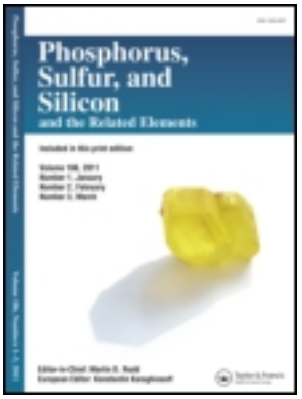


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Vanadatesulfuric Acid: A Novel, Recyclable, and Heterogeneous Catalyst for the One-Pot Synthesis of Dihydropyrimidinones and Dihydropyrimidinthiones Under Solvent-Free Conditions

Masoud Nasr-Esfahani [a] & Tooba Abdizadeh [a]

[a] Department of Chemistry , Yasouj University , Yasouj , Iran

Accepted author version posted online: 24 May 2012.Published online: 31 May 2013.

To cite this article: Masoud Nasr-Esfahani & Tooba Abdizadeh (2013): Vanadatesulfuric Acid: A Novel, Recyclable, and Heterogeneous Catalyst for the One-Pot Synthesis of Dihydropyrimidinones and Dihydropyrimidinthiones Under Solvent-Free Conditions, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:5, 596-608

To link to this article: http://dx.doi.org/10.1080/10426507.2012.694001

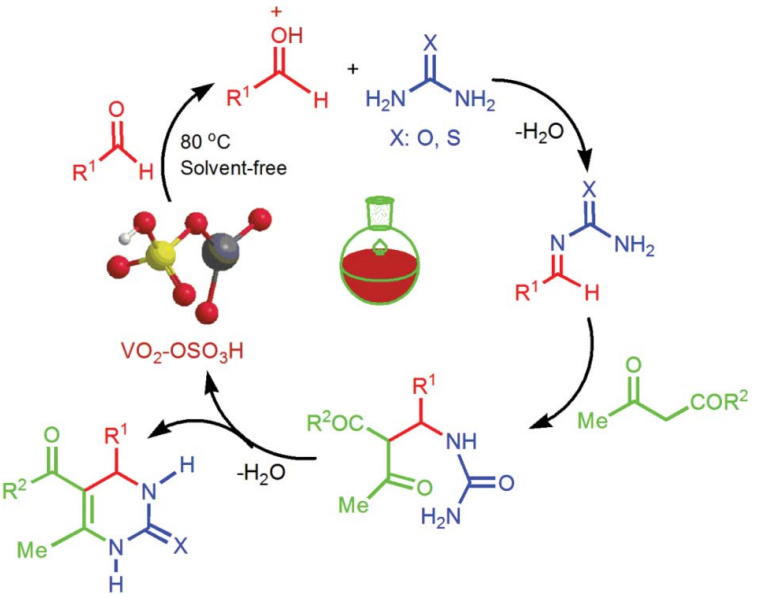
Phosphorus, Sulfur, and Silicon, 188:596–608, 2013

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.694001

VANADATESULFURIC ACID: A NOVEL, RECYCLABLE, AND HETEROGENEOUS CATALYST FOR THE ONE-POT SYNTHESIS OF DIHYDROPYRIMIDINONES AND DIHYDROPYRIMIDINTHIONES UNDER SOLVENT-FREE CONDITIONS

Masoud Nasr-Esfahani and Tooba Abdizadeh
Department of Chemistry, Yasouj University, Yasouj, Iran

GRAPHICAL ABSTRACT



Abstract *Vanadatesulfuric acid (VSA), as a novel and heterogeneous catalyst, was used for an efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones (thiones) using an aldehyde, urea, or thiourea and an acyclic β-dicarbonyl compound under solvent-free conditions. VSA is prepared via the reaction of sodium metavanadate and chlorosulfonic acid in high purity. The catalyst was characterized by FTIR, X-ray diffraction (XRD), and transmission electron microscopy (TEM) analysis. Compared to the classical Biginelli reactions, this method consistently has the advantage of high yields, simple workup, short reaction times, and reusability of the catalyst.*

Received 28 January 2012; accepted 9 May 2012.
We are thankful to Yasouj University for partial support of this work.
Address correspondence to Masoud Nasr-Esfahani, Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran. E-mail: manas@mail.yu.ac.ir

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Vanadatesulfuric acid; 3,4-dihydropyrimidin-2(1*H*)-ones (thiones); reusable catalyst; solvent-free; heterogeneous catalyst

INTRODUCTION

Multicomponent condensation reactions (MCRs) are powerful synthetic tools in organic and medicinal chemistry because of the fact that different products can be synthesized by varying the substrate in a one-pot procedure.[1] In the drug discovery process, multicomponent reaction strategies offer significant advantages over conventional linear-type syntheses.[2] From a synthetic point of view, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. Therefore, the discovery of new MCRs, or the full exploitation of the already known multicomponent reactions is of considerable current interest. One such MCR that belongs to the latter category is the synthesis of dihydropyrimidinone (DHPM) derivatives.

The Biginelli reaction is a well-known, simple, and straightforward acid-catalyzed procedure for the three-component condensation of β-ketoesters, an aliphatic or aromatic aldehyde, and an urea leading to the formation of 3,4-dihydropyrimidinones (DHPMs), first reported by Pietro Biginelli in 1893.[3] DHPMs and their derivatives possess a wide range of pharmacological and therapeutic properties such as calcium channel modulation,[4] mitotic kinesin Eg 5 inhibition,[5] antiviral,[6] antibacterial and antifungal,[7] and anticancer activities.[8] Recently, DHPMs have been used as starting material for the synthesis of so-called ''superstation'' rosuvastatin selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme responsible for the biosynthesis of cholesterol.[9] Several alkaloids, such as batzelladine alkaloids containing the DHPMs core unit, have been found to be potent human immunodeficiency virus (HIV) (gp-CD4) inhibitors.[10a] Moreover, the DHPM motif is present in many products isolated from natural material such as several species of sponges.[10b]

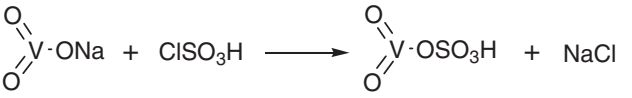
In the last few years, many synthetic methods have been developed for preparing these compounds by using Lewis acids or Brønsted acids promoters as well as microwave[11] and ultrasound irradiation[12] to improve and modify this reaction.

