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A Click Chemistry Approach to Tetrazoles via Huisgen 1,3-Dipolar Cycloaddition, Part 1: Synthesis of 5-Sulfonyltetrazoles from Azides and Sulfonylcyanides

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Experimental Section

All ^{1}H NMR spectra were taken on a Bruker AMX-400 spectrometer in $CDCl_3$ with TMS as a standard at 0.00 ppm unless otherwise noted. All ^{13}C NMR spectra were taken on the same machine at 100 MHz in $CDCl_3$ with $CDCl_3$ as a standard at 77.00 ppm, unless otherwise noted. All ^{15}N NMR spectra taken on the same machine in THF with CD_3NO_2 as an external standard at 0.0 ppm. All melting points were taken on a Thomas Hoover Uni-melt melting point apparatus and are uncorrected. All Mass Spectral data were obtained using MALDI ionization. Reagents were used unpurified.

Synthesis of Azides (1a-18a):

Most of the azides have been reported in literature before. Below is a representative example of the synthesis of each class of azides.

(**2-Azidoethyl)benzene (1a):**[1] A 250 mL roundbottomed flask was charged with a stir bar, (2-bromoethyl)benzene (9.25 g, 50 mmol), sodium azide (6.5 g, 100 mmol), potassium iodide (168 mg, 1 mmol), and 50 mL DMF. The suspension was stirred in an oil

bath set to 90°C for 16 hours, and the solvent was then evaporated under reduced pressure. The solid was dissolved in 50 mL ethyl acetate, and 50 mL water. The organic layer was isolated, dried over $MgSO_4$, and evaporated to give **1a** (7.27 g, 49.5 mmol, 99%) as a yellow oil. The product had ^{1}H NMR 7.35-7.20 (m, 5H), 3.51 (t, 2H, *J*= 7.0 Hz), 2.99 (t, 2H, *J*= 7.0 Hz); ^{13}C NMR 137.86, 128.56, 128.44, 126.58, 52.20, 35.11.

Azide **9a** was also made using this protocol.

Pentafluorobenzylazide (8a): A 250 mL roundbottomed flask was charged with a stir bar, pentafluorobenzylbromide (3.8 g, 15 mmol), sodium azide (2.0 g, 30 mmol), potassium iodide (50 mg), and 50 mL acetonitrile. The reaction was stirred at reflux for 16 hours. The solvent was evaporated, and the residue was dissolved in 50 mL water and 50 mL CH_2Cl_2, and shaken with sodium sulfite (100 mg). The organic layer was isolated, dried over $MgSO_4$, and evaporated to yield **1a** (3.31 g, 14.83 mmol, 99%) as a clear oil. The product had ^{1}H NMR 4.46 (s, 2H); ^{13}C NMR 145.36 (dm, *J*= 1007 Hz), 141.52 (dm, *J*= 1020 Hz), 137.58 (dm, *J*= 1007 Hz), 109.34 (m), 41.60.

Other azides made using this protocol include **3a, 4a**, **5a**, **6a**, **7a**, **12a**, **13a**.

4-Azidotoluene (15a)[2]: A 100 mL roundbottomed flask was charged with a stir bar, 50 mL 2N HCl, and 4-toluidine (3.75 g, 35 mmol). The solution was chilled to -5°C in a salt-ice bath. An ice-cold solution of sodium nitrite (2.90 g, 42 mmol) in 10 mL water was slowly added over five minutes such that the temperature of the reaction did not rise above -3°C. After a further five minutes, 250 mg urea was added to destroy the excess nitrous

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(1) The spectral data match reported values. See: A. R. Katritzky, G. Liso, E. Lunt, R. C. Patel, S. S. Thind, A. Zia, *J. Chem. Soc., Perkin Trans. 1* **1980**, *(4)*, 849-50.

acid. The diazonium salt was then added over five minutes to a stirred ice-cold solution of sodium azide (4.55 g, 70 mmol) and sodium acetate (8.4 g, 105 mmol) in 50 mL water. The mixture was stirred for 2 hours at 0°C, and the dark oily product was extracted into diethyl ether (2x100 mL). The ethereal solution was washed with water (2x100 mL), dried over $MgSO_4$, and evaporated to dryness to yield **15a** (4.73 g, 33.1 mmol g, 95%) as an yellow oil. The product had ^{1}H NMR 7.16 (d, 2H, *J*=8.5 Hz), 6.93 (d, 2H, *J*=8.8 Hz), 2.32 (s, 3H); ^{13}C NMR 137.06, 134.46, 130.22, 118.72, 20.67.

