ORGANIC
LETTERS

2000
Vol. 2, No. 1
73−76

Sequential Diels–Alder Reaction of in Situ Generated 2,3-Dimethylenepyrrole and Carbodienophiles: Rapid Synthesis of 2,3,6,7-Tetrasubstituted Carbazoles

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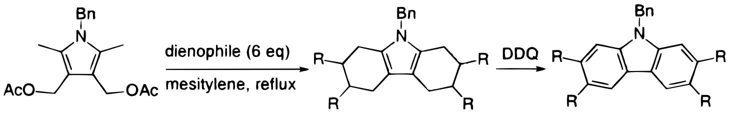
Received November 4, 1999

ABSTRACT



1 2 3

2,3,6,7-Tetrasubstituted-1,2,3,4,5,6,7,8-octahydrocarbazoles 2 were synthesized in 46–90% yields by sequential Diels–Alder reactions from *N*-benzyl-2,5-dimethyl-3,4-bisacetoxymethylpyrrole (1) and dienophiles such as maleic anhydride, maleimides, ethyl maleate, fumaronitrile, and ethyl acrylate. The 2,3,6,7-tetrasubstituted carbazoles 3 were then synthesized in 32–87% yields from 2 by oxidation with DDQ.

The carbazole ring system and its hydrogenated analogues form the core of a wide range of alkaloids, and several strategies exist for their construction.[1] Carbazoles are also important building blocks for the construction of polymers with thermal,[2] electrical,[3] and photoelectrical properties[4] and as polymer-blend additives for the fabrication of photorefractive materials.[5] Despite the importance of carbazoles in natural products and materials applications, methodology for the rapid, selective synthesis of 2,3,6,7-tetrasubstituted carbazoles has not been developed. To date, only a limited number of reports describe the efficient construction of highly substituted symmetric skeletons[6−8] and no general methodology exists for the synthesis of functionalized 2,3,6,7-tetrasubstituted-1,2,3,4,5,6,7,8-octahydrocarbazoles **2** and 2,3,6,7-tetrasubstituted carbazoles **3**.[9] Such methodology may prove important for the generation of new carbazole polymers with more refined material properties.

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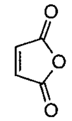
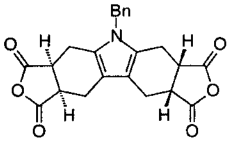
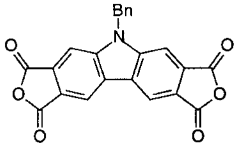
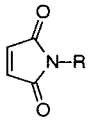
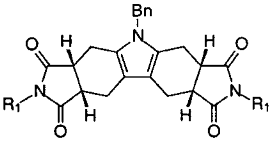
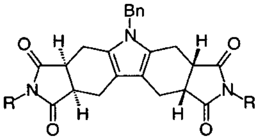
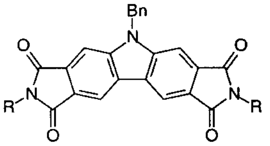
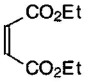
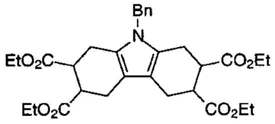
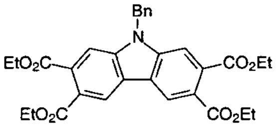
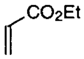
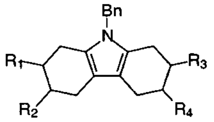
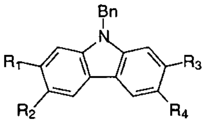
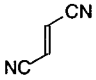
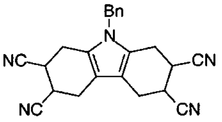
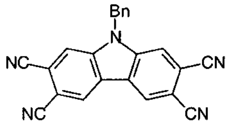
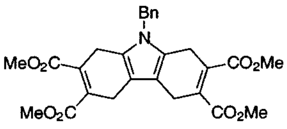
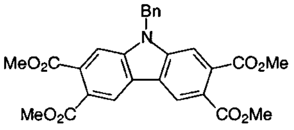
(8) (a) Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2435−2437. (b) Simpson, J. E.; Baub, G. H.; Hayes, F. N. *J. Org. Chem.* **1973**, *38*, 4428−4431.

