Journal of Fluorine Chemistry 136 (2012) 32–37

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Interaction of quinolines polyfluorinated on the benzene moiety with sodium and potassium amides in liquid ammonia

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ARTICLE INFO

Article history:
Received 23 November 2011
Received in revised form 17 January 2012
Accepted 25 January 2012
Available online 4 February 2012

Keywords:
Polyfluorinated quinolines
Methylquinolines
Aminoquinolines
Potassium (sodium) amide
Deprotonation
Polyfluorinated quinolinyl anions
Oxidative dehydroamination

ABSTRACT

The interaction of 5,6,7,8-tetrafluoro- (**1**) and 5,7,8-trifluoro-6-(trifluoromethyl)quinoline (**2**) with sodium or potassium amide in liquid ammonia proceeds as a nucleophile (NH_2^-) addition on the 2-position of the pyridine ring, the respective adducts being oxidized to give the respective quinoline-2-amines. In the case of **1** the amide addition is concurrent with aminodefluorination on the 6- and 7-positions. 5,6,8- (**3**), 5,7,8-trifluoro- (**4**) and 5,7-difluoroquinolines (**5**) with one amide equivalent undergo deprotonation of the C–H bond flanked by two *ortho*-fluorine atoms to produce the respective long-lived quinolinyl anions, which can be used as nucleophilic synthons as exemplified by their methylation to yield respective 6- and 7-methylpolyfluoroquinolines. With an excess of potassium amide the originally generated quinolinyl anions add an amide anion on the 2- or 4-position.

1. Introduction

Fluorine containing heterocyclic compounds are of increased interest because many of them possess biological activity [1]. An appreciable place among them is being held by quinolines with one or two fluorine atoms in the benzene fragment [2–4]. Quinolines with three or four fluorine atoms in the benzene ring were studied sporadically for a long time [5], obviously owing to their small availability. However, the research of this field was markedly activated recently [6–8] thanks to developing the simple and concise synthesis of their precursors – polyfluorinated anilines nonsubstituted in *ortho*-position to the amino group, based on selective *ortho*-hydrodehalogenation of their more accessible *ortho*-halogenated analogues.

The obvious general approach to functionalization of quinolines polyfluorinated on the benzene ring is based on their reaction with nucleophiles. Earlier these quinolines were shown to undergo fluorine substitution in the benzene fragment by neutral N-centered (aqueous ammonia [5,8], piperidine, N_2H_4–H_2O [8]), P- and As-centered (Me_3MEMe_2; E = P, As; M = Si, Sn [7]) and charged O-centered (MeONa) [5,7,9] nucleophiles. Unlike this, charged C-nucleophiles (organic Mg- and Li-compounds) at −72 °C added to the 2-position of the pyridine moiety to yield corresponding 2-substituted quinolines after oxidation of initially formed 1,2-dihydroquinolines [7]. However, at 18 °C quinoline **1** with PhMgBr gave some amount of the phenyldefluorination product. This suggests the primary fast addition of the nucleophile at the 2-position to be reversible and followed by fluorine replacement in the benzene ring.

Finding-out a dependence of these competing reactions from the nature of the nucleophile and reaction conditions is of the paramount value to plan syntheses using polyfluorinated quinolines as "building blocks". In this context, charged N-centered nucleophiles (metal amides) are of significant interest as the aminofunctionalization of both the hetero- and carbocyclic parts of the quinoline skeleton is important for the molecular design of potentially bioactive fluorinated quinoline derivatives. Aiming on this, the present work is devoted to study the reaction of quinolines polyfluorinated on the benzene moiety with potassium and sodium amides in liquid ammonia at −55 ÷ −33 °C.

2. Results and discussion

The reaction of quinoline **1** with three equivalents of sodium or potassium amide in liquid ammonia at −55 ÷ −33 °C after quenching with ammonium chloride gave a mixture of the aminodefluorination products – previously known 6-amino-5,7,8-trifluoro (**6**) and 7-amino-5,6,8-trifluoroquinoline (**7**) (1:3 ratio, corresponding to the regioselectivity of fluorine substitution

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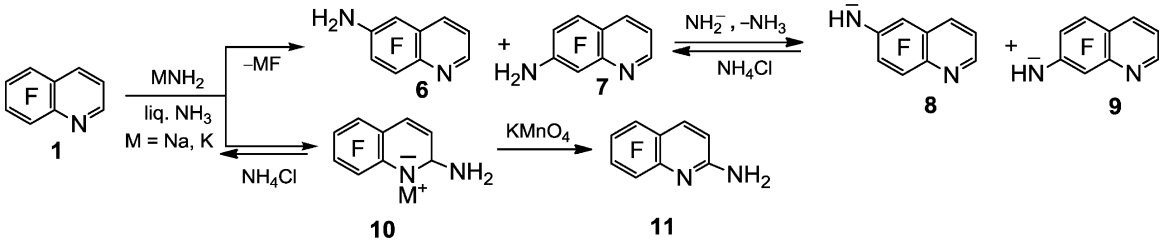
doi:10.1016/j.jfluchem.2012.01.007

Table 1
Interaction of quinolines polyfluorinated via benzene moiety with $Na(K)NH_2$ in liquid ammonia.

