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Convenient synthesis of linear pyrano[3,2-*g*]-, [2,3-*g*]- and angular pyrano[3,2-*f*]coumarins from 4[(1,1-dimethyl-2-propynyl)oxy]phenol☆

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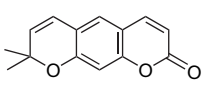
Abstract—An easy preparation of new 4-alkoxycarbonyl angular and linear pyranocoumarins starting from 4-[(1,1-dimethyl-2-propynyl)-oxy]phenol and their transformation to the known coumarins xanthyletin, 8,8-dimethylpyrano[3,2-*f*]chromen-3(8*H*)-one and 7,7-dimethyl-pyrano[2,3-*g*]chromen-2(7*H*)-one is described.

1. Introduction

Several linear and angular pyranocoumarins, like xanthyletin (**I**) and seselin (**II**) have been isolated from natural sources.[1–5] These compounds are known to possess useful biological activities.[3–6] Thus, xanthyletin shows[4] antifungal, insecticidal, anticancer, and anti-HIV activities, while seselin is used as a photoactive drug for skin disorders.[5] For the syntheses of these compounds various methods have been developed.[4–11]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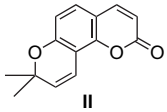
II

Thus, the 7-(1,1-dimethyl-prop-2-ynyl)ethers of coumarins, when heated, at reflux in *N*,*N*-dimethylaniline, gave the angular pyranocoumarins with cyclization taking place at the more reactive 8-position. If the 8-position is substituted however, the corresponding 8-substituted linear pyranocoumarins are obtained.[6–8] Thermal [3,3]-sigmatropic rearrangement of 6-prop-2-ynyloxycoumarins also resulted in the efficient synthesis of angular pyrano[3,2-*f*]chromen-2(7*H*)-ones.[9] Angular pyranocoumarins were also obtained from both 5- and 7-hydroxycoumarins and 1,1-diethoxy-3-methyl-2-butene,[10] while seselin and seselin derivatives were conveniently prepared in a two-step approach from 2,4-dihydroxybenzaldehyde and 2,4-dihydroxyacetophenone, using Claisen rearrangement and Wittig reaction.[5] 6-Hydroxy-2,2-dimethyl-2*H*-chromen-7-carbaldehyde and 7-hydroxy-2,2-dimethyl-2*H*-chromen-6-carbaldehyde, prepared earlier by the formylation of the corresponding 6-methoxy- and 7-methoxy-chromene derivatives and subsequent demethylation, were effectively converted into the corresponding linear pyranocoumarins by refluxing with *N*,*N*-dimethylacetamide dimethylacetal.[11]

4-Alkoxycarbonylcoumarins have been prepared earlier,[12,13] mainly by our group, from the reaction of *o*-quinones with alkoxycarbonylmethylene(triphenyl)phosphoranes ($Ph_3P{=}CHCOOR$) via an initial Wittig monoolefination to the corresponding *o*-quinonemethide, which by further Michael addition of a second ylide species followed by Hofmann elimination of Ph_3P, and finally by δ-lactonization gives rise to the corresponding coumarins. Recently Yavari and co-workers reported[14] that reactions of phenols with DMAD in the presence of Ph_3P lead to the corresponding 4-methoxycarbonylcoumarins via an initial addition of Ph_3P to the acetylenic ester and a concominant protonation of the reactive 1:1 adduct, followed by electrophilic attack of the vinyltriphenylphosphonium cation formed to the aromatic ring, in the *ortho* position relative to the strongly activating PhO-group.

Brown and co-workers in 1990 reported[15] the synthesis of 4-[(1,1-dimethyl-2-propynyl)oxy]phenol **1** from hydroquinone, which by refluxing in *o*-xylene afforded 2,2-dimethylchromen-6-ol **2**. Oxidation of **2** with Fremy's salt gave 2,2-dimethyl-2*H*-chromene-6,7-dione (**3**).

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Keywords: Pyranocoumarins; Xanthyletin; Phenols; DMAD; Ph_3P; Wittig reaction; δ-Lactonization; Dealkoxycarbonylation.

