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Transition-metal-free regioselective C–H halogenation of imidazo[1,2-*a*]pyridines: sodium chlorite/bromite as the halogen source†

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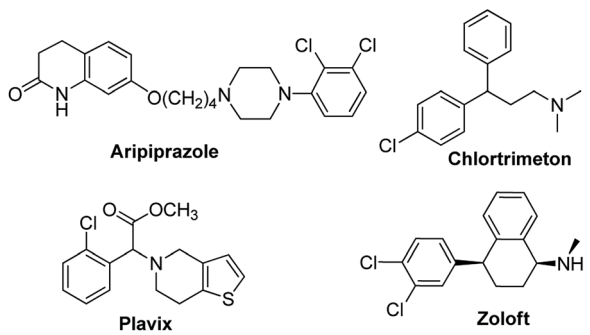
A facile transition-metal-free regioselective halogenation of imidazo[1,2-*a*]pyridines using sodium chlorite/bromite as the halogen source is presented. The reaction has provided an efficient method for the formation of C–Cl or C–Br bonds to synthesize 3-chloro or 3-bromo-imidazo[1,2-*a*]pyridines which were then efficiently transformed into imidazo[1,2-*a*]pyridine core π-systems by Suzuki–Miyaura reactions.

Aryl halides as a structural skeleton are present in a large number of natural products, pharmaceuticals, and biologically active compounds.[1] Significant drugs such as Aripiprazole, Chlortrimeton, Plavix and Zoloft all included the aryl chlorides motif (Scheme 1). Apart from this, aryl bromides have always been extremely important synthetic intermediates and building blocks in organic chemistry[2] for the construction of diverse and highly functionalized compounds. In the past few years, aryl halides have been used as substrates to form carbon–carbon and carbon–heteroatom bonds *via* transition-metal-catalyzed cross-coupling reactions. There are some classical methods: Heck, Suzuki, Negishi, Stille, Sonogashira, Ullmann, Buchwald–Hartwig, Kumada, *etc.*[3–10] Consequently, the development of a new route for the construction of these scaffolds is highly desirable, especially those based on assembling structures directly from readily available raw materials. In the last few years, several transition-metal-catalyzed halogenation transformations[11,12] have been developed, employing Pd, Rh or Cu as the catalysts and carboxylic acid, amide, nitrile, or pyridine as the directing groups (Scheme 1a). Recently, NH_4X, NaX and HX have been also employed as the halogen sources[13] in transition-metal-free conditions for the halogenation of several arenes and heteroarenes (Scheme 1b). Nevertheless, directing groups and additional oxidants were usually needed in these transformations and the halogen sources were very limited.



Scheme 1 Chlorine containing drugs.

In order to expand the richness of green synthetic methods, we tried to hunt for other atom-economical and easy-to-obtain halogen sources. As we know, sodium chlorite or bromite are commodity chemicals that are widely used as main effective components of bleaches or desizing agents.[14] On the other hand, imidazo[1,2-*a*]pyridines represent an important class of molecules and show unique bioactivities and chemical properties[15] that lead them to broad applications in organic synthesis and pharmaceutical chemistry.[16] Recent significant advances[17] have been achieved in this field. We have also developed novel strategies for the construction of imidazo[1,2-*a*]pyridines.[18] Herein, our current interest is focused on developing an efficient transition-metal-free selective halogenation of imidazo[1,2-*a*]pyridines without direct group, in which process sodium chlorite or bromite were used as both halogen sources and oxidants (Scheme 2c).

Our initial investigation focused on the halogenation of imidazo[1,2-*a*]pyridine **1a**. The results of the optimized reaction conditions are summarized in Table 1. The reaction was conducted in the presence of $NaClO_2$ (1 equiv.), AcOH (2 mmol), in toluene at 60 °C for 10 h (Table 1, entry 1). To our delight, the desired product **2a** was formed in 64% yield. No regioisomeric products were observed by GC-MS and ^{1}H NMR spectroscopy. Being delighted by this result, we then carried out the different optimization experiments to obtain the optimal reaction conditions. Various amounts of $NaClO_2$ were next survey for this transformation (Table 1, entries 2–3). A similar yield was

