Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6082

www.rsc.org/obc

PAPER

Copper(I)-catalyzed cycloaddition of silver acetylides and azides: Incorporation of volatile acetylenes into the triazole core†

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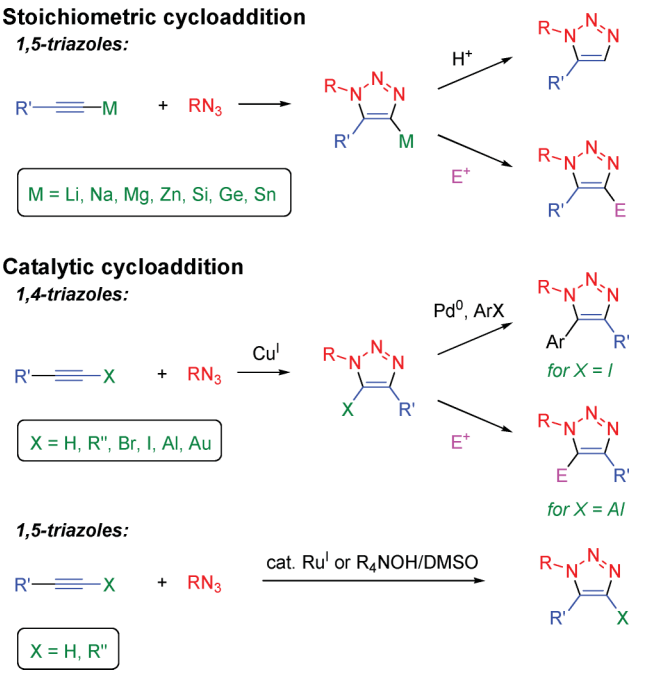
Received 8th March 2011, Accepted 3rd June 2011
DOI: 10.1039/c1ob05360d

Silver acetylides and organic azides react under copper(I) catalysis to afford 1,4-disubstituted 1,2,3-triazoles. Mechanistic studies implicate a process involving transmetallation to copper acetylides prior to cycloaddition. This work demonstrates that silver acetylides serve as suitable precursors for entry into copper-mediated coupling reactions. This methodology allows the incorporation of volatile and difficult-to-handle acetylenes into the triazole core.

Introduction

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction[1,2] is a conjugation strategy notable for its fidelity and breadth of scope, lending to its use in a broad range of applications.[3] The reaction provides 1,4-disubstituted-1,2,3-triazoles as the sole product, and is typically applied to terminal alkynes (RCCH) but can also be performed on non-terminal alkynes (RCCR′) including internal alkynes (R′ = alkyl),[4] 1-bromo-[5] and 1-iodoalkynes[6] (R′ = Br, I), and aluminium[7] and gold[8] acetylides (R′ = Al, Au), affording 1,4,5-trisubstituted triazoles in which the alkyne substituent (R′) is found in the 5 position of the resulting 1,2,3-triazole (Scheme 1). 5-Iodo- and 5-aluminotriazoles serve as versatile synthetic intermediates for the introduction of electrophilic groups at the position initially occupied by the iodine or metal by Suzuki–Miyuara coupling[6] or nucleophilic substitution,[7] yielding 1,4,5-trisubstituted triazoles.[7–9] The CuAAC reaction is complemented by the ruthenium(I)-catalyzed azide–alkyne cycloaddition (RuAAC) reaction, which provides 1,5-disubstituted and 1,4,5-trisubstituted triazoles.[10] The catalytic CuAAC and RuAAC processes extend the reactivity of preformed metal acetylides with azides. Thus, lithium,[11] sodium,[11] magnesium,[11] zinc,[12] silicon,[13] germanium[13] and tin[13] acetylides undergo reaction with azides to afford triazoles in which the acetylenic group and azide group are found at the 1 and 5 positions and the metal/metalloid is located at the 4 position. 4-Magnesiotriazoles can undergo reaction with suitable electrophiles and the 4-zincotriazoles are suitable substrates for Negishi reaction.[12] A metal-free protocol employing catalytic tetraalkylammonium hydroxide in DMSO also affords 1,5-triazoles exclusively.[14]



Scheme 1 Summary of metal-mediated stoichiometric and catalytic azide-alkyne cycloaddition reactions affording 1,4- and 1,5-disubstituted triazoles and their elaboration to 1,4,5-trisubstituted triazoles.

Whereas the cycloaddition chemistry of acetylides of the group 11 metals copper and gold with azides have been well studied, the corresponding reactions of the intervening element silver have been largely overlooked.[15] Silver acetylides are among the oldest known organometallic species[16] and are relatively stable solids that can be stored in air and are easily prepared from the reaction of ammoniacal aqueous silver nitrate and terminal acetylenes[17] or TMS-acetylenes and silver salts.[18] Stimulated by the similar

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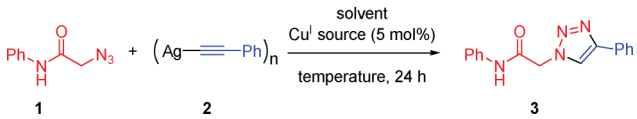
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05360d

Table 1 Optimization of copper(I)-catalyzed cycloaddition of silver phenylacetylide and azidoacetanilide



Entry	Cu(I) source	Solvent	Temp	Yield (%)
1	—	NMM[a]	rt	0
2	—	NMM[a]	115 °C	5[b]
3	—	Pyridine	rt	0
4	$CuSO_4$ (5 mol%), NaAsc (10 mol%)	Pyridine/H_2O (10 : 1)	rt	27
5	$[Cu(MeCN)_4]PF_6$ (5 mol%)	Pyridine	rt	54
6	$[Cu(MeCN)_4]PF_6$ (5 mol%)	Pyridine	rt	75[c]
7	$[Cu(MeCN)_4]PF_6$ (10 mol%)	$CHCl_3$	rt	45[d]

[a] NMM = *N*-methylmorpholine. [b] 1 : 1 mixture of 1,4- and 1,5-triazoles was formed. [c] Reaction under nitrogen. [d] 1 eq Ph_3P was added.

electronic configurations of the congeners copper(I), silver(I) and gold(I) (s^0d^{10}) we investigated the reactivity of silver acetylides in azide/alkyne cycloaddition reactions with and without copper(I) catalyst.