To replace the strong protic acid used in the classic Biginelli reaction, triflates,[13] aluminum hydrogen sulfate ($Al(HSO_4)_3$),[14] silicasulfuric acid,[15] *p*-toluenesulfonic acid (*p*-TSA),[16] L-prolines,[17] Nafion-50,[18] propanephosphoric acid,[19] *p*-dodecylbenzenesulfonic acid (DBSA),[20] polystyrenepoly(ethylene glycol) sulfuric acid (PS–PEG–SO_3H),[21] imidazol-1-yl-acetic acid,[22] N,N′-dichlorobis(2,4,6-trichlorophenyl)urea,[23] *p*-sulfonic acid calixarenes,[24] and ytterbium perfluorooctanoate ($Yb(PFO)_3$)[25] have been used.

However, many of the existing methods suffer from the use of expensive catalysts, longer reaction time, tedious workup, and low yields.[26] Therefore, the search for improved catalysts that are recyclable and capable of performing the reaction under mild conditions have gained particular attention.

Solid acids have emerged as potential alternate catalysts to the common liquid acids due to their safe nature, enhanced selectivity, requirements in catalytic amounts, and easier work-up.[27] The ease of separation without resulting into problem of waste disposal and option of reuse of the solid acid catalysts render the processes employing solid acid catalysts as green processes.

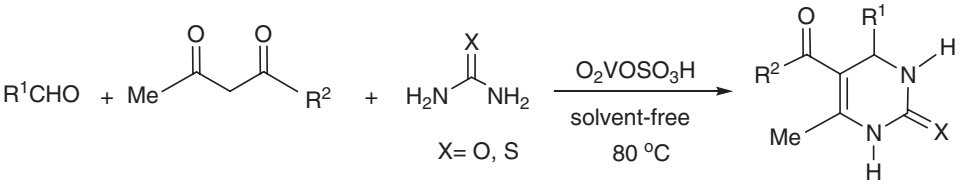
In continuation of the above and of our studies on the application of solid acids,[28] we found that anhydrous sodium metavanadate reacts with chlorosulfonic acid (1:1 mole ratio) to give vanadatesulfuric acid (VSA). The reaction is performed easily and cleanly and the product, VSA, was isolated by dilution of the mixture with water and then simple filtration (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

In connection with our recent interest in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones),[29,30] herein, we wish to report a simple and efficient method for such a reaction by using VSA as a new, green, recyclable, and heterogeneous catalyst under solvent-free conditions (Scheme 2).



Scheme 2

Characterization of VSA

In the infrared (IR) spectrum of $NaVO_3$, several absorptions appear, which are apparently the result of V–O stretching modes for each of several, different oxygen atoms according to the particular location or arrangement within the lattice.[31] At lower frequency, a broad and general absorption occurs, which is apparently caused by lower frequency V–O bonding. Here, the V–O stretching mode is observed as a medium band located at 950 cm^{-1}. These two spectra tend to locate the ''normal" position for this stretching vibration between oxygen and vanadium. Other broad bands are present in the spectrum of sodium metavanadate, centering at 845 and 690 cm^{-1}. The VO_3^- structure consists of V–O bonding of variable bond lengths, some of which vibrate at lower frequencies than others. The 950 cm^{-1} band has been assigned to a V–O bond, which is considerably shorter than other bonds in the structure; the 845 cm^{-1} band very probably arises from the stretching modes of the longer V–O bonds (Figure 1).

For VSA, the IR vibration bands are consigned as follows: the bands found at 3450 and 1640 cm^{-1} are attributed to the stretching and bending vibration of –OH group, respectively. The bands at 1050 and 1180 cm^{-1} are assigned for the sulfonic acid bonds, S–OH, S = O

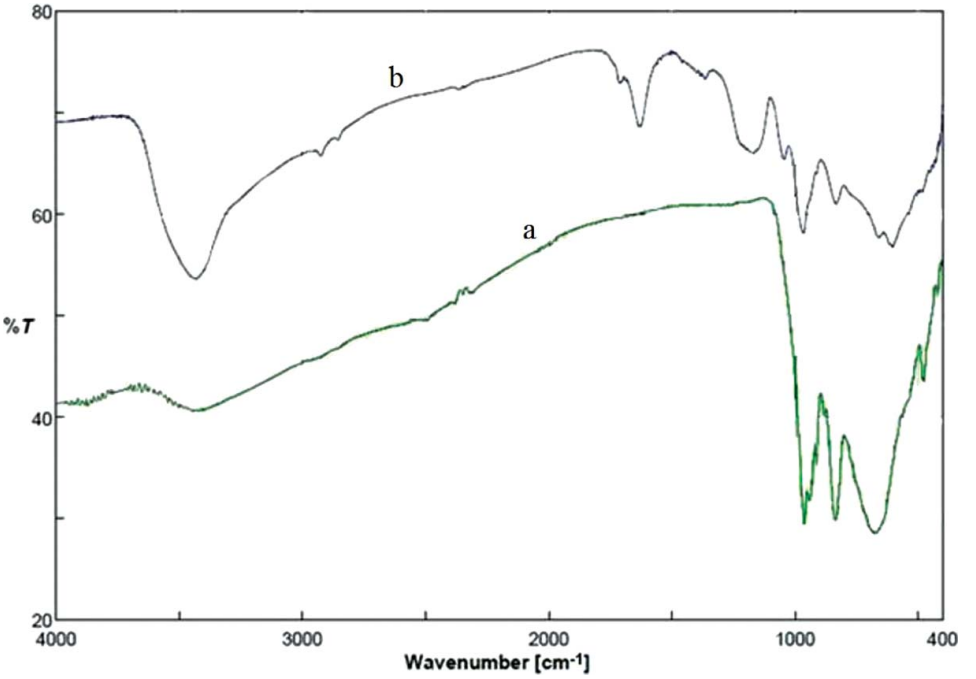


Figure 1 FTIR spectra of (a) sodium metavanadate; (b) vanadatesulfuric acid.

stretching, and S = O asymmetric stretching, respectively. The bands appearance in 960, 840, and 603 cm^{-1} related to V = O and V–O stretching (Figure 1).

