

Natural HEU type zeolite catalyzed Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1H) one derivatives

Mahmood Tajbakhsh^a, Bagher Mohajerani^b,
Majid M. Heravi^{c,*}, Amir N. Ahmadi^a

^a Department of Chemistry, School of Sciences, Mazandaran University, Babolsar, Iran

^b Chemical and Petrochemical Research Division, Research Institute of Petroleum Industry, Tehran, Iran

^c Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

Received 29 November 2004; received in revised form 20 April 2005; accepted 20 April 2005

Abstract

A new method for Biginelli reaction via heterogenous catalyst has been developed. This method uses natural Heulandite type zeolite (HTMA) as a catalyst for the one pot condensation of an aldehyde, urea and a 1,3-dicarbonyl compound under mild conditions in excellent yields.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Biginelli reaction; Zeolite; Heulandite; Dihydropyrimidinones; One pot condensation

1. Introduction

Dihydropyrimidinones have attracted considerable attention because of their wide spectrum of biological and therapeutic activities. Functionalized dihydropyrimidinones have been used as potent calcium channel blockers [1], antihypertensive agents [2] and neuropeptide Y antagonist [3]. Some marine natural products containing the dihydropyrimidinone-5-carboxylate unit such as the batzelladine alkaloid have been found to be potent HIV gp-120-CD4 inhibitors [4].

The first protocol to prepare the compounds of this type was presented by Biginelli [5] more than a century ago and made use of three components, one pot condensation of a β -ketoester, an aldehyde, and urea under strongly acidic conditions. This method has its own merits and drawbacks. A major drawback of the classical Biginelli reaction is the poor to moderate yields, particularly when the reaction is performed with an aliphatic aldehyde [6]. This important disadvantage has led to the disclosure of several improved

and modified methods using Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ [7], lanthanide triflate [8], indium trichloride [9], lanthanum trichloride [10], NiCl_2 , FeCl_3 [11], boric acid [12], vanadium (III) chloride [13], supported FeCl_3 [14], and *N*-butyl-*N,N*-dimethyl- α -phenylethyl ammonium bromide [15]. Several combinatorial applications of the Biginelli condensation have been advanced [16] using solid phase on fluorous phase reaction conditions. Recently there have been a number of reports concerning the microwave assisted, high speed, Biginelli reaction, using poly phosphate ester (PPE) [17a] and FeCl_3 or TsOH [17b]. In addition KSF montmorillonite [18] and zeolite [19] in refluxing toluene have been used for Biginelli cyclocondensation to give dihydropyrimidinones although this reaction took a long time and gave low to moderate yields.

Due to the importance of Biginelli reaction products, the discovery and introduction of milder, faster, eco-friendly conditions resulting in high yields whilst using inexpensive reagents are in great demand.

Zeolites are crystalline hydrated aluminosilicates of the alkaline earths. Natural zeolites are formed in several geological environments such as hydrothermal, burial metamorphic, closed system (including alkaline earths), open system,

* Corresponding author. Tel.: +98 218041347; fax: +98 218047861.
E-mail address: mmh1331@yahoo.com (M.M. Heravi).

and weathering profiles. Due to their remarkable physical and chemical properties, zeolites have been utilized successfully by the chemical industry and in environmental protection over the last 40 years [20].

2. Experimental

2.1. General procedure for the synthesis of derivatives of 4-aryl, 3,4-dihydropyrimidin-2(1H)-one

A three-necked round bottom flask fitted with a thermocouple and a reflux condenser was charged with β -ketoester (6 mmol), arylaldehyde (6 mmol), urea (7.2 mmol), and HMTA catalyst (0.2 g) in glacial acetic acid (30 ml). The mixture was heated at 100 °C for 4–5 h. The mixture was cooled to room temperature. The catalyst was then removed by filtration and the solution poured onto ice-water (60 ml). The resulting solid product was filtered and recrystallized from ethanol to give pure product.

