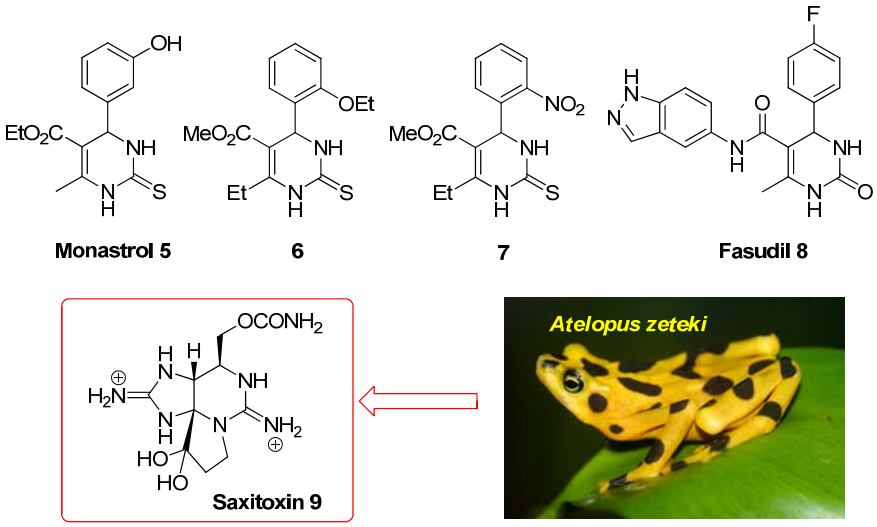


Fig. 1. Structure of some biologically active DHPM which synthesized through Biginelli reaction.

GC-Mass analysis was performed on a model 5973/6890 network mass-selective detector (Agilent). Scanning electron microscope (SEM) analysis was performed on a PhilipsXL-30 field-emission SEM operated at 16 kV, while TEM was carried out on a Tecnai G2 F30 at 300 kV. Weight change curve in nitrogen was measured on a TA instrument of TGA Q50 V6.3 with the maximum heating rate of 20 ºC/min. Low-angle X-ray scattering measurements were accomplished on X'Pert Pro MPD diffractometer using Cu K_α radiation (λ=1.5418 Å).

2.2. Synthesis and functionalization of SBA-15

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report [15] and the modified SBA-Pr-SO_3H was used as nanoporous solid acid catalyst in the following reaction. For this aim, in a typical synthesis batch, triblock copolymer surfactant as a template (P123= $EO_{20}PO_{70}EO_{20}$, Mac =5800) (4.0 g) was completely dissolved in water (30 ml) and HCl solution (120 g, 2 M). Then, TEOS (tetraethylorthosilicate) (8.50 g) was added to it and stirred for 8 h at 40 ºC. The resulting mixture was poured into a Teflon-lined stainless steel autoclave and kept at 100ºC for about 20 h without stirring. The composition of P123:HCl:H_2O:TEOS gel was 0.0168:5.854:162.681:1 in molar ratio. After cooling down to room temperature, the product was filtered, washed with distilled water and dried overnight at 60ºC in air. The synthesized sample was calcinated at 550ºC for 6 h in air atmosphere to remove the template.

In order to functionalize SBA-15, the calcined SBA-15 (2 g) and (3-mercaptopropyl)trimethoxysilane (10 mL) were refluxed in dry toluene (20 mL) for 24 h. The product was filtered and washed with CH_2Cl_2 for 6 h using a soxhlet apparatus, then dried under vacuum. The solid product (SBA-Pr-SH) was oxidized with H_2O_2 (excess) and one drop of H_2SO_4 in methanol (20 mL) for 24 h at ambient temperature. Afterwards, the mixture was filtered and washed with H_2O, and acetone. The modified SBA-Pr-SO_3H was dried and characterized using TGA, SEM, TEM and back-titration. It was then used as mesoporous solid acid catalyst in the following reactions.

