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New Types of *o*-Carboranyl Heterocyclic Compounds: Synthesis and Characterization of Morpholino and Di(methoxyethyl)amino Substituted 1,3,5-Triazine Derivatives

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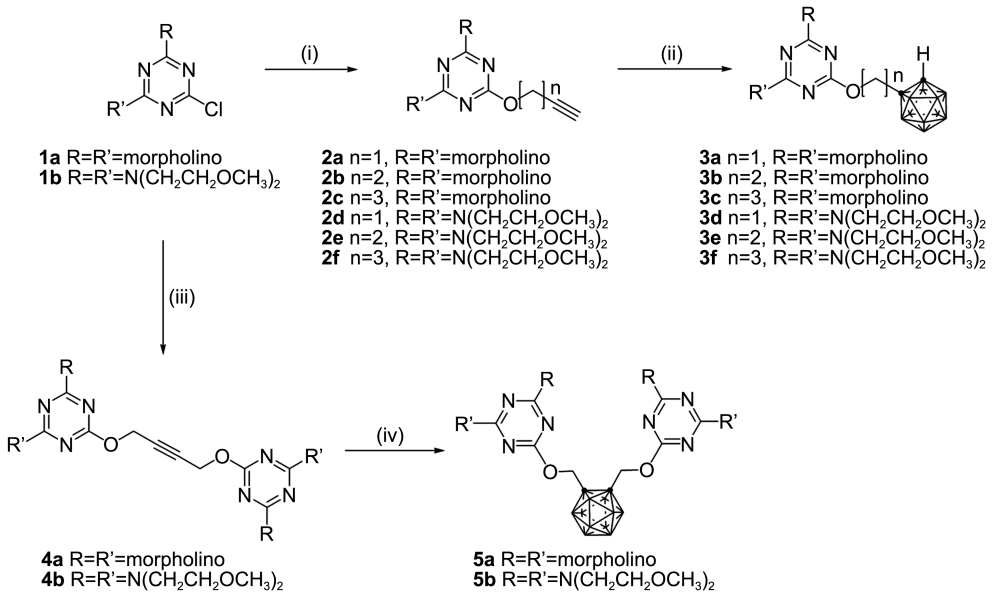
The class of *s*-triazine derivatives contains compounds possessing various types of biological activity. It has been suggested that one of these compounds, hexamethylmelamine, be used for the treatment of lung carcinoma.[1] Another 1,3,5-triazine derivative (5-azacytidine) is used for the treatment of acute lymphoblastic leukemia.[2,3] The antitumor activity of some 1,3,5-triazine derivatives is believed to be related to the fact that these compounds represent antimetabolites of pyrimidine bases and are capable of accumulating in tumor cells.[4]

Currently, the delivery of boron-containing molecular fragments to tumor tissues and the accumulation of these agents within the framework of boron neutron capture therapy (BNCT) is the subject of a great deal of attention.[5] BNCT was first proposed as a potential cancer therapy in 1936,[6] but successful application of BNCT to the treatment of cancer still presents a challenge in medical research.[7] Additionally, most compounds that have developed for BNCT to date are not suitable due to their low water solubility, stability, and selectivity toward cancer cells.[8] We believe that *s*-triazines comprise a promising group of heterocyclic carriers of such boron-containing molecular fragments for multivariate chemical modification. For example, *o*-carborane-containing derivatives can be synthesized using propargyl substituted *s*-triazines. We previously reported that tetrahydroisoquinolines (THIQ),[9] *s*-triazines,[10] ethylamines,[11] and piperidines[12] containing the *o*-carborane moiety were potential BNCT agents. Here, we report the synthesis and characterization of *s*-triazinyl morpholine and di(methoxyethyl)amine derivatives and their related *o*-carborane moieties with good yields as potential BNCT agents as an extension of our ongoing investigations into the biological behavior of bio-molecules based on *o*-carboranes.

