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FAST AND GREEN SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES AND –THIONES USING NANOMETASILICA DISULFURIC ACID AS RECYCLABLE CATALYST IN WATER

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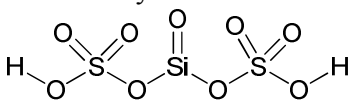
ABSTRACT
Biginelli reaction of *β*-ketoesters, an aryl aldehyde, and urea or thiourea in the presence of nanometasilica disulfuric acid (NMSDSA), as an efficient catalyst in refluxing water is reported. The catalyst was prepared according to a previously published literature procedure using inexpensive and readily available starting materials. Furthermore, the catalyst could be recovered conveniently and reused efficiently such that a considerable catalytic activity still could be achieved after fourth run. Other beneficial features of this new synthetic approach include short reaction times, high yields, clean reaction profiles, and a simple work-up procedure.

KEY WORDS: Biginelli reaction; 3,4-Dihydropyrimidin-2(1*H*)-ones and –thiones; Fast and green synthesis; Nanometasilica disulfuric acid (NMSDSA).

INTRODUCTION
Acid-catalysts are one of the most frequently applied processes in chemical industry, which has been a major area of research interest[1]. Commonly, liquid inorganic acids including H_2SO_4, HCl and H_3PO_4 are part of the homogeneous acid catalysts. Despite their application in the wide production of industrial chemicals, many disadvantages such as high toxicity, corrosive nature, hazards in handling and difficult separation from the products make them not so useful. Furthermore, the synthesis using homogeneous catalysts have major problem of catalyst recovery and reuse. These difficulties are not in the range of green chemistry. According to these disadvantages, in order to improve drawbacks of these catalysts, replacement of them by novel, nontoxic, eco-friendly, recyclable heterogeneous catalysts with improved efficiency have been the important topics of researchers during the last decades. Heterogeneous catalysts show important role in many aspects of environmental and economic in many industrial processes. They presented some excellence including great reactivity, operational simplicity, low toxicity, non-corrosive nature and the potential of the

recyclability. Furthermore, most of the heterogeneous catalysts show better product selectivity, so that by-product can be easily separated[ii]. In this regard, a wide range of catalysts and their supported heterogeneous forms are reported in the last few years for various chemical and biochemical processes and extensively have been reviewed. Among the reported solid catalysts, solid inorganic and natural-based acids have been also used widely for various organic functional group transformations[iii, iv]. One of the most important strategies to combine economic aspects with the environmental concerns is the use of silica or its corresponding derivatives as a core or coating agent in the synthesis of porous materials and nanocatalysts[v]. Silica sulfuric acid (SSA) as a familiar example has been prepared via reaction between silica gel and chlorosulfonic acid at room temperature[vi]. SSA and its different forms as a superior proton source of all of the reported acidic solid supports or acidic resins have been widely used for a various functional groups transformations[vii] and extensively reviewed[viii].

In this research, sodium metasilicate has reacted with two equivalents of chlorosulfonic acid to synthesize nanometasilica disulfuric acid (NMSDSA). It is fascinating to note that the reaction is simple and safe without any workup process because NaCl salt is performed as a solely byproduct. The structure of this catalyst is shown in scheme 1.



Scheme 1. Structure of NMSDSA

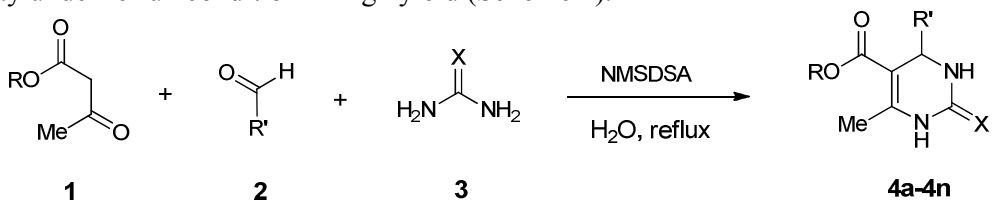
Multicomponent reactions (MCRs) are one-pot processes in which three or more available components react to form a new product that contains basically most or all atoms of the reactants used[ix]. Dihydropyrimidinones and thiones (DHPMs) are an important class of organic compounds with low molecular weight that synthesized *via* MCR includes the condensation of *β*-ketoester, aldehyde, and urea or thiourea as primary reagents[x]. These structures attract tremendous concentration in medicinal chemistry research because of their large range of pharmacological effects and providing important ligands for biological receptors.

