Catalyst-Free Highly Regio- and Stereoselective Ring Opening of Epoxides and Aziridines with Sodium Azide Using Poly(ethylene glycol) as an Efficient Reaction Medium[1]

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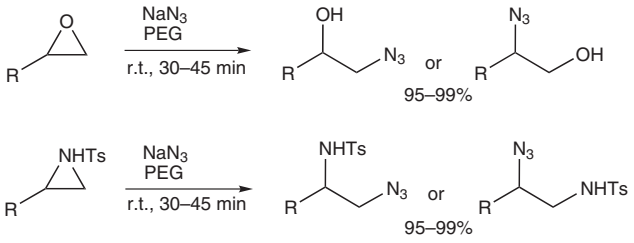
Abstract: Ring opening of epoxides and aziridines has readily been carried out at room temperature using poly(ethylene glycol) (PEG-400) as the efficient reaction medium to form the corresponding 2-azido alcohols and 2-azido amines, respectively, in excellent yields (95–99%) within 30–45 minutes and with high regio- and streoselectivity.

Key words: epoxide, aziridine, PEG-400, 2-azido alcohol, 2-azido amine



Scheme 1

2-Azido alcohols are valuable precursors for 2-amino alcohols which are present in various natural products and different bioactive compounds.[2] They are also useful for the synthesis of amino sugars and carbocyclic nucleosides.[3] 2-Azido amines are important as intermediates for the preparation of vicinal diamines which are medicinally valuable[4] and also have different applications in organic syntheses.[5] The useful synthetic route to 2-azido alcohols and 2-azido amines involves ring opening of epoxides and aziridines, respectively, with azide anion. The classical protocol for the preparation of azidohydrins using NaN_3 and NH_4Cl requires a longer reaction time (12–48 h) and forms side products.[2a,b] The modified methods for azidolysis of epoxides[6] and aziridines[6f,7] use a combination of NaN_3 or $TMSN_3$ and a Lewis acid or a transition-metal complex. Although these methods are valuable for the preparation of 2-azido alcohols and 2-azido amines, many are associated with drawbacks, such as longer reaction times, high temperature, unsatisfactory yields and poor regioselectivity. Thus, an improved protocol for the preparation of these compounds is essential.

In continuation of our work[8] on the development of useful synthetic methodologies we have recently observed that azidolysis of epoxides and aziridines can efficiently be carried out with NaN_3 in poly(ethylene glycol) (PEG-400) (Scheme 1).

Several epoxides and *N*-tosylaziridines underwent ring cleavage readily with NaN_3 in PEG at room temperature to form the corresponding azido alcohols and *N*-tosylazido amines respectively (Table 1). No additional catalyst was required. The products were formed in excellent yields and no side products were detected. The conversion was complete within a short period of time. Both epoxides and azidridines afforded the products with equal ease.

The ring opening of epoxides and aziridines took place with high regio- and stereoselectivity. 2-Alkylepoxides and 2-alkyl-*N*-tosylaziridines yielded the products formed by opening at the terminal position while 2-phenylepoxide (styrene oxide) and 2-phenyl-*N*-tosylaziridine afforded the products formed by cleavage at the benzylic position. The structures of 2-azido alcohols and 2-azido-*N*-tosyl amines were established from their spectral (IR, ^{1}H NMR and MS) and analytical data.

The ring opening of bicyclic epoxides and aziridines with NaN_3 afforded the products with *trans*-configuration indicating the conversion to be *anti*-stereoselective. In the ^{1}H NMR spectra, the ring protons of **2j** appeared at δ = 3.35 (1 H, ddd, *J* = 9.8, 9.2, 4.2 Hz) (C*H*OH) and 3.12 (1 H, ddd, *J* = 9.5, 9.2, 4.2 Hz) (CHN_3), while those of **2p** at δ = 3.73 (1 H, m) (C*H*NHTs) and 3.34 (1 H, ddd, *J* = 9.5, 9.2, 4.1 Hz) (CHN_3).

Poly(ethylene glycol) (PEG-400)[9] has been used in the present conversion as an efficient reaction medium. This is a biologically acceptable polymer and is inexpensive and eco-friendly. However, its applications as a reaction medium in organic syntheses have not yet been fully explored. In absence of PEG it was found that azidolysis of epoxides and aziridines did not take place. The role of PEG is possibly to activate these compounds through hydrogen bonding. The PEG was recovered from the reaction mixture and was reused without loss of activity.

