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Copper nanoparticles in click chemistry: an alternative catalytic system for the cycloaddition of terminal alkynes and azides

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ABSTRACT

Readily prepared copper nanoparticles have been found to effectively catalyse the 1,3-dipolar cycloaddition of a variety of azides and alkynes furnishing the corresponding 1,2,3-triazoles in excellent yields. Both the preparation of the nanoparticles and the click reaction proceed in short reaction times.

Few reactions in organic chemistry have experienced the revival and great splendour achieved by the Huisgen 1,3-dipolar cycloaddition reaction of organic azides and alkynes[1] in the dawn of the 21st century. The enormous attention recently gained by this reaction began with the pivotal discovery by the groups of Meldal[2] and Sharpless,[3] in which copper(I) catalysis was found to dramatically accelerate the reaction under mild conditions at the same time that a high regioselectivity was achieved towards the 1,4-regioisomer of the triazole product.[4] This powerful, highly reliable and selective reaction is the paradigm of a click reaction, as it meets the set of stringent criteria required in click chemistry as defined by Sharpless et al.[5] Consequently, this protocol has found increasing application in a variety of disciplines[4b,6] such as organic chemistry,[4] drug discovery and medicinal chemistry,[7] polymer and materials science,[8] or bioconjugation.[7a,9]

In spite of the fact that some copper-free azide-alkyne cycloaddition strategies have been recently reported, the kinetics is rather low and the regioselectivity unpredictable.[10] Therefore, the copper(I)-catalysed process is still the preferred choice. The sources of copper(I) include: (a) copper(I) salts, normally in the presence of a base and/or a ligand, (b) in-situ reduction of copper(II) salts (e.g., copper sulfate with sodium ascorbate) and (c) comproportionation of copper(0) and copper(II), generally limited to special applications (e.g., biological systems).[4] The results obtained by any of these methods are, in general, excellent. There are, however, some issues that should be addressed in order to further improve the efficiency of the reaction and to fulfil the requirements of a truly click reaction. For instance, reactions performed in some of the common solvents used (e.g., water–alcohol solvent mixtures) can be problematic especially for insoluble reagents or too soluble products, thus reducing the application scope. Another aspect of consideration is the reaction time, which, in general, is relatively rather long if we take into account that many of the protocols need 12–24 h for completion. The addition of some copper complexes[11] or ligands[4,12] was found to enhance the reaction rate, but it was with the application of microwave chemistry (75–140 °C) that reaction times were dramatically reduced to less than 1 h.[4a,13] New and interesting advances in the title reaction involve heterogeneous catalysis.[14] Thus, copper(I) in charcoal showed to be an efficient heterogeneous catalyst for the title reaction in the presence of triethylamine in dioxane at 60 °C, the reaction times being reduced to only 10–120 min.[14a] Copper(I) in zeolite USY was recently found to catalyse the cycloaddition reaction with a wide substrate scope under ligand-free conditions in toluene (15 h, rt).[14b]

Since the discovery that copper metal (turnings or powder in stoichiometric quantity) can be a source of the catalytic species,[15] an increasing attention has been devoted to the application of copper nanoparticles (CuNPs) as substitutes of bulk copper metal in order to reduce both the catalyst loading and the reaction times.[16] Although the use of CuNPs has shown a general beneficial effect in the cycloaddition of alkynes and azides, some arguments can curtail the application, competitiveness and general acceptance of

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some of these methods, namely: (a) rather tedious CuNPs preparation due to the multiple steps, long time, high temperatures or use of non-commercially available reagents; (b) presence of stabilising agents or solid supports to prevent nanoparticle agglomeration during the cycloaddition reaction; (c) presence of an additive to create an acidic medium that induces copper dissolution; (d) limited substrate scope or (e) insufficient high yields that require chromatographic purification. Although the reaction times have been considerably reduced in some cases, they are still relatively long (2–18 h).[16a–d,f] It is noteworthy that the PVP-stabilised CuNPs reached high product yields for benzyl and aryl azides in very short reaction times (15–50 min) using formamide as the solvent at room temperature.[16e]

On the other hand, and due to our ongoing interest on active metals,[17a] we reported that active copper, generated from copper(II) chloride dihydrate, lithium metal and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) in THF, was successfully applied to the reduction of carbonyl compounds and imines,[17b] sulfonates,[17c] and to the hydrodehalogenation of organic halides, all at room temperature.[17d] We have recently discovered that, under the above conditions or in the case of using anhydrous copper(II) chloride, copper nanoparticles are formed. We wish to present herein a catalytic system composed of readily generated copper nanoparticles in THF which, in the presence of triethylamine at 65 °C, allows the fast and high yielding 1,3-dipolar cycloaddition of terminal alkynes and azides.

