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Brønsted acid catalyzed Diels–Alder reactions of 2-vinylindoles and 3-nitrocoumarins: an expedient synthesis of coumarin-fused tetrahydrocarbazoles

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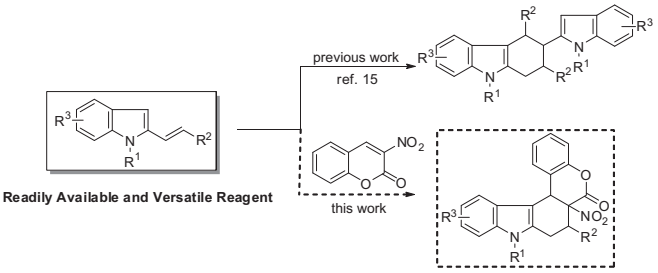
ABSTRACT

A Brønsted acid catalyzed Diels–Alder reaction of 2-vinylindoles and 3-nitrocoumarins has been described. The methodology allows a rapid and expedient synthesis of a variety of coumarin-fused polycyclic indoles in good yields (up to 82%) with high diastereoselectivities (up to >19:1).

1. Introduction

Structurally unique and functionality-enriched heterocyclic systems are of great significances in chemically and biologically related research areas.[1] In particular, the polycyclic indoles,[1c,2] coumarins[3] and their derivatives are two important classes of compounds and have been widely found in biologically active molecules and drug candidates. Moreover, diversely functionalized polycyclic indoles and coumarins have also been identified as versatile synthetic building blocks for the construction of complex molecules and natural products. Therefore, great efforts have been devoted to their preparation.[4,5] However, direct and efficient protocols allowing for the combinatorial assembly of these two 'privileged' structural motifs into one molecule are very limited.[2e]

During the last decade, organocatalysis has become one of the most active and attractive research fields in the modern synthetic organic chemistry.[6,7] Particularly, since the MacMillan's[8] fundamental and pioneering work on imidazolidinone salt-catalyzed enantioselective Diels–Alder reaction[9] of α,β-unsaturated aldehydes with dienes, organocatalytic [4+2] cycloadditions[10] have been well documented and widely used to generate cyclic and polycyclic compounds with various diene/dienophile combinations.[11,12] For example, the Chen group[11d,e] has developed an elegant aza-Diels–Alder reaction of aza-1,3-butadienes and aldehydes, which provided an efficient approach to chiral piperidine derivatives in a highly enantioselective manner. Recently, Ricci and co-workers[12f,g] firstly disclosed an asymmetric Diels–Alder reaction of 3-vinylindoles with the use of chiral amine thiourea as the catalyst, affording a variety of optically active tetrahydrocarbazoles. Notably, the MacMillan group ingeniously developed a novel Diels–Alder/cyclization cascade reaction of 2-vinylindoles and successfully applied this protocol to the synthesis of (−)-minifiensine.[13] Along this line, we also reported a Brønsted acid catalyzed tandem Diels–Alder/aromatization reaction of 2-vinylindoles (Scheme 1).[14] Despite these great advances, the development of more efficient and practical strategy for the synthesis of densely functionalized heterocyclic systems with vinyl indole[15] is still highly desirable.



Scheme 1. Brønsted acid catalyzed Diels–Alder reaction of 2-vinylindoles and 3-nitrocoumarins.

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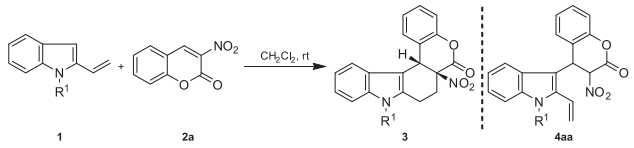
As part of our ongoing research programs directed toward the development of efficient methods for the synthesis of biologically active carbon and heterocyclic compounds,[16] we describe herein the first example of Brønsted acid catalyzed Diels–Alder reaction of 2-vinylindoles with 3-nitrocoumarins.[17] The process allows an expedient synthesis of diversified coumarin-fused polycyclic indoles from readily accessible substrates.

2. Results and discussion

Initially, we investigated the possible cycloaddition with various *N*-substituted 2-vinylindoles **1** and 3-nitrocoumarin **2a** with CH_2Cl_2 as the solvent in absent of Brønsted acid (Table 1). In the case of N-free 2-vinylindole **1a**, only the Friedel–Crafts alkylation product **4aa** was formed in a yield of 54% (Table 1, entry 1). Gratifyingly, when a methyl group was introduced on N-1 position, the Diels–Alder reaction proceeded smoothly and gave the desired cycloadduct in good yield with excellent diastereoselectivity (>19:1 dr; Table 1, entry 2). Notably, no simple Friedel–Crafts product was detected. Further experiments revealed that the reaction was compatible with diverse protecting group on the nitrogen (R^1=Me, Allyl, Ts, or Bn). The corresponding [4+2] cycloadducts were obtained in good yields with variable diastereoselectivities (Table 1, entries 3–5, 10:1 to >19:1 dr; 73–80% yield). Considering the reaction efficiency, stereoselectivity, and the stability of the 2-vinylindole, **1e** was chosen as the model substrate for further optimizations.

