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An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Ju Hui Lee, Hye Im Jung & Dae Young Kim (2019): Visible light-mediated photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines using CBr_4 as bromine source, Synthetic Communications, DOI: 10.1080/00397911.2019.1691738

To link to this article: https://doi.org/10.1080/00397911.2019.1691738

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Visible light-mediated photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines using CBr_4 as bromine source

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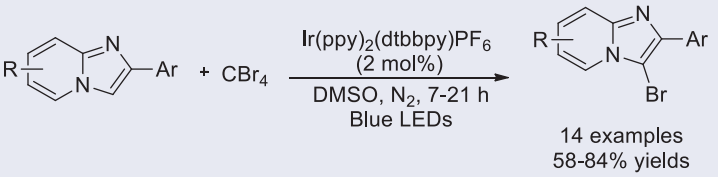
ABSTRACT

The photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines is described in this paper. This reaction uses the readily accessible and shelf-stable CBr_4 as a bromine source. This photocatalytic system is shown to serve as a convenient and practical synthetic protocol for the preparation of 2-aryl-3-bromoimidazo[1,2-*a*]pyridines.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 14 October 2019

KEYWORDS
Bromination; photoredox reaction; 2-arylimidazo[1,2-a]pyridines; 3-bromoimidazo[1,2-a]pyridines

Introduction

The imidazo[1,2–*a*]pyridine scaffold is found as a privileged core in a wide variety of biologically active compounds.[1] These derivatives exhibit a broad range of pharmaceutical activities, such as antibacterial,[2] antifungal,[3] anti-inflammatory,[4] antitumor,[5] and antiviral.[6] In recognition of these pharmaceutical properties of C-3 substituted imidazo[1,2–*a*]pyridines, a number of C-3 functionalization methods have been developed over the last decade.[7] Among C-3 substituted imidazo[1,2-*a*]pyridine derivatives, 3-bromoimidazo[1,2-a]pyridines have attracted substantial attention for use as common intermediates enabling the displacement of bromide at C-3 position.[8] The 3-Bromination of imidazo[1,2-*a*]pyridines with various halogen sources is a typical procedure used for the synthesis of 3-bromo-imidazo[1,2-*a*]pyridine derivatives.[9–12] Various C-3 bromination methods have been developed to date, with most of them including the bromination of 2-aryl imidazo[1,2-*a*]pyridines with $CuBr_2$, *N*-bromosuccinimide,[9] and $NaBrO_2$ (Scheme 1(1)).[10] In recent years, several groups have reported on the bromination of 2-arylimidazo[1,2-*a*]pyridines with alkali and ammonium bromides in the presence of various oxidizing agents (Scheme 1(2)).[11] Very recently, Lei and coworkers reported on the electrochemical bromination of 2-

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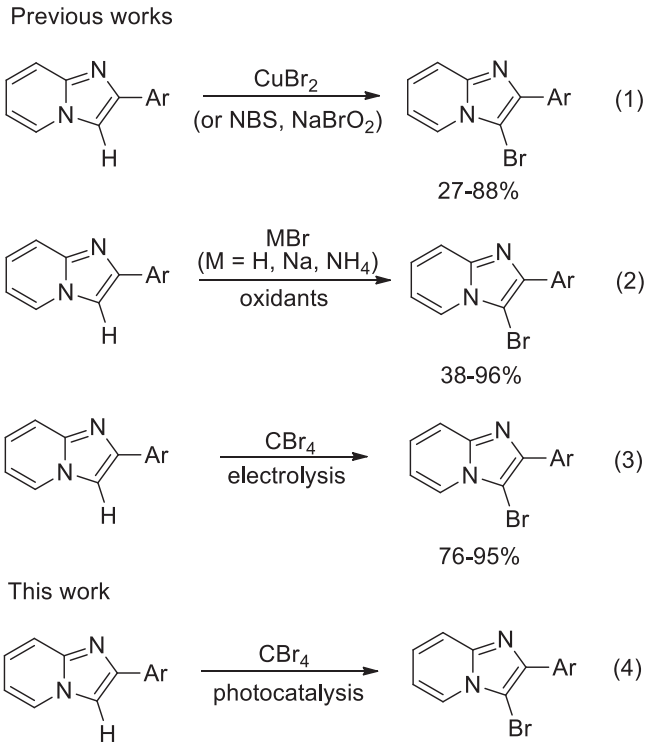


