# Energy transfer-driven regioselective synthesis of functionalized phenanthridines by visible-light Ir photocatalysis

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Energy transfer-driven regioselective synthesis of functionalized phenanthridines by visible-light Ir photocatalysis

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A photocatalytic strategy for regioselective synthesis of phenanthridine derivatives from N-(2-arylbenezidenedamino)pyridinium salts has been developed. Utilization of an Ir photocatalyst, [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 (dF(CF3)ppy = 3,5-difluoro-2-(5-(trifluoromethyl)-2-pyridyl)phenyl, dtbbpy = 4,4’-di-tert-butyl-2,2’-bipyridine), is a key to successful reactions. The excited Ir catalyst does not serve as a 1e-redox reagent but as an energy donor toward the pyridinium salts. The present system can be also applied to one-pot synthesis of Trisphaeridine, an anti-cancer drug.

Introduction

Phenanthridine scaffolds are frequently observed in natural alkaloids and therapeutically active compounds. Thus, a variety of synthetic strategies have been developed so far and new methodologies for selective synthesis are still in demand.1 Recently, radical-mediated protocols from several precursors have been reported as depicted in Scheme 1. Radical addition to biaryl isonitrile (Scheme 1a)3b,4 and vinyl azide (Scheme 1b)5 followed by cyclization is an attractive method for synthesis of phenanthridines, with which selective introduction of various functional groups at the 6-position is viable. In addition, 1e-redox reactions of oxime or imine precursors (Scheme 1c and d),4,5,6d which are easily accessible and less hazardous and toxic than the above-mentioned chemicals, also have become useful methods for construction of nitrogen-containing polyaromatics including phenanthridines. Interestingly, according to the seminal works by the groups of Yu and Xu, the cationic radical of oxime or imine precursors.

Results and discussion

various C1, O1, and N-centered radicals.7 We developed aroyloxlation and amidation with the corresponding N-aryloxoy- and amidyl-pyridinium salts by visible-light photoredox catalysis.8 In this context, we designed N-(2-arylbenezidenedamino)pyridinium salts 1 as the precursors for photocatalytic synthesis of phenanthridines (Scheme 1e). Herein we will describe photocatalytic reaction of 1, leading to regioselective synthesis of functionalized phenanthridines, especially, 2-substituted products. It is notable that the reaction turned out to be initiated by energy transfer from the photoexcited catalyst rather than electron transfer.
We initially examined photocatalysts for the reaction of (E)-N-(2-phenylbenzylidenamino)pyridinium salt (E-1a)\(^{1,2}\) at room temperature under visible-light irradiation with blue LEDs (\(\lambda = 425 \text{ nm}\)). Taking account of the redox potential of 1a (\(E_{\text{irr}} = -1.26 \text{ V vs. } \text{Cp}_2\text{Fe}\)) and photocatalysts with high reducing power (\(E_{\text{irr}} < -1.30 \text{ V vs. } \text{Cp}_2\text{Fe}\)) was estimated by the emission spectra (\(\lambda_{\text{em}}\)). Taking account of the redox potential of \(\text{Ir}^{\text{III}}\) (\(E_{\text{irr}} = -1.26 \text{ V vs. } \text{Cp}_2\text{Fe}\)).

The scope of the present photocatalytic reaction is shown in Table 1. Examination of the reaction conditions (a) Reaction conditions: A mixture of photocatalyst (2.5 mmol, 0.50 mL) dissolved in a deuterated solvent was irradiated by 3 W blue LEDs (\(\lambda = 425 \text{ nm}\)) for 4 h at rt. The reaction was estimated by NMR spectroscopy for the crude reaction mixture. b) Reaction temperature = -80 \(^\circ\)C. c) MeCN was used as a solvent. d) Reaction time = 8 h. e) Reaction temperature = rt, 4 h. f) Reaction temperature = rt, 4 h. g) NMR scale. h) Reaction time = 96 h. i) Isolated yield of the major isomer. j) The isolated yield of the major isomer. k) MeCN was the solvent. l) Reaction temperature = rt, 48 h. m) Isolated yield of the major isomer. n) Isolated yield of the major isomer.