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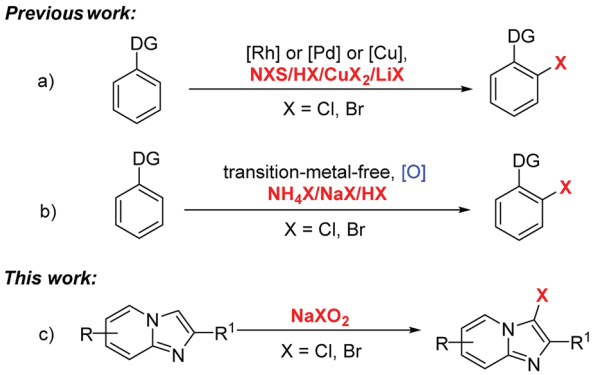
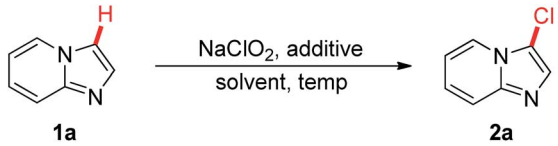


Scheme 2 Selective halogenation reactions.

Table 1 Optimization of the reaction conditions[a]



Entry	$NaClO_2$ (equiv.)	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	2	AcOH	Toluene	60	64
2	3	AcOH	Toluene	60	62
3	1	AcOH	Toluene	60	43
4	2	CF_3COOH	Toluene	60	40
5	2	PivOH	Toluene	60	29
6	2	TsOH	Toluene	60	31
7	2	—	Toluene	60	Trace
8	2	AcOH	Dioxane	60	69
9	2	AcOH	NMP	60	45
10	2	AcOH	CH_3CN	60	37
11	2	AcOH	DMSO	60	63
12	**2**	**AcOH**	**DMF**	60	**87**
13	2	AcOH	DCE	60	14
14	2	AcOH	DMF	40	74
15	2	AcOH	DMF	80	85
16[c]	2	AcOH	DMF	60	n.r.

[a] Reaction conditions: **1a** (0.5 mmol), $NaClO_2$ (1–3 mmol), AcOH (2 mmol), solvent (2 mL), 40–80 °C for 10 h. [b] Determined by GC analysis. [c] Without $NaClO_2$.

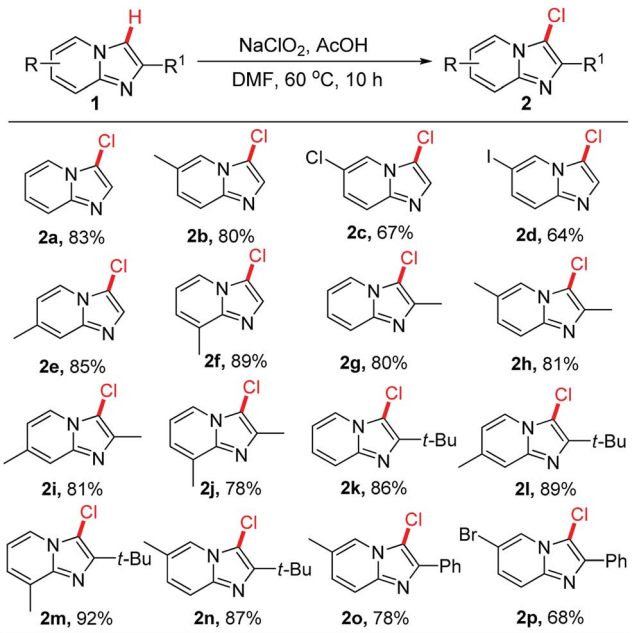
obtained after increasing the amount of $NaClO_2$ to 3 equiv., while a decreased yield was observed after decreasing the amount from 2 to 1 equiv. Among the set of additives examined, AcOH gave the desired product **2a** in good yield, while CF_3-COOH, PivOH and TsOH were found to be less effective in affording the corresponding product **2a** in 29–40% yield (Table 1, entries 4–6). It was worth noting that if acid was not added, only trace amount of target product was generated (Table 1, entry 7). The effect of solvents was further tested. It was found that DMF was the best choice in comparison to toluene, 1,4-dioxane, NMP, CH_3CN, DMSO and DCE (Table 1, entries 8–13). We then screened the reaction temperature and found the reaction performed at 40 °C or 80 °C gave a lower yield of the product **2a** (Table 1, entries 14–15). The control experiment indicated that product **2a** was not generated in the absence of $NaClO_2$ (Table 1, entry 16).

