A New Simplified Protocol for Copper(I) Alkyne–Azide Cycloaddition Reactions Using Low Substoichiometric Amounts of Copper(II) Precatalysts in Methanol

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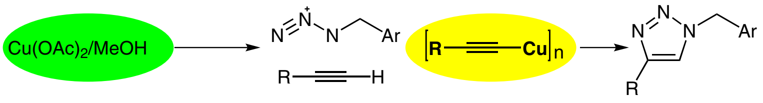

Dedicated to Professor Steven V. Ley FRS for his excellent achievements in organic chemistry on the occasion of his 70th birthday

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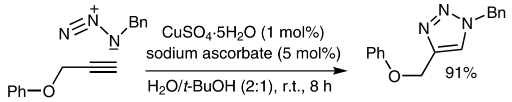
Abstract Copper(II) carboxylates are reduced efficiently by methanol in the presence of alkynes and form yellow alkynylcopper(I) polymeric precatalysts that are involved with azides, in the absence of added ligands, in the catalytic cycles that result in the formation of 1,4-disubstituted 1,2,3-triazoles.

Key words alkyne, azide, copper(I), cycloaddition, triazole

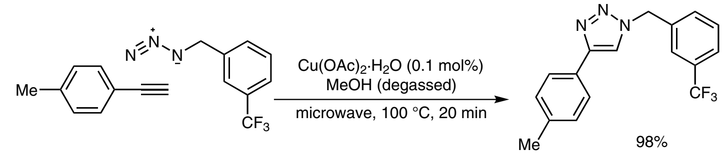
The disclosure of highly regioselective copper(I)-catalysed intermolecular alkyne–azide cycloaddition (CuAAC) reactions by Meldal and Sharpless and their co-workers[1] has been followed each year by a very large number of reports of the preparation of triazoles that have been used for a variety of purposes. Click CuAAC reactions have become perhaps the most widely studied of all copper-catalysed reactions.[2] The use of sodium ascorbate together with copper(II) sulfate, in aqueous *tert*-butanol,[1c] is probably the most currently used CuAAC protocol.

However, in addition to examples involving the direct use of copper(I) salts,[1a,b,3] there are other ways of generating the copper(I) state. For example, reactions of metallic copper together with copper(II) salts provides a method where the presence of ascorbate or its oxidation product may have a deleterious effect.[4] Other catalyst systems include a copper nanocluster,[5] copper(I) zeolites,[6] a copper-manganese spinel oxide,[7] copper(I) oxide 'on water',[8] and copper on carbon.[9a,b] Our previous studies of CuAAC reactions centred on copper(II) precatalysts in the absence of ligands, using copper(II) hydroxyacetate,[10] and more recently Gerhardite [copper(II) hydroxynitrate], the copper(II) species present in 'Copper-in-Charcoal'.[11]

The use of copper(II) acetate in CuAAC reactions has been studied in considerable detail by Zhu and his co-workers, paying particular attention to reactions involving chelating azides as well as other ligands.[12] The reduction of a copper(II) 1,10-phenantholine complex to the related copper(I) complex in propan-2-ol implicated the alcohol as the reducing agent.[13] In an earlier study we established that the phenylethynylcopper(I) polymer was involved in CuAAC reactions by the interaction of phenylacetylene with copper(II) hydroxyacetate in easily oxidisable alcohols, including isopropanol.[10b] The present investigation was undertaken for a number of reasons. First, the original protocol, shown in Scheme 1, involved the addition of a solution of copper(II) sulfate to a solution of an alkyne and an azide in a mixture of *tert*-butanol, water, and a fivefold excess of sodium ascorbate. Second, no additional ligands were used. Third, the acidities of ascorbic acid (pK_a ca. 4.1) and acetic acid (pK_a 4.76) are almost identical, and fourth, π complexation of alkynes by metallic ions such as copper(I) reduce the acidity of alkynes by ca. 10 pK_a units.[14] The recent report of the use of a copper(II)-tren precatalyst[15] in CuAAC reactions, and the use of copper(I) oxide in the presence of dioxygen,[16] prompts this report of a highly efficient and simple protocol that uses copper(II) carboxylates in methanol.



