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VISIBLE-LIGHT-PROMOTED *Se*-ARYLATION OF DIARYL DISELENIDES WITH 2-PHENYLIMIDAZOPYRIDINES IN THE PRESENCE OF AMMONIUM IODIDE: SYNTHESIS OF 2-PHENYL-3-(ARYLSELANYL)IMIDAZO[1,2-*a*]PYRIDINES

Yuki Murata,[1] Keiko Kanasaki,[1] Kaito Kondo,[1] Naoki Kakusawa,[2] Mio Matsumura,[1] and Shuji Yasuike[1]*

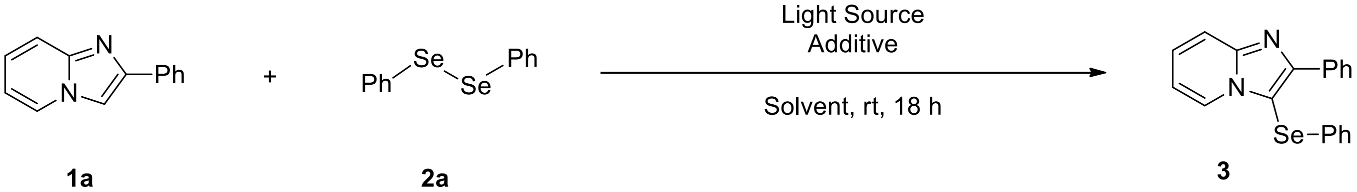
[1] School of Pharmaceutical Sciences, Aichi Gakuin University, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan. [2] Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan. E-mail: s-yasuik@dpc.agu.ac.jp

Abstract – Photoreaction of diaryl diselenides and 2-phenylimidazo[1,2-*a*]pyridine in the presence of ammonium iodide (20 mol%) using blue LED light led to the formation of 3-(arylselanyl)imidazopyridines in good-to-excellent yields under aerobic conditions. By using various diselenides, this reaction efficiently introduces the selanyl group at the 3-position of the imidazopyridine scaffold.

Functionalized imidazo[1,2-*a*]pyridines have gained growing interest in the fields of medicinal chemistry and materials science.[1,2] A number of drugs and clinical candidates, such as zolpidem and alpidem, contain an imidazo[1,2-*a*]pyridine scaffold.[3] 3-(Arylselanyl)imidazo[1,2-*a*]pyridines, which bear a selenium substituent, have potential antioxidant properties.[4] Consequently, they have aroused much attention and new synthetic methodologies have been actively pursued. Past synthetic routes have mainly utilized the reaction of imidazopyridines and diphenyl diselenide as selanyl source to cause the direct C–H *Se*-arylation of the 3-position of the imidazopyridine skeleton. In 2011, Zhou et al. reported the synthesis of 3-(phenylselanyl)imidazopyridines *via* a Cu-catalyzed directed C–H selenation.[5] Since then, alternative methods that do not use transition metal catalyst have been investigated, and effective reagents and systems such as Cs_2CO_3–ionic liquid,[6] I_2–H_2O_2[7] and I_2–DMSO[8] have been found. However, these reactions have some disadvantages such as using oxidant reagents or stoichiometric amounts of base. Visible-light mediated reactions have emerged as an attractive strategy in organic synthesis because these methods are safe, clean, and environmentally friendly offering a green chemistry approach.[9] Furthermore, the *Se*-arylation of aromatic heterocyclic rings has also been reported. In 2014, Ranu et al. developed a *Se*-heteroarylation of diaryl diselenides with diazonium salts containing pyridines, thiazoles, and quinolones generated from heteroarylamines using a blue LED as the light source and eosin Y as photocatalyst.[10] Later, Liu[11] and Braga[12] independently reported the visible-light induced reaction of imidazopyridines and diphenyl diselenide in the presence of an iridium complex or rose bengal as a photocatalyst at room temperature using blue LED light to afford 2-aryl-3-(phenylselanyl)imidazopyridines. However, these reactions have drawbacks such as using expensive photocatalysts and/or giving low reaction yields (35–54%). Moreover, the substrate scope and scalability of these reactions are problems that remain unsolved. Here, we report the visible-light promoted *Se*-arylation of various diaryl diselenides and 2-phenylimidazo[1,2-*a*]pyridines in the presence of iodide reagents under aerobic conditions for the formation of 3-selanylimidazopyridines.

