J. Indian Chem. Soc.,
Vol. 92, October 2015, pp. 1553-1556

Synthesis of dihydropyrimidinones derivatives by Biginelli reaction in basic medium

Nivedita Srivastava*, Arti Mehrotra and Anil Kumar

Bioorganic & Heterocyclic Research Laboratory, Department of Applied Chemistry, Faculty of Engineering & Technology, M. J. P. Rohilkhand University, Bareilly-243 006, Uttar Pradesh, India

E-mail : drnimjpru@rediffmail.com, niveditacdri2000@yahoo.com

Manuscript received online 12 December 2014, accepted 04 March 2015

Abstract : A simple, clean and convenient one-pot method has been developed for the synthesis of 4-substituted-3,4-dihydropyrimidinone by multicomponent condensation of ethyl acetoacetate, aromatic aldehydes and urea in basic medium in the presence of ethanol under refluxing conditions. The yield of all products is ≥ 90%. The synthesized compounds have been characterized on the basis of their spectroscopic data.

Keywords : Biginelli reaction, 3,4-dihydropyrimidines, multicomponent condensation.

Introduction

Pyrimidine is the important heterocyclic compounds, which have attracted attention from long time. It has significant attention due to its synthetic and important medicinal property and also due to its presence in many biological systems. Certain pyrimidine derivatives like 3,4-dihydropyrimidines (DHPM) shows great attention in organic synthesis. It is an important class of compounds due to their biological properties[1–3] as anticoagulant[4], antihypertensive[5], anti-inflammatory, antimicrobial, antibacterial[6], antifungal and antioxidant activities[7]. It also inhibits the propagation of the malaria parasite *Plasmodium falciparum*[8]. Along with these properties, it is also the backbone of several calcium channel blocker[9]. Due to the versatile properties of dihydropyrimidnones, it always shows the topic of interest by the researchers in developing a versatile cheap method of economic utility.

In last two decades, Biginelli's reaction for the synthesis of DHPM's has received interest and several improved procedures have been reported[10]. The use of Lewis acids catalyst such as indium(III) chloride[11], indium(III) bromide[12], $CuCl_2/CuSO_4$ or $CuCl_2/HCl$[13], cupric(II) triflate[14], copper(II) acetate/sodium ascorbate/acetic acid[15], strontium(II) triflate[16], bismuth(III) nitrate[17], $BiCl_3$[18], BF_3[19], calcium chloride[20], sulfate zirconia[21], $Co(HSO_4)_2$[22], chlorotrimethylsilane[23], iron(III) tosylate[24], $FeCl_3$[25], $LaCl_3$[26], $LiClO_4$[27], CAN[28] have been successfully used in Biginelli reaction. Biginelli reaction was also catalyzed by bases such as t-BuOK[29]. Now nanoparticles[30] have been successfully applied to the Biginelli products synthesis. Some calcium antagonists such as nifedipine and verapamil, which are used as antihypertensive agents, have a serious disadvantage in the treatment of hypertension. These drugs were replaced by dihydropyrimidines derivatives as these are known to possess calcium antagonists with potent and long-lasting vasodilative, hypotensive or antihypertensive activity[31]. Apart from this DHPM unit also have potential application in the treatment of AIDS[32].

Many reaction methods have several drawbacks such as use of expensive and dangerous catalysts, long reaction times, use of high boiling point and toxic solvents and low yield of products. It is important to adopt such experimental conditions which may remove all these limitations and to obtain a better yield of product. Our efforts are in the direction of search of simple, efficient, environmentally friendly, inexpensive methods with better yields of products.

The most general and widely employed route to prepare pyrimidines involves the combination of a reagent containing the N-C-N skeleton with C-C-C unit. Urea is used as N-C-N reagents and ethyl acetoacetate as the typical

C-C-C reagents in different reaction conditions.

