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One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal acetylenes and in situ generated azides

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Abstract—1,4-Disubstituted 1,2,3-triazoles were obtained by a high-yielding copper(I) catalyzed 1,3-dipolar cycloaddition reaction between in situ generated azides and terminal acetylenes. This one-pot, two-step procedure tolerates most functional groups and circumvents the problems associated with the isolation of potentially toxic and explosive organic azides.

Multi-component reactions have received much attention lately, and have proven to be a very elegant and rapid way to access highly functional molecules from simple building blocks. Multi-component, one-pot reactions generally afford good yields and are fundamentally different from two-component reactions in several aspects.[1] Over the past decade, several sequential multi-component reactions have been developed into multi-component one-pot variants involving Passerini-,[2] Ugi-,[3] and Mannich-type[4] reactions. Moreover, multi-component one-pot reactions result in fewer operations by avoiding isolation, handling and chromatography. Hence, better yields are usually achieved.

The recently discovered copper(I) catalyzed azide-acetylene ligation reaction[5] produces exclusively 1,4-disubstituted 1,2,3-triazoles.[6] This reaction has recently received considerable attention due to its regiospecificity, quantitative yields and the capacity to tolerate a wide variety of other functional groups. Despite its growing impact in the field of bioconjugation and materials science,[7] the application of this reaction is still hampered by the apprehension of handling organic azides since hydrazoic acid is toxic and potentially explosive.[8]

In connection with our efforts in developing one-pot copper(I) catalyzed cycloaddition reactions,[9] we discovered that conversion of α-bromo ketones to the corresponding azides was facile at ambient temperature in aqueous solutions. Herein, we report that the product azide from reacting sodium azide with ethyl bromoacetate under neutral conditions can be further transformed to 1,4-disubstituted 1,2,3-triazoles in a one-pot procedure.

Mixing ethyl bromoacetate with one equivalent of sodium azide in aqueous *t*-BuOH solution (H_2O/*t*-BuOH 1:1, 0.25 M) produced the desired organic azide in quantitative yield with short reaction times at ambient temperature. In the presence of one equivalent of phenyl acetylene and 5 mol % $CuSO_4 \cdot 5H_2O$ and 10 mol % sodium ascorbate, the in situ generated azide was converted to the desired 1,4-disubstituted 1,2,3-triazole **1** in 91% yield. By applying this methodology to other terminal acetylenes several 1,4-disubstituted 1,2,3-triazoles were obtained in 80–94% yields (Scheme 1).[10]

The rich variety of terminal acetylenes employed demonstrates the scope and functional group tolerance of this protocol. LC–MS and ^{1}H NMR analyses of the crude reaction products confirmed the formation of a single regioisomer,[10] and the presence of N–H triazoles in the reaction mixtures was never observed. In all cases, the products were isolated either by simple filtration or by aqueous workup. Trace amounts of copper in the final product was removed by washing with 10% ammonia buffer solution (pH = 8.5).

In summary, a one-pot procedure for the direct conversion of α-halo esters to 1,4-disubstituted 1,2,3-triazoles has been developed. These reactions were efficiently performed in neutral aqueous solutions (pH = 7–8) at

