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REVIEW

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

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Synthetic routes;
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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.

Contents

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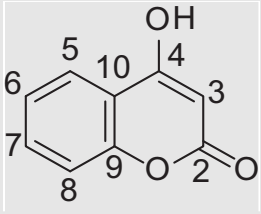
1. Introduction

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; Ziarani and Hajiabbasi, 2013), but it constitutes the structural nucleus of many natural products (Awe et al., 2009; Oganesyan et al., 2007; Orlovskaya et al., 2007).

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 Rettie, 2008; Ganguly et al., 2013; Guo et al., 2013; Palareti and Legnani, 1996; Pelz et al., 2005; Simon and Shaughnessy, 2004; Van Walraven et al., 2002), antibacterial (Brahmbhatt et al., 2013; 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 (Kirkiacharian et al., 2008; Zavrsnik et al., 2011), antitumor (Arya et al., 2014; Bi et al., 2013; Dorababu et al., 2013; Farghaly et al., 2014; Kawaii et al., 2001; Kumar et al., 2013; Pingaew et al., 2014; Salinas-Jazmin et al., 2010; Loa et al., 2009), anticonvulsant (Jaweed Mukarram et al., 2005), antiprotozoal (Tasdemir et al., 2006), insecticidal (Wang et al., 2009), fungicide (Oliva et al., 2003), antimycobacterial (Abou-Melha and Faruk, 2008; Kotharkar and Shinde, 2006; Mostafa, 2008; Sukdolak et al., 2005; Zavrsnik et al., 2008), antimutagenic (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 et al., 2006, 2007a, 2007b, 2007c; Jandera et al., 2005, 2008; Jin et al., 2007; Joseph et al., 2009; Li and McGuffin, 2007; Meaney and McGuffin, 2008; Novakova et al., 2010; Spacil et al., 2008; Subbiah et al., 2005; Sun et al., 2009; Zhang et al., 2010) and other products of technical importance such as plant growth regulating modulators (Abdou et al., 2013; Brooker et al., 2007; Gerasov et al., 2008; Graciet, 2005; Metwally et al., 2012a, 2012b, 2012c, 2012d, 2013; Stanchev et al., 2010; Trivedi et al., 2001; Wang et al., 2000), and dye stuff.

On typing "4-hydroxycoumarin" in any chemistry database a countless number of records appear as proof of its importance and long history; thus, it has been impracticable to survey the literature of 4-hydroxycoumarin completely from the beginning. In continuation of our studies in exploring the utilization of cyclic 1,3-dicarbonyl compounds as versatile precursors for the synthesis of organic compounds (Abdou, 2014a, 2014b, 2014c, 2014d), in the present review, we have thus chosen to summarize the most relevant advances in the construction of 4-hydroxycoumarin (without any substituents attached) reported in the literature from 1996 until now. The monograph of the chemistry of 4-hydroxycoumarin, structure,

Table 1 ^{1}H NMR and ^{13}C NMR spectra of 4-hydroxycoumarin (Solvent: DMSO-d_6).



^{1}H NMR				^{13}C NMR	
H	δ (ppm)	Multiplicity	J (Hz)	C	δ
3	5.61	s	–	2	161.79
				3	90.87
5	7.84	d	7.80	4	165.52
				5	123.85
6	7.66	t		6	123.10
				7	132.63
7	7.36	t		8	116.28
				9	153.41
8	7.39	d		10	116.67

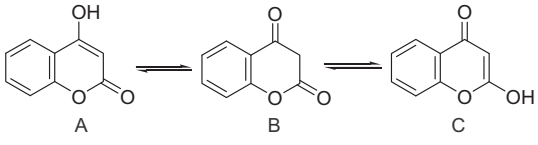


Figure 1 Possible tautomeric structures of 4-hydroxycoumarin **1** (A–C).

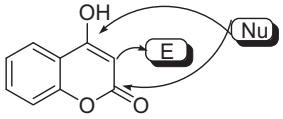


Figure 2 Reactive sites in 4-hydroxycoumarin.

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., 1997b). 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, typical chemical shift for hydrogens on non-aromatic double bonds and no other signal is observed with the exception of the four aromatic hydrogens (H-5, H-6, H-7, and H-8). It shows two complex multiplets, of equal intensity, at 7.66 and 7.84 ppm due to the C-5 and C-6 protons, and two others at 7.36 and 7.39 ppm for the C-7 and C-8 protons, respectively. The coupling constants for the C-5, C-6 protons (J = 7.8 Hz) and C-7, C-8 protons (J = 7.8 Hz). It is also interesting to note that the hydrogen of the hydroxy group was not visible, because of fast hydrogen/deuterium exchange (Špirtović-Halilović et al., 2014).

A ^{13}C NMR study (Traven et al., 1997a) of the 4-hydroxycoumarin (Table 1) indicated that the C-2, C-4 and C-9 carbons resonate downfield, compared to the other carbons. Splitting pattern analysis shows the signal of the C-2 atom to be doublet due to its interaction with the only proton at position 3. The signals of C-4 are multiplets (doublets of doublets) due to splitting on H-3 and H-5 atoms.

The LRMS (Aguirre-Pranzoni et al., 2011) showed an M^+ of m/z 162. Substitution (—OH or C═O) in C-4 was confirmed by analyzing the mass spectrum which shows that the fragment at m/z 120, corresponding to the loss of the ketene moiety, is 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 HC_2O. The loss of CO (M-28) and HCO (M-29), is even below the 2%. The absence of fragments corresponding to M-17 (m/z145) and M-18 (m/z 144) is attributable to the loss of HO and H_2O 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.

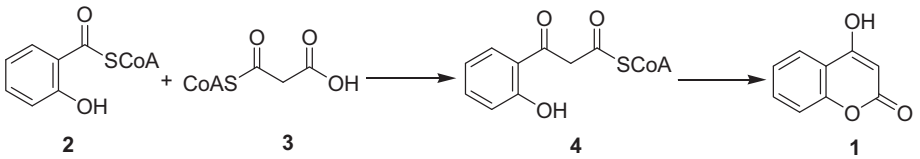
4. Chemical reactivity

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 alkylating agents. It seemed that hard nucleophiles attack preferentially oxygen atom, while soft ones attack preferentially carbon atom (Fig. 2).

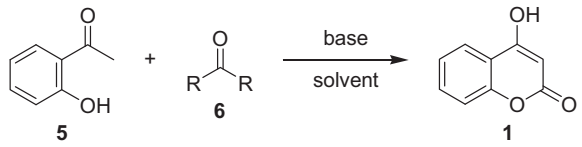
5. Synthesis

5.1. The biosynthetic pathway

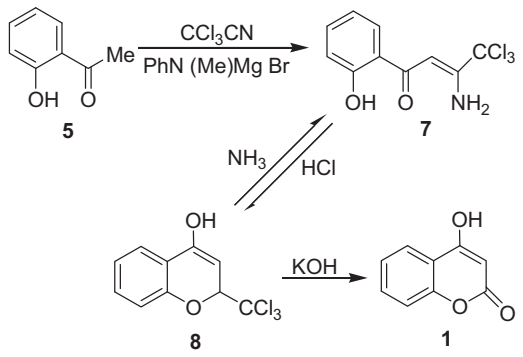
Biosynthesis of 4-hydroxycoumarin **1** involves BIS-catalyzed reaction of salicyl-CoA **2** with malonyl-CoA **3** to form a diketone intermediate **4** which undergoes intramolecular cyclization by nucleophilic attack of the phenolic group on the CoA- or cysteine-tethered C-1 thioester yielding 4-hydroxycoumarin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



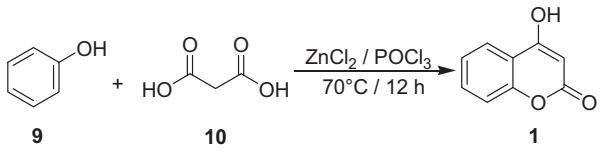
Scheme 1



Scheme 2 **1a–f** (Toluene): R = OEt; base/yield(%) = NaOEt/80, NaH/85, NAPA/51, KAPA/63, Na/50/, NaH/85; **1g** (Xylene): R = OEt; base/yield (%) = Na/93; **1h–k** (Toluene): R = OMe; base/yield (%) = KAPA/55, NAPAb/60, NaH/84, NaOEt/71; **1i,m** (Toluene): R = Cl; base/yield (%)/ref = NaH/69, NaOEt/66.



Scheme 3



Scheme 4

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 trichloroacetonitrile in the presence of *N*-methylanilinomagnesium 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-phenoxypropanoic 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** in 90% yield *via* the acid-catalyzed deacylation 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).

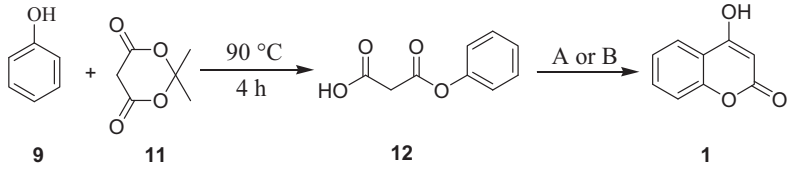
6. Chemical reactions

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

6.1. Reactions involving carbon–carbon bond formation

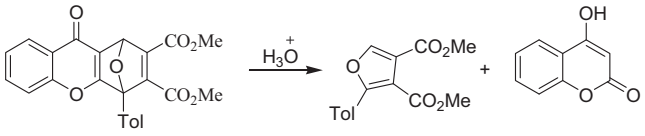
6.1.1. C—C Bond formation reactions

6.1.1.1. C_3-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



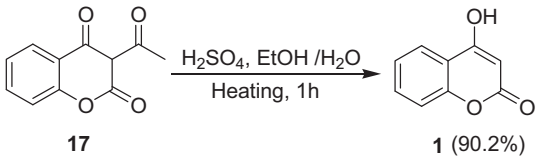
A : Eaton's reagent, 70 °C, 1 h.
B : 116% PPA, 120 °C, 15 h.

Scheme 5



Tol = toluene

Scheme 6



Scheme 8

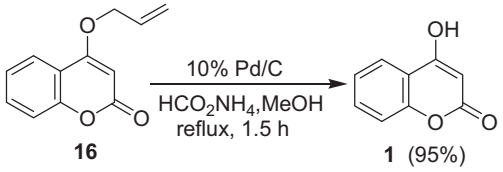
potential advantages, such as the wide availability of the starting materials and the generation of H_2O as the only side product. Such strategy has been elegantly applied to the synthesis of allyl and benzyl-substituted 4-hydroxycoumarin compounds (Chatterjee and Roy, 2012; Gan et al., 2008; Huang et 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).

