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Highly Stereocontrolled Access to Trifluoromethylbenzylic Alcohols Possessing *p*-Substituents by the Bakers' Yeast Reduction

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Abstract: The bakers' yeast reduction of *p*-amino- or hydroxy-substituted trifluoroacetylbenzene derivatives proceeded in a highly enantioselective manner to give (*R*)-trifluorobenzyl alcohols in up to 92 %ee, which is in a strong contrast to the results obtained in the cases with simple trifluoroacetylbenzene and the naphthalene analogues. The optically active alcohols obtained were readily converted into enantiomerically pure forms by recrystallization.

In conjunction with the growing interest in the field of chiral triflurormethyl containing materials[1] we have embarked on the new efficent method for the preparation of trifluorormethylated benzyl alcohols. For the preparation of optically active secondary alcohols, the bakers' yeast reduction of prochiral ketones offers one of the most straightforward and reliable methods, and many useful procedures have been reported.[2] Although chiral trifluoromethyl benzyl alcohols are useful synthons for ferroelectric crystals,[3] the preparation by the use of bakers' yeast reduction of the simple trifluoroacetylbenzene and naphthalene did not meet with satisfactory enantiofacial discrimination, and the optical purity of the reduced alcohols were in the range of 44-66%ee due to the substrate specificity encountered in the yeast reduction.[4] We have already reported a simple solution to this problem by modification of the substrates by introducing para-substituents[5] which also offer good access for the construction of ferroelectric crystals. For application to more efficient ferroelectric crystals other para-substituents besides carboxylate were needed. For this purpose amino and hydroxyl derivatives intrigued us from the standpoint of case of functional group manipulations, which may improve substrate specificity in the bakers' yeast reduction.

The starting materials were readily prepared from *p*-tolylmagnesium bromide by trifluoroacetylation with trifluoroacetic acid followed by oxidation with chromium trioxide to give *p*-trifluoroacetylbenzoic acid in good yield,[6] which upon chlorination with thionyl chloride and Curtius rearrangement after conversion into the acyl azide afforded the *p*-trifluoroacetylaniline derivative in good yield. The phenol derivative was also readily prepared from the trifluoroacetylation of *p*-anisylmagnesium bromide under the same conditions as for the *p*-tolyl analogue, and the thus obtained *p*-methoxy-α,α,α-trifluoroacetophenone was hydrolyzed to the corresponding phenol by borone tribromide in good overall yield. Further protection of the amino and hydroxyl groups with acetyl, benzoyl, and *p*-tosyl groups was readily carried out via standard procedures to

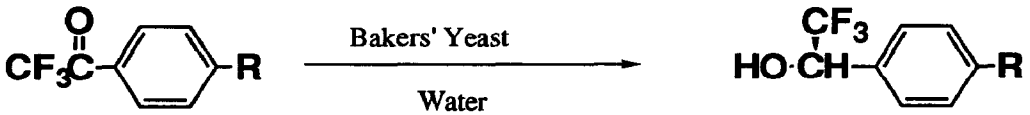

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Table 1. Bakers' Yeast Reduction of *p*-Substituted Trifluoroacetylbenzene Derivatives

Entry	R	Saccharose[a)]	Time(d)	Yield[b)]	%ee[c)]	Configuration
1	NH_2	+	4	76	56	*R*
2	NHBz	+	4	67	68	*R*
3	NHTs	+	4	46	59	*R*
4	NHAc	+	1	63	92	*R*
5	NHAc	-	1	59	80	*R*
6	OH	-	1	85	34	*R*
7	OMe	-	2	88	51	*R*
8	OAc	-	1	85[d)]	21	*R*
9	OTs	-	3	17	48	*R*
10	OBz	+	2	40	87	*R*
11	OBz	-	2	55	91	*R*

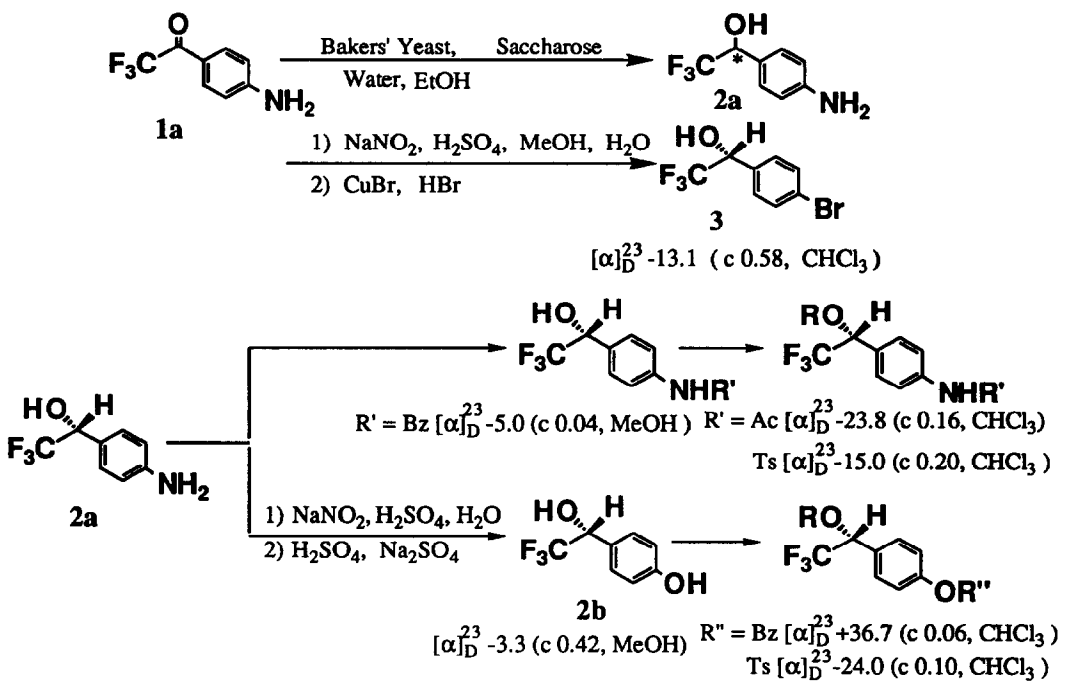
a) The marks of + or - represent in the presence or in the absence of saccharose, respectively. b) Isolated by preparative TLC. c) Determined by capillary GLC (SE-30, 50 m) or HPLC (Hibar RT 240) analysis of the corresponding (*R*)-MTPA esters. d) Product was obtained as deacetylated form.

