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# KI-catalyzed oxidative cyclization of $\alpha$ -keto acids and 2-hydrazinopyridines: efficient one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyridines†

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A one-pot approach to substituted 1,2,4-triazolo[4,3-*a*]pyridines has been developed that is based on a KI-catalyzed oxidative cyclization of  $\alpha$ -keto acids and 2-hydrazinopyridines. This transition-metal-free procedure was highly efficient and shows good economical and environmental advantages.

## Introduction

Triazolo pyridines represent an important class of nitrogen containing fused-ring heterocycles, which exist as core scaffolds in many natural products and bioactive molecules.<sup>1</sup> Among them, 1,2,4-triazolo[4,3-*a*]pyridines display versatile biological activities and possess attractive applications in the fields of pharmaceutical and pesticide chemistry.<sup>2</sup> For example, functionalized 1,2,4-triazolo[4,3-*a*]pyridines have been investigated as human 11 $\beta$ -hydroxysteroid dehydrogenase-type 1 (ref. 2a) (Fig. 1a) and P38 $\alpha$  mitogen-activated (MAP) kinase inhibitors<sup>2b</sup> (Fig. 1b), as well as an effective antimalarial agent<sup>2c</sup> (Fig. 1c). Moreover, 1,2,4-triazolo[4,3-*a*]pyridines also have found wide applications in the fields of coordination chemistry and material chemistry.<sup>3</sup> As a consequence, the development of effective and practical methods for the construction of substituted 1,2,4-triazolo[4,3-*a*]pyridines has attracted considerable interests. Generally, classic methods for the synthesis of 1,2,4-triazolo[4,3-*a*]pyridines including cyclodehydration of acylated 2-hydrazinopyridines<sup>4</sup> and oxidative cyclization of 2-pyridylhydrazones.<sup>5</sup> In recent years, some elegant one-pot, two-steps synthesis of 1,2,4-triazolo[4,3-*a*]pyridines were developed.<sup>6</sup> Chang and co-workers reported condensation of aldehydes and 2-hydrazinopyridine in EtOH and followed by iodine-induced oxidative cyclization.<sup>6a</sup> Very recently, Reddy developed a I<sub>2</sub>/DMSO system to oxidize  $\alpha$ -aryl methyl ketones to give aldehydes, sequential cyclization with 2-hydrazinopyridines.<sup>6b</sup> However, a really one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyridines is still seldom reported.<sup>7</sup> Thus, the development of practical one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyridines is highly desirable.

## Results and discussion

Due to the unique variable-valent and environment friendly natures of iodides, a variety of useful iodide-containing catalytic systems such as XI/TBHP (X = I, Na, K, *n*Bu<sub>4</sub>N...), I<sub>2</sub>/H<sub>2</sub>O<sub>2</sub>, ArI/*m*CPBA and NaI/<sup>t</sup>BuOCl have been developed rapidly in recent years.<sup>8</sup> In this respect, XI/TBHP systems have found wide applications in the preparation of functionalized heterocyclic compounds.<sup>9</sup> Wang and co-workers developed a NIS/TBHP-mediated intermolecular oxidative amination providing substituted quinazolines in high yields.<sup>9a</sup> Kalita and co-workers reported an I<sub>2</sub>/TBHP-induced synthesis of 4,3-fused 1,2,4-triazoles *via* azomethine imine 1,3-dipolar cycloaddition with aromatic N-heterocycles.<sup>9b</sup> Although iodine-promoted procedures have been developed for the synthesis of 1,2,4-triazolo[4,3-*a*]pyridines, excess amount of iodine as well as two-steps are required, which highly increased the cost of the method. As part of our studies on transition-metal-free oxidative cyclization reactions,<sup>10</sup> we previously found hydrazides hardly tolerated under oxidative conditions, especially at high reaction temperatures. Aiming at these problems, we surmise that a quick transformation of 2-hydrazinopyridines with active carbonyl compounds may inhibit the production of the oxidative byproducts, and sequentially realize the construction of 1,2,4-triazolo[4,3-*a*]pyridines. Herein, we demonstrate an efficient oxidative cyclization of  $\alpha$ -keto acids and 2-

