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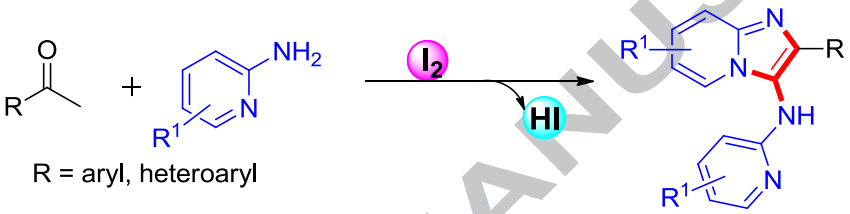

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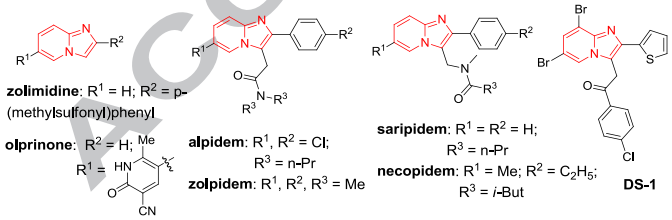
ABSTRACT

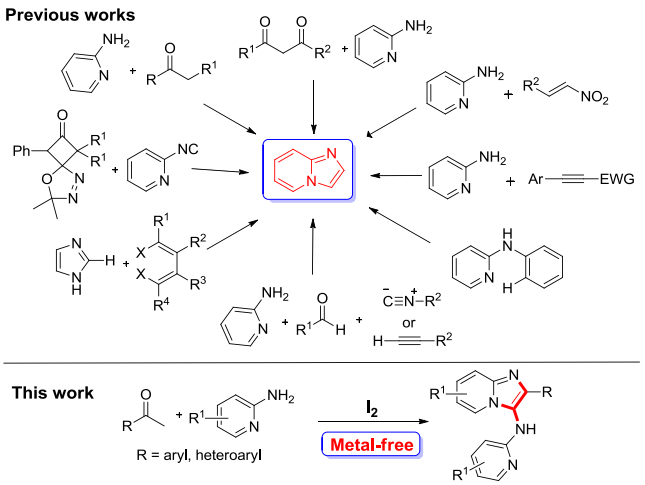
An I_2-promoted one-pot protocol was proposed for the synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-a]pyridines from aromatic ketones and 2-aminopyridines. The present reaction proceeded well in the presence of I_2 in DMSO, and it avoided the requirement of any metal, base, and ligand.

Imidazo[1,2-a]pyridines have attracted much attention since the beginning of the last century. Due to their important biological activity, they have, in recent years, been broadly investigated and utilized in the pharmaceutical industry. They also be used in bioimaging probes, and molecular recognition because of their structural characters.[1] In addition, the imidazo[1,2-a]pyridine scaffolds have been found to be the core structure of many natural products and drugs such as zolpidem, alpidem, zolimidine, saripidem, necopidem, olprinone, and DS-1 (Scheme 1).[2]



Scheme 1. The drugs containing imidazo[1,2-a]pyridine unit.

Consequently, many synthetic methods have been reported for the synthesis of imidazo[1,2-a]pyridines (Scheme 2).[3] In recent times, some novel synthetic approaches have been proposed to access imidazo[1,2-a]pyridines. For example, an efficient method involving condensation of aldehydes, 2-aminopyridines, and isonitriles or alkynes in one-pot has been established.[4] Metals catalyzed C-H activation or coupling methods have also been developed.[5] Moreover, transition-metal free domino protocols were also proposed by some research groups.[6–9] Despite these achievements, the development of further diverse methods to construct various imidazo[1,2-a]pyridines is still desirable. In addition, the molecules of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-a]pyridines are rarely reported in literature.



Scheme 2. The methods for the synthesis of imidazo[1,2-a]pyridines.

In our previous studies, we found that I_2 could promote quantitative conversion of aryl methyl ketones to aryloxoethanals in DMSO.[10] The aryloxoethanals generated in situ were easily captured by 2-aminopyridines to afford imidazo[1,2-a]pyridines.

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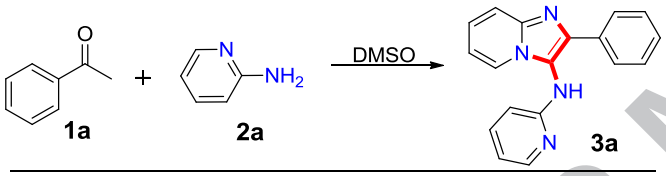
Based on these results, we aimed to investigate if it would be possible to develop an I_2 promoted one-pot protocol to synthesis of imidazo[1,2-a]pyridines via sp^3 C-H bonds functioalization from aromatic ketones (Scheme 2).

