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Formation of *N*-sulfonylamidines by copper-catalyzed coupling of sulfonyl azides, terminal alkynes, and trialkylamines

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ABSTRACT

A copper-catalyzed synthesis of *N*-sulfonylamidines via three-component coupling of sulfonyl azides, terminal alkynes, and trialkylamines is reported.

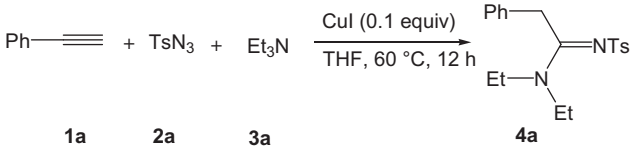
Amidines have fascinating chemical properties by virtue of their structures, and they have been widely applied in medicinal and synthetic chemistry.[1] Substituted amidines are useful intermediates for the synthesis of heterocyclic compounds and metal complexes.[2,3] Traditional methods for the preparation of amidine derivatives are based on functional group transformation of precursors such as thioamides,[4] isocyanides,[5] and aldoximes.[6]

Tandem reactions of sulfonyl azides, terminal alkynes, and secondary amines have been reported and the structures of the resulting amidines were confirmed unambiguously by an X-ray crystallographic analysis, which disclosed the *E*-form of the C=N double bond.[7] In this Letter, we report a one-pot synthesis of *N*-sulfonylamidines via the Cu-catalyzed three-component coupling of trialkylamines, sulfonyl azides, and terminal alkynes. Trialkylamines are frequently applied as bases, but rarely used as the nucleophile in these reactions.[8–10]

The formation of ketenimine intermediates from terminal alkynes, sulfonyl azides, and triethylamine, as the base, in the presence of copper catalysts,[11,12] has encouraged us to trap these intermediates using trialkylamines. It should be mentioned that the ketenimine intermediate can be generated using activated azides such as sulfonyl, carbonyl, and phosphoryl azides.[13,14] Thus, the reaction of phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), and triethylamine (**3a**) gave N^1,N^1-diethyl-2-phenyl-N^2-tosylacetamidine (**4a**) in 83% yield (Scheme 1). This result prompted us to optimize the reaction conditions for the synthesis of other sulfonylamidine derivatives[15] (Table 1).

While only a trace of product was obtained at ambient temperature, heating at 60 °C was found to be effective for complete conversion. Also, an increased loading of the tertiary amine gave better yields. Several catalysts such as CuI, CuBr, CuCl, Cu_2O, and copper powder were tested with CuI and CuBr giving the best results. Among several solvents screened, THF was the best; nonpolar solvents such as toluene and hexane were not suitable for the formation of sulfonylamidine derivatives. Thus, the optimized reaction conditions used were 10 mol % of CuI relative to the alkyne and 3 equiv of the trialkylamine in THF at 60 °C.

Phenylacetylene readily participates in the coupling to furnish the corresponding amidine in good yields (Table 1, entries 1–3). Aliphatic acetylenes served as low-yielding substrates compared to phenylacetylene (Table 1, entries 4–8). Aromatic sulfonyl azides reacted efficiently with **1a** and the corresponding products were obtained in good yields. Several types of aliphatic acyclic trialkylamines were utilized successfully.



Scheme 1. Copper-catalyzed three-component coupling of phenyacetylene, *p*-toluenesulfonyl azide, and triethylamine.

