Catalysis Communications 114 (2018) 6–9

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short communication

The studies on the chemoenzymatic synthesis of 2-benzyl-3-butenoic acid

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ARTICLE INFO

Keywords:
Alkylation
Enzyme catalysis
Dienolates

ABSTRACT

The studies on the chemoenzymatic synthesis of 2-benzyl-3-butenoic acid 3 were performed. The alkylation of dienolates derived from the crotonic and vinylacetic acids with different types of alkylating agents was examined. In all cases the inseparable mixture of isomeric acids 3 and 4 were obtained. Chemoselective enzymatic esterification of those mixtures provides ester 6 in 86% yield as a single product without double bond isomerization. None common method can be used for its hydrolysis since under basic conditions only isomeric acid 5 is formed. To overcome this limitation enzyme catalysed hydrolysis process was design. This protocol afforded isomerically pure acid 3 in 98% yield.

1. Introduction

The β,γ-unsaturated carboxylic acids are valuable building blocks for the synthesis of numerous relevant biologically active compounds, e.g. factor Xia inhibitors [1], *dl*-bisnorvernolepin [2], vineomycinone B_2 [3], and many other. Among other species, *rac*-2-benzyl-3-butenoic acid 3 is an important starting material for the synthesis of various medicaments such as carboxypeptidase A inhibitors [4], functionalized piperidinones – HIV protease inhibitors [5], lignin-related tetrahydrofurans [6], γ-resorcylates [7], (*Z*)-ethylenic pseudopeptides [8]. So high functionality of unsaturated carboxylic acids is among others a result of possibility of transforming double bond in to the oxirane, thiirane, aziridine or cyclopropane ring [4], moreover double bond can contribute in olefin metathesis reaction [8,9] (Fig. 1). Various available methods towards β,γ-unsaturated carboxylic derivatives including reduction of triple bond [10], nickel-catalysed coupling reactions [11], indium-mediated addition [12], palladium-catalysed alkylation of ketone enolates [13], Cu-catalysed allylic alkylations [14] and many others are detailed described in literature. However, all the previously mentioned methods suffer from some serious disadvantages such as necessity of use environmentally polluting metal complexes or many chemical transformations resulting in low overall yield. In this context alkylation of dienolates still remains useful method for preparation of this class of compounds due to its wide generality and versatility. [15,16]. However the major drawback of mentioned method is associated with low regioselectivity and difficult separation procedure of obtained complex reaction mixture, using common purification methods such as vacuum distillation or column chromatography. Moreover, it is well known that β,γ-unsaturated carboxylic acids and their derivatives are very prone to the double bond isomerization (eg. under basic or acidic conditions, elevated temperatures) [17,18]. It is well recognized that an addition of copper (I) salts to lithium unsaturated carboxylic acid dienediolates results mainly in alkylation on γ-carbon position [19]. The introduction of regiodirective groups, e.g. silyl, sulfonyl group improves γ-regioselectivity of aldol additions of esters, but not for alkylation [20]. Despite of numerous studies devoted to this synthetic matter [21–23] including enantioselective alkylation with chiral auxiliaries [24], condensation of dienolates with aldehydes and ketones [25] as well as Michael addition of dienolates to unsaturated ketones [26], the development of simple and efficient synthetic pathways towards this class of compounds still remain challenging. Several attempts have been made to develop biocatalitic routes towards β,γ-unsaturated carboxylic acids. Recently, Okrasa et al. obtained a new crystal structure of arylmalonate decarboxylase isolated from the *B. bronchiseptica* and designed mutants which showed increased activity with α-aryl and α-alkenyl malonates [27]. Gao, et al. used microbial whole-cell catalyst *Rhodococcus erythropolis* AJ270 containing a nitrile hydratase/amidase for biotransformation of various functionalized racemic nitriles. This protocol provide a synthetic route to highly enantiopure carboxylic acids and amides functionalized with an allyl, propargyl, allenyl, or vinyl group [28]. Herein, we describe the studies on preparative, isomerically pure, chemoenzymatic synthesis of 2-benzyl-3-butenoi acid 3.