New *o*-carborane-based *s*-triazine derivatives (75-78% for **2** and 36-38% for **4**) were synthesized as outlined in Scheme 1. As shown in Scheme 1, the starting materials **1** and alkynyloxy-*s*-triazine **2** and **4** can be easily prepared as previously described.[10,13]

Compound **2** exhibit characteristic absorption bands in the infrared spectra at 3025-3090 cm^{-1} reflecting the C-H bond of the alkynyl group (see Experimental Section). The ^1H NMR spectra of compounds **2** and **4** contain a broadened



Scheme 1. *Reagent and condition*: (i) alkynyl alcohol, *t*-BuOK, DMF, 70-75 °C, 5 h; (ii) decaborane ($B_{10}H_{14}$), aniline, toluene, reflux, 24 h; (iii) alkynyl alcohol, *t*-BuOK, DMF, 70-75 °C 24 h; (iv) decaborane, aniline, toluene, reflux, 36 h.

singlet due to C*H* groups of the propargyl fragment at 1.97-2.42 ppm, singlets reflecting OCH_2 groups at 4.35-4.89 (**2**) and 4.86 and 4.91 ppm (**4**), and multiplets due to protons of the morpholine substituent in the region of 1.94-2.43 (**2**) and 4.86 and 2.43 ppm (**4**). Treatment of **2** or **4** with decaborane ($B_{10}H_{14}$) and dimethylaniline in toluene produced the target compounds, **3** and **5**, respectively, in moderate yields (35-50%). Compounds **3** and **5** show characteristic absorption bands in the infrared spectra at 2586-2596 cm^{-1} for the B-H group (see Experimental Section). In the ^{1}H NMR spectra of compound **3**, the proton chemical shift for the OCH_2 group (δ = 4.21-4.86 ppm) almost coincides with the value observed for the initial compound (**2**) (see Experimental Section). Additionally, the signal produced by protons of the C*H* group of this carborane was observed in a weaker field (δ = 3.58-4.26 ppm) than the value for the corresponding fragment in the initial compound (δ = 3.55 ppm). In addition to the signals of protons of the morpholine substituent [δ = 3.65-3.77 (**3**), 3.68 and 3.74 ppm (**5**)], the spectra of compounds **3** and **5** contained a broad signal caused by B-H peaks of the *o*-carborane moieties from 0.5 to 3.4 ppm.

In conclusion, the sequential replacement of three chlorine atoms on cyanuric chloride with cyclic or secondary amine nucleophiles provides the synthesis of a variety of alkynyl-oxo-substituted *s*-triazine molecules Thus, we have developed a general and versatile method for the preparation of triazines flanked with an *o*-carborane. In light of its operational simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the *s*-triazines.

Experimental Section

General Consideration. All manipulations were carried out using standard Schlenk techniques. Starting materials, **1**, **2a**, and **3a**, were prepared as previously described.[10] NMR spectra were collected using a JEOL (500 MHz) FT-NMR spectrometer and referenced based on the residual protons of the solvent ($CDCl_3$, 7.26 ppm). Infrared (IR) spectra were obtained on a JASCO FT/IR-5300 spectrophotometer. Low-resolution mass spectra were acquired with a Quattro AC spectrometer.

Preparation of Compounds 2 and 4.

General Procedure: A DMF (50 mL) solution of 2,4-dimorpholino- or bis[di(methoxyethylamino)]-1,3,5-triazine **1** (10 mmol) and alkynyl alcohol (15 mmol for **2**) or 2-butyn-1,4-diol (8 mmol for **4**) was added to potassium *tert*-butoxide (1.2 mmol for **2** or 8.0 mmol for **4**) at room temperature. The reaction mixture was then stirred at room temperature for 1 h, followed by stirring at 70 °C for an additional 6 h. Next, the reaction mixture was cooled to room temperature and quenched with distilled H_2O (50 mL × 3). The reaction mixture was subsequently extracted with ethyl acetate (30 mL × 2). The organic layer was washed with H_2O (30 mL × 3), dried with anhydrous Na_2SO_4, and concentrated *in vacuo.* The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 1:1) to give **2** and **4** in yields of 75-78% and 36-38%, respectively.

2a: Yield: 2.37 g (78%); IR (KBr pellet, cm^{-1}) ν(C–H) 3290; ^{1}H NMR ($CDCl_3$, ppm) δ 2.42 (t, *J* = 5.0 Hz, 1H), 3.70 (t, *J* = 10.0 Hz, 8H), 3.78 (t, *J* = 10.0 Hz, 8H), 4.89 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 43.9, 54.1, 66.8, 74.5, 78.6, 166.03, 170.0.

