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Zirconia Sulfuric Acid: An Efficient Heterogeneous Catalyst for the One-Pot Synthesis of 3,4-Dihydropyrimidinones Under Solvent-Free Conditions

Maliheh M. Hosseini[1] · Eskandar Kolvari[1] · Nadiya Koukabi[1] · Maryam Ziyaei[1] · Mohammad Ali Zolfigol[2]

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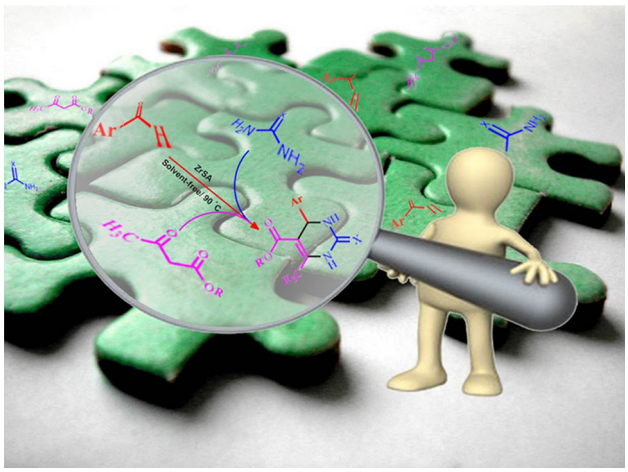
Abstract In this article, zirconia sulfuric acid (ZrSA) has been synthesized from the reaction of ZrO_2 with chlorosulfonic acid. It was characterized by (FT-IR, XRD, TGA, SEM, EDS, BET, BJH, ICP and pH analysis). This catalyst was employed for the synthesis of 3,4-dihydropyrimidinones via cyclocondensation of β-ketoester, aromatic aldehydes and urea/thiourea under solvent-free conditions. Main advantages of the catalyst were non toxic nature, high stability and reusability.

Graphical Abstract



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✉ Eskandar Kolvari
kolvari@semnan.ac.ir

Mohammad Ali Zolfigol
zolfi@basu.ac.ir

[1] Department of Chemistry, Semnan University, Semnan, Iran

[2] Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran

Keywords Zirconia sulfuric acid · Solid acid catalyst · Biginelli · 3,4-Dihydropyrimidinones · Recyclability

1 Introduction

Acid-catalyzed reactions are overwhelming favorite topics in terms of widespread applications in the chemical industry. Conventional liquid inorganic acids including H_2SO_4, HCl and H_3PO_4 are part of the homogeneous acid catalysts. Despite their usage in the large-scale production of industrial chemicals, they suffer from several disadvantages such as high toxicity, corrosive nature, hazards in handling and difficult separation from the products. These disadvantages are far from the concept of "Green Chemistry". In this respect, in order to solve or minimize drawbacks of these catalysts, replacement of them by novel, nontoxic, eco-friendly, recyclable heterogeneous catalysts with improved efficiency have been the subject of intensive investigation during the past decade. Heterogeneous catalysts play crucial role in aspects of environmental and economic in many industrial activities. They offer some advantages including high reactivity, operational simplicity, low toxicity, non-corrosive nature and the potential of the catalyst to be recyclable. Additionally, most of the heterogeneous catalysts show higher "target" product selectivity, so that waste production can be avoided [1–4]. Immobilizing of homogenous precursors on a solid support is one of the important routes for developing novel heterogeneous catalysts [5, 6].

Currently, the commonly used support for heterogeneous catalysts are polymers [7], mesoporous materials [8], zeolites [9], active carbon [10], ion-exchange resins [11] and metal oxides [12]. Metal oxides such as ZrO_2 with high surface area, mechanical strength and thermal stability

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have attracted attention as promising support materials. Zirconia (ZrO_2) is one of the most important ceramic materials that are widely used in chemical industry due to their unique electrical, mechanical, optical and thermal properties [13–16]. Hence, there has been an intensified focus towards new heterogeneous catalysts for multicomponent reactions that would reinforce environmental benefits.

Synthesis of 3,4-dihydropyrimidin-2(1H)-one (DHPMs) are important for therapeutic and pharmacological properties [17–20]. The Biginelli reaction which was reported for the first time by the Italian chemist Pietro Biginelli in 1891 [21], is an easy and useful multicomponent reaction (MCR) for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs). The reaction is accomplished from one-pot condensation of β-dicarbonyl compound, aldehyde and urea or (thiourea) in the presence of various catalyst such as Bronsted acids [22], Lewis acids [23], heteropolyacids [24] and nanocatalysts [25]. The improvement of the reaction catalyst has received much attention in recent years.

Growing concern about environmental damage leads to an urgent requirement for the development of ecofriendly technology and economic processes. In this regard, here in, we report preparation of ZrO_2–SO_3H as newly acid catalyst for the facile synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (DHPM) under solvent-free conditions.