All products are known compounds and were characterized by mp, IR, ¹H NMR and EA. Data for **1**: mp 202–204 °C; ¹H NMR (DMSO-d₆): 1.1 (t, *J* = 7.2 Hz, 3H, CH₃CH₂O), 2.24 (s, 3H, CH₃), 4.00 (q, *J* = 7.2 Hz, 2H, OCH₂), 5.16 (s, 1H, CH), 7.18–7.30 (m, 5H, arom CH), 7.78 (s, 1H, NH), 9.25 (s, 1H, NH); IR (KBr): 3244, 1724, 1639 cm⁻¹; Anal. calcd. for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.79. Found: C, 64.69; H, 6.28; N, 10.90.

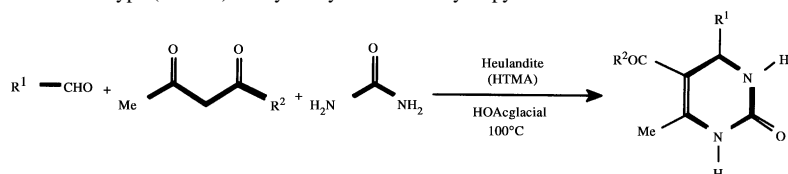
3. Results and discussion

In view of emerging importance of zeolites as catalysts and our general interest in solid acid catalyzed chemical reactions [21], we envisioned expedited Biginelli reactions using an available zeolite. Herein we wish to disclose our results, studying the application of our natural zeolite, which has recently been found in Iran (Semnan Province). This type of zeolite may determined to be Heulandite type [22] by XRD. We have named this commercially available zeolite, with the formula (CaAl₂Si₇O₁₈·6H₂O), HTMA. It has a surface area of 44 m²/g and a chemical composition of SiO₂ (55%), Al₂O₃ (11%), Na₂O (1.5%), K₂O (1.8%), CaO (0.64%), Fe₂O₃ (0.81%), and an acidity of 1.95 mmol NH₃/g_{cat}. The crystal size of catalyst was determined to be below 3 μm using SEM technique (Fig. 2).

Solid phase zeolite type catalysts are interesting since they are environmentally friendly and convenient to perform reactions with. However, reactions involving such catalysts take long times and often give low yields. Thus, a natural, cheap, and commercially available catalyst with appropriate aluminum sites which can act as a suitable Lewis acid to stabilize the imine intermediate and result in the formation of dihydropyrimidinones [19].

An aldehyde, urea, and an appropriate β -ketoester in the ratio of 1:1.2:1 were heated at 100 °C in glacial acetic acid in the presence of HTMA (0.2 g per 0.006 mol aldehyde) for the indicated time (Table 1). After completion of the reaction

Table 1
Heulandite type (HTMA) catalyzed synthesis of dihydropyrimidinones



Entry	R ₁	R ₂	<i>t</i> (h)	Yield (%)	mp (°C)		Ref.
					Found		
1	C ₆ H ₅	OEt	4–5	75	202–204		202–203 [7]
2	3-NO ₂ -C ₆ H ₄	OEt	4–5	73	225–226		226–227 [23]
3	4-F-C ₆ H ₄	OEt	4–5	72	176–177		175–177 [8]
4	4-HO-C ₆ H ₄	OEt	4–5	74	226–228		227–229 [8]
5	2-HO-C ₆ H ₄	OEt	4–5	69	202–205		201–203 [10]
6	4-MeO-C ₆ H ₄	OEt	4–5	75	200–202		199–201 [8]
7	4-Cl-C ₆ H ₄	OEt	4–5	80	207–210		210–212 [8]
8	C ₆ H ₅ C=C	OEt	4–5	60	234–236		232–235 [8]
9	3-MeO C ₆ H ₄	OEt	4–5	75	207–209		207–208 [9]
10	C ₆ H ₅	OMe	4–5	76	208–210		207–210 [8]
11	4-Cl-C ₆ H ₄	OMe	4–5	78	205–207		204–207 [7]
12	4-OMe-C ₆ H ₄	OMe	4–5	87	192–194		192–194 [7]
13	2-Methyl-C ₆ H ₄	OMe	4–5	81	239–242		240–242 [17a]
14	4-F-C ₆ H ₄	OMe	4–5	70	193–196		192–194 [8]
15	2-NO ₂ -C ₆ H ₄	OMe	4–5	70	280–283		280–282 [12]
16	Furyl	OMe	4–5	67	201–202		202–204 [11]
17	CH ₃ CH ₂ CH ₂	OEt	12	46	153–155		152–155 [11]
18	(CH ₃) ₂ CH	OEt	12	44	170–172		171–173 [11]

Table 2
Investigation of catalyst recyclability

Run	<i>t</i> (h)	Yield (%)	mp (°C)
1 ^a	4–5	75	202–204
2	4–5	75	202–205
3	4–5	74–75	201–204
4	4–5	74	202–204
5	4–5	72	201–204
6	4–5	51	200–205

^a Results refer to entry 1 in Table 1.

