Asian Journal of Chemistry Vol. 17, No. 3 (2005), 1858–1862

A Suitable Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones by Microwave Irradiation

M.A. PA SHA* and V.P. JAYA SHANKARA
Department of Studies in Chemistry,
Central College Campus, Bangalore University, Bangalore-560 001, India

Zinc acetate dihydrate ($Zn(OAc)_2 \cdot 2H_2O$) efficiently catalyzes the three-component coupling of β-keto ester, substituted aryl adehyde and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones respectively, the new protocol for the Biginelli reaction under microwave irradiation works in the absence of solvent. The yields are high and the reaction goes to completion within 40–60 sec.

Key Words: Microwave irradiation, 3,4-Dihydropyrimidin-2(1H)ones, β-Keto ester, Aryl benzaldehyde, Urea, Thiourea.

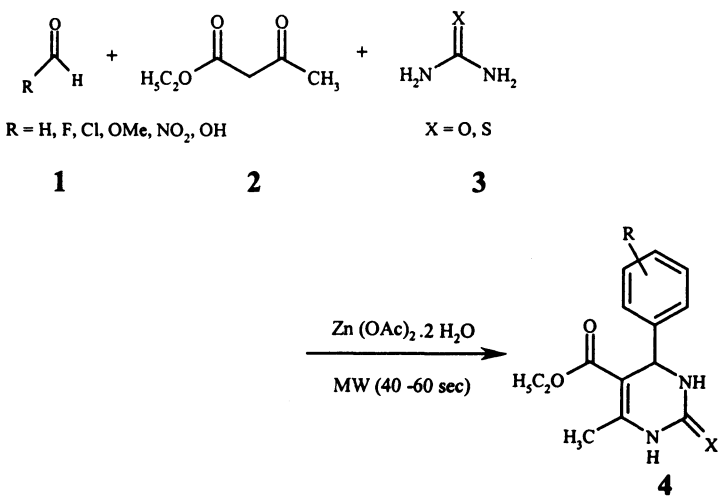
INTRODUCTION

Recently, the interest in synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and related compounds exhibits a wide range of biological activities such as antiviral, antitumour, antibacterial and antiinflammatory properties[1a]. These compounds have also emerged as the integral backbones of several calcium channel blockers, antihypertensive agents, α_{1a}-adrenergic antagonists and neuropeptide antagonists[2]. Several alkaloids containing the 3,4-dihydropyrimidin-2(1*H*)-one unit which have been isolated from marine sources are found to be potent HIV gp-120-CD4 inhibitors[2]. The synthesis of this heterocyclic nucleus is thus important, and the most simple and straightforward procedure reported by Biginelli[1b] involves one-pot condensation of β-keto ester, benzaldehyde and urea under strongly acidic conditions.

Numerous synthetic methods for preparing these compounds have been reported by using Lewis acids, protic acids as well as promoters and ionic liquids; some of them include ceric ammonium nitrate (CAN) under the influence of ultrasound[3], montmorillonite KSF[4], $InCl_3$[5], $InBr_3$, $LnCl_3$[7], $Yb(OTf)_3$[8], $Cu(OTf)_3$[9], H_2SO_4[10], zirconium(IV) chloride[11], ytterbium(III) resin[12], 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$) in ionic liquids[13], $Mn(OAc)_3 \cdot 2H_2O$[14], phosphotungstic acid/EtOH[15a], polyphosphate ester (PPE)[15b], polyaniline-bismoclite complex[15c], BF_3-OEt_2/CuCl/HOAc[16], silica/H_2SO_4[17], $NiCl_2/FeCl_3$[18], NH_4Cl[19], LiBr[20], $KHSO_4$/glycol[21], $CdCl_2$[22], $ZnCl_2$[23a], $FeCl_3$/HCl[23b], $SnCl_2 \cdot 2H_2O$[24a] and I_2/CH_3CN[24b]. Many of the existing methods involve expensive reagents, stoichiometric amount of catalyst, strongly acidic conditions, longer reaction times, higher

temperatures, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation and environmental pollution. Therefore, there is a need for versatile, simple and environmentally friendly processes for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

Currently, microwave irradiation has become a very useful tool in organic synthesis. Microwave technology in organic chemistry has been explored extensively within the last decade. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, easier work up matching with green chemistry protocols. There are a few reports on the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation; these methods involve use of $CuCl_2 \cdot 2H_2O/CuSO_4 \cdot 5H_2O$ (60–120 s)[25a], polyphosphate ester (PPE, 60–90 s)[25b], Amberlyst-15/Nafion-H/HOAc (120–130 s)[25c]. In this report a method of synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones **4**, under microwave irradiation using catalytic amounts of $Zn(OAc)_2 \cdot 2H_2O$ for a three-component coupling of substituted aldehyde **1**, β-keto ester **2** and urea or thiourea **3** have been described. The new protocol under microwave irradiation works in the absence of solvent. The yields are high and the reaction goes to completion within 40–60 s **(Scheme-1).**



Scheme-1.

