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Synthesis and characterization of 2*H*-pyrano[3,2-*c*]coumarin derivatives and their photochromic and redox properties

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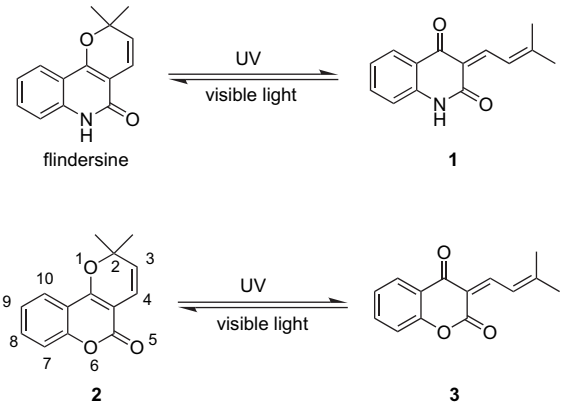
Abstract—A series of 2*H*-pyrano[3,2-*c*]chromen-5-one derivatives were synthesized and characterized. Their photochromic and redox properties were investigated by the UV–vis absorption spectroscopy. While compounds with one or two phenyl groups incorporated at the 2-position were present in both ring-opened (**5a** and **10a**) and ring-closed (**6a** and **11a**) forms, the incorporation of an *N*,*N*-dimethylamino group on either side of the aromatic ring resulted in formation of the ring-opened (**5b** and **10b**) forms only. The ring-closed forms **13** and **18** with a methyl substituent at the 3-position of the pyran moiety failed to exhibit photochromic behavior. Compound **23** with an *N*,*N*-dimethylamino group on the aromatic ring displayed increasing shoulder absorption in the visible region and a distinct change of color upon UV irradiation. The non-fluorescent **10b** instantly changed from dark red to colorless, when treated with sodium borohydride. The reduced **28** was blue fluorescent with a quantum yield of 0.46 and could be returned to its original color via DDQ oxidation.

1. Introduction

Photochromism[1] refers to a reversible phototransformation of a chemical species between two forms having different absorption spectra. Compounds with photochromic properties may have a wide range of applications in the area of photonic materials. Flindersine, a pyrano[3,2-*c*]quinoline derivative, was proven to possess photochromic properties half a century ago due to the presence of a light-sensitive pyran functionality.[2] The corresponding coumarin derivative **1** (Scheme 1) exhibited similar photochemical behavior.[3] While much effort has been made to improve the photochromic properties of chromenes,[4] diarylethenes,[5] and spiropyrans[6] for practical applications, little attention has been paid to the photochromism of pyrano[3,2-*c*]quinoline and pyrano[3,2-*c*]coumarin derivatives. One possible explanation is that the ring-closed and ring-opened forms of these molecules do not differ substantially in their absorption spectra, which is a prerequisite for practical applications. For instance, the negligent color variance prior to and after the irradiation of flindersine hampers its potential to serve as materials used in photochromic ophthalmic lenses.[7] In this paper, we describe the synthesis of various substituted pyrano[3,2-*c*]coumarins in an aim to find molecules with the desired photochromic property, which is that the photogenerated forms exhibit broad absorption in the visible region. The effects of the conjugative substitution at the 2-position, the bulky substituents at the 3-position, the benzo annelation at the 7,8-positions, and the conjugative substitution at the 8,9- and 9,10-position of 2*H*-pyrano[3,2-*c*]-chromen-5-ones on their photochemical properties were investigated. Moreover, the redox switch property of some ring-opened compounds was also explored.



Scheme 1. Photochromism of flindersine and a coumarin derivative **2**.

2. Results and discussion

The incorporation of aromatic substituents at the 2-position of 2*H*-pyrano[3,2-*c*]chromen-5-one represents a simple way to cause the photogenerated forms **1** and **3** to exhibit broad absorption in the visible region. Although several 2-phenyl-substituted 2*H*-pyrano[3,2-*c*]chromen-5-ones have been previously prepared, whether they existed in either

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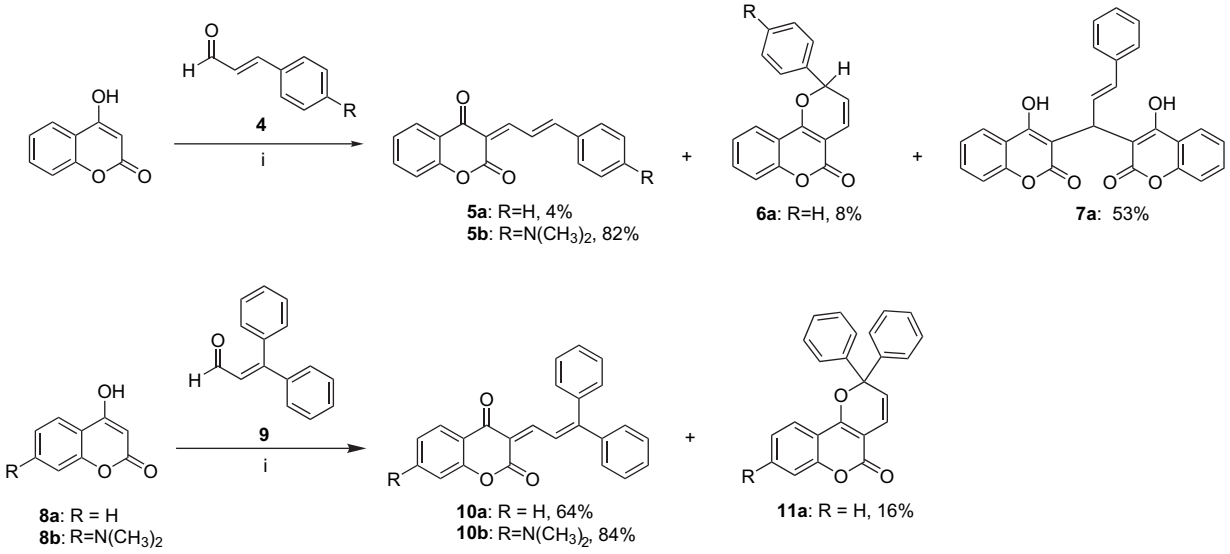
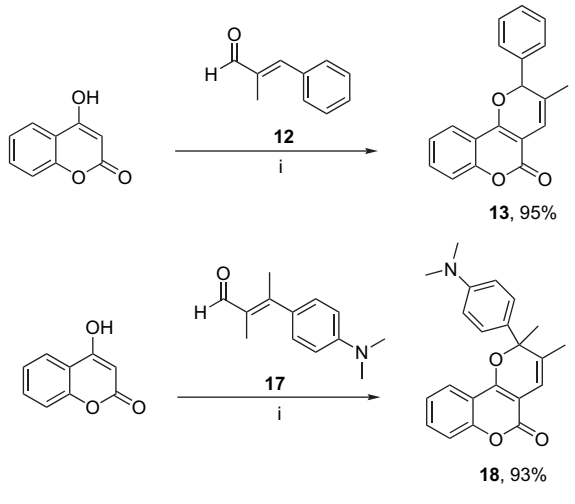
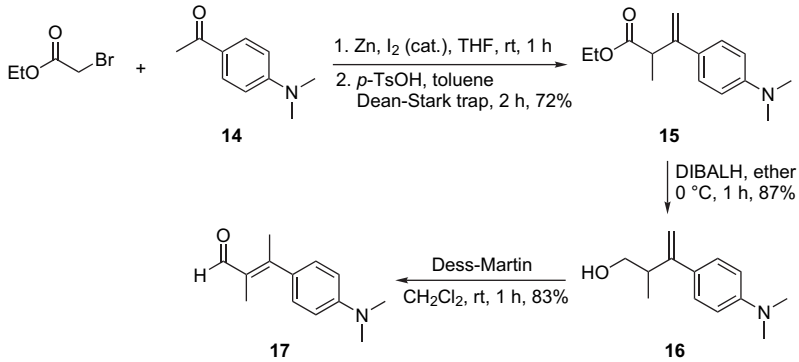


