## Coumarin(Benzopyrone)-Fused Five-Membered Aromatic Heterocycles

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Contributor: Eslam El-Sawy , Gilbert Kirsch

Coumarins are a family of benzopyrones (1,2-benzopyrones or 2*H*-[1]benzopyran-2-ones), which represent an important family of oxygen-containing heterocycles, widely distributed in nature. Since coumarins have versatile applications, the synthesis trials of different structures of the coumarin-based scaffold were attempted. Among all the heterocycles built on  $\alpha$ -pyrone moiety of coumarin, the furan ring was the only available structure in nature. Thus, it has inspired a lot of researchers to replace the oxygen with other heteroatoms. Wide varieties of heterocycles were constructed by a synthetic pathway to introduced furans, pyrroles, thiophenes, and selenophenes as a fused ring that characterized by a single heteroatom to the  $\alpha$ -pyrone moiety of coumarin.

coumarins benzopyrones five-membered aromatic heterocycles

### 1. Introduction

Coumarins are a family of benzopyrones (1,2-benzopyrones or 2*H*-[1]benzopyran-2-ones), which represent an important family of oxygen-containing heterocycles, widely distributed in nature <sup>[1][2][3][4]</sup>. Coumarins display a broad range of biological and pharmacological activities, <sup>[5][6]</sup> such as antiviral <sup>[7][8][9][10]</sup>, anticancer <sup>[11][12][13]</sup>, antimicrobial <sup>[14][15]</sup>, and antioxidant <sup>[16][17][18]</sup> activities. On the other hand, coumarin represents an ingredient in perfumes <sup>[19]</sup>, cosmetics <sup>[20]</sup>, and as industrial additives <sup>[21][22]</sup>. Furthermore, coumarins play a pivotal role in science and technology as fluorescent sensors, mainly due to their interesting light-emissive characteristics, which are often responsive to the environment <sup>[23][24][25][26]</sup>. The coumarin (benzopyrane)-fused, membered aromatic heterocycles built on the α-pyrone moiety are an important scaffold. The only fused heterocycle with an α-pyrone moiety of coumarin that can be found in nature is the furan ring. One example is the naturally occurring furan 4*H*-furo[3,2-*c*]benzopyran-4-one, which provides the main core of many natural compounds of so-called coumestans. These comestans include coumestan, wedelolactone, and coumestrol. The coumestans are found in a variety of plant species that are commonly used in traditional medicine <sup>[27]</sup>.



Naturally occurring furan, so-called coumestans

In order to enrich the limited versatility of the structures found in nature, synthesis of coumarin (benzopyrane)fused, membered aromatic heterocycles has received considerable attention, including numerous reported routes.

# 2. Synthesis of Benzopyrone-Fused, Five-Membered Aromatic Heterocycles

#### 2.1. Five-Membered Aromatic Rings with One Heteroatom

#### 2.1.1. Furans

Furobenzopyrone (or furocoumarins) comprises an important class of coumarins found in a wide variety of plants, particularly in the carrot (*Apiaceae/Umbelliferae*), legume (*Fabaceae*), and citrus families (*Rutaceae*) <sup>[27]</sup>. The chemical structure of furobenzopyrone (furocoumarins) consists of a furan ring fused with coumarin. The fusion of the furan ring to the  $\alpha$ -pyrone moiety of coumarin forms the core structure of the three most common isomers, viz. 4*H*-furo[2,3-*c*]chromen(benzopyran)-4-one, 4*H*-furo[3,4-*c*]chromen(benzopyran)-4-one, and 4*H*-furo[3,2-*c*]chromen (benzopyran)-4-one (Figure 1).



4H-furo[2,3-c]chromen-4-one 4H-furo[2,3-c]benzopyran-4-one



4H-furo[3,4-c]chromen-4-one 4H-furo[3,4-c]benzopyran-4-one



4H-furo[3,2-c]chromen-4-one 4H-furo[3,2-c]benzopyran-4-one

**Figure 1.** The three most common isomers of a furan ring fused to the  $\alpha$ -pyrone moiety of coumarin.

4*H*-Furo[2,3-*c*]benzopyran-4-one

Furan Construction

The basic building block for the formation of 4H-furo[2,3-*c*]benzopyran-4-one is the 3-hydroxycoumarin (1) <sup>[28][29]</sup>. Pandya and coworkers <sup>[30]</sup> developed a method to synthesize some 4H-furo[2,3-*c*]benzopyran-4-ones starting with

3-hydroxycoumarin using the Nef reaction. Thus, the reaction of 3-hydroxycoumarin (**1**) with various 2-aryl-1-nitro ethenes **2a**,**b**, in the presence of piperidine and methanol as a solvent, followed the Nef reaction condition and afforded a series of 1-aryl-furo[2,3-*c*]benzopyran-4-ones **3a**,**b** and 1-phenyl-2-methyl-furo[2,3-*c*]benzopyran-4-one (**4**), respectively (<u>Scheme 1</u>). The formation of these products was explained by the reaction mechanism (<u>Scheme 1</u>).



