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Photochemical multicomponent transformation of acceptor-only diazoalkanes by merging their cycloaddition and carbene reactivities

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ABSTRACT

Herein, we report an efficient photochemical method for the synthesis of poly-substituted pyrazoles through a multicomponent reaction of acceptor-only diazoalkanes, alkynes, and solvents (cyclic ethers or nitriles). The key to this success was driven by the photolysis of acceptor-only diazoalkanes to form free carbene species and the fast *in situ* [3 + 2]-cycloaddition formation of nucleophilic N–H pyrazole derivatives. This work also serves as an entry to allow future reaction design on the combination of carbene reactivity of diazoalkanes with their other reaction modes.

Diazoalkanes have been witnessed as one of the most significant synthetic building blocks in organic synthesis since they were discovered by Curtius in the 1890s [1]. From their reactivity perspective, diazoalkanes could serve as carbene precursors (under thermal, UV-light irradiation or transitions-metal conditions), 1,3-dipoles, nucleophiles, or electrophiles, which enables a large number of useful organic transformations [2–9]. Among them, the classic reactions of metal-catalyzed carbene transfer have been well-developed and provided an effective way to construct carbon-carbon and carbon-heteroatom bonds. Recently, visible-light promoted transformation of diazoalkanes with the formation of free carbene as the key intermediate has gained increasing interest in organic synthesis and has been extensively developed (Scheme 1a) [10–25]. However, the reaction substrates are mostly limited to the use of donor-acceptor diazo compounds. In addition, for all of those developed photochemical processes, diazoalkanes only served as carbene precursors. To the best of our knowledge, rational utilization of multiple reactivities of diazoalkanes in one visible light promoted reaction still remained as a challenging task.

Acceptor-only diazoalkanes, such as the ethyl diazoacetate, are cheap and commercially available chemical feedstock. In contrast to donor-acceptor diazo compounds, photochemical conversion of acceptor-only diazoalkanes was rarely reported which might be due to their weak absorption in visible light region [10–13,26]. On the other hand, without the stabilization with an aryl group, the reactivity of acceptor-only diazoalkanes are relatively low compared with donor-acceptor diazo compounds [8]. Recently, the group of Li [27] and our group [28] independently realized the visible-light-promoted three component reaction of acceptor-only diazoalkanes, nitriles, and carboxylic acids. We found that the photogenerated high reactive carbene species from acceptor-only diazoalkanes could be quickly trapped by nitrile solvents to give a relatively stable nitrile ylide intermediates, which then reacted with carboxylic acids to give the final imides in good yields. Based on the above findings, we anticipated that those highly reactive free carbene species should also be captured by other nucleophilic solvents, such as cyclic ethers, to give the oxonium ylide intermediates [29–36], thus further expanding the synthetic potential of acceptor-only diazoalkanes for the rapid construction of valuable complex organic molecules. Specifically, we presumed that a [3 + 2]-cycloaddition of acceptor-only diazoalkanes with alkynes could provide easy access to N–H pyrazole derivatives in the same reaction system [37–40], which in turn reacted with the photogenerated ylide intermediates to complete the designed multicomponent reaction (Scheme 1b). The obtained multi-substituted pyrazoles are important heterocycles that have numerous applications ranging from biological, medicinal, to synthetic organic chemistry [41,42].