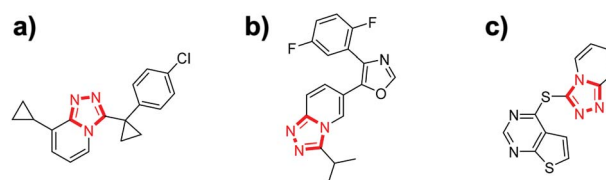


Fig. 1 Selected examples of functional 1,2,4-triazolo[4,3-*a*]pyridines. (a) Inhibitor of 11 $\beta$ -HSD-1, (b) inhibitor of P38 $\alpha$  MAP kinase, (c) anti-malarial agent.

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hydrazinopyridines *via* KI/TBHP system which afforded good yields of substituted 1,2,4-triazolo[4,3-*a*]pyridines in one-pot.

In the initial study, a screen of the active carbonyl compounds was preceded. A one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyridines requires the condensation reaction rate  $k_1$  much larger than the oxidative cyclization reaction rate  $k_2$  and the functional group easy to be removed. Therefore, some electron-withdrawing-groups were tested in the reaction such as  $-\text{CO}_2\text{H}$ ,  $-\text{COMe}$ ,  $-\text{CHO}$ ,  $-\text{COPh}$ ,  $-\text{CN}$  and  $-\text{CO}_2\text{Me}$ , which enhanced the electrophilicity of the  $\alpha$ -carbonyl group and could be removed by C–C bond cleavage under oxidative conditions (Fig. 2).<sup>11</sup> After several trials, we were delight to find that the desired 1,2,4-triazolo[4,3-*a*]pyridine **4a** could be obtained in 82% yield *via* oxidative cyclization of  $\alpha$ -keto acid **1a** and 2-hydrazinopyridine **2a** in the presence of 20 mol% of KI, 2 equiv. of TBHP and 2 equiv. of  $\text{Na}_2\text{CO}_3$  in 1,4-dioxane at 130 °C for 12 h.

Around the optimized conditions, the reaction parameters were varied and the results were summarized in Table 1. Further investigation of iodides revealed that NaI, TBAI and  $\text{I}_2$  were less reactive than KI (entries 2–4). Subsequently, changing the oxidants into others such as  $\text{H}_2\text{O}_2$ , DTBP and  $\text{K}_2\text{S}_2\text{O}_8$  would decrease the outcomes of the reaction (entries 5–7). Next, the

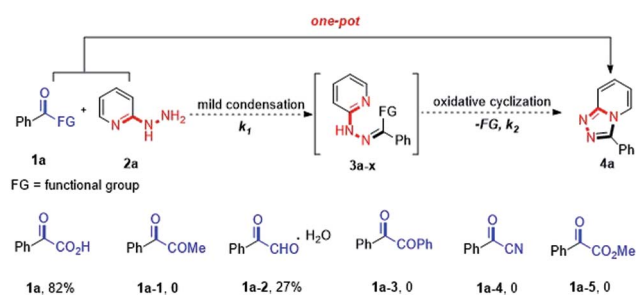


Fig. 2 Screened active carbonyl compounds.

