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Enantio-, Regio-, and Chemoselective Reduction of Aromatic α-Diketones by Baker's Yeast

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Summary. The enantio- and regioselective reduction of several symmetric and nonsymmetrically *para*-substituted benzil derivatives (21–92%) was achieved by means of *Saccharomyces cerevisiae* (baker's yeast). After modification of the reaction conditions reduction of nonsymmetric α-diketones led chemoselectively to chiral α-hydroxy ketones with up to 82% *ee*.

Keywords. Asymmetric synthesis; Chemoselectivity; Chiral α-hydroxy ketones; α-Diketone; Yeast.

Introduction

Chiral α-hydroxy ketones constitute a significant structural block in many biologically active natural products. They are also remarkable synthons for the asymmetric synthesis of natural products [1, 2]. Several methods have been developed for the synthesis of optically active α-hydroxy ketones. For example, the oxidation of prochiral enolates using optically active oxaziridines [3], stereoselective oxidation of optically active enolates [4], selective oxidation of chiral titanum enolates [5], symmetric oxidation of silyl enol ethers [6], enzymatic synthesis of optically active benzoins by reduction of α-diketones, by kinetic resolution of racemic α-hydroxy and acetoxy ketones [7], and by selective hydrolysis of the acetoxy ketones by the fungus *R. oryzae* [8, 9]. To prepare chiral α-hydroxy ketones, reduction mediated by yeast is a potent tool [10, 11].

In previous investigations on the microbial reduction of several aliphatic 1,2-diketones by means of baker's yeast, reactions have been found to occur forming either hydroxyketones or diols [11–18]. The stereoselectivity of these reactions has been quite variable [19]. Racemic benzoin has been obtained with a low yield *via* reduction of benzil [19]. Racemic benzoin has been further reduced by using

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Saccharomyces and *Rhodotorula*. With *R. mucilaginosa* the *meso* form and the (*R,R*)-enantiomer have been obtained in the ratio 2:3 [20].

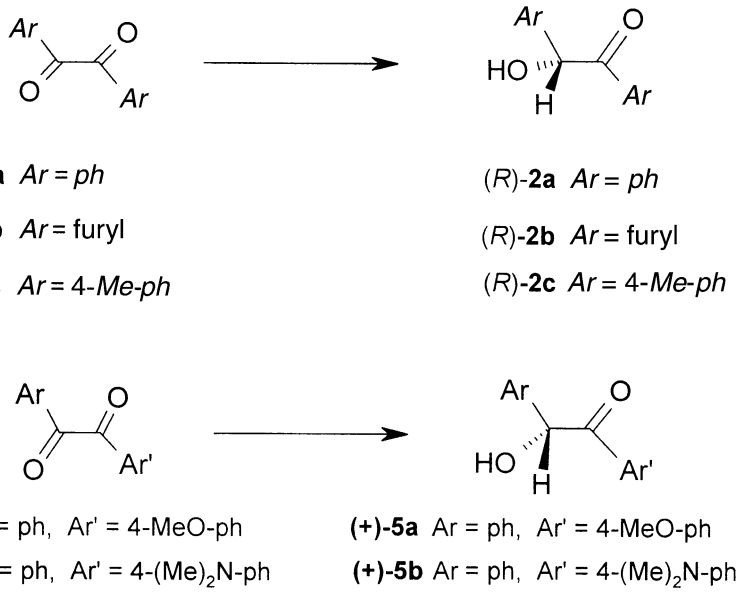
The microorganism *Xanthomonas oryzae* reduced benzil to (*R*)-benzoin in modest yield and low optical purity [21]. Recently, we stereoselectively reduced several prochiral aliphatic and aromatic β-diketones, β-ketoesters, and α-diketones in the presence of *S. cerevisiae* [22c, 22d]. However, although *X. oryzae* has been reported to reduce benzil derivatives to some extent, no communication was found for the application of baker's yeast, *S. cerevisiae*, for the reduction of symmetric and nonsymmetrically *para*-substituted benzils.

Results and Discussion

We now present the first examples of enantio- and regioselective reduction of the symmetric and nonsymmetrically *para*-substituted benzil derivatives **3a**–**3c**, **6a**, and **6b**. The two aromatic rings together with the α-diketone group are necessary that the compound would be an appropriate substrate for *S. cerevisiae*. To improve the yield of the α-hydroxy ketones, modifications of reaction conditions has been attempted, *e.g.* using acidic buffer solution [19], lowering the reaction temperature [23], and use of methyl vinyl ketone as an enzyme inhibitor preventing the production of the diol [17]. However, we found that these methods were not reproducible and resulted in formation of the *vic*-diol. The difference in their results and ours conceivably originate from the difference in the baker's yeast employed for the experiments. Selectivities of yeast reductions are not always satisfactory, different methods have been developed to improve the stereochemical result [24].

