Tetrahedron Letters,Vol.30,No.29,pp 3811-3812,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

A NOVEL CARBON-CARBON BOND FORMATION IN THE COURSE OF BAKERS' YEAST REDUCTION OF CYANOACETONE

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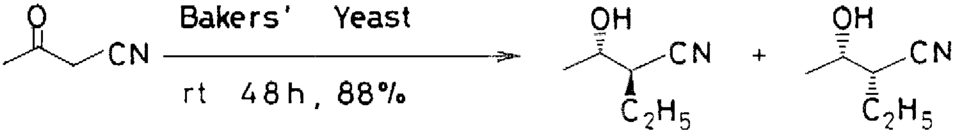
Summary: A novel carbon-carbon bond formation, i.e. ethylation at the α-position of the nitrile was occurred in the bakers' yeast reduction of cyanoacetone, to give optically pure (3S)-3-hydroxy-2-ethylbutyronitrile.

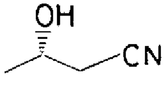
It has been well recognized that the bakers' yeast is a useful reagent to reduce various functionalized ketones, providing optically active secondary alcohol derivatives which were employed successfully as chiral building blocks for the natural products synthesis.1) We now wish to report here a new interesting reaction of 3-oxobutyronitrile (cyanoacetone) 1 with bakers' yeast under the usual fermenting conditions not to afford the 3-hydroxybutyronitrile 3, but to give (3S)-2-ethyl-3-hydroxybutyronitrile 2 in excellent yield with high optical purity (Eq. 1). Although the reduction of cinnamaldehyde with bakers' yeast has been reported to give the product in which the ethylhydroxy group added on its molecule in low yield,2) the present ethylation by yeast is the first case of alkylation to occure in the course of the reduction.

The fermenting method of the present reaction is described as follows: To a stirred solution of 54 g of D-glucose in 390 ml of water was added 49 g of bakers' yeast (Oriental Yeast Co.) and the suspension was stirred for 30 min, then 10 ml of ethanol solution of the ketone 1 (0.813 g, 9.77 mmol) was added. The mixture was stirred at room temperature for 48 h, and filtered through a celite pad. The filtrate was saturated with NaCl, and extracted with ethyl acetate. The extracts were concentrated in vacuo and the residue was subjected to silica-gel flash column chromatography to give a mixture of



(1)

1 anti-2 syn-2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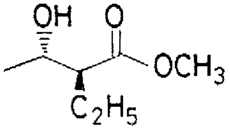
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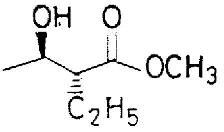
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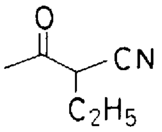
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two diastereomers of 2-ethyl-3-hydroxybutyronitrile 2 (0.968 g, 88%). The intermediate 6 was obtained when the reaction was stopped for 4 hours in 58% yield. The product 2, consisted of 34:66 of *syn* and *anti* isomers,³⁾ was converted into the corresponding ester for the separation of the two isomers ⁴⁾ by silica-gel flash column chromatography, by the treatment with 3,5-dinitrobenzoyl chrolide in the presence of pyridine. Then the benzoyl esters were further transformed into anti-nitrile 2 ($[\alpha]_D^{23}$ -18.8° (c 1.04, EtOH)) and syn-nitrile 2 ($[\alpha]_D^{23}$ +9.50° (c 1.05, EtOH)) by lithium aluminum hydride reduction in THF at -50° C. The optical purities of both of diastereomers of the nitrile 2 were found to be more than 99 %ee confirmed by 470MHz ^{19}F-NMR analysis of the corresponding (+)-MTPA esters. To determine the absolute configuration, the anti- 2 was converted into the corresponding hydroxy ester 4 ($[\alpha]_D^{23}$ +8.48° (c 0.825, $CHCl_3$)), and the configuration at C-3 position of the yeast reduction product was assigned as S by the comparison with the specific rotation of methyl (2R,3R)-3-hydroxybutanoate 5 ($[\alpha]_D^{23}$ -9.21° (c 1.09, $CHCl_3$)) which was derived from the anti selective ethylation to the dianion of methyl (3S)-3-hydroxybutanoate.⁵⁾

Although the mechanism of this interesting yeast mediated reaction has not been clear yet, the alkylation might occur prior to the reduction of ketone, which is confirmed by the isolation of the intermediate 6.

The modification of the substrate for the yeast reduction allow us to use the yeast as a synthetic reagent which has capability to use wide variety of reactions under mild reaction conditions and easy operation to produce a useful compound in optically active state.

References and Notes

1) For example: K. Mori and S. Kuwahara, J. Synth. Org. Chem. Jpn., 46, 467 (1988); T. Fujisawa, T. Sato, and T. Itoh, ibid., 44, 519 (1986) and references cited therein.
2) C. Fuganti and P. Grasselli, "Stereochemistry and Synthetic Application of Products of Fermentation of α,β-Unsaturated Aromatic Aldehydes by Bakers' Yeast" in "Enzymes in Organic Synthesis", Ed. by R. Porter and S. Clark, Pitman, London, 1985, 112. and references sited therein.
3) The ratio was determined by the capillary glpc analysis using SE-30 50m column.
4) E. Hungerbühler, D. Seebach, and D. Wasmuth, Helv. Chim. Acta, 64, 1467 (1981).
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(Received in Japan 12 May 1989)