Click Chemistry: Copper Clusters Catalyse the Cycloaddition of Azides with Terminal Alkynes

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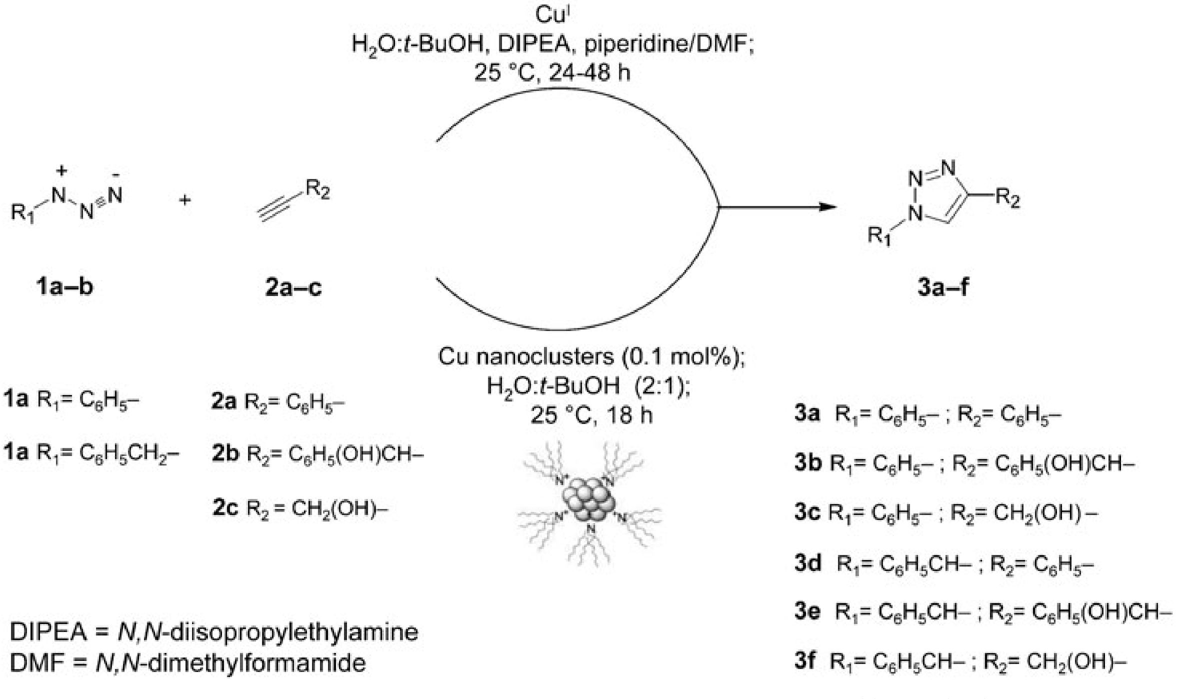
Abstract: Air-stable copper nanoclusters are good catalysts in the Cu(I)-catalysed “click” cycloaddition of azides with terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles. No additional base or reducing agent is required. The reaction kinetics using various copper catalyst types and the function of copper particles in this system are studied and discussed.

Keywords: azides; cycloaddition; kinetics; mechanism; nanoclusters; triple bonds

Introduction

‘Click chemistry’, a term recently coined by Sharpless and co-workers,[1] denotes a growing family of powerful chemical reactions that are based on ‘spring–loaded’ energy-intensive substrates that can, under the right conditions, unload their energy to form stable products in high selectivity. Ever since their debut in 2001, click reactions are finding more and more applications in organic synthesis and drug discovery.[2] Perhaps the most remarkable example is the copper-catalysed version of the Huisgen 1,3-dipolar cycloaddition of azides to terminal alkynes (Scheme 1, top).[3,4] This reaction tolerates a variety of functional groups, is insensitive to water and oxygen, and gives easy access to regiospecific 1,4-disubstituted 1,2,3-triazoles. The 100% atom economy and simple product isolation make this reaction useful in various applications ranging from bio-orthogonal bioconju-



Scheme 1. Huisgen-type 1,3-cycloaddition of azides to terminal alkynes catalyzed by Cu(I) ions (*top*) and by Cu nanoclusters (*bottom*).