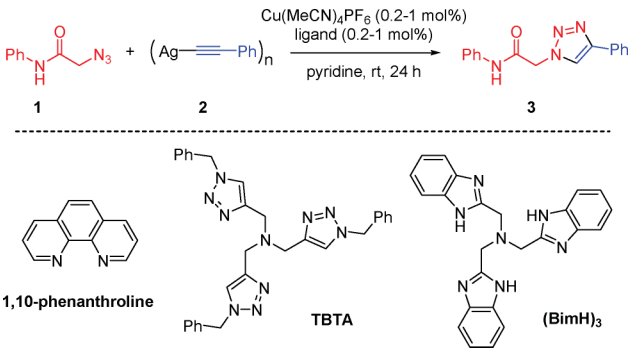
Results and discussion

Reaction optimization and scope

We initially investigated whether silver phenylacetylide **2** would undergo reaction with a model azide, azidoacetanilide **1**. Silver acetylides are polymeric species with limited solubility[19] and we investigated the reaction in both *N*-methylmorpholine, which has seen use as a solvent in nucleophilic substitution reactions of silver acetylides,[20] and pyridine.[17] The latter solvent dissolves the Ag-acetylide most likely as a consequence of Ag–N(pyridine) coordinate bond formation breaking up aggregates. As reported in Table 1 little or no reaction was observed under these conditions. In the case of entry 2, the observation that 1,4- and 1,5-disubstituted triazoles are formed in equal measure suggests that product formation was occurring by protonation of the silver acetylide followed by a non-regiospecific thermal Huisgen [3 + 2] cycloaddition. These results are in agreement with an exploratory study of Aucagne and Leigh.[15] We next studied the ability of copper(I) to catalyze the cycloaddition reaction. Both preformed copper(I) in $[Cu(MeCN)_4]PF_6$ and *in situ* generated copper(I) from $Cu^{II}SO_4$/sodium ascorbate were used. In the latter case (entry 4) pyridine/H_2O (10 : 1) was required to dissolve the sodium ascorbate reductant. Entry 6 shows that $[Cu(MeCN)_4]PF_6$ provides the 1,4-triazole **3** in the best yield. It was shown that performing the reaction under nitrogen improves the yield (compare entries 5 and 6). Exclusive formation of the 1,4-triazole was confirmed by analytical data[21] and comparison with authentic material prepared by CuAAC reaction.[22] The inclusion of triphenylphosphine (1 eq) allowed the reaction to be performed in chloroform (entry 7); however, the yield was inferior relative to reaction in pyridine (entry 6).

We next examined the effect of ligands on the reaction. 1,10-Phenanthroline[23] and $(BimH)_3$ (*tris*(2-benzimidazolylmethyl)amine)[24,25] ligands (Table 2) in conjunction with Cu^{I} are reported to accelerate the rate of CuAAC reactions, although in both cases the cycloaddition reactions are sensitive to oxygen.

Table 2 Effect of ligands on the copper(I)-catalyzed cycloaddition of silver phenylacetylide and azidoacetanilide



Entry	$[Cu(MeCN)_4]PF_6$ (mol%)	Ligand (mol%)	Yield (%)
1	1	—	57
2	1	TBTA (1)	57
3	1	$(BimH)_3$ (1)	69
4	1	1,10-Phenanthroline (1)	81
5	0.2	—	14
6	0.2	TBTA (0.2)	19
7	0.2	$(BimH)_3$ (0.2)	66
8	0.2	1,10-Phenanthroline (0.2)	66

On the other hand the *tris*-triazole ligand TBTA (*tris*(1-benzyl-1*H*-1,2,3-triazol-4-ylmethyl)amine) (Table 2) has emerged as a popular auxiliary ligand that enhances reaction yields through stabilizing the copper(I) oxidation state,[22,26] thereby improving the turnover number of the catalytic copper centers, although no rate enhancement is observed.[24] The effect of these three ligands on the yield of the reaction of **1** and **2** was examined using reduced copper loadings with a 1 : 1 ratio of ligand to copper. Reducing the amount of $[Cu(MeCN)_4]PF_6$ to 1 mol% and 0.2 mol% had a significant effect upon yield (entries 1 and 5). The inclusion of TBTA provided little improvement in yield (entries 2 and 6), whereas the rate accelerating ligands $(BimH)_3$ and 1,10-phenanthroline both afforded significant improvement at both 1 and 0.2 mol% $[Cu(MeCN)_4]PF_6$. The preferred conditions for the copper(I)-catalyzed silver acetylide azide cycloaddition (CuAgAAC) reaction were using 1 mol% $[Cu(MeCN)_4]PF_6$ and

1,10-phenanthroline, under nitrogen at room temperature in pyridine (entry 4).

