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Stereochemical Control in Yeast Reduction of Fluorinated β-Diketones

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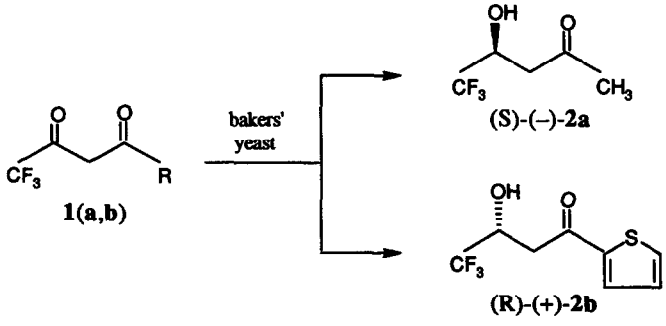
Abstract. The presence of additives in bakers' yeast reductions of fluorinated β-diketones turns the stereochemistry of the reaction towards the (R) or (S) enantiomers of the corresponding ketols.

The asymmetric Bakers' yeast reduction of prochiral carbonyl compounds is one of the most useful reactions for the synthesis of chiral alcohols. Bakers' yeast is inexpensive, its use does not require microbiological experience or special equipment and it works over a wide range of unnatural substrates.[1] However, the stereochemical results of the reaction are not always satisfactory, since the process is often only partially stereoselective. The reason for this behaviour can be ascribed to two or more competing dehydrogenases which may operate simultaneously on the same substrate to produce alcohols of opposite configuration.[2] Several methods have therefore been developed to control the stereochemistry of the reaction in order to obtain both the enantiomers of the reduction products in high enantiomeric excesses. Among these, the use of enzyme-highly selective inhibitors has turned out to be very effective.[3]

In our recent research we observed that the yeast reduction of 1,1,1-trifluoro-2,4-pentandione (**1a**), and 4,4,4-trifluoro-1-(2-thienyl)-1,3-butandione (**1b**), gives the corresponding 5,5,5-trifluoro-4-hydroxy-2-pentanone (**2a**), and 4,4,4-trifluoro-3-hydroxy-1-(2-thienyl)-1-butanone (**2b**), respectively, in regioselective way and in good enantiomeric excesses, ee. 38-72% (Scheme 1).[4]



Scheme 1

Moreover, the absolute stereochemistry of the reduction products depends on the R substituent: *i.e.*, when R is the methyl group, we recovered the levorotatory hydroxyketone **2a** having the (S) absolute configuration at

the chiral carbon atom; when R is the thienyl group, we obtained the dextrorotatory hydroxyketone **2b** with the (R) configuration at the same chiral center.[4] We now report the results of the yeast reduction of the same β-diketones **1a** and **1b**, carried out in the presence of several additives in order to improve the enantiomeric excesses and to verify the possibility of obtaining both enantiomers of the carbinols **2a** and **2b**.

RESULTS AND DISCUSSION

The reductions were performed by adding the diketones **1a** or **1b** to a yeast-water suspension preincubated for 1h with the selected additive: methylvinylketone, allyl alcohol, acetic- fumaric- or oleic-acid, ethylchloroacetate and allyl bromide; *i.e.*, additives which are reported to affect the stereochemical course of bakers' yeast reductions.[5] In some cases, both the influence of the yeast/substrate ratio and the influence of the presence of glucose were considered. Allyl bromide was tested also with 2h of preincubation.

Table 1. Comparison of the effects of additives in bakers' yeast reduction of β-diketone **1a**.[a]

Method[b]	Additive	(gl^{-1})	Product		
			conv.%[c]	ee.%[d]	conf.[e]
1	–		97	44	(S)-(–)
1G	–		97	63	(S)-(–)
2	–		50	38	(S)-(–)
2G	–		97	72	(S)-(–)
1	allyl alcohol	(3)	100	86	(S)-(–)
1G	allyl alcohol	(3)	100	86	(S)-(–)
2	allyl alcohol	(3)	94	88	(S)-(–)
2G	allyl alcohol	(3)	100	87	(S)-(–)
2G	allyl alcohol	(6)	82	92	(S)-(–)
1	methylvinylketone	(1.5)	100	76	(S)-(–)
1G	methylvinylketone	(1.5)	100	83	(S)-(–)
2G	methylvinylketone	(1.5)	14	69	(S)-(–)
1G	methylvinylketone	(3)	82	86	(S)-(–)
1	acetic acid	(3)	93	44	(S)-(–)
2G	acetic acid	(3)	95	61	(S)-(–)
1	fumaric acid	(3)	97	47	(S)-(–)
2G	fumaric acid	(3)	94	77	(S)-(–)
1	oleic acid	(3)	100	31	(S)-(–)
2G	oleic acid	(3)	99	77	(S)-(–)
1	ethylchloroacetate	(3)	100	9	(R)-(+)
1G	ethylchloroacetate	(3)	76	20	(R)-(+)
1	allyl bromide	(1.5)	46	57	(R)-(+)
1G	allyl bromide	(1.5)	74	64	(R)-(+)
1	allyl bromide	(3)	37	81	(R)-(+)
1G	allyl bromide	(3)	48	60	(R)-(+)
2G	allyl bromide	(3)	70	40	(R)-(+)

