



Full paper/Mémoire

An appropriate one-pot synthesis of dihydropyrimidinones catalyzed by heteropoly acid supported on zeolite: An efficient and reusable catalyst for the Biginelli reaction

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ABSTRACT

A mild and efficient catalytic method has been developed for the synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones (DHPM) by a one-pot three-component cyclocondensation reaction using molybdophosphoric acid (MPA) supported on Y zeolite in high to excellent yields. The reaction investigated in the presence of molybdophosphoric acid encapsulated in the supercage of zeolite for comparison. In the second method, no appreciable progress was observed due to large size of dihydropyrimidinone compounds towards the supercage dimension of Y zeolite. In addition, the catalyst was recovered and reused for several times without efficient loss in catalytic activity.

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1. Introduction

Dihydropyrimidinones derivatives known as “Biginelli compounds” have received significant attention because of their wide range of pharmacologically potent calcium channel blockers, antihypertensive agents and α -adrenergic antagonists, and neuropeptide Y (NPY) antagonists.

These compounds also have been found to have a broad range of biological activities such as antiviral, antitumor, cardiovascular antibacterial, anti-inflammatory and anti-oxidant properties [1–4]. Therefore, the preparation of these materials has attracted the significant attention of many chemists. The classical Biginelli synthesis involves three-component one-pot condensation of β -ketoester with an aldehyde and urea under strongly acidic conditions, but the reaction suffer from drawbacks such as low yields, long reaction time, and strong corrosion equipment [5]. In order to improve the efficiency of these reactions, many efforts including various solid-phase modifications and use of a

variety of Lewis acid catalysts have been devoted. These catalytic systems involve ytterbium(III) resin [6], Mn(OAc)₃·2H₂O [7], trifluoroacetic acid (TFA) [8], boric acid [9], CeCl₃·7H₂O [10], Cu(OTf)₂ [11], lithium bromide [12], silica/sulfuric acid [13], indium (III) bromide [14], lanthanum chloride [15], vanadium(III) chloride [16], ionic liquids BMImPF₆ and BMImBF₄ [17], montmorillonite-KSF [18], zinc triflate [19], I₂ [20], NBS [21], bismuth triflate [22], LiClO₄ [23], NH₄Cl [24], zirconium(IV) chloride [25], indium(III) bromide [26], heteropolyacid Ag₃PW₁₂O₄₀ [27], supported polyoxometal [28], benzyltriethylammonium chloride [29], Y(OAc)₃ [30], AlCl₃:ZnCl₂ (3:1) [31], etidronic acid [32], silica-chloride [5] and -SmCl₃·6H₂O [33].

Among support systems, zeolite Y is an appropriate candidate for the immobilization of HAP because it produces heterogeneous catalysts that are recoverable and reusable.

In a continuation of our previous work on heterogeneous catalysts [34–36], we wish to report a cheap, recoverable and efficiency catalytic system for the synthesis of dihydropyrimidinone from aldehyde in the presence of supported polyoxometal on external zeolite surface as a solid acid catalyst.

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2. Experimental

Polyoxometalates including molybdophosphoric acid, tangestophosphoric acid and tangestosilicic acid, denoted as molybdophosphoric acid (MPA), tangestophosphoric acid (TPA) and tangestosilicic acid (TSA), respectively, were purchased from Merck and purified by extraction with dimethyl ether from aqueous solution and then dried under reduced pressure. Other materials were of the commercial reagent grade and used without further purification. The NaY-zeolite was purchased from Sigma-Aldrich Chemical Company. Melting points were recorded on a Barnstead Electrothermal 9200 apparatus and are uncorrected. All of the reactions were performed under magnetically stirring and the progress of the reactions was monitored by thin layer chromatography (TLC). All products were known compounds and identified by comparing their physical data to their authentic samples.