Scheme 2. Reagents and conditions: (i) ethylenediammonium diacetate (cat.), CH_2Cl_2/MeOH, rt, 3 h.

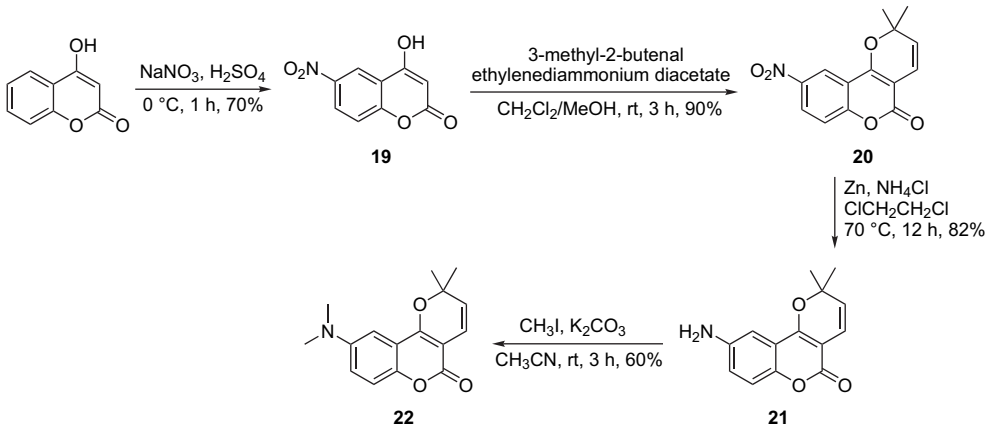
the ring-opened or the ring-closed forms remains uncertain.[8] We repeated the synthesis according to the literature procedure, as shown in Scheme 2. The results demonstrated that the condensation products were present in both ring-opened and ring-closed forms when one or two phenyl groups were incorporated at the 2-position of 2*H*-pyrano[3,2-*c*]chromen-5-ones. Based on proton NMR integrations, the ratios of ring-opened forms (**5a** and **10a**) to ring-closed forms (**6a** and **11a**) are 1 to 2 and 4 to 1, respectively. Incorporation of an *N*,*N*-dimethylamino group on either side of the aromatic ring, however, resulted in the formation of ring-opened forms **5b** and **10b** only, presumably due to the enhancement of the mesomeric effects by the substituents. In an effort to switch the products to the ring-closed pyran forms for photochromic studies, a methyl group at the 3-position of 2*H*-pyrano[3,2-*c*]chromen-5-one was introduced to destabilize the ring-opened form by increasing the steric hindrance between the methyl group and the phenyl group. Compounds **13** and **18** were prepared by reacting 4-hydroxycoumarin with **12** and **17**, respectively, as shown in Scheme 3. Scheme 4 describes the preparation of **17**.[9] The results indicated that both **13** and **18** existed in the ring-closed forms only, suggesting that the methyl group at the 3-position can indeed switch their presence to the ring-closed form. Unfortunately, the irradiation of **13** and **18** with UV light (354 nm) revealed no photochromic behavior. Since the desired photochromic properties had not been obtained by 2- and 3-position substitutions, the effects of substitution at the 8- and 9-position of the coumarin moiety were considered. Scheme 5 shows the synthesis of 9-*N*,*N*-dimethylamino-substituted **22**, which began with the nitration



Scheme 3. Reagents and conditions: (i) ethylenediammonium diacetate (cat.), MeOH, rt, 3 h.

