

Three component solvent-free synthesis of substituted pyrimido [4,5-*d*] pyrimidine-2-(1*H*)-one

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Abstract : A novel three component condensation of aromatic aldehyde, urea or thiourea and barbituric acid or *N,N*-1,3-dimethylbarbituric acid was carried out using *L*-proline as an organo-catalyst under solvent-free microwave conditions.

Keywords: barbituric acid, *L*-proline, solvent-free microwave conditions.

I. INTRODUCTION

The great biological importance of DHPM nucleus has over the years prompted the development of various strategies for the synthesis of diversely functionalized dihydropyrimidine derivatives.¹ Making the variations in the original three reacting components can modify the classical Biginelli reaction.² The following building blocks have so far been documented as the variations of original Biginelli reaction.

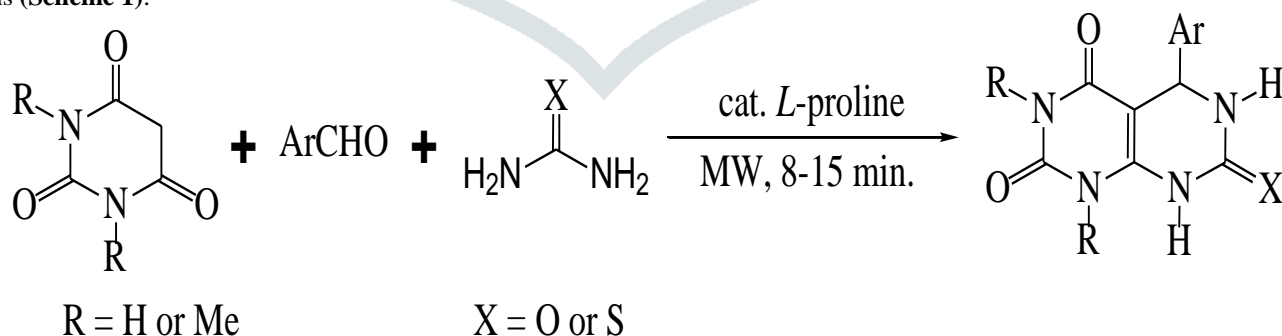
II. Experimental Section:

Reaction vessels were flame-dried or oven dried. Barbituric acid, *N,N*-1,3-dimethyl barbituric acid and *L*-proline were purchased from Aldrich chemicals. Analytical TLC was performed on glass plates coated with silica gel. For the microwave irradiation experiments described below a conventional (unmodified) household microwave oven equipped with a turntable was used (Samsung, code number C 103 FL, 450 W) and operating at 2450 MHz.

Typical procedure: Barbituric acid (5 mmol) or *N,N*-1,3-dimethyl barbituric acid, appropriate aromatic aldehyde (5 mmol), urea or thiourea (5 mmol) and *L*-proline (5 mol%) were mixed thoroughly in a mortar. The reaction mixture was then transferred to 100 mL conical flask and was then irradiated in a domestic microwave oven for 8-15 min. at 450 W. The progress of the reaction was monitored by TLC. After the completion of the reaction, it was poured into crushed ice. The resulting solid was filtered off and recrystallized from ethanol to afford pyrimido[4,5-*d*]pyrimidine-2-1*H*-one in reasonable purity.

Present work:

There are several improved protocol for Biginelli reaction, including transition metal Lewis acid catalysis, solid phase synthesis and activation with certain additives, ionic liquids, heterogeneous catalysis, microwave irradiation and grinding techniques. All of the above improved procedures for the three component Biginelli reaction *mainly* utilize open chain β -dicarbonyl compounds (particularly, β -keto ester) as one of the substrate. The literature survey has revealed that there is limited number of Biginelli reaction variations, which utilizes cyclic 1,3-diketone to afford pyrimidine-fused heterocycles. Owing to the importance of fused pyrimidine ring in natural products and drug chemistry, herein we wish to report one-pot three component condensation of barbituric acid, aldehyde and urea or thiourea using *L*-proline as an efficient organo-catalyst under solvent free microwave conditions (Scheme 1).

