

Copyright WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2002.  
Supporting Information for *Angew. Chem. Int. Ed.* Z18693

**A Click Chemistry Approach to Tetrazoles via Huisgen 1,3-Dipolar Cycloaddition,  
Part 2: Synthesis of 5-Acyltetrazoles from Azides and Acylcyanides**

*Zachary P. Demko, K. Barry Sharpless*

**Experimental Section**

All  $^1\text{H}$  NMR spectra were taken on a Bruker AMX-400 spectrometer in  $\text{CDCl}_3$  with TMS as a standard at 0.00 ppm unless otherwise noted. All  $^{13}\text{C}$  NMR spectra were taken on the same machine at 100 MHz in  $\text{CDCl}_3$  with  $\text{CDCl}_3$  as a standard at 77.00 ppm, unless otherwise noted. 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. Azides were synthesized as described in the previous communication. Most acyl cyanides are commercially available; *p*-methoxybenzoyl cyanide and diethylcyanoformamide were synthesized using the procedure found in reference 11g, and 2,6-difluorobenzoylcyanide was synthesized using the procedure found in reference 11a.

General Synthesis of Acyl Tetrazoles:

A vial was charged with a stir bar, azide (5.0 mmol), and acylcyanide (7.5 mmol), and tightly capped. The reagents were stirred in an oil bath set to 120°C, neat, for 40 hours.

If the reactions was not complete at this time, it was continued, in some cases with an increase in temperature to 130°C, until the reaction was complete. The reaction mixture was then cooled, and dissolved in ethyl acetate (10 mL) and added to an aqueous solution of sodium carbonate (10% w/w, 50 mL) and stirred for one hour. In some cases, longer stirring times and the addition of acetone (20 mL) was necessary to effect the full hydrolysis of the acyl cyanide. The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were diluted with hexanes (60 mL) and run through a short plug of silica gel. The silica plug was washed with an equal amount and composition of solvent. The solvent was evaporated to yield the product.

**1-(2-Methylbenzyl)-5-benzoyl tetrazole (1):** The reaction was heated for 60 hours. The product (1.37 g, 4.92 mmol, 98%) was a tan powder with m.p. 80 °C; <sup>1</sup>H NMR 8.35-8.32 (m, 2H), 7.71-7.66 (m, 1H), 7.55-7.50 (m, 2H), 7.22-7.17 (m, 2H), 7.13-7.08 (m, 1H), 7.02-6.98 (m, 1H), 5.95 (s, 2H), 2.43 (s, 3H); <sup>13</sup>C NMR 182.18, 149.96, 136.90, 135.61, 135.27, 132.44, 131.44, 131.29, 129.37, 129.25, 128.83, 126.94, 51.23, 19.75; HRMS (MALDI) calc'd for C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>ONa (MNa<sup>+</sup>) 301.1060, found 301.1062.

**1-(3-Methoxybenzyl)-5-benzoyl tetrazole (2):** The product (1.38 g, 4.69 mmol, 94%) was a yellow oil; <sup>1</sup>H NMR 8.39-8.35 (m, 2H), 7.70-7.65 (m, 1H), 7.54-7.50 (m, 2H), 7.25-7.20 (t, 1H, *J* = 7.9 Hz), 6.95-6.90 (m, 2H), 6.85-6.81 (m, 1H), 5.91 (s, 2H), 3.74 (s, 3H); <sup>13</sup>C NMR 181.41, 159.85, 149.10, 135.07, 134.94, 134.79, 130.99, 130.00, 128.49,

120.49, 114.39, 113.83, 55.17, 52.85; HRMS (MALDI) calc'd for C<sub>16</sub>H<sub>15</sub>N<sub>4</sub>O<sub>2</sub> (MH<sup>+</sup>) 295.1189, found 295.1195.

