Azidotrimethylsilane-mediated Schmidt rearrangement of 2-aryl-1,2,3,4-tetrahydro-1-methylsulfonyl-4-quinolones: non-regioselectivity of carbon migration

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Azidotrimethylsilane-mediated Schmidt rearrangement of 2-aryl-1-methylsulfonyl-1,2,3,4-tetrahydro-4-quinolones in trifluoroacetic acid was investigated. In contrast to the corresponding 2-aryl-1,2,3,4-tetrahydro-4-quinolone precursors, the *N*-methylsulfonyl derivatives displayed non-regioselectivity of carbon migration during nitrogen insertion affording the isomeric ring-expanded derivatives *via* alkyl and aryl migration.

Since the introduction of Librium as a minor tranquiliser a large number of seven-membered heterocyclic compounds with the benzodiazepine moiety have been synthesized and tested for psychotropic properties.[1] This moiety has been found to represent a versatile template in peptidomimetic design and it is also found in several other compounds of biological importance including antitumor antibiotics and inhibitors of HIV-1 transcriptase.[2] New methods continue to appear in the literature describing the synthesis of novel benzodiazepine analogues, and emphasis is placed on the alteration and replacement of heteroatoms with the aim of modifying the pharmacological activity. We have previously reported the synthesis and spectroscopic studies of: 1,4-benzoxazepinones,[3] 1,4-benzodiazepinones,[4] 1,4- and 1,5-benzothiazepinones,[5] and their tetrazolo derivatives.[3–6] These benzodiazepine analogues were accessed through the Schmidt rearrangement of specially prepared flavanone precursors and some of them have been found to exhibit receptor binding properties.[7] When flavanone analogues **1** (X = O, NH, S; R = Ar) were subjected to azidotrimethylsilane (TMSA) in TFA, various isomeric products were isolated depending on the nature of heteroatom X in the precursors. Flavanones (X = O)[3] and quinolones (X = NH)[4] afforded 1,4-benzoheterazepinones **2** and their tetrazolo[1,5-*d*] derivatives **4** *via* alkyl (C-3) shift, regioselectively (Scheme 1). On the other hand, thiaflavanones (X = S) displayed non-regioselectivity of carbon migration in their reactivity affording 1,4- **2** and 1,5-benzothiazepinone **3** isomers *via* alkyl (C-3) and aryl (C-4a) migration.[5] A similar non-regioselectivity of carbon migration was reported for the Schmidt rearrangement of 1,2,3,4-tetrahydroquinolin-4-ones (X = NR′, R = H)[8] and thiochromanones (X = S, R = H).[9] On the other hand, under similar reaction conditions applied to tetraquinolinones and thiochromanones, thiochromanone 1-oxide (X = SO, R = H) afforded 1,5-isomer as the sole product.[10]

We have previously reported a kinetic mechanistic study of the TMSA-mediated Schmidt rearrangement of the A- and B-ring substituted flavanones in TFA using ^{1}H NMR spectroscopy, which was undertaken to elucidate the observed regioselectivity of alkyl carbon migration.[11] This observation in the case of flavanones was rationalized in terms of the electronic effect of the ethereal oxygen. Presumably, the lone pair electron delocalization of X would result in a partial double bond formation between the fused ring and the migration origin (C4a–C4) and this would inhibit aryl migration [Fig. 1(*a*)].[12] The increased lone pair electron delocalization by X would instead stabilize the incipient carbocation [Fig. 1(*b*)] and

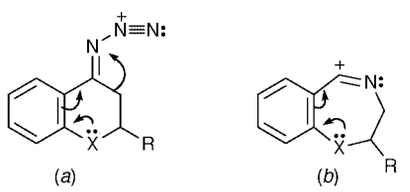
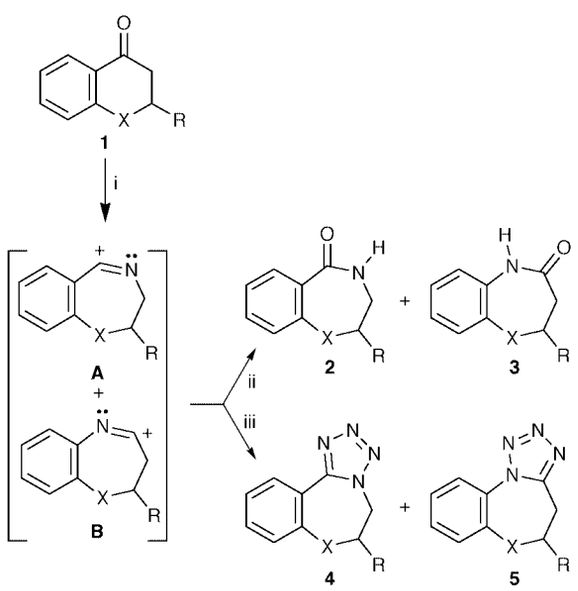


Fig. 1 Involvement of X in: (*a*) inhibiting aryl migration and (*b*) stabilizing the carbocation generated *via* alkyl migration.



Scheme 1 *Reagents and conditions*: (i) Me_3SiN_3, TFA; (ii) H_2O; (iii) TMSA.

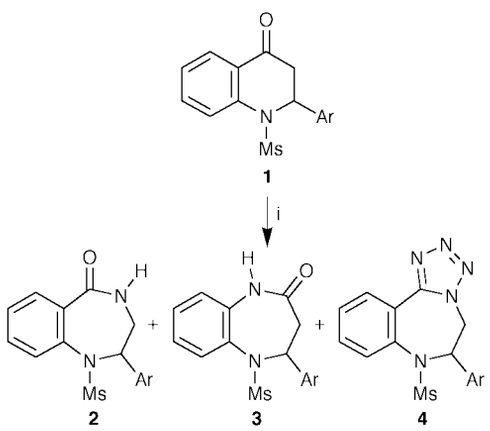
enhance alkyl migration. We believe that the enhanced propensity for lone pair electron delocalization by O or N accounts for the observed regioselectivity of alkyl carbon (C–3) shift in the case of flavanones and quinolones. On the other hand, the non-regioselectivity of carbon migration in the case of thiaflavanones presumably reflects the poor π-electron delocalization by sulfur involving the incompatible C_{2P}–S_{3P} orbital interaction.[13]

Our interest in the Schmidt reaction of flavanoid compounds prompted us to investigate the application of the azidotrimethylsilane–trifluoroacetic acid reaction conditions to

2-aryl-*N*-methylsulfonyl-4-quinolones. This investigation was undertaken to establish the effect of reducing the propensity of nitrogen for lone pair electron delocalization in systems **1** on the mode of carbon migration (*i.e.* alkyl *versus* aryl migration) and to employ NMR (^{1}H and ^{13}C) and mass spectroscopic techniques to distinguish between isomeric ring-expanded products.

