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Original Resarch Article

Nano-*N,N,N′,N′*-tetramethyl-*N*-(silica-n-propyl)-*N′*-sulfo-ethane-1,2-diaminium chloride as an efficient and recyclable catalyst for the green synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones

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KEYWORDS

Nanocatalyst
Nano-*N,N,N′,N′*-tetramethyl-*N*-(silica-n-propyl)-*N′*-sulfo-ethane-1,2-diaminium chloride (nano-[TSPSED][Cl]$_2$)
3,4-Dihydropyrimidin-2-(1*H*)-one
3,4-Dihydropyrimidin-2-(1*H*)-thione;
Solvent-free

ABSTRACT

In this work, efficient and high-yielding green synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and 3,4-dihydropyrimidin-2-(1*H*)-thiones was achieved by a one-pot three-component reaction between aldehydes, ethyl acetoacetate, and urea/thiourea, using a recyclable mesoporous nanocatalyst entitled nano-*N,N,N′,N′*-tetramethyl-*N*-(silica-n-propyl)-*N′*-sulfo-ethane-1,2-diaminium chloride (nano-[TSPSED][Cl]$_2$). High yields, short reaction times, solvent-free conditions, easy purification of the products, compliance with green chemistry protocols and recyclability of the catalyst are the benefits of this work. The products were obtained in 80-98 % yields and in 10-45 min.

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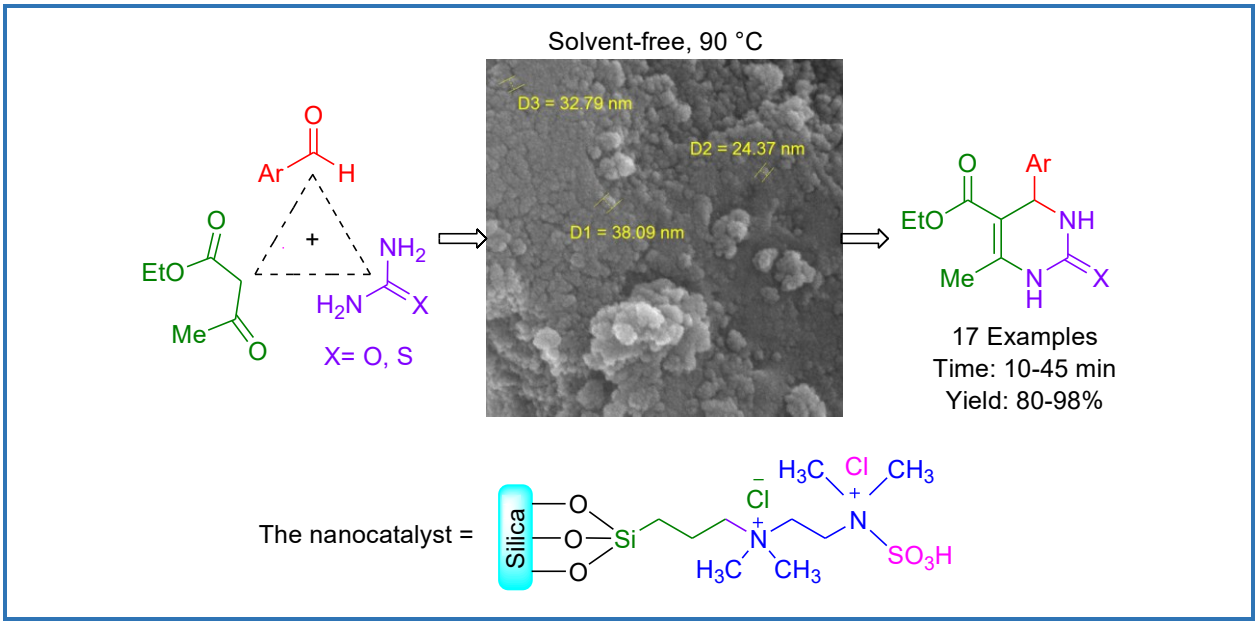
Graphical Abstract



Introduction

Nowadays, nanocatalysts, an important class of nanomaterials, have become a noticeable topic in synthetic chemistry due to their capacity to outperform traditional catalysts with their ability to quickly catalyze the bulk materials. Nanocatalysts have considered as materials with high catalytic activity due to their small size, large surface area, and catalyst loading capacity. Nanocatalysts have prominent options such as low density, low toxicity, high mechanical stability, easy functionalization, high selectivity, reactivity and yields of products. [1–18]. Important class of nanocatalysts is ionic liquids immobilized on silica supports. Silica-supported ILs as heterogeneous catalysts have advantages of two groups such as non-flammability, suitable thermal, chemical and electrochemical stability, non-volatility, green nature, and recyclability [19–22], easy usage and simple isolation [23–25].

