Alkynylcopper(I) polymers and their use in a mechanistic study of alkyne–azide click reactions†

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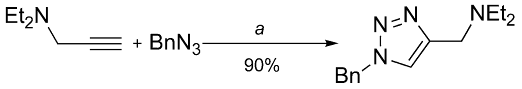
Polymeric dinuclear alkynylcopper(I) complexes, for example phenylethynylcopper(I), can be prepared by a robust method involving the interaction of terminal alkynes with copper(II) salts in acetonitrile. The use of the ladder polymers provides heterogeneous catalysts for copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions and provides important mechanistic information.

Dipolar cycloaddition reactions of terminal alkynes and organic azides were found by Sharpless and Fokin and by Meldal and their co-workers to be accelerated by the use of copper(I) catalysts:[1] the most widely used protocol involving the reduction of Cu(II) to Cu(I) using sodium ascorbate is exemplified in Scheme 1.[1a]

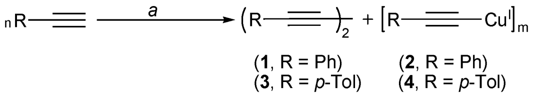
The reactions have been widely exploited and find wide use in organic synthesis, biology and materials science.[2] Although the reviews on the subject indicate that the copper(I) oxidation state is required,[3] there are a limited number of reports of the direct use of copper(II) salts.[4] A careful investigation of the kinetics of the CuAAC reaction of phenylacetylene and benzylazide revealed a second order dependence on copper(I).[5] Recent calculations,[6] based on the requirement of two copper atoms in the transition state complex, gave a low value for the activation energy for the reaction of methylazide and propyne coordinated to two copper(I) atoms each of which had identical spectator ligands. We were interested to obtain additional experimental evidence on the mechanism of alkyne–azide click reactions and to establish how copper(II) salts could function as pre-catalysts. Of importance, in connection with the present communication, is the calculation that indicated the involvement of dinuclear copper complexes with short distances between the two copper atoms in both the alkynecopper complex (2.85 Å) and the transition state complex (2.64 Å). We now report our preliminary results.



Scheme 1 *Reagents and conditions:* (a) $CuSO_4{\cdot}H_2O$ (1 mol%), sodium ascorbate (5 mol%), H_2O–^tBuOH (1 : 1), rt, 8 h.

Acetylenic coupling,[7] including the oxidative dimerisation of copper(I) acetylides discovered by Glaser,[8] has been studied extensively. The Eglinton–Glaser variation uses copper(II) acetate.[9] We argued that, since Glaser coupling reactions are stoichiometric in copper(II) in the absence of dioxygen, it would be fruitful to investigate Glaser coupling under reaction conditions that were likely to generate a copper(I) catalytic species required for CuAAC reactions. We envisaged that acetonitrile would be a good solvent because of its polarity and as a known ligand for copper(I),[10] as well as copper(II).[11] Experiment has confirmed that reasoning. We have focused on heterogeneous catalytic systems because of the ability to recycle such catalysts, as well as their ease of removal at the end of reactions. Our investigations began by subjecting a suspension of copper(II) hydroxyacetate, a layered hydroxide,[12] that was obtained pure as shown by its X-ray powder diffraction (XRD) pattern, to microwave irradiation in the presence of an excess of phenylacetylene in acetonitrile and were pleased to obtain 1,4-diphenylbuta-1,3-diyne (**1**) in 95% yield based on the copper(II) hydroxyacetate used, together with a yellow insoluble product.

A number of yellow or orange organocopper(I) species are polymeric and have short inter Cu(I)–Cu(I) distances: some of the compounds are stabilised by ligands.[13] Polymeric alkynylcopper(I) complexes have been known for many years.[14] While originally prepared by the interaction of copper(I) iodide with



Scheme 2 *Reagents and conditions:* (a) $Cu_2(OH)_3OAc$, microwave or reflux, MeCN.

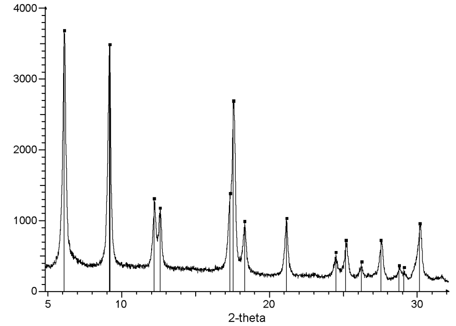


Fig. 1 XRD pattern of (**2**) compared with the pattern (vertical tick marks) generated from the structure of phenylethynylcopper(I) after Che and co-workers.[17]

