Cycloaddition Reaction of 2-Allenylindoles with Diethyl Acetylenedicarboxylate under Thermal and High Pressure Conditions Minoru Ishikura,* Harue Uchiyama, Ayako Hino, and Nobuya Katagiri

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The cycloaddition reaction of 2-allenylindoles 2 with diethyl acetylenedicarboxylate 6 was undertaken under both thermal and high pressure reaction conditions, leading to carbazole derivatives 5.

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Various new synthetic strategies for the construction of carbazoles have been extensively studied, mainly due to the biological properties of many naturally occurring and unnatural representatives of this class of compounds [1]. Among these strategies, electrocyclic reaction of an in situ generated allene intermediate was applied to the synthesis of carbazole alkaloids by Hibino [2], and most straightforward studies (*i.e.*, those based on the Diels-Alder reaction of vinylindoles and dienophiles) have been performed on the preparation of carbazoles [3]. High pressure protocol is well known to affect affect the Diels-Alder reaction, which has been successfully applied to the synthesis of natural products [4]. There have been several studies on the use of functionalized allenes as dienophiles and the use of simple vinylallenes as diene components for the Diels-Alder reaction [5], whereas Diels-Alder reactions using allenyl derivatives under high pressure have been practically unexplored. We have previously reported a concise procedure for the preparation of 2-allenvlindoles [6] and our recent work on the synthetic development of 2-allenylindoles 4 has given rise to the question of whether a Diels-Alder reaction of 2-allenylindoles 4 as a diene component with dienophiles can be effective in the construction of carbazoles, as well. In this paper, we describe our initial experiment on the reaction of 4 with diethyl acetylenedicarboxylate 6 under both thermal and high pressure reaction conditions that verifies the underlying viability of this approach to the preparation of carbazoles 5 (Scheme 1).

The requisite allenylindoles **4** were prepared by the palladium catalyzed cross-coupling reaction of indolylborates **2**, derived from the corresponding indoles **1** *in situ*, with prop-2-ynyl carbonates **3** [6]. First, the thermal Diels-Alder reaction of **4** with **6** (2 equivalents) in toluene at 150° was carried out in a sealed tube, leading to carbazoles **5** in good to moderate yields, except for the case of **4g** (Table).

Subjection of 4 to a high pressure Diels-Alder reaction with 6 (2 equivalents) in toluene under 980 MPa at room temperature provided 5 in good to moderate yields, as well. Several reports demonstrate that the Diels-Alder reactions in combination with a Lewis acid under high pressure are potentially effective [7]; however, the presence of europium (III) trifluoromethanesulfonate as a Lewis acid did not have any impact on the reaction of 4b with 6 under high pressure or thermal conditions. The reaction of 4c and 4e with 6 under both thermal and high pressure reaction conditions provided carbazoles 5c, 5c', and 5e, 5e' in good yields. The structure of 5c and 5c' was established based on their nmr spectrum. The proton nmr spectrum of 5c showed a singlet for the methine proton at position 4a (4.94 ppm). Notable features are the lack of a methoxyl group in carbazoles 5d-f, and the isolation of 5e' possessing a hydroxymethyl group at the nitrogen in the indole ring under the high pressure condition, which seems to be explicable as depicted in Scheme 2. The splitting of the methoxyl group in the Diels-Alder adduct 7, arising from 4e and 3, to formaldehyde leads to 8, where a similar splitting path is depicted on the reaction of 1-(2-oxoalkyl)oxyindoles [8]. Thus, 5e arises from 8 through double bond migration, and the combination of 8 with the *in situ* generated formaldehyde affords 5e'.





[a] Isolated yields (%); [b] A: 150°/sealed tube/20 hours B: room temperature/980 MPa/20 hours; [c] No isolable products.

In summary, we have developed a concise method for constructing carbazoles **5** based on the Diels-Alder reaction

of 2-allenylindoles 4 with diethyl acetylenedicarboxylate 6 under thermal and high pressure conditions, in which the efficacy of 4c and 4e has been demonstrated.

Although there was little difference in the effectiveness between thermal and high pressure conditions, utilization of the high pressure condition could be advantageous in terms of simplicity in the reaction manipulation and the easy purification of the reaction mixture.

