Pergamon

Tetrahedron Letters, Vol. 35, No. 26, pp. 4635-4638, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00844-2

An Efficient Biocatalyzed Kinetic Resolution of Methyl (Z)-3-Arylsulphinylpropenoates

Cosimo Cardellicchio[a], Francesco Naso*[a], and Antonio Scilimati[b]

[a] C. N. R., Centro di Studio sulle *Metodologie Innovative di Sintesi Organiche*, Dipartimento di Chimica, Università di Bari, Via Amendola 173, 70126 Bari, Italy.

[b] Dipartimento Farmaco-Chimico, Università di Bari, via Orabona 4, 70125 Bari, Italy.

Abstract: The enzymatic hydrolysis of racemic methyl (*Z*)- and (*E*)-3-arylsulphinylpropenoates by several microbial lipases and α-chymotrypsin (α-CHT) was studied. High enantioselectivity values (up to 99%) were obtained using (*Z*)-methyl esters.

Optically active sulfoxides are widely used in asymmetric synthesis,[1] as they can efficiently control the formation of a new stereogenic center. Therefore, several methods for the preparation of these useful compounds in an optical active form are known.[1,2]

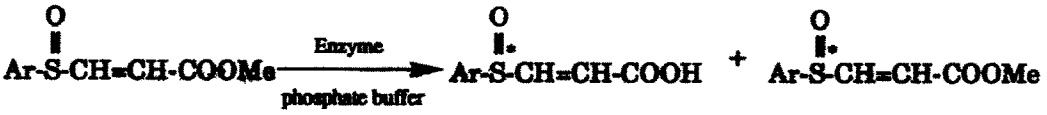
Recently, we reported that 1- and 2-halovinyl aryl sulfoxides[3] react with aryl or alkylmagnesium reagents to give diaryl or alkyl aryl sulfoxides, the halovinyl moiety behaving as a leaving group. This displacement proved to be fully enantiospecific. These results, besides shedding light on the stereochemical course of the novel sulfoxide forming process, suggest that such a process could be considered a competitive candidate among the procedures leading to optically active sulfoxides, if ready methods for obtaining the optically active starting materials were found. Therefore, with the aim of synthesizing potential optically active precursors of our substrates, we decided to investigate the enzyme-catalyzed hydrolysis of alkyl esters of both (*Z*)- and (*E*)-3-arylsulphinylpropenoic acids.[4]

We tested α–chymotrypsin (α-CHT) and a variety of microbial lipase enzymes from *Candida cylindracea* (OF-360 from Meito Sangyo), *Mucor miehei* (MAP), *Pseudomonas sp.* (AK and K-10), *Humicola sp.* (CE-10), *Rhizopus delemar*, *Aspergillus niger* (AP), and *Pancreas pig lipase* (PPL), and methyl esters as starting substrates.[5]

The lipases showed low enantioselectivity in the enzyme-catalyzed hydrolysis of methyl ester of (*E*)- and (*Z*)-3-phenylsulphinylpropenoic acids, in water-saturated isooctane, *n*-hexane (either anhydrous or with different amounts of water, in all cases less than 1%), and chloroform. However, in the α-CHT-catalyzed

hydrolysis of the same (*E*)- and (*Z*)-sulfinylesters, the enantioselectivity values were found to depend on the configuration of the substrate, with better values for the (*Z*)-isomer (Table, entries 1-2, C=Conversion, E=enantioselectivity factor[6]).

Table: Enzyme-Catalyzed Hydrolysis of Methyl (*E*)- and (*Z*)-3-Arylsulfinylpropenoates.



