Synlett C. Li, F. Zhang Letter

L-Proline-Catalyzed Cyclization of 6-Aminopyrimidine-4(3*H*)-ones with Nitroolefins: Synthesis of Polysubstituted 5-Arylpyrrolo[2,3-*d*]pyrimidin-4-ones

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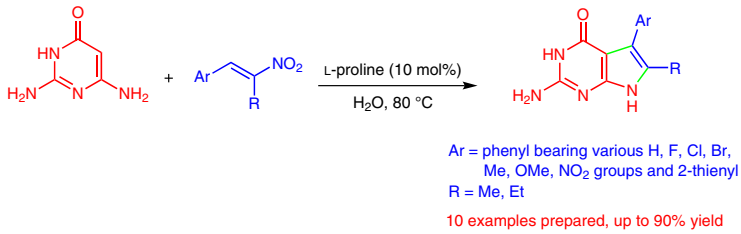

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Abstract A simple and efficient one-pot procedure for the synthesis of new pyrrolo[2,3-*d*]pyrimidine derivatives has been established through an L-proline-catalyzed cyclization of 6-aminopyrimidine-4(3*H*)-one with nitroolefins in water. The reaction at 80 °C in water gives various highly substituted pyrrolo[2,3-*d*]pyrimidines in good to excellent yields. This procedure has the advantages of environmental friendliness, good yields, and convenient operation.

Key words proline, nitroalkenes, organocatalysis, cyclization, pyrrolopyrimidinones, Michael addition

Pyrrolo[2,3-*d*]pyrimidines, as an important class of heterocyclic compounds, have attracted increased attention in both the organic chemistry and pharmaceutical communities, due to the presence of these moieties in numerous naturally occurring products,[1] synthetic drugs,[2] and industrial materials.[3] A survey of the literature revealed the presence of a pyrrolo[2,3-*d*]pyrimidine core in many promising pharmaceuticals that exhibit a broad spectrum of biological activities, such as antiviral,[4] antiinflammatory,[5] antifolate,[6] antitumor,[7] antibacterial,[8] antifungal,[9] or receptor tyrosine kinase-inhibitory activities.[10] Representative examples (Figure 1) include pemetrexed (Pmx; Alimta), a unique antifolate used in the treatment of hematological malignancies and solid tumors (Type I);[11] toyocamycin, a naturally occurring nucleoside antibiotic (Type II);[12] TNP-351, a strong inhibitor of dihydrofolate reductase that has been applied clinically as an anticancer agent (Type III);[13] and PF-06459988, which functions as a third-generation epidermal growth factor receptor inhibitor (Type IV).[14]

In view of their interesting properties, the chemistry of pyrrolopyrimidines has been developed significantly, and considerable efforts have been devoted to developing more

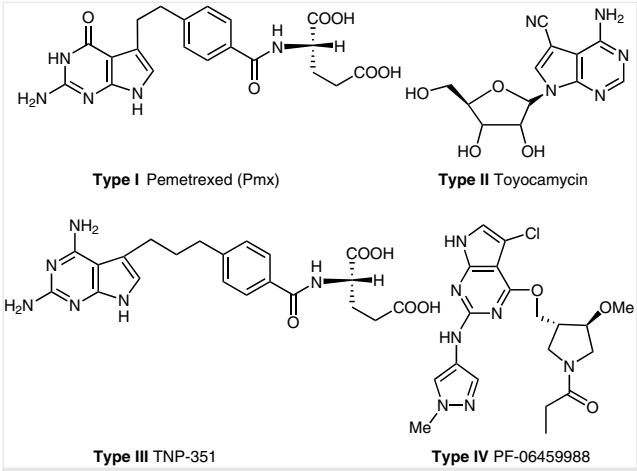


Figure 1 Structures of biologically active pyrrolo[2,3-*d*]pyrimidine derivatives

