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PII: S0040-4039(19)30209-6
DOI: https://doi.org/10.1016/j.tetlet.2019.03.008
Reference: TETL 50649

To appear in: *Tetrahedron Letters*

Received Date: 14 January 2019
Revised Date: 26 February 2019
Accepted Date: 3 March 2019

Please cite this article as: Katrun, P., Kuhakarn, C., $K_2S_2O_8$-Mediated halogenation of 2-arylimidazo[1,2-*a*]pyridines using sodium halides as the halogen sources, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.03.008

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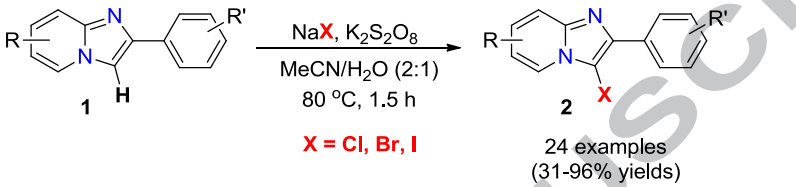

Tetrahedron Letters
journal homepage: www.elsevier.com

$K_2S_2O_8$-Mediated halogenation of 2-arylimidazo[1,2-*a*]pyridines using sodium halides as the halogen sources

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Bromination
Potassium persulfate
Imidazo[1,2-*a*]pyridine
Nitrogen-heterocycle

ABSTRACT

A convenient halogenation of 2-arylimidazo[1,2-*a*]pyridines using sodium chloride/bromide/iodide as the halogen sources in the presence of $K_2S_2O_8$ as an easy-to-handle oxidizing agent was developed. The present work offers an efficient and rapid access to 3-chloro-, 3-bromo- and 3-iodo-2-arylimidazo[1,2-*a*]pyridines which can be readily converted to *C*3-substituted imidazo[1,2-*a*]pyridines by cross-coupling reactions.

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Among various types of nitrogen-containing organic molecules, imidazo[1,2-*a*]pyridine is an important structural scaffold commonly found in biologically active natural products and pharmaceutical molecules. Compounds bearing imidazo[1,2-*a*]pyridine core were shown to exhibit a variety of biological activities and pharmacological effects such as antibacterial,[1] antiviral,[2] antitumor[3] and anti-inflammatory[4] activities. Imidazo[1,2-*a*]pyridine-containing molecules also act as GABA and benzodiazepine receptor agonists, GnRH antagonist and cardiotonic agents.[5] Therefore, imidazo[1,2-*a*]pyridine scaffold was found in many commercially available drugs such as Zolpiden, Zolimidine, Saripidem, Alpidem, Necopidem, Miroprofen, Olprione and GSK812397 as shown in Figure 1.[6]

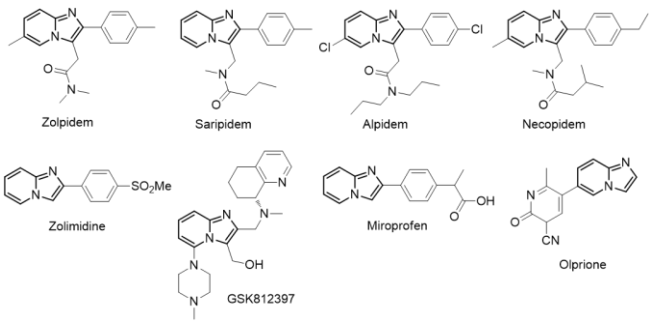
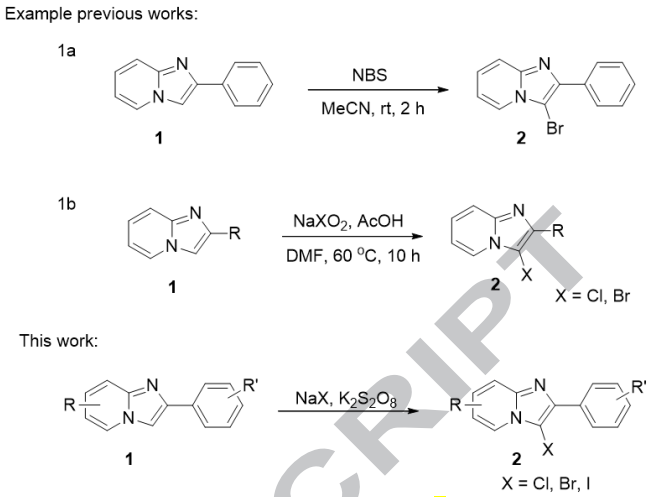


Figure 1. Selected examples of drugs bearing an imidazo[1,2-*a*]pyridine scaffold.