Entry	Reagents (g, mmol)		Quencher (g, mmol)	Conditions		Mass of product mixture (g)	Products distribution: content (mol.%)[a], NMR yield (%)
	Quinoline	Metal		T (°C)	t (min)		
1	**1** (0.13, 0.65)	K (0.08, 2.05)	NH_4Cl (0.22, 4.11)	−33	5	0.11	**1**, 35, 30; **6**, 21, 18; **7**, 44, 38
2	**1** (0.17, 0.85)	K (0.10, 2.56)	$KMnO_4$ (0.61, 3.84)	−33	5	0.07	**1**, 83, 34; **11,** 17, **7**
3	**1** (0.20, 1.00)	K (0.12, 3.08)	NH_4Cl (0.33, 6.17)	−55	10	0.18	**1**, 41, 37; **6**, 15, 14; **7**, 43, 39
4	**1** (0.14, 0.70)	Na (0.056, 2.43)	NH_4Cl (0.26, 4.86)	−33	10	0.13	**1**, 34, 32; **6**, 18, 17; **7**, 46, 43
5	**1** (0.13, 0.65)	K (0.09, 2.31)	NH_4Cl (0.25, 4.67)	−33	10	0.12	**1**, 29, 27; **6**, 19, 18; **7**, 49, 45
6	**1** (0.32, 1.59)	K (0.19, 4.87)	$KMnO_4$ (1.08, 6.82)	−33	10	0.07	**1**, 3, 0.7; **6**, 3, 0.7; **7**, 9.5, 2; **11**, 82, 18
7	**1** (0.17, 0.84)	Na (0.062, 2.70)	NH_4Cl (0.29, 5.42)	−33	60	0.16	**1**, 22, 22; **6**, 20, 21; **7**, 58, 60
8	**1** (0.13, 0.65)	K (0.08, 2.05)	$KMnO_4$ (0.48, 3.04)	−33	60	0.05	**1**, 2, 0.8; **6**, 5, 2; **7**, 16, 6; **11**, 68, 25
9	**2** (0.20, 0.80)	Na (0.056, 2.42)	NH_4Cl (0.26, 4.86)	−33	60	0.19	**2**, 85, 81; **12**, 5.5, 5
10	**2** (0.22, 0.88)	Na (0.071, 3.09)	$KMnO_4$ (0.68, 4.33)	−35	18	0.17	**2**, 7, 5; **14**, 90, 69
11	**2** (0.25, 1.00)	K (0.13, 3.33)	$KMnO_4$ (0.74, 4.67)	−33	18	0.19	**2**, 12, 9; **14**, 82, 62
12	**3** (0.22, 1.20)	Na (0.037, 1.61)	CH_3I (0.23, 1.60)	−33	30	0.24	**15**, 90, 96
13	**3** (0.20 1.09)	Na (0.075, 3.28)	NH_4Cl (0.35, 6.56)	−33	180	0.19	**3**, 92, 87; **17**, 5, 5
14	**3** (0.20, 1.12)	K (0.18, 4.62)	$KMnO_4$ (0.99, 6.26)	−33	30	0.03	**3**, 7, 1; **18**, 89, 13
15	**4** (0.20, 1.09)	Na (0.031, 1.33)	CH_3I (0.23, 1.60)	−33	30	0.21	**20**, 95, 99
16	**4** (0.29, 1.58)	K (0.075, 1.91)	CH_3I (0.34, 2.41)	−55	30	0.29	**4**, 13, 13; **20**, 85, 83
17	**4** (0.13, 0.74)	K (0.115, 2.95)	$KMnO_4$ (0.65, 4.13)	−55	30	0.085	**4**, 50, 33; **21**, 46, 30; **22**, 4, 2.5
18	**4** (0.22, 1.20)	K (0.19, 4.87)	$KMnO_4$ (1.07, 6.77)	−33	30	0.06	**4**, 16, 5; **21**, 46, 13; **22**, 35, 10
19	**5** (0.28, 1.70)	Na (0.048, 2.09)	CH_3I (0.30, 2.09)	−33	30	0.28	**5**, 2, 2; **24**, 90, 88
20	**5** (0.33, 2.00)	K (0.094, 2.41)	CH_3I (0.34, 2.41)	−33	30	0.35	**5**, 4, 4; **24**, 88, 93
21	**5** (0.12, 0.73)	K (0.11, 2.82)	$KMnO_4$ (0.62, 3.95)	−33	30	0.05	**5**, 81, 34; **25**, 13, 5; **26**, 5, 2

[a] In the cases, when total content of the named compounds is below 100%, unidentified components are present.



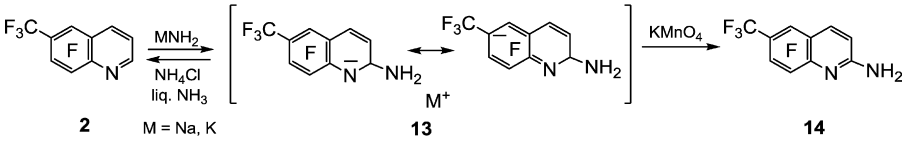
Scheme 1.

in quinoline **1** by various nucleophiles [7,8]) in 60–80% total NMR yield with the appreciable amount of **1** (Table 1, entries 1, 3–5, 7). Certainly, amines **6** and **7** react with the second NH_2^- equivalent to produce the respective quinolinylamide anions **8** and **9** (Scheme 1).

