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Merging catalyst-free synthesis and iodine catalysis: one-pot synthesis of dihydrofuropyrimidines and spirodihydrofuropyrimidine pyrazolones†

Ya-Yun Zheng, Kai-Xiang Feng, Ai-Bao Xia,* Jie Liu, Cheng-Ke Tang, Zhan-Yu Zhou and Dan-Qian Xu*

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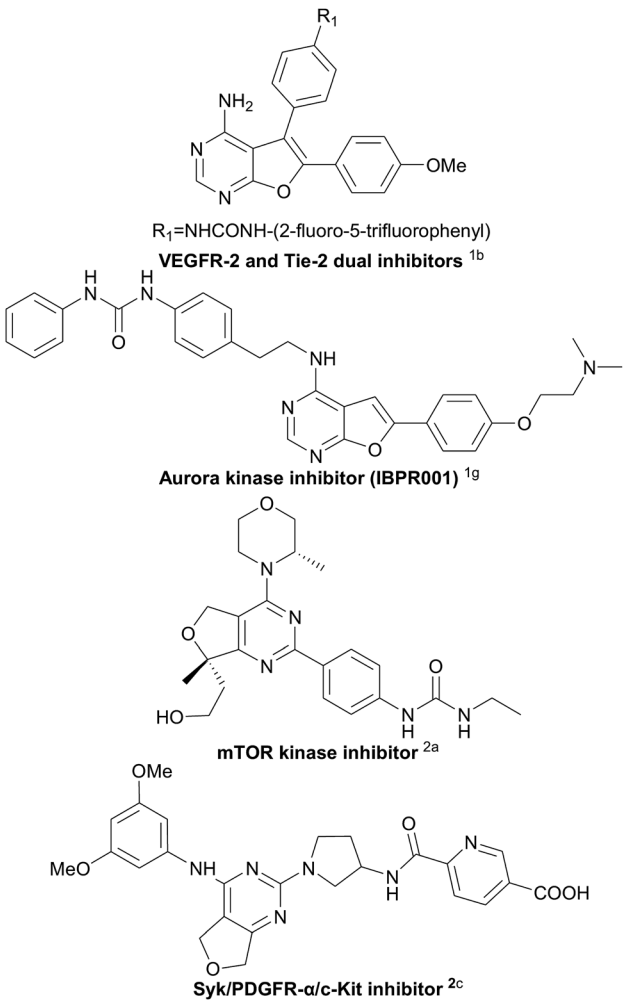
A new and efficient one-pot strategy combining catalyst-free synthesis and iodine catalysis has been developed for the synthesis of dihydrofuropyrimidines and spirodihydrofuropyrimidine pyrazolones. This approach affords products in moderate to high yields (up to 96%) with excellent diastereoselectivities (up to >25 : 1 dr). The reaction is simple to carry out and is metal-free.

Furo fused pyrimidines[1] and dihydrofuro fused pyrimidines,[2] derivatives of the pyrimidine species,[3] are prevalent heteroaromatic core structures found in a broad variety of natural products, pharmaceuticals, and other biologically active molecules (Scheme 1). In particular, dihydrofuropyrimidine derivatives have shown a diverse range of useful biological and pharmacological activities such as anticancer, anti-inflammatory, antiproliferative, and antirheumatic activities. The substituent group on the dihydrofuran moiety significantly influences the biological activity. However, efficient procedures for the synthesis of dihydrofuropyrimidines are not well developed. In 1987, Taylor *et al.* reported intramolecular Diels–Alder reactions of 1,2,4-triazines to synthesize dihydrofuro fused pyrimidines under very high temperature condition (Scheme 2A).[4] Alternatively, dihydrofuropyrimidine derivatives can be prepared in relatively low yields from pre-synthesized 2,4-dichloro-dihydrofuropyrimidines *via* further substitution reactions and coupling reactions (Scheme 2B). However, several steps are required to prepare highly functionalized starting materials with different furan groups.[2a,5] Both of these methods have some well-known drawbacks: (a) harsh reaction conditions and the requirement of multistep synthetic sequences; (b) the use of poisonous or expensive reagents such as $COCl_2$, $POCl_3$, and transition metal Pd; and (c) low yields and limited substrate scope. Therefore, it is highly desirable to find an efficient and general synthetic methodology for the construction of various substituted dihydrofuropyrimidines, from easily accessible raw



Scheme 1 Selected important biologically active heterocycles containing fused pyrimidine moieties.

