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# New and versatile syntheses of 3-alkyl- and 3-aryl-1,2,4-benzotriazine 1,4-dioxides: preparation of the bioreductive cytotoxins SR 4895 and SR 4941

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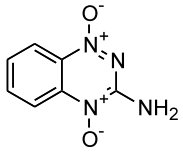
**Abstract**—Palladium-mediated coupling of 3-chloro-1,2,4-benzotriazine 1-oxide with a variety of stannanes in the presence of $Pd(PPh_3)_4$ gives 3-alkyl derivatives in good yields. Suzuki reaction of the 3-chloro compound with phenylboronic acids gives 3-aryl-1,2,4-benzotriazine 1-oxides. Oxidation of 1-oxides with trifluoroperacetic acid gives the 1,4-dioxides. This method provides a better route to the potential anti-cancer agents SR 4895 and SR 4941. 

Tirapazamine **1** (TPZ, 3-amino-1,2,4-benzotriazine 1,4-dioxide, Tirazone™) is a bioreductive drug[1] undergoing clinical trials as a cytotoxic agent for the potentiation of radiotherapy and chemotherapy. TPZ **1** is currently in Phase II trials in combination with radiotherapy and in Phase III trials with cisplatin.[2] TPZ is activated by one-electron reductases[3] to form a radical anion. This radical anion may be oxidized by molecular oxygen under aerobic conditions, generating superoxide radical, which mediates aerobic toxicity. Under hypoxic conditions the radical anion may be protonated[4] and species derived from the radical anion interact with DNA, although the exact mechanism is unclear.[5] TPZ causes DNA double-strand breaks under anoxic conditions[5a] and these correlate with cytotoxicity.[6] Thus, one-electron reduction of TPZ, reversible in the presence of oxygen, results in selective cytotoxicity to hypoxic cells, often found in solid tumours and considered responsible for relapse after radiotherapy.[7]

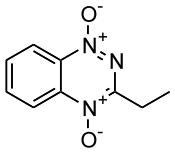
An analogue development programme identified several second-generation analogues suitable as 'backup' clinical candidates for TPZ **1**.[8] The 3-ethyl-1,4-dioxide (SR 4895) **2** and the 3-(2-methoxyethyl)-1,4-dioxide (SR 4941) **3** showed increased aqueous solubility, increased electron affinity and equivalent in vivo activity compared to TPZ **1**. Synthesis of these 3-alkyl derivatives via the Bamberger synthesis[9] required the preparation and cyclization of appropriately substituted formazans to give 1,2,4-benzotriazines, which were then oxidized to the corresponding dioxides.[10] This approach required a separate synthesis for each derivative.

The application of palladium-mediated Stille[11] and Suzuki[12] couplings to heterocyclic chemistry has grown rapidly in recent years,[13] leading us to consider the 1,2,4-benzotriazine 1-oxide system as a useful substrate for such chemistry, directed towards the synthesis of 3-alkyl- and 3-aryl-derivatives.

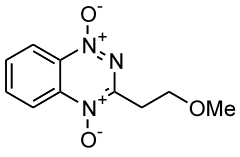
We wish to report a novel, versatile, and efficient synthesis of 3-alkyl 1,2,4-benzotriazine 1,4-dioxides that utilizes Stille coupling with a key 3-chloro-1,2,4-benzotriazine 1-oxide intermediate **6**. Further elaboration gives access to a range of derivatives exemplified by the




**1**




**2** (SR4895)




**3** (SR4941)

*Keywords*: antitumour compounds; Stille reaction; Suzuki reaction; benzotriazoles.

