Iranian Journal of Catalysis .2(1), 2012, 17-21

IRANIAN JOURNAL OF CATALYSIS

Nano-Silica phosphoric acid: an efficient catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones) under solvent-free or sonication conditions

Abdolhamid Bamoniri*[a], Bi Bi Fatemeh Mirjalili[b], Sedigheh Nazemian[a]

[a] *Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, I.R.Iran.*
[b] *Department of Chemistry, College of Science, Yazd University, I. R. Iran .*

Received 7 Dec 2011; received in revised form 27 Feb 2012; accepted 3 March 2012

ABSTRACT

Two simple protocols for the synthesis of three-component condensation reaction of an aldehyde, β-ketoester and urea or thiourea to obtain the 3, 4-dihydropyrimidin-2(1*H*)-ones (thiones) using nano silica phosphoric acid are reported. Short reaction times, high yields, reusability of catalyst and easy workup are some advantages of these protocols.

Keywords: *Biginelli reaction, 3,4-Dihydropyrimidin-2(1H)-ones, 3,4-Dihydropyrimidin-2(1H)-thiones, Heterogeneous catalyst, Multi-component reactions, Nano silica phosphoric acid, Sonication condition.*

1. Introduction

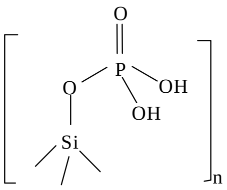
During the last decade, multi-component reactions have increasingly become important in organic and medicinal chemistry as efficient and low-cost tools for combinatorial synthesis. Biginelli has reported a multi-component reaction of ethyl acetoacetate, benzaldehyde and urea to obtain dihydropyrimidinone (DHPM). The DHPM derivatives have attracted considerable interest in recent years due to promising activities as calcium channel blockers, antihypertensive, antibacterial, antitumor and anti-inflammatory agents [1]. The Biginelli reaction could be catalyzed by acids such as $H_3PMo_{12}O_{40}$ [2], 12-tungstophosphoric acid [3], chloroacetic acid [4], CuI [5], $Fe(CF_3CO_2)_3$ [6], CaF_2 [7], trichloroisocyanuric acid [8], $ZrCl_4$ [9], NH_2SO_3H [10], $Y(NO_3)_3.6H_2O$ [11] and nano-$BF_3.SiO_2$ [12].

Silica phosphoric acid (SPA) [13] is an efficient and reusable catalyst. It was prepared by reaction of silica chloride [14] with dry phosphoric acid. It is noted that, silica chloride was prepared via reaction of silica gel and thionyl chloride. By using nano silica gel instead of silica gel, according to above pathway, nano silica phosphoric acid (nano-SPA) was prepared. The particle size of nano-silica gel and nano-SPA was measured by SEM photography (Fig. 1). The acidic capacity of nano-SPA is 10.32 mmol.g-1 and was determined via titration of 0.2 g of catalyst with standard solution of NaOH. The FT-IR (ATR) spectra of silica chloride, nano-SPA, and $H_3PO_4.SiO_2$ were shown in Fig. 2. In all ATR spectrums, the Si-O-H and Si-O-Si stretching bonds are appeared in 900 until 1100 cm^{-1}. In silica chloride spectrum, the Si-Cl stretching bond is appeared in 700 cm^{-1}. In ATR spectra of nano-SPA and $H_3PO_4.SiO_2$, the P-O-H, P=O, P-O stretching bonds are appeared 910-1040, 1637 and 2400-2800 cm^{-1} respectively. According to above data, we suggested one structure for nano-SPA with PO_3H_2 on silica gel (Scheme 1).

2. Experimental

2.1. General.

The materials were purchased from Merck company and were used without any additional purification. Products were characterized by FT-IR, ^{1}H-NMR and comparison of their physical properties with those reported in the literature.



Scheme 1.

