*Vietnam Journal of Science and Technology* ***63*** *(5) (2025) 864-874*

doi:10.15625/2525-2518/18669

# Synthesis of some *bis*(styryl) containing coumarin ring from substituted 3-acetyl-4-methylcoumarin

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Received: 18 August 2023; Accepted for publication: 29 August 2025

**Abstract.** This study presents an efficient synthetic methodology for novel coumarin derivatives containing *bis*(styryl) groups, with potential applications in materials science and biology. Three 3-acetyl-4-methylcoumarin precursors were synthesized in 40 - 55 % yields via Pechmann condensation of substituted *o*-hydroxyacetophenones with ethyl acetoacetate, using sodium acetate as catalyst under optimized conditions (120 - 130 °C, 35 h). Subsequent Claisen-Schmidt condensation reactions with various aromatic aldehydes (1:2 molar ratio) in chloroform, catalyzed by piperidine (0.5 mol.%), afforded eleven 3-((*E*)-arylprop-2-enoyl)-4-((*E*)-styryl)coumarin derivatives in 35 - 57 % yields after 25 - 35 h of reflux.

The synthesized *bis*(styryl) containing coumarins exhibit extended π-conjugation systems and high thermal stability (m.p. 190 - 287 °C), making them promising candidates for pharmaceutical development and materials science applications. This work not only expands the library of functionalized coumarins but also provides valuable insights into the reactivity of 3-acetyl-4-methylcoumarin derivatives.

*Keywords*: *bis*(styryl), *α,β*-unsaturated ketones, coumarin, *o*-hydroxyacetophenone, ethyl acetoacetate.

*Classification numbers*: 1.1.2, 1.1.3, 1.1.6, 1.2.1.

## 1. INTRODUCTION

Coumarins display a wide range of biological activities, including antidiabetic [1], anticancer [2], antifungal [3], anti-HIV, and antibacterial effects [4, 5], as well as platelet aggregation [6] and steroid 5α-reductase inhibition [7]. They also find applications as optical brighteners [8], photosensitizers [9], fluorescent and laser dyes [9,10]. Several 3-acetylcoumarin derivatives show strong bioactivity, such as EGFR inhibition [11] and tyrosinase inhibition [12], alongside notable physicochemical properties including strong fluorescence [13], high thermal stability [14], and green synthetic accessibility [15]. Incorporation into polymers enables reversible photodimerization and self-healing materials [16].

Structural modification via styryl groups enhances biological activity through Michael addition [17], while *bis*(styryl) compounds, though underexplored, offer extended conjugation and applications in optical materials [18]. The combination of coumarin and *bis*(styryl) scaffolds may yield multi-target agents for cancer and antimicrobial therapy. This work reports the synthesis of *bis*(styryl) derivatives from 3-acetyl-4-methylcoumarins, exploiting the reactive

acetyl group and the electronic/steric role of the 4-methyl substituent. Although 3-acetylcoumarin is known to generate various active heterocycles [19, 20], *bis*(styryl) derivatives remain largely unexplored.

## 2. EXPERIMENTAL

The melting points of the synthesized compounds were determined using a Stuart SMP3 melting point apparatus. Infrared (IR) spectra were recorded on an Impact 410-Nicolet (Nicolet Instrument Corporation, USA) Spectrometer using potassium bromide (KBr) pellets. Nuclear magnetic resonance (NMR) spectra were acquired at 500 MHz for $^{1}$H-NMR on an Avance AV500 Spectrometer (Bruker, Germany) using deuterated dimethyl sulfoxide (DMSO-$d_6$) as the solvent and tetramethylsilane (TMS) as the internal standard.

Liquid chromatography-mass spectrometry (LC-MS) data were obtained using an LC-MS-ORBITRAP-XL system (Thermo Fisher Scientific, USA), while mass spectrometry (MS) data were recorded on a 5989B Hewlett–Packard Mass Spectrometer (Hewlett-Packard, USA). High-resolution mass spectrometry (HR-MS) data were collected using a Micromass AutoSpec Premier Instrument (Waters, USA). Thin-layer chromatography (TLC) was performed using Merck Kieselgel 60F254 pre-coated silica gel plates.

Computational studies were conducted using HyperChem Release 8.0 software (Hypercube, Inc., USA). The charge density of the synthesized compounds was calculated using semi-empirical methods. All molecular structures were built and geometrically optimized using the RM1 method [21], with a convergence limit of $10^{-4}$ and an iteration limit of 50. The Polak-Ribiere algorithm was employed with a termination condition of the root-mean-square (RMS) gradient set at 0.1000 kcal/(Å·mol) and the restricted Hartree-Fock (RHF) calculation method.

All reagents and solvents used in the synthesis were of high purity and were purchased from Merck Chemical Company. The substituted 3-acetyl-4-methylcoumarins (**2a-c**) were synthesized via Pechmann condensation, following the reaction pathway illustrated in Scheme 1. In this reaction, substituted *o*-hydroxyacetophenones (**1a**–**c**) were reacted with ethyl acetoacetate in the presence of sodium acetate as a base catalyst. The reaction was carried out under reflux conditions until completion, as monitored by TLC. Upon completion, the reaction mixture was cooled, and the precipitate was filtered and purified by recrystallization from ethanol to afford the desired coumarin derivatives **2a-c** in good yields.

