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Three-component cascade reaction synthesis of polycyclic 1,4-dihydropyridine derivatives in water

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ABSTRACT

An efficient and straightforward synthesis of polycyclic 1,4-dihydropyridine derivatives has been developed by reacting heterocyclic ketene aminals (HKAs) with 1,3-cyclohexanedione derivatives and a number of substituted salicylaldehyde, respectively, via three-component cascade reactions in water. This strategy provides an efficient and environmentally friendly approach for easy access to various new fused polycyclic 1,4-dihydropyridine derivatives without the need of organic solvents in moderate to good yields.

1. Introduction

Polycyclic 1,4-dihydropyridines are of importance in discovering new bioactive compounds because they bear 1,4-dihydropyridines, a class of building blocks of a variety of biological agents, which could treat Alzheimer's disease (Fig. 1, Tacripyrimedone),[1] open potassium channels (Fig. 1, A-278637 and ZM244085),[2] as well as show anti-tumor (Fig. 1, **1**),[3] anti-diarrhea (Fig. 1, **2**),[4] and antimicrobial properties (Fig. 1, **3**),[5] among others.[6] To synthesize these compounds, nucleophilic addition of pyridinium species and Hantzsch synthesis by condensation of three different components in one pot are two of the most well-known methods.[7,8] While a lot of research efforts have continuously been made, the synthesis of new and diverse polycyclic 1,4-dihydropyridines derivatives with high atom economy and ease of preparation is still needed for drug discovery and research.

The employment of one pot multicomponent reactions (MCRs) and cascade reactions are of interest due to the demand of the development of efficient chemical processes.[9] Compared with the conventional organic reactions, MCRs provide the advantages of simplicity, synthetic efficiency, synthetic convergence, and atom economy, while cascade reactions, as a process, in which several bonds are formed in sequence without isolating intermediates, changing conditions or adding reagents, require minimum human intervention, and offer the ease of reaction scale-up and industrial production.[8d,10,11]

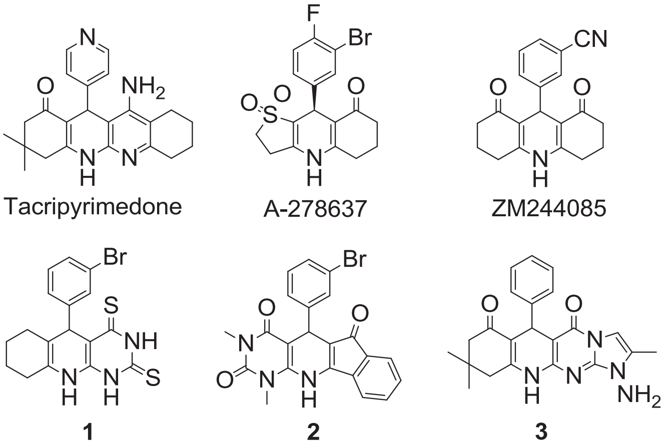

Fig. 1. Biologically active polycyclic 1,4-dihydropyridine derivatives.

Recently, we combined these green processes and developed effective cascade multicomponent reactions in aqueous systems or

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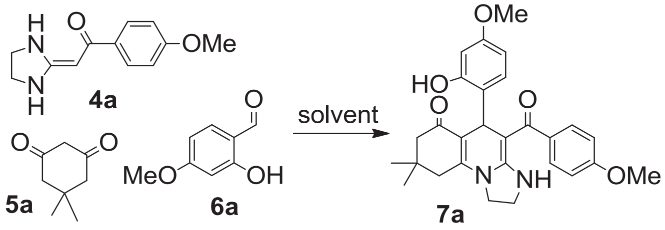
solvent free systems, and synthesized a series of fused heterocyclic compounds using HKAs. HKAs are frequently found in a large number of biologically active pharmacophores such as antianxiety, anticancer, and antituberculosis agents.[12–17] Thus they have been utilized for the synthesis of a wide variety of functional heterocyclic and fused heterocyclic compounds.[18,19] We noticed that 1,4-dihydropyridine derivatives bearing another nitrogen atom on the second position, which have shown important biological activity in a number of compounds such as Tacripyrimedone, **1**, **2**, and **3** in Fig. 1, could be afforded directly using HKAs as the nitrogen sources. We herein describe a novel synthesis method for fused polycyclic 1,4-dihydropyridines derivatives by reacting HKA **4** with 1,3-cyclohexanedione derivatives **5** and various substituted salicylaldehyde **6** via three-component cascade reactions in water. This process is operationally simple and functional groups tolerant. Meanwhile, using non-toxic and almost zero-cost water as the reaction medium renders the synthesis more environmentally benign and sustainable.[20]

2. Result and discussion

In the initial experiment, HKAs **4a**, 5,5-dimethyl-1,3-cyclohexanedione **5a**, and salicylaldehyde **6a** were chosen as the model substrates to optimize the reaction conditions. Specifically, the solvent, catalyst, and temperature were screened as shown in Table 1. First, the model reaction was performed in various solvents including toluene, 1,4-dioxane, THF, CH_3CN, CH_2Cl_2, DMF, DMSO, EtOH, and H_2O, respectively (Table 1, entries 1–9). H_2O proved to be the best solvent, with which the yield of **7a** reached 90% (Table 1, entry 9). Next, we studied the catalytic effect of adding acid or base to the reaction and found that both the acid (Table 1, entries 10 and 11) and base (Table 1, entries 12–14) decreased the yields. Finally, the model reaction was performed at three temperatures different from the reflux temperature of H_2O (ambient temperature, 45 °C and 60 °C) and it was demonstrated that lower temperatures decreased the yield of **7a** (Table 1, entries 15–17). Thus, the optimum reaction conditions were found to be refluxing **4a** (1.0 mmol), **5a** (1.1 mmol), and **6a** (1.1 mmol) in H_2O without any catalyst.