2.1. General procedure for the preparation of supported polyoxometalate

The catalysts were prepared by the incipient wetness method [28]. The framework of Y zeolite involves aluminum atoms that show basicity. Thus, they may decompose as a heteropolyacid structure [37]. Therefore, Y zeolite was modified by acid treatment. In the typical procedure, aqueous NaY suspension was prepared (8 wt%) and dealuminated by adding HClO₄ to suspension of zeolite in water following 0.5 mM heteropolyacid (HPA) addition [38]. The mixture of HPA was supported on dealuminated zeolite (HY), stirred for 24 h followed by drying at 383 K and calcined for 4 h at 250 °C to obtain the support catalyst.

2.2. General procedure for the synthesis of dihydropyrimidinones

In a typical procedure, ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea (1.5 mmol) were mixed with HPA supported on Y zeolite (8 wt% NaY + 0.5 mM HPA) and refluxed in the presence of acetonitrile (10 mL) as a solvent for an appropriate time. The progress of reaction was monitored by TLC. At the end of reaction, heteropoly acid (HPA) supported on HY filtered off and washed with hot water and ethanol to remove urea from the surface of the catalyst. Then, the catalyst dried and was maintained for new runs. The filtrate was concentrated and the crude product was recrystallized from ethanol to afford the pure

Table 1

Synthesis of ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in the presence of zeolite-supported molybdophosphoric acid in various solvent after 6 h under reflux conditions.^a

Yield ^b (%)	Solvent	Entry
55	Ethylacetate	1
25	dichloromethane	2
45	Chloroform	3
74	Methanol	4
97	Acetonitrile	5

^a Reaction conditions: 4-Nitro benzaldehyde (1 mmol), acetoacetate (1 mmol), urea (1.5 mmol), solvent (10 mL), catalyst (0.7 mol%).

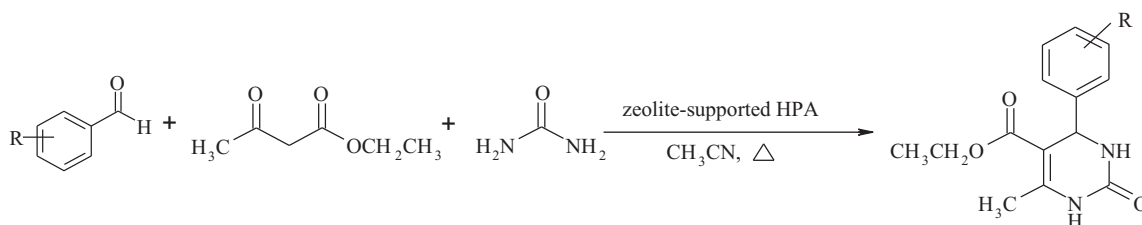
^b Isolated yield.

product. Products were identified by comparison with melting points of the authentic compounds.

In addition, the Biginelli reaction was performed in the presence of zeolite-encapsulated HPA for comparison. Synthesis of this catalyst is discussed in our previous works [34–36].

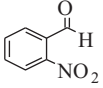
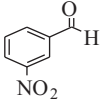
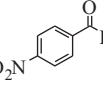
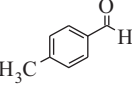
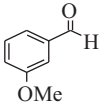
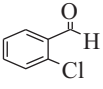
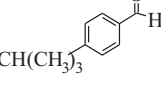
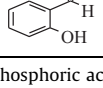
3. Results and discussion

Catalysts were prepared by the impregnation of HPA in an acidic suspension with zeolite as a support. The zeolite structure shows basicity because of aluminum atoms so that it causes the decomposition of HPA. Therefore, Y zeolite was dealuminated by adding perchloric acid according to the reported procedure [38]. The reaction of aldehydes with acetoacetate and urea in the presence of HPA supported on dealuminated zeolite produced corresponding dihydropyrimidinone compounds (Scheme 1). Several solvents were used with 4-Nitro benzaldehyde as a model substrate and zeolite supported-MPA as a model catalyst at reflux conditions. The best results were obtained with acetonitrile (Table 1). Under this condition, a wide range of aromatic aldehyde bearing electron-withdrawing or electron-donating groups was reacted to obtain the corresponding compounds in good to excellent yield (Table 2). Zeolite-encapsulated HPA was used in these reactions for comparison. The result proved in the presence of zeolite-encapsulated HPA, the yield of dihydropyrimidinone is very negligible that proved dihydropyrimidinone molecules cannot be formed in the supercage of zeolite because of the large size of these molecules. Therefore, the supported system was chosen as the catalytic system. The reusability of catalyst was investigated using 3-nitrobenzaldehyde (1 mmol) as a model



Scheme 1. Synthesis of conventional dihydropyrimidinones in the presence of zeolite-supported heteropolyacid under reflux condition.