---

* Corresponding author: E-mail: bamoniri@kashanu.ac.ir.
Tel.: +98-361 5912305; Fax: +98-361 5552930.

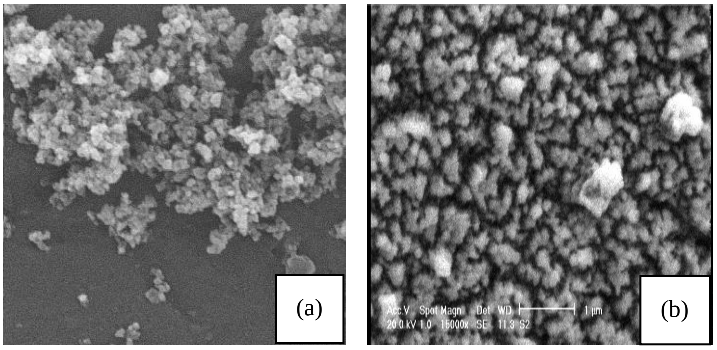


Fig. 1. The SEM photograph of (a) nano silica-gel and (b) nano-SPA.

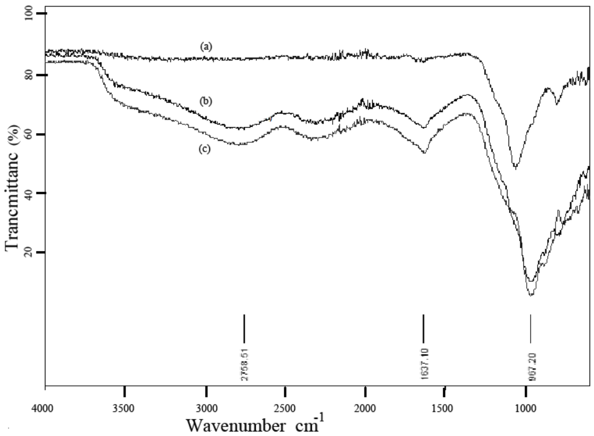


Fig. 2. ATR of (a) silica chloride, (b) nano-SPA and (c) $H_3PO_4.SiO_2$

FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the ^1H NMR spectra.The SEM of nano particles determined with VEGA/TESCAN scanning electron microscope.A BANDELIN Sonopulse HD 3200 ultrasonic apparatus was used for sonication.

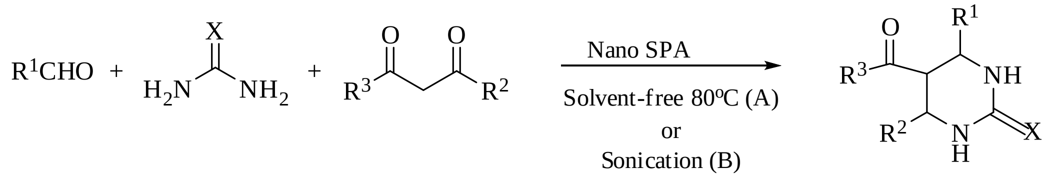
2.2. Typical Procedures for the Preparation of 3, 4-dihydropyrimidinones/thiones in the presence of nano-SPA

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.25 mmol) and nano-SPA (0.01 g) was heated with stirring at 80 °C. The progress of the reaction was monitored by TLC. After completion of reaction, the product was dissolved in hot ethanol and filtered to recover the catalyst. The filtrate was concentrated to obtain the product. The crude product recrystallized from ethanol.