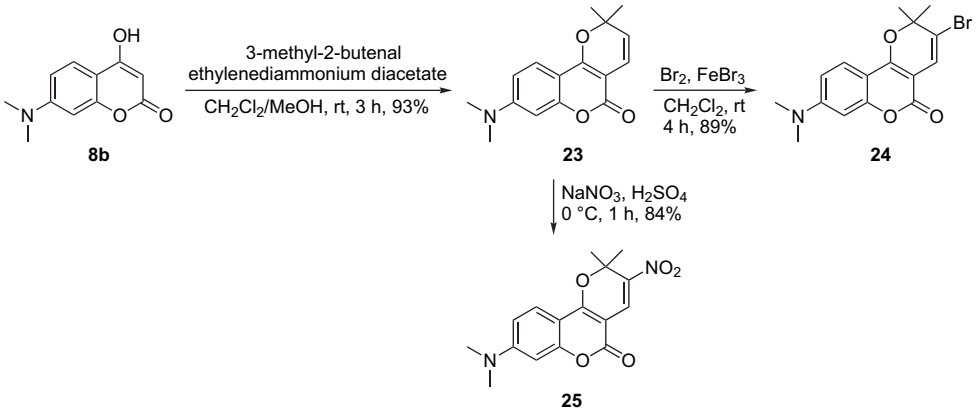


Scheme 4. Preparation of compound **17**.



Scheme 5. Preparation of compound **22**.

of 4-hydroxycoumarin to give the 9-nitro-substituted **19**, followed by coupling with 3-methyl-2-butenal to yield **20**. The nitro group was reduced by treating **20** with zinc and ammonium chloride to afford the 9-amino-substituted **21**. Final methylation of the amino group with excess methyl iodide using potassium carbonate as a base in acetonitrile furnished the target **22**. Scheme 6 presents the preparation of 8-*N*,*N*-dimethylamino-substituted **23** and corresponding 3-bromo- and 3-nitro-substituted derivatives **24** and **25** from **8b**.[10] The annelation of 7-*N*,*N*-dimethylamino-4-hydroxycoumarin with 3-methyl-2-butenal afforded **23** in a favorable yield. A routine bromination and nitration of **23** with bromine and sodium nitrate gave compounds **24** and **25**, respectively. The irradiation results demonstrated that neither **24** nor **25** was sensitive to light, indicating that the incorporation of a substituent at the 3-position is detrimental to its photochromism. Although compounds **20**–**22** exhibited photochromic property, none had a distinct change in color. The only compound that exhibited photochromic behavior with a noticeable color change was compound **23**. It turned from colorless to yellow within seconds upon UV irradiation (Fig. 1). The resulting ring-opened **26** can cyclize back to **23**



Scheme 6. Preparation of compounds **23**–**25**.

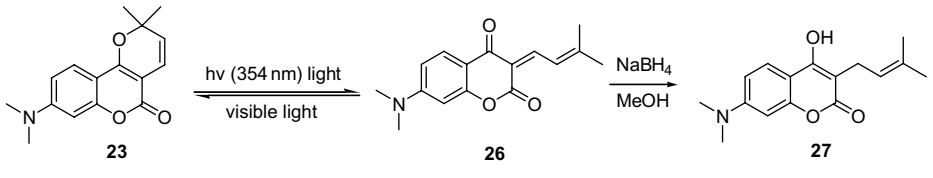


Figure 1. The photochromic switch of **23** and the color difference prior to and after photoirradiation (λ=354 nm).

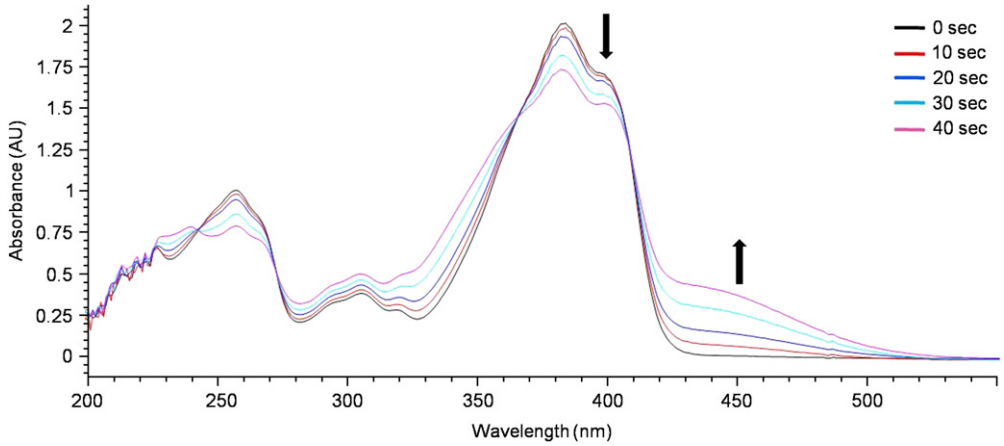


Figure 2. Time course of the UV–vis absorption spectra of **23** (3.68×10^{-5} M) in CH_2Cl_2 under continuous irradiation using 354 nm light at 25 °C.

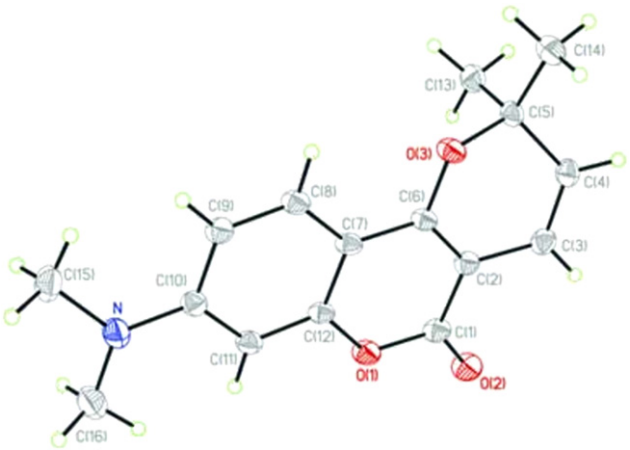


Figure 3. X-ray crystal structure of compound **23**.

within seconds under visible light. Figure 2 displays the time course of the UV–vis absorption spectra of **23** in CH_2Cl_2 under continuous irradiation (354 nm) with four clear isosbestic points (242, 273, 368, and 419 nm). The structure of compound **23** was unambiguously verified by X-ray crystallography (Fig. 3). The structure of photogenerated **26** was indirectly confirmed by reducing it in situ with sodium borohydride in methanol to give compound **27** (Fig. 1), which was stable enough to be further characterized.

