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Cu-catalyzed tandem reactions of fluorinated alkynes with sulfonyl azides en route to 2-trifluoromethylquinolines†

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A novel method for the synthesis of 2-trifluoromethylquinolines *via* Cu-catalyzed tandem reactions was reported. A strong electronic effect was observed, but the steric effect was negligible.

Quinolines are common structural motifs and appear in a wide range of natural products and drug molecules.[1,2] Among them, 2-trifluoromethylquinoline derivatives have attracted great attention in drug design because of the unique properties of the fluorine atom.[3] For example, Mefloquine which contains a 2-trifluoromethylquinoline skeleton is one of the main drugs for anti-malaria.[4]

Although 2-trifluoromethylquinoline derivatives are of great interest, methods for the synthesis of these compounds are limited.[5] The most frequently utilized strategy is the Combes' method.[6] Recently, transition-metal-catalyzed synthesis of 2-trifluoromethylquinolines has become increasingly attractive.[7,8] For example, in 2001, Uneyama *et al.* reported an intermolecular synthesis of 2-trifluoromethylquinolines by rhodium-catalyzed cyclization of trifluoroacetimidoyl chlorides with alkynes at an elevated temperature.[8e] In 2008, the same group developed an altered method to access 2-trifluoromethylquinolines by palladium-catalyzed intramolecular chloroimination reactions.[8c] In order to avoid or reduce the use of noble metals and to enrich the strategies for the synthesis of 2-trifluoromethylquinolines, our group has developed several routes to 2-trifluoromethylquinolines.[9] In 2010, a palladium-catalyzed tandem Sonogashira–alkyne carbocyclization of β-trifluoromethyl β-enaminoketones with aryl alkynes was reported. 2-Trifluoromethylquinolines could be achieved in excellent yields under mild conditions.[9a] In the same year, a milder way to obtain 2-trifluoromethylquinolines catalyzed by cheap and abundant copper metal was disclosed.[9b] This strategy was proposed to undergo a tandem reaction mechanism that involves isomerization to form allene, followed by a Friedel–Crafts reaction to give the products. However, despite the significant progress, the reactions suffer from harsh conditions (high reaction temperature), limited availability of starting materials, and poor functional-group compatibility. Methods that feature mild conditions and easy operation with easily accessible starting materials are still required to be developed.

As part of our continuous studies on the synthesis of fluorinated heterocyclic compounds, herein we report a copper-catalyzed azide–alkyne cycloaddition (CuAAC)[10] to synthesize 2-trifluoromethylquinolines through tandem reactions of fluorinated terminal alkynes with sulfonyl azides at room temperature.[11,12]

As shown in Table 1, fluorinated terminal alkyne **1a** and tosyl azide **2a** were chosen as the model substrates to screen the optimal reaction conditions. An initial experiment was performed using 1.2 equiv. of tosyl azide **2a** and 1.5 equiv. of Et_3N with 10 mol% of CuI in CH_3CN at room temperature under a nitrogen atmosphere for 24 h. Substrate **1a** was consumed completely, and no corresponding product **3aa** was observed (Table 1, entry 1). When an inorganic base K_2CO_3 was used, substrate **1a** was also fully converted, and only a trace amount of product **3aa** was detected (Table 1, entry 2). To our delight, the product **3aa** was obtained in 11% yield when THF was used as the solvent, although **1a** was fully consumed (Table 1, entry 3). However, almost all of substrate **1a** remained when CH_2Cl_2 was used as the solvent (Table 1, entry 4). An encouraging result was achieved when toluene was used, yielding 36% of the product and recovering 58% of the substrate (Table 1, entry 5). These results suggest that non-polar solvents benefit the transformation. Other inorganic bases were also studied and no better results were achieved (Table 1, entries 6–8). Then copper catalysts were studied. To our satisfaction, an

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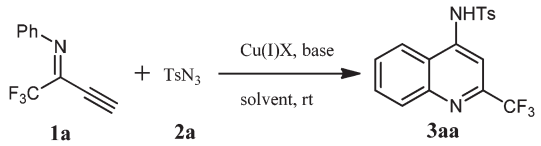
Table 1 Reaction condition optimization[a]



