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Visible Light-Induced Cyclization Reactions for the Synthesis of 1,2,4-Triazolines and 1,2,4-Triazoles

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A novel method for concisely synthesizing 1,2,4-triazolines via [3+2] cyclization under visible light is reported. These compounds can be easily converted into 1,2,4-triazoles under basic or photoredox conditions. The application of the 1,2,4-triazoles was also investigated via mild operations.

Nitrogen-containing moieties are vital parts of a large number of medicinal compounds and naturally biological products.[1] Thus, the development of novel strategies for the efficient synthesis of these heterocyclic compounds is highly important in the field of synthetic chemistry. Notably, 1,2,4-triazolines and 1,2,4-triazoles represent important structural units that exhibit anticancer and anticonvulsant properties and which exist in numerous biologically active compounds (Figure 1).[2] Due to the significance of these molecules, some strategies for their efficient synthesis have been developed based on the metal-catalysis and organocatalysis.[3] In addition, due to being readily available, azodicarboxylates have been employed as important reagents for the synthesis of these compounds. For example, Tepe and co-workers reported the efficient synthesis of 1,2,4-triazoles utilizing oxazolones and azodicarboxylate (Scheme 1A) via two steps.[4] Heinrich's group realized the [3+2] cyclization between azomethines ylides and phenylazocarboxylates yielding the 1,2,4-triazoles via three steps (Scheme 1B).[5] To the best of our knowledge, although large number of methods for preparing these products has been reported in the past decades, mild operating conditions with metal-free, room temperature, and fewer experimental steps are still challenging projects for chemists.

Recently, photoredox catalysis has emerged as a powerful approach in organic synthesis, and various novel reactions have begun to be fully realized under visible light.[6] Therefore, cyclization reactions induced by visible light for the synthesis of 1,2,4-triazoles would be an interesting and significant method. 2H-azirines, as highly important valuable intermediates for preparing various functional compounds, could be catalyzed by transition metal catalysts or induced by UV light irradiation.[7] Recently, Xiao and co-workers found that 2H- azirines could be excited by a photosensitizer under visible light, in order to synthesize oxazoles and pyrroles.[8] Inspired by the works, we speculated that 1,2,4-triazoles might be synthesized by photoredox catalysis using 2H-azirines and azodicarboxylates. Herein, we report the efficient synthesis of 1,2,4-triazolines and 1,2,4-triazoles under visible light via one step.

Initially, we examined the reaction of 2H-azirine **1a** with azodicarboxylate **2a** in the presence of **I** (9-mesityl-10-methyl-acridinium perchlorate). DCE was used as the solvent under blue LED illumination. To our delight, the reaction was completed in 10

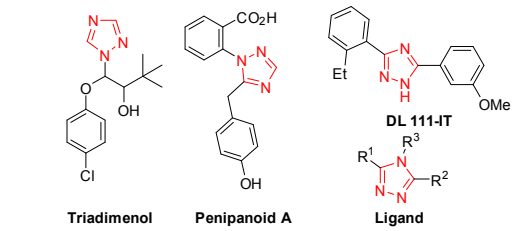
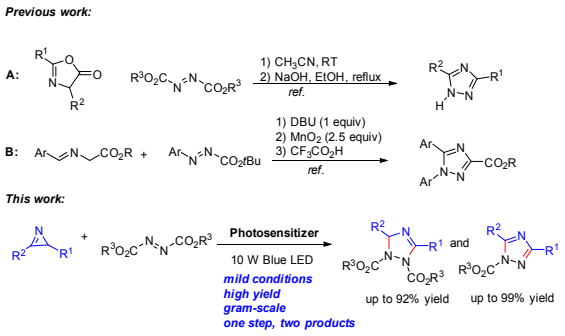


Figure 1. Represent biological active compounds and ligands.



Scheme 1. The synthesis of 1,2,4-triazoles.