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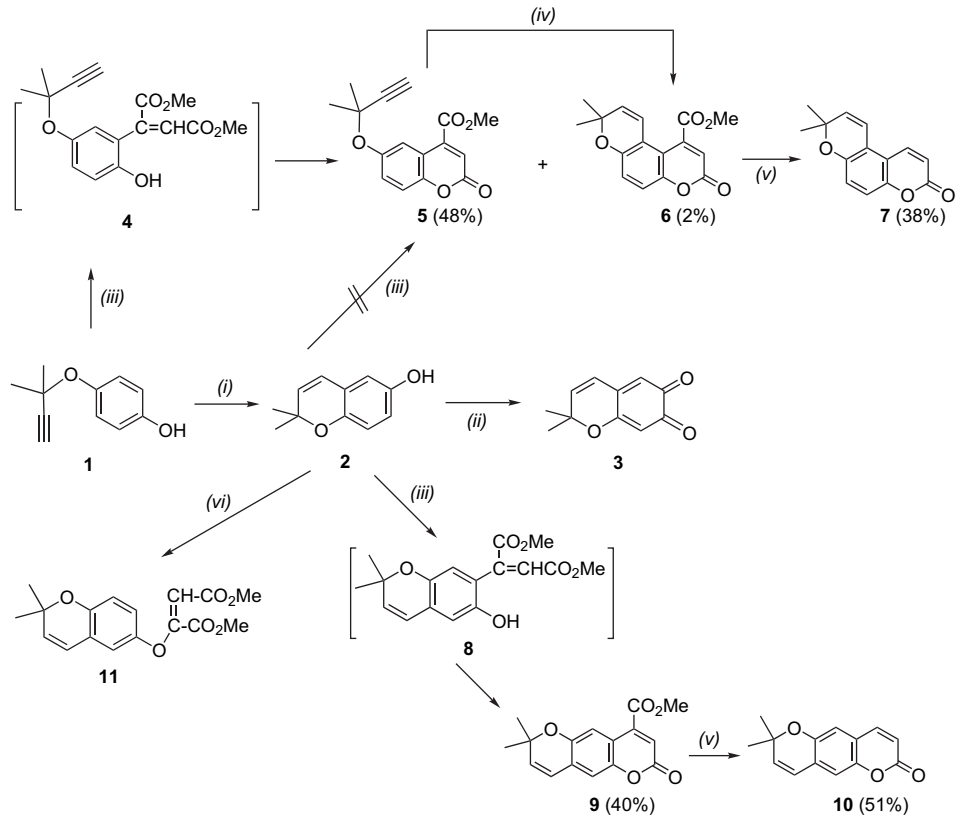
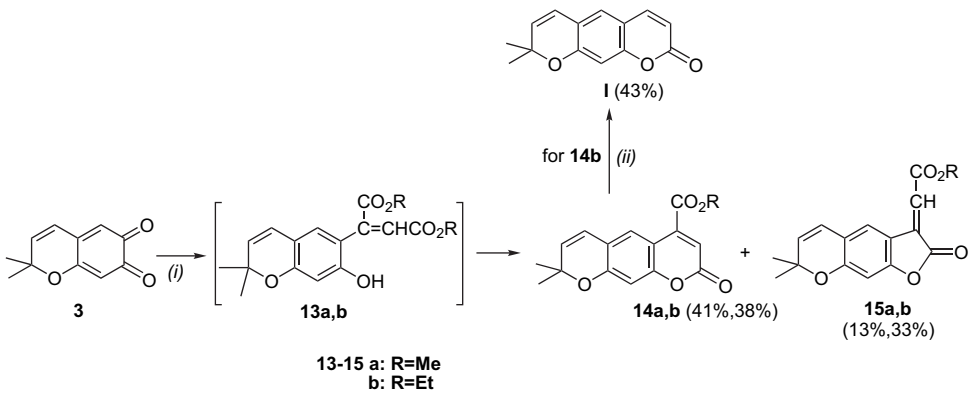


Scheme 1. Reagents and conditions: (i) Ref. 15, *o*-xylene, reflux, N_2 (91%); (ii) Ref. 15, Fremy's salt (68%); (iii) Ph_3P, DCM, DMAD (at −5 °C), reflux; (iv) *o*-xylene, reflux (77%); (v) Cu, quinoline, N_2, 175–180 °C, 19 h and (vi) DMAD, $ZnCl_2$, N_2, 100 °C, 1.5 h (23%).



