Tetrahedron Letters,Vol.23,No.17,pp 1767-1770,1982 0040-4039/82/171767-04$03.00/0
Printed in Great Britain

PREPARATION OF DIASTEREOMERIC 2-DEUTERIO-3-HYDROXY BUTYRATE. A GENERAL METHOD FOR HYDROGENATION OF β-ACYLOXY-α,β-UNSATURATED CROTONATES

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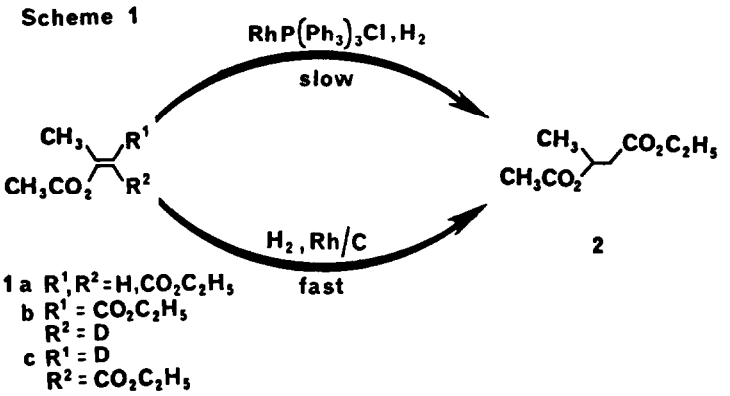
Summary: Both erythro- and threo-2-deuterio-3-hydroxybutyrate are prepared selectively, with a hydrogenation over 5% rhodium on carbon catalyst serving as a key step. This hydrogenation is general for β-acyloxy-α,β-unsaturated crotonates.

During the course of some stereochemical studies, we needed to synthesize specimens of 2-deuterio-3-hydroxybutyrates of known relative configuration at C-2 and C-3. This problem had been encountered previously, but a satisfactory solution had not been devised. Earlier approaches involved the openings of an epoxide with hydride[1] or the hydroboration of crotonic esters[2] and were characterized by low regioselectivity and poor yield.

An alternative approach, direct hydrogenation of 3-acetoxy crotonate, was initially considered to be unpromising due to the inherent stability of its carbon-carbon double bond[3,4] and the susceptibility of such molecules to hydrogenolysis.[5] For example, attempted hydrogenation of 1 with PtO_2 and hydrogen gave only ethyl butyrate. Furthermore, the acid- and base-sensitivity of such compounds and their hydrogenation products precluded the use of non-neutral conditions. We report here a solution to the specific synthetic problem mentioned above. Because this problem is a common one encountered in synthetic work, we further report that the method has broad scope permitting the hydrogenation of a wide range of β-acyloxy-α,β-unsaturated compounds.

While Wilkinson's catalyst, $Rh(PPh_3)_3Cl$,[6a,b] was found to catalyze the hydrogenation of 1a[7] to 2, the reaction displayed an induction period of 1-2 days, proceeded sluggishly thereafter, succeeded only irregularly, and always was accompanied by a darkening of the reaction mixture. However, under the same conditions (room temperature, 1 atm H_2) using 5% rhodium metal on carbon,[8] the reduction proceeded rapidly to give the desired 2 quantitatively (Scheme 1). These observations suggest that in the case of $Rh(PPh_3)_3Cl$ reduction, a disproportionation of $Rh(PPh_3)_3Cl$ to Rh(0) and, most likely, Rh (III) was responsible for the coincidence of a darkening of the reaction mixture and reduction of the substrate and that Rh(0) was in fact the active catalyst.

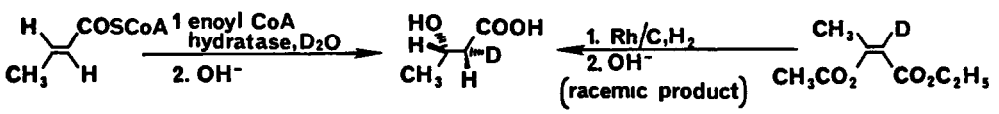
Scheme 1



In order to demonstrate the stereoselectivity of this reaction, both the E- and Z- enol acetates 1b,c were prepared enriched with deuterium at C-2,[9] and hydrogenated over 5% rhodium on carbon. Examination of the resulting 2-deuterio-3-acetoxy butyrates by 270 MHz ^{1}H NMR indicated complete stereoselectivity of reduction. The signals for the diastereotopic protons at C-2 are readily distinguishable; thus, the hydrogenation products of E- and Z- of enol acetates which contained 78% ^{2}H at C-2 showed relative ratios of 78:22 and 22:78 respectively for the downfield:upfield diasterotopic protons. It remained to determine whether the reduction was selectively syn or anti. This was accomplished by an enzymatic synthesis of 2-^{2}H-3-hydroxybutyrate from crotonyl coenzyme A[10] using enoyl CoA hydratase,[11] a reaction whose stereochemistry has been investigated by Eggerer.[2]

In D_2O, crotonyl CoA was converted in the presence of enoyl CoA hydratase to 2R,3S-2-^{3}H-3-hydroxybutyryl CoA. The product was hydrolyzed at pH 11, and the resulting deuterated hydroxybutyric acid was isolated by ion exchange chromatography. Racemic synthetic samples were produced by hydrogenation of 1b and 1c followed by hydrolysis. Based on Eggerer's assignment of the enzyme catalyzed addition of water to crotonyl CoA as syn, we can assign the chemical shifts of the diastereotopic protons in 3S-3-hydroxybutyrate by observing that the more downfield signal in our deuterated, enoyl CoA hydratase-derived product is absent. Comparison of the same region in spectra of the synthetically derived specimen shows the hydrogenation to be selectively syn (Scheme 2).

