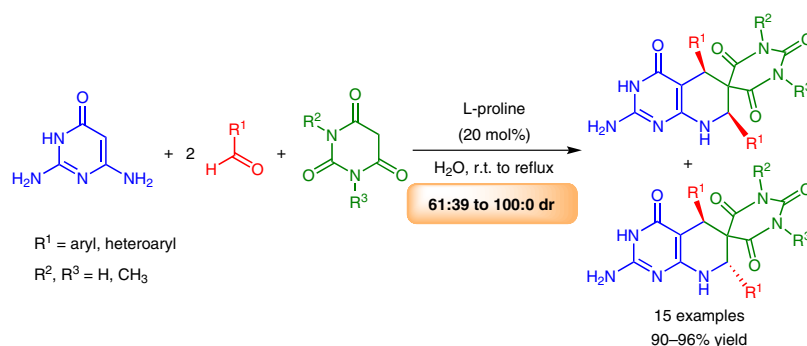


# L-Proline-Catalysed One-Pot Regio- and Diastereoselective Synthesis of Spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] in Water

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**Abstract** A simple L-proline-catalysed regio- and diastereoselective synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] in water through a strategy of one-pot multicomponent domino reaction of 2,6-diaminopyrimidin-4-one, aldehydes and barbituric acids is described. The notable advantages of the protocol are operational simplicity, mild reaction conditions, simple purification process involving no chromatographic techniques, wide substrate scope, and high yields. The method delivers the desired product within short reaction time and with a diastereoselectivity of 61:39 to 100:0, which makes the protocol highly attractive.

**Key words** spiro compounds, organocatalysis, multi-component reaction, L-proline, aqueous medium

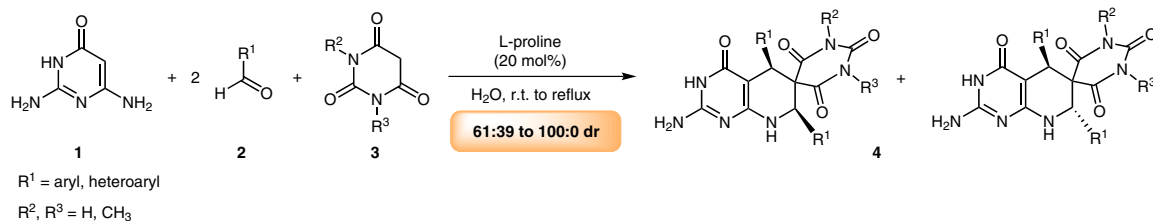
The development of simple, efficient, environmentally benign and economically viable reaction protocols with high regio- and diastereoselectivity continues to be an important area of research. In this context, development of multicomponent domino reactions have become an increasingly powerful tool in organic synthesis because the protocol allows flexible, convergent, atom- and step-economic synthesis.<sup>1</sup> Furthermore, due to the adverse implications of organic solvents, efforts to design efficient synthetic methodology in aqueous medium are of interest. Water can also regulate the course of a reaction by its unique physiochemical properties; polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions.<sup>2</sup>

In this area, organocatalysis has emerged as a powerful strategy, whereby chemical reactions are accelerated by the application of small organic molecules in substoichiometric amounts. Ideal organocatalysts are easy to handle, air- and

water-stable, relatively non-toxic, work under mild conditions, are easily separated from the crude reaction mixture and overcome the major drawbacks of heterogeneous catalysts, such as metal-leaching, long reaction times and structural stability.<sup>3</sup>

Pyrido[2,3-*d*]pyrimidines and their spiro analogues exhibit a wide range of biological activities such as antibacterial,<sup>4</sup> antitumor,<sup>5</sup> antihypertensive,<sup>6</sup> cardiogenic,<sup>7</sup> antiproliferative,<sup>8</sup> vasodilator,<sup>9</sup> antifolating,<sup>10</sup> antimalarial,<sup>11</sup> analgesic<sup>12</sup> and antifungal<sup>13</sup> properties. Furthermore, the presence of the spiro-carbon atom provides structural rigidity, can induce steric strain and helps the parent molecule to undergo thermal, base- or acid-promoted rearrangements, often resulting in new and unexpected products.<sup>14</sup>