**Scheme 1.** The Nef reaction to synthesize furo[2,3-*c*]benzopyran-4-ones **3a**,**b** and **4**. *Reagents and conditions*: MeOH, piperidine, reflux, five outputs in 55%–61% yield.

#### Pyrone Construction

Dong et al., 2020 developed a novel and facile rhodium(III)-catalyzed process of sulfoxonium ylide (5) with hydroquinone (6). The carbonyl in the sulfoxonium ylide assisted the ortho-C–H functionalization of the sulfoxonium ylide, followed by intramolecular annulation with hydroquinone to afford 8-hydroxy-4*H*-furo[2,3-*c*]benzopyran-4-one (7) (Scheme 2) <sup>[31]</sup>.



**Scheme 2.** Rhodium(III)-catalyzed sequential ortho-C–H oxidative arylation/cyclization of sulfoxonium ylide to afford 4*H*-furo[2,3-c]benzopyran-4-one (7). *Reagents and conditions*: [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (5 mol %), AgBF<sub>4</sub> (20 mol %),

Zn(OAc)<sub>2</sub> (0.225 mmol), AcOH (0.3 mmol), and acetone (2 mL), 12 h, in a sealed Schlenk tube under N<sub>2</sub> at 100 °C, 25% yield. 4*H*-Furo[3,4-*c*]benzopyran-4-one

#### Furan and Pyrone Construction

In the literature, a large number of reports described the synthesis of 4*H*-furo[2,3-*c*] and 4*H*-furo[3,2-*c*]benzopyran-4-ones, while synthesis of the 4*H*-furo[3,4-*c*]benzopyran-4-one was reported by only one study, that of Brahmbhatt and his coworkers <sup>[32]</sup>. The first 4*H*-furo[3,4-*c*]benzopyran-4-ones (**10**) was synthesized by the demethylation– cyclization reaction of intermediates, 3-substituted-4-ethoxycarbonyl furans **9** (<u>Scheme 3</u>). For the demethylation and in situ lactonization steps, several reagents were tried, of which pyridine hydrochloride and HBr in acetic acid were found to be the most promising.



**Scheme 3.** Demethylation and in situ lactonization steps to prepare the first 4*H*-furo[3,4-*c*]benzopyran-4-one **10**. *Reagents and conditions*: (a) ethyl acetoacetate or ethyl benzoylacetate, piperidine, and MeOH (the Nef reaction condition); (b) HBr, AcOH concentration, 130 °C, 4 h, 16 outputs with 50%–65% yield.

4*H*-Furo[3,2-*c*]benzopyran-4-one

#### Furan Construction

A wide range of research has demonstrated that 4-hydroxycoumarin is the key compound for the synthesis of 4H-furo[3,2-*c*]benzopyran-4-ones, which can readily react with the C=C bond of the alkene, or the C=C bond of the alkyne [33][34][35][36][37].

Reisch reported the condensation of 4-hydroxycoumarin (**11**) with 1-phenyl-2-propyn-1-ol (**12**) under acidic conditions (a mixture of glacial acetic and concentrated sulfuric acid) to deliver the corresponding 2-methyl-3-phenylfuro[3,2-c]benzopyran-4-one (**13**) (<u>Scheme 4</u>) <sup>[38]</sup>.



**Scheme 4.** Synthesis of 2-methyl-3-phenylfuro[3,2-*c*]benzopyran-4-one (**13**). *Reagents and conditions*: AcOH, conc. H<sub>2</sub>SO<sub>4</sub>, 110 °C, 1 h, 70% yield.

A few studies employed the aliphatic aldehydes as building blocks with 4-hydroxycoumarin (**11**) to synthesize 4*H*-furo[3,2-*c*]benzopyran-4-ones <sup>[25][39]</sup>. This method was ineffective as it gave a poor yield as well as a mixture of 2,3-dihydrofuran, 4*H*-furo[3,2-*c*]benzopyran-4-ones, and 4*H*-furo[3,2-*c*]benzopyran-4-ones <sup>[39]</sup>. Conversely, in the case of using the aromatic aldehyde as a building block, the 4*H*-furo[3,2-*c*]benzopyran-4-one was obtained <sup>[40]</sup>. Kadam et al. developed atom-efficient multicomponent reactions (MCRs) and step-efficient, one-pot synthesis of 3-(4-bromophenyl)-2-(cyclohexylamino)-4*H*-furo[3,2-*c*]benzopyran-4-one (**16**) using 4-hydroxycoumarin (**11**) with 4-bromobenzaldehyde (**14**) and cyclohexyl isocyanide (**15**) as an alkylene source (<u>Scheme 5</u>) <sup>[40]</sup>.



