Pergamon

Tetrahedron Letters 43 (2002) 7925–7928

TETRAHEDRON
LETTERS

3-Cyanomethyl-2-vinylindoles as thermal indole-2,3-quinodimethane equivalents: synthesis of functionalized 1,2,3,4-tetrahydrocarbazoles

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Received 10 July 2002; revised 2 September 2002; accepted 5 September 2002

Abstract—Electron-donating substituted 3-cyanomethyl-2-vinylindoles were found to rearrange via thermal [1,5]H shift into the corresponding indole-2,3-quinodimethanes which were trapped by dienophiles to afford tetrahydrocarbazoles. © 2002 Elsevier Science Ltd. All rights reserved.

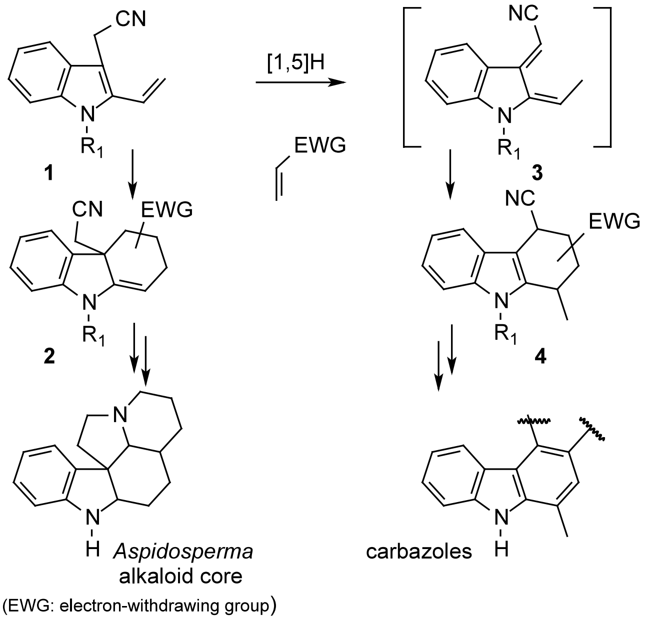
2-Vinylindoles[1] have proved to be versatile 4π-electron components in Diels–Alder reactions aiming at regio- and stereoselective syntheses of indole alkaloids,[2] carbazoles,[3] and non-natural [*b*]annelated indole derivatives[4] of pharmacological interest.

In continuation of our interest in the chemistry of 2-vinylindoles **1**,[5] we decided to study their thermal Diels–Alder reactivity toward electron deficient dienophiles. According to Pindur's analyses[6] Diels–Alder reactions between 2-vinylindoles and acrylate type dienophiles would be a $\mathrm{HOMO_{diene}}$–$\mathrm{LUMO_{dienophile}}$ controlled process via the energetically favored *endo* transition state with a predictable regioselectivity.

Normal Diels–Alder reactivity of **1** should afford cycloadducts of type **2**, possible intermediates toward *Aspidosperma* alkaloids. However, alternatively, a second pathway to tetrahydrocarbazoles **4**, involving an indole-2,3-quinodimethane intermediate **3** via thermal [1,5]H shift, could also be envisaged (Scheme 1). A few related transformations on 2-alkyl-3-vinyl-,[7] and 2-vinyl-3-alkylindoles[8] have already been observed, and molecular modelling calculations[9] evidenced that [1,5]-sigmatropic migration of one of the benzyl protons of 2-vinylindoles **1** was energetically favored.

Herein we disclose our preliminary results illustrating the synthetic utility of 3-cyanomethyl-2-vinylindoles (**1**) as indole-2,3-quinodimethane[10] equivalents in thermal Diels–Alder reactions (Scheme 2).

Unprotected **1a** and electron-withdrawing group substituted 2-vinylindoles **1b** and **1c** failed to react, whereas introduction of electron-donating groups resulted in a



Scheme 1.

Keywords: Diels–Alder reaction; 3-cyanomethyl-2-vinylindole; indole-2,3-quinodimethane; [1,5]-sigmatropic hydrogen shift; tetrahydrocarbazoles.