Multi-component reactions (MCRs) have been used as an important protocol for preparation of potential biologically active substances. In comparison with the classical stepwise strategies in organic synthesis, multi-component reactions as processes in which three or more materials compose to yield a product. MCRs have many advantages such as synthesizing various products with different molecular structures in brief reaction time, developing of green chemistry, simplicity, synthetic efficiency and atom efficient nature [26–36].

The best solvent from the green chemistry point of view is no solvent due to minimization of environmental impact factor. Due to the high concentration of the reactants, these reactions proceed

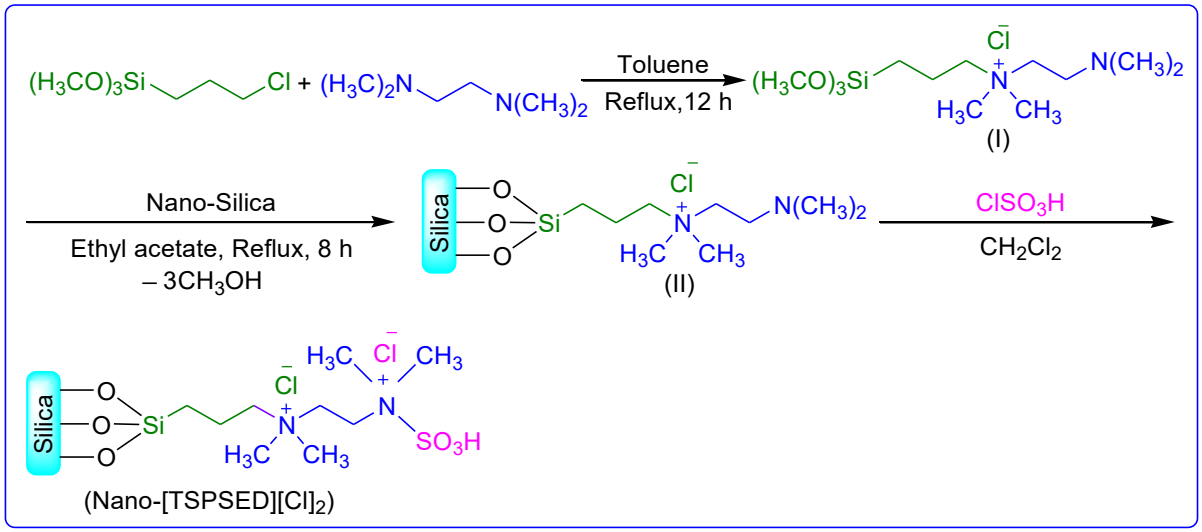
with higher yield and often lead to short reaction times. Combination of the solvent-free conditions with multi-component reaction has been shown to be a powerful strategy to yield complex molecular structures in few synthetic steps [37]. Solvent-free, multi-component reactions with reusable heterogeneous catalysts reduce the consumption of environmentally hazardous solvents and utilize scaled-down reaction vessels. It also satisfies green chemistry protocols, and may enhance the region selectivity and stereo selectivity of reactions. Less energy consumption to perform reaction, easier work-up and purification of product is further interest of solvent-free reactions [38–40]. Due to increasing the environmental concerns, development of clean synthetic procedures has become crucial.

Dihydropirimidines have attracted much attention due to their interesting biologically activities and properties such as anti-inflammatory, cytotoxic properties, cardiovascular activity and antihypertensive agents, antitumor, antiviral, antibacterial, analgesic, blood palette aggregation inhibitor, and calcium channel blockers [41–44]. 3,4-Dihydropyrimidine-2-(1*H*)-ones and 3,4-dihydropyrimidine-2-(1*H*)-thiones could be obtained through the Biginelli reaction involving aldehyde, β-ketoesters and urea/thiourea are of important interest in both industrial and academic communities. Because of high importance of Biginelli products, some catalysts have been used for this transformation such as Boehmite nanoparticle [45], SiO_2–$CuCl_2$ [46], iron (III) tosylate [43], Ammonium Dihydrogen Phosphate [47], Melamine trisulfonic acid [48], polystyrenesulfonic acid (PSSA) [49], $H_3PW_{12}O_{40}$ [50], [bmim][$MeSO_4$] [51], p-sulfonic acid calixarenes [52] and sulfonated carbon [53]. However, these often require relatively harsh reaction conditions such as high reaction temperature, expensive, highly acidic catalysts, long reaction time, tedious work-up procedures and column purification and indifferent yields. Therefore, developing a new method that gives substituted DHPMs by an efficient and convenient procedure is of interest.

