Res Chem Intermed
DOI 10.1007/s11164-014-1766-7

Phthalimide-*N*-sulfonic acid: a new and efficient organocatalyst for the Biginelli reaction under solvent-free conditions

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Received: 30 May 2014 / Accepted: 7 July 2014

Abstract Phthalimide-*N*-sulfonic acid (PISA) was straightforwardly synthesized via addition of chlorosulfonic acid to a solution of potassium phthalimide in dry dichloromethane. This reagent is found to be an efficient solid acidic catalyst in the Biginelli reaction. The three-component reaction of aryl aldehydes, urea/thiourea, and ethyl acetoacetate or acetylacetone occurs by means of 10 mol % of PISA in solvent-free reaction conditions (SFRCs) at 120 °C. The present methodology is a green approach to access a series of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in high yields. In addition, the use of PISA as the catalyst offers several notable features such as simple operational procedure, no use of hazardous organic solvents, and recyclability of catalyst.

Keywords Phthalimide-*N*-sulfonic acid · Organocatalyst · Biginelli-3CR · 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones · Solvent-free conditions

Introduction

The one-pot multicomponent reaction (MCR) was an attractive broad area of research in the synthesis of *N*-containing heterocyclic scaffolds such as the 3,4-dihydropyridin-2-1*H*-(ones)/3,4-dihydropyridin-2-1*H*-(thiones) (DHPMs) and their heterocyclic derivatives [1–19]. A one-pot process in organic synthetic chemistry that generates DHPMs via MCR in a single operation is called the Biginelli 3-component reaction (Biginelli-3CR). Since the 3CR synthesis of ethyl-6-methyl-

Electronic supplementary material The online version of this article (doi:10.1007/s11164-014-1766-7) contains supplementary material, which is available to authorized users.

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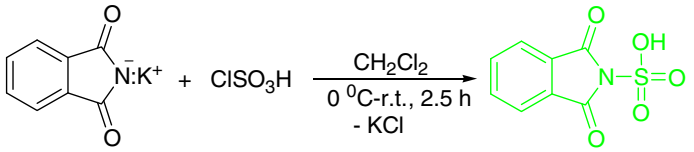
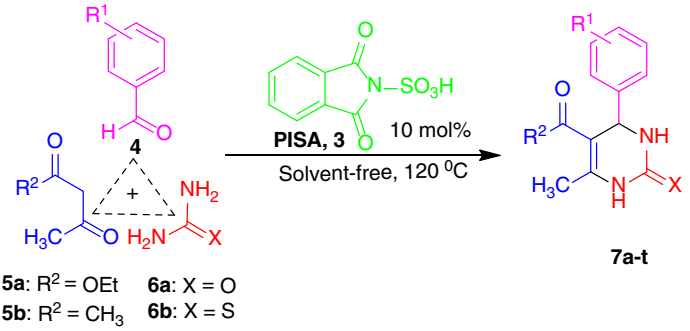
Published online: 27 July 2014