2.2. General procedure for the preparation of DHPMs

The SBA-Pr-SO_3H was firstly activated in vacuum at 100ºC for 10 min, and then, after cooling of the catalyst to room temperature, aryl aldehydes **2** (1 mmol), ethyl acetoacetate **3** (0.13 ml, 1 mmol) and urea **4** (0.09 gr, 1.5 mmol) were added to it. The mixture was heated in an oil bath (80°C) in appropriate time as shown in Table 2. After completion of the reaction, which was monitored by TLC, the crude product was dissolved in hot ethanol and then filtered to remove the solid catalyst. Filtrate was cooled to room temperature to give the pure product. The solid acid catalyst subsequently was washed with diluted acid solution, distilled water and then acetone, dried under vacuum, which can be used for several times without a loss of significant activity.

Selected spectral data

*5- (Ethoxycarbonyl)-6- methyl- 4- phenyl- 3,4-dihydro pyrimidin-(1H)-one (**1a**):*

FT-IR (KBr): $\bar{\nu}$ = 3244, 3116, 1726, 1701 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.07-1.12 (t, 3H, $\underline{CH_3}CH_2O$), 2.25 (s, 3H, CH_3), 3.97-4.04 (q, 2H, $CH_3\underline{CH_2}O$), 5.14-5.15 (d, 1H, CH), 5.41 (s, 1H, NH), 7.21-7.35 (m, 5 CH, arom), 7.74 (s, 1H, NH) ppm. ^{13}CNMR (62.5 MHz, DMSO-d_6): δ= 14.10, 17.80, 53.98, 59.21, 99.28, 126.27, 127.29, 128.41, 144.89, 148.38, 152.16, 165.36 ppm. MS (m/e)= 260 [$M^{+\cdot}$], 245, 231, 215, 183, 169, 155.

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

FT-IR (KBr): $\bar{\nu}$ = 3370, 3104, 2931, 1702, 1642 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 0.95-1.00 (t, 3H, $\underline{CH_3}CH_2O$), 2.28 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.84-3.90 (q, 2H, $CH_3\underline{CH_2}O$), 5.39-5.40 (d, 1H, CH), 7.09-7.16 (m, 4CH, arom), 7.61 (s, 1H, NH), 9.14 (s, 1H, NH) ppm. ^{13}CNMR (62.5 MHz, DMSO-d_6): δ= 13.90, 17.66, 18.63, 54.42, 59.04, 99.15, 126.50, 127.13, 130.07, 134.64, 143.23, 148.41, 151.53, 165.22 ppm. MS (m/e)= 274 [$M^{+\cdot}$], 259, 245, 229, 201, 183, 155, 91.

*5-(Ethoxycarbonyl)-6- methyl-4- (4-methylphenyl)-3,4-dihydropyrimidin-(1H)-one (**1g**):*

FT-IR (KBr): $\bar{\nu}$ = 3245, 3116, 1705, 1647 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.14-1.20 (t, 3H, $\underline{CH_3}CH_2O$), 2.31 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.02-4.10 (q, 2H, $CH_3\underline{CH_2}O$), 5.32-53.4 (d, 1H, CH), 6.02 (s, 1H, NH), 7.08-7.11 (d, 2CH, arom), 7.20-7.23 (d, 2CH, arom), 8.05 (s, 1H, NH) ppm. MS (m/e)= 274 [$M^{+\cdot}$], 259, 245, 229, 215, 201, 215, 183, 155, 91.

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

FT-IR (KBr): $\bar{\nu}$ = 3272, 3109, 2935, 1702, 1641 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.07-1.13 (t, 3H, $\underline{CH_3}CH_2O$), 2.42 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.99-4.08 (q, 2H, $CH_3\underline{CH_2}O$), 5.67-5.68 (d, 1H, CH), 5.89 (s, 1H, NH), 6.84-7.79 (m, 4CH, arom), 8.46 (s, 1H, NH) ppm.

*4- (4- N,N- Dimethylaniline)- 5- (Ethoxycarbonyl)- 6-methyl)-3,4-dihydropyrimidin-(1H)-one (**1k**):*

FT-IR (KBr): $\bar{\nu}$ = 3242, 3113, 1704, 1648 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.15-1.21 (t, 3H, $\underline{CH_3}CH_2O$), 2.32 (s, 3H, CH_3), 2.92 (s, 6H, 2 CH_3), 4.01-4.09 (q, 2H, $CH_3\underline{CH_2}O$), 5.25 (d, 1H, CH), 6.19 (s, 1H, NH), 6.63-6.66 (d, 2CH, arom), 7.16-7.44 (d, 2CH, arom), 8.27 (s, 1H, NH) ppm.

