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DERIVATIVES OF THE PRODUCT OF BAKER'S YEAST REDUCTION OF ETHYL ACETOACETATE AS PRECURSORS OF FREE RADICAL CHIRONS OF THE 2(S)-HYDROXYPROPYL MOIETY

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Abstract: Baker's yeast reduction of ethyl acetoacetate provided in good yield ethyl 2(S)-hydroxybutanoate. The hydrolysis of the ester function after protection of the hydroxyl yielded an acid which, under BARTON's free radical decarboxylation conditions, produced a free radical chiron of 2(S)-hydroxypropyl moiety; according to the reaction medium various chiral products from reaction of this entity were produced.

BARTON (1) discovered several years ago an efficient method of decarboxylation of acids which also provided a clean method of production of alkyl radicals. In the following years, he developed new free radical chemistry, allowing an easy transformation of acids into thio-derivatives, halides, hydroperoxides, alcohols...(2).

The reduction of ethyl acetoacetate by Baker's yeast has been widely studied in the last ten years (3). This reaction has proved to be a good source of the ethyl 3(S)-hydroxybutanoate with an enantiomeric excess higher than 95%.

The existence of these two reactions prompted us to consider their combination in order to generate the chiral 2(S)-hydroxypropyl radical, which could be a good precursor of chiral compounds:

$$CH_3C(O)CH_2CO_2Et \xrightarrow[\text{Yeast}]{\text{Baker's}} CH_3CH(OH)CH_2CO_2Et \xrightarrow[\text{Reaction}]{\text{Barton's}} CH_3CH(OH)CH_2^{\circ}$$

Taking into account the inhibition effect of the presence of high concentrations of starting ethyl acetoacetate in the biological medium (4), the need of large amounts of this hydroxyester led us to define conditions for the large scale reduction. This has been possible by a continuous addition of the ketoester with a syringe pump to the microorganism culture (5). The ethyl 3(S)-hydroxypropanoate was isolated with a yield of 70% relative to the starting material and an enantiomeric excess higher than 95%.

Since the reaction of Barton necessitates the preparation of acyl derivatives capable of reacting with the hydroxyl group, it was necessary to protect the alcohol before the transformation of the ester to acid. Three ways were used:

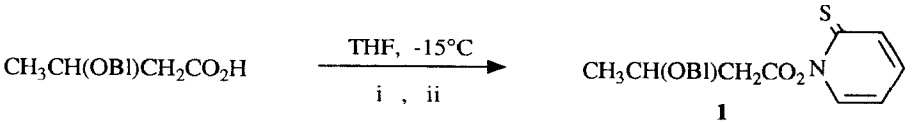
-addition to dihydropyran (6) (yield = 100%)

-reaction on chloromethylethyl ether (7) (yield = 90%)

-condensation with isopropylisocyanate (8) (yield = 75%)

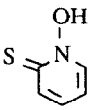
The saponification by potassium hydroxide of the tetrahydropyranyl derivative was easily done with a yield of 80%. For the two other compounds the enzymatic hydrolysis (Pig Liver Esterase) was the best method of obtaining the corresponding acids (yield = 90%) without formation of crotonic acid (9).

Esters **1a-c** were prepared *in situ* by the following reaction (10):

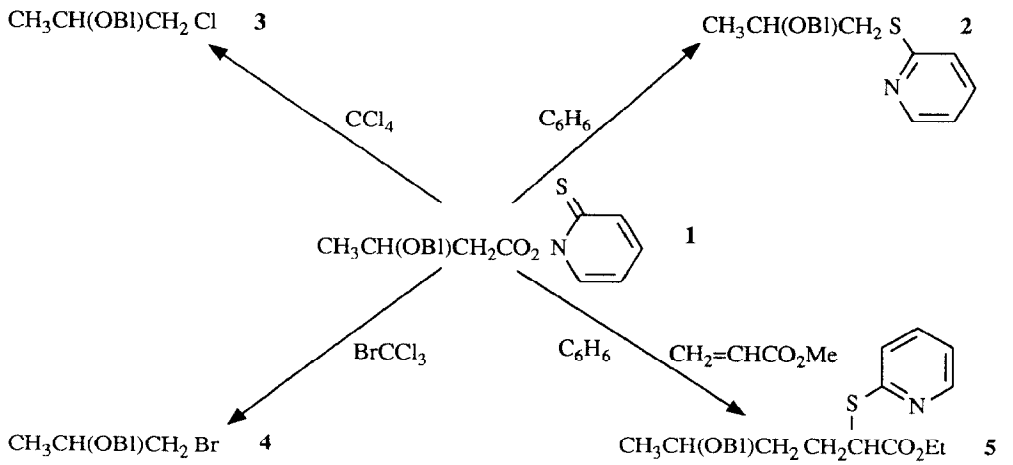


Bl = 2-THP ; CH_2OEt ; C(O)NHi-Pr

i - i-BuOC(O)Cl , N-Methylmorpholine ii - Et_3N ,



Their photolyses were performed in different media producing various functional chiral alcohols as depicted in the following scheme :



Bl = 2-THP (a) ; CH_2OEt (b) ; C(O)NHi-Pr (c)

The photolysis of benzene solutions of the three esters **1a-c** led to the three thioderivatives **2a-c** in better yields for the acetals (73 % and 85 %) than for the urethane (65%) (11). These results prompted us to perform the other photolyses only with the ketal-esters **1a** and **1b**.

