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ORIGINAL PAPER

Immobilized [Cu(cdsalMeen)] on silica gel: a highly efficient heterogeneous catalyst for 'Click' [3 + 2] Huisgen cycloaddition

Elham Zarenezhad[1] · Mohammad Navid Soltani Rad[2] · Somayeh Behrouz[2] · Sheida Esmaielzadeh[3] · Mojtaba Farjam[1]

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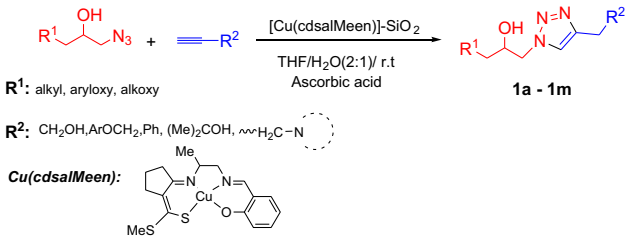
Abstract A facile and simple protocol for the 'Click' cycloaddition of organic azides with terminal alkynes catalyzed by immobilized [Cu(cdsalMeen)] on silica as a new and convenient heterogeneous catalyst is described. In this synthetic methodology, [Cu(cdsalMeen)]–SiO_2 catalyzes 1,3-dipolar Huisgen cycloaddition of different functionalized β-azido alcohols and alkynes in the presence of ascorbic acid and a solution of THF/H_2O (2:1, V/V) at room temperature. Good to excellent yields of β-hydroxytriazolylalkyl derivatives were afforded using [Cu(cdsalMeen)]–SiO_2. Immobilization of [Cu(cdsalMeen)] on silica was approved as a chemically and thermally stable catalyst that can be reused for many consecutive trials without a significant decline in its reactivity.

Graphical Abstract



Keywords Click' cycloaddition · Heterogeneous catalyst · β-azido alcohols · Terminal alkynes · β-hydroxytriazolylalkyl

Introduction

1,2,3-Triazoles are an attractive class of heterocyclic compounds because of their wide range of applications including use as agrochemicals, pharmaceutical agents, industrial applications as well as in organometallic chemistry [1, 2]. Heterocyclic compounds containing 1,2,3-triazole structure are known as bioactive compounds, exhibiting a broad spectrum of biological activities, such as antiviral [3], anticancer [4], anti-HIV [5], antibiotic [6], antibacterial [7] and antimicrobial [8]. The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is one of the most widely used method for the synthesis of 1,2,3-triazoles [9]. This type of reaction gives poor regiospecificity which normally leads to a mixture of 1,4- and 1,5-substituted triazoles [10, 11]. Separately, Meldal and Sharpless discovered a modification of the Huisgen reaction, in which addition of Cu $^{(I)}$ to the reaction mixture produced in only 1, 4-substituted triazoles [12, 13]. Various copper $^{(I)}$ sources were applied as catalyst such as CuOTf and CuI. Cu $^{(I)}$ can be in situ produced

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✉ Elham Zarenezhad
El_Zarenezhad@yahoo.com

[1] Non-communicable Diseases Research Center, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran

[2] Medicinal Chemistry Research Laboratory, Department of Chemistry, Shiraz University of Technology, Shiraz 71555-313, Iran

[3] Department of Chemistry, Darab Branch, Islamic Azad University, Darab, Iran

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by using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a reducing agent [14]. Whereas, enriching the metal core with electrons can accelerate the investigated reaction, a stable copper $^{(II)}$ complex with an electron-donating ligand is a useful surrogate for copper $^{(I)}$ systems [15].

Immobilization of organometallic complexes on inorganic supports appears to be a good way to render them practicable and to improve their stability, selectivity and the control of their reactivity through the microenvironment created by the support [16–22]. For these reasons, a common progress in catalysis is the transformation of successful homogeneous catalysts into recoverable catalytic systems that can easily be separated from the reaction mixture by simple filtration and reused multiple times without the loss of the activity and selectivity characteristic of the original catalyst. The development of complex supported on silica gel has attracted attention in recent years because industry seeks more environmentally friendly chemical manufacturing processes. Silica gel as an inorganic support has a high surface area (5–800 $m^2\ kg^{-1}$) compared with other inorganic supports, ranking these materials at the top of the list of high surface area solids [23–25].

Silica-based supports have been widely utilized for preparing heterogeneous Cu catalysts, which opens up new opportunities for the environmentally benign synthesis of clicked compounds. Wang's group immobilized Cu $^{(I)}$ catalyst on primary amine-modified silica gel and utilized this $Cu^{(I)}$ complex as the promoter for the three-component reactions between alkyl halides, sodium azide and terminal alkynes [26]. Li and coworkers also employed *N*-heterocyclic carbene (NHC)-modified silica particles as efficient and recyclable ligands for the Huisgen cycloaddition [27]. Shamim and Paul found that the silica modified by a Schiff base–type ligand promoted the Cu-catalyzed, three-component synthesis of 1,2,3-triazoles in water at room temperature [28]. Several silica-supported chelating absorbents containing multidentate nitrogenated ligands were developed by Santoyo-Gonzalez et al., and their Cu $^{(I)}$ complexes could be utilized for the click synthesis of the triazole products [29]. Our group have also utilized copper-doped silica cuprous sulfate (CDSCS) as a highly efficient and new heterogeneous nano catalyst for Huisgen cycloaddition, CDSCS catalyzes 1,3-dipolar Huisgen cycloaddition of different functionalized β-azido alcohols and alkynes at room temperature [30].

In recent years, a great deal of drug research activity has focused upon the development of selective adrenergic agonists and antagonists, which widely were used to control the hypertension [31–33]. These drugs belong to the group of β-blocking agents known as aryloxy propranolamines. The general features of all of these compounds can be easily visualized as structure (**I**). Various aryloxypropanol amines have been synthesized so far, and many of them are now clinically approved drugs that used as cardiovascular agents [34]. Many approved drugs with cardiovascular property including propranolol (**II**), alprenolol (**III**), metoprolol (**IV**) and carazolol (**V**) having aryloxypropanol amine framework (Fig. 1).