The crystalline structure of the VSA was determined by powder X-ray diffraction (XRD) (Figure 2). A number of prominent Bragg reflections reveal that the resultant particles of VSA have a monoclinic structure (space group: *P*2/*m*; $a = 12.170$ Å, $b = 3.602$ Å, $c = 7.780$ Å, JCPDS card no. 16–0601). The size of the VSA particles was also determined from X-ray line broadening using the Debye–Scherrer formula ($D = k\lambda/\beta\cos\theta$, where k is Scherrer constant, λ the X-ray wavelength, β the peak width of half-maximum, and θ is the Bragg diffraction angle). For the (0 0 1) reflection the average size of the VSA particles was estimated to be around 16 nm.

The morphology and size of VSA were investigated by transmission electron microscopy (TEM) (Figure 3). They had needle-like morphology with a narrow size distribution from 15 to 20 nm and a mean size of 17 nm. The presence of some larger particles should be attributed to aggregating or overlapping of smaller particles. In addition, elemental analysis of catalyst was performed by means of X-ray fluorescence analysis (XRF) such that the obtained result confirmed the elemental composition of VSA.

Effect of Solvent and Catalyst Concentration on the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

Initially, in order to evaluate the catalytic activity of VSA, the three-component reaction of benzaldehyde, urea, and ethyl acetoacetate under solvent-free condition as a model reaction was investigated. The corresponding product was obtained in 92% yield

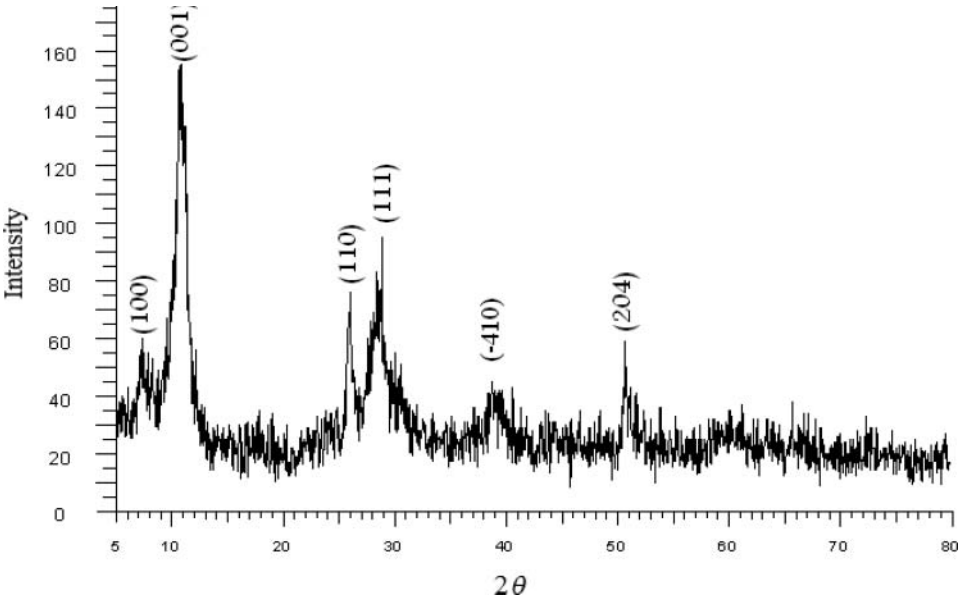


Figure 2 Powder X-ray diffraction pattern of the VSA particles.

during 30 min. This compound has been synthesized under various conditions by other researchers, some of which are presented in Table 1 that have comparable or lower yield/time ratios in comparison to current conditions.

Then, the solvent effect in the condensation of benzaldehyde (1 mmol), urea (1.5 mmol), and ethyl acetoacetate (1mmol) in the presence of VSA (0.15 mmol) as a

Table 1 Comparison of efficiency of various catalysts in synthesis of 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-ones

Entry	Catalyst	Amount of catalyst[a]	Conditions	Yield/time[b]	Ref.
1	$Sr(OTf)_2$	5	Solvent-free/70 °C	97/4	32
2	$[Al(H_2O)_6](BF_4)_3$	10	CH_3CN (reflux)	81/20	33
3	$Zr(H_2PO_4)_2$	7	Solvent-free/90 °C	88/1	34
4	LiBr	10	CH_3CN (reflux)	92/3	35
5	$SbCl_3$	100	CH_3CN (reflux)	90/18	36
6	$Cu(OTf)_2$	1	CH_3CN/25 °C	95/6	13
7	SiO_2-$KAl(SO_4)_2$	25	Solvent-free/80 °C	92/4	14
8	CaF_2	10	C_2H_5OH/(reflux)	98/2	37
9	Chloroacetic acid	10	Solvent-free/90 °C	92/3	38
10	NH_4Cl	40	Solvent-free/100 °C	90/3	39
11	Triphenylphosphine	10	Solvent-free/100 °C	70/10	40
12	PS–PEG–SO_3H[c]	0.99	Dioxane/2-propanol (reflux)	80/10	21
13	$TiCl_4$–$MgCl_2$	10	Solvent-free/100 °C	90/3	41
14	VSA	15	Solvent free/80 °C	94/0.5	–

[a]Amount of catalysts are in mol%.
[b]Values refer to yield (%)/time (h).
[c]0.3 g (0.99 mmol –SO_3H) of the catalyst vs. 1 mmol aldehyde.

