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Efficient Synthesis of 1-Sulfonyl-1,2,3-triazoles

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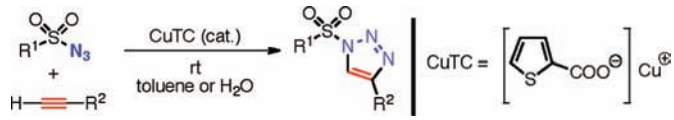
ABSTRACT



An efficient room-temperature method for the synthesis of 1-sulfonyl-1,2,3-triazoles from in situ generated copper(I) acetylides and sulfonyl azides is described. The copper(I) thiophene-2-carboxylate (CuTC) catalyst produces the title compounds under both nonbasic anhydrous and aqueous conditions in good yields.

As latent diazo compounds, 1-sulfonyl-1,2,3-triazoles serve as convenient progenitors of reactive azavinyl carbenes.[1] These electron-deficient heterocycles stand out as an important exception in the family of generally stable and unreactive 1,2,3-triazoles: the weakened N1−N2 bond in 1-sulfonyl derivatives facilitates their ring−chain isomerism, which leads to the formation of diazoimines and subsequent decomposition to the transition metal stabilized carbenes.

Copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC)[2] could well be the most direct and practical route to 1-sulfonyl-1,2,3-triazoles. High fidelity, efficiency, and compatibility with a broad range of functional groups and conditions have made it a widely utilized method for the synthesis of small molecules, bioconjugates, and complex molecular architectures.[3] However, the outcome of the CuAAC reaction of electron-deficient azides is affected by a wide variety of factors. Mirroring the well-known Dimroth rearrangement,[4−6] reaction medium,[7] temperature,[8] triazole ring substituents,[9,10] and ligand choice[11,12] all influence the outcome of the reaction (Scheme 1). Judicious choice of reaction conditions currently enables isolation of either *N*-acyl sulfonamides **7**[7] or 1-sulfonyl triazoles **4**. Although several recent reports have described syntheses of 1-sulfonyl triazoles,[8,12] none offer the level of generality and simplicity required for wide adoption. In search of a practical, simple, and robust synthesis of sulfonyl triazoles, we examined effects of various ligands on the outcome of the CuAAC reaction of sulfonyl azides. This communication reports our findings.

In general, ligands that exhibit the most dramatic effect on the course of the reaction contain nitrogen heterocycles, (e.g., tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA)

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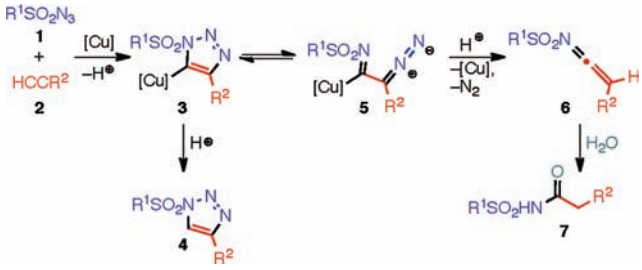
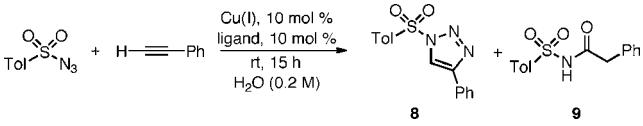
Scheme 1. Proposed Intermediates in the Copper(I)-Catalyzed Reaction of Alkynes and Sulfonyl Azides



or 2,6-lutidine).[8,11] However, as a "borderline soft" Lewis acid, copper(I) also partners well with sulfur ligands, for example, methionine in copper transport proteins and copper-containing enzymes.[13] Herein, we report that copper(I) thiophene-2-carboxylate (Liebeskind's reagent)[14] is a convenient, bench-stable catalyst for the synthesis of 1-sulfonyl-1,2,3-triazoles effective at ambient temperature both under anhydrous conditions and as a heterogeneous suspension in water.

Table 1. 1-Sulfonyl Triazole Synthesis: Effect of Copper(I) Source and Sulfur Ligand



entry	copper(I) source	ligand	PhCCH consumed (%)[a]	ratio **8**:**9**[a]
1	$CuSO_4$/NaAsc[b]	–	89[c]	6:1
2	CuBr	*t*-Bu_2S	40	10:1
3	CuBr	BnSPh	43	12:1
4	CuBr	thiophene	37	14:1
5	CuBr	thiolane	85	2:1
6	CuBr	Bn_2S	44	3:1
7	CuBr	Met	23	1:1
8	Cu_2O	*t*-Bu_2S	13	1:1
9	$CuSO_4$/NaAsc	*t*-Bu_2S	85[c]	13:1
10	$CuPF_6$·$(MeCN)_4$	*t*-Bu_2S	86[c]	13:1
11	CuSCN	–	17	2:1
12	CuBr·SMe_2	–	32	2:1
13	**CuTC**[d]	–	**95**[c]	**>100:1**

[a] As determined by LC/MS analysis; see Supporting Information for details. [b] NaAsc = sodium ascorbate. [c] TsN_3 undetected by LC/MS. [d] CuTC = copper(I) thiophene-2-carboxylate. Tol = tolyl.