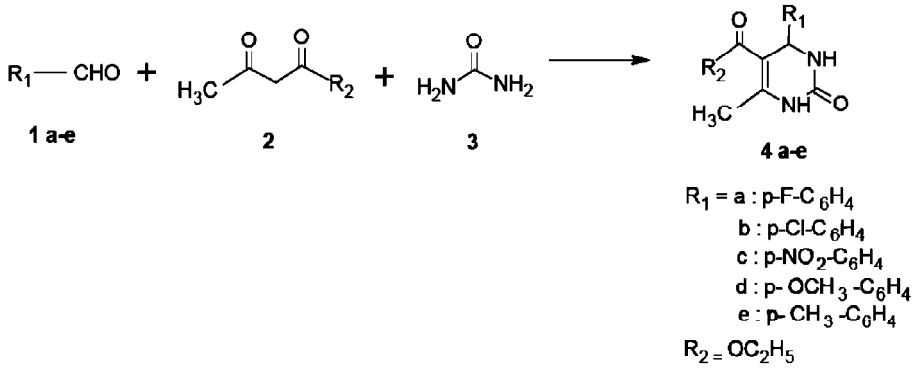
Here we have carried out the condensation of *para*-substituted aromatic aldehydes **1a-e** (-C- unit) and ethyl acetoacetate **2** (C-C unit) with urea **3** (N-C-N unit) in presence of potassium carbonate in ethanol (Scheme 1). Using such condition 3,4-substituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine derivatives **4a-e** are formed in good yield (≥ 90%).

Results and discussion

It is interested to report that the one pot reaction of substituted benzaldehyde **1a-e** with ethyl acetoacetate **2** and urea **3** in the presence of cheap K_2CO_3/ethanol resulted in the formation of 4-substituted-3,4-dihydropyrimidinone **4a-e** in ≥ 90% yield (Scheme 1). Melting point of **4a-e** is represented in Table 1. Structures of **4a-e** were confirmed by Mass, IR, ^{1}H NMR.

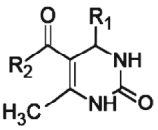
Experimental

Spectral data were recorded as follows : IR spectra was run on a Perkin-Elmer and Schimadzu 8201 PC, FT Infrared spectrophotometer (ν_{max} in cm^{-1}). Mass spectra were recorded on Waters UPLC-TOD Triple Quadrupole. ^{1}H NMR has been recorded on Bruker Avance-300 (300 MHz). Signals were designated as follows : s, singlet; bs, broad signal; d, doublet; t, triplet; m, multiplet.



Scheme 1. General synthetic procedure for synthesis of 4-substituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine **4a-e**.

Table 1. Compounds formed by efficient synthesis of dihydropyrimidines



Sr. no.	R_1	R_2	Nomenclature of synthesized compounds	M.p. (°C) Found	M.p. (°C) Reported
1.	*p*-F-C_6H_4	OEt	Ethyl-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine	173–175	172
2.	*p*-Cl-C_6H_4	OEt	Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine	215–216	213
3.	*p*-NO_2-C_6H_4	OEt	Ethyl-4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine	206–208	208
4.	*p*-OCH_3-C_6H_4	OEt	Ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine	199–201	202
5.	*p*-CH_3-C_6H_4	OEt	Ethyl-4-(4-methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine	170–172	171

Melting points were determined in open capillary method and were uncorrected. All reagents used were of commercial grade and were used as received without further purification unless otherwise specified. Reagent grade solvents were used in all other cases unless otherwise specified. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure.

General procedure for 3,4-dihydropyrimidines (**4a-e**) :

A mixture of *para*-substituted benzaldehyde **1a-e** (0.010 *M*), ethylacetoacetate **2** (0.010 *M*), urea **3** (0.010 *M*) and potassium carbonate (0.010 *M*) in ethanol (15 ml) were refluxed for 12 h. Solvent was evaporated and reaction product was poured into ice cold water with stirring. The reaction mixture was neutralized with glacial acetic acid, which causes the separation of solid. Solid was collected by filtration, washed with water and recrystallized from aqueous ethanol.

Spectral data :

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

Solid, (91%), (Found : C, 60.42; H, 5.40; N, 10.05. $C_{14}H_{15}N_2O_3F$ Calcd. for : C, 60.43; H, 5.43; N, 10.06%); ν_{max} : 3220, 3200, 3115, 1702, 1642, 1560, 1500, 1200, 775 cm^{-1}; δ (DMSO-d_6) : 1.26 (3H, t, CH_3), 2.26 (3H, s, CH_3), 4.02 (2H, m, OCH_2), 5.18 (1H, d, CH), 7.50–8.20 (5H, 3d, Ar and NH), 9.32 (1H, s, NH); *m/z* 278 (M^+).

