Copper Free Click: 1,3 Dipolar Cycloaddition of Azides and Arynes

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Supplementary Information

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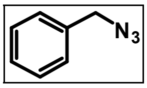
General Information

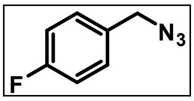
All reactions were carried out in oven dried glassware. THF was distilled from sodium, CH_2Cl_2 and CH_3CN were distilled from CaH_2. CsF and KF were dried for one hour at 110 ºC in a vacuum oven (0 mbar) to remove any traces of moisture. TBAF, 18-crown-6, and 15-crown-5 were purchased from Aldrich and used as received. ^1H-, ^{13}C-, and ^{19}F-NMR were recorded on a Varian AMX400 (400, 100.59 MHz, and 200 MHz respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^1H and δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, dt=doublet of triplets, td=triplet of doublets, m=multiplet), coupling constants (Hz), and integration. Flash chromatography was performed on silica gel . All reactions were monitored by thin layer chromotography on Merck F-254 silica gel plates. Visualization of the TLC plates was performed with $KMnO_4$ reagent and UV (254 nm). Conversion of reactions was determined by GC-MS (GC HP6890, MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer by EI (70 eV) measurements. Benzyne precursor *o*-(trimethylsilyl)phenyl triflate was commercially available and used as received. The remaining benzyne precursors were synthesized according to literature procedures.[1] Melting points are uncorrected.

Experimental Procedure for the Preparation of Azides

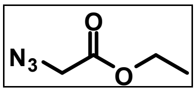
General Procedure: to a stirred solution of the corresponding bromide (1.0 eq) in a 50 cm^3 water/acetone mixture (1:4) was added NaN_3 (1.5 eq). The resulting suspension was stirred at room temperature for 24 hours. DCM was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 x 10 cm^3 aliquots of DCM and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure, and the azide was sufficiently pure to use without further work up.



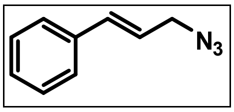
Benzyl azide. Yellow oil. From 2.5 mmol benzyl bromide, 100 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.43 (m, 5H), 4.35 (s, 2H); ^{13}C (100.59 MHz, $CDCl_3$): δ 135.5, 129.3, 128.3, 128.2, 54.8.



1-(Azidomethyl)-4-fluorobenzene. Pale yellow oil. From 2.5 mmol 1-(bromomethyl)-4-fluorobenzene, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.39 (m, 2H), 7.00-7.11 (m, 2H), 4.30 (s, 2H); ^{13}C (100.59 MHz, $CDCl_3$): δ 162.5 (d, *J*=1307 Hz), 131.4, 129.9 (d, J= 45.2 Hz), 115.7 (d, *J*=110.0 Hz), 54.0; ^{19}F NMR (200 MHz, $CDCl_3$): δ -112.3.



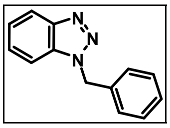
Ethyl 2-azidoacetate. Colorless oil. From 2.5 mmol ethyl bromoacetate, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, *J*=6.8 Hz, 2H), 3.77 (d, *J*= 1.2 Hz, 2H), 1.20 (td, *J*=7.2, 1.2 Hz, 3H). ^{13}C (100.59 MHz, $CDCl_3$): δ 168.1, 61.5, 50.0, 13.8.



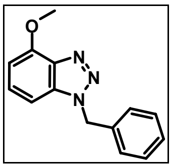
Cinnamyl azide. Colorless oil. From 2.5 mmol cinnamyl bromide, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.45 (m, 5H), 6.67 (d, *J*=16 Hz, 1H), 6.26 (dt, *J*=16, 6.4 Hz, 1H), 3.95 (d, *J*=6.4 Hz, 2H); ^{13}C (100.59 MHz, $CDCl_3$): δ 135.7, 134.5, 128.7, 128.2, 126.7, 122.4, 53.0; HRMS (EI) calcd for $C_9H_9N_3$ 159.0796, found 159.0790.

Experimental Procedure for the Cycloaddition of Azides and Arynes

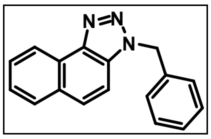
General Procedure: to a stirred solution of azide (0.60 mmol, 3.0 eq) in 3 cm^3 of solvent in a 10 cm^3 glass roundbottom flask was added a fluoride source (0.40 mmol, 2.0 eq) and crown ether (0.40 mmol, 2.0 eq) as stated. After ten minutes of stirring at room temperature, the aryne precursor (0.20 mmol, 1.0 eq) in 1 cm^3 of solvent was added dropwise to the reaction mixture. The roundbottom was sealed and the reaction was monitored by TLC or GC. Upon completion, the reaction mixture was poured into saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography (heptane/ethyl acetate (7:1)) yielding pure products with the exception of 1-benzyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole and 1-benzyl-1*H*-naphtho[1,2-*d*][1,2,3]triazole, which could not be separated by column chromatography.



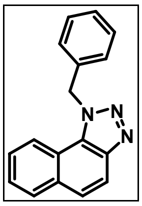
1-Benzyl-1*H*-benzo[*d*][1,2,3]triazole. White solid: mp 114-115 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J*=8.0 Hz, 1H), 7.26-7.41 (m, 8H), 5.85 (s, 2H); ^{13}C (100.59 MHz, $CDCl_3$): δ 146.3, 134.7, 132.8, 129.0, 128.4, 127.6, 127.4, 123.9, 120.0, 109.7, 52.2; HRMS (EI) calcd for $C_{13}H_{11}N_3$ 209.0953, found 209.0945.