Experimental

Materials and methods

All solvents and reagents were purchased from Fluka, Merck and Iranian Chemical Companies with high-grade quality and used without any purification. Nano-*N*,*N*,*N*′,*N*′-tetramethyl-*N*-(silica-n-propyl)-*N*′-sulfo-ethane-1,2-diaminium chloride (nano-[TSPSED][$Cl]_2$) was synthesized by our recently published procedure [54] (Scheme 1). The FE-SEM (field emission scanning electron microscopy) micrograph of the catalyst is shown in Figure 1; the particles sizes were in below 100 nm. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel. The melting points were recorded



Scheme 1. The synthesis of nano-[TSPSED][Cl]$_2$

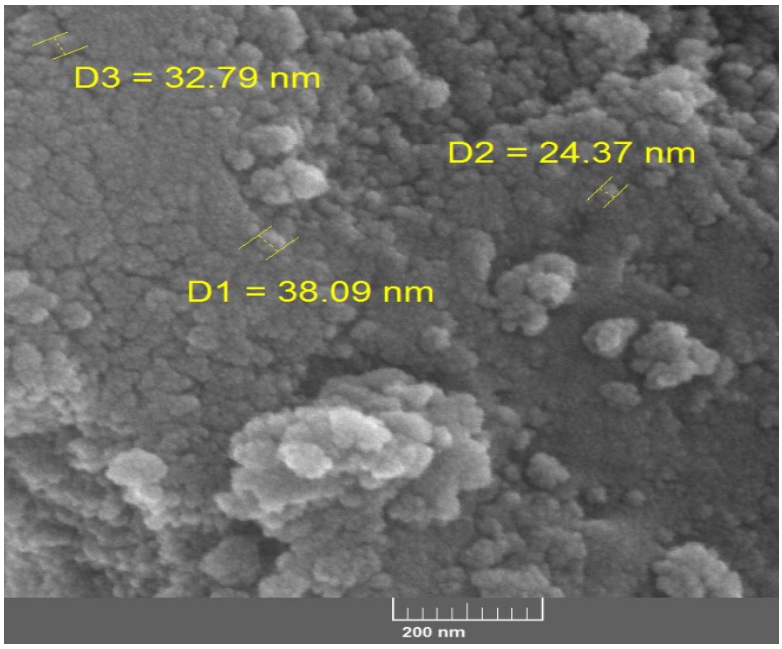


Figure 1. The FE-SEM image of nano-[TSPSED][Cl]$_2$

using a Büchi B-545 apparatus in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded by a Bruker Avance DPX spectrometer.

General procedure for the preparation of 3, 4-dihydropyrimidinones/thiones using nano-[TSPSED][Cl]$_2$

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol, 0.13 g), urea/thiourea (1.4 mmol) and nano-[TSPSED][Cl]$_2$ (0.024 g) was firstly stirred magnetically at 90 °C. After solidification of the reaction mixture, it was stirred using a small rod at 90 °C. Upon completing the condensation, as

monitored by TLC, the reaction mixture was cooled to room temperature, acetone was added, stirred for 2 min in reflux conditions, followed by centrifugation and decanting to separate the nanocatalyst. The resulting solution was evaporated, and the residue precipitate was recrystallized from EtOH (95%) to give the pure product.