Scheme 1 The copper(II) sulfate/sodium ascorbate protocol for a CuAAC reaction



Scheme 2 The copper(II) acetate/methanol protocol for CuAAC reactions

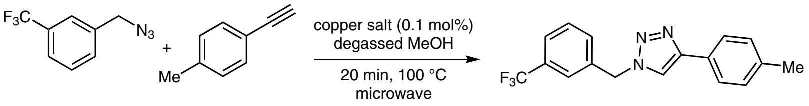
We observed, at an early stage of the present investigation, that a solution of phenylacetylene and copper(II) acetate in wet degassed methanol at ambient temperature gave the yellow polymeric phenylethynylcopper(I),[17] in an almost quantitative yield after ca. two days; similarly, copper(II) formate gave the same product more rapidly. The absence of the Glaser reaction product, 1,4-diphenylbuta-1,3-diyne, as shown by GC–MS, confirmed that methanol was the reducing agent.[10c,18] Reactions using copper(II) salts in solvents such as acetonitrile result in the formation of Glaser products in order to reduce copper(II) salts to the copper(I) precatalyst required to catalyse CuAAC reactions.[10a]

Our earlier studies of CuAAC reactions[10] showed that arylethynylcopper(I) polymers are efficient precatalysts that are formed in high yields and that reactions carried out at ambient temperature, in the absence of added ligands, were complete after ca. 15 hours.[10b] CuAAC reactions were shown to proceed more rapidly in microwave-assisted reactions. Importantly, that alkynylcopper(I) polymers are involved in the catalytic cycle in the absence of ligands was established by crossover reactions.[10a,b,2f] For example, in a reaction of *p*-tolylethyne with benzylazide using a catalytic amount of phenylethynylcopper(I), we recovered *p*-tolylethynylcopper(I).

We therefore carried out reactions of phenylacetylene with benzylazide at ambient temperature using 1 mol% of copper(II) acetate in methanol, in order to establish that methanol could be used as the reducing agent and obtained 1-benzyl-4-phenyl-1,2,3-triazole in 71% yield after three days: A similar reaction, carried out at 50 °C for 4 hours gave the same product in 78% yield. Reactions of benzylazide with octa-1,7-diyne or nona-1,8-diyne were also carried out at 50 °C for 4 hours and gave the expected products in 72% and 69% yields, respectively.[19,21] The reaction of 3-trifluoromethylbenzyl azide with phenylacetylene or *p*-tolyl-acetylene and copper(II) acetate (1 mol%), at ambient temperature in degassed methanol, proceeded very slowly and gave, after 12 hours, the expected triazole derivatives in only 37% and 51%, respectively. We then carried out a series of microwave-assisted reactions, using a mixture of *p*-tolylacetylene and 3-trifluoromethylbenzyl azide together with amounts of copper(II) acetate, starting with 5 mol%, in order to establish the minimum reasonable amount of the precatalyst required. Reactions using 0.1 mol% of copper(II) acetate gave the expected triazole derivative, shown in Scheme 2, in an almost quantitative yield.[23] As our earlier results had shown that CuAAC reactions can be carried out at ambient temperatures using preformed alkynylcopper(I) polymers,[10b] in the absence of added ligands, the present results suggest that the reduction of copper(II) to give the precatalytic copper(I) species, is the slow step in our new protocol.

Reactions using other copper(II) carboxylates as precatalysts for CuAAC reactions were carried out; but none was found to be superior to copper(II) acetate.

Table 1 Influence of Copper(II) Salts on the CuAAC Reaction[a]



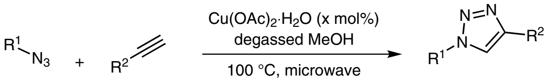
Entry	Copper Salt	Yield (%)[b]
1	$Cu(HCO_2)_2 \cdot 4H_2O$	92
2	$Cu(n\text{-}C_6H_{11}CO_2)_2$	78
3	$Cu(C_6H_5CO_2)_2$	72
4	$Cu(C_6H_{11}O_7)_2$	54
5	$Cu(acac)_2$	52
6	$Cu(OAc)_2 \cdot 5H_2O$	98

[a] General conditions: copper salt (0.1 mol%), alkyne (1.5 equiv), azide (1.0 equiv), degassed MeOH, 100 °C, microwave, 20 min.
[b] Isolated yield after chromatography.

