Pergamon

Tetrahedron Letters 42 (2001) 2901–2905

TETRAHEDRON LETTERS

The synthesis of functionalised β- and γ-lactams by cyclisation of enamides using copper(I) or ruthenium(II)

Justin S. Bryans,[a] Nicola E. A. Chessum,[b] Andrew F. Parsons[b,*] and Franco Ghelfi[c]

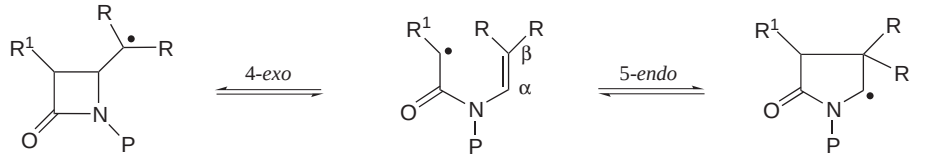
[a]*Pfizer Global Research and Development, Forvie Site, Robinson Way, Cambridge CB2 2QB, UK*
[b]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[c]*Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41100 Modena, Italy*

Received 25 January 2001; accepted 21 February 2001

Abstract—Cyclisation of a variety of halo-enamides with copper(I) or ruthenium(II) complexes has been investigated. The regioselectivity of the radical cyclisation, which can proceed via either a 4-*exo* or 5-*endo* pathway, to form β- or γ-lactam products respectively, is determined by the nature of the metal oxidant and the reaction conditions. Thus, whereas copper(I)/bipyridine reactions give predominantly γ-lactams, the use of copper(I)/TMEDA or dichlorotris(triphenylphosphine)ruthenium(II) affords mainly β-lactams. © 2001 Elsevier Science Ltd. All rights reserved.

Radical cyclisation of unsaturated organohalides to form *N*-heterocycles has attracted considerable synthetic interest in recent years.[1] A wide variety of five- and six-membered rings in particular, can be prepared under mild reaction conditions using a variety of cyclisation methods. For example, γ-lactams can be prepared from tributyltin hydride-mediated cyclisation of *N*-allyl or *N*-vinyl (enamide) halo-amides, by 5-*exo*[2] or 5-*endo*[3] pathways, respectively (Scheme 1). The 5-*endo*-*trig* cyclisation of halo-enamides is intriguing because the initial carbamoylmethyl radical **1** prefers to form γ-lactam **2** rather than undergo the more favourable 4-*exo*-*trig* cyclisation leading to β-lactam **3**. Indeed, the 4-*exo*-*trig* reaction is generally only observed when bulky radical-stabilising (e.g. R = aromatic) groups are introduced on the β-position of the enamide double bond. These R groups can stabilise β-lactam radical **2** (by electronic effects) and also hinder attack at the β-position of carbamoylmethyl radical **1** (by steric effects).[4] The R^1 substituents are also important and, for example, the introduction of radical stabilising groups at this position favours the formation of γ-lactam radical **2**.[5] These results have been explained on the basis of a reversible cyclisation mechanism; the 4-*exo* cyclisation produces the kinetically favoured β-lactam while the 5-*endo* cyclisation produces the thermodynamically more stable γ-lactam.[5]

As part of a programme to develop alternative radical reagents to tributyltin hydride, we recently reported the cyclisation of enamides using copper(I) chloride/bipyridine or dichlorotris(triphenylphosphine)ruthenium(II).[6,7] Hence, cyclisation of chloro-enamides such as **4** was observed to give dienes in excellent yield by a 5-*endo* radical cyclisation (Scheme 2). No β-lactams were isolated from these reactions, which were pro-

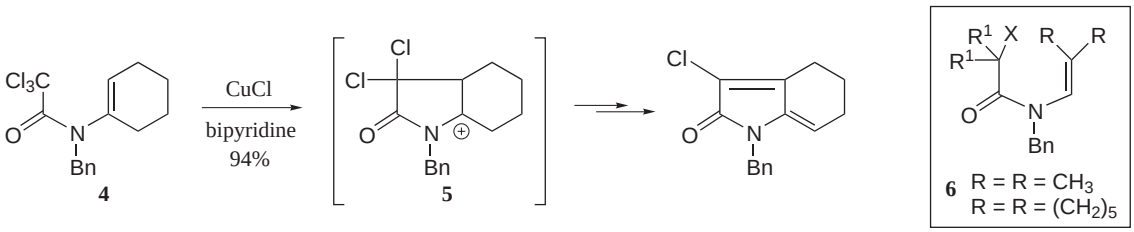


kinetic product **3** — **1** — *thermodynamic product* **2**

Scheme 1.

