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Synthesis of Biscoumarin Derivatives as Biological Compounds Using Cellulose Sulfonic Acid

Masoumeh Sedighi and Naser Montazeri*

Department of Chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
*Corresponding author

Abstract

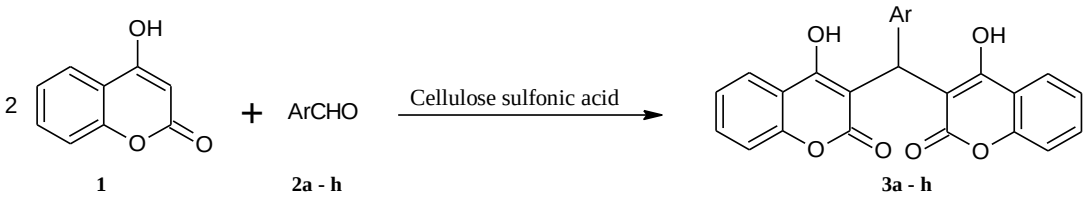
Cellulose sulfonic acid efficiently catalyzes the one-pot reaction of 4-hydroxycoumarin and aryl aldehydes under mild reaction conditions to yield biscoumarin derivatives in high yields. This method is of great value because of its easy processing, short reaction time and high yields. We anticipate the present method will receive the attention of medicinal chemists and be used for elaborate synthesis and pharmaceutical screening of biscoumarin based molecules.

Keywords: Biscoumarin, Aryl aldehydes, 4-hydroxycoumarin, Cellulose sulfonic acid

1 Introduction

Biscoumarin and coumarin derivatives have attracted strong interest to their useful biological and pharmacological properties [1-5]. Compounds with these ring systems have long been the subject of numerous studies on account of their pharmacological and biological activities such as anti-fungal, anti-anthelmintic, anti-coagulants, analgesic, anti-tumor, anti-HIV, anti-apoptotic, antioxidant and cytotoxic [6-8]. A number of structurally different natural and synthetic coumarin derivatives have been reported to exert notably antimicrobial as well as antifungal activity [9-11]. In view of different biological and chemical applications of biscoumarin, the development of suitable synthetic methodologies for their generation has been a topic of great interest in recent times. The general method for synthesis of biscoumarin derivatives involves the reaction of 4-hydroxycoumarin with aryl aldehydes in the presence of different catalysts such

as tetrabutylammonium bromide [12], molecular iodine [13], [bmin] BF_4 [14], SO_3H-functionalized ionic liquid [15], sodium dodecyl sulfate [16], piperidine [17], n-dodecylbenzene sulfonic acid (DBSA) [18], nano silica chloride [19], ruthenium (III) chloride hydrate [20] and Zn $(proline)_2$ [21]. Although these methods may be effective, some of them have relatively long reaction times and tedious work up. These finding prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of biscoumarins under simpler experimental set up and eco-friendly conditions. Cellulose is a polymer raw material used for two general purposes. For many centuries it has served mankind as a construction material, mainly in the form of intact wood and textile fibers such as cotton or flax, or in the form of paper and board. On the other hand, cellulose is a versatile starting material for chemical conversions, being used at the production of artifact, cellulose-based thread and films as well as a variety of stable cellulose derivatives used in many areas of industry and domestic life.
Cellulose and its derivatives have some unique properties such as biodegradable, inexpensive, extremely inert and environmentally benign, which make them attractive catalysts for organic or inorganic transformations [22]. Recently, cellulose sulfonic acid has emerged as a promising biopolymeric solid support acid catalyst for various acid-catalyze reactions [23]. However, there are no reports on the use of cellulose sulfonic acid for one-pot synthesis of biscoumarins. In continuation of our previous work on the applications of solid acid catalysts in the synthesis of heterocyclic compounds [24], in this article, we report cellulose sulfonic acid as a highly efficient, clean and economically valuable catalyst for the one-pot synthesis of biscoumarin derivatives from reaction of 4-hydroxycoumarin and aryl aldehydes (Scheme 1).



1 **2a - h** **3a - h**

Scheme 1

2 Material & methods

All of the chemical material used in this work purchased from Fluka or Merck and without further purification. Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer in KBr disks. The ^1H NMR (500 MHz) spectra were recorded on a Bruker-Ac-500 spectrometer.

