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Tetrahedron 61 (2005) 8746–8751
Tetrahedron

Ring opening of 2-(bromomethyl)-1-sulfonylaziridines towards 1,3-heteroatom substituted 2-aminopropane derivatives

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Received 12 April 2005; revised 10 June 2005; accepted 13 June 2005

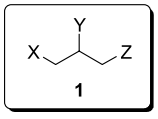
Available online 25 July 2005

Abstract—1,3-Heteroatom substituted 2-aminopropane derivatives have been prepared from 2-(bromomethyl)-1-sulfonylaziridines for the first time using sodium azide or different potassium phenoxides in water in the presence of silica gel. The applicability of 1-arenesulfonyl-2-(bromomethyl)aziridines for the synthesis of functionalized sulfonamides has also been demonstrated towards different 1,3-dialkoxy-2-(tosylamino)propanes and 1,3-dialkylthio-2-(tosylamino)propanes upon treatment with the appropriate sodium alkoxide or sodium alkylthiolate in the corresponding alcohol or in methanol, respectively.

1. Introduction

A key element present in a whole range of physiologically active natural products and their synthetic analogues comprises a 1,2,3-heteroatom substituted three-carbon unit **1** (Fig. 1; X, Y, Z=O, N, S). Many drugs accommodate such a moiety in their structure, hence the interest in the development of new entries towards compounds bearing a 1,2,3-trisubstituted propane skeleton. Aryloxypropanolamines (X=OAr, Y=OH, Z=NHR, Fig. 1) are used as β-blockers for the treatment of hypertension, angina pectoris, glaucoma, obesity, and arrhythmia,[1] but also as antidiabetic,[2] antihypertensive and vasorelaxing agents.[3] Sphingolipids (X=Z=OH, Y=NH_2, Fig. 1), membrane compounds of essentially all eukaryotic cells, comprise a 2-amino-1,3-dihydroxypropane subunit as part of a longer (unsaturated) carbon chain.[4] Also 2-[(arylmethyl)amino]-propanediols (X=Z=OH, Y=NHR, Fig. 1) or shortly AMAP's have been reported as antitumor DNA intercalators with promising prospects in medicine.[5] Moreover, compounds containing a 2-amino-1,3-propanediol subunit are important constituents of broad-spectrum antibiotics such as thiamphenicol and florfenicol.[6] Finally, also some sulfur containing analogues are known for their biological activity, especially in agriculture as pest control agents (acaricides and insecticides).[7–9]

In recent years, the demand for environmentally benign processes has become an important element in the design of new synthetic methodologies. From an ecological point of view, organic reactions in aqueous media constitute an attractive alternative for the use of classical solvents. The present report describes an efficient approach towards 1,3-difunctionalized 2-aminopropane derivatives in water as a solvent in the presence of silica gel, starting from 2-(bromomethyl)-1-sulfonylaziridines, a versatile but fairly unknown class of substrates in organic synthesis. The molecular diversity of these aziridines originates from the presence of two electrophilic moieties, namely two carbon atoms of the aziridine ring on the one hand and the halogenated carbon atom on the other hand, which enables a variety of different synthetic transformations towards cyclic and acyclic target compounds. It has already been demonstrated in the literature that the closely related 1-tosyl-2-(tosyloxymethyl)aziridines suffer from ring opening upon treatment with organocuprate reagents by attack at the least hindered carbon atom of the aziridine moiety, immediately followed by ring closure by displacement of the tosylate in a straightforward manner.[10] Also for *N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine, an aziridine with a different electron-withdrawing substituent at nitrogen, comparable results were published.[11]



X, Y, Z = heteroatoms
e.g. O, N, S

Figure 1.

Keywords: 2-(Bromomethyl)aziridines; 2-Aminopropanes; Water; Ring opening; Nucleophiles.
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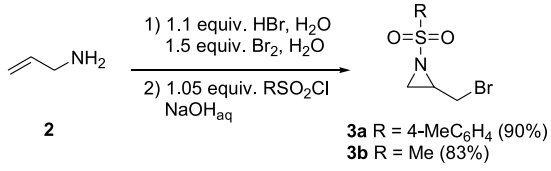
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.06.036

1-Arenesulfonyl-2-(bromomethyl)aziridines can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon upon treatment with lithium cuprate reagents towards α-branched *N*-tosylamides.[12] In the present report, the 2-aminopropane dication synthon equivalency of 2-(bromomethyl)-1-sulfonylaziridines will be further evaluated upon treatment with heteroatom centered nucleophiles. In the literature, a limited number of reports dealing with ring opening reactions of 2-(alkoxymethyl)aziridines and 2-(hydroxymethyl)aziridines towards 2-amino-1,3-dioxypropanes have been reported up to now.[13] Only one example of the conversion of an aziridine into a 1,3-dialkylthio-2-aminopropane derivative has been published, in which *N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine was treated with 3 equiv of lithium thiophenoxide in THF at −42 °C, giving rise to 2-(diphenylphosphinamido)-1,3-bis(thiophenyl)propane in 70% yield.[11]

