Synthesis of Functionalized Azet-2(1*H*)-imines through [2+2] Cycloaddition of Imines and Ketenimines

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Abstract: The reaction between ketenimine intermediates, generated from terminal alkynes and sulfonyl azides, trichloroacetonitrile, and sodium arylsulfinates in *N*,*N*-dimethylformamide at room temperature affords *N*-[3-aryl(alkyl)-4-arylazet-2(1*H*)-ylidene]-arene(alkane)sulfonamides in moderate to good yields.

Key words: 2-azetines, copper iodide, trichloroacetonitrile, sodium arylsulfinates, ketenimines, sulfonyl azides, terminal alkynes

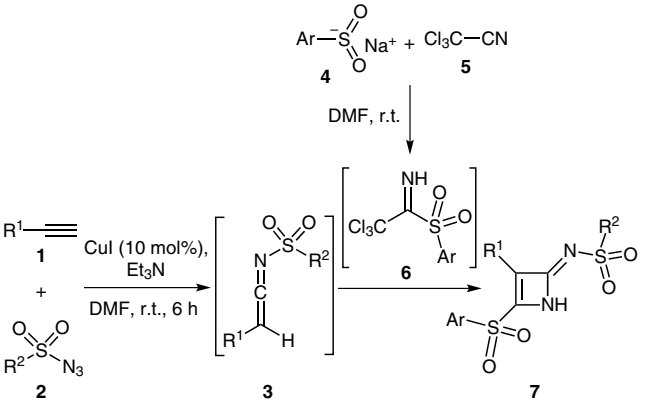
The replacement of carbon atoms of cyclobutane by heteroatoms introduces functionalities which exhibit increased reactivity resulting from the ring strain. This often leads to unusual properties which make four-membered heterocycles useful as synthetic intermediates.[1–3] However, it also adds a new dimension of difficulty concerning the synthesis of these heterocycles. Azetines comprise a rare class of constrained azaheterocycles with high synthetic potential due to their usually unstable nature. This class can be divided into 1-azetines and 2-azetines, depending on the position of the double bond. The chemistry of azetines is still not much developed, despite the fact that since the early 1980s fundamental information was available for the further unraveling of this class of compounds.[4] Herein, we report a simple and efficient procedure for the synthesis of *N*-[3-aryl(alkyl)-4-arylazet-2(1*H*)-ylidene]arene(alkane)sulfonamides **7** via the copper-catalyzed four-component coupling reaction of terminal alkynes **1**, sulfonyl azides **2**, sodium arylsulfinates **4**, and trichloroacetonitrile **5** (Table 1).[5] This protocol builds on works published by Fokin[6] and Xu,[7] using a different imine for the [2+2] reaction. This allows subsequent elimination of chloroform to give the azetine products **7**.

Among several methods leading to the generation of ketenimines, the copper-catalyzed azide–alkyne cycloaddition reaction attracted much attention because of its mild formation conditions.[8] The ketenimine intermediates generated in this reaction could be trapped by various nucleophiles.[9,10] In this way, skeletons of various heterocycles were successfully synthesized.[11–14]

Initially, phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), sodium *p*-tolylsulfinate (**4a**), and **5** were selected as the model substrates. Several catalysts such as CuI, CuBr, CuCl, and copper powder were tested with CuI giving the best results. Among several solvents screened, *N*,*N*-dimethylformamide (DMF) was the best. When the reaction was performed in DMF in the presence of one equivalent of Et_3N at room temperature for six hours, it was found that the desired product **7a** was indeed obtained in 84% yield (Table 1). Thus, the optimized reaction conditions used were 10 mol% of CuI, 1 mmol of alkyne, 1.2 mmol of sulfonyl azide, 1 mmol of sodium arylsulfinate, and 1 mmol of **5** in DMF at room temperature.

Phenylacetylene readily participates in these coupling reactions to furnish the compounds **7a**–**f** in good yields (Table 1). Butylacetylene served as low-yielding substrate compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently, and the corresponding products were obtained in good yields.