(9) There is a report of 9-acetylcarbazole-2,3,6,7-tetracarboxylic acid 2,3;6,7-dianhydride. However, the preparation and characterization of this compound was not reported. Kampar, V. E.; Mazere, I. V.; Meirovits, I. A.; Neiland, O. Y. *Chem. Heterocycl. Compd.* **1979**, *15*, 153−155.

10.1021/ol991220o CCC: $19.00

Table 1. Products of the Diels–Alder Reaction and Oxidation

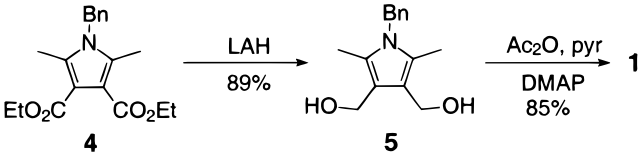
entry	dienophile	time of Diels-Alder	octahydrocarbazole yield(%)[a]	time of oxidation	carbazole yield(%)[a]
1		45 min	 **2a** (90%)	23 h	 **3a** (87%)
2	 R_1 = Me R_2 = 2-Napthyl	2 h ($R = R_1$) 4 h ($R = R_2$)	 **2b** (25%)[b] $R = R_1$  **2c** (52%)[b] $R = R_1$ **2d** (89%) $R = R_2$	24 h[c] ($R = R_1$) 1.5 h[c] ($R = R_2$)	 **3b** (No Product) $R = R_1$ **3d** (32%) $R = R_2$
3		5 h	 **2e** (68%)	20 h	 **3e** (60%)
4		23 h[d]	 **2f-h** (46%) **2f** $R_1,R_3=CO_2Et$ $R_2,R_4=H$ **2g** $R_1,R_4=CO_2Et$ $R_2,R_3=H$ **2h** $R_1,R_3=H$ $R_2,R_4=CO_2Et$	12 h	 **3f** (18%) $R_1,R_3=CO_2Et$ $R_2,R_4=H$ **3g** (29%) $R_1,R_4=CO_2Et$ $R_2,R_3=H$ **3h** (19%) $R_1,R_3=H$ $R_2,R_4=CO_2Et$
5		24 h	 **2i** (75%)	25 h[c]	 **3i** (29%)
6	$MeCO_2—\equiv—CO_2Me$	2 h	 **2j** (69%)	1 h	 **3j** (70%)

(*a*) Isolated yields. (*b*) Total conversion was 90% (2:1 ratio of **2b**:**2c** by ^1H NMR). A mixture (13%) of 2b:2c was not separated after two silica gel columns. (*c*) Reaction performed in refluxing 1,4 dioxane. (*d*) Nine equivalents of dienophile used.

We now report a novel tandem Diels–Alder reaction that assembles **2**[10,11] in one step from pyrrole **1** and 2 equiv of carbodienophile (Table 1).[12,13] The corresponding carbazole **3** is subsequently generated by the action of DDQ (Table 1). This methodology provides for the rapid construction of a variety of highly substituted carbazoles, including substitution patterns that are difficult to achieve by existing methods. Furthermore, this new methodology can be readily adapted to the formation of polymers by employing bis- or polydienophiles instead of the simple carbodienophiles described herein.

Reduction of pyrrole ethyl ester **4** followed by acetylation under standard conditions readily provides **1** on scales as large as 0.1 mol (Scheme 1). The heating of a solution of **1** and any acid stronger than acetic acid (e.g., TsOH, maleic acid, or HCl) results in the rapid decomposition of **1** and the formation of an intractable black solid. We believe this is due to the rapid formation of diene **6** or **7**, which undergoes stereorandom [4 + 2] cycloadditions between dienes (vide infra).

Scheme 1. Synthesis of Pyrrole **1**



The formation of **2d** was systematically examined, revealing that the transformation is sensitive to the concentration of **1**, and acid impurities (e.g., maleic acid), but is insensitive to light and small amounts of O_2. The formation of octahydrocarbazoles **2a−j** employed a variety of dienophiles with yields ranging from 46 to 90%.[14] When fumaronitrile was employed and the reaction prematurely halted, a mixture of **2i** and **8a** was isolated. When **8a** was reintroduced to the reaction conditions, **2i** was obtained, suggesting that the two Diels−Alder reactions are sequential. Compound **8a** could potentially allow access to unsymmetrically substituted octahydrocarbazoles simply by utilizing a different dienophile after isolation of monoadduct **8a**.

