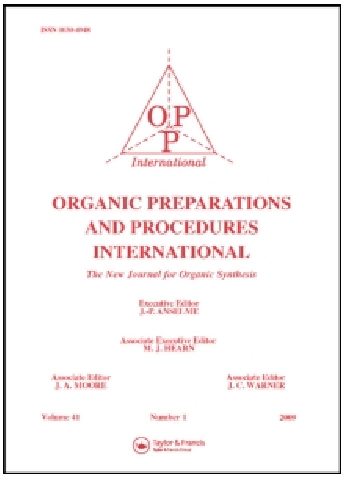


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF L-HISTIDINOL

K. W. Bentley[a]; E. H. Creaser[a]
[a] Research School of Biological Sciences, The Australian National University, Canberra, Australia

To cite this Article Bentley, K. W. and Creaser, E. H.(1973) 'AN IMPROVED SYNTHESIS OF L-HISTIDINOL', Organic Preparations and Procedures International, 5: 1, 5 — 7

To link to this Article: DOI: 10.1080/00304947309356454

URL: http://dx.doi.org/10.1080/00304947309356454

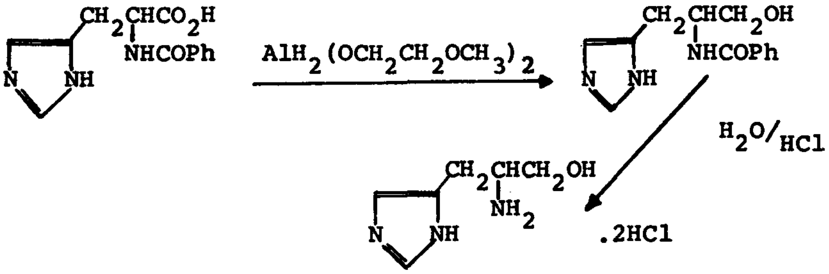
ORGANIC PREPARATIONS AND PROCEDURES INT. 5(1), 5-7 (1973)

AN IMPROVED SYNTHESIS OF L-HISTIDINOL

K.W. Bentley and E.H. Creaser

Research School of Biological Sciences
The Australian National University,
Canberra, Australia.

The normal procedure for the conversion of L-histidine to L-histidinol is the reduction of the monobenzoyl-L-histidine methyl ester with lithium aluminium hydride in tetrahydrofuran solution and subsequent hydrolysis of the benzoyl-L-histidinol[1]. This method suffers from the disadvantages associated with the use of lithium aluminium hydride in the presence of ethers. Furthermore, the stepwise preparation of the monobenzoyl-L-histidine methyl ester gives a considerable loss of yield.



For our studies on the inducible histidinol dehydrogenase of Arthrobacter histidinolovorans[2] it was necessary to have a rapid and convenient synthesis for histidinol. We now report an improved method for the synthesis of L-histidinol dihydrochloride based upon reduction of monobenzoyl-L-histidine by sodium bis-(2-methoxyethoxy) aluminium hydride (RED-AL, VITRIDE), followed by acid hydrolysis[3].

EXPERIMENTAL

Monobenzoyl-L-Histidine.- Monobenzoyl-L-histidine was prepared in 77% yield by the method of Gerngross[4] mp.244-246° (after drying at 110° for 4 hours to remove water of crystallisation). The pure compound could be obtained by crystallisation from water, mp. 248° (dec.), lit. mp.247° (dec.)

Benzoyl-L-Histidinol.- The tetrahydrofuran used in this preparation was dried over sodium for several days and then distilled. A 3-necked 3 litre round bottom flask was provided with mechanical stirrer, reflux condenser and dropping funnel, the last two being protected with calcium chloride drying tubes. A suspension of 30 g. (0.12 moles) of monobenzoyl-L-histidine was heated in 1.0 l of tetrahydrofuran until most of it had dissolved. To this mixture was added 110 ml. of a 70% benzene solution of sodium bis-(2-methoxyethoxy) aluminium hydride (Eastman Kodak) at such a rate as to keep the mixture gently boiling. After the addition was complete, the solution was refluxed for two hours. The solution was cooled to 0°, and after ascertaining that little reductant remained, taken to dryness under reduced pressure at 35°. Then 150 ml. of 5M hydrochloric acid was added to the residue and the mixture refluxed under nitrogen for 90 min. After cooling the solution was extracted three times with ether to remove benzoic acid and the aqueous layer concentrated to dryness under reduced pressure. This histidinol dihydrochloride was recovered by heating the residue in 800 ml. of 95% ethanol filtering through a sintered glass funnel and concentrating the filtrate until crystallisation commenced. The yield of product, mp. 194-196° was 84%. The pure compound mp. 197-199° was obtained in 76% yield by recrystallisation from 95% ethanol. $[\alpha]_D^{25} = -4.0$ (H_2O); lit. $[\alpha]_D^{18} = -3.7$ (H_2O).

The overall yield of the conversion of histidine to histidinol was 58%. This compared favourably with that previously obtained 31%[1].

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(Received December 19, 1972; in revised form February 6, 1973)