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SHORT COMMUNICATION

Nano TiO_2@KSF as a high-efficient catalyst for solvent-free synthesis of *Bis*coumarin derivatives

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ABSTRACT: An efficient, simple and convenient route is described for the synthesis of *bis*coumarin (3,3'-(arylmethylene)*bis*(4-hydroxy-2*H*-chromen-2-one)) by using recyclable catalyst TiO_2@KSF. In this procedure, we synthesize a *bis*coumarin derivative *via* the three multi-component reactions (3MCRs) of two equivalent 4-hydroxycoumarin with one equivalent of various aromatic aldehydes in the presence of 20 mg nano TiO_2@KSF as homogeneous catalyst under solvent-free conditions at 100 °C for the convinced reaction times (8–15 min). The advantages of this protocol towards the synthesis of *bis*coumarin derivatives are: a) use of solvent-free conditions, b) inexpensive catalyst, c) using commercially available precursors, d) reusability of TiO_2@KSF up to four cycles without much loss in reactivity, e) simple work-up, f) high yields of pure products, g) short reaction times. The structure of all *bis*coumarin derivatives were confirmed by M.p., TLC, FT-IR, ^{1}H NMR spectra and were compared with reliable references.

Keywords: *Aromatic aldehydes; Biscoumarins; Nano TiO_2@KSF; Solvent-free conditions; 4-Hydroxycoumarin.*

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INTRODUCTION

*Bis*couumarin and coumarin derivatives are a heterocyclic moiety that is found in many natural compounds [1]. *Bis*coumarin derivatives are distinguished derivatives of coumarin which are widely found in the bioactive metabolites of terrestrial and marine organisms [2,3]. *Bis*coumarins and coumarin derivatives possess various biological activities such as anticancer [4], antioxidant [5], antibacterial [6], cytotoxic [7] and anti-HIV agents [8]. One of the most used methods in synthesis of *bis*coumarin involves reaction of aldehyde derivatives with 4-hydroxycoumarin derivatives. A survey in literature showed that there are many protocols in preparation of *bis*coumarins that have used different homogenous and heterogeneous catalysts and different reaction conditions, for example nickel nanoparticles [9], n-dodecylbenzene sulfonic acid (DBSA) [10], nano silica chloride [11], tetrabutylammonium bromide (TBAB) [12], $[MIM(CH_2)_4SO_3H][HSO_4]$ [13], I_2 [14], Phosphotungstic acid [15], $B(HSO_4)_3$ [16], TiO_2/SO_4^{2-}[17], methanesulfonic acid [18], sodium dodecyl sulfate (SDS) [19], cellulose sulfonic acid [20], Ru@imine-Z [21]. Although all of them are useful and valuable, however many of these protocols suffer from low yields of products, long reaction times, non-recyclable catalyst, and harmful and corrosive solvents. Therefore, the development of simple, clean, high yielding and environmentally friendly approaches to the synthesize this compound are important tasks for an organic chemist. During the course of our studies towards the development of new routes to the synthesis of heterocyclic

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compounds [22-31] here, we report a new and efficient synthesis of *bis*coumarins in the presence of premade nano-TiO_2@KSF as a solid catalyst under solvent-free conditions (Fig. 1).

EXPERIMENTAL

Material and Instruments

All commercially available chemicals were obtained from Merck and used without further purification. FT-IR spectra were recorded on Shimadzu IR-470 spectrophotometer. ^{1}H NMR spectra were determined on a Bruker Advance DRX-400 MHz spectrometer using TMS as the internal standard and $CHCl_3$ as solvent. The scanning electron microscope (SEM, model Sigma-IJMA) was used to characterize the nano-TiO_2@KSF.

