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ORIGINAL PAPER

Effective and Rapid Synthesis of Pyrido[2,3-*d*:6,5-*d*′]Dipyrimidines Catalyzed by a Mesoporous Recoverable Silica-Based Nanomaterial

Alireza Kohzadian[1] · Abdolkarim Zare[1]

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Abstract
A simple, rapid and effective protocol for the synthesis pyrido[2,3-*d*:6,5-*d*′]dipyrimidines has been developed via the one-pot multi-component reaction of arylaldehydes, 2-thiobarbituric acid and NH_4OAc using nano-[SiO_2-R-NMe_2SO_3H][Cl] as a mesoporous nanaocatalyst in solvent-free conditions. The remarkable features of this protocol include superiority relative to the reported methods in terms of two or more of these items: the reaction times, yields, the reaction temperature and conditions.

Keywords Pyrido[2,3-*d*:6,5-*d*′]dipyrimidines. Nano-[SiO_2-R-NMe_2SO_3H][cl]. Mesoporous nanocatalyst. Multi-component reaction. Solvent-free

1 Introduction

Currently, nanocatalysis is a significant field of nanoscience [1]. Nanoparticles as active and stable catalysts or supports could substitute bulk materials for a variety of catalytic applications [2–5]. Owing to their small sizes, nanoparticles have higher surface area and exposed active sites, and consequently increased contact areas with starting materials; this behavior is similar to homogeneous catalysts. Nanostructured catalysts can simultaneously act as heterogeneous catalysts; because, they are insoluble in reaction medium, and can simply segregate from reaction mixture [6–10].

Nowadays, an applied method for decreasing the ecological harms of chemical reactions is accomplishing them in solvent-free conditions. Beside this, elimination of solvent affords other profits, including: decrement of reaction time, economic and energy savings, increment of yield and selectivity, and a remarkable decrease in the size of reactor [11–14].

The reactions in which at least three reactants are treated in one pot to produce a material that has all essential moieties of the reactants, are called multi-component reactions (MCRs). MCRs are in accordance with green chemistry protocols, affordable and high effectual, and produce less waste compared with multi-steps reactions [15–19]. Moreover, it is clear, if MCRs are performed in solvent-free conditions, their importance will be doubled, because their benefits merge together [15–19].

Pyrimidines are attractive heterocyclic frameworks showing a variety of biological and medicinal activities [20, 21]. Pyrimidines and their fused derivatives are sources to synthesize therapeutic agents and new drugs [22, 23]. Additionally, pyrimido-pyrimidine derivatives are applied as tyrosine kinase inhibitory [24], antitumor [25], antiviral [26], antiallergic [27], anti-inflammatory [28], antifolate [29], antihypertensive [30], antimicroibial [31], fibroblast growth factor receptor [32], anti-HIV [33], anticonvulsants [34], antibacterial [35], analgesic [36] and antioxidant [37] agents. An important group of heterocycles containing pyrido-pyrimidine core is pyrido[2,3-*d*:6,5-*d*′]dipyrimidines which can prepared via the one-pot pseudo five-component reaction of arylaldehydes, 2-thiobarbituric

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✉ Alireza Kohzadian
akohzadian@yahoo.com

✉ Abdolkarim Zare
abdolkarimzare@pnu.ac.ir; abdolkarimzare@yahoo.com

[1] Department of Chemistry, Payame Noor University, Box 19395-3697, Tehran, PO, Iran

acid and NH_4OAc; few catalysts have been reported to perform this reaction, consisting of nano-[DMSPDE][Cl] [38], γ-Fe_2O_3@HAp-SO_3H [39], Fe-MCM-41-ionic liquid [40], $CuFe_2O_4$ nanospheres [41], $[H\text{-}NMP]^+[HSO_4]^-$ [42], and nano $CuFe_2O_4$ (under ultrasonic or microwave irradiation) [43, 44].

Considering the high importance of pyrido[2,3-*d*:6,5-*d'*]dipyrimidines, existing few catalysts for their synthesis in the literature, and high significance of nanocatalysis and solvent-free technique, search for finding efficient nanocatalysts to achieve this reaction in solvent-free conditions is demanded; in the present research, we have achieved this, and reported an easy-to-follow, quick, eco-friendly and highly effectual protocol for the production of pyrido[2,3-*d*:6,5-*d'*-]dipyrimidines through the one-pot multi-component condensation of arylaldehydes, 2-thiobarbituric acid and ammonium acetate using nano-[SiO_2-R-NMe_2SO_3H][Cl] as a mesoporous recoverable nanocatalyst in solvent-free conditions.