From the standpoint of asymmetric diaryl synthesis, the reduction has three problems: chemoselectivity, regioselectivity, and enantioselectivity. Nonetheless, these α-hydroxy ketones or corresponding benzil compounds have been used for one pot syntheses of series of phenytoin-like analogues (5,5-diphenyl hydantoin) as antiepileptic drugs [22b, 22e, 22f].

Reduction of α-diketones **3a**–**3c**, **6a**, and **6b** utilizing baker's yeast was stereoselective and for nonsymmetric α-diketones chemoselectivity as well as stereoselectivity afforded the related chiral α-hydroxy ketones (*R*)-**2a**, (*R*)-**2b**, (*R*)-**2c**, (+)-**5a**, and (+)-**5b** (Scheme 1). The chemoselectivity was confirmed by means of ^{1}H NMR spectra of (+)-**5a** and (+)-**5b** after shaking with D_2O. The doublet peaks at 4.7 ppm due to the α-hydrogen adjoining the unsubstituted phenyl rings in both spectra disappeared. However, initially the reduction procedure did not afford satisfactory results. To improve the yield of chiral hydroxy ketones the reaction conditions were modified. Potassium phosphate as a buffer at $pH = 7$ for three days and thermal pre-treatment of baker's yeast were found to be the most satisfactory and led to the related chiral α-hydroxy ketones (*R*)-**2a** ($ee = 50\%$), (*R*)-**2b** ($ee = 82\%$), (*R*)-**2c** ($ee = 36\%$), (+)-**5a**, and (+)-**5b** (the absolute configurations and *ee* values for **5a** and **5b** could not be assigned since the specific rotation values have not been reported so far). The results indicate that reduction does not afford the *vic*-diol and only one of the α-hydroxy ketones was obtained. Consequently, in principle the yeast reduction without using any inhibitor terminates at the mono reduction stage.



Scheme 1

Experimental

Chemicals were purchased from Fluka, Merck, and Aldrich. Commercial baker's yeast, natural yeast, *S. cerevisiae*, as active and dry material (Saf-levure, S.I. Lesaffre 59703, Mareq, France) was used. Products were characterized by comparison with authentic samples (IR, NMR, GC, TLC, and mp). Yields refer to isolated pure center cut from column chromatography or for material scratched from preparative TLC plates. Melting points are uncorrected and were determined on a Mettler Fp5 melting point apparatus. The specific rotation, $[\alpha]_D$, was determined on a commercial polarimeter ATAGO (POLAX) (cell path lengths of 5 and 10 cm were used). IR spectra were obtained on a Shimadzu IR-470. All NMR data were recorded in $CDCl_3$ or in CD_3COCD_3 on either a Brucker MA2.FT.80 or a Brucker DRX 500 Avance spectrometer, using *TMS* as internal reference. The high-resolution mass spectra were obtained on a Fisons Trio-1000 instrument. The UV/Vis spectra were recorded on a Shimadzu UV-2100.

Compounds **3a**–**3c**, **6a**, and **6b** were prepered from their respective α-hydroxy ketones **2a**–**2c**, **5a**, and **5b** by oxidation with NH_4NO_3, in the presence of $Cu(CH_3COO)_2$ in acetic acid according to Ref. [26], for the oxidation of **5b** $CuSO_4$ and pyridine were utilized [27]. These α-hydroxy ketone adducts were obtained by benzoin condensation [28].

Reduction of **3a** *by Baker's Yeast. (R)-2-Hydroxy-1,2-diphenylethanone*
((*R*)-**2a**, $C_{14}H_{12}O_2$)

To a 250 cm^3 round bottom flask was added 5 g of D-(+)-glucose monohydrate (25.2 mmol), 50 cm^3 of tap H_2O and 7 cm^3 of potassium phosphate buffer ($pH = 7$, 0.01 *M*). The resulting mixture was stirred at room temperature for several minutes to produce a homogeneous solution whereupon 5 g of active dry yeast were added. The solution was stirred for 30 min at 50°C. After the mixture was cooled to room temperature with an ice bath it was stirred at 30°C for 30 min and then 0.7 g of **3a** (3.3 mmol) were added. The flask was equipped with a bent glass tube that through a trap dips below the surface of a saturated aqueous solution of $Ba(OH)_2$ in a 200 cm^3 *Erlenmeyer* flask. The solution was stirred

vigorously for 72 h at 30°C. After this time the solution was extracted three times with 40 cm^3 portions of *Et*OAc. For better separation of the phases the extraction mixtures were centrifuged. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to leave the crude product as a residue. The crude product was purified on a silica gel column. The elution solvent was 1:3 (*v*:*v*) of *Et*OAc:ligroin to afford 0.3 g of (*R*)-**2a** (43%), mp 137°C, $[\alpha]_D^{25} = -57.5°cm^2g^{-1}$ ($c = 1.4$, CH_3COCH_3), $ee = 50\%$ (commercially available product $[\alpha]_D^{25} = -115°cm^2g^{-1}$ ($c = 1.5$, CH_3COCH_3), mp 134–136°C.

