



Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via Three Component Coupling of Alcohol, Azide and Alkynes Using CuO Nanoparticles

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A one-pot reaction for the synthesis of 1,4-disubstituted 1,2,3-triazoles from the alcohols via copper oxide nanoparticles (nano CuO) catalyzed nucleophilic substitution of alcohol with azide, followed by azide-alkyne 1,3-dipolar cycloaddition (click reaction) is reported. 1,4-Disubstituted 1,2,3-triazoles are obtained in good to excellent yields from a variety of readily available alcohols without the need for the preactivation and isolation of the azide intermediates.

Key Words: 1,4-Disubstituted 1,2,3-triazoles, Azide, 1,3-Dipolar cycloaddition, CuO nanoparticles.

INTRODUCTION

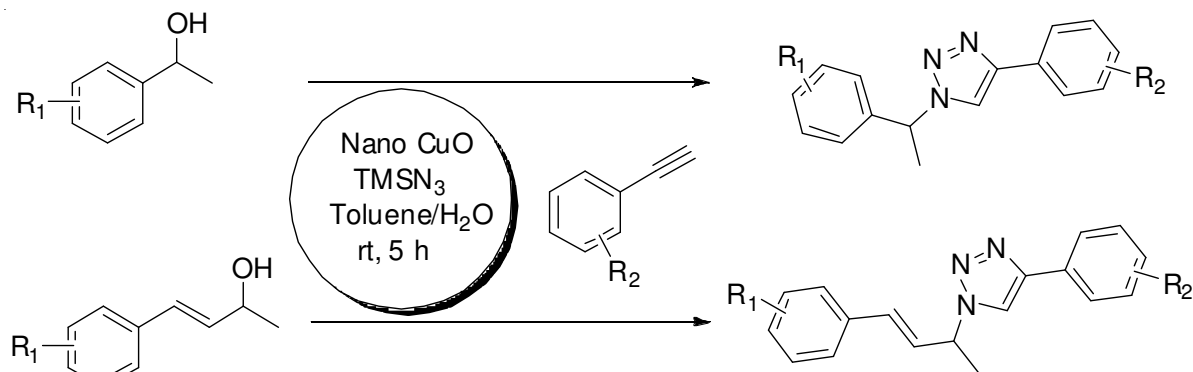
The ever increasing demand for the novel medicinally active compounds and the laborious process of lead discovery and optimization have resulted in the continuous search for simple and efficient methods for generation of libraries for biological screening. Click chemistry has emerged as a fast and efficient approach to synthesize novel compounds with desired function making use of selected "near perfect" reactions¹. The Huisgen 1,3-dipolar cycloaddition² of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions.

Copper catalyzed ligation of organic azides and terminal alkynes has enjoyed much use since its discovery. Exclusive regioselectivity, wide substrate scope, mild reaction conditions and very high yields³ have made it the method of choice for making permanent connections by means of 1,4-disubstituted 1,2,3-triazoles. Since then, this reaction has been used for the construction of a variety of multivalent structures such as sugar heterodimers, glycoconjugates⁴, calix-sugars⁵ and dendritic and polymeric materials⁶. Furthermore, the one-pot multistep reaction involving the Wittig olefination, the Knoevenagel condensation, the Diels-Alder cyclization and Cu(I)-catalyzed alkyne-azide coupling has been explored⁷. Gratifyingly, the same level of success has been found when compared to the traditional methodology. In another variation, microwave-assisted one-pot reaction has generated a variety of triazoles directly from activated aryl halides and sodium azide⁸. In a similar fashion, taking advantage of anomeric activation, rapid

one-pot syntheses of triazole-linked glycoconjugates have also been developed from readily available unprotected saccharides or saccharide acetates⁹. Several members of the 1,2,3-triazole family have indeed shown interesting biological properties, such as antiallergic¹⁰, antibacterial¹¹ and anti-HIV activity¹². Additionally, 1,2,3-triazoles are found in herbicides, fungicides and dyes¹³.