EXPERIMENTAL

Melting points were recorded on Yamato MP21 and are uncorrected. Mass spectra were recorded on a Micromass AutoSpec 3100 mass spectrometer. Infrared spectra were measured on a Hitachi Model 270-30 spectrometer. The nmr experiments were performed with a JEOL JNM-LA300 or JNM-EX400 spectrometer, and chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal reference. Medium pressure liquid chromatography was performed on silica gel (Silica gel 60N, Kanto Chemical Co., Inc.). Dehydrated tetrahydrofuran was purchased from Kanto Chemical Co., Inc.

Allenylindoles **4a** [6], **4b** [6], **4c** [6], **4d**, **4e**, **4f**, **4g** were prepared according to our previous report [6].

2-(2-Cyclohexylidenevinyl)-1-methoxyindole (4d).

This compound was obtained as colorless prisms (recrystallized from petroleum ether) and had mp 56-58°; ir (chloroform): 1954 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.50-1.73 (m, 6H), 2.22-2.31 (m, 4H), 3.97 (s, 3H), 6.10-6.20 (m, 1H), 6.23 (s, 1H), 7.05 (t, 1H, J = 7.3 Hz), 7.15 (t, 1H, J = 7.3 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.47 (d, 1H, J = 7.8 Hz); ¹³C nmr (deuteriochloroform): δ 26.0, 27.2, 31.3, 64.6, 81.4, 96.4, 105.3, 107.8, 120.2, 121.7, 124.2, 131.6, 133.1, 201.1; ms: m/z 253 (molecular ion).

Anal. Calcd for C₁₇H₁₉NO: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.41; H, 7.76; N, 5.41.

2-(2-Cyclohexylidene-1-methylvinyl)-1-methoxyindole (4e).

This compound was obtained as colorless crystals (recrystallized from pentane) and had mp 53-55°; ir (neat): 1950 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.50-1.80 (m, 6H), 2.11 (s, 3H), 2.20-2.38 (m, 4H), 3.89 (s, 3H), 6.22 (s, 1H), 7.05 (t, 1H, J = 7.8 Hz), 7.17 (t, 1H, J = 7.8 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.49 (dd, 1H, J = 1, 8.3 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 19.3, 22.6, 26.1, 27.1, 31.6, 64.1, 88.8, 96.9, 102.8, 107.9, 120.0, 120.3, 122.0, 123.8, 137.7, 134.5, 199.7; ms: m/z 267 (molecular ion).

Anal. Calcd for C₁₈H₂₁NO: C, 80.85; H, 7.92; N, 5.24. Found: C, 80.96; H, 8.14; N, 5.15.



Methyl 3-Cyclohexylidene-2-(1-methoxyindol-2-yl)prop-2enoate (**4f**).

This compound was obtained as viscous oil; ir (neat): 1948, 1724 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.56-1.61 (m, 2H), 1.68-1.73 (m, 4H), 2.27-2.40 (m, 4H), 3.80 (s, 3H), 3.89 (s, 3H), 6.66 (s, 1H), 7.07 (t, 1H, J = 7.3 Hz), 7.20 (t, 1H, J = 7.3 Hz), 7.37 (d, 1H, J = 7.8 Hz), 7.54 (d, 1H, J = 8.3 Hz); ¹³C nmr (deuteriochloroform): δ 25.7, 26.6, 30.4, 52.4, 64.3, 91.2, 100.4, 107.3, 108.2, 120.2, 120.9, 122.4, 124.0, 128.8, 133.0, 166.4, 207.2; hrms: Calcd for C₁₉H₂₁NO₃: 311.1521. Found: 311.1523.

tert-Butyl 2-(2-Cyclohexylidene-1-methylvinyl)indole-1-carboxylate (**4g**).

This compound was obtained as colorless prisms (recrystallized from ethyl acetate-hexane) and had mp 95-96°; ir (chloroform): 1730 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.50-1.70 (m, 6H), 1.64 (s, 9H), 2.02 (s, 3H), 2.08-2.30 (m, 4H), 6.38 (s, 1H), 7.10-7.35 (m, 2H), 7.43 (d, 1H, J = 7.8 Hz), 8.07 (d, 1H, J = 8.3 Hz); ¹³C nmr (deuteriochloroform): δ 20.8, 26.1, 27.4, 28.0, 31.4, 83.5, 92.9, 102.3, 108.3, 115.2, 120.1, 122.6, 123.6, 129.4, 139.8, 198.2; ms: m/z 337 (molecular ion).

Anal. Calcd for C₂₂H₂₇NO₂: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.27; H, 8.17; N, 4.22.

