Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2779–2781
Tetrahedron Letters

Synthesis of L-aminohomohistidine (L-Ahh)

Manuel Friedel and Thomas Lindel*

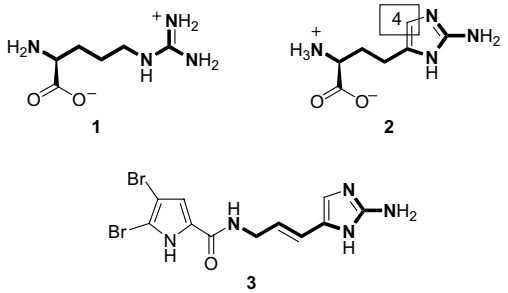
Ludwig-Maximilians-Universität, Department of Chemistry, D-81377 Munich, Germany

Received 22 January 2004; revised 5 February 2004; accepted 6 February 2004

Abstract—A short synthesis of L-aminohomohistidine (L-Ahh) is described, which starts from readily available δ-hydroxy-L-lysine. The embedding of the basic guanidino moiety in the aromatic imidazole lowers the basicity of the side chain to a pK_a of 8.3. It is proposed that L-Ahh may be employed as an arginine-mimetic in medicinal chemistry.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The guanidinium group occurs in the side chain of the proteinogenic amino acid L-arginine (**1**, Scheme 1) and is involved in many physiological and pathophysiological processes. Peterlin-Mašič and Kikelj have compiled a comprehensive review on arginine-mimetics for which there is a constant demand.[1] Enzymes with a preference for guanidinium groups include trypsin-like serine proteases,[2] for example, thrombin, factor Xa, trypsin, many integrin receptors,[3] and NO synthases.[4] Interactions with the guanidinium moiety are mediated by the carboxylate groups of the side chains of aspartic or glutamic acid.



Scheme 1. Structures of L-arginine (**1**), L-aminohomohistidine (**2**, L-Ahh), and oroidin (**3**) sharing an agmatin partial structure.

At physiological pH guanidinium groups are protonated. Their high pK_a-value and polarity hamper their therapeutic use due to poor bioavailability after peroral application.[1] Options to circumvent this problem include the use of aminopyrimidine, benzamidine,[5] or amidinohydrazone[6] moieties, among others.

It may be worthwhile to analyze natural products in this respect. The guanidino motif of the marine pyrrole–imidazole alkaloid oroidin (**3**) is embedded in a 2-aminoimidazole moiety, with the interesting consequence of exhibiting a pK_a-value lowered by about four magnitudes.[7,8] The aromaticity of the imidazole ring overwhelms the basicity of a free guanidino group.

2-Aminoimidazoles have only rarely been considered as guanidinium mimetics.

The free amino acid L-aminohomohistidine (**2**, L-Ahh) has, surprisingly, not been described, yet.[9] In this paper we report a short synthesis and the determination of the pK_a-values of L-Ahh (**2**), which should prove useful as an arginine-mimetic in medicinal chemistry. Formally, one additional carbon atom (C-4, Scheme 1) is introduced into the structure of arginine.

2. Results and discussion

Our synthesis has the advantage of making use of the widely available, nonproteinogenic amino acid (5*S*)-hydroxy-L-lysine (**4**), which can be obtained from collagene in large scale.[10] Moreover, it follows one of the proposals on the biogenesis of oroidin (**3**), which may

Keywords: Amino acids; Aminoimidazoles; Arginine-mimetic; Bioisosteres; Medicinal chemistry.
* Corresponding author. Tel.: +49-89-2180-77733; fax: +49-89-2180-77734; e-mail: thomas.lindel@cup.uni-muenchen

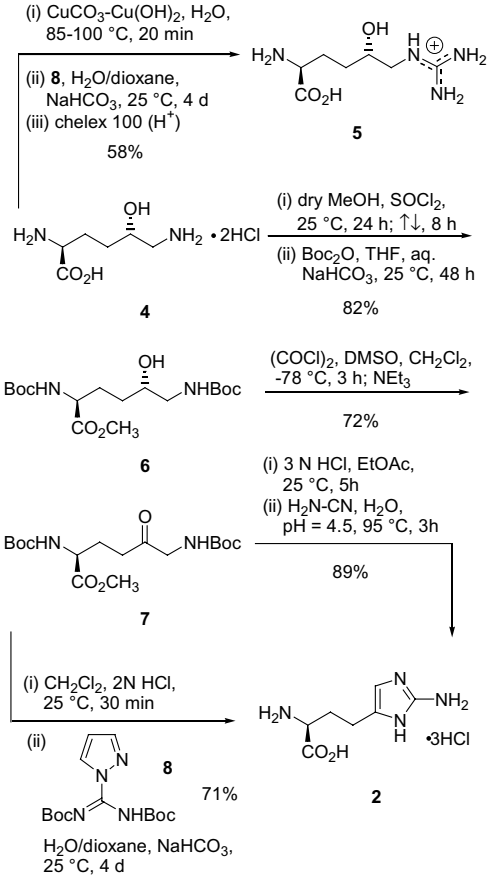
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.027

involve homoarginine, which in turn is derived from lysine.[7b,11]

