Copper-Catalyzed One-Pot Synthesis of Functionalized Pyrroles from Sulfonyl Azides, Alkynes, and (*p*-Toluenesulfonyl)methyl Isocyanide

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Ketenimine intermediates generated by the addition of copper acetylides to sulfonyl azides are trapped by (*p*-toluenesulfonyl)methyl isocyanide ($TsCH_2NC$), in the presence of Et_3N, to afford functionalized pyrroles in moderate-to-good yields.

Introduction. – Due to the reactivity of the central C-atom of ketenimines towards various nucleophiles [1][2], they are applied in the construction of heterocycles. Among several methods leading to the generation of ketenimines, the Cu-catalyzed azide–alkyne cycloaddition attracted much attention due to its mild conditions [3]. The *in situ* generated ketenimine intermediates *via* this reaction could be trapped by various nucleophiles [4–8]. Applying this procedure, we present a novel Cu^I-catalyzed synthesis of functionalized pyrroles from *N*-sulfonyl ketenimines (generated, *in situ*, by addition of Cu acetylides to sulfonyl azides) and (*p*-toluenesulfonyl)methyl isocyanide (**3**) in the presence of Et_3N (*Scheme 1*). Herein, we report the details of this study.

Results and Discussion. – In our initial investigations, Phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), and **3** were selected as the model substrates. Several catalysts such as CuI, CuBr, CuCl, Cu_2O, and Cu powder were tested, with CuI leading to the best results. Among several solvents screened, DMF was the best. When the reaction was performed in DMF in the presence of 2 equiv. of Et_3N at room temperature for 6 h, it was found that the desired product **4a** was indeed obtained in 83% yield. Thus, the optimized reaction conditions used were 10 mol-% of CuI, 1 mmol of alkyne, 1.2 mmol of sulfonyl azide, and 1 mmol of **3** in 3 ml of DMF at room temperature.

Phenylacetylene readily participated in the coupling reaction to furnish the corresponding alkyl(aryl)-*N*-(4-phenyl-2-tosyl-1*H*-pyrrol-3-yl)sulfonamide **4** in good yields (*Scheme 1*). Aliphatic acetylenes were low-yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently, and the corresponding products were obtained in good yields.

The structure of compounds **4a**–**4i** was elucidated by IR, ^{1}H- and ^{13}C-NMR, and MS data. The ^{1}H-NMR spectrum of **4a** exhibited five *singlet*s for Me (δ(H) 2.34 and 2.42), NH (δ(H) 5.60 and 8.71), and pyrrole (δ(H) 7.01 ppm) H-atoms, along with characteristic *multiplet*s for the aromatic H-atoms. The ^{13}C-NMR spectrum of **4a** exhibites 18 signals in agreement with the proposed structure. The mass spectrum of **4a**

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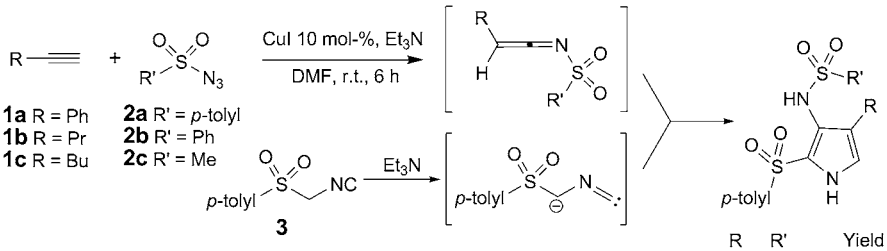
Scheme 1

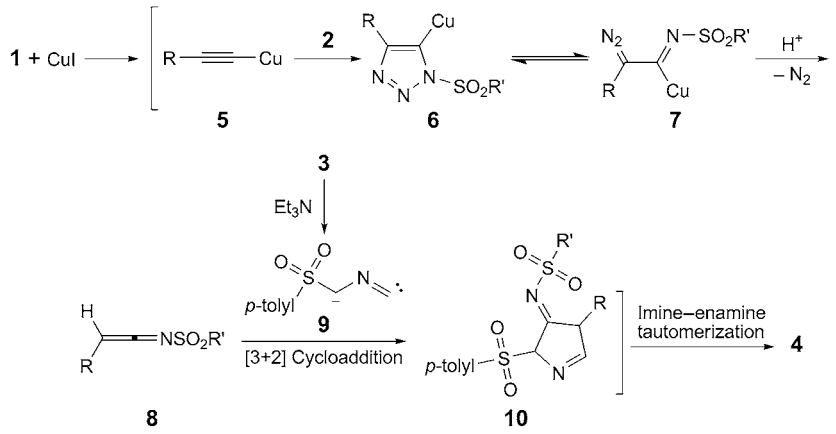


	R	R'	Yield [%]
4a	Ph	*p*-Tolyl	83
4b	Ph	Ph	87
4c	Ph	Me	79
4d	Pr	*p*-Tolyl	65
4e	Pr	Ph	63
4f	Pr	Me	60
4g	Bu	*p*-Tolyl	60
4h	Bu	Ph	57
4i	Bu	Me	52