Preparation of nano TiO_2@KSF

Catalyst was prepared according to the reported literature [32] with some modifications. A mixture of 1.5 g of montmorillonite, 9.37 mL of AcOH and 5 mL titanium (IV) isopropoxide was stirred at r.t. then, 106 mL deionized water added slowly to the mixture. After 30 minutes a clear solution was formed. The mixture was stirred in an oil bath (100 ºC) until a gel formed. The solution was filtered, washed with EtOH and dried at 80 ºC for 4h to yield a gray powder (1 g, 66%). The catalyst was characterized by IR spectra (Fig. 2) and TEM image (Fig. 2).

General procedure for preparation of biscoumarins 3a-j

A mixture of 4-hedroxycoumarin (2 mmol), aldehyde (1 mmol) and TiO_2@KSF (20 mg) was stirred at 100 ºC under solvent-free condition. The progress of the reaction was monitored using a thin layer chromatography (TLC) (petroleum ether : EtOAc 3:1). After completion of the reaction, EtOH (10 mL) was added to the mixture to dissolve a product, at this stage the catalyst removed by filtration.

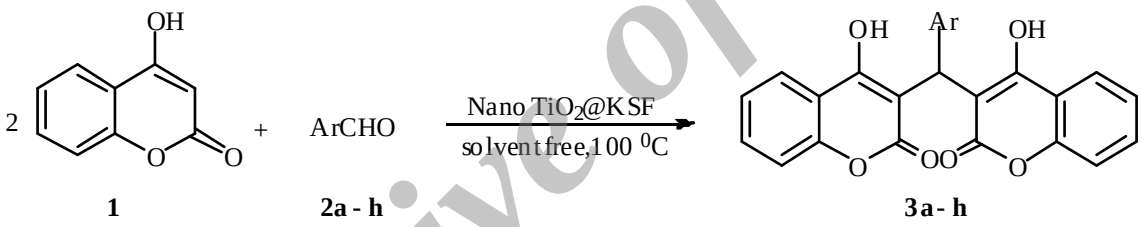

Fig. 1: Synthesis of *bis*coumarins at the presence nano-TiO_2@KSF in solvent free-condition.

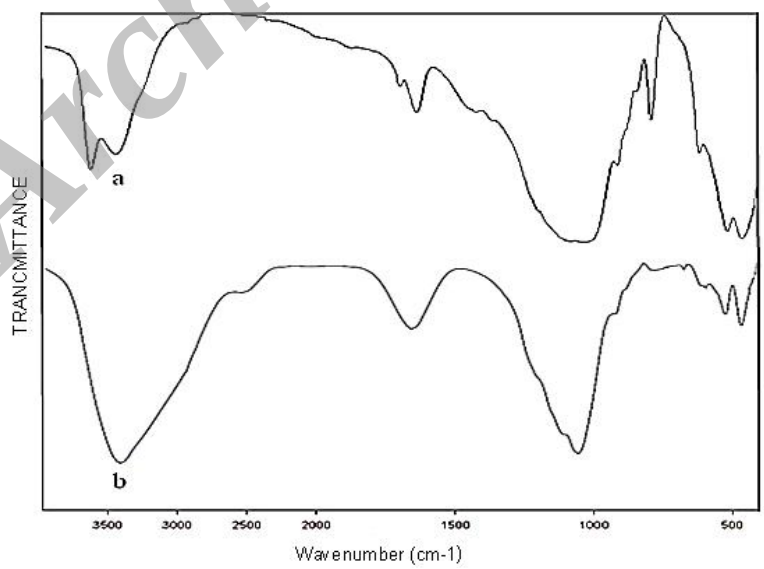

Fig. 2: FT-IR spectra of natural nontmorillonite (a), nano-TiO_2@ksf (b).

The product obtained by evaporation EtOH under reduced pressure as pure solid without further purification.