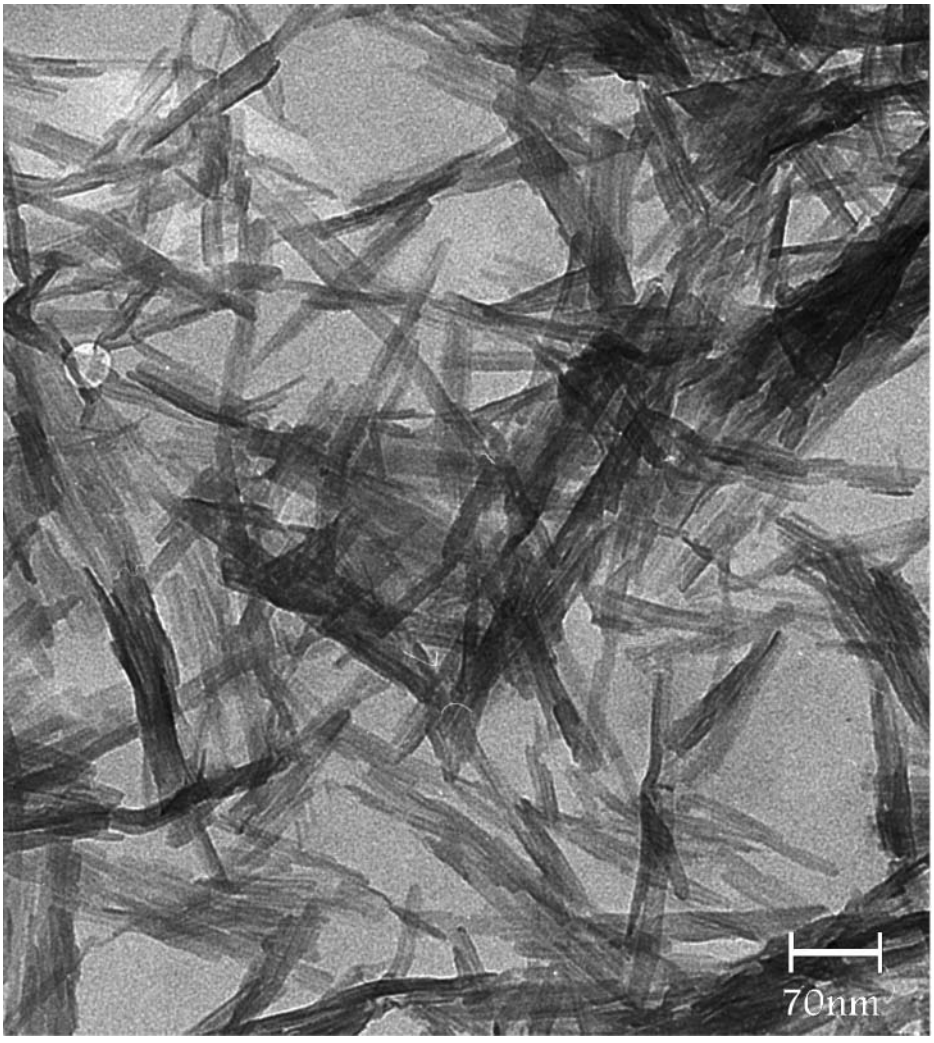


Figure 3 The TEM image showing needle-like VSA particles of 15–20 nm in size.

Table 2 Solvent effect on the reaction of benzaldehyde, urea, and ethyl acetoacetate catalyzed by VSA

Entry	Solvent (reflux)	Time (h)	Yield[a] (%)
1	CH_3CH_2OH	20	73
2	CH_3OH	20	70
3	CH_3CN	20	62
4	H_2O	20	65
5	CH_3Cl	20	55
6	Solvent-free[b]	0.5	94

[a]Isolated yields.
[b]At 80 °C.

Table 3 The influence of the amount of catalyst and heat on the synthesis of 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-ones

Entry	VSA (mol%)	Temperature (°C)	Time (min)	Yield[a] (%)
1	None	80	24 h	Trace
2	5	80	60	85
3	7.5	80	50	87
4	10	80	42	90
5	15	80	30	94
6	20	80	35	94
7	25	80	37	92
8	15	25	60	75
9	15	40	55	80
10	15	60	45	85
11	15	80	30	94
12	15	100	20	93

[a]Isolated yields.

model reaction has been studied. As shown in Table 2, among the tested solvents, such as ethanol (EtOH), methanol (MeOH), acetonitrile, water, chloroform, and a solvent-free system, the best result was obtained after 30 min under solvent-free conditions in excellent yield (94%).

The reaction condition was then optimized by conducting the reaction in different temperature and employing different catalyst loading. The best result was obtained by carrying out the reaction with 15 mol% of catalyst under solvent-free condition at 80 °C (Table 3, entry 5).

In the absence of VSA, according to thin layer chromatography (TLC) monitoring, the model reaction gives only trace of the product after 24 h at 80 °C under solvent-free condition (Table 3, entry 1). The conversion and yield of the corresponding DHPM increased with incremental increase in the catalyst concentration from 5 to 25 mol%. Further addition of catalyst had no noticeable effect on the yield. This was due to the fact that beyond a certain concentration, there exist excess of catalyst sites over what are actually required by the reactant molecules, and hence, the additional catalyst does not increase the rate of the reaction. Therefore, in all further reactions 15 mol% of the catalyst were used because of satisfactory yield of the product (94%) in reasonably short time.

In other to improve the yields, the reaction is performed using different quantites of reagents. The best results were obtained with a 1:1:1.5 ratio of benzaldehyde, ethyl acetoacetate, and urea, respectively.

To generalize this procedure, a series of Biginelli compounds were synthesized with benzaldehyde derivatives and the results are shown in Table 4. The reaction worked well with electron withdrawing (NO_2, Br, Cl, etc.) as well as electron donating (Me, OMe, etc.) substituents giving various DHPMs in 80–95% yields. Moreover, acid sensitive aldehydes such as furyl (entry 10), thienyl carbaldehyde (entry 11), and cinammaldehyde (entry 14) furnished products in yield of 83%, 80%, and 81%, respectively.