5-(Ethoxycarbonyl)-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5)

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (t, J = 8.6 Hz, 3H, OCH_2CH_3), 2.25 (s, 6H, CH_3Ar and CH_3C=C), 3.97 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 5.12 (s, 1H, methine CH), 7.12 (s, 4H, Ar), 7.71 (s, 1H, NH), 9.19 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 14.5, 18.2, 21.1, 54.1, 59.6, 99.9, 126.6, 129.3, 136.8, 142.4, 148.6, 152.7, 166.8.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7)

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.23 (s, 3H, CH_3C=C), 3.71 (s, 3H, OCH_3), 3.97 (q, J = 7.6 Hz, 2H, OCH_2CH_3), 5.09 (s, 1H, methine CH), 6.86 (d, J = 8.7 Hz, 2H, Ar), 7.14 (d, J = 11.4 Hz, 2H, Ar), 7.67 (s, 1H, NH), 9.15 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO-d_6): δ 14.6, 18.2, 53.8, 55.5, 59.6, 100.0, 114.2, 127.8, 137.5, 148.5, 152.6, 158.9, 166.8.

5-(Ethoxycarbonyl)-4-(4-flurophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (10)

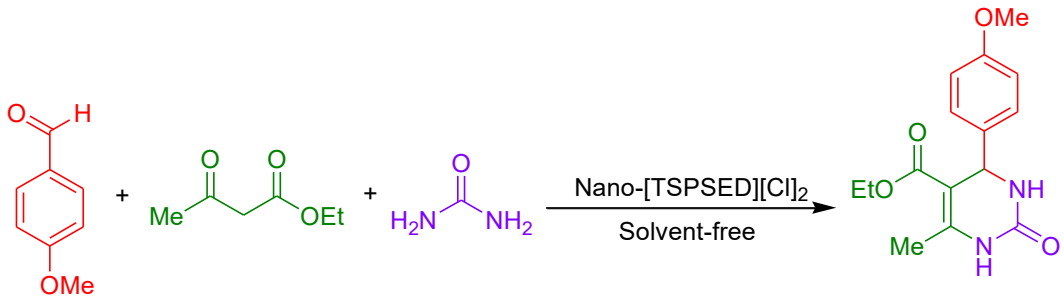
^{1}H NMR (500 MHZ, DMSO-d_6): δ 1.08 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, CH_3C=C), 3.97 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.15 (s, 1H, methine CH), 7.14 (t, J = 8.9 Hz, 2H, Ar), 7.27 (t, J = 8.5 Hz, 2H, Ar), 7.75 (s, 1H, NH), 9.22 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.5, 18.2, 53.8, 59.7, 99.6, 116.9, 128.7, 141.7, 148.9, 152.4, 160.8, 166.7.

Results and Discussion

To optimize the conditions, the reaction of 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.4 mmol) was chosen as a model system under solvent-free conditions (Scheme 2), and studied in the presence of different amounts of nano-*N*,*N*,*N*′,*N*′-tetramethyl-*N*-(silica-n-propyl)-*N*′-sulfo-ethane-1,2-diaminium chloride (nano-[TSPSED][Cl]$_2$) at range of 80-100 °C. The respective results are summarized in Table 1. The logical results were obtained when the reaction was performed using 0.024 g of the catalyst at 90 °C.

To assess the generality and efficacy of the nano-[TSPSED][Cl]$_2$ for the production of 3,4-dihydropyrimidin-2-(1*H*)-ones, arylaldehydes (with various substituents) were reacted with ethyl acetoacetate and urea under the optimal reaction conditions. The results are summarized in Table 2. As seen in Table 2, the catalyst was general and highly efficient for the reaction; all aromatic

aldehydes (containing electron-withdrawing substituents, electron-donating substituents and halogens) afforded the corresponding products in high yields within short reaction times. Nano-[TSPSED][Cl]$_2$ was also efficient when thiourea was used instead of urea (Compounds 13–17).



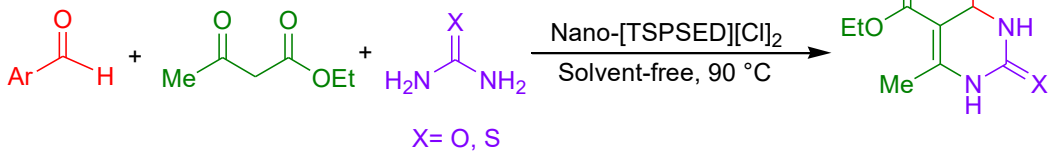
Scheme 2. The model reaction

Table 1. Effect of the catalyst amount and temperature on the reaction of 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.4 mmol)

Entry	The catalyst amount (g)	Temperature (°C)	Time (min)	Yield (%)[a]
1	0.020	90	30	87
2	0.024	90	25	96
3	0.030	90	15	96
4	0.024	80	30	84
5	0.024	100	20	96

