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Highly selective synthesis of 1-polyfluoroaryl-1,2,3-triazoles via a one-pot three-component reaction

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ABSTRACT

A series of 1-polyfluoroaryl-1,2,3-triazoles were synthesized in moderate to good yields by an efficient copper-catalyzed one-pot three-component reaction of polyfluoroarenes, sodium azide, and terminal alkynes. The method involves a polyfluoroarylated azide intermediate produced in situ by the selective C—F bond cleavage of polyfluoroarene with sodium azide.

1,2,3-Triazole scaffolds are ubiquitous structural moieties in the synthetic chemistry, which find widespread applications in medicinal chemistry and materials science.[1] Owning to their vast importance, much attention has been devoted to the synthesis of 1,2,3-triazoles and their derivatives. To date, there are a large number of well-designed studies on the construction of 1,2,3-triazoles. Among the strategies presented, the transition-metal catalyzed or mediated 1,3-dipolar cycloadditions of organic azides with alkynes represent one of the most useful approaches.[2] However, usually this methodology leads to a mixture of 1,4-disubstituted- and 1,5-disubstituted-1,2,3-triazoles. Later, copper-catalyzed azide–alkyne cycloaddition (CuAAC) reported by the Sharpless[3] and Meldel[4] groups has proved to be an outstanding procedure for the access to 1,4-disubstituted 1,2,3-triazoles. This reaction occurs reliably under mild conditions, displaying superb substrate scope and exquisite selectivity. However, the organic azide molecules utilized in the reaction were generally prepared beforehand, which increased the operational complexity of the reaction procedure. It is known that the low molecular weight organic azides tend to be explosive and are difficult to handle. Therefore, it is highly desirable to find a facile method that avoids handling the neat hazardous organic azides for the synthesis of the 1,2,3-triazoles.

One-pot three-component cascade reaction catalyzed by a transition-metal was considered to be an efficient strategy in the organic chemistry, especially for the construction of complex organic compounds.[5] Recently, intensive attention has been devoted to the methodology involving the in situ generation of required azides in the Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition reaction.[6] For instance, the Fokin group reported a microwave-enhanced, fast, and efficient three-component reaction for the generation of 1,4-disubstituted-1,2,3-triazoles from corresponding alkyl halides, sodium azide, and alkynes.[7] Alonso and co-workers reported an interesting multicomponent click synthesis of 1,2,3-triazoles from epoxides in water catalyzed by copper nanoparticles on activated carbon.[8] Well-designed Cu(II)–β-cycldextrin complex-based catalytic strategy reported by Kaboudin enables us to produce the 1,2,3-triazoles via a one-pot reaction of an aryl boronic acid with sodium azide in water.[9] Kumar and co-workers developed an efficient and simple tandem protocol for the synthesis of structurally complex and novel 1,2,3-triazole-fused imidazo-[1,2-*a*]pyridines via CuAAC, Ullmann-type C—N coupling.[10] Although these elegant advances have been achieved, the organic azide intermediates were mainly prepared by the coupling reaction of aryl amines, halides, and boronic acids with an azide source such as NaN_3, TMSCN, and TfN_3.[11] Consequently, the development of in situ generation methods of organic azides to create 1,2,3-triazole compounds remains an interesting challenge.

Polyfluoroarenes are a class of electron-deficient compounds which are prone to be attacked by the electron-rich atoms or groups to form the new carbon–carbon bonds or carbon–heteroatom bonds via the selective C—F bond cleavage.[12] Our group has

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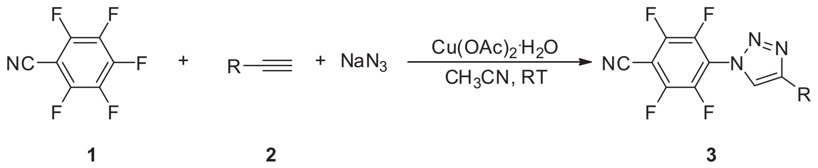


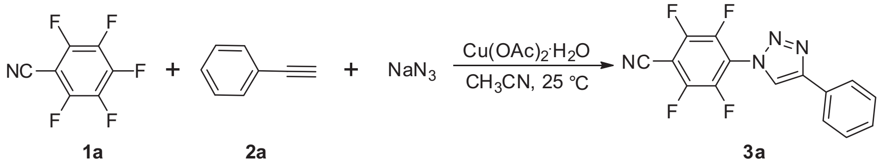
Scheme 1. Synthesis of 1-polyfluoroaryl-1,2,3-triazole via a one-pot three-component reaction.

