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New possibilities of 1,2,4-triazines functionalization: first examples of synthesis and structure of boron-containing 1,2,4-triazines

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Abstract—By oxidation of 3-thioderivatives of 1,2,4-triazine **1a**,**b** 3-alkylsulfonic derivatives **2a**,**b** were obtained. Interaction of the sulfonic derivative **2a** with indole leads to 3-oxo-5-indolyl-5-phenyl-as-triazine **4**. The sulfone **2a** reacts with 1-ethyl-2,6-dimethylquinolinium iodide to give 3-(1-ethyl-6-methyl-1,2-dihydroquinoline-2-methylene)-5-phenyl-1,2,4-triazine **5**. The 3-morpholino- **3** and 3-thioderivatives **6**, **7a**,**b** of as-triazine were obtained by interaction of the sulfone **2** with morpholine and organic boron-containing thiols. The crystal structure of boron-containing derivative of as-triazine **7b** was investigated by X-ray analysis.

The 1,2,4-triazine derivatives glyacitidine and tetracitidine in their nucleotide forms suppress the synthesis of pyrimidine bases and possess antitumour activity[1,2]. The as-triazine cycle is part of the pyrimidotriazine nucleus in natural antibiotics, such as fervenuline, xantotricine, reumicine and 2-methylfervenuline (MSD-92)[3].

The transport and accumulation of boron-containing compounds into tumour tissue, which is necessary for further improvement of BNCT (boron neutron cancer therapy), is a continuing challenge.[4] It seems advantageous to use 1,2,4-triazines as heterocyclic carriers of boron-containing fragments.

In the present work we investigated the possibilities of synthesis of various derivatives starting from 2-thio-substituted as-triazines. It was intended to change the nucleofugacity of the 2-thiogroup by its oxidation to alkylsulfone, and also to activate the triazine cycle by its protonation. Activation of the nucleophilic agent was realized by generation of the corresponding anion by means of treatment of the reaction mixture with an organic base.

By oxidation of the 3-alkylthioderivatives of 1,2,4-triazine **1a**,**b** (Scheme 1) with gaseous chlorine in a water suspension at 5–10 °C the corresponding 3-alkylsulfonyl derivatives **2a**,**b** were obtained.[‡]

Keywords: Triazine; Boranes; Boron neutron capture therapy; Mass spectrometry.