(monitored by TLC), the catalyst was removed by filtration and the filtrate poured onto crushed ice. The resulting solid was collected by filtration and recrystallized from ethanol to afford the pure product in high yield. The amount of catalyst was lowered from the reported 14% based on the total weight for synthetic zeolites [19] to 11% for Heulandite and no changes in purities or yields were observed. However, when less than 11% of the catalyst was used, the reaction did not seem to proceed to completion.

The results disclosed in Table 1, show the scope and generality of the method. One of the salient features of this method is that electron poor or rich arylaldehydes give excellent yields and purities. Aliphatic aldehydes also give acceptable yields compared with other catalysts. In this table, yields refer to isolated products. All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples. The catalyst can be used up to five times without any activity loss or appreciable changes in product yields. These results are summarized in Table 2.

Small crystal size of the catalyst indicates a large external surface area which causes its improved catalytic performance.

As shown in Table 3, natural HEU type catalyst gives higher yield in considerably shorter reaction time compared with homogeneous catalysts. This catalyst is also favored over classical zeolites because such a cheap catalyst gives comparable yields in shorter reaction times and under the same conditions. The model reaction (entry 1, Table 1) was carried out in toluene solvent at 100 °C merely to investigate the solvent effect and resulted in a product yield of 74%. This shows how zeolites function in a similar solvent.

Our discussion for this priority is given by comparing the Si/Al ratio of three zeolites in this section (Table 4).

As shown in Table 4, HY and HEU have been more efficient in this reaction because of the greater number of the Lewis acid sites (Al). On the other hand, the TPD profiles

Table 3
Comparison of Biginelli reaction using different solid acid catalysts

Entry	Catalyst	<i>t</i> (h)	<i>T</i> (°C)	Yield (%)
1	HZSM-5 ¹⁹	12	100	21
2	HY ¹⁹	12	100	80
3	Montmorillonite KSF ¹⁸	10, 48	100, 100	35, 72
4	Natural Zeolite Heulandite	4–5	100	75
5	HCl ^a	18	78	78

^a Classical Biginelli reaction. Results refer to entry 1 in Table 1.

Table 4
Comparison of Si/Al in some zeolite used in this reaction

Catalyst	Si/Al	Ref.
HY	2.5	[19]
HEU	5.0	
H-ZSM5	15	[19]

for HZSM-5, HY and Heulandite in Fig. 1 show that the TDP curve for HZSM-5 consists of two low temperature (LT) and high temperature (HT) peaks corresponding to weak and strong acidic sites, respectively, and the acidity equals 1.41 mmol NH₃/g_{cat}.

However, no HT peaks are observed for HY and Heulandite zeolites. Since the Biginelli reaction gives a higher yield using the latter catalysts, it can be concluded that the existence of strong acidic sites does not favor this reaction and

