Molbank **2014**, M833; doi:10.3390/M833

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

N^2-*tert*-Butoxycarbonyl-N^5-[*N*-(9-fluorenylmethyloxycarbonyl)-2-aminoethyl]-(*S*)-2,5-diaminopentanoic Acid

Jyotirmoy Maity * and Roger Stromberg *

Department of Biosciences and Nutrition, Karolinska Institute (KI), Novum, Huddinge SE-141 83, Sweden

* Authors to whom correspondence should be addressed; E-Mails: Roger.Stromberg@ki.se (R.S.); Jyotirmoy.Maity@ki.se (J.M.); Tel.: +46-8-5248-1024 (R.S.); +46-8-5248-1219 (J.M.).

Received: 3 April 2014 / Accepted: 7 August 2014 / Published: 22 August 2014

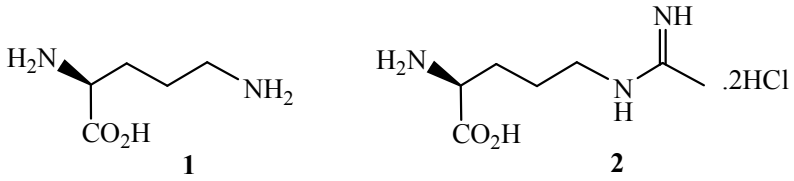
Abstract: N^2-*tert*-Butoxycarbonyl-N^5-[*N*-(9-fluorenylmethyloxycarbonyl)-2-aminoethyl]-(*S*)-2,5-diaminopentanoic acid (**5**) has been synthesized by the reaction of N^2-*tert*-butoxycarbonyl-L-2,5-diaminopentanoic acid (Boc-L-ornithine, **3**) and *N*-Fmoc-2-aminoacetaldehyde (*N*-Fmoc-glycinal, **4**) in the presence of sodium cyanoborohydride in methanol containing 1% acetic acid at room temperature.

Keywords: reductive amination; N^2-*tert*-butoxycarbonyl-N^5-[*N*-(9-fluorenylmethyloxycarbonyl)-2-aminoethyl]-(*S*)-2,5-diaminopentanoic acid; $^{\delta}$N-(2-aminoethyl)-L-ornithine

Introduction

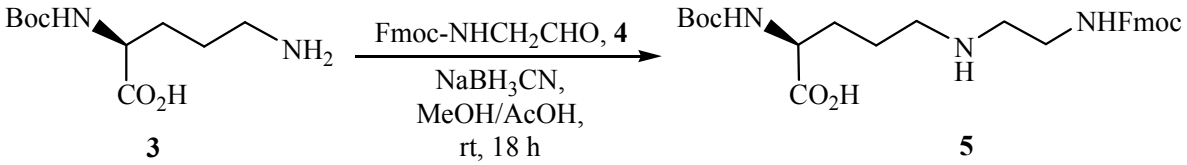
Ornithine (**1**, Figure 1) is a non proteinogenic amino acid, which plays an important role in ammonia metabolism via the urea cycle. Its intake has been recommended as a nutritional supplement for its antifatigue effect [1,2]. N^5-Ornithine derivatives showed their potential as orally active non-peptide fibrinogen receptor antagonists [3] and selective prostaglandin EP_4 receptor antagonists [4]. L-N^5-(1-Iminoethyl)-ornithine dihydrochloride (**2**, Figure 1) was used for studies of bactericidal activity of human eosinophilic granulocytes against *Escherichia coli* [5]. The capability of the N^5-ornithine derivatives as biologically active agents inspired us to synthesize its new-fangled derivatives.

Figure 1. Structures of L-ornithine (**1**) and L-N^5-(1-iminoethyl)-ornithine dihydrochloride (**2**).



Reductive amination has become a versatile and practical method for the preparation of amines in organic synthesis. New catalysts for reductive amination exemplify organocatalysts, complexes of transition metals (Ru, Rh, Ir), reagents involving boron, tin and silicon [6]. This reaction has found its application for the synthesis of natural products, drug molecules and chiral ligands. In this short note, we describe a reductive amination between N^2-*tert*-butoxycarbonyl-L-2,5-diaminopropionic acid (**3**) and *N*-Fmoc-2-aminoacetaldehyde (*N*-Fmoc-glycinal, **4**) to derivatize the ornithine moiety by converting its N^5-primary amine into a secondary amine and extending it with an aminoethyl group; thus producing the building block for the new triamino acid $^{\delta}$N-(2-aminoethyl)ornithine (Scheme 1). As judged by thin layer chromatography (TLC), the Fmoc seems to survive the conditions, but it is possible that some of the aldehyde was consumed by direct reaction with the borohydride, resulting in a moderate yield. Although a change of reagent perhaps could have improved the outcome, we found the isolated yield after chromatography quite acceptable, considering that only 0.9 equivalents of aldehyde was used (for simplicity of purification).

Scheme 1. Synthesis of title compound **5** from Boc-L-ornithine.