The activity of the recycled VSA was also examined according to the typical experimental condition. After completion of the reaction of benzaldehyde, urea, and ethyl acetoacetate, the catalyst was recovered from the reaction mixture. The recovered catalyst

Table 4 Preparation of substituted DHPMs catalyzed by VSA under solvent-free conditions

Entry	R^1	X	R^2	Time (min)	Yield[b] (%)	mp (°C) Found[a]	mp (°C) Reported
1	C_6H_5	O	OEt	30	94	203–205	202–203[26]
2	4-O_2N-C_6H_4	O	OEt	35	93	207–209	207–210[42]
3	4-CH_3-C_6H_4	O	OEt	30	91	213–215	215–216[43]
4	4-CH_3O-C_6H_4	O	OEt	30	88	201–202	210–202[26]
5	4-Cl-C_6H_4	O	OEt	35	95	212–214	215–216[44]
6	2-CH_3O-C_6H_4	O	OEt	45	85	252–254	255–257[50]
7	2,4-Cl-C_6H_3	O	OEt	35	90	249–251	248–250[44]
8	3-O_2N-C_6H_2	O	OEt	40	94	227–229	229–231[43]
9	2-O_2N-C_6H_2	O	OEt	45	91	213–215	210–212[45]
10	2-Furyl	O	OEt	50	83	207–209	208–210[44]
11	2-Thienyl	O	OEt	55	80	214–216	215–217[44]
12	$CH_3CH_2CH_2$	O	OEt	75	75	177–179	180–182[44]
13	2-Cl-C_6H_4	O	OEt	45	92	216–218	215–216[51]
14	$C_6H_5CH=CH$	O	OEt	70	81	228–230	227–230[44]
15	4-BrC_6H_4	O	OEt	15	92	230–232	231–233[20]
16	2-HO-5-$O_2NC_6H_3$	O	OEt	45	89	229–231	–
17	2,4-$(CH_3)_2C_6H_3$	O	OEt	30	90	236–238	–
18	C_6H_5	O	OMe	35	90	191–193	191–193[42]
19	2-$CH_3OC_6H_4$	O	OMe	55	85	285–287	283–285[46]
20	4-$CH_3OC_6H_4$	O	OMe	40	87	193–195	194–196[44]
21	4-$O_2NC_6H_4$	O	OMe	45	90	232–234	236–238[54]
22	2,4-$(CH_3)_2C_6H_3$	O	OMe	35	87	254–256	–
23	C_6H_5	O	Me	45	93	232–234	234–235[40]
24	4-$CH_3C_6H_4$	O	Me	45	85	250–253	256–257[52]
25	4-$CH_3OC_6H_4$	O	Me	50	90	171–169	168–170[40]
26	C_6H_5	S	OEt	30	93	205–207	208–210[43]
27	4-HOC_6H_4	S	OEt	35	85	197–199	202–203[53]
28	4-$CH_3OC_6H_4$	S	OEt	40	88	147–149	150–152[43]
29	4-$CH_3C_6H_4$	S	OEt	45	90	187–189	192–194[44]
30	4-ClC_6H_4	S	OEt	35	95	207–209	208–210[32]
31	3-O_2NC6H_4	S	OEt	40	93	205–206	206–207[32]
32	C_6H_5	S	OMe	40	91	223–225	221–222[44]
33	4-$CH_3OC_6H_4$	S	OMe	50	87	151–153	149–150[55]
34	2-$O_2NC_6H_4$	S	OMe	40	90	223–225	–
35	2-BrC_6H_4	S	OMe	45	90	186–188	–
36	3-CH_3O-4-ClC_6H_3	S	OMe	50	86	219–221	–

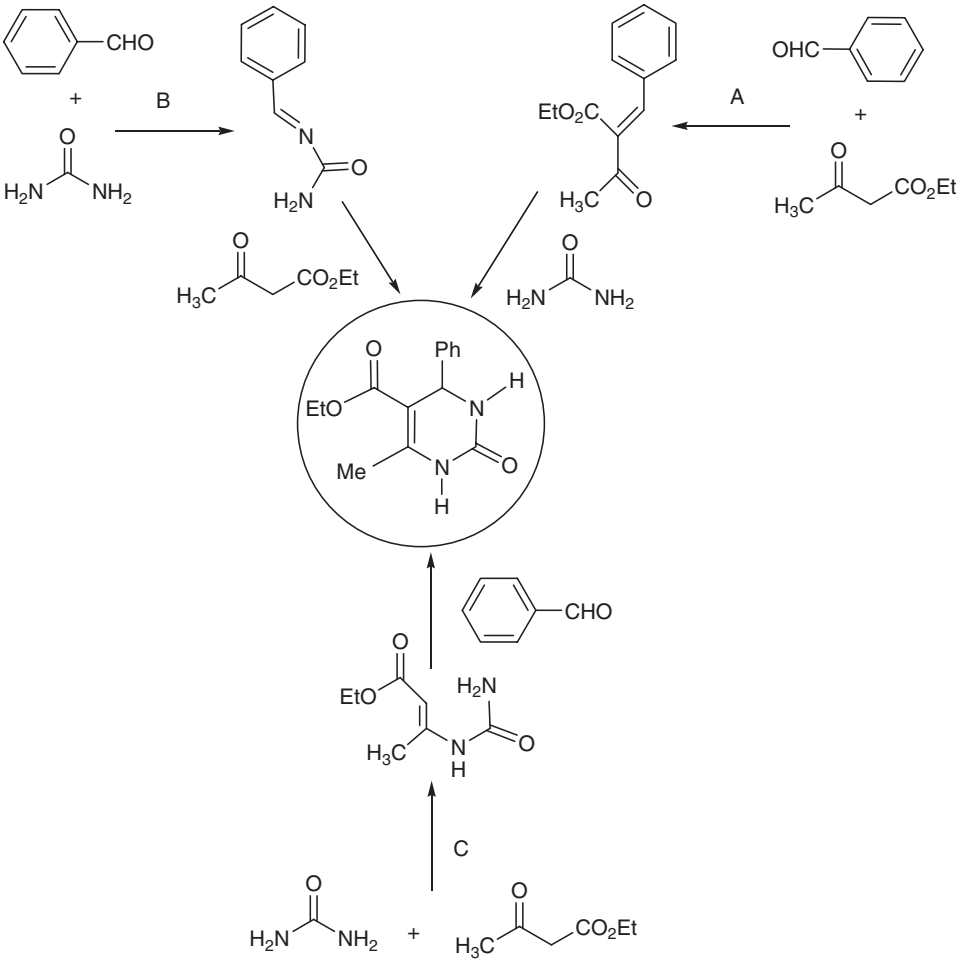
[a]All products were characterized by ^1H NMR and IR spectroscopy and comparison with these reported in the literature.

