Sankar C Bhunia,[a] Sutanuka Pal,[b] Gopal C Patra,[a] and Sudhir C Pal[a]*

[a]Chemistry Department, Midnapore College, Midnapore 721 101, West Bengal, India
[b]School of Chemistry, University of Hyderabad, Hyderabad 500046, Andhra Pradesh, India
*E-mail: sudhirpal08@gmail.com

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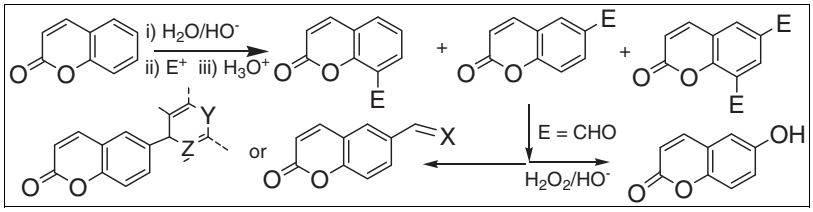

Some 6-disubstituted, 8-disubstituted, and/6,8-disubstituted compounds have been prepared from coumarin, 7-methylcoumarin, and 3,4-benzocoumarin. The Reimer–Tiemann reaction, Lederer–Manasse reaction, bromination using molecular bromine as well as 2,4,4,6-tetrabromocyclohex-2,5-dien-1-one, Elbs reaction, and diazocoupling have been carried under controlled conditions to obtain various derivatives. Further, several reactions of aldehyde derivatives of these coumarins have been carried on to prepare important functional compounds including some heterocycles. It is noteworthy that these aldehydes behave as phenolic aldehydes under alkaline conditions to undergo the Dakin reaction. The reactions are mostly carried in aqueous media involving a dianionic intermediate and hence fulfill one important criterion of green chemistry.

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INTRODUCTION

It has been observed that a saponified solution containing the dianion (**DA**) of coumarin gave back coumarin almost quantitatively upon acidification [1]. Hence, it is expected that any electrophilic reaction at the benzenoid ring performed with the saponified solution of coumarins would result in the formation of 6-disubstituted, 8-disubstituted, and/6,8-disubstituted coumarins after acidification. Our goal was to functionalize coumarins at the benzenoid ring by using the activating effect of the oxide group. This is important because the coumarin ring is a fluorophore and many compounds have been derived from it for use as sensors [2], and some have been tested to possess medicinal properties [3]. Accordingly, we proposed to carry out systematic studies on coumarins with reactions that could be carried out under alkaline condition. We decided to perform Reimer–Tiemann reaction, bromination using various brominating agents, Lederer–Manasse reaction [4], persulfate oxidation (Elbs reaction) [5], and diazocoupling on coumarin, 7-methylcoumarin, and 3,4-benzocoumarin. We have succeeded in preparing several derivatives by using very controlled conditions under which the olefinic bond in coumarin and 7-methylcoumarin remained unaffected. The reactions fulfill one of the important principles of green chemistry, that is, use of nonhazardous solvent [6] because the reactions are all carried in aqueous medium. The principle is depicted in Scheme 1.

We also wanted to examine the behavior of coumarin-6-carbaldehyde towards different nucleophiles: to see whether it prefers addition of these nucleophiles to the aldehydic carbon or to the β-carbon of the enoate moiety under a variety of conditions. Reactions with hydrazine and semicarbazide and condensations with acetone and malonic acid have been studied. Under mild basic to mild acidic conditions, most nucleophiles add to the –CHO group. The aldehyde group in this compound also responded favorably to three-component Biginelli condensation [7] and a three-component Hantzsch dihydropyridine synthsesis [8]. We carried out Dakin reaction [9] with the saponified solutions of coumarin-6-carbaldehyde, 7-methylcoumarin-6-carbaldehyde, and 3,4-benzocoumarin-6-carbaldehyde successfully to show that these compounds behave as a *para*-phenolic compounds under these conditions.

RESULTS AND DISCUSSION

Reimer–Tiemann reaction. Reimer–Tiemann reaction of coumarin (**I**) has been reported earlier [10]. We repeated the reaction with the given procedure, and the yield was found to be not satisfactory. We modified the conditions and have been able to improve the yield. Similar results were observed for 7-methylcoumarin (**II**) and 3,4-benzocoumarin (**III**). A further improvement in overall yield was recorded using a catalytic amount of crown ether. Under these conditions, dialdehydes were also formed in the case of coumarin and 7-methylcoumarin [1]. This was the first time report of the formation of dialdehydes in any Reimer–Tiemann reaction. The results of Reimer–Tiemann reactions are summarized in Scheme 2(a–c).

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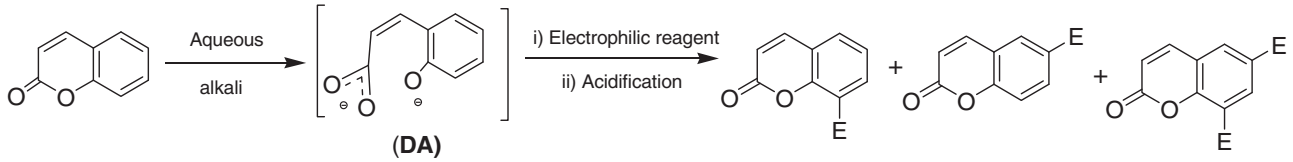
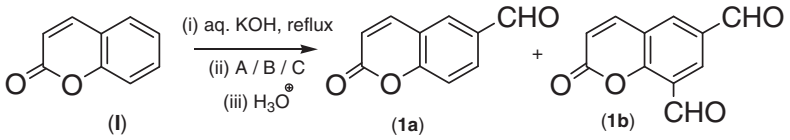
Scheme 1. The principle of derivatization of coumarins.

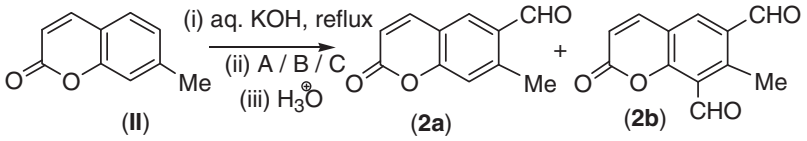


Scheme 2. (a) Reimer–Tiemann reaction of coumarin (**I**). (b) Reimer–Tiemann reaction of 7-methylcoumarin (**II**). (c) Reimer–Tiemann reaction of 3,4-benzocoumarin (**III**).