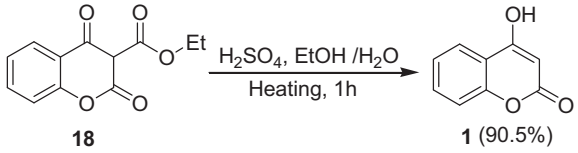
It was also shown that the 4-hydroxy-3-(1,3-diphenylallyl)-2H-chromen-2-one **23** was obtained by the reaction of 1,3-diphenylprop-2-en-1-ol **22** with 4-hydroxycoumarin **1** in the presence of 5 mol% ytterbium (III) triflate in a mixture of 1,4-dioxane and nitromethane (Huang et al., 2007b) (Scheme 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)-2*H*-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).

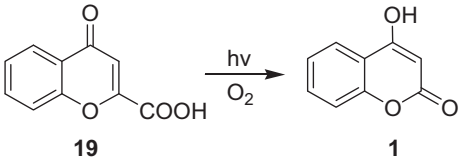
6.1.1.2. C_3-Benzylation. Theerthagiri and Lalitha (2010) reported that the direct benzylation of 4-hydroxycoumarin **1** with a wide variety of secondary benzylic alcohols **26** was achieved using trimethylsilyltrifluoromethane sulfonate



Scheme 7



Scheme 9



Scheme 10

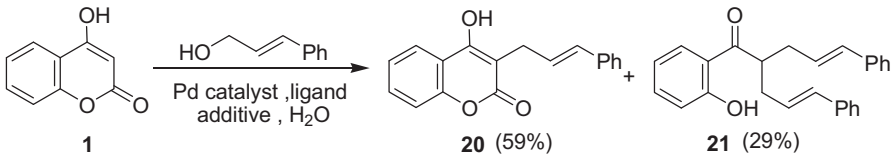
(TMSOTf) as an efficient catalyst at room temperature providing the desired products **27** in good to excellent yields (Scheme 14).

Iron (III) perchlorate efficiently catalyzes benzylation of 4-hydroxycoumarin **1** with various secondary benzylic alcohols **28** in acetonitrile. The reaction proceeds smoothly to give the corresponding C_3-benzylated products (Thirupathi and Kim, 2010) (Scheme 15).

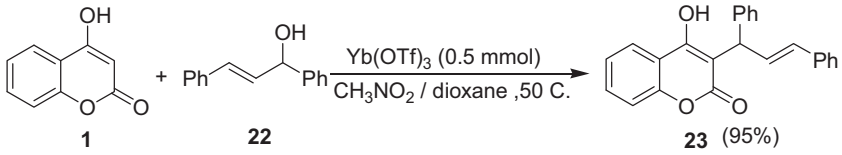
The above methodology was successfully applied for the benzylation of 4-hydroxycoumarin **1** with, the sterically hindered alcohol, 1-(2-naphthyl)ethanol **30** in acetonitrile containing 5 mol% of iron (III) perchlorate monohydrate to afford the 4-hydroxy-3-(1-(naphthalene-2-yl)ethyl)-2*H*-chromen-2-one **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 benzylic alcohols **32** in methylene chloride containing a catalytic amount of $FeCl_3{\cdot}6H_2O$ (Scheme 17).

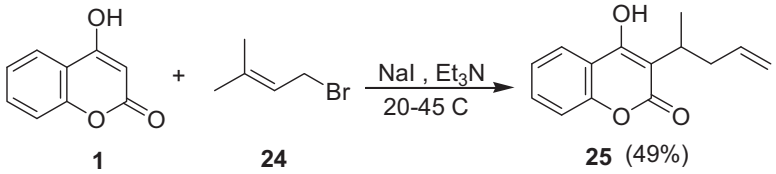
3-Alkylated-4-hydroxycoumarins **35**, used as anticoagulants phenprocoumon, were achieved in high yield by the



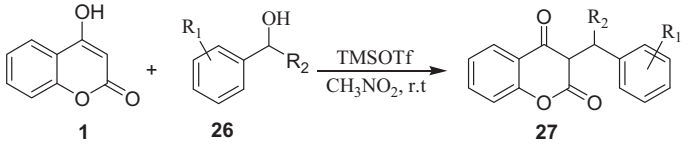
Scheme 11



Scheme 12



Scheme 13



26, 27	a	b	c	d	e	f	g	h	I
R_1	H	4-CH_3O	4-F	H	H	4-CH_3	4-CH_3O	2-Br	2-CH_3O
R_2	CH_3	4-$CH_3OC_6H_4$	4-FC_6H_4	3,4-Cl C_6H_4	3,4-CH_3 C_6H_4	CH_3	CH_3	CH_3	CH_3
Conditions (time, yield)	(0.5h,91%)	(0.5h, 83%)	(0.5h,71%)	(0.5h, 81%)	(0.5h, 87%)	(0.5h,71%)	(0.5h,60%)	(0.45h,55%)	(0.5h,78%)

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

Scheme 14

reaction of 4-hydroxycoumarin **1** with *sec*-benzylic alcohols **34** 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 **37** 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 **38** 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 **42** were produced in 3-component cascade reaction involving aryl/heteroaryl/vinyl iodides **41**, 4-hydroxycoumarin **1,** and allene **40** 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 benzylic, benzhydrylic, allylic, and propargyl alcohols **43** at 50 °C in nitromethane. The 3-

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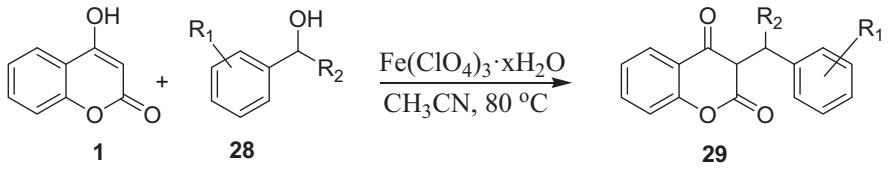
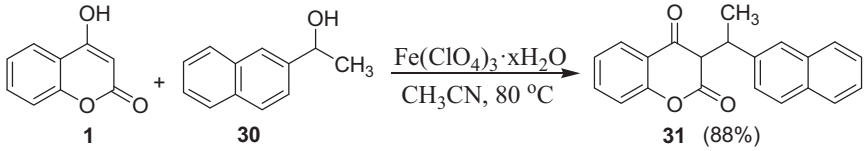


1 28 29

28, 29	a	b	c	d	e	f	g	h
R_1	H	4-CH_3O	4-CH_3	2-CH_3O	H	4-Cl	4-CH_3O	4-F
R_2	H	CH_3	CH_3	CH_2CH_3	C_6H_5	4-Cl C_6H_4	4-$CH_3OC_6H_4$	4-FC_6H_4
Conditions (time, yield)	(4h,86%)	(3.5h,92%)	(4h,89%)	(3.5 h, 90%)	(3 h, 91%)	(2.5 h,93%)	(2 h, 98%)	(2.5h, 95%)

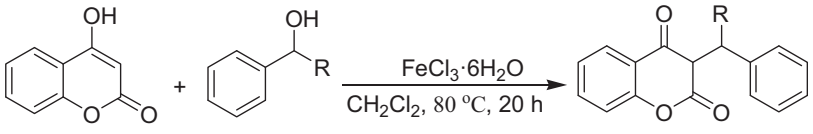
Reaction condition: **28** (1.0 mmol), **1** (equiv.).

Scheme 15



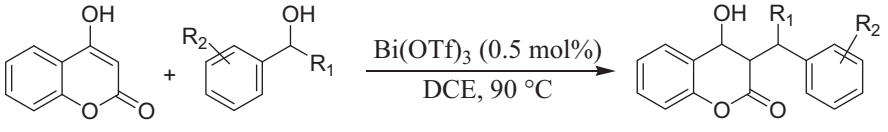
1 30 **31** (88%)

Scheme 16



1 32 **33**
32,33a: R=Me (86%)
32,33b: R=Et (92%)

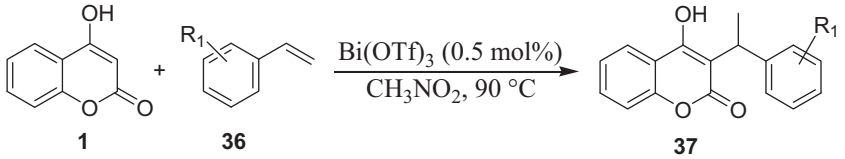
Scheme 17



1 34 35

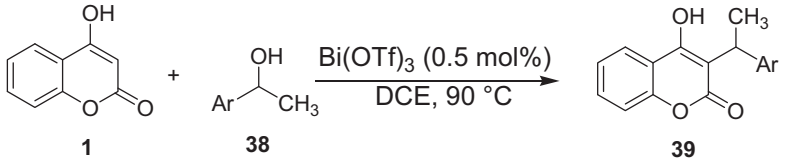
34, 35	a	b	c	d	e	f
R_1	Me	Me	Me	Me	Et	Me
R_2	H	4-Br	2-Me	Ph	H	4-MeO
Conditions (time, yield)	(5 h, 89%)	(8 h, 61%)	(3 h, 88%)	(5 h, 80%)	(4 h, 62%)	(3 h, 97%)

Scheme 18



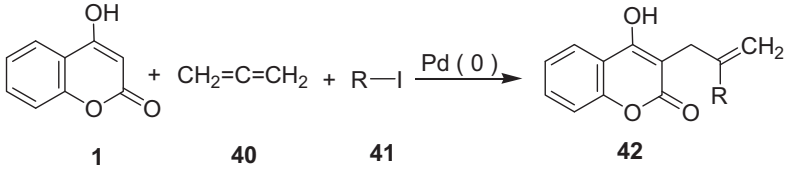
36, 37	a	b	c	d
R_1	H	4-Cl	4-Me	2-F
Conditions (time, yield)	(4 h, 75%)	(7 h, 80%)	(5 h, 58%)	(4 h, 67%)

Scheme 19



38, 39	a	b
Ar	1-naphthyl	2-naphthyl
Conditions (time, yield)	(6 h, 60%)	(5 h, 93%)

Scheme 20



41, 42	a	b	c	d	e
R	F_3C, CF_3, I	Cl, Cl, I	F, Cl, I	I, Cl, N	I, N
Yield (%)	97	91	91	65	92

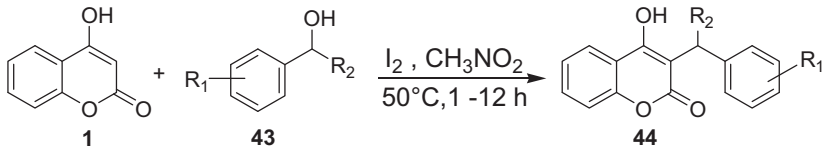
Scheme 21

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)arylmethyl]-4-hydroxy coumarin **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 $(C_6F_5)_3B$ (Reddy et al., 2010), $Yb(OTf)_3$ (Chatterjee