RESULTS AND DISCUSSION

Primary, the solid catalyst nano-TiO_2@KSF was characterized by FT-IR spectra and TEM technique. The FT-IR spectra of natural montmorillonite (Fig. 2a), nano-TiO_2@KSF (Fig. 2b) are shown. These spectra revealed that, nano-TiO_2@KSF formation was confirmed, as a result of Ti–OH strong vibration at 3400 cm^{-1}, H–O–H bending vibration at 1654 cm^{-1}. The SEM images of nano-TiO_2@KSF (Fig. 3) show that TiO_2-nanoparticles have been supported on the KSF. The XRD patterns of titanium (Fig. 4) and nano-TiO_2@KSF (Fig. 5) indicate the diffraction peaks at 2θ = 26°, 36°-39°, 48° and 54° that confirmed translocation of Ti on KSF surface. Following our prior efforts in the design and click synthesis of heterocyclic compounds here, we introduce nano TiO_2@KSF as an efficient catalyst in preparation of *bis*coumarins under solvent-free condition in high yields and short reaction time with high purity.

In order to obtain the optimum reaction conditions in preparation of *bis*coumarins, the reaction of 2 mmol 4-hydroxycoumarin and 1mmol benzaldehyde was selected as a typical reaction and different conditions such as amount of catalyst, temperature of reaction and type of the solvent were studied. In Table 1, yield and time of the model reaction are investigated in the presence of 20 mg of nanoTiO_2@KSF in some solvents such as $CHCl_3$, H_2O, EtOH, also in solvent-free condition at different temperatures. According to Table 1 for entries 1-4 performing the model reaction *e.g.* at room temperature for solvents and solvent-free conditions led to the low yield of product. Increasing the temperature of reactions improved the yield and time