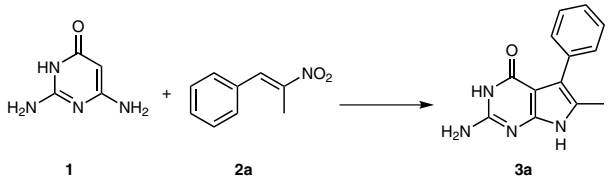
efficient synthetic methods or improving existing synthetic routes to these substances, as well as to the introduction of various substituents onto the core.[15] Among these methods, the Sonogashira reaction, followed by tandem cyclization in a one- or two-pot manner, is the conventional approach to constructing the pyrrolo[2,3-*d*]pyrimidine scaffold.[2b–d,16] Some other strategies have also been developed for the synthesis of these heterocycles. For example, Taylor and Liu reported the synthesis of derivatives of 5-arylpyrrolo[2,3-*d*]pyrimidine by a four-step process in modest yields.[17] Recently, Thakur and co-workers reported the synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidines in a one-pot two-step manner from an aminopyrimidine and nitrostyrenes.[18] Despite these advances, most of these approaches suffer from one or more drawbacks such as the need for a transition-metal catalyst, the use of a strong base or acid, the use of hazardous or expensive reagents, multistep sequences, or the need

for special apparatus, which are not compatible with some biological applications, are uneconomical, or are not eco-friendly. Consequently, there still remains a necessity to develop a new environmentally friendly method to realize the preparation of polysubstituted pyrrolo[2,3-*d*]pyrimidines.

L-Proline, as a versatile organocatalyst, has been effectively used for C–C bond formation in various organic transformations.[19] In a continuation of our efforts to develop new methods for the synthesis of useful heterocyclic blocks from common starting materials,[20] we recently reported the synthesis of tetrahydro-4*H*-indol-4-one derivatives through an L-proline-catalyzed domino approach.[20a] Here, we wish to report a cyclization for the synthesis of new pyrrolo[2,3-*d*]pyrimidine derivatives by using L-proline as a catalyst in water. To the best of our knowledge, this convenient and efficient procedure has not been reported before.

Initially, we examined the reaction of 2,6-diaminopyrimidin-4(3*H*)-one with [(1*E*)-(2-nitroprop-1-en-1-yl)]benzene as a model reaction for optimization of the conditions. As is well known, the selection of an appropriate catalyst is of critical importance for the synthesis of heterocyclic compounds. First, the model substrates were mixed in water in the absence of any catalyst; unfortunately, the desired product was not obtained, even after 24 hours at 80 °C (Table 1, entry 1). However, when L-proline (10 mol%) was added as a catalyst, 2-amino-6-methyl-5-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**3a**) was obtained in 82% yield after two hours (entry 2). Subsequently, various other catalysts (DL-alanine, triethylamine, 4-dimethylaminopyridine, *N*-methylmorpholine, pyridine, and potassium carbonate) were tested for the reaction in water (entries 3–8). However, none of these catalysts showed a better catalytic activity than L-proline under the same experimental conditions. Screening of the amount of catalyst showed that 10 mol% of L-proline was sufficient to push the reaction forward successfully (entries 2, 9 and 10).

Table 1 Optimization of the Conditions for the Model Reaction[a]



