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Copper(I)-Catalyzed Interrupted Click Reaction with $TMSCF_3$: Synthesis of 5-Trifluoromethyl 1,2,3-Triazoles

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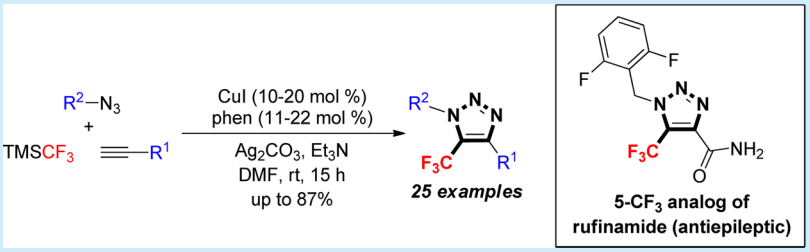
Supporting Information

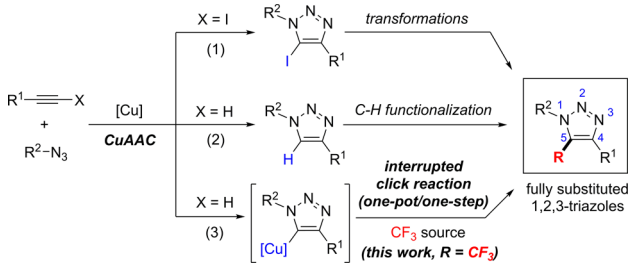


ABSTRACT: We herein describe a Cu(I)-catalyzed interrupted click reaction, using (trifluoromethyl)trimethylsilane ($TMSCF_3$) as a nucleophilic CF_3 source, to synthesize 5-trifluoromethyl 1,2,3-triazoles in one step from readily available terminal alkynes and azides. The reaction shows complete regioselectivity, broad substrate scope, and good functional group tolerability. The application of the reaction has been demonstrated in the synthesis of a trifluoromethylated analog of antiepileptic drug rufinamide.

Since its initial discovery,[1] the Cu(I)-catalyzed azide−alkyne 1,3-dipolar cycloaddition (CuAAC)[2] has been established as one of the most reliable methods for assembling complex molecules and a prime example of "click chemistry".[3] Contrary to thermal reactions, CuAAC regioselectively delivers 1,4-disubstituted 1,2,3-triazoles from terminal alkynes under exceedingly mild conditions.[2a] Complementary RuAAC and IrAAC offer 1,5-disubstituted products, but the regioselectivities are highly substrate-dependent.[4] The efficient synthesis of *fully substituted* 1,2,3-triazoles with a high level of regiocontrol has been an important yet challenging priority,[5] especially given that such compounds are indispensable motifs in drug discovery.[6]

1-Iodoalkynes have been utilized to form 5-iodo-1,2,3-triazoles that can undergo subsequent transformations to give the fully substituted triazoles (Scheme 1, eq 1).[7] Alternatively, catalytic C−H functionalization of 1,4-disubstituted triazoles avoids the use of stoichiometric amounts of halogenated alkynes (Scheme 1, eq 2).[8] The *interrupted* click reaction is the most direct approach in which the 5-cuprated-1,2,3-triazole intermediates are intercepted *in situ* by a trapping reagent (Scheme 1, eq 3). Both electrophilic (ICl,[9a] benzoyl/acetyl chloride and allyl bromide/iodide[9b]) and nucleophilic (terminal alkyne[9c−e] and *H*-phosphate[9f]) trapping reagents have been employed. More recently, aryl halides,[9g,h] *N*-tosylhydrazones,[9i] and S-, Se-, N-,[9j] and Sn-based[9k] electrophiles have also been used. However, to the best of our knowledge, there is no example of intercepting the click catalytic cycle with a CF_3 source for the synthesis of 5-trifluoromethyl 1,2,3-triazoles.