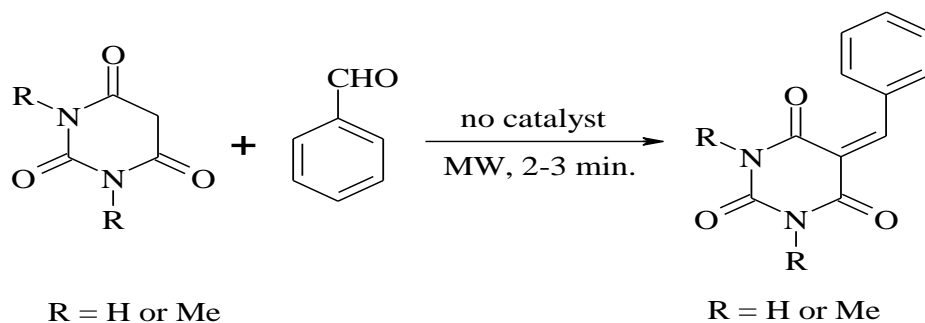


Scheme 1

III. RESULTS AND DISCUSSION:

In a typical experimental procedure, barbituric acid (3 mmol), aromatic aldehyde (3 mmol) and thiourea (3 mmol) was intimately mixed in 25 mL beaker and *L*-proline (5 mol%) was added. This reaction mixture was subjected to intermittent microwave irradiation for the time period of 1 min interval in an unmodified domestic microwave oven at 450 W. This intermittent irradiation-mixing cycle was repeated for the total irradiation time as mentioned in **Table 1**, to afford the highly functionalized pyrimido[4,5-*d*]pyrimidine-2-1*H*-thione in excellent yields (79-92%). In all the cases, the products were purified

by the recrystallization method from ethanol. After the microwave irradiation of every 1 min. interval, a glass thermometer was immediately immersed in the reaction mixture and the final reaction temperature under microwave activation was found to be less than 85 °C. Based upon this observation, we carried out the solvent free reaction of barbituric acid (2 mmol), benzaldehyde (2 mmol), and thiourea (2 mmol) using *L*-proline (5 mol%) under conventional heating at 80-90 °C for the time period of 2-3 hr. In this case the yield of **4m** was significantly low (18-29%). Thus, microwave irradiation was found to be very efficient for the rapid synthesis of **4a-q** in excellent yields. It is worth mentioning that in the absence of *L*-proline, the reaction does not proceed to form pyrimido[4,5-*d*]pyrimidine-2-1*H*-thione and only the condensation of barbituric acid and aromatic aldehyde was observed.



The generality of the method was tested by making variations in all the three components. Thus, barbituric acid as well as *N,N*-1,3-dimethylbarbituric acid reacted with variously substituted aromatic aldehyde and urea or thiourea in the presence of *L*-proline under microwave irradiation to afford a range of diversely functionalized pyrimido [4,5-*d*] pyrimidine-2-1*H*-one in good to excellent yields. The results are shown in **Table 1**.

The structures of all pyrimido[4,5-*d*]pyrimidine-2-1*H*-thione (**4a-q**) were confirmed from the spectroscopic data and elemental analysis. The NMR spectra showed the absence of the methylene proton (δ 2.54 ppm) of the barbituric acid and the presence of a proton at δ 5.26-5.44 ppm.

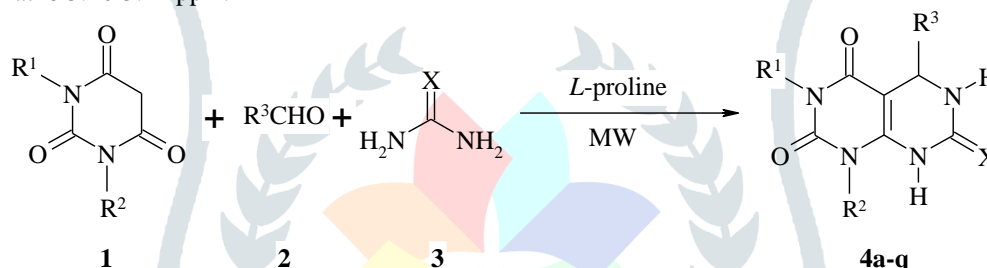


Table 1: *L*-Proline catalyzed multi-component synthesis of pyrimido[4,5-*d*]pyrimidine-2-1*H*-one under solvent-free