The scope of the CuAgAAC reaction was examined with the results outlined in Fig. 1. In general, the 1,4-disubstituted triazoles **4–17** were obtained in good yields (69–96%). Satisfactory yields were obtained with both aryl and alkylacetylenes. The presence of an *ortho* methoxy group did not appreciably affect the yield of **8** and **13**. The synthesis of the *bis*-triazoles **16** and **17** required more forcing conditions to effect formation of two triazole groups, with the silver acetylide increased to 3 equivalents with respect to the azide and 15 mol% $[Cu(MeCN)_4]PF_6$ and 6 mol% phenanthroline. Certain silver acetylides, such as silver butylacetylide, are known to be soluble in non-coordinating organic solvents such as CCl_4, $CHCl_3$ and benzene.[17] Treatment of silver butylacetylide and **1** in $CHCl_3$ with 10 mol% $[Cu(MeCN)_4]PF_6$ and 10 mol% phenanthroline afforded the triazole **9** in 75%. A benefit of the CuAgAAC reaction is its ability to utilize silver acetylides of low molecular weight alkynes such as propyne and 1-butyne, which are generally under-represented as substrates for the CuAAC reaction leading to sparse reports of 4-methyl and 4-ethyl-substituted 1,4-triazoles.[27] For example, silver butynylide can be prepared in minutes by passing a stream of 1-butyne over a stirred solution of ammoniacal silver nitrate, affording the easily handled silver acetylide as a solid, or from the reaction of a non-gaseous precursor, 1-trimethylsilylbutyne with silver nitrate. By contrast, CuAAC reactions using gaseous alkynes require maintenance of an atmosphere of an excess of the alkyne over the reaction mixture using a balloon or a Parr apparatus.[27]

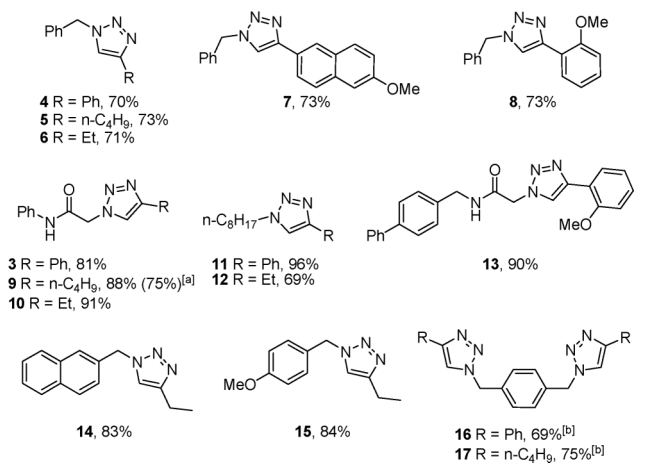


Fig. 1 Scope of the copper(I)-catalyzed silver acetylide azide cycloaddition. Conditions: silver acetylide (1 eq), azide (1 eq), $[Cu(MeCN)_4]PF_6$ (1 mol%), 1,10-phenanthroline (1 mol%), pyridine, rt, 24 h. [a] Silver butylacetylide (1.5 eq), $[Cu(MeCN)_4]PF_6$ (10 mol%), 1,10-phenanthroline (10 mol%) in $CHCl_3$.[b] Silver acetylide (3 eq), azide (1 eq), $[Cu(MeCN)_4]PF_6$ (15 mol%), 1,10-phenanthroline (6 mol%) in pyridine.

We also established a one-pot procedure that allowed the direct use of azides and TMS-alkynes (TMS-phenylacetylene, TMS-hexyne, TMS-propyne) in pyridine in the presence of stoichiometric silver to form the silver acetylide, followed by addition of $[Cu(MeCN)_4]PF_6$ to promote the CuAgAAC reaction (Fig. 2).

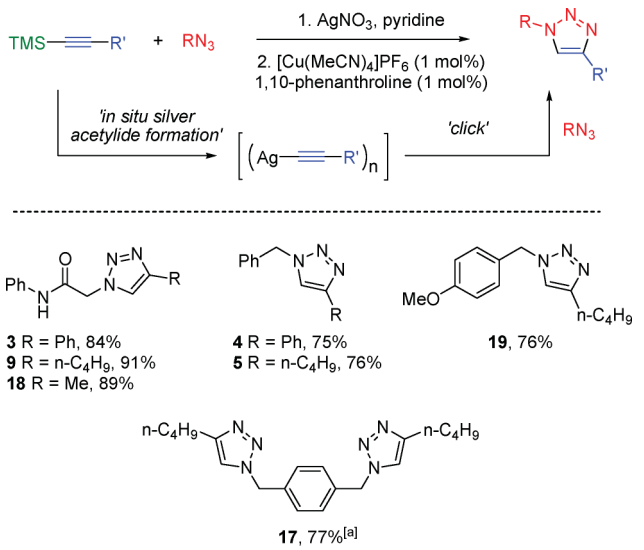
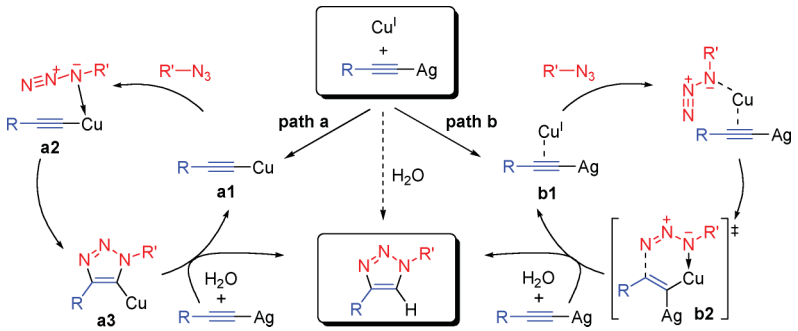


Fig. 2 One-pot conversion of TMS-alkynes and azides to 1,4-triazoles. [a] 1-Trimethylsilyl-1-hexyne (3 eq), azide (1 eq), $[Cu(MeCN)_4]PF_6$ (5 mol%), 1,10-phenanthroline (2 mol%).

