A Microwave-Assisted Click Chemistry Synthesis of 1,4-Disubstituted 1,2,3-triazoles via a Copper(I)-Catalyzed Three-Component Reaction

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Supporting Information

General Remarks: ^{1}H, ^{13}C and DEPT NMR spectra were recorded on a Bruker-300 Avance instrument. All spectra were recorded in a 1:1 mixture of $CDCl_3$ and CD_3OD, unless otherwise stated. The ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference and ^{13}C with $CDCl_3$ as internal standard. The low resolution mass spectra were obtained with a HP5989A MS instrument. The ion source temperature was 150-250°C as required. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70-230 mesh silica gel (E. M. Merck)) were used. All new compounds have been characterized by ^{1}H, ^{13}C and DEPT NMR / EI-MS. All commercially available starting materials were purchased from Sigma-Aldrich and were used without any further purification.

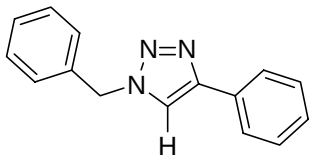
Microwave Irradiation Experiments: All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The machine was used in the standard configuration as delivered, including proprietary software. The reactions were

carried out in 10 mL glass vials sealed with an aluminum/Teflon® crimp top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60-120 s) to ambient temperature by gas jet cooling.

General procedure for the microwave-assisted three-component reactions

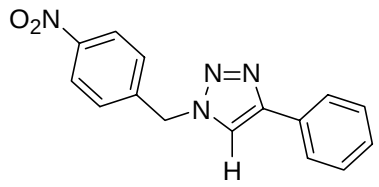
An appropriate halide (1.0 mmol), acetylene (1.1 mmol) and sodium azide (1.1 mmol) were suspended in a 1:1 mixture of water and *tert*-BuOH (1.5 mL each) in a 10 mL glass vial equipped with a small magnetic stirring bar. To this was added the copper wire (50 mg) and copper sulphate solution (1N, 200 µL), and the vial was tightly sealed with an aluminum/Teflon® crimp top. The mixture was then irradiated for the time and temperature indicated in Tables **1** & **2**, using an irradiation power of 100 W. After completion of the reaction, the vial was cooled to 50 ˚C by gas jet cooling before it was opened. The mixture was then diluted with water (20 mL) and filtered. The residue was washed with cold water (20 mL), 0.25 N HCl (10 mL) and finally with petroleum ether (50 mL) to furnish the product triazoles **3a-m**, in yields indicated as in Tables **1** & **2**.

Synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole 3a :



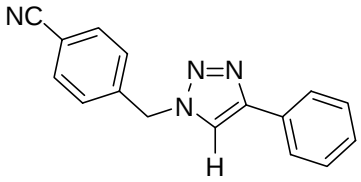
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 5.46 (s, 2H), 7.25 – 7.39 (m, 8H), 7.67 (s, 1H), 7.77 (d, 2H, J = 7.3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 53.8, 119.6, 125.4, 127.7, 127.9, 128.4, 128.6, 128.8 , 130.4, 134.6, 147.9 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = -54.5, 120.2, 126.1, 128.4, 128.6, 129.1, 129.3, 129.5 ppm. EI - MS [M+]: 235 (100%).

Synthesis of 1-(4-nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole 3b:



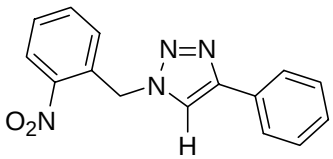
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 5.70 (s, 2H), 7.41-7.47 (m, 4H), 7.72 - 7.88 (m, 6H), 8.19 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 53.6, 119.9, 123.9, 124.3, 125.7, 128.5, 128.7, 129.9, 141.7, 142.7, 148.7 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = -53.6, 120.3, 124.4, 124.7, 126.2, 128.9, 129.0 ppm. EI - MS [M+]: 290 (100%).

