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Communication

Three-Component Reactions of 7-Hydroxy Coumarin Derivatives, Acetylenic Esters and Aromatic Aldehydes in the Presence of NEt_3

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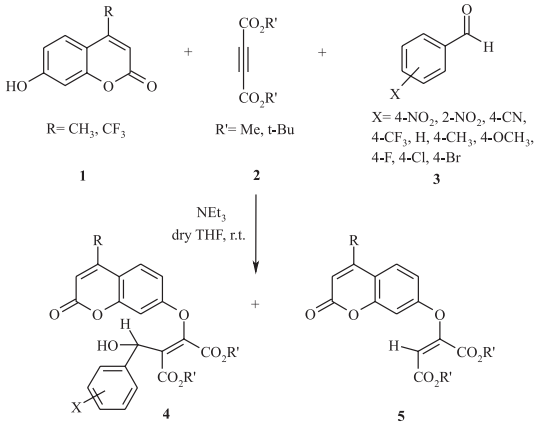
Three-component reactions of 7-hydroxy-4-methyl coumarin or 7-hydroxy-4-(trifluoromethyl) coumarin, dialkyl acetylenedicarboxylates and aromatic aldehydes in the presence of NEt_3 lead to dialkyl (2*E*)-2-[aryl(hydroxy)methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-ene dioate or dialkyl (2*E*)-2-[aryl(hydroxy)methyl]-3-{(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)oxy} but-2-ene dioate in good yields under mild reaction conditions.

Keywords: 7-hydroxy coumarins, dialkyl acetylenedicarboxylates, aromatic aldehydes, three-component reaction

Introduction

Coumarins form an exceptional class of oxygen-containing heterocyclic compounds, which exhibit significant biological activities, such as inhibitory of platelet aggregation,[1,2] inhibitory of steroid 5α-reductase,[3] inhibitory of HIV-1 protease,[4] antibacterial and anticancer activities.[5,6] Coumarin derivatives have been applied for treatment of various cancerous diseases including malignant melanoma, leukemia, renal cell carcinoma, prostate and breast cancer.[7-12] Moreover, coumarins were used as intermediates in the synthesis of chromenes, coumarones and 2-acylresorcinols.[13] Owing to their important applications, various synthetic methodologies for the synthesis of coumarin derivatives have been developed. However, further scientific efforts are still on demand to seek for synthetic methodologies of novel coumarin-based scaffolds.

Recently, the reactions of phenols including phenol, 1-naphthol, 2-naphthol, 8-hydroxyquinoline, 1,6-dihydroxynaphthalene and hydroxybenzaldehydes as *OH*-acids with dimethyl acetylenedicarboxylate (DMAD) in the presence of a catalytic amount of triethylamine,[15] pyridine[16] and triphenylphosphine[17] have been reported. In continuation of our general interest in the synthesis of heterocyclic compounds via three-component reactions,[17-20] we have investigated the reactions of 7-hydroxycoumarins **1** with acetylenic diesters **2** and arylaldehydes **3** in the presence of NEt_3 in tetrahydrofuran (THF) at ambient temperature to afford the corresponding three-component products (1:1:1 adduct) as novel coumarin derivatives **4** and compound **5** as 1:1 adduct in good yields (Scheme 1).



Scheme 1. Preparation of *O*-substituted coumarin derivatives.

Results and Discussion

Initially, the reaction of 7-hydroxy-4-methyl coumarin and DMAD with 4-nitro benzaldehyde as a model reaction was examined in the absence of base at room temperature, in which the starting materials were recovered intact without the formation of the expected multi-component reaction (MCR) product **4**. When the reaction was carried

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out in the presence of NEt_3, the expected product **4** (1:1:1 adduct) was formed as light yellow powder. In order to find the appropriate base for the synthesis of **4a**, the model reaction was investigated in THF using different bases and the results are presented in Table 1. Although all the bases (K_2CO_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and NEt_3) promote the reaction, the highest yield of the product was obtained using NEt_3.

Table 1. Effect of different bases in the synthesis of **4a**

Base	Yield of **4a** / %
K_2CO_3	35
DBU	50
DABCO	40
NEt_3	60

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO: 1,4-diazabicyclo[2.2.2] octane.

