Regio- and stereocontrolled synthesis of novel 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines from 2-(bromomethyl)- or 2-(sulfonyloxymethyl)aziridines†

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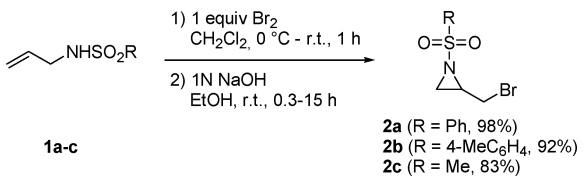
2-(Bromomethyl)-1-sulfonylaziridines were converted into novel 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines upon treatment with 2-aminothiophenol in THF in the presence of K_2CO_3. Starting from 3-substituted 2-(sulfonyloxymethyl)aziridines, a regio- and stereocontrolled synthesis of *trans*-2-phenyl- and *trans*-4-(phenyl or propyl)-3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines was developed in good yields *via* two different reaction pathways, depending on the nature of the sulfonyloxy group.

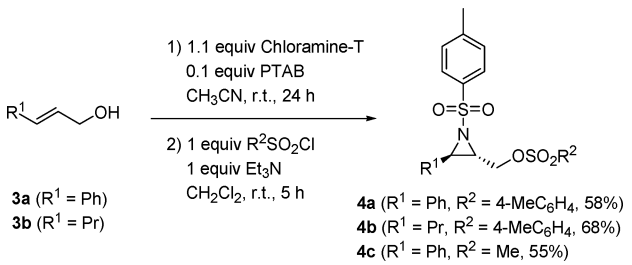
1,5-Benzothiazepines[1] comprise an important class of heterocycles due to the existence of several biologically active representatives such as Diltiazem[2] and Thiazesim.[3] Also their 3-amino derivatives have received considerable interest, especially from a medicinal point of view.[4] Whereas several approaches are available towards the synthesis of 1,5-benzothiazepines,[5] the preparation of the 3-amino-1,5-benzothiazepine skeleton remains an unexplored field of chemistry.[4a] In continuation of our interest in 2-(halomethyl)aziridines[6] and 2-(halomethyl)oxiranes[7] as three-carbon building blocks in organic synthesis, their reactivity with regard to 2-aminothiophenol was investigated in the present report.

2-(Bromomethyl)aziridines **2a–c** were prepared in high yields starting from allylsulfonamides **1** upon treatment with 1 equiv of bromine in dichloromethane, followed by ring closure of the resulting intermediate 2,3-dihalopropylsulfonamides by means of aqueous sodium hydroxide in ethanol at room temperature for 0.3 to 15 hours (Scheme 1).[8]



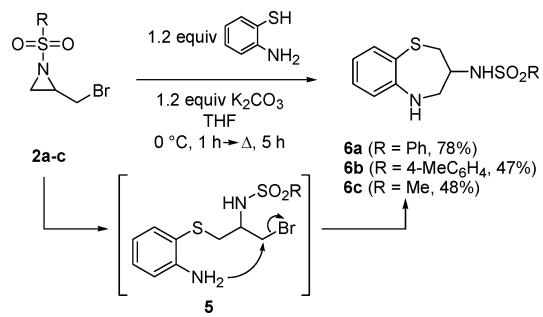
Scheme 1

Also *trans*-3-substituted 2-(sulfonyloxymethyl)aziridines were prepared as substrates for the synthesis of 3-amino-1,5-benzothiazepines. Aziridination of allylic alcohols **3** by treatment with 1.1 equiv of chloramine-T trihydrate[9] in acetonitrile in the presence of 0.1 equiv of phenyltrimethylammonium bromide (PTAB) afforded the corresponding 2-(hydroxymethyl)-1-tosylaziridines, which were subsequently sulfonylated upon reaction with 1 equiv of tosyl or mesyl chloride in dichloromethane in the presence of Et_3N at room temperature towards 2-(sulfonyloxymethyl)aziridines **4a–c** (Scheme 2).



Scheme 2

Treatment of 2-(bromomethyl)aziridines **2** with 1.2 equiv of 2-aminothiophenol in THF in the presence of potassium carbonate provided an easy access to 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines **6** after reflux for 5 hours (Scheme 3). Starting from 1-arenesulfonylaziridines **2a–b**, the presence of the corresponding acyclic intermediates **5** could be confirmed by means of ^1H NMR spectroscopy, implying that the formation of benzothiazepines **6** proceeds through initial attack of the sulfur atom of 2-aminothiophenol onto the less hindered aziridine carbon atom in substrates **2**, followed by nucleophilic displacement of bromide by the amino group (Scheme 3). Benzothiazepine **6a** was obtained as a 5 : 2 mixed crystal with toluene upon recrystallization from toluene.[10]



Scheme 3

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† Electronic supplementary information (ESI) available: Experimental details and characterisation data for compounds **6**–**8**. See DOI: 10.1039/b804246m

