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LETTERS

Syntheses of carboranylpyrroles

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Abstract—The syntheses of three carboranylpyrroles (**5**, **10** and **14**) bearing carborane cages in 3-position and/or 4-position of the pyrrole ring, either directly linked or through a methylene spacer, are described. Tetramerization of two carboranylpyrroles afforded the corresponding β-carboranylporphyrins, as mixtures of type I–IV isomers. © 2001 Elsevier Science Ltd. All rights reserved.

For some time boron-containing molecules with varying degrees of tumor-specificity have been synthesized for application in the boron neutron capture therapy (BNCT) modality for treatment of cancer, and in particular of malignant brain tumors.[1,2] Among these compounds, carborane-containing porphyrins are particularly promising BNCT agents[3–6] because of their selectively for tumor cells, their ability to deliver therapeutic boron concentrations, and their persistence within tumors. The basis of BNCT relies on the capture reaction of slow neutrons by boron-10 nuclei, which produces highly cytotoxic particles [$^{4}He^{2+}$ and $^{7}Li^{3+}$] and releases approximately 2.4 MeV of energy. The destructive effect is highly localized to ^{10}B-containing tissue, since these high linear energy transfer particles possess short mean paths of travel, thus expending their energy within the cells where they are generated. The only two boron neutron capture agents currently in clinical trials are disodium mercapto-*closo*-dodecaborate (BSH)[7] and L-4-dihydroxyborylphenylalanine (BPA),[8] which have shown only moderate selectivity for brain tumors. Herein, we report the total syntheses of three carboranylpyrroles, featuring carbon–carbon linkages between the carborane and the 3- and/or 4-positions of the pyrrole rings. Carboranylpyrroles are key building blocks in the synthesis of symmetrical and unsymmetrical β-carboranylporphyrins; type I–IV porphyrins were also obtained from the cyclotetramerization of two carboranylpyrroles.

1-Allyl-2-methyl-*o*-carborane **1** (R = Me), the precursor of carboranylpyrrole **5**, was prepared in 84% yield from 1-lithium-2-methyl-*o*-carborane (prepared in situ from 1-methyl-*o*-carborane and 1 equiv. of *n*-butyllithium)[9] and allylbromide, in THF at −78°C. Under the same reaction conditions, *o*-carborane produced **1** (R = H) in 70% yield; the slightly lower yield obtained in this case is presumably due to the known disproportionation reaction of the lithium anion of *o*-carborane. Compound **1** (R = Me) reacted at −78°C with in situ generated phenylsulfenyl chloride[10] to produce exclusively the anti-Markovnikov product **2**, in 84% yield (Scheme 1); the preference for anti-Markovnikov addition could be steric (due to the large size of the carborane cage), electronic (due to the electron-withdrawing capacity of the carborane group), or a mixture of both. At higher temperatures the Markovnikov product was also obtained and the combined yield of both products was lower because of an obligatory chromatographic separation; for example at 45°C, a 2:3 mixture of **2** and the corresponding Markovnikov product was obtained in 60% yield. Oxidation of **2** using an excess of *m*-CPBA produced the corresponding sulfone in high yield, which was selectively dehydrochlorinated at 0°C with 1 equiv. of DBU to give **3**, or using a slight excess of DBU (1.1–2 equiv.) at room temperature to give **4**, quantitatively. Presumably, compound **4** is produced as a result of based-catalyzed equilibration to give the most stable (internal) alkene. Both unsaturated sulfones **3** and **4** produced carboranylpyrroles **5** in 68–90% yields under Barton–Zard reaction conditions,[11] in the presence of sodium *tert*-butoxide and isocyanoacetate esters. Base-catalyzed double bond isomerization of **4** to give **3** is required in order to provide pyrrole **5** from **4**. When NaH was used as the base, the yields obtained for **5** were considerably lower and a side product of this reaction, sulfone **6**, was also isolated. Compound **6** was obtained as the major product when the reaction was