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	Catalyst	*t* (°C)[b]	Time (h)	Yield (%)[c]
1	Toluene	—	Reflux	13	69
2	Dioxane	—	Reflux	10	71
3	THF	—	Reflux	18	75
4	CH_3CN	—	Reflux	16	60
5	CH_2Cl_2	—	Reflux	23	48
6	DMF	—	120	6	80
7	DMSO	—	120	8	77
8	EtOH	—	Reflux	9	72
9	H_2O	—	Reflux	4	90
10	H_2O	HOAc (10%)	Reflux	4	88
11	H_2O	*p*-TSA (10%)	Reflux	4	80
12	H_2O	K_2CO_3 (10%)	Reflux	4	65
13	H_2O	Et_3N (10%)	Reflux	4	74
14	H_2O	Piperidine (10%)	Reflux	4	68
15	H_2O	—	rt	24	n.r.
16	H_2O	—	45	24	Trace
17	H_2O	—	60	24	Trace

n.r.=no reaction.

[a] The reaction was performed with **4a** (1.0 mmol), **5a** (1.1 mmol), and **6a** (1.1 mmol).

[b] rt=room temperature.

[c] Isolated yield based on **4a**.

Next we explored the scope and limitations of the cascade reactions involving different HKAs **4**, 1,3-cyclohexanedione derivatives **5**, and various substituted salicylaldehyde **6** (Table 2). First, we tested the scope of substrates **4** (Table 2, entries 2, 3, 8, 12, 18, 20, 22). It was shown that the substituent on the aromatic HKAs had some influence on the yield. Specifically, the substituted aromatic HKAs with electron-donating groups such as methyl and methoxyl groups (Table 2, entries 2, 3) reacted faster and gave higher yields than those with electron-withdrawing groups such as fluoro and chloro groups (Table 2, entries 12, 18, 22). Next, the 1,3-cyclohexanedione derivatives **5b** (Table 2, entries 4, 19) were also employed in this process, and all reactions proceeded well, giving the corresponding polycyclic pyridines **7d** and **7s**. Compared to **7d** and **7o**, for example, the yields of the **7c** and **7r** were almost the same and the reaction time was identical to the corresponding reaction (Table 2, entries 3 vs 4 and 18 vs 19). Therefore the substitutes of the 1,3-cyclohexanedione have no significant influence on the reaction. In order to further explore the influence of the size of cycles of substrates **5**, the 1,3-cyclopentanedione **5c** was employed in this process to afford **7w** with the yield of 75%, which was similar to the yield of **7v** (Table 2, entries 22 vs 23). However it is worth noting that **5a** as the substrate participates in the reaction faster than **5c**, presumably owing to the higher tension of the ring to form the fused products **7**.

In an endeavor to expand the scope of salicylaldehyde derivatives **6** (Table 2, entries 1, 5, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 21), a series of substituted salicylaldehyde **6** with both electron-withdrawing and electron-donating groups were used as the substrates. The reactions proceeded successfully and the corresponding products **7** were obtained in moderate to excellent yields. As can be seen from Table 2, the substituents on the aryl rings of salicylaldehyde **6** used in our experiments did not have an obvious impact on the reaction yields.

In order to further investigate the scope of HKAs, six-membered HKAs **4h** and seven-membered HKAs **4i–j**, respectively, were also employed as the substrates to react with **5** and **6** (Scheme 1). The reactions proceeded smoothly under the same reaction condition and we got the final product **7x–z** with good yields (73–94%). It was found the size of heterocycles of heterocyclic ketene aminals played a significant role on the reactions. Generally, six-membered HKAs gave higher yields than five-membered and seven-membered ones. For example, the yield of **7y** and **7z** were only 75% and 73% (Scheme 1) and the yield of **7x** was 94% (Scheme 1).

Products **7a–z** were characterized by ^1H HMR, ^{13}C NMR, IR, and HRMS. They were all in agreement with the proposed structures. We obtained a single crystal of product **7q** and performed X-ray diffraction analysis on **7q** (Fig. 2).[21]

On the basis of the above experimental results together with the related reports, a proposed mechanism of the cascade reaction is described in Scheme 2. Take **7a** as an example. Firstly, salicylaldehyde **5a** reacts with 5,5-dimethyl-1,3-cyclohexanedione **6a** through Knoevenagel condensation to give the intermediates **8**. Then the heterocyclic ketene aminals **4a** act as heteroene components and react with **8** to form the intermediates **9**. This step is followed by a rapid imine–enamine tautomerization to give **10**. Next, the N-cyclization is realized by having amino group attack the carbonyl group in **10** and the following dehydration affords **7a** (Scheme 2).

3. Conclusion

In summary, we have successfully developed a concise and environmentally friendly three-component cascade synthesis of fused polycyclic 1,4-dihydropyridines derivatives **7** by heterocyclic