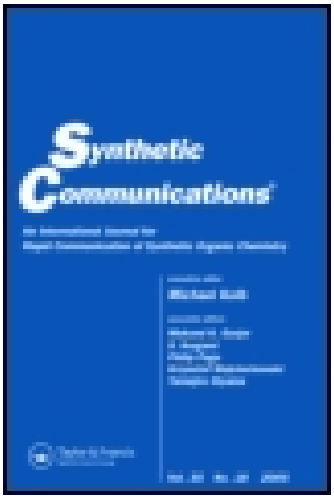

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# SYNTHESIS OF FUNCTIONALIZED DIHYDROFUROCOUMARIN DERIVATIVES FROM 3-AMINOALKYL-4-HYDROXYCOUMARIN

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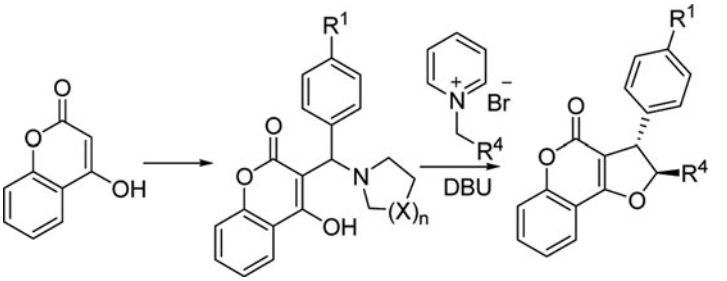
## GRAPHICAL ABSTRACT




**Abstract** *Some dihydrofuro-fused coumarin derivatives were synthesized from 3-aminoalkyl-4-hydroxycoumarin via in situ generation of* N*-ylide. The 3-aminoalkylated 4-hydroxycoumarin derivatives were synthesized from one-pot, three-component reaction of 4-hydroxycoumarin, aryl aldehydes, and secondary amines in ethanol at room temperature. Again, when salicylaldehyde was employed instead of benzaldehyde, interestingly pyranocoumarins were obtained. The reaction protocol can be further explored toward the synthesis of many other heterocyclic fused dihydrofurans.*

**Keywords** Aryl aldehyde; dihydrofurocoumarins; 4-hydroxycoumarin; pyrano[3,2-*c*]-coumarins; ylides

## INTRODUCTION

Fused coumarin system, in particular furocoumarins, are secondary metabolites found in some higher plants such as celery (*Apium graveolens*), parsnip (*Pastinaca sativa*), and carrot (*Daucus carota*).[1] Naturally occurring furocoumarins exist either in the linear form where the furan is attached at the C(6) and C(7) or in the angular form, carrying the substituent at C(7) and C(8). The most abundant

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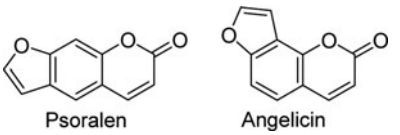



