

Letter

Photochemical Doyle-Kirmse Reaction: A Route to Allenes

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Supporting Information

ABSTRACT: This Letter describes the metal-free, blue-lightinduced [2,3]-sigmatropic rearrangement of sulfonium ylides generated from donor/acceptor diazoalkanes and propargyl sulfides. The reaction furnishes highly functionalized allenes from a broad range of starting materials in decent yield. Mechanistic experiments supported by the literature data suggest singlet carbenes as intermediates in this reaction.

he unique reactivity of the 1,2-diene moiety and its presence in a number of natural products have attracted considerable attention over the last several decades.^{1–3} Allenes undergo a wide variety of reactions including cycloisomerization,^{4,5} cycloaddition,⁶⁻⁸ and cross-coupling⁹⁻¹¹ reactions furnishing a valuable collection of small and complex molecules with impressive regio- and diastereoselectivities.^{12,13} As a result, this functionality has often been installed in biologically active molecules, such as steroids¹⁴ or nucleosides,¹⁵ to tune their pharmacological properties.

The appealing chemistry of allenes results in a variety of synthetic methods for their preparation, starting from classical procedures¹⁶ to more recent reports on enantioselective methods promoted by metal catalysts (e.g., copper,¹⁷ palladium,¹⁸ or gold¹⁹). Prominent among these are rearrangement reactions involving sulfonium or oxonium propargyl ylides. Typically, these reactive intermediates are generated from propargyl sulfides or alcohols and extremely electrophilic metal carbenes derived from diazocarbonyl compounds.²⁰⁻²⁴

Unlike carbene chemistry induced by metal catalysts,^{25,26} photolytic reactions are less explored, with only a few examples being promoted by visible light.²⁷ Our group developed photocatalytic procedures for the functionalization of aldehydes,²⁸ ketones,²⁹ and indoles,³⁰ evidencing that in the presence of blue light, α -diazo esters can act as efficient alkylating reagents. On the contrary, the decomposition of aryl diazoacetates to free carbenes under blue-light irradiation proved to be feasible because these compounds absorb light in the wavelength region of 400-500 nm.^{31,32} As a consequence, the reactivity of donor/acceptor diazo compounds under bluelight irradiation has been extensively studied. Indeed, visiblelight-induced cyclopropanation,³³ cyclopropenation,³⁴ benzan-nulation,³⁵ and cross-coupling³⁶ as well as C-H,³² O-H,³² and $N-H^{32,37}$ insertion reactions have been recently reported.

Photochemically generated carbenes react with propargyl tertiary alcohols,³⁸ giving cyclopropenes in contrast with metalcatalyzed [2,3]-sigmatropic rearrangement involving ylide intermediates (Scheme 1A).24







Such ylides, in general, can undergo either [1,2]- or [2,3]sigmatropic rearrangements, but for allyl sulfides, the Doyle–Kirmse reaction predominates (Scheme 1B).^{39,40,34}

In this line, we questioned whether in the presence of blue light propargyl sulfides would follow a pattern of propargyl alcohols and undergo a photochemical cyclopropenation reaction or rather furnish [2,3]-sigmatropic rearrangement products, as reported by Kirmse⁴¹ and Doyle⁴² in metalcatalyzed reactions.

Herein we report that under blue-light irradiation the Doyle-Kirmse reaction of propargyl sulfides with donor/ acceptor diazoalkanes leads to allenes, valuable building blocks toward complex molecules (Scheme 1C).

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^{*a*}Reaction conditions: 1 (0.15 mmol), 2 (9 equiv), DCM (0.5 mL), single blue LED, 24 h, rt. ^{*b*}Isolated yields. ^{*c*}Methylene blue (1 mol %) was added. ^{*d*}Eosin Y (1 mol %) was added. ^{*e*}Reaction time: 8 h. ^{*f*}Benzophenone (20 mol %) was added. ^{*g*}Reaction was started with 1 (0.075 mmol) in DCM (0.25 mL); a second portion of 1 (0.075 mmol) in DCM (0.25 mL) was added after 3 h.

Taking into consideration the optical properties of donor/ acceptor diazo compounds (see the SI), specifically, the local absorbance maximum for the lowest energy absorption, we selected methyl (4-cyano)phenyl diazoacetate (1) as a model diazoalkane and reacted it with phenyl propargyl sulfide (2) under blue-light irradiation (Table 1). To our delight, the reaction furnished allene 3 in 76% yield (entry 1). Control experiments demonstrated the crucial role of light (entry 2) and revealed that the addition of a photosensitizer to the reaction performed under blue light did not significantly affect the reaction yield (entry 3). Consequently, because some diazo compounds absorb in the wavelength around 500 nm, the model reaction was irradiated with green light. The desired product 3 formed, however, in diminished yield. Keeping in mind that suitable sensitizers induce the generation of carbenes, we examined whether the addition of eosin Y, an organic photocatalyst, improved the reaction outcome. The yield indeed increased up to 65% (entry 5). On the contrary, reactions with and without the addition of benzophenone (a photosensitizer) under high-energy UV light were less efficient and led to the decomposition of starting materials just after 8 h (entries 6 and 7). Presumably, in these cases, the photoexcitation of not only diazo ester 1 but also propargyl sulfide 2 contributed to the loss of reaction selectivity. Dichloromethane (DCM) ensured the formation of product in the highest yield. Notably, there was no need to use dry, degassed solvents. (For details, see the SI.) The yield further improved when diazo compound 1 was added portionwise to the solution of 9 equiv of sulfide 2 in DCM (second portion after 3 h, entry 8).