With respect to the redox property of the ring-opened molecules, compound **10b** instantly changed from dark red to colorless, when treated with sodium borohydride in methanol at room temperature. Figure 4 depicts the redox switch between **10b** and **28**, and the corresponding colors in the oxidized (dark red) and the reduced (colorless) forms. Figure 5 presents the UV–vis absorption spectra of **10b** prior to and after reduction. It displays two long-wavelength broad bands at 410 (ε=30,791 $M^{-1}\,cm^{-1}$) and 490 nm (ε=28,938 $M^{-1}\,cm^{-1}$) before reduction, which is associated with the increased π-delocalization of the chromophore. A different spectrum was obtained when **10b** was reduced to **28**. The reduction of **10b** to **28** caused the complete disappearance of long-wavelength absorbance by the disruption of the conjugation, and the appearance of a single intense band at 340 nm (ε=33,812 $M^{-1}\,cm^{-1}$), which resembles the absorption behavior of **8b**. Additionally, the reduced **28** can swiftly revert to its original color via 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation. The reversible redox switch process was repeated 10 times without significant changes in the UV spectra. While **10b** emitted no fluorescence at room temperature, the corresponding reduced **28** was blue fluorescent in methanol with a quantum yield of 0.46. Figure 6 displays the excitation and emission spectra of **28**. The reversible redox process between **10b** and **28** can be regarded as a molecular switching system, in which the absorption and emission characteristics are controlled by the redox state of the 4-hydroxycoumarin moiety. This

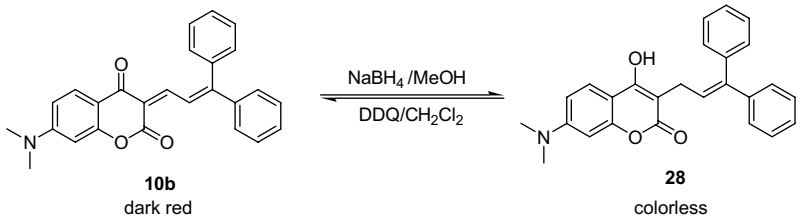


Figure 4. The redox switch between **10b** and **28** and the corresponding colors in the oxidized (left) and the reduced form (right).

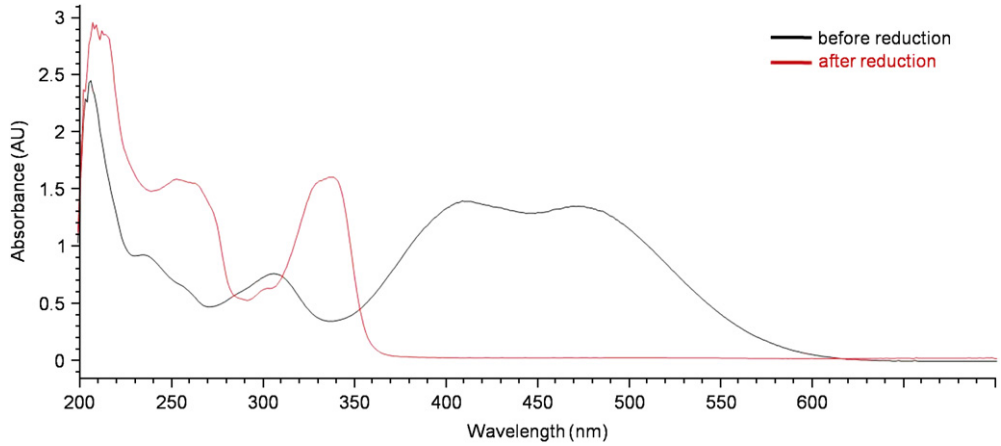


Figure 5. UV–vis spectra of **10b** (3.8×10^{-5} M in MeOH) prior to and after reduction.

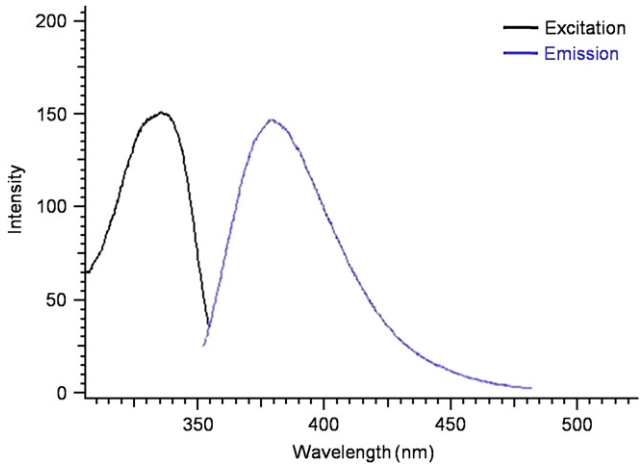


Figure 6. The excitation (339 nm) and emission (383 nm) spectra of **28** (6.54×10^{-6} M) in CH_2Cl_2 at room temperature.

redox switch system is quite unique because the redox reaction occurs at the fluorophore rather than the fluorescent quencher, as in most reported donor–acceptor systems.[11]

3. Conclusions

This study synthesized and characterized a series of 2*H*-pyrano[3,2-*c*]chromen-5-one derivatives. The incorporation of either phenyl groups at the 2-position or a methyl substituent at the 3-position of 2*H*-pyrano[3,2-*c*]chromen-5-one eliminated their photochromic behavior. Compound **23** with an *N*,*N*-dimethylamino group substituted at the 8-position on the benzene ring exhibited a distinct change of color within seconds upon UV irradiation, and can potentially be used as a material in photochromic ophthalmic lenses. Moreover, the reversible redox conversion between **10b** and **28** has the potential to function as an active fluorescence redox switch.

4. Experimental

4.1. General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Mass spectra were recorded on JOEL JMS-SX/SX 102A spectrometer. Infrared spectra were obtained using a 1725XFT-IR spectrophotometer. Absorption spectra were acquired using an HP8453 spectrophotometer. Single-crystal structures were determined by a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H). Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use.