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gation,[5–8] polymer[9,10] and dendrimer[11] syntheses to the construction of peptide bond surrogates[12] and powerful pharmacophores. The reaction is catalysed by Cu(I) species that are either added directly as cuprous salts (with or without ligands[13]), or generated by the reduction of Cu(II) salts, or by the *in situ* oxidation of copper metal turnings to give Cu(I) species. The last option is particularly attractive, as copper metal is inexpensive, and there is no need for a reducing agent as in the case of Cu(II). However, reactions are relatively slow and require a significant amount of catalyst. These drawbacks are increasingly important when large-scale production is considered.

The fact that both Cu(0) and Cu(II) can be used as catalyst precursors, plus the ubiquitous presence of Cu(I)-alkyne intermediates in similar chemical systems,[14] such as the Glaser homocoupling and the Stephens–Castro[15] and Sonogashira[16,17] reactions, led us to think that copper nanoclusters could be efficient catalysts for Huisgen-type cycloadditions. Our previous studies showed that Cu clusters are particularly suited to Suzuki,[18,19] and Sonogashira[20] cross-coupling reactions. In this paper, we show the use of nanometric copper clusters as efficient ligand-free catalysts for 1,3-dipolar cycloaddition reactions between azides and terminal alkynes.[21–25] These clusters are active and stable, and comply with the requirements of 'click chemistry'. We demonstrate the application of the system to a variety of substrates, compare the reaction rates using different types of copper catalysts, and examine whether copper atoms and/or ions are leaching into the solution or not.

Results and Discussion

The copper nanoclusters were prepared by reducing cuprous chloride in solution with tetraoctylammonium formate (TOAF). This method gives a stable suspension that can be kept for months, with a narrow cluster size distribution and is very easy to handle.[18]

In a typical cluster-catalysed cycloaddition reaction (Scheme 1, bottom), one equivalent of azide **1** was mixed at 25 °C and pressure with two equivalents of alkyne **2** and 0.001 equivalents of copper clusters, in 50 mL of 2:1 water:*t*-butyl alcohol. Good conversions and yields were observed for a variety of azide/alkyne combinations (Table 1). The 1,4-disubstituted 1,2,3-triazoles **3a**–**f** were easily isolated by filtration, followed by recrystallisation, and identified by their melting points and ^{1}H NMR spectra.

Aliphatic alkynes gave higher yields than aromatic ones (typically 85–100% *vs.* ~80%, respectively). The presence of an electron-withdrawing hydroxy group increased the product yield. The phenyl group in the 1-phenylprop-2-yn-1-ol (entries 2 and 5) was found to slightly impede the reaction, probably because of steric effects, i.e., interfering with the formation of the terminal alkyne-Cu(I) species. This effect was observed for both aromatic and aliphatic azides.[2]

Sharpless and co-workers recently reported that the Cu(I)-catalysed synthesis of 1,2,3-triazoles from azides and terminal alkynes could also be catalysed by Cu(0) turnings,[3] as well as by $CuSO_4$/sodium ascorbate.[6,7] In both cases it was suggested that the Cu(0) and Cu(II) precursors are oxidised or reduced to give the active Cu(I) catalytic species. Such switching between the Cu(0)/Cu(I)/Cu(II) oxidation states was also observed by one of us in the catalytic oxidation of allylic olefins with *t*-butyl hydroperoxide (TBHP), which could also be catalysed by copper clusters as catalyst precursors.[26] The interesting point about the azide-alkyne cycloadditions, however, is that copper clusters may play a special role here, rather than just serving as 'reservoirs' for Cu(I) ions. This is analogous to our findings on Sonogashira cross-coupling, where copper clusters exhibited very different catalytic properties compared to Cu(I) salts.[20]

To gain further insight into the role of the copper clusters in azide-alkyne cycloadditions we monitored the kinetics of the model reaction between benzyl azide (**1b**) and prop-2-yn-1-ol (**2c**). We compared profiles for four cases, catalysed by copper shavings, copper powder, copper nanoclusters, and $CuSO_4$/ascorbate, respectively (Figure 1). All other reaction conditions were kept constant and blank experiments were performed to exclude systemic effects.