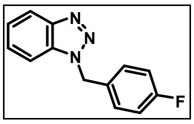
1-Benzyl-4-methoxy-1*H*-benzo[*d*][1,2,3]triazole. White solid: mp 93-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.27-7.33 (m, 6H), 6.90 (d, *J*=11.2 Hz, 1H), 6.65 (d, *J*=10.4 Hz, 1H), 5.81 (s, 2H), 4.11 (s, 3H); ^{13}C (100.59 MHz, $CDCl_3$): δ 138.4, 134.8, 134.5, 128.7, 128.4, 128.1, 127.2, 103.1, 101.7, 56.0, 52.0; HRMS (EI) calcd for $C_{14}H_{13}N_3O$ 239.1059, found 239.1061.



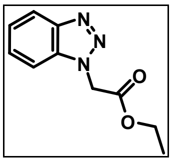
1-Benzyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole. White solid: mr 147-154 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, *J*=8 Hz, 1H), 7.94 (d, *J*=7.6 Hz, 1H), 7.71-7.74 (m, 2H), 7. 58 (t, *J*=6.4 Hz, 1H), 7.26-7.36 (m, 5H), 7.18 (s, 1H), 5.93 (s, 2H). ^{13}C (100.59 MHz, $CDCl_3$): δ 135.7, 134.8, 133.1, 130.5, 129.3, 129.0, 128.5, 128.2, 127.4, 127.0, 126.3, 122.3, 118.5, 109.2, 52.4. HRMS (EI) calcd for $C_{17}H_{13}N_3$ 259.1109, found 259.1115.



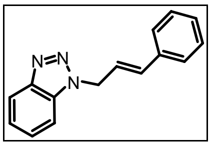
1-Benzyl-1*H*-naphtho[1,2-*d*][1,2,3]triazole. White solid: mr 147-154 ºC; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (m, 2H), 7.71-7.74 (m, 2H), 7.51-7.54 (m, 1H), 7.26-7.36 (m, 5H), 7.16 (s, 1H) 6.28 (s, 2H). ^{13}C (100.59 MHz, CDCl$_3$): δ135.7, 134.9, 133.1, 130.9, 129.3, 129.1, 128.6, 128.2, 127.4, 127.1, 126.4, 122.3, 118.1, 115.7, 54.0. HRMS (EI) calcd for $C_{17}H_{13}N_3$ 259.1109, found 259.1115.



1-(4-Fluorobenzyl)-1*H*-benzotriazole. White solid: mp 92-93 ºC; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, *J*= 9.02 Hz, 1H), 7.26-7.43 (m, 5H), 7.04 (t, *J*=8.4 Hz, 2H), 5.82(s, 2H); ^{13}C (100.59 MHz, CDCl$_3$): δ 162.6 (d, *J*=985 Hz), 146.3, 132.6, 130.5, 129.4 (d, *J*=30.4 Hz), 127.5, 123.9, 120.1, 116.0 (d, *J*=88.4), 109.4, 51.4. HRMS (EI) calcd for $C_{13}H_{10}FN_3$ 227.0859, found 227.0851.



Ethyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acetate. Pale yellow solid: mp 76-78 ºC. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.11(d, *J*=8.4, 1H), 7.48-7.52 (m, 2H), 7.39-7.42 (m, 1H), 5.42 (s, 2H), 4.26 (q, *J*=6.8 Hz, 2H), 1.26 (t, *J*=6.8 Hz, 3H); ^{13}C (100.59 MHz, CDCl$_3$): δ 166.6, 146.3, 133.6, 128.2, 124.4, 120.5, 109.4, 62.6, 49.3, 14.3. HRMS (EI) calcd for $C_{10}H_{11}N_3O_2$ 205.0851, found 205.0852.



1-Cinnamyl-1*H*-benzo[*d*][1,2,3]triazole. White solid: mp 72-73 ºC. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, *J*=11.2 Hz, 1H), 7.57 (d, 8.4 Hz, 1H), 7.45 (t, *J*=7.2 Hz, 1 H), 7.26-7.40 (m, 6H), 6.69 (d, *J*=15.6 Hz, 1H), 6.41 (dt, *J*=15.6, 6.4 Hz, 1H), 5.45 (dd, *J*=6.8, 1.6 Hz, 2H). ^{13}C (100.59 MHz, CDCl$_3$): δ 146.2, 135.5, 134.4, 132.9, 128.6, 128.3, 127.3, 126.6, 123.9, 122.1, 120.0, 109.6, 50.6. HRMS (EI) calcd for $C_{15}H_{13}N_3$ 235.1109, found 235.1116.

References

1. D. Peña, S. Escudero, D. Pérez, E. Guitián and L. Castedo, *Angew. Chem., Int. Ed.*, 1998, **37**, 2659; D. Peña, D. Pérez, E. Guitián and L. Castedo, *J. Am. Chem. Soc.*, 1999, **121**, 5827; D. Peña, D. Pérez, E. Guitián and L. Castedo, *J. Org. Chem.*, 2000, **65**, 6944; H. Yoshida, J. Ikadai, M. Shudo, J. Ohshita and A. Kunai, *J. Am. Chem. Soc.*, 2003, **125**, 6638.