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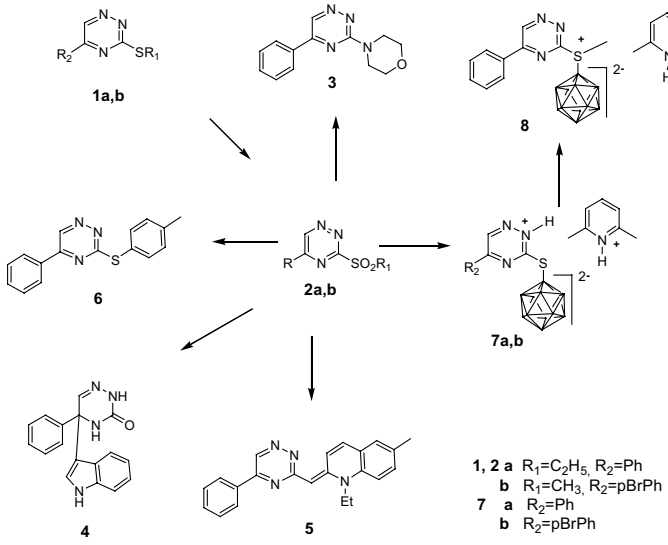
‡ All new compounds gave satisfactory mass spectra. Spectra with boron fragments gave the expected isotope distribution pattern. These ions are indicated with ‡; the indicated masses correspond to the maximum intensity peak of a fragment showing the expected isotope distribution pattern for 10 boron atoms with natural abundance of ^{10}B and ^{11}B. Structure was established by ^1H NMR. Indicated are: No of compound, yield %, mp °C (solvent for crystallization). Molecular ion mass, m/z (relative intensity, %). ^1H NMR in DMSO-d_6, 200 MHz: **2a**, 65–70, 139–140 (ethanol). 249 (8), $[M]^{+\cdot}$. 1.33 (t, 3H, $J = 7.3$ Hz, CH_3), 3.80 (kv, 2H, $J = 7.3$ Hz, CH_2), 7.55–7.85 (m, 3H, $3 \times CH_{arom}$), 8.35–8.55 (m, 2H, $2 \times CH_{arom}$). **2b**, 60–65, 171–172 (ethanol). 315 (17), $[M]^{+\cdot}$. 3.60 (s, 3H, CH_3), 7.86 (d, 2H, $J = 8.8$ Hz, $2H_{arom}$), 8.36 (d, $2 \times CH$, $J = 8.8$ Hz, $2H_{arom}$), 10.35 (s, 1H, $CH_{triazin}$). **5**, 60–65, 142–143 (ethanol). 340 (80) $[M]^{+\cdot}$. 1.37 (t, 3H, $J = 6.8$ Hz, CH_3); 2.32 (s, 3H, CH_3), 4.17 (kv, 2H, $J = 6.8$ Hz, CH_2), 5.75 (s, 1H, H), 7.20–9.10 (m, 10H, CH_{arom}), 9.38 (s, 1H, $CH_{triazin}$). **6**, 75–80, 168–170 (ethanol). 279 (46) $[M]^{+\cdot}$. 2.39 (s, 3H, CH_3), 7.34 (d, 2H, $J = 7.8$ Hz, $2 \times CH_{arom}$), 814 (d, 2H, $J = 7.8$ Hz, $2 \times CH_{arom}$), 9.82 (s, 1H, $CH_{triazine}$). **7a**, 40–45, 199–200, 329‡ (75), $[M]^{+\cdot}$. −0.50–2.50 (br b 11H, $B_{12}H_{11}$), 2.66 (s, 6H, $2CH_{3lutidine}$), 7.50–7.90 (m, 5H, CH_{arom}), 8.34 (t, 1H, $J = 7.6$ Hz, 4-$CH_{lutidine}$), 8.49 (d, 2H, $J = 7.6$ Hz, C_3H, $C_5H_{lutidine}$), 9.62 (s, 1H, $CH_{triazin}$). **7b**, 30–35, 227–229, 408‡ (25) $[M]^{+\cdot}$. −0.50–2.50 (br b, 11H, $B_{12}H_{11}$), 2,68 (s, 6H, $2 \times CH_{3lutidine}$), 7.72 (d, 2H, $J = 7.8$ Hz, C_3H, $C_5H_{lutidine}$), 7.83 (d, 2H, $J = 8.8$ Hz, 2CH), 8.36 (t, 1H, $J = 7.8$ Hz, $CH_{lutidine}$), 8.43 (d, 2H, $J = 8.8$ Hz, $2CH_{arom}$), 9.60 (s, 1H, $CH_{triazine}$). **8**, 75–80, 96–97. 344‡ (100), $[M]^{+\cdot}$. −0.50–2.50 (br b, 11H, $B_{12}H_{11}$), 2.68 (s, 6H, $2 \times CH_{3lutidine}$), 3.08 (s, 3H, $3 \times SH_3$), 7.55–7.85 (m, 5H, CH_{arom}), 8.20–8.50 (m, 3H, $CH_{lutidine}$), 10.27 (s, 1H, $CH_{triazin}$).



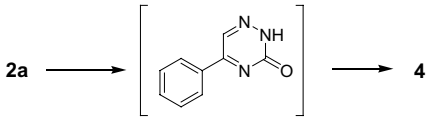
Scheme 1.

Upon short heating of compounds **2a** with morpholine in ethanol the alkylsulfonic group was smoothly substituted and the described[5] morpholyl derivative **3a** was formed.

We discovered a unusual transformation of the sulfone **2a** when it was heated with indole in ethanol in presence of trifluoroacetic acid. In result of this reaction 3-oxo-5-indolyl-5-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine **4** was obtained. In this case, probably at first a hydrolysis of the sulfonic group occurred, resulting in the formation of 3-oxo-5-phenyl-2,3-dihydro-1,2,4-triazine; then indole was added and compound **4** was formed as described in Ref. 6 (Scheme 2).

