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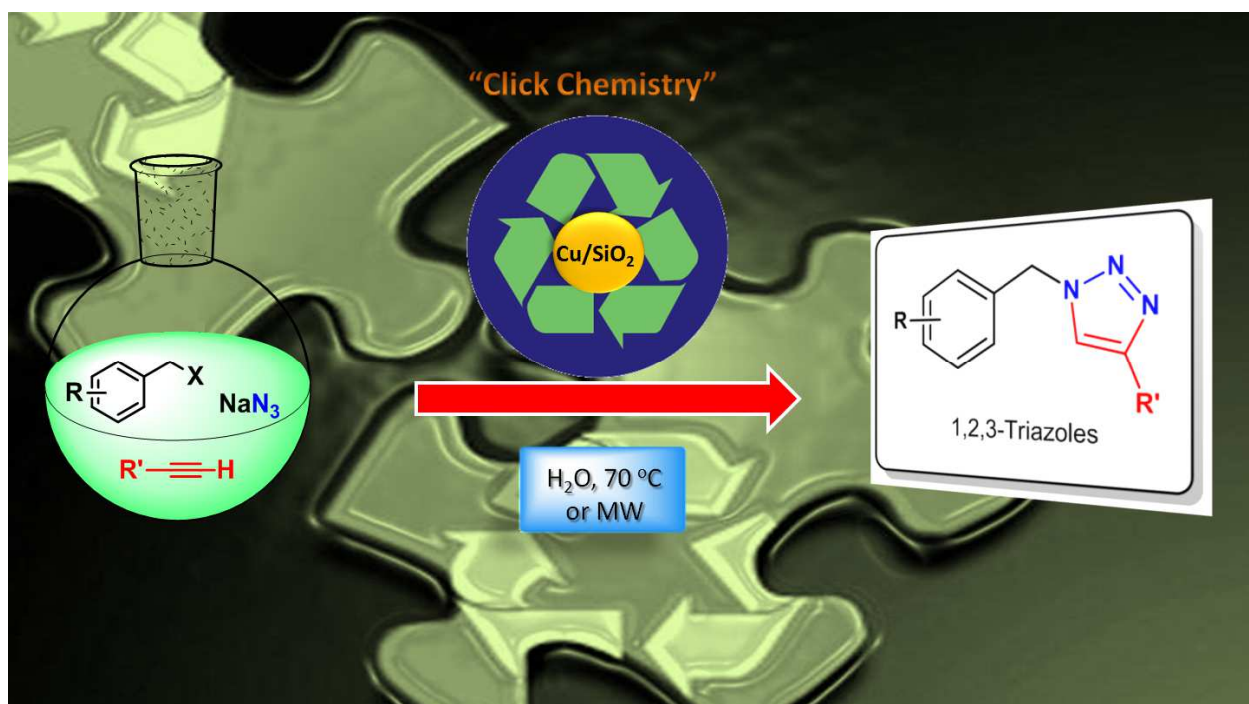
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Graphical Abstract

Recoverable Cu/SiO$_2$ Composite-Catalyzed the Click Synthesis of1,2,3-Triazoles in Water Media.

Cátia Schwartz Radatz,[a] Liliana do Amaral Soares,[a] Estéfano Fernando Vieira,[b] Diego Alves,[c] Dennis Russowsky[b,*] and Paulo Henrique Schneider[a,*]

ARTICLE TYPE

Recoverable Cu/SiO₂ Composite-Catalysed Click Synthesis of 1,2,3-Triazoles in Water Media

Cátia Schwartz Radatz,[a] Liliana do Amaral Soares,[a] Estéfano Roberto Vieira,[b] Diego Alves,[c] Dennis Russowsky, *[b] and Paulo Henrique Schneider *[a]

An eco-friendly multicomponent reaction for the synthesis of 1,2,3-triazoles using a recoverable and recyclable Cu/SiO₂ composite as the catalyst is reported. The reaction proceeds by mixing the benzyl halide, sodium azide, the alkyne and the catalyst in an aqueous medium to afford the desired products in ₁₀ excellent yields. The heterogeneous catalytic system showed highly efficiency, performing the multicomponent Huisgen reaction in a green approach based on recoverability, recyclability and avoidance of wastes. Microwave irradiation was also applied, substituting for conventional heating, resulting in excellent yields of the products with a dramatic reduction in the reaction time.

Introduction

₁₅ 1,2,3-Triazoles are typical nitrogen-containing heterocyclic molecules that have attracted increasing interest due to their wide range of applications. The 1,2,3-triazole unit is present in several classes of compounds that display different biological activities.[1-3] These molecules are commonly employed in many fields of ₂₀ chemistry such as drug discovery, including the development of new drugs as well as the modulation of their activities.[4-9] Within the industry, 1,2,3-triazoles have been applied to the development of new materials[10,11] or the design of new catalysts,[12,13] among other uses.[14,15]