2 Experimental Section

2.1 General Remarks

All reagents were purchased from Merck and Aldrich and used without further purification. Zirconium oxide (ZrO_2) was purchased from Aldrich. Fourier transform infrared spectroscopy (FT-IR) was recorded on a Shimadzu 8400 s spectrometer using KBr pressed powder discs. The TGA curve of catalyst was recorded by using a thermogravimetric analyzer on a Du Pont 2000 thermal analysis apparatus at heating rate of 5 °C min^{-1} under air atmosphere over the temperature range of 25–800 °C. X-ray diffraction (XRD) patterns of samples were taken on a Siemens D5000 (Siemens AG, Munich, Germany) X-ray diffractometer using Cu-Kα radiation of wave-length 1.54 Å. Scanning electron Microscopy, SEM-EDX, analysis was performed using Tescanvega II XMU Digital Scanning Microscope. BET surface areas were acquired on a Beckman Coulter SA3100 surface area analyzer. The loading value of sulfur in the catalyst was estimated by inductively coupled plasma ICP analysis with an ICP MS ELAN DRC-e. Products were characterized by spectroscopy data (FTIR, 1H NMR and 13C NMR spectra) and melting points. NMR spectra were recorded on a Bruker Avance 300 MHz instruments (1H NMR 300 MHz) in pure deuteriated chloroform and dimethyl sulfoxide with tetramethylsilane (TMS) as the internal standard. Melting points were recorded on a THERMO SCIENTIFIC 9100 apparatus. All reactions were monitored by TLC and all yields refer to isolated products.

2.2 Preparation of ZrO_2–SO_3H (ZrSA)

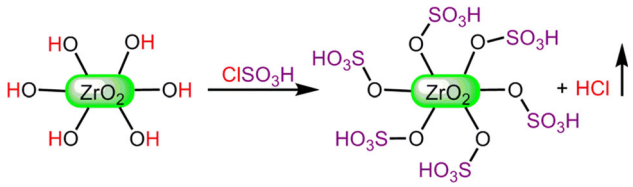
A suction flask equipped with a constant-pressure dropping funnel and a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water) was used. It was charged with ZrO_2 (1 g, 12.5 mmol) and dry CH_2Cl_2 (20 ml). Then chlorosulfonic acid (0.25 ml, 3.76 mmol) was added dropwisely over a period of 30 min in an ice bath (0 °C). HCl gas immediately evolved from the reaction vessel. The mixing was continued over one hour to evaluation of HCl was seized. Then, the CH_2Cl_2 was removed under reduced pressure and the solid powder was washed with water (10 ml) and dried at 100 °C. The prepared ZrSA stored in vacuum desiccator over anhydrous silica gel, then, was dried in 100 °C for 6 h.

2.3 General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones

A mixture of aromatic aldehyde (1 mmol), β-dicarbonyl compounds (1 mmol), and urea (or thiourea) (1.5 mmol) was stirred at 90 °C utilizing ZrSA (0.05 g, 15 wt%) for the appropriate time in solvent free condition until the reaction was complete. The reaction was monitored by thin layer chromatography (TLC) [7:3 hexane:ethyl acetate]. After the completion of the reaction the resulting mixture was cooled, eluted with hot ethanol (5 ml), centrifuged and filtrated to collect the formed precipitate. The crude product was recrystallized from ethanol to yield pure 3,4-dihydopyrimidin-2(1H)-ones derivatives.

3 Results and Discussion

Herein, we report the synthesis of zirconia sulfuric acid (ZrSA) and discuss its performance as a novel solid acid catalyst as a part of our ongoing investigation in developing new and efficient heterogeneous solid acid catalysts [26–28]. This catalyst was prepared by the reaction of ZrO_2 with chlorosulfonic acid at room temperature (Scheme 1). The loading process proceeded cleanly and HCl evolved from the reaction vessel immediately as the only by-product. The synthesized catalyst was characterized by IR, XRD, TGA, SEM, EDS, BET, BJH, ICP and acid–base titration.



Scheme 1 Schematic representation of the synthesis of zirconia sulfuric acid (ZrSA)

3.1 Catalyst Characterization

3.1.1 PH Analysis of Catalyst

The amounts of sulfonic acid groups on ZrSA were determined by acid–base potentiometric titration of the aqueous suspension of the washed catalyst with standard NaOH solution. For this purpose 100 mg ZrSA was dispersed in 20 ml H_2O by ultrasonic bath for 60 min. The amount of the acid was neutralized by addition of standard NaOH solution (0.1 N) to the equivalence point of titration. The required volume of NaOH to this point was 2.89 ml. The optimum concentration of H^+ sites was 2.89 mmol/g of catalyst (values calculated by the weight of ZeSA) at 25 °C. The value of H^+ per gram of acid corresponds to ratio of mmol of chlorosulfonic acid to total mass of ZrSA.

3.1.2 FT-IR Spectra

Figure 1 shows the FT-IR results of ZrO_2 particles with and without SO_3H loading, respectively. For the bare ZrO_2 (Fig. 1a), the vibration band at 746 and 588 cm^{-1} are the typical IR absorbance induced by structure Zr–O vibration. The vibration band at around 1616 cm^{-1} is due to Zr–OH vibration and the absorbance band at around 3431 cm^{-1} was certified to the adsorbed water which is consistent with the reported IR spectra for ZrO_2 [29]. In the case of ZrSA (Fig. 1b), some new bands appeared at 1338, 1286, 1172, 1072, 1006, 891 and 852 cm^{-1}, which are attributed to the O=S=O asymmetric and symmetric stretching vibration and S–O stretching vibration of the sulfonic groups (–SO_3H), respectively [27]. The spectrum also shows a relatively broad band around 2700–3600 cm^{-1} due to OH stretching absorption of the SO_3H group. All these observations confirm that the sulfonic groups have functionalized the surface of the ZrO_2.

