

Photo-Driven Synthesis of C6-Polyfunctionalized Phenanthridines from Three-Component Reactions of Isocyanides, Alkynes, and Sulfinic Acids by Electron Donor–Acceptor Complex

Yang Li,[†] Tao Miao,^{*,†} Pinhua Li,[†] and Lei Wang^{*,†,‡}

[†]Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P.R. China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P.R. China

Supporting Information



ABSTRACT: A novel and efficient photoinduced synthesis of C6-polyfunctionalized phenanthridines from three-component reactions of isocyanides, alkynes and sulfinic acids was developed. The reactions generated the corresponding products with high selectivity through the photochemical activity of the formed electron donor–acceptor (EDA) complex during the reaction via a radical tandem process under mild conditions.

S ince the pivotal work of Melchiorre and co-workers in 2013,¹ the photochemical transformations by electron donor-acceptor (EDA) complexes, which are the transient combination of electron-rich with electron-accepting substrates,² as the alternative photocatalysts for the photoinduction of electron transfer without the need for external photosensitizer have received great attention.³ To date, the reported EDA complexes are mainly focused on using alkyl halide as electron acceptor and enamine, indole or enolate as electron donor. It is desirable to explore the novel EDA complexes for the new photoreactions.

Phenanthridines are widespread in natural products and pharmaceuticals with remarkable biological activities⁴ and draw considerable interest from synthetic chemists. Recently, a cascade radical pathway through a radical addition to 2-isocyanobiphenyls from an imidolyl radical, followed by an intramolecular homolytic aromatic substitution, has been established, providing the rapid assembly of C6-functionalized phenanthridines.⁵ Most recently, valuable approaches to phenanthridines from isocyanides via photoredox catalysis with external photocatalysts have been developed by Yu et al.⁶

Vinyl sulfones, as important biologically active molecules and synthetic intermediates,⁷ and their preparation directly from the reactions of alkenes or alkynes with sodium sulfinates or sulfinic acids have received substantial attention.⁸ Compared with stepwise chemical process, radical cascade reaction, in which a series of consecutive radical steps occur and several chemical bonds are formed, has proven to be a powerful strategy for efficient building molecular architectures in high selectivity and atom economy.⁹ However, the direct introduction of two different functional groups to a carbon–carbon triple bond via a radical cascade reaction is limited. To develop novel methodology for the difunctionalization of alkyne in good selectivity

through a radical cascade procedure is highly valuable and more challenging.

In this paper, we disclose a novel EDA complex generated from arylsulfinic acid and biaryl isocyanide. To our delight, a unique three-component reaction of arylsulfinic acid, alkyne, and biaryl isocyanide can be driven by the photochemical activity of the formed EDA complex to provide C6-(vinyl sulfone) phenanthridines in high selectivity via a radical tandem process. The reactivity and selectivity of the reaction are dependent on the reaction conditions (Scheme 1).

Scheme 1. EDA-Complex Photo-Driven Three-Component Reaction



Initially, a model reaction of *p*-toluenesulfinic acid (1a), 1heptyne (2a), and 2-isocyanobiphenyl (3a) was chosen to optimize the reaction conditions (Table S1). When the model reaction was performed in a mixed solvent (DMSO/H₂O) in the presence of pyridine under air with blue LED irradiation for 16 h, a product of the three-component reaction of 1a, 2a, and

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3a, (E)-6-(1-tosylhept-1-en-2-yl)phenanthridine (4a), was generated in 48% yield (Table S1, entry 1). When the reaction was carried out under O2 atmosphere, 4a was isolated in 71% yield with 10:1 of E/Z ratio (Table S1, entry 2). It is important to note that no product was detected in the absence of light even when the reaction was heated at 60 °C for 16 h (Table S1, entries 3 and 4). Following this, the yield of 4a was decreased to 38% under the irradiation with green LED (Table S1, entry 5). Notably, (Z)-6-(1-tosylhept-1-en-2-yl)phenanthridine (4a'), a Z-isomer of 4a, was obtained in 73% yield under UV irradiation for 24 h (Table S1, entry 6).¹⁰ While the model reaction was irradiated with UV light for 24 h under N₂ atmosphere, no desired product 4a or 4a' was observed (Table S1, entry 7). Further optimization of solvent and base indicated that a mixed-solvent DMSO/H2O in 8:1 (V/V) and pyridine was the best choice among the tested parameters (Table S1, entries 8–19). Furthermore, reducing the amount of 1a or 2a led to decreased yields of 4a (Table S1, entries 20 and 21).

