Organic LETTERS
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Thermally Induced [3 + 2] Cycloaddition of Alkynyl-Tethered Diazoamides: Synthetic and Mechanistic Insights

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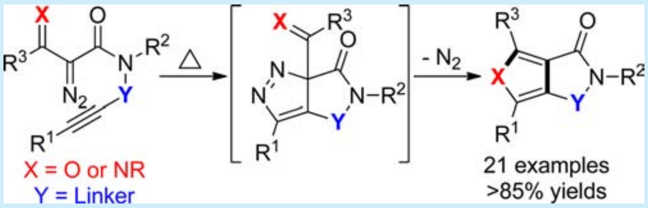
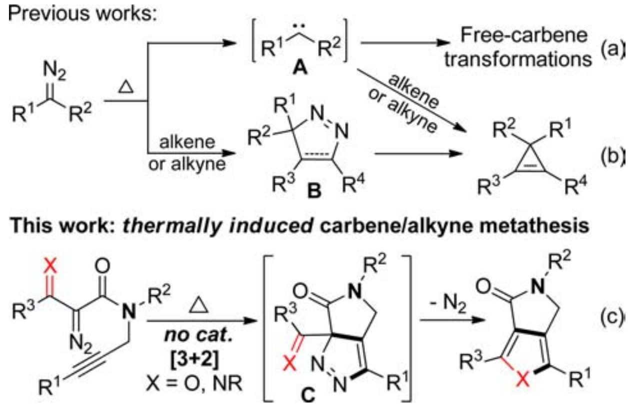
Ⓢ *Supporting Information*

ABSTRACT: A general and unprecedented thermally induced formal [3 + 2] cycloaddition has been developed that provides a general access to fused lactam derivatives in high to excellent yields with broad substrate scope. In comparison with the reported metal-catalyzed carbene/alkynyl metathesis, this is the only example in this area under catalyst-free conditions with excellent selectivity. Mechanistic studies indicate that the 3*H*-pyrazole is the key intermediate in this cascade reaction, which is confirmed spectroscopically for the first time.



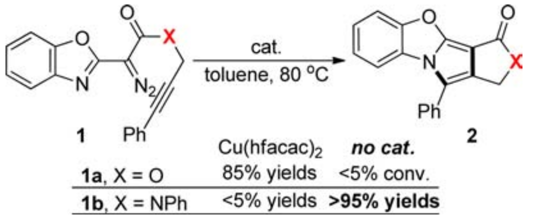
Diazo compounds, as common metal carbene precursors, have shown broad applications in modern synthetic organic chemistry.[1] In contrast to typical metal-catalyzed transformations, thermally induced dinitrogen extrusion reactions of diazo compounds have emerged as a complementary paradigm in recent years,[2−8] including aromatic substitution,[2] C−H insertion,[3] N−H insertion,[4] S−S insertion,[5] geminal difunctionalization,[6] cyclopropanation,[7] and cyclopropenation.[8] In most of these transformations, the corresponding free carbene **A** has been proposed or favored as the intermediate (Scheme 1a). Meanwhile, 3*H*-pyrazole **B** was proposed to be the key intermediate by Doyle and co-workers in the thermally induced intramolecular cyclopropenation of enoldiazo compounds (Scheme 1b).[9] Recently, the diazole intermediate was observed in intermolecular cyclopropanation under thermal conditions by Xiao[10a] and Jiang.[10b] In addition, better selectivity control is obtained in the reactions via intermediate **B**, which first occurs at the C−C π bond dominantly, and other potential reactions in the free carbene pathway could be avoided. Inspired by these works and as a continuation of our own interest in the synthesis of polycyclic heterocycles,[11] herein we report a thermally induced [3 + 2] cycloaddition of alkynyl-tethered diazoamides via the corresponding 3*H*-pyrazole **C** (Scheme 1c) that provides a general access to fused lactams with structural diversity. In comparison with the reported metal-catalyzed carbene/alkyne metathesis process,[11−13] this work is the only example of a complementary approach in this area under catalyst-free conditions.

