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Efficient room temperature copper(I) mediated 5-*endo* radical cyclisations

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Abstract

Reaction of bromo-enamides with catalytic Cu(Me_6-trien)Br at room temperature furnishes regioisomeric mixtures of unsaturated pyrrolidinones in a highly efficient manner via an initial 5-*endo* radical cyclisation reaction followed by an oxidation and elimination of H^+. Bromo-enamide **3f** furnishes the β-lactam via a 4-*exo* cyclisation pathway.

Keywords: radicals; radical reactions; cyclisations; copper; copper compounds; enamides.

In recent years, the growth of transition metal mediated free radical processes has gained in importance.[1] In particular the atom transfer radical cyclisation reactions (ATRC) of 2,2,2-trichlorinated carbonyl compounds have been reported with a range of metal catalysts. By far the most popular methods to mediate atom transfer cyclisations have been those utilising CuCl(bpy)[2] or CuCl(TMEDA)$_2$.[3] The majority of published atom transfer radical cyclisation reactions have involved the 5-*exo* cyclisation of trichloro- or dichloro-acetamides and acetates at elevated temperatures.[2,3] The use of CuCl(bpy)[4] and CuCl(*N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine)[5] to make medium sized rings via 8–10-*endo* cyclisations has also been reported. While there are a number of Bu_3SnH mediated 5-*endo* cyclisations in the literature[6] there are very few reports of cyclisations under atom transfer conditions proceeding in the 5-*endo* mode. Zard has recently reported that by using Ni powder in refluxing AcOH and *i*PrOH[7] (typical atom transfer conditions) trichloroacetamides can undergo an unexpected 5-*endo* cyclisation followed by double elimination of HCl (Scheme 1).

We recently reported that complexes derived from copper halides and ligands **1** and **2** (Me_6-trien) were active catalysts for mediating the 5-*exo* atom transfer radical cyclisation of activated trichloro-, dichloro- and monohalo-acetamides at room temperature.[8] As a consequence, we investigated whether these new catalysts could also be used to mediate efficient atom transfer 5-*endo* cyclisations of halo-acetamides at room temperature.

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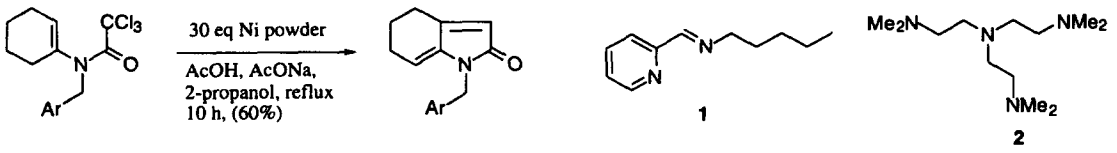
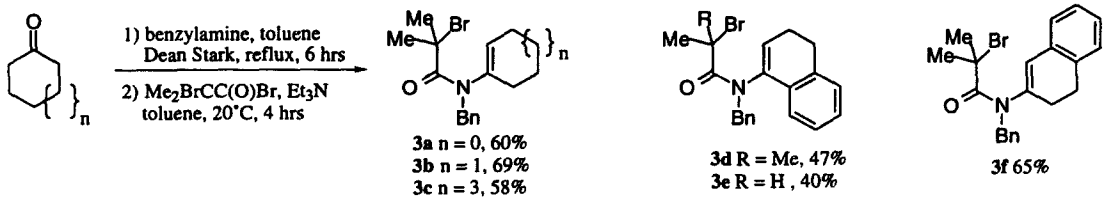
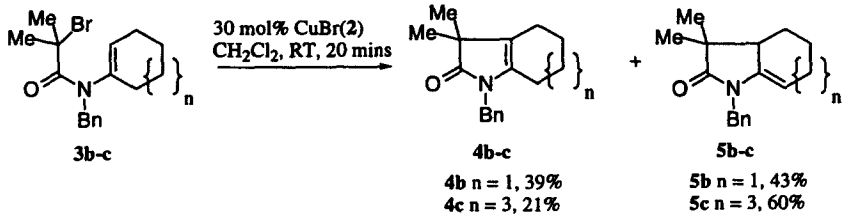


Scheme 1.

