Tetrahedron: Asymmetry Vol. 4, No. 6, pp. 1229-1232, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

DERIVATIVES OF THE PRODUCT OF BAKER'S YEAST REDUCTION OF ETHYL 2-ALKYL 3-OXOBUTANOATES AS PRECURSORS OF FREE RADICAL CHIRONS OF THE 2(S)-HYDROXYALKYL MOIETY

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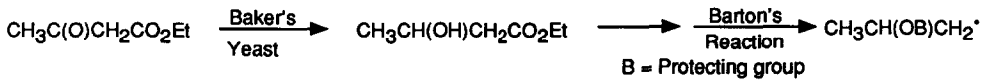
(*Received* 26 *November* 1992; *accepted* 4 *January* 1993)

Abstract : Baker's yeast reductions of ethyl 2-alkyl 3-oxobutanoates provided ethyl 2-alkyl 3(S)-hydroxybutanoates. Such compounds were used as sources for precursors of 2(S)-ethoxymethoxyalkyl radicals whose reactions towards halogen donors, tin hydride and methyl acrylate have been studied.

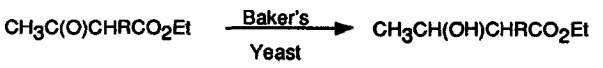
In a previous paper (1) we described the use of the Baker's yeast reduction of ethyl 3-oxobutanoate, in connection with BARTON's reactions (2), to produce a "protected" 2(S)-hydroxypropyl radical, whose reactivity has been applied to various syntheses.



The efficiency of this sequence prompted us to extend this work to ethyl 2-alkyl 3-oxobutanoates since the corresponding radicals would be interesting chiral intermediates.

Reduction of ethyl 2-alkyl acetoacetates

Numerous studies of the reduction of alkyl 2-substituted β-ketoesters by baker's yeast have been published (3) but few have dealt extensively with the influence of the nature of the substituent : ethyl 2-methyl, 2-ethyl, 2-allyl, 2-thiomethyl and 2-thiophenyl 3-oxobutanoates were submitted to this microorganism. Using the reaction conditions previously defined (1), ethyl 2-alkyl 3-oxobutanoates **1a-e** were treated to provide the corresponding β-hydroxyesters **2a-e**. Table 1 summarizes the chemical and optical yields for the formation of these products.



1 **2**

R	Me	Et	All	Bu	i-Pr
	a	**b**	**c**	**d**	**e**

Table 1 : Baker's yeast reduction of ethyl 2-alkyl acetoacetates **1a-e**

Keto-ester	Hydroxy-ester	Amount (g)	(%)	(%) syn/anti (2S,3S)/(2R,3S)	e.e %	
					syn	anti
1a	**2a**	10 [a]	65	90/10	96	90
1b	**2b**	6 [a]	70	60/40	97	97
1c	**2c**	10 [a]	75	22/78	95	97
1d	**2d**	3 [b]	55	85/15	86	75
1e	**2e**	2 [b]	50	51/49	96	96

a Same procedure as in (1) for this amount of ketoester

b Similar to (1) with 3 additions of 100g of sucrose and 100g of baker's yeast over 2 days at a keto addition rate of 0.166 ml/h

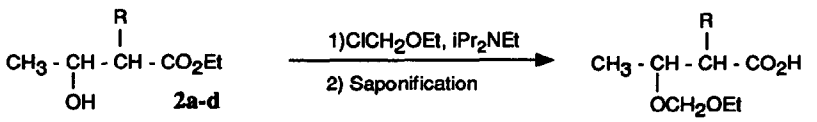
The results obtained were in accordance with the previous studies of the reduction of **1a, 1b** and **1c** by baker's yeast (3). Under the conditions of reduction used for ethyl 3-oxobutanoate, not all of the substituted keto-esters were completely reduced. However, a complete conversion of the amounts of ketoesters mentioned in Table 1 could be obtained using a larger quantity of baker's yeast, with a slower rate of addition of the compound. Only ethyl 2-octyl 3-oxobutanoate could not be reduced : it seems that the increase of the length and the size of the substituent disfavoured the reduction in this case.

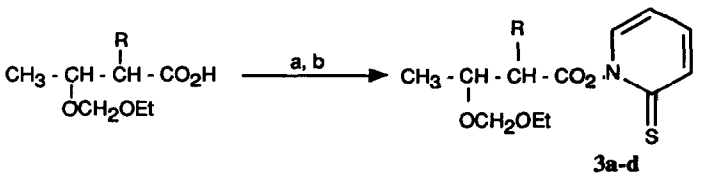
Diastereoisomer assignment was achieved by gas chromatography, by comparison with a sample obtained in the diastereospecific alkylation of ethyl 3(S)-hydroxybutanoate, according to FRATER (4) and confirmation was obtained from ^{1}H and ^{13}C NMR studies of these compounds (4, 5, 6). It appears that the diastereoisomeric excess was affected by the structure of the ketoester. Ethyl 2-allyl 3-oxobutanoate **1c** was efficiently reduced but the major isomer obtained was (2S,3S), in contrast to the saturated compounds where it was (2R, 3S), a finding previously mentioned by NAKAMURA (7) and FRATER (4).

