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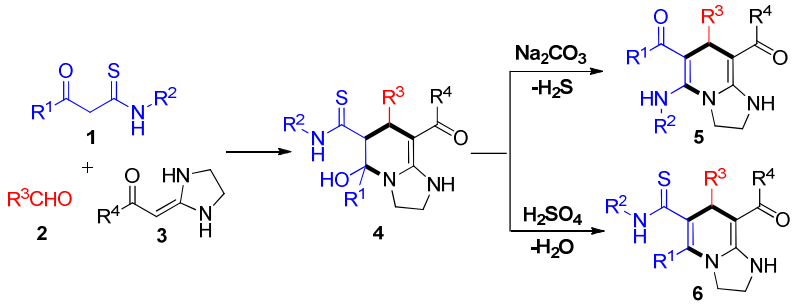
Graphical abstract

Acid/base-controlled chemodivergent synthesis of two differently functionalized imidazo[1,2-*a*]pyridines

Wei-Si Guo, Xing Xin, Ke-Long Zhao, Li-Rong Wen* and Ming Li *



Two differently substituted type of imidazo[1,2-*a*]pyridine derivatives were synthesized chemodivergently using *β*-ketothioamides, aldehydes and heterocyclic ketene aminals through acid/base regulation.

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Acid/base-controlled chemodivergent synthesis of two differently functionalized tetrahydroimidazo[1,2-*a*]pyridines

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A new approach for the facile chemodivergent synthesis of tetrahydroimidazo[1,2-*a*]pyridines from *β*-ketothioamides, aldehydes and heterocyclic ketene aminals is described. In the presence of a base, an unprecedented ring-opening, tautomerization, recyclization cascade is observed and the H_2S eliminated tetrahydroimidazo[1,2-*a*]pyridines were formed in good yields. With catalytic amount of acid, another type of different substituted tetrahydroimidazo[1,2-*a*]pyridines were obtained through dehydration.

Imidazo[1,2-*a*]pyridine is an important heterocyclic skeleton which can be found in a broad spectrum of pharmaceuticals,[1] such as insecticide against pea aphids (I),[2] and the inhibitors of TNF-α expression in T cells (II) (Figure 1).[3] Therefore, a variety of methodologies have been developed for the construction of imidazo[1,2-*a*]pyridines.[4] Recently, diverse metal-catalyzed methods for the construction of this privileged structure have been reported.[5] Multicomponent reactions (MCRs) are an important strategy in the synthesis of heterocyclic scaffolds.[6] The diversity and easy accessibility to a large number of compounds, make MCRs a very important tool in modern organic synthesis.[7] However, there is only limited number of reports on imidazo[1,2-*a*]pyridines synthesis through multicomponent reactions under metal-free conditions.[8]

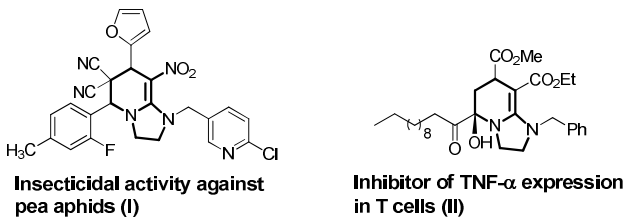


Fig. 1 Selected biologically active imidazo[1,2-*a*]pyridines.

β-Ketothioamides (KTAs)[9] and heterocyclic ketene aminals (HKAs)[10] are versatile building blocks for the rapid construction of various heterocyclic compounds.[11] The previous reports of KTAs participated reactions mainly involved four types (Figure 2, modes A−D). In continuation of our interests in the utilization of HKAs and KTAs,[12] and based on our recent works in exploring metal-free MCRs,[13] herein, we report a metal-free acid/base controlled chemodivergent synthesis of tetrahydroimidazo[1,2-*a*]pyridines by another reaction mode of KTAs (Figure 2, mode E).

