The first synthesis of boron-containing stable σ-adducts of 5-nitropyrimidine

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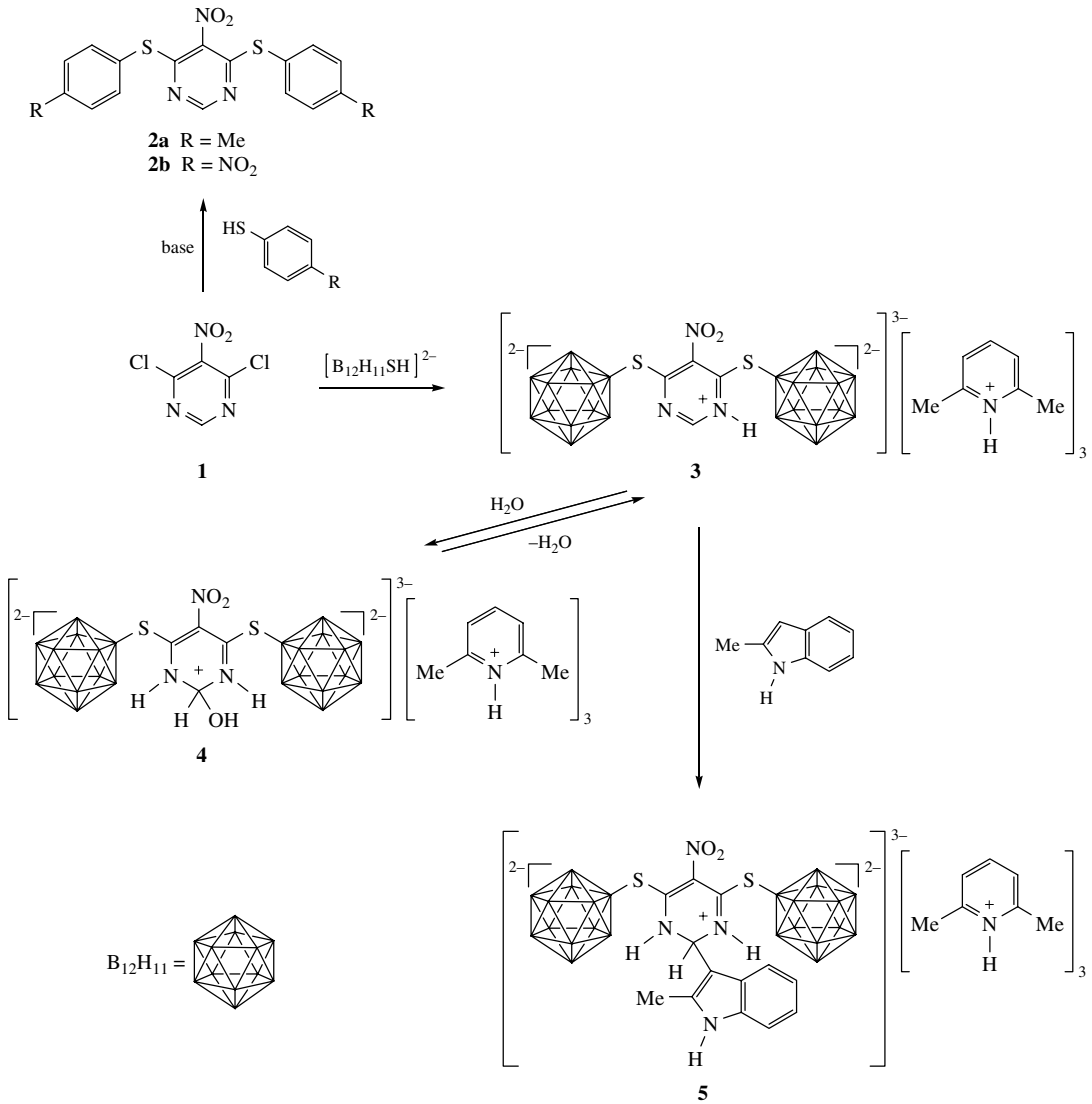
The interaction of a boron-containing thio derivative of 5-nitropyrimidine with nucleophiles led to the first boron-containing σ-adduct of 5-nitropyrimidine; the structures of the test compounds were investigated by NMR spectroscopy, mass spectrometry and X-ray analysis.