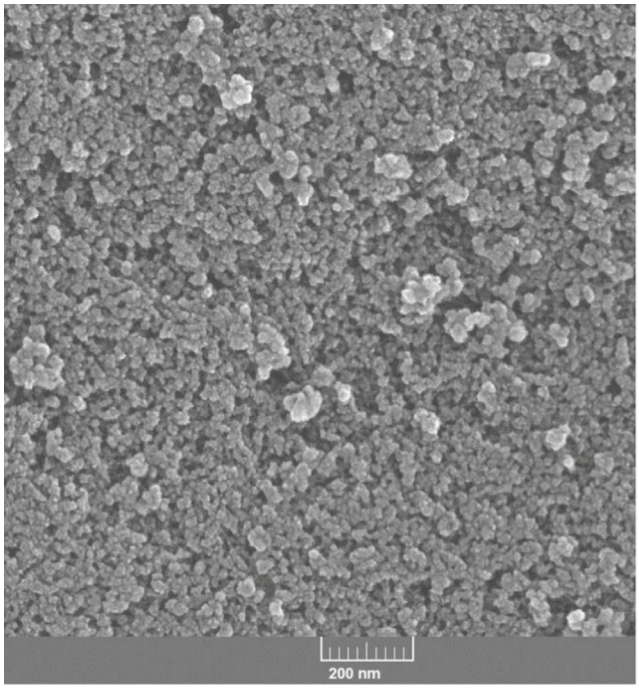
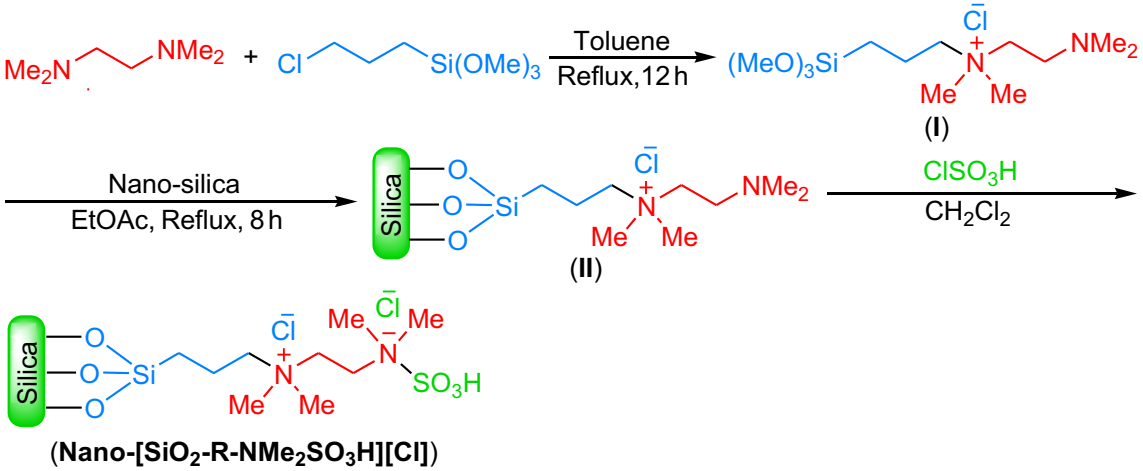


Fig. 1 The FE-SEM image of nano-[SiO_2-R-NMe_2SO_3H][Cl]

2 Results and Discussion

Nano-[SiO_2-R-NMe_2SO_3H][Cl] was synthesized according to Scheme 1 [10]. The FE-SEM (field emission scanning electron microscopy) and TEM (transmission electron microscopy) micrographs of the nanocatalyst are shown in Figs. 1 and 2. The organic moiety loading on the silica surface was 1.32 mmol/g [10].

To acquire the optimized catalyst quantity, reaction temperature and solvent, the reaction of 4-chlorobenzaldehyde (1 mmol), 2-thiobarbituric acid (2 mmol) and NH_4OAc (1.4 mmol) was checked in the presence of 0.01–0.03 g of nano-[SiO_2-R-NMe_2SO_3H][Cl] at range of 80–95 °C in solvent-free conditions, and also in 3 mL of ethanol, ethyl acetate and acetonitrile (Scheme 2); the results are tabulated in Table 1. As the Table exemplifies, the best results were acquired by utilization of 0.02 g of the nanocatalyst at 90 °C in the absence of solvent (Table 1, entry 2). Enhancing the catalyst quantity or temperature didn't improve the results (Table 1, entries 3 and 5). Furthermore, performing the reaction in solvent conditions didn't afford good results (Table 1, entries 6–8). Besides, the reaction was studied using *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine, nano-silica and chlorosulfonic acid (the starting materials for the synthesis of nano-[SiO_2-R-NMe_2SO_3H][Cl]) as catalysts (Table 1, entries 9–11); it is clear that the starting



Scheme 1 The preparation of nano-[SiO_2-R-NMe_2SO_3H][Cl]

