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Solvent effects in copper(I)-mediated 5-*endo* cyclisation of secondary bromo-enamides

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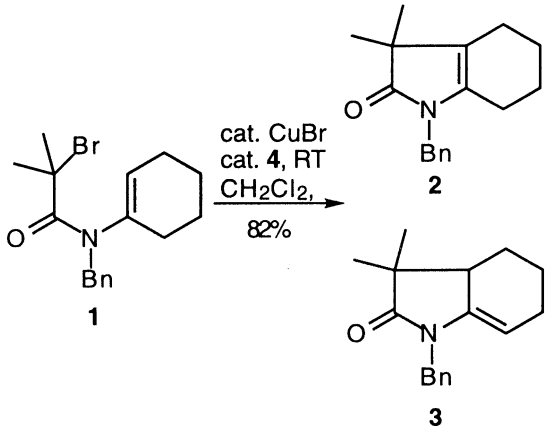
Abstract – Secondary bromoenamides **5**, **14-18**, **32** and **33** undergo efficient 5-*endo* cyclisation reactions to give α,β-unsaturated monoene lactams **9**, **19–23**, **34** and **35** under atom transfer conditions mediated by CuBr and the tripyridylamine **6** in refluxing toluene (59–87%). Changing the solvent to refluxing 1,2-dichloroethane furnishes α,β-unsaturated diene lactams **26-31**, **36**, and **37** instead (42–86%). © 2001 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

bromoenamines / 5-endo cyclisations / radical reactions / atom transfer / solvent effect / copper(I) complexes

Résumé – Les bromoénamines **5**, **14–18**, **32** et **33** subissent, dans des conditions de transfert d'atome induit par le CuBr et la tripyridylamine **6** dans le toluène au reflux, une cyclisation efficace de type 5-*endo* pour donner les lactames α,β-insaturés **9**, **19–23**, **34** et **35** avec de bons rendements (59–87 %). Lorsque le toluène est remplacé par le 1,2-dichloroéthane, on obtient alors les lactames diéniques **26–32**, **36** et **37** (42–86 %). © 2001 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

bromoénamines / cyclisations 5-endo / réactions radicalaires / transfert d'atome / effet de solvant / complexes du cuivre(I)

The use of radical cyclisation protocols to prepare heterocyclic compounds continues to be widespread [1]. 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. In addition these protocols are terminated under reductive conditions. Functionality can be retained if cyclisations are conducted under atom transfer conditions. While a number of groups have reported that catalytic amounts of ruthenium halides [2–6], copper halide complexes of bipyridine [7–10], *N*-alkylpyridylimines [11–13], TMEDA [14–16], multidentate amines and multidentate pyridines [17–18] mediate 5-*exo* atom transfer radical cyclisation of a range of haloacetamides onto alkene functional groups, there are very few reports on the application of this type of methodology to 5-*endo* cyclisation onto enamides [19–27] (*scheme 1*).



Scheme 1.

We recently reported that tertiary bromoenamides of type **1** undergo rapid radical-polar crossover reactions to furnish unsaturated pyrrolidi

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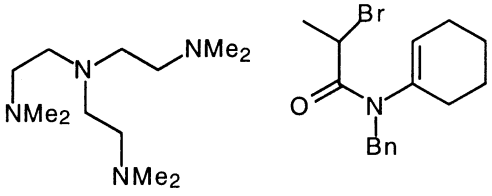
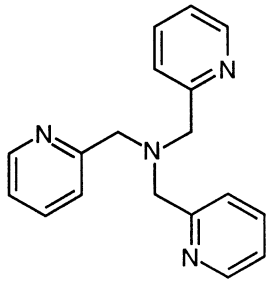
none derivatives at room temperature with the activated copper complex derived from CuBr and **4**. During the course of this work we reported that it was not possible to cyclise secondary bromoenamides (e.g. **5**) using this methodology.



4 **5**



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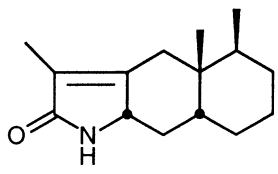
As part of a programme towards the synthesis of the natural products **7–8** [28], we re-investigated the cyclisation of secondary bromides using the alternative more activated ligand **6** at elevated temperatures.



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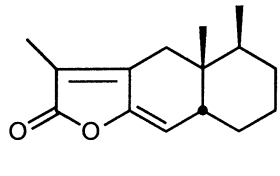

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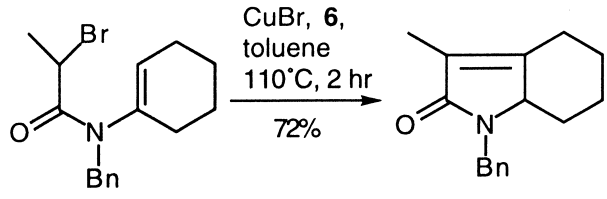
Preliminary studies investigated the cyclisation of the precursor **5**. Hence, reaction of **5** with CuBr and **6** in refluxing toluene for 2 hours furnished the corresponding alkene **9** in 72 % yield [29] (*scheme 2*).