In the aggregate with literary data on high reactivity of quinolines [10] with alkaline metal amides, the significant return of the starting compound suggested that, besides the attack on the polyfluorobenzene moiety, the NH_2^- addition to the pyridine ring occurs to yield the anionic adduct **10** (Scheme 1). This adduct is obviously stable under the reaction conditions but decomposes to **1** by NH_4Cl. Such a viewing was born out by the fact that the reaction of **1** with an excess of KNH_2 at −33 °C, being completed by adding $KMnO_4$, gave a mixture of the previously unknown 2-amino-5,6,7,8-tetrafluoroquinoline (**11**) (for 10 min ~80% in the product mixture and 13% isolated yield) together with small quantities of **6** and **7** (Table 1, entries 6 and 8). Quenching of the reaction with $KMnO_4$ is accompanied by abundant tarring, which evidently results from oxidation of the principal part of anions **8** and **9** and probably from their interaction with the starting and formed quinolines. This assumption accords with the decrease in the total mass of identified products compared to quenching with NH_4Cl and with correspondence of the content of amine **11** in the product mixture with the quantity of recovered **1** in entries 3–5.

One may consider two ratiocinations of the above results. The first one suggests the initial fast reversible addition of NH_2^- to C-2 of quinoline **1** followed by the slower but irreversible aminodefluorinations on C-6 and C-7. In this case, assuming the back decay of **10** to be fast, one could expect the compounds originating from **10** (quinoline **1** upon quenching by NH_4Cl or amine **11** upon quenching by $KMnO_4$) to disappear from the product mixtures soon with the reaction progress, amines **6** and **7** being formed only. However, it is evident from the data presented in Table 1 that the product distribution was only little dependent on the reaction time and temperature. Even after 5 min (the time needed for the substrate to dissolve) comparable quantities of amines **2** and **6**/**7** were formed, the appreciable amount of **1** being returned (entries 1, 2). In these experiments, the total conversions of **1** in a mixtures of adduct **10** and amines **6**/**7** (presuming that the quantity of **10** in entry 1 is proportional to that of **11** in entry 2 and the quantities of **6** and **7** in entry 2 are proportional to those in entry 1) were calculated as 75–80% and 65–70%, respectively. These evaluations are satisfactorily consistent (at least, not contradictive) with each other, taking into account the short reaction time and that the work-up procedure can somewhat adulterate the initial composition of the mixture (Table 1, entries 3–8). However, within 10 min, at almost full conversion of **1** (entry 6), both **1** and **11** are present in the product mixtures obtained after the respective reaction quenching (entries 3–6). Moreover, even within 60 min (entries 7, 8) the product distribution changes (if any) rather slowly in favor of **6** and **7**. This prompts one to prefer the alternative conclusion, consisting in the NH_2^- additions to C-2 to be practically irreversible within the monitoring time and to occur in parallel with its additions to C-6 and C-7. In this case the observed product ratio is basically caused by similar rates of the competing reactions (Scheme 1).

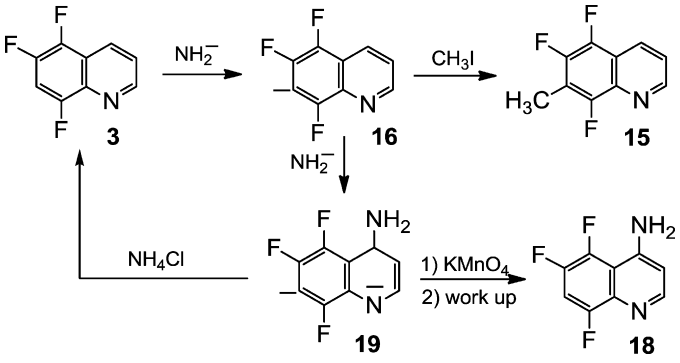
Unlike this, 5,7,8-trifluoro-6-(trifluoromethyl)quinoline (**2**) with three equivalents of $NaNH_2$ in liquid ammonia at −33 °C for 1 h after quenching by NH_4Cl gave mainly the starting material



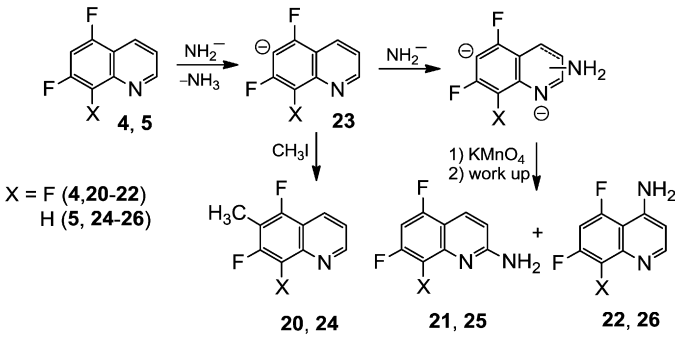
Scheme 2.

with a trace admixture of previously known 5-amino-7,8-difluoro-6-(trifluoromethyl)quinoline (**12**) as shown by ^{19}F NMR [8] (Table 1, entry 9). That the return of the starting compound is due to back transformation of the stable adduct **13** is illustrated by obtaining the previously unknown 2-amino-5,7,8-trifluoro-6-(trifluoromethyl)quinoline (**14**) (49% isolated yield) as the only product after oxidizing the reaction mixture by $KMnO_4$ (Scheme 2, Table 1, entries 10, 11). Comparison of this result with that for **1** suggests the 6-CF_3 group to effectively stabilize adduct **13** (Scheme 2) and to favor its formation in the competition with aminodefluorination.

