Reactions of 5,6,7,8-tetrafluoro-4-hydroxycoumarin derivatives with benzylamine and aniline

*K. V. Shcherbakov, Ya. V. Burgart, and V. I. Saloutin**

I. Ya. Postovskii Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22/20 ul. S. Kovalevskoi/Akademicheskaya, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 5954. E-mail: saloutin@ios.uran.ru

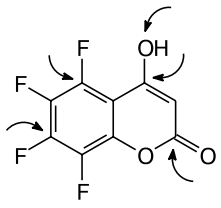
5,6,7,8-Tetrafluoro-4-hydroxycoumarin reacted with benzylamine under mild conditions to give a stable salt, while its refluxing with aniline or benzylamine in xylene afforded 5,6,7,8-tetrafluoro-4-phenyl(benzyl)aminocoumarins. Reactions of 3-acetyl(acetimidoyl)-5,6,7,8-tetrafluoro-4-hydroxycoumarins with benzylamine followed different pathways, depending on the solvent. Condensation at the acyl substituent can be accompanied by replacement of the F atom in position 7. 3-Acetylcoumarin formed a salt, while 3-acetimidoylcoumarin yielded a 7-monosubstituted product. 3-Acetyl(acetimidoyl)-5,6,7,8-tetrafluoro-4-hydroxycoumarins reacted with aniline to give only 5,6,7,8-tetrafluoro-4-hydroxy-3-(*N*-phenylacetimidoyl)coumarin.

Key words: coumarins, amines, organofluorine compounds, nucleophilic substitution.

4-Hydroxycoumarin derivatives find applications as luminescent markers, dyes, drugs, and agricultural chemicals.[1] In connection with this, 4-hydroxycoumarins are considered to be promising objects of modification aiming at obtaining substances that would possess practically useful properties. Earlier,[2] we have developed efficient methods for the synthesis of 5,6,7,8-tetrafluoro-4-hydroxycoumarin and its 3-substituted derivatives. These compounds have been studied[3] only in reactions with ammonia and morpholine, the major process in these transformations being aromatic nucleophilic substitution for the F atoms at the position C(7). 4-Hydroxycoumarins are known to react with primary and secondary amines at the OH group to give *N*-substituted 4-aminocoumarins. Opening of the α-pyrone ring into 3-hydroxy-3-(2-hydroxyphenyl)prop-2-enamides is also possible.[4] It is also known[5] that primary amines react with 3-acetyl-4-hydroxycoumarin at its acetyl substituent. Modification of fluorine-containing 4-hydroxycoumarins have not been studied hitherto.

Here we studied reactions of 4-hydroxy- (**1**), 3-acetyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin (**2**), and 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin (**3**) with primary amines **4** (benzylamine (**4a**) and aniline (**4b**)). Since these amines differ in basicity, the outcome of their reactions with coumarins **1**—**3** would reveal efficient ways of modifying the compounds of this series.

Coumarin **1** contains three nonequivalent electrophilic reactive sites to be attacked by a nucleophile: the lactone C(2) atom, the C(4) atom bound to the hydroxy group,



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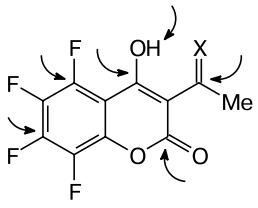

2, **3**

X = O (**2**), NH (**3**)

the C(5) and C(7) atoms of the aromatic ring, and the hydroxy H(4) proton. 3-Substituted coumarins **2** and **3** have the fourth electrophilic site: the C(9) atom of the acetyl (or acetimidoyl) group.

We found that 4-hydroxycoumarin **1** reacts with benzylamine **4a** at room temperature in acetonitrile, ethanol, or DMSO to give stable product **5** (Scheme 1).

Four alternative structures can be proposed for the reaction product. These are benzopyran **A** (addition of amine **4a** to the C(3)=C(4) bond), benzopyran **B** (addition of amine **4a** to the C(2)=O group), *N*-benzylpropenamide **C** (opening of the α-pyrone ring), and ammonium salt **D**. Compounds **A**—**C** can exist in different tautomeric forms.