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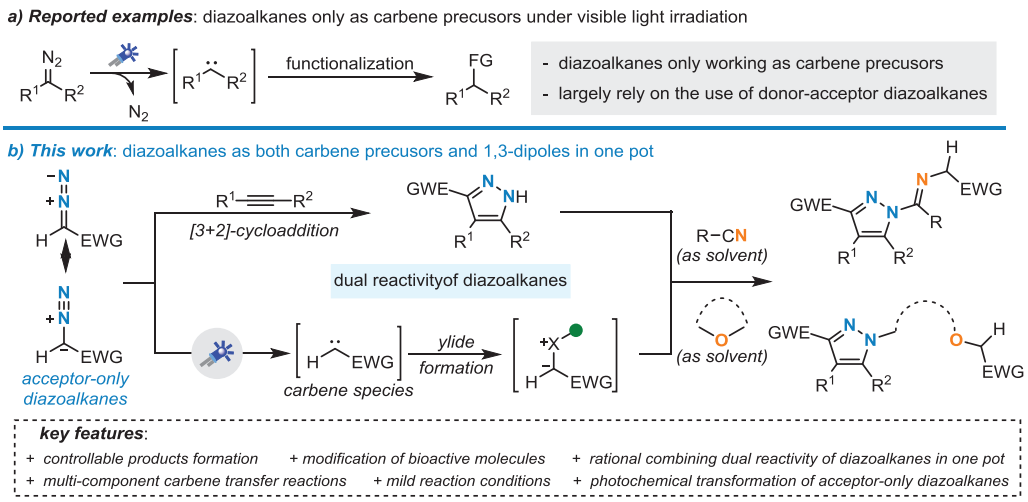
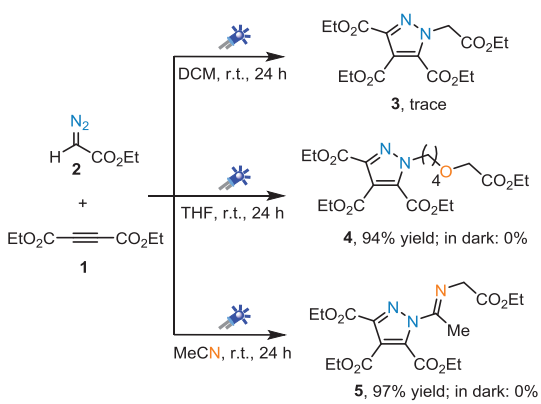


Scheme 1. Photochemical transformation of diazoalkanes.

As our ongoing research programs on the photochemical transformation of diazoalkanes [43–47], we herein describe our studies on visible-light promoted multicomponent reaction of acceptor-only diazoalkanes by merging their cycloaddition and carbene reactivities in one pot. To our delight, both cyclic ether and nitrile solvents were suitable trapping reagents to form the key ylide intermediates. The method featured good functional group tolerance, and broad substrate scope with successfully modification of natural isolates.

We initially examined the reaction by using ethyl 2-diazoacetate **1** and diethyl acetylenedicarboxylate **2** as model substrates under irradiation with 24 W blue LEDs at room temperature (Scheme 2). To validate our hypothesis on the reactivity of carbene species derived from acceptor-only diazo compounds, DCM was first used as reaction media. As expected, only one step [3 + 2]-cycloaddition of diethyl acetylenedicarboxylate and ethyl 2-diazoacetate was obtained as major product, together with a trace amount of the anticipated N–H insertion product **3**. In contrast, we could obtain the target multi-component product **4** in 94% yield by replacement of DCM with nucleophilic solvent THF. It should be pointed out that the reaction is also the first example of utilizing cyclic ethers to stabilize the highly reactive acceptor-only free carbene intermediates. Not surprisingly, CH_3CN could also participate in the designed reaction to give **5** in 97% yield. Importantly, control experiments indicated that blue LED irradiation was essential for this multi-component transformation in either THF or CH_3CN (for other detail optimization, see Supporting information).

