Exclusive β-Substitution in the Reaction of Octafluoronaphthalene with Secondary Amines

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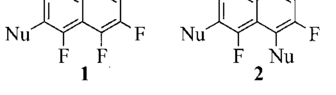
The reaction between octafluoronaphthalene and dimethylamine, pyrrolidine or piperidine in DMF, dimethyl(ethylene)urea (DMEU) or without solvent leads to the exclusive substitution of β-fluorine atoms giving naphthalene derivatives with four NR_2 groups. This was proved by ^{19}F NMR of the products and a crystal structure determination for 1,4,5,8-tetrafluoro-2,3,6,7-tetrakis(piperidin-1-yl)naphthalene. The main feature of the reaction in DMF was a transamidation process. The remaining four fluorine atoms in the synthesised tetraamines could be smoothly replaced by reduction with $LiAlH_4$.

Introduction

There is little information available regarding the reaction between octafluoronaphthalene (OFN) and neutral nucleophiles. The action of hydrazine, diethylamine and some saturated cyclic secondary amines has been investigated previously.[1] However, in all those cases, no more than two functionalities were introduced to the OFN core, consecutively at positions 2 and 6. Until now, the scope of this reaction in the preparation of polysubstituted naphthalenes and the position of the third and subsequent nucleophilic substitution are unknown. This is of general interest, because preliminary semiempirical calculations have shown that positions 1 and 4 of 2,6-disubstituted hexafluoronaphthalenes are almost equally susceptible to nucleophilic attack theoretically leading to structures **1** and **2** (Scheme 1).[2] In connection with this, and since we have a continuing interest in polyaminonaphthalenes,[3] the interaction between OFN and some secondary neutral amines has been investigated.



1 **2**

Scheme 1

Results and Discussion

Initial reactions between OFN and secondary amines were conducted at 95 °C in DMF with excess dimethylamine, piperidine, or pyrrolidine (see Exp. Sect. for details). After heating for 2 d, the crude reaction mixture contained several partially substituted derivatives: **3** (0.6%), **4** (58%) and **5** (23%) for dimethylamine, **6** (2%), **7** (15%), **8** (63%) and **9** (19%) for piperidine and **10** (0.3%), **11** (66%), **12** (14%) and **13** (20%) for pyrrolidine (Scheme 2). Compounds **8**, **9**, **12** and **13** are substituted with dimethylamino groups in addition to the dialkylamino group derived from the secondary amine. This is due to a transamidation reaction between DMF and the secondary amine, yielding dimethylamine, which then competes with the secondary amine in the nucleophilic substitution.[4] It is important to note that the enhanced nucleophilicity of pyrrolidine leads to lower yields of "mixed" substitution products. After 5−7 d at 95 °C, the reaction mixtures contain mainly the tetrasubstituted products **5**, **9** or **13**. In the case of piperidine, compound **14** (ca. 20%) was also formed.

The influence of higher temperature (190 °C) and prolonged reaction time (up to 20 d) was tested only with dimethylamine because of the byproduct formation for the other secondary amines. Even under these vigorous conditions the main products of the reaction were compound **5** (77%) and a substance assigned, after GC/MS, as the pentasubstituted derivative (yield < 20%). No attempts to optimize the preparation of the latter were made.

Subsequently, 1,3-dimethylimidazolidine-2-one [dimethyl(ethylene)urea, DMEU] was used as the reaction medium. This is widely used along with 1,3-dimethylhexahydropyrimidin-2-one to replace carcinogenic HMPTA in nucleophilic substitution reactions.[5] We found that heating OFN for 1 week with piperidine in DMEU at 95 °C resulted in the formation of the tri- and tetraamines **7** (63%) and **15** (37%), respectively. When piperidine is replaced by pyrrolidine or dimethylamine under the same reaction conditions only tetrasubstituted products **16** and **5** were ob-

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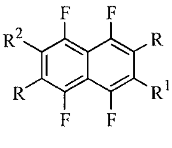


	3	4	5	6	7	8	9	10
R	NMe_2	NMe_2	NMe_2	piperidin-1-yl	piperidin-1-yl	piperidin-1-yl	piperidin-1-yl	pyrrolidin-1-yl
R^1	F	NMe_2	NMe_2	F	piperidin-1-yl	NMe_2	NMe_2	F
R^2	F	F	NMe_2	F	F	F	NMe_2	F