Table 1 Synthesis of *N*-[3-aryl(alkyl)-4-arylazet-2(1*H*)-ylidene]arene(alkane)sulfonamides **7**



1–**4**, **6**, **7**	R^1	R^2	Ar	Yield (%) of **7**
a	Ph	4-Tol	4-Tol	84
b	Ph	Ph	4-Tol	80
c	Ph	Me	4-Tol	74
d	Ph	4-Tol	Ph	78
e	Ph	Ph	Ph	73
f	Ph	Me	Ph	70
g	*n*-Bu	4-Tol	4-Tol	67
h	*n*-Bu	Ph	4-Tol	60
i	*n*-Bu	Me	4-Tol	58

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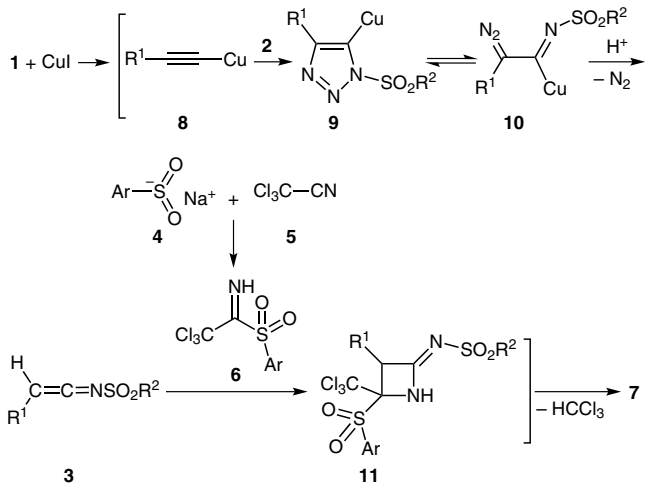
Structures of compounds **7a–i** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **7a** exhibited three singlets for methyl (δ = 2.47, 2.48 ppm), and NH (δ = 5.07 ppm) protons, along with characteristic multiplets for the phenyl protons. The ^{13}C NMR spectrum of **7a** showed 17 signals in agreement with the proposed structure. The mass spectrum of **7a** displayed the molecular ion peak at *m/z* = 452. The NMR spectra of compounds **7b–i** are similar to those of **7a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

A plausible mechanism for the formation of compounds **7** is given in Scheme 1. The yellow copper acetylide **8**, formed from **1** and CuI, is converted into ketenimine **3** by well-documented transformations.[15–17] Susequently, a [2+2] cycloaddition reaction[6,7,18] takes place between **3** and **6** (generated in situ from **4** and **5**) to produce **11**. Intermediate **11** affords product **7** by loss of chloroform.



Scheme 1

In summary, we have developed a multicomponent reaction involving ketenimine intermediates, trichloroacetonitrile, and sodium arylsulfinates, which affords a new route to the synthesis of *N*-[3-aryl(alkyl)-4-arylazet-2(1*H*)-ylidene]arene(alkane)sulfonamides in moderate to good yields. The present method may be considered as a practical route for the synthesis of functionalized azet-2(1*H*)-imines. The potential diversity of this reaction and available starting materials are the main advantages of this methodology.

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(5) **General Procedure for the Synthesis of Compounds 7**

To a mixture of sulfonyl azide **2** (1.2 mmol), alkyne **1** (1 mmol), and CuI (0.1 mmol), Et_3N (1 mmol) in DMF (2 mL) was slowly added **5** (1 mmol) and sodium arylsulfinate **4** (1 mmol) stirred at r.t. under N_2 atmosphere. After completion of the reaction [about 6 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.

4-Methyl-*N*-[3-Phenyl-4-tosylazet-2(1*H*)-ylidene]-benzenesulfonamide (7a)

