REVIEW

Recent advances in 4-hydroxycoumarin chemistry. Part 1: Synthesis and reactions

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KEYWORDS
4-Hydroxycoumarin; Synthetic routes; Chemical reactivity; Tautomeric structure; Reactions

Abstract This review aimed to document the publications concerning 4-hydroxycoumarin, its synthesis, chemical reactivity and reactions during the period from 1996 up to now.
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1. Introduction

The 4-hydroxycoumarins represent, nowadays, an important precursor in the realm of organic synthesis. Interest in it has been amplified because, not only they are significant synthetic endpoints (Siddiqui, 2014; Ziari and Hajjibbsi, 2013), but it constitutes the structural nucleus of many natural products (Awe et al., 2009; Oganesyan et al., 2007; Orlovskaya et al., 2006).

These derivatives have shown a remarkably broad spectrum of pharmacological and physiological activities and they are used as anticoagulant (Abdelhafez et al., 2010; Au and Reittie, 2008; Ganguly et al., 2013; Guo et al., 2013; Palareti et al., 2013; Kidwai et al., 2014; Kumari et al., 2013; Metwally et al., 2012a, 2012b, 2012c, 2012d, 2013; Stanchev et al., 2005), anticoagulant (Abou-Melha and Faruk, 2008; Kotharkar and Shinde, 2006; Mostafa, 2008; Sukdolak et al., 2005; Zavrsnik et al., 2008), antimitugenic (Edenharder and Tang, 1997), antioxidant (Foti et al., 1996; Jung and Park, 2009; Kaneko et al., 2001; Senol et al., 2010; Vukovic et al., 2010a, 2010b), and anti-inflammatory agents (Ahmad et al., 2009; Luchini et al., 2008). Also, in recent years there are references to derivatives with HIV protease inhibitors (Chiang et al., 2007; Khan et al., 2004a, 2004b; Kostova et al., 2004; Liu et al., 2009; Manolov et al., 2004; Mao et al., 2002; Mitra et al., 1998; Raleva et al., 2005; Skulnick et al., 1996; Su et al., 2006), and tyrosine kinase inhibitors (Yang et al., 1999). Additionally, these kinds of compounds are also extensively studied in analytical chemistry (Beldean-Galea et al., 2008; Bieganowska, 1997; Blahova et al., 2006; Cacciola and Legnani, 2007; Cespedes et al., 2006; El-Dean et al., 2013; Kidwai et al., 2014; Kumari et al., 2013; Musthafa et al., 2013; Pansuriya and Patel, 2007; Prasad et al., 2014), antifungal (Chohan et al., 2006; Rehman et al., 2005), antiviral (Kirkiaherian et al., 2008; Zavrsnik et al., 2011), antitumor (Arya et al., 2014; Bi et al., 2013; Dorababu et al., 2013; Farghaly et al., 2014; Kawai et al., 2001; Kumar et al., 2013; Pingaew et al., 2014; Salinas-Jazmin et al., 2010; Loa et al., 2009), anticonvulsant (Jaweed et al., 2010; Loa et al., 2009), anticonvulsant (Jaweed et al., 2001; Kumar et al., 2013; Pingaew et al., 2014; Salinas-Jazmin et al., 2010; Loa et al., 2009).

Table 1: 1H NMR and 13C NMR spectra of 4-hydroxycoumarin (Solvent: DMSO-d6).

<table>
<thead>
<tr>
<th>H</th>
<th>δ (ppm)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>C</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5.61</td>
<td>s</td>
<td>–</td>
<td>2</td>
<td>161.79</td>
</tr>
<tr>
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<td>7.84</td>
<td>d</td>
<td>7.80</td>
<td>4</td>
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<tr>
<td>6</td>
<td>7.66</td>
<td>t</td>
<td>6.12</td>
<td>5</td>
<td>123.85</td>
</tr>
<tr>
<td>7</td>
<td>7.36</td>
<td>t</td>
<td>10.80</td>
<td>6</td>
<td>123.10</td>
</tr>
<tr>
<td>8</td>
<td>7.39</td>
<td>d</td>
<td>10.80</td>
<td>7</td>
<td>132.63</td>
</tr>
<tr>
<td>9</td>
<td>7.36</td>
<td>t</td>
<td>10.80</td>
<td>8</td>
<td>116.28</td>
</tr>
<tr>
<td>10</td>
<td>7.36</td>
<td>t</td>
<td>10.80</td>
<td>9</td>
<td>153.41</td>
</tr>
</tbody>
</table>

Figure 1 Possible tautomeric structures of 4-hydroxycoumarin 1 (A–C).
synthesis and reactions is a comprehensive survey of this vast field. The discussion is supported by numerous lucid diagrams and the extensive reaction schemes are supported by relevant and up-to-date references from the original literature.

2. Molecular structures and spectral properties

A series of papers have investigated the structures of 4-hydroxycoumarin using UV, IR, LRMS and NMR spectroscopy. The UV spectrum of 4-hydroxycoumarin revealed one characteristic absorption peak at 308 nm (Traven et al., 1997a). The analysis of IR spectrum of it shows characteristic bands in Nujol mull at 3380 cm\(^{-1}\) (OH), 1650 (C=O), and 1530 (C=C, arom.) (Sosnovskikh et al., 2000). The carbonyl stretching frequency of 4-hydroxycoumarin underwent bathochromic shift at 1660 cm\(^{-1}\) in chloroform or dioxane solution (Hamdi et al., 2008b). The position of this band does not alter when the infrared spectrum is recorded in potassium bromide pellet (Jung et al., 1999).

The proton NMR spectrum of 4-hydroxycoumarin (Traven et al., 1997a) (Table 1) revealed only one signal is observed as a singlet at 5.61 ppm (Table 1), seems likely. The hydrogen of the hydroxy group was not visible, because of fast hydrogen/deuterium exchange (Sˇpirtovic´-Halilovic´ et al., 2014). The MS spectrum base peak. Furthermore, the intensity of the fragment at m/z 121 resulted to be two times higher than the expected intensity for the isotopic contribution to m/z 120, being that a clear evidence of the elimination of a 41 fragment whose composition must necessarily be HC2O. The loss of CO (M-28) and HCO (M-29), is even below the 2%. The absence of fragments corresponding to M-17 (m/z 145) and M-18 (m/z 144) is attributable to the loss of HO and H2O respectively. This matches with the tautomeric equilibrium between the enol and the keto forms.

3. Tautomeric structure(s)

4-Hydroxycoumarin can exist in three tautomeric keto-enol forms (Fig. 1) namely, 4-hydroxy-2-chromenone (A), 2,4-chromandione (B), and 2-hydroxy-4-chromenone (C). These three possible prototropic transformations have been intensively examined by various chemical reactivity, spectral, thermochemical, and computational methods (Aguirre-Pranzoni et al., 2011; Jacquot et al., 2001; Sousa et al., 2010; Traven et al., 2002). A glance at these standard reference works, the involvement of the tautomeric forms of 4-hydroxycoumarin, that is, 2,4-chromandione (B) or 2-hydroxy-4-chromenone (A), seems likely.