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

Solid, (92%), (Found : C, 57.23; H, 5.12; N, 9.49. $C_{14}H_{15}N_2O_3Cl$ Calcd. for : C, 57.05; H, 5.13; N, 9.50%); ν_{max} : 3205, 3130, 1710, 1650, 1600, 1530, 1300, 700 cm^{-1}; δ (DMSO-d_6) : 1.10 (3H, t, CH_3), 2.25 (3H, s, CH_3), 3.99 (2H, m, OCH_2), 5.22 (1H, d, CH), 7.28–7.79 (5H, 3d, Ar and NH), 9.28 (1H, s, NH); *m/z* 294 (M^+).

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

Solid, (93%), (Found : C, 55.06; H, 4.94; N, 13.74. $C_{14}H_{15}N_3O_5$ Calcd. for : C, 55.08; H, 4.95; N, 13.76%); ν_{max} : 3215, 3100, 1700, 1640, 1590, 1520 cm^{-1}; δ (DMSO-d_6) : 1.16 (3H, t, CH_3), 2.26 (3H, s, CH_3), 3.99 (2H, m, OCH_2), 5.27 (1H, d, CH), 7.50–8.20 (5H, 3d, Ar and NH), 9.65 (1H, s, NH); *m/z* 305 (M^+).

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

Solid, (92%), (Found : C, 62.04; H, 6.23; N, 9.63. $C_{15}H_{18}N_2O_4$ Calcd. for : C, 62.06; H, 6.24; N, 9.64%); ν_{max} : 3205, 3120, 1690, 1630, 1580, 1510, 1190 cm^{-1}; δ (DMSO-d_6) : 1.12 (3H, t, CH_3), 2.25 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 3.97 (2H, m, OCH_2), 5.10 (1H, d, CH), 6.86–7.72 (5H, 3d, Ar and NH), 9.15 (1H, s, NH); *m/z* 290 (M^+).

Ethyl-4-(4-methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4e**) :

Solid, (90%), (Found : C, 65.66; H, 6.60; N, 10.19. $C_{15}H_{18}N_2O_3$ Calcd. for : C, 65.68; H, 6.61; N, 10.21%); ν_{max} : 3300, 3250, 3125, 1715, 1650, 1590, 1505 cm^{-1}; δ (DMSO-d_6) : 1.20 (3H, t, CH_3), 2.3 (6H, s, CH_3), 4.05 (2H, q, OCH_2), 5.35 (1H, d, CH), 6.8 (1H, brs, NH), 7.15–7.25 (5H, 3d, Ar and NH), 8.85 (1H, s, NH); *m/z* 274 (M^+).

All products were characterized by IR, ^1H NMR, Mass spectra and by comparison of physical characteristics with authentic samples.

Conclusion

In this work, we have synthesized 4-substituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine **4a-e** by the one pot condensation of *para*-substituted benzaldehyde **1a-e**, ethyl acetoacetate **2** and urea **3** by the use of easily available K_2CO_3. The yield of product **4a-e** is very good ≥ 90%.

Acknowledgement

We gratefully acknowledge the financial support provided by University Grants Commission (UGC), New Delhi, Grant no. 31-128/2005 SR and Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute, Lucknow (India) for providing spectral data on payment basis.

References

1. R. V. Chikhale, R. P. Bhole, P. B. Khedekar and K. P. Bhusari, *European Journal of Medicinal Chemistry*, 2009, **44**, 3645.
2. M. M. Alam, M. Akhter, A. Husain, A. Marella, O. P. Tanwar, R. Ali, S. M. Hasan, H. Kumar, R. Haider and M.

Shaquiquzzaman, *Acta Pol. Pharm.*, 2012, **69**, 1077.