2. Results and discussion

2-(Bromomethyl)-1-sulfonylaziridines **3** are very easily accessible, and thus very attractive starting materials in organic synthesis.[14] 2-(Bromomethyl)-1-(4-methylbenzenesulfonyl)aziridine **3a** and 2-(bromomethyl)-1-(methanesulfonyl)aziridine **3b** were prepared from allylamine **2** in a very efficient two-step procedure adapted from the literature (Scheme 1).[15]



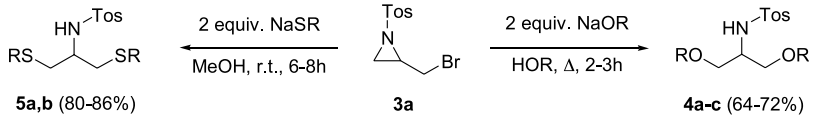
Scheme 1.

When 2-(bromomethyl)-1-tosylaziridine **3a** was treated with 2 equiv of an alkoxide or an alkylthiolate, the corresponding ring opened 1,3-dialkoxy- or 1,3-dialkylthiopropanamines **4** and **5** were isolated in high yield (Scheme 2). *N*-(2-Methoxy-1-(methoxymethyl)ethyl)-4-methylbenzenesulfonamide **4a** and *N*-(2-ethoxy-1-(ethoxymethyl)ethyl)-4-methylbenzenesulfonamide **4b** were obtained upon treatment of aziridine **3a** with 2 equiv of sodium methoxide, respectively, sodium ethoxide, in the corresponding alcohol (2 N) after reflux for 3 h (Table 1). Similarly, *N*-(2-(2-propenyloxy)-1-((2-propenyloxy)methyl)ethyl)-4-methylbenzenesulfonamide **4c** was prepared in 64% yield utilizing 2 equiv of sodium allyloxide in refluxing allyl alcohol (1 N). The sulfur analogues **5a**,**b** of the former dialkoxypropane derivatives were synthesized by treatment of 2-(bromomethyl)-1-tosylaziridine **3a** with 2 equiv of sodium isopropylthiolate or sodium allylthiolate in methanol (0.3 N) at room temperature for 6–8 h, affording *N*-(2-((1-methylethyl)thio)-1-(((1-methylethyl)thio)methyl)ethyl)-4-methylbenzenesulfonamide **5a** and *N*-(2-(2-propenylthio)-1-((2-propenylthio)methyl)ethyl)-4-methylbenzenesulfonamide **5b** in high yields (Table 1).

Very recently, a new protocol for the synthesis of 1-tosylaziridines in water as a solvent in the presence of silica has been reported, exploiting the adsorptive nature of silica gel.[16] Also the ring opening of 1-tosyl-2-hexylaziridine with sodium azide in water in the presence of silica was mentioned in the same reference. This reaction did not proceed in the absence of silica. The applicability of this approach using 2-(bromomethyl)-1-tosylaziridines **3**, however, has not been investigated up to now.

An attempt to prepare 2-(azidomethyl)-1-tosylaziridine **6** selectively by reaction of 1-tosyl-2-bromomethyl)aziridine **3a** with 1 equiv of sodium azide in water failed, since this aziridine **6** was further consumed as a substrate in a ring opening reaction with azide, probably due to activation of the aziridine ring by silica. In this way, a mixture of unreacted 2-(bromomethyl)-1-tosylaziridine **3a** (44%), 2-(azidomethyl)-1-tosylaziridine **6** (25%) and tosylamide **7a** (31%) was obtained (Scheme 3).

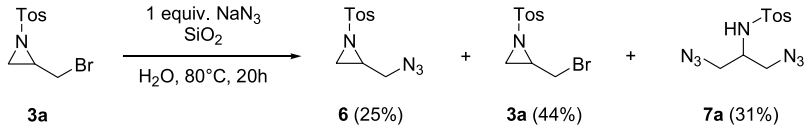
Consequently, the diazido compounds **7a**–**b** were obtained very easily and in high yields after treatment of 2-(bromomethyl)aziridines **3** with 2 equiv of sodium azide in water in the presence of silica (0.5 g for 1 mmol of substrate) (Caution: the azido compounds should be handled with care, utilizing a safety shield). After heating for 16–20 h at 80 °C, *N*-(2-azido-1-(azidomethyl)ethyl)-4-methylbenzenesulfonamide **7a** and *N*-(2-azido-1-(azidomethyl)ethyl)-4-methanesulfonamide **7b** were isolated as the sole reaction products (Scheme 4).