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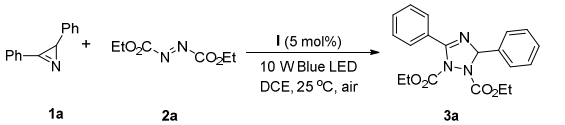
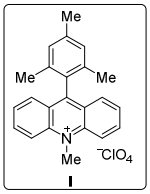
min to give **3a** in 91% yield (Table 1, entry 1). However, when the reaction was catalyzed by $Ru(bpy)_3Cl_2 \cdot 6H_2O$, $Ir(ppy)_2(dtbbpy)PF_6$ and EY, no products could be obtained (Table 1, entries 4-6). After screening the solvents, no better results were obtained, and DCE was determined to be the superior choice (Table 1, entries 7-9). Control experiments were also performed, and no reaction occurred in the absence of the photosensitizer or visible light (Table 1, entry 2,3). Taken together, these results indicated that the [3+2] cyclization was induced by photoredox catalysis.

Table 1. Screening the reaction conditions.a



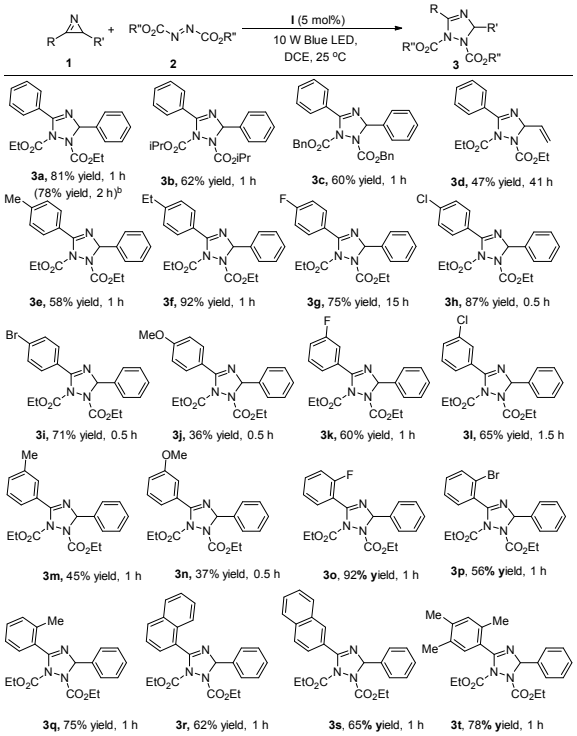
1a 2a 3a

Entry	Change from the "standard conditions"	Yield (%)
1	none	**10 min, 91**
2	no light	1 h, trace
3	no photocatalyst	1 h, trace
4	$Ru(ppy)Cl_3 \cdot 6H_2O$, instead of **I**	1 h, trace
5	$[Ir(ppy)_2(dtbbpy)]PF_6$, instead of **I**	1 h, trace
6	EY, instead of **I**	1 h, trace
7	in toluene	1 h, trace
8	in CH_2Cl_2	10 min, 87
9	in DMF	1 h, NR
10	in $CHCl_3$	10 min, 78
11	in CH_3CN	10 min, 89
12	in acetone	10 min, 89



[a]Unless otherwise noted, in all reactions, **1a** (0.05 mmol) and **2a** (0.075 mmol) were catalyzed by **I** (5 mol%) in DCE (1 mL) under blue LED at 25 °C. DCE: ClCH2CH2Cl.