We initially focused our attention on determining suitable experimental conditions for the visible-light-promoted *Se*-arylation reaction of diphenyl diselenide **2a** with 2-phenylimidazo[1,2-*a*]pyridine **1a** using a catalytic amount of an iodine reagent as additive. Table 1 shows the results of screening of various additives, solvents, and wavelengths of visible light. Initially, the reaction of diphenyl diselenide **2a** and imidazopyridine **1a** in the presence of 20 mol% of an additive such as I_2, NaI, KI, tetrabutylammonium iodide (TBAI), or ammonium iodide (NH_4I) was performed with the irradiation from a 5W blue LED lamp in MeCN at room temperature under aerobic conditions (entries 1–5). All these additives afforded expected product **3** in good-to-excellent yields. Among these, NH_4I appeared to be the best additive for this reaction in terms of yield (92%) (entry 5). Notably, both selanyl groups of the diselenide participated in the reaction. Tetrabutylammonium bromide gave inferior results to NH_4I (entry 6). When the reaction was carried out without NH_4I, the yield of **3** remarkably decreased (entry 7). A solvent screen showed that the reaction took place effectively in MeCN, DMSO, DMF, and EtOH, among which MeCN gave the highest yield of product **3** (entries 5, 8–10). However, the reaction in EtOAc, THF, toluene, and CH_2Cl_2 gave inferior results (entries 11–14). The wavelength of visible light also affected this reaction, and irradiation with blue LED (470 nm) gave better results than with green (525 nm) (entries 5 and 15). On the other hand, the reaction using fluorescent lamp was low yield (25%) (entry 16). Decreasing the loading of NH_4I from 20 to 10 mol% significantly decreased the yield of **3** (entry 17). The reaction under an argon atmosphere showed a significant decrease in the yield of **3**, and even in the reaction under a pure oxygen atmosphere, a decrease of yield was observed (entries 18 and 19). Consequently, the best results were obtained when **1a** and **2a** were irradiated with blue LED visible light in the presence of NH_4I under aerobic conditions. This reaction could also be scaled up to 10 mmol and desired product **3** was obtained in excellent yields of up to 91%, generating up to 3.12 g of product.

Table 1. Photoreaction of 2-phenylimidazopyridine **1a** with diphenyl diselenide **2a**[a]