Despite these advances, there is a need to broaden the scope of one-pot multistep reaction in combination with click chemistry. Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle¹⁴. This is especially true for small molecules with several azide functionalities that would be of much interest for the generation of polyvalent structures. Thus, a methodology that avoids isolation of organic azides is desirable. Aliphatic azides can be readily prepared from the corresponding halides by nucleophilic displacement or, in cases of aryl and vinyl azides, by a Cu(I)-catalyzed reaction (vide infra) with sodium azide.

The substitution is especially facile when activated halides, such as allylic, propargylic and benzylic, are used. In present study we have studied the reactivity of alcohols in such reactions, which generally requires preactivation of hydroxyl group to convert in to azides¹⁵. Herein, we report a one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles via three component coupling of secondary alcohol, trimethylsilyl azide and terminal alkynes in the presence of a catalytic amount of a CuO nanoparticles (**Scheme-I**).



Scheme-I

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals, Pvt. Ltd. India and used as received. ACME silica gel (100-200 mesh) was used for column chromatography. All the other chemicals and solvents were obtained from commercial sources and purified using standard methods. The IR spectra of all compounds were recorded on a Perkin-Elmer, Spectrum GX FTIR spectrometer. The ^1H , ^{13}C NMR spectra were recorded on a Varian-400 MHz, Bruker-Avance 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in CDCl_3 . ESI mass spectra were recorded on a Finnigan LCQ Advantagemax spectrometer.

General experimental procedure: A mixture of alcohol (1 mmol), trimethylsilyl azide (2 mmol) and CuO nanoparticles (3 mol %) in toluene (3 mL) was stirred at 60°C for 3 h. After complete consumption of the alcohol as indicated by TLC, alkyne (1.2 mmol) and water (2 mL) was added and continued the reaction. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and purified by column chromatography on silica gel to afford the pure product. The product was well characterized by ^1H NMR, ^{13}C NMR and mass spectroscopic analysis.

4-Phenyl-1-(1-phenyl-ethyl)-1H-[1,2,3]triazole (Table-1, entry 1): ^1H NMR (300 MHz, CDCl_3): δ (ppm) 2.03 (d, 3H, $J = 7.554$ Hz), 5.79-5.86 (q, 1H, $J = 7.6$ Hz), 7.23-7.39 (m, 8H), 7.55 (s, 1H), 7.75 (d, 2H, $J = 8.309$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 21.23, 60.25, 118.20, 125.62, 126.52, 128.0, 128.56, 128.73, 128.99, 130.68, 139.90, 147.76. ESI MS (m/z): 250 ($\text{M}+\text{H}$) $^+$.

1-[1-(4-Bromo-phenyl)-ethyl]4-phenyl-1H-[1,2,3]triazole (Table-1, entry 2): ^1H NMR (300 MHz, CDCl_3) δ (ppm) 2.01 (d, 3H, $J = 7.6$ Hz) 5.75-5.82 (q, 1H, $J = 7.6$ Hz), 7.17 (d, 2H, $J = 8.309$ Hz), 7.27-7.39 (m, 3H), 7.48 (d, 2H, $J = 8.309$ Hz) 7.56 (s, 1H), 7.74 (d, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 21.24, 59.70, 118.21, 120.19, 125.71, 127.98, 128.18, 128.65, 128.77, 132.26, 139.80, 147.75. ESI MS (m/z): 329 ($\text{M}+2$) $^+$.

4-Phenyl-1-(1-*p*-tolyl-ethyl)-1H-[1,2,3]triazole (Table-1, entry 3): ^1H NMR (300 MHz, CDCl_3) δ (ppm) 2.01 (d, 3H, $J = 7.2$ Hz), 2.35 (s, 3H) 5.76-5.86 (q, 1H, $J = 7.2$ Hz), 7.12

(d, 2H, $J = 7.9$ Hz), 7.26-7.37 (m, 5H), 7.5 (s, 1H), 7.61 (d, 2H, $J = 7.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 21.26, 21.34, 60.19, 117.97, 125.54, 126.59, 127.93, 128.52, 128.95, 129.43, 137.88, 139.92, 147.78. ESI MS (m/z): 264 ($\text{M}+\text{H}$) $^+$.