[a] Reactions were performed in water at 27-30 °C with 1h of preincubation of the system yeast-additive. [b] Method 1: substrate 1 m.mole (0.02 M); BY 224 gl^{-1}. Method 1G: method 1 with additional glucose 60 gl^{-1}. Method 2: substrate 1 m.mole (0.04 M); BY 112 gl^{-1}. Method 2G: method 2 with additional glucose 60 gl^{-1}. [c] Conversion estimated by glc after 20-24 h. [d] Enantiomeric excess determined by glc on chiral G-DEX 120 capillary columnn. [e] Absolute configuration from ref. 4a.

In the presence of acetic- fumaric- and oleic-acid we did not observe any significant effect. On the contrary, the addition of methylvinylketone, allyl alcohol, ethylchloroacetate and allyl bromide, to the reaction system did affect the stereochemical course of the reduction by controlling both the synthesis of the (S) or (R) enantiomeric form of **2a**. The results of the yeast-reduction of diketone **1a**, carried out in the presence of the additives, are compared in Table 1 together with the results obtained in the control reaction without any additive. In particular, (S)-(–)-**2a** was obtained when the reactions were carried out in the presence of allyl alcohol, methylvinylketone, acetic- fumaric- or oleic-acid, as well as in the control reduction; on the other hand, (R)-(+)-**2a** was obtained when we used the ethylchloroacetate or the allyl bromide as additive. In the first case, the best chemical and stereochemical results for (S)-(–)-**2a**, 82-100% of conversion and 86-92% of enantiomeric excess, were obtained when the reactions were carried out in the presence of allyl alcohol; in the second case, the best results of conversion and ee. for (R)-(+)-**2a**, 37-74% and 40-81%, respectively, were obtained when allyl bromide was used as additive.

Table 2. Effects of preincubation time of yeast-allyl bromide system on the reduction of β-diketone **1a**.[a]

Method	Additive	(gl^{-1})	p.t.[b]	Product		
				conv.%	ee.%	conf.
1	allyl bromide	(1.5)	1	46	57	(R)-(+)
1	allyl bromide	(1.5)	2	50	62	(R)-(+)
1	allyl bromide	(3)	1	37	81	(R)-(+)
1	allyl bromide	(3)	2	86	70	(R)-(+)
1	allyl bromide	(6)	2	74	74	(R)-(+)
1G	allyl bromide	(1.5)	1	74	64	(R)-(+)
1G	allyl bromide	(1.5)	2	75	75	(R)-(+)
1G	allyl bromide	(1.5)	4	77	71	(R)-(+)
1G	allyl bromide	(3)	1	48	60	(R)-(+)
1G	allyl bromide	(3)	2	84	70	(R)-(+)
1G	allyl bromide	(6)	2	67	77	(R)-(+)

[a] The reduction conditions are described in Table 1. [b] Preincubation time in hours.

Moreover, in the presence of allyl alcohol the results of the reductions do not seem strongly dependent on the yeast/substrate ratio and/or on the presence of glucose: *i.e.*, very high conversions and appreciable ee. of (S)-(–)-**2a** were obtained, independently of whether methods 1 or 1G, 2 or 2G, were applied to the reaction. On the other hand, in the presence of allyl bromide the conversions and, in a lesser degree, the enantiomeric excesses, can be improved with a longer incubation time (Table 2), as also observed in other cases.[5e] Finally, no synergic effect has been observed in presence of either the additives methylvinylketone and allyl alcohol or ethylchloroacetate and allyl bromide.