Some literatures demonstrated pharmacological and therapeutic effects of DHPMs structure such as calcium channel blockers[xi], antihypertensive drugs[xii], α1a-adrenergic antagonists[xiii], neuropeptide antagonists[xiv]. Recently, DHPMs have also been found as potential antioxidant agents and considered for the development of new anticancer drugs[xv, xvi]. Furthermore, their specific structure has been found in natural marine alkaloid batzalladines, which are the first low-molecularweight natural products reported in the literature to inhibits the binding of HIVgp-120 to CD4 cell. This could be a new path for the development of AIDS therapy[xvii, xviii].

Many synthetic protocols were developed to accelerate the rate of DHPMs reaction and to improve the yield. These compounds have been synthesized in the presence of various Lewis and Brønsted acid catalyst such as $M(NTf)_2$ (M = Ni, Cu, Yb)[xix], $[bmim][FeCl_4]$[xx], $InCl_3$[xxi], $FeCl_3$[xxii], $BF_3{\cdot}OEt_2$[xxiii], $LaCl_3$[xxiv], $InBr_3$[xxv], $ZrOCl_2$[xxvi], $Fe(ClO_4)_3$[xxvii], CuI[xxviii], $ZrCl_4$[xxvi] have been utilized in the construction of the DHPMs skeleton. Major drawbacks of these procedures include expensive reagents, use of large amounts of toxic organic solvents, prolonged heating and side reactions.

All of these disadvantages make further improvement of the synthesis of such molecules essential. Therefore, the development of a new greener and more convenient method using a new catalyst with high catalytic activity for the synthesis of DHPMs is highly desirable.

As part of our research program on the development of convenient methods using reusable catalysts for the synthesis of organic compounds[xxix–xxxviii], and as a result of global interest in the ongoing research towards the development of environmentally friendly methods for the synthesis of organic compounds especially compounds that are frequently used in pharmaceutical industry, we report herein facile and efficient green synthesis of DHPMs with short reaction time by the three-component condensation of *β*-ketoesters **1**, an aryl aldehyde **2**, and urea or thiourea **3** using NMSDSA, as heterogeneous catalysts with high catalytic activity under reflux condition in high yield (Scheme 2).



Scheme 2. NMSDSA catalyzed synthesis of DHPMs.

RESULTS AND DISCUSSION

Characterization of the catalyst

For our investigations, the NMSDSA catalyst was prepared according to the literature procedure[xxxviii]. The NMSDSA was characterized by FT-IR, and thermal gravimetric (TG) analysis. The FT-IR spectrum of the NMSDSA is shown in (Fig. 1 (1)). The characteristic vibrational bands of the SiO_3 at 524 and 1103 cm^{-1} are related to the stretching vibration of Si–O groups. The two abroad peaks at 3472 and 3421 cm^{-1} which can be related to O–H stretching on $–SO_3H$ group. Also, the two peaks at 1296 and 1183 cm^{-1} are related to vibrational modes of $O–SO_2$ bonds. The absorption peak related to S=O bond vibration appeared at 1048 cm^{-1}.

In the TG curve of NMSDSA (Fig. 2) Two-stage decomposition is seen corresponding to different mass lose ranges. In the first region, a mass loss approximately 3% weight occurred between room temperature and 120 °C is attributable to the loss of trapped water and organic solvents, which were used in making the catalyst. A mass loss of approximately 13% weight occurred between 120 and 190 °C that related to the slow mass loss of SO_3H groups. Finally, a mass loss of approximately 14% weight occurred between 190–415 °C that it was related to the thermal decomposition of the catalyst. From the TG, it can be concluded that NMSDSA could be safety used in organic reactions due to high thermal stability about 415 °C.

Evaluation of catalytic activity of NMSDSA in the synthesis of DHPMs.