Scheme 2. Reagents and conditions: (i) Ph_3P=CHCOOR (**12a**: R=Me, **b**: R=Et), DCM, rt, N_2, 30 min and (ii) Cu, quinoline, N_2, 175–180 °C, 19 h.

As a continuation of our investigation on the syntheses of coumarin derivatives,[13] we now report the easy preparation of the new coumarin derivatives **6**, **9**, and **14a**,**b** from the compounds **1**, **2**, and **3**, respectively. The reactions studied and the products obtained are depicted in Schemes 1–2.

2. Results and discussion

Treatment of phenol **1** with DMAD in the presence of Ph_3P in refluxing DCM for two days, and separation of the reaction mixture by column chromatography afforded methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (**5**) and methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (**6**) in 48% and 2% yields, respectively. Compound **5** by refluxing in *o*-xylene for 20 h gave coumarin **6** in 77% yield (Scheme 1). Obviously product **5** was obtained by δ-lactonization of the intermediate **4** and gave the angular coumarin **6** by further cyclization.[9]

When compound **1** was previously cyclized to phenol **2** according to the lit. 15 and the latter was then subjected to a similar treatment with Ph_3P and DMAD in refluxing DCM for five days, ethyl 7,7-dimethyl-2-oxo-2,7-dihydropyrano[2,3-*g*]chromene-4-carboxylate (**9**) was obtained in 40% yield. The linear coumarin **9** was obviously produced by further δ-lactonization of the intermediate **8**. Both key intermediates **4** and **8** are formed via an electrophilic attack of the vinyltriphenylphosphonium cation[14] on the aromatic

ring *ortho* to the –OH substituent of **1** and **2**, respectively. In contrast to the formation of **4** from the symmetrically substituted phenol **1**, the formation of **8** can be attributed to the attack of the vinyltriphenylphosphonium cation to the less sterically hindered 7-position (in comparison to the 5-position) of the non-symmetric phenol **2**.

We considered as an alternative path for the preparation of linear pyranocoumarins the initial transformation of phenol **2** to the known[15] quinone **3** and the reaction[12,13] of the latter with the phosphoranes $Ph_3P{=}CHCOOR$ **12a**,**b** (Scheme 2). Treatment of quinone **3** with $Ph_3P{=}CHCOOCH_3$ (**12a**) at room temperature afforded methyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[3,2-*g*]chromene-4-carboxylate (**14a**) (41%) along with methyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (**15a**) (13%) via the δ- and γ-lactonization, respectively, of the intermediate **13a**. Similarly, the reaction of **3** with $Ph_3P{=}CHCOOC_2H_5$ (**12b**) gave compounds **14b** and **15b** in 38% and 33% yield, respectively. The formation of intermediate **13** instead of **8** can be predicted from the lower electrophilicity of the C-7 C=O, due to the +R effect of the pyran ring O-atom, since this intermediate is formed by the initial Wittig monoolefination of the C-6 C=O of **3**, followed by Michael addition of a second ylide and Hofmann elimination of Ph_3P.[11,12] The IR spectra of compounds **15a**,**b** exhibited the characteristic[13a] absorption at ν_{max} ~1790 cm^{-1} for a five-member lactone carbonyl.

We also studied the reaction of phenol **2** with DMAD in the presence of $ZnCl_2$, which resulted in the formation of dimethyl 2-[(2,2-dimethyl-2*H*-chromen-6-yl)oxy]-2-butenedioate (**11**) in 23% yield, but no cyclization product was isolated.