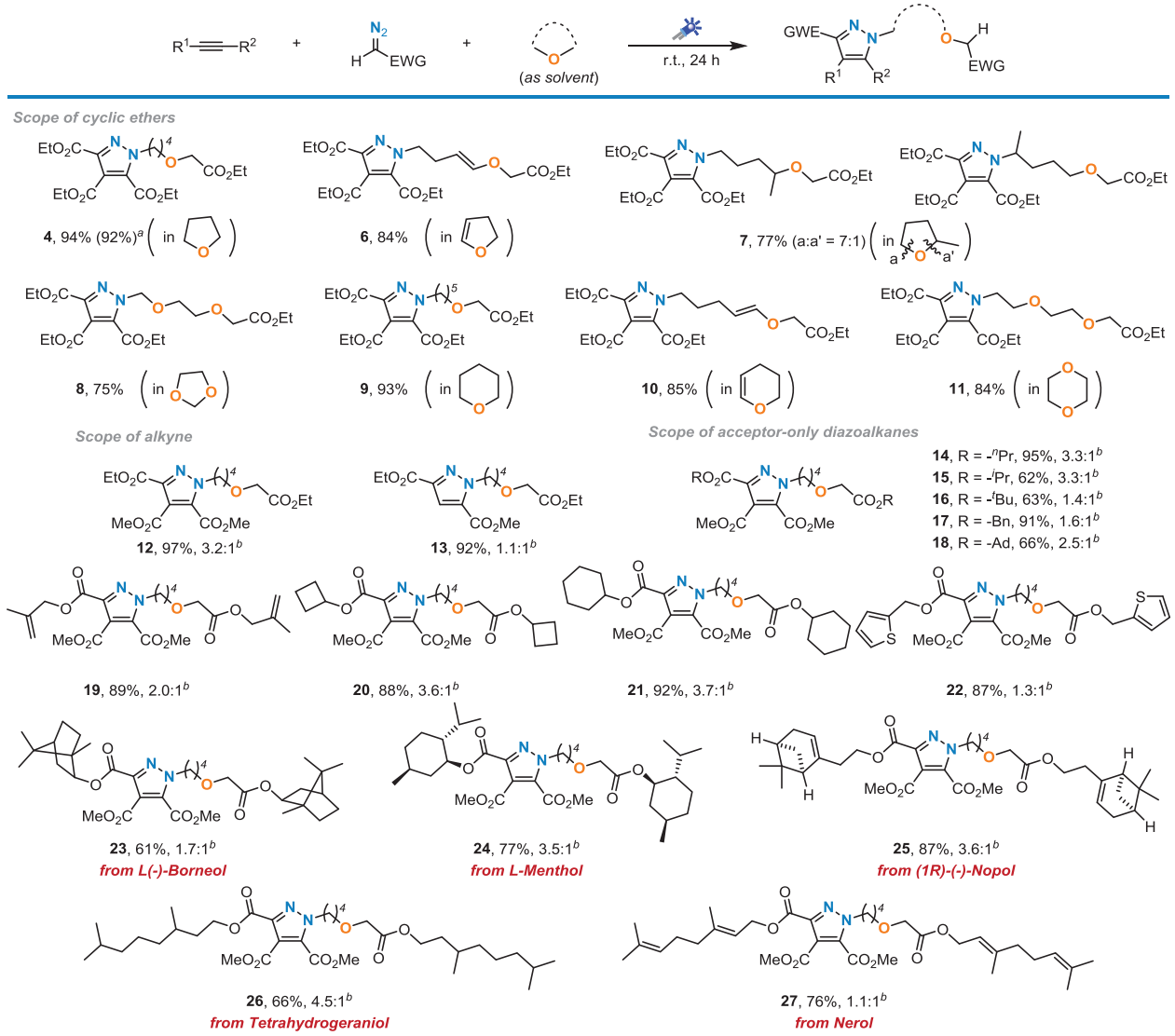


Scheme 2. Reactions of diethyl acetylenedicarboxylate with ethyl diazoacetate in different solvents.