To gain a better understanding of this photoinduced radical process, a series of optical absorption spectra of the solution were recorded. As shown in Figure 1a, the solution developed a



Figure 1. (a) Optical absorption spectra of the reaction components. (b) Job's plot for ratio between 1a and 3a. (c) Reaction of 1a and 3a. (d) Reaction of N-methyl-N-phenylmethacrylamide (7) with 1a and 3a. (e) Visible-light-triggered generation of S-centered radical A' and the imidoyl radical C by EDA complex.

yellowish color change from colorless when 1a was mixed with 3a and pyridine in DMSO/ H_2O (8:1), and its optical absorption spectra showed a bathochromic displacement in the visible region, which is diagnostic of an EDA complex.^{1,3} Then a Job's plot using UV/vis absorption experiments was drawn to evaluate the stoichiometry of the EDA complex I between 1a and 3a. The maximal absorption at 50% molar fraction of 3a suggested a 1:1 ratio of 1a and 3a (Figure 1b). The dissociation constant K_{EDA} between 1a and 3a was found to be 5.29 M^{-1} in DMSO/H₂O (8:1) via the Benesi-Hildebrand method.¹¹ To further understand the structure of the EDA complex, a reaction of 1a and 3a was stirred in a mixture of $DMSO/H_2O$ (8:1) without 2a under blue LED irradiation for 8 h, providing 5 and 6. The deuterium experiments indicated H₂O and acid are the sources of proton, and methylation is not coming from methyl radicals produced by DMSO (Figure 1c). Therefore, 5 and 6 probably originated from H_2O , H^+ , and radical intermediate C', which was generated from intermediate B' via an abstraction of H^+ (see

Figure S7 for details). Furthermore, sulfonylated oxindole 8 was obtained in 55% yield when *N*-methyl-*N*-phenylmethacrylamide 7 was added to the reaction of 1a and 3a with 3 W blue LED irradiation for 16 h, indicating that sulfonyl radical intermediate A' was involved in the reaction (Figure 1d). These observations demonstrate that the formation of EDA complex I and the dissociation of radical ion pair II to produce sulfonyl radical intermediate A' and radical intermediate C are the key drivers in this photochemical process (Figure 1e).

With the optimal reaction conditions established, we then examined the substrate scope of this radical tandem reaction. In general, this tandem reaction exhibited high regio- and stereoselectivity, and E- or Z-products were isolated in good yields under blue LED or UV irradiation. As described in Scheme 2, a variety of arylsulfinic acids with electron-donating



^{*a*}Reaction conditions: 1 (0.75 mmol), 2a (0.50 mmol), 3a (0.25 mmol), pyridine (6.0 equiv), DMSO/H₂O (8:1, 4.5 mL) in O₂ at room temperature under 3 W blue LED (450 \pm 5 nm) irradiation for 16 h (method A) or 3 W UV (365 \pm 5 nm) irradiation for 24 h (method B). ^{*b*}Isolated yield based on 3a. ^{*c*}E/Z ratio determined by isolated yield of 4 or ¹H NMR analysis of the crude products 4a and 4a'. ^{*d*}In 5.0 mmol scale.

groups or electron-withdrawing groups on the aryl rings reacted efficiently with 2a and 3a to give the corresponding products 4a-k and 4a'-k' in good yields. The structures of products (Z)-4a' and (E)-4d were further characterized by X-ray crystallographic analysis. *o*-Chlorophenylsulfinic acid gave the products 4i and 4i' in 51% and 56% yield, respectively. Furthermore, 2-naphthyl and 2-thienylsulfinic acid were also

successful in this transformation with 53-61% yields of the corresponding products. Importantly, *n*-butylsulfinic acid, an aliphatic sulfinic acid, was also a suitable substrate for the reaction, providing the corresponding products **4n** and **4n'** in 70 and 66\% yields. When the reaction of **1a**, **2a**, and **3a** was performed on a 5.0 mmol scale with irradiation of 3 W UV for 24 h, the product **4a'** was obtained in 69% yield.

We then turned our attention to exploring the scope of the alkynes (2) and isocyanides (3), as shown in Scheme 3. First,



^aReaction conditions: **1a** (0.75 mmol), **2** (0.50 mmol), **3** (0.25 mmol), pyridine (6.0 equiv), DMSO/H₂O (8:1, 4.5 mL) in O₂ at room temperature under 3 W blue LED (450 \pm 5 nm) irradiation for 16 h (Method A) or 3 W UV (365 \pm 5 nm) irradiation for 24 h (Method B). ^bIsolated yield based on **3**. ^cE/Z ratio determined by isolated yield of **4** or ¹H NMR analysis of the isolated crude products **4**.

other aliphatic alkynes including *n*-propyl, *n*-butyl, *n*-hexyl, and *n*-heptylacetylene worked well with **1a** and **3a**, providing the desired products **4o**-**r** and **4o'**-**r'** in 65–72% yields. In particular, cyclopropropylacetylene was also effective in the reactions, leading to the products **4s** and **4s'** in 51% and 53% yields. Subsequently, the substitution effect on the aromatic rings of isocyanides **3** was examined. The results indicated that the reactions were not sensitive to the nature of the substituent groups, as evidenced by the yields of **4t**-**ab** and **4t'**-**ab'**. 2-Isocyanobiphenyls containing Me, Cl, CF₃, and CO₂Me at the *para*-position of the nonisocyanide phenyl rings reacted with **1a** and **2a**, affording the corresponding phenanthridine derivatives

(4w-z and 4w'-z') in 52–71% yields. 2,4-Dichloro-2'isocyano-1,1'-biphenyl also gave good results (4aa and 4aa'). For isocyanide with a *m*-methyl on the phenyl ring, the reaction preferentially took place at the more crowded position, and 4ab was isolated in 52% yield with 2.6:1 selectivity. Meanwhile, a more hindered isomer 4ab-1' was the exclusive product in 47% yield with irradiation of 3 W UV for 24 h.

