

## An Efficient Catalyst-Free Ring Opening of Epoxides in PEG-300: A Versatile Method for the Synthesis of Vicinal Azidoalcohols

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Efficient and regioselective conversion of epoxides to 1,2-azidoalcohols has been carried out by treatment of sodium azide using polyethylene glycol as the reaction medium. The reaction afforded the corresponding products with high regioselectivity under mild reaction conditions.

**Keywords:** 1,2-Azidoalcohol, Epoxide, Polyethylene glycol, Sodium azide, Azidohydrin, Ring opening

### INTRODUCTION

Vicinal azidoalcohols are precursors of aminoalcohols [1], which are well known as  $\beta$ -blockers and present in various natural products and different bioactive compounds [2]. They are also useful for the synthesis of amino sugars [3], carboxylic nucleosides [4], lactames [5] and oxazolines [6]. Azidation of epoxides as the most common synthetic route to 1,2-azidoalcohols are often performed in aqueous solutions under alkaline or acidic conditions [7] and several different methods have been devised in order to obtain the direct azidolysis of epoxides in the literature. The reaction of epoxides with triethylaluminium/ $\text{HN}_3$  [8],  $\text{NaN}_3$ /calcium cation exchange Y-type zeolite [9], tributyltin azide [10], dibutyltin diazide [11],  $\text{NaN}_3/\text{LiClO}_4$  [12],  $\text{TMSN}_3/\text{Ti}(\text{O}^i\text{Pr})_4$  [13],  $\text{TMSN}_3/\text{Cr}(\text{salen})$  [14],  $\text{TMGA}/\text{Hf}(\text{OTf})_4$ ,  $\text{Zr}(\text{OTf})_4$  or  $\text{Yb}(\text{OTf})_4$  [15], diethylaluminium azide [16],  $\text{NaN}_3/\text{CAN}$  [17],  $\text{TMSN}_3/\beta$ -Cyclodextrin [18],  $\text{NaN}_3/\text{PTC}$  [19],  $\text{NaN}_3/\text{halohydrin dehalogenase}$  [20],  $\text{NaN}_3/\text{CeCl}_3$  [21],  $\text{NaN}_3/\text{Oxone}$  [22],  $\text{NaN}_3/\text{LiBF}_4$  [23], Azide exchange resin [24],  $\text{NaN}_3/\text{PVA}$  (or PAA) [25],  $\text{HN}_3/\text{Co}(\text{salen})$  [26],

$\text{NaN}_3/(\text{TBA})_4\text{PFeW}_{11}\text{O}_{39}\cdot 3\text{H}_2\text{O}$  [27] have been reported.

However, many of these methods involve the use of expensive and stoichiometric amounts of reagents or catalysts, suffer from poor regioselectivity, strongly acidic conditions and also require extended reaction times. Therefore, the development of a new and efficient protocol for this transformation under mild and more convenient conditions is still needed.

"Pollution control" demands are a source of inspiration to design and develop new solvent media for achieving high efficiency. Towards this goal, many attention has been drawn to the development of environmentally benign solvents such as ionic liquids [28], supercritical carbon dioxide [29], poly(ethylene glycol) [30] and water [31]. The value of a new solvent medium primarily depends on its environmental impact, the ease with which it can be disposed and the number of times the solvent can be recycled. Secondary issues concern a low vapor pressure, nonflammability, and high polarity for solubilization. Room temperature ionic liquids are one of the recent additions, which meet several of the above requirements. However the high cost and unproven disposal issues limit their use in industry [32].

PEG and its aqueous solutions represent interesting solvent

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systems for solvent replacement, and may stand comparison to other currently favored systems. Low molecular weight liquid PEGs can be regarded as protic solvents with aprotic sites of binding constituted. A few inorganic salts and many organic substrates are soluble in low molecular weight liquid PEG, and thus, they have been proposed as solvents for organic reactions [33]. PEGs have been termed “host” solvents [33] due to their ability to form complexes with metal cations.

In this work, we have described a mild and efficient method for the nucleophilic ring-opening of epoxides with sodium azide in PEG, which afforded the corresponding vicinal azidoalcohols in high regioselectivity. As described here, a variety of azidoalcohols can be synthesized under mild and non-toxic conditions.