5 **9**

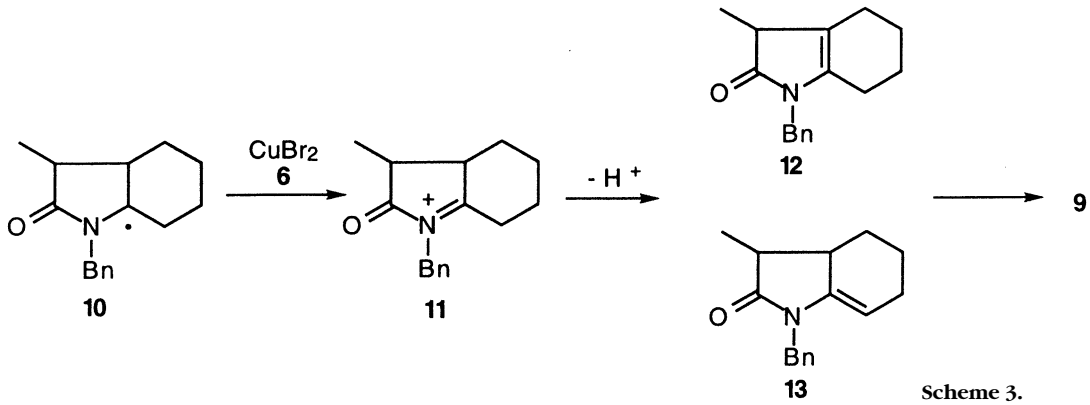
Scheme 2.

Mechanistically, it is likely that the observed products arise via a 5-*endo* cyclisation of the initially generated radical to give tertiary radical **10**, which upon oxidation to the cation **11** by Cu(II) (generated in the initiation step) gives initially the alkenes **12** and **13** which undergo isomerisation to the more stable α,β-unsaturated ketone **9** under the reaction conditions (*scheme 3*).

We then probed the generality of the reaction by investigation of the cyclisation of a variety of precursors **14–18** (*table I*). In all cases the corresponding α,β-unsaturated products were obtained in good yields. Evidence for the intermediacy of alkenes such as **12** and **13** was obtained by detection of 7 % of the regio-isomeric alkene **24** during the cyclisation of **17**.

The *p*-methoxybenzyl derivative **21** could be readily deprotected in good yield using ceric ammonium nitrate in aqueous acetonitrile to give the secondary amide **25** in 96 % yield (*scheme 4*).

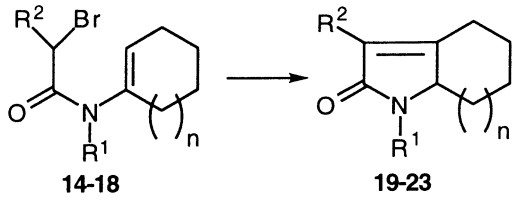
During the course of this work an interesting solvent effect was uncovered. If the cyclisation reactions were repeated using 1,2-dichloroethane as solvent (at 80 °C), then, instead of the monoenes **19–23**, the corresponding dienes **26–31**, arising from further oxidation were isolated (*table II*). Mechanistically, it is uncertain how this further oxidation takes place. Presumably under the reaction conditions further oxidation of the tertiary position to generate another acyl iminium ion is facile thus leading to the observed dienes. Whether radicals



10 **11** **12** **13**

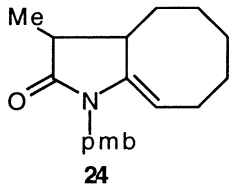
Scheme 3.

Table I. Cyclisation of enamides



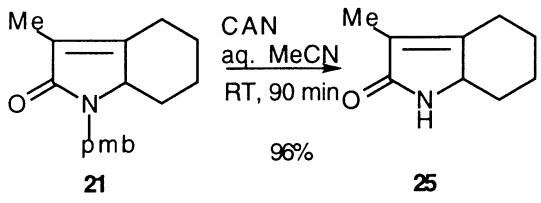
Compound	R^1	R^2	n	Yield %
5	Bn	Me	1	**9** (72)
14	Bn	Me	3	**19** (78)
15	Bn	Ph	1	**20** (59)
16	pmb	Me	1	**21** (86)
17	pmb	Me	3	**22** (82)[1]
18	pmb	Ph	1	**23** (87)

