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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Ranjeet V. Nair [a] , Prashant N. Patil [a] & Manikrao M. Salunkhe [a]

[a] Department of Chemistry, The Institute of Science, 15-Madam Cama Road, Mumbai, 400032, India

Version of record first published: 25 Sep 2007.

To cite this article: Ranjeet V. Nair , Prashant N. Patil & Manikrao M. Salunkhe (1999): Novel Synthesis And Enzymatic Resolution of (±) -2,3 - Epoxy Propyl Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:15, 2559-2566

To link to this article: http://dx.doi.org/10.1080/00397919908086413

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SYNTHETIC COMMUNICATIONS, 29(15), 2559-2566 (1999)

# Novel Synthesis And Enzymatic Resolution of ( ± ) - 2,3 - Epoxy Propyl Esters

Ranjeet V. Nair, Prashant N. Patil, Manikrao M. Salunkhe*

Department of Chemistry, The Institute of Science,15-Madam Cama Road, Mumbai-400032, India

Abstract: A novel method of synthesizing glycidyl esters ( ± ) -2,3-epoxy propyl esters has been developed involving reaction of epichlorohydrin with sodium salt of carboxylic acids in the presence of 15-crown-5 as catalyst with excellent yields. Enzymatic resolution of these glycidyl esters by lipasePS-C has been achieved with remarkable substrate selectivity.

Glycidyl esters have received much attention as functional monomers and cross linking agents.[1] Further homochiral glycidol and its derivatives have found widespread applications as chiral building blocks in assymmetric synthesis.[2a-c] Previously Otera *et al.* had carried out the reaction of sodium salt of carboxylic acids with epichlorohydrin in the presence of Sn-P catalyst to yield glycidyl esters.[1] This method has drawbacks because of lower yields due to side product, reflux conditions and long reaction time in both the steps.

* To whom correspondence should be addressed.



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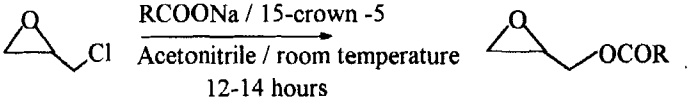
We have developed a simple one pot novel method, for the synthesis of (±)-2,3-epoxy propyl esters by reacting sodium salt of carboxylic acid with epichlorohydrin using 15-crown-5 as phase transfer catalyst at room temperature.(Scheme-1) The reaction was sluggish without 15-crown-5. The poor nucleophilicity of acetate ion towards various substrates in condensed system has been attributed to a combination of polarizability, basicity and solvation factors.[3] The acetate ion solubilized as sodium salts in acetonitrile, toluene, or benzene containing 15-crown-5 are sufficiently nucleophilic to react smoothly and quantitatively, even at room temperature. (Scheme-1)

Scheme-1




1(a-f) (±)-2 ( a-f )

| 1(a-f) | R |
|---|---|
| a = | $C_6H_5$ |
| b = | $C_6H_5$-CH=CH- |
| c = | p-$NO_2C_6H_4$ |
| d = | $CH_3$ |
| e = | $C_2H_5$ |
| f = | $C_3H_7$ |

We have investigated the effect of solvent on the above phase transfer reaction. For this purpose 1a was chosen as a model substrate and 15-crown-5 was taken as phase transfer catalyst. The reaction was carried out using various solvents as shown in Table1. Thus, by increasing the polarity of the solvent both, the reaction time decreases and the yield increases. Acetonitrile was found to be the ideal

Table-1: Preparation of (±)-2,3-epoxy propyl esters (2a-f)

| Product | Yield % | bp$^0$C at NTP♣ | solvent (dry) | reaction time (hours) |
|---|---|---|---|---|
| 2a | 80<br>85<br>95 | 125 | benzene<br>toluene<br>acetonitrile | 20<br>16<br>12 |
| 2b | 94 | 221 | acetonitrile | 12 |
| 2c | 92 | 60♦ | acetonitrile | 12 |
| 2d | 92 | 168 | acetonitrile | 13 |
| 2e | 91 | 180 | acetonitrile | 13 |
| 2f | 92 | 197 | acetonitrile | 14 |

♦= mp ♣bp and mp are uncorrected and taken at NTP (normal temperature and pressure)

solvent for the above reaction and further all the reactions were carried out in dry acetonitrile with the same quantity of 15-crown-5. The structures were confirmed by physical constants and spectral analysis. The results are summarised in Table 1.

