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Short Communication

Skraup-like cyclization of polyfluoro-2-naphthylamines: Vicarious electrophilic substitution of fluorine

Galina A. Selivanova, Alexey V. Reshetov, Irina Yu Bagryanskaya, Vitalij D. Shteingarts *

N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, Lavrentiev Ave. 9, Novosibirsk 630090, Russia

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ABSTRACT

Treatment of polyfluoro-2-naphthylamines with glycerol in H_2SO_4 or CF_3SO_3H at 150–160 °C gives respective polyfluorobenzo[f]quinolines. The reaction is suggested to proceed via intramolecular vicarious electrophilic substitution of fluorine at the α-position of polyfluorinated naphthalene core.

1. Introduction

Azaheterocycles fused with a fluorinated naphthalene skeleton, in particular, fluorinated benzoquinolines with one or two fluorine atoms, are of interest as potentially bioactive compounds [1]. As precursors for benzoquinolines with polyfluorinated carbocyclic moiety, polyfluorinated naphthylamines having an unsubstituted *ortho*-position to the amino group could be presumably involved in the Skraup synthesis. The recent development of the selective hydrodehalogenation of polyfluoroarenes [2] afforded a possibility of hydrodefluorination of heptafluoro-2-naphthylamine [3] or its *N*-acetyl derivative [4] by zinc in aqueous ammonia to expeditiously prepare their previously inaccessible less fluorinated analogs with an unsubstituted position which is β in the naphthalene core and *ortho* to the NHR group (R = Ac or H).

In this paper we examined a possibility of the Skraup pyridinization of polyfluorinated 2-naphthylamines.

2. Results and discussion

Unexpectedly, 1,4,5,6,8-pentafluoro-2-naphthylamine (**1**) reacted with glycerol in H_2SO_4 at 150–160 °C (the conditions previously used for pyridinization of *ortho*-unsubstituted polyfluorinated anilines [5]) to undergo cyclization with the F^1 rather than H^3 substitution and to give 6,7,8,10-tetrafluorobenzo[f]quinoline (**2**) in ~55% NMR yield (Scheme 1). A significant amount of the starting material remained intact (the ^{19}F NMR data), obviously due to dilution of the reaction mixture by liberated water. The oxidant (*m*-nitrobenzenesulfonic acid) proved needless, but using CF_3SO_3H instead of H_2SO_4 somewhat increased the conversion degree.

One could believe the pyridinization thus found to be generally typical for 2-naphthylamines with the 1-position occupied by fluorine. Indeed, heptafluoro-2-naphthylamine (**3**) with glycerol in CF_3SO_3H at 150–160 °C gave (after the work-up) 5,6,7,8,9,10-hexafluorobenzo[f]quinoline (**4**) and the product of its hydroxydefluorination on the 6-position – 5,7,8,9,10-pentafluorobenzo[f]quinoline-6-ol (**5**) in total ~55% NMR yield (Scheme 1). Under the same conditions only 5,6,7,8,10-pentafluoro-9-aminobenzo[f]-quinoline (**7**) was obtained in 40% isolated yield from hexafluoro-2,7-naphthylenediamine (**6**). Compared to the formation of quinolinol **5** from amine **3**, in this case the hydrolysis is prevented obviously due to the presence of the 9-NH_2 group in **7**.

The structures of all polyfluorobenzo[f]quinolines obtained were proved by their ^1H and ^{19}F NMR characteristics, which are typical for pyridine [6], polyfluorinated quinolines [7], naphthalenes [8] and, in the case of **2**, by the X-ray analysis (Fig. 1). The ^1H NMR spectra of **5** and **7** display the broadened resonances typical for the hydroxy (9.9 ppm) and amino (4.3 ppm) group, respectively. In all the NMR spectra there are also doublet splittings of *J* 1.5–5 Hz in the ^1H and ^{19}F signals due to the inter-ring spin couplings [8b,c].

* Corresponding author. Fax: +7 383 3309752.
E-mail address: shtein@nioch.nsc.ru (V.D. Shteingarts).

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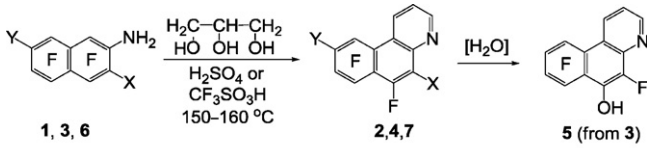


1,2 X,Y = H; **3,4** X,Y = F; **6,7** X = F, Y = NH_2

Scheme 1.

