Cu(I)-Catalyzed Three-Component Coupling of Trifluoromethyl Ketone *N*-Tosylhydrazones, Alkynes and Azides: Synthesis of Difluoromethylene Substituted 1,2,3-Triazoles

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A CuI-catalyzed three-component coupling of trifluoromethyl ketone *N*-tosylhydrazones, alkynes and azides has been developed. The reaction represents a straightforward method to access difluoromethylene substituted 1,2,3-triazoles. Mechanistically, it has been proposed that the reaction follows a pathway involving the formation of Cu(I) triazolide intermediate, Cu(I) carbene formation, migratory insertion, and β -fluoride elimination. The transformation is featured by mild conditions, wide substrate scope and high efficiency.

Keywords Cu(I)-catalysis, metal carbene, migratory insertion, β -fluoride elimination, triazole

Introduction

Owing to their unique properties, the organofluorine compounds have found wide applications in various fields, ranging from material sciences, pharmaceutical chemistry and biological sciences.^[1] Therefore, significant attentions and efforts have been devoted to the development of efficient synthetic methods toward fluorine-containing organic compounds.^[2] Among them, the synthesis based on transition-metal-catalyzed reaction has attracted increasing attentions in the past decade.

On the other hand, transition-metal-catalyzed cross coupling reactions involving migratory insertion of metal carbene have been extensively studied by our group and other groups recently.^[3] The key process of this type of transformations is the formation of metal carbene species and the subsequent migratory insertion. The process has been proved to be a versatile method to construct C–C bonds and C–X bonds. One of the major current focuses in this field is the finding of new organometallic species from which the metal carbene intermediate can be generated. Another focus is the application of this novel type of coupling reactions for the synthesis of functional organic compounds, such as fluorine-containing compounds.

In this context, we and others have previously demonstrated that CF₃-bearing *N*-tosylhydrazones or diazo-compounds are versatile building blocks for the synthesis of compounds containing trifluoromethyl groups^[4a-4d] and difluoromethylene groups.^[4e-4f] In 2015,

we reported a Cu(I)-catalyzed three-component coupling of *N*-tosylhydrazones, alkynes and azides (Scheme 1a).^[5] The Cu(I) triazolide intermediate **A** has been proposed to react the *in situ*-generated diazo compounds to form Cu(I) carbene species. We further conceived that the intermediate **A** can react with other diazo compounds, such as CF₃-bearing diazo-compounds, to generate Cu(I) carbene intermediate (Scheme 1b). According to the previous reports,^[4e-4f,6] the Cu(I) carbene migratory insertion will be followed by β -fluoride elimination to afford 1,1-difuoroolefins as the products.

Scheme 1 Cu(I)-catalyzed three-component reaction involving triazolide copper carbene intermediate



Experimental

General procedure for the Cu(I)-catalyzed reaction

Under nitrogen atmosphere, CuI (7.6 mg, 0.04 mmol, 20 mol%), LiO^tBu (32 mg, 0.4 mmol, 2.0 equiv.) CF₃-bearing *N*-tosylhydrazones (1, 0.20 mmol) were succes-



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sively added to a flame-dried 10 mL Schlenk tube. The reaction flask was degassed three times with nitrogen and dry dioxane (2.0 mL) was added using a syringe. Then alkyne **2** (1.3 equiv., 0.26 mmol) and azide **3** (1.3 equiv., 0.26 mmol) were added by microsyringe, successively. If the alkynes or azides were solid, they should be added before degassing. At last, the reaction tube was immersed in 65 °C bath oil. The reaction was heated with stirring for 4 h, and it was then cooled to room temperature and filtered through a short plug of silica gel [V(petroleum ether) : V(acetone) : V(dichloromethane)=3:1:1 as eluents]. Solvent was then removed *in vacuo* to leave a crude mixture, which was purified by silica gel column to afford pure product triazoles **4**, **5** and **6**.

Results and Discussion

According to previous reaction conditions,^[5] the initial experiment was carried out at 65 °C with 0.2 mmol CF₃-bearing *N*-tosylhydrazone **1a** and terminal alkyne **2a** and benzyl azide **3a** as substrates in the ratio of 1 : 1, LiO'Bu (2.0 equiv.) as the base and dioxane (2.0 mL) as the solvent. To our delight, 73% isolated yield of product **4a** was obtained through silica gel chromatography. When the amount of *N*-tosylhydrazone **1a** was

increased to 1.3 equiv., the isolated yield of **4a** was diminished to 43%. However, by increasing the amount of alkyne **2a** and azide **3a** to 1.3 equiv., the isolated yield of **4a** could be improved to 83%. Thus, this was selected as the standard condition for the following experiments.