Mechanistic studies

Two possible mechanistic pathways for the CuAgAAC reaction can be proposed based on the analogous processes for CuAAC reactions of terminal acetylenes[2] and non-terminal acetylenes.[6,7] One pathway (Scheme 2, **path a**) involves the transmetallation of the silver acetylide to a copper acetylide intermediate **a1**,[28] which then undergoes reaction with an azide to afford the metal complex **a2**.[2] This complex contracts to form a 5-cuprotriazolide **a3**,[29] which is protonated to afford the 1,4-triazole. The second pathway (Scheme 2, **path b**) invokes the formation a π-complex with the alkyne **b1**, which undergoes cycloaddition to **b2**, followed by expulsion of copper(I). In order to test the potential for silver acetylides to undergo transmetallation, we studied a member of a family of previously described discrete molecular species $[(RCC)_{12}Ag_{14}X]^+$ (X = F, Cl, Br).[30] These consist of a cage compound with 14 silver atoms arranged in a rhombic dodecahedron surrounding a central halide atom.[30] The silver atoms are held together by a combination of bridging alkynyl groups and argentophilic Ag···Ag interactions. As molecular species they comprise a useful model for the less tractable polymeric silver acetylides, as they are likely to possess similarities in their bonding patterns. $[(C_3H_7CC)_{12}Ag_{14}Cl]^+$ can be generated by reformation of polymeric silver pentynide and conveniently studied by electrospray ionization mass spectroscopy (ESI-MS).[31] Treatment of $[(C_3H_7CC)_{12}Ag_{14}Cl]^+$ with increasing concentrations of $[Cu(MeCN)_4]PF_6$ in acetonitrile/water afforded a series of copper(I) exchanged clusters $[(C_3H_7CC)_{12}Ag_nCu_mCl]^+$ (n = 8–13, m = 1–6, $n + m$ = 14), in which a maximum of 6 silver(I) centres are exchanged to afford $[(C_3H_7CC)_{12}Ag_8Cu_6Cl]^+$ (Fig. 3). Varying the time of incubation did not alter the degree of incorporation, suggesting that the exchange process is rapid. We conclude that partial Cu^I/Ag^I exchange is a facile process, and that it may also occur in polymeric silver acetylides or silver acetylides dissolved in pyridine.

To gain evidence that copper acetylides formed by transmetallation of silver acetylides are bonafide reaction intermediates,



Scheme 2 Proposed mechanisms for the copper(I)-catalyzed silver acetylide azide cycloaddition. Possible oligomeric/polymeric states have not been included for purposes of clarity.

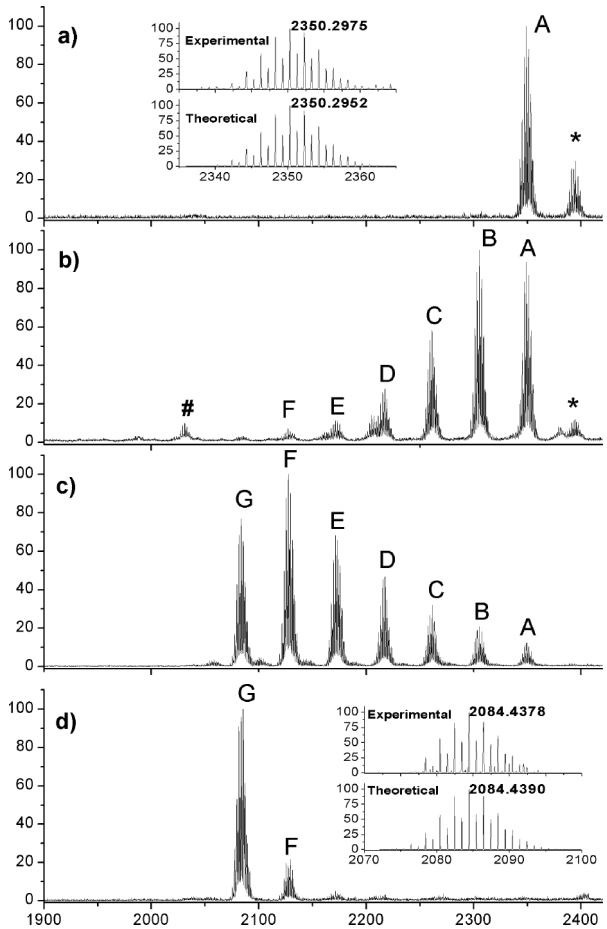


Fig. 3 ESI-MS (Finnigan hybrid LTQ-FT-MS) spectra of solutions of $AgCCC_3H_7$:$Cu(MeCN)_4PF_6$ in $MeCN/H_2O$. Concentration ratio (a) 1 : 0; (b) 1 : 0.2; (c) 1 : 0.5; (d) 1 : 1. Peaks observed correspond to the general formula $[Ag_nCu_mCl(CCC_3H_7)_{12}]^+$ ($n = 8$–14, $m = 0$–6, $n + m = 14$). **A**: $n = 14$, $m = 0$; **B**: $n = 13$, $m = 1$; **C**: $n = 12$, $m = 2$; **D**: $n = 11$, $m = 3$; **E**: $n = 10$, $m = 4$; **F**: $n = 9$, $m = 5$; **G**: $n = 8$, $m = 6$. * = $[(AgCCC_3H_7)_{13}Ag]^+$, # = $[(AgCCC_3H_7)_{10}Ag]^+$. The insets in (a) and (d) correspond to experimental and theoretical isotope distributions and mass of peaks **A** and **G**, respectively.

we investigated the Glaser coupling of silver acetylides under Cu(I) catalysis (Fig. 4a). The Glaser reaction is a classical method to prepare 1,3-diynes through the oxidative homocoupling of terminal alkynes.[32] Treatment of silver phenylacetylide **1** with stoichiometric $[Cu(MeCN)_4]PF_6$ in pyridine at 80 °C in the