Since the considerable therapeutic activities of triazole derivatives [35], we incorporated the triazole cores instead of amine-derived moieties in compounds (**I**) to obtain β-hydroxytriazoles (VI), (Fig. 1). Herein, we report a new and reusable catalyst system based on $Cu^{(II)}$ on silica gel and ascorbic acid as reducing agent. This heterogeneous catalyst system exhibits a potent catalytic activity for regioselective 1,3-dipolar Huisgen cycloaddition reaction to access diverse 1,2,3-triazole cores.

Experimental

General Remarks: All preliminary chemicals were purchased from either Fluka or Merck. Solvents were purified by standard procedures, and stored over 3 Å molecular sieves. The catalyst was prepared due to reported procedure [36]. Reactions were followed by TLC using SILG/UV 254 silica gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H-, and ^{13}C-NMR spectra were obtained using a Brüker Avance-DPX-400 spectrometer operating at 400/100 MHz also, using a Brüker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively (δ in ppm, J in Hz). GC/MS were performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m/z*; rel. %). Elemental analyses were performed on a Perkin–Elmer 240-B microanalyzer.

Procedure for immobilization of [Cu(cdsalMeen)] on silica

To a solution of [Cu(cdsalMeen)] (0.4 g, 1 mmol) in anhydrous dichloromethane (50 mL), it was added a fresh and active silica gel (0.6 g, 10 mmol) in 0.063–0.200 mm or 70–230 mesh size. The suspension solution was stirred for 48 h at room temperature. Afterward, the suspension solution was flash filtered (sintered glass) and the solid residue (catalyst) was washed with anhydrous dichloromethane (2 × 50 mL). The catalyst was then dried in a vacuum oven at 60 °C for 4 h and stored in a refrigerator. Inductively coupled plasma (ICP) analysis indicated that in each gram of catalyst, there is 0.032 g of active Cu catalyst (0.05 mol-%).

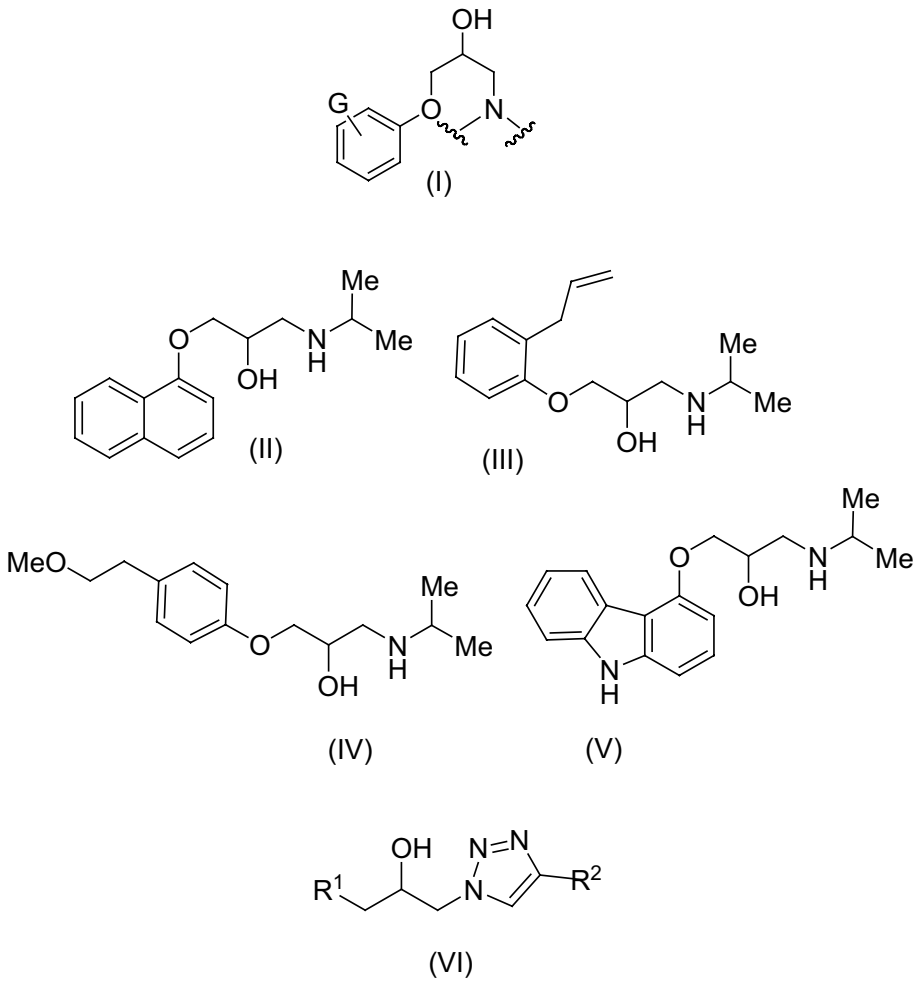


Fig. 1 General structure of famous classes of β-adrenergic blocking agents (*I*), clinically approved drugs: propranolol (*II*), alprenolol (*III*), metoprolol (*IV*), and carazolol (*V*) and their 1,2,3-triazolyl analogs (*VI*)

General procedure for catalytic test

To a round bottom flask (50 mL) was added a mixture of alkyne (0.012 mol), catalyst (0.3 g), the appropriate β-azido alcohol (0.01 mol), and ascorbic acid (0.18 g, 1 mmol) in a mixture of THF/H_2O (2:1 V/V, 20 mL). The reaction mixture was stirred at room temperature until TLC monitoring indicated no further progress in the conversion. The catalyst was filtered off, washed with THF/H_2O (5 × 10 mL), and the filtrate was evaporated under vacuum to remove the solvent. The remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel and eluted with proper solvents. Characterization data of all synthesized compounds are described below.