In the next step, lipase catalysed hydrolysis of the synthesized glycidyl esters were carried out using lipase PS-C.[4] Previously Whitesides *et al.* had carried out lipase (PPL) catalysed hydrolysis of several racemic esters of epoxy alcohols.[5] Interestingly, in our case ( ± )-2,3-epoxy propyl esters( 2a-c ) underwent hydrolysis in good yield giving ( S ) -Glycidols 94-95% ee along with unreacted ( R )-2,3-

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epoxy propyl esters 91-97% ee. This enzyme shows remarkable substrate selectivity as it does not catalyse substrates (2d-f). The substrates (2d-f) were recovered quantitatively and showed no optical activity.( Scheme-2)

The enantiomeric excess was calculated by correlation of optical rotation [ $\alpha$ ] with literature values[6 a-c] and by derivatization. The results are compiled in Table 2 .

(S)- Glycidol obtained in the chiral form can be converted to (S)-Aryl epoxy ether which is a chiral building blocks for β-blockers.[7] (S)-Glycidol are also building blocks for lipids and phospholipids.[8] Further compound 3c i.e (R)-2,3-epoxy propyl p-nitrobenzoate is a chiral building block, reacting at C-3 with nucleophiles.[9]

In order to optimise the reaction on a larger scale, hydrolysis of 2a (i.e 2,3-epoxy propyl benzoate ) (0.056 mole,10 gms) was carried by lipase PS-C (2 gms) by using usual procedure to give (S)-Glycidol (97% ee, 4.56 gms, 46% yield) along with unreacted (R)-2,3-epoxy propyl benzoate. (95% ee, 4.68 gms, 47% yield) This reaction was completed in 17 hours as compared to the same reaction performed on a small scale (1.5 m mole) which required 12 hours for completion.

Finally we can conclude this substrate selective enzymatic hydrolysis by using lipase PS-C is an efficient alternative route, with simple work up and high enantiomeric excess.

## Experimental:

$^1$H-NMR spectra were recorded on Perkin Elmer 300 Mhz spectrometer, using $CDCl_3$ as solvent. Optical rotation values were noted on JASCO-390 Polarimeter.

**General procedure for the synthesis of (R/S) -2,3-epoxy propyl esters:**

15-crown-5 (25μl) was dissolved in dry acetonitrile and sodium salt of carboxylic acid (0.05mole) was added to it. The solution was kept for stirring for

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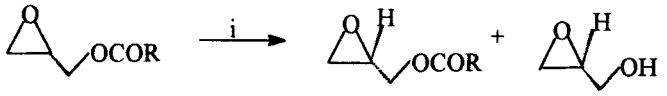
Scheme-2




| ( R/S ) - 2,3-epoxy propyl esters | ( R ) -2,3-epoxy propyl esters | ( S ) - glycidol |
|---|---|---|
| 2 a - f | 3 a - f | 4 a - f |

2 a - f R

a = $C_6H_5$
b = $C_6H_5$-CH=CH-
c = p-$NO_2C_6H_4$
d = $CH_3$
e = $C_2H_5$
f = $C_3H_7$

i = lipase PS-C, THF/ room temperature, phosphate buffer 0.1 M, pH=7

Table-2

| Reactant | Conversion* (%) | Reaction time (hours) | Product formation | |
|---|---|---|---|---|
| 2 | | | 3 ee (%) | 4 ee (%) |
| a | 93 | 12 | 97 % $[\alpha]_D^{25}$ -26.6$^0$ (c=0.15, pyridine ) | 95% $[\alpha]_D^{25}$ -14.3 $^0$ (c=1, chloroform) |
| b | 92 | 13 | 91 % $[\alpha]_D^{25}$ -31.2$^0$ (c=1, chloroform) | 95 % $[\alpha]_D^{25}$ -14.2$^0$ (c=1, chloroform) |
| c | 94 | 11 | 92 % $[\alpha]_D^{25}$ -32.0$^0$ (c=0.25, chloroform) | 94 % $[\alpha]_D^{25}$ -14.1$^0$ (c=1, chloroform) |

* taking into account amount of products isolated (3a-c) and (4a-c)

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30 minutes. Then excess of epichlorohydrin (0.1 mole) was added. The reaction progress was monitored by TLC The organic extract was washed with water, then with aqueous $NaHCO_3$. The organic extract was collected, dried over $MgSO_4$ and evaporated under vacuum to yield corresponding ( $\pm$ )- 2,3- epoxy propyl esters. The products were purified by column chromatography using petroleum ether: ethyl acetate (7:3) as the eluent.