3. Results and Discussion

In continuation of our investigation on application of solid acids in organic synthesis [15-20], we have used nano-SPA in Bigenelli multi-component reaction. Initially, we studied the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3-4-dihydropyrimidin-2(1*H*)-one using benzaldehyde, ethyl acetoacetate, urea and SPA as a catalyst under various conditions (Table 1). The best conditions were obtained by using 0.04 g of SPA for 1 mmol of each substrate under solvent-free conditions at 80 °C (Table 1, entry 2). We repeated the above mentioned reaction with 0.01 g of nano-SPA and we found that the activity of nano-SPA was four times as much as SPA (Table 1, entry 3). To examine the reusability of nano-SPA in solvent free condition, after each run, the product was dissolved in $CHCl_3$ and filtered. Then, the catalyst residue was washed with acetone and reused. Treatment with acetone removes the tar from the catalyst surface more efficiently (Table 1, entries 14 and 15). The catalyst was reusable although a gradual decline was observed in its activity.

The leeching of the catalyst was low and studied by stop the present reaction in 50% progress, isolation the catalyst and continuation of the reaction in ethyl acetate as solvent. After, 120 minutes, the progress of the reaction was 65%. The ultrasonic assisted synthesis of the present reaction was studied by using SPA or nano-SPA in ethyl acetate under reflux conditions (Table 1, entries 11 and 12). It was found



Scheme 2.

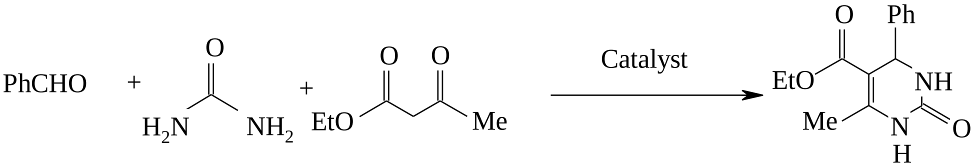


Table 1. Synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one under various conditions[a]

Entry	Catalyst (g)	Solvent	Condition	Time (min)	Yield (%)	Ref.
1	SPA (0.03)	-	80 °C	120	52	-
2	SPA (0.04)	-	80 °C	120	94	-
3	Nano-SPA (0.01)	-	80 °C	120	95	-
4	SPA (0.04)	$CHCl_3$	40 °C	120	48	-
5	SPA (0.04)	H_2O	60 °C	120	63	-
6	SPA (0.04)	n-Hexane	40 °C	120	88	-
7	SPA (0.04)	EtOH	40 °C	120	85	-
8	SPA (0.04)	HOAc	40 °C	120	75	-
9	SPA (0.04)	MeOH	40 °C	120	86	-
10	SPA (0.04)	Acetone	40 °C	120	87	-
11	SPA (0.04)	-	Ball mill	30	65	-
12	SPA (0.04)	Ethyl acetate	Ultrasound	30	96	-
13	Nano-SPA (0.01)	Ethyl acetate	Ultrasound	30	95	-
14	Nano-SPA (0.01), 2nd run	-	80 °C	120	65	-
15	Nano-SPA (0.01), 3rd run	-	80 °C	120	50	-
16	Silica chloride (0.02)	-	90 °C	70	80	-
17	37% nano-$BF_3.SiO_2$ (0.3)	-	80 °C	15	85	12
18	$H_3PMo_{12}O_{40}$ (2 mol %)	HOAc	Reflux	240	75	2
19	12-Tungstophosphoric acid (2 mol %)	HOAc	Reflux	360	70	3
20	Chloroacetic acid (10 mol %)	-	90 °C	180	86	4
21	CuI (15 mol %)	-	90 °C	25	87	5
22	$Fe(CF_3CO_2)_3$ (5 mol %)	-	70 °C	20	95	6
23	CaF_2(10 mol %)	EtOH	Reflux	120	98	7
24	Trichloroisocyanuric acid (15 mol %)	EtOH	Reflux	720	92	8
25	$ZrCl_4$ (10 mol %)	EtOH	Reflux	240	88	9
26	NH_2SO_3H (75 mol %)	EtOH	Ultrasound	40	87	10

[a]Benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.25 mmol) were applied.

that under sonication conditions, the reaction time decreased to 30 minutes. Then, the synthesis of various 3,4-dihydropyrimidin-2(1H)-ones (thiones) were done (scheme 2) and the obtained results summarized in Table 2. All products were known and characterized through comparison of their FT-IR, 1H-NMR and physical properties with those reported in the literature. The obtained results have shown that the electron withdrawing groups on aldehyde caused the high yields of products in short reaction times (Table 2, entries 1 and 2). Ethyl acetoacetate is more reactive than ethyl benzoyl acetate in Biginelli reaction (Table 2, entries 8, 9 and 10).

