Journal of Materials Science and Engineering A 1 (2011) 219-223
Formerly part of Journal of Materials Science and Engineering, ISSN 1934-8959

Simple, One Pot Synthesis of 3,4-Dihydropyrimidin-2-ones under Microwave Irradiation Using EPIC Catalyst

Makone Sangita Sanjay, Bunnawar Laxman Yeshwantrao and Niwadange Sandeep Nivruttirao

Chemistry Research Lab., School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded 431606, Maharashtra, India

Received: January 23, 2011 / Accepted: March 05, 2011 / Published: July 10, 2011.

Abstract: A general and practical route for the synthesis of 3, 4-dihydropyrimidinones by one pot cyclocondensation of aldehydes and β-ketoesters and urea is described using EPIC as catalyst in eco-friendly solvent, water under microwave irradiation. Use of alternate energy source such as microwave accelerates the rate of formation of the Biginelli product. Excellent yields, wide applicability, short reaction time and environmentally benign reaction conditions are important features of this method. The present method provides a novel and improved protocol for synthesis of 3, 4-dihydropyrimidinones.

Key words: 3,4-Dihydropyrimidinones, EPIC, microwave irradiation, aqueous media.

1. Introduction

In the past decayed dihydropyrimidines has been the focus of considerable due to their biological activities and pharmacological profile [1-2]. A wide range of biological effect in the areas of antimicrobial, antiviral, anti-tumor, anti-inflammatory and cardiovascular activities has been established for Biginelli compounds. For example, several functionalized derivatives are used as calcium channel modulators, antihypertensive agents and α̃antagonist [3-6]. A number of marine alkaloids with broad spectrum of biological activities contain dihydropyrimidines as a part of their structures [7-9]. The most simple and straightforward procedure, first reported by Biginelli, involves the one-pot cyclocondensation of β- ketoester with an aldehyde, and urea under strongly acidic conditions [10].

Within the past few years several groups developed new methods using Lewis acids BF$_3$-OEt$_2$, FeCl$_2$, LaCl$_3$, La(OTf)$_3$, Yb(OTf)$_3$, InX$_3$, ZrCl$_4$,BiCl$_3$ Mn(Oac)$_3$, LiClO$_4$ or a combination of Lewis acids with transition metal salts, clays, etc. have been reported [11]. More recently one-pot synthesis of Biginelli compounds have been reported and claimed to effective yield of process [12-14]. Shalehi et al. had introduced silica-sulfuric acid as an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidinones [15], Hu [16] and Kappe [17] reported the use of BF$_3$·OEt$_2$/CuCl and PPE (polyphosphate ester) mediated variations of the Biginelli reaction giving high yields of dihydropyrimidines, but the reaction requires long reaction time. In addition, there are some other methods such as using dodecyl sulfonic acid [18], solid-phase synthesis [19-20] and microwave-assisted [21] synthesis of Biginelli compounds. However, despite the potential utility of these catalysts, many of these methodologies for the synthesis of dihydropyrimidinones associated with several shortcomings such as long reaction time, high temperature, low yields, occurrence of several side

---

Corresponding authors: Makone Sangita Sanjay, associated professor, research fields: green chemistry, physical chemistry. E-mail: ss_makone@rediffmail.com.

products, high sensitivity to ambient air and moisture, use of organic solvents and toxic and hazardous transition metals. Recently *N*, *N'*-dichlorobis (2, 4, 6-trichlorophenyl) urea (CC-2) also reported as a new reagent for Biginelli reaction in place of urea [22].

Now a days Development of non-hazardous synthetic methodologies for organic reactions are one of the latest challenge to the organic chemists. Recently, organic reactions conducted in aqueous media have received much attention [23-26], because water is non-toxic, cheap, abundantly available and being to the environment. Because of our interest in envirocats, new solid-supported catalysts which is a part of our continual efforts to develop green strategies, herein we wish to report the use of envirocat EPIC [27], along with microwave irradiation in an aqueous media. This protocol offers a simple, green, economic and environmentally benign route for the three component condensation synthesis of dihydropyrimidinones using EPIC catalyst in an aqueous media under microwave irradiation.