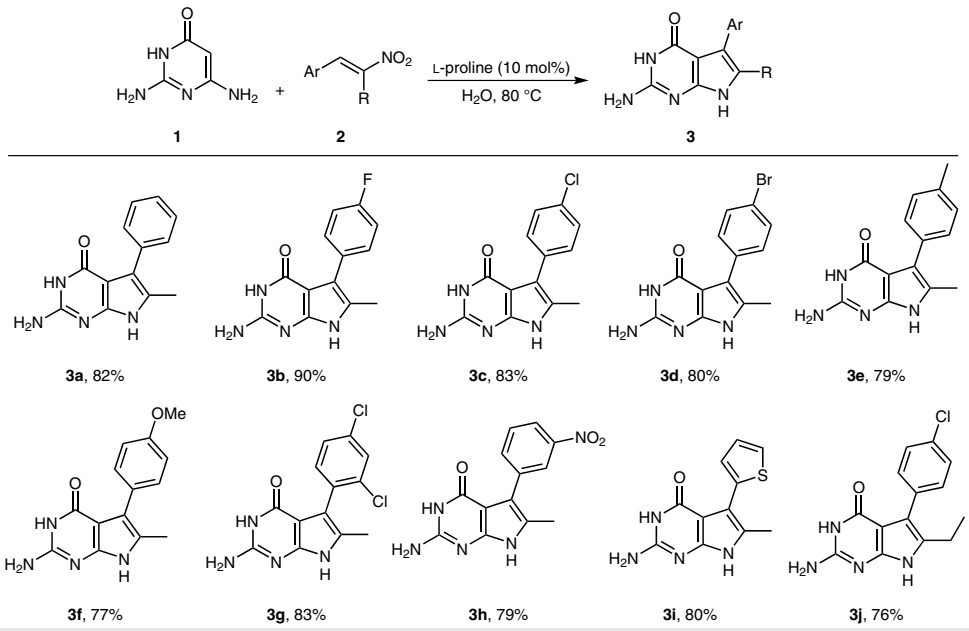
1 **2a** **3a**

Entry	Solvent	Catalyst (mol%)	Temp (°C)	Yield[b] (%)
1[c]	H_2O	–	80	–
2	H_2O	L-proline (10)	80	82
3	H_2O	DL-alanine (10)	80	52
4	H_2O	Et_3N (10)	80	33
5	H_2O	DMAP (10)	80	21
6	H_2O	NMM (10)	80	<10
7	H_2O	pyridine (10)	80	<10
8[c]	H_2O	K_2CO_3 (10)	80	–
9	H_2O	L-proline (20)	80	84
10	H_2O	L-proline (5)	80	56
11	MeOH	L-proline (10)	reflux	62
12	EtOH	L-proline (10)	reflux	71
13	$HO(CH_2)_2OH$	L-proline (10)	80	80
14	chloroform	L-proline (10)	reflux	40
15	THF	L-proline (10)	reflux	33
16	DMF	L-proline (10)	80	41
17	MeCN	L-proline (10)	reflux	37
18	toluene	L-proline (10)	80	17
19[c]	H_2O	L-proline (10)	60	44
20	H_2O	L-proline (10)	100	84

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), solvent (2.5 mL), 2 h.
[b] Isolated yield.
[c] Reaction time: 24 h.

Next, we repeated the model reaction in various solvents (Table 1, entries 11–18), and we found that reactions in protic solvents gave higher yields than did those in non-protic solvents and that the reaction in water gave the highest yield (entry 2). The same model reaction was then carried out at temperatures of 60, 80, and 100 °C for two hours. The yield of product **3a** rose from 44% to 82% when the temperature was increased from 60 to 80 °C (entries 2 and 19), but then almost leveled off when the temperature was increased further to 100 °C (entry 20); 80 °C is therefore a suitable temperature, and a higher temperature is not necessary.

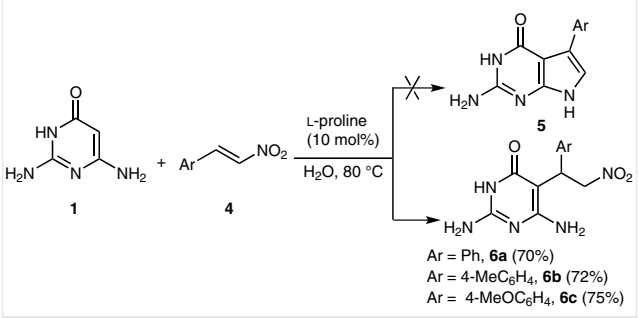
The generality of the protocol was explored by using the optimized conditions (Scheme 1).[21] A range of nitroolefins bearing various substituents, including electron-deficient and electron-rich groups on the aromatic ring, were subjected to the reaction to examine the efficiency and applicability of the method. The reaction was found to be compatible with various nitroolefin substrates with either electron-withdrawing groups (such as halide or nitro) or electron-donating groups (such as methyl or methoxy).[22] We also noted that nitroolefins bearing electron-withdrawing groups gave higher yields than did those bearing electron-donating groups. We attributed the high activities of nitroolefins bearing electron-deficient groups to the low electronic cloud density at their α-carbon atoms. Particularly noteworthy was the fact that the heterocyclic nitroolefin [(1*E*)-2-(2-nitroprop-1-en-1-yl)]thiophene tolerated this procedure and gave the corresponding product in 80% yield. Additionally, the substrate [(1*E*)-1-chloro-4-(2-nitrobut-1-en-1-yl)]benzene gave the corresponding product, 2-



Scheme 1 Synthesis of products **3**. *Reagents and conditions*: **1** (0.5 mmol), **2** (0.5 mmol), L-proline (10 mol%), H_2O (2.5 mL), 80 °C, 2 h.

