

Radical Cascade Multicomponent Minisci Reactions with Diazo Compounds

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rapid assembly with various heteroarenes. A delicate balance has been achieved between the activation of heteroarenes through protonation and the decomposition of diazo compounds by the same acid. This multicomponent Minisci reaction shows high functional group tolerance, especially in the incorporation of biologically active molecules. Detailed mechanistic studies that include photophysical measurements elaborate this radical cascade reaction. Furthermore, this transformation provides new opportunities for versatile reactions of diazo compounds in radical cascade multicomponent coupling reactions.

KEYWORDS: diazo compounds, alkenes, radical cascade, Minisci reaction, multicomponent reaction, photocatalysis

INTRODUCTION

Diazo compounds are versatile building blocks that have been used extensively in organic synthesis.^{1,2} Their multicomponent reactions (MCRs),³ which incorporate two or more functional groups into one molecule with the release of dinitrogen, have shown features of high synthetic efficiency, atom economy, and convergence that provide an economical and useful tool for the construction of complex target compounds.⁴ Previous endeavors toward MCRs of diazo compounds focused on trapping protic onium ylides with various electrophiles followed by delayed proton transfer (Scheme 1a(i))^{4a} and on the combination of traditional cross-coupling with carbene migratory insertion (Scheme 1a(ii)).^{4b} Both of them enrich the diazo chemistry through carbene intermediates and have found remarkably wide applications in building complicated organic molecules.

with alkenes provide nucleophilic radicals, which enable the further

Radical chemistry has made great progress during the past decade, and many new radical processes have been developed with photoredox catalysis.⁵ Unlike the carbene process, the radical chemistry of diazo compounds makes MCRs possible through radical propagation. Though formation of carbon-centered radicals from diazo compounds with the release of N₂ has been reported, their subsequent reactions with alkenes are rare.⁶ Gryko,^{6a} Zhang,^{6b} Li,^{6c} and their co-workers reported the generation of radical species from diazo compounds either through a cobalt(III)-carbene radical intermediate or homolytic bond cleavage of a C–I bond. Their further reaction with alkenes delivered C_{sp2} –H alkylation products or traditional

cyclopropanation products (Scheme 1b). Recently, we reported the functionalization of alkenes with diazo compounds by radical pathways,⁷ through which photocatalytic hydroalkylation products by thio-assisted hydrogen atom transfer (HAT) and azidoalkylation products through an iron catalytic cycle were selectively formed (Scheme 1b). Since the carbon radical generated from a diazo compound stabilized by one or two electron-withdrawing groups (EWG) is electrophilic,⁸ its addition to a carbon–carbon double bond produces an alkyl radical that is nucleophilic.⁹ We envisioned that a radical cascade reaction utilizing this radical polarity reversal could be designed to achieve a new MCR pathway with diazo compounds.

Heteroarene groups exist widely in natural products, pharmaceuticals, and agrochemicals.¹⁰ The Minisci reaction,¹¹ in which nucleophilic radicals undergo addition to heteroarenes, provides an efficient and direct method for the functionalization of heteroarenes. The three-component Minisci reaction was first disclosed in 1978, in which alkenes were oxidized by $Ag^+/S_2O_8^{2-}$ in the presence of H_2O , and the resulting radical was added to lepidine (4-methylquinoline).¹²

Received:December 7, 2021Revised:December 23, 2021Published:January 7, 2022





Scheme 1. Designs for the Radical Cascade Multicomponent Minisci Reaction with Diazo Compounds



While radical species such as H^{\bullet} , N_3^{\bullet} , phosphinyl radical, and alkyl radicals from aliphatic halides have been utilized,¹³ the use of easily accessible diazo compounds to afford a desirable spectrum of functionalization in multicomponent Minisci reaction has not been reported.