Results and discussion

Series of 2-aryl-*N*-methylsulfonyl-4-quinolones **1** (X = NSO_2-Me) prepared as described before[14] were subjected to TMSA in TFA, the reaction conditions previously applied to the corresponding quinolone precursors (X = NH, R = Ar; see Scheme 1).[4] Under these reaction conditions, substrates **1** afforded the 1,4- **2** and 1,5-benzodiazepinone derivatives **3**, as well as the 1,4-tetrazolo derivatives **4** (Scheme 2). In the case of the

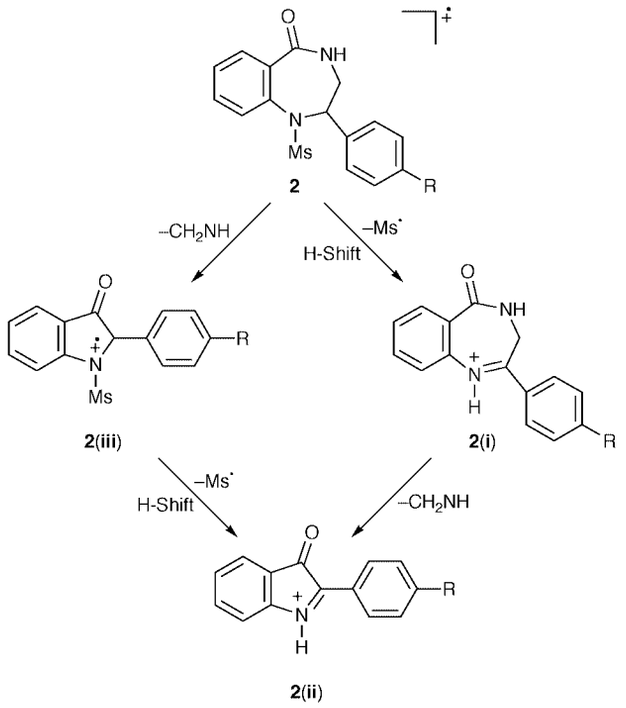


Scheme 2 *Reagents and conditions*: (i) $(CH_3)_3SiN_3$/TFA.

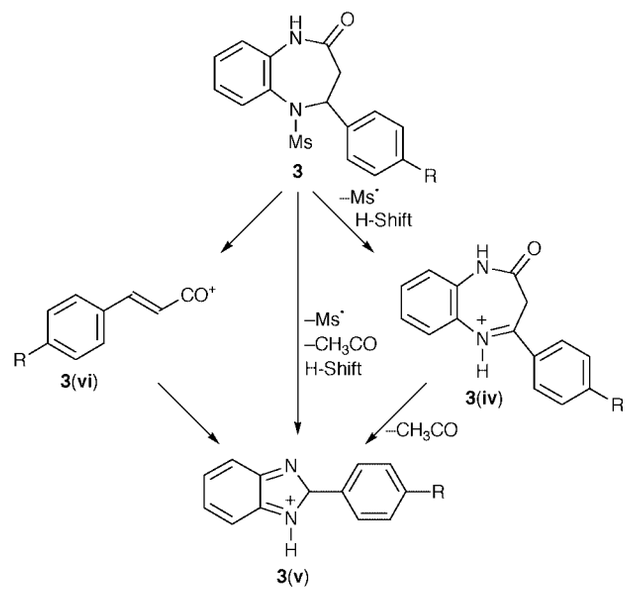
methoxy derivative **1e**, traces of the 1,5-benzodiazepinone were detected in the reaction mixture, but could not be isolated by careful column or preparative chromatographic techniques. In order to distinguish between the isomeric products and to establish the mode of carbon shift (1,4 *versus* 1,5), it was necessary to investigate the ^{1}H NMR and ^{13}C NMR chemical shifts and the mass spectroscopic fragmentation patterns of the ring-expanded derivatives **2**–**4**. ^{1}H NMR, ^{13}C NMR and mass spectra of the 1,4-benzodiazepinones **2**, the 1,5-regioisomers **3** and the 1,4-tetrazolo derivatives **4** exhibit distinct differences from one another and also from those of the 2-aryl-*N*-methylsulfonyl-4-quinolone precursors **1**.

^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic analysis of the rearrangement products

1,4-Benzodiazepinones 2 and 1,5-benzodiazepinones 3. The isomeric 1,4- **2** and 1,5-benzodiazepinones **3** were distinguished from the corresponding precursors **1** and the tetrazolo derivatives **5** by the presence of the amide proton signal in their ^{1}H NMR spectra. The lactam functionality was also confirmed by the presence in the IR spectra of the NH absorption band at *ca.* ν 3250–3350 cm^{-1}. The significant downfield shift of the methylene resonances in the ^{1}H NMR (*ca.* δ 3.42) and ^{13}C NMR (*ca.* δ 45.6) spectra of the 1,4-benzodiazepinones **2** reflect the deshielding effect of the adjacent amide nitrogen and confirmed ring-expansion *via* alkyl migration. On the other hand, the formation of the isomeric 1,5-benzodiazepinones **3** *via* aryl migration was confirmed by the high field absorption of the diastereotopic methylene protons (*ca.* δ 2.6 and 2.8) and the downfield shift of the C–9a signal (*ca.* δ 136–140) due to deshielding by the adjacent amide nitrogen. The carbonyl carbons of the ring-expanded derivatives **2** and **3** resonate in the region δ_C 170–173, confirming the lactam nature of the carbonyl functionality and thus distinguishing these compounds from the corresponding precursors (^{13}C=O, at



