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# Efficient Radical Cyclisation of Secondary Amides: An Enantioselective Synthesis of Phenyl Allokainoid

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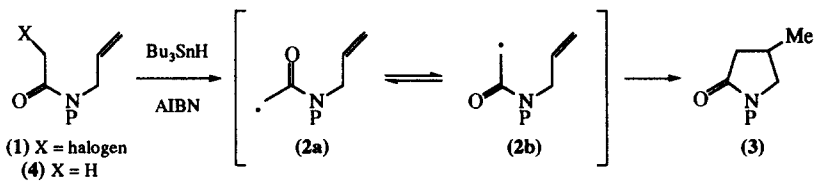
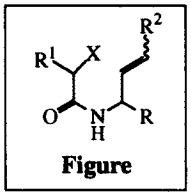
***Abstract:*** Cyclisation of various unsaturated haloamides with tributyltin hydride/AIBN has been explored. Substituted pyrrolidinones were isolated in good to excellent yield and the cyclisation of a serine-derived amide was utilised as the key step in an enantioselective synthesis of phenyl allokainoid.


***Keywords:*** Tin and compounds; Radicals and radical reactions; Cyclisation; Kainoids.

The free-radical cyclisation of unsaturated haloamides (**1**) to produce pyrrolidinones (**3**) has attracted the attention of many research groups (Scheme 1).[1] These reactions, which proceed *via* a 5-*exo-trig* cyclisation pathway, commonly employ tributyltin hydride/AIBN in boiling benzene. Work by Ikeda[2] and Stork[3] highlighted the need for bulky protecting groups on nitrogen (P=$COCF_3$, Ph or Bn etc); when unsubstituted allyl ethanamides (P=H) were reacted, the products of simple reduction (**4**) were predominantly or exclusively formed. The poor cyclisation yields were explained by the (intermediate) carbamoylmethyl radical adopting the *syn*– conformation (**2a**); the introduction of a large *N*-protecting group shifted the equilibrium in favour of the *anti*–conformer (**2b**) which could then cyclise. We became interested in developing an efficient cyclisation of secondary amides and envisaged that the amide conformer population and/or the rate of 5-*exo* cyclisation would be influenced by substitution at positions other than nitrogen. These were at the α–carbon (R), at the site of radical generation ($R^1$) and at the acceptor alkene ($R^2$) (Figure).




**Scheme 1**




**Figure**

Initial studies concentrated on the synthesis and tin–mediated cyclisation of haloethanamides (**5a, c-g**) in boiling benzene or toluene (Table 1).[4] Reaction of (**5a**) at 80°C gave predominantly acyclic amide (**6a**) derived from simple reduction (entry 1). This can be compared to reaction of the related α–methylthio derivative (**5b**) which has been reported to undergo exclusive simple reduction to (**6b**) in 36% yield (entry 2).[2] When (**5a**) was reacted with $Bu_3SnH$ at 110°C in boiling toluene the cyclisation was more efficient and the desired pyrrolidinone (**7a**) was isolated as the major product (entry 3). The increased temperature is expected

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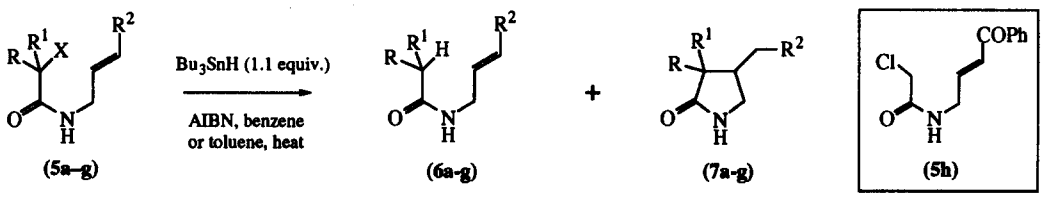
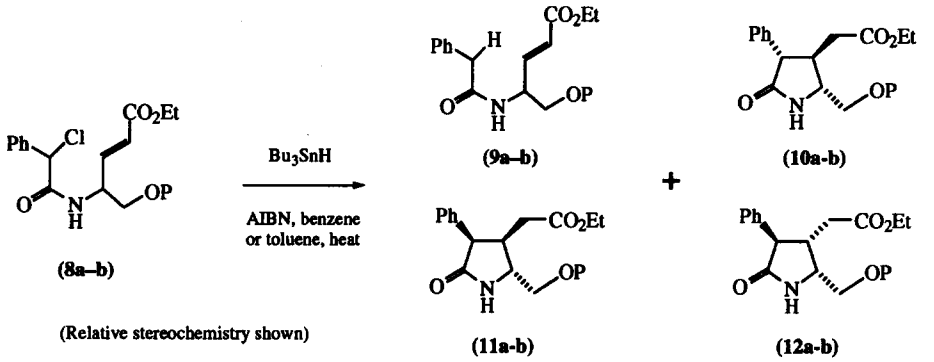
to alter the conformer population and cyclised product (**7c-g**) could also be isolated from reaction of similar precursors with, for example, phenyl and chloro substituents at the site of radical generation (entries 4 to 8). Cyclisation was observed using electron rich or poor alkenes even though the intermediate α-carbamoylmethyl radical is electrophilic in nature.[6] It should also be noted that the *trans*– pyrrolidinone isomers (**7d, e, g**) were formed predominantly and this is consistent with a reversible cyclisation, the reaction being under thermodynamic control.[7] Unexpectedly, reaction of the unsaturated ketone (**5h**) with $Bu_3SnH$ at 110°C resulted in reduction of the alkene double bond,[8] rather than carbon–chlorine bond cleavage, to give the corresponding butanone in (an unoptimised) 40% yield.




