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Visible-Light Induced Isoindoles Formation To Trigger Intermolecular Diels–Alder Reactions in the Presence of Air

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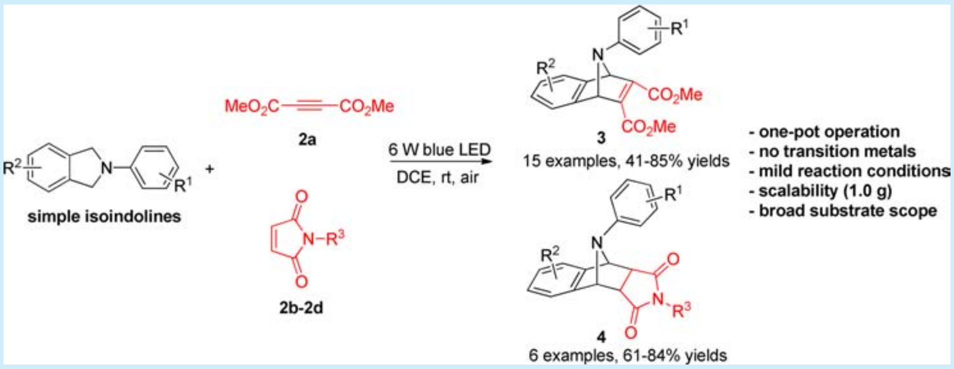
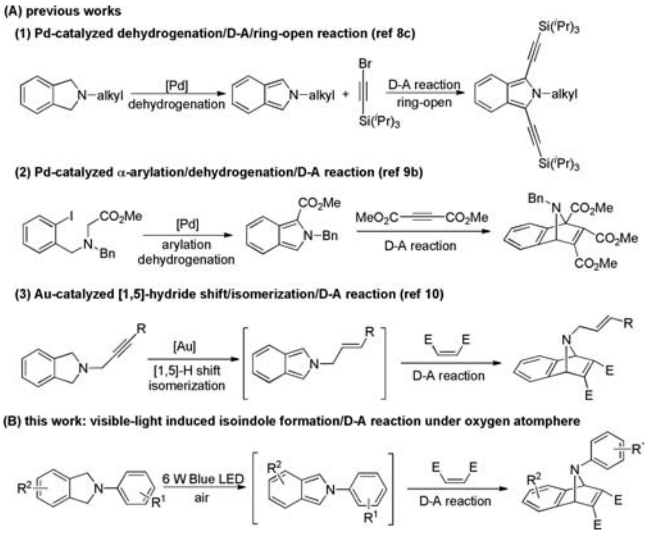
Ⓢ *Supporting Information*



ABSTRACT: Visible-light induced isoindole formation triggered an intermolecular Diels–Alder reaction with dienophiles such as acetylenedicarboxylate and maleimides in the presence of air. The reaction resulted in excellent diastereoselctivity and high yields under mild reaction conditions. This protocol provides an atom-economical, transition-metal-free (TM-free) and straightforward approach to structurally diverse bridged-ring heterocycles from easily accessible molecules.

Isoindoles as interesting nitrogen-containing heterocycles have attracted considerable attention from organic chemists, due to their high level of reactivity in cycloaddition reactions,[1,2] their fluorescent and electroluminescent properties, and potential pharmaceutical activity.[3,4] The reasons for their limited applications are mainly due to their relatively unstable structure and the lack of a general methodology for the synthesis of their derivatives.[5] Because of the instability of the isoindole nucleus, recent studies mainly focus on applying isoindoles as latent dienes allowing for intermolecular Diels–Alder (D–A) reactions with dienophiles,[6] directly giving access to bridged- and fused-ring heterocycles (Scheme 1A), which are of important biological interest.[7] For instance, Suginome's group reported a palladium-catalyzed dehydrogenation/Diels–Alder sequence to realize this protocol (Scheme 1A-1).[8] Additionally, palladium-catalyzed α-arylation/dehydrogenation/Diels–Alder reaction sequences have been established by Solé et al. (Scheme 1A-2).[9] Moreover, Gong and co-workers recently used a Au-catalyzed [1,5]-hydride shift/Diels–Alder cascade to provide these bridged-ring heterocycles (Scheme 1A-3).[10] To expand the scope of the Diels–Alder reaction with isoindoles, the development of a convenient, efficient, transition-metal-free, and atom-economical approach for the rapid construction of these bridged-ring heterocycles is highly desirable.