The use of pyrimidine bases as a transport vehicle for the delivery of active molecules or their fragments is caused by an easier metabolism of pyrimidines in tumoral cells than in healthy tissues.[1] 4,6-Bis(benzylthiopyrimidines) show an antitumor activity.[2] The anticarcinogenic action of condensed pyrimidines (purinethiols) is related to their ability to be included in nucleic acids of tumoral cells.[1] The transport and accumulation of boron-containing compounds in tumor tissues, which is necessary for further improvement of boron neutron cancer therapy (BNCT), is of considerable current interest.[3]

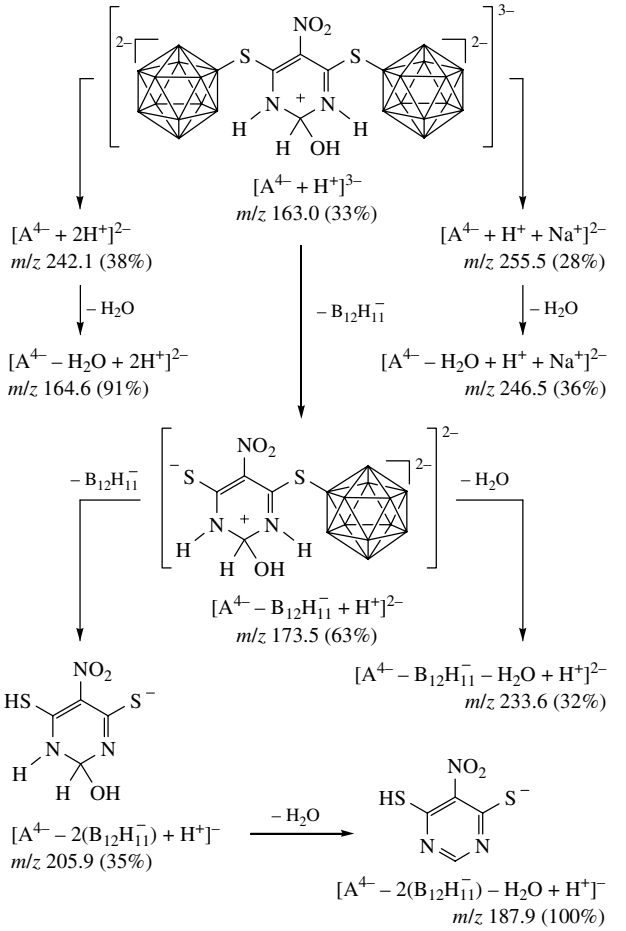
We investigated the synthesis and properties of thio derivatives of 5-nitropyrimidine, which can be used for the synthesis of thiopurines and their analogues.[4]

The interaction of 4,6-dichloro-5-nitropyrimidine **1** (Scheme 1) with arylthiols in the presence of lutidine in dimethylsulfoxide (DMSO) at room temperature leads to the formation of corresponding arylthio derivatives of 5-nitropyrimidine **2a**,**b**.† Under similar reaction conditions, the addition of **1** to the boron-containing thiol $Na_2B_{12}H_{11}SH$ (sodium mercaptododecaborate) occurs. In this case, boron-containing derivative of 5-nitropyrimidine **3** is obtained.

Interestingly, product **3** crystallises from an aqueous solution of DMSO as covalent hydrate **4**, which gradually eliminates water and turns into unhydrated species **3** upon storage in dry



Scheme 1



Scheme 2

DMSO. This transformation could be observed by ^{1}H NMR spectroscopy. Actually, after the dissolution of compound **4** in [$^2H_6$]DMSO, the ^{1}H NMR spectrum‡ showed a broad signal at 6.2 ppm due to the proton at the *sp*^{3}-hybridised C(2) atom of covalent hydrate **4**, and a weak signal at 8.9 ppm due to the proton at the C(2) atom of unhydrated form **3** was observed. After 5–7 h, the signal at 6.2 ppm disappeared, and the signal at 8.9 ppm became more intense.

In the negative electrospray ionisation (ESI) mass spectrum of compound **4**,§ doubly and triply charged molecular ions (*m*/*z* 242.1 and 163.0) are observed, corresponding to $[A^{4-} + H]^{3-}$ (*m*/*z* 163.0), $[A^{4-} + 2H]^{2-}$ (*m*/*z* 242.1) and $[A^{4-} + H + Na]^{2-}$ (*m*/*z* 255.5). The triply charged anion sequentially loses both $[B_{12}H_{11}]^-$ moieties, yielding the ions $[A^{4-} – B_{12}H_{11} + H]^{2-}$ (*m*/*z* 173.5) and $[A^{4-} – 2(B_{12}H_{11}) + H]^-$ (*m*/*z* 205.9). All ions, except for the triply charged anion, show loss of water, which leads to the formation of an aromatic cyclic structure (Scheme 2).