₂₅ Different methods are available for the synthesis of 1,2,3-triazoles. The most attractive involves the thermal 1,3-dipolar cycloaddition of azides with alkynes, discovered by Huisgen[16] and popularized independently by Sharpless[17] and Meldal.[18] The process is based on a copper-catalysed reaction protocol, which ₃₀ proceeds with high regioselectivity. The development of the copper-catalysed azide-alkyne cycloaddition process (CuAAC) was a milestone in the synthesis of 1,2,3-triazoles, and represents the most illustrative example of "click-type reactions" within the concept of "Click Chemistry".[19-25]

₃₅ Organic azides are generally safe compounds; however, those of low molecular weight are unstable and difficult to handle.[26-28] Therefore, developing a methodology that avoids their isolation is desirable. In this context, Van der Eycken and co-workers developed an efficient method for a practical multicomponent ₄₀ reaction in which an organic azide was generated *in situ* from the corresponding bromides and sodium azide.[29] With regard to metal catalysis, a great number of studies have focused on the use of copper salts as catalytic systems for this purpose.[30-41] Most of these catalytic systems are involved in homogeneous catalysis ₄₅ processes, and sometimes the difficulty of separating the catalyst

as well as the requirement for reducing agents and stabilizing ligands pose difficult problems to circumvent. Thus, from an environmental point of view, the search for new efficient methods offering high yield, selectivity, mild conditions, recoverability ₅₀ and waste avoidance is highly desirable. In this regard, heterogeneous catalysis emerges as an important tool and has been frequently used as a green alternative for a broad range of chemical transformations. Additionally, it brings important advantages, especially those regarding removal of the catalyst ₅₅ from the reaction media, which can be done by simple filtration.

Although the main methodologies have been based on the active Cu[I] species,[42] few reports have been dedicated to the direct use of Cu[II] species in preparing the catalyst. Some classical examples use CuSO₄ as a precatalyst and sodium ascorbate as the ₆₀ reducing agent to generate the active Cu[I] species.[17] Alternatively, a Cu(OAc)₂/ascorbate system was also effective in catalysing the Huisgen Reaction.

Lipshutz and co-workers introduced an inexpensive Cu/Charcoal heterogeneous catalyst prepared from Cu(NO₃)₂ as ₆₅ the metal source.[43] In this case, formation of the CuO and Cu₂O species within a charcoal matrix was proposed. On the other hand, the *in situ* generation of the catalytically active Cu[I] species from Cu[II] was also proposed through an alkyne homocoupling reaction or *in situ* oxireduction reaction.[44,45,46]

₇₀ Regarding our continuous search for new reactions catalysed by Lewis acids,[47-51] we dedicated our efforts to developing a safe, easy to handle heterogeneous Lewis acid catalyst that could be easily separated from the crude reaction mixture and recycled in a given process. Previous studies showed that a Cu/SiO₂ composite, ₇₅ synthesized by the sol-gel method, was successfully employed to promote the multicomponent dihydropyrimidinone synthesis known as Biginelli's reaction.[52] More recently, a series of dihydropyridines were easily prepared in one step synthesis through catalysis by an analogous In/SiO₂ composite.[53] In this

report, we wish to disclose our results towards the development of a new eco-friendly multicomponent approach, in which 1,2,3-triazoles were synthesized in high yields and with high regioselectivities promoted by the heterogeneous Cu/SiO_2 composite catalyst. Thus, the reaction of benzyl halide **1**, sodium azide (**2**) and the terminal alkynes **3** was performed in water media to afford the respective 1,2,3-triazole **4** as depicted below in Scheme 1.
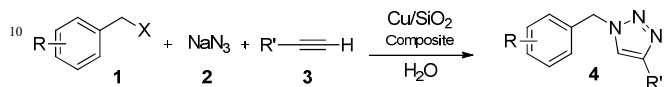
Scheme 1 General Synthesis of 1,2,3-triazoles.

Results and discussion

Preparation of the Catalyst

The heterogeneous Cu/SiO_2 Lewis acid catalyst was readily prepared through the sol-gel method, mixing the metal halide ($CuCl_2$ as the metal source) and tetraethyl orthosilicate (TEOS) under acidic catalysis. The TEOS was gelated in the presence of an aqueous ethanolic solution of $CuCl_2$ and a few drops of HCl at room temperature for approximately 5 days. The obtained green vitreous solid material was powdered and submitted to a thermal treatment at 180 °C for 24 h, and then successively washed with ethyl alcohol, water and diethyl ether. The washed powder material was dried in an oven at 100 °C for 24 h to afford a pale green powdered material. Electron Dispersive Spectroscopy (EDS) elemental analysis of the composite showed the average molar ratio of Cu/Si was 1:5.9 (Figure 1).The calculations indicated 2.59 mmol of Copper per gram of composite material.
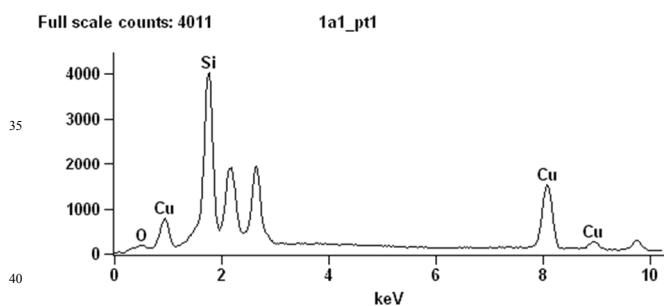

Figure 1. The EDS spectra of Cu/SiO_2 Composite

The specific surface area was determined using the BET method,[54] yielding a value of 120 ± 12 m^2g^{-1} for Cu/SiO_2. The average pore diameter distribution in this material was obtained from N_2 adsorption-desorption isotherms through the BJH method[55] and showed a distribution range from 4 nm to 13 nm, characterizing the composite material as a mesoporous material.

