Synthesis of Carborane-containing Nitroimidazole Compounds *via* Mild 1,3-Dipolar Cycloaddition

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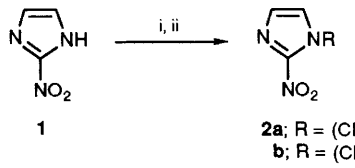
Nitroimidazole-linked carboranes are synthesised in good yield from ω-alkenyl- and ω-alkynyl-2-nitroimidazoles and a carborane nitrile oxide by 1,3-dipolar cycloaddition under mild conditions.

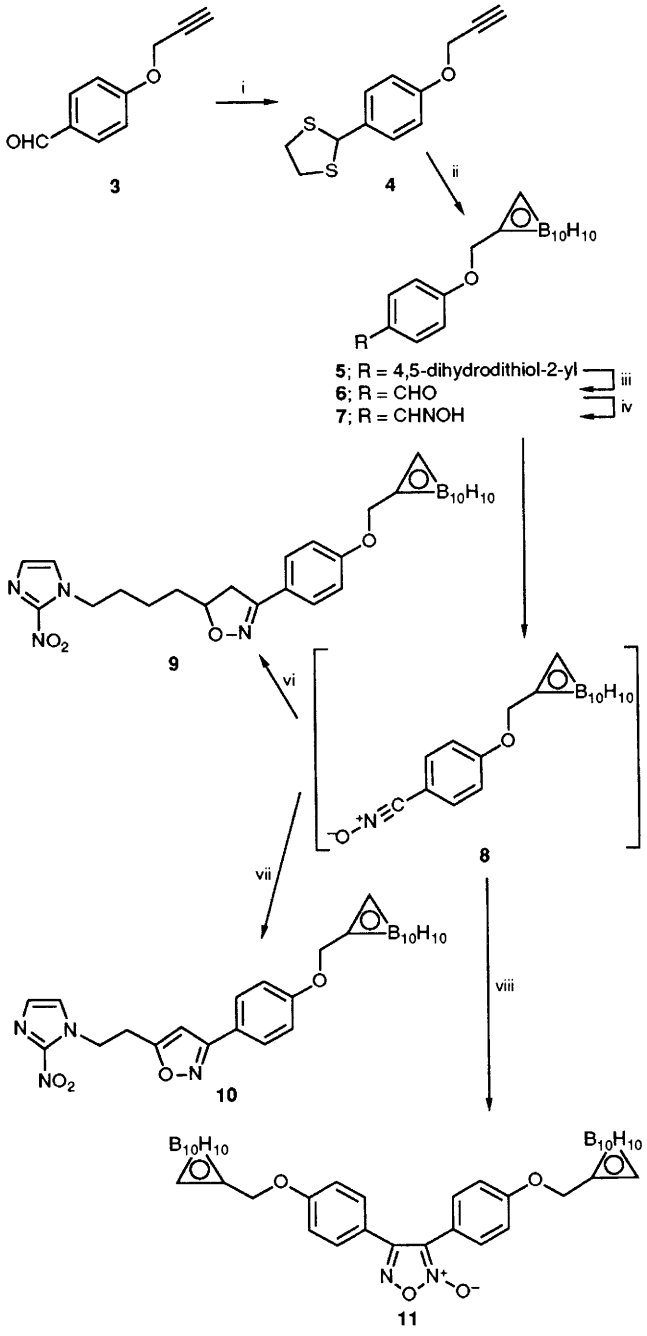
Boron neutron capture therapy (BNCT) is of increasing interest as a strategy for treatment of various cancers[1] and is based on the $^{10}B(n,\alpha)^{7}Li$ reaction of the ^{10}B isotope. Early studies of BNCT using non-targeted boron compounds gave mixed results.[2] Failures were attributed to inadequate concentrations of ^{10}B in the tumour tissue or lack of selectivity of disposition of ^{10}B, leading to damage to normal tissue. Recently, carboranes have been linked to nucleosides[3] and to porphyrins[4] in attempts to target boron to tumours. 2-Nitroimidazoles are selectively retained in poorly vascularised hypoxic tumour tissue by reductive metabolism to electrophiles.[5] As an extension of a programme of synthesis and evaluation of nitroimidazoles in the treatment of cancer,[6,7] we propose that a compound containing 10–12 boron atoms linked to 2-nitroimidazole would form a useful method of concentrating boron in solid tumours. Nitroimidazoles bearing boron are hitherto unreported.

Simple and complex boranes are widely used as reducing agents but 1-substituted-2-nitroimidazoles are themselves readily reduced (E^{1}_{7} = −389 mV);[7] thus assembly of a molecule containing both moieties must be achieved under mild conditions. Alkylation of 2-nitroimidazole **1** requires vigorous conditions and the *closo*-1,2-dicarbadodecarboranes are prepared[8] by reaction of alkynes and decarborane(14) ($B_{10}H_{14}$) in the presence of boiling Lewis bases for long reaction times. 1,3-Dipolar cycloadditions of nitrile oxides to



1 **2a**; R = $(CH_2)_4CH{=}CH$ **b**; R = $(CH_2)_2C{\equiv}CH$

Scheme 1 *Reagents and conditions*: i, KOBu^t, DMF, 100 °C; ii, $BrCH_2CH_2CH_2CH_2CH{=}CH_2$ or $TsOCH_2CH_2C{\equiv}CH$, DMF, 130 °C



Scheme 2 *Reagents and conditions*: i, $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; ii, $B_{10}H_{14}$, MeCN, reflux 3 days; iii, $Hg(ClO_4)_2{\cdot}3H_2O$, THF, 5 min; iv, $NH_2OH{\cdot}HCl$, Na_2CO_3, EtOH; v, NaOCl, H_2O, CH_2Cl_2; vi, **2a**; vii, **2b**; viii, PhMe, reflux

alkenes and alkynes proceed[9] under mild conditions; hence this method was chosen to link appropriate nitroimidazoles and carboranes for the final assembly step.

