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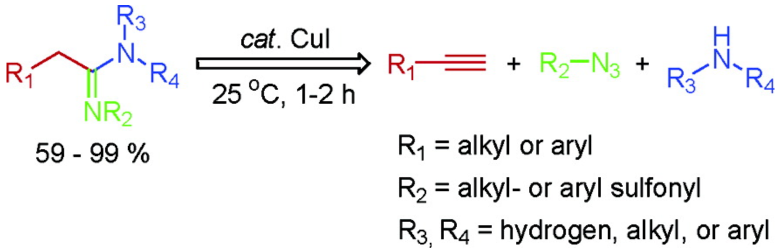

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Highly Efficient One-Pot Synthesis of *N*-Sulfonylamidines by Cu-Catalyzed Three-Component Coupling of Sulfonyl Azide, Alkyne, and Amine

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A multicomponent reaction (MCR), offering a straightforward route to generate complexity and diversity in a single operation, is an extremely powerful tool in combinatorial chemistry and drug discovery.[1] However, only a few highly useful MCRs are available for applications,[2] and rapid advances in this area lead to searches for new types of target molecules. Amidines could be well-fitted for these criteria since they are prominent structural motifs in numerous bioactive natural products.[3] Furthermore, they serve as important pharmacophores, synthetic intermediates, and efficient coordinating ligands.[4] Whereas traditional syntheses of amidines largely rely on the simple functional group transformation from some precursors such as (thio)amides,[5] (iso)nitriles,[6] or (ald)oximes,[7] only a few reports have adopted one-pot MCR approaches, albeit with limited scope and generality.[8] Herein, we describe a new type of three-component synthesis of *N*-sulfonylamidines and preliminary mechanistic discussion of the reaction.

In the context of our studies aimed for the development of efficient catalytic nitrogen transfer,[9] we have focused on the utility of sulfonyl azides. When *p*-toluenesulfonyl azide and phenylacetylene were treated with diisopropylamine, an amidine was unexpectedly produced in high yields by the action of copper catalysts (Scheme 1). This result contrasts significantly with the click chemistry,[10] wherein reactions of alkyl(aryl) azides with alkynes furnish mainly 1,4-triazoles. We assumed that this difference is originated from the entirely dissimilar reactivity between sulfonyl- and alkyl(aryl) azides toward Cu-acetylides (vide infra). While no reaction took place in the absence of a Cu catalyst, a number of Cu sources were tested to reveal that certain species including CuI, CuCl, CuBr•SMe$_2$, CuOAc, and Cu(acac)$_2$ were almost equally effective in the coupling. Among them, CuI was chosen herein as a catalyst for practical reasons. Although 10 mol % of CuI was used, reduced loading of the catalyst was also acceptable to get a complete conversion, albeit with a longer time; for example, 30 min with 10 mol % CuI versus 8−12 h with 1 mol % for >99% conversion at ambient temperature in THF. Among various solvents examined, THF, 1,4-dioxane, or CH_2Cl_2 turned out to be the best, whereas use of nonpolar solvents such as toluene and hexane resulted in more sluggish conversion.

Under the optimized conditions, a wide range of three components were successfully coupled to afford the corresponding *N*-sulfonylamidines (Table 1). The structure of amidine was unambiguously conformed by an X-ray crystallographic analysis, which discloses an *E*-form of the generated C=N double bond.[11]

Scheme 1

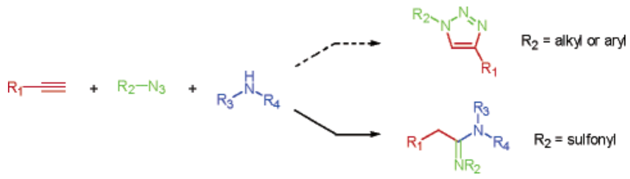
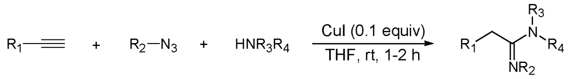
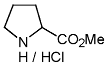
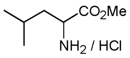


Table 1. Copper-Catalyzed Three-Component Coupling[a]



entry	R$_1$	R$_2$	amine	yield (%)[b]
1	Ph	4-$MeC_6H_4SO_2$	(i-Pr)$_2$NH	89
2	4-$CF_3C_6H_4$			99
3	4-MeC_6H_4			90
4	4-$PhOC_6H_4$			84
5	2-Pyridyl			66
6	3-Pyridyl			92
7	3-Thienyl			86
8	$CH_3(CH_2)_3$			90
9	t-Bu			79
10	$HOCH_2(CH_2)_2$			78
11	$ClCH_2(CH_2)_2$			91
12[c]	1,7-Octadiyne			92
13	Me_3Si			85
14	CO_2Et			94
15	1-Cyclohexenyl			90
16	CH_2=$CHCH_2C(CO_2Et)_2CH_2$			92
17	Ph	2-$C_5H_4NSO_2$	(i-Pr)$_2$NH	59[d]
18		$MeSO_2$		90
19		4-$MeC_6H_4SO_2$	$PhCH_2NH_2$	68
20			i-$PrNH_2$	75
21[e, f]			PhNHMe	91
22[e]			 CO_2Me H / HCl	70
23[e]			 CO_2Me NH_2 / HCl	95

[a] A mixture of alkyne (0.5 mmol), azide (0.6 mmol), amine (0.6 mmol), and CuI (0.05 mmol) in THF (1.0 mL) was stirred at room temperature for 1 h (aromatic alkynes) or 2 h (aliphatic acetylenes). [b] Isolated yield. [c] Diamidine product. [d] 1.0 equiv of azide was used. [e] Et_3N (1.2−1.5 equiv to alkyne) was added. [f] Run for 6 h.