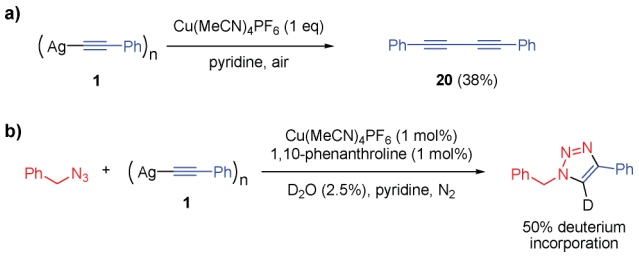


Fig. 4 Mechanistic investigations into the CuAgAAC reaction. (a) Copper-promoted Glaser reaction of silver phenylacetylide. (b) C5-deuterium incorporation from D_2O.

presence of O_2 afforded 1,4-diphenylbuta-1,3-diyne **20** in an unoptimized 38% yield. In the absence of copper, only traces of the diyne could be observed. Together with the ESI-MS study of Cu^I/Ag^I exchange in the molecular silver acetylide cluster we conclude that transmetallation of silver acetylides to copper acetylides can occur readily, although the precise nature of the silver alkynyls formed when silver acetylides are dissolved in pyridine is not known.[33] We next studied the origin of the proton at C5 of the triazole. Inclusion of D_2O into a standard reaction of silver phenylacetylide **1** and benzyl azide in dry pyridine resulted in 50% incorporation of deuterium as determined by ^1H NMR and mass spectrometric analysis (Fig. 4b). As the CuAgAAC reaction we have developed utilizes non-dried pyridine, the C5-triazole proton originates from the solvent.

Conclusions

This work demonstrates a new copper(I)-catalyzed cycloaddition reaction of silver acetylides with azides. The key to this reaction is the judicious choice of pyridine as solvent, which possesses powerful solvating properties for a wide range of silver acetylides. Mechanistic evidence supports a pathway proceeding by way of transmetallation to copper acetylides, consistent with **path a** (Scheme 2). This work represents only the second case for which transmetallation of silver acetylides has been observed, extending the seminal work showing that silver acetylides can enter the palladium catalytic cycle of cross-coupling reactions[34] and demonstrating that silver acetylides can participate in other Cu(I)-catalyzed processes such as the Glaser reaction. The new catalytic CuAgAAC reaction provides a practical synthesis of 1,4-triazoles derived from low molecular weight alkynes by their conversion to readily handled polymeric silver acetylides, and is complementary

to other recently reported processes using copper(I)-catalyzed cycloaddition of TMS-alkynes[35] and of calcium carbide.[36]

Experimental Section

Petroleum spirits refers to a mixed fraction boiling at 40–60 °C. Thin layer chromatography (t.l.c) was performed with Merck Silica Gel 60 F_{254}, using mixtures of petroleum spirits-ethyl acetate unless otherwise stated. Detection was effected by either charring in a mixture of 5% sulfuric acid-MeOH and/or by visualization in UV light. Melting points were obtained on a Reichert-Jung hot-stage apparatus. NMR spectra were obtained on Varian Inova 400 or 500 instruments (Melbourne, Australia). Flash chromatography was performed according to the method of Still *et al.* with Merck Silica Gel 60, using adjusted mixtures of ethyl acetate-petroleum spirits unless otherwise stated.[37] Solvents were evaporated under reduced pressure using a rotary evaporator. High resolution mass spectrometry was performed on a Finnigan hybrid LTQ-FT mass spectrometer (Thermo Electron Corp.). Azides were prepared as described in the literature.[22,38,39]

Preparation of silver acetylides

Silver acetylides were prepared according to the procedures of Davies and Scheiber[17] or Viterisi *et al.*[18]

(a) A solution of $AgNO_3$ (5 mmol) in a mixture 1 : 1 of EtOH and 15 M aqueous NH_3 (10 ml) was added to a stirred solution of the alkyne (5 mmol) in EtOH (5 ml) at rt. The resulting precipitate was collected, washed with EtOH, ether and petroleum spirits and dried in the dark.

(b) A solution of $AgNO_3$ (1 eq) in a mixture of CH_3CN and Et_3N (2 : 1, 10 ml) was added to a stirred solution of the alkyne (1 eq) in CH_3CN (5 ml) at rt. The resulting precipitate was collected, washed with CH_3CN and dried in the dark.

(c) TMS-alkyne (1 eq) was added to a solution of silver nitrate (1 eq) in ethanol (10 ml) at rt. The resulting precipitate was filtered, washed with ethanol and dried in the dark.

General procedure for Cu(I)-catalyzed silver acetylide and azide cycloaddition

Silver acetylide (1 eq.) was added to a solution of azide (1 eq.) in pyridine (4 ml). The reaction mixture was sparged with N_2 for 10 min, then $[Cu(MeCN)_4]PF_6$ (1 mol%) and 1,10-phenanthroline (1 mol%) were added. The reaction mixture was stirred for 24 h at rt in the dark under N_2, then diluted with dichloromethane (15 ml) and 15 M aqueous NH_3 (15 ml). The mixture was filtered through Celite and the filtrate was sequentially washed with 15 M aqueous NH_3 (15 ml) and water (2 × 15 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford the product.