In principle, differentiation between the α- and ε-amino groups had to be achieved. Initially, we made use of the protecting copper complexation of the α-amino group,[12] which was applied for the particular case of (5*S*)-hydroxy-L-lysine (**4**) by Kihlberg and co-workers.[13] It was indeed possible to subsequently achieve regioselective ε-amidinylation to the guanidino compound **5**. However, it turned out to be difficult to then oxidize the secondary alcohol moiety.

Interestingly, the regioselective amidinylation of the ε-amino group was possible as soon as the secondary alcohol had been oxidized to the ketone. Our synthesis of **2** starts with the reaction of **4** with thionylchloride in dry methanol, followed by conversion of the resulting ester into the twice Boc-protected derivative **6** with Boc_2O in aqueous solution (82% overall yield, Scheme 2). Oxidation of **6** under Swern conditions led to ketone **7** (72% yield).

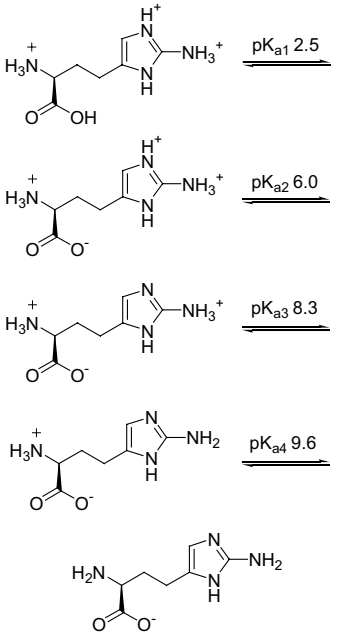
Ketone **7** can be converted to L-Ahh (**2**) by two different means. Boc-deprotection of **7** with aqueous HCl in EtOAc or CH_2Cl_2 followed by reaction with cyanamide at pH 4.5 in aqueous solution led to L-Ahh (**2**) in 89% overall yield.[14] Alternatively, amidinylation of Boc-deprotected ketone **7** with the pyrazole **8**[15] at room temperature (4 d), followed by chromatography on silica gel with *n*-BuOH/H_2O/AcOH (3:1:1) afforded L-Ahh (**2**) in 71% overall yield. In both cases, regioselective amidinylation of the ε-amino group takes place making the differential deprotection of the amino groups unnecessary. The synthesis of L-Ahh (**2**)[16] was accomplished in five steps with an overall yield of 53%, respectively, 42%.



Scheme 2. Synthesis of L-Ahh (**2**).

The pK_a-values of L-Ahh (**2**) will be of key importance to its further use. Titration of a solution of **2** in 0.02 N HCl with 0.1 N NaOH led to the identification of four pK_a-values, which can be assigned as shown in Scheme 3. The first pK_a value of L-Ahh (**2**) (pK_{a1} 2.5, Scheme 3) corresponds well to the first pK_a-value of arginine (pK_{a1} 2.2)[17] and is associated with the deprotonation of the carboxylic acid moiety. The pK_{a2} value of 6.0 corresponds to the loss of the imidazolium N–H and is in good accordance with the pK_a of substituted imidazolium cations as in histidine (pK_a 6.0).[17] The pK_{a4} of the α-amino moiety in **2** is 9.6 compared to a pK_a of 9.04 in arginine.[17] As the major difference to arginine, the monoprotonated side chain of **2** possesses a pK_{a3} of 8.3 compared to a pK_a of 12.48 of the guanidinium moiety of arginine. Comparison with other aminoimidazoles shows that pK_a values of aminoimidazolium cations usually range between 8 and 9, which is in good accordance with our results.[6] The isoelectric point of **2** was determined to be at pH = 8.97, compared to the isoelectric point of arginine at pH = 10.76.[17]

In summary, we have developed a convenient synthetic access to the unknown amino acid 2-aminohomohistidine as an analog of arginine. The protocol can be run with only two work-ups. Investigations concerning the incorporation of L-Ahh (**2**) as a bioisostere in arginine-containing biologically active compounds are currently under way.