Pale yellow powder, mp 120–123 °C; yield 0.38 g (84%). IR (KBr): ν_{max} = 3430, 2921, 1516, 1392, 1275, 1132, 1080 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (3 H, s, Me), 2.48 (3 H, s, Me), 5.07 (1 H, s, NH), 7.26–7.30 (3 H, m, Ph), 7.34–7.40 (4 H, m, Ph), 7.47 (2 H, d, ^3J = 7.9 Hz, Ar), 7.83 (2 H, d, ^3J = 7.7 Hz, Ar), 7.91 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.2 (Me), 27.3 (Me), 122.5 (C), 127.5 (2 CH), 128.0 (2 CH), 128.7 (2 CH), 129.2 (CH), 130.6 (2 CH), 130.7 (2 CH), 132.5 (2 CH), 135.0 (C), 136.0 (CH), 142.1 (C), 146.7 (C), 147.3 (C), 166.7 (C), 167.3 (C). MS (EI): *m/z* (%) = 452 (2) [M$^+$], 375 (8), 361 (12), 297 (14), 196 (23), 155 (100), 91 (70), 77 (51). Anal. Calcd (%) for $C_{23}H_{20}N_2O_4S_2$ (452.09): C, 61.04; H, 4.45; N, 6.19. Found: C, 61.49; H, 4.52; N, 6.28.

***N*-[3-Phenyl-4-tosylazet-2(1*H*)-ylidene]benzene-sulfonamide (7b)**

Pale yellow powder, mp 111–113 °C; yield 0.35 g (80%). IR (KBr): ν_{max} = 3437, 2939, 1528, 1400, 1271, 1140, 1084 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.48 (3 H, s, Me), 5.08 (1 H, s, NH), 7.29–7.36 (3 H, m, Ph), 7.40 (2 H, d, ^3J = 7.7 Hz, Ar), 7.48 (2 H, d, ^3J = 7.7 Hz, Ar), 7.62 (2 H, t, ^3J = 7.9 Hz, Ar), 7.75 (1 H, t, ^3J = 7.9 Hz, Ar), 7.91 (2 H, d, ^3J = 7.6 Hz, Ar), 8.03 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.2 (Me), 122.6 (C), 127.4 (2 CH), 127.5 (2 CH), 128.7 (2 CH), 129.2 (CH), 130.2 (2 CH), 130.7 (2 CH), 132.5 (2 CH), 135.7 (CH), 136.2 (C), 142.1 (C), 144.8 (C), 147.3 (C), 165.1 (C), 168.8 (C). MS (EI): *m/z* (%) = 438 (3) [M$^+$], 361 (11), 283 (13), 256 (15), 155 (76), 141 (100), 91 (34), 77 (44). Anal. Calcd (%) for $C_{22}H_{18}N_2O_4S_2$ (438.07): C, 60.26; H, 4.14; N, 6.39. Found: C, 60.06; H, 4.18; N, 6.45.

***N*-[3-Phenyl-4-tosylazet-2(1*H*)-ylidene]methane-sulfonamide (7c)**

Pale yellow powder, mp 98–100 °C; yield 0.28 g (74%). IR (KBr): ν_{max} = 3425, 2945, 1541, 1401, 1279, 1126 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (3 H, s, Me), 3.65 (3 H, s, Me), 5.08 (1 H, s, NH), 7.29–7.34 (3 H, m, Ph), 7.40 (2 H, d, ^3J = 7.7 Hz, Ar), 7.49 (2 H, d, ^3J = 7.8 Hz, Ar), 7.91 (2 H, d, ^3J = 7.8 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.2 (Me), 33.0 (Me), 122.5 (C), 127.5 (2 CH), 128.8 (2 CH), 129.3 (CH), 130.7 (2 CH), 132.5 (2 CH), 135.0 (C), 142.1 (C), 147.4 (C), 162.8 (C), 167.1 (C). MS (EI): *m/z* (%) = 376 (M$^+$, 2), 299 (10), 256 (14), 221 (12), 155 (40), 78 (100), 77 (44). Anal. Calcd (%) for $C_{17}H_{16}N_2O_4S_2$ (376.06): C, 54.24; H, 4.28; N, 7.44. Found: C, 54.66; H, 4.34; N, 7.56.

