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The synthesis of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines from 1,2-thiazine 1-oxides—sulfonamide analogues of the pyrrolobenzodiazepine antitumour natural products

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Abstract—Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) and the corresponding pyrrolobenzothiadiazepines (PBTDs) are attractive targets as natural and synthetic antitumour antibiotics and as non-nucleosidic reverse transcriptase inhibitors. A concise synthesis of the PBTD class is presented, which starts from *o*-azidobenzenesulfonamide and its conversion into 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine 1-oxides via Diels–Alder reaction. After a one-pot ring contraction, desulfurisation and aromatisation process, accompanied by concomitant same pot conversion of the azide group into a primary amine via the Staudinger reaction, these 1,2-thiazine-1-oxides yield a 1-(*o*-aminobenzenesulfonyl)pyrrole. *N*-Formylation of the amine and Bischler–Napieralski ring closure onto the pyrrole completes the PBTD synthesis.

The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are of interest[1,2] due the antitumour antibiotic activity of the PBD natural products, of which DC-81 **1** and prothracarcin **2** (Fig. 1) are typical, and synthetic analogues of which are in clinical development.[3] The related pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTD) **3** have received much less interest, but are attractive as sulfonamide analogues of the antitumour antibiotic PBDs,[4] and also as non-nucleosidic inhibitors of reverse transcriptase.[5] The 1,2,5-benzothiadiazepines have also attracted attention for the range of activities that they possess as analogues of the CNS-active 1,4-benzodiazepines[6] and also as tumour necrosis factor-alpha converting enzyme (TACE) inhibitors, and as inhibitors of metalloproteinases in general.[6c,7] Almost all reported syntheses of the PBDs and PBTDs use proline as the source of the five-membered ring,[1–5] with only a few methods relying on a de novo pyrrole construction methodology,[1,8] and there are no methods, which construct the pyrrole from a diene. Although relatively unexploited, the synthesis of simple (unfused) pyrroles from dienes has proven its importance to the synthetic chemist.[9] In this letter we report that 2-arylsulfonyl substituted 1,2-thiazine-1-oxides **4** (see Fig. 1), which are easily constructed from a diene via a Diels–Alder reaction, can be transformed in a one-pot process into the 1-arylsulfonyl-substituted pyrroles **5**, which can then be easily converted into the PBTD nucleus.

Our interest in this area came about as part of a programme of studies aimed at exploring the uses of 1,2-thiazine-1-oxides in heterocyclic synthesis.[10–12] We previously reported that 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides **4** are precursors for the synthesis of unsaturated bicyclic 1,2,5-benzothiadiazepines via conversion into α,ω-iminophosphoranyl ketones and subsequent aza-Wittig reaction.[12] One of the key transformations in this process was the construction of 1-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides **4** via a Diels–Alder reaction, which relied upon the in situ generation of the unstable *N*-sulfinyl dienophile **6** (see Fig. 1) by treating the sulfonamide with pyridine and thionyl chloride. The Diels–Alder reaction was high yielding but gave, on occasion, the 1-(*o*-azidobenzenesulfonyl)pyrrole **7** (Fig. 1) as a minor product (<5%). We became interested in optimising the yield of this pyrrole as it is a potential intermediate for the synthesis of PBTDs. The origin of this pyrrole product would seem to be base

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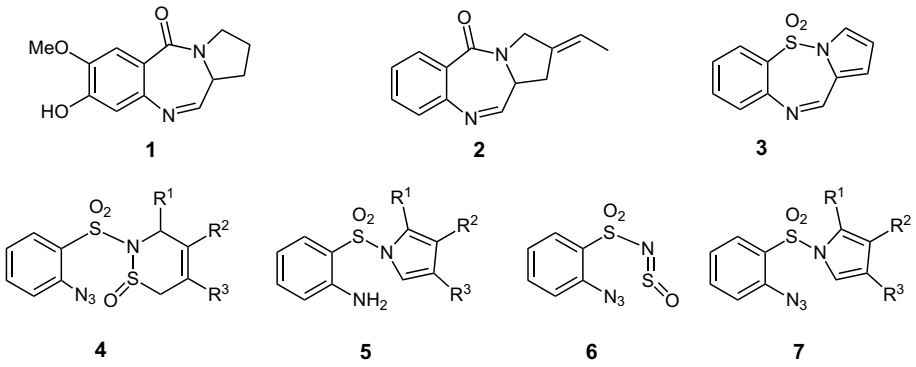
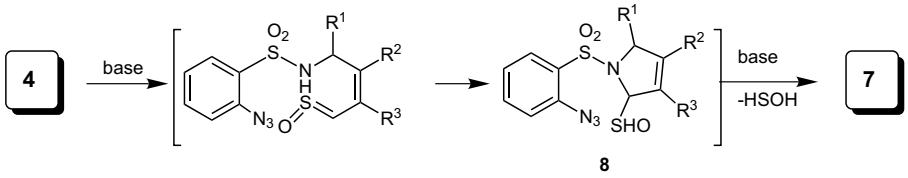