With this idea in mind, we selected acetophenone (**1a**) and 2-aminopyridine (**2a**) as a model reaction (Table 1). The reaction of acetophenone (**1a**) and 2-aminopyridine (**2a**) with I_2, CuO at 80-100 ℃ could not perform to give the desired product (entries 1–3). It was found, however, the desired product was obtained in 68% yield when acetophenone **1a** and I_2 were heated at 100 ℃ for 1–2 h, with the subsequent addition of **2a** for another 2 h (entry 4). The yield was up to 73% when the does of I_2 was increased to 150-200 mol % (entries 5–6). To our delight, the reaction still performed well with only 150 mol % of I_2 (entry 7). However, no desired product was obtained in the absence of I_2 or I_2/CuO (entries 8–9). Further elevation or reduction of temperature could not enhance the yield (entries 10–11). After several experimental optimization processes, we found that a mixture of **1a** (1.0 mmol) and I_2 (1.5 mmol) in DMSO was heated to 100 ℃ for 1-2 h. Addition of **2a** (2.0 mmol) to this and heating to 100 ℃ for 1 h produced product **3a** in 75% isolated yield.

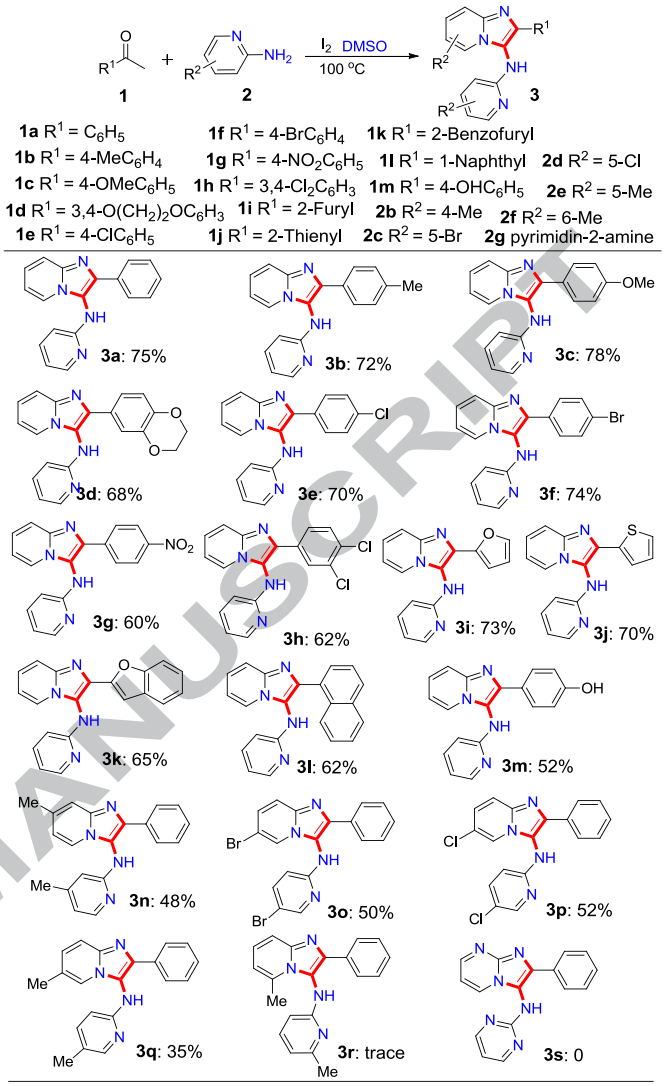
Table 1. Optimization of the reaction conditions



Entry	I_2 (mmol)	CuO (mmol)	Temp. (℃)	Yield (%) [c]
1[a]	1.1	1.1	80	n.r.
2[a]	1.1	1.1	90	n.r.
3[a]	1.1	1.1	100	n.r.
4[b]	1.1	1.1	100	68
5[b]	1.5	1.1	100	73
6[b]	2.0	1.1	100	72
7[b]	1.5	-	100	75
8[b]	-	1.1	100	n.r.
9[b]	-	-	100	n.r.
10[b]	1.5	-	110	69
11[b]	1.5	-	80	60

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), I_2, and CuO were heated in DMSO (3–5 mL). [b] **1a** (1.0 mmol), I_2, and/or CuO were heated for 1–2 h in DMSO (3–5 mL), and then added **2a** (2.0 mmol) for another 1 h. [c] Isolated yield. n.r. = no reaction.

Table 2 The scope of ketones and 2-aminopyridines[a, b]



[a] Reaction conditions: A mixture of **1** (1.0 mmol) and I_2 (1.5 mmol) in DMSO (3–5 mL) was heated at 100 ℃ for 1–6 h, and then for an additional 1–2 h after addition of **2** (2.0 mmol). [b] Isolated yield.

