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Highly efficient and easy synthesis of biscoumarin catalyzed by pentafluoropropionic acid (PFPA) as a new catalyst in aqueous medium

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Pentafluoropropionic acid efficiently catalyzes the one-pot reaction of 4-hydroxycoumarin and aryl aldehydes under mild reaction conditions to yield biscoumarin derivatives in high yields. The products were obtained in short reaction times. We believe this applicability of pentafluoropropionic acid with mentioned advantages makes our method superior over previous reported methods to the synthesis of biscoumarins.

Keywords: Biscoumarins, 4-hydroxycoumarin, Aryl aldehydes, Pentafluoropropionic acid.

INTRODUCTION

Coumarin derivatives and especially biscoumarins are important classes of heterocyclic compounds because their biological activities [1-5]. Compounds with these ring system have diverse pharmaceutical activities such as cytotoxicity, antithrombotic, anticancer, anti-HIV, antioxidant, anticoagulant, urease inhibitory and enzyme inhibitory [6-10]. A number of structurally different natural and synthetic coumarin derivatives have been reported to exert notably antimicrobial as well as antifungal activity [11-13]. Moreover a number of biscoumarins are useful as malignant melanoma, metastatic renal cell carcinoma and prostate cancer drugs [14-16]. Therefore, the development of new and efficient methodologies for the synthesis of biscoumarin derivatives will be interesting in both synthetic organic and medicinal chemistry. The general method for synthesis of biscoumarin derivatives involves the reaction of 4-hydroxycoumarin with aryl aldehydes in the presence of different catalyst such as cellulose sulfonic acid [17], nano TiO_2 [18], $Zn(proline)_2$ [19], ruthenium (III) chloride hydrate [20], tetrabutylammonium bromide (TBAB) [21], molecular iodine [22], $[bmin]BF_4$ [23], SO_3H-functionalized ionic liquid [24], nano silica chloride [25], sodium dodecyl sulfate [26], piperidine [27], n-dodecylbenzene sulfonic acid (DBSA) [28], heteropolyacids [29], phosphotungstic acid [30], $POCl_3$ in dry DMF [31], 1,8-diazabicyclo [5.4.0] undec-7-ene(DBU) [32], manganous chloride [33], and tetrabutylammonium hexatungstate [34]. Although these methods may be effective, some of them have relatively long reaction times and tedious work up. These finding prompted us toward further investigation in seach for a new catalyst, which will carry out the synthesis of biscoumarins under simpler experimental set up and eco-friendly conditions. In this article, we present a one-pot reaction for the synthesis of biscoumarin derivatives in the presence of pentafluoropropionic acid (PFPA) in aqueous medium (Scheme 1).

Scheme 1. PFPA catalyzed synthesis of biscoumarins.

EXPERIMENTAL

Chemical were purchased from Merck and used without further purification. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by thin layer chromatography (TLC) on Silica-gel Polygram SILG-UV 254 plates. 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.

TYPICAL PROCEDURE

A mixture of 4-hydroxycoumarin **1** (2 mmol), an aromatic aldehyde **2a-h** (1 mmol) and PFPA (0.4 mmol) in H_2O (10 mL) was heated on the oil bath under reflux with stirring for the time period as indicated in Table 1. The progress of the reaction

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was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and the solid product was collected by filtration, and washed with cold water. The solid product was obtained by recrystallization in ethanol. Products were characterized by their physical constants (m.p.), IR and ^{1}H NMR spectroscopy and comparison with authentic samples.

RESULT AND DISCUSSION

In order to optimize the reaction conditions, including solvents and temperature, the reaction was conducted under various conditions and the results are listed in Table 1. In an optimized reaction condition, 4-hydroxycoumarin (2 mmol) and benzaldehyde (1 mmol) in H_2O (10 mL) were mixed in the presence of PFPA (0.4 mmol) as catalyst for 60-100 min. The reaction proceeds very cleanly under reflux and was free of side products. After completion of the reaction (monitored by TLC), a simple work up affords the products in high yields (Table 2).

