Pergamon

Tetrahedron Letters 39 (1998) 2815–2818

TETRAHEDRON LETTERS

Radical Reactions Leading to Substituted Pyroglutamates

S. Richard Baker[b], Andrew F. Parsons[a]* and Michelle Wilson[a]

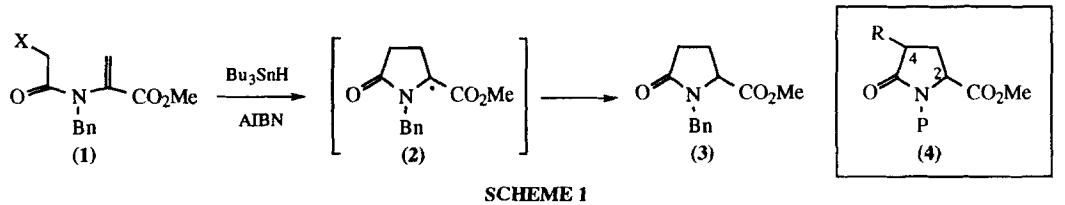
[a]Department of Chemistry, University of York, Heslington, York, YO1 5DD, U.K.

[b]Eli Lilly and Company Ltd, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, U.K.

Received 22 December 1997; revised 13 January 1998; accepted 30 January 1998

Abstract: The Bu_3SnH mediated cyclisation of a serine-derived dehydroalanine was shown to provide an efficient approach to a protected 4-phenylpyroglutamate which was elaborated to 4-phenylglutamic acid in good yield. Cyclisation reactions of this type were shown to proceed *via* an intermediate captodative radical which could be trapped intermolecularly using an alkene *e.g.* styrene or methyl methacrylate. This method has potential for the synthesis of various 4- and/or 2-substituted glutamic acids.

Radical cyclisation of haloamides to form substituted pyrrolidinones of biological importance has attracted considerable attention in recent years. A variety of radical initiators including Bu_3SnH,[1] BEt_3,[2] Fe^0-$FeCl_3$,[3] $Mn(OAc)_3$,[4] $CuCl$,[5] $(Ph_3P)_3RuCl_2$[6] and Ni/CH_3CO_2H[7] have been employed and these reactions generally involve cyclisation of the intermediate carbamoylmethyl radical on to an *N*-allyl double bond in a favoured 5-*exo-trig* manner. Recently however, Ikeda and co-workers[8] demonstrated that pyrrolidinones could also be prepared from the corresponding *N*-vinyl precursors. This remarkable reaction was reported to result from the carbamoylmethyl radical undergoing a geometrically disfavoured 5-*endo-trig* mode of cyclisation.[9,10] The regioselectivity of this reaction could be attributed to the high stability of the product α-acylamino radical. We have recently demonstrated the application of this method in pyroglutamate synthesis and hence reaction of dehydroalanine **(1)** with Bu_3SnH resulted in the formation of **(3)** (Scheme 1).[11] This reaction could proceed *via* the captodative radical **(2)** and these type of radicals are known to be relatively stable and comparatively easy to form.[12]

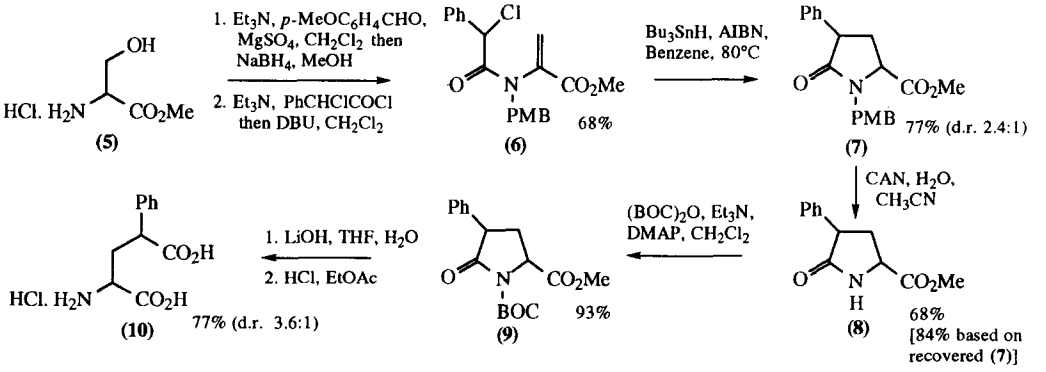


SCHEME 1

It was envisaged that this method could be applied to the preparation of various medicinally important glutamic acids *via* intermediate 4-substituted pyroglutamates **(4)**. This is indeed possible, as exemplified in Scheme 2, where the synthesis of 4-phenylglutamic acid **(10)** from serine **(5)** is reported for the first time.[13] The key radical cyclisation reaction to give pyrrolidinone **(7)** proceeded in 77% yield when Bu_3SnH (1.1 equivalents)/AIBN (0.1 equivalents) was added slowly (over 5 h) to a boiling solution of **(6)** [prepared in good yield from **(5)**] in benzene (0.02 M). This was found to be the optimum addition time and the use of alternative

