Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2137–2139

TETRAHEDRON LETTERS

Electrochemical synthesis of diaminodicarboxylic acid derivatives

Paula M. T. Ferreira, Hernâni L. S. Maia and Luís S. Monteiro*

Department of Chemistry, University of Minho, Gualtar, P-4710-057 Braga, Portugal

Received 19 December 2002; accepted 15 January 2003

Abstract—Diaminoadipic acid derivatives were synthesized in good yields by electrolysis of *N*,*N*-diacyldehydroalanines. Cyclic voltammetry measurements on the precursors are presented and interpreted as supporting formation of a nucleophilic intermediate generated by electrochemical reduction.

1. Introduction

Diaminodicarboxylic acid derivatives (bis-amino acids) are an important class of biologically active compounds. 2,6-Diaminopimelic acid is the key cross-linking amino acid in the cell wall peptidoglycan layer in many Gram-negative organisms and a precursor of lysine, which is formed via this intermediate in many Gram-positive organisms.[1,2] These diaminodicarboxylic acid derivatives give rise to conformational constraints stabilizing the secondary structures of peptides,[3] and have also been used as building blocks for development of peptidomimetics.[4]

The methods described for the synthesis of these compounds are generally multi-step and/or low yielding. The electrochemical synthesis of diaminodicarboxylic acid derivatives using Kolbe electrolysis has been described by Hiebl et al.[5] In this work oxidative decarboxylation of aspartic and glutamic acid derivatives gave rise to a radical intermediate, which produced 2,5-diaminoadipic acid and 2,7-diaminosuberic acid derivatives by dimerization, but only low yields were obtained. Now, we describe a single step electrochemical method for the synthesis of 2,5-diaminoadipic acid derivatives in good yields using *N*,*N*-diacyldehydroalanine derivatives as starting materials.

2. Results and discussion

Following previous results obtained in the electrochemical cleavage of the *p*-toluenesulfonyl (tosyl, Tos) and *p*-nitrobenzyloxycarbonyl [Z(NO_2)] groups from *N*,*N*-diacyldehydroalanine and *N*,*N*-diacyldehydroaminobutyric acid derivatives,[6] we decided to investigate further the electrochemical behaviour of dehydroamino acid derivatives. Thus, the activation potentials of several *N*-acyl- and *N*,*N*-diacyldehydroamino acid derivatives (Table 1, entries 4–6 and 7–9, respectively) were determined by cyclic voltammetry and compared with those for the respective β-hydroxyamino acid derivatives (Table 1, entries 1–3).[7]

As expected from our previous experience,[8] the peak potentials found with all the Z(NO_2) amino acid derivatives investigated fell within a fairly narrow range (0.15 V); the reduction potential of this group is not affected by the neighbourhood of either a *tert*-butyloxycarbonyl group (Boc) group or a double bond. However, this was not the case of both benzoyl (Bz) and tosyl dehydroamino acid derivatives, which exhibit reduction potentials shifted to significantly less negative values than those of the corresponding β-hydroxyamino acid compounds. We assign this behaviour to stabilisation of the radical anion by conjugation of the aromatic ring of these two groups with the α,β-double bond (entries 4–6) and with the Boc carbonyl group (entries 7–9), which would not occur in the case of the nitrophenyl species. This effect is enhanced in the dehydrophenylalanine (ΔPhe) series (entries 3, 6 and 9) by further conjugation with the amino acid β-phenyl ring and markedly weakened in the dehydroaminobutyric acid (ΔAbu) series (entries 1, 4 and 7), certainly due to the electron donating effect of the β-methyl group.

Keywords: dehydroamino acids; cyclic voltammetry; electrolysis; diaminodicarboxylic acids; 2,5-diaminoadipic acid.

