

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

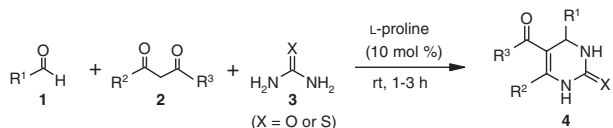
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A Novel efficient and simple synthetic protocol for the Biginelli reaction has been developed for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones in a one-pot three-component condensation of aldehydes, β -dicarbonyl compounds, and urea or thiourea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

In recent years, 3,4-dihydropyrimidin-2(1H)-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 agents² and α_{1a} adrenoceptor-selective antagonists.³ Moreover several recently isolated marine alkaloids⁴ with interesting biological activities containing the dihydropyrimidinone-5-carboxylate core. Most importantly among these are the batzelladine alkaloids 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 kinase 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 led 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

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 ₆ H ₄	Me	OEt	O	4b	3.0	80	11m
3	4-(OMe)-C ₆ H ₄	Me	OEt	O	4c	2.0	88	11m
4	3,4,5-(OMe) ₃ -C ₆ H ₂	Me	OEt	O	4d	2.5	82	11q
5	C ₆ H ₅ -CH=CH	Me	OEt	O	4e	2.0	90	11b
6	4-Cl-C ₆ H ₄	Me	OEt	O	4f	1.5	92	11m
7	4-F-C ₆ H ₄	Me	OEt	O	4g	1.5	90	11d
8	2-Cl-6-F-C ₆ H ₃	Me	OEt	O	4h	2.0	89	
9	4-(NO ₂)-C ₆ H ₄	Me	OEt	O	4i	1.0	91	11m
10	C ₂ H 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 ₆ H ₄	Me	OMe	O	4n	3.0	82	11b
15	4-(F)-C ₆ H ₄	Me	OMe	O	4o	2.0	90	11f
16	4-(OMe)-C ₆ H ₄	Me	OMe	O	4p	2.5	81	11m
17	2,4-(Cl) ₂ -C ₆ H 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 ₆ H ₄	Me	Me	O	4t	2.5	85	11b
21	2-pyridyl	Me	Me	O	4u	2.5	88	11b
22	4-(OMe)-C ₆ H ₄	Me	Ph	O	4v	3.0	82	11b
23	3-(OMe)-C ₆ H ₄	Me	OEt	S	4w	2.5	87	11b
24	4-Cl-C ₆ H ₄	Me	OEt	S	4x	1.0	93	11a
25	4-(OMe)-C ₆ H ₄	Me	OEt	S	4y	3.0	87	11c
26	Ph	Me	Me	S	4z	2.5	90	11b

^aAll reactions were carried at ambient temperature. ^bAll products were characterized by ¹H NMR, ¹³C NMR, IR, and mass spectroscopy.

^cIsolated and unoptimized yields.

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(1H)-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

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(1H)-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 ¹H NMR). Another important feature of this protocol is survival of a variety of functional groups such as OCH₃, OH, NO₂, F, Cl, and conjugated C=C double bond under the reaction conditions.

We propose the mechanism based on an elegant mechanism proposed by List¹³ 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.

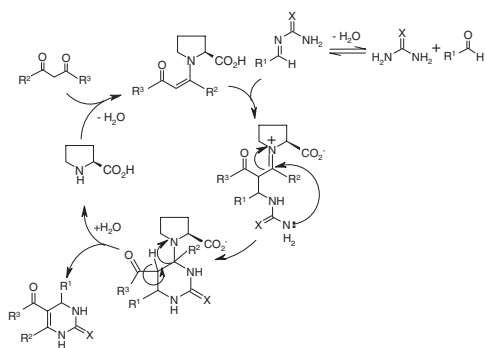


Figure 1. Plausible mechanism (X = oxygen or sulphur).

In summary, we have developed a novel and simple protocol, for the synthesis of 3,4-dihydropyrimidin-2(1H)-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.

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