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Nano-cellulose-OSO_3H as a green and effective nano catalyst for one-pot synthesis of pyrano [2,3-*D*] pyrimidines

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A straightforward and efficient synthetic methodology has been developed for the preparation of biologically important pyrano [2,3-*d*] pyrimidines using nano-Cellulose-OSO_3H as a new catalyst. The reaction involves the use of barbituric acid, ethylcyanoacetate and aldehydes. A wide range of aldehydes is compatible in this reaction, producing excellent yields in short time. The morphology of nanocatalyst (nano-Cellulose-OSO_3H) was observed using a transmission electron microscopy (TEM). The Cellulose-OSO_3H surface was studied by energy dispersive X-ray spectroscopy (EDX) method to find out the chemical composition. Also, the vibrational spectrum analysis (FT-IR) of the catalyst has been performed.

Keywords: Pyranopyrimidines; Barbituric acid; Ethylcyanoacetate; Green chemistry; Nano-Cellulose-OSO_3H

INTRODUCTION

Recently, multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation [1]. These reactions are widely applied in pharmaceutical chemistry for producing different structures and combinatorial libraries for drug discovery. One such reaction, is the synthesis of Pyrano[2,3-*d*]pyrimidines. Pyrimidine is a core section in many biological systems because they generally show pharmacological properties such as antibacterial, antitumor and analgesic activities [2-4].

In recent years, there has been growing interest in finding inexpensive and effective solid acid nano catalyst such as nanocrystalline TiO_2-$HClO_4$ [5], nano-$TiCl_4.SiO_2$ [6-9], nano-$SnCl_4.SiO_2$ [10,11], nano-$BF_3.SiO_2$ [12-15], $HClO_4$-SiO_2 nanoparticles [16,17], nano-Cellulose-OSO_3H [18], nano silica sulfuric acid [19-22] and $SbCl_5/SiO_2$ nanoparticles [23, 24]. Cellulose is one of the most abundant biopolymers on the earth used in various industries such as packaging and automobile manufactures and many other applications such as biomedical and chemistry [25]. Cellulose sulfuric acid, as a bio-supported and recyclable solid acid catalyst, has been applied for in various organic transformations such as the synthesis of α-amino nitriles [26], 4-aryl-1,4-dihydropyridines [27], 5-hydroxymethylfurfural and 5-ethoxymethylfurfural [28], 3,4-dihydropyrimidinones/thiones [29] and quinoxaline derivatives [30]. New technologies are making it possible to produce nano cellulose from wood [31], cotton [32], wheat straw [33] and bacteria [34].

Nano cellulose has different attractive properties including high strength and stiffness, low weight and biodegradability that can be used as a potential adsorbent [35].

In this study, the cellulose has been used as adsorbent for the preparation of nano-Cellulose-OSO_3H whose average size is small and is well distributed. The presence of new functional groups on the surface of Cellulose-OSO_3H resulted in a dramatic increase of surface polarity and acidity, thereby improving the catalytic efficiency of the nano-Cellulose-OSO_3H.

In continuation of our previous research on the use of solid acids in organic synthesis [14-23], the nano-Cellulose-OSO_3H as a catalyst has been applied for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives.

RESULTS AND DISCUSSION

Following the previous report about the application of solid acids in organic synthesis, in this work, we studied the application of cellulose as a green, cheap and available surface to synthesis of solid acid nano catalyst. In this study, cellulose-OSO_3H nanoparticles were prepared and characterized. The catalytic activity of nanoparticles was investigated for synthesis of pyrano [2,3-*d*] pyrimidines derivatives, by the condensation of a aldehyde **1a-j**, ethylcyanoacetate **2** and barbituric acid **3** (Scheme 1).