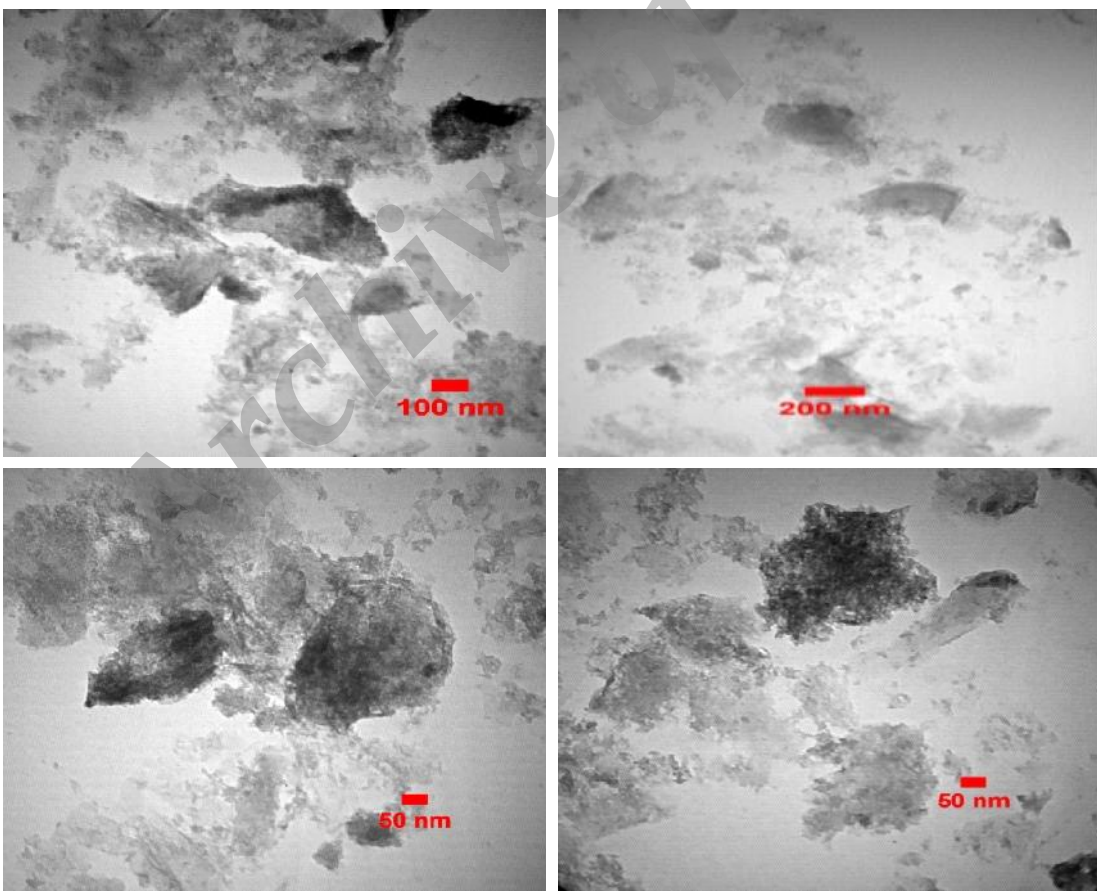

Fig. 3: Images of nano-TiO_2@KSF using electronic microscopic (TEM).

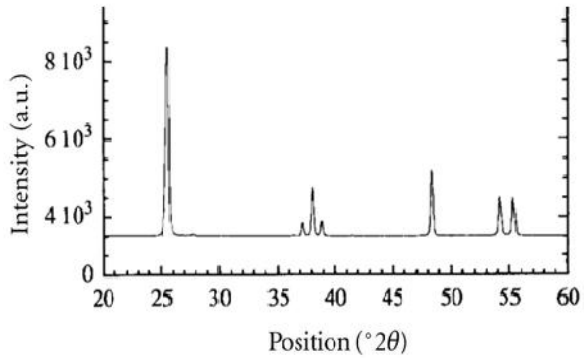

Fig. 4: X-ray diffraction spectrum of catalyst titanium

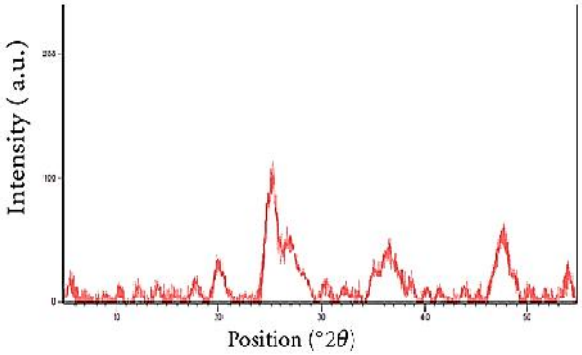

Fig. 5: X-ray diffraction spectrum of catalyst TiO_2@ KSF

Table 1: The results of using different promoter in solvent-free synthesis of 3a.

Entry	Solvent	Temperature (°C)	Time (min)	Yield %
1	$CHCl_3$	r.t.	50	25
		35	35	45
		reflux	20	60
2	H_2O	r.t.	35	25
		70	30	30
		reflux	20	55
3	EtOH	r.t.	35	60
		70	20	70
		reflux	20	85
4	solvent free	r.t.	35	60
		70	20	75
		100	10	98

of reaction. Moreover, under reflux condition the product obtained at high yield and short reaction time. However, entry 4 indicates that the highest yield and shorter reaction time could be obtained under solvent-free condition at 100 °C.

In addition, the amount of catalyst was investigated (Table 2). Entry 1 indicated that the model reaction was not completed in absence of catalyst even within 10 min. Entries 2-5 showed that, increasing the amount of catalyst from 5 to 20 mg significantly improved the yield of products. However, entry 7 indicates that the yield of product decreased by increasing the amount of catalyst from 25 to 30 mg.

In order to study the recyclability of catalyst, nanoTiO_2@KSF was separated from the reaction mixture and was washed with EtOH, dried in oven and reused. According to Table 3 the efficiency of nanoTiO_2@KSF almost remained constant even after three cycles. These results confirm that the nano-TiO_2@KSF is efficient and a reusable catalyst to synthesize some compounds such as *bis*coumarins 3a-j. These results prompted us to investigate preparation of various *bis*coumarins 3a-j under optimized reaction conditions. The three multi-component reactions (3MCRs) of two equivalent of 4-hydroxycoumarin and one equivalent of aromatic aldehydes 2a-j led to preparation of 3a-j in high yields and short reaction times (Table 4). According to Table 4 entries 1, 3 and 10, aldehydes bearing electron withdrawing substituent reacted in shorter reaction time. However, our results revealed that other entries withdrawing or electron releasing substituent had not shown any significant effect on the yield of products. The work-up procedure was rather simple e.g. catalyst was simply removed by addition of hot EtOH to the reaction mixture, filtering the catalyst and collecting a product by evaporation of EtOH.

