Pergamon

Tetrahedron Letters 42 (2001) 4409–4412

TETRAHEDRON LETTERS

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

Andrew J. Clark,[a,*] Gary M. Battle[a] and Andrew Bridge[b]

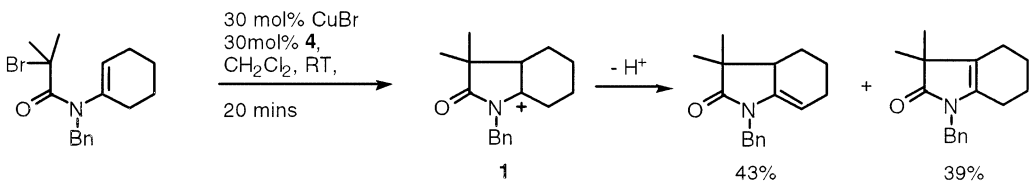
[a]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*
[b]*Aventis Pharma Ltd, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

Received 7 February 2001; accepted 2 May 2001

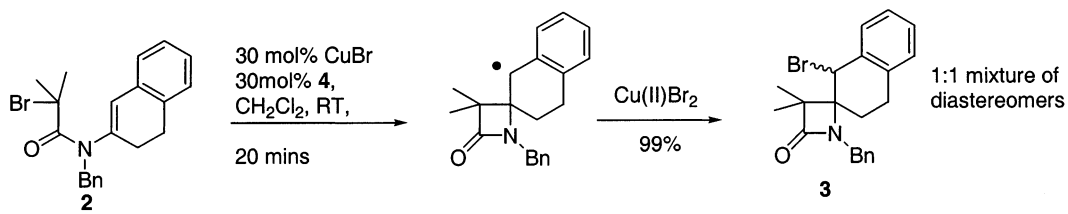
Abstract—The tripyridylamine copper(I) halide complex mediates the atom transfer radical cyclisation of bromo-enamides to give β-lactams exclusively with no formation of γ-lactams. Initial products **7** arise from 4-*exo* bromine atom transfer but elimination can be readily achieved by reaction with DBU to furnish alkenes **8** in high yields (92–98%).

The use of radical cyclisation protocols to prepare heterocyclic compounds continues to be widespread.[1,2] Cyclisation using stannane methods, although still popular, suffers from many problems including the toxicity of the reagent itself and the difficulty in reaction work-up procedures. While a number of groups have reported that catalytic amounts of ruthenium halides,[3] copper halide complexes of bipyridine,[4] *N*-alkylpyridylimines,[5] TMEDA,[6] multidentate amines and multidentate pyridines[7] mediate 5-*exo* 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 4-*exo* versus 5-*endo* cyclisation onto enamides.[8,9] In all these examples the substrates contained functionality at the α-carbon of the enamide and, in general, an oxidative 5-*endo* cyclisation was observed, with products arising not from atom transfer but from pathways postulated to arise via *N*-acyl iminium ions **1** (Scheme 1). Products arising from β-lactams **3** were only detected if the radical was stabilised (i.e. cyclisation of **2**)[8] (Scheme 2).

Consequently, we were interested in investigating the cyclisation of enamides that were substituted at the terminal end of the alkene only. We recently reported



Scheme 1.

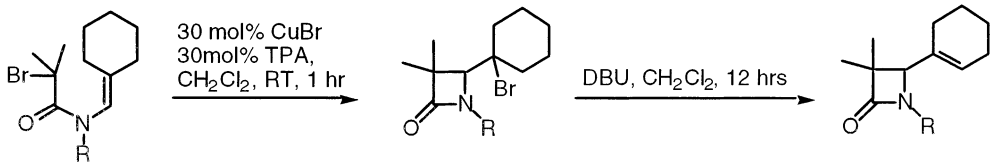


Scheme 2.

Keywords: radicals and radical reactions; cyclisations; copper and compounds.
* Corresponding author.

PII: S0040-4039(01)00737-7

Table 1. Yield of cyclisation and elimination reactions

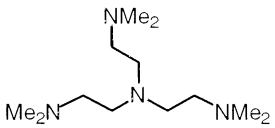


6a-e **7a-e** **8a-e**

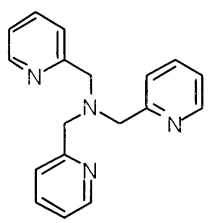
6	R	Yield 7 (%)	Yield 8 (%)
a	Bn	96	94
b	PMB	98	92
c	*t*-Bu	0[a]	–[b]
d	*i*-Bu	98[c]	–[b]
e	*o*-BrBn	98	98

[a] No reaction.
[b] Elimination not attempted.
[c] Reaction took 2 h to go to completion.

that the nature of the ligand in copper(I) mediated atom transfer cyclisations can have a dramatic effect upon the rate of atom transfer cyclisation reactions. Thus, the tetradentate ligands **4** and **5** were found to be the most active in simple 5-*exo* radical cyclisations[7] allowing reactions to be carried out under milder conditions (room temperature or below) than existing copper–bipyridine,[4] copper–TMEDA,[6] or $RuCl_2(PPh_3)_3$ technologies[3] (refluxing toluene). In this letter we describe an investigation into the 4-*exo* cyclisation of enamides containing β-substitution only. In this way we hoped to impede the rate of any competing 5-*endo* cyclisation. In addition, the use of highly activated atom transfer catalysts at low temperatures would also be expected to facilitate reaction to give the kinetic 4-*exo* products.