4. Chemical reactivity

It is evident from the topography of 4-hydroxycoumarin (Fig. 2) that it possesses both electrophilic and nucleophilic properties. The most significant reactivity is the nucleophilicity of carbon atom at position 3. This was noted since more than hundred years. Thus reactions such as Mannich reaction, coupling reaction and halogenation took place readily at such carbon. The oxygen atom of the hydroxyl group however remains the main site for attack by acylating and alkylation agents. It seemed that hard nucleophiles attack preferentially oxygen atom, while soft ones attack preferentially carbon atom (Fig. 2).

5. Synthesis

5.1. The biosynthetic pathway

Biosynthesis of 4-hydroxycoumarin 1 involves BIS-catalyzed reaction of salicyl-CoA 2 with malonyl-CoA 3 to form a diketone intermediate 4 which undergoes intramolecular cyclization by nucleophilic attack of the phenolic group on the CoA- or cysteine-tethered C-1 thioester yielding 4-hydroxycoumarin 1 (Beerhues and Liu, 2009; Liu et al., 2010) (Scheme 1).
5.2. The chemical synthetic pathway

Many synthetic approaches to 4-hydroxycoumarin 1 have been reported, mainly using hydroxyacetophenone or phenol as starting material.

5.2.1. Using 2-hydroxyacetophenone

Treatment of 2-hydroxyacetophenone 5 with acylating agents 6 such as phosgene, dimethylcarbonate, or diethylcarbonate in the presence of stoichiometric amount of base in anhydrous toluene or xylene afforded 4-hydroxycoumarin 1 in variable yield (Scheme 2). It was found that sodium hydride was the most effective base among sodium ethoxide, sodium metal, freshly prepared sodium 3-aminopropylamide (NaAPA), and potassium 3-aminopropylamide (KAPA) (Jung et al., 2001; Kasabe et al., 2010; Payne et al., 2010; Zhao et al., 2010).

On the other hand, condensation of 2-hydroxyacetophenone 5 with trichloroacetanilidrile in the presence of N-methylaminomagnesium bromide afforded (Z)-3-amino-4,4,4-trichloro-1-(2-hydroxyphenyl)but-2-en-1-one 7, which was converted into 2-(trichloromethyl)chromones 8 upon treatment with concentrated hydrochloric acid. The base catalyzed hydrolysis of the later compound gave 4-hydroxycoumarin 1 (Traven et al., 1997b) (Scheme 3).

5.2.2. Using phenol

Heating of phenol with malonic acid in phosphorus oxychloride containing twofold amount of anhydrous zinc chloride yielded 4-hydroxycoumarin 1 (Naveen et al., 2006) (Scheme 4).

Treatment of phenol 9 with Meldrum acid 11 under solvent-free condition at 90 °C afforded 3-oxo-3-phenoxypropionic acid 12 in 92% isolated yield, which transformed to 4-hydroxycoumarin 1 in 75% and 48% isolated yield, upon treatment with Eaton’s reagent or polyphosphoric acid (PPA) (Scheme 5) (Gao et al., 2010; Park et al., 2007; Zhi Qiang et al., 2014).

5.2.3. Hydrolytic retro Diels–Alder (RDA) reaction

Daia et al. (2002) have reported a new synthetic route to achieve 4-hydroxycoumarin 1 and furan derivative via the acid-catalyzed hydrolytic retro Diels–Alder reaction of 7-oxabicyclo[2.2.1]heptadiene 14 (Scheme 6).

5.2.4. Using cleavage of 4-allyl coumarinyl ether

Ganguly et al. (2006) has described an efficient procedure for the synthesis of 4-hydroxycoumarin 1 via the cleavage of 4-allyl coumarinyl ether using a catalytic amount of palladium on activated charcoal in methanol, and in combination with ammonium formate (Scheme 7). Recently, it was reported that the molecular iodine catalyzed this reaction (Nawghare et al., 2014).

5.2.5. Deacetylation of 3-acetyl-4-hydroxycoumarin

Jung et al. (1999) disclosed a simple and inexpensive synthesis of 4-hydroxycoumarin 1 via the acid-catalyzed decacetylation of 3-acetyl-4-hydroxycoumarin 17 (Scheme 8).

5.2.6. Hydrolysis and decarboxylation of 3-carbethoxy-4-hydroxycoumarin

In a similar manner, the acid-catalyzed hydrolysis and decarboxylation of 3-carbethoxy-4-hydroxycoumarin 18 yielded 4-hydroxycoumarin 1 (Jung et al., 1999) (Scheme 9).

5.2.7. Photooxygenation of chromone-2-carboxylic Acid

Another elegant approach to attain 4-hydroxycoumarin 1 with the quantum yield was reported by Kawata et al. (1999) via the photooxygenation of chromone-2-carboxylic acid 19 in aerated ethanol solution. The reaction seems to proceed via the decarboxylation followed by the addition of the oxygen molecule (Scheme 10).

6. Chemical reactions

In this section, chemical transformations have been classified on the basis of the new bond formed.

6.1. Reactions involving carbon–carbon bond formation

6.1.1. C=C Bond formation reactions

6.1.1.1. C=C Allylation reaction. The Allylation of 4-hydroxycoumarin 1 is an important strategy for the formation of C=C bonds in organic synthesis. Recently, considerable interest has been focused on Allylation of 4-hydroxycoumarin 1 using alcohols as electrophiles, since it offers several
potential advantages, such as the wide availability of the starting materials and the generation of H2O as the only side product. Such strategy has been elegantly applied to the synthesis of allyl and benzyl-substituted 4-hydroxycoumarin compounds (Chatterjee and Roy, 2012; Gan et al., 2008; Huang et al., 2007b; Shue and Yang, 2012).

Activator-free and one-pot C-allylation of 4-hydroxycoumarin 1 by simple palladium catalyst in water is now a well-documented process (Gan et al., 2008; Shue and Yang, 2012). Palladium-catalyzed Allylation of 1 using cinnamyl alcohol and heating for 20 min directly gave the corresponding C-allylated products 20, 21 (Scheme 11).

It was also shown that the 4-hydroxy-3-(1,3-diphenylallyl)-2H-chromen-2-one 23 was obtained by the reaction of 1,3-diphenylprop-2-en-1-ol 22 with 4-hydroxycoumarin 1 in the presence of 5 mol% ytterbium (III) triflate in a mixture of 1,4-dioxane and nitromethane (Huang et al., 2007b) (Scheme 12). Also, this allylic activation of 1 can be efficiently performed across an Ir–Sn heterobimetallic catalyst (Chatterjee and Roy, 2012; Huang et al., 2007b).

Allylation of 4-hydroxycoumarin 1 with 3,3-dimethylallylbromide 24 in the presence of sodium iodide and triethylamine provided 4-hydroxy-3-(pent-4-en-2-yl)-2H-chromen-2-one 25, which was considered as an intermediate for the preparation of (M5) ARQ 501 (β-Lapachone) human blood metabolites (Yang et al., 2008) (Scheme 13).