4-Phenyl-1-(1-phenyl-propyl)-1H-[1,2,3]triazole (Table-1, entry 4): ^1H NMR (300 MHz, CDCl_3) δ (ppm) 0.98 (t, 3H, $J = 7.6$ Hz), 2.27-2.42 (m, 1H), 2.48 - 2.63 (m, 1H), 5.46 (t, 1H, $J = 6.798$ Hz), 7.302-7.38 (m, 8H), 7.59 (s, 1H), 7.75 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 11.0, 28.36, 66.85, 118.52, 125.59, 127.02, 128.50, 128.70, 128.94, 130.68, 138.83, 147.64. ESI MS (m/z): 264.1 ($\text{M}+\text{H}$) $^+$.

1-Benzhydryl-4-phenyl-1H-[1,2,3]triazole (Table-1, entry 5): ^1H NMR (300 MHz, CDCl_3) δ (ppm) 6.73 (s, 1H) 7.28-7.50 (m, 12H) 7.80 (d, 2H), 7.95 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 68.09, 76.57, 77.00, 77.42, 119.57, 125.66, 128.53, 128.71, 128.88, 130.51, 138.09, 147.49. ESI MS (m/z): 312.1 ($\text{M}+\text{H}$) $^+$.

(E)-4-Phenyl-1-(4-phenylbut-3-en-2-yl)-1H-1,2,3-triazole (Table-1, entry 6): ^1H NMR (300 MHz, CDCl_3): δ 1.85 (d, 3H, $J = 6.8$ Hz), 5.37-5.46 (m, 1H), 6.40 (dd, 1H, $J = 6.8$ Hz, 15.8 Hz), 6.60 (d, 1H, $J = 15.8$ Hz), 7.24-7.40 (m, 8H), 7.74 (s, 1H), 7.79 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 20.7, 58.4, 117.8, 125.6, 127.6, 127.9, 128.3, 128.6, 129.7, 130.6, 132.6, 135.5, 147.6. ESI MS (m/z): 276 ($\text{M}+\text{H}$), 298 ($\text{M} + \text{Na}$).

(E)-1-(4-(4-bromophenyl)but-3-en-2-yl)-4-phenyl-1H-1,2,3-triazole (Table-1, entry 7): ^1H NMR (300 MHz, CDCl_3): δ 1.86 (d, 3H, $J = 6.8$ Hz), 5.38-5.45 (m, 1H), 6.40 (dd, 1H, $J = 6.5$ Hz, 16.1 Hz), 6.51 (d, 1H, $J = 16.1$ Hz), 7.22-7.30 (m, 3H), 7.36-7.40 (m, 2H), 7.44 (d, 2H, $J = 8.5$ Hz), 7.93 (s, 1H), 7.80 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 20.7, 58.3, 117.8, 122.2, 125.6, 128.1, 128.5, 128.7, 130.5, 131.4, 131.7, 134.5, 147.7. ESI MS (m/z): 354 (M) $^+$, 256 ($\text{M} + 2$).

(E)-4-phenyl-1-(4-*p*-tolylbut-3-en-2-yl)-1H-1,2,3-triazole (Table-1, entry 8): ^1H NMR (300 MHz, CDCl_3): δ 1.85 (d, 3H, $J = 6.8$ Hz), 2.35 (s, 3H), 5.37-5.43 (m, 1H), 6.34 (dd, 1H, $J = 6.8$ Hz, 15.6 Hz), 6.57 (d, 1H, $J = 16.5$ Hz), 7.09 (d, 2H, $J = 7.8$ Hz), 7.23-7.29 (m, 3H), 7.35-7.39 (m, 2H), 7.74 (s, 1H), 7.79 (d, 2H, $J = 7.8$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 20.8, 21.1, 58.4, 117.7, 125.6, 126.5, 126.6, 127.9, 128.7, 129.3, 130.6, 132.6, 132.7, 138.3, 147.6. ESI MS (m/z): 290 ($\text{M} + \text{H}$).

