New Route to Pyroglutamates *via* α-Chloro Amide Radical Cyclisation

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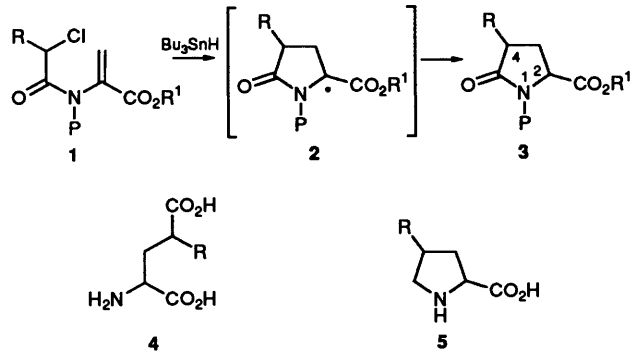
The tributyltin hydride mediated radical cyclisation of *N*-(α-chloroacetamido)dehydroalanine derivatives prepared from serine proceeds regioselectively to give pyroglutamates in 47–74% yield—the cyclisation of the intermediate carbamoylmethyl radical proceeds in a 'disfavoured' 5-*endo-trig* manner.

The 5-*exo-trig* radical cyclisation of α-halogeno amides to form pyrrolidinones has attracted considerable interest in recent years.[1] This cyclisation has been mediated by a variety of reagents[2] including tributyltin hydride[3] and applied to the synthesis of a number of natural products.[4] Recently, Ikeda and co-workers[5] demonstrated that certain α-halogeno amides can undergo radical cyclisation in a 'disfavoured' 5-*endo-trig* process. Thus, the cyclisation of various 2-chloro-*N*-(cycloalk-1-enyl)acetamides was shown to afford pyrrolidinones and/or β-lactams in good yield. This was applied to the synthesis of perhydroerythrinane.[6]

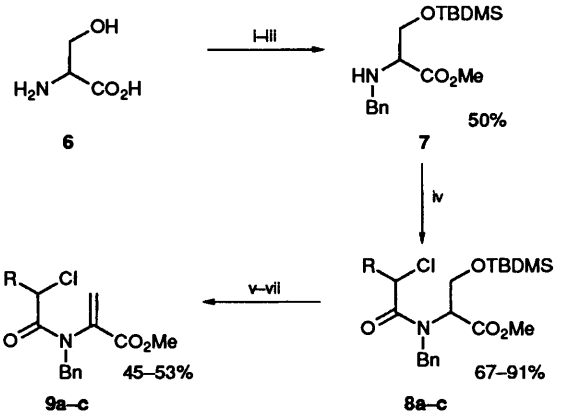
We envisaged that the 5-*endo-trig* radical cyclisation of halogeno amides could provide a new approach to pyroglutamates (5-oxopyrrolidine-5-carboxylic acids). Thus, on treatment of α-chloro amide **1** with tributyltin hydride, *endo* cyclisation to afford pyroglutamates of type **3** was expected to occur regioselectively *via* the captodative[7] stabilised radical **2** (Scheme 1). Pyroglutamates of type **3**, with substituents (R) at



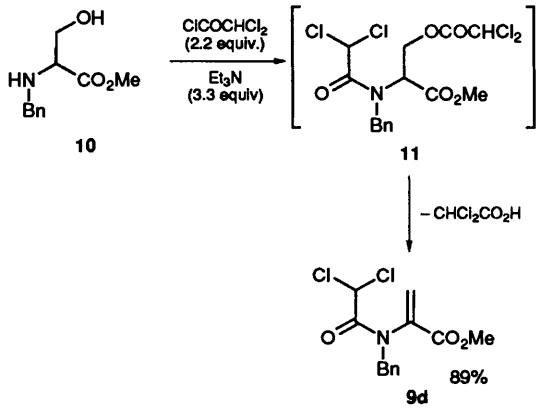
Scheme 1

the C-4 position, are valuable intermediates in the synthesis of biologically important non-proteinogenic amino acids. This includes glutamic acid analogues **4**[8] and proline derivatives **5**[9] which are useful pharmacological probes for excitatory amino acid receptors. Previous approaches to **4** and **5** based on the alkylation of pyroglutamic acid **3** (R = H) are limited by both the reactivity and availability of the electrophile.[10]

To investigate the feasibility of this approach the α-chloro amides **9a–d** were prepared from DL-serine **6**. For the synthesis of **9a–c** the protected serine derivative **7** was first treated with the appropriate chloroacetyl chloride to afford the amides **8a–c** in good yield (Scheme 2). On desilylation, primary alcohol chlorination and finally triethylamine mediated elimination,[11] the desired dehydroalanine derivatives **9a–c** were isolated in reasonable yield. A more efficient synthesis was developed for dichloro amide **9d** which involved the reaction of *N*-benzylserine methyl ester **10** with dichloroacetyl chloride and triethylamine (Scheme 3). This 'one-pot' procedure was shown to involve the intermediacy of diester **11** which on subsequent



Scheme 2 **a**, R = H; **b**, R = Me; **c**, R = Ph; Bn = benzyl *Reagents:* i, MeOH, HCl; ii, PhCHO, Et_3N, $MgSO_4$, CH_2Cl_2 then $NaBH_4$, MeOH; iii, TBDMSCl, Et_3N, DMAP, CH_2Cl_2; iv, RCHClCOCl, Et_3N, Et_2O; v, TsOH, MeOH; vi, PCl_5, $CHCl_3$; vii Et_3N, EtOAc



Scheme 3

elimination of dichloroacetic acid afforded **9d** in excellent yield. We are currently exploring the scope of this reaction in dehydroamino acid synthesis.

