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Visible-Light-Promoted and One-Pot Synthesis of Phenanthridines and Quinolines from Aldehydes and *O*-Acyl Hydroxylamine

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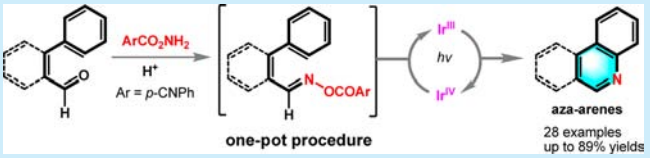
Supporting Information

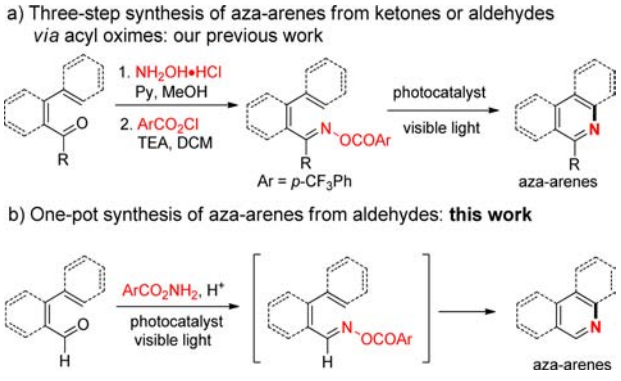
ABSTRACT: A one-pot synthesis of phenanthridines and quinolines from commercially available or easily prepared aldehydes has been reported. *O*-(4-Cyanobenzoyl)-hydroxylamine was utilized as the nitrogen source to generate *O*-acyl oximes in situ with aldehydes catalyzed by Brønsted acid. *O*-Acyl oximes were then subjected to visible light photoredox catalyzed cyclization via iminyl radicals to furnish aza-arenes. A variety of phenanthridines and quinolines have been prepared assisted by Brønsted acid and photocatalyst under visible light at room temperature with satisfactory yields.



N-Containing 6-membered arenes, such as quinolines and phenanthridines, are ubiquitous in natural products, pharmaceuticals, and other biologically active molecules.[1] Traditional methods to prepare these heterocycles primarily rely on ionic transformations from amines and carbonyl compounds, such as Combes, Povarov, and Skraup reactions.[2,3] Transition-metal-mediated reactions have also been developed prosperously to achieve these motifs from diverse precursors for recent years.[4]

Compared to the flourish of ionic condensation and transition-metal catalysis, there are fewer reported methods using radical approaches in the construction of aza-arenes.[5] Very recently, we have developed a visible-light-promoted synthesis of *N*-containing 6-membered arenes from *O*-acyl oximes via an iminyl radical (Scheme 1a).[6] This strategy affords an efficient method for the exclusive 1 e reduction of acyl oximes[7] under mild conditions, which can furnish a class of ubiquitous aza-arenes in high yields, including pyridines, quinolines, and phenanthridines. However, *O*-acyl oximes must be preformed from corresponding ketones or aldehydes in two steps (oximation and acylation). To improve the overall efficiency of this transformation, we would like to investigate the possibility of a one-pot procedure for the synthesis of aza-arenes from carbonyl compounds and a nitrogen source. In this regard, selection of the nitrogen source is crucial to this transformation. The nitrogen source must be able to generate *O*-acyl oximes with carbonyl compounds in situ.[8] It was found that *O*-acyl hydroxylamines, which could easily be prepared from readily available hydroxylamine and the corresponding acyl chlorides, could condense with aldehydes to give *O*-acyl oximes. Thus, we believed that *O*-acyl hydroxylamines could serve as the nitrogen source in the one-pot synthesis of aza-arenes from aldehydes under visible light photoredox catalysis (Scheme 1b).[9]

Scheme 1. Visible-Light-Promoted Synthesis of Aza-arenes



Our initial efforts toward this goal focused on the use of *O*-(4-cyanobenzoyl)hydroxylamine (**2a**) as the nitrogen source. Reaction of biphenyl-2-carbaldehyde (**1a**) with **2a** (3.0 equiv) under our previously established conditions[6] gave desired phenanthridine **3a** in 37% yield based on ^{1}H NMR spectroscopy analysis (Table 1, entry 1). The poor yield was due to low conversion of aldehyde **1a** to the corresponding acyl oxime. To accelerate the formation of the acyl oxime, a variety of additives were examined (entries 2−9). Organic base, such as Et_3N, could not improve this reaction (entry 2). To our delight, Brønsted acids were efficient additives to this transformation (entries 3−9). *p*-Cl-benzenesulfonic acid (CBSA) was proven to be the best additive with 72% NMR yield of **3a** (entry 9). The dosage of the nitrogen source was then investigated. The use of less **2a** did not affect the yield of this reaction significantly (entries 10−11), and 1.5 equiv of **2a** gave the optimal result with 74% NMR yield (72% isolated yield) (entry 10). The solvent effect was then evaluated (entries 12−17). No solvent was superior to DMF. *O*-(4-CF_3-benzoyl)-hydroxylamine (**2b**) was investigated as the nitrogen source,