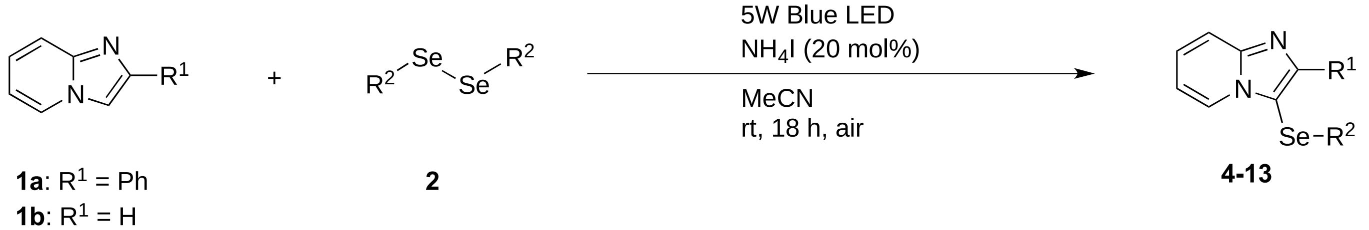


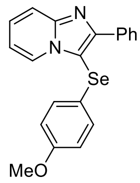
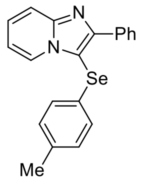
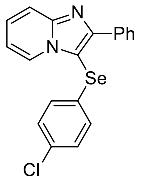
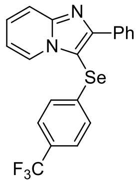
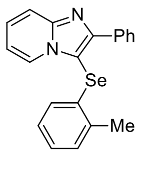
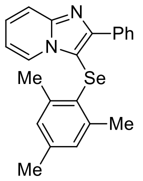
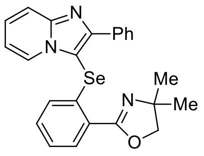
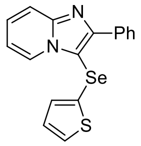
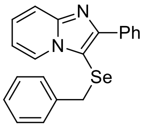
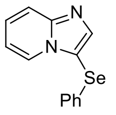
Entry	Light Source[b]	Additive (mol%)	Solvent	Yield of **3** (%)[c]
1	470 nm	I_2 (20)	MeCN	61
2	470 nm	NaI (20)	MeCN	65
3	470 nm	KI (20)	MeCN	74
4	470 nm	TBAI (20)	MeCN	78
5	470 nm	NH_4I (20)	MeCN	92
6	470 nm	NH_4Br (20)	MeCN	41
7	470 nm	---	MeCN	45
8	470 nm	NH_4I (20)	DMSO	78
9	470 nm	NH_4I (20)	DMF	59
10	470 nm	NH_4I (20)	EtOH	56
11	470 nm	NH_4I (20)	EtOAc	50
12	470 nm	NH_4I (20)	THF	49
13	470 nm	NH_4I (20)	toluene	15
14	470 nm	NH_4I (20)	CH_2Cl_2	51
15	525 nm	NH_4I (20)	MeCN	71
16	fluorescent lamp[d]	NH_4I (20)	MeCN	25
17	470 nm	NH_4I (10)	MeCN	56
18[e]	470 nm	NH_4I (20)	MeCN	41
19[f]	470 nm	NH_4I (20)	MeCN	76

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol). [b] Blue (470 nm) or Green LED (525 nm). [c] Isolated yield. [d] 22W. [e] Under Ar. [f] Under O_2.

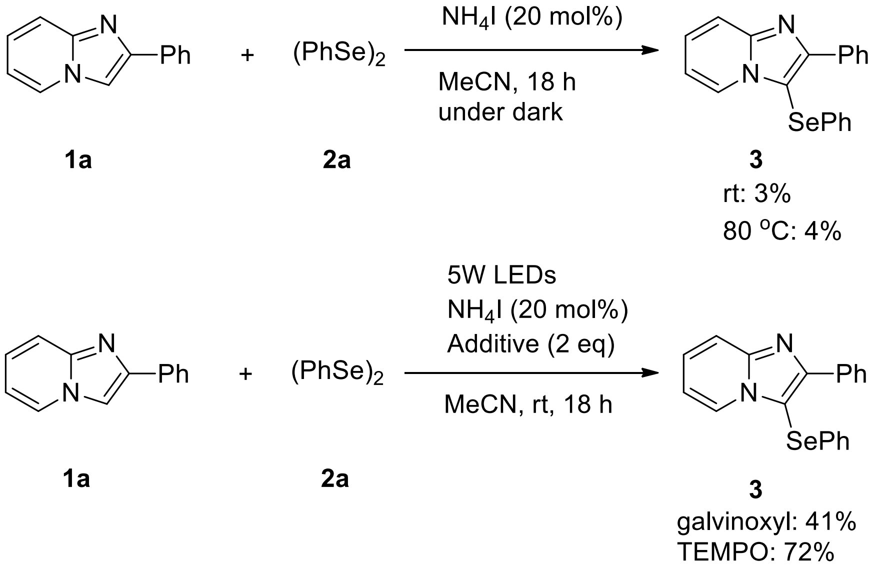
In order to investigate the efficiency and generality of this reaction, various diselenides **2** were reacted with imidazopyridines **1a** and **1b** under the above optimal experimental conditions. The results are summarized in Table 2. The reactions of 2-phenylimidazopyridine **1a** and diaryl diselenides gave the corresponding 3-selanylimidazopyridine **4**–**7** in good-to-excellent yields (78–93%). The nature of the substituent on the benzene ring of the diselenides did not significantly affect the outcome of the reaction. Sterically hindered *ortho*-substituted diselenides (including a dihydrooxazole moiety) reacted to give the corresponding imidazopyridine **8**–**10** without any difficulty, and the reaction with a diaryl diselenide bearing thiophene rings gave **11** in excellent yield. Dibenzyl diselenide gave **12** in a lower yield than those observed for diaryl diselenides. The reaction of unsubstituted imidazopyridine **1b** with diphenyl diselenide **2a** proceeded regioselectively, giving only 3-selanylimidazopyridine **13** in excellent yield (89%).

