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N-Sulfonyl Amidine Synthesis via Three-Component Coupling Reaction Using Heterogeneous Copper Catalyst Derived from Metal-Organic Frameworks

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ABSTRACT

Three-component coupling reaction of terminal alkyne, sulfonyl azide, and amine for the synthesis of *N*-sulfonyl amidine was developed using heterogeneous Cu@C catalyst, which was generated by pyrolysis of HKUST-1 ($Cu_3(BTC)_2$, BTC = 1,3,5-benzenetricarboxylate). A variety of terminal alkynes, sulfonyl azides, and amines underwent three-component coupling in the presence of 5 mol % Cu@C. The used Cu@C catalyst was readily separated by centrifugation and could be reused at least three times with no loss of reactivity. Filtration experiments revealed that the developed Cu@C catalysis is basically heterogeneous.

Amidines are important and versatile functional groups in organic chemistry.[1] They have been widely utilized as building blocks in the synthesis of heterocycles[2] and biologically active compounds.[3] In addition, they also serve as ligands for transition metals due to their unique structure.[4] General methods for the synthesis of amidines depend on functional group transformations from precursors such as nitrile and aldoxime.[5] Recently, diverse methods for the construction of amidine have been developed by virtue of transition metal catalysis.

In 2005, Chang's group reported Cu-catalyzed three-component coupling reaction with terminal alkyne, sulfonyl azide, and amine for the synthesis of *N*-sulfonyl amidine.[6] The mechanism of the three-component coupling reaction looks like Cu-catalyzed regioselective cycloaddition for 1,4-disubstituted 1,2,3-triazole[7] at first glance, however, the electron withdrawing effect of sulfonyl group causes triazole ring opening to produce ketenimine intermediate upon releasing nitrogen gas.[8] Finally, nucleophilic addition of amine to the generated ketenimine intermediate produces *N*-sulfonyl amidine.[9] After Chang's pioneering contribution to the *N*-sulfonyl amidine synthesis, several synthetic methods for *N*-sulfonyl amidine using sulfonyl azide have been developed. Li and others observed that 1,3-dipolar cycloaddition of sulfonyl azides with vinyl amines, which was generated by oxidative dehydrogenation of tertiary amines, produced *N*-sulfonyl amidines.[10] And, Ashfeld utilized sulfonyl azides in a phophite-mediated Beckmann-type rearrangement for the synthesis of *N*-sulfonyl amidines.[11] In addition, some examples of amidine synthesis without sulfonyl azide have been reported. These examples are including a rearrangement of ynamide catalyzed by palladium,[12] a condensation of sulfonamide with formamide or DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal),[13] and an aerobic oxidative coupling.[14] However, Chang's Cu-catalyzed three-component coupling reaction[6] is still regarded as a practical and atom efficient reaction, because an inexpensive copper catalyst is required without any additives under mild conditions and a nitrogen gas is the sole byproduct.

Because heterogeneous catalysts have advantages of the practicality and reusability, we envisioned that the use of heterogeneous catalyst would make Cu-catalyzed three-component coupling reaction more attractive. To the best of our knowledge, however, only few examples of heterogeneous Cu-catalyzed three-component coupling for *N*-sulfonyl amidine were described.[15] Recently, Lee and our group developed heterogeneous Cu@C catalyst which was generated by pyrolysis of HKUST-1 ($Cu_3(BTC)_2$, BTC = 1,3,5-benzenetricarboxylate). The developed Cu@C catalyst showed good reactivity and reusability in the aerobic alcohol oxidation[16] and aerobic oxidative conversion of aldehydes to nitriles.[17] These interesting results of Cu@C prompted us to investigate the reactivity of Cu@C in the three-component coupling. Herein, we describe the synthesis of *N*-sulfonyl amidine through heterogeneous Cu@C-catalyzed three-component coupling.

