Novel Short-Step Synthesis of Functionalized γ-Phenyl-β-hydroxybutenoates and their Cyclization to 4-Hydroxycoumarins via the *N*-Hydroxybenzotriazole Methodology

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Abstract: A novel method for the synthesis of functionalized 3-substituted 4-hydroxycoumarins is reported. *C*-Acylation compounds were derived from the reaction of the *N*-hydroxybenzotriazole ester of the functionalized acetyl salicylic acids and a variety of active methylene compounds and cyclized to the title compounds. The synthesis is simple and the compounds are produced in yields varying from 39 to 80%. The structure of the newly prepared *C*-acylation compounds was thoroughly studied through NMR spectroscopy for the first time in the literature.

Key words: coumarins, *N*-hydroxybenzotriazole, natural products, acylations, NMR spectroscopy, heterocycles

4-Hydroxy 3-substituted coumarins (Figure 1), a class of fused ring heterocycles, occur widely among natural products and have importance in medicine.[1–3] Several natural products with the coumarinic moiety exhibit interesting biological and pharmacological properties. They are antibacterial, anti-HIV active,[4] antiviral, intisecticidal[5] and anticoagulant.[6,7] Additionally, coumarin derivatives have been used as food additives, perfumes, cosmetics, dyes[8,9] fluorescent probes and triplet sensitizers,[10] herbicides and anticancer agents.[7] More specifically, we could mention the preparation of a series of 3-cyano-4-hydroxycoumarins as inhibitors of passive cutaneous anaphylaxis in rats.[11] In addition, a series of coumarins bearing different groups on the aromatic ring were synthesized and tested as caspase activators and apoptosis inducers,[12] showing that these compounds can be used to induce cell death under a variety of conditions in which uncontrolled growth and spread of abnormal cells occurs. Among the variety of 4-hydroxycoumarins which have been isolated as natural products, we could mention robustic acid,[13] ferulenol and its analogues[14,15]and two sesquiterpenecoumarins isolated from *Ferula pallida*.[16]

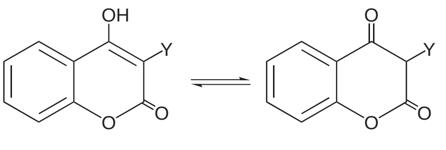

Figure 1 3-Substituted 4-hydroxycoumarins

From what was said above, it is obvious why the synthesis of coumarin heterocycles is of great importance for many research groups. The classical von Pechmann synthetic route to 4-substituted coumarins consists of the condensation of phenols with β-keto esters[17] in the presence of a variety of reagents[18] including several catalysts.[19–21] Also, coumarins have been synthesized by methods including Perkin,[22] Reformatsky,[23] Knoevenagel,[24] and Wittig reactions.[25] However, most of the above methods are less convenient, since they require several steps and vigorous conditions.

Over the last years, we have been involved in a one-step synthesis of tetramic[26] and tetronic acids[27] employing *N*-hydroxybenzotriazole esters of α-amino or α-hydroxy acids as acylating agents of active methylene compounds. The reaction was used to produce a wide variety of γ-amino-[28] or γ-hydroxybutenoates,[29] which can be converted to five-membered heterocycles of biological interest. With the previously discussed convenient preparation of a variety of activated systems from α-amino or α-hydroxy acids in hand, we are in a position now to approach the synthesis of 3-substituted 4-hydroxycoumarins with several substituents on the aromatic ring, and their *C*-acylation precursors using as activated building blocks the *N*-hydroxybenzotriazole esters of functionalized acetyl salicylic acids.

In this paper, we describe an efficient short-step synthesis for producing 3-substituted 4-hydroxycoumarins with several substituents on the aromatic ring via a *C*-acylation–cyclization reaction of active methylene compounds with the *N*-hydroxybenzotriazole esters of functionalized acetyl salicylic acids. In addition, the functionalized 'intermediates', γ-phenyl-β-hydroxybutenoates, have been isolated and their structure was studied by NMR spectroscopy revealing their existence in different tautomeric forms. The synthetic route leading to the *C*-acylation products and the corresponding functionalized coumarins is summarized in Scheme 1 and Table 1.

Our strategy involves the condensation of the *N*-hydroxybenzotriazole esters of the functionalized acetyl salicylic acids **1a**–**e** with the anions of active methylene compounds **3a**–**f**. The important intermediates **4a**–**f** were converted to the corresponding 3-alkoxycarbonyl-4-hydroxycoumarins **5a**–**f** via an intramolecular lactoniza-

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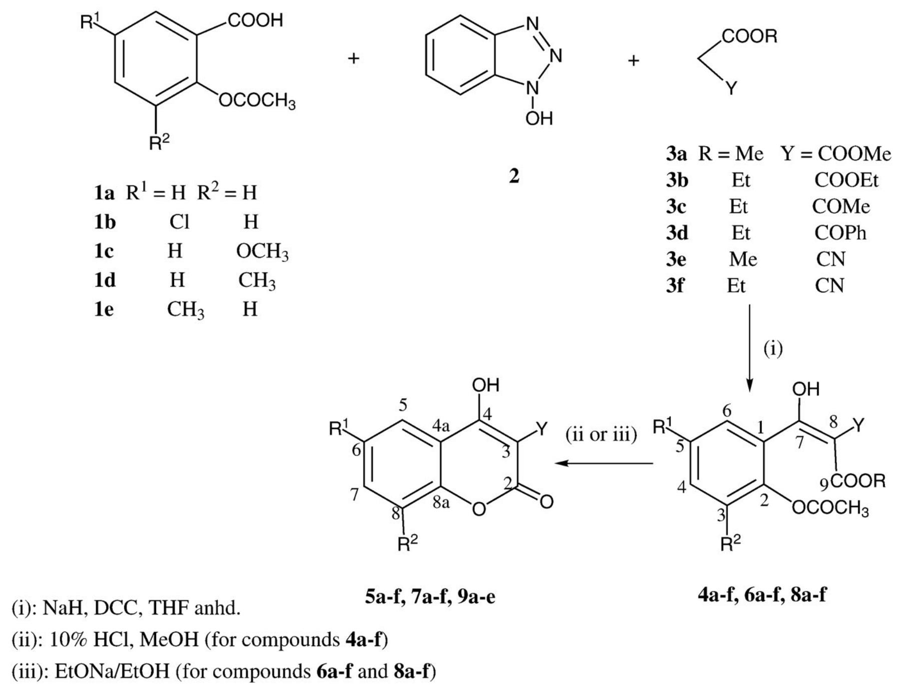