2. Experiment

A mixture of benzaldehyde (5 mmol), ethyl acetoacetate or methyl acetoacetate (5 mmol), urea (11mmol) and EPIC (300 mg) in 5 ml water was taken in beaker and heated in a microwave oven at power 50% for appropriate time (Table 1). After completion (monitored by TLC), the reaction mixture was poured in to hot ethanol and catalyst is recovered by filtration and the solvent was removed under vacuum to collect the crude product. Further, the product is washed with water (2 × 5ml) and filtered, and then residue is recrystallized in ethanol which gives pure product.

3. Results and Discussion

The reaction of benzaldehyde (entry a) gives high yield (85%) and needs shorter reaction time. Even for aliphatic aldehydes (entry g, h) the present method gives good yields as compared to the reported method which gave poor yields in standard Biginelli reaction. Aromatic aldehydes carrying electron withdrawing substitutions also afforded excellent yields of products (entry c,e,f,j). The method is also effective for aldehyde such as furfural aldehyde which generally create problem in highly acidic condition.

The advantage of use of EPIC for this reaction lies in the fact that various functional groups like, nitro, methoxy, remained intact under the given reaction conditions.

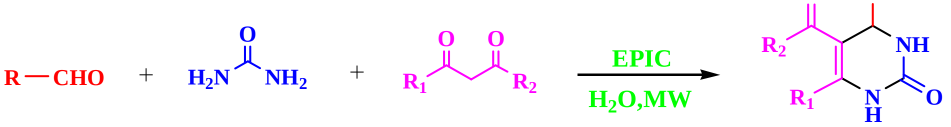
Compounds were characterized by ^{1}H NMR and IR spectral analysis and physical constant with reported literature.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate

M.P. 201 °C, KBr: v = 3240, 3120,2950,2925,1720,1702,1641,1589 cm^{-1}, ^{1}HNMR (DMSO) δ=1.17 (t, 3H, J=6.7 Hz) 4.05 (q, 2H, J=6.61 Hz), 5.20 (s, 1H), 7.15-7.35(m, 6H), 8.95 (br., s, NH), m/z = 260 (M$^+$), 232, 182, 155, 137, 43.

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate

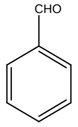
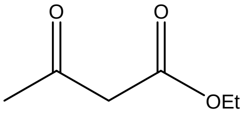
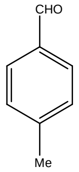
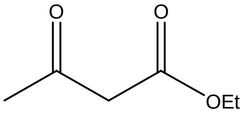
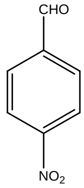
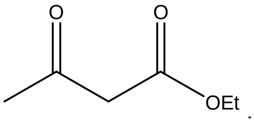
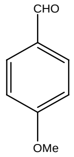
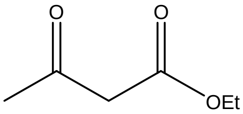
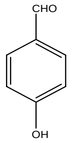
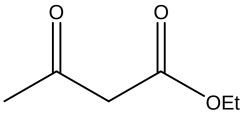
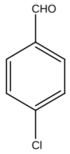
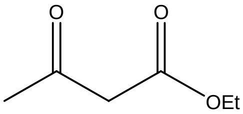
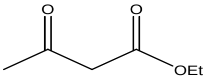
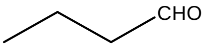
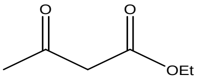
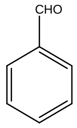
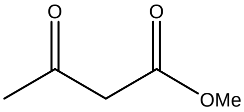
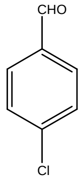
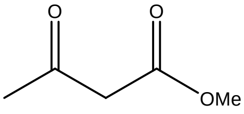
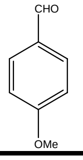
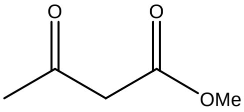
M.P. 204 °C, KBr:v = 3235, 3109, 2970, 1701, 1645, 1558 cm^{-1}, ^{1}HNMR (DMSO) δ = 1.20 (t,3H, J=6.9 Hz), 2.28 (s, 3H), 4.05 (q, 2H J = 7 Hz), 5.39 (d. 1H,J = 2.4 Hz), 7.50 (d, 2H, J = 8.7Hz),7.35 (br. s, NH), 8.20 (d, 2H, J = 8.7 Hz), 9.30(br., s, NH) m/z = 306 (M$^+$), 276,232,183,151,138.