displayed the molecular-ion peak at *m*/*z* 466. The NMR spectra of compounds **4b**–**4i** are similar to those of **4a**, except for the substituents, which gave rise to characteristic signals in the appropriate regions of the spectra.

A plausible mechanism for the formation of compounds **4** is depicted in *Scheme 2*. The yellow Cu acetylide **5**, formed from **1** and CuI, undergoes a 1,3-dipolar cycloaddition reaction with sulfonyl azide **2**, to generate the triazole derivative **6**[1]).

Scheme 2



[1]) Recently, *Sharpless* and co-workers [9] established anhydrous conditions with CuI in $CHCl_3$/2,6-lutidine at 0° to prevent decomposition of intermediate **6** and to provide selective formation of the desired 1-sulfonyltriazoles.

This intermediate undergoes ring opening to afford the α-diazoimino species **7** and, thereafter, ketenimine **8** by elimination of N_2 [10][11]. Anion **9** (formed from **3** and Et_3N) undergoes [3 + 2] dipolar cycloaddition with ketenimine **8** to afford 3(4*H*)-(sulfonylimino)-2*H*-pyrrole **10**, which is converted to **4** by imine–enamine tautomerization.

In conclusion, a one-pot Cu^I-catalyzed reaction of sulfonyl azides, terminal alkynes, and **3** is successfully established. The reaction described here is mild, general, and efficient, thus providing a simple path for the synthesis of substituted pyrroles.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; band positions in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer; at 70 eV; in m/z (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for Synthesis Compounds **4**. The isocyanide **3** (0.195 g, 1 mmol) and Et_3N (0.100 g, 1 mmol) were dissolved in DMF (3 ml), and stirred for 10 min. Then, sulfonyl azide **2** (1.2 mmol), alkyne **1** (1 mmol), CuI (0.019 g, 0.1 mmol), and Et_3N (0.100 g, 1 mmol) in DMF (2 ml) were slowly added to the mixture, which was stirred at r.t. under N_2. After completion of the reaction (*ca.* 6 h; TLC (AcOEt/hexane 1:3) monitoring), the mixture was diluted with CH_2Cl_2 (2 ml) and aq. NH_4Cl soln. (3 ml), stirred for 30 min, and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 3 ml), and the combined org. fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash CC (SiO_2; 230–400 mesh, *Merck*; hexane/AcOEt 3:1) to give product **4**.

4-Methyl-N-*{2-[(4-methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrrol-3-yl}benzenesulfonamide* (**4a**). Pale-yellow powder. Yield: 0.39 g (83%). M.p. 124–126°. IR (KBr): 3385, 3231, 1597, 1530, 1461, 1367, 1257, 1170, 1099. ^1H-NMR: 2.36 (*s*, Me); 2.42 (*s*, Me); 5.60 (*s*, NH); 7.03 (*t*, ^3J = 7.5, 1 arom. H); 7.06 (*s*, CH); 7.16 (*d*, ^3J = 7.5, 2 arom. H); 7.28–7.33 (*m*, 6 arom. H); 7.76 (*d*, ^3J = 8.2, 2 arom. H); 7.91 (*d*, ^3J = 8.2, 2 arom. H); 8.71 (*s*, NH). ^{13}C-NMR: 32.1 (Me); 32.3 (Me); 120.1 (C); 122.3 (CH); 124.3 (C); 127.5 (2 CH); 127.9 (2 CH); 128.2 (C); 129.3 (CH); 129.7 (2 CH); 129.8 (2 CH); 130.1 (2 CH); 130.7 (2 CH); 140.1 (C); 141.1 (C); 142.2 (C); 147.3 (C); 155.2 (C). MS: 466 (2, M^+), 311 (9), 296 (17), 170 (16), 155 (100), 141 (23), 91 (58), 77 (50), 64 (32). Anal. calc. for $C_{24}H_{22}N_2O_4S_2$ (466.57): C 61.78, H 4.75, N 6.00; found: C 62.25, H 4.81, N 6.09.

