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Synthesis of Substituted Coumarins via Brønsted Acid Mediated Condensation of Allenes with Substituted Phenols or Anisoles

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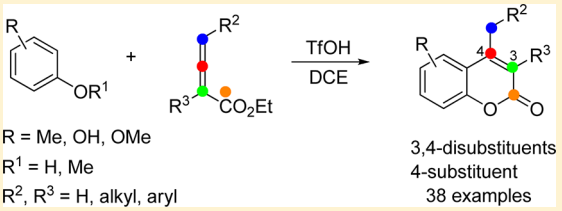
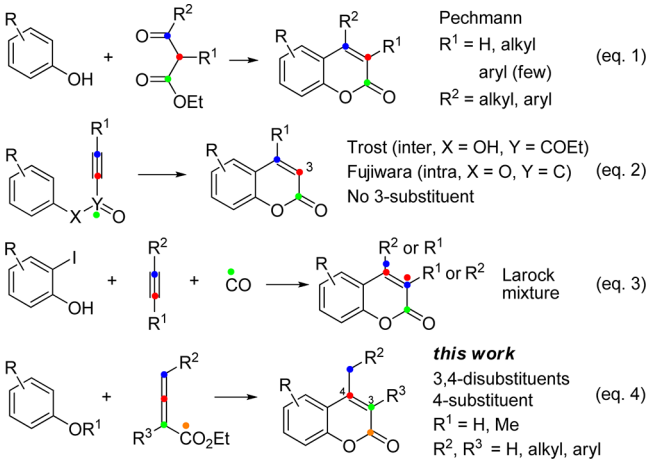
Supporting Information

ABSTRACT: Coumarins were obtained from the condensation of electron-rich arenes with allenes in the presence of TfOH in good yield. Depending on the substituent pattern of allenes employed, the general synthetic method of 4-substituted and 3,4-disubstituted 3-arylcoumarins has been developed. Readily available allenes were employed as the three-carbon atom sources constituting the coumarin skeleton.



INTRODUCTION

While coumarins have been used as an important phamacophore displaying interesting biological activities,[1] they are also frequently employed in materials science as highly efficient organoelectroluminescent materials, especially in recent years.[2] This aspect has led to extensive synthetic efforts to obtain more diverse coumarin derivatives. For example, Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions were conventionally employed for the synthesis of the coumarin skeleton.[3] Among these, the Pechmann reaction is the most widely used method (eq 1), consisting of the condensation of phenols with β-ketoesters in the presence of a variety of reagents, mainly producing 4-substituted coumarins.[3,4] Several acid catalysts have been used in the Pechmann reaction, including sulfuric acid, aluminum chloride, phosphorus pentoxide, or trifluoroacetic acid.[3−5] However, these catalysts have to be used in excess and, in some cases, the reaction provides undesired side products, such as chromones, in addition to coumarins. Recently, a wide range of Lewis acids have been examined as an alternative to the conventional acids in the Pechmann reaction for the formation of coumarins.[6] More recent research emphasis has been centered on the use of Pd-catalyzed C−C bond formation producing 3- or 4-substituted coumarins.[7] Trost et al. developed an atom-economic synthesis of coumarins from the intermolecular reaction of propiolic acids with phenols in the presence of palladium catalysts in formic acid (eq 2).[8] Fujiwara et al. also reported a direct synthesis of coumarins by Pd-catalyzed inter- and intramolecular hydroarylation of aryl propiolates.[9] Unfortunately, these methods could not be applied to the synthesis of coumarins having substituents at the 3-position. Larock et al. described that Pd-catalyzed annulation of internal alkynes by *o*-iodophenols in the presence of CO results in formation of coumarins (eq 3).[10] However, the generation of regioisomeric mixtures is unavoidable when unsymmetrical alkynes are employed. Although the synthetic strategies to functionalized coumarins by using other transition-metal-catalyzed reactions have also been reported,[11] most of them depend on the functionalization of a preformed coumarin nucleus.[12] Thus, it is of great interest to develop a novel synthetic route to coumarins having diverse substituents from intermolecular reaction of a new precursor without using preformed coumarins. Herein, we report a versatile synthetic method of coumarins using allenes, and depending on the substituent pattern of those readily available starting materials, a general synthetic method of 4-substituted and 3,4-disubstituted 3-arylcoumarins is also described (eq 4).



RESULTS AND DISCUSSION

Recently, we have been interested in the transition-metal-catalyzed intermolecular hydroarylation and, thus, examined the reaction of 1,3,5-trimethoxybenzene (**1a**) with ethyl 2-benzyl-2,3-butadienoate (**2a**). However, a condensing product, 3-benzyl-5,7-dimethoxy-4-methylcoumarin (**3a**), was unexpectedly detected instead of a desired hydroarylated product. Considering the fact that there are few synthetic methods of coumarins using allenes[13] and that a direct introduction of 3,4-

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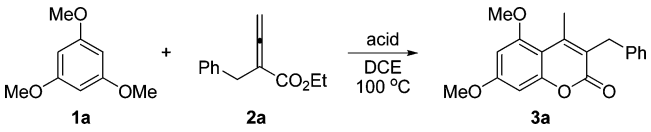
disubstituents, including the 3-aryl group, on coumarins from an intermolecular reaction is highly challenging, we decided to further investigate the condensation reaction of **1a** with **2a** under various conditions (Table 1). Another important

Table 1. Optimization for Preparation of Coumarins



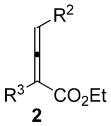
entry	acid (equiv)	time (h)	yield (%)
1	CH_3CO_2H (1)	24	0
2	CF_3CO_2H (1)	24	0
3	*p*-TsOH (1)	15	0
4	PPTS[a] (1)	15	0
5	TfOH (0.05)	48	21
6	TfOH (0.1)	24	35
7	TfOH (1)	10	86

[a]Pyridinium *p*-toluene sulfonate.

motivation for this study is the ready availability of allenes with wide structural diversity based on our previous work,[14] in which highly practical syntheses of allenes were achieved by the Pd-catalyzed cross-coupling reactions of organoindium reagents. Reactions of **1a** with **2a** in the presence of a wide range of acids, such as acetic acid, trifluoroacetic acid, *p*-toluenesulfonic acid, and PPTS, in DCE at 100 °C did not proceed (Table 1, entries 1−4). Treatment of **1a** and **2a** with trifluoromethanesulfonic acid (TfOH, 5 mol %) furnished **3a** in 21% yield (entry 5). Increasing the amount of TfOH to 10 mol % in DCE (100 °C, 24 h) afforded the better result (35% yield, entry 6). Finally, the best result was obtained with 1 equiv of TfOH, producing **3a** in 86% yield in DCE at 100 °C after 10 h (entry 7).