	11	12	13	14	15	16
R	pyrrolidin-1-yl	pyrrolidin-1-yl	pyrrolidin-1-yl	piperidin-1-yl	piperidin-1-yl	pyrrolidin-1-yl
R^1	pyrrolidin-1-yl	NMe_2	pyrrolidin-1-yl	piperidin-1-yl	piperidin-1-yl	pyrrolidin-1-yl
R^2	F	F	NMe_2	NMe_2	piperidin-1-yl	pyrrolidin-1-yl

Scheme 2. Products of nucleophilic substitution by secondary amines on octafluoronaphthalene in DMF

tained, although in the second case trace amounts (< 1%) of pentasubstituted product could be detected by GC/MS. The yields of compounds **5** and **16** were about 85% when the reaction was conducted at 190 °C for 1 week. Currently, the only isolated product from the reaction with piperidine is **15**. Attempts to substitute more fluorine atoms in **5**, **15**, or **16** by increasing the reaction time up to 2 weeks failed, giving an intractable tar.

In order to observe the influence of solvent on the substitution reaction, we also investigated the reaction in pure amines. When OFN was treated with piperidine or pyrrolidine at 95 °C for 1 week, only tri- [**7** (65%), **11** (67%)] and tetrasubstituted products [**15** (12%), **16** (7%)] were found in the reaction mixture. Elevating the temperature to 190 °C led to exclusive formation of **15** and **16** together with some tarring. Tarring was the dominant process in reactions performed for 2 weeks at this temperature and no products with more than four amino groups were detected.

The composition of the reaction mixtures was determined by NMR spectroscopy and GC/MS. The exclusive formation of β-substituted derivatives in the reaction of OFN with secondary amines was confirmed by the ^{19}F NMR spectra of the neutral products and an X-ray crystal structure of tetraamine **15** (Figure 1). This molecule is centrosymmetric with the piperidinyl rings skewed out of the naphthalene plane by an average torsion angle of 58°.

Further evidence for exclusive β-substitution comes from the chemical shift of the ammonium proton resonance in the ^1H NMR spectrum of protonated **5** or **15** which appears at $\delta = 9-10$ ppm (cf. with protonated defluorinated analogs of type **17**[6]). It is apparent that the course of the reaction disagrees with that predicted and may be explained in the light of an *ortho,meta*-activation and *para*-deactivation effect of the fluorine atom(s): the site having the most fluorine atoms in neighbouring *ortho*- and, especially, *meta*-positions undergoes nucleophilic substitution preferentially.[7]

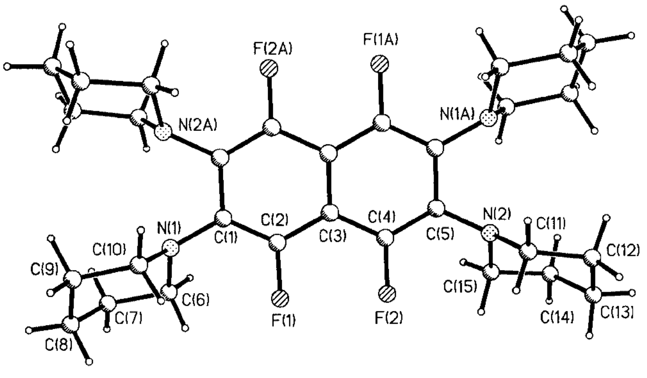
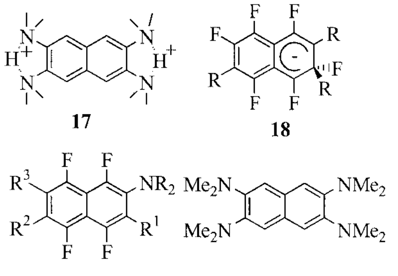


Figure 1. The X-ray crystal structure of **15** viewed perpendicular to the central bond of the naphthalene unit; selected bond lengths [Å] and angles [°]: N(1)−C(1) 1.409(2), N(2)−C(5) 1.419(2), N(1)···N(2A) 2.749(2), F(1)···F(2) 2.502(2), C(1)−C(2) 1.378(2), C(2)−C(3) 1.414(2), C(4)−C(5) 1.372(2), C(2)−F(1) 1.356(2); N(1)−C(1)−C(2) 124.38(15), C(1)−C(2)−C(3) 123.95(15), C(2)−C(3)−C(4) 124.49(15), C(2)−C(3)−C(3A) 118.02(16); N(1)−C(1)−C(2)−F(1) −1.9(2), F(2)−C(4)−C(5)−N(2) 3.8(2), C(3)−C(4)−C(5)−C(1A) 1.1(2)