The catalytic activity of this material was evaluated in the synthesis of DHPMs. At first, the synthesis of compound **4d** was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by mixture of ethyl acetoacetate (1 mmol), 4-chlorobenzaldehydes (1 mmol), and urea (1 mmol) in the presence of different amounts of NMSDSA, and various solvents such as H_2O, EtOH, MeOH, CH_3CN, CH_2Cl_2, and also under solvent-free conditions at different temperature. Long reaction times (up to100 min) and poor yields (below 45 %) of the product **4d** were obtained in the absence of the catalyst in all cases. On the other hand, different amounts of the catalyst (0.01, 0.03, 0.05, 0.07, and 0.09) in the presence of the solvents or solvent-free condition in various temperatures caused to improve the yields and times of the reaction. Moreover, the best results in the presence of different amounts of the catalyst found in refluxing solvents. These outcomes show that catalyst, solvent, and temperature are necessary for this reaction as well polar solvents were better than other non-polars. Also, the best yields and short reaction times were obtained in 0.07 g of the catalyst in water at different temperature. Whereas, further increase in catalyst

amount to 0.09 g, did not improve the product yield and reaction time. Among the tested solvents and also solvent-free conditions and various amounts of the catalyst, the reaction was more facile and proceeded to give the highest yield (96 %), and short reaction time (17 min), using 0.07 g of NMSDSA in H_2O (5 ml) at reflux temperature. All subsequent reactions were carried out in these optimized conditions.

According to these results, and in order to generalize this model reaction, we developed the reaction of *β*-ketoesters and urea or thiourea with a range of other aromatic aldehydes under the optimized reaction conditions (Table 1). The NMSDSA efficiently catalyzed the reactions, giving the products 4a-4m in high yields over relatively short reaction times. Easy separation of obtained products from the catalyst makes this method useful for the synthesis of DHPMs. Purity checks with melting points, TLC and the ^{1}H NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **4a-4n** were deduced from their ^{1}H NMR and FT-IR spectral data and a comparison of their melting points with those of authentic samples.

Table 1. NMSDSA catalyzed synthesis of DHPMs [a].

Entry	R	R'	X	Product[b]	Time /min	Isolated Yield %	m.p. (ºC) Found	m.p. (ºC) Reported
1	Et	Ph	O	**4a**	15	93	203-205	202-204[xxiii]
2	Me	Ph	O	**4b**	20	95	208-210	209-212[xxiii]
3	Et	Ph	S	**4c**	18	91	207-209	208-210[xxv]
4	Et	4-ClC_6H_4	O	**4d**	17	96	213-215	212-214[xxv]
5	Me	4-ClC_6H_4	O	**4e**	16	89	155-157	149-152[xxiii]
6	Et	4-ClC_6H_4	S	**4f**	17	95	192-194	192-194[xxv]
7	Et	3-BrC_6H_4	O	**4g**	20	94	196-198	195-196[xxxix]
8	Et	4-FC_6H_4	O	**4h**	15	95	174-176	173-176[xl]
9	Et	4-MeC_6H_4	O	**4i**	16	92	213-215	216-218[xxxix]
10	Me	4-MeC_6H_4	O	**4j**	15	93	203-205	204-206[xxv]
11	Et	4-MeC_6H_4	S	**4k**	19	89	193-195	192-194[xxv]
12	Et	4-$MeOC_6H_4$	O	**4l**	18	94	201-203	198-200[xl]
13	Et	4-$MeOC_6H_4$	S	**4m**	17	95	154-156	150-152[xxv]
14	Et	4-$NO_2C_6H_4$	O	**4n**	14	91	207-209	206-208[xl]

[a]Reaction conditions: *β*-ketoesters **1** (1 mmol), aromatic aldehyde **2** (1 mmol), urea or thiourea **3** (1 mmol) and NMSDSA (0.07 g) in refluxing water.
[b]All the products were characterized according to their FT-IR and ^{1}H NMR spectral data and comparison of their melting points with those of authentic samples.

We also used the model reaction under optimized reaction conditions to evaluate the reusability of the NMSDSA catalyst. After completion of the reaction, the catalyst was recovered as described in the experimental section. The separated catalyst was dried at 50 ºC under vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least four times without significant reduction in its activity (96, 95, 94, 94 % yields in first to fourth use, respectively) which clearly demonstrates the practical reusability of this catalyst.

Furthermore, the FT-IR spectra of the recovered catalysts (Fig. 1(2)–(4)) were almost identical to the spectrum of the fresh catalyst (Fig. 1(1)), indicating that the structure of the catalyst was unchanged by the reaction.

