Highly Regioselective Hydrolysis of Substituted 2-Benzylidene-1,3-propylene Diacetates Using Porcine Pancreas Lipase

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Hydrolysis of substituted 2-benzylidene-1,3-propylene diacetates in the presence of 100 w/w % of porcine pancreas lipase (PPL) Type II proceeded to afford the corresponding *Z*-monoacetates in excellent yields with high regioselectivities.

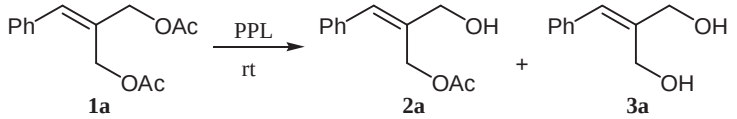
We have just reported regiospecific acetylation of substituted 2-benzylidene-1,3-propanediols with vinyl acetate using 50 w/w % of porcine pancreas lipase (PPL) Type II.[1] The corresponding *E*-monoacetates were obtained as a sole product in excellent yields without over acetylation. It is interesting to develop methodology for preparation of the corresponding *Z*-monoacetates. Although Takabe and co-workers have found regioselective hydrolysis of 2-alkylidene-1,3-propylene diacetates using several kinds of lipases, the corresponding *Z*-monoacetates were afforded only in moderate yields (24–52%) because the corresponding diols and *E*-monoacetates were obtained as by-products in all cases.[2] Herein, we describe preparation of *Z*-monoacetates by highly regioselective hydrolysis of substituted 2-benzylidene-1,3-propylene diacetates **1a**–**1h** using 100 w/w % of PPL Type II.

In a preliminary investigation, the reaction of 2-benzylidene-1,3-propylene diacetate (**1a**) in the presence of 100 w/w % of PPL in a 1:1 mixture of DMSO (dimethyl sulfoxide)–PB (1/15 M phosphate buffer, pH 7.0) afforded the corresponding *Z*-isomer **2a** in 98% yield as indicated in Entry 6 of Table 1. In the case of using methanol as a solvent, no reaction was observed (see Entry 1). Ethanol and 2-propanol work as a solvent for solvolysis of **1a** to afford poorer yields as shown in Entries 2 and 3, respectively. Hydrolysis of **1a** proceeded in PB to give 59% yield of the corresponding *Z*-acetate with 19% yield of 2-benzylidenepropane-1,3-diol (**3a**) (see Entry 4). The *E*-isomer was not detected from ^{1}H NMR analysis of the crude products in all Entries of Table 1.

Next, the regioselective hydrolysis of 2-benzylidene-1,3-propylene diacetates substituted on the benzene ring by electron-donating or electron-withdrawing groups was examined: the results from hydrolysis of various substituted 2-benzylidene-1,3-propylene diacetates **1b**–**1h** and 2-alkylidene-1,3-propylene diacetate **1i** in the presence of 100 w/w % of PPL in a 1:1 mixture of DMSO–PB are collected in Table 2. We selected methoxy and methyl substituents as representative electron-donating groups (see Entries 2 and 5–8), trifluoromethyl and chloro substituents as electron-withdrawing groups (see Entries 3 and 4), and 2-(3-phenylpropylidene)-1,3-propylene diacetate (**1i**) for an aliphatic species (see Entry 9). Fortunately, all monosubstituted 2-benzylidene-1,3-propylene diacetates **1b**–**1g** reacted in the presence of 100 w/w % of PPL in a 1:1 mixture of DMSO–PB to afford the corresponding *Z*-monoacetylated products in excellent yields with high regioselectivities. 2-(2,4,6-Trimethylbenzylidene)-1,3-propylene diacetate (**1h**) was a poor substrate for hydrolysis using PPL probably due to its steric hindrance by ortho-substituents on the benzene ring and the corresponding *Z*-monoacetate **2h** was obtained in 17% yield.

The reaction of the 2-(3-phenylpropylidene)-1,3-propylene diacetate (**1i** in Entry 9) afforded *Z*-monoacetate in lower regioselectivity than ones of substituted 2-benzylidene-1,3-propylene diacetates **1a**–**1h**. Although the corresponding *Z*-isomer **2i** was obtained in 67% yield, the diol **3i** was produced as a by-product in 13% yield and the starting material **1i** was recovered in 11%

Table 1. *E*-Hydrolysis of 2-benzylidene-1,3-propylene diacetate (**1a**) in the presence of PPL[a]

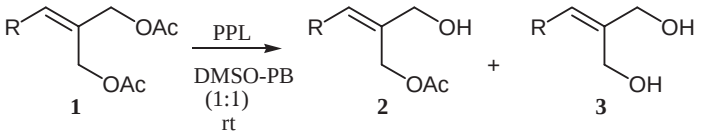


1a **2a** **3a**

Entry	Solvent	Reaction time	Yield **2a**/%	Yield **3a**/%	Recovery **1a**/%
1	MeOH	5 days	trace	N.D.[c]	99
2	EtOH	5 days	35	N.D.	55
3	*i*-PrOH	5 days	24	N.D.	67
4	PB[b]	23 h	59	19	13
5	DMSO–PB[b] (1:4)	21 h	61	16	16
6	DMSO–PB[b] (1:1)	25 h	98	trace	N.D.
7	Acetone–PB[b] (1:1)	25 h	75	N.D.	22
8	MeCN–PB[b] (1:1)	25 h	4.3	N.D.	93
9	THF–PB[b] (1:1)	25 h	N.D.	N.D.	98

[a]All reactions were carried out with 1 equivalent of 2-benzylidene-1,3-propylene diacetate (**1a**) and 100 w/w % of PPL in 3 mL of solvent at rt. [b]1/15 M Phosphate buffer (pH 7.0). [c]Not detected.