General Procedure for the Thermal Reaction of **4** with Diethyl Acetylenedicarboxylate.

A mixture of 4 (2 mmol) and diethyl acetylenedicarboxylate (4 mmol) in toluene (10 mL) was placed in a sealed tube, and heated at 150° for 20 hours. After cooling, the solvent was removed, and the residue was separated by medium pressure liquid chromatography with ethyl acetate-hexane as an eluent to give 5.

General Procedure for the Reaction of **4** with Diethyl Acetylenedicarboxylate under High Pressure.

High pressure reaction was carried out by using a piston-cylinder apparatus equipped with a K.P.15.B pump (Hikari Koatsu KiKi Ltd., Co., Japan). A solution of 4 (2 mmol) and diethyl acetylenedi-carboxylate (4 mmol) in toluene (5 mL) was placed in a Teflon tube with Teflon stopper. The tube was placed in a high pressure reactor and pressurized to 980 MPa at room temperature for 20 hours. After the pressure was released, the solvent was removed and the residue was separated by medium pressure liquid chromatography with ethyl acetate-hexane as an eluent to give 5.

Ethyl 2-Cyclohexyl-4-(ethoxycarbonyl)-9-methylcarbazole-3-carboxylate (**5a**).

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 123-124°; ir (chloroform): 1720 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.25-1.62 (m, 5H), 1.41 (t, 3H, J = 7.3 Hz), 1.44 (t, 3H, J = 7.3 Hz), 1.80 (d, 1H, J = 12.2 Hz), 1.88 (d, 2H, J = 12.7 Hz), 2.01 (d, 2H, J = 12.7 Hz), 3.06 (tt, 1H, J = 2.9, 11.7 Hz), 3.85 (s, 3H), 4.40 (q, 2H, J = 7.3 Hz), 4.52 (q, 2H, J = 7.3 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.39 (d, 1H, J = 7.8 Hz), 7.40 (s, 1H), 7.49 (t, 1H, J = 8.3 Hz), 8.15 (d, 1H, J = 7.8 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 14.2, 26.3, 27.0, 29.2, 35.0, 41.4, 61.3, 61.7, 107.8, 108.5, 117.7, 119.6, 121.1, 122.8, 123.4, 126.5, 142.0, 142.2, 144.3, 168.7, 169.2; ms: m/z 407 (molecular ion).

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.53; H, 7.24; N, 3.31. Ethyl 2-Cyclohexylidene-4-(ethoxycarbonyl)-1,9-dimethyl-1,9-dihydro-4a*H*-carbazole-3-carboxylate (**5b**).

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 126-127°; ir (chloroform): 1740, 1716 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.20 (d, 3H, J = 7.3 Hz), 1.32 (t, 3H, J = 7.3 Hz), 1.38 (t, 3H, J = 7.3 Hz), 1.57-1.70 (m, 6H), 2.04-2.10 (m, 2H), 2.30-2.37 (m, 1H), 2.45-2.52 (m, 1H), 3.74 (s, 3H), 4.04-4.20 (m, 2H), 4.24-4.34 (m, 1H), 4.34 -4.50 (m, 2H), 7.13 (t, 1H, J = 8.3 Hz), 7.19 (t, 1H, J = 7.3 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.64 (d, 1H, J = 7.8 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 14.2, 18.0, 26.8, 27.4, 28.2, 29.6, 30.2, 30.6, 33.1, 60.7, 61.4, 105.3, 109.4, 116.5, 119.1, 121.2, 121.7, 123.8, 135.9, 137.7, 142.8, 146.0, 167.8, 168.7; ms: m/z 421 (molecular ion).

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.14; H, 7.50; N, 3.26.

Ethyl 2-Cyclohexylidene-3-(ethoxycarbonyl)-1-(methoxycarbonyl)-9-methyl-9-hydro-4a*H*-carboxylate (**5c**).

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 114-116°; ir (chloroform): 1728 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.31 (t, 3H, J = 7.3 Hz), 1.36 (t, 3H, J = 7.3 Hz), 1.28-1.44 (m, 2H), 1.54-1.76 (m, 4H), 2.00-2.20 (m, 2H), 2.40-2.58 (m, 2H), 3.65 (s, 3H), 3.76 (s, 3H), 4.05-4.19 (m, 1H), 4.25-4.36 (m, 1H), 4.37-4.50 (m, 2H), 4.94 (s, 1H), 7.14 (t, 1H, J = 7.3 Hz), 7.22 (dt, 1H, J = 1, 8.3 Hz), 7.30 (d, 1H, J = 7.8 Hz), 7.67 (d, 1H, J = 8.3 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 14.2, 26.6, 27.3, 27.9, 30.2, 31.4, 33.2, 41.3, 52.7, 60.7, 61.4, 107.6, 109.7, 117.4, 117.5, 119.5, 121.4, 122.3, 123.6, 136.4, 137.7, 138.0, 147.4, 166.9, 168.4, 169.3; ms: m/z 465 (molecular ion).

