

One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition catalysed by SiO₂–Cu(I) oxide and single crystal X-ray analysis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole

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Abstract A one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition reaction between terminal alkynes, benzyl/allyl/alkyl halides, and NaN₃ in water at room temperature using silica-supported copper(I) oxide (SiO₂–Cu₂O) has been developed. Various supported copper(I) oxide catalysts have been tested for this reaction where silica-supported copper(I) oxide works well in this reaction. The catalyst being heterogeneous can be easily recovered at the end of reaction and can be reused making the process completely economical. A single crystal X-ray analysis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole has revealed that the compound crystallizes in the monoclinic space group P21.

Keywords Crystal structure · Heterogeneous catalysis · One-pot synthesis · Transition metal compounds · SiO₂–Cu₂O

Introduction

The introduction of Cu(I) catalysis in 2001 for the Huisgen 1,3-dipolar cycloaddition reaction of organic azides and alkynes [1] has gained much attention in recent years [2].

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This catalytic species further improves both the rate and regioselectivity of the reaction due to its quantitative, very robust, general, and insensitive nature [3]. Various copper species were used as a copper source for this azide/alkyne-“click”-reaction or CuAAC-reaction such as Cu(0)/oxidizing agent, Cu(0) on charcoal, Cu(0) nano particles [3], Cu(0) catalyst [4], Cu(II)-TD@nSiO₂ [5], Cu(I)/auxiliary ligand [3], and the use of Cu(I) species alone [3].

Although various catalytic systems, both homogenous as well as heterogeneous, have been explored heterogeneous catalysis in organic reactions is of great interest to organic chemists because of their synthetic utility [6], easy isolation of product, simple work-up procedure, recovery and reusability of the catalyst, thus making the process green and economical [7]. The use of silica as a support for heterogeneous catalyst takes the advantage due to its excellent stability (both chemical and thermal), high surface area, good accessibility, and also because organic groups can be robustly anchored to the surface [8–15]. Further, water provides an excellent medium for this CuAAC-reaction due to its non-toxic, non-flammable, abundant, inexpensive nature, and rate enhancement property. Further, silica supported heterogeneous catalysts have been successfully used in the aqueous medium [16, 17].

The multicomponent reaction of alkynes and azides yielding 1,2,3-triazoles is a powerful one-pot three-component click reaction as the afforded triazoles show anti-allergical [18], anti-infective [19], anti-malarial [20], anti-HIV [21], and anti-bacterial biological activities [22]. The low-molecular-weight organic azides are difficult to handle due to their explosive nature. Therefore, a method which involves the in situ formation of organic azides from the starting materials in the reaction medium will be advantageous. Further, avoiding the use of any base makes the process more useful.

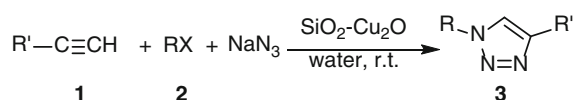
Herein, we report a silica-supported copper(I) oxide catalysed one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes, benzyl/allyl/alkyl halides, and NaN_3 in water at room temperature (Scheme 1). The catalyst is easy to prepare, inexpensive, and can be reused for five times without significant loss of catalytic activity. Use of additional base for this CuAAC reaction is avoided.

Results and discussion

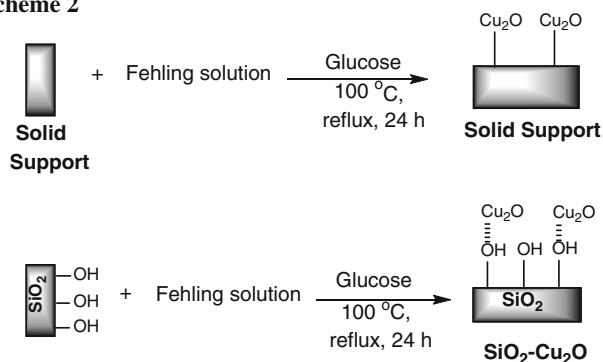
Preparation and characterization of $\text{SiO}_2\text{-Cu}_2\text{O}$

All the supported copper(I) oxide catalysts such as $\text{SiO}_2\text{-Cu}_2\text{O}$ (1), HAP/ Cu_2O (2), basic $\text{Al}_2\text{O}_3/\text{Cu}_2\text{O}$ (3), and cellulose/ Cu_2O (4) have been prepared following the earlier reported procedure [23] as shown in Scheme 2. Among the various supported copper(I) oxide catalysts, $\text{SiO}_2\text{-Cu}_2\text{O}$ was found to be most active and was further characterized by FTIR, thermogravimetric analysis (TGA), X-ray diffractometry (XRD), X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic absorption spectroscopic analysis (AAS). Complete characterization of the catalyst has been reported [23] (see Supplementary Material).

