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An efficient catalyst-free regio- and stereoselective ring-opening of epoxides with phenoxides using polyethylene glycol as the reaction medium☆

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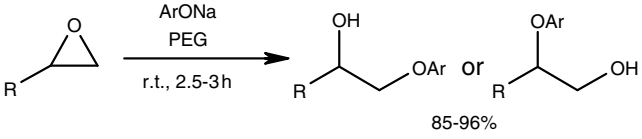
Abstract—A catalyst-free regio- and stereoselective ring-opening of epoxides with phenoxides has been carried out efficiently using polyethylene glycol as the reaction medium to form the corresponding β-aryloxyalcohols in high yields at room temperature.

β-Aryloxyalcohols are key intermediates in the preparation of various pharmaceutically important compounds.[1] A convenient synthetic route to β-aryloxy alcohols involves the ring-opening of epoxides with phenols. However, there are only a few methods reported[2] for such conversions and most of these have been conducted under alkaline conditions at high temperature. Epoxides have also recently been opened with phenoxide ions using $Ce(OTf)_4$ in micellar media[3a] and utilizing β-cyclodextrin in water.[3b] However, the first method requires a costly reagent while the second method suffers from long reaction times (8 h) at 60 °C. For the ring-opening of epoxides with polymer supported phenoxide anions, the preparation of the nucleophiles is a tedious task and the conversion is conducted at 50 °C.[3c] In every case, a catalyst has been used.

In continuation of our work[4] on the development of useful synthetic methodologies, we have observed that a catalyst-free ring-opening of epoxides with phenoxide ions can be carried out efficiently using polyethylene glycol (PEG-400)[5] as the reaction medium (Scheme 1).



Scheme 1.

Various epoxides were converted into the corresponding β-aryloxyalcohols on treatment with sodium phenoxides in PEG (Table 1). The reactions were carried out at room temperature and were completed within 2.5–3 h. The conversion time for glycidal ethers having substituted rings was 3 h and 2.5 h for the other epoxides. The products were formed in high yields (85–96%). 2-Phenyl, 2-alkyl and bicyclic epoxides underwent the conversion smoothly. 2-Alkylepoxides with an aryloxy group containing electron-donating as well as electron-withdrawing groups in the aryl ring furnished the products with equal ease.

The conversion of epoxides into β-aryloxyalcohols occurred with high regio- and stereoselectivity. 2-Alkyl epoxides gave products by nucleophilic attack of the phenoxide ions at the terminal position while styrene oxide formed the product by attack at the benzylic position. A careful examination of the ^1H NMR spectra of the crude products clearly indicated the formation of only one regioisomer in each case (except in entries 18 and 19) and no other product could be detected. The ^1H NMR and mass spectral data of the pure compounds

Keywords: Epoxide; β-Aryloxyalcohols; PEG-400; Regio- and stereoselectivity; Catalyst-free conversion.

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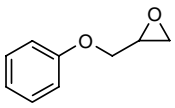
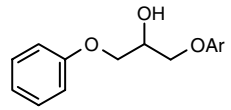
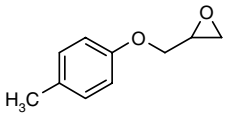
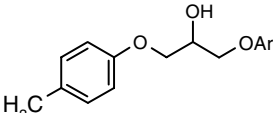
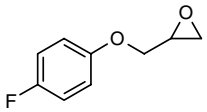
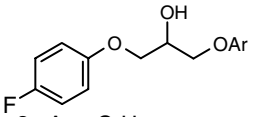
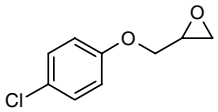
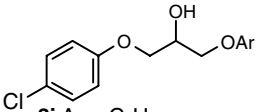
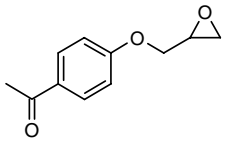
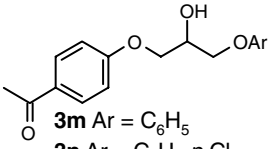
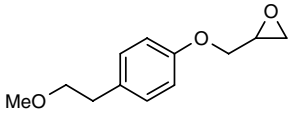
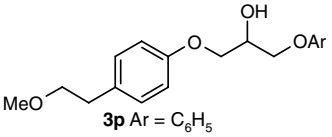
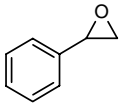
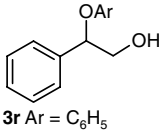
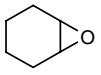
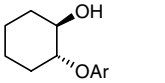
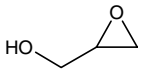
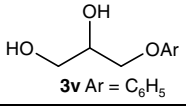
Table 1. Ring-opening of epoxides with ArONa using PEG[a]

