Copper-Catalyzed One-Pot Synthesis of Functionalized 1,4-Dihydroazete Derivatives from Sulfonyl Azides, Terminal Alkynes, and Tetramethylguanidine

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Abstract: Ketenimine intermediates generated by the addition of copper acetylides to sulfonyl azides are trapped by tetramethylguanidine to afford 1,4-dihydro-*N*,*N*-dimethyl-3-aryl(alkyl)-4-aryl(alkyl)sulfoniminoazet-2-amine derivatives in moderate to good yields.

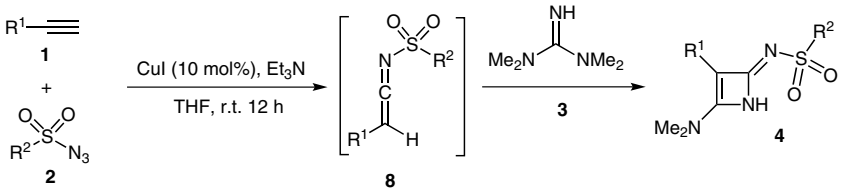
Key words: 1,4-dihydroazete, copper iodide, tetramethylguanidine, sulfonyl azide, terminal alkyne, ketenimine

Four-membered nitrogen heterocycles possess a wide range of biological activities and are used as antibiotic and antibacterial agents.[1] These strained ring systems have found increasing applications as intermediates in the synthesis of pharmaceuticals.[2,3] Among them, the 2-azetine series, especially azetinones, has gained much attention.[4,5] It has been reported that monocyclic azet systems are remarkably active, not only as antibacterials, but also as inhibitors of cytomegalovirus protease,[6] cholesterol absorption,[7] and human tryptase.[8] Moreover, scaffolds derived from monocyclic azet have been exploited for their utility as versatile synthetic intermediates.[9–12]

The ketenimine intermediates generated in the copper-catalyzed azide–alkyne cycloaddition reaction can be trapped by various nucleophiles.[13–15] In this way, skeletons of various heterocycles were successfully synthesized.[16–20] Applying this strategy, we used tetramethylguanidine to trap the in situ generated ketenimines and obtained 1,4-dihydro-*N*,*N*-dimethyl-3-aryl(alkyl)-4-aryl(alkyl)sulfoniminoazet-2-amine derivatives (Table 1). Herein, we report the details of this work.[21]

First, we studied the reaction between the ketenimine generated from phenylacetylene (**1a**) and *p*-toluensulfonyl azide (**2a**) with tetramethylguanidine (**3**). This reaction proceeded smoothly at room temperature and afforded 1,4-dihydro-*N*,*N*-dimethyl-3-phenyl-4-tosyliminoazet-2-amine (**4a**) in 80% yield. This result prompted us to optimize the reaction conditions for the synthesis of other derivatives (Table 1).

Table 1 Synthesis of Compounds **4a–i**



Entry	**1**, **2**, **4**	R^1	R^2	Yield of **4** (%)
1	**a**	Ph	4-Tol	80
2	**b**	Ph	Ph	82
3	**c**	Ph	Me	74
4	**d**	*n*-Pr	4-Tol	67
5	**e**	*n*-Pr	Ph	60
6	**f**	*n*-Pr	Me	57
7	**g**	*n*-Bu	4-Tol	62
8	**h**	*n*-Bu	Ph	57
9	**i**	*n*-Bu	Me	53

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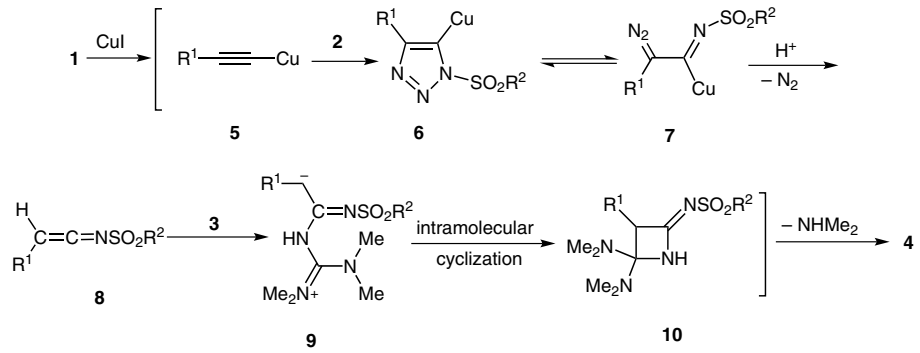

Scheme 1

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, tetrahydrofuran (THF) was the best. Thus, the optimized reaction conditions used were 10 mol% of CuI, 1 mmol of the alkyne, 1.2 mmol of sulfonyl azide, and 1 mmol of tetramethylguanidine in THF at room temperature.