Synthesis of 4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile 3c:



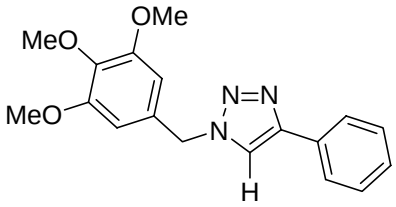
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 5.82 (s, 2H), 7.38 - 7.49 (m, 6H), 7.61 (s, 1H), 7.73 (d, 1H, J = 5.1 Hz), 7.89 (d, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): 51.5, 111.3, 116.5, 125.1, 127.7, 128.3, 128.8, 128.9, 130.2, 132.6, 133.2, 137.8 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = -53.2, 126.8, 129.4, 130.1, 130.5, 130.7, 134.3, 134.9 ppm. EI - MS [M+]: 260 (100%).

Synthesis of 1-(2-nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole 3d:



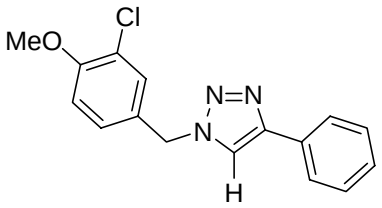
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 5.99 (s, 2H), 7.14 (d, 1H, J = 7.3 Hz), 7.32 - 7.44 (m, 3H), 7.52 (t, 1H, J = 7.7 Hz), 7.61 (t, 1H, J = 7.7 Hz), 7.86 (d, 2H, J = 5.1 Hz), 8.13 (d, 1H, J = 8.05 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 50.7, 124.7, 125.1, 127.7 , 128.3, 129.1, 129.7, 130.0, 130.02, 133.8, 147.0 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = -52.5, 126.5, 126.8, 129.5, 130.1, 130.9, 131.5, 135.6 ppm. EI - MS [M+]: 290 (100%).

Synthesis of 4-phenyl-1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazole 3e:



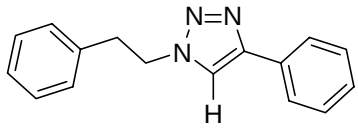
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 3.61 (s, 3H), 3.74 (s, 6H), 5.71 (s, 2H), 6.64 (s, 2H), 7.45 - 7.57 (m, 5H), 8.56 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 55.5, 56.2, 60.6, 106.1, 120.0, 125.6, 128.2, 128.4, 128.6, 139.0, 139.4, 147.9, 154.1 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 55.5, 56.2, 60.6, 106.1, 120.0, 128.2, 128.4, 128.6 ppm. EI - MS [M+]: 325 (100%).

Synthesis of 1-(3-chloro-4-methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole 3f



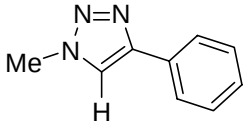
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 3.93 (s, 3H), 5.54 (s, 2H), 7.17 (d, 1H, J = 8.3 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.44 – 7.58 (m, 6H), 8.54 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 55.0, 56.0, 114.1, 120.0, 124.2, 125.6, 128.2, 128.4, 128.6, 128.9, 129.8, 134.8, 147.9, 155.3 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 55.0, 56.0, 114.1, 120.0, 125.6, 128.2, 128.6, 128.9, 129.8 ppm. EI - MS [M+]: 299 (100%).

Synthesis of 4-phenyl-1-(2-phenylethyl)-1*H*-1,2,3-triazole 3g:



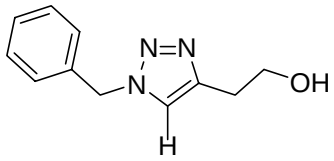
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 3.13 (t, 2H, J = 7.4 Hz), 4.58 (t, 2H, J = 7.4 Hz), 7.16 – 7.57 (m, 10 H), 8.38 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 34.5, 50.1, 119.7, 125.8, 126.6, 127.7, 128.2, 128.5, 128.6, 130.0, 139.0, 146.8 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 34.5, 50.1, 119.7, 125.8, 126.6, 128.2, 128.5, 128.6, 130.0 ppm. EI - MS [M+]: 249 (100%).

