Synthesis of 1-(2-polyfluoroacylaminophenyl)-3-polyfluoroalkylpropane-1,3-diones and 2-polyfluoroalkyl-4-quinolones

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The condensation of 2-aminoacetophenone with R^FCO_2Et ($R^F = CF_3$, CF_2H, CF_2CF_2H) in the presence of LiH in THF or Bu^tOK in Bu^tOH affords either 2-polyfluoroalkyl-4-quinolones or 1-(2-polyfluoroacylaminophenyl)-3-polyfluoroalkylpropane-1,3-diones, depending on the ratio of the initial reactants. The latter are hydrolyzed in an acidic medium to produce 2-polyfluoroalkyl-4-quinolones. *N*-Methyl-2-trifluoromethyl-4-quinolone was synthesized from 2-aminoacetophenone, CF_3CO_2Et, and MeI in the presence of Bu^tOK.

Key words: 2-aminoacetophenone, ethyl polyfluorocarboxylates, condensation, 1-(2-polyfluoroacylaminophenyl)-3-polyfluoroalkylpropane-1,3-diones, 2-polyfluoroalkyl-4-quinolones, tautomerism.

The antibacterial activity of compounds of the fluoroquinolone series is well known.[1,2] This work is devoted to the polyfluoroacylation of 2-aminoacetophenone with the purpose to synthesize 2-polyfluoroalkyl-4-quinolones, which have recently received much attention. 2-Trifluoromethyl-[3,4] and 2-trichloromethyl-4-quinolones[5] have previously been synthesized by the reactions of aromatic amines with ethyl trifluoro- and trichloroacetoacetates, whereas 2-polyfluoroalkyl-4-quinolones were obtained by the reactions of aromatic amines with $R^FC{\equiv}CCO_2Et$ [6,7] and $R^FCFXCH_2CO_2Et$ (X = F, Br).[8] The condensation of fluorine-containing imidoyl chlorides with esters of malonic,[9,10] acetoacetic,[9] and cyanoacetic[10] acids in the presence of sodium hydride affords derivatives of 2-polyfluoroalkyl-4-quinolone-3-carboxylic acid, which are also formed from the trifluoroacetyl derivative of Meldrum´s acid and substituted anilines.[11]

Results and Discussion

It is well known that the condensation of 2-hydroxyacetophenones with ethyl trifluoroacetate in the presence of bases occurs as *C*-trifluoroacetylation to form 1-(2-hydroxyaryl)-4,4,4-trifluorobutane-1,3-diones,[12] which exist in a solution and in the crystalline state as 2-hydroxy-2-(trifluoromethyl)chroman-4-ones.[13] Published data on the use of 2-aminoacetophenones in *C*-polyfluoroacylation are lacking. Only *N*-trifluoroacetylations of anilines by ethyl trifluoroacetate in the presence of 4-dimethylaminopyridine[14] and of 2-aminoacetophenones by the treatment with trifluoroacetic anhydride[15] are described. 2-(Trifluoroacetylamino)acetophenones formed in the latter case undergo cyclization in the presence of alkylating agents and KOH to form *N*-alkyl-2-trifluoromethyl-4-quinolones.[15]

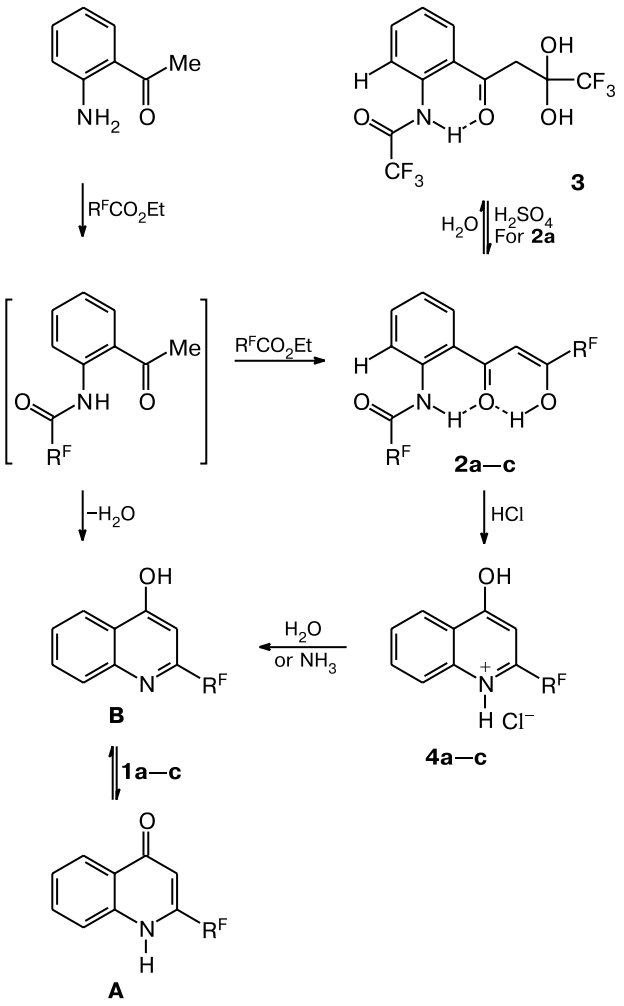
We found that the reaction of 2-aminoacetophenone with R^FCO_2Et on boiling in THF in the presence of LiH using the 1 : 1.2 molar ratio of ketone to ester affords 2-polyfluoroalkyl-4-quinolones **1a—c** (form **A**) in 12—19% yields. Form **A** exists in a solution in equilibrium with the 4-hydroxyquinoline form **B**.[4] Taking into account the known data,[14,15] we can assume that polyfluoroacylation occurs primarily at the N atom of the amino group followed by intramolecular cyclization to quinolones **1a—c** (Scheme 1).