Table 2
Synthesis of 3,4-dihydropyrimidin-2 (1H)-ones, catalyzed by zeolite-supported heteropolyacid.

Entry	Substrate	MPA-supported HY		TPA-supported HY		TSA-supported HY		Melting point	
		Time (h)	Yield ^a (%)	Time (h)	Yield ^a (%)	Time (h)	Yield ^a (%)	Found ^b	Reported
1		10	94	7	65	11	72	223	220 [7]
2		8.5	95	9.5	95	10.5	94	225–227	227–228 [14]
3		6	97	5	80	6	92	208–210	209–211 [13]
4		6.5	95	6.5	95	8.5	92	213–215	214–216 [26]
5		7.5	93	7.5	95	8.5	93	206	207–208 [30]
6		7.5	90	92	4.5	8.5	90	213	215–216 [7]
7		7.5	95	8	80	12	97	198	199–202 [17]
8		11	70	5	70	11	70	157–159	156–158 [30]
9		8	90	9.5	93	10	80	217–218	215–216 [7]
10		7.5	80	6	90	5.5	90	198–199	199–201 [28]

MPA: molybdophosphoric acid; TPA: tangestophosphoric acid; TSA: tangestosilic acid; HY: dealuminated zeolite.

^a Isolated yield.

^b Compounds are known and were characterized by their physical and spectral data.

Table 3

The results obtained in the reusability of zeolite-supported molybdophosphoric acid catalyst in the synthesis of ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate after 6 h.

Yield ^a (%)	Run
97	1
95	2
94	3
95	4
90	5

^a Isolated yield.

substrate in the presence of recovered catalyst (0.7 mol%) and acetonitrile (10 mL) as solvent under reflux conditions. At the end of the reaction, the catalyst was filtered and washed by hot water and ethanol to remove unreacted species. Then, the catalyst was activated by drying at 120 °C for 3 h and was used for new runs. No appreciable loss in the catalytic activity was detected, which means that HPA is still present on the support system (Table 3).

4. Conclusion

In conclusion, in this paper, we reported a mild and efficient protocol for the synthesis of dihydroprimidinone compounds that utilizes a multicomponent coupling reaction catalyzed by HPA supported on Y zeolite in refluxing acetonitrile. In the presence of zeolite-encapsulated HPA, the yield of reaction is very negligible due to the size of dihydropyrimidinone compounds being larger than the supercage of zeolite. Then, support system was chosen as the catalytic system. The catalyst was recoverable and reused for several times without losing effective catalytic activity.

References

- [1] K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyed, S. Moreland, A. Hedberg, B.C. O'Reilly, *J. Med. Chem* 34 (1991) 806.
- [2] C.O. Kappe, W.M.F. Fabian, M.A. Semones, *Tetrahedron* 53 (1997) 2803.