Scheme 1 Synthesis of the *C*-acylation compounds and the corresponding functionalized coumarins by using *N*-hydroxybenzotriazole

tion, using a methanolic hydrochloric acid solution (10%). On the other hand, the intermediates **6a**–**f** and **8a**–**f** were converted to the corresponding 3-acyl-4-hydroxycoumarins **7a**–**f** and 3-cyano 4-hydroxycoumarins **9a**–**e** via a cyclization reaction using sodium ethoxide in ethanol. The *N*-hydroxybenzotriazole esters of α-amino acids are

Table 1 *C*-Acylation Compounds and the Corresponding Functionalized Coumarins

Compound	R^1	R^2	R	Y	Compound	R^1	R^2	Y
4a	H	H	Me	COOMe	**5a** (from **4a**)	H	H	COOMe
4b	H	H	Et	COOEt	**5b** (from **4b**)	H	H	COOEt
4c	Cl	H	Et	COOEt	**5c** (from **4c**)	Cl	H	COOEt
4d	H	OMe	Et	COOEt	**5d** (from **4d**)	H	OMe	COOEt
4e	H	Me	Et	COOEt	**5e** (from **4e**)	H	Me	COOEt
4f	Me	H	Et	COOEt	**5f** (from **4f**)	Me	H	COOEt
6a	H	H	Et	COMe	**7a** (from **6a**)	H	H	COMe
6b	H	H	Et	COPh	**7b** (from **6b**)	H	H	COPh
6c	Cl	H	Et	COMe	**7c** (from **6c**)	Cl	H	COMe
6d	H	OMe	Et	COMe	**7d** (from **6d**)	H	OMe	COMe
6e	H	Me	Et	COMe	**7e** (from **6e**)	H	Me	COMe
6f	Me	H	Et	COMe	**7f** (from **6f**)	Me	H	COMe
8a	H	H	Me	CN	**9a** (from **8a**)	H	H	CN
8b	H	H	Et	CN	**9b** (from **8c**)	Cl	H	CN
8c	Cl	H	Et	CN	**9c** (from **8d**)	H	OMe	CN
8d	H	OMe	Et	CN	**9d** (from **8e**)	H	Me	CN
8e	H	Me	Et	CN	**9e** (from **8f**)	Me	H	CN
8f	Me	H	Et	CN				

well-known activated synthons used in peptide synthesis.[30] The requisite *N*-hydroxybenzotriazole esters of the functionalized acetyl salicylic acids were synthesized by condensation of equimolar amounts of functionalized O-protected salicylic acids **1a**–**e** with *N*-hydroxybenzotriazole **2** and dicyclohexylcarbodiimide (DCC) in anhydrous tetrahydrofuran at 0 °C. After a reaction time of 24 h, the reaction mixture was filtered off and the filtrate containing the non-isolated active ester was used as acylating agent in the next step. In a typical *C*-acylation reaction, the active methylene compounds **3a**–**f** (1 equiv) was treated with sodium hydride (2 equiv) in anhydrous tetrahydrofuran at room temperature. After stirring for 2.5 h, the solvent was removed under reduced pressure, the residue was diluted with water, washed with diethyl ether and the aqueous layer was acidified with aq hydrochloric acid (10%) to give the functionalized intermediates **4a**–**f**, **6a**–**f** and **8a**–**f** after extraction with dichloromethane. These intermediates, the functionalized γ-phenyl-β-hydroxybutenoates, were purified by flash chromatography and their structure was assigned on the basis of their ^{1}H NMR spectral data (see Experimental). Cyclization of the *C*-acylation compounds **4a**–**f** to the corresponding functionalized 3-alkoxycarbonyl-4-hydroxycoumarins **5a**–**f** was affected by treatment with a methanolic hydrochloric acid solution (10%) at room temperature for 48 h. On the other hand, the *C*-acylation compounds **6a**–**f** and **8a**–**f** were treated with a solution of sodium ethoxide in absolute ethanol at room temperature for 24 h to afford the corresponding functionalized 3-acyl-4-hydroxycoumarins **7a**–**f** and 3-cyano-4-hydroxy coumarins **9a**–**e**, respectively. According to the proposed methodology, the active carbon of the methylene compound ultimately becomes the 3-carbon of the coumarin ring, and any substituents attached to this carbon will subsequently reside in the correct position, while the functionalized salicylic acid ring supplies the remainder of the molecule.

An important feature of the proposed methodology has been the use of *N*-hydroxybenzotriazole esters as useful precursors for the synthesis of compounds with interesting biological properties. The activation of acetyl salicylic acid as its hydroxybenzotriazole ester is an attractive alternative to other activated salicylic acid species[6,7] permitting mild reaction conditions. Another advantage is that there is no need for isolating the intermediate active ester; this fact reduces the reaction time, in contrast to previously described methodologies and is beneficial for the overall yield of the reaction. Additionally, the absence of active sites on the *N*-hydroxybenzotriazole molecule is a way to control the chemoselectivity of the reaction, a feature which was studied in one of our previous papers.[29] Finally, the methodology is simple, inexpensive and easily scaled up.

All compounds that are presented in this paper have been studied by means of ^{1}H NMR spectroscopy and their elemental analyses have been acquired. In addition, we have acquired representative ^{13}C NMR and IR spectra of some compounds.

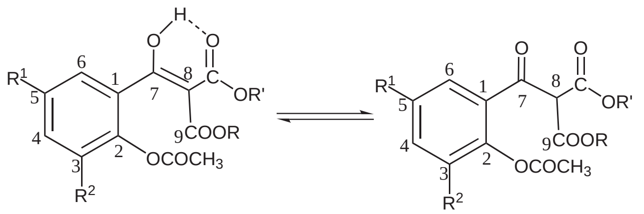

Figure 2 Keto–enol equilibrium of the *C*-acylation compounds derived from malonates

Starting the discussion of the NMR spectra with the *C*-acylation intermediates **4a**–**f** derived from the use of malonates, we should mention their existence in enol and keto tautomers in different ratios (Figure 2, see Experimental).

