Efficient Synthesis of *N*-Sulfonylacetamidines from Propiolic Acid by Copper-Catalyzed Three-Component Coupling Reactions

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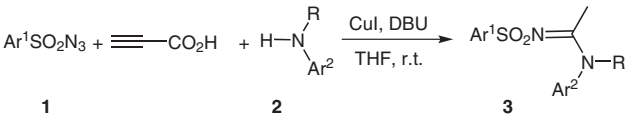
Abstract: Using propiolic acid as one of the reacting components, a copper-catalyzed three-component reaction of sulfonyl azide and amines affords *N*-sulfonylacetamidines via a decarboxylation process in high yields under mild conditions. This one-pot method is efficient, general, and versatile.

Key words: amidine, azides, copper, catalysis, propiolic acid

Amidines are found in numerous bioactive natural products[1] and are widely applied in medicinal and synthetic chemistry due to their prominent structural motifs.[2] Furthermore, substituted amidines serve as important pharmacophores, synthetic intermediates, and efficient metal complexes.[3] The transition-metal-catalyzed multicomponent reactions (MCRs) have frequently offered a rapid and efficient route to generate complex molecular frameworks from simple and readily available substrates because they have excellent catalytic efficiency in most cases.[4,5] Recently, a highly efficient copper-catalyzed MCR[6] was reported concerning sulfonyl azides or phosphoryl azides,[7] alkynes, and the third components such as amines,[8] water,[9] alcohols,[10] pyrroles,[11] iminophosphoranes,[12] or ammonium salts[13] under mild conditions. Synthetically interesting applications including intermolecular or intramolecular reactions have been also achieved on the basis of the same approach.[14,15] On the other hand no example of utilizing propiolic acid as a source of terminal alkyne in the catalytic three-component coupling reactions has been shown to afford amidine derivatives. To our surprise, an unexpected decarboxylation product of *N*-ethyl-*N*-phenyl-*N*′-tosylacetamidine was observed while synthesizing *N*-ethyl-*N*-phenyl-*N*′-tosyl-2-amidinoacetic acid through three-component coupling reaction using *p*-toluenesulfonyl azide, propiolic acid, and *N*-ethylbenzenamine catalyzed by CuI in the presence of Et_3N. Herein we report a new, mild, and efficient method for the preparation of *N*-sulfonylacetamidines **3**, in which propiolic acid was reacted with sulfonyl azide **1** and amine **2** via copper-catalyzed three-component reactions in the presence of DBU (Scheme 1).



Scheme 1 Synthesis of *N*-sulfonylacetamidines **3**

We started from the study of the reaction of *p*-toluenesulfonyl azide with propiolic acid and *N*-ethylbenzenamine. The reaction proceeds in THF with CuI as a catalyst in the presence of DBU to yield *N*-ethyl-*N*-phenyl-*N*′-tosylacetamidine **3a** in 90% yield (Table 1, entry 1). Among the various solvents it was found that DMF and CH_2Cl_2 were less satisfactory than THF. Coupled product was not generated in the absence of additional amine bases. Moreover, the use of triethylamine resulted in a lower yield of desired product than DBU.

With the suitable reaction conditions in hand, we next tested the feasibility of the protocol using various amine, sulfonyl azides, and propiolic acid (Table 1). As shown in Table 1, the one-pot three-component reaction afforded the *N*-sulfonylacetamidines **3** in moderate to excellent yields (55–92%). Generally, electronic effects and the positions of substitutents did not appear to exert much appreciable influence on the efficiency. Substrates with several functional groups such as methoxy or chloro on the *para* or *meta* positions of the aromatic ring could afford the corresponding *N*-sulfonylacetamidines in high yields (entries 1–5). However, the yield was decreased when the arylamine was substituted with *ortho* substituents (entry 6). Using 4-methyl-*N*-(4-methylbenzyl)benzenamine as the amine having large steric hindrance at nitrogen atom lower the yield of the product even after a much longer reaction time (entry 7). Furthermore, the desired products were not observed in the reactions of diphenylamine or 10*H*-phenothiazine under the standard reaction conditions. Thus steric hindrance effects play an important role in this reaction. In comparison to phenylsulfonyl azide, no obvious electronic effect was observed compared with TsN_3 (entries 8–10). Several kinds of amines including primary, aliphatic, or aromatic were also efficient substrates (entries 11 and 12).