| Entry | (5) | R | $R^1$ | $R^2$ | X | Temp. (°C) | Yield of (6) (%) | Yield of (7) (%) | (7) *trans*– : *cis*–[‡] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | a | Cl | Cl | H | Cl | 80 | 56 | 16 | – |
| 2 | b[2] | MeS | H | H | Cl | 80 | 36 | – | – |
| 3 | a | Cl | Cl | H | Cl | 110 | 18 | 30 | – |
| 4 | c | Cl | Cl | $CO_2Et$ | Cl | 110 | 13 | 61 | – |
| 5 | d | Ph | H | H | Cl | 110 | 29 | 45 | 8.5:1 |
| 6 | e | Ph | H | $CO_2Et$ | Cl | 110 | 20 | 42 | 3.1:1 |
| 7 | f | Me | Me | $CO_2Et$ | Br | 110 | 27 | 30 | – |
| 8 | g | Cl | H | $CO_2Et$ | Cl | 110 | 24 | 53 | 1.4:1 |

[‡]Determined from the $^{13}C$ NMR spectrum.[7]

**Table 1:** Tin-mediated cyclisations leading to disubstituted pyrrolidinones (**7a-g**)



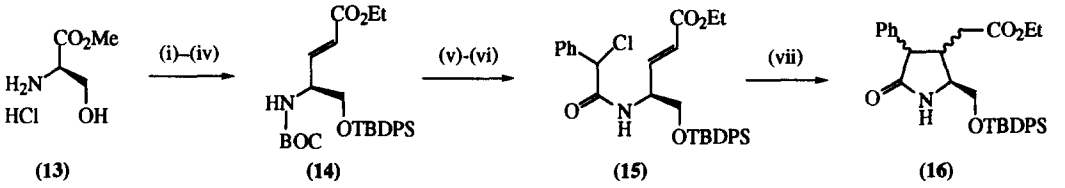

| (8) | P | Temp. (°C) | (9) (%) | (10) (%) | (11) (%) | (12) (%) | Cyclisation Yield (%) |
|---|---|---|---|---|---|---|---|
| a | TBDMS | 80 | 18 | 40 | 21 | 4 | 65 |
| a | TBDMS | 110 | – | 52 | 27 | 6 | 85 |
| b | TBDPS | 110 | – | 56 | 22 | 6 | 84 |

**Table 2:** Tin-mediated cyclisations leading to trisubstituted pyrrolidinones (**10-12**)

Encouraged by these results, we then explored the effect of substitution at the carbon atom α– to nitrogen.[9] A protected primary alcohol substituent was chosen because the size of the alcohol protecting group

