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Communications

Transition-metal-free, visible-light induced cyclizations of arylsulfonyl chlorides with 2-isocyanobiphenyls to produce phenanthridines

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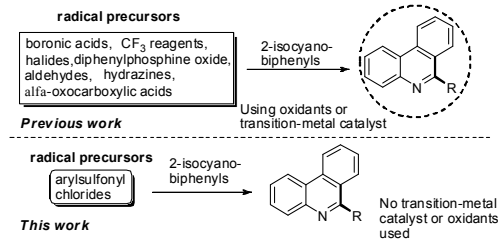
6-Aryl substituted phenanthridines were synthesized by a visible-light-catalyzed cyclization of 2-isocyanobiphenyls with arylsulfonyl chlorides under oxidants-free and transition-metal-free conditions. This transformation represents an efficient and attractive synthetic utilization of arylsulfonyl chlorides.

The expedient synthesis of substituted aromatic heterocycles has been a major goal for organic chemistry for decades, owing to the bioactive properties of heterocycles and their prevalence in natural products. As such, the development of new methods to synthesize heterocycles has been at the forefront of our discipline.[1] Of these techniques, radical-mediated reactions are among the most important in the development of new technologies for the synthesis of heterocycles.[2] The phenanthridine ring system represents one class of the most abundant and ubiquitous heterocycles in nature.[3] Owing to their structural diversity and remarkable biological functions, the synthesis and transformation of phenanthridines has been and continues to be a topic of research interest for synthetic organic chemists.[4]

Aryl isonitriles are highly versatile reagents which have found widespread application in organic, medicinal, and combinatorial chemistry (e.g. multicomponent reactions, heterocycle synthesis, and cycloadditions). Aryl isonitriles have gained renewed attention as radical acceptors in cascade reactions for the construction of heteroarenes.[5] Recently, a cascade radical pathway involving C-radical addition to 2-isocyanobiphenyls and subsequently intramolecular hemolytic aromatic substitution has been developed, which allows the rapid construction of substituted phenanthridines with high efficiency. However, only a few studies have been focused on this field and limited radical precursors were developed such as boronic acids,[6] CF_3 reagents,[5,7] halides,[8] aldehydes,[9] diphenylphosphine oxide,[10] α-oxocarboxylic acids and hydrazines.[11-12] Thus, it is still necessary to develop more radical precursors to realize isocyanide insertion *via* a radical process.

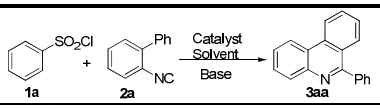
Visible light photoredox catalyst initiated organic transformations are emerging as uniquely powerful tools for constructing new chemical bonds in organic synthesis due to their more environmentally benign sustainability and mild operating conditions.[13-14] However, despite progress in this area, the in situ generation of aryl radicals for C-C(aryl) bond formation by visible light photoredox catalysis is quite rare.[15] Arylsulfonyl chlorides which are readily available commercially by sulfonylation of arenes have been utilized as aryl radical precursors for the sequential arylation of alkynes and carbocyclization with benzylic C(sp^3)-H bonds.[16] We hypothesized that 2-isocyanobiphenyls might serve as a platform to trap aryl radicals. In connection with our broader interest in the synthesis of nitrogen-containing heterocycle compounds,[17] herein, we disclose our preliminary results on visible-light promoted transformation of 2-isocyanobiphenyls and arylsulfonyl chlorides for the synthesis of phenanthridines under oxidants-free and transition-metal-free conditions. This transformation represents an efficient and attractive synthetic utilization of arylsulfonyl chlorides.



Scheme 1 Cyclization of 2-isocyanobiphenyls with various radical precursors including our work

The effort was initiated by using benzenesulfonyl chloride **1a** and 2-isocyanobiphenyl **2a** as a model reaction in the presence of $[Ru(bpy)_3Cl_2]$ (5 mol%), Na_2CO_3 (1.5 equiv), and 36 W compact fluorescent light in MeCN at room temperature. The desired phenanthridine **3aa** was obtained, albeit in low yield, after 10 h (Table 1, entry 1). Interestingly, the yield of **3aa** dramatically enhanced to 64% when the reaction was performed with 5 W blue LED light (Table 1, entry 2). The yield of **3aa** was lowered to 51% when reaction was irradiated with 5 W green LED light (Table 1, entry 3). Extensive screening of bases revealed that K_2HPO_4 provided the best results (Table 1, entries 4-7). Of the solvents tested, MeCN proved particularly suitable (Table 1, entries 8-10). Three other visible-light photoredox catalysts $[Ir(ppy)_3]$, Eosin Y and Rose Bengal (RB), were also tested (Table 1, entries 11-13). With Eosin Y, a good yield was still achieved (Table 1, entry 12). However, the reaction did not take place in the absence of either the visible-light photoredox catalysts (Table 1, entry 14) or additional visible light (Table 1, entry 15).