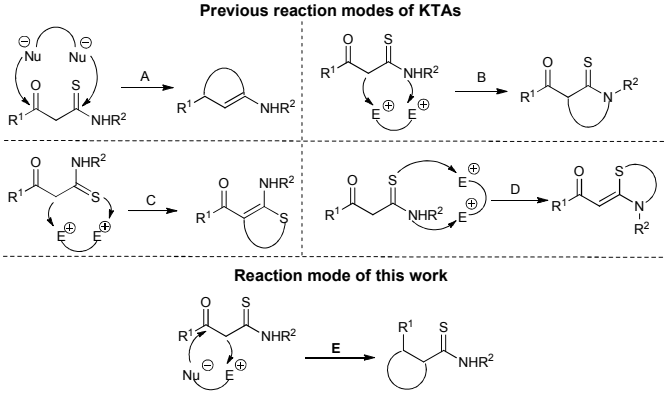
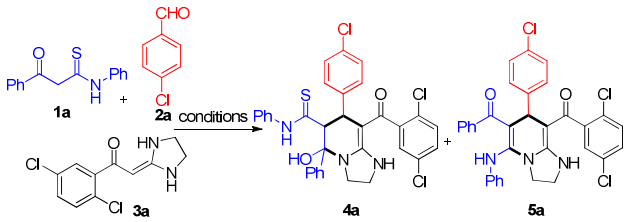


Fig. 2 Reaction modes of *β*-ketothioamides

Initially, a mixture of KTA **1a**, aldehyde **2a**, and HKA **3a** was stirred in refluxing toluene in the presence of Na_2CO_3 for 8 h, a yellow powder **5a** was obtained in 28% yield after column chromatography (Table 1, entry 1). Then a series of other bases, including Et_3N, DABCO, DBU, CH_3ONa and K_2CO_3, were screened. Disappointedly, all these bases gave lower yields than Na_2CO_3 (entries 2−7). Subsequently, the model reaction was performed in various solvents. When the solvent was changed to methanol, another compound **4a** was obtained besides **5a**, albeit in low yield (entry 8). Interestingly, the selectivity of the reaction was changed from **5a** to **4a** without addition of any base (entry 9).

Through carefully reaction conditions screening (entries 10−15), **4a** was obtained in high yield in refluxing methanol (entry 10). Furthermore, we found that **4a** could be transformed to **5a** in high yield using Na_2CO_3 as a base in DMF. Fortunately, the structure of **4a** was determined by single crystal X-ray analysis (see ESI). Thus we reasoned that an interesting ring-opening, tautomerization, recyclization cascade could be involved in the transformation.

Table 1 Optimization of the reaction conditions [a]