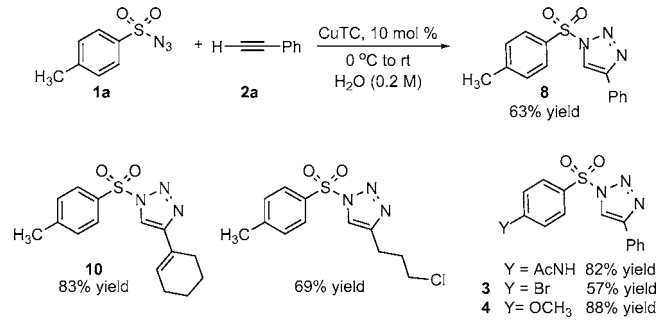
A variety of sulfur σ-donating ligands (Table 1) were screened under heterogeneous aqueous conditions for their ability to effect selective formation of the 1-sulfonyl triazole **8** over *N*-acyl sulfonamide **9** (presumably formed via a highly reactive *N*-sulfonyl ketenimine intermediate such as **6**). All results were compared to the $CuSO_4$/sodium ascorbate system (entry 1), which generates and maintains copper in its +1 oxidation state in situ.[2b]

Relative to the control reaction (entry 1), *tert*-butyl sulfide, benzyl phenyl sulfide, and thiophene (entries 2−4) in conjunction with CuBr showed improved selectivity for triazole **8** at the expense of conversion. In contrast, thiolane (entry 5) exhibited high conversion with diminished selectivity. Addition of *tert*-butyl sulfide to the $CuSO_4$/sodium ascorbate system (entry 9) resulted in an improved ratio and maintained high conversion. Attempts to achieve high conversion and selectivity by screening different copper(I) sources in the presence of *tert*-butyl sulfide were modestly successful (entries 9 and 10). Finally, screening other sulfur-containing copper(I) complexes (entries 11−13) led to the identification of copper(I) thiophene-2-carboxylate (CuTC, entry 13), which dramatically influenced the course of the reaction. Conversion remained high, as seen in entries 1, 9, and 10, yet no *N*-acyl sulfonamide **9** was detected by LC/MS—resulting in *exclusive selectivity* under heterogeneous aqueous conditions.

Examination of a panel of solvents (see Supporting Information) for the CuTC-catalyzed 1-sulfonyl triazole synthesis identified water and toluene as optimal solvents, with both leading to complete reactions in 2 h. Interestingly, traditional CuAAC mixed cosolvent conditions (2:1 *tert*-butyl alcohol:H_2O) resulted in both poorer conversions and selectivity. Acetonitrile, a strongly coordinating solvent for copper(I), entirely suppressed product formation, while dichloromethane and chloroform led to complete conversion after 5 h. At lower catalyst loadings (2 mol %), complete conversion and selectivity were achieved in 15 h, attesting to the stability of the catalyst.

A variety of 1-sulfonyl triazoles were synthesized (Scheme 2) using water as the solvent.[16] Despite cooling in an ice water bath, an observed exotherm, most pronounced in the presence of excess sulfonyl azide, prompted a change to toluene as the solvent of choice.

Scheme 2. Synthesis of 1-Sulfonyl-1,2,3-triazoles in Water[a]



[a] 1.0 mmol scale: CuTC (10 mol %), H_2O (0.2 M), alkyne (1−1.3 equiv), azide (1 equiv), 0 °C to rt, 2−18 h.

The general procedure[15] for the synthesis of 1-sulfonyl triazoles results in good isolated yields over a range of alkynes with tosyl azide (Table 2). Both aryl alkynes (entry

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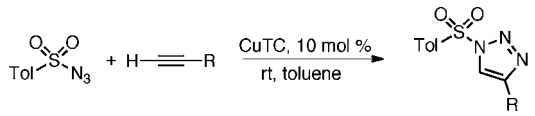
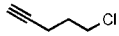
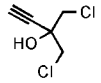
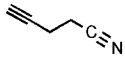
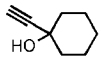
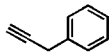
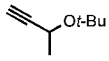
Table 2. 1-Sulfonyl Triazole Synthesis: Scope with Respect to Alkyne[a]