The model reaction was further studied using different amounts of NEt_3 under the same reaction conditions (Table 2). The results in Table 2 clearly show that 100 mol% of NEt_3 give the highest yield of the product **4a**.

Table 2. Effect of NEt_3 mol% in the synthesis of **4a**

NEt_3 / mol%	Yield of **4a** / %
50	30
60	40
70	45
100	60

In order to examine the scope and limitations of this method, we extended our study to a variety of aromatic aldehydes with electron-withdrawing and electron-donating substituents. The results in Table 3 clearly indicate the significant role of the substituent groups of the benzaldehyde ring in the reaction pathway for the synthesis of three-component products **4a**-**j** (1:1:1 adduct). The reactions of 7-hydroxy-4-methyl coumarin and DMAD with benzaldehyde and electron-donating substituted benzaldehydes (X = H, CH_3, OCH_3, F, Cl, Br) in the presence of NEt_3 in THF at room temperature did not afford the corresponding product **4** and only compound **5** (1:1 adduct) was collected as sole product. Electron-withdrawing substituted benzaldehydes (X = NO_2, CN) reacted with 7-hydroxy-4-methyl or trifluoromethyl coumarins and dialkyl acetylenedicarboxylates under similar reaction conditions to give the corresponding three-component products **4a**-**j** in good yields (38-60%). However, 4-trifluoromethylbenzaldehyde under similar condition unexpectedly gave only compound **5**.

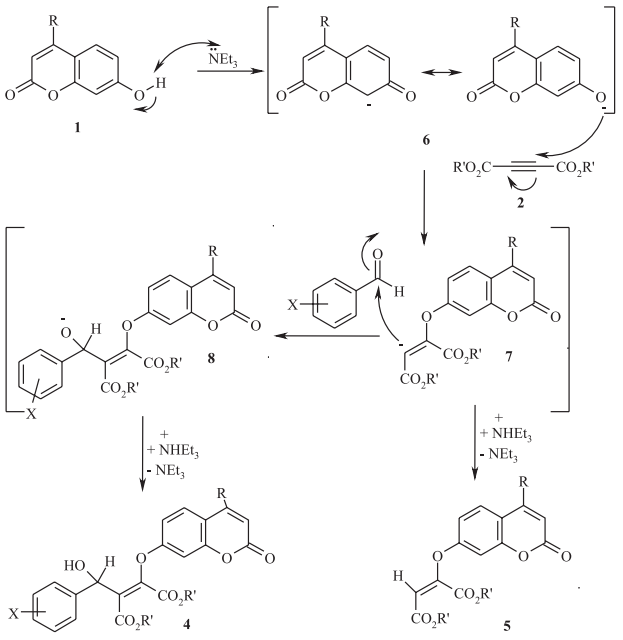
Table 3. Three-component reactions of 7-hydroxy-4-methyl coumarin or 7-hydroxy-4-(trifluoromethyl) coumarin with dialkyl acetylenedicarboxylates and aromatic aldehydes in the presence of NEt_3 in THF

Compound	R	R'	X	Yield of **4**[a] / %	Yield of **5**[a] / %
4a	Me	Me	4-NO_2	60	35
4b	Me	*t*-Bu	4-NO_2	53	–
4c	Me	Me	2-NO_2	50	47
4d	Me	*t*-Bu	2-NO_2	41	–
4e	Me	Me	4-CN	55	42
4f	Me	*t*-Bu	4-CN	51	–
4g	CF_3	Me	4-NO_2	50	–
4h	CF_3	*t*-Bu	4-NO_2	30	–
4i	CF_3	Me	2-NO_2	42	–
4j	CF_3	Me	4-CN	38	–
5	Me	Me	4-CF_3	–	92
5	Me	Me	H	–	94
5	Me	Me	4-CH_3	–	97
5	Me	Me	4-OCH_3	–	98
5	Me	Me	4-F	–	97
5	Me	Me	4-Cl	–	92
5	Me	Me	4-Br	–	94

[a]Isolated yields.

