Tetrahedron Letters Vol. 21, pp 2467 - 2470 0040-4039/80/0622-2467$02.00/0

HIGHLY STEREOSELECTIVE REDUCTIONS OF α-ALKOXY-β-KETO ESTERS. ASPECTS OF THE MECHANISM OF SODIUM BOROHYDRIDE REDUCTION OF KETONES IN 2-PROPANOL[1]

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Reduction of α-alkoxy-β-keto esters with sodium borohydride in 2-propanol proceeds with high stereoselectivity via a five-membered ring chelated sodium ion.

The principal methods for stereo-controlled synthesis of α,β-dihydroxy carboxylic acids and esters are hydroxylation of α,β-unsaturated acids or esters and hydrolysis of glycidic esters.[3] Aldol synthesis using enolate ions 1 derived from α-alkoxy or hydroxy carboxylic acids or esters with unsymmetrical carbonyl compounds ($R^3 \neq R^4$), illustrated below, has been reported [4,5] to give

$$ROCR^1{=}C(OLi)OR^2 + R^3R^4C{=}O \rightarrow R^3R^4C(OH)CR^1(OR)CO_2R^2$$

1 2

mixtures of diastereomeric α,β-dihydroxy or α-alkoxy-β-hydroxy carboxylic acids or esters 2. For example, t-butyl O-alkylglycolate forms the corresponding enolate 1, R^1=H, R^2=t-Bu on treatment with LDA in THF and on reaction with aldehydes gives mixtures of erythro and threo diastereomers of t-butyl α-alkoxy-β-hydroxy carboxylates 2, $R^1=R^3$=H, R^2=t-Bu with almost no or modest stereoselectivity depending on substituents.[5]

This paper presents a new, highly stereoselective method for preparing α-alkoxy-β-hydroxy carboxylate esters 2, $R^1=R^3$=H by reduction of t-butyl α-alkoxy-β-keto carboxylates 3 with sodium borohydride in 2-propanol. This procedure is of additonal interest because it extends the application of the cyclic model postulated by Cram and coworkers[6] and it suggests a crucial role for the sodium cation in sodium borohydride reductions in 2-propanol.

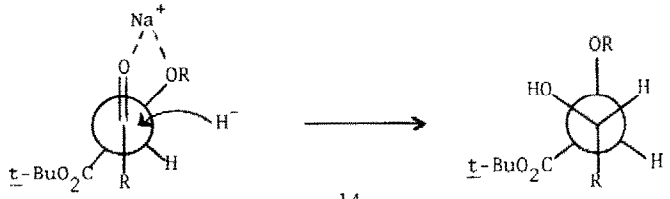
The t-butyl α-alkoxy-β-keto carboxylates listed in the Table were prepared by Collins' oxidation[7,8] of the corresponding t-butyl α-alkoxy-β-hydroxy carboxylates or in the case of 3a and 3b by acylation of the enolate of the appropriate t-butyl O-alkylglycolate with benzoyl chloride. The isolated yields in the reductions with sodium borohydride in 2-propanol and the ratio of diastereomeric products are given in the Table. Care had to be taken to add the requisite amount of

sodium borohydride because excess reagent resulted in overreduction, i.e. reduction of the ester moiety.[9]

The stereochemistry of the diastereomers was assigned as indicated for the previous study on the aldol reaction.[5] Furthermore, it is assumed that the same model accounts for the major diastereomer produced in the sodium borohydride reduction of all of the t-butyl α-alkoxy-β-keto carboxylates studied.

In addition to the reductions reported in the Table keto ester 3a was reduced with excess lithium borohydride. Only a single diastereomeric triol was produced as detected by ^{1}H NMR. Since this triol was the same as that formed with excess sodium borohydride it was assigned the erythro configuration.

To gain more insight into the mechanism for these reductions the following experiment was performed. A solution of sodium borohydride and 15-crown-5 in 2-propanol was stirred for 6 h and then allowed to react with keto ester 3e. The diastereomeric ratio of the product α-alkoxy-β-hydroxy ester was 1:1 in contrast to the 7:1 ratio obtained in the absence of 15-crown-5. This evidence clearly requires a crucial role for the sodium ion in the stereochemical course of this reduction. However, it is clear that sodium ion is not required for reduction, i.e. reduction occurs even in the presence of 15-crown-5. An attractive explanation for the stereochemical results[10] is that reduction of t-butyl α-alkoxy-β-keto carboxylates 3 proceeds via a chelate in which the sodium ion is coordinated by the carbonyl oxygen atom and the oxygen atom of the α-alkoxy group.[11] Delivery of hydride from the less hindered direction generates the erythro diastereomer as shown.[12] This is in contrast to the chelation by boron suggested by Yamada and Koga[13] but



similar to the suggestion of Handel and Pierre[14] for the sodium borohydride reduction of α-aziridinyl ketones. Wigfield and Gowland[12b] noted that "...there is, as far as we are aware, no evidence for a role for Na^+ in $NaBH_4$ reductions in 2-propanol." However, on the basis of the evidence presented in this paper and the work of Handel and Pierre,[14] it is clear that sodium ions play an important role in controlling the stereochemistry in the reduction of these α-heteroatom substituted ketones by sodium borohydride in 2-propanol although they are not required for reduction.

TABLE. Reduction of t-Butyl α-Alkoxy β-Keto Carboxylates 3, $R^1COCH(OR)CO_2t$-Bu with Sodium Borohydride in 2-Propanol

Compound	R^1	R	Yield[a] %	Ratio[b]
3a	Ph	Me	93	20:1
3b	Ph	t-Bu	85	10:1
3c	Me	Me	42[c]	7:1
3d	Me	t-Bu	66[c]	5:3
3e	n-C_6H_{13}	Me	89	7:1
3f	n-C_6H_{13}	t-Bu	84	10:4.5
3g	i-Pr	Me	68	10:1.5
3h	i-Pr	t-Bu	80	2:1
3i	t-Bu	Me	84	5:1

[a]Yield of isolated, distilled products

[b]Diastereomer (erythro: threo) product ratio

[c]Modest yield apparently due to relatively high water solubility of product

REFERENCES AND NOTES

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10. This stereochemistry is predicted by the five-membered cyclic model shown and the open-chain model. *The opposite stereochemistry is predicted by the dipolar model and six-membered cyclic* model (sodium ion chelated by the ketone and ester oxygen atoms). The stereochemical results rule out the latter two models for the predominant pathway. The five-membered cyclic model is invoked rather than the open chain model because of the demonstrated importance of sodium ions on the stereochemistry and the generally high stereoselectivity in the reductions.

11. Additional support for this suggestion is gleaned from the data in the Table. For each pair of compounds 3 in which R^1 is the same but R is Me in one case and t-Bu in the other, the stereoselectivity is less when R=t-Bu than when R=Me. Coordination of the oxygen atom of the α-alkoxy group by the sodium ion is expected to be less favored when R=t-Bu than when R=Me for steric reasons.

12. The product shown is that isolated after workup. It is not known whether the initial product is the corresponding sodium alkoxide or whether i-PrOH participates in the transition state for hydride transfer to generate initially the alcohol as suggested by Wigfield and Gowland: (a) D.C. Wigfield and F. W. Gowland, Tetrahedron Lett., 3373 (1976); (b) D.C. Wigfield and F. W. Gowland, J. Org. Chem., 42, 1108 (1977); but see also C. Adams, V. Gold, and D.M.E. Reuben, J. Chem. Soc., Perkin Trans. 2, 1472 (1977).

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(Received in USA 12 March 1980)