According to the literature,[17] a proposed reaction mechanism is shown in Scheme 2. In the initial stage, deprotonation of propiolic acid by DBU and reaction with sulfonyl azide **1** produces a five-membered cyclic trizole intermediate **B**, in which the Cu metal is coordinated to the oxygen atom from carbonate ion and to one carbon

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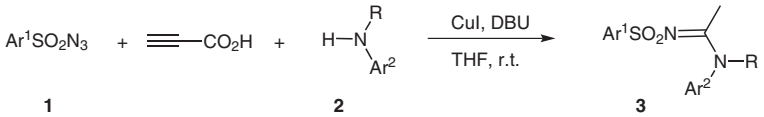
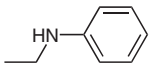
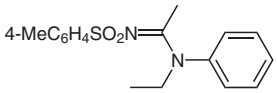
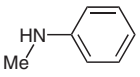
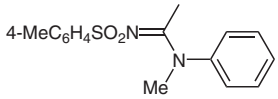
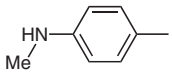
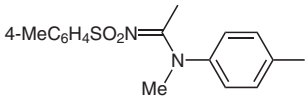
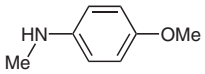
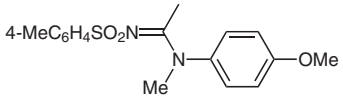
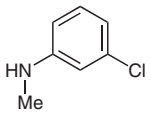
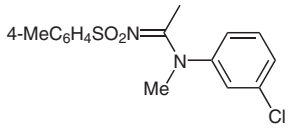
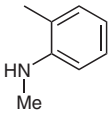
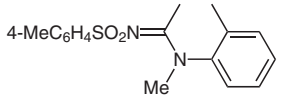
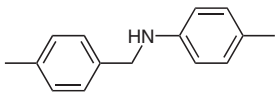
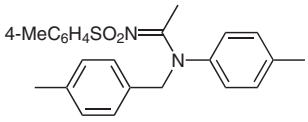
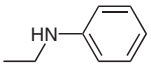
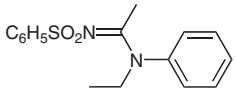
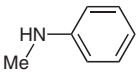
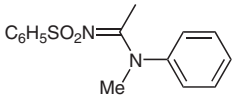
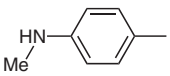
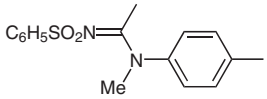
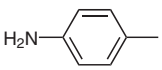
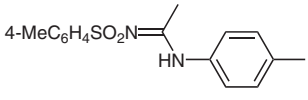
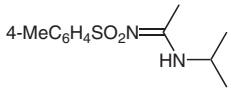
atom of the triazole. Extrusion of molecular nitrogen and carbon dioxide from **B** followed by the hetero-Wolff rearrangement provides the key ketenimine intermediate **C**. Then an addition of amines **2** to **C** leads to the desired *N*-sulfonylacetamidines **3**.

In conclusion, we have developed a mild and efficient method for synthesis of a variety of *N*-sulfonylacetamidines derivatives using propiolic acid as a new type of reacting partner in the copper-catalyzed three-component

Table 1 Synthesis of *N*-Sulfonylacetamidines **3**[a]

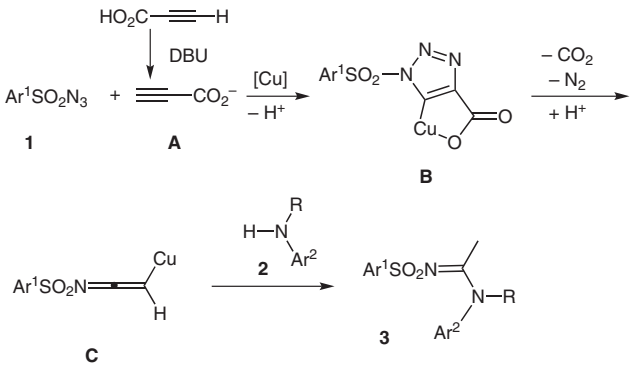


1 2 3

Entry	Ar^1	Amine **2**	**3**		Yield of **3** (%)[b]
1	4-MeC_6H_4		3a		90
2	4-MeC_6H_4		3b		87
3	4-MeC_6H_4		3c		85
4	4-MeC_6H_4		3d		84
5	4-MeC_6H_4		3e		86
6	4-MeC_6H_4		3f		64
7	4-MeC_6H_4		3g		55
8	Ph		3h		92
9	Ph		3i		87
10	Ph		3j		84
11	4-MeC_6H_4		3k		85
12	4-MeC_6H_4		3l		80

