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Stereocontrolled Synthesis of *p*-Substituted Trifluoromethylbenzylic Alcohol Derivatives of High Optical Purity by the Baker's Yeast Reduction

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Abstract: The enantioselectivity of the bakers' yeast reduction of *p*-substituted trifluoroacetylbenzene derivatives could be improved by the introduction of some functional groups at the para-position to give the corresponding (*R*)-trifluoromethyl-substituted benzylic alcohols in high chemical and optical yields. The optically active alcohols obtained were readily converted into optically pure forms by recrystallization.

Although the bakers' yeast reduction of ketones provides a chemo-, and stereoselective preparation of secondary alcohols,[1] the substrate specificity encountered in the yeast mediated methodologies often makes this useful tool less utilizable. In particular, for the preparation of the optically active trifluoromethyl-substituted benzylic alcohols, some difficulties have been reported in the reduction of α,α,α-trifluoroacetylated aryl derivatives with bakers' yeast, and the optical purities of the reduced alcohols were not satisfactorily good.[2] Our ongoing interest in the reduction of sulfur-functionalized ketones[1b] and particularly sulfur-containing trifluoroacetylbenzene coupled with the fact that little is known about the yeast-mediated reduction of trifluoroacetylbenzene derivatives bearing a functional group at the para-position[2-4] led us to anticipate that the introduction of a functional group into the para-position would improve the enantioselectivity of the bakers' yeast reduction of trifluoroacetylbenzene derivatives. In addition, the manipulation of one of the carbonyl groups with sulfur-containing moieties would be suitable for the chemo- and stereoselective reduction of the diketones with yeast. Optically pure trifluoromethyl-substituted benzylic alcohols represent an important class of functionalized precursors useful in ferroelectric liquid crystals having a stereogenic center directly connected to the core aromatic ring, which have a potentiality of a large spontaneous polarization and a short response time towards electric field,[5] and a reported access to one of the

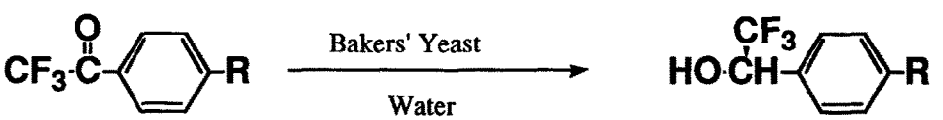


Table 1. Bakers' Yeast Reduction of *p*-Substituted Trifluoroacetylbenzene Derivatives

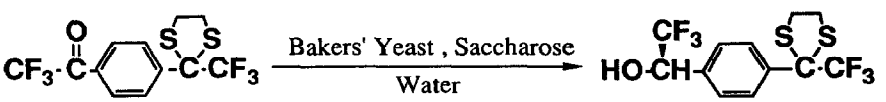
Entry	R	Saccharose[a)]	Time(d)	Yield[b)]	%ee[c)]	Configuration
1	CO_2H	+	5	57	80	*R*
2	CO_2CH_3	+	6	47	80	*R*
3	CO_2H	-	6	75	91	*R*
4	CO_2CH_3	-	7	59	90	*R*

a) The marks of + and - represent in the presence and in the absence of saccharose, respectively. b) Isolated by preparative TLC. c) Determined by capillary GLC analysis (SE-30, 50 m) of the corresponding (*R*)-MTPA esters.

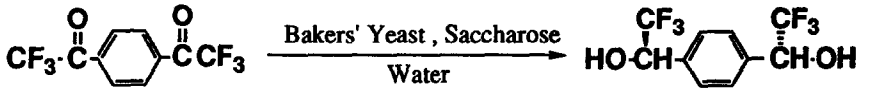
invaluable synthons of such a class is provided by the enzymatic resolution of the racemic *p*-substituted benzylic alcohols with a lipase,[6] where the absolute configuration of the product has not been addressed. We report herein that trifluoroacetylbenzene derivatives preferentially give upon bakers' yeast reduction (*R*)-trifluoromethyl-substituted benzylic alcohol derivatives in high enantiomeric excess when the appropriate functional groups were introduced at the para-position.

