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Metal-Free Mediated C-3 Methylsulfanylation of Imidazo[1,2-*a*]-pyridines with Dimethyl Sulfoxide as a Methylsulfanylating Agent

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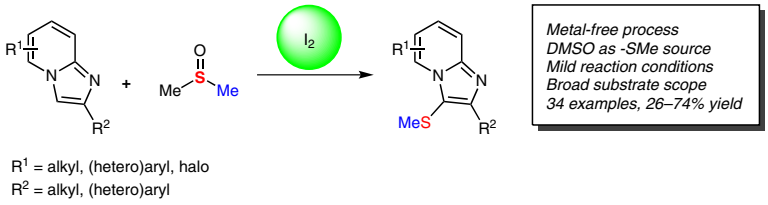

R^1 = alkyl, (hetero)aryl, halo
R^2 = alkyl, (hetero)aryl

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Abstract A simple approach is described for the regioselective C-3 methylsulfanylation of imidazo[1,2-*a*]pyridines through diiodine-mediated, acetone-promoted, C–S bond construction with dimethyl sulfoxide as both the source of the methylsulfanyl moiety and the solvent. Preliminary mechanistic investigations indicated that three different reaction mechanisms might be involved in the transformation.

Key words methylsulfanylation, C–S bond formation, imidazopyridines, dimethyl sulfoxide, iodine

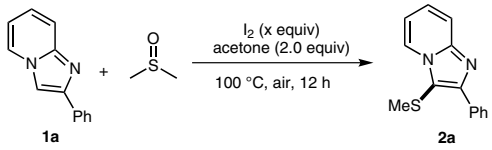
The introduction of a methylsulfanyl moiety into aromatic or heteroaromatic rings represents a fundamental and attractive area of research because of the remarkable biological activities of (hetero)aryl methyl thioethers, which are regarded as versatile and privileged structures in pharmaceutical chemistry.[1] (Hetero)aryl methyl thioethers are also used in a range of transition-metal-catalyzed cross-coupling reactions.[2] The conventional methods for the construction of (hetero)aryl methyl thioethers include the reduction of sulfoxides, the nucleophilic substitution of iodomethane, the electrophilic substitution of dimethyl disulfide, and the nucleophilic aromatic substitution (S_NAr) of thiolate anions, all of which suffer from a range of drawbacks.[3] In recent years, much progress has been made in the use of the environmentally benign and readily available solvent dimethyl sulfoxide (DMSO) as a methylsulfanylation agent to form C–SMe bonds. The methylsulfanylation of aryl halides by using DMSO as a source of the methylsulfanyl moiety in the presence or absence of a transition metal has been described by Cheng and others.[4] Notably, a direct methylsulfanylation of C(sp^2)–H bonds with DMSO through C–H activation has been developed by Qing and co-workers and by other groups.[5] From the viewpoints of the environment and atom economy, a combination of a C–H functionalization strategy and the use of green DMSO constitutes a straightforward and sustainable approach for the efficient assembly of structurally diverse (hetero)aryl methyl thioethers.

Functionalized imidazo[1,2-*a*]pyridine derivatives are ubiquitous heterocyclic scaffolds that possess numerous biological activities and serve as versatile building blocks for several pharmaceutically significant compounds.[6] For instance, some C-3 substituted imidazo[1,2-*a*]pyridines have been successfully applied as neuroactive drugs; these include necopidem, saripidem, zolpidem, alpidem, and olprinone.[6e,7] In the past few years, substantial steps have been made toward the regioselective functionalization of imidazo[1,2-*a*]pyridines, especially in C-3 sulfanylation, by the use of various promoters and sulfanylating reagents.[8] Unlike the C-3 sulfanylation of imidazo[1,2-*a*]pyridines, the corresponding methylsulfanylation has been rarely reported.[8b,9] The C-3 methylsulfanylation of imidazo[1,2-*a*]pyridines was explored by Roychowdhury[9a] and Wu[9b] and their respective co-workers; however, the reactions involved toxic $POCl_3$ or NH_2CN. Encouraged by our continuing efforts in iodine-mediated tandem reactions,[10] we have developed a nontoxic, mild, and operationally simple approach to the C-3 methylsulfanylation of imidazo[1,2-*a*]pyridines by using DMSO as both methylsulfanylating agent and solvent in the presence of inexpensive molecular iodine.