The trend summarized in Table 1 has also been observed in the synthesis of **2b** by bakers' yeast reduction of β-diketone **1b** carried out in the presence of the same additives (Table 3). Namely, allyl alcohol and methylvinylketone, which contributed to increase the ee. of the (S) form of ketol **2a**, afforded, in this case, a lowering of the ee. of the (R) form of ketol **2b**, the highest effect still being related to the allyl alcohol. Conversely, the presence of ethylchloroacetate and, in a more pronounced way, of allyl bromide, also caused a shift to higher values of the ee. of the (R) enantiomer of ketol **2b**, with respect to the results obtained in the

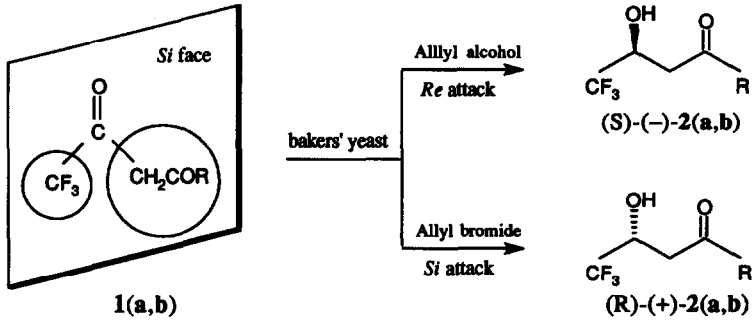
absence of additives. Moreover, with allyl bromide a longer preincubation time enhances the ee. values of the **2b** product.

Table 3. Comparison of the effects of additives in bakers' yeast reduction of β-diketone **1b**.[a]

Method	Additive	(gl^{-1})	p.t.[b]	Product		
				conv.%	ee.%	conf.[c]
1	-			97	49	(R)-(+)
1G	-			74	66	(R)-(+)
1	allyl alcohol	(1.5)	1	68	22	(R)-(+)
1G	allyl alcohol	(1.5)	1	61	31	(R)-(+)
1	methylvinylketone	(1.5)	1	52	32	(R)-(+)
1	acetic acid	(1.5)	1	65	39	(R)-(+)
1	ethylchloroacetate	(1.5)	1	32	50	(R)-(+)
1	allyl bromide	(1.5)	1	70	54	(R)-(+)
1G	allyl bromide	(1.5)	1	19	70	(R)-(+)
1	allyl bromide	(1.5)	2	15	62	(R)-(+)
1G	allyl bromide	(1.5)	2	34	81	(R)-(+)

[a] The reduction conditions are described in Table 1. [b] Preincubation time in hours. [c] Absolute configuration from ref. 4b.

In summary, the *pro-S* and *pro-R* additives reported in Table 1, for diketone **1a**, work with diketone **1b** in the same direction even if in minor extent (Table 3). The most representative of these additives are, on one side, the allyl alcohol, which seems to inhibit the *Si* attack of the hydride and, on the other side, the allyl bromide, which inhibits the *Re* attack (Scheme 2). By assuming that CF_3 is sterically less demanding than CH_2COR substituent, one can notice that Prelog's rule[6] holds for the yeast reductions carried out with allyl bromide additive, whereas it is not followed when the additive is allyl alcohol.



a) R = CH_3; b) R = thienyl

Scheme 2

The Prelog's rule seems to apply also for the recently reported yeast reductions of ethyl 3-oxoalkanoates carried out in the presence of allyl bromide, whereas opposite stereochemical course of the same reductions is

observed when the additive is allyl alcohol.[5e] These results, together with the results of the present work, clearly indicate the effectiveness of the methods described in this paper for the preparation of both the enantiomeric forms of a larger series of chiral compounds, and the possibility of also making configurational assignments to the optically active derivatives obtained in the same reactions.

EXPERIMENTAL

Fresh bakers' yeast (FALA, Strasbourg) and commercially available glucose were used for the reactions. 1,1,1-Trifluoro-2,4-pentandione (**1a**) and 4,4,4-trifluoro-1-(2-thienyl)-1,3-butandione (**1b**) were purchased from Janssen Chimica. Methylvinylketone and allyl bromide were purchased from Merck, allyl alcohol from Aldrich Chemical Co. Other chemicals used as additives and solvents were obtained from Carlo Erba. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20 °C in $CHCl_3$ solution (c 1.0). Glc analyses were performed on a Hewlett-Packard 5890 A gas chromatograph; the conversions were evaluated on a DB1 column (30 m x 0.53 mm I.D. and 5 μm film phase) from J&W Scientific, whereas the enantiomeric excesses were evaluated on a chiral G-DEX 120 column (30 m x 0.25 mm I.D. and 0.25 μm film phase) from Supelchem. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer, chemical shifts being reported in δ values from TMS as internal standard. Elemental analyses were determined with a Carlo Erba Elemental Analyser Mod. 1106.