Entry	Epoxide **1**	Phenoxide **2**	Product **3**	Isolated yield[b] (%)
1		C_6H_5ONa	 **3a** Ar = C_6H_5 **3b** Ar = C_6H_4-*p*-Cl **3c** Ar = C_6H_4-*p*-OMe	92
2		*p*-Cl–C_6H_4ONa		88
3		*p*-OMe–C_6H_4ONa		90
4		C_6H_5ONa	 **3d** Ar = C_6H_5 **3e** Ar = C_6H_4-*p*-Cl **3f** Ar = C_6H_4-*p*-OMe	94
5		*p*-Cl–C_6H_4ONa		89
6		*p*-OMe–C_6H_4ONa		91
7		C_6H_5ONa	 **3g** Ar = C_6H_5 **3h** Ar = C_6H_4-*p*-Cl **3i** Ar = C_6H_4-*p*-OMe	93
8		*p*-Cl–C_6H_4ONa		87
9		*p*-OMe–C_6H_4ONa		86
10		C_6H_5ONa	 **3j** Ar = C_6H_5 **3k** Ar = C_6H_4-*p*-Cl **3l** Ar = C_6H_4-*p*-OMe	89
11		*p*-Cl–C_6H_4ONa		87
12		*p*-OMe–C_6H_4ONa		86
13		C_6H_5ONa	 **3m** Ar = C_6H_5 **3n** Ar = C_6H_4-*p*-Cl **3o** Ar = C_6H_4-*p*-OMe	89
14		*p*-Cl–C_6H_4ONa		86
15		*p*-OMe–C_6H_4ONa		87
16		C_6H_5ONa	 **3p** Ar = C_6H_5 **3q** Ar = C_6H_4-*p*-Cl	88
17		*p*-Cl–C_6H_4ONa		85
18		C_6H_5ONa	 **3r** Ar = C_6H_5 **3s** Ar = C_6H_4-*p*-Cl	90(6)
19		*p*-Cl–C_6H_4ONa		86(7)
20		C_6H_5ONa	 **3t** Ar = C_6H_5 **3u** Ar = C_6H_4-*p*-Cl	96
21		*p*-Cl–C_6H_4ONa		94
22		C_6H_5ONa	 **3v** Ar = C_6H_5	87

[a] The structures of the products were established from their spectral (^{1}H NMR and MS) data.
[b] Yield reported in parentheses is for other regioisomer.

obtained by purification of the crude products established their structures. In the ^{1}H NMR spectra of β-aryloxyalcohols derived from 2-alkyl epoxides, the $\rangle CHOH$ and $-CH_2(OAr)$ protons resonated at ca δ 4.3 and 4.0, respectively. On the other hand, in the ^{1}H NMR spectra of β-aryloxyalcohols produced from styrene oxide, the $\rangle CH(OAr)$ and $-CH_2OH$ protons appeared at ca. δ 5.2 and 3.7, respectively. These values clearly established the regiochemistry of the β-aryloxyalcohols obtained from 2-alkyl epoxides and styrene oxide. The ring-opening of bicyclic epoxides took place with *anti*-selectivity to furnish the products with the trans-configuration. In the ^{1}H NMR spectra of the products, the coupling constants of the ring protons adjacent to the –OAr and –OH groups provided evidence for this stereochemical assignment. For example, the *J* values of these two protons for **3u** are 9.5, 9.0 and 4.0 Hz and 9.2, 9.0 and 4.0 Hz, suggesting the trans-configuration of the compound.

Polyethylene glycol (PEG-400) has been used here for the preparation of β-aryloxy alcohols from epoxides.[6] It is an eco-friendly, biologically acceptable, inexpensive polymer. However, its applications as a reaction medium in organic syntheses are still limited. In the present conversion, the role of PEG is possibly to activate the epoxide ring by hydrogen bonding thus facilitating the nucleophile attack by the phenoxide ion. The PEG was recovered from the reaction mixture and was recycled without loss of activity.

The ring-opening of epoxides with phenoxides was also carried out using diethyl ether, methanol and ethanol in the absence of any catalyst. However, with the first solvent no conversion occurred under the present experimental conditions, while with the other two solvents the reaction afforded complex mixtures which were difficult to purify.

In conclusion, we have described a novel and efficient protocol for conversion of epoxides into β-aryloxyalcohols using PEG as the reaction medium at room temperature.

Acknowledgement

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6. *General experimental procedure*: To the suspension of an epoxide (1 mmol) in PEG (2 g), the phenoxide (1.1 mmol) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC. After completion, the mixture was poured onto water and extracted with EtOAc (3×10 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, ethyl acetate–hexane 2:8) to obtain the pure β-aryloxyalcohol. The PEG was recovered from the water and recycled without affecting the yields of the products.