The sulfone **2a** reacts with 1-ethyl-2,6-dimethylquinolinium iodide in presence of triethylamine in DMSO at room temperature to form 3-(1-ethyl-6-methyl-1,2-dihydroquinoline-2-methylene)-5-phenyl-1,2,4-triazine **5**. The sulfonic group in **2a** was substituted by reaction with thiocresol in presence of lutidine at room temperature. As result of this reaction 3-*p*-methylphenylthio-4-phenyl-1,2,4-triazine **6** was obtained with high yield.

Interaction of the sulfones **2** in CH_3CN with the boron-containing thiol $Na_2B_{12}H_{11}SH$ as nucleophile[7] at room temperature in presence of lutidine gave the first boron-containing derivatives of 1,2,4-triazine **7a**,**b**, analogous to the reaction with morpholine. Sulfone **2** (0.078 g, 0.3 mmol) was stirred with 0.095 g (0.43 mmol) $Na_2B_{12}H_{11}SH$ in 2 mL of acetonitrile in the presence of 0.05 mL lutidine for 3 h at room temperature. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was treated with 2 mL of



Scheme 2.

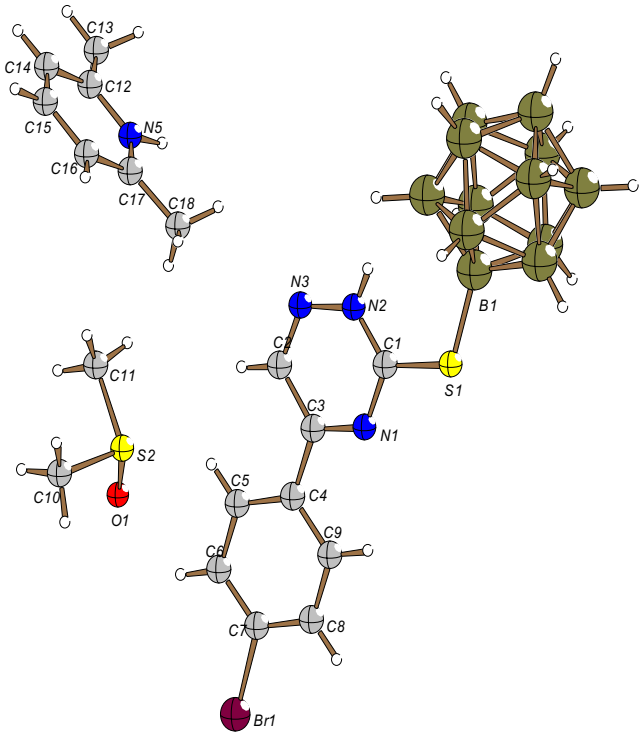
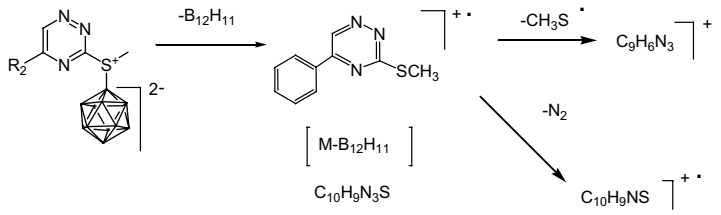