1a 2a 3aa

Entry	Cu(I)X	Base	Solvent	Yield[b]/%
1	CuI	Et_3N	CH_3CN	0
2	CuI	K_2CO_3	CH_3CN	Trace
3	CuI	K_2CO_3	THF	11
4	CuI	K_2CO_3	CH_2Cl_2	Trace
5	CuI	K_2CO_3	Toluene	36
6	CuI	K_3PO_4	Toluene	21
7	CuI	Na_2CO_3	Toluene	14
8	CuI	Cs_2CO_3	Toluene	10
9	CuCl	K_2CO_3	Toluene	98(94)[c]
10	CuBr	K_2CO_3	Toluene	64
11	CuCN	K_2CO_3	Toluene	23

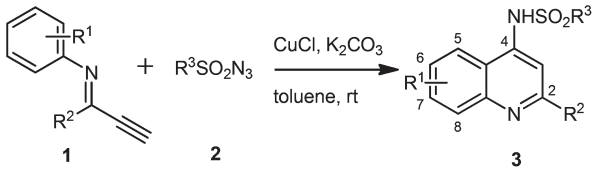
[a] Reaction condition: **1a**, 1.2 equiv. of **2a**, 1.5 equiv. of base, 10 mol% of Cu(I)X, in solvent at room temperature under a nitrogen atmosphere for 24 h. [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c] Isolated yield in parentheses.

almost quantitative yield (98%) was detected when CuCl was used as the catalyst (Table 1, entry 9). Other copper catalysts such as CuBr and CuCN were less efficient compared to CuCl (Table 1, entries 10 and 11). Finally, the optimized reaction conditions were identified as **1a**, 1.2 equiv. of **2a**, 10 mol% of CuCl, and 1.5 equiv. of K_2CO_3 in toluene at room temperature under a nitrogen atmosphere.

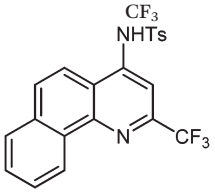
To investigate the scope and limitations of the established strategy, a number of fluorinated terminal alkynes **1** and sulfonyl azides **2** were tested. The results are summarized in Table 2. It should be noted that the electronic effect of substituents on the N-aromatic moiety of substrates **1** significantly affects the yield of desired products, while the steric effect has little effect on that.

As can be seen from Table 2, the reaction occurs smoothly in toluene at room temperature, reaching completion within 24 h. The method has a broad scope and good functional-group compatibility. Firstly, we studied various sulfonyl azides **2a–e**. Both electron-rich aryl sulfonyl azides and electron-poor aryl sulfonyl azides gave excellent results (Table 2, entries 1–4). Even alkyl sulfonyl azides afforded the desired product in moderate yield (Table 2, entry 5). Then the effect of substituents on the N-aromatic moiety of substrates **1** was studied. Many different substituents were tolerated in the reactions, such as alkyl groups (Table 2, entries 6, 11 and 14), amino group (Table 2, entry 7), halides (Table 2, entries 8, 9, 12 and 13), ester group (Table 2, entry 10) and aryl groups (Table 2, entries 15 and 16). The halides could be used for further transformation. However, while electron-rich substituents afforded excellent results, electron-poor substituents only delivered moderate results. These results suggest that the electronic effect of substituents on the N-aromatic moiety of substrates **1** has a great influence on the yield of desired products. For

Table 2 Scope and limitations of Cu-catalyzed tandem reactions between fluorinated terminal alkynes and sulfonyl azides[a]



1 2 3

Entry	R^1	R^2	R^3	Yield[b]/%
1	H	CF_3	*p*-Me-Ph	**3aa**, 94
2	H	CF_3	Ph	**3ab**, 90
3	H	CF_3	*p*-Cl-Ph	**3ac**, 82
4	H	CF_3	*p*-NO_2-Ph	**3ad**, 93
5	H	CF_3	Me	**3ae**, 44
6	6-Me	CF_3	*p*-Me-Ph	**3ba**, 94
7	6-NMe_2	CF_3	*p*-Me-Ph	**3ca**, 89
8	6-Br	CF_3	*p*-Me-Ph	**3da**, 46
9	6-I	CF_3	*p*-Me-Ph	**3ea**, 42
10	6-CO_2Et	CF_3	*p*-Me-Ph	**3fa**, 33
11	5-Me : 7-Me (1 : 1.7)	CF_3	*p*-Me-Ph	**3ga** + **3ga′**, 75
12	5-Cl : 7-Cl (1 : 1.8)	CF_3	*p*-Me-Ph	**3ha** + **3ha′**, 45
13	8-F	CF_3	*p*-Me-Ph	**3ia**, 21
14	8-Me	CF_3	*p*-Me-Ph	**3ja**, 83
15	8-Ph	CF_3	*p*-Me-Ph	**3ka**, 91
16				**3la**, 96
17	H	C_2F_5	*p*-Me-Ph	**3ma**, 84
18	H	C_3F_7	*p*-Me-Ph	**3na**, 81
19	6-OMe	CF_2Cl	*p*-Me-Ph	**3oa**, 62
20	6-OMe	CF_2Br	*p*-Me-Ph	**3pa**, 54
21	H	CF_2H	*p*-Me-Ph	**3qa**, trace

