Catalysis by Di-n-butyltin Oxide of a Tertiary Ketol Rearrangement: Synthesis of Intermediates and Analogues of Valine and Isoleucine Biosynthesis

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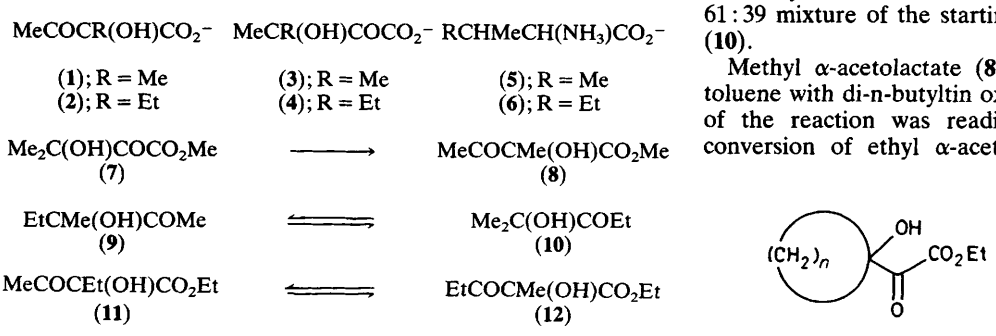
Di-n-butyltin oxide efficiently catalyses the rearrangement of 3-hydroxy-2-oxocarboxylic acid esters into the corresponding 2-hydroxy-3-oxo-esters, in a reaction that simulates the reversible rearrangement catalysed by the enzyme reductoisomerase.

Interest in the biosynthesis of the branched-chain amino acids has been heightened recently by the development of powerful new herbicides[1] that act by inhibiting the first common enzyme in the pathway of valine and isoleucine biosynthesis, acetolactate synthase [acetolactate pyruvate lyase (carboxylating), E.C. 4.1.3.18].[2] This enzyme catalyses the formation of α-acetolacetate (2-hydroxy-2-methyl-3-oxobutanoate) (**1**) and its homologue α-acetohydroxybutyrate (2-hydroxy-2-ethyl-3-oxobutanoate) (**2**), which are precursors of valine (**5**) and isoleucine (**6**), respectively. The intermediates (**1**) and (**2**) undergo tertiary ketol rearrangement to the β-hydroxy-α-keto isomers (**3**) and (**4**), respectively, in a reaction catalysed by the enzyme reductoisomerase [(*R*)-2,3-dihydroxy-3-methylbutanoate: $NADP^+$ oxidoreductase (isomerizing), E.C. 1.1.1.86], Scheme 1. We report here a synthetically useful reaction which represents a laboratory analogy of the reverse reaction, reported to occur at high pH,[3] of the reductoisomerase-catalysed step in valine–isoleucine biosynthesis. The rearrangement is catalysed by di-n-butyltin oxide. Thus when the methyl ester (**7**) of the valine precursor (**8**) was boiled under reflux in toluene with 4.6 mol% di-n-butyltin oxide it was quantitatively converted into methyl α-acetolactate, which was isolated in 81% distilled yield (Table 1).

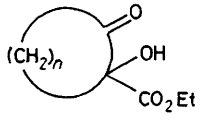
Although participation by the methoxycarbonyl group cannot be ruled out, it is not essential for the rearrangement as shown by the conversion of the simple tertiary ketol (**9**) into a 61 : 39 mixture of the starting compound (**9**) and its isomer (**10**).

Methyl α-acetolactate (**8**) was unchanged on boiling in toluene with di-n-butyltin oxide, but thermodynamic control of the reaction was readily demonstrated by the clean conversion of ethyl α-acetohydroxybutyrate (**11**) into an



Scheme 1

(**13**); $n = 4$ (**14**); $n = 5$



(**15**); $n = 4$ (**16**); $n = 5$

Table 1. Rearrangement, catalysed by di-n-butyltin oxide, of 3-hydroxy-2-oxocarboxylic acid to 2-hydroxy-3-oxo-esters.

Starting material	Product	Catalyst /mol%	Time[a] /h	Yield/% [b]
(7)	(8)	3	22	81
(13)	(15)	2	18	90
(14)	(16)	2	60	79

[a] All reactions were carried out under nitrogen in boiling toluene. [b] Yields quoted are for isolated, distilled (bulb–tube) material; yields estimated by g.l.c. are all >95%.

equilibrium mixture of (**11**) and its isomer (**12**) in a 1 : 1 ratio as indicated by ^{1}H n.m.r. spectroscopy.

The rearrangement described here provides a useful method for ring expansion. Thus the cyclic ketol esters (**13**) and (**14**) were converted, essentially quantitatively, into the α-hydroxy-β-keto isomers (**15**) and (**16**) respectively. The yields of isolated (distilled) products are given in Table 1.

The tertiary ketol rearrangement of α-keto-β-hydroxy esters has not previously been described. Methods for this rearrangement of simple tertiary ketols described in the literature failed with this system.[4] Thus the reagents Al(O-Bu^t)$_3$,[5] BF_3·Et_2O–HOAc–Ac_2O,[6] $AlCl_3$–HOAc–Ac_2O,[6] and alumina (in large excess)[5] failed to give any trace of α-hydroxy-β-keto ester. Methods involving aqueous acids and alkalis[4] are not applicable as ester hydrolysis would inevitably occur with subsequent decarboxylation.

The only available general method for generating the α-hydroxy-β-keto ester system is by the introduction of an oxygen function at the α-carbon of β-keto esters. For biochemical studies the classical α-acetoxylation method of Krampitz[7] has normally been used. However, the best recently described method[8] fails with simple aliphatic systems such as α-acetolactate itself. The method described here constitutes a mild, catalytic method for the generation of α-acetolactate esters and analogues from readily accessible[9] β-hydroxy-α-keto esters.

Hanessian has described the tertiary ketol rearrangement of benzyloxycarbonylspectinomycin in a reaction brought about by a mixture of bis(tri-n-butyltin)oxide and bromine, each in molar excess.[10] Although the rearrangement was reported not to occur in the presence of bromide or the tin oxide individually, nevertheless it may be related mechanistically to the di-n-butyltin oxide-catalysed reaction described above.

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