In going from quinolines **1** and **2** to **3–5**, besides nucleophilic attacks of NH_2^- on the pyridine and benzene moieties, the opportunity appears of deprotonation of the C–H bond neighbored by two *ortho*-fluorine atoms (analogously to polyfluorinated benzenes [11]). It turned out that precisely this reaction channel is strongly prevailing. So, after quinoline **3** was kept with an equivalent quantity of $NaNH_2$ in liquid ammonia at −33 °C for 30 min and subsequent treatment of the reaction mixture with CH_3I led to 5,6,8-trifluoro-7-methylquinoline (**15**) as the only product isolated in 72% yield (Scheme 3, Table 1, entry 12). To check whether the initially formed 7-quinolinyl anion **16** can further react with NH_2^-, **3** was involved in the reaction with three equivalents of $NaNH_2$ under the same conditions for 3 h. After quenching with NH_4Cl the starting quinoline was almost completely recovered (Table 1, entry 13) and only traces of known [8] 8-amino-5,6-difluoroquinoline (**17**) were detected by ^{19}F NMR. However, quenching the reaction with $KMnO_4$ led to previously unknown 4-amino-5,6,8-trifluoroquinoline (**18**) isolated in 11% yield (Scheme 4, Table 1, entry 14), while the major part (~85%) of the reacting material being tarred. These results reveal that anion **16** adds the excess NH_2^- on the 4-position to give dianion **19**. Protonation of **19** by NH_4Cl regenerates quinoline **3**, whereas oxidation produces mainly tar, probably due to oxidation of both **16** and **19**, and affords a minor amount of **18** (Scheme 3). The aminodefluorination of anion **16** does obviously not occur, as otherwise one could reasonably expect the quenching by NH_4Cl to give corresponding aminoquinoline(s). The evident reason for this is the nucleophile repulsion by the negative σ-charge located in the benzene moiety.



Scheme 3.



Scheme 4.

The reaction of quinoline **4** with one equivalent of $NaNH_2$ at −33 °C or KNH_2 at −55 °C in liquid ammonia and subsequent quenching with CH_3I gave 5,7,8-trifluoro-6-methylquinoline (**20**) almost exclusively (97% and 85% isolated yield, respectively) (Scheme 4, X = F; Table 1, entries 15 and 16). Using an excess of KNH_2 at −55 °C and oxidizing the mixture with $KMnO_4$ gave a ~12:11:1 mixture of quinoline **4**, 2-amino-5,7,8-trifluoroquinoline (**21**) and 4-amino-5,7,8-trifluoroquinoline (**22**) in ~60% overall yield calculated on the consumed starting material (Table 1, entry 17). The reaction of **4** with an excess of KNH_2 at −33 °C completed by oxidation gave amines **21** and **22** in a ~1.3:1 ratio and 12% and 6% isolated yield, respectively (Table 1, entry 18). Thus, the initially formed 6-quinolinyl anion **23** (X = F) adds NH_2^- just as **16**, however, with slightly different and obviously temperature dependent orientation. Analogous temperature dependence was reported for the NH_2^- addition to nonfluorinated quinoline [10].

Keeping quinoline **5** with one equivalent of $NaNH_2$ or KNH_2 at −33 °C and quenching the reaction with CH_3I gave 5,7-difluoro-6-methylquinoline (**24**) in 39% isolated yield (Scheme 4; Table 1, entries 19, 20), whereas oxidation of the mixture, which was obtained with an excess of KNH_2 gave mainly the starting compound and small amounts (less than 20% in total) of 2-amino-5,7-difluoroquinoline (**25**) and 4-amino-5,7-difluoroquinoline (**26**) in a ratio of ~2.5:1 (Scheme 4; Table 1, entry 21). It is not excluded that the lower yield of these amines compared to similar products from **4** reflects a dependence of the 2- and 4-position electrophilicities of originally formed anions **23** on the fluorination degree of the benzene moiety.

Quinolines **20**–**22** and **24** have been obtained for the first time.