Quiroga et al. reported a triethylamine-catalysed synthesis of pyridopyrimidin-spirocyclohexanotrienes from 6-aminopyrimidines, dimedone and formaldehyde under microwave irradiation but with no diastereoselectivity.<sup>15</sup> Barua and Bhuyan developed a two-step procedure for the synthesis of spiro-substituted pyrido[2,3-*d*]pyrimidines. However, the use of organic solvents and piperidine and diisopropylethylamine (DIPEA) as catalysts reduce its green credentials.<sup>16</sup> In 2009, Jiang et al. developed an elegant procedure for the synthesis of 6-spiro-substituted pyrido[2,3-*d*]pyrimidines from 2,6-diaminopyrimidin-4-one, aldehydes and barbituric acids under microwave irradiation. However, this procedure is compatible only with aryl aldehydes.<sup>17</sup> Herein, we report a new and simple L-proline-catalysed regio- and diastereoselective synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] by one-pot multicomponent domino reaction of 2,6-diaminopyrimidin-4-one, aldehydes and barbituric acids in water with diastereoselectivity from 61:39 to 100:0 under mild reaction conditions (Scheme 1).<sup>18</sup>



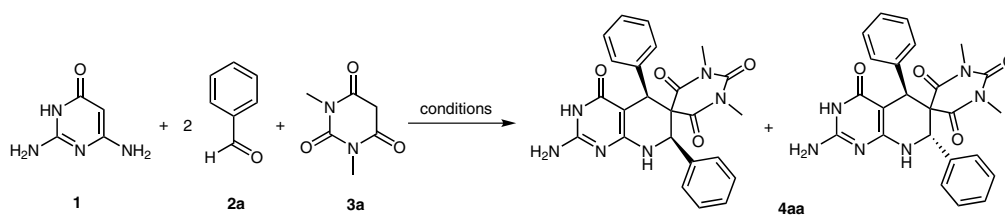
**Scheme 1** Synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines]

The present work is the result of our continuous efforts on the development of new protocols involving greener methodologies for the synthesis of biologically active heterocyclic molecules.<sup>19</sup> L-Proline is the catalyst of choice because it is not only a mild and readily available bifunctional organocatalyst but it also catalyses a range of reactions by its different activation modes such as by enamine and iminium cation formation. Moreover, it has been described as the simplest molecule that can facilitate chemical transformations similar to those catalysed by complex enzymes and has shown remarkable efficiency in promoting diverse synthetic transformations including enantio- and diastereoselective aldol, Mannich, and Michael reactions.<sup>20</sup>

Initially, a mixture of 2,6-diaminopyrimidin-4-one (**1**, 1 mmol), benzaldehyde (**2a**, 2 mmol) and 1,3-dimethylbarbituric acid (**3a**, 1 mmol) was stirred at room temperature and only 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione was isolated along with the unreacted starting materials (Table 1, entry 1). With this observation, we stirred a

mixture of 1,3-dimethylbarbituric acid (**3**, 1 mmol) and benzaldehyde (**2a**, 1 mmol) at room temperature until the generation of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione was indicated by TLC. Next, another 1 mmol of benzaldehyde (**2a**) followed by 1 mmol of 2,6-diaminopyrimidin-4-one (**1**) were added to the reaction mixture and the reaction was heated to reflux, which resulted in the formation of 2-amino-1',3'-dimethyl-5,7-diphenyl-7,8-dihydro-1'*H*,3*H*-spiro[pyrido[2,3-*d*]pyrimidine-6,5'-pyrimidine]-2',4,4',6'(3'*H*,5'*H*)-tetraone (**4aa**) in 70% yield in 3 h, with 84:16 diastereoselectivity (entry 2). However, when the same reaction was carried out using 10 mol% L-proline, the yield of **4aa** increased to 80% and diastereoselectivity increased to 90:10 in 1.5 h (entry 3). Further increasing the catalyst load to 20 mol% led to **4aa** being isolated in 95% yield within 45 min with 97:3 diastereoselectivity (entry 4). No further improvement in yield or diastereoselectivity was observed when the catalyst load was increased to 30 mol% (entry 5). To assess the effect of solvent, when the re-

