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Direct Access to Pyrimidines through Organocatalytic Inverse-Electron-Demand Diels-Alder Reaction of Ketones with 1,3,5-Triazine

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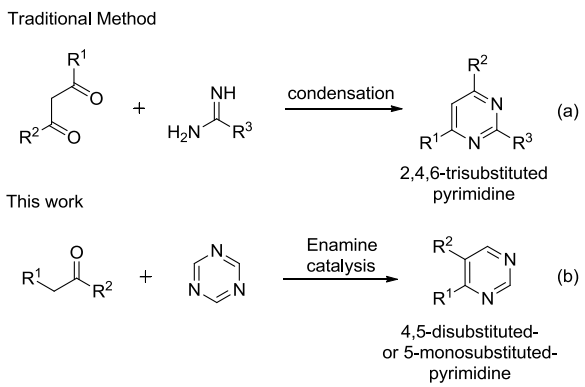
An organocatalytic inverse-electron-demand Diels-Alder reaction of ketones with 1,3,5-triazine through enamine catalysis has been developed. This method could furnish 4,5-disubstituted pyrimidines in good yields and high levels of regioselectivities.

Pyrimidines are ubiquitous heterocyclic moieties present in natural products, drugs and functional materials.[1] A number of pyrimidines exhibit biologically important activities.[2] As shown in Figure 1, sulfadiazine is a sulfonamide antibiotic that contains a 5-aminopyrimidine.[3] Trimethoprim is a bacteriostatic antibiotic known as dihydrofolate reductase inhibitor, mainly used in the prevention and treatment of urinary tract infections.[4] Bosentan is a drug for treating cardiovascular pathology.[5]

Although a number of approaches for the preparation of pyrimidine frameworks have been developed,[6-7] a general and highly selective method for the synthesis of 4,5-disubstituted pyrimidine skeleton has rarely been investigated. One of the most efficient strategies for making such a structure is mainly focused on the basis of N−C−N condensations. For examples, condensation of an amidine with a 1,3-diketone or derivative is one of major methods for the direct preparation of the six-membered-ring pyrimidine (Scheme 1a).[8] Notably, easily preparation of the prerequisite diketones or dicarbonyl derivatives makes this a more attractive strategy for synthesis of substituted pyrimidines. Condensation of an amidine with a nitrile derivative, a common N-C source, is another versatile approach. Despite these advances, due to the significance of pyrimidines in drug discovery, preparations of diversely substituted pyrimidines are still in high demand.[9] Therefore, developing new efficient method for the constructuion of various substituted pyrimidines would be of high interest.



Scheme 1. Strategies in preparation of pyrimidines.

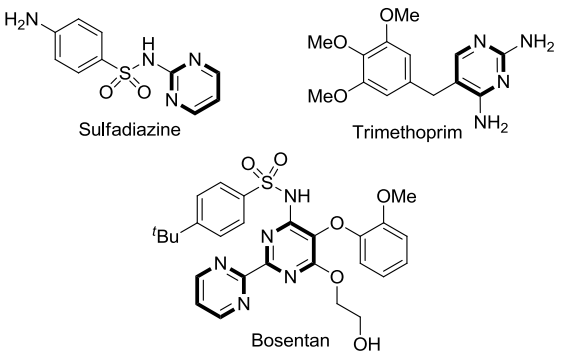


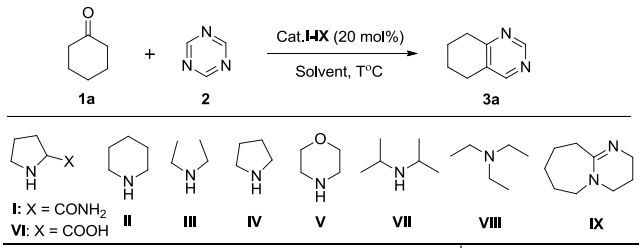
Fig 1: Examples of important pyrimidines.