The corresponding carbazoles **3a−j**, with the exception of **3b**,[15] were generated in 29−87% yield by oxidation of the octahydrocarbazoles **2a−j** with DDQ (Table 1).[16] Structural confirmation was provided by an X-ray crystal structure of **3d** (Figure 1). The oxidation of **2f−h** afforded three structural isomers, **3f** (18%), **3g** (29%), and **3h** (19%), that were assigned by HMBC and HMQC NMR spectroscopy experiments. There does not appear to be electronic regiochemical control for the formation of the octahydrocarbazoles with unsymmetrical dienophiles.

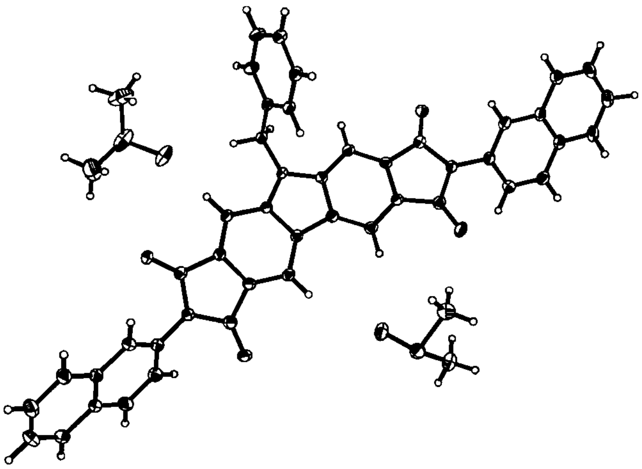


Figure 1. Crystal structure of **3d**.

The mechanism for the formation of **2** appears to be two sequential [4 + 2] cycloadditions between the exocyclic diene portion of **6** and **9** and a dienophile (Scheme 2).[17] The 2,3-dimethylenepyrrole required for the Diels−Alder reaction can be generated by the thermal elimination of acetic acid to form **6** (Scheme 2), which is observed by mass spectroscopy.[18] There are two possible pathways by which **6** can

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(10) **2a**: ^{1}H NMR (399.95 MHz, DMSO-d_6) 2.65 (dd, J = 15.3, 7.49 Hz; 2H), 2.70 (dd, J = 15.82, 7.86 Hz; 2H), 2.82 (dd, J = 15.3, 2.18 Hz; 2H), 2.95 (dd, J = 15.82, 1.91 Hz; 2H), 3.66 (ddABq, J = 9.86, 7.49, 2.18 Hz; 2H), 3.73 (ddABq, J = 9.86, 7.86, 1.91 Hz; 2H), 4.95 (ABq, J = 16.77 Hz, 1H), 5.08 (ABq, J = 16.77 Hz, 1H), 6.88−6.93 (m, 2H), 7.20−7.32 (m, 3H); ^{13}C NMR (100.58 MHz, DMSO-d_6) 20.47, 20.68, 40.20, 40.39, 45.82, 111.79, 124.25, 126.28, 127.20, 128.60, 138.29, 175.39, 175.57; MS (EI, 70 eV) exact mass calcd for $C_{23}H_{19}NO_6$ 405.1204, found 405.1212.

(11) The relative stereochemistry of **2a**, **2b**, **2c**, and **2d** was assigned on the basis of the splitting pattern of the benzylic protons. The trans arrangement of the anhydrides or imides makes the protons on the benzylic carbon diastereotopic, thus giving rise to an ABq in the ^{1}H NMR. If the anhydrides or imides were oriented cis, the benzylic protons would be homotopic, giving rise to a singlet in the ^{1}H NMR.

(12) Diels−Alder reactions with in situ generated 2,3-dimethylenepyrroles and dienophiles for the generation of 4,5-carbodisubstituted-2,3,4,5-tetrahydroindoles. Chou, T.; Chang, R. *J. Chem. Soc., Chem. Commun.* **1992**, 549−551.

