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Cyanuric and thiocyanuric esters as carriers of boron-containing fragments and their fragmentation in mass spectrometry

Yuri A. Azev,[a,b] Thomas Dülcks[a] and Detlef Gabel[a,*]

[a]*Department of Chemistry, University of Bremen, PO Box 330440, D-28334 Bremen, Germany*
[b]*Ural Scientific Research Institute of the Technology of Medicinal Preparations, Ekaterinburg, Russia*

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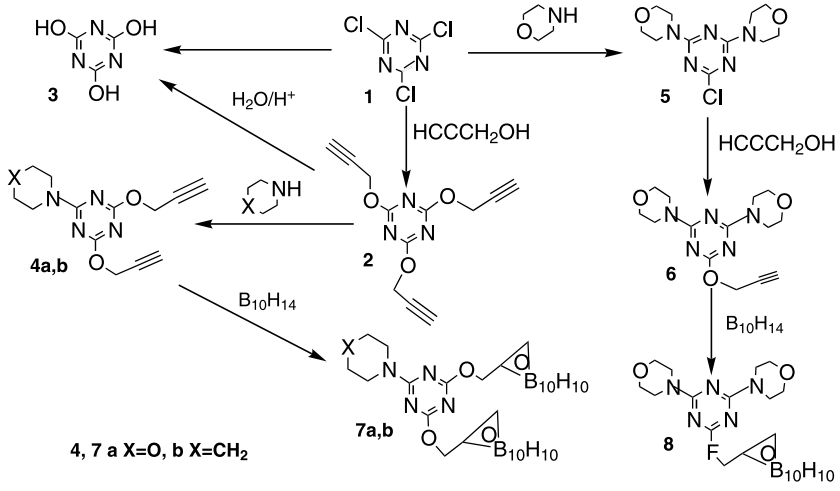
Abstract—Tripropargylic esters **2** and **10** of cyanuric and thiocyanuric acids were synthesized. Interaction of these compounds with disubstituted amines gives monoaminoderivatives of dipropargyloxy-*s*-triazine **4** and **11**. Diaminosubstituted propargyloxy-*s*-triazine **6** was prepared from the corresponding diaminochloroderivative **5**. First examples of boron-containing *s*-triazines **7**, **8**, **12**, **13** were prepared by reaction of propargyl esters **4**, **6**, **10**, **11** with decaborane. New rearrangements of the molecular ions of the 2-aminoderivatives of 4,6-dipropargyloxy-1,3,5-triazine in mass spectrometry were found.

The transport and accumulation of boron-containing compounds into tumor tissue, which is necessary for further improvement of BNCT (boron neutron cancer therapy), is a continuing challenge.[1] It seems advantageous to use *s*-triazines as heterocyclic carriers of boron-containing fragments. These compounds may act as antimetabolites of pyrimidine bases and can accumulate in cancer cells.[2] *s*-Triazines are also being investigated as anticancer drugs[3].

In the present work synthesis of the known 2,4,6-tripropargyloxy-1,3,5-triazine **2**[4] was performed by interaction of cyanur chloride **1** with propargyl alcohol in acetone with alkali (Scheme 1). Short heating of propargyl cyanurate **2** in dilute HCl gave cyanuric acid **3**.

Upon heating of 2,4,6-tripropargyloxyderivative **2** with disubstituted amines (morpholine and piperidine) in



Scheme 1.

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* Corresponding author. Tel.: +49-421-2182200; fax: +49-421-2182871; e-mail: azural@dialup.utk.ru; gabel@chemie.uni-bremen.de

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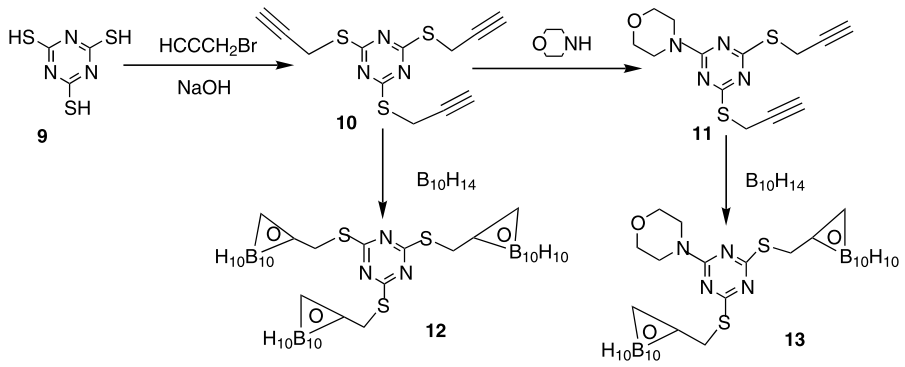


Scheme 2.

boiling ethanol the corresponding monoaminoderivatives of 4,6-dipropargyloxy-*s*-triazine **4a**,**b** were obtained.[†]

The synthesis of diaminopropargylderivatives was carried out conveniently in another way. Thus, interaction of cyanuric chloride **1** with morpholine at a stepwise increase of temperature from 0 to 40°C gives the known 2,4-dimorpholyl-6-chloro-*s*-triazine **5**.[5] 2,4-Dimorpholyl-6-propargyloxy-*s*-triazine **6** was obtained by reaction of **5** with propargyl alcohol with alkali at 40–45°C.