**Table 1** Optimization of the Reaction<sup>a</sup>



Entry	Catalyst (mol%)	Solvent <sup>b</sup>	Time (min)		Yield (%) <sup>c</sup>	<i>cis/trans</i> <sup>d</sup>
			RT	Reflux		
1	–	H <sub>2</sub> O	720	0	0	–
2	–	H <sub>2</sub> O	30	150	70	84:16
3	L-Proline (10)	H <sub>2</sub> O	20	70	80	90:10
4	L-Proline (20)	H <sub>2</sub> O	15	30	95	97:3
5	L-Proline (30)	H <sub>2</sub> O	15	30	95	97:3
6	L-Proline (20)	EtOH	15	30	80	93:7
7	L-Proline (20)	MeOH	15	30	82	91:9

<sup>a</sup> Reaction scale: **1** (1 mmol), **2a** (2 mmol) and **3a** (1 mmol).

<sup>b</sup> Solvent (5 mL) used.

<sup>c</sup> Isolated yield.

<sup>d</sup> Based on <sup>1</sup>H NMR spectroscopic analysis.

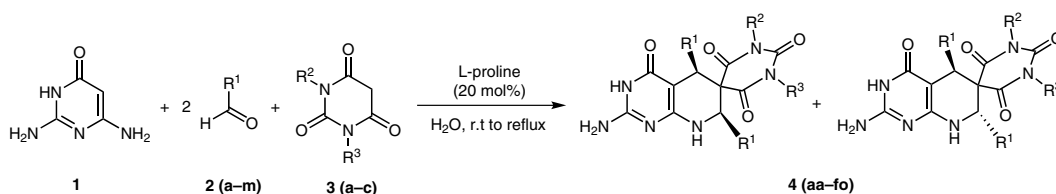
action was executed in EtOH and MeOH the desired product was obtained in 80 and 82% yield, respectively (entries 6 and 7). Thus, the above studies led to the conclusion that 20 mol% L-proline in water under room temperature to reflux are the optimum conditions in terms of yield and diastereoselectivity. It may be noted that simultaneous mixing of **1** (1 mmol), **2a** (2 mmol) and **3a** (1 mmol) using 20 mol% L-proline also yielded the desired product in 95% yield in 45 min under reflux conditions, but the two-step procedure reduces the required reflux time.

Having established the optimised reaction conditions, the scope of the reaction was explored by reacting 2,6-diaminopyrimidin-4-one (**1**) with various aldehydes **2** and barbituric acids **3**; the results are presented in Table 2. Various aromatic aldehydes participated well in the reaction and the target products were obtained in good to excellent yields. The electronic and steric effects from the substituents on the benzene ring have no significant impact on the course of the reaction, as is evident from the fact that benzaldehydes with electron-withdrawing and -donating groups in *ortho*-, *meta*- and *para*-positions reacted effi-

ciently (Table 2). Much to our satisfaction, heteroaromatic aldehydes such as thiophene-2-carboxaldehyde and pyridine-4-carboxaldehyde also reacted efficiently to give their corresponding products **4gg** and **4hh** in 90% and 94% yields, respectively (entries 7 and 8). The generality of the protocol was further expanded when 1-methylbarbituric acid (**3b**) and barbituric acid (**3c**) were reacted with 2,6-diaminopyrimidin-4-one and various aldehydes under the same reaction conditions, and their corresponding products were obtained in high yields (entries 9–15).

Assessment of the <sup>1</sup>H NMR spectra revealed that the reaction is highly diastereoselective and the products **4bb**, **4ee**, **4fk**, **4kl**, **4mn** and **4fo** were obtained in 100:0 diastereoselectivity. A comparison of the diastereoselectivity and product yields of the present methodology with the reported procedures for the synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] is shown in Table 3. Interestingly, the use of L-proline increases the diastereoselectivity and the product yield significantly. However, all products were racemic.