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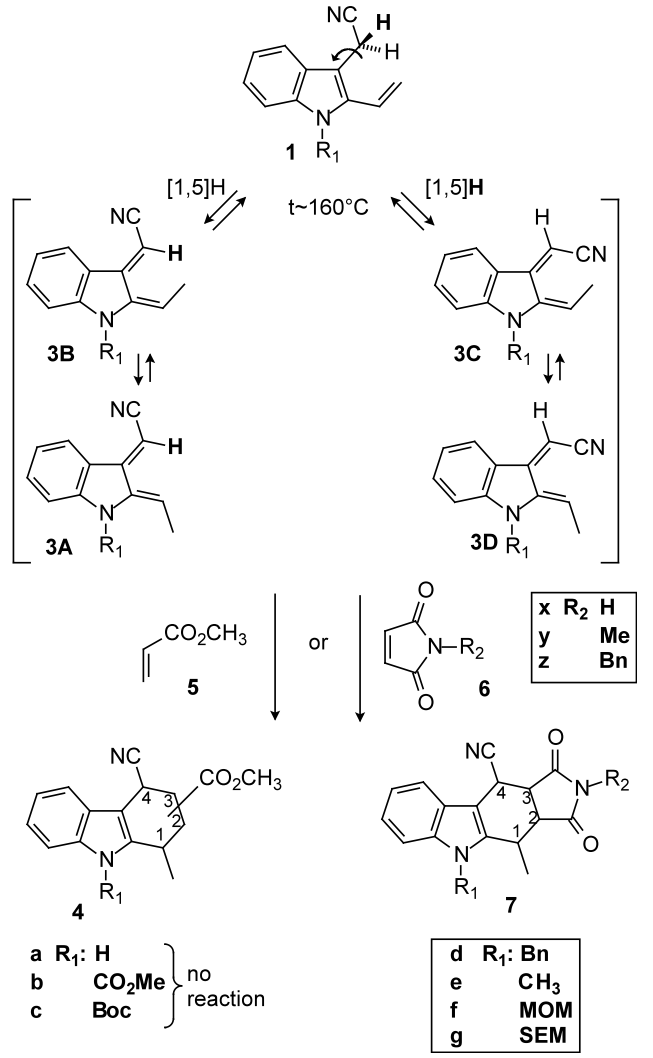
PII: S0040-4039(02)01907-X



Scheme 2.

breakthrough in reactivity. Thus, exposure of **1d** in toluene to methyl acrylate **5** at 160°C in a sealed tube for 44 h gave rise to a complex mixture of adducts, from which *endo* adducts **4-d-A** and **4-d-B**,[11] derived, respectively, from the indole-2,3-quinodimethanes **3A** and **3B**, could be isolated (Table 1, entry 1).[12]

From the ^{1}H NMR spectrum the three proton doublets at δ: 1.33 ppm ($J=6.7$ Hz) for the minor (**4-d-A**), and at δ: 1.23 ppm ($J=7.6$ Hz) for the major diastereomer (**4-d-B**) could be attributed to the methyl groups situated on C-1 of the tricyclic ring systems.

The relative stereochemistry was determined by usual combination of NMR experiments and by comparison of coupling constants. Thus, the observed coupling constants, $J_{\text{H-3–H-4}}=5.5$ Hz in **4-d-A** and **4-d-B** were in accordance with the H-3/H-4 *cis* relative configuration, resulting from an *endo* transition state, while the two small vicinal couplings of H-1 ($J_{\text{H-1–H-2}}=5.3$ and $J_{\text{H-1–H-2}'}=2.5$ Hz) in **4-d-B** agreed with a quasi-axially oriented CH_3 group. In **4-d-A** the opposite relative configuration of C-1 carbon was assigned on the basis of a large coupling constant ($J_{\text{H-1–H-2}}=9.5$ Hz).