Where, R= alkyl, phenyl
R_1= Me
R_2= OEt, OMe

Scheme. 1.

Table 1 Synthesis of dihydropyrimidinones.

Entry	Aldehydes	β-Dicarbonyls	Time/min	Yield(%)[a]	mp(°C)[b]
a			5	85	201
b			6	80	197
c			5.5	81	204
d			6	80	191
e			6.5	82	226
f			6	82	213
g			6	80	154
h			5	81	152
i			6	84	234
j			5	82	191
k			4.5	81	193

[a] Yields are of pure isolated products; [b] Products are characterized by their physical constants (mp with their authentic compounds reported in literature.) and by spectral analysis.

Ethyl 1,2,3,4-tetrahydro-6-methyl -2-oxo-4-*p*-tolylpyrimidine-5-carboxylate

M.P. 197 °C, KBr:v = 3240, 3110, 1691,1664,1560 cm^{-1}, ^{1}HNMR (DMSO) δ = 2.23 (s, 3H) 2.28 (s.3H), 4.10 (q, 2H, J = 6.9 Hz), 5.40 (d, 1H, J = 2.2 Hz), 6.95 (m, 4H), 7.61(br. s, NH), 9.10 (br. s, NH), m/z = 274(M^{+}), 244, 228, 201, 155, 137, 91.

4. Conclusions

In summary, the present procedure demonstrates the synthesis of dihydropyrimidinones in excellent yield with no side reaction. The use of green catalyst, high yield, general applicability to a variety of aldehydes makes this method an attractive to the existing methods.

Acknowledgment

The authors thank DST (Department of Science and Technology, New Delhi, India) for providing financial support for this research work.

References

[1] P. Biginelli, Gazz, Chim. Ital. 23 (1893) 360.

[2] C.O.Kappe, 100 years of the Biginelli dihydropyridines Synthesis, Tetrahedron 49 (32) (1993) 6937-6963.

[3] K.S. Atwal, G.C. Rovnyak, B. C.O'Reilly, J. Schwartzm Synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidines, J. Org. Chem. 54 (25) (1989) 5898-5907.

[4] K.S. Atwal, B.N. Swamson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg, et al., 3.3-carbamoyl-4-aryl-1,2,3,4-tetrahyrdo-6-methyl-5-pyrimidine carboxylic acid esters as orally effective antihypertensive agents, J. Med. Chem. 34 (2) (1991) 806-811.

[5] G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, et al., Basic 3-substituted-4-aryl-1,4-dihyrdopyrimidine-5-carboxylic acid esters. Potent antihypertensive agents, J. Med. Chem. 35 (17) (1992) 3254-3263.

[6] C.O. Kappe, W.M.F. Fabian, Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators: a comparison of abinitio, semi-empirical and X-ray crystallographic studies, Tetrahedron Letters 53 (8) (1997) 2803-2816.

[7] A.L.E. Overman, M.H. Rabinowitz, P.A. Renhowe, Enantioselective Total Synthesis of (-)-Ptilomycalin, J. Am. Chem. Soc. 117 (9) (1995) 2657-2658.

[8] L. Heys, C.G. Moore, P.J. Murphy, The guanidine metabolites of Ptilocaulis spiculifer and related compounds: isolation and synthesis, Chem. Soc. Rev. 29 (1) (2000) 57-67.