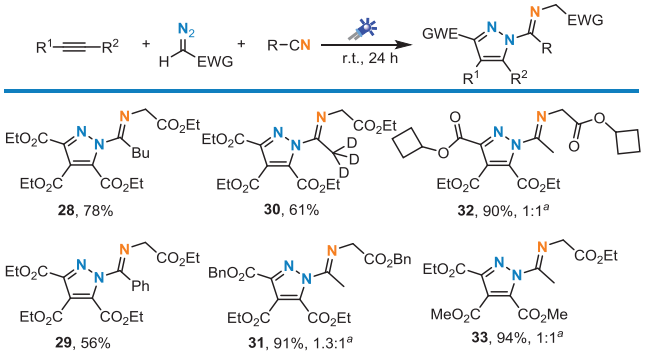
After establishing the optimal reaction conditions, the scope of the transformation was investigated (Scheme 3). We first examined a range of cyclic ethers. It was found that most of the commonly used cyclic ethers, such as 2,3-dihydrofuran, 2-methyltetrahydrofuran, 1,3-dioxolane, tetrahydro-2*H*-pyran, 3,4-dihydro-2*H*-pyran, and 1,4-dioxane, all reacted well under the optimal reaction conditions, affording the corresponding pyrazole **4–9** in good to excellent yields. Dimethyl acetylenedicarboxylate and methyl propiolate also proved to be suitable substrates for this transformation, affording inseparable N^1 and N^2 functionalization product **12** and **13** in 97% and 92% yield, respectively. We next turned our attention to the scope of acceptor-only diazoalkanes. It was found that alkyl diazoacetates containing both alkyl groups (**14–18**, 62%–95% yield) and cycloalkyl groups (**20** and **21**, 88%–92% yield) showed good compatibility to produce the corresponding poly-substituted pyrazoles in good to excellent yields and moderate N^1 and N^2 regioselectivity. Notably, substrates containing sensitive carbon double bond (**19**) and thiophene heterocycle (**22**) showed good compatibility to give the corresponding products in good yields. Next, we employed this photochemical multicomponent poly-substituted pyrazole synthesis reaction with a set of biologically active molecules, and derivatives of L-(−)-borneol (**23**), L-menthol (**24**), (1*R*)-(−)-nopol (**25**), tetrahydrogeraniol (**26**), and nerol (**27**) could be successfully accessed, which further illustrated the benefits of the current method.

Further studies then focused on the scope of nitriles as a carbene stabilizing reagent to stabilize the acceptor-only free carbene species (Scheme 4). We found that different nitriles, such as pentanenitrile (**28**), benzonitrile (**29**), and even CD_3CN (**30**) all could serve as reaction medias to yield the corresponding poly-substituted pyrazoles in good yield. Furthermore, we simply modified the substituents on acceptor-only diazo compounds by using benzyl and cycloalkylderived substrates as examples. Under the optimal reaction conditions, the anticipated multi-component reaction products **31** and **32** in excellent yield and moderate regioselectivity. Finally, this reaction was applied to dimethyl acetylenedicarboxylate to yield the desired product **33** in 94% isolated yield and 1:1 of N^1:N^2-product ratio.

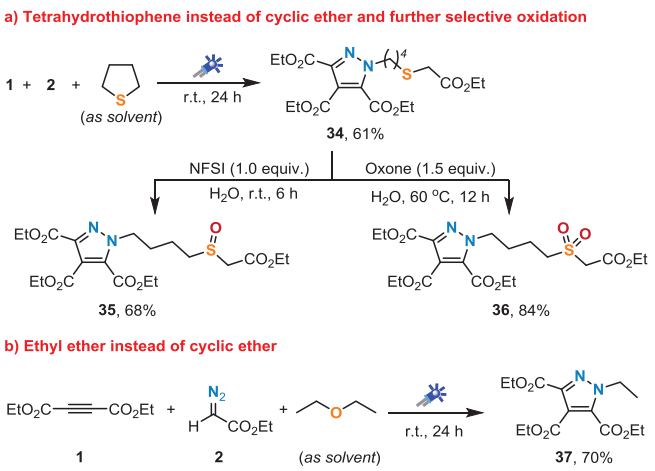
We were pleased to find that tetrahydrothiophene was also an effective substrate for this transformation, with the formation of poly-substituted pyrazole containing a sulfur ether fragment in good yield (**34**, 61% yield, Scheme 5a). Note that, this is the first reported example with the utilization of cyclic sulfide as a free carbene trapping reagent under photochemical reaction conditions. More significantly, sulfide **34** could easily be converted into other