Both the NH_2 and Me groups are acylated under the same conditions, but at the ketone : ester molar ratio of 1 : 2.8, to form β-diketones **2a—c** in high (68—87%) yields. In a solution of $CDCl_3$ compounds **2a—c** exist entirely in the enole form. The reaction with CF_3CO_2Et affords a mixture of diketone **2a** and the corresponding covalent hydrate **3**, and the first compound is completely transformed into the second product upon crystallization from aqueous AcOH. Diketone **2a** (which adds water being dissolved in DMSO-d_6 and transforms into **3** by 10%) was isolated after the treatment of hydrate **3** with concentrated H_2SO_4 for several minutes at ~20 °C. The authors of several works[16—18] pointed to the formation of *gem*-diols from the CF_3-containing β-dicarbonyl compounds. Note that the reaction of CF_3CO_2Et with 2-aminoacetophenone in the presence of Bu^tOK in Bu^tOH affords diketone **2a** in 86% yield omitting the formation of hydrate **3**. Refluxing of compounds **2a—c** in a water-alcoholic solution of HCl

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1954—1960, November, 2002.

1066-5285/02/5111-2109 $27.00

Scheme 1



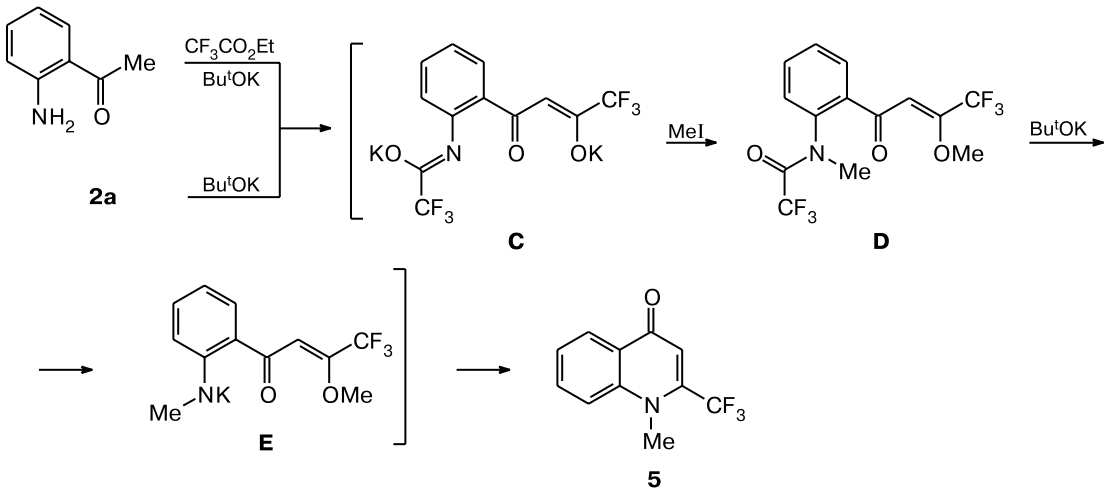
R = CF_3 (**a**), CF_2H (**b**), $(CF_2)_2H$ (**c**)

for 2 h affords 4-hydroxyquinoline hydrochlorides **4a—c** in 35—65% yields. The hydrolysis of hydrochlorides **4a—c** (refluxing in water for 1 day) or their treatment with aqueous ammonia produces quinolones **1a—c**. The latter were also obtained directly from diketones **2a—c** and hydrate **3** in 40—82% yields without isolation of salts **4a—c** (see Scheme 1).

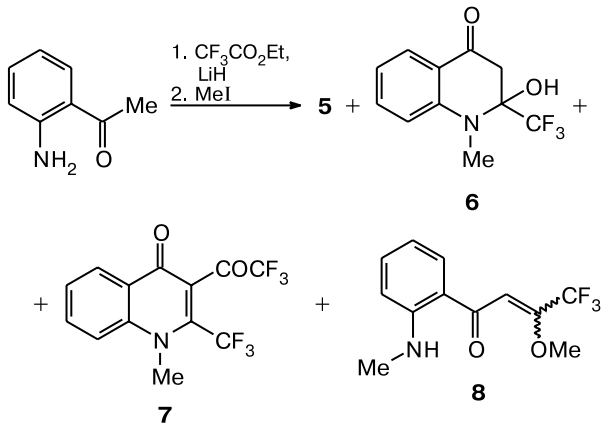
Thus, the condensation of 2-aminoacetophenone with an excess of R^FCO_2Et in the presence of LiH or Bu^tOK allows the synthesis of 1-(2-polyfluoroacylaminophenyl)-3-polyfluoroalkylpropane-1,3-diones **2a—c**, which easily afford *N*-unsubstituted 2-polyfluoroalkyl-4-quinolones **1a—c**. In this connection, it was of interest to elucidate the possibility of application of this reaction to the synthesis of *N*-substituted 2-polyfluoroalkyl-4-quinolones. We found that the treatment of 2-aminoacetophenone with a threefold excess of CF_3CO_2Et in the presence of Bu^tOK followed by refluxing of the reaction mixture with a fivefold excess of MeI produced *N*-methyl-2-trifluoromethyl-4-quinolone (**5**) in 51% yield (Scheme 2). This compound has previously been synthesized from 2-(trifluoroacetylamino)acetophenone.[15] The reaction proceeds, most likely, through dipotassium salt **C** because diketone **2a** also forms compound **5** under similar conditions. A possible reaction mechanism includes *N*- and *O*-methylations of salt **C** followed by the detrifluoroacetylation of intermediate **D** by the alkoxide anion, which leads to quinolone **5** through the stage of formation of salt **E**. Note that only hydrate **3** was isolated in a low yield (14%) along with allyl iodide instead of the expected *N*-allylquinolone.