With this newly developed protocol, a variety of allenes (Scheme 1), which can be readily prepared by a Pd-catalyzed

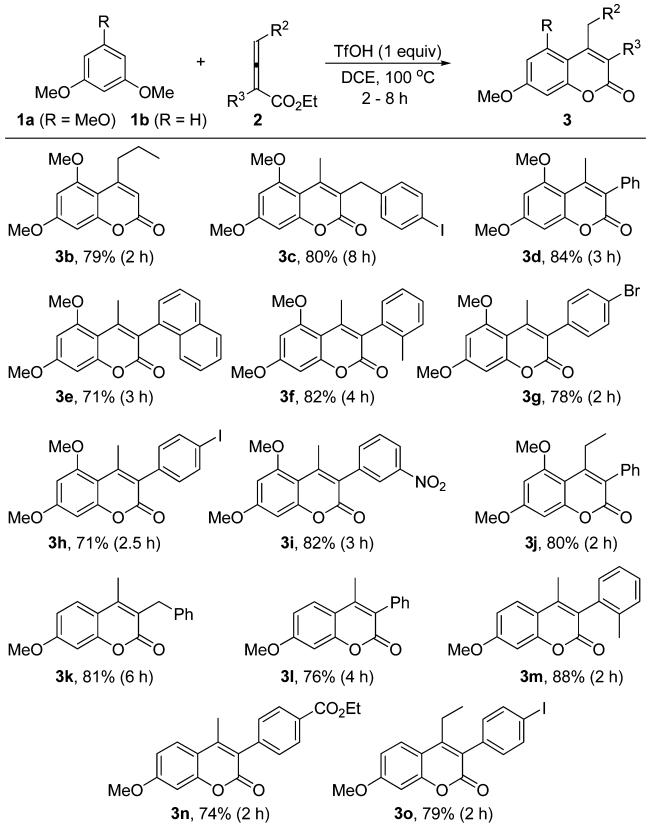
Scheme 1. A Variety of Allenes



2a : R^2 = H, R^3 = Bn
2b : R^2 = Et, R^3 = H
2c : R^2 = H, R^3 = 4-I-$C_6H_4CH_2$
2d : R^2 = H, R^3 = Ph
2e : R^2 = H, R^3 = 1-Naph
2f : R^2 = H, R^3 = 2-Me-C_6H_4
2g : R^2 = H, R^3 = 4-Br-C_6H_4
2h : R^2 = H, R^3 = 4-I-C_6H_4
2i : R^2 = H, R^3 = 3-NO_2-C_6H_4
2j : R^2 = Me, R^3 = Ph
2k : R^2 = H, R^3 = 4-EtO_2C-C_6H_4
2l : R^2 = Me, R^3 = 4-I-C_6H_4
2m : R^2 = H, R^3 = H
2n : R^2 = Ph, R^3 = H
2o : R^2 = H, R^3 = 4-Br-$C_6H_4CH_2$
2p : R^2 = H, R^3 = 2-Naph-CH_2
2q : R^2 = Me, R^3 = Bn
2r : R^2 = H, R^3 = 4-Me-$C_6H_4CH_2$

cross-coupling reaction with organoindium reagents, were subjected to undergo the intermolecular condensation reaction (Table 2). Treatment of electron-rich arene **1a** with 1,3-disubstituted allene **2b** in the presence of TfOH (1 equiv) produced 4-*n*-propylcoumarin **3b** in 79% yield. 1,1-Disubstituted allene **2c** bearing a 4-iodo benzyl group at the 2-position proceeded efficiently to provide 3,4-disubstituted coumarin **3c** in 80% yield. Although the introduction of an aryl group on the 3-position of coumarin is generally difficult, 4-methyl-3-phenylcoumarin (**3d**) was obtained in 84% yield when **1a** was treated with **2d** under the optimized reaction conditions. Encouraged by these results, we extended the scope of the reaction further with a wide range of 1,1-disubstituted allenes **2** having an aryl group. 2-(1-Naphthyl)allenoate (**2e**) underwent

Table 2. TfOH-Mediated Preparation of Coumarins



the condensation reaction with similar efficiency, producing **3e** in 71% yield. Electronic variation (2-methyl, 4-bromo, 4-iodo, and 3-nitro groups) on the phenyl ring did not much influence the reaction efficiency, although an iodo substituent slightly lowered the product yield. Direct introduction of bromo- and iodo-phenyl groups at the 3-position of coumarin is very important for further functionalizations via cross-coupling reactions. Reaction of ethyl 2-phenyl-2,3-pentadienoate (**2j**), which is a 1,1,3-trisubstituted allene, with **1a** afforded 4-ethyl-3-phenylcoumarin (**3j**) in 80% yield. 1,3-Dimethoxybenzene (**1b**) underwent the regioselective condensation with **2a** to give 3-benzyl-7-methoxy-4-methylcoumarin (**3k**) in 81% yield. Importantly, a constitutional isomer of **3k**, 3-benzyl-5-methoxy-4-methylcoumarin, was not detected in this reaction. 1,1-Disubstituted allenes (**2d** and **2f**) bearing phenyl and *o*-tolyl groups also gave good yields of the desired coumarins (**3l** and **3m**). High functional group tolerance was observed, as demonstrated in the reaction of allenes bearing an ethoxycarbonyl group. The condensation reaction of 1,1,3-trisubstituted allenes **2l** took place in high yield to afford **3o**.