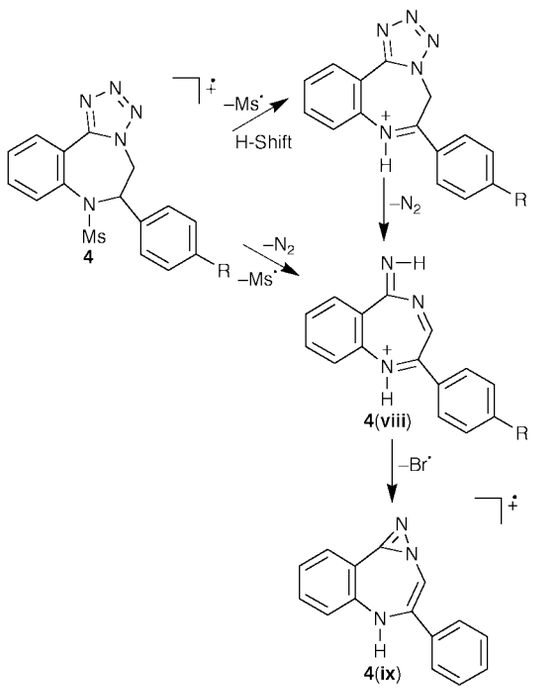
Scheme 3 MS Fragmentation patterns for 2-aryl-2,3,4,5-tetrahydro-1-methylsulfonyl-1*H*-1,4-benzodiazepin-5-ones **2**.



Scheme 4 MS Fragmentation patterns for 4-aryl-2,3,4,5-tetrahydro-5-methylsulfonyl-1*H*-1,5-benzodiazepin-2-ones **3**.

ca. δ 192). The major fragmentations characteristic of the *N*-methylsulfonylbenzodiazepinones **2** and **3** are summarized in Schemes 3 and 4, respectively. Loss of CH_2NH from the 1,4-benzodiazepinones **2** to form the ring contracted fragment **2(ii)** parallels a fragmentation observed for the corresponding parent 1,4-benzodiazepinones[3] and confirms formation *via* alkyl migration during the Schmidt reaction of the precursors. The two ions tentatively formulated as **3(v)** and **3(vi)** in the mass spectra of systems **3** confirm the molecular ions to be the result of nitrogen insertion *via* aryl migration. Systems **3** exhibit fragmentation patterns similar to those reported for the analogous 4-aryl-3,4-dihydro-1,5-benzodioxepin-2-ones.[15] The molecular formulae of the fragments cited in Schemes 3–5 represent, in each case, the closest fit (consistent with available atoms) to the experimentally determined accurate *m*/*z* values.

Tetrazolo[1,5-*d*][1,4]benzodiazepine derivatives 4. The splitting patterns of the methylene and methine protons in the ^{1}H NMR spectra of the tetrazolo derivatives **4** are characterized by three sets of double doublets at *ca.* δ 4.4, 5.2 and 5.9, respectively. The significant downfield shift of the signals corresponding to the nonequivalent methylene protons in the ^{1}H NMR spectra of compounds **4**, which is due to the increased electron-withdrawing effect of the tetrazolo ring, distinguishes them from the corresponding precursors and from the lactam derivatives. The increased magnetic anisotropy of the tetrazolo ring also shifts the 11-H signal further downfield (to *ca.* δ 8.1) than in the corresponding 1,4- and 1,5-benzodiazepinones. The ^{13}C NMR spectra of the tetrazolo derivatives **4** are characterized by the absence of a ^{13}C=O signal and the presence of the ^{13}C=N resonance at *ca.* δ 153.0. Nitrogen insertion *via* alkyl migration in compounds **4** was also confirmed by the significant downfield shift (to *ca.* δ 49.3) of the resonance corresponding to the methylene carbon (C-5). The absence in the IR spectra of the NH and C=O absorption bands and the presence of the C=N absorption bands at *ca.* ν 1600 cm^{-1} distinguish the tetrazolo derivatives from the corresponding precursors and from the lactam derivatives. The generalized mass fragmentation patterns of the tetrazolo derivatives **4** are summarized in Scheme 5. Precedence for the fragmentation of the tetrazolo



Scheme 5 MS Fragmentation patterns for 6-aryl-6,7-dihydro-7-methylsulfonyl-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepines **4**.

derivatives **4** is provided by the mass spectral analyses of the 6-aryltetrazolo[1,5-*d*][1,4]benzodiazepines (X = NH).[4]

Much work has been carried out aimed at elucidating the mechanism of the Schmidt reaction in order to explain the formation of either one or both isomers. According to earlier reports the configuration of the iminodiazonium ion [see Fig. 1(*a*)], *i.e. anti* or *syn* relative to the benzo ring, is believed to determine the ratio of the final products and the migrating group is suggested to be the one *anti* to the diazonium nitrogen.[16] In the case of flavanones[3] and quinolones,[4] the regioselectivity of formation of 1,4-benzoheterazepinones and the tetrazolo[1,5-*d*] derivatives *via* alkyl migration was attributed to the transition state factors rather than equilibrium populations of the *syn*- and *anti*-iminodiazonium ions.[11] *N*-Methylsulfonylquinolones **1** and thiaflavanone derivatives[5] exhibit similar behavior of carbon migration under TMSA–TFA conditions to afford mixtures of 1,4- and 1,5-benzoheterazepinones and the tetrazolo[1,5] derivatives. A comparison of the results of Schmidt rearrangement of flavanones, thiaflavanones, quinolones and their *N*-methylsulfonyl derivatives demonstrates that the mode of nitrogen insertion into their C-rings depends largely on the electronic effect/nature of the endocyclic heteroatom (X, see Fig. 1) and not on steric factors.[11] A theoretical study of formamido analogues has indicated that the magnitude of the nitrogen barriers precludes rapid isomerization between *syn*- and *anti*-iminodiazonium ions at room temperature.[17] Delocalization effects [*e.g.* Fig. 1(*a*)] and remote functions (R) may, however, be expected to reduce the inversion barrier significantly. The reduced propensity of nitrogen for lone pair delocalization in systems **1** also favours the formation of the 1,5-benzodiazepine isomers **3** *via* aryl migration. On the other hand, an electron-donating group (R) at the *para* position of the B-ring is expected to increase the electron density at the methine carbon. This effect, in turn, will oppose the electron-withdrawing inductive effect of the amide nitrogen and lead to increased nucleophilicity of the migrating 1° alkyl group. For strong electron-donating group such as the *p*-methoxy substituent, alkyl migration will be favoured over aryl migration, hence only traces of 4-(4′-methoxyphenyl)-1,5-benzodiazepinone isomer were detected in the crude reaction mixture.