Scheme 2.

Table 1. Ring opening reactions of 2-(bromomethyl)-1-tosylaziridine **3a** with alkoxides and alkylthiolates

Entry	Conditions	Product	R	Yield (%)
1	2 equiv NaOMe/MeOH (2 N), △, 3 h	**4a**	Me	72
2	2 equiv NaOEt/EtOH (2 N), △, 3 h	**4b**	Et	77
3	2 equiv $NaOCH_2CH{=}CH_2$/allyl alcohol (1 N), △, 2 h	**4c**	$CH_2CH{=}CH_2$	64
4	2 equiv NaSiPr/MeOH (0.3 N), rt, 6 h	**5a**	*i*Pr	80
5	2 equiv $NaSCH_2CH{=}CH_2$/MeOH (0.3 N), rt, 8 h	**5b**	$CH_2CH{=}CH_2$	86

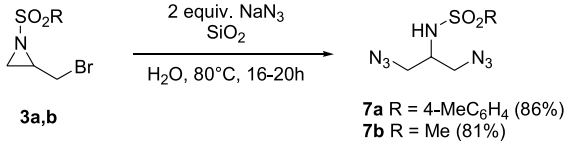


3a — 6 (25%) — 3a (44%) — 7a (31%)

Scheme 3.

A stepwise approach based on this methodology enables the synthesis of 2-aminopropane derivatives with a different substitution pattern at C1 and C3. 2-(Bromomethyl)-1-tosylaziridine **3a** was converted into the corresponding 2-(methoxymethyl)aziridine **8** upon reaction with 1.05 equiv of NaOMe in MeOH (2 N) after stirring at room temperature for 5 h (Scheme 5). This reaction proceeds through ring opening and subsequent ring closure of the resulting β-bromosulfonamide. Treatment of the latter aziridine **8** with 2 equiv of sodium azide in water in the presence of silica gel afforded *N*-(2-azido-1-(methoxymethyl)ethyl)-4-methylbenzenesulfonamide **9** after heating for 20 h at 80 °C (Scheme 5).

Furthermore, also other water-compatible nucleophiles besides sodium azide have been evaluated using this water–silica based methodology. Oxygen-centered nucleophiles such as potassium phenoxides were applied successfully towards 1,3-diaryloxy-2-aminopropane derivatives **10** in good yields upon treatment of 2-(bromomethyl)aziridines **3** with 2.2 equiv of a substituted phenol in water in the presence of silica (0.5 g for 1 mmol of substrate) and 5 equiv of potassium carbonate after heating for 16–20 h at 80 °C (Scheme 6). When the same reactions were performed with less then 5 equiv of K_2CO_3 (e.g. 2 equiv), the intermediate 2-(aryloxymethyl)aziridines were also isolated (25%), besides the desired 1,3-diaryloxy-2-aminopropane derivatives **10** (75%). The use of phenoxides clearly extends the scope of the presented water–silica based methodology towards a large variety of possible target compounds, and water can be used as a suitable green alternative for other solvents in ring opening reactions of 2-(bromomethyl)-1-sulfonylaziridines with heteroatom centered nucleophiles.



3a,b

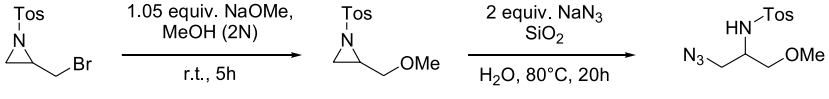
7a R = 4-MeC$_6$H$_4$ (86%)
7b R = Me (81%)

Scheme 4.

In summary, the versatility of 2-(bromomethyl)-1-sulfonylaziridines **3** as substrates in organic synthesis has been demonstrated by the development of a straightforward approach towards different 1,3-heteroatom substituted 2-aminopropane derivatives using water as a solvent in the presence of silica gel. In this way, monoazido- and diazidopropane derivatives have been synthesized using sodium azide in water, as well as 1,3-diaryloxypropane sulfonamides by means of different potassium phenoxides as reagents. The potential of 2-(bromomethyl)-1-sulfonylaziridines has been further demonstrated by the synthesis of 1,3-dialkoxy-2-(tosylamino)propanes and 1,3-dialkylthio-2-(tosylamino)propanes upon treatment with the appropriate sodium alkoxide or sodium alkylthiolate. As plentiful methods are available for *N*-detosylation of sulfonamides, the presented methodology offers a suitable access to the synthesis of the corresponding amines.