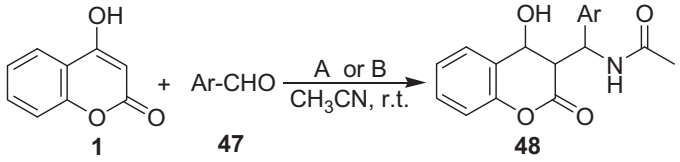


43, 44	a	b	c	d	e	f	g
R_1	4-OMe	H	H	H	4-Me	H	H
R_2	Me	Me	CH=CH-C_6H_5	C≡C-C_6H_5	Me	4-OMeC_6H_5	C_6H_4
Conditions (time, yield)	(12 h, 84%)	(12 h, 74%)	(4 h, 92%)	(1 h, 80%)	(12 h, 76%)	(4 h, 82%)	(4 h, 97%)

Scheme 22

45, 46	a	b	c	d	e	f
R_1	H	H	OMe	H	OMe	H
R_2	C_6H_4	Me	CH_2-CH-CH_2	C≡C-C_6H_5	C≡C-C_6H_5	CH=CH-C_6H_5
Conditions (time, yield)	(2 h, 86%)	(2 h, 81%)	(2 h, 78%)	(2.5 h, 84%)	(2 h, 83%)	(3 h,78%)

Scheme 23



	a	b	c	d	e	f	g	h
Ar	C_6H_5	4-Cl-C_6H_4	4-Br-C_6H_4	2-Cl-C_6H_4	3-NO_2-C_6H_4	4-NO_2-C_6H_4	2-MeO-C_6H_4	2-HO-C_6H_4
Yield (%) (A/B)	98/95	95/95	100/90	98/90	98/95	95/95	95/97	98/90

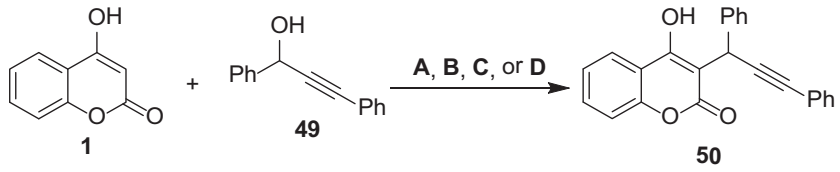
Reaction condition: A: $ClSO_3H$
B: P_2O_5-HMDS

Scheme 24

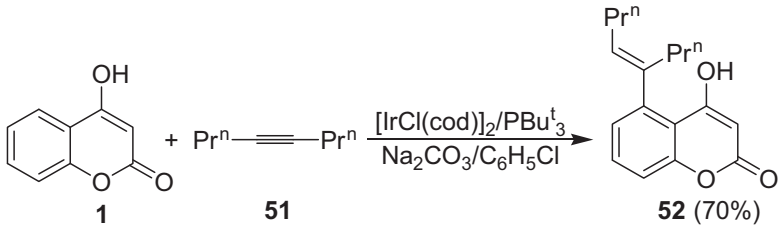
and Roy, 2012; Huang et al., 2007b), $FeCl_3$ (Maiti et al., 2011), and iodine in nitromethane (Lin et al., 2009) (Scheme 25).

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-octen-4-yl]coumarin **52** was produced as the single coupling product (Nishinaka et al., 2001) (Scheme 26).

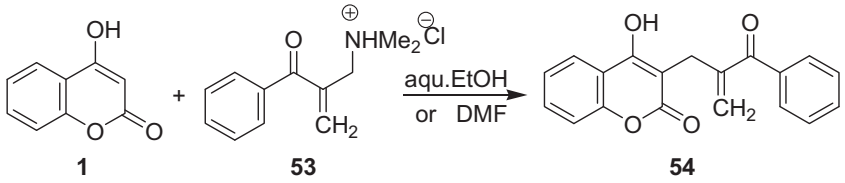
In recent years, 1-aryl-2-dimethylaminomethyl-prop-2-en-1-ones (ADMP reagents) **53** have gained remarkable attention



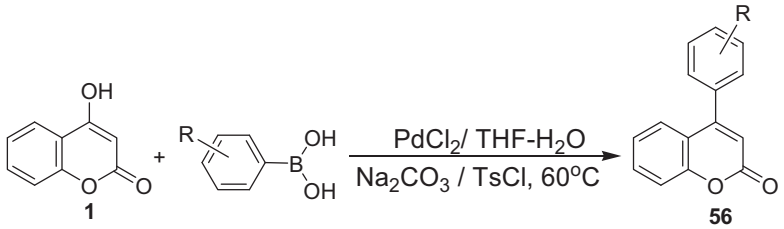
Scheme 25 Methods: **A**: $(C_6F_5)_3B$, CH_3CN, reflux, 15 min, 89% yield; **B**: $Yb(OTf)_3$, dioxane, CH_3NO_2, 50 °C, 2 h, 85% yield; **C**: $FeCl_3$, dioxane, CH_2Cl_2, 50 °C, 3 h, 77% yield, **D**: I2, CH_3NO_2, 50 °C, 1 h, 80%.



Scheme 26



Scheme 27



55, 56	a	b	c	d	e	f	g
Ar	H	4-Me	4-OMe	2-Cl	3-CN	3-NO_2	4-CF_3
Yield (%)	91	98	98	88	90	68	52

Scheme 28

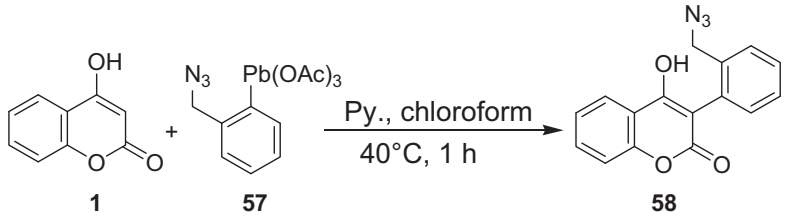
in organic, and medicinal chemistry. Girreser and Heber (2000) succeeded in preparing 3-(2-benzoylallyl)-4-hydroxycoumarin **54** *via* the reaction of 4-hydroxycoumarin **1** with ADMP **51** in dimethylformamide or ethanol as solvent (Scheme 27).

6.1.1.4. Arylation. Luo and Wu (2009) demonstrated that 4-aryl coumarins **56** can be synthesized *via* palladium-catalyzed direct arylation of 4-hydroxycoumarin **1** with arylboronic acids **55**. 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).

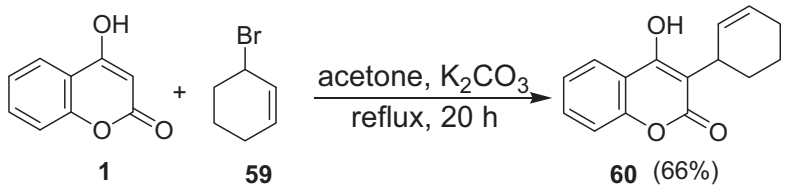
Ganina et al. (2005) reported that the reaction of 4-hydroxycoumarin **1** with 2-(azidomethyl)phenylleadtriacetate **57** in chloroform containing catalytic amount of pyridine yielded 3-(2-azidomethylphenyl)-4-hydroxycoumarin derivatives **58** (Scheme 29).

A simple procedure for the preparation of 3-(cyclohex-2-enyl)-4-hydroxycoumarin **60** by refluxing 4-hydroxycoumarin **1** with 3-bromocyclohexene **59** in acetone containing anhydrous potassium carbonate was described by Majumdar and Sarkar (2002) (Scheme 30).

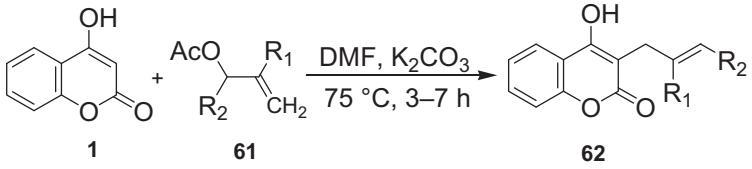
The nucleophilic addition of 4-hydroxycoumarin **1** to Baylis–Hillman acetate adducts **60** has been described for the



Scheme 29

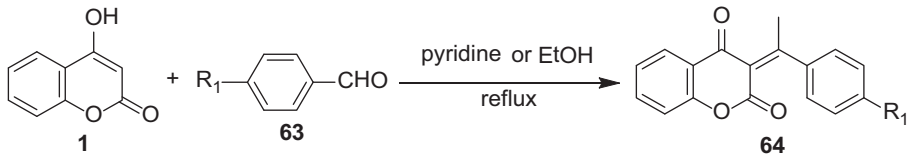


Scheme 30



61, 62	a	b	c	d	e	f	g	h
R_1	CO_2Et	CN	CO_2Et	CO_2Et	CO_2Et	CO_2Et	CO_2Et	CN
R_2	C_6H_5	C_6H_5	3-BrC_6H_4	3-$NO_2C_6H_4$	4-$MeOC_6H_4$	3-$AcOC_6H_4$	CH_2CH_2Ph	2-$NO_2C_6H_4$
Conditions (time, yield)	(3.5h,92%)	(4 h,82%)	(3.5 h, 85%)	(6 h, 72%)	(5 h, 89%)	(6 h,73%)	(6 h, 78%)	(4 h, 82%)

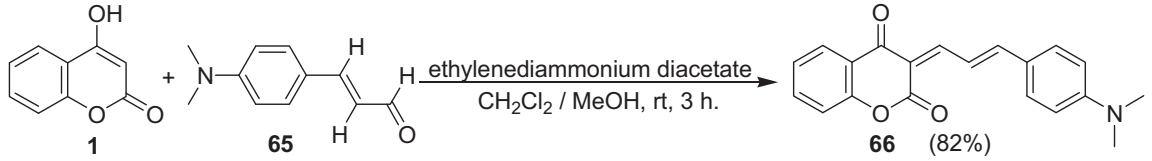
Scheme 31



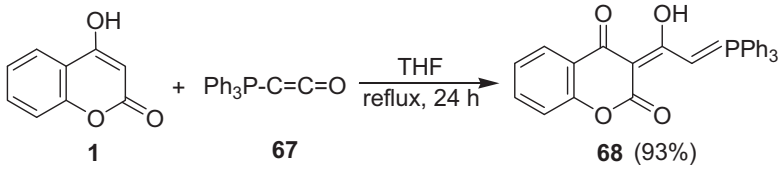
Scheme 32 **64a,b** (Solvent: Pyridine): R = H (75%), 4-Me (70%); **64c–g** (Solvent: Ethanol): R (Yield%) = H (78), 4-OMe (80), 4-Cl (80), 3-NO_2 (76), 4-OH (83).

first time by Reddy et al. (2009) as an efficient route to obtain 3-substituted 4-hydroxycoumarin **61** in good yields (Scheme 31).