Scheme 1



Scheme 2



Catalyst testing for the azide/alkyne-“click”-reaction or CuAAC-reaction

To optimise the reaction conditions for this CuACC reaction, phenylacetylene, benzyl chloride, and sodium azide were selected as a test substrate to examine the catalytic effect of supported copper(I) oxide.

To select the most appropriate heterogeneous solid supported copper(I) oxide catalyst, Huisgen 1,3-dipolar cycloaddition reaction was carried out using different supported copper(I) oxide catalysts (1–4) at room temperature in aqueous medium. The results are summarised in Table 1. It has been seen that silica-supported copper(I) oxide gave good yields whereas for basic alumina supported copper(I) oxide, yield is quite low. After carrying out series of reactions, 5 mol% of Cu in $\text{SiO}_2\text{-Cu}_2\text{O}$ was found to be sufficient to carry out the reaction in good to excellent yields. Further, the use of different solvents (water, ethanol, acetonitrile) has been investigated using the test substrates (phenylacetylene, benzyl chloride, and sodium azide). The results are evaluated through TLC (Table 2). It has been assumed that water proves to be an activator for Cu_2O catalyst. The product, i.e. 1-benzyl-4-phenyl-1*H*-1,2,3-triazole obtained from the reaction has been subjected to single crystal X-ray studies. It is important to note that the reaction proceeds under neat conditions but the yield is very poor, i.e. 60 % in 20 h at

Table 1 Effect of different supported catalysts for CuACC reaction

S. no.	Support	Time/h	Yield ^b /%
1	Silica- Cu_2O	3.5	96
2	Hydroxyapatite- Cu_2O	3.5	90
3	Cellulose- Cu_2O	3.5	75
4	Basic alumina- Cu_2O	3.5	70

Reaction conditions: phenylacetylene (1.2 mmol), benzyl chloride (1 mmol), NaN_3 (1 mmol), 0.2 g catalyst (5 mol% Cu), and 5 cm^3 water by stirring at room temperature

^a Yields refer to column chromatography yield

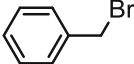
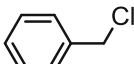
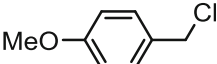
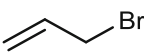
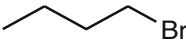
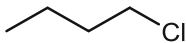
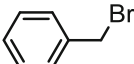
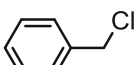
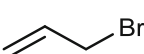
Table 2 Effect of different solvents for CuACC reaction

S. no.	Solvent	Time/h	Yield ^b /%
1	Toulene	3.5	70
2	Acetonitrile	3.5	82
3	Water	3.5	96

Reaction conditions: phenylacetylene (1.2 mmol), benzyl chloride (1 mmol), NaN_3 (1 mmol), 0.2 g $\text{SiO}_2\text{-Cu}_2\text{O}$ (5 mol% Cu), and 5 cm^3 solvent by stirring at room temperature

^a Yields refer to column chromatography yield

Table 3 SiO₂-Cu₂O catalyzed azide alkyne cycloaddition at room temperature in aqueous medium

Comp. ^a	RX	Alkyne R'	Time/h	Yield ^b /%	M.p. (lit. m.p.)/°C
3a		C ₆ H ₅ -	4	95	128–130 (128–129 [29])
3b		C ₆ H ₅ -	3.5	96	128–130 (128–129 [29])
3c		C ₆ H ₅ -	3.5	97	126–127 (127–129 [30])
3d		C ₆ H ₅ -	2	92	40–41 (40–42 [31])
3e	C ₂ H ₅ I	C ₆ H ₅ -	6.5	92	59–60 (61–62 [32])
3f		C ₆ H ₅ -	8	91	45–46 (46–47 [29])
3g		C ₆ H ₅ -	8	92	45–46 (46–47 [29])
3h		HOCH ₂ -	4.5	95	75–76 (76–77 [33])
3i		HOCH ₂ -	4.5	96	75–76 (76–77 [33])
3j		HOCH ₂ -	3	92	44–45 (43–45 [31])