Table 2. Synthesis of 3-selanylimidazo[1,2-*a*]pyridines[a,b]



				
4: 78%	**5**: 87%	**6**: 85%	**7**: 93%	**8**: 87%
				
9: 70%	**10**: 75%	**11**: 91%	**12**: 66%	**13**: 89%

[a] Conditions: **1** (0.5 mmol), **2** (0.25 mmol), NH_4I (0.1 mmol). [b] Isolated yield.



Scheme 1. Control reactions

To understand this reaction, the following control experiments were carried out (Scheme 1). The reaction of **1a** and **2a** in the presence of NH_4I under dark conditions at room temperature afforded **3** in only 3% yield. Furthermore increasing the reaction temperature to 80 °C did not increase the yield of **3** (4%). These results demonstrate that irradiation with visible light is essential for the reaction to occur. The photoreaction cannot be fully suppressed and desired product **3** was obtained in 41% yield even when two equivalents of galvinoxyl free radical were added to the reaction mixture. The suppression of the reaction using TEMPO as additive was less effective than when using galvinoxyl free radical.

At present, the mechanism of this photoreaction is unclear. We speculate that the mechanism might be similar to that of the visible-light-mediated *S*-arylation of diaryl disulfides with indoles in the presence of sodium iodide described by Yan et al.[13] Moreover, it is known that the electrophilic substitution of imidazo[1,2-*a*]pyridines with phenylselenyl bromide affords 3-selanylimidazopyridines.[14] Figure 1 shows a possible mechanism for the synthesis of 3-selanylimidazopyridines through visible-light-promoted *Se*-arylation from imidazopyridines and diselenides in the presence of a catalytic amount of an iodide reagent. The first step of the reaction would be the generation of diselenide anion radical **A** and iodine radical **B** from diselenides **2** and iodide ion (I^-) by single electron transfer. Anion radical **A** would then cleave into selenide radical **C** and anion ($R\text{–}Se^-$), and the coupling of **C** and iodine radical would afford selanyl iodine **D**. Finally, the electrophilic substitution of **D** with imidazopyridine **1a** gives 3-selanylimidazopyridine and selenol **F** *via* **E**. Selenol **F** converts to diselenide **2** by air oxidation. Therefore, the reaction proceeds with 0.5 equivalents of diselenide, and both selanyl groups are used in the reaction. On the other hand, selenide radical **C** has been reported to be generated by homolytic cleavage of diselenide utilizing visible-light irradiation (> 300 nm) and easily recombined.[15] Photoreaction of diphenyl deselenide **2a** and imidazopyridine **1a** without NH_4I gave 3-selanylimidazopyridine **3** in moderate yield (Table 1, entry 7). This result suggests the existence of another potential pathway *via* intermediate **G** from selenide radical **C** and **1**.

