J Incl Phenom Macrocycl Chem (2008) 60:353–357
DOI 10.1007/s10847-007-9384-2

ORIGINAL ARTICLE

# Zeolite an efficient catalyst for the Biginelli condensation reaction

**Mojgan Zendehdel · A. Mobinikhaledi · A. Asgari**

Received: 6 August 2007 / Accepted: 24 October 2007 / Published online: 21 February 2008
© Springer Science+Business Media B.V. 2008

**Abstract** A zeolite catalyzed, single step and environmentally friendly process for synthesis of classical Biginelli reaction was investigated. For this reaction Transition metal/Y zeolites were prepared by microwave solid-state and aqueous solution ion-exchange methods. The yield of reactions was increased in order of CuY > CoY > NiY > MnY ≈ FeY > VY > CrY > ZnY for the solid-state zeolite ion-exchange and CuY > CoY > NiY > MnY > CrY > VY > ZnY > FeY for the aqueous solution ion-exchange. The solid-state ion-exchange zeolite by microwave irradiation showed higher activity compared to the aqueous solution exchange. The yield of the product in the present of CuY zeolite was in order of 22–50%.

**Keywords** Tetrahydropyrimidinones · Zeolite · Acid sites · Biginelli

## Introduction

3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) have received significant attentions due to their diverse range of therapeutic and pharmacological activities [1–9] such as antiviral [5], antimitotic [6], anticarcinogenic [7], antihypertensive [8, 9] and calcium channel modulators [10]. Moreover, several natural marine alkaloids with interesting biological activities contain the dihydropyrimidine-5-carboxylate moiety [11, 12]. The original method for the synthesis of 3,4-Dihydropyrimidin-2(1H)-ones, which was firstly reported by Biginelli in 1893, involves one-pot reaction of $\beta$-ketoester or $\beta$-diketone, arylaldehyde and urea [13]. This has led to the recent development of several improved reaction protocols by using different acid catalysts including inorganic solid acids such as nafion-H [14], HEU [15], zeolite [16], MCM-41 [17] and heterogeneous catalytic method [18]. However the most of these protocols seem to be mainly concerned with the enhancing of the yields reaction. Very rarely attention has paid to the role of different used inorganic solid acids as catalyst in the mechanism of the Biginelli reaction.

Recently, there has been interested in the use of inorganic solid acids in the organic synthesis [19–21]. Among the various solid acid catalysts, zeolites have received an increasing attention because of their suitable acidity, thermal stability and low cost.

The acidity of zeolite could be due to the Bronsted and Lewis acid sites [22]. Exchange of monovalent cations with polyvalent ion creates strong Bronsted centers by the hydrolysis phenomena [23], which is useful for some of acid catalyst reactions such as alcohol dehydration, acylation [24], estrification [25], and Diels–Alder reaction [26]. We can decrease the number of proton sites and increase the number of Lewis sites by dehydration reaction, which is carried out above 875 K° [27]. The time of the cation exchange process can be reduced under microwave irradiation [28].

The Lewis sites can be increased when the metal/zeolite is prepared in the solid state phase ion-exchange under microwave irradiation [29, 30]. Interestingly, in some reactions, including intramolecular acylation [25], isomerization [31] and conversion of acids to benzimidazoles [32], the Lewis sites are the active centers.

In view of these reports, effort have been made to carry out the Biginelli reaction by different zeolite catalysts in

M. Zendehdel (✉) · A. Mobinikhaledi · A. Asgari
Chemistry Department, Arak University, Dr. Beheshti Ave, Arak, Iran
e-mail: mojganzendehdel@yahoo.com

order to find the role of zeolite in the mechanism of the reaction.

## Experimental

$^{1}$H-NMR and $^{13}$C-NMR were recorded on Bruker (300 MHz) spectrometer. TMS was used as an internal standard. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III). The IR spectra were recorded by Galaxy Series FT-IR 5000 spectrometer. All products were characterized by NMR and IR spectra, and elemental analysis.

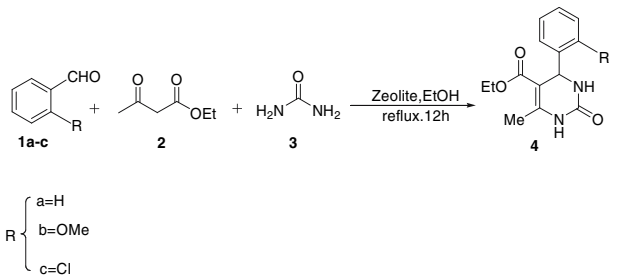
Zeolite NaY was prepared and activated according to the procedure described previously [33]. Two different routes were used for preparation of metal/Y zeolites.