In order to bias the diastereoselectivity of the reaction towards the formation of the 3(S)-hydroxycompounds, ethyl chloroacetate was added to the reaction mixtures (8). Reduction of ketoester **1a** with various amounts of this halogenoester were examined. At 10 mmolar concentration of the additive, total inhibition of the reaction was observed while, at 5 mmolar of additive, reduction occurred but without effect on the diastereoisomeric excess.

Chiral compounds from free radical transformations of β-hydroxyesters

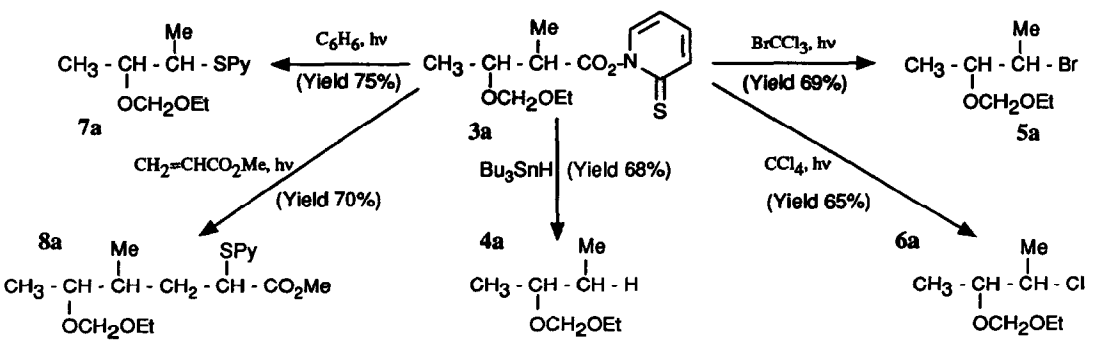
The Barton esters **3a-d** were prepared from the β-hydroxyesters **2a-d**, in the manner used for 3(S)-hydroxybutanoate (1), by the following sequence :



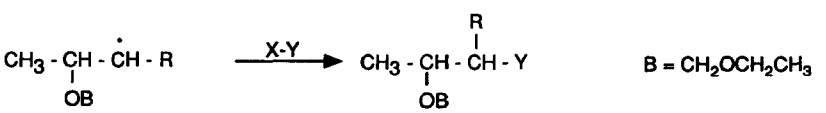


a) iPrCH$_2$OCOCl, N-methylmorpholine b) N-hydroxypyridine-2-thione, Et$_3$N

Compound **3a** was photolytically decomposed under various conditions in order to produce new chiral compounds :

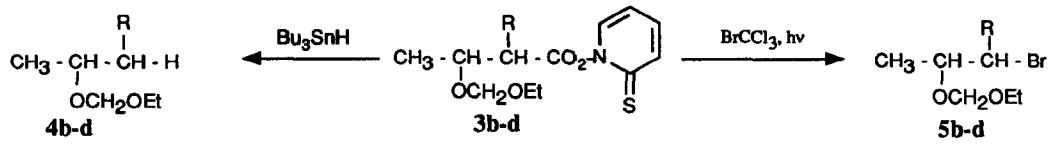


The intermediate chiral radical involved in all these reactions bears a prochiral free radical center which could in principle react to produce two diastereoisomers provided the transferred moiety was not a hydrogen atom :



The reactions studied occurred with no stereoselectivity, as is generally the case for acyclic radicals (9). Only **7a** was obtained with a significant diastereoisomeric excess (30%), but initiation (BEt_3-O_2) over a range of temperature (-30°C to +60°C) did not alter this value.

In order to show the generality of these free radical reactions, the photodecomposition of Barton's esters **3b-d** were achieved in the presence of tri-n-butyltin hydride or bromotrichloromethane :



Barton esters **3b-d** were easily prepared but the compound derived from **2e** could not be obtained since neither enzymatic hydrolysis nor saponification provided the free acid. Diastereoselectivity during the halogenation was very low (d.e.<10%) as was the case for **5a**. Table 2 summarizes the yields of formation of the protected chiral secondary alcohols **4b-d** and bromhydrins **5b-d**.

Table 2 :Yields of the transformation of Barton esters **3b-d**

Product	**4b**	**4c**	**4d**	**5b**	**5c**	**5d**
Yield (%)	75	64	58	68	64	58

Taking account of the fact that these free radical reactions do not affect the configuration of the stereogenic carbon linked to the oxygen, the reactions products **4b-d** were the 2(S) enantiomers of the protected alcohols while **5b-d** corresponded to a mixture of single enantiomers of each diastereoisomer, which should be therefore separable by achiral liquid-solid phase chromatography.

In conclusion, the combination of baker's yeast reduction of 2-alkyl acetoacetates in conjunction with Barton's degradation of the resultant hydroxyester provides a useful synthesis of chiral compounds but appears unfortunately limited to small n-alkyl groups.

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