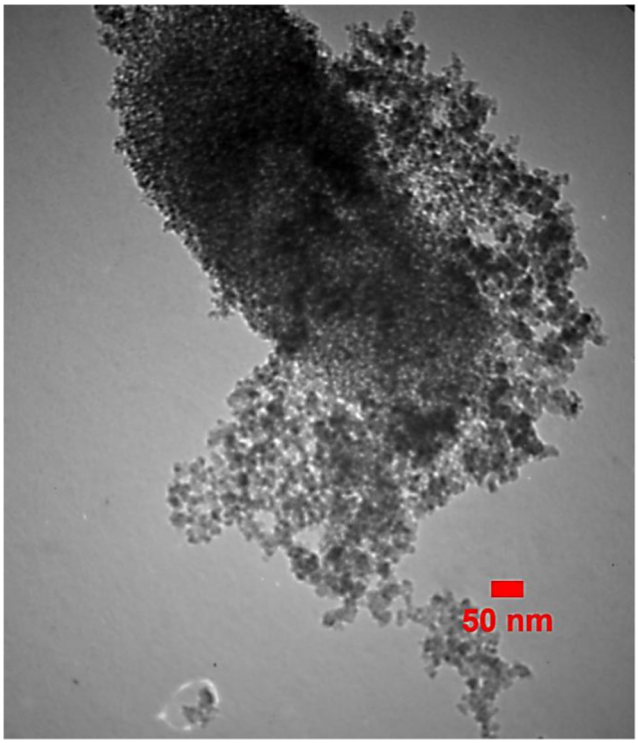


Fig. 2 The TEM micrograph of nano-[SiO_2-R-NMe_2SO_3H][Cl]

materials could not effectively catalyze the reaction, even at 110 °C; these results verified that our plan to anchor the diamine and chlorosulfonic acid on the surface of nano-silica for the synthesis of nano-[SiO_2-R-NMe_2SO_3H][Cl] was rational and fruitful.

After finding the best reaction conditions, the condensation of miscellaneous arylaldehydes with 2-thiobarbituric acid and NH_4OAc was investigated in the presence of nano-[SiO_2-R-NMe_2SO_3H][Cl]; the relevant reaction times and yields are indicated in Table 2. Considering the attained results, effectuality and generality of the nanocatalyst were high, since high yields of the corresponding pyrido[2,3-*d*:6,5-*d'*]dipyrimidines were acquired in short times in the case of all aldehydes, i.e. benzaldehyde, and electron-deficient as well as electron-reach arylaldehydes. In the other hand, the results were very good when arylaldehydes with ortho, para and meta substituents were utilized.

A literature-based mechanism was proposed for the synthesis (Scheme 3) [40]. Firstly, the carbonyl group of aldehyde is activated by the acidic group of nano-[SiO_2-R-NMe_2SO_3H][Cl], and then reacts with the tautomer of 2-thiobarbituric acid to provide intermediate **III**. In the other hand, ammonia reacts with another molecule of 2-thiobarbituric (which activated by the catalyst) to produce intermediate **IV** after removal of a H_2O molecule (the nanocatalyst also helps removing H_2O). Following that, Michael type addition of intermediate **IV** to intermediate **III** (which activated with nano-[SiO_2-R-NMe_2SO_3H][Cl]), and tautomerization produces intermediate **V**. Intermolecular nucleophilic addition of the amino group of intermediate **V** to its activated carbonyl group, and elimination of a H_2O molecule affords pyrido[2,3-*d*:6,5-*d'*]dipyrimidine.

To recognize superiority of nano-[SiO_2-R-NMe_2SO_3H][Cl] with respect to the reported catalysts for the production of pyrido[2,3-*d*:6,5-*d'*]dipyrimidines, the reaction conditions and results when compound **10** has been prepared, using these catalysts, are tabulated in Table 3. According to the Table data, the reaction time of our catalyst is shorter than the catalysts showed as entries 2–7; the yield of nano-[SiO_2-R-NMe_2SO_3H][Cl] is higher than the others; and the reaction temperature of our protocol is lower than entries 2 and 3. Furthermore, in our method, ultrasound and microwave energies, that require especial devices, have not been exploited. Application of solvent-free technique is another benefit of our work.