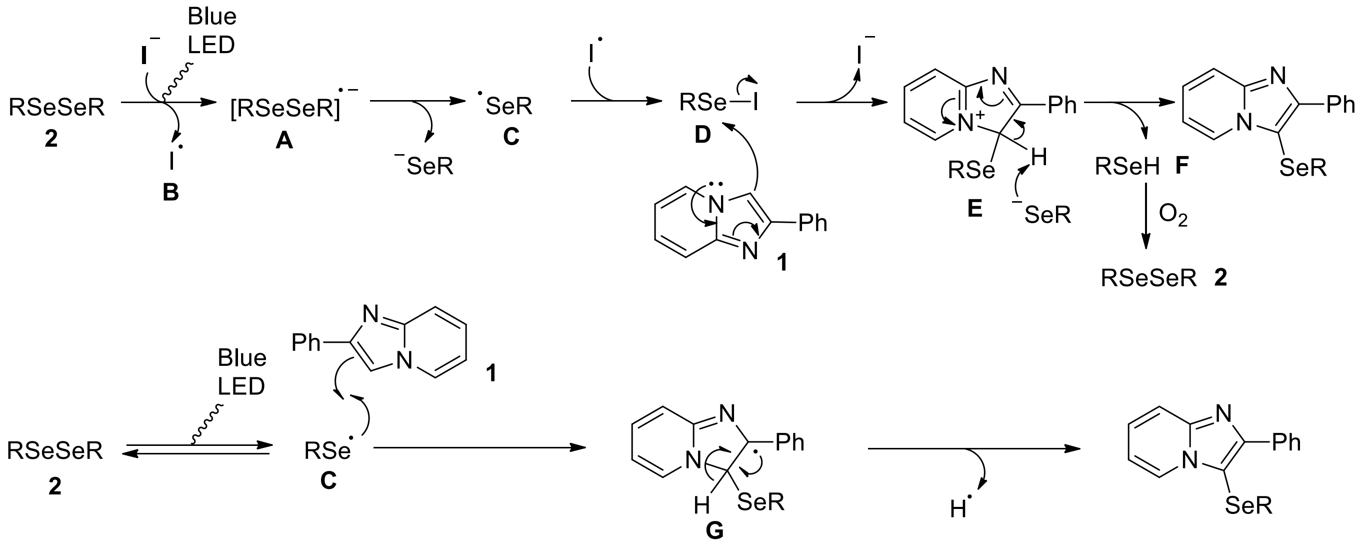


Figure 1. Possible mechanism

In summary, we have developed the visible-light promoted reaction of imidazopyridines and diaryl diselenides in the presence of inexpensive NH_4I (20 mol%) at room temperature using blue LED light to afford 3-selanylimidazopyridines. This reaction efficiently introduces the selanyl group at the 3-position of imidazopyridines. The iodine reagents utilized in this reaction, such as NH_4I, gave better results than the addition of photocatalysts reported so far. The synthetic application of this reaction and a detailed investigation of the reaction mechanisms are in progress.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro melting point hotstage apparatus (MP-S3) and are not corrected. ^1H NMR (TMS: δ: 0.00 as an internal standard) and ^{13}C NMR ($CDCl_3$: δ: 77.00 as an internal standard) spectra were recorded on a JEOL JNM-AL400 (400 MHz and 100 MHz) spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra (MS) were obtained on a JEOL JMS-SX-102A instrument. IR spectras were recorded on a SHIMADZU FTIR-8400S spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR peaks are reported. All chromatographic separations were accomplished with Silica Gel 60N (Kanto Chemical Co., Inc.). Thin-layer chromatography (TLC) was performed with Macherey-Nagel Pre-coated TLC plates Sil G25 UV_{254}. Most of reagents were used without further purification unless otherwise specified. PhSeSePh (**2a**), BnSeSeBn (**2j**) and imidazopyridine (**1b**) were purchased from TCI Fine Chemicals, Japan. 2-Phenylimidazo[1,2-*a*]pyridine (**1a**)[16] and diaryldiselenides such as **2b-d**,[17] **2e**,[18] **2f**,[17] **2g**,[19] **2h**[20] and **2i**[21] were prepared according to the reported procedures and spectroscopic data are in accordance with the literature, respectively.