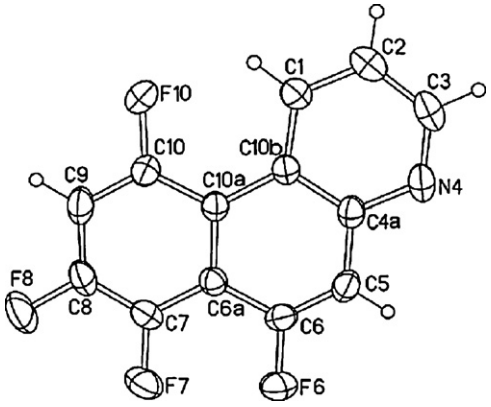
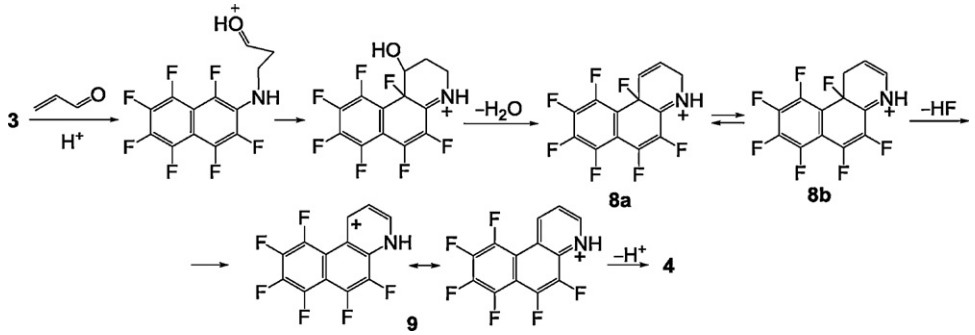


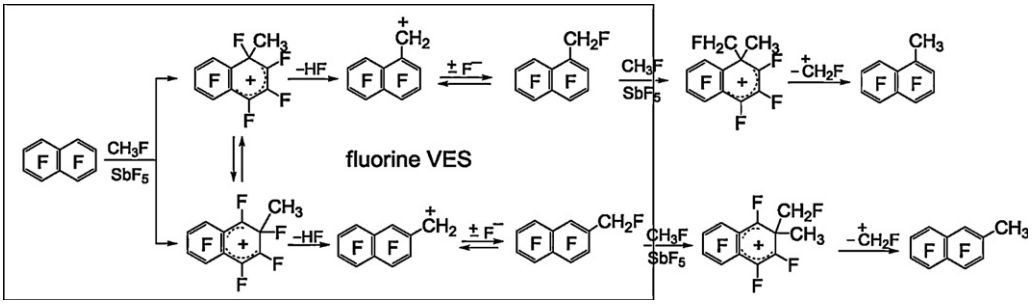
Fig. 1. The X-ray structure of **2**.

Regardless of moderate yields of the isolated products, the above results are believed significant for the following reasons. Compounds **2**, **4**, **5** and **7** are the first representatives of benzo[f]quinolines with perfluorinated carbocyclic moiety. However, it seems more fundamental that their formation in the reaction under study is a rare case of fluorine *ipso*-substitution under clearly electrophilic conditions. Earlier benzo[f]quinolines were documented to form via the Skraup-like cyclization of 1-X-2-naphthylamines with the *ipso*-substitution of X = Br, NO_2 [9]. These transformations were not rationalized mechanistically, but the nature of groups replaced admits their true electrophilic substitution with removal as cations. However, for the substitution of fluorine such an admission is unreasonable. Therefore, the *ipso*-to-fluorine pyridinization of polyfluoro-2-naphthylamines is assumed to proceed via a mechanism of vicarious electrophilic substitution (VES) depicted for amine **3** in Scheme 2. The distinctive key stages of VES are (1) an electrophilic *ipso*-attack (in this case – intramolecular and directed on the naphthalene α-position) and (2) subsequent aromatization of the intermediate cationic σ-complex (tautomers **8a**,**b** in this case) by eliminating HY (Y is generally an *ipso* displaced group, being a fluorine atom in this certain case) to produce an arylmethyl cation (**9** in this case) [10].