Scheme 1. General Methods for the Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles



Installing a trifluoromethyl group at a strategic position of a drug candidate can significantly enhance its pharmacological properties.[10] The 5-trifluoromethyl 1,2,3-triazoles belong to the class of trifluoromethylated heterocycles that have substantial applications in pharmaceuticals and agrochemicals.[11,12] The most common synthetic approach toward these triazoles involves 1,3-dipolar cycloaddition of azides and CF_3-containing building blocks.[13a−g] The starting materials were usually tedious to prepare, and the products might be obtained as inseparable regioisomeric mixtures. Metal-mediated trifluoromethylation of 5-iodotriazoles[13h] and 5-stannyl triazoles[9k] avoided the regioselectivity problem but required two separate steps using stoichiometric amounts of halogen and tin.

We envisioned that a catalytic protocol could be developed by incorporating a trifluoromethylation step into the CuAAC cycle thereby providing direct access to 5-trifluoromethyl 1,2,3-triazoles regioselectively. Copper-mediated/-catalyzed oxidative trifluoromethylation using (trifluoromethyl)trimethylsilane ($TMSCF_3$) as a nucleophilic source is well-documented yet has

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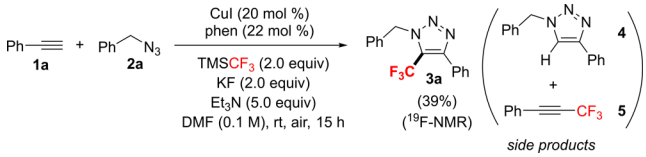
not been applied to CuAAC.[14] We therefore began our studies by reacting phenylacetylene **1** with benzyl azide **2** using copper(I) iodide and 1,10-phenanthroline (phen) as the catalyst, in the presence of $TMSCF_3$ as the CF_3 source, KF as the activator, and Et_3N as the base, in DMF solution open to air at room temperature (Scheme 2). Gratifyingly the desired product 5-

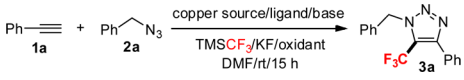
Scheme 2. Preliminary Result



trifluoromethyl 1,2,3-triazole **3a** was obtained in 39% yield by NMR. Side products including the protonated triazole **4** and trifluoromethylated acetylene **5** were also detected.

Subsequent optimization studies were carried out to improve the yield of **3a** (Table 1; see Supporting Information for full

Table 1. Optimization Studies[a]