[a] Reaction conditions: sulfonyl azide (0.3 mmol), propiolic acid (0.45 mmol), amine (0.12 mmol), CuI (0.06 mmol), and DBU (0.15 mmol) in 2 mL of THF were stirred in a flask at r.t. under N_2 for 10 h.[16]
[b] Isolated yield.

reaction of with sulfonyl azides and amine in the present of DBU via a decarboxylation process.



Scheme 2 A proposed mechanism of the reaction

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) **General Procedure for the Synthesis of 3**
A solution of sulfonyl azide (1.2 mmol), amine (1.2 mmol), propiolic acid (1.0 mmol), DBU (1.5 mmol), and CuI (0.1 mmol) in THF (2 mL) was stirred at r.t. under N_2 for 10 h. After the reaction was completed, which was monitored with TLC, the reaction solution was diluted with CH_2Cl_2 (2 mL) and then with aq NH_4Cl solution (3 mL). The mixture was stirred for an additional 30 min at r.t., and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography with EtOAc–PE to give *N*-sulfonylacetamidines **3a–l**.
Selected Data
***N*-Ethyl-*N*-phenyl-*N′*-tosylacetamidine (3a)**
Light yellow solid, mp 130.0–131.0 °C. IR (KBr): 3458, 2929, 1547, 1495, 1267, 1139, 1089, 685 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): d = 7.88 (2 H, d, *J* = 8.2 Hz), 7.45 (2 H, t, *J* = 7.8 Hz), 7.39 (1 H, t, *J* = 7.5 Hz), 7.29 (2 H, d, *J* = 8.0 Hz), 7.12 (2 H, d, *J* = 7.5 Hz), 3.83 (2 H, q, *J* = 14.2 Hz,), 2.42 (3 H, s), 2.24 (3 H, s), 1.12 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): d = 165.4, 141.9, 141.6, 140.3, 130.0, 129.1, 128.6, 127.7, 126.3, 47.2, 21.4, 19.8, 11.9. ESI-MS: *m/z* (%) = 316 [M^+]. HRMS: *m/z* calcd for $C_{17}H_{21}N_2O_2S$: 317.1324 [M + H]$^+$; found: 317.1321.
***N*-*p*-Tolyl-*N′*-tosylacetamidine (3k)**
Light yellow solid (a mixture of two isomers with a ratio 1:3, which is tentatively assigned as *Z*/*E* of the generated imino C=N double bond), mp 109.6–127.9 °C. IR (KBr): 3750, 3308, 1535, 1457, 1275, 1143, 1089, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.7 (0.7 H, br, *Z*/*E*), 7.87 (1.9 H, d, *J* = 8.2 Hz, *E*), 7.82 (0.6 H, d, *J* = 8.0 Hz, *Z*), 7.36 (0.6 H, d, *J* = 8.5 Hz, *Z*), 7.31 (2 H, d, *J* = 8.1 Hz, *E*), 7.26 (0.6 H, d, *J* = 8.0 Hz, *Z*), 7.20 (2 H,d, *J* = 8.0 Hz, *E*), 7.08 (0.6 H, d, *J* = 8.5 Hz, *Z*), 7.02 (2 H, d, *J* = 8.2 Hz, *E*), 2.61 (0.9 H, s, *Z*), 2.43 (3 H, s, *E*), 2.41 (1.0 H, s, *Z*), 2.37 (3 H, s, *E*), 2.30 (1.0 H, s, *Z*), 2.01 (2.9 H, s, *E*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6, 162.9, 143.0, 142.2, 140.4, 139.3, 138.2, 135.2, 134.8, 134.0, 130.2, 129.4, 129.3, 129.2, 126.4, 126.3, 126.1, 121.7, 22.0, 21.7, 21.5, 21.4, 20.9, 20.8. ESI-MS: *m/z* (%) = 302 [M^+]. HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_2S$: 303.1167 [M + H]$^+$; found: 303.1170.
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