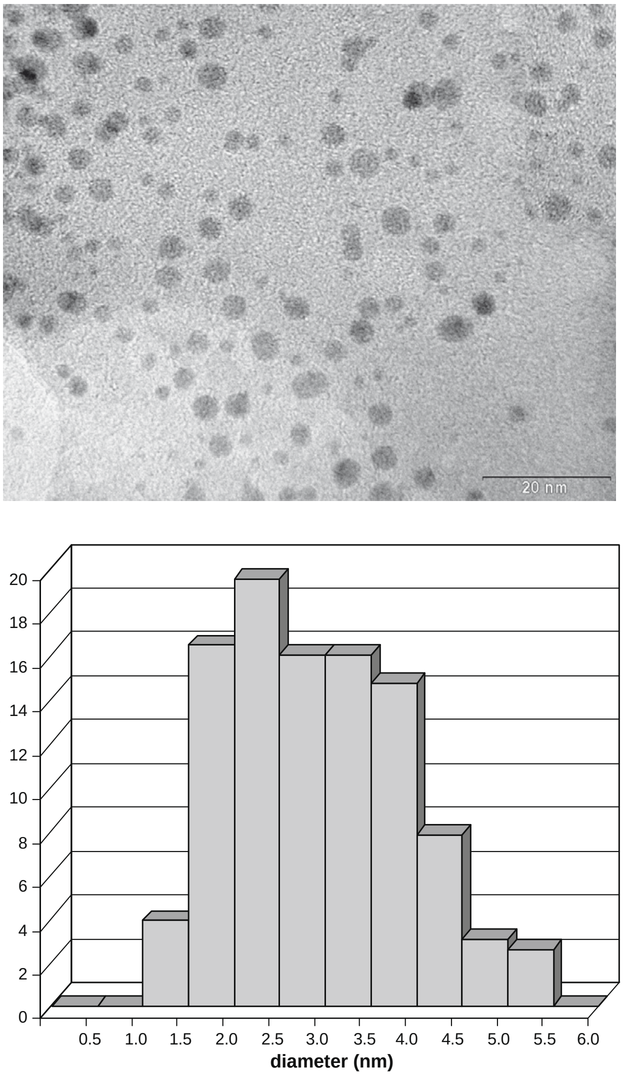
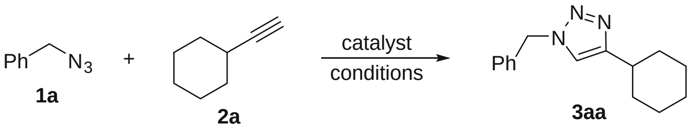


Figure 1. TEM micrograph and size distribution of the CuNPs. The sizes were determined for 230 nanoparticles selected at random.

The CuNPs suspension was instantaneously generated by mixing copper(II) chloride, lithium metal and a catalytic amount of DTBB (10 mol %) in THF at room temperature.[18] The CuNPs were characterised by transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS) and X-ray powder diffraction (XRD). Droplets of this suspension analysed by TEM showed well-defined spherical nanoparticles with a particle size distribution of ca. 3.0 ± 1.5 nm (Fig. 1). Energy-dispersive X-ray (EDX) analysis on various regions confirmed the presence of copper, with energy bands of 8.04, 8.90 keV (K lines) and 0.92 keV (L line) (Supplementary data). The XPS spectrum showed a single Cu $2p_{3/2}$ peak at 932.9 eV, which despite the close proximity of the binding energies for the Cu(0), Cu(I) and Cu(II) states, it was clearly different from that obtained for a sample exposed to air during prolonged time (Supplementary data). The XRD spectrum and selected area electron diffraction (SAED) pattern were in agreement with the presence primarily of metallic copper (Supplementary data), albeit the formation of copper oxides (especially Cu_2O) on the surface during the sample handling cannot be ruled out.