On the other hand, this transformation was applicable to various aromatic alkynes, giving (*Z*)-C6-(vinyl sulfone) phenanthridines only in good yields under N_2 atmosphere with UV irradiation for 24 h, and the results are listed in Scheme 4. A variety of arylacetylenes with different functional





^{*a*}Reaction conditions: **1** (0.75 mmol), **2** (0.25 mmol), **3a** (0.50 mmol), pyridine (6.0 equiv), DMSO (4.0 mL), and H₂O (15 equiv) in N₂ with 3 W UV (365 \pm 5 nm) for 24 h. ^{*b*}Isolated yield based on **2**. ^{*c*}3 W blue LED (450 \pm 5 nm) for 24 h.

groups (alkyl, methoxyl, and halogen) on the phenyl rings underwent the reactions smoothly to give the corresponding products (4ac'-al') in 51–73% yields. As expected, arylsulfinic acids containing alkyl and halogen substituents on the benzene rings are amenable to the current protocol, generating the products (4am'-ar') in good yields. When phenylacetylene reacted with 1a and 3a with irradiation of 3W blue LED, the reaction also proceeded smoothly to give the desired product 4am' in 53% yield. It is important to note that the high stereoselectivity for a sole isomer 4am' was obtained with irradiation of 3 W UV (365 ± 5 nm) or 3 W blue LED (450 ± 5 nm). The structure of 4am' was unambiguously confirmed by X-ray crystallography. Furthermore, β -keto sulfone was obtained as a byproduct when 2a was reacted with 1a and 3a under O₂ atmosphere with UV irradiation.^{9d}

To gain mechanistic insights, a radical-trapping experiment was conducted. The reaction was completely inhibited by the radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). More importantly, the vinyl radical formed in situ was trapped by TEMPO to form radical adduct **10** (determined by HPLC–HRMS analysis), supporting the proposed radical pathway of the reaction (Scheme 5a). In addition, optical absorption of the product **4a** was also examined in DMSO/ H_2O (8:1) (Figure S9). The UV–vis spectrum exhibits a strong absorption band in the ultraviolet range below 365 nm. Under UV light irradiation at 365 nm for 24 h, **4a** was converted into its (Z)-isomer (**4a**') in 93% yield (Scheme 5b).

On the basis of the results of our studies and previous related reports, $^{1-3}$ a plausible mechanism is proposed (Scheme 6).

Scheme 5. Control Experiments



Scheme 6. Proposed Mechanism for the Formation of 4



With the assistance of pyridine and H₂O, an arylsulfinate anion can form an EDA complex (I) with isocyanide 3a. The formed EDA complex I undergoes a SET process upon light excitation to generate dipolar species II. Subsequent fragmentation of II produces an oxygen-centered radical A and a radical anion B. The generated A can resonate with sulfonyl radical A', which reacts with the carbon-carbon triple bond of terminal alkyne 2 to afford a vinyl radical D, which is trapped by TEMPO. Thereafter, an addition of D to the terminal carbon of 3a generates the imidoyl radical E, which undergoes an intramolecular homolytic aromatic substitution to give a radical F. Then F is oxidized by O_2 to form cationic intermediate G and O2^{•-}. Ultimately, a base-assisted deprotonation yields final product phenanthridine 4. On the other hand, the generated \mathbf{B}' from B through a resonance can abstract a hydrogen cation to form an imidoyl radical C, which can store a hydrogen radical. Under an O_2 atmosphere, radical C can be captured by $O_2^{\bullet-}$ to produce 3a and HO_2^{-} .

A divergent strategy for the highly regio- and stereoselective synthesis of (E)- and (Z)-C6-(vinyl sulfone)phenanthridines was developed by a light-controlled three-component reaction of biaryl isocyanides, alkynes, and arylsulfinic acids via a radical tandem process under O₂ atmosphere. The reaction was driven by the photochemical activity of the novel electron donor– acceptor (EDA) complex generated from the reaction of arylsulfinic acid and biaryl isocyanide in the presence of pyridine and water. This approach is operationally simple, uses mild conditions, has a broad substrate scope, and provides good yields of the desired products. The established new EDA complexes from arylsulfinate anions as electron donors and isocyanides as electron acceptors will open new avenues for their applications in photochemical transformations. Further effort on the reaction mechanism is underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00171.

Full experimental details and characterization data for all products (PDF)

Accession Codes

CCDC 1564340–1564342 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: taomiaochem@163.com.

*E-mail: leiwang88@hotmail.com.

ORCID [®]

Lei Wang: 0000-0001-6580-7671

Notes

The authors declare no competing financial interest.

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