With the optimal conditions in hand, we next examined the scope and limitation of our method (Table 3). 1,3-Dihydroxybenzene (**1c**) was condensed with ethyl 2,3-butadienoate (**2m**) to produce selectively 7-hydroxy-4-methylcoumarin (**4a**) in 81% yield. When **1c** was reacted with 1,3-disubstituted allenes (**2b** and **2n**), the corresponding coumarins (**4b** and **4c**) having 4-*n*-propyl and benzyl groups were obtained. 1,1-Disubstituted allenes (**2a**, **2o**, and **2p**) worked equally well in the condensation with **1c**, producing 3,4-disubstituted coumarins, including 3-benzyl-7-hydroxy-4-methylcoumarin derivatives (**4d**, **4e**, and **4f**), in good yields. In addition, we were pleased to obtain 3-benzyl-4-ethyl-7-

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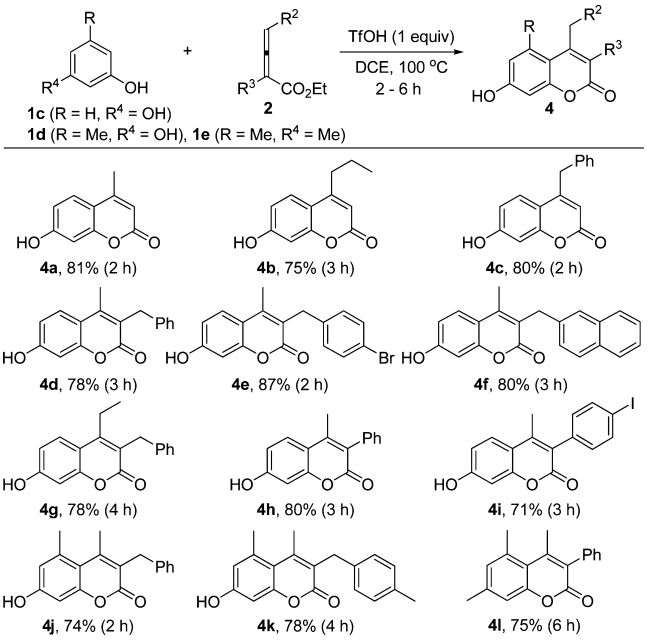
Table 3. TfOH-Mediated Preparation of Coumarins

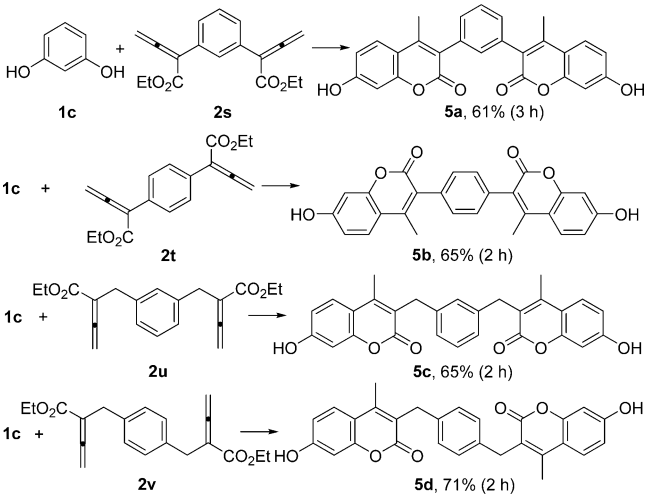


hydroxycoumarin (**4g**) from 1,1,3-trisubstituted allene (**2q**). In addition, phenyl or 4-iodophenyl groups at the 3-position of coumarin could be efficiently introduced by the current method, which was demonstrated by obtaining the 3,4-disubstituted coumarins (**4h** and **4i**). No regioisomeric coumarin products, such as 5-hydroxycoumarin, were isolated in all cases. The present method turned out to be compatible with the reaction of 1,3-dihydroxy-5-methylbenzene (**1d**) with **2a** and **2r**, resulting in selectively **4j** and **4k** in 74% and 78% yields, respectively. 3,5-Dimethylphenol (**1e**) did not diminish the condensation efficiency, albeit requiring a longer reaction time (6 h).

We were also interested in the synthesis of bis(coumarins) from the reaction of electron-rich arenes with bis(allenes) through a 2-fold condensation reaction in one pot (Scheme 2). Treatment of **1c** (1 equiv) with 0.5 equiv of 1,3- or 1,4-bis(allenes) (**2s** and **2t**) in the presence of TfOH (1 equiv) produced efficiently bis(coumarins) **5a** and **5b** in 61% and 65% yields, respectively. In the case whereby one more carbon between the phenyl and allenyl groups was extended, **1c** underwent the 2-fold condensation with **2u** and **2v**, leading to bis(coumarins) **5c** and **5d** in moderate yield under the standard reaction conditions.

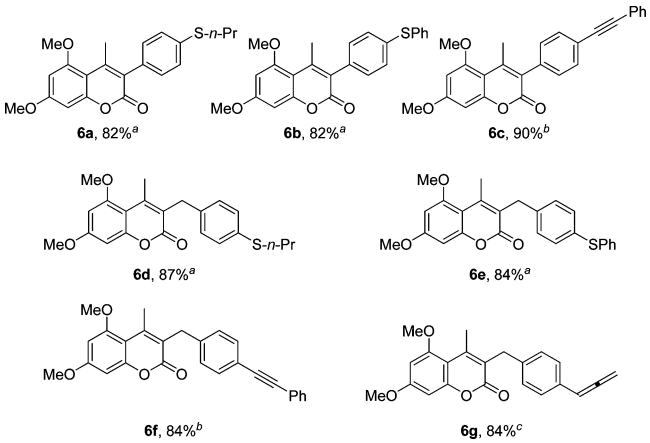
Since 3-(4-bromophenyl)coumarin (**3g**) or 3-(4-iodophenyl)coumarin (**3h**) are in hand now, we explored the possibility of further transformation via a cross-coupling reaction (Table 4). The reaction of **3h** with $In(S\text{-}n\text{-}Pr)_3$,

Scheme 2. TfOH-Catalyzed Preparation of Bis(coumarins)[a]



[a]Conditions: **2s**–**2v**, (50 mol %) and TfOH (100 mol %) were used, DCE, 100 °C.

