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Copper(I) reactions in *N*-heterocycle synthesis: efficient preparation of substituted pyrrolidinones

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Abstract

Reaction of halo-enamides with copper(I) chloride in boiling toluene has been shown to produce unsaturated pyrrolidinones in excellent yield (81–94%). Both di- and trichloroamide precursors can be used to form dienes via an initial 5-*endo*-trig radical cyclisation. © 1999 Elsevier Science Ltd. All rights reserved.

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Copper(I)-based halogen atom transfer reactions, particularly cyclisations, have attracted considerable interest in recent years.[1] This method can offer a number of advantages over alternative reductive methods for mediating free-radical processes e.g. using Bu_3SnH or $HSi(SiMe_3)_3$ and AIBN. These include: (i) only a catalytic amount of copper(I) is required; (ii) copper(I) chloride is inexpensive; (iii) the metal catalyst can be easily removed and (iv) a halogen functional group is introduced after carbon–carbon bond formation. These atom transfer cyclisations involve a redox reaction between copper(I) and (II) oxidation states. Electron transfer from copper(I) chloride to the substrate generates a carbon-centred radical which can then cyclise to give a new (more reactive) carbon radical that reacts with copper(II) chloride. This regenerates copper(I) chloride and forms a cyclic product containing a versatile chlorine atom. Reactions are generally carried out in the presence of amines, such as bipyridine, that coordinate and solubilise the copper(I) chloride and alter the redox potential so that reactions can be carried out at reasonable temperatures (<150°C).[2] The most commonly used precursors for copper(I)/bipyridine-based cyclisations are polyhalogenated compounds with a weak carbon–chlorine bond and, for example, unsaturated trichloroamides have been shown to cyclise in a 5-*exo*-trig manner to give trichlorinated pyrrolidinones.[2,3] These studies prompted us to explore the formation of substituted pyrrolidinones via a 5-*endo*-trig cyclisation of halo-enamides. Previous work had shown that Bu_3SnH,[4] Ni/AcOH[5] or $Mn(OAc)_3$[6] could be used to mediate this unusual (disfavoured) cyclisation process but the use of copper(I) has not previously been reported.[7]

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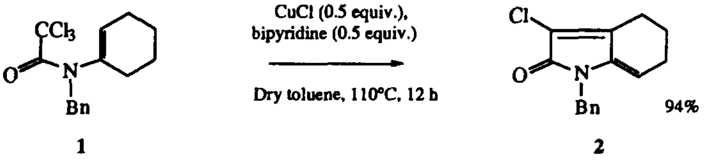
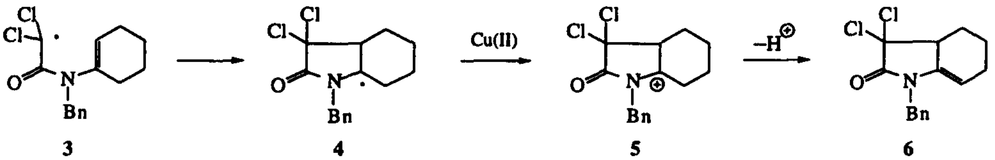
Initial studies centred on the cyclisation of trichloro-enamide **1** which was formed on acylation of the enamine derived from cyclohexanone and benzylamine (Scheme 1).[8] Reaction of **1** with 0.25 equivalents of copper(I) chloride/bipyridine in boiling toluene resulted in the formation of diene **2** in 83% yield together with some unreacted starting material (4%). When the equivalents of copper(I) chloride/bipyridine were increased to 0.5, complete consumption of **1** was observed to give **2** in an excellent 94% yield. The formation of a diene[9] can be explained by a mechanism involving initial 5-*endo* cyclisation of carbamoylmethyl radical **3** to form tertiary radical **4** (Scheme 2). Related manganese(III)[6] and nickel[5] reactions have shown that these types of radical are very susceptible to oxidation and electron transfer to copper(II) could yield the *N*-acyliminium ion **5**. Deprotonation of **5** could give rise to enamide **6** and this can produce diene **2** on loss of HCl (which could be mediated by the bipyridine). This sequence requires only a catalytic amount of the copper(I) complex as the copper(II), formed on generation of **3**, is reduced back to copper(I) on reaction with radical **4**. It is not clear why more than 0.25 equivalents of the copper(I) complex is required although the formation of **2** requires the loss of HCl and this may well disrupt the redox cycle.