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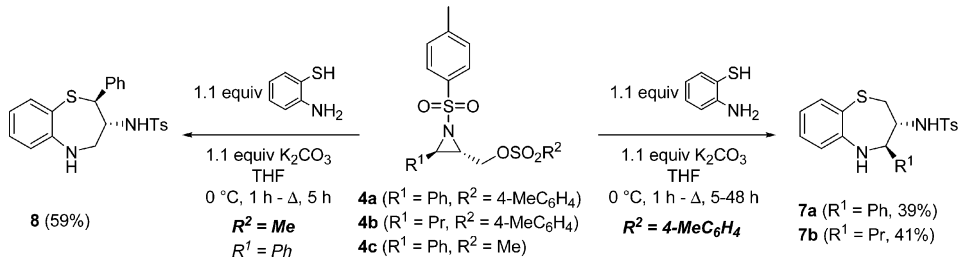
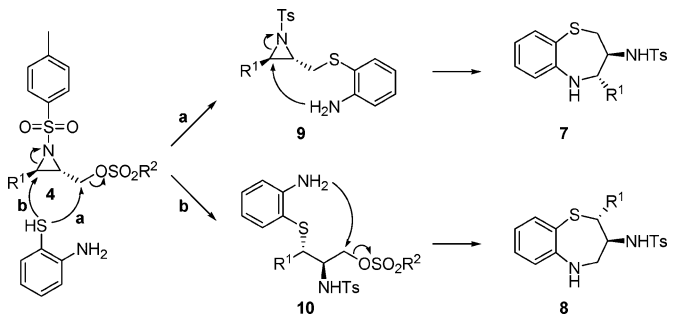


Scheme 4

This approach was further elaborated towards *trans*-disubstituted 2,3,4,5-tetrahydro-1,5-benzothiazepines **7** and **8** starting from *trans*-2,3-disubstituted aziridines **4**. Surprisingly, treatment of 2-(sulfonyloxymethyl)aziridines **4a** and **4b** with 1.1 equiv of 2-aminothiophenol in THF in the presence of 1.1 equiv of K_2CO_3 afforded 4-substituted 3-aminobenzothiazepines **7a,b**, whereas aziridine **4c** was transformed into 2-phenyl-3-aminobenzothiazepine **8** applying the same reaction conditions (Scheme 4). In both cases, no traces of the other regioisomers were identified in the reaction mixtures.

Apparently, tosylates **4a** and **4b** are more reactive as compared to mesylate **4c**. Indeed, 2-(tosyloxymethyl)aziridines **4a**,**b** undergo initial nucleophilic displacement of the tosyloxy group by means of 2-aminothiophenol towards intermediate aziridines **9**, which cyclise spontaneously to afford 4-substituted 3-aminobenzothiazepines **7** (pathway **a**, Scheme 5). On the other hand, 2-(mesyloxymethyl)aziridine **4c** suffers from initial ring opening by 2-aminothiophenol at the benzylic position towards acyclic intermediate **10**, followed by cyclization upon nucleophilic substitution of the mesyloxy moiety (pathway **b**, Scheme 5).



Scheme 5

The structural identity of benzothiazepines **7** and **8** was confirmed by means of detailed one- and two-dimensional NMR spectroscopic analysis. For example, the presence of cross-peaks in the COSY-spectrum of 4-phenylbenzothiazepine **7a** between the NH and the C-4 benzylic proton supported the assigned substitution pattern (Fig. 1). A NOE-effect of 3.8% between the same two protons proved this assignment to be correct. Similarly, cross-peaks between the NH proton and the adjacent methylene protons supported the structure of benzothiazepine **8** bearing a phenyl group at the 2-position. For both benzothiazepines **7** and **8**, the relative configuration was assigned as *trans* based on the large vicinal coupling constants of 9.6 Hz between H-3 and H-4 for

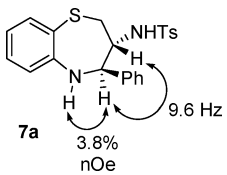


Fig. 1

compounds **7** and of 9.2 Hz between H-2 and H-3 for compound **8**.

In conclusion, a highly efficient synthesis of 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines has been accomplished starting from easily accessible aziridine substrates. Furthermore, this approach can be applied successfully for the regio- and stereocontrolled synthesis of *trans*-2- or *trans*-4-substituted 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines by choice of the appropriate leaving group.

Notes and references

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10 Spectroscopic data for 3-aminobenzothiazepine **6a**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.60 (1H, ddd, $J = 14.5$, 4.9, 1.3 Hz); 2.75 (1H, dd, $J = 14.5$, 2.6 Hz); 2.93 (1H, dd, $J = 13.9$, 1.6 Hz); 3.31 (1H, m); 3.64 (1H, m); 3.91 (1H, m); 6.00 (1H, d, $J = 10.2$ Hz); 6.77 (1H, dd, $J = 7.9$, 1.0 Hz); 6.85 (1H, td, $J = 7.9$, 1.0 Hz); 7.10 (1H, td, $J = 7.9$, 1.0 Hz); 7.36 (1H, dd, $J = 7.6$, 1.3 Hz); 7.56 (3H, m); 7.96 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 37.0, 51.4, 52.0, 120.6, 122.1, 125.1, 126.9, 128.5, 129.3, 132.8, 132.9, 141.6, 151.3. IR (neat, cm^{-1}): $\nu = 3320$, 1588, 1475, 1323. MS (70 eV): m/z (%): 320 (M^+, 5); 243 (39); 203 (100). Anal. Calcd for $C_{15}H_{16}N_2O_2S_2 \cdot 0.4C_7H_8$: C 59.84, H 5.42, N 7.84. Found: C 58.86, H 5.65, N 7.76%.