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Short Communication

Synthesis of 1-Aminomethyl- and 1-(2-Aminoethyl)-*o*-carborane

Jonas Malmquist, Hadi Ghaneolhosseini and Stefan Sjöberg*

Institute of Chemistry, Department of Organic Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden

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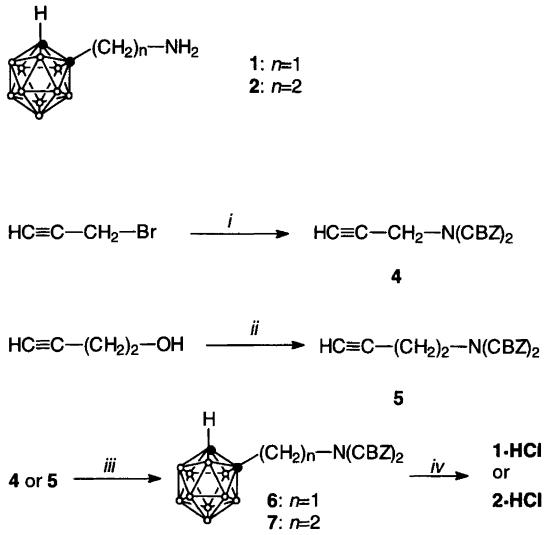
The synthesis of some 1-(ω-aminoalkyl)-*o*-carboranes including the 1-aminomethyl compound **1·HCl** has been reported previously.[1] The overall yield for **1·HCl** was 27% in three steps from *N,N*-di-*tert*-butyl iminodicarboxylate. Independently, Soloway *et al.* reported an alternative synthesis for this compound in three steps from *N*-propargylphthalimide.[2] The overall yield was 36%. Both approaches require decaborane(14), a very costly compound. Therefore, development of an alternative synthetic route with a higher total yield of **1·HCl** was undertaken. Described herein is an improved synthesis of **1·HCl** and its aminoethyl analogue **2·HCl**. The total yields of **1·HCl** and **2·HCl** from the *o*-carborane-forming step with decaborane(14) were 48% and 42%, respectively.

The synthesis of amine **2·HCl**, starting from ethyl 3-butynoate via *o*-carboranylethanoic[3] acid and the corresponding nitrile,[3] was first reported by Zakharkin *et al.*[4] The yield was 25%. The synthesis of the acetamide derivative of **2·HCl** from 3-(*p*-tolylsulfonyloxy)butyne and an acetonitrile–decaborane complex in 44% yield was reported later.[2]

In the preparations of **1·HCl** and **2·HCl** described here, the Gabriel reagent *N,N*-dibenzylimidodicarbonate [$HN(CBZ)_2$][5,6] (**3**) was used for the introduction of the amino function (Scheme 1). Ion-pair alkylation of **3**[5,7] with propargyl bromide in the two-phase system dichloromethane–water gave the protected propargylamine **4** in 87% yield. The same procedure was used for 4-iodo-1-butyne, which gave the corresponding protected amine **5**, but in only 5% yield. The low yield is due to the competing elimination of hydrogen iodide from 4-iodo-3-butyne reaction giving vinylacetylene. However, alkylation of $HN(CBZ)_2$ with 3-butyn-1-ol using Mitsunobu conditions,[8,9] afforded the protected amine **5** in an 80% yield.

The doubly protected aminoalkyl carboranes **6** and **7** were formed in 63% and 59% yield, respectively, by reacting the acetylenes **4** or **5** with 6,9-bis(diethyl sulfide)·decaborane.[10] Acetonitrile was also used as the decaborane ligand,[10] but a decreased yield and mono deprotection of the amine were observed. Under the reaction conditions described for the synthesis of **6** and MeCN as the decaborane-ligand, the product ratio of **6** to mono deprotected **6** was roughly 2:1 according to the ^1H NMR spectrum of the crude product.[11] Similar mono deprotection had been observed earlier when di-BOC



Scheme 1. *i*, $HN(CBZ)_2$ (**3**), $QHSO_4$, 2 M NaOH, CH_2Cl_2; *ii*, 1. **3**-PPh_3, 2. DEAD; *iii*, $B_{10}H_{10}\cdot 2Et_2S$, toluene; *iv*, Pd-H_2, abs. EtOH.

