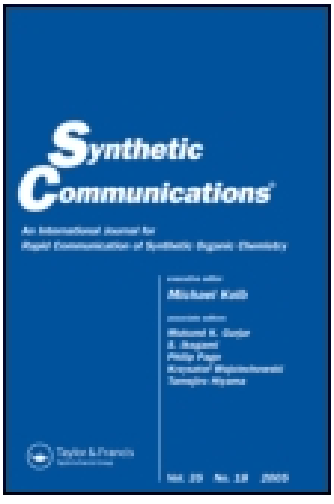


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Regiospecific Acetylation of Substituted α,α′-Benzylidenedimethanols with Vinyl Acetate using Porcine Pancreas Lipase

Tsuyoshi Miura [a], Yuya Kawashima [a], Mauko Takahashi [a], Yasuoki Murakami [a] & Nobuyuki Imai [a]

[a] Faculty of Pharmacy, Chiba Institute of Science, Chiba, Japan

Published online: 10 Sep 2007.

To cite this article: Tsuyoshi Miura, Yuya Kawashima, Mauko Takahashi, Yasuoki Murakami & Nobuyuki Imai (2007) Regiospecific Acetylation of Substituted α,α′-Benzylidenedimethanols with Vinyl Acetate using Porcine Pancreas Lipase, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:18, 3105-3109, DOI: 10.1080/00397910701544760

To link to this article: http://dx.doi.org/10.1080/00397910701544760

Synthetic Communications®, 37: 3105–3109, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701544760

Regiospecific Acetylation of Substituted α,α′-Benzylidenedimethanols with Vinyl Acetate using Porcine Pancreas Lipase

Tsuyoshi Miura, Yuya Kawashima, Mauko Takahashi, Yasuoki Murakami, and Nobuyuki Imai
Faculty of Pharmacy, Chiba Institute of Science, Chiba, Japan

Abstract: Acetylation of substituted α,α′-benzylidenedimethanols with 10 equivalents of vinyl acetate in the presence of 50 w/w% of porcine pancreas lipase (PPL) type II regiospecifically proceeded to afford only the corresponding *E*-monoacetates in excellent yields without *Z*-monoacetates, diacetate, or the starting materials.

Keywords: acylation, diol, enzyme, lipase, regioselectivity

INTRODUCTION

The acetyl group is one of the most popular protecting groups and plays an important role in organic synthesis.[1] Therefore, development of highly selective acetylation is an attractive research field. Among the many methods for selective acetylation, the enzymatic acetylation using lipase and vinyl acetate is an excellent methodology. Although many articles reported enantioselective acetylation of racemic alcohols in the presence of lipase,[2] there is only one example where researchers have developed a highly regioselective acetylation of α,α′-alkylidenedimethanols using several kinds of lipases such as AK and PS-D.[3] In this method, diacetates and *Z*-monoacetates were obtained as by-products in all cases, and exactly 1 equivalent of vinyl acetate has to be used to avoid production of diacetates. Regioselective acetylation of α,α′-alkylidenedimethanols is very difficult with common conditions

Received in the USA November 16, 2006
Address correspondence to Nobuyuki Imai, Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan. E-mail: nimai@cis.ac.jp

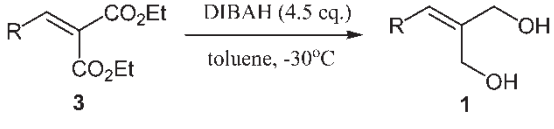
using acetic anhydride/pyridine.[3] In this article, we describe a regiospecific acetylation of substituted α,α'-benzylidenedimethanols **1a–h** with vinyl acetate using 50 w/w% of porcine pancreas lipase (PPL) type II.

Porcine pancreas lipase (PPL) type II is commercially available from Sigma.