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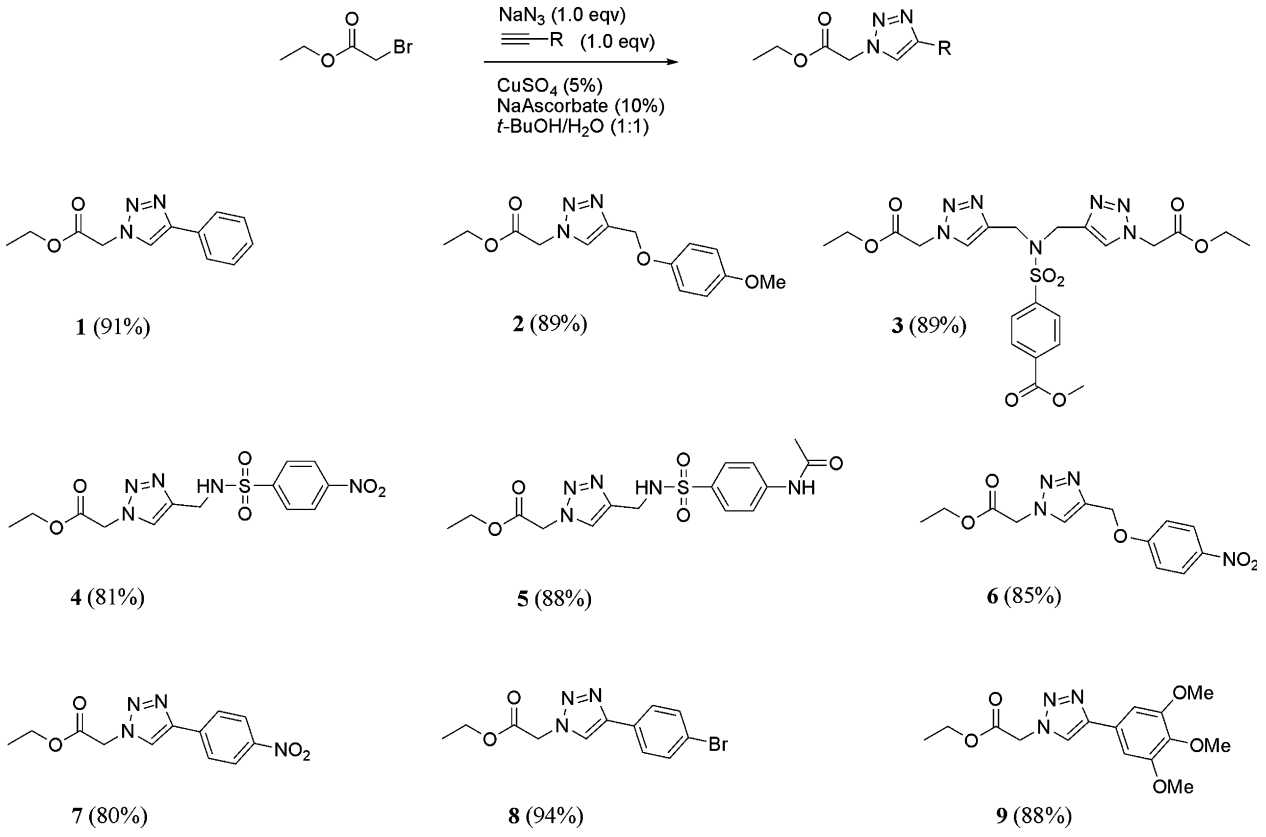

Scheme 1.

ambient temperature. Molar equivalents of the halide, sodium azide, and alkyne were employed in this mild 1,3-dipolar cycloaddition reaction. The method circumvents the problems encountered with the isolation of organic azides, and complements other recently published methods for the preparation of 1,2,3-triazoles.[11] The operational simplicity of this method makes it attractive for preparative applications as well as for the synthesis of screening libraries for drug discovery.