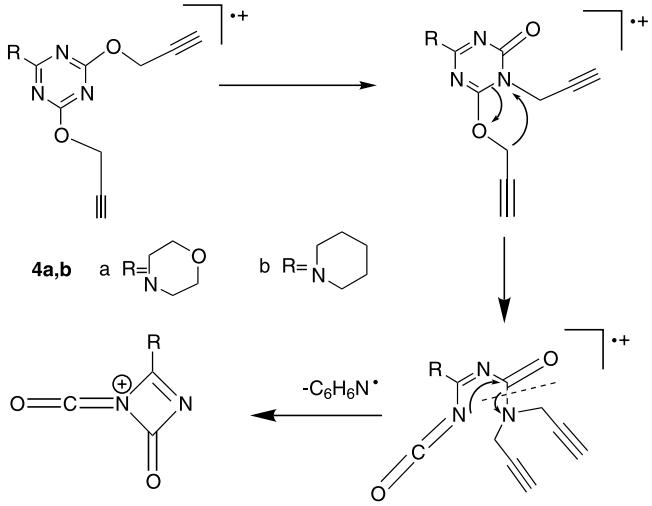
We synthesized the 2,4,6-tripropargylthioderivative **10** by interaction of the thiocyanuric acid **9** in 2% aqueous NaOH with propargyl bromide at room temperature for 3 h (Scheme 2). Upon heating of **10** with morpholine in boiling ethanol, the corresponding morpholyl derivative **11** was produced.

Synthesis of the carboranes was achieved by heating the propargyl derivatives **4**, **6**, **10**, and **11** with decaborane and acetonitrile in toluene for 15–18 h in analogy to the procedure described elsewhere.[6] After evaporation of the reaction solution the corresponding boron-containing derivatives **7**, **8**, **12**, and **13** were obtained (Schemes 1 and 2).

o-Carboranyl derivatives of 1,3,5-*s*-triazines have been described recently.[7] The derivatives described here were obtained by the addition of decaborane to a triple bond, and contain an additional methylene group between the triazine ring and the carborane, whereas the structures described in Ref. 7 have been obtained by the action of lithium carboranes with cyanuric chlorides.

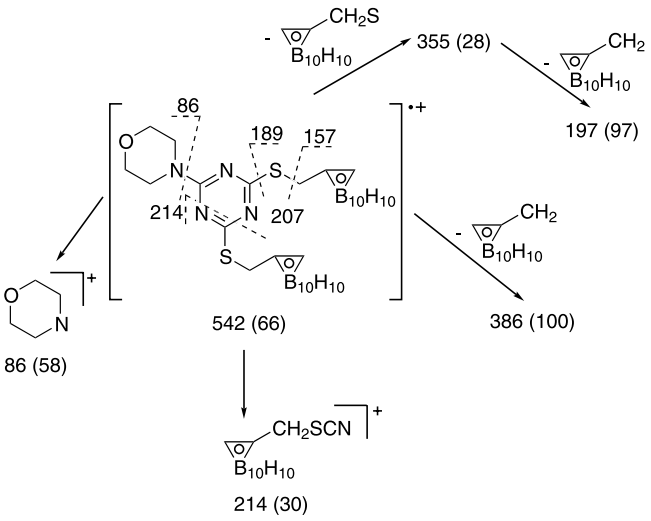
The electron impact (EI) mass spectra of the propargyloxy and propargylthio derivatives of 1,3,5-triazine show fragment ions $[M-OCH_2-CCH]^+$ and $[M-CH_2-CCH]^+$, resulting from cleavages of the bonds on both sides of the O- or S-atom.

For the aminopropargyl cyanurates **4a**,**b** we observed an unusual fragmentation of the molecular ion. Both molecules gave intensive fragment ions at $[M-92]^+$



Scheme 3.