^a Optimized reaction conditions: alkyne (1.2 mmol), halide (1 mmol), NaN₃ (1 mmol), 0.2 g SiO₂-Cu₂O (5 mol% Cu), and 5 cm³ water by stirring at room temperature

^b Yields refer to column chromatography yield

room temperature. To study the generality of the developed protocol, various benzyl/allyl/alkyl halides with phenylacetylene or propargyl alcohol were chosen and results are presented in Table 3. It has been observed that benzyl halides provide the best results, whereas alkyl halides take much time for the reaction to proceed to completion.

Crystal and molecular structure of 3b

An ORTEP view of the title compound with atomic labelling is shown in Fig. 1 [24]. The geometry of the molecule was calculated using PLATON [25] and PARST [26] software. The selected bond lengths and bond angles are given in Table 4.

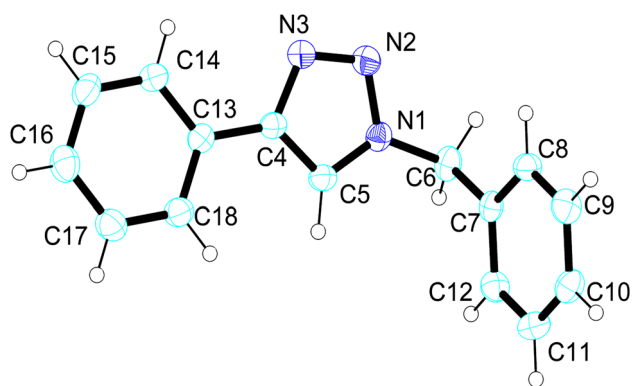


Fig. 1 ORTEP view of the molecule with displacement ellipsoids drawn at 40 %

Table 4 Selected bond lengths/Å and bond angles/°

N1–C5	1.332(2)	C5–N1–N2	110.38(17)
N1–N2	1.346(2)	C5–N1–C6	128.99(18)
N1–C6	1.462(3)	N2–N1–C6	120.57(17)
N2–N3	1.320(2)	N3–N2–N1	106.83(16)
N3–C4	1.351(2)	N2–N3–C4	109.42(17)
C4–C5	1.371(3)	N3–C4–C5	107.33(17)
C4–C13	1.470(3)	N3–C4–C13	122.89(17)
C6–C7	1.506(3)	C5–C4–C13	129.77(19)
C7–C8	1.380(3)	N1–C5–C4	106.03(18)
C7–C12	1.387(3)	N1–C6–C7	111.34(15)
C8–C9	1.377(3)	C8–C7–C12	118.48(18)
C9–C10	1.378(3)	C8–C7–C6	120.9(2)
C10–C11	1.367(3)	C12–C7–C6	120.57(18)
C11–C12	1.377(3)	C9–C8–C7	120.6(2)
C13–C18	1.383(3)	C8–C9–C10	120.4(2)
C13–C14	1.387(3)	C11–C10–C9	119.5(2)
C14–C15	1.375(3)	C10–C11–C12	120.3(2)
C15–C16	1.374(3)	C11–C12–C7	120.70(19)
C16–C17	1.377(3)	C18–C13–C14	118.23(19)
C17–C18	1.374(3)	C18–C13–C4	120.44(18)
C14–C13–C4	121.33(1)	C15–C14–C13	120.7(2)
C16–C15–C14	120.6(2)	C15–C16–C17	119.3(2)
C18–C17–C16	120.3(2)	C17–C18–C13	121.0(2)

The title molecule comprises of a triazole ring and two phenyl rings (Fig. 1). Bond lengths and angles of the title molecules are within normal ranges [27]. Triazole ring (N1/N2/N3/C4/C5) makes a dihedral angle of 79.02(7)° and 9.63(7)° with phenyl rings (C7–C12) and (C13–C18), respectively. Dihedral angle between the phenyl rings is 77.67(7)°. Packing view of the molecules in the unit cell viewed down the *b* axis is shown in Fig. 2.