3.1.3 X-ray Diffraction (XRD) Analysis

The powder XRD patterns of ZrO_2 and ZrSA are shown in Fig. 2. It seems that the peak intensities of ZrO_2 and ArSA are almost same and the peaks remained intact under the conditions used for modification. These results indicate that mesoporosity of the support remains intact after modification.

3.1.4 Thermo Gravimetric Analysis (TGA)

Thermo gravimetric analysis (TGA) of ZrSA in comparison with ZrO_2 is shown in Fig. 3. The TGA curve of ZrO_2 (Fig. 3a) reveals an initial weight loss, occurring below 200 °C, quite likely due to the removal of adsorbed water. The second weight loss occurring in the range 180–800 °C, is attributed to the dehydroxylation of ZrO_2.

As shown in Fig. 3b the TGA of ZrSA shows two-stage decomposition. The weight loss below 200 °C is related to the loss of adsorbed solvent or trapped water from the catalyst and a mass loss of weight occurred between 590 and 700 °C that is related to the sudden mass loss of SO_3H groups [30–32]. From the evaluation of the weight loss in the mentioned temperature range, it can be understood that ZrSA has a great thermal stability (up 160 °C) confirming that it could be safely used in organic reactions at temperatures in the range of 80–150 °C.

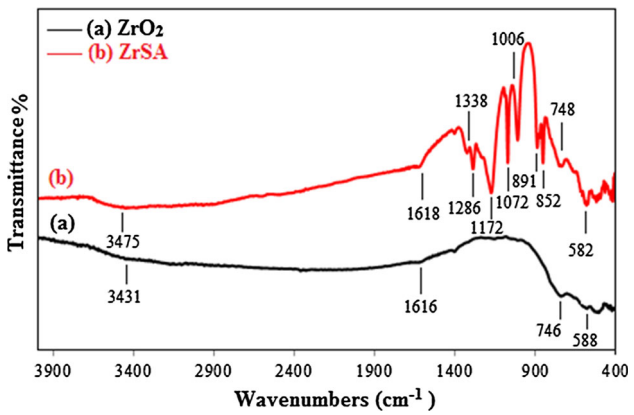


Fig. 1 FT-IR spectra of **a** ZrO_2, **b** ZrSA

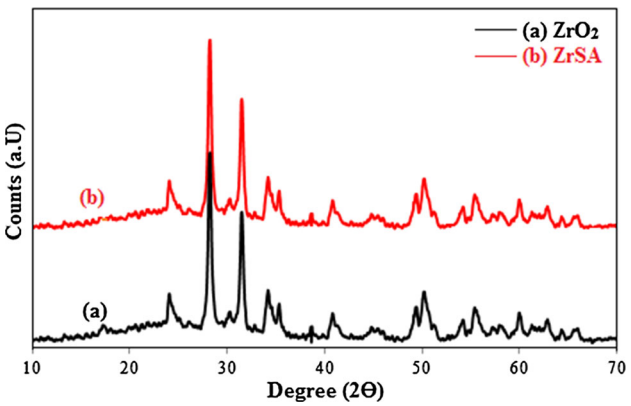


Fig. 2 Powder XRD patterns of (*a*) ZrO_2 (*b*) ZrSA

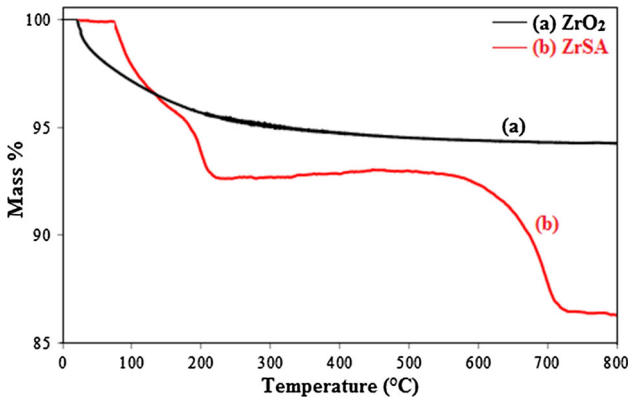


Fig. 3 TGA weight loss curves of (*a*) ZrO_2 (*b*) ZrSA

3.1.5 FESEM-EDS Analysis

The surface features and elementary composition of ZrO_2 and ZrSA were examined with FESEM and EDS, as shown in Fig. 4. EDS spectrum of ZrSA (Fig. 4b) reveals the appearance of sulfur and excess oxygen elements that reconfirm the formation of SO_3H groups after modification of ZrO_2 (Fig. 4d) by sulfunation agent.

FESEM spectrum shows that the pure ZrO_2 (Fig. 4a) has been composed of the micron-size sphere particles. According to the FESEM image of the modified material (Fig. 4c), it was found that there is no clear change in the morphology of the obtained modified material. The material is still sphere structure and the particles sizes were smaller than that for pure material.