Figure 1. Molecular structure of compound **7b**. Selected bond lengths (Å): S(1)–C(1) 1.703(5), S(1)–B(1) 1.900(6), N(1)–C(3) 1.315(6), N(1)–C(1) 1.355(6), C(1)–N(2) 1.328(6), N(2)–N(3) 1.337(6), N(3)–C(2) 1.303(6), C(2)–C(3) 1.430(7), C(3)–C(4) 1.471(7), C(4)–C(5) 1.392(7), C(4)–C(9) 1.404(7), C(5)–C(6) 1.393(7), C(6)–C(7) 1.380(7), C(7)–C(8) 1.372(7), C(7)–Br(1) 1.884(5), C(8)–C(9) 1.388(7), N(5)–C(17) 1.343(7), N(5)–C(12) 1.347(7), C(12)–C(14) 1.372(7). Selected bond angles (°): C(1)–S(1)–B(1) 108.0(3), B(5)–B(1)–S(1) 113.3(4), B(9)–B(1)–S(1) 125.1(4), B(11)–B(1)–S(1) 116.3(4), B(2)–B(1)–S(1) 128.9(4), B(3)–B(1)–S(1) 121.0(4), C(3)–N(1)–C(1) 117.9(4), N(2)–C(1)–N(1) 119.3(5), N(2)–C(1)–S(1) 123.3(4), N(1)–C(1)–S(1) 117.3(4), C(1)–N(2)–N(3) 125.4(5), C(2)–N(3)–N(2) 115.7(5), N(3)–C(2)–C(3) 121.0(5), N(1)–C(3)–C(2) 120.4(5), N(1)–C(3)–C(4) 117.4(5), C(2)–C(3)–C(4) 122.1(5), C(5)–C(4)–C(9) 119.4(5), C(5)–C(4)–C(3) 122.0(5), C(9)–C(4)–C(3) 118.6(5), C(4)–C(5)–C(6) 120.2(5), C(7)–C(6)–C(5) 119.3(5), C(8)–C(7)–C(6) 121.4(5), C(8)–C(7)–Br(1) 118.2(4), C(6)–C(7)–Br(1) 120.4(4), C(7)–C(8)–C(9) 119.9(5), C(8)–C(9)–C(4) 119.8(5).



Scheme 3.

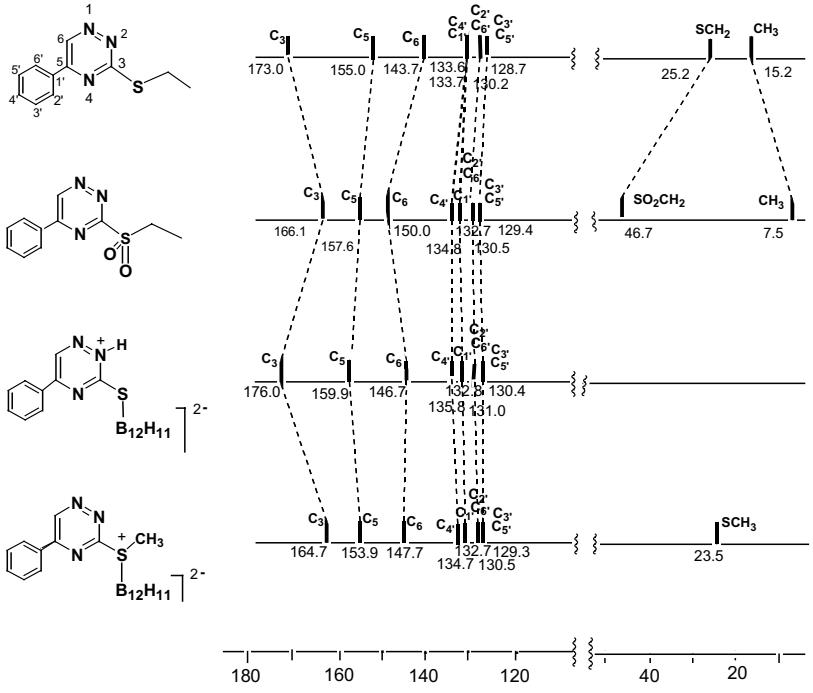


Figure 2. Chemical shifts of C-atoms in the ^{13}C NMR spectra of the 3-thioderivatives of as-triazine.

water and **7** was obtained as solid. It was filtered, redissolved in dimethylsulfoxide and precipitated with ethanol.

The negative fast atom bombardment (FAB) mass spectrum of compound **7a**,**b** shows an ion, which corresponds to the boron-containing molecular anion of this compound. In the positive-ion FAB spectrum an ion at m/z 108 corresponding to the protonated lutidine ($C_7H_{10}N^+$) is observed.