One-pot CuAgAAC procedure from 1-trimethylsilyl-1-alkynes

Azide (1.0 equiv.) was added into a mixture of TMS-alkyne (1.0 equiv.) and silver nitrate (1.2 equiv.) in pyridine (4 ml). The reaction mixture was purged with N_2 for 10 min. $[Cu(MeCN)_4]PF_6$ (1 mol%) and 1,10-phenanthroline (1 mol%) were added and the resultant mixture was stirred at rt under N_2 for 24 h. Conc. aq. ammonia (20 ml) was added to the mixture followed by stirring for 5 min. The reaction mixture was filtered through filter aid. The aqueous phase was extracted with dichloromethane (3 × 15 ml), washed with conc. aq. ammonia and water, dried ($MgSO_4$) and solvent removed under reduced pressure.

N-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide 3

White needles from DMSO/H_2O, mp 244.5–246.5 °C (lit.[22] 243–245 °C). ^{1}H NMR (500 MHz, d_6-DMSO): δ = 5.38 (2H, s, CH_2), 7.09 (1H, t, *J* 7.5 Hz), 7.33 (3H, t, *J* 8.0 Hz), 7.45 (2H, t, *J* 8.0 Hz), 7.59 (2H, d, *J* 7.5 Hz), 7.88 (2H, d, *J* 8.0 Hz), 8.59 (1H, s, triazole-H), 10.49 (1H, s, NH); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 52.4 (1C, CH_2), 119.2, 123.0, 123.8, 125.1, 127.8, 128.9, 130.2, 138.4, 146.2 (14C, Ar), 164.1 (1C, C═O).

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole 4

White crystals from DMSO/H_2O, mp 120–122.5 °C (lit.[40] 122–124 °C). ^{1}H NMR (500 MHz, d_6-DMSO): δ = 5.64 (2H, s, CH_2), 7.37 (8H, m, Ar–H), 7.84 (2H, dd, *J* 1.5, 7.5 Hz, Ar–H), 8.63 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 53.0 (1C, CH_2), 121.5, 125.1, 127.9, 128.1, 128.4, 128.8, 128.9, 130.6, 136.0, 146.6 (14C, Ar).

1-Benzyl-4-butyl-1*H*-1,2,3-triazole 5

White crystals from DMSO/H_2O, mp 60–62 °C, (lit.[35] 62–63 °C). ^{1}H NMR (500 MHz, d_6-DMSO): δ = 0.87 (3H, t, *J* 7.5 Hz, CH_3) 1.30 (2H, m, CH_2), 1.55 (2H, m, CH_2), 2.59 (2H, t, *J* 7.5 Hz, CH_2C═C), 5.52 (2H, s, CH_2Ph), 7.26–7.38 (5H, m, Ar–H), 7.87 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 13.7, 21.7, 24.6, 31.1, 52.6 (5C, 4 × CH_2,1 × CH_3), 121.9, 127.8, 128.0, 128.7, 136.3, 147.2 (8C, Ar).

4-Ethyl-1-benzyl-1*H*-1,2,3-triazole 6

White crystals, mp 53–55 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 1.17 (3H, t, *J* 7.5 Hz, CH_3), 2.62 (2H, q, *J* 7.5 Hz, C**H**$_2$CH$_3$), 5.55 (2H, s, C**H**$_2$Ph), 7.32 (5H, m, Ph), 7.88 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 13.6, 18.5, 52.7 (3C, 2 × CH_2, 1 × CH_3), 121.5, 127.8, 127.9, 128.7, 136.3, 148.7 (8C, Ar); HR-ESIMS: *m*/*z* = 188.11793 $[M+H]^+$, calcd. 188.11822 for $C_{11}H_{14}N_3$.

1-Benzyl-4-(2-methoxynaphthalen-7-yl)-1*H*-1,2,3-triazole 7

Colourless crystals, mp 215.5–218 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 3.87 (3H, s, CH_3), 5.66 (2H, s, CH_2), 7.17 (1H, dd, *J* 2.5, 9.0 Hz, Ar–H), 7.32–7.41 (6H, m, Ar–H), 7.85–7.87 (2H, m, Ar–H), 7.93 (1H, dd, *J* 2.5, 9.0 Hz, Ar–H), 8.31 (1H, d, *J* 2.5 Hz, Ar–H), 8.67 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 53.0, 55.1 (CH_2, CH_3), 106.1, 118.8, 121.2, 123.3, 124.0, 125.8, 127.1, 127.8, 128.0, 128.4, 128.6, 129.3, 133.8, 135.8, 146.7, 157.4 (Ar); HR-ESIMS: *m*/*z* = 316.14438 $[M+H]^+$, calcd. 316.14444 for $C_{20}H_{18}N_3O$.

1-Benzyl-4-(2-methoxyphenyl)-1*H*-1,2,3-triazole 8

White crystals from DMSO/H_2O, mp 167.5–169.5 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 3.88 (3H, s, CH_3), 5.66 (2H, s, CH_2), 7.04 (1H, t, *J* 7.5 Hz, Ar), 7.15 (1H, dd, *J* 1.0, 8.0 Hz, Ar), 7.30–7.38 (6H, m, Ar), 8.15 (1H, dd, *J* 2.0, 8.0 Hz, Ar), 8.46 (1H,

s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 52.7 (1C, CH_2), 55.5 (1C, OMe), 111.5, 119.0, 120.6, 124.1, 126.5, 127.8, 128.1, 128.8, 129.0, 136.3, 142.0, 155.3 (14C, Ar); HR-ESIMS: m/z = 266.12872 $[M+H]^+$, calcd. 266.12879 for $C_{16}H_{16}N_3O$.

