Synthesis of Benzothiadiazines, Benzothiadiazepines, and Benzothiadiazocines from Intramolecular Azide Reactions and Iodocyclisations

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Abstract: N-Homoallyl-substituted (2-aminoaryl)sulfonamides undergo intramolecular iodocyclisation to furnish aziridine-fused 1,2,6-benzothiadiazocines. The identical aziridine-fused 1,2,6-benzothiadiazocines were also available from an intramolecular azide to alkene 1,3-diploar cycloaddition involving the corresponding N-homoallylic (2-azidoaryl)sulfonamides in boiling carbon tetrachloride. The use of boiling DMF as solvent for the same reaction gave pyrrolo-fused benzothiadiazines. Intramolecular azide–alkene cycloadditions also allowed access to aziridine-fused pyrrolobenzothiadiazepines and pyrrolobenzodiazepines.

Key words: aziridine, azide, benzodiazocine, benzodiazepine

1,4-Benzodiazepines are one of the most studied and successful motifs in medicinal chemistry.[1] The 1,2,5-benzothiadiazepines **1** (Figure 1) are less well studied but have, nonetheless, attracted interest[2] as inhibitors of metalloproteinases and farnesyl protein transferases, as CNS active compounds, as non-nucleosidic reverse transcriptase inhibitors (NNRTI),[3–5] and as TACE inhibitors.[6] The pyrrolobenzothiadiazepine (PBTD) nucleus **2** is an analogue of the well-studied antitumour antibiotic pyrrolobenzodiazepines (PBD) **3**,[7] and has also attracted interest as a non-nucleosidic reverse transcriptase inhibitor.[2,3] As part of a series of studies[8] utilising 1,2-thiazine 1-oxides as precursors to bicyclic 1,2,5-benzothiadiazepines **1**, we became interested in developing methodologies that would allow access to the tricyclic PBTD **2**, and have already published one such route.[9]

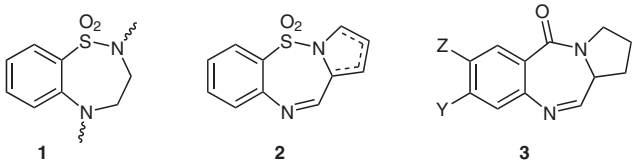

Figure 1

In our search for further routes to the PBTD nucleus, we sought to take advantage of the fact that the 1,2-thiazine-1-oxide **4** (X = NH_2, Scheme 1) should,[10] on hydrolysis, yield a sulfinic acid **5**, which, after spontaneous retro-ene-type loss of sulfur dioxide would furnish a homoallylic sulfonamide **6**. We anticipated that a 5-*endo*-trig iodocyclisation[11] would then yield the corresponding pyrrolidine system **7**, which would serve as a useful precursor for the synthesis of the PBTD nucleus **2**, via, for example, loss of HI, oxidation to the pyrrole,[12] N-formylation and Bischler–Napieralski ring closure. In the event we were surprised to discover that compound **6** underwent an entirely different mode of cyclisation to form an eight-membered ring and we report the results of this study herein.

