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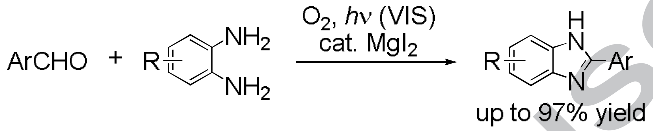

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Aerobic photooxidative synthesis of benzimidazoles from aromatic aldehydes and diamines using catalytic amounts of magnesium iodide

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ABSTRACT

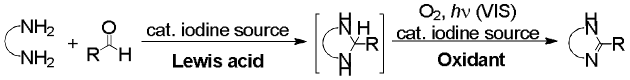
This paper proposes a safe, mild, and environmentally benign method for the synthesis of benzimidazoles from aromatic aldehydes and diamines by aerobic photooxidation using irradiation with visible light, a catalytic amount of magnesium iodide, which serves as both a Lewis acid and an oxidant, and molecular oxygen as the terminal oxidant.

Benzimidazoles are one of the significant organic chemical structures in medicinal and industrial chemistry. In particular, they are potential PPI drugs,[1] hypotensive drugs,[2] anti-HIV drugs,[3] and molecular target drugs.[4] Thus, benzimidazoles are considered to be promising in drug discovery. Therefore, the development of efficient methods for the synthesis of benzimidazoles is an important research area. Numerous methods have been reported for the construction of benzimidazoles on the basis of condensation reactions between aldehydes and diamines followed by oxidation of the aminal intermediates.[5] However, these methods usually require the use of stoichiometric amounts of oxidants such as $PhI(OAc)_2$[6] and iodine[7] or transition-metal catalysts such as $Co(OH)_2$[5] and $Sc(OTf)_2$[8] using molecular oxygen as terminal oxidant. Furthermore, metal free reaction have been reported including sulfamic acid/air,[9] KHF_2/O_2,[10] and air.[11] However, these methods have some problems such as low yield, glass corrosion, and high temperature.

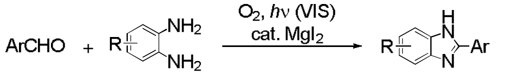
The catalytic amounts of iodine-source-catalyzed C–H oxidation with stoichiometric amounts of various oxidants has attracted great interest because iodine sources tend to exhibit low toxicity and are inexpensive compared with transition-metal catalysts. For example, Ishihara *et al.*[12] and others[13] have reported novel C–H oxidation reactions using a catalytic amount of quaternary ammonium iodide with aq H_2O_2 or *tert*-butyl hydroperoxide as terminal oxidants, which generate only water or *tert*-butanol waste products. This mild C–H oxidation can produce C–O bonds, C–N bonds, or both. Recently, combination of tetrabutylammonium iodide and hydrogen peroxide was applied to synthesis of benzimidazoles from diamine and aldehyde.[14] To the best of our knowledge, however, synthesis of benzimidazoles from aldehydes and diamines using catalytic amounts of iodine sources and molecular oxygen as terminal oxidant has not been reported to date.

We have been developed various oxidation methods that involve the use of catalytic amounts of iodine sources and molecular oxygen, which has received considerable attention as an ideal oxidant because it is photosynthesized by plants, produces little waste, is inexpensive, and exhibits greater atom efficiency than other oxidants when used as a terminal oxidant under visible light irradiation.[15] Furthermore, molecular iodine has served various functions in organic synthesis, including those of an oxidant and a Lewis acid.[16] Thus, we propose a one-pot and metal-free synthetic protocol for the preparation of acetophenones from styrenes using molecular iodine, which serves as an oxidant in the aerobic photooxidation step and a Lewis acid in the deiodination step.[17] Furthermore, one-pot synthesis of bis-indolylmethane from benzyl alcohol and indoles was also performed using a catalytic amount of iodine, which catalyzes the aerobic photooxidation of benzyl alcohol and the condensation step between an indole and benzaldehyde.[18] From the perspective of green chemistry, the reagent used in the upstream reaction of a multistep synthesis should be recycled to catalyze the downstream reaction.[19]

Given this background, we hypothesized that the successive iodine-catalyzed cyclization of aldehyde with diamine and the subsequent oxidation of the aminal intermediate would enable the synthesis of *N*-heteroaromatics (Scheme 1). Herein, we describe an aerobic photooxidative synthesis of benzimidazoles from aromatic aldehydes and aromatic diamines using a catalytic amount of magnesium iodide as both a Lewis acid and an oxidant (Scheme 2).