**Table 2** Scope of the Synthesis<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	4	Time (min)		Yield (%) <sup>b</sup>	<i>cis/trans</i> <sup>c</sup>
					RT	Reflux		
1	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4aa</b>	15	30	95	97:3
2	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4bb</b>	10	25	93	100:0
3	2-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4cc</b>	15	30	90	84:16
4	3-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4dd</b>	15	30	91	92:8
5	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4ee</b>	15	25	96	100:0
6	4-MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<b>4ff</b>	10	30	94	92:8
7	2-Thienyl	CH <sub>3</sub>	CH <sub>3</sub>	<b>4gg</b>	15	30	90	61:39
8	4-Pyridyl	CH <sub>3</sub>	CH <sub>3</sub>	<b>4hh</b>	15	30	94	98:2
9	2-ClC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	<b>4ii</b>	15	30	91	71:29
10	3-BrC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	<b>4jj</b>	15	35	94	93:7
11	4-MeOC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	<b>4fk</b>	10	30	91	100:0
12	4-MeC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	<b>4kl</b>	15	25	93	100:0
13	3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	H	<b>4lm</b>	10	25	90	98:2
14	3-MeC <sub>6</sub> H <sub>4</sub>	H	H	<b>4mn</b>	15	30	91	100:0
15	4-MeOC <sub>6</sub> H <sub>4</sub>	H	H	<b>4fo</b>	10	25	93	100:0

<sup>a</sup> Reaction scale: **1** (1 mmol), **2** (2 mmol), **3** (1 mmol).

<sup>b</sup> Isolated yield.

<sup>c</sup> Based on <sup>1</sup>H NMR spectroscopic analysis.

**Table 3** Comparison of Present Methodology with Reported Methodology

Entry	4	Yield (%) <sup>a</sup>		<i>cis/trans</i> <sup>b</sup>	
		This work	Ref. <sup>17</sup>	This work	Ref. <sup>17</sup>
1	4aa	95	85	97:3	94:6
2	4ee	96	83	100:0	80:20
3	4ff	94	88	92:8	86:14
4	4fk	91	88	100:0	96:4
5	4kl	93	82	100:0	96:4
6	4fo	93	89	100:0	93:7
7	4gg	90	No reaction	61:39	–
8	4hh	94	No reaction	98:2	–

<sup>a</sup> Isolated yield.<sup>b</sup> Based on <sup>1</sup>H NMR spectroscopic analysis.

All products synthesised were characterised by <sup>1</sup>H and <sup>13</sup>C NMR, IR spectroscopy, mass spectrometry and elemental analysis. Known compounds were further authenticated by comparison with analytical data from previous reports.

In summary, we have developed a straightforward synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] by L-proline-catalysed one-pot multicomponent domino reaction of 2,6-diaminopyrimidin-4-one, aldehydes and barbituric acids in water. The protocol is highly regio- and diastereoselective and works under mild reaction conditions. The use of water as reaction medium and L-proline as organocatalyst has expanded the scope of aqueous medium organocatalysed reactions. Operational simplicity, high yields, shorter reaction time, wide substrate scope, simple purification process and diastereoselectivity from 61:39 to 100:0 make this protocol highly attractive.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588456>.

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- (18) **General procedure for the synthesis of spiro[pyrido[2,3-*d*]pyrimidin-2-amine-6,5'-pyrimidines] (4aa–o)**: A mixture of aldehyde **2** (1 mmol) and barbituric acid **3** (1 mmol) was stirred at room temperature in the presence of 20 mol% L-proline as catalyst in water (5 mL) until the generation of 5-arylidenebarbituric acid was indicated by TLC. This was then followed by the addition of another 1 mmol of aldehyde **2** and 1 mmol of 2,6-diaminopyrimidin-4-one **1**, then the reaction mixture was heated to reflux for the appropriate time (Table 2). On completion of the reaction, as indicated by TLC, the mixture was cooled and the solid product formed was filtered out and washed with water (3 × 10 mL) to afford pure **4**
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