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KI-catalyzed oxidative cyclization of α-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 α-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.[1] 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.[2] For example, functionalized 1,2,4-triazolo[4,3-*a*]pyridines have been investigated as human 11β-hydroxysteroid dehydrogenase-type 1 (ref. 2*a*) (Fig. 1a) and P38α mitogen-activated (MAP) kinase inhibitors[2*b*] (Fig. 1b), as well as an effective antimalarial agent[2*c*] (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.[3] 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[4] and oxidative cyclization of 2-pyridylhydrazones.[5] In recent years, some elegant one-pot, two-steps synthesis of 1,2,4-triazolo[4,3-*a*]pyridines were developed.[6] Chang and co-workers reported condensation of aldehydes and 2-hydrazinopyridine in EtOH and followed by iodine-induced oxidative cyclization.[6*a*] Very recently, Reddy developed a I_2/DMSO system to oxidize α-aryl methyl ketones to give aldehydes, sequential cyclization with 2-hydrazinopyridines.[6*b*] However, a really one-pot synthesis of 1,2,4-triazolo[4,3-*a*]pyridines is still seldom reported.[7] 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, nBu$_4$N…), I_2/H_2O_2, ArI/*m*CPBA and NaI/^{t}BuOCl have been developed rapidly in recent years.[8] In this respect, XI/TBHP systems have found wide applications in the preparation of functionalized heterocyclic compounds.[9] Wang and co-workers developed a NIS/TBHP-mediated intermolecular oxidative amination providing substituted quinazolines in high yields.[9*a*] Kalita and co-workers reported an I_2/TBHP-induced synthesis of 4,3-fused 1,2,4-triazoles *via* azomethine imine 1,3-dipolar cycloaddition with aromatic N-heterocycles.[9*b*] 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,[10] 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 α-keto acids and 2-

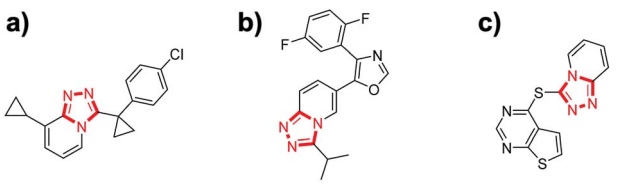

Fig. 1 Selected examples of functional 1,2,4-triazolo[4,3-*a*]pyridines. (a) Inhibitor of 11β-HSD-1, (b) inhibitor of P38*a* MAP kinase, (c) antimalarial agent.

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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 $-CO_2H$, –COMe, –CHO, –COPh, –CN and $-CO_2Me$, which enhanced the electrophilicity of the α-carbonyl group and could be removed by C–C bond cleavage under oxidative conditions (Fig. 2).[11] 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 α-keto acid **1a** and 2-hydrazinopyridine **2a** in the presence of 20 mol% of KI, 2 equiv. of TBHP and 2 equiv. of Na_2CO_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 I_2 were less reactive than KI (entries 2–4). Subsequently, changing the oxidants into others such as H_2O_2, DTBP and $K_2S_2O_8$ would decrease the outcomes of the reaction (entries 5–7). Next, the influence of the bases was studied. The product yields were highly improved when Na_2CO_3 and K_2CO_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 α-keto acids were employed to react with 2-hydrazinopyridine **2a** under the optimized conditions. Aryl α-keto acids with electron-donating groups (–Me, –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 α-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-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 α-keto acids. Next, an array of 2-hydrazinopyridine derivatives were investigated. To our satisfaction, the developed method was successfully applied to

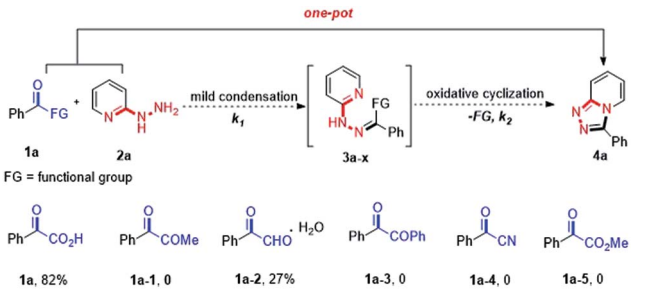
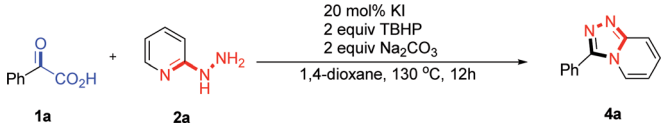