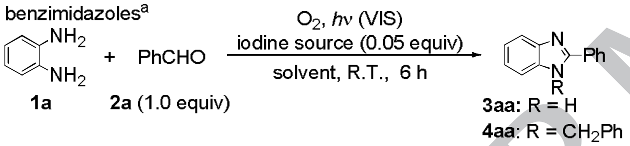
Scheme 1. Catalytic aerobic photooxidative cyclization using iodine source



Scheme 2. Catalytic aerobic photooxidative synthesis of benzimidazoles

First, we optimized the reaction conditions for the synthesis of benzimidazole **3aa**, as shown in Table 1. The reaction conditions for the photooxidative cyclization were optimized with 1,2-phenylenediamine (**1a**) and benzaldehyde (**2a**) in the presence of a catalytic amount of an iodine source under an oxygen atmosphere and under irradiation by a general-purpose fluorescent lamp. In this reaction, EtOAc was the most effective solvent, and MgI_2 was the most suitable reagent, which afforded **3aa** in 93% isolated yield with side-product **4aa** in only 2% yield (entries 1–14). Interestingly, this reaction also proceeded under an air atmosphere instead of O_2 (entry 15). Notably, magnesium iodide, visible-light irradiation, and molecular oxygen are necessary for this reaction because **3aa** was not obtained or was obtained in low yields in the absence of one or more of these ingredients (entries 16–18).[20]

Table 1. Optimization of reaction conditions for the synthesis of benzimidazoles[a]



Entry	Iodine source	Solvent	Yield (%)[b]	
			3aa	**4aa**
1	MgI_2	EtOAc	(93)	2
2	MgI_2	MeCN	(86)	trace
3	MgI_2	PhMe	84	trace
4	MgI_2	MeOH	72	4
5	MgI_2	$CHCl_3$	70	3
6	MgI_2	Hexane	40	trace
7	MgI_2	DMF	9	trace
8	MgI_2	THF	trace	0
9	I_2	EtOAc	86	2
10	CaI_2	EtOAc	79	trace
11	CI_4	EtOAc	85	7
12	LiI	EtOAc	33	8
13	NaI	EtOAc	8	trace
14	NIS	EtOAc	49	25
15[c]	MgI_2	EtOAc	81	trace
16	-	EtOAc	0	0
17[d]	MgI_2	EtOAc	29	7
18[e]	MgI_2	EtOAc	36	6

[a] The reaction conditions: **1a** (0.15 mmol) and **2a** (1.0 equiv) in solvent (3 mL) was stirred under argon atmosphere for 30 min. Then it was added iodine source (0.05 equiv) in solvent (2 mL) and was stirred and irradiated with a fluorescent lamp under O_2 atmosphere for 6 h.

[b] ^{1}H NMR yields. Numbers in parentheses are isolated yields.

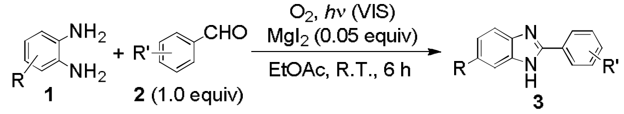
[c] Reaction was conducted under air.

[d] Reaction was conducted in the dark.

[e] Reaction was conducted under argon.