Scheme 1. Bromination of 2-arylimidazo[1,2-*a*]pyridines

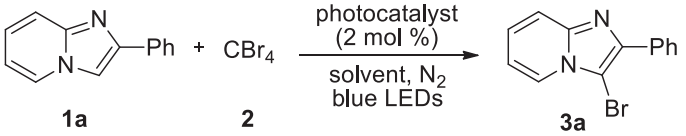
arylimidazo[1,2-*a*]pyridines with carbon tetrabromide (Scheme 1(3)).[12] Despite the above advancements, more efficient and mild approaches for the bromination of 2-arylimidazo[1,2-*a*]pyridines are still desired. Photocatalysis reactions have emerged as an efficient protocol to introduce functional groups to organic molecules due to their environmental friendliness and potential application in industry.[13] To our knowledge, no studies have reported on the photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines. Thus, we envisioned the bromination of 2-arylimidazo[1,2-*a*]pyridines to 2-aryl-3-bromo-imidazo[1,2-*a*]pyridines by visible light-mediated photoredox bromination with carbon tetrabromide as the bromine source (Scheme 1(4)).

Results and discussion

In connection with our ongoing research program investigating the C-H bond functionalization via redox reactions, of alkene derivatives,[14] we recently reported on the visible light-mediated photoredox functionalization of alkenes and aromatics.[15] Herein, we present the visible light-mediated photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines.

To determine the optimized reaction conditions for the photocatalytic bromination of 2-arylimidazo[1,2-*a*]pyridines, we examined the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with carbon tetrabromide (**2**) in DMSO in the presence of photocatalyst (2 mol%) with blue LEDs (5 W, λ_{max} = 455 nm). We conducted this reaction with several different metal photocatalysts and organic dyes (Table 1, entries 1–9).

Table 1. Reaction condition optimization[a].



1a 2 3a

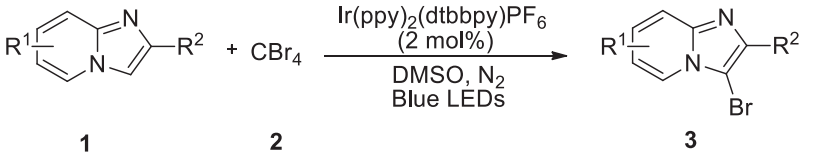
Entry	Photocatalyst	Solvent	Time (h)	Yield (%)[b]
1	$[Ru(bpy)_3](PF_6)_2$	DMSO	18	66
2	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	DMSO	16	75
3	$[Ru(phen)_3Cl_2]\cdot H_2O$	DMSO	16	69
4	*fac*-Ir(ppy)$_3$	DMSO	16	73
5	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	7	84
6	Na_2 EosinY	DMSO	16	trace
7	Eosin Y	DMSO	20	23
8	Rose Bengal	DMSO	18	33
9	Rhodamine B	DMSO	18	43
10	Ir(ppy)$_2$(dtbbpy)PF_6	DMF	18	81
11	Ir(ppy)$_2$(dtbbpy)PF_6	MeCN	18	63
12	Ir(ppy)$_2$(dtbbpy)PF_6	MeOH	17	trace
13	Ir(ppy)$_2$(dtbbpy)PF_6	THF	18	49
14	Ir(ppy)$_2$(dtbbpy)PF_6	DCM	17	20
15	Ir(ppy)$_2$(dtbbpy)PF_6	DCE	17	6
16	Ir(ppy)$_2$(dtbbpy)PF_6	PhMe	17	3
17[c]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	18	12
18[d]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	18	64
19[e]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	18	66
20[f]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	18	56
21[g]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	7	84
22[h]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	12	71
23[i]	–	DMSO	15	trace
24[j]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	15	trace
25[k]	Ir(ppy)$_2$(dtbbpy)PF_6	DMSO	15	79