[b]Isolated yields.

was then added to fresh substrates under the same experimental conditions for four runs without a noticeable decrease in the product yield and its catalytic activity.

As shown in Scheme 3, three possible mechanisms are proposed for Biginelli reaction according to the literature, but generally accepted reaction mechanism includes the acid-catalyzed formation of C–N bond from the benzaldehyde and urea (pathway B).[49] According to reported results, the pathway B is characteristic for the Brønsted type of catalysts, whereas Lewis acid type of catalysts follow the pathway C (ureido-crotonate mechanism).[36] To clarify the role of VSA, three separated reactions were conducted (pathways A–C) under

the optimized reaction condition (15 mol% of VSA at 80 °C in solvent-free condition and reflux temperature in acetonitrile during 30 min and 20 h, respectively). The prolonged heating of benzaldehyde and ethyl acetoacetate (pathway A) or ethyl acetoacetate and urea (pathway C) did not undergo the expected reactions to yield products, whereas the reaction of benzaldehyde and urea furnished the arylidene–urea (pathway B). These observations clearly indicate that Biginelli reaction catalyzed by VSA proceeds predominately through arylidene–urea intermediate (pathway B), which supports the prediction that Biginelli reaction is catalyzed by Brønsted type catalysis.



Scheme 3

CONCLUSIONS

We have found an efficient, nonhygroscopic, and inexpensive catalyst, and a straightforward procedure for one-pot synthesis of DHPMs (thiones) using VSA as a catalyst. Also, it was found that the performance of the catalytic system is greatly improved when

used without solvents, which is important from the viewpoint of green chemistry. The attractive features of this simple protocol are short reaction time, high yields, simple workup, reusability of the catalyst, and simple purification of the products.

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. TEM was studied using a Philips, CM-10 TEM instrument operated at 100 kV. Melting points (mp) were determined using a Barnstead Electrothermal (BI 9300) apparatus and are uncorrected. The IR spectra were obtained using a FTIR JASCO-680 spectrometer instrument. The NMR spectra were taken with a Bruker 400 MHz Ultrashield spectrometer at 400 MHz (^{1}H) and 125 MHz (^{13}C) using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent with tetramethylsilane (TMS) as the internal standard. Sample ^{1}H and ^{13}C NMR spectra for 5-methoxycarbonyl-4-(2-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione are given in Figures S1 and S2 (available online in Supplemental Materials).

Preparation of VSA

Anhydrous sodium metavanadate was prepared by drying of sodium metavanadate monohydrate ($NaVO_3 \cdot H_2O$, MW = 139.94) in the oven at 200 °C for 4 h. To chlorosulfonic acid (0.1 mol, 11.6 g, 7.7 mL) in 250 mL round bottom flask in an ice-bath, anhydrous sodium metavanadate (0.1 mol, 12.2 g) was added gradually with stirring. After the completion of addition of anhydrous sodium metavanadate, the reaction mixture was shaken for 1 h. Then cold water (50 mL) was added to the reaction mixture and stirred for 10 min. The mixture was filtered and a dark red solid of VSA, 16.3 g (91%), mp 256 °C (dec.) was obtained. Characteristic IR bands (KBr, cm^{-1}): 3540–3300 (OH, bs), 1640 (OH, m), 1250–1140 (S = O, bs), 1050 (S–O, m), 960 (V = O, m), 840 (V = O, m), 630 (V–O, m).

General Procedure for Preparation of DHPMs

A mixture of aldehyde (1 mmol), β-dicarbonyl (1 mmol), urea or thiourea (1.5 mmol), and VSA (0.15 mmol) was heated at 80 °C under stirring for an appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate:*n*-hexane (1:3) as eluent. After completion of the reaction, the crude product from the reaction mixture was dissolved in hot EtOH and the catalyst was separated by filtration and was poured into cold water and the solid was collected and washed with water and recrystallized from EtOH to give pure product in 75–95% yields (Table 4). The physical and spectroscopic data of the novel compounds is given below:

5-Ethoxycarbonyl-4-(2-hydroxy-5-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Table 4, entry 16). Mp: 229–231 °C; R_f = 0.49 (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3402, 3237, 3115, 2988, 1727, 1694, 1642, 1523, 1489,1434, 1336, 1226, 1160, 837, 787, 638 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.02 (t, J = 6.8 Hz, 3H), 2.26 (s, 3H), 3.91 (q, J = 6.8 Hz, 2H), 5.45 (s, 1H),6.95 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 8.03 (dd, J = 6.4, J = 2.4 Hz, 1H), 9.25(s, 1H), 11.37 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 14.3, 18.2, 50.4, 59.6, 97.1, 116.4, 124.4, 125.4, 131.5, 139.6, 149.7, 152.3, 162.1, 165.6; Anal. calcd. for $C_{14}H_{15}N_3O_6$: C, 52.34; H, 4.71; N, 13.08; O, 29.88; found: C 52.40, H 4.78, N 13.02.