Thus, the aggregate of the above results reveals the excess NH_2^- addition on the 2- an 4-positions of the 6- and 7-quinolinyl anions generated by deprotonation of quinolines **3**–**5**. The data obtained do not present a reliable basis to rigorously judge about the real regioselectivity of this reaction, first of all due to the low product yields achieved by the oxidative quenching, and about the factors governing this regioselectivity. Nevertheless, comparing the product distributions displayed by quinoline **4** at −55 and −33 °C allows one to surmise that the kinetically favored addition occurs at the 2-position, being followed by a partial isomerization of the initially formed dianionic 2-NH_2-adduct to the 4-NH_2-adduct. Taking into account the high nucleophilicity of the amide anion, the kinetically preferable 2-addition is assumed to proceed via an early transition state and to be directed mainly by factors associated with the substrate, first of all by the nitrogen inductive effect. As for theoretical evaluation of the relative stability of the dianionic 2- and 4-NH_2-adducts, respective quantum chemical calculations should be performed. However, some preliminary

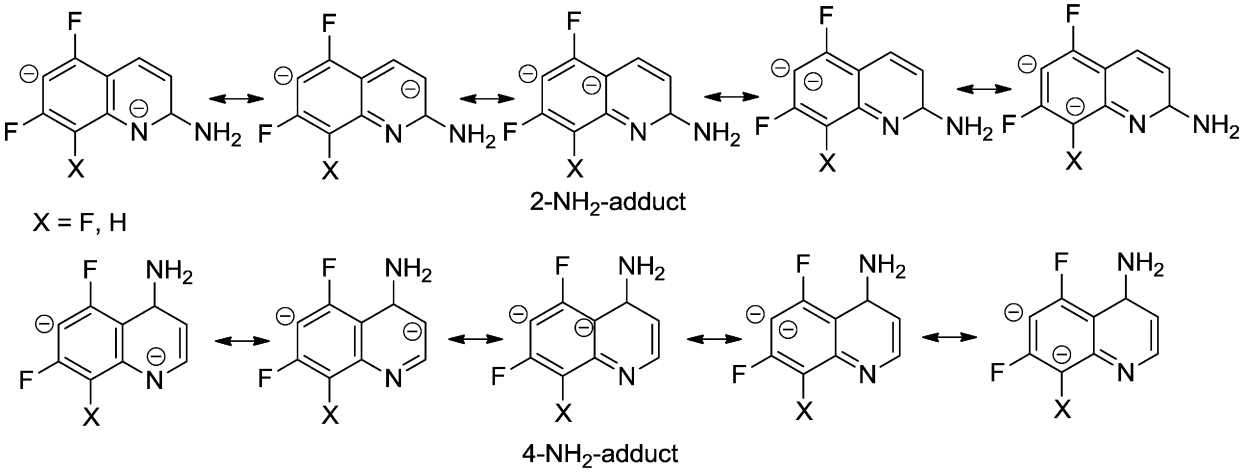
Table 2
^{1}H[a] and ^{19}F NMR chemical shifts (ppm) and coupling constants (Hz) for amino- and methylpolyfluoroquinolines.

