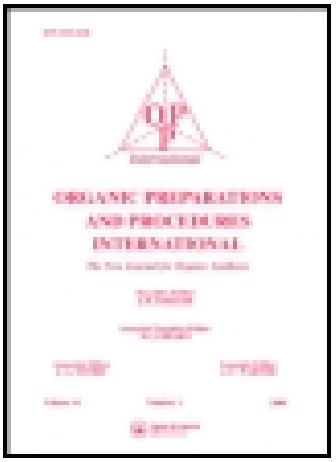


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A FACILE SYNTHESIS OF W-BENZYLOXYCARBONYL-(S)-2-AMINO-3-(DIMETHYLAMINO)PROPANOICACID

Ryszard Andruszkiewicz [a] & Aleksandra Walkowiak [a]

[a] Department of Pharmaceutical Technology and Biochemistry , Technical University of Gdańsk , 80-952, Gdańsk, POLAND

Published online: 18 Feb 2009.

To cite this article: Ryszard Andruszkiewicz & Aleksandra Walkowiak (2001) A FACILE SYNTHESIS OF W-BENZYLOXYCARBONYL-(S)-2-AMINO-3-(DIMETHYLAMINO)PROPANOICACID, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 33:4, 379-381, DOI: 10.1080/00304940109356605

To link to this article: http://dx.doi.org/10.1080/00304940109356605

10. R. C. Haddon and S. V. Chichester-Hicks, *Macromolecules*, **22**, 1027 (1989).

11. H. R. Allcock and S. Kwon, *Macromolecules*, **22**, 75 (1989).

12. H. R. Allcock, D. C. Ngo, M. Parvez, R. R. Whittle and W. J. Birdsall, *J. Am. Chem. Soc.*, **113**, 2628 (1991).

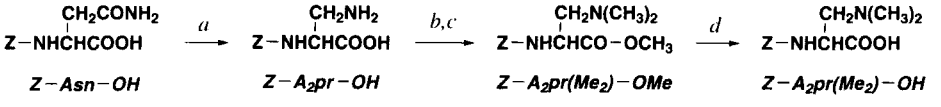
****

A FACILE SYNTHESIS OF N^2-BENZYLOXYCARBONYL-(S)-2-AMINO-3-(DIMETHYLAMINO)PROPANOIC ACID

Submitted by (02/20/01) Ryszard Andruszkiewicz* and Aleksandra Walkowiak

Department of Pharmaceutical Technology and Biochemistry
Technical University of Gdańsk, 80-952 Gdańsk, POLAND

In our research program aimed at the design and synthesis of selective inhibitors of glucosamine-6-phosphate synthase[1,2] and edeine antibiotics,[3] we required a wide range of functionalized (S)-2,3-diaminopropanoic acids that could be converted into N,N-dimethylated residues. Several methods for the preparation of (S)-2-amino-3-(dimethylamino)propanoic acid have been published recently. Application of chiral Co(III) complexes with (S)-aspartic acid or (S)-2,3-diaminopropanoic acid[4] has been shown to be a multi-step and tedious preparative method. The ring opening of protected serine β-lactones with N,N-dimethylamine seems to be a convenient and attractive route to optically pure $A_2pr(Me_2)$ derivatives.[5,6,7] However, despite its simplicity, nucleophilic ring opening of Boc- or Z-serine-β-lactone with N,N-dimethylamine under various reaction conditions (THF, acetonitrile and methylene chloride as solvents and temperatures 0° and 20°) resulted in the formation of the corresponding amides in high yield arising from acyl-oxygen cleavage, and traces of products arising from alkyl-oxygen cleavage. Moreover, reaction of N,N-dimethyl-N-(trimethylsilyl)amine with the same β-lactones, in our hands, gave a mixture of both amino acids and amides, the latter only in 37-45% yield respectively. Reductive methylation[8] of protected A_2pr with formaldehyde and sodium cyanoborohydride thus appeared to be the method of choice. Herein, we report a complete description of the preparation of Z-$A_2pr(Me_2)$-OH[9] in high yield and purity.



a) PIDA b) CH_2O,$NaBH_3CN$ c) MeOH/$SOCl_2$ d) NaOH

Z-A_2pr-OH was prepared from protected asparagine using iodosobenzene diacetate (PIDA) according to the published procedure.[10] Alkylation of the primary N^3-amine of Z-A_2pr-OH with formaldehyde and $NaBH_3CN$ in acetonitrile/acetic acid afforded the dimethylated derivative Z-A_2pr(Me_2)-OH in high yield. Then, in order to isolate the desired derivative and to remove inorganic salts, dimethylated compound was smoothly converted into the methyl ester Z-A_2pr(Me_2)-OMe with methanol using $SOCl_2$ as a catalyst. The crude product was extracted with ethyl acetate, the methyl ester was saponified and the final product purified on AG 1X2 anion exchange resin column. The residue was crystallized from a mixture of MeOH/Et_2O gave Z-A_2pr(Me_2)-OH. The good overall yield (80%) achieved for the reaction sequence (b → c → d), thus makes the present procedure a practical and useful one.