A plausible mechanism for the synthesis of compounds **4** and **5** is depicted in Scheme 2. It is assumed that deprotonation of coumarin **1** by NEt_3 generates anion **6** that can subsequently perform Michael addition with dialkyl acetylenedicarboxylate **2** to give intermediate **7**. Intermediate **7** could either protonate by ammonium salt to produce compound **5** or react with aldehyde **3** to form intermediate **8**, which then protonates by ammonium salt to afford the coumarin derivatives **4**.

The structure of **4a** was deduced from infrared (IR), ^1H, ^{13}C, ^{19}F nuclear magnetic resonance (NMR) and mass spectra, as well as elemental analysis. The IR spectrum of **4a** showed a broad band between 3300-3400 cm^{-1} corresponding to OH stretching absorption and a strong peak at 1740 cm^{-1} attributed to C=O vibrations of the ester groups. The ^1H NMR spectrum of **4a** exhibited a doublet at δ 2.44 ppm ($^4J_{HH}$ 1.2 Hz) for the methyl group, a singlet at δ 3.32 ppm for the OH group, two singlets at δ 3.72 and 3.79 ppm for the two methoxy groups, a singlet at δ 6.02 ppm for the aliphatic methine group (CH), a quartet at δ 6.26 ppm ($^4J_{HH}$ 1.2 Hz) for the CH group of heterocyclic moiety, a doublet of doublet at δ 6.94 ppm ($^3J_{HH}$ 8.8 Hz,

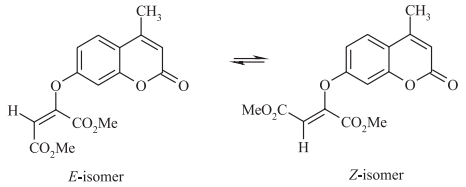


Scheme 2. Proposed mechanism of preparation of *O*-substituted coumarin derivatives.

$^4J_{HH}$ 2.4 Hz), a doublet at δ 6.97 ppm ($^4J_{HH}$ 2.4 Hz) and a doublet at δ 7.57 ppm ($^3J_{HH}$ 8.8 Hz) for the three CH groups of the benzene ring of coumarin and two doublets at δ 7.63 and 8.20 ppm ($^3J_{HH}$ 8.4 Hz) for the four CH groups of the *para*-substituted benzene ring. The ^{13}C NMR spectrum of **4a** exhibited twenty one signals in agreement with the proposed structure. The mass spectrum of this compound displayed a molecular ion peak at *m/z* 469 (M^+, 7) and other fragments at 437, 378, 287, 176 and 150 in accordance with the structure of **4a**.

Similarly, the ^{1}H and ^{13}C NMR spectra of **4b-4j** displayed the expected characteristic resonances related to their structure.

The structure of the compound **5** is *E* and *Z* configuration isomers, as shown in Scheme 3.



Scheme 3. Geometric isomers of **5**.

Although the carbon-carbon double bond in **5** is conjugated to the adjacent oxygen atom, the rotation about the C=C bond for the *E* and *Z* isomers is slow on the NMR time scale at room temperature, as confirmed by ^{1}H and ^{13}C NMR spectra of **5**. The assignment of the *Z*-configuration to the major geometric isomer of **5** is based on the ^{1}H NMR chemical shift of the olefinic proton, which migrated to lower field for the *Z* isomer due to the anisotropic effect of the adjacent ester group.

The ^{1}H NMR spectrum of the *Z*-isomer exhibited a doublet at δ 2.42 ppm ($^4J_{HH}$ 1.2 Hz) for the methyl group, two sharp singlets at δ 3.74 and 3.81 ppm for the two methoxy groups and a singlet at δ 6.77 ppm for the olefinic proton, and the spectrum of the *E*-isomer displayed a doublet at δ 2.46 ppm ($^4J_{HH}$ 1.2 Hz) for the methyl group, two singlets at δ 3.73 and 3.92 ppm for the two methoxy groups and a singlet at δ 5.43 ppm for the olefinic proton. The ^{13}C NMR spectrum of **5** displayed 32 distinct resonances, in agreement with the presence of two *E* and *Z* geometric isomers. The structure of **5** was further confirmed by the mass spectrum, which displayed a molecular ion peak at *m/z* 318.