3. N. Annette Chiang, J. C. Valderramos, R. Balachandran, J. C. Raj, B. P. Mead, C. Scheider, L. B. Samantha, G. K. Michael, M. H. Donna, S. C. Xiaojiang, W. D. Billy, A. F. David, W. Peter and L. B. Jeffrey, *Bioorganic & Medicinal Chemistry*, 2009, **17**, 1527; A. Adhikari, B. Kalluraya, K. V. Sujith, G. Chandra and R. Mahmood, *Saudi Pharmaceutical Journal*, 2012, **20**, 75.
4. S. Chitra, D. Devanathan and K. Pandiarajan, *European Journal of Medicinal Chemistry*, 2010, **45**, 1367.
5. M. Ashok, B. S. Holla and N. S. Kumari, *European Journal of Medicinal Chemistry*, 2007, **42**, 380.
6. E. W. Hurst and R. Hull, *Journal of Medicinal Chemistry*, 1961, **3**, 215.
7. T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber and T. J. Mitchison, *Science*, 1999, **286**, 971.
8. C. O. Kappe, *Accounts of Chemical Research*, 2000, **33**, 879.
9. J. Zhu, H. Bienayme, eds. Wiley, Weinheim, 2005; H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.,* 2000, **6**; A. Domling and I. Ugi, *Angew. Chem., Int. Ed.,* 2000, **39**, 3168; C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879; C. Simon, T. Constantieux and J. Rodriguez, *Eur. J. Org. Chem.,* 2004, 4957.
10. S. Sandhu and J. S. Sandhu, *Arkivoc,* 2012, **i**, 66.
11. B. C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.,* 2000, **65**, 6270.
12. N. Y. Fu, Y. F. Yuan, S. W. Wang, J. T. Wang and C. Peppe, *Tetrahedron,* 2002, **58**, 4801.
13. M. Gohain, D Prajapati and J. S. Sandhu, *Synlett,* 2004, **2**, 235; S. Jayakumar and T. K. Sabeer, *J. Chem. Pharm. Res*., 2011, **3**, 1089.
14. A. S. Paraskar, G. K. Dzwkar and A. Sudalai, *Tetrahedron Lett.,* 2003, 3305.
15. P. Saleihi, M. Dbiri, M. Koohshari, S. K. Movahed and M. Bararjanian, *Mol. Divers.,* 2011, **15**, 833.
16. W. Su, J. Li, Z. Zheng and Y. Shen, *Tetrahedron Lett.,* 2005, **45**, 6037.
17. M. M. Khodei, A. R. Khosropour and M. Jowkar, *Synthesis,* 2005, **8**, 1301.
18. K. Ramalinga, P. Vijayalakshmi and T. N. B. Kaimal, *Synlett*, 2001, 863.
19. E. H. Hu, D. R. Sidler and U. H. Dolling. *J. Org. Chem.*, 1998, **63**, 3454.
20. B. Gangadasu, P. Narender, B. C. Raju and V. J. Rao, *Indian J. Chem.,* 2006, **45**, 1259.
21. D. A. Bentran, L. L. Romero, V. H. L. Corona, E. G. Zamora and G. N. Silva, *Molecules,* 2006, **11**, 731.
22. H. R. Memarian and M. Ranjbar, *J. Chin. Chem. Soc.,* 2011, **58**, 522.
23. S. Khodadoost, E. Alipoor and M. Amini, *Org. Chem. J.,* 2010, **2**, 85.
24. J. T. Starcevitch, T. J. Laughlin and R. S. Mohan, *Tetrahedron Lett.*, 2013, **54**, 983.
25. J. Lu and H. Ma, *Synlett*, 2000, 63.
26. J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, 2000, **41**, 9075.
27. J. S. Yadav, B. V. S. Reddy, R. Srinivas, C. Venugopal and T. Ramalingam, *Synthesis,* 2001, 1341.
28. J. S. Yadav, B. V. S. Reddy, K. B. Reddy, K. S. Raj and A. R. Prasad, *J. Chem. Soc., Perkin Trans.,* 2001, **1**, 1939.
29. Z. L. Shen, X. P. Xu and S. J. Ji, *J. Org. Chem.,* 2010, **75**, 1162.
30. S. B. Sapcal, K. F. Shelke, B. B. Shingate and M. S. Shingare, *Bull. Korean Chem. Soc.,* 2010, **31**, 351; M. N. Esfahani, S. J. Hoseini and F. Mohammadi, *Chinese J. Catal.,* 2011, **32**, 1484; R. J. Kalbasi, A. R. Massah and B. Daneshvarnejad, *Appl. Clay Sci.,* 2012, **55**, 1; E. Kolvari, N. Koukabi and O. Armandpour, *Tetrahedron*, 2014, **70**, 1383.
31. K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.
32. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freger, C. Debrossi, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzbery, R. K. Johnson, J. W. Westley and B. C. M. Potts, *J. Org. Chem.,* 1995, **60**, 1182.