

Catalysis-Free Microwave-Assisted Synthesis of Biscoumarins with Chromone Group by a Multicomponent Process [†]

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Abstract

In this work, biscoumarin molecules were obtained by multicomponent reaction, without catalysts, under thermal heating or microwave irradiation. First, optimization tests were performed using benzaldehyde and 4-hydroxycoumarin as starting substrates. The optimal temperature (100 °C), solvent (1-propanol), and reaction time (4 h for conventional heating and 1 h for microwave irradiation) were then employed for the reaction between 4-hydroxycoumarin and different 3-formylchromones to obtain biscoumarins. Good yields and selectivity, which in most cases was greater than 65%, both with conventional thermal heating and microwave radiation were achieved.

Keywords: biscoumarins; chromone substructure; microwaves; multicomponent reactions

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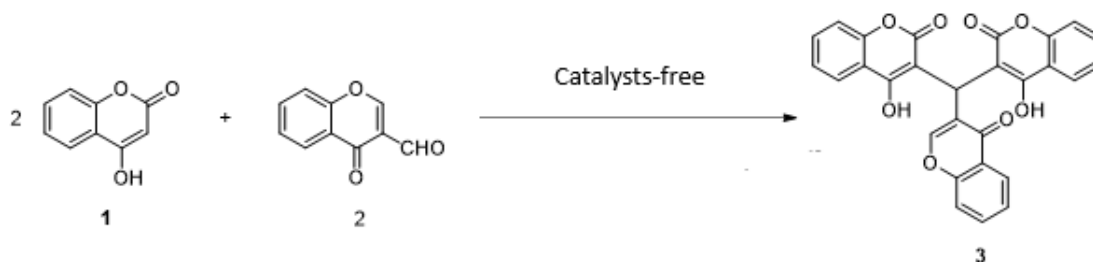
1. Introduction

The development of sustainable chemistry has been possible thanks to numerous studies conducted in both academic and industrial settings by researchers from different fields. This is due to the urgent need to promote processes and develop products that reduce the generation of waste that significantly impacts ecosystems [1]. Among the numerous tools for implementing eco-efficient processes, multicomponent reactions (MCRs) are convergent processes that combine three or more reactants in a single operation to form a single product. They are invaluable in drug development due to their high atom economy and lack of generation of harmless byproducts. They are ideal for constructing heterocyclic structures containing N, O, and S atoms [2,3]. Coumarins are a group of benzopyrones related to the flavonoid group. These compounds have demonstrated diverse bioactivities, for example: antimicrobial, antiviral, fungicidal, vasodilatory, anticoagulant, anti-inflammatory, sedative, hypnotic, analgesic, molluscicides, among others. A widely studied group of compounds associated with coumarins are the so-called bisanalogs, which have been shown to be active as anticoagulants, antiseptics, and urease inhibitors.

Dicumarol, a naturally occurring biscoumarin derived from plants or fungi, is recognized as a powerful anticoagulant [4–6].

2. Results and Discussion

In the present work an efficient process for the synthesis of biscoumarins was developed through a multicomponent process involving the condensation reaction of 2 moles of 4-hydroxycoumarin with 1 mol 3-formylchromones. Initially, optimal reaction conditions were established with benzaldehyde and subsequently, 3-formylchromones were used as starting substrates (Scheme 1). Environmentally friendly reaction conditions were applied, without catalysts, with nontoxic solvents and using microwave radiation as an alternative heat source to reduce reaction times. The compounds are obtained practically pure by simple precipitation of the reaction mixture and filtration.