In order to get only the halogeno-derivatives, the esters **1a-b** were added to the solvent dropwise over two hours for the bromide and four hours for the chloride (12). Indeed, the direct photolyses of the solutions of esters **1a-b** in these polyhalogenomethanes led to a mixture of the halocompounds **3a-b** or **4a-b** with the thioderivatives **2a-b**.

The photolysis of **1a-b** in a benzene solution of methyl acrylate provided the esters **5a-b** (13).

The yields of the isolated products (liquid solid chromatography on silica) and the yields of the deblocking reactions are summarized in the Table.

Although the chiral center was not involved in the free radical reactions, its stereochemical integrity was however verified through the derivatization of the starting alcohol-ester and of the halogenoalcohols to Mosher's esters which confirmed that there had been no racemization (14). In both cases, gas chromatographic analysis indicated that an enantiomeric excess close to 95% had been obtained.

Table

Product	Yield of Formation (%)[a]	Yield of Deprotection (%)[b]
2a	73	65
2b	85	80
3a	55	[c]
3b	65	50[d]
4a	60	45[d]
4b	75	80[d]
5a	60[e]	62
5b	80[e]	80

[a] Determined relative to the starting acid after purification by liquid-solid chromatography over silica.

[b] Determined relative to the protected derivative after purification by liquid-solid chromatography over silica (deprotection of THP derivatives by two hours heating at 40°C in methanol in presence of Amberlyst (15); deprotection of the other acetals by six hours heating at 40°C of a tetrahydrofuran solution of hydrochloric acid (16)).

[c] Difficult to separate from the solvent used for the hydrolysis.

[d] Separation of the deprotected compound by distillation.

[e] Presence of traces of **1a** or **1b**.

In conclusion, the product of reduction of ethyl acetoacetate by Baker's yeast appears to be a good starting material for the preparation of precursors of free radical chirons of the (S) 2-hydroxypropyl moiety. 1-halogeno-2(S)-hydroxypropane, 2(S)-hydroxy-1-(2-pyridyl)thiylpropane and methyl 5(S)-hydroxy-2-(2-pyridyl)thiyl hexanoate and the corresponding hydroxy protected compounds, are easily prepared in good yield by this route. Extension of this work to the products deriving from ethyl 2-alkylacetoacetate is, at the moment, in progress in order to check for possible asymmetric induction of such a chiral moiety during the reaction of an alpha prochiral free radical center.

References:

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(5) A 4 L three-necked round bottom flask equipped with a mechanical stirrer, a dropping funnel, a thermometer and a syringe pump was filled with distilled water (2 L), and sucrose (150 g). The mixture was stirred for one hour at about 35°C before addition of baker's yeast "Active dry yeast S.I. Lessafre" (100 g). After 20 min, ethyl acetoacetate (20 g) was added continuously at a rate of 0.4 mL/h. After complete addition, baker's yeast (50 g) and sucrose (100 g) were poured in the solution and stirring and heating maintained for 13 hours. Cells eliminated by centrifugation (2000 r/min) were washed with 250 mL of ethyl acetate. Then, the aqueous solution was saturated with sodium chloride and extracted with ethyl acetate (3 x 200 mL). The combined organic phases, after drying over magnesium sulphate, were filtered and concentrated under vacuum and the product was isolated by distillation with a Kugelrohr (oven 90-5°C, vacuum 30 mm Hg) with a yield in the range (70-80 %). $[\alpha]_D^{20} = +40.3$ (C=1, $CHCl_3$); e.e (Mosher's salt) >95 %.

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(9) Saponification:

An ethanolic solution (50 mL water - 50 mL ethanol) of KOH (12 g) and 50 mmoles of ethyl 3-(2-tetrahydropyranyloxy) butyrate were stirred for six days at room temperature. After elimination under vacuum of ethanol, the solution was extracted with ether (2 x 30 mL). Chloroform (100 mL) was then added to the aqueous layer which was then acidified with HCl to pH 1 at 0°C. After separation of the organic phase, the water solution was extracted with chloroform (2 x 30 mL). After drying of the extracts, the solvent was eliminated under vacuum and the acid used without any further purification.

Enzymatic hydrolyses:

Ethyl 3-ethoxymethyloxy butyrate and ethyl 3-(2-methylethylaminocarbonyl) butyrate (15 mmoles) were hydrolyzed at controlled pH 8 (25 ml of phosphate buffer) by pig liver esterase (100 µL of commercial solution from Sigma) with automatic addition of 0.5 M NaOH. The acid was separated using the same experimental procedure as in the saponification.

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(11) Crude ester **1** (10 mmoles) dissolved in 30 mL of benzene, was irradiated with a tungsten lamp under argon until discolourisation of the solution. After filtration over celite the solvent was eliminated under vacuum and the product purified by chromatography over silica (Chromagel 60ACC, 230-400 mesh) with mixtures of diethyl ether and light petroleum ether.

(12) Crude ester **1** (10 mmoles) in solution of the polyhalogenomethane (5 mL) was added, under argon, at a rate of 1.6 mL/H (CCl_4) or 2.4 mL/h ($BrCCl_3$) to 15 ml of stirred polyhalogenoalkane irradiated with a tungsten lamp. One hour after the end of the addition, the crude reaction product was then treated as in (11).

(13) Crude ester **1** (10 mmoles) in benzene (10mL) was added over 10 min. under argon to a stirred solution of methyl methacrylate (25 mmoles) in benzene (20 mL) under irriadiation with a tungsten lamp. One hour after the end of the addition, the crude product of the reaction was then treated as in (11).

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