6.1.1.2. C3-Benzylaion. Theerthagiri and Lalitha (2010) reported that the direct benzylaion of 4-hydroxycoumarin 1 with a wide variety of secondary benzyl alcohols 26 was achieved using trimethylsilyltrifluromethane sulfonate (TMSOTf) as an efficient catalyst at room temperature providing the desired products 27 in good to excellent yields (Scheme 14).

Iron (III) perchlorate efficiently catalyzes benzylaion of 4-hydroxycoumarin 1 with various secondary benzyl alcohols 28 in acetonitrile. The reaction proceeds smoothly to give the corresponding C3-benzylated products (Thirupathi and Kim, 2010) (Scheme 15).

The above methodology was successfully applied for the benzylaion of 4-hydroxycoumarin 1 with the sterically hindered alcohol, 1-(2-naphthyl)ethanol 30 in acetonitrile containing 5 mol% of iron (III) perchlorate monohydrate to afford the 4-hydroxy-3-(1-(naphthalene-2-yl)ethyl)-2H-chromen-2-one 31 (Schobert et al., 2000) (Scheme 16).

The one-pot synthesis of phenprocoumon, a current pharmaceutical drug, was reported by Kischel et al. (2007) upon treatment of 4-hydroxycoumarin 1 with benzyl alcohols 32 in methylene chloride containing a catalytic amount of FeCl3·6H2O (Scheme 17).
reaction of 4-hydroxycoumarin 1 with sec-benzylic alcohols in dichloroethylene (DCE) containing catalytic amounts of Bi(OTf)$_3$ (Rueping et al., 2010) (Scheme 18).

Rueping et al. (2010) have devoted considerable attention to a bismuth (III)-catalyzed alkylation of 4-hydroxycoumarin 1 with different styrene derivatives, bearing electron-withdrawing groups or electron-donating groups, resulted in the corresponding products were isolated in good to excellent yields (Scheme 19).

Warfarin derivatives could also be achieved in 60% and 93% yield by warming naphthyl-substituted arylalcohols with 4-hydroxycoumarin 1 in dichloroethylene containing a catalytic amount of Bi(OTf)$_3$ (Rueping et al., 2010) (Scheme 20).

Mono 3-(2'-arylallyl) derivatives of 4-hydroxycoumarin were produced in 3-component cascade reaction involving aryl/heteroaryl/vinyl iodides, 4-hydroxycoumarin 1, and allene using tetrakis(triphenylphosphine) palladium, Pd(PPh$_3$)$_4$ or Pd$_2$(dba)$_3$ as catalyst (Grigg et al., 2004) (Scheme 21).

Molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance. A highly efficient method for the C–C bond formation is via molecular iodine-catalyzed C$_3$-alkylation reaction of 4-hydroxycoumarin 1 with benzyl, benzhydryl, allylic, and propargyl alcohols at 50°C in nitromethane. The 3-

<table>
<thead>
<tr>
<th>Condition (time, yield)</th>
<th>(0.5h, 91%)</th>
<th>(0.5h, 83%)</th>
<th>(0.5h, 71%)</th>
<th>(0.5h, 81%)</th>
<th>(0.5h, 87%)</th>
<th>(0.5h, 71%)</th>
<th>(0.5h, 60%)</th>
<th>(0.45h, 55%)</th>
<th>(0.5h, 78%)</th>
</tr>
</thead>
</table>

Reaction condition: 26 (1 mmol), 1 (2 equiv), TMSOTf (15 mol %) at r.t.

Scheme 14
**Scheme 15**

\[
\text{1} + \text{28} \rightarrow \text{29}
\]

**Scheme 16**

\[
\text{1} + \text{30} \rightarrow \text{31}
\]

**Scheme 17**

\[
\text{1} + \text{32} \rightarrow \text{33}
\]

**Scheme 18**

\[
\text{1} + \text{34} \rightarrow \text{35}
\]

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alkylated-4-hydroxycoumarin 44 was obtained in good yields (Lin et al., 2009) (Scheme 22).

Amberlite IR-120 (H\(^+\) form) was used as the acid catalyst for alkylation of 4-hydroxycoumarin 1 with secondary benzyl alcohols 45 for the synthesis of an anti-coagulant, coumatetralyl 46. The products obtained were successfully utilized in the preparation of 3,4-disubstituted coumarin derivatives (Reddy et al., 2008) (Scheme 23).

Anary-Abbasinejad et al. (2007) published the use of chlorosulfonic acid or phosphorus pentoxide and hexamethyldisiloxane (HMDS) (Anary-Abbasinejad et al., 2008) as an efficient system to induce the three-component reaction of 4-hydroxycoumarin 1 with an aryl aldehydes 47, and acetonitrile led to 3-[(acetylamino)aryl methyl]-4-hydroxycoumarin 48 in excellent yields (Scheme 24).

6.1.1.3. Propargylation and allenylation. Recently, a number of methods have been developed for propargylation of 4-hydroxycoumarin 1 at the 3-position with propargylic alcohol 49 using (C\(_6\)F\(_5\))\(_3\)B (Reddy et al., 2010), Yb(OTf)\(_3\) (Chatterjee

![Scheme 19](image)

<table>
<thead>
<tr>
<th>(R_1)</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
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<td>(7 h, 80%)</td>
<td>(5 h, 58%)</td>
<td>(4 h, 67%)</td>
</tr>
</tbody>
</table>

Scheme 19

![Scheme 20](image)

<table>
<thead>
<tr>
<th>(Ar)</th>
<th>a</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions (time, yield)</td>
<td>(6 h, 60%)</td>
<td>(5 h, 93%)</td>
</tr>
</tbody>
</table>

Scheme 20

![Scheme 21](image)

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<tr>
<th>(R)</th>
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<th>Cl</th>
<th>F</th>
<th>I-Cl</th>
<th>I-N</th>
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<tr>
<td>Yield (%)</td>
<td>97</td>
<td>91</td>
<td>91</td>
<td>65</td>
<td>92</td>
</tr>
</tbody>
</table>

Scheme 21
43, 44 | a | b | c | d | e | f | g  
<table>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R₁</td>
<td>4-OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4-Me</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
| R₂  | Me  | Me  | CH=CH-C₆H₅ | C=C-C₆H₅ | Me  | 4-OMeC₆H₅ | C₆H₄  
| Conditions (time, yield) | (12 h, 84%) | (12 h, 74%) | (4 h, 92%) | (1 h, 80%) | (12 h, 76%) | (4 h, 82%) | (4 h, 97%)  

Scheme 22

45, 46 | a | b | c | d | e | f  
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>R₁</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>
| R₂  | C₆H₄ | Me | CH₂-CH-CH₂ | C=C-C₆H₅ | C=C-C₆H₅ | CH=CH-C₆H₅  
| Conditions (time, yield) | (2 h, 86%) | (2 h, 81%) | (2 h, 78%) | (2.5 h, 84%) | (2 h, 83%) | (3 h, 78%)  

Scheme 23

Reaction condition: A: ClSO₃H  
B: P₂O₅+HMDS

Scheme 24

and Roy, 2012; Huang et al., 2007b), FeCl₃ (Maiti et al., 2011), and iodine in nitromethane (Lin et al., 2009) (Scheme 25).