*5-(Ethoxycarbonyl)-6-methyl-4-(2,4-dimethoxyphenyl)-3,4-dihydropyrimidin-(1H)-one (**1l**):*

FT-IR (KBr): $\bar{\nu}$ = 3232, 3104, 2940, 2839, 1705, 1645 cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.08-1.14 (t, 3H, $\underline{CH_3}CH_2O$), 2.41 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.02-4.10 (q, 2H, $CH_3\underline{CH_2}O$), 5.65 (s, 1H, CH), 6.35-6.39 (d, 1H, NH), 6.45-6.46 (d, 1H, CH), 6.92-6.96 (d, 1H, CH), 7.26 (s, 1H, NH) ppm.

3. Results and Discussion

3.1. Preparation and characterization of SBA-Pr-SO_3H

In this work, SBA-Pr-SO_3H was prepared as mentioned before, and then, characterized. The TGA analysis of SBA-Pr-SO_3H (Fig. 2) proved that the organic functional groups (propyl sulfonic acid) were grafted onto the pores of SBA-15. The weight reduction in TGA analysis in the temperature range between 200-600°C indicates that the amount of propyl sulfonic acid groups is 1.2 mmol/g. Additionally, concentration of the sulfonic acid groups onto the modified SBA-15 was also evaluated through a back titration method by adding a known strength of NaOH solution. To avoid hydrolysis of SBA-15 framework, a very dilute standardized NaOH solution (0.1 M) was applied. The excess amount of NaOH was back titrated with a standardized HCl. This titrimetric experimental data exhibited that each gram of SBA-Pr-SO_3H contained 1.28 mmol sulfonic acid groups. Good agreement between both values of back titration and TGA is clear evidence that the sulfonic groups incorporated onto the pores of SBA-15, where they are accessible for catalytic reaction processes.

The small angle powder XRD pattern of both SBA-15 and SBA-Pr-SO_3H is shown in Fig. 3. As it is clear, both of them (SBA-15 and SBA-Pr-SO_3H) display the three characteristic peaks at the 2θ (°) values of 1.00, 1.69 and 1.93, which are related to the 100 (strong), 110 (weak) and 200 (weak) reflections, respectively, corresponding to the 2D-hexagonal mesoporous. However, a considerable decrease is observed in the intensity of SBA-Pr-SO_3H, which reveals that propyl sulfonic acid groups were successfully incorporated onto the pores of SBA-15.

3.2. Biginelli reaction by the use of SBA-Pr-SO_3H

In this step, preparation of DHPMs **1a-k** was studied using Biginelli condensation of benzaldehyde derivatives **2**, ethylacetoacetate **3** and urea **4** in the presence of heterogeneous nano solid acid catalyst (SBA-Pr-SO_3H) under solvent free conditions (Scheme 1). In this reaction, various DHPMs were prepared and their results are summarized in Table 1.

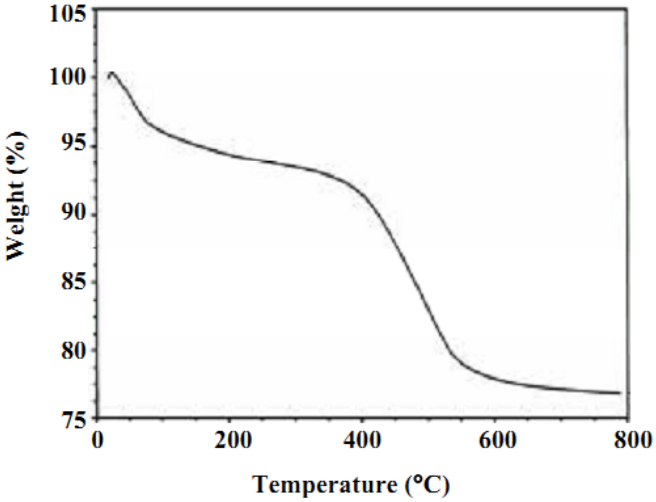


Fig. 2. TGA analysis of SBA-Pr-SO_3H.