Figure 1.

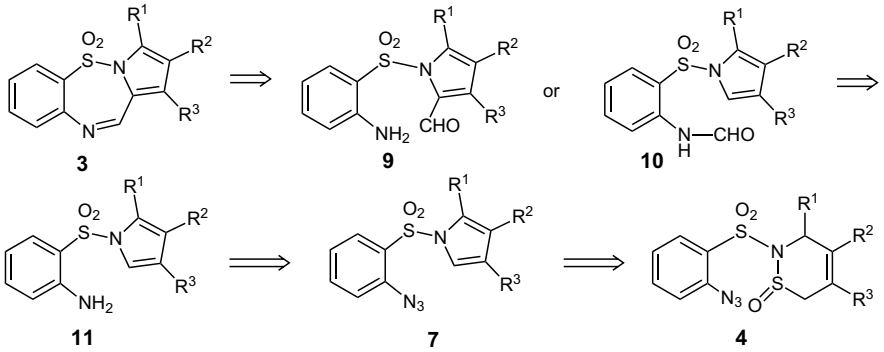


Scheme 1.

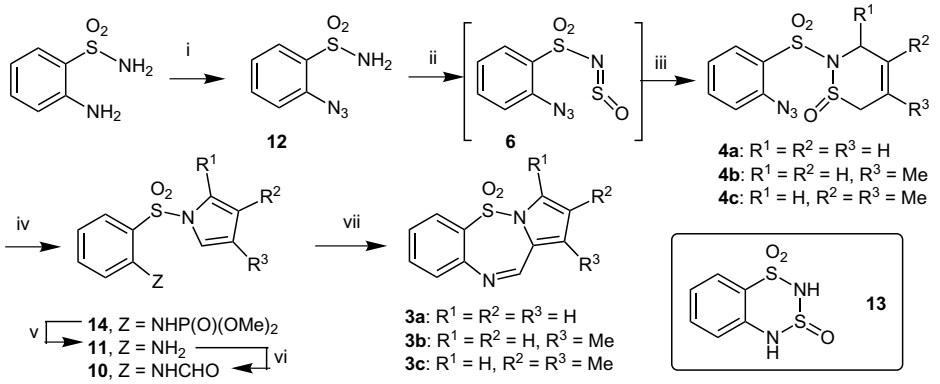
catalysed ring opening of the 1,2-thiazine-1-oxide **4**, subsequent closure to a pyrrolidine **8** and loss of HSOH to give the pyrrole **7**, as shown in Scheme 1. Indeed, Harrington[9a] has also observed the low yielding formation of pyrroles from 1,2-thiazine-1-oxides under similar basic conditions, and went on to optimise the sequence to great effect[9a] via the addition of a thiophile, trimethyl phosphite, in a synthetic approach to simple (unfused) 1-(*p*-toluenesulfonyl)pyrroles.

The use of trimethyl phosphite in this conversion was attractive to us as we anticipated that we could undertake concurrent conversion of the azide group in compound **7** into an amine via the hydrolysis of an intermediate iminophosphorane [ArN=P(OMe)$_3$], formed after Staudinger reaction of the azide with the phosphite.[13] Our retrosynthetic strategy for the PBTD nucleus **3** is shown in Scheme 2 and relies upon the installation of the imine bond as the final step, giving the formylated precursor **9** or **10**, and hence leading to the 1-(*o*-aminobenzenesulfonyl)pyrrole **11** as the key target for formylation. Functional group interconversion (azide to amine) leads back to compound **7**, and the key transformation of 1,2-thiazine-1-oxide into pyrrole gives the readily available (see below) 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides **4** as starting materials.