3.1.6 BET and BJH Texture Analysis

The BET surface area and pore volume and Pore width were calculated using the Brunauer–Emmett–Teller (BET) and BJH equations. BET surface areas were acquired on a Beckman Coulter SA3100 Surface Area Analyzer. Prior to N_2-physical adsorption measurements, the samples were degassed at 150 °C for 120 min in the nitrogen atmosphere. The specific surface area (SBET) of the obtained materials was determined with adsorption–desorption isotherms of N_2 at 77 K. The surface area, pore volumes, pore width and pore diameter size of the material are summarized in Table 1.

The decrease in the surface of the ZrSA proved the presence of $–SO_3H$ as acidic groups on the surface of the solid catalyst (Table 1). It can be concluded that the sulfonation of ZrO_2 has taken place, because the physical adsorption of nitrogen gas after functionalization using chlorosulfonic acid was decreased. Also, Table 2 shows the textural properties of ZrO_2 and ZrSA.

3.2 Catalytic Performances in Multicomponent One-Pot Synthesis of Dihydropyrimidinone Derivatives

After characterization, catalytic activity of the catalyst was examined in multicomponent reactions for the synthesis of dihydropyrimidinone derivatives. The structures of the final products were well characterized by using spectral (IR, 1H NMR) data.

Dihydropyrimidinone was prepared by the reaction of aromatic aldehyde, β-dicarbonyl compound and urea or (thiourea) with 15 wt% of ZrSA at 90 °C under solvent-free conditions (Scheme 2).

In order to optimize the reaction conditions with respect to catalytic efficiency of ZrSA and to examine the effect of solvent and temperature on the reaction yield, initially a model study was carried out on the synthesis of dihydropyrimidinone by the condensation of benzaldehyde (1 mmol), methyl acetoacetate (1 mmol) and urea (1.5 mmol) in different sets of reaction conditions. In preliminary experiment, to minimize the formation of byproducts and to achieve good yield of the desired product, the reaction is optimized by varying the amount of catalyst (5, 10, 15 and 20 mol%). The percentage of the product formation using ZrSA as the catalyst was found 69, 77, 97 and 89 %, respectively (Table 3, entries 2–5). Therefore, it was found that the use of 15 mol% of the catalyst was sufficient to promote the reaction. Larger amounts of the catalyst were found to have an inhibitory effect on the formation of the product. The results show clearly that catalyst is effective for this transformation and in the absence of it, the reaction did not take place even after higher reaction time (Table 3, entry 1).

The effect of temperature was studied by carrying out the model reaction at different temperatures (50, 70, 90 and 110 °C) in the presence of 15 mol% of ZrSA under solvent-free condition and the best results were obtained at 90 °C (Table 3, entries 4, 6–8). This reaction was also carried out in various solvents, with ZrSA (15 wt %) as a catalyst. The reaction could be carried out in refluxing EtOH, H_2O and MeOH as solvents and gave product in moderate yield (Table 3, entries 9–11). It was very surprising that the reaction proceeded in excellent yields (97 %) under solvent-free condition (Table 3, entry 4). Therefore, the solvent-free condition was used for the synthesis of dihydropyrimidinones derivatives.

To establish the generality and applicability of this method, a series of aromatic aldehydes with the electron-donating and electronwithdrawing substituent were reacted with methyl or (ethyl) acetoacetate and urea or (tiourea) under the optimized conditions. The results are presented in Table 4. Aromatic aldehydes containing both electron