Benzyl azide (**1a**) and cyclohexylacetylene (**2a**) were used as model substrates in order to optimise the reaction conditions (Table 1). Two blank experiments carried out in the absence of Cu but under the conditions of generation of the CuNPs (with or without Et_3N) led to the starting **1a** and **2a**. The presence of Et_3N was shown to be indispensable for the reaction to take place (Table 1, entry 1). The CuNPs in stoichiometric amounts were shown to be

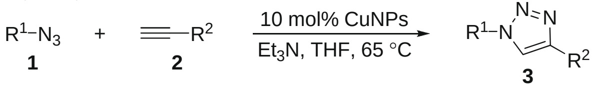
Table 1
Copper-catalysed 1,3-dipolar cycloaddition of benzyl azide and cyclohexylacetylene[a]

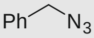
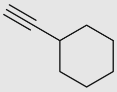
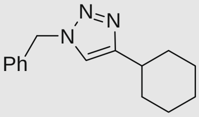
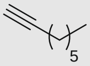
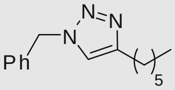
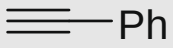
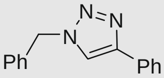
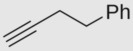
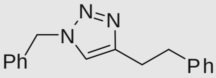
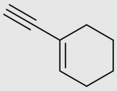
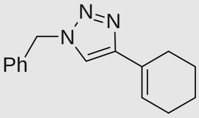
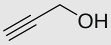
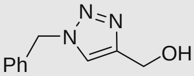
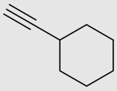
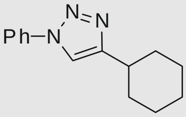
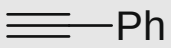
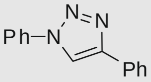
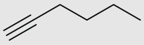
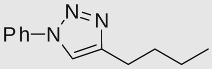
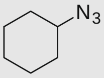
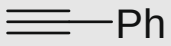
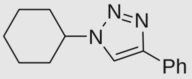
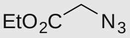
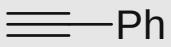
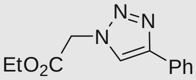
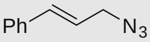
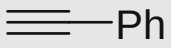
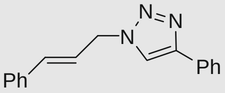


Entry	Catalyst (mol %)	Additive (mmol)	*T* (°C)	Time (h)	Yield[b] (%)
1	CuNPs (100)	none	25	12	0
2	CuNPs (100)	Et_3N (1)	25	1	98
3	Cu (100)[c]	Et_3N (1)	25	2	0
4	CuO (100)	Et_3N (1)	25	2	0
5	Cu_2O (100)	Et_3N (1)	25	2	0
6	$CuCl_2$ (100)	Et_3N (1)	25	2	0
7	CuCl (100)	Et_3N (1)	25	3	85[d]
8	CuNPs (100)	PVP/Et_3N (1)[e]	25	3	58
9	CuNPs (20)	Et_3N (1)	25	6	98
10	CuNPs (10)	Et_3N (1)	25	6	98
11	CuNPs (5)	Et_3N (1)	25	24	98
12	CuNPs (2)	Et_3N (1)	25	24	100
13	CuNPs (1)	Et_3N (1)	25	24	100
14	CuNPs (10)	Et_3N (3)	25	0.5	99
15	CuNPs (10)	Et_3N (2)	25	0.5	99
16	CuNPs (10)	Et_3N (1)	65	0.5	100
17	CuCl (10)	Et_3N (1)	25	24	70
18	CuCl (10)	Et_3N (1)	65	24	80
19	CuNPs (10)	Et_3N (1)[f]	65	24	75
20	CuNPs (10)	Et_3N (1)[g]	65	24	71

[a] **1a** (1 mmol) and **2a** (1 mmol) in THF.
[b] GLC yield.
[c] Cu powder (1–5 μm).
[d] Multiple side products were detected.
[e] 1 g PVP [poly(1-vinylpyrrolidin-2-one), MW ~ 29000].
[f] Reaction in *t*-BuOH/H_2O 1:2.
[g] Reaction under air.