The actuality of this mechanism is substantiated by the following reasons. The arylamine addition to acrolein in the presence of concentrated sulfuric acid is a conventional first stage of the Skraup reaction mechanism, being proved for polyfluoroarylamines by the routine Skraup synthesis of quinolines from polyfluoroanilines with the unsubstituted *ortho*-position to the amino group [5]. The *ipso*-to-fluorine electrophilic attack is amply documented as conjugative electrophilic addition to polyfluoroarenes or as generation of long-lived polyfluorinated arenium cations [11], including those with the ring –$CF(CH_3)$– unit derived by the *ipso*-to-fluorine attack of a carbon-centered electrophile (CH_3F–SbF_5) on polyfluorinated methylbenzenes [11b]. Most importantly, previously described was methyldefluorination of octafluoronaphthalene by the CH_3F–SbF_5 couple to produce isomeric methylheptafluoronaphthalenes [12]. Now this reaction is suggested to occur via the mechanism also including fluorine VES followed by electrophilic displacement of the stabilized carbocation CH_2F^+ (Scheme 3). As for the conversion of **8a**,**b** in Scheme 2 and the initially formed naphthalenium cations in Scheme 3 into the respective arylmethyl cations, the analogous hydrodehalogenations of *gem*-(halo,alkyl)arenium cations were previously reported [13].



Scheme 2.



Scheme 3.

3. Conclusion

In the present article we have reported a rare event of fluorine substitution under distinctly electrophilic conditions which putatively proceeds via the mechanism of vicarious electrophilic substitution. The crucial steps of this mechanism are an (intramolecular in this case) *ipso*-to-fluorine electrophilic attack and subsequent aromatization of the intermediate cationic σ-complex by eliminating HF. Besides, the reaction described demonstrates the basic possibility of Skraup-like pyridinization of polyfluoroarylamines with both *ortho*-positions to an amino group occupied by fluorine. This is of a paramount importance since such starting compounds are in general more easily accessible than the relevant polyfluoroarylamines with an unsubstituted *ortho*-position. These results make the previously scarcely investigated area of quinolines with polyfluorinated carbocyclic moiety more attainable for intensive developing than before and stimulates to outline the feasibility scope of the reaction.

4. Experimental

4.1. General

NMR spectra were recorded on instruments "Bruker AV-300" and "Bruker AM-400"; internal references: nondeuterated solvent admixtures for ^{1}H and C_6F_6 (δ_F = −163.0 ppm) for ^{19}F.

1,4,5,6,8-Pentafluoro-2-naphthylamine (**1**) was prepared according to [4], heptafluoro-2-naphthylamine (**3**) and hexafluoro-2,7-naphthylenediamine (**6**) – according to [14]); other reagents and materials were of commercial origin.

4.2. General experimental procedure

The mixture of a substrate, glycerol and an acid (H_2SO_4 or CF_3SO_3H) was stirred at 150–160 °C for 8 h, then cooled, diluted with water (a 25-fold volume) and alkalified by diluted aqueous NaOH to pH ∼10. The precipitate was filtered off, boiled for 1 h first with CH_2Cl_2 (2 × 50 mL), then with ethanol (3 × 50 mL) to yield, respectively, the solid fractions A and B.