2b: Yield: 2.45 g (77%); LRMS: 319 (36%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(C–H) 3276; ^{1}H NMR ($CDCl_3$, ppm) δ 2.00 (t, *J* = 5.0 Hz, 1H), 2.67 (td, *J* = 15.0 and 6 Hz, 2H), 3.69 (t, *J* = 10.0 Hz, 8H), 3.78 (t, *J* = 10.0 Hz, 8H), 4.38 (t, *J* = 15.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 19.2, 43.9, 64.3, 66.8, 70.0, 79.2, 166.1, 170.5.

2c: Yield: 2.54 g (75%); LRMS: 333 (28%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(C–H) 3285; ^{1}H NMR ($CDCl_3$, ppm) δ 1.94 (m, 2H), 1.94 (t, *J* = 5.0 Hz, 1H), 1.97 (q, *J* = 15.0 Hz, 2H), 2.35 (td, *J* = 15.0 Hz and 5.0 Hz, 2H), 3.70 (t, *J* = 10.0 Hz, 8H), 3.78 (t, *J* = 10.0 Hz, 8H), 4.35 (t, *J* = 15.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 15.4, 28.0, 43.8, 65.2, 66.9, 474768.8, 83.7, 166.1, 170.9.

2d: Yield: 3.05 g (77%); LRMS: 397 (26%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(C–H) 3283; ^{1}H NMR ($CDCl_3$, ppm) δ 2.43 (t, *J* = 3.0 Hz, 1H), 3.31 (s, 12H), 3.55 (t, *J* = 11.0 Hz, 8H), 3.74 (t, *J* = 11.0 Hz, 8H), 4.85 (d, *J* = 3.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 47.6, 47.9, 53.8, 58.9, 70.6, 71.2, 74.2, 79.1, 166.0, 169.5.

2e: Yield: 3.12 g (76%); LRMS: 411 (31%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(C–H) 3225; ^{1}H NMR ($CDCl_3$, ppm) δ 1.98 (t, *J* = 5.0 Hz, 1H), 2.65 (td, *J* = 15.0 Hz and 5.0 Hz, 2H), 3.32 (s, 12H), 3.55 (t, *J* = 10.0 Hz, 8H), 3.76 (t, *J* = 10.0 Hz, 8H), 4.36 (t, *J* = 15.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 19.2, 47.7, 47.8, 58.8, 64.1, 69.9, 70.7, 71.3, 80.4, 166.1, 170.0.

2f: Yield: 3.18 g (75%); LRMS: 425 (28%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(C–H) 3280; ^{1}H NMR ($CDCl_3$, ppm) δ 1.96 (q, *J* = 15.0 Hz, 2H), 2.16 (t, *J* = 5.0 Hz, 1H), 2.33 (td, *J* = 15.0 Hz and 5 Hz, 2H), 3.33 (s, 12H), 3.55 (t, *J* = 10.0 Hz, 8H), 3.76 (t, *J* = 10.0 Hz, 8H), 4.35 (t, *J* = 15.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 15.4, 28.1, 65.0, 68.7, 70.8, 71.3, 75.2, 83.8, 166.1, 170.5.

4a: Yield: 2.22 g (38%); LRMS: 584 (37%), $[M]^{+\bullet}$; ^{1}H NMR ($CDCl_3$, ppm) δ 3.70 (t, *J* = 15.0 Hz, 16H), 3.78 (t, *J* = 15.0 Hz, 16H), 4.91 (s, 4H); ^{13}C NMR ($CDCl_3$, ppm) δ 43.9, 66.9, 77.6, 80.5, 166.0, 170.2.

4b: Yield: 2.26 g (36%); LRMS: 768 (27%), $[M]^{+\bullet}$; ^{1}H NMR ($CDCl_3$, ppm) δ 3.30 (s, 24H), 3.52 (t, *J* = 15.0 Hz, 16H), 3.71 (t, *J* = 15.0 Hz, 16H), 4.86 (s, 4H); ^{13}C NMR ($CDCl_3$, ppm) δ 54.1, 58.9, 58.9, 71.3, 81.4, 166.0, 170.0.

Preparation of 3 and 5.

