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BAKER'S YEAST REDUCTION OF α-HALOACETOPHENONES

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Abstract: The fermenting baker's yeast reductions of α-haloacetophenones were carried out by three different procedures. While the α-fluoro-, α-chloro- and α-bromoacetophenones gave the correspondent (-)-halohydrins, the reduction of α-iodoacetophenone gave acetophenone and (-)-1-phenylethanol.

Introduction

The stereoselective reduction of α-haloacetophenones is potentially an useful process to obtain chiral halohydrins which can be used as chiral building blocks for some optically active natural products[1a] and, to some extend, for important pharmaceutical products.[2]

Baker's yeast *(Saccharomyces cerevisiae)* is a potential candidate in preparing chiral alcohols by reduction of pro-chiral ketones because it is inexpensive, and very efficient in many cases and involves an easy work-up. The asymmetric reductions of a series of aromatic ketones have been previously achieved by actively fermenting baker's yeast.[3]

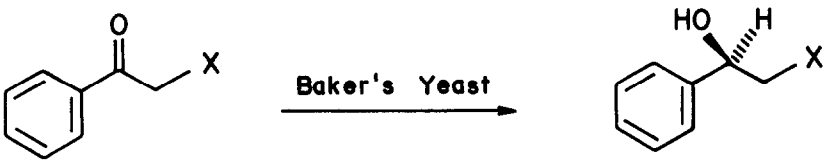
Some α-haloacetophenones have been asymmetrically reduced by organoborane[1] reagents made by mixing aluminum or boron hydrides and various chiral diols or aminoalcohols,[4] reagents prepared from borane and chiral aminoalcohols,[5] oxaborolidine,[6] *Cryptococcus macerans*[7] and nicotinamide adenine dinucleotide dependent horse liver dehydrogenase (NADH/HLADH).[8]

In connection with our projects of asymmetric synthesis of some optically activity symphathomimetic compounds, we report in this paper the results on baker's yeast reduction of α-haloacetophenones. The effects of the halogen and the influence of the sugar addition on the chemical yields are discussed.

Results and Discussion

In some cases the baker's yeast reduction of ketones gives alcohol of high optical purity, while many others afford alcohol with low ee. Further development of the methodology for stereochemical control in the yeast reduction is still required. In this paper the reductions of α-haloacetophenones by baker's yeast were carried out by three different procedures: Procedure A: according to the general procedure described by Seebach *et al.*[9] but with addition of small amount of $ZnSO_4$ as recommended by McLeod *et al.*,[3a] Procedure B: fermenting baker's yeast without addition of sucrose but employing a large quantity of yeast[3g,3h] and Procedure C. a procedure differentiate from B with respect to the ketone addition, i.e., a solution of ketone in ethanol is slowly added (1 to 3 hours) to the fermenting baker's yeast[3b,3h] (see experimental section).

These three procedures were chosen because some of them are frequently used by synthetic organic chemists and because there are some important differences between them. In procedure A, which is the most used, the carbohydrate participates in this process as a electron donor[10] while in the procedure B, although a large quantity of yeast employed, no carbohydrate is added. In the latter case it is assumed that the saccharides present in the baker's yeast cell can produce NADH or NADPH and consequently has reducing power even without added glucose.[11,12] Since it has been shown that the slow addition of the substrate can improve the results of baker's yeast reduction,[3] procedure C was tested for some α-haloacetophenones. The results of these experiments are present in Table 1.



X = F, Cl, Br

Table 1. Reduction of α-haloacetophenones by baker's yeast.

$PhCOCH_2X$	Procedure[a]	Reaction time (h)	$PhCHOHCH_2X$ yield (%)	$[\alpha]_D^{25}$	Optical yield (%)[b]	$PhCOCH_2X$ recovered (%)
F	A	48	44	-50.6 (R)	95	3.3
F	B	24	67	-51.7 (R)	97	-
Cl	A	48	37	-43.3 (R)	90	-
Cl	B	24	74	-39.3 (R)	82	-
Cl	C	4	84	-21.1 (R)	44	4.6
Br	A	96	9	-38.2 (R)	93	-
Br	B	24	9	-39.7 (R)	97	-
Br	C	4	11	-36.9 (R)	90	trace
I	B	24[c]	-	-	-	-

[a] Procedure A: sucrose fermenting baker's yeast; Procedure B: baker's yeast without addition of sucrose; Procedure C: the ketone dissolved in ethanol was added slowly in the sucrose fermenting baker's yeast.

[b] Based on the specific rotation reported in the literature.