[a] Reaction condition: **1**, 1.2 equiv. of **2**, 1.5 equiv. of K_2CO_3, 10 mol% of CuCl, in toluene at room temperature under a nitrogen atmosphere for 24 h. [b] Isolated yields.

substrates containing substituents at the *m*-position on the N-aromatic moiety, both electron-rich and electron-poor substituents gave approximately 2 : 1 regioisomeric products in 75% (Me) and 45% (Cl) yield, respectively. For substrates containing substituents at the *o*-position on the N-aromatic moiety, even the Ph group could afford excellent product yield up to 91% (Table 2, entry 15 *vs.* entries 13, 14 and 16). Moreover, the structure of **3ka** was confirmed by X-ray crystal diffraction studies (Fig. 1).[13] These results implied that the steric

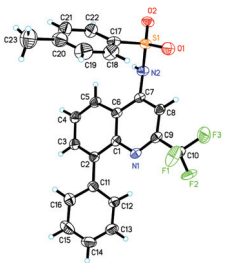
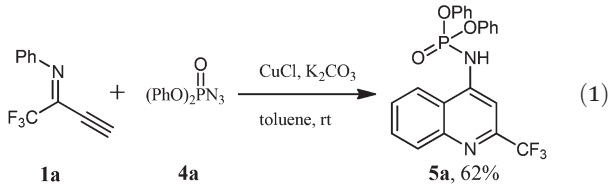


Fig. 1 X-ray crystal structure of **3ka**.

effect has little effect on the yield of desired products. In addition, other fluoroalkyl groups were also examined. Perfluoroalkyl groups were more efficient than others during the transformation (Table 2, entries 1, 17, and 18 *vs.* entries 19–21). When the CF_2H group was employed in the reaction, only a trace amount of the desired product was detected, presumably due to the decomposition of the substrate under the standard conditions (Table 2, entry 21).

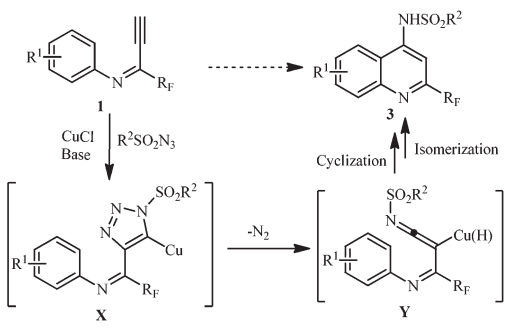


(1)

Furthermore, this catalytic system could be used for the reactions between fluorinated terminal alkynes and phosphoryl azides.[14] When substrate **1a** and phosphoryl azide **4a** were treated under the optimized reaction conditions, the corresponding product **5a** was obtained in moderate yield [eqn (1)]. This reaction broadened the catalytic system to some extent and offered a way to furnish phosphoramidate, which might be used as a directing group for further decoration of 2-trifluoromethylquinoline skeletons.[15]

Based on the above-mentioned studies, a brief mechanism was proposed as shown in Scheme 1. The click reaction of fluorinated terminal alkynes **1** with sulfonyl azides **2** catalyzed by CuCl gave triazole intermediate **X**, which then isomerized to form ketenimine intermediate **Y**. Finally, products **3** were obtained after cyclization and isomerization.

In conclusion, we have developed a convenient method for preparing 2-trifluoromethylquinolines under mild conditions through tandem reactions. The reaction mechanism was supposed to involve copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, cyclization and isomerization. This method has a broad scope and good functional-group compatibility. A strong electronic effect of substituents on the N-aromatic moiety of substrates **1** was observed, while the steric effect was negligible. Furthermore, this method could be used to synthesize 2-trifluoromethyl-4-phosphorylamidoquinolines. This approach provides an efficient route to 2-trifluoromethylquinolines which are useful in life sciences.



Scheme 1 Proposed mechanism.

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13 CCDC-946895 (**3ka**) contains the supplementary crystallographic data for this paper.

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