Highly Efficient Synthetic Method of Optically Active 1,1,1-Trifluoro-2-alkanols by Enzymatic Hydrolysis of the Corresponding 2-Chloroacetates

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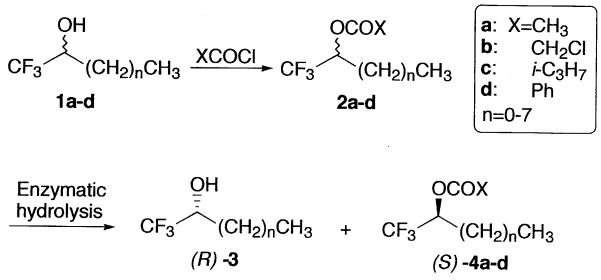
Enantioselective hydrolyses of 2-chloroacetates derived from racemic 1,1,1-trifluoro-2-alkanols were found to proceed very smoothly in the presence of a catalytic amount of lipase MY to yield the corresponding (*R*)-alcohols with high optical purity. In this procedure, purification was easily carried out only by a simple distillation of the reaction mixture, enabling us to extend this reaction in a larger scale.

In recent years, the growing importance of optically active 1,1,1-trifluoro-2-alkanols has often been pointed out as components of ferroelectric liquid crystals.[1] While there are a number of reports on their syntheses via the enzymatic hydrolysis with lipases,[2,3] most of them would not be appropriate as the large scale production method of such alcohols because of the difficulty in separation of the enzyme especially in the case of the asymmetric hydrolysis. Enzymatic esterification would be regarded as an alternative route, while employment of water is much more convenient than organic solvents because of the faster reaction rates and better enantioselectivity from our previous experience. Then we have searched a various type of acyl groups allowing the high enantiomeric discrimination by lipases as wel as the ready separation of the hydrolyzed alcohols from the unreacted esters. Here, the authors would like to report the enzymatic hydrolysis of 1,1,1-trifluoro-2-alkanols via the corresponding 2-chloroacetates and this modification eventually enabled us to significantly reduce the amount of enzyme employed and to isolate the products only by a simple distillation, not via troublesome column chromatography.



Scheme 1.

At first, 1,1,1-trifluoro-2-octanol (**1**, n=5) was selected as a model compound and was converted to a different type of esters **2a-d** (n=5) in a usual manner,[4] which were employed for enzymatic hydrolysis (Scheme 1). The reaction was carried out with 5 g of esters **2a-d** (n=5) and an appropriate amount of lipase MY (supplied by Meito Sangyo Co.) from *Candida rugosa* in 50 ml of 0.5 M phosphate buffer at pH 7 at 38 ℃.

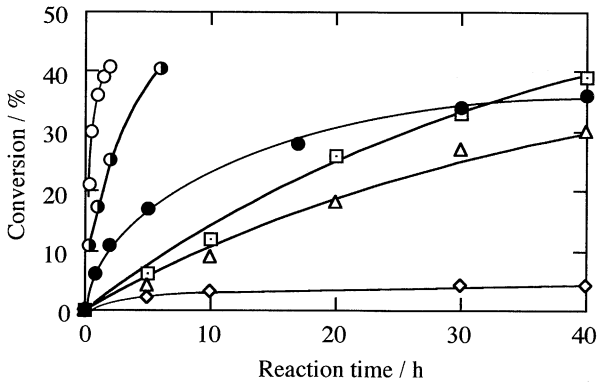


Figure 1. Differences in hydrolysis rates of **2a-d** (n=5). Conditions: the amount of the racemic esters was 5 g in all cases; **2a** (□), **2b** (○), **2c** (△) and **2d** (◇) reacted with 500 mg of lipase MY (30000 units/g) and **2b** reacted with 2 mg (◑) and 0.5 mg (●) of lipase MY.

The liquid phase was periodically analyzed by gas chromatography and the reaction was stopped by addition of 6 N HCl (5 ml) when 40% conversion was attained.

The results are shown in Figure 1. The hydrolysis rates increased in the order of benzoate << *i*-butyrate < acetate << 2-chloroacetate. Because the most preferable substrate **2b** (n=5) in the present system smoothly transformed into the corresponding chiral alcohol (*R*)-**3**, the effective reduction of an amount of the enzyme was realized to less than 0.1% compared with our previously reported conditions.[3] This high efficiency was also understood from the comparison of reaction time-conversion relationship of acetate **2a** (□) and 2-chloroacetate **2b** (●), the latter using only a thousandth amount of lipase MY.