We began our study by using 2-phenylimidazo[1,2-*a*]pyridine (**1a**) as a model substrate. First, we examined the treatment of **1a** with 20 mol% I_2 and 2.0 equivalents of acetone in DMSO at 100 °C under air for 12 hours. Unfortunately, only a trace of the desired product **2a** was detected (Table 1, entry 1). To our delight, however, the yield of the methylsulfanylated product **2a** was markedly enhanced by increasing the amounts of I_2, and 2.0 equivalents of I_2 were found to give the highest yield (74%) of **2a** (entries 2–5). A

further increase in the amount of iodine resulted in an obvious decrease in the reaction efficiency (entry 6). Notably, no reaction occurred in the absence of iodine (entry 7). The effect of the volume of the DMSO solvent was also tested, and 1.0 mL of DMSO was found to the optimal quantity (entries 8–10). The transformation proceeded sluggishly in the absence of acetone, highlighting the crucial role of acetone in the reaction (entry 11). Replacement of I_2 with NH_4I totally inhibited the reaction (entry 12). Further investigations on the reaction temperature revealed that the reaction did not take place at room temperature, and that a reduced or elevated temperature (80 or 120 °C) gave slightly inferior results (entries 13–15).

Table 1 Optimization of the Reaction Conditions[a]

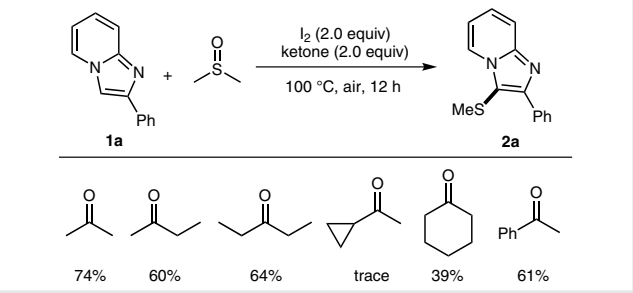


1a 2a

Entry	I_2 (equiv)	DMSO (mL)	Yield[b] (%)
1	0.2	1.0	trace
2	0.5	1.0	25
3	1.0	1.0	42
4	1.5	1.0	64
5	2.0	1.0	74
6	3.0	1.0	64
7	–	1.0	NR[c]
8	2.0	0.5	51
9	2.0	1.5	63
10	2.0	2.0	71
11[d]	2.0	1.0	22
12[e]	2.0	1.0	NR
13[f]	2.0	1.0	NR
14[g]	2.0	1.0	65
15[h]	2.0	1.0	60

[a] Reaction conditions: **1a** (0.3 mmol), I_2, acetone (0.6 mmol), DMSO, under air, 100 °C, 12 h.
[b] Isolated yield.
[c] NR = no reaction.
[d] In the absence of acetone.
[e] I_2 was replaced with NH_4I.
[f] At r.t.
[g] At 80 °C.
[h] At 120 °C.