2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate by Italian chemist Pietro Biginelli in 1893 [20], synthesis and biological evaluation of different classes of these heterocyclic rings have been widely and extensively studied. DHPMs and associated heterocyclic molecules have attracted a lot of attention due to their unique characteristics. Some examples of heterocyclic structures with a dihydropyrimidine (DHPM) core have been established a wide scope of important applications in biological and pharmacological fields [21–27]. A large number of various heterocyclic compounds containing DHMP exhibit broad ranges of medicinal properties, including antibacterial, antihypertensive, calcium channel modulation, antiviral, antitumor, antifungal, anti-tubercular, mitotic kinesin Eg5 inhibition, anti-HIV, anti-HSV, and anti-inflammatory [28–32]. Moreover, some DHPMs and their derivatives can be found as the structural motif in a wide range of natural marine alkaloids such as batzelladine A and B as well as drug candidates. Among the best-known examples of DHMP-containing heterocycles, which are considered as drug candidates, include monastrol, enanstrone, piperastrol, dimethylenastron, fluorastrol, L-771688, SNAP-7941, SQ 32926, SQ32547, mon 97, and SWO2. Taking into consideration the importance of 3,4-dihydropyrimidin-containing heterocycles, many researchers in the synthetic organic chemistry and pharmaceutical research institutions were interested in developing newer approaches for the synthesis of these types of eye-catching heterocyclic compounds. A literature survey indicates that novel protocols to perform the Biginelli reaction using various catalysts, reagents, reaction conditions, and nonconventional techniques, such as microwave, ultrasound, high-pressure, and grindstone chemistry, have been developed by different research groups. To date, a huge number of important reviews about the different synthetic methods towards of 3,4-dihydropyrimidin-containing heterocycles have been presented [32–39]. A large part of the catalysts, reagents, and conditions/techniques for the Biginelli-3CR has also been reported elsewhere in the literature [40–42]. Also, metal-free organocatalytic multicomponent reactions (OMCRs) are one of the effective green catalytic synthetic approaches to preparation of Biginelli adducts [43]. In the last few years, newer metal-free organocatalytic versions of Biginelli-3CR have also been described. Some of these metal-free catalysts are listed as follows: *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and dicyclohexyl carbodimide (DCC) [44], ethylene glycol [45], triphenylphosphine (PPh_3) [46], choline-based ionic liquids (CIL) [47], oxalic acid [48], *N*-sulfonic acid poly(4-vinylpyridinium) chloride (NSPVPC) [49], PEG_{1000}-DAIL/toluene [50], β-cyclodextrin [51], poly(SIL) [52], bovine serum albumin (BSA) [53], pentafluorophenyl-ammonium triflate (PFPAT) [54], bioglycerol-based sulfonic acid functionalized carbon [55], nitrite ionic liquid [56], trifluoroethanol [57], sulfonated carbon [58], tartaric acid [59], citric acid [59, 60], Me_3SiCl [61], xanthan sulfuric acid [62], acidic ionic liquids [63–67], 1,3,5-triazine-2,4,6-triyltrisulfamic acid (TTSA) [68], deep eutectic solvent [69], chiral bisphosphorylimides [70], 3-[(3-(trimethoxysilyl)propyl)thio]propane-1-oxy-sulfonic acid [71], amino acid functionalized ionic liquid [72], phase transfer catalysis [73], trimethylsilyl chloride (TMSCl) in ethyl lactate (EL) [74], iodine under microwave irradiation [75], sulfonic acid-functionalized polypropylene fiber [76], and phytic acid [77].

Organocatalysts, on the other hand, are classically small organic molecules that are able to facilitate chemical transformations with a substoichiometric amount of an organic compound. Organocatalytic strategies have attracted attention for their application in organic synthesis due to their efficiency and selectivity. Compared with metallic catalysts, the preparation and handling of most organocatalysts is easier, cheaper, and relatively stable [78–81]. Organocatalysts possess other advantages, for example, cost-effectiveness, ready availability, a metal-free environment, relatively low toxicity, simple functionality, non-sensitivity to air and moisture, promotion of a variety of chemical transformations via various activation modes, mildness of the reaction conditions required, huge potential for the development of large-scale production [82–84]. Alternatively, implementation of organic transformations under solvent-free reaction conditions (SFRCs) have gained in popularity in recent years because of their simple workup procedure, high efficiency, mild conditions, environmental friendliness, cleanliness, low cost, handling, and economical friendliness [85, 86]. Recently, we have explored the Biginelli-type cyclocondensation of substituted benzaldehydes with cyclopentanone and urea/thiourea [87] and Biginelli compounds [88]. Followed by our research work, this article describes preparation of phthalimide-*N*-sulfonic acid (PISA) (Scheme 1) as well as a solvent-free and solid PISA-catalyzed synthesis of several derivatives of Biginelli compounds via a simple one-vessel 3-CR condensation between substituted benzaldehydes (**4**), β-dicarbonyl compounds (**5a,b**), and urea/thiourea (**6a,b**) (Scheme 2). Phthalimide-*N*-sulfonic acid (PISA) acts as highly



Scheme 1 The synthesis of phthalimide-*N*-sulfonic acid (PISA) (**3**)



Scheme 2 Biginelle-3C synthesis of 3,4-dihydropyrimidin-5(1*H*)-ones/thiones (**7a–t**) catalyzed by PISA (**3**)

efficient solid acidic organocatalyst for the synthesis of the Biginelli products under SFRCs.