EXPERIMENTAL

All the chemicals were purchased from BDH/Merck and used as received. Reactions were monitored on TLC by comparison with the authentic samples. For the microwave irradiation experiments a conventional (unmodified) household microwave oven was used (LG, Electronics, India). The IR spectra of the products were recorded on Nicolet 400D FTIR spectrophotometer. Melting points are determined on a Buchi melting point apparatus.

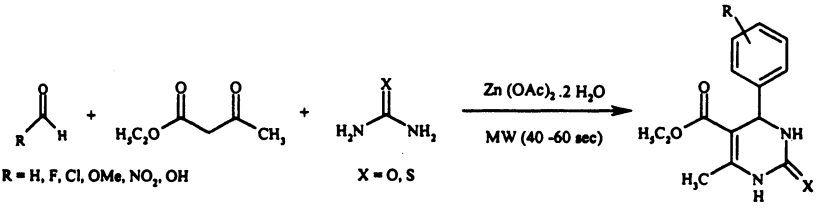
General procedure for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones: A mixture of benzaldehyde (**1a**, 1.06 g, 10 mmol), ethyl acetoacetate (**2**, 1.30 g, 10 mmol), urea (**3**, 0.6 g, 10 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (1.10 g, 5 mmol) was

taken in a Pyrex cylindrical tube, heated in a microwave oven (320 W). At the end of irradiation or after completion [(40–60 s, monitored by TLC (5% ethyl acetate : pet ether)] the contents were cooled to room temperature and ice-cold water was added, the residue was filtered through a sintered funnel to get the crude product. The crude product was further purified by recrystallization (EtOH or *i*-PrOH) to afford pure 3,4-dihydropyrimidin-2(1*H*)-one **(4a).**

RESULTS AND DISCUSSION

In a typical experiment, a mixture of β-keto ester, an aryl aldehyde, urea and catalytic amount of non-hazardous zinc acetate dihydrate was subjected to microwave irradiation for 40–60 s under solvent free condition to get 3,4-dihydropyrimidin-2(1*H*)-ones in high yields (Table-1). Clearly, it is seen that a

TABLE-1
$Zn(OAc)_2{\cdot}2H_2O$ CATALYZED SYNTHESIS OF
3,4-DIHYDRO FYRIMIDIN-2(1*H*)-ONES/-THIONES



1(a-l) 2 3 4(a-l)

S. No.	1 R	3 X	Time (s)	Product[a] 4	Yields[b] (%)	m.p. (°C) Found	m.p. (°C) Reported[c]
1	C_6H_5	O	50	4a	95	201–203	202–203
2	4-$NO_2C_6H_4$	O	60	4b	92	209–210	208–210
3	4-$H_3CC_6H_4$	O	35	4c	90	214–215	214–216
4	4-ClC_6H_4	O	50	4d	93	211–212	211–212
5	4-$H_3COC_6H_4$	O	40	4e	94	200–201	199–201
6	4-OHC_6H_4	O	60	4f	90	227–228	227–229
7	2-Furyl	O	45	4g	91	204–205	204–205
8	C_6H_4—CH=CH	O	45	4h	90	232–233	232–235
9	4-F-C_6H_4	O	50	4i	93	185–186	185–186
10	C_6H_5	S	60	4j	95	208–210	208–210
11	4-H_3CO—C_6H_4	S	50	4k	94	150–152	150–152
12	4-Cl—C_6H_4	S	60	4l	92	192–195	192–195

[a]All the products are known, were characterised by IR spectral analysis and by comparison of their physical properties with those of the authentic compounds.
[b]Isolated yields.
[c]Melting points of compounds are consistent with reported values [reference (14, 19, 22–24)].

wide range of structurally varied aldehydes and urea are coupled with a β-keto ester to produce the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones. It is also clear that aromatic aldehydes, carrying either electron-withdrawing or electron-donating substituents afford high yields of products with high purity. Acid sensitive aldehyde like 2-furaldehyde also works well without formation of side products. α,β-unsaturated aldehyde also produces 3,4-dihydropyrimidin-2(1*H*)-one in good yield and there is no decomposition or polymerization under our reaction conditions. Thiourea has been used with similar success to provide the corresponding thio-derivatives of 3,4-dihydropyrimidin-2(1*H*)-ones, which are also of much interest with respect to their biological activities. Thus, the method utilizes readily available low cost reagents and affords high yields of different substituted 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones in short reaction times.