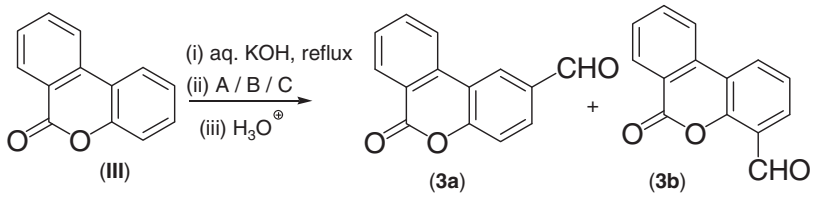
A : $CHCl_3$, 12 hr. reflux	35%	—
B : diluted with water; $CHCl_3$, 8 hr reflux	52%	—
C : Condition B + 5 mol% 18-Crown-6	50%	22%

(a) Reimer-Tiemann reaction of coumarin (**I**)



A : $CHCl_3$, 12 hr. reflux	30%	—
B : diluted with water; $CHCl_3$, 8 hr reflux	49%	—
C : Condition B + 5 mol% 18-Crown-6	44%	20%

(b) Reimer-Tiemann reaction of 7-methylcoumarin (**II**)



A : $CHCl_3$, 12 hr. reflux	15%	15%
B : diluted with water; $CHCl_3$, 8 hr reflux	19%	19%
C : Condition B + 5 mol% 18-Crown-6	26%	24%

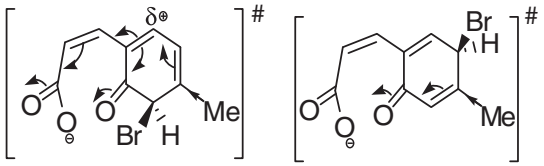
(c) Reimer-Tiemann reaction of 3,4-benzocoumarin (**III**)

Bromination. Molecular bromine that forms hypobromite in cold alkaline condition gave a mixture of two products in each case. Both coumarin (**I**) and 3,4-benzocoumarin (**III**) gave an approximately 2 to 1 ratio of two monobromo compounds namely 6-bromo- (**1c** and **3c**, respectively) and 8-bromo derivatives (**1d** and **3d**, respectively). 7-Methylcoumarin (**II**), on the other hand, yielded one monobromo (8-bromo-7-methylcoumarin, **2c**) and one dibromo (6,8-dibromo-7-methylcoumarin, **2d**) product. We studied bromination by using 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one (TBCO), which has been reported [11] to give controlled as well as regioselective bromination products. Indeed this happened in these cases too. Coumarin and 3,4-benzocoumarin gave 6-bromoderivative (**1c** and **3c**, respectively), whereas 7-methylcoumarin afforded 8-bromoderivative (**2c**) only when treated with one

equivalent of TBCO. The bromination at C-8 in preference to C-6 in case of 7-methylcoumarin is not very clear. A possibility may be the electronic effect of the methyl group stabilizing the transition state ($\mathbf{TS_1}$) for C-8 substitution better than that ($\mathbf{TS_2}$) for C-6 substitution (Scheme 3) [12].

In contrast to treatment of coumarin with bromine in chloroform that results in addition at the double bond [13], our methods give nuclear substitution product(s). This is the first report of the preparation of 6-bromoderivatives and 8-bromoderivatives of coumarins via bromination of parent compounds. The results are summarized in Scheme 4. Previously, these compounds were mostly synthesized from suitable bromosubstituted benzenoid compounds [14].

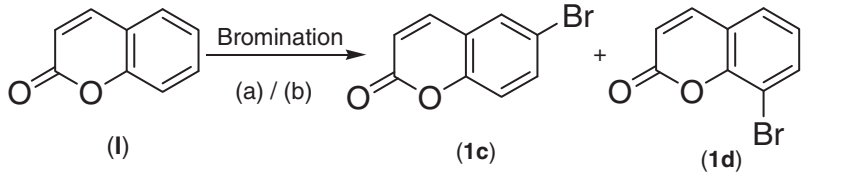
Scheme 3. Transition states for bromination for 7-methylcoumarin.



$\mathbf{TS_1}$ $\mathbf{TS_2}$

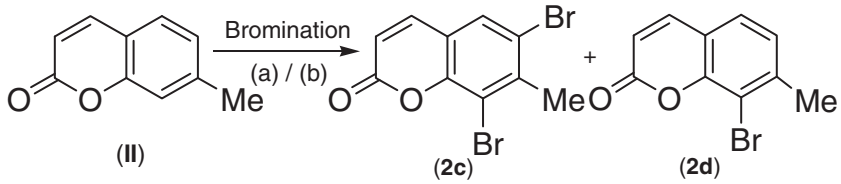
Lederer–Manasse reaction. Although coumarin–formaldehyde polymers were derived from salicyladehyde–formaldehyde polymerization reaction [15], a direct reaction of coumarin with formaldehyde has not been reported. Because in the saponified solution, the phenoxide moiety of coumarins is "free," we decided to study the reactions of these with formaldehyde (Lederer–Manasse reaction). Under strongly alkaline conditions, the compounds gave polymeric products. Attempts were made to obtain simple hydroxymethylated products. This was performed by carrying out the reactions at reduced pH (~8–10) by diluting the saponified solution of the substrates. Monohydroxymethyl as well as dihydroxymethyl derivatives were isolated in all the three cases (**1e** and **1f** from coumarin, **2e** and **2f** from 7-methylcoumarin, and **3e** from 3,4-benzocoumarin). However, major products from coumarin (**I**) and 7-methylcoumarin (**II**) were the precipitated dimeric products namely 6,6′-methylenebis-[coumarin-8-methanol] (**1g**) and 6,6′-methylenebis-[7-methylcoumarin-8-methanol] (**2g**), respectively. The reactions were slow at mild alkaline conditions, and 10–12 days were needed for complete reaction. For 3,4-benzocoumarin, the dimeric product could

Scheme 4. Bromination of coumarins (**I–III**) using bromine or 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one.



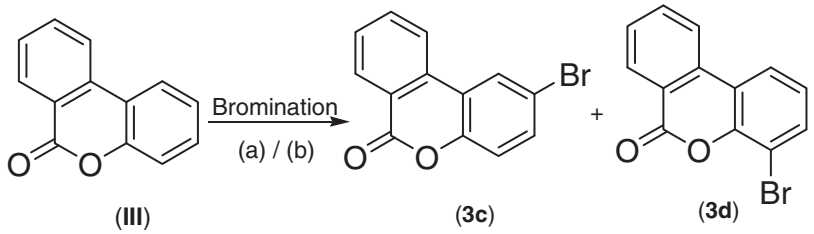
(**I**) (**1c**) (**1d**)

(a) Molecular Br_2	56%	30%
(b) TBCO (one equiv.)	81%	—



(**II**) (**2c**) (**2d**)

(a) Molecular Br_2	44%	25%
(b) TBCO (one equiv.)	—	58%



(**III**) (**3c**) (**3d**)

(a) Molecular Br_2	50%	27%
(b) TBCO (one equiv.)	76%	—

not be found possibly because the product (**3e**) was precipitated out and hence could not react further. All these compounds (Scheme 5) are reported here for the first time.

