Tetrahedron Letters 56 (2015) 1696–1698

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and enzymatic resolution of racemic 2,3-epoxy propyl esters obtained from glycerol

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ARTICLE INFO

Article history:
Received 22 November 2014
Revised 6 February 2015
Accepted 13 February 2015
Available online 19 February 2015

Keywords:
Enantioselectivity
Glycerol
Glycidyl esters
Kinetic resolution
Lipase

ABSTRACT

A method is described for the synthesis of (±)-2,3-epoxy propyl esters from glycerol, involving reaction of epichlorohydrin with sodium or potassium salts of carboxylic acids in the presence of TBAB as catalyst, with moderate to excellent yields. Kinetic resolution of glycidyl butyrate by lipase of *Thermomyces lanuginosa* has been achieved with remarkable enantiomeric excess (ee >99%) using 1,4-dioxane as a co-solvent in pure buffer solution (30 and 50 °C, pH = 7.0).

The 2,3-epoxypropanol (glycidol **1**) and its optically active epoxide derivatives (Fig. 1) have been used as important chiral building blocks in synthetic routes to compounds of great interest such as carmegliptin which is a potent oral antidiabetic single daily dose,[1] chiral degradable polymers for biomedical and pharmaceutical applications such as poly(1,2-glycerol carbonate),[2] the preparation of optically active beta-blockers[3] and, anticancer drugs.[4] Various strategies have been designed for the synthesis of chiral glycidols such as the hydrolytic kinetic resolution by Jacobsen methology[5] and Sharpless epoxidation of allylic alcohol.[6]

Pursuing the preparation of those important products with high optical purity, many papers describe the use of lipases in the resolution of (±)-glycidol (**1**) and its esters, however, low yields are obtained, long reaction time are required[7] or it is necessary extremely anhydrous conditions to obtain good yields.[8]

Reaction of epichlorohydrin (**4**), which is obtained industrially from propylene and, more recently, from glycerol,[9,10] with carboxylic acid salts in the presence of a phase transfer catalyst can be used as a strategy for the synthesis of glycidyl esters.

Considering that the biodiesel production is increasing exponentially and glycerol is a by-product of this industry, its generation is also happening in a large scale. Therefore, there is a consensus in the scientific community that the placement of glycerol is a serious problem for the production of biodiesel in bulk and it is crucial to seek alternatives for the consumption of this extra volume either in its raw form or as derivatives with high added value. On the other hand, the increase in biodiesel production can be economically made feasible if new applications and market for glycerol are found. Accordingly, studies aiming to new industrial applications for glycerol are of great industrial, social, economic, and environmental interest.[10,11] Given that, as our research group focuses on the possibilities of converting simple and versatile molecules to a variety of chemicals with high added value, we have chosen to work on the synthesis and bioconversion of derivatives of glycerol, using lipases as catalyst to obtain chiral building blocks of pharmaceutical interest.

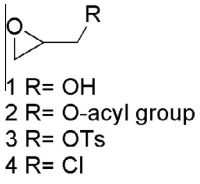

Figure 1. Glycidol (**1**) and its epoxide derivatives.

In this Letter, we present a simple and direct method for the synthesis of (±)-2,3-epoxypropyl esters from glycerol and kinetic resolution of some these racemic esters using lipases from *Thermomyces lanuginosa* and *Candida rugosa*.

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http://dx.doi.org/10.1016/j.tetlet.2015.02.046
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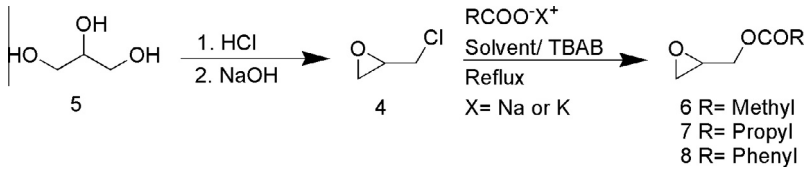


Scheme 1. Preparation of epichlorohydrin from glycerol and production of esters.

