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Electrochemical-induced regioselective C-3 thiomethylation of imidazopyridines *via* a three-component cross-coupling strategy†

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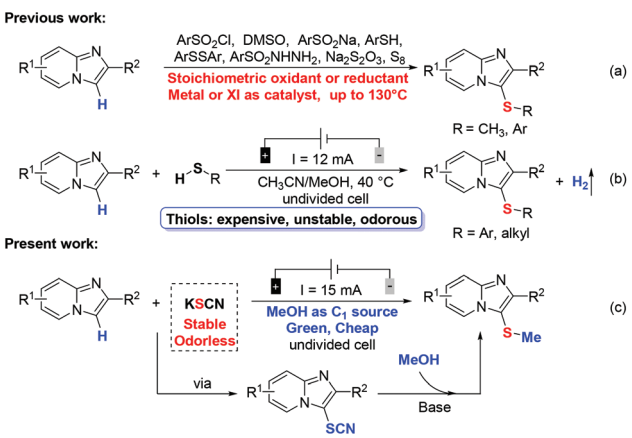
The electrochemical-induced regioselective C-3 thiomethylation of imidazopyridines has been initially accomplished *via* a three-component cross-coupling strategy using thiocyanate as the sulfur source and methanol as the methyl reagent. This protocol provides a green method for the thiomethylation of imidazopyridines without the need for any exogenous oxidants and metal catalysts under room temperature conditions. A wide range of functional groups were tolerated to produce regioselective C-3 thiomethylated products in high yields. Importantly, such an electrochemical-oxidation-induced thiomethylated reaction could be easily scaled up with excellent efficiency.

As one of the most important N-heterocyclic compounds, imidazo[1,2-*a*]pyridines are considered to be privileged scaffolds that have attracted great attention from chemists because their derivatives show varied biological activities, such as antiviral, antitumor, antiparasitic, and antimicrobial activities, and act as fungicidal agents.[1] Their varied biological activities and wide applications have stimulated the development of new synthetic approaches to obtain functionalized imidazole derivative compounds.[2] Consequently, given the electron-rich nature of imidazopyrine rings, substantial efforts have been devoted to the transition-metal or stoichiometric oxidant-mediated direct C–H functionalization of imidazo[1,2-*a*]pyridines, such as alkoxylation,[3] thiocyanation,[4] sulfenylation,[5] sulfonation,[4b] phosphorylation,[6] carbonylation[7] and amination.[8] In contrast, employment of thiocyanate derivatives as the sulfur source to achieve the thiomethylation of imidazopyridines is relatively less investigated.

Sulfur-containing compounds have attracted considerable attention due to their prevalence in a variety of natural products, pharmaceuticals, and materials.[9] Moreover, organosulfur architectures are considered as versatile precursors for further functionalizations of many bioactive products.[10] Therefore, the sulfenylation of imidazopyridines by using sulfonyl chloride,[11] sulfinic acids,[5f] disulfides,[12] thiols,[5i] dimethyl sulfoxide[5a,c,d,h] and elemental sulfur[5g] as the sulfur source (Scheme 1a) has gained much research interest. Nevertheless, most of these methods suffer from some limitations such as the need for smelly and expensive sulfur reagents, stoichiometric amounts of oxidants or reductants, harsh reaction conditions, and/or the use of metal catalysts (*i.e.*, Ir, Cu, Co). To address these limitations, electroorganic chemistry as a powerful and fascinating protocol has attracted considerable attention from chemists because the conventional chemical oxidizing or reducing agents can be replaced by electric current as an inexpensive and sustainable reagent.[13] Recently, Lei and coworkers have successfully achieved C-3 sulfenylation of imidazopyridines with thiols under electrochemical conditions (Scheme 1b).[5i] As far as we know, there is no report on the thiomethylation of imidazopyridines *via* a three-component cross-coupling strategy using cheap, stable, and odorless thio-



Scheme 1 Thiolation of imidazo[1,2-*a*]pyridines using different sulphenylating reagents.

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cyanate as the sulfur source and methanol as the methyl reagent in the absence of metal catalysts and any exogenous oxidants. In continuation of our efforts in constructing sulfur-containing compounds,[14] here, we wish to report a new and efficient thiomethylation of imidazopyridines with thiocyanate and methanol by a one-pot three-component oxidative cross-coupling strategy under electrochemical conditions (Scheme 1c). The present protocol provides a convenient and efficient approach to synthesize a series C-3 thiomethylated imidazopyridine derivatives in moderate to high yields using an undivided electrolytic cell under metal- and external oxidant-free conditions.

