DIRECT SYNTHESES OF β-HYDROXYVALINE AND [4,4'-$^2H_6$]-β-HYDROXYVALINE

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SUMMARY

The anion of N,N-dibenzylglycine ethyl ester was condensed with acetone to afford N,N-dibenzyl-β-hydroxyvaline ethyl ester which was debenzylated and hydrolyzed to yield β-hydroxyvaline in 72% overall yield. A variety of β-hydroxyvalines labelled on the isopropyl group can be prepared by this procedure as shown by the preparation of [4,4'-$^2H_6$]-β-hydroxyvaline from d_6-acetone.

Key Words: β-Hydroxyvaline, Amino Acids, Acetone, Deuterium, Hydrogenolysis.

INTRODUCTION

In connection with our studies on the biosynthesis of penicillin, we required a method for preparing labelled β-hydroxyvaline. This compound was first prepared by Schrauth and Geller[1] by the ammonolysis of α-bromo-β-methoxyisovaleric acid, derived from β,β-dimethylacrylic acid. Since labelled β,β-dimethylacrylic acid would be required as the starting material, this procedure is not suited for preparing a variety of labelled β-hydroxyvalines. More recently, Harada[2] reported a synthesis of β-hydroxyvaline in which acetone and ethyl chloroformate were condensed to form a glycidic ester. Opening of the epoxide of the glycidic acid salt by benzylamine, followed by hydrogenolysis, gave β-hydroxyvaline. Unfortunately, this procedure cannot be used for preparing β-hydroxyvaline labelled with deuterium or tritium on its methyl groups since the deuterium or tritium atoms would be lost by exchange from acetone during the condensation reaction. Other syntheses of β-hydroxyvaline

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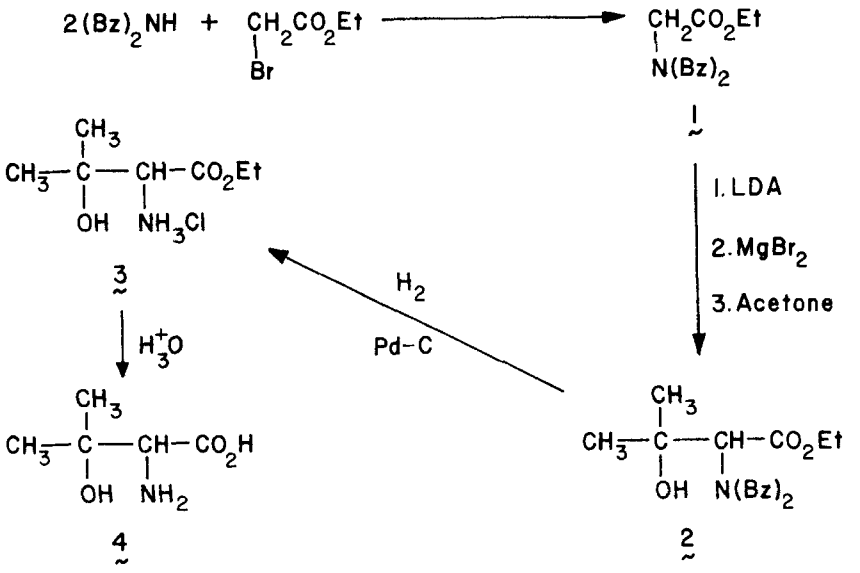
have been reported[3,4] but for obvious reasons are unsatisfactory for preparing labelled β-hydroxyvaline.

A variety of α-alkylamino acids have been prepared by alkylation of anions derived from N-protected amino acid esters. In those cases where the anion is delocalized through a nitrogen protecting group, no reaction with carbonyl compounds occurs.[5,6] In contrast, localized anions, in which the nitrogen is masked as an isocyanate[7] or protected by dimethyl groups,[8] react with carbonyl compounds to afford β-hydroxy adducts in fair yields. The isocyanate and N,N-dimethyl groups, however, are not easily converted to free amino groups.

RESULTS AND DISCUSSION

We wish to report a direct synthesis of β-hydroxyvaline based on the condensation of the anion of N,N-dibenzylglycine ethyl ester (1) with acetone (Scheme 1). This procedure can also be used for preparing labelled β-hydroxyvaline from labelled acetone as shown by the preparation of [4,4'-$^2H_6$]-β-hydroxyvaline from d_6-acetone.