Accordingly, there has been of great interest in the development of synthetic methods for the construction and functionalization of the imidazo[1,2-*a*]pyridine core.[7] Halogenated arenes are important synthetic intermediates and building blocks in organic transformation through cross-coupling reactions. Thus, halogenated imidazo[1,2-*a*]pyridines have been widely employed as versatile synthetic intermediates[8] which could be readily converted to highly complex compounds.[9] In the past decades, there have been a number of studies towards the development of synthetic methodologies for the construction of a core structure of imidazo[1,2-*a*]pyridines **1**. On the other hand, fewer works have addressed general methods to access *C*2- or *C*3-halogenated imidazo[1,2-*a*]pyridines.[10-17] 2-Aryl-3-bromoimidazo[1,2-*a*]pyridines **2** were readily prepared by treatment of *C*2-substituted [1,2-*a*]pyridines **1** with *N*-bromosuccinimide (NBS) (Scheme 1a).[16] A facile transition-metal-free regioselective halogenation of imidazo[1,2-*a*]pyridines **1** using sodium chlorite/bromite as the halogen sources yielded the corresponding *C*3-halogenated derivatives **2** (Scheme 1b).[17] Although the previous works disclosed for the synthesis of *C*3-halogenated imidazo[1,2-*a*]pyridines are useful, it is still desirable, in the perspective view of the development of new synthetic methodology, to develop alternative and general procedure to access halogenated imidazo[1,2-*a*]pyridines under simple and convenient reaction conditions. Herein, the present work described our findings on halogenation of imidazo[1,2-*a*]pyridines **1** employing readily available and inexpensive sodium halides as halogen sources in the presence of easy-to-handle $K_2S_2O_8$ as an oxidizing agent under mild conditions and short reaction time.

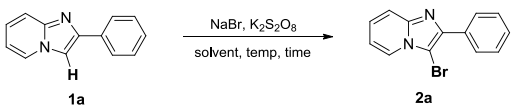
We began our study employing 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and sodium bromide (NaBr) as the model substrates to screen for optimum reaction conditions. A variety of reaction parameters including solvent, reaction temperature, bromide source and reagent stoichiometry were screened and the results are summarized in Table 1. First, the effect of solvents was primarily evaluated. The reactions were screened employing 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 0.5 mmol), NaBr (4 equiv.)



Scheme 1. The halogenation of imidazo[1,2-*a*]pyridines scaffold.

and $K_2S_2O_8$ (1.5 equiv.) in solvent (3 mL) and the reactions were carried out at either at 80 °C or at refluxing temperature for 1.5 h. Pleasingly, the reaction performed in a mixture of EtOH:H_2O (2:1 v/v) gave the corresponding 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**2a**) in 80% yield (Table 1, entry 1). Next, a few choices of combination of organic solvents (THF, 1,4-dioxane and 1,2-dichloroethane) with water in a ratio of 2:1 v/v were screened (Table 1, entries 2−5). Compound **2a** was obtained in highest yield (85% yield) when the reaction was carried out in MeCN:H_2O (2:1 v/v). Unfortunately, the reaction poorly proceeded when it was carried out in water solely leading to **2a** in 40% yield (Table 1, entry 6). Attempts to increase the water to MeCN ratio by employing 1:2 v/v MeCN:H_2O as the solvent gave unsatisfactory result; **2a** was isolated in 32% yield with recovery of compound **1** (44% yield) (Table 1, entry 7). Next, the reaction temperature was briefly investigated. Although the reaction carried out at 100 °C did not provide a better yield, the reaction performed at room temperature gave poorer results (Table 1, entries 8 and 9). After the solvent was identified (MeCN/H_2O, 2:1 v/v), we then examined the effect of a stoichiometry of NaBr and $K_2S_2O_8$ (Table 1, entries 10−16). While increasing the amount of NaBr employed (from 4 equiv. to 5 equiv.) did not significantly enhance the yield of **2a**, lowering the amount of NaBr (from 4 to 3 and 2 equiv.) significantly decreased the yield of **2a** (Table 1, entries 10−12). The stoichiometry of $K_2S_2O_8$ employed also displayed similar scenario to those of the NaBr (Table 1, entries 13−15). It is worth to emphasize that the desired product **2a** was not observed when the reaction was carried out in the absence of $K_2S_2O_8$ (Table 1, entry 16). Finally, after screening of other bromide sources, it was found that *n*-Bu_4NBr and Et_4NBr gave **2a** in poorer yields while KBr gave comparable results to those obtained when NaBr was employed as a halogen source (Table 1, entries 17−19). Based on the results shown in Table 1, the optimum reaction conditions were chosen as the following: imidazo[1,2-*a*]pyridine **1** (0.5 mmol), NaBr (4.0 equiv.) and $K_2S_2O_8$ (1.5 equiv.) in MeCN:H_2O (2:1 v/v, 3 mL) at 80 °C for 1.5 h (Table 1, entry 5).

