Switchable Reactivity between Vinyl Azides and Terminal Alkyne by Nano Copper Catalysis

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Supporting Information



ABSTRACT: A novel nano copper-catalyzed substrate-dependent chemodivergent transformation of vinyl azides with a terminal alkyne is disclosed. 2,5-Disubstituted pyrroles were selectively obtained in high yield with aryl alkynes and aliphatic alkynes, whereas 2,3,4-trisubstituted pyrroles were formed with silylated alkynes. This switchable method provides a controllable and facile access to both multisubstituted pyrrole scaffolds with high efficiency, excellent regioselectivity, and good functional group compatibility.

ransition-metal-catalyzed C-C and C-N bond formations are indispensable tools in organic synthesis allowing for the constitution of basis backbones that are prevalent building blocks of active molecules in the life sciences and in many material precursors.¹ Recently, vinyl azides as a pivotal three-atom synthon for the construction of C-C and C-N bonds have attracted considerable attention in synthetic chemistry,² since they are readily available from azides and the corresponding alkenes or alkynes.³ Moreover, the synergy of the azides group and the alkene makes vinyl azides exhibit unique reactivity which is not found in azides or alkene alone.⁴

Generally, azides and alkynes tend to undergo Huisgen 1,3dipolar cycloaddition (one of the most popular click reactions) under thermal,⁵ strain promoted,⁶ and transition-metalcatalyzed conditions (Scheme 1a).⁷ Among them is a classic example of a Cu-catalyzed azide-alkyne cycloaddition (CuAAC) independently reported by Meldal and Sharpless in 2002.

In line with our interest in the conformation of nitrogen heterocycles with vinyl azides,⁹ we were curious about the reactivity of vinyl azides with unactivated terminal alkyne under copper catalysis. However, when conducting the reaction with vinyl azides and terminal alkynes in our copper catalytic system, we obtained multisubstituted pyrroles instead of the 1,2,3-triazoles from CuAAC disclosed separately by Bi and Kirshning, respectively.¹⁰ Furthermore, an interesting switchable reaction was observed in this conversion by varying the substituent R^4 of the terminal alkyne (Scheme 1b). We speculate that these unexpected consequences might be attributed to the combination of the unique features of vinyl azides and a special copper catalytic system. Compared to the

Scheme 1. Reactions between Azides and Terminal Alkyne

1) Click reaction between azides and termianl alkyne to triazoles (well established)



Cu-catalyzed azide-terminal alkyne cycloaddition to form 1,2,3-triazole which is well established, the Cu-catalyzed cascade reaction of vinyl azides and terminal alkynes to generate pyrroles is still unknown and remains a challenge. In this paper, we present a novel nano copper-catalyzed switchable reaction between vinyl azides and terminal alkynes to synthesize multisubstituted pyrroles. Significantly, aliphatic and aromatic alkynes were selectively transformed into the corresponding 2,5-disubstitued pyrroles, while silyl-alkynes were converted into 2,3,4-trisubstituted pyrroles.

We embarked on the investigation with the reaction of 1ethynyl-4-methoxybenzene 1a and (1-azidovinyl) benzene 2a in the presence of 30 mol % of catalyst, at 135 °C in DCE



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under a nitrogen atmosphere (Table 1). The click reaction product 3a' was obtained in 76% yield with CuTC as the



"Reactions were run with **la** (0.1 mmol) and **2a** (0.18 mmol), catalyst (30 mol %) in 4 mL of DCE under a nitrogen atmosphere. Yields were determined by ¹H NMR using bromochloromethane as the internal standard. ^bIsolated yields.

catalyst (Table 1, entry 1). Interestingly, 2,5-disubstituted pyrrole 3a was observed when copper(I) halides were used (Table 1, entries 2–3). Furthermore, the yield of 3a rose to 60% using CuSCN as the catalyst (entry 4). Other copper salts such as CuBr and CuCN could also execute this reaction but with lower efficiencies (see the Supporting Information (SI)). Gratifyingly, the reaction gave full conversion with 77% isolated yield of 3a when using copper nanoparticles (CuNPs) as the catalyst (entry 5). In contrast, only a 23% yield of 3a was produced when commercial Cu dust was chosen as the catalyst (entry 6). A control experiment confirmed that the omission of copper salts completely shut down the cascade reactions (entry 7). Moreover, the CuNPs catalyst was found to be recyclable without loss of activity (for details, please see SI).

With the established cascade reaction conditions in hand, we examined the scope of alkynes, and the results are summarized in Scheme 2. For aryl alkynes the position of the substituents on the aromatic ring (para, meta, and ortho positions) did not significantly affect the reaction efficiency. This transformation could also tolerate aryl alkynes with electron-donating as well as electron-withdrawing substituents on the aryl rings. For instance, the 4-Me₂N and 4-CF₃ alkynes could be converted into the desired products in 82% and 56% yields, respectively (3d and 3g). To our delight, the free amino group and fluoride containing groups were compatible functional groups for these transformations (3c, 3e, 3j). It is noteworthy that the reaction of alkyl alkynes worked efficiently in the current protocol, and the corresponding 2,5-disubstituted pyrroles were obtained in moderate yields (3m-3u). When 1 mmol of 1a was used as the substrate, the pyrrole product 3a was obtained in 70% yield (Scheme 2). Unfortunately, an attempt to extend this approach to the coupling of an internal alkyne (3v) was unsuccessful.

Various vinyl azides were also studied (Scheme 3). We were pleased to find that common functionalities including the halogens (4c-4e, 4j, 4k), cyano (4g), and acetoxyl (4h) were able to be incorporated into the desired products. Unexpectedly, vinyl azides bearing the *ortho* methyl substituent performed poorly along with deactivating the catalyst (4l).

