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Pig Liver Esterase Catalyzed Hydrolyses of Diesters. A New Route to the Syntheses of Achiral Half-Esters

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PIG LIVER ESTERASE CATALYZED HYDROLYSES OF DIESTERS. A NEW ROUTE TO THE SYNTHESES OF ACHIRAL HALF-ESTERS.

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ABSTRACT: Pig liver esterase catalyzed hydrolyses of diesters of alkanes, aromatic and heterocyclic compounds gave high yields of the corresponding half-esters under mild reaction conditions.

Pig liver esterase (PLE), an economical and readily available hydrolytic enzyme, has been widely used as a practical catalysts for the synthesis of chiral molecules *via* enantioselective ester hydrolysis.[1] PLE catalyzed hydrolysis of cyclic *meso* diesters to prepare chiral half-esters has been well documented.[2] This enzyme has also been used for the hydrolysis of ester groups of labile molecules but its utility in the synthesis of achiral molecules has been very limited.[3] Now we wish to report an efficient, simple and high yield synthesis for the preparation of achiral half-esters through the hydrolysis of diesters by PLE.[4]

Generally the acid-esters, or half esters are prepared by the esterification or transesterification with alcohols in the presence of an acids catalysts, [5] by the hydrolysis of the corresponding cyclic anhydride with alcohols [6] or by the hydrolysis of diesters with barium hydroxide.[7] In all these cases either the yields are moderate at best, or it is difficult to purify the product due to the formation of diester, diacid and half-ester during the isolation procedure.In addition, many of these methods provide a statistical distribution of these three components, at best. In contrast, PLE catalyzed hydrolysis of dimethyl esters of alkanes (**1**), phthalic acid (**3**) and pyridine dicarboxylic acid (**5**) gave high yields and clean product by a simple work-up under mild reaction conditions (Table 1). The rate of hydrolysis is faster in aliphatic series than in aromatic. The reaction proceeds even if the substrate is a suspension.

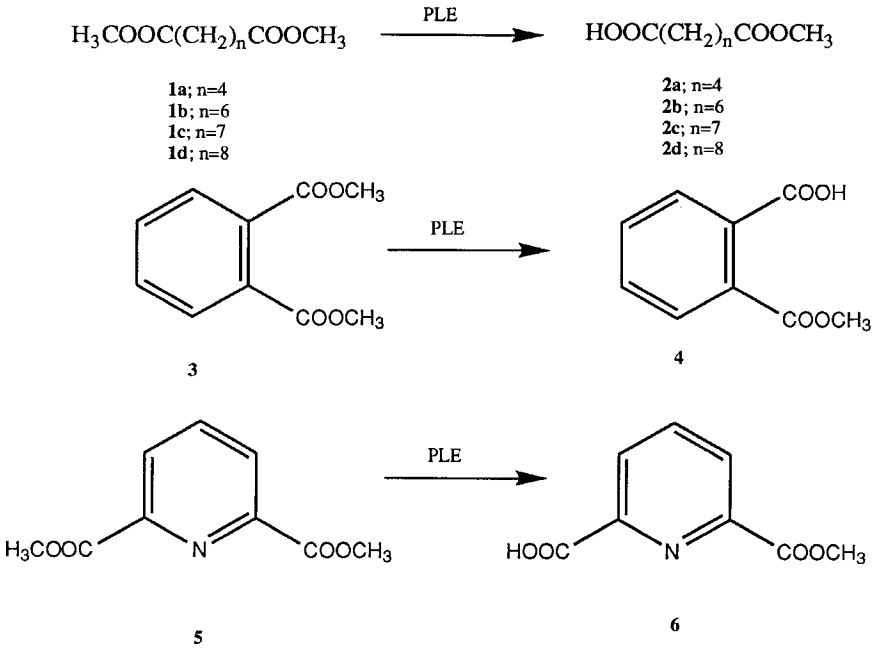
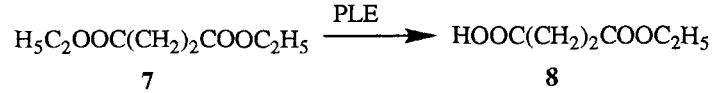


