

## A Highly Efficient Free Radical Approach to Trisubstituted Pyrrolidinones

A. F. Parsons and R. J. K. Taylor

School of Chemical Sciences, University of East Anglia, Norwich, UK NR4 7TJ

The radical-mediated cyclisation of serine derived  $\alpha$ -chloroamides has been found to be influenced in both yield and stereoselectivity by the nature of the substituent at the site of radical generation—radicals substituted at the  $\alpha$ -position by methyl, phenyl and dichloro groups underwent smooth cyclisation to give excellent yield of pyrrolidinones in which the *trans*-C-2 : C-3 isomer predominated—this procedure has potential application to a new synthesis of the kainoid amino acids.

Considerable interest has been devoted recently to the development of new synthetic routes to natural products containing pyrrolidinone and pyrrolidine rings,<sup>1</sup> such as the pyrrolidine amino acids, the kainoids.<sup>2</sup> Since the isolation of the parent kainoid, kainic acid **1**, in 1953 a number of structurally related compounds (*e.g.* the domoates<sup>3</sup> and acromelates<sup>4</sup>) have been isolated and found to exhibit powerful biological properties (insecticidal, anthelmintic and principally neuroexcitatory<sup>5</sup>). The effects and patterns of nerve failure observed after injection of kainoids have been shown to mimic the symptoms observed in patients suffering from diseases such as epilepsy, Huntington's disease and Alzheimer's disease. Recently, the acromelate analogue **2** has been prepared<sup>6</sup> and on biological testing shown to exhibit the most potent neuroexcitatory activity among the kainoids known to-date. This has prompted interest in the synthesis of acromelate analogues with the ultimate aim of designing an antagonist, which can be used therapeutically in cases of excessive neuronal excitation.

Interest in the cyclisation of amide radicals has recently been rekindled and several radical-mediated approaches to lactams have appeared in the literature.<sup>7</sup> We envisaged that the kainoid amino acid nucleus could be constructed *via* a tin-mediated amide radical cyclisation<sup>8</sup> of precursors of type **3** (where X is a leaving group) to give pyrrolidinone **4**. Subsequent lactam reduction and oxidative elaboration of the C-2 side chain would furnish the desired amino acids. This novel approach to the kainoids would allow flexibility in the nature of the C-4 substituent (R) allowing for the synthesis of a number of kainoid analogues.

To test the feasibility of this approach a number of  $\alpha$ -chloroamides (**6a–d**)<sup>†</sup> were prepared (in 93–99% yield) by reaction of the known amine **5**,<sup>9</sup> prepared from serine, with the appropriate acid chloride (Scheme 1).

On treatment of  $\alpha$ -chloroamide **6a** with Bu<sub>3</sub>SnH and AIBN (catalytic) in boiling benzene‡ a number of products were isolated after column chromatography (Scheme 2, entry 1, Table 1). The desired pyrrolidinone **7a** was isolated in only 31% yield (as predominantly the *trans*-isomer) while the reduced substrate **8a** was formed in 35% yield. In addition the 1,4-aryl migration product **9**, presumably resulting from an intramolecular *ipso*-attack,<sup>10</sup> was formed in 13% yield. When the same reaction was carried out in boiling toluene (entry 2,

Table 1) although the yield of **7a** was improved, its formation was less diastereoselective<sup>11</sup> and the by products **8a** and **9** were still evident. However, the efficient formation of **7a** could be achieved using the trichloroamide **6b**. Thus, on reaction of **6b** with 1.1 equiv. of Bu<sub>3</sub>SnH pyrrolidinone **7b** was isolated in 77% yield (entry 3, Table 1) while on reaction with 3.3 equiv. **7a** was formed in 82% yield (entry 4, Table 1). This is surprising considering the electrophilic nature of the radical derived from **6b**, which was expected<sup>12</sup> to cyclise in low yield onto the electron-poor double bond.