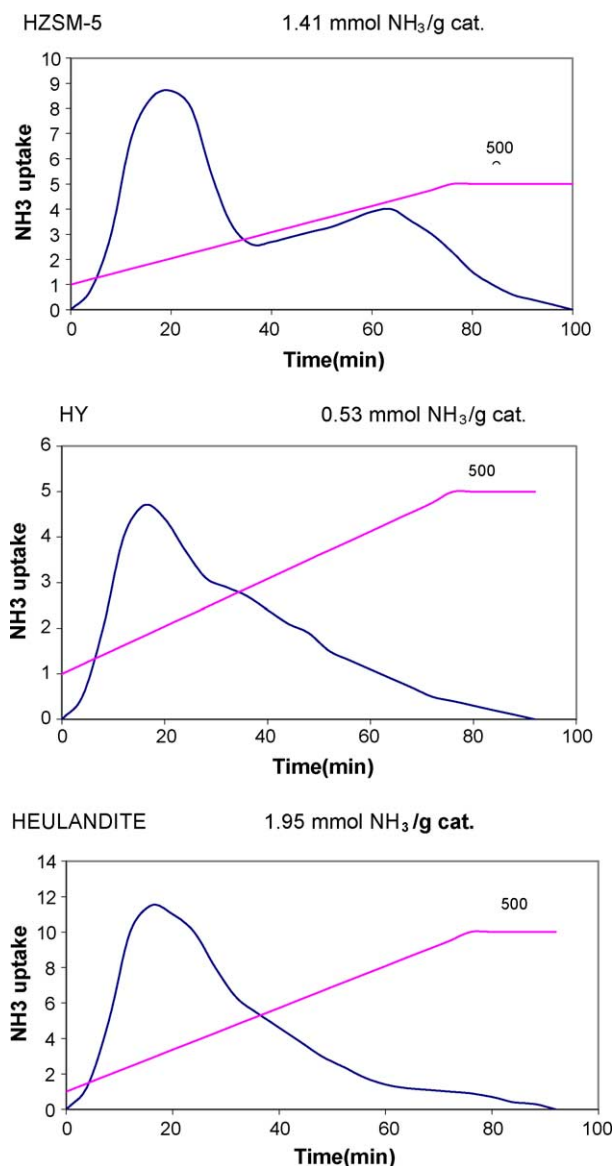


Fig. 1. TPD profiles for HZSM-5, HY, and Heulandite.

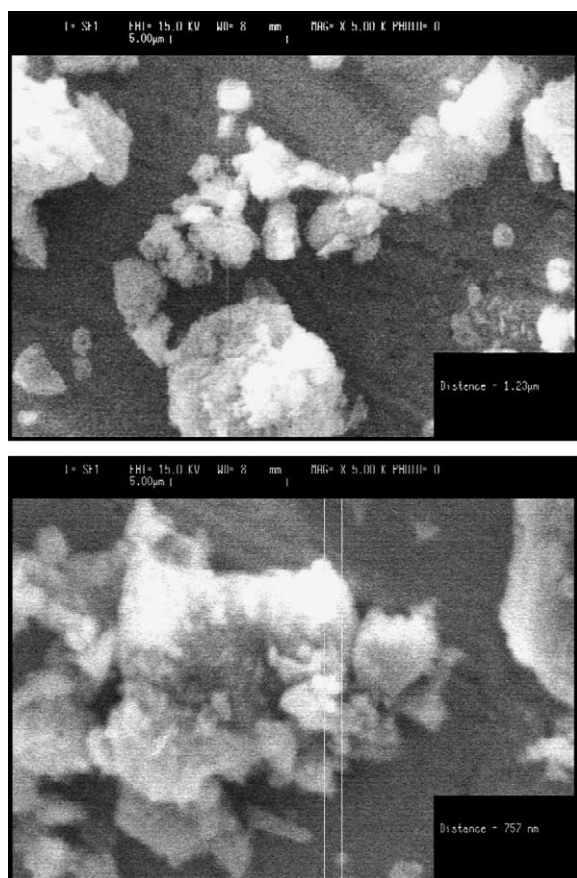


Fig. 2. The histogram of particle distribution for Heulandite by SEM technique.

suppresses the catalytic performance due to the possibility of the denseness of the active sites.

The acidity of Heulandite is 1.95 mmol $\text{NH}_3/\text{g}_{\text{cat}}$ and that of HY equals 0.53 mmol $\text{NH}_3/\text{g}_{\text{cat}}$. Given the identical pattern of TPD profiles for both zeolites, it can be concluded that the Biginelli reaction takes a shorter time using HEU compared with HY because there is a greater number of acidic sites in HEU catalyst. Thus, this catalyst has catalyzed the reaction in a shorter time compared with HY.

The SEM experiment for this new type of zeolite has been also performed. The typical pictures are given in Fig. 2.

4. Conclusion

In conclusion, we have developed a method using a commercially available, inexpensive and reusable solid catalyst. The reasonable reaction times, high yields, simple workup procedure and product isolation are main merits of this

method. We believe this methodology will find application in organic synthesis.