The 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides **4** were constructed using a hetero Diels–Alder reaction[14] between the appropriate diene and the *N*-sulfinyl heterocumulene[15] **6**, derived from *o*-azidobenzenesulfonamide **12**, as shown in Scheme 3. *o*-Azidobenzenesulfonamide **12** was obtained from *o*-aminobenzenesulfonamide in over 90% yield via diazotisation and treatment with sodium azide. *o*-Aminobenzenesulfonamide could not be used directly as the starting material for the sulfinylation reaction as this resulted in the formation of the dithiadiazine **13**. The *N*-sulfinyl **6** was best formed from a 1:1:2 ratio of sulfonamide **12**, thionyl chloride and pyridine,



Scheme 2.



Scheme 3. Reagents and conditions: (i) $NaNO_2$, HCl(aq) then NaN_3. (ii) $SOCl_2$, pyridine, THF, 0 °C, 3 h. (iii) $R^1HC{=}CR^2{-}CR^3{=}CH_2$. (iv) $P(OMe)_3$, Et_3N, MeOH, 25 °C, then 2 M NaOH(aq). (v) HCl(g), THF, room temp. (vi) HCO_2H, $(MeCO)_2O$, THF. (vii) $P(O)Cl_3$, $(CH_2Cl)_2$.

and had to be formed in situ, as attempted isolation resulted in its hydrolysis back to the sulfonamide. Thus, the 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides **4a–c** were obtained from *o*-azidobenzenesulfonamide in yields of 78%, 82% and 93%, respectively, and were next treated with a 2:1 molar equivalent mixture of trimethyl phosphite:triethylamine in methanol. The desired 1-(*o*-aminobenzenesulfonyl)pyrroles **11a–c** were isolated in yields of 50%, 73% and 50%, respectively, after basic aqueous (2 M NaOH) work-up, good yields considering the multi-step nature of the process. The phosphoramidates **14a–c** were the only other products of this reaction and were isolated in yields of 23%, 10% and 18%, respectively, and are probably the result of partial basic hydrolysis of the iminophosphorane. The phosphoramidates **14** could be converted into the amine **11** in 85–90% yields using gaseous hydrogen chloride in THF.[16]

The conversion of the 1-(*o*-aminobenzenesulfonyl)pyrroles **11** into the PBTD nucleus required the introduction of a single carbon. Vilsmeier formylation of the pyrrole ring in compound **11** gave the desired product **9** (shown in Scheme 2) but, in the event, this would not cyclise, probably due to the deactivation of the aldehyde by delocalisation into the pyrrole ring. However, *N*-formylation using a preformed mixture of acetic anhydride and formic acid[17] gave the *N*-formylated products **10a–c** (Scheme 3) in yields of 98%, 77% and 83%, respectively. The final ring closure was effected by the Bischler–Napieralski reaction using phosphorus oxychloride in 1,2-dichloroethane and gave the desired PBTDs **3a–c** in 55%, 59% and 43% yields, respectively.[18,19]

To conclude, a concise route to the pyrrolobenzothiadiazepine (PBTD) nucleus has been reported via the one-pot conversion of 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine-1-oxides into 1-(*o*-aminobenzenesulfonyl)pyrroles followed by formylation and Bischler–Napieralski ring closure. The PBTDs are attractive as sulfonamide analogues of the synthetic and natural antitumour pyrrolobenzodiazepines (PBDs). We are now adapting this route to allow access to such PBDs.