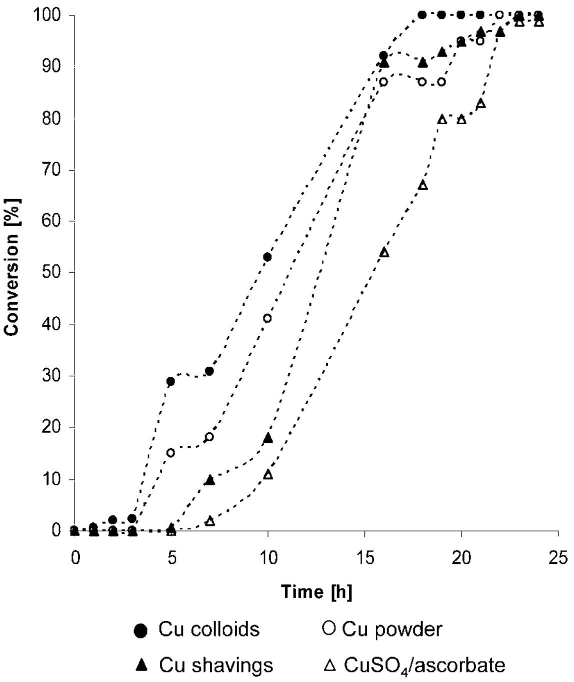
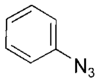
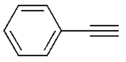
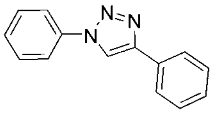
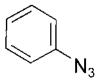
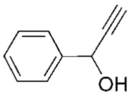
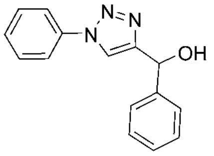
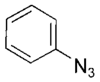
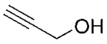
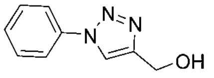
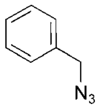
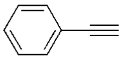
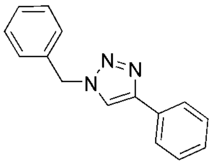
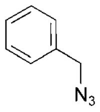
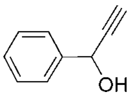
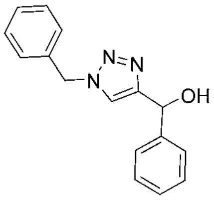
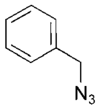
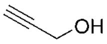
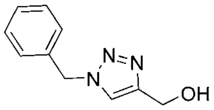


Figure 1. Time-resolved reaction profiles observed for the 1,3-cycloaddition of prop-2-yn-1-ol to benzyl azide using various copper catalytic systems. Reaction conditions are as in Table 1. All reactions were performed in duplicate (with error of ±2.3%).

Table 1. Huisgen-type cycloadditions catalysed by copper nanoclusters.[a]

Entry	Azide		Alkyne		Product		Yield [%][b]
1		**1a**		**2a**		**3a**	80
2		**1a**		**2b**		**3b**	85
3		**1a**		**2c**		**3c**	> 99[c]
4		**1b**		**2a**		**3d**	82
5		**1b**		**2b**		**3e**	97
6		**1b**		**2c**		**3f**	> 99[c]

[a] Reaction conditions: 10 mmol azide, 20 mmol alkyne, 0.1 mmol Cu nanoclusters, 50 mL H_2O/*t*-BuOH (2 : 1), 25 °C; 18 h.
[b] Yields of isolated products, reported in mol % based on azide starting material.
[c] Yields calculated based on GC values, corrected for the presence of an internal standard.

Several interesting things can be observed in Figure 1. Perhaps the most significant are the differences between the reaction rates of the various catalyst types. This indicates that the role of Cu particles in the Huisgen 1,3-dipolar cycloadditions is similar to that in the Sonogashira cross-coupling. If the Cu particles were mere 'reservoirs' for Cu(I) and/or Cu(II) ions, one would expect similar reaction profiles regardless of the copper source {*cf.* the oxidative Cu/TBHP system where the kinetic profiles for Cu(0) clusters, Cu(I) salts and Cu(II) salts are indistinguishable[26]}.

Copper nanoclusters displayed the highest activity of the four systems tested, affording 100% conversion after 18 h. The activity trend is Cu(0) clusters > Cu(0) powder > Cu(0) shavings > Cu(II) /ascorbate. This is in good agreement with the catalyst surface area [in the case of Cu(0)]. The specific surface area of the clusters and the powder was 168 m^2/g and 0.15 m^2/g, respectively.