**Scheme 5.** Atom-efficient multicomponent reactions (MCRs) and step-efficient, one-pot synthesis of 4*H*-furo[3,2*c*]benzopyran-4-one (**16**). *Reagents and conditions*: DMF or toluene, μw, 80 °C, 20 min, 97% yield.

4-Hydroxycoumarin derivatives have received significant attention from researchers, as these derivatives possess 1,3-dicarbonyl systems. It allows for the easy generation of  $\alpha, \alpha'$ -dicarbonyl radicals, which can be readily added to the C=C bond of the alkene <sup>[41]</sup>. The first example of this reaction was described in 1998, by Lee and his coworkers. They reported an efficient way to prepare 4*H*-furo[3,2-*c*]benzopyran-4-ones **19** by Ag<sub>2</sub>CO<sub>3</sub>/celite (Fetizon's reagent)-mediated oxidative cycloaddition of 4-hydroxycoumarin **17** to olefins, such as vinyl sulfide and phenyl propenyl sulfide. The resulting dihydrofuro[3,2-*c*]benzopyran-4-ones **18** was treated by sodium periodate in aqueous methanol to form the corresponding sulfoxides, which, upon refluxing with pyridine in carbon tetrachloride, directly delivered the 4*H*-furo[3,2-*c*]benzopyran-4-one **19** in good yields (<u>Scheme 6</u>) <sup>[41]</sup>.



**Scheme 6.** A facile synthesis of 4*H*-furo[3,2-*c*]benzopyran-4-ones **19** by silver(I)/celite promoted an oxidative cycloaddition reaction. *Reagents and conditions*: (a)  $CH_2$ =CHSPh and/or  $CH_3CH$ =CHSPh,  $Ag_2CO_3$ /celite, acetonitrile, reflux, 3 h; (b) NalO<sub>4</sub>, MeOH,  $CCl_4$ , pyridine,  $Al_2O_3$ , four outputs with 71%–82% yield.

Recently, different catalytic methodologies have been developed for the synthesis of 2*H*-chromenes, and they are based on three main approaches: catalysis with (transition) metals, metal-free Brønsted catalysis, and Lewis acid/base catalysis, which includes examples of nonenantioselective organocatalysis and enantioselective organocatalysis <sup>[42][43][44]</sup>. Alkynes have been widely employed as building blocks for this reaction in most cases.

To date, different transition metal (Au, Pt, and Cu) catalyzed/mediated methodologies for benzopyrane synthesis have been reported <sup>[27][42][45][46]</sup>. Cheng and Hu described a one-pot cascade of an addition/cyclization/oxidation sequence using CuCl<sub>2</sub> as the oxidant and CH<sub>3</sub>SO<sub>3</sub>H as the acid for regioselective synthesis of 2-substituted-4*H*-furo[3,2-*c*]benzopyran-4-ones **22** from the substituted 3-alkynyl-4*H*-benzopyran-4-one **20** (Scheme 7) <sup>[47]</sup>. This strategy included the CH<sub>3</sub>SO<sub>3</sub>H-acid-catalyzed construction of the furan ring, followed by oxidation of **21** with CuCl<sub>2</sub> (Scheme 7) <sup>[47]</sup>. When the reaction was carried out in the presence of a catalytic amount of CuCl as a Lewis acid and atmospheric oxygen as an oxidative reagent, compound **22** was provided directly. On the other hand, the presence of 10% CuBr and an excess of CuCl<sub>2</sub> as the oxidant afforded the corresponding 3-chloro-2-substituted-4*H*-furo[3,2-*c*]benzopyran-4-ones **23** (Scheme 7) <sup>[48]</sup>.



**Scheme 7.** Transition metal Cu catalyzed/mediated methodologies for synthesis of the 4*H*-furo[3,2-*c*]benzopyran-4-ones **22** and **23**. *Reagents and conditions*: (a) CH<sub>3</sub>SO<sub>3</sub>H, H<sub>2</sub>O, DMF, 90 °C, 1–3 h; (b) CuCl<sub>2</sub>, 90 °C, 20 h; (c) CuCl, O<sub>2</sub>, DMF, H<sub>2</sub>O, 90 °C, 10–20 h, 10 outputs with 37%–88% yield; (d) CuBr, CuCl<sub>2</sub>, DMF, H<sub>2</sub>O, 75 °C, 10 h, 13 outputs with 45%–81% yield.