Anal. Calcd for C₂₇H₃₁NO₆: C, 69.65; H, 6.72; N, 3.01. Found: C, 69.76; H, 6.82; N, 2.99.

Methyl 3,4-Bis(ethoxycarbonyl)-2-cyclohexyl-9-methylcarbazole-1-carboxylate (5c').

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 194-195°; ir (chloroform): 1726 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.20-1.50 (m, 5H), 1.42 (t, 3H, J = 7.3 Hz), 1.44 (t, 3H, J = 7.3 Hz), 1.65-2.00 (m, 5H), 2.70-2.85 (m, 1H), 3.76 (s, 3H), 4.03 (s, 3H), 4.38 (q, 2H, J = 7.3 Hz), 4.52 (q, 2H, J = 7.3 Hz), 7.22 (t, 1H, J = 7.3 Hz), 7.38n(d, 1H, J = 8.3 Hz), 7.51 (t, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 7.8 Hz); ¹³C nmr (deuteriochloroform): δ 14.0, 14.1, 26.0, 27.7, 30.3, 32.0, 45.2, 52.3, 61.7, 62.0, 108.9, 118.9, 120.1, 120.3, 122.3, 127.1, 127.4, 137.9, 139.1, 142.6, 168.1, 169.4, 169.8; ms: m/z 465 (molecular ion).

Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.65; H, 6.72; N, 3.01. Found: C, 69.48; H, 6.85; N, 2.97.

Ethyl 2-Cyclohexyl-3-(ethoxycarbonyl)carbazole-4-carboxylate (**5d**).

This compound was obtained as colorless crystals (recrystallized from methanol) and had mp 170-172°; ir (chloroform): 3380, 1720 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.10-1.45 (m, 5H), 1.40 (t, 3H, J = 7.3 Hz), 1.41 (t, 3H, J = 7.3 Hz), 1.65-1.80 (m, 5H), 2.85-3.00 (m, 1H), 4.40 (q, 2H, J = 7.3 Hz), 4.52 (q, 2H, J = 7.3 Hz), 7.17 (t, 1H, J = 7.3 Hz), 7.24 (s, 1H), 7.29 (d, 1H, J = 7.8 Hz), 7.35 (t, 1H, J = 7.3 Hz), 8.13 (d, 1H, J = 7.8 Hz), 8.75 (br s, 1H); ¹³C nmr (deuteriochloroform): δ 14.1, 14.2, 26.1, 27.0, 34.7, 41.2, 61.4, 61.8, 110.4, 110.9, 118.0, 119.8, 121.4, 122.6, 123.7, 126.0, 126.5, 140.6, 141.1, 144.0, 168.9, 169.7; ms: m/z 393 (molecular ion).

Anal. Calcd for C₂₄H₂₇NO₄: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.13, H, 7.07; N, 3,55.

Ethyl 2-Cyclohexylidene-3-(ethoxycarbonyl)-1-methyl-1,9dihydro-4a*H*-carbazole-4-carboxylate (**5e**).

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 154-155°; ir (chloroform): 3468, 1724 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.16 (d, 3H, J = 6.8 Hz), 1.31 (t, 3H, J = 7.3 Hz), 1.38 (t, 3H, J = 7.3 Hz), 1.27-1.40 (m, 2H), 1.42-1.64 (m, 4H), 1.95-2.03 (m, 2H), 2.11-2.20 (m, 1H), 2.30-2.38 (m, 1H), 4.00 (q, 1H, J = 6.8 Hz), 4.08-4.20 (m, 1H), 4.24-4.35 (m, 1H), 4.35-4.52 (m, 2H), 7.07-7.15 (m, 2H), 7.27-7.32 (m, 1H), 7.60-7.66 (m, 1H), 8.70 (br s, 1H); ¹³C nmr (deuteriochloroform): δ 14.1, 19.3, 26.7, 27.4, 28.1, 30.5, 32.0, 33.0, 60.8, 61.5, 105.8, 111.4, 117.5, 118.9, 121.1, 122.0, 123.8, 124.0, 135.6, 136.2, 143.1, 145.2, 168.1, 169.0; ms: m/z 407 (molecular ion).