Table 2. *E*-Hydrolysis of substituted 2-benzylidene-1,3-propylene diacetates **1a**–**1h** and 2-alkylidene-1,3-propylene diacetate **1i** in the presence of PPL[a]



Entry	1	R	Reaction time/h	Yield 2/%	Yield 3/%	Recovery 1/%
1	**1a**	Ph	25	98	trace	N.D.[b]
2	**1b**	4-$MeOC_6H_4$	20	95	N.D.	1.7
3	**1c**	4-$CF_3C_6H_4$	24	92	N.D.	1.7
4	**1d**	4-ClC_6H_4	4	84	N.D.	3.7
5	**1e**	4-MeC_6H_4	18	85	N.D.	1.6
6	**1f**	3-MeC_6H_4	19	98	N.D.	0.8
7	**1g**	2-MeC_6H_4	21	92	N.D.	0.4
8	**1h**	2,4,6-$Me_3C_6H_2$	48	17	N.D.	66
9	**1i**	$PhCH_2CH_2$	19	67	13	11

[a]All reactions were carried out with 1 equivalent of substituted 2-benzylidene-1,3-propylene diacetates **1** and 100 w/w % of PPL in 3 mL of a 1:1 mixure of DMSO–PB at rt. [b]Not detected.

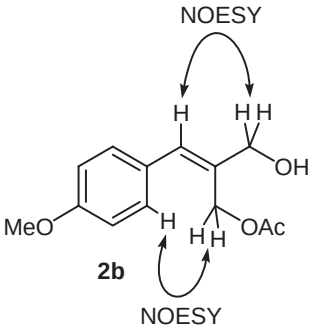


Figure 1. Determination of the structure of **2b**.

yield. The *E*-isomers were not detected from the crude products in all Entries of Table 2.

The structure of monoacetate **2b**[3] was determined to be the *Z*-isomer by NOESY analysis as shown in Figure 1. The NOESY correlationships were observed between the olefin and the methylene protons adjacent to the hydroxy group, and between the aromatic and the methylene protons adjacent to the acetate group. All other monoacetates (**2a** and **2c**–**2i**) were also determined to be *Z*-isomer by NOESY analysis.

In summary, porcine pancreas lipase (PPL) efficiently works in hydrolysis of substituted 2-benzylidene-1,3-propylene diacetates **1a**–**1h** and 2-alkylidene-1,3-propylene diacetate **1i**, and the corresponding *Z*-monoacetates were obtained in high yields.[4] Monoacetates of 2-benzylidene-1,3-propanediols are potential useful intermediates in organic synthesis and may be used as building blocks in syntheses of natural products.[5]

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References and Notes

1 T. Miura, Y. Kawashima, M. Takahashi, Y. Murakami, N. Imai, *Synth. Commun.* **2007**, *37*, in press. Porcine pancreas lipase (PPL) Type II is commercially available from Sigma.

2 a) T. Hisano, K. Onodera, Y. Toyabe, N. Mase, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2005**, *46*, 6293, and the references cited therein. b) K. Takabe, N. Mase, T. Hisano, H. Yoda, *Tetrahedron Lett.* **2003**, *44*, 3267.

3 Compound **2b**: ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s), 2.57 (1H, brs), 3.80 (3H, s), 4.26 (2H, s), 4.83 (2H, s), 6.74 (1H, s), 6.88 (2H, d, $J = 8.8$ Hz), 7.19 (2H, d, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 55.3, 61.1, 65.7, 113.9, 128.3, 130.1, 131.5, 134.0, 159.1, 171.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{13}H_{16}O_4Na$, 259.0941; found, 259.0913.

4 A typical procedure of hydrolysis using PPL is as follows. To a pale yellow suspension of 124 mg (0.500 mmol, 1 equivalent) of 2-benzylidene-1,3-propylene diacetate (**1a**) and 124 mg (100 w/w %) of PPL in 3 mL of a 1:1 mixture of DMSO–1/15 M phosphate buffer (pH 7.0) was stirred at rt for 25 h. The reaction mixture was filtered on Celite, and washed with AcOEt. The filtrate was added to water, and then extracted three times with AcOEt. The combined AcOEt layers were washed with brine, and dried over anhydrous $MgSO_4$. The mixture was filtered, and the filtrate was evaporated. The crude product was chromatographed on silica gel with a 2:3 mixture of AcOEt and hexane to afford 101 mg (98% yield) of **2a**.

5 G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen, C. T. Maxey, M. S. Wells, A. S. Goldstein, M. J. Dibley, C. J. Wang, D. P. Ostercamp, S. Chung, P. S. Cunningham, M. A. Berliner, *J. Org. Chem.* **1997**, *62*, 1976.

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