Scheme 2. Substrate Scope of Alkynes^a



^{*a*}Reaction conditions: CuNPs (30 mol %), alkyne 1 (0.2 mmol), vinyl azides **2a** (0.36 mmol), DCE (5 mL) were stirred for 3 h at 135 $^{\circ}$ C under a nitrogen atmosphere. Isolated yields. ^{*b*}1 mmol scale.





"Reaction conditions: CuNPs (30 mol %), alkyne 1 (0.2 mmol), vinyl azides 2 (0.36 mmol), DCE (5 mL) were stirred for 3 h at 135 °C under a nitrogen atmosphere. Isolated yields. ^bDetected by GC-MS.

The erosion in yields might be attributed to increased steric hindrance. Unfortunately, substrates such as α -alkyl vinyl azides and β -methyl vinyl azides failed to be transferred into the corresponding products (**4n** and **4o**).

To extend the scope of this strategy, an intriguing question is whether silylated alkynes can be used as a coupling partner and consequently afford 2,5-disubstituted pyrroles. To our surprise, the reaction gave 2,3,4-trisubstituted pyrroles instead of 2,5disubstituted pyrroles under the standard conditions (Scheme 4). The structural analysis indicated that two vinyl azides were involved in the generation of the major product. As expected, the reaction efficiency could be significantly enhanced by simply increasing the amount of vinyl azides. A series of silylated alkynes including TMS-, TES-, and TIPS-substituted alkynes were shown to be viable substrates. The structure of **5c** was further confirmed by single-crystal X-ray analysis (CCDC:

Scheme 4. Synthesis of 2,3,4-Trisubstituted Pyrroles^a



"Reaction conditions: CuNPs (30 mol %), alkyne 1 (0.2 mmol), vinyl azides 2 (0.50 mmol), DCE (5 mL) were stirred for 3 h at 135 °C under a nitrogen atmosphere. Isolated yields.

1865535). Notably, when a β -substituted vinyl azide and a terminal vinyl azide were chosen to be the substrates, the cross-coupled product (**5**i) was obtained as the major product.

To obtain a better understanding of these transformations, several control experiments were performed (Scheme 5, eqs 1-6). 2H-Azirine was proposed as an intermediate of the transformations;¹¹ therefore, the 2H-azirine 6a was prepared and subjected to the reaction with alkyne 1a and 1w in the presence of Cu NPs. The corresponding products 3a and 5c were obtained in 86% and 84% yields, respectively (eqs 1 and 2). These results indicate that 2H-azirine could be a key intermediate in both reactions. Considering that the copper acetvlide might be the intermediate in these reactions. (phenylethynyl)copper 7a and ((triisopropylsilyl)ethynyl)copper 10a were prepared and reacted under the standard conditions. However, the reaction gave no 2,5-disubstituted pyrroles but only 2,3,4-trisubstituted pyrroles as the main product (eqs 3 and 4). These results indicate that the copper acetylide was the intermediate in the assembly of 2,3,4trisubstituted pyrroles but not for the synthesis of 2,5disubstituted pyrroles. Furthermore, when the 1,2,3-triazole 3a' which is potentially generated through a [3 + 2]cycloaddition was employed as the substrate, the reaction did not proceed (eq 5). This result excludes a 1,2,3-triazole intermediate in this transformation. In addition, an intermolecular competition experiment was conducted by subjecting an equivalent amount of 1a and 1w with vinyl azides 2a. To our surprise, the reaction gave the corresponding products 3a and 5c without any crossover product (eq 6). Moreover, both reactions were completely suppressed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (for details, see SI).

Based on the reported literature¹² and the above experimental observations, a plausible mechanism for these

Letter





chemodivergent transformations is depicted in Scheme 6. The vinyl azides 2 undergo thermal decomposition to form 2*H*-azirine I. In the generation of the 2,5-disubstituted pyrrole (path a), the 2*H*-azirine initially undergoes an SET reduction with CuNPs to produce the iminyl Cu(II) intermediate II. This C-radical is trapped by the terminal alkyne *via* intermolecular radical addition to generate intermediate III.

Scheme 6. Mechanism for the Chemodivergent Reaction



Subsequently, the radical is captured by the intramolecular copper(II) species to afford the copper adduct IV, which then undergoes reductive elimination to regenerate the active copper species and produces the 3H-pyrroles. Finally, 2,5disubstituted pyrrole 3 is achieved via the isomerization of the 3*H*-pyrrole. For the synthesis of the 2,3,4-trisubstituted pyrrole (path b), the CuNPs initially react with the terminal alkyne to form a copper acetylide V. Subsequently, the 2H-azirine undergoes a nucleophilic ring opening with copper acetylide V, resulting in the iminyl copper intermediate VI, which is protonated to give the NH imine (detected by GCMS; see SI). Then the iminyl copper intermediate VI reacts with another 2H-azirine molecule, leading to intermediate VII and VIII, which are keto-enol tautomers. Intramolecular cyclization of VIII furnishes intermediate IX, which undergoes protonolysis to release intermediate X along with the initial copper species. Further elimination of NH₃ and isomerization provide the 2,3,4-trisubstituted pyrrole 5.

In conclusion, we have developed a nano copper-catalyzed switchable reaction to assemble 2,5-disubstituted pyrroles and 2,3,4-trisubstituted pyrroles with simple and readily accessible starting materials. The utilization of inexpensive, readily available, recyclable, and environmentally friendly a copper nanoparticle catalyst makes this reaction particularly attractive. Further efforts to elucidate the detailed mechanism and to explore the difference between common alkynes and silylated alkynes are currently underway in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00373.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

Accession Codes

CCDC 1865535 contains 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.

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Notes

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