When 4-hydroxycoumarin 1 was treated with 4-octyne 52 in the presence of [IrCl(cod)]₂ and sodium carbonate, in refluxing chlorobenzene using monodentate phosphines as ligand, 4-hydroxy-5-[(E)-4-oct-4-enyl]coumarin 52 was produced as the single coupling product (Nishinaka et al., 2001) (Scheme 26).

In recent years, 1-aryl-2-dimethylaminomethyl-prop-2-en-1-ones (ADMP reagents) 53 have gained remarkable attention.
in organic, and medicinal chemistry. Girreser and Heber (2000) succeeded in preparing 3-(2-benzoylallyl)-4-hydroxycoumarin via the reaction of 4-hydroxycoumarin with ADMP in dimethylformamide or ethanol as solvent (Scheme 27).

6.1.1.4. Arylation. Luo and Wu (2009) demonstrated that 4-aryl coumarins can be synthesized via palladium-catalyzed direct arylation of 4-hydroxycoumarin with arylboronic acids. The reactions were performed in the presence of palladium dichloride or palladium saccharinate (Luo and Wu, 2009; Shah et al., 2013) in the presence of sodium carbonate in tetrahydrofuran at 60–70 °C (Scheme 28).

Ganina et al. (2005) reported that the reaction of 4-hydroxycoumarin with 2-(azidomethyl)phenylleadtriacetate in chloroform containing catalytic amount of pyridine yielded 3-(2-azidomethylphenyl)-4-hydroxycoumarin derivatives (Scheme 29).

A simple procedure for the preparation of 3-(cyclohex-2-ynyl)-4-hydroxycoumarin by refluxing 4-hydroxycoumarin with 3-bromocyclohexene in acetone containing anhydrous potassium carbonate was described by Majumdar and Sarkar (2002) (Scheme 30).

The nucleophilic addition of 4-hydroxycoumarin to Baylis–Hillman acetate adducts has been described for the

### Scheme 27

**A**: (C₆F₅)₃B, CH₃CN, reflux, 15 min, 89% yield; **B**: Yb(OTf)₃, dioxane, CH₃NO₂, 50 °C, 2 h, 85% yield; **C**: FeCl₃, dioxane, CH₃Cl₂, 50 °C, 3 h, 77% yield; **D**: I₂, CH₃NO₂, 50 °C, 1 h, 80%.

### Scheme 28

<table>
<thead>
<tr>
<th>Ar</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
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</thead>
<tbody>
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<td>H</td>
<td>4-Me</td>
<td>4-OMe</td>
<td>2-Cl</td>
<td>3-CN</td>
<td>3-NO₂</td>
<td>4-CF₃</td>
</tr>
<tr>
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<td>98</td>
<td>88</td>
<td>90</td>
<td>68</td>
<td>52</td>
</tr>
</tbody>
</table>

### Scheme 29

- **Table 28**
first time by Reddy et al. (2009) as an efficient route to obtain 3-substituted 4-hydroxycoumarin in good yields (Scheme 31).

6.1.1.5. Olefination. One of the most successful strategies for constructing 3-benzylidene coumarins is the Knoevenagel condensation. Heterocondensation reaction between 4-hydroxycoumarin and a substituted benzaldehyde in the presence of a base such as K2CO3 gives the corresponding 3-benzylidene coumarins in good yields. For example, reaction of 4-hydroxycoumarin with benzaldehyde in acetone/ K2CO3 gives 3-benzylidene coumarin in 66% yield (Scheme 30).

<table>
<thead>
<tr>
<th>61, 62</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
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<td>R2</td>
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<td>C6H5</td>
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<td>3-NO2C6H4</td>
<td>4-MeOC6H4</td>
<td>3-AcOC6H4</td>
<td>CH2CH2Ph</td>
<td>2-NO2C6H4</td>
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<tr>
<td>Conditions (time, yield)</td>
<td>(3.5 h, 92%)</td>
<td>(4 h, 82%)</td>
<td>(3.5 h, 85%)</td>
<td>(6 h, 72%)</td>
<td>(5 h, 89%)</td>
<td>(6.7 h, 73%)</td>
<td>(6 h, 78%)</td>
<td>(4 h, 82%)</td>
</tr>
</tbody>
</table>

Scheme 31

(Solvent: Pyridine): R = H (75%), 4-Me (70%); (Solvent: Ethanol): R (Yield%) = H (78), 4-OMe (80), 4-Cl (80), 3-NO2 (76), 4-OH (83).

(Scheme 32) 64a,b (Solvent: Pyridine): R = H (75%), 4-Me (70%); 64c–g (Solvent: Ethanol): R (Yield%) = H (78), 4-OMe (80), 4-Cl (80), 3-NO2 (76), 4-OH (83).
hydroxycoumarin 1 and several substituted benzaldehydes 63 in pyridine (Refouvelet et al., 2004) or ethanol (Kidwai et al., 2004, 2007, 2008) under reflux led to the formation of 3-arylidene derivatives 64 in high yields and dimeric coumarin derivatives will be formed as a by-product (Zavrsnik et al., 2011) (Scheme 32).

In a similar manner, (E,E)-3-[3-(4N,N-[dimethylaminophenyl]prop-2-enylidene)-2H-1-benzopyran-2,4(3H)-dione 66 was obtained via reaction of 4-hydroxycoumarin 1 with (E)-3-(3-(dimethylamino)phenyl)acrylaldehyde 65 in a mixture of methylene chloride and methanol containing catalytic amount of ethylenediammonium diacetate (Huang et al., 2007a) (Scheme 33).

Heating 4-hydroxycoumarin 1 with ketylidenetriphenylphosphorane 67 in tetrahydrofuran led to the formation of the corresponding 3-(triphens phosphora-nylideneoxoethyl) derivatives 68 (Schobert et al., 2000) (Scheme 34).

The acid-catalyzed microwave irradiation of 4-hydroxycoumarin 1 and triethyl orthoformate 69 gave 3-ethoxymethylene-3H-2,4-dione 70 in moderate yield.
An efficient stereoselective Wittig olefination of 4-hydroxycoumarin 1 with ethoxycarbonylmethylene-(triphenyl) phosphorane 71 assisted with microwave irradiation afforded (E)-ethyl 2-(4-hydroxy-2H-chromen-2-ylidene)-acetate 72 in 82% yield in 110 s (Sabitha et al., 1999) (Scheme 36).

**Scheme 39**

**Scheme 40**

**Scheme 41**

**Scheme 42**

(Pansuriya et al., 2010; Rad-Moghadam and Mohseni, 2004) (Scheme 35).

An efficient stereoselective Wittig olefination of 4-hydroxycoumarin 1 with ethoxycarbonylmethylene-(triphenyl) phosphorane 71 assisted with microwave irradiation afforded (E)-ethyl 2-(4-hydroxy-2H-chromen-2-ylidene)-acetate 72 in 82% yield in 110 s (Sabitha et al., 1999) (Scheme 36).
Coupling of 2-phenyl-4H-thiochromen-4-one \( \text{1} \) with 4-hydroxycoumarin \( \text{1} \) in acetic anhydride and ethyl acetate under reflux yielded the (3)-3-(2-phenyl-4H-thiochromen-4-ylidene)-3H-chromene-2,4-dione \( \text{74} \) (Huang et al., 2008) (Scheme 37).