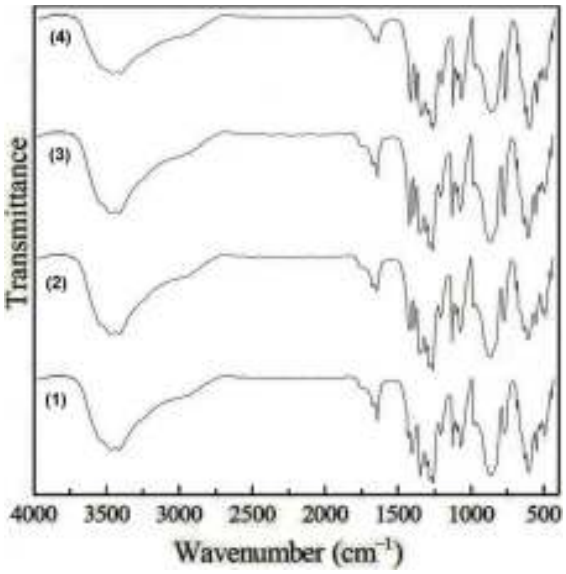


Fig. 1. FT-IR spectra of the fresh catalyst NMSDSA ((1), first run), and the recovered catalyst ((2–4), runs 2–4).

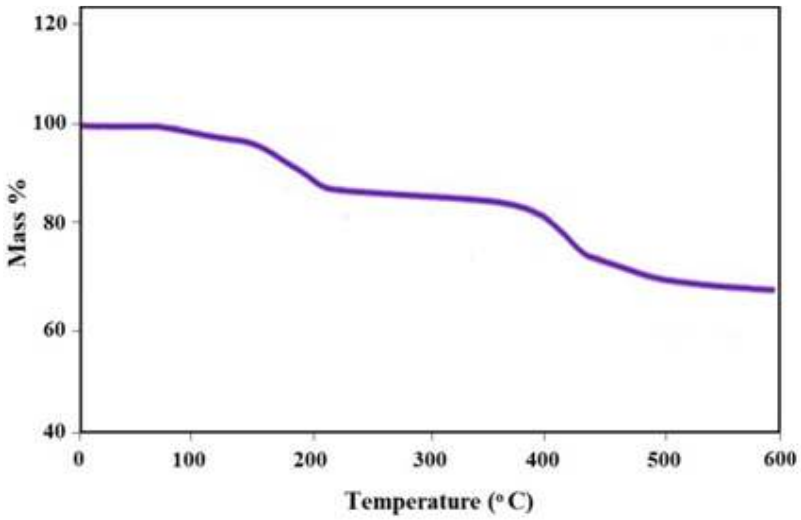


Fig. 2. Thermal gravimetric (TG) analysis of the NMSDSA

We compared the results we obtained using NMSDSA as catalyst with previously reported results for the synthesis of DHPMs in the presence of various catalysts (Table 2). Our reaction conditions showed shorter reaction times than all the other conditions and gave high yields of the desired products.

Table 2. Comparison of the efficiencies of different catalysts for the synthesis of DHPMs.

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T/ºC	Other			
$M(NTf)_2$ (M = Ni, Cu, Yb)	Water	r.t	-----	1440	25-88	xix
[bmim][FeCl4]	-----	100	-----	30	56-99	xx
$InCl_3$	THF	Reflux	-----	360-540	75-95	xxi
$FeCl_3$	-----	90	-----	240	53-96	xxii
$BF_3{\cdot}OEt_2$	THF	r.t	-----	1080	70-96	xxiii
$LaCl_3$	EtOH	Reflux	-----	300	56-97	xxiv
$InBr_3$	EtOH	Reflux	-----	420	68-98	xxv
$ZrOCl_2$	-----	90-100	-----	30-180	40-99	xxvi
$Fe(ClO_4)_3$	CH_3CN	Reflux	-----	120-300	73-94	xxvii
CuI	Water	90	-----	240-360	65-71	xxviii
$ZrCl_4$	-----	100	-----	120-300	78-92	xxvi
NMSDSA	Water	Reflux	-----	14-20	89-96	This work

Although we did not investigate the reaction mechanism, the NMSDSA could acts as Brönsted acid related to the $–SO_3H$ groups and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature[xxxviii]. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker 400 and 500 spectrometers.