4



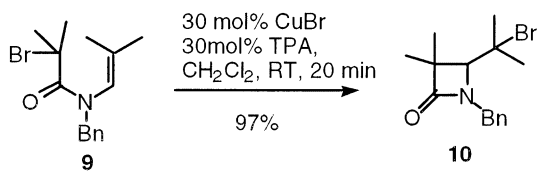
5

In 5-*exo* ATRC of haloacetamides onto alkenes the nature of the *N*-substituent often affects the efficiency of the cyclisations. Thus, we prepared a range of enamides in which we initially varied the *N*-alkyl substituent (see Table 1) to ascertain if this would have any effect on the cyclisation.

Hence, reaction of the substrates **6a–e** with 30 mol% CuBr and 30 mol% **5** (TPA) in CH_2Cl_2 at room temperature for 1 h followed by work-up by passing through a silica plug furnished the bromo 4-*exo* atom transfer products **7a–e** in high yields.[10] No products arising from 5-*endo* cyclisation or reduction of the initial radical were detected. However, the cyclisations of **6d–e** (2 h) were slower than both **6a–b** indicating that the steric bulk of the *N*-alkyl group plays a role in determining the rate of the cyclisation, indeed the substrate with the most hindered *N*-alkyl group (compound **6c**) did not undergo cyclisation at all (even after 12 h at reflux). The synthetic utility of the process could be expanded by manipulation of the tertiary bromides **7** to the corresponding alkenes **8**. Thus stirring the bromides **7** with one equivalent of DBU in CH_2Cl_2 at room temperature for 12 h furnished the elimination products **8** again in excellent (92–98%) yields.

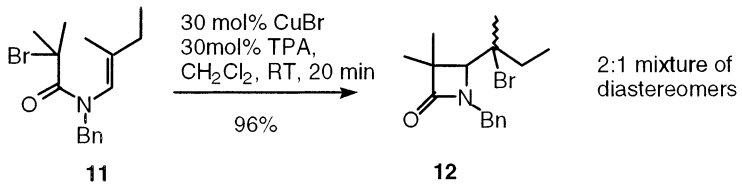
Having investigated the effect of the *N*-substituent we next turned our attention to the effect of the substituents on the enamide itself. We were encouraged to discover that cyclisation of both **9** and **11** were facile giving rise to the expected bromo-functionalised products **10** and **12**, respectively (Schemes 3 and 4) (with **12** being produced as an inseparable 2:1 mixture of diastereomers).

Interestingly, it was not possible to cyclise the monosubstituted precursor **13** even after extended reaction times and at reflux. Only starting material was recovered and no reduction was detected (Scheme 5). Next, we investigated the cyclisation of the secondary bromide **14** (Scheme 6). Cyclisation of secondary halides using atom transfer is often quite difficult and elevated temperatures are often required, even with the activated ligands **4–5**. In our hands, heating the substrate **14** in refluxing CH_2Cl_2 did not lead to any reaction and only starting material was recovered. However, heating at a higher temperature in refluxing toluene for 24 h gave a 2.8:1 mixture of diastereomers **15** in 82% yield. Interestingly elimination of the tertiary bromide



9 **10**

Scheme 3.

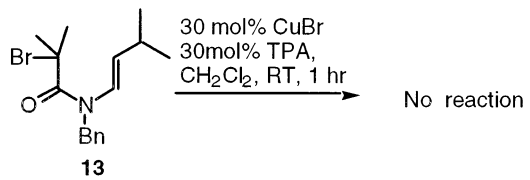


Scheme 4.

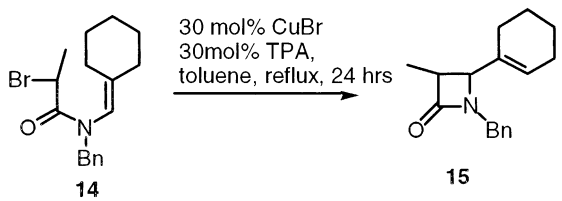
occurred under the reaction conditions giving rise to the alkene **15** directly without the need for DBU mediated elimination. Reaction of the chiral substrate **16** was next examined. Cyclisation occurred as expected to give a 0.8:1 ratio of diastereomers of the bromide **17** (Scheme 7).

Finally, we investigated the cyclisation of the substrate **18** containing a cyclopentyl ring appended to the alkene. This too underwent exclusive cyclisation to give the β-lactam **19** in 99% yield (Scheme 8).