Method A

About 200 mL of 0.01 M solution of metal salts ($VCl_3$, $CrCl3 \cdot 6H_2O$, $FeCl_3 \cdot 4H_2O$, $MnCl_2 \cdot 4H_2O$, $CoCl_2 \cdot H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$ and $ZnCl_2$) was added to 2.0 g of NaY zeolite in a 250-mL flask. The mixture was stirred for 24 h and then filtered. The obtained solid was washed with water until a colorless filtrate observed. The final zeolite products were dried at room temperature.

Method B

A mixture of 2.0 g of NaY zeolite and 2 mmol of each metal salts listed above was mechanically mixed, ground and heated in microwave oven for 10–20 min at 900 W powers. Recently study in our laboratory showed that metal salts are completely dispersed and ion exchanged onto zeolite [32].




**Scheme1**

General preparation of 3,4-Dihydropyrimidin-2(1H)-ones **4(a-c)**

To a solution of urea (0.02 mol) and ethyl acetoacetate (0.02 mol) in ethanol (10 mL), appropriate aldehyde (0.02 mol) and metal/Y zeolite (0.25 g) was added. The reaction mixture was refluxed for 12 h. The used catalyst was collected by filtration and then washed with ethanol. The crude product was recrystallized from ethanol.

## Results

3,4-Dihydropyrimidin-2(1H)-ones **4(a-c)** were prepared by reaction of appropriate aldehyde, ethyl acetoacetate and urea in the present of the zeolite as shown in Scheme 1.

Tables 1, 2 and 3 show the results of the Biginelli reaction with benzaldehyde, 2-methoxy benzaldehyde and 2-chloro benzaldehyde, respectively. The zeolite, which was used as catalyst in these reactions, was ion exchanged by microwave in the solid state and in the aqueous solution. The catalyst activated for 2 h and reactions were carried out to 3–4 times. In each case, yield was decreased about 5–6%. The results for concentration of cations in metal/

**Table 1** The yield (%) of Biginelli reaction for benzaldehyde, urea and ethyl acetoacetate

| | VY | CrY | FeY | MnY | CoY | NiY | CuY | ZnY | NaY | HY | NaA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aq[a] | 14.3 | 20.0 | 5.3 | 23.8 | 24.2 | 21.7 | 34.2 | 13.0 | 48.2 | 19.4 | 17.2 |
| MW[b] | 28.2 | 25.1 | 32.5 | 32.5 | 37.0 | 34.2 | 38.1 | 20.3 | – | – | – |

[a] Aqueous solution

[b] Solid state

**Table 2** The yield (%) of Biginelli reaction for 2-methoxy benzaldehyde, urea and ethyl acetoacetate

| | VY | CrY | FeY | MnY | CoY | NiY | CuY | ZnY | NaY | HY | NaA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aq[a] | 16.4 | 25.2 | 10.0 | 26.1 | 28.4 | 28.3 | 30.2 | 15.8 | 62.5 | 27.2 | 18.0 |
| MW[b] | 55.7 | 31.8 | 40.5 | 40.8 | 43.0 | 41.2 | 48.2 | 24.8 | – | – | – |

[a] Aqueous solution

[b] Solid state

**Table 3** The yield (%) of Biginelli reaction for 2-chloro benzaldehyde, urea and ethyl acetoacetate

| | VY | CrY | FeY | MnY | CoY | NiY | CuY | ZnY | NaY | HY | NaA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aq[a] | 13.5 | 15.7 | 5.4 | 17.4 | 19.0 | 18.0 | 22.4 | 8.0 | 36.1 | 19.3 | 15.3 |
| MW[b] | 23.3 | 22.0 | 26.0 | 25.0 | 29.1 | 26.8 | 32.1 | 11.3 | – | – | – |

[a] Aqueous solution

[b] Solid state

zeolite after reaction were also similar to those reported before [34].

Ethyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4a**)

Mp 205–207 °C. IR (KBr): $\nu$ = 3238, 3113, 2980, 1724, 1649, 1465, 1290 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): $\delta$ (ppm) = 1.09 (t, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$), 3.99 (q, 2H, $CH_2$), 5.13 (d, 1H, H-4), 7.21–7.34 (m, 5H, $H_{arom}$), 7.73 (s, 1H, NH), 9.19 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ (ppm) = 14.5, 18.2, 54.5, 59.7, 99.8, 126.7, 127.7, 128.8, 145.3, 148.8, 152.8, 165.8. Anal. cald. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%. Found: C, 64.25; H, 6.51; N, 10.62%.

Ethyl-6-methyl-4-(2-methoxyphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4b**)

Mp 258–259 °C. IR (KBr):$\nu$ = 3267, 3109, 2958, 1726, 1703, 1639, 1487, 1286 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): $\delta$ (ppm) = 1.04 (t, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 3.789 (s, 3H, $CH_3$), 3.93 (q, 2H, $CH_2$), 5.50 (d, 1H, H-4), 6.87–7.28 (m, 4H, $H_{arom}$, 1H, NH), 9.1 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ (ppm) = 14.5, 18.2, 49.3, 55.8, 59.4, 98.0, 111.6, 120.6, 127.5, 129.1, 132.1, 149.3, 152.7, 157.0, 165.8. Anal. cald. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65%. Found: C, 62.29; H, 6.45; N, 9.60%.

Ethyl-6-methyl-4-(2-chlorophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4c**)

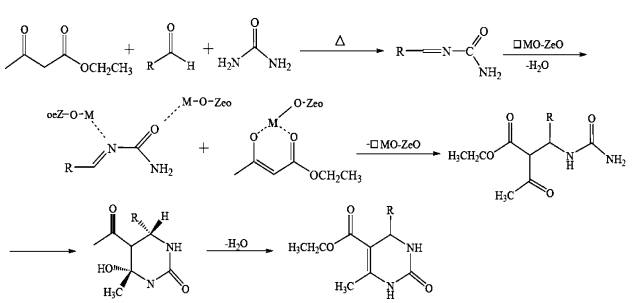
Mp 221–222 °C. IR (KBr): $\nu$ = 3354, 3236, 3111, 2978, 1693, 1641, 1226, 1095 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): $\delta$ (ppm) = 0.99 (t, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 3.90 (q, 2H, $CH_2$), 5.63 (d, 1H, H-4), 7.25–7.41 (m, 4H, $H_{arom}$), 7.71 (s, 1H, NH), 9.27 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ (ppm) = 14.4, 18.1, 51.9, 59.5, 98.3, 128.2, 129.2, 129.5, 129.8, 132.1, 142.2, 149.8, 151.8, 165.4. Anal. cald. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50%. Found: C, 57.10; H, 5.44; N, 9.54%.

## Discussion

With note to Tables 1, 2 and 3 we have seen the following catalytic activity for exchange zeolite in aqueous solution: CuY > CoY > NiY> MnY> CrY> VY> ZnY> FeY. Hence, the yield of the reaction with zeolite, which is ion exchanged under microwave irradiation increased in the order of CuY > CoY > NiY> MnY> FeY> VY> CrY > ZnY. The CuY zeolite shows the highest yield and activity for two sets of catalysts.

The yield of these reactions was high when solid ion-exchanged metal zeolite under microwave irradiation was used. Since these reactions catalyzed by an acid, the acidity is strongly linked with the type of cation and so will vary with the degree of cation exchange. On the other hand the water molecule bonded to the zeolite decreases at high temperature and consequently the number of Lewis acid sites increase. Therefore, the nature of the acid sites is related to the type of metal centers in addition to thermal pretreatment. The ion exchange in solid state under microwave irradiation increases the Lewis sites [35], which may be formed through the following mechanism: Scheme 2

Condensation of aldehyde, urea and ethyl acetoacetate forms an intermediate which is stabilized by framework M and all Lewis sites zeolite. The intermediate cylices with zeolite and forms product. It seems that created hydrogen bond between OMe group of 2-methoxy benzaldehyde and the framework zeolite is a factor, which causes the yield of reaction increased.



**Scheme2**

Further more, pervious work showed a synergy between the Bronsted and Lewis sites. The number of Bronsted sites is increased by adsorption of water molecules on Y zeolite [34]. Interestingly, in the present study, we found that by using hydrated zeolite ion-exchange under microwave condition, the yield of the reaction decreased by 10–11%. Hence, as the Bronsted sites in HY zeolite is increased, the yield is decreased. This shows that the establishing Lewis sites is better sites for this reaction.