### *General procedure for preparing* 2a-c

In a reaction flask, 0.01 moles of substituted *o*-hydroxyacetophenones (**1a**–**c**) were dissolved in 0.03 moles (5.85 mL) of ethyl acetoacetate. Subsequently, 2.0 g of sodium acetate was added to the reaction mixture. The reaction was carried out under reflux with continuous stirring at a temperature range of 120 - 130 °C for 35 hours. Upon completion, the reaction mixture was allowed to cool to room temperature before being poured onto crushed ice to precipitate the product. The crude solid was collected by vacuum filtration, thoroughly washed with distilled water to remove residual reagents and impurities, and then air-dried. The crude products (**2a-c**) were purified by recrystallization using ethanol as the solvent. Each solid was dissolved in a minimal volume of hot ethanol, and the resulting solution was allowed to cool slowly to room temperature, followed by further cooling in an ice bath to enhance crystallization. The purified products were collected via vacuum filtration, washed with small portions of cold ethanol, and dried under reduced pressure to obtain the final pure substituted 3-

acetyl-4-methylcoumarins (**2a-c**) in high purity. The physical properties, along with IR, MS, and NMR spectral data of compounds **2a-c**, are reported as follows:

**3-Acetyl-6-hydroxy-4-methylcoumarin (2a)** [23]

From **1a** (0.01 mol, 1.52 g): Yield 1.09 g (50 %) of **2a** as brown-yellow crystals. M.p: 225 - 227 $^{o}$C. IR (KBr, cm$^{-1}$): 3209 (O-H br.str.); 1698 and 1672 (C=O str.); 1616 and 1576 (C=C str.); 1241 and 1179 (C-O str.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ9.82 (1H, s, OH); 7.29 (1H, d, *J* = 8.5 Hz, H$_{benzo}$); 7.14 (1H, d, *J* = 2.5 Hz, H$_{benzo}$); 7.12 (1H, dd, 1H, *J* = 8.5, 2.5 Hz, H$_{benzo}$); 2.46 (3H, s, COCH$_3$); 2.31 (3H, s, CH$_3$). MS (*m/z)*: 218 (M$^{+\cdot}$, 92.5 %); 203 [M-CH$_3$]$^+$ (80.7 %); 176 [M-CH$_2$CO]$^+$ (100 %), etc.

**3-Acetyl-6-methoxy-4-methylcoumarin (2b)**

From **1b** (0.01 mol, 1.66 g): Yield 1.27 g (55 %) of **2b** as light blue crystals. M.p: 134-135 $^{o}$C. IR (KBr, cm$^{-1}$): 1720 and 1690 (C=O str.); 1621 and 1587 (C=C str.); 1222 and 1182 (C-O str.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ7.41(1H, d, *J* = 7.0 Hz, H$_{benzo}$); 7.32-7.28 (2H, m, H$_{benzo}$); 3.85 (3H, s, OCH$_3$); 2.47 (3H, s, COCH$_3$); 2.38 (1H, s, CH$_3$). MS (*m/z)*: 232 (M$^{+\cdot}$, 86.6 %); 217 [M-CH$_3$]$^+$ (75.8 %); 190 [M-CH$_2$CO]$^+$ (100 %), etc.

**3-Acetyl-7-hydroxy-4-methylcoumarin (2c**)

From **1c** (0.01 mol, 1.52 g): Yield 87.2 mg (40 %) of **2c** as pale-yellow crystals. M.p: 240-241 $^{o}$C. IR (KBr, cm$^{-1}$): 3208 (O-H br.str.); 1682 (C=O str.); 1591 and 1554 (C=C str.); 1267 and 1182 (C-O str.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ10.76 (1H, s, OH); 7.74 (1H, d, *J* = 8.5 Hz, H$_{benzo}$); 6.85 (1H, dd, *J* = 8.5, 2.5 Hz, H$_{benzo}$); 6.74 (1H, d, *J* = 2.5 Hz, H$_{benzo}$); 2.45 (3H, s, COCH$_3$), 2.34 (3H, s, CH$_3$). MS (*m/z)*: 218 (M$^{+\cdot}$, 48.6 %); 203 [M-CH$_3$]$^+$ (100 %); 175 [203-CO]$^+$ (27.6 %), etc.

***General procedure for preparing bis(styryl):***

To synthesize *bis*(styryl) compounds, a mixture of compounds **2a-c** (5 mmol) and aromatic aldehydes (10 mmol) were combined with chloroform (25 mL) and 0.5 mol% piperidine (0.5 mL). The mixture was heated under reflux in a water bath for 25 - 35 hours. During heating, the reactants dissolved and subsequently formed products that precipitated out of the solution. The resulting precipitate was filtered and washed three times with hot chloroform. The obtained products were air-dried and recrystallized from a mixture of 30 % DMF and 70 % ethanol. Physical properties and IR, MS, and NMR spectral data of the *bis(*styryl) derivatives are reported as follows:

**6-Hydroxy-3-((*E*)-phenylprop-2-enoyl)-4-((*E*)-styryl)coumarin (3a)** [23]

From 1.09 g of **2a** and 1.06 g of benzaldehyde: Reaction time 32 h. Yield 82.74 mg (42 %) of **3a**, which formed into pale-yellow crystals. Mp 201 - 203 $^{o}$C; IR (KBr, cm$^{-1}$): 3221 (O-H br.str.), 1670 (C=O, str.), 1572 (C=C, str.), 1211 (C-O str.) and 973 (=CH$_{trans}$ bend.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ9.81 (1H, s, OH); 7.72 (2H, t, *J* = 7.5 and 1.5 Hz, H$_{phenyl}$); 7.68 (1H, d, *J* = 16.0 Hz, H$_{\beta vinyl\ ketone}$); 7.57 (2H, d, *J* = 7.0 Hz, H$_{phenyl}$); 7.429-7.327 (7H, m, 6H$_{phenyl}$ and 1H$_{benzo}$); 7.28 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.27 (1H, d, *J* = 2.5 Hz, H$_{benzo}$); 7.15 (1H, dd, *J* =9 .0 and 3.0 Hz, H$_{benzo}$); 7.06 (1H, d, *J* = 16.5 Hz, -CH=C*H*-Ar); 6.97 (1H, d, *J* = 16.0 Hz, H$_{\alpha vinylketone}$). ESI-MS: m/z 395.27 [M+H]$^+$, 48.83 % and 417.22 [M + Na]$^+$, 66.11 %.

**3-((*E*)-4-Bromophenylprop-2-enoyl)-4-((*E*)-4-bromostyryl)-6-hydroxycoumarin (3b)** [23]

From 1.09 g of **2a** and 1.85 g of 4-bromobenzaldehyde: Reaction time 30 h.Yield 1.57 g (57 %) of **3b**, which formed into yellow crystals. M.p: 285 - 287 $^{o}$C. IR (KBr, cm$^{-1}$): 3345 (O-H br.str.); 1674 (C=O str.); 1587 and 1525 (C=C str.), 1224 (C-O str.) and 977 (=CH$_{trans}$ bend.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ9.79 (1H, s, OH); 7.68 (2H, d, *J* = 9.0 Hz, H $_{phenyl}$); 7.65 (1H, d, *J* = 16.5 Hz, H$_{\beta vinyl\ ketone}$); 7.60 (2H, d, *J* = 9.0 Hz, H$_{phenyl}$); 7.58 (2H, d, *J* = 9.0 Hz, H$_{phenyl}$); 7.547-7.530 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.36 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.36 (1H, d, *J* = 9.0 Hz, H$_{benzo}$); 7.24 (1H, d, *J* = 3.0 Hz, H$_{benzo}$); 7.14 (1H, dd, *J*=9.0 and 3.0 Hz, H$_{benzo}$); 7.08 (1H, d, *J* = 16.0 Hz, -CH=C*H*-Ar), and 6.92 (1H, d, *J* = 16.5 Hz, H$_{\alpha.vinyl\ ketone}$).

**3-((*E*)-4-Chlorophenylprop-2-enoyl)-4-((*E*)-4-chlorostyryl)-6-hydroxycoumarin (3c)** [23]

From 1.09 g of **2a** and 1.40 g of 4-chlorobenzaldehyde: Reaction time 35 h. Yield 85.65 mg (37 %) of **3c**, which formed into yellow crystals. M.p: 267 - 269 $^{o}$C. IR (KBr, cm$^{-1}$): 3252 (O-H br.str.); 1668 (C=O str.); 1601, 1542 (C=C str.), 1244 (C-O str.) and 978 (=CH$_{trans}$ bend.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ9.79 (1H, s, OH); 7.75 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.67 (1H, d, *J* = 16.5 Hz, H$_{\beta vinyl\ ketone}$); 7.61 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.46 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.43 (2H, d, *J* = 9.0 Hz, H$_{phenyl}$); 7.36 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.35 (1H, d, *J*=8.0 Hz, H$_{benzo}$); 7.25 (1H, d, *J*=3.0 Hz, H$_{benzo}$); 7.14 (1H, dd, *J* = 9.0 and 3.0 Hz, H$_{benzo}$); 7.08 (1H, d, *J* = 16.0 Hz, -CH=C*H*-Ar,) and 6.94 (1H, d, *J* = 16.5 Hz, *H*$_{\alpha vinyl\ ketone}$).