In cases where the substituent on the aromatic ring is the methoxy or 5-methyl group, the keto form is favorable whereas the 3-chloro and 3-methyl derivatives show a preference for the enolic form. In an effort to correlate the signals of each group to the enol and keto form, we have also taken into account a relevant paper which presented ^{1}H NMR data for some of these compounds without giving signals for both forms but only for the dominant one.[31]

Based on the NMR spectra, the *C*-acylation compounds **7a**–**f** were found to exist, in $CDCl_3$ solution, in the enolic form. The ^{1}H NMR spectra of the intermediates derived from acetylacetate are not so simple since these compounds participate in the enol–enol equilibrium of tautomers having a hydrogen bond between the enolic proton at C-7 and the oxygen of acetyl group (tautomers **A**, **B**) or ethoxycarbonyl group (tautomers **C**, **D**) (Figure 3).

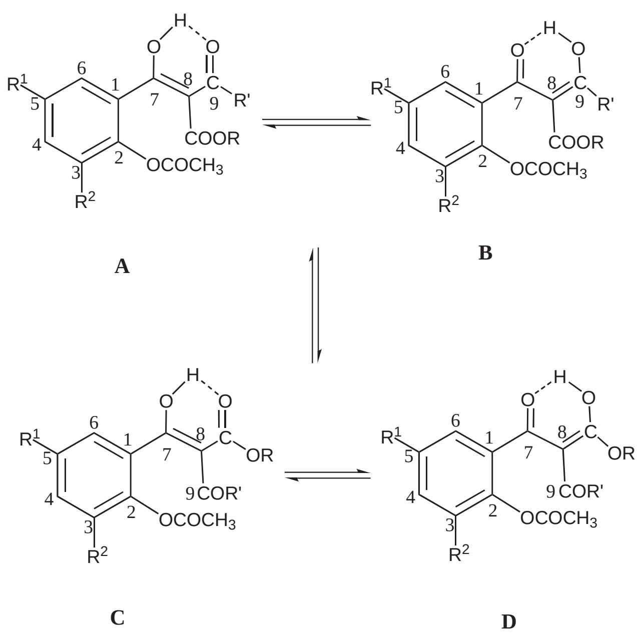

Figure 3 Enol–enol equilibrium of the *C*-acylation compounds derived from acylacetates

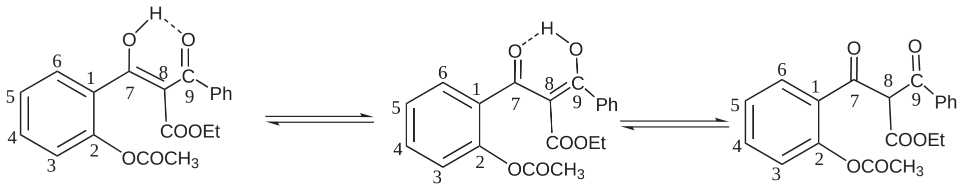

Figure 4 Tautomers of ethyl [(2-acetoxyphenyl)hydroxymethylidene]benzoylacetate

On the other hand, in the case of compound **6b** (when benzoyl acetate was used) the keto form is observed in favor of the enolic tautomer (Figure 4).

The NMR and IR spectra of the *C*-acylation compounds **8a–e** bearing a cyano group show some interesting features. There is no signal for the methine proton of the keto tautomer, since these compounds are found only in their enolic form. This observation is fully in accordance with the strong electron withdrawing character of the cyano group and the observation which was made for the *C*-acylation compounds of cyano acetates with the *N*-hydroxybenzotriazole esters of α-hydroxy acids.[28] In addition, the hydrogen bond between the alkoxycarbonyl and the hydroxy group appears at δ = 13.68 in compounds **8a** and **8b**, as expected for hydrogen bonds of alkoxycarbonyl groups.

Total assignments on the ^{1}H and ^{13}C NMR spectra of 4-hydroxycoumarins were accomplished by utilizing HETCOR experiments for compound **5b** and the data mentioned in a related paper referring to quinolinones.[32] So, correlations were observed between carbons resonating at δ = 14.1 ($COOCH_2CH_3$), 62.8 ($COOCH_2CH_3$), 116.9 (C-8), 124.3 (C-6), 125.1 (C-5) and 135.6 (C-7), and protons resonating at δ = 1.46 ($COOCH_2CH_3$), 4.51 ($COOCH_2CH_3$), 7.30–7.36 (H-8), 7.30–7.36 (H-6), 8.02 (H-5) and 7.68 (H-7), respectively.

In conclusion, we have successfully synthesized a series of functionalized 3-substituted 4-hydroxycoumarins and the *C*-acylation compounds which are used as precursors for their synthesis using a short-step methodology. The methodology makes use of the *N*-hydroxybenzotriazole ester of the functionalized acetyl salicylic acid as acylating agent and the desired active methylene compounds. The reaction gives high yields and a short reaction time is required in contrast to previous methodologies. In addition, the functionalized intermediate γ-hydroxybutenoates have been isolated in pure form after column chromatography and their structure was studied by means of ^{1}H NMR spectroscopy, and revealed their existence in different tautomeric forms for the first time. Work currently in progress includes application of the proposed methodology on the preparation of other heterocyclic ring systems with known biological activity. Also, the application of this methodology in the synthesis of natural products containing the coumarin nucleus is in our future plans.

Mps were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The FT-IR spectra were recorded on a Nicolet Magna IR 560. The NMR spectra were recorded on a Varian Gemini-2000 300 MHz and a Bruker AC 300 300 MHz spectrometer; chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyser.

Petroleum ether refers to the fraction with bp (40–60 ºC). Commercially available THF was dried prior to use by refluxing over Na. All other solvents (puriss quality) were used without further purification. Origin and purity of the other reagents are as follows: salicylic acid, purum; active methylene compounds, puriss; DCC, puriss; HOBt, purum.

Functionalized 2-Acetoxybenzoic Acids 1b–e; General Procedure[33]

In a typical reaction, the functionalized salicylic acid (20 mmol) was mixed with acetic anhydride (15 mL) and a few drops of aq phosphoric acid (85%). The mixture was stirred under reflux for 2 h. Subsequently H_2O (3 mL) was added. The reaction was continued for 5 min and the mixture was poured into cold H_2O (30 mL) and brought to r.t.. The precipitate formed was filtered off, washed with H_2O and dried in vacuo.