Table 1
Effect of the protecting group on the Diels–Alder reaction of 2-vinylindole **1** and 3-nitrocoumarin **2a**[a]



Entry	R^1	*t* (h)	Product	Yield[b] (%)	dr[c]
1	H (**1a**)	120	**4aa**	54	—
2	Me (**1b**)	3	**3ba**	66	>19:1
3	Allyl (**1c**)	4.5	**3ca**	80	11:1
4	Ts (**1d**)	19	**3da**	73	>19:1
5	Bn (**1e**)	4	**3ea**	79	10:1

[a] Reactions were carried out with 2-vinylindole **1** (0.3 mmol), 3-nitrocoumarin **2a** (0.2 mmol) in CH_2Cl_2 (1.0 mL) for the indicated time.
[b] Isolated yield for both diastereomers.
[c] Determined by ^{1}H NMR analysis.

To further improve the reaction efficiency and selectivity, we examined a variety of Brønsted acid catalysts, such as thioureas, urea, and some common protonic acids (Fig. 1).[18] As shown in Table 2, the addition of a catalytic amount of Brønsted acid played an important role on the reaction efficiency and diastereoselectivity (Table 2, entries 1–8). However, the use of strong hydrogen-bonding catalysts such as thiourea **5** and urea **6**, gave only a trace amount of the cycloadduct even after 24 h (Table 2, entries 1 and 2). After screening of several other simple thioureas, it was found that

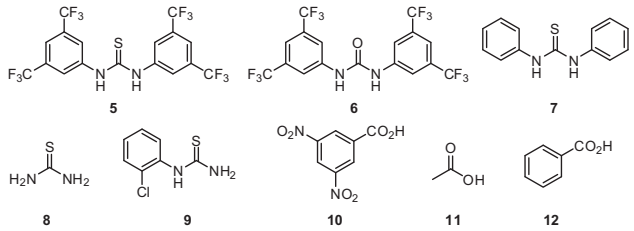
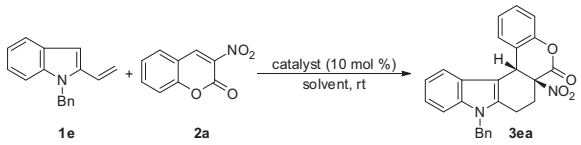


Fig. 1. Brønsted acid catalysts examined in this study.

Table 2
Optimization studies for the Diels–Alder reaction of 1-benzyl-2-vinyl-1*H*-indole **1e** and 3-nitrocoumarin **2a**[a]



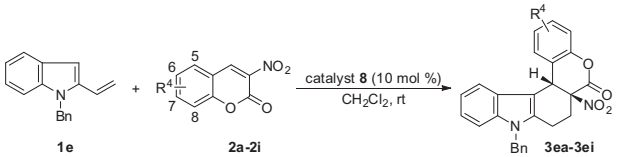
Entry	Catalyst	Solvent	*t* (h)	Yield[b] (%)	dr[c]
1	**5**	CH_2Cl_2	24	<5	—
2	**6**	CH_2Cl_2	24	<5	—
3	**7**	CH_2Cl_2	6	75	11:1
4	**8**	CH_2Cl_2	3.5	82	12:1
5	**9**	CH_2Cl_2	12	74	10:1
6	**10**	CH_2Cl_2	8	68	8:1
7	**11**	CH_2Cl_2	12	62	9:1
8	**12**	CH_2Cl_2	12	69	11:1
9	**8**	$Cl(CH_2)_2Cl$	6	69	8:1
10	**8**	$CHCl_3$	6	61	7:1
11	**8**	Toluene	16	61	10:1
12	**8**	Xylenes	12	61	12:1
13	**8**	CH_3CN	12	44	7:1
14	**8**	Et_2O	12	61	11:1
15	**8**	THF	24	60	8:1
16	**8**	MeOH	16	48	4:1
17	**8**	DMF	24	<5	—
18	**8**	H_2O	24	<5	—

[a] Reactions were carried out with 1-benzyl-2-vinyl-1*H*-indole **1e** (0.3 mmol), 3-nitrocoumarin **2a** (0.2 mmol), and 10 mol % catalyst in solvent (1.0 mL) for the indicated time.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.

the simplest thiourea **8** was the best promoter and gave the corresponding product in 82% yield with 12:1 dr. Protonic acids, DNBA, HOAc, and $PhCO_2H$ could also efficiently catalyze the reaction (Table 2, entries 6–8), but with poorer results. Thus, in terms of reaction efficiency and stereoselectivity, a brief survey of solvents was carried out in the presence of thiourea **8**, and CH_2Cl_2 was identified as the optimal reaction media (Table 2, entry 4).