(13) Diels−Alder reactions have been reported with in situ generated indole-2,3-quinodimethanes for the generation of 2,3-carbodisubstituted-1,2,3,4-tetrahydrocarbazoles. (a) Gallagher, T.; Magnus, P. *Tetrahedron* **1981** *37*, 3889−3897. (b) Marinelli, E. R. *Tetrahedron Lett*. **1982**, *23*, 2745−2748. (c) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett*. **1983**, *24*, 5435−5438. (d) Saroja, B.; Srinivaan, P. C. *Tetrahedron Lett*. **1984**, *25*, 5429−5430. (e) Vice, S. F.; Carvalho, H. N.; Taylor, N. G.; Dmitrienko, G. I. *Tetrahedron Lett*. **1989**, *30*, 7289−7292. (f) Pindur, U.; Haber, M. *Tetrahedron* **1991**, *47*, 1925−1936. (g) Pindur, U.; Haber, M. *Heterocycles* **1991**, *32*, 1463−1470. (h) Fray, E. B.; Moody, C. J.; Shah, P. *Tetrahedron* **1993**, *49*, 439−450.

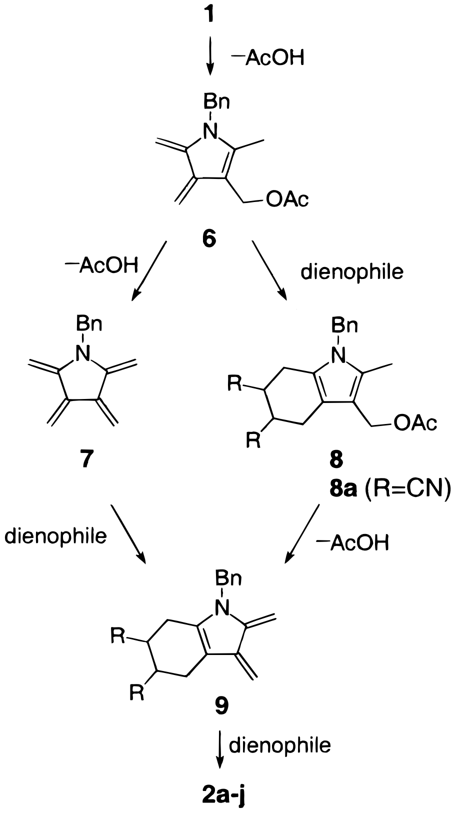
(14) **General experimental for 2a−j**: A solution of **1** (50 mg, 0.151 mmol) and dienophile (0.81 mmol, free of acid) in mesitylene (4 mL, distilled from Na°) was refluxed in a dry round-bottom flask fitted with an air-cooled reflux condenser under Ar until all of **1** was consumed. The solution was cooled, and the solvent was removed in vacuo.

(15) Carbazole **3b** was not observed in attempts to oxidize a mixture of **2b** and **2c** with DDQ.

(16) **Representative Oxidation. Synthesis of 3a:** A solution of **2a** (50 mg, 0.151 mmol) and DDQ (112 mg, 0.49 mmol) in 1,4 dioxane (8.5 mL, distilled from Na°) was stirred at room temperature under Ar in a dry round-bottom flask for 23 h. The precipitated 4,5-dichloro-3,6-dihydroxyphthalonitrile was filtered, and the dioxane was removed in vacuo to afford a brown solid, which was purified by flash chromatography (SiO_2, THF:CH_2Cl_2, 1:1) to afford 42.6 mg (0.11 mmol, 87%) of **3a** as a yellow solid: mp >310 °C; ^{1}H NMR (499.70 MHz, DMSO-d_6) 6.04 (s, 1H), 7.18−7.20 (m, 2H), 7.25−7.30 (m, 3H), 8.55 (s, 2H), 9.26 (s, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6) 46.65, 108.67, 120.98, 122.71, 126.80, 127.27, 127.92, 128.88, 130.44, 136.16, 145.53, 163.31, 163.45; MS (EI, 70 eV) exact mass calcd for $C_{23}H_{11}NO_6$ 397.0586, found 397.0581.