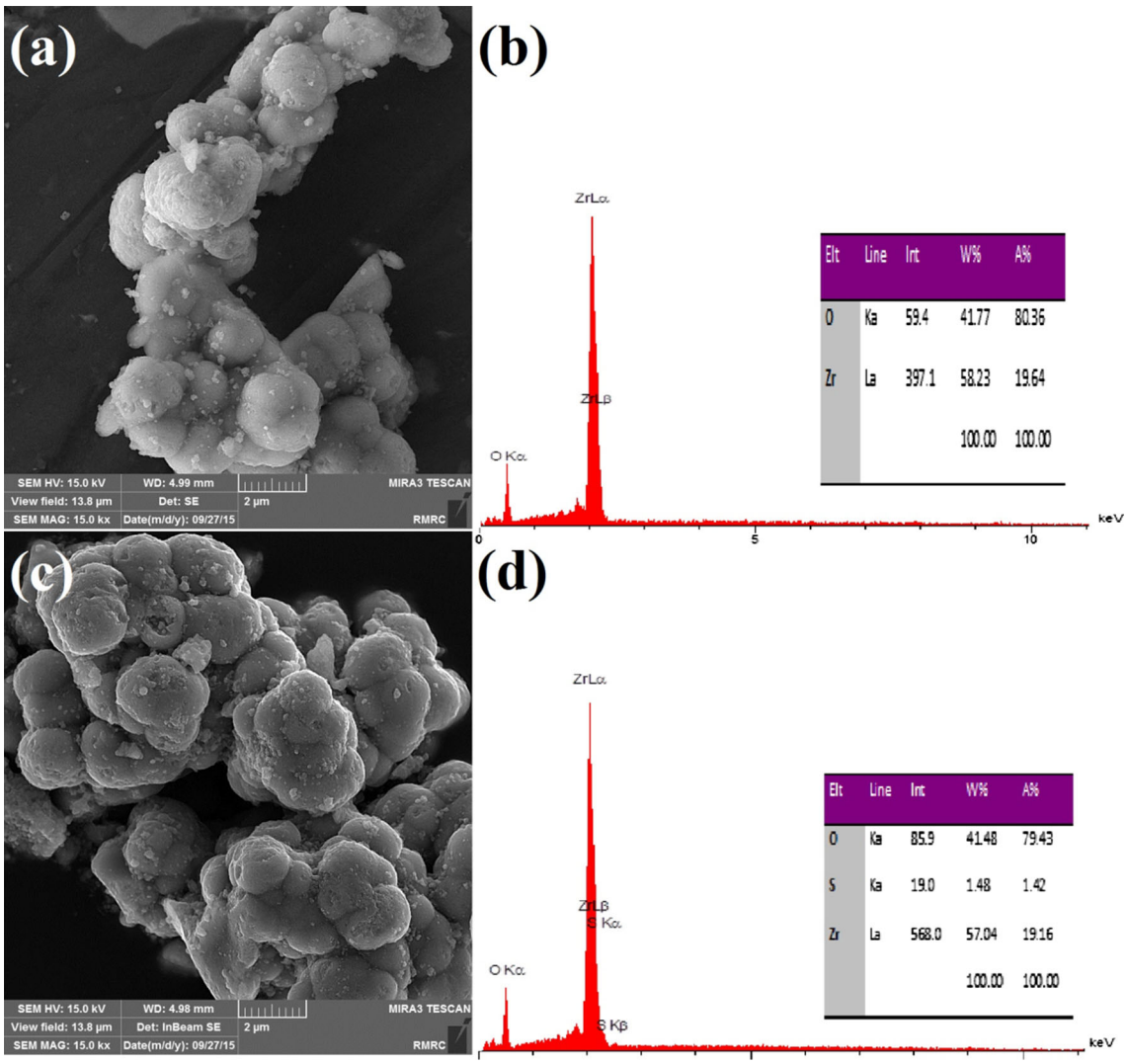


Fig. 4 FESEM-EDS analysis of **a** and **b** ZrO_2 **c** and **d** ZrSA

Table 1 BET data showing the textural properties of the obtained materials

Sample	BET surface area ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)	Pore width (nm)
ZrO_2	6.7	0.0051	1.7
ZrSA	1.9	0.0016	4.2

Table 2 BJH data showing the textural properties of the obtained materials

Property	ZrO_2	ZrSA
Desorption surface area	11.8 $m^2\ g^{-1}$	5.419 $m^2\ g^{-1}$
Cumulative desorption pore volume	0.014 $cm^3\ g^{-1}$	0.0094 $cm^3\ g^{-1}$
Desorption pore diameter	3.6 nm	3.5 nm

donating and electron withdrawing groups afforded high yields of the desired products.

A plausible mechanism for the Biginelli reaction in the presence of ZrSA is shown in Scheme 3. ZrSA facilitates the formation of the intermediate I by Knoevenagel condensation of aldehydes 1 and β-ketoester 2, and I after dehydration gives the olefin II. Nucleophilic attack of the amino group in urea or thiourea 3 at the β-carbon of the α,β-unsaturated carbonyl group followed by cyclization yields the product 4.

Scheme 2 Synthesis of dihydropyrimidinone using of zirconia sulfuric acid (ZrSA)

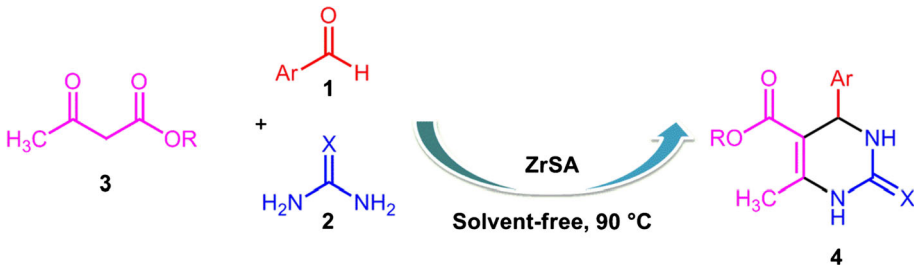


Table 3 Optimization of synthesis of dihydropyrimidinones

Entry	Solvent	Condition	Amount of catalyst (mol%)	Time (min)	Yield (%)[a]
1	Solvent-free	90 °C	–	50	Trace
2	Solvent-free	90 °C	5	95	69
3	Solvent-free	90 °C	10	70	77
4	Solvent-free	90 °C	15	50	97
5	Solvent-free	90 °C	20	55	89
6	Solvent-free	50 °C	15	55	56
7	Solvent-free	70 °C	15	50	48
8	Solvent-free	110 °C	15	45	77
9	Ethanol	Reflux	15	60	89
10	Methanol	Reflux	15	50	85
11	Water	Reflux	15	65	20

Reaction condition: benzaldehyde (1 mmol), methyl acetoacetate (1 mmol), urea (1.5 mmol)

[a] Isolated yields

The efficiency of ZrSA was compared with some other published works in literature for the Biginelli reaction (Table 5). Each of these methods has their own advantages, but they often suffer from some troubles including reaction conditions, time and product yields. As can be seen in this table, the present catalyst was found to be the most efficient catalyst for the synthesis of dihydropyrimidinones.