RESULTS AND DISCUSSION

α,α'-Alkylidenedimethanols **1** were easily prepared from diethyl alkylidenedicarboxylates **3**, which can be obtained by Knoevenagel condensation of the corresponding aldehydes with diethyl malonate,[4] followed by diisobutylaluminium hydride (DIBAH) reduction in 20–62% yields as shown in Scheme 1.[5]

In a preliminary investigation, the reaction of 2-benzylidenepropane-1,3-diol (**1a**) with vinyl acetate in the presence of 50 w/w% of porcine pancreas lipase (PPL) in 1,4-dioxane afforded the corresponding *E*-isomer **2a** as a sole product in 95% yield as indicated in entry 1 of Table 1. The overacetylated product and the *Z*-isomer were not detected from ^{1}H NMR analysis of the crude product. The regioselective acetylation of α,α'-benzylidenedimethanols substituted on the benzene ring by electron-donating or electron-withdrawing groups was then examined: the results from the acetylation of various substituted α,α'-benzylidenedimethanols **1b–h** and α,α'-alkylidenedimethanol **1i** with vinyl acetate in the presence of 50 w/w% of PPL in 1,4-dioxane are collected in Table 1. 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)propane-1,3-diol (**1i**) for an aliphatic species (see entry 9). Fortunately, all *para*-monosubstituted α,α'-benzylidenedimethanols **1b–e** were reacted with vinyl acetate in the presence of 50 w/w% of PPL in 1,4-dioxane to afford the corresponding *E*-monoacetylated products in excellent yields with complete regioselectivities. The high regioselectivities were also observed in the reaction of substrates (**1f** and **1g**) with the methyl group at *meta*- and *ortho*-positions on the benzene ring (see entries 6

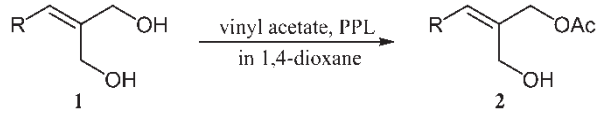


3 **1**

1a (R= Ph): 62%, **1b** (R= 4-MeOC$_6$H$_4$): 48%,
1c (R= 4-CF$_3$C$_6$H$_4$): 34%, **1d** (R= 4-ClC$_6$H$_4$): 53%,
1e (R= 4-McC$_6$H$_4$): 57%, **1f** (R= 3-McC$_6$H$_4$): 55%,
1g (R= 2-MeC$_6$H$_4$): 57%, **1h** (R= 2,4,6-Me$_3$C$_6$H$_2$): 58%,
1i (R= PhCH$_2$CH$_2$): 20%

Scheme 1. Preparation of α,α'-alkylidenedimethanols **1**.

Table 1. *E*-Acetylation of substituted α,α'-benzylidenedimethanols **1a**–**h** and α,α'-alkylidenedimethanol **1i** in the presence of PPL[a]



1 **2**

Entry	1	R	Reaction time (h)	Isolated yield (%)
1	**1a**	Ph	23	95
2	**1b**	4-$MeOC_6H_4$	23	94
3	**1c**	4-$CF_3C_6H_4$	47	90
4	**1d**	4-ClC_6H_4	48	94
5	**1e**	4-MeC_6H_4	31	97
6	**1f**	3-MeC_6H_4	20	92
7	**1g**	2-MeC_6H_4	26	95
8	**1h**	2,4,6-$Me_3C_6H_2$	72	30[b]
9	**1i**	$PhCH_2CH_2$	28	80[c]

[a]All reactions were carried out with 1 equivalent of substituted α,α'-benzylidenedimethanol **1**, 10 equivalents of vinyl acetate, and 50 w/w% of PPL in 3 mL of 1,4-dioxane at rt.

[b]The starting material was recovered in 61% yield.

[c]The starting material was recovered in 3.7% yield, and the *Z*-isomer **4** and the diacetate **5** were obtained in 4.6% and 5.6% yields, respectively.

and 7, respectively). 2-(2,4,6-Trimethylbenzylidene)propane-1,3-diol (**1h**) was a poor substrate for acetylation using PPL, probably because of its steric hindrance by *ortho*-substituents on the benzene ring, and the corresponding *E*-monoacetate **2h** was obtained in 30% yield. The reaction of the 2-(3-phenylpropylidene)propane-1,3-diol (**1i** in entry 9) afforded *E*-monoacetate in lower regioselectivity than ones of substituted α,α'-benzylidenedimethanols **1a**–**h**. Although the corresponding *E*-isomer **2i** was obtained in 80% yield, the *Z*-isomer **4** and the diacetate **5** were produced as by-products in 4.6% and 5.6% yields, respectively (Fig. 1).