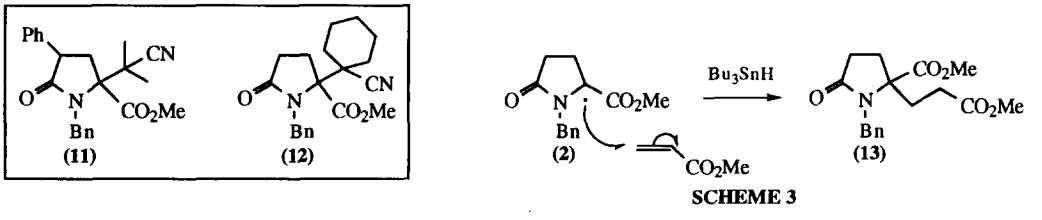
0040-4039/98/$19.00
PII: S0040-4039(98)00254-8

solvents[14] resulted in poorer cyclisation yields [*e.g.* a 69% yield of **(7)** was isolated when using EtOAc]. The PMB group[15] was then oxidatively removed to afford **(8)** which was then converted to the *N*-BOC derivative **(9)**. The ^{1}H NMR spectrum of the pyrrolidinone **(9)** showed the formation of both *trans*- and *cis*- isomers in the ratio of 2.8:1. The lactam and ester groups of **(9)** were then hydrolysed under basic conditions (which can epimerise the C-4 centre) and *N*-deprotection gave rise to the desired amino acid **(10)**. Although eight reactions are employed in this synthesis, the overall yield is very respectable (26%). The method thus offers a novel approach to 4-aryl glutamic acid derivatives which are problematic to prepare[16] using previously reported methods *e.g.* by electrophilic quenching of the C-4 anion of pyroglutamic acid.[17]



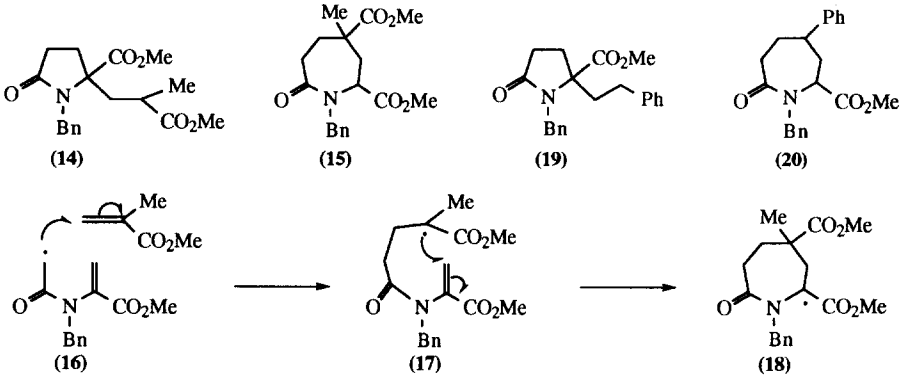
SCHEME 2

We then explored the application of this cyclisation reaction in the formation of C-2 or α-substituted pyroglutamates/glutamic acids. There are few approaches to these types of compound even though, as conformationally restricted amino acids, they have the potential to induce structural modifications in peptides and proteins.[18] As mentioned earlier, the 5-*endo* cyclisation reaction was thought to proceed *via* radicals of type **(2)** which on trapping could allow the formation of a carbon-carbon bond at the C-2 position. Initial studies concentrated on the cyclisation of the *N*-benzyl analogue of **(6)** using Bu_3SnH (1.1 equivalents) and >0.1 equivalents of AIBN. It was found that when 0.6 equivalents of AIBN was used [in addition to the formation of methyl *N*-benzyl-4-phenylpyroglutamate in 75% yield] the C-2 substituted pyroglutamate **(11)** was formed in 18% yield. This arises from a radical termination reaction involving coupling of the C-2 pyroglutamate radical [of type **(2)**] with the radical produced on decomposition of AIBN. The formation of **(11)** confirms that the cyclisation does indeed proceed *via* radicals of type **(2)** and further highlights the importance of radical processes to construct carbon-carbon bonds in sterically hindered environments. Other precursors and radical initiators could be employed and, for example, reaction of **(1, X=Cl)** with ACN (0.6 equivalents) produced [in addition to **(1, X=H)** and **(3)** in 17 and 38% yield respectively] the cyclohexane analogue **(12)** in 11% yield.