The treatment of the dilithium salt of diketone **2a** (obtained from 2-aminoacetophenone and LiH in THF) with MeI leads to a mixture of compounds with m.p. 80—85 °C, which, according to the ^{1}H NMR spectroscopic data, consists of *N*- and *O*-methylation and

Scheme 2



Scheme 3



C-trifluoroacetylation products **5—8** in the 38 : 35 : 10 : 17 ratio (Scheme 3). Methyl ester of enole **8** exists as *Z*- and *E*-isomers in a ratio of 3 : 1. Recrystallization from hexane with a CCl_4 additive produced a mixture of quinolones **5** and **7** in the ~7 : 3 ratio, which was not separated further (for the data of the ^1H and ^{19}F NMR spectra for quinolone **7**, see Experimental). Thus, unlike the dipotassium salt, the methylation of diketone **2a** dilithium salt is not selective and cannot serve as a preparative method for the synthesis of *N*-methyl-2-polyfluoroalkyl-4-quinolones.

N-Methylquinolone **5**, which is incapable of tautomeric transformations, can be used as a model compound in the estimation of the approximate composition of a tautomeric mixture of compounds **1a—c** in different solvents. For example, the resemblance of the ^1H NMR spectra of compounds **5** and **1a,b** (Table 1) in $CDCl_3$ shows that substances **1a,b** (**1c** is insoluble in $CDCl_3$) exist predominantly in the quinolone form **A** ($\delta_{H(3)}$ ~6.5, $\delta_{H(5)}$ ~8.4), and the broadening of the signals from H(3) and H(8) in the case of **1a** is attributed, most likely, to the inhibition of prototropism under the effect of the CF_3 group.[19] The data of the IR spectra (in Nujol) of compounds **1a—c** and **5** suggest that in the crystal-

Table 1. ^1H NMR spectra of compounds **1a—c**, **4a—c**, and **5**

Compound	Solvent	δ (*J*/Hz)						
		H(3)	H(5)	H(6)	H(7)	H(8)	OH/NH	R^F
1a	$CDCl_3$	6.73 (br.s)	8.37 (d, J_o = 8.0)	7.47 (t, J_o = 7.5)	7.72 (ddd, J_o = 8.4, J_o = 7.0, J_m = 1.3)	7.60 (br.s)	9.40 (br.s)	−68.73 (s)[a]
1a	DMSO-d_6	7.16 (br.s, 0.8 H); 6.20—7.00 (br.s, 0.2 H)	8.23 (d, J_o = 7.5)	7.65 (br.s)	7.85 (t, J_o = 7.1)	8.01 (br.s)	12.30 (br.s)	−67.73 (s)[a]
1a	DMSO-d_6—D_2O	7.05 (br.s, 0.85 H)	8.23 (d, J_o = 8.0)	7.65 (t, J_o = 7.2)	7.87 (ddd, J_o = 8.3, J_o = 7.0, J_m = 1.3)	8.00 (d, J_o = 8.0)	—	—
1b	$CDCl_3$	6.41 (s)	8.36 (d, J_o = 7.9)	7.39—7.42 (m)	7.68 (ddd, J_o = 8.4, J_o = 7.1, J_m = 1.3)	7.39—7.42 (m)	8.50 (br.s)	6.57 (t, $^2J_{H,F}$ = 54.5)
1b	DMSO-d_6	6.37 (br.s, 0.8 H); 6.80—7.20 (br.s, 0.2 H)	8.10 (d, J_o = 8.2)	7.40 (br.s)	7.67—7.74 (m)		12.20 (br.s)	7.02 (t, $^2J_{H,F}$ = 53.8)
1b	DMSO-d_6—CCl_4	6.30 (br.s, 0.7 H); 6.70—7.10 (br.s, 0.3 H)	8.10 (d, J_o = 7.6)	7.35 (br.s)	7.65 (t, J_o = 7.0)	7.72 (br.s)	12.00 (br.s)	6.88 (t, $^2J_{H,F}$ = 54.2)
1b	DMSO-d_6—CCl_4—CD_3CO_2D	6.47 (br.s, 0.85 H)	8.13 (d, J_o = 8.1)	7.37 (t, J_o = 7.3)	7.65 (t, J_o = 7.6)	7.75 (d, J_o = 8.0)	—	6.87 (t, $^2J_{H,F}$ = 54.1)
1c	DMSO-d_6	7.17 (br.s, 0.8 H); 6.20—6.80 (br.s, 0.2 H)	8.21 (d, J_o = 7.3)	7.62 (br.s)	7.82 (t, J_o = 7.1)	7.96 (br.s)	12.10 (br.s)	6.98 (tt, $^2J_{H,F}$ = 52.1, $^3J_{H,F}$ = 5.1)
4a	DMSO-d_6	7.15 (s)	8.22 (dd, J_o = 8.2, J_m = 1.0)	7.64 (ddd, J_o = 8.2, J_o = 6.9, J_m = 1.0)	7.85 (ddd, J_o = 8.4, J_o = 6.9, J_m = 1.5)	8.00 (d, J_o = 8.4)	—	—