6.1.1.6. Allylindation. Colombo et al., 2008 developed a three-component domino allylindation reaction of 1H-indole-3-carbaldehyde \( \text{75} \) with allyl bromide and 4-hydroxycoumarin \( \text{1} \) in the presence of indium metal in a mixture of tetrahydrofuran and water (1:1) which afforded the desired adduct \( \text{76} \) (Scheme 38).

Multicomponent reaction of aldehydes, indole \( \text{77} \) and 4-hydroxycoumarin \( \text{1} \) showed a surprising dependence on the
solvent, with CHCl₃–H₂O (1:1) giving the best yield of heterodimeric adducts 78 (Appendino et al., 2009) (Scheme 39). Catalysts (indium(III) or 1-proline) (Brahmachari and Das, 2014; Rao et al., 2012) have also been used as another catalysts for this reaction.

Deb and Bhuyan (2008) have exploited a very simple, novel, and efficient method for the synthesis of 3-[1(1H-indol-3-yl)(phenyl)methyl]-2H-1-benzopyran-2,4(3H)-dione 80 via the reaction of 4-hydroxycoumarin 1 and 3-alkylated indoles 79 (Scheme 40).

Baron et al. (2012) have investigated the solvent-free Michael addition of 3-(2-nitrovinyl)indole 81 to 1 by ultra-sound activation gave 4-hydroxy-3-[1-(1H-indol-3-yl)-2-nitroethyl]chromen-2-one 82 (Scheme 41).

Yamamoto et al. showed that indole-containing coumarins were prepared via three component reaction from 4-hydroxycoumarin 1, indole derivatives 83, and aldehydes 84 in acetic acid. The products showed promising antibacterial activities (Yamamoto and Kurazono, 2007; Yamamoto and Harimaya, 2004) (Scheme 42).

6.1.1.7. Synthesis of thioamides. Makhloufi-Chebli et al. (2009) showed that the condensation of 4-hydroxycoumarin 1 with arylisothiocyanates 86 in DMSO containing triethylamine as basic catalyst gave the corresponding N-aryl-4-hydroxycoumarin-3-carbothioamides 85 and N,N′-dihalogen-4-hydroxycoumarin-3-carboximidamides 86 (Scheme 43).

6.1.1.8. Synthesis of enaminones. Chohan et al. (2006) studied the antibacterial, antifungal and cytotoxic activities of a new series of 4-[[2,4-dioxo-2H-chromene-3(4H)-ylidene)methyl]aminosulfonamides 90 which have been obtained by the condensation reaction of 4-hydroxycoumarin 1 with various sulfonamides 89 in the presence of an excess of triethyl ortho-formate (Scheme 44).

The reaction of 4-hydroxycoumarin 1 with an excess of N,N-dimethylformamide dimethyl acetal (DMFDMA) 91 in refluxing toluene afforded the corresponding 3-(dimethylamino methylene)chromane-2,4-dione derivative 92 (Hamdi et al., 2006) (Scheme 45).

6.1.1.9. Formylation reaction. The broad range of applications of 4-hydroxy-2-oxo-2H-1-benzopyran-3-carboxaldehydes 93 has led to the development of its synthetic method. Several workers have reported the synthesis of 4-hydroxy-2-oxo-2H-1-benzopyran-3-carboxaldehydes 93 via the Vilsmeier Haack reaction by refluxing 4-hydroxycoumarin 1 with dimethyl formamide and phosphorous oxychloride. This compound 93 is useful for the synthesis of oxadiazolo[1,3,5]-triazine, 1,2,4-triazolo and thiadiazolo 1,3,4 oxadiazole derivatives (Gangadhar and Krupadanam, 1998; Mulwad and Chaskar, 2006; Mulwad, 2003; Rajanna et al., 1996) (Scheme 46).

On the contrary, Elgamal et al. (1997) reported that the same reaction yielded bis(3-formylocoumarin-4-yl)ether hydrate 94 (Scheme 47).

6.1.1.10. Acetylation reaction. The direct acetylation of 4-hydroxycoumarin 1 with acetyl chloride using pyridine or piperidine as a catalyst gave the 3-acetyl-4-hydroxycoumarin 95 (Stadlbauer and Hojas, 2004) (Scheme 48).

Moreover, several reports on new synthetic routes for these derivatives have been published during the last decade. A regioselective 3-acetyl-4-hydroxycoumarin 96 was obtained via the reaction of 4-hydroxycoumarin 1 with acetic acid or acetic anhydride containing phosphorous oxychloride as catalyst (Hamdi et al., 2008a; Li et al., 2012a, 2012b; Mulwad and Hegde, 2009b; Sukdolak et al., 2004; Vazquez-Rodriguez et al., 2013) (Scheme 49).

3-(10'-Undecenoyl)chroman-2,4-dione 98 was prepared by acetylation of 4-hydroxycoumarin 1 with 10-undecenoyl chloride 97 in pyridine containing a catalytic amount of piperidine (Cravotto et al., 2004a, 2004b) (Scheme 50).
The reaction of 4-hydroxycoumarin 1 with several long chain acyl chlorides 99 in pyridine containing a catalytic amount of piperidine under sonochemical conditions afforded 3-acyl-4-hydroxycoumarins 100 (Cravotto et al., 2006) (Scheme 51).

Cordaro et al. (2003) published the solvent-free reaction of 4-methyl-2-phenyl-2-oxazolin-5-one 101 with 4-hydroxycoumarin 1 afforded N-(1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1-oxopropan-2-yl)benzamide 102 in 40% yield (Scheme 52).

6.2. Reactions involving carbon–heteroatom bond formation

6.2.1. C–N bond formation

6.2.1.1. Coupling reactions. A series of new azo coumarin dyes were prepared by coupling of basic solution (sodium hydroxide or pyridine) (Metwally et al., 2012e; Shoair, 2007; Yazdanbakhsh et al., 2007) of 4-hydroxycoumarin 1 with diazotized arylamines (Scheme 53).

![Scheme 52](image)

![Scheme 53](image)

![Scheme 54](image)

![Scheme 55](image)

![Scheme 56](image)
Some novel hetarylazocoumarin dyes 106 were achieved by coupling 4-hydroxycoumarin 1 with diazonium salt of heterocyclic amines 105 (Jashari et al., 2014; Karci, 2005; Karci and Ertan, 2005) (Scheme 54).

6.2.1.2. Nitration reaction. Nitration of 4-hydroxycoumarin 1 with a mixture of glacial acetic acid and concentrated nitric acid afforded 3-nitro-4-hydroxycoumarin 107 (Brady et al., 2004; Butler and Brown, 2002; Dekic et al., 2010; Gao et al., 2010; Park et al., 2007; Zhi Qiang et al., 2014). Also, this nitration reaction was reported by Lei et al. (2004) via the reaction of 4-hydroxycoumarin 1 with nitrogen oxide and oxygen in dichloromethane (Scheme 55).