previously reported the base-promoted SNAr reaction of N—H and O—H containing compounds with polyfluoroarenes via the selective C—F bond cleavage.[13] The interesting results encouraged us to expand the application of the SNAr protocol to fabricate the novel polyfluoroarylated compounds. Given the importance of the 1,2,3-triazoles and the ongoing interest of the C—F bond cleavage strategy, herein, we reported the first copper-catalyzed one-pot three-component tandem reaction of terminal alkynes, sodium azide, and polyfluoroarenes at room temperature. This strategy enables a practical one-step access to a variety of 1-polyfluoroaryl-1,2,3-triazoles, which are important fluorine-containing compounds and the polyfluoroaryl skeletons were prevalent in a large number of drug molecules and material compounds.[14] Additionally, our method involves a polyfluoroarylated azide intermediate produced in situ by the selective C—F bond cleavage of polyfluoroarene with sodium azide (Scheme 1).[15]

Based on our previous work, we speculated that the sodium azide may directly react with polyfluoroarenes to give the polyfluoroarylated azide intermediate in suitable conditions, which was then followed by the domino reaction with terminal alkynes to generate the 1-polyfluoroaryl-1,2,3-triazoles in one-pot. In order to validate the feasibility of the one-pot three-component process, we treated 1.0 equiv of sodium azide, 1.1 equiv of pentafluorobenzonitrile 1a, and 1.5 equiv of phenylacetylene **2a** utilizing 10 mol % $Cu(OAc)_2{\cdot}H_2O$ as the catalyst without a reducing agent in 0.5 mL DMSO stirred at room temperature for 8 h. Delightedly, we observed that the desired product was obtained in 57% isolated yield (Table 1, entry 1). This satisfied result inspired us to search the suitable conditions for this interesting reaction. After the preliminary screening of solvent (Table 1 entries 1–6), we found only CH_3CN was critical for the reaction efficiency, which gave 92% yield of the product (Table 1, entry 6). Other solvents such as DMF, CH_3OH, THF, and even the mixed solvents of ^{t}BuOH/H_2O (1:1) led to a lower yield (Table 1, entries 1–5). Under otherwise identical conditions, we then investigated the other copper catalysts on the efficiency of this reaction. It was revealed that the selected Cu(I) sources were less favorable than $Cu(OAc)_2{\cdot}H_2O$ in this reaction (Table 1, entries 7–9), and the other Cu(II) sources were also ineffective or even delivered a trace amount of **3a**, which were used with the association of sodium ascorbate as the reducing agent (Table 1, entries 10–13). The above screening results illustrated that the solvent and the catalyst played an important role in this one-pot three-component cascade transformation. Increase or decrease in the loading of the catalyst led to unsatisfactory results (Table 1, entries 14 and 15). Hence, the optimal conditions include employing CH_3CN as the solvent in combination with 10 mol % $Cu(OAc)_2{\cdot}H_2O$ as the catalyst.

With the optimized conditions in hand, we continued to investigate the generality and substrate scope of this facile one-pot three-component reaction. The results are summarized in Table 2.

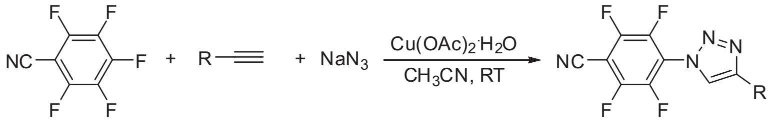
Table 1
Optimization of reaction conditions for the synthesis of **3a**[a]