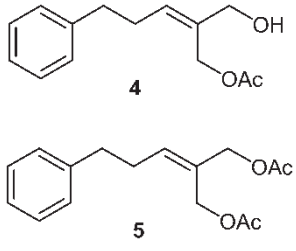


Figure 1. By-products in acetylation of **1i**.

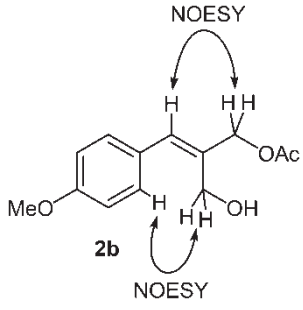


Figure 2. Determination of the structure of **2b**.

The structure of monoacetate **2b** was determined to be the *E*-isomer by nuclear overhauser effect spectroscopy (NOESY) analysis as shown in Fig. 2. The NOESY correlationships were observed between the olefin and the methylene protons adjacent to the acetate group and between the aromatic and the methylene protons adjacent to the hydoroxyl group. All other monoacetates (**2a**, **2c**–**i**) were also determined to be *E*-isomer by NOESY analysis.

In summary, porcine pancreas lipase (PPL) efficiently works as a catalyst in acetylation of substituted α,α'-benzylidenedimethanols **1a**–**h** and α,α'-alkylidenedimethanol **1i**. Although a large excess of vinyl acetate (10 equiv) was used, the corresponding *E*-monoacetates were obtained as a sole product in high yields without overacetylation. Monoacetates of α,α'-alkylidenedimethanols are potential useful intermediates in organic synthesis and may be used as building blocks in syntheses of natural products. In our procedure, it is possible to prepare various *E*-monoacetates of α,α'-benzylidenedimethanols and α,α'-alkylidenedimethanols. We are now working on preparation of *Z*-monoacetates these diols.

EXPERIMENTAL

Compound 2b Data

Compound **2b**: ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.23 (1H, brs), 3.82 (3H, s), 4.33 (2H, s), 4.80 (2H, s), 6.67 (1H, s), 6.89 (2H, d, $J = 8.7$ Hz), 7.26 (2H, d, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 55.3, 59.4, 67.8, 113.8, 128.2, 130.3, 132.8, 133.8, 159.2, 171.4; HRMS (ESI-TOF): calcd. for $C_{13}H_{16}O_4$ ($M + Na^+$): 259.0941; found: 259.0958.

Typical Acetylation Procedure

A typical procedure of acetylation using PPL is as follows. To a pale yellow suspension of 194 mg (1.00 mmol, 1 equiv) of 2-(4-methoxybenzylidene)propane-1,3-diol **1b**, 0.92 mL (10.0 mmol, 10 equiv) of vinyl acetate and 97 mg

(50 w/w%) of PPL in 3 mL of 1,4-dioxane was stirred at rt for 23 h. The reaction suspension was diluted with 10 mL of ethyl acetate and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was evaporated. The crude product was chromatographed on silica gel with a 2:3 mixture of ethyl acetate and hexane to afford 222 mg (94% yield) of **2b**.

ACKNOWLEDGMENT

This work was supported in part by Ajinomoto Award in Synthetic Organic Chemistry, Japan, and Grants-in-Aid for Scientific Research (C) (No. 18590014) from the Japan Society for the Promotion of Science. This work was performed through the Scientific Research Project by CIS (Chiba Institute of Science).

REFERENCES

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd edn.; John Wiley and Sons: New York, 1999.
2. (a) Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, 2000; (b) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
3. (a) Hisano, T.; Onodera, K.; Toyabe, Y.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 6293, and the references cited therein; (b) Takabe, K.; Mase, N.; Hisano, T.; Yoda, H. *Tetrahedron Lett.* **2003**, *44*, 3267.
4. (a) Gu, J.-X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305; (b) Hon, Y.-S.; Lu, L. *Tetrahedron* **1995**, *51*, 7937.
5. Cho, J.-H.; Ko, S. Y.; Oh, E.; Park, J. C.; Yoo, J. U. *Helv. Chim. Acta* **2002**, *85*, 3994.