(*to be continued*)

Table 1 (*continued*)

Compound	Solvent	δ (*J*/Hz)						
		H(3)	H(5)	H(6)	H(7)	H(8)	OH/NH	R^F
4b	DMSO-d_6	6.87 (s)	8.20 (dd, J_o = 8.2, J_m = 1.1)	7.57 (ddd, J_o = 8.2, J_o = 7.0, J_m = 0.9)	7.87 (ddd, J_o = 8.4, J_o = 7.0, J_m = 1.4)	7.98 (d, J_o = 8.4)	—	7.22 (t, $^2J_{H,F}$ = 53.7)
4c	DMSO-d_6—CCl_4	6.99 (s)	8.18 (dd, J_o = 8.3, J_m = 1.0)	7.53 (ddd, J_o = 8.1, J_o = 6.9, J_m = 1.1)	7.74 (ddd, J_o = 8.4, J_o = 6.9, J_m = 1.5)	7.93 (d, J_o = 8.4)	—	6.84 (tt, $^2J_{H,F}$ = 52.5, $^3J_{H,F}$ = 5.6)
5	$CDCl_3$	6.79 (s)	8.44 (dd, J_o = 8.0, J_m = 1.7)	7.47 (ddd, J_o = 8.0, J_o = 7.0, J_m = 0.8)	7.79 (ddd, J_o = 8.7, J_o = 7.0, J_m = 1.7)	7.61 (d, J_o = 8.7)	3.88 (q, $^5J_{H,F}$ = 0.7)[b]	—
5	DMSO-d_6—CCl_4	6.55 (s)	8.19 (ddd, J_o = 8.0, J_m = 1.7, J_p = 0.5)	7.47 (ddd, J_o = 8.0, J_o = 6.7, J_m = 1.2)	7.83 (ddd, J_o = 8.5, J_o = 6.7, J_m = 1.7)	7.88 (d, J_o = 8.5)	3.87 (q, $^5J_{H,F}$ = 0.8)[b]	—
5	DMSO-d_6	6.62 (s)	8.20 (ddd, J_o = 8.0, J_m = 1.6, J_p = 0.5)	7.53 (ddd, J_o = 8.0, J_o = 6.7, J_m = 1.2)	7.88 (ddd, J_o = 8.5, J_o = 6.7, J_m = 1.6)	7.93 (d, J_o = 8.5)	3.87 (q, $^5J_{H,F}$ = 0.8)[b]	—

[a] ^{19}F NMR.
[b] NMe.

line state **1a—c** also exist as quinolones **A** (ν(C=O) = 1615—1645 cm^{-1} and ν(C=C) = 1560—1595 cm^{-1}).

In solutions of compounds **1a—c** in DMSO-d_6, the slow (in the NMR time scale) exchange between the NH and OH tautomers occurs already at ~20 °C, which allows the observation of broadened singlets from the H(3) protons of both forms and the calculation of their ratio in the mixture. The signal from the minor tautomer looks much more broadened because the rate of its transformation into the main tautomer is higher. It is probable that the presence of both tautomers in a solution of DMSO-d_6 is a consequence of the S=O...H—O(N) intermolecular hydrogen bonding between molecules of the solvent and solute. Quinoline form **B** ($\delta_{H(3)}$ ~7.2 ppm, 75—80%) is predominant for compounds **1a,c**, while quinolone form **A** ($\delta_{H(3)}$ ~6.4, 70—75%) predominates for **1b**. This can be explained by a lower electron-withdrawing ability of the CF_2H group, resulting in a decrease in the NH acidity of quinolone **1b** compared to **1a,c** and hindering of the formation of a conjugated anion, through which, most likely, the tautomeric process occurs in a basic solvent.[20]

Upon addition of D_2O to a solution of compound **1a** in DMSO-d_6, one could expect the disappearance of the OH/NH and H(3) protons (in the latter case, partial or complete) and a decrease in the rate of tautomeric transformations due to the kinetic isotope effect, which is sometimes observed during deuterium exchange.[21] This would be manifested as the further broadening of aromatic protons. In fact, however, the exchange process was accelerated due to an increase in the medium polarity, and the earlier masked *ortho*-constants of the H(6) and H(8) protons were manifested. In addition, a singlet with an intensity of 0.85 H (due to partial deuteration) from the H(3) protons of both forms with the averaged chemical shift (δ 7.05) was observed in the spectrum, which agrees with the ~80% content of tautomer **B** calculated from the relative intensities of signals from H(3) before the addition of D_2O. A similar pattern was observed for a solution of compound **1b** in DMSO-d_6—CCl_4—CD_3CO_2D with the only exception that $\delta_{H(3)}$ was in the region characteristic of the quinolone form **A** (δ 6.47) and corresponded to the ~75% content of tautomer **A**.