Catalytic Hydrogenation Research Centre, State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou, 310014, China. E-mail: xiaaibao@zjut.edu.cn; chrc@zjut.edu.cn

† Electronic supplementary information (ESI) available: Experimental procedures, data, and NMR spectra of all compounds. CCDC 1893720 and 1893721. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra01665a

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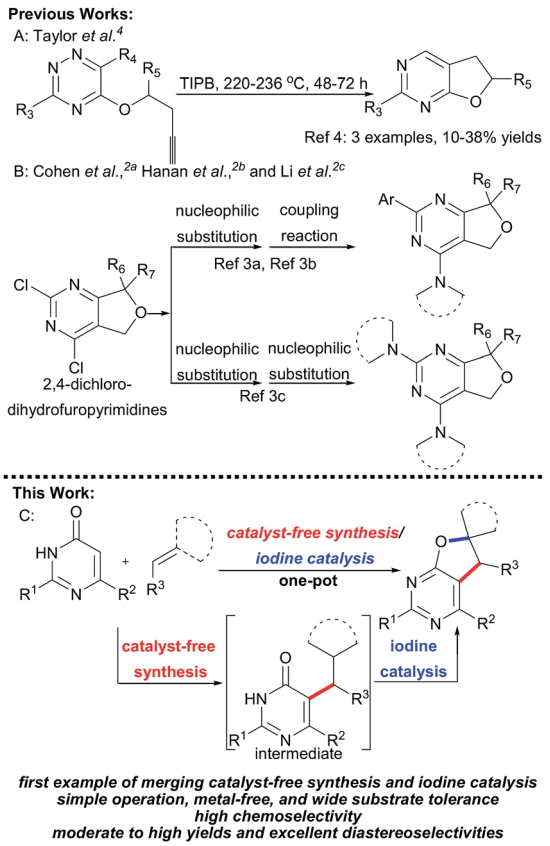


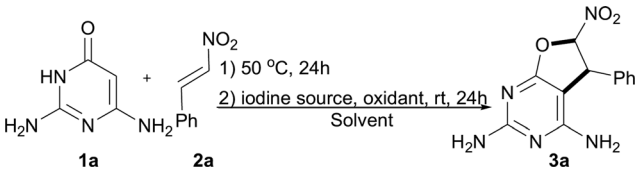
Scheme 2 General methods for the synthesis of dihydrofuropyrimidine derivatives.

materials, under simple and mild reaction conditions, and without the use of potentially toxic transition metals.

In past decades, catalyst-free synthesis has been extensively studied and applied to the construction of complex molecules, as it tends to be inexpensive and environmentally friendly.[6a,b,c] For example, Deb, Baruah, and co-workers described two procedures for the synthesis of 1,3-oxazines[6d] and pyrimidine ring compounds[6f] under the catalyst-free conditions. In 2017, the group of Brahmachari presented a catalyst-free protocol for the construction of functionalized pyridodipyrimidines.[6e] In recent years, iodine catalysis has also emerged as an efficient, metal-free methodology for chemical bond construction which has low toxicity, is environmentally benign, and is readily available.[7] Very recently, we presented a new and efficient catalytic strategy that combined organocatalysis and iodine catalysis for the one-pot sequential catalytic synthesis of spirodihydrobenzofurans.[8] The success of that approach suggested that it might be possible to prepare the biologically important dihydrofuro fused pyrimidines using a new strategy that combines catalyst-free synthesis and iodine catalysis. Herein, we report a facile and efficient methodology for the synthesis of dihydrofuro fused pyrimidine derivatives using 2,6-diaminopyrimidin-4(3*H*)-ones,[9] versatile building blocks in organic synthesis which can be easily prepared,[10] nitroolefins, and unsaturated pyrazolones (Scheme 2C), in which the intermolecular reaction can be easily induced under very mild and catalyst free conditions, and the subsequent step of intramolecular cyclization can then be easily realized *via* iodine catalysis.