**Figure 1.** Linear and angular isomers for furocoumarins.

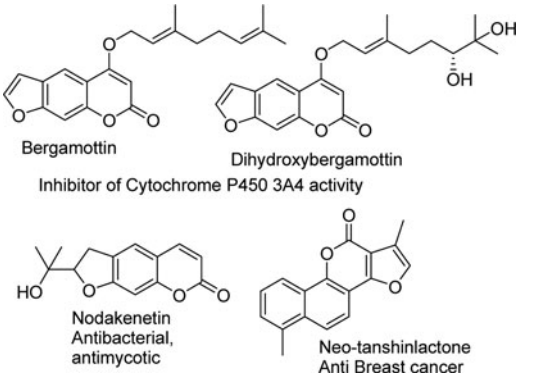



**Figure 2.** Some bioactive furocoumarins.

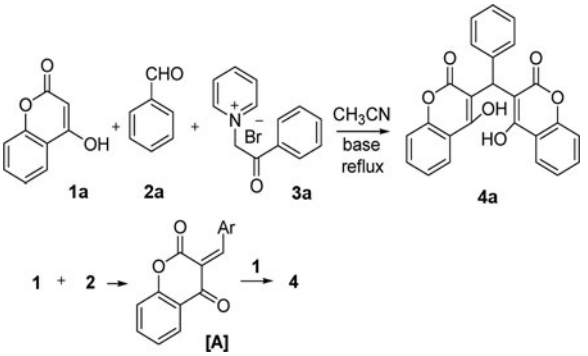
linear furocoumarins are psoralen, xanthotoxin, and bergapten, whereas the angular form is mostly represented by angelicin, sphondin, and pimpinellin (Fig. 1).

Furocoumarin derivatives possess diverse biological activities such as antifungicidal,[2] insecticidal,[3] insect antifeedant,[4] anti-HIV,[5] and anticancer activities.[6] They have also attracted considerable attention because of their photochemical, photophysical, and photobiological activities.[7] Furocoumarins are photosensitizers of plant origin and increase the sensitivity of biological objects to UVA radiation. Because of these properties, furocoumarins have a wide range of applications as drugs for skin and autoimmune disease and thus are useful for molecular manipulation.[8] Some of the biologically important furocoumarins are shown in Fig. 2.

As a part of our continuing efforts toward the synthesis of various heterocyclic compounds,[9] particularly annelated coumarins of biological importance,[10] we report here the synthesis of some functionalized dihydrofurocoumarin derivatives **7** from the reaction of 3-aminoalkyl-4-hydroxycoumarin **6** and pyridinium salt **3** in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile under refluxing condition (Scheme 2).

## DISCUSSION

We initiated our study with the three-component reaction of 4-hydroxycoumarin **1a**, benzaldehyde **2a,** and pyridinium salt **3a** under refluxing conditions in acetonitrile in the presence of DBU (Scheme 1). Unfortunately, the reaction produced simply biscoumarin compounds **4a** instead of the expected furocoumarins.[11] This might be because of the highly reactive 4-hydroxycoumarin, which undergoes Michael addition to the Knoeveagal condensed product **[A]** before the

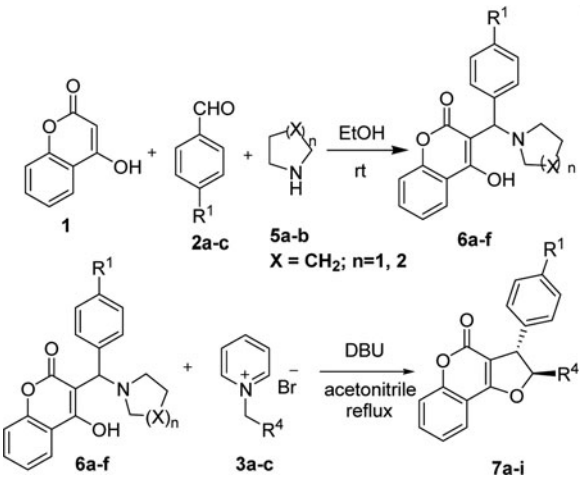



**Scheme 1.** Formation of biscoumarin derivatives.



expected attack of the pyridinium ylide forms in the reaction process (Scheme 1). In fact, formation of such biscoumarin is well precedented.[12]

Then, we planned to utilize 3-aminoalkyl-4-hydroxycoumarins **6** with pyridinium salts **3** to achieve the furan fused coumarin derivatives **7** (Scheme 2). The 3-aminoalkyl-4-hydroxycoumarin derivative **6a** was first prepared from one-pot, three-component reaction of 4-hydroxycoumarin **1**, benzaldehyde **2a,** and pyrrolidine **5a** in ethanol at room temperature following the reported method.[13] Interestingly, when the compound **6a** so obtained was reacted with pyridinium salt **3a** in the presence of a catalytic amount of DBU in ethanol under refluxing conditions, it afforded the dihydrofuro[2,3-*c*]coumarin derivative **7a** in very good yield (Scheme 2). The structure of the compound was ascertained from the spectroscopic data and elemental analysis. The $^1$H NMR spectra showed the absence of the singlet peak at δ 5.23 and presence of two doublets at δ 4.72 ($J = 4.86$ Hz) and δ 6.10 ($J = 6.96$ Hz), which indicate the formation of cyclized dihydro furan fused product. The coupling constants of the $^1$H NMR spectra of these two protons further indicate