We initially examined photocatalysts for the reaction of (E)-N-(2-phenylbenzylidenamino)pyridinium salt (E-1a)\(^{1,2}\) at room temperature under visible-light irradiation with blue LEDs (\(\lambda = 425 \text{ nm}\)). Taking account of the redox potential of 1a (\(E_{\text{irr}} = -1.26 \text{ V vs. } \text{Cp}_2\text{Fe}\)), Ir photocatalysts with high reducing power (\(E_{\text{irr}} < -1.30 \text{ V vs. } \text{Cp}_2\text{Fe}\)) in the excited state, 1a (\(E_{\text{irr}} = -2.14 \text{ V}\)) and 1b (\(E_{\text{irr}} = -2.14 \text{ V}\)) were tested in CDCl\(_3\). But, to our surprise, the reactions did not proceed at all (entries 1 and 2 in Table 1). In contrast, 1c (\(E_{\text{irr}} = -2.14 \text{ V}\)) and 1d (\(E_{\text{irr}} = -2.14 \text{ V}\)) efficiently gave the desired phenanthridine product 2a in 85 and 78% NMR yields, respectively (entries 3 and 4). A preparative-scale experiment afforded 2a in 76% isolated yield (entry 3). It is noteworthy that monitoring the reaction in the presence of 1c and 1d by NMR spectroscopy revealed formation of an intermediate, which is assigned to Z-1a. Efficient isomerization from E-1a to Z-1a was observed prior to formation of 2a (see the Supporting Information). In addition, photocatalysts with a larger triplet energy (\(E_T = 254 \text{ kJ mol}^{-1}\) (1r-3), 253 kJ mol\(^{-1}\) (1r-4), 232 kJ mol\(^{-1}\) (1r-1), and 209 kJ mol\(^{-1}\) (1r-2) promoted the present reaction smoothly (entries 1–4).

The scope of the present photocatalytic reaction is shown in Table 2. Examination of the reaction conditions (a) Reaction conditions: A mixture of photocatalyst (2.5 mmol, 0.50 mL) dissolved in a deuterated solvent was irradiated by 3 W blue LEDs (\(\lambda = 425 \text{ nm}\)) for 4 h at rt. The reaction was estimated by NMR spectroscopy for the crude reaction mixture. b) Reaction temperature = -80 \(^\circ\)C. c) MeCN was used as a solvent. d) Reaction time = 8 h. e) Reaction temperature = rt, 4 h. f) Reaction temperature = rt, 4 h. g) NMR scale. h) Reaction time = 96 h. i) Isolated yield of the major isomer. j) The isolated yield of the major isomer. k) MeCN was the solvent. l) Reaction temperature = rt, 48 h. m) Isolated yield of the major isomer. n) Isolated yield of the major isomer. o) MeCN was used as a solvent. p) Reaction time = 48 h. q) Reaction temperature = 0 \(^\circ\)C. r) Reaction temperature = rt, 48 h. s) NMR scale. t) Reaction time = 96 h. u) Isolated yield of the major isomer. v) The crude mixture contained a trace amount of an unidentified product.

For the details of the conditions, see the Supporting Information. a) Yield was obtained after purification. Isomer ratios were determined by \(^1\text{H}\) NMR spectroscopy for crude reaction mixtures. b) MeCN was used as a solvent. c) Reaction time = 48 h. d) Reaction temperature = 0 \(^\circ\)C. e) Reaction temperature = rt, 48 h. f) NMR scale. g) Reaction time = 96 h. h) Isolated yield of the major isomer.
A Ru photocatalyst, [Ru(bpy)_3](PF_6)_2, with lower reducing power (E_{ox} = -1.22 V)[a] and triplet energy (E_T = 196 KJ mol^{-1}) did not induce the reaction at all (entry 5). Examination of solvent revealed that dichloromethane was the best (entries 6–8). Irradiation with visible light and the presence of the photocatalyst are vital for efficient reaction (entries 9 and 10).

Next, we explored the reaction scope, especially reactions of precursors bearing one substituent at the meta-position of the aromatic ring A, which would cyclize at the two different positions, thus creating regioisomers (2- (2) or 4-substituted phenanthridines (2').) First, the reaction of the precursor bearing MeO group (1b) at room temperature afforded the phenanthridine resulting from the favorable cyclization at the para-position with respect to the MeO group (93% NMR yield, 2b:2b' = 1.4:1.0). The selectivity was improved by carrying out the reaction at lower temperature. The preparative-scale reaction at ~80 °C afforded the corresponding phenanthridine (2b and 2b') in 63% yield with better regioselectivity (6:1, entry 1 in Table 2). The present reaction system preferentially afforded 2-substituted phenanthridines 2 with good to excellent regioselectivity regardless of the electronic nature of the substituent (entries 1–9 in Table 2). On the other hand, reactivity of 1 was significantly dependent on the substituent. In particular, electron-withdrawing groups required higher temperature than ~80 °C and longer reaction time for production of the phenanthridines, (entries 6–9) and NO_2 derivative (1k) did not yield the product even at room temperature (entry 10). Noticeably, all precursors underwent the E-to-Z isomerization. The acetamido (1c), methyl (1d), Pr (1e), Ph (1f), F (1g), Cl (1h), and CF_3 (1j) substituted derivatives regioselectively gave the corresponding phenanthridines (30–82% yields, 2:1 to a single isomer). (entries 2–9). It should be noted that this selectivity was in contrast to phenanthridines (30–82% yields, 2:1 to a single isomer). (entries 2–9). It should be noted that this selectivity was in contrast to phenanthridines (30–82% yields, 2:1 to a single isomer).