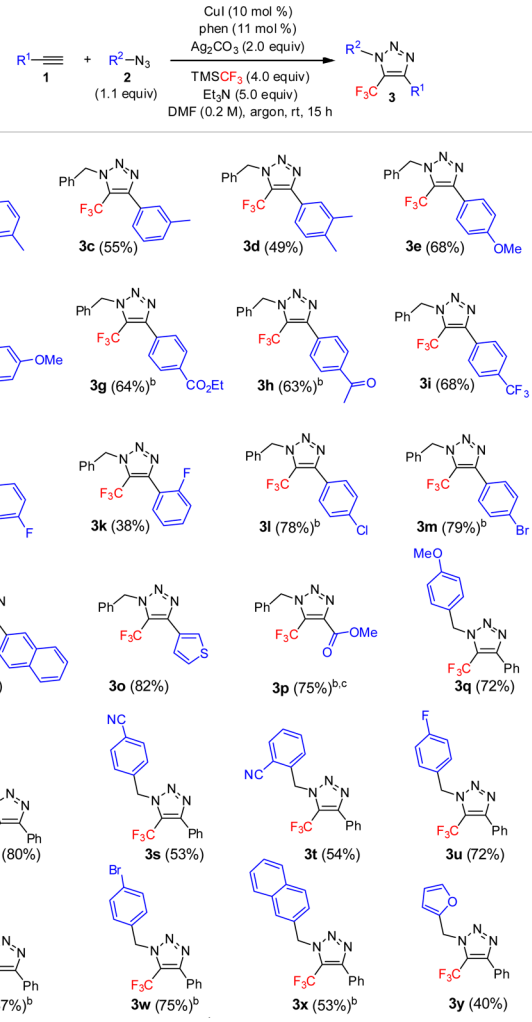
entry	copper source/ligand	oxidant	base	yield (%)[b]
1	CuI/phen	none	Et_3N	<5
2	CuI/phen	Ag_2CO_3	Et_3N	46
3[c]	CuI/phen	Ag_2CO_3	Et_3N	56
4[c]	CuI/phen	Ag_2CO_3	none	<5
5[c]	CuBr/phen	Ag_2CO_3	Et_3N	15
6[c]	CuCl/phen	Ag_2CO_3	Et_3N	7
7[c]	CuTc/phen	Ag_2CO_3	Et_3N	6
8[c]	CuCN/phen	Ag_2CO_3	Et_3N	27
9[c]	$(CuOTf)_2{\cdot}C_6H_6$/phen	Ag_2CO_3	Et_3N	26
10[c]	$Cu(MeCN)_4PF_6$/phen	Ag_2CO_3	Et_3N	11
11[c]	CuI/–	Ag_2CO_3	Et_3N	38
12[c]	CuI/TMEDA	Ag_2CO_3	Et_3N	27
13[c]	CuI/bpy	Ag_2CO_3	Et_3N	46
14[c]	CuI/*t*Bu-bpy	Ag_2CO_3	Et_3N	36
15[c,d]	CuI/phen	Ag_2CO_3	Et_3N	62
16[c,d,e]	**CuI/phen**	**Ag_2CO_3**	**Et_3N**	**70, 67**[f]

[a]Unless specified otherwise, reactions were carried out using **1a** (0.2 mmol), **2a** (0.22 mmol), copper (20 mol %), ligand (22 mol %), base (5.0 equiv), $TMSCF_3$ (2.0 equiv), KF (2.0 equiv), and oxidant (2.0 equiv) in DMF (0.1 M) at room temperature under argon. [b]Yield was determined by ^{19}F NMR using benzotrifluoride as the internal standard. [c]Used 5.0 equiv of $TMSCF_3$ without KF. [d]Reaction was cooled to 0 °C during the addition of $TMSCF_3$, then warmed up to room temperature, and stirred at room temperature for 15 h. [e]Used CuI (10 mol %), phen (11 mol %), 4.0 equiv of $TMSCF_3$ without KF, in DMF (0.2 M). [f]Isolated yield.

details). Oxidative conditions were necessary, as reactions without air gave no desired product (Table 1, entry 1). Among other oxidants, such as DDQ, *p*-benzoquinone, $PhI(OAc)_2$, benzoyl peroxide, *t*BuOO*t*Bu, and $Cu(OAc)_2$, silver carbonate gave significantly higher yield by suppressing the formation of alkynyl CF_3 side product **5** (Table 1, entry 2). Interestingly, Et_3N alone was sufficient as an activator for $TMSCF_3$ avoiding the use of expensive and hygroscopic KF (Table 1, entry 3).[15] Increasing the equivalents of $TMSCF_3$ from 2.0 to 5.0 equiv also improved the yield. The requirement of Et_3N was important (Table 1, entry 4), and other bases (DIPEA, pyridine, KO*t*Bu, K_2CO_3) were found to be less effective. Various copper sources were screened and showed inferior catalytic activities compared to CuI (Table 1, entries 5–10, versus entry 3). The yield decreased without added ligand, and ligands such as tetramethylethylenediamine (TMEDA) and 2,2′-bipyridine (bpy) were not as effective as phen (Table 1, entries 11–14, versus entry 3). The yield was somewhat improved by adding $TMSCF_3$ at 0 °C and then warming the reaction to room temperature, possibly due to a slower decomposition of $TMSCF_3$ (Table 1, entry 15).[14a,b] Finally, we were able to lower the catalyst loading to 10 mol % CuI by increasing the concentration and isolated 67% of the desired 5-trifluoromethyl 1,2,3-triazole **3a** (Table 1, entry 16).