[c] In this case the isolated products were $PhCHOHCH_3$, $[\alpha]_D^{25}$ - 36.3 (S) (73% optical yield) in 32% yield and $PhCOCH_3$ in 67% yield.

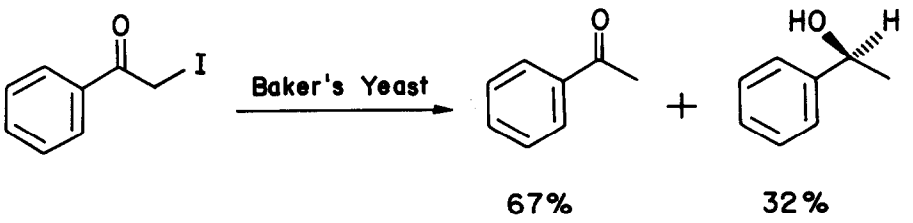
On the mechanism of the baker's yeast reduction.

α-Haloacetophenones have been used as mechanistic probes for differentiation between reduction processes which proceed *via* electron transfer or by hydride transfer mechanisms, since acetophenone is the reduction product obtained by electron transfer while halohydrin is obtained by hydride transfer mechanism[13]. Since no free radical reduction was observed which did not involve carbon-halogen bond cleavage,[8] our results presented in Table 1 indicate, in light of the above mentioned studies, that the α-fluoro-, α-chloro-, and α-bromoacetophenones are baker's yeast reduced by a hydride transfer mechanism, since no acetophenone was detected in the reaction products. This is an expected result because it is generally assumed that enzymic reductions proceed *via* hydride transfer mechanism.[13a] Taking into account that the phenyl moiety is larger than the halomethyl moiety, these reductions obey the Prelog rule[14] since (-)-(R)-2-halo-1-phenylethanol was obtained.

While the baker's yeast reductions of α-chloro- and α-fluoro-acetophenones are in agreement with the results of the NADH/HLADH reductions,[8] the α-bromoacetophenone reduction show remarkable differences: i. α-bromoacetophenone was reduced by NADH to give acetophenone by an electron transfer process, while the system NADH/HLADH was not able to produce bromohydrin;[8] ii. the baker's yeast reduction of α-bromoacetophenone gave (-)-(R)-2-bromo-1-phenylethanol, isolated in 9 to 11% yield,[15] and no acetophenone were isolated or even detected by ^1H nmr spectra of the extracted material. This is an indication that

the enzymatic complex of the baker's yeast has more reduction power than the NADH/HLADH system by a hydride transfer mechanism for this substrate. *Cryptococcus macerans* is also able to reduce α-bromoacetophenone to optical active bromohydrin.[7]

Now we comment the results of the α-iodoacetophenone reduction where acetophenone and (-)-(S)-1-phenylethanol were isolated in 67 and 32% yield, respectively. In this reaction the α-iodoacetophenone was reduced to acetophenone and the acetophenone was partially and asymmetrically reduced to (-)-(S)-1-phenylethanol. It is known that acetophenone is slowly reduced by baker's yeast to give (-)-(S)-1-phenylethanol.[3a] The addition of *m*-dinitrobenzene (DNB), a frequently used inhibitor of radical chain processes[8] in amounts of 6 to 100% in relation to the substrate, did not inhibit the formation of acetophenone. Thus this experiment does not prove evidence for an alectron transfer mechanism in this reduction. It is important to mention that α-iodoacetophenone was reduced to optically active iodohydrin in 67% ee.[1d]



The influence of sucrose addition.

For the baker's yeast reduction of α-fluoro- and α-chloroacetophenones there is a remarkable difference between procedures A and B on the chemical yields of the halohydrins produced (see Table 1). The enhancement of the halohydrins yields from sucrose activated to no sucrose activated baker's yeast reduction was from 44 to 67% for α-fluoroacetophenone and from 38 to 74% for α-chloroacetophenone. The optical yields remain practically unchanged for α-fluoroacetophenone and were slightly decreased for α-chloroacetophenone. So for synthetic purposes, procedure B has an obviously advantage. The alcohol/ketone ratios, determined from the ^{1}H nmr spectra of the extract of samples withdrawn from the reaction mixture, show that the reduction by procedure B is faster than that of procedure A. The α-chloroacetophenone reduction was almost completed in 3 hours and no ketone was recovered after 24 hours of reaction for procedure B, while some ketone was recovered after 48 hours of reaction for procedure A. Similar results were obtained with α-fluoroacetophenone. Procedure C was optimized for α-chloroacetophenone reduction with a reaction time of 4 hours after total addition of the ketone. The chemical yield increased from 74% (method B) to 84% while the optical yield decreased from 82 to 44%.

