Pergamon

Tetrahedron Letters 39 (1998) 4333–4336

TETRAHEDRON
LETTERS

Microwave-Promoted Lipase-Catalyzed Reactions

Gialih Lin* and Wen-Yuan Lin

Department of Chemistry, National Chung-Hsing University, Taichung 402, Taiwan

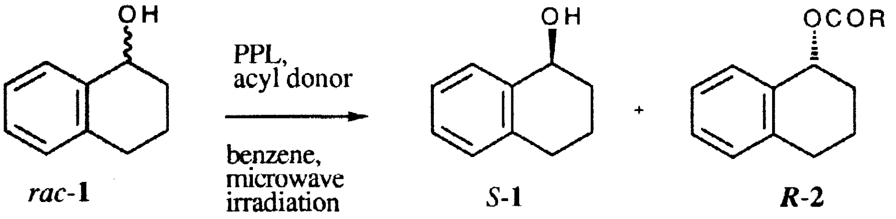
Received 9 March 1998; revised 7 April 1998; accepted 8 April 1998

Abstract: Lipase from porcine pancreas is demonstrated to catalyze acylation reactions in organic media under microwave irradiation. Reaction rates and enantioselectivities are significantly enhanced 1-14 and 3-9 fold, respectively.

The recent development of enzyme catalysis in organic synthesis for kinetic resolutions of racemates has attracted the attention of organic chemists because of their synthetic utility.[1-5] The lipase-catalyzed acylations and transacylations have become popular methods in asymmetric synthesis.[3] A major drawback of applying lipase-catalyzed reactions in organic synthesis is the low reaction rate. Thus, we reported a method based on azeotropic distillation to increase the lipase-catalyzed transacylation reaction rate by 4-70 fold[6-8] and the other method based on ultrasonication to increase the lipase-catalyzed reaction rates by 7-83 fold[9,10] in organic solvents. Parker et al. reported recently that microwave irradiation can increase the rate of lipase-catalyzed hydrolysis reactions by 2-3 fold.[11] Therefore, we are inspired to study the effect of microwave irradiation on lipase-catalyzed acylation reactions in organic solvents.

Porcine pancreatic lipase (PPL) catalyzed acylations of *(R)*-1,2,3,4-tetrahydro-1-naphthol (*R*-**1**) from its racemates (*rac*-**1**) to produce *(R)*-1,2,3,4-tetrahydro-1-naphthylacylate (*R*-**2**) and recover *(S)*-1,2,3,4-tetrahydro-1-naphthol (*S*-**1**) with high stereoselectivity. Under microwave irradiation, reaction rates and stereoselectivities of these reactions increased 4-6 and 3-9 fold, respectively, as ultrasonic conditions[9] (Table 1).

Scheme I. Lipase-Catalyzed Acylation of 1,2,3,4-Tetrahydro-1-Naphthol by Microwave Irradiation



0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00765-5

Table 1. PPL-catalyzed acylations of *rac*-**1** with acyl donors in benzene under microwave irradiation[13]

reaction condition	acyl donor	first order rate constants[a](s^{-1})	% ee (*S*-**1**)[b]	% ee (*R*-**2**)[b]	conv.[c]	E[d]
control, 25°C	vinyl acetate	$(2.2\pm0.2)x10^{-5}$	43	85	0.33	19
W-MW,[e] 35°C	vinyl acetate	$(7.3\pm0.6)x10^{-5}$	28	98	0.22	142
ultrasound,[f] 33°C	vinyl acetate	$(6.9\pm0.3)x10^{-5}$	92	96	0.49	152
control, 25°C	vinyl butyrate	$(3.0\pm0.2)x10^{-5}$	94	90	0.51	64
W-MW,[e] 35°C	vinyl butyrate	$(1.6\pm0.2)x10^{-4}$	44	98	0.31	196
control, reflux-DS[g]	palmitic acid	$(1.5\pm0.1)x10^{-5}$	65	78	0.45	16
S-MW,[h] reflux	palmitic acid	$(5.8\pm0.4)x10^{-5}$	54	97	0.36	117
control, reflux-DS[g]	palmitic anhydride	$(6.9\pm0.8)x10^{-5}$	47	85	0.35	20
S-MW,[h] reflux	palmitic anhydride	$(3.8\pm0.8)x10^{-4}$	33	98	0.25	174

