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Letter

Visible-Light-Mediated Tandem Sulfonylation/Cyclization of Vinyl Azides with Sulfonyl Hydrazines for the Synthesis of 6-(Sulfonylmethyl)phenanthridines under Mild Conditions

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Liu-Liang Mao^{*a} Li-Xia Quan^b Xian-Hong Zhu^a Cong-Bin Ji^b An-Xi Zhou^{*a} Fayun Chen^b Da-Gui Zheng^a



TBPB = tert-butyl peroxybenzoate

28 examples, up to 84%

^a Key Laboratory of Applied Organic Chemistry, Higher Institutions of Jiangxi Province, Shangrao Normal University, Shangrao 334001, P. R. of China maoll14@lzu.edu.cn zhouanxi@hotmail.com

^b Shangrao Normal University, College of Chemistry and Environment Science, Shangrao 334001, P. R. of China

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Abstract A visible-light-mediated tandem sulfonylation/cyclization of vinyl azides with sulfonyl hydrazines was developed that provides an efficient and simple strategy for the synthesis of valuable 6-(sulfonyl-methyl)phenanthridines with a broad substrate scope and satisfactory yields under mild conditions.

Key words photochemical reaction, tandem reaction, sulfonylation, cyclization, sulfonyl hydrazines, phenanthridines

Phenanthridine and its derivatives represent privileged subunits in materials chemistry and in medical chemistry that have gained extensive attention due to their optoelectronic properties and unique biological activities [Scheme 1(a)].¹ Therefore, a considerable number of strategies have been developed for the construction of functionalized phenanthridines. Since its discovery in the 1980s, the Bischler-Napieralski cyclization has been used extensively to provide access to phenanthridines; however, this approach suffers from poor functional-group tolerance due to the harsh conditions required.² To overcome this limitation, considerable efforts have been made to develop efficient and simple strategies for the synthesis of phenanthridines. Examples include the Morgan–Walls cyclization,³ the aza-Wittig reactions,⁴ Pictet-Hubert condensation,⁵ Pd-catalyzed tandem reactions,⁶ cyclization reactions employing arynes,7 transition-metal-catalyzed annulations of imines,8 radical-mediated cyclizations,9 and microwave-promoted cyclizations.¹⁰ Although these reports constitute significant achievements, further exploration of mild and convenient protocols is still highly desirable because of the extensive uses of functionalized phenanthridines.

Visible-light-mediated organic photochemical synthesis has recently attracted particular attention due to its environmentally friendly and sustainable nature, as well as its mild operating conditions; consequently, great progress has been made in this area.¹¹ In particular, the synthesis of the phenanthridine skeleton through photoredox catalysis has received a large amount of attention.¹² However, the majority of the resulting methodologies exhibit limited substrate scopes, and only a few examples using vinyl azide substrates have been explored.¹³

For instance, the Yu and Liu groups have reported the preparation of functionalized phenanthridines through visible-light-mediated alkylations and trifluoromethylations of vinyl azides [Scheme 1(b)].^{13a,b} Visible-light-promoted syntheses of phenanthridines through tandem sulfonylation and phosphorylation of vinyl azides have also been demonstrated by the Yang and Wu groups, respectively [Scheme 1(b)].^{13c,d} Additionally, our group has successfully used the same strategy to realize a cascade/tandem reaction of vinyl azides for the construction of functionalized phenanthridines by using arylsulfonyl chlorides as the sulfonylating reagent [Scheme 1(b)].^{13e} Here, we report a visible-light-mediated tandem sulfonylation/cyclization of vinyl azides with sulfonyl hydrazines to provide efficient and simple access to 6-(sulfonylmethyl)phenanthridines [Scheme 1(c)].

We first investigated the visible-light-mediated tandem sulfonylation/cyclization of the vinylic azide **1a** with the hydrazine source **2** in MeCN. Because the structure of the hydrazine source is crucial for the production of a N/C/S-

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Scheme 1 Examples of bioactive molecules containing a phenanthridine skeleton (a) and examples of visible-light-mediated radical tandem cyclizations of vinyl azides (b and c)

centered radical,¹⁴ a variety of hydrazine sources were prepared and evaluated under photoredox conditions. When azide **1a** (1.3 equiv) was exposed to 5 W blue LED irradiation in the presence of Ru(bpy)₃Cl₂·6H₂O (2 mol%), *tert*-butyl peroxybenzoate (TBPB; 2.0 equiv), Na₂CO₃ (1.2 equiv), and the sulfonyl hydrazine **2a** (0.2 mmol) as a hydrazine source, the corresponding sulfonylation/cyclization product **3aa** was obtained in 74% yield. Other hydrazine sources such as phenylhydrazine (**2b**), methyl hydrazinecarboxylate (**2c**), and acetohydrazide (**2d**) were also examined, but none of the desired products were detected (Scheme 2).

Following this, vinyl azide 1a and hydrazine 2a were taken forward for further optimization of the reaction conditions. The effects of varying the oxidant, solvent, and base employed in the transformation were examined (see Supporting Information, Tables S2-S4), but in all cases the changes were found to be detrimental to the yield of 3aa. The Ru(bpy)₃Cl₂·6H₂O photocatalyst was found to be essential, as the reaction did not proceed when rhodamine B was used instead (SI; Table S5, entry 1). Reactions conducted with the photocatalyst under an air atmosphere or in the absence of blue LED irradiation also failed to generate 3aa, as did a reaction carried out in the absence of Ru(bpy)₃Cl₂·6H₂O (SI; Table S5, entries 2–4). The best result was therefore obtained by using 2 mol% of

 $Ru(bpy)_3Cl_2\cdot 6H_2O$, 1.20 equivalents of Na_2CO_3 , and 2.0 equivalents of TBPB in MeCN under 5 W blue LED irradiation, which gave **3aa** in 74% yield.