Experimental

General

All chemicals were purchased from Alfa Aesar and Aldrich and were used without further purification, with the exception of 4-methylbenzaldehyde, 4-methoxylbenzaldehyde, and benzaldehyde, which were distilled before using. All solvents were distilled before using. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected. NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-500 and 400 MHz using $CDCl_3$ or DMSO-d_6 as the solvent. FT-IR spectra were recorded on a Perkin-Elmer RXI spectrometer. Elemental microanalyses were performed on an Elementar Vario EL III analyzer. The development of reactions was monitored by thin-layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

Preparation of the phthalimide-*N*-sulfonic acid (PISA)

In a fume hood, a clean and oven-dried 50-mL suction flask was cooled at 0 °C in an ice bath. This flask charged with a solution of potassium phthalimide (3.704 g, 20 mmol) in anhydrous dichloromethane (15 mL) was equipped with a constant pressure-dropping funnel containing chlorosulfonic acid (2.33 g, 20 mmol). Chlorosulfonic acid was added dropwise over a period of 20 min with slow stirring at the same temperature. After addition was complete, the reaction mixture was heated to room temperature and stirred for a further 2.5 h. The reaction mixture was filtered off and the solid residue was washed with water (4 mL) as well as diethyl ether (3 × 6 mL) and dried under vacuum. PISA was achieved as a cream-colored solid. Yield: 92 %, 4.18 g; M.p. 156–157 °C; IR (KBr, cm^{-1}): ν 3,500–2,500 (O–H), 1,706 (C=O), 1,298 and 1,128 (S=O), 718 (S–O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (m, 4H, Ar–H), 11.35 (s, 1H, SO_3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.4, 133.0, 134.8, 169.6, 169.7. Anal. Calcd. For. $C_8H_5NO_5S$ (%): C, 42.29; H, 2.22; N, 6.17; S, 14.11. Found: C, 42.28; H, 2.20; N, 6.20; S, 14.05.

Typical procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones and–thiones (**7a–t**)

To a mixture of aryl aldehyde **4** (1 mmol), β-dicarbonyl **5** (1 mmol), and urea or thiourea **6** (1.2 mmol) was added 10 mol % of phthalimide-*N*-sulfonic acid (PISA). The reaction mixture was heated to 120 °C on a heating mantle for the appropriate time. After completion of the reaction, as indicated by TLC analysis, the system was cooled to room temperature. Ethanol (5 mL) was added to the reaction mixture, and

the mixture was heated until a homogeneous solution was obtained. Next, ethyl acetate was added to the resulting mixture and then cooled to RT, and the catalyst was recovered by filtration and washed thoroughly with ethyl acetate and then diethyl ether. The recovered catalyst was then reused under the same conditions as above for at least five reactions. After this, the organic phase was concentrated by evaporation, distilled water was added to the residue, and the solid thus obtained. The resulting solid product was filtered off, washed with cold water, and then the reaction mixture was subjected to isolation with preparative TLC using a mixture of ethyl acetate and *n*-hexane (3:10) as eluent. Selected spectral data are listed below.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7c**)

IR (KBr, cm^{-1}): *v* 3,220 (N–H), 3,102 (N–H), 2,980 (CH), 2,931 (CH), 1,724 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (t, 3H, $J = 7.1$ Hz, CH_3), 2.35 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.08–413 (m, 2H, CH_2), 5.37 (s, 1H, CH), 5.92 (s, 1H, NH), 6.84–6.87 (m, 2H, Ar–H), 7.25–7.30 (m, 2H, Ar–H), 8.41 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.3, 18.7, 50.7, 53.6, 98.7, 128.0, 128.5, 131.7, 143.5, 148.9, 151.9, 165.6.

Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7i**)

IR (KBr, cm^{-1}): *v* 3,330 (N–H), 3110 (N–H), 1,706 (C=O), 1,550 (NO_2), 1,345 (NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, $J = 7.0$ Hz, CH_3), 2.25 (s, 3H, CH_3), 3.90 (q, 2H, $J = 7.0$ Hz, CH_2), 5.57 (s, 1H, CH), 7.45–7.88 (m, 4H, Ar–H), 7.05 (s, 1H, NH), 8.42 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.9, 17.7, 53.3, 59.4, 99.4, 115.1, 118.7, 120.1, 129.3, 146.9, 147.5, 150.2, 155.7, 163.5.

