The synthesis of a monoammonium derivative of fullerenopyrrolidine

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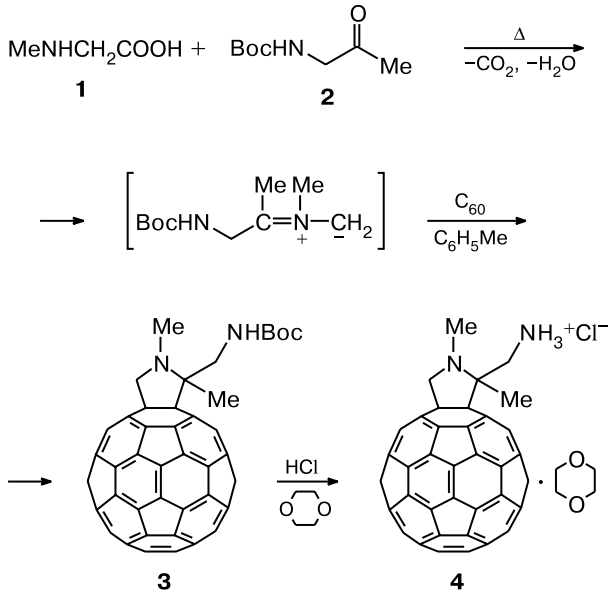
The Prato reaction was used to synthesize a monoammonium derivative of fullerenopyrrolidine.

Key words: [60]fullerene, amino ketone, cycloaddition reaction.

Among biologically active organic functionalized fullerenes, special attention has been recently given to water-soluble substituted fullerenopyrrolidines containing polar groups in the nitrogen-containing ring. Interest in such compounds has extremely risen after some of them were reported[1—3] as possibly exhibiting an anti-HIV activity. Bisammonium salts of fullerenopyrrolidine were obtained by Prato[4] using 1,3-dipolar cycloaddition of azomethine ylides (formed from glycines and *N*-Boc-protected diamino ketones) to [60]fullerene. However, the described[4] general scheme includes no detailed procedures for the synthesis and, chiefly, separation of mono-, di-, and polyadducts.

The goal of the present work was to find a route to monoammonium salts of fullerenopyrrolidine *via* the reaction of C_{60} with azomethine ylide formed from sarcosine (**1**) and 1-(*N*-Boc-amino)propan-2-one **2** in toluene (Scheme 1).

Scheme 1



We also developed a high-yielding procedure for the synthesis of the starting amino ketone **2** by oxidation of an amino alcohol.

To find the optimal conditions for the synthesis of ammonium derivatives of fullerenopyrrolidine, we varied the molar ratio of the reagents while monitoring the reaction by TLC. The best results were obtained for the 1 : 2 : 1 ratio of fullerene, sarcosine, and amino ketone. However, in this case too, the reaction yielded a mixture of cycloadducts, the monoadduct being dominant. The reaction products were separated off by column chromatography: first, the unreacted fullerene was eluted with toluene and then monoadduct **3** was eluted with toluene—chloroform (2 : 3). After the Boc-protection was removed, monoammonium salt of fullerenopyrrolidine **4** was obtained as a solvate with dioxane. Compound **4** is a brown crystalline substance, which is stable in air and soluble in water with a low content of DMSO.

Experimental

Fluka chemicals (1-aminopropan-2-ol, oxalyl chloride, triethylamine (99.5%), and di-*tert*-butyl dicarbonate (Boc_2O; 98%)) were used as purchased. The course of the reaction was monitored by TLC on Macherey-nagel plates (SiO_2, 0.2 mm). Cycloadducts were separated off on Merck silica gel-60.

The electronic absorption spectrum of compound **4** is typical of fullerenopyrrolidines.[5] ^{1}H NMR spectra were recorded on a Bruker Avance DPX-200 instrument.