With the optimal reaction conditions established, the scope of the present transformation was investigated in DMSO.[15] As summarized in Table 2, various aromatic ketones were found to participate in this reaction. The electronic and steric nature of aromatic methyl ketones had little influence on the reaction efficiency, and all the corresponding products were obtained in moderate to good yields (52–78%; Table 2). For example, various aromatic ketones bearing electron-rich (**3b–3d**) and electron-deficient (**3e–3h**) substituents on the aryl ring could perform smoothly to give the corresponding products in generally good yields (60–78%). In addition, the scope of the substrates was further extended to various heteroaryl methyl ketones, such as 2-acethyl furan, -thiophen, -benzofuran. To our delight, the corresponding products **3i–3k** were furnished in 65–73% yields. Meanwhile, steric hindrance substrate 1-naphthyl methyl ketone **1l** was also tolerant to this reaction to afford the desired product **3l** in 62% yield. The substrate bearing a phenolic hydroxy group (OH) could be used and was successfully converted to the corresponding product **3m** in 52% yield. Subsequently, the substituted 2-aminopyridines **2b**, **2c**, **2d**, **2e**, **2f**, and 2-aminepyrimidin **2g** were also employed. **2b**-**2e** could perform to afford the corresponding products **3n-3q** in 35-52% yields. However, **2f** and **2g** were not suitable for the reaction and no desired products were observed. The target compound **3j** was further determined by X-ray crystallographic analysis (Figure 1).

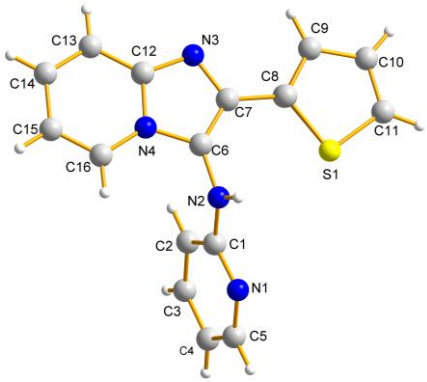


Figure 1 The X-Ray crystal structure of compound **3j**

To probe the reaction process, the reaction of **1a** (0.1 mmol) with I_2 (0.15 mmol), and **2a** (0.2 mmol) in DMSO-d_6 was monitored by ^{1}H NMR spectroscopic analysis (Figure 2). The signal at 4.6 ppm that appeared at 5-15 mins was unambiguously assigned to the -CH_2- group of α-iodo aryl methyl ketone **4** by comparison with that of an authentic sample of **4 (**Figure S2**)**. Meanwhile, the signals at 9.54 ppm and 5.70 ppm were assigned to the characteristic peaks of phenylglyoxal (**5**) and its hemiacetal (**6**), respectively.[10c, 11] When the reaction was performed for 35 mins, the substrate **1a** was absolutely transformed into intermediates **5** and **6**. After the addition of **2a**, the characteristic peaks of **5** and **6** disappeared immediately. The characteristic peaks of product **3a** were also clearly observed. Thus, Figure 2 indicates a high conversion of the reaction without formation of any byproduct.

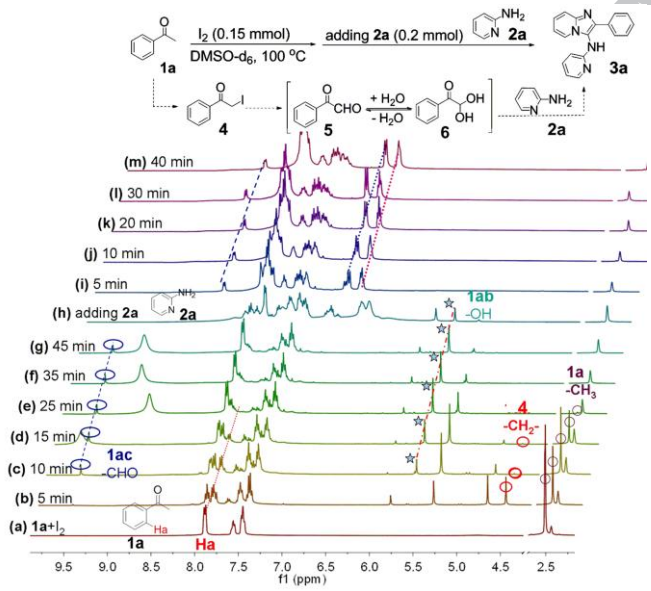
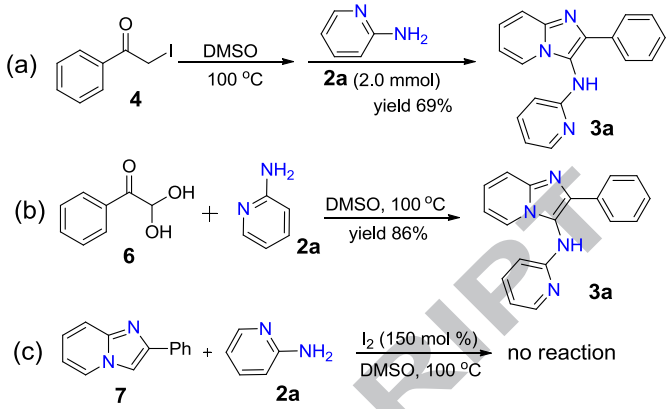