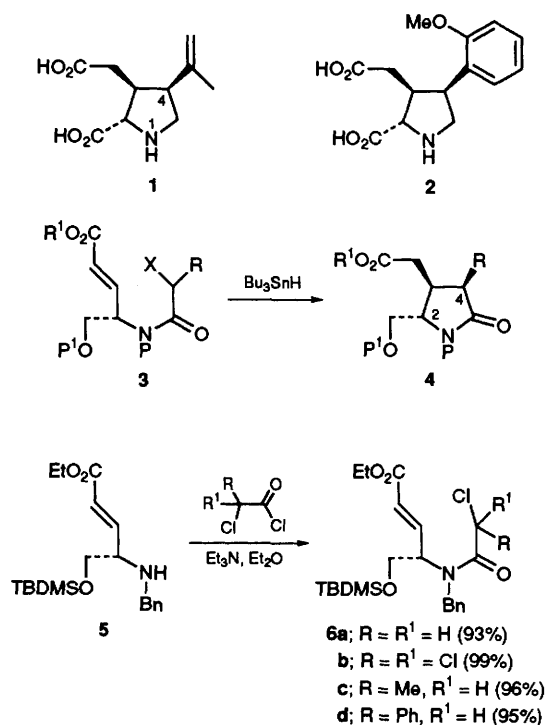


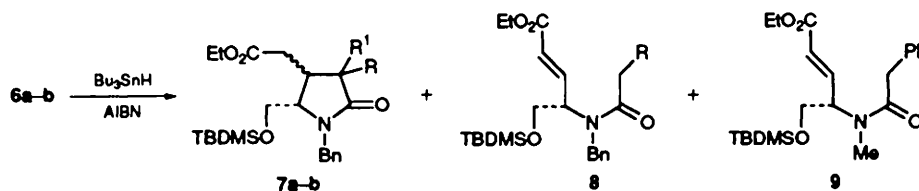
Table 1

Entry	Chloride (6)	Reaction temp./°C	Products (yield %)	C-2 : C-3 <i>trans</i> - <i>cis</i> -ratio
1	a	80	<b>7a</b> (31) + <b>8a</b> (35) + <b>9</b> (13)	15 : 1
2	a	110	<b>7a</b> (38) + <b>8a</b> (15) + <b>9</b> (18)	4.2 : 1
3	b	80	<b>7b</b> (77)	5 : 2
4	b	110 <sup>a</sup>	<b>7a</b> (82)	2.7 : 1
5	c	80	<b>8c</b> (4) + <b>10c</b> (25) + <b>11c</b> (28) + <b>12c</b> (28)	2.2 : 1
6	d	80	<b>10d</b> (31) + <b>11d</b> (31) + <b>12d</b> (31)	2 : 1
7	d	110	<b>10d</b> (32) + <b>11d</b> (32) + <b>12d</b> (32)	2 : 1

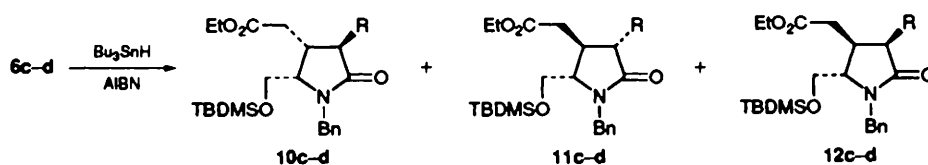
<sup>a</sup> Reaction performed using 3.3 equiv. of Bu<sub>3</sub>SnH.

<sup>†</sup> All new compounds exhibited satisfactory spectral (<sup>1</sup>H and <sup>13</sup>C NMR, IR) and analytical (high-resolution mass and/or combustion) data.

<sup>‡</sup> A 0.02 mol dm<sup>-3</sup> solution containing Bu<sub>3</sub>SnH (1.1 equiv.) and AIBN (azoisobutyronitrile) (0.1 equiv.) in benzene (20 ml) was added dropwise over 1 h to a 0.03 mol dm<sup>-3</sup> solution of chloride **6a** (150 mg, 0.34 mmol, 1.0 equiv.) in boiling benzene (10 ml) while stirring under nitrogen. The solution was then refluxed for a further 2 h and the solvent removed *in vacuo*. Diethyl ether (15 ml) and aqueous KF (8%, 15 ml) was added to the residue and the mixture stirred for 2 h. The organic layer was separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to afford crude product which was purified by column chromatography (silica).



Scheme 2



Scheme 3

After initial success with  $\alpha$ -chloroamides **6a-b** the cyclisation of amides **6c-d** was attempted (Scheme 3). Thus, on reaction of **6c** with  $\text{Bu}_3\text{SnH}$  the separable pyrrolidinones **10c-12c** were isolated in a combined yield of 81%, while the non-cyclised byproduct **8c** was only formed in 4% yield (entry 5, Table 1). This represented a much more efficient cyclisation than that of **6a**. Reaction of the phenyl substituted chloride **6d** with  $\text{Bu}_3\text{SnH}$  in refluxing benzene $\S$  or toluene (entries 6 and 7) gave excellent 94 and 97% yields, respectively, of the desired separable pyrrolidinones **10d-12d** with none of the reduced compound **8d** apparently being formed. $\P$

This work has demonstrated the importance of substituents at the site of radical generation on the efficiency of cyclisation of  $\alpha$ -chloroamides and shown that extremely efficient pyrrolidinone ring formation (with potential application to the kainoid and allokainoid amino acids for example) can be achieved from precursors of type **6**. Although good to reasonable relay of stereochemistry from C-2 to C-3 was observed further work is needed to optimise the relative stereochemistry between C-3 and C-4.