The baker's yeast reductions of α-bromoacetophenone do not show any significant differences between the three procedures. The (-)-(R)-2-bromo-1-phenylethanol was obtained in chemical yield around 10%. These low yields are probably due to parallel reactions of

α-bromoacetophenone since no bromoacetophenone was recovered and the bromohydrin is very stable in the reaction mixture.

Conclusion.

The baker's yeast reduction of α-fluoro- and α-chloroacetophenones gives the corresponding (-)-(R)-halohydrins in reasonable good chemical and optical yields by the procedure B (without sucrose addition), which can be used to easily prepare these important chiral building blocks. The baker's yeast reduction of α-bromoacetophenone gave (-)-(R)-bromohydrin in poor chemical yields and the reduction of α-iodoacetophenone was not able to produce the iodohydrin.

EXPERIMENTAL PART

IR spectra were recorded on a Perkin-Elmer Model 1430 spectrometer. ^{1}H NMR spectra were obtained on a Bruker AW-80 or on a Varian XL-100 spectrometer with tetramethylsilane (TMS) as the internal standard. Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter at a wavelength of 589 nm. Mass spectra were determined on a Varian MAT 311 A spectrometer.

MATERIALS: α-chloro- and α-bromoacetophenone (Aldrich), *m*-dinitrobenzene (Carlo Erba) and baker's yeast (Fleischmann or Itaiguara) were used without any treatment. α-Fluoro- and α-iodoacetophenone were prepared using the procedures described in the literature.[16,17] All other solvents and reagents were reagent grade.

General procedure for reduction of α-haloacetophenones by baker's yeast.

Method A: A solution of sucrose (10 g) in water (38 ml) and a solution of $ZnSO_4.H_2O$ (0.0128 g) in water (1.3 ml) were added with stirring at 30°C to a mixture of baker's yeast (20 g) with water (10 ml). After 30 minutes the ketone (1 mmol) was added and 24 hours later a solution of sucrose (3 g) in water (13 ml) and a mixture of baker's yeast (7 g) with water (3 ml) were added and the stirring was continued at 30°C for an additional 24 hours. After this period the reaction mixture was saturated with sodium chloride and the products were extracted with chloroform in a liquid-liquid extractor during 48 hours. The halohydrin and the remaining ketone were isolated by silica gel column chromatography using chloroform as eluent.

Method B: The ketone (1 mmol) was added with stirring at 30°C to a mixture of baker's yeast (35 g) and water (20 ml). The stirring was continued at 30°C for 24 hours. The procedures used for the extraction and isolation of the products are the same as those described in method A.

Method C: The ketone (1 mmol) dissolved in ethanol (1.5 ml) was added slowly during 1 hour with stirring at 30°C to a mixture of baker's yeast (35 g) and water (20 ml). The stirring was continued at 30°C for 2 to 4 hours more. The products were extracted and isolated as described in method A.

Baker's yeast reduction of α-fluoroacetophenone: i. When α-fluoroacetophenone (0.15 g, 1.09 mmol) was subjected to procedure A during 48 hours, the following products were isolated: a. α-fluoroacetophenone (5 mg, 3.62 mmol, 3.3% recovered) with the NMR and IR spectra identical with an authentic sample; b. (-)-(R)-2-fluoro-1-phenylethanol (67.2 mg, 0.48 mmol, 44% yield) as a colorless oil: $[\alpha]_D^{25}$ -50.6° (c 1.5, $CHCl_3$) (lit. -53.2)[8], giving an optical purity of 95%; ^1H NMR δ (8= MHz, CCl_4): 2.7 (br s, 1H, OH); 4.23 (double dd, 1H, CH_2, J=47.8, 9.2 and 7.4 Hz); 4.40 (double dd, 1H, CH_2, J=47.8, 9.2 and 3.6 Hz), 4.86 (double dd, 1H, CH, J=13, 7.4 and 3.6 Hz), 7.25 (s, 5H, Ph).

ii. When α-fluoroacetophenone (0.155 g, 1.12 mmol) was subjected to procedure B the unique product isolated was (-)-(R)-2-fluoro-1-phenylethanol (0.105 g, 0.75 mmol, 67% yield) as a colorless oil, $[\alpha]_D^{25}$ -51.7° (c 1.6, $CHCl_3$), the optical purity was 97%.