Table 2. The scope of the [3+2] reactions.a

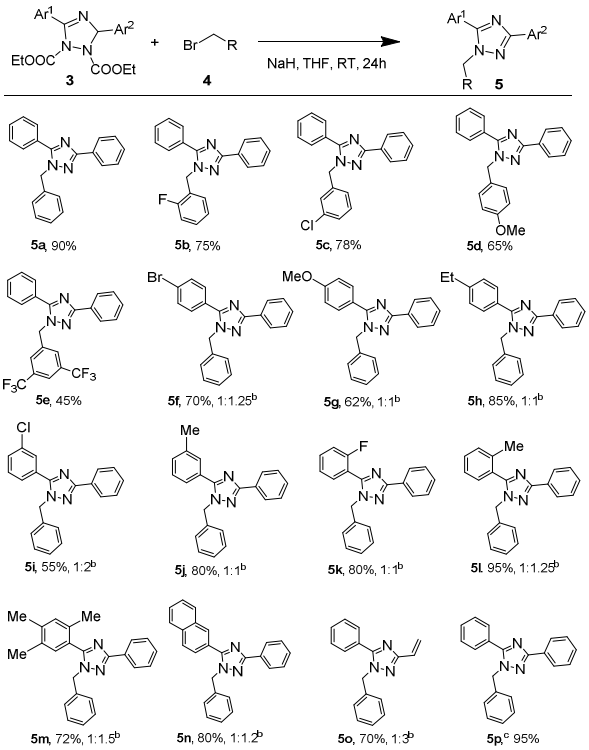


[a]Unless otherwise noted, in all reactions, **1** (0.5 mmol) and **2** (0.75 mmol) were catalyzed by **I** (5 mol%) in DCE under blue LED at 25 °C. [b]**1a** (5 mmol) and **2a** (7.5 mmol) were catalyzed by **I** (5 mol%) in DCE under blue LED at 25 °C.

Under the optimized conditions, we next investigated the scope of the [3+2] cyclization reactions with various azodicarboxylate and 2H-azirines. In general, all of the reactions proceeded smoothly to afford the desired products in good and excellent yields. Different protecting groups of the azodicarboxylate, including ethyl, isopropyl, and benzyl groups, were all tolerated in the reactions. The electron-withdrawing groups and electron-donating groups on the benzene ring of the 2H-azirines all furnished the corresponding products with good to excellent yields within the desired time period. The naphthyl moiety of the 2H-azirines was also tolerated, with 62% yield and 65% yield in 1h (Table 2). In particular, **3a** can be scaled up to gram-level affording 1.4g with 78% yield in 2 h. To further explore the applications of the products **3**, we subsequently performed reactions between **3** and **4** under basic conditions. We found that 1,2,4-triazoles with alkyl groups on the "N" site can be obtained with good to excellent yields, irrespective of the electronic and steric nature of the substituents on the benzene ring of **3** and **4** (Table 3).

When we were exploring the [3+2] cyclization reactions under visible light, the desired 1,2,4-triazoles can be obtained stirring for a longer time. Encouraged by the result, we then continued to explore the direct aromatization of **3** induced by visible light under photoredox catalysis. After screening the conditions of the reaction, the reaction was efficiently catalyzed by **I** in the air with 99% yield (in Ar, 35% yield), affording the corresponding product with high

Table 3. Substrates scope of the tri-substituted 1,2,4-triazoles.[a]



[a]Unless otherwise noted, the reactions were carried out with **3** (0.05 mmol) and **4** (0.10 mmol) using NaH (0.10 mmol) in THF. [b]the regioselectivity ratio determined by ^{1}H-NMR. [c]the reactions were carried out with **3b** (0.05 mmol) and **4** (0.10 mmol) using NaH (0.10 mmol) in THF.

