DOI 10.5012/bkcs.2010.31.7.1843

Articles

Azide/Alkyne Resins for Quick Preparation of 1,4-Disubstituted 1,2,3-Triazoles

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Received October 14, 2009, Accepted November 16, 2009

An efficient method for the preparation of 1,4-disubstituted 1,2,3-triazole compounds is described using polymeric quaternary ammonium salts having azide or alkyne functionality to remove unreacted excess starting molecules (azide/alkyne). Copper metal could easily be removed by simple filtration with a short Na_2SO_4/silica cartridge, affording highly regioselective products in high yield and excellent purity without the need for work-up, extraction and chromatographic purification.

Key Words: Click chemistry, Azide/alkyne resins, 1,2,3-Triazole, Huisgen 1,3-dipolar cycloaddition reaction

Introduction

Copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction, described by the Meldal[1] and Sharpless[2] groups, has been used extensively as a powerful tool in various fields of applied chemistry[3-5] due to its rapid, mild, specific, and air/moisture-tolerant reaction. The triazole ring is stable to acid/basic hydrolysis as well as reductive/oxidative conditions, and displays desirable features for use as a drug.[7] Several bioconjugations have utilized triazole moiety as an isostere of the amide bond.[8] This heterocyclic ring has received increasing research attention in the fields of synthetic organic chemistry, medicinal chemistry, and material science. The development of new process for rapid purification has become an important challenge from practical, economical, and environmental points of view. Although click reaction is carried out readily with high yield, purification of product still requires high research cost. Generally, one excess starting molecule, copper metal, some additives such as sodium ascorbate, amine bases, ligands, and solvent remain after complete click reaction and require typical purification procedures such as extraction and chromatographical separation, consuming expensive time and cost. Some efforts have been made to achieve efficient purification-free methods. Recently, Girard *et al.* have reported dimethylaminomethyl polystyrene-supported Cu(I) for the efficient removal and reuse of the Cu(I) catalyst.[9] Similarly, in our previous work we prepared CuI-immobilized ionic polymers as a reusable catalyst for Huisgen 1,3-dipolar cycloaddition reaction.[10] This catalyst showed good catalytic activity up to 10 reuses without significant leaching of CuI and any loss of yield. In addition, Smith *et al.* described the successful removal of CuI and excess azide using a modular flow reactor system comprised of three continuous columns containing different polymer resins.[11]

Herein, we report a very simple and expedient method for the rapid preparation of 1,4-disubstituted 1,2,3-triazole using scavenger resins to remove unreacted azide/alkyne after the solution-phase click reaction. Subsequently, copper catalyst is also removed by simple filtration. This work was motivated by the necessary requirements that must be satisfied for potential application to high throughput synthesis of 1,4-disubstituted 1,2,3-triazoles.

Experimental Section

General methods. All chemicals were purchased from commercial sources and used without further purification. Quaternization of resins and reaction process were carried out using a speed control shaker, BTS-1500/RB-20/RBTC-T/150-T of J-KEM Scientific, Inc. ^{1}H and ^{13}C NMR spectra were recorded using both Varian Gemini-2000 (200 MHz) and Varian UNITY-INOVA 400 (400 MHz). ICP-MS (Inductively Coupled Plasma - Mass Spectrometer) data were obtained to quantify copper metal using ELAN6100/Perkin Elmer. Low-resolution mass spectra were obtained using VK Quattro II GC-MS/MS spectrometer (ESI or EI). Elemental Analyzer (EA), Flash EA1112/Thermo Electron was used to calculate nitrogen content of azide (**A**) and acetylene (**B**) resins. High-resolution mass spectra (HRMS) data were recorded at the Korea Basic Science Institute using Jeol-JMS 700. Melting Points were checked with OptiMelt apparatus (Stanford research systems). High performance liquid chromatography (HPLC) was performed using a Varian ProStar, HPLC Condition: (Polaris 5C 18-A, batch: 2620101, SS 250 mm × 4.6 mm) at the flow-rate of 1 mL/min eluting with CH_3CN/H_2O (45/55).