Keywords: copper and compounds; lactams; radicals and radical reactions; ruthenium and compounds.
* Corresponding author. Tel.: +44-1904-432608; fax: +44-1904-432516; e-mail: afp2@york.ac.uk

PII: S0040-4039(01)00320-3

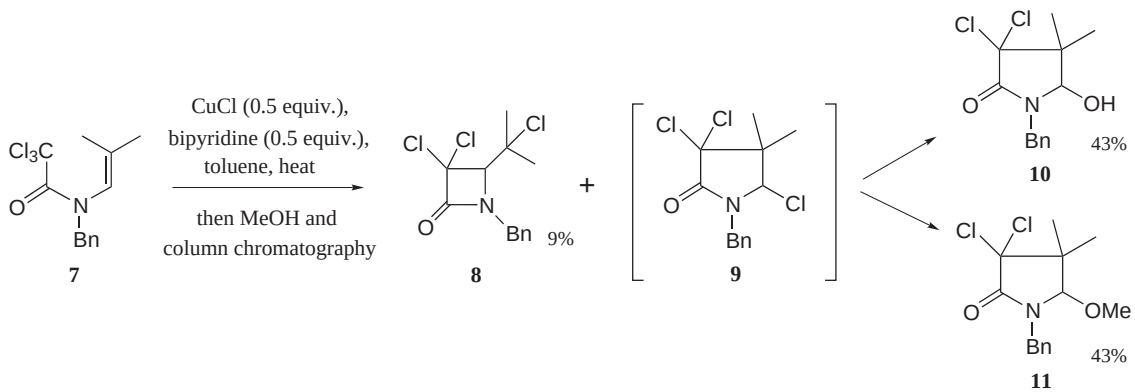


Scheme 2.

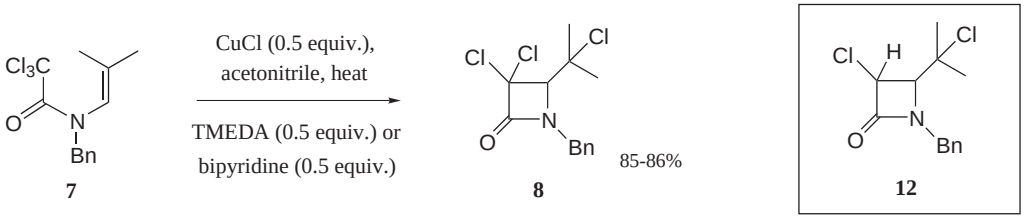
posed to involve deprotonation of an intermediate *N*-acyliminium ion of type **5**. With a view to increasing the generality and flexibility of this cyclisation method, as well as probing the mechanism of these types of reaction, we now report the novel cyclisation of enamides of type **6** using copper(I) or ruthenium(II) complexes. These enamides possess some important structural features. To encourage 4-*exo* cyclisation they contain two β-substituents and to prevent deprotonation of an intermediate *N*-acyliminium ion they have no α-substituent.[8]

Our preliminary work focused on the cyclisation of trichloro-enamide **7** [prepared by *N*-acylation of the imine derived from benzylamine and isobutyraldehyde] using copper(I) chloride/bipyridine in boiling toluene (Scheme 3).[9] After heating overnight and (acidic) workup, the ^{1}H NMR spectrum of the crude reaction mixture showed the complete disappearance of starting material and the clean formation of β-lactam **8** and γ-lactam **9**. This reaction was carried out a number of times and on each occasion γ-lactam **9** was the major product, although the ratio of **9**:**8** did vary from 9.6 to 2.6:1. Purification of the crude product using column chromatography (on silica) resulted in the hydrolysis of α-chloro-γ-lactam **9** to give α-hydroxy-γ-lactam **10**, while reaction with methanol gave α-methoxy-γ-lactam **11**. Hence when **7** was reacted with copper(I) chloride/bipyridine (0.5 equiv./0.5 equiv.) and the crude product stirred with methanol (for 24 h at rt), column chromatography afforded **8**, **10** and **11** in 9, 43 and 43% yields, respectively. It should be noted that **11** is converted to **10** on column chromatography. This was indicated by the ^{1}H NMR spectrum of the crude product, which showed a 6.7:1 ratio of **11**:**10** prior to chromatography.