3.3 Reusability of the Catalyst

The recovery and reuse of catalysts are highly preferable for a green process. In this regard, reusability of the catalyst was evaluated in the model reaction. After completing the reaction, ZrSA was recovered from the reaction mixture via centrifuge, washed with ethanol and dried in oven at 100 °C and was reused for another batch of the reaction. This process has been repeated for 4 consecutive runs without observable decrease in catalytic activity of the catalyst. ICP analysis of fresh and recycled catalyst showed 3.8 and 2.7 % of S content respectively. Moreover, the XRD pattern of recycled catalyst showed that the ZrSA was the similar to the initial one after four runs (Fig. 5).

3.4 Physical and Spectroscopic Data for Selected Compounds

*3.4.1 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**4n**)*

Mp: 205–207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz):d (ppm): 8.62 (s, 1H, NH), 7.24e7.31 (m, 5H, ArH), 6.1 (s, 1H, NH), 5.38 (s, 1H, CH), 4.03 (q, 2H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 1.13 (t, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): d (ppm): 14.12, 18.55, 55.59, 59.97, 101.23, 126.56, 127.88, 128.66, 143.73, 146.48, 153.73, 165.65. IR (KBr) cm^{-1}: 3247.90, 3116.75, 2977.89, 1720.39, 1643.24.

*3.4.2 5-(Ethoxycarbonyl)-6-methyl-4-(p-tolyl)-3,4-dihydropyrimidin-2(1H)-one (**4q**)*

Mp: 215–217 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm): 8.75 (s, 1H, NH), 7.09e7.21 (m, 4H, ArH), 6.22 (s,1H, NH), 5.34 (s, 1H, CH), 4.04 (q, 2H, OCH_2CH_3), 2.3 (s, 3H, CH_3),1.15(t, 3H, OCH_2CH_3).^{13}C NMR ($CDCl_3$, 75 MHz): d (ppm): 14.16, 18.50, 21.09, 55.18, 59.93, 101.35, 126.45, 129.30, 137.52, 140.91, 146.41, 153.99, 165.74. IR (KBr) cm^{-1}: 3245.97, 3114.82, 2979.82, 1724.24, 1649.02.

Table 4 ZrSA-catalyzed one-pot synthesis of dihydropyrimidinones

Entry	Ar	R	X	Product	Time (min)	Yield (%)[a]	MP	MP(Ref)
1	C_6H_5	Me	O	4a	25	99	216–218	209–216 [33]
2	4-HO–C_6H_4	Me	O	4b	50	91	239–241	241–242 [34]
3	4-$(CH_3)_2NC_6H_4$	Me	O	4c	50	83	215–217	213–215 [35]
4	2-Cl–C_6H_4	Me	O	4d	60	92	252–253	252–253 [36]
5	4-Cl–C_6H_4	Me	O	4e	45	98	204–206	204–207 [37]
6	2-MeO–C_6H_4	Me	O	4f	45	88	280–283	283–285 [38]
7	4-MeO–C_6H_4	Me	O	4g	50	94	193–194	192–194 [39]
8	4-Me–C_6H_4	Me	O	4h	60	86	214–216	214–215 [40]
9	4-O_2N–C_6H_4	Me	O	4i	50	82	234–236	235–237 [33]
10	3-O_2N–C_6H_4	Me	O	4j	60	92	279–281	279–280 [36]
11	2-O_2N–C_6H_4	Me	O	4k	55	84	224–226	224–225 [41]
12	3-EtO-4-HO–C_6H_3	Me	O	4l	60	81	252–254	253–254 [35]
13	3,4-(OMe)2–C_6H_3	Et	O	4m	60	72	176–179	178 [42]
14	C_6H_5	Et	O	4n	30	92	205–207	205–206 [43]
15	4-HO–C_6H_4	Et	O	4o	25	96	230–231	228 [44]
16	4-O_2N–C_6H_4	Et	O	4p	50	91	213–215	208–211 [39]
17	4-Me–C_6H_4	Et	O	4q	60	85	215–217	215–216 [45]
18	4-Cl–C_6H_4	Et	O	4r	70	90	214–216	213–215 [46]
19	2-Cl–C_6H_4	Et	O	4s	70	92	216–218	216–218 [47]
20	3-EtO–4-HO–C_6H_3	Et	O	4t	50	93	232–234	232–233 [48]
21	C_6H_5	Et	S	4u	45	81	206–208	208–209 [49]
22	4-HO–C_6H_4	Et	S	4v	45	95	204–206	202–203 [50]
23	4-O_2N–C_6H_4	Et	S	4w	50	90	193–195	193–194 [51]
24	C_6H_5	Me	S	4x	40	91	227–229	221–222 [38]