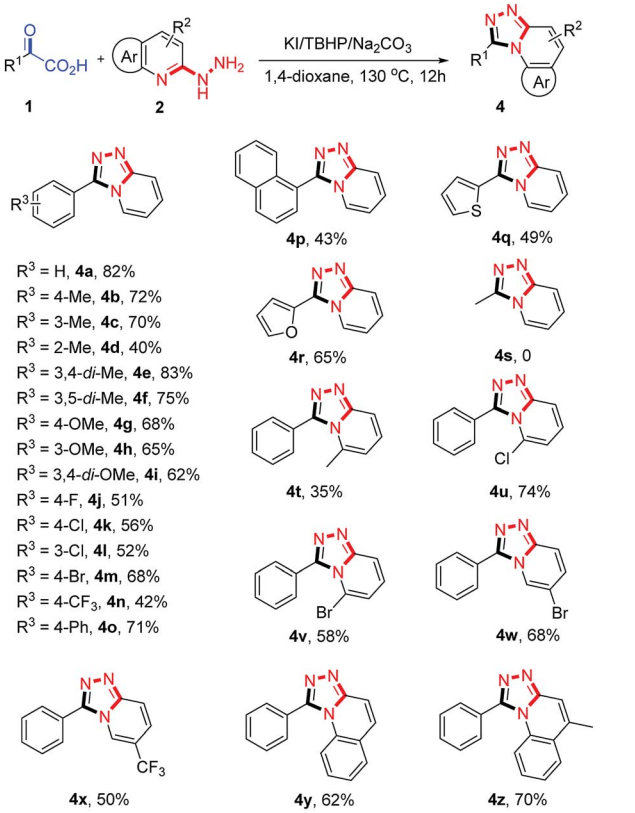
Fig. 2 Screened active carbonyl compounds.

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from standard conditions	Yield[b]
1	None	82
2	NaI, instead of KI	68
3	TBAI, instead of KI	56
4	I_2, instead of KI	55
5	H_2O_2, instead of TBHP	37
6	DTBP, instead of TBHP	0
7	$K_2S_2O_8$, instead of TBHP	0
8	K_2CO_3, instead of Na_2CO_3	63
9	Without Na_2CO_3	41
10	TEA, instead of Na_2CO_3	18

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), KI (20 mol%), TBHP (70% aqueous solution, 1 mmol) and Na_2CO_3 (1 mmol) in 1,4-dioxane (2 mL) at 130 °C for 12 h. [b] Isolated yield.

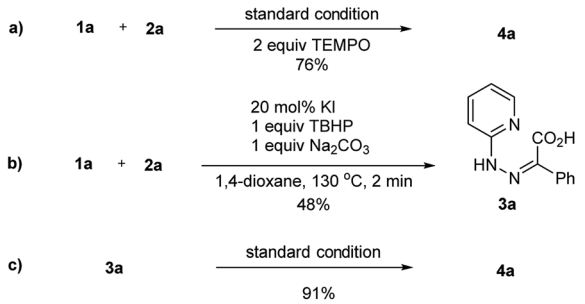


Scheme 1 Substrate scope.

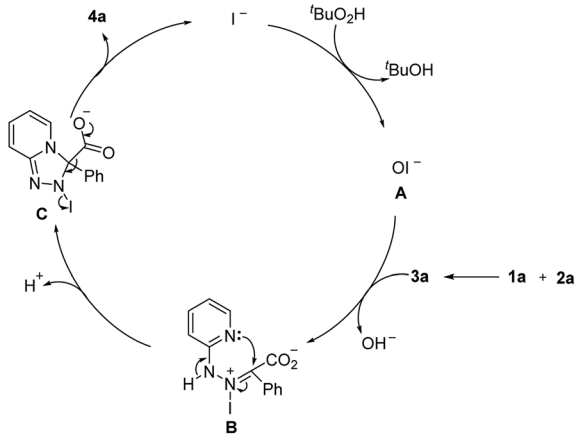
different Me–, Cl–, Br– and CF_3– substituted 2-hydrazinopyridines, providing the desired products in 35–74% yields (**4t–4x**). It was noted that 6-Me substituted 2-hydrazinopyridines gave a lower yield of product, probably due to the steric hindrance. However, steric effects had a little impact on 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,[8,9,12] a plausible mechanism is proposed in Scheme 3. Hypoiodate **A** is initially generated from oxidation of iodide by ^{t}BuO$_2$H.[9b,12] Then, oxidation of the *in situ* generated intermediate **3a** by **A** forms **B**, which could be further transferred to **C** through intermolecular nucleophilic cyclization.[9] Finally, decarboxylation aromatization of **C** gives **4a** and completed the catalytic circle of iodide. Bases may affect the key steps **B** to **C**, thus, enhancing the reaction outcomes.[8a,e]



Scheme 2 Mechanistic investigation.



Scheme 3 Proposed mechanism.

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 ^{t}BuO$_2$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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