4-Methyl-*N*-[3-phenyl-4-(phenylsulfonyl)azet-2(1*H*)-ylidene]benzenesulfonamide (7d)

Pale yellow powder, mp 129–132 °C; yield 0.34 g (78%). IR

(KBr): ν_{max} = 3436, 2925, 1512, 1397, 1278, 1131, 1082 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.48 (3 H, s, Me), 5.08 (1 H, s, NH), 7.29-7.36 (3 H, m, Ph), 7.40 (2 H, d, ^3J = 7.7 Hz, Ar), 7.49 (2 H, d, ^3J = 7.6 Hz, Ar), 7.62 (2 H, t, ^3J = 7.7 Hz, Ar), 7.75 (1 H, t, ^3J = 7.7 Hz, Ar), 7.91 (2 H, d, ^3J = 7.9 Hz, Ar), 8.05 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.2 (Me), 122.6 (C), 127.4 (2 CH), 127.5 (2 CH), 128.7 (2 CH), 129.2 (CH), 130.1 (2 CH), 130.7 (2 CH), 132.6 (2 CH), 135.7 (C), 136.0 (CH), 142.1 (C), 144.8 (C), 147.3 (C), 164.8 (C), 167.7 (C). MS (EI): *m/z* (%) = 438 (2) [M^+], 361 (14), 347 (13), 283 (16), 196 (14), 155 (100), 141 (68), 91 (55), 77 (44). Anal. Calcd (%) for $C_{22}H_{18}N_2O_4S_2$ (438.07): C, 60.26; H, 4.14; N, 6.39. Found: C, 60.69; H, 4.21; N, 6.44.

***N*-[3-Phenyl-4-(phenylsulfonyl)azet-2(1*H*)-ylidene]-benzenesulfonamide (7e)**

Pale yellow powder, mp 114–117 °C; yield 0.31 g (73%). IR (KBr): ν_{max} = 3450, 2922, 1511, 1264, 1140, 1082 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.06 (1 H, s, NH), 7.31–7.36 (5 H, m, Ph), 7.51–7.53 (3 H, m, Ph), 7.59 (2 H, t, ^3J = 7.7 Hz, Ar), 7.72 (1 H, t, ^3J = 7.7 Hz, Ar), 7.98 (2 H, d, ^3J = 7.9 Hz, Ar), 8.05 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 122.6 (C), 127.4 (2 CH), 127.9 (2 CH), 128.8 (2 CH), 129.3 (CH), 130.2 (2 CH), 130.7 (CH), 132.6 (2 CH), 135.3 (CH), 135.7 (2 CH), 139.0 (C), 142.2 (C), 144.8 (C), 166.4 (C), 168.3 (C). MS (EI): *m/z* (%) = 424 (3) [M^+], 347 (13), 283 (8), 242 (10), 182 (21), 141 (100), 77 (34). Anal. Calcd (%) for $C_{21}H_{16}N_2O_4S_2$ (424.06): C, 59.42; H, 3.80; N, 6.60. Found: C, 59.69; H, 3.84; N, 6.57.

***N*-[3-Phenyl-4-(phenylsulfonyl)azet-2(1*H*)-ylidene]-methanesulfonamide (7f)**

Pale yellow powder, mp 90–93 °C; yield 0.25 g (70%). IR (KBr): ν_{max} = 3439, 1513, 1269, 1145, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.60 (3 H, s, Me), 5.08 (1 H, s, NH), 7.29–7.36 (3 H, m, Ph), 7.47 (2 H, d, ^3J = 7.7 Hz, Ar), 7.63 (2 H, t, ^3J = 7.8 Hz, Ar), 7.74 (1 H, t, ^3J = 7.8 Hz, Ar), 8.04 (2 H, d, ^3J = 7.8 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 33.0 (Me), 122.5 (C), 127.4 (2 CH), 128.8 (2 CH), 129.3 (CH), 130.2 (2 CH), 132.6 (2 CH), 135.7 (CH), 142.3 (C), 147.8 (C), 164.6 (C), 167.4 (C). MS (EI): *m/z* (%) = 362 (2) [M^+], 285 (11), 242 (18), 221 (21), 141 (54), 78 (100), 77 (25). Anal. Calcd (%) for $C_{16}H_{14}N_2O_4S_2$ (362.04): C, 53.02; H, 3.89; N, 7.73. Found: C, 53.41.; H, 3.94; N, 7.80.