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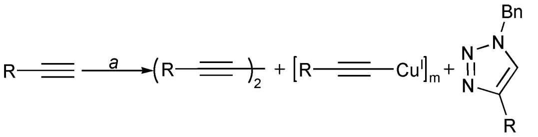


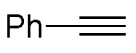
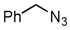
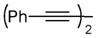
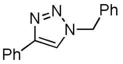
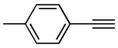
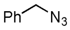
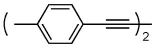
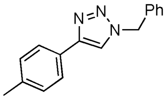
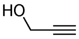
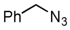
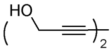
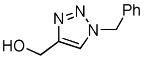
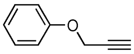
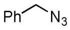
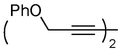
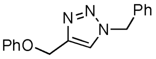
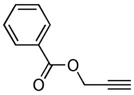
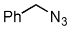
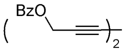
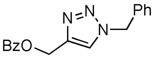
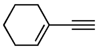
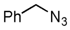
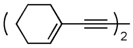
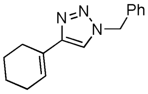
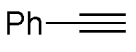
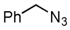
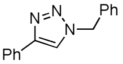
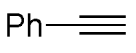
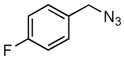
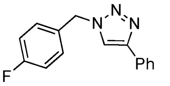
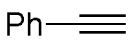
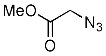
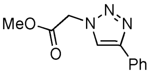
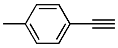
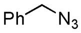
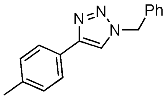
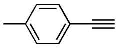
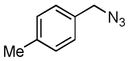
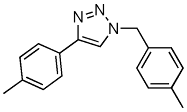
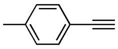
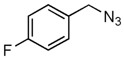
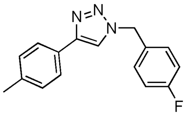
(**1**, R = Ph) (**2**, R = Ph) (**5**, R = Ph)
(**3**, R = *p*-Tol) (**4**, R = *p*-Tol) (**6**, R = p-Tol)

Scheme 3 *Reagents and conditions:* (a) $Cu_2(OH)_3OAc$, R–CCH, BnN_3, microwave or reflux, MeCN.

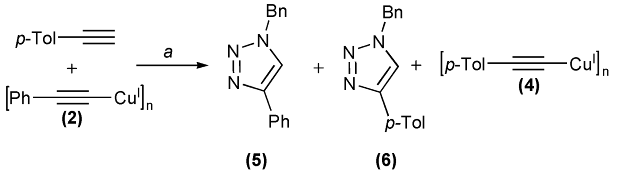
alkali metal derivatives of terminal alkynes,[15] a number of other methods have been used to prepare alkynylcopper(I) derivatives; all involve reactions of copper(I) salts with a terminal alkyne or one of its derivatives.[16] The detailed structure of the stable insoluble yellow polymeric phenylethynylcopper(I) has been reinvestigated by Che and co-workers,[17] using X-ray powder diffraction: it has an extended Cu–Cu ladder structure in which both Cu atoms adopt the same $\mu,\eta^{1,2}$-CC bridging mode in which the two Cu(I) atoms are separated by distances of between 2.49 Å and 2.83 Å, ideally positioned to take part in CuAAC reactions.[6] We showed that the yellow insoluble compound, shown in Scheme 2, was the phenylethynylcopper(I) ladder polymer (**2**), formed in 92% yield, by comparison of its XRD pattern (Fig. 1) with the expected powder diffraction pattern for the polymer calculated from the crystal structure reported by Che and co-workers.[17]

The protocol shown in Scheme 2 provides a novel general method for the preparation of polymeric alkynylcopper(I) derivatives. A comparison of the powder diffraction patterns of (**2**) and the *p*-tolylacetylene derivative (**4**) (see the ESI†) reveals that both patterns show strong reflections associated with better long-range order of the structure within the layers than between them. This behaviour is similar to that normally observed for layered materials (*e.g.* clays) where the preferred orientation is observed for reflections parallel to the 001 plane.