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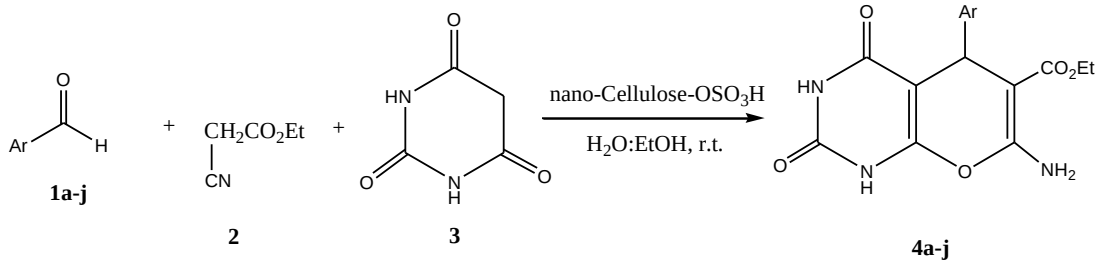


Scheme 1. Synthesis of pyrano [2,3-*d*] pyrimidines derivatives in the presence of nano-Cellulose-OSO_3H as catalyst

The morphology and size of cellulose-OSO_3H was observed by TEM images. As shown in Figure 1, the size of nano-Cellulose-OSO_3H is below 100 nm. The results of EDX analyses of the cellulose and cellulose-OSO_3H are given in the following figure and table.

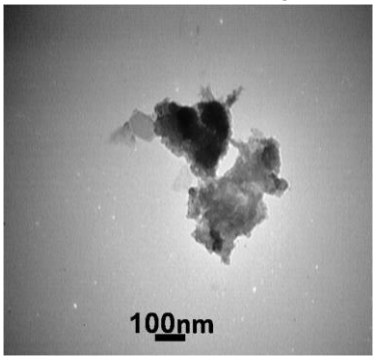


Fig. 1. TEM micrograph of nano-Cellulose-OSO_3H

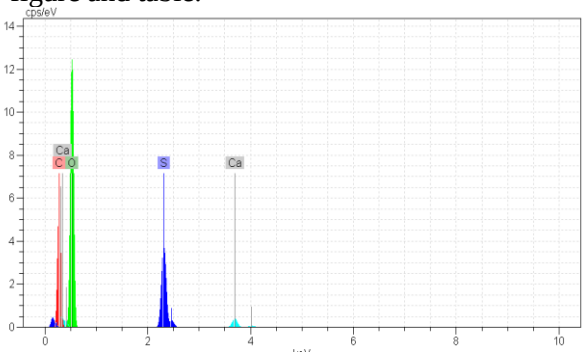


Fig. 2. EDX of nano-Cellulose-OSO_3H

Table 1. Chemical analysis of nano-cellulose and nano-cellulose-OSO_3H

	Nano-Cellulose	Nano-Cellulose -OSO_3H
Element	W%	W%
C	69.20	25.58
O	22.84	66.10
S	-	6.87

In FTIR spectrum of nano-cellulose-OSO_3H (Fig. 3), the hydroxyl bands of cellulose and sulfonic acid appeared at 3428 cm^{-1}. The C-H stretching vibrations of the aliphatic systems for cellulose were observed at 2907 cm^{-1}. The O–H bending of the adsorbed water was observed at 1613 and 1637 cm^{-1}.The symmetric and asymmetric O=S=O stretching vibrations appeared at 1119 and 1378 cm^{-1}. The bridge asymmetric C-O-C stretching vibrations were observed within the range of 1000-1150 cm^{-1}. The S-O stretching vibrations were observed within the range 616-661 cm^{-1}.