N-*{2-[(4-Methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrrol-3-yl}benzenesulfonamide* (**4b**). Pale-yellow powder. Yield: 0.36 g (87%). M.p. 119–121°. IR (KBr): 3354, 3182, 1598, 1539, 1373, 1263, 1097. ^1H-NMR: 2.41 (*s*, Me); 5.55 (*s*, NH); 6.92 (*t*, ^3J = 7.7, 1 arom. H); 7.15 (*s*, CH); 7.23 (*d*, ^3J = 8.2, 2 arom. H); 7.32 (*d*, ^3J = 7.7, 2 arom. H); 7.35 (*t*, ^3J = 7.5, 2 arom. H); 7.39–7.43 (*m*, 3 arom. H); 7.56–7.60 (*m*, 4 arom. H); 8.70 (*s*, NH). ^{13}C-NMR: 31.9 (Me); 120.3 (C); 122.3 (CH); 124.6 (C); 126.7 (2 CH); 128.8 (2 CH); 129.3 (2 CH); 129.8 (CH); 130.2 (2 CH); 130.4 (C); 132.6 (2 CH); 133.2 (2 CH); 138.1 (CH); 138.9 (C); 142.2 (C); 145.4 (C); 155.0 (C). MS: 452 (1, M^+), 311 (10), 272 (20), 155 (100), 141 (80), 91 (50), 77 (55), 64 (31). Anal. calc. for $C_{23}H_{20}N_2O_4S_2$ (452.55): C 61.04, H 4.45, N 6.19; found: C 61.47, H 4.53, N 6.28.

N-*{2-[(4-Methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrrol-3-yl}methanesulfonamide* (**4c**). Pale-yellow powder. Yield: 0.31 g (79%). M.p. 100–103°. IR (KBr): 3351, 3233, 1523, 1370, 1266, 1188, 1015. ^1H-NMR: 2.37 (*s*, Me); 3.64 (*s*, Me); 5.54 (*s*, NH); 6.87 (*t*, ^3J = 7.7, 1 arom. H); 7.03 (*s*, CH); 7.11 (*d*, ^3J = 7.7, 2 arom. H); 7.18 (*d*, ^3J = 7.7, 2 arom. H); 7.27 (*t*, ^3J = 7.5, 2 arom. H); 7.55 (*d*, ^3J = 7.5, 2 arom. H); 8.52 (*s*, NH). ^{13}C-NMR: 29.9 (Me); 33.0 (Me); 120.2 (C); 122.4 (CH); 124.6 (C); 126.6 (2 CH); 129.7 (2 CH); 129.8 (2 CH); 130.1 (CH); 133.0 (2 CH); 138.3 (C); 139.0 (C); 145.3 (C); 155.3 (C). MS: 390 (4, M^+), 311 (10), 235 (19), 180 (25), 155 (100), 91 (50), 78 (38), 77 (65). Anal. calc. for $C_{18}H_{18}N_2O_4S_2$ (390.48): C 55.37, H 4.65, N 7.17; found: C 55.70, H 4.72, N 7.25.

4-Methyl-N-*{2-[(4-methylphenyl)sulfonyl]-4-propyl-1*H-*pyrrol-3-yl}benzenesulfonamide* (**4d**). Pale-yellow powder. Yield: 0.28 g (65%). M.p. 98–101°. IR (KBr): 3370, 3182, 1597, 1510, 1404, 1267, 1168, 1097. ^{1}H-NMR: 0.97 (*t*, ^3J = 7.0, Me); 1.51–1.54 (*m*, CH_2); 2.13 (*t*, ^3J = 7.0); 2.41 (*s*, Me); 2.47 (*s*, Me); 5.54 (*s*, NH); 7.03 (*s*, CH); 7.30 (*d*, ^3J = 7.8, 2 arom. H); 7.38 (*d*, ^3J = 8.0, 2 arom. H); 7.75 (*d*, ^3J = 7.8, 2 arom. H); 7.89 (*d*, ^3J = 8.0, 2 arom. H); 8.66 (*s*, NH). ^{13}C-NMR: 13.7 (Me); 20.8 (CH_2); 22.2 (CH_2); 29.3 (Me); 32.3 (Me); 120.6 (C); 122.6 (CH); 124.4 (C); 127.4 (2 CH); 130.1 (2 CH); 130.3 (2 CH); 130.6 (2 CH); 134.6 (C); 142.1 (C); 146.0 (C); 147.2 (C); 155.4 (C). MS: 432 (4, M^+), 389 (8), 277 (14), 170 (25), 155 (100), 91 (57), 77 (40), 64 (18). Anal. calc. for $C_{21}H_{24}N_2O_4S_2$ (432.56): C 58.31, H 5.59, N 6.48; found: C 58.53, H 5.65, N 6.57.