The requisite 1,2-thiazine 1-oxide precursors **4** were accessed via a hetero-Diels–Alder reaction in good overall yield as described previously.[8,9] Hydrolysis of the 1,2-thiazine 1-oxide moiety in compound **4** was achieved in boiling THF in the presence of 2 M aqueous hydrochloric acid to give the requisite homoallylic sulfonamide derivatives **6** in 70–80% yield, as shown in Scheme 1. With the amino compounds **6** in hand, we subjected them to the standard iodocyclisation conditions,[11,12] namely iodine in the presence of sodium hydrogencarbonate. The products isolated from these reactions were not the desired pyrrolidines **7**, nor any deiodo product derived therefrom. Extensive two-dimensional NMR studies of the products led to the assignment of the structures as the distinctive[13–16] aziridine-fused benzothiadiazocines **8**. As an example, the ^{1}H NMR spectrum of compound **8a** (R^1 = Me, R^2 = H)[17] showed the absence of both of the hydrogens of the amino NH_2 group but showed the presence of the easily identified sulfonamide NH group. The sulfonamide NH was coupled to a methylene group which was in turn coupled to a second methylene unit. This was attached to a quaternary but sp^3 carbon and this in turn was attached to a methyl group and also to a further methylene group. This final methylene had no further carbon or hydrogen couplings, and showed a clear and distinct singlet for each of its two hydrogens, typical of such aziridines.[13–16] This, together with a rational mechanism and alternative synthesis (see below), led to the assignment of the structure as the aziridine-fused benzothiadiazocine **8a**. NOE studies showed that the two methyl groups in compound **8b** were *trans* (or *anti*) to one another, a feature implied the absence of any signal enhancement between the two methyls, and further supported by a strong correlation between the hydrogen on C4 of the 1,2,6-benzothiadiazocine ring and the C5 methyl substituent.

It seems logical to rationalise a mechanism whereby the arylamino nitrogen and not the sulfonamido nitrogen in compound **6** (Scheme 1) is the participating nucleophile

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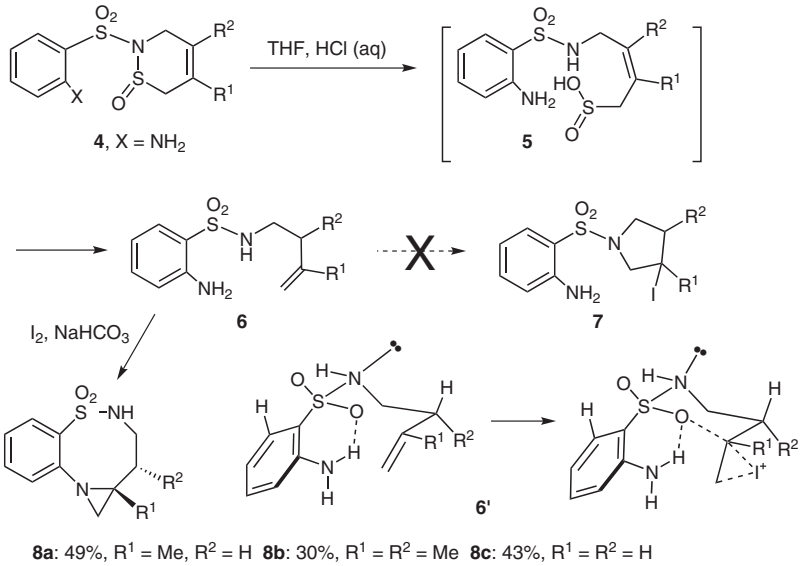


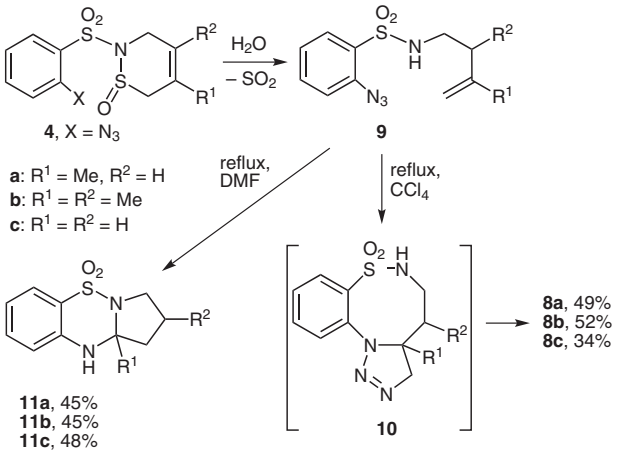
Scheme 1

in the iodocyclisation, thereby giving the thiadiazocine ring. Formation of the aziridine then follows from cyclisation onto the primary alkyl iodide, paralleling well-known methods for the synthesis of aziridines.[13–16] It is of note that homoallylic sulfonamide derivatives **6** can adopt conformations, such as that shown in structures **6′** in Scheme 1, that can encourage cyclisation via the arylamino nitrogen. Scheme 1 also shows a possible explanation for the *trans* relationship of the two methyl groups in compound **8b** in that the R^1 and R^2 groups in intermediate **6′** occupy the two pseudo-equatorial positions shown in the six-membered-ring transition state, leading to the observed *trans* stereochemistry.