Having established the optimal reaction conditions, we then explored the scope of 3-nitrocoumarins. As summarized in Table 3,

Table 3
Diels–Alder reactions of 1-benzyl-2-vinyl-1*H*-indole **1e** with representative 3-nitrocoumarins **2**[a]



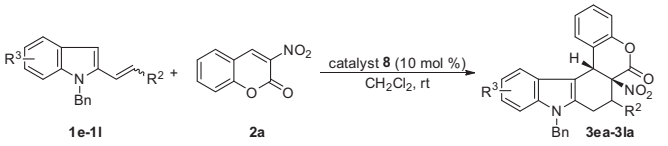
Entry	R^4	*t* (h)	Product	Yield[b] (%)	dr[c]
1	H (**2a**)	3.5	**3ea**	82	12:1
2	6-Me (**2b**)	6	**3eb**	77	11:1
3	6-MeO (**2c**)	6	**3ec**	73	11:1
4	7-MeO (**2d**)	23	**3ed**	66	9:1
5	6-F (**2e**)	2	**3ee**	82	10:1
6	6-Cl (**2f**)	4	**3ef**	67	13:1
7	6-Br (**2g**)	4	**3eg**	80	14:1
8[d]	6,8-Br_2 (**2h**)	1.5	**3eh**	78	>19:1
9[d]	6-NO_2 (**2i**)	94	**3ei**	43	>19:1

[a] Unless otherwise noted, the reactions were carried out with 0.3 mmol of 1-benzyl-2-vinyl-1*H*-indole **1e**, 0.2 mmol of 3-nitrocoumarins **2a–2i** in 1.0 mL of CH_2Cl_2 in the presence of 10 mol % of catalyst **8** for the indicated time.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] With acetone as the solvent.

a wide range of electron-poor and electron-rich 3-nitrocoumarins with variable substitution patterns reacted well with 1-benzy-2-vinyl-1*H*-indole **1e**, giving the corresponding products in generally good yields (67–82%) with high dr values (9:1 to >19:1) (Table 3, entries 2–8). As shown in entries 5–8, we have successfully utilized halogenated coumarin substrates in this reaction. Importantly, these halogenated polycyclic indoles would allow further functionalization through other cross-coupling reactions.[19] In the case of 6-nitro substituted 3-nitrocoumarins **2i**, excellent dr (>19:1) was also obtained albeit with slightly diminished conversion (Table 3, entry 9).

Next, we investigated the functional tolerance of 2-vinylindole component. As shown in Table 4, both electron-rich and electron-poor 2-vinylindoles were suitable substrates for this transformation (Table 4, entries 2–6). Generally good yields and excellent diastereoselectivities were achieved in all cases. Moreover, 2-vinylindole **1k** bearing two substituents could also efficiently participate in this Diels–Alder reaction, affording the desired product in 74% yield with >19:1 dr (Table 4, entry 7). In addition, the 2-vinylindole **1l** with a methyl group at the terminal alkene (*E*/*Z*=2:1) reacted smoothly with 3-nitrocoumarin **2a** to give the cycloadduct in a yield of 60% with 13:1 dr (Table 4, entry 8).

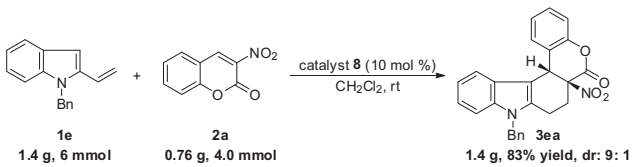
Table 4
Diels–Alder reactions of representative 2-vinyl-1*H*-indole **1** with 3-nitrocoumarins **2a**[a]



Entry	R^2	R^3	*t* (h)	Product	Yield[b] (%)	dr[c]
1	H	H (**1e**)	3.5	**3ea**	82	12:1
2	H	5-Me (**1f**)	3	**3fa**	75	>19:1
3	H	5-MeO (**1g**)	2	**3ga**	66	13:1
4	H	5-F (**1h**)	12	**3ha**	71	13:1
5	H	5-Cl (**1i**)	94	**3ia**	63	10:1
6	H	5-Br (**1j**)	96	**3ja**	64	>19:1
7	H	4-Cl,7-Me (**1k**)	80	**3ka**	74	>19:1
8[d]	Me	H (**1l**)	46	**3la**	60	13:1

[a] Unless otherwise noted, the reactions were carried out with 0.3 mmol of 1-benzyl-2-vinyl-1*H*-indoles **1e**–**1l**, 0.2 mmol of 3-nitrocoumarins **2a** in 1.0 mL of CH_2Cl_2 in the presence of 10 mol % of catalyst **8** for the indicated time.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] (*E*)-**1l**/(*Z*)-**1l**=2:1.

