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Lipase-mediated selective acetylation of primary alcohols in ethyl acetate

Ernane C. de Souza [a], Moises Romero-Ortega [a,b], Horacio F. Olivo [a,*]

[a] Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, USA
[b] Departamento de Química Organica, Facultad de Química, Universidad Autónoma del Estado de México, Toluca, Mexico

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ABSTRACT

An environmental friendly process to selectively acetylate primary alcohols was demonstrated. The esterification process consists of treatment of a primary alcohol in the presence of immobilized *C. antarctica* lipase (Novozyme-435) in ethyl acetate at room temperature. Primary alcohols were acetylated in the presence of secondary alcohols and phenols.

Introduction

Lipases (triacylglycerol ester hydrolases) are versatile enzymes largely employed in synthetic organic chemistry to resolve racemic mixtures of alcohols, leading to highly enantioselective products.[1–5] Furthermore, lipases are promiscuous biocatalysts[1] for several recently found applications such as the aldol reaction,[2] the carbon-carbon Michael addition to α,β-unsaturated carbonyl compounds,[3] the aza-Michael additions of amines to acrylates,[4] the Mannich reaction,[5] and the Ugi multicomponent reaction.[6] Lipases are also used in the amidation of acids[7] and esters.[8]

In principle, the lipase-mediated esterification/hydrolysis of alcohol/ester reactions are reversible.[9] In order to drive the acylation reaction to the products, vinyl acetate is commonly used as the acylating reagent, Scheme 1. Thus, the ene alcohol produced is irreversibly tautomerized to acetaldehyde. On the other hand, when a hydrolysis reaction is carried out for the resolution of esters, the reaction is performed in water, which acts as a nucleophile and also as solvent. Therefore, the reaction equilibrium is displaced towards the alcohol. We have previously employed ethyl acetate, an environmentally benign solvent,[10] in lipase-mediated reactions in the presence of urea-hydrogen peroxide.[11] Ethyl acetate readily reacts in the binding site of the lipase with a serine residue forming an acetyl-enzyme complex. Hydrogen peroxide reacts with the acetyl-enzyme complex forming *in situ* acetylperoxycarboxylic acid. The peroxycarboxylic acid can then oxidize alkenes to oxiranes and also insert oxygen in cyclic ketones (Baeyer-Villiger oxidation) to deliver lactones. In this paper, we describe the use of ethyl acetate as the solvent as well as the acetyl-transfer agent for the acetylation of primary alcohols.[12] This reaction is environmentally friendly, practical, safe, inexpensive, and performed under mild conditions. In most cases, the product does not require chromatographic purification. The reaction is filtered thru a small bed of celite or filter paper to recover the catalyst, and solvent is evaporated.

There are several chemical methods available to carry out the acylation of alcohols. Most of them include the use of acyl halides or anhydrides in the presence of bases such as pyridine or triethylamine,[13] Lewis or protonic acids,[14] as well as solid acid catalysts.[15] Vinyl acetate can also be used as the acetylating agent in the presence of palladium catalyst.[16] Acyl halides and acetic anhydride are lachrymator and corrosive agents, respectively, and less than ideal for industrial applications. The present protocol for acetylating alcohols utilizing ethyl acetate in the presence of an immobilized lipase under mild reaction conditions should complement well other lipase-mediated acylation methods and be considered a cleaner alternative.[17]

Results and discussion

Initially, the acetylation of benzyl alcohol (**1a**) in ethyl acetate was investigated employing a small amount of lipase, Table 1. *C. antarctica* lipase (recombinant enzyme expressed in *Aspergillus*

* Corresponding author.
E-mail address: horacio-olivo@uiowa.edu (H.F. Olivo).

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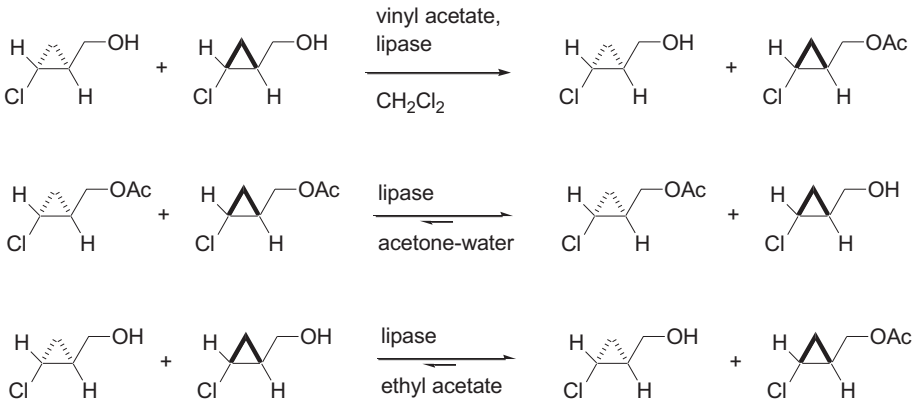
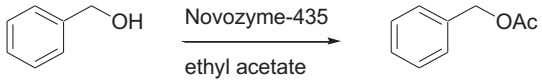


Scheme 1. Lipase-mediated resolution of alcohols.