4.2. UV and fluorescence measurements

Absorption spectra were acquired using an HP8453 spectrophotometer with a 1 cm path length quartz cell and emission spectra were obtained on a Hitachi F-4500 fluorospectrometer.

4.3. Calculation of fluorescence quantum yield

Anthracene (Φ_f=0.27, λ_{max}=345 nm in hexane) was used as an external standard for the measurement of fluorescence quantum yield of **28**. Fluorescence quantum yield was measured by comparing the integrated area under the fluorescence curve for compound **28** and anthracene at equal absorbance at the same excitation wavelength and was corrected for the refractive index of the solvent.

4.4. General procedure for the preparation of compounds 5a,b, 6a, 7a, 10a,b, 11a, 13, 18, 20, and 23

To a solution of 4-hydroxycoumarin (1.00 g, 6.16 mmol) in a mixture of methylene chloride (20 mL) and methanol (10 mL) were added appropriate substituted cinnamaldehyde (6.16 mmol) and a catalytic amount of

ethylenediammonium diacetate (0.01 g, 0.06 mmol). After the mixture was stirred at room temperature for 3 h, water (20 mL) was added and the product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give the pure product.

4.4.1. 3-(3-Phenylprop-2-enylidene)-2*H*-benzopyran-2,4(3*H*)-dione (5a). Orange solid. Yield 4%. R_f=0.40 (30% EtOAc/hexanes). Mp 184–185 °C (lit.[12] 183–185 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.69 (dd, J=15.3, 12.0 Hz, 1H), 8.38 (m, 2H), 7.75–7.30 (m, 9H).

4.4.2. 2-Phenyl-2*H*,5*H*-pyran[3,2-*c*]chromen-5-one (6a). Orange solid. Yield 8%. R_f=0.40 (30% EtOAc/hexanes). Mp 184–185 °C (lit.[12] 183–185 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75–7.30 (m, 9H), 6.61 (dd, J=9.9, 1.5 Hz, 1H), 6.39 (dd, J=3.6, 1.5 Hz, 1H), 5.95 (dd, J=9.9, 3.6 Hz, 1H). Compounds **5a** and **6a** cannot be separated from column chromatography.

4.4.3. (*E*)-3,3-(3-Phenylprop-2-enylidene)bis[4-hydroxy-2*H*-benzopyran-2-one] (7a). White solid. Yield 53%. R_f=0.43 (40% EtOAc/hexanes). Mp 221–222 °C (lit.[12] 220–224 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.92 (d, J=7.8 Hz, 2H), 7.56 (t, J=7.8 Hz, 2H), 7.36–7.16 (m, 9H), 6.76 (dd, J=15.9, 8.7 Hz, 1H), 6.26 (d, J=15.9 Hz, 1H), 5.73 (d, J=8.7 Hz, 1H).

4.4.4. (*E*,*E*)-3-[3-(4-*N*,*N*-Dimethylaminophenyl)prop-2-enylidene]-2*H*-1-benzopyran-2,4(3*H*)-dione (5b). Purple solid. Yield 82%. R_f=0.46 (40% EtOAc/hexanes). Mp 180–181 °C (lit.[13] 180–182 °C). Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (dd, J=15.0, 12.6 Hz, 1H), 8.35 (d, J=12.9 Hz, 1H), 8.11 (dd, J=7.8, 1.5 Hz, 1H), 7.62–7.55 (m, 4H), 7.28–7.21 (m, 2H), 6.70 (dd, J=9.3, 1.5 Hz, 2H), 3.13 (s, 6H). Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (d, J=5.1 Hz, 1H), 8.43 (dd, J=18.6, 12.6 Hz, 1H), 8.08 (dd, J=5.7, 1.8 Hz, 1H), 7.67 (d, J=9.0 Hz, 4H), 7.28–7.21 (m, 2H), 6.70 (dd, J=9.0, 1.8 Hz, 2H), 3.13 (s, 6H).

4.4.5. 3-(3,3-Diphenylallylidene)chromen-2,4-dione (10a). Yellow solid. Yield 64%. R_f=0.35 (20% EtOAc/hexanes). Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, J=12.6 Hz, 1H), 8.39 (d, J=12.6 Hz, 1H), 8.04 (dd, J=7.8, 1.5 Hz, 1H), 7.63–7.20 (m, 13H). Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (d, J=12.3 Hz, 1H), 8.29 (d, J=12.3 Hz, 1H), 8.10 (dd, J=7.8, 1.5 Hz, 1H), 7.63–7.20 (m, 13H).

4.4.6. 2,2-Diphenyl-2*H*-pyrano[3,2-*c*]chromen-5-one (11a). Yellow solid. Yield 16%. R_f=0.35 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (dd, J=8.4, 1.8 Hz, 1H), 7.63–7.20 (m, 13H), 6.86 (d, J=9.9 Hz, 1H), 6.05 (d, J=9.9 Hz, 1H).

4.4.7. 7-*N*,*N*-Dimethylamino-3-(3,3-diphenylallylidene)-3*H*-chromen-2,4-dione (10b). Orange solid. Yield 84%. R_f=0.35 (25% EtOAc/hexanes). Mp 221–222 °C. Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (d, J=12.6 Hz, 1H), 8.33 (d, J=12.6 Hz, 1H), 7.92 (d, J=9.0 Hz, 1H), 7.49–7.25 (m, 10H), 6.57 (dd, J=9.0, 2.4 Hz, 1H), 6.32 (d, J=2.4 Hz, 1H), 3.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.3, 164.3, 161.6, 157.1, 155.8, 155.0, 154.1, 140.9, 137.8, 131.2, 130.5, 129.7, 128.5, 124.8, 108.8, 97.4, 40.1. Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91 (d, J=12.3 Hz, 1H), 8.16 (d, J=12.3 Hz, 1H), 7.87 (d, J=9.0 Hz, 1H), 7.49–7.25 (m, 10H), 6.35 (dd, J=9.0, 2.4 Hz, 1H), 6.30 (d, J=2.4 Hz, 1H), 3.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.3, 164.0, 161.0, 156.4, 155.6, 155.0, 154.0, 140.9, 137.6, 131.2, 129.7, 128.9, 128.4, 125.3, 108.9, 97.4, 40.1. HRMS (EI) m/z calcd for $C_{26}H_{21}NO_3$ 395.1521, found 395.1526 (M^+). IR ν (KBr) 1725, 1643, 1609, 1441, 1203, 1114 cm^{-1}.