(E)-1-(4-(4-Methoxyphenyl) but-3-en-2-yl)-4-phenyl-1H-1,2,3-triazole (Table-1, entry 9): ^1H NMR (300 MHz,

TABLE-1
ONE-POT SYNTHESIS OF 1,4-DISUBSTITUTED 1,2,3-
TRIAZOLES FROM DIFFERENT ALCOHOLS WITH
TMSN₃ AND PHENYL ACETYLENE^a

Entry	Alcohol	Product	Time (h)	Yield (%)
1			5	75
2			5	67
3			5	72
4			5	78
5			3	90
6			4	86
7			4	83
8			4	88
9			4	85

^aReaction conditions: alcohol (1 mmol), TMSN₃ (1.5 equiv), phenyl acetylene (1.2 mmol) and toluene (3 mL), room temperature

CDCl₃): δ 1.83 (d, 3H, *J* = 6.8 Hz), 3.79 (s, 3H), 5.35-5.40 (m, 1H), 6.24 (dd, 1H, *J* = 6.8 Hz, 15.6 Hz), 6.57 (d, 2H, *J* = 15.6 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 7.24-7.29 (m, 3H), 7.34-7.37 (m, 2H), 7.74 (s, 1H), 7.78 (d, 2H, *J* = 7.8 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 20.8, 55.2, 58.5, 113.9, 117.8, 125.3, 125.5, 127.8, 129.9, 128.1, 128.6, 130.6, 132.1, 147.5, 159.6. ESI MS (*m/z*): 306 (M + H).

1-(1-Phenyl-ethyl)-4-*p*-tolyl-1*H*-[1,2,3]triazole (Table-2, entry 1): ¹H NMR (300 MHz, CDCl₃) δ (ppm) 2.01 (d, 3H, *J* = 7.2 Hz), 2.35 (s, 3H), 5.76-5.86 (q, 1H, *J* = 7.21 Hz), 7.12 (d, 2H, *J* = 7.9 Hz), 7.26-7.37 (m, 5H), 7.50 (s, 1H), 7.61 (d, 2H, *J* = 7.9 Hz). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 21.24, 21.30, 60.22, 118.0, 125.59, 126.56, 127.92, 128.53, 129.03, 129.43, 137.87, 140.02, 147.85. ESI MS (*m/z*): 264.1 (M+H)⁺.

4-(4-Methoxy-phenyl)-1-(1-phenyl-ethyl)-1*H*-[1,2,3]triazole (Table-2, entry 2): ¹H NMR (300 MHz, CDCl₃) δ (ppm) 2.02 (d, 3H, *J* = 7.2 Hz), 3.81 (s, 3 H), 5.77-5.84 (q, 1H, *J* = 7.2 Hz), 6.85 (d, 2H, *J* = 8.876 Hz), 7.27-7.36 (m, 5H), 7.46 (s, 1H), 7.66 (d, 2H, *J* = 8.7 Hz). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 21.29, 55.30, 60.19, 114.19, 117.50, 126.53, 126.97, 128.50, 129.02, 139.7, 159.67. ESI MS (*m/z*): 280.1 (M+H)⁺.

4-(4-Pentyl-phenyl)-1-(1-phenyl-ethyl)-1*H*-[1,2,3]triazole (Table-2, entry 3): ¹H NMR (300 MHz, CDCl₃) δ (ppm) 0.85 (t, 3 H, *J* = 6.5 Hz), 1.24-1.33 (m, 4H, *J* = 3.6 Hz), 1.53-1.68 (m, 2H, *J* = 7.9 Hz), 2.01 (d, 3H, *J* = 7.2 Hz), 2.55 (t, 2H, *J* = 7.9 Hz), 5.76-5.86 (q, 1H, *J* = 7.2 Hz), 7.12 (d,

2H, *J* = 7.9 Hz), 7.25-7.37 (m, 5H), 7.5 (s, 1H), 7.63 (d, 2H, *J* = 7.9 Hz). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 13.96, 21.27, 22.49, 30.98, 31.42, 35.67, 60.19, 118.00, 125.59, 126.06, 128.06, 128.47, 128.76, 128.99, 140.02, 142.96, 147.85. ESI MS (*m/z*): 320.2 (M+H)⁺.