Table 4. Coumarin Derivatization via Cross-Coupling Reaction[a,b,c]

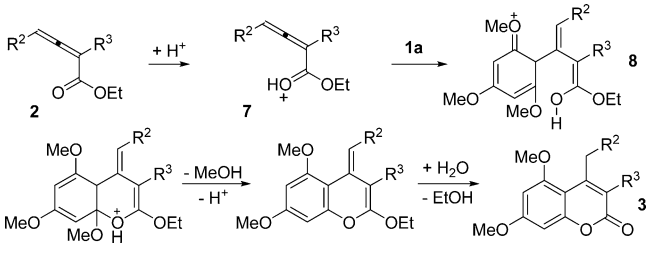


[a]$Pd(OAc)_2$ (4 mol %), Xantphos (4.2 mol %), DIPEA (100 mol %), $In(SR^5)_3$ (34 mol %), DMF, 100 °C, 1 h. [b]$Pd_2(dba_3)CHCl_3$ (2 mol %), Ph_3P (16 mol %), CuI (10 mol %), Et_3N (300 mol %), phenylacetylene (1.2 equiv), DMF, 100 °C, 3 h. [c]$Pd_2(dba_3)CHCl_3$ (2 mol %), Ph_3P (16 mol %), LiCl (300 mol %), In (100 mol %), propargyl bromide (150 mol %), DMF, 100 °C, 3 h

$In(SPh)_3$,[15] and phenylacetylene in the presence of palladium catalyst proceeded efficiently to produce the synthetically valuable 3,4-disubstituted coumarins (**6a**, **6b**, and **6c**), including the π-extended coumarin. Also, **3c** was converted into the functionalized 3,4-disubstituted coumarins (**6d**, **6e**, **6f**, and **6g**) in good yields through indium-mediated thiopropyl, thiophenyl, and allenyl coupling reactions[16] and the Sonogashira reaction.[17]

Although the mechanism of the present reaction has not been fully established at the present stage, a possible reaction pathway is shown in Scheme 3. Nucleophilic 1,4-addition of the aromatic carbon of the trimethoxybenzene (**1a**) to the proton-activated allenyl ester **7** might have occurred to afford **8**. Intramolecular addition and aromatization, followed by hydrolysis, could then give the corresponding 3,4-disubstituted

Scheme 3. Plausible Mechanism



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coumarins **3**. Exclusive formation of coumarins having an oxygen atom on the 7-position can be attributed to steric and electronic effects.

CONCLUSION

In conclusion, we have developed a highly efficient and practical route to substituted coumarins using a Brønsted acid mediated condensation reaction under metal-free conditions. Coumarins having 4-substituents, 3,4-disubstituents, and 2-aryl groups could be obtained, which were not easily accessible through the precedent procedures. Significantly, readily available allenes were employed as a three-carbon atom source constituting the coumarin skeleton. Considering the fact that a wide range of diversely substituted allenes can be easily prepared by our previous Pd-catalyzed cross-coupling reactions, the present synthetic procedure of coumarins is anticipated to be widely applied in organic synthesis, medicinal chemistry, and materials science.

EXPERIMENTAL SECTION

General Methods. A variety of chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out on precoated plates and visualized with UV light or stained with potassium permanganate. ^{1}H and ^{13}C NMR spectra were measured at 298 K on a 400 Fourier Transform NMR spectrometer. Chemical shifts were reported in δ (parts per million), relative to the internal standard of TMS. The signals observed were described as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplets). The number of protons (n) for a given resonance was indicated as nH. Coupling constants are reported as J values in hertz. ^{13}C NMR are reported as δ (parts per million) in downfield from TMS and relative to the signal of chloroform-d (δ 77.00, triplet). Mass spectrometry was performed on a GC/HRMS spectrometer (KBSI) under the electron impact (EI) ionization technique (magnetic sector−electric sector double focusing mass analyzer).

Synthesis of 3-Benzyl-5,7-dimethoxy-4-methylcoumarin (3a). In a V-vial, 1,3,5-trimethoxybenzene (50.0 mg, 0.3 mmol) was added to a solution of ethyl 2-benzyl-2,3-butadienoate (61.0 mg, 0.3 mmol) and TfOH (45.0 mg, 0.3 mmol) in dichloroethane (1.0 mL). The reaction mixture was stirred at 100 °C for 10 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give 3-benzyl-5,7-dimethoxy-4-methylcoumarin **3a** (80.0 mg, 86%). Yellow solid, melting point 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.26−7.24 (m, 4H), 7.18−7.16 (m, 1H), 6.44 (s, 1H), 6.29 (s, 1H), 4.03 (s, 2H), 3.83 (s, 6H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) 162.5, 162.4, 159.4, 155.8, 150.6, 139.9, 128.8, 128.6, 126.5, 121.2, 105.9, 96.1, 93.5, 56.1, 56.0, 32.9, 20.3; IR (KBr) 2939, 1706, 1597, 1455, 1224, 1205 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{18}O_4$, 310.1205; found, 310.1207.

5,7-Dimethoxy-4-propylcoumarin (3b):[18] 79% yield (58.8 mg), white solid, melting point 117−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 6.46 (s, 1H), 6.31 (s, 1H), 5.97 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.86 (dd, J = 7.5, 7.8 Hz, 2H), 1.64−1.59 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 163.0, 161.7, 159.1, 158.6, 157.7, 111.1, 104.7, 96.0, 94.0, 56.2, 56.1, 38.9, 23.2, 14.5; IR (KBr) 2961, 1709, 1601, 1449, 1156, 1116 cm^{-1}.

3-(4-Iodobenzyl)-5,7-dimethoxy-4-methylcoumarin (3c): 80% yield (104.7 mg), white solid, melting point 110−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.57 (dt, J = 8.25, 2.35 Hz, 2H), 7.00 (d, J = 8.33 Hz, 2H), 6.45 (d, J = 2.46 Hz, 1H), 6.31 (d, J = 2.46 Hz, 1H), 3.96 (s, 2H), 3.85 (d, J = 1.95 Hz, 6H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.1, 162.0, 159.0, 155.5, 139.3, 137.5, 130.3, 120.2, 105.4, 95.8, 93.1, 91.2, 55.8, 55.7, 32.1, 20.0; IR (film) 3006, 2964, 2939, 1704, 1616, 1596, 1158, 1133, 822 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{17}IO_4$, 436.0172; found, 436.0173.

5,7-Dimethoxy-4-methyl-3-phenylcoumarin (3d): 84% yield (74.7 mg), pale yellow solid, melting point 154−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.45−7.41 (m, 2H), 7.38−7.34 (m, 1H), 7.28−7.25 (m, 2H), 6.48 (s, 1H), 6.33 (s, 1H), 3.86 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.8, 161.5, 159.8, 156.3, 150.5, 135.7, 130.8, 128.8, 128.1, 123.8, 105.8, 96.1, 93.6, 56.2, 56.1, 21.9; IR (KBr) 2940, 2843, 1714, 1616, 1592, 1459, 1159, 1113 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{16}O_4$, 296.1049; found, 296.1052.