To demonstrate the practical utility of the current protocol, the reaction of 1-benzyl-2-vinyl-1*H*-indole **1e** and 3-nitrocoumarin **2a** was performed at 4.0 mmol scale (Scheme 2). After 5 h, the desired product **3ea** was isolated in 83% yield with 9:1 dr by simple filtration of the reaction mixture.



Scheme 2. Gram-scale preparation of **3ea**.

Based on the X-ray structure of **3ea**[20] and the ^1H NMR spectral experiments (NOESY and HSQC) of **3la**, a plausible transition state was proposed to explain the observed stereocontrol (Fig. 2).[21] An *endo*-selective Diels–Alder cycloaddition might be favored.

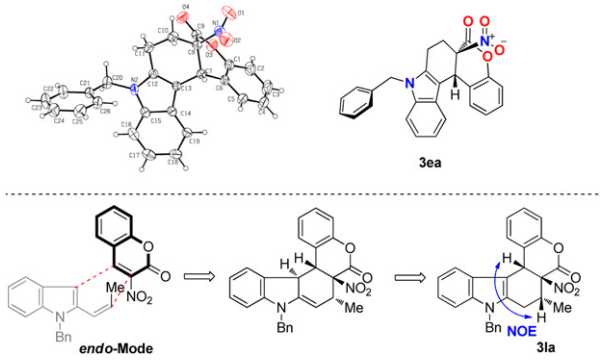


Fig. 2. X-ray crystal structure of **3ea** and proposed transition state.

3. Conclusion

In summary, we have developed a highly diastereoselective Diels–Alder reaction of 2-vinylindoles and 3-nitrocoumarins by the use of simple thiourea catalyst, allowing efficient access to a variety of coumarin-fused tetrahydrocarbazoles. The versatility of the produced polycyclic indole derivatives, the general attractiveness of the method, and the high levels of diastereoselectivity obtained would lead to many applications, especially in the synthesis of biologically important compounds and natural products. Further efforts will be dedicated to expanding the substrate scope and the development of asymmetric version of this transformation.

4. Experimental section

4.1. General methods

Unless otherwise noted, all 3-nitrocoumarins and 2-vinylindoles were prepared according to the known literature.[22,23] Catalysts **5** and **6** were prepared from the known procedure.[16c,24] Catalysts **7**–**12** were purchased from commercial suppliers and used without further purification. Dichloromethane was freshly distilled from calcium hydride, ethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Other solvents were also purified before using. Reactions were monitored by thin layer chromatography (TLC), and column chromatography purifications were performed using 200–300 mesh silica gel, 2-vinylindoles were purified by column chromatography on neutral Al_2O_3 (200–300 mesh).

^1H NMR spectra were recorded on 400 MHz or 600 MHz spectrophotometers. Solvent for NMR is $CDCl_3$ or DMSO, unless the otherwise noted. Chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on 100 MHz or 150 MHz. Chemical shifts are reported in parts per million relative to the central line of the multiplet at 77.0 ppm for $CDCl_3$, 39.5 ppm for DMSO. Mass spectra were measured on a Finnigan Trace MS spectrometer (EI).

4.2. General procedure for the Diels–Alder reaction of 2-vinylindole 1 with 3-nitrocoumarin 2 (Tables 3 and 4)

The thiourea catalyst **8** (1.5 mg, 0.02 mmol), 3-nitrocoumarin **2** (0.2 mmol) were stirred in 1.0 mL of dichloromethane for 20 min at room temperature. 2-Vinylindole **1** (0.3 mmol) was then added and the reaction mixture was stirred for 1.5–96 h. After the complete consumption of **2** (as monitored by TLC), the reaction mixture was

purified directly by flash column chromatography on silica gel (petroleum ether/ethyl acetate (20:1 to 16:1)) to give the corresponding pure Diels–Alder product as a solid. Relative configuration of the product was determined by comparison of ^{1}H NMR, ^{13}C NMR spectra and HRMS.