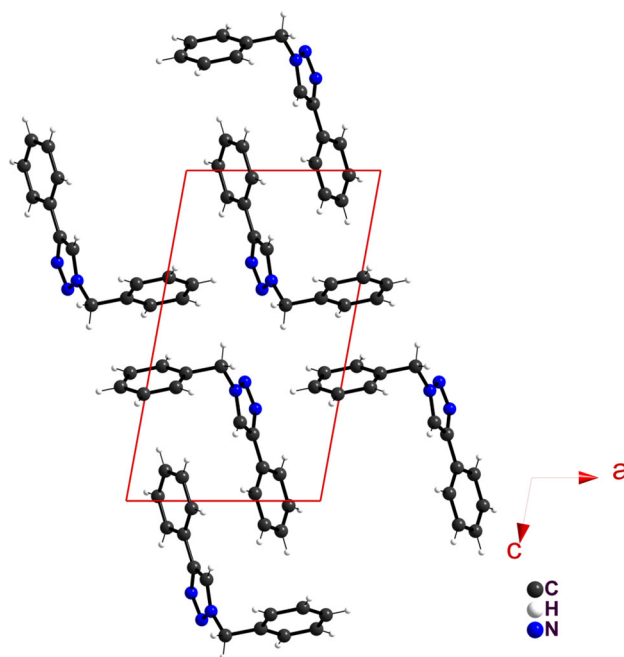


Fig. 2 The packing arrangement of molecules viewed down the *b*-axis

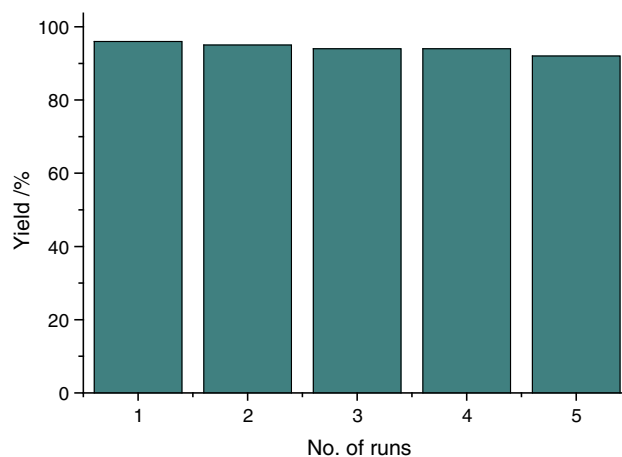


Fig. 3 Recyclability of the SiO₂–Cu₂O for CuACC reaction

Recyclability of SiO₂–Cu₂O for CuAAC-reaction

For heterogeneous catalyst, recyclability is an important factor which made the process cost effective and greener. A series of five consecutive runs were carried out in case of compound **3b**. It was found that there is almost no change in the activity of catalyst up to fifth use: yields were 96, 95, 94, 94, and 92 %, respectively (Fig. 3). The catalyst after fifth use showed the presence of Cu(II), as indicated by magnetic moment measurements.

Conclusion

In conclusion, we have presented a simple, efficient, and greener method for the synthesis of 1,4-disubstituted 1,2,3-triazoles via azide/alkyne-“click”-reaction or CuAAC-reaction using recyclable SiO₂-Cu₂O. This simple procedure afforded the products in good to excellent yields. The catalyst is selective and heterogeneous and therefore its practical use in this reaction makes the process more advantageous. Further, the reaction proceeds in the absence of any ligand and base. The use of water as a solvent in the reaction makes the process environment-friendly.

Experimental

Silica gel was purchased from ACROSS Organics and all other chemicals were purchased from Merck and Sigma Aldrich and were used without further purification. IR spectra of the catalyst and the synthesized compounds were recorded in the range of 4,000–300 cm⁻¹ on a Shimadzu Prestige-21 spectrophotometer. TGA of the catalyst was obtained on a Linesis Thermal Analyser. X-ray diffractograms were recorded in 2θ range of 10°–80° on a Panalyticals X'pert Pro X-ray diffraction spectrometer using CuKα radiation. XPS spectra of the catalyst were recorded on KRATOS ESCA model AXIS 165 (Resolution). SEM was recorded on JSM-6100 (JEOL) and TEM was recorded on Hitachi (H-7500) 120 kV with CCD camera. The atomic absorption spectrometric analysis (AAS) was done on Avanta-M atomic absorption spectrometer. ¹H NMR and ¹³C NMR of the compounds were obtained on Bruker Avance III (400 MHz) spectrometer. Mass spectra of the products were obtained on a Bruker Daltonics Esquire 3000 spectrometer.