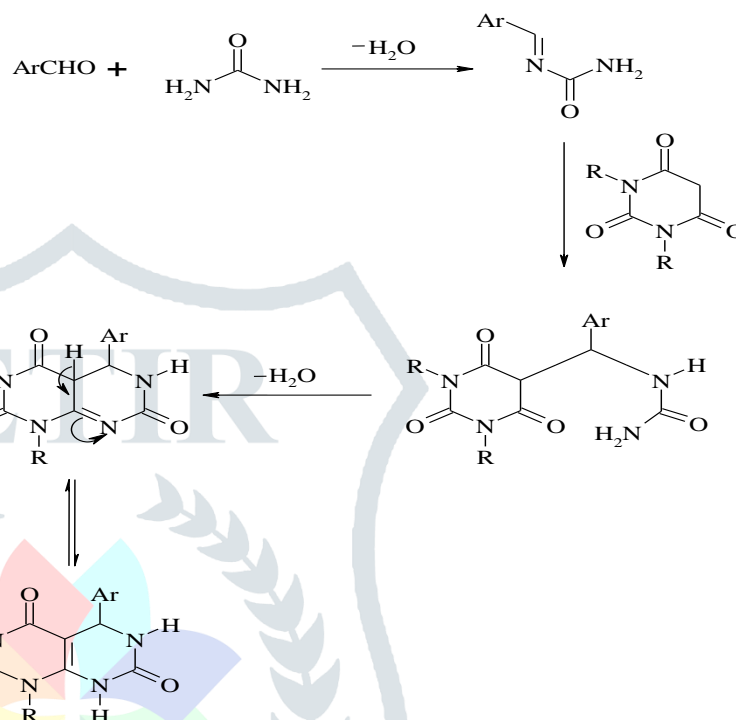
Entry	Product	R ¹	R ²	R ³	X	Reaction Time (min)	Yield ^a (%)
12	4a	H	H	C ₆ H ₅	O	12	87
2	4b	H	H	4-CH ₃ O-C ₆ H ₄	O	14	84
3	4c	H	H	4-Cl-C ₆ H ₄	O	13	76
4	4d	H	H	3-NO ₂ -C ₆ H ₄	O	12	81
5	4e	CH ₃	CH ₃	C ₆ H ₅	O	13	79
6	4f	CH ₃	CH ₃	4-CH ₃ O-C ₆ H ₄	O	17	83
7	4g	CH ₃	CH ₃	4-Cl-C ₆ H ₄	O	14	79
8	4h	CH ₃	CH ₃	3-NO ₂ -C ₆ H ₄	O	15	85
9	4i	CH ₃	CH ₃	3-CH ₃ O-4-HO-C ₆ H ₃	O	15	76
10	4j	CH ₃	CH ₃	C ₆ H ₅	S	13	82
11	4k	CH ₃	CH ₃	4-Cl-C ₆ H ₄	S	12	81
12	4l	CH ₃	CH ₃	4-CH ₃ -C ₆ H ₄	S	14	83
13	4m	H	H	C ₆ H ₅	S	12	78
14	4n	H	H	4-CH ₃ -C ₆ H ₄	S	14	77
15	4o	H	H	3-NO ₂ -C ₆ H ₄	S	13	84

16	4p	H	H	4-Cl-C ₆ H ₄	S	11	83
17	4q	H	H	4-CH ₃ O-C ₆ H ₄	S	12	79

^aIsolated yields after recrystallization.

Reaction Mechanism:

The mechanism of this reaction is assumed to be similar to the original Biginelli reaction as proposed by O. C. Kappe.²



III.CONCLUSION:

Multi-Component synthesis of pyrimido[4,5-*d*]pyrimidine-2-1*H*-one is associated with following important merits:

- Novel synthesis of diversely functionalized bicyclic pyrimidine derivatives.
- Short reaction time.
- Elimination of solvent i. e. solvent-free protocol.
- High yields.
- Purification of the product simply by recrystallization.

In conclusion, we have developed a new, rapid and simple multi-component cyclocondensation protocol for the synthesis of biologically active pyrimido[4,5-*d*]pyrimidine-2-1*H*-one in high yields.

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