With our continuing research interest in the radical chemistry of diazo compounds,^{7,14} we have designed a photocatalytic redox-neutral multicomponent Minisci reaction of diazo compounds (Scheme 1b, below). The diazo compounds are transformed to electrophilic carbon radical species through proton-coupled electron transfer (PCET).¹⁵ Then, selective addition of the carbon radical to diverse unactivated C=C bonds reverses the radical polarity to nucleophilic, which enables their further trapping by heteroarenes. However, several challenges had to be overcome, including (1) the undesirable direct decomposition of diazo compounds by acid (proton-denitrogenation), which is of concern because of the necessary use of acid for the activation of heteroarenes; (2) the competitive two-component reaction between diazo compounds and alkenes that forms cyclopropane derivatives; and (3) different from our previous photocatalytic hydroalkylation process,⁷ the photocatalyst here plays two roles: first as a reductant to transform the diazo compound into radical species and, then, as an oxidant of the heteroarene radical intermediate formed in the Minisci reaction, providing the final functionalized heteroarene after deprotonation. Thus, a photocatalyst with a suitable reduction potential to initiate the reaction as well as an oxidation potential for its oxidized state that can complete the cascade transformation is critical for this reaction.

RESULTS AND DISCUSSION

Reaction Optimization. The three-component adduct **4a** was effectively obtained from the reaction of lepidine (**1a**),

ethyl diazoacetate (EDA, 2a), and 4-phenyl-1-butene (3a) in 1,2-dichloroethane (DCE) at room temperature under blue LED with $[Ir(dtbbpy)(ppy)_2]PF_6$ as a photocatalyst and with 2.0 equiv of TFA to activate lepidine and protonate the diazo compound (Table 1, entry 1). A series of control experiments verified the necessity of each reactant. Thus, the multicomponent adduct 4a was not formed in the absence of the photocatalyst or a blue LED (Table 1, entries 2 and 4), and only a low yield of 4a was observed when TFA was omitted from the reaction system (Table 1, entry 3). Weaker acids than TFA were ineffective. The catalytic systems we used in our previous hydroalkylation and azidoalkylation reactions were also tested,⁷ but either no product or only a trace amount of 4awas formed (Table 1, entries 5-7). This indicates that even though the carbon radical could be formed from the diazo substrate under these conditions, the second catalytic cycle, in which the intermediate derived from addition of the nucleophilic radical to the protonated heteroarene was oxidized to a radical cation, failed with these catalysts. Other photocatalysts were also investigated, but only the iridium catalyst gave this product in a moderate yield (Table 1, entries 8–12). Changing the light source confirmed that the blue LED is the best irradiation source (Table 1, entries 13-15). It should be mentioned that in addition to the desired 4a, byproducts 5 and 6 were also observed under several of these reaction conditions. These cyclopropanation products were presumably generated from either a carbene intermediate or through a free radical process that occurred with the release of N_2 .^{2i,6c,16}

Substrate Scope. With the optimized conditions in hand, we evaluated the scope of olefins appropriate for this photocatalytic multicomponent coupling reaction and found that a wide variety of unactivated alkenes are transformed into the corresponding products in moderate to good yields





^aReactions were carried out using lepidine **1a** (0.2 mmol, 1.0 equiv), ethyl diazoacetate **2a** (0.8 mmol, 4.0 equiv), 4-phenyl-1-butene **3a** (0.8 mmol, 4.0 equiv), $[Ir(dtbby)(ppy)_2]PF_6$ (2 mol %), and TFA (0.4 mmol, 2.0 equiv) in DCE under a blue LED at 25 °C. ^bDetermined by ¹H NMR analysis using CHBr₃ as an internal standard. ^cIsolated yield in parentheses. ^dOur previous catalytic system; see the Supporting Information for more details. dtbbpy: 4,4'di-*tert*-butyl-2,2'-dipyridyl. ppy: 2-phenylpyridine. bpz: 2,2'-bipyrazine. nd: not detected. HE: Hantzsch ester.

(Scheme 2). The mild reaction conditions allowed for high functional group compatibility and tolerance to a variety of functional groups, such as methoxy, chloride, bromide, ketones, esters, amides, and even a free hydroxyl (4f-4l, 4p-4q). The X-ray structure of product 4j was obtained for full structural characterization. Additionally, substrates derived from pyromucic acid and 2-thenoic acid proceeded smoothly under the reaction conditions to deliver products 4m and 4n. The estrone derivative 4o was also obtained in a good yield, which underscores the synthetic utility of this protocol and its compatibility with complex molecules.