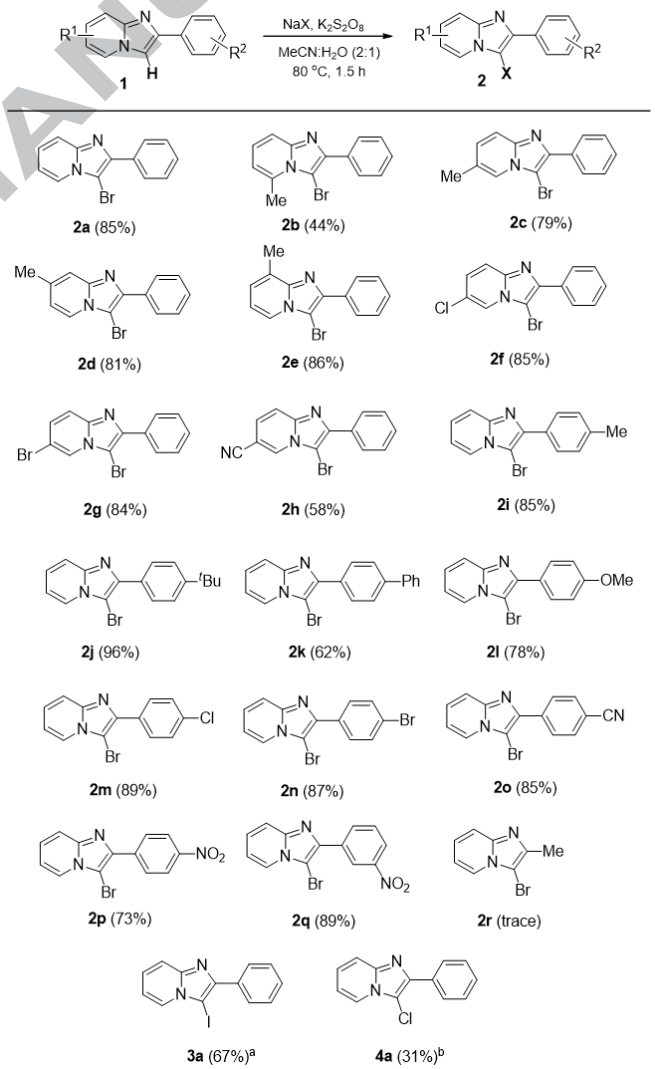
Table 1. Optimization reaction condition for the synthesis of 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**2a**)[a]