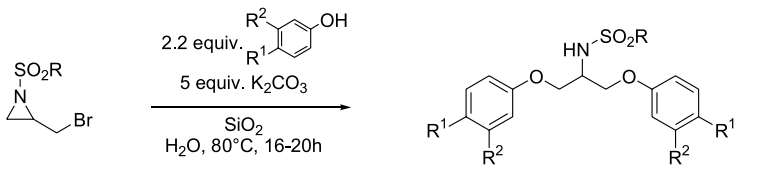
3. Experimental

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or AGILENT 1100, 70 eV. IR spectra were measured with a



3a — 8 (52%) — 9 (74%)

Scheme 5.



3a,b

10a R = Me, R^1 = H, R^2 = Cl (81%)
10b R = 4-MeC$_6$H$_4$, R^1 = F, R^2 = H (84%)
10c R = 4-MeC$_6$H$_4$, R^1 = OMe, R^2 = H (72%)

Scheme 6.

Spectrum One FT-IR spectrophotometer. Dichloromethane was distilled over calcium hydride, other solvents were used as received from the supplier.

3.1. Synthesis of 1,3-dialkoxy-2-(tosylamino)propanes 4a–c

As a representative example, the synthesis of *N*-(2-ethoxy-1-(ethoxymethyl)ethyl)-4-methylbenzenesulfonamide **4b** is described. To 2-(bromomethyl)-1-(4-methylbenzenesulfonyl)aziridine **3a** (0.29 g, 1 mmol) was added sodium methoxide in methanol (1.0 mL, 2 equiv, 2 N in MeOH), and the resulting mixture was heated under reflux for 4 h. The reaction mixture was poured into water (20 mL), extracted with CH_2Cl_2 (3×10 mL) and dried (K_2CO_3). Filtration of the drying agent and evaporation of the solvent afforded *N*-(2-ethoxy-1-(ethoxymethyl)ethyl)-4-methylbenzenesulfonamide **4b** (0.23 g, 77%). These compounds were purified by means of column chromatography: (EtOAc/Hexane 1:4). Purity (NMR) >95%.

3.1.1. *N*-(2-Methoxy-1-(methoxymethyl)ethyl)-4-methylbenzenesulfonamide 4a. Yie1d 72%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3Ar); 3.21 (6H, s, 2×CH_3O); 3.23–3.38 (4H, m, 2×CH_2O); 3.40–3.47 (1H, m, CHN); 5.35 (1H, s(broad), NH); 7.30 and 7.78 (2×2H, 2×d, J=8.3 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.49 (CH_3Ar); 52.36 (CHN); 58.87 (2×CH_3O); 71.18 (2×CH_2O); 127.08 and 129.58 (2×HC_{ortho} and 2×HC_{meta}); 137.93 (CH_3C); 143.30 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3270 (NH), 1609, 1452, 1330, 1165. MS (70 eV) *m/z* (%): 273 (M^+, 1); 229 (81); 171 (31); 155 (44); 139 (81); 91 (100); 73 (67); 65 (27); 45 (60). Anal. Calcd for $C_{12}H_{19}NO_4S$ (%): C 52.73; H 7.01; N 5.12. Found (%): C 52.90; H 7.19; N 4.90.

3.1.2. *N*-(2-Ethoxy-1-(ethoxymethyl)ethyl)-4-methylbenzenesulfonamide 4b. Yie1d 77%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11 (6H, t, J=7.3 Hz, 2×CH_3CH_2); 2.43 (3H, s, CH_3Ar); 3.29–3.48 (9H, m, 4×CH_2O and CHN); 5.05 (1H, s(broad), NH); 7.30 and 7.79 (2×2H, 2×d, J=8.0 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.99 (2×CH_3CH_2); 21.49 (CH_3Ar); 52.61 (CHN); 66.58 (2×CH_3CH_2O); 69.00 (2×$CH_3CH_2OCH_2$); 127.13 and 129.56 (2×HC_{ortho} and 2×HC_{meta}); 137.84 (CH_3C); 143.29 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3277 (NH), 2978, 2878, 1598, 1457, 1423, 1332. MS (70 eV) *m/z* (%): 302 (M^+, 7); 245 (26); 244 (50); 243 (94); 215 (21); 210 (12); 186 (17); 185 (80); 157 (38); 156 (23); 155 (90); 146 (11); 141 (16); 140 (32); 139 (94); 133 (12); 117 (16); 107 (11); 106 (13); 105 (10); 102 (52); 100 (13); 92 (57); 91 (100); 87 (92); 86 (87); 77 (21); 65 (83). Anal. Calcd for $C_{14}H_{23}NO_4S$ (%): C 55.79; H 7.69; N 4.65. Found (%): C 55.96; H 7.88; N 4.48.