The proposed structures of all the new pyranocoumarins **6**, **9**, and **14a**,**b** were in good agreement with their analytical and spectral data (^1H NMR, ^{13}C NMR, IR, and MS) and they are unequivocally proved via their transformation, by heating in quinoline and Cu powder, into the known 8,8-dimethylpyrano[3,2-*f*]chromen-3(8*H*)-one[9,10] (**7**) (38%), 7,7-dimethylpyrano[2,3-*g*]chromen-2(7*H*)-one[11] (**10**) (51%), and 8,8-dimethyl-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one[11] (**I**) [xanthyletin, 43% (from **14b**)], respectively. The yields for the preparation of these coumarins are comparable to the yields of the earlier preparation.[4–11]

The above mentioned synthetic approaches demonstrate their utility for the synthesis of different linear and angular pyranocoumarins, using the same starting material, depending on the reaction conditions.

3. Experimental

3.1. General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 1310 spectrophotometer as Nujol mulls. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz for ^1H and ^{13}C, respectively) using $CDCl_3$ as solvent and TMS as an internal standard. *J* values are reported in Hertz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under Electron Impact (EI) conditions. High-resolution mass spectra (HRMS) were recorded on an Ionspec mass spectrometer under Matrix-Assisted Laser Desorption-Ionization Fourier Transform Mass Spectrometer (MALDI-FTMS) conditions with 2,5-dihydroxybenzoic acid (DHB) as the matrix. Microanalyses were performed on a Perkin–Elmer 2400-II Element analyzer. Silica gel no. 60, Merck A.G. has been used for column chromatography. Compounds **1**, **2**, and **3** were prepared according to the lit. 15.

3.1.1. Procedure for the synthesis of methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (5) and methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (6). 4-[(1,1-Dimethyl-2-propynyl)oxy]phenol **1** (0.6 g, 3.41 mmol) and Ph_3P (0.893 g, 3.41 mmol) were dissolved in DCM (15 ml). A solution of DMAD (0.484 g, 0.418 ml, 3.41 mmol) in DCM (10 ml) was added dropwise over 10 min at −5 °C and the orange solution was heated under reflux for two days. Evaporation of the solvent and separation by column chromatography (hexane/DCM 1:1) followed by PTLC (silica gel, DCM) afforded **5** (0.465 g, 48%) and **6** (15 mg, 2%).

3.1.1.1. Methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (5). Yellow crystals, mp 76–78 °C (DCM/hexane); IR (Nujol) ν (cm^{-1}): 3230, 1725, 1705, 1600, 1550; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.67 (s, 6H), 2.63 (s, 1H), 4.00 (s, 3H), 6.97 (s, 1H), 7.29 (d, *J*=8.9 Hz, 1H), 7.43 (dd, *J*= 2.9 and 8.9 Hz, 1H), 8.18 (d, *J*=2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 29.4, 53.1, 73.4, 74.7, 85.4, 117.4, 118.8, 119.7, 123.8, 126.7, 142.0, 150.1, 152.0, 160.1, 164.2; MS *m/z*: 286 (M^+, 14), 271 (28), 221 (38), 220 (37), 219 (52), 192 (56), 160 (56), 134 (74), 67 (100). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 66.92; H, 4.98.

3.1.1.2. Methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano-[3,2-*f*]chromene-1-carboxylate (6). Yellow crystals, mp 98–100 °C (DCM/hexane); IR (Nujol) ν (cm^{-1}): 1720, 1705, 1600, 1555; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (s, 6H), 3.96 (s, 3H), 5.73 (d, *J*=9.8 Hz, 1H), 6.22 (d, *J*= 9.8 Hz, 1H), 6.52 (s, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 7.17 (d, *J*=8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 26.9, 53.2, 75.5, 111.6, 116.8, 117.1, 117.6, 118.9, 121.7, 131.5, 144.9, 149.2, 150.1, 159.5, 167.0; MS *m/z*: 286 (M^+, 20), 271 (100), 243 (16), 211 (10), 184 (8), 156 (4), 128 (4). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.35; H, 5.12.

3.1.2. Procedure for the preparation of methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (6). A degassed solution of coumarin **5** (0.209 g, 0.73 mmol) in *o*-xylene (40 ml) under an Argon atmosphere was heated at reflux for 20 h. The solvent was evaporated and the residue was separated by PTLC (silica gel, DCM) and gave **6** (0.161 g, 77%).