Compound	Structure	H	F
11[a]	W = 2-NH_2; X, Y, Z = F	8.05 (dd, *J*(H-4, H-3) = 9, *J*(H-4, F-8) = 1, 1H, H-4), 6.77 (d, *J*(H-4, H-3) = 9, 1H, H-3), 5.29 (bs, 2H, NH_2)	−153.0 (dd, *J*(F-5, F-6) = 20, *J*(F-5, F-8) = 14.5, 1F, F-5), −156.6 (bt, *J*(F-7, F-8), *J*(F-7, F-6) ~19.5, 1F, F-7), −157.2 (m, 1F, F-8), −166.5 (bt, J_{F^6,F^5}, J_{F^6,F^7} ~20, 1F, F-6)
14[a]	W = 2-NH_2; X = CF_3; Y, Z = F	8.12 (dd, *J*(H-4, H-3) = 9, *J*(H-4, F-8) = 1, 1H, H-4), 6.79 (d, *J*(H-4, H-3) = 9, 1H, H-3), 5.35 (bs, 2H, NH_2)	−56.6 (dd, *J*(F-5, CF_3) = 25, *J*(F-7, F-8) = 19.5, 3F, CF_3), −126.2 (bqd, 3*J*(F-5, CF_3) = 25, *J*(F-5, F-8) = 18, 1F, F-5), −140.2 (m, 1F, F-7), −158.6 (bt, *J*(F-7, F-8) = 19.5, *J*(F-5, F-8) = 18, 1F, F-8)
15[a]	W = H; X, Z = F; Y = CH_3	8.91 (dd, *J*(H-2, H-3) = 3, *J*(H-2, H-4) = 1, 1H, H-2), 8.36 (dt, *J*(H-4, H-3) = 8.5, *J*(H-4, H-2), *J*(H-4, F-8) 1.5, 1H, H-4), 7.48 (dd, *J*(H-4, H-3) = 8.5, *J*(H-2, H-3) = 4, 1H, H-3), 2.45 (t, 2*J*(CH_3, F) = 2, 3H, CH_3)	−131.9 (bd, *J*(F-8, F-5) = 19, 1F, F-8), −141.8 (bd, *J*(F-6, F-5) = 19, 1F, F-6), −155.5 (t, *J*(F-8, F-5), *J*(F-6, F-5) ≈ 19, 1F, F-5)
18[b]	W = 4-NH_2; X, Z = F; Y = H	8.36 (d, *J*(H-2, H-3) = 5, 1H, H-2), 7.51 (td, 2 ^{ortho}*J*(H, F) = 10, *J*(H-7, F-5) = 7.5, 1H, H-7), 6.77 (d, *J*(H-2, H-3) = 5, 1H, H-3), 6.44 (bs, 2H, NH_2)	−123.3 (dd, *J*(F-5, F-8) = 18, *J*(F-8, H-7) = 10, 1F, F^8), −142.8 (dd, *J*(F-6, F-5) = 19, *J*(F-6, H-7) = 10.5, 1F, F-6), −147.8 to −147.3 (m, 1F, F^5)
20[a]	W = H; X = CH_3; Y, Z = F	8.94 (dd, *J*(H-2, H-3) = 4, *J*(H-2, H-4) = 1, 1H, H-2), 8.32 (dt, *J*(H-4, H-3) = 8.5, *J*(H-4, H-2), *J*(H-4, F-8) ≈ 1, 1H, H-4), 7.45 (dd, *J*(H-4, H-3) = 8.5, *J*(H-2, H-3) = 4, 1H, H-3), 2.41 (t, 2*J*(CH_3, F) = 2, 3H, CH_3)	−131.1 (dm, *J*(F-5, F-8) = 19, 1F, F-5), −138.6 (dm, *J*(F-7, F-8) = 18, 1F, F-7), −158.1 (bt, *J*(F-7, F-8), *J*(F-5, F-8) ≈ 18, 1F, F-8)
21[b]	W = 2-NH_2; X = H; Y, Z = F	8.02 (dd, *J*(H-4, H-3) = 9, *J*(H-4, F-8) = 1, 1H, H-4), 6.96 (ddd, ^{ortho}*J*(H, F) = 11, 9, *J*(H-6, F-8) = 6, 1H, H-6), 6.95 (d, *J*(H-4, H-3) = 9, 1H, H-3), 6.57 (bs, 2H, NH_2)	−125.7 (ddd, *J*(F-5, F-8) = 16.5, *J*(F-5, H-6) = 10, *J*(F-5, F-7) = 2, 1F, F-5), −136.5 (ddd, *J*(F-7, F-8) = 18, *J*(F-7, H-6) = 11, *J*(F-5, F-7) = 2, 1F, F-7), −159.7 (btd, 2*J*(F, F) = 17–18, *J*(F-8, H-6) = 6, 1F, F-8)
22[b]	W = 4-NH_2; X = H; Y, Z = F	8.37 (d, *J*(H-2, H-3) = 5, 1H, H-2), 7.19 (ddd, ^{ortho}*J*(H, F) = 13, 11, *J*(H-6, F-8) = 6, 1H, H-6), 6.71 (d, *J*(H-2, H-3) = 5, 1H, H-3), 6.54 (bs, 2H, NH_2)	−115.1 (m, 1F, F-5), −136.6 (ddd, *J*(F-7, F-8) = 19, *J*(F-7, H-6) = 11, *J*(F-5, F-7) = 2.5, 1F, F-7), −154.8 (btd, 2*J*(F, F) = 18–19, *J*(F-8, H-6) = 6, 1F, F-8)
24[a]	W, Z = H; X = CH_3; Y = F	8.82 (bd, *J*(H-2, H-3) = 4, 1H, H-2), 8.25 (d, *J*(H-4, H-3) = 8.5, 1H, H-4), 7.47 (bd, *J*(H-8, F-7) = 10, 1H, H-8), 7.32 (dd, *J*(H-4, H-3) = 8.5, *J*(H-2, H-3) = 4, 1H, H-3), 2.32 (bt, 2*J*(CH_3, F) = 2, 3H, CH_3)	−112.9 (bt, *J*(F-7, H-8), *J*(F-7, F-5) ≈ 9, 1F, F-7), −125.7 (1F, bd, *J*(F-7, F-5) = 9, F-5)
25[b]	W = 2-NH_2; X, Z = H; Y = F	7.99 (d, *J*(H-4, H-3) = 9, 1H, H-4), 6.98 (dm, *J*(H-8, F-7) = 10.5, 1H, H-8), 6.87 (d, *J*(H-4, H-3) = 9, 1H, H-3), 6.79 (btd, 2 ^{ortho}*J*(H, F) = 10, *J*(H-4, H-2) = 2.5, 1H, H-6), 6.27 (bs, 2H, NH_2)	−109.9 (ddd, ^{ortho}*J*(H, F) = 10, 9.5, *J*(F-5, F-7) = 7.5, 1F, F-7), −120.6 (dd, *J*(F-5, H-6) = 10, *J*(F-5, F-7) = 7.5, 1F, F-5)
26[b,c]	W = 4-NH_2; X, Z = H; Y = F	8.32 (1H, d, J_{H^2,H^3} = 9, H^2), 7.00 (1H, H^6), 6.62 (1H, d, J_{H^2,H^3} = 9, H^3), 6.43 (2H, bs, NH_2)	−109.7 to −109.6 (1F, m, F^5), −110.2 (1F, bq, 3*J* = 9.5, F^7)

[a] Solution in $CDCl_3$.
[b] Solution in acetone-d_6.
[c] The signals of the H^6 and H^8 are hidden by the H^8 signal of aminoquinoline **25** and H^6 signal of quinoline **5**.

speculation is possible, based on the presentation of the dianionic adducts in terms of canonical structures depicting the negative π-charge dispersion over the quinoline core. A peculiar feature of these adducts is the destabilizing interaction of localized σ- and delocalized π-charges. From this point of view, the sets of canonical structures for the 2- and 4-NH_2-adducts formed by 6-quinolinyl anion **23** (X = F) with NH_2^- (Scheme 5) seem approximately equivalent, which is consistent with the ~1.3:1 ratio of quinolines **21** and **22** obtained from **4** at −33 °C (Table 1, entry 18).