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Table 1 Ring Opening of Epoxides and Aziridines with NaN_3 in PEG

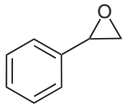
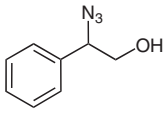
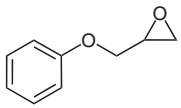
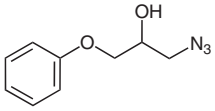
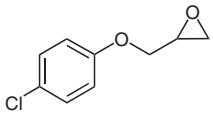
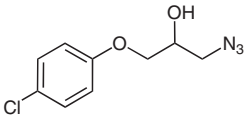
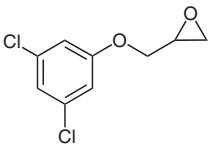
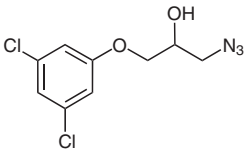
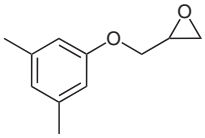
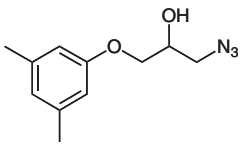
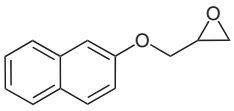
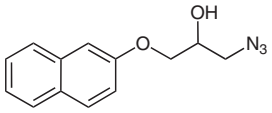
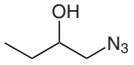
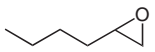
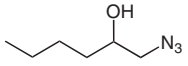
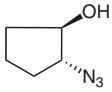
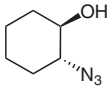
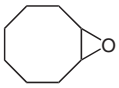
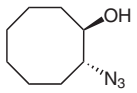
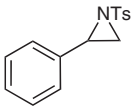
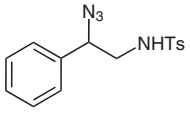
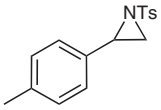
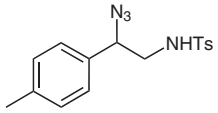
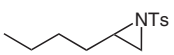
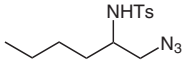
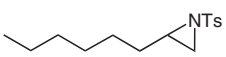
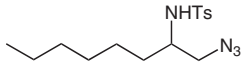
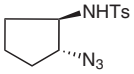
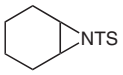
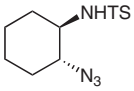
Entry	Epoxide/Aziridine **1**	Product **2**	Time (min)	Isolated yield (%)[a]	Ref.
a			35	98	6f
b			40	96	6f
c			45	95	6g
d			40	95	6f
e			40	96	6f
f			45	95	6f
g			30	97	6f
h			45	95	6f
i			35	99	6f
j			30	98	6f
k			40	95	6f
l			40	99	6f
m			45	98	6f
n			45	96	6f
o			40	95	7e

Table 1 Ring Opening of Epoxides and Aziridines with NaN_3 in PEG (continued)

Entry	Epoxide/Aziridine **1**	Product **2**	Time (min)	Isolated yield (%)[a]	Ref.
p			45	96	7e
q			40	99	6f

[a] The structures of the products were established from their spectral (IR, ^1H NMR and MS) and analytical data.

In conclusion, we have developed a simple and efficient method for azidolysis of epoxides and aziridines with NaN_3 using PEG at room temperature. The mildness and eco-friendly nature of the conversion, shorter reaction times, impressive yields and excellent regio- and stereoselectivity are the considerable advantages to make the present method superior to the existing methods for the preparation of 2-azido alcohols and 2-azido amines.

2-Azido Alcohols or Amines; General Procedure

To a stirred suspension of an epoxide (or *N*-tosyl aziridine) (1 mmol) in PEG-400 (2 g), was added NaN_3 (78 mg, 1.2 mmol) and the mixture was stirred at r.t. The reaction was monitored by TLC. After completion, the mixture was poured onto H_2O (10 mL) and was extracted with EtOAc (2 × 10 mL). The solvent was removed and the crude product was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure azidohydrin (or *N*-tosyl-azido amine) (Table 1). The PEG was recovered from the aqueous layer and was reused without loss of activity.

Acknowledgment

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