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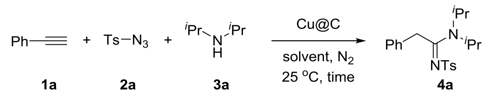
Table 1. Optimization for Cu@C-catalyzed *N*-sulfonyl amidine synthesis[a]

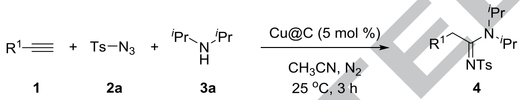


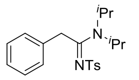
Entry	Solvent	Cu@C (mol %)	Time (h)	Yield (%)[b]
1	THF	5	1	13
2	1,4-dioxane	5	1	5
3	CH_2Cl_2	5	1	10
4	CH_3CN	5	1	47
5	DMF	5	1	4
6	DMSO	5	1	3
7	toluene	5	1	2
8	**CH_3CN**	**5**	**3**	**92**
9	CH_3CN	2.5	3	75
10	CH_3CN	2.5	12	90

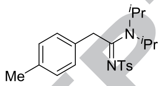
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.6 mmol), and Cu@C in solvent (1.0 mL) under N_2 balloon at 25 °C. [b] Yield determined by ^{1}H NMR.

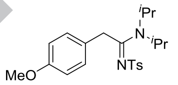
Initially, we tested the reactivity of Cu@C in three-component coupling of phenyl acetylene **1a**, *p*-toluenesulfonyl azide **2a**, and diisopropyl amine **3a** (Table 1). Gratifyingly, it was observed that Cu@C was able to catalyze *N*-sulfonyl amidine synthesis in THF solvent, which turned out to be the best in the homogeneous copper system (entry 1).[6] To enhance the reactivity of Cu@C, solvent screening was conducted. Interestingly, the use of CH_3CN gave the best yield of *N*-sulfonyl amidine (47%), while other solvents such as 1,4-dioxane, CH_2Cl_2, DMF, DMSO, and toluene did not showed satisfactory results (entries 2-7). To achieve full conversion, we increased the reaction time in CH_3CN solvent, and high yield of **4a** was obtained (entry 8). The use of reduced catalyst loading gave a moderate yield in 3 h, however, increased yield of **4a** was observed in prolonged reaction time. (entries 9–10).

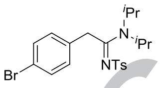
Table 2. Substrate scope of terminal alkynes in the Cu@C-catalyzed three-component coupling[a,b]

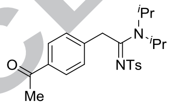


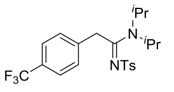

4a, 92%

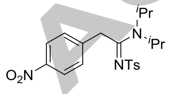

4b, 83%

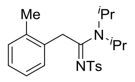

4c, 83%

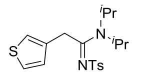

4d, 84%

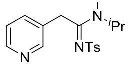

4e, 92%

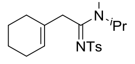

4f, 90%

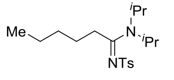

4g, 85%

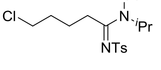

4h, 96%

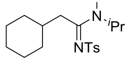

4i, 86%

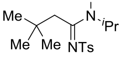

4j, 79%

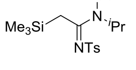

4k, 89%


4l, 96%


4m, 97%


4n, 94%


4o, 89%


4p, 90%

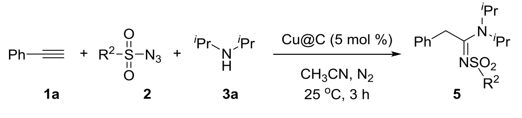
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.6 mmol), and Cu@C (5 mol %, 4 mg) in CH_3CN (1.0 mL) under N_2 balloon at 25 °C. [b] Isolated yield.