Phenylacetylene readily participates in the coupling reaction to furnish the corresponding 1,4-dihydro-*N*,*N*-dimethyl-3-aryl-4-aryl(alkyl)sulfoniminoazet-2-amine derivatives in good yields (Table 1). Aliphatic acetylenes served as low-yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently, and the corresponding products were obtained in good yields.

Structures of compounds **4a**–**i** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **4a** exhibited three singlets for methyl (δ = 2.38 ppm), dimethyl amino (δ = 2.80 ppm), and NH (δ = 3.94 ppm, exchanged with D_2O) protons, along with characteristic multiplets for the aryl groups. The ^{13}C NMR spectrum of **4a** exhibits 13 signals in agreement with the proposed structure. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 341. The NMR spectra of compounds **4b**–**i** are similar to those of **4a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

A plausible mechanism for the formation of compounds **4** is given in Scheme 1. The yellow copper acetylide **5**, formed from **1** and CuI, undergoes a 1,3-dipolar cycloaddition reaction with sulfonyl azide **2**, to generate the triazole derivative **6**.[22] This intermediate undergoes ring opening to afford the α-diazoimino species **7**, which is converted to ketenimine derivative **8** by loss of nitrogen gas and protonation.[23–25] Ketenimine intermediate **8** is trapped by 1,1,3,3-tetramethylguanidine to yield the zwitterionic adduct **9**, which undergoes an intramolecular cyclization reaction and subsequent loss of dimethylamine to generate product **4**.

In summary, ketenimine intermediates generated by the addition of copper acetylides to sulfonyl azides are trapped by 1,1,3,3-tetramethylguanidine to yield 1,4-dihydro-*N*,*N*-dimethyl-3-aryl(alkyl)-4-aryl(alkyl)sulfoniminoazet-2-amine derivatives. The present method may be considered as a practical route for the synthesis of functionalized 4-iminosulfonyl-*N*,*N*-dimethyl-1,4-dihydroazet-2-amine, which may be converted to azetin-2-one derivatives.

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(21) **General Procedure for the Synthesis of Compounds 4**

To a mixture of sulfonyl azide **2**, (1.2 mmol), alkyne **1** (1 mmol), and CuI (0.1 mmol), Et_3N (1 mmol) in THF (2 mL) was slowly added tetramethylguanidine (1 mmol). The mixture was stirred at r.t. After completion of the reaction [about 12 h; TLC (EtOAc–hexane = 1:5) monitoring], the mixture was diluted with CH_2Cl_2 (2 mL) and aq NH_4Cl solution (3 mL), stirred for 30 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane–EtOAc = 5:1] to give the product.

1,4-Dihydro-*N*,*N*-dimethyl-3-phenyl-4-tosyliminoazet-2-amine (4a)

Yellow oil; yield 0.27 g (80%). IR (KBr): ν_{max} = 3438, 2923, 1511, 1396, 1270, 1139, 1083 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.38 (3 H, s, Me), 2.80 (6 H, s, NMe_2), 3.94 (1 H, s, NH), 7.18 (2 H, t, ^3J = 7.5 Hz, Ar), 7.24 (1 H, t, ^3J = 7.5 Hz, Ar), 7.25–7.28 (4 H, m, Ph), 7.76 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.7 (Me), 40.5 (NMe_2), 88.3 (C), 125.7 (CH), 126.4 (2 CH), 128.1 (2 CH), 128.7 (2 CH), 129.6 (2 CH), 137.5 (C), 141.1 (C), 142.3 (C), 166.1 (C), 169.2 (C). MS (EI): *m/z* (%) = 341 (2) [M^+], 297 (8), 271 (12), 155 (100), 145 (22), 91 (70), 77 (54). Anal. Calcd (%) for $C_{18}H_{19}N_3O_2S$ (341.00): C, 63.32; H, 5.61; N, 12.31. Found: C, 63.79; H, 5.54; N, 12.38.