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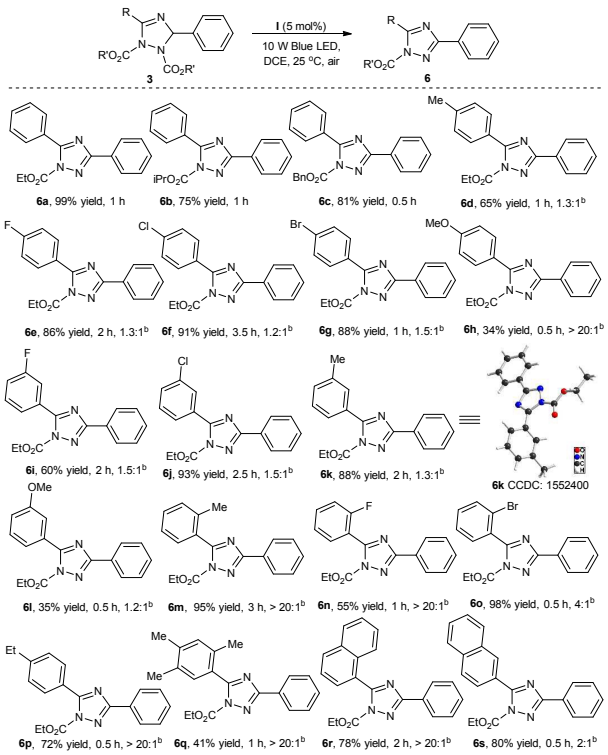
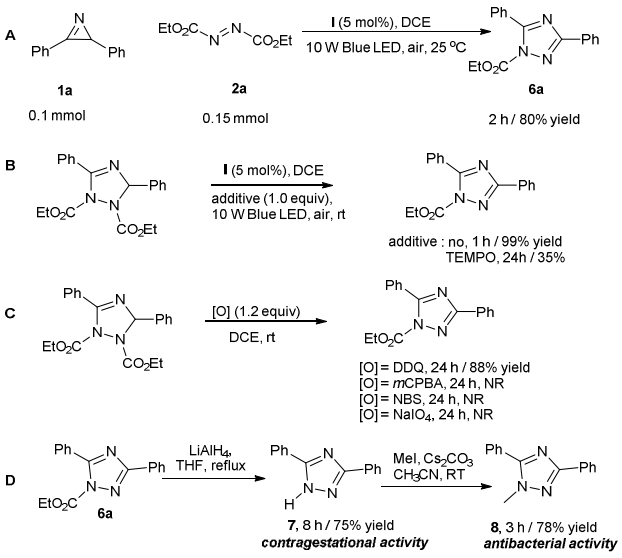
yield in 1 h (*See SI*). Next, we investigated the influences of different substituents, including ethyl ester, isopropyl ester and benzyl ester, on the "N" of **3**. All of the reactions proceeded well and furnished the corresponding products with high yields within a short time period. After the investigation of the electronic and steric nature of the substituents on the benzene ring of **3**, higher yields were obtained when electron-withdrawing groups were present on the benzene ring. By contrast, electron-donating groups, such as a methoxyl, were detrimental to the reactions, as only 34% yield and 35% yield could be obtained (Table 4, **6h**, **6l**). Meanwhile, the naphthyl groups were also tolerated. Furthermore, we also explored the direct synthesis of 1,2,4-triazoles induced by the blue LED via one step without any operations, 80% yield of **6a** was yielded by stirring for a longer time (Scheme 2A).

To gain insights into the aromatization of **3**, we added TEMPO to the reaction. However, only 35% yield was obtained after stirring for 24 h, which suggested that the reaction included a radical step. Though other oxidants were also tested in order to illustrate the importance of this method, only DDQ could oxidize substrate **3a**, resulting in 88% yield over a long reaction time (24 h). Thus, photoredox catalysis under visible light is critical for the aromatization of **3a**. Notably, **6a** could be easily transformed using $LiAlH_4$ into the biologically active molecule **7**,[10] which has contra gestational activity. The subsequent methylation of **7** affords **8**,[11] which has antibacterial activity. We also attempted the asymmetric reaction between **1a** and **2a** using the chiral photosensitizer **9** as the catalyst based on the ion-pair strategy;[12] however, only 20% ee

