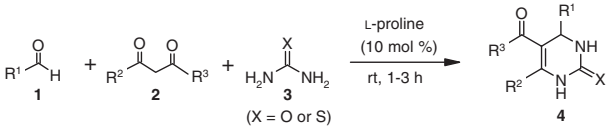
A Novel L-Proline Catalyzed Biginelli Reaction: One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones under Solvent-Free Conditions

J. S. Yadav, S. Praveen Kumar, G. Kondaji, R. Srinivasa Rao, and K. Nagaiah*
Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

(Received December 8, 2003; CL-031166)

A Novel efficient and simple synthetic protocol for the Biginelli reaction has been developed for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in a one-pot three-component condensation of aldehydes, β-dicarbonyl compounds, and urea or thiourea by using 10 mol % L-proline as the catalyst under solvent free condition.

In recent years, 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) and their derivatives occupy an important place in the realm of natural and synthetic organic chemistry due to their broad range of biological activities, including antiviral, antitumor, antibacterial, and anti-inflammatory activities.[1] More recently, appropriately functionalized DHPMs have attracted considerable interest due to their promising activities as calcium channel blockers, orally active antihypertensive agents[2] and α_{1a} adrenoceptor-selective antagonists.[3] Moreover several recently isolated marine alkaloids[4] with interesting biological activities containing the dihydropyriminone-5-carboxylate core. Most importantly among these are the batzelladine alkaloides A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[5] A very recent important highlight in this aspect is the identification of the structurally rather simple DHPM monastrol as a mitotic kinesis Eg5 motor protein inhibitor and potential new lead for the development of anticancer drugs.[6] Hence the synthesis of this heterocyclic nucleus is of much current importance.

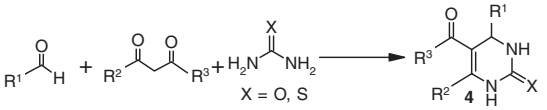


Scheme 1.

In 1891, Italian chemist Pietro Biginelli first reported the synthesis of DHPMs by multi-component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde, and urea under strongly acidic conditions.[7] However, one serious drawback of Biginelli's reaction is low yields in the case of substituted aromatic and aliphatic aldehydes.[8] This has lead to the development of multi-step synthetic strategies that produce somewhat better yields but lack the simplicity of the one-pot, one-step synthesis.[2a,8a,9a,9b,10]

L-proline has been found to be effective for enamine-based direct catalytic asymmetric aldol, Mannich, Michael, Diels–Alder,[11] and α-amination reactions.[12] The scope of these reactions depend upon the nucleophilic enamine catalytic activity of secondary amine and the carboxylic acid moiety as general Brønsted acid co-catalyst presented in L-proline. So we wish to exploit this catalytic activity of L-proline to synthesis chiral DHPMs, unfortunately we ended with racemic DHPMs.[14] Herein we report a novel L-proline catalyzed Biginelli reaction applied to one-pot three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea or thiourea to synthesis DHPMs under solvent-free conditions, which is not only simple and high-yielding (80–96%) but also greatly decreases environmental pollution (Scheme 1). To the best of our knowledge there were no reports for the synthesis of DHPMs catalyzed by L-proline. Treatment of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) in the presence of 10 mol % of L-proline at ambient temperature for 1 h afforded the corresponding 3,4-dihydropyrimidin-2(1*H*)-one 4a in 96% yield. The results are summarized in the Table 1. Most importantly, a variety of aromatic, aliphatic, and heterocyclic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted

Table 1. L-proline catalysed synthesis of dihydropyrimidinones under solvent-free conditions