Interestingly, when trichloro-enamide **7** was reacted with copper(I) chloride/bipyridine (0.5 equiv./0.5 equiv.) or copper(I) chloride/TMEDA (0.5 equiv./0.5 equiv.) in boiling acetonitrile, only β-lactam **8** was formed in 85–86% yield (Scheme 4). The crude ^{1}H NMR spectra showed no evidence for the formation of γ-lactam **9**. It should be noted, however, that an



Scheme 3.



Scheme 4.

increase in the number of equivalents of the copper(I) chloride/TMEDA complex did result in the formation of an alternative product. Hence when **7** was heated with 1 equivalent of copper(I) chloride and 2 equivalents of TMEDA in acetonitrile, β-lactam **8** together with dichloro-β-lactam **12** were formed in 60 and 31% yields, respectively.

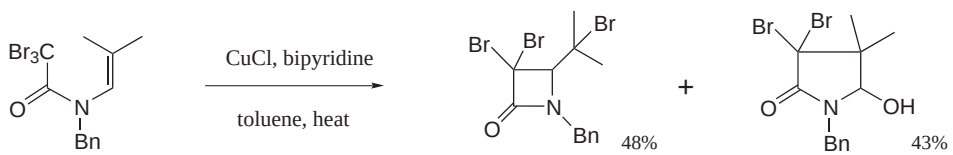
The change in the regioselectivity of the cyclisation can be rationalised by a reversible mechanism[8] in which the β-lactam is the kinetic product and the γ-lactam is the thermodynamic product (Scheme 1). Hence, 4-*exo* cyclisation of radical **1**, to give **3**, is expected to be faster than 5-*endo* cyclisation leading to **2**. The copper(I) complexes are soluble in acetonitrile and so the formation of a tertiary radical of type **3** is expected to be followed by rapid oxidation to form the β-lactam product. However, the copper(I) chloride/bipyridine complex is much less soluble in toluene. As a consequence, the rate of oxidation of **3** is expected to be slower and so equilibration to the more stable radical **2** can take place prior to oxidation leading to a predominance of the γ-lactam product. Further evidence for this mechanism came from reacting **7** with only 0.1 (rather than 0.5) equivalents of copper(I) chloride/bipyridine in boiling toluene. Lowering the copper(I) concentration was expected to facilitate radical equilibration leading to the predominant formation of the thermodynamically favoured (γ-lactam) products. Indeed, after heating for 22 h, only γ-lactams **9** and **10** were formed in 59 and 9% yields, together with unreacted starting material (18%), as determined from the ^{1}H NMR spectrum.

Steric effects also influence the regioselectivity as illustrated by the cyclisation of tribromide **13** (Scheme 5). After heating **13** with copper(I) chloride/bipyridine (0.5 equiv./0.5 equiv.) for 2 h in toluene, β-lactam **14** and γ-lactam **15** were isolated in 48 and 43%, respectively, after column chromatography. The introduction of bromine rather than chlorine substituents (at the site of radical generation) therefore leads to an increase in the amount of β-lactam product. This is presumably because of steric interaction between the (bulky) bromine substituents and a terminal methyl substituent, which lowers the rate of 5-*endo* cyclisation.[10]

The effect of introducing a cyclohexyl group at the terminus of the alkene double bond (in place of the dimethyl substituents) was also investigated (Scheme 6). Thus, heating trichloride **16** with copper(I) chloride/bipyridine (0.5 equiv./0.5 equiv.) in toluene for 12 h afforded predominantly γ-lactam **18** (in an excellent 81% yield) after column chromatography. As for trichloride **7**, the use of copper(I) chloride/bipyridine in toluene therefore leads to a predominance of the thermodynamically more stable γ-lactam.

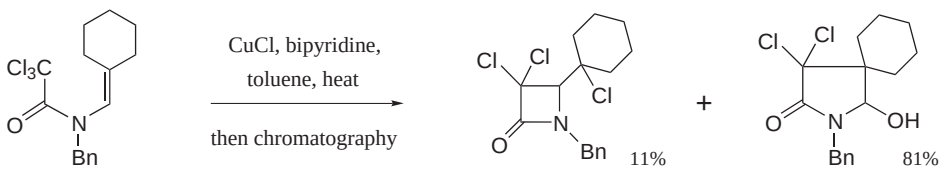
For comparison, the cyclisation of halo-enamides **7**, **19** and **20** with dichlorotris(triphenylphosphine)-ruthenium(II) was also carried out (Scheme 7). For each of these reactions, the main (or exclusive) product was a β-lactam. For example, cyclisation of trichloroenamide **7** gave a combined 48% yield of β-lactams **8** and **21** and only a 17% yield of γ-lactam **10**. When using bromides **19** and **20**, excellent yields of unsaturated β-lactams **23** and **25** were isolated, presumably resulting from bromine atom transfer followed by elimination of hydrogen bromide. This can be compared to the corresponding copper(I) chloride/bipyridine mediated cyclisation of **19**, which gave β-lactam **23** in 36% yield and γ-lactam **24** in 26% yield. The predominance of β-lactams over γ-lactams using the ruthenium(II) complex can be rationalised in a similar way to the copper(I)/acetonitrile reactions. Hence, the ruthenium-(II) complex is soluble in boiling toluene and so the intermediate β-lactam radical (of type **3**) is expected to be rapidly oxidised.