5,7-Dimethoxy-4-methyl-3-(1-naphthyl)coumarin (3e): 71% yield (73.8 mg), pale green solid, melting point 178−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.91−7.84 (m, 2H), 7.62−7.37 (m, 5H), 6.56 (s, 1H), 6.37 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.6, 160.9, 159.5, 156.3, 152.0, 133.8, 133.0, 132.1, 128.6, 128.4, 128.1, 126.4, 125.9, 125.6, 124.9, 121.4, 95.7, 93.3, 55.8, 55.7, 21.5; IR (KBr) 2933, 1708, 1589, 1186, 1156, 1124 cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{18}O_4$, 346.1205; found, 346.1204.

5,7-Dimethoxy-4-methyl-3-(2-methylphenyl)coumarin (3f): 82% yield (76.3 mg), pale yellow solid, melting point 168−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.30−7.23 (m, 3H), 7.10 (d, J = 6.8 Hz, 1H), 6.51 (s, J = 2.42 Hz, 1H), 6.35 (s, J = 2.54 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.8, 160.9, 159.8, 156.5, 151.0, 137.5, 135.3, 130.6, 130.5, 128.5, 126.5, 123.3, 105.6, 95.1, 93.6, 56.2, 56.1, 21.3, 19.9; IR (KBr) 2941, 1714, 1616, 1593, 1158 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{18}O_4$, 310.1205; found, 310.1205.

3-(4-Bromophenyl)-5,7-dimethoxy-4-methylcoumarin (3g): 78% yield (87.8 mg), pale yellow solid, melting point 147−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.56 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.48 (s, 1H), 6.34 (s, 1H), 3.87 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 161.6, 159.8, 158.4, 154.9, 149.5, 133.2, 131.1, 130.6, 104.2, 94.8, 92.2, 54.8, 54,7, 20.5; IR (KBr) 1694, 1613, 1594, 1158, 1093, 822 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{15}BrO_4$, 374.0154; found, 374.0157.

3-(4-Iodophenyl)-5,7-dimethoxy-4-methylcoumarin (3h): 71% yield (89.9 mg), pale brown solid, melting point 178−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.77 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.48 (s, 1H), 6.34 (s, 1H), 3.87 (s, 6H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 163.0, 161.2, 159.8, 156.3, 150.8, 138.0, 135.3, 132.8, 122.8, 105.7, 96.2, 94.1, 93.6, 56.2, 56.1, 22.0; IR (KBr) 1704, 1612, 1593, 1111, 1058, 823 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{15}IO_4$, 422.0015; found, 422.0017.

5,7-Dimethoxy-4-methyl-3-(3-nitrophenyl)coumarin (3i): 82% yield (84.0 mg), white solid, melting point 118−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.15−8.12 (m, 1H), 8.06 (s, 1H), 7.55−7.49 (m, 2H), 6.40 (s, 1H), 6.26 (s, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 163.4, 161.1, 160.0, 156.4, 151.9, 148.7, 121.4, 105.4, 96.4, 93.7, 56.3, 56.2, 22.1; IR (KBr) 2249, 1711, 1608, 1160, 1084 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{15}NO_6$, 341.0899; found, 341.0896.

4-Ethyl-5,7-dimethoxy-3-phenylcoumarin (3j): 80% yield (74.5 mg), white solid, melting point 172−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.46−7.42 (m, 2H), 7.40−7.36 (m, 1H), 7.26−7.24 (m, 2H), 6.52 (s, 1H), 6.36 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.79 (q, J = 7.3 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.3, 161.4, 158.8, 156.6, 155.6, 135.3, 130.0 128.5, 127.7, 123.4, 104.3, 95.8, 93.5, 55.9, 55.7, 26.2, 14.6; IR (KBr) 2977, 1706, 1590, 1378, 1114, 1079 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{18}O_4$, 310.1205; found, 310.1207.

3-Benzyl-7-methoxy-4-methylcoumarin (3k): 81% yield (68.1 mg), white solid, melting point 115−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.49 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 4.4 Hz, 4H), 7.19−7.15 (m, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.80 (s, 1H), 4.03 (s, 2H), 3.85 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.7, 162.3, 154.4, 148.2, 139.6, 128.9, 128.7, 126.7, 126.1, 126.0, 122.5, 114.5, 112.6, 101.0, 56.1, 33.2, 15.8 ; IR (KBr)

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2936, 1712, 1608, 1385, 1285, 1161 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{16}O_3$, 280.1099; found, 280.1097.

7-Methoxy-4-methyl-3-phenylcoumarin (3l):[19] 76% yield (60.7 mg), yellow solid, melting point 96−100 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.57 (d, J = 8.7 Hz, 1H), 7.47−7.43 (m, 2H), 7.40−7.36 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 3.89 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.7, 161.8, 154.8, 148.3, 135.1, 130.6, 128.8, 128.4, 126.6, 124.7, 114.5, 112.8, 101.0, 56.2, 17.0; IR (KBr) 2936, 1714, 1606, 1381, 1269 cm^{-1}.

7-Methoxy-4-methyl-3-(2-methylphenyl)coumarin (3m):[20] 88% yield (74.0 mg), white solid, melting point 109−113 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.58 (d, J = 8.7 Hz, 1H), 7.31−7.26 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 6.92−6.88 (m, 2H), 3.90 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.8, 161.2, 155.0, 149.0, 137.4, 134.7, 130.7, 130.4, 128.8, 126.5, 124.4, 114.3, 112.7, 101.1, 56.2, 20.0, 16.6 ; IR (KBr) 1713, 1607, 1509, 1382, 1286, 1264 cm^{-1}.

3-(4-Ethoxycarbonylphenyl)-7-methoxy-4-methylcoumarin (3n): 74% yield (75.1 mg), white solid, melting point 159−163 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.13 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.9 Hz, 1H), 6.87 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 2.28 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 166.7, 163.0, 161.3, 154.9, 148.8, 139.8, 130.8, 130.5, 130.0, 126.6, 123.8, 114.2, 112.9, 101.1, 61.5, 56.2, 14.8; IR (KBr) 2995, 1702, 1603, 1287, 1257 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{18}O_5$, 338.1154; found, 338.1157.

4-Ethyl-3-(4-iodophenyl)-7-methoxycoumarin (3o): 79% yield (96.3 mg), pale brown solid, melting point 170−174 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.79 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.87 (s, 1H), 2.63 (q, J = 7.6 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 162.8, 161.7, 155.4, 154.4, 138.1, 134.7, 132.1, 122.6, 123.1, 113.0, 112.9, 101.4, 94.5, 56.2, 23.3, 14.7; IR (KBr) 2978, 1701, 1615, 1304, 1158 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{15}IO_3$, 406.0066; found, 406.0063.