Preparation of scavenger resins A and B (Scheme 1). Chloromethyl Merrifield resin (2.00 g, 3.60 mmol of Cl) was placed in a vial pretreated with Sigmacote® and DMA (25 mL) was added. After the resin was fully swollen, dimethylamino-2-

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propyne (768 μL, 7.20 mmol) or dimethylamino-1-azidopropane (923 μL, 7.20 mmol) was added to the suspension. Using a block shaker equipped with speed and temperature controller, the suspension was well shaken at room temperature for 24 h. The resulting ionic resin was collected into a plastic syringe equipped with polyethylene frit, and counter anion, chloride were exchanged by simple ion exchange process with aqueous solution of sodium tetrafluoroborate (0.2 M, 50 mL), this ion exchange procedure was repeated 10 times, and then washed with distilled water, acetone, methanol, THF, and diethyl ether, and dried under reduced pressure to give resin **A** (2.592 g, 1.376 mmol/g of acetylene group determined by nitrogen content of elemental analysis) or resin **B** (2.600 g, 1.249 mmol/g of azide determined by nitrogen content of elemental analysis).

General procedure for 1,2,3-triazole synthesis (Table 2). Aqueous $CuSO_4 \cdot 5H_2O$ (5 mol %, 0.2 M, 125 μL), Cu powder (5 mol %, 2 mg) and Et_3N (5 mol %, 3.5 μL) were added into a vial containing CH_3CN (1.5 mL), and then azide/alkyne compound (0.50 mmol), alkyne/azide compound (0.55 mmol) were added to the solution. The reaction mixture was shaken using a shaker at room temperature and monitored by TLC. After complete conversion, to the reaction mixture was added resin **A** or **B** (depending on type of excess starting molecule), and the suspension was shaken using a shaker at room temperature until the excess starting molecule disappeared on TLC. The reaction mixture was diluted with ethyl acetate (3.0 mL) and filtered with a short silica/Na_2SO_4 column, and then washed with ethyl acetate (5.0 mL × 2). The combined filtrate was concentrated under reduced pressure to give the crude product, whose purity was determined by NMR and HPLC data without further purification.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (entry 1, Table 2). CAS No. 108717-96-0; 99% yield as a white solid: mp 104 - 105 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.82-7.77 (m, 2H), 7.66 (s, 1H), 7.43-7.26 (m, 8H), 5.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.3, 134.7, 130.5, 129.1, 128.7, 128.1, 128.0, 125.7, 119.5, 54.2. HRMS (FAB) *m/z* $C_{15}H_{13}N_3$ $[MH]^+$ calcd: 236.1188, found: 236.1185.

1-Benzyl-4-(phthalimido-2-yl-methyl)-1*H*-1,2,3-triazole (entry 2, Table 2). CAS No. 478555-31-6; 97% yield as a white solid: mp 178 - 179 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.86-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.51 (s, 1H), 7.37-7.26 (m, 5H), 5.48 (s, 2H), 4.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.6, 143.1, 134.4, 134.0, 132.0, 129.0, 128.7, 128.0, 123.4, 122.6, 54.1, 33.1. HRMS (FAB) *m/z* $C_{18}H_{14}O_2$ $[MH]^+$ calcd: 319.1195, found: 319.1195.

1-Benzyl-4-(2-phenylethyl)-1*H*-1,2,3-triazole (entry 3, Table 2). 99% yield as a bright yellow solid: mp 65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.29 (m, 3H), 7.23-7.09 (m, 8H), 5.41 (s, 2H), 2.96-2.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.8, 134.7, 128.8, 128.4, 128.2, 128.1, 127.7, 125.9, 53.8, 35.3, 27.4. HRMS (FAB) *m/z* $C_{17}H_{17}N_3$ $[MH]^+$ calcd: 264.1501, found: 264.1499.

1-Benzyl-4-[bis-*N*,*N*-(*t*-butyloxycarbonylmethyl)aminomethyl]-1*H*-1,2,3-triazole (entry 4, Table 2). 97% yield as a bright yellow solid: mp 59 - 60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (brs, 1H), 7.36-7.26 (m, 5H), 5.51 (s, 2H), 4.00 (brs, 2H), 3.45 (brs, 4H), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 134.5, 128.8, 128.5, 128.2, 128.0, 80.9, 55.0, 54.1, 49.0, 28.0. HRMS (FAB) *m/z* $C_{22}H_{32}N_4O_4$ $[MH]^+$ calcd: 417.2502, found: 417.2504.