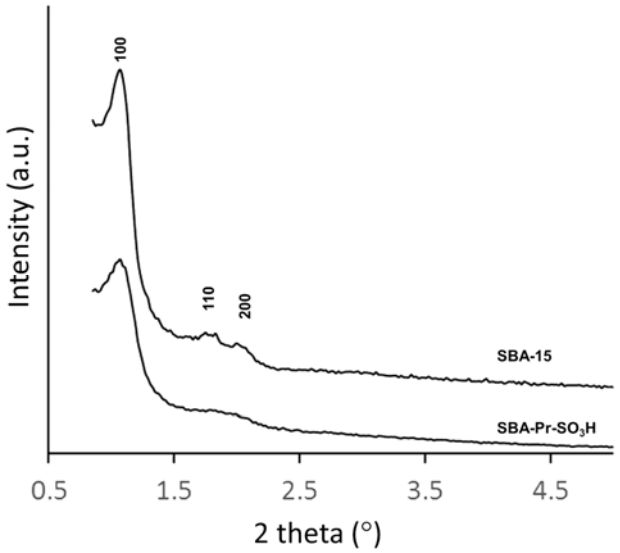


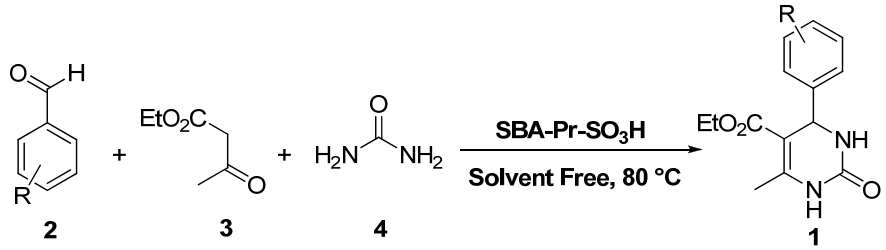
Fig. 3. The small angle powder XRD pattern of both SBA-15 and SBA-Pr-SO_3H.

The reaction time offering high yields of the products which are attributed to the effect of nanopore size about 6 nm of nano solid acid catalyst (Fig. 4).

After the reaction was completed (monitored by TLC), the mixture reaction was dissolved in hot EtOH, and the catalyst was separated by simple filtration, and reactivated by simple washing subsequently with diluted acid solution, water, and acetone, to reuse without noticeable loss of reactivity. Some new and known products were characterized by FT-IR and NMR spectroscopy data. Melting points of the known products were compared with reported values in the literature as shown in Table 1.

SEM image of SBA-Pr-SO_3H (Fig. 5a) shows uniform particles about 1μm. The same morphology was previously detected in SBA-15. It can be concluded that the morphology of modified SBA-15 was saved without change during the modification procedure. Besides this, the TEM image (Fig. 5b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pores of SBA-Pr-SO_3H was not collapsed during two steps reactions.

The most probable mechanism for this reaction is shown in Scheme 2. Initially, SBA-Pr-SO_3H as an acid catalyst protonates the carbonyl group of the aldehyde **2**.



Scheme 1. Biginelli condensation of benzaldehyde derivatives, ethylacetoacetate and urea in the presence of SBA-Pr-SO_3H.

Table 1. SBA-Pr-SO_3H catalyzed the synthesis of DHPMs under solvent free condition.

Entry	Product	R[a]	Time (min)	Yield (%)	m.p. (ºC)		Ref.
					Found	Reported	
1	1a	H	15	90	203-204	200-201	[21]
2	1b	2,3-$(Cl)_2$	12	95	238-240	244-246	[22]
3	1c	4-Cl	20	95	206-208	208-211	[23]
4	1d	2,6-$(Cl)_2$	10	98	229-231	226-227	[24]
5	1e	2-F	15	98	230-232	233-235	[23]
6	1f	2-Me	12	70	202-203	201-203	[4]
7	1g	4-Me	10	80	212-214	214-215	[25]
8	1h	2-OMe	10	70	257-259	262-265	[23]
9	1i	4-OMe	30	60	209-210	206-208	[23]
10	1j	2,3-$(OMe)_2$	30	50	201-202	185-186	[26]
11	1k	4-NMe_2	15	75	248-250	253-254	[27]

[a]All products were characterized by IR, ^{1}HNMR, ^{13}CNMR Mass and comparison of physical characteristics with authentic samples.