Compounds **1a—c** are very weak bases due to the electron-withdrawing influence of the R^F group. This results in the instability of quinolinium chlorides **4a—c** (according to the elemental analysis data, chloride **4a** contained 20% compound **1a**). These salts have no distinct melting points because they readily decompose on heating to free bases, are insoluble in $CDCl_3$, and in a solution of DMSO-d_6 dissociate, according to the ^1H NMR spectroscopic data, to form 4-hydroxyquinoline tautomers **B**. Based on the $\delta_{H(3)}$ value and taking into account the deshielding effect of the R^F group, we can suggest that a freshly prepared solution of **1a** contains virtually only form **B** ($\delta_{H(3)}$ 7.15), whereas in solutions of **1b,c** a thermodynamic equilibrium between tautomers **A** and **B** with

the substantial predomination of the latter ($\delta_{H(3)}$ 6.87 and 6.99, respectively) is immediately established. Under these conditions, the rate of exchange between the tautomers increases to such an extent that even *meta*-constants are observed (see Table 1).

The characteristic feature of the ^{1}H NMR spectra of diketones **2a—c** and hydrate **3** is the unusually downfield signal from the H(3) aromatic proton (δ 8.70—8.74). Such a strong deshielding of the H(3) atom, which is manifested at δ 7.30—7.60 in *N*-acylaminobenzenes, is caused by the formation of the C=O...H—N intramolecular hydrogen bond (see Scheme 1). This bond stabilizes the coplanar conformer in which the amide carbonyl is arranged near H(3) and has the deshielding effect on this atom.[22]

Thus, the condensation of 2-aminoacetophenone with esters of polyfluorocarboxylic acids affords previously unknown β-diketones with the *o*-polyfluoroacylamino group and represents a novel approach to the synthesis of unsubstituted and substituted at the N atom 2-polyfluoroalkyl-4-quinolones.

Experimental

IR spectra were obtained on an IKS-29 instrument in Nujol. ^{1}H NMR spectra were recorded on Bruker DRX-400 and Bruker WM-250 spectrometers (400.13 and 250.13 MHz) in $CDCl_3$ and DMSO-d_6. ^{19}F NMR spectra were recorded on Bruker DPX-200 and Tesla-BS-567A instruments (188.3 and 75.3 MHz, respectively) with Me_4Si (^{1}H) and $CFCl_3$ (^{19}F) as internal standards. The ^{1}H NMR spectroscopic data for compounds **1a—c**, **4a—c**, and **5** are presented in Table 1.

3,3-Dihydroxy-1-(2-trifluoroacetamidophenyl)-4,4,4-trifluorobutan-1-one (3). Anhydrous THF (15 mL), finely powdered LiH (0.4 g, 50 mmol), and CF_3CO_2Et (5.0 mL, 6.0 g, 42 mmol) were placed in a round-bottom flask with a mechanical stirrer, a reflux condenser, and a dropping funnel. A solution of 2-aminoacetophenone (2.0 g, 15 mmol) in anhydrous THF (10 mL) was added dropwise to the resulting mixture with refluxing and stirring for 1 h. The mixture was refluxed for 2 h with stirring, and then the solvent was distilled off to dryness on a water bath under a reduced pressure. The residue was treated with an aqueous solution of AcOH (5 mL of AcOH in 100 mL of water), and the precipitate that formed was filtered off, washed with water, and dried. The product was a mixture of diketone **2a** and its hydrate **3**, and its recrystallization from an AcOH—H_2O (2 : 1) mixture produced the almost pure hydrate form **3** in 68% yield (3.47 g), m.p. 168—169 °C. IR, ν/cm^{-1}: 3420 (OH); 1735, 1660 (C=O); 1615, 1600, 1545 (NH, arom.). ^{1}H NMR for compound **3*** (400 MHz, $CDCl_3$), δ: 3.52 (s, 2 H, CH_2); 4.64 (s, 2 H, 2 OH); 7.35 (ddd, 1 H, H(5), $J_{H(5),H(6)}$ = 8.2 Hz, $J_{H(5),H(4)}$ = 7.3 Hz, $J_{H(5),H(3)}$ = 1.0 Hz); 7.74 (ddd, 1 H, H(4), $J_{H(4),H(3)}$ = 8.5 Hz, $J_{H(4),H(5)}$ = 7.3 Hz, $J_{H(4),H(6)}$ = 1.4 Hz); 7.97 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 8.2 Hz, $J_{H(6),H(4)}$ = 1.4 Hz); 8.74 (dd, 1 H, H(3), $J_{H(3),H(4)}$ = 8.5 Hz, $J_{H(3),H(5)}$ = 1.0 Hz); 12.25 (br.s, 1 H, NH).