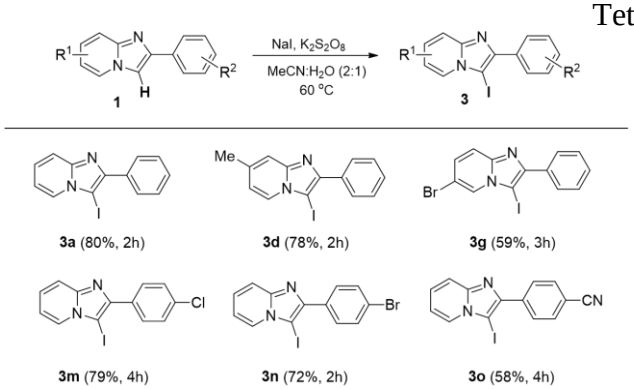
Entry	Br (eq)	$K_2S_2O_8$ (eq)	Solvent	Temp. (^oC)	Time (h)	Yield (%)[b]	
						1a	**2a**
1	NaBr (4)	1.5	EtOH:H_2O (2:1)	80	1.5	-	80
2	NaBr (4)	1.5	THF:H_2O (2:1)	80	1.5	-	78
3	NaBr (4)	1.5	1,4-dioxane:H_2O (2:1)	80	1.5	-	61
4	NaBr (4)	1.5	DCE:H_2O (2:1)	80	1.5	-	55
5	**NaBr (4)**	**1.5**	**MeCN:H_2O (2:1)**	**80**	**1.5**	**-**	**85**
6	NaBr (4)	1.5	H_2O	80	3	-	40
7	NaBr (4)	1.5	MeCN:H_2O (1:2)	80	1.5	44	32
8	NaBr (4)	1.5	MeCN:H_2O (2:1)	100	1.5	-	74
9	NaBr (4)	1.5	MeCN:H_2O (2:1)	rt[c]	18	36	31
10	NaBr (5)	1.5	MeCN:H_2O (2:1)	80	1.5	-	88
11	NaBr (3)	1.5	MeCN:H_2O (2:1)	80	1.5	-	77
12	NaBr (2)	1.5	MeCN:H_2O (2:1)	80	1.5	-	60
13	NaBr (4)	2.0	MeCN:H_2O (2:1)	80	1.5	-	80
14	NaBr (4)	1.1	MeCN:H_2O (2:1)	80	1.5	-	75
15	NaBr (4)	0.6	MeCN:H_2O (2:1)	80	1.5	27	49
16	NaBr (4)	-	MeCN:H_2O (2:1)	80	1.5	98	-
17	KBr (4)	1.5	MeCN:H_2O (2:1)	80	1.5	-	84
18	Bu_4NBr (4)	1.5	MeCN:H_2O (2:1)	80	1.5	-	78
19	Et_4NBr (4)	1.5	MeCN:H_2O (2:1)	80	1.5	-	70

[a]Reaction conditions: **1a** (0.5 mmol), Br sources and $K_2S_2O_8$ in solvent (3 mL) at following temperature for 1.5 h.
[b]Isolated yield after column chromatography on SiO_2.
[c]30-35 ^oC.

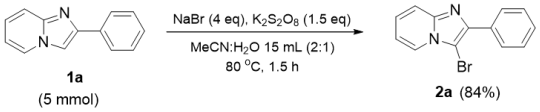
Having established the optimized conditions to access to 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**2a**) employing a combination of NaBr and $K_2S_2O_8$ in aqueous acetonitrile, we next explored the scope and generality of the present reaction and the results are summarized in Scheme 2. First, compounds **1** with various substituents (R^1) on the pyridine ring of 2-phenylimidazo[1,2-*a*]pyridines were evaluated. Compound **1** containing electron-donating groups (5-Me, 6-Me, 7-Me and 8-Me) gave the corresponding products **2b**−**2e** in moderate to good yields (44−86% yields). It is evident that the steric effect arising from the location of the methyl group at *C*5 deteriorated the yield; **2b** was obtained in low yield (44% yield). The bromination reaction of compound **1** bearing electron-withdrawing groups (6-Cl, 6-Br and 6-CN) on the pyridine ring proceed smoothly and delivered the corresponding products **2f**−**2h** in moderate to good yields (58−85% yields). Next, 2-arylimidazo[1,2-*a*]pyridines bearing a series of electronically different groups (R^2, including 4-Me, 4-^{t}Bu, 4-Ph, 4-OMe, 4-Cl, 4-Br, 4-CN, 4-NO_2 and 3-NO_2) on the *C*2-phenyl ring were well tolerated and yielded the corresponding products **2i**−**2q** in high to excellent yield (62−96% yields). Unfortunately, 2-methylimidazo[1,2-*a*]pyridine (**1r**) was not a good substrate; only trace amount of **2r** was observed (TLC monitoring). To expand the utility of the present methodology, we then explored the iodination and chlorination of 2-phenylimidazo[1,2-*a*]pyridine (**1a**). Gratifyingly, under similar reaction conditions when NaI or NaCl were employed in placed of NaBr, 3-iodo-2-phenylimidazo[1,2-*a*]pyridine (**3a**) and 3-chloro-2-phenylimidazo[1,2-*a*]pyridine (**4a**) were obtained in 67% and 31% yields, respectively. To further enhance iodination and chlorination efficiency, optimization of the reaction conditions was revisited. After extensive screening, the optimal conditions for iodination were to expose **1** with NaI (5 equiv), $K_2S_2O_8$ (2 equiv) in MeCN:H_2O (2:1 v/v, 3 mL) at 60 °C (Scheme 3), leading to the iodinated products **3** in moderate to good yields (58−80% yields). Unfortunately, attempts toward the chlorination by employing either excess amount of $K_2S_2O_8$ or NaCl (saturated NaCl 1 mL in place of H_2O)[18] were not satisfactory. Finally, it is worth to note that scaling up experiments (5 mmol scale) for the bromination reaction of **1a** was also investigated under the optimized conditions leading to the product **2a** in similar efficiency (84% yield) (Scheme 4).