Benzophenone *O*-(2-hydroxy-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)propyl) oxime (1a) Column chromatography on silica gel (EtOAc/*n*-hexane, 3:1) afforded the product as a yellow foam; yield: (94%); R_f (EtOAc/*n*-hexane, 3:1) 0.66; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.15 (s, 1H, OH, exchangeable with D_2O), 3.28 (s, 1H, OH, exchangeable with D_2O), 3.34 (dd, J = 6, 11.6 Hz, 2H, N-CH_2), 3.46 (dd, J = 3.2, 11.6 Hz, 2H, OCH_2), 3.83 (m, 1H, C*H*OH), 5.02 (s, 1H, CH_2OH), 6.96 (m, 10H, aryl), 8.12 (s, 1H, C (5)-H, triazole). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 52.8, 68.5, 70.4, 71.0, 114.3, 115.8, 128.2, 128.5, 129.1, 129.3, 129.4, 129.6, 136.9, 137.8, 157.6; IR (KBr) ν cm^{-1}: 3610, 3550, 3080, 3045, 2930, 1620, 1550, 1423; MS [*m/z* (%)]: 352.14; Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90; found: C, 64.75; H, 5.73; N, 15.92.

9*H*-Fluoren-9-one *O*-(2-hydroxy-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)propyl) oxime (1b) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a brown foam; yield: (92%); R_f (EtOAc/*n*-hexane, 2:1) 0.55; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.26 (s, 1H, OH, exchangeable with D_2O), 3.66 (dd, J = 5.6, 11.2 Hz, 2H, N-CH_2), 3.74 (dd, J = 4, 11.6 Hz, 2H, OCH_2), 3.88 (s, 1H, OH, exchangeable with D_2O), 4.11

(m, 1H, C*H*OH), 4.81 (s, 2H, CH_2OH), 7.19 (m, 8H, aryl), 8.25 (s, 1H, C(5)–H, triazole). NMR (100 MHz, DMSO-d_6) δ ppm: 53.1, 68.2, 69.2, 71.0, 119.2, 127.3, 128.0, 128.2, 128.4, 129.1, 129.3, 129.6, 133.1, 136.2, 140.9, 142.4, 143.3, 157.6.; IR (KBr) ν cm^{-1}: 3610, 3550, 3080, 3045, 2930, 1620, 1550, 1423; MS [*m/z* (%)]: 350.14; Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99; found: C, 65.11; H, 5.20; N, 15.98.

(Z)-Acetophenone *O*-(2-hydroxy-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)propyl) oxime (1c) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a creamy foam; yield: (89%); R_f (EtOAc/*n*-hexane, 2:1) 0.55; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.15 (s, 3H, C*H*$_3$), 3.06 (s, 1H, OH, exchangeable with D_2O), 3.51 (dd, J = 5.6, 11.2 Hz, 2H, N-CH_2), 3.59 (dd, J = 4, 11.6 Hz, 2H, OCH_2), 3.78 (s, 1H, OH, exchangeable with D_2O), 3.92 (m, 1H, C*H*OH), 4.98 (s, 2H, CH_2OH), 7.55 (m, 5H, aryl), 7.92 (s, 1H, C(5)–H, triazole). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 18.9, 53.5, 63.7, 69.5, 71.4, 127.9, 128.2, 129.1, 132.5, 136.3, 142.4, 158.2.; IR (KBr) ν cm^{-1}: 3610, 3550, 3080, 3045, 2930, 1620, 1550, 1423; MS [*m/z* (%)]: 290.32; Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30; found: C, 57.90; H, 6.24; N, 19.32.

2-((1-(2-Hydroxy-3-(naphthalen-2-yloxy)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)isoindoline-1,3-dione (1d) Column chromatography on silica gel (EtOAc/*n*-hexane, 4:1) afforded the product as a pale yellow solid; yield: (93%); mp = 208–210 °C; R_f (EtOAc/*n*-hexane, 4:1) 0.56; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm:4.03 (m, 2H, NCH_2CH), 4.28 (s, 1H, OH, exchangeable with D_2O), 4.42 (dd, J = 7.5, 13.8 Hz, 1H, ArO-C*H*$_A$H$_B$), 4.57 (dd, J = 3.6, 13.8 Hz, 1H, ArOCH$_A$*H*$_B$), 4.84 (s, 2H, NCH_2C=C), 5.61 (m, 1H, C*H*OH), 7.12 (m, 4H, aryl), 7.74 (m, 7H, aryl), 8.08 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm:32.8, 52.6, 67.7, 69.5, 106.7, 118.5, 123.1, 123.6, 124.2, 126.3, 126.6, 127.4, 128.5, 129.2, 131.5, 134.1, 134.4, 142.0, 156.1, 167.3; IR (KBr) ν cm^{-1}: 3366, 3152, 3087, 3048, 2931, 1775, 1723, 1628, 1558, 1423; MS [*m/z* (%)]: 428; Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08; found: C, 67.36; H, 4.63; N, 13.19.

2-((1-(2-Hydroxy-3-(4-methoxyphenoxy)-propyl)-1*H*-1,2,3-Triazol-4-yl)methyl)isoindoline-1,3-dione (1e) Column chromatography on silica gel (EtOAc/*n*-hexane, 4:1) afforded the product as a yellow solid; (92%); mp = 141-143 °C; R_f (EtOAc/*n*-hexane, 4:1) = 0.51; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm: 3.64 (s, 3H, OCH_3), 3.81 (m, 2H, NCH_2CH), 4.17 (s, 1H, OH, exchangeable with D_2O), 4.33 (dd, J = 7.8, 13.8 Hz, 1H, ArOCH$_A$H$_B$), 4.50 (dd, J = 3.4, 13.8 Hz, 1H, ArOCH$_A$H$_B$), 4.83 (s, 2H, NCH_2C=C), 5.50 (m, 1H, C*H*OH), 6.81 (m, 4H, aryl), 7.80 (m, 4H, aryl), 8.03 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 32.8, 52.7, 55.2, 67.8, 70.0, 114.5, 115.4, 123.1, 124.1, 131.5, 134.4, 142.0, 152.3, 153.4, 167.3; IR (KBr) ν cm^{-1}: 3326, 3145, 2990, 2971, 1764, 1709, 1506, 1427; MS [*m/z* (%)]: 408; Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72; found: C, 61.70; H, 5.03; N, 13.76.