Table 1 Optimization of the reaction conditions[a]



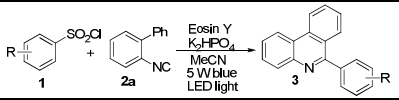
1a 2a 3aa

Entry	Catalyst	Solvent	Base	Yield[b] (%)
1[c]	$Ru(bpy)_3Cl_2$	MeCN	Na_2CO_3	16
2	$Ru(bpy)_3Cl_2$	MeCN	Na_2CO_3	64
3[d]	$Ru(bpy)_3Cl_2$	MeCN	Na_2CO_3	51
4	$Ru(bpy)_3Cl_2$	MeCN	K_2CO_3	47
5	$Ru(bpy)_3Cl_2$	MeCN	$NaHCO_3$	39
6	$Ru(bpy)_3Cl_2$	MeCN	Et_3N	41
7	$Ru(bpy)_3Cl_2$	MeCN	K_2HPO_4	82
8	$Ru(bpy)_3Cl_2$	DMSO	K_2HPO_4	0
9	$Ru(bpy)_3Cl_2$	CH_2Cl_2	K_2HPO_4	22
10	$Ru(bpy)_3Cl_2$	toluene	K_2HPO_4	0
11	$Ir(ppy)_3$	MeCN	K_2HPO_4	68
12	Eosin Y	MeCN	K_2HPO_4	79
13	RB	MeCN	K_2HPO_4	51
14	none	MeCN	K_2HPO_4	0
15[e]	Eosin Y	MeCN	K_2HPO_4	0

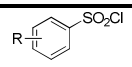
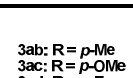
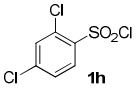
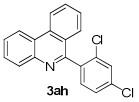
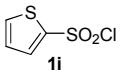
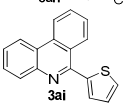
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), base (1.5 equiv), catalyst (5 mol%), 5 W blue LED, solvent (1 mL), r.t. in Ar atmosphere for 10 h. ppy = phenylpyridine. [b] Isolated yield. [c] 36 W compact fluore- scent light used instead of 5 W blue LED light. [c] 5 W green LED. [e] Without additional ligh.

Encouraged by these results, we applied the above visible-light photocatalysis protocol to a range of both arylsulfonyl chlorides **1** and 2-isocyanobiphenyls **2** to investigate the scope. The scope of arylsulfonyl chlorides **1** was initially explored in the presence of substrate **2a**, Eosin Y, K_2HPO_4, and 5 W blue LED light. As summarized in Table 2, Both electron-donating and -withdrawing arylsulfonyl chlorides could be successfully converted to the corresponding phenanthridines in moderate to good yield. In addition, a high level of tolerance by functional groups was observed, and the efficiency of the reaction was not affected in the presence of halides, ether, and alkyl groups. Furthermore, substituents at different positions on the arene group (*para*, *meta*, and *ortho* positions) did not affect the reaction efficiency. It is noteworthy that halo-substituted arylsulfonyl chlorides were tolerated well, thus leading to halo-substituted products, which could be used for further transformations. Interestingly, the polysubstituted arylsulfonyl chloride gave the desired product **3ah** with a good yield. Notably, the introduction of heterocycles into this system made this methodology more useful for the preparation of pharmaceuticals and materials (Table 2, entry 3).

Table 2 Screen of the arylsulfonyl chlorides **1** [a]



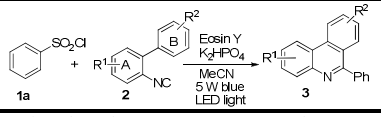
1 2a 3

Entry	Arylsulfonyl chloride	Product	Yield (%)[b]
1	 **1b**: R = *p*-Me **1c**: R = *p*-OMe **1d**: R = *p*-F **1e**: R = *p*-Cl **1f**: R = *o*-Me **1g**: R = *m*-Me	 **3ab**: R = *p*-Me **3ac**: R = *p*-OMe **3ad**: R = *p*-F **3ae**: R = *p*-Cl **3af**: R = *o*-Me **3ag**: R = *m*-Me	**3ab**: 72% **3ac**: 66% **3ad**: 79% **3ae**: 74% **3af**: 61% **3ag**: 68%
2	 **1h**	 **3ah**	77
3	 **1i**	 **3ai**	53

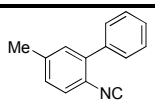
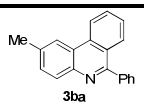
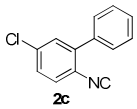
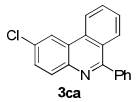
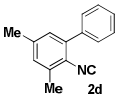
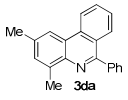
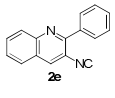
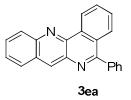
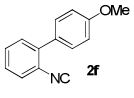
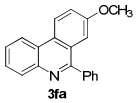
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), Eosin Y (5 mol%), 5 W blue LED, K_2HPO_4 (1.5 equiv), solvent (1 mL), r.t. in Ar atmosphere for 10 h. [b] Isolated yield.

