4,5-Difluoro-1,2-dehydrobenzene: generation and cycloaddition reactions

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The oxidation of 1-amino-5,6-difluorobenzotriazole with $Pb(OAc)_4$ in dry CH_2Cl_2 afforded 4,5-difluoro-1,2-dehydrobenzene, a new active intermediate, which can be used *in situ* for the synthesis of fluorinated carbo- and heterocyclic compounds *via* cycloaddition reactions.

Benzotriazoles are of continuing interest for chemists and biologists as an important class of heterocyclic compounds. Indeed, benzotriazole is a key structural fragment of a number of natural compounds,[1] vitamins (for example, B_{12})[2] and biologically active compounds exhibiting herbicidal,[3] insecticidal,[4] acaricidal[5] and other activities. In particular, some benzotriazoles are active towards G-serotonin receptors (5-HT_{1A}),[6] while others are inhibitors of cytochromes P-450s.[7] On the other hand, N-substituted benzotriazoles are widely used in synthetic organic chemistry as easily modified and good leaving groups, and also as a source of iminium cations.[8–10]

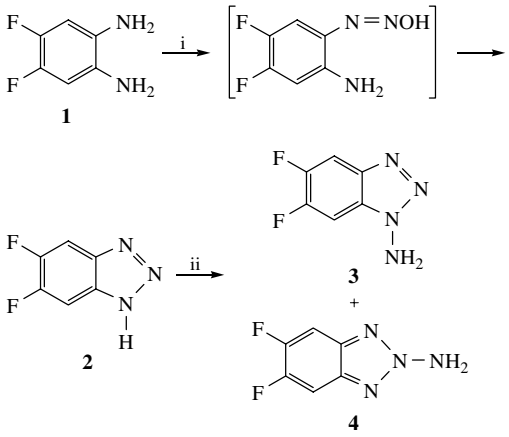
It is well known that the incorporation of fluorine atoms into organic molecules modifies their biological, chemical and physical properties.[11,12] In this respect, derivatives of 1-aminobenzotriazoles bearing fluorine atoms in the benzene ring might be of interest as a source of fluorinated dehydrobenzene. However, fluorinated benzotriazoles have not so far been described in the literature. We have tried to generate 4,5-difluoro-1,2-dehydrobenzene and to demonstrate that it is a useful intermediate for the synthesis of fluorinated carbo- and heterocyclic compounds.

1,2-Dehydrobenzene (DHB) is an important and extremely active intermediate, which is widely used in organic chemistry to functionalise aromatic compounds and to study the mechanisms of chemical and biochemical reactions.[13,14] Both intra- and intermolecular cycloaddition reactions of DHB can be used for the construction of a variety of natural compounds.[15] 4,5-Difluoro-1,2-dehydrobenzene has been generated from 4,5-difluoro-2-trimethylsilanylphenyl trifluoromethanesulfonate in order to be involved in the reaction with alkynes.[16] There are also published data concerning the generation and reactions of tetrafluorodehydrobenzene.[17–19]

One of the well-known ways to generate DHB is the oxidative degradation of 1-aminobenzotriazole, which can be derived from *ortho*-nitroaniline through diazotation with sodium nitrite followed by the interaction with diethyl malonate and subsequent chain of complicated catalytic reactions.[20,21] However, our attempts to obtain 1-amino-5,6-difluorobenzotriazole **3** from 2-nitro-3,4-difluoroaniline using the procedures described[21] were unsuccessful.

We prepared aminotriazoles **3** and **4** through the N-amination of 5,6-difluorobenzotriazole **2** with hydroxylaminosulfonic acid (HASA). Starting 1,2-diamino-4,5-difluorobenzene **1** was converted into corresponding benzotriazole **2** through nitrosation in water/AcOH at 65–80 °C (Scheme 1).† The reaction of **2** with HASA resulted in a mixture of N-1 and N-2 isomeric amino compounds **3** and **4**, which were separated by column chromatography (diethyl ether–petroleum ether, 2:1). The ratio between isomers was found to depend on the reaction temperature and solvents used. The best yield of N-1 isomer **3** (75%) was reached when the reaction was carried out in water at 70–75 °C.

In the ^{1}H NMR spectrum of 1-amino compound **3**, the resonance signals of H-4 and H-7 protons appear as double doublets at δ 8.17 and 7.79 ppm due to coupling constants $^nJ_{(H,F)}$, while in the ^{1}H NMR spectrum of symmetrical N-2 isomer **4** protons H-4 and H-7 are chemically equal, thus, giving rise to a pseudo-triplet at 7.93 ppm.



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, AcOH, 5 °C; ii, aqueous KOH, HASA, 30 °C.

† The ^{1}H NMR spectra in [$^2H_6$]DMSO were recorded on a Bruker WP-250 instrument (250 MHz). Mass spectra were recorded using a Varian MAT 311A spectrometer.