[1] 7% of **24** was isolated



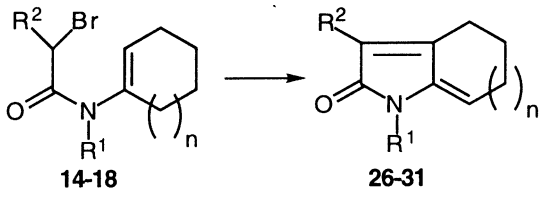
derived from decomposition of the chlorinated solvent under the reaction conditions are responsible for this oxidation or whether the solvent modifies the redox potential of the catalyst facilitating oxidation directly is unclear. However, a reaction using acetonitrile as solvent also furnished the diene, suggesting that the latter may be important.

However, re-submitting the pure monoene **23** to the reaction conditions of CuBr and ligand **6** in refluxing 1,2-dichloroethane for 2 h furnished the diene **31** in 77 % yield, indicating that the monoenes are precursors to the formation of the dienes under theses conditions. The solvent effect was found to be general however, hence reaction of the related substrates **32** and **33** under identical conditions furnished either the monoenes **34–35** or the



Scheme 4.

Table II. Cyclisation of enamides with 1,2-dichloroethane as solvent



Compound	R^1	R^2	n	Yield %[1]
5	Bn	Me	1	**26** (42)
14	Bn	Me	3	**27** (57)
15	Bn	Ph	1	**28** (64)
16	pmb	Me	1	**29** (71)
17	pmb	Me	3	**30** (86)
18	pmb	Ph	1	**31** (74)

[1] Reactions were carried out using CuBr, **6**, in $ClCH_2CH_2Cl$ at reflux for 2 hrs

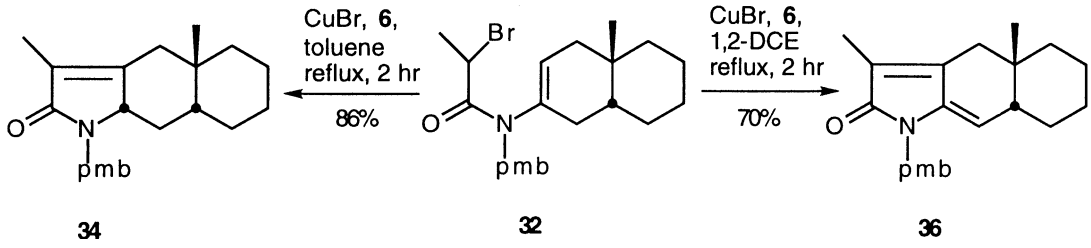
dienes **36–37** depending upon whether toluene or 1,2-dichloroethane (1,2-DCE) was used as solvent (*schemes 5–6*).

In conclusion, we have shown that it is possible to mediate the 5-*endo* cyclisation of secondary bromo-enamides using the activated ligand **6** in conjunction with CuBr. The reaction, which is thought to proceed via a radical-polar crossover mechanism, furnishes either monoene or diene products in excellent yields depending upon the solvent used. Application of this methodology to the synthesis of the natural products **7–8** is currently underway and will be reported at a later date.

. Typical experimental procedures

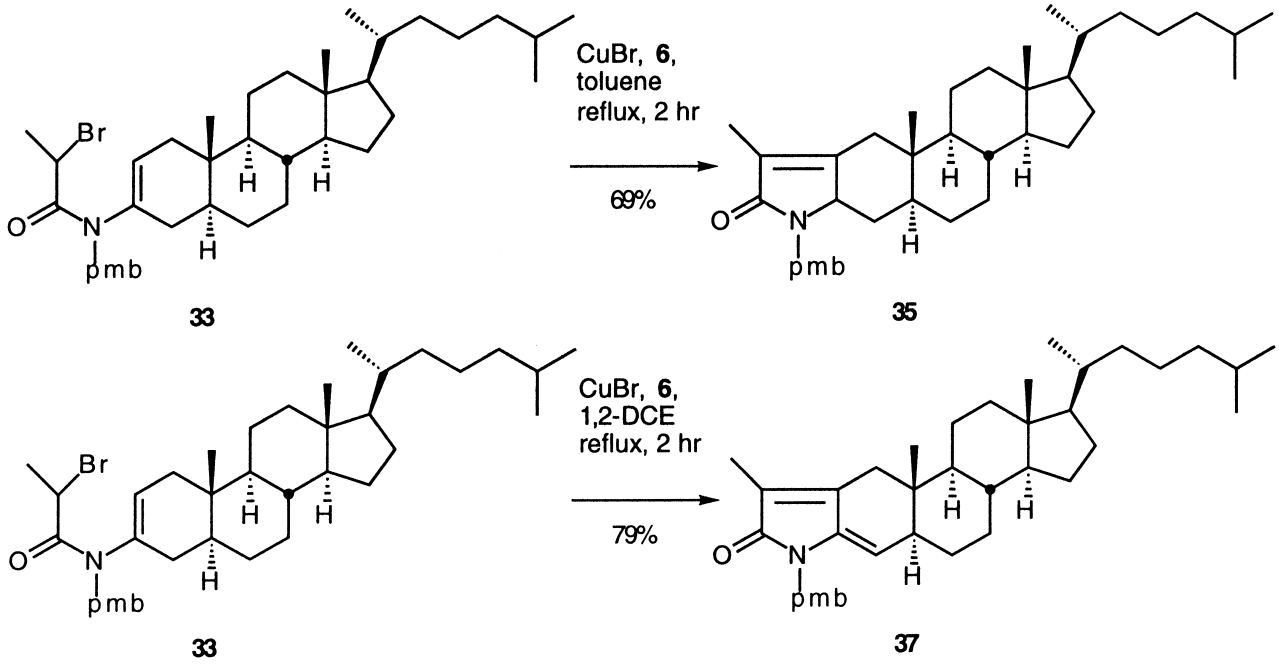
. General method for cyclisation of bromoacetamides