Experimental

Materials and methods

Dialkyl acetylenedicarboxylates, aromatic aldehydes and triethylamine were purchased from Fluka (Buchs, Switzerland) and used without further purification. 7-Hydroxy coumarin derivatives were prepared by known methods.[21] Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a FT-IR Bruker vector 22 spectrometer; NMR spectra were recorded on a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C, 376.5 MHz for ^{19}F NMR) with $CDCl_3$ as solvent. Chemical shifts are given in parts *per* million (δ) relative to tetramethylsilane (TMS), and coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O Rapid analyzer.

General procedure for the preparation of compounds **4a-j**

To a magnetically-stirred solution of 7-hydroxy coumarin derivatives (2 mmol), aromatic aldehydes (2 mmol) and NEt_3 (2 mmol) in THF (8 mL) a mixture of dialkyl acetylenedicarboxylate (2 mmol) in THF (2 mL) was added in 15 min. The reaction mixture was then allowed to stand at room temperature for 0.5-10 h. After completion of the reaction as indicated by thin-layer chromatography (TLC) (*n*-hexane/EtOAc, 1:1), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Merck, 230-400 mesh) using a mixture of *n*-hexane/EtOAc (1:1) as eluent to afford the pure product as a light yellow powder.

Analytical data for dimethyl (2*E*)-2-[hydroxy(4-nitrophenyl) methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**4a**)

Light yellow powder; m.p. 144-146 °C; IR (KBr) ν_{max}/cm^{-1} 3388, 3074, 2955, 2853, 1740, 1655, 1568, 1347, 1260, 1090; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.44 (d, 3H, *J* 1.2 Hz, CH_3), 3.32 (s, 1H, OH), 3.72 and 3.79 (2s, 6H, $2OCH_3$), 6.02 (s, 1H, CH benzylic), 6.26 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.94 (dd, 1H, *J* 8.8, 2.4 Hz, Ar–H), 6.97 (d, 1H, *J* 2.4 Hz, Ar–H), 7.57 (d, 1H, *J* 8.8 Hz, Ar–H), 7.63 (d, 2H, *J* 8.4 Hz, 2Ar–H), 8.20 (d, 2H, *J* 8.4 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7, 53.0, 53.2, 68.8, 105.0, 113.2, 113.9, 116.6, 123.8, 126.2, 126.9, 130.8, 144.1, 147.5, 147.6, 152.0, 154.7, 157.7, 160.4, 161.4, 165.7; MS (EI, 70 eV) (%) 469 (M^+, 7), 437 (7), 378 (15), 319 (11), 287 (38), 262 (15), 234 (16), 176 (43), 150 (100), 104 (23), 76 (15); anal. calcd. for $C_{23}H_{19}NO_{10}$ (469.41): C, 58.85; H, 4.08; N, 2.98%; found: C, 58.79; H, 4.13; N, 2.95%.

Analytical data for di-*tert*-butyl (2*E*)-2-[hydroxy(4-nitrophenyl) methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**4b**)

Light yellow powder; m.p. 147-149 °C; IR (KBr) ν_{max}/cm^{-1} 3425, 2927, 2856, 1728, 1611, 1568, 1346, 1262, 1093; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.26 and 1.36 (2s, 18H, $2CMe_3$), 2.45 (d, 3H, *J* 1.2 Hz, CH_3), 3.88 (s, 1H, OH), 5.98 (s, 1H, CH benzylic), 6.26 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.96 (dd, 1H, *J* 8.6, 2.4 Hz, Ar–H), 7.02 (d, 1H, *J* 2.4 Hz, Ar–H), 7.57 (d, 1H, *J* 8.4 Hz, Ar–H), 7.64 (d, 2H, *J* 8.8 Hz, 2Ar–H), 8.22 (d, 2H, *J* 8.8 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8, 27.6, 27.7, 68.7, 84.1, 84.2, 105.5, 113.4, 113.9, 116.4, 123.5, 125.9, 126.8, 129.5, 145.5, 147.4, 148.2, 152.0, 154.7, 158.2, 159.9, 160.5, 164.8; MS (EI, 70 eV) (%) 553 (M^+, 1), 407 (3), 176 (94), 148 (100), 91 (22), 57 (28); anal. calcd. for $C_{29}H_{31}NO_{10}$ (553.57): C, 62.92; H, 5.64; N, 2.53%; found: C, 62.85; H, 5.61; N, 2.58%.