General procedure for azide/alkyne-“click”-reaction or CuAAC-reaction using SiO₂-Cu₂O

In a round-bottom flask (25 cm³), a mixture of alkyne **1** (1.2 mmol), halide **2** (1 mmol), NaN₃ (1 mmol), and 0.2 g SiO₂-Cu₂O (5 mol% Cu) in 5 cm³ water was stirred at room temperature for an appropriate time. On completion (monitored by TLC), the reaction was cooled to room temperature and filtered. The residue was washed with water followed by EtOAc (3 × 10 cm³). The product was obtained after the removal of solvent under reduced pressure followed by crystallization from petroleum ether or EtOAc: petroleum ether or passing through column of silica and elution with EtOAc: petroleum ether.

Crystal structure determination and refinement

X-ray intensity data of 21,166 reflections (of which 2,427 unique) were collected on X'calibur CCD area-detector

Table 5 Crystal and experimental data

Crystal description	Block-shaped
Crystal colour	White
Crystal size/mm ³	0.3 × 0.2 × 0.2
Empirical formula	C ₁₅ H ₁₃ N ₃
Formula weight	235.28
Radiation, wavelength/Å	MoKα, 0.71073
Unit cell dimensions/Å/°	<i>a</i> = 7.9749(6), <i>b</i> = 5.7607 (4) <i>c</i> = 13.7668(9) <i>β</i> = 100.361(7)
Crystal system	Monoclinic
Space group	P21
Unit cell volume/Å ³	622.15(8)
No. of molecules per unit cell, <i>Z</i>	2
Temperature/ <i>K</i>	293(2)
Absorption coefficient/mm ⁻¹	0.077
<i>F</i> (000)	248
Scan mode	<i>ω</i> scan
<i>θ</i> range for entire data collection/°	3.60 < <i>θ</i> < 26.00
Range of indices	<i>h</i> = -9 to 9, <i>k</i> = -7 to 7, <i>l</i> = -16 to 16
Reflections collected/unique	21,166/2,427
Reflections observed (<i>I</i> > 2σ(<i>I</i>))	1,891
<i>R</i> _{int}	0.0639
<i>R</i> _{sigma}	0.0419
Structure determination	Direct methods
Refinement	Full-matrix least-squares on <i>F</i> ²
No. of parameters refined	163
Final <i>R</i>	0.0429
<i>wR</i> (<i>F</i> ²)	0.0843
Weight	1/[σ ² (<i>F</i> _o ²) + (0.0434 <i>P</i>) ² + 0.0000 <i>P</i>], where <i>P</i> = [<i>F</i> _o ² + 2 <i>F</i> _c ²]/3
Goodness-of-fit	1.025
(Δ/σ) _{max}	0.001 (for U22 N1)
Final residual electron density/Å ⁻³	-0.133 < Δρ < 0.099
Measurement	X'calibur system, Oxford diffraction, UK
Software for structure solution	SHELXS97 [28]
Software for refinement:	SHELXL97 [28]
Software for molecular plotting:	ORTEP-3 [24] PLATON [25]
Software for geometrical calculation	PLATON [25] PARST [26]

diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 × 0.20 × 0.20 mm. The

cell dimensions were determined by least-squares fit of angular settings of 8,109 reflections in the θ range 3.53° – 29.10° . The intensities were measured by ω scan mode for θ ranges 3.60° – 26.00° . 1,891 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarization, and absorption factors. The structure was solved by direct methods using SHELXS97 [28]. All non-hydrogen atoms of the molecule were located in the best E-map. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-hydrogen atoms with C–H = 0.93–0.97 Å. Full-matrix least-squares refinement was carried out using SHELXL97 [28]. The final refinement cycles converged to an $R = 0.0429$ and $wR(F^2) = 0.0843$ for the observed data. Residual electron densities ranged from -0.133 to $0.099 \text{ e}\text{\AA}^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 5.

CCDC-940362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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