Fe_3O_4@ ZrO_2/SO_4^{2-} as a Nano magnetic solid acid catalyst for one pot synthesis of benzylamino coumarin derivatives

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Abstract: A convenient and practical Fe_3O_4@ZrO_2/SO_4^{2-} as a nano magnetic solid acid catalyzed multicomponent synthesis of benzylamino coumarin derivatives. This reaction has been developed from secondary amines, aromatic aldehydes and 4-hydroxycoumarin via mannich type reaction that compared to the classical reactions, this method consistently has the advantages of short reaction times, little catalyst loading, high yields, easy magnetic separation and reusability of the catalyst.

Keywords: Magnetic nanoparticles, Fe_3O_4@ZrO_2/SO_4^{2-} , Benzylamino coumarins, 4-Hydroxycoumarin, Mannich type reaction.

Introduction:

Multicomponent reactions (MCRs) are a dominant tool for atom efficient, time, cost-advantageous and environmentally waste-free synthesis of complex building blocks of bioactive heterocycles [1]. In the synthesis of various chemicals, solvents and catalyst are accountable part of the chemical processes, thus selection of a proper solvent and catalyst should be done for synthesis of compounds. In recent years, much attention has been directed towards the synthesis of 3-benzyl substituted 4-hydroxycoumarins owing to their tremendous application in various research fields including biological science and medicinal chemistry. 3-Benzyl substituted 4-hydroxycoumarin derivatives are components of numerous natural products like warfarin, phenprocoumon, coumatetralyl, carbochromen, bromadialone, etc (Fig. 1). These compounds also exhibit a wide band of biological activities including antibacterial, anti-HIV [2], antiviral [3], anticoagulant [4], antioxidant [5] and anticancer activities [6]. The vast biological importance of the amino derivatives of 4-hydroxycoumarin inspired us to develop a novel protocol for the efficient synthesis of new benzylamino coumarin derivatives.

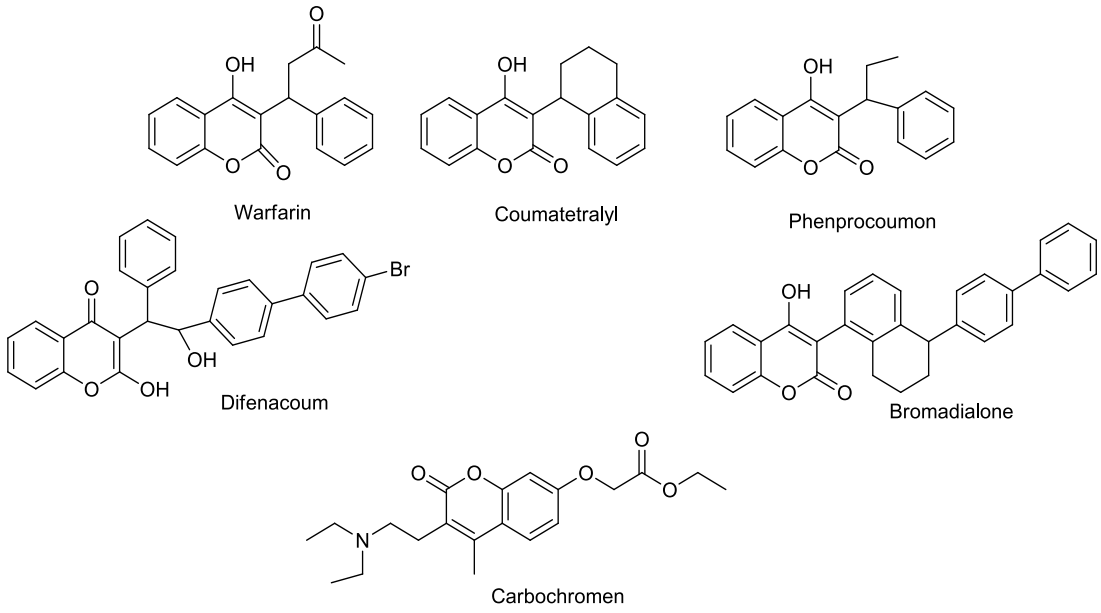
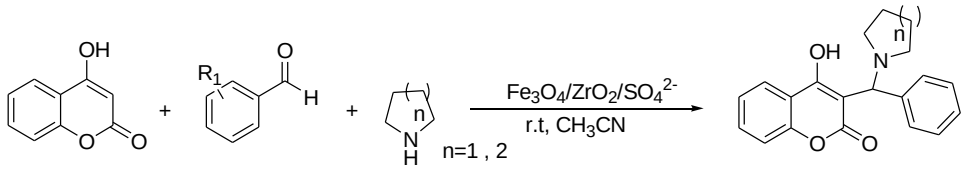