Functionalized *C*-Acylation Compounds 4a–f, 6a–f and 8a–f; General Procedure

In a typical reaction, the functionalized acetyl salicylic acid **1a**–**e** (10 mmol) was treated with *N*-hydroxybenzotriazole (**2**) (1.35 g, 10 mmol), and DCC (2.05 g, 10 mmol) was added dropwise in anhyd THF (40 mL) at 0 °C for 1 h. The resulting suspension was refrigerated overnight at 3–5 °C. The precipitated solid (DCCU) was filtered off and the filtrate was added to a solution of sodium hydride (0.8 g, 20 mmol) and the appropriate active methylene compound **3a**–**f** (10 mmol) in anhyd THF (80 mL). The resulting mixture was stirred at r.t. for 2.5 h and then concentrated in vacuo. The obtained gum was diluted with H_2O and washed with Et_2O. The aq extract was acidified with aq HCl (10%) in an ice–H_2O bath. The precipitated white solid (*N*-hydroxybenzotriazole) was filtered off and the aq filtrate was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the *C*-acylation compounds **4a**–**f**, **6a**–**f** and **8a**–**f** as oils. The oily products **4a**–**f** and **6a**–**f** were purified by flash chromatography (petroleum ether–EtOAc). On the other hand, the cyanoacetates **8a**–**f** were not purified by flash chromatography since they are unstable under such conditions, but they were triturated with pentane and Et_2O for purification.

Functionalized 3-Alkoxycarbonyl-4-hydroxycoumarins; General Procedure

The *C*-acylation compounds **4a**–**f** (5 mmol) were dissolved in MeOH (10 mL) and treated with aq HCl (10%; 10 mL) for 48 h at r.t. to afford the corresponding substituted 3-methoxycarbonyl- **5a** and 3-ethoxycarbonyl-4-hydroxycoumarins **5b**–**f** as white solids. All solid products were filtered off, washed with petroleum ether and dried in vacuo.

Functionalized 3-Acyl- and 3-Cyano-4-hydroxycoumarins 7a–f and 9a–e; General Procedure

The *C*-acylation compounds **6a–f** and **8a–f** (5 mmol) were treated with a solution of sodium (2.3 g, 10 mmol) in absolute EtOH (10 mL) and stirred at r.t. for 24 h. The mixture was evaporated under reduced pressure and the residue was diluted with H_2O and washed with Et_2O. The aq layer was acidified with aq HCl (10%) to afford the functionalized 3-acetyl- **7a**,**c**–**f** and 3-benzoyl-4-hydroxycoumarins **7b** as white solids. All solid products were filtered off, washed with petroleum ether and dried in vacuo.

Analytical and Spectroscopic Data of All Compounds

2-Acetoxy-5-chlorobenzoic Acid (1b)

Yield: 2.8 g, (65%); mp 157–159 °C (lit.[34] 153–154 °C).

^{1}H NMR ($CDCl_3$): δ = 2.34 (s, 3 H, $OCOCH_3$), 7.09 (d, *J* = 8.5 Hz, 1 H, H-3), 7.58 (dd, *J* = 2.4, 8.5 Hz, 1 H, H-4), 8.08 (d, *J* = 2.4 Hz, 1 H, H-6).

2-Acetoxy-3-methoxybenzoic Acid (1c)

Yield: 3.0 g, (71%); mp 140–142 °C.

^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3 H, $OCOCH_3$), 3.86 (s, 3 H, OCH_3), 7.19 (dd, *J* = 1.8, 7.8 Hz, 1 H, H-4), 7.26 (t, *J* = 7.8 Hz, 1 H, H-5), 7.65 (dd, *J* = 1.8, 7.8 Hz, 1 H, H-6).

Anal. Calcd for $C_{10}H_{10}O_5$ (210): C, 57.14; H, 4.76. Found: C, 57.29; H, 4.61.

2-Acetoxy-3-methylbenzoic Acid (1d)

Yield: 2.4 g, (62%); mp 117–118.5 °C.

^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3 H, CH_3), 2.37 (s, 3 H, $OCOCH_3$), 7.24 (t, *J* = 7.8 Hz, 1 H, H-5), 7.49 (dd, *J* = 1.8, 7.8 Hz, 1 H, H-4), 7.95 (dd, *J* = 1.8, 7.8 Hz, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 16.0 (CH_3), 20.7 (OCO*C*H_3), 122.1, 125.8, 130.2, 132.5, 136.5, 149.9 (aromatic carbons), 169.4, 170.4.

Anal. Calcd for $C_{10}H_{10}O_4$ (194): C, 61.86; H, 5.15. Found: C, 62.00; H, 5.01.

2-Acetoxy-5-methylbenzoic Acid (1e)

Yield: 3.5 g (90%); mp 148–151 °C.

^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3 H, $OCOCH_3$), 2.40 (s, 3 H, CH_3), 7.02 (d, *J* = 8.1 Hz, 1 H, H-3), 7.41 (dd, *J* = 1.8, 8.1 Hz, 1 H, H-4), 7.91 (d, *J* = 1.8 Hz, 1 H, H-6).[35]

Methyl [(2-Acetoxyphenyl)hydroxymethylidene]methoxycarbonylacetate (4a)

Yield: 1.6 g (54%); viscous oil [purified by column chromatography (petroleum ether–EtOAc, 7:3)].

^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 2.5 H, $OCOCH_3$ keto), 2.39 (s, 3 H, $OCOCH_3$ enol), 3.51, 3.92 (2 s, 6 H, $COOCH_3$ enol), 3.81 (s, 5 H, $COOCH_3$ keto), 5.27 (s, 0.8 H, methine proton keto), 7.17–7.89 (m, 7 H, aromatic protons enol and keto), 13.67 (s, 1 H, OH enol).

Ethyl [(2-Acetoxyphenyl)hydroxymethylidene]ethoxycarbonylacetate (4b)

Yield: 1.7 g (53%); mp 50–52 °C [(purified by column chromatography (petroleum ether– EtOAc, 93:7)].

^{1}H NMR ($CDCl_3$): δ = 0.82, 1.26 (2 t, *J* = 7.0, 7.0 Hz, 3.6 H, $COOCH_2CH_3$ enol), 1.15 (t, *J* = 7.0 Hz, 6 H, $COOCH_2CH_3$ keto), 2.18 (s, 1.8 H, $OCOCH_3$ enol), 2.28 (s, 3 H, $OCOCH_3$ keto), 3.89, 4.27 (2 q, *J* = 7.0, 7.0 Hz, 2.2 H, $COOCH_2CH_3$ enol), 4.16 (q, *J* = 7.0 Hz, 4 H, $COOCH_2CH_3$ keto), 5.14 (s, 1 H, methine proton keto), 7.07–7.79 (m, 6 H, aromatic protons enol and keto), 13.60 (s, 0.57 H, OH enol).[6]

Ethyl [(2-Acetoxy-5-chlorophenyl)hydroxymethylidene]ethoxycarbonylacetate (4c)

Yield: 1.7 g (48%); gummy solid [purified by column chromatography (petroleum ether– EtOAc, 7.5:2.5)].