* Corresponding author. Fax: 351 253 678983; e-mail: monteiro@quimica.uminho.pt

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00163-1

Table 1. Peak potentials obtained by cyclic voltammetry of amino acid and dehydroamino acid derivatives[a]

	Compound		$-Ep$ (V versus S.C.E.)				
		P	Z(NO_2)	Bz	Tos	Z	Boc
1	P-Thr-OMe		1.14	2.36	2.50	2.82	[b]
2	P-Ser-OMe		1.04	2.42	2.48	2.86	[b]
3	P-Phe(β-OH)-OMe		1.08	2.38	2.53		[b]
4	P-ΔAbu-OMe		0.97	2.21	2.18	2.34	2.46
5	P-ΔAla-OMe		1.10	1.91	1.90	2.29	2.12
6	P-ΔPhe-OMe		1.12	1.87	1.65		1.84
7	P-ΔAbu(*N*-Boc)-OMe		1.02	2.02	2.12	2.19	2.36
8	P-ΔAla(*N*-Boc)-OMe		1.04	1.84	1.88	2.04	2.01
9	P-ΔPhe(*N*-Boc)-OMe		1.02	1.80	1.74		1.84

[a] Cathode: vitreous carbon. Solvent: dimethylformamide. Supporting electrolyte: Bu_4NBF_4 0.1 mol dm^{-3}. Substrate conc.: ≈0.005 mol dm^{-3}.
[b] No reduction peak was detected.

All cyclic voltammograms were consistent with irreversible processes occurring after formation of the radical anions, and previous results obtained in electrolyses of Z(NO_2) and Tos in *N*,*N*-diacyldehydroalanine and dehydroaminobutyric acid derivatives showed that these two protecting groups undergo cleavage at the peak potentials listed in Table 1.[6] However, cyclic voltammograms for dehydroamino acids mono and diacylated with Boc showed peak potentials between −1.84 and −2.46 V versus S.C.E. Since this group is stable to electrochemical reduction,[8] the irreversible voltammograms found for these compounds could not be related to cleavage of Boc. In addition, once the aromatic ring of Z is not conjugated with the rest of the molecule, potential shifts of 0.63 V or more would be related to the α,β-double bond in conjugation with at least two carbonyl groups, and not to the protecting group.

In view of the cyclic voltammetry data now obtained, controlled potential electrolysis of Boc-ΔAla(*N*-Boc)-OMe and Z-ΔAla(*N*-Boc)-OMe at the peak potentials indicated in Table 1 was carried out. With both substrates, a 2,5-diaminoadipic acid derivative was isolated in good yields (85% and 78%, respectively) as diastereomeric mixtures.[9] We believe that the reaction proceeds via formation of a carbanion at the β-carbon atom, which acts as a nucleophile and adds to a molecule of the starting material. In fact, no such reaction was found with Boc-ΔAla-OMe and Boc-ΔPhe(*N*-Boc)-OMe, which are known not to be sufficiently strong electrophiles to undergo nucleophilic attack[10] (electrolysis of the former resulted in decomposition of the starting material without formation of the diaminoadipic acid derivative). In addition, electrolysis of Boc-ΔPhe(*N*-Boc)-OMe gave Boc-ΔPhe-OMe due to cleavage of one of the Boc groups by electrochemically generated bases.

Thus, electrochemical reduction of Boc-ΔAla(*N*-Boc)-OMe and Z-ΔAla(*N*-Boc)-OMe constitutes a valuable method for the preparation of 2,5-diaminoadipic acid derivatives.

Acknowledgements

We wish to thank the Fundação para a Ciência e a Tecnologia for financial support (project no. POCTI/1999/QUI/32689).

