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Lipase-catalyzed monoprotection of 1,4-diols in an organic solvent using vinyl benzoate as acyl transfer agent

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Abstract—Lipase from *Mucor miehei* (MML) has been selected as the most suitable enzyme to catalyze the efficient monobenzoylation of 1,4-diols using vinyl benzoate as acyl transfer reagent in *tert*-butyl methyl ether. The regioselectivity of the monobenzoylation of 2-substituted-1,4-diols has been studied as well. © 2003 Published by Elsevier Science Ltd.

The selective monoprotection of diols is an important operation in organic synthesis[1] and the challenge is even greater in the case of 1,4-diols that possess two chemically equivalent primary hydroxy groups. The protection of these compounds by chemical methods usually generates a mixture of unreacted, mono- and diprotected diols, unless special experimental conditions are adopted, as shown, for instance, by the selective monoacylation that can be achieved either by chemical[2,3] or biocatalytic[4,5] methods. In general, for synthetic purposes a benzoic ester should be preferred as an acyl protecting group of polyhydroxy compounds, owing to the stability of benzoyl moiety, in general higher than that of other acyl derivatives, and to a less pronounced attitude to vicinal migration.[1] The selective benzoylation of 1,4-diols, that can be accomplished by chemical methods,[6] has not been reported using an enzyme-catalyzed reaction although a few examples of enzymatic benzoylation of polyhydroxy compounds has been occasionally described in the literature.[7–9] We have started a project aimed to realize selective benzoylation of diols using lipases as biocatalysts in organic solvents[10] and present here our results on the monobenzoylation of a few 1,4-diols that contain two hydroxy groups identical or similar as in the case of 2-substituted-1,4-diols. Butane-1,4-diol (**1a**) was the substrate used to set up experimental conditions such as choice of the most suitable organic solvent and the proper enzyme/substrate ratio. Microbial lipases from *Pseudomonas cepacia* (PCL), *Mucor miehei* (MML), *Candida antarctica* (CAL), *Candida cylindracea* (or *C. rugosa*, CCL) and the porcine pancreas lipase (pPL) were selected as potential biocatalysts.[11] Commercially available vinyl benzoate (VB) has been used as acylating agent and the VB/substrate ratio established as well. Our results show that MML in *tert*-butyl methyl ether (*t*-BuOMe) is the most active lipase at an enzyme/substrate ratio 100 mg/mmol at 25°C (Fig. 1).[12]

Table 1 reports the results obtained with MML in *t*-BuOMe with diols **2a**–**4a**[13] (Fig. 2) following the

Table 1. MML-catalyzed esterification of 1,4-diols (**1a**–**4a**) in *t*-BuOMe by means of VB[a]

Diols	Time (h)	Products	Ratio[b]	Yield[c] (%)
1a	4.0	**1b**/**1c**	82/18	72
2a	5.0	**2b**/**2c**	93/7	82
3a	0.8	**3b**/**3c**	92/8	80
4a	1.5	**4b**/**4c**	67/33	58

[a] For experimental details, see Ref. 14.
[b] At 90% conversion.
[c] Yields refer to monobenzoates **1b**–**4b** as isolated products after flash chromatography.

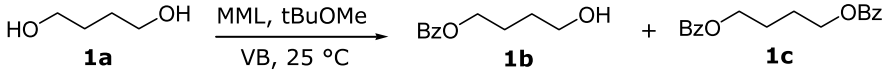

Figure 1.

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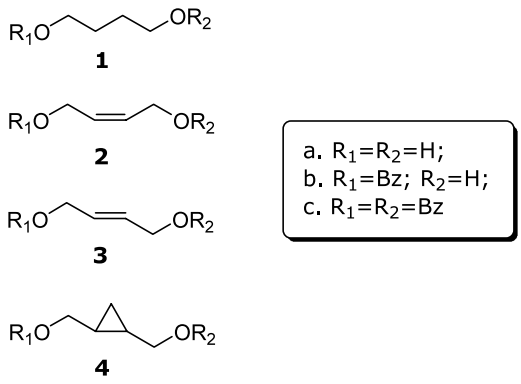

Figure 2.

experimental protocol set up for diol **1a**.[14] It should be observed that (*E*)-diol **3a** reacts faster than the (*Z*)-isomer **2a** and, similarly, the monobenzoylation of the (*E*)-cyclopropyl diol **4a** proceeds at a higher rate than the corresponding reaction with diol **1a**, albeit with less regioselectivity.