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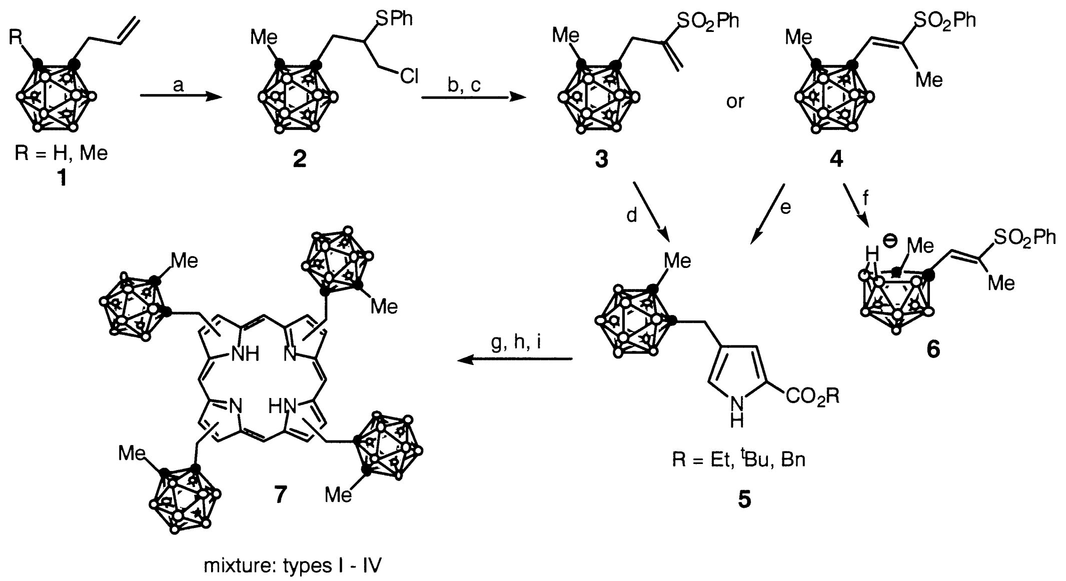


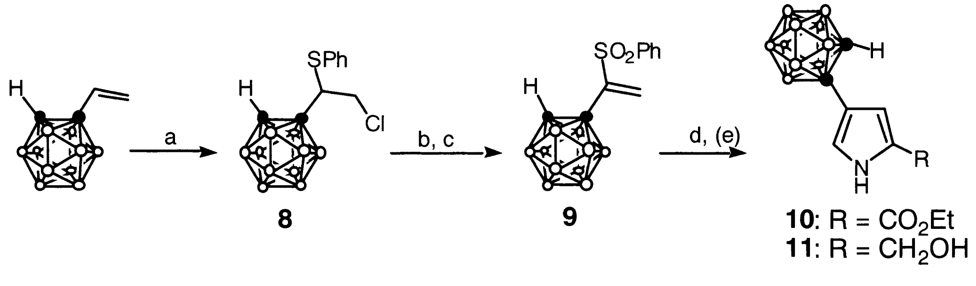
Scheme 1. (a) PhSCl, CH_2Cl_2, −78°C, 8 h (84%); (b) *m*-CPBA, CH_2Cl_2, 0°C, 11 h (95%); (c) DBU (1 equiv.), THF, 0°C, 30 min (98% of **3**) or DBU (2 equiv.), THF, 0°C (20 min) then rt (30 min) (98% of **4**); (d) $CNCH_2CO_2R$, NaO^tBu, THF, reflux, 10 h (R = Et: 68%, R = Bn: 90%); (e) $CNCH_2CO_2{}^tBu$, NaO^tBu, THF, reflux, 20 h (90%); (f) $CNCH_2CO_2Et$, NaH, THF, rt, 8 h (60%); (g) $LiAlH_4$, THF, 0°C, 2.5 h (R = Et, 80%); (h) TFA, $CHCl_3$, 70°C, 15 min; (i) *p*-chloranil, rt.

performed at room temperature in the presence of 3 equiv. of NaH and 2 equiv. of ethyl isocyanoacetate. The unsaturated sulfone **4** failed to produce the corresponding 3-methylcarboranyl-4-methylpyrrole under a variety of reaction conditions; the only products obtained were either **5** or **6**.

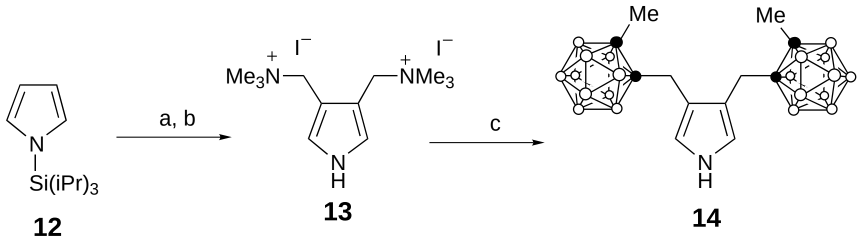
Carboranylpyrrole **5** (R = Et) was treated with $LiAlH_4$ and then tetramerized in the presence of TFA as catalyst, followed by oxidation with *p*-chloranil to produced a mixture of four isomeric porphyrins (type I–IV)[12] in 15% (non-optimized) yield (Scheme 1). Porphyrins **7** showed a single molecular peak in the MALDI-MS spectrum, etio-type visible spectra and multiple *meso*-proton resonances in the NMR spectrum.