Diazocoupling. Coumarin (**I**) was reported to give 6-phenylazocoumarin (**1i**) by coupling with benzenediazonium chloride [10]. We decided to study these coupling reactions in detail with the three coumarins by using our procedure. It has been observed that a saponified solution of coumarin formed azo-products (**1i–1n**) by coupling at C-6 with various aromatic diazonium salts having electron-donating as well as electron-withdrawing groups at the aromatic ring of the diazonium salt. The yields were very good in all the cases (see Scheme 6). Even 7-methylcoumarin (**II**) and 3,4-benzocoumarin (**III**) yielded respective azo-dyes (**2e** and **3d**, respectively) with benzene diazonium chloride quite easily. We studied UV–vis spectra of all these azo-dyes (Table 1). All the dyes except (**1n**) exhibited band in the range 430–440 nm region; however, the intensity of absorption for (**2e**) having a methyl group at the coumarin part appears somewhat higher.

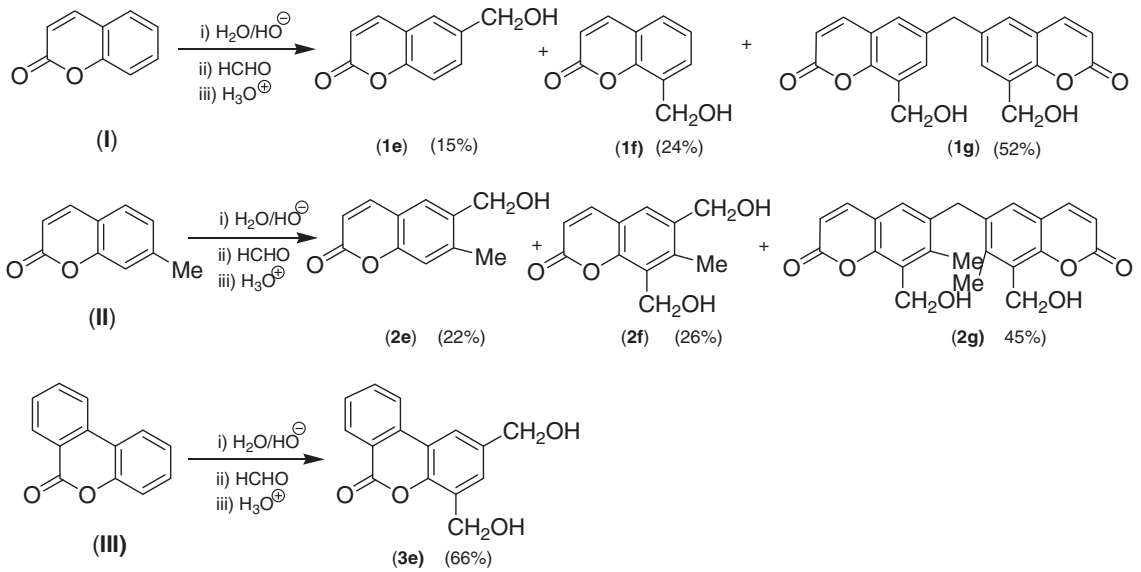
Elbs oxidation. The treatment of saponified solution of the three coumarins with potassium perdisulfate (viz. Elbs oxidation) gave results that are similar with earlier observations [16]. Mainly, 6-position obtained hydroxylated in each case. However, attempt to prepare 6,7-dihydroxycoumarin from 7-hydroxycoumarin (umbelliferrone) by this procedure led to oxidation at the double bond of the enoate chain. A degradation product namely 2,4-dihydroxybenzaldehyde was obtained (Scheme 7).

Condensations of coumarin-6-carbaldehyde. We performed condensation of the coumarin-6-carbaldehyde (**IV**) with acetone but did not find diarylidine product as reported earlier [10]. Instead, we obtained only monoarylidine (viz. 1:1 condensation) product namely 4-[coumarin-6-yl]but-3-en-2-one (**4a**). An attempted Knoevenagel condensation [17] with diethyl malonate did not yield the desired product in satisfactory yield. However, the Doebner variation [18] using malonic acid in pyridine under refluxing condition gave a very good yield of 3-[coumarin-6-yl]propenoic acid (**4b**) [19]. It furnished hydrazone (**4c**) as well as semicarbazone (**4d**) with considerable ease. In all these reactions, carried under mild basic conditions, conjugate addition to enoate moiety did not occur at all. It has been noted that coumarin itself underwent reaction with hydrazine to yield a hydrazide derivative (**CH**) where conjugate addition to C=C bond of enoate moiety also occurs (Scheme 8).

With excess hydrazine coumarin-6-carbaldehyde afforded complex mixture of products that could not be separated. The reaction can be controlled to obatain the product (**4c**) involving condensation only with the aldehyde group. This lactone aldehyde also underwent a three-component cyclo-condensation namely Biginelli condensation [7] with ethyl acetate and urea successfully under mild acidic condition in the presence of $FeCl_3$ to furnish the expected dihydropyrimidine derivative (**4e**) in satisfactory yield [20]. However, a better yield was obtained when Me_3SiCl was used as catalyst in DMF solvent [21]. A three-component tetramolecular Hantzsch synthesis involving the aldehyde, ethyl acetoacetate, and ammonium acetate lead to a dihydropyridine derivative (**4f**) in good yield upon refluxing in ethanol [22]. All these condensation reactions of coumarin-6-carbaldehyde (**IV**) are summarized in Scheme 9.

Dakin reaction of aldehydes derived from the coumarins. Dakin reaction [9] works well for aromatic aldehydes having OH or NH_2 group at *ortho*-position or *para*-position. Its application in organic synthesis has so far been exploited in

Scheme 5. Lederer–Manasse reactions of coumarins (**I–III**).



Scheme 6. Diazocoupling of coumarins (**I–III**).