Scheme I



Ethyl bromoacetate was stirred with two equivalents of dibenzylamine to give N,N-dibenzylglycine ethyl ester (1) in 91% yield. Addition of acetone to the anion of 1 at -78° (generated with lithium diisopropylamide), followed by work-up, gave a 1:1 mixture of N,N-dibenzyl-β-hydroxyvaline ethyl ester (2) and starting material.[9] A much better conversion to product was achieved by the addition of one equivalent of anhydrous $MgBr_2$ to the anion of 1 prior to the addition of acetone.[10] Accordingly, 2 was obtained in 81% yield. The dibenzyl groups were cleaved by hydrogenolysis (5% Pd/C) to afford β-hydroxyvaline ethyl ester hydrochloride (3) which was hydrolyzed with 3 N HCl to β-hydroxyvaline hydrochloride. The free amino acid (4), obtained by ion-exchange chromatography on Dowex 50W, was recrystallized from H_2O-EtOH in 89% yield, based on 2.

[4,4'-$^2H_6$]-β-Hydroxyvaline was similarly prepared from d_6-acetone in 71% overall yield, demonstrating the utility of this procedure for preparing labelled β-hydroxyvalines from labelled acetone. Furthermore, the atom percent of deuterium atoms in the dimethyl groups of d_6-β-hydroxyvaline, estimated from the integrated nmr spectrum, was 99%, corresponding to an essentially quantitative incorporation of deuterium from d_6-acetone.

EXPERIMENTAL

d_6-Acetone (99.5 atom % D) was purchased from Aldrich Chemical Company. Reagent and d_6-acetone were dried with Linde 4A molecular sieves prior to use. Palladium on carbon was purchased from Ventron Corporation. Dowex-50W was purchased from Sigma Chemical Company. Melting points were determined on a Reichert "Thermopan" microscope and are uncorrected. Nmr spectra were recorded on a Varian T-60 instrument. Chemical shifts are expressed in δ units and are relative to TMS in organic solvents and relative to 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) in D_2O. The integrated spectrum of [4,4'-$^2H_6$]-β-hydroxyvaline was recorded on a Varian FT-80 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. Microanalyses were done by M-H-W Laboratories, Phoenix, Arizona.

N,N-Dibenzylglycine ethyl ester (1). Dibenzylamine (78.8 g, 0.40 mol) was added to a stirred solution of ethyl bromoacetate (33.4 g, 0.20 mol) in 250 ml of acetonitrile at 5°. After stirring 24 hr the mixture was filtered and evaporated. The residue was dissolved in Et_2O (300 ml), washed with H_2O, 5% $NaHCO_3$, brine, and dried (Na_2SO_4-K_2CO_3). Removal of solvent in vacuo gave a solid which was recrystallized from 95% EtOH to yield 51.8 g (91%) of 1, mp 56-57°, nmr ($CDCl_3$) δ 7.40 (10H,s,aromatic), 4.18 (2H,q,-CH_2-), 3.85 (4H,s, benzylic), 3.29 (2H,s,-CH_2-), 1.24 (3H,t,-CH_3); ir (KBr) 1725, 1190, 745, 698 cm^{-1}.

Anal. Calcd for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.45; H, 7.49; N, 4.75.

N,N-Dibenzyl-β-hydroxyvaline ethyl ester (2). A solution of 1 (5.66 g, 20 mmol) in 30 ml of dry THF (tetrahydrofuran) was added dropwise to 21.9 mmol of LDA (lithium diisopropylamide) in 20 ml of dry THF [prepared by dropwise addition of a 1.6 M n-butyllithium solution (13.7 ml) in hexane to 3.1 ml of dry isopropylamine in 20 ml of dry THF at -10° under argon] under argon at -78°. After stirring for 15 min, 22.2 mmol of $MgBr_2$ in 60 ml of dry THF [prepared by stirring 0.54 g of Mg turnings with 1.9 ml of ethylene bromide in 60 ml dry THF under argon] was added and the solution was stirred for 15 min at -78°. Acetone (1.54 ml, 21 mmol) in 20 ml of dry THF was added and stirring continued for 15 min. A solution of NH_4Cl (1.5 g in 5 ml H_2O) was added and the reaction was allowed to reach room temperature. The mixture was filtered and THF was removed in vacuo. The residue was dissolved in Et_2O (75 ml), washed with 5% $NaHCO_3$, brine, and dried (Na_2SO_4-K_2CO_3). Evaporation of solvent gave 6.56 g of 2 which was recrystallized from 95% EtOH. Yield, 5.53 g (81%), mp 78-79°, ir (KBr) 3525, 1715, 1195, 1145, 750, 695 cm^{-1}; nmr ($CDCl_3$) δ 7.33 (10H,s,aromatic), 3.80 (4H, AB, $\Delta\nu$ = 26 Hz, J = 13.8 Hz, benzylic), 4.3 (2H,q,-CH_2-), 3.41 (1H,s,-OH), 1.40 (3H,t,-CH_3), 1.24 (3H,s, -CH_3), 1.11 (3H,s,-CH_3).