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-thioxopyrimidine-5-carboxylate (**7o**)

IR (KBr, cm^{-1}): *v* 3,234 (N–H), 3,110 (N–H), 2,942 (CH), 1,670 (C = O), 1,580 (NO_2), 1,340 (NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.48 (t, 3H, $J = 7.2$ Hz, CH_3), 2.24 (s, 3H, CH_3), 4.23 (q, 2H, $J = 7.2$ Hz, CH_2), 5.74 (s, 1H, CH), 7.12 (s, 1H, NH), 7.48–8.35 (m, 4H, Ar–H), 8.41 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 15.7, 54.7, 62.3, 105.8, 123.5, 126.1, 144.2, 150.1, 161.2, 167.3, 175.3.

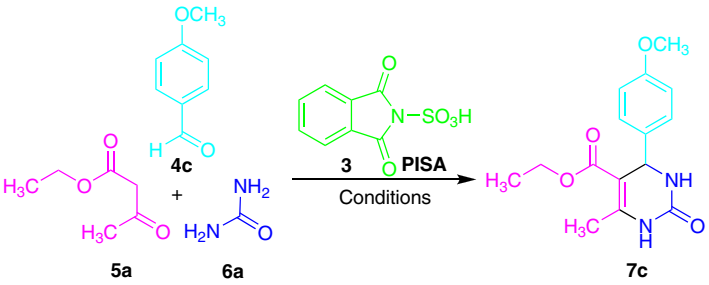
Results and discussion

In the present investigation, as shown in Scheme 1, phthalimid-*N*-sulfonic acid (PISA) was synthesized as a solid acidic organocatalyst and applied to preparation of a series of 3,4-dihydropyrimidin-5(1*H*)-ones/thiones (**7a–t**) by condensing aryl aldehydes (**4**), β-dicarbonyls (ethyl acetoacetate, **5a**, or pentane-2,4-dione, **5b**) and urea (**6a**)/thiourea (**6b**) under conventional heating conditions without any solvent (Scheme 2).

The structure of PISA is supported by spectral data. In the IR spectrum of PISA, the absorption bands characteristic for C=O, S=O, and S–O are visible at 1,706, 1,298, 1,128, and 718 cm^{-1}, respectively. The appearance of a broad band between 3,500 and 2,500 cm^{-1} is attributed to the hydroxyl group (–OH) of sulfunic acid fragment. In ^{1}H NMR spectrum, the resonance of the proton belongs to—SO_3H appeared at $\delta = 11.35$ ppm as a singlet. The multiplet signal appeared at $\delta = 7.85$ ppm integrating for four protons confirms the aromatic protons. The ^{13}C NMR spectrum of synthesized catalyst showed three signals at $\delta = 123.4$, 133.0, and 134.8 ppm attributable to the aromatic carbons. The data revealed the presence of the C = O group at $\delta = 169.6$ and 169.7 ppm. Given the ^{13}C NMR spectrum of the catalyst, it seems that the structure of PISA is not symmetric. Appearance of two peaks at $\delta = 169.6$ and 169.7 ppm support the asymmetric structure of the catalyst. The reaction of the PISA formation is easy and clean as well as needs no special workup and purification methods.

In order to find the most appropriate reaction conditions, 3CR cyclocondensation reaction of 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and

Table 1 Effect of the amounts of the PISA (**3**) and temperature on the synthesis of ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7c**) in the absence of solvent[a]



Entry	Catalyst (mol %)	Temperature (°C)	Time (h)[b]	Yield (%)[c]
1	–	120	10	20
2	2.5	120	5	55
3	5	120	3	82
4[d]	**10**	**120**	**2**	**94**
5	15	120	2	95
6	20	120	2	94
7	10	Ambient	10	0
8	10	50	10	40
9	10	80	10	54
10	10	100	10	70
11	10	130	2	95

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol)