Entry	R^1	R^2	R^3	X	Product[b]	Time /h	Yield /%[c]	Ref
1	Ph	Me	OEt	O	**4a**	1.0	96	11m
2	4-(OH)-C_6H_4	Me	OEt	O	**4b**	3.0	80	11m
3	4-(OMe)-C_6H_4	Me	OEt	O	**4c**	2.0	88	11m
4	3,4,5-$(OMe)_3$-C_6H_2	Me	OEt	O	**4d**	2.5	82	11q
5	C_6H_5–CH=CH	Me	OEt	O	**4e**	2.0	90	11b
6	4-Cl-C_6H_4	Me	OEt	O	**4f**	1.5	92	11m
7	4-F-C_6H_4	Me	OEt	O	**4g**	1.5	90	11d
8	2-Cl-6-F-C_6H_3	Me	OEt	O	**4h**	2.0	89	
9	4-(NO_2)-C_6H_4	Me	OEt	O	**4i**	1.0	91	11m
10	C_2H_5	Me	OEt	O	**4j**	3.0	85	
11	2-furyl	Me	OEt	O	**4k**	2.5	88	11c
12	2-thienyl	Me	OEt	O	**4l**	3.0	83	11a
13	Ph	Me	OMe	O	**4m**	1.5	95	11m
14	4-(OH)-C_6H_4	Me	OMe	O	**4n**	3.0	82	11b
15	4-(F)-C_6H_4	Me	OMe	O	**4o**	2.0	90	11f
16	4-(OMe)-C_6H_4	Me	OMe	O	**4p**	2.5	81	11m
17	2,4-$(Cl)_2$-C_6H_3	Me	OMe	O	**4q**	1.0	93	11r
18	Ph	Ph	OEt	O	**4r**	3.0	80	11m
19	Ph	Me	Me	O	**4s**	2.0	91	11k
20	4-(OMe)-C_6H_4	Me	Me	O	**4t**	2.5	85	11b
21	2-pyridyl	Me	Me	O	**4u**	2.5	88	11b
22	4-(OMe)-C_6H_4	Me	Ph	O	**4v**	3.0	82	11b
23	3-(OMe)-C_6H_4	Me	OEt	S	**4w**	2.5	87	11b
24	4-Cl-C_6H_4	Me	OEt	S	**4x**	1.0	93	11a
25	4-(OMe)-C_6H_4	Me	OEt	S	**4y**	3.0	87	11c
26	Ph	Me	Me	S	**4z**	2.5	90	11b

[a]All reactions were carried at ambient temperature. [b]All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy. [c]Isolated and unoptimized yields.

well, affording excellent yields in high purity. Very highlight of this procedure is the tolerance of acid sensitive aldehydes such as furfural and cinnamaldehyde (4k and 4e) without formation of side products. Also the additional advantage of this protocol is volatile propionaldehyde (4j) yield the corresponding DHPM in excellent yield. Thiourea also gives the corresponding dihydropyrimidin-2(1*H*)-thiones (Entries 4w–4z) which are also of much interest with regard to biological activity.[1a] And also a wide variety of β-ketone esters (4w–4y) and aliphatic β-diketones (4s–4v, 4z) were participated in this reaction. Thus, variations in all the three components have been accommodated very comfortably. This protocol utilizes the use of just 10 mol % of L-proline under solvent-free conditions at ambient temperature. In addition no additive or protic/Lewis acid is necessary in this procedure. The crude products obtained are of high purity (>95% by ^{1}H NMR). Another important feature of this protocol is survival of a variety of functional groups such as OCH_3, OH, NO_2, F, Cl, and conjugated C=C double bond under the reaction conditions.

We propose the mechanism based on an elegant mechanism proposed by List[13] for the direct asymmetric three-component Mannich reaction. The most plausible mechanism of the L-proline catalyzed three components Biginelli reaction is depicted in Figure 1.

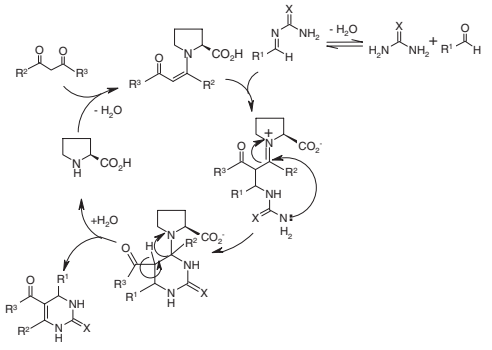


Figure 1. Plausible mechanism (X = oxygen or sulphur).

In summary, we have developed a novel and simple protocol, for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by L-proline catalyzed condensation of β-dicarbonyl compound, aldehyde, and urea under solvent-free condition provided an efficient, eco-friendly and much improved modification of classical Biginelli reaction. We believe, our procedure will find an important application in the synthesis of DHPMs to fulfill the needs of academia as well as pharmaceutical industries.

SPK, GK, and RSR thank CSIR, New Delhi, for the award of fellowships.