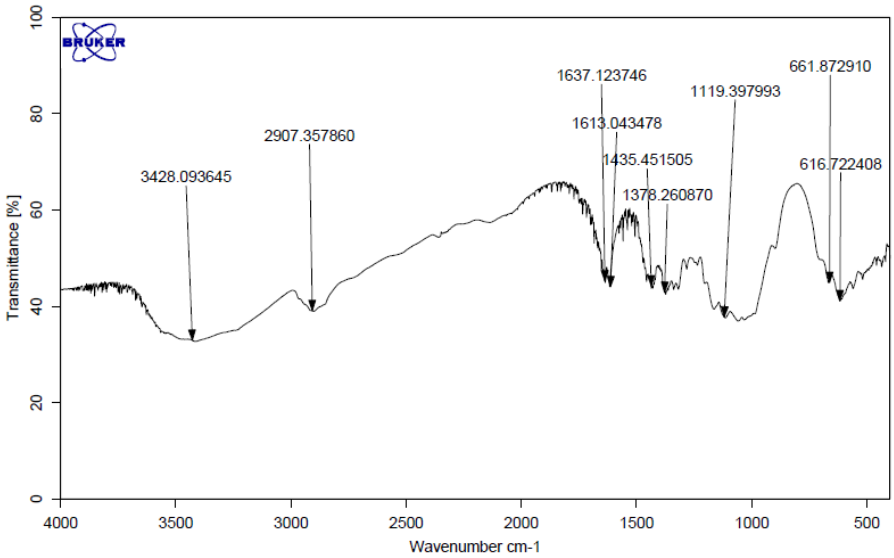


Fig. 3. FT IR spectrum of nano-cellulose-OSO_3H.

In order to determine the optimum quantity of nano-Cellulose-OSO_3H, the reaction of barbituric acid, ethylcyanoacetate and benzaldehyde was carried out at room temperature in H_2O:EtOH using different quantities of nano-Cellulose-OSO_3H. As shown in Table 2, 0.008 g of nano-Cellulose-OSO_3H gives an excellent yield in 45 min.

Table 2. Optimization of the reaction conditions for synthesis of 4a

Entry	Catalyst (amount)	Solvent/Condition	Time(min)	Yield
1	Nano-Cellulose-OSO_3H (0.008 g)	CH_2Cl_2/r.t	45	Trace
2	Nano-Cellulose-OSO_3H (0.008 g)	H_2O:EtOH/ r.t	45	92
3	Nano-Cellulose-OSO_3H (0.008 g)	CH_3CN/ r.t	45	42
4	Nano-Cellulose-OSO_3H (0.008 g)	DMF/ r.t	45	47
5	Nano-Cellulose-OSO_3H (0.008 g)	H_2O/ r.t	45	85
6	Nano-Cellulose-OSO_3H (0.006 g)	H_2O:EtOH/ r.t	45	74
7	Nano-Cellulose-OSO_3H (0.01 g)	H_2O:EtOH/ r.t	45	94
8	Nano-Cellulose-OSO_3H (0.008 g) 2^{nd} run	H_2O:EtOH/ r.t	45	89
9	Nano-Cellulose-OSO_3H (0.008 g) 3^{rd} run	H_2O:EtOH/ r.t	45	86
10	Nano-Cellulose (0.008 g)	H_2O:EtOH/ r.t	45	Trace
11	Cellulose (0.008 g)	H_2O:EtOH/ r.t	45	Trace

To study the scope of the reaction, a series of aldehydes with barbituric acid and ethylcyanoacetate were examined by nano-Cellulose-OSO_3H as catalyst. The results are shown in Table 3. In all cases, aromatic aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and formed products in approving yield.

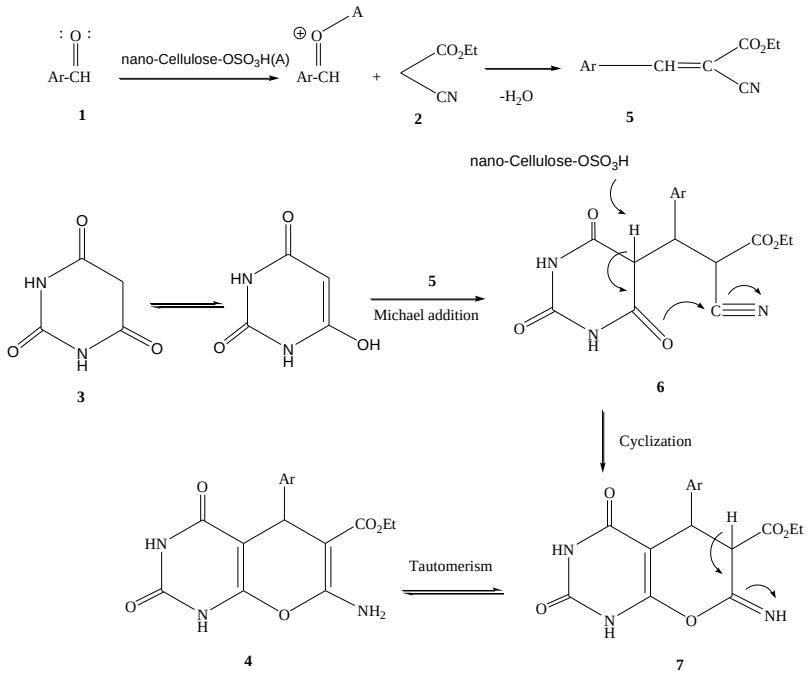
Table 3. Synthesis of pyrano [2,3-*d*] pyrimidines[a]

