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Enzymatic monoesterification of symmetric diols: restriction of molecular conformations influences selectivity†

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We have experimentally demonstrated that by 'locking' the molecular conformation through the introduction of a double or triple bond in the center of a symmetric diol, enzymatic monoesterification can be achieved selectively. The enzyme *Candida antarctica* lipase B, generally used for the transesterification of diols, can be effectively used for the monoesterification of symmetrical diols in an unbuffered system also. By varying the chain length of a carboxylic acid moiety, we have established that optimum selectivity and efficiency can be achieved in the range of 4.8 to 5.0 pK_a values. Selectivity can be improved up to 98.75% for a monoester in an overall 73% yield (mixture of a monoester and a diester) when but-2-yne-1,4-diol reacted with hexanoic acid. Water, a by-product, provides an interfacial environment for the enzyme to work in the organic reaction medium. The uniqueness of the reported monoesterification protocol is that it involves only the mechanical stirring of the reaction mixture at room temperature in the presence of the enzyme for 24 h. High percentage yield with selectivity for a monoester, easier product isolation and overall, environmental sustainability are added advantages. The synthesized monoesters are characterized by using HNMR and high resolution mass spectrometry (HRMS).

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Introduction

Esterification is one of the most important reactions in organic synthesis. Organic esters find application in diverse areas. For example, the fatty acid monoester and diester of 1,3-propanediol are useful in the production of soaps, detergents, shampoos, cosmetics, as well as in several industrial applications. In these products, they find application as surfactants, emulsifiers, dispersants, corrosion inhibitors, lubricants, demulsifiers, and so on.[1] However, the reaction is governed by equilibrium and so, as it proceeds in the forward direction, the reverse reaction *i.e.* the hydrolysis of the ester also competes affecting the overall reaction yield. If water produced during the process is removed continuously using simple apparatus like 'Dean and Stark', the reaction can be shifted to the forward direction to almost completion.[2,3] In most cases, the reaction is carried out in an excess of alcohol as a medium and catalysis by using a mineral acid is a routine practice. However, this simple procedure is not applicable for the monoesterification of symmetrical diols with both hydroxyl groups being chemically equivalent.[4–8] The formation of the by-product diester (in high percentage) is unavoidable. Monoesters of diols are required as they find applications in diverse areas such as precursors in the multistep synthesis of bioactive natural products (such as amphidinolide B, spirastrellolide A, spiculoic acid A *etc.*)[9–12] and pheromones (for example, an epoxide derivative of a monoacylated diol is required during the synthesis of (+)-disparlure – the pheromone of gypsy moth, *Lymantria dispar* and its modified derivative – found as the pheromone of ruby tiger moth, *Phragmatobia fuliginosa*).[13] The monoacylated diol is also useful for the synthesis of 2-piperidones present in many bioactive compounds such as cytisine, tacamonine, yaequinolone *etc.*[14] Hence, the development of a strategy to suppress the production of the diester is needed.

The conventional procedure for the synthesis of a monoester from a symmetric diol is to treat the carboxylic acid with a stoichiometric amount of the diol in the presence of a mineral acid as the catalyst; however, the desired selectivity for monoester formation cannot be achieved. It was demonstrated that the proportion of unreacted diol, monoester and diester present in the mixture is in a 1 : 2 : 1 ratio.[15,16] In this procedure, too, the catalysis is of a homogeneous type and the amount of mineral acid used for the purpose is comparable with that of the reactants; it is not an environment friendly practice and may cause the degradation of the acid sensitive reactants.

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Fe_3O_4@L-Proline/Pd nanocomposite for one-pot tandem catalytic synthesis of (±)-warfarin from benzyl alcohol: synergistic action of organocatalyst and transition metal catalyst†‡

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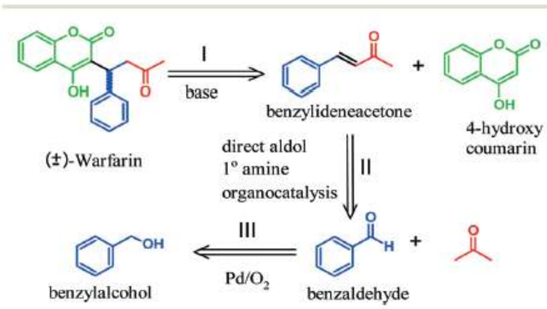
One-pot synthesis of (±)-warfarin, an anticoagulant, has been achieved from benzyl alcohol in a 'green way' by using a multicomponent catalyst. For the purpose, L-proline capped Fe_3O_4 nanoparticles (Fe_3O_4@L-proline NPs) were synthesized and metallic palladium was loaded on its surface (Fe_3O_4@L-proline/Pd NCs). The morphology, particle size and shape were studied by using FESEM and TEM analysis. The Pd present on the surface was responsible for oxidation of benzyl alcohol and its derivatives to the corresponding aldehyde *in situ*. This in turn, condensed with acetone to form the aldol condensation product, benzylideneacetone, at 70 °C due to the presence of the L-proline organocatalyst on the surface of Fe_3O_4 NPs. Later, 4-hydroxycoumarin was introduced to condense with *in situ* generated benzylideneacetone by a Michael addition to form the target product (±)-warfarin. It was established that benzyl alcohol can be converted into the final product, (±)-warfarin, with an overall 35% yield within 5 days in a single-pot process. This process requires a rise in temperature in stages to a maximum of 100 °C and 1 atm pressure of dioxygen gas. An important aspect of the developed process is the avoidance of loss of costly Pd by leaching and catalyst recovery by the use of a magnetic field. The use of a solvent like PEG-400 makes the process green in a true sense. The interaction of L-proline with Fe_3O_4 NPs and the presence of Pd on the surface were confirmed by the FTIR and XRD patterns, respectively. The present study hereby suggests a combined 3-step mechanism for the production of the target product warfarin. Pilot-scale one-pot production of (±)-warfarin was carried out and a flow diagram with various unit processes is presented.