Brønsted-acid-catalyzed propargylations of several organic substrates, including 1,3-dicarbonyl compounds, with alkynols have been reported <sup>[49]</sup>. In most cases, the acid catalyst is required to promote the propargylation process efficiently. Zhou and coworkers developed a one-pot Yb(OTf)<sub>3</sub> propargylation–cycloisomerization sequence of 4-

hydroxycoumarin (**11**) with the propargylic alcohol (**24**) for the synthesis of a 2-benzyl-3- phenyl-4*H*-furo[3,2c]chromen-4-one (**25**) skeleton using Yb(OTf)<sub>3</sub> as a Lewis acid (<u>Scheme 8</u>)  $\frac{[50]}{2}$ .



**Scheme 8.** One-pot synthesis of 4*H*-furo[3,2-*c*]chromen-4-one (**25**) using a Yb(OTf)<sub>3</sub>-catalyzed propargylation and allenylation reaction. *Reagents and conditions*: (a) 5 mol % Yb(OTf)<sub>3</sub>, CH<sub>3</sub>NO<sub>2</sub>, dioxane, 50 °C; (b) K<sub>2</sub>CO<sub>3</sub>, 70 °C, 37% yield.

Similarly, 4*H*-furo[3,2-*c*] benzopyran-4-one formation reactions proceeded in higher yields and in a one-pot manner, employing a catalytic system composed of the 16-electron allyl–ruthenium(II) complex [Ru( $\eta$ 3-2-C<sub>3</sub>H<sub>4</sub>Me)(CO) (dppf)][SbF<sub>6</sub>] (dppf=1,1'-bis(diphenylphosphino)ferrocene) and trifluoroacetic acid (TFA) in the reaction of 4-hydroxycoumarin (**11**), with 1-(4-methoxyphenyl)-2-propyn-1-ol (**26**) as an example. The 4*H*-furo[3,2-*c*]benzopyran-4-one (**27**) was synthesized with a 72% yield (<u>Scheme 9</u>) <sup>[50][51][52]</sup>.



**Scheme 9.** The 16-electron allyl–ruthenium(II) complex in preparation of 4*H*-furo[3,2-*c*]benzopyran-4-one (**27**). *Reagents and conditions*: 16-electron allyl–ruthenium(II) complex [Ru( $\eta$ 3-2-C<sub>3</sub>H<sub>4</sub>Me)(CO)(dppf)][SbF<sub>6</sub>] (5 mol %), trifluoroacetic acid (TFA) (50 mol %), THF, 75 °C, 5 h, 72% yield.

Extensive work has been done to investigate the utility of an aryl alkynyl ether as a furan substrate, instead of arylalkynol, in the synthesis of 4*H*-furo[3,2-*c*]benzopyran-4-one <sup>[29][35]</sup>. The treatment of 3-iodo-4-methoxycoumarin (**28**) with phenylacetylene by means of sequential Sonogashira C–C coupling conditions resulted in a high-yield formation of the 4*H*-furo[3,2-*c*]benzopyran-4-one (**30**) (Scheme 10) <sup>[53]</sup>. In this reaction, the triethylamine was used as a base to induce the S<sub>N</sub>2-type demethylation of the Sonogashira coupling product, followed by an intramolecular attack of the enolate onto the cuprohalide  $\pi$ -complex of the triple bond (Scheme 10).



**Scheme 10.** Et<sub>3</sub>N-induced demethylation–annulation of an aryl alkynyl ether in the synthesis of 4*H*-furo[3,2*c*]benzopyran-4-one (**30**). *Reagents and conditions*: (a) alkyne (3 equiv.), 8 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 8 mol % Cul, Et<sub>3</sub>N/DMF, 80 °C, 48 h, 82% yield; (b) alkyne (3 equiv.), 8 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 8 mol % Cul, Et<sub>3</sub>N/MeCN, 60 °C, 15 h, 70% yield.

As a follow-up to this type of reaction, a novel and rapid assembly of an interesting class of 4*H*-furo[3,2*c*]benzopyran-4-ones, **33**, was successfully achieved using a one-pot sequential coupling/cyclization strategy with 3-bromo-4-acetoxycoumarins **31** and dialkynlzincs **32** prepared in situ as reactive acetylides in transition-metalcatalyzed crosscoupling. The cascade transformation relies on palladium/copper-catalyzed alkynylation and intramolecular hydroalkoxylation (<u>Scheme 11</u>) <sup>[54]</sup>.