*4.2.1. 3-Nitro-4-(2-vinyl-1H-indol-3-yl)chroman-2-one (**4aa**).* Brown solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.39 (d, J=7.7 Hz, 2H), 7.24–7.20 (m, 2H), 7.08 (t, J=7.2 Hz, 1H), 6.98 (t, J=7.4 Hz, 1H), 6.94 (d, J=6.6 Hz, 2H), 6.85–6.80 (m, 1H), 5.98 (d, J=13.1 Hz, 1H), 5.65 (d, J=17.5 Hz, 1H), 5.51 (d, J=13.2 Hz, 1H), 5.44 (d, J=11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.64, 150.19, 148.53, 136.20, 127.94, 128.68, 128.55, 126.77, 125.76, 122.60, 122.52, 119.78, 119.45, 117.82, 117.40, 114.28, 113.86, 99.29, 31.58; HRMS (ESI) calcd for $C_{19}H_{14}N_2O_4$ $[M+Na]^+$: 357.0825; found: 357.0851.

*4.2.2. 9-Methyl-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ba**).* Yellow solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.35 (t, J=7.7 Hz, 1H), 7.25 (s, 1H), 7.22 (s, 2H), 7.17 (t, J=7.3 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 6.98 (s, 1H), 5.27 (s, 1H), 3.60 (s, 3H), 3.12 (s, 2H), 2.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.21, 149.37, 137.58, 133.12, 129.75, 125.96, 125.28, 122.48, 121.70, 119.73, 118.26, 117.22, 109.03, 102.93, 90.26, 40.77, 29.24, 27.34, 19.70; HRMS (ESI) calcd for $C_{20}H_{16}N_2O_4$ $[M+Na]^+$: 371.1033; found: 371.1008.

*4.2.3. 9-Allyl-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ca**).* Yellow solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.37 (t, J=7.5 Hz, 1H), 7.24 (s, 3H), 7.17 (t, J=7.3 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 7.00 (s, 1H), 5.92–5.88 (m, 1H), 5.31 (s, 1H), 5.14 (d, J=10.2 Hz, 1H), 4.77 (d, J=17.1 Hz, 1H), 4.62 (s, 2H), 3.11 (t, J=11.1 Hz, 2H), 2.86 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.84, 149.38, 137.06, 132.96, 132.37, 129.81, 126.11, 125.35, 121.87, 119.89, 118.39, 117.30, 116.64, 109.39, 103.39, 90.24, 45.26, 40.75, 29.65, 27.32, 19.46; HRMS (ESI) calcd for $C_{22}H_{18}N_2O_4$ $[M+Na]^+$: 397.1139; found: 397.1164.

*4.2.4. 6a-Nitro-9-tosyl-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3da**).* Yellow solid, ^{1}H NMR (600 MHz, DMSO): δ 7.51 (s, 1H), 7.34 (t, J=7.6 Hz, 1H), 7.22 (s, 1H), 7.18–7.14 (m, 3H), 7.12–7.09 (m, 2H), 6.86 (s, 1H), 6.81 (d, J=7.4 Hz, 2H), 6.78 (d, J=8.3, 1H), 5.36 (s, 1H), 5.22 (s, 2H), 2.96 (d, J=17.3 Hz, 1H), 2.90–2.77 (m, 1H), 2.76–2.53 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.46, 149.31, 136.84, 135.82, 133.09, 129.74, 129.37, 128.88, 127.52, 126.56, 125.83, 125.33, 123.60, 122.82, 118.18, 117.24, 109.29, 103.30, 90.29, 46.54, 40.52, 26.97, 21.46, 19.61; HRMS (ESI) calcd for $C_{26}H_{20}N_2O_6S$ $[M+Na]^+$: 511.0928; found: 511.0940.

*4.2.5. 9-Benzyl-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ea**).* Pale yellow solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.36 (t, J=7.7 Hz, 1H), 7.28–7.19 (m, 6H), 7.12–7.09 (m, 2H), 6.99 (d, J=7.0 Hz, 1H), 6.92 (d, J=7.2 Hz, 2H), 5.31 (s, 1H), 5.25–5.18 (m, 2H), 3.03 (s, 2H), 2.81 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.13, 149.39, 137.41, 136.65, 133.1, 129.75, 128.87, 127.55, 126.16, 125.91, 125.35, 122.42, 122.04, 120.03, 118.42, 117.29, 109.56, 103.68, 90.23, 46.46, 40.79, 27.25, 19.65; HRMS (ESI) calcd for $C_{26}H_{20}N_2O_4$ $[M+Na]^+$: 447.1292; found: 447.1321.

*4.2.6. 9-Benzyl-2-methyl-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3eb**).* Pale yellow solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28–7.23 (m, 5H), 7.20 (d, J=8.2 Hz, 1H), 7.15–7.10 (m, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.92 (d, J=7.2 Hz, 2H), 5.25–5.17 (m, 3H), 3.02 (s, 2H), 2.80 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.27, 147.45, 137.49, 136.70, 135.11, 133.19, 130.36, 135.12, 133.19, 130.36, 129.96, 128.89, 127.57, 126.53, 125.89, 122.02, 120.04, 118.45, 117.06, 109.55, 103.81, 90.38, 46.53, 40.98, 27.46, 20.90, 19.75; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_4$ $[M+Na]^+$: 461.1470; found: 461.1477.