Bakers' yeast reduction was conducted according to the following typical procedure: dry bakers' yeast (S. I. L. Lesaffre, 5g), saccharose (Wako, 6g) and a pH 7.0 aqueous phosphate buffer solution (KH_2PO_4-Na_2HPO_4) were mixed and stirred vigorously at room temperature for 30 min. In cases where no saccharose was used, dry bakers' yeast was simply stirred with the buffer solution until homogeneity. Then *p*-trifluoroacetylbenzoic acid derivatives[7] (0.66 mmol) dissolved in 5 ml of ethanol was added to the broth with constant stirring. Standard work-up followed by silica gel thin layer chromatography allowed the isolation of optically active (*R*)-*p*-(2,2,2-trifluoro-1-hydroxyethyl)benzoic acid derivatives in moderate yields. In the cases of *p*-trifluoroacetylbenzoic acid and its methyl ester examined, the better results were obtained without saccharose and the isomers were readily separated and isolated by preparative silica gel TLC. The optical purity of the products thus obtained was determined by GLC (SE-30, 50 m) analysis of the corresponding (*R*)-MTPA esters.[8] As shown in Table 1 the bakers' yeast reduction gave the optically active (*R*)-alcohols in good enantiomeric excess, making a contrast to the previous result where the reduction of the simple trifluoroacetylbenzne gave the corresponding benzylic alcohol in 44%ee.[2]

Previously from our laboratory, the improvement of the stereocontrol in the bakers' yeast reduction has been reported to be achieved by the introduction of sulfur functional groups.[1b] Thus, the bakers' yeast reduction of *p*-bis(trifluoroacetyl)benzene possessing a protecting group at one of the ketones as 1,3-dithiolane was carried out in the presence of saccharose for 8 days to give the corresponding optically active secondary alcohol of higher purity in a chemical yield of 78% and in an optical yield of 96%, which was determined by HPLC analysis of the (*R*)-MTPA ester.[9]

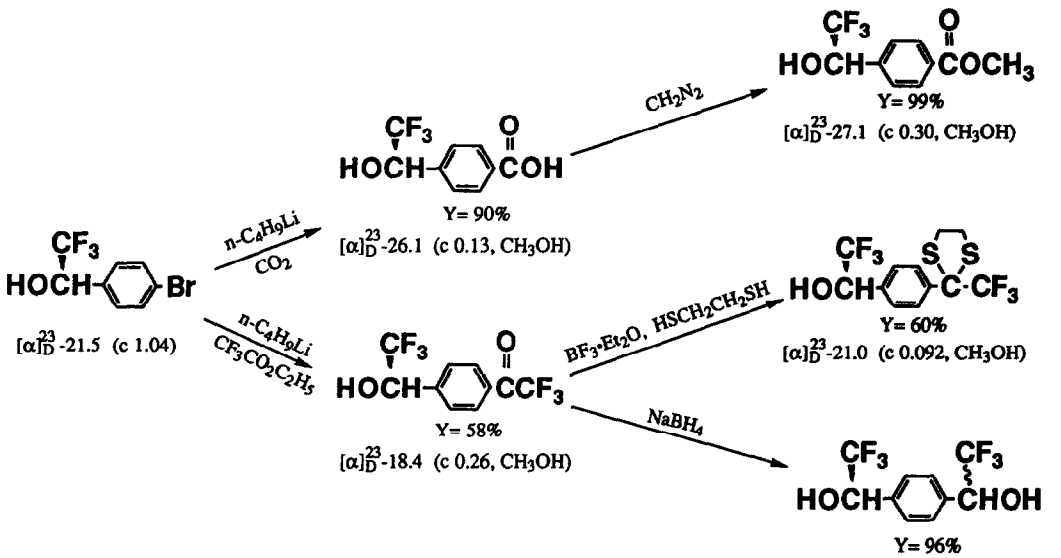


The reduction of the prototype of the diketone, *p*-bis(trifluoroacetyl)benzene, proceeded also in a highly stereodivergent fashion to give the diol in a yield of 59% with a ratio of (*R*,*R*)- to (*R*,*S*)-form of 98 : 2 by conducting the bakers' yeast reduction as described above.[10] In this case the reduction of the second carbonyl was relatively fast, and the diol was obtained as a major product even when the reaction was conducted for a



short time, indicating that the selective protection of one of the carbonyls as described above is one of the better solutions to the selective preparation of hydroxy ketone derivatives. The optical purity of the diol was determined by capillary GLC analysis of the corresponding bis(*R*)-MTPA ester and by comparison with the spectral behavior of the authentic racemic bis(*R*)-MTPA ester. In strong contrast to *p*-bis(trifluoroacetyl)-benzene, the reduction of *p*-diacetylbenzene with bakers' yeast gave the mono-reduction product as a sole product in 65% yield with >99% ee after six days, and the reduction of the second carbonyl proceeded considerably sluggishly to give the diol in 6% yield upon further treatment of the mono-reduction product with yeast for one week. Furthermore, the reduction of the homologous *p*-pentafluoropropionylbenzoic acid with bakers' yeast was less enantioselective to afford the pentafluoroethyl-substituted benzylic alcohol derivative in 40% chemical yield and in 40% optical yield, showing that the bakers' yeast reduction of the perfluoroacylbenzene derivatives possessing a substituent at the para-position appears to be effective particularly for trifluororacetyl derivatives.