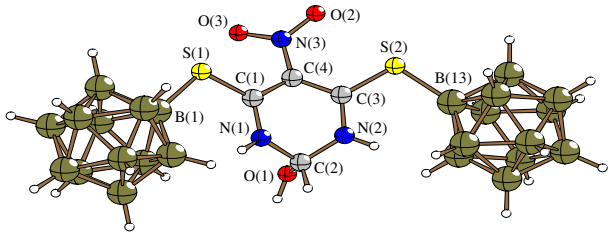


Figure 1 Molecular structure of the triply charged anion of compound **4**. Selected bond lengths (Å): S(1)–C(1) 1.714(4), S(1)–B(1) 1.890(4), C(1)–N(1) 1.320(4), C(1)–C(4) 1.431(5), N(1)–C(2) 1.448(4), C(2)–O(1) 1.403(4), C(2)–N(2) 1.446(4), N(2)–C(3) 1.332(4), C(3)–C(4) 1.413(5), C(3)–S(2) 1.719(3), C(4)–N(3) 1.431(4), N(3)–O(3) 1.225(4), N(3)–O(2) 1.235(4), S(2)–B(13) 1.902(4); selected bond angles (°): C(1)–S(1)–B(1) 108.73(18), N(1)–C(1)–C(4) 115.5(3), N(1)–C(1)–S(1) 121.2(3), C(4)–C(1)–S(1) 122.9(3), C(1)–N(1)–C(2) 122.0(3), O(1)–C(2)–N(2) 108.9(3), O(1)–C(2)–N(1) 111.4(3), N(2)–C(2)–N(1) 106.1(3), C(3)–N(2)–C(2) 121.9(3), N(2)–C(3)–C(4) 115.(3), N(2)–C(3)–S(2) 120.3(3), C(4)–C(3)–S(2) 123.9(3), C(3)–C(4)–C(1) 119(3), C(3)–C(4)–N(3) 121.5(3), C(1)–C(4)–N(3) 119.2(3), O(3)–N(3)–O(2) 121.9(3), O(3)–N(3)–C(4) 119.0(3), O(2)–N(3)–C(4) 119.0(3), C(3)–S(2)–B(13) 109.14(17).

The X-ray investigation of crystals of **4**¶ showed that this compound is a salt of the triply charged anion of the boron-containing sulfide of 5-nitropyrimidine with three molecules of protonated lutidine. Note that one negative charge of the boron moiety is compensated by the protonation of the N(2) [N(6)] atom of the pyrimidine ring (Figure 1).

Both the protonation of the pyrimidine ring of compound **4** and the formation of a heterocyclic cation show that the basicity of the pyrimidine ring is raised considerably as a result of the electron-donating influence of the two boron-containing substituents each carrying a double negative charge.

We discovered an unusual transformation of the boron-con-

† *Preparation of sulfides* **2**, **4**. 4,6-Dichloro-5-nitropyrimidine (0.5 mmol) was stirred with a corresponding thiol (1.0 mmol) in 2 ml of DMSO in the presence of 0.05 ml of lutidine for 4–5 h at room temperature. Products **2**, **4** precipitated from DMSO with water.

Reaction of sulfide **4** *with 2-methylindole*. Sulfide **4** (0.04 mmol) was stirred with 0.1 mmol of 2-methylindole in 2 ml of DMSO for 12 h at room temperature. The reaction mixture was diluted with water (2 ml), and compound **5** was obtained as a solid. The product was washed with water (2 ml).

‡ The ^{1}H NMR spectra were recorded on a Bruker DPX 200 spectrometer. Chemical shifts were measured using DMSO as an internal standard.

2a: 80–85% yield, mp 159–160 °C (ethanol). ^{1}H NMR, δ: 2.36 (s, 6H, 2Me), 7.28 (d, 4H, CH_{arom}, *J* 8.0 Hz), 8.46 (s, 1H, H-2). MS, *m*/*z*: 369 (25%) $[M]^+$.

2b: 75–80% yield, mp 192–194 °C (ethanol). ^{1}H NMR, δ: 7.86 (d, 4H, CH_{arom}, *J* 8.0 Hz), 8.30 (d, 4H, CH_{arom}, *J* 8.0 Hz), 8.53 (s, 1H, H-2). MS, *m*/*z*: 431 (90%) $[M]^+$.