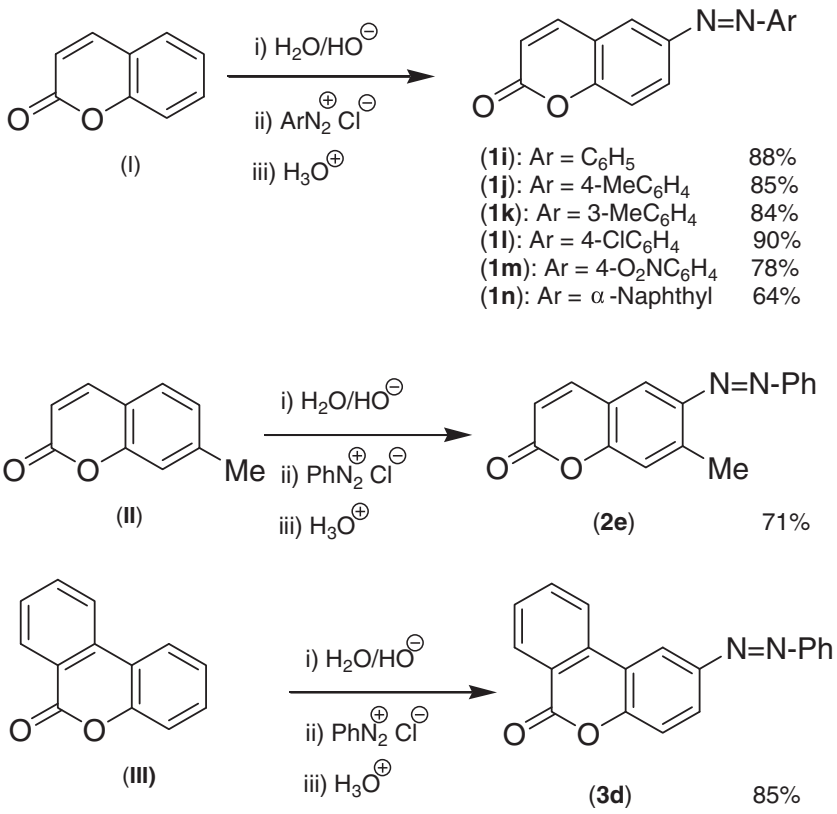
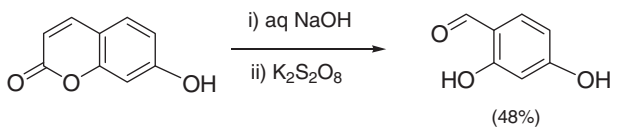


Table 1

UV–vis spectral data of azo-dyes of coumarins.

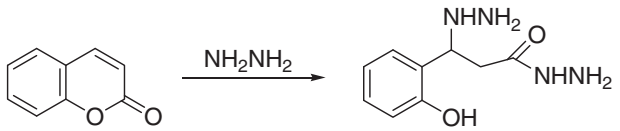
Compound (structure no.)	λ_{max} (nm)	ε_{max}
6-Phenylazocoumain (**1i**)	440.5	1446
6-[4-Methylphenyl]azocoumain (**1j**)	435	1584
6-[3-Methylphenyl]azocoumain (**1k**)	440.5	2310
6-[4-Chlorophenyl]azocoumain (**1l**)	430	2650
6-[4-Nitrophenyl]azocoumain (**1m**)	430	2556
6-[1-Naphthyl]azocoumarin (**1n**)	380	6750
7-Methyl-6-phenylazocoumarin (**2e**)	438.2	4606
6-Phenylazo-3,4-benzocoumarin (**3e**)	432.4	1400

Scheme 7. Elbs reaction of 7-hydroxycoumarin.



only a limited number of cases [23]. Coumarin aldehydes had never been subjected to this reaction. We carried out this reaction (see Scheme 10) with coumarin-6-carbaldehyde (**IV**), 7-methylcoumarin-6-carbaldehyde (**V**), and 3,4-benzocoumarin-6-carbaldehyde (**VI**). Again, the substrates were first hydrolysed with alkali and then diluted prior to treatment with hydrogen peroxide in cold condition. Expected product (i.e., 6-hydroxycoumrin (**4g**), 6-hydroxy-7-methylcoumarin (**5**), and 6-hydroxy-3,4-benzocoumarin (**6**) from (**IV**), (**V**), and (**VI**), respectively) was obtained in each case. The last two compounds are reported here for the first time.

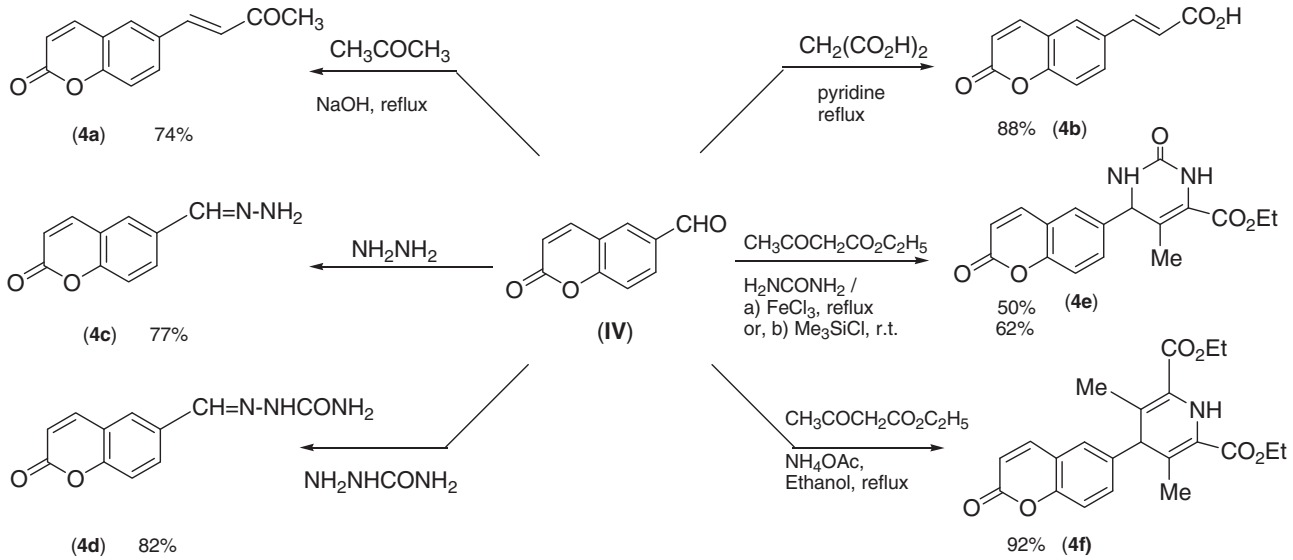
Scheme 8. Reaction of coumarin with hydrazine.



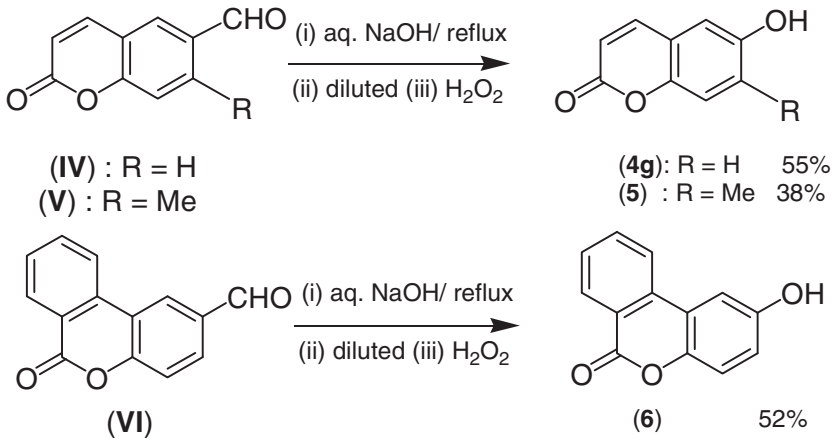
CONCLUSION

In conclusion, it can be said that enoate (and benzoate in 3,4-benzocoumarin) side chain in heterocyclic ring of coumarins behaves as proton of phenols; it is delinked from the O of benzenoid ring in alkaline condition and reunites in acid medium. In between, controlled reactions can

Scheme 9. Condensation reactions of coumarin-6-carbaldehyde (**IV**).



