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Selective lipase-catalyzed preparation of diol monobenzoates by transesterification and alcoholysis reactions in organic solvents

Enzo Santaniello *, Pierangela Ciuffreda, Silvana Casati, Laura Alessandrini, Alessandro Repetto

Dipartimento di Scienze Precliniche LITA, Vialba-Università degli Studi di Milano, Via G.B. Grassi, 74-20157 Milano, Italy

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Abstract

Lipases from *Mucor miehei* (MML) and *Candida antarctica* (CAL) are able to catalyze the monobenzoylation of the primary hydroxy group of 1,2- 1,4- or 1,5-diols with vinyl benzoate in an organic solvent, the reaction proceeding with high regioselectivity and moderate enantioselectivity. The lipase-catalyzed debenzoylation of 1,2-propanediol dibenzoate by alcoholysis with 1-octanol most satisfactorily occurred with *Pseudomonas cepacia* lipase absorbed onto celite that allowed also to prepare (*R*)-1-benzoyloxy-2-methylpropan-3-ol from 2-methyl-1,3-propanediol dibenzoate, a result complementary to MML-catalyzed benzoylation of 2-methyl-1,3-propanediol that affords the (*S*)-monobenzoate.

Keywords: Lipases; Benzoylation; Transesterification; Alcoholysis; Diols

1. Introduction

The selective protection of polyhydroxy compounds still remains a challenge in organic synthesis and, considering an ester as the protecting group of an alcohol, various biocatalytic approaches can be adopted for selective introduction/removal of acyl groups [1]. Among synthetically useful lipase-catalyzed methods for ester synthesis, the transesterification procedure that relies upon vinyl or propenyl esters as acylating reagents [2–4] has enjoyed widespread application in organic synthesis [5,6]. Vinyl acetate (VA) is by far the enol ester more frequently used for introduction of an acetate, although this protecting group is not sufficiently stable for synthetic manipulations and suffers of the disadvantage that migration towards a vicinal hydroxy group frequently occurs under a variety of experimental conditions, as clearly shown for 1,2-diols [7–9]. In this respect, although a benzoic ester is more resistant and less prone to migrate [10], relatively few examples of selective enzymatic benzoylation of polyhydroxylated compounds are currently available [11–14]. On the other hand, such a biocatalytic procedure could constitute a useful alternative to existing chemical approaches that often require special reagents and experimental conditions to achieve an adequate regioselection [15]. Recently, we have published a few papers dealing with the enzymatic monobenzoylation of diols catalyzed by suitable lipases in an organic solvent under transesterification conditions using vinyl benzoate (VB) as acyl transfer [16–18]. Furthermore, a preliminary report on the enzymatic debenzoylation of 1,2- and 1,3-diol diesters [19] has added alcoholysis to the biocatalytic procedures for the selective preparation of monobenzoates of polyhydroxylated compounds.

2. Results and discussion

2.1. Lipase-catalyzed benzoylation of 1,2-propanediol (*1a*)

For the enzymatic benzoylation procedure, 1,2-propanediol (**1a**) was selected as a model substrate to set up experimental conditions such as choice of the most active lipase, suitable organic solvent and correct lipase/VB ratio. Microbial lipases from *Pseudomonas cepacia* (PCL), *Muchor miehei* (MML), *Candida antarctica* (CAL), *Candida cylindracea* (CCL) and the porcine pancreas lipase (pPL) were selected as biocatalysts, CAL and MML being available in an immobilized form. The enzyme/substrate ratio was fixed as 0.1 g of the enzymatic preparation per millimole of **1a**, independently from the hydrolytic activity of the lipase. Blank reactions, carried without enzyme, showed no products in the conditions of lipase-catalyzed benzoylation. The equivalent amount of VB was 1.5 $mmol^{-1}$ of

* Corresponding author. Tel.: +39 0250319691; fax: +39 0250319694.
E-mail address: Enzo.Santaniello@unimi.it (E. Santaniello).

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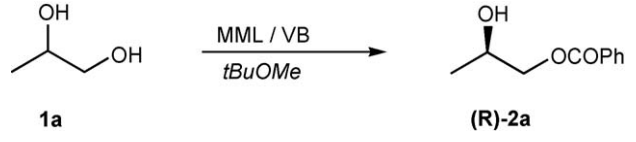
Table 1
Lipase-catalyzed benzoylation of 1,2-propanediol (**1a**)

Lipase[a]	Convn (%)	Time (h)	ee (%)	*E*
MML	100	1	–	–
MML	30	0.10	60[b]	5.3
MML	60	0.25	70[c]	5.5
CAL	100	4.5	–	–
CAL	37	1.5	54[b]	4.5
CAL	63	2.1	64[c]	4.6
PCL	52	72	–	–
CCL	21	72	–	–
pPL	33	72	–	–