Scheme 2. Halogenation of imidazo[1,2-*a*]pyridines **1**. Reaction conditions: **1** (0.5 mmol), NaBr (4 equiv.) and $K_2S_2O_8$ (1.5 equiv.) in MeCN:H_2O (2:1 v/v, 3 mL), at 80 °C for 1.5 h. In parentheses: isolated yield after column chromatography (SiO_2). [a]NaI was employed in placed of NaBr. [b]NaCl was employed in placed of NaBr.

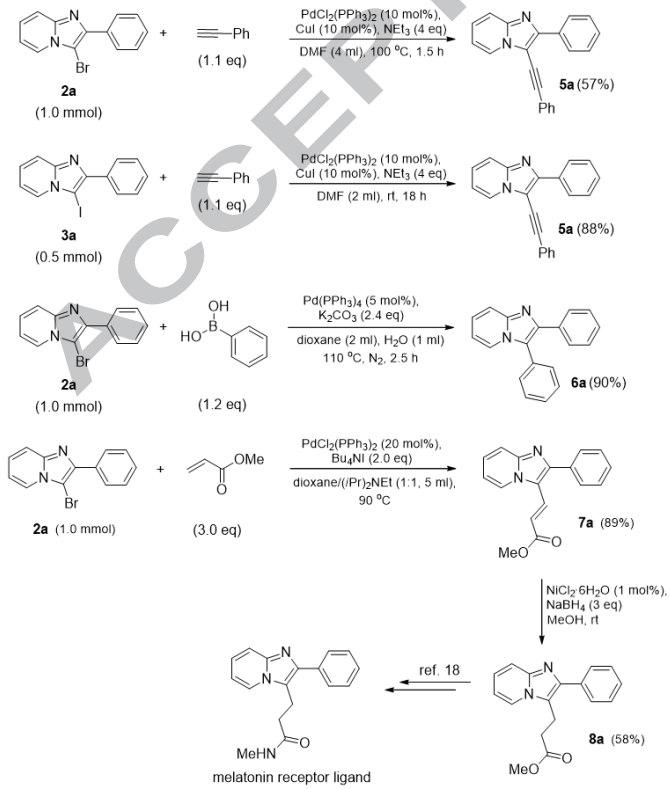


Scheme 3. Iodination of imidazo[1,2-*a*]pyridines **1**. Reaction conditions: **1** (0.5 mmol), NaI (5 equiv.) and $K_2S_2O_8$ (2.0 equiv.) in MeCN:H_2O (2:1 v/v, 3 mL), at 60 °C. In parentheses: isolated yield after column chromatography (SiO_2) and reaction time



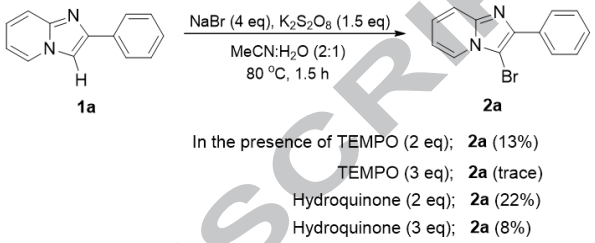
Scheme 4. Gram scale synthesis of 3-bromoimidazo[1,2-*a*]pyridine (**2a**)

Synthetic applications of **2a** and **3a** were conducted employing Pd-catalyzed cross-coupling reactions (Scheme 5). Sonogashira coupling reactions of **2a** and **3a** with phenyl acetylene readily proceeded and gave the product **5a** in 57% yield (from **2a**) and 88% yield (from **3a**). Suzuki-Miyaura reaction of **2a** also worked well providing the corresponding product **6a** in excellent yield (90% yield). The Heck reaction of 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**2a**) with methyl acrylate afforded the product **7a** (89% yield) which can be further reduced to give compound **8a** in 58% yield. Compound **8a** is an intermediate for the synthesis of selective melatonin receptor ligands.[19]