## EXPERIMENTAL

All  $^1\text{H}$  and  $^{13}\text{C}$ NMR data were recorded on a Bruker Advanced DPX 400 MHz instrument spectrometer using  $\text{Me}_4\text{Si}$  as the internal standard in  $\text{CDCl}_3$ . IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. Epoxides and PEG-300 were purchased from Merck Company in high purity. Products were characterized by comparison of their physical and spectroscopic data with those of known samples [17,23]. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

### General Procedure for the Preparation of 1,2-Azidoalcohols from Epoxides

To a suspension of epoxide (1 mmol) in PEG-300 (2 g),  $\text{NaN}_3$  (2 mmol) was added and the mixture was stirred at 60 °C for the lengths of time shown in Table 1. The progress of reaction was monitored by TLC using  $\text{CCl}_4$ -ether (4:1) as eluent. On completion of reaction, the reaction mixture was poured into water (10 ml) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over anhydrous  $\text{CaCl}_2$ , filtered and concentrated. The desired 1,2-azidoalcohols were obtained in good to excellent isolated yields (80-94%). For styrene oxide, further purification was achieved by preparative TLC or by silica gel column chromatography.

## RESULTS AND DISCUSSION




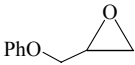
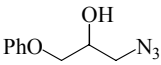
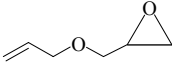
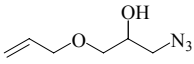
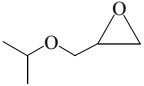
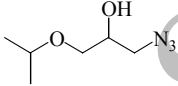
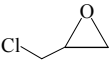
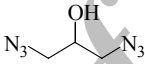

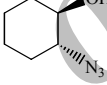
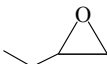
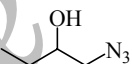
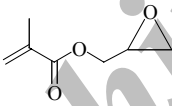
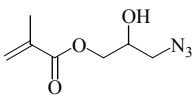
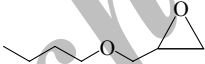
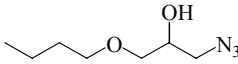
In a typical experiment, phenyl glycidyl ether (1 mmol) and sodium azide (2 mmol) were stirred at room temperature in PEG. TLC analysis of the reaction mixture did not show completion of the reaction after 5 h, but by increasing the temperature to 60 °C, the reaction was completed within 1 h and produced 1-azido-3-phenoxy-2-propanol in quantitative yield (Table 1, entry 2). In order to show the general applicability of the method, we extended it to a variety of epoxides (Table 1) and, in all cases, a very clean reaction was observed. The structure of all the products were settled from their analytical and spectral (IR,  $^1\text{H}$  NMR) data and by direct comparison with authentic samples.

To show the scope of the reaction, we extended it to a variety of epoxides (Scheme 1, Table 1), and in all cases a very clean reaction was observed.

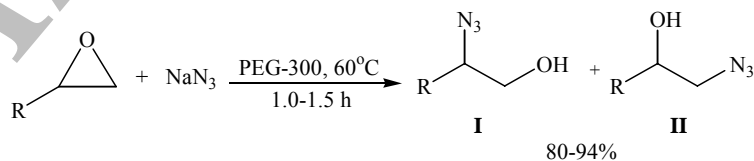
In the present conversion, the role of PEG is to possibly form complexes with cation, much like crown ethers, and these complexes cause the anion to be activated. In addition, polymeric catalyst can probably be facilitated the ring opening of the epoxide by hydrogen bonding as shown in Scheme 2.

The regioselectivity of the ring opening of epoxides is thoroughly dependent on the mechanism of the reaction and particularly on steric and electronic factors. The reaction of styrene oxide with  $\text{NaN}_3$  in PEG was completed after 1.5 h and produced 2-azido-2-phenylalcohol (I) as major product and trace amount of other regioisomer 2-azido-1-phenylalcohol (II). Epoxides carrying electron-withdrawing groups reacted under similar reaction conditions and their corresponding azidoalcohol were produced in excellent yields and regioselectivity. In these cases, with the attack of the azide ion on the less substituted oxirane carbon, the regioselectivity is reversed and the azidoalcohol (II) is obtained. It is shown that, for epoxides carrying electron-donating groups, it is the electronic factor that predominates and the azide ion attacks predominantly at the secondary carbon atom of the epoxide ring, a fact which is reasonably well established [34]. In contrary, in epoxides carrying electron-withdrawing groups, it is the steric factor which predominates and the nucleophilic attack of azide ion is strongly favored on the less substituted carbon of epoxides.