3.1.3. Procedure for the synthesis of methyl 7,7-dimethyl-2-oxo-2,7-dihydropyrano[2,3-*g*]chromene-4-carboxylate (9). 2,2-Dimethylchromen-6-ol (**2**) (0.35 g, 2 mmol) and Ph_3P (0.524 g, 2 mmol) were dissolved in DCM (10 ml). A solution of DMAD (0.284 g, 0.246 ml, 2 mmol) in DCM (5 ml) was added dropwise over 10 min period at −5 °C

and the solution was heated under reflux for five days. Evaporation of the solvent and separation by column chromatography (hexane/DCM 1:1) resulted to **9** (0.23 g, 40%); yellow crystals, mp 181–182 °C (DCM/hexane); IR (Nujol) ν (cm^{-1}): 1705, 1690, 1605, 1520; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (s, 6H), 3.99 (s, 3H), 5.87 (d, J=9.8 Hz, 1H), 6.38 (d, J=9.8 Hz, 1H), 6.87 (s, 1H), 6.97 (s, 1H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.9, 53.1, 77.7, 112.7, 113.8, 115.8, 118.7, 121.2, 125.8, 135.7, 142.1, 149.1, 149.5, 160.3, 164.3; MS *m/z*: 286 (M^+, 15), 272 (11), 271 (100), 241 (18), 156 (10), 128 (12), 91 (10). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.15; H, 4.96.

3.1.4. Procedure for the synthesis of dimethyl 2-[(2,2-dimethyl-2*H*-chromen-6-yl)oxy]-2-butenodioate (11). DMAD (0.69 g, 0.6 ml, 4.88 mmol) was added to a mixture of 2,2-dimethylchromen-6-ol (**2**) (0.5 g, 2.84 mmol) and anhydrous $ZnCl_2$ (0.387 g, 2.84 mmol) and the mixture was heated under an Argon atmosphere at 100 °C for 90 min. After cooling the mixture was partitioned in ethyl acetate (10 ml) and 10% HCl (10 ml). The organic layer was separated, washed with H_2O (10 ml), dried by anhydrous Na_2SO_4, separated by column chromatography (hexane/DCM 1:2) and gave **11** (0.208 g, 23%); colorless crystals, mp 65–66 °C (ethyl acetate/hexane); IR (Nujol) ν (cm^{-1}): 1725, 1690, 1640, 1255, 1195; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.41 (s, 6H), 3.72 (s, 3H), 3.73 (s, 3H), 5.64 (d, J=10.2 Hz, 1H), 6.25 (d, J=10.2 Hz, 1H), 6.50 (s, 1H), 6.62 (d, J=2.5 Hz, 1H), 6.69 (d, J=8.9 Hz, 1H), 6.70 (dd, J_1=2.5 Hz, J_2=8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.7, 51.9, 52.9, 76.1, 113.9, 114.1, 116.6, 116.9, 121.9, 122.0, 131.9, 148.8, 150.3, 150.4, 162.8, 164.0; MS *m/z*: 316 (M^+, 11), 304 (20), 303 (100), 161 (9), 144 (17), 132 (8), 115 (12), 91 (8). HRMS calcd for $C_{17}H_{18}O_6$ $[M]^+$ 318.1097, found: 318.1094.

3.1.5. General procedure for the preparation of the coumarins 14a,b and the furanones 15a,b. A solution of *o*-quinone **3** (1 mmol) and ylides **12a**,**b** (2.2 mmol) in dry DCM (50 ml) was stirred under an Argon atmosphere at room temperature for 1 h. The solvent was evaporated in a rotary evaporator and the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 15:1) to give products **15a**,**b** and **14a**,**b**.