[a] Isolated yield

Table 2. The solvent-free synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using nano-[TSPSED][Cl]$_2$



X= O, S

Compd. No.	X	Ar	Time (min)	Yield (%)[a]	M.p. °C (Lit.)
1	O	C_6H_5	15	97	199-201 (202-204) [55]
2	O	2-$O_2NC_6H_4$	20	95	214-216 (215-217) [56]
3	O	3-$O_2NC_6H_4$	10	89	215-217 (216-218) [57]
4	O	4-$O_2NC_6H_4$	10	93	207-209 (209-211) [48]
5	O	4-MeC_6H_4	20	90	215-217 (216-219) [56]
6	O	3-$MeOC_6H_4$	20	95	208-210 (206-208) [47]
7	O	4-$MeOC_6H_4$	15	98	197-199 (200-202) [48]

8	O	3,4-$(MeO)_2C_6H_4$	15	95	173-175 (175-178) [56]
9	O	4-OHC_6H_4	10	97	235-237 (236-238) [55]
10	O	4-FC_6H_4	20	98	178-180 (181-185) [56]
11	O	4-ClC_6H_4	15	82	213-215 (210-214) [56]
12	O	4-BrC_6H_3	15	80	216-218 (215-217) [56]
13	S	C_6H_4	20	93	207-209 (208-210) [56]
14	S	3-$O_2NC_6H_4$	40	80	198-200 (200-202) [55]
15	S	2-ClC_6H_4	40	91	165-167 (167-169) [48]
16	S	4-$MeOC_6H_4$	45	89	144-146 (145-156) [55]
17	S	3-BrC_6H_4	30	82	184-186 (182-184) [58]