3.1.3. *N*-(2-(2-Propenyloxy)-1-((2-propenyloxy)methyl)ethyl)-4-methylbenzenesulfonamide 4c. Yie1d 64%, colorless crystals. Mp 42 °C. Flash chromatography on silica gel: EtOAc/Hexane 1:4, R_f=0.25. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.42 (3H, s, CH_3Ar); 3.30–3.36 (2H, m, 2×NCH(*H*CH)); 3.46–3.49 (3H, m, 2×NCH(HC*H*) and CHN); 3.86 (4H, d, J=5.3 Hz, 2×CH_2CH=CH_2); 5.07 (1H, s(broad), NH); 5.12–5.21 (4H, m, 2×CH=CH_2); 5.71–5.86 (2H, m, 2×C*H*=CH_2); 7.29 and 7.77 (2×2H, 2×d, J=8.1 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.49 (CH_3Ar); 52.60 (CHN); 68.62 (2×NCH*C*H_2); 71.98 (2×*C*H_2CH=CH_2); 117.05 (2×CH=*C*H_2); 127.08 and 129.58 (2×HC_{ortho} and 2×HC_{meta}); 134.23 (2×*C*H=CH_2); 137.73 (CH_3C); 143.30 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3296 (NH), 1647, 1598, 1485, 1456, 1329, 1161, 1092. MS (70 eV) *m/z* (%): 325 (M^+, 0.3); 254 (100); 195 (16); 170 (6); 155 (60); 91 (96); 82 (19); 71 (4); 65 (13). Anal. Calcd for $C_{16}H_{23}NO_4S$ (%): C, 9.05; H, 7.12; N, 4.30. Found (%): C, 58.83; H, 7.28; N, 4.21.

3.2. Synthesis of 1,3-dialkylthio-2-(tosylamino)propanes 5a,b

As a representative example, the synthesis of *N*-(2-((1-methylethyl)thio)-1-(((1-methylethyl)thio)methyl)ethyl)-4-methylbenzenesulfonamide **5a** is described. To sodium methoxide (12 mL, 4 mmol, 2 equiv, 0.33 N in MeOH) was added propane-2-thiol (0.46 g, 6 mmol, 3 equiv), and the mixture was stirred for 30 min at room temperature. Subsequently, a solution of 2-(bromomethyl)-1-(4-methylbenzenesulfonyl)aziridine **3a** (0.58 g, 2 mmol) in methanol (2 mL) was added to the mixture. After stirring for 6 h at room temperature, the reaction mixture was poured into water (50 mL), extracted with CH_2Cl_2 (3×25 mL) and dried ($MgSO_4$). Filtration of the drying agent and evaporation of the solvent afforded the crude *N*-(2-((1-methylethyl)thio)-1-(((1-methylethyl)thio)methyl)ethyl)-4-methylbenzenesulfonamide **5a**, which was purified by means of column chromatography (EtOAc/Hexane 1:4, R_f=0.43).

3.2.1. *N*-(2-((1-Methylethyl)thio)-1-(((1-methylethyl)thio)methyl)ethyl)-4-methylbenzenesulfonamide 5a. Yie1d 80%, colorless liquid. Flash chromatography on silica gel: EtOAc/Hexane 1:4, R_f=0.43. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.13 and 1.17 (12H, 2×d, J=6.6 Hz, 2×CH(CH_3)$_2$); 2.41 (3H, s, CH_3Ar); 2.62 (2H, d×d, J=13.7, 6.8 Hz, 2×(*H*CH)S); 2.69 (2H, sept, J=6.6 Hz, 2×C*H*(CH_3)$_2$); 2.82 (2H, d×d, J=13.7, 5.4 Hz, 2×(HC*H*)S); 3.35 (1H, m, CHN); 5.42 (1H, d, J=6.6 Hz, NH); 7.31 and 7.80 (2×2H, 2×d, J=8.3 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.47 (CH_3Ar); 23.18 and 23.23 (2×CH(*C*H_3)$_2$); 34.21 (2×CH_2S); 35.74 (CHS); 52.88 (CHN); 127.24 and 129.61 (2×HC_{ortho} and 2×HC_{meta}); 137.10 (CH_3C); 143.47 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3276 (NH), 1598, 1495, 1452, 1337, 1160. MS (70 eV) *m/z* (%): 361 (M^+, 4); 360 (18); 319 (8); 272 (100); 230 (25); 190 (27); 157 (32); 155 (49); 139 (31); 117 (47); 105 (27); 91 (52); 89 (24); 74 (35); 65 (15); 43 (24). Anal. Calcd for $C_{16}H_{27}NO_2S_3$(%): C, 53.15; H, 7.53; N, 3.87. Found (%): C, 53.31; H, 7.70; N, 3.70.