The potassium salt of 2-nitroimidazole **1** was alkylated with 6-bromohex-1-ene and with but-3-ynyl tosylate[10] in hot DMF (dimethylformamide) to give the alkene **2a**[7] (78%) and the alkyne **2b**† (59%), respectively (Scheme 1). As predicted, treatment of **2b** with $B_{10}H_{14}$ gave only polar degradation products.

4-(3-Prop-1-ynyloxy)benzaldehyde **3**[11] was chosen as the bifunctional compound for elaboration to form a carborane and a nitrile oxide. Both aldehyde **3** and the 4,5-dihydro-1,3-dioxole protected form were unstable to $B_{10}H_{14}$. However, protection of the aldehyde as the 4,5-dihydro-1,3-dithiole **4**† was achieved in 80% yield (Scheme 2). This protecting group resisted prolonged treatment with $B_{10}H_{14}$ in refluxing acetonitrile, which furnished carborane **5**† (51%). The aldehyde was unmasked cleanly under very mild conditions using $Hg(ClO_4)_2$, giving carboranylmethoxybenzaldehyde **6**† (90%) in a much shorter sequence than that reported[4] for the synthesis of the *meta* isomer. Oxidation of the corresponding oxime **7**† to give nitrile oxide **8**‡ and 1,3-dipolar cycloaddition with **2a** and **2b** were effected§ as one-pot procedures, affording the required dihydroisoxazole **9**†¶ and the isoxazole **10**†‖ in which both nitroimidazole and carborane moieties are present. Yields were essentially quantitative based on dipolarophile and nitrile oxide consumed.

Formation of the intermediate nitrile oxide **8** was very rapid but prolonged reaction times at ambient temperature were required for acceptable conversion into heterocycles. Even after several days, no boron-containing compounds other than **8, 9** or **10** were evident and it was possible to isolate unreacted **8** from the reaction mixtures by chromatography. This nitrile oxide is remarkably stable, with little decomposition after several weeks at ambient temperature; in contrast, the $t_{\frac{1}{2}}$ of most aromatic nitrile oxides is reported[9] to be only a few hours. Conversion into the dimer, 1,2,5-oxadiazole 2-oxide **11**,†** was effected only on heating in boiling toluene.

The mild conditions of the 1,3-dipolar cycloaddition described here permit the joining of sensitive 2-nitroimidazole and boron cage moieties within one molecule. This strategy represents an opportunity for incorporating chemically sensitive pharmacophores and targeting groups into drug molecules while generating a heterocycle which is itself capable of further elaboration. Compounds **9** and **10** are highly

† New compounds were characterised by ^1H NMR and MS and, for target compounds, microanalysis or high resolution MS.

‡ *Spectroscopic data* **8**: IR ν_{max}/cm^{-1} 2600 (B–H) and 2320 ($C{\equiv}N^+$-O^-); NMR ($CDCl_3$) δ 1.2–3.1 (10 H, br m, B_{10}-H_{10}), 3.97 (1 H, s, carborane 2-H), 4.38 (2 H, s, carborane-CH_2), 6.82 (2 H, d, Ar 3,5-H_2) and 7.40 (2 H, d, Ar 2,6-H_2).

§ Typical experiment: oxime **7** (1 mmol) and alkyne **2b** (1 mmol) in CH_2Cl_2 (20 ml) were treated with aqueous NaOCl for 18 h. Chromatography (silica gel; CH_2Cl_2) of the evaporation residue gave isoxazole **10**.

¶ **9**: NMR ($CDCl_3$) δ 1.3–3.3 (10 H, br m, B_{10}-H_{10}), 1.5–2.0 (6 H, m, imidazole-$CH_2CH_2CH_2CH_2$), 2.93 (1 H, dd) and 3.40 (1 H, dd) isoxazole 4-H_2, 4.09 (1 H, br, carborane 2-H), 4.45 (4 H, m, imidazole-CH_2 + carborane-CH_2), 4.73 (1 H, ddt, isoxazole 5-H), 6.87 (2 H, d, Ar 3,5-H_2) 7.11 (1 H, s) and 7.15 (1 H, s) imidazole 4,5-H_2, and 7.61 (2 H, d, Ar 2,6-H_2).

‖ **10**: NMR ($CDCl_3$) δ 1.3–3.3 (10 H, br m, B_{10}-H_{10}), 3.42 (2 H, t, isoxazole-CH_2), 4.09 (1 H, br, carborane 2-H), 4.46 (2 H, s, carborane-CH_2), 4.82 (2 H, t, imidazole-CH_2), 6.26 (1 H, s, isoxazole 4-H), 6.92 (2 H, d, Ar 3,5-H_2), 6.96 (1 H, s) and 7.09 (1 H, s) imidazole 4,5-H_2, and 7.70 (2 H, d, Ar 2,6-H_2).

** **11**: NMR ($CDCl_3$) δ 1.3–3.3 (20 H, br, m, 2 × B_{10}-H_{10}), 4.07 (2 H, br, 2 × carborane 2-H), 4.46 (2 H, s, carborane-CH_2), 4.47 (2 H, s, carborane-CH_2), 6.92 (4 H, d, Ar 3,5-H_2 + Ar′ 3,5-H_2), 7.47 (2 H, d, Ar 2,6-H_2), and 7.49 (2 H, d, Ar′ 2,6-H_2).

lipophilic; the development of more water-soluble analogues for biological evaluation will be reported elsewhere.

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