Synthesis of Optically Active Trifluorinated Compounds: Asymmetric Michael Addition with Hydrolytic Enzymes

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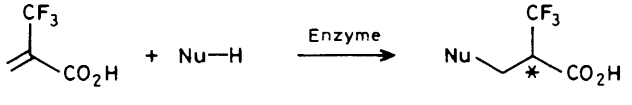
Syntheses of optically active compounds possessing a trifluoromethyl group, *via* enzymatic chiral Michael addition reaction of 2-(trifluoromethyl)propenoic acid and synthesis of trifluoromethylated heterocycles, have been undertaken.

Hydrolytic enzymes as chiral catalysts for asymmetric hydrolysis have been studied over the years.[1,2] However, their catalytic ability for asymmetric synthesis of halogenated compounds remains unexplored from a practical point of view. As far as fluorine compounds are concerned, no enzymatic research has been reported except a few approaches to the transformation of monofluoro-organic compounds and the reduction of aryl perfluoroalkyl ketones.[3—5] Furthermore, the synthetic methods which give high optical purity for a variety of versatile chiral fluorinated materials have not been studied in detail.[6,7]

This work describes a new catalytic reaction of the hydrolytic enzymes, *i.e.* the enzyme-assisted Michael addition



(1)

Nu–H = HOH, $PhNH_2$, EtOH, Et_2NH, PhSH, PhOH

reaction to introduce a centre of chirality into fluorocompounds.

2-(Trifluoromethyl)propenoic acid (**1**), which is the commercially available trifluoromethyl group source with both hydrophobic and hydrophilic sites, readily transforms to produce chiral 3-hydroxy-2-(trifluoromethyl)propanoic acid

Table 1. Asymmetric Michael addition reaction of 2-(trifluoromethyl)propenoic acid.

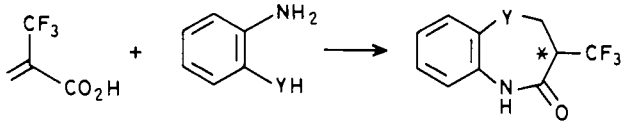
Enzyme	Substrate	Product[a]	Reaction time/h	Yield /%	$[\alpha]_D$/° (MeOH)	Optical purity % e.e.
Candida cylindracea[c]	H_2O	$HOCH_2CH(CF_3)CO_2H$	34	48	+5.70 (*c* 1.52)	70[d]
Pig liver esterase[b]	H_2O	$HOCH_2CH(CF_3)CO_2H$	52	54	+4.90 (*c* 1.50)	60[d]
α-Chymotrypsin[b]	H_2O	$HOCH_2CH(CF_3)CO_2H$	169	77	+3.91 (*c* 1.75)	49[d]
Candida cylindracea[c]	EtOH	No reaction	48			
Pig liver esterase[b]	PhOH	No reaction	48			
Candida cylindracea[c]	Et_2NH	$Et_2NCH_2CH(CF_3)CO_2H$	92	47	+0.61 (*c* 1.56)	71[e]
Pig liver esterase[b]	Et_2NH	$Et_2NCH_2CH(CF_3)CO_2H$	92	39	+0.58 (*c* 1.85)	69[e]
Candida cylindracea[c]	$PhNH_2$	$HOCH_2CH(CF_3)CONHPh$	40	76	+0.51 (*c* 0.77)	39
Pig liver esterase[b]	PhSH	$PhSCH_2CH(CF_3)CO_2H$	24	64	+0.13 (*c* 2.06)	50[e]

[a] Structures of these products are established from spectral data. For the new compound the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.4%). [b] Sigma Co. Ltd. [c] Meito Sangyo Co. Ltd. [d] The optical purity (e.e. = enantiomeric excess) was determined by ^{19}F n.m.r. after conversion of methyl 3-hydroxy-2-(trifluoromethyl)propanoate derived from 3-hydroxy-2-(trifluoromethyl)-propanoic acid and diazomethane to its diastereoisomeric ester by optically active (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. [e] The optical purity was determined by g.l.c. and/or ^{19}F n.m.r. after conversion of optically active acids into their diastereoisomeric amides by optically active α-methylbenzylamine.