In 1975, Neunhoeffer and Bachmann demonstrated that 1,3,5-triazine could undergo a rapidly regiospecific cycloaddition reaction with ynamines, followed with a subsequent loss of hydrogen cyanide, to efficiently form pyrimidines.[10] In 1982, the Boger group reported a regiospecific pyrimidine synthesis via a thermal cycloaddition of 1,3,5-triazine with enamines.[11] Surprisingly, to the best of our knowledge, such a catalytic example of 1,3,5-triazine reacted with in situ generated enamines to assemble pyrimidines has not yet been reported. As a part of our continuing interests in this area,[12] especially in expanding enamine chemistry[13] to generate heterocycles, herein, we report our new progress regarding an enamine-catalyzed inverse-electron-demand Diels-Alder of ketones with 1,3,5-triazine, which provided an efficient and complementary route for pyrimidine synthesis (Scheme 1b).

Initial experiments were conducted by using cyclohexanone **1a** and 1,3,5-triazine **2** in the presence of 10 mol% loading of amine catalysts, such as secondary amines (**I-VII**) and tertiary amines (**VIII** and **IX**). Among the catalysts tested (Table 1), we found that secondary amines are generally more effective than tertiary amines (Table 1-9). Tertiary amines exhibited low catalytic activities (entries 8 and 9, <5% and 18%, respectively). Pleasingly, secondary amine prolinamide **I** showed higher reactivity than other catalysts (entry 1, 81%). Surprisingly, the similar derivative proline **VI** only provided a moderate chemical yield (entry 6, 28%). Finally, prolinamide **I** was cidentified as the most effective catalyst. Further optimization of other reaction parameters revealed that solvent was another crucial factor. When reaction carried out in DMSO, reactivity was positively influenced, leading to the desired product **3a** in 81% yield. Other solvents, such as toluene, MeCN, $CHCl_3$, THF, MeOH, DMA, and DMF, caused a significant decreas in chemical yields (Table

1, 18-65%, entries 10-16). Lowering the reaction temperature to 60 °C resulted in a poor chemical yield (entry 17, 41%, 32 h). Changing the catalyst loading of **I** from 20 mol% to 10 mol% caused a decrease in chemical yield (Table 1, entry 18, 71%). Notably, addition of 10 mol% TEA further promoted the reaction (entry 19, 91%). Finally, the best combination was achieved when the reaction was performed in the presence of 10 mol% of prolinamide **I** as catalyst and 10 mol% of TEA as additive.

Table 1: Optimization of the reaction conditions.[a]

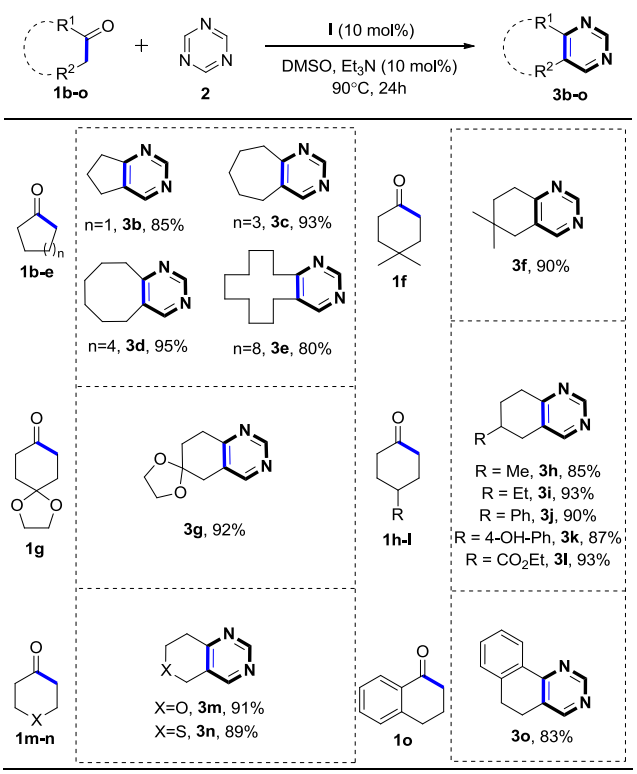


Entry	Cat.	Solvent	Yield/%[b]	Entry
1	**I**	DMSO	81	1
2	**II**	DMSO	54	2
3	**III**	DMSO	36	3
4	**IV**	DMSO	61	4
5	**V**	DMSO	32	5
6	**VI**	DMSO	28	6
7	**VII**	DMSO	24	7
8	**VIII**	DMSO	<5	8
9	**IX**	DMSO	18	9
10	**I**	DMF	65	10
11	**I**	DMA	53	11
12	**I**	Toluene	41	12
13	**I**	MeOH	35	13
14	**I**	THF	62	14
15	**I**	CH_3CN	42	15
16	**I**	$CHCl_3$	43	16
17[c]	**I**	DMSO	41	17[c]
18[d]	**I**	DMSO	71	18[d]
19[e]	**I**	**DMSO**	**91**	**19**[e]
20[f]	**I**	DMSO	63	20[f]