[a]Reaction conditions: 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 0.1 mmol), carbon tetrabromide (**2**, 0.2 mmol), photocatalyst (2 mol%) in solvent (1.0 mL), blue LEDs, room temperature under N_2. [b]Isolated yields. [c]Red LEDs instead of blue LEDs. [d]White LEDs LEDs instead of blue LEDs. [e]Green LEDs LEDs instead of blue LEDs. [f]1 mol% photocatalyst loading. [g]1.5 equiv. of carbon tetrabromide was used. [h]1.2 equiv. of carbon tetrabromide was used. [i]Without photocatalyst. [j]Reaction performed in the dark. [k]3 equiv of TEMPO was added.

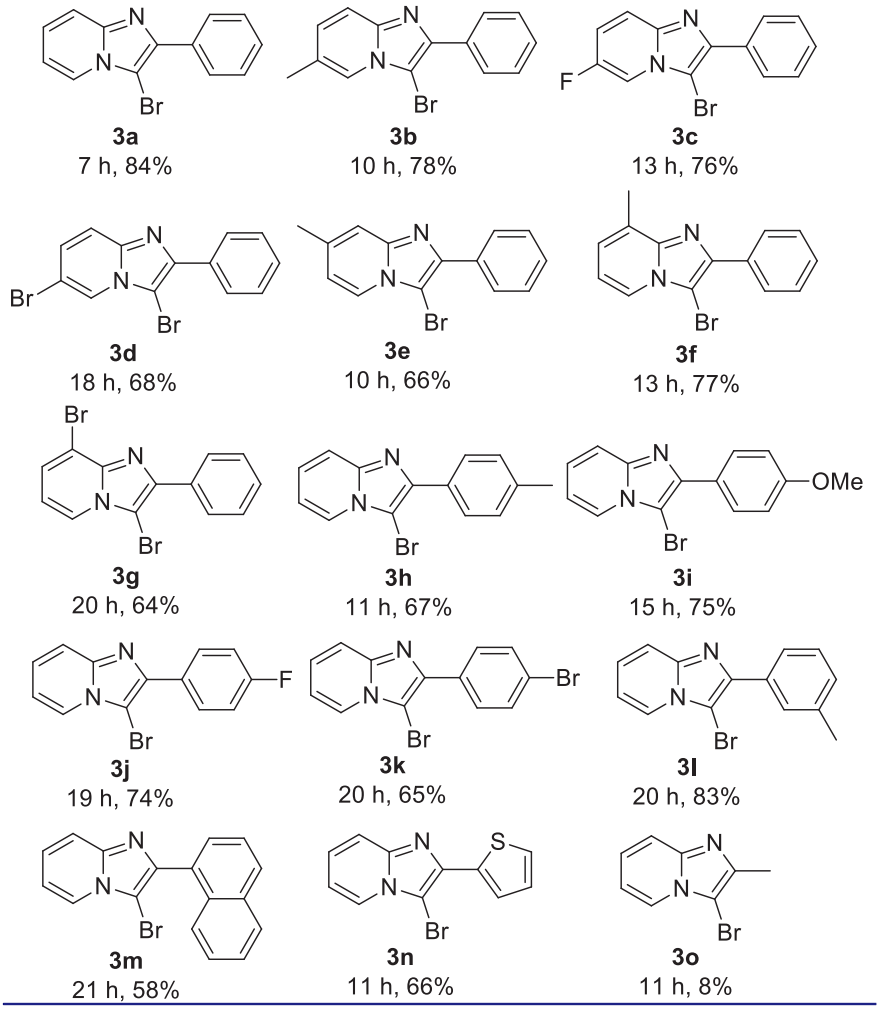
By screening photocatalysts, Ir(ppy)$_2$(dtbbpy)PF_6 was found to be the best photocatalyst for this bromination (84% yield, Table 1, entry 5). Various commonly used solvents were examined: DMSO, DMF, acetonitrile, methanol, THF, dichloromethane, 1,2-dichloroethane, and toluene (entries 5 and 10–16). The results showed that the reaction gave the highest yield in DMSO (entry 5). Furthermore, a lower yield was obtained when the visible light sources were switched to red, white, and green LEDs (Table 1, entries 17–19). Reducing the photocatalyst (Ir(ppy)$_2$(dtbbpy)PF_6) loading to 1 mol % slightly decreased the yield of 3-bromo-2-phenylimidazo[1,2-*a*]pyridines (**3a**, Table 1, entry 20). The optimal amount of carbon tetrabromide (**2**) was determined after the parallel reactions, and 1.5 equiv of **2** was considered to be suitable for this reaction (entries 5 and 21–22). Finally, the controlled experiments demonstrated the critical roles of the photocatalyst and visible light in this bromination (Table 1, entries 23–24).