**Scheme 2.** Synthesis of dihydrofurocoumarins.

the formation of the thermodynamicly stable *trans* isomer of the product. The mass spectra showed a sharp molecular ion peak at 369.3 $(M + H)^+$. Then, we utilized a number of 3-aminoalkyl-4-hydroxy-coumarins **6** with various pyridinium salts bearing COPh, CN, and COOEt groups and synthesized a large number of dihydrofuro[2,3-*c*]coumarin derivatives **7b–i**. All the new products obtained were characterized from their spectroscopic data and elemental analysis. Our observations are recorded in Table 1.

The reaction was also studied in some other solvents, for example, ethanol, tetrahydrofuran (THF), dimethylformamide (DMF), and toluene, but acetonitrile was found as the best solvent for the reaction. DBU was used as base in the reaction process for its nonnucleophilic nature. We studied the reaction by utilizing various aryl aldehydes possessing electron-withdrawing as well as electron-donating groups at the aromatic ring. It was observed that the reactions were smooth in all the cases. However, the aldehyde having the electron-withdrawing substituent produced the product in shorter time with better yield in comparison to the aldehyde with electron-donating substituent. Further increase in the reaction time did not improve the yield of the products.

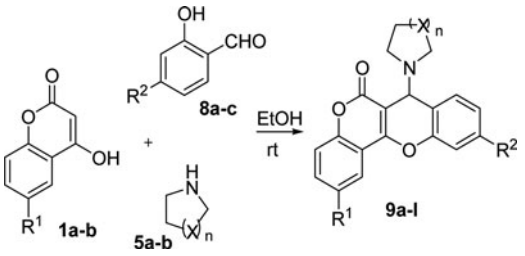
It was very interesting to note that when salicylaldehyde **8a** was used with 4-hydroxycoumarin **1a** and pyrolidine **5a**, we obtained the cyclized pyrano[2,3-*c*]coumarin derivative **9a** instead of 3-aminoalkyl-4-hydroxycoumarins **6**, in good yield (Scheme 3). Notably, pyran-fused coumarins are very important class of naturally occurring bioactive molecules.[14] The structure of the compound was ascertained from spectroscopic data and elemental analysis. Although the formation of a pyran ring was obvious because of the presence of two suitably located hydroxyl groups, notable point is that the cyclization occurred at very mild condition. Subsequently, a series of pyrano[3,2-*c*]coumarins **9b–l** were synthesized by utilizing different substituted salicylaldehydes **8a–c** with 4-hydroxycoumarin **1a,b** and **5a,b** and characterized. The number of generalizations is shown in Table 2. However, unlike the previous reaction, we have not observed any significant effect of substituent in the aromatic ring of the aldehyde in this reaction in terms of yield and reaction time.

The possible mechanism which could account for the formation of products **7a** and **9a** is depicted in Schemes 4 and 5.