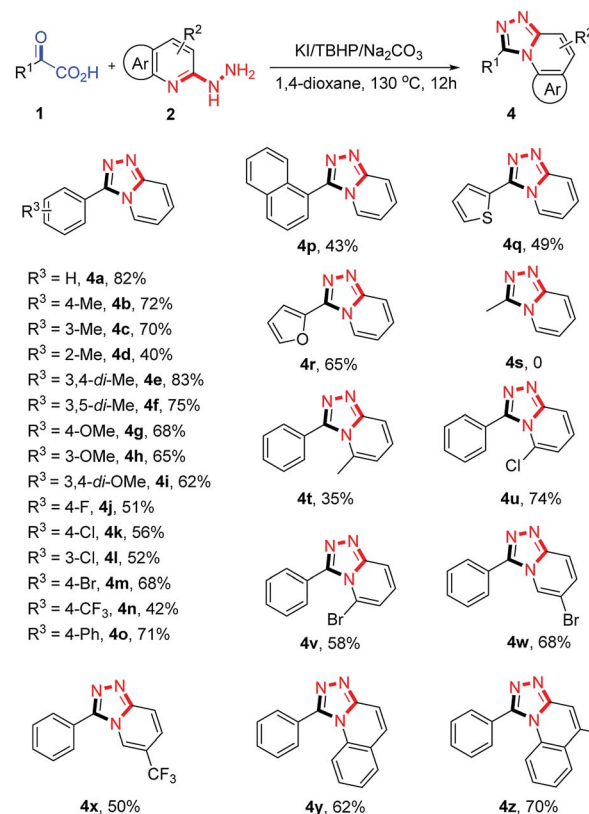
Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Variation from standard conditions	Yield <sup>b</sup>
1	None	82
2	NaI, instead of KI	68
3	TBAI, instead of KI	56
4	$\text{I}_2$ , instead of KI	55
5	$\text{H}_2\text{O}_2$ , instead of TBHP	37
6	DTBP, instead of TBHP	0
7	$\text{K}_2\text{S}_2\text{O}_8$ , instead of TBHP	0
8	$\text{K}_2\text{CO}_3$ , instead of $\text{Na}_2\text{CO}_3$	63
9	Without $\text{Na}_2\text{CO}_3$	41
10	TEA, instead of $\text{Na}_2\text{CO}_3$	18

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), KI (20 mol%), TBHP (70% aqueous solution, 1 mmol) and  $\text{Na}_2\text{CO}_3$  (1 mmol) in 1,4-dioxane (2 mL) at 130 °C for 12 h. <sup>b</sup> Isolated yield.

influence of the bases was studied. The product yields were highly improved when  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$  were employed as bases (entries 8, 9). Other bases such as TEA showed little poor performance (entry 10).

To demonstrate the generality of this one-pot 1,2,4-triazolo[4,3-*a*]pyridine synthesis reaction, we then set out to explore the substrate scope. As shown in Scheme 1, a wide range of aryl  $\alpha$ -keto acids were employed to react with 2-hydrazinopyridine **2a** under the optimized conditions. Aryl  $\alpha$ -keto acids with electron-donating groups ( $-\text{Me}$ ,  $-\text{OMe}$ ) on the aryl ring proceeded smoothly to afford the desired products **4** in moderate to good yields (**4b–4i**, 40–83%). However, *ortho*-methyl substituted substrate gave a comparatively low yield of **4d**; this might be due to the steric hindrance of *ortho*-methyl group. Halogen substituted (4-F, 3-Cl, 4-Cl, 4-Br) aryl  $\alpha$ -keto acids were well-tolerated in this tandem reaction (**4j–4m**), which could be further derivatized in classic cross-coupling reactions. Other electron-withdrawing groups such as 4- $\text{CF}_3$  and 4-Ph were also compatible under the typical conditions, to produce the desired product in 42% and 71% yield (**4o**, **4x**), respectively. Moreover, the ring-fused and heterocyclic substrates also reacted smoothly to deliver the corresponding products (**4p–4r**) in moderate yields. However, the system was not applicable for the cyclization of 2-oxopropanoic acid with **2a**. This could be attributed to a weaker electrophilicity of C2-carbonyl of 2-oxopropanoic acid in compared with the aryl  $\alpha$ -keto acids. Next, an array of 2-hydrazinopyridine derivatives were investigated. To our satisfaction, the developed method was successfully applied to



Scheme 1 Substrate scope.