Recoverability of nano-[SiO_2-R-NMe_2SO_3H][Cl] was studied for the condensation of 4-nitrobenzaldehyde (1 mmol) with 2-thiobarbituric acid (2 mmol) and NH_4OAc (1.4 mmol) to prepare compound **3**. Recycling the nanocatalyst was achieved via the mentioned procedure in the experimental section; it was reusable for 4 times with negligible loss of its activity (Fig. 3). Full characterization of the nanocatalyst has been reported in our previous paper [10]. The recycled nano-[SiO_2-R-NMe_2SO_3H][Cl] was also characterized by FT-IR, FE-SEM and XRD (X-ray diffraction). The FT-IR spectrum is shown in Fig. 4, and the corresponding data are briefed in Table 4; the data showed that the organic groups immobilized on the silica surface were retained (the IR data is accordance with those reported for nano-[SiO_2-R-NMe_2SO_3H][Cl] in our published

Scheme 2 The model reaction

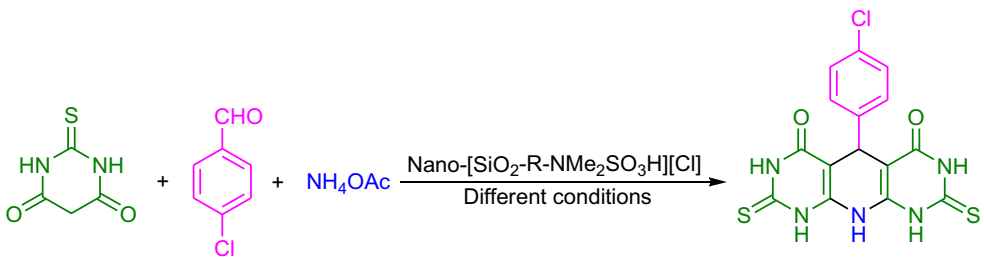


Table 1 The results of optimizing the catalyst quantity, temperature and solvent on the reaction of 4-chlorobenzaldehyde, 2-thiobarbituric acid and NH_4OAc

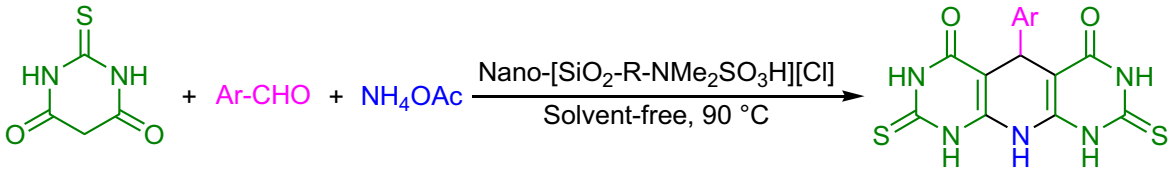
Entry	Catalyst	Catalyst quantity (g)	Temp. (°C)	Solvent	Time (min)	Yield[a] (%)
1	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.01	90	–	10	82
2	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	90	–	5	93
3	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.03	90	–	5	93
4	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	80	–	10	64
5	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	95	–	5	93
6	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	Reflux	EtOH	120	84
7	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	Reflux	EtOAc	120	80
8	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	0.02	Reflux	CH_3CN	120	75
9	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine	0.02	110	–	15	43
10	Nano-silica	0.02	110	–	15	38
11	Chlorosulfonic acid	0.003[b]	90	–	20	82

[a] Yield of isolated product

[b] Considering the amount of the acidic group (SO_3H) immobilized on silica in nano-[SiO_2-R-NMe_2SO_3H][Cl] (1.32 mmol/g) [10], 0.003 g (0.026 mmol) of $ClSO_3H$ was used