Among the solvents tested, the reaction in $CHCl_3$ using 40 mol% of the catalyst gave a low yield of desired product. Ethanol, methanol and CH_3CN gave moderate to good yields under these conditions. Without catalyst, in refluxing EtOH, MeOH, H_2O, $CHCl_3$ and CH_3CN the reactions times are prolonged and the yields are poor. However, the reaction at reflux in H_2O with 40mol% of catalyst afforded desired product in high yield. In the solvent free conditions, even in the presence of 50 mol% of the catalyst at 120 °C, the yields are low. We also evaluated the amount of PFPA required for this transformation. It was found that the yield of product was affected by the catalyst amount. Increasing the amount of the catalyst up to 40 mol% at reflux in H_2O increased the yield of the product. Further increase in the catalyst amount did not increase the yield noticeably. In order to show generality and scope.

Table 1. Optimizing the reaction conditions[a].

Entry	Catalyst (mol%)	Solvent	Condition	Time (min)	Yield (%)
1	--	EtOH	Reflux	180	25
2	--	MeOH	Reflux	180	20
3	--	H_2O	Reflux	180	30
4	--	$CHCl_3$	Reflux	240	Trace
5	--	CH_3CN	Reflux	180	28
6	30	--	120 °C	60	40
7	40	--	120 °C	60	45
8	50	--	120 °C	60	45
9	30	H_2O	Reflux	100	82
10	40	H_2O	Reflux	80	88
11	50	H_2O	Reflux	80	87
12	40	EtOH	Reflux	80	75
13	40	MeOH	Reflux	100	64
14	40	$CHCl_3$	Reflux	100	40
15	40	CH_3CN	Reflux	100	72

[a] Benzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol)
[b] Isolated yields

Table 2. Synthesis of biscoumarins using pentafluoropropionic acid as catalyst [a].

Entry	Ar	Product [b]	Time (min)	Yield (%)[c]	m.p. (°C) [reference]
1	3-$NO_2C_6H_4$	4a	60	92	234-235 [25]
2	4-HOC_6H_4	4b	100	86	223-225 [19]
3	4-$NO_2C_6H_4$	4c	60	90	233-235 [25]
4	C_6H_5	4d	80	88	227-229 [19]
5	4-ClC_6H_4	4e	80	87	250-252 [20]
6	4-$MeOC_6H_4$	4f	80	87	243-245 [20]
7	4-MeC_6H_4	4g	80	89	267-268 [25]
8	2-ClC_6H_4	4h	100	86	221-223 [25]

[a] 4-hydroxycoumarin (2 mmol), aryl aldehyde (1 mmol) and PFPA (40 mol%).
[b] The product were characterized by comparison of their spectroscopic and physical data with those reported in the literature.
[c] Isolated yield.

Table 3. Comparison of efficiency of various catalyst in synthesis of biscoumarin derivatives.

Entry	Catalyst	Conditions	Time (min)	Yield (%)[c]	Reference
1	Cellulose sulfonic acid	H_2O, reflux	100-150	80-90	[17]
2	Nano TiO_2	H_2O, reflux	5-10	84-96	[18]
3	$Zn[proline]_2$	H_2O, reflux	5-9	91-96	[19]
4	$RuCl_3.nH_2O$	H_2O, 80 °C	25-35	75-95	[20]
5	Nano SiO_2Cl	CH_2Cl_2 , 40 °C	60-360	68-95	[25]
6	SDS	H_2O, 60 °C	138-180	84-98	[26]
7	DBSA	H_2O, 40 °C	60	78-92	[28]
8	$[TBA]_2[W_6O_{19}]$	EtOH, reflux	5-10	85-92	[34]
9	PFPA	H_2O, reflux	60-100	86-92	This work

Of this new protocol, we used various substituted aromatic aldehydes and the results obtained are summarized in table 2. 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. The efficiency of PFPA as a catalyst for the synthesis of the biscoumarin derivatives was compared with that of other catalysts reported in the literature. Some of the results are summarized in table 3. It is clear from this table that PFPA is an efficient catalyst which could be useful in the synthesis of a series of biscoumarin derivatives.

CONCLUSION

In conclusion, we have developed new method for the one-pot synthesis of biscoumarin derivatives from 4-hydroxycoumarin and aryl aldehydes using pentafluoropropionic acid (PFPA) catalyst. Easy work up, ready commercial availability of the catalyst, short reaction time and high yield, make the procedure an attractive alternative to the existing methods for the synthesis of biscoumarin derivatives.

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