7-((1-(2-Hydroxy-3-(4-methoxyphenoxy)-propyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (1f) Column chromatography on silica gel (EtOAc) afforded the product as a white solid; yield: (83%); mp = 183–186 °C; R_f (EtOAc) = 0.21; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm: 3.16 (s, 3H, N(3)-CH_3), 3.35 (s, 3H, N(1)-CH_3), 3.65 (s, 3H, OCH_3), 3.80 (m, 2H, NCH_2CH), 4.15 (s, 1H, OH, exchangeable with D_2O), 4.35 (dd, J = 7.5, 13.8 Hz, 1H, ArOCH$_A$H$_B$), 4.51 (dd, J = 3.3, 13.8 Hz, 1H, ArOCH$_A$H$_B$), 5.49 (m, 1H, CHOH), 5.54 (s, 2H, NCH_2C=C), 6.75 (m, 4H, aryl), 8.07 (s, 1H, C(5)–H, triazole), 8.13 (s, 1H, C(8)-H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 27.4, 29.3, 41.0, 52.7, 55.2, 67.7, 70.0, 105.7, 114.4, 115.3, 124.8, 142.0, 142.3, 148.2, 150.9, 152.2, 153.4, 154.3; IR (KBr) ν cm^{-1}:3222, 3127, 2931, 1725, 1710, 1657, 1549, 1439; MS [*m/z* (%)]: 441 (10.3); Anal. Calcd for $C_{20}H_{23}N_7O_5$: C, 54.42; H, 5.25; N, 22.21; found: C, 54.31; H, 5.39; N, 22.27.

7-((1-(2-Hydroxybutyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (1g) Column chromatography on silica gel (EtOAc) afforded the product as a white solid; (81%); mp = 144–146 °C; R_f (EtOAc) 0.17; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm: 0.82 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.13 (m, 2H, CH_2CH_3), 3.16 (s, 3H, N(3)-CH_3), 3.35 (s, 3H, N(1)-CH_3), 3.68 (s, 1H, OH, exchangeable with D_2O), 4.12 (dd, J = 7.6,13.7 Hz, 1H, NCH$_A$H$_B$), 4.28 (dd, J = 3.2, 13.7 Hz, 1H, NCH$_A$H$_B$), 4.94 (m, 1H, C*H*OH), 5.52 (s, 2H, NCH_2C=C), 8.00 (s, 1H, C(5)–H, triazole), 8.11 (s, 1H, C(8)-H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 9.6, 27.0, 27.4, 29.3, 41.0, 55.0, 70.2, 105.7, 124.5, 141.9, 142.3, 148.2, 150.9, 154.3; IR (KBr) ν cm^{-1}: 3252, 3107, 2961, 1719, 1708, 1665, 1542, 1431; MS [*m/z* (%)]: 333; Anal. Calcd for $C_{14}H_{19}N_7O_3$: C, 50.44; H, 5.75; N, 29.41; found: C, 50.49; H, 5.87; N, 29.54.

1-((1-(3-Butoxy-2-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl) methyl)indoline-2,3-dione (1h) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a scarlet foam; (91%); R_f (EtOAc/*n*-hexane, 4:1) 0.45, ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 0.53 (t, $J = 7.2$ Hz, 3H, CH_3), 0.95 (m, 2H, CH_2CH_3), 1.13 (m, 2H, OCH_2CH_2), 3.08 (m, 4H, CH_2OCH_2), 3.49 (m, 1H, C*H*OH), 3.84 (s, 1H, OH, exchangeable with D_2O), 4.02 (dd, $J = 7.3$, 14.0 Hz, 1H, NCH_AH_B), 4.20 (dd, $J = 3.4$, 14.0 Hz, 1H, NCH_AH_B), 4.65 (s, 2H, $NCH_2C{=}C$), 6.72 (m, 2H, aryl), 7.18 (m, 2H, aryl), 7.58 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 13.8, 18.8, 31.5, 35.3, 53.2, 69.0, 71.3, 71.6, 111.4, 117.4, 123.9, 124.6, 125.1, 138.5, 141.3, 150.2, 157.9, 183.1; IR (liquid film) ν cm^{-1}: 3419, 3035, 2950, 1739, 1614, 1585, 1471; MS [*m/z* (%)]: 358; Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63; found: C, 60.47; H, 6.13; N, 15.68.

1-((1-(3-(Allyloxy)-2-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione (1i) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a scarlet foam; (93%); R_f (EtOAc/*n*-hexane, 4:1) 0.39; ^{1}H NMR (250 MHz, $CDCl_3$): δ ppm: 3.18 (m, 2H, OCH_2CHOH), 3.58 (m, 1H, C*H*OH), 3.73 (m, 2H, $CH_2CH = C$), 3.96 (s, 1H, OH, exchangeable with D_2O), 4.13 (dd, $J = 7.2$, 14.0 Hz, 1H, NCH_AH_B), 4.29 (dd, $J = 3.6$, 14.0 Hz, 1H, NCH_AH_B), 4.75 (s, 2H, $NCH_2C{=}C$), 4.89 (m, 2H, $=CH_2$), 5.53 (m, 1H, CH), 6.86 (m, 2H, aryl), 7.28 (m, 2H, aryl), 7.67 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 35.3, 53.2, 69.0, 71.0, 72.3, 111.4, 117.4, 117.5, 123.9, 124.6, 125.2, 134.1, 138.6, 141.3, 150.2, 158.0, 183.1; IR (liquid film) ν cm^{-1}: 3400, 3083, 2984, 1734, 1625, 1591, 1468; MS [*m/z* (%)]: 342; Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; found: C, 59.60; H, 5.21; N, 16.46.