Preparation of cellulose sulfonic acid

To a magnetically stirred mixture of cellulose (5.00 g) and n-hexane (20 mL), chlorosulfonic acid (1.00 g, 9 mmol) was added drop wise at 0 °C during 2h. HCl gas was removed from the reaction. The reaction mixture was stirred for 2h and filtered. The residue was washed with acetonitrile (30 mL) and dried at room temperature to afford 5.15g of cellulose sulfonic acid as a white powder [23].

General procedure for the synthesis of biscoumarins (3a-h)

A mixture of 4-hydroxycoumarin 1 (2mmol), an aromatic aldehyde 2a-h (1mmol) and cellulose sulfonic acid (0.02 g) in H_2O (10 mL) was heated on the oil bath under reflux with stirring for 2h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and the solid product was collected by filtration and washed with cold water. The solid residue was diluted with boiling ethanol (5 mL) and the catalyst was separated. The filtrate was concentrated on Rota-evaporator to give a solid products 3a-h in high yields. All the products were identified by comparing the analytical data (Melting point, IR, ^1H NMR) with those reported or with authentic samples prepared by the conventional method, in which we used cellulose sulfonic acid as the catalyst. The results are summarized in Table 1.

3 Results & discussion

Cellulose sulfonic acid as a solid acid catalyst play prominent role in the synthesis of biological heterocyclic compounds. Cellulose sulfonic acid with high reactivity, high stability, low toxicity and easy preparation is one of the most attractive catalysts for organic synthesis prompted by these finding. We decided to investigate the efficiency of cellulose sulfonic acid as a catalyst in the synthesis of biscoumarin derivatives. To optimize the reaction conditions, the reaction of 4-hydroxycoumarin (2 mmol) and banzaldehyde (1 mmol) was used as a model reaction. In order to determine the optimum quantity of cellulose sulfonic acid, model reaction was carried out at reflux in H_2O condition. The efficiency of the reaction is mainly affected by different amounts of catalyst. In the absence of the catalyst low yield of product was obtained even after 5h. The observations, indicate that catalyst is necessary for completing the reaction. Increasing in amount of the catalyst until 0.02g increased the yield of the product, whereas the higher amount of the catalyst did not increase the yield noticeably. The model reaction was also examined in various solvents. Among the solvents tested, the reaction in EtOH, $CHCl_3$ and CH_3CN using 0.02g of the catalyst gave a moderate yield of the desired product at reflux. However, the best results were obtained when H_2O was used as a solvent at reflux. In the solvent free conditions, even in the presence of 0.05g of the catalyst at 100 °C, the yields are low. In order to show generality and scope of this protocol, we used various substituted aromatic aldehydes and the results obtained are summarized in Table 1.

Table 1. Synthesis of biscoumarins using cellulose sulfonic acid 3a-h[a]

Entry	Ar	Product[b]	Time (min)	Yield (%)[c]	m. p. (°C)	
					Found	Reported
1	C_6H_5	3a	120	90	230-232	228-230 [21]
2	3-$NO_2C_6H_4$	3b	100	85	235-237	234-236 [19]
3	4-$MeOC_6H_4$	3c	150	82	244-246	242-244 [20]
4	4-ClC_6H_4	3d	120	80	253-255	252-254 [20]
5	4-$NO_2C_6H_4$	3e	100	84	230-232	232-234 [19]
6	2-ClC_6H_4	3f	100	89	220-222	224-226 [19]
7	4-MeC_6H_4	3g	120	83	265-266	266-268 [19]
8	4-HOC_6H_4	3h	150	81	224-226	222-225 [21]

[a] 2 mmol 4-hydroxycoumarin, 1 mmol aryl aldehyde and 0.02g cellulose sulfonic acid in H_2O (10 mL) under reflux.
[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedure.
[c] Isolated yield.

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in high yields. The type of aldehyde had no significant effect on the reaction.

4 Conclusion

In conclusion, we have developed new method for the one-pot synthesis of biscoumarin derivatives from aromatic aldehydes and 4-hydroxycoumarin using cellulose sulfonic acid as an efficient solid acid catalyst in high yields. Simple experimental procedure, noncorrosive, inexpensive solid acid catalyst, and eco-friendly have made this approach distinctly superior over to many other protocols reported earlier.

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