TITLE: Novel and Efficient Organocatalytic Biginelli Reaction Using 2-Ethylhexanoic Acid

AUTHORS: Rahim HEKMATSHOAR,Mojgan KARGAR,Zahra HASHEMI,Fereshteh GOLI,Abdoljalil MOSTASHARI

PAGES: 617-621

Gazi University Journal of Science
GU J Sci
25(3):617-621 (2012)

ORIGINAL ARTICLE

Novel and Efficient Organocatalytic Biginelli Reaction Using 2-Ethylhexanoic Acid

Rahim HEKMATSHOAR[1,♠], Mojgan KARGAR[1], Zahra HASHEMI[1], Fereshteh GOLI[1]
Abdoljalil MOSTASHARI [2]

[1]*School of Chemistry, College of Science, University of Alzahra, Tehran, IRAN*
[2]*Industrial Chemical R&D Organization, Tehran, IRAN*

Received: 15.10.2011 Revised: 04.05.2012 Accepted: 24.05.2012

ABSTRACT

A highly efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones in 2-ethylhexanoic acid as green, low cost and recoverable catalytic medium, illustrates good synthetic utility of this method.

Key Words: *2-ethylhexanoic acid, 3,4-dihydropyrimidin-2(1H)-ones/thiones, organocatalyst.*

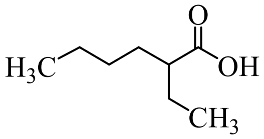
[♠] Corresponding author, e-mail: rhekmatus@yahoo.com

1. INTRODUCTION

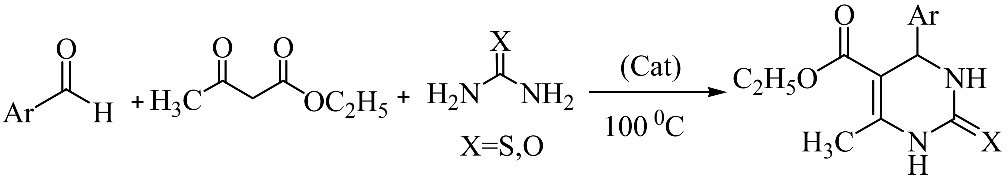
The multifunctionalized dihydropyrimidine scaffold represents a heterocyclic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial and anti-inflammatory activities, [1-3] has been ascribed to these partly reduced pyrimidine derivatives. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents.[4] A very recent highlight in this context has been the identification of the structurally rather simple DHPM Monastrol as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[5] Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated.[6]

The most simple and straight forward procedure for the synthesis of DHPMs was first reported by the Italian chemist Pietro Biginelli more than 100 years ago; it involves a three-component one-pot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions.[7] In recent years several methods for the synthesis of DHPMs have been developed to improve and modify this reaction by means of microwave irradiation,[8] ultrasound irradiation,[9] promoted by PPh_3,[10] Lewis acids such as Boric acid,[11] $KAl(SO_4)_2.12H_2O$ supported on silica gel,[12] $Sr(OTf)_2$,[13] Indium(III) halides,[14] $Bi(NO_3)_3$,[15] $Y(NO_3)_3\cdot 6H_2O$,[16] $In(OTf)_3$,[17] $TaBr_5$,[18] $Ce(NO_3)_3\cdot 6H_2O$,[19] silica chloride,[20] CaF_2,[21] 12-tungstophosphoric acid,[22] $Cu(OTf)_2$,[23] sulfonated β-cyclodextrine[24] and sulfated tungstate[25]. Some of the above protocols suffer from drawbacks such as the use of expensive and/or unrecoverable catalysts, strong acidic conditions and long reaction times. To avoid these limitations, the introduction of a milder and more efficient methods accompanied with higher yields are needed.

Very recently we have developed a simple and green organocatalytic Biginelli reaction that involves the use of imidazol-1-yl-acetic acid as a new organocatalyst. [25] In continuation of our interest in methodology for the organocatalytic Biginelli reaction, herein we describe a simple organocatalytic Biginelli reaction that involves the use of 2-ethylhexanoic acid (Fig 1) as a new organocatalytic medium. The reactions afforded various 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (Scheme 1), with good-to-excellent yields (86-93%).



< Fig 1 >



Scheme 1

2. EXPERIMENTAL

The physical data of all known compounds were compared with those of authentic samples and found to be identical. Structure and identity of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones were confirmed by spectroscopic methods such as IR and ^{1}HNMR. The spectral and analytical data for the selected compounds are presented.