***N*-BOC-*cis*-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-L-proline methyl ester (entry 5, Table 2).** 98% yield as a white solid: mp 45 - 46 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.01 (s, 1H), 7.83-7.77 (m, 2H), 7.45-7.28 (m, 3H), 5.23-5.17 (t, *J* = 12.8 Hz, 1H), 4.48-4.41 (m, 1H), 4.18 (dd, *J* = 11.4, 7.4 Hz, 1H), 4.00-3.89 (m, 1H), 3.69 (s, 3H), 3.03-2.88 (m, 1H), 2.70-2.61 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.9, 153.1, 147.8, 130.1, 128.6, 128.1, 125.5, 118.6, 80.7, 57.4, 52.1, 51.0, 35.9, 28.0. HRMS (FAB) *m/z* $C_{19}H_{24}N_4O_4$ $[MH]^+$ calcd: 373.1876, found: 373.1877.

***N*-BOC-*cis*-4-[4-(phthalimido-2-yl-methyl)-1*H*-1,2,3-triazol-1-yl]-L-proline methyl ester (entry 6, Table 2).** 97% yield as a white solid: mp 61 - 62 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85-7.70 (m, 5H), 5.16 (s, 1H), 5.00 (s, 2H), 4.46-4.39 (m, 1H), 4.17 (dd, *J* = 11.4, 7.4 Hz, 1H), 3.90-3.80 (m, 1H), 3.70 (s, 3H), 3.02-2.87 (m, 1H), 2.67-2.57 (m, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.8, 167.3, 153.5, 152.9, 133.9, 132.6, 131.8, 123.2, 80.7, 57.5, 52.1, 50.8, 35.8, 35.0, 32.8, 27.9. HRMS (FAB) *m/z* $C_{22}H_{25}N_5O_6$ $[MH]^+$ calcd: 456.1883, found: 456.1887.

***N*-BOC-*cis*-4-[4-(2-phenylethyl)-1*H*-1,2,3-triazol-1-yl]-L-proline methyl ester (entry 7, Table 2).** 99% yield as a white solid: mp 82 - 83 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32-7.15 (m, 6H), 5.10-5.03 (m, 1H), 4.44-4.37 (m, 1H), 4.12 (dd, *J* = 11.4, 7.4 Hz, 1H), 3.82-3.73 (m, 1H), 3.69 (s, 3H), 3.05-2.81 (m, 5H), 2.66-2.42 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.0, 153.2, 140.9, 128.3, 128.2, 126.0, 80.8, 57,5, 52.2, 51.0, 35.9, 35.3, 28.1, 27.4. HRMS (FAB) *m/z* $C_{21}H_{28}N_4O_4$ $[MH]^+$ calcd: 401.2189, found: 401.2185.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-phenyl-1*H*-1,2,3-triazole (entry 8, Table 2). 94% yield as a white solid: mp 124 - 125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 7.85-7.83 (m, 2H), 7.45-7.42 (m, 2H), 7.38-7.33 (m, 1H), 5.95 (d, *J* = 9.6 Hz, 1H), 5.54 (t, *J* = 9.6 Hz, 1H), 5.45 (t, *J* = 9.6 Hz, 1H), 5.28 (t, *J* = 9.2 Hz, 1H), 4.34 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.17 (dd, *J* = 12.8, 2.0 Hz, 1H), 4.05 (ddd, *J* = 10.0, 4.8, 2.0 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 169.9, 169.3, 168.9, 148.5, 129.8, 128.8, 128.5, 125.9, 117.7, 85.7, 75.1, 72.7, 70.2, 67.7, 61.5, 20.6, 20.5, 20.47, 20.1. HRMS (FAB) *m/z* $C_{22}H_{25}N_3O_9$ $[MH]^+$ calcd: 476.1669, found: 476.1665.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(phthalimido-2-yl-methyl)-1*H*-1,2,3-triazole (entry 9, Table 2). 95% yield as a white solid: mp 203 - 204 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.87-7.85 (m, 2H), 7.74-7.72 (m, 2H), 5.94 (d, *J* = 8.8 Hz, 1H), 5.50-5.42 (m, 2H), 5.26 (t, *J* = 10.0 Hz, 1H), 5.06-4.96 (m, 2H), 4.30 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.15 (dd, *J* = 12.8, 2.4 Hz, 1H), 4.07 (ddd, *J* = 10.4, 4.8, 2.4 Hz, 1H), 2.06 (s, 6H), 2.01 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 169.7, 169.1, 168.6, 167.3, 143.2, 133.9, 131.8, 123.2, 121.4, 85.3, 74.8, 72.4, 70.0, 67.5, 61.4, 32.7, 20.4, 20.3, 20.3, 19.9. HRMS (FAB) *m/z* $C_{25}H_{26}N_4O_{11}$ $[MH]^+$ calcd: 559.1676, found: 559.1683.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(2-phenylethyl)-1*H*-1,2,3-triazole (entry 10, Table 2). 99% yield as a white solid: mp 179 - 180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ

7.44 (s, 1H), 7.30-7.25 (m, 2H), 7.21-7.17 (m, 3H), 5.87 (dd, J = 6.4, 2.4 Hz, 1H), 5.42 (dd, J = 6.8, 2.8 Hz, 2H), 5.24 (ddd, J = 10.0, 6.4, 2.8 Hz, 1H), 4.30 (dd, J = 12.4, 4.8 Hz, 1H), 4.14 (dd, J = 12.8, 2.4 Hz, 1H), 4.01 (ddd, J = 10.0, 5.2, 2.4 Hz, 1H), 3.07-2.97 (m, 4H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 169.7, 169.2, 168.6, 147.8, 140.7, 128.2, 125.9, 119.0, 85.3, 74.7, 72.5, 70.0, 67.5, 61.4, 35.0, 27.2, 20.5, 20.3, 20.3, 19.9. HRMS (FAB) *m/z* $C_{24}H_{29}N_3O_9$ $[MH]^+$ calcd: 504.1982, found: 504.1981.

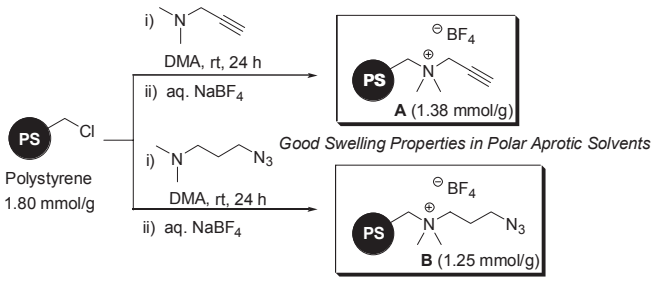
1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-[bis-*N*,*N*-(*t*-butyloxycarbonylmethyl) aminomethyl]-1*H*-1,2,3-triazole (entry 11, Table 2). 93% yield as a bright yellow solid: mp 130 - 131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 5.92 (d, J = 8.8 Hz, 1H), 5.48-5.40 (m, 2H), 5.25 (t, J = 9.6 Hz, 1H), 4.32 (dd, J = 12.8, 4.8 Hz, 1H), 4.15 (dd, J = 12.4, 2.0 Hz, 1H), 4.09-4.06 (m, 3H), 3.44 (s, 4H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.87 (s, 3H), 1.47 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 170.0, 169.6, 169.0, 168.4, 146.0, 121.3, 85.4, 80.7, 74.6, 72.3, 70.2, 67.5, 61.3, 54.9, 48.5, 27.9, 20.4, 20.24, 20.21, 19.8. HRMS (FAB) *m/z* $C_{29}H_{44}N_4O_{13}$ $[MH]^+$ calcd: 657.2983, found: 657.2986.

4-Phenyl-1-[2-(phthalimido-2-yl)ethyl]-1*H*-1,2,3-triazole (entry 12, Table 2). 97% yield as a bright yellow solid: mp 157 - 158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (s, 1H), 7.80-7.77 (m, 4H), 7.69-7.67 (m, 2H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 1H), 4.73 (t, J = 6.4 Hz, 2H), 4.20 (t, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 147.9, 134.2,131.6, 130.4, 128.7, 128.1, 125.7, 119.9, 47.8, 37.6. HRMS (FAB) *m/z* $C_{18}H_{14}N_4O_2$ $[MH]^+$ calcd: 319.1195, found: 319.1190.

