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Nano Al_2O_3: An efficient catalyst for the multi-component synthesis of Pyrano [2, 3-d] Pyrimidinone derivatives

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ABSTRACT

Pyrano [2,3-d] pyrimidinone derivatives have received considerable interest from the pharmaceutical industry due to their wide range of interesting biological and therapeutic properties. Nano Al_2O_3 was found to be a highly efficient solid acid catalyst for the preparation of pyrano [2,3-d] pyrimidinone derivatives from the reaction of barbituric acid, aryl aldehyde and malononitrile. Al_2O_3 nanoparticles with the average diameter of 15 nm were used four different contents of 10, 15, 20 and 25 mol%. Present methodology offers several advantages, such as high yields, short reaction time, simple procedure with an easy work-up and mild reaction conditions. The products were obtained in high yields under reflux in H_2O:EtOH (1:1). We believe this applicability of nano Al_2O_3 with mentioned advantages makes our method superior over all previous reported methods to the synthesis of pyrano [2,3-d] pyrimidinone derivatives. The structures of the products were characterized by their physical constants and comparison of their melting points with those of authentic samples.

Keywords: *Nano Al_2O_3; Barbituric acid; Aryl Aldehyde; Malononitrile; Catalyst.*

INTRODUCTION

Multi-component reactions (MCRs) have emerged as an efficient and powerful tools in modern synthetic organic chemistry. MCRs allow to chemists for reaction of several new bonds in a one-pot reaction. Strecker was the first chemist that used MCRs for the synthesis of amino acids [1]. In the past decade, there have occurred tremendous developments in MCRs and great efforts are continually being made to develop new MCRs [2-6]. One such multi-component reactions is the synthesis of pyrano [2, 3-d] pyrimidinones. Due to the diverse biological properties of this compound class, there is a widespread in their synthesis. Compounds with a pyrimidine moiety, have shown antibacterial, analgesic, antitumor and fungicidal activities [7-10].

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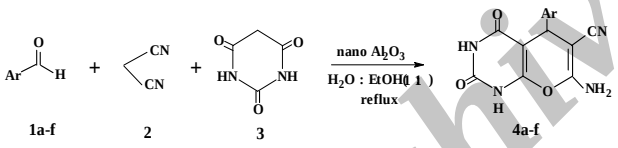
The pyran derivatives were also ubiquitous in agrochemicals such as diuretic and spasmolytic [11]. These heterocyles are used as cosmetics, pigments and photoactive materials [12, 13]. In view of different biological and chemical applications of pyranopyrimidinones, the developments of suitable synthetic methodologies for their generation have been a topic of great interest in recent times. Pyranopyrimidinone derivatives are generally synthesized via one-pot three-component reaction of an aryl aldehyde, malononitrile and barbituric acid in the presence of several catalysts such as diammonium hydrogen phosphate [14], L-proline [15], tetrabutylammonium bromide in water [16], electrocatalytic [17], DABCO [18] and ultrasound irradiation [19]. Also Mashkouri and Naimi-Jamal accomplished this reaction by use of mechanochemical solvent-free and catalyst-free conditions [20]. In continuation of our previous works on the applications of catalysts in the synthesis of heterocyclic compounds [21], in this article, we present a one-pot, three-component method for the preparation of pyrano [2, 3-d] pyrimidinone derivatives in the presence of nano Al_2O_3 under reflux in H_2O: EtOH (scheme 1).



Scheme. 1. Nano Al_2O_3 catalyzed for synthesis of pyrano[2,3-d]pyrimidinones

EXPERIMENTAL

All chemicals and solvents were purchased from Merck or Fluka and used as received 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 (500MHz) spectra were recorded on a Brucker-Ac-500 spectrometer. The purity determinations of the reaction monitoring were accompanied by thin layer chromatography (TLC) on silica gel polygram SILG-UV 254 plates.

Nano Al_2O_3 particles

Nano Al_2O_3 with average particle size of 15nm was used as received. The properties of nano Al_2O_3 particles are shown in Table 1.