With the establishment of the optimal conditions, the scope of this transition-metal-free chlorination reaction was next investigated. And the results have been described in Scheme 3. A variety of 2-unsubstituted imidazo[1,2-*a*]pyridines were first employed under the optimized conditions. Different position substituted groups on the pyridine ring of imidazo[1,2-*a*]pyridine, having 6-CH_3, 6-Cl, 6-I, 7-CH_3, 8-CH_3 substitution, were well-tolerated under the optimized conditions. The results indicated that selective C-3 chlorination products **2a–2f** were formed in good to excellent yields. This catalytic system was further found to be successfully applied to catalyze the chlorination of 2-CH_3, 2-$C(CH_3)_3$, and 2-Ph substituted imidazo[1,2-*a*]pyridines, generating the desired products in moderate to good yields (**2g–2p**). It was worth noting that when imidazo[1,2-*a*]pyridines substituted with sterically hindered 2-$C(CH_3)_3$ were employed as substrates, the transformation worked well and led to a beneficial effect on the reaction outcome.

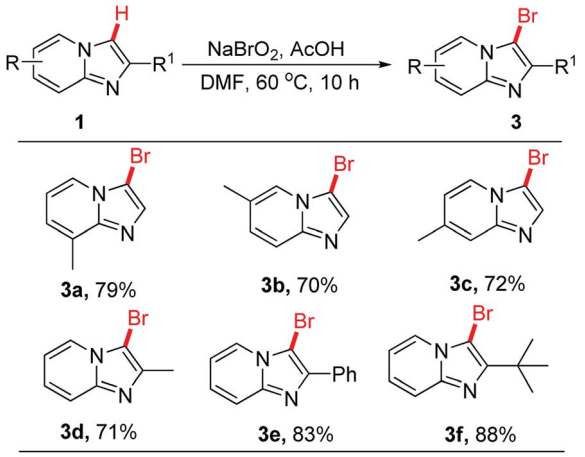
We next examined the bromination of imidazo[1,2-*a*]pyridines derivatives in the presence of $NaBrO_2$ and AcOH in DMF at 60 °C for 10 h. The results were summarized in Scheme 4. As we expected, the optimal conditions could also be applied to bromination of imidazo[1,2-*a*]pyridines and afforded the brominated products **3a–3f** in 70–88% yields. It was found that the reaction was also with great regioselective in the case of 2-unsubstituted imidazo[1,2-*a*]pyridines.

The reactions of **2a** or **3d** with phenylboronic acid were conducted in the presence of Pd-catalyst (Scheme 5). The Suzuki–Miyaura reactions were performed very well, affording the product **5a** or **6a** in 74% or 79% yields, respectively.

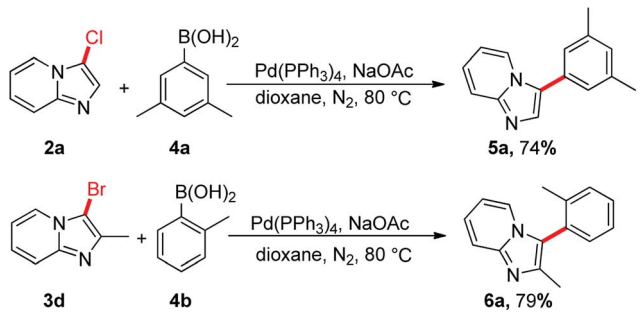
In order to text whether this method is compatible with other aromatic species or not, we have tried to use indoles, 1-methyl-



Scheme 3 Chlorination of imidazo[1,2-*a*]pyridines.



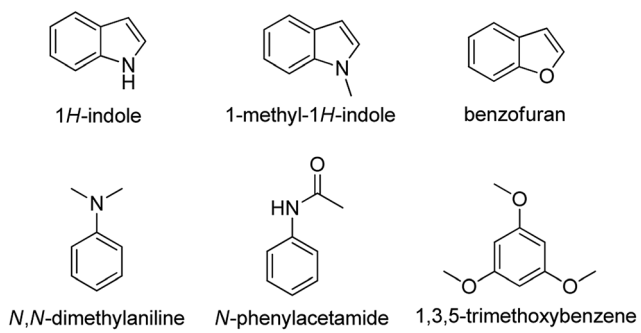
Scheme 4 Bromination of imidazo[1,2-*a*]pyridines.