3.2.2. *N*-(2-(2-Propenylthio)-1-((2-propenylthio)methyl)ethyl)-4-methylbenzenesulfonamide 5b. Yie1d 86%, colorless liquid. Flash chromatography on silica gel: EtOAc/Hexane 1:4, R_f=0.25. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.44 (3H, s, CH_3Ar); 2.62 and 2.71 (4H, 2×d×d, J=13.8, 6.6, 5.2 Hz, 2×NCH(*HC*H)); 2.89–3.00 (4H, m, 2×SCH_2CH=CH_2); 3.36–3.45 (1H, m, NCH); 5.02–5.12 (5H, m, 2×CH=CH_2 and NH); 5.60–5.75 (2H, m, 2×C*H*=CH_2); 7.33 and 7.78 (2×2H, 2×d, J=8.4 Hz, C_6H_4). ^{13}C NMR (68 MHz, ref=$CDCl_3$): δ 21.44 (CH_3Ar);

34.67 and 35.11 (4×CH_2S); 52.06 (CHN); 117.68 (2×CH=CH_2); 127.21 and 129.60 (2×HC_{ortho} and 2×HC_{meta}); 133.64 (2×CH=CH_2); 137.22 (CH_3C); 143.52 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3279 (NH), 1635, 1598, 1495, 1407, 1331, 1160. MS (70 eV) *m/z* (%): 357 (M^+, 1); 202 (4); 201 (54); 155 (74); 91 (100); 65 (21). Anal. Calcd for $C_{16}H_{23}NO_2S_3$ (%): C, 53.75; H, 6.48; N, 3.92. Found (%): C, 53.96; H, 6.63; N, 3.81.

3.3. Ring opening of 1-tosylaziridines with sodium azide in water

As a representative example, the synthesis of *N*-(2-azido-1-(azidomethyl)ethyl)-4-methylbenzenesulfonamide **7a** is described. 2-(Bromomethyl)-1-(4-methylbenzenesulfonyl) aziridine **3a** (1.45 g, 5 mmol), sodium azide (0.66 g, 2 equiv) and silica gel (2.5 g) were suspended in water (7.5 mL) and stirred at 80 °C for 16 h. The reaction mixture was filtered over Celite and the filter cake was washed with CH_2Cl_2 (2×20 mL). Isolation of the organic phase, extraction of the water phase with CH_2Cl_2 (20 mL), drying of the combined organic extracts ($MgSO_4$), filtration and evaporation of the solvent afforded the crude *N*-(2-azido-1-(azidomethyl)ethyl)-4-methylbenzenesulfonamide **7a**, which was recrystallized from methanol, yielding pure **7a** (1.27 g, 86%).

3.3.1. *N*-(2-Azido-1-(azidomethyl)ethyl)-4-methylbenzenesulfonamide 7a. Yie1d 86%, colorless crystals. Mp 77.8 °C. Recrystallized from methanol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3Ar); 3.27–3.50 (5H, m, 2×CH_2N_3 and CHN); 5.06 (1H, s(broad), NH); 7.33–7.36 and 7.76–7.80 (2×2H, 2×m, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.57 (CH_3Ar); 51.91 (2×CH_2N_3); 52.23 (CHN); 127.11 and 129.98 (2×HC_{ortho} and 2×HC_{meta}); 137.24 (CH_3C); 144.09 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν= 3262 (NH), 2106 (N_3), 2936, 2863, 1597, 1449, 1328, 1162, 1093, 733. MS (70 eV) *m/z* (%): 296 (M^++1, 54); 239 (56); 225 (39); 155 (100). Anal. Calcd for $C_{10}H_{13}N_7O_2S$ (%): C, 40.67; H, 4.44; N, 33.20. Found (%): C, 40.85; H, 4.67; N, 33.47.

3.3.2. *N*-(2-Azido-1-(azidomethyl)ethyl)methanesulfonamide 7b. Yie1d 81%, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.07 (3H, s, CH_3); 3.53–3.55 (4H, m, 2×CH_2N_3); 3.64–3.68 (1H, m, CHN); 5.04 (1H, s(broad), NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.73 (CH_3); 52.78 (2×CH_2N_3); 52.97 (CHN). IR (NaCl, cm^{-1}): ν=3277 (NH), 2106 (N_3), 2936, 2874, 1443, 1319, 1154, 993. MS (70 eV) *m/z* (%): no M^+, 218 (7), 149 (30); 87 (63). Anal. Calcd for $C_4H_9N_7O_2S$ (%): C, 21.91; H, 4.14; N, 44.72. Found (%): C, 22.07; H, 4.01; N, 44.93.