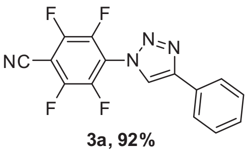
Entry	Solvent	Catalyst	Yield[b] (%)
1	DMSO	$Cu(OAc)_2{\cdot}H_2O$	57
2	DMF	$Cu(OAc)_2{\cdot}H_2O$	45
3	THF	$Cu(OAc)_2{\cdot}H_2O$	60
4	CH_3OH	$Cu(OAc)_2{\cdot}H_2O$	65
5	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$	92
6	^{t}BuOH/H_2O (1:1)	$Cu(OAc)_2{\cdot}H_2O$	40
7	CH_3CN	CuCl	83
8	CH_3CN	CuBr	74
9	CH_3CN	CuI	85
10	CH_3CN	$CuSO_4{\cdot}5H_2O$/NaAsc[c]	Trace
11	CH_3CN	$Cu(NO_3)_2{\cdot}3H_2O$/NaAsc	Trace
12	CH_3CN	$CuCl_2{\cdot}2H_2O$/NaAsc	42
13	CH_3CN	$Cu(acac)_2$/NaAsc	91
14[d]	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$	85
15[e]	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$	87

[a] Reaction conditions: pentafluorobenzonitrile (0.22 mmol), phenylacetylene (0.30 mmol), sodium azide (0.2 mmol), catalyst (10 mol %), solvent (0.5 mL), room temperature, 8 h.
[b] Isolated yields.
[c] NaAsc = sodium ascorbate (20 mol %).
[d] $Cu(OAc)_2{\cdot}H_2O$ (5 mol %).
[e] $Cu(OAc)_2{\cdot}H_2O$ (20 mol %).

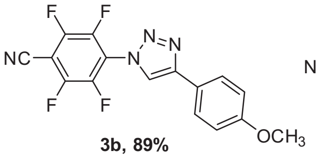
Table 2
One-pot three-component synthesis of 1-polyfluoroaryl-1,2,3-triazoles[a]



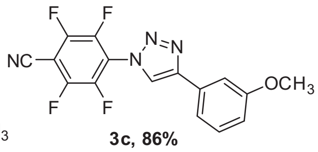
1a **2** **3**



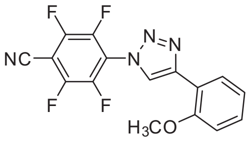
3a, 92%



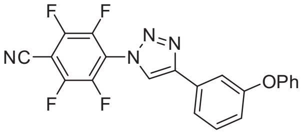
3b, 89%



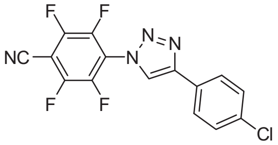
3c, 86%



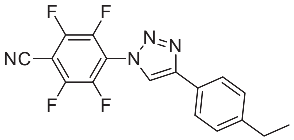
3d, 83%



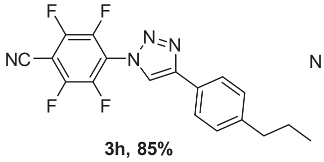
3e, 78%



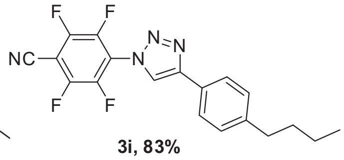
3f, 80%



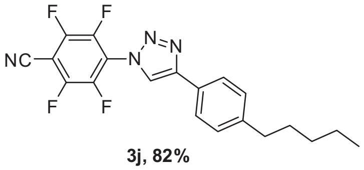
3g, 87%



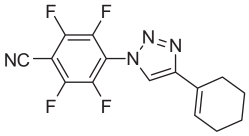
3h, 85%



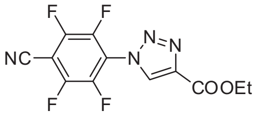
3i, 83%



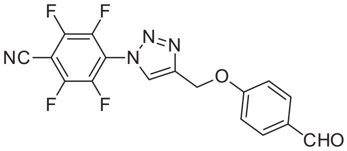
3j, 82%



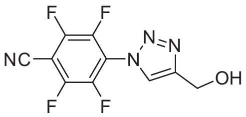
3k, 83%[b]