Entry	Ar	Product	Time(min)	Yield[b]	M.P.(˚C) Ref.[c]
1	C_6H_5	4a	45	92	206-208(206-210) [36]
2	3-Cl-C_6H_4	4b	45	86	282-284(283-284) [37]
3	4-Cl-C_6H_4	4c	40	88	297-299(>300) [37]
4	3-NO_2-C_6H_4	4d	40	91	262-264(237-240) [36]
5	4-NO_2-C_6H_4	4e	40	92	290-292(289-293) [36]
6	4-CH_3-C_6H_4	4f	50	89	295-298(296-298) [36]
7	4-CH_3O-C_6H_4	4g	50	89	293-295(297-298) [38]
8	3,4-CH_3O-C_6H_3	4h	55	91	>300 (303-306) [36]
9	3-OH-C_6H_4	4i	40	92	172-174(170-174) [36]
10	4-OH-C_6H_4	4j	40	93	169-170(163-167) [36]

[a]ratio of aldehyde (mmol): barbituric acid (mmol): ethylcyanoacetate (mmol): catalyst (g) is 1:1:1:0.008. [b]Isolated yield. [c]All products are known and were identified by their melting points, IR and ^1H, ^{13}C NMR spectra.

With the above-mentioned results in hand, a plausible mechanism of this reaction was proposed in Scheme 2. The initiation step of this chain process was begun with the interaction of aldehyde **1** and nano-Cellulose-OSO_3H as a solid acid catalyst. The subsequent step was Knoevenagel condensation between the activated aldehyde and ethylcyanoacetate **2** to form intermediate **5**. Then the Michael addition of barbituric acid **3** to intermediate **5** would furnish intermediate **6**. Finally, the product **4** was obtained by an intramolecular cyclization and tautomerism.

Recently some catalysts such as DABCO [36], $CaCl_2$ [37] and Glycerol [38] have been applied for the pyrano[2,3-*d*]pyrimidine synthesis. Although many of the reported methods are effective, but, some of them suffer from disadvantages such as harsh reaction conditions, long reaction times, complex working and purification procedures, long volume of catalyst loading and moderate yields. Therefore, the development of a simple, mild and efficient method is still needed. In order to establish better catalytic activity of nano-Cellulose-OSO_3H, the synthesis of pyrano [2,3-*d*] pyrimidine derivatives was compared with other catalysts reported in literature [36-38]. As shown in Table 4, synthesis of these compounds catalyzed by nano-Cellulose-OSO_3H in H_2O:EtOH offers production of the corresponding products in shorter time, much efficient yield and milder condition is done, while other methods require more amount of catalyst or longer reaction time for synthesis of pyrano [2,3-*d*] pyrimidines.



Scheme 2. Plausible mechanism for the formation of pyrano [2,3-*d*] pyrimidine derivatives.

Table 4. Comparison of nano-Cellulose-OSO$_3$H and various catalyst in the synthesis of pyrano [2,3-*d*] pyrimidine derivatives.

Entry	Catalyst	Solvent	Condition	Time (min)	Yield[a]	Ref.
1	DABCO, 10 mol%	H_2O:EtOH	r.t	30-40	82-94	[36]
2	$CaCl_2$, 20 mol%	EtOH	US	10	90-93	[37]
3	$CaCl_2$, 20 mol%	EtOH	r.t	120-170	90-92	[37]
4	Glycerol, 1 mL	-	80 °C	100-150	90-92	[38]
5	nano-Cellulose-OSO$_3$H	H_2O:EtOH	r.t	40-55	86-93	This work

[a]Isolated yield

The present investigation shows that nano-Cellulose-OSO$_3$H a capable nanocatalyst to be used for pyrano[2,3-*d*]pyrimidine synthesis via one-pot reaction of aldehydes, ethylcyanoacetate and barbituric acid. Nano-Cellulose-OSO$_3$H was successfully prepared and characterized using EDX, FT-IR and TEM. Prominent among the advantages of this method are such as shorter reaction times, simple work-up, affords excellent yield, and re-usable for a number of times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^{1}H NMR spectra were recorded on Bruker DRX-300 Avance spectrometer at solution in DMSO-d_6 using TMS as internal standard. The morphologies of the nanoparticles were observed using TEM of Philips CM10. The EDX analysis was done using a SAMx-analyser. The chemicals for this work were purchased from Fluka and were used without further purification.