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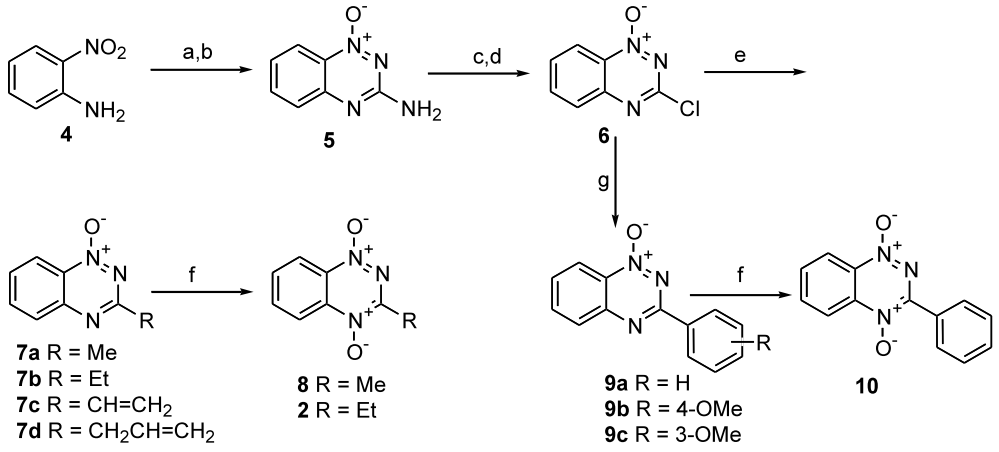
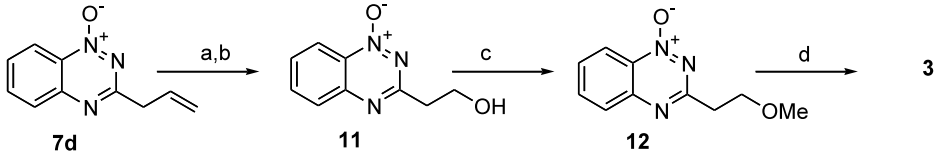



**Scheme 1.** *Reagents and conditions*: (a) $NH_2CN$, *c*HCl, 100°C; (b) 30% aq. NaOH, 100°C; (c) $NaNO_2$, HCl; (d) $POCl_3$, $PhNMe_2$, 80°C; (e) $SnR_4$ or *n*-$Bu_3SnR$, $Pd(PPh_3)_4$, DME, 85°C; (f) $CF_3CO_3H$, DCM; (g) $RC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, $Cs_2CO_3$, DME, water, 85°C.




**Scheme 2.** *Reagents and conditions*: (a) $O_3$, DCM/MeOH; (b) $NaBH_4$, EtOH; (c) $TMSCH_2N_2$, $HBF_4$, DCM; (d) $CF_3CO_3H$, DCM.

synthesis of **2** and **3**. Thus, conversion of 2-nitroaniline **4** to 3-amino-1,2,4-benzotriazine 1-oxide **5** using the method of Mason and Tennant[14] and subsequent diazotization and chlorination of the intermediate phenol gave the key chloride **6**[15] in 68% overall yield (Scheme 1).

Chloride **6** was sufficiently activated to undergo Stille coupling readily with a variety of stannanes in the presence of $Pd(PPh_3)_4$ in DME at 85°C to give good yields (66–86%) of 3-alkyl 1-oxides **7a**–**d**. Oxidation of 3-methyl-1-oxide **7a** and 3-ethyl-1-oxide **7b** with trifluoroperacetic acid gave the dioxides **8** and **2**,[16] respectively. Further elaboration of the 3-vinyl-1-oxide **7c** and the 3-allyl-1-oxide **7d**[17] gave access to a range of substituted derivatives. In particular, ozonolysis of **7d**, followed by a reductive workup gave the 3-(2-hydroxyethyl)-1-oxide **11** that was methylated[18] to give **12** and oxidized to **3**[19] with trifluoroperacetic acid (Scheme 2).

The chloride **6** also allows access to 3-aryl derivatives, previously prepared by a Bamberger cyclization.[9] Thus, Suzuki coupling of **6** with arylboronic acids in the presence of $Pd(PPh_3)_4$ and $Cs_2CO_3$ in DME/water at 85°C gave the 3-aryl-1-oxides **9a**–**c** in good (56–65%) yields[20] (Scheme 1). Oxidation of **9a** with trifluoroperacetic acid gave dioxide **10**.

