Tetrahedron Letters,Vol.25,No.14,pp 1425-1428,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A NOVEL AND EFFICIENT SYNTHESIS OF L-VINYLGLYCINE

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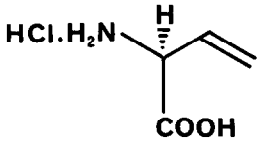
Summary - A simple and practical synthesis of the title compound starting with L-glutamic acid is described.

Naturally-occurring amino acids and their derivatives[1] are enjoying renewed popularity as synthetically useful chirons[2] in a variety of chemically and biochemically directed projects. Vinylglycine is a unique amino acid which has been isolated from mushrooms[3] and implicated in a number of biochemical processes.[4,5] It has been the subject of several synthetic studies[5,6] which produced it in racemic form or in a partially resolved form, in modest to poor yield. The most recent synthesis by the Rapoport group[8] devised an elegant entry to the optically pure L-amino acid hydrochloride 1, using L-methionine as starting material. In this scholarly study, several facets of the chemical and physico-chemical properties of the amino acid were discussed and experimentally studied. It is evident that



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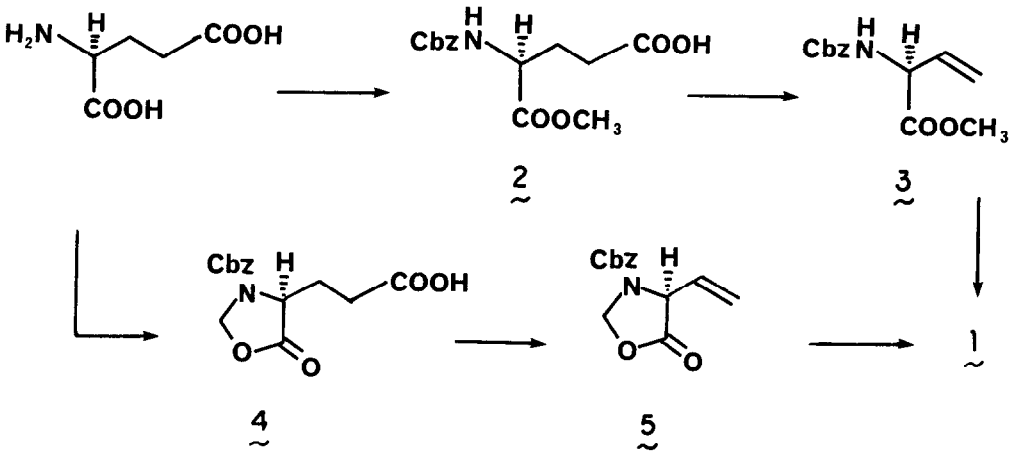
any synthetic or manipulative exercise concerned with L-vinylglycine or its derivatives is earmarked for two major setbacks, namely, racemization (if only partial) and isomerization to the corresponding dehydroamino acid. Hence any attempts at synthesis must take into account the delicate balance of functionality and chirality in this intriguing molecule.



We wish to report on a simple and practical synthesis of optically pure crystalline L-vinylglycine hydrochloride from the inexpensive and readily available L-glutamic acid, by a process that can be adapted to a multi-gram scale. This involves a decarboxylative elimination[9] of the readily obtainable N-[(benzyloxy)carbonyl] L-glutamic acid monomethyl ester[10] 2 with lead tetraacetate, catalyzed by cupric acetate.