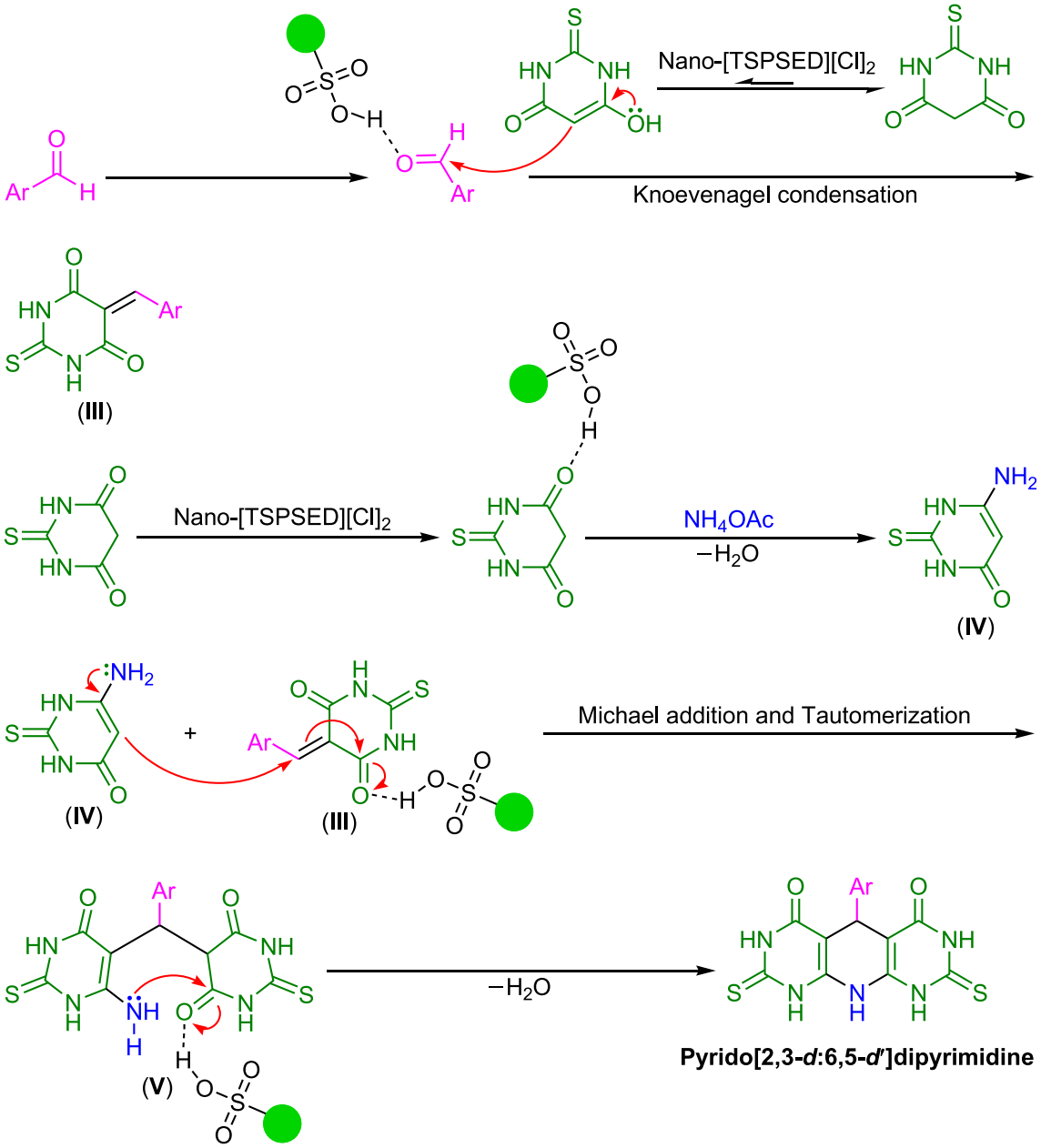
paper [10]). Nonetheless, the FE-SEM micrograph of the recycled catalyst (Fig. 5) indicated that the nanoparticles have slightly aggregated during recycling, and their sizes have slightly increased, when compared

Table 2 The production of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines using nano-[SiO_2-R-NMe_2SO_3H][Cl]



Comp. no	Ar	Time (min)	Yield[a] (%)	M.p. (°C)	
				Found	Reported
1	C_6H_5	5	89	208-210	211 [43]
2	2-$O_2NC_6H_4$	10	92	228-230	230 [43]
3	4-$O_2NC_6H_4$	5	94	329-331	330 [43]
4	4-MeC_6H_4	10	91	316-318	-
5	3-$MeOC_6H_4$	15	88	237-239	242 [43]
6	4-$MeOC_6H_4$	10	90	277-279	280 [42]
7	3,4-$(MeO)_2C_6H_3$	10	91	>300	>300 [39]
8	4-ClC_6H_4	5	93	254-256	257 [43]
9	4-FC_6H_4	5	88	227-229	-
10	2-FC_6H_4	5	95	239-241	240 [43]
11	2-BrC_6H_4	15	91	255-257	253-255 [38]
12	3-BrC_6H_4	10	93	248-250	246-248 [38]

[a] Isolated yield



Scheme 3 The suggested mechanism for the preparation of pyrido[2,3-*d*:6,5-*d'*]dipyrimidines

Table 3 Comparison of the reaction conditions and results of nano-[SiO_2-R-NMe_2SO_3H][Cl] with the reported catalysts in the preparation of product **10**

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	Nano-[SiO_2-R-NMe_2SO_3H][Cl]	Solvent-free, 90 °C	5	95	–
2	Nano-[DMSPDE][Cl]	Solvent-free, 110 °C	15	86	[38]
3	γ-Fe_2O_3@HAp-SO_3H[a]	DMF, 110 °C	20–75	70–95	[39]
4	Fe-MCM-41-IL	H_2O, r.t.	45	80	[40]
5	Nano $CuFe_2O_4$	H_2O, r.t.	35	85	[41]
6	$[HNMP]^+[HSO_4]^-$	H_2O, ultrasonic (26.5 W)	8	90	[42]
7	Nano $CuFe_2O_4$	H_2O, ultrasonic (40 W)	10	90	[43]
8	Nano $CuFe_2O_4$	H_2O, microwave (100 W)	2	90	[44]

[a] In this work, product **10** has not been synthesized; thus, we have tabulated the range of times and yields