1-(*tert*-Butoxycarbonyl)aminopropan-2-ol. A stirred solution of 1-aminopropan-2-ol (0.78 g, 10 mmol) in a mixture of dioxane (20 mL) and 1 *N* NaOH (10 mL, 10 mmol) was cooled in an ice bath. Then Boc_2O (2.4 g, 11 mmol) was added and the reaction mixture was stirred at ~20 °C for 18 h and concentrated *in vacuo* to ~7 mL. The resulting paste was diluted with water to 50 mL and the product was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over Na_2SO_4

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and concentrated *in vacuo* to an oily product (1.71 g), which was used unpurified for the next step.

1-(*tert*-Butoxycarbonyl)aminopropan-2-one (2). Oxalyl chloride (0.98 mL, 11.45 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C and anhydrous DMSO (1.7 mL, 23.9 mmol) in CH_2Cl_2 (5 mL) was added. The solution was stirred at −73 °C for 2 min and Boc-aminopropanol (1.71 g, 9.71 mmol) in CH_2Cl_2 (10 mL) was added dropwise, while preventing the temperature from rising above −50 °C. Then the reaction mixture was stirred at the same temperature for 15 min, triethylamine (6.9 mL, 49.8 mmol) was added, and stirring was continued for an additional 5 min at −50 °C. The mixture was warmed to room temperature, diluted with CH_2Cl_2 (50 mL), and washed with water (4×50 mL). The organic layer was separated off and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was fractionated to collect a light liquid with b.p. 80—85 °C (0.1 Torr), which then crystallized (m.p. 44—46 °C). The yield of compound **2** was 1.38 g (80%). Found (%): C, 55.31; H, 8.51. $C_8H_{15}NO_3$. Calculated (%): C, 55.49; H, 8.67. ^{1}H NMR ($CDCl_3$), δ: 1.42 (s, 9 H, Me_3C); 2.16 (s, 3 H, MeC(O)); 4.00 (d, 2 H, CH_2, J = 4.6 Hz); 5.23 (br.s, 1 H, NH).

1-*tert*-Butoxycarbonylaminomethyl-1,2-dimethyl[60]fullereno[*c*]pyrrolidine (3). Sarcosine (**1**) (0.25 g, 2.80 mmol) and Boc-aminopropan-2-one **2** (0.4 g, 2.31 mmol) were added to a solution of fullerene (1 g, 1.38 mmol) in toluene (600 mL). The reaction mixture was refluxed with stirring for 8 h, cooled to ~20 °C, and filtered. The resulting solution was separated by column chromatography on silica gel with toluene and toluene—chloroform (2 : 3) as the eluents for the unreacted fullerene and the major product, respectively. Polyadducts were eluted with chloroform. The solvents were removed *in vacuo* to give a red-brown solid (0.11 g, 60% with respect to the consumed fullerene), m.p. >400 °C. Found (%): C, 90.80; H, 2.37. $C_{70}H_{20}N_2O_2$. Calculated (%): C, 91.30; H, 2.17.

1,2-Dimethyl-1-methylammonio[60]fullereno[*c*]pyrrolidine chloride, a solvate with dioxane (4). Compound **3** (0.15 g, 0.16 mmol) was added at 0 °C to a solution of 4 *M* HCl (2 mL) in dioxane. The reaction mixture was stirred at this temperature for 2 h. The solution was decanted and the precipitate was repeatedly washed with dioxane until a neutral reaction and dried *in vacuo*. The yield of a brown product was 0.13 g (96%). Found (%): C, 86.30; H, 2.36; Cl, 3.65. $C_{65}H_{13}ClN_2 \cdot C_4H_8O_2$. Calculated (%): C, 87.60; H, 2.22; Cl, 3.75. UV (DMSO), λ_{max}/nm: 340, 430. ^{1}H NMR (DMSO-d_6), δ: 1.62 (s, 3 H, NMe); 2.86 (s, 3 H, C—Me); 3.57 (s, 8 H, H of dioxane); 3.80, 4.37 (both d, 1 H each, $C\underline{H}_2NH_3^+$, J = 13.3 Hz); 4.41, 4.70 (both d, 1 H each, CH_2, J = 10.5 Hz); 6.98 (s, NH_3^+). The integral intensity of the signal at δ 6.98 is lower than the expected value, probably, because of the isotope exchange with the solvent.

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