Scheme 2



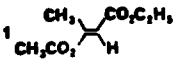
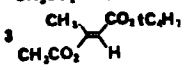
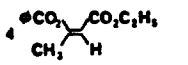
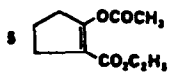
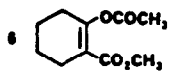
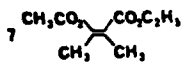
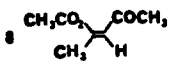
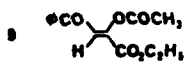
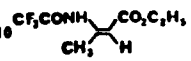
The scope of this method was investigated by reducing a variety of β-acyloxy-α,β-unsaturated compounds; the results are shown in Table I. Both β-acyloxy-α,β-unsaturated esters and ketones were hydrogenated cleanly by this method. Even tetra-substituted compounds of this class (5,6,7) were successfully hydrogenated, to our knowledge the first report of such a

hydrogenation. Hydrogenation of ethyl β-aminocrotonate failed, but after treatment with trifluoroacetic anhydride in CH_2Cl_2, the resulting trifluoroacetaminde 10 underwent rapid reduction. Hydrolysis afforded the corresponding β-amino acid.

The following is a typical procedure. A flask containing anhydrous tetrahydrofuran and 5% Rh on carbon (approximately 0.05 equivalents) is thoroughly purged with hydrogen and fitted with a hydrogen balloon. Substrate is added via syringe, and the reaction mixture is stirred vigorously at room temperature under 1 atmosphere H_2. When the reaction is judged complete[12] the product is isolated by filtration through Celite to remove catalyst followed by bulb to bulb distillation, with yields ranging routinely between 90-100%.

The use of 5% rhodium on carbon to catalyze the stereoselective syn hydrogenation of β-acyloxycrotonates provides a straightforward solution to what has been up to now a challenging synthetic problem. With the reduction of tetra-substituted β-acyloxycrotonates, this method offers an approach to a synthetic unit common to many natural products.[13] Additionally, the above route to β-aminobutyric acid represents a simple procedure for the synthesis of β-amino acids.

TABLE I: Compounds hydrogenated over 5% Rh/C[a].

	Substrate	% yield
1		100
3		98
4		90
5		95
6		95
7		90
8		98
9		96
10		95

a. All compounds listed gave satisfactory NMR data.

Acknowledgement: I am indebted to Professor F. H. Westheimer, in whose laboratories this work was done, for financial support and scientific guidance. I am also grateful to Dr. Steven A. Benner for many valuable discussions and suggestions and to the NSF for a pre-doctoral fellowship.

References

1. Personal communication from Professor Duilio Arigoni; J. R. Mohrig, P. T. Vreede, S. C. Schultz, and C. A Fierke, J. Org. Chem., 46, 4655-4658 (1981).
2. P. Willadsen and H. Eggerer, Eur. J. Biochem., 54, 247-252 (1975).
3. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, J. Am. Chem. Soc., 74, 4223-4251 (1952).
4. Paul Rylander, Catalytic Hydrogenation in Organic Synthesis, Academic Press (1979).
5. L. J. Roll and R. Adams, J. Am. Chem. Soc., 53, 3469-3476 (1931); R. H. Baker and P. C. Weiss J. Am. Chem. Soc., 66, 343-345 (1944).
6. a) J. A. Osborn and G. Wilkinson, Inorg. Syn., 10, 67 (1967); b) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, J. Chem. Soc. (A), 1711-1732 (1966).
7. The E- and Z- β-acetoxycrotonates were prepared selectively as in C. P. Casey and D. F. Marten, Tet. Lett., 925-928 (1974).
8. Obtained from Englehard Industries, Inc.
9. The deuterium enriched E- and Z- β-acetoxycrotonates were prepared in a 70:30 ratio by reaction of $CH_3COCD_2CO_2Et$ with acetyl chloride in pyridine at 0 °C. The dideuterio β-keto ester was prepared by exchange of the active methylene protons of ethyl acetoacetate in D_2O/THF.
10. Crotonyl coenzyme A was prepared by reaction of the CoA lithium salt with crotonic anhydride in cold, aqueous 50 mM $KHCO_3$ solution.[11] Crotonic anhydride was prepared by the reaction of crotonic acid with dicyclohexylcarbodiimide in tetrahydrofuran.
11. J. R. Stern and A. del Campillo, J. Biol. Chem., 218, 985-1002 (1956).
12. The reaction could be conveniently followed by TLC or by filtering small aliquots through celite to remove catalyst and examining the product by NMR.
13. M. C. Pirrung and C. H. Heathcock, J. Org. Chem., 45, 1727-1728 (1980); D. A. Evans, E. Vogel and J. V. Nelson, J. Am. Chem. Soc., 101, 6120-6123 (1979); M. Hirama and S. Masamune, Tet. Lett., 2225-2228 (1979).

(Received in USA 19 January 1982)