2. Results and discussion

The common substrates for synthesis of 2-benzyl-3-butenoic acid 3 are usually crotonic 1a or vinylacetic 1b acids. The treatment of those

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https://doi.org/10.1016/j.catcom.2018.05.020
Received 16 April 2018; Received in revised form 25 May 2018; Accepted 26 May 2018
Available online 29 May 2018
1566-7367/

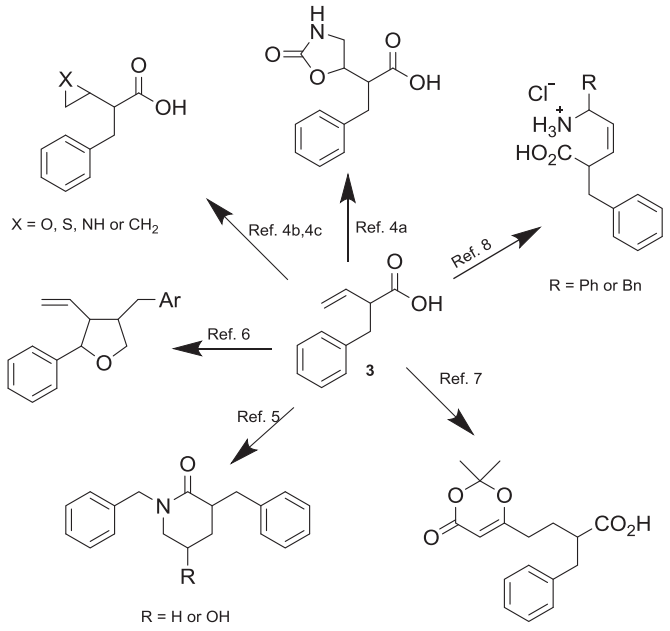
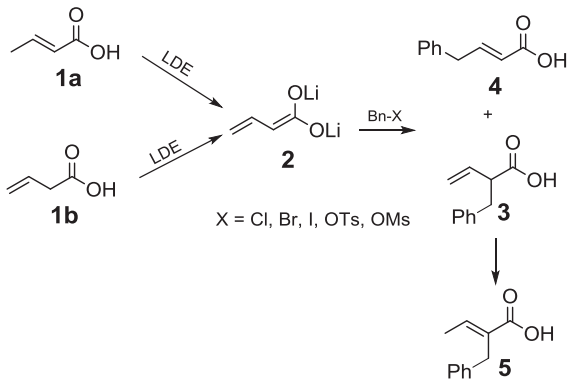


Fig. 1. Synthetic applications of rac-2-benzyl-3-butenoic acid.



Scheme 1. Alkylation of dienolate 2 with different types of alkylating agents.

compounds with strong base (e.g. LDE – lithium diethylamide), lead to respective lithium dienolates 2 which can subsequently react at the α- or γ-carbon atom, resulting in the mixture of isomeric acids 3 and 4. The ratio between products dependent on both: type of alkylating agents used and reaction conditions. Furthermore, β,γ-unsaturated carboxylic acid 3 undergoes double bond isomerization to thermodynamically more stable α,β-unsaturated acid 5 (Scheme 1). This synthetic problem is well recognized in literature, unfortunately most available data are based mostly on the analysis of ^{1}H NMR [21–23] spectra of crude reaction products. Results obtained using this method are often ambiguous, due to complex composition of reaction mixture and low accuracy of NMR measurement. Initially we employed methodology proposed by Aurell et al. for the synthesis of model compounds using 2-benzylbut-3-enoic acid 3 and 5-phenylpent-2-enoic acid 4 as analytical standards for further research [22]. Unfortunately, the method reported was difficult to reproduce, and provided, after tedious and time consuming purification, the acid 3 with low, 40% yield. Despite of many efforts, we were not be able to directly isolate pure acid 4 by this method. Thus, this compound was synthesized by Knoevenagel condensation of 3-phenylpropanal with malonic acid, which provided pure acid 4 in 90% yield.