One key scientific question is whether the Cu(0) clusters and powder are leaching copper atoms into the solution or not. Indeed, this question stands at the heart of many an argument in heterogeneous catalysis.[27] To try to answer this question, we performed a separate set of reactions to give **3f** catalysed by Cu(0) powder. As before, reactions were monitored by GC. This time, however, we filtered the powder out of the reaction vessel after 7 h, continued to stir, and added the powder back after 20 h. Figure 2 shows the resulting kinetic profile ('●' symbols), together with a control reaction with no filtration (broken curve).

The clear difference between the reaction curves in Figure 2 supports our hypothesis that the reaction occurs on the surface of the copper particles, rather than *via* Cu(0) atoms or Cu(I)/Cu(II) ions that are leached into the reaction mixture. Furthermore, all four profiles in Figure 1 exhibit an induction period, from 1 h in the case of Cu clusters, and up to 5 h in the case of Cu(II)/ascorbate. For the Cu(0) catalysts, the duration of the induction period corresponds to the catalysts' surface area. This fact is also in agreement with a reaction that

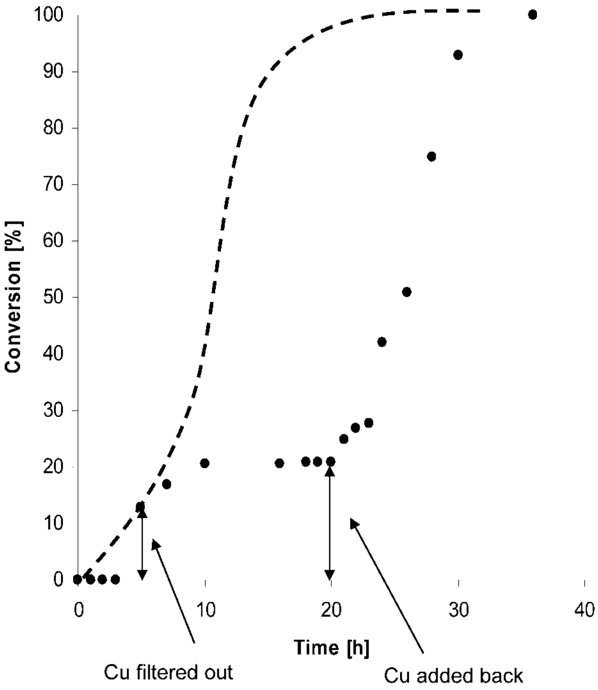


Figure 2. Time-resolved reaction profile observed for the 1,3-cycloaddition of prop-2-yn-1-ol and benzyl azide using Copper powder as catalyst. Reaction conditions are as in Table 1. '●' symbols represent the kinetic profile of the experiment filtering and adding back Cu powder. The broken line shows a control experiment without filtering of the copper catalyst.

occurs at the catalyst surface. The reaction is probably mediated *via* a Cu(I) ion on the surface, similar to the mechanism of the Sonogashira coupling.[20]

Notwithstanding this evidence, two more points should be considered: First, it may be that after the copper powder is filtered off, some Cu(I) and/or Cu(II) may still remain in solution, but as there is no more reducing agent, it will rapidly convert all Cu(II) (in Figure 2 we see that after 7 h, when the copper powder is filtered off, the reaction slows down considerably, but does not stop). Second, recent studies on the mechanism of the homogeneously-catalysed reaction show that Cu(I) acetylide is almost certainly an intermediate in the catalytic cycle.[28] If this is the case, it means that Cu(0) by itself cannot catalyze the reaction – one way or another, Cu(I) has to form.[29]

Conclusion

In conclusion, we show here that Cu nanoclusters are efficient catalysts for 1,3-cycloadditions of azides to terminal alkynes. Reaction conditions are improved in comparison with previous catalytic systems. There is evidence that the catalysis occurs on the particles' surface, but the mechanism is complex, and more work is needed to ascertain the specific role of the clusters. It is possible that a Cu(I)-alkyne intermediate is involved, similar to the case with Sonogashira reactions. Further studies to elucidate the mechanism of these cluster-catalysed click reactions will be the subject of future research in our laboratory.