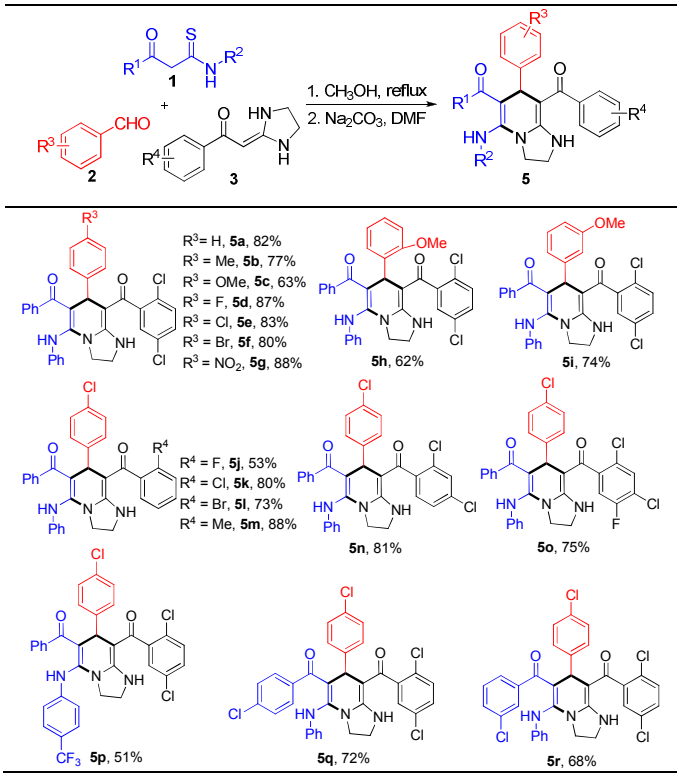


Entry	Base	Solvent	Temp (°C)	Time (h)	yield (%)[b] 4a	5a
1	Na_2CO_3	toluene	110	8	trace	28
2	Et_3N	toluene	110	8	trace	20
3	DABCO	toluene	110	8	trace	23
4	Pyridine	toluene	110	8	trace	18
5	DBU	toluene	110	8	trace	16
6	CH_3ONa	toluene	110	8	trace	13
7	K_2CO_3	toluene	110	8	trace	21
8	Na_2CO_3	MeOH	65	8	23	15
9		**MeOH**	**65**	**8**	**83**	**trace**
10		toluene	110	8	30	trace
11		MeCN	80	8	70	trace
12		EtOH	80	8	80	trace
13		dioxane	100	8	50	Trace
14		MeOH	r.t.	20	trace	Trace
15		MeOH	50	20	20	Trace

[a] The mixture of **1a** (0.5 mmol), **2a** (0.5 mmol), and **3a** (0.5 mmol) was stirred in solvent at indicated temperature in the presence of air. [b] Isolated yield.

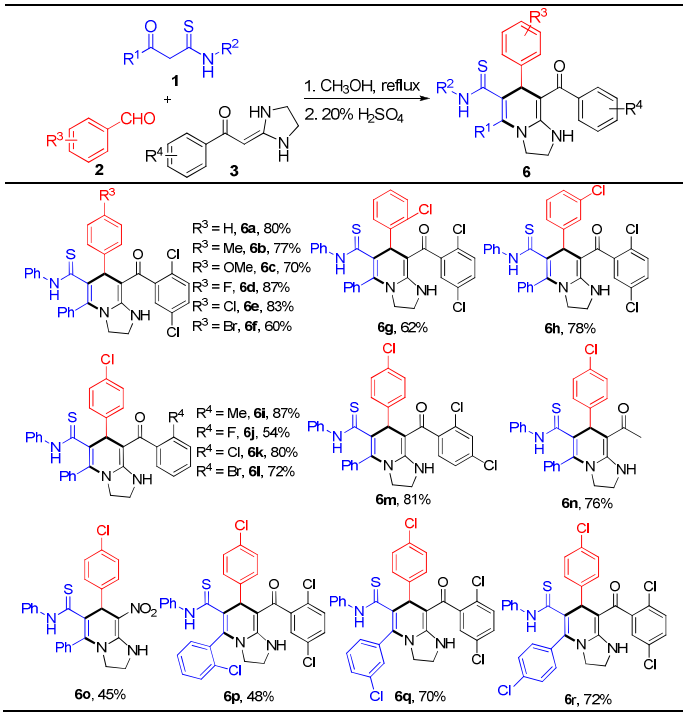
Under the optimal conditions, the scope of the reaction was examined using a broad range of substituted arylaldehydes (Table 2). Products **5a-i** were obtained in moderate to good yields regardless of electron-withdrawing or electron-donating groups on the benzaldehydes. Next, substituted aryl-HKAs were employed to provide the desired products **5j-o** in moderate to good yields. Interestingly, tetrahydroimidazo[1,2-*a*]pyridines **5** were just obtained from *ortho* substituted aryl-HKAs. No desired products were formed when non-, *meta*- or *para*-substituted aryl-HKAs were used as reactants. The reason for this phenomenon is still unclear. The reaction also proceeded smoothly with three other substituted KTAs to afford the tetrahydroimidazo[1,2-*a*]pyridines **5p-r**. The structures of **5** were confirmed by X-ray crystallographic analysis of **5c** (see ESI).