The results of azidotrimethylsilane-mediated Schmidt rearrangement of flavanones, thiaflavanones, quinolones and their *N*-methylsulfonyl derivatives appear to support the theoretical study by Bach and Wolber[17] that this reaction involves non-isomerizing very short-lived iminodiazonium ions. In our previous kinetic mechanistic study of TMSA-mediated Schmidt rearrangement of flavanones using ^{1}H NMR spectroscopy,[11] the spectra clearly indicated the presence of substrate and products, but no accumulation of intermediates was apparent. We believe that the ratio of products formed in the case of flavanone analogues depends on the migratory aptitudes of the aryl and/or alkyl carbons, which in turn depend largely on the charge stabilization ability of the heteroatom X. The *N*-methylsulfonylbenzodiazepine analogues synthesized in this work can serve as substrates for further studies of chemical transformation, conformational effects and biological activity.

Experimental

Solvents and commercially available reagents were purified by conventional methods before use. Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used as stationary phase. IR Spectra were recorded as KBr pellets using a Hitachi 270-30 Infrared spectrophotometer. NMR spectra were obtained using a Varian Gemini 200 MHz spectrometer and the chemical shift values are referenced relative to TMS or the solvent peak (^{1}H: 7.25 ppm and ^{13}C: 77.0 ppm); *J* values are given in Hz. Low-resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer (University of Natal, Pietermaritzburg). High-resolution mass spectra were recorded at Cape Technikon Mass Spectrometry Unit using a VG-70 SEQ MASPEC II[32] (scanning at RP 10 000). Combustion analyses (C, H and N) were carried out at the Department of Chemistry, University of Cape Town. The 2-aryl-1,2,3,4-tetrahydro-1-methylsulfonyl-4-quinolone **1** were prepared as described before.[14]

Reactions of *N*-substituted quinolones 1 with azidotrimethylsilane: Schmidt rearrangement. General procedure

Azidotrimethylsilane (1.5 mol equiv.) was added dropwise to a solution of quinolone (1 mol equiv.) in trifluoroacetic acid (4.5 ml per mmol of **1**) and the solution was stirred at room

temperature for 3 days with the exclusion of moisture. The mixture was evaporated under reduced pressure and the residue was purified by column chromatography yielding sequentially three–four fractions.

Reaction of 1a with TMSA in TFA

Eluted with AcOEt–toluene (1:1 v/v). Four fractions were obtained: starting material and compounds **4a**, **3a** and **2a**.

6,7-Dihydro-7-methylsulfonyl-6-phenyl-5*H*-tetrazolo[1,5-*d*]-[1,4]benzodiazepine 4a. White solid (20%); mp 239–241 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.36 (3H, s, SO_2Me), 4.40 (1H, dd, *J* 11.4 and 14.6, 5-H), 5.20 (1H, dd, *J* 6.0 and 14.2, 5-H), 5.98 (1H, dd, *J* 6.0 and 11.4, 6-H), 7.38 (5H, s, C_6H_5), 7.62–7.67 (3H, m, 8-H, 9-H and 10-H) and 8.05 (1H, dd, *J* 2.4 and 5.8, 11-H); δ_C(50 MHz, $CDCl_3$) 38.7 (SO_2Me), 49.2 (C-5), 66.3 (C-6), 123.8 (C-11a), 126.6 (C-2′ and C-6′), 129.2 (C-4′), 129.3 (C-3′ and C-5'), 130.1 (C-8), 130.3 (C-10), 133.2 (C-9), 134.3 (C-11), 135.0 (C-1′), 136.8 (C-7a) and 153.4 (C=N); ν_{max}/cm^{-1} 1145 (SO_2) 1340 (SO_2) and 1600 (C=N); *m*/*z* 341 (M^+, 19.8%), 262 (14.0), 234 (100) and 206 (33.5) (calc. for $C_{16}H_{15}N_5O_2S$ (341.394), C, 56.26; H, 4.43; N, 20.51. Found: C, 56.50; H, 4.42; N, 19.79%).

2,3,4,5-Tetrahydro-5-methylsulfonyl-4-phenyl-1*H*-1,5-benzodiazepin-2-one 3a. White solid (25%); mp 242–243 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.52 (1H, dd, *J* 1.4 and 13.7, 3-H), 2.78 (1H, t, *J* 13.2, 3-H), 2.87 (3H, s, SO_2Me), 5.71 (1H, dd, *J* 4.8 and 13.2, 4-H), 7.18 (1H, t, *J* 8.3, 7-H), 7.26–7.45 (8H, m, C_6H_5, 6-H, 8-H and 9-H) and 9.98 (1H, s, NH); δ_C(50 MHz, DMSO-d_6) 39.0 (SO_2Me), 39.4 (C-3), 64.2 (C-4), 123.0 (C-1′) 125.5 (C-6), 125.9 (C-2′ and C-6′), 127.8 (C-8), 128.6 (C-3′ and C-5'), 129.3 (C-4′), 129.5 (C-7), 133.4 (C-9), 138.2 (C-5a), 141.5 (C-9a) and 170.3 (C=O); ν_{max}/cm^{-1} 1149 (SO_2), 1340 (SO_2), 1685 (C=O) and 3250 (NH); *m*/*z* 316 (M^+, 21.9%), 237 (13.3), 195 (64.9), 131 (100), 103 (23.3) and 65 (22.6) (calc. for $C_{16}H_{16}N_2O_3S$ (316.379), C, 60.74; H, 5.10; N, 8.85. Found: C, 60.83; H, 5.08; N, 8.81%).