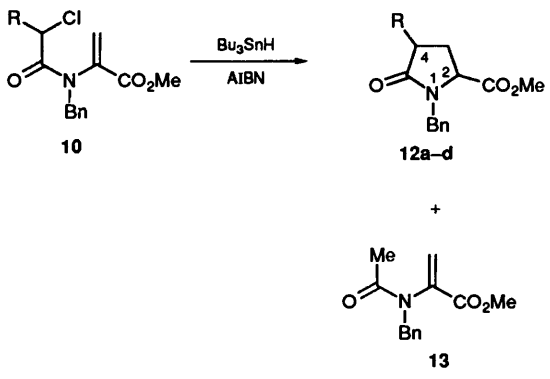
On treatment of α-chloro amide **9a** with tributyltin hydride (1.1 equiv.) and azoisobutyronitrile (AIBN) (catalytic) in boiling benzene the desired pyroglutamate **12a** resulting from a 5-*endo-trig* cyclisation was isolated in 52% yield after column chromatography (Scheme 4, Table 1, entry 1). In addition the dehydroalanine derivative **13** derived from simple chloro amide reduction was isolated in a very low 8% yield.† It is noted that the cyclisation of **9a** to form γ-lactam **12a** was regioselective; no product resulting from a 4-*exo-trig* cyclisation (*i.e.* β-lactam)

† No phenyl migration (to form the NMe product) as observed on related substrates[3] was evident.

Table 1

Entry	Chloride **9**	Reaction temp./(°C)	Products (yield %)	C-2:C-4 *trans*/*cis*- ratio[a]
1	**a**	80	**12a**(52) + **13**(8)	—
2	**b**	80	**12b**(47)	1.75:1
3	**c**	80	**12c**(56)	1:2.1
4	**c**	110	**12c**(52)	1:2.1
5	**d**	80	**12d**(33) + **12a**(36)	3:1
6	**d**	80[b]	**12a**(70)	—

[a] Isomer ratio determined from the ^{1}H NMR spectrum. The *cis*/*trans*-assignments were made by comparison with literature data of related compounds[12] and should therefore be regarded as tentative. [b] Reaction performed using 2.2 equiv. of Bu_3SnH.



Scheme 4

was formed. Indeed the absence of β-lactam formation was characteristic of the cyclisations of **9a–d** (see later).

The tin-mediated cyclisations of **9b** and **9c** were then investigated. Thus, on cyclisation of **9b** in boiling benzene the 4-methylpyroglutamate **12b** was formed in 47% yield (Scheme 4, Table 1, entry 2).* This was isolated as an inseparable mixture of diastereoisomers in the approximate ratio 1.75:1 as indicated from the ^{1}H NMR spectrum. The 4-phenylpyroglutamate **12c** was isolated in similar yield (52–56%) and diastereoselectivity (2.1:1) from the cyclisation of **9c** in benzene or toluene (Scheme 4, Table 1, entries 3 and 4). No products resulting from the simple reduction of chloro amides **9b–c** were apparently formed in these reactions.

Pyroglutamate formation was also realised on cyclisation of dichloroamide **9d** (Scheme 4, Table 1, entries 5 and 6). Thus, on reaction with 1.1 equiv. of tributyltin hydride in boiling benzene the desired 4-chloro derivative **12d** was formed in 33% yield. In addition the unsubstituted pyroglutamate **12a**, formed on tin hydride reduction of **12d**, was isolated in 36% yield. The yield of **12a** could be increased to 70% when 2.2 equiv. of tin hydride were treated with **9d**.

In conclusion, this work describes a new approach to pyroglutamates based on a 5-*endo-trig* radical cyclisation of α-chloro amides. The application of this approach in amino acid synthesis is currently being investigated.

Experimental

Tributyltin hydride was purchased from Lancaster Chemical Company and distilled before use. All new compounds were characterised by a full range of spectroscopic data, including IR, ^{1}H and ^{13}C NMR studies and high resolution mass spectrometry.

* The *N*-benzyl substituent was found to be necessary for cyclisation; reaction of the corresponding N–H derivative (with tributyltin hydride in boiling benzene or toluene) afforded no pyroglutamate.

General Procedure for the Radical Cyclisations.—A 0.014 mol dm^{-3} solution containing tributyltin hydride (1.1 equiv.) and azoisobutyronitrile (0.1 equiv.) in benzene or toluene (29–81 cm^3) was added dropwise over 1 h *via* a syringe pump to a 0.024 mol dm^{-3} solution of the alkene **9a–d** (0.36–0.63 mmol, 1 equiv.) in boiling benzene or toluene whilst the latter was stirred under nitrogen. The solution was then heated at reflux for a further 3 h and the solvent removed under reduced pressure. Diethyl ether (10–15 cm^3) and aqueous potassium fluoride (8%, 10–15 cm^3) were added to the residue and the mixture stirred for 2 h. The organic layer was separated, washed with water and brine, dried (magnesium sulfate) and evaporated under reduced pressure to afford crude product which was purified by column chromatography (silica) to afford the pyroglutamate **12a–d** (33–70%).

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