1,6-ELECTROCYCLIZATION REACTIONS OF ACCEPTOR-SUBSTITUTED 2,3-DIVINYLINDOLES TO FUNCTIONALIZED CARBAZOLES

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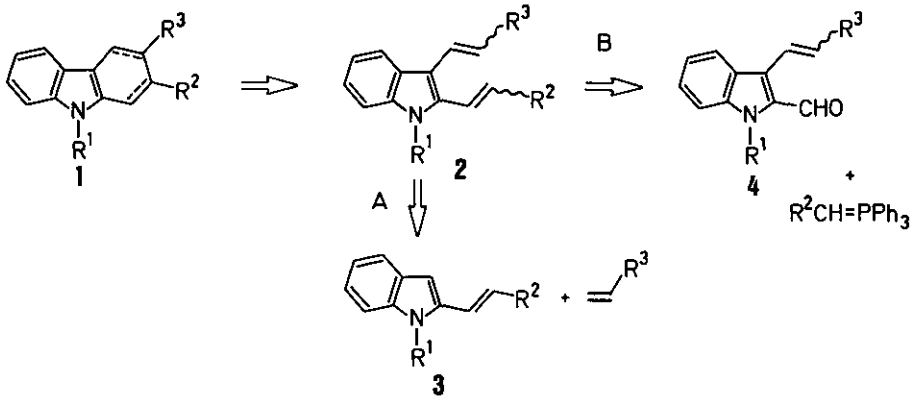
Abstract —— The syntheses and thermal 1,6-electrocyclization reactions of acceptor-substituted 2,3-divinylindoles, which give rise to functionalized carbazole derivatives, are described.

Functionalized and/or annellated carbazoles and carbazole alkaloids have now attained considerable interest as pharmacologically active lead substances as well as being, for example, compounds with antibiotic and anti-tumour activities.[1-6] Hence, there is a still a major requirement for short and highly selective syntheses of these classes of heterocyclic compounds starting from readily available substrates. In continuation of our work on convergent pericyclic methods for the synthesis of carbazoles (e.g. Diels-Alder reactions),[5,6] we now report on a further, recent pericyclic strategy for carbazoles,[7,8] namely the 1,6-electrocyclization of selectively acceptor-functionalized 2,3-divinylindoles which serve as highly interesting building blocks (Scheme 1, retrosynthetic analysis).

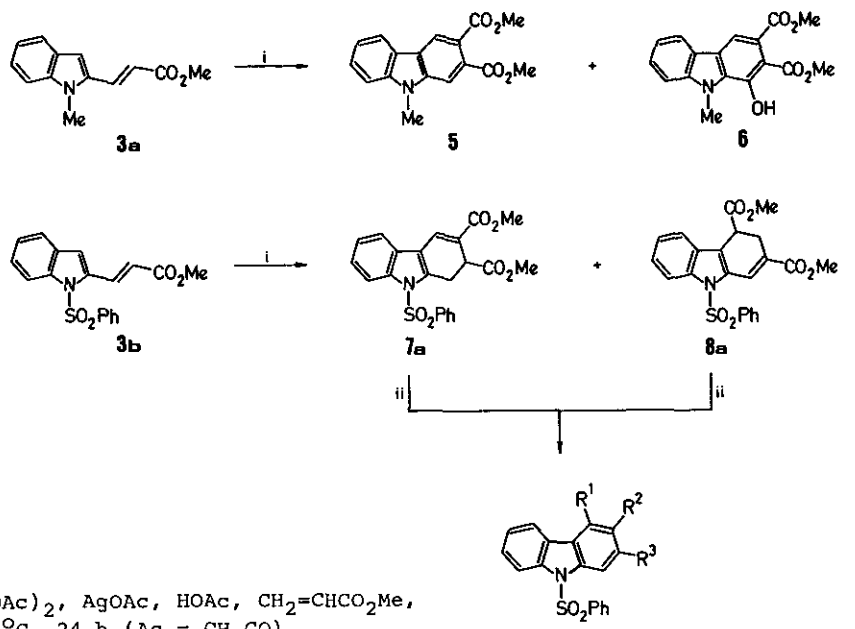
Syntheses of the previously unknown starting materials, the acceptor-substituted 2,3-divinylindoles (**2**; R^1 = Me, SO_2Ph; R^2 = CO_2Me, COMe; R^3 = CO_2Me, CN) were attempted by two routes: (**A**) the $Pd(OAc)_2$-catalyzed vinylation[9,10] of 2-vinylindoles **3** and (**B**) the salt-free Wittig reaction of 2-formyl-3-vinylindoles **4** with the appropriate ylides (Scheme 1).