At the outset of our investigations, a pilot electrocatalytic thiomethylation reaction of **1b** was carried out in an undivided cell with a stoichiometric amount of KSCN using MeOH as the methyl reagent in CH_3CN solvent (Table 1). To our delight, by optimizing the key reaction parameters, the best results were obtained by performing electrolysis at room temperature under a constant current of 15 mA cm^{-2} in an undivided cell, which was equipped with a graphite rod anode and a platinum plate cathode and conducting lithium perchlorate ($LiClO_4$) as the electrolyte at room temperature. Under these conditions, the desired product **2b** was obtained in 98% yield (Table 1, entry 1). As expected, the control experiments demonstrate that both electricity, and KSCN and MeOH play decisive roles in accessing the desired products (Table 1, entries 2–4). However, the desired product **2b** was obtained in a yield of only35% when KSCN was replaced with NH_4SCN under the standard conditions (Table 1, entry 5). In order to investigate the reasons behind this, cyclic voltammetry (CV) experiments were carried out, showing that the oxidation potentials of KSCN, NH_4SCN, **1b** and **2b** were 0.95 V, 1.1 V, 1.0 V and 1.2 V ($E_{p/2}$ *vs.* Ag/AgCl), respectively. The results demonstrate that NH_4SCN has a higher oxidation potential than KSCN and **1b**,

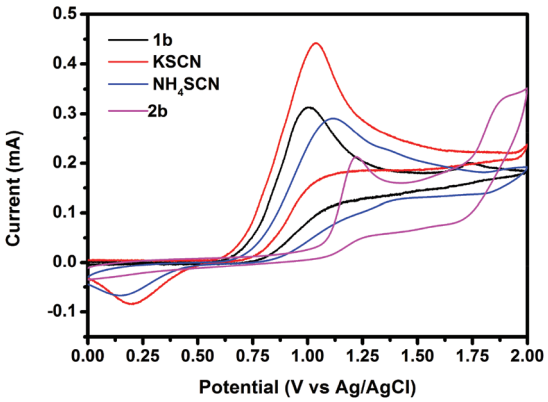


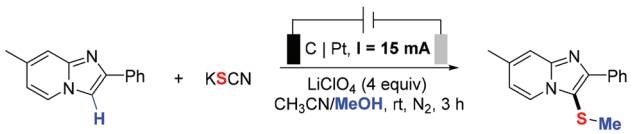
Fig. 1 Cyclic voltammetry experiments.

so the formation of $(SCN)_2$ on the electrode surface should be more difficult, resulting in lower yields (Fig. 1). Subsequently, slightly reduced but still acceptable yields were obtained when the reaction was performed in ammonium salt (Table 1, entries 6–8). Both increasing and decreasing the constant current would dramatically decrease the reaction yields (Table 1, entry 9). Also, the effects of the electrode materials were investigated. Lower reaction yields were obtained on exchanging the cathode and anode or switching to a platinum plate anode with a surface area much lower than that of the graphite rod anode (Table 1, entries 10 and 11).

With the optimized conditions described above, the substrate scope was investigated and restrictive analysis was conducted by varying the peripheral substituents (R^1 and R^2) of scaffold **1** (Table 2). The electrolysis reaction exhibited excellent compatibility with a variety of electron-donating and electron-withdrawing groups at different positions of the imidazo[1,2-*a*]pyridine ring (**2a–2i**). Unfortunately, no desired product was obtained when KSeCN instead of KSCN was subjected to the standard conditions. Also, the effects of the C-2 substituents on the phenyl ring were examined. As expected, both electron-donating and electron-withdrawing groups at different positions of the substituents on the phenyl ring afforded the corresponding methylated products in excellent yields (**2j–2n**). Moreover, the structure of **2n** was unambiguously confirmed by single-crystal X-ray analysis (Fig. 2). These results indicate that the developed protocol is not affected by the electronic and steric effects. It should be noted that imidazo[1,2-*a*]pyridines substituted by the steric hindrance, heterocyclic or alkyl, groups can still react well under the established conditions (**2o–2u**). More importantly, the commercially available imidazo[1,2-*a*]pyridine could also give the desired product in a moderate yield (**2v**).