The results indicated that CuY zeolite shows the highest activity for the Biginelli reaction using a set of catalysts in three reactions. It seems that small ions, such as $Cu^{2+}$, have high degrees of ion exchange and $CuCl_2$ has dispersed completely onto the NaY zeolite under microwave irradiation. Also some of these dispersed ions reacted with the oxygen ions of zeolite to form –O–M–Cl under microwave irradiation, which are as new Lewis acid sites [36].

## Conclusion

We consider the nature of cation and method of exchange on the catalytic activities of transition metal cation-exchange zeolite. The good correlation between the yields of Biginelli reaction in presence of transition metal/zeolite cation exchange in aqueous solution suggests that the active centers are mostly Lewis sites.

## References


1. A review on DHPMs: C.O. Kappe, 100 years of the Biginelli dihydropyrimidine synthesis. Tetrahedron, **49**, 6937–6963 (1993)
2. Weber, L.: Multi-component reactions and evolutionary chemistry. Drug. Discov. Today **7**, 143–147 (2002)
3. Domling, A.: Recent advances in isocyanide-based multicomponent chemistry. Curr. Opin. Chem. Biol. **6**, 306–313 (2002)
4. A review, Kappe, C.O. Kappe, Biologically active dihydripyrimidones of the Bignelli-type. A literature survey. Eur. J. Med. Chem., **35**, 1043 (2000)
5. Hurst, E.W., Hull, R.J.: Med. Pharm. Chem. **3**, 215 (1961)
6. Mayer, T.U., Kapoor, T.M., Haggarty, S.J., King, R.W., Schreiber, S.I., Mitchison, T.J.: Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science **286**, 971–974 (1999)
7. Kato, T.: Jpn. Kokay Tokkyo Koho, 1984, 974, 59190 (CA 102:132067)
8. Atwal, K.S., Swanson, B.N., Unger, S.E., Floyd, D.M., Moreland, S., Hedberg, A., O'Reilly B.C.: Dihydropyrimidine calcium channel blockers. 3. 3-carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidenecarboxylic acid esters as orally effective antihypertensive agents. J. Med. Chem. **34**, 806–811 (1991)
9. Rovinyak, G.C., Atwal, K.S., Hdberg, A., Kimbal, S.D., Moreland, S., Gougoutas, J.Z., O'Reilly, B.C., Schwarts, J., Malley, Malley, M.F.: Dihydropyrimidine calcium channel blockers. 4, basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. J. Med. Chem. **35**, 3254–3263 (1992)
10. Kappe, C.O.: Design and synthesis of a conformationally rigid mimic of the dihydropyrimidine calcium channel modulator SQ 32,926. Molecules **5**, 227–239 (2000)
11. Overman, L.E., Rabinowitz, M.H., Renhowe, P.A.: Enantioselective total synthesis of (−)-Ptilomycalin A. J. Am. Chem. Soc. **117**, 2657–2658 (1995)
12. Snider, B.B., Shi, Z.: Biomimetic syntheses of Crambines A, B, C1, and C2. Revision of the structures of Crambines B and C1. J. Org. Chem. **58**, 3828 (1993)
13. Gazz Biginelli, P.: Aldehyde-urea derivatives of aceto- and oxaloacetic acids. Chim. Itall. **23**, 360–413 (1893)
14. Lin, H.X., Zhao, Q.J., Xu, B., Wang, X.H.: A green synthesis of dihydropyrimidinones by Biginelli reaction over Nafion-H catalyst. Chin. Chem. Lett. **18**(5), 502–504 (2007)
15. Tajbakhsh, M., Mohajerani, B., Heravi, M.M., Ahmadi, A.N.: Natural HEU type zeolite catalyzed Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*) one derivatives. J. Mol. Catal. A: Chem. **236**(1–2), 216–219 (2005)
16. Radha Rani, V., Srinivas, N., Radha Kishan, M., Kulkarni, S.J., Raghavan, K.V.: Zeolite-catalyzed cyclocondensation reaction for the selective synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. Green Chem. **3**, 305–306 (2001)
17. Choudhary, V.R., Tillu, V.H., Narkhede, V.S., Borate, H.B., Wakharkar, R.D.: Microwave assisted solvent-free synthesis of dihydropyrimidinones by Biginelli reaction over Si-MCM- 41 supported $FeCl_3$ catalyst. Catal. Commun. **4**(9), 449–453 (2003)
18. Adrienn, H., Zoltán, H., Ilona, V.: Convenient one-pot heterogeneous catalytic method for the preparation of 3,4-Dihydropyrimidin-2(1*H*)-ones. Synth. Commun. **36**(1), 129–136 (2006)
19. Salehi, P., Dabiri, M., Zolfigol, M.A., Fard, M.A.B.: Efficient synthesis of 3,4-Dihydropyrimidin-2(1 H)-ones over silica sulfuric acid as a reusable catalyst under solvent-free conditions. Heterocycles **60**, 2435–2440 (2003)
20. Lin, H., Ding, J., Chen, X., Zhang, Z.: An efficient synthesis of 5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones catalyzed by KSF montmorillonite. Molecules **5**, 1240–1243 (2000)
21. Mobinikhaledi, A., Foroughifar, N., Karimi, G.: One-pot synthesis of tetrahydropyrimidines catalyzed by zeolite. Synth. React. Inorg. Metal-Org. Nano-Metal Chem. **37**, 279–282 (2007)
22. Thomas, J.M., catlow, C.R.A.: Prog. Inorg. Chem. **35**, 1 (1987)
23. Corma, A.: Inorganic solid acids and their use in acid-catalyzed hydrocarbon reactions. Chem. Rev. **95**, 559 (1995)
24. Kooti, M., Zendehdel, M., Mohammadpour Amini, M.: Interaction of pesticides with a $\beta$-Cyclodextrin derivative studied by reversed-phase thin-layer chromatography and principal component analysis. J. Incl. Phen. Macrocycl. Chem. **42**, 265–268 (2002)
25. Gauthier, C., Chiche, B., Finiels, A., Genste, P.: Influence of acidity in friedel-crafts acylation catalyzed by zeolites. J. Mol. Catal. **50**, 219–229 (1989)
26. Zendehdel, M., Fouroghfar, N., Gaykani, Z.: Diels-alder reaction with transition metal/zeolites. J. Incl. Phen. Macrocycl. Chem. **53**, 47–49 (2005)
27. Forster, H., Hatje, U.: Investigations on the solid-state ion exchange of $Ni^{2+}$, $Cu^{+}$ and $Zn^{2+}$ ions into zeolite Y using EXAFS techniques. Solid State Ionic **101**, 425–430 (1997)
28. Xiao, F.S., Wu, W., Qiu, S., Xu, R.: The microwave technique: a new route for high dispersion of inorganic salts onto supports. J. Mat. Sci. Lett. **14**, 598–599 (1993)
29. Zendehdel, M., Amini, M.M., Emami Khansairi, M.: Asian J. Chem. **19**, 3 (1988)
30. Zendehdel, M., Amini, M.M., Emami Khansairi, M.: Asian J. Chem. (2007)