Scheme 3. Control experiments (a) photocatalytic reaction of O-acyl oxime using Ir catalysts (b) computational analysis for Z-1a (only cationic part).

Then, we also applied the present reaction to precursors linked at the meta- and para-position of the aromatic ring A. The 2,3-substituted phenanthridine 2l was obtained in 70% yield as a single regioisomer from the reaction of methylenedioxybenzene derivative 1l (entry 11). To our delight, selective synthesis of benzo-fuzed and heteroatom-doped phenanthridines was also viable. Benzo[c]phenanthridine (2m), benzo[c][1,8]naphthyridine derivatives 2n and thieno[2,3-c]isoquinoline 2o were obtained in 74, 50, and 62% yields, respectively (entries 12–14). These results show that the present photocatalytic system is highly compatible with various functionalities such as ether, amide, halogen, acetal, and heteroaromatic groups.11

To demonstrate utility of the present reaction system, one-pot synthesis of Trisphaeridine (2p) from the corresponding aldehyde was studied (Scheme 2). As a result, 2p was obtained in 67% isolated yield from the corresponding aldehyde without purification at the stage of intermediate 1p.

The triplet energy (E_T) of E-1a was estimated by DFT calculation (UB3LYP/6-311G+(2d,p)/CH_2Cl_2) to be 234 KJ mol^{-1}, which was lower in energy than E_T of the photoexcited catalysts *Ir-3 and *Ir-4, indicating that, taking into account of the irrelevance to the E_{ox} values discussed above, photoisomerization of E-1a was triggered by energy transfer from *Ir rather than electron transfer, as was also supported by the emission quenching experiment (see the Supporting Information). Simple cyclization of the iminyl radical intermediate can be excluded, because the photocatalytic...
Conclusions
We have developed a synthetic method for selectively substituted phenanthridines from N-(2-arylbenzylidenamino)pyridinium salts, in which the pyridinium moiety in the photoexcited Z-1 accepts an electron from the terminal aryl group of the biaryl skeleton to generate the key radical intermediate. The Ir photocatalyst with higher triplet energy plays a vital role in the sensitization of the precursors through energy transfer. Further studies on photocatalytic synthesis of nitrogen-containing polyaromatics are underway in our laboratory.

Conflicts of interest
There are no conflicts to declare.

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Notes and references

2. For selected examples of radical reaction of biaryl isonitriles, see: (a) M. Tobisu, T. I. Furukawa and N. Chatani, Modular synthesis of phenanthridine derivatives by oxidative cyclization of 2-isocyanoaromatics with organoboron reagents, Angew. Chem. Int. Ed., 2012, 51, 11363; (b) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, Synthesis of 6-alkylated phenanthridine derivatives using photoredox neutral somophilic isocyanide insertion, Angew. Chem. Int. Ed., 2013, 52, 13289; (c) D. Leifert, C. D. Daniliuc and A. Studer, 6-Aryllylated phenanthridines via base promoted homolytic aromatic substitution (BHAS), Org. Lett., 2013, 15, 6286; (d) Q. Wang, X. Dong, T. Xiao and L. Zhou, Ph(OAc)2-mediated synthesis of 6-(trifluoromethyl)phenanthridines by oxidative cyclization of 2-isocyanoaromatics with CF3SiMe3 under...
metal-free conditions. 


9. CCDC 1978371, 1978373, and 1978372 contain the supplementary crystallographic data for 1a, 2c’ (4-isomer) and 2d, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

11. When the yields were moderate, the corresponding aldehydes and nitriles were observed as by-products. In addition, the corresponding ketimine-type substrate, which does not afford the nitrile by-product, was obtained in a very low yield according to the method for preparation of an aldime-type substrate.


15. (a) C. G. S. Lima, T. de M. Lima, M. Duarte, I. D. Jurberg and M. W. Paixão, Organic synthesis enabled by light-irradiation of EDA complexes: theoretical background and synthetic