3.1.5.1. Methyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano-[3,2-*g*]chromene-4-carboxylate (14a). Yellow crystals (from EtOAc/hexane); mp 186–187 °C; yield 41%; IR (Nujol) ν (cm^{-1}): 1725, 1675, 1605, 1545; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.47 (s, 6H), 3.99 (s, 3H), 5.70 (d, J=10.2 Hz, 1H), 6.36 (d, J=10.2 Hz, 1H), 6.74 (s, 2H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.2, 53.0, 77.9, 104.5, 109.5, 115.6, 118.7, 121.1, 123.9, 131.2, 142.0, 155.8, 157.2, 160.4, 164.6; MS *m/z*: 286 (M^+, 10), 272 (17), 271 (81), 244 (10), 243 (11), 184 (7), 156 (11), 128 (14), 91 (100). HRMS calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0914, found: 287.0910.

3.1.5.2. Methyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (15a). Yellow crystals (from EtOAc/hexane); mp 129–131 °C; yield 13%; IR (Nujol) ν (cm^{-1}): 1795, 1702, 1625, 1598; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (s, 6H), 3.86 (s, 3H), 5.62 (d, J=10.2 Hz, 1H), 6.37 (d, J=10.2 Hz, 1H), 6.55 (s, 1H), 6.70 (s, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.4, 29.7, 52.2, 78.3, 99.8, 113.6, 117.1, 120.2, 121.6, 126.8, 129.4, 133.5, 157.7, 158.9, 166.0, 168.2; MS *m/z*: 286 (M^+, 14), 272 (17), 271 (100), 243 (10), 184 (7), 156 (9), 128 (10), 115 (7). HRMS calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0914, found: 287.0910.

3.1.5.3. Ethyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[3,2-*g*]-chromene-4-carboxylate (14b). Yellow crystals (from Et_2O/hexane); mp 151–152 °C; yield 38%; IR (Nujol) ν (cm^{-1}): 1720, 1690, 1605, 1550; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.42 (t, J=7.6 Hz, 3H), 1.47 (s, 6H), 4.44 (q, J=7.6 Hz, 2H), 5.70 (d, J=10.2 Hz, 1H), 6.37 (d, J=10.2 Hz, 1H), 6.74 (s, 2H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 28.4, 62.3, 77.9, 104.5, 109.6, 115.5, 118.7, 121.2, 124.0, 131.2, 142.4, 155.8, 157.2, 160.6, 164.1; MS *m/z*: 300 (M^+, 46), 285 (100), 257 (49), 229 (8), 213 (8), 185 (42), 156 (12), 128 (16). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.86; H, 5.34.

3.1.5.4. Ethyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (15b). Yellow crystals (from EtOAc/hexane); mp 138–140 °C; yield 33%; IR (Nujol) ν (cm^{-1}): 1788, 1705, 1600, 1575; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.37 (t, J=7.6 Hz, 3H), 1.47 (s, 6H), 4.31 (q, J=7.6 Hz, 2H), 5.61 (d, J=10.2 Hz, 1H), 6.37 (d, J=10.2 Hz, 1H), 6.55 (s, 1H), 6.70 (s, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.2, 28.4, 29.7, 61.2, 78.2, 99.7, 113.6, 117.7, 120.8, 121.6, 126.8, 129.4, 133.3, 157.6, 158.8, 165.6, 168.3; MS *m/z*: 300 (M^+, 14), 285 (100), 259 (14), 258 (30), 257 (27), 229 (10), 213 (12), 185 (45), 156 (22), 128 (55), 115 (29), 69 (60). HRMS calcd for $C_{17}H_{17}O_5$ $[M+H]^+$ 301.1070, found: 301.1060.

3.1.6. General procedure for the dealkoxycarbonylation of the coumarin derivatives 6, 9, and 14b. A mixture of coumarin derivative **6** or **9** or **14b** (0.32 mmol) and copper powder (0.66 mmol) in dry quinoline (5 ml) was heated under an Argon atmosphere at 175–180 °C for 19 h. After cooling, ethyl acetate (50 ml) was added, the copper powder was filtered and the residue was treated with 5% HCl (50 ml). The water layer was washed with ethyl acetate (50 ml) and the combined organic layers were washed with water (50 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated in a rotary evaporator and the residue was subjected to column chromatography (silica gel, DCM) to give the coumarin derivatives **7**[9,10] (38%), **10**[11] (51%), and **I**[11] (43%).

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