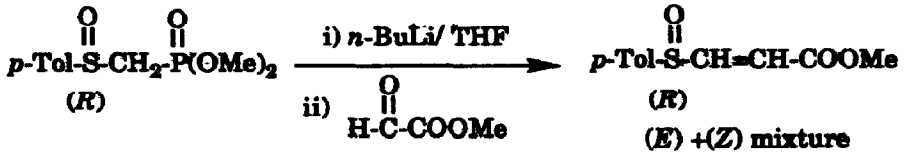
Ar=Phenyl, 2-Naphthyl, *p*-Tolyl

Entry	Config.	Ar	Enzyme	Co-Solvent	e.e. (ester)	e.e. (acid)	C	E	Time (h)
1	(E)	Ph	CHT	None	12%	14%	46%	1	9
2	(Z)	Ph	CHT	None	43%	52%	45%	5	42
3	(Z)	Ph	CHT	10% DMSO	31%	45%	41%	4	20
4	(Z)	Ph	CHT	20% DMSO	63%	7%	90%	2	100
5	(Z)	Ph	CHT	10% t-BuOH	15%	72%	17%	7	20
6	(Z)	Ph	CHT	20% t-BuOH	73%	60%	55%	8	48
7	(Z)	Ph	CHT	10% t-BuOMe	27%	80%	25%	12	70
8	(Z)	Ph	CHT	20% t-BuOMe	91%	65%	58%	14	50
9	(Z)	2-Np	OF-360	None	29%	91%	24%	28	47
10	(Z)	2-Np	OF-360	None	99%	68%	59%	26	94
11	(Z)	p-Tol	OF-360	None	85%	44%	66%	6	48
12	(Z)	p-Tol	CHT	None	37%	77%	32%	11	68

The activity of α–CHT is not particularly affected in moderately polar solvents. In fact, α-CHT-catalyzed peptide synthesis and other processes have been accomplished in a wide variety of organic solvents.[7] The conformational stability of α-chymotrypsin and the promising E values in the hydrolysis of the (*Z*)-isomer prompted us to evaluate the possibility of enhancing the α-CHT enantioselectivity by adding a co-solvent to the phosphate buffer used as reaction medium.[8] Thus, we examined the dependence of the E values from the reaction medium, selecting some representative organic solvents, including dimethyl sulfoxide, *t*-butanol, *t*-butyl methyl ether. The relevant data (Table, entries 3-8) show that the addition of a suitable co-solvent (*i.e.* *t*-BuOMe) can increase to a great extent the e.e. values of the kinetic resolution of the (*Z*)-methyl ester, thus making the process useful from the synthetic point of view [for entry 8, the isolated yield of the recovered methyl ester of (*Z*)-3-phenylsulphinylpropenoic acid was 39%; recrystallization from *n*-hexane afforded the ester with 99% e.e., $[\alpha]_D$=+546° (c=1, acetone); the isolated yield of (*Z*)-3-phenylsulphinylpropenoic acid, $[\alpha]_D$=-371° (c=1, acetone), was 41%].

Further attention was devoted to the enzymatic hydrolysis of methyl (*Z*)-3-arylsulfinylpropenoates. If Ar=2-naphthyl, the best enantioselectivity was obtained with the OF-360 lipase, and controlling the reaction time it was possible to obtain either the acid or the ester with high e.e. values (Table, entry 9-10). If Ar=*p*-tolyl, the methyl ester was obtained in higher e.e. values with the OF-360 lipase (Table, entry 11), recovering the substrate with an $[\alpha]_D$=-370° (c=1, acetone). α–CHT gave low conversion (Table, entry 12) and in this case the produced acid has $[\alpha]_D$=-361° (c=1, acetone).

With the aim of establishing the configuration of the resolved sulfoxide, we compared the optical rotation of methyl (*Z*)-*p*-tolylsulphinylpropenoate with the value observed for the same compound obtained in the chemical synthesis *via* Horner-Wadsworth-Emmons reaction:[9]



In this reaction it is assumed that the configuration of the sulphur centre is fully preserved. Surprisingly, we found that the value reported in the literature is exceedingly low ($[\alpha]_D$=-28° for the (*R*) configuration) and according to our data it would correspond to an e.e. value of 6%. Indeed, we repeated the HWE synthesis in the conditions reported[9] and the separated (*Z*)-isomer was found to have $[\alpha]_D$=-22°and an e.e. value of almost 5%, determined both by NMR chiral shift reagent experiments and by chiral HPLC (Chiralcel OD column).

Thus, it appears that extensive isomerization of the sulphinyl centre occurs in the conditions reported in the literature and reproduced in our experiments.[10] Undoubtedly, these findings stress the importance of our biocatalytic route.

Enzymatic Enantioselective Hydrolysis: General Procedure.

The reaction mixture containing 200 mg of enzyme powder in 20 ml of 0.2 N phosphate buffer, pH=7.0 (or a mixture of the buffer and the appropriate amount of an organic solvent, see Table), and 200 mg of racemic substrate were placed in a screw-cap bottle and shaken on an orbit shaker at 250 rpm and 37 °C. After the time specified in the Table, the mixture was acidified with aqueous 1N HCl to pH=2 and then extracted with diethyl ether. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The unreacted substrate and the product were separated by preparative TLC (silica gel; diethyl ether/*n*-hexane=40/60 as eluent). The ester was directly used for the determination of ee_S values, whereas the product was methylated by 10% BF_3-MeOH treatment at room temperature and then used for the determination of ee_P values. The kinetic resolution of methyl (*Z*)-phenylsulphinylpropenoate was also successfully performed on a 5 g scale. In this case the separation of the produced acid from the remaining ester was achieved by extracting with diethyl ether only the ester from the reaction mixture. This was then acidified with 1N HCl to pH=2 and finally the acid was extracted with chloroform.

