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# Copper-Catalyzed Cycloaddition of Sulfonyl Azides with Alkynes to Synthesize *N*-Sulfonyltriazoles 'on Water' at Room Temperature

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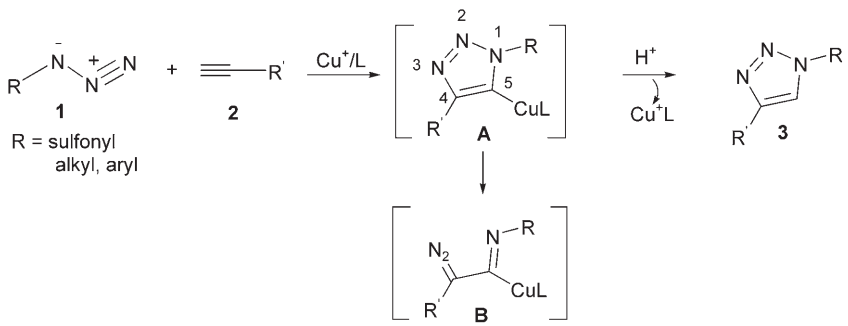
**Abstract:** We have developed a green and practical method for the Huisgen cycloaddition of water-insoluble sulfonyl azides with alkynes 'on water' at room temperature under catalysis of the inexpensive catalyst system CuX/PhSMe, and addition of the ligand (thioanisole) greatly inhibited cleavage of the $N^1$–$N^2$ bond in the 5-cuprated *N*-sulfonyltriazole intermediates to amides and improved the yields of *N*-sulfonyltriazoles.

**Keywords:** copper-catalyzed reaction; on water; S ligands; sulfonyl azides; *N*-sulfonyltriazoles

## Introduction

Compounds containing triazole building blocks find various applications in both materials science and drug discovery because of the stability of triazole part in strongly acidic and basic media, as well as towards oxidizing and reducing conditions.[1] The Huisgen [3+2]cycloaddition,[2] especially the copper-catalyzed cycloaddition of azides and alkynes,[3,4] offers an almost unlimited array of inert triazole-containing architectures. As shown in Scheme 1, the copper-catalyzed coupling reaction of azides with alkynes firstly produces 5-cuprated *N*-substituted triazole intermediates (**A**) whose stability is governed by various factors including the type of azides and alkynes, reaction medium, temperature and so on.[5–7] Among them, the type of azides is especially important.[8] When R is alkyl or aryl, the $N^1$–$N^2$ bond is stable, and the corresponding 1,2,3-triazoles are easily obtained. However, when R is a strong electron-withdrawing group (such as sulfonyl), the electron density on the $N^1$ atom of the intermediate **A** is low, and the $N^1$–$N^2$ bond is readily cleaved. For example, the copper-catalyzed three-component coupling of sulfonyl azides, alkynes with amines, alcohols or water produced amidines, imidates, or amides, respectively, because of cleavage of the $N^1$–$N^2$ bond.[9] Very recently, Fokin and Chang have cooperatively developed a useful copper-cata-



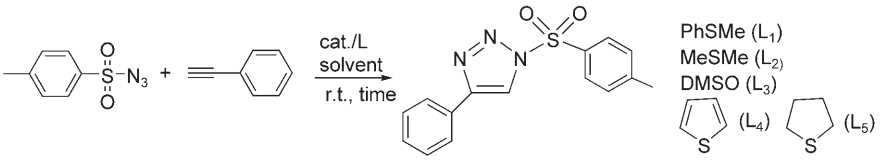

**Scheme 1.** Possible copper-catalyzed cycloaddition of azides with alkynes and opening process of triazoles[8].

lyzed approach to *N*-sulfonyltriazoles, but the reactions were carried out in anhydrous chloroform, and a lower temperature (0 °C) was required.[8] Herein, we report a simple, inexpensive and highly efficient catalyst system, CuBr/PhSMe, for cycloadditions of water-insoluble sulfonyl azides with alkynes 'on water' at room temperature.