Huang et al. (2007a) observed that nitration of 4-hydroxycoumarin 1 in the presence of a solution of sodium nitrite and sulfuric acid at 0°C afforded 4-hydroxy-6-nitro-2H-chromen-2-one (Scheme 56).

On the other hand, use of CAN on montmorillonite K-10 clay under microwave irradiation for expeditious solvent-free regioselective nitration of 4-hydroxycoumarin 1 has been revealed for the first time by Ganguly et al. (2003) (Scheme 57).

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6.2.1.3. Formation of substituted amine (Amination). Recently, several workers have demonstrated the synthesis of 4-aminocoumarin 111 via the reaction of 4-hydroxycoumarin 1 with ammonium acetate 110 under reflux (Miri et al., 2011; Stamboliyska et al., 2010). Also, this condensation can be efficiently performed under microwave irradiation in solvent-free conditions and the products were isolated in 92% yield (Chavan, 2006) (Scheme 58).

Similarly, Glasnov and Ivanov (2008) achieved 4-aminocoumarin 111 by the reaction of 4-hydroxycoumarin 1 with acidic solution of ammonia. A simple and facile amination of 4-hydroxycoumarin 1 with equimolar amounts of 4-aminothiophenol or 4-aminophenol 112 in toluene yielded the corresponding 4-arylaminocoumarin derivatives 113 in high yields (Hamdi et al., 2006) (Scheme 59). Jacquot et al. (2007) described the condensation of 4-hydroxycoumarin 1 with alkyl(aryl)amines 114 in refluxing ethoxyethanol gave the 4-alk(aryl)coumarins 115 (Scheme 60). A short and being environmental-friendly synthesis of \(N\)-substituted 4-aminocoumarins 117 was accomplished by the reaction of 4-hydroxycoumarin 1 with primary amines 116 under microwave irradiation without use of any catalyst (Stoyanov and Ivanov, 2004) (Scheme 61).

Chavan (2006) synthesized a series of 4-aryl- and 4-alkylaminocoumarins 119 in good to excellent yields by the microwave assisted solvent-free reaction of 4-hydroxycoumarin 1 with aryl- or alkylamines 118 (Scheme 62).

Karagiosov et al. (1999) synthesized the \(N\)-(2-[(2-Oxo-2H-chromen-4-yl)amino]ethyl) acetamide 121 via the reaction of
4-hydroxycoumarin 1 with ethylenediamine 120 in boiling glacial acetic acid (Scheme 63).

6.2.1.4. Reaction with Schiff base. Manolov (1998) succeeded in preparation of benzylidenephenyliminochroman 123 from the condensation 4-hydroxycoumarin 1 with benzalaniline 122 in refluxing glacial acetic acid (Scheme 64).

6.2.2. C–S bond formation
6.2.2.1. Sulfonation reaction. 4-Hydroxy-3-coumarinsulfonic acid 125 was obtained by the reaction of 4-hydroxycoumarin 1 with chlorosulfonic acid 124 in dioxane (Jashari et al., 2007; Kovac et al., 2001) (Scheme 65).

6.2.2.2. Sulfenylation reaction. 6.2.2.2.1. Thiophenols formation. When a mixture of 4-hydroxycoumarin 1 and phosphorus pentasulfide in dry toluene was boiled under reflux, it yielded 3,3-bis-(4-thiohydroxycoumarin)[4-mercapto-3-(4-mercapto-2-oxo-2H-chromen-3-yl)-2H-chromen-2-one] 126 (Ibrahim, 2006) (Scheme 66).

6.2.2.2.2. Sulfides formation. Peng et al. (2009) have described a green, efficient, and novel route for the synthesis of 4-sulfanylcoumarins 128 via direct sulfanylation of 4-hydroxycoumarin 1 with thiols 127 in the presence of p-toluensulfonyl chloride (Scheme 67).

On the other hand, tetraalkylthiuram disulfides 131 reacted with 4-hydroxycoumarin 1 to yield 3-dimethylaminothiocarbonylthio-4-hydroxycoumarin 132 (Schnell and Kappe, 1999) (Scheme 68).

6.2.2.3. Thiocyanation reaction. Yadav et al. (2007) noted that 4-hydroxycoumarin 1 undergoes a novel and highly selective thiocyanation with ammonium thiocyanate 133 in the presence of K2CO3 / DMF (Scheme 69).

4-hydroxycoumarin 1 with diaryl disulfides 129 in dimethylformide in the presence of potassium carbonate yielded 3-arylsulfenyl derivative of 4-hydroxycoumarin 130 (Schnell and Kappe, 1999) (Scheme 68).

Treatment of 4-hydroxycoumarin 1 with diaryl disulfides 129 in dimethylformide in the presence of potassium carbonate yielded 3-arylsulfenyl derivative of 4-hydroxycoumarin 130 (Schnell and Kappe, 1999) (Scheme 68).

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6.2.2.4. Thionation reaction. Treatment of 4-hydroxycoumarin 1 with Lawesson’s reagent in boiling toluene afforded 4-mercapto-2H-chromene-2-thione 136 (Ibrahim, 2006) (Scheme 71).

Avetisyan and Alvandzhyan (2006) have reported that 4-hydroxy-2H-chromene-2-thione 137 is achieved from treatment of 4-hydroxycoumarin 1 with diphosphorus pentasulfide in boiling pyridine (Scheme 72).

6.2.3. $C\equiv O$ bond formation

6.2.3.1. Esterification. Esterification of 4-hydroxycoumarin 1 with acetic anhydride in the presence of pyridine at room temperature afforded the 4-acetoxycoumarin 138 in an excellent yield (Talapatra et al., 2001). Also, it was reported that the iodine or antimony trichloride or 4-dimethylaminopyridine (DMAP) (Ahmed and van Lie, 2006; Bhattacharya et al., 2008; Liu et al., 2014) catalyzed this acylation reaction. The advantages of these catalysts include their simplicity, fast and clean reactions, high yield, and the absence of organic solvent (Scheme 73).

In addition, O-acylation of 4-hydroxycoumarin 1 can occur with various acyl chlorides 139 or DMAP (Kappe and Schnell, 1996; Kuo et al., 2006; Liao et al., 2003; Liu et al., 2014; Lin et al., 2002) afforded corresponding esters 140 (Scheme 74). Also, it was reported that the SmCl$_3$ catalyzed this acylation reaction (Shen et al., 2007).

6.2.4. Claisen condensation

Treatment of 4-hydroxycoumarin 1 with methylenetriazine in refluxing methanol to produce the corresponding 3-thiocyanato-chroman-2,4-dione 134 in excellent yield with high selectivity (Scheme 70).

6.2.2.4. Thionation reaction. Treatment of 4-hydroxycoumarin 1 with Lawesson’s reagent in boiling toluene afforded 4-mercapto-2H-chromene-2-thione 136 (Ibrahim, 2006) (Scheme 71).