3-[1-(1-Phenyl-ethyl)-1*H*-[1,2,3]triazol-4-yl]-pyridine (Table-2, entry 4): ¹H NMR (300 MHz, CDCl₃) δ (ppm) 2.01 (d, 3H, *J* = 7.6 Hz), 5.75-5.79 (q, 1H, *J* = 7.6 Hz), 7.28-7.34 (m, 5H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.57 (s, 1H), 8.09 (d, 1H, *J* = 8.4 Hz), 8.75 (d, 1H, *J* = 4.8 Hz), 8.92 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 21.19, 60.20, 118.20, 124.2, 125.52, 127.52, 128.01, 133.51, 135.42, 140.26, 147.94, 149.24. ESI MS (*m/z*): 251.1 (M+H)⁺.

(E)-4-(3-Fluorophenyl)-1-(4-phenylbut-3-en-2-yl)-1*H*-1,2,3-triazole (Table-2, entry 5): ¹H NMR (300 MHz, CDCl₃): δ 1.87 (d, 3H, *J* = 6.8 Hz), 5.38-5.48 (m, 1H), 6.40 (dd, 1H, *J* = 6.8 Hz, 16.1 Hz), 6.62 (d, 1H, *J* = 15.8 Hz), 6.91-7.01 (m, 1H), 7.27-7.39 (m, 6H), 7.50-7.59 (m, 1H), 7.75 (s, 1H), 7.80 (d, 1H, *J* = 8.3 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 20.7, 58.5, 114.6, 114.9, 121.2, 125.5, 126.6, 127.4, 127.6, 128.4, 128.6, 130.2, 130.4, 132.8, 146.6, 161.4. ESI MS (*m/z*): 294 (M+H).

TABLE-2
ONE-POT SYNTHESIS OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES
FROM DIFFERENT ALKYNES WITH TMSN₃ AND ALCOHOLS^a

Entry	Alcohol	Alkyne	Product	Time (h)	Yield (%)
1				5	80
2				5	78
3				5	80
4				6	65
5				4	82
6				4	85
7				5	72
8				4	80
9				5	75

^aReaction conditions: alcohol (1 mmol), TMSN₃ (1.5 equiv), alkyne (1.2 mmol) and toluene (3 mL), room temperature.

(E)-1-(4-Phenylbut-3-en-2-yl)-4-*p*-tolyl-1*H*-1,2,3-triazole (Table-2, entry 6): ¹H NMR (300 MHz, CDCl₃): δ 1.85 (d, 3H, *J* = 6.6 Hz), 2.37 (s, 3H), 5.38-5.45 (m, 1H), 6.40 (dd, *J* = 6.6 Hz, 16.1 Hz), 6.60 (d, 1H, *J* = 16.1 Hz), 7.17 (d, 2H, *J* = 8.1 Hz), 7.24-7.37 (m, 5H), 7.68 (d, 2H, *J* = 8.1 Hz),

7.70 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 20.7, 21.2, 58.3, 117.4, 125.4, 126.5, 127.6, 127.8, 128.3, 128.6, 129.3, 132.6, 135.5, 137.7, 147.7. ESI MS (*m/z*): 290 (*M* + *H*).

(E)-2-(1-(4-Phenylbut-3-en-2-yl)-1*H*-1,2,3-triazol-4-yl)pyridine (Table-2, entry 7): ^1H NMR (300 MHz, CDCl_3): 1.87 (d, 3H, *J* = 6.8 Hz), 5.41-5.50 (m, 1H), 6.41 (dd, 1H, *J* = 6.8 Hz, 16.1 Hz), 6.63 (d, 1H, *J* = 16.1 Hz), 7.16-7.20 (m, 1H), 7.25-7.37 (m, 5H), 7.76 (ddd, *J* = 1.8 Hz, 7.7 Hz, 9.4 Hz), 8.17-8.21 (m, 2H), 8.51 (brd, 1H, *J* = 4.9 Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 20.9, 58.7, 120.6, 121.0, 122.9, 126.6, 127.3, 128.4, 128.6, 133.1, 138.0, 148.1, 149.5. ESI MS (*m/z*): 277 (*M* + *H*).