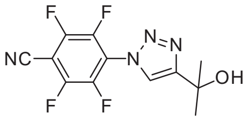
3l, 72%



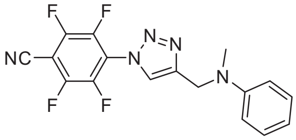
3m, 71%



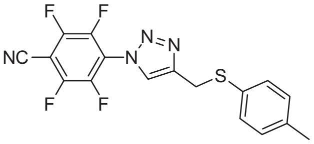
3n, 74%



3o, 73%



3p, 76%



3q, 70%

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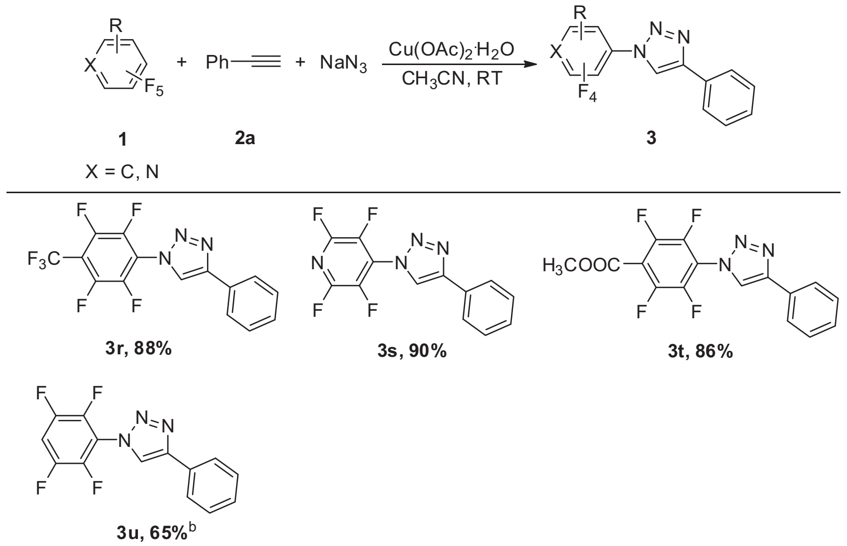
[a] Reaction conditions: pentafluorobenzonitrile (0.22 mmol), alkyne (0.30 mmol), sodium azide (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), CH_3CN (0.5 mL), room temperature, 8 h.
[b] $Cu(acac)_2$/NaAsc.

Various alkynes including the aromatic alkynes and the aliphatic alkynes smoothly reacted with pentafluorobenzonitrile and sodium azide under the optimized conditions to form the desired 1-ployfluoroaryl-4-substituted-1,2,3-triazoles (Table 2, **3a**–**q**). Aromatic alkynes with electron-donating groups or with electron-withdrawing groups on the aryl ring were all tolerated under the optimal conditions, affording the corresponding products in good yields (Table 2, **3b**–**j**). The high efficiency of this reaction is fully achieved for the substrates with the same substituent at different positions, (e.g. methoxy, Table 2, **3b**–**d**). Interestingly, the aliphatic alkynes were also suitable in this reaction, which gave rise to the products in acceptable to moderate yields (Table 2, **3k**–**q**).

Table 3
One-pot three-component synthesis of 1-polyfluoroaryl-1,2,3-triazoles[a]



3r, 88%

3s, 90%

3t, 86%

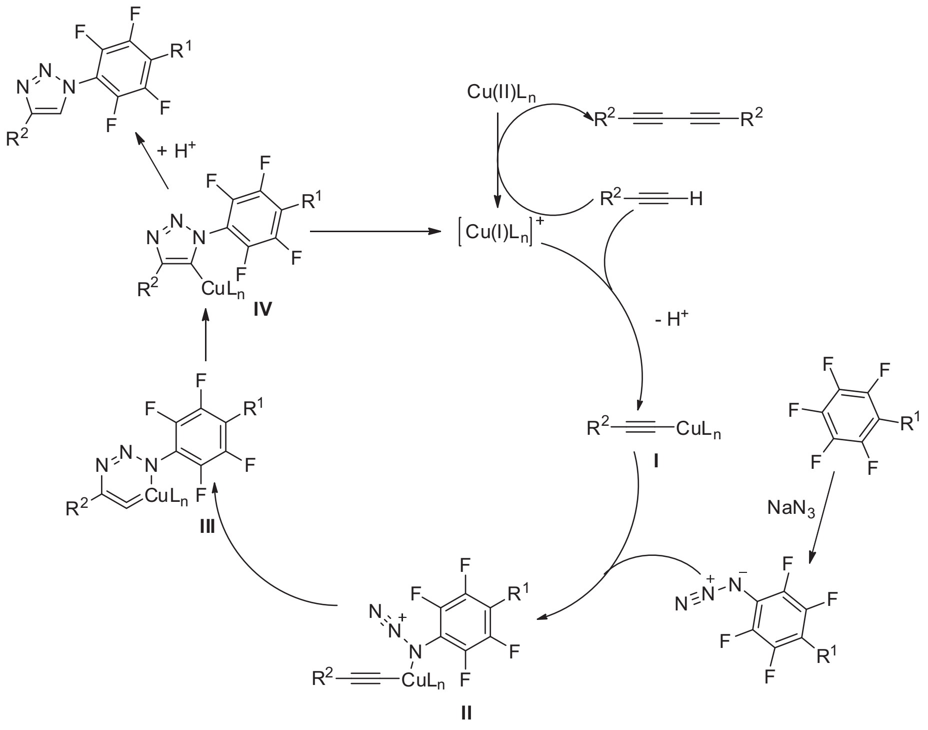
3u, 65%[b]