Scheme 1. Isoindole Derivatives Generated in Situ in Diels–Alder Reaction



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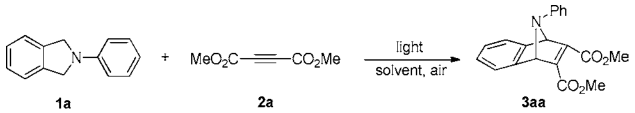
In the past decade, progress in the field of visible-light photoredox reactions with amines has attracted considerable interest from the chemical community.[11] As part of our research interest in the development of C−H functionalization at the α position to the nitrogen atom, a variety of *N*-aryl pyrrole derivatives have been prepared via a [1,5]-hydride shift/isomerization process.[12] Herein, we describe an intermolecular Diels−Alder reaction based on visible-light induced formation of isoindoles in the presence of air as latent dienes, which react with dienophiles to afford bridged-ring heterocycles under mild reaction conditions.

Table 1. Evaluation of Various Reaction Conditions[a]

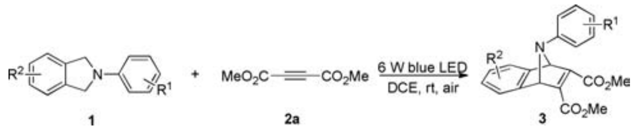


entry	light	temp (°C)	solvent	time (h)	yield (%)[b]
1	sunlight	20	DCE	107	44
2	orange	20	DCE	143	41
3	green	20	DCE	84	50
4	blue	20	DCE	43	83
5	–	20	DCE	72	trace
6[c]	blue	20	DCE	72	trace
7	blue	20	DCM	71	72
8	blue	20	THF	61	75
9	blue	20	DMF	48	81
10	blue	20	PhMe	69	78
11	blue	50	DCE	48	69
12	blue	80	DCE	48	67

[a] **1a** (0.3 mmol), **2a** (1.2 equiv), light, solvent (3 mL). [b] Isolated yield. [c] Under a N_2 atmosphere.

A dichloroethane (DCE) solution of *N*-phenylisoindoline **1a** and dimethyl acetylenedicarboxylate **2a** was stirred at room temperature in the presence of sunlight (entry 1, Table 1). After 107 h, the desired product bridged-ring heterocycle **3aa** was obtained in 44% yield. Encouraged by this result, under other identical conditions, different types of light were examined (entries 2−4, Table 1). To our delight, **3aa** was obtained in 83% yield after 43 h of irradiation with a 6 W blue LED at room temperature (entry 4, Table 1). In sharp contrast, the reaction almost did not take place in the dark (entry 5, Table 1). When the reaction was carried out under a N_2 atmosphere, only a trace amount of product was observed (entry 6, Table 1). These results indicated that both visible-light and air played critical roles in this reaction. Furthermore, solvent optimization revealed that DCE was the best solvent, enabling the reaction completion at room temperature within 43 h. Other solvents, such as DCM, THF, DMF, and toluene, could also give satisfactory results (entries 7−10, Table 1). To examine the temperature effect, the reaction was carried out at 50 and 80 °C under otherwise identical conditions, respectively, providing **3aa** in lower yields (entries 11, 12, Table 1). Together, the optimized reaction conditions were determined as follows: DCE as a solvent, under air condition, room temperature, in the presence of blue LED.