[a] Isolated yield

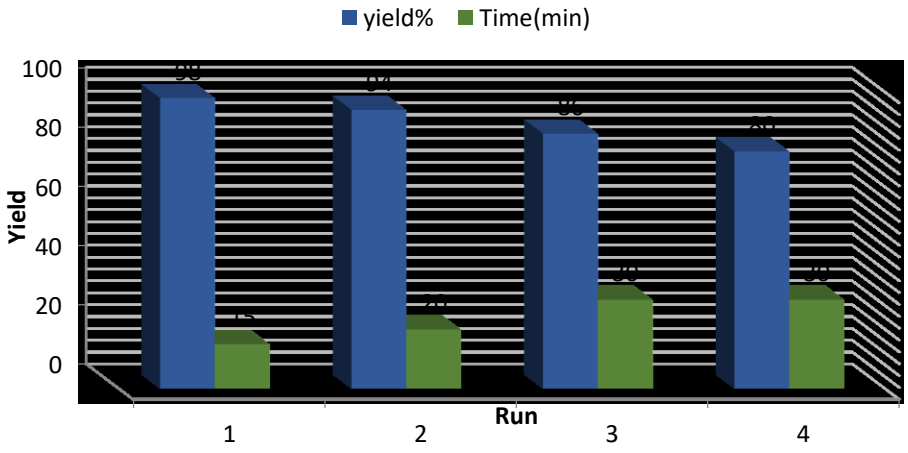
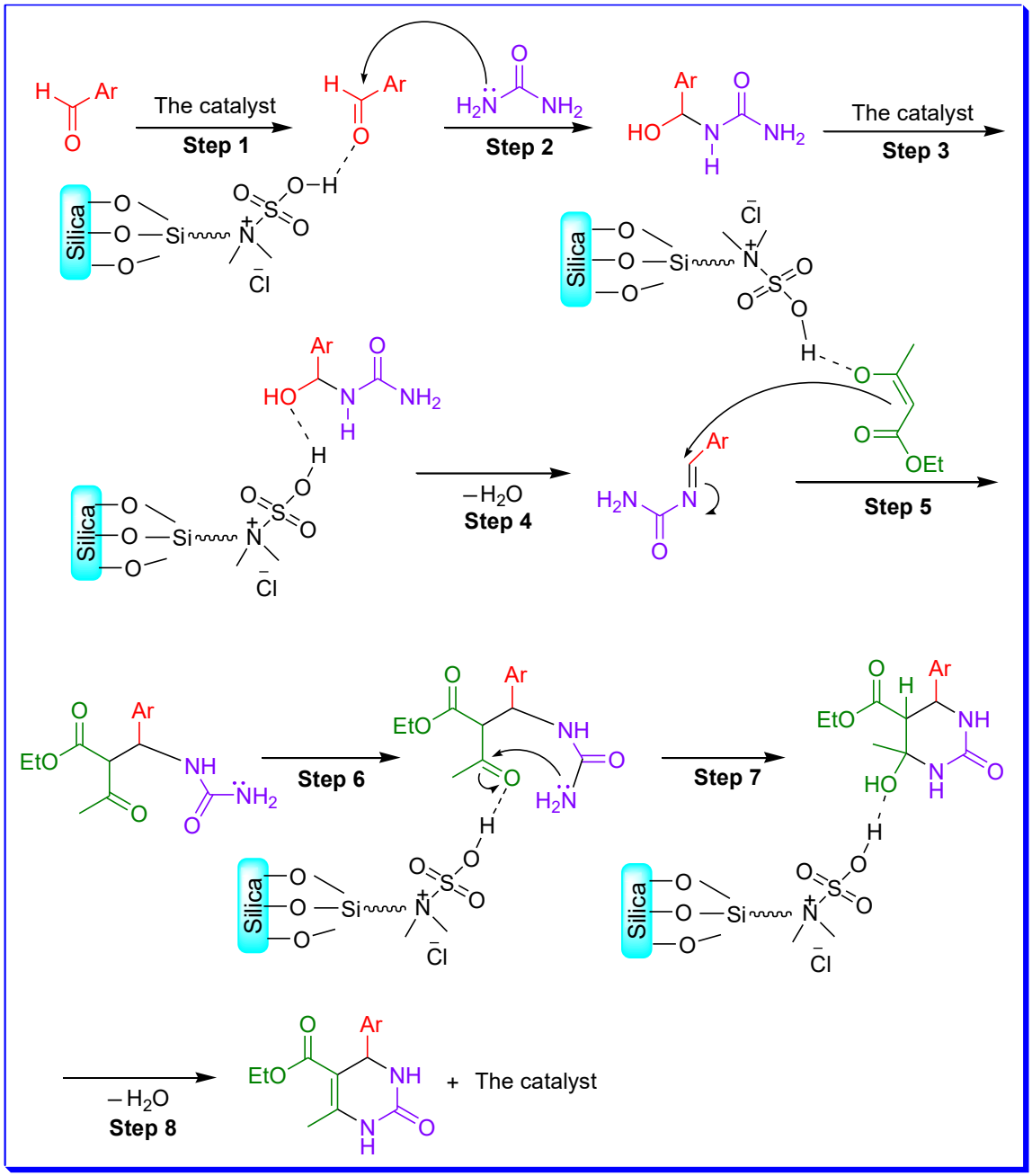


Figure 2. Recyclability of nano-[TSPSED][Cl]$_2$ on the reaction of 4-methoxybenzaldehyde with ethyl acetoacetate and urea

The possibility of recycling the catalyst was examined using the condensation of 4-methoxybenzaldehyde with ethyl acetoacetate and urea. The nanocatalyst was separated according to the procedure mentioned in the experimental section. Nano-[TSPSED][Cl]$_2$ could be reused for 2 times with logical and acceptable retaining catalytic activity (Figure 2). However, in third recycling, the yield decreased up to 18%.

A plausible mechanism, based on the literature, of the reaction is shown in Scheme 3 [56]. The acidic group of nano-[TSPSED][Cl]$_2$ can accelerate the reaction by two roles: (*I*) activation of the carbonyl group of aldehyde for nucleophilic addition (step 1 and 6), (*II*) assistance for removing H_2O (step 4 and 8), and (*III*) activating the carbonyl group of ethyl acetoacetate and converting keto to enol for addition to imine group (step 5).



Scheme 3. The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in the presence of nano-[TSPSED][Cl]$_2$

Conclusions

In this research study, we have developed a methodology for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones from aldehydes (1 mmol), ethyl acetoacetate (1 mmol) and urea/thiourea (1.4 mmol) using nano-[TSPSED][Cl]$_2$ as nanostructured mesoporous material at 90 °C. The benefits of the protocol include short reaction times, high yields, tolerance for various

functional groups of aldehydes, recyclability of the catalyst, no need to column chromatography for purification of the products, application of solvent-free conditions, and compliance with green chemistry protocols. The products were obtained in 80-98 % yields and in 10-45 min.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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