4-[Bis-*N*,*N*-(*t*-butyloxycarbonylmethyl)aminomethyl]-1-[2-(phthalimido-2-yl)ethyl]-1*H*-1,2,3-triazole (entry 13, Table 2). 97% yield as a pale yellow solid: mp 131 - 132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.71 (m, 5H), 4.69 (brs, 2H), 4.16 (brs, 2H), 4.01 (brs, 2H), 3.42 (brs, 4H), 1.46 (brs, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 167.3, 145.6, 134.0, 131.4, 123.2, 80.8, 54.9, 48.6, 47.7, 37.5, 27.9. HRMS (FAB) *m/z* $C_{25}H_{33}N_5O_6$ $[MH]^+$ calcd: 500.2509, found: 500.2513.

Results and Discussion

Primarily, polymeric ammonium salts having azide or alkyne functionality were designed as scavenger resins instead of a neutral polymer because of their better swelling properties in polar reaction media, in which the click reaction is usually carried out. These resins were prepared by quaternization of high chloromethyl-loaded (1.80 mmol/g) Merrifield resin with excess amine having acetylene or azide functional group in dimethylacetamide (DMA) solvent at room temperature for 24 h, followed by anion exchange with aqueous sodium tetrafluoroborate ($NaBF_4$).

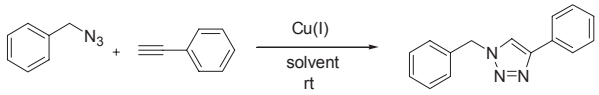


Scheme 1. Preparation of scavenger resins **A** and **B**

The ammonium BF_4 resin was chosen due to its better swelling property in polar aprotic solvent compared to ammonium Cl resin.[12] Consequently, the resins **A** and **B** were obtained in 1.38 mmol/g for **A** and 1.25 mmol/g for **B** as determined by elemental analysis (calculated by nitrogen content) (Scheme 1). Both resins showed good swelling properties in several polar solvents such as acetonitrile, DMF, and DMSO over 5 fold swollen compared to dry resins.

To find out a suitable condition for both solution- and solid-phase click reactions, we optimized the reaction condition using a simple click reaction of benzyl azide (**1**) and phenyl acetylene (**2**) (Table 1). The catalyst, base, and reaction solvent were varied for fast reaction completion, high regioselectivity, reducing byproducts such as oxidatively coupled acetylene dimer,[13] and facile removal of other residues. Firstly, the Sharpless protocol, 10 mol % of $CuSO_4 \cdot 5H_2O$ (aqueous 0.2 M)/Na-ascorbate (aqueous 0.2 M), was tried in DMF solvent (Table 1, entry 1). The reaction was completed within 1 h, but it was difficult to remove the DMF solvent after the reaction. Thus, the same reaction was performed in more volatile acetonitrile solvent (entry 2). However, the reaction proceeded very slowly. On the next attempt, the Meldal protocol, CuI/triethylamine (Et_3N) was tested in acetonitrile solvent, and the reaction was completed within 3 h. Problematically, an oxidatively coupled acetylene dimer and a 1,5-disubstituted triazole regioisomer were also formed (entry 3). Therefore, the catalytic system was returned back to the Sharpless condition, similar to entry 2 in Table 1. Although the addition of Et_3N accelerated the reaction, it remained slow (entry 4). As shown in entry 5, the efficiency of the reaction was improved when 10 mol % of $CuSO_4 \cdot 5H_2O$ (aqueous 0.2 M)/Cu power was used in the presence of Et_3N, affording fast reaction completion within 3 h with no byproducts. Furthermore, 5 mol % of catalyst allowed the reaction to be completed within 6 h (entry 6). Consequently, 5 mol % of $CuSO_4$

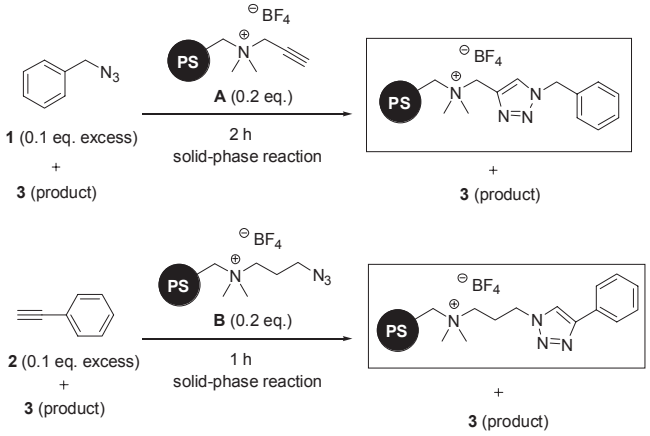
Table 1. Optimization of solution-phase click reaction[a]