The one-pot reaction was initially performed with 2,6-diaminopyrimidin-4(3*H*)-one **1a** and nitroolefin **2a** as model substrates to demonstrate the feasibility of the designed approach. The overall synthesis proceeded smoothly, when the catalyst-free synthesis was conducted at 50 °C and the intramolecular cyclization was performed in the presence of I_2 and *tert*-butyl hydroperoxide in CH_3CN at room temperature, the reaction proceeded smoothly, affording the desired product **3a** in 82% isolated yield (Table 1, entry 1). A representative range of iodine sources were then tested for the second cyclization step (entries 2–6). The yield could be improved to 86% by using potassium iodide (entry 3). The second step was tested further using KI and a range of oxidants: TBPB, DTBP, $NaClO_2$, $K_2S_2O_8$, and even H_2O_2 (entries 7–11). Although the reaction tolerated

Table 1 Screening of reaction conditions[a,g]



Entry	Iodine source	Oxidant	Solvent	Yield[b] (%)
1	I_2	TBHP	CH_3CN	82
2[c]	NaI	TBHP	CH_3CN	84
3[c]	**KI**	**TBHP**	**CH_3CN**	**86**
4[c]	NH_4I	TBHP	CH_3CN	72
5[c]	nBu$_4$NI	TBHP	CH_3CN	80
6[c]	NIS	TBHP	CH_3CN	83
7[c]	KI	TBPB	CH_3CN	54
8[c]	KI	DTBP	CH_3CN	23
9[c]	KI	$NaClO_2$	CH_3CN	28
10[c]	KI	$K_2S_2O_8$	CH_3CN	32
11[c]	KI	H_2O_2	CH_3CN	76
12[c]	KI	TBHP	DMF	Trace
13[c]	KI	TBHP	THF	82
14[c]	KI	TBHP	1,4-Dioxane	Trace
15[c]	KI	TBHP	MeOH	68
16[c]	KI	TBHP	H_2O	63
17[c,d]	KI	TBHP	CH_3CN	55
18[c,e]	KI	TBHP	CH_3CN	73
19[c,f]	KI	TBHP	MeOH	65
20[c,f]	NH_4I	TBHP	MeOH	50
21[c,f]	nBu$_4$NI	TBHP	MeOH	70
22[c,f]	NIS	TBHP	MeOH	52
23[c,f]	**nBu$_4$NI**	**H_2O_2**	**MeOH**	**77**

[a] Unless otherwise stated, all the reactions were conducted in solvent (1 mL) using **1a** (0.1 mmol) and **2a** (0.1 mmol) with stirring for 24 h at 50 °C, this was followed by the addition of iodine source (0.01 mmol) and oxidant (0.2 mmol), and the solution was then stirred for 24 h at room temperature. [b] Isolated yield. [c] The reaction was conducted in the presence of 20 mol% iodine source. [d] First step was conducted at 40 °C for 24 h. [e] First step was conducted at 60 °C for 24 h. [f] First step was conducted at room temperature for 24 h. [g] The dr value is >25 : 1 for all the isolated products.

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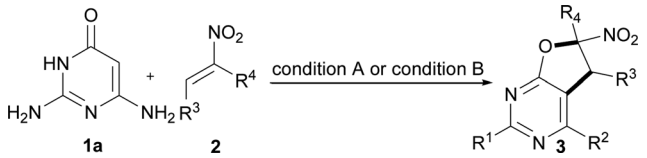
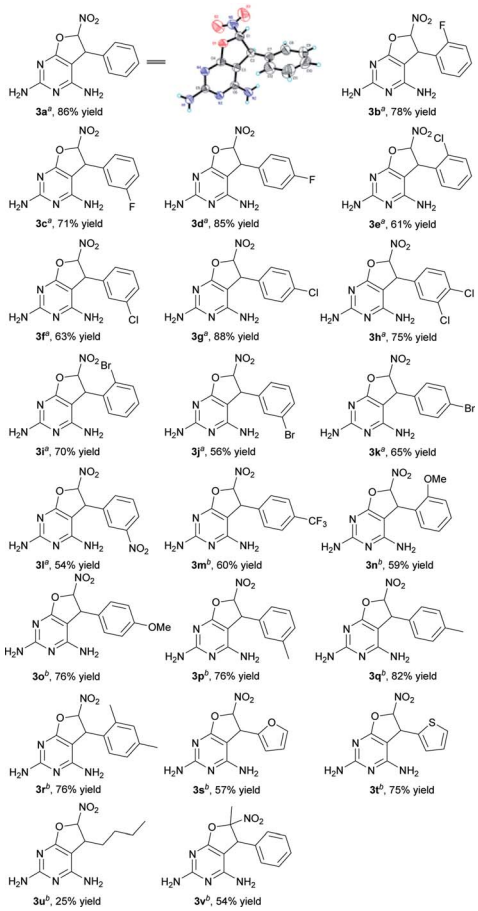
all of these oxidants, none produced as high a yield with KI as TBHP had. This combination was then examined in other solvents (entries 3 and 12–16) and it was found that CH_3CN was best. With these optimal conditions in hand, further investigation was performed to study the influence of the reaction temperature on the catalyst-free synthesis step (entries 17–18). When the reaction was conducted at 40 or 60 °C, the product **3a** was obtained at 55% and 73% yields, respectively. Interestingly, at room temperature, the first catalyst-free synthesis step went well in MeOH to give the final product **3a** in 65% yield (entry 19). Further screening of the reaction conditions (entries 20–23) showed that the combination of TBAI and H_2O_2 in the second step, at room temperature, afforded product **3a** in 77% yield (entry 23).