Figure 1. Biologically active 3-substituted coumarins.

The methods reported previously for the synthesis of benzylamino coumarin derivatives suffer from severe disadvantages such as longer reaction time, inadequate yields and use of expensive catalyst [7,8]. Thus, the development of environmentally benign, high-yielding, and fast synthesis of benzylamino coumarin derivatives still remains a desired goal in organic synthesis. In our preliminary work on multicomponent reactions (MCRs) for the synthesis of various biologically important heterocyclic compounds [9], we wish to report herein a highly efficient procedure for the preparation of 3-substituted coumarin derivatives via one pot three-component Mannich type reaction using $Fe_3O_4@ZrO_2/SO_4^{2-}$ as an efficient nano magnetic sulfated zirconia solid acid catalyst,in acetonitrile solvent at room temperature (Scheme 1). Nano magnetic sulfated zirconia is an ecofriendly and inexpensive catalyst with high surface acidity and reusable capacity.



Scheme 1. Synthesis of benzylamino coumarin derivatives catalysed by $Fe_3O_4@ZrO_2/SO_4^{2-}$ at room temperature

2. Results and discussions

Initially, benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol) and piperidine (1 mmol) were employed as reactants for the model reaction to synthesize benzylamino coumarin derivatives in the presence of catalytic amount of $Fe_3O_4@ZrO_2/SO_4^{2-}$ (70 mg) (Table 1).

In our initial study for the optimization of the reaction condition, a screening was performed with a variety solvents like ethanol, methanol, H_2O and acetonitrile (Table 1). The results showed that acetonitrile was the solvent of choice. The effect of catalyst amount on reaction yield was determined, too. finally The best outcome, in terms of yield and the reaction time was obtained with 70 mg/mmol of $Fe_3O_4@ZrO_2/SO_4^{2-}$.

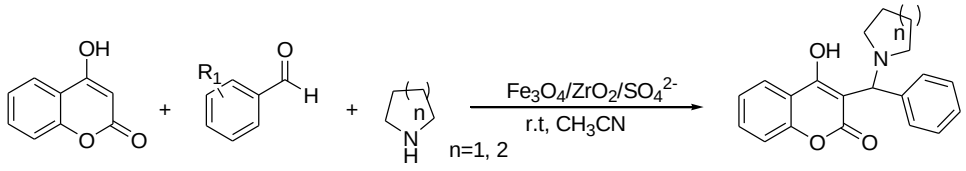
Table 1. Optimization of the solvent for the Synthesis of benzylamino coumarine .

Entry	Solvent	Time (min)	Isolated yield (%)
1	H2O	10	30
2	EtOH	10	70
3	MeOH	10	60
4	CH3CN	10	97
5	No Solvent	10	–