2,3,4,5-Tetrahydro-1-methylsulfonyl-2-phenyl-1*H*-1,4-benzodiazepin-5-one 2a. White solid (35%); mp 263–265 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.88 (3H, s, SO_2Me), 3.10 (1H, dddd, *J* 6.0 and 11.2, 3-H), 3.41 (1H, ddd, *J* 5.8 and 10.4, 3-H), 5.38 (1H, dd, *J* 5.0 and 11.8, 2-H), 7.29 (5H, s, C_6H_5), 7.38–7.67 (4H, m, 6-H, 7-H, 8-H and 9-H), 8.55 (1H, t, *J* 6.0, NH); δ_C(50 MHz, DMSO-d_6) 38.6 (SO_2Me), 45.2 (C-3), 66.8 (C-2), 126.4 (C-2′ and C-6′), 127.8 (C-1′), 128.6 (C-3′ and C-5′), 129.2 (C-9), 129.6 (C-7), 131.9 (C-8), 132.8 (C-4′), 133.6 (C-6), 134.8 (C-5a), 139.4 (C-9a) and 169.6 (C=O); ν_{max}/cm^{-1}1159 (SO_2), 1339 (SO_2), 1680 (C=O) and 3350 (NH); *m*/*z* 316 (M^+, 4.5%), 237 (27.6), 208 (100), 152 (10.6), 119 (4.4) and 77 (10.9) (calc. for $C_{16}H_{16}N_2O_3S$ (316.379), C, 60.74; H, 5.10; N, 8.85. Found: C, 60.72; H, 5.08; N, 8.38%).

Reaction of 1b with TMSA in TFA

Eluted with $CHCl_3$–EtOAc (4:1 v/v). Four fractions were obtained: starting material and compounds **4b**, **3b** and **2b**.

6-(4-Fluorophenyl)-6,7-dihydro-7-methylsulfonyl-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine 4b. White solid (20%); mp 222–224 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.35 (3H, s, SO_2Me), 4.36 (1H, dd, *J* 11.6 and 14.7, 5-H), 5.19 (1H, dd, *J* 6.0 and 14.6, 5-H), 5.97 (1H, dd, *J* 6.0 and 11.4, 6-H), 7.09 (2H, t, *J* 8.6, 3′-H and 5′-H), 7.36 (2H, t, *J* 6.9, 2′-H and 6′-H), 7.62–7.73 (3H, m, 8-H, 9-H and 10-H) and 8.06 (1H, d, *J* 7.7, 11-H); δ_C(50 MHz, $CDCl_3$) 38.4 (SO_2Me), 48.7 (C-6), 65.1 (C-5), 116.4 (d, $^2J_{CF}$ 21.7, C-3′ and C-5′), 123.5 (C-11a), 128.6 (d, $^3J_{CF}$ 8.4, C-2′ and C-6′), 129.9 (C-8), 130.9 (C-10), 132.5 (d, $^4J_{CF}$ 3.5, C-1′), 132.9 (C-9), 133.7 (C-11), 134.3 (C-7a), 153.4 (C=N) and 162.0 (d, $^1J_{CF}$ 245.0, C-4′); ν_{max}/cm^{-1}1140 (SO_2), 1340 (SO_2) and 1605 (C=N); *m*/*z* 359 (M^+, 13.8%), 330 (11.4), 280 (11.8) and 252 (100) (Found: M^+, 359.0842. $C_{16}H_{14}O_2N_5FS$ requires *M*, 359.0852).

4-(4-Fluorophenyl)-2,3,4,5-tetrahydro-5-methylsulfonyl-1*H*-1,5-benzodiazepin-2-one 3b. White solid (10%); mp 216–218 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.69 (1H, dddd, *J* 1.6, 5.0 and 13.2, 3-H), 2.86 (3H, s, SO_2Me), 2.94 (1H, t, *J* 13.2, 3-H), 5.83 (1H, dd, *J* 5.0 and 13.6, 4-H), 7.03 (2H, t, *J* 8.8, 3′-H and 5′-H), 7.20 (1H, d, *J* 7.8, 9-H), 7.26–7.31 (3H, m, 6-H, 7-H and 8-H), 7.45 (2H, t, *J* 7.7, 2′-H and 6′-H) and 8.70 (1H, s, NH); δ_C(50 MHz, $CDCl_3$) 39.9 (SO_2Me), 40.3 (C-3), 64.5 (C-4), 115.8 (d, $^2J_{CF}$ 21.3, C-3′ and C-5′), 123.0 (C-6), 127.0 (C-8), 127.8 (d, $^3J_{CF}$ 8.4, C-2′ and C-6′), 129.3 (C-7), 130.2 (C-9), 133.8 (C-5a), 136.6 (d, $^4J_{CF}$ 3.4, C-1′), 136.9 (C-9a), 162.5 (d, $^1J_{CF}$ 246.2, C-4′) and 172.1 (C=O); ν_{max}/cm^{-1} 1180 (SO_2), 1345 (SO_2), 1695 (C=O) and 3350 (NH); *m*/*z* 334 (M^+, 42.3%), 255 (19.1), 213 (74.0) and 149 (100) (Found: M^+, 334.0774. $C_{16}H_{15}O_3N_2FS$ requires *M*, 334.0787).