## Results and Discussion

Since the type of ligand in intermediates **A** in Scheme 1 can affect the distribution of electron density on the copper, $C^5$ and $N^1$ atoms, the addition of an electron-rich ligand increases the electron density at copper and $N^1$ and decreases the binding energy of the $C^5$–Cu bond, which improves the stability of the $N^1$–$N^2$ bond and desorption of CuL from **A**. In addition, the solvent also affects this dissociative process, and the protonic solvents are usually favored. Therefore, we initialized the copper-catalyzed optimum conditions for coupling of sulfonyl azides with alkynes. Because compounds containing sulfur (such as MeSMe) are efficient ligands in the copper-catalyzed cross-coupling reactions,[10] addition of a ligand containing sulfur can be a good choice. Very recently, we found that thioanisole could greatly promote the copper-catalyzed cycloaddition of aliphatic or aryl azides with alkynes.[11] Chang and co-workers found that the copper-catalyzed three-component reaction of terminal alkynes, sulfonyl azides in the presence of water produced amides.[9b] Herein, we want to find out whether thioanisole can inhibit the hydrolysis of the 5-cuprated *N*-sulfonyltriazole intermediates to amides and promote the formation of *N*-sulfonyltriazoles in aqueous medium. As shown in Table 1, thioanisole was firstly used as the ligand with CuBr in the cycloaddition of *p*-toluenesulfonyl azide with phenylacetylene in water as medium; a good yield (88%) was obtained in the presence of 10 mol% CuBr and 20 mol% thioanisole (relative to sulfonyl azide) for 12 h (entry 1) (***caution:*** *p-toluenesulfonyl azide and phenylacetylene are insoluble in water*). Other organic solvents (*tert*-butanol, $CHCl_3$, $CH_3CN$ and *tert*-butanol/$H_2O$ mixed solvent) were also investigated, and they provided lower yields than water (entries 2–5). When the reaction time was prolonged to 16 h in water, the yield increased to 92%. Reaction efficiency greatly improved when the amounts of CuBr and ligand were increased (entry 7). Other copper salts (CuI, CuCl, $CuSO_4$) were tested in the presence of thioanisole (entries 8–10), and copper (I) salts showed higher activity. No *N*-sulfonyltriazole was found in the absence of copper catalyst (entry 11). The effect of ligands was also investigated, various compounds containing sulfur (dimethyl sulfide, thiophene, tetrahydrothiophene and dimethyl sulfoxide) were evaluated (entries 12–15 in Table 1), but they are inferior to thio-

**Table 1.** Copper-catalyzed cycloaddition of *p*-toluenesulfonyl azide with phenylacetylene: optimization of conditions.[a]

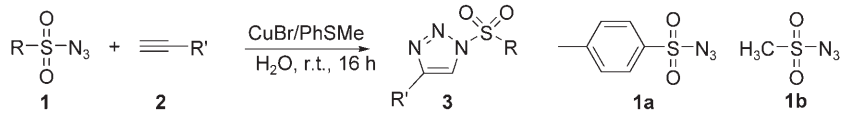



| Entry | Catalyst/Ligand | Solvent | Time | Yield [%][b] |
|---|---|---|---|---|
| 1 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | $H_2O$ | 12 h | 88 |
| 2 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | *t*-BuOH | 12 h | 22 |
| 3 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | $CHCl_3$ | 12 h | 6 |
| 4 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | $CH_3CN$ | 12 h | 24 |
| 5 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | *t*-BuOH/$H_2O$ (2:1) | 12 h | 61 |
| 6 | 0.1 equiv. CuBr/0.2 equiv. $L_1$ | $H_2O$ | 16 h | 92 |
| 7 | 0.2 equiv. CuBr/0.4 equiv. $L_1$ | $H_2O$ | 2 h | 94 |
| 8 | 0.1 equiv. CuI/0.2 equiv. $L_1$ | $H_2O$ | 12 h | 34 |
| 9 | 0.1 equiv. CuCl/0.2 equiv. $L_1$ | $H_2O$ | 12 h | 62 |
| 10 | 0.1 equiv. $CuSO_4$/0.2 equiv. $L_1$ | $H_2O$ | 12 h | 0 |
| 11 | 0.2 equiv. $L_1$ | $H_2O$ | 12 h | 0 |
| 12 | 0.1 equiv. CuBr/0.2 equiv. $L_2$ | $H_2O$ | 12 h | 50 |
| 13 | 0.1 equiv. CuBr/0.2 equiv. $L_3$ | $H_2O$ | 12 h | 36 |
| 14 | 0.1 equiv. CuBr/0.2 equiv. $L_4$ | $H_2O$ | 12 h | 32 |
| 15 | 0.1 equiv. CuBr/0.2 equiv. $L_5$ | $H_2O$ | 12 h | 63 |
| 16 | 0.1 equiv. CuBr | $H_2O$ | 12 h | 3 |

[a] *Reaction conditions: p*-toluenesulfonyl azide (0.5 mmol), phenylacetylene (0.6 mmol), solvent (0.5 mL).
[b] Conversion yield determined by $^1H$ NMR using 1,3-benzodioxole as the internal standard.