Analytical data for dimethyl (2*E*)-2-[hydroxy(2-nitrophenyl) methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**4c**)

Light yellow powder; m.p. 104-106 °C; IR (KBr) ν_{max}/cm^{-1} 3429, 3084, 2956, 2855, 1734, 1610, 1527, 1349, 1262, 1085; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.41 (d, 3H, *J* 0.8 Hz, CH_3), 3.37 (s, 1H, OH), 3.68 and 3.77 (2s, 6H, $2OCH_3$), 6.20 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.48 (1H, s, CH benzylic), 6.76 (d, 1H, *J* 2.4 Hz, Ar–H), 6.87 (dd, 1H, *J* 8.8, 2.4 Hz, Ar–H), 7.43 (td, 1H, *J* 7.4, 1.2 Hz, Ar–H), 7.51 (d, 1H, *J* 8.8 Hz, Ar–H), 7.67 (td, 1H, *J* 8.0, 1.2 Hz, Ar–H), 7.91 (dd, 1H, *J* 8.0, 1.2 Hz, Ar–H), 8.00 (dd, 1H, *J* 8.0, 0.8 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7, 52.9, 53.1, 66.1, 104.3, 113.0, 113.4, 115.0, 124.6, 126.0, 129.1, 129.3, 133.6, 133.8, 135.3, 142.0, 147.7, 152.2, 154.5, 158.1, 160.7, 161.4, 165.7; MS (EI, 70 eV) (%) 469 (M^+, 7), 392 (19), 364 (16), 348 (32), 333 (18), 316 (13), 277 (23), 259 (30), 230 (12), 202 (16), 176 (81), 148 (100), 120 (33), 59 (49); anal. calcd. for $C_{23}H_{19}NO_{10}$ (469.41): C, 58.85; H, 4.08; N, 2.98%; found: C, 58.91; H, 4.11; N, 2.94%.

Analytical data for di-*tert*-butyl (2*E*)-2-[hydroxy(2-nitrophenyl) methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**4d**)

Light yellow powder; m.p. 149-151 °C; IR (KBr) ν_{max}/cm^{-1} 3428, 2925, 2855, 1730, 1611, 1528, 1346, 1265, 1089; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.24 and 1.33 (2s, 18H, $2CMe_3$), 2.43 (d, 3H, *J* 1.2 Hz, CH_3), 3.43 (s, 1H, OH), 6.23 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.49 (s, 1H, CH benzylic), 6.91 (d, 1H, *J* 2.4 Hz, Ar–H), 6.95 (dd, 1H, *J* 8.2, 2.4 Hz, Ar–H), 7.46 (td, 1H, *J* 7.4, 1.2 Hz, Ar–H), 7.53 (d, 1H, *J* 8.8 Hz, Ar–H), 7.68 (td, 1H, *J* 8.2, 1.2 Hz, Ar–H), 7.98 (dd, 1H, *J* 8.4, 1.2 Hz, Ar–H), 8.03 (d, 1H, *J* 8.1 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8, 27.5, 27.6, 66.5, 83.5, 83.7, 105.1, 113.4, 113.5, 115.9, 124.6, 125.6, 128.8, 129.2, 131.7, 133.5, 135.8, 143.5, 147.8, 152.1, 154.6, 158.8, 160.0, 160.8, 164.8; MS (EI, 70 eV) (%) 553 (M^+, 1), 423 (2), 316 (15), 201 (26), 176 (100), 148 (100), 119 (15), 91 (25), 57 (21); anal. calcd. for $C_{29}H_{31}NO_{10}$ (553.57): C, 62.92; H, 5.64; N, 2.53%; found: C, 62.88; H, 5.69; N, 2.47%.