2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-1-methylsulfonyl-1*H*-1,4-benzodiazepin-5-one 2b. White solid (30%); mp 206–209 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.90 (3H, s, SO_2Me), 3.09 (1H, dddd, *J* 5.9 and 10.4, 3-H), 3.46 (1H, ddd, *J* 5.9 and 11.9, 3-H), 5.40 (1H, dd, *J* 5.2 and 11.6, 2-H), 7.17 (2H, t, *J* 8.9, 3′-H and 5′-H), 7.29–7.68 (6H, m, 2′-H, 6-H, 6′-H, 7-H, 8-H and 9-H) and 8.57 (1H, t, *J* 5.9, NH); δ_C(50 MHz, DMSO-d_6) 39.9 (SO_2Me), 45.1 (C-3), 66.0 (C-2), 115.5 (d, $^2J_{CF}$ 21.3, C-3′ and C-5′), 128.6 (d, $^3J_{CF}$ 8.4, C-2′ and C-6′), 129.4 (C-9), 129.7 (C-7), 132.0 (C-8), 132.8 (C-6), 133.4 (C-5a), 134.9 (C-9a), 135.8 (d, $^4J_{CF}$ 3.4, C-1′), 161.7 (d, $^1J_{CF}$ 242.8, C-4′) and 169.7 (C=N); ν_{max}/cm^{-1}1160 (SO_2), 1360 (SO_2), 1689 (C=O) and 3200 (NH); *m*/*z* 334 (M^+, 6.4%), 255 (31.4) and 226 (100) (Found: M^+, 334.0777. $C_{16}H_{15}O_3N_2FS$ requires *M*, 334.0787).

Reaction of 1c with TMSA in TFA

Eluted with $CHCl_3$–EtOAc (9:1, v/v). Four fractions were obtained: starting material and compounds **4c**, **3c** and **2c**.

6-(4-Chlorophenyl)-6,7-dihydro-7-methylsulfonyl-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine 4c. White solid (30%); mp 243–246 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.35 (3H, s, SO_2CH_3), 4.35 (1H, dd, *J* 11.2 and 14.7, 5-H), 5.19 (1H, dd, *J* 6.2 and 14.7, 5-H), 5.96 (1H, dd, *J* 6.0 and 11.5, 6-H), 7.25–8.08 (8H, m, Ar-H); δ_C(50 MHz, $CDCl_3$) 38.6 (SO_2CH_3), 48.9 (C-5), 65.6 (C-6), 123.7 (C-11a), 128.0 (C-3′ and C-5′), 129.6 (C-2′ and C-6′), 130.3 (C-8), 130.4 (C-10), 133.4 (C-11), 134.3 (C-1′), 134.5 (C-4′), 135.3 (C-7a) and 153.3 (C=N); *m*/*z* 375 (5.5%), 346 (5.7), 296 (9.6), 268 (100) and 233 (27) (Found: M^+ 375.050. $C_{16}H_{14}N_5O_2{}^{35}ClS$ requires *M*, 375.0557).

4-(4-Chlorophenyl)-2,3,4,5-tetrahydro-5-methylsulfonyl-1*H*-1,5-benzodiazepin-2-one 3c. White solid (20%); mp 241–243 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.51 (1H, dd, *J* 1.4 and 13.1, 3-H), 2.77 (1H, t, *J* 13.2, 3-H), 2.86 (3H, s, SO_2Me), 5.71 (1H, dd, *J* 5.0 and 13.1, 4-H), 7.17 (1H, td, *J* 1.4 and 7.7, 9-H), 7.24 (1H, dd, *J* 1.6 and 7.6, 6-H), 7.34 (4H, s, 2′-H, 3′-H, 5′-H and 6′-H), 7.38 (1H, dd, *J* 1.6 and 3.8, 1-H), 7.35–7.45 (2H, m, 7-H and 8-H) and 9.97 (1H, s, NH); δ_C(50 MHz, DMSO-d_6) 39.3 (C-3), 40.4 (SO_2Me), 63.5 (C-4), 123.0 (C-9), 125.4 (C-1′), 127.7 (C-3′ and C-5′), 128.4 (C-2′ and C-6′), 128.9 (C-7), 129.5 (C-6), 132.5 (C-8), 133.4 (C-4′), 138.1 (C-5a), 140.2 (C-9a) and 170.1 (C=O); ν_{max}/cm^{-1} 1145 (SO_2), 1325 (SO_2), 1690 (CO) and 3340 (NH); *m*/*z* 350 (M^+, 46.2%), 317 (10.7), 271 (29.0), 229 (79.6), 65 (100), 133 (66.5) and 92 (22.7) (Found: M^+, 350.0491. $C_{16}H_{15}O_3N_2{}^{35}ClS$ requires *M*, 350.0492).

2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-1-methylsulfonyl-1*H*-1,4-benzodiazepin-5-one 2c. White solid (35%); mp 263– 265 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.86 (3H, s, SO_2Me), 2.95 (1H, dddd, *J* 3.2, 5.6, 11.9 and 14.9, 3-H), 3.20 (1H, ddd, *J* 5.4 and 14.9, 3-H), 5.13 (1H, dd, *J* 5.4 and 11.9, 2-H), 6.94 (2H, d, *J* 8.8, 3′-H and 5′-H), 7.02 (2H, d, *J* 8.6, 2′-H and 6′-H), 7.13 (1H, d, *J* 7.0, 9-H), 7.21–7.35 (2H, m, 7-H and 8-H), 7.48 (1H, d, *J* 2.1 and 7.1, 6-H) and 8.03 (1H, t, *J* 6.0, NH); δ_C(50 MHz, DMSO-d_6) 39.5 (SO_2Me), 44.9 (C-3), 65.9 (C-2), 128.5 (C-3′ and C-5′), 128.7 (C-2′ and C-6′), 129.4 (C-5a), 129.7 (C-9), 132.0 (C-7), 132.5 (C-8), 132.8 (C-6), 133.4 (C-1′), 134.9 (C-4′), 138.4 (C-9a) and 169.6 (C=O); ν_{max}/cm^{-1} 1180 (SO_2), 1360 (SO_2), 1675 (CO) and 3250 (NH); *m*/*z* 350 (M^+, 10.8%), 271 (36.0) and 242 (100) (Found: M^+, 350.0482. $C_{16}H_{15}O_3N_2{}^{35}ClS$ requires *M*, 350.0492).