***N*-[3-Butyl-4-tosylazet-2(1*H*)-ylidene]-4-methylbenzenesulfonamide (7g)**

Yellow oil; yield 0.29 g (67%). IR (KBr): ν_{max} = 3452, 2932, 1525, 1461, 1278, 1118 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3 H, t, ^3J = 6.9 Hz, Me), 1.28–1.45 (2 H, m, CH_2), 1.47–1.53 (2 H, m, CH_2), 2.18 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.43 (3 H, s, Me), 2.48 (3 H, s, Me), 5.10 (1 H, s, NH), 7.39–7.41 (4 H, m, Ph), 7.83 (2 H, d, ^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), 18.5 (CH_2), 22.1 (CH_2), 22.2 (CH_2), 31.0 (Me), 32.3 (Me), 122.2 (C), 127.5 (2 CH), 128.0 (2 CH), 130.6 (2 CH), 130.7 (2 CH), 132.3 (C), 136.0 (C), 144.3 (C), 146.6 (C), 162.6 (C), 166.2 (C). MS (EI): *m/z* (%) = 432 (2) [M^+], 375 (16), 341 (13), 277 (21), 196 (31), 155 (100), 91 (51), 77 (41), 57 (52). Anal. Calcd (%) for $C_{21}H_{24}N_2O_4S_2$ (432.12): C, 58.31; H, 5.59; N, 6.48. Found: C, 58.71; H, 5.65; N, 6.55.

***N*-[3-Butyl-4-tosylazet-2(1*H*)-ylidene]benzenesulfonamide (7h)**

Yellow oil; yield 0.25 g (60%). IR (KBr): ν_{max} = 3411, 2924, 1518, 1471, 1298, 1145, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (3 H, t, ^3J = 6.9 Hz, Me), 1.39–1.45 (2 H, m, CH_2), 1.48–1.53 (2 H, m, CH_2), 2.17 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.48 (3 H, s, Me), 5.09 (1 H, s, NH), 7.39 (2 H, d, ^3J = 7.8 Hz, Ar), 7.62 (2 H, t, ^3J = 7.8 Hz, Ar), 7.76 (1 H, t, ^3J = 7.8 Hz, Ar), 7.91 (2 H, d, ^3J = 8.0 Hz, Ar), 8.05 (2 H, d, ^3J = 8.0 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 18.5 (CH_2), 22.1 (CH_2), 22.5 (CH_2), 31.0 (Me), 122.4 (C), 127.4 (2 CH), 127.5 (2 CH), 130.1 (2 CH), 130.7 (2 CH), 135.7 (CH), 142.1 (C), 144.8 (C), 147.2 (C), 164.9 (C), 167.6 (C). MS (EI): *m/z* (%) = 418 (2) [M^+], 361 (10), 341 (16), 277 (32), 155 (34), 141 (100), 91 (49), 77 (35), 57 (50). Anal. Calcd (%) for $C_{20}H_{22}N_2O_4S_2$ (418.10): C, 57.39; H, 5.30; N, 6.69. Found: C, 57.76; H, 5.44; N, 6.75.

***N*-[3-Butyl-4-tosylazet-2(1*H*)-ylidene]methanesulfonamide (7i)**

Yellow oil; yield 0.21 g (58%). IR (KBr): ν_{max} = 3513, 2934, 1524, 1408, 1279, 1118, 1044 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3 H, t, ^3J = 6.9 Hz, Me), 1.38–1.43 (2 H, m, CH_2), 1.47–1.51 (2 H, m, CH_2), 2.17 (2 H, t, ^3J = 7.0 Hz, CH_2), 2.48 (3 H, s, Me), 3.66 (3 H, s, Me), 5.07 (1 H, s, NH), 7.39 (2 H, d, ^3J = 7.9 Hz, Ar), 7.91 (2 H, d, ^3J = 7.9 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 18.5 (CH_2), 22.1 (CH_2), 22.3 (CH_2), 31.0 (Me), 33.0 (Me), 122.6 (C), 127.5 (2 CH), 130.7 (2 CH), 142.1 (C), 147.3 (C), 162.2 (C), 167.5 (C). MS (EI): *m/z* (%) = 356 (2) [M^+], 277 (12), 236 (10), 155 (39), 91 (45), 78 (100), 57 (46). Anal. Calcd (%) for $C_{15}H_{20}N_2O_4S_2$ (356.46): C, 50.54; H, 5.66; N, 17.86. Found: C, 50.76; H, 5.74; N, 18.01.

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