[a] Reaction conditions: polyfluoroarene (0.22 mmol), phenylacetylene (0.30 mmol), sodium azide (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), CH_3CN (0.5 mL), room temperature, 8 h.

[b] Reaction conditions: pentafluorobenzene (0.22 mmol), phenylacetylene (0.30 mmol), sodium azide (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), DMF (0.5 mL), 70 °C, 8 h.

Although the 1-ethynylcyclohex-1-ene was slightly incompatible with the standard conditions, replacing $Cu(OAc)_2 \cdot H_2O$ with $Cu(acac)_2$ and addition of NaAsc gave a promising yield (Table 2, **3k**). Furthermore, the successful production of **3m**, **3n**, and **3o** in mild yields with the aldehyde and hydroxy groups provided a good opportunity for further formation of oxygen–carbon or oxygen heteroatom bonds by transition-metal-catalyzed coupling and other reactions.

To further explore the generality of the one-pot synthetic strategy, we applied this system to the other polyfluoroarenes such as perfluorotoluene, perfluoropyridine, methyl 2,3,4,5,6-pentafluorobenzoate, and pentafluorobenzene (Table 3). Our optimal conditions were well tolerated with the polyfluoroarene substrates bearing electron withdrawing groups. The reaction of perfluorotoluene, perfluoropyridine, and methyl 2,3,4,5,6-pentafluorobenzoate with phenylacetylene produced the corresponding 1-ployfluoroaryl-4-substituted-1,2,3-triazoles in good yields (Table 3, **3r**–**t**). Unfortunately, the standard conditions were less suitable for pentafluorobenzene, and no detectable amount of the product was observed. Slightly elevating the reaction temperature to 70 °C and



Scheme 2. Proposed mechanism.

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using DMF as the solvent were essential to furnish the product in 65% yield (Table 3, **3u**).

Based on the mechanism studies by the reported literatures,[1e,3,16] a possible mechanism for the synthesis of 1-polyfluoroaryl-1,2,3-triazoles is proposed as shown in Scheme 2. Firstly, the copper(II) catalyst is reduced to the copper(I) reagent via the alkyne oxidative homocoupling (OHC) reaction.[17] Subsequently, the copper(I) reagent combines terminal alkyne to form the copper(I) acetylide I. Then the polyfluoroarylated azide intermediate, which is generated in situ by the selective C—F bond cleavage of polyfluoroarene with sodium azide, is coordinated to the copper center, forming intermediate II. The coordinated polyfluoroarylated azide (see Fig. S1, ESI†) then undergoes a cyclization to give a six-membered metallacycle III, which subsequently rearranges to copper(I) triazolide IV. Finally, protonation of copper(I) triazolide IV results in the desired product and regenerates the copper(I) catalyst for the next catalytic cycle.

In summary, we have successfully developed a simple and efficient approach for the synthesis of 1-polyfluoroaryl-1,2,3-triazoles via a one-pot three-component tandem reaction. With this method, a series of the corresponding products were synthesized in moderate to excellent yields. The reaction shows high generality and functional group tolerance. Most significantly, a polyfluoroarylated azide intermediate was produced via the selective C—F bond cleavage of polyfluoroarene with sodium azide, avoiding the direct utilization of organic azide, which provided an important complementary method for the synthesis of organic azide followed by the domino reaction with alkynes to form the 1,2,3-triazole compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.041.

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