Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c0xx00000x

ARTICLE TYPE

www.rsc.org/xxxxxx

Organopromoted direct synthesis of 6-iodo-3-methylthioimidazo[1,2-*a*]pyridines via convergent integration of three self-sorting domino sequences

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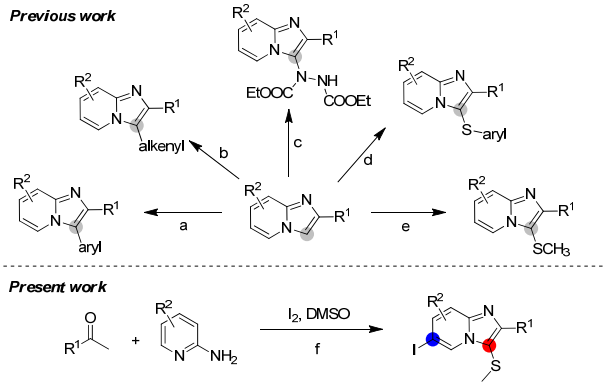
Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An NH_2CN-promoted convergent integration of three self-sorting domino sequences is described for the construction of 6-iodo-3-methylthioimidazo[1,2-*a*]pyridines from aryl methyl ketones and 2-aminopyridines. This strategy allows the construction of imidazo[1,2-*a*]pyridine ring along with methylthiolation at C-3 and iodination at C-6. Preliminary mechanistic studies indicate that this process terminates at the iodination stage without Kornblum oxidation in the presence of I_2 and DMSO.

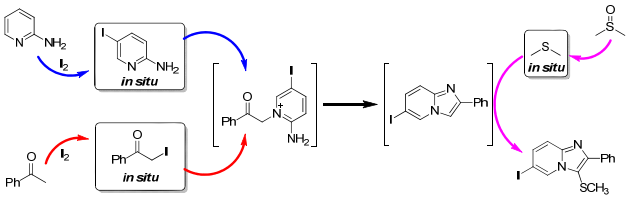
The imidazo[1,2-*a*]pyridine moiety is a privileged fragment present in various biologically active and pharmaceutically important compounds.[1] In particular, numerous commercially available drugs bear this core scaffold, including zolpidem,[2] alpidem,[3] zolimidine,[4] necopidem and saripidem.[5] Consequently, much attention has been paid to the synthesis of substituted imidazo[1,2-*a*]pyridines through the construction of the requisite ring structure.[6] However, the electron-rich nature of the C-3 of the imidazo[1,2-*a*]pyridine ring enables it to undergo direct C-H bond functionalization with electrophiles to form both C-C and C-heteroatom bonds.[7] Over the past several years, the transition metal-catalyzed direct arylation of imidazo[1,2-*a*]pyridines with aryl halides or arenes has been realized (Scheme 1a).[8] In 2009, a Pd/Cu-catalyzed oxidative C–H alkenylation of imidazo[1,2-*a*]pyridines with alkenes was first reported (Scheme 1b).[9] More recently, the hydrazination of such compounds with diethyl azodicarboxylate in the absence of metal catalysts was described (Scheme 1c).[10] As well, the regioselective C-3 sulfenylation of imidazo[1,2-*a*]pyridines has been achieved with various sulfenylating reagents,[11] including disulfides, thiophenols, sodium sulfinates and sulfonyl hydrazides (Scheme 1d). In addition, methylthiolation using a DMSO-$POCl_3$ complex has been demonstrated (Scheme 1e).[12] Nevertheless, to the best of our knowledge, the construction of imidazo[1,2-*a*]pyridine ring along with methylthiolation at C-3 and iodination at C-6 in one-pot has not yet been reported (Scheme 1f).