Table 2 Synthesis of tetrahydroimidazo[1,2-*a*]pyridines **5** under basic conditions [a,b]



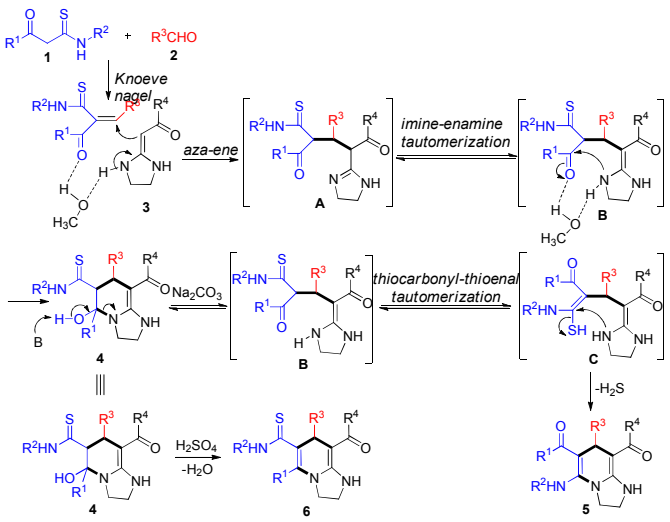
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5mmol), CH_3OH (2 mL), 70 °C, 8 h. Na_2CO_3 (1.0 mmol), DMF (2 mL), 100 °C, 2 h. [b] Isolated yield.

Table 3 Synthesis of tetrahydroimidazo[1,2-*a*]pyridines **6** under acid conditions [a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), CH_3OH (2 mL), 70 °C, 8 h. Then 0.1 mmol H_2SO_4, 2 h. [b] Isolated yields.

Under the conditions of catalytic sulfuric acid, another different substituted type of tetrahydroimidazo[1,2-*a*]pyridine **6a** could be formed in high yield from intermediate **4a**. The substrate scope of this reaction was also evaluated (Table 3). First, a variety of arylaldehydes **2** were reacted with HKA **1** and KTA **3**, and products **6a-h** were obtained in good yields. Subsequently, tetrahydroimidazo[1,2-*a*]pyridines **6i-m** were formed in moderate to good yields with substituted aryl-HKAs. In addition, products **6n** and **6o** were also obtained when methyl-HKA and nitro-HKA were used as starting materials. Next, three substituted KTAs were employed with products **6q** and **6r** formed in good yields, whereas **6p** was obtained in relatively low yield. The structures of **6** were confirmed by X-ray crystallographic analysis of **6h** (see ESI). Notably, the ^{1}H NMR spectra of some compounds **6** (such as **6a-g**) are messy due to rotamers when an ortho-chlorine atom was performed on the aromatic ring of HKAs **3**. The reason for this phenomenon was explained in detail in our previous report.[12a]



Scheme 1 A plausible reaction mechanism

Based on the structure of the crucial intermediate **4**, a plausible mechanism for the reactions is outlined in Scheme 1. Initially, the Knoevenagel adduct, which is readily formed in situ from aldehyde **2** and *β*-ketothioamide **3**, reacts with HKA **1** via aza-ene process to form intermediate **A**. After imine-enamine tautomerization and intramolecular cyclization, the intermediate **4** is obtained. The formation of **4** is due to the *α*-carbon and the carbonyl group of KTAs participated in the reaction under neutral conditions. Notably, in this process, CH_3OH would play an important role in increasing the electrophilicity of the carbonyl group of KTAs by hydrogen bond-driven effect,[14] which is preferentially attacked by nucleophilic reagent giving the ring-closing product **4**. Subsequently, in the presence of sodium carbonate, the semi-aminal group would collapse to regenerate the ring-open intermediate **B**. Then the thiocarbonyl group would tautomerize to form the more stable conjugated thioenol intermediate **C** under basic conditions. Finally, the tetrahydroimidazo[1,2-*a*]pyridine **5** is afforded irreversibly through intramolecular cyclization with elimination of H_2S. Otherwise, in the presence of acid, the tetrahydroimidazo[1,2-*a*]pyridine **6** is obtained directly through dehydration.

In conclusion, a chemodivergent metal-free multicomponent synthesis of two differently functionalized tetrahydroimidazo[1,2-*a*]pyridine derivatives has been developed by adjusting reaction conditions. The ring-opening, tautomerization, recyclization cascade was also first observed in the study of KTAs reactions. The approach features high chemoselectivity, broad substrate scope, and mild reaction conditions, which provides a convenient method for construction of tetrahydroimidazo[1,2-*a*]pyridine derivatives from readily available starting materials.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, and crystal data for **4a, 5c** and **6h** (CIF). See DOI: 10.1039/c000000x/

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