Efficient β-lactam synthesis via 4-exo atom transfer radical cyclisation using CuBr(tripyridylamine) complex

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Abstract
The tripyridylamine copper(I) halide complex mediates the atom transfer radical cyclisation of bromo-enamides to give b-latams exclusively with no formation of g-latams. No evidence for γ-lactam products. While cyclisation of trichloro- and dichloro-acetamide 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.

Keywords: Radicals and radical reactions, cyclisations, copper and compounds, alkynes

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 hydrostannation 2 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 3 Sn) 2 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-alkylpyridyllimines 7 or multidentate amines 8 mediate atom transfer radical cyclisation (ATRC) of a range of haloacetamides onto alkeno 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 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. 11
Initial work focused on the reactions of trichloro- and dichloro-acetamide derivatives 5, 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 hrs. 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%). 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 hrs 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. 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. 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 CH$_2$Cl$_2$ for 24 hrs 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. 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 CH$_2$Cl$_2$. 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 the intermediate vinyl radical is less reactive towards hydrogen abstraction than those derived from the corresponding reactions of terminal alkynes 14a-b. 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 hrs giving a 1:1 mixture of the two products 22 and 23 in 35% isolated yield (70% based on recovered starting material).
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.

References

11) Typical procedure is as follows: To a mixture of 14a (0.1g, 0.28mmol) and CuBr (0.012g, 0.08mmol) under N2 was added a solution of 2 (0.015g, 0.08mmol) in dry CH2Cl2 (2.3ml). The resulting solution was stirred at ambient temperature for 24 hrs. 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.
Scheme 5

$14a \quad R = \text{Ts}$

$14b \quad R = \text{Boc}$

Scheme 6

$18$

Scheme 7

$21$

Table 1

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligand</th>
<th>Solvent</th>
<th>$15:16^a$</th>
<th>$15 \ (E:Z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$14a$</td>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>25:1 (96)</td>
<td>2:5</td>
</tr>
<tr>
<td>$14a$</td>
<td>2</td>
<td>C$_6$H$_6$</td>
<td>74:1 (94)</td>
<td>1:4</td>
</tr>
<tr>
<td>$14a$</td>
<td>17</td>
<td>THF</td>
<td>1:20 (95)</td>
<td>1:4</td>
</tr>
<tr>
<td>$14b$</td>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>10:1 (96)</td>
<td>1:2</td>
</tr>
</tbody>
</table>

$^a$ Percentage yield of combined products in brackets

Table 1