1-(2-Trifluoroacetamidophenyl)-4,4,4-trifluorobutane-1,3-dione (2a). ***A.*** Compound **3** (200 mg, 0.58 mmol) was triturated with concentrated H_2SO_4 (1 mL) for 5 min, and ice-cold water (7 mL) was added. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from hexane. The yield was 170 mg (90%), m.p. 102—103 °C. Found (%): C, 44.08; H, 2.09; N, 4.10. $C_{12}H_7F_6NO_3$. Calculated (%): C, 44.05; H, 2.16; N, 4.28. IR, ν/cm^{-1}: 3140 (NH); 1735, 1650 (C=O); 1630, 1600, 1535 (NH, arom.). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 6.73 (s, 1 H, =CH); 7.34 (ddd, 1 H, H(5), $J_{H(5),H(6)}$ = 8.1 Hz, $J_{H(5),H(4)}$ = 7.3 Hz, $J_{H(5),H(3)}$ = 1.0); 7.72 (ddd, 1 H, H(4), $J_{H(4),H(3)}$ = 8.5, $J_{H(4),H(5)}$ = 7.3 Hz, $J_{H(4),H(6)}$ = 1.4 Hz); 7.90 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 8.1 Hz, $J_{H(6),H(4)}$ = 1.4 Hz); 8.70 (dd, 1 H, H(3), $J_{H(3),H(4)}$ = 8.5 Hz, $J_{H(3),H(5)}$ = 1.0 Hz); 12.06 (br.s, 1 H, NH); 14.30 (br.s, 1 H, OH). ^{1}H NMR for compound **2a*** (400 MHz, DMSO-d_6), δ: 6.44 (s, 1 H, =CH); 7.42—7.87 (m, 4 H, H arom.); 11.91 (s, 1 H, NH).

B. Metallic potassium (2.0 g, 51 mmol), which was dissolved with stirring in boiling Bu^tOH (40 mL, water content 0.1%), was placed in a round-bottom flask with a mechanical stirrer, a reflux condenser, and a dropping funnel. The mixture was cooled to ~20 °C, and CF_3CO_2Et (5.4 mL, 6.4 g, 45 mmol) was added. The resulting solution was brought to boiling, and a solution of 2-aminoacetophenone (2.0 g, 15 mmol) in Bu^tOH (5 mL) was added dropwise with stirring for 10 min. The mixture was refluxed for 15 min, and then EtBr (7.5 mL, 10.9 g, 0.10 mol) was introduced to remove an excess of Bu^tOK. The mixture was refluxed for 2 h, the solvent was distilled off to dryness on a water bath under a reduced pressure, and the residue was treated with an aqueous solution of AcOH (5 mL of AcOH in 100 mL of water). The precipitated product was filtered off, washed with water, dried, and recrystallized from a hexane—CCl_4 (1 : 1) mixture. Diketone **2a** obtained by this procedure contained no admixture of hydrate **3**. The yield of diketone **2a** was 4.55 g (94%, m.p. 100—105 °C) before recrystallization and 4.17 g (86%, m.p. 102—103 °C) after recrystallization.

1-(2-Difluoroacetamidophenyl)-4,4-difluorobutane-1,3-dione (2b) was synthesized from ethyl difluoroacetate and 2-aminoacetophenone under the conditions described for the synthesis of compound **3** with the exception that the product was purified by filtration of the hot solution in CCl_4 through a silica gel layer with further crystallization of diketone **2b** from the filtrate. The yield was 87%, m.p. 108—109 °C (from CCl_4). Found (%): C, 49.80; H, 3.12; N, 4.80. $C_{12}H_9F_4NO_3$. Calculated (%): C, 49.50; H, 3.12; N, 4.81. IR, ν/cm^{-1}: 3180 (NH); 1715, 1635 (C=O); 1620, 1590, 1520 (NH, arom.). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.01 (t, 1 H, HCF_2C=O, $^2J_{H,F}$ = 54.3 Hz); 6.12 (t, 1 H, HCF_2C=C, $^2J_{H,F}$ = 54.0 Hz); 6.62 (s, 1 H, =CH); 7.27 (ddd, 1 H, H(5), $J_{H(5),H(6)}$ = 8.1 Hz, $J_{H(5),H(4)}$ = 7.2 Hz, $J_{H(5),H(3)}$ = 1.0 Hz); 7.64 (ddd, 1 H, H(4), $J_{H(4),H(3)}$ = 8.5 Hz, $J_{H(4),H(5)}$ = 7.2 Hz, $J_{H(4),H(6)}$ = 1.4 Hz); 7.86 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 8.1 Hz, $J_{H(6),H(4)}$ = 1.4 Hz); 8.70 (dd, 1 H, H(3), $J_{H(3),H(4)}$ = 8.5 Hz, $J_{H(3),H(5)}$ = 1.0 Hz); 11.94 (br.s, 1 H, NH); 14.50 (br.s, 1 H, OH).

4,4,5,5-Tetrafluoro-1-[2-(2,2,3,3-tetrafluoropropionylamino)phenyl]pentane-1,3-dione (2c) was synthesized from ethyl

* The data are presented according to the spectrum of the sample containing compounds **3** and **2a** in a ratio of 9 : 1.

* The data are presented for a mixture of compounds **2a** and **3** in a ratio of 9 : 1.