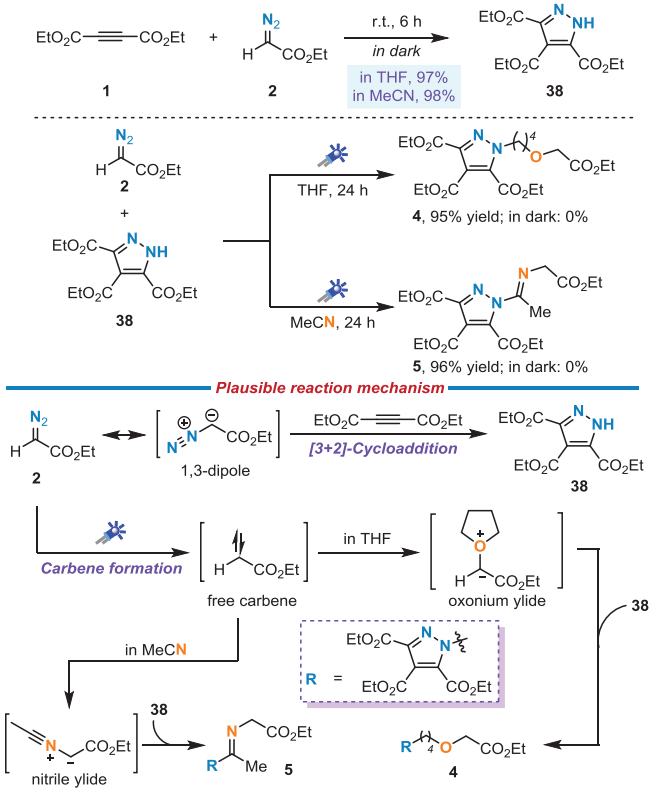
Scheme 3. Reactivity exploration of cyclic ethers. Reaction conditions: alkyne (0.3 mmol), diazoalkanes (1.8 mmol), cyclic ethers (3 mL), under the irradiation with 24 W blue LED for 24 h. [a] Performed at a 1.0 mmol scale. [b] Ratio of N^1- to N^2-product.



Scheme 4. Reactivity exploration of nitriles. Reaction conditions: alkyne (0.3 mmol), diazoalkanes (1.8 mmol), nitriles (3 mL), under the irradiation with 24 W blue LED for 24 h. [a] Ratio of N^1- to N^2-product.



Scheme 5. Follow-up chemistry.



Scheme 6. Mechanism studies.

useful organosulfur compounds, such as sulfoxide **35** and sulfone **36**, in good yields after one-step simple operation [48,49]. To our delight, Et_2O also reacted well under the optimal reaction conditions, affording the corresponding pyrazole **37** in 70% isolated yield (Scheme 5b).

Some control experiments were conducted in Scheme 6 to better understand the reaction mechanism. Firstly, the reaction of **1** and **2** in dark reaction conditions resulted in a highly efficient form of triethyl 1*H*-pyrazole-3,4,5-tricarboxylate **38** within 6 h in either THF or MeCN solvent. Next, we examined the reaction of diazo **2** with pyrazole **38**. Under irradiation with blue LED, the multicomponent reaction product **4** and **5** were obtained in excellent yields. In contrast, no reaction occurred without light irradiation. The results clearly revealed that the in situ formed [3 + 2]-cycloaddition product **38** is the key intermediate for the formation of the final poly-substituted pyrazoles.

Based on the above mechanism investigations and literature reports, a plausible reaction mechanism was proposed in Scheme 6. Initially, [3 + 2]-cycloaddition of ethyl 2-diazoacetate **2** and diethyl acetylenedicarboxylate **1** generated the 1*H*-pyrazole-3,4,5-tricarboxylate **38** [37–40]. Under light reaction conditions, photolysis of acceptor-only diazo compounds lead to the formation of carbene intermediates. Then, the reactive species could either be trapped by THF to form oxonium ylide [29–36] or by CH_3CN to give nitrile ylide [27,28] depending on the reaction media used. The nucleophilic ring opening of oxonium ylide with **38** gave the multi-substituted pyrazole **4**. The reaction of **38** with nitrile ylide afforded **5** which might go through with the formation of nitrilium ion intermediate [27,28].

In summary, we have developed a photochemical multicomponent reaction of acceptor-only diazoalkanes which leads to a wide range of poly-substituted pyrazoles in good to excellent yields. Both of cyclic ether and nitrile solvents can stabilize the activities acceptor-only free carbene species through the formation of ylide intermediates. Compared to previously developed reactions for photochemical transformation of diazoalkanes, the method developed herein rationally utilized two distinguish reactivities of diazoalkanes−cycloaddition reactivity and the carbene reactivity, in one pot. The current process would serve as an entry to further study the synthetic potential of acceptor-only diazo compounds, especially their applications in photochemical multicomponent transformations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108335.

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