5,6-Difluorobenzotriazole **2**. 1,2-Diamino-3,4-difluorobenzene **1**[22] (0.14 g, 1.00 mmol) was dissolved in AcOH (0.12 ml, 2.00 mmol) and 5 ml of water on heating. The reaction mixture was cooled, and a solution of $NaNO_2$ (0.08 g, 1.09 mmol) in 2 ml of water was added at 5 °C. The reaction mixture became immediately dark-green, and it was stirred at room temperature for 1 h. The precipitate obtained after cooling was filtered off, dried in air and recrystallised from water. Yield, 74%; mp 183–184 °C. ^{1}H NMR, δ: 15.85 (br. s, 1H, NH), 7.90 (t, 2H, H-4, H-7, J_{HF} 9.0 Hz). MS, *m/z* (%): 155 (100) [M$^+$], 127 (32), 100 (41), 75 (10), 50 (16). Found (%): C, 46.24; H, 1.89; N, 27.16. Calc. for $C_6H_3F_2N_3$ (%): C, 46.46; H, 1.94; N, 27.09.

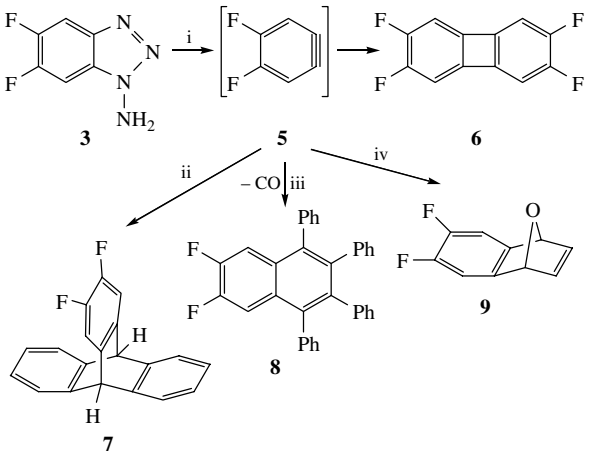
1-Amino-5,6-difluorobenzotriazole **3** *and 2-amino-5,6-difluorobenzotriazole* **4**. 5,6-Difluorobenzotriazole (0.16 g, 10.00 mmol) **2** was dissolved in 3 ml of aqueous KOH (0.17 g, 30.00 mmol) at 30 °C. HASA (0.20 g, 16.00 mmol) was added in portions at 70–75 °C for 1 h, and the reaction mixture was cooled. The precipitate obtained was filtered off and dried in air. A mixture of N-1 and N-2 isomers was separated by column chromatography (silica gel 5–40 μm, petroleum ether–diethyl ether, 1:2; R_f 0.50 (**3**) and 0.63 (**4**). Yields of 67% (**3**) and 27% (**4**).

For **3**: mp 157–159 °C. ^{1}H NMR, δ: 8.17 (dd, 1H, H-4, $^3J_{HF}$ 10.1 Hz, $^4J_{HF}$ 7.1 Hz), 7.79 (dd, 1H, H-7, $^3J_{HF}$ 10.1 Hz, $^4J_{HF}$ 7.0 Hz), 7.15 (br. s, 2H, NH_2). MS, *m/z* (%): 170 (8) [M$^+$], 155 (72), 142 (26), 141 (43), 127 (27), 126 (19), 114 (16), 113 (100), 100 (38), 99 (18), 88 (14), 81 (15), 76 (13), 75 (30), 63 (39), 62 (13), 56 (12), 50 (22). Found (%): C, 42.41; H, 2.13; N, 33.04. Calc. for $C_6H_4F_2N_4$ (%): C, 42.36; H, 2.37; N, 32.93.

For **4**: mp 144–146 °C. ^{1}H NMR, δ: 8.95 (br. s, 2H, NH_2), 7.93 (t, 2H, H-4, H-7, J_{HF} 9.1 Hz).

In order to generate 4,5-difluoro-1,2-dehydrobenzene **5**, 1-amino-5,6-difluorobenzotriazole **3** was oxidised with $Pb(OAc)_4$ in dry CH_2Cl_2 at room temperature (Scheme 2).‡

We found that oxidation is accompanied by the release of nitrogen. In the absence of any 'traps' in the reaction mixture, the dimerisation of dehydrobenzene **5** takes place to give 2,3,6,7-tetrafluorobiphenylene **6** in a nearly quantitative yield. A very intense peak of the molecular ion [M^+ = 224 (100%)] and the ^{1}H NMR data for biphenylene **6** are in a full agreement with its aromatic structure.



Scheme 2 *Reagents and conditions*: i, $Pb(OAc)_4$, dry CH_2Cl_2, 20 °C; ii, anthracene, dry CH_2Cl_2, $Pb(OAc)_4$, 20 °C; iii, tetracyclone, dry CH_2Cl_2, $Pb(OAc)_4$, 20 °C; iv, furan, dry CH_2Cl_2, $Pb(OAc)_4$, 20 °C.

Anthracene, tetraphenylcyclopentadienone (tetracyclone) and furan have also been used as dienes to trap 4,5-difluoro-1,2-dehydrobenzene **5**.