ACKNOWLEDGEMENT

One of the authors (V.P.J.S.) wishes to thank Sri Souwmyanath Swamiji of Sri Adichunchanagiri Muth, Vijayanagara, Bangalore-560 078, for his blessings and constant encouragement.

REFERENCES

1. (a) C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993) and references cited therein. (b) P. Biginelli, *Gazz Chim. Ital.*, **23**, 360 (1893).
2. (a) C.O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000). (b) C.O. Kappe, O.V. Shishkin, G. Uray and P. Verdin, *Tetrahedron*, **56**, 1859 (2000). (c) A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C. De-Brosse, S. Mai, A. Truneh, D.J. Faulkner, B. Carte, A.L. Breen, R.P. Hertzberg, R.K. Johnson, J.W. Westly and B.C. Potts, *J. Org. Chem.*, **60**, 1182 (1995).
3. J.S. Yadav, B.V.S. Reddy, K.B. Reddy, K.S. Raj and A.R. Prasad, *J. Chem. Soc. Perkin Trans. 1*, **42**, 7975 (2001).
4. F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, **40**, 3465 (1999).
5. B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.*, **65**, 6270 (2000).
6. N.Y. Fu, Y.F. Yuan, Z. Cao, S.W. Wang, J.T. Wang and C. Peppe, *Tetrahedron*, **58**, 4801 (2002).
7. J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, **41**, 9075 (2000).
8. Y. Ma, C. Qian, L. Wang and M. Yang, *J. Org. Chem.*, **65**, 3864 (2000).
9. A.S. Paraskar, G.K. Dewkar and A. Sudalai, *Tetrahedron Lett.*, **44**, 3305 (2003).
10. (a) J.C. Bussolari and P.A. McDonnell, *J. Org. Chem.*, **65**, 6777 (2000). (b) K.S. Atwal, B.C. O'Reilly, J.Z. Gougoutas and M.F. Malley, *Heterocycles*, **26**, 1189 (1987); K.S. Atwal, B.C. O'Reilly and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1985).
11. C.V. Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu and V.V.N. Reddy. *Tetrahedron Lett.*, **43**, 2657 (2002).
12. A. Dondoni and A. Massi, *Tetrahedron Lett.*, **42**, 7975 (2001).
13. J. Peng and Y. Deng, *Tetrahedron Lett.*, **42**, 5917 (2001).
14. K.A. Kumar, M. Kasthuraiah, C.S. Reddy and C.D. Reddy, *Tetrahedron Lett.*, **42**, 7873 (2001).
15. (a) C.O. Kappe and S.F. Falsone, *Synlett.*, 718 (1998). (b) T.S. Jin, J.C. Xiao, Y.X. Chen and T.S. Li, *J. Chem., Res. (S)*, **3**, 190 (2004). (c) B. Gangadasu, S. Palaniappan and V.J. Rao, *Synlett.*, **7**, 1285 (2004).

16. E.H. Hu, D.R. Sidler and U.H. Dolling, *J. Org. Chem.*, **63**, 3454 (1998).
17. P. Salehi, M. Dabiri, M.A. Zolfigol and M.A.B. Fard, *Tetrahedron Lett.*, **44**, 2889 (2003).
18. J. Lu and Y. Bai, *Synthesis*, **4**, 466 (2002).
19. A. Shaabani, A. Bazgir and F. Teimouri, *Tetrahedron Lett.*, **44**, 857 (2003).
20. G. Maiti, P. Kundu and C. Guin, *Tetrahedron Lett.*, **44**, 2757 (2003).
21. S. Tu, F. Fang, S. Zhu, L. Tuanjie, X. Zhang and Q. Zhuang, *Synlett.*, **3**, 537 (2004).
22. A.V. Narsaiah, A.K. Basak and K. Nagaiah, *Synthesis*, **8**, 1253 (2004).
23. (a) Q. Sun, Y.Q. Wang, Z.M. Ge, T.M. Cheng and R.T.Li, *Synthesis*, 1047 (2004). (b) J. Lu and H. Ma, *Synlett.*, 63 (2000).
24. (a) S. Kumar, A. Saini and J.S. Sandhu, *Indian J. Chem.*, **43B**, 1485 (2004). (b) K.V.N.S. Srinivas and B. Das, *Synthesis*, 2091 (2004).
25. (a) M. Gohain, D. Prajapati and J.S. Sandhu, *Synlett.*, 235 (2004). (b) C.O. Kappe, D. Kumar and R.S. Verma, *Synthesis*, 1799 (1999). (c) J.S. Yadav, B.V.S. Reddy, E.J. Reddy and T. Ramalingam, *J. Chem. Res.(S).*, **5**, 354 (2000).

(*Received*: 16 October 2004; *Accepted:* 16 April 2005) AJC-4180