A similar pattern was observed with 2-methylbutane-1,4-diol (**5a**), for which the benzoylation of the hydroxy group more distant from the methyl group was only slightly preferred (**5b**/**5c** ratio, 6:4) (Fig. 3).

Compared to the previous result with diol **5a**, the reaction of 2-methylpentane-1,5-diol (**6a**) is slower and the more accessible 5-hydroxy group is benzoylated with higher regioselectivity (**6b**/**6c** ratio, 85:15). Interestingly, 2-methylene diol (**7a**) was benzoylated exclusively at the C-1 hydroxy group with a regioselective outcome similar to that observed for the *Pseudomonas cepacia* lipase-catalyzed acetylation of the same substrate **7a**.[15] Apparently, the presence of the π electrons of the methylene moiety in the diol **7a** is a determining factor in this peculiar behavior that, in the case of the MML-catalyzed reaction, is opposite to that observed for diols **5a** and **6a**. All the above results of the enzymatic benzoylation of diols **5a**–**7a**[16] are collected in Table 2.

In conclusion, also if compared to the recently reported chemical approach,[3] the MML-catalyzed monobenzoylation of 1,4-diols in an organic solvent here reported results in a fast and easy to perform procedure that

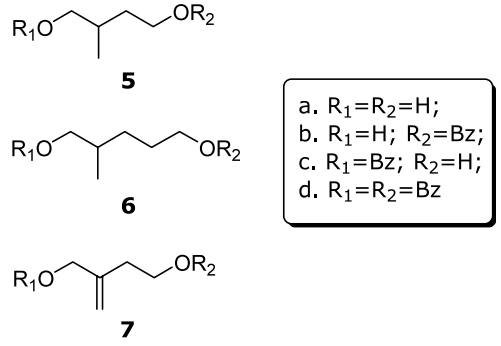

Figure 3.

Table 2. Enzymatic esterification of diols (**5a**–**7a**) in *t*-BuOMe by means of VB[a]

Diol	Time (h)	Yield (%)	Products	Regioselectivity
5a	2.0	80[b]	**5b**/**5c**	60/40
6a	6.5	90[b]	**6b**/**6c**	85/15
7a	0.5	92	**7b**/**7c**	0/100

[a] For experimental details, see Ref. 14.
[b] Yields refer to monobenzoates isolated as a mixture of regioisomers after flash chromatography at 100% conversion.

may open interesting perspectives for the selective benzoylation of other diols that possess primary and/or secondary hydroxy groups.

Acknowledgements

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11. Porcine pancreatic lipase (24 U/mg solid) was purchased from Fluka. Lipase from *Pseudomonas sp.* (Lipase PS 'Amano', 30 U/mg solid) and from *Candida cylindracea* (Lipase AYS 'Amano', 31.6 U/mg solid) were purchased from Amano Pharmaceutical. *Candida antarctica* lipase (Novozym 435®, acrylic resin supported lipase, 11.4 U/mg solid) was purchased from Novo Nordisk Bioindustrial Group. Lipase from *Mucor miehei* (Chirazyme® L-9,c.-f., C2, lyo, carrier-fixed lipase, 8 U/mg solid) was purchased from Roche Molecular Biochemicals.
12. When the reaction was carried out at 0°C, longer reaction time was required but regioselectivity was not enhanced.
13. Butane-1,4-diol (**1a**) and (*Z*)-2-butene-1,4-diol (**2a**) were commercially available (Fluka); (*E*)-1,2-cyclopropanedimethanol (**4a**) was purchased from Aldrich.