(E)-4-hexyl-1-(4-phenylbut-3-en-2-yl)-1*H*-1,2,3-triazole (Table-2, entry 8): ^1H NMR (300 MHz, CDCl_3): 0.88 (t, 3H, *J* = 6.5 Hz), 1.27-1.37 (m, 6 H), 1.59-1.70 (m, 2H), 1.79 (d, 3H, *J* = 6.9 Hz), 2.67 (t, 2H, *J* = 7.9 Hz), 5.29-5.37 (m, 1H), 6.34 (dd, 1H, *J* = 6.6 Hz, 15.8 Hz), 6.53 (d, 1H, *J* = 16.4 Hz), 7.24-7.37 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 13.9, 20.7, 22.4, 25.7, 28.9, 29.4, 31.4, 50.1, 118.6, 126.5, 128.0, 128.2, 128.6, 132.3, 135.6, 148.4. ESI MS (*m/z*): 284 (*M* + *H*).

(E)-1-(1-(4-Phenylbut-3-en-2-yl)-1*H*-1,2,3-triazol-4-yl)cyclohexanol (Table-2, entry 9): ^1H NMR (300 MHz, CDCl_3): 1.31-2.19 (m, 14H), 5.30-5.39 (m, 1H), 6.35 (dd, 1H, *J* = 6.8 Hz, 15.8 Hz), 6.56 (d, 1H, *J* = 15.8 Hz), 7.23-7.43 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 20.7, 21.8, 25.3, 37.9, 58.3, 69.4, 117.6, 126.5, 127.7, 128.3, 128.6, 132.6, 135.5, 155.5. ESI MS (*m/z*): 298 (*M* + *H*).

RESULTS AND DISCUSSION

Our study began with the direct conversion of an alcohol with trimethylsilyl azide into a alkyl azide intermediate which, without isolation, was treated with phenylacetylene to furnish the 1,3-dipolar cycloaddition product 1,4-disubstituted 1,2,3-triazole in an one-pot operation using nano CuO as a catalyst. Water plays an important role in this reaction for (a) quenching of excess trimethylsilyl azide and (b) formation of copper acetylide from nano CuO and acetylene without any amine base. Table-1 shows that the reaction proceeds smoothly to completion and the products were obtained in good yields. The reaction of various secondary benzylic alcohols bearing electron-rich and electron-poor substituents underwent the reaction smoothly and gave the products in good yield (Table-1, entries 1-4). The reaction with benzhydrol and various allyl alcohols were even more faster and the products were formed in good to excellent yields (Table-1, entries 5-9).

In order to extend the scope of the reaction, several terminal alkynes were reacted with the azides of benzylic

alcohol and allylic alcohol, which were generated *in situ*. It was observed that the reaction with a range of terminal alkynes, such as substituted phenyl acetylenes as well as aliphatic and hetero aromatic terminal alkynes, were equally effective and the resulting triazoles were obtained in good yields (85-65 %). Among the different terminal alkynes used in this present study, 4-methyl-, 4-methoxy-, 4-pentyl- and 3-fluoro-substituted phenyl acetylenes were found to be more reactive when compared to the heteroaromatic alkyne (Table-2, entries 1-7). In addition, aliphatic alkynes underwent the reaction smoothly to give the corresponding products in excellent yield under these optimized reaction conditions (Table-2, entries 8 and 9).

Conclusion

In conclusion, an efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles from a variety of benzylic alcohol/allylic alcohol, trimethylsilyl azide and terminal alkynes has been developed *via* a simple one-pot, two-step procedure involving the azidation of alcohols, followed by 1,3-dipolar cycloaddition with terminal alkynes using nano CuO as the catalyst.

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