Optimization under Conventional Heating and Microwave Irradiation

After preparing the catalyst, we examined its ability to promote the formation of the organic azide *in situ*, and subsequent 1,3-dipolar cycloaddition with the alkyne in water as the solvent. We defined three parameters of analysis in order to optimize the reaction conditions. As can be seen in Table 1, the

influence of temperature, reaction time and catalyst loading were analysed. For the initial studies, we selected the reaction of benzyl halides **1a-b**, sodium azide **2** and phenyl acetylene **3a** as a model reaction to yield the 1,2,3-triazole **4a**.

Table 1. Optimization of the reaction conditions using Cu/SiO_2[a]

Entry	Temp. (°C)	Catalyst	mol%	Time (h)	Yield 4a (%)[b]
1	r.t.	Cu/SiO_2	20	12	72
2	70	Cu/SiO_2	20	12	93
3	70	Cu/SiO_2	20	6	95
4	70	Cu/SiO_2	10	6	81
5	70	Cu/SiO_2	10	12	93
6[c]	70	Cu/SiO_2	10	12	95
7	70	Cu/SiO_2	5	12	75
8	70	SiO_2	77 mg	12	-

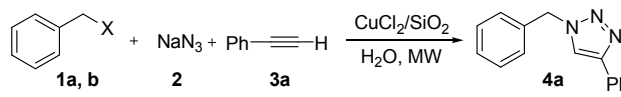[a] Reactions were performed using benzyl bromide **1a** (1.0 mmol), NaN_3 (**2**, 1.2 mmol), phenyl acetylene **3a** (1.0 mmol) Cu/SiO_2 in H_2O (2.0 mL). [b] Yields are determined by GC. [c] Reaction performed with benzyl chloride (**1b**).

In a first experiment, benzyl bromide **1a**, sodium azide **2**, phenyl acetylene **3a**, and Cu/SiO_2 (20 mol%, 77 mg of composite material) were mixed together in water, and after 12 hours at room temperature the corresponding triazole **4a** was obtained in 72% yield (Table 1, entry 1). It is worth noting that the reaction proceeded without an inert atmosphere and the triazole **4a** was obtained in high yield, in a single step in an aqueous medium. Next, we evaluate the influence of temperature and found that performing the reaction at 70 °C for 12 hours furnished the product with an increase in yield to 93% (Entry 2). By shortening the reaction time from 12 to 6 hours, no change in the yield was observed (Entry 3). However, a decrease in the yield was observed when the reaction was performed for 6 hours with 10 mol % of catalyst loading (Entry 4). This first set of experiments indicated that the yield depends on a close relationship between the three variables: time, catalyst loading and temperature. On the other hand, using 10 mol % of the catalyst and extending the reaction time to 12 hours lead to the formation of the product in excellent yields (Entry 5). In order to evaluate the reactivity with other benzyl halide sunders the same conditions as entry 5, we performed a reaction with benzyl chloride **1b** and, to our delight, triazole **4a** was obtained in 95% yield, showing the good reactivity of the catalyst independent of the halogen atom (Entry 6). An additional experiment performed with a decrease in the catalyst loading to 5 mol%, even for 12 hours, at 70 °C caused a decrease in the yield (Entry 7). We should note that the reaction does not proceed in presence of pure SiO_2, evidencing that the presence of the copper metal atom plays a crucial role as a

catalytic species. Additionally, triazole **4a** was completely formed in a selective manner, with no contamination of the 1,5-regioisomer. Although the Cu/SiO$_2$ (10 mol%) composite catalyst showed a good performance in 12 hours of reaction at 70 °C, we
5 decided to investigate another protocol to reduce the reaction times. For this purpose we carried out the reaction under microwave irradiation, a known alternative to a thermal energy source.[56-60] Substitution of traditional heating (oil bath, sand bath, heating jacket, water bath or hot air) by microwave irradiation is
10 a convenient method to accelerate organic reactions and thus reduce their reaction times.[61-63] The use of microwave irradiation has been applied successfully in organic synthesis and, in particular, in the synthesis of heterocyclic compounds, among others.[64-66]
15 In order to develop an efficient protocol for this multicomponent reaction under microwave irradiation, a mixture of benzyl bromide **1a**, NaN$_3$ **2**, phenyl acetylene **3a** and Cu/SiO$_2$ (20 mol%) in H$_2$O (2.0 mL) were irradiated with different powers, temperatures and times (Table 2).
20

Table 2. Optimization of the reaction conditions under microwave irradiation using CuCl$_2$/SiO$_2$.[a]

Entry	X	Power (W)	Temp. (°C)	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	Br	30	70	20	10	73
2	Br	50	70	20	10	92
3	Br	50	50	20	10	35
4	Br	50	90	20	10	89
5	Br	100	70	20	10	67
6	Br	50	70	10	10	95
7	Br	50	70	7	10	85
8	Br	50	70	5	10	30
9	Br	50	70	10	8	84
10	Br	50	70	10	7	83
11	Br	50	70	10	5	43
12	Br	50	70	10	3	n.d.
13	Cl	50	70	10	10	17
14	Cl	50	70	10	20	68
15	Cl	50	70	10	30	83

[a] Reactions were performed using benzyl halide **1a-b** (1.0 mmol), NaN$_3$ (**2**, 1.2 mmol), phenylacetylene **3a** (1.0 mmol), Cu/SiO$_2$ in H$_2$O (2.0 mL).
25 [b] Yields are determined by GC.