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6.2.3.2. O-Alkylation reaction. A mixture of 4-methoxycoumarin 141 and 2-methoxychromone 142 was obtained by the reaction of 4-hydroxycoumarin 1 with diazomethane in the presence of a catalytic amount of triethylamine (Sulko, 2000) (Scheme 75).

Takaishi et al. (2008) reported selective methylation of 4-hydroxycoumarin 1 upon treatment of 1 with diazomethane at room temperature. O-methylation of 4-hydroxycoumarin 1 is also readily performed under microwave irradiation in the presence of dry dimethyl sulfate to give 4-methoxycoumarin 143 (Cao et al., 2014; Garro Hugo et al., 2014; Mitra et al., 2000) (Scheme 76).

The base catalyzed alkylation of 4-hydroxycoumarin 1 with ethyl bromoacetate or chloroacetic acid 143 afforded ethyl (coumarin-4-oxo)acetate 144 (Abd Elhafez et al., 2003; Chimichi et al., 2002; Dahiya et al., 2010) (Scheme 77).

The reaction of 4-hydroxycoumarin 1 with 3-chloro-2-butanone 145 in acetone in the presence of anhydrous K$_2$CO$_3$ gave 4-(3-oxobutan-2-yloxy)-2H-chromen-2-one 146 in 75% yield (Ali-Sehemi and El-Gogary, 2012) (Scheme 78).

O-alkylation of 4-hydroxycoumarin 1 is possible also with isoureas. Due to the benzoannulation in 4-hydroxycoumarin 1 both ease and yield of this reaction strongly depend on the steric demands of the carbodiimide components. In the case of secondary alcohols only isoureas derived from diisopropylcarbodiimide give decent yields in the corresponding 4-alloxycoumarins 148 (Schobert and Siegfried, 2000) (Scheme 79).

4-Octadecyloxycoumarin 150 was synthesized by the reaction of 4-hydroxycoumarin 1 with 1-bromoctadecane 149 in ethanolic potassium carbonate solution (Guo et al., 2007) (Scheme 80).

Vasudevan et al. (2010) have published the O-alkylation of 4-hydroxycoumarin 1 with various alkenyl bromides 151 in DMF containing catalytic amount of potassium carbonate (Scheme 81).

4-Allyloxycoumarin 154 was obtained by the reaction of 4-hydroxycoumarin 1 with allylic alcohol or allyl bromide 153 in the presence of Bi(OTf)$_3$ or Cs$_2$CO$_3$ or indium (Carta et al., 2012; Chowdhury et al., 2014; Rueping et al., 2010) (Scheme 82).

A number of studies have investigated the O-alkylation of 4-hydroxycoumarin 1 with allyl halides 155 in acetone (Avetisyan and Alvandzhan, 2006; Majumdar et al., 2005; Patent, 2005) or DMF (Vasudevan et al., 2010) containing catalytic amounts of anhydrous potassium carbonate led to the formation of the corresponding allyl ethers 156 (Scheme 83).

Coumarin-4-yl-prop-2-ynyl ether 158 was obtained via refluxing of 4-hydroxycoumarin 1 with propargyl bromide 157 and potassium carbonate in dry acetone or in the presence of tetrabutylammonium bromide (Anand et al., 2011; Arcau et al., 2014; Majumdar et al., 2007) (Scheme 84).

Heating 4-hydroxycoumarin 1 with each of 2-bromobenzyl bromides 161a,b (Majumdar et al., 2003) and 4-vinylbenzylchloride 161c (Abd El-Aziz et al., 2008) in acetone containing anhydrous potassium carbonate afforded 4-(2'-bromo-2-hydroxybenzoyl)methylenephenan-7-one 162a,b and styrene monomers containing etheric-bound coumarin molecules 162c, respectively (Scheme 86).

6.2.3.3. Heteroethers formation. Tandon and Maurya (2009) described the reaction of 2,3-dichloro-1,4-naphthoquinone 163 with 4-hydroxycoumarin 1 in DMSO containing Na$_2$CO$_3$ gave a mixture of the 2-chloro-3-(2-oxo-2H-chromen-4-yl)napthalene-1,4-dione 164 and 2,3-bis(2-oxo-2H-chromen-4-yl) napthalene-1,4-dione 165 in 72% and 11% yields, respectively (Scheme 87).

Kaswala et al. (2009) reported that treatment of cyanuric chloride 166 in acetone with 4-hydroxycoumarin 1 in 10% aqueous sodium carbonate solution led to the formation of 2-(coumarinyl-4-oxo)-4,6-dichloro-s-triazine 167 (Scheme 88).

Condensation of 4-hydroxycoumarin 1 with one and two molar ratios of 2,3-dichloroquinoline 168 in aqueous sodium hydroxide solution gave the 2-chloro-3-(coumarin-4-oxo)quinoxaline 169 and 2,3-(dicyanomethylene)-4-oxoquinolines 170, respectively (El-Deen and Abd El-Fattah, 2000) (Scheme 89).

6.2.3.4. Sulfonates ether formation. Several groups have developed general methodology for the one step formation of 4-(p-
toluenesulfonyloxy)coumarin 172 via tosylation reaction of 4-hydroxycoumarin 1 with tosyl chloride 171 in the presence of base at room temperature (Gallagher et al., 2009; Hansen and Skrydstrup, 2005; Kuroda et al., 2009; Majumdar and Samanta, 2002; Patent, 2005; Saito et al., 1998; Shepard and Carreira, 1997) (Scheme 90).

There are several reports on the synthesis of 4-trifluoromethylsulfonyloxy)coumarin 174 in high yield through treatment of the 4-hydroxycoumarin 1 with triflic anhydride 173 under reflux in pyridine (Seganish and DeShong, 2004) or triethylamine in dichloromethane (Boland et al., 1996; Donnelly et al., 1999; Pierson et al., 2010) (Scheme 91).

Payne et al. (2010) introduced a rapid and efficient microwave irradiation method to prepare 176 via the reaction of 4-hydroxycoumarin 1 with triisopropylbenzenesulfonyl chloride 175 in THF containing catalytic amount of triethylamine (Scheme 92).

6.2.3.5. Silylation (Silyl ether formation). Iaroshenko et al. (2011) found that 4-hydroxycoumarin 1 was silylated by trimethylsilylchloride 177 in dioxane containing catalytic amount of dry pyridine (Scheme 93).

6.2.3.6. Phosphorylation reaction. A series of new piperazine phosphoramidate derivatives of 4-hydroxycoumarin 180 were synthesized through a facile phosphorylating reaction starting from 4-hydroxycoumarin 1 and various phosphorylating
Recent advances in 4-hydroxycoumarin chemistry

Scheme 86

\[
\text{1} + R_2\text{Br} \rightarrow \text{reflux, 6-8 h} \quad \text{162}
\]

<table>
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<tr>
<th>161, 162</th>
<th>R_1</th>
<th>R_2</th>
<th>X</th>
<th>Yield %</th>
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<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>72</td>
</tr>
<tr>
<td>b</td>
<td>OCH_3</td>
<td>H</td>
<td>Br</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>CH_2=CH_2</td>
<td>Cl</td>
<td>33</td>
</tr>
</tbody>
</table>

Scheme 87

\[
\text{1} + 163 \rightarrow \text{164 (11%)} + \text{165 (72%)}
\]

Scheme 88

\[
\text{1} + 166 \rightarrow \text{167 (78%)}
\]

Scheme 89

Please cite this article in press as: Abdou, M.M. et al., Recent advances in 4-hydroxycoumarin chemistry. Part 1: Synthesis and reactions. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.06.012
agents in the presence of triethylamine at room temperature (Chen et al., 2012) (Scheme 94).