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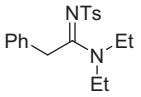
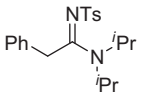
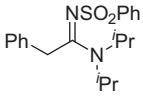
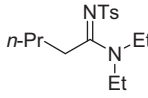
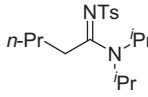
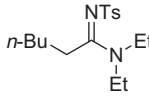
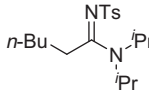
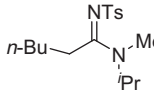
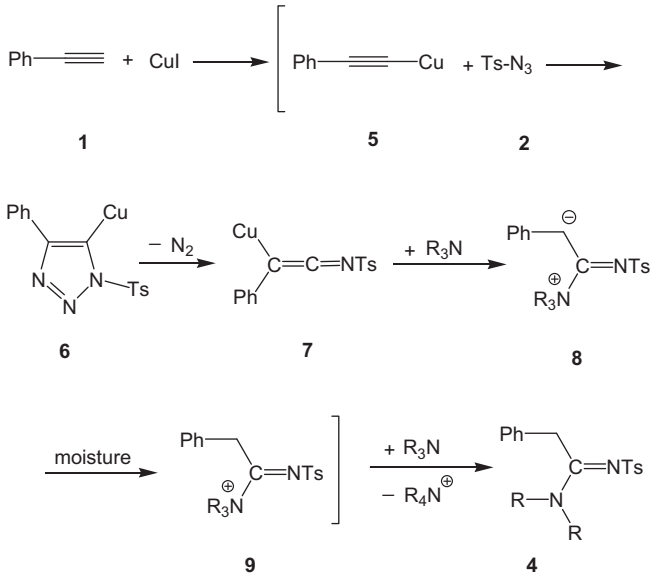
Table 1
Copper-catalyzed three-component coupling

Entry	Alkyne	Sulfonyl azide	Amine	Amidine		Yield (%)
1	Ph— ≡ **1a**	*p*-Tolyl(SO$_2$)N$_3$ **2a**	Et_3N		**4a**	83
2	**1a**	**2a**	$(^iPr)_2NEt$		**4b**	86
3	**1a**	Ph(SO$_2$)N$_3$ **2b**	$(^iPr)_2NEt$		**4c**	73
4	*n*-Pr— ≡ **1b**	*p*-Tolyl(SO$_2$)N$_3$ **2a**	Et_3N		**4d**	31
5	**1b**	**2a**	$(^iPr)_2NEt$		**4e**	34
6	*n*-Bu— ≡ **1c**	**2a**	Et_3N		**4f**	51
7	**1c**	**2a**	$(^iPr)_2NEt$		**4g**	45
8	**1c**	**21a**	$(^iPr)NMe_2$		**4h**	42



Scheme 2. A plausible mechanism for the reaction.

A plausible rationalization for the formation of compounds **4** is given in Scheme 2. The yellow copper acetylide **5**, formed from **1** and CuI,[7] undergoes a 1,3-dipolar cycloaddition reaction with sulfonyl azide **2** to generate the triazole derivative **6**.[16,17] This intermediate can then be converted into the ketenimine derivative **7**,[18] which is attacked by the trialkylamine to afford the zwitterion **8**. This intermediate is converted into salt **9**, presumably by moisture. Dealkylation of intermediate **9** by the trialkylamine would produce the desired product **4**.

In conclusion, ketenimine intermediates generated by the addition of copper acetylides to tosyl azides are trapped by trialkylamines to yield *N*-sulfonylamidine derivatives. The present method may be considered a practical route for the synthesis of functionalized *N*-sulfonylamidines.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.135.

