Regiospecific Normal Diels–Alder Reaction of *trans*-1,2-Biscoumarinylethenes

Kailas K. Sanap, Shriniwas D. Samant*

Department of Chemistry, Institute of Chemical Technology, N. Parekh Marg, Matunga, Mumbai 400 019, India
Fax +91(22)33611020; E-mail: samantsd@yahoo.com; E-mail: sd.samant@ictmumbai.edu.in

Received: 07.05.2012; Accepted after revision: 27.06.2012

Abstract: The reaction of different 7,8-substituted coumarin 4-acetic acids with 7-diethylaminocoumarin-3-carbaldehyde in the presence of piperidine in methanol gives 1,2-biscoumarinylethenes. These compounds undergo regiospecific Diels–Alder reactions at their electron-rich diene components C_3–C_4–C_{10}–C_9, with electron-deficient dienophiles. The feasibility of normal electron-demand Diels–Alder reactions could be explained on the basis of the HOMO–LUMO gap. All the compounds are new and are intensely colored.

Key words: coumarins, cycloaddition reaction, Diels–Alder reaction, 3,4-annulated coumarin, regiospecific reaction

Coumarins (2*H*-1-benzopyran-2-ones) and polycyclic compounds containing coumarin moiety occur in many plants[1] and have important applications in biology. They form a group of more than 40 drugs, which are used in medicine and have diverse biological activities, viz. anticoagulant, antifungal, hypertensive, CNS depressant, antihelmintic, hypnotic, antitumor agents, and HIV protease inhibition.[2] Coumarin compounds are used as additives in foods, perfumes, cosmetics, pharmaceuticals, cigarettes, and alcoholic beverages.[3] They find application in fluorescent dyes, as they are effective fluorophores, characterized by high fluorescence quantum yields.[4] Undeniably, they constitute the largest class of fluorescent dyes[5] and are widely used as emission layers in organic light-emitting diodes (OLED),[6] optical brighteners,[7] and nonlinear optical chromophores.[8]

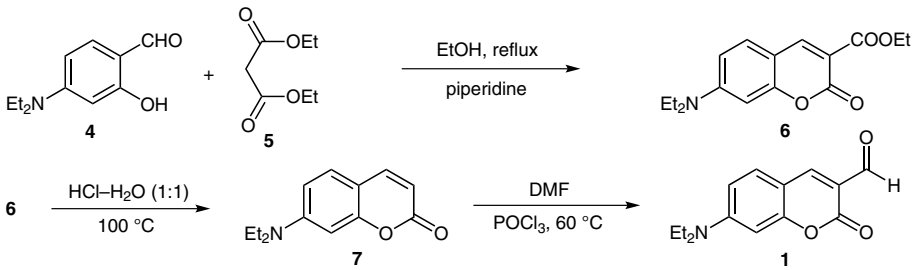
One of the sites of coumarins that attracts the attention of chemists is the 3–4 double bond. It shows the properties of an olefinic double bond and undergoes addition reactions.[9] Due to activation by the adjacent carbonyl group, it also functions as a dienophile.[10] Coumarins containing a vinyl substituent at the 3- and styryl substituent at the 4-position behave as dienes, and the corresponding Diels–Alder reaction gives 3,4-annulated coumarins.[11] Coumarin-containing electron-deficient diene at the 3-position undergoes an inverse-electron-demand Diels–Alder reaction with electron-rich dienophiles and gives 3,4-annulated coumarins.[12]

As a part of our ongoing interest in biscoumarinylethenes and their applications in cycloaddition reactions to build polycyclic compounds, we herein report the regiospecific Diels–Alder reactions of (*E*)-1-(7-diethylaminocoumarin-3-yl)-2-(7,8-substituted coumarin-4-yl)ethenes **3a**–**h**. We thought **3** to be interesting substrates for the Diels–Alder reaction as it contains two distinct dienes, $C_{4'}$–$C_{3'}$–C_9–C_{10} and C_3–C_4–C_{10}–C_9, with different orbital characteristics and different electron demands; possibly providing the regiospecificity in the reaction.