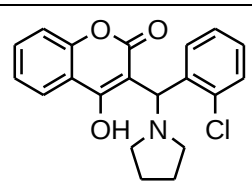
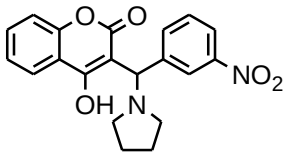
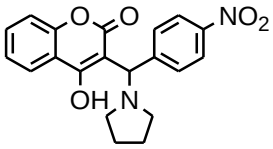
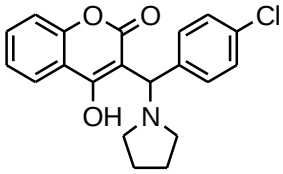
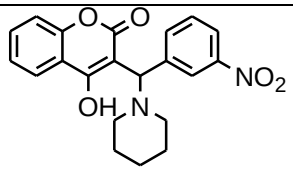
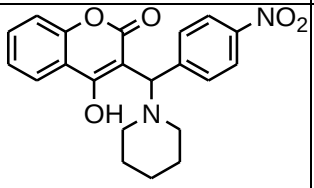
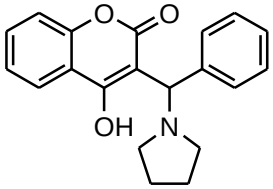
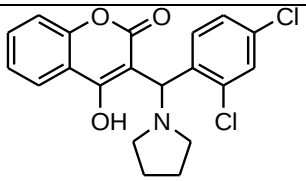
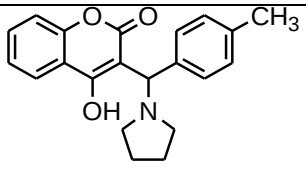
a Conditions: 1 mmol benzaldehyde, 1 mmol 4-hydroxycoumarin , 1 mmol secondary amine and 3 mL solvent.

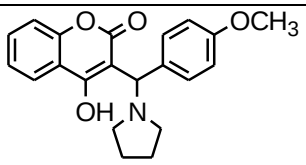
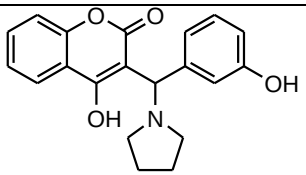
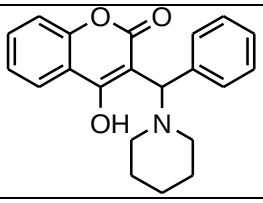
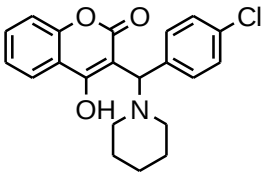
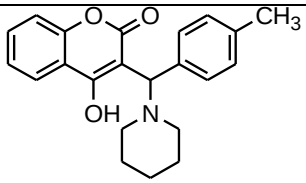
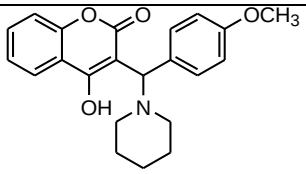
The scope and generality of synthesis of benzylamino coumarin derivatives are well showed with structurally diverse aldehydes. The results are summarized in Table 2.

Table 2. Synthesis of benzylamino coumarin in the presence of $Fe_3O_4@ZrO_2/SO_4^{2-}$.



Entry	Aldehyde	Amine	Product	Time (min)	Yield (%)	MP(°C)	
						Found	Reported

1	2-Cl benzaldehyde	Pyrrolidine		15	95	155-157	157-158 [10]
2	3-Nitro benzaldehyde	Pyrrolidine		10	92	186-188	188-190[10]
3	4-Nitro benzaldehyde	Pyrrolidine		5	92	175-177	170-172[11]
4	4-Cl benzaldehyde	Pyrrolidine		8	90	175-179	176-178[11]
5	3-Nitro benzaldehyde	Piperidine		5	94	187-189	184-186[12]
6	4-Nitro benzaldehyde	Piperidine		12	90	171-174	174-176[11]
7	benzaldehyde	Pyrrolidine		13	90	173-1761	170-172[11]
8	2,4-Cl_2 benzaldehyde	Pyrrolidine		15	80	145-147	148-150[10]
9	4-Methyl benzaldehyde	Pyrrolidine		18	85	177-180	180-182[11]

10	4-Methoxy benzaldehyde	Pyrrolidine		20	87	135-138	140[10]
11	3-Hydroxy benzaldehyde	Pyrrolidine		22	95	161-162	160[13]
12	benzaldehyde	Piperidine		30	87	180-183	182-184[10]
13	4-Cl benzaldehyde	Piperidine		10	95	191-193	188-190[10]
14	4-Methyl benzaldehyde	Piperidine		18	85	186-189	190[13]
15	4-Methoxy benzaldehyde	Piperidine		20	85	140-142	143[13]

[b] Isolated yield

Fig. 2 shows the reusability of the catalyst for the preparation of benzylamino coumarin . The model reaction was carried out under the optimized conditions. After completion of the reaction, the catalyst was extracted by magnetite and washed with acetone. Then used as such for subsequent runs (four times) under the same conditions without significant loss of its catalytic activity.