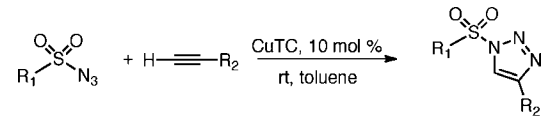


8, 10, 11, 15–22

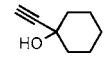
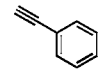
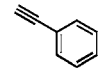
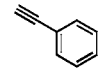
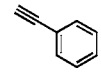
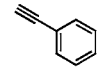
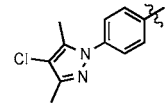
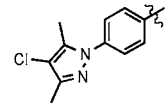
entry	alkyne	product	time (h)	yield (%)[b]
1[c]		**8**	3.5	89
2[d]		**10**	7	64
3[c]		**11**	1	75
4		**15**	2.5	75
5		**16**	3.5	65
6		**17**	4	75
7		**18**	2	83
8[e]		**19**	3	75
9[f]		**20**	1	82
10[e]		**21**	2.5	71
11[g]		**22**	7	75

[a] 1.0 mmol scale unless otherwise noted; CuTC (10 mol %), toluene (0.2 M), alkyne (1 equiv), tosyl azide (1 equiv), rt. [b] Isolated yield. [c] 5.0 mmol scale. [d] 1.1 equiv of alkyne. [e] 1.3 equiv of alkyne. [f] 2.4 equiv of alkyne. [g] 1.2 equiv of alkyne.

Table 3. 1-Sulfonyl Triazole Synthesis: Scope with Respect to Sulfonyl Azide[a]



13, 14, 23–31

entry	R^1	alkyne	product	time (h)	yield (%)[b]
1[c]	4-BrC_6H_4		**13**	3	86
2	4-BrC_6H_4		**23**	4.5	78
3[d]	4-$H_3COC_6H_4$		**14**	6.5	94
4	4-$H_3COC_6H_4$		**24**	7	79
5	Bn		**25**	3.5	87
6[e]	Me		**26**	12	88
7[e]	*i*-Pr		**27**	12	75
8	*n*-C_8H_{17}		**28**	3.5	92
9[f]			**29**	8.5	90
10[g]			**30**	3	82
11[g]			**31**	3	83

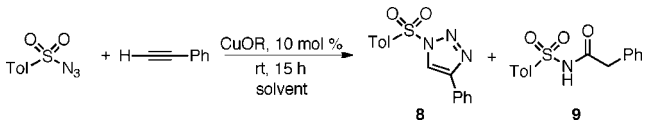
[a] 1.0 mmol scale unless otherwise noted; CuTC (10 mol %), solvent (0.2 M), alkyne (1 equiv), sulfonyl azide (1 equiv), rt. [b] Isolated yield. [c] 1.1 equiv of alkyne. [d] 5.0 mmol scale. [e] 10.0 mmol scale. [f] 1.5 equiv of alkyne. [g] 0.16 mmol scale.

1) and aliphatic alkynes (entries 2−10) are competent substrates, as well as the strongly electron-donating ethyl ethynyl ether (entry 11). The products were isolated via extraction into ethyl acetate and removal of residual copper by treatment with the Cuprisorb resin.[16]

In addition, the general procedure can be applied to a variety of alkyl- and arylsulfonyl azides and alkynes (Table 3).

Further experiments were designed to gain insight into the reactivity of CuTC catalyst. A comparison of three different copper(I) carboxylates (Table 4) revealed decreased conversion and selectivity in aqueous suspensions (entries 2−4). Although selectivity remained high for CuOAc (entry 2) and CuOTf (entry 3) in toluene, conversions were low even after 15 h, requiring days to reach completion at room temperature. In stark contrast, the CuTC-catalyzed reaction (entry 1) reached completion both in toluene and under heterogeneous aqueous conditions in 2 h. The furan analogue of CuTC (CuFC, entry 4) benefits from the same intramolecular arrangement of σ-donors as CuTC and as such performed comparably to CuTC in toluene, despite a small decrease in selectivity under aqueous conditions. Interestingly, the addition of thiophene to CuOAc (entry 5) resulted in little improvement in toluene compared to CuOAc alone (entry 2) and lowered both the selectivity and conversion in an aqueous suspension to that of thiophene and CuBr (Table 1, entry 4).

Table 4. 1-Sulfonyl Triazole Synthesis: Scope with Respect to Copper(I) Carboxylate



		ratio **8**:**9**[a] (PhCCH consumed (%[a]))	
entry	CuOR	toluene	water
1	CuTC	>100:1 (98)[b,c]	>100:1 (95)[b,c]
2	CuOAc	>100:1 (40)	26:1 (88)[b]
3	CuOTf	>100:1 (17)	5:1 (27)
4	CuFC[d]	>100:1 (>99)	31:1 (93)[b]
5	CuOAc[e]	>100:1 (55)	13:1 (32)

[a] As determined by LC/MS; see Supporting Information for details. [b] TsN_3 undetected by LC/MS. [c] 2 h. [d] CuFC = copper(I)-furan-2-carboxylate. [e] With the addition of thiophene (10 mol %).