With the optimized conditions in hand, the substrate scope was then investigated (Table 2).[11] The reaction was found to be compatible with nitroolefins bearing both electron-withdrawing and electron-donating groups. Substrates with electron-withdrawing substituent groups, such as F, Cl, Br, NO_2, or CF_3 on the phenyl ring, afforded moderate to high yields, ranging from 54% to 88% (**3b–m**). It was worth noting that, at room temperature, nitroalkenes bearing electron-rich motifs such as MeO, or Me on the phenyl core, heterocyclic nitroolefins, an aliphatic nitroolefin and α-methyl-substituted nitroolefin all tolerated this transformation, producing the desired dihydrofuropyrimidines in 25% to 82% yields (**3n–v**). For example, by using heterocyclic nitroolefins, products **3s** and **3t** were obtained in 57% and 75% yields, respectively. Aliphatic nitroolefin bearing a butyl group provided **3u** in 25% yield. Furthermore, the α-methyl-substituted nitroolefin was also able to participate in this transformation to afford product **3v** with 54% yield.

Having successfully synthesized an array of dihydrofuropyrimidines, attention was next turned toward the synthesis of biologically interesting spirodihydrofuropyrimidines. In the

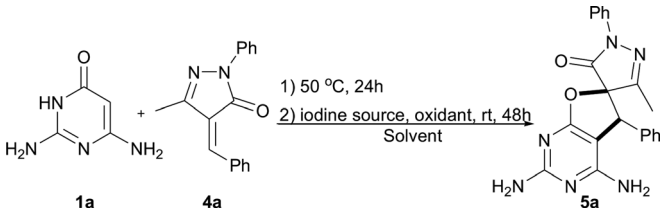
Table 2 Substrate scope for nitroolefins[c,d]





[a] Condition A: the reactions were conducted in CH_3CN (1 mL) using **1a** (0.1 mmol) and **2a** (0.1 mmol) with stirring for 24 h at 50 °C. This was followed by the addition of KI (0.02 mmol) and TBHP (0.2 mmol), and the solution was then stirred for 24 h at room temperature. [b] Condition B: the reactions were conducted in MeOH (1 mL) using **1a** (0.1 mmol) and **2a** (0.1 mmol) with stirring for 24 h at room temperature. This was followed by the addition of nBu$_4$NI (0.02 mmol) and H_2O_2 (0.2 mmol), and the solution was then stirred for 24 h at room temperature. [c] Isolated yield. [d] The dr value is >25 : 1 for all the products.

Table 3 Screening of reaction conditions[a,f]



Entry	Iodine source	Oxidant	Solvent	Yield[b] (%)
1	KI	O_2	CH_3CN	4
2	KI	O_2	1,4-Dioxane	91
3	KI	Open air	1,4-Dioxane	90
4	TBAI	Open air	1,4-Dioxane	85
5[c]	**I_2**	**Open air**	**1,4-Dioxane**	**96**
6	NIS	Open air	1,4-Dioxane	78
7[c]	I_2	Open air	THF	45
8[c]	I_2	Open air	Isopropyl ether	4
9[c]	I_2	Open air	EtOAc	Trace
10[c]	I_2	Open air	CH_3CN	66
11[c]	I_2	Open air	MeOH	Trace
12[c]	I_2	Open air	H_2O	22
13[c,d]	I_2	Open air	1,4-Dioxane	80
14[c,e]	I_2	Open air	1,4-Dioxane	90

[a] Unless otherwise stated, all the reactions were conducted in solvent (1 mL) using **1a** (0.12 mmol) and **4a** (0.1 mmol) with stirring for 24 h at 50 °C. This was followed by the addition of iodine source (0.02 mmol) and oxidant (O_2 balloon), and the solution was then stirred for 48 h at room temperature. [b] Isolated yield. [c] The reaction was conducted in the presence of 10 mol% iodine source. [d] First step was conducted at 40 °C for 24 h. [e] First step was conducted at 60 °C for 24 h. [f] The dr value is >25 : 1 for all the isolated products.