Reduction of **6a** *by Baker's Yeast: (+)-2-Hydroxy-1-(4-methoxyphenyl)-2-phenyl-ethanone* ((+)-**5a**, $C_{15}H_{14}O_3$)

To a 250 cm^3 round bottom flask was added 5 g of D-(+)-glucose monohydrate (25.2 mmol), 70 cm^3 of tap H_2O and 10 cm^3 of potassium phosphate buffer ($pH = 7$, 0.01 *M*). The resulting mixture was stirred at room temperature for several minutes to produce a homogeneous solution whereupon 5 g of active dry yeast were added. The solution was stirred for 30 min at 50°C. After the mixture was cooled to room temperature with an ice bath the mixture was stirred at 30°C for 30 min and then 0.75 g of **6a** (3.1 mmol) were added. The flask was equipped with a bent glass tube that through a trap dips below the surface of a saturated aqueous solution of $Ba(OH)_2$ in a 200 cm^3 *Erlenmeyer* flask. The solution was stirred vigorously for 72 h at 30°C. After this time the solution was extracted three times with 40 cm^3 portions of *Et*OAc. For better separation of the phases the extraction mixtures were centrifuged. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to leave the crude product as a residue. The crude product was purified on a silica gel column. The elution solvent was 1:3 (*v*:*v*) of *Et*OAc:ligroin to afford 0.35 g of (+)-**5a** (47%), mp 106°C, $[\alpha]_D^{25} = +70°cm^2g^{-1}$ ($c = 1$, CH_3COCH_3, the absolute configuration and *ee* value could not be assigned because the specific rotation has not been reported); IR (KBr): $\bar{\nu} = 3460$ (s), 3070 (w), 2920 (m), 2830 (w), 1660 (s), 1600 (s), 1565 (m), 1500 (m), 1260 (s), 1175 (s), 1070 (m), 1060 (m), 975 (s), 820 (m), 740 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.7$ (s, 3H), 4.5 (d, 1H), 5.8 (d, 1H), 6.8 (d, $J = 6.8$ Hz, 2H), 7.2 (m, 5H), 7.8 (d, $J = 6.8$ Hz, 2H) ppm; ^{13}C NMR (CD_3COCD_3): $\delta = 54.58$, 75.16, 113.32, 126.49, 127.02, 127.38, 128.14, 130.93, 140.06, 163.49, 196.96 ppm.

(R)-1,2-(Difuran-2-yl)-2-hydroxyethanone ((*R*)-**2b**, $C_{10}H_8O_3$)

A similar procedure as used for **3a** was applied. The elution solvent was 1:3 (*v*:*v*) *Et*OAc:ligroin to afford 41% of (*R*)-**2b**, mp 139°C, $[\alpha]_D^{25} = -16.5°cm^2g^{-1}$ ($c = 1.2$, CH_3COCH_3), $ee = 82\%$ (commercially available product ((*S*) **2b**) $[a]_D^{25} = +20.1°cm^2g^{-1}$ ($c = 2$, Et_2O) [9d], mp 134–137°C.

(R)-2-Hydroxy-1,2-di(p-tolyl)ethanone ((*R*)-**2c**, $C_{16}H_{16}O_2$)

A similar procedure as used for **3a** was applied. The elution solvent was 1:3 (*v*:*v*) *Et*OAc:ligroin to afford 17% of (*R*)-**2c**, mp 87°C, $[\alpha]_D^{25} = -53°cm^2g^{-1}$ ($c = 0.7$, CH_3COCH_3), $ee = 36\%$ (commercially available product $[\alpha]_D^{25} = -130.8°cm^2g^{-1}$ ($c = 1$, MeOH) [9d], mp 89°C.

(+)-1-(4-Dimethylaminophenyl)-2-hydroxy-2-phenylethanone ((+)-**5b**, $C_{16}H_{17}NO_2$)

A similar procedure as used for **3a** was applied. However, in addition to the previously added yeast each 24 h a solution of 10 cm^3 of distilled H_2O, 1 g of yeast, and 1 g of D-(+)-glucose were added to the reaction mixture. The crude product was purified on a silica gel column. The elution solvent was 1:3 (*v*:*v*) *Et*OAc:ligroin to afford 21% of (+)-**5a**, $[\alpha]_D^{25} = +47°cm^2g^{-1}$ ($c = 0.65$, CH_3COCH_3, the absolute configuration and *ee* value could not be assigned since the specific rotation has not been reported in the literature); IR (KBr): $\bar{\nu} = 3400$ (s), 3070 (w), 2910 (w), 2800 (w), 1650 (s), 1605 (s),

1540 (m), 1440 (m), 1385 (s), 1165 (s), 1090 (m), 1065 (s), 975 (m), 800 (m), 750 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.9$ (s, 6H), 4.8 (d, $J = 6.1$ Hz, 1H), 5.8 (d, $J = 6.1$ Hz, 1H), 6.5 (d, $J = 9$ Hz, 2H), 7.3 (m, 5H), 7.8 (d, $J = 9$ Hz, 2H) ppm.

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