In our case, after substitution by two amino groups, only intermediate **18** satisfies these rules (see Scheme 3). Our confidence in the correctness of structures **8**, **9** and **12−14** is based on the following considerations. As was mentioned above, the introduction of the first two groups at positions 2 and 6 of OFN occurs rapidly even at 30 °C, while the evolution of Me_2NH as a result of the formylation of amines by DMF requires more harsh conditions. Therefore, dimethylaminodefluorination should start from the third stage of the reaction. Indeed, in the reaction mixture we did not observe compounds of type **19**, which could serve as a precursor of isomers different from **8**, **9**, **12**, **14**. Unfortunately, we were unable to obtain good-quality crystals of any of the "mixed" substitution products in order to prove their structure precisely and to distinguish between isomers of the type **20** and **21**. However, the ^{13}C NMR spectrum of **9** shows five peaks in the aromatic region, thus excluding compounds of type **21** which would display six signals.



19 $R^1 = R^3 = F$, $R^2 = NMe_2$
20 $R^1 = R^3 = NMe_2$, $R^2 = NR_2$
21 $R^1 = R^2 = NMe_2$, $R^3 = NR_2$

Scheme 3

Finally, we have found that the four α-fluorine atoms in the tetrakis(dialkylamino)naphthalenes can be reduced with $LiAlH_4$/THF. Thus, **5** gave 2,3,6,7-tetrakis(dimethylamino)naphthalene (**22**) in around 90% yield. It should be noted that the OFN → **5** → **22** sequence is a much more effective route to tetraamines of type **22**, which are known as electron-donor molecules. Previously, these molecules have been prepared by multistep procedures.[6]

Conclusion

In conclusion, the first tetrakis(dialkylamino)naphthalenes with amino groups exclusively in β-positions have been obtained from the reaction of OFN with some secondary amines. It was proved that piperidine and pyrrolidine in DMF are able to produce mixed substitution products with piperidin-1-yl or pyrrolidin-1-yl and dimethylamino groups on one ring. The structure of 1,4,5,8-tetrafluoro-2,3,6,7-tetrakis(piperidin-1-yl)naphthalene was confirmed by X-ray diffraction analysis and the sequence of substitution was established for the first time: 2, followed by 6, 3, 7, 1. Mono-, di-, tri-, and tetrasubstitution can be obtained using easily accessible conditions with the additional possibility of being able to replace the remaining fluorine atoms by hydrogen atoms. This offers obvious advantages in the further functionalisation of these tetraamines.

Experimental Section

General Remarks: ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ with a Varian Unity-300 spectrometer, operating at 300, 75, and 282 MHz, respectively, with internal standards Me_4Si for ^{1}H, ^{13}C and $CFCl_3$ for ^{19}F. GC/MS was performed with a Perkin−Elmer PE-5MS RX apparatus. A 25-m fused silica (methylphenylsilicone) capillary column was used with UHP-grade helium as the carrier gas. Octafluoronaphthalene and pyrrolidine were purchased from Lancaster, DMEU from Acros and $LiAlH_4$ from Aldrich Chemical Co. Inc.

General Procedure: A solution of octafluoronaphthalene (0.1 mmol), amine (8 mmol) and the appropriate solvent (2 mL) was heated in a sealed tube at the reaction temperature during the selected time. The reaction mixture was then poured into 40% KOH (30 mL) and the products were extracted with ethyl acetate (4 × 5 mL). The organic phases were combined, washed with water (2 × 20 mL), dried with Na_2SO_4, concentrated to dryness and either chromatographed on alumina or analysed by GC/MS.

1,4,5,8-Tetrafluoro-2,3,6,7-tetrakis(dimethylamino)naphthalene (5): Optimized conditions: 95 °C, DMF, 7 d; yield 86%; colourless needles with m.p. 169−170 °C (from MeOH/hexanes). $C_{18}H_{24}F_4N_4$ (372.40): calcd. C 58.1, H 6.5, N 15.0; found C 57.8, H 6.4, N 14.5. ^{1}H NMR: $\delta = 2.88$ (s) ppm. ^{13}C NMR: $\delta = 43.0$ (q, $^1J_{C,H} = 135.5$ Hz), 109.6 (m), 134.5 (m), 149.7 (dm, $^1J_{C,F} = 272.7$ Hz) ppm. ^{19}F NMR: $\delta = -135.0$ (s) ppm. MS (EI): *m/z* (%) = 372 (100) [M^+], 355 (16), 328 (18), 310 (31), 162 (36), 44 (70).