With the optimized conditions in hand, the substrate scope was investigated with a series of CF₃-bearing N-tosylhydrazones, alkynes and azides. Firstly, the functional group compatibility of N-tosylhydrazones was studied. As shown in Scheme 2, we found different types of CF₃-bearing N-tosylhydrazones could tolerate this condition to afford the final coupling products. This transformation is not sensitive to steric effect, as shown by the reaction with ortho-methyl substituted aryl *N*-tosylhydrazones **1c**. The yield of coupling product **4c** was only slightly diminished. In general, the electronic effect of aryl ring of N-tosylhydrazones did not show obvious influence on the yields. However, the reaction with the N-tosylhydrazone 1j bearing electron-rich heteroaromatic ring afforded the corresponding product 4j in low yield, which may be attributed to the instability of the in situ-generated diazo compound. The structure of 4i was confirmed by X-ray crystallography.^[7] The alkyl substituted N-tosylhydrazones also gave the corresponding products (4k-4m), while the yields are only moderate.





Next, the substrate scope of alkynes was surveyed with various terminal alkynes. The terminal alkynes substituted by various arvl and alkyl groups can tolerate the reaction conditions, affording the corresponding products in good to moderate yields (Scheme 3). Notably, the alkynes bearing electron-rich aromatic substituents afforded the products in good yields (5a-5c, 5h), while these bearing electron-withdrawing substituents gave low yields of the products (5f-5g). The reaction with alkyne 2i, which bears heteroaromatic substituent, also afforded the coupling product 5i in moderate yield. Gratifyingly, the reaction with envne (2j) and the alkynes (2k-2n) bearing different alkyl substituents, also afforded the expected products in moderate yields.

Furthermore, the substrate scope of azides was ex-

Scheme 3 Substrate scope of terminal alkynes 2a-2n

plored. It was found that the reaction with a series of azides could afford the corresponding products in moderate to good yields (Scheme 4). The transformation was not significantly influenced by the electronic properties of the aryl ring. However, the transformation is sensitive to the steric effect. For example, the sterically hindered substrate 3d only gave the product in moderate yield. The reaction bearing heteroaromatic azide 3f also afforded the product, albeit in low yield. This may be attributed to the fact that the pyridine moiety coordinates to the catalyst to influence the reaction. Moreover, the alkyl azide 3g gave the expected product 6g smoothly.

Furthermore, to show the potential application of this transformation, we scaled up this reaction to 10 mmol. And it gave the product smoothly, albeit in





Scheme 4 Substrate scope of terminal azides 3a-3g



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Scheme 5 Proposed reaction mechanism



diminished yield (Eq. 1).



For gaining insights into the mechanism of this transformation, control experiments were conducted as shown in Eq. 2. In order to substantiate the reaction sequence, **1a** and **2a** were subjected to the reaction first for 4 h, the azide **3a** was added to the reaction system. Under such conditions, the triazole product could not be obtained, but only 1,1-difluoroenyne **7** was detected.^[4e] The results support our initial assumption shown in Scheme 1 that the alkyne reacts first with azide to form the Cu(I) triazolide intermediate **A**, which further reacts with the *in situ* generated diazo substrate.



The proposed reaction mechanism is shown in Scheme 5. The Cu(I) triazolide intermediate **A** reacts with *in situ* generated diazo compound **1a'** to form Cu(I) carbene **C**, followed by migratory insertion of the Cu(I) carbene to form a new Cu(I) species **D**. At last, the intermediate **D** gives the product **4a** through β -fluoride elimination with the regeneration of Cu(I) catalyst (Scheme 5, path *a*). Alternatively, the Cu(I) triazolide intermediate A may be in equilibrium with its protonated counterpart 8 (Scheme 5, path *b*). To verify such possibility, triazolide 8 was prepared and subjected to the standard reactions. However, triazolide 8 remains unchanged, which indicates path *b* can be ruled out.

Conclusions

In summary, we have developed an efficient and regioselective method for the synthesis of difluoromethylene substituted 1,4,5-trisubstituted 1,2,3-triazoles.^[8,9] The reaction is featured by mild conditions, wide substrate scope, and good yields. Mechanistically, this reaction follows a pathway involving [2+3] cycloaddition (click reaction), Cu(I) carbene formation, migratory insertion, and β -fluoride elimination. This reaction further demonstrates the application of CF₃-bearing *N*-tosylhydrazones in the synthesis of fluorine-containing organic compounds.

Acknowledgement

The project is supported by National Basic Research Program of China (973 Program, No. 2015CB856600) and NSFC (Nos. 21472004 and 21332002).

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