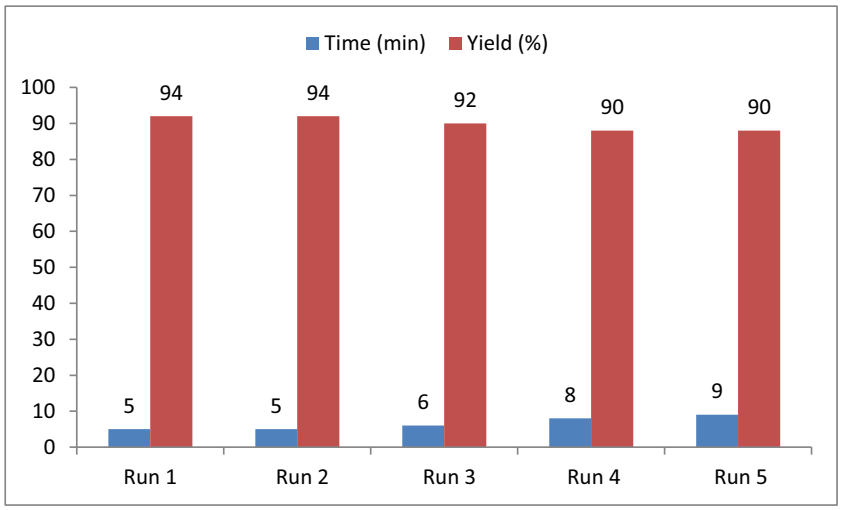


Fig. 3 The results of reusing nano-[SiO_2-R-NMe_2SO_3H][Cl]

with the fresh catalyst [10]. The XRD pattern of recycled nano-[SiO_2-R-NMe_2SO_3H][Cl] (Fig. 6) was slightly different relative to the fresh catalyst [10] (the sharp peaks has decreased); this can attributed to aggregation of the nanoparticles, increment of their sizes and increasing amount of amorphous form, during recycling and reusing.

3 Conclusions

In summary, we have introduced nano-[SiO_2-R-NMe_2SO_3H][Cl] as a mesoporous catalyst for the preparation of a significant class of heterocyles. The profits of our protocol consist of relatively simple preparation of the catalyst, recyclability of the catalyst, easy workup procedure, short reaction times, high yields, generality, effectiveness, convenient one-pot operation, good compliance with green chemistry protocols, and superiority of at least two of these items: yields, the reaction times, the reaction temperature and conditions relative to the reported methods.

4 Experimental

4.1 Materials and Apparatuses

The reactants and solvents were supplied from Merck or Fluka Chemical Companies. Nano-[SiO_2-R-NMe_2SO_3H][Cl] was prepared by our recently published method (Scheme 1) [10]. Identification of known products was accomplished by comparing their melting points and/or NMR data with the reported ones. Thin layer chromatography (TLC) on silica gel SIL G/UV 254 plates was applied for observation of the reaction

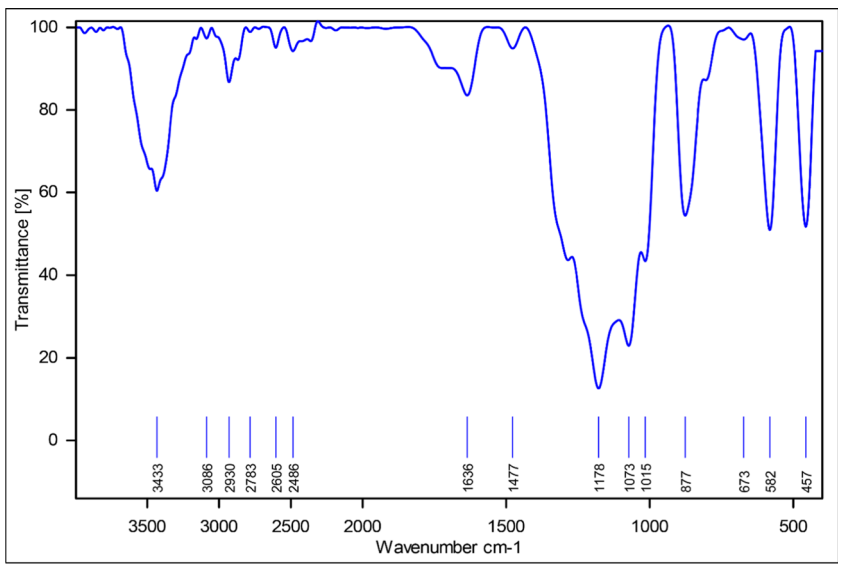


Fig. 4 The FT-IR spectrum of recycled nano-[SiO_2-R-NMe_2SO_3H][Cl]