a. First order rate constants were determined from the number of moles of the product formed (from HPLC) *vs* time plot by nonlinear curve fitting to first order kinetic equation. b. % ee was calculated by % ee = OP - (1- OP). Optical purity of *S*-**1** was calculated by OP = $[\alpha]_{D\ exp.} / [\alpha]_{D\ lit.}$, where $[\alpha]_{D\ exp.}$ of *S*-**1** is measured from a polarimeter at 25°C, c2.5, $CHCl_3$ and $[\alpha]_{D\ lit.}$ at 17°C of *S*-**1** is +32° which is obtained from Aldrich Catalog 1996-1997. % ee values of *R*-**2** is obtained from those of *R*-**1** and *R*-**1** is obtained from basic hydrolysis (0.1 N KOH, EtOH, 25°C, 18h, 96%) of the reactive ester *R*-**2**. c. the extent of conversion[12] d. the enantiomeric ratio[12] e. weak microwave irradiation (10 s' pulse every 30 s) f. reference 9 g. reflux with a Dean-Stark trap h. strong microwave irradiation (continuous pulse)

For the PPL-catalyzed acylation of *rac*-1-indanol (*rac*-**3**) with acyl donors to produce and *(R)*-1-indanylacylate (*R*-**4**) and recover *S*-**3**, enantioselectivities and reaction rates increased 3-5 and 1-14 fold, respectively, by microwave irradiation in benzene (Table 2).

Scheme II. Lipase-Catalyzed Acylation of 1-Indanol by Microwave Irradiation

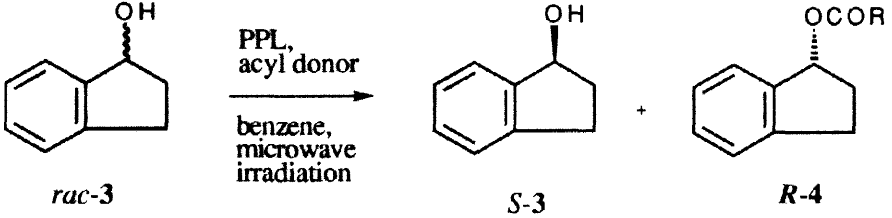


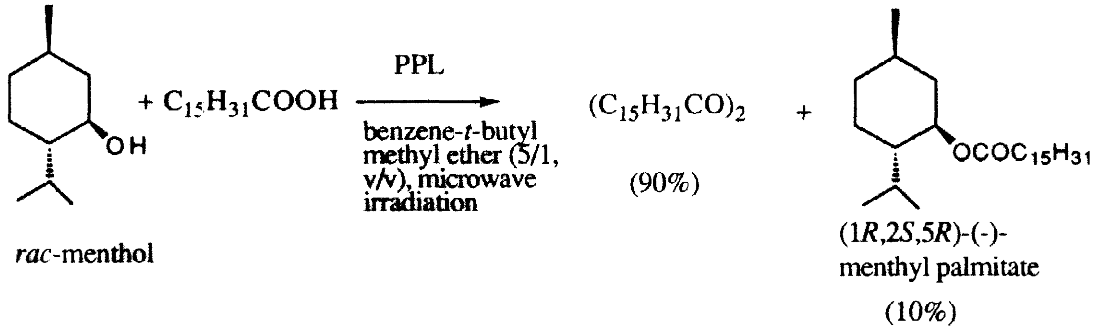
Table 2. PPL-catalyzed acylations of *rac*-**3** with acyl donors in benzene under microwave irradiation[a]

reaction type	acyl donor	first order rate constants(s^{-1})	% ee (*S*-**3**)	% ee (*R*-**4**)	conv.	E
control, 25°C	vinyl acetate	$(1.7\pm0.1)x10^{-5}$	57	94	0.38	54
W-MW, 35°C	vinyl acetate	$(6.1\pm0.2)x10^{-5}$	38	99	0.28	265
control, 25°C	vinyl butyrate	$(1.3\pm0.2)x10^{-5}$	73	88	0.46	34
W-MW, 35°C	vinyl butyrate	$(1.8\pm0.2)x10^{-4}$	81	95	0.46	96
control, reflux-DS	palmitic acid	$(2.8\pm0.6)x10^{-5}$	88	88	0.50	45
S-MW, reflux	palmitic acid	$(4.1\pm0.2)x10^{-5}$	77	97	0.44	166
control, reflux-DS	palmitic anhydride	$(2.3\pm0.8)x10^{-4}$	52	93	0.36	50
S-MW, reflux	palmitic anhydride	$(2.1\pm0.4)x10^{-4}$	33	98	0.25	159

a. All conditions are similar to Table 1.