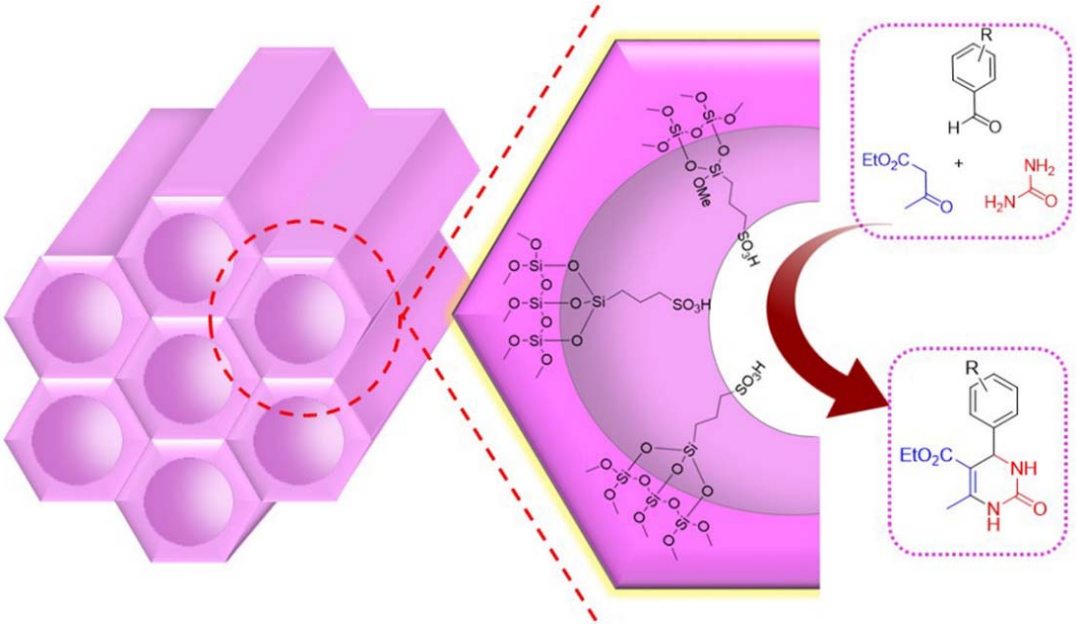


Fig. 4. SBA-Pr-SO_3H acts as a nano-reactor.

Then, urea **4** attacks to the protonated carbonyl groups followed by dehydration to give intermediate **6**. Afterwards, the enol form of ethyl acetoacetate **5** is added to the intermediate **6** to produce **7**. Furthermore, an intra-cyclisation occurs through addition of the amino group of urea moiety to the carbonyl group which affords cyclization product **8** and after dehydration results in the formation of the desired product **1**.

The recyclability of the catalyst was also investigated under optimized conditions for the synthesis of the model compound **1a**. In this regard, the reaction was accomplished in the first run for four times to recover about 0.07 gr SBA-Pr-SO_3H. Subsequently, the catalyst was washed and reactivated as mentioned before and then reused. The process of recycling was repeated for four times and the yields were 90, 83, 80 and 81%. It was found that the catalytic activity drops slightly from the first use to the second use due to some leaching of sulfonic acid groups which were grafted on the outer surface of SBA-15. Additionally, no significant decrease in catalytic activity was observed for the third and fourth cycles, which means the leaching groups were separated from the catalyst in the first stage of the recovery. In fact, this catalyst is completely recoverable.

The Biginelli reaction has been studied in several conditions in the literatures as presented in Table 2. In comparison with other existing methods, the present non-microwave methodology is one of the best methods because of several advantages in term of a greener conditions, short reaction time and easy work-up, reusable catalyst and excellent yields with high purity of the products.