* To whom correspondence should be adressed.

protected propargylamine had been reacted with 6,9-bis(acetonitrile)·decaborane.[1]

The doubly CBZ-protected amines **6** and **7** were deprotected by hydrogenolysis using $Pd(OH)_2$ (Pearlman's catalyst) in the presence of hydrochloric acid to give the hydrochlorides of **1** and **2** in 88% and 87% yield, respectively.

Experimental

General details. THF was distilled from the sodium–benzophenone ketyl radical. The ^1H, ^{13}C and ^{11}B NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Varian Unity-400 spectrometer operating at 400, 100.6 and 128.3 MHz, respectively, or on a Varian XL-300 spectrometer operating at 300, 75.4 and 96.2 MHz, respectively. Boron trifluoride–diethyl ether was used as an external standard for the boron spectra. The IR spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Elemental analyses were determined by Analytische Laboratorien, Gummersbach, Germany. Merck Silica gel 60 (230–400 mesh) and Merck Silica gel 60 F_{254} were used for flash column chromatography and TLC, respectively. Melting points are uncorrected and were obtained using a Büchi capillary melting point. 'Q^+' is used for the tetrabutylammonium ion and 'cb' is used to denote the *o*-carborane-cage.

N,N-*Di(benzyloxycarbonyl)prop-2-ynylamine* (**4**). To a stirred mixture of tetrabutylammonium hydrogen sulfate, $QHSO_4$, (3.92 g, 10.6 mmol) and 2.00 M aqueous sodium hydroxide (12.1 ml), were added, at ambient temperature, dichloromethane (10 ml) and *N,N*-dibenzylimidodicarbonate (**3**)[5] (3.00 g, 10.5 mmol). To this mixture prop-2-ynyl bromide (1.75 ml, 15.7 mmol, 80% in toluene) dissolved in dichloromethane (5 ml), was added dropwise. The mixture was refluxed for 1.5 h and then cooled to room temperature. The layers were separated, the water phase was extracted with dichloromethane (10 ml) and the combined organic phases were evaporated. The QBr was precipitated by adding ether (30 ml) to the residue. The precipitate was washed with ether (3 × 20 ml), the combined washings were dried over sodium sulfate and filtered. The filtrate was concentrated to give crude **4**. The crude product was purified by flash column chromatography using ether–pentane (1:3) as the eluent, $R_f = 0.46$, gave 2.94 g (87%) of **4**. An analytical sample was obtained by bulb-to-bulb distillation (240–250 °C, 3 mmHg). M.p. 36.5–38 °C. Anal. $C_{19}H_{17}NO_4$: C, H, N. ^1H NMR ($CDCl_3$): δ 7.37 (m, 10 H, *arom*), 5.30 (s, 4 H, Ph-CH_2), 4.52 (d, $J = 2$ Hz, 2 H, CH_2), 2.65 (t, $J = 2$ Hz, 1 H, acetylenic *H*). ^{13}C NMR ($CDCl_3$): δ 152.4, 134.9, 128.4, 128.3, 128.0, 78.7, 72.5, 68.9, 36.1. IR (NaCl): 3277, 1761, 1724, 1345, 1213, 1112 cm^{-1}.

N,N-*Di(benzyloxycarbonyl)but-3-ynylamine* (**5**). To an ice-cooled solution of *N,N*-dibenzylimidodicarbonate (**3**)[5] (302 mg, 1.06 mmol) and triphenylphosphine (419 mg, 1.6 mmol) in anhydrous THF (8 ml) was added dropwise 3-butyn-1-ol (69 mg, 0.98 mmol) and a solution of diethyl azodicarboxylate (0.28 ml, 1.8 mmol) in anhydrous THF (3 ml). The resulting yellow solution was stirred for 24 h at RT. and then concentrated. The crude product was purified by flash column chromatography with ether–pentane (1:3), $R_f = 0.38$, to give **5** (266 mg, 80%). Anal. $C_{20}H_{19}NO_4$: C, H, N. ^1H NMR ($CDCl_3$): δ 7.35 (m, 10 H, *arom*), 5.25 (s, 4 H, Ph-CH_2), 3.32 (d, $J = 8$ Hz, 2 H, CH_2-N), 2.50 (dt, $J = 8$, 2 Hz, 2 H, C-CH_2), 1.89 (t, $J = 2$ Hz, 1 H, acetylenic *H*). ^{13}C NMR ($CDCl_3$): δ 153.1, 135.1, 128.6, 128.4, 128.2, 80.4, 70.1, 68.8, 44.9, 18.7. IR (NaCl): 3291, 1752, 1699, 1455, 1385, 1355, 1330, 1281, 1193, 1104 cm^{-1}.