EXPERIMENTAL SECTION

Mp was determined on a Boëtius heating block and is uncorrected. Reactions were monitored and the products checked on silica gel plates (DC Alufolien Kieselgel 60, Merck) in the following solvent systems (v/v): A = ethyl acetate-methanol-water (5:1:0.75), B = *n*-butanol-acetic acid-water (4:1:1). All products are homogenous. Specific rotations were measured at a Polamat A (Carl Zeiss Jena) polarimeter. ^1H and ^{13}C NMR spectra were recorded at 200 MHz on a Gemini Varian spectrometer. Elemental analysis was performed on a Perkin Elmer analyzer.

N^2-Benzyloxycarbonyl-(S)-2-amino-3(dimethylamino)propanoic Acid (Z-A_2pr(Me_2)-OH).- To a vigorously stirred suspension of Z-A_2pr-OH (2.22g, 9.3 mmol) in acetonitrile (30 mL), 30% formaldehyde (4.2 mL) and $NaBH_3CN$ (1.03 g, 16 mmol) were added. After 15 min, acetic acid was added until the pH was neutral and stirring was continued for 24 h. After evaporation of solvents, the residue was dissolved in methanol (50 mL) and $SOCl_2$ (0.2 mL) was added dropwise and the mixture was left standing for 12 h with occasional stirring. After evaporation of methanol, the residue was dissolved in water (5 mL), neutralized with 1 M aqueous $NaHCO_3$ and extracted with chloroform (2x 20 mL). The organic layer was evaporated, the oily residue dissolved in stoichiometric amount of 1M NaOH (8.3 mL) and methanol (10 mL) and kept for 2 h at room temperature. The concentrated solution was adsorbed on AG 1X2 column (OH^-, 0.8 x 10 cm). Elution with 1 M acetic acid and evaporation of eluate to dryness gave the solid residue which was crystallized from methanol-ethyl ether to obtain 1.98 g (80%) of the title compound, mp.138-139° (dec.). TLC: R_f : A - 0.19, R_f : B - 0.31 $[\alpha]^{20}_D$ = -18.2° (c = 1, H_2O)

^1H NMR (D_2O, 200 MHz): δ 2.75 (N(CH_3)$_2$, s,6H), 3.18 (CH_AH_B,dd,1H, J_{AB} = 13.2 Hz, J_{AX} = 8,6 Hz), 3.35 (CH_AH_B, dd, 1H, J_{AX} = 6.2 Hz, J_{AB} = 13.2 Hz), 4.20 (CH, dd, 1H, J_{AX} = 6.2 Hz. J_{BX} = 8.6 Hz), 4.98 (PhCH_2, s, 2H), 7.27 (C_6H_5, m, 5H).

^{13}C NMR (D_2O, 200 MHz): δ 46.02 (CH_2), 53.98 (CH), 61.56 (N(CH_3)$_2$), 70.28 (PhCH_2), 130.79, 131.39, 131.70 (CH arom), 139.01 (CH_{arom}), 160.75 (CO_{ureth}), 177.18 (COOH)

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.82; H, 7.03; N, 10.28

Acknowledgement.- Financial support from the Chemical Faculty, Technical University of Gdańsk is gratefully acknowledged.

REFERENCES

1. R. Andruszkiewicz, S. Milewski and E. Borowski, *J. Enzyme Inhibition*, **9**,123 (1995)

2. R. Andruszkiewicz, R. Jedrzejczak, T. Zieniawa, M. Wojciechowski and E. Borowski, *ibid.*, **15**, 429 (2000)

3. J. Gumieniak, R. Andruszkiewicz, A. Czerwiński, J. Grzybowska and E. Borowski, *J. Antibiot.*, **36**, 1239 (1983)

4. R. Barfod, L. Bendahl, A. Hammershoi, D. K. Jensen, A. M. Sargeson and A. C. Willis, *J. Chem. Soc., Dalton Trans.*, 449 (**1999**)

5. L. D. Arnold, T. H. Kalantar and J. C. Vederas, *J. Am. Chem. Soc.*, **107**, 7105 (1985)

6. N. Kucharczyk, B. Badet and F. LeGoffic, *Synth. Comm.*, **19**, 1603 (1989)

7. E. S. Ratemi and J. C.Vederas, *Tetrahedron Lett.*, **35**, 7605 (1994)

8. R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972)

9. Abbreviations used: Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, Asn = (S)-asparagine, (S)-A_2pr = (S)-2,3-diaminopropanoic acid, Me = methyl, THF = tetrahydrofuran, MeOH = methanol, Et_2O = ethyl ether, PIDA = iodosobenzene diacetate

10. L. H. Zhang, G. S. Kauffman, J. A. Pesti and J. Yin, *J. Org. Chem.*, **62**, 6918 (1997)

****

AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES

Submitted by M. Kidwai* and P. Sapra
(01/26/01)

Department of Chemistry
University of Delhi, Delhi-110007, INDIA

In recent years, organic reactions on solid supports[1] and those assisted by microwaves[2] especially under solventless conditions,[3,4] have attracted attention due to their enhanced selectivity, milder reaction conditions and associated ease of manipulation. Solid phase syntheses can address problems