The absolute configurations of the *p*-substituted trifluoromethylbenzylic alcohols thus prepared were established to be *R*-form in all the cases by an independent synthesis of authentic alcohol derivatives starting from the known (*R*)-*p*-(2,2,2-trifluoro-1-hydroxyethyl)bromobenzene[3] prepared from the bakers' yeast reduction of the parent ketone as depicted below via the standard transformations.



In conclusion, in contrast to the yeast reduction of simple trifluoroacetylbenzene or naphthalene,[2] trifluoroacetylbenzene derivatives, which can be readily synthesized from commercially available starting materials, have been shown to undergo a highly stereoselective reduction with bakers' yeast by the introduction of the appropriate functional groups at the para-position, providing the corresponding *R*-alcohols of high optical purity. The optically pure alcohols were readily obtained by recrystallization of the yeast

reduction products, in which the recrystallization yields were normally in the range of 70-90%. Thus, the present methodology provides a straightforward access to the optically pure benzylic alcohols containing a trifluoro-group useful for chiral dopants, and with the slight modification of the substituents at the benzene ring a series of optically pure benzylic alcohols possessing a suitable functionality for further functional group manipulations necessary for the ferroelectric liquid crystals will be readily accessible.

References and Notes

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7) The starting trifluoroacetylbenzene derivatives were prepared according to the following procedures: *p*-trifluoroacetylbenzoic acid was synthesized by the trifluoroacetylation of *p*-bromotoluene with trifluoroacetic acid under the action of magnesium metal (56%) according to the method of Yagupolskii et al.[11] followed by the Jones oxidation (49%). The corresponding methyl ester was obtained by the esterification with diazomethane (99%). *p*-Bis(trifluoroacetyl)benzene was available in one step by the coupling of the commercially available *p*-dibromobenzene with ethyl trifluoroacetate in the presence of n-butyllithium (63%).[12] Then protection with ethanedithiol in the presence of catalytic amount of borontrifluoride etherate gave mono-protected bis(trifluoroacetyl)benzene (13%).
8) (*R*)-*p*-(2,2,2-Trifluoro-1-hydroxyethyl)benzoic acid; recrystallized from toluene; mp 174-6°C; $[\alpha]_D^{23}$ -28.1 (c 0.08, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 5.13 (q, *J* = 6.6 Hz, 1H), 2.90 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -80.0 (d, *J* = 6.6 Hz); IR ($CHCl_3$) 3400, 3100, 2950, 1730, 1160, and 1140 cm^{-1}. Methyl (*R*)-*p*-(2,2,2-trifluoro-1-hydroxyethyl)-benzoate; recrystallized from n-hexane; mp 75-7°C; $[\alpha]_D^{23}$-28.3 (c 0.12, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 5.10 (q, *J* = 6.6 Hz, 1H), 3.93 (s, 3H), 3.00 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -80.0 (d, *J* = 6.6 Hz); IR ($CHCl_3$) 3450, 3100, 2980, 1740, 1240, 1180, and 1160 cm^{-1}.
9) (*R*)-4-(2,2,2-trifluoro-1-hydroxyethyl)-1-(2-trifluoromethyl-1,3-dithiolan-2-yl)benzene: recrystallized from toluene; mp 77-9°C; $[\alpha]_D^{23}$ -21.0 (c 0.20, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.69 (d, *J* =8 .0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 5.04 (q, *J* = 6.6 Hz, 1H), 3.40-3.60 (m, 4H), 3.10 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -72.0 (s), -79.0 (d, *J* = 6.6 Hz); IR (neat) 3350, 2950, 1360, 1290, and 1140 cm^{-1}.
10) (*R,R*)-*p*-Bis(2,2,2-trifluoro-1-hydroxyethyl)benzene: recrystallized from carbon tetrachloride; mp 78-80°C; $[\alpha]_D^{23}$ -48.0 (c 0.10, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 4H), 5.07 (q, *J* = 6.6 Hz, 2H), 2.75 (s, 2H); ^{19}F NMR ($CDCl_3$) δ -80.0 (d, *J* = 6.6 Hz); IR (neat) 3350, 2920, 2850, 1470, 1430, 1280, 1180, and 1140 cm^{-1}.
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