(*E*)-2-butene-1,4-diol (**3a**) was prepared by reduction of diethyl fumarate, according to: Corlay, H.; Motherwell, W. B.; Pennell, A. M. K.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J.; Binger, P.; Stepp, M. *Tetrahedron* **1996**, *13*, 4883–4902.

14. All new compounds gave spectroscopic data in agreement with the assigned structures. A typical procedure for MML-mediated benzoylation of 1,4-diols: lipase (100 mg) was added to a solution of substrate **4a** (1.0 mmol) and VB (1.2 mmol) in *t*-BuOMe (10.0 ml). The mixture was allowed to react at room temperature under magnetic stirring and the progress of the reaction monitored by TLC (hexane/ethyl acetate, 70:30; v/v) and GLC. After 1.5 h the reaction had reached 90% conversion and the enzyme was filtered off and washed with MeOH, the solvents were distilled under vacuum. After flash chromatography (hexane/ethyl acetate, 70:30; v/v) pure compound **4b** was obtained as a colorless oil (58% yield): R_f 0.25 (hexane/ethyl acetate, 70:30; v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (2H, d, $J=7.7$, *o*-Ph H), 7.53 (1H, dd, $J=7.7$ and 7.7 Hz, *p*-Ph H), 7.42 (2H, dd, $J=7.7$ and 7.7 Hz, *m*-Ph H), 4.21 (1H, dd, $J=6.3$ and 11.2 Hz, C*H*HOBz), 4.16 (1H, dd, $J=7.0$ and 11.2 Hz, CH*H*OBz), 3.53 (1H, dd, $J=6.3$ and 11.2 Hz, C*H*HOH), 3.46 (1H, dd, $J=7.0$ and 11.2 Hz, CH*H*OH), 1.18 (2H, m, cyPr C*H*), 0.64 (1H, ddd, $J=4.9$, 4.9 and 8.4 Hz, cyPr C*H*H), and 0.59 (1H, ddd, $J=4.9$, 4.9 and 8.4 Hz, cyPr CH*H*).
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16. Diols **5a** and **6a** were prepared by lithium aluminum hydride reduction of the corresponding diethyl esters. Diol **7a** was prepared by DIBAL reduction of dimethyl itaconate as described in Ref. 15. Assignment of the structure of each regioisomer of produced monobenzoates was achieved by ^{1}H NMR analysis (500 MHz) and the most significant signals are as follows. **5b**: ($CDCl_3$) δ 4.44–4.33 (2H, m, CH_2OBz), 3.57–3.51 (2H, m, part AB of system ABX, CH_2OH), 1.00 (3H, d, $J=7.0$ Hz, CH_3). **5c**: ($CDCl_3$) δ 4.22 (1H, dd, $J=5.6$ and 10.5 Hz, C*H*HOBz), 4.16 (1H, dd, $J=6.3$ and 10.5 Hz, CH*H*OBz), 3.80–3.70 (2H, m, CH_2OH), 1.06 (3H, d, $J=7.0$ Hz, CH_3). **6b**: ($CDCl_3$) δ 4.29 (2H, t, $J=7.0$ Hz, CH_2OBz), 3.50 (1H, dd, $J=5.6$ and 10.5 Hz, C*H*HOH), 3.46 (1H, dd, $J=6.3$ and 10.5 Hz, CH*H*OH), 0.94 (3H, d, $J=7.0$ Hz, CH_3). **6c**: ($CDCl_3$) δ 4.19 (1H, dd, $J=5.6$ and 10.5 Hz, C*H*HOBz), 4.13 (1H, dd, $J=6.3$ and 10.5 Hz, CH*H*OBz), 3.64 (2H, t, $J=6.3$ Hz, CH_2OH), 1.01 (3H, d, $J=7.0$ Hz, CH_3). **7c**: ($CDCl_3$) δ 5.24 (1H, bs, =C*H*H), 5.09 (1H, bs, =CH*H*), 4.79 (2H, s, CH_2OBz), 3.81 (2H, t, $J=6.3$ Hz, CH_2OH), 2.42 (2H, t, $J=6.3$ Hz, CH_2 CH_2OH).