Table 4 The FT-IR data of nano-[TSPSED][Cl]$_2$

Absorption (cm^{-1})	Related bond or functional group
457	Rocking of Si-O
582	Bending of -SO_2-
673	Stretching of S-O
877	Stretching of N-S
1015	Stretching of Si-C
1073	Stretching of Si-O-Si
1178	Asymmetric stretching of -SO_2-
1477	Bending of C-H
1636	Bending of O–H group of molecular water adsorbed on silica gel
2930	Symmetric stretching of C-H
2400–3650	Stretching of OH group of the SO_3H and OH groups on silica surface

progress. Melting points were measured by a Büchi B-545 apparatus in open capillary tubes. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometers. Shimadzu GC-MS-QP 1100 EX model was utilized for running mass spectra. Apparatuses model MIRA3TESCAN-XMU and Zeiss EM900 980 keV) were applied for recording FE-SEM and TEM images of the catalyst.

4.2 General Method for the Synthesis of Pyrido[2,3-*d*:6,5-*d*′]Dipyrimidines

Aldehyde (1 mmol), 2-thiobarbituric acid (0.288 g, 2 mmol), NH_4OAc (0.108 g, 1.4 mmol) and nano-[SiO_2-R-NMe_2SO_3H][Cl] (0.02 g) were mixed, and stirred forcefully by a rod at 90 °C. After consumption of the reactants, as observed by TLC, MeOH (15 mL) was added to the reaction mixture, refluxed for 2 min (accompanied with stirring), centrifuged and decanted to detach the nanocatalyst {the recycled nano-[SiO_2-R-NMe_2SO_3H][Cl] was washed by MeOH (2 × 3 mL), dried and utilized for the next run}. Evaporation of the resulting solvent from the decanting, and recrystallization of the obtained precipitate from ethanol (95%) afforded the pure product.

4.3 Spectroscopic Data of some Products

Product 1: ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 5.96 (s, 1H, methine CH), 7.00 (d, J = 7.7 Hz, 2H, H_{Ar}), 7.05 (t, J = 7.1 Hz, 1H, H_{Ar}), 7.16 (t, J = 7.5 Hz, 2H, H_{Ar}), 7.55 (br., 1H, NH), 11.53 (br., 3H, NH), 17.15 (br., 1H, NH) (supplementary material, Fig. S1); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 30.9, 96.3, 125.3, 126.9, 128.1, 143.4, 163.1, 164.2, 173.2 (supplementary material, Fig. S2).

Product 4: FT-IR (KBr, cm^{-1}): ν_{max} 3477 (NH), 3089 (C-H, sp^2 stretch), 2919 (C-H, sp^3 symmetric stretch), 1644 (C=O), 1538 and 1433 (C=C), 1302 and 1132 (C=S) (supplementary material, Fig. S3); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.20 (s, 3H, CH_3), 5.90 (s, 1H, methine CH), 6.87 (d, J = 7.8 Hz, 2H, H_{Ar}), 6.96 (d, J = 7.6 Hz, 2H, H_{Ar}), 7.10 (br., 1H, NH), 11.51 (br., 3H, NH), 17.15 (br., 1H, NH) (supplementary material, Fig. S4); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 21.0, 30.5, 96.4, 126.9, 128.7, 134.0, 140.3, 163.0, 163.9, 173.2 (supplementary material, Fig. S5). Mass: m/z 371 $[M]^+$ (supplementary material, Fig. S6).

Product 5: ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.63 (s, 3H, CH_3), 5.91 (s, 1H, methine CH), 6.49 (s, 1H, H_{Ar}), 6.57 (d, J = 7.7 Hz, 1H, H_{Ar}), 6.63 (dd, J = 8.1, 2.3 Hz, 1H, H_{Ar}), 7.07 (a broad peak and a triplet, J = 7.9 Hz, 2H, H_{Ar} and NH), 11.54 (br., 4H, NH) (supplementary material, Fig. S7); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 31.0, 55.4, 96.4,