N,N-*Di(benzyloxycarbonyl)-1-(aminomethyl)-o-carborane* (**6**). Decaborane[10] (0.979 g, 8.02 mmol) and diethyl sulfide (3.5 ml, 33 mmol) were mixed in dry toluene (50 ml) and heated to reflux. After 1.5 h reflux under a nitrogen atmosphere the acetylene **4** (2.15 g, 6.67 mmol) dissolved in toluene (5 ml) was added. After reflux for 16 h the toluene was evaporated off, methanol (50 ml) was added and the mixture was heated for 16 h. The mixture was concentrated to give crude **6** which was purified by flash column chromatography using ether–pentane (1:3), $R_f = 0.38$, to give **6** (1.84 g, 63%). An analytical sample was recrystallized from hexane. M.p. 70–71 °C. Anal. $C_{19}H_{27}B_{10}NO_4$: C, H, N. ^1H NMR ($CDCl_3$): δ 7.37 (m, 10 H, *arom*), 5.27 (s, 4 H, Ph-CH_2), 4.45 (d, $J = 2.4$ Hz, 2 H, CH_2), 3.85 (br s, 1 H, *H*C). ^{13}C NMR ($CDCl_3$): δ 153.9, 134.1, 128.8, 128.7, 128.5, 73.7, 69.8, 60.5, 50.4. ^{11}B NMR ($CDCl_3$): δ −1.7, −4.9, −10.0, −12.0 (sh), −13.2. IR (KBr): 3068, 3034, 2590, 2575, 1770, 1748, 1702, 1384, 1328, 1293, 1215, 1112 cm^{-1}.

N,N-*Di(benzyloxycarbonyl)1-(2-aminoethyl)-o-carborane* (**7**) was obtained from **4** (200 mg, 0.59 mmol) as described for **6**. Crude **7** was purified by flash column chromatography with ether–pentane 2:3 as the eluent, $R_f = 0.48$, to give **7** (160 mg, 59%). M.p. 99–100 °C. Anal. $C_{20}H_{29}B_{10}NO_4$: C, H, N. ^1H NMR ($CDCl_3$): δ 7.35 (m, 10 H, *arom*), 5.22 (s, 4 H, Ph-CH_2), 3.78 (m, 2 H, C-CH_2), 3.38 (br s, 1 H, *H*C), 2.39 (m, 2 H, CH_2-N). ^{13}C NMR ($CDCl_3$): δ 152.6, 134.7, 128.7, 128.4, 72.0, 69.1, 60.5, 45.4, 35.7. ^{11}B NMR ($CDCl_3$): δ −1.6, −4.8, −8.6, −11.4, −12.4. IR (KBr^-): 3392, 2583, 2548, 1728, 1688, 1390, 1342, 1211 cm^{-1}.

*1-(Aminomethyl)-*o*-carborane hydrochloride* (**1·HCl**). The protected amine **6** (1.04 g, 2.36 mmol) was hydrogenated in absolute ethanol (15 ml) containing 12 M HCl (8 drops), in the presence of palladium hydroxide on carbon (200 mg) for 17 h. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude product was purified by precipitation from a methanol solution with ether to give **1·HCl** (454 mg, 2.17 mmol) in 92% yield. The spectroscopic data were in accord with published data.[1]

1-(2-Aminoethyl)-o-carborane hydrochloride (**2·HCl**). was obtained from **7** (190 mg, 0.42 mmol) according to the procedure described for **1·HCl** to give 87% **2** (81 mg). M.p. 247 °C (decomp., beginning sublimation at 200 °C). ^{1}H NMR (CD_3OD): δ 4.79 (br s, 1 H, *H*C), 3.12 (m, 2 H, C-CH_2), 2.69 (m, 2 H, CH_2-N). ^{13}C NMR (CD_3OD): δ 72.7, 63.9, 39.4, 35.3. ^{11}B NMR (CD_3OD): δ −2.0, −4.8, −8.8, −11.4, −12.2. IR (KBr): 3058, 2581, 2475, 1466 cm^{-1}.

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