(2,2,3,3-tetrafluoro)propionate and 2-aminoacetophenone under the conditions described for the synthesis of compound **3** with the exception that the reaction mixture was boiled for 4 h. The yield was 83%, m.p. 73—74 °C (from hexane). Found (%): C, 43.18; H, 2.27; N, 3.59. $C_{14}H_9F_8NO_3$. Calculated (%): C, 42.98; H, 2.32; N, 3.58. IR, ν/cm^{-1}: 3180 (NH); 1725, 1645 (C=O); 1600, 1530 (NH, arom.). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.11 (tt, 1 H, $H(CF_2)_2C$=C, $^2J_{H,F}$ = 52.9 Hz, $^3J_{H,F}$ = 4.8 Hz); 6.23 (tt, 1 H, $H(CF_2)_2C$=O, $^2J_{H,F}$ = 52.8 Hz, $^3J_{H,F}$ = 5.4 Hz); 6.76 (s, 1 H, =CH); 7.33 (ddd, 1 H, H(5), $J_{H(5),H(6)}$ = 8.2 Hz, $J_{H(5),H(4)}$ = 7.2 Hz, $J_{H(5),H(3)}$ = 1.0 Hz); 7.70 (ddd, 1 H, H(4), $J_{H(4),H(3)}$ = 8.5 Hz, $J_{H(4),H(5)}$ = 7.2 Hz, $J_{H(4),H(6)}$ = 1.4 Hz); 7.91 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 8.2 Hz, $J_{H(6),H(4)}$ = 1.4 Hz); 8.70 (dd, 1 H, H(3), $J_{H(3),H(4)}$ = 8.5 Hz, $J_{H(3),H(5)}$ = 1.0 Hz); 12.16 (br.s, 1 H, NH); 14.63 (br.s, 1 H, OH).

4-Hydroxy-2-(trifluoromethyl)quinoline hydrochloride (4a). A mixture of EtOH (10 mL), water (1 mL), concentrated HCl (0.7 mL), and hydrate **3** (500 mg, 1.4 mmol) was refluxed for 2 h, then all volatiles were distilled off under a reduced pressure, and the solid residue was washed with AcOEt. The yield was 180 mg (52%). IR, ν/cm^{-1}: 3090, 2340—2760, 1750, 1640, 1605. Found (%): C, 49.77; H, 2.89; N, 5.81. $C_{10}H_6F_3NO \cdot 0.8$ HCl. Calculated (%): C, 49.57; H, 2.83; N, 5.78.

2-Difluoromethyl-4-hydroxyquinoline hydrochloride (4b) was synthesized similarly to salt **4a** in 65% yield. IR, ν/cm^{-1}: 3090, 2460—2720, 1750, 1655, 1605. Found (%): C, 51.84; H, 3.39; N, 5.94. $C_{10}H_7F_2NO \cdot$HCl. Calculated (%): C, 51.85; H, 3.48; N, 6.05.

4-Hydroxy-2-(1,1,2,2-tetrafluoroethyl)quinoline hydrochloride (4c) was synthesized similarly to salt **4a** in 35% yield. IR, ν/cm^{-1}: 2360—2730, 1725, 1630, 1600. Found (%): C, 46.91; H, 2.92; N, 4.58. $C_{11}H_7F_4NO \cdot$HCl. Calculated (%): C, 46.91; H, 2.86; N, 4.97.

2-Trifluoromethyl-4-quinolone (1a). ***A.*** Anhydrous THF (15 mL) and finely powdered LiH (0.68 g, 86 mmol) were placed in a round-bottom three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. 2-Aminoacetophenone (3.4 g, 25 mmol) and CF_3CO_2Et (3.6 mL, 4.3 g, 30 mmol) were added to the resulting mixture, and the reaction mixture was refluxed for 3 h with stirring, after which the solvent was distilled off to dryness on a water bath under a reduced pressure. The residue was treated with an aqueous solution of AcOH (7 mL of AcOH in 100 mL of water), and the mixture was left for 2 days at ~20 °C. The solidified product was filtered off, washed with water, dried, and recrystallized from $CHCl_3$. The yield was 1.0 g (19%), m.p. 210—212 °C. IR, ν/cm^{-1}: 3260, 3160 (NH); 3090 (=CH); 1645, 1630 (C=O); 1580, 1530 (C=C, arom.). Found (%): C, 56.39; H, 2.99; N, 6.75. $C_{10}H_6F_3NO$. Calculated (%): C, 56.35; H, 2.84; N, 6.57.

B. Hydrochloride **4a** (250 mg, 1.0 mmol) was dissolved on heating in EtOH (3 mL), and a 25% solution of NH_3 was added dropwise to pH 8—9. The alcohol was evaporated, and the residue was washed with water. The yield was 200 mg (90%), m.p. 209—210 °C.

C. A mixture of EtOH (7 mL), water (0.8 mL), concentrated HCl (0.8 mL), and hydrate **3** (300 mg, 0.87 mmol) was refluxed for 6 h, then the solvent was evaporated, and the residue was refluxed for 20 h in water (10 mL). The precipitate that formed upon cooling was filtered off and dried. The yield was 120 mg (65%), m.p. 208—210 °C.

2-Difluoromethyl-4-quinolone (1b) was synthesized similarly to quinolone **1a**. The yield was 85% (from **4b**), 82% (from **2b**), and 14% (from 2-aminoacetophenone), m.p. 205—207 °C. IR, ν/cm^{-1}: 3270, 3180 (NH); 3090 (=CH); 1640, 1615 (C=O); 1570, 1515 (C=C, arom.). Found (%): C, 61.43; H, 3.65; N, 7.40. $C_{10}H_7F_2NO$. Calculated (%): C, 61.54; H, 3.62; N, 7.18.