7-Hydroxy-4-methylcoumarin (4a):[21] 81% yield (42.8 mg), white solid, melting point 186−189 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.71 (s, 1H), 6.13 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.5, 160.7, 155.2, 153.9, 127.0, 113.2, 112.4, 110.6, 102.5, 18.5; IR (KBr) 3231, 3033, 1695, 1585, 1255, 1080 cm^{-1}.

7-Hydroxy-4-propylcoumarin (4b):[22] 75% yield (45.9 mg), white solid, melting point 190−193 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.70 (s, 1H), 6.06 (s, 1H), 2.68 (t, J = 7.4 Hz, 2H), 1.66−1.56 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.4, 160.7, 157.2, 155.5, 126.7, 113.3, 111.6, 109.7, 102.7, 33.2, 21.7, 14.0; IR (KBr) 3350, 3053, 1678, 1615, 1235, 1077 cm^{-1}.

4-Benzyl-7-hydroxycoumarin (4c): 80% yield (60.5 mg), white solid, melting point 214−217 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.35−7.31 (m, 4H), 7.28−7.22 (m, 1H), 6.76 (d, J = 8.7 Hz, 1H), 6.71 (s, 1H), 4.13 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 162.0, 161.2, 156.6, 156.0, 138.1, 129.8, 129.5, 127.7, 127.6, 113.8, 112.0, 111.5, 103.2, 37.8; IR (KBr) 3221, 1690, 1617, 1559, 1291, 1136 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{12}O_3$, 252.0786; found, 252.0785.

3-Benzyl-7-hydroxy-4-methylcoumarin (4d): 78% yield (62.3 mg), white solid, melting point 227−230 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.28−7.14 (m, 5H), 6.80 (d, J = 8.8 Hz, 1H), 6.70 (s, 1H), 3.92 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 162.7, 160.9, 153.8, 148.9, 139.8, 128.8, 128.4, 127.1, 126.4, 120.4, 113.3, 112.8, 102.3, 32.4, 15.5; IR (KBr) 3209, 1660, 1576, 1451, 1236, 1097 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{14}O_3$, 266.0943; found, 266.0946.

3-(4-Bromobenzyl)-7-hydroxy-4-methylcoumarin (4e): 87% yield (90.1 mg), pale brown solid, melting point 254−257 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.70 (s, 1H), 3.92 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.7, 160.9, 153.8, 149.2, 139.3, 131.6, 130.7, 127.2, 112.0, 119.4, 113.3, 112.7, 102.3, 31.9, 15.5; IR (KBr) 3206, 1653, 1571, 1487, 1449, 1384, 1228, 853, 827 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{13}BrO_3$, 344.0048; found, 344.0050.

7-Hydroxy-4-methyl-3-((2-naphthyl)methyl)coumarin (4f): 80% yield (75.9 mg), white solid, melting point 226−229 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.87−7.82 (m, 3H), 7.68 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.49−7.41 (m, 3H), 6.82 (d, J = 8.8 Hz, 1H), 6.73 (s, 1H), 4.10 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.8, 160.9, 153.9, 149.3, 137.5, 133.5, 132.0, 128.3, 127.8, 127.4, 127.2, 126.4, 126.1, 125.7, 120.2, 113.3, 112.9, 102.3, 32.7, 15.6; IR (KBr) 3326, 1665, 1611, 1566, 1304, 1240, 1145, 1087 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{16}O_3$, 316.1099; found, 316.1101.

3-Benzyl-4-ethyl-7-hydroxycoumarin (4g): 78% yield (65.6 mg), white solid, melting point 173−175 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.4 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.29−7.18 (m, 5H), 6.82 (d, J = 8.8 Hz, 1H), 6.73 (s, 1H), 3.92 (s, 2H), 2.82 (q, J = 7.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.6, 160.0, 153.9, 153.7, 139.6, 128.3, 127.8, 126.4, 125.9, 119.1, 113.0, 110.9, 102.1, 31.6, 21.5, 13.4; IR (KBr) 3245, 1668, 1593, 1451, 1381, 1227 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{16}O_3$, 280.1099; found, 280.1096.

7-Hydroxy-4-methyl-3-phenylcoumarin (4h): 80% yield (60.5 mg), white solid, melting point 225−227 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.5 (s, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.46−7.38 (m, 3H), 7.30−7.28 (m, 2H), 6.84 (dd, J = 8.7 Hz, 1H), 6.75 (d, J = 2.39 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.2, 160.6, 154.2, 148.6, 135.2, 130.6, 128.4, 127.9, 127.5, 122.7, 113.3, 112.7, 102.3, 16.7; IR (KBr) 3227, 2921, 2853, 1670, 1375, 1226, 1131, 1106, 1072 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{12}O_3$, 252.0786; found, 252.0784.

7-Hydroxy-3-(4-iodophenyl)-4-methylcoumarin (4i): 71% yield (80.5 mg), white solid, melting point 266−269 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.6 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.3, 160.4, 154.2, 149.0, 137.3, 134.9, 133.0, 127.7, 121.7, 113.5, 112.7, 102.3, 94.5, 16.8; IR (KBr) 3388, 1681, 1608, 1583, 1134, 773 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{11}IO_3$, 377.9753; found, 377.9751.

3-Benzyl-7-hydroxy-4,5-dimethylcoumarin (4j): 74% yield (62.2 mg), pale green solid, melting point 211−214 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.2 (s, 1H), 7.16−7.13 (m, 2H), 7.08−7.03 (m, 3H), 6.50 (s, 1H), 6.45 (s, 1H), 3.81 (s, 2H), 2.49 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.8, 159.9, 155.6, 151.8, 140.3, 139.5, 129.3, 128.7, 126.8, 121.2, 118.1, 113.0, 101.5, 33.0, 25.7, 21.1; IR (KBr) 3163, 1658, 1578, 1385, 1169, 860 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{16}O_3$, 280.1099; found, 280.1102.