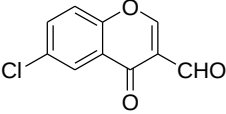
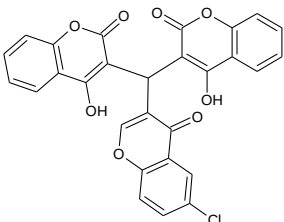
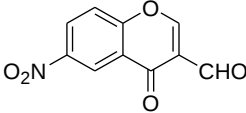
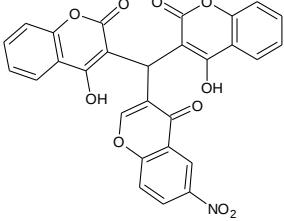
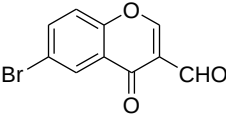
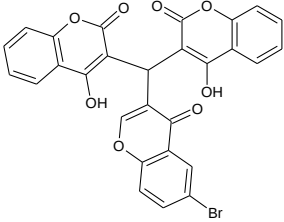
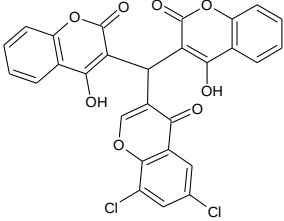
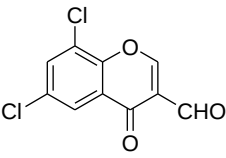
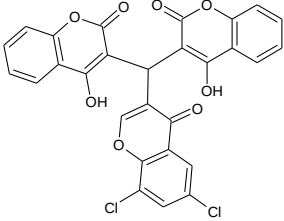
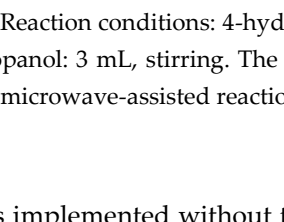
Scheme 1. Biscoumarins synthesis from 3-formylchromone.

To optimize the reaction conditions, the effect of the solvent, temperature, and reaction time were evaluated. It is important to note that all reactions were carried out in the absence of a catalyst. Furthermore, to reduce reaction times, the use of microwave radiation was explored as an alternative heating source.

The optimal reaction conditions were found using 0.5 mmol of benzaldehyde, 1 mmol of 4-hydroxycoumarin, 3 mL of 1-propanol, a temperature of 100 °C, and a time of 4 h. Under these conditions, a biscoumarin yield of 80% was obtained, free of byproducts. Similarly, using microwave radiation at 130 °C, biscoumarin is obtained in 1 h with a comparable yield of 78% and free also of byproducts. These optimized conditions were used to prepare several biscoumarins containing the 3-formylchromone substructure by reacting 4-hydroxycoumarin with substituted 3-formylchromones. Yields for the thermal reaction ranged from 86 to 58%. In some examples, the reaction was carried out using microwave radiation, obtaining comparable results in 1 h at 130 °C. The results obtained are indicated in Table 1.

Table 1. Synthesis of biscoumarin ¹.

Entry	Formylchromone	Time (h)	Product	Yield (%)
1		4		86
		1		74
2		4		67
		1		59

3		4		75
4		4		58
5		4		70
		1		68
6		4		68
		1		67

¹ The yields of pure products 3 are expressed in mol%. Reaction conditions: 4-hydroxycoumarin (1 mmol), 3-formylchromone 2 (0.5 mmol), solvent, 1-propanol: 3 mL, stirring. The 4-h yields correspond to the thermal reaction, and the 1-h yields to the microwave-assisted reaction.

3. Conclusions

In this work, a sustainable methodology was implemented without the use of catalysts to obtain biscoumarins derived from 3-formylchromones with 4-hydroxycoumarin by thermal heating and microwave irradiation. Six biscoumarin molecules were obtained, five of which had not been previously reported in the literature, with yields that, in most cases, exceeded 70%.

Author Contributions: E.X.A.P.: Methodology, data curation, formal analysis. G.A.P.: Methodology, investigation, data curation, formal analysis. V.P.: Investigation, writing—review & editing. M.C.M.: Methodology, data curation, formal analysis. Á.G.S.: Methodology, supervision, data curation, formal analysis, funding acquisition. G.P.R.: Conceptualization, methodology, supervision, formal analysis, writing—review & editing, funding acquisition, project administration. All authors have read and agreed to the published version of the manuscript.

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