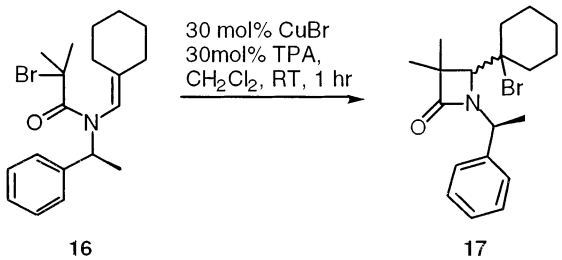
In conclusion, we have demonstrated that cyclisation of terminally substituted enamides using catalytic quantities of CuBr (**5**) furnishes bromo-β-lactams in excellent



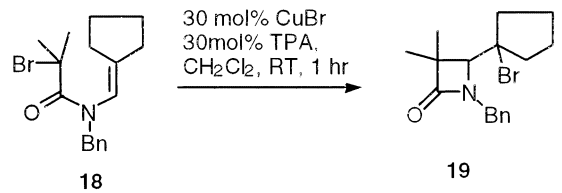
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

yields (82–99%) under mild conditions via a 4-*exo* atom transfer radical cyclisation. No products arising from 5-*endo* cyclisation or reduction of the original radical precursors were detected. The efficient formation of the β-lactams deserves some comment. It is generally accepted that the 4-*exo* products are the kinetically derived products while those arising from 5-*endo* cyclisation are thermodynamically favoured. The ratio of 4-*exo* to 5-*endo* products in Bu_3SnH mediated cyclisations of related precursors has been shown to be temperature dependant with lower temperatures favouring the kinetic 4-*exo* product.[11] In this work the effect of cyclising onto terminally substituted enamides (which will sterically impede 5-*endo* cyclisation), in conjunction with the use of a very active atom transfer catalyst that allows rapid trapping of the intermediate radicals at ambient temperature both favour the production of the kinetic β-lactam products. Interestingly, even at 110°C in toluene, compound **14** furnished the 4-*exo* product exclusively highlighting the efficient nature of the atom transfer catalyst used in trapping out the intermediate cyclised radical.

Acknowledgements

We acknowledge support for this research from both the EPSRC and Aventis Pharma Ltd, (EPSRC Industrial CASE award for G. M. Battle).

References

1. Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1.
2. (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301; (b) Curran, D. P.; Sisko, J.; Yeske, P. E.; Liu, H. *Pure Appl. Chem.* **1993**, *65*, 1153; (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
3. (a) Pirrung, F. O. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 12415; (b) Rachita, M. A.; Slough, G. A. *Tetrahedron Lett.* **1993**, *43*, 6821; (c) Slough, G. *Tetrahedron Lett.* **1993**, *43*, 6825; (d) Hayes, T.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533; (e) Phelps, J. C.; Bergbreiter, D. E.; Lee, G. M.; Villani, R.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3915; (f) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281; (g) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, M.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.

4. (a) Udding, J. H.; Tuijp, K. C. J. M.; Vanzanden, M. N. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 1993; (b) Udding, J. H.; Tuijp, K. C. J. M.; Vanzanden, M. N. A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 1907; (c) Baldovini, N.; Bertrand, M.-P.; Carrière, A.; Nougier, R.; Plancher, J. M. *J. Org. Chem.* **1996**, *61*, 3205; (d) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625.
5. (a) Clark, A. J.; Filik, R. P.; Thomas, G. H. *Tetrahedron Lett.* **1999**, *40*, 4885; (b) Clark, A. J.; Duncalf, D. J.; Filik, R. P.; Haddleton, D. M.; Thomas, G. H.; Wongtap, H. *Tetrahedron Lett.* **1999**, *40*, 3807; (c) Clark, A. J.; Filik, R. P.; Haddleton, D. M.; Radique, A.; Sanders, C. J.; Thomas, G. H.; Smith, M. E. *J. Org. Chem.* **1999**, *64*, 8954.
6. (a) Forti, L.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.* **1996**, *37*, 2077; (b) Forti, L.; Ghelfi, F.; Libertini, E.; Pagnoni, U. M.; Soragni, E. *Tetrahedron* **1997**, *53*, 17761; (c) Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A.; DeBuyck, D.; Parsons, A. F. *Tetrahedron* **1999**, *55*, 1687.
7. (a) De Campo, F.; Lastécouères, D.; Verlhac, J.-B. *Chem. Commun.* **1998**, 2117; (b) Clark, A. J.; De Campo, F.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastécouères, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, *1*, 671.
8. Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619. For the use of organocobalt complexes in the preparation of β-lactams, see: (a) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *Chem. Commun.* **1994**, 369; (b) Pattenden, G.; Reynolds, S. J. *Chem. Commun.* **1994**, 379; (c) Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1991**, *32*, 259.
9. Davies, D. T.; Kapura, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615. For the use of other non-tin methods for the preparation of β-lactams, see: Jackson, L. V.; Walton, J. C. *Chem. Commun.* **2000**, 2327.
10. All new compounds exhibited satisfactory spectroscopic and analytical data.
11. Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763.