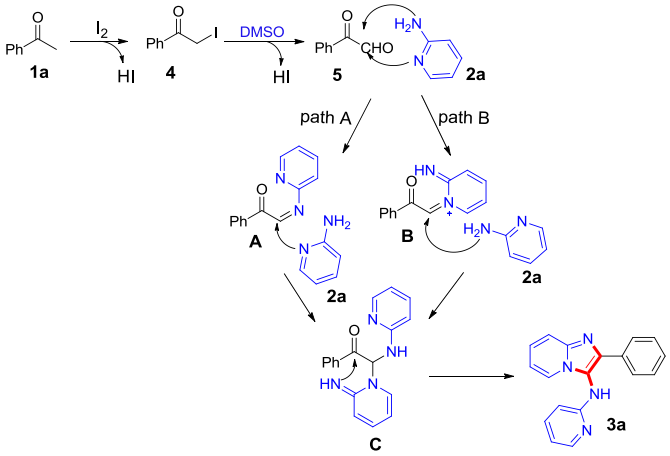
Figure 2 The reaction process of **1a** (0.1 mmol), **2a** (0.2 mmol) with I_2 (0.15 mmol) was monitored by ^{1}H NMR spectroscopy (400 MHz, DMSO-d_6).

Some control experiments were conducted (Scheme 3). It was found that phenacyl iodine **4** (1.0 mmol) reacted with **2a** (2.0 mmol) in DMSO at 100 ℃ to provide product **3a** in 69% yield (Scheme 3a). The reaction of intermediate **6** (1.0 mmol) with **2a** (2.0 mmol) at 100 ℃ also proceeded smoothly to provide product **3a** in good yield (86%) in DMSO (Scheme 3b). The results suggest that phenacyl iodine **4** and phenylglyoxal **5** are proper intermediates for production of **3a**. The reaction of 2-phenyl imidazo[1,2-a]pyridine **7** with **2a** was also performed under the standard conditions; however, no desired product was observed (Scheme 3c). It demonstrated that the reaction did not undergo through the intermediate 2-phenyl imidazo[1,2-a]pyridine **7.**



Scheme 3. The controlled experiments to prove the mechanism.

Possible mechanism for the process is illustrated in Scheme 4. Initially, the acetophenone **1a** takes place α-halogenation to afford α-iodo ketone **4** in the media of I_2 in DMSO.[12] Subsequently, α-iodo ketone **4** is further oxidized by DMSO to yield phenylglyoxal **5**.[10, 13] Phenylglyoxal **5** undergoes two possible pathways to afford intermediate **C**.[14] In pathway A, the amino group of **2a** initially attacks the aldehyde group of **5** to obtain intermediate **A**, which is further attacked by the pyridine group of another molecule of **2a** to yield intermediate **C**. In pathway B, the pyridine group of **2a** first attacks the aldehyde group of **5** to afford intermediate **B**. Then, the amino group of another molecule of **2a** undergoes condensation with **B** to give intermediate **C**. Finally, intermediate **C** experiences an intramolecular condensation to furnish the desired product **3a**.



Scheme 4 The plausible mechanism of the present reaction

In conclusion, a metal-free I_2-promoted protocol was proposed for the synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-a]pyridines from aromatic ketones and 2-aminopyridines. Mechanism investigation demonstrated that the reaction proceeded through α-iodo aryl methyl ketone and aryloxoethanal intermediates. Unlike previous processes, the present protocol avoids the requirement of metal, base, and ligand. In addition, the molecules of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-a]pyridines are rarely reported in literature. Further investigations into the scope of this reaction and its applications are ongoing.

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15 Typical procedure for preparation of **3**: A sealed tube was charged with acetophenone **1a** (120 mg, 1 mmol), iodine (380.7 mg, 1.5 mmol) and DMSO (3 mL) at room temperature. The resulting mixture was stirred at 100 ℃. After disappearance of the reactant (monitored by TLC), 2-aminopyridine **2a** (188 mg, 2.0 mmol) was added and the mixture was heated to 100 ℃ for 2 h. After completion of the reaction and addition of water (50 mL), the mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with 10% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: Petr/EtOAc = 3:1) to yield the desired product **3a** as a white solid (214.6 mg, 75% yield).

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.