The compound **6a** under thermal condition produces the intermediate **[A]** by eliminating pyrrolidine molecule, and on the other hand, the pyridinium ylide **[B]**

**Table 1.** Synthesis of compound **7** catalyzed by DBU

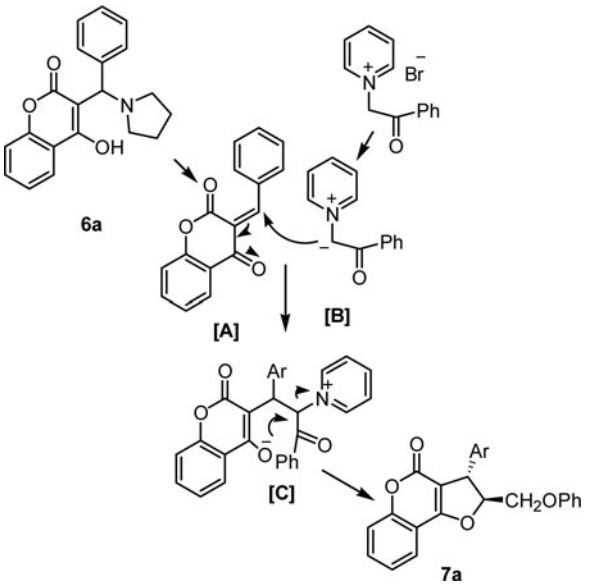
| Product | $R^1$ | $R^4$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **7a** | H | COPh | 3 | 81 |
| **7b** | H | CN | 3 | 78 |
| **7c** | H | COOEt | 3 | 80 |
| **7d** | Cl | COPh | 2.5 | 82 |
| **7e** | Cl | CN | 2.5 | 79 |
| **7f** | Cl | COOEt | 2.5 | 81 |
| **7 g** | Me | COPh | 3 | 80 |
| **7 h** | Me | CN | 3 | 77 |
| **7i** | Me | COOEt | 3 | 78 |



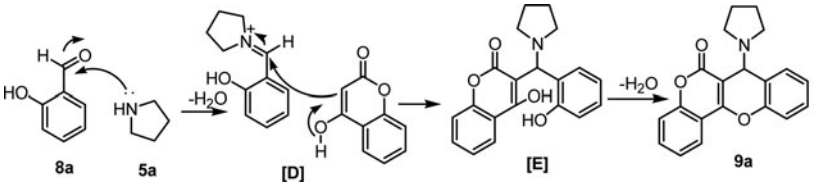

**Scheme 3.** Synthesis of pyranocoumarins **9**.

**Table 2.** Synthesis of compound **9** via one-pot, three-component reaction

| Product | $R^1$ | $R^2$ | $[CH_2]_n$ | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| **9a** | H | H | $[CH_2]_1$ | 3 | 73 |
| **9b** | H | H | $[CH_2]_2$ | 3 | 76 |
| **9c** | H | Br | $[CH_2]_1$ | 2.5 | 75 |
| **9d** | H | Br | $[CH_2]_2$ | 2.5 | 79 |
| **9e** | H | Me | $[CH_2]_1$ | 3.5 | 74 |
| **9f** | H | Me | $[CH_2]_2$ | 3.5 | 77 |
| **9 g** | Me | H | $[CH_2]_1$ | 3.5 | 73 |
| **9 h** | Me | H | $[CH_2]_2$ | 3.5 | 76 |
| **9i** | Me | Br | $[CH_2]_1$ | 3 | 73 |
| **9j** | Me | Br | $[CH_2]_2$ | 3 | 78 |
| **9k** | Me | Me | $[CH_2]_1$ | 4 | 79 |
| **9 l** | Me | Me | $[CH_2]_2$ | 4 | 81 |




**Scheme 4.** Mechanism for the formation of compound **7**.




**Scheme 5.** Mechanism for the formation of compound **9**.

forms in situ from N-phenacylpyridinium bromide **3a** in presence of DBU. The pyridinium ylide **[B]** then undergoes Michael addition to intermediate **[A]** to afford the pyridinium enolate **[C]**. The enolate **[C]** is not isolable, which cyclizes instantly by eliminating pyridine to give the dihydrofurocoumarin derivative **7a.**

For the formation of compound **9a**, the reaction occurs via an initial reaction between salicylaldehyde **8a** and pyrrolidine **5a** in the presence of protic solvent to give the intermediate **[D]**, which subsequently suffers a nucleophilic attack by 4-hydroxycoumarin **1a** to give compound **[E]**. Finally, the intermediate **[E]** eliminates water molecule to afford the pyrano[3,2-*c*]coumarin **9a**.