With the optimal reaction conditions determined, we investigated the substrate scope of imidazopyridines (Table 2). We initially examined the bromination of 2-phenylimidazo[1,2-*a*]pyridines **1** bearing various substituents on the pyridine ring with carbon tetrabromide (**2**) under the optimized conditions. 2-Phenylimidazo[1,2-*a*]pyridines **1** with electron-donating

Table 2. Substrate scope[a,b].

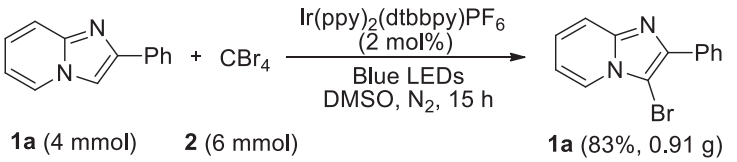


1 2 3



[a]Reaction conditions: imidazo[1,2-*a*]pyridine **1** (0.1 mmol), carbon tetrabromide (**2**, 0.15 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol%) in DMSO (1.0 mL) blue LEDs, room temperature under N_2. [b]Isolated yield.

groups such as 6-methyl, 7-methyl, and 8-methyl substituents on the pyridine ring provided the corresponding 3-brominated products **3b**, **3e**, and **3f** in moderate-to-high yields (66–78%). The bromination of 2-phenylimidazo[1,2-*a*]pyridines **1** having electron-withdrawing groups such as 6-fluoro, 6-bromo, and 8-bromo substituents on the pyridine ring also respectively delivered the desired 3-brominated products **3c**, **3d**, and **3g** in moderate-to-



Scheme 2. Gram-scale synthesis of **3a**.

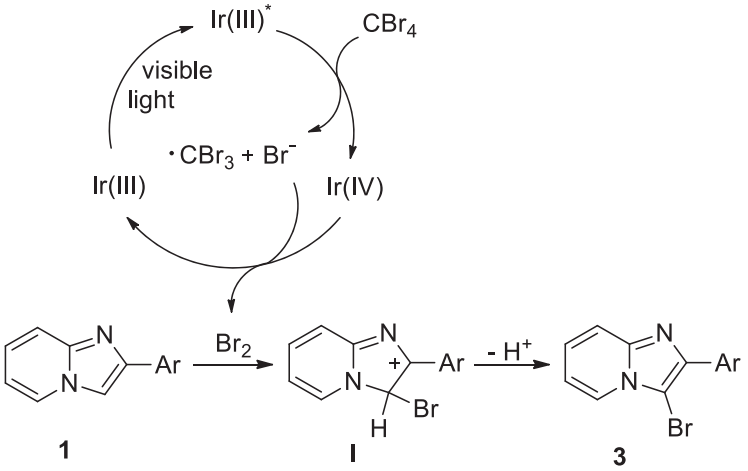


Figure 1. Plausible reaction pathway.

high yields (64–76%). Moreover, 2-arylimidazo[1,2-*a*]pyridines bearing various substituents such as *p*-methyl, *p*-methoxy, *p*-fluoro, *p*-bromo, and *m*-methyl groups of the C-2 aryl ring underwent facile transformation to give the corresponding 3-brominated products **3h–3l** in moderate-to-high yields (65–83%). Notably, the naphthyl- and heteroaryl-substituted cyclobutanols **1m** and **1n** provided the brominated products with moderate yields (58–66%, Table 2, for **3m** and **3n**). Unfortunately, the bromination of 2-alkyl substituted imidazo[1,2-*a*]pyridine, 2-methylimidazo[1,2-*a*]pyridine, gave the corresponding 3-bromo-2-methylimidazo[1,2-*a*]pyridine (**3p**) with low yield (8%).