For synthesis of the desired esters, we replaced the chlorine atom of epichlorohydrin (**4**) by selected carboxylate groups (Scheme 1). Epichlorohydrin (**4**) was prepared by bubbling gaseous and dried HCl in a heated mixture (105–110 °C) of glycerol (**5**) with catalytic amount of acetic acid, followed by dehydro-chlorination with NaOH pellets[12] leading to moderate yields of the desired product (~60%).

Carboxylates of sodium or potassium are not very reactive nucleophiles. However, using the phase-transfer catalysis system (PTC), the rate of this type of reaction can be increased drastically.[13–15] The method induces or accelerates the reaction between compounds that are either solubilized or form different phases by the action of a transfer agent or catalyst.[14] Thus, sodium and potassium acetate, butyrate and benzoate where submitted to reaction with epichlorohydrin in the presence of suitable crown ethers as phase-transfer catalyst in a solid–liquid system.[15,16] It was chosen toluene and acetonitrile to evaluate the effect of solvent polarity.[17] However, in the tested conditions the yields were very low (<3%). Take in account that tetra-*n*-butylammonium bromide (TBAB) has been used as a catalyst in allylation of sodium phenoxide in a solid–liquid system,[16] we decided to make use of it in place of crown ethers (Scheme 1) and, the results are presented in Table 1.

With respect to ester **6** the best results were obtained when acetonitrile was used as solvent (20% and 45% for sodium and potassium salts, respectively), while in toluene, the yields were very poor (10% and 15%, respectively). The reaction in toluene produced a good yield (90%) of ester **7**, especially in the presence of sodium butyrate (70% when used potassium butyrate). As for the benzoate **8**, no significant differences in yields were observed (~60%) using either toluene or acetonitrile. All the experiments were dealt under triplicate basis and, it was observed that the reactions are not successful without the catalyst.

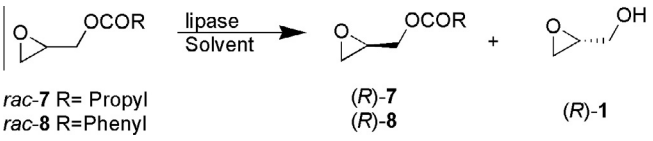
The acetate salts present low solubility in both used solvents; however they are more soluble in the more polar solvent acetonitrile, resulting in acceleration of the reaction and higher yields. On the other hand, carboxylate ions of longer carbon chain, as the butyrate, are more soluble in the hydrophobic solvent toluene, reflecting in an excellent yield for the sodium salt, but only moderate for potassium salt. This difference of reactivity is likely due to the slightly higher solubility of sodium salt in organic solvents. The aggregation of the ionic pair/complex reduces the reactivity by reducing the effective concentration of the nucleophile in the organic phase.[17,18]

The benzoates reactivity was similar in both polar and nonpolar solvents, leading to moderate yields after 5 h reaction. The benzoates and butyrates are close in solubility, but are less reactive since its nucleophilicity is attenuated by electronic delocalization effect of the aromatic ring.

The great stereoselectivity of lipases make them very important catalysts in organic chemistry. Even used as a single type of enzyme, they can recognize different substrates promoting many type of reactions such as the preparation of enantiomerically pure compounds.[19]

In the present study we focused our attention to lipase *Thermomyces lanuginosa* (TLL) and *Candida rugosa* (CRL). TLL is thermostable, commercially available in solution or immobilized. It is widely used in the food and fine chemical industries as well as for the production of biodiesel.[19] Despite the great potential of TLL in chemical process, we could not find any report in the literature of its use in kinetic resolution of 2,3-epoxy propyl esters.