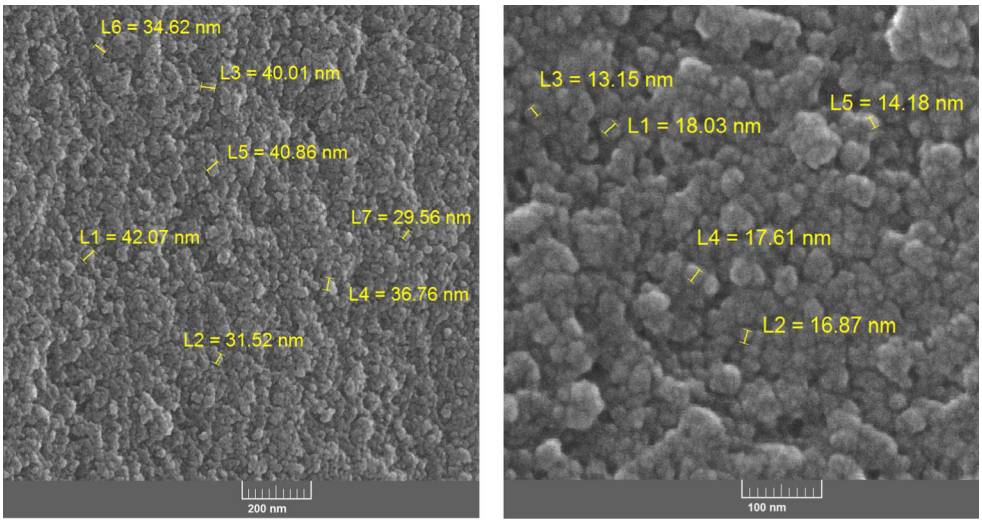


Fig. 5 The FE-SEM micrographs of the recycled catalyst

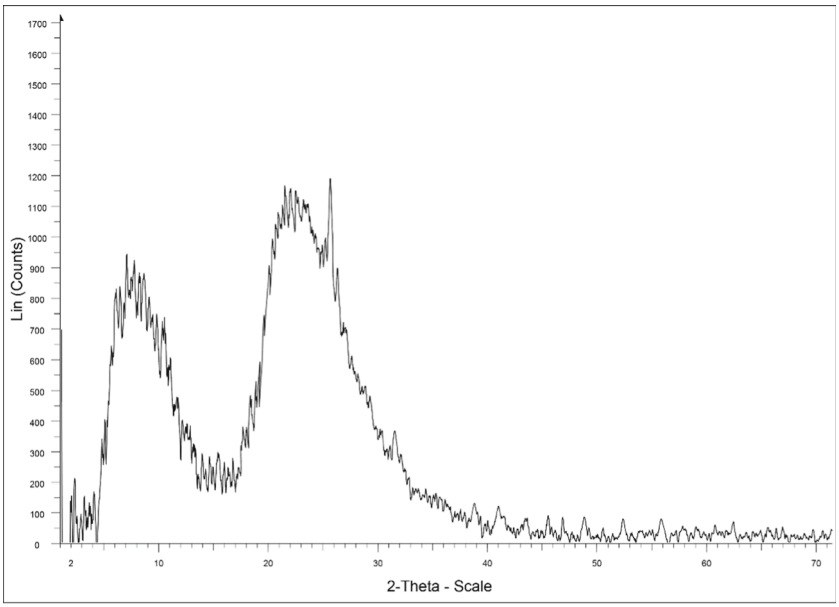


Fig. 6 The XRD pattern of recycled nano-[SiO_2-R-NMe_2SO_3H][Cl]

109.9, 113.8, 119.8, 129.3, 145.4, 159.6, 163.3, 172.9, 173.4 (supplementary material, Fig. S8).

Product 6: ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.66 (s, 3H, CH_3), 5.89 (s, 1H, methine CH), 6.72 (d, J = 8.5 Hz, 2H, H_{Ar}), 6.89 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.08 (br., 1H, NH), 11.47 (br., 2H, NH), 11.61 (br., 2H, NH) (supplementary material, Fig. S9); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 30.1, 55.4, 96.5, 113.5, 127.9, 135.3, 157.2, 163.0, 164.1, 173.2 (supplementary material, Fig. S10).

Product 9: FT-IR (KBr, cm^{-1}): ν_{max} 3475 (NH), 3142 (C-H, sp^2 stretch), 2880 (C-H, sp^3 symmetric stretch), 1617 (C=O), 1537 and 1437 (C=C), 1304 and 1132 (C=S) (supplementary material, Fig. S11); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 5.93 (s, 1H, methine CH), 6.95–6.99 (m, 4H, H_{Ar}), 10.48 (br., 1H, NH), 11.53 (br., 3H, NH), 17.14 (br., 1H, NH) (supplementary material, Fig. S12); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 30.4, 96.2, 114.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 128.6 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 139.3 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 160.5 (d, $^1J_{C\text{-}F}$ = 238.8 Hz), 163.1, 164.5, 173.3 (supplementary material, Fig. S13). Mass: m/z 375 $[M]^+$ (supplementary material, Fig. S14).

Product 10: ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 6.03 (s, 1H, methine CH), 6.94–7.01 (m, 2H, H_{Ar}), 7.12 (d, J = 6.8 Hz, 2H, H_{Ar}), 10.59 (br., 1H, NH), 11.49 (br., 3H, NH), 16.97 (br., 1H, NH) (supplementary material, Fig. S15); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 25.9, 94.4, 114.3 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 122.5, 126.5 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 129.0 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 129.6 (d, $^3J_{C\text{-}F}$ = 12.5 Hz), 159.8 (d, $^1J_{C\text{-}F}$ = 242.5 Hz), 162.2, 163.5, 172.3 (supplementary material, Fig. S16).

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