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5-exo Atom transfer cyclisation onto alkynes mediated by copper(I) complexes

Andrew J. Clark,^{a,*} Gary M. Battle^a and Andrew Bridge^b

^aDepartment of Chemistry, University of Warwick, Coventry CV4 7AL, UK ^bAventis Pharma Ltd, Rainham Road South, Dagenham, Essex RM10 7XS, UK

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Abstract—Multidentate amine derived copper(I) halide complexes mediate the atom transfer radical cyclisation of 1-halo-Npropargylacetamides. While cyclisation of trichloro- and dichloroacetamide derivatives leads to α , β -unsaturated γ -lactams containing the gem-dihalide functional group, monohaloacetamides give rise to either cyclised atom transfer or reduction products depending upon the solvent and catalyst used. © 2001 Elsevier Science Ltd. All rights reserved.

The use of radical cyclisation protocols to prepare heterocyclic compounds continues to be widespread.^{1,2} Cyclisation onto terminal alkyne functional groups using organostannane methods can be complicated by competing hydrostannation² and with amides significant amounts of *endo* products are often observed.^{2,3} In addition these protocols are terminated under reductive conditions. Functionality can be retained in products if cyclisations are conducted under atom transfer conditions. One of the most popular mediators for atom transfer radical cyclisations is $(Bu_3Sn)_2^4$ and this has been reported to mediate efficient cyclisations onto alkynes.⁵ However, due to the toxicity of tin reagents, alternative mediators are required. While a number of groups have reported that catalytic amounts of copper halide complexes of bipyridine,⁶ N-alkylpyridylimines⁷ or multidentate amines⁸ mediate atom transfer radical cyclisation (ATRC) of a range of haloacetamides onto alkene functional groups; there are very few reports on the application of this type of methodology to cyclisation onto alkynes.⁹ Ghelfi recently reported that attempted cyclisation of 1 using CuCl/TMEDA failed, although no explanation of how the reaction 'failed' was given.^{8b} One problem of this approach is that



Scheme 2.

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terminal alkynes are known to undergo facile oxidative dimerisation and intermolecular coupling reactions at the terminal carbon when subjected to copper halide/ pyridine complexes.¹⁰ In fact, in our hands, the product from reacting **1** in the presence of 1 equivalent of CuCl(**2**) at room temperature overnight was not the desired atom transfer product **3**, but the dimer **4** in 98% yield. In 5-exo ATRC of haloacetamides onto alkenes the nature of the N-substituent often affects the efficiency of the cyclisations. Nagashima et al. reported that efficiencies were highest when tosyl or Boc substituents were used as the N-protecting group.^{6a-b} As a consequence we prepared a range of N-tosyl and N-Boc cyclisation precursors and investigated their ATRC reactions onto alkynes (Scheme 1).¹¹

Initial work focused on the reactions of trichloro- and dichloroacetamide derivatives 5 and 9a-b with CuCl(2). Satisfyingly these substrates underwent cyclisation with 30 mol% of CuCl(2) and no dimerisation products were detected. Cyclisation of the trichloroacetamide 5 at room temperature proceeded relatively slowly (compared to cyclisation of the corresponding alkene derivative) giving a mixture of products in a mass balance of 96% after 24 h. This mixture consisted of the cyclised products 6 (75%) and 7 (11%), N-tosyl amide 8 (3%), as well as a small amount of unreacted starting material (11%) (Scheme 2). Cyclisation of the related dichloroacetamides 9a-b under the same conditions provided much cleaner reactions furnishing only one cyclised product 10a-b without any trace of amide cleaved product 8, although the reactions did not go to completion (giving a 1:1 mixture of product:starting material after 24 h at room temperature—100% mass balance). Stirring 9a with 1 equivalent of CuCl(2) furnished an 8:1 ratio of 10a:9a. The gem dihalide 10a could be converted in to the corresponding aldehyde derivative 11a with aqueous silver nitrate in refluxing THF, thus providing a useful functional group for further synthetic manipulation (Scheme 3). The formation of the two major products can be rationalised by initial atom transfer cyclisation to give vinyl chloride 12 followed by abstraction of a second halogen atom furnishing an allyl radical 13 which then undergoes a second atom transfer reaction to give the observed product 6 (Scheme 4). Alternatively, reduction of 13 (either from the solvent or via the ligand) would give rise to the minor cyclised product 7.

Next we investigated the cyclisation of the less activated monobromoacetamides 14a-b, 18 and 21. Cyclisation of 14a with CuBr(2) in CH₂Cl₂ for 24 h furnished two products, the atom transfer product 15a (E:Z=2:5) as well as the reduced product 16a. Thus the intermediate vinyl radical may undergo either bromine atom transfer to produce 15a or hydrogen atom transfer to give 16a (Scheme 5). As a consequence the ratio of these products could be significantly altered if the reaction was carried out with different solvents or ligand (Table 1). For example, repeating the reaction in benzene gave almost exclusively the atom transfer product 15a, presumably due to the poorer hydrogen atom donating ability of benzene compared to CH₂Cl₂, while the use of a better hydrogen atom donor (e.g. THF) and the ligand 17 lead to 16a as the major product (Table 1). Interestingly, cyclisation of the disubstituted alkyne 18 proceeded to give a 1:1 mixture of (E:Z) isomers of the atom transfer product 19 only (94%), suggesting that



Scheme 4.

Scheme 3.



^a Percentage yield of combined products in brackets.



Scheme 6.



Scheme 7.

the intermediate vinyl radical is less reactive towards hydrogen abstraction than those derived from the corresponding reactions of terminal alkynes 14a-b(Scheme 6). Finally, we investigated the reaction of the deactivated 2-bromo-precursor 21. Reaction with 30 mol% CuBr(2) at room temperature did not lead to any observed reaction. Instead stirring with the more activated ligand system CuBr(17) was required. Even with this more activated catalyst system the reaction only proceeded to 50% conversion after 48 h giving a 1:1 mixture of the two products 22 and 23 in 35% isolated yield (70% based on recovered starting material) (Scheme 7).

In conclusion, we have demonstrated that a range of haloacetamides may undergo 5-exo atom transfer radical cyclisations onto alkynes mediated by CuX(2) or CuX(17) complexes at room temperature. No cyclisation products arising from 6-endo cyclisation were observed in this study for either the terminal or disubstituted alkynes. The relatively slow rate of conversion

(compared to their alkene analogues) is not surprising and often characteristic of cyclisation onto alkynes.^{2,3}

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- 11. Typical procedure is as follows: To a mixture of **14a** (0.1 g, 0.28 mmol) and CuBr (0.012 g, 0.08 mmol) under N_2 was added a solution of **2** (0.015 g, 0.08 mmol) in dry CH₂Cl₂ (2.3 ml). The resulting solution was stirred at ambient temperature for 24 h. The crude mixture was passed through a short silica plug eluting with CH₂Cl₂. After evaporation of the solvent and chromatography **15a** and **16a** were isolated in a combined 96% yield.