For the PPL-catalyzed hydrolysis of *rac*-1-indanyl butyrate in *t*-butyl methyl ether and acylation of menthol with palmitic acid (Scheme III) in *t*-butyl methyl ether-benzene (1/5, v/v), microwave irradiations enhanced neither reaction rates nor enantioselectivities. Interestingly, the latter reaction yielded primarily palmitic anhydride under microwave irradiation.

Scheme III. Lipase-Catalyzed Acylation of menthol by Microwave Irradiation



Microwave heating involves directed absorption of energy by functional groups that bear ionic conductivity or a dipole rotational effect, and this energy is then released into the surrounding solution. This absorption of energy causes the functional groups involved to have higher reactivity with surrounding reactants than they are simply incubated at the same temperature.[14] However, in many systems the reasons for this are not well understood. In our systems, microwave irradiation results in higher reaction rates compared to those of conventional heating probably because the alcohol substrates in the former reactions are tremendously activated by absorption of microwave energy while the substrates in the latter reactions are not. The rate enhancements from microwave irradiation of PPL-catalyzed reactions are also probably due to the locally high pressures or the increase in usable surface area for catalysis as those ultrasonic reactions.[15,16] In microwave irradiation reactions, the increment in enantioselectivities is probably due to the activation of the reactive alcohol substrates (*R*-**1** and *R*-**3**) while still little participation of the unreactive, recovered alcohol substrates (*S*-**1** and *S*-**3**) into the reactions although they are also activated.

In summary, microwave irradiation is a simple, effective method to promote reaction rates and stereospecificities in lipase-catalyzed transacylation reactions.

Acknowledgement: We thank the National Science Council of Republic of China for financial support.

REFERENCES AND NOTES

1. Wong, C.-H. *Science*, **1989**, *244*, 1145-1152.
2. Jones, J. B. *Tetrahedron*, **1986**, *42*, 3351-3403.
3. Chen, C.-S.; Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695-707.
4. Whitesides, G. M.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638.
5. Martinek, K.; Semenov, A. N. *J. Appl. Biochem.* **1981**, *3*, 93-126.
6. Lin, G.; Liu, S.-H. *Org. Prep. Proc. Int.* **1993**, *25*, 463-480.

7. Lin, G.; Liu, S.-H.; Chen, S.-J., Wu, F.-C.; Sun, H.-L. *Tetrahedron Lett.* **1993**, *34*, 6057-6058.
8. Lin, G.; Chen, S.-J.; Sun, H.-L. *J. Chin. Chem. Soc.* **1994**, *41*, 459-465.
9. Lin, G.; Liu, H.-C. *Tetrahedron Lett.* **1995**, *36*, 6067-6068.
10. Lin, G.; Liu, H.-C.; Liu, S.-H. *J. Chin. Chem. Soc.* **1995**, *42*, 957-961.
11. Parker, M.-C.; Besson, T.; Lamare, S.; Legoy, M.-D. *Tetrahedron Lett.* **1996**, *37*, 8383-8386.
12. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299.
13. General procedures: a) *Microwave irradiation reactions.* To a benzene (15 mL) solution of *rac*-**1** (3.4 mmol), an acyl donor (vinyl acetate, 5 eqs.; vinyl butyrate, 2.5 eqs.; palmitic acid, 1.2 eqs.; palmitic anhydride, 1.2 eqs.) and PPL (6 mass eqs., Sigma L0382) were added. A conventional cooking microwave oven (Tatung, 700 W) was used. For vinyl acetate and vinyl butyrate reactions, weak microwave irradiation (10 s' pulse every 30 s) was used. For palmitic acid and palmitic anhydride reactions, strong microwave irradiation (continuous pulse) was used. The oven was equipped with a glass reaction vessel inside and a condenser outside. The reaction was bubbled by argon and maintained at 35°C in the case of weak microwave irradiation or at reflux temperature in the case of strong microwave irradiation for 2.5 h. The resulting mixtures were concentrated and separated by medium pressure liquid chromatography (LiChroprep Si 60, Merck; hexane/ethyl acetate, 4/1, v/v). b) *Classical heating (control) reactions.* Identical substrate volumes as those described above. The procedures for the reflux (distillation) with a Dean-Stark trap were described before.[6]
14. Yu, H.-M.; Chen, S.-T.; Suree, P.; Nuansri, R.; Wang, K.-T. *J. Org. Chem.* **1996**, *61*, 9608-9609.
15. Lee, J.; Synder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522-1524.
16. Lindley, L.; Mason, T. J.; Lorimer, J. P. *Ultrasonics* **1987**, *25*, 45-48.