Analytical data for dimethyl (2*E*)-2-[(4-cyanophenyl) (hydroxy)methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy] but-2-enedioate (**4e**)

Light yellow powder; m.p. 138-140 °C; IR (KBr) ν_{max}/cm^{-1} 3426, 3050, 2925, 2855, 2229, 1735, 1263, 1091; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.42 (d, 1H, *J* 0.8 Hz, OH), 2.44 (d, 3H, *J* 1.2 Hz, CH_3), 3.72 and 3.79 (2s, 6H, $2OCH_3$), 5.96 (s, 1H, CH benzylic), 6.26 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.91 (dd, 1H, *J* 8.8, 2.4 Hz, Ar–H), 6.95 (d, 1H, *J* 2.4 Hz, Ar–H), 7.56 (d, 1H, *J* 7.2 Hz, Ar–H), 7.57 (d, 2H, *J* 8.4 Hz, 2Ar–H), 7.64 (d, 2H, *J* 8.4 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7, 52.0, 53.2, 68.9, 105.0, 111.9, 113.1, 113.9, 116.6, 118.6, 126.2, 126.7, 130.9, 132.4, 144.1, 145.6, 152.0, 154.7, 157.7, 160.4, 161.5, 165.0. MS (EI, 70 eV) (%) 449 (M^+, 19), 417 (12), 358 (42), 319 (23), 287 (100), 259 (15), 242 (11), 214 (13), 187 (52), 148 (45), 130 (88), 102 (29), 59 (8); anal. calcd. for $C_{24}H_{19}NO_8$ (449.42): C, 64.14; H, 4.26; N, 3.12%; found: C, 64.07; H, 4.31; N, 3.08%.

Analytical data for di-tert-butyl (2*E*)-2-[(4-cyanophenyl)(hydroxy)methyl]-3-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**4f**)

Light yellow powder; m.p. 129-131 °C; IR (KBr) ν_{max}/cm^{-1} 3431, 2925, 2855, 2230, 1728, 1610, 1261, 1095; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.28 and 1.34 (2s, 18H, $2CMe_3$), 2.45 (d, 3H, *J* 0.8 Hz, CH_3), 3.78 (d, 1H, *J* 8.8 Hz, OH), 5.93 (d, 1H, *J* 7.6 Hz, CH benzylic), 6.26 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.94 (dd, 1H, *J* 8.8, 2.8 Hz, Ar–H), 7.02 (d, 1H, *J* 2.4 Hz, Ar–H), 7.56 (d, 1H, *J* 8.4 Hz, Ar–H), 7.58 (d, 2H, *J* 8.4 Hz, 2Ar–H), 7.66 (d, 2H, *J* 8.4 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8, 27.7, 29.7, 68.8, 84.0, 84.1, 105.5, 111.5, 113.3, 113.9, 116.4, 118.7, 125.9, 126.7, 129.7, 132.1, 145.4, 146.2, 151.9, 154.7, 158.2, 159.9, 160.5, 164.9; MS (EI, 70 eV) (%) 533 (M^+, 2), 459 (3), 433 (13), 403 (4), 358 (4), 316 (7), 288 (4), 227 (17), 176 (100), 148 (80), 130 (30), 102 (18), 57 (16); anal. calcd. for $C_{30}H_{31}NO_8$ (533.58): C, 67.53; H, 5.86; N, 2.63%; found: C, 67.58; H, 5.90; N, 2.59%.

Analytical data for dimethyl (2*E*)-2-[hydroxy(4-nitrophenyl)methyl]-3-{(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)oxy}but-2-enedioate (**4g**)

Light yellow powder; m.p. 168-170 °C; IR (KBr) ν_{max}/cm^{-1} 3513, 3089, 2955, 2852, 1739, 1567, 1346, 1263, 1088; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 3.58 (m, 1H, OH), 3.75 and 3.80 (2s 6H, $2OCH_3$), 5.98 (s, 1H, CH benzylic), 6.76 (s, 1H, CH heterocylic), 7.00-7.03 (m, 2H, 2Ar–H), 7.62 (d, 2H, *J* 8.4 Hz, 2Ar–H), 7.72 (dd, 1H, *J* 8.0, 2.0 Hz, Ar–H), 8.21 (d, 2H, *J* 8.8 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.1, 53.4, 68.9, 105.2, 110.0, 113.9, 114.5 (q, *J* 5.5 Hz, CH), 121.3 (q, *J* 275.6 Hz, CF_3), 123.8, 126.9, 127.2, 132.3, 141.1 (q, *J* 33.4 Hz, C), 142.9, 147.0, 147.7, 155.7, 158.5, 158.7, 161.1, 165.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ –64.77; MS (EI, 70 eV) (%) 523 (M^+, 3), 432 (22), 341 (89), 241 (39), 202 (74), 173 (12), 150 (100), 104 (21), 59 (16); anal. calcd. for $C_{23}H_{16}F_3NO_{10}$ (523.38): C, 52.78; H, 3.08; N, 2.68%; found: C, 52.84; H, 3.04; N, 2.61%.