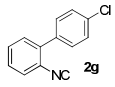
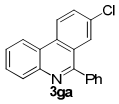
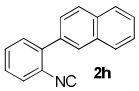
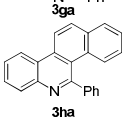
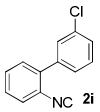
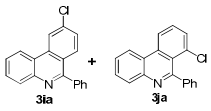
The cyclocoupling method was also successfully applied to a variety of 2-isocyanobiphenyls **2**. As shown in Table 3, a broad range of 2-isocyanobiphenyl compounds reacted smoothly with **1a** to give the corresponding phenanthridine derivatives in good yields. The isocyanides bearing either electron-rich or electron-deficient substituent on the benzene ring A afforded 6-phenyl phenanthridines with satisfactory yields (Table 3, entries 1-3). Replacement of the benzene ring A with a quinoline ring did not affect the efficiency of the reactions (Table 3, entry 4). To highlight the utility of this transformation, the isocyanides having different functional groups on the benzene ring B were also investigated. Electronically different isocyanides underwent annulation with **1a** successfully (Table 3, entries 5-6). When an isocyanide bearing a 2-naphthyl group was used, the cyclization occurred only at the 1-position and not at the 3-position (Table 3, entry 7). The regioselectivity observed in this particular case is a characteristic outcome of homolytic aromatic substitution. Notably, when 2-isocyanobiphenyl derivative **2i** was employed, the reaction afforded the two regioisomers **3ia** and **3ja** in a ratio of 1.3: 2 (Table 3, entry 8).

Table 3 Screen of the 2-isocyanobiphenyls **2**[a]



1a 2 3

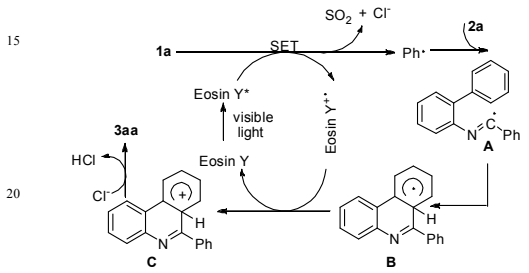
Entry	2-Aminophenol	Product	Yield[b] (%)
1	 **2b**	 **3ba**	57
2	 **2c**	 **3ca**	64
3	 **2d**	 **3da**	70
4	 **2e**	 **3ea**	51
5	 **2f**	 **3fa**	75

6			78
7			72
8			71

3ia+**3ja**, (ratio 1: 1.5)[c]

[a] Reaction conditions: Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), Eosin Y (5 mol%), 5 W blue LED, K_2HPO_4 (1.5 equiv), solvent (1 mL), r.t. in Ar atmosphere for 10 h. [b] Isolated yield. [c] The ratio was determined by the isolated yield.

On the basis of these observations and previous studies,[5, 14a, 15] a plausible mechanism was proposed as shown in Scheme 2. Initially, photoexcitation of Eosin Y by visible light generates excited [Eosin Y*]. Then An phenyl radical (Ph·) is formed by a single-electron transfer (SET) from the excited state [Eosin Y*] to an arylsulfonyl chloride and subsequent addition of the phenyl radical (Ph·) to isocyanide **2a** to form the imidoyl radical **A** *via* intermolecular addition, followed by an intramolecular attack of the imidoyl radical **A** on the pendant aromatic ring to give the cyclized radical intermediate **B**. A single-electron oxidation of **B** by the Eosin Y radical cation regenerates the photocatalyst and forms the cation intermediate **C**. Finally, deprotonation of **C** leads to the desired phenanthridine **3aa**.



Scheme 3 Plausible mechanism

In summary, we have successfully executed a 2-isocyanobiphenyl cyclization that involves arylsulfonyl chlorides and is triggered by visible-light photoredox catalysis to construct functionalized phenanthridines, a ubiquitous component of many natural products, biomolecules and materials applications. Most importantly, simple and readily available Eosin Y emerges as an efficient catalyst, rather than a metal catalyst, which is often expensive and is required to be completely removed from products, especially in the synthesis of pharmaceutical compounds. What's more, high functional-group tolerance under mild conditions. Mechanistic, scope, and limitation studies of the reaction are in progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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