[b] Reaction progress monitored by TLC analysis

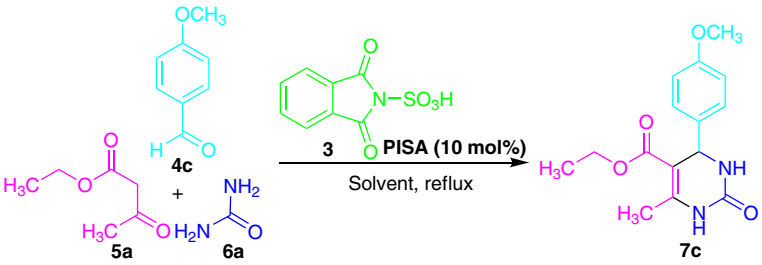
[c] Isolated yields

[d] Optimized conditions shown in *bold*

urea (1.2 mmol) was selected as the model reaction. The mentioned reaction was implemented under neat conditions at 120 °C using 2.5, 5, 10, 15, and 20 mol % of PISA as the solid acid organocatalyst (Table 1).

Table 1 shows the results of the optimization. When the reaction was carried out in the absence of the catalyst, the product **7c** was only formed in 20 % of the reaction yield for 10 h. Implementation of the reaction using 2.5 % of PISA catalyst at 120 °C led to the enhancement of the reaction yield to 55 % and shortening reaction time from 10 h into 5 h (Table 1, entry 2). As a result, the rise in the reaction yield as well as shortening of the reaction time means that the catalytic amount of the PISA for performing this reaction is mandatory. When the amount of the catalyst was increased from 2.5 to 10 mol %, the yield of the formation of compound **7c** was improved from 55 to 94 % and the reaction time was further reduced to 2 h (Table 1, entries 2–4). Hence, the 2-h period was enough time for the conducting of the model reaction. Otherwise, increasing the catalyst loading from 10 to 15 and 20 mol % does not significantly change the yield (Table 1, entries 5–6). Consequently, the amount of 10 mol % of PISA was chosen as the catalyst for conduction the other reactions. The temperature dependence study was also investigated (Table 1, entries 7–11). When the reaction was carried out at ambient temperature, formation of the product was not observed. Increasing of the temperature from ambient temperature to 50, 80, and 100 °C, the yield of the product **7c** was improved. Increasing the temperature from 100 to 130 °C does not significantly effect the yield of the reaction. It was found that the reaction temperature should be 120 °C in the presence of 10 mol % of PISA. In the next section of this exploration, the solvent effect was investigated by means of the

Table 2 The synthesis of ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7c**) using PISA (10 mol %) in various solvents under reflux conditions[a]



Entry	Solvent	Time (h)[b]	Isolated Yield (%)
1	CH_3CN	22	80
2	EtOH	22	78
3	CH_2Cl_2	72	76
4	H_2O	22	55
5	$CHCl_3$	22	65

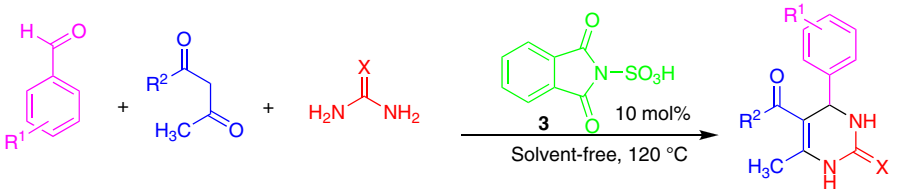
[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol)

[b] Reaction progress monitored by TLC analysis

model reaction in various solvents using 10 mol % of PISA in reflux conditions (Table 2).

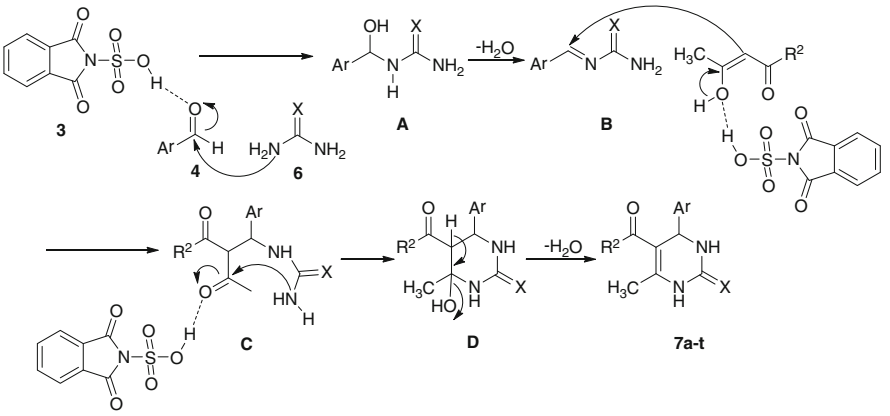
As can be seen in Table 2, both the yields and the reaction times suggested that solution conditions were not efficient. In addition, increasing the reaction times did not have a significant effect on the yields. As a consequence, based on the results of the screening study of the temperature, the amount of PISA (Table 1), and the solvent effect (Table 2) showed that 10 mol % of PISA was sufficient. Also, 120 °C as well as solvent-free were the optimal reaction temperature and conditions for completion of the reaction. Therefore, all further reactions were carried out using