With the optimal conditions in hand, we investigated the scope of aryl diazoacetates (Scheme 2) and propargyl sulfides (Scheme 3). The visible-light-induced Doyle–Kirmse reaction works well for a broad range of aryl diazo compounds regardless of the position and electronic effects of a substituent in the phenyl ring. In the case of electron-donating substituents (allenes 15-17), as compared with those with electron-withdrawing groups (products 3-6), yields slightly decrease as a result of the lower electrophilicity of carbenes generated from diazo reagents. Halogen substituents on the phenyl ring within the diazo compound structure (7-11) are also well tolerated,

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Scheme 2. Scope of Reaction: Aryl Diazocarbonyl

^{*a*}Reaction conditions: diazoalkane (0.15 mmol, added in two portions), phenyl propargyl sulfide (2, 9 equiv), DCM (0.5 mL), single blue LED, 24 h. ^{*b*}Reaction performed on a 1 mmol scale.

with the 4-fluoro derivative giving the best result (9, 88%). Furthermore, the substitution position does not strongly affect the reaction yield; for two- and three-substituted products 10 and 11, yields decrease to some extent, as compared with four-substituted diazoalkane derivative 9.

The reaction is also efficient for diazoacetates bearing unsubstituted aryl and naphthyl aromatic rings, affording products 12-14 in good yield. Even allene 18 bearing a heteroaromatic moiety can be synthesized in satisfactory yield, in contrast with allene bearing the pyridine unit.

Various esters of aryl diazoacetate including (–)-menthyl are well tolerated with benzyl diazoester ($\lambda_{max} = 430$ nm) giving allene **20** in the highest yield. Additionally, the reaction is easily scalable, and the synthesis of compound **4** on a 1 mmol scale gives product **4** in even slightly better yield (**4**, 84% compared with 78% on the 0.15 mmol scale).





"Reaction conditions: diazoalkane 1 (0.15 mmol, added in two portions), propargylic sulfide (9 equiv), DCM (0.5 mL), single blue LED, 24 h.

It is noteworthy that under developed conditions, aryl diazoketone also absorbing blue light gives allene **22** in 43% yield (Figure 1). In contrast, methyl 2-diazo-3-phenyl-propionate ($\lambda_{max} = 410$ nm, Figure 1) is not reactive under developed conditions, suggesting that the absorption of light in the blue region is not the only prerequisite for an efficient reaction.

As far as propargyl sulfides are concerned, the reaction tolerates not only derivatives with substituted phenyl rings



Figure 1. Absorption spectra of various diazoalkanes (6 μ mol·mL⁻¹ in DCM) and phenyl propargyl sulfide **2** (3.6 μ mol·mL⁻¹ in DCM). For UV–vis spectra of other aryl diazocarbonyl compounds, see the SI.

giving allenes 23-25 in good yield but also nitrogencontaining heteroaromatics, for example, pyridine, tetrazole, quinolone (26-29), and aliphatic sulfides, for which products form (30-32) in only slightly diminished yield (Scheme 3). A valuable example is allene 33 bearing the cysteine moiety, which was obtained in 58% yield with, as expected, no diastereoselectivity. The effect of substitution on the propargyl moiety was also examined, and due to steric hindrance, allenes 34 and 35 were obtained but in moderate yield.

On the basis of recent reports on the reactivity of aryl diazoacetates under blue-light irradiation,³² we assume that the photoexcitation of an aryl diazocarbonyl compound is also the initial step in their reaction with propargyl sulfides (Scheme 4).





Under light irradiation, nitrogen extrusion occurs, leading to a singlet carbene that can either undergo intersystem crossing to the triplet state or, as such, react with a propargyl sulfide, generating a sulfonium ylide. The subsequent [2,3]-sigmatropic rearrangement furnishes the desired allene. Exploring the mechanistic aspects of the reaction, we questioned the nature of carbene species involved in the visible-light-induced Doyle-Kirmse reaction. Our recent studies on the porphyrinphotocatalyzed α -alkylation of ketones with α -diazo esters suggest the generation of triplet carbenes detected as an adduct with TEMPO.²⁸ Concurrently, the reported reaction is not halted by the addition of TEMPO, and no adducts with carbenes can be observed. (See the SI.) Taking into consideration the fact that direct photolysis of diazo compounds leads to the generation of singlet carbenes, whereas photosensitization furnishes triplet carbenes, 43,44 we performed the reaction with and without the addition of a triplet sensitizer, tetraphenyl porphyrin (TPP, Scheme 5A). When TPP was added, a decrease in the yield was indeed observed compared with the porphyrin-free reaction. More-





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over, blue-light irradiation of aryl diazoacetate with *cis*-stilbene led to the diastereoselective cyclopropanation reaction (Scheme 5B).

This outcome is typical for singlet carbene species, as cyclopropanations engaging triplet carbenes are believed to be two-step processes with a loss of stereospecifity.⁴⁵ Consequently, the predominant generation of singlet carbenes in the reaction course is assumed.

In summary, we have shown that the Doyle-Kirmse reaction of propargyl sulfides with diazo compounds can be induced by visible light and does not require any catalyst. Our method enables the synthesis of a broad range of highly functionalized allenes in good to excellent yield under mild reaction conditions.

Mechanistic considerations support the involvement of singlet carbenes that react with propargyl sulfides, forming ylides. The subsequent [2,3]-sigmatropic rearrangement leads to allenes. Our investigations contribute to broadening the knowledge of visible-light-induced processes employing diazo compounds, as only comprehensive studies will fulfill this research area.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04560.

Full description of optimization and mechanistic studies, general procedure for [2,3]-sigmatropic rearrangement to allenes, UV-vis spectra of aryl diazocarbonyl compounds, compound characterization (NMR, HRMS, AE), and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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