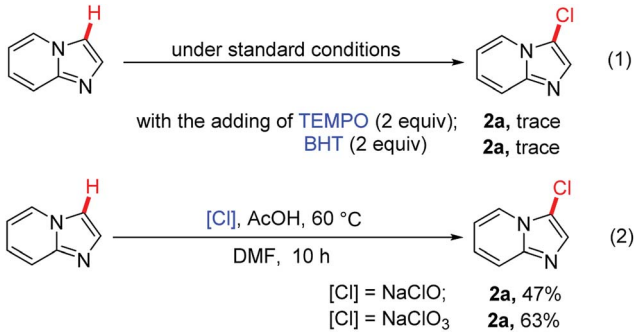
Scheme 5 Suzuki–Miyaura reactions of **2a** or **3d** with phenylboronic acid.

1*H*-indoles, benzofurans, *N*,*N*-dimethylaniline, *N*-phenylacetamide and 1,3,5-trimethoxybenzene to perform under the present reaction conditions, while no target products were obtained. We supposed that the specificity of this reported method is because of the rich electronic ethene-1,2-diamine moiety of imidazo[1,2-*a*]pyridine (Scheme 6).

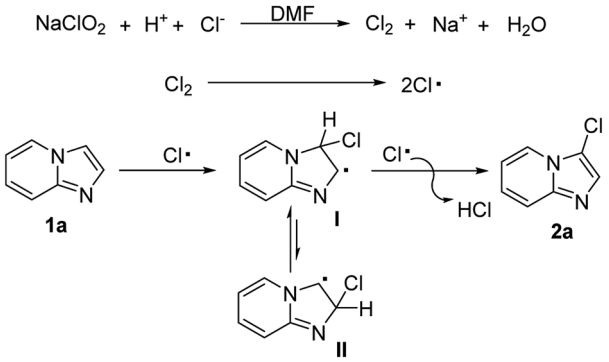
Gaining insight into the mechanism, control experiments were carried out for this transition-metal-free halogenation reaction. To prove a radical species involved in transformation, the reactions were conducted by adding radical-trapping reagent



Scheme 6 Applications for other aromatic species.



Scheme 7 Control experiments for investigation of the mechanism.



Scheme 8 Possible mechanism.

(TEMPO) or radical inhibitor (BHT) (Scheme 7, eqn (1)) in the reaction, and only trace amount of product **2a** was observed. The result clearly showed that this reaction had been inhibited and a radical process was involved for this transformation, which was consistent with previous reported.[17] To further investigated the chlorine source, NaClO and $NaClO_3$ were employed to react with imidazo[1,2-*a*]pyridine **2a** under the standard conditions. The results showed that the chlorination products were obtained in yields of 47% or 63% respectively, which means chlorine ions having a charge of 1+ or 5+ can also proceed this transformation, albeit with low yields (Scheme 7, eqn (2)).

Base on the above results and previous works,[19] a possible mechanism was proposed to account for this transition-metal-free regioselective halogenation reaction (Scheme 8). Firstly, oxidation–reduction reaction of sodium chlorite happened in the presence of AcOH to produce chlorine, NaOAc and H_2O. Subsequently, the chlorine radical was easily formed *via* homolysis of chlorine, which then attack the double bond between C2 and C3 of imidazo[1,2-*a*]pyridine, resulting in free radical intermediate **I** (more stable than **II** because of the p–π conjugation). Finally, the free radical intermediate **I** underwent an aromatization with chlorine free radical to give the target product **2a**.

Conclusions

In conclusion, we have developed an efficient transition-metal-free regioselective C–H functionalization approach. The

reaction provides a new selective route to synthesize 3-Cl or 3-Br-imidazo[1,2-*a*]pyridines without directing groups. The use of cheap sodium chlorite or bromite as both halogenic sources and oxidants is a major advantage. The 3-Cl or 3-Br-imidazo[1,2-*a*]pyridines as the substrates can successful apply to Suzuki–Miyaura reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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