Other azides made using this protocol include **16a** , **17a** and **18a**. Azides **10a**,[3] and **11a**[4] are reported in literature, and azide **14a** is a commerically available sample.

5-Methylthio-1-phenethyl-*1H*-tetrazole (1):[5] A glass pressure tube was charged with a stir bar, (2-azidoethyl)benzene (670 mg, 4.55 mmol), methylthiocyanate (2 mL, 27 mmol), sealed, submerged and stirred in an oil bath set to 136°C for 40 hours. The methylthiocyanate was evaporated under reduced pressure, and the crude material was purified by silica gel chromatography eluting with a mixture of 20% ethyl acetate and 80% hexanes to yield **1** (322 mg, 1.47 mmol, 32%) as a clear oil. The product had ^{1}H NMR 7.32-7.22 (m, 3H), 7.12-7.08 (m, 2H), 4.43 (t, 2H, *J*= 7.0 Hz), 3.19 (t, 2H, *J*= 7.4 Hz), 2.71 (s, 3H); ^{13}C NMR 154.54, 135.93, 128.65, 128.53, 127.05, 48.37, 35.10, 15.18; ^{15}N NMR 7.93, -9.55, -60.74, -150.07; HRMS (MALDI) calc'd for $C_{10}H_{13}N_4S$ (MH^+) 221.0855, found 221.0856.

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(2) Prepared as in: H. Tomioka, T. Matsuhsita, S. Murata, S. Koseki, *Liebigs Ann.* **1996**, p. 1971-1980.
(3) G. Swift, D. Swern, *J. Org. Chem.* **1967**, *32(3)*, 511-517.
(4)A. Converso, K. Burow, A. Marzinzik, K. B. Sharpless, M. G. Finn, *J. Org. Chem.* **2001**, *66*(12), 4386-4392.

General Synthesis of Sulfonyl Tetrazoles:

A vial was charged with a stir bar, toluene sulfonylcyanide (905 mg, 5.0 mmol), and azide (5.0 mmol), and tightly capped. The reagents were stirred in an oil bath set to 80°C, neat, for 16 hours. If the reaction was not complete at this time, stirring was continued, in some cases with the temperature reset to 100°C. In cases of unhindered azides, the crude product, a light yellow solid, was analytically pure. To remove the color, the product is dissolved in 30% ethyl acetate, and 70% hexanes, and run down a short plug of silica gel to yield a white solid. If excess toluene sulfonylcyanide is present, the product is crushed and placed under a vaccuum at 80°C for four hours. In the case of hindered azides, the product is purified by column chromatography eluting with 10% ethyl acetate and 90% hexanes to give the product as a white or light tan solid. In some cases (**9, 14**) the product was sufficiently insoluble that trituration with 10% ethyl acetate and 90% hexanes was sufficient to purify the compound.

5-Toluenesulfonyl-1-(2-phenethyl)tetrazole (2):[5] The product (1.63 g, 4.98 mmol, 99%) had m.p. 101-103°C (crude solid); ^{1}H NMR 7.91 (d, 2H, *J*= 8.5 Hz), 7.42 (d,

(5) Regiochemical assignment based on ^{15}N NMR spectra comparison with compounds in H A. Dabbagh, W. Lwowski, *J. Org. Chem.* **2000**, *65*(22), 7284-7290.

2H, *J*= 8.2 Hz), 7.35-7.27 (m, 3H), 7.23-7.19 (m, 2H), 5.00-4.95 (m, 2H), 3.36-3.31 (m, 2H), 2.49 (s, 3H); ^{13}C NMR 154.86, 147.46, 135.65, 134.13, 130.37, 129.15, 128.93, 128.84, 127.38, 50.93, 36.30, 21.89; ^{15}N NMR 13.50, -3.94, -40.47, -143.87; HRMS (MALDI) calc'd for $C_{16}H_{16}N_4O_2SNa$ (MNa^+) 351.0886, found 351.0881.

5-Toluenesulfonyl-1-benzyltetrazole (3): The product (1.57 g, 5.0 mmol, 99%) had m.p. 137-138°C (crude solid); ^{1}H NMR 7.76 (d, 2H, *J*= 8.5 Hz), 7.39-7.35 (m, 5H), 7.31 (d, 2H, *J*= 8.8 Hz), 5.94 (s, 2H), 2.44 (s, 3H); ^{13}C NMR 154.57, 147.29, 134.14, 132.76, 130.23, 129.15, 129.06, 128.44, 53.08, 21.82; ; HRMS (MALDI) calc'd for $C_{15}H_{15}N_4O_2S$ (MH^+) 315.0910, found 315.0881.