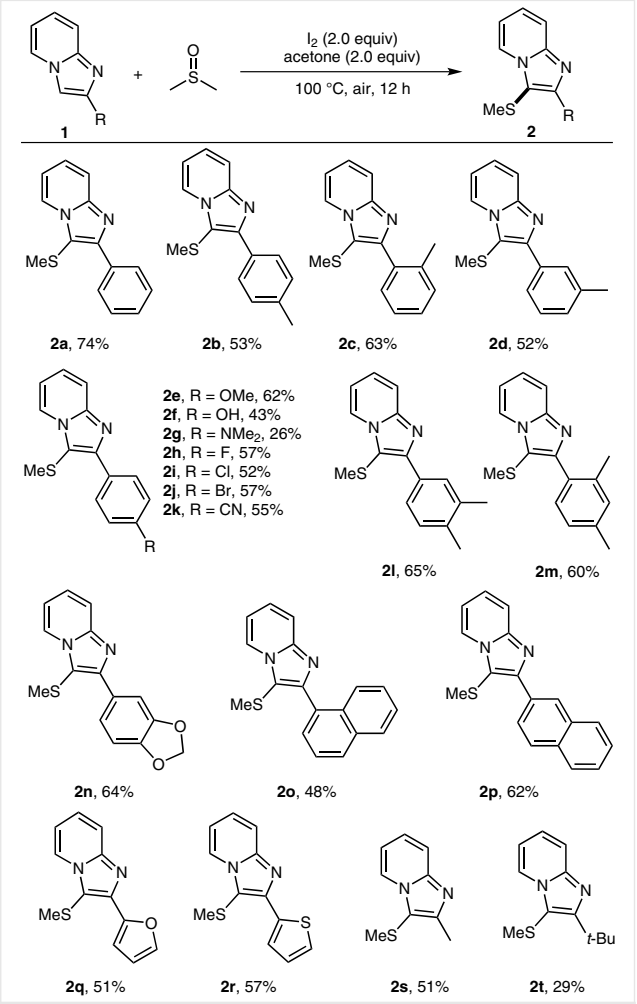
Because of the dramatically promotive role of acetone, we examined the effects of a range of ketone analogues (Scheme 1). Interestingly, butanone, pentan-3-one, or acetophenone produced comparatively efficient reactions, whereas a relatively lower reactivity was observed with cyclohexanone. With 1-cyclopropylethanone, however, only a trace of the methylsulfanylated product **2a** was obtained. Although the exact role of the ketones remains elusive, we speculate that they facilitate the formation of an active methylsulfanyl moiety during the reaction.