7-Diethylaminocoumarin-3-carbaldehyde (**1**) was synthesized from 4-(diethylamino)salicylaldehyde (**4**) in two steps according to a literature procedure (Scheme 1).[13]

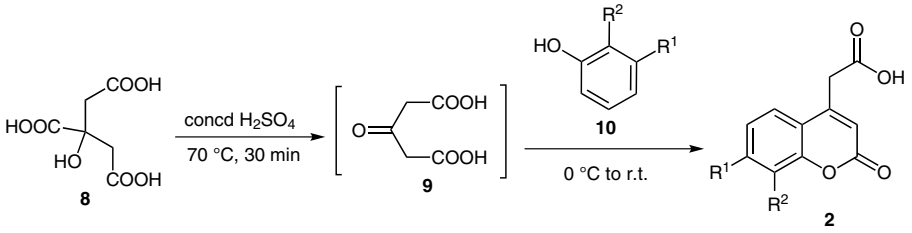
Coumarin-4-acetic acids **2** were prepared by the condensation of phenols **10** with acetone dicarboxylic acid (**9**), which in turn was prepared in situ by reacting citric acid (**8**) with concentrated sulfuric acid (Scheme 2).[14]

Coumarin-4-acetic acids **2** are known to react with aromatic aldehydes in the presence of piperidine to form 4-styrylcoumarins.[15] Taking inspiration from this, reaction of **2a** with **1** was carried out in the presence of piperidine in methanol at ambient temperature when (*E*)-1-(7-diethylaminocoumarin-3-yl)-2-(7-methyl coumarin-4-yl)ethane (**3a**) was obtained (Scheme 3). Different biscoumarinylethenes were thus prepared using optimized conditions (Table 1). Compounds **3c** and **3e** were methylated using DMS and K_2CO_3 by the standard procedure to obtain **3g** and **3h**, respectively.

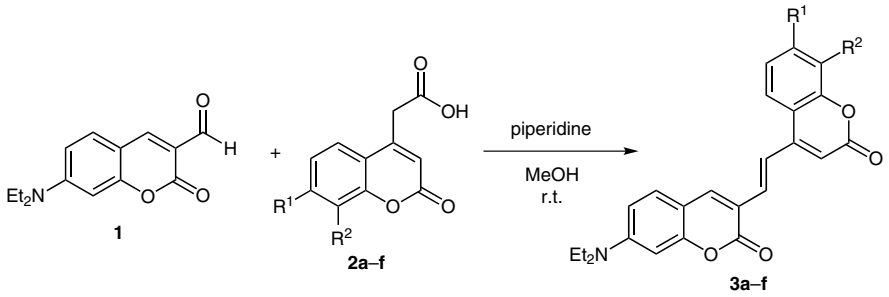


Scheme 1 Synthesis of diethylaminocoumarin-3-carbaldehyde

SYNLETT 2012, 23, 2189–2194
Advanced online publication: 21.08.2012
DOI: 10.1055/s-0031-1290454; Art ID: ST-2012-B0397-L



Scheme 2 Synthesis of coumarin-4-acetic acids



Scheme 3 Synthesis of biscoumarinylethenes

Compound **3a** was reacted with electron-deficient dienophiles – tetracyanoethylene (**11**), *N*-phenylmaleimide (**12**), maleic anhydride (**13**), and diethyl acetylene dicarboxylate (**14**) (Table 2). Tetracyanoethylene (**11**) was used with a specific aim to investigate regiospecificity in the reaction of **3a**. Due to 1,2-tetracyanosubstitution in the product, the structure could be deciphered easily.

Table 1 Reaction of **1** with **2a–f**[a]

Entry	R^1	R^2	Product **3**	Time (h)[b]	Yield of **3** (%)[c]
1	Me	H	**3a**[17]	19	64
2	H	H	**3b**	18	65
3	OH	H	**3c**	21	61
4	$NHCO_2Et$	H	**3d**	24	67
5	OH	OH	**3e**	28	61
6	Cl	H	**3f**	16	71
7	OMe	H	**3g**	–	–
8	OMe	OMe	**3h**	–	–

[a] Reaction conditions: molar ratio of **1**/**2** = 1:1, piperidine (1 equiv), MeOH.
[b] Time for total consumption of **1**.
[c] Isolated yield.