*4.2.7. 9-Benzyl-2-methoxy-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ec**).* Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J=6.9 Hz, 1H), 7.25 (d, J=7.4 Hz, 3H), 7.19 (d, J=8.3 Hz, 1H), 7.10 (t, J=7.3 Hz, 1H), 7.01 (d, J=7.6 Hz, 3H), 6.90 (d, J=6.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 1H), 5.26 (s, 1H), 5.18 (t, J=10.4, 2H), 3.77 (s, 3H), 3.00 (s, 2H), 2.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.37, 143.29, 137.47, 136.70, 133.20, 128.90, 127.58, 126.20, 125.87, 123.53, 122.10, 120.14, 118.27, 114.96, 114.51, 109.59, 103.66, 90.24, 55.70, 46.53, 40.92, 27.18, 19.70; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_5$ $[M+H]^+$: 455.1580; found: 455.1607.

*4.2.8. 9-Benzyl-3-methoxy-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ed**).* Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J=7.7 Hz, 1H), 7.26 (d, J=7.3 Hz, 4H), 7.19 (d, J=8.3 Hz, 1H), 7.10 (t, J=7.4 Hz, 1H), 6.98 (t, J=7.2 Hz, 1H), 6.91 (d, J=6.7 Hz, 2H), 6.79 (d, J=7.8 Hz, 1H), 6.63 (s, 1H), 5.26–5.16 (m, 3H), 3.78 (s, 3H), 3.01 (s, 2H), 2.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.70, 150.28, 137.46, 136.72, 133.05, 130.30, 128.88, 127.56, 126.17, 125.99, 125.88,, 122.00, 119.99, 118.56, 114.06, 111.55, 109.54, 104.22, 102.68, 90.47, 55.54, 46.50, 40.49, 27.51, 19.74; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_5$ $[M+H]^+$: 455.1602; found: 455.1607.

*4.2.9. 9-Benzyl-2-fluoro-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ee**).* Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.22 (m, 6H), 7.15 (t, J=7.6 Hz, 1H), 7.08–7.02 (m, 3H), 6.92 (d, J=6.9 Hz, 2H), 5.32 (s, 1H), 5.29–5.19 (m, 2H), 3.08–2.98 (m, 2H), 2.87–2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.66, 145.36, 137.48, 136.57, 133.30, 128.93, 127.63, 126.01, 125.86, 124.41, 122.27, 120.32, 118.89, 118.81, 118.16, 116.75, 116.51, 116.40, 116.16, 109.71, 103.09, 89.84, 46.55, 40.59, 26.99, 19.60; HRMS (ESI) calcd for $C_{26}H_{19}FN_2O_4$ $[M+H]^+$: 433.1397; found: 433.1407.

*4.2.10. 9-Benzyl-2-chloro-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3ef**).* Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.34–7.27 (m, 4H), 7.23 (d, J=8.1 Hz, 2H), 7.15 (t, J=7.6 Hz, 1H), 7.07–7.04 (m, 2H), 6.93 (d, J=6.9 Hz, 2H), 5.30 (s, 1H), 5.23 (t, J=12.1 Hz, 2H), 3.04 (t, J=6.3 Hz, 2H), 2.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.57, 147.94, 137.48, 136.52, 133.32, 130.56, 129.87, 129.38, 128.89, 127.60, 125.85, 124.23, 122.23, 120.32, 118.73, 118.15, 109.69, 102.89, 89.86, 46.52, 40.78, 27.12, 19.61; HRMS (ESI) calcd for $C_{26}H_{19}ClN_2O_4$ $[M+H]^+$: 459.1105; found: 459.1112.

*4.2.11. 9-Benzyl-2-bromo-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3eg**).* Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J=8.1 Hz, 1H), 7.29–7.20 (m, 6H), 7.13 (t, J=7.5 Hz, 1H), 7.03 (t, J=7.2 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H), 6.91 (d, J=7.0 Hz, 2H), 5.26–5.16 (m, 3H), 3.01 (d, J=6.1 Hz, 2H), 2.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.45, 148.52, 137.51, 136.52, 133.34, 132.87, 132.31, 128.91, 127.63, 125.87, 124.60, 122.26, 120.36, 119.10, 118.18, 118.04, 109.70, 109.35, 102.90, 89.87, 46.55, 40.75, 22.62, 19.66; HRMS (ESI) calcd for $C_{26}H_{19}BrN_2O_4$ $[M+H]^+$: 503.0581; found: 503.0606.

