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Application of nano TiO_2@KSF as an efficient and reusable catalyst for the synthesis of pyrano-pyrimidines

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Abstract

In this work, Nano TiO_2@KSF was used as an efficient, heterogeneous and reusable catalyst for the synthesis of pyrano[2,3-*d*]-pyrimidinone derivatives via three-component reactions of malononitrile, barbituric acid and various aldehydes in water. The products were prepared in high yields within short reaction times. Also, this catalyst can be reused several times without loss of its catalytic activity. All of the products were characterized using melting point and several common techniques, including infrared spectra (FT-IR), and were compared with trusty references.

Keywords: TiO2@KSF; pyrano[2,3-d]-pyrimidinone; malononitrile; barbituric acid.

Introduction

During the past decade, multi-component reactions (MCRs) have been of considerable interest to organic chemists because the structure of complex molecules with various biological and pharmaceutical activities can easily be achieved from available starting materials. MCRs are cost-effective, time-efficient reactions, environmentally benign and economic [1,2]. The synthesis of pyrano[2,3-*d*]-pyrimidinone using multi-component reactions can be considered as a domain of carbonyl condensation chemistry.

The development of environmentally friendly catalysts and efficient methods for catalyst separation and recycling are the most important goals in the designing of catalysts. A convenient way to achieve these goals is the use of heterogeneous catalyst system for various organic reactions [3]. We have recently reported TiO_2@KSF as an effective heterogeneous acidic catalyst for the preparation of biscoumarin derivatives. Highly efficient catalyst activity, cost efficiency, ease of preparation, wide substrate scope, reusability and low toxicity are the major advantage of nano-TiO_2@KSF [4].

Pyrano-pyrimidinones as one of the most important derivatives of barbituric acid show significant biological and pharmaceutical activities including antitumor, antimalarial, antibacterial, antifungal, vasodilator, analgesic, sedative-hypnotic, bronchiodilator, anti parkinsonian and anti-allergic activities [5–8]. As well, these compounds are orderly structural subunits in several important natural products, including alkaloids, carbohydrates, pheromones,

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polyether antibiotics and iridoids [9,10].

There are various reports for the synthesis of pyrano-pyrimidinones including the use of *L*-proline [11], Zn[(*L*)proline]$_2$ [12], KAl(SO$_4$)$_2$.12H$_2$O [13], DBA [14], (NH$_4$)$_2$.HPO$_4$[15],[DABCO](SO$_3$H)$_2$(HSO$_4$)$_2$ [16], [BMIm]BF$_4$ [17], KBr/Electrolysis [18], and Succinimidinium hydrogensulfate ([H-Suc] HSO$_4$) [19]. Moreover, microwave irradiation methods were also used for the preparation of pyrano-pyrimidinones in the absence of catalyst [20].

Experimental

General

All of the aldehydes, malononitrile, and barbituric acids were purchased from Merck chemical company (Munich) and were used without further purification. Montmorillonite and titanium (IV) isopropoxide were purchased from Sigma-Aldrich (Mumbai). Melting points were recorded by capillary tubes on an electrothermal 9100 apparatus and are uncorrected. The FT-IR and IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. All yields refer to the isolated products and the known products were characterized by their physical constants and comparison to authentic samples.

General procedure for the preparation of TiO$_2$@KSF [4]

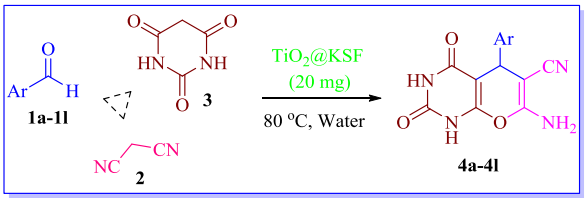
A mixture of montmorillonite (1.5 g), AcOH (9.37 mL) and titanium (IV) isopropoxide (5 mL) was stirred at r.t. Then, 106 mL deionized H$_2$O was added slowly to the mixture and after 30 minutes a clear solution was formed. The reaction mixture was stirred at 100 ºC until a gel formed. The mixture was filtered, washed with EtOH and dried at 80 ºC for 4 h to yield a gray powder.