The application of the electrochemical-oxidation-induced thiomethylation for other kinds of heterocyclic compounds was explored, including benzo[*d*]imidazo[2,1-*b*]thiazole and imidazo[1,2-*a*]pyrimidine (Table 3). Satisfactorily, the corresponding thiomethylated products could be obtained in satisfactory yields (**4a–4c**). Yet, no or trace amounts of the desired

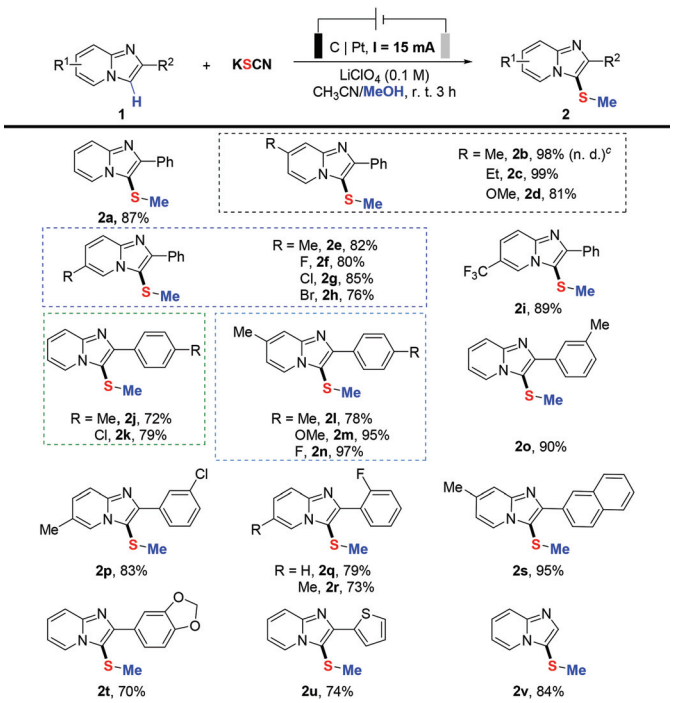
Table 1 Optimization of the reaction conditions[a]



Entry	Deviation from standard conditions	Yield[b] (%)
1	None	98
2	Without current	n.d.
3	Without KSCN	n.d.
4	Without MeOH	n.d.
5	NH_4SCN instead of KSCN	35
6	nBu_4NClO_4 instead of $LiClO_4$	78
7	nBu_4NBF_4 instead of $LiClO_4$	84
8	nBu_4NPF_6 instead of $LiClO_4$	96
9	Entry 1 but 12 mA or 17 mA	60–49
10	Pt (+)|C (−) instead of C (+)|Pt (−)	63
11	Pt (+)|Pt (−) instead of C (+)|Pt (−)	62

[a] Standard conditions: C anode, Pt cathode, constant current = 15 mA, **1b** (0.25 mmol), KSCN (2.0 equiv.), $LiClO_4$ (4.0 equiv.), MeOH (0.5 mL), MeCN (9.5 mL), r.t., N_2, 3 h. n.d. = not detected. [b] Isolated yields.

Table 2 Scope of imidazopyridines[a,b]



[a] Standard conditions: C anode, Pt cathode, constant current = 15 mA, **1** (0.25 mmol), KSCN (2.0 equiv.), $LiClO_4$ (4.0 equiv.), MeOH (0.5 mL), MeCN (9.5 mL), r.t., N_2, 3 h. n.d. = not detected. [b] Isolated yields. [c] KSeCN instead of KSCN.

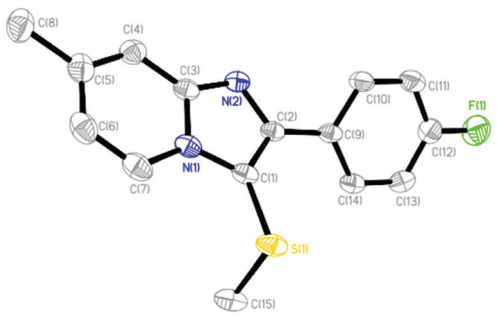
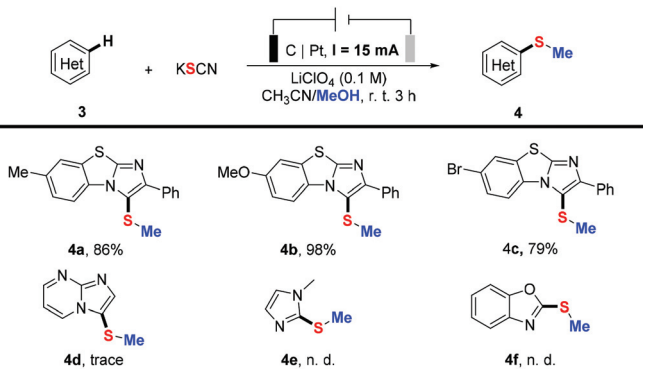