We would like to thank Dr O. W. Howarth of the SERC NMR service, University of Warwick, for running the NOE experiments, and the SERC MS service for high resolution measurements.

Received, 4th May 1993; Com. 3/02532B

$\S$  On addition of  $\text{Bu}_3\text{SnH}$  to **6d** in benzene at 40°C, only starting material was evident on TLC analysis. Pyrrolidinone formation was only observed when the reaction temperature was raised to 80°C, whereupon **10d-12d** were isolated as a 1:1:1 mixture in a combined yield of 73% (determined from the  $^1\text{H}$  NMR spectrum).

$\P$  The stereochemistry of the three diastereoisomers **10d-12d** was deduced from NOE experiments and confirmed by base-induced epimerisation experiments using 1,8-diazabicyclo[5.4.0]undec-7-ene in boiling benzene.

## References

- For example A. I. Meyers and L. Snyder, *J. Org. Chem.*, 1993, **58**, 36; T. Naito, Y. Honda, O. Miyata and I. Ninomiya, *Chem. Pharm. Bull.*, 1993, **41**, 217; S. Hanessian and V. Ratovelomanana, *Synlett*, 1990, 501; Y. Hirai, T. Terada, Y. Amemiya and T. Momose, *Tetrahedron Lett.*, 1992, **33**, 7893; J. E. Baldwin, M. G. Moloney and S. B. Shim, *Tetrahedron Lett.*, 1991, **32**, 1579.
- Synthesis of Optically Active  $\alpha$ -Amino Acids*, ed. R. M. Williams, Pergamon, 1989, p. 306.
- Y. Ohfuné and M. Tomita, *J. Am. Chem. Soc.*, 1982, **104**, 3511; J. L. C. Wright, M. Falk, A. G. Innes and J. A. Walter, *Can. J. Chem.*, 1990, **68**, 22; M. Maeda, T. Kodama, T. Tanaka, H. Yoshizumi, T. Takemoto, K. Nomoto and T. Fujita, *Tetrahedron Lett.*, 1987, **28**, 633.
- K. Konno, K. Hashimoto, Y. Ohfuné, H. Shirahama and T. Matsumoto, *J. Am. Chem. Soc.*, 1988, **110**, 4807; S. Fushiyama, S. Sato, T. Kanazawa, G. Kusano and S. Nozoe, *Tetrahedron Lett.*, 1990, **31**, 3901.
- Kainic Acid as a Tool in Neurobiology*, ed. E. G. McGeer, J. W. Olney and P. L. McGeer, Raven Press, New York, 1978; M. Ishida and H. Shinozaki, *Brain Res.*, 1988, **474**, 386.
- K. Hashimoto and H. Shirahama, *Tetrahedron Lett.*, 1991, **32**, 2625.
- D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723; T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1989, 879; T. Sato, N. Nakamura, K. Ikeda, M. Okada, H. Ishibashi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2399.
- For related free radical approaches to the kainoids see J. E. Baldwin, M. G. Moloney and A. F. Parsons, *Tetrahedron*, 1990, **46**, 7263 and 1991, **47**, 155; S. Hatakeyama, K. Sugawara and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1993, 125.
- A. Barco, S. Benetti, G. Spalluto, A. Casolari, G. P. Pollini and V. Zanirato, *J. Org. Chem.*, 1992, **57**, 6279.
- H. Ishibashi, N. Nakamura, K. Ito, S. Kitayama and M. Ikeda, *Heterocycles*, 1990, **31**, 1781; J. Aube, X. Peng, Y. Wang and F. Takusagawa, *J. Am. Chem. Soc.*, 1992, **114**, 5466.
- Radical cyclisations of *N*-(but-1-en-3-yl)trichloroacetamide derivatives using Ru or Cu catalysts are known to yield *trans-cis*-pyrrolidinones, the isomeric ratio of which is dependant on the reaction temperature. See H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.*, 1993, **58**, 464.
- L. Belvisi, C. Gennari, G. Poli, C. Scolastico, B. Salom and M. Vassallo, *Tetrahedron*, 1992, **48**, 3945; Y. Hirai, A. Hagiwara, T. Terada and T. Yamazaki, *Chem. Lett.*, 1987, 2417.