different Me-, Cl-, Br- and CF<sub>3</sub>- substituted 2-hydrazinopyridines, providing the desired products in 35–74% yields (**4t–4x**). It was noted that 6-Me substituted 2-hydrazinopyridines gave a lower yield of product, probably due to the steric hindrance. However, steric effects had a little impact on the reaction 2-Cl and 2-Br substituted 2-hydrazinopyridines, which gave yields similar to the *para*-substituted ones. Furthermore, 2-hydrazinoquinoline derivatives were also compatible with the optimized conditions, affording the corresponding products **4y** and **4z** in 62% and 70% yield, respectively. Additionally, the model reaction can be easily performed on 10 mmol scale, producing 1.40 g (72% yield) of **4a**.

To gain further insight into the reaction mechanism, some control experiments were carried out. Addition of 2 equiv. of TEMPO into the model reaction, which is a known radical scavenger, a slightly decreased yield of product **4a** was obtained (Scheme 2a). The results suggested that the reaction might follow a hypervalent iodine-catalytic mechanism than a radical pathway. When the reaction was preceded for 2 min, the condensation product **3a** was isolated in 48% yield. As expected, further reaction of **3a** under standard conditions furnished the desired product **4a** in 91% yield. These observations identified that **3a** was a key intermediate of the reaction.

Based on the above experiments and previous studies,<sup>8,9,12</sup> a plausible mechanism is proposed in Scheme 3. Hypoiodate **A** is initially generated from oxidation of iodide by <sup>t</sup>BuO<sub>2</sub>H.<sup>9b,12</sup> Then, oxidation of the *in situ* generated intermediate **3a** by **A**

forms **B**, which could be further transferred to **C** through intermolecular nucleophilic cyclization.<sup>9</sup> Finally, decarboxylation/aromatization of **C** gives **4a** and completed the catalytic cycle of iodide. Bases may affect the key steps **B** to **C**, thus, enhancing the reaction outcomes.<sup>8a,e</sup>

## Conclusions

In summary, we have developed a one-pot method for the synthesis of 1,2,4-triazolo[4,3-*a*]pyridines using KI as the catalyst and <sup>t</sup>BuO<sub>2</sub>H as the terminal oxidant. This transition-metal-free methodology shows good economical and environmental advantages. Furthermore, the mildness of this approach also makes it appealing for further application in organic synthesis.

## Conflicts of interest

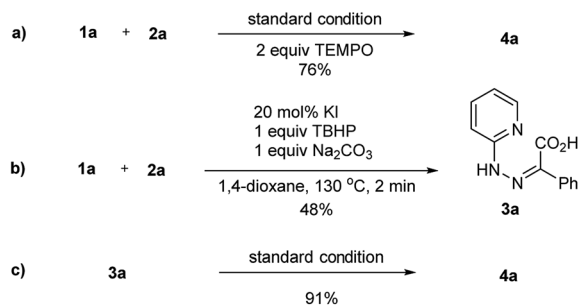
There are no conflicts to declare.

## Acknowledgements

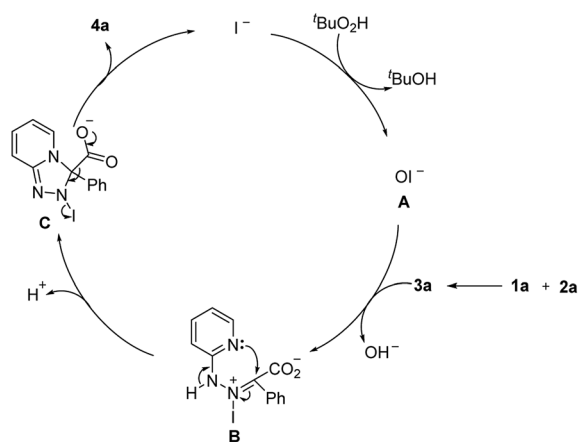
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Scheme 2 Mechanistic investigation.



Scheme 3 Proposed mechanism.



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