3.3.3. *N*-(2-Azido-1-(methoxymethyl)ethyl)-4-methylbenzenesulfonamide 9. Yie1d 74%, colorless crystals. Mp 67–68 °C. Flash chromatography on silica gel: EtOAc/Hexane 1:4, R_f=0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (3H, s, CH_3Ar); 3.18–3.51 (5H, m, CH_2N_3, CH_2O and CHN); 3.24 (3H, s, CH_3O); 5.15–5.27 (1H, m, NH); 7.29–7.33 and 7.74–7.84 (2×2H, 2×m, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.55 (CH_3Ar); 51.74 (CH_2N_3); 52.51 (CHN); 58.97 (CH_3O); 71.05 (CH_2O); 127.09 and 129.80 (2×HC_{ortho} and 2×HC_{meta}); 137.54 (CH_3C); 143.74 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3257 (NH), 2102 (N_3), 2935, 2898, 2832, 1596, 1416, 1326, 1162, 1086, 983, 820, 682. MS (70 eV) *m/z* (%): no M^+; 239 (M^+-CH_2OMe, 9); 228 (28); 155 (49); 139 (30); 91 (100); 65 (20); 45 (19). Anal. Calcd for $C_{11}H_{16}N_4O_3S$ (%): C 46.47; H 5.67; N 19.70. Found (%): C 46.61; H 5.83; N 19.59.

3.3.4. 2-(Methoxymethyl)-1-(4-methylbenzenesulfonyl) aziridine 8. To 2-(bromomethyl)-1-(4-methylbenzenesulfonyl)aziridine **3a** (0.29 g, 1 mmol) was added sodium methoxide in methanol (0.53 mL, 1.05 equiv, 2 N in MeOH), and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was poured into water (20 mL), extracted with CH_2Cl_2 (3×10 mL) and dried ($MgSO_4$). Filtration of the drying agent and evaporation of the solvent afforded the crude 2-(methoxymethyl)-1-(4-methylbenzenesulfonyl)aziridine **8**, which was purified by means of column chromatography (EtOAc/Hexane 1:4, R_f=0.08).

Yie1d 52%, colorless liquid. Flash chromatography on silica gel: EtOAc/Hexane 1:4, R_f=0.08. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.20 (1H, d, J=4.3 Hz, (H_{trans}CH)N); 2.43 (3H, s, CH_3Ar); 2.61 (1H, d, J=7.2 Hz, (HCH_{cis})N); 2.92–3.01 (1H, m, CHN); 3.29 (3H, s, CH_3O); 3.38 and 3.53 (2H, 2×d×d, J=6.9, 4.3, 1.4 Hz, (HCH)O); 7.32 and 7.81 (2×2H, 2×d, J=8.1 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21. 62 (CH_3Ar); 30.85 (CH_2N); 38.40 (CHN); 58.92 (CH_3O); 71.21 (CH_2O); 128.01 and 129.68 (2×HC_{ortho} and 2×HC_{meta}); 134.79 (CH_3C); 144.65 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=2253, 1916, 1596, 1490, 1448, 1322, 1290, 1226. MS (70 eV) *m/z* (%): 241 (M^+, 4); 211 (3); 155 (25); 91 (79); 65 (33); 56 (97); 45 (100). Anal. Calcd for $C_{11}H_{15}NO_3S$ (%): C 54.75; H 6.27; N 5.80. Found (%): C 54.93; H 6.44; N 5.64.

3.4. Synthesis of diaryloxysulfonamides 10

As a representative example, the synthesis of *N*-(2-(3-chlorophenoxy)-1-((3-chlorophenoxy)methyl)ethyl)methanesulfonamide **10a** is described. 2-(Bromomethyl)-1-(4-methanesulfonyl)aziridine **3b** (0.54 g, 2.5 mmol) was added to a mixture of 3-chlorophenol (0.70 g, 2.2 equiv), K_2CO_3 (1.73 g, 5 equiv) and silica gel (1.25 g) and stirred at 80 °C for 16 h. The reaction mixture was filtered over Celite and the filter cake was washed with CH_2Cl_2 (2×20 mL). Isolation of the organic phase, extraction of the water phase with CH_2Cl_2 (20 mL), drying of the combined organic extracts ($MgSO_4$), filtration and evaporation of the solvent afforded the crude *N*-(2-(3-chlorophenoxy)-1-((3-chlorophenoxy)methyl)ethyl)methanesulfonamide **10a**, which was recrystallized from methanol/CH_2Cl_2 (1:1), yielding pure **10a** (0.79 g, 81%).