Table 2
1,3-Dipolar cycloaddition of azides and alkynes catalysed by CuNPs[a]



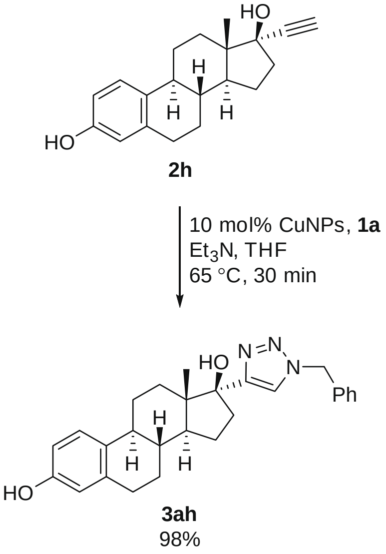
Entry	Azide	Alkyne		Time (min)	Triazole		Yield[b] (%)
1	 **1a**		**2a**	30		**3aa**	95[c]
2	**1a**		**2b**	10		**3ab**	98
3	**1a**		**2c**	10		**3ac**	98[c]
4	**1a**		**2d**	10		**3ad**	90[d]
5	**1a**		**2e**	30		**3ae**	97[c]
6	**1a**		**2f**	30		**3af**	97[c]
7	Ph–N_3 **1b**		**2a**	30		**3ba**	94
8	**1b**		**2c**	10		**3bc**	98
9	**1b**		**2g**	10		**3bg**	98
10	 **1c**		**2c**	30		**3cc**	87
11	 **1d**		**2c**	30		**3dc**	88[d]
12	 **1e**		**2c**	10		**3ec**	97

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), CuNPs (10 mol %), Et_3N (1 mmol) in THF at 65 °C.
[b] Isolated yield after crystallisation from Et_2O.
[c] Isolated yield after filtration and solvent evaporation.
[d] Isolated yield after column chromatography.

superior to other sources of copper, leading to **3aa** in the highest yield and shortest reaction time (Table 1, entries 2–8). The product yields were also excellent by decreasing the amount of CuNPs up to 1 mol %, albeit longer reaction times were required (Table 1, entries 9–13). It is noteworthy that the addition of >1 equiv Et_3N shortened the reaction time to only 30 min at 25 °C maintaining an excellent yield (Table 1, entries 14 and 15). This reduction in time, however, was not generally observed for some other substrates tested at 25 °C but it was at 65 °C, in the case of **1a** and **2a** with the same result (Table 1, entry 16). CuCl, under the above conditions, or CuNPs in the solvent mixture *t*-BuOH/H_2O 1:2 or under air, led to lower product yields and much longer reaction times (Table 1, entries 17–20). Therefore, the reaction conditions in entry 16 were considered the most appropriate in order to have a method of more general application maintaining the short reaction time.

The optimised reaction conditions were successfully applied to a variety of terminal alkynes and azides (Table 2).[19] Benzyl azide, phenyl azide, cyclohexyl azide, ethyl 2-azidoacetate and cinnamyl azide were combined with several terminal alkynes bearing alkyl, cycloalkyl, phenyl, alkenyl or hydroxyalkyl substituents. All reactions were highly regioselective towards the 1,4-disubstituted triazoles and were completed in 10–30 min. Furthermore, the corresponding 1,2,3-triazoles were obtained in excellent isolated yields, generally, after simple work-up involving filtration and crystallisation or solvent evaporation. We checked some of the 10-min reactions and observed that they really proceeded almost instantaneously (during the first minute), though a standard time of 10 min has been given. It is worthwhile mentioning that, under the reaction conditions, cinnamyl azide did not undergo a [3,3]-sigmatropic rearrangement leading to the secondary allylic azide,[20] since compound **3ec** was the only detected product (Table 2, entry 12). Moreover, this methodology exhibited the same efficiency for more complex substrates such as 17-ethynyloestradiol (**2h**), which by reaction with benzyl azide, under the standard conditions, furnished the corresponding triazole-substituted steroid derivative in practically quantitative yield after 30 min (Scheme 1).