**1-(4-Fluorobenzyl)-5-benzoyl tetrazole (3):** The reaction was heated for 60 hours. The product (1.34 g, 4.75 mmol, 95%) was a yellow solid with m.p. 90-91 °C; <sup>1</sup>H NMR 8.39-8.35 (m, 2H), 7.70-7.64 (m, 1H), 7.54-7.49 (m, 2H), 7.45-7.39 (m, 2H), 7.02-6.97 (m, 2H), 5.89 (s, 2H); <sup>13</sup>C NMR 181.26, 162.71 (d, *J* = 988 Hz), 148.90, 135.03, 134.62, 130.89, 130.50 (d, *J* = 36 Hz), 129.39, 128.65, 115.79 (d, *J* = 85 Hz), 52.14, 22.46; HRMS (MALDI) calc'd for C<sub>15</sub>H<sub>11</sub>F<sub>1</sub>N<sub>4</sub>ONa (MNa<sup>+</sup>) 305.0809, found 305.0811.

**1-(Pentafluorobenzyl)-5-benzoyl tetrazole (4):** The product (1.66 g, 4.69 mmol, 94%) was a yellow solid with m.p. 99-101 °C; <sup>1</sup>H NMR 8.48-8.44 (m, 2H), 7.77-7.73 (m, 1H), 7.62-7.56 (m, 2H), 6.06 (s, 2H); <sup>13</sup>C NMR 181.34, 149.31, 145.54 (dm, *J* = 1040 Hz), 142.12 (dm, *J* = 1025 Hz), 137.64 (dm, *J* = 1015 Hz), 135.43, 134.47, 131.06, 128.86, 107.19 (m), 40.90; HRMS (MALDI) calc'd for C<sub>15</sub>H<sub>7</sub>F<sub>5</sub>N<sub>4</sub>ONa (MNa<sup>+</sup>) 377.0432, found 377.0437.

**Benzyl ((5-benzoyl)-1-tetrazolyl) acetate (5):** The reaction was heated for 60 hours. The product (1.54 g, 4.78 mmol, 96%) was a yellow oil; <sup>1</sup>H NMR 8.46-8.40 (m, 2H), 7.72-7.67 (m, 1H), 7.56-7.51 (m, 2H), 7.33-7.25 (m, 5H), 5.58 (s, 2H), 5.17 (s, 3H); <sup>13</sup>C NMR 181.28, 165.00, 149.81, 135.19, 134.34, 134.11, 131.03, 128.73, 128.69, 128.56, 128.41, 68.22, 50.47; HRMS (MALDI) calc'd for C<sub>17</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> (MH<sup>+</sup>) 323.1139, found 323.1139.

**1-(2-Phenethyl)-5-benzoyl tetrazole (6):** The reaction was heated for 60 hours. The product (1.34 g, 4.82 mmol, 96%) was a yellow oil;  $^1\text{H}$  NMR 8.22-8.18 (m, 2H), 7.69-7.63 (m, 1H), 7.52-7.47 (m, 2H), 7.17-7.13 (m, 2H), 7.8-7.03 (m, 3H), 4.99 (t, 2H,  $J = 7.3$  Hz), 3.22 (t, 2H,  $J = 7.3$  Hz);  $^{13}\text{C}$  NMR 181.47, 149.56, 135.73, 134.91, 134.53, 130.86, 128.68, 128.65, 128.50, 127.07, 50.43, 36.26; HRMS (MALDI) calc'd for  $\text{C}_{16}\text{H}_{15}\text{N}_4\text{O}$  ( $\text{MH}^+$ ) 279.1240, found 279.1238.

**1-Cyclohexyl-5-benzoyl tetrazole (7):** The product (1.09 g, 4.25 mmol, 85%) was a yellow oil;  $^1\text{H}$  NMR 8.36-8.33 (m, 2H), 7.72-7.67 (m, 1H), 7.58-7.53 (m, 2H), 4.96 (tt, 1H,  $J = 11.4, 4.1$  Hz), 2.20-2.12 (m, 2H), 2.09-2.01 (m, 2H), 2.00-1.92 (m, 2H), 1.81-1.74 (m, 1H), 1.55-1.42 (m, 2H), 1.41-1.31 (m, 1H);  $^{13}\text{C}$  NMR 182.05, 148.94, 134.99, 134.96, 130.86, 128.68, 59.98, 32.91, 25.10, 24.77; HRMS (MALDI) calc'd for  $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}$  ( $\text{MH}^+$ ) 257.1397, found 257.1400.