Baker's yeast reduction of α-chloroacetophenone: i. When α-chloroacetophenone (0.5 g, 3.23 mmol) was subjected to procedure A the following products were isolated: a. α-chloroacetophenone (37 mg, 0.24 mmol, 8% recovered); b. (-)-(R)-2-chloro-1-phenylethanol (180 mg, 1.15 mmol, 37% yield) as a colorless oil; $[\alpha]_D^{25}$ -43.3° (c 1.8, cyclohexane) (lit. -48.1)[7], giving an optical purity of 90%; IR (film) 3390, 3040, 2960, 1495 cm^{-1}; ^1H NMR (100 MHz, CCl_4) δ 2.9 (br s, 1H, OH), 3.5 (dd, 1H, J=11 and (Hz, CH_2), 3.7 (dd, 1H, J=11 and 4 Hz, CH_2), 5.1 (dd, 1H, J=8 and 4 Hz, CH), 7.8 (s, 5H, Ph); m/z 156 (M^+).

ii. When α-chloroacetophenone (1.0 g, 6.47 mmol) was subjected to procedure B the unique product isolated was (-)-(R)-2-chloro-1-phenylethanol (749 mg, 4.79 mmol, 74% yield): $[\alpha]_D^{25}$ -39.3° (c 1.7, cyclohexane), the optical purity was 82%.

iii. When α-chloroacetophenone (1.01 g, 6.54 mmol) was subjected to procedure C the following products were isolated: a. α-chloroacetophenone (46 mg, 0.30 mmol, 4.5% recovered); b. (-)-(R)-2-chloro-1-phenylethanol (863 mg, 5.51 mmol, 84% yield) as a colorless oil; $[\alpha]_D^{25}$ -21.1° (c 1.7, cyclohexanone), the optical purity was 44%.

Baker's yeast reduction of α-bromoacetophenone: 1. When α-bromoacetophenone (0.5 g, 2.51 mmol) was subjected to procedure A the product isolated was (-)-(R)-2-bromo-1-phenylethanol (46.6 mg, 0.23 mmol, 9.1% yield) as an oil; $[\alpha]_D^{25}$ -38.2 (c 6.3, $CHCl_3$) (lit. $[\alpha]_D^{25}$ -39°)[7] giving an optical purity of 93% based on the specific rotation and the optical purity reported in reference 7; IR (film) 3400 (OH), 1490 (C=C) cm^{-1}; NMR (80 MHz, CCl_4) δ 2.7 (br s, 1H, OH), 3.38 (dd, 1H, J=10.4 and 8.0 Hz, CH_2), 3.56 (dd, 1H, J=10.4 and 4.0 Hz, CH_2), 4.80 (dd, 1H, J=8.0 and 4.0 Hz, CH), 7.3 (s, 5H, Ph); m/z 200-202 (M^+).

ii. When α-bromoacetophenone (1 g, 5.01 mmol) was subjected to procedure B the product isolated was (-)-(R)-2-bromo-1-phenylethanol (83.3 mg, 0.417 mmol, 8.8%); $[\alpha]_D^{25}$ -39.7° (c 8.4, $CHCl_3$). The optical purity was 97%.

iii. When α-bromoacetophenone (1 g, 5.02 mmol) was subjected to procedure C the product isolated was (-)-(R)-2-bromo-1-phenylethanol (84.2 mg, 0.42 mmol, 11%); $[\alpha]_D^{25}$ -36.9° (c 7.73, $CHCl_3$) giving an optical yield of 90%.

Baker's yeast reduction of α-iodoacetophenone: When α-iodoacetophenone (643 mg, 2.61 mmol) was subjected to procedure B the following products were isolated: a. acetophenone

(209 mg, 1.74 mmol, 67%); b. (-)-(S)-1-phenylethanol (101 mg, 0.83 mmol, 32%): $[\alpha]_D^{25}$ -36.3° (c 1.9, C_6H_6) (lit. $[\alpha]_D$ +43.5°)[3a] giving an optical yield of 73%; IR (film) 3350 (OH), 1495 (C=C) cm^{-1}; NMR (80 MHz, CCl_4) δ 1.2 (d, 3H, J=6.4 Hz, CH_3), 2.1 (br s, 1H, OH), 4.6 (q, 1H, J=6.4 Hz, CH), 7.2 (s, 5H, Ph).

Reduction of α-iodoacetophenone by baker's yeast in the presence of *m*-dinitrobenzene: Following method B, DNB (in amounts of 6 to 100% in relation to ketone) was added to the mixture of baker's yeast-water 30 minutes before the ketone addition. NMR of the extract clearly showed that acetophenone was the principal product.

Stability of the (±)-2-bromo-1-phenylethanol in the baker's yeast-water mixture: The racemic bromohydrin (1 mmol) was shaken with baker's yeast water mixture (same quantities as method B) for a period of 24 hours. The extraction and isolation procedure were the same as described in method A. 98% of the racemic bromohydrin was recovered.

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