In conclusion, we have reported an efficient method for the synthesis of dihydrofurocoumarin derivatives starting from the reaction of 3-aminoalkyl-4-hydroxycoumarin and pyridinium ylides generated in situ from pyridinium salt. Moreover, a series of novel pyrano[3,2-*c*]-coumarin derivatives were synthesized via one-pot, three-component reaction of 4-hydroxycoumarin, aryl aldehydes, and secondary amines at room temperature. This reaction protocol can be explored for the synthesis of some other furan-fused heterocyclic compounds.

## EXPERIMENTAL

### Representative Procedure for the Synthesis of Compound 7

A mixture of 4-hydroxy-3-(phenyl-pyrrolidin-1-yl-methyl)coumarin **6a** (321 mg, 1 mmol), pyridinium salt **3a** (278 mg, 1 mmol), and DBU (152 mg, 1 mmol) in acetonitrile (10 ml) under $N_2$ atmosphere was refluxed for 3 h. After completion of the reaction (monitored by thin-layer chromatography, TLC), the solvent was removed under reduced pressure. The product was purified by silica-gel column chromatography by using 8:2 petroleum ether (PE) and ethylacetate as eluent. The product was ascertained as **7a** from various spectroscopic data. Similarly other compounds **7b–i** were synthesized and characterized.

Compound **7a**: Yield: 298 mg (81%); mp 167 °C; IR ($CHCl_3$): $\nu_{max}$ 1711, 1745, 2868 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.72 (d, $J = 4.86$ Hz, 1H), 6.10 (d, $J = 6.96$ Hz, 1H), 7.19–7.96 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 38.17, 81.67, 93.49, 121.31, 125.24, 125.91, 126.32, 127.49 (2C), 127.81, 128.10, 128.76 (2C), 128.84 (4C), 132.66, 138.69, 140.22, 146.69, 161.91, 167.23, 186.43; MS ($m/z$): 369.3 $[M+H]^+$. Anal. calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38%. Found: C, 78.21; H, 4.29%.

### Representative Procedure for the Synthesis of Compound 9

A mixture of 4-hydroxycoumarin **1a** (162 mg, 1 mmol), salicylaldehyde **8a** (122 mg, 1 mmol), and pyrrolidine **5a** (70 mg, 1 mmol) was taken in a round-bottomed

flask containing ethanol. Then the reaction mixture was stirred vigorously at room temperature for 3 h. After completion of the reaction (monitored by TLC), the solid compound was filtered off and crude products were recrystallized from ethanol. The product **9a** was obtained in 73% yield. The structure of the compound was ascertained from the spectroscopic data and elemental analysis. Similarly, other compounds **9b–l** were synthesized and characterized.

Compound **9a**: Yield: 240 mg (75%); mp 209 °C; IR ($CHCl_3$): $\nu_{max}$ 1221, 1745.1, 2884.3 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.12 (br s, 4H), 2.93 (br s, 1H), 3.24 (br s, 1H), 3.70 (br s, 1H), 3.96 (br s, 1H), 5.31 (s, 1H), 7.26–8.08 (m, 8H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 22.79 (2C), 45.63 (2C), 50.93, 97.31, 119.38, 121.47, 122.32, 124.68, 125.21, 126.37, 127.73, 127.91, 128.11, 129.35, 149.39, 153.63, 160.09, 164.69; MS (*m*/*z*): 320.7 $[M+H]^+$. Anal. calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39%. Found: C, 75.09; H, 5.18; N, 4.31%.



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## SUPPORTING INFORMATION

Full experimental details and $^1H$ and $^{13}C$ NMR spectra of **7a, 7b, 7c**, and **9a** can be accessed on the publisher's website.

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