4.3. 6,7,8,10-Tetrafluorobenzo[f]quinoline 2

The workup of the mixture obtained from **1** (400 mg, 1.40 mmol), glycerol (2.3 g, 25.0 mmol), H_3BO_3 (340 mg, 5.2 mmol) and CF_3SO_3H (6 mL) gave fractions A (140 mg), containing **2** (91%, here and after according to the ^{19}F NMR analysis), and B (280 mg), consisting of **1** (15%), **2** (30%) and an unidentified substance containing a CF_3-group (42%). The total NMR yield of the title compound on consumed **1** is ∼55%. Fraction A was crystallized from $CHCl_3$ to afford **2** (85 mg, 24% yield): mp 191–193 °C. ^{1}H NMR ($CDCl_3$): δ 7.4 (ddd, $J_H9,_F10$ 13, $J_H9,_F8$ 10, $J_H9,_F7$ 6, H-9), 7.6 (dd, $J_H2,_H1$ 8.5, $J_H2,_H3$ 4, H-2), 7.7 (dm, $J_H5,_H6$ 13, H-5), 9.0 (br.s, H-3), 9.2 (dd, $J_H1,_H2$ 8.5, $J_H1,_H3$ 2.5, H-1). ^{19}F NMR ($CDCl_3$): δ −111.3 (ddd, $J_F10,_F7$ 17, $J_F10,_H9$ 13, $J_F10,_F8$ 7, F-10), −115.3 (dm, $J_F6,_F7$ 77, F-6), −134.9 (dddd, $J_F8,_F7$, $J_F8,_F9$ ∼ 19, $J_F8,_H9$ 10, $J_F8,_F10$ 7, F-8), −147.0 (dddm, $J_F7,_F6$ 77, $J_F7,_F8$ 19, $J_F7,_F10$ 17, F-7). MS (EI) *m*/*z*: 251 [M$^+$] (100), 252 (16), 232 (10), 224 (15). Anal. Calcd. for $C_{13}H_5F_4N$: C 62.16; H 1.99; F 30.28; N 5.58. Found: C 62.77; H 1.95; F 30.69; N 5.48.

4.4. 5,6,7,8,9,10-Hexafluorobenzo[f]quinoline 4 and 5,7,8,9,10-pentafluorobenzo[f]quinoline-6-ol 5

The workup of the mixture obtained from **3** (500 mg, 1.85 mmol), glycerol (3.0 g, 33 mmol), H_3BO_3 (2.7 g, 43 mmol) and CF_3SO_3H (6 mL) gave fractions A (30 mg), containing **4** (90%), and B (340 mg), consisting of **5** (72%) and some unidentified CF_3-substance (28%). The combined NMR yield of the title compounds is ∼50%. Fraction A was crystallized from $CHCl_3$ to afford **4** (21 mg, 4% yield): mp 105–108 °C. ^{1}H NMR ($CDCl_3$): δ 7.7 (dd, $J_H2,_H1$ 8.5, $J_H2,_H3$ 4, H-2), 9.1 (dd, $J_H3,_H2$ 4, $J_H3,_H1$ 1.5, H-3), 9.3 (dd, $J_H1,_H2$ 8.5, $J_H1,_H3$ 1.5, H-1). ^{19}F NMR ($CDCl_3$): δ −139.3 (dddm, $J_F10,_F9$ 19, $J_F10,_F7$ 13, $J_F10,_F8$ 8, F-10), −143.7 (ddm, $J_F6,_F7$ 72, $J_F6,_F5$ 15, F-6), −145.0 (dddm, $J_F7,_F8$ 19, $J_F7,_F10$ 13, $J_F7,_F9$ 6, F-7), −150.3 (dm, $J_F5,_F6$ 15, F-5), −154.6 (dddm, $J_F9,_F8$, $J_F9,_F10$ ∼19, $J_F9,_F7$ 6, F-9), −155.6 (dddm, $J_F8,_F7$, $J_F8,_F9$ ∼ 19, $J_F8,_F10$ 8, F-8). MS (EI) *m*/*z*: 287 [M$^+$] (100), 287 (15), 268 (10), 267 (10), 260 (15). Anal. Calcd. for $C_{13}H_3F_6N$: C 54.36; H 1.05; N 4.88. Found: C 54.57; H 1.28; N 4.44.

Fraction B was boiled with a mixture of conc.aq. NaOH (30 mL, 25%) and ethanol (15 mL) for 10 min, diluted with water (50 mL), a precipitate was filtered off to give **5** (240 mg, 46% yield): mp 219–221 °C. ^{1}H NMR ($(CD_3)_2CO$): δ 7.7 (dd, $J_H2,_H1$ 8.5, $J_H2,_H3$ 4, H-2), 9.0 (dd, $J_H3,_H2$ 4, $J_H3,_H1$ 3, H-3), 9.3 (dd, $J_H1,_H2$ 8.5, $J_H1,_H3$ 3, H-1), 10.7 (m, H-5), 9.9 (br.s, OH). ^{19}F NMR ($(CD_3)_2CO$): δ −139.0 (dddm, $J_F10,_F9$ 20, $J_F10,_F7$ 15, $J_F10,_F8$ 5, F-10), −141.6 (dddm, $J_F7,_F8$ 18, $J_F7,_F10$ 15, $J_F7,_F9$ 6, F-7), −157.1 (dddm, $J_F8,_F9$ 20, $J_F8,_F7$ 18, $J_F8,_F10$ 5, F-8), −157.8 (dddm, $J_F9,_F8$, $J_F9,_F10$ ∼ 20, $J_F9,_F6$ 6, F-9). MS (EI) *m*/*z*: 285 [M$^+$] (100), 286 (16), 237 (17), 236 (11), 218 (10). Calcd for $C_{13}H_4F_5NO$: M 285.0208. Found: M$^+$ 285.0211.