1 2 3

entry	Cu(I)[b]	solvent	time	comments
1	A	DMF	1 h	non volatile DMF
2	A	CH_3CN	3 d	slow
3	B	CH_3CN	3 h	regioisomer & acetylene dimer
4	C	CH_3CN	> 24 h	slow
5	D	CH_3CN	3 h	
6	E	CH_3CN	6 h	

[a]All reactions were carried out on a 0.5 mmol of **1** and 1.1 equiv of **2**. [b]A: 10 mol % $CuSO_4 \cdot 5H_2O$, 10 mol % Na-ascorbate. B: 10 mol % CuI, 10 mol % Et_3N. C: 10 mol % $CuSO_4 \cdot 5H_2O$, 10 mol % Na-ascorbate, 10 mol % Et_3N. D: 10 mol % $CuSO_4 \cdot 5H_2O$, 10 mol % Cu, 10 mol % Et_3N. E: 5 mol % $CuSO_4 \cdot 5H_2O$, 5 mol % Cu, 5 mol % Et_3N.



Scheme 2. Heterogeneous click reactions

(aqueous 0.2 M)/Cu/Et_3N in acetonitrile solvent was chosen as the optimal condition for the solution-phase click reaction.

After optimization of the solution-phase click reaction, the heterogeneous click reaction was investigated by adding corresponding acetylene or azide resin (**A** or **B**) to the reaction mixture. The reaction was completed within 2 h and 1 h, respectively, in which 0.2 equiv of scavenger resin **A** or **B** was used for complete scavenging of 0.1 equiv of unreacted starting molecule azide (**1**) or acetylene (**2**), respectively (Scheme 2).

After the solid-phase click reaction, we attempted to remove impurities such as copper species, Et_3N, and acetonitrile solvent that remained in the reaction mixture. Recently, our group reported that CuI can be immobilized onto polystyrene-based ammonium salt resin for heterogeneous solid catalyst.[10] Soluble copper residue could be consistently immobilized onto scaven-

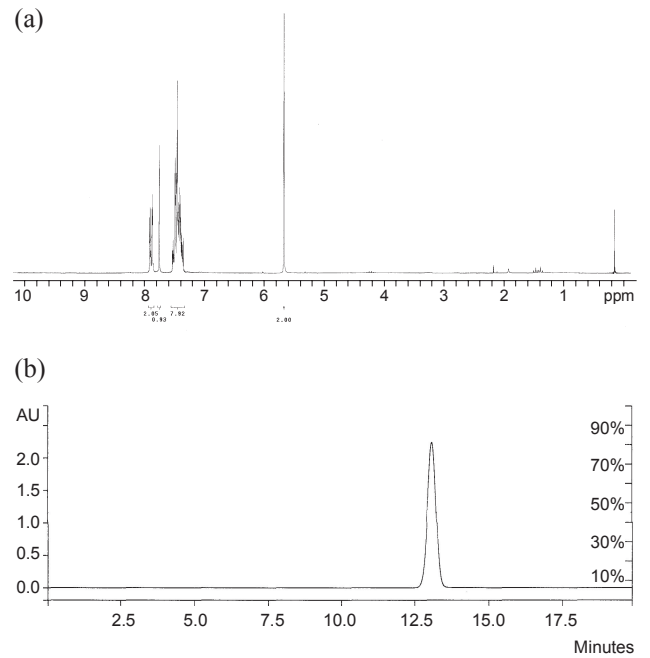
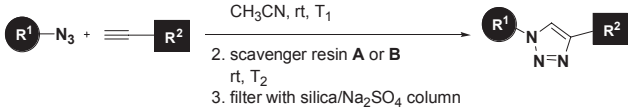
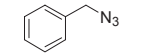
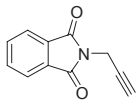
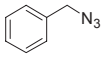
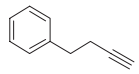
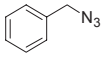
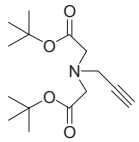
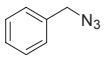
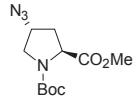
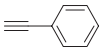
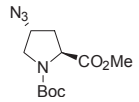
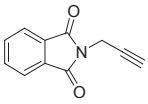
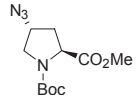
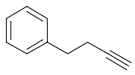
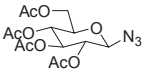
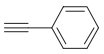
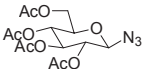
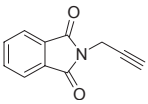
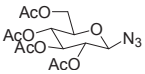
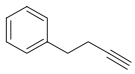
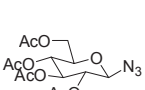
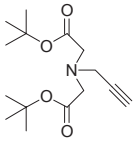
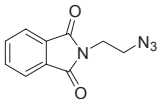
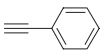
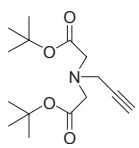
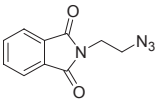