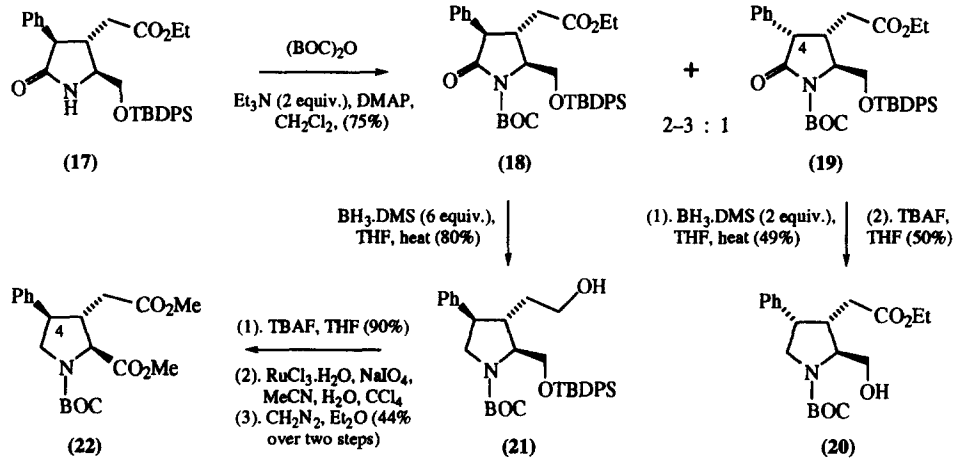
could be easily varied and this could influence the amide conformer population and yield of cyclisation. In addition, the primary alcohol could be oxidised (after cyclisation) to allow the synthesis of biologically important cyclic amino acids. Precursors (**8a–b**) containing a silyl protected alcohol were therefore prepared from DL–serine and reacted with $Bu_3SnH$ (Table 2). Reaction of (**8a**) in benzene gave predominantly cyclised product (in 65% yield) together with ethanamide (**9a**), derived from simple reduction, in 18% yield. The yield of pyrrolidinone could be improved to an excellent 85% using boiling toluene and a similar yield was achieved using a TBDPS (rather than TBDMS) protecting group. The cyclisations gave predominantly the all *trans*–pyrrolidinone diastereomer (**10a–b**) and, as before, this is consistent with a reversible radical cyclisation.[10]

This cyclisation reaction was then applied to the synthesis of an unnatural kainoid amino acid.[11] These compounds have attracted considerable attention because of their pronounced biological properties. Aromatic analogues are of particular interest because of their potent neuroexcitatory activity[12] and we envisaged that this cyclisation approach could be used to prepare a 4–phenyl kainoid amino acid.




(i) $(BOC)_2O$, $Et_3N$, $CH_2Cl_2$ (85%); (ii) TBDPSCl, DMAP (cat.), $Et_3N$, $CH_2Cl_2$ (87%); (iii) DIBAL-H, toluene, -78°C; (iv) $Ph_3P{=}CHCO_2Et$, $CH_2Cl_2$ (74% over two steps); (v) TFA, $CH_2Cl_2$, 0°C to r.t.; (vi) PhCH(Cl)COCl, $Et_3N$, $Et_2O$, 0°C to r.t. (81% over two steps); (vii) $Bu_3SnH$, AIBN, toluene, heat (79%; d.r. 8.9:3.5:1).

**Scheme 2**




**Scheme 3**

The D-serine derivative (**13**) was initially protected and converted to the *trans*–unsaturated ester (**14**) *via* Wittig reaction of the intermediate α–amino aldehyde (Scheme 2). The $^1H$ and $^{19}F$ NMR spectra of MTPA derivatives, prepared on desilylation (TBAF) of (**14**) followed by reaction with either (+) or (±)–MTPA chloride, indicated an e.e. of ≥95% for (**14**). *N*–Deprotection of (**14**) followed by acylation of the crude primary amine afforded chloroamide (**15**) which on reaction with $Bu_3SnH$ cyclised to give (**16**) in 79% yield.[13]

As expected from the racemic cyclisations (Table 2), three separable diastereoisomers of **(16)** were isolated, the all *trans*– pyrrolidinone **(17)** (Scheme 3) being the major product. The *cis*– C-3:C-4 isomer [of type **(11b)**] could also be epimerised to pyrrolidinone **(17)** using DBU in boiling toluene (in 75% yield).

*N*–Protection of pyrrolidinone **(17)** under basic conditions, gave the desired carbamate **(18)** together with epimer **(19)**. Clearly epimerisation at the C–4 position had occurred, presumably after *N*–protection, to give a mixture of C–4 isomers. Reduction of lactam **(19)** using two equivalents of borane–methyl sulfide complex gave the corresponding pyrrolidine in moderate yield and subsequent desilylation (using TBAF) to give **(20)** was of similar yield (50%).[14] A much cleaner transformation was observed when **(18)** was reacted with 6 equivalents of the reducing agent to promote both lactam and ester reduction. The resultant alcohol **(21)** was cleanly desilylated and oxidised to the dicarboxylic acid. For ease of characterisation, this was reacted with diazomethane and the dimethyl ester **(22)** was isolated in 44% yield from **(21)**. The deprotection of very similar compounds to **(22)**, to form kainoid amino acids, has previously been reported.[11,12,14]

This work has demonstrated that secondary haloamides can be efficiently cyclised using tributyltin hydride without the need for *N*–protection. The cyclisation has been utilised in a new approach to the C–4 phenyl allokainoid **(22)**.

**Acknowledgements**

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