Table 2. Visible-Light Induced Isoindole Formation/D−A Reaction of Isoindolines 1 with 2a in the Presence of Air[a]



entry	1	R^1	R^2	3	yield (%)[b]
1	**1a**	H	H	**3aa**	83
2	**1b**	4-Me	H	**3ba**	76
3	**1c**	2,4-Me_2	H	**3ca**	73
4	**1d**	2-OMe	H	**3da**	81
5	**1e**	3-OMe	H	**3ea**	71
6	**1f**	4-OMe	H	**3fa**	85
7	**1g**	2-Cl	H	**3ga**	74
8	**1h**	3-Cl	H	**3ha**	76
9	**1i**	4-Br	H	**3ia**	70
10	**1j**	1-naphthyl	H	**3ja**	63
11	**1k**	H	5-Me	**3ka**	72
12	**1l**	H	5-OMe	**3la**	65
13	**1m**	H	4-Cl	**3ma**	64
14	**1n**	H	5-Cl	**3na**	71
15	**1o**	H	4-NO_2	**3oa**	41

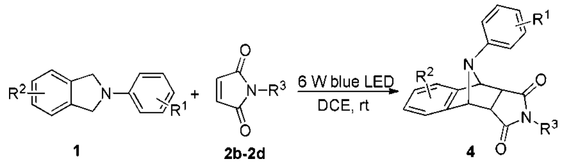
[a] **1** (0.3 mmol) and **2** (1.2 equiv), 6 W blue LED, DCE (3 mL), rt under an air atmosphere for 43 h. [b] Isolated yields.

With the optimal reaction conditions in hand, we turned our attention to explore the reaction of various isoindolines **1** with **2a** as the dienophile (Table 2). It was found that both electron-donating and -withdrawing substituents on the benzene ring linked to the nitrogen atom of **1** were suitable for this reaction, affording the corresponding products **3aa**−**3ia** in 70−85% yields (entries 1−9, Table 2). The reaction of *N*-(1-naphthyl)-isoindoline **1j** gave the corresponding product **3ja** in a slightly lower yield (63% yield, entry 10, Table 2). The structural assignment of **3ia** was supported by the X-ray crystallography (see the Supporting Information for details). Next, *N*-phenylisoindoline derivatives with various R^2 substituents were subjected to the visible-light triggered D−A reaction (entries 11−15, Table 2). We found that methyl, methoxyl, and chloro groups did not affect the reactivity, giving the corresponding products **3ka**−**3na** in good yields (entries 11−14, Table 2). However, the reaction with 4-NO_2 substituted substrate **1o** gave the corresponding product **3oa** in only 41% yield (entry 15, Table 2). Meanwhile, we found that *N*-alkylisoindoline was an inappropriate substrate for this conversion.

To broaden the generality of the above reaction with isoindolines **1**, maleimides **2b**−**2d** were used as the dienophiles (entries 1−3, Table 3). Therefore, reaction of *N*-phenylisoindoline **1a** with *N*-methylmaleimide **2b** provided the corresponding product **4ab** in 67% yield with perfect *endo*-selectivity (entry 1, Table 3).[13] When *N*-phenylmaleimide **2c** and *N*-benzylmaleimide **2d** were reacted with **1a**, products **4ac** and **4ad** were isolated in 83% and 84% yield, respectively (entries 2, 3, Table 3), both only affording the *endo*-products. The relative configuration of **4ad** was confirmed by X-ray crystallography (see the Supporting Information for details). Reaction of **2d** with 2-methoxyl, 4-methoxyl, and 4-bromide substituted isoindolines (**1d**, **1f**, **1i**) gave products **4dd**, **4fd**, and **4id** in 76−84% yields, respectively (entries 4−6, Table 3).

To demonstrate the practical utility of this methodology, a gram-scale reaction (1.0 g) was carried out to furnish the desired product **3aa** in 77% yield (Scheme 2). Interestingly, treatment of **3aa** with 20 mol % TsOH·H_2O in DCE at 80 °C resulted in 1-naphthylamine derivative **5** in 78% yield (Scheme 3).