Scheme 10. Dakin reactions of coumarin-6-carbaldehydes (**IV–VI**).



be performed to introduce suitable group at the 6-position and/or 8-position. A general method to functionalize coumarins has therefore been established.

EXPERIMENTAL

General. Melting points were recorded in metal bath and are uncorrected. IR spectra were recorded in Perkin-Elmer (Spectrum 2), and UV–vis spectra were recorded with Shimadzu (UV-1800) spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in Bruker Instruments. LCMS were taken in Micromass (Water) apparatus. HRMS spectra were taken with help of Micromass Q-TOF Micro mass spectrometer. Elemental analyses were made on a Thermo-Finnigan Flash EA 1112 analyzer.

7-Methylcoumarin, 3,4-benzocoumarin, and TBCO were prepared in our laboratory (see supporting information file). Other chemicals were purchased and used as such.

Hydrolysis of coumarins. In general, all the three coumarins were refluxed in 30% aqueous ethanolic alkali. A total of 4–8 h was needed for complete hydrolysis (completion was TLC monitored). The solutions were diluted with water to lower the pH required for the particular reactions.

Reimer–Tiemann reactions of coumarins [1]. Given in the supporting information file 1.

Bromination using molecular bromine. The hydrolysed solution (reduced to pH 10–11) containing 4 mmol of substrate was cooled in an ice bath to 5°C. To this solution, stirred magnetically, a dilute solution containing 0.03 g mole bromine was added very slowly during 10 min. After 1 h, the mixture was acidified to pH ~ 1 with dilute HCl in cold. The precipitated solid was chromatographed in a column over silica gel (60–120 mesh size), and the separated products were isolated.

Coumarin (**I**) gave two products namely 6-bromocoumarin (**1c**) and 8-bromocoumarin (**1d**). 7-Methylcoumarin (**II**) also gave

two products, which are 6,8-dibromo-7-methylcoumarin (**2c**) and 8-bromo-7-methylcoumarin (**2d**). 3,4-Benzocoumarin (**III**) furnished 6-bromo-3,4-benzocoumarin (**3c**) and 8-bromo-3,4-benzocoumarin (**3d**). Structures of all these brominated products have been established by spectral analyses.

6-Bromocoumarin (1c). Colorless solid, mp 164–165°C (lit. 165–167°C [14]); yield 502 mg, 56%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63 (d, J = 9.6 Hz, 1H), 7.62 (m, 2H), 7.23 (d, J = 10 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H).

8-Bromocoumarin (1d). Colorless solid, mp 137–138°C (lit. 136.5–137°C [14]); yield 268 mg, 30%. IR: ν_{max} (KBr) 1732, 1616, 1173, 1107, 922, 842, 741, and 636 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (dd, J = 8 and 1.6 Hz, 1H), 7.67 (d, J = 9.6 Hz, 1H), 7.44 (dd, J = 8 and 1.6 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H). HRMS: *m/z* calculated for $C_9H_5BrO_2Na$ 246.9370 [M^+ + Na] and 248.9350; found 246.9380 and 248.9366 in the intensity ratio of 1:1.

6,8-Dibromo-7-methylcoumarin (2c). Colorless solid, mp 133–34°C; yield 556 mg, 44%. IR: ν_{max} (KBr) 1746, 826, and 637 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.59 (d, J = 9.6 Hz, 1H), 6.43 (d, J = 9.6 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 154.5, 150.1, 142.0, 141.9, 129.5, 119.7, 118.7, 117.3, 113.7, and 24.4. HRMS: *m/z* calculated for $C_{10}H_7Br_2O_2$ 316.8807 [M^+ + H], 318.8787, and 320.8767; found 316.8815, 318.8787, and 320.8784 in the intensity ratio of 1:2:1.

8-Bromo-7-methylcoumarin (2d). Colorless soild, mp 185°C; yield 238 mg, 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 10 Hz, 1H), 7.20 (d, J = 10 Hz, 1H), 6.42 (d, J = 9.6 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 151.0, 143.2, 143.1, 126.3, 126.1, 117.8, 116.0, 112.7, and 23.5. HRMS: *m/z* calculated for $C_{10}H_7BrO_2Na$ 260.9527 [M^+ + Na] and 262.9507; found 260.9527 and 262.9507 in the intensity ratio of 1:1.

6-Bromo-3,4-benzocoumarin (3c). Colorless solid, mp 170–72°C; yield 548 mg, 50%. IR: ν_{max} (KBr) 1741 and 768 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.45 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.90 (m, 2H), 7.68 (t, J = 7.8 Hz, 1H), 7.28 (merged with $CHCl_3$ signal, 1H). HRMS: *m/z* calculated for $C_{13}H_7BrO_2Na$ 296.9527 [M^+ + Na] and 298.9507; found 296.9460 and 298.9445 in the intensity ratio of 1:1.

8-Bromo-3,4-benzocoumarin (3d). Colorless solid, mp 220°C; yield 296 mg, 27%. IR: ν_{max} (KBr) 1744, 750, and 634 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.44 (dd, J = 8 and 1 Hz, 1H), 8.14 (d, J = 8 Hz, 1H), 8.02 (dd, J = 8 and 1 Hz, 1H), 7.86 (dt, J = 8 and 1.4 Hz, 1H), 7.60–7.76 (m, 2H), 7.23 (merged with $CHCl_3$ signal, 1H). HRMS: *m/z* calculated for $C_{13}H_7BrO_2Na$ [M^+ + Na] 296.9527 and 298.9507; found 296.9521and 298.9501.

Bromination using 2,4,4,6-tetrabromocyclohexa-2,4-dien-1-one [24]. The hydrolysed solution of a coumarin substrate (3 mmol) at pH ~10 was treated with a molar proportion of an ethanolic solution of the reagent and stirred overnight. The reaction mixture was then acidified, the precipitated solid was dissolved in ethyl acetate and washed free from 2,4,6-tribromophenol with Na_2CO_3. The extract was dried with anhydrous Na_2SO_4, solvent removed, and finally the product was recrystallized. All the three substrates yielded a single product each. The product (yield 544 mg, 81%) from coumarin (**I**) matched with (**1a**); the one (yield 414 mg, 58%) from 7-methylcoumarin (**II**) was found to be identical with (**2d**), and that (yield 625 mg, 76%) from 3,4-benzocoumarin (**III**) was identical with (**3c**).