On the basis of our previous studies,[13] we envisioned that methyl ketones could be converted *in situ* to the corresponding acyl iodine compounds in the presence of I_2, which would be primed for the cross-trapping of 5-iodopyridin-2-amine generated *in situ* from 2-aminopyridine to afford the 2-aminopyridinium salt. Following the sequential intramolecular cyclization and



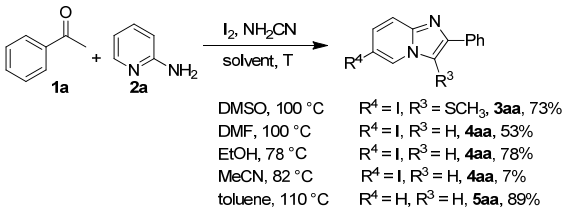
Scheme 1 Functionalization of the C-3 of imidazo[1,2-*a*]pyridines.

aromatization, DMS generated *in situ* from DMSO would be trapped to realize the methylthiolation of the C-3 of the resulting imidazo[1,2-*a*]pyridine. The present work provides the first known example of the organopromoted direct synthesis of 6-iodo-3-methylthioimidazo[1,2-*a*]pyridines via convergent integration of three self-sorting domino sequences (Scheme 2).



Scheme 2 Design strategy: four-component coupling reaction of aryl methyl ketones and 2-aminopyridines in the presence of I_2 and DMSO.

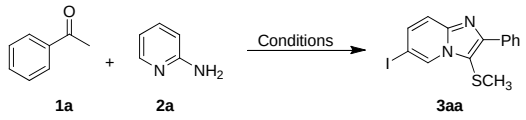
Initially, the reaction of acetophenone (**1a**) with 2-aminopyridine (**2a**) was performed in various solvents to assess the feasibility of our new strategy (Scheme 3). Fortunately, both the direct annulation reaction and the functionalization of imidazo[1,2-*a*]pyridine occurred in DMSO to afford the expected 6-iodo-3-(methylthio)-2-phenylimidazo[1,2-*a*]pyridine (**3aa**) in 73% yield (Table 1, entry 1). The structure of **3aa** was unambiguously confirmed by X-ray crystallography analysis (see Supporting Information). In contrast, the reaction was not very



Scheme 3 The effects of the reaction solvent.

successful in the absence of NH_2CN (Table 1, entry 2). To our surprise, a reduction in the quantity of NH_2CN to 2.0 equiv. provided **3aa** in 87% yield (Table 1, entry 6), whereas further decreases in the charge of NH_2CN resulted in significant decreases in the yields (Table 1, entries 3-5). Accordingly, various amines and other bases were also evaluated, but none had a positive impact on the outcome of the reaction (see Supporting Information). These results indicated that NH_2CN is an important mediator in this transformation. It was established that the reaction would not proceed in the absence of I_2 (Table 1, entry 11), suggesting that I_2 also plays a crucial role in the reaction. A range of different temperatures was assessed with the aim of improving the yield (Table 1, entries 12-16), and 100 °C was determined to be optimal for the formation of **3aa**. After screening on different parameters, the optimized conditions were determined as **1a** (0.5 mmol) with **2a** (0.5 mmol) in the presence of NH_2CN (1.0 mmol) and I_2 (0.8 mmol) in DMSO at 100 °C for 24 h (Table 1, entry 6)

Table 1 Optimization of the reaction conditions[a]