We thought it relevant to devise an alternative synthetic sequence to the aziridino-fused benzothiadiazocines **8** and predicted that the azides **9**, shown in Scheme 2, might, on heating, furnish directly the aziridines **8**. Azides **9** were easily synthesised in yields of 71–82% by treating the 1,2-thiazine 1-oxides **4** (X = N_3) in hot THF in the presence of 2 M aqueous hydrochloric acid. Heating azides **9a–c** in carbon tetrachloride for 7.5 hours allowed the isolation of the aziridino-fused benzothiadiazocines **8a–c** in 49%, 52%, and 34% yields, respectively. The products were identical in all respects (including the stereochemistry of compound **8b**) to those obtained by iodocyclisation in Scheme 1.

This route presumably proceeds via an azide–alkene 1,3-dipolar cycloaddition reaction to give an intermediate triazoline **10** which, on extrusion of molecular nitrogen, furnishes the desired aziridines **8**, a sequence shown to be successful for other aziridine syntheses based upon intramolecular azide–alkene reactions.[13–16] The conversion of the azides **9a–c** into the aziridino-fused benzothiadiazocines **8a–c** required exacting conditions by heating in carbon tetrachloride at 85 °C for 7.5 hours. Heating at reflux in acetonitrile, THF, chloroform, or toluene gave complex mixtures of the azide **9**, aziridine **8**, and other unidentified products, from which the pure aziridines could only be isolated in low yield (<10%). Interestingly, heating at reflux in DMF gave a reasonably clean reaction in which the azides **9** were converted into single new products that were not the aziridines **8**, and were found in fact to be the pyrrolo-fused 1,2,4-benzothiadiazines **11**, formed in yields of 45–48%, as shown in Scheme 2.[18,19]

The structures of the products **11** were assigned on the basis of their COSY, HMBC, and HSQC NMR spectra, infrared observations (NH), and accurate mass measurements. All doubt was removed by X-ray crystallographic studies (Figure 2), which confirmed[19] that the products were indeed the pyrrolobenzothiadiazines **11**.



Scheme 2

A possible mechanism, which would explain the formation of compounds **11a–c** is shown in Scheme 3, and involves a rearrangement of the carbon backbone. Thus, nitrene insertion into the alkene gives the primary carbon radical **12**. Hydrogen extrusion by the nitrogen followed by rearrangement of the resulting primary carbon radical

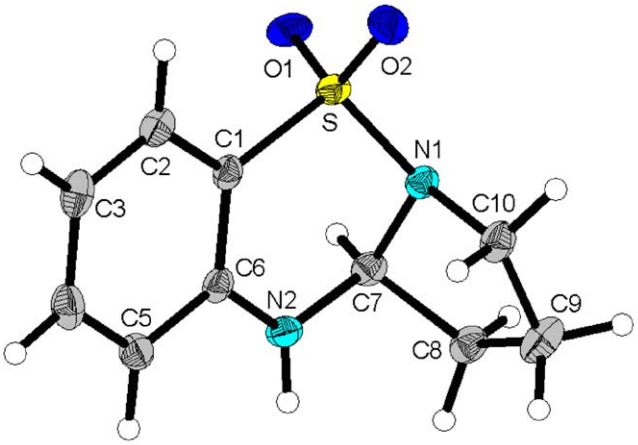
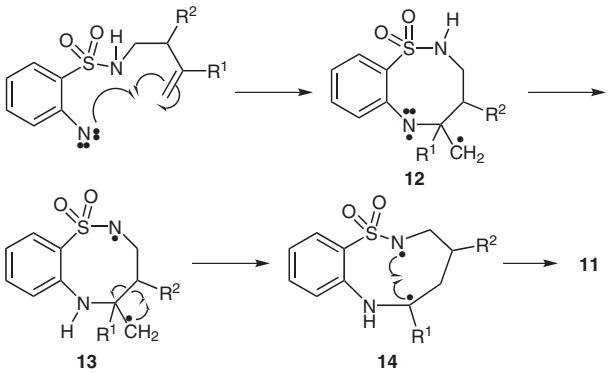


