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Polyethylene glycol (PEG) as an efficient recyclable medium for the synthesis of β-amino sulfides

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Abstract—Aziridines undergo ring opening readily with various thiols in the presence of polyethylene glycol (PEG) to afford the corresponding β-amino sulfides in high yields with good regioselectivity under mild and neutral conditions. The PEG can be recovered and reused.

The chemistry of aziridines continues to attract the attention of the synthetic community.[1] In fact, this interest is driven by the useful properties of aziridines centred around their ring-opening transformations.[2] The reactivity of aziridines as carbon electrophiles makes them versatile nitrogen containing building blocks for the synthesis of biologically important compounds.[3] The cleavage of tosylaziridines with thiols is interesting because the resultant β-amino sulfides are important for the synthesis of many biologically interesting molecules such as amino acids,[4] heterocycles[5] and alkaloids.[6] The simple and most straightforward route to β-amino sulfides involves the regioselective ring opening of tosylaziridines with thiols using acid or base catalysts.[7] Lewis acids such as boron trifluoride etherate and zinc chloride as well as Bronsted acids-like trifluoromethanesulfonic acid have been employed as acid catalysts.[7,8] However, many of these methods suffer from the fact that a Lewis acid or strong base was necessary to effect the reaction.[9] Moreover, varied reaction conditions are needed for various aziridines because of the different reactivity of substrates and reagents, as well as the complexity of the structure of aziridines.[10–12] Furthermore, these reagents cannot be recovered and recycled because they decompose or are deactivated under quenching conditions. The development of environmentally benign and clean synthetic procedures is important in organic synthesis and organic reactions without the use of harmful organic solvents are of great interest in organic synthesis.[13] Recently, attention has been drawn to the development of environmentally benign solvents such as ionic liquids,[14] water[15] and polyethylene glycol.[16] The value of a new solvent medium primarily depends on its environmental impact, the ease with which it can be recycled, nonflammability and high polarity for solubilization. Moreover, in performing the majority of organic transformations, solvents play an important role in mixing the ingredients to make the system homogeneous so allowing molecular interactions to be more efficient. Initially, our efforts directed towards the cleavage of tosylaziridines in ethanol and ethylene glycol with thiophenol. In this direction, we used N-substituted aziridines (Table 1, entry 3, 6, 7 and 16) for cleavage with thiophenol in ethanol and ethylene glycol. The desired products are not obtained after longer reaction times and the starting materials were recovered.

Polyethylene glycol (PEG) a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tool for diagnostics, has hitherto not been widely used as a solvent medium but has been used as a support for various transformations.[16,17] More recently, we demonstrated PEG as an efficient recyclable reaction medium.[18] With this background, we wish to highlight our results on the application of PEG as a recyclable reaction medium in the regioselective ring-opening reaction of tosylaziridines with various thiols. To the best of our knowledge, this is the first report on the use of PEG as a reaction medium for the cleavage of tosylaziridines with various thiols resulting in the

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Table 1. PEG-mediated ring opening of tosylaziridines with thiophenols

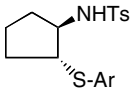
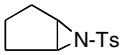
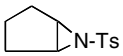
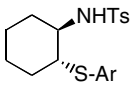
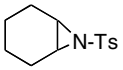
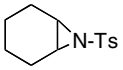
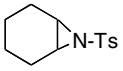
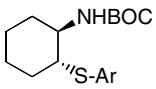
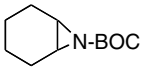
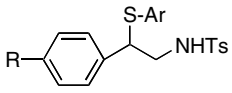
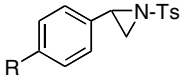
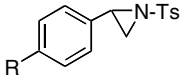
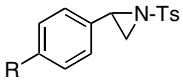
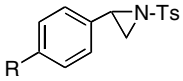
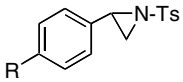
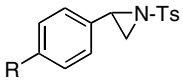
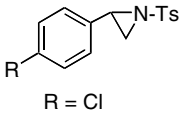
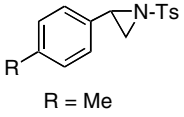
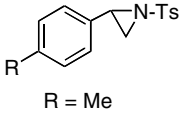
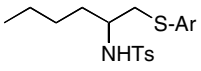
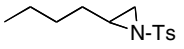
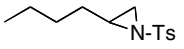
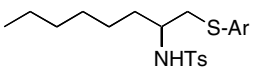
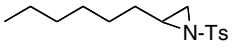
Entry	Aziridine	Product	Time (h)	Yield[a] (%)
				
1		**2a** Ar = Ph	1.0	95
2		**2b** Ar = C_6H_4-*p*-Cl	1.2	95
				
3		**2c** Ar = Ph	1.0	92
4		**2d** Ar = C_6H_4-*p*-Cl	1.5	90
5		**2e** Ar = C_6H_4-*p*-OMe	1.3	95
				