[9] Z.D. Arou, L.E. Overman, The tethered Biginelli condensation in natural product synthesis, Chem. Commun. (2004) 253-265.

[10] K. Folkar, H.J. Harwood, T.B. Johnson, CXXX synthesis of 2-Keto-1,2,3,4-tetrahydropyridines, J. Am. Chem. Soc. 54 (9) (1932) 3751-3758.

[11] A.S. Parakar, G.K. Dewkar, A. Sudalai $Cu(OTf)_2$: a reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, Tetrahedron Letters 44 (16) (2003) 3305-3308.

[12] P.P. Baruah, S. Gadhwal, D. Prajapati, J.S. Sandhu, The biginelli condensation: a novel and efficient regioselective synthesis of dihydropyrimidin-2(1*H*)-ones using lithium bromide, Chem. Lett. 31 (10) (2002) 1038-1039.

[13] G. Sabitha., G.S.K.K. Reddy, J.S. Yadav, Vanadium(III) chloride catalyzed Biginelli condensation: solution phase library generation of dihydropyrimidin-(2H)-ones, Tetrahedron Letters 44 (34) (2003) 6497-6499.

[14] I. Saxena, C. Dilip, J.S. Sarma, Three component condensations catalyzed by iodine-alumina for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation and solvent-free conditions, Tetrahedron Letters 46 (7) (2005) 1159-1160.

[15] P. Salehi, M. Dabir, M.A. Zolfigel, M.A.B.F. Silica, sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, Tetrahedron Letters 44 (14) (2003) 2889-2891.

[16] E.H. Hu, D.R. Sidler, U.H. Dolling, Unprecedented catalytic three component one-pot condensation reaction: an efficient synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones, J. Org. Chem. 63 (10) (1998) 3454-3457.

[17] C.O. Kappe, S.F.F. Synlett, Polyphosphate ester-mediated synthesis of dihydropyrimidines, Improved Conditions for the Biginelli Reaction 7 (1998) 718-720.

[18] S. D. Sharma, P. Gogoi, D. Konwar, A highly efficient and green method for the synthesis of 3,4-dihydropyrimidin-2-ones and 1,5-benzodiazepines catalyzed by dodecyl sulfonic acid in water, Green Chem. 9 (2007) 153-157.

[19] A. Studer, S. Hadida, R. Ferritto, S.Y. Kim, P. Jeger, P. Wipf, et al., Curran fluorous synthesis: a fluorous-phase strategy for improving separation efficiency in organic synthesis, Science 275 (1997) 823-826.

[20] A. Studer, P. Jeger, D.P. Curran, fluorous synthesis: fluorous protocols for the ugi and biginelli multicomponent condensations, J. Org. Chem. 62 (9)

(1997) 2917-2924.

[21] K.K. Pasunooti, H. Chai, Ch.N. Jensen, B.K. Gorityala, S. Wang, X.W. Liu, A microwave-assisted, copper-catalyzed three-component synthesis of dihydropyrimidinones under mild conditions, Tetrahedron Letters 52 (2011) 80-84.

[22] G.B.D. Rao, B.N. Acharya, S.K. Verma, M.P. Kaushik, *N*,*N′*-Dichlorobis(2,4,6-trichlorophenyl)urea (CC-2) as a new reagent for the synthesis of pyrimidone and pyrimidine derivatives via Biginelli reaction, Tetrahedron Letters 52 (2011) 809-812.

[23] C.J. Li, T.H. Chan, Organic Reactions in Aqueous Media, John Wiley & Sons, New York, 1997.

[24] P.A. Grieco (Ed.), Organic Synthesis in Water, Blackie Academic and Professional, London, 1998.

[25] U.M. Lindstrom, Sterioselective organic reaction in water, Chem. Rev. 102 (2002) 2751-2772.

[26] S. Kobayashi, K. Manabe, Development of novel lewis acid catalyst for selective organic reactions in aqueous media, Acc. Chem. Rev. 35 (2002) 209-217.

[27] Contract Chemical, UK Product information, 1994.