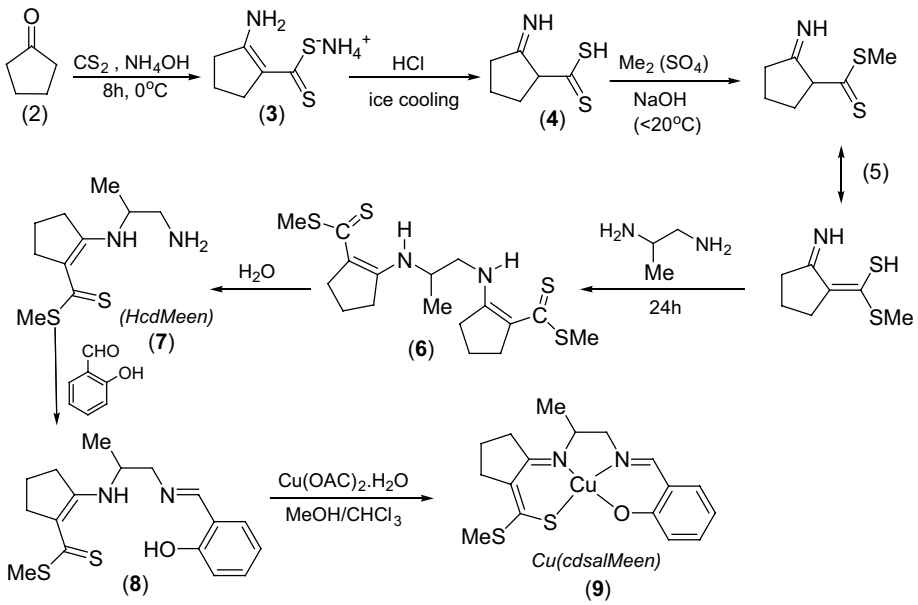
1-(4-((4-Chlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-3-(2,4-dichlorophenoxy)propan-2-ol (1j) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a pale-yellow solid; (88%); mp = 129–132 °C; R_f (EtOAc/*n*-hexane, 4:1) 0.62; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm: 3.97 (m, 2H, NCH_2CH), 4.28 (s, 1H, OH, exchangeable with D_2O), 4.45 (dd, $J = 7.5$, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.61 (dd, $J = 3.2$, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.13 (s, 2H, $OCH_2C{=}C$), 5.66 (m, 1H, C*H*OH), 7.02 (m, 6H, aryl), 7.51 (s, 1H, aryl), 8.19 (s1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 52.5, 61.3, 67.6, 70.6, 115.2, 116.4, 122.5, 124.5, 124.7, 125.6, 128.0, 128.7, 129.1, 142.1, 152.8, 156.8; IR (KBr) ν cm^{-1}: 3264, 3028, 2921, 1647, 1590, 1491, 1036; MS MS [*m/z* (%)]: 428; Anal. Calcd for $C_{18}H_{16}Cl_3N_3O_3$: C, 50.43; H, 3.76; Cl, 24.81; N, 9.80; found: C, 50.57; H, 3.81; Cl, 24.87; N, 9.71.

1-(4-Benzylphenoxy)-3-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-ol (1k) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; (91%); mp = 86–89 °C; R_f (EtOAc/*n*-hexane, 4:1) 0.36; ^{1}H NMR(250 MHz, DMSO-d_6) δ ppm: 1.22 (s, 6H, $2CH_3$), 3.18 (s, 2H, $PhCH_2$), 3.63 (m, 2H, NCH_2CH), 3.95 (s, 1H, CHOH, exchangeable with D_2O), 4.09 (dd, $J = 7.5$, 13.7 Hz, 1H, $ArOCH_AH_B$), 4.25 (dd, $J = 2.7$, 13.4 Hz, 1H, $ArOCH_AH_B$), 4.88 (s, 1H, $(CH_3)_2COH$, exchangeable with D_2O), 5.29 (m, 1H, C*H*OH), 6.60 (d, $J = 8.2$ Hz, 2H, aryl), 6.86 (m, 7H, aryl), 7.61 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 30.7, 40.4, 52.4, 67.0, 67.9, 69.5, 114.5, 121.6, 125.8, 128.3, 128.5, 129.7, 133.5, 141.6, 155.7, 156.6; IR (KBr) ν cm^{-1}: 3329, 3065, 2971, 1643, 1584, 1511, 1453; MS [*m/z* (%)]: 367; Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44; found: C, 68.50; H, 6.81; N, 11.53.

1-(4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-3-phenoxypropan-2-ol (1l). Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; (90%); mp 92–95 °C; R_f (EtOAc/*n*-hexane, 4:1) 0.35; ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm: 1.39 (s, 6H, $2CH_3$), 3.84 (m, 2H, NCH_2CH), 4.15 (s, 1H, CHOH, exchangeable with D_2O), 4.29 (dd, $J = 7.3$, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.44 (dd, $J = 3.8$, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.03 (s, 1H, $(CH_3)_2COH$, exchangeable with D_2O), 5.48 (m, 1H, CHOH), 6.85 (m, 3H, aryl), 7.18 (m, 2H, aryl), 7.78 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d6): δ ppm: 30.7, 52.4, 67.0, 67.9, 69.4, 114.5, 120.7, 121.4, 129.4, 155.5, 158.3; IR (KBr) ν cm^{-1}: 3316, 3100, 2970, 1597, 1588, 1468; MS [*m/z* (%)]: 277; Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15; found: C, 60.75; H, 6.83; N, 15.10.