General procedure for the preparation of pyrano-pyrimidinones

A mixture of the aromatic aldehyde (1 mmol), malononitrile (1 mmol), barbituric acid (1 mmol) and TiO$_2$@KSF (20 mg) in H$_2$O (3 mL) was stirred at 80 °C for the appropriate time. After completion of the reaction (monitored by TLC (*n*-hexane:etheylacetate; 3:2)) the mixture was cooled to r.t. and, then, the solvent was evaporated. Afterwards, the solid product was dissolved in EtOH (5 mL) and filtered to separate the catalyst.

Results and discussion

Here, and in continuation of our recent research group-efforts [21-26], we wish to report the synthesis of pyrano-pyrimidinones (**4a**-**4l**) using TiO$_2$@KSF. At first, in order to optimize the amount of the catalyst, temperature and solvent, the reaction of 4-boromobenzaldehyde (**1e**) with malononitrile (**2**) and barbituric acid (**3**) was studied in the presence of TiO$_2$@KSF at different conditions. The obtained results are tabulated in Table 1. After careful studies, optimum conditions were selected as shown in Scheme 1. It is noteworthy that higher amounts of TiO$_2$@KSF did not affect the reaction yield while slighter amounts of the catalyst led to the lower yields.



Scheme 1. Preparation of pyrano[2,3-*d*]-pyrimidinone derivatives catalyzed by TiO_2@KSF

After optimization of the reaction conditions and in order to generalize the efficiency of TiO_2@KSF in this reaction, various aromatic aldehydes (**1a-1l**) were reacted with malononitrile (**2**) and barbituric acid (**3**) under the best conditions to furnish the preparation of corresponding pyrano[2,3-*d*]pyrimidin-ones in short reaction times (25–45 min) with high yields (Table 2). As shown in Table 2, aldehydes containing electron-withdrawing or electron-donating substituent successfully reacted and afforded high yields of the pure products.

Table 1. Optimization of the reaction condition catalyzed by TiO_2@KSF

Entry	Catalyst (mg)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
1	20	Solvent-free	100	120	Trace
2	20	CH_3CN	Reflux	120	35
3	20	*n*-Hexan	Reflux	120	40
4	20	H_2O	Reflux	25	93
5	20	EtOH	Reflux	50	78
6	5	H_2O	Reflux	30	68
7	10	H_2O	Reflux	30	90
8	30	H_2O	Reflux	35	90
9	10	H_2O	50	40	87
10	10	H_2O	r.t.	120	Trace
11	20[b]	H_2O	Reflux	120	30
12	20[c]	H_2O	Reflux	120	Trace

[a]Isolated yields
[b]TiO_2 catalyst used
[c]KSF catalyst used

Table 2. Preparation of pyrano[2,3-*d*]-pyrimidinone in water [a, b]

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (ºC) [ref]
1	C_6H_4CHO	4a	30	89	220-222 [25]
2	4-ClC_6H_4CHO	4b	25	92	240-243 [25]
3	3-ClC_6H_4CHO	4c	30	90	241-242 [15]
4	2-ClC_6H_4CHO	4d	35	91	211-214 [26]
5	4-BrC_6H_4CHO	4e	25	93	228-230 [14]
6	4-FC_6H_4CHO	4f	25	92	264-266 [27]
7	4-$NO_2C_6H_4CHO$	4g	40	86	236-239 [27]
8	3-$NO_2C_6H_4CHO$	4h	40	85	264-266 [10]
9	4-OHC_6H_4CHO	4i	45	88	>300 [25]
10	3-OHC_6H_4CHO	4j	45	84	159-161 [27]
11	4-$OCH_3C_6H_4CHO$	4k	40	86	276-278 [26]
12	4-$NMe_2C_6H_4CHO$	4l	45	87	230-233 [17]