This work has shown that halo-enamides of type **6** can undergo both 4-*exo* and 5-*endo* radical cyclisations to form a variety of highly substituted β- and γ-lactams using copper(I) or ruthenium(II). The use of copper(I) or ruthenium(II) has a number of advantages over related cyclisation methods including nickel/acetic acid[8] or tributyltin hydride.[4,5] This includes mild reaction



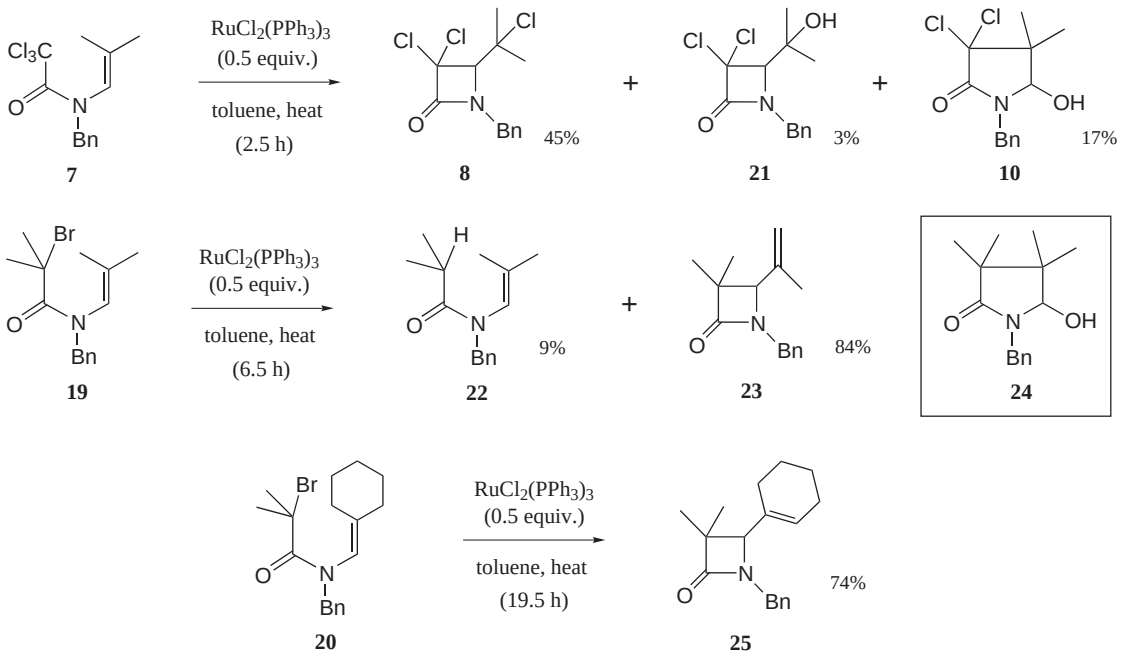
13 **14** **15**

Scheme 5.



16 **17** **18**

Scheme 6.



Scheme 7.

conditions, efficient conversions, simple purification of products and the ability to easily change the regioselectivity of the cyclisation by varying the reaction solvent and the nature of the redox catalyst. Thus, although we found that **7** could be efficiently cyclised to *N*-benzyl-β-isopropyl-β-lactam (18%) and *N*-benzyl-β,β-dimethyl-γ-lactam (58%) using tributyltin hydride (1.1 equivalent added over 1 h followed by immediate addition of 2.2 further equivalents), this required high dilution conditions and rigorous purification to remove the tin residues. The use of copper(I) or ruthenium(II) also produces highly functionalised lactams bearing halogen or alkene functional groups. The formation of highly substituted/sterically congested γ-lactams is particularly noteworthy and these types of compounds could act as precursors to, for example, *N*-acyliminium ions.[11] Further studies directed towards the application of this methodology in amino acid synthesis are currently underway.

Acknowledgements

We thank Parke-Davis/Pfizer (Cambridge) and the BBSRC for funding.

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