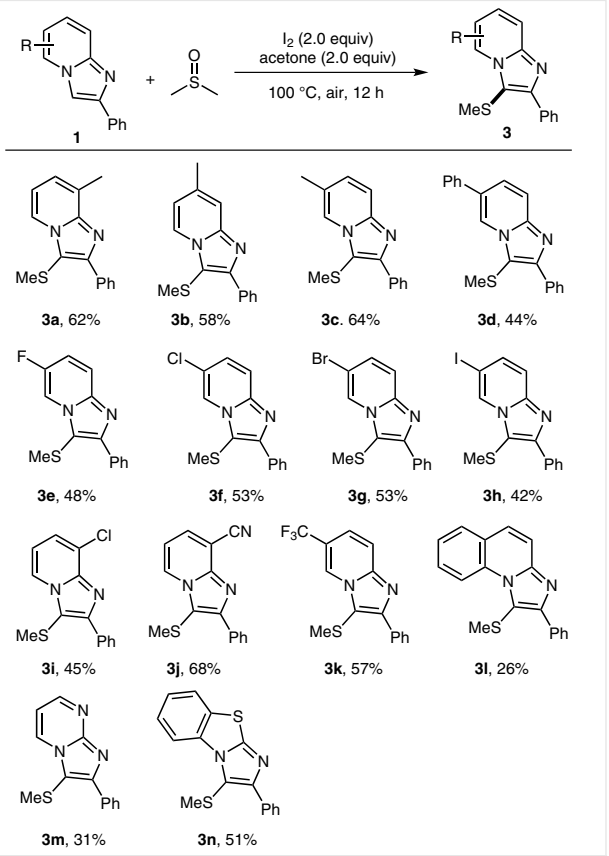
Scheme 1 The effects of various ketones

With the optimized reaction conditions in hand, we investigated the scope and limitations of the transformation.[11] A wide variety of substituents attached to the imidazole ring were examined. Gratifyingly, various substituents and functional groups on the aryl ring were smoothly tolerated under the reaction conditions, and the corresponding methylsulfanylated products **2a–n** were obtained in moderate to good yields (Scheme 2). *Ortho*- and *meta*-substituted substrates showed similar reactivities to *para*-substituted ones, suggesting that steric hindrance in the aryl ring has a marginal influence on the reaction (**2b–d**). Impressively, the sensitive hydroxy and dimethylamino functional groups were compatible with the reaction system, albeit with relatively low efficiencies (**2f** and **2g**). Note that halogenated substituents showed acceptable reactivities and provide an opportunity for further derivatization of the products (**2h–j**). Overall, the electronic nature of the aryl ring had a negligible effect on the reaction, as illustrated by the similar reactivities of substrates bearing electron-donating or electron-withdrawing groups (**2b–n**). Furthermore, a naphthalene ring and several heterocyclic moieties, such as furan or thiophene, were each incorporated into the target methylsulfanylated molecules in satisfactory yields (**2o–r**). More significantly, alkyl-substituted imidazo[1,2-*a*]pyridines are viable substrates for the methylsulfanylation process (**2s** and **2t**). The low yield of product **2t** might be attributable to steric hindrance by the vicinal *tert*-butyl group.

The generality of the present protocol was subsequently explored by an examination of the scope of imidazo[1,2-*a*]pyridines with various substituents on the pyridine ring (Scheme 3). A series of electron-donating or electron-withdrawing groups at various positions of the pyridine ring of the imidazo[1,2-*a*]pyridine were compatible with the reaction, leading to the corresponding methylsulfanylated products **3a–k** in moderate to good yields. Strongly electron-withdrawing cyano or trifluoromethyl groups (**3j–k**) were tolerated under the optimized conditions, indicating that



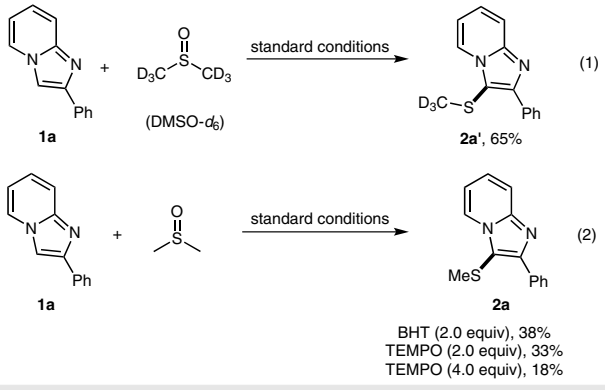
Scheme 2 The scope of imidazo[1,2-*a*]pyridines. *Reagents and conditions*: **1** (0.3 mmol), I_2 (0.6 mmol), acetone (0.6 mmol), DMSO (1.0 mL), under air, 100 °C, 12 h. Isolated yields are reported.



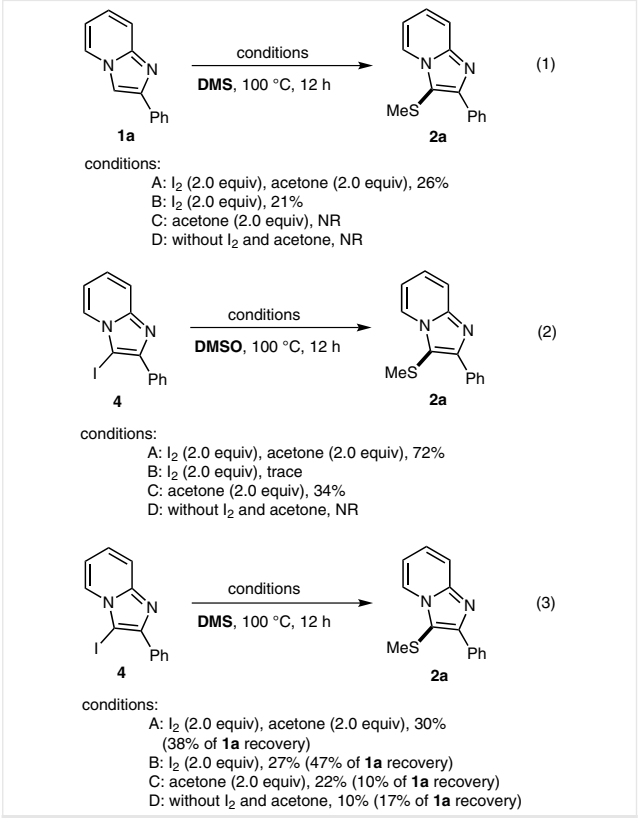
Scheme 3 The scope of imidazo[1,2-*a*]pyridines with modifications of the pyridine core. *Reagents and conditions*: **1** (0.3 mmol), I_2 (0.6 mmol), acetone (0.6 mmol), DMSO (1.0 mL), under air, 100 °C, 12 h. Isolated yields are reported.