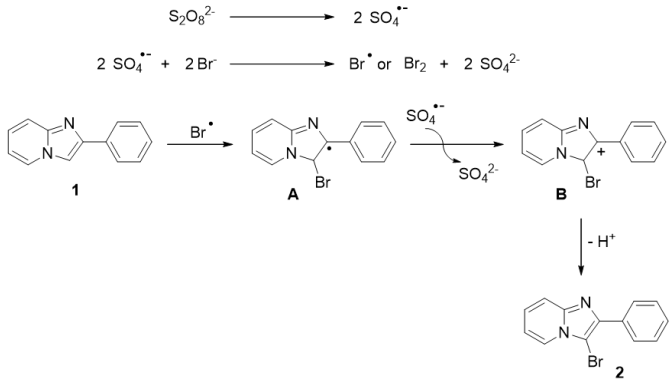
Scheme 5. Synthetic applications of 3-haloimidazo[1,2-*a*]pyridine

To help to better understand the reaction mechanism, some control experiments were carried out. The reactions of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with NaBr/$K_2S_2O_8$ were carried out under standard reaction conditions but in the presence of radical inhibitors including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone (Scheme 6). From the experimental results, it was clearly showed that the reaction was suppressed by both radical scavengers. Thus, there should be radical species involved in the present transformation.



Scheme 6. Control experiments

On the basis of the control experiments in Scheme 6 and the previously reports concerning oxidative halogenation,[17,18,20] we proposed possible reaction mechanism for this transformation as shown in Scheme 7. Initially, decomposition of $K_2S_2O_8$ generates sulfate radical anion which then oxidizes bromide ion to bromine radical or molecular bromine. Then, bromine radical regioselectively added to the *C*3 of imidazo[1,2-*a*]pyridine **1** to produce benzylic radical intermediate **A**. Subsequently, the oxidation of intermediate **A** by sulfate radical anion takes place to provide benzylic cation intermediate **B**. Finally, intermediate **B** undergoes deprotonation to give the observed product **2**.



Scheme 7. Possible reaction mechanism

In conclusion, we have described a facile and convenient method to synthesize 3-chloro-, 3-bromo- or 3-iodo-2-arylimidazo[1,2-*a*]pyridines by using sodium chloride/bromide/iodide as the halogen source in the presence of $K_2S_2O_8$ as an easy-to-handle oxidizing agent under convenient reaction conditions and short reaction time. Additionally, the reaction can be scaled up to 5 mmol scale and the prepared halogenated products can be converted to more complex imidazo[1,2-*a*]pyridine compounds through cross-coupling reactions.

Acknowledgments

We thank the Natural Products Research Unit, Department of Chemistry and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Khon Kaen University and the Center for Innovation in Chemistry (PERCH-CIC), Mahidol University for financial support.

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21. *General procedure for the synthesis of 3-haloimidazo[1,2-a]pyridines* ***2*****:** Potassium persulfate ($K_2S_2O_8$) (202.7 mg, 0.75 mmol) was added to a suspension of imidazo[1,2-*a*]pyridines **1** (0.5 mmol) and sodium bromide (205.8 mg, 2.0 mmol) in acetonitrile/H_2O (2:1 v/v, 3 mL), and the reaction mixture was stirred at 80 °C for 1.5 h. After completion of the reaction, the reaction mixture was quenched by the addition of sat. aq $Na_2S_2O_3$ (5 mL). Further stirring was followed by extraction with EtOAc (2 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated (aspirator). The residue was purified by column chromatography using EtOAc/hexanes as eluent to afford the corresponding product. *3-Bromo-2-phenylimidazo[1,2-a]pyridine (**2a**)***:*** Prepared from 2-phenylimidazo[1,2-*a*]pyridine (**1a**) (97.1 mg, 0.5 mmol), $K_2S_2O_8$ (202.7 mg, 0.75 mmol) and NaBr (205.8 mg, 2.0 mmol). Colorless solid; yield: 116.1 mg (85%); mp 62.0−64.0 °C (lit.[10] 63−64.5 °C); R_f = 0.50 (30% EtOAc in hexanes). IR (neat): 2918, 1628, 1491, 1466, 1440, 1343, 980, 748, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 7.0 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 9.1 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 6.94 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5 (C), 142.7 (C), 132.9 (C), 128.6 (2×CH), 128.4 (CH), 128.0 (2×CH), 125.2 (CH), 124.1 (CH), 117.7 (CH), 113.2 (CH), 91.8 (C). HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}BrN_2$: 273.0027; found: 273.0020.

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.

Highlight

- Convenient procedure for halogenation of 2-arylimidazo[1,2-*a*]pyridines.
- Rapid preparation of 3-halo-2-arylimidazo[1,2-*a*]pyridines in a short reaction time.
- $K_2S_2O_8$ as an easy-to-handle oxidizing agent.

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