**1-(1-Adamantyl)-5-benzoyl tetrazole (8):** The reaction was heated for 80 hours. The crude product was dissolved in ethyl acetate (10 mL) and the product was collected by filtration, washed once with ethyl acetate (5 mL) and dried. The product (1.15 g, 3.73 mmol, 75%) was a tan solid with m.p. 187-189 °C;  $^1\text{H}$  NMR 7.94-7.90 (m, 2H), 7.74-7.68 (m, 1H), 7.57-7.52 (m, 2H), 2.34-2.31 (m, 6H), 2.25-2.20 (m, 3H), 1.76-1.72 (m, 6H);  $^{13}\text{C}$  NMR 186.00, 150.00, 135.42, 130.52, 129.02, 129.00, 63.65, 42.18, 35.48, 29.55; HRMS (MALDI) calc'd for  $\text{C}_{18}\text{H}_{20}\text{N}_4\text{ONa}$  ( $\text{MNa}^+$ ) 331.1529, found 331.1533.

**1-Benzyl-5-benzoyl tetrazole (9):** The product (1.30 g, 4.92 mmol, 98%) was a yellow oil;  $^1\text{H}$  NMR 8.38-8.34 (m, 2H), 7.70-7.65 (m, 1H), 7.54-7.51 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.28 (m, 3H), 5.94 (s, 2H);  $^{13}\text{C}$  NMR 181.40, 149.08, 135.05, 134.78, 133.55, 130.99, 128.92, 128.86, 128.71, 128.38, 52.96; HRMS (MALDI) calc'd for  $\text{C}_{15}\text{H}_{13}\text{N}_4\text{O}$  ( $\text{MH}^+$ ) 265.1084, found 265.1085.

**1-Benzyl-5-(4-methoxybenzoyl) tetrazole (10):** The product (1.46 g, 4.96 mmol, 99%) was a light yellow solid with m.p. 98 °C;  $^1\text{H}$  NMR 8.40 (d, 2H,  $J = 9.1$  Hz), 7.40-7.29 (m, 5H), 6.98 (d, 2H,  $J = 9.1$  Hz), 5.92 (s, 2H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR 179.47, 165.25, 149.37, 133.75, 133.70, 128.89, 128.80, 128.39, 127.86, 114.11, 55.64, 52.84; HRMS (MALDI) calc'd for  $\text{C}_{16}\text{H}_{15}\text{N}_4\text{O}_2$  ( $\text{MH}^+$ ) 295.1189, found 295.1192.

**1-Benzyl-5-(2,6-difluorobenzoyl) tetrazole (11):** The product (1.49 g, 4.97 mmol, 99%) was a light yellow solid with m.p. 61-65 °C;  $^1\text{H}$  NMR 7.52 (tt, 1H,  $J = 8.5, 6.2$  Hz), 7.39-7.31 (t, 2H,  $J = 8.5$  Hz), 5.95 (s, 2H);  $^{13}\text{C}$  NMR 177.33, 160.24 (dd, 2H,  $J = 1020, 24$  Hz), 149.53, 134.63 (t, 1H,  $J = 36$  Hz), 133.09, 128.94, 128.92, 128.21, 115.06 (t, 1H,  $J = 72$  Hz), 112.14 (d, 2H,  $J = 97$  Hz), 52.82; HRMS (MALDI) calc'd for  $\text{C}_{15}\text{H}_{10}\text{F}_2\text{N}_4\text{O}$  ( $\text{MNa}^+$ ) 323.0715, found 323.0718.