In Table 1 are depicted the results of enzymatic hydrolysis using esters **2a** and **2b** under the above standard reaction conditions. It was quite apparent that the latter was transformed much faster than the other, but the equally high performance (E>100) was established for both compounds. In many cases, the absolute configurations of the products **3** were determined by chemical correlation method[5] using chiral 3,3,3-trifluoropropeneoxide and ethyl 4,4,4-trifluoro-3-hydroxybutyrate as reference materials. The diastereomeric MTPA (α -methoxy- α -(trifluoromethyl)phenylacetyl) esters from **3** with both (*R*)- and (*S*)-MTPA-Cl showed the similar NMR chemical shift difference tendency (Δ δ), which, on the basis of the Modified Mosher methods,[6] assumed the same stereochemistries for compounds not chemically determined. Now, *R* preference in the present hydrolysis was demonstrated in all examples in this Table, while the enantioselection was lowered for such

Table 1. Enantioselective hydrolysis of acetates (**2a**, n=1-7) and chloroacetates (**2b**, n=0-5) with lipase MY

Substrate	Lipase/g[a]	Time/h[b]	$[\alpha]^{25}_{D}$/deg[c]	e.e./%[d]	E[e]
2a (n=7)	0.5	45	+25.4 (c 1.62)	98	>100
2a (n=6)	0.5	43	+23.8 (c 1.54)	98	>100
2a (n=5)	0.5	41	+28.6 (c 1.52)	97	>100
2a (n=4)	0.5	28	+28.0 (c 1.55)	97	>100
2a (n=3)	0.5	27	+31.8 (c 1.52)	97	>100
2a (n=2)	0.5	22	+32.4 (c 1.60)	97	>100
2a (n=1)	0.5	6[f]	j	95	55
2a (n=1)	0.5	15[g]	+29.4 (c 1.53)	91	67
2b (n=5)	0.002	6	+24.0 (c 1.59)	97	>100
2b (n=4)	0.003	5	+29.8 (c 1.54)	97	>100
2b (n=3)	0.003	6	+29.5 (c 1.47)	98	>100
2b (n=2)	0.003	5	+30.6 (c 1.47)	97	>100
2b (n=1)	0.010	1[h]	+28.9 (c 1.51)	91	61
2b (n=0)	0.003	3[i]	j	71	20

[a]Activity was 30000 unit/g. [b]Stoped at 40% conversion unless otherwise noted. [c]In methanol. [d]Determined by gas chromatography after conversion of (*R*)-**3** to their MTPA esters. [e]E value=ln[1-(conv.){1+(e.e.)}]/ln[1-(conv.){1-(e.e.)}]. [f]At 27% conversion. [g]At 50% conversion. [h]At 49% conversion. [i]At 57% conversion. [j]Not isolated.

substrates with shorter alkyl chain as **2a** (n=1) and **2b** (n=1 or 0) which hydrolyzed too fast to stop the reaction at 40% conversion. As long as the authors concern, hydrolysis of esters (acetates or 2-chloroacetates) from 1,1,1-trifluoro-2-alkanols furnished alcohols possessing *R* stereochemistry without any exception,[2,3] where a strongly electronegative trifluoromethyl moiety might play a significantly important role for the interaction with the enzyme at its active site.

As described above, we demonstrated the high efficiency of the hydrolyses of 2-chloroacetates derived from 1,1,1-trifluoro-2-alkanols,[7] which allowed us to employ a very small amount of enzyme and led us to readily isolate the hydrolyzed products by a simple distillation. This modification allowed us to isolate up to 100 g of the hydrolyzed alcohols **3** in a single enzymatic optical resolution.

References and Notes

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4 Typical procedure for (±)-**2b** (n=3). To a mixture of (±)-**1** (n=3) (40.6 g, 260 mmol) and chloroacetyl chloride (35.3 g, 310 mmol) in methylene dichloride (400 ml), pyridine (29.3 g, 370 mmol) was added under cooling with ice water. After 2 h of stirring at room temperature, the mixture was quenched with 1 N HCl (400 ml), and then the organic layer was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$, followed by evaporation of the solvent. The residue was distilled to give (±)-**2b** (n=3) in 91% yield (54.8 g, bp 92-93 ℃/40 mmHg). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.91 (m, 3H), 1.36 (m, 4H), 1.80 (m, 2H), 4.13 (s, 2H), 5.34 (m, 1H).

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7 Typical procedure for (*R*)-(+)-1,1,1-trifluoro-2-hexanol [(*R*)-(+)-**3**, n=3]. A mixture of (±)-**2b** (n=3) (50.0 g, 215 mmol) and 0.5 M phosphate buffer pH7 (500 ml) was vigorously stirred at 38 ℃, and powdered lipase MY (20 mg) was added. After 6 h of stirring at 38 ℃, 6 N HCl (50 ml) was added. The reaction mixture was extracted with ether (500 ml), and then washed with saturated $NaHCO_3$ solution and brine. The ether layer was dried with $MgSO_4$, followed by evaporation of the solvent. The residue was distilled to give (*R*)-(+)-**3** (n=3) in 38% yield (12.6 g, bp 61-62 ℃/53 mmHg), 98%ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H), 1.32-1.75 (m, 6H), 2.01 (d, 1H), 3.91 (m, 1H).