1,4-Dihydro-*N*,*N*-dimethyl-3-phenyl-4-benzenesulfoniminoazet-2-amine (4b)

Yellow oil; yield 0.27 g (82%). IR (KBr): ν_{max} = 3437, 2929, 1520, 1400, 1273, 1142, 1087 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.85 (6 H, s, NMe_2), 3.98 (1 H, s, NH), 7.15 (2 H, t, ^3J = 7.5 Hz, Ar), 7.20 (1 H, t, ^3J = 7.5 Hz, Ar), 7.23 (2 H, d, ^3J = 7.5 Hz, Ar), 7.25–7.29 (3 H, m, Ph), 7.78 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.6 (NMe_2), 88.5 (C), 125.6 (CH), 126.5 (2 CH), 128.3 (2 CH), 128.8 (2 CH), 129.7 (2 CH), 137.5 (CH), 140.2 (C), 142.5 (C), 165.7 (C), 170.8 (C). MS (EI): *m/z* (%) = 327 (3) [M^+], 283 (12), 257 (17), 145 (31), 141 (100), 77 (54). Anal. Calcd (%) for $C_{17}H_{17}N_3O_2S$ (327.05): C, 62.36; H, 5.23; N, 12.83. Found: C, 62.06; H, 5.18; N, 12.75.

1,4-Dihydro-*N*,*N*-dimethyl-3-phenyl-4-methanesulfoniminoazet-2-amine (4c)

Yellow oil; yield 0.20 g (74%). IR (KBr): ν_{max} = 3435, 2925, 1531, 1401, 1271, 1120 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.81 (3 H, s, Me), 2.93 (6 H, s, NMe_2), 4.01 (1 H, s, NH), 7.26 (2 H, t, ^3J = 7.4 Hz, Ar), 7.30 (1 H, t, ^3J = 7.4 Hz, Ar), 7.42 (2 H, d, ^3J = 7.4 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.2 (Me), 40.4 (NMe_2), 87.2 (C), 124.4 (CH), 125.7 (2 CH), 126.4 (2 CH), 140.9 (C), 162.3 (C), 172.5 (C). MS (EI): *m/z* (%) = 265 (2) [M^+], 221 (10), 195 (14), 145 (30), 79 (100), 77 (44). Anal. Calcd (%) for $C_{12}H_{15}N_3O_2S$ (265.00): C, 54.32; H, 5.70; N, 15.06. Found: C, 54.66; H, 5.64; N, 15.16.

1,4-Dihydro-*N*,*N*-dimethyl-3-propyl-4-tosyliminoazet-2-amine (4d)

Yellow oil; yield 0.20 g (67%). IR (KBr): ν_{max} = 3436, 2924, 1510, 1397, 1271, 1138, 1084 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, t, ^3J = 6.9 Hz, Me), 1.57–1.62 (2 H, m, CH_2), 2.38 (3 H, s, Me), 2.52 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.91 (6 H, s, NMe_2), 3.94 (1 H, s, NH), 7.24 (2 H, d, ^3J = 8.0 Hz, Ar), 7.81 (2 H, d, ^3J = 8.0 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (Me), 21.4 (CH_2), 22.7 (CH_2), 29.7 (Me), 40.5 (NMe_2), 86.1 (C), 126.5 (2 CH), 128.4 (2 CH), 139.0 (C), 142.0 (C), 166.6 (C), 172.5 (C). MS (EI): *m/z* (%) = 307 (2) [M^+], 263 (14), 197 (14), 155 (100), 111 (28), 91 (55), 77 (44), 43 (22). Anal. Calcd (%) for $C_{15}H_{21}N_3O_2S$ (307.01): C, 58.61; H, 6.89; N, 13.67. Found: C, 58.89; H, 6.94; N, 13.54.

1,4-Dihydro-*N*,*N*-dimethyl-3-propyl-4-benzenesulfoniminoazet-2-amine (4e)

Yellow oil; yield 0.17 g (60%). IR (KBr): ν_{max} = 3455, 2925, 1513, 1269, 1142, 1087 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, t, ^3J = 7.0 Hz, Me), 1.57–1.60 (2 H, m, CH_2), 2.51 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.89 (6 H, s, NMe_2), 3.93 (1 H, s, NH), 7.39 (1 H, t, ^3J = 8.0 Hz, Ar), 7.43 (2 H, t, ^3J = 8.0 Hz, Ar), 7.91 (2 H, d, ^3J = 8.0 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 21.1 (CH_2), 22.8 (CH_2), 40.5 (NMe_2), 86.1 (C), 124.3 (CH), 125.6 (2 CH), 128.2 (2 CH), 135.7 (C), 162.9 (C), 172.4 (C). MS (EI): *m/z* (%) = 293 (3) [M^+], 249 (13), 223 (8), 141 (100), 111 (18), 77 (34), 43 (35). Anal. Calcd (%) for $C_{14}H_{19}N_3O_2S$ (293.00): C, 57.31; H, 6.53; N, 14.32. C, 57.16; H, 6.48; N, 14.21.