2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide 9

White crystals from DMSO/H_2O, mp 167.5–169.5 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 0.81 (3H, t, *J* 7.5 Hz, CH_3), 1.23 (2H, m, CH_2), 1.51 (2H, m, CH_2), 2.58 (2H, t, *J* 7.5 Hz, CH_2), 5.18 (2H, s, CH_2CO), 7.07 (1H, t, *J* 7.5 Hz, Ar–H), 7.29 (2H, t, *J* 7.5 Hz, Ar–H), 7.44 (2H, d, *J* 8.5 Hz, Ar–H), 7.76 (1H, s, triazole-H), 10.41 (1H, s, NH); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 14.1, 22.1, 25.6, 31.6, 52.5 (5C, 4 × CH_2, 1 × CH_3), 119.6, 123.9, 124.2, 129.3, 138.8, 147.1 (8C, Ar), 164.8 (1C, C═O); HR-ESIMS: m/z = 259.15527 $[M+H]^+$, calcd. 259.15534 for $C_{14}H_{19}N_4O$.

2-(4-Ethyl-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide 10

White crystals, mp 158–160 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 1.21 (3H, t, *J* 7.5 Hz, CH_3), 2.65 (2H, q, *J* 7.5 Hz, C**H**$_2$CH$_3$), 5.26 (2H, s, CH_2CO), 7.08 (1H, t, *J* 7.5 Hz, Ar), 7.33 (2H, t, *J* 7.5 Hz, Ar), 7.58 (2H, d, *J* 7.5 Hz, Ar), 7.86 (1H, s, triazole-H), 10.4 (1H, s, NH); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 13.7 (CH_3), 18.4, 52.1 (CH_2), 119.2, 123.0, 123.7, 128.9, 138.4, 148.1 (Ar), 164.3 (C═O); HR-ESIMS: m/z = 231.12399 $[M+H]^+$, calcd. 231.12404 for $C_{12}H_{15}N_4O$.

4-Phenyl-1-octyl-1*H*-1,2,3-triazole 11

White crystals, mp 76–78 °C (lit.[38] 74–75 °C). ^{1}H NMR (500 MHz, d_6-DMSO): δ = 0.83 (3H, t, *J* 7 Hz, CH_3), 1.22–1.28 (10H, m, 5 × CH_2), 1.84 (2H, t, *J* 7 Hz, C**H**$_2$CH$_2$N), 4.37 (2H, t, *J* 7 Hz, C**H**$_2$–N), 7.31 (1H, t, *J* 8 Hz, Ar), 7.43 (2H, t, *J* 8 Hz, Ar), 7.83 (2H, d, J 8.5 Hz, Ar), 8.57 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 13.9 (CH_3), 22.0, 25.8, 28.3, 28.5, 29.6, 31.1, 49.5 (8C, 8 × CH_2), 121.2, 125.1, 127.7, 128.8, 130.9, 146.2 (8 C, Ar).

4-Ethyl-1-octyl-1*H*-1,2,3-triazole 12

Yellow solid, mp 37.5–39 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3H, t, *J* 7.0 Hz, $(CH_2)_7$C**H**$_3$), 1.19–1.26 (13H, m, 5 × CH_2, 1 × CH_3), 2.70 (2H, q, ArC**H**$_2$CH$_3$), 4.25 (2H, t, *J* 7.5 Hz, CH_2N), 7.23 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 13.6, 13.9, 18.9, 22.5, 26.4, 28.3, 28.9, 30.2, 31.6, 50.1 (10C, 10 × CH_2), 119.9, 149.6 (2C, Ar); HR-ESIMS: m/z = 210.19646 $[M+H]^+$, calcd. 210.19647 for $C_{12}H_{24}N_3$.

2-(4-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-(*N*-(4-biphenyl))acetamide 13

Colourless crystals, mp 182–183 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 3.91 (3H, s, CH_3), 5.24 (2H, s, CH_2), 7.04 (1H, t, *J* 8.0 Hz, Ar–H), 7.05 (1H, d, *J* 8.0 Hz, Ar–H), 7.31–7.38 (4H, m, Ar–H), 7.39–7.47 (2H, m, Ar–H), 7.62–7.65 (4H, m, Ar–H), 8.16 (1H, dd, *J* 1.5, 7.5 Hz, Ar–H), 8.38 (1H, s, triazole-H); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 42.1, 51.6, 55.5 (3C, 2 × CH_2, 1 × CH_3), 111.5, 119.1, 120.6, 125.5, 126.5, 126.6, 126.7, 127.4, 128.0, 128.8, 128.9, 138.0, 139.0, 139.9, 141.5, 155.3 (20C, Ar), 165.6 (1C, C═O); HR-ESIMS: m/z = 399.18148 $[M+H]^+$, calcd. 399.18155 for $C_{24}H_{23}N_4O_2$.

4-Ethyl-1-((naphthalen-6-yl)methyl)-1*H*-1,2,3-triazole 14

White solid, mp 73.5–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (3H, t, *J* 7.5 Hz, $(CH_2)_7$C**H**$_3$), 2.72 (2H, q, C**H**$_2$CH$_3$), 5.62 (2H, s, CH_2N), 7.21 (1H, s, triazole-H), 7.34 (1H, dd, *J* 1.5, 8.5 Hz, H7), 7.48–7.51 (2H, m, Ar), 7.18 (1H, d, *J* 1.5 Hz, H5), 7.80–7.83 (3H, m, Ar); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 13.5, 19.0 (2C, CH_2CH_3), 54.1 (1C, CH_2N), 120.1, 125.3, 126.5, 126.6, 127.2, 127.7, 127.8, 129.0, 132.3, 133.0, 133.1, 150.2 (12C, Ar); HR-ESIMS: m/z = 238.13385 $[M+H]^+$, calcd. 238.13387 for $C_{15}H_{16}N_3$.