Compound **16a** was analyzed by ^{1}H NMR spectroscopy; C_4'H and C_3H protons in **3a** were decisive in locating the placement of dienophile in **16a**. In the ^{1}H NMR spectrum of **3a** C_4'H and C_3H appeared at δ = 7.79 and 6.49 ppm, respectively. In the ^{1}H NMR of **16a**, the C4′H appeared at δ = 7.93 ppm, which is close to the position where it appeared in the ^{1}H NMR spectrum of **3a**. On the other hand the peak due to C_3H disappeared. This indicated that the Diels–Alder reaction of **3a** took place on the C_3–C_4–C_{10}–C_9 diene system. The ^{1}H NMR spectrum of **16a** did not show the presence of any olefinic hydrogen; instead it showed methylene and methine protons (i.e., C_{10}H and C_9H) at δ = 3.59 and 4.29, respectively. It meant that after the Diels–Alder reaction a 1,3-prototropic shift took place to form the more stable adduct **16a** instead of **15a**, and such a 1,3-prototropic shift is known.[16]

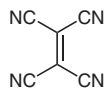
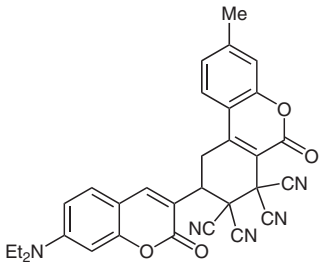
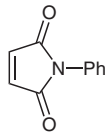
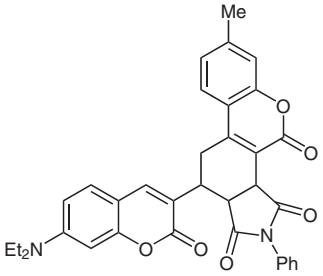
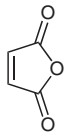
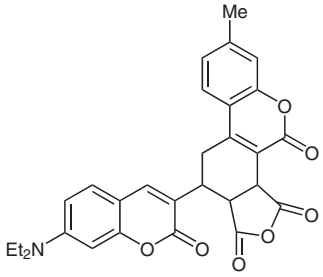
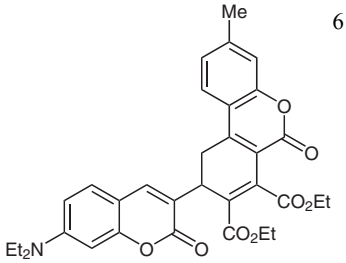
It can be seen that **3** can be represented by many charge-separated resonance structures (Figure 1). The diethylamino group in the donor ring and the carbonyl group in the acceptor ring form two termini of an extended conjugation, which incorporates both the diene systems. Resonance structures **I**–**IV** well represent this situation, and structure **V** show that the positive charge is located at C_4'. This indicates that the diene system C_3–C_4–C_{10}–C_9 is electron rich as compared to diene system C_4'–C_3'–C_9–C_{10} and hence the former is susceptible to undergo the normal electron-demand Diels–Alder reaction.

The HOMO and LUMO energies of **3** and **11** were computed at Accelrys Material Studio using the Dmol^3 programme (MS 5.2, Table 3). It was found that the energy gap between the HOMO of **3** and the LUMO of **11** is smaller than that between the LUMO of **3** and HOMO of **11**. Hence, it was concluded that the reaction proceeded by the normal electron-demand Diels–Alder pathway.

To widen the scope of reaction, dienes **3a**–**h** were allowed to react with **11** (Scheme 4, Table 4). Good yield of the products were obtained in all the cases. The reaction of **3e** and **3h** took place rapidly to furnish **16e** and **16h** in 73%

and 83% yield, respectively, while **3d** and **3f** were found to be less reactive.

Table 2 Diels–Alder Reaction of **3a** with Different Dienophiles[a,b]

Entry	Dienophile	Product ($\lambda_{max,\ nm}$)	Time (h)[c]	Yield (%)[d]
1	 **11**	 **16a** (400)	2	85
2	 **12**	 **17** (380)	4	79
3	 **13**	 **18** (382)	6	77
4[e]	 **14**	 **19** (380)	6	81

[a] Reaction conditions: molar ratio of **3a**/dienophile = 1:2.
[b] Reflux in dioxane.
[c] Time for the total consumption of **3a**.
[d] Isolated yield.
[e] Reflux in *o*-dichlorobenzene. For UV: DMSO, 10^{-3} M (10 ppm), 28–30 °C.

In conclusion, condensation of coumarin-4-acetic acids with diethylaminocoumarin-3-carbaldehyde gave *trans*-1,2-biscoumarinylethenes which have two different diene components. Reaction of *trans*-1,2-biscoumarinylethenes with electron-deficient dienophiles took place regiospecifically on the electron-rich diene component, that is, C_3–C_4–C_{10}–C_9.