Next, we investigated substrate scope of terminal alkynes with the optimized conditions (Table 1, entry 8) in hands (Table 2). Various substituted phenyl acetylenes, regardless of electronic environment, underwent heterogeneous copper-catalyzed three-component coupling reaction to produce the corresponding *N*-sulfonyl amidines in good to high yields (**4a-4h**). To show practicality of the developed catalysis, the synthesis of **4a** was carried out on 10 mmol scale (1.0 g of phenyl acetylene), and the product **4a** was obtained in a 92% yield (3.4 g). Slightly lower yields were observed in the reaction of hetero-aromatic alkynes such as **1i** and **1j**, presumably due to coordination of hetero-atom to copper. Not only vinyl alkyne but also aliphatic alkynes could be employed in the present protocol with good reactivity. (**4k-4p**). Sterically bulky alkynes such as **1o** and **1p**, which showed poor reactivity in the previously reported heterogeneous Cu-catalyzed three-component coupling reaction due to size effect of catalyst,[15a] showed high yields.

The substrate scope of sulfonyl azides was also investigated (Table 3). Although aromatic sulfonyl azides showed good results, it was observed that *N*-sulfonyl amidine synthesis with aliphatic sulfonyl azides were sluggish. Instead of sulfonyl azides, we also examined phosphoryl azides as coupling partners in the developed Cu@C-catalyzed three-component coupling reaction,[18] however, the use of phosphoryl azides, such as diphenyl phosphoryl azide and diethyl phosphoryl azide failed to produce *N*-phosphoryl amidines.

A variety of amines were employed in the Cu@C-catalyzed three-component coupling reaction (Table 4). Symmetric diamines such as diethylamine, dibutylamine, and dibenzylamine produced the corresponding *N*-sulfonyl amidines in high yields (**6a**–**6c**). In case of diphenylamine, the yield of **6d** was low in the optimized conditions, however, acceptable yield (54%) was obtained in the presence of triethylamine (1.2 equiv.). We thought that the addition of triethylamine facilitated the

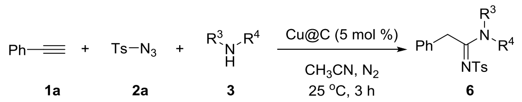
Table 3. Substrate scope of sulfonyl azides in the Cu@C-catalyzed three-component coupling[a,b]

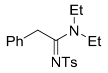


Entry	R^2 =	Yield (%)[b]
1	Phenyl	93
2	4-bromophenyl	93
3	methyl	33
4	n-butyl	63
5	cyclohexyl	50

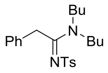
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), **3a** (0.6 mmol), and Cu@C (5 mol %, 4 mg) in CH_3CN (1.0 mL) under N_2 balloon at 25 °C. [b] Isolated yield.

Table 4. Substrate scope of amines in the Cu@C-catalyzed three-component coupling[a,b]

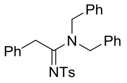




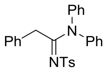
6a, 80%



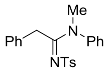
6b, 92%



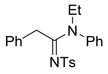
6c, 94%



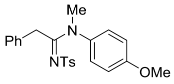
6d, 54%[c]



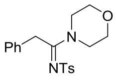
6e, 93%[c]



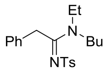
6f, 93%[c]



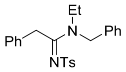
6g, 86%[c]



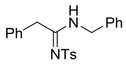
6h, 50%



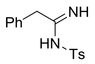
6i, 79%



6j, 96%



6k, 72%[c]



6l, 74%[c,d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3** (0.6 mmol), and Cu@C (5 mol %, 4 mg) in CH_3CN (1.0 mL) under N_2 balloon at 25 °C. [b] Isolated yield. [c] Et_3N (0.6 mmol) was added. [d] Aqueous ammonia (25-28%) was used.

generation of copper acetylide which is an important intermediate for the three-component coupling reaction.[8] Other aniline derivatives could be employed as amine nucleophile to produce the corresponding amidines (**6e**–**6g**). Cu@C-catalyzed three-component coupling with cyclic amine such as morpholine gave a moderate product yield regardless of the existence of triethylamine (**6h**). Asymmetric diamines such as **3i** and **3j** showed good reactivities. Not only primary amine such as benzyl amine but also ammonia could be successfully employed as nucleophile in the present protocol (**6k** and **6l**).[9d]

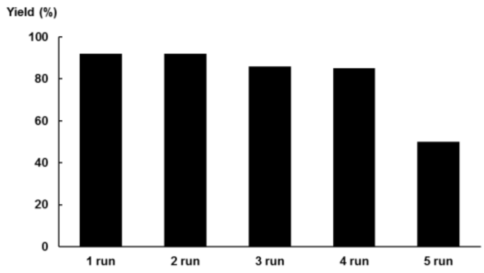


Figure 1. Recycling test of Cu@C in the three-component coupling reaction.

