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On the Synthesis of 2-Amino-4,6-difluorobenzonitrile: Highly Selective Formation of 5-Fluoro-3-nitro-1,2-benzoquinone 2-Diazide in the Attempted Sandmeyer Cyanation of 2,4-Difluoro-6-nitrobenzenediazonium Cation†

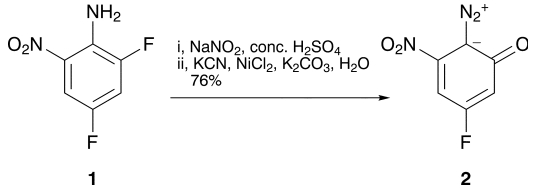
Pelayo Camps,* Jordi Morral and Diego Muñoz-Torrero

Laboratori de Química Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal s/n, E-08028 Barcelona, Spain

Attempted cyanation of a diazonium salt derived from 2,4-difluoro-6-nitroaniline gives 5-fluoro-3-nitro-1,2-benzoquinone 2-diazide‡ in good yield by selective nucleophilic substitution of the 2-fluoride group by hydroxide, instead of the desired 2-amino-4,6-difluorobenzonitrile, which can be obtained by the reaction of 2,4,6-trifluorobenzonitrile with ammonia.

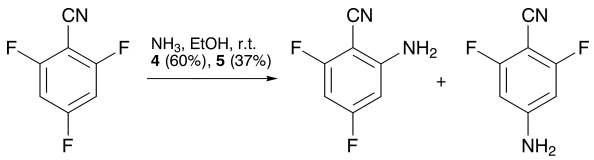
In connection with the preparation of tacrine related compounds of potential interest for the treatment of Alzheimer's disease, we required 2-amino-4,6-difluorobenzonitrile **4**, a compound which has been used for the synthesis of 4-aminoquinoline derivatives but for which a preparation has not been described. A general procedure to prepare 2-aminobenzonitriles from the corresponding 2-nitroanilines involves the amino group being replaced by cyanide *via* the corresponding diazonium salt followed by reduction of the nitro groups which yields the amine function.[2] It is known that diazonium salts having leaving groups at the *ortho* or *para* position can give products derived from nucleophilic substitution of these groups by nucleophiles present in the reaction medium, in competition with nucleophilic substitution of the diazo group.[3] When the attacking nucleophile in these reactions is hydroxide, the substitution product is a 1,2- or 1,4-benzoquinone diazide.[4]

When we attempted the preparation of **4** from **1** by the above cited general procedure, we obtained a brown solid in 76% yield which was characterized as 5-fluoro-3-nitro-1,2-benzoquinone 2-diazide **2**.‡ Especially significant were its IR [ν/cm^{-1} 2149 (diazo group st), 1641 (C=O st), 1519 and 1350 (NO_2 st)] and ^{13}C NMR spectra [two quaternary carbon atoms (δ 175.6 and 79.4) and only one C-F carbon atom (δ 167.0, J 267.3 Hz)], which suggested the presence of benzoquinone diazide and nitro functions and only one fluorine atom. The value of the $J_{H,F}$ and $J_{C,F}$ coupling constants were only compatible with the 1,2-benzoquinone 2-diazide structure. The rest of the spectroscopic data and elemental analysis were also concordant with the proposed structure. Worthy of note is the highly selective formation of **2**, which implies not only the selective substitution of a fluoride *vs.* a nitrite group but also the selective substitution of the *o*- *vs.* the *p*-fluoride.[3,5]



1 2

Scheme 1 Selective formation of 1,2-benzoquinone 2-diazide **2** from a diazonium salt derived from **1** under Sandmeyer reaction conditions



3 4 5

Scheme 2 Synthesis of isomeric aminodifluorobenzonitriles **4** and **5**

Aminobenzonitrile **4** could be obtained by the reaction of 2,4,6-trifluorobenzonitrile with an ethanolic solution of ammonia at room temperature following a modification of the method described for the preparation of 2-amino-6-fluorobenzonitrile.[6] In this reaction, a mixture of the two possible monosubstitution products **4** and **5** in a ratio close to the statistical one was obtained. This mixture was easily separated by column chromatography, isolating both products in 60 and 37% yield, respectively. Aminonitrile **4** is being used for the preparation of tacrine-related products through Friedländer reactions.

Experimental

General.—Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus, 500 MHz. ^{1}H NMR spectra were performed on a Varian VXR 500 spectrometer, 75.4 MHz, ^{13}C NMR spectra on a Varian Gemini 300 and 200 MHz ^{1}H and 50.3 ^{13}C NMR spectra on a Varian Gemini 200. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. IR spectra were recorded on a FTIR Perkin-Elmer spectrometer, model 1600. Silica gel SDS 60 (60–200 μm) was used for the column chromatography. Commercial solvents for column chromatography were purified by distillation at atmospheric pressure. Elemental analyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo (C.I.D.), Barcelona, Spain.