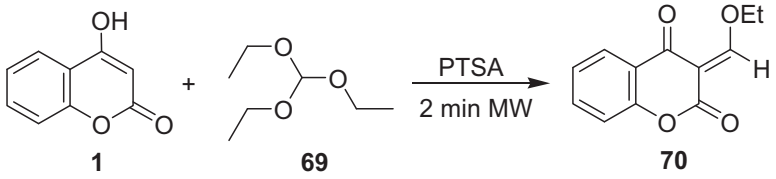
6.1.1.5. Olefination. One of the most successful strategies for constructing 3-benzylidenecoumarins **64** is the Knoevenagel condensation. Heterocondensation reaction between 4-



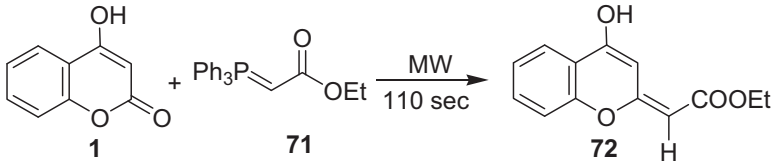
Scheme 33



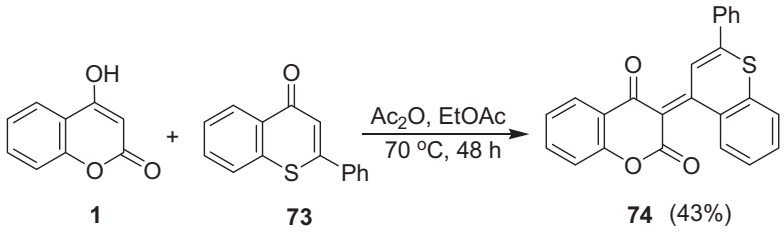
Scheme 34



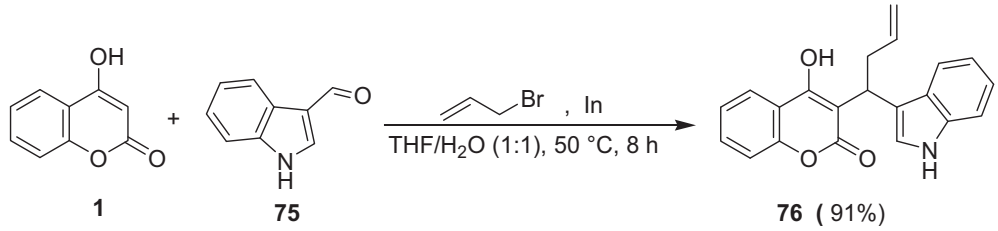
Scheme 35



Scheme 36



Scheme 37



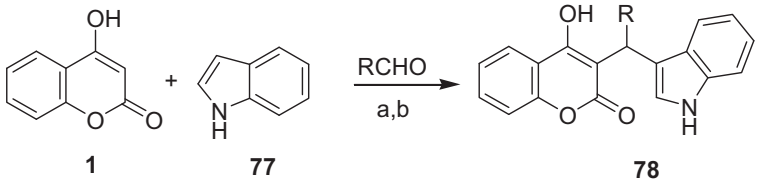
Scheme 38

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-(4*N*,*N*-[dimethylaminophenyl)prop-2-enylidene]-2*H*-1-benzopyran-2,4(3*H*)-dione **66** was obtained *via* reaction of 4-hydroxycoumarin **1** with (*E*)-3-(4-(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 ketenylidenetriphenylphosphorane **67** in tetrahydrofuran led to the formation of the corresponding 3-(triphenylphosphora-nylideneoxoethyl) derivatives **68** (Schobert et al., 2000) (Scheme 34).

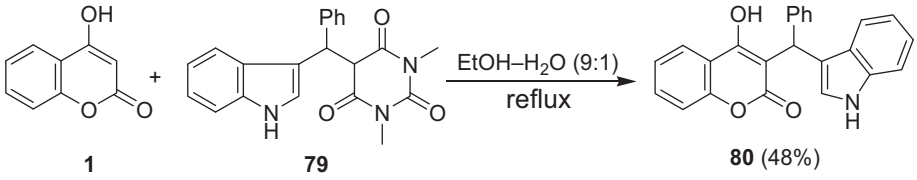
The acid-catalyzed microwave irradiation of 4-hydroxycoumarin **1** and triethyl orthoformate **69** gave 3-ethoxymethylene-3*H*-2,4-dione **70** in moderate yield



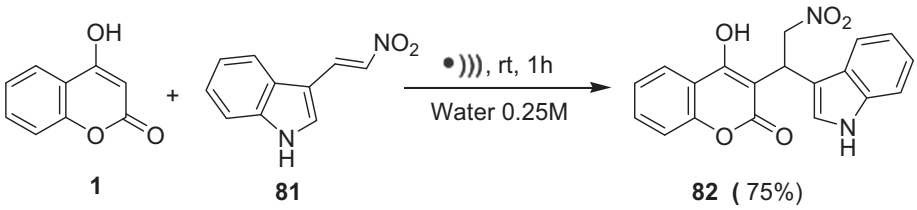
	a	b	c	d	e
R	CH_3	C_6H_{13}	C_6H_5	4-NO_2Ph	4-OMePh
Conditions (time, yield)*	a (5 h, 88%)	a (48 h, 70%)	a (24 h, 41%) b (48 h, 57%)	a (24 h, 25%) b (48 h, 85%)	a (24 h, 18%) b (48 h, 28%)

*a: $CHCl_3$, 40 °C; b: $CHCl_3$–water 1:1, 40 °C.

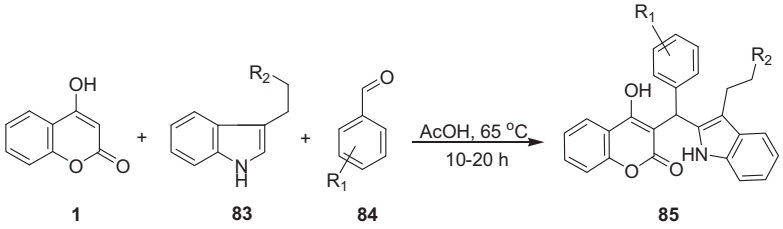
Scheme 39



Scheme 40



Scheme 41

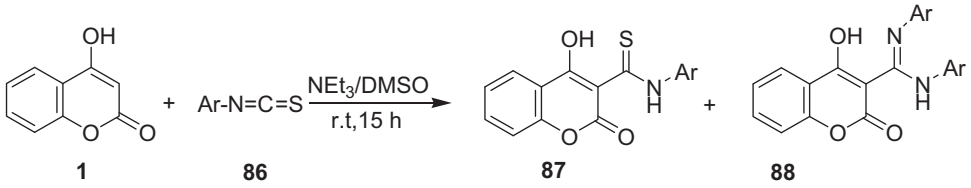


	a	b	c	d	e	f	g	h	i	k	l	m	n	o	p	q
R_1	3-Br	3-Br	3-Br	H	3-F	3-Me	3-CF_3	4-Br	4-SMe	4-Me	3-CF_3	4-OMe	4-OCF_3	4-OCF_3	4-Me	4-CF_3
R_2	NHAc	OAc	OBz	OBz	OBz	OBz	OBz	OBz	OBz	OBz	OBz	OBz	OBz	NHAc	$NHSO_2Ph$	$NHSO_2Ph$
Yield (%)	53	69	85	81	98	97	85	62	86	88	84	87	85	93	90	85

Scheme 42

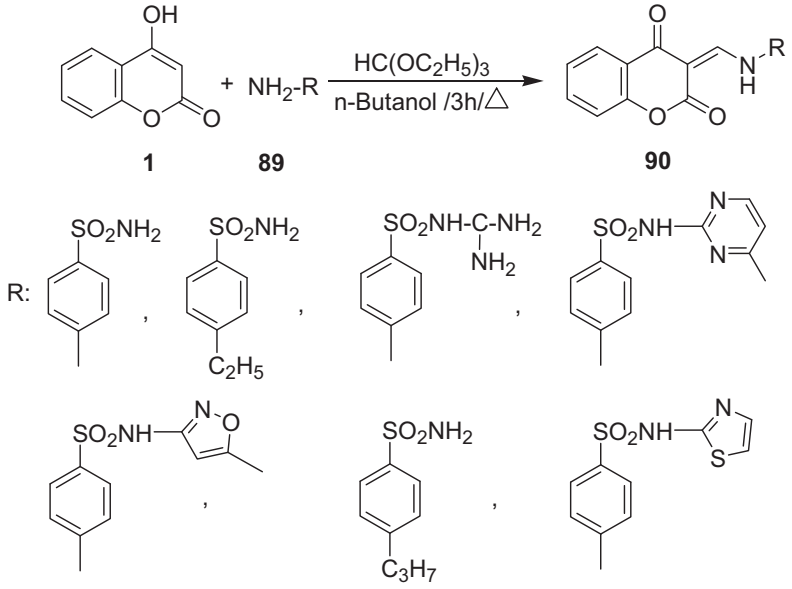
(Pansuriya et al., 2010; Rad-Moghadam and Mohseni, 2004) (Scheme 35).

An efficient stereoselective Wittig olefination of 4-hydroxycoumarin **1** with ethoxycarbonylmethylene-(triphenyl) phosphorane **71** assisted with microwave irradiation afforded (*E*)-ethyl 2-(4-hydroxy-2*H*-chromen-2-ylidene)-acetate **72** in 82% yield in 110 s (Sabitha et al., 1999) (Scheme 36).

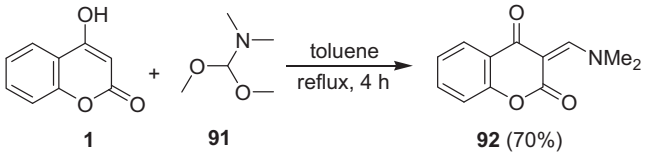


87, 88	a	b
Ar	Ph	4-Br-Ph
Yield % (87/88)	30/55	35/45

Scheme 43



Scheme 44

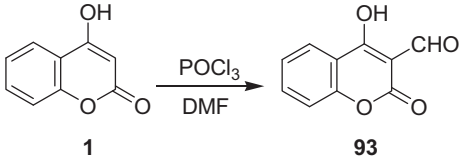


Scheme 45

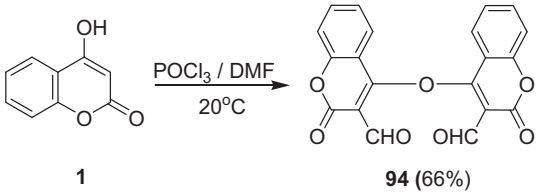
Coupling of 2-phenyl-4*H*-thiochromen-4-one **73** with 4-hydroxycoumarin **1** in acetic anhydride and ethyl acetate under reflux yielded the (3)-3-(2-phenyl-4*H*-thiochromen-4-ylidene)-3*H*-chromene-2,4-dione **74** (Huang et al., 2008) (Scheme 37).