N-*{2-[(4-Methylphenyl)sulfonyl]-4-propyl-1*H-*pyrrol-3-yl}benzenesulfonamide* (**4e**). Pale-yellow powder. Yield: 0.26 g (63%). M.p. 94–96°. IR (KBr): 3358, 3286, 1526, 1461, 1399, 1256, 1168, 1099. ^{1}H-NMR: 1.02 (*t*, ^3J = 7.0, Me); 1.56–1.60 (*m*, CH_2); 2.19 (*t*, ^3J = 7.0, CH_2); 2.42 (*s*, Me); 5.58 (*s*, NH); 6.88 (*t*, ^3J = 7.5, 1 arom. H); 7.04 (*s*, CH); 7.14 (*d*, ^3J = 7.5, 2 arom. H); 7.19 (*d*, ^3J = 7.9, 2 arom. H); 7.30 (*t*, ^3J = 7.5, 2 arom. H); 7.56 (*d*, ^3J = 7.9, 2 arom. H); 8.64 (*s*, NH). ^{13}C-NMR: 13.8 (Me); 20.8 (CH_2); 21.8 (CH_2); 29.3 (Me); 120.4 (C); 122.1 (CH); 124.3 (C); 126.6 (2 CH); 129.7 (2 CH); 129.8 (2 CH); 130.6 (2 CH); 133.0 (CH); 138.3 (C); 139.0 (C); 145.2 (C); 155.5 (C). MS: 418 (4, M^+), 375 (9), 262 (12), 157 (30), 155 (54), 141 (100), 91 (80), 77 (77), 64 (21), 43 (19). Anal. calc. for $C_{20}H_{22}N_2O_4S_2$ (418.53): found: C 57.39, H 5.30, N 6.69; found: C 57.63, H 5.24, N 6.76.

N-*{2-[(4-Methylphenyl)sulfonyl]-4-propyl-1*H-*pyrrol-3-yl}methanesulfonamide* (**4f**). Pale-yellow powder. Yield: 0.21 g (60%). M.p. 90–93°. IR (KBr): 3323, 3222, 1596, 1461, 1367, 1257, 1170, 1098. ^{1}H-NMR: 0.98 (*t*, ^3J = 7.0, Me); 1.52–1.56 (*m*, CH_2); 2.14 (*t*, ^3J = 7.0, CH_2); 2.48 (*s*, Me); 3.66 (*s*, Me); 5.56 (*s*, NH); 7.05 (*s*, CH); 7.41 (*d*, ^3J = 7.9, 2 arom. H); 7.92 (*d*, ^3J = 7.9, 2 arom. H); 8.60 (*s*, NH). ^{13}C-NMR: 13.8 (Me); 20.8 (CH_2); 22.2 (CH_2); 29.3 (Me); 33.0 (Me); 120.1 (C); 122.4 (CH); 124.5 (C); 127.5 (2 CH); 130.7 (2 CH); 142.1 (C); 147.3 (C); 155.2 (C). MS: 356 (2, M^+), 329 (10), 295 (20), 141 (100), 91 (54), 79 (33), 77 (50), 64 (18). Anal. calc. for $C_{15}H_{20}N_2O_4S_2$ (356.46): C 50.54, H 5.66, N 7.86; found: C 50.95, H 5.72, N 7.95.