Figure 2 X-ray crystal structure for compound **11c**

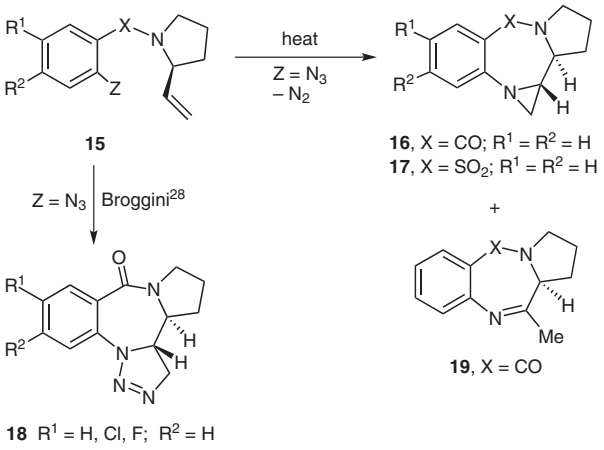
13 gives a rearranged carbon backbone together with the more stable carbon radical **14**. Ring closure then furnishes the final product.

1,5-Benzodiazocines have attracted attention as analogues of the 1,4-benzodiazepines,[20] as novel antibacterial compounds[21] and as positive ionotropic calcium sensitising agents,[22] whilst the corresponding 1,2,6-benzothiadiazocines are attractive as sulfur analogues of this system and have also attracted particular attention as potential NNRTI.[23] Aziridine-fused systems are of general and widespread utility in synthesis and as DNA alkylating agents and potential antitumour agents.[13,24] The pyrrolobenzothiadiazines **11** are a subclass of the larger 1,2,4-benzothiadiazine class that has attracted interest as hepatitis C virus RNA polymerase inhibitors,[25] modulators of AMPA receptors,[26] and as potassium ATP channel activators.[27]



Scheme 3

The successful formation of aziridino-fused systems from the iodocyclisation and intramolecular azide processes led us to investigate the possibility of accessing aziridino-fused analogues of the much sought after[7–9] antitumour antibiotic pyrrolobenzodiazepines (PBD) **3**, a system in which we have been interested for some time.[2,8,9] We thought it of interest to explore the possibility of using intramolecular iodocyclisation or azide cycloaddition as methods of installing an aziridine in the place of the usual imine to give the aziridino-PBD **16** and **17**, as outlined in Scheme 4. The imine behaves as an electrophile in the presence of nucleophilic residues in DNA and is responsible for the biological activity of the PBD[7] – replacement with an aziridine is thus of interest. We are aware of only one other attempt at such a process, in which Broggini[28] was able to show that the azides **15** (Z = N_3; R^1 = H, Cl, F; R^2 = H; X = CO) give stable triazolines **18** in carbon tetrachloride or toluene at 80 °C. With the analogous azide (**15**, R^1, R^2 = H, X = CO) we were repeatedly unable to isolate the triazoline but obtained instead (after heating in acetonitrile at gentle reflux for 20 h) an ca. 1:1 mixture of the aziridine (**16**, R^1 = R^2 = H) and imine **19** in combined yields of 51–60%. Imines are common products from azide–alkene cycloadditions.[15,29] Interestingly, the sulfonamide (**15**, Z = N_3; R^1, R^2 = H; X = SO_2) gave the aziridine **17** (R^1, R^2 = H) as the only isolated product in 44% yield.[30] The stereochemical assignment of compounds **16** and **17** was suggested by coupling constants in the range of 8–9 Hz, by NOESY (aziridine CH_2 to pyrrolidine CH correlation and no CH-to-CH correlation) and by Broggini's unequivocal assignment of the stereochemistries of compounds **18** by X-ray crystallography. These preliminary results with intramolecular azide cycloadditions of precursors **15** are most encouraging, and we are currently exploring the scope of this process in more detail. All attempts to access compounds **16** and **17** by iodination of precursors **15** (Z = NH_2) were unsuccessful due to some unexpected iodination of the aromatic ring.