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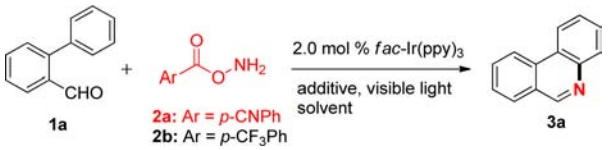
Table 1. Optimization of Reaction Conditions[a]



entry	additive	solvent	yield/%[b]
1		DMF	37
2	Et_3N	DMF	<10
3	AcOH	DMF	55
4	TsOH	DMF	64
5	TfOH	DMF	41
6	Cl_3CCO_2H	DMF	57
7	oxalic acid	DMF	46
8	CSA	DMF	70
9	CBSA	DMF	72
10[c]	**CBSA**	**DMF**	**74 (72**[f]**)**
11[d]	CBSA	DMF	72
12[c]	CBSA	DMSO	71
13[c]	CBSA	NMP	68
14[c]	CBSA	toluene	trace
15[c]	CBSA	CH_3CN	trace
16[c]	CBSA	MeOH	trace
17[c]	CBSA	THF	trace
18[e]	CBSA	DMF	16

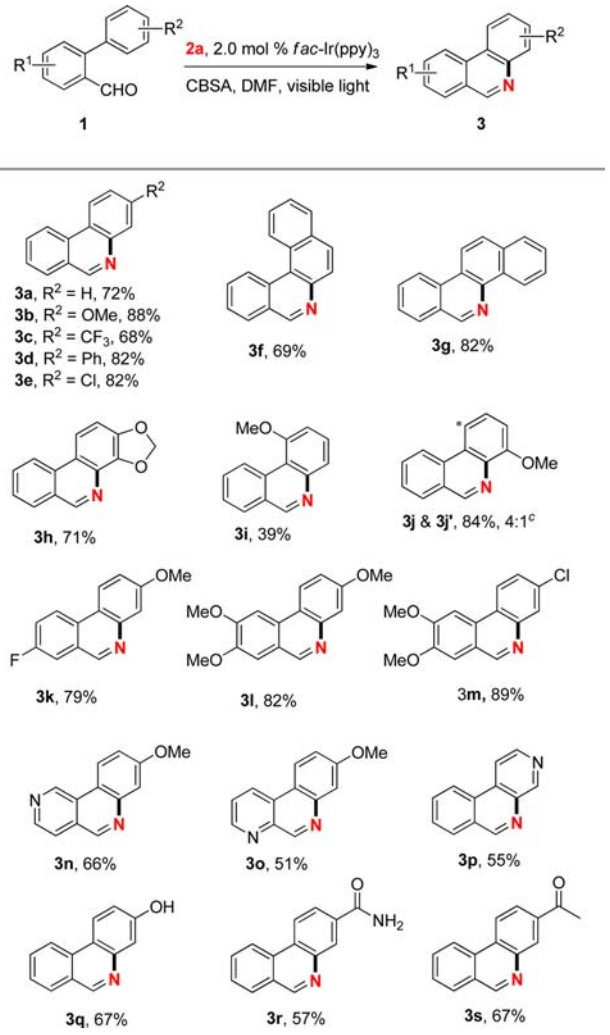
[a]Reaction condition: A solution of **1a** (0.2 mmol), **2a** (0.6 mmol), *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol %) and additive (0.02 mmol) in the indicated solvent (2.0 mL) was irradiated by white LED strips for 10 h. [b]^{1}H NMR yield. [c]1.5 equiv of **2a** (0.3 mmol) was used. [d]1.2 equiv of **2a** (0.24 mmol) was used. [e]**2b** (0.3 mmol) was used instead of **2a**. [f]Isolated yield. CSA = camphorsulfonic acid; CBSA = *p*-Cl-benzenesulfonic acid.

and it turned out to be much less efficient than **2a**. The corresponding *O*-acyl oxime could be generated smoothly, but visible-light-promoted cyclization was sluggish and the desired product was isolated in 16% yield after 10 h (entry 18).