The scope of the reaction was investigated under the optimized conditions (Scheme 3). In one step, 24 fully substituted 5-

Scheme 3. Scope of 5-Trifluoromethyl 1,2,3-Triazoles[a]



[a]Isolated yields, 0.2 mmol of **1**. [b]Used CuI (20 mol %) and phen (22 mol %). [c]Used 0.3 mmol of alkyne **1p**.

trifluoromethyl 1,2,3-triazoles **3** were synthesized by the click reaction from easily accessible terminal alkynes **1** and azides **2**. The reaction exhibited great functional group tolerance for both alkyne and azide substituents. Electron-rich (**3e,q**) and -poor (**3g–k, r–u**) substituent groups were tolerated. Besides the *para*-substituted benzenes, substituents at *meta* (**3c–d,f**) and *ortho* (**3k,t**) positions were also compatible. Sensitive groups such as

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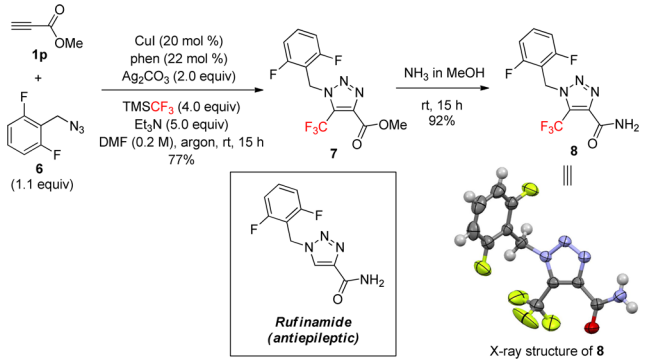
chloride (**3l,v**), bromide (**3m,w**), ester (**3g,p**), and ketone (**3h**), which were known to react with $TMSCF_3$,[14b,15] remained intact in the reactions. Naphthyl (**3n,x**), thienyl (**3o**), and furyl (**3y**) ring systems could also be present in the products. Compound **3p** containing a methyl ester group directly attached to the triazole core, which could be a useful functional handle for further transformations (*vide infra*), was obtained from the corresponding alkynyl ester **1p**. Some of the substrates required increased catalyst loadings to reach reasonable yields. It is worth-mentioning that alkyl substituents on the alkyne were not tolerated. Phenyl and tosyl azides were unreactive under the reaction conditions.

The utility of the reaction was demonstrated in an expedient synthesis of the 5-trifluoromethyl analog of rufinamide, a marketed drug for treating Lennox–Gastaut syndrome, a severe form of childhood epilepsy (Scheme 4).[16] Readily available alkyne

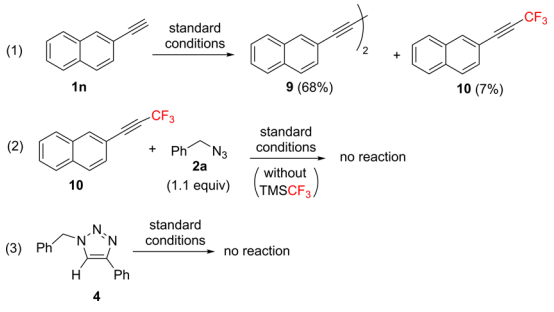
Scheme 4. Synthesis of the 5-Trifluoromethyl Analog of Antiepileptic Drug Rufinamide



1p and azide **6** reacted smoothly under the standard conditions to afford the trifluoromethylated triazole **7**. Further treatment with methanolic ammonia furnished the 5-trifluoromethyl analog **8**. The structure of **8** and the CF_3 group at the C-5 position were unambiguously confirmed by X-ray crystallography. This highly efficient (two steps, 71% overall yield) and regioselective (5-CF_3) synthetic route toward the rufinamide analog would be attractive to medicinal chemists in drug development.[13b,c]