3,7-Bis(dimethylamino)-1,4,5,8-tetrafluoro-2,6-bis(piperidin-1-yl)-naphthalene (9): 95 °C, DMF, 7 d; yield 83%; colourless powder with m.p. 256−257 °C (from MeOH/hexanes). $C_{24}H_{32}F_4N_4$ (452.53): calcd. C 63.7, H 7.1, N 12.4; found C 63.4, H 6.9, N 12.5. ^{1}H NMR: $\delta = 1.64$ (br. m, 12 H, $CH_2CH_2CH_2$), 2.90 [s, 12 H, $N(CH_3)_2$], 3.11 [br. m, 8 H, $N(CH_2)_2$] ppm. ^{13}C NMR: $\delta = 24.5$ (m), 27.0 (t, $^1J_{C,H} = 126.4$ Hz), 43.5 (q, $^1J_{C,H} = 134.2$ Hz), 52.3 (t, $^1J_{C,H} = 134.9$ Hz), 109.8 (m), 134.6 (m), 147.3 (m), 147.8 (m), 150.7 (m) ppm. ^{19}F NMR: $\delta = -134.2$ (br. d, $J_{F,F} = 61.8$ Hz, 2 F, 1,5-*F*), −134.6 (br. d, $J_{F,F} = 61.7$ Hz, 2 F, 4,8-*F*) ppm. MS (EI): *m/z* (%) = 452 (100) [M^+], 347 (10), 338 (12), 84 (61), 44 (24).

1,4,5,8-Tetrafluoro-2,3,6,7-tetrakis(piperidin-1-yl)naphthalene (15): 190 °C, DMEU, 7 d; yield 84%; colourless needles with m.p. 321−322 °C (from $CHCl_3$). $C_{30}H_{40}F_4N_4$ (532.66): calcd. C 67.7, H 7.6, N 10.5; found C 67.5, H 7.3, N 10.5. ^{1}H NMR: $\delta = 1.66$ (m, 24 H, $CH_2CH_2CH_2$), 3.13 [m, 16 H, $N(CH_2)_2$] ppm. ^{19}F NMR: $\delta = -134.2$ (s) ppm.

1,4,5,8-Tetrafluoro-2,3,6,7-tetrakis(pyrrolidin-1-yl)naphthalene (16): (95 °C, DMEU, 7 d); yield 86%; colourless crystals with m.p. 215−216 °C (from MeOH/hexanes). $C_{26}H_{32}F_4N_4$ (476.56): calcd. C 65.5, H 6.8, N 11.8; found C 65.5, H 6.5, N 11.7. ^{1}H NMR: $\delta = 1.89$ (m, 16 H, CH_2CH_2), 3.32 [m, 16 H, $N(CH_2)_2$] ppm. ^{19}F NMR: $\delta = -135.9$ (s) ppm. MS (EI): *m/z* (%) = 476 (100) [M^+], 448 (11), 420 (18), 338 (12), 70 (45).

2,3,6,7-Tetrakis(dimethylamino)naphthalene (22): $LiAlH_4$ (30 mg, 0.8 mmol) was added to a solution of fluoronaphthalene **5** (37 mg, 0.1 mmol) in anhydrous THF (3 mL). The resulting suspension was refluxed for 24 h, then quenched with MeOH (5 mL) and diluted with water (10 mL). The product was extracted with benzene. The organic layer was washed with water, dried with Na_2SO_4 and the solvents were evaporated to dryness. This gave a residue, which after recrystallization from *n*-hexane afforded 26 mg (87%) of pure **22**, which was identical in its properties to an authentic sample prepared by another method.[6]

X-ray Crystallographic Study of 15: $C_{30}H_{40}F_4N_4$, $M = 532.66$, triclinic, $a = 6.7176(14)$, $b = 8.9069(19)$, $c = 12.089(3)$ Å, $\alpha = 95.216(4)$, $\beta = 105.703(4)$, $\gamma = 103.505(5)°$, $V = 667.8(2)$ Å^3, $T = 120(2)$ K, space group $P\bar{1}$, $Z = 1$, $\mu(\text{Mo-}K_\alpha) = 0.098$ mm^{-1}, 5083 reflection collected, 3150 unique ($R_{int} = 0.0184$). The final $wR(F^2)$ was 0.2080 (all data). CCDC-209303 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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