4.4.8. 3-Methyl-2-phenyl-2*H*-pyrano[3,2-*c*]chromen-5-one (13). Yellow solid. Yield 95%. R_f=0.40 (20% EtOAc/hexanes). Mp 143–144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (dd, J=7.2, 1.5 Hz, 1H), 7.48–7.25 (m, 6H), 7.18 (td, J=7.2, 1.2 Hz, 1H), 6.60 (q, J=1.5 Hz, 1H), 5.94 (s, 1H), 1.75 (d, J=1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 156.4, 152.6, 137.6, 131.5, 129.3, 128.8, 127.6, 123.7, 122.4, 116.3, 115.0, 113.7, 100.7, 82.6, 19.6. HRMS (EI) m/z calcd for $C_{19}H_{14}O_3$ 290.0943, found 290.0940 (M^+). IR ν (KBr) 1707, 1661, 1540, 1187 cm^{-1}.

4.4.9. 2-(4-*N*,*N*-Dimethylaminophenyl)-2-methyl-2*H*-pyrano[3,2-*c*]chromen-5-one (18). Yellow solid. Yield 93%. R_f=0.30 (30% EtOAc/hexanes). Mp 218–219 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (dd, J=8.1, 1.5 Hz, 1H), 7.45 (td, J=8.4, 1.5 Hz, 1H), 7.38 (d, J=9.0 Hz, 1H), 7.25 (dd, J=8.1, 0.9 Hz, 1H), 7.19 (td, J=8.4, 0.9 Hz, 1H), 6.68 (d, J=9.0 Hz, 1H), 6.53 (d, J=1.5 Hz, 1H), 2.94 (s, 6H), 1.95 (s, 3H), 1.79 (d, J=1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.8, 158.0, 155.0, 153.0, 138.3, 129.1, 128.8, 127.7, 125.9, 123.4, 114.3, 108.7, 103.9, 97.7, 96.6, 82.5, 40.1, 19.6. HRMS (EI) m/z calcd for $C_{22}H_{21}NO_3$ 347.1521, found 347.1520 (M^+). IR ν (KBr) 1718, 1645, 1478, 1126, 1167 cm^{-1}.

4.4.10. 2,2-Dimethyl-9-nitro-2*H*-pyrano[3,2-*c*]chromen-5-one (20). Yellow solid. Yield 90%. R_f=0.30 (20% EtOAc/hexanes). Mp 181–182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (d, J=2.7 Hz, 1H), 8.38 (dd, J=9.0, 2.7 Hz, 1H), 7.43 (d, J=9.0 Hz, 1H), 6.52 (d, J=9.9 Hz, 1H), 5.64 (d, J=9.9 Hz, 1H), 1.61 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3, 157.2, 156.2, 143.8, 127.7, 126.5, 119.0, 117.8, 115.9, 115.8, 101.3, 81.7, 28.6. HRMS (EI) m/z calcd for $C_{14}H_{11}NO_5$ 273.0638, found 273.0637 (M^+). IR ν (KBr) 3082, 1725, 1641, 1486, 1219 cm^{-1}.

4.4.11. 8-*N*,*N*-Dimethylamino-2,2-dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (23). Yellow solid. Yield 93%. R_f=0.40 (30% EtOAc/hexanes). Mp 148–149 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J=9.0 Hz, 1H), 6.61 (dd, J=9.0, 2.7 Hz, 1H), 6.52 (d, J=9.9 Hz, 1H), 6.48 (d, J=2.7 Hz, 1H), 5.40 (d, J=9.9 Hz, 1H), 3.05 (s, 6H), 1.51 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 160.0, 155.2, 153.1, 123.6, 123.5, 117.2, 108.7, 104.1, 97.6, 95.9, 79.8, 40.0, 28.4. HRMS (EI) m/z calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1208 (M^+). IR ν (KBr) 2925, 1706, 1612, 1417, 1197 cm^{-1}. Crystallographic data (excluding structural factors) of this compound have been deposited at

the Cambridge Crystallographic Data Center as supplementary publication number CCDC-622320. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

4.5. 3,3-Diphenyl-2-propenal (9)

To a solution of benzophenone (2.0 g, 11.0 mmol) and $TiCl_4$ (4.8 mL, 43.9 mmol) in methylene chloride (100 mL) was added dropwise a solution of triethylamine (6.1 mL, 43.9 mmol) at 0 °C. The resulting mixture was stirred for 12 h at room temperature. An aqueous NH_4Cl solution was then added to quench the reaction. The product was extracted twice with methylene chloride. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to give a yellow liquid with an 86% Yield. R_f=0.50 (15% EtOAc/hexanes). Mp 46–47 °C (lit.[14] 46–47 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (d, J=8.1 Hz, 1H), 7.47–7.30 (m, 10H), 6.60 (d, J=8.1 Hz, 1H).

4.6. Ethyl 3-(4-*N*,*N*-dimethylaminophenyl)-2-methyl-crotonate (15)

To a solution of 4-dimethylaminoacetophenone (1.00 g, 8.32 mmol) and ethyl 2-bromoacetate (1.81 g, 9.99 mmol) in benzene (30 mL) were added activated zinc (0.82 g, 12.48 mmol) and a catalytic amount of iodine. The mixture was stirred at 80 °C for 8 h, and the solvent was concentrated in vacuo. To this mixture in toluene (50 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The mixture was then refluxed in a Dean-Stark trap. After completion of the reaction within 2 h, it was cooled down to room temperature and the solvent was concentrated in vacuo. The resulting residue was poured into water, and the product was then extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (1:9 EtOAc/hexanes) to give a yellow liquid with a 72% yield. R_f=0.45 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (dd, J=6.6, 2.1 Hz, 2H), 6.68 (dd, J=6.6, 2.1 Hz, 2H), 5.30 (s, 1H), 5.06 (s, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.66 (q, J=6.9 Hz, 1H), 2.95 (s, 6H), 1.38 (d, J=0.9 Hz, 3H), 1.18 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 149.4, 145.6, 131.1, 128.4, 127.8, 123.7, 111.8, 60.1, 40.4, 21.6, 17.5. HRMS (EI) m/z calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1569 (M^+). IR ν (KBr) 1734, 1610, 1523, 1189 cm^{-1}.