Using the same synthetic strategy as above, 3-carboranylpyrrole **10** was prepared according to Scheme 2. Commercially available 1-vinyl-*o*-carborane produced sulfide **8** upon reaction with in situ generated phenylsulfenyl chloride,[10] which after oxidation with *m*-CPBA and dehydrochlorination using DBU, afforded sulfone **9** in 76% overall yield. Under Barton–Zard reaction conditions[11] sulfone **9** was converted into carboranylpyrrole **10** in 55% yield. Reduction as before using $LiAlH_4$ produced an unusually stable pyrrolecarbinol **11**, which also produced a mixture of porphyrins, in low yield, upon tetramerization in the presence of TFA followed by oxidation with *p*-chloranil.

Another methodology for the synthesis of carboranylpyrroles is outlined in Scheme 3. Tri(isopropyl)-silyl-protected pyrrole **12** reacts with *N*,*N*-dimethylaminomethyl iodide (Eschenmoser reagent) regioselectively at the 3- and 4-positions of the pyrrole ring.[13] After deprotection and methyl iodide quaternization, pyrrole **13** is obtained in 60% overall yield. Reaction of pyrrole **13** with 1-lithium-2-methyl-*o*-carborane in refluxing THF produced carboranylpyrrole **14** in 21% yield. The low yield obtained is probably due to self-condensation and polymerization reactions of pyrrole **13**. In fact, a considerable amount of polar side products were detected by TLC.



Scheme 2. (a) PhSCl, CH_2Cl_2, reflux (30 min), then rt (30 min) (75%); (b) *m*-CPBA, CH_2Cl_2, 0°C, 20 h (78%); (c) DBU (1.1 equiv.), THF, −10°C, 30 min (98%); (d) $CNCH_2CO_2Et$, THF, NaO^tBu, THF, rt, 20 h (55%); (e) $LiAlH_4$, THF, 0°C, 2.5 h (80%).



Scheme 3. (a) CH_2=NMe_2I, CH_3CN, reflux (2 h) then rt (4 h) (75%); (b) *n*-Bu_4NF, THF, rt (15 min) then 0°C, excess MeI, overnight (60%); (c) 1-lithium-2-methyl-*o*-carborane, THF, 0°C (1 h), then 80°C (24 h) (21%).

All new compounds synthesized possessed spectroscopic data in accord with the assigned structures.[14] The new carboranylpyrroles **5**, **10** and **14** described herein are currently being employed in the stepwise synthesis of unsymmetrical β-carboranylporphyrins.

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14. Selected spectroscopic data: compound **5**, mp 110°C; MS (EI) *m*/*z* 309.2 [M^+]; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.36 (t, 3H, $J=7.2$ Hz, CH_3), 1.20–3.18 (m, 10H, BH), 2.11 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 4.32 (q, 2H, $J=7.2$ Hz, CH_2), 6.75 (d, 1H, $J=1.8$ Hz, PyrH), 6.80 (d, 1H, $J=2.7$ Hz, PyrH), 9.11 (broad s, 1H, NH). Porphyrins **7**, MS (MALDI) *m*/*z* 989.9 $[M+1]^+$; UV–vis ($CHCl_3$) λ_{max}: 404 nm, 499, 531, 572, 625. Compound **10**, mp 95°C, MS (EI) *m*/*z* 281.9 [M^+]; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.37 (t, 3H, $J=7.2$ Hz, CH_3), 1.20-3.50 (m, 10H, BH), 3.73 (s, 1H, CH), 4.35 (q, 2H, $J=7.2$ Hz, CH_2), 6.91 (s, 1H, PyrH), 7.06 (d, 1H, $J=1.8$ Hz, PyrH), 9.35 (broad s, 1H, NH). Compound **14**, mp 140°C; MS (EI) *m*/*z* 407.5 [M^+]; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.25–3.34 (m, 20H, BH), 2.18 (s, 6H, CH_3), 3.40 (s, 4H, CH_2), 6.64 (d, 2H, $J=2.7$ Hz, PyrH), 8.23 (broad s, 1H, NH).