Reactions with formaldehyde (Lederer–Manasse reaction). Each of the saponified solution of a substrate (containing 1 g of each substrate) was diluted with water to a pH 9–10 and cooled to a temperature ~10°C to which an excess of formaldehyde solution was added. The mixture was left in the fridge at 15°C for 10–12 days. The solution assumed yellow color (red in case of 3,4-benzocoumarin), and a solid was precipitated out in each case. The solid was filtered off; the filtrate was acidified with dil. HCl and then extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate, concentrated, and chromatographed over silica gel (230–400 mesh) to separate the products.

Coumarin (**I**) gave two products, (**1e**) and (**1f**), from the extract. The dimeric product (**1g**) was obtained from the precipitated solids. The organic extract from 7-methylcoumarin (**II**) was separated into two compounds, (**2e**) and (**2f**), The precipitated solid was purified to give the dimeric product (**2g**). From the 3,4-benzocoumarin (**III**) reaction mixture, the main isolated product, obtained as a precipitate, was (**3e**).

Spectral characteristics of all these new compounds are given below.

6-Hydroxymethylcoumarin (1e). White solid, mp 123°C ($CHCl_3$); yield 180 mg, 15%. IR: ν_{max} (KBr) 3200 (br.) and 1715 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, J = 9.6 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 7.51 (s, 1H), 7.33 (d, J = 9 Hz, 1H), 6.44 (J = 9.6 Hz, 1H), 4.77 (s, 2H), and 1.71 (s, 1H). LCMS: *m/z* 177.1 (M^+ + 1). *Anal.* Calcd for $C_{10}H_8O_3$ C 68.18, H 4.58; found C 68.32, H 4.51.

8-Hydroxymethylcoumarin (1f). White solid, mp 151°C ($CHCl_3$); yield 286 mg, 24%. IR: ν_{max} (KBr) 3417 and 1700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, J = 9.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 6.44 (J = 9.6 Hz, 1H), 4.96 (s, 2H), and 1.71 (s, 1H).LCMS: *m/z* 177.1 (M^+ + 1).

6,6′-Methylenebis-[coumarin-8-methanol] (1g). White solid, mp 310°C (CH_3OH); yield 643 mg, 52%. IR: ν_{max} (KBr) 3746, 3650 (br.), 1699, and 1538 cm^{-1}. ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.87, (d, J = 9.6 Hz, 2H), 7.55 (s, 2H), 7.35 (s, 2H), 6.36 (d, J = 9.6 Hz, 2H), 5.36 (broad s, 2H), 4.68, (s with fine splitting, 4H), and 4.06 (s, 2H). ^{13}C NMR (100 MHz, d_6-DMSO + $CDCl_3$): δ 160.4, 149.5, 144.7, 137.0, 131.0, 130.2, 126.2, 118.5, 116.2, 79.1, and 57.5. HRMS: *m/z* calculated for $C_{21}H_{17}O_6$ 365.1020 [M^+ + H]; found 365.1023.

6-Hydroxymethyl-7-methylcoumarin (2e). White solid, mp 135°C ($CHCl_3$); yield 260 mg, 22%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 9.6 Hz, 1H), 7.52 (s, 1H), 7.15 (s, 1H), 6.36 (J = 9.6 Hz, 1H), 4.77 (s, 2H), 2.44 (s, 3H), 1.91 (br. s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 153.4, 143.4, 141.1, 135.6, 126.2, 118.1, 116.7, 115.7, 62.5, and 19.1. HRMS: *m/z* calculated for $C_{11}H_{10}O_3Na$ 213.0527 [M^+ + Na]; found 213.0493.

6,8-Bis-(hydroxymethyl)-7-methylcoumarin (2f). White solid, mp 155°C (CH_3OH); yield 356 mg, 26%. ^{1}H NMR (200 MHz, d_6-DMSO): δ 8.02 (d, J = 9.6 Hz, 1H), 7.58 (s, 1H), 6.36 (d, J = 9.6 Hz, 1H), 4.67 (s, 2H), 4.50 (s, 2H), and 2.33 (s, 3H). HRMS: *m/z* calculated for $C_{12}H_{12}O_4Na$ 243.0633 [M^+ + Na]; found 243.0627.

6,6′-Methylenebis-[7-methylcoumarin-8-methanol] (2g). White solid, mp 280°C (CH_3OH); yield 548 mg, 45%. IR: ν_{max} (KBr) 3403 (br.), 1716, and 1612 cm^{-1}. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.12 (d, J = 9.5 Hz, 2H), 7.12 (s, 2H), 6.39 (d, J = 9.5 Hz, 2H), 4.75 (s, 4H), 4.07 (s, 2H), 2.51 (s merged with

HDO, 2H), and 2.37 (s, 6H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 166.3, 160.6, 150.8, 145.2, 142.2, 135.2, 127.9, 127.8, 116.8, 115.2, 53.8, 36.4, and 15.9. HRMS: *m/z* calculated for $C_{23}H_{21}O_6$ 393.1333 [M^+ + H]; found 393.1320.

6,8-Bis-(hydroxymethyl)-3,4-benzocoumarin (3e). White solid, mp 185°C (CH_3OH); yield 856 mg, 66%. IR: ν_{max} (KBr) 3334 (br.) and 1726 cm^{-1}. ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.40 (d, *J* = 8 Hz, 1H), 8.26 (d, *J* = 8 Hz, 1H), 8.15 (s, 1H), 7.96 (t, *J* = 8 Hz, 1H), 7.68 (t, *J* = 8 Hz, 1H), 7.65 (s, 1H), 539–5.34 (m, 2H), 4.75 (d, *J* = 5.5 Hz, 2H), and 4.62 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 160.6, 147.0, 139.0, 135.9, 135.1, 130.8, 130.3, 129.6, 127.7, 123.1, 120.9, 119.9, 127.1, 63.1, and 57.9. HRMS: *m/z* calculated for $C_{15}H_{13}O_4$ 257.0808 [M^+ + H]; found 257.0866.

Diazocoupling reactions. The pH of saponified solution of a coumarin substrate containing 1 mmol of the compound was set at 13–14 and cooled to −5°. Diazotized solution of aniline (excess) was added slowly so that the final pH was maintained at 8–9. After half an hour, the dye was filtered and washed with water. The yield is very good in all the cases. All the dyes were characterized by spectral analyses. The UV–vis data are given in the discussion (Table 1).