Table 3 HOMO and LUMO Energies for **3**[a]

3	HOMO (eV)	LUMO (eV)	$Diene_{HOMO}$ – $dienophile_{LUMO}$	$Dienophile_{HOMO}$ – $diene_{LUMO}$
3a	–4.862	–3.008	0.761	5.308
3b	–4.887	–3.127	0.736	5.189
3c	–4.860	–3.013	0.763	5.303
3d	–4.850	–2.969	0.773	5.347
3e	–4.910	–3.086	0.713	5.23
3f	–4.995	–3.262	0.628	5.054
3g	–4.857	–3.039	0.766	5.277
3h	–4.889	–3.012	0.734	5.304

[a] Tetracyanoethylene (**11**): HOMO: –8.316 eV, LUMO: –5.623 eV.

Table 4 Diels–Alder Reaction of **3** with **11** in Dioxane[a,b]

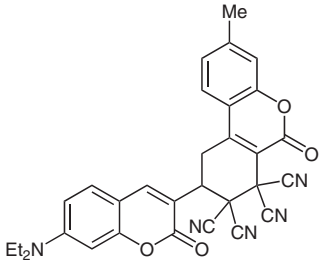
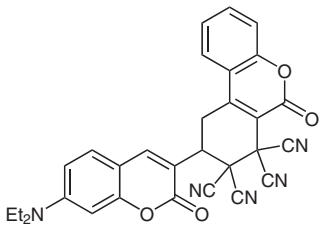
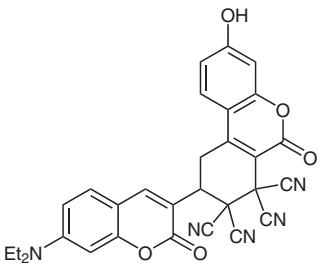
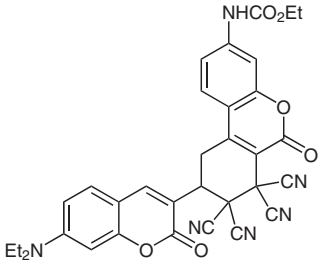
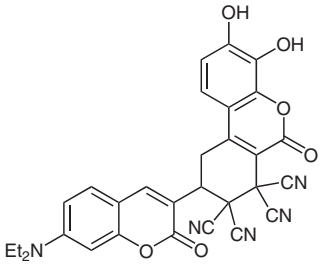
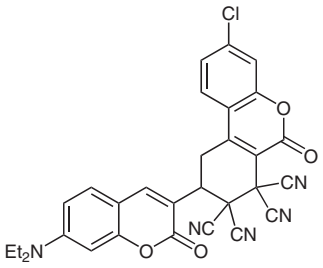
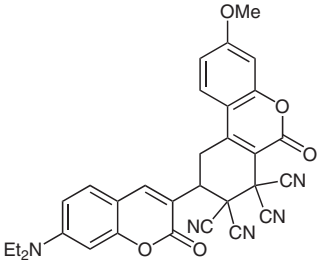
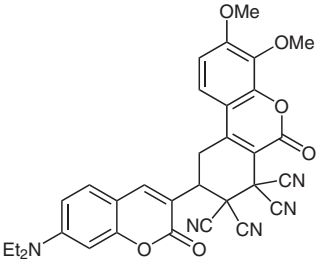
Entry	Substrate **3**	Product ($\lambda_{max,nm}$)	Time (h)[c]	Yield (%)[d]
1	**3a**	 **16a**[18] (400)	2	85
2	**3b**	 **16b** (401)	2	81
3	**3c**	 **16c** (398)	2.25	80

Table 4 Diels–Alder Reaction of **3** with **11** in Dioxane[a,b] (continued)

Entry	Substrate **3**	Product ($\lambda_{max,nm}$)	Time (h)[c]	Yield (%)[d]
4	**3d**	 **16d** (400)	2.5	74
5	**3e**	 **16e** (399)	1.5	73
6	**3f**	 **16f** (402)	2.5	76
7	**3g**	 **16g** (401)	2.25	81
8	**3h**	 **16h** (402)	1.5	83

[a] Reaction conditions: molar ratio of **3**/**11** = 1:2.
[b] Reflux temperature.
[c] Time for total consumption of **3**.
[d] Isolated yield. For UV: DMSO, 10^{-3}M (10 ppm), 28–30 °C.