General Procedure: Decaborane (0.88 g, 11 mmol) and *N*,*N*-dimethylaniline (1.75 g, 14 mmol) were added to a dried toluene (20 mL) solution containing alkynyloxy-1,3,5-triazines **2** or **4** (2.0 g, 10 mmol). The resulting solution was then heated at reflux for 24 h and filtered. Next, the filtrate was diluted with water (1:1), after which the precipitate was separated by filtration and recrystallized to give **3** or **5**.

3a: Yield: 2.11 g (50%); IR (KBr pellet, cm^{-1}) ν(B–H) 2588; ^{1}H NMR ($CDCl_3$, ppm) δ 3.65 (t, *J* = 10.0 Hz, 8H),

3.70 (t, J = 10.0 Hz, 8H), 3.97 (br s, 1H), 4.86 (s, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 43.9, 58.1, 66.2, 66.7, 72.3, 165.8, 170.5.

3b: Yield: 2.14 g, (49%); LRMS: 438† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2596; ^{1}H NMR ($CDCl_3$, ppm) δ 2.67 (t, J = 12.0 Hz, 2H), 3.70 (t, J = 10.0 Hz, 8H), 3.77 (t, J = 10.0 Hz, 8H), 3.84 (br s, 1H), 4.34 (t, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 36.6, 43.9, 60.7, 66.8, 67.0, 72.4, 165.9, 170.1.

3c: Yield 2.20 g, (49%); LRMS: 451† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2591; ^{1}H NMR ($CDCl_3$, ppm) δ 1.93 (q, J = 12.0 Hz, 2H), 2.39 (t, J = 12.0 Hz, 2H), 3.58 (br s, 1H), 3.70 (t, J = 12.0 Hz, 8H), 3.76 (t, J = 12.0 Hz, 8H), 4.24 (t, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 28.7, 305.2, 44.9, 61.6, 65.2, 66.8, 74.7, 166.0, 170.1.

3d: Yield: 2.42g (47%); LRMS: 515† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2592; ^{1}H NMR ($CDCl_3$, ppm) δ 3.33 (s, 12H), 3.55 (t, J = 12.0 Hz, 8H), 4.26 (br s, 1H), 3.75 (t, J = 12.0 Hz, 8H), 4.82 (s, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 47.9, 58.6, 66.1, 70.6, 71.0, 73.2, 166.0, 169.5.

3e: Yield: 2.48 g (47%); LRMS: 530† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2588; ^{1}H NMR ($CDCl_3$, ppm) δ 2.70 (t, J = 12.0 Hz, 2H), 3.32 (s, 12H), 3.55 (t, J = 10.0 Hz, 8H), 3.76 (t, J = 10.0 Hz, 8H), 3.79 (br s, 1H), 4.35 (t, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 36.4, 47.8, 60.8, 63.8, 70.7, 71.1, 72.5, 166.0, 169.6.

3f: Yield: 2.60 g (48%); LRMS: 544† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2594; ^{1}H NMR ($CDCl_3$, ppm) δ 1.92 (q, J = 12.0 Hz, 2H), 2.36 (t, J = 12.0 Hz, 2H), 3.35 (s, 12H), 3.53 (t, J = 10.0 Hz, 8H), 3.73 (br s, 1H), 3.75 (t, J = 10.0 Hz 8H), 4.21 (t, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 28.8, 35.2, 58.9, 61.6 , 64.9, 70.7, 71.2, 74.9, 166.0, 170.2.

5a: Yield: 2.44 g (35%); LRMS: 702† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2586; ^{1}H NMR ($CDCl_3$, ppm) δ 3.68 (t, J = 15.0 Hz, 16H), 3.74 (t, J = 15 Hz, 8H) 5.00 (s, 4H); ^{13}C NMR ($CDCl_3$, ppm) δ 43.9, 64.7, 66.8, 72.6, 165.9, 169.7.

5b: Yield: 3.62 g (41%); LRMS: 888† (100%), $[M]^{+\bullet}$; IR (KBr pellet, cm^{-1}) ν(B–H) 2593; ^{1}H NMR ($CDCl_3$, ppm) δ 3.31 (s, 24H), 3.55 (t, J = 12.0 Hz, 16H), 3.75 (t, J = 12.0 Hz, 16H), 5.05 (s, 4H); ^{13}C NMR ($CDCl_3$, ppm) δ 47.2, 59.0, 64.2, 70.6, 71.2, 75.6, 166.0, 169.3.

†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.

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