Table 3 The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (**7a–t**) catalyzed by PISA (**3**) under SFRCs



4 (1 mmol) **5** (1 mmol) **6** (1.2 mmol) **7a-t**

Entry	R^1	R^2	X	Product **7a–t**	Time (h)	Isolated yield (%)	Mp (°C)	
							Observed	Reported [ref.]
1	H	OCH_2CH_3	O	**7a**	1.25	85	204–207	200–201 [59]
2	4-CH_3	OCH_2CH_3	O	**7b**	1.5	92	214–215	215–216 [91]
3	4-OCH_3	OCH_2CH_3	O	**7c**	2	94	200–202	201–202 [59]
4	2-OCH_3	OCH_2CH_3	O	**7d**	2	98	258–260	262–263 [90]
5	4-OH	OCH_2CH_3	O	**7e**	2.5	90	210–211	200–201 [89]
6	3-OH	OCH_2CH_3	O	**7f**	2.5	92	165–166	163–164 [89]
7	4-Cl	OCH_2CH_3	O	**7g**	3	88	214–215	215–217 [58]
8	4-NO_2	OCH_2CH_3	O	**7h**	3	92	206–208	207–208 [59]
9	3-NO_2	OCH_2CH_3	O	**7i**	3.2	90	225–226	225–226 [89]
10	2-NO_2	OCH_2CH_3	O	**7j**	3	88	209–211	207–210 [59]
11	H	OCH_2CH_3	S	**7k**	2	89	211–214	205–208 [59]
12	4-OCH_3	OCH_2CH_3	S	**7l**	3	92	154–155	153–154 [59]
13	4-OH	OCH_2CH_3	S	**7m**	3.2	90	194–196	200–202 [58]
14	3-OH	OCH_2CH_3	S	**7n**	3	90	185–186	184–187 [89]
15	4-NO_2	OCH_2CH_3	S	**7o**	3.5	91	110–112	108–110 [89]
16	2-NO_2	OCH_2CH_3	S	**7p**	4	79	195–197	196–198 [92]
17	H	CH_3	O	**7q**	1	88	230–233	230–231 [89]
18	4-CH_3	CH_3	O	**7r**	1	90	200–202	203–205 [93]
19	4-OCH_3	CH_3	O	**7s**	1	94	167–168	168–170 [89]
20	4-OH	CH_3	O	**7t**	3	93	228–230	220–224 [89]



Scheme 3 The proposed mechanism for the formation of 3,4-dihydropyrimidin-5(1*H*)-ones/thiones (**7a–t**)

Table 4 Reusability of PISA in the synthesis of **7c**[a]

Catalyst recycle	Time (h)[b]	Yield (%)[c]
Fresh	2	94
1	2	92
2	2	92
3	2.5	90
4	2.5	88
5	3.5	86

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol)

[b] Reaction progress monitored by TLC analysis

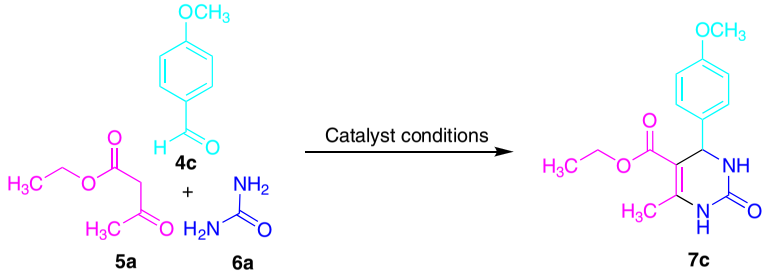
[c] Isolated yields

10 mol % of the catalyst in solid state at 120 °C. The activity and reusability of the catalyst were found to be excellent.