**3-((*E*)-3-(3,4-methylenedioxyphenyl)prop-2-enoyl)-4-((*E*)-3,4-methylenedioxystyryl)-6-hydroxycoumarin (3d)** [23]

From 1.09 g of **2a** and 1.50 g ofpiperonaldehyde: Reaction time: 35 h. Yield 1.084 g (45 %) of **3d**, which formed into yellow crystals. M.p: 265 - 267 $^{o}$C. IR (KBr, cm$^{-1}$): 3272 (O-H br. str.); 1711 and 1656 (C=O str.); 1585 (C=C str.); 1252 (C-O str.) and 987 (=CH$_{trans}$ bend.). $^{1}$HNMR (500MHz, DMSO-d$_6$): δ9.76 (1H, s, OH); 7.55 (1H, d, *J* = 16.5 Hz, H$_{\beta vinyl\ ketone}$); 7.39 (1H, d, *J* = 1.5 Hz, H$_{phenyl}$); 7.35 (1H, d, *J* = 1.5 Hz, H$_{phenyl}$); 7.34 (1H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.28 (1H, d, *J* = 3.0 Hz, H$_{benzo}$); 7.22 (1H, dd, *J* = 8.0, 1.5 Hz, H$_{phenyl}$); 7.18 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.13 (1H, dd, *J*=8.5 and 3.0 Hz, H$_{benzo}$); 6.955-6.866 (5H, m, -CH=C*H*-Ar, *H*$_{\alpha.vinyl\ ketone}$, 3H$_{phenyl}$); 6.07 (2H, s, ArO$_2$C*H*$_2$) and 6.04 (2H, s, ArO$_2$C*H*$_2$). ESI-MS: m/z 483.06 [M+H]$^{+}$, 17.21 % and 505.19 [M + Na]$^{+}$, 83.70 %.

**3-((*E*)-4-Nitrophenylprop-2-enoyl)-4-((*E*)-4-nitrostyryl)-6-hydroxycoumarin (3e)** [23]

From 1.09 g of **2a** and 1.51 g of 4-nitrobenzaldehyde: Reaction time 25 h. Yield 1.098 g (45 %) of **3e**, which formed into yellow crystals. M.p: 248 - 250 $^{o}$C. IR (KBr, cm$^{-1}$): 3469 (O-H br. str.); 1701 (C=O str.); 1577 (C=C str.); 1525 and 1347 (NO$_2$ ν$_s$, ν$_{as}$); 1237 (C-O str.); 1031 and 972 (=CH$_{trans}$ bend.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ9.86 (1H, s, OH); 8.23 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 8.22 (2H, d, *J* = 8.0 Hz, H$_{phenyl}$); 8.00 (2H, d, *J* = 8.5 Hz, H$_{phenyl}$); 7.87 (2H, d, *J* = 9.0 Hz, H$_{phenyl}$); 7.82 (1H, d, *J* = 16.5 Hz, *H*$_{\beta vinyl\ ketone}$); 7.61 (1H, d, *J*=16.5 Hz, -C*H*=CH-Ar); 7.40 (1H, d, *J* = 9.0 Hz, H$_{benzo}$); 7.26 (1H, d, *J* = 16.5 Hz, -CH=C*H*-Ar); 7.24 (1H, d, *J* = 3.0 Hz, H$_{benzo}$); 7.17 (1H, dd, *J* = 9.0 and 3.0 Hz, H$_{benzo}$) and 7.06 (1H, d, *J* = 16.5 Hz, *H*$_{\alpha vinyl\ ketone}$).

**6-Methoxy-3-((*E*)-phenylprop-2-enoyl)-4-((*E*)-styryl)coumarin (3f)**

From 1.16 g of **2b** and 1.06 g of benzaldehyde: Reaction time 30 h. Yield 71.40 mg (35 %) of **3f**, which formed into pale-yellow crystals. M.p: 190 - 191 $^{o}$C; IR (KBr, cm$^{-1}$): 1717 (C=O str.); 1610, 1578 (C=C str.); 1249 (C-O str.); 1006 and 963 (=CH$_{trans}$, bend.). $^{1}$HNMR (500 MHz, DMSO-d$_6$): δ7.54 (1H, d, *J* = 16.5 Hz, H$_{\beta vinyl\ ketone}$); 7.51 (1H, d, *J* = 9.0 Hz, H$_{benzo}$); 7.43 (10H, m, H$_{phenyl}$); 7.25 (1H, d, *J* = 2.0 Hz, H$_{benzo}$); 7.19 (1H, dd, *J* = 9.0 and 2.5 Hz, H$_{benzo}$); 7.13

(1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.07 (1H, d, *J* = 16.5 Hz, -CH=C*H*-Ar); 6.99 (1H, d, *J* = 16.0 Hz, $H_{\alpha vinyl\ ketone}$), and 3.84 (3H, s, $OCH_3$).

**3-((*E*)-4-Chlorophenylprop-2-enoyl)-4-((*E*)-4-chlorostyryl)-6-methoxycoumarin (3g)**From 1.16 g of **2b** and 1.40 g of 4-chlorobenzaldehyde: Reaction time 30 h. Yield 95.40 mg (40 %) of **3g**, which formed into yellow crystals. M.p: 248 - 249 $^oC$. IR (KBr, $cm^{-1}$): 1703 (C=O str.), 1596, 1518 (C=C str.); 1177 (C-O str.); 1045 and 972 (=$CH_{trans}$ bend.). $^1$HNMR (500 MHz, DMSO-$d_6$): δ7.80 (1H, d, *J* = 16.5 Hz, $H_{\beta vinyl\ ketone}$); 7.69 (8H, m, $H_{phenyl}$); 7.44 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.35 (1H, d, *J* = 9.0 Hz, $H_{benzo}$); 7.24 (2H, d, *J*=16.5 Hz, -CH=C*H*-Ar); 7.26 (1H, d, *J* = 2.0 Hz, $H_{benzo}$); 7.15 (1H, dd, *J* = 9.0 and 2.0 Hz, $H_{benzo}$), 6.97 (2H, d, *J* = 16.5 Hz, $H_{\alpha vinylketone}$) and 3.85 (3H, s, $OCH_3$). HR-MS (m/z, %): $M^+$ = 475.5459 (100 %); 477.5389 (65.55 %) and 479.5446 (13.79 %).