4. Conclusion

In summary, we have presented the nano-SPA is an efficient, eco-friendly and reusable catalyst for synthesis of Biginelli-type compounds under solvent-free condition or sonication in ethylacetate. Short reaction times, high yields, simplicity of operation, and easy work-up are some advantages of this method.

Acknowledgements

The Research Council of University of Kashan is gratefully acknowledged for the financial support for this work.

Table 2. Synthesis of dihydropyrimidinones/thiones in the presence of nano- SPA under solvent free condition at 80 °C.

Entry	R^1	R^2	R^3	X	Yield^b (%)		mp (^{o}C) found	mp (^{o}C)· reported ^{Ref}
					Normal heating^a	sonication^b		
1	2-NO_2-C_6H_4	CH_3	OCH_2CH_3	O	92	90	218-220	220[3]
2	4-NO_2-C_6H_4	CH_3	OCH_2CH_3	O	93	89	209-211	211[2]
3	4-Cl-C_6H_4	CH_3	OCH_2CH_3	O	91	88	214-215	216[3]
4	4-MeO-C_6H_4	CH_3	OCH_2CH_3	O	89	87	203-205	203–205[4]
5	3-MeO-C_6H_4	CH_3	OCH_2CH_3	O	87	86	219-222	220-221[21]
6	4-Me-C_6H_4	CH_3	OCH_2CH_3	O	89	88	215-216	214[22]
7	C_6H_5	CH_3	OCH_2CH_3	O	91	89	204-205	204[2]
8	2,6-$(Cl)_2$-C_6H_3	Ph	OCH_2CH_3	O	89	87	275-276	274-276[24]
9	4-Cl-C_6H_4	Ph	OCH_2CH_3	O	87	85	267-268	267-269[24]
10	Ph	Ph	OCH_2CH_3	O	88	87	154-158	155-157[25]
12	4-Cl-C_6H_4	CH_3	OCH_2CH_3	S	90	90	184-185	184-185[4]
13	2-Cl-C_6H_4	CH_3	OCH_2CH_3	S	89	88	168-170	168-169[23]
14	4-MeO-C_6H_4	CH_3	OCH_2CH_3	S	86	85	152-153	153[3]
15	4-Me-C_6H_4	CH_3	OCH_2CH_3	S	87	86	190-192	191-193[12]
16	Ph	CH_3	OCH_2CH_3	S	92	90	205-206	206[3]
17	2-Cl-C_6H_4	CH_3	CH_3	S	91	92	171-173	173-174[23]
18	4-MeO-C_6H_4	CH_3	CH_3	S	88	87	162-164	161-163[12]
19	Ph	Ph	OCH_2CH_3	S	88	87	184-185	183-185[23]
20	4-MeO-C_6H_4	Ph	OCH_2CH_3	S	87	85	152-154	151-152[23]

[a] A mixture of aldehyde (mmol): β-keto ester (mmol): urea or thiourea (mmol): nano-SPA (g) equal to 1:1:1.25:0.01 was heated in 80 °C for 120 minutes.

[b] A mixture of aldehyde (mmol): β-keto ester (mmol): urea or thiourea (mmol): nano-SPA(g) equal to 1:1:1.25:0.01 in ethyl acetate was sonicated under power 100 for 30 minutes.

References

[1] (a) H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda,T. Ishihara, K. Funahashi, F. Satoh, M. Morita, T. Noguchi, J. Med. Chem. 32 (1989) 2399-2406 (b) K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A.O. Hedberg, B.C. Reilly, J. Med. Chem. 34 (1991) 806-811.