**Table 2.** Copper-catalyzed cycloaddition of sulfonyl azides with alkynes.[a]




1 2 3 1a 1b

| Entry | Alkyne | Product | Yield [%][b] |
|---|---|---|---|
| 1 | **2a** | **3a** | 90 |
| 2 | **2b** | **3b** | 86 |
| 3 | **2c** | **3c** | 61[c]; 88[d] |
| 4 | **2d** | **3d** | 84 |
| 5 | **2e** | **3e** | 90 |
| 6 | **2f** | **3f** | 87 |
| 7 | **2g** | **3g** | 90 |
| 8 | **2h** | **3h** | 85 |
| 9 | **2i** | **3i** | 92 |
| 10 | **2j** | **3j** | 86 |
| 11 | **2k** | **3k** | 45[c]; 80[d] |
| 12 | **2a** | **3l** | 91 |
| 13 | **2g** | **3m** | 94 |

[a] *Reaction conditions:* sulfonyl azide (0.5 mmol), alkyne (0.6 mmol), PhSMe (0.1 mmol), CuBr (0.05 mmol), $H_2O$ (0.5 mL).
[b] Isolated yield.
[c] Reaction time 30 h.
[d] Solid alkyne was previously dissolved in 1 mL of ethyl acetate, and then the resulting solution was added to the flask.

anisole. Only a trace amount of cycloaddition product was obserevd in the absence of ligand (entry 16). The experiments showed that the reaction was not influenced by oxygen in air.

Therefore, the copper-catalyzed cycloadditions of sulfonyl azides with alkynes were performed under our standard conditions: 10 mol% CuBr as the catalyst, 20 mol% thioanisole as the ligand relative to sulfonyl azide, water as the reaction medium at room temperature without exclusion of air. As shown in Table 2, the coupling reactions performed quite well for all the substrates examined, and the desired *N*-sulfonyltriazoles were obtained in excellent yields. We found that the reaction rates depended on the states (solid and liquid) of the substrates. The liquid substrates showed higher reaction rates, while the reactions with the solid substrates were slower. For example, reactions of the solid alkynes **2c** and **2k** with sulfonyl azides for 30 h provided the corresponding products in 61% and 45% yields, respectively. When **2c** or **2k** was previously dissolved in ethyl acetate, the resulting solution was added to the flask with water, and the coupling reaction was complete within 16 h (entries 3 and 11). The reactions of the hydrophobic and generally highly insoluble substrates in water were named as organic synthesis 'on water' by Sharpless.[12] In fact, water is not a good solvent for the substrates, but it shows excellent solubility for copper salts which is favorable for the coordination of copper(I) ion with alkyne and ligand, and the addition of water could improve the desorption of CuL from intermediates **A** in Scheme 1. Electronic variation in the alkynes and sulfonyl azides did not obviously affect the efficiency of the reactions, and the coupling reactions tolerated a variety of functional groups, such as hydroxy (entries 5 and 6) and amide (entry 11). Since some of *N*-sulfonyl heterocyclic compounds are bioactive molecules,[13] and the sulfonyl group can be easily removed with magnesium in methanol under mild conditions[14] to provide 4-substituted *N*-H-triazoles,[9] this method has potential for many practical applications.

## Conclusions

We have developed a highly efficient catalytic system (CuBr/PhSMe) for the Huisgen cycloaddition of sulfonyl azides with alkynes, and addition of the ligand (thioanisole) greatly inhibited cleavage of the $N^1$–$N^2$ bond in the 5-cuprated *N*-sulfonyl triazole intermediates to amides and improved the yields of *N*-sulfonyl triazoles. The method has the following advantages: (a) an inexpensive catalytic system; (b) high reaction yields; (c) high regioselectivity (only 1,4-triazole products); (d) water as the medium; (e) all the reactions were performed at room temperature without exclusion of air; (f) heterogeneous reactions are feasible; (g) outstanding functional group tolerance; (h) easy work-up procedure. All these results show that the method will be of wide practical applications in many research fields. Further synthetic applications of the catalyst system are currently ongoing in our laboratory.

## Experimental Section

### General Procedure for the Preparation of *N*-Sulfonyltriazoles 3a–m

Water (0.5 mL), alkyne (0.6 mmol) (solid alkynes **2c, 2k** or the solution of **2c, 2k** in 1 mL of ethyl acetate), *p*-toluenesulfonyl azide or methylsulfonyl azide (0.5 mmol), CuBr (0.05 mmol), anisole (0.1 mmol, 13 mg) were added to a flask with a stir bar, and the mixture was stirred at room temperature (~25 °C) without exclusion of air. After 16 h (30 h for solid alkynes **2c** and **2k**), most of the starting azides (determination by TLC) were consumed. The resulting solution was poured into water/ethyl acetate mixture. After extraction of the aqueous phase with ethyl acetate, the combined organic phase was dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation, and the crude product was isolated on a short silica gel column (using EtOAc/petroleum ether as eluent) to afford the pure triazole.

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