5-Ethoxycarbonyl-4-(2,4-dimethylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Table 4, entry 17). Mp: 236–238 °C; $R_f = 0.48$ (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3367, 3218, 3104, 2966, 1697, 1644, 1498, 1455, 1320, 1222, 1092, 812, 657, 544 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.10 (t, $J = 6.4$ Hz, 3H), 2.30 (s, 3H), 2.45 (s, 6H), 4.02 (q, $J = 6.4$ Hz, 2H), 5.66 (s, 1H), 6.97–7.00 (m, 2H), 7.15 (d, $J = 6.8$ Hz, 1H), 7.68 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 13.9, 17.6, 18.5, 20.5, 50.1, 59.0, 99.3, 126.5, 127.0, 130.6, 134.4, 136.1, 140.3, 148.2, 151.6, 165.2; Anal. calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; O, 16.65; found: C 66.70, H 7.05, N 9.76.

5-Methoxycarbonyl-4-(2,4-dimethylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Table 4, entry 22). Mp: 254–256 °C; $R_f = 0.46$ (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3370, 3216, 3100, 2947, 1698, 1644, 1498, 1455, 1321, 1223, 1095, 812, 662 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.20 (s, 3H), 2.72 (s, 3H), 2.35 (s, 3H), 3.34 (s, 3H), 5.34 (s, 1H), 6.91–6.94 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.59 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 18.2, 19.0, 21.0, 50.6, 51.2, 99.7, 126.9, 127.5, 131.3, 134.9, 136.7, 140.8, 148.8, 152.2, 166.2; Anal. calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21; O, 17.50; found: C 65.71, H 6.67, N 10.26.

5-Methoxycarbonyl-4-(2-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (Table 4, entry 34). Mp: 223–225 °C; $R_f = 0.46$ (*n*-hexane:ethyl acetate = 3:1) ; IR (KBr): 3329, 3216, 3103, 2965, 1707, 1629, 1525, 1455, 1223, 1087, 704 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) : 2.28 (s, 3H), 3.33 (s, 3H), 5.89 (s, 1H), 7.50–7.89 (m, 4H), 9.70 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) : 17.6, 49.6, 51.5, 100.3, 124.6, 129.6, 129.8, 134.6, 138.5, 146.3, 147.8, 165.5, 174.8; Anal. calcd. for $C_{13}H_{13}N_3O_4S$: C, 50.81; H, 4.26; N, 13.67; O, 20.82; S, 10.43; found: C 50.88, H 4.32, N 13.70.

5-Methoxycarbonyl-4(2-boromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (Table 4, entry 35). Mp: 186–187 °C; $R_f = 0.56$ (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3345, 3227, 3112, 2977, 1695, 1640, 1566, 1456, 1371, 1227, 1096, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) : 2.31 (s, 3H), 3.33 (s, 3H), 5.59 (s, 1H), 7.20–7.57 (m, 4H), 9.63 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) : 22.3, 56.2, 59.2, 105.2, 127.4, 133.8, 134.5, 135.0, 138.0, 147.6, 150.9, 170.5, 179.1; Anal. calcd. for $C_{13}H_{13}BrN_2O_2S$: C, 45.76; H, 3.84; Br, 23.42; N, 8.21; O, 9.38; S, 9.40; found: C 45.82, H 3.90, N 8.18.

5-Methoxycarbonyl-4-(3-methoxy-4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (Table 4, entry 36). Mp: 219–221 °C; $R_f = 0.50$ (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3349, 3235, 3122, 2983, 1698, 1636, 1520, 1454, 1230, 1089, 890, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.48 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 4.54 (s, 1H),6.70–7.10 (m, 3H), 9.08–9.21 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 23.8, 42.5, 48.5, 52.5, 55.8, 81.7, 112.4, 120.5, 121.3, 124.7, 140.1, 148.3, 168.8, 176.9; Anal. calcd. for $C_{14}H_{15}ClN_2O_3S$: C, 51.45; H, 4.63; Cl, 10.85; N, 8.57; O, 14.69; S, 9.81; found: C 51.40, H 4.70, N 8.52.

REFERENCES

1. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996,** 29, 123–131.
2. Kappe, C. O. *Acc. Chem. Res.* **2000,** 33, 879–888.
3. Biginelli, P. *Gazz. Chim. Ital.* **1893,** 23, 360–413.