Acknowledgement

We gratefully acknowledge financial support of this work by the Research Institute of Petroleum Industry of Iran.

References

- [1] G.C. Rovnyak, S.D. Kimball, B. Beyer, G. Cucinotta, D.J. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J.P. McCarthy, R. Zhang, S. Mareland, *J. Med. Chem.* 38 (1995) 119.
- [2] G.J. Grover, S. Dzwomczyk, D.M. McMullen, C.S. Normadinam, P.G. Sleph, S. Moreland, *J. Cardiovasc. Pharmacol.* 26 (1995) 289.
- [3] M.A. Bruce, G.S. Pointdexter, G. Johnson, *PCT Int. Appl. WO* 33,791 (1998).
- [4] B.B. Sinder, Z.J. Shioz, *Org. Chem.* 58 (1993) 3828.
- [5] R. Biginelli, *Gazz. Chim. Ital.* 23 (1893) 360.
- [6] J. Barluenga, M. Thomas, A. Ballesterus, A. Lopez, *Tetrahedron Lett.* 30 (1989) 4573.
- [7] E.H. Hu, D.R. Silder, U.H.J. Dolling, *Org. Chem.* 63 (1998) 3454.
- [8] Y. Ma, C.T. Qian, L.M. Wang, M.J. Yang, *Org. Chem.* 65 (2000) 3864.
- [9] A. Brindaban, J. Unasish Jana, *Org. Chem.* 65 (2000) 6270.
- [10] Y. Junlu, Z. Bai, B. Wag, H. Yang, Ma, *Tetrahedron Lett.* 41 (2000) 9075.
- [11] J. Lu, Y.J.Z. Bai, *Synthesis* 4 (2002) 66.
- [12] S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang, *Tetrahedron Lett.* 44 (2003) 6153.
- [13] G. Salitha, G.S. Kiran Kreemar Reddy, K. Bhashar Reddy, J.S. Yadar, *Tetrahedron Lett.* 44 (2003) 6497.
- [14] V.R. Choudhary, V.H. Tellu, V.S. Narkhede, H.B. Borate, R.D. Warkharkar, *Catal. Commun.* 4 (9) (2003) 449.
- [15] K. Rosi Reddy, C. Venkoleshwar Reddy, M. Mahesh, P.V.K. Rayu, V.V. Narayana Reddy, *Tetrahedron Lett.* 44 (2003) 8173.
- [16] P.C. Wipf, A. Cunningham, *Tetrahedron Lett.* 36 (1995) 7819.
- [17] (a) C.O. Kappe, D. Kumar, R.S. Varma, *Synthesis* 10 (1999) 1799; (b) S.J. Tu, J.F. Zhau, D.J. Cai, H. Wang, J.C. Feng, *Synth. Commun.* 32 (2002) 147.
- [18] F. Bigi, S. Carloni, B. Frullanti, R. Maggi, G. Sartori, *Tetrahedron Lett.* 40 (1999) 3465.
- [19] V. Radha Rani, N. Srinivas, M. Radhakishan, S.J. Kulkarni, K.V. Raghavan, *Green Chem.* 3 (2001) 305.
- [20] G.E. Christidis, D. Moraetis, E. Keheyan, L. Akholbedashrili, N. Kekebdze, R. Evarkyan, H. Yeritsyan, H. Sargsyan, *Appl. Clay Sci.* 24 (2003) 79, and references listed therein.
- [21] (a) M.M. Heravi, D. Ajami, M. Ghassemzadeh, *Synthesis* 3 (1999) 393; (b) M.M. Heravi, D. Ajami, K. Aghapoor, M. Ghassezadeh, *Chem. Commun.* (1999) 833; (c) M.M. Herava, D. Ajami, M.M. Mojtahedi, M. Ghassemzadeh, *Tetrahedron Lett.* 40 (1999) 561.
- [22] D.W. Breck, *Zeolite Molecular Sieves, Structures; Chemistry and Uses*, Wiley, NewYork, 1984, p. 154.
- [23] K. Folkers, H.J. Harwood, T.B. Johnson, *J. Am. Chem. Soc.* 54 (1932) 3751.