4: 30–35% yield, mp 170–172 °C (ethanol). ^{1}H NMR, δ: –0.50–2.50 (br. b, 22H, $2B_{12}H_{11}$), 2.69 (s, 18H, 3×2-$Me_{lutidine}$, 3×6-$Me_{lutidine}$), 6.24 (s, 1H, H-2), 7.69 (d, 6H, 3×H-$3_{lutidine}$, 3×H-$5_{lutidine}$, *J* 8.0 Hz), 8.32 (t, 3H, 3×H-$4_{lutidine}$, *J* 8.0 Hz), 9.64 (s, 1H, H-2).

5: 45–50% yield, mp 134–135 °C. ^{1}H NMR, δ: –0.50–2.50 (br. b, 22H, $2B_{12}H_{11}$), 2.49 (s, 3H, Me_{indole}), 2.68 (s, 18H, 3×2-$Me_{lutidine}$, 3×6-$Me_{lutidine}$), 6.14 (s, 1H, H-2), 6.90–7.60 (m, 4H, CH_{indole}), 7.72 (d, 6H, 3×H-$3_{lutidine}$, 3×H-$5_{lutidine}$, *J* 8.0 Hz), 8.25–8.40 (m, 3H, $3CH_{lutidine}$), 9.14 (s, 2H, NH), 11.49 (s, 1H, NH_{indole}).

§ The mass data were acquired on a Finnigan MAT 8200 double-focusing mass spectrometer (electron energy, 70 eV; ion source temperature, 200 °C; resolution R ≈ 9000). Metastable ion analyses were performed on a Finnigan MAT 95 double-focusing mass spectrometer using the above ionisation conditions. The ESI mass spectra were measured on a Bruker Esquire-LC ion trap mass spectrometer.

All new compounds gave satisfactory mass spectra. Mass spectra with boron fragments gave the expected isotope distribution pattern.

¶ Crystals of compound **4** for X-ray analysis were obtained by crystallization from aqueous DMSO. *Crystal data for* **4**: at 173(2) K, a crystal of $C_{27}H_{66}N_6B_{24}O_6S_3 \cdot Me_2SO \cdot 2H_2O$ (0.40×0.25×0.10 mm) is monoclinic, a = 2948.2(6), b = 890.43(18), c = 3850.7(8) pm, α = 90°, β = 98.79(3)°, γ = 90°, V = 9.99(1) nm^3, space group *C*2/*c*, Z = 8, d_{calc} = 1.232 g cm^{-3}, μ = 0.194 mm^{-1}, wavelength of 71.073 pm, $F(000)$ = 3888, Siemens P4 diffractometer, θ range for data collection, 2.37–26.00°, index ranges $-35 \le h \le 35$, $-10 \le k \le 10$, $-47 \le l \le 47$, reflections collected, 17079; independent reflections, 7453 (R_{int} = 0.0673); completeness to θ = 26.00°, 76.1%; refinement method, full-matrix least-squares on F^2; data/restraints/parameters, 7453/13/657; Goodness-of-fit on F^2, 0.844; final R indices [$I > 2\sigma(I)$], R_1 = 0.0532, wR_2 = 0.1122; R indices (all data), R_1 = 0.1082, wR_2 = 0.1282; largest diff. peak and hole 0.335 and –0.221 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 non-hydrogen 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.[6] The figure was done with the program DIAMOND.[7]

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 275757. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.

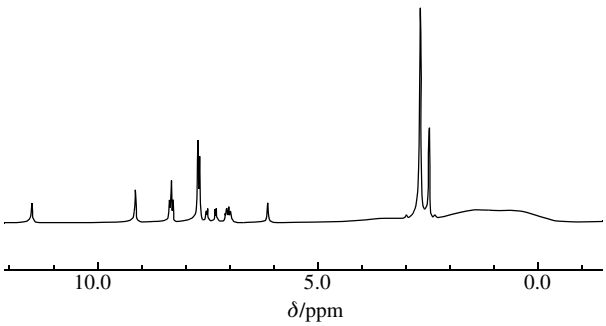
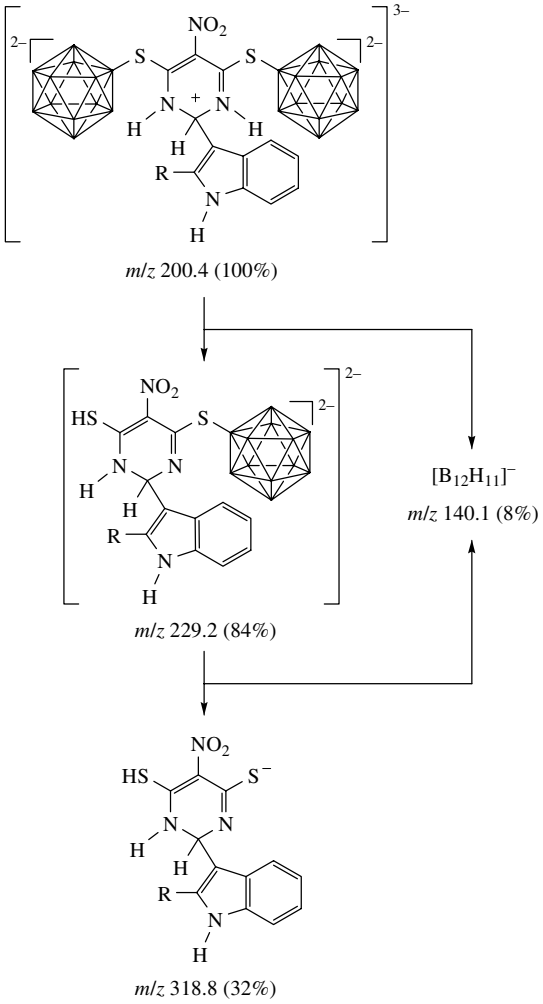