**Table 1.** Reaction of Different Epoxides with NaN<sub>3</sub> Using PEG as the Reaction Medium at 60 °C

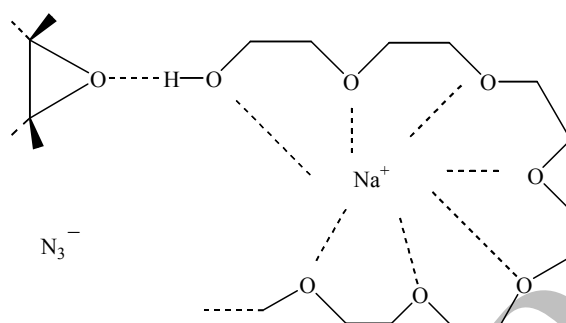
Entry	Substrate	Product(s) <sup>a</sup>	Time (h)	Yields (%) <sup>b</sup>
1		 + 	1.5	85 (90:10) <sup>c</sup>
2			1.0	90
3			1.0	90
4			1.5	87
5			1.5	80
6			1.0	85
7			1.5	80
8			1.5	94
9			1.5	84

<sup>a</sup>Products were identified by comparison of their physical and spectral data with those of authentic samples [17]. <sup>b</sup>Isolated yields. <sup>c</sup>According to GC analysis.

*Scheme 1*

The ring-opening of bicyclic epoxides with NaN<sub>3</sub> furnished the azidoalcohols with *trans*-configuration indicating the conversion to be *anti*-stereoselective. Also, in the case of epichlorohydrin, the diazido alcohol was produced (Table 1, entry 5).

In order to show the merit of our procedure for the synthesis of 1,2-azidoalcohols, we have shown the advantages of present procedure by comparing our results with those previously reported in the literature (Table 2). In conclusion, this method can be applied for conversion of variety of



Scheme 2

**Table 2.** Comparison of Azidolysis of Styrene oxide with Different Methods

Entry	Reagent and reaction conditions	Time (h)	Regioselectivity (%)		Yield (%)	Ref.
			$\alpha$ -attack (I)	$\beta$ -attack (II)		
1 <sup>a</sup>	NaN <sub>3</sub> /PEG/60 °C	1.5	90	10	85	-
2	NaN <sub>3</sub> /DMSO/80 °C	3	99	1	99	[1]
3	NaN <sub>3</sub> /LiClO <sub>4</sub> /CH <sub>3</sub> CN/80 °C	5	82	18	92	[12]
4	NaN <sub>3</sub> /Mg(ClO <sub>4</sub> ) <sub>2</sub> /CH <sub>3</sub> CN/80 °C	2	83	17	78	[12]
5	NaN <sub>3</sub> /NH <sub>4</sub> Cl/MeOH-H <sub>2</sub> O/reflux	5	81	19	90	[12]
6	LiN <sub>3</sub> /CH <sub>3</sub> CN/80 °C	20	79	21	94	[12]
7	TMGA/Hf(OTf) <sub>4</sub> /CH <sub>3</sub> CN/r.t.	42	78	22	65	[15]
8	TMGA/Yb(OTf) <sub>4</sub> /CH <sub>3</sub> CN/r.t.	96	72	28	82	[15]
9	TMGA/Zr(OTf) <sub>4</sub> /CH <sub>3</sub> CN/r.t.	42	74	26	67	[15]
10	TMSN <sub>3</sub> / $\beta$ -CD/H <sub>2</sub> O/37 °C	5	-	-	45	[18]
11	NaN <sub>3</sub> /PTC/H <sub>2</sub> O/r.t.	6	91	9	95	[19]
12	NaN <sub>3</sub> /CeCl <sub>3</sub> /CH <sub>3</sub> CN-H <sub>2</sub> O/reflux	3	88	12	96	[21]
13	Azide exchange resin/EtOH/50 °C	1	-	-	30	[24]
14	HN <sub>3</sub> /Co(salen)/TBME/0 °C	8	8	92	49.6	[26]
15	NaN <sub>3</sub> /(TBA) <sub>4</sub> PfW <sub>11</sub> O <sub>39</sub> .3H <sub>2</sub> O/ CH <sub>3</sub> CN-H <sub>2</sub> O/80 °C	4.5	80	20	85	[27]
16	NaN <sub>3</sub> /H <sub>2</sub> O (pH = 9.5)/30 °C	13	97	3	90	[35]

<sup>a</sup>Present method.

epoxides carrying activated and deactivated groups into their corresponding 1,2-azidoalcohols. The advantages of present protocol, such as environmentally friendly alternative, short reaction times, simplicity in operation, the low cost of reagents, highly regioselectivity, and high yields of products, make this new process an attractive alternative to current methodologies.

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