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18. All new compounds gave satisfactory $^{1}H/^{13}C$ NMR spectra, mass spectra and HRMS/microanalysis.
19. Experimental procedures and typical spectroscopic details: preparation of 1,2-thiazine 1-oxides **4**. To a stirred solution of *o*-azidobenzenesulfonamide (2.00 g, 10.1 mmol) and anhydrous pyridine (2.0 equiv) in anhydrous tetrahydrofuran (50 mL), under an atmosphere of dry nitrogen at 0 °C, was added, dropwise with stirring over a period of 3 h, a solution of thionyl chloride (1.0 equiv) in anhydrous tetrahydrofuran (10 mL), to yield the crude *N*-sulfinyl compound **6**. The appropriate 1,3-diene (1.6 equiv) was added, and the mixture was allowed to warm to room temperature overnight. The solvent was removed by rotary evaporation and the crude product was purified by flash silica column chromatography (petroleum ether–ethyl acetate/1:1). For example, 2-(*o*-azidobenzenesulfonyl)-4,5-dimethyl-1,2-thiazine-1-oxide **4c** was obtained as a yellow solid (3.06 g, 93% yield). Mp: 137–138 °C. δ_H (400 MHz, $CDCl_3$): 1.71 (3H, s, Me), 1.79 (3H, s, Me), 3.23 (1H, d, *J* 15.9, CH_2), 3.63 (1H, d, *J* 14.2, CH_2), 3.68 (1H, d, *J* 14.2, CH_2), 3.86 (1H, d, *J* 16.2), 7.28 (1H, t, *J* 7.8, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.66 (1H, dt, *J* 7.8, 1.1, Ar*H*), 8.01 (1H, dd, *J* 8.0, 0.9, Ar*H*). δ_C (100 MHz, $CDCl_3$): 16.9 (Me), 19.7 (Me), 42.9 (*C*H_2), 55.5 (*C*H_2), 115.0 (q), 120.3 (*C*H), 123.5 (q), 124.6 (*C*H), 127.5 (q), 131.6 (*C*H), 135.1 (*C*H), 139.0 (q). ν_{max} (chloroform, cm^{-1}): 3006 (w), 2918 (w), 2134 (s, N_3), 1585 (m), 1575 (m), 1472 (s), 1444 (m), 1351(s), 1291 (m), 1171 (s), 1102 (s), 885 (m), 758 (s), 614 (m). EI+ mass spectrum (*m*/*z*, %): 326 ([M]$^+$, 9%), 298 (12%), 278 (10%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). HRMS (ESI+): found [M+H$^+$] 327.0587, $C_{12}H_{14}N_4O_3S_2$ requires 327.0585.
Preparation of 1-(2-aminobenzenesulfonyl)pyrroles **11**: to a rapidly stirring solution of triethylamine (1 equiv) and trimethylphosphite (2 equiv) in anhydrous methanol (10 mL) was added the 1,2-thiazine 1-oxide **4** (0.30–0.50 g, 1 equiv) in one portion and the mixture was stirred at room temperature under an atmosphere of dry nitrogen for 2 h. The volatiles were removed by rotary evaporation and the crude mixture was purified by silica column chromatography (petroleum ether–ethyl acetate 40:60+10% triethylamine). For example, compound **11c** (0.135 g, 50%) was obtained as pale yellow oil from 1,2-thiazine 1-oxide **4c** (0.350 g, 1.07 mmol). δ_H (400 MHz, $CDCl_3$): 1.91 (6H, s, 2 × Me), 4.5–4.7 (2H, br s, NH_2), 6.63 (1H, d, *J* 8.2, Ar*H*), 6.71 (1H, t, *J* 7.6, Ar*H*), 6.84 (2H, s, 2 × pyrrole-*H*), 7.25 (1H, t, *J* 7.4, Ar*H*), 7.61 (1H, d, *J* 8.1, Ar*H*). δ_C (100 MHz, $CDCl_3$): 10.1 (Me), 117.4 (*C*H), 117.6 (*C*H), 117.8 (*C*H), 120.0 (q), 124.2 (q), 129.2 (*C*H), 135.0 (*C*H), 145.6 (q). ν_{max}(thin film, cm^{-1}): 3457 (s, NH_2), 3377 (s, NH_2), 2966 (m), 2919 (m), 1636 (s), 1599 (m), 1484 (s), 1455 (m), 1348 (m), 1296 (m), 1068 (s), 1034 (s), 829 (s), 744 (m), 699 (m), 610 (m), 588 (m). EI+ mass spectrum (*m*/*z*, %): 250 ([M]$^+$, 70%), 185 (25%), 156 (20%), 108 (35%), 94 (100%), 65 (80%), 39 (50%). HRMS (ESI+): Found [M+H$^+$] 251.0845, $C_{12}H_{14}N_2O_2S$ requires 251.0849.
