), 8.18–8.21 (m, 2H), 8.33–8.39 (m, 1H), 8.61 (s, 1H). MS (EI) *m/z* (%): 379 (M^+, 100%), 239 (68), 194 (42), 165 (72). Elemental Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69; S, 8.45. Found: C, 66.52; H, 4.59; N, 3.74; S, 8.31.
For **3c**: mp 174 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.45 (t, $J = 7.08$ Hz, 3H), 2.83 (s, 3H), 4.38–4.43 (q, $J = 6.84$ Hz, 2H), 7.32–7.39 (m, 2H), 7.45–7.49 (m, 2H), 7.81–7.83 (d, $J = 7.32$ Hz, 2H), 7.91–7.93 (d, $J = 7.84$ Hz, 1H), 8.20 (s, 1H), 8.28–8.30 (d, $J = 8.32$ Hz, 2H), 8.48 (s, 1H). MS (EI) *m/z* (%): 393 (M^+, 100%), 349 (17), 209 (73), 181 (37). Elemental Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 67.28; H, 5.02; N, 3.83; S, 8.42.
For **3d**: mp 171 °C; IR (KBr) ν_{max}: 1720, 1369, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H), 3.96 (s, 3H), 7.28–7.50 (m, 5H), 7.84–7.94 (m, 3H), 8.23 (s, 1H), 8.30–8.33 (d, $J = 8.17$ Hz, 1H), 8.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.74, 51.96, 115.02, 117.23, 120.03, 122.93, 124.09, 124.27, 126.41, 127.58, 129.17, 134.03, 135.21, 137.73, 138.59, 140.12, 140.49, 167.74. MS (EI) *m/z* (%): 379 (M^+, 92%), 238 (100), 206 (34). Elemental Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69; S, 8.45. Found: C, 66.38; H, 4.72; N, 3.72; S,8.57.
For **3e**: mp 183 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.97 (s, 3H), 7.10–7.13 (m, 2H), 7.31–7.34 (t, $J = 7.82$ Hz, 1H), 7.39–7.40 (d, 1H), 7.45–7.48 (t, $J = 7.56$ Hz, 1H), 7.77–7.79 (d, $J = 7.32$ Hz, 2H), 8.15–8.17 (d, $J = 8.8$ Hz, 1H), 8.21–8.23 (d, $J = 8.8$ Hz, 1H), 8.33–8.35 (d, $J = 8.8$ Hz, 1H), 8.56 (s, 1H). MS (EI) *m/z* (%): 396 (80), 254 (100), 240 (46). Elemental Anal. Calcd for $C_{21}H_{17}NO_5S$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.69; H, 4.39; N, 3.94.