SCHEME 3

Encouraged by these results, we then explored the trapping of radical (**2**) using alkene acceptors. Thus slow addition of a solution of Bu_3SnH/AIBN to a mixture of iodide (**1, X=I**) and methyl acrylate (3 equivalents) in boiling benzene gave rise to three compounds after column chromatography.[19] These were the *N*-acetyl derivative (**1, X=H**) derived from simple reduction (in 17% yield), the pyroglutamate (**3**) in 20% yield and the desired methyl propanoate derivative (**13**) in 12% yield (Scheme 3). The formation of (**13**) was expected to arise from regioselective 1,4-addition of the pyroglutamate radical (**2**) to methyl acrylate followed by H-atom abstraction from Bu_3SnH. Reaction of (**1, X=I**) with methyl methacrylate (MMA) followed a similar course and the substituted pyroglutamate (**14**) was isolated in 22% yield. Unexpectedly, the reaction also produced the seven-membered lactam (**15**) (as one diastereomer) in 23% yield. This remarkable result could be attributed to an intermolecular reaction of the initial carbamoylmethyl radical (**16**) followed by an intramolecular 7-*endo-trig* cyclisation[20] of (**17**) to give (**18**) as outlined in Scheme 4. The reaction is unusual as tandem (or domino) radical reactions generally employ a rapid (entropically favoured) intramolecular cyclisation followed by subsequent intra- or intermolecular reactions.[21] This is an unusual example of the reverse situation. Indeed this reaction was found not to be specific to MMA and reaction of (**1, X=I**) with stryene produced the desired pyroglutamate (**19**) in 9% yield and the seven-membered lactam (**20**) (as one diastereomer[22]) in 13% yield.



SCHEME 4

Similar tandem reactions were attempted using *iso*-butyl vinyl ether, an electron-rich alkene. However, no products derived from the intermolecular trapping of radical (**2**) using this acceptor could be isolated. These results can be understood if radical (**2**) is considered to be nucleophilic in character and hence adds more rapidly to electron-poor alkenes.[23]

The intermediacy of radicals of type (**2**) has also been supported using ESR to investigate the reaction of (**1, X=I**) with Bu_6Sn_2/*hν* in benzene. Although the initial carbamoylmethyl radical could not be observed, the spectrum showed the presence of the tertiary radical (**2**).[24] The same radical was generated by reaction of (**3**) with $^tBuOO^tBu$/*hν*.[25]

This work has demonstrated the importance of the 5-*endo-trig* cyclisation of dehydroalanines in the formation of 4- and/or 2-substituted pyroglutamates. The haloamide cyclisation followed by reaction of the intermediate captodative radical allows the formation of C-2 substituted pyroglutamates in a one-pot reaction. Future work will investigate the intramolecular trapping of radicals of type (**2**).

Acknowledgements

We thank the EPSRC and Eli Lilly for a CASE award to M.W.. We would also like to thank Dr Will Prowse (Eli Lilly) for carrying out NMR experiments and Dr Adrian Whitwood (York) for conducting the ESR studies.