Table 1 Alkyne–azide click reactions carried out with $Cu_2(OH)_3OAc^a$ or $[(CuCCR)_2]_n{}^b$

Entry	Catalyst/pre-catalyst (mol%)	Alkyne	Azide	Glaser product	Yield[c,d] (%)	Click product	Yield[c] (%)
1	$Cu_2(OH)_3OAc$ (10 mol%)				77		92
2	$Cu_2(OH)_3OAc$ (10 mol%)				70		89
3	$Cu_2(OH)_3OAc$ (10 mol%)				74		79
4	$Cu_2(OH)_3OAc$ (10 mol%)				81		73
5	$Cu_2(OH)_3OAc$ (10 mol%)				79		85
6	$Cu_2(OH)_3OAc$ (10 mol%)				87		86
7	$[(CuCCPh)_2]_n$ (10 mol%)			—	—		86
8	$[(CuCCPh)_2]_n$ (10 mol%)			—	—		82
9	$[(CuCCPh)_2]_n$ (10 mol%)			—	—		88
10	$[(CuCC\text{-}p\text{Tol})_2]_n$ (10 mol%)			—	—		75
11	$[(CuCC\text{-}p\text{Tol})_2]_n$ (10 mol%)			—	—		74
12	$[(CuCC\text{-}p\text{Tol})_2]_n$ (10 mol%)			—	—		88

[a] General conditions: $Cu_2(OH)_3OAc$ (10 mol%), alkyne (1.5 eq.), azide (1.0 eq.), MeCN, 100 °C microwave, 10 min. [b] General conditions: $[(CuCCR)_2]_n$ (10 mol%), alkyne (1.5 eq.), azide (1.0 eq.), MeCN, 100 °C microwave, 10 min. [c] Isolated yield. [d] Calculated w.r.t. mol% Cu added.



Scheme 4 *Reagents and conditions:* (a) $[(PhCCCu)_2]_n$ (10 mol%), BnN_3, microwave, MeCN.

We next carried out a microwave reaction with a solution of benzylazide and an excess of phenylacetylene in acetonitrile in the presence of 10 mol% of copper(II) hydroxyacetate. As anticipated, GC/MS analysis showed that 1,4-diphenylbuta-1,3-diyne (**1**) and 1-benzyl-4-phenyltriazole (**5**) were both formed and that the ratio of (**1**) : (**5**) was 1 : 10, isolated in 77% and 92% yields, respectively, together with the conversion of the copper(II) hydroxyacetate into the phenylethynylcopper(I) (**2**) in 82% yield; shown in Scheme 3.

A similar reaction, but using 1 mol% of copper(II) hydroxyacetate, gave the compound (**2**), and a 72% yield of 1-benzyl-4-phenyltriazole (**5**): 1,4-diphenylbuta-1,3-diyne (**1**) was not detected in this reaction, presumably because it was formed in a yield below the level of detection using GC/MS. A series of experiments was conducted using different alkynes, the results of some of which are given in Table 1 (entries 1–6) (additional results are given in the ESI†).

We investigated next the function of the phenylethynylcopper(I) ladder polymer.[18] A reaction in carefully degassed acetonitrile, using a mixture of benzylazide, phenylacetylene and phenylethynylcopper(I) (**2**), using our established microwave reaction conditions, gave the triazole (**5**) in 86% yield. Use of the recovered phenylethynylcopper(I) gave a similar yield. A reaction in which 10 mol% of phenylethynylcopper(I) (**2**) together with a solution of *p*-tolylacetylene and benzylazide in acetonitrile gave 1-benzyl-4-phenyltriazole (**5**) (10%) and 1-benzyl-4-*p*-tolyltriazole (**6**) (85%) (Scheme 4); thus showing that the alkyne attached to copper is replaced during the reaction. The recovered yellow material was then used in a reaction with *p*-tolylacetylene and benzylazide and gave the triazole (**6**) in 85% yield. The recovered yellow insoluble material was shown by XRD to be compound (**4**), shown in Scheme 4, by comparison with the material prepared earlier. As anticipated, a reaction of 1-[^{2}H]-2-phenylethyne with benzylazide in the presence of the phenylethynylcopper(I) (**2**) gave 1-benzyl-4-phenyl-5-[^{2}H]-triazole in 65% yield with a quantitative incorporation of deuterium; the above result confirms that under our reaction conditions the proton source in the triazole product is derived from the added alkyne *e.g.* phenylacetylene. A reaction of the compound (**2**) with benzylazide gave the triazole (**5**) in 85% yield together with a brown insoluble residue that regenerated the yellow phenylethynylcopper(I) (**2**), after the addition of a solution of phenylacetylene in acetonitrile. Some of the reactions of phenylacetylene with a series of different azides, using the compound (**2**), and of *p*-tolylacetylene with the compound (**4**) and the different azides are also shown in Table 1 (entries 7–12) (additional results are given in the ESI†).

In summary, we have shown that copper(II) hydroxyacetate acts as a pre-catalyst that generates efficient polymeric bi-nuclear copper(I) catalytic species for CuAAC reactions. Our results support the involvement of intermediates calculated to have short Cu–Cu internuclear distances. In our continuing work we are exploring other heterogeneous reactions involving the use of the polymeric alkynecopper(I) catalysts.

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Notes and references

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