1-(4-Benzylphenoxy)-3-(4-((4-chlorophenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)propan-2-ol (1m) Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; (92%); mp = 201–205 °C; R_f (EtOAc/*n*-hexane, 4:1) 0.31; ^{1}H NMR(250 MHz, DMSO-d_6) δ ppm: 3.85 (s, 2H, $ArCH_2Ph$), 3.88 (m, 2H, NCH_2CH), 4.10 (s, 1H, CHOH, exchangeable with D_2O), 4.89 (dd, $J = 7.6$, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.25 (dd, $J = 3.3$, 13.4 Hz, 1H, $ArOCH_AH_B$), 5.13 (s,2H, $OCH_2C{=}C$), 5.57 (m, 1H, CHOH), 6.83 (d, $J = 8.2$ Hz,

Scheme 1 Routes to prepare the [Cu(cdsalMeen)]



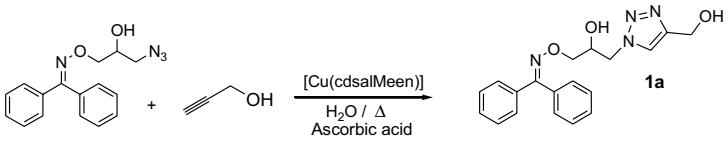
2H, aryl), 7.04 (m, 10H, aryl), 8.1 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ ppm: 52.6, 61.3, 67.77, 69.4, 114.4, 116.4, 124.5, 125.6, 128.1, 129.1, 129.6, 133.5, 141.6, 142.0, 156.6, 156.8; IR (KBr) ν cm^{-1}: 3358, 3059, 2971, 1640, 1510, 1450; MS [*m/z* (%)]: 449; Anal. Calcd for $C_{25}H_{24}ClN_3O_3$: C, 66.74, H, 5.38; Cl, 7.88; N, 9.34; O, 10.67; found: C, 66.72, H; 5.36, Cl; 7.87, N, 9.35; O, 10.69.

Results and discussion

Initially, we prepared an active catalyst due to procedure reported in a literature [36]. As is shown in Scheme 1, the ammonium salt of the thioacid **3** was prepared by stirring a mixture of cyclopentanone **2** (0.3 mol), carbon disulfide (0.39 mol) and 28% aqueous ammonia (100 mL) at 0 °C for eight hours. The yellow crude product was collected, washed with ether. The ammonium salt **3** is not stable at room temperature and loses ammonia on standing. The acid **4** was prepared by dissolving the crude product in water and slowly neutralizing with HCl (2N) under ice-cooling. The yellow prismatic crystals were collected, washed with water and dried. The crude acid was dissolved in air-free cold ethanol until saturation, an equal volume of water was added to the filtered solution and kept in an ice bath for half an hour and the shining yellow crystals **4** were collected, washed with water–ethanol (1:1,V:V) and dried over $CaCl_2$. Yellow crystals (0.03 mol) of **4** were dissolved in a solution of sodium hydroxide (0.03 mol) in 50 mL of water. Dimethylsulfate (0.03 mol) was added in portions under cooling and vigorous stirring, with the temperature being kept below 20 °C. The brown product **5** was then separated, dried and recrystallized from (1:1,V:V) methanol–water. The brown powder was dissolved in 35 mL of methanol, and 0.1 mol of 1,2-diaminopropane was added. After 24 h, the red solution gradually turned pale yellow. The yellow crystalline product **6** was separated, washed with water, dried and recrystallized from dioxane. Then, water (120 mL) was added to the filtrate. The yellow crystals **7** were separated, washed with water and dried. The crude product was recrystallized from 3:2 (V:V) water/methanol. The yellow plates are Methyl-2-(1-methyl-2′-aminoethane) amino-1-cyclopentenedithiocarboxylate (HcdMeen). Ligand **7** (in methanol) was added to a methanolic solution containing the stoichiometric amount of salicylaldehyde. The resultant yellow powder **8** was recrystallized from methanol/chloroform 2:1 (V:V). For synthesis of [Cu(cdsalMeen]) **9** complex, solution of copper acetate in 10 mL of methanol was added to a solution of the appropriate ligand **8** (yellow color) (0.1 mmol) in 10 mL of chloroform/methanol 2:1 (V:V). The solution was stirred for 15 min and then allowed to stand at room temperature for 24 h. After filtering, the crude was recrystallized from acetonitrile/methanol 1:1 (V:V), the $Cu^{(II)}$ complex has brown color.

After synthesis and supporting the catalyst on silica gel, we applied this catalyst in synthesis of some 1,2,3-triazole derivatives. The first step of this synthetic approach was started by optimizing the reaction conditions. At first, we carried out the cycloaddition reaction of benzophenone *O*-(3-azido-2-hydroxypropyl) oxime and prop-2-yn-1-ol as a model reaction to acquire the corresponding 1,2,3-triazole (**1a**) (Table 1). The 1,3-dipolar cycloaddition of model reaction was carried out in the presence of ascorbic acid (1 mmol) and [Cu(cdsalMeen)]–SiO_2 (0.05 mol%) in H_2O

Table 1 Influence of various temperatures on conversion of O-(3-azido-2-hydroxypropyl) oxime into **1a** using [Cu(cdsalMeen)]–SiO_2 in H_2O



Entry	Temperature (°C)	Time (h)	Yield[a] (%)
1	25	4	46
2	50	2	61
3	80	1. 5	70
4	90	1.25	73
5	100	1	79
6	110[b]	1	79
7	155[b]	1	80
8	200[b]	1	80
9	220[b]	1	80

[a] Isolated yield

[b] The reaction is conducted in a pressure bottle

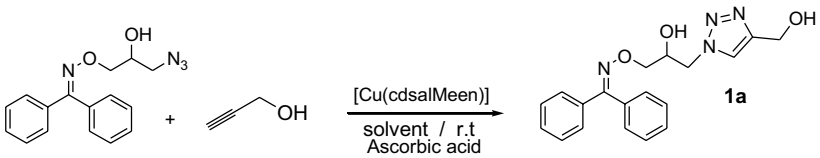
at room temperature, which was afforded **1a** in 46% yield after stirring for 4 h (Table 1, entry 1).