α,α'-bis-(1-(5-Toluenesulfonyl)tetrazole)-*p*-xylene (4): The product (2.75 g, 5.0 mmol, 99%) decomposed slowly above 160°C; ^{1}H NMR 7.80 (d, 4H, *J*= 8.5 Hz), 7.41 (s, 4H), 7.33 (d, 4H, *J*= 7.9 Hz), 5.95 (s, 4H), 2.44 (s, 6H); ^{13}C NMR 154.69, 147.66, 133.92, 130.34, 129.23, 129.09, 52.46, 21.84; HRMS (MALDI) calc'd for $C_{24}H_{22}N_8O_4S_2Na$ (MNa^+) 573.1098, found 573.1084.

5-Toluenesulfonyl-1-(4-methoxybenzyl)tetrazole (5): The product (1.65 g, 5.0 mmol, 99%) had m.p. 124-126°C (crude solid); ^{1}H NMR 7.81 (d, 2H, *J*= 8.5 Hz), 7.37-7.32 (m, 4H), 6.88 (d, 2H, *J*= 8.0 Hz), 5.86 (s, 2H), 3.81 (s, 3H), 2.45 (s, 3H); ^{13}C NMR 160.23, 154.41, 147.26, 134.22, 130.23, 130.17, 129.08, 124.79, 114.35, 55.31, 52.73, 21.83; HRMS (MALDI) calc'd for $C_{16}H_{16}N_4SO_3$ (MNa^+) 367.0835 found 367.0825.

Benzyl ((5-toluenesulfonyl)-1-tetrazolyl acetate (6): The product (1.86 g, 5.0 mmol, 99%) had m.p. 98°C (crude solid); ^{1}H NMR 7.90 (d, 2H, *J*= 8.5 Hz), 7.42-7.34 (m,

7H), 5.57 (s, 2H), 5.27 (s, 2H), 2.46 (s, 3H); ^{13}C NMR 164.83, 155.23, 147.59, 134.26, 134.14, 130.33, 129.28, 128.93, 128.77, 128.53, 68.64, 50.24, 21.91; HRMS (MALDI) calc'd for $C_{17}H_{17}N_4SO_4$ (MH^+) 373.0965, found 373.0958.

5-Toluenesulfonyl-1-(4-fluorobenzyl)tetrazole (7): The product (1.64 g, 4.94 mmol, 99%) had m.p. 99°C (crude solid); ^{1}H NMR 7.81 (d, 2H, *J*= 8.5 Hz), 7.43-7.39 (m, 2H), 7.36 (d, 2H, *J*= 7.9 Hz), 7.09-7.03 (m, 2H), 5.90 (s, 2H), 2.45 (s, 3H); ^{13}C NMR 154.54, 147.53, 134.03, 130.74, 130.65, 130.32, 129.10, 128.59, 116.11 (*m*), 52.36, 21.87; HRMS (MALDI) calc'd for $C_{15}H_{13}F_1N_4O_2SNa$ (MNa^+) 355.0635, found 355.0647.

5-Toluenesulfonyl-1-(pentafluorobenzyl)tetrazole (8): The product (2.00 g, 4.95 mmol, 99%) had m.p. 136-137°C (crude solid); ^{1}H NMR 8.01 (d, 2H, *J*= 8.5 Hz), 7.47 (d, 2H, *J*= 8.2 Hz), 7.26 (s, 2H), 2.51 (s, 3H); ^{13}C NMR 154.78, 147.90, 145.57 (dm, *J*= 1001 Hz), 142.47 (dm, *J*= 1025 Hz), 137.67 (dm, *J*= 1019 Hz), 133.80, 130.46, 129.20, 106.30 (m), 40.86, 21.86; HRMS (MALDI) calc'd for $C_{15}H_9F_5N_4O_2SNa$ (MNa^+) 427.0259, found 427.0280.

5-Toluenesulfonyl-1-cyclohexyltetrazole (9): The product (1.39 g, 4.54 mmol, 91%) had m.p. 116°C; ^{1}H NMR 7.98 (d, 2H, *J*= 7.9 Hz), 7.45 (d, 2H, *J*= 7.9 Hz), 5.08-5.00 (m, 1H), 2.50 (s, 3H) 2.19-2.11 (m, 2H), 2.08-1.93 (m, 4H), 1.84-1.77 (m, 1H), 1.57-1.44 (m, 2H), 1.40-1.25 (m, 1H); ^{13}C NMR 154.34, 147.35, 134.20, 130.28, 129.16, 60.61, 32.87, 25.06, 24.64, 21.83; HRMS (MALDI) calc'd for $C_{14}H_{18}N_4O_2SNa$ (MNa^+) 329.1043, found 329.1053.