General experimental procedure for the synthesis of DHPMs 4a-4n catalyzed by NMSDSA

A mixture of *β*-ketoesters **1** (1 mmol), aromatic aldehydes **2** (1 mmol), urea or thiourea **3** (1 mmol) and NMSDSA (0.07 g) as catalyst was heated in refluxing water for 14–20 min. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate (5 mL) was added to the reaction mixture, stirred and refluxed for 10 min. Since the reaction mixture was soluble in hot ethyl acetate and NMSDSA catalyst was soluble in water, the two layers were separated through separating funnel. The solvent of the organic layer was evaporated, and the crude product was purified *via* recrystallization from ethanol. Also, the catalyst could be readily recovered from the evaporation aqueous phase to dryness under reduced pressure and washing with hot ethanol.

^{1}H NMR and FT-IR data:

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H, *J* = 7.1 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 7.1 Hz, CH_2), 5.13 (d, 1H, *J* = 3.2 Hz, CH), 7.20-735 (m, 5H, arom-H), 7.76 (s, 1H, NH), 9.23 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3231 (NH), 3113 (NH), 1701 (C=O), 1651 (C=O).

Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 5.14 (d, 1H, *J* = 2.8 Hz,

CH), 7.22-7.35 (m, 5H, arom-H), 7.74 (s, 1H, NH), 9.22 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3239 (NH), 3115 (NH), 1708 (C=O), 1656 (C=O).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H, *J* = 6.9 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.98 (q, 2H, *J* = 6.9 Hz, CH_2), 5.15 (d, 1H, *J* = 2.8 Hz, CH), 7.23-7.42 (m, 5H, arom-H), 9.62 (s, 1H, NH), 10.31 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3247 (NH), 3126 (NH), 1664 (C=O).

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d) ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (t, 3H, *J* = 7.1 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.95-4.05 (m, 2H, CH_2), 5.15 (d, 1H, *J* = 3.2 Hz, CH), 7.25 (d, 2H, *J* = 7.7 Hz, arom-H), 7.39 (d, 2H, *J* = 7.7 Hz, arom-H), 7.75 (s, 1H, NH), 9.22 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3233 (NH), 3114 (NH), 1703 (C=O), 1650 (C=O).

Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 5.11 (d, 1H, *J* = 2.8 Hz, CH), 7.24 (d, 2H, *J* = 8.4 Hz, arom-H), 7.40 (d, 2H, *J* = 8.4 Hz, arom-H), 7.79 (s, 1H, NH), 9.28 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3234 (NH), 3115 (NH), 1709 (C=O), 1653 (C=O).

Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 7.1 Hz, CH_3), 2.29 (s, 3H, CH_3), 3.95‑4.05 (m, 2H, CH_2), 5.17 (s, 1H, CH), 7.40 (d, 2H, *J* = 8.4 Hz, arom-H), 7.78 (d, 2H, *J* = 8.4 Hz, arom-H), 9.65 (s.br., 1H, NH), 10.36 (s.br., 1H, NH); IR (KBr, cm^{-1}): υ 3328 (NH), 3175 (NH), 1673 (C=O).

Ethyl 4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g) ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 7.0 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.95-4.05 (m, 2H, CH_2), 5.14 (d, 1H, *J* = 3.2 Hz, CH), 7.23 (d, 1H, *J* = 7.7 Hz, arom-H), 7.31 (t, 1H, *J* = 7.8 Hz, arom-H), 7.39 (s, 1H, arom-H), 7.45 (dt, 1H, *J* = 7.9, 0.9 Hz, arom-H), 7.77 (s, 1H, NH), 9.25 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3238 (NH), 3114 (NH), 1706 (C=O), 1654 (C=O).

Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h) ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (t, 3H, *J* = 7.2 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.95-4.00 (m, 2H, CH_2), 5.13 (d, 1H, *J* = 3.2 Hz, CH), 7.20-7.40 (m, 4H, arom-H), 7.75 (s, 1H, NH), 9.24 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3238 (NH), 3079 (NH), 1703 (C=O), 1650 (C=O).

Ethyl 6-methyl-2-oxo-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 7.1 Hz, CH_3), 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H, CH_2), 5.12 (d, 1H, *J* = 3.2 Hz, CH), 7.01 (d, 2H, *J* = 7.9 Hz, arom-H), 7.15 (d, 2H, *J* = 7.9 Hz, arom-H), 7.93 (s, 1H, NH), 9.15 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3241 (NH), 3117 (NH), 1711 (C=O), 1656 (C=O).

Methyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 5.10 (d, 1H, *J* = 3.2 Hz, CH), 6.99 (d, 2H, *J* = 8.0 Hz, arom-H), 7.15 (d, 2H, *J* = 8.0 Hz, arom-H), 7.82 (s, 1H, NH), 9.18 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3240 (NH), 3115 (NH), 1709 (C=O), 1655 (C=O).