1. Introduction

Warfarin (Coumadin® or Marevan®) is an anticoagulant drug most commonly prescribed by physicians for the prevention of thrombosis and embolism. It functions by inhibiting the vitamin K-mediated biosynthetic pathway leading to the formation of blood clotting proteins. Most commonly, it is synthesized by Michael addition of 4-hydroxycoumarin to benzylideneacetone in the presence of a base. Various organocatalysts having primary amines, amino acid functionalities and natural cinchona-derived chiral amines and diamines are reported to favor the asymmetric synthesis of one of the enantiomers.[1–4] The *S*-enantiomer is shown to be 2–5 times more active than the *R*-enantiomer. Moreover, it has a different metabolic pathway in humans and also has a shorter half-life than the *R*-enantiomer (21–40 h for *S*- and 37–89 h for *R*-warfarin).[5–7] However, in general, it is



Scheme 1 Planning for one-pot synthesis of (±)-warfarin from benzyl alcohol through 3-way catalysis by using a single nanocomposite catalyst having multiple components (I, II and III).

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† This work is dedicated to Dr. D. P. Bharambe, a humble teacher and mentor, on the occasion of his 62nd birthday and retirement.

‡ Electronic supplementary information (ESI) available: XRD patterns, TEM images with SAED pattern, FTIR spectra of all synthesized materials, synthesis scheme, combined reaction mechanism, ^1H NMR and ^{13}C NMR are provided in the ESI. See DOI: 10.1039/c9cy01497g

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Cinchona alkaloid derivative modified Fe_3O_4 nanoparticles for enantioselective ring opening of *meso*-cyclic anhydrides†

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In the present work, the molecular framework of quinidine was modified at the methoxy functional group of the C6′ carbon of the quinoline moiety with a long-chain carboxylic acid group (–COOH) and it was used as a capping agent during the synthesis of Fe_3O_4 NPs. The resulting modified quinidine capped Fe_3O_4 (Fe_3O_4@mQD) NPs were characterized by different techniques and used for enantio-selective ring opening (ERO) by methanolysis in a heterogeneous mode of catalysis. The interactions of mQD with the Fe_3O_4 surface, as well as its % loading, were studied using FTIR spectroscopy and thermal analysis techniques. Reaction parameters like the solvent system, temperature, and substrate were optimized. ERO of succinic and glutaric anhydrides by methanolysis was carried out in the presence of Fe_3O_4@mQD NPs. The optimized protocol can produce a chiral hemiester with high enantioselectivity (up to 98% ee) and excellent % yield (more than 90% in most of the cases).

1. Introduction

Enantioselective *meso*-cyclic anhydride ring opening or desymmetrization of cyclic anhydride is one of the most important protocols in the field of asymmetric synthesis.[1–5] It allows the direct access to products with multiple stereocentres in a single step with high stereoselectivity (almost 99% ee) and yield.[6,7] Due to this protocol, many steps (*e.g.* protection-deprotection of essential functional groups) and precious chiral auxiliaries involved in a total synthesis can be saved.[8] Total synthesis of (+)-biotin (a member of the series of water-soluble vitamin B, widely distributed in microorganisms, animals, and plants and necessary for the metabolism of fatty acids, α-amino acids, and sugars) through the Goldenberg–Strenbatch approach is a well-known example (Scheme 1).[9,10]

As can be seen from Scheme 1 the monoesterification of diacid 1 to 4 is very difficult and the available methods are inefficient to achieve complete conversion and selectivity. For example, (i) mineral acid-catalyzed esterification in which the diacid treated with a stoichiometric amount of alcohol lacks the selectivity of the desired monoester and yields a mixture of monoester, diester, and unreacted alcohol[11,12] and (ii) the reactivity of the two carboxylic groups can be differentiated by adsorbing the diacid on a suitable support (like alumina or silica). The chemisorption of one of the two carboxylate ions on the surface (either monodentate or bidentate mode) of the support makes the other group move away which can be esterified easily using the esterification toolkit.[13] However, monocarboxylate desorption from the surface is time-consuming, and different dicarboxylic acids may have different affinities for the support depending on the hydrocarbon chain length. Hence, substrate-wise special methods must be developed for this purpose. A single protocol that is universally applicable to all kinds of diacids is lacking; hence, (iii) enzyme-mediated methods are designed for these kinds of protocols.[14,15] But they have their own drawbacks regarding the stability and storage of the available expensive enzymes and their recovery. Another method to synthesize a monoester is to convert diacid completely into diester with excess alcohol under normal esterification conditions. Then the resulting diester 3 is asymmetrically hydrolyzed with lipase type enzymes into a chiral hemiester 4. However, this approach is not feasible and riddled with extra steps and a high total synthesis cost.

One of the most innovative ideas towards the synthesis of a hemiester is to start with *meso*-cyclic anhydride 2 instead of diester 3. ERO of such *meso*-cyclic anhydride 2 would result in chiral hemiester 4 in a single step.[16] The chiral hemiester can easily be converted into lactone 5 of either configuration by the chemoselective reduction of the ester group using a suitable reducing agent (lithium borohydride/dry THF or BH_3–Me_2S/dry THF) and cyclization.[17] Many approaches have been developed for the ERO of anhydride to date. However, they have met with

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