3.4.1. *N*-(2-(3-Chlorophenoxy)-1-((3-chlorophenoxy) methyl)ethyl)methanesulfonamide 10a. Yie1d 81%, colorless crystals. Mp 99.7–100.7 °C. Recrystallized from methanol/CH_2Cl_2 (1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (3H, s, CH_3); 4.13–4.21 (5H, m, 2×CH_2O and CHN); 5.12–5.14 (1H, m, NH); 6.77–6.81, 6.90–6.91, 6.96–6.99 and 7.19–7.26 (8H, 4×m, HC_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.93 (CH_3); 52.49 (CHN); 67.71 (2×CH_2O); 112.85, 115.06, 121.90 and 130.50 (HC_{arom}); 135.15 (2×

CCl); 158.65 (2×OC_{quat}). IR (NaCl, cm^{-1}): ν=3351 (NH), 3071, 3011, 2962, 2931, 1597, 1486, 1311, 1251, 1151, 770. MS (70 eV) *m/z* (%): 389/91/93 (M^+, 16); 261/3 (10); 167 (22); 153/5 (100); 134 (15); 111 (23); 96 (24). Anal. Calcd for $C_{16}H_{17}Cl_2NO_4S$ (%): C 49.24; H 4.39; N 3.59. Found (%): C 49.41; H 4.52; N 3.44.

3.4.2. *N*-(2-(4-Fluorophenoxy)-1-((4-fluorophenoxy) methyl)ethyl)-4-methylbenzenesulfonamide 10b. Yie1d 84%, colorless crystals. Mp 154.4–155.5 °C. Recrystallized from Hexane/CH_2Cl_2 (1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3Ar); 3.84–3.96 (3H, m, 2×(*H*CH)O and CHN); 4.05–4.09 (2H, m, 2×(HC*H*)O); 5.41 (1H, d, *J*= 7.4 Hz, NH); 6.66–6.73 and 6.87–6.96 (8H, 2×m, 4×$OHC_{ortho}HC_{meta}$); 7.25 and 7.78 (4H, 2×d, *J*=8.3 Hz, 2×$SHC_{ortho}HC_{meta}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.51 (CH_3Ar); 51.91 (CHN); 66.92 (2×CH_2O); 115.54 (d, *J*= 8.1 Hz, 4×OHC_{ortho}); 115.93 (d, *J*=23.1 Hz, 4×OHC_{meta}); 127.20 and 129.78 (2×$SHC_{ortho}HC_{meta}$); 137.55 (CH_3C); 143.75 (SC); 154.10 (2×OC_{quat}); 157.64 (d, *J*=238.8 Hz, 2×CF). IR (NaCl, cm^{-1}): ν=3360 (NH), 3057, 2930, 8875, 1506, 1220, 831, 810. MS (70 eV) *m/z* (%): 434 (M^++1, 100). Anal. Calcd for $C_{22}H_{21}F_2NO_4S$ (%): C, 60.96; H, 4.88; N, 3.23. Found (%): C, 61.13; H, 5.01; N, 3.09.

3.4.3. *N*-(2-(4-Methoxyphenoxy)-1-((4-methoxyphenoxy) methyl)ethyl)-4-methylbenzenesulfonamide 10c. Yie1d 72%, colorless crystals. Mp 91.1–92.3 °C. Recrystallized from methanol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3Ar); 3.75 (6H, s, 2×CH_3O); 3.85–3.94 (3H, m, 2×(*H*CH)O and CHN); 4.05–4.09 (2H, m, 2×(HC*H*)O); 5.25–5.28 (1H, m, NH); 6.69–6.80 (8H, m, 4×$OHC_{ortho}HC_{meta}$); 7.26 and 7.78 (4H, 2×d, *J*=8.4 Hz, 2×$SHC_{ortho}HC_{meta}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.53 (CH_3Ar); 52.02 (CHN); 55.70 (2×CH_3O); 66.97 (2×CH_2O); 114.68 and 115.47 (4×MeO$HC_{ortho}HC_{meta}$); 127.18 and 129.75 (2×$SHC_{ortho}HC_{meta}$); 137.57 (CH_3C); 143.61 (SC); 152.15 and 154.28 (2×CH_2OC_{quat} and 2×$MeOC_{quat}$). IR (NaCl, cm^{-1}): ν=3307 (NH), 2940, 2834, 1508, 1228, 1162, 1039, 818. MS (70 eV) *m/z* (%): no M^+, 333 ($M^+-MeOC_6H_4OH$, 42); 210 (45); 155 (100); 123 (32); 91 (99). Anal. Calcd for $C_{24}H_{27}NO_6S$ (%): C 63.00; H 5.95; N 3.06. Found (%): C 63.19; H 6.11; N 2.90.

Acknowledgements

The authors are indebted to the 'Fund for Scientific Research—Flanders (F.W.O.-Vlaanderen)' (Belgium) and Ghent University (GOA) for financial support.

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