References and Notes

1 a) Review: C. O. Kappe, *Tetrahedron*, **49**, 6937 (1993). b) Review: C. O. Kappe, *Acc. Chem. Res.*, **33**, 879 (2000). c) Review: C. O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000).

2 a) K. S. Atwal, G. C. Rovnyak, B. C. O'Reilly, and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1989). b) G. J. Grover, S. Dzwonczyk, D. M. McMullen, D. E. Normandin, C. S. Arham, P. G. Sleph, and S. Moreland, *J. Cardiovasc. Pharmacol.*, **26**, 289 (1995) and references cited therein.

3 a) C. O. Kappe, W. M. F. Fabian, and M. A. Semones, *Tetrahedron*, **53**, 2803 (1997). b) J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, R. M. Freidinger, R. W. Ransom, S. S. O'Malley, P. Eppert, D. Nagarathnam, and C. Forray, *J. Med. Chem.*, **43**, 2703 (2000) and references cited therein.

4 a) B. B. Snider and Z. Shi, *J. Org. Chem.*, **58**, 3828 (1993) and references cited therein. b) L. E. Overman, M. H. Rabinowitz, and P. A. Renhowe, *J. Am. Chem. Soc.*, **117**, 2657 (1995). c) Review: L. Heys, C. G. Moore, and P. Murphy, *Chem. Soc. Rev.*, **29**, 57 (2000).

5 a) A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, and D. Faulkner, *J. Org. Chem.*, **60**, 1182 (1995). b) A. V. Rama Rao, M. K. Gurjar, and J. Vasudevan, *J. Chem. Soc., Chem. Commun.*, **1995**, 1369. c) B. B. Snider, J. Chen, A. D. Patil, and A. Freyer, *Tetrahedron Lett.*, **37**, 6977 (1996).

6 a) T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Screiber, and T. J. Mitchison, *Science*, **286**, 971 (1999). b) S. J. Haggarty, T. U. Mayer, D. T. Miyamoto, R. Fathi, R. W. King, T. J. Mitchison, and S. L. Screiber, *Chem. Biol.*, **7**, 275 (2000).

7 a) P. Biginelli, *Ber.*, **24**, 1317 (1891). b) P. Biginelli, *Ber.*, **26**, 447 (1893). c) P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893).

8 a) J. Barluenga, M. Tomas, A. Ballesteros, and L. A. Lopez, *Tetrahedron Lett.*, **30**, 4573 (1989). b) K. S. Atwal, G. C. Rovnyak, B. C. O'Reilly, and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1989).

9 a) B. C. O'Reilly and K. S. Atwal, *Heterocycles*, **26**, 1185 (1987). b) K. R. Reddy, Ch. V. Reddy, M. Mahesh, P. V. K. Raju, and V. V. N. Reddy, *Tetrahedron Lett.*, **44**, 8173 (2003).

10 a) Review: C. O. Kappe, *Tetrahedron*, **49**, 6937 (1993). b) A. Shaabani, A. Bazgir, and F. Teimouri, *Tetrahedron Lett.*, **44**, 857 (2003) and references cited therein. c) J. T. Li, J. F. Han, J. H. Yang, and T. S. Li, *Ultrason. Sonochem.*, **10**, 119 (2003). d) D. Alessandro, M. Alessandro, S. Simona, and B. Valerio, *J. Org. Chem.*, **67**, 6979 (2003). e) D. Alessandro, M. Alessandro, M. Erik, S. Simona, and B. Valerio, *J. Org. Chem.*, **67**, 6172 (2003).

11 B. List, *Synlett*, **2001**, 1675 and references cited therein.

12 a) A. Bogevig, N. Kumaragurubaran, K. Juhl, W. Zhuang, and K. A. Jorgensen, *Angew. Chem., Int. Ed. Engl.*, **41**, 1790 (2002). b) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bogevig, and K. A. Jorgensen, *J. Am. Chem. Soc.*, **124**, 6254 (2002). c) B. List, *J. Am. Chem. Soc.*, **124**, 5656 (2002).

13 B. List, P. Pojarliev, W. T. Biller, and H. J. Martin, *J. Am. Chem. Soc.*, **124**, 827 (2002).

14 The racemic nature of DHPMs confirmed by HPLC analysis.

Published on the web (Advance View) August 14, 2004; DOI 10.1246/cl.2004.1168