Scheme 3. Experimentally determined pK_a-values of L-Ahh (**2**). Structural assignment was made according to literature values.[8,17]

Acknowledgements

We would like to thank Prof. Dr. Karlheinz Drauz and Dr. Franz-Rudolf Kunz from Degussa AG for the generous supply of (5*S*)-hydroxy-L-lysine and for the determination of the pK_a-values. We also thank the Fonds der Chemischen Industrie for financial support.

References and notes

1. Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron* **2001**, *57*, 7073–7105.
2. Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341.
3. Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1374–1389.
4. Alderton, W. K.; Cooper, C. E.; Knowles, R. G. *Biochem. J.* **2001**, *357*, 593–615, and references cited therein.
5. For a leading reference, see: Lam, P. Y. S.; Clark, C. G.; Li, R.; Pinto, D. J. P.; Orwat, M. J.; Galemmo, R. A.; Fevig, J. M.; Teleha, C. A.; Alexander, R. S.; Smallwood, A. M.; Rossi, K. A.; Wright, M. R.; Bai, S. A.; He, K.; Luettgen, J. M.; Wong, P. C.; Knabb, R. M.; Wexler, R. R. *J. Med. Chem.* **2003**, *46*, 4405–4418.
6. Soll, R. M.; Lu, T.; Tomczuk, B.; Illig, C. R.; Fedde, C.; Eisennagel, S.; Bone, R.; Murphy, L.; Spurlino, J.; Salemme, F. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1–4.
7. Reviews on the pyrrole–imidazole alkaloids: (a) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237–243; (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753–1783.
8. Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118–3120.
9. (a) Patent claims on derivatives: Conolly, C.; Doherty, A. M.; Hamilton, H. W.; Patt, W. C.; Sircar, I. (Warner-Lambert Co., USA). Eur. Pat. Appl. EP 399556, 1990; (b) Haik, G. M., Jr. (Redox Inc., USA.). PCT Int. Appl. WO 9717081, 1997; (c) Haik, G. M., Jr. (Redox Inc., USA). PCT Int. Appl. WO 9851260, 1998.
10. (5*S*)-Hydroxy-L-lysine (**4**) is also commercially available.
11. Lindel, T.; Hochgürtel, M.; Assmann, M.; Köck, M. *J. Nat. Prod.* **2000**, *63*, 1566–1569.
12. Schwyzer, R.; Rittel, W. *Helv. Chim. Acta* **1961**, *44*, 161.
13. Broddefalk, J.; Bäcklund, J.; Almqvist, F.; Johansson, M.; Holmdahl, R.; Kihlberg, J. *J. Am. Chem. Soc.* **1998**, *120*, 7676–7683.
14. Lancini, G. C.; Lazzari, E. *J. Heterocycl. Chem.* **1966**, *3*, 152–154.
15. (a) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389–3392; (b) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497–2502.
16. Selected physical and spectroscopical data of L-Ahh (**2**): Mp 184 °C (decomposition). $[\alpha]_{20}^{365}$ +37.2 ($c=$ 5 mg/mL in MeOH). UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon) = 266$ nm (496 mol^{-1} dm^3 cm^{-1}). IR (KBr): $\tilde{\nu} = 3402$ (s), 2533 (w), 1678 (s), 1635 (s), 1420 (w), 1210 (w), 541 (m). ^{1}H NMR (400 MHz, D_2O): $\delta = 6.51$ (s, 1H, CC*H*NH), 3.96 (t, $^3J = 6.18$ Hz, 1H, C*H*CH_2), 2.67–2.59 (m, 2H, CH_2CH_2C), 2.23–2.06 (m, 2H, $CHCH_2CH_2$). ^{13}C NMR (100 MHz, D_2O): $\delta = 71.8$ (1C, *C*O_2H), 146.7 (1C, N*C*NN), 125.0 (1C, N*C*CH), 109.7 (1C, C*C*HNH), 52.0 (1C, *C*$CHCH_2$), 28.5 (1C, CH_2CH_2C), 20.0 (1C, $CHCH_2CH_2$). MS (FAB): $m/z = 185$ $[M+H]^+$. HRFABMS $C_7H_{12}N_4O_2[M+H]^+$: calcd 185.1039; found 185.1026.
17. Lide, D. R. *Handbook of Chemistry and Physics*, 76th ed.; CRC: Boca Raton, 1995; p 7-1.