Probably, the situation is similar for the reaction of **5** with excess NH_2^- (Scheme 5) also producing comparable amounts of



Scheme 5.

2- and 4-aminoquinolines (Table 1, entry 21). However, contrary to this in the case of quinoline **3**, despite the analogous consideration in terms of canonical structures leads to the same prediction, only 4-aminoquinoline **18** was obtained. Thus, only a more comprehensive experimental and computational study can explain this disparity.

3. ^{1}H and ^{19}F NMR spectral data

The NMR characteristics of the first synthesized fluorinated amino- and methylquinolines presented in Table 2 are as a whole in line with those of both nonfluorinated [12] (including aminoquinolines [12b,c]) and fluorinated on the benzene ring [7,9,13] quinolines. A specific feature of 2- and 4-aminoquinolines is the influence of an amino group on fluorine chemical shifts (δ_F). Comparing the δ_F values of 2-aminoquinolines **11**, **14**, **21** and **25** and their precursors **1**, **2**, **4** [13] and **5** [12b], respectively, one can see that all fluorine resonances are high-field shifted due to the electron donating effect of the 2-NH_2 group. The shifts of F-6 (~8 ppm for **11**) and F-8 (4–5 ppm for **11** and **14**, ~3 ppm for **21**) are naturally larger than those of F-5 and F-7 (0–2 ppm, ~3 ppm for F-5 of **14**). The 4-NH_2 group similarly influences the chemical shift values of F-6 and F-7 of **18**, **22** and **26**, but its effect toward F-5 in going to these amines from their precursors **3**–**5** is qualitatively different: the F-5 signal, contrary to the electron donating effect of 4-NH_2, is low-field shifted by 6–10.5 ppm. This seems to be reasonably accounted for by the through-space interaction of F-5 and 4-NH_2. In so doing, the F-5 substituent effect is obviously modified in such a manner that F-8 of **18** and **22** also experience a low-field shift of 2–3.5 ppm.

The influence of the methyl group on δ_F values of polyfluoroquinolines is consistent with relevant literature data for polyfluorinated benzene [14] and naphthalene [15] derivatives. Upon its substitution for hydrogen in going from precursors **3**–**5** to quinolines **15**, **20** and **24**, respectively, the near-by fluorine resonances are broadened and high-field shifted by 4–5 ppm. The imaginary introduction of a methyl group instead of fluorine in going from **1** to **15** and **20** and from 5,6,7-trifluoroquinoline [16] to **24** causes deshielding of the neighboring fluorines, more strongly for F-5 and F-8 (~21 ppm) than for F-6 and F-7 (16–18.5 ppm), obviously, because the C_α–C_β bond is shorter than the C_β–C_β one (cf. [7,13,15]).

4. Conclusions

The quinolines **1** and **2** react with sodium or potassium amides in liquid ammonia to add NH_2^- at the 2-position of the pyridine fragment, the corresponding quinoline-2-amines being obtained by oxidation of thus formed adducts. Concurrently, quinoline **1** is aminodefluorinated at C-6 and C-7. Unlike this, quinolines **3–5** undergo deprotonation on the C–H bond neighbored by two fluorine atoms to generate respective quinolinyl anions. These anions were shown to be useful substrates for electrophilic functionalization as exemplified by their methylation with CH_3I to afford the respective methylquinolines in good yields. The excess KNH_2 adds to the 2- or 4-position of the pyridine fragment of initially formed quinolinyl anions.

5. Experimental

The quinolines **1** [13], **2** [13], **3** [13], **4** [13], **5** [17] were prepared according to the literature protocols. Liquid NH_3 was purified by distillation over metallic sodium to a cooled (−70 °C) reaction vessel.

^{1}H and ^{19}F NMR spectra were recorded on a NMR spectrometer Bruker AV-300 (300.13 MHz and 282.36 MHz for ^{1}H and ^{19}F correspondingly) using residual protons in the solvents $CDCl_3$ (δ_H 7.24 ppm), acetone-d_6 (δ_H 2.04 ppm), DMSO-d_6 (δ_H 2.50 ppm) and C_6F_6 (δ_F −163 ppm) as internal standards.

GC–MS was performed using an Hewlett-Packard HP 5890 Series II gas chromatograph and HP 5971 (EI, 70 eV) mass-selective detector using a HP5 MS capillary column (30 mm × 0.25 mm × 0.25 mm); the carrier gas was He, 1 mL/min.

Exact molecular masses were determined by HRMS on a Thermo Scientific DFS instrument, ionizing energy 70 eV.