When performed at 70 °C for 10 minutes at 30 W of power, the reaction led to the formation of **4a** in 73% yield (Table 2, entry 1). Raising the power to 50 W produced an increase in the yield of product **4a** (Entry 2). Maintaining the power at 50 W and
30 changing the temperature to 50 °C (Entry 3) or 90°C (Entry 4), resulted in lower yields of **4a**. The use of higher power (100 W) did not lead to improvements in the yield (Entry 5). To our satisfaction, by reducing the amount of catalyst to 10 mol%, an excellent yield of 94% for product **4a** was observed (Entry 6). A
35 further decrease in the catalyst load to either 7 mol% or 5 mol% caused also a dramatic decrease in product yield (Entries 7 and 8, respectively). Decreases in the product yield were also observed in reactions performed for reduced reaction times of 8, 7, 5 or 3 minutes (Entries 9–12, respectively). In contrast to the previous
40 results, when benzyl chloride **1b** was employed poor yields were observed (Entries 13 and 14, respectively), and only after the reaction time was extended to 30 minutes were appreciable yields obtained (Entry 15).

After independent optimization of the reaction conditions
45 (conventional heating – Method A and microwave irradiation – Method B), we extended these conditions for a series of different benzyl halides (**1a-g**) and terminal alkynes (**3a-h**) to check the versatility of the protocols under Cu/SiO$_2$ catalysis. The results are summarized in Table 3.
50 In general, all reactions proceeded smoothly using both developed protocols, generating the products with good to excellent yields. At first, reactions were performed under conventional heating (Method A). Starting from benzyl bromide with variations in the terminal alkynes, we could observe that the
55 products were obtained in high yield with both aromatic and aliphatic ones (Table 3, entries 1, 5, 7 and 9, respectively). By using functionalized terminal alkynes, slight decreases in the reaction yields were obtained (Entries 11, 13, 15 and 17, respectively). The use of the less reactive benzyl chlorides as
60 starting materials did not cause significant changes in the reactivity and 1,2,3-triazoles were obtained in good yields, revealing the efficacy of the Cu/SiO$_2$ composite as a catalyst. Also, the reaction did not seem to be influenced by electronic or steric properties regarding the benzyl chloride, since no
65 significant changes in yields were observed (cf. entries 3, 19, 21, 23, 25 and 27, respectively).

Further studies of this multicomponent reaction carried out under microwave irradiation confirmed the efficiency of the developed protocol (Method B). The microwave heating was
70 performed with a single-mode cavity microwave in sealed heavy-walled Pyrex tubes. The generalizability of the method was extended by reacting several terminal alkynes **3a-h** with a variety of substituents, including aryl, alkyl, vinyl, alcohol and ester. All those alkynes were successfully employed in combination with
75 benzyl bromides **1a**, and benzyl chlorides **1b-g.** These reactions and the corresponding products were obtained in good yields (Entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 26, respectively).
80