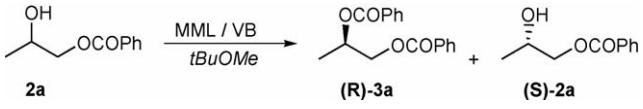
[a] 100 mg enzyme/mmol substrate.
[b] Determined by ^{1}H NMR analysis of MTPA ester of monobenzoate **2a**.
[c] Determined by ^{1}H NMR analysis of MTPA esters of unreacted **1a**.

substrate and was kept as such for all following substrates. All the reactions were stopped after 72 h and *tert*-butyl methyl ether (*t*BuOMe) was selected as solvent. The results of the enzymatic benzoylation of **1a** with all selected lipases (Table 1) show that CAL and MML are able to catalyze the regioselective acylation to the monobenzoate **2a** much faster than other enzymes, MML being the most active biocatalyst. The monobenzoate **2a** is a stable compound and ^{1}H NMR analysis of the ester obtained by reaction with (*S*)-MTPACl [20] indicated 60% enantiomeric excess (ee) at 30% conversion of diol **1a** that corresponds to a value of 5.3 of enantiomeric ratio *E* [21]. The (*R*)-configuration was assigned to enzymatically prepared monobenzoate **2a** (Scheme 1) by analysis of ^{1}H NMR data of (*R*)- and (*S*)-MTPA esters of **2a**, according to the Mosher's modified method [22]. Comparison of the optical rotation of enzymatically prepared **2a** with the value reported in literature [23] confirmed the assigned configuration. The reaction catalyzed by CAL proceeded at slower rate, but no improvement of the enantioselectivity was observed.

It has been previously reported [24] that also in the lipase-catalyzed acetylation of racemic 1,2-diols, the resulting 1-monoacetate is not optically pure and in order to achieve a stereoselective resolution the diol has to be converted into the corresponding diacetate. This so called "sequential acetylation" allows to prepare the diacetate or the unreacted diol in an enantiomerically pure form [25]. We considered the possibility that also the enantioselectivity of the lipase-catalyzed benzoylation could be enhanced by converting the chemically prepared racemic monobenzoate **2a** to the dibenzoate **3a** (Scheme 2). The



Scheme 1. MML-catalyzed benzoylation of 1,2-propanediol (**1a**) in *t*BuOMe.



Scheme 2. MML-catalyzed benzoylation of monobenzoate **2a**.

Table 2
MML-catalyzed benzoylation of monobenzoate **2a** in different solvents

Solvent	Convn (%)	Time (h)	ee[a] (%)	*E*
Hexane	61	4	85	8.7
Toluene	63	29	82	6.9
*t*BuOMe	62	40	88	9.2
$CHCl_3$	17	168	–	–
THF	26	168	–	–

[a] Determined by ^{1}H NMR analysis of MTPA esters of unreacted monobenzoate **2a**.

dibenzoylation was slow (30% in 24 h) but the enatioselectivity was improved to *E* 9.2, a value that can be considered significant for the stereochemical outcome of an enzymatic resolution. This prompted us to further study the dependence of the enantioselectivity on the nature of the solvent and results are shown in Table 2.

The reaction was faster in apolar solvents such as hexane or toluene with no improvement of *E* whereas in polar solvents such as $CHCl_3$ or THF the reaction was considerably slower and the enantioselectivity not further examined.

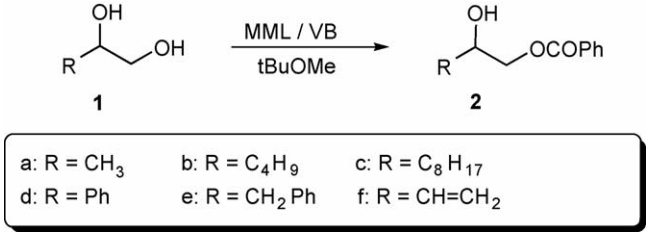
2.2. Monobenzoylation of 1,2-diols *1b–f*

We extended the above preliminary observations to a few additional 1,2-diols (Scheme 3) that were characterized by the presence of residues R that correspond to aliphatic (**1b** and **1c**), phenyl (**1d**), benzyl (**1e**) or unsaturated (**1f**) moieties.

For all substrates we examined only the MML-catalyzed benzoylation in *t*BuOMe that proceeded to a quantitative conversion in 1–3 h with high regioselectivity and low enantioselectivity (Table 3). For aliphatic diols **1b** and **1c**, fast benzoylations were more easily monitored at >50% conversion and compared with **1a** at the same extent. Furthermore, MML- and CAL-catalyzed dibenzoylation of monobenzoates **2b–f** proceeded at slow rate and enantioselectivity that was lower than the one observed for **2a**.

2.3. Lipase-catalyzed benzoylation of 1,4- and 1,5-diols

The selective monoprotection of two chemically equivalent primary hydroxy groups in 1,4-diols constitutes a challenge in organic synthesis and chemical methods usually lead to a mixture of unreacted, mono- and diprotected diols, unless special experimental conditions are developed. When the MML-catalyzed benzoylation procedure was applied to 1,4-diols **9–12a** (Fig. 1), selective monobenzoylation was observed [16].



Scheme 3. MML-catalyzed benzoylation of diols **1a–f**.