6-Phenylazocoumain (1h). Red solid, mp 144°C ($CHCl_3$); yield 220 mg, 88%. IR: ν_{max} (KBr)1728, 1693, 1260, and 1207 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.8 and 2.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.93–7.88 (m, 2H), 7.80 (d, *J* = 9.6 Hz, 1H), 7.55–7.46 (m, 4H) and 6.48 (d, *J* = 9.6 Hz, 1H). LCMS: *m/z* 251 (M^+ + 1).

6-[4-Methylphenyl]azocoumain (1i). Red solid, mp 270°C ($CHCl_3$); yield 224 mg, 85%. IR: ν_{max} (KBr) 1718, 1616, and 1084 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.8 and 2.2 Hz, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 9.6 Hz, 1H), and 2.45 (s, 3H).

6-[3-Methylphenyl]azocoumain (1j). Red solid, mp 255° ($CHCl_3$); yield 222 mg, 84%. IR: ν_{max} (KBr) 1717, 1637, and 1065 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11–8.05 (m, 2H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.74 (br. s, 2H), 7.49–7.25 (m, 3H), 6.51 (d, *J* = 9.6 Hz, 1H), and 2.47 (s, 3H).

6-[4-Chlorophenyl]azocoumain (1k). Red solid, mp 235–37°C ($CHCl_3$); yield 256 mg, 90%. IR: ν_{max} (KBr) 1721, 1702, and 1620 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.8 and 2.2 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.91–7.85 (m, 2H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.54–7.44 (m, 3H), and 6.52 (d, *J* = 9.6 Hz, 1H).

6-[4-Nitrophenyl]azocoumain (1l). Red solid, mp 188°C ($CHCl_3$); yield 230 mg, 78%. IR: ν_{max} (KBr) 1722, 1602, 1344, and 1178 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.6 Hz, 2H), 8.08 (d, *J* = 8.6 Hz, 2H), 8.14 (s, 1H), 7.85 (d, *J* = 9.6 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), and 6.55 (d, *J* = 9.6 Hz, 1H).

6-[1-Naphthyl]azocoumarin (1m). Deep red solid, mp 220°C (dec.); yield 192 mg, 64%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.92 (d, *J* = 8 Hz, 1H), 8.27 (dd, *J* = 8.8 and 2.2 Hz, 1H), 8.18 (d, *J* = 2 Hz, 1H), 8.65–7.90 (m, 4H), 7.72–7.53 (m, 4H), and 6.54 (d, *J* = 9.6 Hz, 1H).

7-Methyl-6-phenylazocoumarin (2h). Red solid, mp 168–70°C (dec.); yield 187 mg, 71%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.79 (s, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.55–7.50 (m, 3H), 7.30 (s, 1H), 6.42 (d, *J* = 9.6 Hz, 1H), and 2.82 (s, 3H). LCMS: *m/z* 265.1 (M^+ + 1). *Anal*. Calcd for $C_{16}H_{12}N_2O_2$ C 72.72, H 4.58, N 10.60; found C 72.32, H 4.63, N 10.55.

6-Phenylazo-3,4-benzocoumarin (3f). Red solid, mp 178°C ($CHCl_3$); yield 255 mg, 85%. IR: ν_{max} (KBr) 1736, 1605, 1239, 1068, and 687 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.64 (d, *J* = 2.0 Hz, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.06 (dd, *J* = 8.6 and 2.2 Hz, 1H), 7.92–8.00 (m, 3H), 7.46–7.68 (m, 5H). HRMS: *m/z* calculated for $C_{19}H_{12}N_2O_2Na$ 323.0791[M^+ + Na]; found 323.0801.

Elbs reaction. The hydrolysed solution of 7-hydroxycoumarin (324 mg, 2 mmol) was diluted (pH ~ 10), treated with $K_2S_2O_8$ (3 mmol) with constant stirring at 0–5°C for 2 h. The mixture was then acidified, and product purified by chromatography.

2,4-Dihydroxybenzaldehyde. Colorless solid, mp 136°C (lit. 137°C). Yield 130 mg, 48%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.19 (s, disappeared on D_2O shaking, 1H), 10.02 (br. s, disappeared on D_2O shaking, 1H), 9.46 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.29 (dd, *J* = 8.4 and 2.2 Hz, 1H), and 6.18 (d, *J* = 2.2 Hz, 1H).

Reaction products from coumarin-6-carbaldehyde (IV).

Condensation with acetone. This was prepared by heating a mixture of the aldehyde (**IV**: 500 mg; 2.87 mmol) in excess acetone (5 mL) in the presence of 20% NaOH solution at 70–80°C for 5 h. The mixture was then acidified. A yellowish precipitate was formed. This was then purified by chromatography over silica gel. The physical and spectral data are as follows.

4-[Coumarin-6-yl]but-3-en-2-one (4a). Colorless solid, mp 168–70°C ($CHCl_3$); yield 452 mg, 74%. IR: ν_{max} (KBr) 1725, 1716, 1669, and 1621 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.64 (s, 1H), 7.51 (d, *J* = 16 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 16 Hz, 1H), 6.47 (d, *J* = 9.6 Hz, 1H), and 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 159.9, 155.1, 142.9, 141.0, 131.1, 131.0, 127.9, 127.6, 119.2, 117.7, 117.6, and 27.8. LCMS: *m/z* 215.2 (M^+ + 1). *Anal*. Calcd for $C_{13}H_{10}O_3$ C 72.89, H 4.71; found C 72.81, H 4.72.

Doebner reaction

3-[Coumarin-6-yl]propenoic acid (4b). The compound was prepared from the aldehyde (**IV**: 500 mg; 2.87 mmol) by refluxing with excess malonic acid in the presence of piperidine and a little *β*-alanine for 12 h in pyridine solvent. Yield 545 mg (88%). Details are given in the supporting information file 1.

Condensations with hydrazine and semicarbazide.

Hydrazone (4c) and semicarbazone (4d). Hydrazone (4c) and semicarbazone (4d) of Coumarin-6-carbaldehyde were prepared using standard procedure [25]. These structures were supported by spectral data.

(4c). Pale yellow solid, mp 295°C. IR: ν_{max} (KBr) 3421 (br.), 1698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.68 (m, 3H), 7.63 (s, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), and 5.62 (s, 2H).

(4d). Colorless solid, mp 235°C. IR: ν_{max} (KBr) 3481 (br.), 1693 cm^{-1}. ^{1}H NMR (200 MHz, d_6-DMSO): δ 10.33 (s, 1H), 8.05–7.98 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.54 (s, 2H), and 6.51 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (50 MHz, d_6-DMSO): δ 160.2, 157.2, 154.2, 144.5, 138.1, 131.9, 130.1, 127.0, 119.3, 117.2. LCMS: *m/z* 231.9 (M^+ + 1).

Reaction of coumarin with hydrazine.