*4.2.12. 9-Benzyl-2,4-dibromo-6a-nitro-7,8,9,13c-tetrahydrochromeno[3,4-c]carbazol-6(6aH)-one (**3eh**).* Pale yellow solid, ^{1}H NMR (600 MHz, DMSO): δ 8.06 (s, 1H), 7.46 (d, J=7.6 Hz, 1H), 7.29 (d, J=6.8 Hz, 2H), 7.24 (d, J=6.5 Hz, 1H), 7.10 (s, 2H), 6.96 (d, J=6.5 Hz, 4H), 5.64 (s, 1H), 5.40 (s, 2H), 3.11 (s, 1H), 3.00–2.98 (m, 1H), 2.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ 159.82, 145.39, 138.13, 137.48, 137.08, 136.86, 135.29, 134.25, 133.43, 128.65, 127.30, 126.20, 125.48, 121.85, 119.98, 117.72, 111.29, 110.37, 102.00, 90.14, 45.85, 40.12,

26.47, 19.26; HRMS (ESI) calcd for $C_{26}H_{18}Br_2N_2O_4$ $[M+Na]^+$: 602.9518; found: 602.9531.

*4.2.13. 9-Benzyl-2,6a-dinitro-7,8,9,13c-tetrahydrochromeno[3,4-c] carbazol-6(6aH)-one (**3ei**).* Yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 8.50 (d, J=1.9 Hz, 1H), 8.18–8.16 (m, 1H), 7.82 (d, J=8.1 Hz, 1H), 7.29–7.27 (m, 3H), 7.24–7.21 (m, 2H), 7.14 (d, J=8.8 Hz, 1H), 6.95 (d, J=7.0 Hz, 2H), 5.44 (s, 1H), 5.31–5.24 (m, 2H), 2.95–2.84 (m, 3H), 2.81 (d, J=9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.35, 153.76, 144.64, 137.66, 136.36, 133.56, 128.97, 127.73, 125.87, 125.69, 125.59, 123.70, 122.49, 120.59, 118.60, 117.96, 109.89, 102.09, 89.67, 46.66, 41.43, 27.66, 19.77; HRMS (ESI) calcd for $C_{26}H_{19}N_3O_6$ $[M+Na]^+$: 492.1156; found: 492.1172.

*4.2.14. 9-Benzyl-12-methyl-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3fa**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.35 (d, J=7.3 Hz, 1H), 7.24 (d, J=7.4 Hz, 3H), 7.10–7.09 (m, 3H), 6.95 (d, J=7.5 Hz, 1H), 6.90 (d, J=5.9 Hz, 2H), 5.33 (s, 1H), 5.22–5.16 (m, 2H), 3.01 (t, J=20.0 Hz, 2H), 2.81 (d, J=5.9 Hz, 1H), 2.73 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.46, 149.31, 136.84, 135.81, 133.10, 129.74, 129.72, 129.35, 128.86, 127.50, 126.55, 125.83, 125.31, 123.59, 122.81, 118.17, 117.21, 109.29, 103.28, 90.29, 46.50, 40.45, 26.93, 21.44, 19.58; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_4$ $[M+Na]^+$: 461.1469; found: 461.1477.

*4.2.15. 9-Benzyl-12-methoxy-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3ga**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.28–7.22 (m, 4H), 7.11 (d, J=8.1 Hz, 1H), 7.07 (d, J=8.9 Hz, 1H), 6.90 (d, J=7.2 Hz, 2H), 6.76–6.74 (m, 1H), 6.69 (s, 1H), 5.29 (s, 1H), 5.21–5.14 (m, 2H), 3.65 (s, 3H), 3.01 (d, J=6.0 Hz, 2H), 2.81 (d, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.12, 154.20, 149.55, 136.79, 133.66, 132.60, 129.86, 129.64, 128.89, 127.56, 126.55, 125.83, 125.16, 122.52, 117.42, 111.66, 110.28, 103.22, 100.68, 90.30, 55.53, 46.63, 40.89, 27.30, 19.77; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_5$ $[M+Na]^+$: 477.1426; found: 477.1426.

*4.2.16. 9-Benzyl-12-fluoro-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3ha**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.29–7.24 (m, 4H), 7.10 (t, J=8.7 Hz, 2H), 6.89 (d, J=7.1 Hz, 2H), 6.85–6.82 (m, 2H), 5.24 (s, 1H), 5.19 (t, J=12.6 Hz, 2H), 3.03 (s, 2H), 2.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.87, 149.44, 136.31, 134.85, 133.93, 130.04, 129.50, 128.90, 127.65, 126.34, 125.73, 125.47, 121.90, 117.38, 110.28, 110.18, 110.06, 103.77, 103.53, 90.12, 46.68, 40.78, 27.29, 19.78; HRMS (ESI) calcd for $C_{26}H_{19}FN_2O_4$ $[M+H]^+$: 443.1401; found: 443.1407.