(17) The formation of **2a**, **2b**, **2c**, and **2d** are stereospecific and arise from two sequential [4 + 2] cycloaddition reactions. When fumaronitrile is used as a dienophile, two diastereomers of **2i** are observed that were not separated, and thus, the relative configurations of the nitriles were not determined. The transformation with ethyl maleate affords six diastereomers of **2e**. We hypothesize that the **2e** mixture arises from isomerization of the dienophile and/or epimerization of each cycloadduct.

Scheme 2. Mechanism of Formation of Octahydrocarbazole **2**



proceed to **2**. The first is the elimination of a second molecule of acetic acid from **6** to form 5-benzyl-aza[5]radialene (**7**), which is also observed by mass spectroscopy.[19,20] Radialene **7** can subsequently undergo the tandem Diels−Alder reactions with 2 equiv of dienophile to generate **2**. In the second pathway, **6** reacts with a dienophile to form **8**,[21] which undergoes a second elimination of acetic acid to form **9** (observed in MS of **8a**).[22] This is followed by a second Diels−Alder reaction to form **2**. Attempts to improve the yield of **2** by accelerating the elimination of acetic acid by acid or base catalysis failed.[23]

The yields for the formation of **2a**, **2e**, **2f**−**h**, and **2i** appear to be related to the relative reactivity of the dienophiles toward cyclopentadiene in a Diels−Alder reaction.[24] The reactivity of maleic anhydride and *N*-methylmaleimide, which show the best yields, are approximately 2 orders of magnitude greater than the dienophiles in entries 3−6. The reduced yields in entries 3−6 may be due to the reduced reactivity of the dienophiles, allowing the diene concentration to increase. Therefore, nonproductive [4 + 2] cycloadditions between dienes to form dimers and polymer would be more likely to occur.[25,26] This is consistent with the observation that a reduction in the concentration of **1** results in an increase in the yield of **2**.

In conclusion, this study demonstrates the effective synthesis of 2,3,6,7-tetrasubstituted-1,2,3,4,5,6,7,8-octahydrocarbazoles **2** and 2,3,6,7-tetrasubstituted carbazoles **3**. The generation of **2** proceeds through the sequential generation of **6** and **9**, each of which undergoes a [4 + 2] cycloaddition reaction.

Acknowledgment. This work has been supported by the UIUC Research Board and a Procter and Gamble Fellowship in Synthetic Organic Chemistry. NMR spectra were obtained in the Varian Oxford Instrument Center for Excellence in NMR Laboratory.

Supporting Information Available: X-ray structure tables for **3d**. Full experimental details and characterization data for compounds **1**, **2a**−**j**, **3a**−**j**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] Triene **6** was observed in the high-resolution mass spectrum of **1**: MS (EI, 70 eV) exact mass calcd for $C_{17}H_{19}NO_2$ 269.1415, found 296.1416.

[19] Radialene **7** was observed in the high-resolution mass spectrum of **1**: MS (EI, 70 eV) exact mass calcd for $C_{15}H_{15}N$ 209.1205, found 209.1210.

[20] In an analogous reaction, Trahanovsky and Cassady isolated furanoradialene at −60 °C via the flash vacuum pyrolysis of 3,4-bis-(acetoxymethyl)-2,5-dimethylfuran. Trahanovsky, W. S.; Cassady, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 8197−8201.

[21] The monoadduct **8a** was isolated when the reaction was not allowed to go to completion.

[22] Triene **9** (R = CN) was observed in the mass spectrum: MS (EI, 70 eV) mass calcd for $C_{19}H_{17}N_3$ 287, found 287.

[23] Use of pyridine in the formation of **2d** resulted in a reduction of the yield from 89% to 70%. Use of DBU and KHMDS resulted in the rapid decomposition of **1**. The use of acids such as TsOH, maleic acid, or HCl resulted in the decomposition of **1**.

[24] Sauer, J.; Wuest, H.; Mielert, A. *Chem. Ber*. **1964**, *97*, 3183−3207.

[25] In an analogous reaction, dimers were isolated for indole-2,3-quinodimethanes[12] and furanoradialene.[20]

[26] The yield of the dimers of indole-2,3-quinodimethanes increased as with the less reactive dienophiles.[12g]