4.7. 2-Methyl-3-(4-*N*,*N*-dimethylaminophenyl)-3-buten-1-ol (16)

To a solution of **15** (1.0 g, 8.32 mmol) in dry ether (20 mL) was added DIBALH (5 mL, 20% in hexane) at 0 °C. The mixture was stirred for 1 h and the product extracted twice with methylene chloride. The extract was dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give a yellow liquid with an 87% yield. R_f=0.30 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (dd, J=6.6, 2.1 Hz, 2H), 6.71 (dd, J=6.6, 2.1 Hz, 2H), 5.27 (d, J=0.9 Hz, 1H), 4.96 (d, J=0.9 Hz, 1H), 3.65, 3.53 (ABdq, J=10.8, 6.3 Hz, 2H), 2.96–2.91 (m, 1H), 2.95 (s, 6H), 1.17 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 149.9, 129.8, 127.1, 112.1, 109.5, 66.6, 40.4, 40.1, 16.8. HRMS (EI) m/z calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1460 (M^+). IR ν (KBr) 3420, 1611, 1522 cm^{-1}.

4.8. 3-(4-*N*,*N*-Dimethylaminophenyl)-2-methyl-2-butenal (17)

To a solution of **16** (1.0 g, 6.16 mmol) in methylene chloride (20 mL) was added Dess–Martin reagent (5 mL, 15% in methylene chloride) at 0 °C. The mixture was stirred for 1 h and water was then added to quench the reaction. The product was extracted twice with methylene chloride. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give a yellow liquid with an 83% yield. R_f=0.50 (15% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (s, 1H), 7.13 (dd, J=6.6, 2.1 Hz, 2H), 6.71 (dd, J=6.6, 2.1 Hz, 2H), 2.99 (s, 6H), 2.27 (q, J=1.2 Hz, 3H), 1.91 (q, J=1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.2, 149.5, 138.0, 134.6, 129.8, 129.3, 122.4, 40.2, 13.5, 10.6. HRMS (EI) m/z calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1316 (M^+). IR ν (KBr) 1683, 1623, 1450 cm^{-1}.

4.9. 4-Hydroxy-6-nitro-2*H*-chromen-2-one (19)

To a solution of $NaNO_3$ (0.52 g, 6.17 mmol) in an ice-cooled sulfuric acid (20 mL) was added 4-hydroxycoumarin (1.00 g, 6.17 mmol). After stirred at 0 °C for 1 h, the mixture was poured into an ice-cooled water to precipitate the product. Upon filtration, the crude product was recrystallized from EtOAc/hexanes (7:3) to give a white solid with a 70% yield. R_f=0.4 (70% EtOAc/hexanes). Mp 253–254 °C (lit.[12] 253–254 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, J=0.9 Hz, 1H), 8.28 (d, J=8.7 Hz, 1H), 7.42 (dd, J=8.7, 0.9 Hz, 1H), 5.55 (s, 1H).

4.10. 9-Amino-2,2-dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (21)

To a solution of **20** (1.00 g, 3.66 mmol) were added sequentially activated zinc (0.48 g, 7.32 mmol), NH_4Cl (0.59 g, 10.98 mmol, in 100 mL of 1,2-dichloroethane), and acetic acid (three drops). The mixture was refluxed for 3 h and then cooled to room temperature. The product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (3:7 EtOAc/hexanes) to give a yellow solid with an 82% yield. R_f=0.30 (30% EtOAc/hexanes). Mp 136–137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J=9.0 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 6.89 (dd, J=9.9, 2.4 Hz, 1H), 6.52 (d, J=9.9 Hz, 1H), 5.50 (d, J=9.0 Hz, 1H), 3.80 (br s, 2H), 1.52 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 158.6, 146.3, 142.9, 125.8, 120.0, 117.2, 116.7, 115.8, 106.2, 100.1, 80.2, 28.4. HRMS (EI) m/z calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0896 (M^+). IR ν (KBr) 3353, 1678, 1570, 1456, 1205 cm^{-1}.

4.11. 9-*N*,*N*-Dimethylamino-2,2-dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (22)

To a solution of **21** (1.00 g, 4.11 mmol) in dry acetonitrile (30 mL) were added K_2CO_3 (0.88 g, 6.62 mmol) and excess CH_3I. After the mixture was stirred at room temperature for 24 h, water was added to quench the reaction. The product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give a yellow solid with a 60% yield. R_f=0.35 (20% EtOAc/hexanes). Mp 153–154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (dd, J=8.7, 0.9 Hz, 1H), 6.98 (d, J=8.7 Hz, 1H), 6.96 (d, J=0.9 Hz, 1H), 6.55 (d, J=9.9 Hz, 1H), 5.51 (d, J=9.9 Hz, 1H), 2.99 (s, 6H), 1.55 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1, 158.2, 127.9, 127.3, 126.4, 125.8, 123.7, 116.6, 116.2, 114.3, 100.1, 80.8, 39.2, 22.5. HRMS (EI) m/z calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1203 (M^+). IR ν (KBr) 1702, 1615, 1152, 1195, 1110 cm^{-1}.