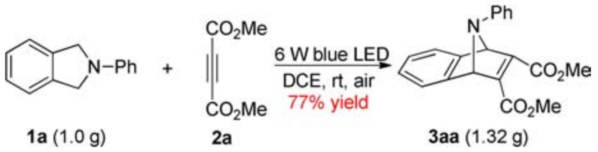
Table 3. Visible-Light Induced Isoindoles Formation/D−A Reaction with Maleimides 2b−2d in the Presence of Air[a]



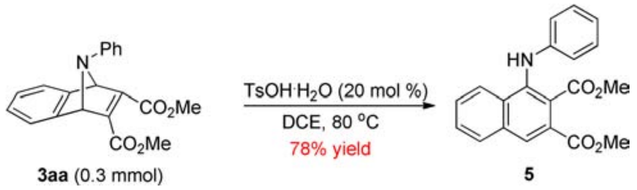
entry	1	R^1	R^2	2, R^3	4	yield (%)[b]
1	**1a**	H	H	**2b**, Me	**4ab**	67
2	**1a**	H	H	**2c**, Ph	**4ac**	83
3	**1a**	H	H	**2d**, Bn	**4ad**	84
4	**1d**	2-OMe	H	**2d**, Bn	**4dd**	78
5	**1f**	4-OMe	H	**2d**, Bn	**4fd**	84
6	**1i**	4-Br	H	**2d**, Bn	**4id**	76

[a] **1** (0.3 mmol), **2** (1.2 equiv), 6 W blue LED, DCE (3 mL), rt under an air atmosphere for 43 h. [b] Isolated yield.

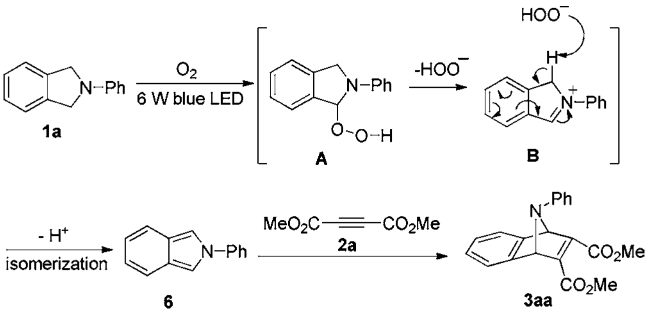
Scheme 2. Gram-Scale Preparation of Product 3aa



Scheme 3. Formation of 1-Naphthylamine 5 Derivative *via* Ring Opening



Scheme 4. Proposed Mechanism



A plausible mechanism for forming product **3aa** is shown in Scheme 4. Initially, visible-light irradiation of O_2 in the presence of *N*-phenylisoindoline **1a** generates isoindoline hydroperoxide **A**. This process is similar to the autoxidation reaction, which is a well-known reaction of nitrogen-containing compounds in the presence of oxygen.[14] Elimination of a hydrogen peroxide ion from **A** provides iminium cation intermediate **B**, which undergoes isomerization to give isoindole **6**.[15] Finally, the desired product **3aa** is formed via an intermolecular Diels−Alder reaction between diene **6** and dienophile **2a**. It was noted that the reaction could be converted completely in 5 h in the atmosphere of oxygen under blue LED, demonstrating that both oxygen and blue LED play critical roles in the reaction.

In conclusion, we herein present the first visible-light induced isoindole formation from isoindolines in the presence of air, which enable an intermolecular Diels−Alder reaction between the latent dienes and dienophiles under mild reaction conditions. This protocol ends up with excellent diastereoselectivity and high yields, providing a facile, transition-metal-free, and atom-economical approach to structurally diverse bridged-ring heterocycles from easily accessible compounds. Additionally, the resulting products could be easily converted to a 1-naphthylamine derivative in good yields. Further investigations on the application of this transformation are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds and a CIF file for compounds **3ia** and **4ad**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01078.

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Notes

The authors declare no competing financial interest.

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