2.1. Chemicals and Apparatus

All the chemicals were purchased from Merck Company. Melting points were measured using Barnstead Electro thermal. IR spectra were recorded as KBr disc on the FT-IR Brucker Tensor 27 spectrometer. ^{1}HNMR spectra were recorded on a Bruker DRX-500 AVANCE Spectrometer.

2.2. General Procedure for Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones

A solution of ethyl acetoacetate (10 mmol), aldehyde (10 mmol) and urea or thiourea (15 mmol) in 10 mL 2-ethylhexanoic acid was heated at 100 °C. The progress of the reaction was monitored by TLC (hexane/ethyl acetate 8:2). After completion of the reaction, the reaction mixture was cooled to room temperature, water (10 ml) and petroleum ether (10 ml) were added and the precipitated products were filtered. The precipitate was washed with 5 ml of petroleum ether. The products were recrystallized from 70% aqueous ethanol. The filtrates formed two layers, from which the organic layer was separated and evaporated to recover 2-ethylhaxanoic acid almost quantitatively.

2.3. Spectral Data for Selected Compounds

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Entry1):

mp 206-208 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.20 (s, 1H, NH), 7.75 (s, 1H, NH), 7.28 (m, 5H, arom CH), 5.14 (s, 1H, CH), 3.97 (q, *J* 7.1 Hz, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, *J* 7.1 Hz, 3H, CH_3); IR (KBr): 3242, 1721, 1637 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.25; N, 10.92.

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

mp 203 °C; ^{1}HNMR (500 MHz, DMSO-d_6): δ = 9.17 (s, 1H, NH), 7.68 (s, 1H, NH), 7.15 (d, *J* 8.6 Hz, 2H; arom CH), 6.88 (d, *J* 8.5 Hz, 2H; arom CH), 5.09 (s,1H, CH), 3.98 (q, *J* 7.0 Hz, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3), 1.10 (t, *J* 7.0 Hz, 3H, CH_3); IR (KBr): 3241,1700, 1637 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.20; N, 9.66. Found: C, 61.65; H, 6.21; N 9.58.

3. RESULT AND DISCUSSION

Due to the mild conditions and operational simplicity, organocatalysis has received great attention in industry.

The interest in this field has increased spectacularly in the last few years as result of both the novelty of the concept and more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic transformations.[25]

Our interest in the use of 2-ethylhexanoic acid, is in line with our focus on the application of available carboxylic acids as novel, benign and recyclable organocatalysts for Beginelli and similar multi-component reactions.

Our attempt has been focused on applying novel green organocatalyst for practical Biginelli reaction and we were interested in using 2-ethylhexanoic acid. Extensive literature survey indicates that 2-ethylhexanoic acid has never been reported as a catalyst for "Biginelli Reaction" or any other organic transformation and the present work is the first report that introduces it as a catalyst. This catalyst is eco-friendly and easily accessible. Facile recoverability in pure state and good yield makes it infinitely reusable.

In order to evaluate the catalytic efficiency of 2-ethylhexanoic acid; the condensation reactions of benzaldehyde, ethyl acetoacetate and urea (thiourea) with mole ratios of 1:1:1.5 were chosen as model systems. In these experiments, different amounts of 2-ethylhexanoic acid, namely 4, 6 and 10 mL relative to the 10 mmol of benzaldehyde at 100° C were used. Isolated yields of 75, 84 and 92%, respectively, could be achieved after the reaction had only proceeded for 1h. This indicates that the conversion was increased with increasing amounts of 2-ethylhexanoic acid. With 10 mL of 2-ethylhexanoic acid as catalytic media, reactivity of different aromatic aldehydes with either electron-donating or electron-withdrawing substituents (Entries 3, 4 and 7 in Table 1) were also examined. It can be seen that all reacted very well, although yields achieved from the aromatic aldehydes with electron-withdrawing substituents were slightly higher than aromatic aldehydes with electron-donating substituents. The results of 2-ethylhexanoic acid catalyzed Biginelli reactions are shown in Table 1.

Table 1. 2-Ethylhexanoic acid catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding 2(1*H*)thiones.