5-Toluenesulfonyl-1-(1-*trans*-(2-cyclohexanol))tetrazole (10): The product (1.23 g, 3.80 mmol, 76%) decomposed from 148-152°C; ^{1}H NMR 8.00 (d, 2H, *J*= 8.5 Hz), 7.42

(d, 2H, *J*= 8.1 Hz), 4.98 (ddd, 1H, *J*= 14.1, 10.0, 4.4 Hz), 4.12-4.06 (m, 1H), 2.48 (s, 3H), 2.27-2.18 (m, 2H), 2.05 (dq, 2H, *J*= 12.3, 2.9 Hz), 1.97-1.86 (m, 3H), 1.58-1.45 (m, 3H); ^{13}C NMR 155.51, 147.25, 134.42, 130.20, 129.26, 72.60, 66.43, 34.61, 31.78, 24.54, 23.90, 21.84; HRMS (MALDI) calc'd for $C_{14}H_{19}N_4O_3S$ (MH^+) 323.1172, found 323.1168.

5-Toluenesulfonyl-1-(1,5-(9-thiabicyclo[3.3.1]nonane))tetrazole (11): The product (1.96 g, 3.35 mmol, 67%) decomposed from 178-182°C; ^{1}H NMR (600 MHz, 2 isomers at room temperature due to ring rearrangenment; see reference 24; a:b :: 5:3) 8.06 (d, 4H(a), *J*= 8.5 Hz), 7.97 (d, 4H(b), *J*= 8.5 Hz), 7.61 (d, 4H(a), *J*= 8.1 Hz), 7.53 (d, 4H(b), *J*= 7.9 Hz), 5.92-5.85 (m, 2H(a)), 5.74-5.67 (m, 2H(b)), 3.52- 3.48 (m, 1H(b)), 3.47-3.43 (m, 1H(a)), 3.28-3.25 (m, 1H(a)), 3.22-3.19 (m, 1H(b)), 3.13-3.04 (m, 1H(a&b)), 2.97-2.90 (m, 1H(a)), 2.83-2.76 (m, 1H(b)), 2.48 (s, 6H(a)), 2.43 (s, 6H(b)), 2.30-2.24 (m, 2H(a&b)), 2.24-2.16 (m, 2H(a&b)); ^{13}C NMR 156.04, 155.93, 149.02, 147.90, 136.17, 135.20, 132.02, 131.89, 130.40, 129.74, 80.52, 80.30, 67.74, 63.67, 35.84, 35.26, 28.96, 27.29, 22.68, 22.56; HRMS (MALDI) calc'd for $C_{24}H_{26}N_8O_4S_3Na$ (MNa^+) 609.1131, found 609.1122.

5-Toluenesulfonyl-1-(1-phenethyl)tetrazole (12): The product (972 mg, 2.96 mmol, 59%) had m.p. 114-115°C; ^{1}H NMR 7.73 (d, 2H, *J*= 8.2 Hz), 7.36-7.25 (m, 7H), 7.48 (q, 1H, *J*= 7.0 Hz), 2.41 (s, 3H), 2.06 (d, 3H, *J*= 6.8 Hz); ^{13}C NMR 154.28, 147.13, 138.28, 134.11, 130.12, 128.91 (2H), 128.79, 126.76, 60.50, 22.12, 21.72; HRMS (MALDI) calc'd for $C_{16}H_{16}N_4O_2SNa$ (MNa^+) 351.0886, found 351.0899.

5-Toluenesulfonyl-1-(diphenylmethyl)tetrazole (13): The product (930 mg, 2.38 mmol, 48%) had m.p. 122-125°C; ^{1}H NMR 8.01 (d, 2H, *J*= 8.5 Hz), 7.39-7.34 (m, 8H),

7.29 (s, 1H), 7.27-7.23 (m, 4H), 2.43 (s, 3H); ^{13}C NMR 166.42, 146.23, 135.81, 135.31, 130.14, 129.09, 128.94, 128.87, 128.15, 72.69, 21.74; HRMS (MALDI) calc'd for $C_{21}H_{18}N_4O_2SNa$ (MNa^+) 413.1043, found 413.1058.