Copper(II) acetylacetonate in methanol did function as a precatalyst; however, as anticipated, it was poor by comparison to the copper(II) carboxylates that we studied. The results of the trial reactions are shown in Table 1.

The optimum conditions (Table 1, entry 6) were then applied to a range of alkyne–azide combinations to afford the corresponding triazoles. In some cases a higher loading of copper acetate was required to obtain the best yields in the cycloaddition reactions (Table 2). Although many of the reactions reported were carried out using degassed methanol; reactions can be carried out in the presence of air since the reducing agent methanol, like ascorbate in the Sharpless protocol,[1c] is present in a very large excess.

Table 2 Application to a Range of Substrates[a]



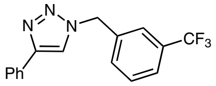
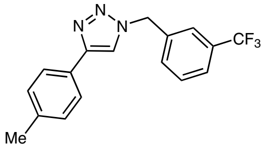
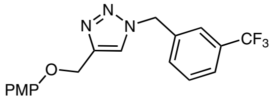
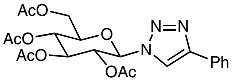
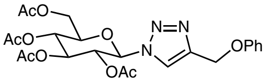
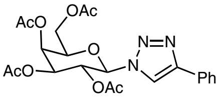
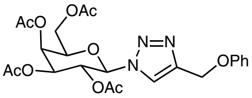
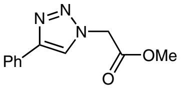
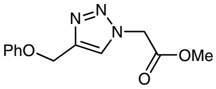
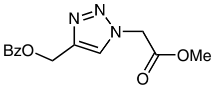
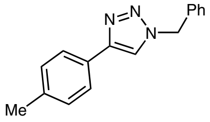
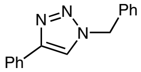
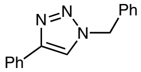
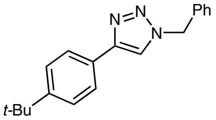
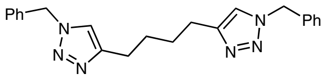
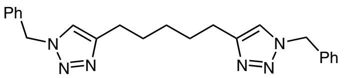
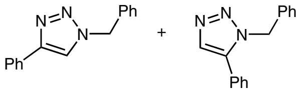
Entry	Catalyst loading (mol%)	Time	Product	Yield (%)[b]
1	0.1	10 min		71
2	0.1	10 min		98
3	0.1	10 min		70
4	1.0	20 min		46
5	1.0	30 min		99
6	1.0	60 min		92
7	1.0	30 min		96
8	1.0	20 min		86
9	0.1	20 min		65
10	0.1	20 min		70

Table 2 (continued)

Entry	Catalyst loading (mol%)	Time	Product	Yield (%)[b]
11	0.1	20 min		85
12	1.0	20 min		72
13	1.0	72 h		71[c]
14	1.0	30 min		65
15	1.0	4 h		72[d,19]
16	1.0	4 h		69[d,21]
17	0.0	30 min		12[e,f]

[a] General conditions: Copper salt (0.1 mol%), alkyne (1.5 equiv), azide (1.0 equiv), degassed MeOH, 100 °C, microwave, 20 min.
[b] Isolated yield after chromatography.
[c] Conditions: Copper salt (1.0 mol%), alkyne (1.5 equiv), azide (1.0 equiv), MeOH, r.t., 3 d.
[d] Conditions: Copper salt (1.0 mol%), diyne (2.2 equiv), azide (1.0 equiv), MeOH, conventional heating 50 °C, 4 h.
[e] Conversion evaluated by ^{1}H NMR spectroscopy by integration of benzylazide CH_2 vs. benzyl CH_2 in the triazole products.
[f] Sum of both regioisomers.

In summary, we have shown that a simple protocol can be used to obtain good to excellent yields of 1,4-disubstituted 1,2,3-triazoles, that involve alkynylcopper(I) polymeric precatalysts in the CuAAC reactions carried out in the absence of added ligands. Also, that whereas phenylethynylcopper(I) has been prepared by a number of methods,[17] our present results demonstrate that reactions of alkynes in methanol in the presence of, for example copper(II) acetate, provides the simplest method of preparing the alkynylcopper(I) polymers. The new protocol may also stimulate the use of alkynylcopper(I) compounds as precatalysts in a variety of other reactions. In addition to other recent examples,[24] alkynylcopper(I) polymers may be involved for example in the flow generation of azides used in the copper(I)-catalysed preparation of allenes from terminal alkynes.[25]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560526.

