

0040-4039(94)E0136-L

Synthesis of Enantiomerically Pure 2,2-Disubstituted-2-Amino-ethanols by Dissolving Metal Reduction of a,a-Disubstituted Amino Acid Amides

Harold M. Moody, Bernard Kaptein', Quirinus B. Broxterman, Wilhelmus H. J. Boesten and Johan Kamphuis

> DSM Research, Bio-organic Chemistry Section, PO Box 18, 6160MD Geleen, The Netherlands

Abstract: Enantiomerically pure 2,2-disubstituted 2-amino-ethanols are prepared in 65 - 99% yield by reduction of a, a-disubstituted amino acid amides using liquid sodium metal in refluxing 1-propanol.

Chiral amino alcohols are versatile starting materials in asymmetric synthesis¹ and for the synthesis of biologically active compounds². In general the 2-substituted 2-amino-ethanols are readily prepared by reduction of amino acids or their corresponding esters by LiAlH₄, BH₃, or NaBH₄ either in combination with a protic or a Lewis acid^{3.4}. 2,2-Disubstituted 2-amino-ethanols are less frequently mentioned in literature despite the fact these amino alcohols too, are of interest for new pharmaceuticals like Fedotozine tartrate⁵ and Cericlamine hydrochloride⁶.

We wish to report here our results on the synthesis of this type of amino alcohol by a new method, namely by reduction of enantiomerically pure amino acid amides using liquid sodium metal in refluxing alcohols. Mono- and disubstituted amino acid amides are readily available in high enantiomeric excesses by enzymatic methods⁷.

In the course of our studies on chiral 1,2-diamines from amino acid amides our attention was drawn to a recent article by Chatterjee *et al*⁸. In the reduction of amides using sodium, amines were isolated as the sole product. The formation of mixtures of alcohols and amines has also been described however⁹. We used liquid sodium metal in refluxing 1-propanol for the reduction of amino acid amides but to our suprise no 1,2-diamine was formed and only amino alcohols were isolated¹⁰.



Although the reduction of amino acid amides containing an α -hydrogen proceeded in only moderate yields and with extensive racemization, the yields with α , α -disubstituted amino acid amides were nearly quantitative. In addition, no racemization was observed. Different solvents were tested in this reduction (e.g. THF, dioxane, liquid NH₃, NH₃/MeOH, EtOH, 1-propanol, 2-propanol, 1-butanol and t-butanol). Complete conversion was only achieved when sodium in refluxing 1-propanol (97°C) was used. Under these conditions 5-6 equivalents of sodium metal are sufficient to accomplish the reduction in 15 to 60 minutes. Although 1-butanol can be used the reduction is more sluggish and more sodium is needed.

In a typical experiment 50 mmol of the amino acid amide is dissolved in 80-100 ml of 1-propanol. This solution was heated to reflux under a nitrogen atmosphere and 300 mmol of sodium metal added in portions over a period of 15 minutes. The sodium was completely dissolved after refluxing for an additional hour (ammonia is liberated from the cooler). After cooling, 10 ml of water was added and the solution concentrated *in vacuo*. The residue was dissolved in water and extracted with CH₂Cl₂ or CHCl₃. The organic layers were washed with water, dried (MgSO₄) and concentrated to yield pure amino alcohols. The results are listed in Table 1.

Many functional groups are tolerant of these reducing conditions as can be seen from our results. Aromatic groups and double bonds are not reduced and sulfur substituted substrates are not dealkylated. However, a chloro-substituted substrate (see Table) was found to be dechlorinated as well as reduced. As a consequence a mixture of products was obtained. Using a large excess of sodium (17 eq.) complete reduction as well as complete dehalogenation occurred¹¹. The reduction is not restricted to amino acid amides; phenylacetamide is also reduced to 2-phenethyl alcohol in 78% yield.

Although sodium reduction is described for esters (Bouveault-Blanc reduction)⁹, the conversion of amides to alcohols does not proceed by transformation of the amides into the propyl ester (by NaOⁿPr) and subsequent reduction. Transformation of amino acid amides into propyl esters is sluggish (80% conversion for phenylacetamide and only 14% conversion for *a*-methylhomophenylalanine amide after 24 hours reflux) while the sodium reductions are completed within 1 hour. We believe that reduction most likely proceeds by electron transfer to the amide and protonation of the radical anion. Subsequent electron transfer and protonation yields the *geminal* amino alcohol which loses NH₃. The aldehyde is then reduced to the alcohol. This mechanism via electron transfer is supported by the work of Kamochi and Kudo who used Sml₂ in the reduction of amides to primary alcohols¹².

In conclusion, 2,2-disubstituted 2-amino-ethanols can be synthesized in high yields from the corresponding amino acid amides without racemization using the cheap reagents sodium¹³ and 1-propanol.