**3-((*E*)-3-Nitrophenylprop-2-enoyl)-4-((*E*)-3-nitrostyryl)-7-hydroxycoumarin (3h)**

From 1.09 g of **2c** and 1.51 g of 3-nitrobenzaldehyde: Reaction time 28 h. Yield 1.041 g (43 %) of **3h**, which formed into yellow crystals. M.p: 247 - 248 $^oC$. IR (KBr, $cm^{-1}$): 3450 (O-H br. str.); 1699 (C=O str.); 1610 (C=C str.); 1527 and 1355 ($NO_2$ $\nu_s$ and $\nu_{as}$); 1244 (C-O str.), 1071, and 979 (=$CH_{trans}$ bend.). $^1$HNMR (500 MHz, DMSO-$d_6$): δ8.69 (1H, d, *J* = 1.5 Hz, $H_{phenyl}$); 8.58 (1H, s, $H_{phenyl}$); 8.38 (1H, dd, *J* = 8.0 and 1.5 Hz, $H_{phenyl}$); 8.35 (1H, d, *J* = 7.5 Hz, $H_{phenyl}$), 8.31 (1H, dd, *J* = 8.0 and 1.5 Hz, $H_{phenyl}$); 8.19 (1H, d, *J* = 7.5 Hz, $H_{phenyl}$), 8.00 (1H, d, *J* = 8.5 Hz, $H_{benzo}$); 7.98 (1H, d, *J* = 16.5 Hz, $H_{\beta vinyl\ ketone}$); 7.84 (1H, d, *J* = 8.0 and 7.0 Hz, $H_{phenyl}$); 7.81 (1H, t, *J* = 7.5 and 7.0 Hz, $H_{phenyl}$); 7.76 (1H, d, *J*=16.5 Hz, -C*H*=CH-Ar); 7.43 (1H, d, *J* = 16.5 Hz, -CH=C*H*-Ar); 7.21 (1H, d, *J* = 16.5 Hz, $H_{\alpha vinyl\ ketone}$); 7.04 (1H, dd, *J* = 9.0 and 2.5 Hz, $H_{benzo}$), and 6.99 (1H, d, *J* = 2.5 Hz, $H_{benzo}$).

**3-((*E*)-4-Nitrophenylprop-2-enoyl)-4-((*E*)-4-nitrostyryl)-7-hydroxycoumarin (3i)**

From 1.09 g of **2c** and 1.51 g of 4-nitrobenzaldehyde: Reaction time 32 h. Yield 0.968 g (40 %) of **3i**, which formed into browncrystals. M.p: 260 - 261 $^oC$. IR (KBr, $cm^{-1}$): 3276 (O-H str.); 1703, 1669 (C=O str.); 1617 (C=C str.); 1513, 1342 ($NO_2$ $\nu_s$, $\nu_{as}$); 1069 (=$CH_{trans}$, bend.). $^1$HNMR (500 MHz, DMSO-$d_6$): δ8.22 (4H, t, *J* = 8.5 and 8.5 Hz, $H_{phenyl}$); 7.99 (2H, d, *J* = 9.0 Hz, $H_{phenyl}$); 7.87 (2H, d, *J* = 8.5, $H_{phenyl}$); 7.81 (1H, d, *J* = 8.5 Hz, $H_{benzo}$); 7.78 (1H, d, *J* = 16.0 Hz, $H_{\beta vinyl\ ketone}$); 7.62 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.30 (1H, d, *J*=16.5 Hz, -CH=C*H*-Ar); 7.03 (1H, d, *J* = 16.0 Hz, $H_{\alpha vinyl\ ketone}$); 6.88 (1H, dd, *J* = 9.0 and 2.5 Hz, $H_{benzo}$), and 6.84 (1H, d, *J* = 2.5 Hz, $H_{benzo}$).

**3-((*E*)-4-Chlorophenylprop-2-enoyl)-4-((*E*)-4-chlorostyryl)-7-hydroxycoumarin (3j)**

From 1.09 g of **2c** and 1.40 g of 4-chlorobenzaldehyde: Reaction time 32 h. Yield 81.02 mg (35 %) of **3j**, which formed into yellow crystals. M.p: 271 - 272 $^oC$. IR (KBr, $cm^{-1}$): 3274 (O-H, str.); 1675 (C=O str.); 1627 (C=C str.); 1071, 976 (=$CH_{trans}$ bend.). $^1$HNMR (500 MHz, DMSO-$d_6$): δ7.80 (1H, d, *J* = 8.5 Hz, $H_{benzo}$); 7.74 (2H, d, *J* = 8.5 Hz, $H_{phenyl}$); 7.64 (1H, d, *J* = 16.0 Hz, $H_{\beta vinyl\ ketone}$); 7.60 (2H, d, *J* = 8.5 Hz, $H_{phenyl}$); 7.46 (2H, d, *J* = 8.5 Hz, $H_{phenyl}$); 7.43 (2H, d, *J* = 8.5 Hz, $H_{phenyl}$); 7.38 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.06 (1H, d, *J* = 16.0 Hz, -CH=C*H*-Ar), 6.92 (1H, d, *J* = 16.5 Hz, $H_{\alpha vinyl\ ketone}$); 6.87 (1H, dd, *J* = 9.0 and 2.5 Hz, $H_{benzo}$), and 6.82 (1H, d, *J* = 2.0 Hz, $H_{benzo}$).