Nair et al.[8] observed the enantioselective hydrolysis of various (±)-2,3-epoxy propyl esters catalyzed by lipase from *Pseudomonas cepacia* (PS-C 'Amano' II), and their kinetic resolution were selective for aromatic esters, however, lipase PS-C was not capable of catalyzing the aliphatic esters hydrolysis (acetate, butyrate and propionate). Nevertheless, in our work, (±)-glycidyl butyrate **7** was obtained in a good enantiomeric excess of (*R*)-ester (99%) when phosphate buffer was used as solvent and 1,4-dioxane as co-solvent in the presence of lipase from *Thermomyces lanuginosa* (Scheme 2 and Table 2). Similar results were obtained by Li et al.[20] using lipase from *Bacillus subtilis* (BSL2) where the authors reported an ee >98% of (*R*)-butyrate when the conversion was above 52%.



Scheme 2. Enzymatic resolution by hydrolysis of (±)-glycidyl esters.

Table 1
Preparation of (±)-2,3-epoxy propyl esters using TBAB as a phase transfer catalyst in toluene and acetonitrile

Salt	Solvent[a]	Product	Time (h)	Yield (%)
CH_3CO_2Na	MeCN	**6**	5	20
	Toluene		5	10
CH_3CO_2K	MeCN		5	45
	Toluene		5	15
$CH_3(CH_2)_2CO_2Na$	MeCN	**7**	5	35
	Toluene		5	90
$CH_3(CH_2)_2CO_2K$	MeCN		5	30
	Toluene		5	70
$C_6H_5CO_2Na$	MeCN	**8**	5	60
	Toluene		5	60
$C_6H_5CO_2K$	MeCN		5	65
	Toluene		5	60

[a] Anhydrous, at reflux.

Table 2
Kinetic resolution of **7** and **8** by lipases from *Thermomyces lanuginosa* and *Candida rugosa*, respectively

Compound	Lipase from	Temp (°C)	Time (h)	ees* (%)
7	*T. lanuginosa*	30	2	>99[a] (*R*)
7	*T. lanuginosa*	50	2	>99[a] (*R*)
8	*C. rugosa*	30	6	34[b] (*R*)

[a] Determined by GC (Chiraldex B-PM Column).
[b] Determined by HPLC (Chiraldex G-TA column).
* ees = substrate enantiomeric excess.

The enzymatic resolution by hydrolysis of (±)-glycidyl benzoate **8** using lipase from *Candida rugosa* as catalyst showed poor enantiomeric excess of (*R*)-ester (34%) (Table 2).

The enantiomeric excess of the remaining glycidyl esters was determined by integration of peak areas of individual enantiomers in their chromatograms.

In summary, a simple method for preparing glycidyl esters from glycerol was developed involving reaction of epichlorohydrin with salts of carboxylic acids having TBAB as phase transfer catalyst. The yields obtained were reasonable, especially for butyrate **7** (90%). A kinetic resolution process to achieve (*R*)-butyrate **7** and (*R*)-glycidyl benzoate **8** from their racemates using lipases from *Thermomyces lanuginosa* and *Candida rugosa* was investigated. The results showed that the lipase from *Thermomyces lanuginosa* led to enzymatic hydrolysis of the ester butyrate with a high enantiomeric excess ($\geqslant$99%). As for lipase from *Candida rugosa* the hydrolysis of (±)-benzoate **8** gave low enantiomeric excess (ee 34%).

Acknowledgments

Y.J.K.A. would like to acknowledge Foundation to Support Development of Education, Science and Technology of the State of Mato Grosso do Sul (FUNDECT, Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul) for the scholarships. A.B. gratefully acknowledge FUNDECT for the financial support. The authors thank Maxwell Parrela Andreu for assistance in the GC analysis and Professors Luiz Henrique Viana (UFMS, Universidade Federal de Mato Grosso do sul) and Leandro H. de Andrade (USP, Universidade de São Paulo) for making available their laboratories for determination of enantiomeric excesses.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.046.

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