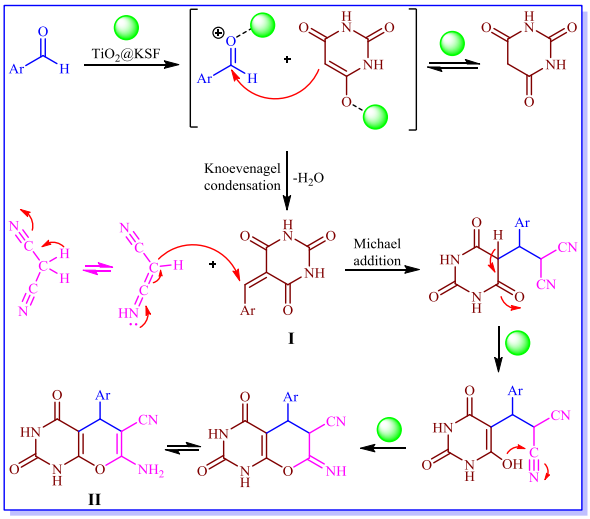
[a]The desired products were characterized by comparison of their IR spectra with those of the known compounds.
[b]Isolated yield.

A comparison of the catalytic efficiency of TiO_2@KSF in the synthesis of 7-amino-5-(4-bromophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (**4e**) with the other catalysts is shown in Table 3. This comparison indicates that our methods are better than some of the reported methods in terms of the reaction time, catalyst amount, reaction conditions and yield product.

Table 3. Compared efficiency of various catalysts in preparation of pyrano-pyrimidinones of 4 BrC_6H_4CHO

Entry	Catalyst	Conditions	Time (min)	Yield (%)[Ref.]
1	L-Proline	EtOH, r.t.	90	75 [10]
2	Tetrabutylammonium bromide	H_2O, reflux	30	95 [15]
3	$KAl(SO_4)_2.12H_2O$ (alum)	H_2O, 80 °C	40	91 [12]
4	SBA-Pr-SO_3H	Solvent-free, 140 °C	15	81 [18]
5	Zn[(L)proline]$_2$	EtOH, reflux	35	92 [11]
6	DBA	EtOH, reflux	83	87 [14]
7	TiO_2@KSF	Water, 80 °C	32	91 [this work]

In a proposed mechanism, the carbonyl group of the aldehyde is firstly activated by TiO_2@KSF.



Scheme 2. The reasonable mechanism in preparation of pyrano[2,3-*d*]pyrimidine

Next, the carbonyl group is attacked by barbituric acid and the related products (**I**) were formed. The subsequent addition of malononitrile to Knoevenagel compound (**I**) led to the acyclic intermediate which undergoes intramolecular cyclization to afford the products (**II**) (Scheme 2).

Finally, the reusability of the catalyst was investigated in the synthesis of 7-amino-5-(4-bromophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile under the optimized reaction conditions. After completion of the reactions, the catalyst was filtered and was washed with EtOH, dried and reused for the same reactions.

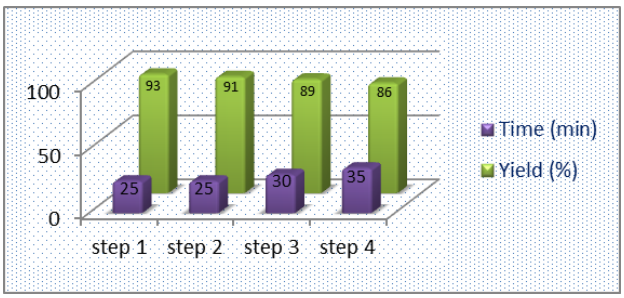


Figure 1. Reusability of TiO_2@KSF in the synthesis of pyrano[2,3-*d*]pyrimidine (**4e**)

This method was used at least for four runs with only slim reduction in the catalytic activity (Figure 1).

Conclusion

In summary, TiO_2@KSF was developed as a versatile and highly efficient catalyst for organic transformation reactions. Notably, it displayed a marked enhancement in catalytic activity for the preparation of pyrano[2,3-*d*]pyrimidinone (**4a-4l**) derivatives in presence of TiO_2@KSF. The target products were obtained under mild conditions and green method. Besides, it could be reused at least four times without an obvious decrease in catalytic performance. The notable advantages of our catalyst are high catalytic activity, generality

reaction profile, non-toxic nature, easy work-up procedure, short reaction times and excellent yields of products.

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