Scheme 1. Thermally Induced Dinitrogen Extrusion of Diazo Compounds



Initial experiments were inspired by our recent studies of copper-catalyzed carbene/alkyne metathesis for the synthesis of pyrroles (Scheme 2).[11a] When an alkynyl-tethered diazoacetate (e.g., **1a**) was used, the fused polycyclic pyrrole was obtained in 85% yield. However, when the corresponding diazoamide **1b** was evaluated under these conditions, only decomposition of the material was observed, and no identical product could be isolated. As a continuing effort in this context, the control reaction with **1b** in the absence of metal catalyst gave the expected product **2b** in quantitative yield, and the product was confirmed by single-crystal X-ray diffraction analysis.[14] In addition, the obtained product was pure enough for character-

Scheme 2. Reactivity of Diazoacetate versus Diazoamide



Received: November 2, 2016
Published: November 22, 2016

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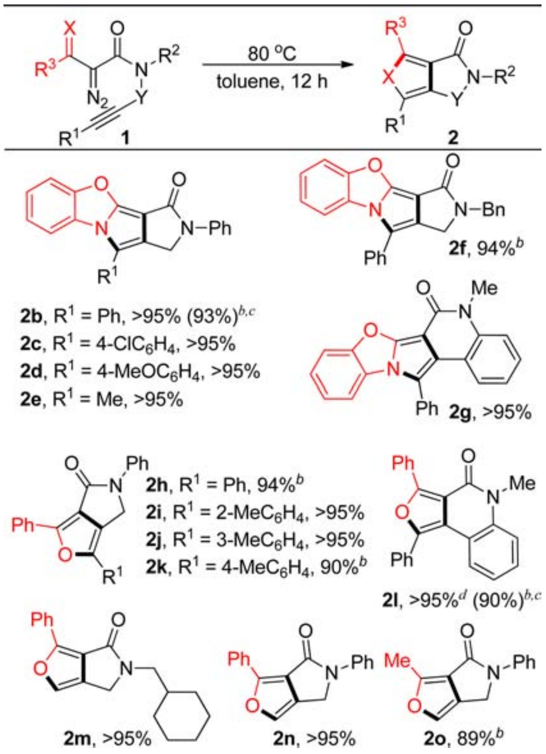
DOI: 10.1021/acs.orglett.6b03288

ization after evaporation of the solvent in vacuum, and no column chromatography was needed for further purification in this case. It is worth mentioning that these thermally induced reaction conditions were fit for diazoamides only, and the corresponding diazoacetate **1a** turned out to be inert at 80 °C.

With the above effective thermally induced reaction conditions in hand, the scope of diazoamides was explored (Scheme 3). All of the other tested amide derivatives were well-tolerated under these conditions and produced the polycyclic products in >93% yield (**2b**–**g**). In addition, the reaction showed excellent chemoselectivity, and typical free carbene transformations, including aromatic substitution[2] and C–H insertion[3] for *N*-aryl (**2b**–**d**) and *N*-benzyl (**2f**)-substituted substrates, respectively, were not observed under these conditions.[15] Encouraged by these results, we further extended the substrates from *α*-imino diazoamides to the *α*-carbonyl diazoamides, and similar reactivity with these materials was observed to give the corresponding fused furans in high to excellent yields.[16] Notably, no further purification was needed for most of these products (>95% yield), and recrystallization was applied when necessary in high yield (as indicated by footnote *b* in Scheme 3). Additionally, the reaction was found to perform well on a gram scale, and pure products **2b** and **2l** were obtained in 93% and 90% yield, respectively, after recrystallization.