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Table 3. Scope of 1,3-dipolar cycloaddition reaction using Cu/SiO$_2$.[a]
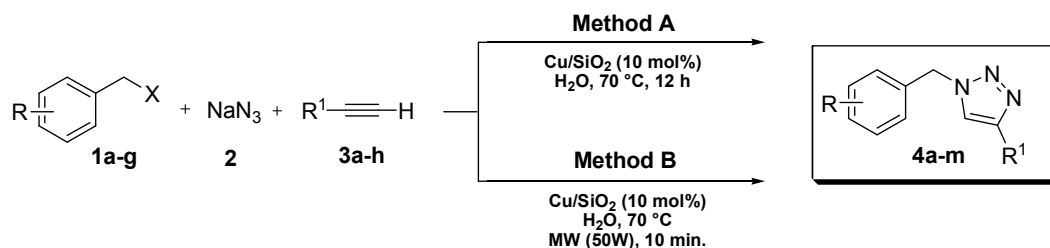
Entry	Method	Benzyl Halide 1			Alkyne 3		Product 4			Yield (%)[b]
			R	X		R^1		R	R^1	
1	A	1a	H	Br	3a	Ph	4a	H	Ph	93
2	B	1a	H	Br	3a	Ph	4a	H	Ph	92
3	A	1b	H	Cl	3a	Ph	4a	H	Ph	95
4[c]	B	1b	H	Cl	3a	Ph	4a	H	Ph	83
5	A	1a	H	Br	3b	nC$_4$H$_9$	4b	H	nC$_4$H$_9$	81
6	B	1a	H	Br	3b	nC$_4$H$_9$	4b	H	nC$_4$H$_9$	95
7	A	1a	H	Br	3c	nC$_8$H$_{17}$	4c	H	nC$_8$H$_{17}$	87
8	B	1a	H	Br	3c	nC$_8$H$_{17}$	4c	H	nC$_8$H$_{17}$	90
9	A	1a	H	Br	3d		4d	H		96
10	B	1a	H	Br	3d		4d	H		95
11	A	1a	H	Br	3e	HO(CH$_3$)$_2$C	4e	H	HO(CH$_3$)$_2$C-	70
12	B	1a	H	Br	3e	HO(CH$_3$)$_2$C	4e	H	HO(CH$_3$)$_2$C-	93
13	A	1a	H	Br	3f		4f	H		52
14	B	1a	H	Br	3f		4f	H		96
15	A	1a	H	Br	3g	HO(CH$_2$)$_2$-	4g	H	HO(CH$_2$)$_2$-	89
16	B	1a	H	Br	3g	HO(CH$_2$)$_2$-	4g	H	HO(CH$_2$)$_2$-	84
17	A	1a	H	Br	3h	EtO$_2$C-	4h	H	EtO$_2$C-	83
18	B	1a	H	Br	3h	EtO$_2$C-	4h	H	EtO$_2$C-	92
19	A	1c	4-Me	Cl	3a	Ph	4i	4-Me	Ph	95
20[c]	B	1c	4-Me	Cl	3a	Ph	4i	4-Me	Ph	79
21	A	1d	2-Me	Cl	3a	Ph	4j	2-Me	Ph	93
22[c]	B	1d	2-Me	Cl	3a	Ph	4j	2-Me	Ph	78
23	A	1e	4-Cl	Cl	3a	Ph	4k	4-Cl	Ph	92
24[c]	B	1e	4-Cl	Cl	3a	Ph	4k	4-Cl	Ph	75
25	A	1f	2-Cl	Cl	3a	Ph	4l	2-Cl	Ph	90
26[c]	B	1f	2-Cl	Cl	3a	Ph	4l	2-Cl	Ph	75
27	A	1g	3-CF$_3$	Cl	3a	Ph	4m	3-CF$_3$	Ph	86

[a] Reactions were performed using benzyl halide **1a-g** (1.0 mmol), NaN$_3$ (**2**, 1.2 mmol), terminal alkyne **3a-h** (1.0 mmol) and CuCl$_2$/SiO$_2$ (10 mol%) in H$_2$O (2.0 mL) under conditions previously determined for methods A or B. [b] Yields are given for isolated products. [c] Reactions were performed in 30 min.

The Reciclability of the Catalyst

An important feature of the use of supported catalysts is that they are readily recyclable, which makes their use an excellent alternative, especially considering economic and environmental aspects. Thus, as a further extension of this work, we verified the possibility of recycling the Cu/SiO$_2$ composite catalyst, using a model reaction performed under microwave heating comprised of benzyl bromide **1a**, NaN$_3$ **2** and phenyl acetylene **3a** as depicted in Figure 2.

As can be seen in Figure 2, the catalytic system can be recovered and reused in this multicomponent reaction at least four times without significant loss of activity in producing the 1,2,3 triazoles selectively. Moreover, TEM images of the recycled catalyst showed a homogeneous distribution of the Cu/SiO$_2$ composite similar to the initial one, and with the BET surface area exactly the same as that obtained from the fresh catalyst.
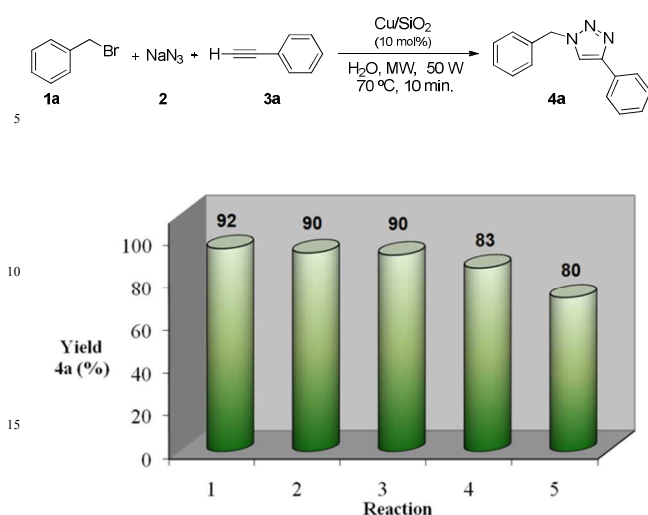
**Figure 2.** Recyclability of the Cu/SiO$_2$ catalytic system.