Ethyl 6-methyl-2-thioxo-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k) ^{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), 2.28 (s, 3H, CH_3), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 5.12 (d, 1H, *J* = 3.2 Hz, CH), 7.03 (d, 2H, *J* = 7.8 Hz, arom-H), 7.17 (d, 2H, *J* = 7.8 Hz, arom-H), 9.56 (s, 1H, NH), 10.25 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3320 (NH), 3180 (NH), 1671 (C=O).

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (t, 3H, *J* = 7.1 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.72 (s,

3H, CH_3O), 3.99 (q, 2H, *J* = 7.1 Hz, CH_2), 5.25 (d, 1H, *J* = 2.4 Hz, CH), 6.20 (s, 1H, NH), 6.75 (d, 2H, *J* = 8.7 Hz, arom-H), 7.18 (d, 2H, *J* = 8.7 Hz, arom-H), 7.66 (s, 1 H), 9.14 (s, 1 H); IR (KBr, cm^{-1}): υ 3247 (NH), 3118 (NH), 1703 (C=O), 1649 (C=O).

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, 3H, *J* = 7.1 Hz, CH_3), 2.28 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.00 (q, 2H, *J* = 7.1 Hz, CH_2), 5.11 (d, 1H, *J* = 3.6 Hz, CH), 6.89 (d, 2H, *J* = 8.6 Hz, arom-H), 7.12 (d, 2H, *J* = 8.6 Hz, arom-H), 9.57 (s, 1H, NH), 10.26 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3314 (NH), 3171 (NH), 1667 (C=O).

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H, *J* = 7.1 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H, CH_2), 5.25 (d, 1H, *J* = 3.2 Hz, CH), 7.56 (d, 2H, *J* = 8.4 Hz, arom-H), 7.90 (s, 1H, NH), 8.23 (d, 2H, *J* = 8.4 Hz, arom-H), 9.36 (s, 1H, NH); IR (KBr, cm^{-1}): υ 3324 (NH), 3092 (NH), 1721 (C=O), 1657 (C=O).

CONCLUSION

In summary, we showed that NMSDSA, efficiently catalyzed the synthesis of Biginelli reaction by one-pot, three-component reaction of *β*-ketoesters, an aryl aldehyde, and urea or thiourea at in water. The method was relatively fast and high yielding, and the work-up was easy. The catalyst can be recycled after simple handling, and used at least four times without any substantial reduction in its catalytic activity. The procedure is also advantageous in the sense that it is a fast reaction in refluxing water and therefore operates under environmentally friendly conditions.

REFERENCES

i. K. Tanabe and W.F. Hölderich, *Appl. Catal. A Gen.*, **181**, 399 (1999).
ii. A. Davoodnia, A. Nakhaei and N. Tavakoli-Hoseini, *Z. Naturforsch. B*, **71**, 219 (2016).
iii. T. Ahmadi, A. Davoodnia, M. Pordel, M. Fattahi, M. Ebrahimi, N. Tavakoli-Hoseini and A. Nakhaei, *Heterocycl. Lett.*, **7**, 27 (2017).
iv. S. Yadegarian, A. Davoodnia and A. Nakhaei, *Orient. J. Chem.*, **31**, 573 (2015).
v. M. Rohaniyan, A. Davoodnia and A. Nakhaei, *Appl. Organometal. Chem.*, **30**, 626 (2016).
vi. M.A. Zolfigol, *Tetrahedron*, **57**, 9509 (2001).
vii. M. Daraei, M.A. Zolfigol, F. Derakhshan-Panah, M. Shiri, H.G. Kruger and M. Mokhlesi, J. *Iran. Chem. Soc.*, **12**, 855 (2015).
viii. A. Davoodnia and A. Nakhaei, *Synth. React. Inorg. Metal-Org. Nano-Met. Chem.*, **46**, 1073 (2016).
ix. J. Zhu and H. Bienaymé, Multicomponent reactions, John Wiley & Sons, (2006).
x. S.V. Ryabukhin, A.S. Plaskon, E.N. Ostapchuk, D.M. Volochnyuk and A.A. Tolmachev, *Synthesis*, **2007**, 417 (2007).
xi. K., Singh, D. Arora and S. Singh, *Mini Rev. Med. Chem.,* **9**, 95 (2009).
xii. G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz and M.F. Malley, *J. Med. Chem.,* **35**, 3254 (1992).
xiii. D. Nagarathnam, S.W. Miao, B. Lagu, G. Chiu, J. Fang, T.G. Murali Dhar, J. Zhang, S. Tyagarajan, M.R. Marzabadi, F. Zhang and W.C. Wong, *J. Med. Chem.,* **42**, 4764 (1999).
xiv. J.P. Wan and Y. Pan, *Mini Rev. Med. Chem.*, **12**, 337 (2012).
xv. H.A. Stefani, C.B. Oliveira, R.B. Almeida, C.M. Pereira, R.C. Braga, R. Cella, V.C. Borges, L. Savegnago and C.W. Nogueira, *Eur. J. Med. Chem.,* **41**, 513 (2006).