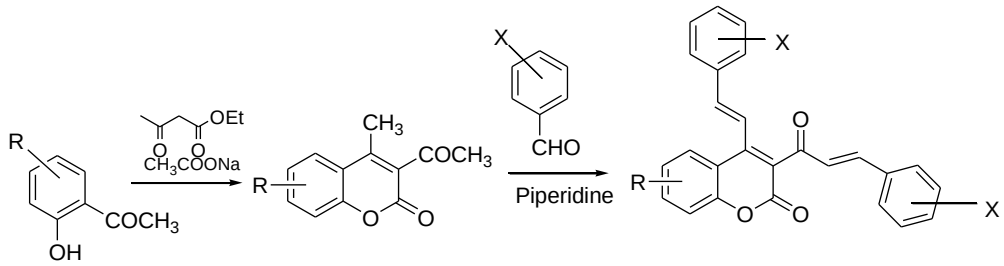
**3-((*E*)-3-(3,4-methylenedioxyphenyl)prop-2-enoyl)-4-((*E*)-3,4-methylenedioxystyryl)-7-hydroxycoumarin (3k)**

From 1.09 g of **2c** and 1.50 g of piperonaldehyde: Reaction time 30 h. Yield 1.132 g (47 %) of **3k**, which formed into yellow crystals. M.p: 242 - 243 $^oC$. IR (KBr, $cm^{-1}$): 3292 (H-O. br.

str.); 1703 (C=O str.); 1623, 1582 (C=C str.); 1040, 989 (=$CH_{trans}$, bend.). $^1$HNMR (500 MHz, DMSO-$d_6$): δ7.95 (1H, s, OH); 7.83 (1H, d, *J* = 9.0 Hz, $H_{benzo}$); 7.52 (1H, d, *J* = 16.0 Hz, $H_{\beta.\ vinyl\ ketone}$); 7.38 (1H, d, *J* = 1.0 Hz, $H_{phenyl}$); 7.35 (1H, d, *J* = 1.5 Hz, $H_{phenyl}$); 7.21 (1H, d, *J* = 16.5 Hz, -C*H*=CH-Ar); 7.21 (1H, dd, *J* = 8.5 and 2.0 Hz, $H_{benzo}$); 6.945-6.854 (5H, m, $4H_{phenyl}$, -CH=C*H*-Ar), 6.87 (1H, d, *J* = 16.0 Hz, $H_{\alpha vinyl\ ketone}$); 6.80 (1H, d, *J* = 2.5 Hz, $H_{benzo}$); 6.07 (2H, s, -$ArO_2CH_2$) and 6.04 (2H, s, -$ArO_2CH_2$).

## 3. RESULTS AND DISCUSSION

Three substituted 3-acetyl-4-methylcoumarin derivatives (**2a-c**) were prepared in 40 - 55 % yields by coindensing substituted *o*-hydroxyacetophenones (**1a–c**) with ethyl acetoacetate at 120 - 130 °C, using sodium acetate as a catalyst [22]. In this protocol, ethyl acetoacetate functions as both the reagent and the solvent; accordingly, a 1:3 molar ratio of **1a–c** to ethyl acetoacetate and a reflux time of 35 hours were found to provide optimal conversion. When fewer than three equivalents of ethyl acetoacetate are used, the acetophenone substrates fail to dissolve completely, making it difficult to maintain a consistent reflux temperature. Conversely, an excess of ethyl acetoacetate undergoes self-condensation in the presence of sodium acetate to form dehydroacetic acid, which complicates the isolation and purification of the desired coumarins and thus reduces the yields of compounds **2a-c** [24].




**1a**: R=5-OH
**1b**: R=5-$OCH_3$
**1c**:R=4-OH

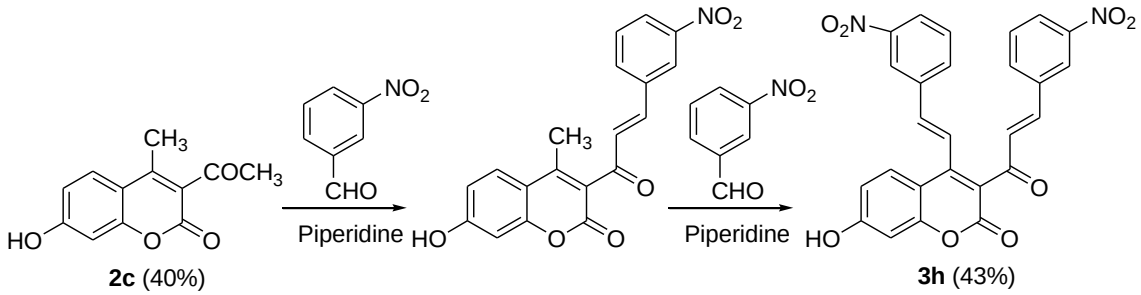
**2a:** R=6-OH (50%);
**2b:** R=6-$OCH_3$(55%)
**2c:** R=7-OH (40%)