Scheme 1.



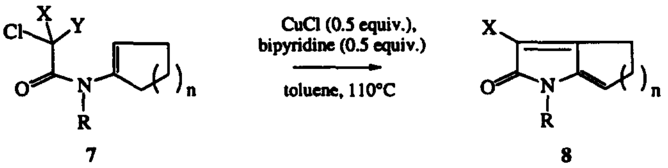
Scheme 2.

A variety of related enamides **7** could be cyclised using this method to give dienes **8** in excellent yield (Table 1). Surprisingly, dichloroenamides produced the same chloro-dienes as that derived from trichloride precursors.[10] Substrates with unsaturated *N*-protecting groups, such as an *N*-allyl precursor (entry 2), underwent exclusive 5-*endo* cyclisation; no products derived from 5-*exo* cyclisation on to the allyl double bond was isolated. Reaction of *N*-homoallyl precursors (entries 3 and 4) produced similar bicyclic dienes and no tandem cyclisation was observed as oxidation of the intermediate radical (of type **4**) was faster than 5-*exo* cyclisation on to the homoallyl double bond. α-Chloroesters were found to cyclise efficiently (entries 6 to 10) and these reactions could also be mediated using dichloro-tris(triphenylphosphine)ruthenium(II) rather than copper(I) chloride/bipyridine (entries 7 and 10).

Acyclic as well as cyclic enamides can be used and treatment of enamide **9** with copper(I) chloride/bipyridine afforded diene **10** in good yield (Scheme 3). This product was thought to result from isomerisation of the alkene double bond in **9** to form the more substituted alkene **11** which could then undergo 5-*endo* cyclisation and radical oxidation as described previously. Indeed heating **9** with bipyridine in toluene did promote isomerisation to give **11** and, as expected, this could be cyclised on reaction with copper(I) chloride/bipyridine to produce **10** in 87% yield.

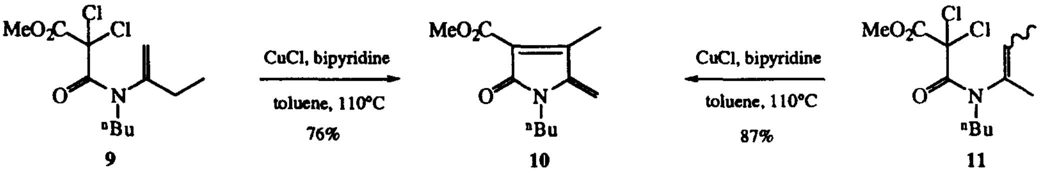
Some unexpected products were isolated from the cyclisation of dichloro-enamide **12**, containing a substituted cyclohexene ring (Scheme 4). Thus, reaction of carbamate **12** with copper(I)/bipyridine produced the expected diene **13** together with oxindoles **15** and **16**. The oxindoles were presumably formed on hydrolysis and decarboxylation[11] (on silica gel chromatography) of methyl ester **14**. A similar compound, namely oxindole **18**, was the only product isolated (in 35% yield) from reaction of acetal