xvi. T.U. Mayer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.L. Schreiber and T.J. Mitchison, *Science*, **286**, 971 (1999).

xvii. A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C.D. Brosse, S. Mai, A. Truneh and B. Carte, *J. Org. Chem.*, **60**, 1182 (1995).

xviii. B.B. Snider, J. Chen, A.D. Patil, and A.J. Freyer, *Tetrahedron Lett.,* **37**, 6977 (1996).

xix. I. Suzuki, Y. Suzumura and K. Takeda, *Tetrahedron Lett.,* **47**, 7861 (2006).

xx. J. Peng and Y. Deng, *Tetrahedron Lett.*, **42**, 5917 (2001).

xxi. B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.*, **65**, 6270 (2000).

xxii. J. Lu and H. Ma, *Synlett,* **2000**, 63 (2000).

xxiii. E.H. Hu, D.R. Sidler and U.H. Dolling, *J. Org. Chem.,* **63**, 3454 (1998).

xxiv. J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, **41**, 9075 (2000).

xxv. N.Y. Fu, Y.F. Yuan, Z. Cao, S.W. Wang, J.T. Wang and C. Peppe, *Tetrahedron*, **58**, 4801 (2002).

xxvi. J.C. Rodríguez-Domínguez, D. Bernardi, and G. Kirsch, *Tetrahedron lett.,* **48**, 5777 (2007).

xxvii. M.M. Heravi, F.K. Behbahani and H.A. Oskooie, *Chin. J. Chem.*, **26**, 2203 (2008).

xxviii. H.R. Kalita and P. Phukan, *Catal. Commun.*, **8**, 179 (2007).

xxix. A. Nakhaei and A. Davoodnia, *Chin. J. Catal.*, **35**, 1761 (2014).

xxx. A. Nakhaei, A. Davoodnia and A. Morsali, *Res. Chem. Intermed.*, **41**. 7815 (2015).

xxxi. A. Nakhaei, A. Davoodnia and S. Yadegarian, *Russ. J. Gen. Chem.*, **86**, 2870 (2016).

xxxii. A. Nakhaei, N. Hosseininasab and S. Yadegarian, *Heterocycl. Lett.*, **7**, 81 (2017).

xxxiii. A. Nakhaei, A. Davoodnia and S. Yadegarian, *Heterocycl. Lett.*, **6**, 601 (2016).

xxxiv. A. Nakhaei, A. Davoodnia and S. Yadegarian, *Heterocycl. Lett.*, **7**, 35 (2017).

xxxv. A. Nakhaei, S. Yadegarian and A. Davoodnia, *Heterocycl. Lett*., **6**, 329 (2016).

xxxvi. A. Nakhaei, A. Davoodnia, S. Yadegarian and N, Tavakoli-Hoseini, *Iran. J. Org. Chem*., **8**, 1919 (2016).

xxxvii. A. Davoodnia, S. Yadegarian, A. Nakhaei and N. Tavakoli-Hoseini, *Russ. J. Gen. Chem.*, **86**, 2849 (2016).

xxxviii. M.A. Zolfigol, H. Ghaderi, S. Baghery and L. Mohammadi, *J. Iran. Chem. Soc*., **14**, 121 (2017).

xxxix. N. Mohammadzadeh-Dehsorkh, A. Davoodnia, N. Tavakoli-Hoseini and M. Moghaddas, *Synth. React. Inorg. Metal-Org. Nano-Met. Chem*., **41**, 1135 (2011).

xl. C.V. Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu and V.N. Reddy, *Tetrahedron lett.,* **43**, 2657 (2002).

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