Table 1
Acetylation of benzyl alcohol.[a]



1a **2a**

Entry	EtOAc (mL)	Time (h)	Conv. (%)
1	1	16	77
2	2	16	80
3	3	16	85
4	4	16	83
5	5	16	79
6	5	24	93
7	5	48	93

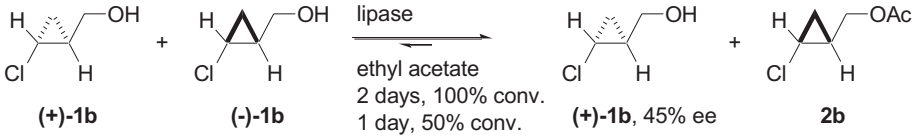
[a] The reactions were performed with 100 mg of benzyl alcohol and 5 mg of Novozyme-435.

niger and immobilized in acrylic resin, Novozyme-435) is a popular serine-lipase that has shown to accept a large variety of alcohols in its binding site.[18] The lipase-mediated acetylation was carried out at different concentrations of ethyl acetate at room temperature for up to 24 h (entries 1–6). Conversion was determined by ^{1}H NMR signal integration of the benzylic hydrogens of the alcohol and ester. The NMR signals for the benzylic hydrogens of the alcohol appear at 4.70 ppm, while the upfield signals for the same hydrogens of the ester appear at 5.15 ppm. No significant conversion difference was observed varying the amount of ethyl acetate. A maximum conversion was achieved after 24 h (entries 6 and 7).

The *trans*-chlorocyclopropyl methanol (**1b**) is an important intermediate for the synthesis of the macrocyclic marine lactone callipeltoside, Scheme 2.[19] This compound is easily prepared in racemic form. The lipase-mediated acetylation of chlorocyclopropyl methanol in ethyl acetate was completed after two days (100% conversion). When the reaction was stopped at 50% conversion, the alcohol and the ester were separated by column chromatography. The unreacted alcohol was converted to its Mosher ester.[20] Enantiomeric excess of the alcohol was determined by integration of the methylene hydrogens of both diastereomers by ^{1}H NMR. No difference in enantioselectivity was found when running the reaction under classical conditions.

We expanded this lipase-mediated acetylation to several aliphatic alcohols, Table 2. Acetylation of long-chain hydrocarbon alcohols, octanol and lauryl alcohol reached very good and high conversions after one day (entries 1 and 2). It took one day for 1,4-butanediol and 1,5-pentanediol to reach 94% and 92% conversions, respectively (entries 3 and 4). 4-Methyl-pentanol **1 g** reached very high conversion after one day and *N,N*-dimethylaminopropanol **1 h** did too after two days (entries 5 and 6). Acetylation of aminoethoxyethanol **1i** occurred both on the amino and the hydroxy group reaching completion after two days (entry 7). Acetylation of 2-methyl-butanol **1j** reached almost completion after two days and one day for the more lipophilic cyclohexylmethanol **1 k** (entries 8 and 9). However, the more hindered and hydrophilic 2,2-dimethylpropanediol **1 L** only reached 70% conversion after seven days (entry 10). Both *trans* and *cis*-geraniols were acetylated respectively in two and three days in 75 and 73% conversions (entries 11 and 12). Interestingly, no acetylation was observed for secondary alcohols (3-pentanol, cyclopentanol, cyclohexanol and 1,4-cyclohexanediol) under the general reaction conditions even after seven days (not shown on the table). These secondary alcohols can be acylated when the lipase-mediated reaction is carried out with vinyl acetate as the acylating agent.[21]

We also investigated the lipase acetylation of aromatic alcohols in ethyl acetate, Table 3. The 2-methylbenzylic alcohol was more difficult to acetylate than the unsubstituted benzylic alcohol (entry 1). The *p*-methoxybenzylic alcohol was completely acetylated in two days (entry 2), while the 3,5-ditrifluoromethylbenzylic alcohol took three days to reach a 94% conversion (entry 3). The three phenolbenzylic alcohols were acetylated exclusively on the benzylic hydroxyl group after three days (entries 4–6). Longer chain on the primary alcohol possessing an aromatic ring favored the acetylation (entries 7–9). Also, benzylic biphenols were good substrates for acetylation after three days (entries 10 and 11). In general, acetylation of aromatic alcohols took longer than the ones of aliphatic alcohols.



(+)-1b **(-)-1b** **(+)-1b**, 45% ee **2b**

Scheme 2. Lipase resolution of *trans*-chlorocyclopropylmethanol.