Acknowledgment

K.K.S. is thankful to the CSIR, New Delhi, for a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Geissman, T. A. *The Chemistry of Flavonoid Compounds*; Pergamon Press: Oxford, 1962. (b) Harborne, J. B. *The Flavonoids: The Advances in Research since 1980*; Chapman and Hall: London, **1988**. (c) Harborne, J. B. *The Flavonoids: The Advances in Research since 1980*; Chapman and Hall: London, **1994**.
(2) Rastogi, R. P.; Mehrotra, B. N. In *Compendium of Indian Medicinal Plants*, Vol. 3; Rastogi, R. P., Ed.; Central Drug Research Institute and Publications and Information Directorate: Lucknow/New Delhi, **1993**, 273.
(3) Izquierdo, M. E. F.; Granados, J. Q.; Mir, V. M.; Martinez, M. C. L. *Food Chem.* **2000**, *70*, 251.
(4) Kuznetsova, N. A.; Kaliya, O. L. *Usp. Khim.* **1992**, *61*, 1243.
(5) (a) Jones, G.; Jackson, W. R.; Choi, C.; Bergmark, W. R. *J. Phys. Chem.* **1985**, *89*, 294. (b) Koefod, R. S.; Mann, K. R. *Inorg. Chem.* **1989**, *28*, 2285. (c) Jagtap, A. R.; Satam, V. S.; Rajule, R. N.; Kanetkar, V. R. *Dyes Pigm.* **2009**, *82*, 84.
(6) (a) Lee, M. T.; Yen, C. K.; Yang, W. P.; Chen, H. H.; Liao, C. H.; Tsai, C. H.; Chen, C. H. *Org. Lett.* **2004**, *6*, 1241. (b) Yu, T. Z.; Zhang, P.; ZhaoY, L.; Zhang, H.; Meng, J.; Fan, D. W. *Org. Electron.* **2009**, *10*, 653.
(7) (a) Dorlars, A.; Schellhammer, C. W.; Schroeder, J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 665. (b) Keskin, S. S.; Aslan, N.; Bayrakceken, N. *Spectrochim. Acta, Part A* **2009**, *72*, 254. (c) Kido, J.; Iizumi, Y. *Appl. Phys. Lett.* **1998**, *73*, 2721.
(8) (a) Moylan, C. R. *J. Phys. Chem.* **1994**, *98*, 13513. (b) Painelli, A.; Terenziani, F. *Synth. Met.* **2001**, *124*, 171.
(9) (a) Hassan, M. A.; Shiba, S. A.; Harb, N. S.; Abou-El-Regal, M. K.; El-Metwally, S. A. *Synth. Commun.* **2002**, *32*, 679. (b) Raji Reddy, C.; Kiranmai, N.; Johny, K.; Pendke, M.; Naresh, P. *Synthesis* **2009**, 399.
(10) (a) Prabhakar, M.; Reddy, G. N.; Srinu, G.; Manjulatha, K.; Prasad, J. V.; Kumar, S. P.; Srinivas, O.; Iqbal, J.; Kumar, K. A. *Synlett* **2010**, 947. (b) Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2006**, *71*, 70. (c) Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem.* **2010**, *75*, 4251. (d) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263. (e) Jung, M. E.; Allen, D. A. *Org. Lett.* **2009**, *11*, 757. (f) Flores-Larios, I. Y.; Lizbeth-Lopez, G.; Martínez-Martínez, F. J.; González, J.; García-Báez, E. V.; Cruz, A.; Padilla-Martínez, I. I. *Molecules* **2010**, *15*, 1513. (g) Amantini, D.; Fringuelli, F.; Pizzo, F. *J. Org. Chem.* **2002**, *67*, 7238.
(11) (a) Yasuda, M.; Kishi, T.; Goto, C.; Satoda, H.; Nakabayashi, K.; Minami, T.; Shima, K. *Tetrahedron Lett.* **1992**, *33*, 6465. (b) Minami, T.; Matsumoto, Y.; Nakamura, S.; Koyanagi, S.; Yamaguchi, M. *J. Org. Chem.* **1992**, *57*, 167. (c) Mustafa, A.; Kamel, M. *J. Am. Chem. Soc.* **1955**, *77*, 1828. (d) Mustafa, A.; Kamel, M.; Allam, M. A. *J. Am. Chem. Soc.* **1956**, *78*, 4692. (e) El-Shafei, A.; Fadda, A. A.; Abdel-Gawad, I. I.; Youssif, E. H. E. *Synth. Commun.* **2009**, *39*, 2954.
(12) (a) Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, 477. (b) Pottie, I. R.; Nandaluru, P. R.; Bodwell, G. J. *Synlett*