Electronic variation on aryl acetylenes causes no appreciable change in the efficiency of the couplings (Table 1, entries 1−4). Heteroaromatic alkynes also served as high-yielding substrates (entries 5−7). While reactions of aliphatic alkynes were slightly slower compared to those of aryl acetylenes, the corresponding amidines were isolated still in high yields after 2 h (entries 8−12). It is noteworthy that a range of functional groups including halo-, free hydroxyl-, and silyl groups were completely tolerated. In addition, alkynes directly conjugated with carboxylate or double bond readily participated in the coupling to afford the desired products in excellent yields (entries 14 and 15). As demonstrated in entry 16, the reaction is completely chemoselective so that a double bond was intact under the reaction conditions.

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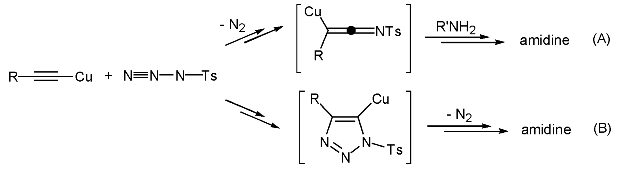
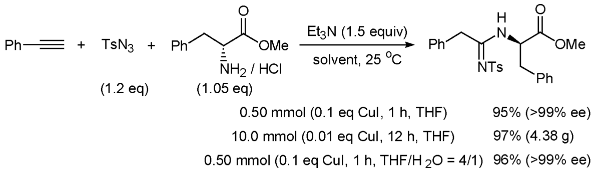
Scheme 2. Two Plausible Pathways in the Cu-Catalyzed Three-Component Coupling Reaction



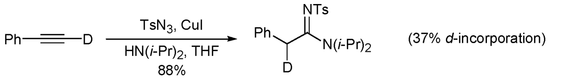
It was revealed that the azide component is not limited only to tosyl azide, but other types such as pyridine- and methanesulfonyl azide were also successfully utilized (Table 1, entries 17 and 18). The scope of the amine components appeared to be extremely broad, and an array of amines including primary, secondary, aliphatic, aryl, acyclic, and/or cyclic types were all efficiently coupled to furnish the corresponding amidines (entries 19−23). Amino esters were likewise incorporated with almost the same efficiency (entries 22 and 23).

Interestingly, reaction with an optically active amino ester was performed without racemization (eq 1). Moreover, it could be readily scaled up (10.0 mmol of alkyne) with the same efficiency (1 mol % of CuI, 97%, 4.4 g). It should be mentioned that the reaction proceeded smoothly even in an aqueous cosolvent system (THF/H_2O = 4/1). These results render further weight on our reaction and broaden its application to chiral compounds.

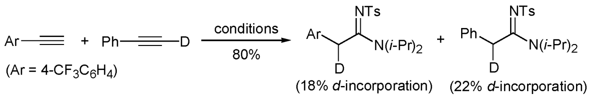


(1)

Reaction of phenylacetylene-*d* offered the desired amidine with *d*-incorporation at the benzylic position (eq 2), and a cross scrambling of deuterium was observed in a reaction employing two arylacetylene substrates (eq 3), suggesting that acetylenic proton does not migrate in a putative “closed” intramolecular manner.[12]



(2)



(3)

Because an immediate color change to yellow was observed upon addition of Cu-catalyst to the reaction mixture containing terminal alkynes, formation of Cu-acetylide is obviously regarded to take place in the first step. Although other possibilities still remain to envision,[13] a subsequent coupling reaction of Cu-acetylide with sulfonyl azide and amine may be assumed to proceed through one of the following intermediates (Scheme 2). The first putative intermediate would be a ketenimine species which is formed by a nucleophilic attack of Cu-acetylide to azide nitrogen followed by a rearrangement. This conversion may be accelerated by the concurrent release of an N_2 molecule. Amination across the C=N bond of the resulting ketenimine adduct and subsequent tautomerization may consist of the final steps in pathway (A).[14] However, more sophisticated examination on the involvement of this reactive intermediate is required in that the reaction also proceeds efficiently even in an aqueous system.

The second possible pathway (B) includes a triazole intermediate similar to the case of click chemistry. Recent DFT calculation has revealed that the stepwise formation of the Cu-triazole species is initiated by the attack of the proximal nitrogen to alkyl(aryl) group on Cu-acetylide.[15] More importantly, triazoles with an electron-withdrawing group such as tosyl at N1 are known to undergo the Dimroth rearrangement[16] via α-diazoimine species which can readily react with an amine leading to amidine moiety.[17] However, when sulfonyl azide was allowed to react in the presence of diisopropylamine under the Sharpless−Fokin conditions,[10] no triazole was observed in our experiments. Independent preparation of and subjecting both 1,4- and 1,5-triazoles[18] to the reaction system resulted in no changes of the heterocycles even after prolonged time presumably because the isolated triazoles are fairly stable under the employed conditions.

In conclusion, we have developed a highly efficient, mild, practical, and catalytic method for the synthesis of *N*-sulfonylamidines. This MCR has an extremely broad scope with all three coupling components of alkyne, sulfonyl azide, and amine. Further mechanistic details and applications, especially for the combinatorial purposes, are now under investigation.

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Supporting Information Available: Spectral data and copies of ^1H and ^{13}C NMR spectra for new compounds and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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