SYNTHESIS OF NANO-CELLULOSE-OSO$_3$H

The nano-cellulose-OSO$_3$H was prepared according to the following procedure: To a magnetically stirred mixture of nano-cellulose (1 g) in n-hexane (10 ml), chlorosulfonic acid (0.4 ml) was added dropwise at 0°C during 20 min. N-hegxane was adopted as a nonpolar solvent to prevent active OH-group nanocelloluse.

After addition was complete, the mixture was stirred for 2h at room temperature until HCl was removed from reaction vessel. Then the mixture was filtered and the collected solid washed with 30 ml of methanol and dried at room temperature to afford ashy powder of nano cellulose sulfuric acid

GENERAL PROCEDURE FOR THE PREPARATION OF COMPOUNDS 4A-J

Nano-Cellulose-OSO_3H (0.008g) was added to a stirred mixture of the aromatic aldehyde (1 mmol), ethylcyanoacetate (1 mmol) and barbituric acid (1 mmol) in EtOH:H_2O (5 mL). The materials were mixed at room temperature for the appropriate time. The progress of the reaction was followed by TLC (*n*-hexane:ethyl acetate 3:1). After completion of the reaction, the mixture was filtered to remove the catalyst. After evaporation of the solvent, the crude product was re-crystallized from hot ethanol to obtain the pure compound. Spectral data of products are listed below:

Selected spectrul data:

*Ethyl 7-amino-5-(3-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4b**)*: IR (KBr, cm^{-1}): 3376, 3343, 3192, 1727; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.73 (s, 1H), 6.99 (s, 2H, ArH), 7.11-7.25 (m, 2H, ArH), 7.21 (s, 2H, NH_2), 9.10 (br s, 1H, NH), 11.17 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.7, 52.8, 76.9, 78.8, 124.8, 125.2, 127.9, 129.6, 133.5, 137.4, 143.0, 150.2, 160.1, 160.3, 163.2, 165.4 ppm.

*Ethyl 7-amino-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4e**)*: IR (KBr, cm^{-1}): 3422, 3374, 3106, 1730; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 4.92 (s, 1H), 7.26 (s, 2H, NH_2), 7.32 (m, 2H, ArH), 8.09 (m, 2H, ArH), 9.67 (s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.2, 61.7, 79.5, 121.0, 128.0, 130.1, 131.2, 145.4, 148.3, 150.5, 160.3, 162.3, 163.8, 167.2 ppm.

*Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4g**)*: IR (KBr, cm^{-1}): 3413, 3389, 3106, 1732; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 3.32 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2), 4.41 (s, 1H), 6.93 (m, 2H, ArH), 7.65 (m, 2H, ArH), 9.07 (br s, 2H, NH_2), 10.03 (s, 1H, NH), 11.09 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.0, 37.2, 55.8, 75.6, 114.2, 126.0, 128.4, 130.1, 134.2, 143.9, 150.5, 157.2, 162.4, 167.3 ppm.

*Ethyl 7-amino-5-(3-hydroxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4i**)*: IR (KBr, cm^{-1}): 3493, 3337, 3106, 1723; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.6 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.10 (s, 1H), 6.56 (s, 2H, NH_2), 6.59 (m, 1H, ArH), 7.04-7.10 (m, 3H, ArH), 9.33 (br s, 1H, OH), 11.1 (s, 1H, NH), 12.1 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6, 59.9, 89.5, 114.7, 114.9, 118.8, 120.1, 127.4, 128.0, 130.1, 146.5, 150.4, 153.1, 158.1, 158.5, 163.3 ppm.

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