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(19) **Bistriazole Prepared from 1,7-Octadiyne and Benzyl Azide**[20]
Benzyl azide (0.15 g, 1.1 mmol) and 1,7-octadiyne (0.053 g, 0.5 mmol) were added to a 3 mL vial containing MeOH (2 mL) which was fitted with a magnetic stirrer bar. Copper(II) acetate mono-hydrate was added (1 mg, 0.005 mmol, 0.1 mL from a stock solution in MeOH containing 10 mg/mL), and the vial was closed. The reaction mixture was then stirred and heated at 50 °C for 4 h on a stirrer hotplate fitted with an aluminium vial holder and allowed to cool. The colourless precipitate was filtered, washed with cold MeOH (2 × 5 mL), Et_2O (5 mL), and allowed to dry in air to give colourless crystals (0.13 g, 72%); mp 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.34$ (6 H, m), 7.26–7.22 (4 H, m), 7.17 (2H, s), 5.47 (4 H, s), 2.72–2.68 (4 H, m), 1.72–1.69 (4 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.7$, 135.2, 129.3, 128.8, 128.2, 120.9, 54.2, 29.1, 25.7 ppm. HRMS: *m/z* calcd for $C_{22}H_{24}N_6Na$ [M + Na]: 395.1960; found: 3955.1959.

(20) Saha, S.; Kaur, M.; Bera, J. K. *Organometallics* **2015**, *34*, 3047.

(21) **Bistriazole Prepared from 1,8-Nonadiyne and Benzyl Azide**[22]
A similar reaction gave colourless crystals (0.13 g, 69%); mp 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37–7.35$ (6 H, m), 7.26–7.22 (4 H, m), 7.17 (2 H, s), 5.48 (4 H, s), 2.67 (4 H, t, $J = 9.6$ Hz), 1.71–1.60 (4 H, m), 1.40–1.37 (2 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.9$, 135.2, 129.3, 128.8, 128.2, 120.8, 54.2, 29.3, 28.9, 25.8 ppm. HRMS: *m/z* calcd for $C_{23}H_{26}N_6Na$ [M + Na]: 409.2117; found: 409.2113.

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(23) **Triazole Prepared from *p*-Tolylethyne and 3-Trifluoromethylbenzyl Azide (Table 2, Entry 2)**
3-Trifluoromethylbenzyl azide (0.34 g, 1.7 mmol) and *p*-tolylethyne (0.30 g, 2.6 mmol) were added to a microwave tube (5 mL) fitted with a magnetic stirrer bar. Copper (II) acetate monohydrate (3.4 mg, 0.017 mmol) was added and the mixture suspended in MeOH (5 mL). The reaction mixture was then heated in the microwave apparatus at 100 °C for 20 min and allowed to cool. The reaction mixture was added to EtOAc (50 mL) and H_2O (50 mL), separated, and the aqueous layer extracted with EtOAc (2 × 50 mL). The EtOAc layers were evaporated under reduced pressure to give an off-white solid which after recystallisation from Et_2O gave the product as colourless crystals (0.53g, 98%); mp 128–130 °C. IR: $\nu_{max} = 3135$, 2982, 1665, 1448, 1386 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74–7.72$ (3 H, m), 7.66–7.61 (2 H, m), 7.55–7.48 (2 H, m), 7.25 (2 H, d, $J = 7.6$ Hz), 5.65 (2 H, s), 2.39 (3 H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.6$, 138.2, 135.8, 131.5 (q, $J = 32.2$ Hz), 131.3, 129.8, 129.6, 127.4, 125.67 (q), 125.62, 124.7 (q, $J = 3.7$ Hz), 123.5 (q, $J = 271.2$ Hz), 122.3, 119.6, 119.2, 53.6, 21.4 ppm. HRMS: *m/z* calcd for $C_{15}H_{24}N_3F_3Na$ [M + Na]: 340.1032; found: 340.1040.

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