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

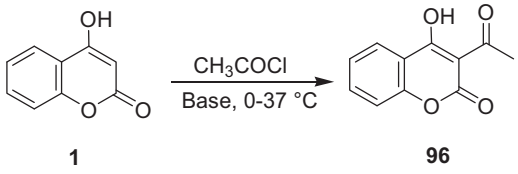
Multicomponent reaction of aldehydes, indole **77** and 4-hydroxycoumarin **1** showed a surprising dependence on the



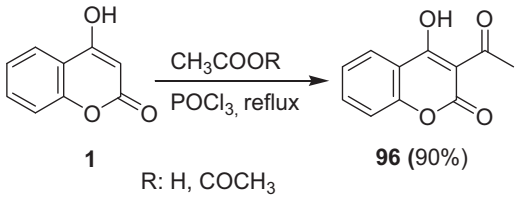
Scheme 46



Scheme 47



Scheme 48



Scheme 49

solvent, with $CHCl_3$–H_2O (1:1) giving the best yield of heterodimeric adducts **78** (Appendino et al., 2009) (Scheme 39). Catalysts (indium(III) or L-proline) (Brahmachari and Das, 2014; Rao et al., 2012) have also been used as another catalysts for this reaction.

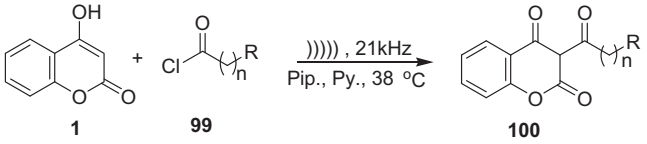
Deb and Bhuyan (2008) have exploited a very simple, novel, and efficient method for the synthesis of 3-[(1*H*-Indol-3-yl)(phenyl)methyl]-2*H*-1-benzopyran-2,4(3H)-dione **80** *via* the reaction of 4-hydroxycoumarin **1** and 3-alkylated indoles **79** (Scheme 40).

Baron et al. (2012) have investigated the solvent-free Michael addition of 3-(2-nitrovinyl)indole **81** to **1** by ultrasound activation gave 4-hydroxy-3-[1-(1*H*-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*$^{-}$-diaryl-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-2*H*-chromen-3(4H)-ylidene]methyl}amino)sulfonamides **90** which have been obtained by the condensation reaction of 4-hydroxycoumarin **1** with various



99, 100	a	b	c
n	8	7	14
R	C≡CH	CH=CH-$(CH_2)_7$-CH_3	CH_3

Scheme 51

sulfonamides **89** in the presence of an excess of triethyl orthoformate (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).

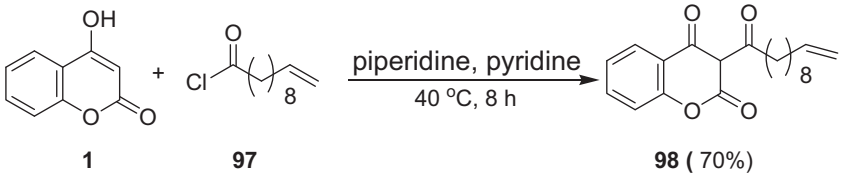
6.1.1.9. Formylation reaction. The broad range of applications of 4-hydroxy-2-oxo-2*H*-1-benzopyran-3-carboxaldehydes **93** has led to the development of its synthetic method. Several workers have reported the synthesis of 4-hydroxy-2-oxo-2*H*-1-benzopyran-3-carboxaldehydes **93** *via* the Vilsmeier 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-formylcoumarin-4-yl)ether hydrate **94** (Scheme 47).

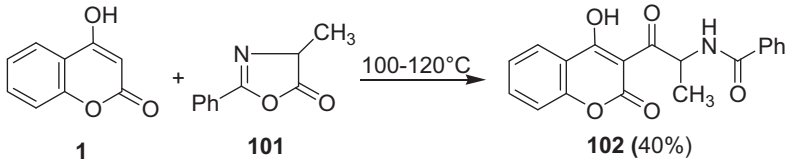
6.1.1.10. Acetylation reaction. The direct acetylation of 4-hydroxycoumarin **1** with acetyl chloride using pyridine or piperidine as a catalyst gave the 3-acetyl-4-hydroxycoumarin **95** (Stadlbauer and Hojas, 2004) (Scheme 48).

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).

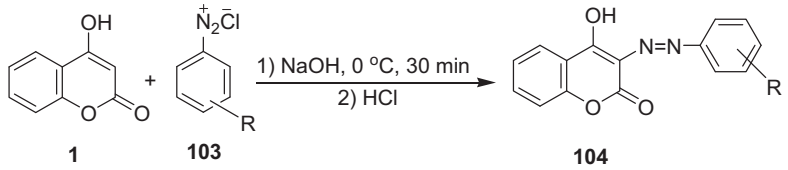
3-(10′-Undecenoyl)chroman-2,4-dione **98** was prepared by acetylation of 4-hydroxycoumarin **1** with 10-undecenoyl chloride **97** in pyridine containing a catalytic amount of piperidine (Cravotto et al., 2004a, 2004b) (Scheme 50).



Scheme 50

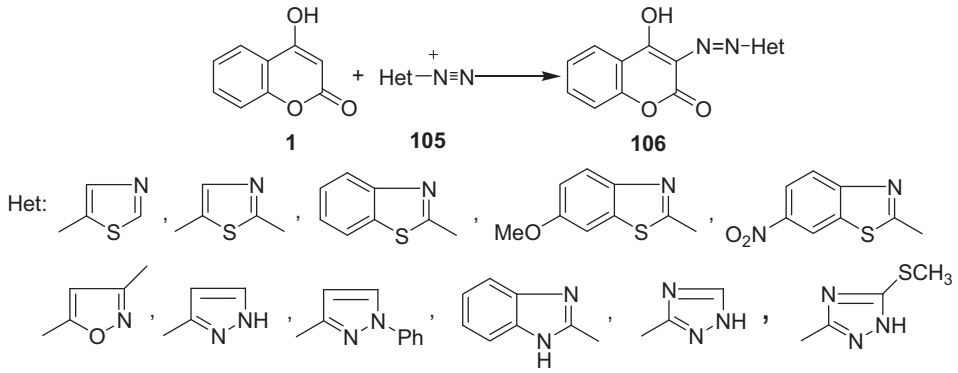


Scheme 52

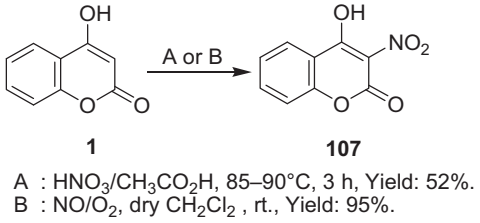


103, 104	a	b	c	d	e	f	g	h	j	k	l
R	*p*-OC_2H_5	*o*-CH_3	*m*-CH_3	*p*-CH_3	–H	*o*-CF_3	*m*-CF_3	*p*-CF_3	*p*-CN	*p*-NO_2	*m*-CH_3, *p*-Cl
Yield(%)	85	75	75	70	75	75	82	65	85	70	70

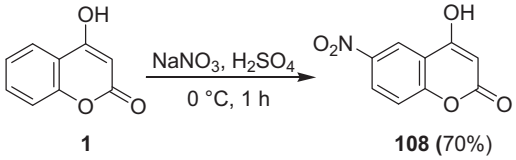
Scheme 53



Scheme 54



Scheme 55



Scheme 56

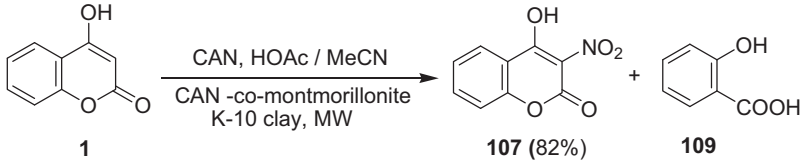
The reaction of 4-hydroxycoumarin **1** with several long chain acyl chlorides **99** in pyridine containing a catalytic amount of piperidine under sonochemical conditions afforded 3-acyl-4-hydroxycoumarins **100** (Cravotto et al., 2006) (Scheme 51).

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-2*H*-chromen-3-yl)-1-oxopropan-2-yl)benzamide **102** in 40% yield (Scheme 52).

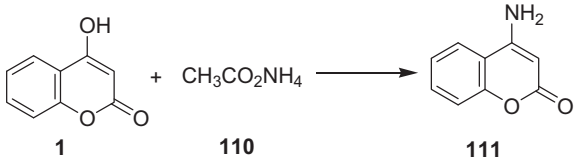
6.2. Reactions involving carbon–heteroatom bond formation

6.2.1. C—N bond formation

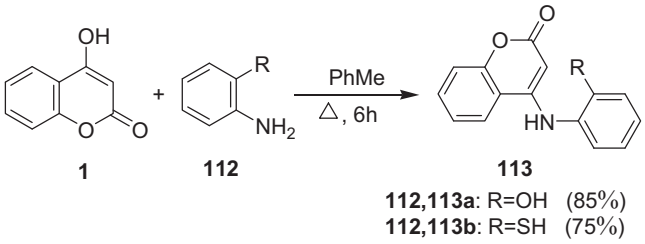
6.2.1.1. Coupling reactions. A series of new azo coumarin dyes were prepared by coupling of basic solution (sodium hydroxide or pyridine) (Metwally et al., 2012e; Shoair, 2007; Yazdanbakhsh et al., 2007) of 4-hydroxycoumarin **1** with diazotized arylamines (Scheme 53).