4.12. 3-Bromo-2,2-dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (24)

To a solution of **23** (1.00 g, 3.69 mmol) in methylene chloride were added $FeBr_3$ (1.09 g, 3.69 mmol) and bromine (0.71 g, 4.42 mmol). After the mixture was stirred at room temperature for 4 h, water was added to quench the reaction. The product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give a yellow solid with an 89% yield. R_f=0.35 (20% EtOAc/hexanes). Mp 138–139 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, J=9.0 Hz, 1H), 6.88 (s, 1H), 6.61 (d, J=9.0, 2.7 Hz, 1H), 6.46 (d, J=2.7 Hz, 1H), 3.06 (s, 6H), 1.65 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5, 158.9, 155.3, 153.4, 123.5, 120.6, 116.8, 108.9, 103.4, 97.7, 96.8, 83.3, 40.1, 27.0. HRMS (EI) m/z calcd for $C_{16}H_{16}BrNO_3$ 349.0314, found 349.0316 (M^+). IR ν (KBr) 1709, 1521, 1121, 671 cm^{-1}.

4.13. 2,2-Dimethyl-3-nitro-2*H*-pyrano[3,2-*c*]chromen-5-one (25)

To a solution of $NaNO_3$ (0.32 g, 3.69 mmol) in an ice-cooled sulfuric acid (20 mL) was added **23** (1.00 g, 3.69 mmol). After stirred at 0 °C for 1 h, the mixture was poured into an ice-cooled water to precipitate the product. Upon filtration, the product was further recrystallized from EtOAc/hexanes (7:3) to give a red solid with an 84% yield. R_f=0.30 (30% EtOAc/hexanes). Mp 233–234 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.61 (d, J=9.0 Hz, 1H), 6.64 (dd, J=9.0, 2.4 Hz, 1H), 6.45 (d, J=2.4 Hz, 1H), 3.13 (s, 6H), 1.87 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.8, 158.0, 155.0, 152.9, 128.8, 127.7, 114.3, 108.7, 103.9, 97.7, 96.6, 82.5, 40.1, 19.6. HRMS (EI) m/z calcd for $C_{16}H_{16}N_2O_5$ 316.1059, found 316.1051 (M^+). IR ν (KBr) 3077, 1661, 1606, 1489, 1188 cm^{-1}.

4.14. 4-Hydroxy-7,7-*N*,*N*-dimethylamino-3-(3-methyl-2-butenyl)coumarin (27)

To a solution of **23** (300 mg, 1.10 mmol) in methanol (15 mL) was added sodium borohydride (83 mg, 2.20 mmol) at room temperature. The resulting mixture was irradiated in a photoreactor under a 354 nm light for 2 h. The solvent was then concentrated in vacuo and water (40 mL) was added. The product was extracted with methylene chloride. The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (2:8 EtOAc/hexanes) to give a white solid **27** with a 10% yield (compound **23** was recovered in a 78% yield). R_f=0.40 (30% EtOAc/hexanes). Mp 99–100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J=9.0 Hz, 1H), 6.61 (dd, J=9.0, 2.4 Hz, 1H), 6.48 (d, J=2.4 Hz, 1H), 5.44 (tq, J=7.5, 1.5 Hz, 1H), 3.38 (d, J=7.5 Hz, 2H), 3.04 (s, 6H), 1.85 (s, 3H), 1.83 (d, J=1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 162.1, 154.5, 152.9, 138.2, 123.3, 121.0, 108.7, 104.7, 98.0, 97.6, 40.2, 25.8, 23.7, 18.1. HRMS (EI) m/z calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1362 (M^+). IR ν (KBr) 2923, 1700, 1616, 1528, 1380, 1232, 1120 cm^{-1}.

4.15. Procedure for the reduction of 10b and oxidation of 28

To a solution of **10b** (500 mg, 1.26 mmol) in methanol (20 mL) was added sodium borohydride (57.4 mg, 1.52 mmol). The mixture was stirred at room temperature for 5 min and water was then added. The reduced product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a white solid **28**, quantitatively. R_f=0.25 (30% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (d, J=8.7 Hz, 1H), 7.39–7.05 (m, 10H), 6.48 (dd, J=9.0, 2.4 Hz, 1H), 6.24 (d, J=2.4 Hz, 1H), 6.05 (t, J=6.9 Hz, 1H), 3.11 (d, J=6.9 Hz, 2H), 2.90 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.8, 155.0, 151.6, 143.5, 140.2, 137.7, 132.6, 130.2, 128.0, 126.8, 126.5, 126.3, 125.2, 107.0, 97.4, 40.3, 24.9. HRMS (EI) m/z calcd for $C_{26}H_{23}NO_3$ 397.1678, found 397.1682 (M^+). IR ν (KBr) 1725, 1643, 1609, 1441, 1203, 1114 cm^{-1}. To a solution of **28** (500 mg, 1.25 mmol) in methylene chloride (30 mL) was added DDQ (286 mg, 1.25 mmol) at room temperature. The oxidation was monitored by TLC and completed within 3 min.

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References and notes

1. Bouas-Laurent, H.; Dürr, H. *Pure Appl. Chem.* **2001**, *73*, 639–665.
2. Becker, R. S.; Michl, J. *J. Am. Chem. Soc.* **1966**, *88*, 5931–5933.
3. Ahluwalia, V. K.; Arora, K. K.; Mukherjee, I. *Heterocycles* **1984**, *22*, 223–227.
4. Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741–1753.
5. Peters, A.; Vitols, C.; McDonald, R.; Branda, N. R. *Org. Lett.* **2003**, *5*, 1183–1186.
6. Fischer, E.; Hirshberg, Y. *J. Chem. Soc.* **1952**, 4522–4524.
7. Davis, R.; Tamaoki, N. *Org. Lett.* **2005**, *7*, 1461–1464.

8. Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, *1*, 49–51.
9. (a) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360–366; (b) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Asami, K.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1717–1718.
10. Chen, Y. S.; Kuo, P. Y.; Shie, T. L.; Yang, D. Y. *Tetrahedron* **2006**, *62*, 9410–9416.
11. Illos, R. A.; Shamir, D.; Shimon, L. J.; Zibermann, I. W.; Bittner, S. *Tetrahedron Lett.* **2006**, *31*, 5543–5546.
12. Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1990**, *73*, 1865–1878.
13. Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Synthesis* **2003**, *8*, 1286–1291.
14. Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857–859.