With the optimal reaction conditions in hand, we investigated the reactions of a variety of vinyl azides to define the scope and limitations of our sulfonylation/cyclization reaction (Scheme 3). Vinyl azides containing either electron-donating or electron-withdrawing groups at the C3 position (phenanthridine numbering) reacted smoothly





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Scheme 3 Substrate scope for vinyl azides. *Reaction conditions*: 2a (0.2 mmol), 1 (1.3 equiv), Ru(bpy)₃Cl₂·6H₂O (2 mol%), TBPB (2.0 equiv), Na₂CO₃ (1.2 equiv), MeCN (2.0 mL), r.t., 5 W blue LED, under Ar. Isolated yields are reported.

with **2a** to provide the products **3aa–ae** in moderate to good yields. Pleasingly, sterically hindered C1-substituted biphenyl vinyl azides bearing methyl (**1f**), phenyl (**1g**), or methoxy (**1h**) groups were also suitable substrates for this transformation. Vinyl azide substrates containing two methyl groups (**1i**) or a naphthalene moiety (**1j**) also reacted smoothly with **2a** to give good yields of the corresponding annulated phenanthridines. Methyl substitution at the R¹ position was tolerated in **1k**, and phenanthridine **3ak** was isolated in 80% yield; however, a substrate containing a phenyl group in this position (**1l**) proved intractable. An isocyano group was found to be an unsuitable analogue for the vinyl azide moiety used in this reaction (**1m**) and, likewise, a cyclization onto a heteroaromatic ring (**1m'**) failed to generate a significant amount of the desired product.

Next, a series of sulfonyl hydrazines **2** were explored under the optimized reaction conditions to examine this area of the substrate scope (Scheme 4). To our delight, sulfonyl hydrazines with either electron-rich (**3an** and **3ao**) or electron-deficient (**3aq–at**) groups at the *para*-position of the benzene ring were suitable for the reaction, and the target phenanthridines were obtained in yields of 70–84%. Additionally, the reaction tolerated sulfonyl hydrazines containing a sterically hindered aromatic group (**3ap**), a naphthyl group (**3au**), or a thienyl group (**3av**) to provide the corresponding products in good yields. Aliphatic sulfonyl hydrazines, such as 1-phenylmethanesulfonohydrazide also reacted with vinyl azide **1a** to afford the expected products (**3aw**, **3ax**), albeit in reduced yields.

To test the scalability of this tandem sulfonylation/cyclization reaction, we carried out a gram-scale experiment under the standard conditions (Scheme 5). Remarkably, the product was isolated in 72% yield, which demonstrates the suitability of this reaction for scaling up.

To gain valuable insights into the visible-light-mediated tandem sulfonylation/cyclization reaction, we conducted some mechanistic experiments. When TEMPO was introduced under the standard reaction conditions, the sulfonylation/cyclization of vinyl azide **1a** was suppressed completely [Scheme 5(b)]. Furthermore, the yield of **3aa** decreased to 40% in the presence of 1,1-diphenylethene, and the sulfonyl-radical-trapping product **4aa** was isolated in 5% yield [Scheme 5(c)]. These results indicate that this visible-light-mediated sulfonylation/cyclization reaction probably proceeds via a sulfonyl radical intermediate.

By combining the results of the above experiments with previous reports in the literature,^{13e,15} we proposed a plausible mechanism for the visible-light-mediated tandem sulfonylation/cyclization reaction, which is shown Scheme 6. First, irradiation of the photocatalyst produces the excited Ru(II)* complex, which reduces TBPB to generate a tert-butoxy radical A and a Ru(III) complex. The tert-butoxy radical A then oxidizes the sulfonyl hydrazine **2a** to form sulfonyl radical C after release of N₂. Subsequently, the sulfonyl radical C reacts with the vinyl azide moiety of 1a to produce an iminyl radical intermediate **D** after the loss of another molecule of N₂. Finally, intramolecular radical addition to the aromatic group occurs from intermediate **D**; this affords radical E, which is then oxidized by Ru(III) and deprotonated by the base to generate the final product **3aa**, with closure of the catalytic cycle.

To summarize, we have developed an efficient and simple method for the synthesis of functionalized phenanthridines through visible-light-mediated tandem sulfonylation/annulation of vinyl azides and sulfonyl hydrazines under mild reaction conditions. In this reaction, simple and commercially available sulfonyl hydrazines emerge as efficient sulfonylating reagents for the construction of new C–S bonds with concomitant C–N bond formation. Further research on the reactivity of vinyl azides is underway in our laboratory.

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D

Scheme 4 Substrate scope for sulfonyl hydrazines. *Reaction conditions*: 2 (0.2 mmol), 1a (1.3 equiv), Ru(bpy)₃Cl₂·6H₂O (2 mol%), TBPB (2.0 equiv), Na₂CO₃ (1.2 equiv), MeCN (2.0 mL), r.t., 5 W blue LED, under Ar. Isolated yields are reported.



Scheme 5 Gram-scale reaction and mechanistic experiments



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Supporting Information

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