The best yield of cycloadduct **7** (39%) derived from the reaction of **3** with anthracene in dry CH_2Cl_2 at room temperature was obtained with a twofold molar excess of anthracene relative to aminotriazole **3**. With a twofold molar excess of **3** relative to anthracene, the yield of **7** decreased to 18%, while yield of biphenylene **6** increased up to 43%. In the ^{1}H NMR spectra, the resonance signal of the bridge head protons H-9 and H-10 of adduct **7** can be easily distinguished as a singlet at 5.56 ppm, thus enabling the ratio of compounds **6** and **7** to be determined by measuring the integral intensities of corresponding signals.

The reaction of **3** with tetracyclone was carried out in a minimal volume of dry CH_2Cl_2 to give 6,7-difluoro-1,2,3,4-tetraphenylnaphthalene **8** in a very good yield (96%) after several minutes of stirring at room temperature. The mass spectrum of fluorinated naphthalene **8** exhibits a very intense peak of the molecular ion, which is in agreement with its aromatic structure.

Interaction of **3** with furan was found to result in the formation of a mixture of **6** and **9**. In order to obtain **9** in a good yield, the reaction has to be carried out in furan as a solvent. In the mass spectrum of cycloadduct **9**, the molecular ion peak with *m/z* 180 was observed. Some plausible ways for degradation of the molecular ion of **9** are consistent with the structure.

In conclusion, note that we generated 4,5-difluoro-1,2-dehydrobenzene from 1-amino-5,6-difluorobenzotriazole and demonstrated its ability to undergo cycloaddition reactions, which can be used for the synthesis of new fluorinated compounds.

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‡ *Generation of 4,5-difluoro-1,2-dehydrobenzene* **5**. 1-Amino-5,6-difluorobenzotriazole **3** (0.02 g, 0.10 mmol) was dissolved in 1 ml of dry CH_2Cl_2 and $Pb(OAc)_4$ powder (0.05 g, 0.12 mmol) was added with stirring. After additional stirring for 5 min, the precipitate of lead oxide was filtered off, and the filtrate was evaporated to dryness to give 2,3,6,7-tetrafluorobiphenylene **6**. Yield, 97%, mp 146–147 °C. ^{1}H NMR, δ: 6.47 (t, 4H, H-1, H-4, H-5, H-8, J_{HF} 8.8 Hz). MS, *m/z* (%): 224 (100) [M^+], 149 (12), 112 (13). Found (%): C, 64.38; H, 1.69. Calc. for $C_{12}H_4F_4$ (%): C, 64.30; H, 1.80.

Cycloaddition reactions of **5** *with anthracene and tetracyclone*. 1-Amino-5,6-difluorobenzotriazole **3** (0.02 g, 0.10 mmol) and diene (0.02 mmol) were dissolved in 2 ml of dry CH_2Cl_2, and $Pb(OAc)_4$ powder (0.05 g, 0.12 mmol) was added with stirring. After additional stirring for 5 min, the precipitate of lead oxide was filtered off, and the filtrate was evaporated to dryness to give the corresponding products **7** or **8**. Yields of 39% (**7**) and 96% (**8**).

9,10-Dihydro-2,3-difluoro-9,10-benzoanthracene **7**: mp 207–209 °C. ^{1}H NMR, δ: 7.38 (m, 6H, Ar–H), 6.97 (m, 4H, Ar–H), 5.56 (s, 2H, H-9, H-10). MS, *m/z* (%): 290 (100) [M^+], 289 (49), 271 (12), 270 (12), 179 (12), 178 (73), 176 (12), 144 (22), 89 (12). Found (%): C, 82.81; H, 4.09. Calc. for $C_{20}H_{12}F_2$ (%): C, 82.74; H, 4.17.

6,7-Difluoro-1,2,3,4-tetraphenylnaphthalene **8**: mp 212–213 °C. ^{1}H NMR, δ: 7.21 (m, 20H, 4Ph), 6.90 (m, 2H, H-5, H-8). MS, *m/z* (%): 468 (100) [M^+], 385 (20), 384 (60), 356 (15), 179 (11), 178 (71). Found (%): C, 86.94; H, 4.49. Calc. for $C_{34}H_{22}F_2$ (%): C, 87.16; H, 4.73.

1,4-Dihydro-6,7-difluoro-1,4-epoxynaphthalene **9**. 1-Amino-5,6-difluorobenzotriazole **3** (0.02 g, 0.10 mmol) was dissolved in 1–2 ml of furan, and $Pb(OAc)_4$ powder (0.05 g, 0.12 mmol) was added. After stirring for 5 min, the precipitate of lead oxide was filtered off, and the filtrate was evaporated to dryness to give **9**. Yield 94%, mp 71–73 °C. ^{1}H NMR, δ: 7.35 (t, 2H, H-5, H-8, J_{HF} 7.8 Hz), 6.41 (d, 2H, H-1 and H-4, $^5J_{HF}$ 8.0 Hz), 5.75 (s, 2H, =CH). MS, *m/z* (%): 180 (43) [M^+], 154 [$M - C_2H_2$]$^+$ (41), 152 [M – CO] (70), 151 [M – CO – H$^\cdot$] (100), 125 (13), 101 (11), 60 (17). Found (%): C, 66.74; H, 3.41. Calc. for $C_{10}H_6F_2O$ (%): C, 66.67; H, 3.36.

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