A Rationale for the Activity of the Catalyst and Mechanistic Pathways

Several sources of the active Cu^I catalyst in the alkyne-azide cycloaddition were noticed. On the other hand, copper (II) sulphate has also been successfully used as a catalytic precursor in the presence of sodium ascorbate to generate the catalytically active Cu^I species *in situ*.[67] Concerning these catalytic species some specific are important to mention. In a pioneering work, Lipshutz considered the preparation of a Cu/Carbon catalyst by mixing charcoal and Cu(NO$_3$)$_2$ and applied it in the Huisgen reaction in water with surprising efficiency.[43,68] The activity of this catalyst was attributed to both Cu$_2$O and CuO species being present within a charcoal matrix.[68] Therefore, the presence of Cu^I in the matrix suggested that an additional reducing agent might not be necessary. More recently, Alonso and co-workers reported an interesting study showing the catalytic ability of CuO and Cu$_2$O in the multicomponent click synthesis of 5-alkynyl 1,2,3-triazoles under ambient conditions.[69] The formation of copper species such as CuO and Cu$_2$O can be associated with the process of preparing the Cu/SiO$_2$ composites generated by the sol-gel method and subsequent thermal treatment.[70,71] Although these species are generally formed under high temperatures, we cannot discard their formation under the conditions of synthesis of Cu/SiO$_2$. No less important is the fact reported by Kantam that postulated a direct participation of Cu(II) in the synthesis of 1,2,3-triazoles using 20 mol % catalyst loading in aqueous solutions for 20 h.[46] We also need to consider the ability of Cu^{II} species to catalyse the oxidative homocoupling of terminal alkynes to afford diynes, known as the Glaser reaction.[72] An interesting study about supported Cu^{II}-Catalyzed Azide-Alkyne cycloaddition in water has also appeared in the literature recently.[73] In this work, Liu and Xia showed that Cu^{II} species dispersed in a silica matrix are able to be reduced to Cu^I species during an *in situ* terminal alkyne homocoupling process. Previous studies involving a Cu^{II} catalyst precursor in azide-alkyne cycloaddition reactions immobilized in TiO$_2$ or in a β–Kegg silicotungstate matrix were performed with excellent results.[74,75]

Based on this previous discussion, we envisaged a rationale for the possible mechanistic pathway for the Cu/SiO$_2$ catalysed three-component Huisgen reaction (Scheme 2). Different events can occur simultaneously:

1. Nucleophilic substitution on benzyl halides affording the respective benzyl azides;

2. The homocoupling of the terminal alkyne by Cu^{II} leading to the formation of a diyne and the active catalytic Cu^I species for the Huisgen reaction.

3. The generated active catalytic Cu^I species participates in the cycloaddition, likely proceeding via the reaction mechanism proposed initially by Sharpless.
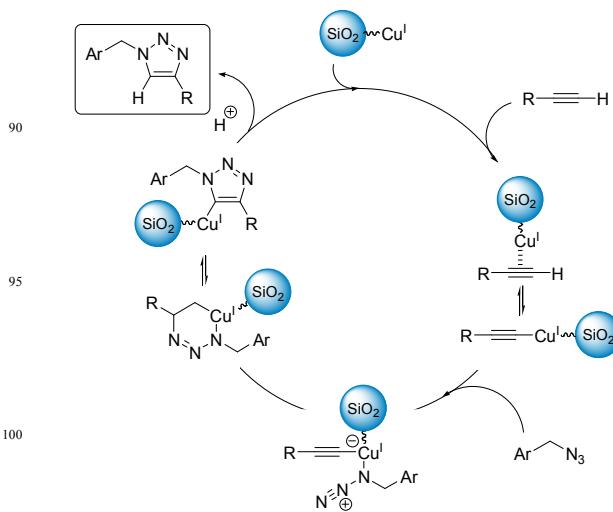
Event 1.
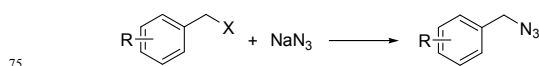
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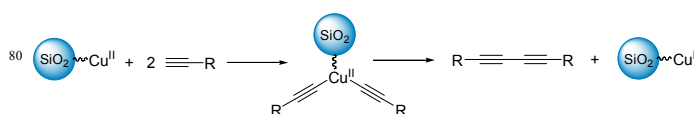
Event 3. The catalytic Cycle

Scheme 2. Mechanistic considerations.

Conclusion

In conclusion, we have successfully developed a clean, eco-friendly, inexpensive and high yield synthesis of 1,2,3-triazoles in an aqueous medium. The synthesis proceeded with full control of the regiochemistry through a multicomponent reaction between benzyl halides, sodium azide and a terminal alkyne catalysed by a Cu/SiO$_2$ composite. The catalyst proved to be efficient for different benzyl halides and terminal alkynes. It is noteworthy that that by using microwave irradiation in substitution of

conventional heating, the products were obtained in good yields with a dramatic reduction in the reaction times. The catalyst was readily prepared through the sol-gel method and shown to be easily recoverable from the reaction. Another important feature shown by the catalyst is that it can be reused at least four times without significant loss of activity.

Experimental section

General

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz or on a Bruker 400 MHz instruments. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). For thin layer chromatography (TLC), Whatman pre-coated TLC plates (Whatman 250 μm layer, UV254) were used, and compounds were visualized with a UV light at 254 nm. Chromatographic separations were performed on Merck (70-230 mesh) silica gel. Microwave reactions were conducted using a CEM Discover, mode operating systems working at 2.45 GHz, with a power programmable from 1 to 300 W.