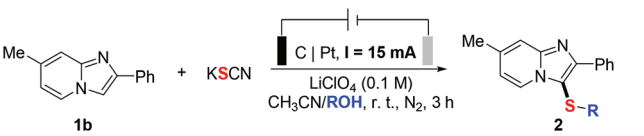
Fig. 2 Crystal structure of **2n**. ORTEP drawing of $C_{15}H_{13}FN_2S$ with 30% probability ellipsoids showing the atomic numbering scheme.

Table 3 Scope of imidazoheterocycles[a,b]

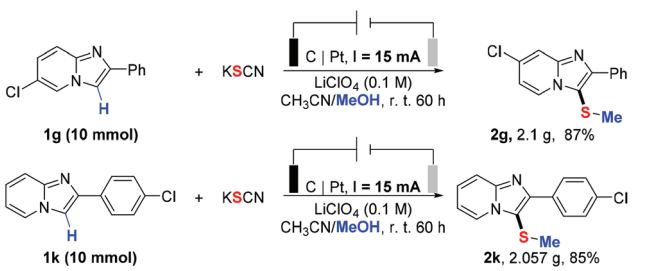


[a] Standard conditions: C anode, Pt cathode, constant current = 15 mA, **3** (0.25 mmol), KSCN (2.0 equiv.), $LiClO_4$ (4.0 equiv.), MeOH (0.5 mL), MeCN (9.5 mL), r.t., N_2, 3 h. n.d. = not detected. [b] Isolated yields.

Table 4 Investigation of other alcohols



Entry	ROH	Yield (%)
1	MeOH	**2b**, 98%
2	EtOH	**2w**, 70%
3	1-Propanol	**2x**, n.d.
4	^{n}BuOH	**2y**, n.d.



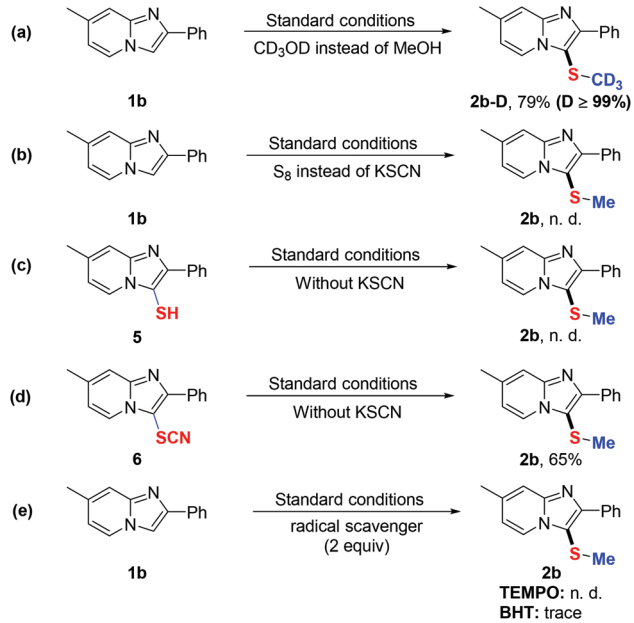
Scheme 2 Gram-scale experiments.

products **4d**, **4e** and **4f** were obtained when imidazo[1,2-*a*]pyrimidine, 1-methyl-1*H*-imidazole and benzo[*d*]oxazole were used as substrates under the standard conditions.

Furthermore, to extend the scope of the developed methodology, other alcohols such as ethanol, *n*-propanol and *n*-butanol have also been examined by using the established protocols. Unfortunately, only the use of ethanol could give 70% yield, whereas using other alcohols might not result in the desired corresponding products (Table 4).

The synthetic applicability of the present protocol on a gram-scale reaction was investigated in the usual laboratory setup. As shown in Scheme 2, under the standard conditions, by using **1g** and **1k** as the substrates the corresponding products of **2g** and **2k** were obtained in excellent yields of 87% and 85%, respectively. The results confirm that the present protocol can serve as a practically efficient strategy to obtain thiomethylated imidazopyridine products *via* an electrochemical-induced methodology with alcohol as the alkylating agent.