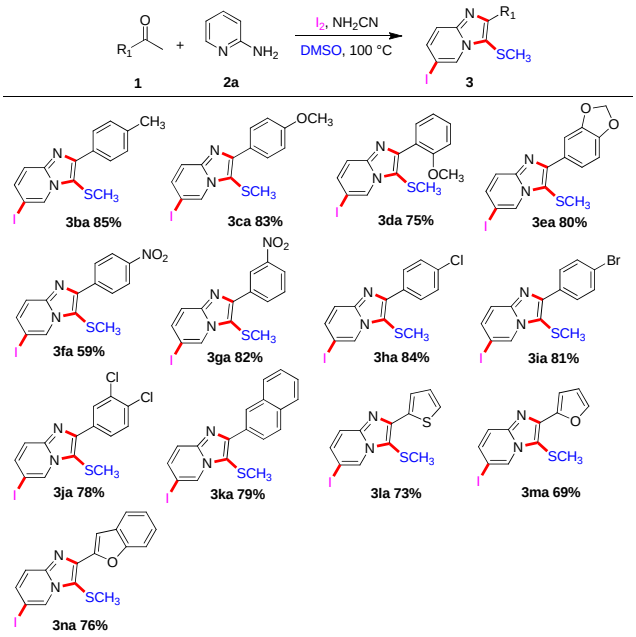


Entry	I_2 (equiv.)	Temp. (°C)	NH_2CN (equiv.)	Yield[b] (%)
1	1.6	100	4.0	73
2	1.6	100	—	8
3	1.6	100	0.5	23
4	1.6	100	1.0	31
5	1.6	100	1.5	35
6	**1.6**	**100**	**2.0**	**87**
7	1.6	100	2.5	82
8	2.0	100	2.0	78
9	1.0	100	2.0	80
10	0.5	100	2.0	<5
11	—	100	2.0	0
12	1.6	130	2.0	83
13	1.6	110	2.0	84
14	1.6	90	2.0	75
15	1.6	80	2.0	63
16	1.6	60	2.0	15

[a] Reaction Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), heated in DMSO (2 mL) for 24 h. [b] Isolated yields.

With the optimized conditions in hand, the substrate generality of this protocol was next evaluated with a variety of different aryl methyl ketones (Table 2). It was gratifying to find that aryl methyl ketones bearing electronically neutral (4-Me), electron-donating (4-OMe, 2-OMe, 3,4-OCH_2O) and electron-withdrawing (4-NO_2, 3-NO_2) substituents all reacted smoothly to afford the corresponding products in moderate to good yields (59-85%; **3ba-ga**). In addition, the optimized conditions were mild enough to be compatible with halogenated (4-Cl, 4-Br, 3,4-Cl_2) substrates (78-84%; **3ha-ja**), thus demonstrating the possibility of further functionalization. The sterically hindered 2-naphthyl methyl ketone also furnished the expected product (**3ka**) in 79% yield. Furthermore, the optimal conditions were successfully applied to the heteroaryl methyl ketones, such as thiophenyl, furanyl and benzofuryl, giving the corresponding products in good yields (69-76%; **3la-na**).

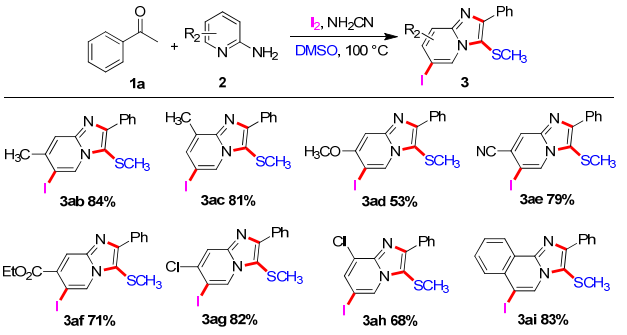
Table 2 Scope of aryl methyl ketones[a,b]



[a] Reaction Conditions: **1** (1.0 mmol), **2a** (1.0 mmol), NH_2CN (2.0 mmol), and I_2 (1.6 mmol) in DMSO (2 mL) at 100 °C for 24 h. [b] Isolated yields.

The scope of this reaction was further expanded to substituted 2-aminopyridines (Table 3). As expected, 2-aminopyridines substituted at the 3 or 4 positions were found effective under the present reaction conditions. Substrates with electron neutral (3-CH_3, 4-CH_3), electron-rich (4-OMe), and electron-deficient (4-CN, 4-COOEt) groups were all compatible and provided the corresponding products in moderate to good

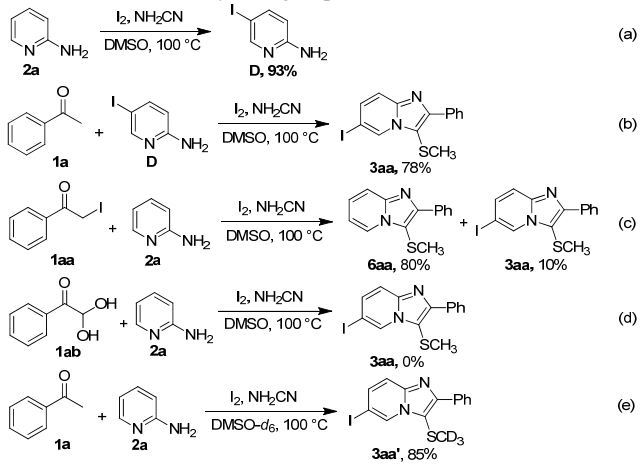
Table 3 Scope of 2-aminopyridines[a,b]