Scheme 3. Thermally Induced [3 + 2] Cycloaddition of Diazoamides[a]



[a] The reactions were carried out on a 0.2 mmol scale in 1.5 mL of toluene. [b] Yields after crystallization. [c] The result in parentheses is for a reaction carried out on a 4.0 mmol scale. [d] The reaction was carried out at 60 °C for 8 h in 1.5 mL of $CDCl_3$.

According to the reported literature[9,10] and the observed high chemoselectivity in this thermally induced dinitrogen extrusion transformation, a general reaction mechanism through a consecutive [3 + 2] cycloaddition process via intermediate 3*H*-pyrazole **C** has been proposed (Scheme 1c)[17] rather than the free carbene pathway, which could lead to other side reactions, including aromatic substitution, C–H insertion, etc. To gain insight into this stepwise mechanism, a control reaction with **1m** was carried out in NMR tube with $CDCl_3$ as the solvent at 60 °C (Figure 1).[18] After 4 h, all of the material had decomposed, and the corresponding intermediate **3m** was obtained via [3 + 2] cycloaddition was observed. Although the diazole intermediate was observed and isolated in the reported cyclopropanation reaction of diazo compounds under thermal conditions,[10] the corresponding 3*H*-pyrazole intermediate (**3m**) was observed in this transformation for the first time.[9] Efforts to purify this intermediate gave the isomerized product **4m** through debenzoylation in 90% yield after column chromatography, and this product was confirmed by single-crystal X-ray diffraction analysis.[14] Additionally, after the crude reaction mixture of intermediate **3m** was heated at higher temperature (60–80 °C) for additional hours, the final furan product **2m** was obtained via cycloisomerization in quantitative yield with simultaneous dinitrogen release. These results provided direct evidence for the stepwise mechanism via the 3*H*-pyrazole intermediate. Another testimony for the existence of this intermediate is the direct isolation of pyrazole **4p** from the corresponding material **1p**, which does not have the terminating reaction site (e.g., imino or carbonyl) installed at the vicinal position of the diazo group (Scheme 4a).

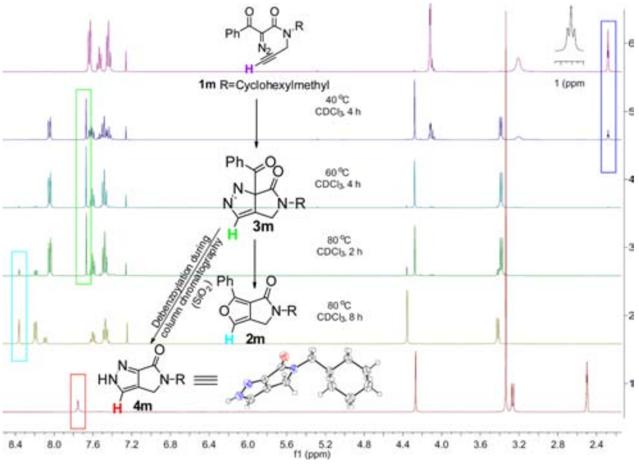
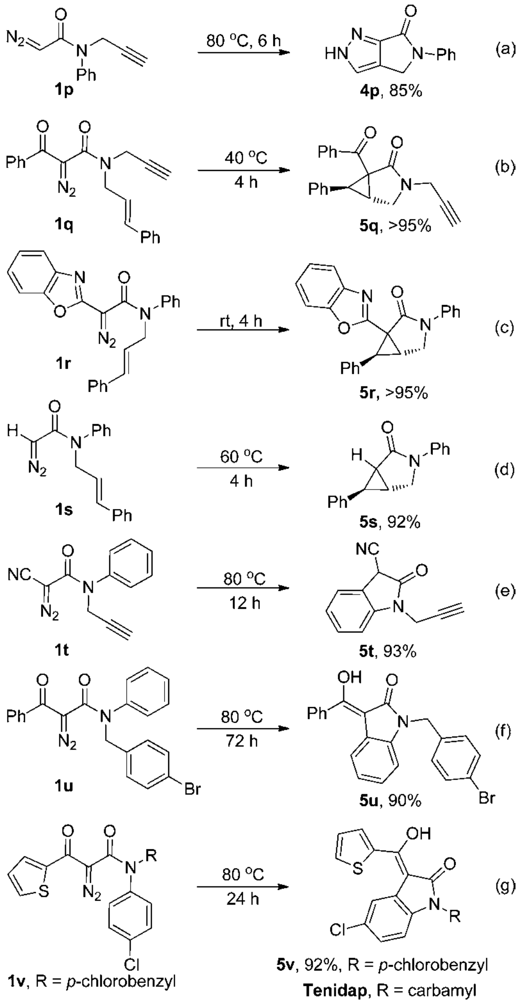