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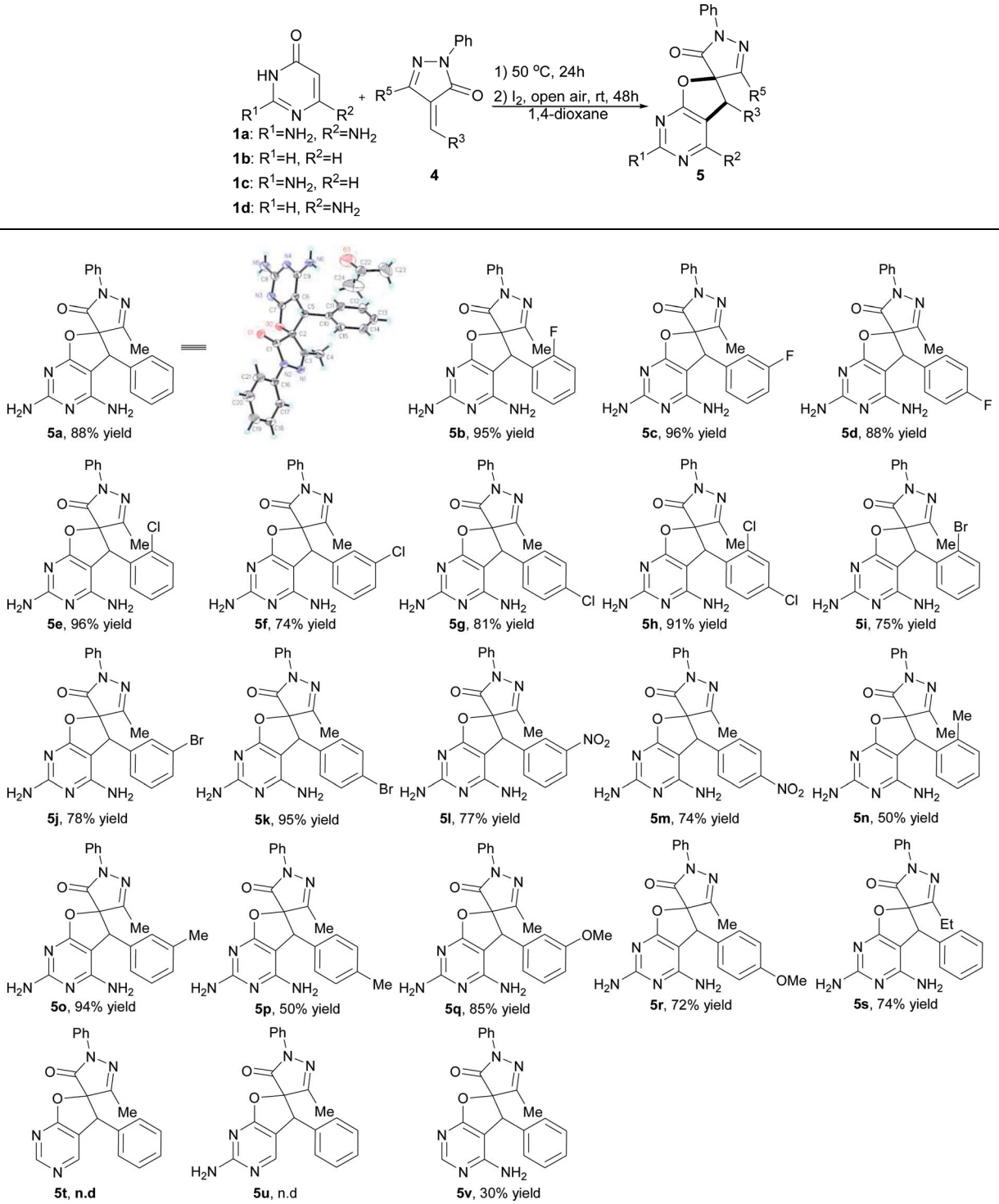
Table 4 Substrate scope of the spirodihydrofuropyrimidine formation reaction[a]