Anal. Calcd for $C_{21}H_{27}O_3N$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.13; H, 8.11; N, 3.86.

β-Hydroxyvaline (4). N,N-Dibenzyl-β-hydroxyvaline ethyl ester (2) (5.12 g, 15 mmol) in 50 ml of MeOH and 1.5 ml of con HCl was hydrogenolyzed with 5% palladium on carbon (1 g) at room temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered and the filtrate was refiltered on a Metricel GA-6 membrane filter. The solvent was evaporated to give β-hydroxyvaline ethyl ester hydrochloride (3) as an oil. The hydrochloride was refluxed 6 hr with 3N HCl and the solution was evaporated to dryness. The residue was dissolved in 1 ml of H_2O and applied to a Dowex 50W ion-exchange column (H^+ form, 1.7 x 25 cm). The column was flushed with H_2O until the eluate was free of chloride ion and then eluted with 1N NH_4OH. The fractions containing 4 were pooled, evaporated to dryness, and dried to a constant weight in vacuo, 1.92 g (96%) of 4. The product was dissolved in 2 ml of hot H_2O and 50 ml of absolute ethanol was added. After cooling overnight the product was filtered and dried. Yield, 1.77 g (89%), mp 222-223° (decomp.) [lit.[1] 218°], nmr (D_2O) δ 3.65 (1H,s,-CH), 1.46 (3H,s,-CH_3), 1.28 (3H,s,-CH_3); ir (KBr) 3200, 1670, 1600, 1560, 1420 cm^{-1}.

Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.32; N, 10.52. Found: C, 45.04; H, 8.49; N, 10.36.

[4,4'-$^2H_6$]-β-hydroxyvaline. N,N-Dibenzyl-[4,4'-$^2H_6$]-β-hydroxyvaline ethyl ester was prepared from d_6-acetone (1.54 ml, 20.9 mmol) by the same procedure and quantities as for 2, yield, 5.65 g (82%). This material (5.21 g, 15 mmol) was hydrogenolyzed, hydrolyzed, and purified by the same procedure used for the preparation of 4. Yield, 1.80 g (86%), mp 222-223°, nmr (D_2O) δ 3.65 (1.0 H, s, -CH), 1.46 (0.031 H, s,-CH_3), 1.27 (0.031 H, s,-CH_3); ir (KBr) 2222 cm^{-1} and absorbencies of 4.

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REFERENCES

1. Schrauth W. and Geller H. - Ber. 55: 2789 (1922).
2. Ohashi J. and Harada K. - Bull. Chem. Soc. Japan 39: 2287 (1966).
3. Berse C. and Bessette P. - Can. J. Chem. 49: 2610 (1971).
4. Kawamata M. - C.A. 83: (21) P178324k 510 (1975).
5. Fitt J. and Gschwend H. - J. Org. Chem. 42: 2639 (1977).
6. Stork G., Leong A. Y. W. and Touzin, A. M. - J. Org. Chem. 41: 3491 (1977). Although not reported, we found no reaction of the benzylidene derivative of glycine ethyl ester with acetone even under forcing conditions.
7. Schöllkopf U. and Frasnelli H. - Angew. Chem. Int. Ed. 9: 301 (1970).
8. Touzin A. M. - Tetrahedron Lett. 18: 1477 (1975).
9. The nmr spectrum of $\underset{\sim}{1}$, recovered from a reaction with d_6-acetone, showed a loss of one α-proton. This suggests a competing deuterium (hydrogen) abstraction of the anion of $\underset{\sim}{1}$ on acetone.
10. Anhydrous $MgBr_2$ has been previously used with preformed lithium enolates in aldol condensations. House H., Crumrine D., Teranishi A. and Olmstead H. - J. Am. Chem. Soc. 95: 3310 (1973).