Scheme 1

However, we have found that the Pd(II)-catalyzed coupling reactions of **3a** and **3b** with methyl acrylate in a one-pot procedure gave rise directly to the novel carbazole derivatives **5/6** and **7a/8a** (Scheme 2). Product **6** was formed additionally by way of an autoxidation process.[11] The isomeric dihydrocarbazoles **7a/8a** were oxidized by DDQ to **7b** and **8b**, respectively. According to MNDO calculations on the parent compounds, the 1,2-dihydrocarbazole structure is generally thermodynamically more stable than the 3,4-dihydrocarbazole form[12] (see also compounds **9b**, **9e**, and **9g**).

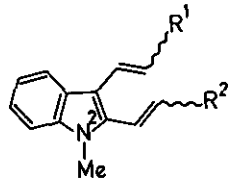
From the Wittig reactions (Method B) of the appropriate indole-2-carbaldehydes **4** with acceptor-stabilized Wittig reagents, the novel 2,3-divinylindoles **2a-e** were isolable in varying degrees of selectivity.[13] In boiling bromobenzene and, in most cases, in the presence of Pd/C as a dehydrogenation catalyst, these products underwent electrocyclization to furnish the functionalized carbazoles **9a-g** in low to high yields (Table 1). The 2,3-dihydrocarbazoles primarily anticipated from the 1,6-electrocyclization process are stabilized probably by subsequent [1,5]-H shifts and in all cases certainly by elimination of hydrogen. In the case of the electrocyclization of **2c**, an additional elimination of acetaldehyde took place to produce compound **9d** together with the products **9c** and **9g**. In the cases of the electrocyclizations of **2a/2b**, **2c**, and **2d/2e**, the more stable 1,2-dihydrocarbazoles could also be isolated as the formal precursors of the cyclization procedure to furnish the fully aromatized carbazole heterocycles (Table 1).



i: $Pd(OAc)_2$, AgOAc, HOAc, CH_2=$CHCO_2Me$, 100 °C, 24 h (Ac = CH_3CO)
ii: DDQ, BrPh, 150 °C

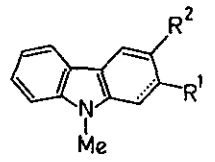
	R^1	R^2	R^3	yield [%]
7b	H	CO_2Me	CO_2Me	18
8b	CO_2Me	H	CO_2Me	22

Scheme 2



2*	R^1	R^2	yield [%]
(EE) **a**	CO_2Me	CO_2Me	43
(ZE) **b**	CO_2Me	CO_2Me	11
(EE) **c**	CO_2Me	COMe	58
(EE) **d**	CN	CO_2Me	57
(EZ) **e**	CN	CO_2Me	28

* The first configuration term refers in all cases to the 2-vinyl function on the indole nucleus.



9	R^1	R^2
a	CO_2Me	CO_2Me
b*	CO_2Me	CO_2Me
c	COMe	CO_2Me
d	H	CO_2Me
e*	CO_2Me	CN
f	CO_2Me	CN
g*	COMe	CO_2Me

* 1,2-Dihydro derivative.

Table 1. Carbazole derivatives **9a-g** *from the electrocyclizations of the* 2,3-divinylindoles **2a-e**.

Substrate	Product	Yield (%)
2a, 2b	**9a**[a]	8
2a, 2b	**9b**[b]	77
2c	**9c**[a]	61
2c	**9d**[a]	7
2d, 2e	**9e**[a]	24
2d, 2e	**9f**[a]	11
2c	**9g**[b]	84

[a] Reaction conditions and time: BrPh, 10% Pd/C, 156 °C; 6 h.

[b] Reaction conditions and time: BrPh, 156 °C; 4 h.

The constitutions of compounds **2** and **5-9**[14] were elucidated primarily by 400 MHz ^{1}H-nmr spectroscopy using several techniques such as, e.g., NOE experiments. For the example of compound **9g**, an energetically low conformation was demonstrated by MMX force field calculations and the diagnostically relevant ^{1}H-NOE's for establishing the constitution[15] were indicated.