The Stille coupling of the key chloride **6** provides access to an efficient synthesis of the potential anticancer agents SR 4895 **2** and SR 4941 **3** as well as providing access to a wide variety of substituted analogues. Suzuki coupling of **6** with a variety of phenylboronic acids to give 3-aryl 1,2,4-benzotriazine 1-oxides extends the utility of this approach. Biological evaluation of these derivatives will be reported in a forthcoming publication.

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17. Experimental data for **7d**: mp (EtOAc/pet. ether) 57–58°C; $^1$H NMR ($CDCl_3$): $\delta$ 8.45 (dd, $J=8.6$, 1.4 Hz, 1 H, H 8), 8.10 (dd, $J=8.4$, 1.4 Hz, 1 H, H 5), 7.94 (ddd, $J=8.4$, 7.1, 1.4 Hz, 1 H, H 6), 7.70 (ddd, $J=8.6$, 7.1, 1.4 Hz, 1 H, H 7), 6.15–6.24 (m, 1 H, H 2′), 5.31 (dq, $J=17.0$, 1.5 Hz, 1 H, H 3′), 5.24 (dq ($J=10.1$, 1.5 Hz, 1 H, H 3′), 3.80 (dq, $J=6.8$, 1.5 Hz, 2 H, H 1′); $^{13}$C NMR ($CDCl_3$): $\delta$ 165.2 (C 3), 147.5 (C 4a), 135.6 (C 6), 133.3 (C 8a), 132.7 (C 2′), 130.1 (C 5), 128.8 (C 7), 120.8 (C 8), 118.5 (C 3′), 41.8 (C 1′). Anal. calcd for $C_{10}H_9N_3O$: C, 64.2; H, 4.9; N, 22.5. Found: C, 63.9; H, 4.9; N, 22.7%.
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19. Experimental data for **3**: mp 102–103°C; $^1$H NMR [$(CD_3)_2SO$]: $\delta$ 8.35–8.39 (m, 2 H, H 5, H 8), 8.12 (ddd, $J=8.7$, 7.1, 1.4 Hz, 1 H, H 6), 7.96 (ddd, $J=8.7$, 7.1, 1.4 Hz, 1 H, H 7), 3.80 (t, $J=6.7$ Hz, 2 H, $CH_2$), 3.26–3.31 (m, 5 H, $CH_2O$, $OCH_3$); $^{13}$C NMR: $\delta$ 152.3 (C 3), 139.2 (C 4a), 135.5 (C 6), 134.4 (C 8a), 132.0 (C 7), 121.0 (C 8), 118.8 (C 5), 66.7 ($CH_2O$), 57.8 ($OCH_3$), 30.1 ($CH_2$). Anal. calcd for $C_{10}H_{11}N_3O_3$: C, 54.3; H, 5.0; N, 19.0. Found: C, 54.1; H, 5.2; N, 19.0%.
20. Experimental data for **9b**: mp (EtOAc/pet. ether) 168–170°C; $^1$H NMR ($CDCl_3$): $\delta$ 8.44–8.49 (m, 3 H, H 8, H 2′, H 6′), 8.02 (d, $J=8.7$ Hz, 1 H, H 5), 7.90 (ddd, $J=8.7$, 7.2, 1.4 Hz, 1 H, H 6), 7.64 (ddd, $J=8.5$, 7.2, 1.4 Hz, 1 H, H 7), 7.20 (ddd, $J=9.0$, 2.9, 2.1 Hz, 2 H, H 3′, H 5′), 3.90 (s, 3 H, $OCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 162.8 (C 4′), 160.5 (C 3), 147.8 (C 4a), 135.5 (C 6), 133.2 (C 8a), 130.3 (C 3′, C 5′), 129.5 (C 5), 129.1 (C 7), 126.5 (C 1′), 120.3 (C 8), 114.3 (C 2′, C 6′), 55.4 ($OCH_3$). Anal. calcd for $C_{14}H_{11}N_3O_2$: C, 66.4; H, 4.4; N, 16.6. Found: C, 66.5; H, 4.4; N, 16.7%.