[a] All the reactions were conducted in 1,4-dioxane (1 mL) using **1** (0.12 mmol) and **4** (0.1 mmol) with stirring for 24 h at 50 °C. This was followed by the addition of I_2 (0.01 mmol) under open air condition, and the solution was then stirred for 48 h at room temperature. Stated yields are isolated yields. The dr value is >25 : 1 for all the products.

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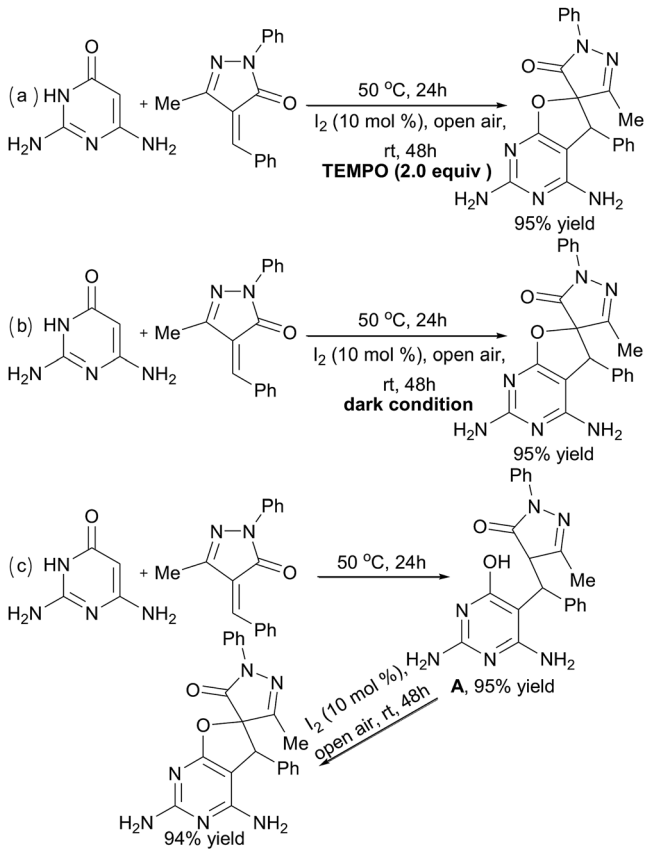
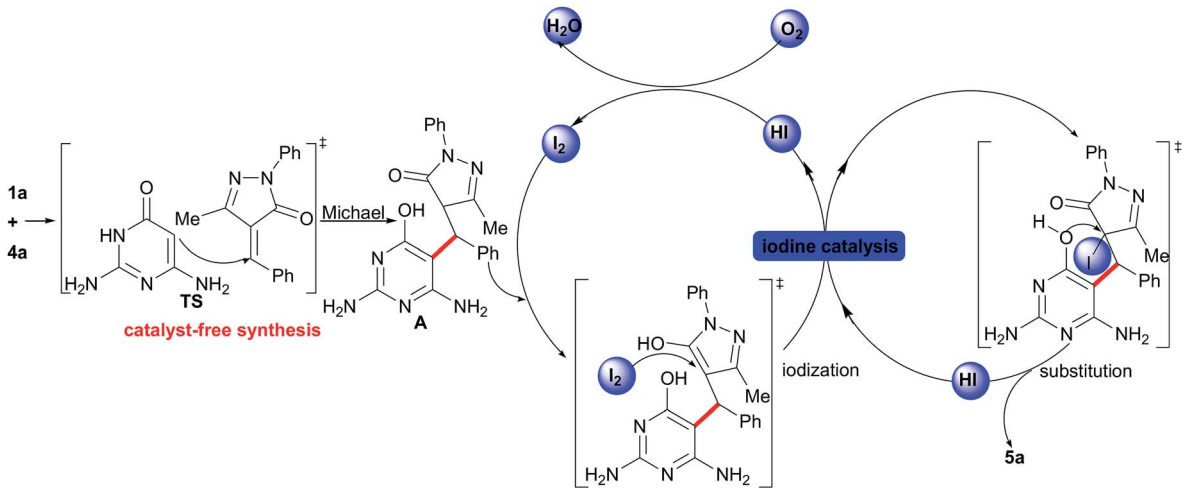