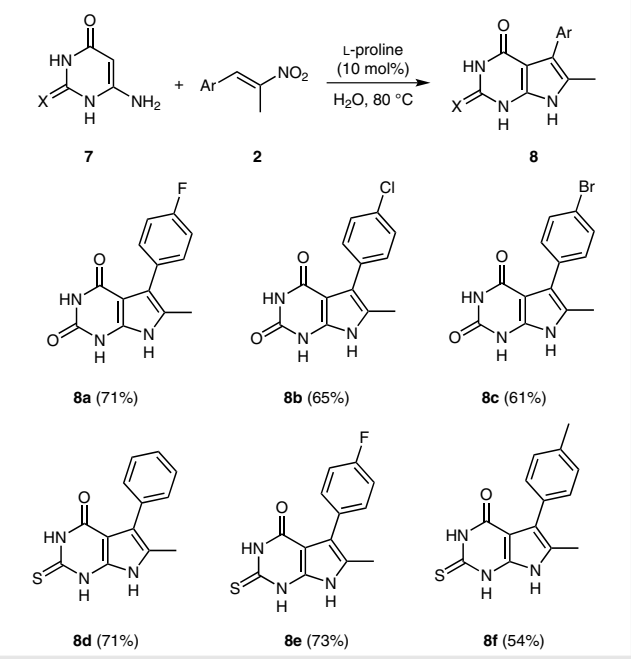
amino-5-(4-chlorophenyl)-6-ethyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**3j**), in 76% yield, which highlighted the wide scope of this condensation.

However, the reaction of optionally substituted [(*E*)-(2-nitrovinyl])benzenes **4a–c** with 2,6-diaminopyrimidin-4(3*H*)-one (**1**) under the same conditions did not give the expected 2-amino-5-aryl-3,7-dihydro-4H-pyrrolo[2,3-*d*]pyrimidin-4-ones **5**; instead, the corresponding 2,6-diamino-5-(2-nitro-1-arylethyl)pyrimidin-4(3*H*)-ones **6a–c** were obtained in 70–75% yield (Scheme 2). The active proton-bearing nitro group probably destabilized the cyclic intermediate, indirectly impeding the elimination of the nitro group.



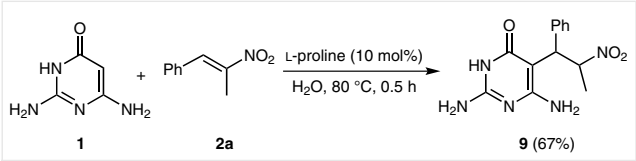
Scheme 2 The synthesis of unexpected 2,6-diamino-5-(1-aryl-2-nitroethyl)pyrimidin-4(3*H*)-ones

With acceptable results in hand, we proceeded to probe the substrate diversity of the reactions of 6-aminopyrimidine-2,4(1*H*,3*H*)-dione (**7a**; X = O) or 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**7b**; X = S) with various nitroolefins **2**. To our delight, the reactions proceeded smoothly and afforded the desired products in good yields (Scheme 3). The reactions of 6-aminopyrimidine-2,4(1*H*,3*H*)-dione (**7a**) with substituted nitroolefins bearing electron-withdrawing groups such as fluoro, chloro, or bromo worked well, and gave the corresponding products **8a–c** in 61–71% yields. 6-Amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**7b**) reacted with a variety of substituted nitroolefins bearing either an electron-deficient group such as fluoro or an electron-rich group such as methyl to give the desired products **8d–f**. The difference in bond strength between C=O and C=S bonds might affect the activity of the pyrimidine substrate. In addition, to further expand the substrate scope, we examined the reaction of [(1*E*)-(2-nitroprop-1-ene-1,3-diyl)]dibenzene with 2,6-diaminopyrimidin-4(3*H*)-one (**1**); unfortunately, no target product was obtained under the optimized conditions, probably as a result of steric hindrance in the nitroolefin substrate.

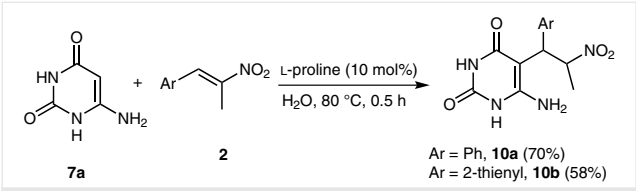


Scheme 3 Expanding the scope of the pyrimidine substrate

Generally, the reactions proceeded rapidly to completion within two hours at 80 °C. In most cases, the desired products were obtained in good yields after workup of the mixture with water and ethanol. However, we also noted that lower reaction temperatures or shorter reaction times could lead to the generation of Michael addition products. Ring-opening product **9** were obtained when the time for the reaction of diamine **1** with nitroolefin **2a** was reduced to 30 minutes (Scheme 4), and the same products, with different yields, were also obtained when the reaction temperature was reduced to 50 °C for two hours. The corresponding reaction of the amino dione **7a** with nitroolefins **2** (R = Ph, 2-thienyl) at 80 °C for 30 minutes similarly gave the corresponding Michael addition products **10a** and **10b** (Scheme 5). Products **9** and **10** can therefore be separately and smoothly obtained in good yields by controlling the reaction process. The structures of all products and intermediates were determined by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.