Anal. Calcd for C₂₅H₂₉NO₄: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.67; H, 7.34; N, 3.39.

Ethyl 2-Cyclohexylidene-3-(ethoxycarbonyl)-9-(hydroxymethyl)-1,9-dihydro-4a*H*-carbazole-4-carboxylate (**5e**').

This compound was obtained as viscous oil; ir (chloroform): 3464, 1722 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.24 (d, 3H, J = 6.8 Hz), 1.31 (t, 3H, J = 7.3 Hz), 1.37 (t, 3H, J = 7.3 Hz), 1.52-1.63 (m, 6H), 2.00-2.06 (m, 2H), 2.28-2.50 (m, 2H), 3.00 (br s, 1H), 4.06-4.50 (m, 5H), 5.56-5.65 (m, 1H), 5.65-5.74 (m, 1H), 7.11-7.22 (m, 2H), 7.39 (d, 1H, J = 7.8 Hz), 7.64 (dd, 1H, J = 1, 6.8 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 18.6, 26.7, 27.4, 28.1, 30.2, 30.6, 33.0, 60.9, 61.5, 66.5, 106.7, 109.4, 118.3, 119.3, 121.8, 122.3, 123.5, 124.3, 135.3, 136.6, 143.4, 145.4, 167.8, 168.7; hrms: Calcd for C₂₆H₃₁NO₅: 437.2202. Found: 437.2216.

Ethyl 2-Cyclohexylidene-3-(ethoxycarbonyl)-1-(methoxycarbonyl)-9-hydro-4aH-carbazole-4-carboxylate (**5f**).

This compound was obtained as colorless crystals (recrystallized from ethyl acetate-hexane) and had mp 103-105°; ir (chloroform): 3464, 1724 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.31 (t, 3H, J = 7.3 Hz), 1.37 (t, 3H, J = 7.3 Hz), 1.24-1.43 (m, 1H), 1.50-1.72 (m, 5H), 2.02-2.18 (m, 2H), 2.25-2.38 (m, 1H), 2.38-2.50 (m, 1H), 3.65 (s, 3H), 4.09-4.19 (m, 1H), 4.27-4.50 (m, 3H), 4.91 (s, 1H), 7.12 (dt, 1H, J = 1.5, 8.3 Hz), 7.17 (dt, 1H, J = 1.5, 8.3 Hz), 7.32 (d, 1H, J = 7.8 Hz), 7.65 (d, 1H, J = 7.8 Hz), 8.70 (br s, 1H); ¹³C nmr (deuteriochloroform): δ 14.1, 14.2, 26.5, 27.4, 27.8, 31.4, 33.2, 43.0, 52.7, 60.9, 61.6, 108.2, 111.6, 117.4, 118.5, 119.3, 121.4, 122.7, 123.7, 135.8, 136.5, 147.9, 167.2, 168.4, 169.7; ms: m/z 451 (molecular ion).

Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.15; H, 6.48; N, 3.10. Found: C, 69.09; H, 6.45; N, 3.13.

Ethyl 9-[(*tert*-Butyl)oxycarbonyl]-2-cyclohexyl-3-(ethoxycarbonyl)-1-methylcarbazole-4-carboxylate (**5g**).

This compound was obtained as viscous oil; ir (chloroform): 1724, 1662 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.20-150 (m, 9H), 1.66 (s, 9H), 1.70-2.10 (m, 7H), 2.52 (s, 3H), 2.98 (t, 1H, J = 12.2 Hz), 4.39 (q, 2H, J = 7.3 Hz), 4.49 (q, 2H, J = 7.3 Hz), 7.29

(t, 1H, J = 7.3 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.94 (d, 1H, J = 7.8 Hz), 8.03 (d, 1H, J = 8.3 Hz); ¹³C nmr (deuteriochloroform): δ 14.1, 19.0, 26.2, 27.7, 28.1, 28.3, 31.1, 61.5, 61.9, 84.3, 114.8, 122.3, 123.3, 124.4, 127.6, 128.3, 141.1, 141.5, 141.6, 150.8, 168.1, 169.9; hrms: Calcd for C₃₀H₃₇NO₆: 507.2620. Found: 507.2634.

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