[a] Reaction conditions: A mixture of **1a** (0.20 mmol), **2** (0.10 mmol) and catalyst (20 mol%) in the solvent (0.25 mL) was stirred at 90 °C for 24h. [b] Isolated yield. [c] The reaction was conducted at 60 °C for 32h. [d] 10 mol% catalyst **I** used. [e] 10 mol% catalyst **I** and 10 mol% Et_3N as additive. [f] 10 mol% catalyst **I** and 10 mol% AcOH as additive.

With the optimized reaction conditions in hand, we then investigated a variety of ketones **1** with **2**. The results are summarized in Table 2. Interestingly, among the various examined ketones, cyclic ketones (e.g. five-, six-, seven-, eight- and twelve-membered rings), all gave high to excellent yields under standard conditions (Table 2, **3a-3p**, 80-95%). The best yield was obtained with cyclooctanone, which afforded the corresponding pyrimidine **3d** in 95% isolated yield (Table 2, **3d**). It is worth noting that phenyl ring fused cyclohexanone **1o** also worked with 1,3,5-triazine **2** and afforded the corresponding product **3o** in 83%. To further indicate the generality and potential of our approach, we turned our attention to examine other types of ketones (*e.g.* acylic ketones). Acetophenone **4a** was employed to react with triazine 2 in the presence of catalyst prolinamide **I**. However, only 54% yield was achieved after 72h. In order to improve reaction efficiency, a further reaction optimization was conducted (see Supporting Information). Finally, amine **V** was found to be the most efficient catalyst for this type of ketones (Table 2, 87%, 72h). As indicated in Table 2, aryl methyl ketones **4b-i** gave good to excellent yields (**5b-i**, 84-92%). Pleasingly, heteroaryl methyl ketones **4j-l** also afforded the corresponding pyrimidine products in high yields (**5j-l**). Propiophenones and butanophenone were also well tolerated (**5n-p**). Other alkyl ketones (e.g. symmetric and dissymmetric alkyl ketones) were also investigated and the desired products was obtained in moderate chemical yields (**5q** and **5r**, 56% and 62%, respectively). Notably, all above reactions provided excellent levels of regioselectivity. This phenomenon can be explained by the Diels-alder reaction occurring with most stabilized enamine.

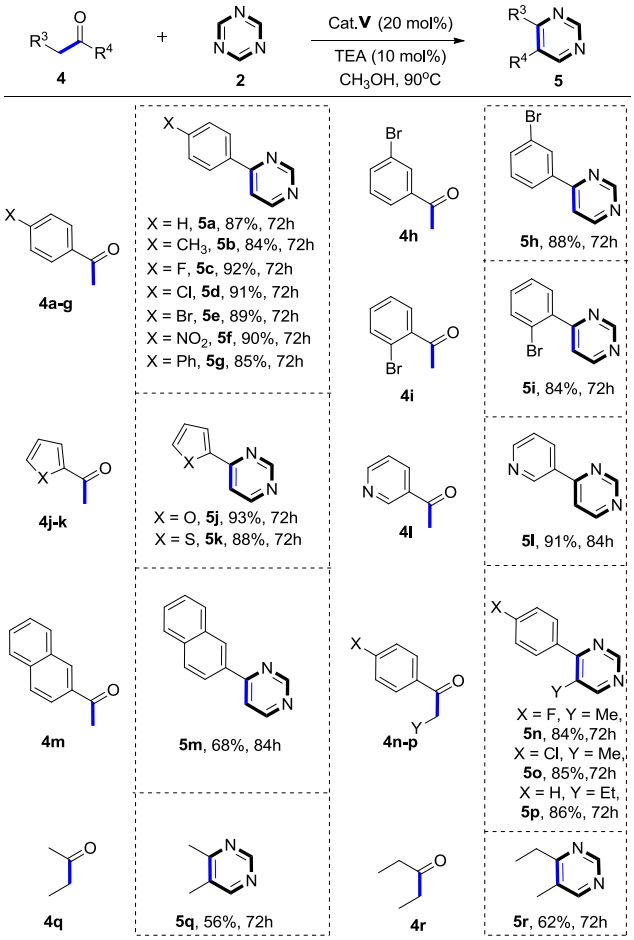
Table 2: Scope of cyclic ketones.[a]