*4.2.17. 9-Benzyl-12-chloro-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3ia**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.38 (d, J=6.9 Hz, 1H), 7.27–7.20 (m, 5H), 7.11 (t, J=9.2 Hz, 2H), 7.03 (d, J=7.8 Hz, 1H), 6.88 (d, J=6.3 Hz, 2H), 5.28 (s, 1H), 5.24–5.17 (m, 2H), 3.02 (d, J=14.4 Hz, 2H), 2.78 (d, J=33.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.57, 147.94, 137.48, 136.52, 133.32, 130.56, 129.87, 129.38, 128.89, 127.60, 125.85, 124.23, 122.23, 120.32, 118.73, 118.15, 109.69, 102.89, 89.86, 46.52, 40.78, 27.12, 19.61; HRMS (ESI) calcd for $C_{26}H_{19}ClN_2O_4$ $[M]^+$: 458.1029; found: 458.1033.

*4.2.18. 9-Benzyl-12-bromo-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3ja**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.39–7.37 (m, 2H), 7.27–7.24 (m, 4H), 7.17 (d, J=8.3 Hz, 1H), 7.10 (d, J=7.9 Hz, 1H), 7.04 (d, J=8.5 Hz, 1H), 6.87 (d, J=6.8 Hz, 2H), 5.26 (s, 1H), 5.21–5.14 (m, 2H), 3.01 (s, 2H), 2.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.45, 148.52, 137.51, 136.52, 133.34, 132.87, 132.31, 128.91, 127.63, 125.87, 124.60, 122.26, 120.36, 119.10, 118.18, 118.04, 109.70, 102.90, 89.87, 46.55, 40.75, 27.26, 19.66; HRMS (ESI) calcd for $C_{26}H_{19}BrN_2O_4$ $[M+H]^+$: 503.0596; found: 503.0606.

*4.2.19. 9-Benzyl-12-bromo-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3ka**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J=7.0 Hz, 1H), 7.24 (d, J=7.4 Hz, 2H), 7.22–7.19 (m, 1H), 7.11–7.08 (m, 3H), 7.01 (d, J=7.8 Hz, 1H), 6.81 (d, J=7.8 Hz, 1H), 6.69 (d, J=7.4 Hz, 2H), 6.32 (s, 1H), 5.49–5.43 (m, 2H), 3.08–3.02 (m, 1H), 2.83 (dd, J=14.6, 7.6 Hz, 1H), 2.70 (dd, J=17.2, 8.1 Hz, 1H), 2.47 (s, 3H), 2.28–2.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.36, 147.87, 137.83, 136.81, 134.36, 129.44, 129.08, 127.49, 125.80, 125.73, 125.67, 124.67,124.62, 123.05, 121.12, 119.98, 116.24, 104.43, 90.07, 47.97, 37.96, 23.18, 19.26, 18.72; HRMS (ESI) calcd for $C_{27}H_{21}ClN_2O_4$ $[M+Na]^+$: 495.1073; found: 495.1088.

*4.2.20. 9-Benzyl-7-methyl-6a-nitro-7,8,9,13c-tetrahydrochromeno [3,4-c]carbazol-6(6aH)-one (**3la**).* Pale yellow solid, ^1H NMR (600 MHz, $CDCl_3$): δ 7.69 (d, J=7.3 Hz, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.32 (d, J=7.4 Hz, 1H), 7.28 (t, J=7.4 Hz, 2H), 7.26–7.22 (m, 1H), 7.15 (d, J=8.2 Hz, 1H), 7.08–7.03 (m, 2H), 6.99 (d, J=8.1 Hz, 1H), 6.93 (d, J=7.3 Hz, 2H), 6.85 (t, J=7.5 Hz, 1H), 5.27–5.17 (m, 2H), 5.07 (s, 1H), 3.19–2.98 (m, 3H), 1.43 (d, J=4.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.07, 149.94, 137.54, 136.65, 134.05, 130.17, 130.01, 128.90, 127.57, 125.82, 125.59, 124.96, 121.89, 121.41, 119.85, 118.65, 117.49, 109.59, 103.41, 93.46, 46.50, 44.67, 37.07, 28.52, 16.07; HRMS (ESI) calcd for $C_{27}H_{22}N_2O_4$ $[M+Na]^+$: 495.1073; found: 495.1088.

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Supplementary data

Experimental details, characterization of all products, NMR spectra of Diels–Alder products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.11.019. These data include MOL files and InChIKeys of the most important compounds described in this article.

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