Reaction of 1d with TMSA in TFA

Eluted with $CHCl_3$–EtOAc (4:1 v/v). Four fractions were obtained: starting material and compounds **4d**, **3d** and **2d**.

6-(4-Bromophenyl)-6,7-dihydro-7-methylsulfonyl-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine 4d. White solid (20%); mp 256–258 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.57 (3H, s, SO_2Me), 4.54 (1H, dd, *J* 10.8 and 14.6, 5-H), 5.33 (1H, dd, *J* 6.0 and 14.7, 5-H), 6.08 (1H, dd, *J* 6.0 and 10.7, 6-H), 7.52 (2H, d, *J* 8.6, 3′-H and 5′-H), 7.58–7.74 (5H, m, 2′-H, 6′-H, 8-H, 9-H and 10-H) and 7.96 (1H, d, *J* 7.4, 11-H); δ_C(50 MHz, DMSO-d_6) 38.9 (SO_2Me), 48.5 (C-5), 63.9 (C-6), 121.8 (C-4′), 123.7 (C-1′), 128.9 (C-2′ and C-6′), 129.5 (C-8), 129.8 (C-10), 131.5 (C-3′ and C-5′), 132.6 (C-9), 133.4 (C-11), 134.9 (C-11a), 136.5 (C-7a) and 152.9 (C=N); ν_{max}/cm^{-1} 1124 (SO_2), 1325 (SO_2) and 1600 (C=N); *m*/*z* 419 (M^+, 23.0%), 390 (9.3), 340 (35.6), 283 (13.7), 233 (76.2), 169 (33.4), 119 (31.0) and 69 (100) (calc. for $C_{16}H_{14}N_5O_2{}^{79}BrS$ (419.01), C, 45.74; H, 3.36; N, 16.66. Found: C, 45.82; H, 3.22; N, 16.77%).

4-(4-Bromophenyl)-2,3,4,5-tetrahydro-5-methylsulfonyl-1*H*-1,5-benzodiazepin-2-one 3d. White solid (25%); mp 276 °C (EtOH); δ_H(200 MHz, DMSO-d_6) 2.53 (1H, dd, *J* 5.0 and 13.1, 3-H), 2.78 (1H, t, *J* 13.2, 3-H), 2.90 (3H, s, SO_2Me), 5.71 (1H, dd, *J* 5.0 and 13.1, 4-H), 7.15 (1H, dd, *J* 1.4 and 7.7, 9-H), 7.24 (1H, dt, *J* 1.6 and 7.6, 7-H), 7.32 (2H, d, *J* 8.4, 3′-H and 5′-H), 7.37 (1H, dd, *J* 1.6 and 7.6, 6-H), 7.43 (1H, dt, *J* 1.6 and 7.6, 8-H), 7.54 (2H, d, *J* 8.4, 2′-H and 6′-H) and 9.98 (1H, s, NH); δ_C(50 MHz, DMSO-d_6) 39.3 (C-3), 40.6 (SO_2Me), 63.4 (C-4), 121.0 (C-6), 123.1 (C-8), 125.6 (C-4′), 128.3 (C-2′ and C-6′), 129.1 (C-7), 129.7 (C-9), 131.5 (C-3′ and C-5′), 133.5 (C-1′), 138.2 (C-5a), 140.9 (C-9a) and 170.2 (C=O); ν_{max}/cm^{-1} 1145 (SO_2), 1325 (SO_2), 1690 (CO) and 3345 (NH); *m*/*z* 396 (M^+, 51.7%), 394 (49.9), 317 (27.6), 315 (28.7), 275 (74.2), 273 (80) and 209 (100) (Found: M^+, 393.9995. $C_{16}H_{15}O_3N_2{}^{79}BrS$ requires *M*, 393.9987).

2-(4-Bromophenyl)-2,3,4,5-tetrahydro-1-methylsulfonyl-1*H*-1,4-benzodiazepin-5-one 2d. White solid (40%); mp 265– 268 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 3.38 (1H, dddd, *J* 5.6 and 15.3, 3-H), 3.52 (1H, dddd, *J* 5.8 and 15.2, 3-H), 5.48 (1H, dd, *J* 5.6 and 11.7, 2-H), 6.90 (1H, t, *J* 5.8, NH), 7.16 (2H, d, *J* 8.5, 3′-H and 5′-H), 7.47 (2H, d, *J* 8.6, 2′-H and 6′-H), 7.50 (1H, dt, *J* 2.0 and 7.4, 7-H), 7.58 (1H, dd, *J* 2.0 and 7.1, 9-H), 7.64 (1H, dt, *J* 2.0 and 7.4, 8-H) and 7.83 (1H, dd, *J* 2.0 and 7.4, 6-H); δ_C(50 MHz, DMSO-d_6) 38.7 (SO_2Me), 45.5 (C-3), 67.0 (C-2), 122.6 (C-4′), 128.3 (C-3′ and C-5′), 129.9 (C-9), 130.4 (C-7), 132.1 (C-2′ and C-6′), 133.0 (C-8), 133.3 (C-6), 133.5 (C-5a), 133.7 (C-1′), 137.7 (C-9a) and 171.1 (C-5); ν_{max}/cm^{-1} 1180 (SO_2), 1360 (SO_2), 1680 (C=O) and 3250 (NH); *m*/*z* 394 (M^+, 64.2%), 365 (2.0), 315 (38.5), 286 (100), 207 (5.6), 179 (11.1) and 152 (9.9) (Found: M^+, 393.9990. $C_{16}H_{15}O_3N_2{}^{79}BrS$ requires *M*, 393.9987).

Reaction of 1e with TMSA in TFA

Eluted with EtOAc–toluene (1:9 v/v). Three fractions were obtained: starting material and compounds **4e** and **3e**.