[a] Reaction Conditions: **1a** (1.0 mmol), **2** (1.0 mmol), NH_2CN (2.0 mmol), and I_2 (1.6 mmol) in DMSO (2 mL) at 100 °C for 24 h. [b] Isolated yields.

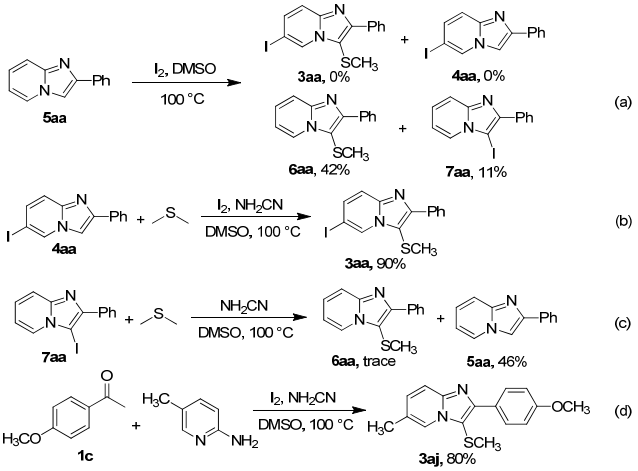
yields (53-84%; **3ab-af**). In general, 2-aminopyridines with electron-withdrawing groups proceeded more efficiently than those containing electron-donating groups. Halogen-substituted substrates (3-Cl, 4-Cl) also afforded the desired products (68-82%; **3ag-ah**). Moreover, 1-aminoisoquinoline (**2i**) was found to readily undergo the transformation, producing the target product **3ai** in 83% yield.

To gain mechanistic insight into this reaction, some control experiments were performed (Scheme 4). When the reaction was carried out without acetophenone, 5-iodopyridin-2-amine (**D**) was isolated in 93% yield (Scheme 4a). The use of **D** as the substrate instead of 2-aminopyridine under the standard conditions led to the formation of 6-iodo-3-(methylthio)-2-phenylimidazo[1,2-*a*]pyridine (**3aa**) in 78% yield (Scheme 4b), indicating that **D** is an important intermediate in this transformation. When phenacyl iodine (**1aa**) was subjected to the optimized conditions, **3aa** was obtained as a minor product in 10% yield (Scheme 4c). This result suggests that iodination might occur prior to the construction of the imidazo[1,2-*a*]pyridine ring. Furthermore, the reaction was unable to proceed when hydrated species (**1ab**) was employed (Scheme 4d), indicating that phenylglyoxal is not an intermediate in the transformation, which is different from our previous work on the *in situ* iodination-based oxidative coupling of aryl methyl ketones.[14] In addition, the reaction of **1a**, **2a** and DMSO-d_6 was carried out, and the deuterated product **3aa**-d_3 was generated (Scheme 4e), clearly confirming that DMSO serves as the source of the methylthio group.



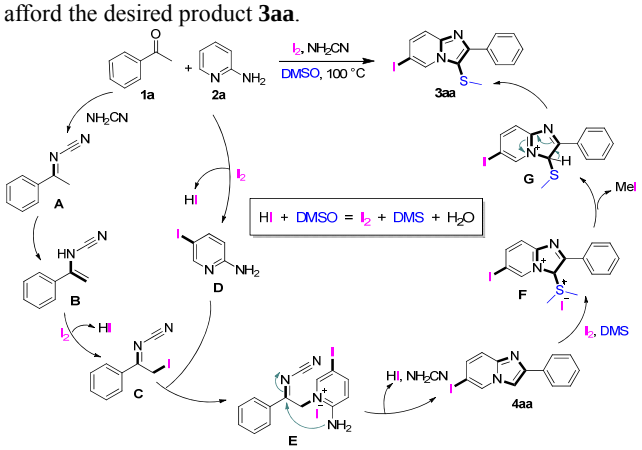
Scheme 4 Control experiments.