- [3] K.S. Atwal, C.G. Rovnyak, B.C. O'Reilly, A.J. Schwartz, *Org. Chem* 54 (1989) 5898.
- [4] C.O. Kappe, *Tetrahedron* 49 (1993) 6937.
- [5] H.N. Karade, M. Sathe, M.P. Kaushik, *Molecules* 12 (2007) 1341.
- [6] A. Dondoni, A. Massi, *Tetrahedron Lett* 42 (2001) 7975.
- [7] K.A. Kumar, M. Kasthuraiah, C.S. Reddy, C.D. Reddy, *Tetrahedron Lett* 42 (2001) 7873.
- [8] J.C. Bussolari, P.A. McDonnel, *J. Org. Chem* 65 (2000) 6777.
- [9] S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang, *Tetrahedron Lett* 44 (2003) 6153.
- [10] D.S. Bose, L. Fatima, C. Miao, H. Jiang, Y. Feng, D. Shi, X.J. Wang, *Org. Chem* 68 (2003) 587.
- [11] A.S. Paraskar, G.K. Dewkar, A. Sudalai, *Tetrahedron Lett* 44 (2003) 3305.
- [12] G. Maiti, P. Kundu, C. Guin, *Tetrahedron Lett* 44 (2003) 2757.
- [13] P. Salehi, M. Dabiri, M.A. Zolfigol, M.A. Bodaghi Fard, *Tetrahedron Lett* 44 (2003) 2889.
- [14] N.Y. Fu, M.L. Pang, Y.F. Yuan, J.T. Wang, *Chin. Chem. Lett* 13 (2002) 921.
- [15] J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, *Tetrahedron Lett* 41 (2000) 9075.
- [16] G. Sabitha, G.S.K. Reddy, K.B. Reddy, J.S. Yadav, *Tetrahedron Lett* 44 (2003) 6497.
- [17] J. Peng, Y. Deng, *Tetrahedron Lett* 42 (2001) 5917.
- [18] F. Bigi, S. Carloni, B. Frullanti, R. Maggi, G. Sartori, *Tetrahedron Lett* 40 (1999) 3465.
- [19] H. Xu, Y. Wang, *Chin. J. Chem* 21 (2003) 327.
- [20] K.V.N. Srinivas, B. Das, *Synthesis* 13 (2004) 2091.
- [21] H. Hazarkhani, B. Karimi, *Synthesis* 8 (2004) 1239.
- [22] R. Varala, M.M. Alam, S.R. Adapa, *Synlett* 1 (2003) 67.
- [23] J.S. Yadav, B.V.S. Reddy, R. Srinivas, C. Venugopal, T. Ramalingam, *Synthesis* 9 (2001) 1341.
- [24] A. Shaabani, A. Bazgir, F. Teimouri, *Tetrahedron Lett* 44 (2003) 857.
- [25] C.V. Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu, V.V.N. Reddy, *Tetrahedron Lett* 43 (2002) 2657.
- [26] N.Y. Fu, Y.F. Yuan, Z. Cao, S.W. Wang, J.T. Wang, *Tetrahedron* 58 (2002) 4801.
- [27] J.S. Yadav, B.V.S. Reddy, P. Sridhar, J.S.S. Reddy, K. Nagaiah, N. Lingaiah, P.S. Saiprasad, *Eur. J. Org. Chem* 3 (2004) 552.
- [28] R. Fazaeli, S. Tangestaninejad, H. Aliyan, M. Moghadam, *Appl. Catal. A: General* 309 (2006) 44.
- [29] D.S. Bose, M. Sudharshan, S.W. Chavhan, *ARKIVOC* iii (2005) 228.
- [30] G. Aridoss, Y.T. Jeong, *Bull. Korean Chem. Soc* 31 (2010) 863.
- [31] S. Balalaie, M. Soleiman-Beigi, F.J. Rominger, *Iran. Chem. Soc* 2 (2005) 319.
- [32] A.M. Pansuriya, M.M. Savant, C.V. Bhuvu, J. Singh, Y.T. Naliapara, *ARKIVOC* vii (2009) 79.
- [33] Y.X. Li, W.L. Bao, *Chinese Chem. Lett* 14 (2003) 993.
- [34] M. Moghadam, S. Tangestaninejad, V. Mirkhani, I. Mohammadpoor, M. Moosavifar, *C. R. Chimie* 14 (2011) 489.
- [35] M. Moghadam, S. Tangestaninejad, V. Mirkhani, I. Mohammadpoor, M. Moosavifar, *Appl. Catal. A: general* 358 (2009) 157.
- [36] M. Moosavifar, S. Tangestaninejad, M. Moghadam, V. Mirkhani, I. Mohammadpoor, *C. R. Chimie* 14 (10) (2011) 953.
- [37] S.R. Mukai, T. Masuno, I. Ogina, K. Hashimoto, *Appl. Catal. A: general* 165 (1997) 219.
- [38] R.R. Ozer, J.L. Ferry, *J. Phys. Chem. B* 106 (2002) 4336.