Analytical data for di-tert-butyl (2*E*)-2-[hydroxy(4-nitrophenyl)methyl]-3-{(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)oxy}but-2-enedioate (**4h**)

Light yellow powder; m.p. 143-145 °C; IR (KBr) ν_{max}/cm^{-1} 3488, 2980, 2856, 1748, 1728, 1567, 1346, 1266, 1085; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.31 and 1.36 (2s, 18H, $2CMe_3$), 3.78 (d, 1H, *J* 9.2 Hz, OH), 5.98 (d, 1H, *J* 8.4 Hz, CH benzylic), 6.76 (s, 1H, CH heterocylic), 7.04 (d, 1H, *J* 2.4 Hz, Ar–H), 7.07 (dd, 1H, *J* 6.6, 2.4 Hz, Ar–H), 7.63 (d, 2H, *J* 8.4 Hz, 2Ar–H), 7.72 (dd, 1H, *J* 7.2, 1.6 Hz, Ar–H), 8.24 (d, 2H, *J* 8.2 Hz, 2Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.6, 27.7, 68.8, 84.3, 84.4, 105.7, 109.7, 114.3, 114.5 (q, *J* 5.6 Hz, CH), 120.3 (q, *J* 217.5 Hz, CF_3), 123.6, 126.8, 126.9 (q, *J* 2.9 Hz, C), 130.6, 141.2 (q, *J* 31.2 Hz, C), 144.6, 147.5, 147.8, 155.7, 158.5, 159.2, 159.6, 164.6; MS (EI, 70 eV) (%) 607 (M^+, 2), 495 (29), 432 (8), 403 (4), 345 (13), 316 (9), 230 (96), 202 (28), 175 (8), 151 (39), 105 (5), 57 (100); anal. calcd. for $C_{29}H_{28}F_3NO_{10}$ (607.54): C, 57.33; H, 4.65; N, 2.31%; found: C, 57.29; H, 4.72; N, 2.26%.

Analytical data for dimethyl (2*E*)-2-[hydroxy(2-nitrophenyl)methyl]-3-{(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)oxy}but-2-enedioate (**4i**)

Light yellow powder; m.p. 142-144 °C; IR (KBr) ν_{max}/cm^{-1} 3448, 3098, 2975, 2855, 1737, 1612, 1529, 1349, 1265, 1083; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 3.1 (s, 1H, OH), 3.71 and 3.78 (2s, 6H, $2OCH_3$), 6.46 (s, 1H, CH benzylic), 6.72 (s, 1H, CH heterocylic), 6.85 (d, 1H, *J* 2.8 Hz, Ar–H), 6.92 (dd, 1H, *J* 8.8, 2.4 Hz, Ar–H), 7.46 (td, 1H, *J* 7.8, 1.2 Hz, Ar–H), 7.64-7.70 (m, 2H, 2Ar–H), 7.94 (dd, 1H, *J* 8.4, 1.2 Hz, Ar–H), 8.00 (d, 1H, *J* 6.8 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 52.9, 53.2, 66.2, 104.7, 109.5, 113.8, 114.1 (q, *J* 5.3 Hz, CH), 119.1, 121.4 (q, *J* 280.7 Hz, CF_3), 124.6, 126.8, 129.2, 129.3, 133.7, 134.9, 135.1, 141.2 (q, *J* 34.4 Hz, C), 147.7, 155.6, 158.7, 159.0, 161.1, 165.5; MS (EI, 70 eV) (%) 523 (M^+, 1), 492 (3), 446 (24), 418 (23), 402 (60), 371 (11), 331 (21), 241 (100), 202 (41), 173 (23), 157 (52), 59 (28); anal. calcd. for $C_{23}H_{16}F_3NO_{10}$ (523.38): C, 52.78; H, 3.08; N, 2.68%; found: C, 52.82; H, 3.05; N, 2.70%.