General procedure for visible light promoted synthesis of 3-selanylimidazo[1,2-*a*]pyridines (3-13). NH_4I (0.1 mmol) was added to a solution of imidazo[1,2-*a*]pyridine (**1a**, 0.5 mmol) and diaryl diselenide (0.25 mmol) in MeCN (3 mL), and the reaction mixture was stirred under blue LED (5 W) irradiation for 18 h under ambient air. The progress of the reaction was monitored by TLC. After completion of the reaction, EtOAc (10 mL) and water (10 mL) were added and the reaction mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed water (10 mL) and brine (20 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under vacuum to get the crude residue. The residue was purified by column chromatograph on silica gel (Hexane-EtOAc = 4:1-1:4) to afforded **3-13** (66-93%). Known products (**3-9**, **11**, **13**) were confirmed by comparison of mp, NMR data, and MS spectra with that in literature (See Supporting Information).

3-[2-(4,4-Dimethyl-2-oxazolinyl)phenylselanyl]-2-phenylimidazo[1,2-*a*]pyridine (10): Yield: 157 mg (75%). Yellow plates (CH_2Cl_2-Hexane). Mp 186-187 °C; R_f = 0.5 (Hexane-EtOAc, 3:2). ^1H NMR (400

MHz, $CDCl_3$): δ = 1.47 (s, 6H, Me), 4.16 (s, 2H, CH_2), 6.64 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.81 (td, *J* = 7.8, 1.1 Hz, 1H, Ar-H), 7.05 (td, *J* = 7.8, 1.6 Hz, 1H, Ar-H), 7.20 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 7.29-7.39 (m, 2H, Ar-H), 7.43 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.74 (d, *J* = 9.2 Hz, 1H, Ar-H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H, Ar-H), 8.12 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.26 (d, *J* = 7.2 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (q), 68.7 (s), 79.0 (t), 106.2 (s), 112.7 (d), 117.4 (d), 125.5 (d), 125.9 (d), 126.3 (d), 126.5 (s), 127.3 (d), 128.2 (d), 128.3 (d), 128.7 (d), 130.2 (d), 131.4 (d), 134.0 (s), 135.2 (s), 147.8 (s), 152.1 (s), 161.1 (s). IR (KBr): 3064, 2968, 1629, 1464, 1352, 1230, 752, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 104 (8), 194 (100), 281 (14), 447 (10) $[M]^+$. HRMS: *m/z* $[M]^+$ calcd for $C_{24}H_{21}N_3OSe$: 447.0850; Found: 447.0856.

3-Benzylselanyl-2-phenylimidazo[1,2-*a*]pyridine (12): Yield: 119 mg (66%). Red oil; R_f = 0.5 (Hexane-EtOAc, 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 2H, CH_2), 6.66 (t, *J* = 7.0 Hz, 1H, Ar-H), 6.88 (dd, *J* = 5.6, 2.4 Hz, 2H, Ar-H), 7.01-7.04 (m, 3H, Ar-H), 7.18 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.37 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.11 (d, *J* = 7.2 Hz, 1H, Ar-H), 8.12 (d, *J* = 7.6 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0 (t), 112.2 (d), 117.1 (d), 125.2 (d), 125.8 (d), 127.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.6 (d), 134.1 (s), 137.9 (s), 147.2 (s), 151.0 (s). IR (film): 3064, 1550, 1342, 1215, 754, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 91 (95), 194 (32), 274 (76), 364 (100) $[M]^+$. HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{16}N_2Se$: 364.0479; Found: 364.0472.

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