(CH). Gray-colored solid, mp 57°C. ν_{max} (KBr) 3229 (br.), 1677, 1458, and 755 cm^{-1}. ^{1}H NMR (500 MHz, d_6-DMSO):

δ 9.23 (br. s, 1H), 7.30 (d with fine splitting, 1H), 7.06 (t with fine splitting, 1H), 6.81 (d with fine splitting, 1H), 6.74 (t with fine splitting, 1H), 5.72 (br s, 1H), 4.69 (t, $J = 7.5$ Hz, 1H), 2.99 (somewhat merged with DMSO H, 2H), 2.87 (m, 1H), 2.50–2.52 (m, 3H); 2.33 (m, 1H) and 2.20 (m, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 176.0, 155.4, 128.5, 127.4, 127.3, 119.0, 115.69, 56.5, and 39.2.

Biginelli condensation. The aldehyde (**IV**, 174 mg; 1 mmol) was heated under reflux with 1.1 equivalent ethyl acetoacetate (143 mg; 1.1 mmol) and 1.5 equivalent urea (90 mg; 1.5 mmol) in the presence of 10 mol% $FeCl_3$ (16 mg) in ethanol medium for 6 h [19]. Then, the mixture was poured into cold water and neutralized with bicarbonate. The precipitated ferric hydroxide was removed, and the filtrate was extracted with ethyl acetate. Upon chromatography (silica gel, 60–100 mesh), pure product (**4e**) was obtained (160 mg; 50% yield) in ethyl acetate–petroleum ether (1:1) eluate.

By stirring at room temperature for 24 h the same reactants in dry dimethyl formamide in the presence of 6 equivalents (0.7 g) of chlorotrimethyl silane [20], an improved yield (202 mg; 62%) of the product was recorded. The structure was settled by spectral studies.

Ethyl 6-methyl-2-oxo-4-[coumarin-6-yl]dihydropyrimidine-5-carboxylate (4e). Colorless solid, mp 248°C (CH_3OH). IR: ν_{max} (KBr) 3367, 3210, 1729, 1698, 1660, 1243, 1089, and 818 cm^{-1}. ^{1}H NMR (500 MHz, d_6-DMSO): δ 9.26 (s, 1H), 8.11, (d, $J = 9.6$ Hz, 1H), 7.80 (s, 1H), 7.537 (s, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 7.39(d, $J = 8.5$ Hz, 1H), 6.48 (d, $J = 9.6$ Hz, 1H), 5.25 (d, $J = 2.6$ Hz, 1H), 3.97 (q, $J = 7$ Hz, 2H), 2.28 (s, 3H), and 1.09 (t, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 165.2, 159.9, 152.7, 151.8, 148.8, 144.3, 141.3, 130.3, 125.9, 118.5, 116.5, 116.3, 98.8, 59.2, 53.6, 17.9, and 14.1. LCMS: *m/z* 329 ($M^+ + 1$). *Anal*. Calcd for $C_{17}H_{16}N_2O_3$ C 62.19, H 4.91, N 8.53; found C 62.81, H 4.77, N 8.50.

Hantzsch synthesis. A mixture of coumarin-6-carbaldehyde (174 mg, 1 mmol.), ethyl acetoacetate (260 mg, 4 mmol), and ammonium acetate (110 mg, 1.5 mmol) in 20 mL ethanol was refluxed for 2 h. After the reaction was over, ~50 mL water was added and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4, solvent was removed, and the residue recrystallized from chloroform.

Diethyl 4-[coumarin-6-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f). Light yellow crystalline solid, mp 198°C ($CHCl_3$). Yield was 365 mg, 92%. IR: ν_{max} (KBr) 3287, 3242, 1700, 1684, and 1110 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, $J = 9.6$ Hz, 1H), 7.48 (d, $J = 8$ Hz, 1H), 7.40 (s, 1H), 7.19 (d, $J = 8$ Hz, 1H), 6.37 (d, $J = 9.6$ Hz, 1H), 6.14 (br. S, 1H), 5.06 (s, 1H), 4.10 (m, 4H), 1.23 (d, J = 6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 161.3, 152.5, 144.7, 144.4, 144.1, 132.1, 127.1, 118.2, 116.3, 116.0, 103.6, 59.9, 39.4, 19.6, and 14.3. HRMS: *m/z* calculated for 420.1418 $C_{21}H_{23}NO_6Na$ [$M^+ + Na$]; found 420.1417.

Dakin reaction. The saponified solution containing 1 mmol of aldehyde (**IV** or **V** or **VI**) in 20% NaOH was cooled to −10°C. A slight excess (~1.2 equivalent) of 30% H_2O_2 solution was added dropwise. The mixture was allowed to attain room temperature and kept stirring for 2 h. An excess of H_2O_2 was ensured (detected by acidified permanganate solution). Then, the solution was acidified, extracted with ethyl acetate, and finally purified by chromatography. The structures were established by spectral analyses.

6-Hydroxycoumarin (4g). Colorless solid, mp 249°C ($CHCl_3$) (lit. 243–47°C [26]); yield 84 mg, 52%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.74 (s, disappeared on deuteration, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 7.22 (d, $J = 9.0$ Hz, 1H), 7.04–6.99 (m, 2H), and 6.42 (d, $J = 9.6$ Hz, 1H). LCMS: *m/z* 162.9 ($M^+ + 1$).

6-Hydroxy-7-methylcoumarin (5). Colorless solid, 179°C ($CHCl_3$); yield 66 mg, 38%. ^{1}H NMR (200 MHz, d_6-DMSO): δ 7.60 (d, $J = 9.6$ Hz, 1H), 7.12 (s, 1H), 6.85 (s, 1H), 6.36, (d, $J = 9.6$ Hz, 1H), 5.44 (br. s, 1H), and 2.43 (s, 3H). LCMS: *m/z* 177 ($M^+ + 1$). *Anal*. Calcd for $C_{10}H_8O_3$ C 68.18, H 4.58; found C 68.32, H 4.51.

6-Hydroxy-3,4-benzocoumarin (6). Colorless solid, mp 218°C (CH_3OH); yield 117 mg, 55%. IR: ν_{max} (KBr) 3387, 1698 cm^{-1}. ^{1}H NMR (200 MHz, d_6-DMSO): δ 9.80, (s, disappeared on deuteration, 1H), 8.30–8.22 (m, 2H), 7.94 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 2.6$ Hz, 1H), 7.27 (d, $J = 9$ Hz, 1H), and 6.99 (dd, $J = 9$ and 2.6 Hz, 2H). ^{13}C NMR (50 MHz, d_6-DMSO): δ 160.9, 154.7, 144.4, 135.8, 134.7, 130.7, 129.7, 122.9, 11.0, 118.9, 118.7, 108.6. LCMS: *m/z* 235.1 ($M^+ + 23$). *Anal*. Calcd for $C_{13}H_8O_3$ C 73.58, H 3.80; found C 73.48, H 3.81.

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