Unfortunately, the CuNPs could not be reused due to the homogeneous nature of the resulting mixture (colourless solution) at the end of the reaction. The reaction mechanism in the alkyne-azide cycloaddition catalysed by copper nanoparticles is not well understood.[16] The formation of copper(I) acetylide is generally invoked (but not demonstrated) by dissolution of Cu(0) to Cu(I) or by reaction with Cu(I) on the nanoparticle surface. We have carried out a series of experiments that demonstrate that dissolution of CuNPs did not occur in the absence of Et_3N and that Et_3N itself have no capability of dissolution over the CuNPs. In the presence of Et_3N and phenylacetylene but in the absence of an azide, however, the CuNPs suspension was transformed into a yellow precipitate and a colourless supernatant. This yellow precipitate could be attributed to Cu(I) phenylacetylide,[22] which proves that the corresponding copper(I) acetylides are the real intermediate species in the reactions reported herein.



Scheme 1. 1,3-Dipolar cycloaddition of 17-ethynyloestradiol and **1a**.

In conclusion, we have introduced a catalytic system, based on CuNPs, that effectively catalyses the 1,3-dipolar cycloaddition of azides and terminal alkynes. The CuNPs are quickly prepared from commercially available reagents under mild conditions in the absence of any stabilising additive or support. We believe that the herein described methodology fulfils the requirements of a truly click reaction, namely: a) wide in scope, b) simple reaction conditions, c) readily available starting materials and reagents, d) easily removed solvent and e) simple removal of by-products and product isolation. In view of the results presented above, we also believe that this is one of the fastest procedures ever reported for the title reaction, comparable to some microwave-based methodologies, but involving milder conditions (65 vs 75–140 °C) and without the inherent limitations of microwave chemistry (e.g., generally restricted to small-scale reactions). Further research to extend the substrate scope and on the reaction mechanism is underway and will be reported in due course.

Acknowledgements

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Supplementary data

Experimental procedures as well as the characterisation of the copper nanoparticles (TEM, XPS, XRD) and new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.220.

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18. *Typical procedure for the preparation of CuNPs*: Anhydrous copper(II) chloride (135 mg, 1 mmol) was added over a suspension of lithium (14 mg, 2 mmol) and DTBB (27 mg, 0.1 mmol) in THF (2 mL) at room temperature under argon. The reaction mixture, which was initially dark blue, changed to black indicating that the CuNPs suspension was formed. This suspension was then diluted with more THF (8 mL).
19. *General procedure for the CuNPs-catalysed 1,3-dipolar cycloaddition of azides and alkynes*: Et_3N (1 equiv), azide (1 equiv) and alkyne (1 equiv) were added over 10 mol % of the CuNPs suspension in THF under argon. The reaction mixture was warmed up to 65 °C and monitored by TLC until total conversion of the starting materials. The resulting solution was passed through a pad of Celite or alternatively subjected to aqueous work-up and extraction with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo to give the corresponding triazole which was pure enough or was purified by crystallisation (Et_2O) or column chromatography (hexane/EtOAc) (see footnotes in Table 2). Triazoles **3ab**,[21a] **3ac**,[21a] **3ae**,[16f] **3af**,[21a] **3bc**,[21a] **3bg**,[21b] **3dc**,[21c] and **3ec**,[21c] were characterised by comparison of their physical and spectroscopic data with those described in the literature.*1-Benzyl-4-cyclohexyl-1*H*-1,2,3-triazole* (**3aa**): white solid; mp 110.2–112.0 °C; IR (KBr) 3118, 2918, 2844, 1539, 1495, 1452, 1050, 755, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.41 (m, 5H), 7.16 (s, 1H), 5.48 (s, 2H), 2.67–2.80 (m, 1H), 1.15–2.10 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 134.9, 129.0, 128.5, 127.8, 119.1, 53.9, 35.3, 32.9, 26.1, 25.9; HRMS (EI) calcd for $C_{15}H_{19}N_3$ 241.1579, found 241.1577.
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