[a] Conditions see Table 1.

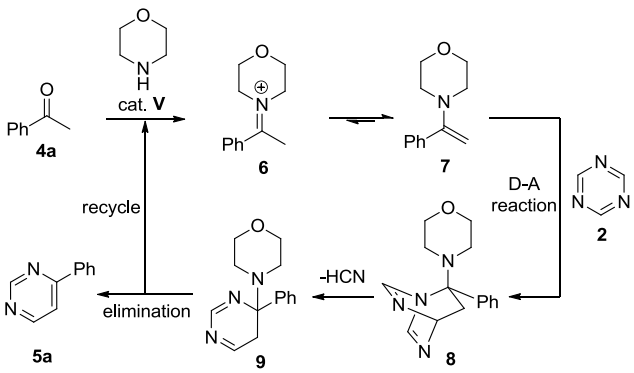
Our postulated reaction pathway is summarized in Scheme 2. While the reaction mechanism is unclear at this stage, it is still believed that the sequence is triggered by the generation of iminium **6** via the condensation of **4a** and catalyst **V**. Iminium **6** rapidly converts to intermediate enamine **7** via a tautomerization. Enamine **7** continuously reacts with 1,3,5-triazine **2** via an inverse-electron-demand Diels-Alder reaction to access the intermediate **8**. Notably, this cycloaddition process demonstrates a high regioselectivity, which leading to directly introduce a diverse set of substituents to pyrimidine scaffold. Intermediate **8** then transfers to intermediate **9** after an elimination of HCN. Last, a liberation of catalyst **V** leads to the formation of final product **5a**.

Table 3: Scope of acyclic ketones.[a]



[a] Reaction conditions: A mixture of **4** (0.20 mmol), **2** (0.10 mmol) and catalyst **V** (20 mol%), TEA (10 mol%) in MeOH (0.50 mL) was stirred at 90 °C for 72h.

Scheme 2. Proposed mechanism.



In summary, an organocatalytic inverse-electron-demand Diels-Alder reaction between various ketones and 1,3,5-triazine has been developed. The reaction is catalyzed by second amines to generate 4,5-disubstituted- or 5-monosubstituted pyrimidines with high levels of regioselectivity. It is noteworthy that this Diels-Alder reaction proceeds efficiently with a simple and inexpensive amine catalyst. Considering the large variety and ready availability of the starting materials and the operational simplicity, a convenient, practical and highly modular pyrimidine synthesis has been developed. We believe that this work will arouse more research interest in organocatalytic synthesis of other biologically active heterocycles. Such studies are actively under way in this laboratory, and more results will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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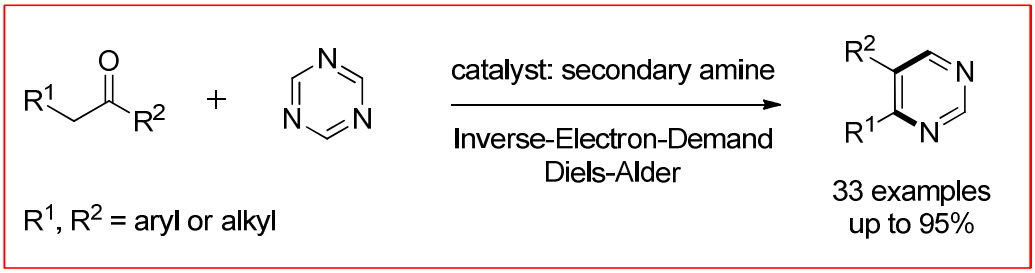

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