The substrate scope of diazo compounds was next examined (Scheme 3). These multicomponent Minisci reactions with different diazoacetates were accommodated under the mild reaction conditions to furnish the corresponding products in good to high yields (7a-7j). Additionally, other potentially reactive functional groups such as allyl (7e), propargyl (7f), and pentynyl (7g) were well tolerated on the ester group in diazo compounds. This methodology is successful with various naturally occurring alcohols in their derived diazoacetate esters, including dihydroconiferyl alcohol, epiandrosterone, and cholesterol (7h-7i), highlighting the generality and potential utility of this methodology. Furthermore, this reaction was not limited to α -diazo esters. Diazoacetamides (7k, 7l), diazoketones (7m, 7n), acceptor/acceptor disubstituted diazo ester (7o), phosphonate (7p), and fluorinated (7q) diazo alkanes were also reactive under the reaction conditions, providing the products smoothly and in moderate to high yields.

Scheme 2. Substrate Scope of Alkenes^a



^{*a*}Conditions identical to those of entry 1, Table 1. ^{*b*}dr value was determined by HPLC.

Scheme 3. Substrate Scope of Diazo Compounds^a



"Conditions identical to those of entry 1, Table 1. ^bdr value was determined by HPLC. ^cdr value was determined by analogy with 7i.

We further assessed the reaction generality with various heteroarenes (Scheme 4). For quinolines bearing phenyl, isopropyl, cyclohexyl, chloro, and methyl substituents at either the C-2 or C-4 position, the reaction proceeded regioselectively at the alternative ortho or para position (8a-8h), while the unsubstituted quinoline gave mixtures of regioisomers (8i-8i') in comparable yields as well as the 2,4-disubstituted





^aConditions identical to those of entry 1, Table 1. ^bdr value was determined by ¹H NMR. ^{*c*}1-Methylbenzimidazole (66%) was recovered. ^dEthyl 2,4-dimethylnicotinate (50%) was recovered.

product 8i". The scope of the reaction was further extended to a series of isoquinolines including unsubstituted isoquinoline and those with methyl-, ester-, methoxy-, and chlorosubstitution at different positions, and all of these substrates underwent regioselective C-2 addition (8j-8p). Phenanthridine was also found to be a competent substrate, affording product 8q in a high yield, and its X-ray structure provided full characterization. Reaction with hydroquinine was performed and gave the desired product 8r in a good yield, albeit with no diasteroselectivity. More importantly, this methodology was not limited to quinolines, isoquinolines, or phenanthridine. Benzimidazole (8s) and pyridine (8t) also proved to be compatible, corroborating the broad generality of the reaction.

Scheme 5. Mechanistic Experiments

However, heterocycles such as guinazoline and guinoxaline and failed diazo compounds and alkenes show some limitations with this method (see the Supporting Information for details).

Mechanistic Investigations. To obtain insights into the mechanism of this novel multicomponent Minisci reaction, a series of control experiments were carried out (Scheme 5, also see the Supporting Information). The yield of 4a from the model reaction in the presence of TEMPO decreased significantly from 73 to 5%, and the related radical-trapping product 9 was separated and characterized (Scheme 5a). However, the yields of the cyclopropanation byproducts 5 and 6 and their ratio were not influenced, which excluded a radical pathway for their formation.¹⁶ A radical clock experiment using vinylcyclopropane 3r formation produced the multicomponent product 4r with complete cyclopropane ring opening (Scheme 5b), and the *cis/trans* ratio from the cyclopropane ring opening was always 1:1. Additionally, a competition experiment between 1a and $1a-d_1$ was conducted giving a primary kinetic isotope effect (KIE) of 1.0, which is consistent with deprotonation not being the rate-determining step (Scheme $5c\bar{)}.^{13f}$

To identify if, as expected, the protonated diazo compound was the species that quenched the photoexcited iridium catalyst, steady-state Stern-Volmer luminescence-quenching experiments were conducted by the addition of different concentrations of EDA 2a to $[Ir(dtbbpy)(ppy)_2]PF_6$ (Figure 1a). The results showed that the iridium photocatalyst was quenched and a linear correlation was found, as presented in the Stern–Volmer plot (Figure 1b). The quenching experiment with the combination of EDA and TFA also showed a quenching effect but decayed with the progression of time (Figure S4). This was due to the decomposition of EDA by TFA. Further investigation with other substrates including lepidine 1a, alkene 3a, and TFA showed that they were not the effective quencher for the Ir photocatalyst (Figure 1b). In addition, a lifetime measurement of the excited Ir* catalyst using time-resolved emission spectroscopy was also performed (Figure 1a, inset). A long-lived phosphorescence from Ir* was observed (τ° = 807 ns, also see the Supporting Information for more details), which decreased monotonically with the increase in the EDA 2a concentration. Moreover, the slopes of the steady-state and time-resolved Stern-Volmer plots are