give the corresponding starting materials in good yield.

Bakers' yeast reduction was carried out 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 a *p*-trifluoroacetylaniline derivative (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)-aniline derivatives in moderate yields. The enantiomeric excess of the products thus obtained was determined by GLC (SE-30, 50 m) or HPLC (Hibar RT 240) analysis of the corresponding (*R*)-MTPA esters. As shown in Table 1, the bakers' yeast reduction gave the optically active (*R*)-alcohols in good enantiomeric excess, depending on the protecting group on the amino and hydroxyl groups. In the cases with aniline derivatives the free amine gave moderate enantiofacial discrimination (entry 1), whereas substrate specificity was improved by introducing an electron-withdrawing group on the amino group, and among the protecting groups the acetyl derivative recorded excellent enantiofacial discrimination to give the benzylic alcohol in 92%ee (entry 4).[7] In this case the presence of the added saccharose was shown to be essential for better discrimination. As to the phenol derivatives the free hydroxyl was not suitable for the bakers' yeast reduction, and the reduction product was obtained in low

enantiomeric excess (entry 6). The protection with acetate was not satisfactory, and the reaction gave the hydrolyzed free phenol in low optical purity (entry 8), whereas the benzoyl derivative was found to be suitable, giving the reduced alcohol in 91%ee (entry 11)[8] when the reduction was conducted in the absence of succharose, which is in contrast to the cases with aniline derivatives.

The absolute configurations of the *p*-substituted trifluoromethylbenzylic alcohols thus prepared were established to be *R* by direct comparison of the sign of the optical rotation with that reported in the case of the *p*-methoxy derivative[9] or in the other cases by the transformation into authentic alcohol derivatives starting from the known (*R*)-*p*-(2,2,2-trifluoro-1-hydroxyethyl)bromobenzene **3**[9] prepared from the bakers' yeast reduction of the parent ketone as depicted below via the standard transformations: The aniline derivative **1a** was reduced with bakers' yeast to give the alcohol **2a**, which upon the Sandmeyer reaction[11] gave the bromo derivative **3**. The comparison of the optical rotation of the bromo derivative with that reported established the absolute configuration of the alcohol **2a** to be *R*. The protection of the amino group also unambiguously established the configuration of each of the aniline derivatives to be *R*. The absolute configurations of the phenol derivatives were also assigned to be *R* by transforming the amino derivative **2a** into the phenol analogue **2b** via the Sandmeyer reaction[10] followed by suitable protection on the hydroxyl group, and comparison of the signs of the optical rotation with those obtained in the present study.



In conclusion, a solution to the problem of the substrate specificity in the bakers' yeast reduction of simple trifluoroacetylbenzene[4] was found by introducing a functionality derived from hydroxyl or amino moiety into para-position of the benzene ring, which can be readily synthesized from commercially available starting materials, and the bakers' yeast reduction provided the corresponding *R*-alcohols in high enantiomeric

excess. Such functional groups may serve also as a good access for the construction of the ferroelectric crystals. 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 60-90%. Thus, the present Bakers' yeast reduction of *p*-amino- and hydroxyl-substituted trifluoroacetylbenzene derivatives provides a straightforward access to the enantiomerically pure benzylic alcohols containing a trifluoro-group, which are useful for chiral dopants for the ferroelectric liquid crystals. Given the simplicity of the experimental procedure and the ease for the modification of the substrate, the present methodology offers a good addition to the existing procedures for the chiral trifluoromethylated alcohols.

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7. (*R*)-4'-(1-Hydroxy-2,2,2-trifluoroethyl)acetanilide: $[\alpha]_D^{23}$ -27.0 (c 0.20, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 4.88 (q, *J* = 6.6 Hz, 1H) 2.19 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -79.3 (d, *J* = 6.6 Hz); IR (neat) 3300, 2910, 2850, 1700, 1200, and 690 cm^{-1}.
8. (*R*)-4'-(1-Hydroxy-2,2,2-trifluoroethyl)benzoyloxybenzene; $[\alpha]_D^{23}$ -20.0 (c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.20 (d, *J* = 8.58Hz, 2H), 7.49-7.68 (m, 5H), 7.26 (d, *J* = 8.58 Hz, 2H), 5.01 (q, *J* = 6.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ -79.5 (d, *J* = 6.6 Hz); IR ($CHCl_3$) 3600, 3350, 2930, 1745, 1615 and 1140 cm^{-1}.
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