Scheme 4

In conclusion, we have found that *N*-(*o*-arylamino)-substituted homoallylic sulfonamides undergo iodocyclisation to furnish aziridino-fused 1,2,6-benzothiadiazocines. The same aziridino-1,2,6-benzothiadiazocines were also available from the intramolecular azide–alkene cycloaddition of the corresponding *N*-(*o*-arylazido)-substituted homoallylic sulfonamides in boiling carbon tetrachloride, whereas the use of boiling DMF gave pyrrolobenzothiadiazines. Intramolecular azide–alkene cycloadditions also allowed access to aziridinopyrrolobenzothiadiazepines and pyrrolobenzodiazepines.

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(17) **Typical Procedure for the Synthesis of Compounds 8a–c**
To a stirred solution of the homoallylic 2-aminobenzenesulfonamide **6a–c** (0.15–0.30 g, 1.0 equiv) and $NaHCO_3$ (3.0 equiv) i n dry MeCN (10 mL) was added portionwise finely powdered iodine (3.0 equiv). The reaction mixture was stirred at r.t. until TLC showed no starting material (ca. 4 h) at which point the reaction mixture was treated with sat. aq $Na_2S_2O_3$ until decolourisation occurred. The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude product was purified by gravity column chromatography (SiO_2) using PE–EtOAc (3:2) as the eluent. Compound **8a** was obtained single spot pure [R_f = 0.3 (PE–EtOAc, 2:3)] as a yellow oil (0.161 g, 49% yield) from the *N*-(butenyl)-2-aminobenzenesulfonamide (**6a**, 0.320 g).
Analytical Data
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (3 H, s, Me), 1.51 (1 H, dd, *J* = 11.2, 8.4 Hz, CMeC*H*$_2$CH$_2$NH), 2.02 (1 H, ddd, *J* = 8.4, 5.9, 2.5 Hz, CMeC*H*$_2$CH$_2$NH), 2.11 (1 H, s, aziridino CH), 2.33 (1 H, s, aziridino CH), 3.36 (1 H, m, CH$_2$C*H*$_2$NH), 3.79 (1 H, ddd, *J* = 15.0, 7.5, 6.1 Hz, CH$_2$C*H*$_2$NH), 5.32 (1 H, t, *J* = 6.1 Hz, SO_2NH), 6.85 (1 H, d, *J* = 7.9 Hz, ArH), 6.98 (1 H, dt, *J* = 8.4, 0.8 Hz, ArH), 7.35 (1 H, dt, *J* = 8.4, 1.4 Hz, ArH), 7.83 (1 H, dd, *J* = 7.9, 1.3 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (CH_3), 35.8 (CH_2), 39.2 (CH_2), 40.2 (CH_2), 43.9 (q), 121.7 (CH), 122.0 (CH), 128.6 (CH), 129.6 (q), 133.0 (CH), 147.8 (q). IR: ν_{max} = 3101 (br m), 2953 (m), 2896 (m), 1591 (m), 1472 (s), 1439 (m), 1333 (s), 1216 (s), 1158 (s), 866 (m) cm^{-1}. HRMS (ES$^+$): *m/z* calcd for $C_{11}H_{14}N_2O_2S$: 239.0849; found: 239.0845 (100%) [M + H]$^+$.