31. Holderich, W., Hesse, M., Naumann, F.: Zeolites: catalysts for organic syntheses. Angew Chem. Int. Ed. Engl. **27**, 226–246 (2007)
32. Zendehdel, M., Mobinikhaledi, A., Hasanvand Jamshidi, F.: Conversion of acids to benzimidazoles with transition metal/zeolites. J. Incl. Phen. Macrocycl. Chem. **59**, 41–44 (2007)
33. Breck, D.W., Tonawanda, N.Y.: Assigned to union carbide, Pat. No.3130007, patented, April 21, 1964
34. Zendehdel, M., Kooti, M., Amini, M.M.: Dispersion and solid state ion exchange of $VCl_3$, $CrCl_3{\cdot}6H_2O$, $MnCl_2{\cdot}4H_2O$ and $CoCl_2{\cdot}6H_2O$ onto the surface of NaY zeolite using microwave irradiation. J Pores Mater. **12**, 143–149 (2005)
35. Lohose, U., Bertran, R., Jancke, K., Kurzawski, L., Parlitz, B., Lofler, E., Schreier, E: Acidity of aluminophosphate structures. Part 2.—Incorporation of cobalt into CHA and AFI by microwave synthesis. J.Chem.Soc. Faraday Trans. **91**, 1163–1172 (1995)
36. Liu, J., Yin, D., Yin, D., Fu, Z., Li, Q., Lu, G.: $ZnCl_2$ supported on NaY zeolite by solid-state interaction under microwave irradiation and used as heterogeneous catalysts for high regioselective Diels-Alder reaction of myrcene and acrolein. J. Mol Catal A, Chem. **209**, 171–177 (2004)