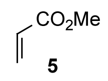
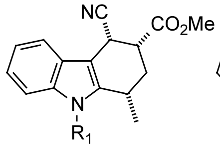
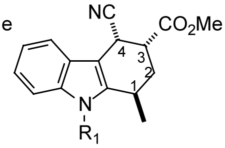
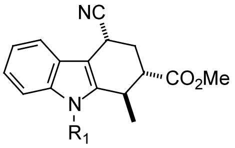
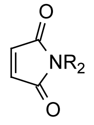
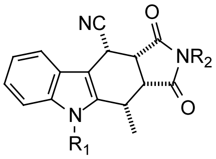
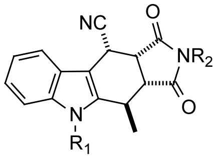
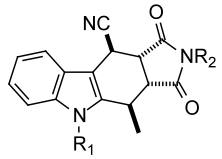
Higher temperature favored the relatively more stable diene **3A**, affording **4-d-A** as major product (entry 2). Formation of such a functionalized tetrahydrocarbazoles by cycloaddition confirmed the expected thermal induced (measured $T_{\text{min}}=140$–150°C) [1,5]-sigmatropic shift of the methylene protons in **1** leading to 'primary' dienes **3B** and **3C**, capable of isomerising at this temperature to **3A** and **3D**, respectively (Scheme 2).

As even in a longer reaction important quantity of non-reacted starting material **1d** was recovered, we tried to enhance the reactivity of **1**, and consequently that of **3**, by varying the electron-donating indole NH protecting groups. Significant improvements in conversion and diastereoselectivity were achieved by MOM (methoxymethyl) **1f**, and even more by SEM (trimethylsilylethoxymethyl) **1g** substitution (entries 3 and 4). In this latter case both isolated cycloadducts derived from the so-called 'primary diene' **3-B**, resulting from an '*ortho*'–*endo* (**4-g-B**) or '*meta*'–*endo* approach (**4-g-meta**). Relative stereochemistry of these acrylate type cycloadducts was deduced by the same manner.[13]

In order to avoid the formation of regioisomers for the further experiences symmetrical maleimides were chosen. Methyl substituted 2-vinylindole **1e** heated in a sealed tube at 165°C with 2 equiv. of *N*-methylmaleimide gave rise to a mixture of cycloadducts from which **7-e-B-y** as main product (31%), resulting from diene **3B**, could be isolated (entry 5). Cycloaddition in *N*-MOM series (**1f**) with *N*-methylmaleimide showed similar behavior (entry 6). Cycloaddition of SEM substituted diene **1g** with different maleimides (entries 7–9) allowed us to enhance the overall yield and in some extent the diastereoselectivity. Consistently, cycloadducts with CH_3 and CN groups in 1,4-*trans* relative configuration deriving from **3B** dienes were obtained as major compounds. As expected, overall yield and selectivity were sensible to both R_1 and R_2 substitutions: in the SEM series *N*-methylmaleimide (**6y**) provided the best results with 68% yield of **7-g-B-y** (entry 8). However, in each case at least three '*endo*' cycloadducts could be identified, originating from indolo-2,3-quinodimethanes **3A**, **3B**, and **3C**. Structural assignments of tetracyclic adducts[14] were based on combined NMR methods supported by NOE measurements. It is noteworthy that in racemic series formation of **7-e-C-y**, **7-f-C-y**, **7-g-C-x**, **7-g-C-y**, and **7-g-C-z**, may result from **3A** by an *exo* transition state, instead of the constrained 'primary diene' **3C**.

In summary, we have found that 3-cyanomethyl-2-vinylindoles **1d-g** could be considered as thermal indole-2,3-quinodimethane equivalents (**3**), and consequently useful diene partners for the preparation of functionalized tetrahydrocarbazoles by [4+2] type cycloadditions. To the best of our knowledge thermally induced [1,5]H shift of **1d-g** coupled with intermolecular Diels–Alder reaction is the first example for the preparation of the 1,4-*trans* disubstituted tetrahydrocarbazole core.[15] Moreover, we evidenced that chemical yield and stereochemical outcome strongly depended on the indole

Table 1. Preparation of tetrahydrocarbazoles (**4**, **7**) from 3-cyanomethyl-2-vinylindoles (**1**) by Diels–Alder reaction[12]