6,7-Dihydro-7-methylsulfonyl-6-(4-methoxyphenyl)-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine 4e. White solid (35%); mp 215–217 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.36 (3H, s, SO_2Me), 3.80 (3H, s, OMe), 4.39 (1H, dd, *J* 11.3 and 14.5, 5-H), 5.16 (1H, dd, *J* 6.1 and 14.7, 5-H), 5.94 (1H, dd, *J* 6.0 and 11.4, 6-H), 6.90 (2H, d, *J* 8.8, 2′-H and 6′-H), 7.27 (2H, d, *J* 8.8, 3′-H and 5′-H), 7.65–7.70 (3H, 8-H, 9-H and 10-H) and 8.06 (1H, d, *J* 7.6, 11-H); δ_C(50 MHz, $CDCl_3$) 38.8 (SO_2Me), 49.3 (C-5), 55.3 (C-6), 65.7 (OMe), 114.6 (C-3′ and C-5′), 123.8 (C-11a), 128.0 (C-2′ and C-6′), 128.7 (C-8), 130.1 (C-10), 130.3 (C-9), 133.2 (C-11), 134.2 (C-1′), 134.9 (C-7a), 152.3 (C-4′) and 155.5 (C=N); ν_{max}/cm^{-1}1158 (SO_2), 1340 (SO_2) and 1605 (C=N); *m*/*z* 371 (M^+, 17.7%), 292 (28.4), 264 (100) and 235 (29.0) (Found: M^+, 371.1040. $C_{17}H_{17}N_5O_3S$ requires *M*, 371.1052).

2,3,4,5-Tetrahydro-5-methylsulfonyl-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepin-2-one 3e. White solid (30%); mp 254 °C (EtOH); δ_H(200 MHz, $CDCl_3$) 2.88 (3H, s, SO_2Me), 3.36 (1H, dddd, *J* 5.6, 11.7 and 15.3, 3-H), 3.51 (1H, ddd, *J* 5.7 and 15.2, 3-H), 3.79 (3H, s, OMe), 5.48 (1H, dd, *J* 6.4 and 11.5, 4-H), 6.86 (2H, d, *J* 8.8, 3′-H and 5′-H), 6.96 (1H, t, *J* 6.0, NH), 7.19 (2H, d, *J* 8.8, 2′-H and 6′-H), 7.46 (2H, m, 6-H and 8-H), 7.58 (1H, dt, *J* 2.0 and 7.1, 7-H) and 7.82 (1H, dd, *J* 2.6 and 6.8, 9-H); δ_C(50 MHz, $CDCl_3$) 38.9 (SO_2Me), 45.7 (C-3), 55.3 (C-4), 67.2 (OMe), 14.3 (C-3′ and C-5′), 127.3 (C-9a), 127.8 (C-2′ and C-6′), 129.6 (C-6), 130.2 (C-8), 130.8 (C-1′), 132.8 (C-7), 133.3 (C-9), 133.8 (C-5a), 159.6 (C-4′) and 171.3 (C=O); ν_{max}/cm^{-1}1160 (SO_2), 1345 (SO_2), 1685 (N–H) and 3210 (N–H); *m*/*z* 346 (M^+, 2.7%), 267 (34.6), 238 (100), 209 (4.5), 149 (18.1) and 119 (23.9) (Found: M^+, 346.0987. $C_{17}H_{18}N_2O_4S$ requires *M*, 346.0985).

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References

1 J. T. Sharp, *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 7, p. 608.
2 G. Marc and S. Pecar, *Synth. Commun.*, 1998, **28**, 1143 and references cited therein.
3 P. T. Kaye and R. D. Whittal, *S. Afr. J. Chem.*, 1991, **44**, 30; P. T. Kaye and R. D. Whittal, *S. Afr. J. Chem.,* 1991, **44**, 56.
4 P. T. Kaye and M. J. Mphahlele, *J. Chem. Res.*, 1994, (*S*) 62; (*M*) 367.
5 P. T. Kaye and M. J. Mphahlele, *Synth. Commun.*, 1995, **25**, 1495.
6 R. B. English, P. T. Kaye, M. J. Mphahlele and R. D. Whittal, *J. Chem. Res.*, 1995, (*S*) 388; (*M*) 2319; R. B. English, P. T. Kaye and M. J. Mphahlele, *S. Afr. J. Chem.*, 1997, **50**, 55; M. J. Mphahlele and P. T. Kaye, *Magn. Reson. Chem.*, 1998, **36**, 69.
7 S. Daya, P. T. Kaye and M. J. Mphahlele, *Med. Sci. Res.*, 1996, **24**, 137.
8 D. Msiti, F. Gatta and R. Landi-Vittory, *J. Heterocycl. Chem.*, 1971, **81**, 231.
9 K. H. Wunsch, K. H. Stahnke and A. Ehlers, *Chem. Ber.*, 1970, **103**, 2302.
10 I. W. J. Still, M. T. Thomas and A. M. Clish, *Can. J. Chem.*, 1975, **53**, 276.
11 P. T. Kaye, M. J. Mphahlele and M. E. Brown, *J. Chem. Soc., Perkin Trans. 2*, 1995, 835.
12 D. Evans and I. M. Lokhart, *J. Chem. Soc.*, 1965, 4806.
13 J. March, in *Advanced Organic Chemistry: Reaction Mechanism and Structure*, 4th edn., Wiley, New York, 1992, p. 509.

14 M. J. Mphahlele and M. R. C. Mabusela, *S. Afr. J. Chem.*, in the press.
15 A. C. Gelebe and P. T. Kaye, *S. Afr. J. Chem.*, 1992, **45**, 109.
16 (*a*) U. T Bhalerao and G. Thyagarajan, *Can. J. Chem.*, 1968, **46**, 3367; (*b*) D. Msiti and V. Rimatori, *Ann. Ist. Super. Sanita*, 1973, **9**, 150; (*c*) A. Levai and R. Bogna, *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 77; (*d*) A. Levai, *Acta Chim. Acad. Sci. Hung.*, 1980, **104**, 385; (*e*) A. Levai, T. Timor, L. Frank and S. Hosztafi, *Heterocycles*, 1992, **34**, 1523.
17 R. Bach and G. J. Wolber, *J. Org. Chem.*, 1982, **47**, 239.
18 J. A. Donnelly and D. F. Farrell, *Tetrahedron,* 1990, **46**, 885.

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