References and Notes

1. (a) Parsons, A.F.; Taylor, R.J.K. *J. Chem. Soc., Perkin Trans. 1*, 1994, 1945. (b) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Heterocycles*, 1994, **38**, 2663. (c) Sato, T.; Matsubayashi, K-i.; Yamamoto, K.; Ishikawa, H.; Ishibashi, H.; Ikeda, M. *Heterocycles*, 1995, **40**, 261. (d) Curran, D.P.; Tamine, J. *J. Org. Chem.*, 1991, **56**, 2746. (e) Stork, G.; Mah, R. *Heterocycles*, 1989, **28**, 723. (f) Jolly, R.S.; Livinghouse, T. *J. Am. Chem. Soc.*, 1988, **110**, 7536. (g) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron*, 1992, **48**, 3945. (h) Ishibashi, H.; Su So, T.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.*, 1991, **56**, 95. (i) Sato, T.; Wada, Y.; Nishimot, M.; Ishibashi, H; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, 1989, 879.
2. Ikeda, M.; Teranishi, H.; Iwamura, N.; Ishibashi, H. *Heterocycles*, 1997, **45**, 863.
3. Benedetti, M.; Forti, L.; Ghelfi, F.; Maira Pagoni, U.; Ronzoni, R. *Tetrahedron*, 1997, **53**, 14031.
4. Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron*, 1996, **52**, 1069.
5. (a) Seijas, J.A.; Vázquez-Tato, M.P.; Castedo, L.; Estévez, R.J.; Ónega, M.G.; Ruiz, M. *Tetrahedron*, 1992, **48**, 1637. (b) Baldovini, N.; Bertrand, M.-P.; Carriére, A.; Nouguier, R.; Plancher, J.-M. *J. Org. Chem.*, 1996, **61**, 3205. (c) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.*, 1993, **58**, 464.
6. (a) Slough, G.A. *Tetrahedron Lett.*, 1993, **34**, 6825. (b) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.*, 1992, **57**, 1682. (c) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.*, 1993, **58**, 2360. (d) Rachita, M.A.; Slough, G.A. *Tetrahedron Lett.*, 1993, **34**, 6821.
7. Boivin, J.; Yousfi, M.; Zard, S.Z. *Tetrahedron Lett.*, 1994, **35**, 5629.
8. Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, 1992, 2399. (b) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, 1995, 1115. (c) Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles*, 1992, **33**, 139. (d) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron: Asymmetry*, 1996, **7**, 2531.
9. (a) Baldwin, J.E. *J. Chem. Soc., Chem. Commun.*, 1976, 734. (b) Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.*, 1980, 482. (c) Beckwith, A.L.J. *Tetrahedron*, 1981, **37**, 3100.
10. For examples of alternative 5-*endo* radical cyclisations see (a) Gimisis, T.; Chatgilialoglu, C. *J. Org. Chem.*, 1996, **61**, 1908. (b) Tanner, D.D.; Rahimi, P.M. *J. Org. Chem.*, 1979, **44**, 1674. (c) Capella, L.; Montevecchi, P.C.; Navacchia, M.L. *J. Org. Chem.*, 1996. **61**, 6783. (d) Clive, D.L.J.; Cantin, M. *J. Chem. Soc., Chem. Commun.*, 1995, 319. (e) Mendenhall, G.D.; Protasiewicz, J.D.; Brown, C.E.; Ingold, K.U.; Lusztyk, J. *J. Am. Chem. Soc.*, 1994, **116**, 1718.
11. (a) Goodall, K.; Parsons, A.F. *J. Chem. Soc., Perkin Trans. 1*, 1994, 3257. (b) Goodall, K.; Parsons, A.F. *Tetrahedron*, 1996, **52**, 6739. (c) Goodall, K.; Parsons, A.F. *Tetrahedron Lett.*, 1997, **38**, 491.
12. Easton, C.J. *Chem. Rev.*, 1997, **97**, 53.
13. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
14. Bekali, B.; Parsons, A.F. unpublished results.
15. Attempted deprotection of the corresponding *N*-benzyl derivative (using $Pd/C/H_2$, $N_2H_4/Pd/C$ or Na/NH_3) was unsuccessful.
16. A previous synthesis of 4-phenylglutamic acid (**10**) has been reported [starting from tropic acid] although the overall yield was not quoted. Gershon, H.; Parmegiani, R.; Giannasio, V.R.; Krull, I.S. *J. Med. Chem.*, 1975, **64**, 1855.
17. See for example Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sánchz-Ferrando, F. *Tetrahedron*, 1993, 49, 8665.
18. Alvarez-Ibarra, C.; Csákÿ, A.G.; de Silanes, I.L.; Quiroga, M.L. *J. Org. Chem.*, 1997, **62**, 479.
19. A solution of Bu_3SnH (110 mg, 0.38 mmol) and AIBN (6 mg, 0.04 mmol) in degassed benzene (4 ml) was added dropwise over 9 h to a boiling solution of iodide (**1, X=I**) (127 mg, 0.35 mmol) and methyl acrylate (95 mg, 1.05 mmol) in degassed benzene (14 ml). The mixture was heated at reflux until the starting material had completely reacted (12 h) as indicated by TLC analysis. The solvent was then removed *in vacuo* and diethyl ether (20 ml) and DBU (0.2 ml) added to the residue. After stirring for 0.5 h, filtration and evaporation afforded crude product which was purified by column chromatography (silica).
20. For a related reaction see: Colombo, L.; Di Giacomo, M.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.*, 1994, **35**, 4031.
21. (a) Tietze, L.F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131. (b) Tietze, L.F. *Chem. Rev.*, 1996, **96**, 115 and following papers. (c) Bunce, R.A. *Tetrahedron*, 1995, **51**, 13103.
22. This is tentatively assigned as the *cis*- isomer based on NMR experiments.
23. Walbiner, M.; Wu, J.Q.; Fischer, H. *Helv. Chim. Acta*, 1995, **78**, 910.
24. Hyperfine splittings: $a_{\beta\text{-}1H}$ 2.0, $a_{\beta\text{-}1H}$ 2.24, a_N 0.145, $a_{\gamma\text{-}2H}$ 0.345, $a_{\gamma\text{-}1H}$ 0.19 mT; g 2.0037.
25. Obata, N.; Niimura, K. *J. Chem. Soc., Chem. Commun.*, 1977, 238.