[2] M.M. Amini, A. Shaabani, A. Bazgir, Catal. Commun. 7 (2006) 843–847.

[3] M.M. Heravi, F. Derikvand, F. Bamoharram, J. Mol. Catal. A: Chem. 242 (2005) 173-175.

[4] Y. Yu, D. Liu, C. Liu, G. Luo, Bioorg. Med. Chem. Lett. 17 (2007) 3508-3510.

[5] H.R. Kalita, P. Phukan, Catal. Commun. 8 (2007) 179–182.

[6] H. Adibi, H.A. Samimi, M. Beygzadeh, Catal. Commun. 8 (2007) 2119–2124.

[7] S. Chitra, K. Pandiarajan, Tetrahedron Lett. 50 (2009) 2222–2224.

[8] M.A. Bigdeli, S. Jafari, G.H. Mahdavinia, H. Hazarkhani, Catal. Commun. 8 (2007) 1641–1644.

[9] C.V. Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu, V.V.N. Reddy, Tetrahedron Lett. 43 (2002) 2657–2659.

[10] J.T. Li, J.F. Han, J.H. Yang, T.S. Li, Ultrasonics Sonochem. 10 (2003) 119 –122.

[11] N.S. Nandurkar, M.J. Bhanushali, M.D. Bhor, B.M. Bhanage, J. Mol. Catal. A: Chem. 271 (2007) 14-17.

[12] B.F. Mirjalili, A. Bamoniri, A. Akbari J. Iran. Chem. Soc. 8 (2011)135-140.

[13] M.A. Zolfigol, F. Shirini, K. Zamani, E. Ghofrani, S. Ebrahimi, Phosphourus, Sulfur, Silicon Relat. Elem.179 (2004) 2177-2182.

[14] M.A. Zolfigol, F. Shirini, A. Ghorbani Choghamarani, A. Shiri, H. Keypour, S. Salehzadeh Asian, J. Chem. 13 (2001) 849-853.

[15] A. Bamoniri, M.A. Zolfigol, I. Mohammadpoor-Baltork, B.F. Mirjalili, J. Iran. Chem. Soc. 3 (2006) 85-88.

[16] A. Bamoniri, B.F. Mirjalili, M.A. Zolfigol, I. Mohammadpoor-Baltork, J. Iran. Chem. Soc. 4 (2007) 332-335.

[17] B.F. Mirjalili, A. Bamoniri, A. Akbari, N. Taghavinia, J. Iran. Chem. Soc. 8 (2011) 129-134.

[18] B. Sadeghi, B.F. Mirjalili, M.M. Hashemi, J. Iran. Chem. Soc. 5 (2008) 694-698.

[19] A. Bamoniri, B.F. Mirjalili, A. Ghorbani-Ch., M. E. Yazdanshenas, A. Shayanfar, A. Akbari, Iran. J. Catal. 2 (2011) 51-54.

[20] B.F. Mirjalili, A. Bamoniri, A. Akbari, Iran. J. Catal. 2 (2011) 87-92.

[21] F.L. Zumpe, M.B. Flu, K. Schmitz, A. Lender, Tetrahedron Lett. 48 (2007) 1421-1423.

[22] M. M. Heravi, K. Bakhtiari, F.F. Bamoharram, Catal. Commun. 7 (2006) 373-376.

[23] J.C. Rodrıguez-Domınguez, D. Bernardi, G. Kirsch, Tetrahedron Lett. 48 (2007) 5777-5780.

[24] B. Liang, X. Wang, J-X Wang, Z. Du, Tetrahedron 63 (2007) 1981–1986.

[25] P. Salehi, M. Dabiri, M.A. Zolfigol, M.A. Bodaghi Fard, Tetrahedron Lett. 44 (2003) 2889–2891.