(18) **Typical Procedure for the Synthesis of Compounds 11a–c**
A solution of the *N*-(butenyl)-2-azidobenzenesulfonamide **9a–c** (ca. 100 mg) in DMF (5 mL) was heated at reflux temperature until TLC showed no starting material (2–3 h). The mixture was cooled, the solvent removed by reduced pressure rotary evaporation, and the residue purified by flash silica column chromatography (PE–EtOAc = 3:2). As an example, pyrrolo-1,2,4-benzothiadiazine **11b** (76 mg, 45%) was obtained from azidobenzenesulfonamide **9b** (130 mg).
Analytical Data
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (3 H, s, CH_3), 1.78 (3 H, d, *J* = 7.2 Hz, CH_3), 1.88 (1 H, dd, *J* = 13.0, 10.2 Hz, CMeCH*H*CHMe), 2.21 (1 H, dd, *J* = 13.0, 7.1 Hz, CMeC*H*HCHMe), 2.41–2.48 (1 H, m, [(CH$_2$)$_2$C*H*Me], 3.23 (1 H, dd, *J* = 10.3, 7.0 Hz, NC*H*H), 3.58 (1 H, dd, *J* = 10.0, 7.0 Hz, NCH*H*), 4.56 (1 H, s, NH), 6.61 (1 H, d, *J* = 8.4 Hz, ArH), 6.76 (1 H, t, *J* = 8.0 Hz, ArH), 7.24 (1 H, td, *J* = 8.4, 1.3 Hz, ArH), 7.68 (1 H, dd, *J* = 8.0, 1.3 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_3), 27.2 (CH_3), 28.3 (CH), 51.0 (CH_2), 57.9 (CH_2), 79.8 (q), 115.3 (CH), 117.5 (CH), 129.3 (CH), 133.2 (CH), 142.3 (q), 145.0 (q). IR (thin film): ν_{max} = 3366 (s), 2965 (s), 2932 (s), 1677 (m), 1605 (s), 1484 (s), 1453 (s), 1322 (s), 1157 (s), 751 (s) cm^{-1}. HRMS (ES$^+$): *m/z* calcd for $C_{12}H_{16}N_2O_2S + H^+$: 253.1005; found: 253.1008 [M + H]$^+$.

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(30) **Analytical Data for Compound 16 (X = CO, $R^1 = R^2 = H$)** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (1 H, d, *J* = 3.6 Hz, aziridine CH_2), 2.04–2.16 (3H, m, CH_2 + C*H*H), 2.18–2.26 (1 H, m, CH*H*), 2.53 (1 H, d, *J* = 4.3 Hz, aziridine CH_2), 2.78 (1 H, ddd, *J* = 9.5, 4.3, 3.6 Hz, aziridine CH), 3.34 (1 H, ddd, *J* = 9.5, 2.9, 1.6 Hz, pyrrolidine CH), 3.62–3.69 (1 H, m, NCH_2), 3.81–3.95 (1 H, m, NCH_2), 7.01 (1 H, dt, *J* = 7.9, 0.7 Hz, ArH), 7.11 (1 H, d, *J* = 8.1 Hz, ArH), 7.44–7.52 (1 H, m, ArH), 7.74 (1 H, d, *J* = 7.9 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (CH_2), 29.4 (CH_2), 32.7 (CH_2), 44.8 (CH), 46.1 (CH_2), 58.1 (CH), 122.0 (CH), 122.9 (CH), 126.8 (q), 129.7 (CH), 131.2 (CH), 145.6 (q), 150.3 (q). IR (thin film): ν_{max} = 3063 (m), 2979 (m), 1625 (s), 1456 (s), 1405 (s), 1039 (m), 922 (m), 766 (s), 730 (s), 704 (s) cm^{-1}. HRMS (ESI^+): *m/z* calcd for $C_{13}H_{14}N_2O + H^+$: 215.1179; found: 215.1178 $[M + H]^+$.