Scheme 3 Mechanistic studies.

previous study, it was discovered that 2,6-diaminopyrimidin-4(3*H*)-one **1a** could react with unsaturated pyrazolone **4a** to form a spirodihydrofuropyrimidine **5a** in 4–91% yields under oxygen atmosphere (Table 3, entries 1 and 2). These results suggested a unique opportunity to develop an one-pot approach for the synthesis of spirodihydrofuropyrimidines in an open air atmosphere. Then iodine sources and solvents were screened with these starting materials (**1a** and **4a**) to optimize the reaction outcome under open air conditions (entries 3–12). The best result was obtained (entry 5, 96% yield) when I_2 was utilized as iodine source and 1,4-dioxane was used as the solvent. Next, the influence of temperature on the reaction outcome was studied. The desired product **5a** was produced in 80% and 90% yields when the reaction mixture was heated at 40 and 60 °C, respectively (entries 13 and 14).

Next, the scope of the spirodihydrofuropyrimidine formation reaction was explored with pyrimidin-4(3*H*)-ones **1** and a wide variety of unsaturated pyrazolones **4** (Table 4).[11] Initially, a number of unsaturated pyrazolones **5** were subjected to the reaction under optimized conditions. In general, a variety of unsaturated pyrazolones bearing both electron-withdrawing (F, Cl, Br, and NO_2) and electron-donating (Me and MeO) groups at the phenyl ring were found to be suitable for the reaction, providing the corresponding spirodihydrofuropyrimidines **5a**–**5r** in moderate to excellent yields (50–96%). The reaction of unsaturated pyrazolone containing an ethyl group substitution on the pyrazolone ring proceeded smoothly to afford the desired product **5s** in 74% yield. Subsequently, to establish the generality of the one-pot reaction, some other amino substituted pyrimidin-4(3*H*)-ones were also employed under the optimized reaction conditions. When pyrimidin-4(3*H*)-one **1b** and **1c** were introduced as partners with unsaturated pyrazolone **4a**, respectively, the desired products **5t** and **5u** were not formed, because the first step of catalyst-free synthesis did not take place. Substrate **1d** reacted well and furnished the spirodihydrofuropyrimidine **5v** in 30% yield.

To understand the mechanism of the reaction, some control experiments were performed under modified conditions in 1,4-dioxane (Scheme 3). High yields could still be obtained in the presence of radical scavenger (TEMPO) (Scheme 3a) or under dark conditions for the second I_2-catalyzed step (Scheme 3b). Thus, a radical mechanism could be excluded for this kind of transformation. Next, when the product of the first catalyst-free synthesis step, intermediate **A**, was separated and used for the



Scheme 4 A proposed mechanism for the one-pot reaction.

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I_2-catalyzed step under the standard conditions, compound **5a** was obtained in 89% yield (Scheme 3c).

Then, based on the aforementioned studies,[8] a presumptive mechanism for the synthesis of dihydrofuropyrimidines from 2,6-diaminopyrimidin-4(3*H*)-ones and unsaturated pyrazolones is proposed (Scheme 4). The initial step should be a catalyst-free Michael addition of **1a** to **4a**, which generates an intermediate **A** *via* a transition state (**TS**). Then, this intermediate **A** can be transformed into **5a** through the I_2-catalyzed cyclization (*via* the iodization reaction and then the nucleophilic substitution). Finally, the HI reacts with O_2 to give I_2 for the next cycle.

Conclusions

In summary, a novel strategy that combines catalyst-free synthesis and iodine catalysis in the presence of oxidant was developed for the one-pot synthesis of dihydrofuropyrimidines and spirodihydrofuropyrimidine pyrazolones from 2,6-diaminopyrimidin-4(3*H*)-ones, nitroolefins, and unsaturated pyrazolones. Dihydrofuro fused pyrimidine derivatives were synthesized in moderate to good yields with excellent diastereoselectivities using TBHP, or H_2O_2 as the oxidants. Spirodihydrofuropyrimidine pyrazolones were produced in high to excellent yields with good functional group tolerance and excellent diastereoselectivities under open air conditions (molecular oxygen as the oxidant). This reaction features simple operation and is metal-free. Further studies on the applications of this methodology to organic synthesis are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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