Table 2 shows the scope and limitations of benzimidazole synthesis from several aromatic diamines and aromatic aldehydes. Most of the reactions of 1,2-phenylenediamines and aromatic aldehydes resulted in good-to-high yields, irrespective of whether an electron-withdrawing or an electron-donating group was present (entries 1–16).[21] 4-nitro-1,2-phenylenediamine (**1f**) afforded **3fa** in moderate yield when 0.2 equivalents of I_2 was used for 20 h because of the weak nucleophilicity of **1f** (entry 17). Unfortunately, aliphatic aldehyde, propanal, and diamine, ethylene diamine, were poor substrates, probably because the oxidation step is slow. Notably, this reaction also produced 2-phenyl benzothiazole (**3ga**) in high yield when 2-aminobenzenethiol (**1g**) was used (Scheme 3). This result suggests that this aerobic reaction condition is suitable for the synthesis of sulfur containing heterocycles.[14] On the other hand, we have already reported the aerobic photooxidation of benzyl alcohols to benzaldehydes using molecular iodine.[15g] Thus, we attempted the one-pot synthesis of benzimidazole from benzyl alcohol and obtained **3aa** in 93% yield (Scheme 4).

Table 2. Catalytic aerobic photooxidative synthesis of benzimidazoles[a]



Entry	R		R'		Product	Yield (%)[b]
1	H	**1a**	H	**2a**	**3aa**	93
2	H	**1a**	3-Me	**2b**	**3ab**	91
3	H	**1a**	4-Me	**2c**	**3ac**	80
4	H	**1a**	4-tBu	**2d**	**3ad**	68
5	H	**1a**	4-Cl	**2e**	**3ae**	97
6	H	**1a**	4-OH	**2f**	**3af**	79[c]
7	H	**1a**	4-OMe	**2g**	**3ag**	77
8	H	**1a**	4-CF_3	**2h**	**3ah**	80
9	H	**1a**	4-CN	**2i**	**3ai**	77
10	H	**1a**	4-NO_2	**2j**	**3aj**	71
11	H	**1a**	3-Me	**2k**	**3ak**	87
12	H	**1a**	3-OMe	**2l**	**3al**	71
13	3-Me	**1b**	H	**2a**	**3ba**	90
14	4-Me	**1c**	H	**2a**	**3ca**	75
15	4-Br	**1d**	H	**2a**	**3da**	86
16	4-OMe	**1e**	H	**2a**	**3ea**	89

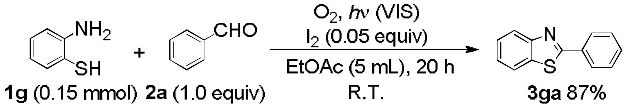
17[d]	4-NO_2	**1f**	H	**2a**	**3fa**	57

[a] The reaction conditions: **1** (0.15 mmol) and **2** (1.0 equiv) in EtOAc (3 mL) was stirred under argon atmosphere for 30 min. Then it was added MgI_2 (0.05 equiv) in EtOAc (2 mL) and was stirred and irradiated with fluorescent lamp under O_2 atmosphere for 6 h.

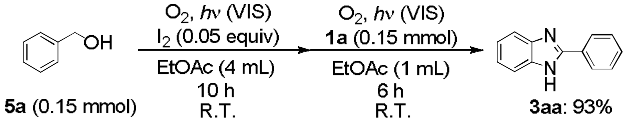
[b] Isolated yields.

[c] ^{1}H NMR yield. The isolated product was 31.3 mg (3ae : 4ae : 1a = 200 : 7 : 10).

[d] I_2 (0.2 equiv) was used for 20 h.