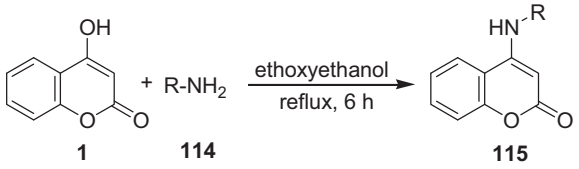
Scheme 57



Scheme 58

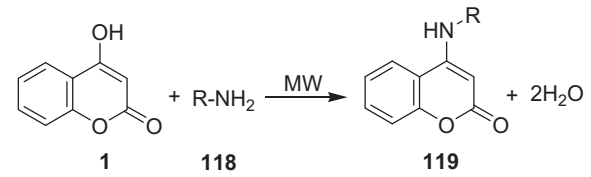


Scheme 59



114, 115	a	b	c	d
R	C_5H_9	C_6H_{11}	$C_{12}H_{25}$	C_8H_9
Yield %	78	80	30	74

Scheme 60



118,119	a	b	c	d	e
R	Ph	4-MeO-Ph	4-Cl-Ph	3-NO_2-Ph	n-C_5H_{11}
Yield %	94	90	92	85	88

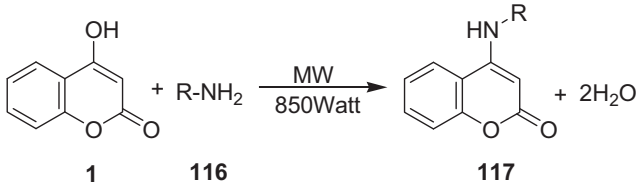
Scheme 62

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).

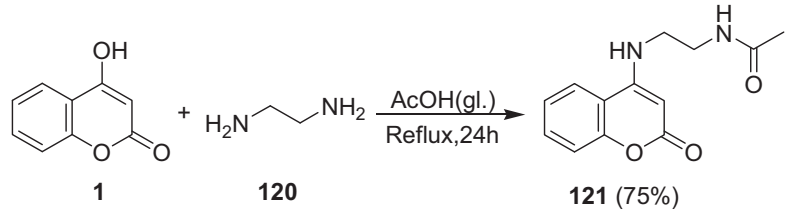
Huang et al. (2007a) observed that nitration of 4-hydroxycoumarin **1** in the presence of a solution of sodium nitrite and sulfuric acid at 0 °C afforded 4-hydroxy-6-nitro-2*H*-chromen-2-one (Scheme 56).

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).

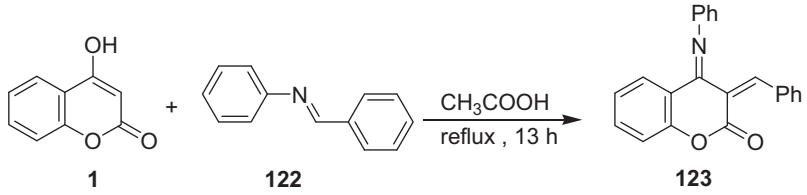


116, 117	a	b	c	d	e	f	g	h
R	n-C_4H_9	n-C_5H_{11}	o-C_5H_{11}	C_6H_5	$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	$C_6H_5(CH)CH_3$	$C_6H_5(CH_2)_3$
Yield %	90	83	40	97	98	97	95	94

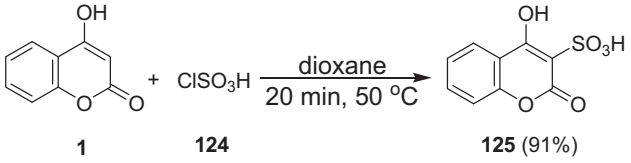
Scheme 61



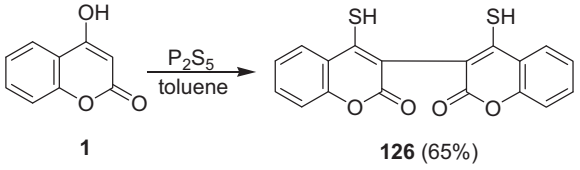
Scheme 63



Scheme 64



Scheme 65



Scheme 66

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.

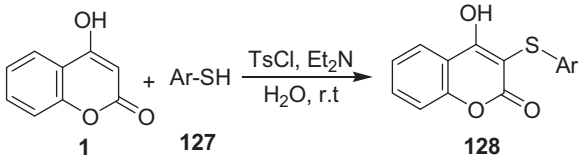
A simple and facile amination of 4-hydroxycoumarin **1** with equimolar amounts of 4-aminothiophenol or 4-aminophenol **112** in toluene yielded the corresponding 4-arylaminocoumarin derivatives **113** in high yields (Hamdi et al., 2006) (Scheme 59).

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).

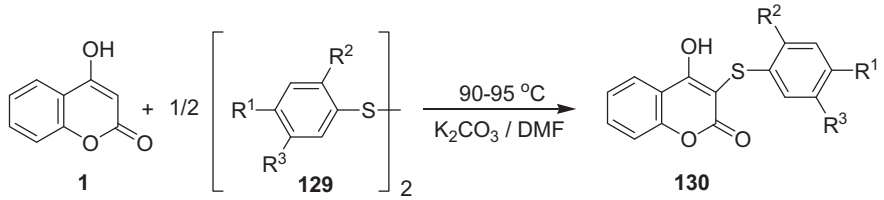
Chavan (2006) synthesized a series of 4-aryl- and 4-alkylaminocoumarins **119** in good to excellent yields by the microwave assisted solvent-free reaction of 4-hydroxycoumarin **1** with aryl- or alkylamines **118** (Scheme 62).

Karagiosov et al. (1999) synthesized the *N*-{2-[(2-Oxo-2*H*-chromen-4-yl)amino]ethyl} acetamide **121** *via* the reaction of



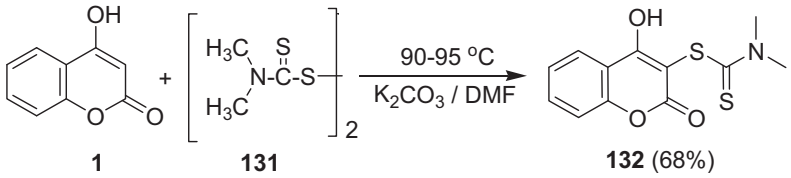
127,128	a	b	c	d	e	f	g	h
Ar	Ph	4-Me-Ph	2-Cl-Ph	4-Cl-Ph	4-F-Ph	$PhCH_2$	$CH_3CH_2CH_2$	$HOCH_2CH_2$
Yield %	80	76	70	80	83	65	63	64

Scheme 67

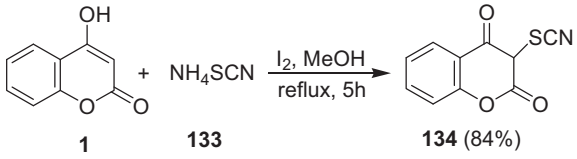


129,130	a	b	c	d
R_1	H	Cl	H	H
R_2	H	H	NO_2	COOH
Yield %	75	77	57	91

Scheme 68



Scheme 69



Scheme 70

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).

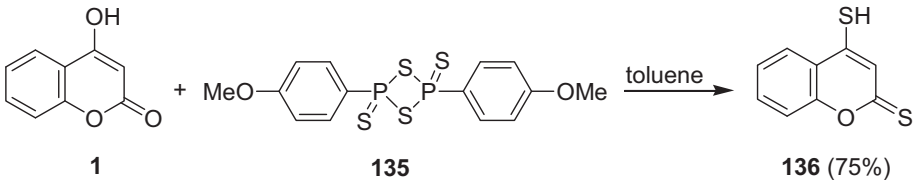
6.2.2.2. Sulfenylation reaction. 6.2.2.2.1. Thiophenols formation. When a mixture of 4-hydroxycoumarin **1** and phosphorus pentasulfide in dry toluene was boiled under reflux, it yielded 3,3-bis-(4-thiohydroxycoumarin)[4-mercapto-3-(4-mercapto-2-oxo-2*H*-chromen-3-yl)-2*H*-chromen-2-one] **126** (Ibrahim, 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*-toluenesulfonyl chloride (Scheme 67).

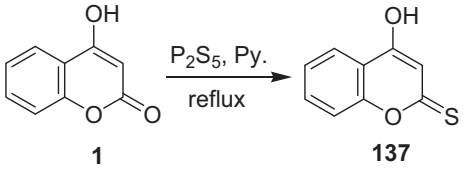
Treatment of 4-hydroxycoumarin **1** with diaryl disulfides **129** in dimethylformide in the presence of potassium carbonate yielded 3-arylsulfenyl derivative of 4-hydroxycoumarin **130** (Schnell and Kappe, 1999) (Scheme 68).

On the other hand, tetraalkylthiuram disulfides **131** reacted with 4-hydroxycoumarin **1** to yield 3-dimethylaminothiocarbonylthio-4-hydroxycoumarin **132** (Schnell and Kappe, 1999) (Scheme 69).

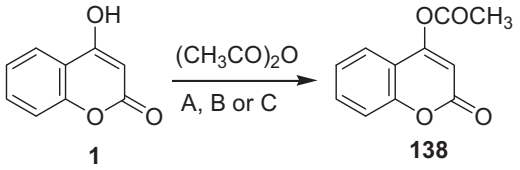
6.2.2.3. Thiocyanation reaction. Yadav et al. (2007) noted that 4-hydroxycoumarin **1** undergoes a novel and highly selective thiocyanation with ammonium thiocyanate **133** in the presence



Scheme 71

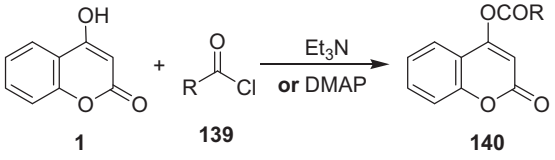


Scheme 72



A : Pyridine, r.t, Yield: 95%.
B : I_2 (cat), 85-90 °C,10 min, Yield: 95%.
C : $SbCl_3$ (10 mol%), r.t, 1.75 h, Yield: 86%.

Scheme 73



R = Me, *t*-butyl, Ph, cyclopropane

Scheme 74

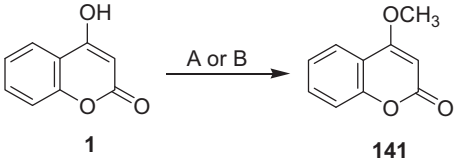
of molecular iodine in refluxing methanol to produce the corresponding 3-thiocyanato-chroman-2,4-dione **134** in excellent yield with high selectivity (Scheme 70).

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

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

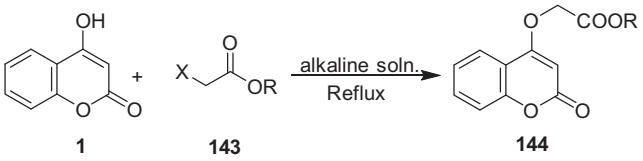
6.2.3. C—O bond formation

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



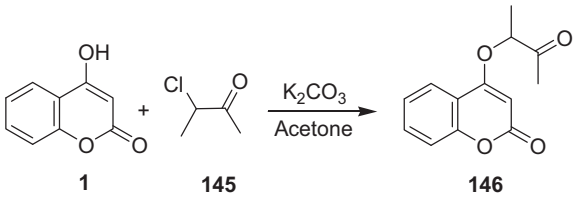
A : CH_2N_2 in Et_2O, r.t, Yield : 23%.
B : Me_2SO_4, K_2CO_3, acetone, MW, 3-15 min, Yield : 78%.