5-Toluenesulfonyl-1-(1-adamantyl)tetrazole (14): The product (818 mg, 2.29 mmol, 46%) decomposed from 201-204°C; ^{1}H NMR 7.95 (d, 2H, *J*= 8.5 Hz), 7.44 (d, 2H, *J*= 8.1 Hz), 2.57-2.54 (m, 6H), 2.51 (s, 3H), 2.37-2.32 (m, 3H), 1.88-1.78 (m, 6H); ^{13}C NMR 155.98, 146.89, 135.22, 129.95, 129.72, 66.21, 41.85, 35.49, 29.81, 21.90; HRMS (MALDI) calc'd for $C_{18}H_{22}N_4O_2SNa$ (MNa^+) 381.1356, found 381.1363.

5-Toluenesulfonyl-1-(4-tolyl)tetrazole (15): The product (980 mg, 3.12 mmol, 62%) had m.p. 141-143°C; ^{1}H NMR 7.82 (d, 2H, *J*= 8.5 Hz), 7.47 (d, 2H, *J*= 8.5 Hz), 7.40-7.36 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H); ^{13}C NMR 155.44, 147.38, 141.96, 134.10, 130.59, 130.17, 130.17, 129.41, 125.43, 21.87, 21.38; HRMS (MALDI) calc'd for $C_{15}H_{14}N_4O_2SNa$ (MNa^+) 337.0730, found 337.0734.

5-Toluenesulfonyl-1-(1-(3-trifluoromethylphenyl)tetrazole (16): The product (1.23 g, 3.34 mmol, 67%) had m.p. 120-122°C; ^{1}H NMR 7.94-7.88 (m, 2H), 7.85-7.76 (m, 4H), 7.41 (d, 2H, *J*= 8.0 Hz), 2.49 (s, 3H); ^{13}C NMR 155.65, 147.88, 133.63, 133.52, 132.30 (q, *J*= 133 Hz), 130.46, 130.35, 129.41, 129.18, 128.26, 122.87, 21.89; HRMS (MALDI) calc'd for $C_{15}H_{11}F_3N_4O_2Sna$ (MNa^+) 391.0447, found 391.0455.

5-Toluenesulfonyl-1-(1-(5-dimethylisophthalyl)tetrazole (17): The product (890 mg, 2.14 mmol, 43%) decomposed from 198-200°C; ^{1}H NMR 8.95 (t, 1H, *J*= 1.4 Hz), 8.45 (d, 2H, *J*= 1.5 Hz), 7.89 (d, 2H, *J*= 8.5 Hz), 7.44 (d, 2H, *J*= 8.2 Hz), 4.02 (s, 6H), 2.50 (s,

3H); ^{13}C NMR 155.68, 147.85, 133.72, 133.63, 133.11, 132.40, 130.67, 130.43, 129.47, 52.99, 21.92; HRMS (MALDI) calc'd for $C_{18}H_{17}N_4O_6S$ (MH^+) 417.0863, found 417.0866.

5-Toluenesulfonyl-1-(4-anisyl)tetrazole (18): The product (491 mg, 1.49 mmol, 30%) had m.p. 108-110°C; ^{1}H NMR 7.82 (d, 2H, *J*= 8.4 Hz), 7.49 (d, 2H, *J*= 8.8 Hz), 7.39 (d, 2H, *J*= 8.1 Hz), 7.07 (d, 2H, *J*= 8.8 Hz), 3.91 (s, 3H), 2.48 (s, 3H); ^{13}C NMR 161.71, 155.49, 147.39, 134.12, 130.20, 129.43, 127.14, 125.70, 114.61, 55.72, 21.90; HRMS (MALDI) calc'd for $C_{15}H_{14}N_4O_2SNa$ (MNa^+) 353.0679, found 353.0680.

5-Thiophenyl-1-benzyltetrazole (19): A 100 mL roundbottomed flask was charged with **3** (1.57 g, 5.0 mmol), thiophenol (1.10 g, 10 mmol), potassium carbonate (1.0 g, 7.2 mmol), and acetonitrile (20 mL) and the contents were stirred at room temperature for 16 hours. The solvent was evaporated, and the slurry was placed on a silica gel plug, which was washed with hexanes (500 mL) and then the product was eluted with a mixture of 25% ethyl acetate and 75% hexanes (500 mL). The solvent was evaporated to give **20** (1.28g, 95% yield) as a white powder. The product had m.p. 59-60 °C; ^{1}H NMR 7.46-7.42 (m, 2H), 7.37-7.30 (m, 6H), 7.24-7.21 (m, 2H), 5.50 (s, 2H); ^{13}C NMR 152.26, 132.85, 132.50, 129.70, 129.42, 128.97, 128.83, 127.94, 127.62, 51.29; HRMS (MALDI) calc'd for $C_{14}H_{13}N_4SNa$ (MH^+) 269.0855, found 269.0854.