4.5. 9-Amino-5,6,7,8,10-pentafluorobenzo[f]quinoline 7

The reaction between **6** (266 mg, 1.00 mmol) and glycerol (1.24 g, 13.5 mmol) in CF_3SO_3H (10 mL) was carried out accordingly to the general procedure, except the precipitate formed after alkalifying the reaction mixture was boiled three times with hexane (30 mL) for 30 min to remove starting **6** (151 mg, 0.57 mmol), then crystallized from $CHCl_3$ to afford **7** (50 mg, 40% on the consumed **6**): mp 271–272 °C. ^{1}H NMR ($CDCl_3$): δ 4.3 (br.s NH_2), 7.6 (dd, $J_H2,_H1$ 8.5, $J_H2,_H3$ 4.5, H-2), 9.0 (dd, $J_H3,_H2$ 4.5, $J_H3,_H1$ 1, H-3), 9.2 (dd, $J_H1,_H2$ 8.5, $J_H1,_H3$ 1, H-1). ^{19}F NMR ($CDCl_3$): δ −137.6 (dd, F^7F^{10}, F^8F^{10} ∼ 13, F-10), −144.3 (ddm, $J_F6,_F7$ 69, $J_F6,_F5$ 16, F-6), −148.9 (dddm, $J_F6,_F7$ 69, $J_F7,_F8$ 19, $J_F7,_F10$ 13, F-7), −153.5 (dd, $J_F8,_F7$ 19, $J_F8,_F10$ 13 F-8), −156.5 (dm, $J_F5,_F6$ 16, F-5). MS (EI) *m*/*z*: 284 [M$^+$] (100), 285 (13), 18 (16). Calcd. for $C_{13}H_5F_5N_2$: M 284.0367. Found: M$^+$ 284.0368. Anal. Calcd for $C_{13}H_5F_5N_2$: N 9.86. Found: N 9.33.

5. Crystallography

XRD data were obtained on a Bruker P4 diffractometer with graphite monochromated Mo Kα radiation using $2\theta/\theta$ scans with $2\theta < 50°$. The structure of **2** was solved using direct method (SIR2002) [15] and refined by a full matrix least-squares procedure using anisotropic thermal parameters for all non-hydrogen atoms (SHELXL-97) [16]. The hydrogen atom positions were calculated geometrically. Compound **2** is triclinic, space group $P\ -1$, a = 7.6409(7), b = 8.433(1), c = 9.1938(8) Å, α = 69.414(7)°, β = 82.957(7)°, γ = 64.184(7)°, V = 498.88(9) Å^3, Z = 2, $C_{13}H_5F_4N$, D_c = 1.672 r/cm^3, μ = 0.152 mm^{-1}, F(0 0 0) = 252, crystal size 0.80 × 0.30 × 0.10 mm^3, independent reflections 1821, wR_2 = 0.1412, S = 1.05 for all reflections (R = 0.0430 for 1184 $F > 4\sigma$). Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no CCDC 761339. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. The obtained crystal structures were analyzed for short contacts between non-bonded atoms using the PLATON program [17]. Bond lengths are the same as the analogs literature bonds [18]. In the homo-crystals of RESH

molecules demonstrate a face-to-face π-stacking of the aromatic rings with featuring some offset. The pyridine–benzene separation within the stack is 3.44 Å (the distance between the ring centers is 3.633(1) Å), the benzene–benzene separation within the stack is 3.42 Å (the distance between the ring centers is 3.653(1) Å. The π-stacks connected by H-bond C–H···N (H(5)···N(4) 2.45 Å, C(9)···N(4) 3.380(3) Å, C(9)–H(5)···N(4) 178°).

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