**$^1$H-N M R ($CDCl_3$/TMS $_{int}$) $\delta$ [ppm] of 2,3-epoxy propyl esters**

a) 2,3-epoxy propyl benzoate: 2.75-2.82 (m, 2H); 3.12-3.41 (m, 1H);4.1 (d of diasterotopic AB, 2H, J=12Hz, 6Hz or 3Hz); 7.4 (m,3H, aromatic); 8.1 (m, 2H, aromatic)

b) 2,3-epoxy propyl cinammate: 2.44-2.75 (m, 2H); 2.94-3.19 (m, H); 4.07 (d of diasterotopic AB, 2H, 12 Hz, 6Hz or 4Hz); 6.24 (d, 1H, J=8Hz); 7.06-7.44 (m,5H); 7.50 (d, 1H, J=8Hz)

c) 2,3-epoxy propyl p-nitrobenzoate: 2.74-2.81 (m,1H); 3.30 (m,1H) 4.4 (d of diasterotopic AB, J=12Hz, 6Hz or 3Hz); 8.21-8.35 (m, 4H, aromatic)

d) 2,3-epoxy propyl acetate: 1.94 (s, 3H); 2.36-2.72 (m,2H); 2.81-3.07(m,1H); 3.90 (d of diasterotopic AB, 2H, J=12Hz, 6Hz or 3hz )

e) 2,3-epoxy propyl propanoate:1.11(t, 3H, J=Hz); 2.27(q, 2H, J=9Hz); 2.40-2.73 (m,2H); 2.87-3.11 (m, 1H); 3.92 (d of diasterotopic AB,12Hz, 6Hz or 3Hz)

f) 2,3-epoxy propyl butanoate: 0.9-1.1 (t, 3H, J=6hz); 1.5-1.9 (m,2H J=6.5Hz); 2.2-2.5 (t, 2H, J=6Hz); 2.9-3.21 (m, 1H); 2.52- 2.75 (m, 2H); 3.93 (d of diasterotopic AB, 2H, J=12Hz, 6Hz or 3Hz)

g) 2,3-epoxy propanol (glycidol): 2.32-2.71(m,3H); 2.79-3.05(m,1H); 3.90 (d of diasterotopic AB, 2H, J=12Hz, 6Hz or 3Hz)

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**Enzymatic hydrolysis of (R/S)- 2,3-epoxy propyl esters:**

The (R/S)- 2,3-epoxy propyl esters was dissolved in dry THF (5ml) and kept for stirring. Then phosphate buffer of (0.1M, pH=7)was added. After about 30 minutes, lipase PS-C was added and kept for stirring. The reaction progress was monitored by TLC. The enzyme was filtered through celite pad. The solution is then extracted with ethyl acetate. The organic phase was collected and dried over $MgSO_4$ and then evaporated under vacuum. The products thus obtained where isolated and purified by column chromatography using n-hexane: petroleum ether (1:1) as eluent. To a small amount of isolated compound thiophenol and Ti (0-i-Pr)$_4$ in $CH_2Cl_2$ was added. The opening product, 3-thiophenyl-1,2-propanediol, isolated after acidification with 10% $H_2SO_4$,was peracetylated with acetic anhydride in pyridine. Analysis of the diacetate by $^1$H-NMR($C_6D_6$) in the presence of the chiral shift reagent Eu(hfc)$_3$ indicated a selectivity >90 % ee.

Acknowledgment: We are grateful to Lady Tata Memorial Trust, Mumbai (India) for financial assistance and also to Amano Pharmaceutical Company, Japan for gift of the enzyme.

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Accepted 12-12-1998

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