^{1}H NMR ($CDCl_3$): δ = 0.97, 1.35 (2 t, *J* = 6.7, 6.7 Hz, 6 H, $COOCH_2CH_3$ enol), 1.25 (t, *J* = 7.3 Hz, 2.6 H, $COOCH_2CH_3$ keto), 2.25, 2.34 (2 s, 4.3 H, $OCOCH_3$ enol and keto), 4.15, 4.35 (2 q, *J* = 6.7, 6.7 Hz, 4 H, $COOCH_2CH_3$ enol), 4.22 (q, *J* = 7.3 Hz, 1.8 H, $COOCH_2CH_3$ keto), 5.12 (s, 0.4 H, methine proton keto), 7.07–7.12, 7.38–7.58 (2 m, 4.3 H, aromatic protons enol and keto), 13.66 (s, 1 H, OH enol).[31]

Ethyl [(2-Acetoxy-3-methoxyphenyl)hydroxymethylidene]ethoxycarbonylacetate (4d)

Yield: 2.0 g (57%); mp 49–52 °C [purified by column chromatography (petroleum ether– EtOAc, 7:3)].

^{1}H NMR ($CDCl_3$): δ = 0.93, 1.34 (2 t, *J* = 7.3, 7.3 Hz, 4 H, $COOCH_2CH_3$ enol), 1.24 (t, *J* = 7.3 Hz, 6 H, $COOCH_2CH_3$ keto), 2.27 (s, 2 H, $OCOCH_3$ enol), 2.35 (s, 3 H, $OCOCH_3$ keto), 3.83, 3.84 (2 s, 4.5 H, OCH_3, enol and keto), 3.98, 4.33 (2 q, *J* = 7.3, 7.3 Hz, 2.4 H, $COOCH_2CH_3$ enol), 4.23 (q, *J* = 7.3 Hz, 4 H, $COOCH_2CH_3$ keto), 5.12 (s, 1 H, methine proton keto), 6.99–7.43 (m, 5 H, aromatic protons enol and keto), 13.54 (s, 0.6 H, OH enol).[31]

Ethyl [(2-Acetoxy-3-methylphenyl)hydroxymethylidene]ethoxycarbonylacetate (4e)

Yield: 2.1 g (62%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 8:2)].

^{1}H NMR ($CDCl_3$): δ = 0.91, 1.33 (2 t, *J* = 7.3, 7.3 Hz, 6 H, $COOCH_2CH_3$ enol), 1.23 (t, *J* = 7.3 Hz, 2.4 H, $COOCH_2CH_3$ keto), 2.18 (s, 4.2 H, CH_3 enol and keto), 2.27 (s, 3 H, $OCOCH_3$ enol), 2.36 (s, 1.2 H, $OCOCH_3$ keto), 3.97, 4.33 (2q, *J* = 7.3, 7.3 Hz, 4 H, $COOCH_2CH_3$ enol), 4.23 (q, *J* = 7.3 Hz, 1.6 H, $COOCH_2CH_3$ keto), 5.17 (s, 0.4 H, methine proton keto), 7.14–7.30 (m, 4.2 H, aromatic protons enol and keto), 13.60 (s, 1 H, OH enol).[31]

^{13}C NMR ($CDCl_3$): δ = 13.4, 13.8, 14.0 ($COOCH_2CH_3$ enol and keto), 16.1, 16.2 (CH_3 enol and keto), 20.5 ($OCOCH_3$ enol), 20.7 ($OCOCH_3$ keto), 60.9, 61.8, 62.3 ($COOCH_2CH_3$ enol and keto), 63.7 (C-8 keto), 101.7 (C-8 enol), 125.6, 125.8, 125.9, 126.8, 127.7, 128.1, 129.2, 130.0, 131.4, 132.8, 133.2, 135.9, 146.3, 148.2 (aromatic carbons enol and keto), 164.5 ($COOCH_2CH_3$ enol), 165.1 ($COOCH_2CH_3$ keto), 168.5, 168.8 ($OCOCH_3$ enol), 171.1 ($OCOCH_3$ keto), 174.9 (C-7 enol), 188.3 (C-7 keto).

Ethyl [(2-Acetoxy-5-methylphenyl)hydroxymethylidene]ethoxycarbonylacetate (4f)

Yield: 1.5 g (45%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 8:2)].

^{1}H NMR ($CDCl_3$): δ = 0.93, 1.33 (2 t, *J* = 7.0, 7.0 Hz, 4.5 H, $COOCH_2CH_3$ enol), 1.23 (t, *J* = 7.0 Hz, 6 H, $COOCH_2CH_3$ keto), 2.23 (s, 2.2 H, $OCOCH_3$ enol), 2.33 (s, 5.3 H, CH_3 enol and keto), 2.36 (s, 3 H, $OCOCH_3$ keto), 3.97, 4.33 (2 q, *J* = 7.0, 7.0 Hz, 3 H, $COOCH_2CH_3$ enol), 4.23 (q, *J* = 7.0 Hz, 4 H, $COOCH_2CH_3$ keto), 5.16 (s, 1 H, methine proton keto), 7.00–7.63 (m, 5.3 H, aromatic protons enol and keto), 13.63 (s, 0.7 H, OH enol).

4-Hydroxy-3-methoxycarbonylcoumarin (5a)

Yield: 0.76 g (69%); mp 139–140 °C (lit.[36] 139–140.5 °C).

^{1}H NMR ($CDCl_3$): δ = 4.04 (s, 3 H, $COOCH_3$), 7.30–7.36 (pt and dd, 2 H, H-6, H-8), 7.68 (pt, *J* = 8.1 Hz, 1 H, H-7), 8.02 (d, *J* = 8.1 Hz, 1 H, H-5), 14.61 (s, 1 H, OH).

3-Ethoxycarbonyl-4-hydroxycoumarin (5b)

Yield: 0.77 g (66%); mp 100–101 °C (lit.[36] 98.5–100 °C).