To study the influence of temperature, the model reaction was carried out at different temperatures (Table 1, entries 2–9). Due to Table 1, an increase in the temperature resulted in the promotion of cycloaddition reaction. The best result obtained when the cycloaddition reaction was conducted at 100 °C for 1 h (Table 1, entry 5). However, increasing the temperature up to 220 °C (in a pressure bottle) did not affect the reaction yield, considerably.

In order to optimize the reaction conditions, the influence of various 2:1 (V/V) organic solvents/H_2O was examined in the presence of [Cu(cdsalMeen)]–SiO_2 at room temperature (Table 2).

From Table 2, it is well demonstrated the solvent has a significant role in progress of reaction. Among the

Table 2 Influence of various miscible organic solvents on conversion of *O*-(3-azido-2-hydroxypropyl) oxime into **1a** using [Cu(cdsalMeen)]–SiO_2 at room temperature[a]

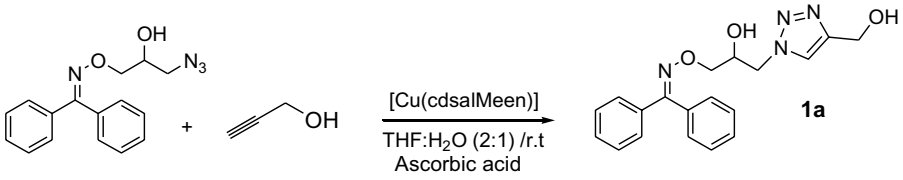


Entry	Solvent[a]	Time (h)	Yield[b] (%)
1	H_2O/DMSO	0.75	89
2	H_2O/DMF	0.75	83
3	H_2O/*t*-BuOH	1.5	70
4	H_2O/MeCN	1.25	73
5	H_2O/THF	0.5	94
6	H_2O/DMSO	1	79
7	H_2O/acetone	2	55
8	H_2O	4	46
9	THF	4	63

[a] For entries 1–7, a mixture of 1:2 (V/V) solvents was used

[b] Isolated yield

Table 3 Influence of time on conversion of *O*-(3-azido-2-hydroxypropyl) oxime into **1a** using [Cu(cdsalMeen)]–SiO_2



Entry	Time (h)	Yield[a] (%)	Conversion[b] (%)
1	0.1	55	61
2	0.2	72	79
3	0. 3	82	90
4	0.4	90	96
5	0.5	94	100
6	0.7	94	100
7	0.8	94	100

[a] Isolated yield

[b] GC yield

examined solvents, a solution of THF/H_2O (2:1, V/V) (Table 2, entry 5) afforded the best result.

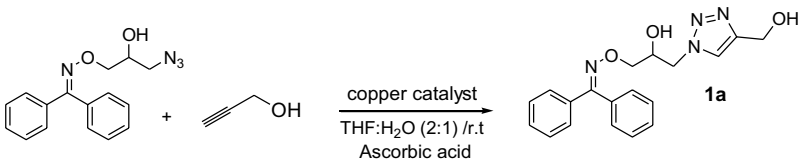
Moreover, using the ratio of organic solvents/water (2:1, V/V), such as DMSO (Table 2, entry 1) and/or DMF (Table 2, entry 2) also yielded the product in reasonable time. Employing the other mixtures afforded a moderate yield of product over longer periods of time (>0.5 h). Additionally, when water and THF were used alone, the yields of 46 and 63% for **1a** were obtained after 4 h, respectively (Table 2, entries 8 and 9). The low yield obtained for **1a** using water is attributed to lack of organic solubility in H_2O.

The optimized stoichiometric ratio of azide/alkyne found to be 1:1.2 for **1a** when 0.3 g (0.05 mol%) of catalyst was applied. It is important to use nearly an equimolar ratio of azide/alkyne. The use of large quantities of alkyne can lead to the appearance of by-products because of alkyne–alkyne homo-coupling reaction in the presence of $Cu^{(I)}$ salts.

Additionally, the influence of time on the progress of reaction for model substrates was investigated (Table 3). As the results in Table 3 indicate, the reaction proceeds smoothly and the best result was obtained when the reaction was terminated after 0.5 h (Table 3, entries 5). Prolonging the reaction time had no distinguishable effect on the progress of the reaction.

To investigation the catalytic potency of homogeneous and heterogeneous [Cu(cdsalMeen)] catalyst and other

Table 4 Comparison of various copper catalysts with [Cu(cdsalMeen)]–SiO_2 on conversion of O-(3-azido-2-hydroxypropyl) oxime into **1a**



Entry[ref]	Catalyst	Time (h)	Yield[a] (%)
1	–	2	0
2	Hetero[b]	0.5	94
3	Homo[c]	0.5	94
4[36]	CuI	8	84
5[37]	$Cu(OAc)_2$	7	73
6[14]	Cu/C	1	87

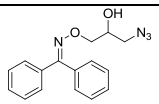
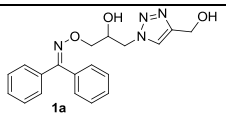
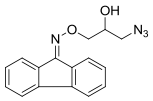
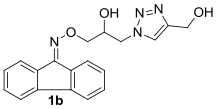
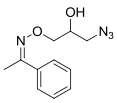
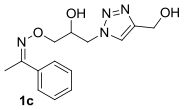
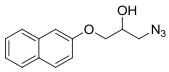
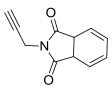
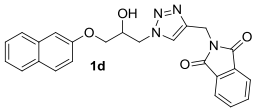
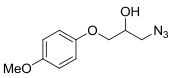
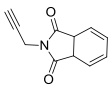
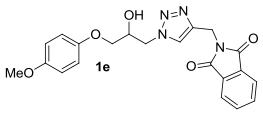
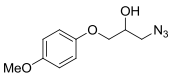
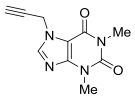
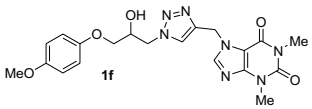
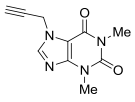
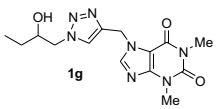
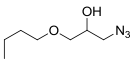
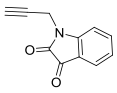
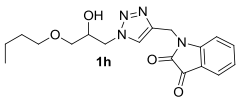
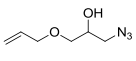
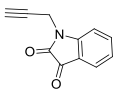
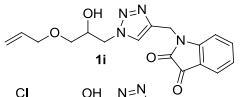
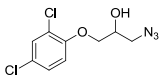
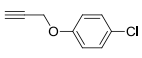
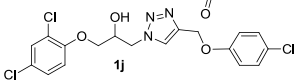
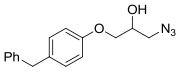
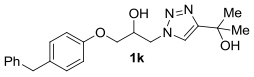
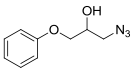
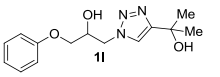
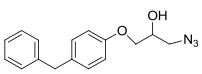
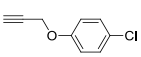
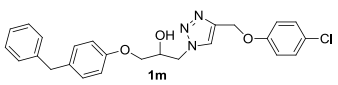
[a] Isolated yield