To demonstrate the practicality and synthetic utility of the visible light-mediated photocatalytic bromination of imidazopyridines investigated here, the gram-scale reaction was conducted under the optimized reaction conditions. As shown in Scheme 2, the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with carbon tetrabromide under the optimized conditions (**2**) afforded the desired 3-bromo-2-phenylimidazo[1,2-*a*]pyridines (**3a**) with 83% yield.

After gaining insight into the mechanism, some controlled experiments were conducted. In these experiments, the absence of the photocatalyst ($Ir(ppy)_2(dtbbpy)PF_6$) or dark condition suppressed the reaction. These reaction factors play an important role in this bromination reaction (Table 1, entries 23–24). In the presence of 3 equiv of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), a high yield of desired product **3a** was obtained (Table 1, entry 25). Therefore, the possibility of a radical pathway was neglected. Based on the preliminary experimental results obtained here as well as the related literature, we propose the plausible reaction pathway shown in Figure 1.[12,16]

Irradiation of the photocatalyst Ir(III) with visible light leads to the excited-state Ir(III)*. The initial reduction of carbon tetrabromide (**2**) by Ir(III)* via a single-electron transfer process should generate bromide ion (Br^-) and tribromomethyl radical. This bromide ion is then oxidized by Ir(IV) to afford the molecular bromine. The reaction of imidazopyridines with Br_2 affords the corresponding 3-bromoimidazo[1,2-a]pyridines **3**.

Conclusion

In conclusion, we have described a practical synthetic method that can be used to synthesize 3-bromoimidazo[1,2-*a*]pyridines by employing carbon tetrabromide under photoredox conditions. This protocol is environmentally friendly because it uses inexpensive and easily handled carbon tetrabromide as the molecular bromine source and visible light as the source of energy. This reaction represents a convenient and mild method for the preparation of 3-bromo-2-arylimidazo[1,2-*a*]pyridine derivatives.

Experimental

General procedure for the photocatalytic bromination of 2-arylimidazo [1,2-a]pyridines

An oven-dried flask was equipped with a magnetic stir bar, 2-arylimidazo[1,2-*a*]pyridines **1** (0.1 mmol), carbon tetrabromide (**2**, 49.7 mg, 0.15 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1.8 mg, 0.002 mmol), and DMSO (1 mL) under N_2 atmosphere. The reaction mixture was then stirred for 7–21 h under irradiation using 5 W blue LEDs (λ_{max} = 455 nm). Upon completion of the reaction, the mixture was concentrated in vacuum and purified by chromatography on silica gel (ethyl acetate:*n*-hexane = 1:5) to afford 3-bromo-2-arylimidazo[1,2-*a*]pyridines **3**.

Yield: 84%; white solid; mp 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 6.8 Hz, 1 H), 8.13 (d, J = 7.2 Hz, 2 H), 7.66 (d, J = 9.2 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 1 H), 7.32–7.26 (m, 1 H), 6.95 (td, J = 6.9 Hz, 1.1 Hz, 1 H); 13C NMR (100 MHz, $CDCl_3$): δ 145.4, 142.6, 132.8, 128.5, 128.3, 127.9, 125.2, 124.0, 117.6, 113.1, 91.8; HRMS (ESI) calcd for $C_{13}H_{10}BrN_2$ $[M+H]^+$ 273.0027; found 273.0031.

Funding

This research was supported by Soonchunhyang University Research Fund and Basic Science Research Program through the National Research Foundation of Korea [NRF-2019R1F1A1059821].

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