^{1}H NMR ($CDCl_3$): δ = 1.46 (t, *J* = 6.9 Hz, 3 H, $COOCH_2CH_3$), 4.51 (q, *J* = 6.9 Hz, 2 H, $COOCH_2CH_3$), 7.30–7.36 (pt and dd, 2 H, H-6, H-8), 7.68 (pt, *J* = 8.1 Hz, 1 H, H-7), 8.02 (dd, *J* = 8.1, 1.8 Hz, 1 H, H-5), 14.76 (s, 1 H, OH).

6-Chloro-3-ethoxycarbonyl-4-hydroxycoumarin (5c)
Yield: 0.73 g (54%); mp 181–184 °C (lit.[34] 181–183 °C).

^{1}H NMR ($CDCl_3$): δ = 1.46 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 4.51 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.26 (d, *J* = 9.1 Hz, 1 H, H-8), 7.61 (dd, *J* = 2.4, 9.1 Hz, 1 H, H-7), 7.98 (s, 1 H, H-5), 14.77 (s, 1 H, OH).

3-Ethoxycarbonyl-4-hydroxy-8-methoxycoumarin (5d)
Yield: 0.92 g (70%); mp 177–180 °C.

^{1}H NMR ($CDCl_3$): δ = 1.45 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 3.95 (s, 3 H, OCH_3), 4.49 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.16–7.58 (m 3 H, aromatic protons), 14.74 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{12}O_6$ (264): C, 59.09; H, 4.55. Found: C, 59.20; H, 4.51.

3-Ethoxycarbonyl-4-hydroxy-8-methylcoumarin (5e)
Yield: 0.70 g (56%); mp 104–106 °C.

^{1}H NMR ($CDCl_3$): δ = 1.46 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 2.44 (s, 3 H, CH_3), 4.50 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.21 (t, *J* = 7.3 Hz, 1 H, H-6), 7.50 (d, *J* = 7.3 Hz, 1 H, H-7), 7.85 (d, *J* = 7.9 Hz, 1 H, H-5), 14.67 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{12}O_5$ (248): C, 62.90; H, 4.84. Found: C, 63.02; H, 4.91.

3-Ethoxycarbonyl-4-hydroxy-6-methylcoumarin (5f)
Yield: 0.77 g (62%); mp 124–126 °C.

^{1}H NMR ($CDCl_3$): δ = 1.44 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 2.41 (s, 3 H, CH_3), 4.49 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.18 (d, *J* = 8.5 Hz, 1 H, H-8), 7.45 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-7), 7.77 (s, 1 H, H-5), 14.71 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{12}O_5$ (248): C, 62.90; H, 4.84. Found: C, 63.04; H, 4.90.

Ethyl [(2-Acetoxyphenyl)hydroxymethylidene]acetylacetate (6a)
Yield: 1.2 g (41%); mp 54–57 °C [purified by column chromatography (petroleum ether– EtOAc, 9:1)].

^{1}H NMR ($CDCl_3$): δ = 0.78, 0.83 (2 t, *J* = 6.7, 6.7 Hz, 3 H, $COOCH_2CH_3$), 2.18, 2.20, 2.43 (3 s, 6 H, $OCOCH_3$, $COCH_3$), 3.89, 4.00 (2 q, *J* = 6.7, 6.7 Hz, 2 H, $COOCH_2CH_3$), 7.00–7.70 (m, 4 H, aromatic protons), 13.63, 17.46 (2 s, 0.25 + 0.75 H, OH).

Anal. Calcd for $C_{15}H_{16}O_6$ (292): C, 61.64; H, 5.48. Found: C, 61.44; H, 5.60.

Ethyl [(2-Acetoxyphenyl)hydroxymethylidene]benzoylacetate (6b)
Yield: 1.4 g (40%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 8:2)].

^{1}H NMR ($CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 1.3 H, $COOCH_2CH_3$ keto), 1.17, 1.25 (2 t, *J* = 7.2, 7.2 Hz, 3 H, $COOCH_2CH_3$ enol), 2.27, 2.29, 2.31 (3 s, 4.3 H, $OCOCH_3$ enol and keto), 3.89 (q, *J* = 7.2 Hz, 0.9 H, $COOCH_2CH_3$ keto), 4.19–4.34 (2 q, 2 H, $COOCH_2CH_3$ enol), 6.11 (s, 0.3 H, methine proton keto), 7.01–7.95 (m, 12.9 H, aromatic protons enol and keto), 13.46, 13.64, 17.24 (3 s, 0.7 H, OH enol).

Ethyl [(2-Acetoxy-5-chloro phenyl)hydroxymethylidene]acetylacetate (6c)
Yield: 1.6 g (49%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 9:1)].

^{1}H NMR ($CDCl_3$): δ = 0.84, 0.86 (2 t, *J* = 7.0, 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.15, 2.18, 2.19, 2.43 (4 s, 6 H, $COCH_3$, $OCOCH_3$), 3.92, 4.01 (2 q, *J* = 7.0, 7.0 Hz, 2 H, $COOCH_2CH_3$), 6.86–7.42 (m, 3 H, aromatic protons), 13.76, 17.35 (2 s, 0.3 + 0.7 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.3 ($COOCH_2CH_3$), 20.4, 20.6, 24.6 ($OCOCH_3$, $COCH_3$), 60.8, 61.2 ($COOCH_2CH_3$), 106.7, 109.3 (C-8), 118.6, 119.1, 123.7, 124.1, 128.4, 129.7, 119.7, 129.9, 131.2, 131.6, 132.1, 132.7, 134.9, 136.0, 145.4, 146.8 (aromatic carbons), 166.3, 168.5 ($COOCH_2CH_3$), 169.1, 171.4 ($OCOCH_3$), 183.6, 188.9 (C-7), 183.6, 195.8 ($COCH_3$).

Ethyl [(2-Acetoxy-3-methoxy phenyl)hydroxymethylidene]acetylacetate (6d)
Yield: 1.5 g (47%); mp 90–92 °C [purified by column chromatography (petroleum ether– EtOAc, 8:2)].