Reaction condition aromatic aldehyde (1 mmol), β-dicarbonyl compound (1 mmol), urea or (thiourea) (1.5 mmol), ZrSA (15 mol%), solvent-free, 90 °C

[a] Isolated yields

*3.4.3 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4r**)*

Mp: 214–216 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm): 8.44 (s, 1H, NH), 7.22e7.29 (m, 4H, ArH), 6.1 (s, 1H, NH), 5.36 (s, 1H, CH), 4.04 (q, 2H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 1.15 (t, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): d (ppm): 14.15, 18.63, 55.02, 60.14, 101.02, 127.99, 128.84, 133.69, 142.19, 146.54, 153.48, 165.45. IR (KBr) cm^{-1}: 3240.19, 3116.75, 2977.89, 1704.96, 1650.95.

*3.4.4 5-(Ethoxycarbonyl)-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4m**)*

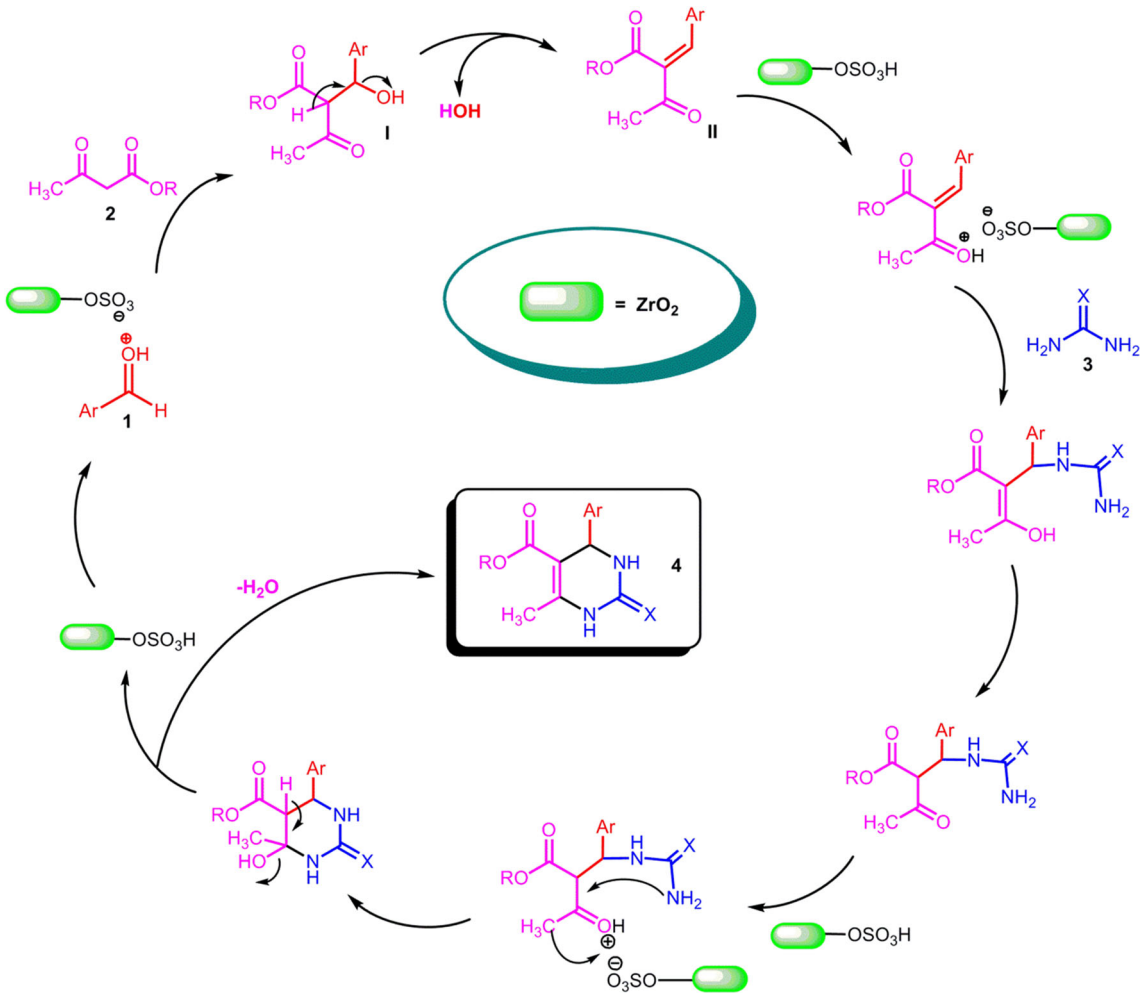
Mp: 176–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm): 9.15 (s, 1H, NH), 7.68 (s, 1H, NH), 5.09 (s, 1H, CH), 3.95 (q, 2H, OCH_2CH_3), 3.37 (s, 3H, CH_3), 3.95 (q, 2H, OCH_2CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): d (ppm): 14.15, 17.76, 53.49, 55.4, 55.52, 59.19, 99.39, 110.45, 111.72, 117.9, 137.35, 148.06, 148.15, 148.48, 152.29, 165.43. IR (KBr) cm^{-1}: 3247.90, 3116.75, 1712.67, 1650.95.