Entry	Ar	X	Time (h)	Yield(%)^a	Mp ^{0}C Found^b	Mp ^{0}C Lit. [ref]
1	C_6H_5	O	1	92	200-203	201-204[]
2	4-Cl- C_6H_4	O	1.5	91	213-215	214-217[]
3	4-OCH_3-C_6H_4	O	2.5	90	201-203	203[22]
4	3-NO_2- C_6H_4	O	1	93	228-230	230[22]
5	4-CH_3-C_6H_4	O	2	88	212-214	214[22]
6	4-Br- C_6H_4	O	2	86	211-213	215[22]
7	2-OH- C_6H_4	O	3	89	200-202	200-202[23]
8	4-$N(CH_3)_2$- C_6H_4	O	2.5	87	230-232	230-232[23]
9	2-Furyl	O	1.5	90	208-210	208-210[25]
10	C_6H_5	S	1.5	91	204-206	206[22]
11	4-OCH_3-C_6H_4	S	2.5	89	153	153[22]
12	3-NO_2-C_6H_4	S	1	90	203-205	205[25]

We have also examined the recoveribility and reusability of the catalytic medium. The performance of the recovered catalyst was found to be as good as the same amount of fresh catalyst

In order to show the merit of the present work, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 1 in Table1) with some previously reported catalysts. The yield of product in the presence of 2-ethylhexanoic acid is comparable to reported catalysts. However, reaction in the presence of these catalysts required longer reaction times than this work (Table 2).

Table 2 Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3, 4-dihydropyrimidin-2(1H)-one using different catalysts.

Entry	Catalyst	Reaction time	Yield% [ref]
1	$Bi(NO_3)_3$	6h	80 [15]
2	PPh_3(10%)	10h	70 [10]
3	$InBr_3$(10%)	10h	79[14]
4	H_3PMoO_{40} (2%)	5h	75 [22]
5	Montmorilonite KSF	48h	82[27]
6	Zeolite	12h	80[28]
7	Yb(III)-resin	48h	80[29]
8	2-ethylhexanoic acid	1h	92(This work)

4. CONCLUSION

2-Ethylhexanoic acid as a catalytic medium has some advantages including low toxicity, low cost and commercial availability. In addition, it possesses a number of other interesting properties, especially low vapor pressure and a widely accessible temperature range with low flammability and ease of recycling that facilitates recovery and may reduce environmental emissions. Reusability of 2-ethylhexanoic acid, ease of separation of pure products, selectivity and high yields in comparison to the classical Biginelli reaction are some of the unique features of this process.

ACKNOWLEDGMENT

We gratefully acknowledge the partial financial support from Alzahra University Research Council.

REFERENCES

1. Kappe, C.O., “Recent advances in the Biginelli dihydropyrimidine synthesis: new tricks from an old dog”, ***Acc. Chem. Res***., 33: 879-888 (2000).

2. Kappe, C.O., “100 years of the Biginelli dihydropyrimidine synthesis”, ***Tetrahedron***., 49: 6937-6963 (1993).

3. Kappe, C.O., Fabian, W.M.F., Semones, M.A., “Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators A comparison of ab initio, semi-empirical and X-ray crystallographic studies”, ***Tetrahedron***., 53: 2803-2816 (1997).

4. 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-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents”, ***J. Med. Chem***., 34: 806-811 (1991).

5. Kappe, C.O., Shishkin, O.V., Uraya, G., Verdinoa, P., “X-Ray Structure, conformational analysis, enantioseparation, and determination of absolute configuration of the mitotic kinesin Eg_5 inhibitor monastrol”, ***Tetrahedron***., 56: 1859-1862 (2000).

6. Heys, L., Moore, C.G., Murphy, P.J., “The guanidine metabolites of Ptilocaulis spiculifer and related compounds; isolation and synthesis”, ***Chem. Soc. Rev***., 29: 57-67 (2000).

7. Biginelli, P., “Derivati aldeiduredici degli eteri acetil-e dossal-acetico”, ***Gazz .Chim. Ital***., 23: 360-416 (1893).

8. Banik, B.K., Reddy, A.T., Datta, A., Mukhopadhyay, C., “Microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones via Biginelli condensation under solventless conditions”, ***Tetrahedron Lett***., 48: 7392-7394 (2007).

9. Li, J.T., Han, J.F., Yang, J.H., Li, T.S., “An efficient synthesis of 3,4-dihydr- opyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation”, ***Ultrason .Sonochem***., 10: 119-122 (2003).

10. Debache, A., Amimour, M., Belfaitah, A., Rhouati, S., Carboni, B., “A one-pot Biginelli synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones/thiones catalyzed

by triphenylphosphine as Lewis base”, ***Tetrahedron Lett***., 49: 6119-6121 (2008).

11. Tu, Sh., Fang, F., Miao, Ch., Jiang, H., Feng, Y., Shi, D., Wang, X., “One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using Boric acid as catalyst”, ***Tetrahedron Lett***., 44: 6153-6155 (2003).