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10. General procedure as exemplified for ethyl 2-(4-((4-nitrophenylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**4**): ethyl bromoacetate (167 mg, 1 mmol), sodium azide (65 mg, 1 mmol), and 4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (240 mg, 1 mmol) were mixed with *t*-BuOH: water solution (4 mL, 1:1) in a 20 mL screw-top scintillation vial. Sodium ascorbate (19 mg, 10 mol %) and copper(II) sulfate solution (50 μL, 1 M, 5 mol %) were added sequentially and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with cold water (15 mL) and 10% aqueous ammonia (2 mL, pH = 8.5) was added. After stirring for another 5 min, the precipitate was collected with a Büchner filter and dried under vacuum. This afforded **4** (299 mg, 81%) as white crystals; mp 154–155 °C; $R_f = 0.41$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.38 (s, 2H), 5.31 (s, 2H), 7.92 (s, 1H), 8.06 (dd, $J = 1.9$, 8.8 Hz, 2H), 8.42 (dd, $J = 1.9$, 8.8 Hz, 2H), 8.67 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.86$, 37.79, 50.09, 61.13, 124.34, 127.93, 142.97, 146.10, 149.38, 166.98; HRMS calcd for $C_{13}H_{15}N_5O_6S$ (M^+): 369.0743, found 369.0729. Spectral data of new compounds: ethyl 2-(4-((4-methoxyphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**2**): white crystals (89%); mp 103–104 °C; $R_f = 0.66$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.21$ (t, $J = 7.0$ Hz, 3H), 3.70 (s, 3H), 4.19 (q, $J = 7.0$ Hz, 2H), 5.10 (s, 2H), 5.40 (s, 2H), 6.62 (dd, $J = 1.9$ Hz, 8.9 Hz, 2H), 6.96 (dd, $J = 1.9$ Hz, 8.9 Hz, 2H), 8.19 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.94$, 50.35, 55.32, 61.42, 75.12, 114.47, 115.65, 125.81, 142.98, 152.00, 153.56, 167.19; HRMS calcd for $C_{14}H_{17}N_3O_4$ (M^+): 291.1219, found 291.1231; diethyl 2,2′-(4,4′-(4-(methoxycarbonyl)-phenylenesulfonamido)bis(methylene)-bis-(1*H*-1,2,3-triazole-4,1-diyl))diacetate (**3**): white crystals (89%); mp 141–143 °C; $R_f = 0.35$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.22$ (t, $J = 7.0$ Hz, 6H), 3.89 (s, 3H), 4.17 (q, $J = 7.0$ Hz, 4H), 4.52 (s, 4H), 5.33 (s, 4H), 7.81 (d, $J = 8.3$ Hz, 2H), 7.96 (s, 2H), 8.04 (d, $J = 8.3$ Hz, 2H);^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.85$, 41.57, 50.19, 52.49, 61.36, 125.51, 127.24, 129.47, 132.97, 141.67, 143.02, 165.05, 167.00; HRMS calcd for $C_{22}H_{27}N_7O_8S$ (M^+): 549.1642, found 549.1691; ethyl 2-(4-((4-acetamidophenylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5**): white crystals (88%); mp 176-178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 1.22$ (t, $J = 7.1$ Hz, 3H), 2.09 (s, 3H), 4.03 (s, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 5.32 (s, 2H), 7.65–7.80 (m, 4H), 7.92 (s, 1H), 8.03 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.88$, 24.04, 38.60, 50.17, 61.35, 118.48, 124.61, 127.64, 133.82, 142.67, 167.02, 168.87; HRMS calcd for $C_{15}H_{19}N_5O_5S$ (M^+): 381.1107, found: 381.1074; ethyl 2-(4-((4-nitrophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**6**): white crystals (85%); mp 133–134 °C; $R_f = 0.58$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.22$ (t, $J = 7.1$ Hz, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 5.36 (s, 2H), 5.42 (s, 2H), 7.82 (dd, $J = 2.0$ Hz, 9.1 Hz, 2H), 7.98 (dd, $J = 2.0$ Hz, 9.1 Hz, 2H), 8.29 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.85$, 50.33, 61.42, 71.70, 115.24, 125.74, 126.31, 140.95, 141.65, 163.06, 167.25; HRMS calcd for $C_{13}H_{14}N_4O_5$ (M^+): 306.0964, found 306.0981; ethyl 2-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)acetate (**7**): yellow crystals (80%); mp 144–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.24$ (t, $J = 7.0$ Hz, 3H), 4.18 (q, $J = 7.0$ Hz, 2H), 5.52 (s, 2H), 8.13 (d, $J = 9.0$ Hz, 2H), 8.32 (d, $J = 9.0$ Hz, 2H), 8.85 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.89$, 50.63, 61.58, 123.70, 124.32, 125.90, 136.79, 144.38, 146.53, 166.98; HRMS calcd for $C_{12}H_{12}N_4O_4$ (M^+): 276.0859, found: 276.0841; ethyl 2-(4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)acetate (**8**): white crystals (94%); mp 129–131 °C; $R_f = 0.57$ (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 1.23$ (t, $J = 7.1$ Hz, 3H), 4.20 (q, $J = 7.1$ Hz, 2H), 5.46 (s, 2H), 7.66 (d, $J = 8.6$ Hz, 2H), 7.82 (d, $J = 8.6$ Hz, 2H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.90$, 50.52, 61.53, 120.86, 123.03, 127.08, 129.69, 131.84, 145.25, 167.07; HRMS calcd for $C_{12}H_{12}BrN_3O_2$(M^+): 309.0113, found 309.0113; ethyl 2-(4-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)acetate (**9**): yellow crystals (88%); mp 95–96 °C; $R_f = 0.18$ (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.24$ (t, $J = 7.1$, 3H), 3.69 (s, 3H), 3.85 (s, 6H), 4.21 (q, $J = 7.1$ Hz, 2H), 5.45 (s, 2H), 7.17 (s, 2H), 8.58 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.91$, 50.47, 55.85, 60.00, 61.50, 102.44, 122.69, 126.04, 137.19, 146.39, 153.26, 167.16; HRMS calcd for $C_{15}H_{19}N_3O_5$ (M^+): 321.1325, found: 321.1325.
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