the current method has excellent functional-group compatibility. A methylsulfanyl group was incorporated into the C-3 position of the imidazo[1,2-*a*]pyridine derived from quinolin-2-amine, albeit with relatively lower efficiency (**3l**). Note that two structurally complicated imidazoheterocycles underwent methylsulfanylation to give the desired products **3m** and **3n**, albeit in low to moderate yields. We speculate that the low yields from some substrates resulted from the unavoidable formation of 3-iodinated or dimeric products during the reaction.

To verify the exact source of the methylsulfanyl group, we used deuterated dimethyl sulfoxide as a solvent for the reaction and we detected fully deuterated methylsulfanyl groups in the desired product, confirming that DMSO acts as the terminal source of the methylsulfanyl group (Scheme 4, eq. 1). Furthermore, when a radical-trapping experiment was carried out, the yield of the reaction showed a dramatic decrease in the presence of the radical scavengers 2,4-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (Scheme 4, eq. 2). These observations indicated that a radical process might be involved in the transformation, but other pathways were not entirely ruled out.



Scheme 4 Mechanistic investigations



Scheme 5 Control experiments

To gain further insights into the reaction mechanism, we conducted a series of control experiments (Scheme 5). Substrate **1a** was treated under various conditions with dimethyl sulfide (DMS) as solvent. The reaction did not proceed in the absence of I_2, showing that a combination of I_2 and DMS was essential for the conversion of substrate **1a** into product **2a** (Scheme 5, eq. 1). When the C-3 iodinated imidazo[1,2-*a*]pyridine **4** was prepared and subjected to various reaction conditions, the transformation proceeded smoothly under the standard conditions, but only a trace of product **2a** was obtained when **4** was treated with DMSO and I_2 in the absence of acetone (Scheme 5, eq. 2). These results show that compound **4** might be an intermediate in the reaction, and demonstrated that acetone plays a crucial role. We also used compound **4** as a substrate in the reaction in DMS as solvent under various conditions (Scheme 5, eq. 3). We observed that the desired product **2a** was obtained in only a relatively low yield, and a certain amount of **1a** was recovered. The product **2a** was isolated in 10% yield, even in the absence of I_2 and acetone, suggesting that an atypical S_NAr-type reaction between compound **4** and DMS might have occurred (Scheme 5, eq. 3, conditions D).

On the basis of the aforementioned mechanistic investigations and previous relevant studies,[5d,9,12] a plausible reaction mechanism was proposed, as depicted in Scheme 6. First, α-iodination of acetone generates hydrogen iodide, which subsequently reacts with DMSO to give DMS. Thermal decomposition of DMSO might give CH_3SH and HCHO.[5b,13] Then, homolysis of I_2 releases an iodine radical[14] that undergoes subsequent reaction with CH_3SH to release a methylsulfanyl radical $CH_3S^{\bullet}$.[15] In path A, the radical $CH_3S^{\bullet}$ adds to the C-3 atom of imidazo[1,2-*a*]pyridine to give intermediate **A**, which is converted into intermediate **B** through a resonance effect. The desired product **2a** is obtained by elimination of $H^{\bullet}$ assisted by $I^{\bullet}$. In path B, **1a** reacts with DMS and I_2 to give the sulfonium intermediate **C**, which undergoes loss of CH_3I and subsequent deprotonation to afford product **2a**.[9b] In path C, the atypical nucleophilic aromatic substitution of compound **4** with DMS delivers the complex **E**,[4c] which releases CH_3I to give the final product **2a**.