Preparation of 1-(2-formamidobenzenesulfonyl)pyrroles **10**: formic acid (2.25 equiv) was added into acetic anhydride (2 equiv) at 0 °C and the solution was stirred at room temperature for 2 h. This solution was added to a solution of the 1-(2-aminobenzenesulfonyl)pyrrole **11** (0.10–0.20 g, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and the reaction mixture was stirred at room temperature for 20 h. The crude product was purified by silica column chromatography (petroleum ether–ethyl acetate 40:60). As an example, compound **10c** (0.120 g, 83%) was obtained as a pale yellow oil from 1-(2-aminobenzenesulfonyl)pyrrole **11c** (0.130 g, 0.52 mmol). δ_H (400 MHz, $CDCl_3$): 1.97 (6H, s, 2 × Me), 6.85 (2H, s, 2 × pyrrole-*H*), 7.23 (1H, t, *J* 7.7, Ar*H*), 7.61 (1H, t, *J* 7.7, Ar*H*), 7.77 (1H, d, *J* 8.0, Ar*H*), 8.52 (1H, d, *J* 7.9, Ar*H*), 8.56 (1H, s, C*H*O), 9.45 (1H, br s, N*H*). δ_C (100 MHz, $CDCl_3$): 10.1 (Me), 117.5 (*C*H), 123.0 (*C*H), 124.2 (*C*H), 125.7 (q), 125.8 (q), 126.1 (q), 128.8 (*C*H), 135.1 (*C*H), 158.8 (*C*HO). ν_{max} (thin film, cm^{-1}): 3290 (m, NH), 3020 (w), 2921 (w), 1706 (s), 1674 (s), 1579 (m), 1514 (m), 1403 (m), 1358 (m), 1290 (m), 1216 (s), 1160 (s), 1071 (m), 669 (m), 611 (m). EI+ mass spectrum (*m*/*z*, %): 278 ([M$^+$], 60%), 250 (10%), 228 (60%), 184 (85%), 156 (20%), 120 (50%), 95 (100%), 65 (85%). HRMS (CI+NH_3): Found [M+NH_4^+] 296.1063, $C_{13}H_{14}N_2O_3S$ requires 296.1063.
Preparation of pyrrolobenzothiadiazepines **3**: A solution of 1-(2-formamidobenzenesulfonyl)pyrrole **10** (~0.10 g, 1 equiv) and phosphorus oxychloride (21.6 equiv) in 1,2-dichloroethane (2 mL) was heated at reflux temperature for 3 h. Evaporation of the solvent gave a residue, which was purified by silica column chromatography (petroleum ether–ethyl acetate, 40:60). For example, compound **3c** (0.040 g, 43%) was obtained from 1-(2-formamidobenzenesulfonyl)pyrrole **10c** (0.100 g, 0.36 mmol) as a bright orange oil. δ_H (400 MHz, $CDCl_3$): 2.06 (3H, s, Me), 2.26 (3H, s, Me), 7.33 (1H, s, pyrrole-*H*), 7.42 (1H, dt, *J* 8.0, 1.0, Ar*H*), 7.60–7.73 (2H, m, 2 × ArH), 8.04 (1H, dd, *J* 7.9, 1.2, Ar*H*), 8.62 (1H, s, N=C*H*). δ_C (100 MHz, $CDCl_3$): 9.6 (Me), 9.9 (Me), 120.8 (*C*H), 123.6 (q), 124.9 (q), 125.3 (*C*H), 126.2(*C*H), 129.9(*C*H), 130.1 (q), 132.5 (q), 134.4 (*C*H), 144.1 (q), 148.6 (*C*H). ν_{max} (cm^{-1}): 2924 (w), 1603 (s), 1582 (s), 1458 (m), 1365 (s), 1294 (m), 1181 (s), 1137 (m), 1107 (m), 910 (s), 832 (m), 767 (m), 733 (m). HRMS (ESI+): Found [M+H$^+$] 261.0691, $C_{13}H_{12}N_2O_2S$ requires 261.0692.