With the optimized conditions in hand, the synthetic potential of this one-pot procedure was then investigated and the results are summarized in Schemes 2 and 3. To find the scope of aldehydes leading to phenanthridines, a variety of biaryl aldehydes were then subjected to the optimized conditions (Scheme 2). Generally, acceptable to good isolated yields (39−89%) were obtained no matter the substituents on the biphenyl moiety (**3a**−**3m**). Aza-arenes with more than one nitrogen atom (**3n**−**3p**) were also prepared by means of this method. Pyridine-derived aldehydes were also tolerated in this reaction, and several interesting aza-arenes **3n**−**3p** were prepared in 51−66% yields. Functional groups such as hydroxyl (**3q**), keto carbonyl (**3r**), amide (**3s**), which could not be tolerated in our previous stepwise procedure, could go through this one-pot transformation. To our disappointment, biaryl ketones were not compatible with these conditions and all ketones we tried were fully recovered (for more unsuccessful examples, see Supporting Information).

We next sought to explore the applicability of this strategy to other important functionalized *N*-containing arenes such as quinoline derivatives (Scheme 3). We found that cinnamaldehyde-type substrates could also go through this one-pot transformation to give quinolines **5a**−**5h** in acceptable yields (45−63%) irradiated by blue LED strips. It is noteworthy that the light source was important to these reactions. The use of

Scheme 2. Scope of Aldehydes Leading to Phenanthridines[a,b]



[a]Reaction conditions: A solution of **1** (0.2 mmol), **2a** (0.3 mmol) *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol %) and CBSA (0.02 mmol) in dry DMF (2.0 mL) was irradiated by white LED strips. [b]Isolated yields. [c]The major product is shown and the asterisk indicates the position of the C−N bond to this ring in the minor isomer.

blue LED strips instead of white LEDs could suppress the formation of side products.

To demonstrate the practicability of this newly established method, a gram scale and two-step synthesis of alkaloid trisphaeridine (**8**),[10] which possessing excellent antitumor effects and antiretroviral activity,[11] was conducted (Scheme 4). Suzuki coupling of commercially available aldehyde **6** with phenyl boronic acid gave biphenyl aldehyde **7** in nearly quantitative yield. Irradiation of **7** (1.81 g) under white LEDs in the presence of *fac*-Ir(ppy)$_3$ and CBSA allowed the preparation of trisphaeridine (**8**, 1.43 g) in 80% yield. The route described here represents the shortest route for trisphaeridine with highest overall yield to date.

In summary, we have described a one-pot synthesis of phenanthridines and quinolines from commercially available or easily prepared aldehydes. *O*-(4-Cyanobenzoyl)hydroxylamine was utilized as the nitrogen source to generate *O*-acyl oximes in situ, which was then subjected to photoredox catalyzed cyclization. Various phenanthridines and quinolines have been

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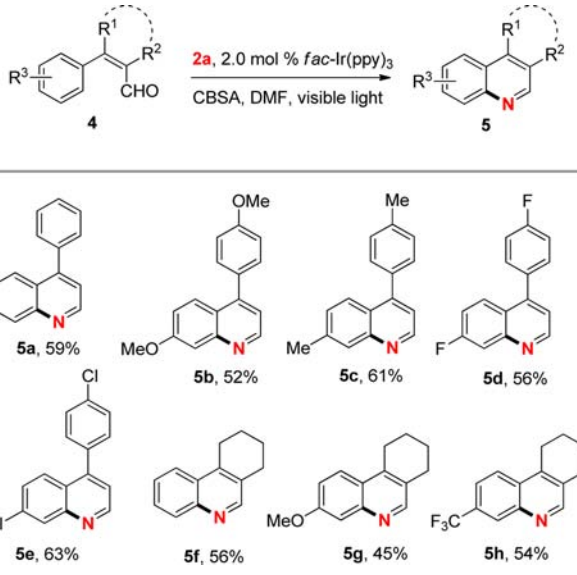
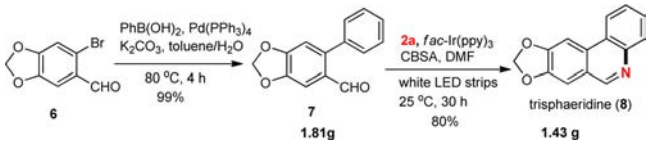
Scheme 3. Scope of Aldehydes Leading to Quinolines[a,b]



[a]Reaction conditions: A solution of **4** (0.2 mmol), **2a** (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol %) and CBSA (0.02 mmol) in dry DMF (2.0 mL) was irradiated by blue LED strips. [b]Isolated yields.

Scheme 4. A Gram Scale and Two-Step Synthesis of Alkaloid Trisphaeridine



achieved assisted by Brønsted acid and photocatalyst under visible light at room temperature with satisfactory yields. These advantages may bring this method a foreseeable application in the synthesis of biologically important *N*-containing heterocycles, as well as natural products. Exploration on other *O*-acyl hydroxylamine-involved important transformation is underway.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data for all compounds are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01096.

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Notes

The authors declare no competing financial interest.

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