Table 1



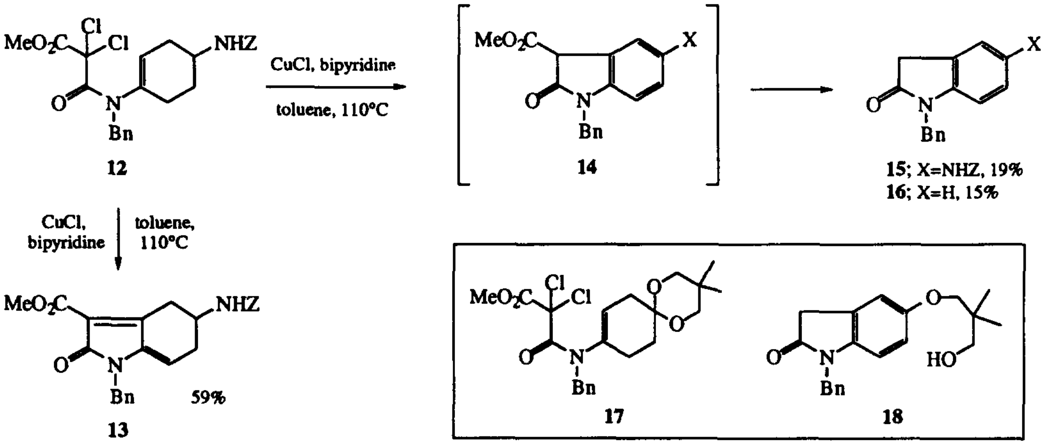
Entry	X	Y	R	n	Yield of 8 (%)
1	Cl	H	Bn	2	87
2	Cl	H	$CH_2CH=CH_2$	2	91
3	Cl	Cl	$CH_2CH_2CH=CH_2$	2	89
4	Cl	H	$CH_2CH_2CH=CH_2$	2	81
5	Cl	Cl	Bn	1	92
6	CO_2Me	Cl	Bn	1	89
7	CO_2Me	Cl	Bn	2	84 (76[a])
8	CO_2Me	Cl	Bn	3	86
9	CO_2Me	Cl	Bn	4	90
10	CO_2Me	H	Bn	2	80 (74[a])

[a] Reaction carried out using $RuCl_2(PPh_3)_3$ (0.5 equiv.) in toluene at 110°C



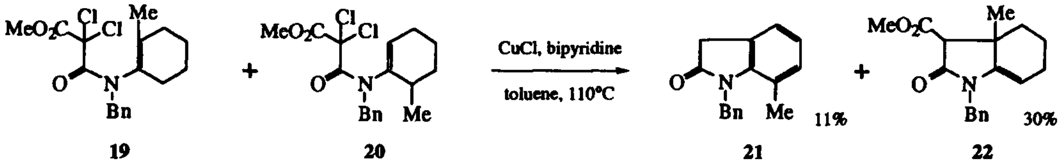
Scheme 3.

17 under the same conditions. It therefore appears that when a substituent is incorporated in the six-membered ring of the enamide, the intermediate diene (of type **8**) can be oxidised further to form a benzene ring.



Scheme 4.

The cyclisation of an inseparable mixture of 2- and 6-methylcyclohexenyl dichlorides, **19** and **20** (in a ratio of 2.6:1) was then investigated (Scheme 5). Oxindole **21** and alkene **22** were isolated and these were thought to be derived from cyclisation of **20** and **19**, respectively. Isomerisation of **20** to (the more stable) alkene **19** leads to the predominant formation of **22**, and the methyl substituent in **22** prevents further oxidation to a diene or oxindole. The presence of an α-hydrogen (rather than chlorine) substituent in **22** presumably results from radical generation followed by hydrogen atom abstraction (from an unidentified donor).[12]



Scheme 5.

This work has demonstrated the novel application of copper(I) promoted halo-enamide cyclisations in pyrrolidinone synthesis. The reaction provides a quick, easy, mild and generally efficient approach to a variety of functionalised *N*-heterocycles in a one-pot reaction. Further studies directed towards the synthesis of alkaloids (and related compounds) using this method are currently underway.

1. Typical procedure

To a stirred solution of the enamine **1** (73 mg, 0.22 mmol) and copper(I) chloride (10 mg, 0.11 mmol) in dry degassed toluene (1.5 cm^3) under nitrogen was added a solution of 2,2′-bipyridine (16 mg, 0.11 mmol) in toluene (0.5 cm^3) and the mixture was heated at reflux for 12 h (until all the starting material had been consumed as indicated by TLC). The solvent was removed in vacuo and the residue purified by column chromatography (silica; petroleum ether:diethyl ether 3:1) to afford diene **2** (54 mg, 94%).

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8. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
9. The same product has been isolated from a related tin hydride-mediated cyclisation: Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75–78.
10. Reaction of a (mono)chloroenamide was unsuccessful, only unreacted starting material was recovered.
11. Similar esters are known to be unstable: Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447–2455.
12. When the reaction was carried out in d_8-toluene, no deuterium was incorporated into either **21** or **22**.