4. Conclusions

In conclusion, our work presents a new application of SBA-Pr-SO_3H as a nano and green solid acid catalyst for the synthesis of DHPMs in solvent-free conditions, which makes the present catalytic reaction as an environmentally friendly method for the Biginelli reaction.

Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Alzahra University and the University of Tehran.

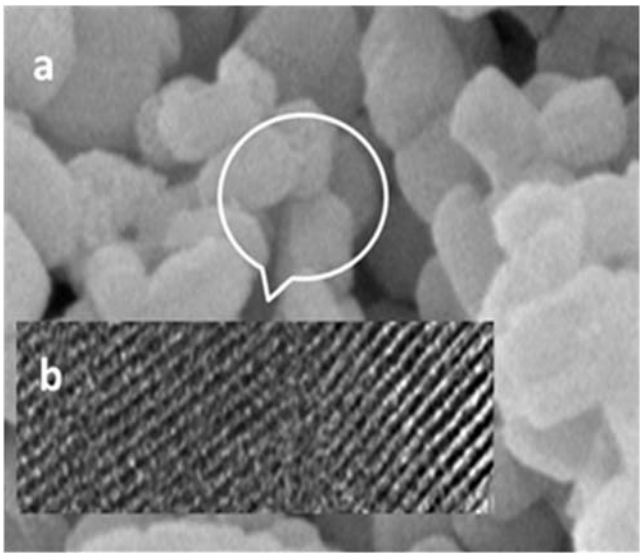
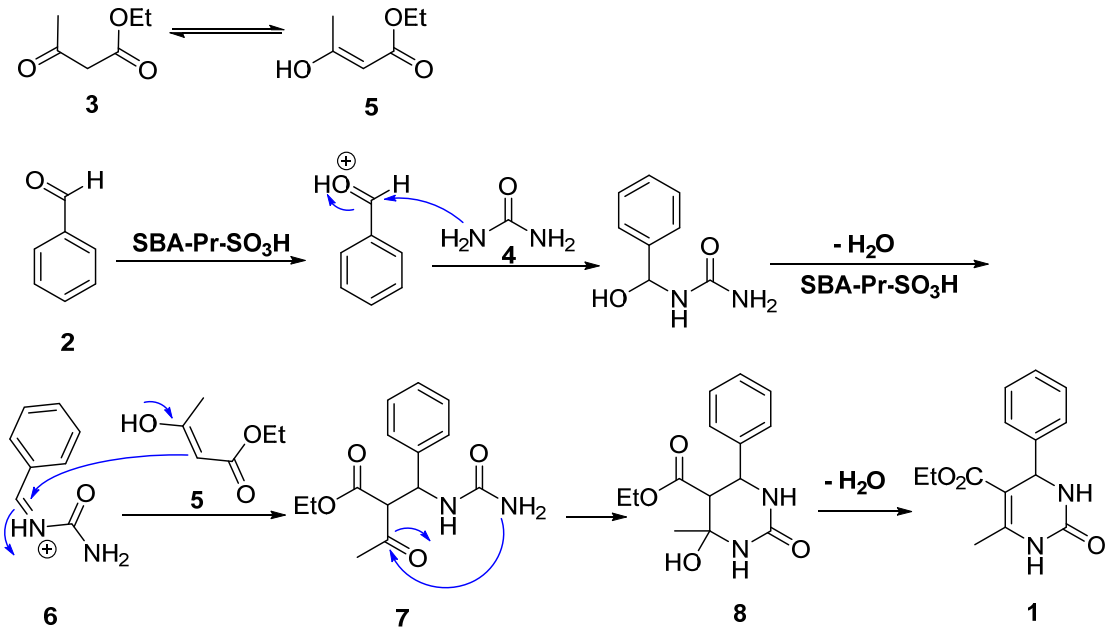


Fig. 5. SEM (a) and TEM (b) images of SBA-Pr-SO_3H.



Scheme 2. The proposed mechanism for Biginelli reaction in the presence of SBA-Pr-SO_3H.

Table 2. Comparison of different conditions in the synthesis of **1a**.