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15. *General procedure*. To a mixture of azide **2** (1.2 mmol), alkyne **1** (1 mmol), and CuI (0.1 mmol) in THF (2 mL) was slowly added the tertiary amine (3 mmol). The mixture was stirred at 60 °C. After completion of the reaction [about 12 h; TLC (AcOEt/hexane 1:4) monitoring], the mixture was diluted with CH_2Cl_2 (2 mL) and aqueous NH_4Cl solution (3 mL), stirred for 30 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 3) and the combined organic fractions were dried ($NaSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane/AcOEt 5:1] to give the product. *N*-sulfonylamidines **4b** and **4g** are known.[7]
N^1,N^1-Diethyl-2-phenyl-N^2-tosylacetamidine (**4a**). Colorless solid, mp 136–139 °C, 0.28 g, yield: 83%. IR (KBr) (ν_{max}, cm^{-1}): 2977, 1549, 1455, 1360, 1272, 1142, 1090, 761, 589. Anal. Calcd for $C_{19}H_{24}N_2O_2S$ (344.47): C, 66.25; H, 7.02; N, 8.13%. Found: C, 66.23; H, 6.99; N, 8.11%. MS (EI, 70 eV): *m*/*z* (%): 345.5 (M+1, 3), 238 (7), 190 (9), 162 (2), 155 (33), 91 (100), 72 (59), 44 (63). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.95 (3H, t, ^3J = 7.0 Hz, Me), 1.15 (3H, t, ^3J = 7.0 Hz, Me), 2.36 (3H, s, Me), 3.20 (2H, q, ^3J = 7.0 Hz, CH_2N), 3.50 (2H, q, ^3J = 7.0 Hz, CH_2N), 4.38 (2H, s, CH_2), 7.11 (2H, d, ^3J = 7.9 Hz, Ar), 7.16–7.26 (5H, m, Ph), 7.77 (2H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.8 (Me), 13.9 (Me), 21.9 (Me), 22.4 (CH_2), 36.5 (CH_2N), 41.8 (CH_2N), 126.2 (CH), 126.8 (2CH), 128.7 (2CH), 129.4 (2CH), 131.7 (2CH), 139.4 (C), 141.6 (C), 143.6 (C), 164.5 (C=N).
N^1,N^1-Diethyl-N^2-tosylpentanamidine (**4d**). Colorless solid, mp 107–108 °C, 0.09 g, yield: 31%. IR (KBr) (ν_{max}, cm^{-1}): 2928, 1567, 1432, 1317, 1287, 1129, 1074, 755, 541. Anal. Calcd for $C_{16}H_{26}N_2O_2S$ (310.45): C, 61.90; H, 8.44; N, 9.02%. Found: C, 61.89; H, 8.43; N, 9.01%. MS (EI, 70 eV): *m*/*z* (%): 311.5 (M+1, 2), 204 (5), 156 (10), 155 (63), 128 (43), 91 (100), 72 (81), 44 (51). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.92 (3H, t, ^3J = 7.2 Hz, Me), 1.10 (3H, t, ^3J = 7.0 Hz, Me), 1.23 (3H, t, ^3J = 7.0 Hz, Me), 1.40–1.46 (2H, m, CH_2), 1.58–1.63 (2H, m, CH_2), 2.39 (3H, s, Me), 2.83–2.86 (2H, m, CH_2), 3.45 (2H, q, ^3J = 7.0 Hz, CH_2N), 3.49 (2H, q, ^3J = 7.0 Hz, CH_2N), 7.23 (2H, d, ^3J = 8.1 Hz, Ar), 7.81 (2H, d, ^3J = 8.1 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 12.1 (Me), 13.6 (Me), 14.2 (Me), 21.0 (Me), 21.3 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 43.1 (CH_2), 43.2 (CH_2), 126.0 (2CH), 129.3 (2CH), 137.1 (C), 139.2 (C), 167.6 (C=N).
N^1-Isopropyl-N^1-methyl-N^2-tosylhexanamidine (**4h**). Colorless solid, mp 110–112 °C, 0.13 g, yield: 42%. IR (KBr) (ν_{max}, cm^{-1}): 2973, 1545, 1313, 1256, 1128, 1063, 841, 753, 558. Anal. Calcd for $C_{17}H_{28}N_2O_2S$ (324.5): C, 62.93; H, 8.70; N, 8.63%. Found: C, 62.95; H, 8.73; N, 8.61%. MS (EI, 70 eV): *m*/*z* (%): 325.5 (M+1, 2), 218 (3), 170 (5), 156 (4), 155 (3), 91 (100), 72 (81), 58 (49). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.85 (3H, t, ^3J = 7.1 Hz, Me), 1.09 (6H, d, ^3J = 6.8 Hz, CMe_2), 1.23 (6H, d, ^3J = 6.8 Hz, CMe_2), 1.28–1.37 (4H, m, $2CH_2$), 1.49–1.60 (2H, m, CH_2), 2.39 (3H, s, Me), 2.83 (3H, s, Me), 2.91 (3H, s, Me), 2.93 (2H, m, CH_2), 3.65 (1H, m, CH), 4.11 (1H, m, CH), 7.24 (2H, d, ^3J = 7.9 Hz, Ar), 7.85 (2H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.8 (Me), 18.9 (CMe_2), 20.5 (CMe_2), 22.2 (Me), 26.2 (CH_2), 27.0 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 31.8 (MeN), 47.2 (CHN), 48.7 (CHN), 126.1 (2CH), 129.0 (2CH), 141.3 (C), 143.5 (C), 172.0 (C=N).
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18. Although a 1,3-dipole or a carbene (without migration of the Cu) would fit the data, we prefer the mechanism shown in Scheme 2.