[b] Heterogeneous

[c] Homogeneous

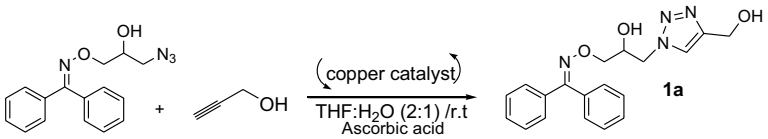
reported copper catalysts in the 1,3-dipolar cycloaddition, the comparative results are summarized in (Table 4). When the reaction was carried out in the absence of catalyst, no products were formed even if the reaction time was prolonged (Table 4, entry 1). According to the results in Table 4, higher yield of **1a** and shorter reaction time were obtained using homogeneous and heterogeneous [Cu(cdsalMeen)] (Table 4, entry 2, 3) in comparison with other examined copper catalysts. Using the other catalysts afforded the satisfactory results of **1a**, however, the reactions were required longer reaction times. As can be seen in Table 4, entry 2, 3, both of homogeneous and heterogeneous [Cu(cdsalMeen)] catalysts are effective, but we applied immobilized [Cu(cdsalMeen)] on silica as a heterogeneous

Table 5 'Click' cycloaddition of β-azido alcohols with alkynes

Entry	ß-Azido alcohol	Alkyne	Product	Time (h)	Yield (%) [a]
1				0.5	94
2				0.5	92
3				0.5	89
4				0.5	93
5				0.5	92
6				1	83
7				1	81
8				0.5	93
9				0.5	91
10				0.5	87
11				0.5	83
12				0.5	81
13				0.5	88

[a] Isolated yield

Table 6 Reusability of [Cu(cdsalMeen)]–SiO_2 in successive trails for synthesis of **1a**



Run	Time (h)	Yield[a] (%)
1	0.5	94
2	0.5	94
3	1. 0	86
4	1.25	84
5	1.5	80

[a] Isolated yield

catalyst, because of its thermal and chemical stability, environmentally compatibility and low catalyst loading that can be easily prepared and reused for many consecutive runs without a significant decrease in its catalytic reactivity.

To illustrate the scope of this method, we extended the optimized reaction condition to other azides and alkynes cycloadditions (Table 5). As the results in Table 5 indicate, [Cu(cdsalMeen)]–SiO_2 proved to be useful catalyst for Huisgen cycloaddition between the structurally diverse β-azido alcohols and alkynes. Using [Cu(cdsalMeen)]–SiO_2, compounds **1a**–**m** were regioselectively synthesized as 1,4-disubstituted 1,2,3-triazoles in excellent yields and short reaction times. The chemistry works well with various β-azido alcohols involving aryloxy, alkoxy and alkyl residues, and also tolerates a wide spectrum of electron-donating and electron-withdrawing functional groups in both alkyne and azide molecules (Table 5). Most of β-azido alcohols used in these experiments were pre-synthesized by the regioselective ring opening reaction of corresponded epoxides with sodium azide, whereas the majority of terminal alkynes were prepared via S_N2-type reaction of propargyl bromide and corresponded nucleophiles.

All synthesized compounds **1a**–**m** were fully characterized, and their structures were confirmed by ^1H and ^{13}C NMR, elemental analysis, mass spectrometry and IR spectroscopy methods.

The reusability of the immobilized [Cu(cdsalMeen)] on silica gel was studied during the synthesis of **1a** (Table 6). In this context, prior to use and also final testing of the catalyst for determination of its activity in many subsequent runs, the catalyst was recycled from the reaction mixture through a sintered glass funnel (vacuum-filtering). The catalyst was then washed successively with THF/H_2O (2:1, V/V, 5 × 10 mL) and dried in a vacuum oven at 100 °C for 30 min. The catalyst was tested for five consecutive runs and through each run, no fresh catalyst was added. Furthermore, the ICP analysis has confirmed the reusability of the [Cu(cdsalMeen)]–SiO_2 without significant desorption of Cu species from silica matrix. As it is well indicated, the amount of leached Cu from [Cu(cdsalMeen)]–SiO_2 is extremely negligible (0.006% after five consecutive runs). As the results in Table 6 indicate, the catalyst can be reused for many consecutive runs without considerable decrease in its catalytic reactivity.

Conclusions

In conclusion, we have reported a robust and recyclable heterogeneous catalysts that contributes to expanding the reliability and scope of the Huisgen 1,3-dipolar cycloaddition. The process showed the considerable synthetic advantages in terms of product diversity, mild reaction condition, simplicity of the reaction procedure and good to excellent yields. Furthermore, copper (II) catalyst can be recovered and recycled by simple filtration of the reaction mixture and reused for at least five consecutive trials without decrease in activity.

Supporting information

More experimental details including characterization data, ^1H NMR and ^{13}C NMR for all new and known compounds are available online.

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