References

1. Roberts, J. L.; Chan, C. *Tetrahedron Lett*. **2002**, *43*, 7679–7682.
2. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 1259–1262.
3. Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem*. **1999**, *64*, 1947–1952.
4. Sutherland, A.; Vederas, J. C. *Chem. Commun*. **2002**, 224–225.
5. Hiebl, J.; Blanka, M.; Guttman, A.; Kollmann, H.; Leitner, K.; Mayrhofer, G.; Rovenszky, F.; Winkler, K. *Tetrahedron* **1998**, *54*, 2059.
6. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3697–3703.
7. Cyclic voltammetry experiments were carried out using a Hi-Tek potentiostat type DT 2101, and a Hi-Tek wave generator type PPRl, connected to a Philips recorder type PM 8043 and to a three electrode, home-built glass cell.
8. Maia, H. L. S.; Monteiro, L. S.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 495–500.
9. A solution of Et_4NCl (0.1 mol dm^{-3}; supporting electrolyte) and Et_3NHCl (0.04 mol dm^{-3}; proton donor) in MeCN was added to a three-electrode cell. To its cathodic compartment Boc-ΔAla(*N*-Boc)-OMe (150.5 mg, 0.5 mmol) was added and a cyclic voltammogram recorded. The potential was adjusted to a value 50 mV more negative than that corresponding to the CV peak and the electrolysis started, the reaction being monitored by HPLC. When all starting material had disappeared, the content of the cathodic compartment was concentrated at reduced pressure and the residue partitioned between 100 cm^3 of ethyl acetate and 50 cm^3 of citric acid 5%. The organic phase was then washed with citric acid

5%, $NaHCO_3$ 1 mol dm^{-3} and brine (three times 30 cm^3 each) and then dried over $MgSO_4$. Removal of the solvent afforded the dimethyl ester of *N*,*N*,*N*′,*N*′-tetra(*tert*-butyloxycarbonyl) 2,5-diaminoadipic acid as a mixture of white solid diastereomers (85%) (found C, 55.68%; H, 8.00%; N, 4.42%. Calcd for $C_{28}H_{48}N_2O_{12}$ C, 55.62%; H, 8.00%; N, 4.63%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.48, 1.50 (36H, 2s, C*H*$_3$ Boc), 1.83–2.02 (2H, m, βC*H*$_2$), 2.08–2.16 (2H, m, βC*H*$_2$), 3.70 (6H, s, C*H*$_3$ OMe), 4.84–4.87 (1H, m, αC*H*), 5.00–5.03 (1H, m, αC*H*); δ_C (75.4 MHz; $CDCl_3$) 26.10, 27.91, 52.13, 57.27, 83.19, 151.84, 171.04. The same procedure as described above was followed with Z-ΔAla(*N*-Boc)-OMe (167.7 mg, 0.5 mmol) to give the dimethyl ester of *N*,*N*′-bis(benzyloxycarbonyl) *N*,*N*′-bis(*tert*-butyloxycarbonyl) 2,5-diaminoadipic acid as an oily mixture of diastereoisomers (78%) (found C, 60.26%; H, 6.26%; N, 4.05%. Calcd for $C_{34}H_{44}N_2O_{12}$ C, 60.70%; H, 6.59%; N, 4.16%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.42 (18H, s, C*H*$_3$ Boc), 1.44 (18H, s, C*H*$_3$ Boc), 1.80–2.18 (2H, m, βC*H*$_2$), 2.19–2.43 (2H, m, βC*H*$_2$), 3.61 (3H, s, C*H*$_3$ OMe), 3.62 (3H, s, C*H*$_3$ OMe), 4.89–4.92 (1H, m, αC*H*), 5.03–5.08 (1H, m, αC*H*), 5.22 (2H, d, $J=3.6$, C*H*$_2$ Z), 5.24 (2H, d, $J=3.0$, C*H*$_2$ Z), 7.32–7.40 (10H, m, Ar*H* Z); δ_C (75.4 MHz; $CDCl_3$) 27.74, 27.77, 52.17, 57.48, 58.30, 68.83, 68.86, 83.83, 128.21, 128.23, 128.32, 128.48, 135.02, 135.10, 151.13, 153,63, 153.70, 170.45, 170.56.

10. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167–3174.