**1-Benzyl-5-(2-furoyl) tetrazole (12):** The reaction was only heated for 20 hours. The product was purified by silica gel chromatography eluting with 10% ethyl acetate and 90% hexanes. The product (1.16 g, 4.56 mmol, 91%) was a light yellow solid with m.p. 96-97 °C;  $^1\text{H}$  NMR 8.28 (d, 1H,  $J = 3.8$  Hz), 7.83 (d, 1H,  $J = 1.8$  Hz), 7.47-7.42 (m, 2H),

7.37-7.31 (m, 3H), 6.69 (dd, 1H,  $J = 3.5, 1.5$  Hz), 6.00 (s, 2H);  $^{13}\text{C}$  NMR 166.93, 150.05, 147.97, 133.41, 128.86 (2H), 128.83, 128.59, 126.36, 113.33, 52.99; HRMS (MALDI) calc'd for  $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$  ( $\text{MNa}^+$ ) 277.0696, found 277.0697.

**1-Benzyl-5-(2-pivaloyl) tetrazole (13):** The reaction was heated for 60 hours at 130 °C. The product (1.12 g, 4.62 mmol, 92%) was a light yellow solid with m.p. 60 °C;  $^1\text{H}$  NMR 7.35-7.26 (m, 5H), 5.83 (s, 2H), 1.32 (s, 9H);  $^{13}\text{C}$  NMR 196.96, 148.05, 133.67, 128.85, 128.80, 128.29, 52.78, 45.48, 26.13; HRMS (MALDI) calc'd for  $\text{C}_{13}\text{H}_{17}\text{N}_4\text{O}$  ( $\text{MH}^+$ ) 245.1397, found 245.1394.

**1-Benzyl-5-acetyl tetrazole (14):** Ten equivalents of pyruvoyl cyanide were used, and the reaction was only heated for 24 hours. The product was purified by silica gel chromatography eluting with 10% ethyl acetate and 90% hexanes. The product (625 mg, 3.09 mmol, 62%) was a yellow oil;  $^1\text{H}$  NMR 7.39-7.32 (m, 5H), 5.88 (s, 2H), 2.80 (s, 3H);  $^{13}\text{C}$  NMR 188.19, 148.72, 133.38, 128.95, 128.92, 128.47, 52.78, 28.77; HRMS (MALDI) calc'd for  $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}$  ( $\text{MH}^+$ ) 203.0927, found 203.0925.

**1-Benzyl-5-(diethylcarbamoyl) tetrazole (15):** The reaction was heated for 60 hours at 130 °C. The product was purified by silica gel chromatography eluting with 10% ethyl acetate and 90% hexanes to give (1.10 g, 4.25 mmol, 85%) as a yellow oil;  $^1\text{H}$  NMR 7.35-7.30 (m, 5H), 5.77 (s, 2H), 3.49 (q, 2H,  $J = 7.0$  Hz), 3.31 (q, 2H,  $J = 7.0$  Hz), 1.14 (t, 3H,  $J = 7.0$  Hz), 1.00 (t, 3H,  $J = 7.0$  Hz);  $^{13}\text{C}$  NMR 156.18, 147.77, 133.58, 128.70, 128.65,

128.26 (2H), 51.93, 43.15, 40.51, 13.82, 12.13; HRMS (MALDI) calc'd for C<sub>13</sub>H<sub>18</sub>N<sub>5</sub>O (MH<sup>+</sup>) 260.1506, found 260.1506.

**1-Benzyl-5-(ethyloxycarbonyl) tetrazole (16):** The product was purified by silica gel chromatography eluting with 10% ethyl acetate and 90% hexanes. The product (960 mg, 4.14 mmol, 83%) was a yellow oil; <sup>1</sup>H NMR 7.38-7.33 (m, 5H), 5.92 (s, 2H), 3.49 (q, 2H, *J* = 7.0 Hz), 3.31 (q, 2H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz), 1.00 (t, 3H, *J* = 7.0 Hz); <sup>13</sup>C NMR 156.18, 147.77, 133.58, 128.70, 128.65, 128.26 (2H), 51.93, 43.15, 40.51, 13.82, 12.13; HRMS (MALDI) calc'd for C<sub>13</sub>H<sub>18</sub>N<sub>5</sub>O (MH<sup>+</sup>) 260.1506, found 260.1506.