12. Azizian, J., Mohammadi, A.A., Karimi, A.R., Mohammadizadeh, M.R., “$KAl(SO_4)_2.12H_2O$ supported on silica gel as a novel heterogeneous system catalyzed biginelli reaction One-pot synthesis of di-hydropyrimidinones under solvent-free conditions”, ***Appl. Catal. A. Gen***., 300: 85-88 (2006).
13. Su, W., Li, J., Zheng, Zh., Shen, Y., “One-pot synthesis of dihydropyrimi- diones catalyzed by strontium(II) triflate under solvent-free conditions”, ***Tetrahedron Lett***., 46: 6037-6040 (2005).

14. Fu, N.Y., Yuan, Y.F., Pang, M.L., Wang, J.T., Peppe, C., “Indium (III) halides-catalyzed preparation of ferrocenedihydropyrimidinones”, ***J. Organomet. Chem.,*** 672: 52-57 (2003).

15. Ming, L., Si, G. W., Rong, W.L., Feng, L.Y., Zheng, Y.H., “One-pot synthesis of Biginelli and Hantzsch products catalyzed by non-toxic ionic liquid (BMImSac) and structural determination of two products”, ***J. Mol. Catal. A: Chem***., 258: 133-138 (2006).

16. Nandurkar, N.S., Bhanushali, M.J., Bhor, M.D., Bhanage, B.M., “$Y\ (NO_3)_3.6H_2O$: A novel and reusable catalyst for one pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions”, ***J .Mol. Catal .A. Chem***., 271: 14-17 (2007).

17. Ghosh, R., Maiti, S., Chakraborty, A., “$In(OTf)_3$-catalysed one-pot synthesis of 3,4-dihydropyrimidin-2(l*H*)-ones”, ***J. Mol. Catal. A. Chem***., 217: 47-50 (2004).

18. Ahmed, N., Lier, J.E.V., “$TaBr_5$-catalyzed Biginelli reaction: one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones under solvent-free conditions ”, ***Tetrahedron. Lett***., 48: 5407-5409 (2007).

19. Adib, M., Ghanbary, K., Mostofi, M., Ganjali, M.R., “Efficient $Ce(NO_3)_3{\cdot}6H_2O$-catalyzed solvent-free synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones”, ***Molecules***., 11: 649-654 (2006).

20. Karade, H.N., Sathe, M., Kaushik, M.P., “Synthesis of 4-aryl substituted 3, 4-dihydropyrimidinones using silica-chloride under solvent free conditions”, ***Molecules***., 12: 1341-1351 (2007).

21. Pandiarajan, C.K., “Calcium fluoride: an efficient and reusable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding 2(1*H*)thione: an improved high yielding protocol for the Biginelli reaction”, ***Tetrahedron. Lett***., 50: 2222-2224 (2009).

22. Heravi, M.M., Derikvand, F., Bamoharram, F., “A catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2(1*H*)-one using 12-tungstophosphoric acid”, ***J. Mol. Catal. A. Chem***., 242: 173-175 (2005).

23. Paraskar, A.S., Dewkar, G.K., Sudalai, A., “$Cu(OTf)_2$: a reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones”, ***Tetrahedron. Lett***., 44: 3305-3308 (2003).

24. Asghari, S., Tajbakhsh, M., Kenari, B.J., Khaksar, S., “Supramolecular synthesis of 3,4-dihydropyrimidine-2(1*H*)-one/thiones under neat conditions”, ***Chin. Chem. Lett.,*** 22: 127-130 (2011).
25. Salim, S.D., Akamanchi, K.G., “Sulfated tungstate: An alternative, eco-friendly catalyst for Biginelli reaction”, ***Catal. Commun***. 12: 1153-1156 (2011).

26. Kargar, M., Hekmatshoar, R., Mostashari, A.J., Hashemi, Z., “Efficient and green synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones using imidazol-1-yl-acetic acid as a novel, reusable and water-soluble organocatalyst”, ***Catal. Commun***., 15: 123–126 (2011).

27. Bigi, F., Carloni, S., Frullanti, B., Maggi, R., Sartori, G., “A revision of the Biginelli reaction under solid acid catalysis. Solvent-free synthesis of dihydropyrimidines over montmorillonite KSF”, ***Tetrahedron Lett***., 40: 3465-3468 (1999).

28. Rani, V.R., Srinivas, N., Kishan, M.R., Kulkarni, S.J., Raghavan, K.V., “Zeolite-catalyzed cyclocondensation reaction for the selective synthesis of 3,4-dihydropyrimidin-2(1H)-ones”, ***Green. Chem***., 3: 305-306 (2001).

29. Dondoni, A., Massi, A., “Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent-free conditions. A green chemistry approach to the Biginelli reaction”, ***Tetrahedron Lett***., 42: 7975–7978 (2001).