6.2.3.7. Synthesis of the podands. The synthesis of the podands could be achieved via the base-catalyzed reaction of 2 equivalents of 4-hydroxycoumarin with oligoethylene glycol diglycidyl ether in refluxing methanol afforded directly the expected coumarin hydroxy ether in good yield (Hamdi et al., 2008a; Li et al., 2012a, 2012b) (Scheme 95).

Tuncer and Erk (2003) disclosed that bis-(4-oxa)coumarin ended polyglycols were synthesized by the reaction of 4-hydroxycoumarin with bis-dihalides of polyglycols in DMF containing catalytic amount of potassium carbonate (Scheme 96).

6.2.4. Carbon–halogen bond formation

Halogenoheteroarenes are useful intermediates for the syntheses of bioactive natural products and pharmaceutical drugs.

6.2.4.1. Bromination. The broad range of applications of 3-bromo-4-hydroxycoumarin has led to the development of numerous synthetic methods. Bromination of 4-hydroxycoumarin with bromine in acetic acid (Anand et al., 2011; Arcau et al., 2014) or chloroform (Kotharkar and Shinde, 2006) at low temperature yielded 3-bromo-4-hydroxycoumarin (Scheme 97).

Many existing bromination processes have recently advanced the goal of non-toxic, waste-free chemistry. Hence, the development of an efficient, eco-friendly, atom economic
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**Scheme 94**

<table>
<thead>
<tr>
<th>179, 180</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C$_6$H$_5$O</td>
<td>4-CH$_2$C$_6$H$_4$</td>
<td>85</td>
</tr>
<tr>
<td>b</td>
<td>C$_6$H$_5$O</td>
<td>4-ClC$_6$H$_4$</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>C$_6$H$_5$O</td>
<td>CH$_3$</td>
<td>80</td>
</tr>
<tr>
<td>d</td>
<td>C$_6$H$_5$O</td>
<td>(CH$_3$)$_3$C-O-CO</td>
<td>83</td>
</tr>
<tr>
<td>e</td>
<td>(ClCH$_2$CH$_2$)$_2$N</td>
<td>4-CH$_2$C$_6$H$_4$</td>
<td>83</td>
</tr>
<tr>
<td>f</td>
<td>(ClCH$_2$CH$_2$)$_2$N</td>
<td>4-ClC$_6$H$_4$</td>
<td>85</td>
</tr>
<tr>
<td>g</td>
<td>(ClCH$_2$CH$_2$)$_2$N</td>
<td>CH$_3$</td>
<td>87</td>
</tr>
<tr>
<td>h</td>
<td>(ClCH$_2$CH$_2$)$_2$N</td>
<td>(CH$_3$)$_3$C-O-CO</td>
<td>84</td>
</tr>
</tbody>
</table>

**Scheme 95**

<table>
<thead>
<tr>
<th>179, 180</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>65 75 70</td>
</tr>
</tbody>
</table>

**Scheme 96**

<table>
<thead>
<tr>
<th>181, 182</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
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<tr>
<td>X</td>
<td>Br</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
</tr>
</tbody>
</table>
(100% with respect to bromine) and selective procedure for the monobromination remains a major challenge in organic synthesis. Several procedures and reagent combinations have been reported for the bromination of 4-hydroxycoumarin. N-bromosuccinimide (NBS) is generally utilized for bromination of 4-hydroxycoumarin at room temperature using different catalysts such as polyethylene glycol (PEG-400) (Venkateswarlu et al., 2009), sulfonic-acid-functionalized silica (Das et al., 2006), ammonium acetate (Das et al., 2007), anhydrous magnesium perchlorate (Zhang et al., 2007) or tetrabutylammonium bromide (TBAB) (Ganguly et al., 2005) (Scheme 98). Ammonium bromide and Oxone® (Kumar et al., 2010) or tetrabutylammonium bromide and phosphorus pentoxide (Jung and Allen, 2009; Kato et al., 2001) have also been used as another brominating agents for this reaction (Scheme 53).

When the bromination of 4-hydroxycoumarin 1 is carried out using vanadium pentoxide as effective promoters with tetrabutylammonium bromide in the presence of hydrogen peroxide, it afforded 2,2-dibromo-2-hydroxyacetophenone 184 (Bora et al., 2000) (Scheme 99).

**6.2.4.2. Chlorination.** It is known that the selectivity of the reaction of 4-hydroxycoumarin 1 with phosphorous oxychloride is low because a considerable amount of 4-chloro-3,4',3',4''-tercoumarin 185 was formed as a by-product. The yield of 4-chlorocoumarin 186 can be improved by treatment of 1 with phosphorous oxychloride under reflux (Kovac et al., 2001; Majumdar and Bhattacharyya, 2001; Zhang et al., 2014). Also, this reaction can be efficiently performed under inert atmosphere in the presence of benzyltriethylammonium chloride in acetonitrile (Xiao et al., 2011) (Scheme 100).

**6.2.4.3. Chloroformylation.** Recently, several workers (Bochkov et al., 2013; Borah et al., 2012; Dawara and Singh, 2011; Iaroshenko et al., 2012; Ibrahim et al., 2009; Ivanov et al., 2013; Kapoor et al., 2012; Kasabe et al., 2010; Li et al., 2012a, 2012b; Milevskii et al., 2013; Mulwad and Hegde, 2009a; Patil et al., 2011; Rehman et al., 2005; Sabetie et al., 2001; Strakova et al., 2003; Wang et al., 2013) have demonstrated the synthesis of 4-chlorocoumarin-3-carbaldehyde 187 via the Veilsmeyer Haack reaction by treatment of 4-hydroxycoumarin 1 with anhydrous N,N-dimethylformamide and phosphorous oxychloride. The chloroformylocoumarin is useful for the synthesis of aromatic and heteroaromatic annelated [1,4]diazepines (Scheme 101).
7. Conclusion

We hope to have conveyed to the readers of this review the current interest of the synthetic community in the synthesis, and chemical reactivity of 4-hydroxycoumarin from 1996 onward. It seems likely that 4-hydroxycoumarin will remain as popular building blocks for the synthetic chemists, and that further elegant and innovative developments and applications will emerge in the future.

References


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Jashari, A., Hey-Hawkings, E., Mikhova, B., Draeger, G., Popovski, E., 2007. An improved synthesis of 4-chlorocoumarin-3-sulfonyl chloride and its reactions with different bidentate nucloephiles to give pyrido[1’-2’;2-3’;1,2,4-thiazolo[3’-2’;3-2]-1,2-thiadiazadino[6,5-c]benzopyran-6-one 7,7-dioxides. Molecules 12 (8), 2017–2028.


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