5.1. General procedure

Polyfluoroquinoline was added to $NaNH_2$ or KNH_2 prepared in liquid ammonia (30 mL) by the routine procedure and the mixture was stirred at a given temperature for the required time (Table 1). Then the reaction mixture was quenched by adding NH_4Cl, $KMnO_4$ (in both cases by portions during 5 min) or MeI (single portion) and stirred for 10 min. After evaporation of NH_3 products were extracted with CH_2Cl_2 (5 mL × 15 mL). The extract was dried with $MgSO_4$ and analyzed by ^{19}F and ^{1}H NMR, GC–MS. Individual compounds were isolated by TLC on a fixed sorbent (silica gel LSL254 5/40 μ with 13 wt.% of gypsum). The separation result was visualized by irradiation of a dried plate with UV light. The separated fractions were extracted from the sorbent with acetone or CH_2Cl_2.

5.2. 2-Amino 5,6,7,8-tetrafluoroquinoline (11)

From the mixture formed after reaction of quinoline **1** with KNH_2 and quenching with $KMnO_4$ (Table 1, entry 6) by 7-fold TLC (CH_2Cl_2; intermediate air-drying of the plate) isolated was amine **11** (0.046 g, 13%); m.p. 201–203 °C (benzene). Anal. calcd for $C_{10}H_6F_3N$: C, 50.0; H, 1.9; F, 35.2; N, 13.0; found: C, 50.2; H, 2.0; F, 35.4; N, 13.0.

5.3. 2-Amino-5,7,8-trifluoro-6-(trifluoromethyl)quinoline (14)

The residual parent compound was sublimated (50–70 °C/10 mm Hg) from the mixture, formed after reaction of quinoline **2** with KNH_2 and quenching with $KMnO_4$ (Table 1, entry 10), to give amine **14** (0.13 g, 49%); m.p. 214–215.5 °C (benzene). Anal. calcd for $C_{10}H_4F_6N_2$: C, 45.1; H, 1.5; F, 42.5; N, 10.5; found: C, 45.2; H, 1.6; F, 42.6; N, 10.5.

5.4. 5,6,8-Trifluoro-7-methylquinoline (15)

From the mixture formed after reaction of quinoline **3** with $NaNH_2$ and quenching with CH_3I (Table 1, entry 11) by 3-fold TLC (hexane–CH_2Cl_2, 1:3; intermediate air-drying of the plate) isolated was methylquinoline **15** (0.17 g, 72%); m.p. 104.5–106 °C (sublimation at 55–65 °C/10 mm Hg). Anal. calcd for $C_{10}H_6F_3N$: C, 60.9; H, 3.1; F, 28.9; N, 7.1; found: C, 61.0; H, 3.3; F, 29.0; N, 6.9.

5.5. 4-Amino-5,6,8-trifluoroquinoline (18)

Sublimation (100–105 °C/10 mm Hg) of the parent compound from the mixture, formed after reaction of quinoline **3** with KNH_2 and quenching with $KMnO_4$ (Table 1, entry 13), gave amine **18** (0.025 g, 11%); m.p. 193–195 °C. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_9H_5F_3N_2$: 198.0399; found 198.0401.

5.6. 5,7,8-Trifluoro-6-methylquinoline (20)

Prepared according to the general procedure (Table 1, entry 14) in 97% yield; m.p. 103–105 °C (sublimation at 65–75 °C/10 mm Hg). Anal. calcd for $C_{10}H_6F_3N$: C, 60.9; H, 3.1; F, 28.9; N, 7.1; found:

C, 61.4; H, 3.1; F, 28.6; N, 7.0. HRMS (EI): m/z $[M]^+$ calcd. for $C_{10}H_6F_3N$: 196.0369; found 196.0368.

5.7. 2-Amino- (21) and 4-amino 5,7,8-trifluoroquinoline (22)

From the mixture, obtained after reaction of quinoline **4** with potassium amide and $KMnO_4$ (Table 1, entry 17), by 3-fold TLC (hexane–ethylacetate, 2:1; intermediate air-drying of the plate) isolated were:

Amine **21** (0.027 g, 12%); m.p. 236–238 °C (benzene). Anal. calcd for $C_9H_5F_3N_2$: C, 54.2; H, 2.9; F, 28.8; N, 14.1; found: C, 54.6; H, 2.5; F, 28.8; N, 14.1.

Amine **22** (0.014 g, 6%); m.p. 171.0–173.5 °C (EtOH–H_2O, 1:1). HRMS (EI): m/z $[M]^+$ calcd. for $C_9H_5F_3N_2$: 198.0399; found: 198.0400.

5.8. 5,7-Difluoro-6-methylquinoline (24)

Separation by 5-fold TLC (hexane–CH_2Cl_2, 1:2) of the mixture, obtained after interaction quinoline **5** with sodium amide and CH_3I (Table 1, entry 18), gave methylquinoline **24** (0.079 g, 39%); m.p. 49–50 °C (sublimation 40–50 °C/10 mmHg). Anal. calcd for $C_{10}H_7F_2N$: C, 67.0; H, 3.9; F, 21.2; N, 7.8; found: C, 67.0; H, 3.9; F, 21.2; N, 8.0.

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