Figure 1. Quenching experiments of $[Ir(dtbpy)(ppy)_2]PF_6$. (a) Steady-state Stern–Volmer quenching experiments of ([Ir] + EDA). Inset: phosphorescence lifetimes of ([Ir] + EDA). (b) Combined Stern–Volmer analysis of steady-state and time-resolved experiments.



Figure 2. Proposed reaction mechanism.

close, indicating that the major quenching process is the dynamic quenching of the excited-state Ir photocatalyst by the EDA substrate (Figure 1b).¹⁸ The Stern–Volmer constant from the steady-state quenching is ~26 M⁻¹, which affords a bimolecular quenching rate of $k_{\rm q} \sim 3.2 \times 10^{-1}$ M⁻¹ s⁻¹.

Considering the combined results of our mechanistic studies and previous reports,^{7,19} a plausible mechanism for this novel multicomponent reaction is illustrated in Figure 2. Upon irradiation with blue light, the Ir(III) complex is converted into the photoexcited species $Ir(III)^* (E_{1/2}^{IV/III*} = -0.96 \text{ V vs}$ SCE).²⁰ Reduction of ethyl diazoacetate (EDA) by the Ir(III)* complex through proton-coupled electron transfer,¹⁵ or a stepwise pathway in which reduction of the diazonium ion that is generated by protonation of EDA with TFA (but not with HOAc), is feasible due to N_2 extrusion; the reduction peak potential of EDA is slightly more negative (-1.145 V vs)SCE).^{19b} The rate of endothermic photoinduced electron transfer could be accelerated due to the ultrafast dissociation of the reduced diazonium ion.²¹ The formed electrophilic carboncentered radical I⁸ undergoes selective addition to an unactivated alkene, instead of the electron-deficient protonated heteroarene, to furnish nucleophilic radical II. Furthermore, the Minisci reaction between radical II and electrophilic heteroarene III smoothly delivers radical cation IV, which is converted to V by deprotonation. According to the KIE experiment, this step is not the rate-determining step. Subsequently, oxidation of V by the Ir(IV) $(E_{1/2}^{IV/III} = +1.21 \text{ V})$

vs SCE) complex gives rise to the corresponding cation that is deprotonated to afford the product, and the photosensitizer Ir(III) catalyst is regenerated at the same time.

CONCLUSIONS

Different from the traditional carbene process, we have developed a radical-mediated methodology for the multicomponent reaction (MCR) of diazo compounds that should be applicable to other electrophilic radical generators. Utilizing polarity reversal enabled in the reaction between the electrophilic radical derived from diazo compounds and nonactivated alkenes, three-component Minisci reactions of heteroarenes, alkenes, and diazo compounds have been achieved. The high functional group tolerance and the broad substrate scope, especially the incorporation of biologically active molecules, embody the generality and synthetic utility of this protocol. We anticipate that the chemistry reported herein will broaden applications of diazo compounds, especially in the discovery and development of new multicomponent reactions (MCRs) for the construction of valuable complex targets.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c05611.

Experimental procedure and spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for 4j (CIF)

X-ray crystallographic data for 8q (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

M.P.D., Y.-L.S., L.D.A., and A.A.-S. acknowledge the Welch Foundation (AX-1871) for funding this research. G.-X.L., W.-H.H., and H.Q. acknowledge the Guangdong Innovative and Entrepreneurial Research Team Program (No. 2016ZT06Y337), the National Natural Science Foundation of China (21801255 and 22171294), and the Natural Science Foundation of Guangdong Province (2114050000685) for funding this research. The X-ray diffractometer used in this research was supported by a grant from the U.S. National Science Foundation (CHE-1920057). K.S.S. and R.H. acknowledge the Welch Foundation for support through the Welch Chair (AX-0045-20110629).

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