

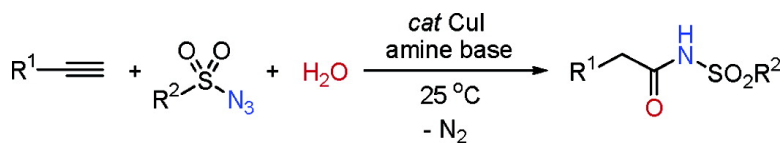
Communication

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 with Terminal Alkyne, Sulfonyl Azide, and Water**

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Copper-Catalyzed Hydrative Amide Synthesis with Terminal Alkyne, Sulfonyl Azide, and Water

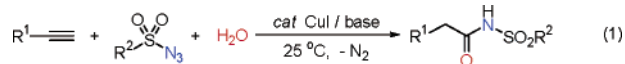
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The amide group is a key motif in chemistry and biology.¹ Although traditional chemical methods for simple amide synthesis rely heavily on an interconversion strategy between carbonyl groups or their equivalent reactive compounds,² lability of those functional groups often restricts its ubiquitous applications. Hence, the development of alternative routes has been challenging to synthetic chemists.³ As a result, the use of thio acids or thioesters as a carbonyl precursor has been actively investigated as a chemical ligation method.⁴ The modified Staudinger reaction of azides with phosphines has also drawn special attention to the chemoselective formation of amides.⁵ Separately, advances in the functionalization of multiple bonds enabled facile conversion of unsaturated hydrocarbons to the corresponding carbonyl compounds.⁶ Especially, the hydration of alkynes is regarded as one of the most promising reactions for this purpose, although the reactions proceed generally at high temperatures.⁷ In this context, catalytic carbonylation of alkynes with amines and CO of high pressure at high temperatures offers a route to the synthesis of homologated amides.⁸

Recently, we devised a highly efficient copper-catalyzed multi-component reaction (MCR), in which sulfonyl azides react with a wide range of alkynes and amines to give amidines.⁹ Whereas electron-rich azides react with 1-alkynes mainly leading to 1,4-triazoles using copper catalyst,¹⁰ the reactivity of sulfonyl azides varies significantly to result in a range of interesting amino group-containing compounds depending on the third coupling partners. In the course of our investigation on the mechanistic details of this MCR, we found that a trace amount of amide was generated ($\leq 5\%$) when aqueous cosolvent was used. This led us to delve into an optimized preparation of amides. Herein we present an interesting procedure for the amide synthesis based on the MCR employing water as one reacting species under very mild conditions (eq 1).



At the outset of our studies, we tried to optimize the reaction conditions for the selective formation of amides (Table 1).¹¹ When the reaction of phenylacetylene (**1a**) with *p*-toluenesulfonyl azide (**2a**) and water was tried with CuI in the absence of an external base, no conversion was observed.¹² In contrast, successful formation of *N*-sulfonyl amide **3a** was observed in chloroform when a tertiary amine base, such as Et₃N, was added. While a stoichiometric amount of triethylamine is required to achieve high efficiency (compare entries 2 and 3), the use of other bases results in significantly reduced yields (entries 4–6). Solvents other than chloroform afforded low yield (entry 7), and copper catalysts other than CuI exhibited reduced activities.

The present approach for amide synthesis turned out to be quite general, and a wide range of alkynes and sulfonyl azides underwent the coupling with water by the action of copper catalyst to furnish

Table 1. Hydrative Amide Synthesis under Various Conditions^a

entry	catalyst	base	solvent	yield (%) ^b
1	CuI		CHCl ₃	<1
2	CuI	Et ₃ N	CHCl ₃	95
3	CuI	Et ₃ N (0.2 equiv)	CHCl ₃	27
4	CuI	(<i>i</i> -Pr) ₂ N ⁺ Et	CHCl ₃	47
5	CuI	pyridine	CHCl ₃	35
6	CuI	K ₂ CO ₃	CHCl ₃	<1
7	CuI	Et ₃ N	THF	30
8	CuBr·SMe ₂	Et ₃ N	CHCl ₃	67

^a Phenylacetylene (0.5 mmol), *p*-toluenesulfonyl azide (1.2 equiv), base (1.2 equiv except entry 3), water (2.5 equiv), and catalyst (0.1 equiv) in solvent (1.0 mL). ^b Based on the integration of ¹H NMR signals using *p*-anisole as an internal standard.

the corresponding *N*-sulfonyl amides in high yields (Table 2). Reactions with both aromatic and aliphatic 1-alkynes were efficient and not influenced by the electronic and steric variations of the reacting substrates. A variety of labile functional groups, such as heterocyclic (entry 6), halide (entry 7), acetate (entry 8), silyloxy (entry 9), propargylic ether (entry 10), conjugated olefin (entry 11), and ester moiety (entry 12), were fully tolerated under the conditions. Intriguingly, in the case of propargylic ether (entry 10), the use of 2,6-lutidine resulted in much higher product yield than Et₃N (34%). It should be mentioned that the reaction is regioselective: only terminal alkynes react, while olefin and internal triple bonds (entries 12 and 13, respectively) are intact.

In addition to aryl sulfonyl azides, aliphatic variants work equally well. For instance, sulfonyl azides of phenylmethane, butane, and 2-trimethylsilylethane took part in the reaction to afford the corresponding *N*-sulfonyl amides in high yields (entries 14–16).¹³ Moreover, *N*-camphorsulfonyl amide **3q** was obtained in good yield under the same conditions (entry 17).

The present approach to amide synthesis was readily amenable to the solid-phase procedure (eq 2).¹⁴ A terminal alkyne (**1r**) attached onto a 2-chlorotrityl resin was readily converted to the corresponding supported *N*-sulfonyl amide under the similar conditions, although the reagents were used in large excess compared to solution-phase cases.¹⁵

After cleaving the resin using CF₃CO₂H, a derivative of hydroxy sulfonamide (**3r**) was isolated in 46% overall yield from three steps, indicating that each step proceeds in 77% on average.¹⁶