Procedure for yeast reductions

Bakers' yeast, 11.2 g (method 1), or 2.8 g (method 2), was suspended in distilled water (50 or 25 ml, respectively) and additive was added in the required quantity. The mixture was kept at 27-30 °C and shaken with a magnetic stirrer for one or two hours. Subsequently, 1 m.mole of diketone **1a** (0.15 g) or 1 ml ethanol solution of 1 m.mole of diketone **1b** (0.22 g), and 6% of glucose, when required, was added and the suspension allowed to stand at the same conditions for 20-24 h. The reaction mixture was then extracted four times with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was analyzed by glc for conversion and enantiomeric excess determination.

The reaction conditions which gave the most interesting results were repeated in gram quantities and the alcohols thus afforded were isolated and characterized as reported in the following.

(S)-(−)-5,5,5-trifluoro-4-hydroxy-2-pentanone (**2a**). Method 2G in presence of allyl alcohol 3 gl^{-1}. Diketone **1a** (2.3 g, 15 m.mol) and 23 g of glucose were added in 380 ml of 1h preincubated water suspension containing 43 g of fresh bakers' yeast and 1.14 g of allyl alcohol. The same procedure described above was then followed. The crude product, showing absence of diketone **1a**, was chromatographed on silica gel column (diethyl ether/petroleum ether 80:20 eluent) and 1.8 g (yield 77%) of alcohol were recovered. The distilled ketol **2a**, $Kp_{\ 20\ mmHg}$ 84-85 °C, showed $[\alpha]_D$ −29.0 ($CHCl_3$) ee. 85%; ^{1}H-NMR ($CDCl_3$), δ: 2.25 (3H, s), 2.76 (1H, dd), 2.89 (1H, dd), 3.35 (1H, b), 4.50 (1H, m). Anal. calcd. for $C_5H_7F_3O_2$: H 4.52, C 38.47; found: H 4.87, C 38.40.

(R)-(+)-5,5,5-trifluoro-4-hydroxy-2-pentanone (**2a**). Method 1G in presence of allyl bromide 1.5 gl^{-1}. A 500 ml water suspension containing 112 g of fresh bakers' yeast and 0.75 g of allyl bromide were preincubated at 27-30 °C for 2 h; then diketone **1a** (1.5 g, 10 m.mol) and 30 g of glucose were added. The same procedure described above was followed. The crude product showed a conversion of 71% and ee. 70%; it was

chromatographed on silica gel column (diethyl ether/petroleum ether 50:50 eluent) and 0,68 g (yield 45%) of alcohol were recovered. The distilled ketol **2a**, Kp $_{20\ mmHg}$ 83-84 °C, showed $[\alpha]_D$ +24.4 ($CHCl_3$); ^{1}H-NMR ($CDCl_3$), δ: 2.25 (3H, s), 2.76 (1H, dd), 2.89 (1H, dd), 3.35 (1H, b), 4.50 (1H, m). Anal. calcd. for $C_5H_7F_3O_2$: H 4.52, C 38.47; found: H 4.74, C 38.43.

(R)-(+)-4,4,4-trifluoro-3-hydroxy-1-(2-thienyl)-1-butanone (**2b**). Method 1G in presence of allyl bromide 1.5 gl^{-1}. A 250 ml water suspension containing 56 g of fresh bakers' yeast and 0,375 g of allyl bromide was preincubated at 27-30 °C for 2 h; then diketone **1a** (1.1 g, 5 m.mol) dissolved in 4 ml of ethyl alcohol and 15 g of glucose were added. The same procedure described above was followed. The crude product showed a conversion of 35% and ee. 76%; it was chromatographed on silica gel column (diethyl ether/petroleum ether 30:70 eluent) and 0.3 g (yield 27%) of alcohol were recovered. The ketol **2b** showed $[\alpha]_D$ +18.3 ($CHCl_3$); ^{1}H-NMR ($CDCl_3$), δ: 3.24 (1H, dd), 3.35 (1H, dd), 3.59 (1H, d), 4.68 (1H, m), 7.19 (1H, dd), 7.74 (1H, dd), 7.79 (1H, dd). Anal. calcd. for $C_8H_7F_3O_2S$: H 3.15, C 42.86, S 14.3; found: H 3.02, C 43.25, S 14.26.

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