CuAAC catalysis is complex and involves multiple dynamic equilibria between copper acetylide species of different coordination geometry, aggregation state, and ligand environment.[17] Controlling these equilibria is of paramount importance for channeling the catalysis in the desired direction. Reactions of sulfonyl azides are further complicated by the instability of (1,2,3-triazol-5-yl)copper species **3** (or its open chain isomer **5**; the opening of the triazole ring is, of course, not sufficient for the formation of ketenimine **6**). Therefore, when synthesis of triazole **4** is the goal, a successful catalyst should (a) stabilize intermediate **3**, thereby disfavoring its irreversible conversion to the ketenimine **6** (a thermodynamic consideration), and/or (b) facilitate the protiolysis step, thus favoring formation of the desired triazole product (a kinetic consideration). We hypothesize that CuTC excels at both. It stabilizes the triazolyl intermediate **3** and its open chain isomer **5**, disfavoring the extrusion of dintrogen. If this irreversible formation of ketenimine **6** does not occur, formation of 5-*H* triazole product **4** would be favored.

Notably, other copper(I) complexes, such as $CuBr{\cdot}SMe_2$ required the addition of 2,6-lutidine in order for the reaction to proceed in toluene.[18] This observation supports our hypothesis that the carboxylate group of CuTC acts as a base in toluene, and may do so in water, forming 2-thiophene carboxylic acid upon the deprotonation of the alkyne. Assuming that the acid remains coordinated to copper throughout the catalytic cycle, the protiolysis step (**3** to **4** in Scheme 1) becomes intramolecular and therefore facile and fast.

The data presented in Table 4 indicate that the intramolecular presentation of sulfur, the five-membered aromatic heterocycle, and a carboxylate are all necessary to achieve both selectivity and rapid conversion. Nevertheless, contributions from the varying solubility of different copper(I) sources and ligands cannot currently be ruled out.

The disclosed method offers an efficient and broad-in-scope means of accessing 1-sulfonyl-1,2,3-triazoles. The procedure is experimentally simple and allows rapid access to these important intermediates, paving the way for future studies of their reactivity and utility as well as for probing the mechanism of the parent CuAAC reaction. These studies are underway and their results will be reported elsewhere.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) CAUTION! The reaction is exothermic, and can be accompanied by dinitrogen release. It should not be performed in a closed vessel, and adequate cooling should always be available. Procedure A: A scintillation vial was charged with copper(I) thiophene-2-carboxylate (CuTC, 0.019 g, 0.1 mmol, 0.1 equiv with respect to alkyne) and water (5 mL) and cooled in an ice-water bath. Subsequently, phenylacetylene (0.110 mL, 1.0 mmol, 1 equiv) then tosyl azide (0.155 mL, 1.0 mmol, 1 equiv) were added and the reaction mixture allowed to warm to room temperature for 2 h. The reaction mixture was diluted with saturated aq NH_4Cl (5 mL) and extracted into EtOAc (2 × 5 mL). The combined organics were dried (Na_2SO_4) and filtered through celite. The eluent was concentrated in vacuo. To remove copper, the concentrate was redissolved in $CHCl_3$ and charged with Cuprisorb resin. The mixture was stirred, filtered through celite and concentrated in vacuo. Pulverizing the crude material in cold cyclohexane and collection by filtration afforded **8** (0.188 g, 63% yield) as an off-white powder. Procedure B: A 125-mL Erlenmyer flask was charged with CuTC (0.191 g, 1.0 mmol) and dry toluene (50 mL). Subsequently, phenylacetylene (1.10 mL, 1.02 g, 10.0 mmol) then tosyl azide (1.55 mL, 10.0 mmol) were added, and the reaction mixture was allowed to stir for 2 h. It was then diluted with saturated aq NH_4Cl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. To remove copper the concentrate was redissolved in $CHCl_3$ and charged with Cuprisorb resin. The mixture was stirred, filtered through celite and concentrated in vacuo. Pulverizing the crude material in cold cyclohexane and collection by filtration afforded **8** (2.67 g, 89% yield) as a white powder: mp 105.2−107.0 °C (lit. 107−108 °C); R_f = 0.44 (silica gel, hexanes:EtOAc 7:3); ν_{max}(HATR)/cm^{-1} 3142, 1386 (SO_2), 1197, 1170 (SO_2), 988; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.37 (m, 3H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.3, 133.0, 130.4, 129.1, 129.0, 128.8, 128.7, 126.0, 118.9, 21.8. Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 59.84; H, 4.47; N, 13.87.

(16) Local dealer information is available at http://www.seachem.com.

(17) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.

(18) Despite attempts to exclude moisture, the formation of *N*-acylsulfonamide was always observed under these conditions.