Cu(I)Br (43 mg, 0.3 mmol) was added to solution of bromoacetamide (100 mg, 0.3 mmol) and TPA-ligand (87 mg, 0.3 mmol) in 2.5 mL of the appropriate solvent. The resulting solution was refluxed with stirring for 2 h. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness in vacuo and purified by flash chromatography (9:1 petroleum ether/ethyl acetate).



34 32 36

Scheme 5.



33 35 33 37

Scheme 6.

. 1-Benzyl-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (9)

Yield (72 %); clear oil; IR (neat, cm^{-1}) 1 687, 803; ^1H NMR (250 MHz, $CDCl_3$) 7.17–7.09 (5H, m, Ar–H), 4.90 (1H, d, J = 15.0 Hz,, C*H*HN), 4.12 (1H, d, J = 15.0 Hz, CH*H*N), 3.39 (1H, m, CH), 2.65 (1H, m, C*H*H), 2.19 (1H, m, CH*H*), 1.95 (1H, m, C*H*H), 1.83 (2H, m, CH_2), 1.74 (3H, m, CH_3), 1.20 (2H, m, CH_2), 0.85 (1H, m, CHH); ^{13}C (75 MHz, $CDCl_3$) d 172.6 (s), 153.4 (s), 138.5 (s), 129.4 (d × 2), 128.2 (d × 2), 127.6 (d), 124.6 (s), 60.3 (d), 44.1 (t), 33.4 (t), 27.5 (t), 26.3 (t), 22.5 (t), 8.8 (q); EI–MS m/z 241 (M^+, 100), 226 (35), 91 (85); HRMS calcd for $C_{16}H_{19}NO$: 241.146 6, found 241.145 9.

. 1-Benzyl-3-methyl-1,4,5,6-tetrahydro-indol-2-one (26)

Yield (42 %); clear oil; IR (neat, cm^{-1}) 1 706, 738; ^1H NMR (250 MHz, $CDCl_3$) 7.23–7.02 (5H, m, Ar–H), 5.00 (1H, t, J = 4.5 Hz, CH=C), 4.69 (2H, s, CH_2N), 1.99 (2H, t, J = 5.5 Hz, CH_2), 1.87 (3H, s, CH_3), 1.74 (2H, q, J = 5.5 Hz, CH_2), 1.34 (2H, quint, J = 5.5 Hz, CH_2); ^{13}C (75 MHz, $CDCl_3$) 164.3 (s), 150.1 (s), 140.0 (s), 138.9 (s), 128.9 (d × 2), 127.6 (d × 2), 127.5 (d), 121.9 (s), 108.5 (d), 43.2 (t), 24.6 (t), 23.7 (t), 22.9 (t), 8.8 (q); EI–MS m/z 239 (M^+, 91), 216 (60), 91 (100); HRMS calcd for $C_{16}H1_7NO$: 239.131 0, found 239.131 6.

. General method for the deprotection of *p*-methoxybenzylamides

Ceric ammonium nitrate (438 mg, 0.8 mmol) was added to a solution of compound **21** (110 mg, 0.32 mmol) in 3.2 mL of 3:1 acetonitrile/H_2O and stirred for 1 h. The resulting solution was added to H_2O (25 mL), extracted with ethyl acetate (25 mL × 3), dried with $MgSO_4$ and reduced to dryness in vacuo. Purification was carried out by flash chromatography (1:1 petroleum ether/ethyl acetate). Yield 80 mg (91 %).

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