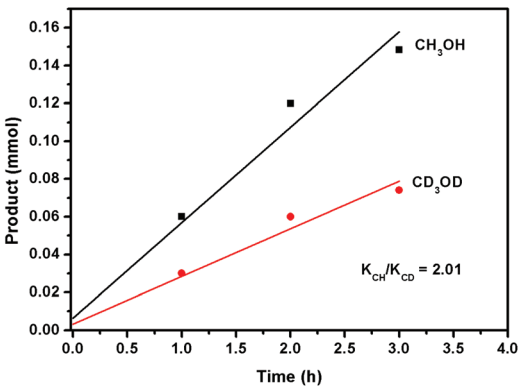
To explore the transformation mechanism, control experiments and deuteration experiments were carried out. Firstly, deuteration experiments show that the methyl group of the product was derived from methanol (Scheme 3a). Furthermore, no desired product **2b** could be obtained when



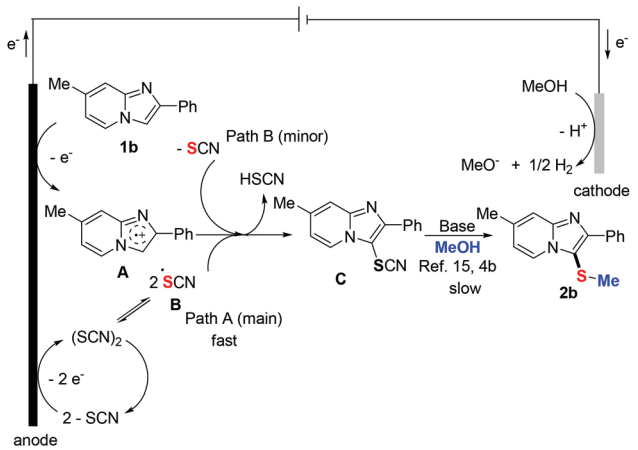
Scheme 3 Control experiments.

elemental sulfur was used under the standard reaction conditions (Scheme 3b). Also, when the reaction of **5** and **6** was carried out under the established conditions, only **6** could afford the desired product in 65% yield, indicating that **6** was an intermediate in the present protocol (Scheme 3c and d). Besides, it was revealed that the methylation reaction was almost inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tertbutyl-4-hydroxytoluene (BHT) was added into the present reaction system, suggesting that the reaction presumably adopted a radical pathway.

To gain a deeper insight into the reaction mechanism, kinetic isotopic effect (KIE) experiments were performed by choosing **1b** as the substrate (Scheme 4). The zero-order rate constant for CH_3OH (k_{CH}), estimated from the initial slope of the plot, is larger than that for CD_3OD (k_{CD}), showing a moderate KIE (k_{CH}/k_{CD}) value of 2.01. The data suggest that the catalytic cycle may involve the dissociation of methanol as a kinetically important step.



Scheme 4 Kinetic isotopic effect experiments.



Scheme 5 Postulated reaction pathway.

Based on the above results and referring to some previous reports,[4b,15] a plausible mechanism is proposed for the regioselective C-3 thiomethylation of imidazopyridines with KSCN and methanol under the electrochemical conditions (Scheme 5). Initially, substrate **1b** undergoes single-electron oxidation at the anode to give intermediate **A**. Subsequently, KSCN is oxidized to form $(SCN)_2$ on the anode surface, and further converted to thiocyanyl radical **B** to cross-couple with **A** yielding intermediate **C**. Finally, intermediate **C** reacts with methanol to furnish the desired product **2b** under the base conditions, of which hydrogen is released as the by-product at the cathode.

Conclusions

In conclusion, we have disclosed an efficient and practical thiomethylation of imidazopyridines by an electrochemical-oxidation-induced three-component cross-coupling strategy. Compared with the previous methods for functionalization of imidazopyridines, this is the first example of C-3 thiomethylation of imidazopyridines by electrochemical oxidation using thiocyanate as the sulfur source. A series of new products of drug candidates can be produced in good to high yields with excellent tolerance for various functional groups under electrochemical oxidation conditions. In particular, the three-component cross-coupling strategy for electrochemical oxidation-induced thiomethylation can be easily scaled up, with promising wide practical applications in the industry. Studies employing the green thiomethylation methodology to synthesize other kinds of bioactive compounds are currently underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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