**3a**: R=6-OH, X=H (42%); **3b**: R=6-OH, X= 4-Br (57%);
**3c**: R=6-OH, X=4-Cl (37%); **3d**: R=6-OH, X=3,4-$O_2CH_2$ (45%);
**3e**: R=6-OH, X= 4-$O_2N$ (45%); **3f**: R=6-$OCH_3$, X=H (35%);
**3g**: R=6-$OCH_3$, X= 4-Cl (40%); **3h:** R=7-OH, X=3-$O_2N$ (43%);
**3i**: R=7-OH, X=4-$O_2N$ (40%); **3j**: R=7-OH, X=4-Cl (35%);
**3k**: R=7-OH, X=3,4-$O_2CH_2$ (47%)

*Scheme 1*. Synthetic pathway for producing coumarin and *bis*(styryl).

*Bis*(styryl) were synthesized through the Claisen–Schmidt condensation of compounds **2a-c** with aromatic aldehydes. The reaction was catalyzed by weak bases, such as piperidine, trimethylamine, and pyridine, in chloroform or ethanol as the solvent. In contrast, the use of strong inorganic bases (KOH, NaOH) resulted in lower yields of *bis*(styryl), as these bases promoted ring-opening reactions of coumarin, leading to undesired byproducts. Reports on the synthesis of *bis*(styryl) derivatives via the condensation of substituted 3-acetyl-4-methylcoumarins (**2a-c**) with aromatic aldehydes are scarce in the literature. Accordingly, the reaction mechanism has not yet been thoroughly investigated or well established. In our recent study [25], the compound 2-(4-hydroxystyryl)-3-((*E*)-3-(4-hydroxyphenyl)prop-2-enoyl)-7-methoxychromone was successfully synthesized. The stages of this synthesis were elucidated by isolating the intermediate product 7-methoxy-2-methyl-3-[(2'*E*)-3' -(*p*-hydroxyphenyl)-prop-2' -enoyl]chromone and analyzing electron density using HyperChem Release 8.0 software.

Therefore, in this study, we propose that the *bis*(styryl) formation reaction follows a similar two-step mechanism, which includes: Step 1 - The 3-acetyl group undergoes condensation with aromatic aldehydes, forming an *α,β*-unsaturated ketone intermediate; Step 2: The *α,β*-unsaturated ketone then undergoes further condensation at the methyl group at position 4 on the *α*-pyrone ring, yielding the final *bis*(styryl) (Scheme 2).




**2c** (40%) **3h** (43%)

*Scheme 2*. The mechanism of synthesis reaction bis(styryl) **3h**.

In some cases, the *α,β*-unsaturated ketone intermediates remained insoluble during reflux and precipitated as solids. Some intermediates, however, were fully soluble, allowing the 4-methyl group on the *α*-pyrone ring to undergo further condensation with aromatic aldehydes, forming *bis*(styryl) derivatives. The reactivity of the 4-methyl group is likely enhanced by: i, Electron-withdrawing effects of the 3-acetyl group, which activates the 4-methyl group and ii, Hyperconjugation with the vinyl ketone group, increasing its reactivity.

Quantum chemical calculations revealed that the 3-acetyl group possesses higher electron density (more negative charge) compared to the 4-methyl group, in agreement with the suggested two-step reaction pathway. For instance, for compound **2a**, the values are -0.270 (3-acetyl) and -0.209 (4-methyl), while for **2b** and **2c**, the values are -0.271/-0.213 and -0.271/-0.218, respectively. This suggests that both groups can react with aromatic aldehydes to form *bis*(styryl) derivatives.

Building on our previous synthesis of key precursors **3a-e** [23], we have developed novel *bis*(styryl) derivatives through a Claisen-Schmidt condensation between 3-acetyl-4-methylcoumarin derivatives and aromatic aldehydes. The synthesis of *bis*(styryl) derivatives proceeds relatively slowly, with reaction times extending up to 25 - 35 hours, as monitored by thin-layer chromatography (TLC). The reaction was carried out using a molar ratio of 1:2 between 3-acetyl-4-methylcoumarin derivatives and aromatic aldehydes. Chloroform served as the reaction solvent, while 0.5 mol% piperidine functioned as a weak base catalyst. The reaction mixture was heated under reflux in a water bath, allowing for gradual product formation.

The reaction progress was tracked based on differences in the solubility of the starting materials and the products, with the latter precipitating as the reaction proceeded. The resulting *bis*(styryl) derivatives containing coumarin were obtained as solid compounds with high melting points. These derivatives exhibited poor solubility in common organic solvents such as ethanol, acetone, and chloroform.

The successful formation of *bis*(styryl) derivatives incorporating the coumarin scaffold was confirmed through spectral analysis, including infrared (IR) spectroscopy, proton nuclear magnetic resonance ($^1$H NMR), and mass spectrometry (MS). These data verified the structural integrity of the synthesized compounds.