Synthesis of 1-methyl-4-phenyl-1H-1,2,3-triazole 3h:



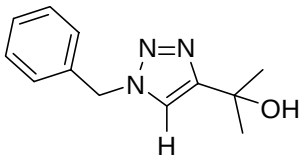
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 4.18 (s, 3H), 7.43 - 7.56 (m, 5H), 8.29 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 37.6, 120.7, 125.8, 128.2, 128.3, 128.6, 146.8 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 37.8, 120.8, 125.8, 128.4, 128.7 ppm. EI - MS [M+]: 159 (100%).

Synthesis of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethanol 3i



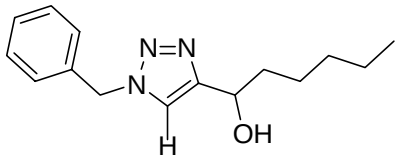
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 2.78 (t, 2H, J = 8.0 Hz), 3.82 (t, 2H, J = 8.0 Hz), 5.43 (s, 2H), 7.21 - 7.40 (m, 5H), 7.87 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 25.5, 54.8, 58.9, 120.5, 127.1, 129.1, 129.3, 133.6, 144.3 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 25.6, 54.8, 58.9, 120.5, 127.1, 129.1, 129.3 ppm. EI - MS [M^+]: 203 (100 %)

Synthesis of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol 3j:



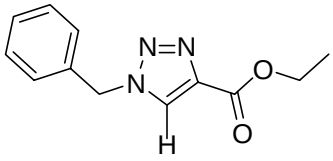
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 1.51 (s, 6H), 5.43 (s, 2H), 7.17 (s, 1H), 7.22 – 7.36 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 27.2, 54.8, 67.3, 119.4, 127.1, 129.2, 129.3, 133.3, 151.2 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 27.2, 54.8, 119.4, 127.1, 129.2, 129.3, ppm. EI - MS [M+]: 216 (100%).

Synthesis of 1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)hexan-1-ol 3k



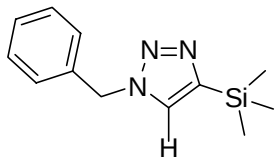
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 0.87 (t, 3H, J = 6.3 Hz), 1.28 - 1.40 (m, 6H), 1.60 - 1.78 (m, 2H), 4.42 (q, 1H, J_1 = 5.4 Hz, J_2 = 9.5 Hz), 5.49 (s, 2H), 7.17 (s, 1H), 7.22 - 7.36 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 13.8, 22.6, 28.7, 33.2, 33.6, 54.8, 63.2, 119.7, 127.1, 129.1, 129.3, 133.3, 147.5 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 13.8, 22.6, 28.7, 33.2, 33.6, 54.8, 63.2, 119.7, 127.1, 129.1, 129.3 ppm. EI - MS [M^+]: 259 (100 %).

Synthesis of ethyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate 3l:



^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 1.39 (t, 3H, J = 6.9 Hz), 4.42 (q, 2H, J_1 = 6.8 Hz, J_2 = 13.7 Hz), 5.55 (s, 2H), 7.25 - 7.40 (m, 5H), 8.06 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 14.0, 55.2, 61.0, 126.9, 128.3, 129.2, 129.4, 133.9, 140.3, 160.2 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 13.9, 55.2, 61.2, 126.7, 128.3, 129.4, 129.5 ppm. EI - MS [M^+]: 231 (100 %).

Synthesis of 1-benzyl-4-trimethylsilanyl-1*H*-1,2,3-triazole 3m:



^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ = 0.39 (s, 9H), 5.49 (s, 2H), 7.22-7.37 (m, 5H), 7.54 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 0.80, 55.5, 127.11, 128.9, 129.1, 129.3, 133.2, 149.7 ppm. DEPT (75 MHz, $CDCl_3$ + CD_3OD): δ = 0.80, 55.5, 127.1, 128.9, 129.1, 129.3 ppm. EI - MS [M^+]: 231 (100 %).