Scheme 76



143,144	R	X	Base	Yield %
a	Et	Br	K_2CO_3	98
b	Et	Br	K_2CO_3	93
c	H	Cl	NaOH	72

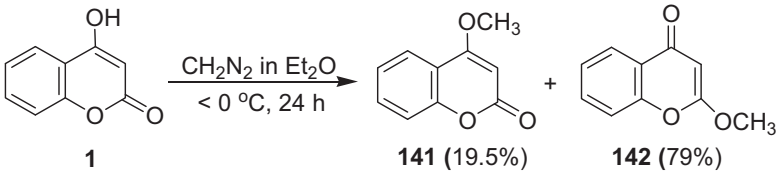
Scheme 77



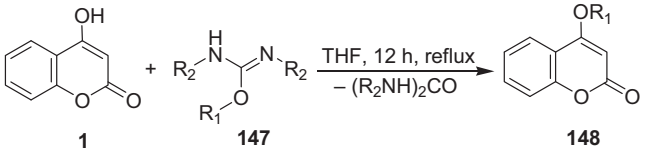
Scheme 78

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** in the presence of 4-dimethylaminopyridine (DMAP) or triethylamine (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).

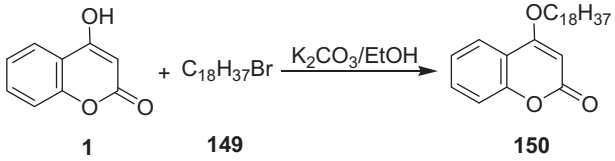


Scheme 75



145,146	R_1	R_2	Yield(%)
a	n-Bu	c-C_6H_{11}	51
b	i-Pr	i-Pr	36
c	i-Bu	c-C_6H_{11}	14
d	i-Bu	i-Pr	37

Scheme 79



Scheme 80

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 **141** (Cao et al., 2014; Garro Hugo et al., 2014; Mitra et al., 2000) (Scheme 76).

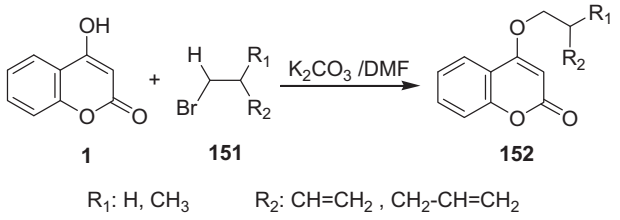
The base catalyzed alkylation of 4-hydroxycoumarin **1** with ethyl bromoacetate or chloroacetic acid **143** afforded ethyl (coumarin-4-oxy)acetate **144** (Abd Elhafez et al., 2003; Chimichi et al., 2002; Dahiya et al., 2010) (Scheme 77).

The reaction of 4-hydroxycoumarin **1** with 3-chloro-2-butanone **145** in acetone in the presence of anhydrous K_2CO_3 gave 4-(3-oxobutan-2-yloxy)-2H-chromen-2-one **146** in 75% yield (Al-Sehemi and El-Gogary, 2012) (Scheme 78).

O-alkylation of 4-hydroxycoumarin **1** is possible also with isoureas **147**. 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-alkoxycoumarins **148** (Schobert and Siegfried, 2000) (Scheme 79).

4-Octadecyloxylcoumarin **150** was synthesized by the reaction of 4-hydroxycoumarin **1** with 1-bromooctadecane **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).



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_2CO_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 Alvandzhyan, 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).

In a similar manner, reaction of 4-hydroxycoumarin **1** with 1,4-dichlorobut-2-yne **159** in dry acetone containing anhydrous potassium carbonate led to the formation of 4-(4-chlorobut-2-ynyloxy)-2*H*-chromen-2-one **160** (Majumdar and Jana, 2007) (Scheme 85).

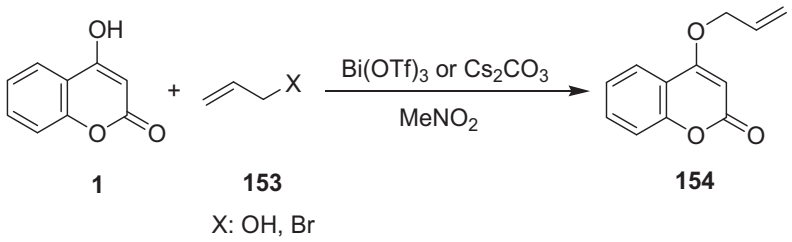
Heating 4-hydroxycoumarin **1** with each of 2-bromobenzyl bromides **161a,b** (Majumdar et al., 2003) and 4-vinylbenzylchloride **161c** (Abd El-Aziz et al., 2008) in acetone containing anhydrous potassium carbonate afforded 4-(2′-bromobenzyloxy)benzopyran-7-ones **162a,b** and styrene monomers containing 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_2CO_3 gave a mixture of the 2-chloro-3-(2-oxo-2*H*-chromen-4-yloxy)naphthalene-1,4-dione **164** and 2,3-bis(2-oxo-2*H*-chromen-4-yloxy) naphthalene-1,4-dione **165** in 72% and 11% yields, respectively (Scheme 87).

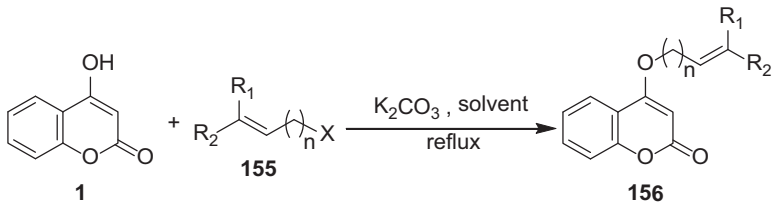
Kaswala et al. (2009) reported that treatment of cyanuric chloride **166** in acetone with 4-hydroxycoumarin **1** in 10% aqueous sodium carbonate solution led to the formation of 2-(coumarinyl-4-oxy)-4,6-dichloro-*s*-triazine **167** (Scheme 88).

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

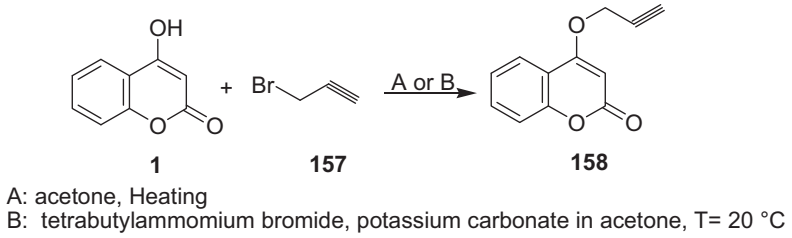
6.2.3.4. Sulfonates ether formation. Several groups have developed general methodology for the one step formation of 4-(*p*-



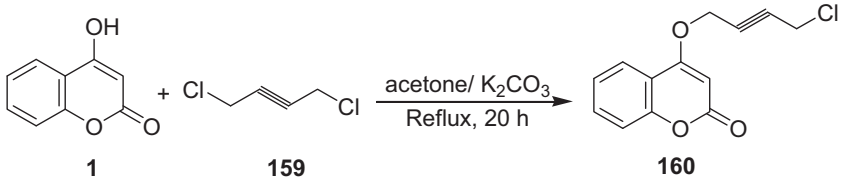
Scheme 82



Scheme 83 **156** (R_1, R_2, X, n, solvent.): **a** (H, H, Br, 2, DMF); **b** (H, H, Br, 2, acetone), **c** (Me, H, Br, 1, acetone); **d** (H, H, Cl, 1, acetone); **e** (Cl, Cl, Cl, 1, acetone); **f** (Cl, Me, Br, 1, acetone); **g** (Me, Me, Br, 2, acetone); **h** (Me, Me, Br, 3, acetone).



Scheme 84



Scheme 85

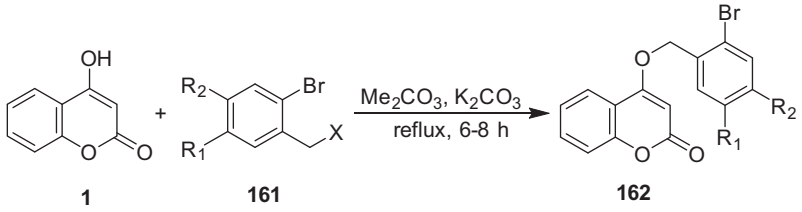
toluenesulfonyloxy)coumarin **172** *via* tosylation reaction of 4-hydroxycoumarin **1** with tosyl chloride **171** in the presence of base at room temperature (Gallagher et al., 2009; Hansen and Skrydstrup, 2005; Kuroda et al., 2009; Majumdar and Samanta, 2002; Patent, 2005; Saito et al., 1998; Shepard and Carreira, 1997) (Scheme 90).

There are several reports on the synthesis of 4-trifluorome thylsulfonyloxycoumarin **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).

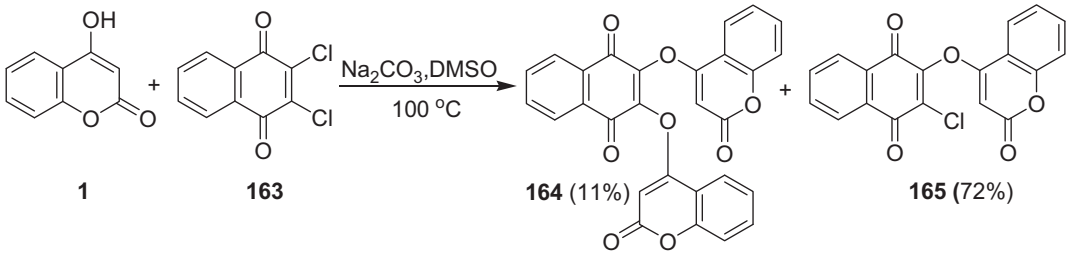
6.2.3.5. *Silylation (Silyl ether formation)*. Iaroshenko et al. (2011) found that 4-hydroxycoumarin **1** was silylated by trimethylsilylchloride **177** in dioxane containing catalytic amount of dry pyridine (Scheme 93).