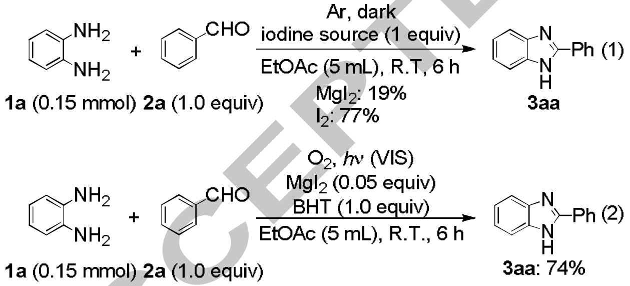


Scheme 3. Catalytic aerobic photooxidative synthesis of benzothiazole



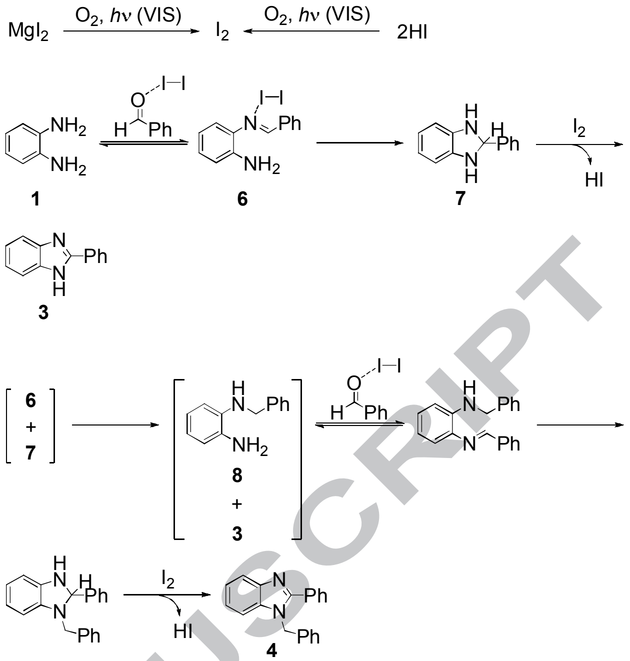
Scheme 4. One-pot photooxidative synthesis of benzimidazoles from benzyl alcohol

To clarify the reaction mechanism, several control experiments were performed. When 1 equivalent of magnesium iodide was used in the absence of both molecular oxygen and visible light, **3aa** was obtained in low yield (Scheme 5, equation 1). In contrast, when 1 equivalent of molecular iodine was used, **3aa** was obtained in good yield (Scheme 5, equation 1). These results suggest that molecular iodine works well as a Lewis acid and that oxidation of aminal intermediate **7** proceeds in the absence of photo irradiation. Notably, this reaction was not suppressed in the presence of 1 equivalent of BHT, and **3aa** was obtained in good yield (Scheme 5, equation 2), which indicates that the reaction probably does not proceed through a radical pathway



Scheme 5. Study of reaction mechanism

Scheme 6 shows a plausible pathway for this reaction. First, magnesium iodide is oxidized to molecular iodine under photooxidative conditions. Molecular iodine acts as a Lewis acid and promotes cyclization of diamine **1** to aminal intermediate **7**,[22] which is oxidized to **3** in the presence of I_2.[23] Hydrogen iodide generated by the oxidation step is oxidized to I_2, and the catalytic cycle is completed. Aminal **7** can be oxidized by **6** to give **3** and **8**; however, this pathway represents a minor pathway because by-product **4** was obtained in low yield.[24]



Scheme 6. Plausible reaction mechanism

In conclusion, in this study, we developed a method for the environmentally benign synthesis of benzimidazoles with a catalytic amount of an iodine source under photooxidative conditions. Furthermore, benzothiazole was obtained in high yield. The one-pot synthesis of benzimidazole from benzyl alcohol was also successful. This method is interesting from the viewpoint of green chemistry because it involves the use of molecular oxygen and visible-light irradiation. Further applications of this approach are under investigation in our laboratory.

Acknowledgments

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20. When 1 g of 1,2-phenylenediamine (**1a**) was used as a scale-up experiment, 2-phenylbenzimidazole (**3aa**) was obtained in 26% yield without further optimization.
21. Typical procedure: A Typical example of the synthesis of benzimidazole (Table 2, entry1). A solution of 1,2-benzenediamine (**1a**, 0.15 mmol) and benzaldehyde (**2a**, 0.15 mmol) in dry EtOAc (3 mL) in a Pyrex test tube was stirred under an argon atmosphere for 30 min. Then magnesium iodide (0.0075 mmol) in dry EtOAc (2 mL) was added, and stirred and irradiated externally with a fluorescent lamp for 6 h with an O_2 balloon. The reaction mixture was concentrated under reduced pressure, and purification of the crude product by PTLC ($CHCl_3$: MeOH= 98 : 2) provided benzimidazole (**3aa**) (Rf = 0.6, 27.1 mg, 93%).
22. We cannot rule out that MgI_2 also works as a Lewis acid because MgI_2 gave slightly higher yield than that of I_2.
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