Figure 1. Analysis of crude compound **3**. (a) ^{1}H NMR, (b) HPLC profile: conditions: C-18 (250 × 4.6 mm), acetonitrile/H_2O (45/55), at 254 nm and 1 mL/min.

Table 2. Various click reactions[a]



entry	azide/acetylene (1.0 eq.)	acetylene/azide (1.1 eq.)	resin	T_1/T_2 (h)	yield (%)	purity (%)[b]
1			**B**	6/1	99	100
2			**A**	8/2	97	99
3			**A**	6/2	99	96
4			**A**	8/2	97	100
5			**B**	18/1	98	100
6			**B**	8/3	97	ND[c]
7			**B**	10/2	99	98
8			**B**	8/1	94	100
9			**B**	8/3	95	ND[c]
10			**B**	10/2	99	100
11			**B**	8/5	93	ND[c]
12			**B**	8/1	97	96
13			**A**	6/2	97	98

[a]All reactions were carried out using 0.5 mmol of acetylene or azide, and 1.1 eq. of counterpart azide or acetylene. After complete solution phase reaction, corresponding resin (0.2 eq.) **A** or **B** was added. [b]Determined by ^{1}H-NMR and confirmed by HPLC. [c]Not determined.

ger resins and removed by filtration, together with insoluble copper metal.

However, a tiny amount of copper still remained in the filtrate solution. This was completely removed by eluting the reaction mixture through a short column packed with Na_2SO_4 and silica gel, in which the Na_2SO_4 was required to remove the small amount of water from the aqueous $CuSO_4$ solution used. The column was washed with additional ethyl acetate (5 mL × 2).

This filtration has proved to be sufficient to remove all copper species by ICP-MS (inductively coupled plasma – mass spectroscopy) analysis to detect Cu metal in the final solution. The analysis sample was prepared in 10 mL acidic aqueous solution (calculated, 157.5 ppm; observed, 0.149 ppm; → 0.095%). The resulting acetonitrile solution obtained after filtration was evaporated to remove the acetonitrile and Et_3N and thereby afford a quantitatively yielded crude product. ^{1}H NMR spectrum (Figure 1a) and HPLC analysis (Figure 1b) confirmed the high purity of almost 100% of the crude product **3**.

Using the aforementioned optimized reaction/ purification condition, the quick preparation of click product was further explored with several substrates in the one-pot reaction of solution-phase and subsequent solid-phase (Table 2). All reactions using 5 mol % of each $CuSO_4$, Cu, and Et_3N in CH_3CN at room temperature afforded corresponding high regioselective products with excellent yield and high purity. While the first solution-phase reaction required a relatively longer reaction time, the solid-phase scavenging step took less time. After each reaction was completed, the reaction mixture was diluted with ethyl acetate and filtered with the Na_2SO_4/silica column to remove the remaining Cu metal and water. The triethylamine base was removed by evaporation under reduced pressure. As shown in Table 2, all desired regioselective 1,4-disubstituted 1,2,3-triazoles were uneventfully obtained in high yield and excellent purity.