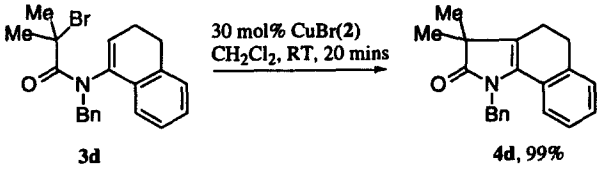
Condensation of either cyclopentanone, cyclohexanone, cyclo-octanone, 1-tetralone or 2-tetralone with benzylamine followed by acylation with 2-bromo-2-methylpropanoyl bromide afforded the monobromoacetamide precursors **3a–d**, and **3f**, respectively (Scheme 2).[9] Acylation of the benzyl imine derived from cyclohexanone with 2-bromopropanoyl bromide furnished the secondary halide precursor **3e**. We had previously reported that 5-*exo* cyclisation of tertiary monobromoacetamides mediated by the CuBr(**2**) complex was rapid at room temperature (less than 15 min)[8] and consequently we initially investigated similar conditions in the 5-*endo* cyclisation of **3a–f**. Hence, to each of the precursors **3a–f** in CH_2Cl_2 at room temperature was added 30 mol% of CuBr and 30 mol% of ligand **2**.[10] The reactions proceeded rapidly and were complete after only 20 min at room temperature with the exception of the reaction of **3e** which did not undergo cyclisation even after 12 h heating at 80°C in 1,2-dichloroethane. In this case only starting material was re-isolated. While the reaction of **3a** gave a complex mixture of unidentified products the other substrates **3b–e** gave excellent yields of the alkene products shown (Schemes 3 and 4).



Scheme 2.



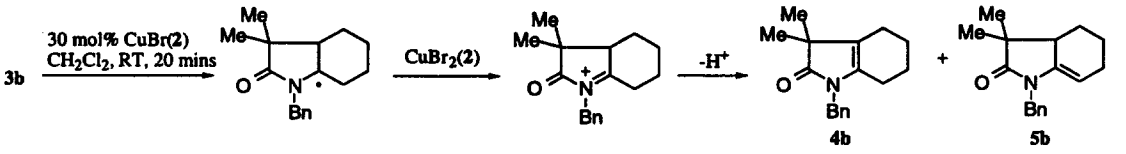
Scheme 3.



Scheme 4.

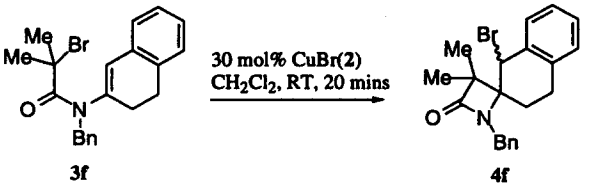
Presumably initial radical formation and 5-*endo* cyclisation is followed by rapid oxidation of the heteroatom stabilised radical to a cation by the $CuBr_2$(**2**) formed in the initial step (Scheme 5).[7a] Elimination of H^+ from the cation can then furnish the observed alkene products. Interestingly, the

overall process represents a formal 'Heck type' cyclisation albeit using substrates that would not normally undergo a palladium mediated Heck process.

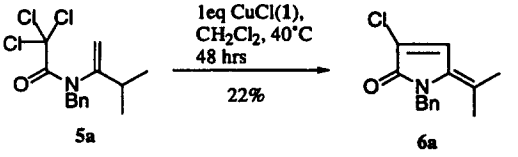


Scheme 5.