N-[(benzyloxy)carbonyl]-L-vinylglycine methyl ester 3 was prepared as follows: To a solution of 2 (2.95g, 10 mmole) in 120ml of benzene was added cupric acetate monohydrate (500 mg, 2.5 mmole) and the suspension was stirred for 1hr, under argon. Freshly prepared lead tetraacetate[11] (8.88g, 20mmole) was added, the suspension was stirred for 1hr under argon, then, stirred at reflux for 15hr. T.L.C. examination (1:1 ethyl acetate/hexanes) indicated the formation of the desired derivative 3 (R_f 0.75)and a minor by-product (N-Cbz-dimethyl glutamate R_f 0.60), with some starting material. After filtration through a celite pad, the benzene solution was diluted with ethyl acetate, and washed three times with water, then with brine, dried over anh.$MgSO_4$ and evaporated. The resulting syrup was purified by flash chormatography (9:1, hexanes-ethyl acetate) to give 1.498 (60%) of N-[(benzyloxy)carbonyl]-L-vinyl glycine methyl ester 3 as an oil, $[\alpha]_D^{21}$-12.4° (c0.5, MeOH)[12,13]; N.M.R. ($CDCl_3$,400MHz) p.p.m.: 3.76 (s,3H, CO_2Me); 4.95 (m, 1H, H-2); 5.12 (s,2H, CH_2Ph); 5.31 (d,1H,H_B; J_{H_B,H_3}= 10Hz); 5.36 (d,1H,H_A; J_{H_A,H_3} = 17Hz); 5.5 (b,1H,

NHCbz); 5.9 (ddd, 1H, J_{H_3}, $H_{B\ cis}$ = 10Hz; $J_{H_3,H_A trans}$= 17Hz),M.S. 250, (M^++1); also recovered were 10% of N-Cbz dimethyl glutamate and 15% of starting material. Treatment of 3 with triethylamine in methanol (5h, 25°) caused complete isomerization to a mixture of the corresponding dehydroamino acids.[8] Interestingly, when the decarboxylative elimination was done in the presence of pyridine, as normally recommended in such reactions[9], varying amounts of isomerization was detected. However, under the conditions described in this work, the intended target was obtained essentially pure after one chromatography without contamination from elimination products.

L-Vinylglycine hydrochloride 1 was obtained from 3 essentially according to the literature procedure[8] (aq. 6N HCl, reflux) to give the pure amino acid in 82% yield, m.p. 171-173°C; $[\alpha]_D$+78.2°(c0.5, H_2O), having spectral characteristics identical to those described.[8]

In connection with this study, we wish to also describe a high yield process for the preparation of 2.[14] Thus, treatment of the readily available formaldehyde adduct 4 (98% from Cbz-L-glutamic acid)[15]with 0.1M sodium methoxide in methanol (2 equiv. at 0°C for 1-2hr) gave the desired monomethyl ester 2 in 90% yield, identical in all respects with an authentic sample. Decarboxylative elimination of 4 under the conditions described above led to the isolation of the corresponding vinylglycine derivative 5 in ~50% yield in addition to starting material (syrup, $[\alpha]_D$ + 89.6, $CHCl_3$).

We believe that the availability of L-vinylglycine and its derivatives by this alternate simple procedure will foster interest in its use as a versatile chiral building block for natural product synthesis.[16] In addition, the mildness of the process described herein, and its mechanistic implications auger well for its extension to an electrochemical process.[17] These and related potentially useful applications are currently under active investigation in our laboratory.

Acknowledgement. We gratefully acknowledge financial support from the National Engineering and Research Council of Canada, Le Ministère de l'Éducation du Québec as well as an unrestricted grant from Hoffmann-La Roche, Nutley, N.J. We also thank Dr. P.M. Tan for recording the high-field n.m.r. spectra, and Michael Evans for the mass spectra.

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11. To ensure optimum conditions, it is important that the lead tetraacetate be freshly prepared and freed from traces of acetic acid. This can be accomplished with an efficient pump.

12. Reported for this material (ref. 8), oil, $[\alpha]_D$-11.8° (MeOH), obtained by pyrolysis of N-[benzyloxy)carbonyl]-L-methionine methyl ester sulfoxide at 148° (3mm) and two column chromatographic purifications.

13. When conducted on a 1mmole scale, the yield was found to as high as 71%, the remainder being starting material.

14. Compound 2 can be prepared from N-Cbz L-glutamic acid in 60% yield,[10] but a chromatographic separation of some diester is necessary.

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(Received in USA 26 January 1984)