To gain mechanistic insights, control experiments were performed (Scheme 5). Under standard conditions (cf. Scheme 3) without the azide, terminal alkyne **1n** underwent a competing dimerization pathway to afford mainly diyne **9** and a small amount of alkynyl CF_3 product **10** (Scheme 5, eq 1).[14c] Independently prepared **10** did not react with azide **2a** therefore ruling out the participation of internal alkynes in the click reaction (Scheme 5, eq 2). Finally, protonated triazole **4** was unreactive under the

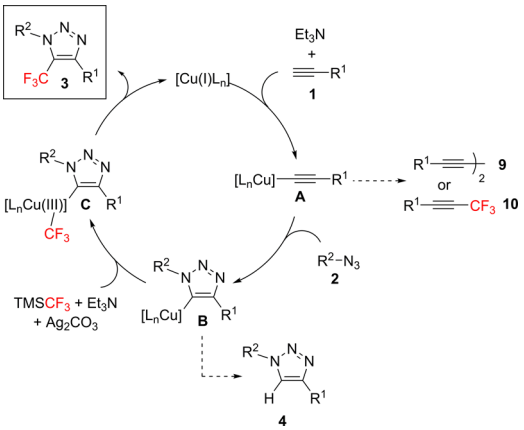
Scheme 5. Control Experiments



standard conditions suggesting that C–H trifluoromethylation of **4** did not take place to form the desired product **3**.

Based on these studies and known literature examples,[9c,f,i,j] we propose the following plausible catalytic cycle for the interrupted click reaction (Scheme 6). The copper(I) acetylide **A** is initially

Scheme 6. Proposed Catalytic Cycle



formed from terminal alkyne **1** with base Et_3N. Under oxidative conditions, intermediate **A** can undergo competitive pathways to form diyne **9** by homocoupling or the alkynyl CF_3 product **10** with $TMSCF_3$,[14c,d,g] the extent of which depends on the conditions. However, in the presence of azide **2**, the expected CuAAC pathway ensues, leading to the formation of 5-cuprated 1,2,3-triazole **B** regioselectively.[2a,5a] Protonolysis of **B** would give rise to triazole **4** as an unproductive side reaction. Alternatively, intermediate **B** can be intercepted by CF_3^-, generated from $TMSCF_3$ and an activator Et_3N, to form the trifluoromethylated copper species **C**. The exact nature of **C** is unclear at the moment; however, in the presence of an oxidant Ag_2CO_3, a copper(III) species is likely to be involved. Evidence exists for the formation of $[Cu(III)(CF_3)_4]^-$ from CuCl and $TMSCF_3$ under oxidative conditions.[17] The phen ligand plays the role of stabilizing $[Cu(III)CF_3]$ by chelation and donating electron density to the copper center.[14c] The use of nucleophilic $TMSCF_3$ is crucial in intercepting **B**; other CF_3 sources such as electrophilic 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (Togni reagent II)[18a] or radical $NaSO_2CF_3$ (Langlois reagent)[18b] were unreactive. Finally, reductive elimination releases product **3** and regenerates the copper(I) catalyst.

In conclusion, we have developed a new protocol for synthesizing fully substituted 5-trifluoromethyl 1,2,3-triazoles regioselectively from simple materials in one step. The reaction relies on intercepting the CuAAC cycle with $TMSCF_3$ as a nucleophilic CF_3 source. The broad reaction scope and applications toward drug analog synthesis should be appealing to industrial chemists in exploring the potential of such types of fluorinated triazoles. Further development of interrupted click reactions using other fluorinating and perfluoroalkylating reagents are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01116.

Crystallographic data for **8** (CIF)
Experimental procedures; spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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