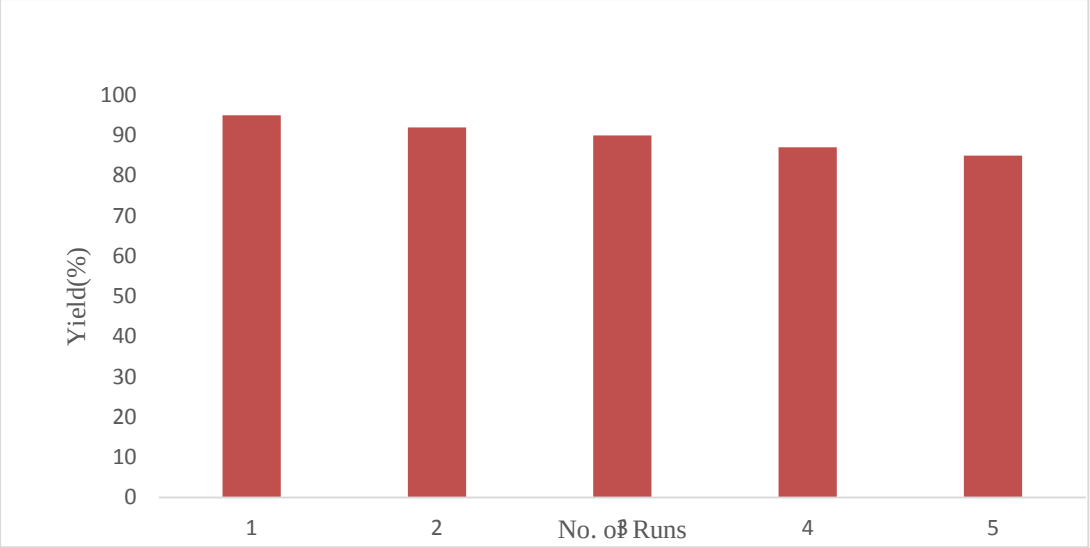


Figure 2. Recyclability of the nanocatalyst.

3. Experimental

3.1. Materials and methods

All chemicals were purchased from Merck, Fluka and Sigma-Aldrich companies and were used without further purification. All reactions and the purity of benzylamino coumarin derivatives were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate , *n*-hexane and methanol as eluents. Melting points were determined in open capillaries using an Electro thermal 9100 instrument. IR spectra were recorded on a Shimadzu FT-IR400s. ^{1}H NMR spectra were recorded on an Avance Bruker DRX-500

3.2. General procedure for the synthesis of benzylamino coumarin

A mixture of aromatic aldehyde (1.0 mmol), 4-hydroxycoumarin (1.0 mmol) and secondary amine (1.0 mmol), were employed as reactants in the presence of catalytic amount of $Fe_3O_4@ZrO_2/SO_4^{2-}$ (70 mg) and 4 mL of CH_3CN as solvent was stirred at room temperature for 5–30 min, the progress of the reaction was monitored by TLC. the catalyst was removed by magnet, then washed with acetone and after drying could be ready to use for the next reaction without loss in activity. The crude product was filtered and extracted in ethyl acetate to give products in good to high yields. The products were characterized by FT-IR and melting point.

4. Conclusion

In summary, we have delineated a highly efficient, procedure for the synthesis of benzylamino coumarin with aldehyde derivatives using $Fe_3O_4@ZrO_2/SO_4^{2-}$ catalyst. In other words, the most important feature of described method is use of organic solvent , reusability of the catalyst, facile conditions, easy isolation of the products with excellent purity, increasing yields, reducing reaction time and waste-free chemical process

Acknowledgements

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