Determination of Enantiomeric Excess Values.

All the e.e. values were measured by 200 MHz ^1H NMR analysis of the esters in the presence of the chiral shift reagent [Eu(hfc)$_3$], or by HPLC. The ^1H NMR analysis was based upon the splitting of the OCH_3 signal in two singlets. The HPLC method for determination of the enantiomeric excess involved the use of a cellulose tris-3,5-dimethylphenylcarbamate chiral stationary phase coated on silica gel (OD-Chiralcel column/Daicel) with a mobile phase of *n*-hexane:2-propanol (90:10) for the (*Z*)-esters, *n*-hexane:2-propanol (95:5) for the (*E*)-ester and *n*-hexane:2-propanol:trifluoroacetic acid (90:9:1) for the (*Z*)-acids. The OD-Chiralcel column resulted not suitable for the (*E*)-acid e.e. determination with a number of solvent mixtures combinations. In the case of methyl (*Z*)-3-phenylsulphinylpropenoate the capacity factor (k') for the first eluted enantiomer and the stereochemical separation factor (α) obtained were 2.9 and 1.74, respectively. k' and α values of 5.7 and 1.43, respectively, were obtained for methyl (*E*)-3-phenylsulphinylpropenoate.

Acknowledgements: We thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Rome) for financial support of this research.

References and Notes

1. Walker, A.J. *Tetrahedron: Asymmetry*, **1992**, *3*, 961-998 and references therein.
2. Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. Synthesis of sulphoxides. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C.J.M. Eds. John Wiley and Sons Ltd.: New York, 1988; pp 233-378.
3. Cardellicchio, C.; Fiandanese, V.; Naso, F. *J. Org. Chem.* **1992**, *57*, 1718-1722
   Cardellicchio, C.; Fiandanese, V.; Naso, F.; Scilimati, A. *Tetrahedron Lett.*, **1992**, *33*, 5121-5124.
4. For the synthesis of the acids, see Albera, D.; Bonincontro, M.; Montanari, F. *Gazz. Chim. Ital.* **1960**, *90*, 709-730.
   Hogeveen, H. *Rec. Trav. Chim.* **1964**, *83*, 813-828 and references therein.
5. (*E*)- and (*Z*)-racemic acids were esterified by standard procedures.
6. The enantioselectivity of biocatalytic reactions is expressed as E. Evaluating the enantiomeric excess of the substrate (ee_S) and the product (ee_P) the extent of conversion (C) can be calculated using the following equation: $C = ee_S/(ee_S+ee_P)$; then the E value can be calculated according to the following equation $E = \ln[(1-C)(1-ee_S)]/\ln[(1-C)(1+ee_S)]$; Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299.
7. Takahashi, K.; Ajima, A.; Yoshimoto, T.; Okada, M. ; Matsushima, A.; Tamaura, Y.; Inada, Y. *J. Org. Chem.* **1985**, *50*, 3414-3415.
   Kullman, W. Proteases as Biocatalysts for the Synthesis of Model Peptides. In *Enzymatic Peptide Synthesis*, CRC Press, Boca Raton, FL 1987, pp 41-59.
8. Butler, L.G. *Enzyme Microb. Technol.* **1979**, *1*, 253-259.
   Zaks, A.; Klibanov, A.M. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 3192-3196.
   Jones, B. *Tetrahedron* **1986**, *42*, 3351-3403.
   Chen, C.-S.; Sih, C.J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695-707.
   Klibanov, A.M. *Acc. Chem. Res.* **1990**, *23*, 114.
9. Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727-1728.
   Guessous, A.; Rouessac, F.; Maignan, C. *Bull. Soc. Chim. Fr.* **1986**, 837-843.
   Guessous, A.; Maignan, C. *Bull. Soc. Chim. Fr.* **1988**, 727-730.
10. The origin of the isomerization remains unclear. However, it seems that it cannot be attributed to the isomerization of the produced ester, since this compound undergoes partial isomerization only over a period of months.[11] Further work is needed in order to elucidate this important point.
11. Maignan, C. private communication.

(*Received in UK* 8 *April* 1994; *accepted* 29 *April* 1994)