Table 2. Preparation of optically active heterocycles.

Substrate	Enzyme	Product[a]	Reaction time/h	Yield /%	$[\alpha]_D$/° (MeOH)	Optical purity[f] % e.e.
2-Aminophenol	*Candida cylindracea*[b]	(**2**)	21	83	+2.74 (*c* 0.45)	41
	Pig liver esterase[c]		16	69	+2.41 (*c* 1.21)	36
	Trichoderma viride[d]		2.5	94	+3.74 (*c* 1.35)	56
	Trichoderma viride[e]		11	61	+2.01 (*c* 0.87)	30
	Aspergillus niger[e]		11	90	+4.48 (*c* 0.47)	67
2-Aminothiophenol	*Candida cylindracea*[b]	(**3**)	20	86	−0.92 (*c* 1.15)	47
	Trichoderma viride[d]		6	72	−0.70 (*c* 0.70)	36
o-Phenylenediamine	*Candida cylindracea*[b]	(**4**)	24	56	+0.66 (*c* 0.89)	38
	Trichoderma viride[d]		24	52	+0.76 (*c* 1.01)	44
4-Methyl-2-aminophenol	*Candida cylindracea*[b]	(**5**)	20	71	+0.56 (*c* 1.54)	25
	Trichoderma viride[d]		20	57	+0.83 (*c* 1.07)	37

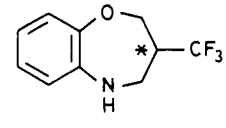
[a] Structures of these products are established from spectral data. For the new compound the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.4%). [b] Meito Sangyo Co. Ltd. [c] Sigma Co. Ltd. [d] Yakult Pharmaceutical Industry Co. Ltd. [e] Amano Seiyaku Co. Ltd. [f] The optical purities were determined by ^{19}F n.m.r. signal intensities by commercially available (+)-tris[di(perfluoro-2-propoxy-propionyl)methanato]europium(III).



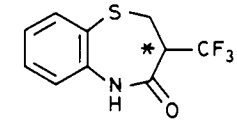
via addition of water, assisted by the hydrolytic enzymes. The results in Table 1 show that chiral Michael addition was also achieved using thiols and secondary amines as nucleophiles, however, alcohols and phenol did not react in this system. When primary amines were used, the condensation and chiral Michael addition reaction were confirmed experimentally.

We have also found a facile route to optically active trifluoromethylated heterocycles. Various kinds of compounds with bifunctional groups were examined to prepare optically active heterocycles. The results shown in Table 2 support a new approach, which is capable of transforming 2-(trifluoromethyl)propenoic acid into optically active heterocycles with a trifluoromethyl group *via* chiral Michael addition and condensation reactions.

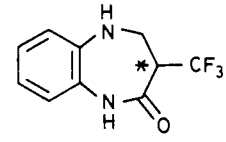
In a typical procedure, a suspension of lipase-MY (*Candida cylindracea*, Meito Sangyo Co. Ltd., 5 g) in buffer solution (50 ml, pH 8.0) was prepared from 1/30 M aq. Na_2HPO_4 and KH_2PO_4 solution, and stirred for 15 min at 40—41 °C. Into the



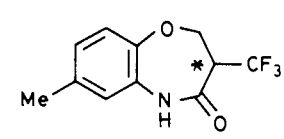
(**2**)



(**3**)



(**4**)



(**5**)

mixture, 2-(trifluoromethyl)propenoic acid (1.5 g, 10 mmol) and *o*-aminophenol (1.3 g, 12 mmol) were added, and then the whole mixture was stirred at 40—41 °C. After 24 h of stirring, the mixture was acidified with 3% HCl and then the oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulphate and then the solvent was removed. The resulting crude products

were chromatographed over silica gel (1 : 1 hexane : diethyl ether) to give optically active heterocycles in the yields shown in Table 2.

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