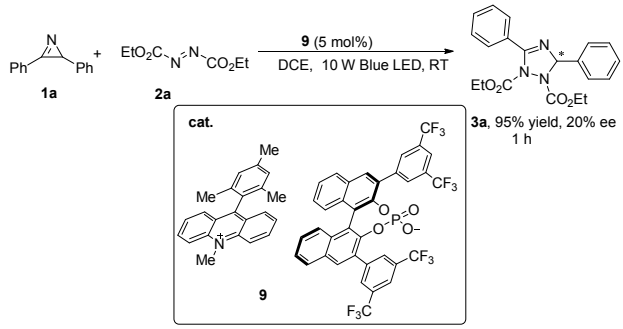
Table 4. The scope of aromatization reactions of **3**.[a]



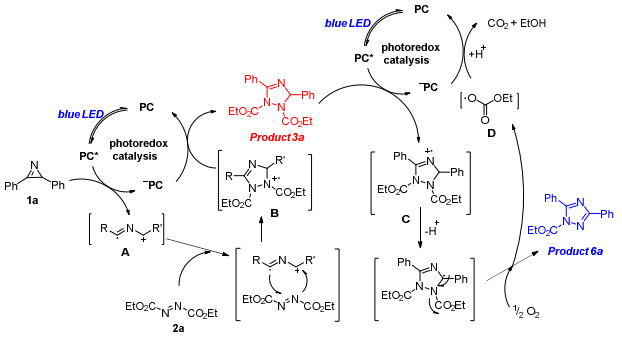
[a]Unless otherwise noted, in all reactions, **3** (0.05 mmol) were catalyzed by **I** (5 mol%) in DCE under blue LED. Supplementary crystallographic data for 6k can be found in CCDC 1552400.[9] [b]the regioselectivity ratio determined by ^{1}H-NMR.



Scheme 2. The mechanistic study and the transformations of 6a.



Scheme 3. The asymmetric [3+2] cyclization reaction.



Scheme 4. The plausible reaction pathway.

was obtained. A detailed exploration of the asymmetric reactions catalyzed by chiral photosensitizers is now underway in our lab. Based on the above results and Xiao's work, a plausible pathway was proposed as shown in Scheme 4. Firstly, 2H-azrine is oxidized by the photoredox catalyst under the visible light, and then 2-azaallenyl radical cation **A** is generated sequentially. After that, 2a will react with the radical cation A to form the new generated **B**, which will be reduced by a low-valent photocatalyst. The corresponding product **3a** is obtained via the catalytic cycle, and then **3a** is continued to be oxidized by the photoredox catalyst to

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form the newly generated **C**. After the abstraction of hydrogen and the aromatization proceeded, the desired compound **6a** is yielded.

In summary, we have developed a novel method in which 2H-azirines and azodicarboxylates are utilized to efficiently synthesize 1,2,4-triazolines, with good to excellent yields, under visible light. The 1,2,4-triazoles could be efficiently furnished when the 1,2,4-triazolines reacted with benzyl bromides under basic conditions or were directly catalyzed by photosensitizers under visible light. Notably, the 1,2,4-triazoles can be transformed into biologically active molecules via additional mild reactions. The asymmetric cyclization reaction was also preliminarily investigated using a chiral organic photosensitizer. Novel methods for synthesizing nitrogen-containing compounds based on azodicarboxylates under visible light are being developed in our lab, and our findings will be reported in due course.

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Visible Light-Induced Cyclization Reactions for the Synthesis of 1,2,4-Triazolines and 1,2,4-Triazoles

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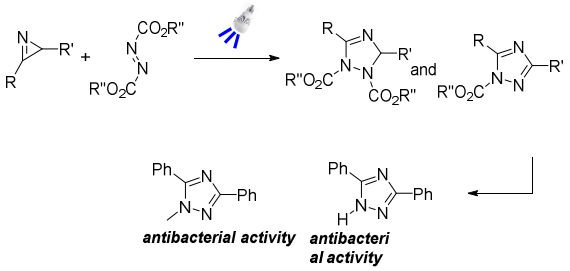

1,2,4-triazolines and 1,2,4-triazoles can be synthesized under the visible light via one step without additional operations, which can be also scaled up to gram-level.