CHEMISTRY LETTERS, pp. 1111-1112, 1985.

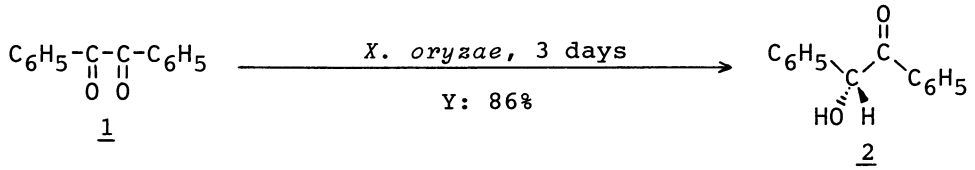
ASYMMETRIC REDUCTION OF BENZIL TO BENZOIN CATALYZED BY THE ENZYME SYSTEM OF A MICROORGANISM

Jin KONISHI, Hiromichi OHTA,* and Gen-ichi TSUCHIHASHI
Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223

Benzil was reduced by incubation with a bacterium in a nutrient medium to afford (R)-benzoin. Substituted benzils were also hydrogenated to the corresponding benzoins in a similar manner.

Optically active α-hydroxyketones constitute a useful group of versatile chiral building blocks for asymmetric synthesis.[1] Although several such building blocks can be derived from naturally occurring products such as lactic acid and amino acids, unnatural type compounds have to be prepared by way of asymmetric synthesis. One of effective methods for these purposes is utilizing enzyme systems of microorganisms in transforming chemical substances.[2] Thus, we screened microorganisms that reduce enantioselectively only one of two carbonyl groups of benzil (1) to give optically active benzoin (2). Although, there have been known a few microorganisms that hydrogenate benzil, the major product is 1,2-diphenylethanediol, the minor product being benzoin of low optical purity.[3] In this letter, we wish to report a highly enantioselective reduction of benzil to give (R)-benzoin.

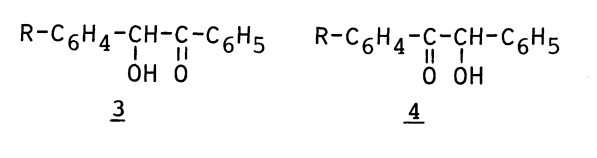
In a nutrient medium,[4] Xanthomonas oryzae IAM 1657, a kind of bacteria which was selected by screening tests among many type cultures, was grown at 30 °C by shake culture for two days. Benzil was added to this suspension (0.2 g/100 ml medium), and the cultivation was continued for additional 3 days. The product was isolated and purified by extraction from the broth, followed by ordinary after-treatments and column chromatography on silica gel. The sole product was benzoin,



1 2

which was identified by comparison of IR, ^{1}H-NMR spectra, and melting point with those of a racemic authentic specimen. No formation of 1,2-diphenylethanediol was confirmed by HPLC. This fact shows the strict chemoselectivity of this enzyme, i.e., it reduces a carbonyl group of diketone but not α-hydroxyketone.[5] Only a few such type of reactions have been demonstrated so far.[6] Moreover, the resulting benzoin was revealed to be optically pure of (R) absolute configuration[7] ($[\alpha]_D^{25}$ -114°, in acetone, c 1.54), within the error of HPLC analysis.[8]

Then, our interest was focused on the regioselectivity of the reaction of the substrates which have a substituent on one phenyl group. Thus, p-methyl-, p-methoxy- and o-methylbenzil were subjected to the microbial reduction. p-Substituted substrates were reduced with moderate regioselectvities, i.e., the carbonyl group attached to the non-substituted phenyl group was preferentially reduced to give a mixture consisting of two possible α-hydroxyketones 3 and 4. Although two isomers could not be separated by column chromatography and PTLC, preparation of racemic 3a, 4a and 4b from the corresponding mandelic amide and arylmagnesium bromide made it possible to determine their molar ratios.[9] Moreover, the optical purities of major isomers 4a and 4b were confirmed to be over 95% by HPLC.[8] To our surprise, o-methylbenzil afforded 3c as a sole product, which was confirmed by comparison of spectral and chromatographic data with those of racemic 3c and 4c prepared by the above mentioned method. Optical purity of 3c was revealed to be 94% by HPLC analysis.



	R	3:4
a	*p*-Me	25:75
b	*p*-MeO	37:63
c	*o*-Me	100:0

In conclusion , reduction of benzil derivatives with X. oryzae was demonstrated to be highly stereoselective. Further substrate specificity, as well as the absolute configuration of products will be presented in the near future.

References

1) G. Tsuchihashi, S. Mitamura, K. Kitajima, and K. Kobayashi, Tetrahedron Lett., 23, 5427 (1982); K. Suzuki, E. Katayama, and G. Tsuchihashi, ibid., 24, 4997 (1983); K. Suzuki, E. Katayama, T. Matsumoto, and G. Tsuchihashi, ibid., 25, 3715 (1984); G. Tsuchihashi, K. Tomooka, and K. Suzuki, ibid., 25, 4253 (1984).

2) For example, A. Fischli, "Modern Synthetic Methods, 1980," ed by R. Scheffold, Verlag, München (1980), pp. 269-350; "Application of Biochemical Systems in Organic Chemistry," ed by J. B. Jones, C. J. Sih, and D. Perlman, John Wiley and Sons, New York (1976).

3) M. Imuta and H. Ziffer, J. Org. Chem., 43, 3319 (1978); W. Acklin, Z. Kis, and V. Prelog, Croat. Chem. Acta, 37, 11 (1965). [Chem. Abstr., 63, 2155e (1965)]; C. Neuberg and F. F. Nord, Ber., 52, 2248 (1919).

4) The medium consists of glucose 10 g, polypepton 7 g, yeast extract 5 g, and K_2HPO_4 5 g in 1000 ml of distilled water, pH 7.2.

5) This bacterium reduced only α,β-diketones. For example, dibenzoylmethane was recovered qauntitatively under the same conditions. Further substrate specificities will be demonstrated elsewhere.

6) C. Neuberg, Biochim. Biophys. Acta, 4, 170 (1950); B. Pfrunder and Ch. Tamm, Helv. Chim. Acta, 52, 1630 (1969).

7) R. Roger and A. McGreger, J. Chem. Soc., 1934, 1545.

8) Analytical conditions: Column, Daicel Chiral Cel OB, 25 cm x 0.46 cm; Solvent, MeOH-H_2O (8/2); Flow rate 0.5 ml/min (15 kg/cm^2).

9) Two pairs of regioisomers were distinguished by the difference in the retention time of HPLC and the chemical shifts due to the methyl groups.

(Received April 25, 1985)