1-(4-Methoxybenzyl)-4-ethyl-1*H*-1,2,3-triazole 15

White solid, mp 65.1–66.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (3H, t, *J* 7.5 Hz, CH_2C**H**$_3$), 2.72 (2H, q, C**H**$_2$CH$_3$), 3.80 (3H, s, OMe), 5.41 (2H, s, CH_2N), 6.88 (2H, d, *J* 9.0 Hz, Ar), 7.15 (1H, s, triazole-H), 7.21 (2H, d, *J* 9.0 Hz, Ar); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 13.6, 19.0 (2C, CH_2CH_3), 53.6, 55.3 (2C, CH_2N, OMe), 114.4, 119.8, 126.9, 129.6, 148.8, 159.8 (8C, Ar); HR-ESIMS: m/z = 218.12877 $[M+H]^+$, calcd. 218.12879 for $C_{12}H_{16}N_3O$.

1,4-*bis*((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzene 16

White crystals from EtOAc/pet. spirit, mp 207–209 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 5.64 (2H, s, CH_2), 7.37 (4H, s, C_6H_4), 7.34–7.30 (2H, m, Ph), 7.44–7.41 (4H, m, Ph), 7.84–7.81 (4H, m, Ph), 8.62 (2H, s, triazole-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ = 52.5 (CH_2), 99.7, 121.3, 125.0, 127.7, 128.2, 128.6, 130.5, 135.8, 146.5 (Ar); HR-ESIMS: m/z = 393.18207 $[M+H]^+$, calcd. 393.18222 for $C_{24}H_{21}N_6$.

1,4-*bis*((4-Butyl-1*H*-1,2,3-triazol-1-yl)methyl)benzene 17

White crystals, mp 168–171 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 0.86 (6H, t, *J* 7.5 Hz, 2 × CH_3), 1.28 (4H, m, C**H**$_2$CH$_2$), 1.53 (4H, m, CH_2CH_3), 2.57 (4H, t, *J* 7.5 Hz, CH_2C═C), 5.51 (2H, s, C**H**$_2$Ar), 7.19 (1H, s, triazole-H), 7.23 (4H, s, C_6H_4); ^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 13.7, 21.7, 24.6, 31.1 (8C, 6 × CH_2, 2 × CH_3), 52.3 (2C, CH_2Ph), 121.9, 128.2, 136.1, 147.3 (10C, Ar); HR-ESIMS: m/z = 353.24484 $[M+H]^+$, calcd. 353.24537 for $C_{20}H_{29}N_6$.

2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide 18

White crystals from EtOAc/pet. spirit, m.p. 179–181 °C. ^{1}H NMR (500 MHz, d_6-DMSO): δ = 2.25 (3H, s, CH_3), 5.26 (2H, s, CH_2), 7.08 (1H, t, *J* 7.5 Hz, Ph), 7.33 (2H, t, *J* 7.5 Hz, Ph), 7.57 (2H, d, *J* 7.5 Hz, Ph), 7.84 (1H, s, triazole-H), 10.4 (1H, s, NH); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 10.4 (CH_3), 52.0 (CH_2), 119.7, 123.7, 123.9, 128.9, 138.4, 141.7 (Ar), 164.3 (C═O); HR-ESIMS: m/z = 239.09031 $[M+Na]^+$, calcd. 239.09033 for $C_{11}H_{12}N_4NaO$.

1-(4-Methoxybenzyl)-4-butyl-1*H*-1,2,3-triazole 19

White solid, mp 72–73.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (3H, t, *J* 7.0 Hz, $(CH_2)_3$C**H**$_3$), 1.30–1.38, 1.57–1.63 (2 × 2H, 2 × m, C**H**$_2$C**H**$_2$CH$_3$), 2.66 (2H, t, *J* 8.0 Hz, CH_2C═C) 3.79 (3H, s, OMe), 5.40 (2H, s, CH_2N), 6.88 (2H, d, *J* 9.0 Hz, Ar), 7.14 (1H, s, triazole-H), 7.20 (2H, d, *J* 9.0 Hz, Ar); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 13.7, 22.2, 25.3, 31.4 (4C, $(CH_2)_3CH_3$), 53.4, 55.2

(2C, CH_2N, OMe), 114.3, 120.2, 126.9, 129.5, 148.8, 159.8 (8C, Ar); HR-ESIMS: m/z = 246.16007 $[M+H]^+$, calcd. 246.16009 for $C_{14}H_{20}N_3O$.

Preparation of 1,4-diphenylbuta-1,3-diyne 20

$[Cu(MeCN)_4]PF_6$ (385 mg, 1.03 mmol) was added to a solution of silver phenylacetylide (214 mg, 1.02 mmol) in pyridine (4.00 ml). The reaction mixture was stirred at 80 °C exposed to air for 18 h. Conc. aq. ammonia (20.0 ml) was added to the mixture followed by stirring for 5 min. The reaction mixture was filtered through filter aid. The aqueous phase was extracted with dichloromethane (3 × 15 ml), washed with conc. aq. ammonia and water, dried ($MgSO_4$) and solvent removed under reduced pressure. Recrystallization (EtOAc/pet. spirit) afforded 1,4-diphenylbuta-1,3-diyne (102 mg, 38%), mp 86–88 °C, lit.[41] 86–87 °C. ^{1}H NMR (500 MHz, d_6-DMSO) δ = 7.33–7.38 (6H, m, Ph), 7.52–7.55 (4H, m, Ph); ^{13}C NMR (125 MHz, d_6-DMSO) δ = 73.9, 81.6 (2C, C≡C), 121.8, 128.4, 129.2, 132.5 (6C, Ph).

Acknowledgements

This work was supported by the Australian Research Council (*via* grants DP1093356 to SJW and DP1096134 to GNK and through the ARC Centre of Excellence in Free Radical Chemistry and Biotechnology), the University of Melbourne and the University of Queensland.

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