2-(1,1,2,2-Tetrafluoroethyl)-4-quinolone (1c) was synthesized similarly to quinolone **1a**. The yield was 40% (from **2c**) and 12% (from 2-aminoacetophenone), m.p. 194—196 °C. IR, ν/cm^{-1}: 3270, 3180 (NH); 3090 (=CH); 1645, 1615 (C=O); 1560, 1515 (C=C, arom.). Found (%): C, 54.00; H, 2.78; N, 5.68. $C_{11}H_7F_4NO$. Calculated (%): C, 53.89; H, 2.88; N, 5.71.

N*-Methyl-2-trifluoromethyl-4-quinolone (5).** ***A. The ethyl ester (CF_3CO_2Et) (2.6 mL, 3.1 g, 22 mmol) was added to a solution of Bu^tOK (0.9 g, 23.0 mmol) in Bu^tOH (20 mL). The resulting mixture was brought to boiling, and a solution of 2-aminoacetophenone (1.0 g, 7.4 mmol) in Bu^tOH (5 mL) was added dropwise with stirring for 15 min. The mixture was refluxed for 0.5 h, and MeI (2.5 mL, 5.7 g, 40 mmol) was introduced after cooling. The resulting mixture was stirred for 2 h at ~20 °C and for 1 h on refluxing. Then the solvent was distilled off on a water bath under a reduced pressure, and the residue was treated with water (100 mL). The product was filtered off, dried, and recrystallized from an EtOH—water (1 : 2) mixture. The yield was 0.85 g (51%), m.p. 137—138 °C (*cf.* Ref. 15: m.p. 137—139 °C). IR, ν/cm^{-1}: 1635, 1610 (C=O); 1595, 1515 (C=C, arom.).

The attempt to obtain *N*-allyl-2-trifluoromethyl-4-quinolone from AllI and 2-aminoacetophenone under similar conditions produced hydrate **3** in 14% yield and a non-identified mixture of products.

B. Diketone **2a** (1.0 g, 3.1 mmol) was introduced into a solution of Bu^tOK (0.39 g, 10.0 mmol) in Bu^tOH (20 mL). The mixture was stirred at ~20 °C until a colorless salt formed (~10 min), and MeI (1.9 mL, 4.26 g, 30 mmol) was added to the suspension. The mixture was stirred for 2 h at ~20 °C and for 1 h on boiling. Then the solvent was distilled off on a water bath under a reduced pressure, and the residue was treated with water (50 mL). The product was filtered off, washed with water, dried, and recrystallized from a toluene—hexane (1 : 1) mixture. The yield was 0.35 g (50%), m.p. 137—138 °C.

Methylation of dilithium salt of 1,3-diketone 2a. Anhydrous THF (20 mL), finely powdered LiH (0.40 g, 50 mmol), and CF_3CO_2Et (5.0 mL, 4.3 g, 30 mmol) were placed in a round-bottom three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. A solution of 2-aminoacetophenone (2.0 g, 15 mmol) in anhydrous THF (10 mL) was added dropwise to the obtained mixture on boiling and with stirring for 0.5 h. The mixture was refluxed for 2 h with stirring, then MeI (5 mL, 10.4 g, 73 mmol) was added dropwise, and the resulting mixture was refluxed for 12 h. The solvent was distilled off to dryness on a water bath under a reduced pressure, and the oily residue was treated with an aqueous solution of AcOH (4.5 mL of AcOH in 100 mL of water). The oily product that crystallized after prolonged stirring was filtered off, washed with water, and dried, m.p. 80—85 °C. According to the ^{1}H NMR spectrum, the product represented a mixture of compounds **5—8** in a ratio of 38 : 35 : 10 : 17, respectively, which, being recrystallized from hexane with an addition of CCl_4, yielded a mixture of quinolones **5** and **7** (was not separated further).

^{1}H NMR* (400 MHz, $CDCl_3$), δ: 3.95 (q, 3 H, MeN, $^5J_{H,F}$ = 1.2 Hz); 7.55 (ddd, 1 H, H(6), $J_{H(6),H(5)}$ = 8.0 Hz, $J_{H(6),H(7)}$ = 7.1 Hz, $J_{H(6),H(8)}$ = 0.8 Hz); 7.68 (d, 1 H, H(8), $J_{H(8),H(7)}$ = 8.8 Hz); 7.87 (ddd, 1 H, H(7), $J_{H(7),H(8)}$ = 8.8 Hz, $J_{H(7),H(6)}$ = 7.1 Hz, $J_{H(7),H(5)}$ = 1.7 Hz); 8.41 (dd, 1 H, H(5), $J_{H(5),H(6)}$ = 8.0 Hz, $J_{H(5),H(7)}$ = 1.7 Hz). ^{19}F NMR (75.3 MHz, $CDCl_3$), δ: −78.0 (q, CF_3CO, $^6J_{F,F}$ = 3.6 Hz, **7** (73%)); −58.7 (br.s, CF_3, **7** (73%)); −63.8 (s, CF_3, **5** (27%)).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 99-03-32960) and in part by the U.S. Civilian Research and Development Foundation (Grant REC-005).

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* The data are presented for compound **7** (70% content); the spectrum of compound **5** (30% content) is presented in Table 1.

Received November 9, 2001;
in revised form April 9, 2002