*3.4.5 5-(Ethoxycarbonyl)-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4s**)*

Mp: 216–218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm): 9.08 (s, 1H, NH), 7.19e7.37 (m, 4H, ArH), 5.98 (s, 1H, NH), 5.86 (s, 1H, CH), 3.97 (q, 2H, OCH_2CH_3), 2.41 (s, 3H, CH_3), 1.02 (t, 3H, OCH_2CH_3).13C NMR ($CDCl_3$, 75 MHz): d (ppm): 13.97, 18.23, 52.06, 59.93, 98.8, 127.51, 128.03, 129.23, 129.75, 132.55, 139.58, 148.56, 153.42, 165.33. IR (KBr) cm^{-1}: 3234.40, 3110.97, 1701.10, 1645.17.

*3.4.6 5-(Ethoxycarbonyl)-4-(3-ethoxy-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4t**)*

Mp: 232–234 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): d (ppm): 7.27 (s, 1H, NH), 6.79 (s, 1H, NH), 5.31(s, 1H, CH), 4.75(s, 1H, OH) 4.03 (q, 2H, OCH_2CH_3), 2.33 (s, 3H, CH_3), 1.39



Scheme 3 Proposed mechanism for the synthesis of dihydropyrimidinones ZrSA

Table 5 Comparing the efficiency of ZrSA with some different reported catalysts in Biginelli reaction

Entry	Catalyst	Condition	Time (h)	Yeild (%)	References
1	SBSSA[a]	Solvent-free/110 °C	1	81	[52]
2	CD-SO_3H[b]	Solvent-free/100 °C	2	89	[53]
3	DBSA[c]	Solvent-free/80 °C	3	94	[54]
4	SSA[d]	EtOH/reflux	6	91	[6]
5	Ce(LS)3[e]	EtOH/80 °C	8	93	[55]
6	Sulfated tungstate	Solvent-free/80 °C	1	92	[56]
7	CSA[f]	H_2O/100 °C	5	80	[57]
8	12-Tungstophosphoric acid	AcOH/reflux	6	98	[58]
9	ZrSA	Solvent-free/90 °C	0.5	92	Peresent work

[a] Silica-bonded s-sulfonic acid

[b] Sulfonated β-cyclodextrine

[c] *p*-dodecylbenzenesulfonic acid

[d] Silica sulfuric acid

[e] Cerium(III) trislaurylsulfonate

[f] Cellulose sulfuric acid

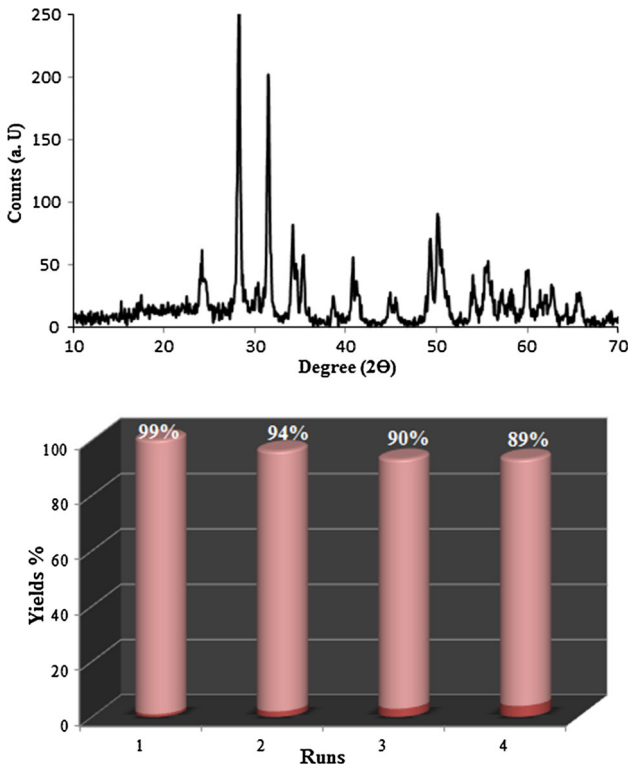


Fig. 5 Reusability of ZrSA in the Biginelli reaction

(t, 3H, OCH_2CH_3), 1.15 (t, 3H, OCH_2CH_3). 13C NMR ($CDCl_3$, 75 MHz): d (ppm): 14.13, 14.77, 17.74, 53.55, 59.15, 63.93, 99.64, 112.3, 115.38, 118.45, 135.9, 146.13, 146.32, 147.84, 152.31, 165.47. IR (KBr) cm^{-1}: 3417, 3263, 2985.60, 1704.96, 1650.95.

4 Conclusion

In the present work, we have introduced zirconia sulfuric acid (ZrSA) as a highly powerful heterogeneous solid acid catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. All the reactions work easily for a variety of aldehydes with both electron-donating and electron-withdrawing groups to give corresponding products in excellent yields. Furthermore, the application of ZrSA as a highly efficient, inexpensive, easy handling and reusable catalyst makes all process more economical and industrially important. The notable advantages of this method are high catalytic activity, short reaction time, mild reaction conditions, excellent yields, reusable catalyst and simple work-up.

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