The infrared (IR) spectra of *bis*(styryl) derivatives (e.g., compound **3h**, supporting data 4) display prominent absorption bands that provide crucial insights into their functional groups. Specifically, the characteristic stretching vibrations of the carbonyl ketone (C=O) and carbonyl pyrone moieties are observed in the region of 1717 - 1670 $cm^{-1}$. These peaks are indicative of strong dipole-dipole interactions within the conjugated system of coumarin. The variation in absorption frequencies within this range is attributed to electronic effects exerted by different substituents on the coumarin ring, which can influence the electron density around the carbonyl functional groups.

Additionally, the presence of *α,β*-unsaturated ketone and vinyl functionalities was confirmed by the IR absorption bands detected in the range of 1071 - 963 $cm^{-1}$. These bands correspond to the out-of-plane bending vibrations of the =C–H bonds in the *trans*-configuration of the styryl moieties. The identification of these absorption peaks provides strong evidence for the retention of a conjugated system within the *bis*(styryl) framework, which plays a crucial role in the compounds' electronic and optical properties.

The $^{1}H$ NMR spectra of *bis*(styryl) derivatives revealed two distinct sets of doublets, exhibiting a roof effect, within the chemical shift range of 6.85 - 8.00 ppm. These doublets are associated with the olefinic (vinyl) protons of the styryl groups and are coupled with each other through a large coupling constant (*J*) of 16.0 - 16.5 Hz. Such a high coupling constant is a well-established criterion for *trans*-alkene configurations, reinforcing the conclusion that both styryl groups adopt an *E*-configuration rather than a *Z*-configuration. Notably, these coupling constant (*J*) values and chemical shift ranges are also in good agreement with our previously reported data [25].

In addition to the signals for the vinyl protons, the $^{1}H$ NMR spectra also displayed resonance signals corresponding to other hydrogen environments present in the *bis*(styryl) derivatives. These included protons in the coumarin core and those attached to the substituted benzene rings. The differentiation and assignment of these aromatic proton signals were based on several spectral characteristics, including: i, Spin–spin splitting patterns: The signals appeared as singlets (s), doublets (d), triplets (t), and potentially more complex multiplets, depending on the neighboring proton interactions. ii, Signal intensity: The integration of each peak provided information about the number of protons contributing to the respective signals (e.g., 1H, 2H, or 3H). iii, Substituent effects: Electron-donating or electron-withdrawing substituents attached to the benzene ring influenced the chemical shifts of aromatic protons, leading to either upfield or downfield shifts depending on their inductive or resonance effects.

Mass spectrometry (MS) confirmed the molecular structure of *bis*(styryl) derivatives, with observed peaks (e.g., compound **3h**) matching calculated formulas. Fragmentation patterns adhered to the nitrogen rule, further validating the results.

One of the most distinctive features observed in the MS spectra is the presence of chlorine-containing *bis*(styryl) derivatives, which can be easily identified by their characteristic isotope patterns. The presence of chlorine in a molecule leads to a predictable isotope distribution due to the natural abundance of its two stable isotopes: chlorine-35 ($^{35}Cl$, ~75.77 %) and chlorine-37 ($^{37}Cl$, ~24.23 %). These isotopes create a three-peak pattern in the molecular ion region, separated by 2 atomic mass units (amu) due to the mass difference between the isotopes. For example, in the case of compound **3g** (supporting data 6), the molecular ion peak appears as a triplet at m/z 475.5459 (100 %), m/z 477.5389 (65.55 %) and m/z 479.5446 (13.79 %). These peaks follow the expected intensity ratios for a single chlorine atom, where the molecular ion peak ($M^{+}$) consists of the base peak ($^{35}Cl$-containing ion), followed by the $(M + 2)^{+}$and (M +

4)$^{+}$peaks due to the presence of $^{37}$Cl. The relative intensities of these peaks (approximately 100:65.55:13.79) align closely with the predicted isotope distribution, reinforcing the presence of a chlorine-containing fragment within the molecular structure.

The ability to detect chlorine through isotope patterns is particularly advantageous in structural elucidation, as it provides unambiguous evidence for the presence of chlorine in *bis*(styryl) derivatives. Furthermore, in combination with other spectral techniques - such as infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy - MS data contribute to a comprehensive characterization of these compounds. The confirmation of molecular weight, and isotope distributions strengthens the structural assignment and ensures the reliability of synthetic results.

## 4. CONCLUSIONS

In summary, this work demonstrates an efficient synthetic route for constructing novel substituted 3-((*E*)-arylprop-2-enoyl)-4-((*E*)-styryl)coumarin derivatives through sequential Pechmann and Claisen–Schmidt condensations. These compounds feature extended π-conjugated systems, making them promising candidates for applications in materials science and medicinal chemistry. However, further studies are required to fully explore their electronic properties, photophysical behavior, and potential biological activities. Future research should focus on in-depth structure – activity relationship (SAR) studies, evaluation of semiconductor or optical properties, and assessment of their therapeutic potential through comprehensive biological assays.

***Acknowledgements.*** The authors would like to thank their colleagues and laboratory staff for their valuable assistance and discussions during the course of this work.

***CRediT authorship contribution statement.*** NguyenNgocThanh: Writing paper, Methodology, Investigation, Funding acquisition, Vu Minh Tan: Formal analysis, Supervision.

***Declaration of competing interest.*** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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