Analytical data for dimethyl (2*E*)-2-[(4-cyanophenyl)(hydroxy)methyl]-3-{(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)oxy}but-2-enedioate (**4j**)

Light yellow powder; m.p. 142-144 °C; IR (KBr) ν_{max}/cm^{-1} 3398, 3081, 2960, 2853, 2238, 1728, 1613, 1262, 1062; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 3.1 (s, 1H, OH), 3.74 and 3.80 (2s, 6H, $2OCH_3$), 5.92 (s, 1H, CH benzylic), 6.75 (s, 1H, CH heterocylic), 6.99-7.01 (m, 2H, 2Ar–H), 7.56 (d, 2H, *J* 8.4 Hz, 2Ar–H), 7.65 (d, 2H, *J* 8.0 Hz, 2Ar–H), 7.71 (d, H, *J* 8.0 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.1, 53.3, 69.0, 105.1, 112.1, 113.9, 114.5 (q, *J* 5.7 Hz, CH), 118.5, 121.3 (q, *J* 275.5 Hz, CF_3), 126.7, 127.1 (q, *J* 2.1 Hz, C), 129.1 (q, *J* 5.1 Hz, C), 132.4, 133.0, 141.1 (q, *J* 32.9 Hz, C), 142.5, 145.2, 155.7, 158.5, 158.8, 161.4, 165.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ –64.76; MS (EI, 70 eV) (%) 503 (M^+, 3), 471 (4), 439 (5), 412 (29), 373 (37), 341 (100), 313 (11), 241 (41), 202 (20), 182 (18), 157 (15), 130 (69), 102 (15), 59 (6); anal. calcd. for $C_{24}H_{16}F_3NO_8$ (503.39): C, 57.27; H, 3.20; N, 2.78%; found: C, 57.31; H, 3.23; N, 2.69%.

Analytical data for dimethyl 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]but-2-enedioate (**5**)

White powder; m.p. 110-112 °C; IR (KBr) ν_{max}/cm^{-1} 3082, 2956, 2852, 1725, 1610, 1265, 1093; (*Z*-isomer, 60%) ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.42 (d, 3H, *J* 1.2 Hz, CH_3), 3.74 and 3.81 (2s, 6H, $2OCH_3$), 6.21 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.77 (s, 1H, CH vinylic), 6.98 (dd, 1H, *J* 8.8, 2.4 Hz, Ar–H), 7.11 (d, 1H, *J* 2.1 Hz, Ar–H), 7.58 (d, 1H, *J* 8.8 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8, 52.2, 53.4, 103.8, 112.8, 113.2, 115.8, 117.1, 126.0, 148.6, 152.2, 154.8, 159.2, 160.7, 161.9, 163.4; (*E*-isomer, 40%) ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.46 (d, 3H, *J* 1.2 Hz, CH_3), 3.73 and 3.92 (2s, 6H, $2OCH_3$), 5.43 (s, 1H, CH vinylic), 6.30 (q, 1H, *J* 1.2 Hz, CH heterocylic), 6.86 (d, 1H, *J* 2.8 Hz, Ar–H), 7.08-7.11 (m, 1H, Ar–H), 7.66 (d, 1H, *J* 8.8 Hz, Ar–H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7, 52.1, 53.3, 103.0, 108.8, 114.7, 116.4, 118.0, 126.4, 151.8, 154.6, 157.9, 155.5, 160.2, 162.6, 165.2; MS (EI, 70 eV) (%) 318 (M^+, 63), 287 (25), 259 (100), 231 (17), 202 (8), 174 (7), 147 (16); anal. calcd. for $C_{16}H_{14}O_7$ (318.28): C, 60.38; H, 4.43; O, 35.19%; found: C, 60.31; H, 4.41; O, 35.24%.

Conclusions

In summary, we have reported a simple and efficient procedure for the synthesis of novel coumarin derivatives via a three-component reaction of 7-hydroxy-4-alkyl coumarins, dialkyl acetylenedicarboxylates and aromatic aldehydes. Scope and limitations of the reaction were studied. The simplicity of the present procedure and the mild reaction conditions make it an interesting alternative to other existing approaches.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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