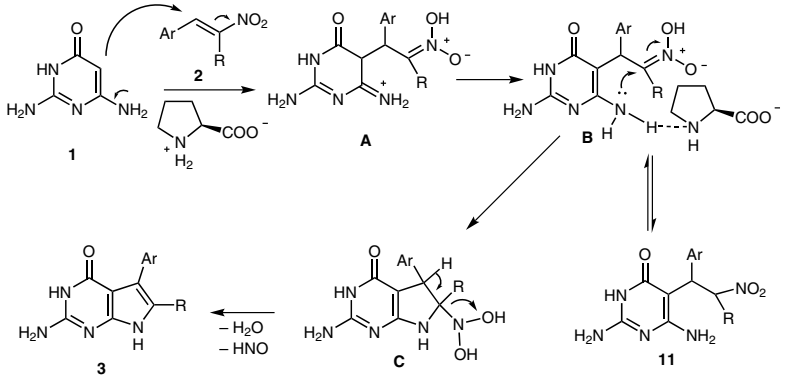
Scheme 4 Control experiment with 2,6-diaminopyrimidin-4(3*H*)-one



Scheme 5 Control experiment with 6-aminopyrimidine-2,4(1*H*,3*H*)-dione

On the basis of the above experimental results and a report in the literature,[23] a mechanism for the reaction is proposed as shown in Scheme 6. 2,6-Diaminopyrimidin-4(3*H*)-one (**1**) first condenses with the nitroolefin **2** to generate intermediate **A**; this reaction is catalyzed by L-proline as an acid catalyst. Subsequently, electron transfer yields the enamine intermediate **B**. This undergoes further transformation into intermediate **11**, which can be separated in a good yield (Schemes 1 and 4). Intramolecular nucleophilic addition of **B** then gives adduct **C**; in this reaction, the amino group is activated by L-proline, which facilitates nucleophilic attack. Finally, aromatization of intermediate **C** occurs with elimination of H_2O and HNO to give the target product **3**.

In summary, we have established novel protocols for rapid access to 2-amino-5-aryl-6-alkyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-ones **3**, 6-methyl-5-aryl-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-diones **8a–c**,



Scheme 6 Proposed mechanism for the formation of pyrrolo[2,3-*d*]pyrimidin-4-ones **3**

and 6-methyl-5-aryl-2-thioxo-1,2,3,7-tetrahydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-ones **8d–f**. The reactions are easy to perform under concise conventional heating conditions. A plausible reaction mechanism for such reaction was proposed and partially confirmed by control experiments. This approach has a broad substrate scope and excellent functional-group tolerance, permitting the rapid construction of highly functionalized products from readily available starting materials. Undoubtedly, this strategy provides a straightforward pathway to construct biologically and pharmacologically interesting target molecules in an effective manner.

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(21) **2-Amino-5-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-ones 3; General Procedure**
A mixture of 2,6-diaminopyrimidin-4(3*H*)-one (**1**, 0.5 mmol), the appropriate nitroolefin **2** (0.5 mmol), and L-proline (10 mol%) in H_2O (2.5 mL) was heated at 80 °C for the appropriate time then cooled to r.t. The mixture was diluted with cold H_2O (30 mL), and the solid was collected by filtration, washed with H_2O and 95% EtOH, dried, and crystallized from 95% EtOH to give the pure product **3**.

(22) **2-Amino-5-(4-methoxyphenyl)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (3f)**
Prepared by following the general procedure from 2,6-diaminopyrimidin-4(3*H*)-one (**1**, 0.5 mmol) and 1-methoxy-4-[(1*E*)-2-nitroprop-1-en-1-yl]benzene (0.5 mmol) as a pale-yellow solid; yield: 104.5 mg (77%); mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.94 (s, 1 H, NH), 10.16 (s, 1 H, NH), 7.33 (d, *J* = 8.0 Hz, 2 H, ArH), 6.88 (d, *J* = 8.4 Hz, 2 H, ArH), 6.00 (br s, 2 H, NH_2), 3.76 (s, 3 H, OMe), 2.17 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 157.4, 152.3, 151.1, 131.3, 127.6, 123.0, 113.2, 98.0, 55.4, 12.1. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_4O_2^+$: 271.1190; found: 271.1194.

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