1,4-Dihydro-*N*,*N*-dimethyl-3-propyl-4-methanesulfoniminoazet-2-amine (4f)

Yellow oil; yield 0.13 g (57%). IR (KBr): ν_{max} = 3436, 1518, 1269, 1142, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3 H, t, ^3J = 6.9 Hz, Me), 1.57–1.61 (2 H, m, CH_2), 2.50 (2 H, t, ^3J = 6.9 Hz, CH_2), 2.76 (3 H, s, Me), 2.90 (6 H, s, NMe_2) 3.92 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (Me), 19.1 (CH_2), 22.6 (CH_2), 29.6 (Me), 40.5 (NMe_2), 86.7 (C), 162.9 (C), 172.5 (C). MS (EI): *m/z* (%) = 231 (2) [M^+], 187 (11), 161 (18), 119 (41), 79 (100), 43 (25). Anal. Calcd (%) for $C_9H_{17}N_3O_2S$ (231.02): C, 46.73; H, 7.41; N, 18.17. Found: C, 47.02; H, 7.34; N, 18.08.

1,4-Dihydro-*N*,*N*-dimethyl-3-butyl-4-tosyliminoazet-2-amine (4g)

Yellow oil; yield 0.20 g (62%). IR (KBr): ν_{max} = 3452, 2933, 1520, 1401, 1270, 1118 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, ^3J = 6.9 Hz, Me), 1.23–1.27 (2 H, m, CH_2), 1.59–1.62 (2 H, m, CH_2), 2.40 (3 H, s, Me), 2.50 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.85 (6 H, s, NMe_2), 3.97 (1 H, s, NH), 7.38 (2 H, d, ^3J = 8.0 Hz, Ar), 7.92 (2 H, d, ^3J = 8.0 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 19.4 (CH_2), 22.4 (CH_2), 27.3 (CH_2), 30.4 (Me), 40.3 (NMe_2), 86.6 (C), 125.6 (2 CH), 128.2 (2 CH), 137.7 (C), 141.2 (C), 166.0 (C), 172.5 (C). MS (EI): *m/z* (%) = 321 (3) [M^+], 277 (16), 251 (13), 155 (100), 125 (20), 91 (51), 77 (41), 57 (52). Anal. Calcd (%) for $C_{16}H_{23}N_3O_2S$ (321.00): C, 59.78; H, 7.21; N, 13.07. Found: C, 59.51; H, 7.27; N, 13.18.

1,4-Dihydro-*N*,*N*-dimethyl-3-butyl-4-benzenesulfoniminoazet-2-amine (4h)

Yellow oil; yield 0.17 g (57%). IR (KBr): ν_{max} = 3413, 2926, 1517, 1401, 1268, 1141, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (3 H, t, ^3J = 6.9 Hz, Me), 1.24–1.28 (2 H, m, CH_2), 1.59–1.62 (2 H, m, CH_2), 2.49 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.92 (6 H, s, NMe_2), 3.98 (1 H, s, NH), 7.26 (1 H, t, ^3J = 7.9 Hz, Ar), 7.39 (2 H, t, ^3J = 7.9 Hz, Ar), 7.80 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (Me), 20.0 (CH_2), 22.5 (CH_2), 27.3 (CH_2), 40.5 (NMe_2), 86.4 (C), 125.6 (CH), 128.7 (2 CH), 129.6 (2 CH), 138.6 (C), 167.3 (C), 172.5 (C). MS (EI): *m/z* (%) = 307 (3) [M^+], 263 (12), 237 (10), 141 (100), 125 (29), 77 (35), 57 (50). Anal. Calcd (%) for $C_{15}H_{21}N_3O_2S$ (307.00): C, 58.61; H, 6.89; N, 13.67. Found: C, 58.86; H, 6.74; N, 13.55.

1,4-Dihydro-*N*,*N*-dimethyl-3-butyl-4-methanesulfoniminoazet-2-amine (4i)

Yellow oil; yield 0.13 g (53%). IR (KBr): ν_{max} = 3513, 2934, 1521, 1403, 1270, 1118, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, ^3J = 6.9 Hz, Me), 1.21–1.29 (2 H, m, CH_2), 1.62–1.66 (2 H, m, CH_2), 2.47 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.82 (3 H, s, Me), 2.90 (6 H, s, NMe_2), 3.96 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 19.8

(CH_2), 22.4 (CH_2), 27.3 (CH_2), 30.7 (Me), 40.4 (NMe_2), 86.2 (C), 166.2 (C), 172.6 (C). MS (EI): *m/z* (%) = 245 (2) [M^+], 201 (12), 175 (10), 125 (39), 79 (100), 57 (46). Anal. Calcd (%) for $C_{10}H_{19}N_3O_2S$ (245.00): C, 48.95; H, 7.81; N, 17.13. Found: C, 48.76; H, 7.75; N, 17.04

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