***p*-Nitrophenyl cyanofornate (17):**<sup>1</sup> A flask was charged with *p*-nitrophenyl chloroformate (10.2 g, 50 mmol), trimethylsilyl cyanide (6.9 g, 75 mmol), 1,4-diazabicyclo[2.2.2]octane (28 mg, 0.5 mol%), and acetonitrile (20mL). The mixture was stirred at 60 °C under an inert atmosphere for 60 hours. The solvent, trimethylsilyl chloride and trimethylsilyl cyanide were evaporated under reduced pressure. The solid was dissolved in 100 mL chloroform, and filtered through a celite pad, evaporated to dryness, and recrystallized in a chloroform (30 mL) to give the product (4.6 g, 24 mmol, 48%) as a tan powder which was 97-98% pure by <sup>1</sup>H-NMR. The product had m.p. 119-120 °C; <sup>1</sup>H NMR 8.38-8.34 (m, 2H), 7.47-7.43 (m, 2H); <sup>13</sup>C NMR 152.87, 146.55, 141.41, 125.72, 121.74, 108.48; MS (EI) calc'd for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>Na (MNa<sup>+</sup>) 215, found 215.

---

(1) Modification from T. V. John, G. L. Larson, C. Subramaniam, US Patent 5,852,207 Dec 22, 1998.

**1-Benzyltetrazolecarboxylic acid *p*-nitrophenyl ester (18):** A vial was charged with *p*-nitrophenyl cyanoformate (1.15 g, 6 mmol) and benzyl azide (665 mg, 5 mmol), and heated at 120°C for 16 hours. The reaction mixture was then dissolved in ethyl acetate (10 mL) and diluted with hexanes (50 mL). The suspension was then filtered and the brown solid collected was found to be pure product (240 mg, 2.15 mmol, 42%). The product decomposed at 99 °C; <sup>1</sup>H NMR 8.36 (d, 2H, *J* = 9.1 Hz), 7.45 (d, 2H, *J* = 9.1 Hz) 7.43-7.35 (m, 5H), 5.97 (s, 2H); <sup>13</sup>C NMR 154.23, 153.65, 146.21, 144.45, 132.76, 129.36, 129.17, 128.50, 125.54, 122.25, 53.31; MS (EI) calc'd for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>Na (MNa<sup>+</sup>) 348, found 348.

**1-Benzyltetrazolecarboxylic acid benzylamide (19):** A vial was charged with *p*-nitrophenyl cyanoformate (1.15 g, 6 mmol) and benzyl azide (665 mg, 5 mmol), and heated at 120°C for 16 hours. The reaction mixture was then cooled and dissolved in dichloromethane (10 mL) and added to a flask containing benzylamine (1.3 g, 12 mmol) and dichloromethane (20 mL), and stirred for two hours. The organic layer was then washed with 1N HCl (3x20 mL) and 1N NaOH (3x20 mL), evaporated, and purified by column chromatography eluting with 10% ethyl acetate and 90% hexanes to give the product as a white solid (1.44 mg, 4.91 mmol, 98%) with m.p. 89-90 °C; <sup>1</sup>H NMR 7.85 (br, 1H), 7.46-7.42 (m, 2H), 7.38-7.26 (m, 8H), 6.00 (s, 2H), 4.63 (d, 2H, *J* = 6.1 Hz); <sup>13</sup>C NMR 154.71, 146.35, 136.61, 133.72, 128.79, 128.67, 128.62, 128.14, 128.06, 127.72, 52.43, 43.44; HRMS (MALDI) calc'd for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>ONa (MNa<sup>+</sup>) 316.1169, found 316.1163.