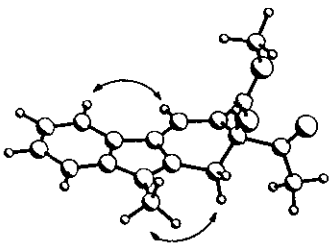


Fig. 1. PLUTO view of the minimum energy conformation of compound **9g** according to MMX force field calculations (ΔH_f = -40.7 kcal/mol).[15] The diagnostically relevant 400 MHz ^{1}H-NOE's for establishing the constitution are demonstrated.

In conclusion, the present results illustrate the scope and limitations of the direct access to acceptor-substituted 2,3-divinylindoles as well as their direct transformation to functionalized carbazoles having substitution patterns that are

not easily attainable by other methods.[3,4] The scope of Pd-catalyzed coupling methodology has been extended and the described reaction type tolerates the presence of a vinyl group at the indole 2 position without any problems. Furthermore, the synthesized carbazole derivatives represent highly interesting building blocks for the synthesis of carbazole alkaloids[1] and compounds for medicinal chemistry.[2]

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14. Satisfactory CHN-elemental analyses (C ± 0.2%; H ± 0.08%; N ± 0.1%) were obtained for products **2** and **5-9**. Selected ^{1}H-nmr spectroscopic data of some compounds: **2c** (400 MHz, DMSO-d_6): δ = 2.43 (s, 3H, CH_3CO), 3.72 (s, 3H, NCH_3 or OCH_3), 3.85 (s, 3H, OCH_3 or NCH_3), 6.50 (d, J = 16 Hz, 1H, vinyl H), 6.55 (d, J = 16 Hz, 1H, vinyl H), 7.24 (dd, J = 7.7 Hz and 7.6 Hz, 1H, 5-H or 6-H), 7.36 (dd, J = 7.3 Hz and 8.1 Hz, 1H, 6-H or 5-H), 7.62 (d, J = 8.3 Hz, 1H, 4-H or 7-H), 7.81 (d, J = 16.4 Hz, 1H, vinyl H), 7.87 (d, J = 16 Hz, 1H, vinyl H), 7.93 (d, J = 8.1 Hz, 7-H or 4-H). **9c** (200 MHz, DMSO-d_6): δ = 2.58 (s, 3H, CH_3CO), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3), 7.32 (dd, J = 7.3 Hz and 7.5 Hz, 1H, 6-H or 7-H), 7.56 (dd, J = 7.2 Hz and 7.7 Hz, 1H, 7-H or 6-H), 7.66 (d, J = 8.1 Hz, 1H, 5-H or 8-H), 7.81 (s, 1H, 1-H or 4-H), 8.32 (d, J = 7.7 Hz, 1H, 8-H or 5-H), 8.67 (s, 1H, 4-H or 1-H). **9d** (400 MHz, CD_2Cl_2): δ = 3.87 (s, 3H, NCH_3 or OCH_3), 3.94 (s, 3H, OCH_3 or NCH_3), 7.30 (dd, J = 7.0 Hz and 7.8 Hz, 1H, 6-H or 7-H), 7.44 (d, J = 8.5 Hz, 1H, 5-H or 8-H), 7.47 (d, J = 8.15 Hz, 1H, 8-H or 5-H), 7.53 (dd, J = 7.0 Hz and 7.1 Hz, 1H, 7-H or 6-H), 8.16 (m, 2H, 1-H and 2-H), 8.81 (d, J = 1.7 Hz, 1H, 4-H). **9g** (200 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3CO), 3.15 (dd, J = 9.1 Hz and 17.6 Hz, 1H, 1-H_β), 3.53 (dd, J = 2.5 Hz and 17.6 Hz, 1H, 1-H_α), 3.75 (s, 3H, NCH_3 or OCH_3), 3.76 (s, 3H, OCH_3 or NCH_3), 3.94 (dd, J = 9.1 Hz and 2.4 Hz, 1H, 2-H_β), 7.1-7.2 (m, 2H, 6-H and 7-H), 7.47 (d, J = 7.52 Hz, 1H, 8-H), 7.70 (dd, J = 1.8 Hz and 6.0 Hz, 1H, 5-H).

15. The MMX molecular mechanics calculations were performed with the program PCMODEL-pi including pi-VESCF routines (Serena Software Ltd., Bloomington, Indiana, USA).

Received, 23rd January, 1990