Figure 2 ^{1}H NMR spectrum of compound **5** in [$^2H_6$]DMSO.

taining sulfide of 5-nitropyrimidine **3** (**4**) when it reacted with 2-methylindole in DMSO at room temperature. This reaction resulted in the formation of a 2-(α-methylindol-3-yl) derivative of 5-nitropyrimidine **5**.

The ^{1}H NMR spectrum of compound **5** (Figure 2) contains proton signals of the pyrimidine moiety and those of three lutidine molecules. For σ-adduct **5**, the characteristic signal of a proton at the sp^3-hybridised C(2) atom is observed at 6.16 ppm. The NH protons of the pyrimidine nucleus are observed as two-proton singlets at 9.16 ppm, which indicate the symmetry of the molecule.

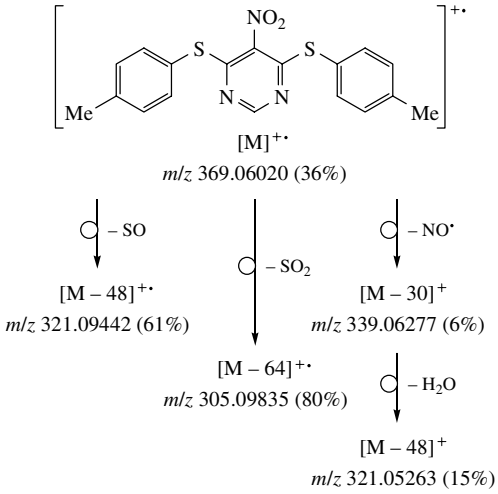
The anions observable in the negative-ion ESI mass spectra confirm the suggested structure of compound **5**. The base peak of the spectrum is a triply charged anion at *m/z* 200.4 corresponding to $[A^{4-} + H^+]^{3-}$. As a result of disintegration of the triply charged anion, the singly charged anion $[B_{12}H_{11}]^-$ (*m/z* 140.1) and the doubly charged anion $[A^{4-} - B_{12}H_{11}^- + H^+]^{2-}$ (*m/z* 229.9) are formed. Fragmentation of the latter yields $[B_{12}H_{11}]^-$ and a singly charged anion of the dithio derivative at *m/z* 318.8 corresponding to $[A^{4-} - 2(B_{12}H_{11}^-) + H^+]^-$ (Scheme 3).



Scheme 3

Note that the σ-adducts obtained are stable boron-containing dihydropyrimidines carrying a positive charge, which is delocalised on the heterocyclic nucleus. At the same time, it is known that 4,6-alkoxy derivatives of 5-nitropyrimidine form anionic σ-complexes with acetone in the presence of potassium hydroxide, which are countered into neutral dihydropyrimidines.[5]

Upon heating in butanol (115 °C, 2 h), arylthio derivatives **2a** do not react with 2-methylindol even in the presence of trifluoroacetic acid.



Scheme 4

The electron impact (EI) mass spectra of the 4,6-diarylthio derivatives of 5-nitropyrimidine **2** show peaks that can be explained by skeletal rearrangements. Thus, intense peaks of [M – 48] and [M – 64] and a weak peak of [M – 30] were observed. To obtain information on these ions, high-resolution (HR) mass measurements and metastable ion analysis were performed. For compound **2a**, the results are shown in Scheme 4.

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