In conclusion, we have developed a general and simple synthetic strategy for the efficient C-3 methylsulfanylation of imidazo[1,2-*a*]pyridines under metal-free conditions by using DMSO as both a source of the methylsulfanyl moiety and a solvent. The protocol features mild operating conditions, a broad substrate scope, and good functional-group compatibility. A number of control experiments were performed to shed light on the reaction mechanism. The transformation provides an alternative for the methylsulfanylation of imidazo[1,2-*a*]pyridines.

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Supporting Information

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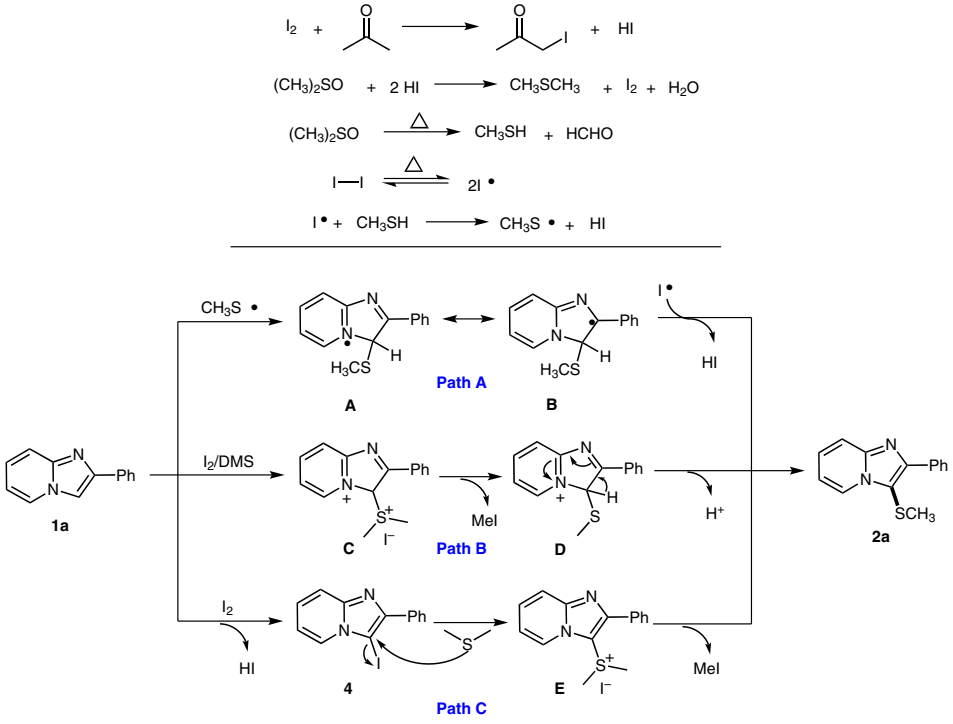

Scheme 6 Plausible reaction mechanism

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(11) **3-(Methylsulfanyl)-2-phenylimidazo[1,2-*a*]pyridine (2a); Typical Procedure**

I_2 (152 mg, 0.6 mmol) and acetone (35 mg, 0.6 mmol) were added to a solution of substrate **1a** (0.3 mmol) in DMSO (1 mL), and the mixture was stirred at 100 °C under air for 12 h. When the reaction was complete (TLC), the mixture was cooled to r.t., the reaction was quenched by H_2O, and the mixture was extracted with EtOAc (3 × 15 mL). The extracts were washed with 10% aq $Na_2S_2O_3$ (2 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by column chromatography (silica gel, PE–EtOAc) to give a brown-yellow solid; yield: 53 mg (74%); mp 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 6.8 Hz, 1 H), 8.29 (m, 2 H), 7.68 (d, *J* = 9.2 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.39 (m, 1 H), 7.30 (m, 1 H), 6.94 (td, J_1 = 6.8, J_2 = 0.8 Hz, 1 H), 2.26 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 146.3, 133.7, 128.4, 128.3, 128.2, 126.0, 124.2, 117.6, 112.7, 111.4, 18.1. HRMS (ES^+–TOF): *m/z* $[M + H]^+$ calcd for $C_{14}H_{13}N_2S$: 241.0799; found: 241.0799.

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