4. Kappe, C. O. *Eur. J. Med. Chem.* **2000,** 35, 1043–1052.
5. Kapoor, T. M.; Mayer, T. U.; Coughlin, M. L.; Mitchison, T. J. *J. Cell. Biol.* **2000,** 150, 975–988.
6. Hurst, E. W.; Hull, R. *J. Med. Pharm. Chem.* **1961,** 3, 215–229.
7. Ashok, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem.* **2007,** 42, 380–385.
8. Fewell, S. W.; Smith, C. M.; Lyon, M. A.; Dumitrescu, T. P.; Wipf, P.; Day, B. W.; Brodsky, J. L. *J. Biol. Chem.* **2004,** 279, 51131–51140.
9. Carswell, C. I.; Plosker, G. L.; Jarvis, B. *Drugs* **2002,** 62, 2075–2085.
10. (a) Overman, L.E.; Rabinowitz, M.H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995,** 117, 2657–2658; (b) Carswell, C. I.; Plosker, G. L.; Jarvis, B. *Drugs* **2002,** 62, 2075–2085.
11. Manhas, M. S.; Ganguly, S. N.; Mukherjee, S.; Jain, A. K.; Bose, A. K. *Tetrahedron Lett.* **2006,** 47, 2423–2425.
12. Stefani, H. A.; Oliveira, C. B.; Almeida, R. B.; Pereira, C. M. P.; Braga, R. C.; Cella, R.; Borges, V. C.; Savegnago, L.; Nogueira, C. W. *Eur. J. Med. Chem.* **2006,** 41, 513–518.
13. Ramalingan, C.; Park, S. J.; Lee, I. S.; Kwak, Y. W. *Tetrahedron* **2010,** 66, 2987–2994.
14. Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. *Appl. Catal. A: Gen.* **2006,** 300, 85–88.
15. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghifard, M. A. *Tetrahedron Lett.* **2003,** 44, 2889–2891.
16. Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakraborty, G.; Manhas, M. S. *Tetrahedron Lett.* **2004,** 45, 8351–8353.
17. Nagaiah, K.; Lingaiah, N.; Saipasad, P. S. *Eur. J. Org. Chem.* **2004**, 552–557.
18. Joseph, J. K.; Jain, S. L.; Sain, B. *J. Mol. Catal. A: Chem.* **2006,** 247, 99–102.
19. Zumpe, F. L.; Flub, M.; Schmitz, K.; Lenderc, A. *Tetrahedron Lett.* **2007,** 48, 1421–1423.
20. Bigdeli, M. A.; Gholami, G.; Sheikhosseini, E. *Chin. Chem. Lett.* **2011,** 22, 903–906.
21. Quan, Z. J.; Da, Y. X.; Zhang, Z.; Wang, X. C. *Catal. Commun.* **2009,** 10, 1146–1148.
22. Kargar, M.; Hekmatshoar, R.; Mostashari, A.; Hashemi, Z. *Catal. Commun.* **2011,** 15, 123–126.
23. Dharma Rao, G. B.; Acharya, B. N.; Verma, S. K.; Kaushik M. P. *Tetrahedron Lett.* **2011,** 52, 809–812.
24. da Silva, D. L.; Fernandes, S. A.; Sabino, A. A.; Fátima, Â. *Tetrahedron Lett.* **2011,** 52, 6328–6330.
25. Wu, M.; Yu, J.; Zhao, W.; Wu, J.; Cao, S. *J. Fluorine Chem.* **2011,** 132, 155–159.
26. Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Carbooni, B. *Tetrahedron Lett.* **2006,** 47, 5697–5699.
27. Clark, J. H. *Acc. Chem. Res.* **2002,** 35, 791–797.
28. (a) Nasr-Esfahani, M.; Montazerozohori, M.; Moghadam, M.; Mohammadpoor-Baltork, I.; Moradi, S. *Phosphorus Sulfur Silicon Relat. Elem.* **2010,** 185, 261–266; (b) Nasr-Esfahani, M.; Montazerozohori, M.; Gholampour, T. *Bull. Korean Chem. Soc.* **2010,** 31, 3653–3657 (c) Nasr-Esfahani, M.; Montazerozohori, M.; Mehrizi, S. *J. Heterocycl. Chem.* **2011,** 48, 249–251; (d) Nasr-Esfahani, M.; Hoseini, S. J.; Mohammadi, F. *Chin. J. Catal.* **2011,** 32, 1484–1489.
29. Nasr-Esfahani, M.; Karami, B.; Montazerozohori, M.; Abdi, K. *J. Heterocycl. Chem.* **2008,** 45, 1183–1185.
30. Nasr-Esfahani, M.; Khosropour, A. R. *Bull. Korean Chem. Soc.* **2005,** 26, 1331–1332.
31. Frederickson, L. D.; Hausen, D. M. *Anal. Chem.* **1963,** 35, 818–827.
32. Su, W.; Li, J.; Zheng, Z.; Shen, Y. *Tetrahedron Lett.* **2005,** 46, 6037–6040.
33. Litvic, M.; Vecenaj, I.; Ladisic, Z. M.; Lovric, M.; Vinkovic, V.; Filipan-Litvic, M. *Tetrahedron* **2010,** 66, 3463–3471.
34. Besoluk, S.; Kukukislamoglu, M.; Zengin, M.; Arsalan, M.; Nebioglu, M. *Turk. J. Chem.* **2010,** 34, 411–416.
35. Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett.* **2003,** 44, 2757–2758.
36. Cepanec, I.; Litvic, M.; Filipan-Litvic, M.; Grungold, I. *Tetrahedron* **2007,** 63, 11822–11827.
37. Chitra, S.; Pandiarajan, K. *Tetrahedron Lett.* **2009,** 50, 2222–2224.
38. Yu, Y.; Liu, D.; Liu, Ch.; Luo, G. *Bioorg. Med. Chem. Lett.* **2007,** 17, 3508–3510.
39. Shaabani, A.; Bazgir, A.; Teimouri, F. *Tetrahedron Lett.* **2003,** 44, 857–859.

40. Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2008,** 49, 6119–6121.
41. Kumar, A.; Maurya, R. A. *J. Mol. Catal. A: Chem.* **2007,** 272, 53–57.
42. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000,** 65, 3864–3868.
43. Reddy, K. R.; Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Reddy, V. V. N. *Tetrahedron Lett.* **2003,** 44, 8173–8175.
44. Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002,** 58, 4801–4807.
45. Chitra, S.; Pandiarajan, K. *Tetrahedron Lett.* **2009,** 50, 2222–2224.
46. Khabazzadeh, H.; Saidi, S.; Sheibani, H. *Bioorg. Med. Chem. Lett.* **2008,** 18, 278–282.
47. Garima, S. V. P.; Yadav, L. D. S. *Tetrahedron Lett.* **2010,** 51, 6436–6438.
48. Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *J. Mol. Catal. A: Chem.* **2007,** 271, 14–17.
49. (a) Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973,** 95, 8741–8749; (b) Kappe, C. O. *J. Org. Chem.* **1997,** 62, 7201–7204.
50. Cepanec, I.; Litvic, M.; Bartolincic, A.; Lovric, M. *Tetrahedron* **2005,** 61, 4275–4280.
51. Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007,** 63, 638–643.
52. Oliver Kappe, C.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000,** 56, 1859–1862.
53. Bandgar, B. P.; More, P. E.; Kamble, V.T.; Totre, J. V. *Arkivoc* **2008,** iv, 1–7.
54. Joseph, J. K.; Jain, S. L.; Sain, B. *J. Mol. Catal. A: Chem.* **2006,** 247, 99–102.
55. Dharma Rao, G. B.; Acharya, B. N.; Verma, S. K.; Kaushik, M. P. *Tetrahedron Lett.* **2011,** 52, 809–812