[†] All new compounds gave satisfactory mass spectra. Spectra with boron fragments gave the expected isotope distribution pattern. These ions are indicated with ‡. Structure was established by ^{1}H NMR. Indicated are: no. of compound, yield %, mp °C (solvent for crystallization). molecular ion mass, *m*/*z* (relative intensity, %). ^{1}H NMR in DMSO-d_6, 200 MHz: **4a**, 45–50. 108–109 (ethanol). 274 (26), $[M]^{+\bullet}$. 3.55 (t, 2H, $J=2.4$ Hz, 2×CH), 3.60–3.75 (m, 8H, 4×CH_2), 4.96 (d, 4H, $J=2.4$ Hz, 2×OCH_2). **4b**, 45–50, 104–105 (ethanol). 272 (21), $[M]^{+\bullet}$. 1.40–1.70 (m, 6H, 3×CH_2), 3.55 (br. s, 2H, 2×CH), 3.60–3.80 (br. s, 4H, 2×CH_2), 4.93 (br. s, 4H, 2×OCH_2). **6**, 30–35, 124–125 (ethanol). 305 (30), $[M]^{+\bullet}$. 3.50 (br. s, 1H, CH), 3.55–3.80 (m, 16H, 8×CH_2), 4.90 (br. s, 2H, OCH_2). **7a**, 40–45, 115–116 (acetic acid). 511‡ (100), $[M]^{+\bullet}$. −0.5–+4.0 (br. m, 20H, 2×$B_{10}H_{10}$), 3.55–3.85 (m, 8H, 4×CH_2), 4.92 (br. s, 4H, 2×OCH_2), 5.24 (br. s, 2H, 2×CH). **7b**, 40–45, 160–161 (acetic acid). 509‡ (100), $[M]^{+\bullet}$. −1.5–+4.5 (br. m, 20H, 20×$B_{10}H_{10}$); 1.30–1.70 (m, 6H, 3×CH_2), 3.74 (br. s, 4H, 2×CH_2), 4.93 (br. s, 4H, 2×OCH_2), 5.26 (br. s, 2H, 2×CH). **8**, 20–25, 145–146 (precipitation from acetic acid by water). 424‡ (100), $[M]^{+\bullet}$. 0–+4.5 (br. m, 10H, $B_{10}H_{10}$), 3.20–4.00 (m, 16H, 8×CH_2), 4.88 (br. s, 2H, OCH_2), 5.24 (br. s, 1H, CH). **10**, 70–75, 77–78 (ethanol). 291 (3), $[M]^{+\bullet}$. 3.22 (t, 3H, $J=2.4$ Hz, 3×CH), 4.02 (d, 6H, $J=2.4$ Hz, 3×SCH_2). **11**, 70–75, 114–115 (ethanol). 306 (1), $[M]^{+\bullet}$. 3.16 (, 2H, $J=2.4$ Hz, 2×CH), 3.45–3.80 (m, 8H, 4×CH_2), 3.92 (d, 4H, $J=2.4$ Hz, 2×SCH_2). **12**, 25–30, 150–151 (precipitation from acetic acid by water). 646‡ (23), $[M]^{+\bullet}$. 0–+4.5 (br. s, 30 H, 3×$B_{10}H_{10}$), 4.19 (br. s, 6H, 3×SCH_2), 5.18 (br. s, 3H, 3× CH). **13**, 35–40, 128–130 (precipitation from acetic acid by water). 542‡ (66), $[M]^{+\bullet}$. 0.4–4.5 (br. s, 20H, 2×$B_{10}H_{10}$), 3.50–4.00 (m, 8H, 4×CH_2), 4.13 (br. s, 4H, 2×CH_2), 5.16 (br. s, 2H, 2×CH).



Scheme 4. The masses followed by parentheses indicate observed ions and their relative intensities.

which could be shown by the DADI (**D**irect **A**nalysis of **D**aughter **I**ons) scanning technique to originate directly from the molecular ions. High resolution measurements of the corresponding molecular and fragment ions showed that in both cases a neutral fragment with an atomic composition of C_6H_6N was ejected from the molecular ion; the fragment probably consists of two propargyl substituents and one N-atom of the triazine cycle. The generation of this fragment may be rationalized by the migration O-CH_2CCH→N-CH_2CCH (analogous to a Claisen rearrangement) and subsequent skeleton rearrangement resulting in formation of a 1,3-diazetin (or opened isomer) as shown in Scheme 3.

Moreover, for the morpholyl (or piperidyl)-substituted cyanurates **4a**,**b** and the thiocyanurate **11** fragmentation and elimination of the amino substituent as a whole or with neighbouring fragments of the heterocycle were observed.

The main fragmentation pathways of the boron-containing cyanurates and thiocyanurates under EI conditions are the elimination of $CH_2CCHB_{10}H_{10}$ ($[M-157]^+$)‡ and of $XCH_2CCB_{10}H_{10}$ (X = O $[M-173]^+$ ‡ or X = X $[M-189]^+$ ‡, see Scheme 4).

Another characteristic fragmentation for 1,3,5-triazines is the elimination of $[NCSCH_2CCHB_{10}H_{10}]^+$ (m/z = 214‡), which leads to a contraction of the triazine cycle to a 1,3-diaziridine. For the amino derivatives of the boron-containing cyanurates and thiocyanurates, fragmentation of the alicyclic amine moiety (ions $[M-CHO]^+$ and $[M-OC_4H_8N]^+$) is observed in addition to cleavage of the propargyl substituents.

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‡ These masses correspond to the maximum intensity peak of a fragment showing the expected isotope distribution pattern for 10 boron atoms with natural abundance of boron-10 and boron-11.