Table 1



Notes: a. Enantiomeric excesses were determined by ¹H NMR (using trifluoroanthrylethanol) or by HPLC (ref 13); b. 6-8 eq. of sodium in 1-propanol containing 4 % of water were used; c. 82 % yield after bulb-tobulb distillation (110-115 °C/0.1 Torr.); d. due to high solubility this compound was isolated via its Schiff base with benzaldehyde (ref 14);e. 17 eq. of sodium were used.

References and notes.

- a) Coppola, G.M.; Schuster, H.F. 'Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids', J. Wiley & Sons, New York, 1987. b) Blaser, U-H. Chem. Rev. 1992, 92, 935. c) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. J. Org. Chem. 1993, 58, 1515.
- Xim, T.H.; Rapoport, H. J. Org. Chem. 1990, 55, 3699. b) Parker, K.A.; Coburn, C.A. J. Org. Chem. 1991, 56, 4601. c) Hobbs, S.H.; Johnson, S.J.; Kesten, S.R.; Pavia, M.R.; Davies, R.E.; Schwarz, R.D.; Coughenour, L.L.; Myers, S.L.; Dudley, D.T.; Moos, W.H. BioOrg. Med. Chem. Lett. 1991, 1, 147.
- a) Karrer, P.; Portmann, P.; Suter, M. Helv. Chim. Acta 1948, 31, 1617. b) Giannis, A.; Sandhoff, K. Angew. Chem., Int. Ed. Engl. 1989, 28, 218. c) Pridgen, L.N.; Prol, J.; Alexander, B.; Gillyard, L. J. Org. Chem. 1989, 54, 3231. d) Abiko, A.; Masamune, S. Tetrahedron Lett. 1992, 33, 5517. e) McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. J. Org. Chem. 1993, 58, 3568.
- 4. Boesten, W.H J.; Roberts, M.J.A.; Schepers, C.H.M. Eur. Pat. 322982 (1989).
- a) Pascaud, X.; Honde, C.; Le Gallou, B.; Chanoine, F; Roman, F.; Bueno, L.; Junien, J.L. Pharm. Pharmacol. 1990, 42, 546. b) Drugs Fut. 1992, 17, 101.
- 6. a) Gouret, C.J.; Wettstein, J.G.; Porsolt, R.D.; Puech, A.; Junien, J L. *Eur. J. Pharmacol.* 1990, 183, 1478.
 b) Gouret, C.J.; Porsolt, R.D.; Wettstein, J.G.; Puech, A.; Pascaud, X.; Junien, J.L. *Arzneim. Forsch/Drug Res.* 1990, 40, 633. c) *Drugs Fut.* 1993, 18, 365.
- 7. a) Kamphuis, J.; Boesten, W.H.J.; Broxterman, Q.B.; Hermes, H.F.M.; Van Balken, J.A.M.; Meijer, E.M., Schoemaker, H.E. Advances in Biochemical Engineering/Biotechnology 1990, 42, 134. b) W.H. Kruizinga, W.H.; Bolster, J.; Kellogg, R.M.; Kamphuis, J.; Boesten, W.H.J.; Meijer, E.M.; Schoemaker, H.E. J. Org. Chem. 1988, 53, 1826 c) Kaptein, B.; Boesten, W.H.J.; Broxterman, Q.B.; Peters, P.J.H.; Schoemaker, H.E.; Kamphuis, J. Tetrahedron Asymm. 1993, 4, 1113 d) Van den Tweel, W.J.J.; Van Dooren, T.J.G.M.; De Jonge, P.H.; Kaptein, B.; Duchateau, A.L.L.; Kamphuis, J. Appl. Microbiol. Biotechnol. 1993, 39, 296.
- 8. Bhandari, K., Sharma, V.L.; Chatterjee, S.K. Chem. Ind. 1990, 547.
- Schröter R. in: 'Methoden der Organischen Chemie, (Houben-Weyl)', Vol XI/1, Thieme Verlag, Stuttgart, 1957, 595-597.
- 10. Boesten, W.H.J.; Moody, H.M.; Broxterman, Q.B. NL Pat. Appl. 9101623 (1991).
- 11. Kaptein, B.; Moody, H.; Broxterman, Q.B.; Kamphuis, J. submitted for publication.
- 12. Kamochi, Y.; Kudo, T; Tetrahedron Lett. 1991, 32, 3511.
- Ashworth, P.; Chetland J.in 'Speciality Chemicals', Ed. B Pearson, Elsevier Appl. Sciences, London, 1992, 259-278.
- 14. Duchateau, A L.L.; Knuts, K.; Boesten, J.M.M.; Guns, J.J J. Chromatogr. 1992, 623, 237.

(Received in UK 1 December 1993; revised 7 January 1994; accepted 14 January 1994)