7-Hydroxy-4,5-dimethyl-3-(4-methylbenzyl)coumarin (4k): 78% yield (68.9 mg), white solid, melting point 225−229 °C; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.4 (s, 1H), 7.07 (s, 4H), 6.61 (s, 1H), 6.56 (s, 1H), 3.83 (s, 2H), 2.62 (s, 3H), 2.51 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.4, 159.4, 155.1, 151.2, 139.0, 136.7, 135.3, 129.4, 128.1, 121.0, 117.6, 112.6, 101.0, 32.1, 25.2, 20.9, 20.5; IR (KBr) 3279, 1672, 1624, 1458, 1272, 1176, 850, 785 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_3$, 294.1256; found, 294.1254.

4,5,7-Trimethyl-3-phenylcoumarin (4l): 75% yield (59.5 mg), white solid, melting point 136−138 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.47−7.43 (m, 2H), 7.40−7.36 (m, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 6.93 (s, 1H), 2.71 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 161.3, 154.4, 150.3, 141.7, 137.0, 135.8, 130.5, 130.4, 129.0, 128.4, 127.7, 118.1, 116.3, 25.4, 22.9, 21.6; IR (KBr) 1693, 1614, 1585, 1384, 1165, 1092 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{16}O_2$, 264.1150; found, 264.1152.

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Synthesis of 3,3′-(1,3-Phenylene-bis(methylene))-bis(7-hydroxy-4-methylcoumarin) (5c). In a V-vial, 1,3-dihydroxybenzene (66.0 mg, 0.6 mmol) was added to a solution of diethyl 2,2′-(1,3-phenylene-bis(methylene))dibuta-2,3-dienoate (98.0 mg, 0.3 mmol) and TfOH (90.0 mg, 0.6 mmol) in dichloroethane (1.0 mL). The reaction mixture was stirred at 100 °C for 2 h. The precipitate was collected by filtration and washed with $CHCl_3$ (10 mL × 3) to give 3,3′-(1,3-phenylenebis(methylene))-bis(7-hydroxy-4-methylcoumarin) **5c** (88.6 mg, 65%). Brown solid, melting point 307−310 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.4 (s, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 7.7 Hz, 1H), 7.08 (s, 1H), 6.99 (d, J = 7.7 Hz, 2H), 6.69 (s, 2H), 3.86 (s, 4H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) 161.7, 160.88, 153.8, 148.8, 139.8, 128.9, 128.2, 127.1, 126.0, 120.4, 113.3, 112.7, 102.3, 32.3, 15.5; IR (KBr) 3249, 1660, 1595, 1448, 1381, 1235, 1163, 1096 cm^{-1}; HRMS (EI) m/z calcd for $C_{28}H_{22}O_6$, 454.1416; found, 454.1413.

3,3′-(1,3-Phenylene)-bis(7-hydroxy-4-methylcoumarin) (5a): 61% yield (78.0 mg), pale brown solid, melting point 367−369 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C) δ 9.43 (s, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.32 (s, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.79 (s, 2H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C) 161.6, 161.1, 155.4, 149.0, 136.0, 133.6, 130.7, 128.6, 127.9, 124.0, 114.2, 113.6, 103.1, 16.8; IR (KBr) 3254, 1612, 1588, 1542, 1509, 1350, 1241, 1164, 1142 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{18}O_6$, 426.1103; found, 426.1104.

3,3′-(1,4-Phenylene)-bis(7-hydroxy-4-methylcoumarin) (5b): 65% yield (83.2 mg), brown solid, melting point above 400 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.6 (s, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.37 (s, 4H), 6.86 (d, J = 8.8 Hz, 2H), 6.77 (s, 2H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) 161.3, 160.6, 154.2, 148.9, 134.5, 130.4, 127.6, 122.4, 113.4, 112.8, 102.3, 16.9; IR (KBr) 3157, 1664, 1594, 1567, 1263, 1134, 992 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{18}O_6$, 426.1103; found, 426.1106.

3,3′-(1,4-Phenylene-bis(methylene))-bis(7-hydroxy-4-methylcoumarin) (5d): 71% yield (96.8 mg), pale brown solid, melting point above 400 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 10.4 (s, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.10 (s, 4H), 6.79 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 7.7 Hz, 2H), 6.69 (s, 2H), 3.87 (s, 4H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) 161.7, 160.8, 153.8, 148.8, 137.5, 128.4, 127.1, 120.5, 113.3, 112.8, 102.3, 32.0, 15.5; IR (KBr) 3119, 1662, 1592, 1446, 1380, 1233, 1166, 1098, 856 cm^{-1}; HRMS (FAB) m/z calcd for $C_{28}H_{22}O_6Na$, 477.1314; found, $[M + Na]^+$ 477.1312.

Synthesis of 5,7-Dimethoxy-4-methyl-3-(4-*n*-propylthio)-phenylcoumarin (6a). To a suspension of $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 4 mol %) and Xantphos (7.3 mg, 0.013 mmol, 4.2 mol %) in DMF (0.5 mL) was added 3-(4-iodophenyl)-5,7-dimethoxy-4-methylcoumarin (126.7 mg, 0.3 mmol) in DMF (0.3 mL) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 5 min, $In(S^nPr)_3$ (34.7 mg, 0.102 mmol) and DIPEA (52.3 μL, 0.3 mmol) in DMF (0.5 mL) were transferred via double-ended needle, and the mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 5,7-dimethoxy-4-methyl-3-(4-*n*-propylthio)phenylcoumarin (**6a**) as a pale brown solid (91.1 mg, 82%). Melting point 90−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.37 (dt, J = 6.51, 1.70 Hz, 2H), 7.18 (dt, J = 8.32, 1.83 Hz, 2H), 6.48 (d, J = 2.47 Hz, 1H), 6.33 (d, J = 2.43 Hz, 1H), 3.86 (d, J = 0.9 Hz, 6H), 2.94 (t, J = 7.17 Hz, 2H), 2.40 (s, 3H), 1.72 (sextet, J = 7.31 Hz, 2H), 1.05 (t, J = 7.38 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 162.8, 161.5, 159.24, 150.62, 137.17, 132.9, 131.3, 128.8, 123.3, 105.9, 96.2, 93.6, 56.2, 56.1, 35.8, 23.0, 22.0, 13.9; IR (film) 3005, 2962, 2933, 2870, 1715, 1616, 1591, 1158, 824 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{22}O_4S$, 370.1239; found, 370.1236.