The next goal of our research was to develop the analytical method for determination of reaction mixture composition (α and γ-substituted acids 3 and 4). Our protocol is based on esterification of carboxylic

Table 1
Alkylation of 1a and 1b with different alkylation agents.

Entry	Substrate	X	3:4 ratio[a]	Yield[a] [%]
1	1a	Cl	27: 1	49
2	1a	Br	5: 1	54
3	1a	I	3: 1	33
4	1a	OTs	49: 1	63
5	1a	OMs	21: 1	46
6	1b	Cl	12: 1	8
7	1b	Br	4: 1	18
8	1b	I	1: 1	16
9	1b	OTs	140: 1	10
10	1b	OMs	9: 1	14

[a] Determined by RP-HPLC after derivatization of crude reaction mixture by diazomethane.

acids mixture to their methyl ester using diazomethane followed by reversed-phase high-performance liquid chromatography (RP-HPLC) chromatogram analysis (for more details see supplementary materials). Diazomethane is a particularly convenient methylating agent because it reacts with carboxylic acids quantitatively at room temperature. Also, the unreacted diazomethane is easy to remove from reaction medium [29]. Having analytical method for determination yield and the α/γ products ratio in hand, we performed experiments to clarify the influence of leaving group present in electrophile structure as well as addition of cooper (I) salts on alkylation reaction of 1a and 1b. As a alkylating agents benzyl halides (X = Cl, Br, I) as well as benzyl tosylates and mesylates (X = OTs, OMs) were used. To validate our results each experiment was repeated at least three times. Obtained results are summarised in Table 1. Benzyl halides, tosylates and mesylates used as alkylating agents tend to react mainly at α-carbon atom of dienolate 2 (Table 1, Entry 1–10). The higher amounts of γ-alkylated products can be obtained by changing leaving group. With increasing of atomic radius of halide present in an alkylating agent the surge of γ-product formation has been observed what is in agreement with literature data for alkylation reaction of dienolates [19,21] (Table 1, Entry 1–3). Tosylates and mesylates are good leaving groups and provided the higher α:γ ratios when compare it to an benzyl halides (Table 1, Entry 4–5 and 9–10).

The analysis of products proportion has been repeated after seven days, and no change in it was observed. The yields varied in a range from 8% to 63%. This results may be explained by high chemical reactivity of enolates witch can easily undergoes site reactions (e.g. polymerisation, multiple alkylation). Reactions carried out with vinylacetic acid 1b (Table 1, Entries 6–10) resulted in much lower yield, than reactions with crotonic acid 1a (Entries 1–5). Presumably it is caused by different rate constant of deprotonation resulting in not equal formation of dienolate 2.

It is well recognized that the exchange of counterion from lithium to the cuprous (I) influences the regioselectivity in alkylation of dienolates [19,30]. This characteristic and still unclear effect has been studied. The distribution of product has been analyzed by RP-HPLC after derivatization with diazomethane. The results showed limited efficiency addition of cuprous (I) additives which do not influenced regioselectivity significantly (Table S1 in SI). The alkylation of dicopper dienolate gives higher amount of γ-alkylated product in comparison with corresponding lithium dienolate, but still approximately 1:1 mixtures of products is obtained.

The results of our studies on alkylation reaction of dienolate 2 showed that this method suffers from a low regioselectivity and requires time-consuming, cumbersome purification steps and cannot be consider as a preparative method for synthesis of 2-benzyl-3-butenoic acid 3. Thus, we turned our attention to an enzymatic process that could lead to overcome this limitations. Biocatalysts exhibit high substrate specificity and require mild operational condition, hence they were promising candidates for selective purification protocol. Taking