To further develop our understanding of the reaction mechanism, the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**5aa**) was performed, which gave neither **3aa** nor the 6-iodoimidazo[1,2-*a*]pyridine (**4aa**), but rather 3-methylthioimidazo[1,2-*a*]pyridine (**6aa**) and 3-iodo-2-phenylimidazo[1,2-*a*]pyridine (**7aa**) (Scheme 5a). This result provides further evidence that 2-aminopyridine might first react with I_2 to form 5-iodopyridin-2-amine (**D**) and that this product is then involved in the construction of the imidazo[1,2-*a*]pyridine. The treatment of 6-iodo-2-phenylimidazo[1,2-*a*]pyridine (**4aa**) with DMS under the optimized conditions afforded the desired product **3aa** in 90% yield (Scheme 5b), suggesting that **4aa** could be an important intermediate in the current reaction. When **7aa** was employed as the reaction substrate, **5aa** was obtained in 46% yield and almost half of the **7aa** was recovered (Scheme 5c), which excludes the possibility that nucleophilic aromatic substitution[15] is involved in the methylthiolation of the C-3 of imidazo[1,2-*a*]pyridine. It is noteworthy that 2-(4-methoxyphenyl)-6-methyl-3-(methylthio)imidazo[1,2-*a*]pyridine (**3aj**) was acquired when 4'-methoxyacetophenone and 5-methylpyridin-2-amine were used as the substrates (Scheme 5d), indicating that the iodination should be selective.



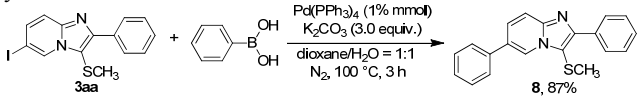
Scheme 5 Control experiments.

On the basis of the aforementioned information and previous work,[16] a plausible mechanism for this reaction is outlined in Scheme 6. The process is initiated by the activation of the carbonyl group of **1a** by NH_2CN to form imine intermediate **A**. Isomerization of **A** then occurs to yield enamine **B**, which would be transformed to **C** via iodination in the presence of I_2. Pyridinium salt **E** is subsequently generated via nucleophilic substitution of **C** with **D**, which results from the iodination of **2a**. Intramolecular cyclization and aromatization occurs to afford **4aa** with the release of HI and NH_2CN. Next, compound **4aa** would react with the DMS generated *in situ* from the reduction of DMSO to give the sulfonium intermediate **F**. Intermediate **F** would then undergo sequential loss of MeI and deprotonation to afford the desired product **3aa**.



Scheme 6 A possible mechanisim.

Considering that 6-iodo-3-methylthioimidazo[1,2-*a*]pyridines could easily undergo further transformation, we treated **3aa** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in dioxane/water = 1:1 at 100 °C, and the resulting Suzuki cross-coupling product **8** was readily prepared in 87% yield.[17]



In summary, we have developed a novel NH_2CN-promoted

four-component coupling reaction for the synthesis of 6-iodo-3-(methylthio)-2-arylimidazo[1,2-*a*]pyridines from aryl methyl ketones and 2-aminopyridines in the presence of I_2 and DMSO. Initial studies of the mechanism suggest that this reaction occurrs via the convergent integration of three self-sorting domino sequences. Remarkably, this reaction allows for the unusual formation of C-I and C-S bonds with imidazo[1,2-*a*]pyridines. Further studies to elucidate a detailed mechanism and identify applications of this protocol are currently underway in our laboratory.

This work was supported by the National Natural Science Foundation of China (Grant Nos. 21272085 and 21472056).

Notes and references

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†Electronic Supplementary Information (ESI) available. CCDC 1408629. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/b000000x/

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