Entry	Catalyst	Solvent	Condition	Yield (%)	Time	Ref.
1	SBA-Pr-SO_3H	-	80ºC	90	15 min	This work
2	$H_5PW_{10}V_2O_{40}$/Pip-SBA-15[a]	-	100ºC	90	20 min	[28]
3	Fe_3O_4@SBA-15	-	90ºC	85	6 h	[29]
4	Aluminium-planted MCM-41[b]	Octane	110ºC	94	10 h	[30]
5	$Mg(NO_3)_2.6H_2O$	-	80ºC	90	90 min	[31]
6	$HClO_4$-SiO_2	-	110 ºC	98	20 min	[32]
7	$SbCl_3$	MeCN	Reflux	75	22 h	[33]
8	TCCA[c]	EtOH	Reflux	94	12 h	[25]
9	ZrO_2/SO_4^{-2}	-	100ºC	94	4 h	[34]
10	Chloro acetic acid	-	90 C	92	3 h	[35]
11	TMSCl/NaI	MeCN	r.t.	98	30 min	[36]
12	$InBr_3$	EtOH	Reflux	98	7 h	[37]
13	$Cu(OTf)_2$	EtOH	MW	75	1 h	[38]
14	TCCA	EtOH	MW	92	3 min	[25]
15	$LaCl_3$	-	MW	85	8 min	[39]
16	-	CH_3COOH	MW	86	2 min	[40]

[a]$H_5PW_{10}V_2O_{40}$ immobilized on SBA-Pr-Piperazine.
[b]Mobil Composition of Matter.
[c]Trichloroisocyanuric acid.