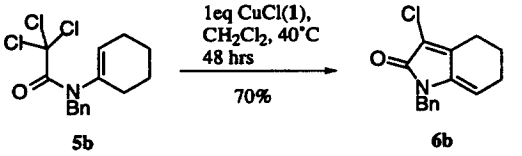
Cyclisation of the 2-tetralone derived precursor **3f** proceeded in a 4-*exo* fashion to give the atom transfer product **4f** as a 1:1 mixture of diastereomers in 99% yield (Scheme 6). Presumably 4-*exo* cyclisation is favoured due to the formation of an intermediate stabilised benzylic radical which then undergoes atom transfer to furnish the observed mixture of diastereomers. The fact that it was possible to cyclise the monobromoacetamides **3b–f** so readily was unexpected and we next examined the cyclisation of the more activated trichloroacetamide substrates **5a–b**. To our suprise when we attempted to cyclise both these substrates using CuCl(**2**) the reactions were extremely slow. In fact stoichiometric amounts of catalyst were required in order to drive the reactions to completion. Unfortunately, we obtained only complex mixtures of unidentified products in both cases. On the other hand if we conducted the reaction with a stoichiometric amount of the less activated atom transfer catalyst based upon the CuCl(**1**) at 40°C it was possible to get low yields of cyclised products **6a–b** (22% and 70%, respectively, see Schemes 7 and 8). In both cases the products arose from cyclisation followed by loss of two equivalents of HCl. This diene formation has been reported for related CuCl(bipyridine) mediated 5-*endo* cyclisations.[11]



Scheme 6.



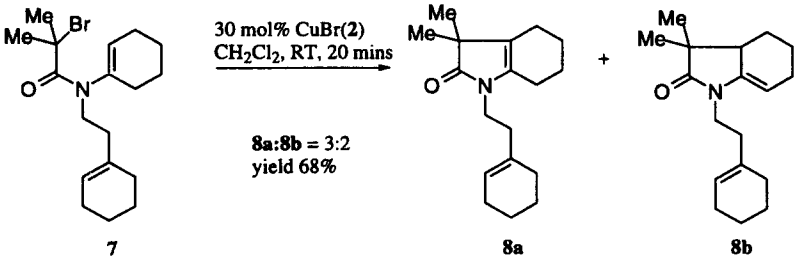
Scheme 7.



Scheme 8.

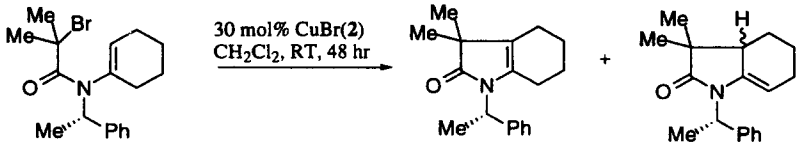
Assuming that the reactions proceed via a formal radical–polar crossover mechanism (Scheme 5), and that cationic intermediates were involved we investigated whether it was possible to mediate a tandem cyclisation via an initial 5-*endo* radical cyclisation of **7** followed by a second electrophilically triggered 5-*exo* cyclisation. Unfortunately, attempts to facilitate this tandem reaction using CuBr(**2**) led only to a mixture of regioisomeric products **8a** and **8b** arising from monocyclisation only (Scheme 9). Recently

an asymmetric synthesis of (−)-γ-lycorane has been reported using a Bu_3SnH mediated 5-*endo* radical cyclisation in which a chiral auxiliary (α-methylbenzylamine) was attached to the nitrogen atom.[12] This prompted us to investigate the cyclisation of the chiral derivative **9** (Scheme 10). Cyclisation at room temperature was slow relative to the other cyclisations (48 h) and gave the two regioisomers (**10**:**11**) as expected (1:1 ratio) with the latter as a 1.9:1 mixture of diastereomers.



7 **8a** **8b**

Scheme 9.



9 **10** **11**

Scheme 10.

In conclusion we have demonstrated that highly efficient room temperature 5-*endo* radical cyclisations of bromo-enamides can be mediated by the CuBr(**2**) complex. Good yields of β-lactams (99%) can be produced if the intermediate cyclised radical is particularly stabilised.

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9. All new compounds exhibited satisfactory spectroscopic and analytical data.
10. A typical experimental procedure is as follows. To the substrate (0.3 mmol) in dichloromethane (2.5 ml) at room temperature under nitrogen was added tris-[2-(dimethylamino)ethyl]amine (0.09 mmol) and CuBr (0.09 mmol). The mixture was stirred at room temperature for 20 min and the crude mixture was filtered through silica and evaporated to dryness.
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