En-try	Starting material	Dienophiles conditions	Cycloadducts				Recov. **1**
	1 R_1	 **5**					
1	**1d** **Bn**	2eq, 160°C, 44h	**4-d-A** (3%)	**4-d-B** (13%)		**4-d-mix** (9%)[a]	47%
2	**1d** **Bn**	2eq, 210°C, 16h	**4-d-A** (31%)	**4-d-B** (19%)		**4-d-mix** (6%)	23%
3	**1f** **MOM**	2eq, 175°C, 44h	**4-f-A** (5%)	**4-f-B** (34%)		**4-f-mix** (5%)	6%
4	**1g** **SEM**	2eq, 165°C, 72h		**4-g-B** (42%)	 **4-g-B-meta** (14%)		4%
		 **6** R_2 **x** H **y** Me **z** Bn					
5	**1e** **Me**	**6y**, 2eq, 165°C, 72h	**7-e-A-y** (1%)	**7-e-B-y** (31%)	**7-e-C-y** (5%)		
6	**1f** **MOM**	**6y**, 2eq, 165°C, 72h	**7-f-A-y** (1%)	**7-f-B-y** (33%)	**7-f-C-y** (3%)		
7	**1g** **SEM**	**6x**, 2eq, 165°C, 72h	**7-g-A-x** (3%)	**7-g-B-x** (35%)	**7-g-C-x** (9%)	**7-g-x-mix** (4%)	5%
8	**1g** **SEM**	**6y**, 2eq, 165°C, 72h	**7-g-A-y** (2%)	**7-g-B-y** (68%)	**7-g-C-y** (9%)		
9	**1g** **SEM**	**6z**, 2eq, 165°C, 72h	**7-g-A-z** (1%)	**7-g-B-z** (59%)	**7-g-C-z** (8%)	**7-g-z-mix** (1%)	

[a] Unseparable mixture of diastereomers (-**mix**).

N-substitution. Application of these findings in the synthesis of functionalized carbazoles of biological interest is currently in progress.

Acknowledgements

Financial support (M.L.) of ADIR and Co. (Laboratoires Servier) is gratefully acknowledged. We thank C. Peterman and P. Sigaut for spectroscopic measurements.

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11. All new compounds were fully characterized by spectroscopic (IR, MS, ^{1}H, ^{13}C NMR) methods. Stereochemical investigations were supported by COSY, HMBC, HMQC, NOE techniques.
12. Numbering of cycloadducts (e.g. **4-d-B**) refers to the nature of indole *N*-substitution (**d**) and that of the intermediate indole-2,3-quinodimethane (**B**). For adducts with maleimides (**6x-z**) R_2 substitution is also considered (e.g. **7-g-B-y**).
13. Selected data for **4-f-B**: mp 118.5–120°C; IR (KBr) 2233, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, d, $J=7.0$ Hz), 2.31 (1H, ddd, $J=1.6$, 3.2, 22.5 Hz), 2.47 (1H, ddd, $J=5.1$, 12.4, 22.5 Hz), 3.18 (1H, ddd, $J=3.2$, 5.3, 12.4 Hz), 3.28 (1H, ddd, $J=1.6$, 5.1, 7.0 Hz), 3.29 (3H, s), 3.87 (3H, s), 4.46 (1H, d, $J=5.3$ Hz), 5.32 and 5.40 (2H, AB system, $J=11.1$ Hz), 7.16–7.29 (2H, m), 7.41 (1H, d, $J=7.1$ Hz), 7.55 (1H, d, $J=7.1$ Hz); MS (EI) m/z 312 (M$^+$), 281, 221.
14. Selected data for **7-g-B-y**: amorphous solid; IR (CH_2Cl_2) 3053, 2953, 2236, 1780, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.02 (9H, s), 0.91 (2H, m), 1.40 (3H, d, $J=7.3$ Hz), 2.88 (3H, s), 3.31 (1H, dd, $J=0.5$, 8.7 Hz), 3.40–3.48 (2H, m), 3.75 (1H, dd, $J=6.8$, 8.7 Hz), 3.98 (1H, qd, $J=0.5$, 7.3 Hz), 4.56 (1H, d, $J=6.8$ Hz), 5.40 and 5.57 (2H, AB system, $J=11.4$ Hz), 7.22 (1H, t, $J=8.0$ Hz), 7.28 (1H, t, $J=8.0$ Hz), 7.46 (1H, d, $J=8.0$ Hz), 8.19 (1H, d, $J=8.0$ Hz); MS m/z 423 (M$^+$), 365, 306, 266, 181.
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