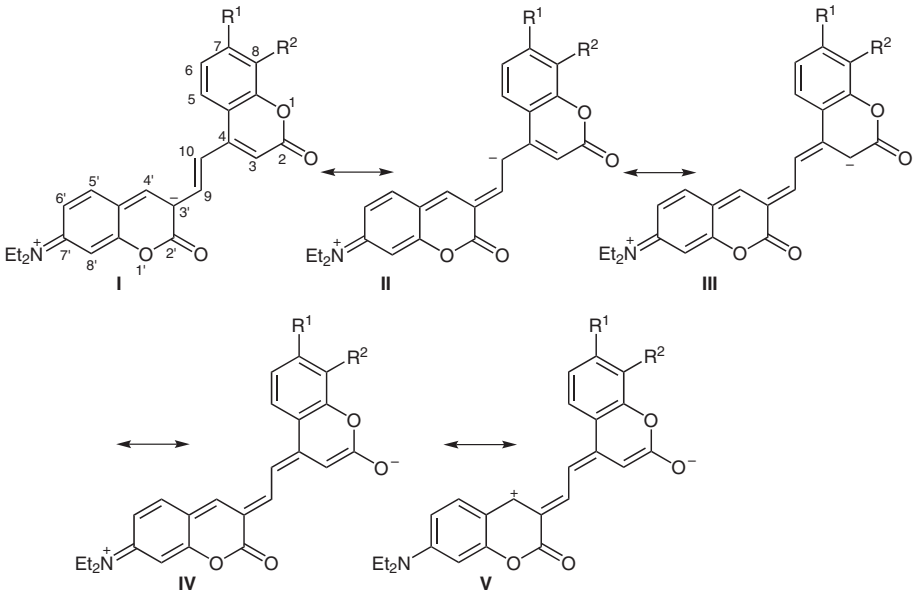
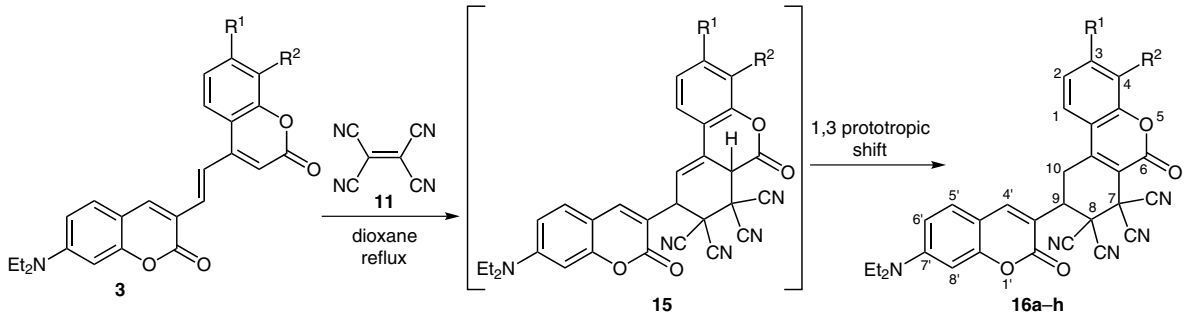


Figure 1 Resonance structures of **3**



Scheme 4 Synthesis of tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one derivatives by the Diels–Alder reaction of **3** and **11**

2011, 2245. (c) Pottie, I. R.; Nandaluru, P. R.; Benoit, W. L.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *J. Org. Chem.* **2011**, *76*, 9015. (d) Nandaluru, P. R.; Bodwell, G. J. *Org. Lett.* **2012**, *14*, 310.

(13) Wu, J.-S.; Liu, W.-M.; Zhuang, X.-Q.; Wang, F.; Wang, P.-F.; Tao, S.-L.; Zhang, X.-H.; Wu, S.; Lee, S.-T. *Org. Lett.* **2007**, *9*, 33.

(14) Laskowski, S. C.; Clinton, R. O. *J. Am. Chem. Soc.* **1950**, *72*, 3987.

(15) Soliman, A. Y.; El-Kafrawy, A. F.; Mohamed, F. K.; Baker, H. M.; Abdel-Gawad, A. M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1991**, *30*, 477.