6		**2f** Ar = Ph	2.0	90
				
7		**2g** Ar = Ph	1.5	85
8		**2h** Ar = C_6H_4-*p*-Cl	1.5	88
9		**2i** Ar = C_6H_4-*p*-OMe	1.5	85
10		**2j** Ar = 2-naphthyl	2.0	85
11		**2k** Ar = Ph	1.3	90
12		**2l** Ar = C_6H_4-*p*-Br	1.3	85

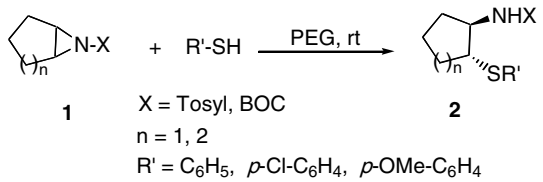
Table 1 (*continued*)

Entry	Aziridine	Product	Time (h)	Yield[a] (%)
13	 R = Cl	**2m** Ar = C_6H_4-*p*-OMe	1.5	85
14	 R = Me	**2n** Ar = Ph	1.3	85
15	 R = Me	**2o** Ar = C_6H_4-*p*-OMe	1.5	85
				
16		**3p** Ar = Ph	2.0	85
17		**3q** Ar = C_6H_4-*p*-Cl	2.0	88
				
18		**3r** Ar = C_6H_4-*p*-Cl	2.0	85

[a] Isolated yields.

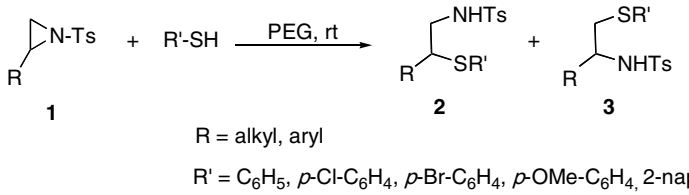
formation of corresponding β-amino sulfides. Accordingly, treatment of tosylaziridine with thiophenol in the presence of PEG 400 (Table 1, entry 1) at room temperature for 1 h, resulted in the generation of β-amino sulfide in 95% yield (Scheme 1).

In a similar fashion, other tosylaziridines reacted smoothly with various thiols to afford the corresponding β-amino sulfides in high yields (Schemes 1 and 2). The reaction proceeds efficiently at room temperature without the use of any further acid or base catalyst and goes to completion in a short time (Table 1).[19] Smaller quantities of the other regioisomer were obtained for unsymmetrical aziridines (5–15%). 2-Aryl substituted aziridines were obtained with the opposite regioselectivity in comparison to 2-alkyl aziridines. In the case of cycloalkyl aziridines, the stereochemistry of the ring cleaved product **2c** was found to be *trans* from the coupling constant values of the ring hydrogen at δ: 2.89 (ddd, 1H, $J = 4.1$, 9.4, 9.8 Hz, CHS) in the ^{1}H NMR spectrum and the peak at δ: 2.98 (ddd, 1H, $J = 4.0$, 9.2, 9.6 Hz) for CHN showed a similar splitting. Bicyclic *N*-tosylaziridines cleaved smoothly with thiols to afford the corresponding β-amino sulfides.



Scheme 1.

The activity of polyethylene glycol (PEG) for the cleavage of tosylaziridines was established by the fact that there was no reaction in the absence of PEG. The role



Scheme 2.

of PEG appears to be not only to activate the tosylaziridine by hydrogen bonding but also to favour α-attack at the tosylaziridine resulting in high regioselectivity.

In summary, PEG has been found to be a useful, cost-effective, environmental friendly and efficient alternative for the regioselective ring opening reactions of tosylaziridines with thiols under mild conditions. Further applications of PEG as a recyclable reaction medium for various organic transformations are under investigation in our laboratory.

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19. General procedure: To a stirred suspension of an aziridine (1 mmol) in PEG 400 (2 g), the thiol (1 mmol) was added and the resulting mixture was stirred at ambient temperature until complete consumption of the aziridine (monitored by TLC). The reaction mixture was extracted with dry ether, the solvent was removed under reduced pressure and the resulting crude product was purified by silica column chromatography using EtOAc and hexane (2:8) as an eluent to obtain the pure product in high yield (Table 1). The recovered PEG was reused for a number of cycles with negligible loss of its activity. Spectral data for the compound **2c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22–1.45 (m, 4H), 1.50–1.74 (m, 2H), 1.94–2.05 (m, 1H), 2.23–2.32 (m, 1H), 2.44 (s, 3H), 2.89 (ddd, 1H, $J = 4.1$, 9.4, 9.8 Hz), 2.98 (ddd, 1H, $J = 4.0$, 9.2, 9.6 Hz), 5.10 (br s, NH, 1H), 7.25–7.40 (m, 7H), 7.77 (d, 2H, $J = 7.8$ Hz); EIMS: $m/z = 361$ [$M^{+\cdot}$].