In the direction of exhibition the scope of these optimal conditions (10 mol % of PISA, 120 °C, and the absence of solvent), this three-component reaction was well evaluated by applying different substituted benzaldehydes bearing electron-donating and electron-withdrawing groups, ethyl acetoacetate or acetylacetone, and urea or thiourea. The results are presented in Table 3. Based on the results indicated in Table 3, it can be seen that the reaction of aryl aldehydes bearing both electron-donating and electron-withdrawing substituents with 1,3-dicarbonyl compounds and urea or thiourea worked well and afforded the corresponding products (**7a–t**) in reasonable yields.

The mechanism of the reaction is not clear. However, based on the literature [49, 66], the imaginable reaction mechanism for the green formation of products (**7a–t**) can be presented in Scheme 3. Probably, aldehyde **4** was activated by PISA catalyst and condensation of activated aldehyde **4** with urea or thiourea (**6**) lead to

Table 5 Comparison of the results of the reaction of 4-methoxybenzaldehyde (**4c**), ethyl acetoacetate (**5a**), and urea (**6a**) using PISA (**3**) with those obtained by reported catalysts



Entry	Catalyst/conditions	Time (h)	Yield (%)	Reference
1	PISA/Solvent-free (100 °C)	2	94	Current work
2	β-Cyclodextrin/Solvent-free (100 °C)	3	86	51
3	Poly(SIL)/EtOH (80 °C)	7	91	52
4	Bovine serum albumin (BSA)/EtOH (60 °C)	8	78	56
5	Pentafluorophenylammonium triflate (PFPAT)/CH_3CN (r.t.)	3.5	85	54
6	Bioglycerol-based sulfonic acid functionalized carbon/CH_3CN (75–80 °C)	4	92	55
7	BSA/Solvent-free (100 °C)	2.33	78	44
8	DCC/Solvent-free (100 °C)	2.5	72	44
9	Choline-based ionic liquid	2	78	47
10	Trifluoroethanol/Reflux	4–6	94	57
11	Citric acid or tartaric acid/absolute EtOH, reflux	4	84	59
12	3-[(3-(Trimethoxysilyl)propyl)thio]propane-1-oxy-sulfonic acid/EtOH, reflux	3	94	69

formation of **A**. This intermediate was dehydrated to generate imine intermediate **B**. Next, compound **C** is formed via addition of enol-form of β-dicarbonyl **5** to imine **B** in the presence of a catalytic amount of PISA. Then, intermediate **C** undergoes an intramolecular cyclization reaction afford the cyclic intermediate **D**, which subsequently undertakes dehydration to form targeted compounds **7a**–**t**.

The reusability of the PISA for the preparation of **7c** was also studied. The catalyst was recovered after each run, washed with ether, dried, and reused for subsequent cycles (Table 4). It showed nearly the same activity as a catalyst along but with a slight decrease of yield. The decrease of the yield of the product is probably related to a slight decrease in the catalytic activity of the catalyst or could be attributed to the loss of catalyst recovery in the course of the reaction.

With the aim of showing the benefit of the catalyst and comparison of the efficiency of the PISA catalyst with other catalysts in the synthesis of 3,4-dihydropyrimidin-4(1*H*)-ones/thiones, results of the reaction of 4-methoxybenzaldehyde (**4c**), ethyl acetoacetate (**5a**), and urea (**6a**) are shown in Table 5. As presented in Table 5, PISA is comparable to the formerly reported approaches in terms of reaction times and yields. Contrasting some of the pervious reported methods, this procedure does not require any additives or anhydrous conditions. Besides these features, this process also does not use hazardous solvents such as acetonitrile.

Conclusions

In summary, a simple, efficient, and environmentally benign method using the PISA for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones by coupling β-ketoesters, aldehydes, and urea or thiourea was developed. The reactions are conducted under thermal SFRCs within 1-4 h yielding the corresponding Biginelli adducts with good to high yields. The use of this catalyst in the synthesis of DHMPs includes benefits such as clean reaction profiles, a simple operational procedure, green, minimization of waste, and recyclability of the new organocatalyst. This work will be valuable for the synthesis of potentially therapeutic agents.

Acknowledgments The authors are thankful to Damghan University Research Council for partial support of this work.

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