(16) Kudale, A. A.; Kendall, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem.* **2008**, *73*, 8437.

(17) **Experimental Procedure for 3a**
Compound **2a** (0.218 g, 1 mmol) and piperidine (0.085 g, 1 mmol) were stirred in MeOH (6 mL) for 15 min and **1** (0.245 g, 1 mmol) was added slowly at r.t. After complete consumption of **1**, the precipitated solid was collected by filtration and washed with a small quantity of cold MeOH followed by H_2O to remove traces of piperidine. Solid **3a** was washed with EtOAc. The second crop of **3a** was obtained from the filtrate; the filtrate was evaporated to obtain a sticky mass which was purified by column chromatography on silica gel using toluene–EtOAc (70:30, v/v); orange solid; 64% yield; mp 231–233 °C. IR (neat): ν = 1698, 1609, 1575, 1513, 1352, 1252, 1192, 1132 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, 6 H, 2 × CH_3, *J* = 7.5 Hz), 2.46 (s, 3 H, CH_3), 3.47 (q, 4 H, 2 × CH_2, *J* = 7.5 Hz), 6.49 (s, 1 H, C3H), 6.51 (d, 1 H, C8′H, *J* = 2.0 Hz), 6.65 (dd, 1 H, C6′H, *J* = 2.0, 9.0 Hz), 7.13–7.15 (m, 2 H, C5′H and C8H), 7.20 (d, 1 H, C10H, *J* = 15.5 Hz), 7.37 (d, 1 H, C6H, *J* = 8.5 Hz), 7.77 (d, 1 H, C5H, *J* = 8.5 Hz), 7.79 (s, 1 H, C4′H), 7.99 (d, 1 H, C9H, *J* = 15.5 Hz). MS: *m/z* = 402.57 [M + 1]. Anal. Calcd (%) for $C_{25}H_{23}NO_4$ (401.45): C, 74.79; H, 5.77; N, 3.49. Found: C, 74.58; H, 5.88; N, 3.52.

(18) **Experimental Procedure for 16a**
Compound **3a** (0.401 g, 1 mmol) and **11** (0.256 g, 2 mmol) were refluxed in dioxane (6 mL) for 2 h. After complete consumption of **3a**, the solution was cooled to r.t. and was evaporated to obtain a sticky mass which was purified by column chromatography on silica gel using toluene–EtOAc (80:20, v/v); buff solid; 85% yield; mp 269–270 °C. IR (neat): δ = 2975, 1702, 1594, 1519, 1251, 1128 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 6 H, 2 × CH_3, *J* = 6.9 Hz), 2.50 (s, 3 H, CH_3), 3.50 (q, 4 H, 2 × CH_2, *J* = 6.9 Hz), 3.59 (d, 2 H, C10H, *J* = 7.2 Hz), 4.29 (t, 1 H, C9H, *J* = 7.2 Hz), 6.44 (d, 1 H, C8′H, *J* = 2.1 Hz), 6.64 (dd, 1 H, C6′H,

J = 2.1, 8.7 Hz), 7.22 (s, 1 H, C8H), 7.24 (d, 1 H, C6H, *J* = 7.8 Hz), 7.38 (d, 1 H, C5′H, *J* = 8.7 Hz), 7.58 (d, 1 H, C5H, *J* = 8.1 Hz), 7.93 (s, 1 H, C4′H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 12.4 (2 × CH_3), 22.0 ($ArCH_3$), 28.3 (C10), 36.9 (C9), 42.3 (C8), 45.1 (2 × CH_2), 46.5 (C7), 97.0 (C8′), 107.5 (C3′), 108.9 (CN), 109.2 (CN), 109.4 (C10b), 109.7 (2 × CN), 109.8 (C6′), 111.6 (C4a′), 114.6 (C6a), 117.7 (C4), 124.8 (C2), 127.2 (C1), 130.1 (C5′), 142.8 (C4′), 147.4 (C3), 152.0 (C7′), 152.3 (C10a), 152.9 (C4a′), 156.5 (C8a′), 157.1 (C2′), 161.5 (C6). MS: *m/z* = 530.46 [M + 1]. Anal. Calcd (%) for $C_{31}H_{23}N_5O_4$ (529.55): C, 70.31; H, 4.38; N, 13.23. Found: C, 70.48; H, 4.47; N, 13.19.