N-*{4-Butyl-2-[(4-methylphenyl)sulfonyl]-1*H-*pyrrol-3-yl}-4-methylbenzenesulfonamide* (**4g**). Pale-yellow powder. Yield: 0.27 g (60%). M.p. 100–104°. IR (KBr): 3235, 3132, 1529, 1461, 1367, 1257, 1171, 1099. ^{1}H-NMR: 0.90 (*t*, ^3J = 7.0, Me); 1.40–1.44 (*m*, CH_2); 1.47–1.53 (*m*, CH_2); 2.17 (*t*, ^3J = 7.0, CH_2); 2.42 (*s*, Me); 2.48 (*s*, Me); 5.47 (*s*, NH); 7.06 (*s*, CH); 7.31 (*d*, ^3J = 7.8, 2 arom. H); 7.39 (*d*, ^3J = 8.0, 2 arom. H); 7.76 (*d*, ^3J = 7.8, 2 arom. H); 7.91 (*d*, ^3J = 8.0, 2 arom. H); 8.58 (*s*, NH). ^{13}C-NMR: 13.9 (Me); 18.5 (CH_2); 22.2 (CH_2); 22.3 (CH_2); 31.0 (Me); 33.0 (Me); 120.1 (C); 121.1 (CH); 124.1 (C); 127.4 (2 CH); 130.1 (2 CH); 130.3 (2 CH); 130.7 (2 CH); 134.7 (C); 142.1 (C); 146.0 (C); 147.2 (C); 154.1 (C). MS: 446 (5, M^+), 389 (9), 276 (12), 170 (25), 155 (100), 91 (50) ,77 (42), 64 (32). Anal. calc. for $C_{22}H_{26}N_2O_4S_2$ (446.58): C 59.17, H 5.87, N 6.27; found: C 59.61, H 5.96, N 6.22.

N-*{4-Butyl-2-[(4-methylphenyl)sulfonyl]-1*H-*pyrrol-3-yl}benzenesulfonamide* (**4h**). Pale-yellow powder. Yield: 0.22 g (57%). M.p. 87–90°. IR (KBr): 3286, 3135, 1553, 1461, 1361, 1251, 1168, 1099. ^{1}H-NMR: 0.90 (*t*, ^3J = 7.0, Me); 1.38–1.44 (*m*, CH_2); 1.48–1.53 (*m*, CH_2); 2.17 (*t*, ^3J = 7.0, CH_2); 2.47 (*s*, Me); 5.59 (*s*, NH); 6.92 (*t*, ^3J = 7.7, 1 arom. H); 7.03 (*s*, CH); 7.14 (*d*, ^3J = 7.7, 2 arom. H); 7.22 (*d*, ^3J = 7.9, 2 arom. H); 7.32 (*t*, ^3J = 7.7, 2 arom. H); 7.57 (*d*, ^3J = 7.9, 2 arom. H); 8.64 (*s*, NH). ^{13}C-NMR: 13.7 (Me); 18.6 (CH_2); 21.9 (CH_2); 22.3 (CH_2); 31.1 (Me); 120.4 (C); 122.4 (CH); 124.4 (C); 126.7 (2 CH); 129.8 (2 CH); 129.9 (2 CH); 130.1 (2 CH); 133.1 (CH); 138.3 (C); 138.9 (C); 145.3 (C); 155.1 (C). MS: 432 (5, M^+), 375 (12), 277 (20), 155 (54), 141 (100), 91 (55), 77 (66), 64 (21), 57 (53). Anal. calc. for $C_{21}H_{24}N_2O_4S_2$ (432.56): C 58.31, H 5.59, N 6.48; found: C 57.95, H 5.70, N 6.59.

N-*{4-Butyl-2-[(4-methylphenyl)sulfonyl]-1*H-*pyrrol-3-yl}methanesulfonamide* (**4i**). Pale-yellow powder. Yield: 0.20 g (52%). M.p. 94–96°. IR (KBr): 3286, 3131, 1597, 1360, 1257, 1170, 1099. ^{1}H-NMR: 0.89 (*t*, ^3J = 7.0, Me); 1.38–1.42 (*m*, CH_2); 1.47–1.51 (*m*, CH_2); 2.15 (*t*, ^3J = 7.0, CH_2); 2.47 (*s*, Me); 3.67 (*s*, Me); 5.54 (*s*, NH); 7.07 (*s*, CH); 7.39 (*d*, ^3J = 7.9, 2 arom. H); 7.89 (*d*, ^3J = 7.9, 2 arom. H); 8.62 (*s*, NH). ^{13}C-NMR: 13.9 (Me); 18.5 (CH_2); 20.1 (CH_2); 22.2 (CH_2); 31.0 (Me); 33.0 (Me); 120.4 (C); 122.5 (CH); 124.4 (C); 127.4 (2 CH); 130.7 (2 CH); 142.0 (C); 147.4 (C); 156.4 (C). MS: 370 (3, M^+), 313 (10), 291 (9), 141 (100), 93 (30), 91 (46), 77 (55), 64 (21). Anal. calc. for $C_{16}H_{22}N_2O_4S_2$ (370.49): C 51.87, H 5.99, N 7.56; found: C 51.46, H 5.85, N 7.67.

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