Table 1. The properties of nano Al_2O_3.

Diameter (nm)	Surface Volume ratio (m^2/g)	Density	Purity (%)
15±3	165±12	<0.1	>99.9

General procedure for the synthesis of pyrano[2,3-d]pyrimidinones 4a-f

A solution of aromatic aldehyde 1a-h (1 mmol), malononitrile 2 (1.2 mmol), barbituric acid 3 (1 mmol) and nano Al_2O_3 (20 mol% based on barbituric acid) in H_2O (5 ml) and EtOH (5 ml) was heated on the oil bath under reflux for the time period as indicated in Table 2. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction 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 (10 ml) and the catalyst was separated. The filtrate was concentrated to give the solid product that washed with cold aqueous ethanol to obtain the pure products.

RESULTS AND DISCUSSION

To initiation our study, the reaction of benzaldehyde, malononitrile and barbituric acid was employed as a model reaction to examine the effect of various solvents Such as acetone, ethanol, methanol, chloroform and H_2O and varying amount of nano Al_2O_3 (10, 15, 20 and 25 mol%) as catalyst. In an optimized reaction conditions, a mixture of benzaldehyde (1 mmol), malononitrile (1.2 mmol) and barbituric acid (1mmol) in ethanol and H_2O (1:1) were heated in presence of nano Al_2O_3 (20 mmol) for 5 h. 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 (Table2).

Table 2. Synthesis of pyrano[2,3-d]pyrimidinones using nano Al_2O_3[a].

Entry	Ar	Product[b]	Time(h)	Yield(%)[c]	m.p.	
					Found	Reported
1	C_6H_5	4a	5	86	207-210	206-209[20]
2	3-$NO_2C_6H_4$	4b	5	89	266-268	255-257[20]
3	4-$NO_2C_6H_4$	4c	4	87	236-238	239-241[16]
4	2-Cl C_6H_4	4d	4	89	215-218	213-215[20]
5	4-Br C_6H_4	4e	5	87	228-230	230-231[16]
6	3-MeO C_6H_4	4f	4	85	233-235	232-234[17]

[a]1 mmol aromatic aldehyde, 1.2 mmol malononitrile, 1 mmol barbituric acid and 20 mol% nano Al_2O_3 in ethanol:H_2O under reflux. [b]The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures. [c]Isolated yields.

The use of acetone and chloroform using 20 mol% of the catalyst gave a low yield of the desired product. Ethanol, methanol and H_2O gave moderate to good yields under these conditions. However, the reaction in mixture of ethanol and H_2O with 20 mol% of catalyst afforded product 4a in 86% yields. Using more than 20 mol% of catalyst, has less effect of the yield and time of the reaction. Therefore, we selected mixture of ethanol and H_2O as solvent and 20 mol% of catalyst for this reaction. No desirable products could be detected in the absence of catalyst for 10 h, which indicated that the catalyst should be absolutely necessary for this reaction. Only a tract product was obtained in the solvent-free conditions in the presence of 20 mol% of the catalyst even at 120 º C.

To evaluate the generality of this model reaction we then prepared a range of pyrano [2, 3-d] pyrimidinone derivatives under the optimized reaction conditions. In all cases the type of aromatic aldehydes had no significant effect on the reaction. The results are summarized in Table 2. Benzaldehyde and other aromatic aldehydes containing electron-with drawing groups or electron-donating groups were employed which were found to react well to give the corresponding pyrano [2, 3-d] pyrimidinone derivatives in high yields.

CONCLUSIONS

In conclusion, we have successfully demonstrated a novel and important catalytic activity of nano Al_2O_3 as an inexpensive, effective and non-corrosive catalyst for the synthesis of pyrano [2, 3-d] pyrimidinones in high yields. In addition to its simplicity and mild reaction conditions, this method has the ability to tolerate a wide variety of substitutions in both components, which can afford different substituted pyrano [2, 3-d] pyrimidinones in high yields. The present practical method is a new candidate for synthetic chemists to apply for the synthesis of pyranopyrimidinones.

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