Typical procedure for the preparation of Cu/SiO_2

In a cup of Becker, adapted with a magnetic stirrer, were placed 5 mL of ethanol, 2 mL of deionized H_2O and 3 drops of HCl conc. Next, 5.0 mmol of $CuCl_2$ was added in one portion. The mixture was vigorously stirred until total dissolution (ca. 15 min). To this clean homogeneous solution was added 20 mmol of TEOS in one time in a continuous flow. This new mixture remained under vigorous stirrer for additional 15 minutes. The magnetic stirrer bar was removed and the flask was covered with a clock glass and leaved in rest until the formation of a glass material (ca. 5 days). After, the glass material was triturated in a mortar and the green solid was submitted to the thermal treatment at 180 °C during 24 hours. After this time, the material was washed with 20 mL of ethanol followed of 20 mL of deionized H_2O. The material was submitted again to the thermal treatment at 100 °C for additional 24 hours.

Characterization of Metal/Silica Composite

The Cu/SiO_2 composite was analyzed through BET method, resulting in 120 ± 12 m^2g^{-1} for Cu/SiO_2 specific surface area. The BJH analysis showed a range of pore size distribution from 4 to 13 nm suggesting a mesopore material. The 1:5.9 ratio of Cu/Si was determined by the EDS analysis, resulting in nearly 2.59 mmols of $CuCl_2$ per gram of silica composite. The TEM images of the catalyst showed a homogeneous distribution of Cu/SiO_2 composite, which were similar to the analysis of the recovered material (see Supplementary Information). The BET surface area showed exactly the same value to that obtained from the fresh catalyst, evidencing the stability of the catalyst during the

reaction conditions it was submitted.

General procedure for the synthesis of 1,2,3-triazoles under conventional heating.

In a 25 mL round-bottom flask were added the appropriate benzyl halide (1.0 mmol), the alkyne (1.0 mmol) and NaN_3 (1.2 mmol). The heterogeneous catalyst Cu/SiO_2 (38 mg, 10 mol%) was added in a single portion and finally 2 mL of water were added. The reaction was carried out at 70 °C for 12 hours. The heterogeneous catalyst was recovered from the reaction media by a simple filtration. The product was extracted from water with ethyl acetate (2 x 5 mL), the organic layers were combined, dried over Na_2SO_4 and the solvent removed. A crude solid product was obtained which was later purified by column chromatography.

General procedure for the synthesis of 1,2,3-triazoles under microwave irradiation

In a Pyrex flask were added the appropriate halide (1.0 mmol), the alkyne (1.0 mmol) and NaN_3 (1.2 mmol). The heterogeneous catalyst Cu/SiO_2 (38 mg, 10 mol%) was added in a single portion and finally 2 mL of water were added. The reaction was carried out at 70 °C under microwave irradiation (50 W) for 10 minutes. The heterogeneous catalyst was recovered from the reaction media by a simple filtration. The product was extracted from water with ethyl acetate (2 x 5 mL), the organic layers were combined, dried over Na_2SO_4 and the solvent removed. A crude solid product was obtained which was later purified by column chromatography.

Spectroscopic data of 1,4-disubstituted 1,2,3-triazoles

1-benzyl-4-phenyl-1H-1,2,3-triazole (4a): Yield 93%; ^{1}H NMR ($CDCl_3$): δ = 5.55 (s, 2H); 7.28-7.42 (m, 8H); 7.66 (s, 1H); 7.79 (d, J = 7.3 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.7; 120.0; 126.1; 127.5; 128.4; 128.7; 129.1; 129.3; 129.5 ppm.

1-benzyl-4-butyl-1H-1,2,3-triazole (4b): Yield 76%; ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, J = 7.7 Hz, 3H); 1.30 (m, 2H); 1.59 (m, 2H); 2. 61 (m, 2H); 5.43 (s, 1H); 7.15-7.29 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7; 22.2; 25.3; 31.1; 54.4; 127.6; 127.9; 128.5; 128.9; 134.7 ppm.

1-benzyl-4-octyl-1H-1,2,3-triazole (4c): Yield 87%. ^{1}H NMR ($CDCl_3$) δ = 0.77 (t, J = 6.0 Hz, 3H); 1.26 (m, 6H); 1.54 (m, 2H); 2.59 (t, J = 7.7 Hz, 2H); 5.39 (s. 2H); 7.12-7.28 (m, 6H); ^{13}C NMR δ = 14.2; 22.4; 25.7; 28.9; 29.3; 31.5; 53.8; 120.4; 127.8; 128.4; 128.9; 135.0; 149.8 ppm.

1-benzyl-4-ciclohexenyl-1H-1,2,3-triazole (4d): Yield: 96%; ^{1}H NMR ($CDCl_3$): δ = 1.55-1.70 (m, 4H); 2.08 (d, J = 3.7 Hz, 2H) 2.26 (d, J = 2.1 Hz, 2H); 5.42 (s, 2H); 6.43 (m, 1H); 7.16-7.19 (m, 2H); 7.24-7.29 (m, 4H) ppm. ^{13}C NMR δ = 22.1; 22.3; 25.2; 26.3; 54.1; 118.3; 125.3; 127.0; 127.9; 128.6; 129.0; 134.8; 149.7 ppm.