In heterogeneous catalysis, the reusability of the used catalyst is important. To investigate the reusability of Cu@C, we carried out the Cu@C-catalyzed three-component coupling reaction with **1a**, **2a**, and **3a** on 2.5 mmol scale in the presence of 20 mg of Cu@C. The used Cu@C was separated by simple centrifugation, and washed by ethyl acetate. After dry using vacuum, about 82% of Cu@C was obtained, and the collected catalyst was reused without further treatment such as calcination. The catalyst could be reused at least three times without significant drop of product yield (Figure 1). The observed low yield in fifth run is presumably due to the loss of the catalyst during separation process.[19]

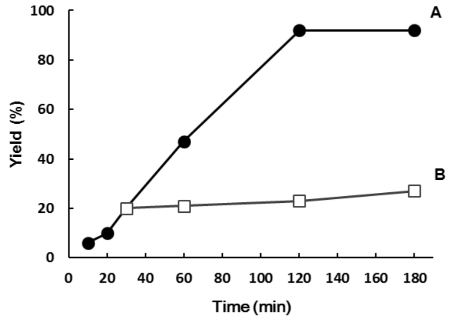


Figure 2. Filtration experiments for Cu@C-catalyzed three-component coupling reaction. (A) The full circle (●) represents the reaction profile of Cu@C catalysis. (B) The open square (□) represents the reaction profile after filtration of the catalyst using syringe filter at 30 min (20% yield).

To study whether the developed catalysis is heterogeneous or homogeneous, filtration experiments were carried out (Figure 2). We set up the Cu@C catalysis with **1a**, **2a**, and **3a** under optimized conditions. After 30 min, the reaction mixture was separated into two portions (A and B). Portion A containing Cu@C was allowed to react for additional 150 min. Whereas, portion B was filtered by using syringe filter to remove heterogeneous copper, and the filtrate was stirred for additional 150 min. After additional 150 min, protion A showed full conversion of **1a** and 92% amidine yield (72%p increase), however, only slight increase was observed in portion B (7%p increase) even with the prolonged reaction time (12 h). When we separated portion A and B in 60 min and stirred them for 12 h, no noticeable increase of the yield was observed in portion B. These results indicated that the Cu@C-catalyzed three-component coupling reaction is basically heterogeneous.[20]

In conclusion, we have developed a new heterogeneous catalysis for three-component coupling using Cu@C, which could be easily accessible by simple pyrolysis of HKUST-1 to generate *N*-sulfonyl amidine. The developed heterogeneous catalysis showed a good substrate scope of terminal alkynes, sulfonyl azides, and amines. Scale up process was able to be achieved on 10 mmol scale. In addition, Cu@C catalyst could be reused at least three times without significant decrease of the reactivity. It was found that the developed Cu@C catalysis is basically heterogeneous from the filtration experiment results.

Acknowledgments

This work was supported by the Incheon National University Research Grant in 2015.

Supplementary Material

Supplementary data (experimental procedures for three-component coupling reaction, ^{1}H and ^{13}C NMR spectra of the products, the characterization of new compounds, and XPS data are described) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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Highlights

- Heterogeneous Cu-catalyzed three-component coupling was achieved using Cu@C which is derived from HKUST-1 MOFs.
- A variety of terminal alkynes, sulfonyl azides, and amines produced *N*-sulfonyl amidines in high yields.
- The Cu@C catalyst could be reused at least three times without significant decrease of the reactivity.

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N-Sulfonyl Amidine Synthesis via Three-Component Coupling Reaction Using Heterogeneous Copper Catalyst Derived from Metal-Organic Frameworks

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