Experimental

N^2-tert-Butoxycarbonyl-N^5-[N-(9-fluorenylmethyloxycarbonyl)-2-aminoethyl]-(S)-2,5-diaminopentanoic acid (**5**)

N^2-*tert*-Butoxycarbonyl-L-2,5-diaminopropionic acid (**3**, Boc-L-ornithine, 0.116 g, 0.5 mmol) was dissolved in a solvent mixture (acetic acid/methanol, 1:99, v/v, 10 mL) at rt under stirring. *N*-Fmoc-2-aminoacetaldehyde (**4**, *N*-Fmoc-glycinal, 0.129 g, 0.46 mmol) [7] was added into the reaction mixture slowly followed by addition of $NaBH_3CN$ (0.072 g, 1.14 mmol) in a single lot. The reaction mixture was stirred at rt and the progress of the reaction was monitored by thin layer chromatography. After 18 h, the reaction mixture was evaporated to dryness under reduced pressure and was dissolved in ethyl acetate (15 mL). Organic layer was washed with water (10 mL) and brine (10 mL × 2), dried over Na_2SO_4 and evaporated to dryness under reduced pressure to get crude compound. Pure compound was obtained by purification of the crude using column chromatography (2%–4% methanol in dichloromethane containing 1% acetic acid) to afford pure compound **5** (0.104 g, 42%).

Physical characteristics: White sticky solid.

Yield: 0.104 g, 42%.

R_f = 0.17 (Methanol/dichloromethane/acetic acid = 1:8.9:0.1, v/v/v).

^{1}H-NMR (400 MHz, CD_3OD) (δ/ppm): 7.70 (2H, d, *J* = 7.6 Hz, Ar-H), 7.55 (2H, d, *J* = 7.6 Hz, Ar-H), 7.29 (2H, d, *J* = 7.6 Hz, Ar-H), 7.21 (2H, d, *J* = 7.6 Hz, Ar-H), 4.32 (2H, d, *J* = 6.8 Hz, NCOOC*H*$_2$CH), 4.11 (1H, t, *J* = 6.8 Hz, NCOOCH$_2$C*H*), 3.86 (1H, br s, 2-CH), 3.31 (2H, t, *J* = 5.6 Hz, NCH$_2$C*H*$_2$NHFmoc), 2.98 (2H, t, *J* = 5.6 Hz, NC*H*$_2$CH$_2$NHFmoc), 2.90 (2H, t, *J* = 5.6 Hz, 5-CH$_2$), 1.74–1.61 (4H, m, 3-CH$_2$, 4-CH$_2$), 1.32 (9H, s, C(CH$_3$)$_3$).

^{13}C-NMR (100 MHz, CD_3OD) (δ/ppm), methine and methyl carbons were distinguished from methylene carbons by ^{13}C-DEPT: 179.5 (COOH), 159.2, 157.6 (2 × NCOO), 145.2, 142.6 (C-Ar), 128.8, 128.1, 126.1, 120.9 (CH-Ar), 80.2 (*C*(CH$_3$)$_3$), 68.0 (NCOO*C*H$_2$CH), 56.2 (C-2), 48.8, 48.6 (C-5, N*C*H$_2$CH$_2$NHFmoc), 48.4 (NCOOCH$_2$*C*H), 38.5 (NCH$_2$*C*H$_2$NHFmoc), 31.3 (C-3), 28.8 (C(*C*H$_3$)$_3$), 23.5 (C-4).

IR (KBr) ν_{max} 3433, 1700, 1570, 1415, 1355, 1250, 1160, 1050, 957, 815, 725, 692 and 620 cm^{-1}.

Optical rotation: $[\alpha]_D^{27}$ +8.2 (*c* 1.0, MeOH).

HRMS (ESI-Tof) *(m/z)* calcd for $C_{27}H_{34}N_3O_6^-$ $[M-H]^-$ 496.2453; found 496.2463.

Acknowledgments

We would like to thank the Swedish Research Council for financial support.

Author Contributions

JM and RS planned the work, JM carried out all experimental work, JM and RS wrote the manuscript together.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Sugino, T.; Shiri, T.; Kajimoto, Y.; Kajimoto, O. L-Ornithine supplementation attenuates physical fatigue in healthy volunteers by modulation lipid and amino acid metabolism. *Nutr. Res.* **2008**, *28*, 738–743.
2. Demura, S.; Yamada, T.; Yamaji, S.; Komatsu, M.; Morishita, K. The effect of L-ornithine hydrochloride ingestion on performance during incremental exhaustive ergometer bicycle exercise and ammonia metabolism during and after exercise. *Eur. J. Clin. Nutr.* **2010**, *64*, 1166–1171.

3. Kottirsch, G.; Zerwes, H.-G.; Cook, N.S.; Tapparelli, C. Beta-amino acid derivatives as orally active non-peptide fibrinogen receptor antagonists. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 727–732.
4. Hattori, K.; Tanaka, A.; Fujii, N.; Takasugi, H.; Tenda, Y.; Tomita, M.; Nakazato, S.; Nakano, K.; Kato, Y.; Kono, Y.; *et al.* Discovery of diphenyloxazole and N^{δ}-Z-ornithine derivatives as highly potent and selective human prostaglandin EP_4 receptor antagonists. *J. Med. Chem.* **2005**, *48*, 3103–3106.
5. Persson, T.; Andersson, P.; Bodelsson, M.; Laurell, M.; Malm, J.; Egesten, A. Bactericidal activity of human eosinophilic granucytes against *Escherichia coli*. *Infect. Immun.* **2001**, *69*, 3591–3596.
6. Tripathi, R.P.; Verma, S.S.; Pandey, J.; Tiwati, V.K. Recent development on catalytic reductive amination and applications. *Curr. Org. Chem.* **2008**, *12*, 1093–1115.
7. Matsumori, N.; Masuda, R.; Murata, M. Amphoteric B covalent dimers bearing a tartarate linkage. *Chem. Biodivers.* **2004**, *1*, 346–352.