^{1}H NMR ($CDCl_3$): δ = 0.83, 0.88 (2 t, *J* = 6.7, 6.7 Hz, 3 H, $COOCH_2CH_3$), 2.16, 2.21, 2.23, 2.43 (4 s, 6 H, $COCH_3$, $OCOCH_3$), 3.81, 3.82 (2 s, 3 H, OCH_3), 3.92, 4.05 (2 q, *J* = 6.7, 6.7 Hz, 2 H, $COOCH_2CH_3$), 6.90–7.07 (m, 3 H, aromatic protons), 13.57, 17.42 (2 s, 0.25 + 0.75 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.3 ($COOCH_2CH_3$), 20.2, 20.3, 20.4, 24.8 ($OCOCH_3$, $COCH_3$), 56.2, 56.3 (OCH_3), 60.6, 61.0 ($COOCH_2CH_3$), 107.5, 109.6 (C-8), 114.3, 115.2, 119.7, 121.3, 126.2, 126.4, 132.3, 134.5, 136.7, 138.1, 151.3, 151.4 (aromatic carbons), 166.7, 168.1 ($COOCH_2CH_3$), 168.6, 171.4 ($OCOCH_3$), 181.5, 189.6 (C-7), 181.5, 195.8 ($COCH_3$).

Anal. Calcd for $C_{16}H_{18}O_7$ (322): C, 60.00; H, 6.00. Found: C, 60.04; H, 5.90.

Ethyl [(2-Acetoxy-3-methylphenyl)hydroxymethylidene]acetylacetate (6e)
Yield: 1.5 g (49%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 8:2)].

^{1}H NMR ($CDCl_3$): δ = 0.82, 0.87 (2 t, *J* = 7.0, 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.18, 2.23, 2.25, 2.45 (4 s, 9 H, $COCH_3$, $OCOCH_3$, CH_3), 3.93, 4.04 (2 q, *J* = 7.0, 7.0 Hz, 2 H, $COOCH_2CH_3$), 7.15–7.37 (m, 3 H, aromatic protons), 13.60, 17.47 (2 s, 0.25 + 0.75 H, OH).

Ethyl [(2-Acetoxy-5-methylphenyl)hydroxymethylidene]acetylacetate (6f)
Yield: 1.2 g (39%); viscous oil [purified by column chromatography (petroleum ether– EtOAc, 93:7)].

^{1}H NMR ($CDCl_3$): δ = 0.80, 0.85 (2 t, *J* = 7.0, 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.14, 2.16, 2.31, 2.41 (4 s, 9 H, $OCOCH_3$, CH_3, $COCH_3$), 3.90, 4.01 (2 q, *J* = 7.0, 7.0 Hz, 2 H, $COOCH_2CH_3$), 6.86–7.49 (m, 3 H, aromatic protons), 13.58, 17.48 (2 s, 0.3 + 0.7 H, OH).

3-Acetyl-4-hydroxycoumarin (7a)
Yield: 0.72 g, (67%); mp 136–137 °C (lit.[37] 138.5 °C, lit.[38] 141 °C, lit.[39] 138 °C, lit.[40] 137 °C)

^{1}H NMR ($CDCl_3$): δ = 2.79 (s, 3 H, $COCH_3$), 7.29–7.37 (pt and dd, 2 H, H-6, H-8), 7.70 (pt, *J* = 8.1 Hz, 1 H, H-7), 8.07 (dd, *J* = 8.1, 1.2 Hz, 1 H, H-5), 17.77 (s, 1 H, OH).

3-Benzoyl-4-hydroxycoumarin (7b)
Yield: 0.81 g, (61%); mp 146–147 °C (lit.[41] 148–151 °C).

^{1}H NMR ($CDCl_3$): δ = 7.32–7.75 (m, 8 H, aromatic protons), 8.12 (dd, *J* = 7.8, 1.2 Hz, 1 H, H-5), 16.74 (s, 1 H, OH).

3-Acetyl-6-chloro-4-hydroxycoumarin (7c)
Yield: 0.74 g (62%); mp 176–178 °C (lit.[42] 170 °C).

^{1}H NMR ($CDCl_3$): δ = 2.78 (s, 3 H, $COCH_3$), 7.25 (d, *J* = 9.1 Hz, 1 H, H-7), 7.62 (dd, *J* = 8.6, 2.4 Hz, 1 H, H-8), 8.01 (d, *J* = 2.4 Hz, 1 H, H-5), 17.81 (s, 1 H, OH).

Anal. Calcd for $C_{11}H_7ClO_4$ (238.5): C, 55.35; H, 2.94. Found: C, 55.26; H, 3.08.

3-Acetyl-4-hydroxy-8-methoxycoumarin (7d)
Yield: 0.7 g (60%); mp 170–172 °C.

^{1}H NMR ($CDCl_3$): δ = 2.77 (s, 3 H, $COCH_3$), 3.96 (s, 3 H, OCH_3), 7.18–7.27 (m, 2 H, H-6, H-7), 7.60 (dd, *J* = 7.3, 1.8 Hz, 1 H, H-5), 17.71 (s, 1 H, OH).

Anal. Calcd for $C_{12}H_{10}O_5$ (234): C, 61.54; H, 4.27. Found: C, 61.46; H, 4.42.

3-Acetyl-4-hydroxy-8-methylcoumarin (7e)
Yield: 0.71 g (65%); mp 108–110 °C.

^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 2.80 (s, 3 H, $COCH_3$), 7.26 (d, *J* = 8.1 Hz, 1 H, H-7), 7.55 (d, *J* = 6.6 Hz, 1 H, H-8), 7.91 (d, *J* = 8.1 Hz, 1 H, H-5), 17.67 (s, 1 H, OH).

Anal. Calcd for $C_{12}H_{10}O_4$ (218): C, 66.06; H, 4.59. Found: C, 65.96; H, 4.45.

3-Acetyl-4-hydroxy-6-methylcoumarin (7f)
Yield: 0.90 g (83%); mp 146–149 °C (lit.[43] 143–145 °C).

^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.79 (s, 3 H, $COCH_3$), 7.20 (d, *J* = 8.1 Hz, 1 H, H-7), 7.51 (d, *J* = 6.3 Hz, 1 H, H-8), 7.85 (s, 1 H, H-5), 17.75 (s, 1 H, OH).

Anal. Calcd for $C_{12}H_{10}O_4$ (218): C, 66.06; H, 4.59. Found: C, 65.99; H, 4.41.

Methyl [(2-Acetoxyphenyl)hydroxymethylidene]cyanoacetate (8a)
Yield: 1.8 g, (69%); viscous oil.