**Scheme 11.** A one-pot sequential coupling/cyclization strategy in the synthesis of 4*H*-furo[3,2-*c*]- benzopyran-4-ones **33**. *Reagents and conditions*: (a) Pd(PPh<sub>3</sub>)<sub>2</sub>, CuI, THF, 60 °C; (b) K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, 13 outputs with 51%–96% yield.

A transition-metal-free approach was developed to achieve 4-*H*-furo[3,2-*c*]benzopyran-4-ones via an iodinepromoted one-pot cyclization between 4-hydroxycoumarins **34** and acetophenones **35**. The transformation spontaneously proceeded to produce (**36**) in the presence of NH<sub>4</sub>OAc. The possible reaction mechanism suggested for the iodine-promoted one-pot cyclization is depicted (<u>Scheme 12</u>) <sup>[55]</sup>.



**Scheme 12.** Metal-free synthesis of 4-*H*-furo[3,2-*c*]benzopyran-4-ones **36**. *Reagents and conditions*: I<sub>2</sub>, NH<sub>4</sub>OAc, PhCI, 120 °C, 18 outputs with 28%–90% yield.

Additionally, Traven et al. <sup>[56]</sup> provided a new short way for the synthesis of 4*H*-furo- [3,2-*c*]benzopyran-4-one, employing the Fries rearrangement of 4-chloroacetoxycoumarin (**37**) to yield two products, namely 3-chloroacetyl4-hydroxycoumarin (**38**) and dihydrofuro[2,3-*c*]coumarin-3-one (**39**), in the ratio of 2:1. Compound (**38**), which underwent cyclization, led to the formation of (**39**). The latter, under reduction and dehydration conditions, afforded 4*H*-furo[3,2-*c*]chromen-4-one (**41**) (Scheme 13). A closely related reaction that allowed for the preparation of (**41**) was developed by Majumdar and Bhattacharyya <sup>[57]</sup>, following a similar procedure but using chloroacetaldehyde instead of chloroactylchloride in the presence of aqueous potassium carbonate to give 3-hydroxy-2,3-dihydrofuro[3,2-*c*]benzopyran-4-one (**40**), which upon treatment with aqueous hydrochloric acid provided 4*H*-furo[3,2-*c*]benzopyran-4-one (**41**) with 72% yield (Scheme 13).



**Scheme 13.** Regioselective synthesis of 4*H*-furo[3,2-*c*]chromen-4-one (**41**). Reagents and conditions: (a) CICH<sub>2</sub>COCI, dry pyridine, 40 min, reflux, 85% yield; (b) AICI<sub>3</sub>, 140–150 °C, 60% yield; (c) AICI<sub>3</sub>, 140–150 °C, 30–40 min or K<sub>2</sub>CO<sub>3</sub>, acetone, 10 min, stirring, r.t., 50% yield; (d) NaBH<sub>4</sub>, 85% yield; (e) H<sub>2</sub>SO<sub>4</sub> (30%), EtOH, heat, 30 min, 80% yield; (f) COCH<sub>2</sub>CI, K<sub>2</sub>CO<sub>3</sub>, 73% yield; (g) HCI, 72% yield.

#### Pyrone Construction

Recently, much effort has been devoted to the development of oxidative intramolecular C–O bond-forming cyclization reactions for the synthesis of bioactive benzopyranones. These methods are limited to being used with arenes building blocks <sup>[58][59][60]</sup>. Fu et al. reported a ligand-enabled, site-selective carboxylation of 2-(furan-3-yl)phenols **42** under the atmospheric pressure of CO<sub>2</sub>. It was performed through an Rh(ii)-catalyzed C–H bond activation, assisted by the ligand chelation of the phenolic hydroxyl group to afford 4*H*-furo[3,2-*c*]benzopyran-4-ones **43** (Scheme 14) <sup>[61]</sup>. This reaction indicates the role of phosphine ligands in combination with Rh<sub>2</sub>(OAc)<sub>4</sub> in promoting the reactivity and the selectivity during C–H carboxylation. The right choice of a suitable basic catalyst is an additional critical point.



**Scheme 14.** Rhodium(II)-catalyzed aryl C–H carboxylation with  $CO_2$  in the synthesis of 4*H*-furo[3,2-*c*] benzopyran-4-ones **43**. *Reagents and conditions*: (a)  $Rh_2(OAc)_4$  (1 mol %), tricyclohexylphosphine  $PCy_3$  (2 mol %), t-BuOK (4.5 equiv.), diglyme, 100 °C, 48 h, six outputs with 70%-86% yield.

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