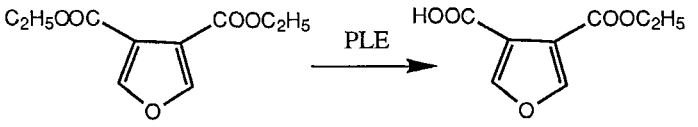
Table 1. PLE catalyzed hydrolyses of diesters

Substrate	Product	Yield(%)	MP °C(Lit.[8] MP)	Reaction Time (hrs)
1a	**2a**	84	28 (28-29)	1
1b	**2b**	87	oil	1
1c	**2c**	81	23 (22-24)	2
1d	**2d**	93	43 (42-43)	3
3	**4**	90	83 (82-84)	8
5	**6**	89	148-149 (147-148)[9]	13
7	**8**	86	oil	0.25
9	**10**	86	137-139(137-139)[10]	3

The methodology was then extended to the hydrolysis of diethyl esters. The PLE catalyzed hydrolysis of diethyl ester of succinic acid (**7**) and furan dicarboxylic acid (**9**) also gave high yields and clean products (Table 1).



7 **8**



9 **10**

Experimental

The melting points are uncorrected. IR spectra (nujol) were recorded on a Nicolet FT-IR spectrometer. ^1H NMR spectra were recorded on a GE 300 spectrometer in $CDCl_3$ using TMS as internal standard. Diesters and Pig Liver Esterase were obtained from Aldrich Chemical Company.

Preparation of achiral half-esters

General Procedure: In a typical experiment, PLE (150 units) was added to a suspension of diester (13 mmol) in 15 mL of 0.01M phosphate buffer (pH 7) at room temperature. The pH value was kept at about 7 by the addition of 1N sodium hydroxide. After consumption of 1 mole equivalent of base, the pH was adjusted to 9, then the aqueous phase was washed with chloroform (2x10 mL). The aqueous phase was acidified to pH 2 with 1 N hydrochloric acid, and extracted with chloroform (2x15 mL). The organic phase was washed with water, dried over anhyd. magnesium sulfate, and evaporated under reduced pressure to yield the product, whose purity was >95% and could be used without further purification (Table 1).

References and notes:

1. Ohno, M. and Otsuka, M. *Organic Reactions*; **1989,** Vol 37; p1.

2. Hultin, P. G.; Mueseler, F. J. and Jones, J. B. *J. Org. Chem.* **1991,** 56, 5375; Tooni, E. J. and Jones, J.B. *Tetrahedron: Asymmetry* **1991**, 2, 207; Kobayashi, S.;

Kamiyama, K. and Ohno, M. *J. Org. Chem.* **1990**, 55, 1169; Metz, P. *Tetrahedron* **1989,** 45, 7311; Van der Eycken, J. *et. al J. Chem. Soc., Chem. Commun.* **1989,** 306; Sabbioni, G. and Jones, J. B. *J. Org. Chem.* **1987**, 52, 4565; Sabbioni, G.; Shea, M. L. and Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 236.

3. Ineyama, T. et. al The 54th Annual Meeting, Chemical Society of Japan, **1987**; Jongejan, J. A. and Duine, J. A. *Tetrahedron Lett.* **1987**, 28, 2767; Hazato, A. *et. al Nippon Kagaku Kaishi* **1983**, 9, 1390; *Chem. Abstr.* **1984**, 100, 120720q.

4. During our work, one report on the hydrolysis of dimethyl phthalate to *mono* methyl phthalate using PLE in acetone-phosphate buffer appeared in a Japanese patent (Yanai, T. et. al *Jpn. Kokai Tokkyo Koho* 04084891, **1992;** *Chem. Abstr.* **1992**, 117, 1490295).

5. Swann, Jr, S.; Oehler, R. and Buswell, R. J. *Org. Syntheses Coll. Vol.* II, 276, **1943** and the references cited therein.

6. March, J. *Advanced Organic Chemistry, Third Ed.* **1985**, p 347.

7. Durham, L. J.; McLeod, D. J. and Cason, J. *Org. Synththeses Coll. Vol.* IV, 635, **1963.**

8. Aldrich catalog 1992-93. All the compounds were confirmed by mp, ir and nmr spectra.

9. Johansen, J. E.; Christie, B. D. and Rapoport, H. *J. Org. Chem.* **1981**, 46, 4914.

10. Boyd, M. R.; Harris, T. M. and Wilson, B. J. *Synthesis* **1971**, 545.

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