In order to investigate the efficiency of TiO_2@KSF and optimize reaction condition, we compared our condition with some other reported catalysts for model reaction, 1 mmol 4-hydroxycoumarin with 2 mmol benzaldehyde (Table 5). As it is shown, our condition has the advantageous of shorter reaction time, comparable yield, low amount of catalyst and no use of solvent in comparison to other reported procedures.

Table 2: Effect of amount of TiO_2@KSF on the yield of compound 3a

Entry	Catalyst (mg)	Temperature (º C)	Time (min)	Yield %
1	0	100	10	-
2	5	100	10	55
3	10	100	10	70
4	15	100	10	85
5	20	100	10	98
6	25	100	10	98
7	30	100	10	90
8	20	110	10	98

Table 3: Recyclability of TiO_2@KSF in yield of compound 3a under optimized condition

Entry	Number of cycles	Yield %
1	1	95
2	2	95
3	3	94
4	4	88

Table 4: The reaction of 4-hydroxycoumarin 1 with aryl benzaldehyd 2a-j over TiO_2@KSF at solvent-free condition.

Comp. NO.	Aldehyde	Time (min)	Yield (%)	m.p. (˚C)	
				Found	Reported [ref]
3a	C_6H_5CHO	10	98	227-228	227-229 [11]
3b	3-OCH_3-C_6H_4CHO	15	93	235-236	238 [12]
3c	4-NO_2-C_6H_4CHO	8	98	233-235	230-232 [20]
3d	3-NO_2-C_6H_4CHO	12	95	260-262	258-260 [19]
3e	4-Cl-C_6H_4CHO	10	95	253-105	252-254 [11]
3f	2-Cl-C_6H4CHO	12	96	202-205	201-203 [13]
3g	4-$CH_3C_6H_4CHO$	15	94	249-50	251-253 [19]
3h	4-OH-C_6H_4CHO	15	95	223-225	224-226 [20]
3i	2-F-C_6H_4CHO	12	96	218-220	215-217 [17]
3j	2,4-di-Cl-C_6H_3CHO	8	97	200-203	200-202 [9]

Table 5: Comparison of our results for synthesis of *bis*coumarins with previously reported data

Entry	Catalyst (amount)	Amount of catalyst	Time (min)	Yield (%)	Condition	Reference
1	Phosphotungstic acid	20mol%	20	93	Water, 80 °C	[15]
2	SDS	20mol%	120	85	water, 60 ºC	[19]
3	I_2	25 mol%	17	50	water, reflux	[14]
4	$[TBA]_2[W_6O_{19}]$	0.15 g	5	91	EtOH, reflux	[33]
5	$RuCl_3 \cdot nH_2O$	5 mol%	25	84	water, 80 ºC	[11]
6	Cellulose sulfonic acid	0.02 g	120	90	water, reflux	[20]
7	$CoCl_2 \cdot 6H_2O$	10 mol%	2	92	H_2O:EtOH, 70 °C	[34]
8	TiO_2@KSF	20 mg	10	98	solvent free, 100 °C	this work

CONCLUSIONS

In conclusion, an efficient, simple, practical and easy set-up method to synthesize *bis*coumarins using nanoTiO_2@KSF under solvent free condition was reported. The products obtained in high yields as pure solid without further purification. Premade nano-TiO_2@KSF is an efficient catalyst for one-pot 3MCRs of *bis*coumarins 3a-j.

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