Experimental Section

Materials and Instrumentation

^{1}H NMR was measured on a Varian Mercury vx300 NMR spectrometer at 25 °C. Chemical shifts of spectra are referenced to Me_4Si and internal solvent resonances. GC analysis was performed on a GC-8000 gas chromatograph with a 100% dimethylpolysiloxane capillary column (DB-1, 30 m × 0.325 mm). All products were identified by their GC retention times and their ^{1}H NMR spectra. Samples for GC were diluted with 1 mL dimethylformamide (DMF) and filtered through an alumina plug prior to injection. GC conditions: isotherm at 110 °C (2 min); ramp at 30 °C/min to 280 °C; isotherm at 280 °C (15 min). A Coulter Multisizer Isoton II particle counter was used to measure the particle size of copper powder. Unless noted otherwise, chemicals were purchased from commercial firms and were used as received. Tetra-*n*-octylammonium formate (TOAF) was prepared as published previously.[18] Azides were synthesised following literature procedures.[30,31]

Procedure for 1,3-Dipolar Cycloaddition of Azides with Terminal Alkynes

***Example (1)*: 1,4-diphenyl-1*H*-1,2,3-triazole (3a):** A solution of phenyl azide (**1a**; 10 mmol, 1.33 g) and phenylacetylene (**2a**; 20 mmol, 2.04 g) in 50 mL of 2:1 H_2O:*t*-BuOH was stirred in a round-bottomed flask equipped with a magnetic stirring bar. A pre-prepared suspension of copper nanoclusters (0.1 mL, 10 mM, equivalent to 0.1 mol % of copper relative to 1a) was then added in one portion and the reaction mixture was stirred at 25 °C for 18 h. Reaction progress was monitored by GC. The product precipitated in the reaction mixture and was collected by filtration, washed (2 × 20 mL H_2O), and dried under vacuum to obtain colourless needles of the product; yield: 1.77 g (80% yield based on **1a**); mp 176–179 °C (lit., 181–183 °C); ^{1}H NMR (Me_4Si): $\delta = 7.26-7.58$ (m, 7H, Ph), 7.79–7.95 (m, 3H, Ph), 8.27 (s, 1H, CH). Good agreement was found with literature values.[32]

***Example (2):* (1-benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (3e):** Reaction and work-up were performed as above, but using benzyl azide (**1b**; 10 mmol, 1.19 g) and 1-phenyl-2-propyn-1-ol (**2b**; 20 mmol, 2.64 g), to give the product as a white solid; yield: 2.21 g (97%); mp 120–123 °C; ^{1}H NMR (Me_4Si): $\delta = 2.24$ (1H, OH), 5.46 (s, 2H, CH_2), 6.01 (s, 1H, CH), 6.91–7.93 (m, 10H, Ph).

Reaction Profiles and Kinetic Analysis

The reaction profiles were obtained for the model reaction between benzyl azide (**1b**) and prop-2-yn-1-ol (**2c**) for four different catalytic systems: copper shavings, copper powder, copper nanoclusters, and $CuSO_4$/ascorbate (see Figure 1 above). All other reaction conditions were kept constant and appropriate blank experiments were performed to exclude systemic effects. In this analysis, the correlation coefficient, R^2, gives a measure of the amount of variability in the data that is accounted for by a given model (in this case, a 2nd–order rate equation). The R^2 values and the second-order rate constants (k) were as follows: Cu colloids: $R^2 = 0.886$, $k = 8.3 \times 10^{-3}$ (four observations); Cu powder: $R^2 = 0.912$, $k = 6.7 \times 10^{-3}$ (four observations); Cu shavings: $R^2 = 0.921$, $k = 3.1 \times 10^{-3}$ (five observations); Cu sulfate/sodium ascorbate: $R^2 = 0.908$, $k = 0.9 \times 10^{-3}$ (six observations).

Surface Analysis and Calculation Procedures

The surface area of copper powder was calculated assuming spherical particles (4.483 μm of diameter measured in a size particle counter and 8.92 g/mL of density) obtaining 0.15 m^2/g. The same procedure was used to calculate the surface area of copper nanoclusters (assuming spherical particles of 4 nm of diameter and 8.92 g/mL of density) giving 168 m^2/g.

Acknowledgements

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[29] Another factor that may play a role in the efficiency of heterogeneous copper catalysts is that the surface of copper metal is usually coated by a monolayer of Cu(I) oxide, a dark red powder when in bulk, but virtually unnoticeable when on the metal, which may serve as the source of Cu(I). This may explain why the reaction slows down and eventually stops, but does not stop immediately, after copper metal is removed.
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