6.2.3.6. Phosphorylation reaction. A series of new piperazine phosphoramide derivatives of 4-hydroxycoumarin **180** were synthesized through a facile phosphorylating reaction starting from 4-hydroxycoumarin **1** and various phosphorylating

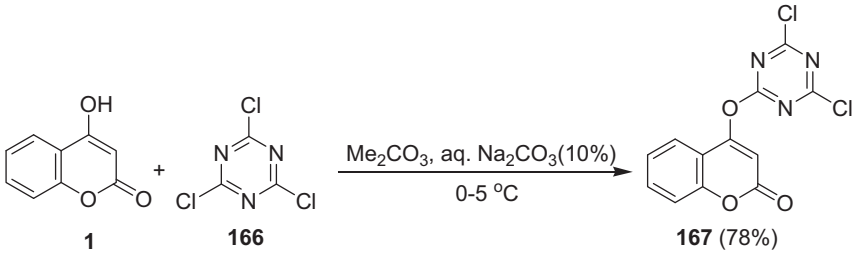


161, 162	R_1	R_2	X	Yied %
a	H	H	Br	72
b	OCH_3	H	Br	75
c	H	CH_2=CH_2	Cl	33

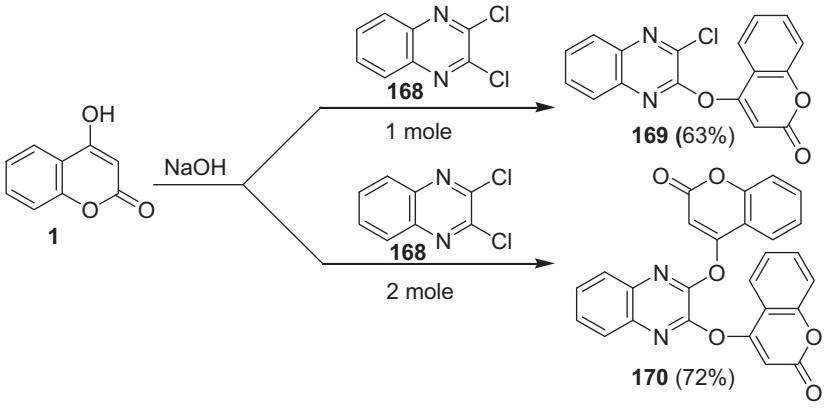
Scheme 86



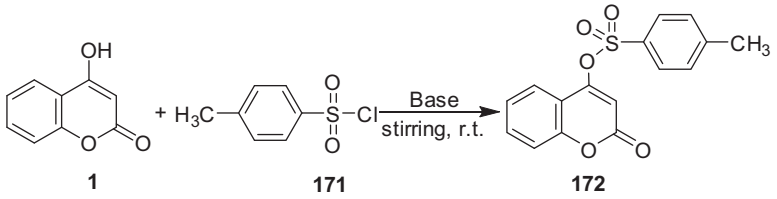
Scheme 87



Scheme 88

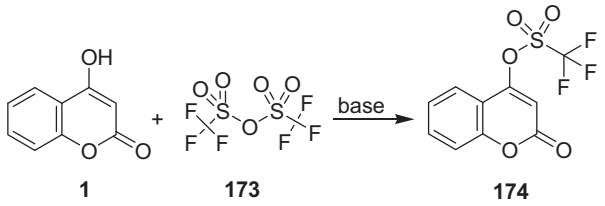


Scheme 89

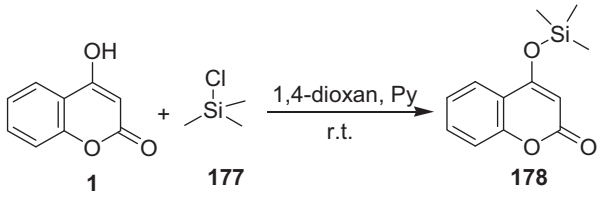


171,172	Base & Solvent	Time/min.	Yield %
a	TEA / THF	90	79
b	TEA / THF	30	97
c	TEA / DCM	30	94
d	TEA / DCM	30	83
e	Pyridine	35	95
f	Pyridine	30	90

Scheme 90



Scheme 91



Scheme 93

agents **179** 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 **180** could be achieved *via* the base-catalyzed reaction of 2 equivalents of 4-hydroxycoumarin **1** with oligoethylene glycol diglycidyl ether **179** in refluxing methanol afforded directly the expected coumarin hydroxy ether in good yield (Hamdi et al., 2008a; Li et al., 2012a, 2012b) (Scheme 95).

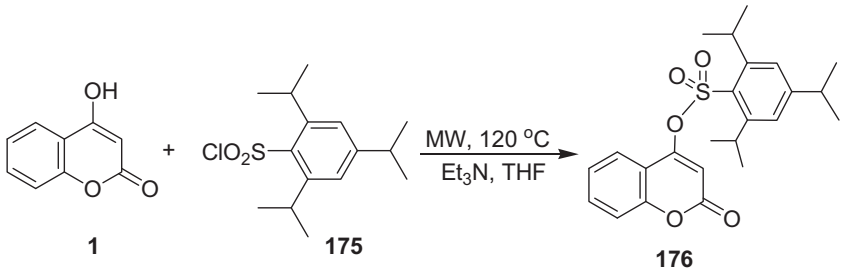
Tuncer and Erk (2003) disclosed that bis-(4-oxa)coumarin ended polyglycols **182** were synthesized by the reaction of 4-hydroxycoumarin **1** with bis-dihalides of polyglycols **181** in DMF containing catalytic amount of potassium carbonate (Scheme 96).

6.2.4. Carbon–halogen bond formation

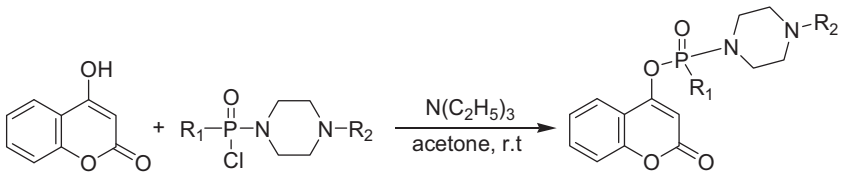
Halogenoheteroarenes are useful intermediates for the syntheses of bioactive natural products and pharmaceutical drugs.

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 **1** 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 **183** (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



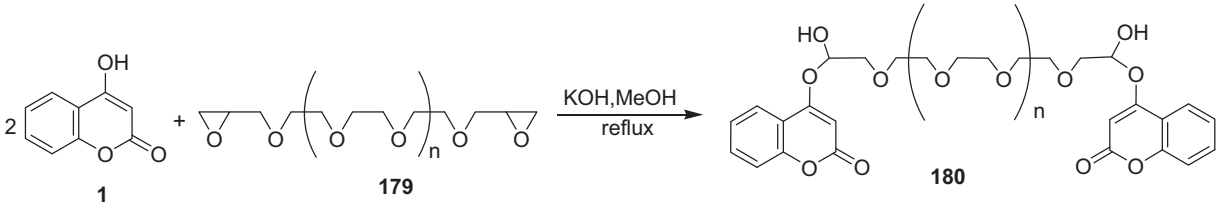
Scheme 92



1 179 180 (75%)

179, 180	R_1	R_2	Yield%
a	C_6H_5O	4-$CH_3C_6H_4$	85
b	C_6H_5O	4-ClC_6H_4	85
c	C_6H_5O	CH_3	80
d	C_6H_5O	$(CH_3)_3C$-O-CO	83
e	$(ClCH_2CH_2)_2N$	4-$CH_3C_6H_4$	83
f	$(ClCH_2CH_2)_2N$	4-ClC_6H_4	85
g	$(ClCH_2CH_2)_2N$	CH_3	87
h	$(ClCH_2CH_2)_2N$	$(CH_3)_3C$-O-CO	84

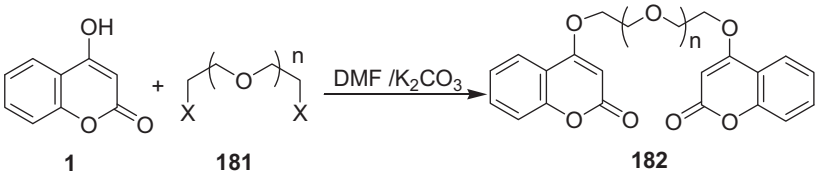
Scheme 94



1 179 180

179, 180	a	b	c
n	2	3	4
Yield %	65	75	70

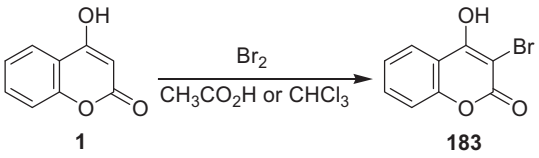
Scheme 95



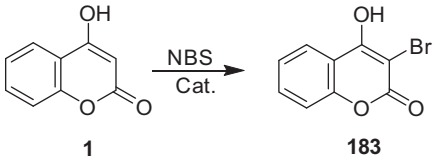
1 181 182

181, 182	a	b	c	d
n	0	1	2	3
X	Br	Cl	Cl	Cl

Scheme 96

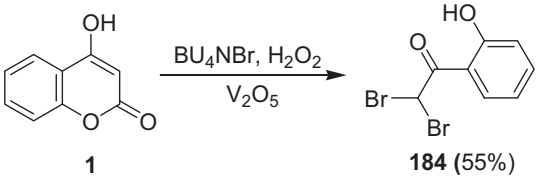


Scheme 97



	Cat. / reaction medium	Yield %
1	PEG-400	90
2	sulfonic acid-functionalized silica	78
3	NH_4OAc/CH_3CN	91
4	$Mg(ClO_4)_2/CH_3CN$	
5	TBAB	76

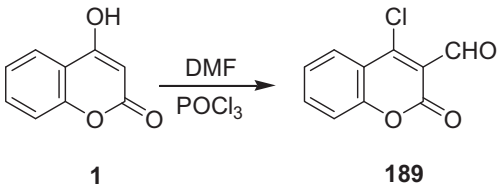
Scheme 98



Scheme 99

(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 **1** 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 tetrabutylammomium 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).

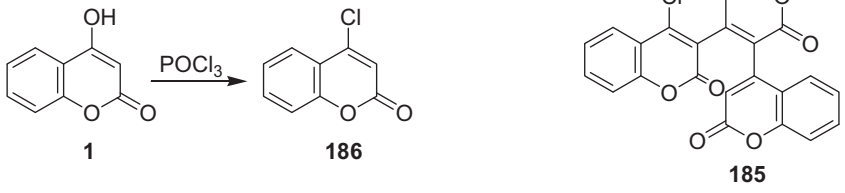
When the bromination of 4-hydroxycoumarin **1** is carried out using vanadium pentoxide as effective promoters with tetrabutylammonium bromide in the presence of hydrogen peroxide, it afforded α,α-dibromo-2-hydroxyacetophenone **184** (Bora et al., 2000) (Scheme 99).



Scheme 101

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 chloroformylcoumarin is useful for the synthesis of aromatic and heteroaromatic annelated [1,4]diazepines (Scheme 101).



Scheme 100

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.

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