2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-ol (4e): Yield 70%;

^{1}H NMR (CDCl$_3$): δ = 1.53 (s. 6H); 3.13 (s, 1H); 5.42 (s, 2H); 7.18-7.21 (m, 3H), 7.28-7.34 (m, 3H) ppm. ^{13}C NMR (CDCl$_3$): δ = 30.3; 54.2; 68.4; 119.2; 128.1; 128.7; 129.1; 134.4; 155.9 ppm.

1-(1-benzyl-1H-1,2,3-triazol-4-yl)cyclohexanol (4f): Yield 52%; ^{1}H NMR (CDCl$_3$): δ = 1.28 (m, 2H); 1.48-1.97 (m, 8H); 2.75 (s, 1H); 5.41 (s, 2H); 7.17-7.31 (m, 6H) ppm. ^{13}C NMR (CDCl$_3$): δ = 22.1; 25.6; 38.5; 54.6; 128.4; 129.0; 129.4; 134.8 ppm.

2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethanol (4g): Yield 89%; ^{1}H NMR (CDCl$_3$) δ = 2.90 (t, *J* = 5.9 Hz, 2H); 3.42 (s, 1H); 3.89 (m, 2H); 5.47 (s, 2H); 7.23-7.28 (m, 3H); 7.32-7.39 (m, 3H) ppm. ^{13}C NMR (CDCl$_3$) δ = 28.1; 52.9; 61.0; 126.9; 127.6; 127.8; 128.5; 128.9; 133.8 140.8 ppm.

1-ethyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate (4h): Yield 83%; ^{1}H NMR (CDCl$_3$) δ = 1.31 (t, *J* = 7.1 Hz, 3H); 4.32 (m, 2H); 5.50 (s, 2H); 7.19-7.29 (m, 5H); 7.90 (s, 1H)ppm. ^{13}C NMR (CDCl$_3$) δ = 14.3; 54.4; 61.3; 127.3; 128.0; 128.2; 129.1; 129.3; 133.4; 160.7 ppm.

1-(4-methylbenzyl)-4-phenyl-1H-1,2,3-triazole (4i): Yield 79%; ^{1}H NMR (CDCl$_3$) δ = 2.28 (s, 3H); 5.46 (s, 2H); 7.13 (s, 4H) 7.24 (d, *J* = 7.1 Hz, 1H) 7.31 (t, *J* = 7.3 Hz, 2H); 7.57 (s, 1H); 7.18 (d, *J* = 7.03 Hz, 2H) ppm. ^{13}C NMR (CDCl$_3$) δ = 21.2; 54.1; 119.4; 125.7; 128.1; 128.2; 129.8; 130.4; 131.5; 138.8; 148.0 ppm.

1-(2-methylbenzyl)-4-phenyl-1H-1,2,3-triazole (4j): Yield 78%; ^{1}H NMR (CDCl$_3$) δ = 2.22 (s, 3H); 5.9 (s, 2H); 7.12-7.24 (m, 5H); 7.31 (t, *J* = 7.3 Hz, 2H) 7.48 (s, 1H); 7.71 (d, *J* = 7.0 Hz, 2H) ppm. ^{13}C NMR (CDCl$_3$) δ = 19.3; 52.2; 119.7; 125.9; 127.0; 128.5; 129.1; 129.5; 129.7; 130.6; 131.3; 132.7; 137.3; 148.2 ppm.

1-(4-chlorobenzyl)-4-phenyl-1H-1,2,3-triazole (4k): Yield 75%; ^{1}H NMR (CDCl$_3$) δ = 5.45 (s, 2H); 7.15 (d, *J* = 7.7 Hz, 2H) 7.21-735 (m, 5H); 7.61 (s, 1H); 7.71 (d, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (CDCl$_3$) δ = 53.4; 119.5; 125.6; 128.3; 128.8; 129.2; 129.3; 130.2; 133.1; 134.8; 148.6 ppm.

1-(2-chlorobenzyl)-4-phenyl-1H-1,2,3-triazole (4l): Yield 72%; ^{1}H NMR (CDCl$_3$) δ = 5.62 (s, 2H); 7.11-7.37 (m, 7H); 7.70-7.75 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (CDCl$_3$) δ = 51.4; 119.9; 125.7; 127.6; 128.2; 128.8; 129.9; 130.2; 132.4; 133.4; 148.0 ppm.

4-phenyl-1-(3-(trifluoromethyl)benzyl)-1H-1,2,3-triazole (4m): Yield 69%; ^{1}H NMR (CDCl$_3$) δ = 5.56 (s, 2H); 7.18-7.47 (m, 5H); 7.54 (t, *J* = 7.6 Hz, 2H); 7.66 (s, 1H); 7.74 (d, *J* = 7.9 Hz, 2H) ppm. ^{13}C NMR (CDCl$_3$) δ = 53.6; 119.6; 124.7; 125.7; 128.4; 128.8; 129.8; 130.1; 131.3; 135.6; 148.4 ppm.

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Notes and references

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