IR (in MeOH): 2229 (CN), 1771, 1663 (C=O), 1614 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3 H, $OCOCH_3$), 3.96 (s, 3 H, $COOCH_3$), 7.26 (d, *J* = 8.1 Hz, 1 H, H-6), 7.36 (pt, *J* = 8.1 Hz, 1 H, H-5), 7.58 (pt, *J* = 8.1 Hz, 1 H, H-4), 7.70 (dd, *J* = 8.1, 1.5 Hz, 1 H, H-3), 13.68 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 20.8 (OCO*C*H_3), 53.3 (COO*C*H_3), 82.0 (C-8), 114.6 (CN), 123.8 (C-1), 124.8 (C-3), 126.1 (C-5), 130.2 (C-6), 133.6 (C-4), 148.3 (C-2), 168.9 (O*C*OCH_3), 171.1 (*C*OOCH_3), 182.3 (C-7).

Ethyl [(2-Acetoxyphenyl)hydroxymethylidene]cyanoacetate (8b)
Yield: 2.2 g, (80%); viscous oil.

IR (in MeOH): 2229 (CN), 1771, 1657 (C=O), 1614 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, *J* = 6.9 Hz, 3 H, $COOCH_2CH_3$), 2.31 (s, 3 H, $OCOCH_3$), 4.41 (q, *J* = 6.9 Hz, 2 H, $COOCH_2CH_3$), 7.25 (d, *J* = 7.8 Hz, 1 H, H-6), 7.36 (pt, *J* = 7.8 Hz, 1 H, H-5), 7.59 (pt, *J* = 7.8 Hz, 1 H, H-4), 7.70 (dd, *J* = 7.8, 1.8 Hz, 1 H, H-3), 13.69 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.9 ($COOCH_2CH_3$) 20.8 ($OCOCH_3$), 63.0 ($COOCH_2CH_3$), 82.2 (C-8), 114.7 (CN), 123.8 (C-1), 125.0 (C-3), 126.1 (C-5), 130.2 (C-6), 133.6 (C-4), 148.3 (C-2), 168.9 (O*C*OCH_3), 170.8 (*C*OOCH_2CH_3), 182.3 (C-7).

Ethyl [(2-Acetoxy-5-chlorophenyl)hydroxymethylidene]cyanoacetate (8c)
Yield: 1.6 g (52%); viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 2.30 (s, 3 H, $OCOCH_3$), 4.41 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.23 (d, *J* = 8.5 Hz, 1 H, H-6), 7.52 (dd, *J* = 2.4, 8.5 Hz, 1 H, H-4), 7.63 (d, *J* = 2.4 Hz, 1 H, H-3).

Ethyl [(2-Acetoxy-3-methoxyphenyl)hydroxymethylidene]cyanoacetate (8d)
Yield: 1.5 g (49%); viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.39 (t, *J* = 7.3 Hz, 3 H, $COOCH_2CH_3$), 2.28, 2.32 (2 s, 3 H, $OCOCH_3$), 3.83 (s, 3 H, OCH_3), 4.39 (q, *J* = 7.3 Hz, 2 H, $COOCH_2CH_3$), 7.12–7.24 (m, 3 H, aromatic protons).

Ethyl [(2-Acetoxy-3-methylphenyl)hydroxymethylidene]cyanoacetate (8e)
Yield: 1.4 g (48%); viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.37 (t, *J* = 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.20 (s, 3 H, CH_3), 2.28 (s, 3 H, $OCOCH_3$), 4.37 (q, *J* = 7.0 Hz, 2 H, $COOCH_2CH_3$), 7.24 (t, *J* = 7.3 Hz, 1 H, H-5), 7.41 (d, *J* = 6.7 Hz, 1 H, H-6), 7.51 (d, *J* = 7.3 Hz, 1 H, H-4).

Ethyl [(2-Acetoxy-5-methylphenyl)hydroxymethylidene]cyanoacetate (8f)
Yield: 1.4 g (48%); viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.37 (t, *J* = 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.26, 2.36 (2 s, 6 H, $OCOCH_3$, CH_3), 4.37 (q, *J* = 7.0 Hz, 2 H, $COOCH_2CH_3$), 6.83–7.40 (m, 3 H, aromatic protons).

3-Cyano-4-hydroxycoumarin (9a)
Yield: 0.6 g (64%); mp 262–262 °C (lit.[11] 267–269 °C).

^{1}H NMR (DMSO-d_6): δ = 7.21 (pt and dd, 2 H, H-6, H-8), 7.51 (pt, *J* = 8.1 Hz 1 H, H-7), 7.83 (d, *J* = 8.1 Hz, 1 H, H-5).

6-Chloro-3-cyano-4-hydroxycoumarin (9b)
Yield: 0.79 g (71%); mp >300 °C.

^{1}H NMR (DMSO-d_6): δ = 7.23 (d, *J* = 8.4 Hz, 1 H, H-8), 7.53 (dd, *J* = 2.4, 8.4 Hz, 1 H, H-7), 7.72 (d, *J* = 2.4 Hz, 1 H, H-5).

Anal. Calcd for $C_{10}H_4ClNO_3$ (221.5): C, 54.18; H, 1.81; N, 6.32. Found: C, 54.00; H, 1.83; N, 6.53.

3-Cyano-4-hydroxy-8-methoxycoumarin (9c)
Yield: 0.62 g (57%); mp 254–256 °C.

^{1}H NMR (DMSO-d_6): δ = 3.85 (s, 3 H, OCH_3), 7.10–7.21 (m, 2 H, H-6, H-7), 7.40 (dd, *J* = 1.8, 7.9 Hz, 1 H, H-5).

Anal. Calcd for $C_{11}H_7NO_4$ (217): C, 60.83; H, 3.23; N, 6.45. Found: C, 60.80; H, 3.33; N, 6.53.

3-Cyano-4-hydroxy-8-methylcoumarin (9d)
Yield: 0.59 g (59%); mp 213–215 °C (lit.[11] 211–214 °C).

^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3 H, CH_3), 7.16 (t, *J* = 7.3 Hz, 1 H, H-6), 7.45 (d, *J* = 7.3 Hz, 1 H, H-7), 7.73 (d, *J* = 7.9 Hz, 1 H, H-5).

3-Cyano-4-hydroxy-6-methylcoumarin (9e)
Yield: 0.67 g (67%); mp 235–237 °C (lit.[11] 238–241 °C).

^{1}H NMR (DMSO-d_6): δ = 2.32 (s, 3 H, CH_3), 7.08 (d, *J* = 8.4 Hz, 1 H, H-8), 7.33 (dd, *J* = 2.1, 8.4 Hz, 1 H, H-7), 7.62 (d, *J* = 1.2 Hz, 1 H, H-5).

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