Figure 1. Intermediate observation in the thermally induced transformation.

To further evaluate the reaction scope and the chemoselectivity order of this thermally induced reaction, various N-substituted diazoamides **1q**–**v** were prepared. As summarized in Scheme 4, cyclopropanation has the priority compared with [3 + 2] cycloaddition (Scheme 4b) and aromatic substitution (Scheme 4c,d).[10] Also, aromatic substitution is preferred over [3 + 2] cycloaddition (Scheme 4e) and C–H insertion (Scheme 4f). To illustrate the utility of this general thermally induced reaction, diazoamide **1v** without the alkynyl group was also subjected to the reaction conditions, and to our delight, the corresponding 3-acyloxindole **5v** was obtained in 92% yield. The 3-acyloxindoles constitute a common structural motif in a considerable number of natural products and pharmaceutically interesting compounds,[19] for example, the antirheumatic drug tenidap.[19a] It is worth mentioning that although many metal-

Scheme 4. Thermally Induced Transformations of Diazoamides

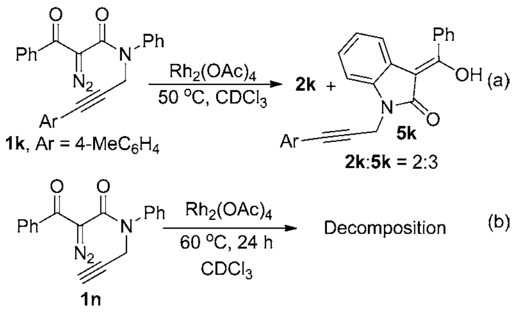


catalyzed approaches have been reported for the synthesis of 3-acyloxindoles,[20] this is the only example under thermal conditions.

Finally, the advantages of this general thermally induced reaction of diazoamides are further demonstrated by comparison with the corresponding Rh-catalyzed reactions (Scheme 5). Lower selectivity (Scheme 5a) or no identifiable product (Scheme 5b) was observed in these cases even at lower temperature.[18]

In conclusion, we report an unprecedented thermally induced [3 + 2] cycloaddition of alkynyl-tethered diazoamides that provides a general access to fused lactams with structural diversity. Although metal-catalyzed carbene/alkynyl metathesis has been well-studied, this is the only example under catalyst-free conditions. In addition, a novel mechanism through the 3*H*-pyrazole has been proposed, and the corresponding intermediate was confirmed spectroscopically for the first time. Further application of diazoamides via this novel transformation under thermal conditions for the synthesis of useful heterocyclic compounds is ongoing in our laboratory.

Scheme 5. Rh-Catalyzed Transformations of Diazoamides



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03288.

General experimental procedures, X-ray structures of **2b** and **4m**, and spectroscopic data for all new compounds (PDF)
Crystallographic data for **2b** (CIF)
Crystallographic data for **4m** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this research from the National Natural Science Foundation of China and the NSFC of Jiangsu Province (SBK20150315, 15KJD150004, and NSFC21602148) and the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions is gratefully acknowledged.

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(14) CCDC 1475370 and CCDC 1504909 contain the supplementary crystallographic data for **2b** and **4m**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Org. Lett. 2016, 18, 6208−6211