In conclusion, a new technique for rapid purification of the click reaction was developed using azide/acetylene scavenger resins. These resins were prepared by quaternization of high chloromethyl-loaded, Merrifield resin with azide/acetylene amine. The corresponding ammonium salt resins showed excellent swelling properties in polar aprotic solvents such as acetonitrile, DMF and DMSO. The copper metal and water residue that remained after the reaction were removed by using Na_2SO_4/ silica cartridge column. The optimal condition, including reaction and purification, was applied to 13 additional click reactions, giving high yield and excellent purity. We expect this method to become the general procedure for the high throughput synthesis of 1,4-disubstituted 1,2,3-triazoles without conventional purification.

Acknowledgments. This work was supported by the Converging Research Program (2009-0081956) and the Real-Time Molecular Imaging Project (2009-0065588) through the National Research Foundation (NRF) of Korea funded by the Ministry of Education, Science and Technology and Korea Health 21 R&D Project, Ministry of Health & Welfare (A062254).

Supporting Information. ^{1}H and ^{13}C NMR spectra and HPLC chromatograms are available on request from the correspondence authors. Fax: +82-2-715-2411 (DYC); E-mail: bslee@futurechem.co.kr (BSL); dychi@sogang.ac.kr (DYC).

References

1. Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
2. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
3. for small molecule synthesis: (a) Ng, S. L.; Yang, P.-Y.; Chen, K. Y.-T.; Srinivasan, R.; Yao, S. Q. *Org. Biomol. Chem.* **2008**, *6*, 844. (b) Chen, J.; Nikolovska-Coleska, Z.; Yang, C. Y.; Gomez, C.; Gao, W.; Krajewski, K.; Jiang, S.; Roller, P.; Wang, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3939.
4. for bioconjugation: (a) Geng, J.; Mantovani, G.; Tao, L.; Nicolas, J.; Chen, G.; Wallis, R.; Mitchell, D. A.; Johnson, B. R. G.; Evans, S. D.; Haddleton, D. M. *J. Am. Chem. Soc.* **2007**, *129*, 15156. (b) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192.
5. for polymerization: (a) Qin, A.; Jim, C. K. W.; Lu, W.; Lam, J. W. Y.; Häussler, M.; Dong, Y.; Sung, H. H. Y.; Williams, I. D.; Wong, G. K. L.; Tang, B. Z. *Macromolecules* **2007**, *40*, 2308. (b) Lee, J. W.; Han, S. C.; Kim, J. H.; Ko, Y. H.; Kim, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 1837. (c) Lee, J. W.; Kim, B.-K.; Jin, S.-H. *Bull. Korean Chem. Soc.* **2005**, *26*, 833. (d) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928.
6. for radiolableling: (a) Li, Z.-B.; Wu, Z.; Chen, K.; Chin, F. T.; Chen, X. *Bioconjugate Chem.* **2007**, *18*, 1987. (b) Sirion, U.; Kim, H. J.; Lee, J. H.; Seo, J. W.; Lee, B. S.; Lee, S. J.; Oh, S. J.; Chi, D. Y. *Tetrahedron Lett.* **2007**, *48*, 3953.
7. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Medicinal Research Reviews* **2008**, *28*, 278.
8. (a) Brik, A.; Alexandratos, J.; Lin, Y. C.; Elder, J. H.; Olson, A. J.; Wlodawer, A.; Goodsell, D. S.; Wong C. H. *ChemBioChem* **2005**, *6*, 1167. (b) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, *70*, 9595. (c) Bock, V. D.; Speijer, D.; Hiemstra, H.; van Maarseveen, J. H. *Org. Biomol. Chem.* **2007**, *5*, 971. (d) Hitotsuyanagi, Y.; Motegi, S.; Hasuda, T.; Takeya, K. *Org. Lett.* **2004**, *6*, 1111. (e) Horne, W. S.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 9372. (f) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 15366.
9. Girard, C.; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689.
10. Sirion, U.; Bae, Y. J.; Lee, B. S.; Chi, D. Y. *Synlett* **2008**, 2326.
11. Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559.
12. Lee, B. S.; Mahajan, S.; Janda, K. D. *Tetrahderon Lett.* **2005**, *46*, 807.
13. Tregre, G. J.; Mathias, L. J. *J. Polym. Sci. Pol. Chem.* **1997**, *35*, 587.