5,7-Dimethoxy-4-methyl-3-(4-phenylthio)phenylcoumarin (6b): 82% yield (99.5 mg), pale yellow solid, melting point 100−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.46−7.42 (m, 2H), 7.36−7.32 (m, 4H), 7.30−7.28 (m, 1H), 7.19 (dt, J = 8.34, 1.97 Hz, 2H), 6.49 (d, J = 2.46 Hz, 1H), 6.33 (d, J = 2.43 Hz, 1H), 3.86 (d, J = 0.94 Hz, 6H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 162.9, 161.4, 159.8, 156.3, 150.8, 136.3, 135.2, 134.2, 132.3, 131.6, 130.4, 129.7, 127.9, 123.1, 105.8, 96.2, 93.6, 56.2, 56.1, 20.0; IR (film) 3056, 3003, 2924, 2851, 1715, 1615, 1590, 1158, 1113, 824 cm^{-1}; HRMS (EI) m/z calcd for $C_{24}H_{20}O_4S$, 404.1082; found, 404.1083.

5,7-Dimethoxy-4-methyl-3-(4-phenylacetylenyl)-phenylcoumarin (6c): 90% yield (107.0 mg), pale brown solid, melting point 180−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.59 (dt, J = 8.14, 1.78 Hz, 2H), 7.56−7.53 (m, 2H), 7.38−7.33 (m, 3H), 7.27 (d, J = 8.17 Hz, 2H), 6.48 (d, J = 2.37 Hz, 1H), 6.33 (d, J = 2.44 Hz, 1H), 3.85 (s, 6H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 163.0, 161.3, 159.9, 156.3, 150.8, 1358, 132.1, 132.0, 131.0, 128.8, 1287, 123.7, 123.2, 123.1, 105.8, 96.2, 93.6, 90.2, 89.7, 56.2, 56.1, 22.0; IR (film) 3054, 2986, 1714, 1616, 1594, 1265, 739, 704 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{20}O_4$, 396.1362; found, 396.1361.

5,7-Dimethoxy-4-methyl-3-(4-*n*-propylthio)benzylcoumarin (6d): 87% yield (100.4 mg), pale yellow solid, melting point 95−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.23 (dt, J = 8.32, 1.81 Hz, 2H), 7.16 (d, J = 8.23 Hz, 2H), 6.45 (d, J = 2.45 Hz, 1H), 6.31 (d, J = 2.43 Hz, 1H), 3.99 (s, 2H), 3.84 (s, 6H), 2.84 (t, J = 7.14 Hz, 2H), 2.56 (s, 3H), 1.63 (sextet, J = 7.45 Hz, 2H), 0.99 (t, J = 7.43 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 162.49, 162.42, 159.4, 155.9, 150.6, 137.8, 134.5, 130.1, 129.1, 121.0, 105.8, 96.1, 93.5, 56.14, 56.07, 365, 32.4, 23.0, 20.4, 13.8; IR (film) 2961, 2929, 2850, 1705, 1617, 1596, 1459, 1159, 823, 800 cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{24}O_4S$, 384.1395; found, 384.1396.

5,7-Dimethoxy-4-methyl-3-(4-phenylthio)benzylcoumarin (6e): 84% yield (105.5 mg), pale brown solid, melting point 130−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.28−7.23 (m, 6H), 7.20−7.17 (m, 3H), 6.44 (d, J = 2.45 Hz, 1H), 6.30 (d, J = 2.44 Hz, 1H), 4.00 (s, 2H), 3.84 (s, 6H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 162.49, 162.45, 159.4, 155.9, 150.7, 139.4, 136.9, 132.9, 132.3, 130.6, 129.52, 129.47, 127.0, 120.7, 105.8, 96.2, 93.5, 56.2, 56.1, 32.6, 20.4; IR (film) 3055, 3006, 2939, 2841, 1703, 1616, 1595, 1158, 1092, 743 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{22}O_4S$, 418.1239; found, 418.1242.

5,7-Dimethoxy-4-methyl-3-(4-phenylacetylenyl)-benzylcoumarin (6f): 84% yield (103.4 mg), pale brown solid, melting point 150−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.52−7.49 (m, 2H), 7.42 (d, J = 8.24, 2H), 7.34−7.30 (m, 3H), 7.22 (d, J = 8.15 Hz, 2H), 6.45 (d, J = 2.44 Hz, 1H), 6.30 (d, J = 2.44 Hz, 1H), 4.04 (s, 2H), 3.84 (d, J = 1.74 Hz, 6H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 162.5, 159.4, 155.9, 150.8, 140.4, 132.1, 132.0, 128.7, 128.6, 128.5, 123.8, 121.4, 120.7, 105.8, 96.2, 93.5, 89.9, 89.4, 56.2, 56.1, 32.9, 20.4; IR (film) 3053, 2987, 1699, 1617, 1598, 1264, 895, 748 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{22}O_4$, 410.1518; found, 410.1519.

Synthesis of 3-(4-Allenylbenzyl)-5,7-dimethoxy-4-methyl-coumarin (6g). To a suspension of $Pd_2dba_3CHCl_3$ (6.2 mg, 0.006 mmol, 2 mol %), PPh_3 (12.6 mg, 0.048 mmol, 16 mol %), and LiCl (38.2 mg, 0.9 mmol) in DMF (0.5 mL) was added 5,7-dimethoxy-3-(4-iodobenzyl)-4-methylcoumarin (130.9 mg, 0.3 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 10 min, an organoindium reagent generated in situ from indium (34.4 mg, 0.3 mmol) and propargyl bromide (20.0 μL, 0.45 mmol) in DMF (0.5 mL) was added, and the mixture was stirred at 100 °C for 3 h. The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3-(4-allenylbenzyl)-5,7-dimethoxy-4-methylcoumarin (**6f**) as a yellow solid (87.8 mg, 84%). Melting point 100−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.18 (s, 4H), 6.44 (d, J = 2.37 Hz, 1H), 6.29 (d, J = 2.36 Hz, 1H), 6.11 (t, J = 6.71 Hz, 1H), 5.10 (d, J = 6.82 Hz, 2H), 4.00 (s, 2H), 3.83 (d, J = 2.85 Hz, 6H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 210.1, 162.5, 162.4, 159.4, 155.9, 150.5, 138.7, 132.1, 128.9, 127.2, 121.2, 105.9, 96.1, 94.1, 93.6, 79.0, 56.1, 56.0, 32.6, 20.3;

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IR (film) 3004, 2938, 2844, 1941, 1703, 1617, 1596, 1206, 1159, 823, 735 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{20}O_4$, 348.1362; found, 348.1359.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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