5-*Fluoro*-3-*nitro*-1,2-*benzoquinone* 2-*Diazide* **2**.—To a solution of sodium nitrite (150 mg, 2.2 mmol) and conc. sulfuric acid (1.10 ml), a cold solution of 2,4-difluoro-6-nitroaniline **1** (340 mg, 1.95 mmol) in acetic acid (2.2 mL) was added. The solution was stirred at 0 °C for 30 min and then poured onto a cold (ice bath) solution of $NiCl_2 \cdot 6H_2O$ (600 mg), KCN (700 mg) and Na_2CO_3 (1.85 g) in water (15 mL). The mixture was heated at 70 °C for 30 min and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give **2** as a brown solid (270 mg, 76%). The analytical sample was obtained by crystallization from hexane, mp 74–75 °C; ν_{max} (KBr) cm^{-1} 2149 (s), 1641 (s), 1585 (s), 1519 (s), 1350 (s), 1325 (s), 1211 (s), 1160 (m), 1114 (s), 1008 (m), 943 (m), 891 (m), 854 (s), 774 (m) and 739 (m); δ_H (200 MHz, $CDCl_3$) 6.70 (dd, J 10.7, J' 2.2 Hz, 1 H, 6-H), 7.19 (dd, J 7.8, J' 2.2 Hz, 1 H, 4-H); δ_C (50.3 MHz, $CDCl_3$) 79.4 (C, br s, C-2), 107.7 (CH, d J 35.6 Hz, C-6), 114.1 (CH, d,

*To receive any correspondence (*e-mail:* camps@farmacia.far.ub.es).

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡*Systematic name:* 6-diazo-3-fluoro-5-nitrocyclohexa-2,4-dien-1-one.

J 16.6 Hz, C-4), 142.7 (C, d, *J* 14 Hz, C-3), 167.0 (C, d, *J* 267.3 Hz, C-5), 175.6 (C, d, *J* 17.4 Hz, C-1) (Found: C, 39.38; H, 1.17; N, 23.01%. $C_6H_2FN_3O_3$ requires: C, 39.36; H, 1.10; N, 22.95%).

2-*Amino*-4,6-*difluorobenzonitrile* **4** *and* 4-*Amino*-2,6-*difluorobenzonitrile* **5**.—A mixture of 2,4,6-trifluorobenzonitrile **3** (216 mg, 1.4 mmol) and a saturated ethanolic solution of ammonia (20 mL) was heated at 35 °C for 18 h in a closed glass vessel. The solution was then concentrated *in vacuo*, water (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid residue (250 mg) which was chromatographed through silica gel (10 g) eluting with hexane–ethyl acetate mixtures of increasing polarity. On elution with hexane–ethyl acetate (9:1) **4** (130 mg, 60% yield) was obtained. On elution with hexane–ethyl acetate (8:2), **5** (80 mg, 37% yield) was isolated. **4**: Mp 144.5–145 °C (sublimed); ν_{max}/(KBr) 2 cm^{-1} 3460 (s), 3360 (s), 3230 (m), 3112 (m), 2224 (s), 1652 (s), 1576 (s), 1491 (m), 1476 (s), 1394 (m), 1313 (m), 1217 (m), 1139 (s). 1103 (s), 1052 (m), 990 (m), 833 (s), 810 (s) and 713 (m); δ_H (500 MHz, CD_3COCD_3) 6.21 (br s, 2 H, NH_2), 6.38 (ddd, *J* 10.2, *J′* 9.5, *J″* 2.5 Hz, 1 H, 5-H), 6.48 (ddd, *J* 11.0, *J′* 2.5 *J″* 2.0 Hz, 1 H, 3-H); δ_C (75.4 MHz, CD_3COCD_3) 82.5 (C, d, *J* 19.5 Hz, C-1), 92.8 (CH, dd, *J* 24.4, *J′* 24.3 Hz, C-5), 98.0 (CH, d, *J* 26.1 Hz, C-3), 112.9 (C, CN), 154.8 (C, dd, *J* 6.0, *J′* 6.1 Hz, C-2), 165.6 (C, dd, *J* 252.6, *J′* 17.0 Hz, C-6), 167.2 (C, dd, *J* 250.3, *J′* 16.1 C-4) (Found: C, 54.57; H, 2.67; N, 18.01%. $C_7H_4F_2N_2$ requires: C, 54.45; H, 2.62; N, 18.18%). **5**: Mp 139.5–140 °C (chloroform); ν_{max} (KBr)/cm^{-1} 3512 (s), 3407 (s), 3065 (m), 2220 (s), 1639 (s), 1569 (s), 1511 (s), 1476 (s), 1388 (m), 1342 (m), 1220 (s), 1184 (s), 1083 (m), 1017 (s), 845 (s) and 723 (s); δ_H (500 MHz CD_3OD) 6.36 [dm, *J* 10.5 Hz, 3(5)-H]; δ_C (75.4 MHz, CD_3OD) 77.3 (C, t, *J* 20.5 Hz, C-1), 97.1 [CH, d, *J* 23.8 Hz, C-3(5)], 112.1 (C, CN), 157.5 (C, t, *J* 15.0 Hz, C-4), 165.9 [C, dd, *J* 252.2 *J′* 8.5 Hz, C-2(6)] (Found: C, 54.57; H, 2.61; N, 17.92%. $C_7H_4F_2N_2$ requires: C, 54.55; H, 2.62; N, 18.18%).

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