References

[1] S.L. Jain, J.K. Joseph, S. Singhal, B. Sain, J. Mol. Catal. A: Chem. 268 (2007) 134-138.
[2] C. Oliver Kappe, Tetrahedron 49 (1993) 6937-6963.
[3] J.P. Wan, Y. Pan, Mini-Rev. Med. Chem. 12 (2012) 337-349.
[4] İ.S. Zorkun, S. Saraç, S. Çelebi, K. Erol, Bioorg. Med. Chem. 14 (2006) 8582-8589.
[5] K.B. Goodman, H. Cui, S.E. Dowdell, D.E. Gaitanopoulos, R.L. Ivy, C.A. Sehon, R.A. Stavenger, G.Z. Wang, A.Q. Viet, W. Xu, G. Ye, S.F. Semus, C. Evans, H.E. Fries, L.J. Jolivette, R.B. Kirkpatrick, E. Dul, S.S. Khandekar, T. Yi, D.K. Jung, L.L. Wright, G.K. Smith, D.J. Behm, R. Bentley, C.P. Doe, E. Hu, D. Lee, J. Med. Chem. 50 (2006) 6-9.
[6] C.O. Kappe, Acc. Chem. Res. 33 (2000) 879-888.
[7] C.Y. Hong, Y. Kishi, J. Am. Chem. Soc. 114 (1992) 7001-7006.
[8] M. Wiese, P.M. Dagostino, T.K. Mihali, M.C. Moffitt, B.A. Neilan, Mar. Drugs 8 (2010) 2185-2211.
[9] C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli, J.S. Beck, Nature 359 (1992) 710-712.
[10] J.S. Beck, J.C. Vartuli, W.J. Roth, M.E. Leonowicz, C.T. Kresge, K.D. Schmitt, C.T.W. Chu, D.H. Olson, E.W. Sheppard, S.B. McCullen, J.B. Higgins, J.L. Schlenker, J. Am. Chem. Soc. 114 (1992) 10834-10843.
[11] D. Zhao, J. Feng, Q. Huo, N. Melosh, G.H. Fredrickson, B.F. Chmelka, G.D. Stucky, Science 279 (1998) 548-552.
[12] K. Bahrami, M.M. Khodaei, P. Fattahpour, Catal. Sci. Technol. 1 (2011) 389-393.
[13] P. Gholamzadeh, G.M. Ziarani, A. Badiei, Z. Bahrami, Eur. J. Chem. 3 (2012) 279-282.
[14] G. Mohammadi Ziarani, A. Abbasi, A. Badiei, Z. Aslani, E-J. Chem. 8 (2011) 293-299.
[15] G. Mohammadi Ziarani, A. Badiei, Y. Khaniania, M. Haddadpour, Iran. J. Chem. Chem. Eng. 29 (2010) 1-10.
[16] G. Mohammadi Ziarani, A.R. Badiei, M. Azizi, Sci. Iran. 18 (2011) 453-457.
[17] P. Gholamzadeh, G. Mohammadi Ziarani, A. Badiei, A. Abolhassani Soorki, N. Lashgari, Res. Chem. Intermed. 39 (2013) 3925-3936.
[18] G. Mohammadi Ziarani, N. Lashgari, A.R. Badiei, Sci. Iran. 20 (2013) 580-586.
[19] G. Mohammadi Ziarani, A. Badiei, S. Mousavi, N. Lashgari, A. Shahbazi, Chin. J. Catal. 33 (2012) 1832-1839.
[20] G.M. Ziarani, A. Badiei, M. Azizi, N. Lashgari, J. Chin. Chem. Soc. 60 (2013) 499-502.
[21] M. Adib, K. Ghanbary, M. Mostofi, M. Ganjali, Molecules 11 (2006) 649-654.
[22] F.S. Falsone, C.O. Kappe, Arkivoc 2 (2001) 122-134.
[23] M. Li, W.-S. Guo, L.-R. Wen, Y.-F. Li, H.-Z. Yang, J. Mol. Catal. A: Chem. 258 (2006) 133-138.
[24] J.K. Joseph, S.L. Jain, B. Sain, J. Mol. Catal. A: Chem. 247 (2006) 99-102.
[25] M.A. Bigdeli, S. Jafari, G.H. Mahdavinia, H. Hazarkhani, Catal. Commun. 8 (2007) 1641-1644.
[26] Ş. Beşoluk, M. Küçükislaoğlu, M. Zenğin, M. Arslan, M. Nebioğlu, Turk. J. Chem. 34 (2010) 411-416.
[27] W. Su, J. Li, Z. Zheng, Y. Shen, Tetrahedron Lett. 46 (2005) 6037-6040.
[28] R. Tayebee, M.M. Amini, M. Ghadamgahi, M. Armaghan, J. Mol. Catal. A: Chem. 366 (2013) 266-274.
[29] J. Mondal, T. Sen, A. Bhaumik, Dalton Trans. 41 (2012) 6173-6181.
[30] H. Murata, H. Ishitani, M. Iwamoto, Org. Biomol. Chem. 8 (2010) 1202-1211.
[31] T. Boumoud, B. Boumoud, S. Rhouati, A. Belfaitah, A. Deache, P. Mosset, Acta Chim. Slov. 55 (2008) 617-622.
[32] M. Maheswara, S.H. Oh, K. Kim, J.Y. Do, Bull. Korean Chem. Soc. 29 (2008) 1752-1754.
[33] I. Cepanec, M. Litvić, M. Filipan-Litvić, I. Grüngold, Tetrahedron 63 (2007) 11822-11827.
[34] D. Angeles-Beltrán, L. Lomas-Romero, V. Lara-Corona, E. González-Zamora, G. Negrón-Silva, Molecules 11 (2006) 731-738.
[35] Y. Yu, D. Liu, C. Liu, G. Luo, Bioorg. Med. Chem. Lett. 17 (2007) 3508-3510.
[36] G. Sabitha, G.S.K. Kumar Reddy, C.S. Reddy, J.S. Yadav, Synlett (2003) 0858-0860.
[37] N.-Y. Fu, Y.-F. Yuan, Z. Cao, S.-W. Wang, J.-T. Wang, C. Peppe, Tetrahedron 58 (2002) 4801-4807.
[38] K.K. Pasunooti, H. Chai, C.N. Jensen, B.K. Gorityala, S. Wang, X.-W. Liu, Tetrahedron Lett. 52 (2011) 80-84.
[39] H. Khabazzadeh, K. Saidi, H. Sheibani, Bioorg. Med. Chem. Lett. 18 (2008) 278-280.
[40] J.S. Yadav, B.V.S. Reddy, E.J. Reddy, T. Ramalingam, J. Chem. Res. 2000 (2000) 354-355.