The ^1H NMR-spectrum of compound **7** contains proton signals of the as-triazine moiety and those of one molecule of lutidine.

The X-ray investigation of crystals of **7b**[§] showed that this compound is a salt of the singly-charged anion of the boron-containing sulfide of as-triazine with the cation of the protonated lutidine. It is important to note that one negative charge of the boron moiety is compensated by protonation of the N-2-atom of the triazine cycle (Fig. 1). Both protonation of the triazine cycle of compound **7** and formation of a stable salt show that the basicity of the triazine cycle is raised considerably as a result of the electron-donating influence of the boron-containing substituent.[¶]

[§] Crystals of compound **7b** for X-ray analysis were obtained by crystallization from DMSO and are the solvate with one molecule of DMSO.

[¶] Crystal data for **7b**: At 173(2) K, a crystal of $C_{18}H_{33}N_4B_{12}BrOS_2 \times (CH_3)_2SO$ ($0.60 \times 0.30 \times 0.10$ mm) is monoclinic, $a = 1424.7(1)$, $b = 1175.3(1)$, $c = 1783.7(2)$ pm, $\alpha = 90$, $\beta = 100.65(1)$, $\gamma = 90°$, $V = 2.9353(5)$ nm^3, space group $P2_1/c$, $Z = 4$, $D_c = 1.347$ Mg/m^3, $\mu = 1.565$ mm^{-1}, wavelength 71.073 pm, $F(000) = 1216$, diffractometer Siemens P4, theta range for data collection 2.50°–25.00°, index ranges $-16 \leqslant h \leqslant 1$, $-13 \leqslant k \leqslant 1$, $-21 \leqslant l \leqslant 20$, reflections collected 6521, independent reflections 5128 [$R_{int} = 0.0336$], completeness to $\theta = 25.00°$ 99.4%, refinement method full-matrix least-squares on F^2, data/restraints/parameters 5128/0/368, Goodness-of-fit on F^2 1.013, final R indices [$I > 2\sigma(I)$] $R1 = 0.0620$, $wR2 = 0.1122$, R indices (all data) $R1 = 0.1359$, $wR2 = 0.1411$, largest diff. peak and hole 0.389 and -0.446 eÅ^{-3}. The structure was solved by direct methods, subsequent least-squares refinement located the positions of the remaining atoms in the electron density maps. All nonhydrogen atoms were refined with individual anisotropic deflection parameters. H-atoms were calculated with common isotropic temperature factors. All calculations were performed with the SHELX program package.[8] The figure was done with the program DIAMOND.[9]

Treatment of the boron-containing derivative **7a** (0.044 g, 0.1 mmol) with methyl iodide (0.03 g, 0.2 mmol) in 0.3 mL dimethylformamide at room temperature for 24 h gave the *S*-methylderivative **8**, which was isolated by dilution with water and washing of the oil with ethanol and water.

In the electron impact (EI) mass spectra of compound **8** the following ions were registered: m/z 203 ($C_{10}H_9N_3S[M-B_{12}H_{11}]$, meas. 203.05225 amu, theor. 203.05171 amu, $\Delta = 2.6$ ppm) and ions resulting from the cleavage of N_2 and $SCH_3^{\cdot}$ from this ion: m/z 175 ($C_{10}H_9NS$, meas. 175.04535 amu, theor. 175.04558 amu, $\Delta = 1.3$ ppm) and m/z 156 ($C_9H_6N_3$, meas. 15,605,635 amu, theor. 156.05617, $\Delta = 1.2$ ppm) (Scheme 3).

Figure 2 shows a diagram of chemical shifts (CS) of the ^{13}C-atoms in 3-thiosubstituted 1,2,4-triazines. It is seen that a variation of the substituent at the S-atom has a noticeable influence on CS of the C-3- and C-6-atoms (mutual para-position), while the change of CS of C-5 is insignificant; it must be marked that the alkylsulfonic group essentially decreases CS of the C-3-atom, while on the contrary the electron-donating boron-containing substituent essentially increases it.

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