Salt structure **D** was assigned to compound **5** from IR and ^{1}H and ^{13}C NMR data. The ^{13}C NMR spectrum of compound **5** in DMSO-d_6 shows one set of signals containing two low-field signals at δ 172.21 and 161.99 due to the C(2) and C(4) atoms of salt **D**. The spectra of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1170—1174, July, 2006.

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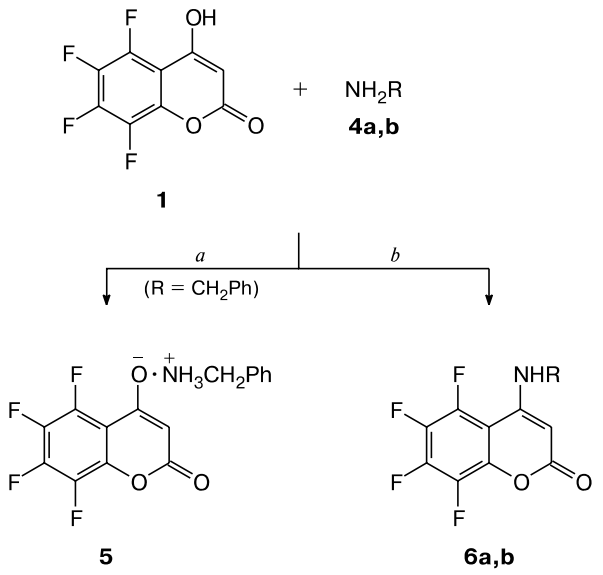
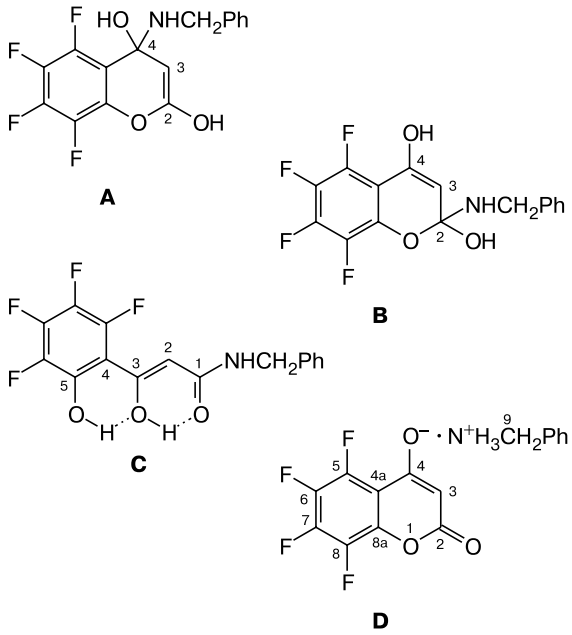
Scheme 1



R = CH_2Ph (**a**), Ph (**b**)

Reagents and conditions: *a*. MeCN or EtOH or DMSO, 20 °C; *b*. *o*-xylene, 144 °C.

coumarins **A** and **B** would each contain only one low-field signal (for the C(2) or C(4) atom, respectively). In the case of amide **C**, three low-field signals for the C(1), C(3), and C(5) atoms would appear in the spectrum. The IR spectrum of compound **5** shows characteristic bands of the C=O group at 1673 cm^{-1} and characteristic bands of the NH_3^+ group. The ^1H NMR spectrum also contains a broadened singlet at δ 8.14 corresponding to the NH_3^+ group, which agrees with the literature data.[6]



When refluxed in toluene or *o*-xylene, salt **5** gave an unidentified mixture of products.

Unlike benzylamine (**4a**), aniline (**4b**) did not react with coumarin **1** under mild conditions.

The formation of stable salt **5** in the reaction of coumarin **1** with benzylamine (**4a**) and the unsuccessful reaction with aniline (**4b**) can most likely be explained by the higher basicity of benzylamine (pK_b 4.67) compared to aniline (pK_b 9.37) (see Ref. 7).

Refluxing of coumarin **1** with amines **4a,b** in *o*-xylene afforded 4-aminocoumarins **6a,b** (see Scheme 1), by analogy with transformations of nonfluorinated 4-hydroxycoumarin.[4]

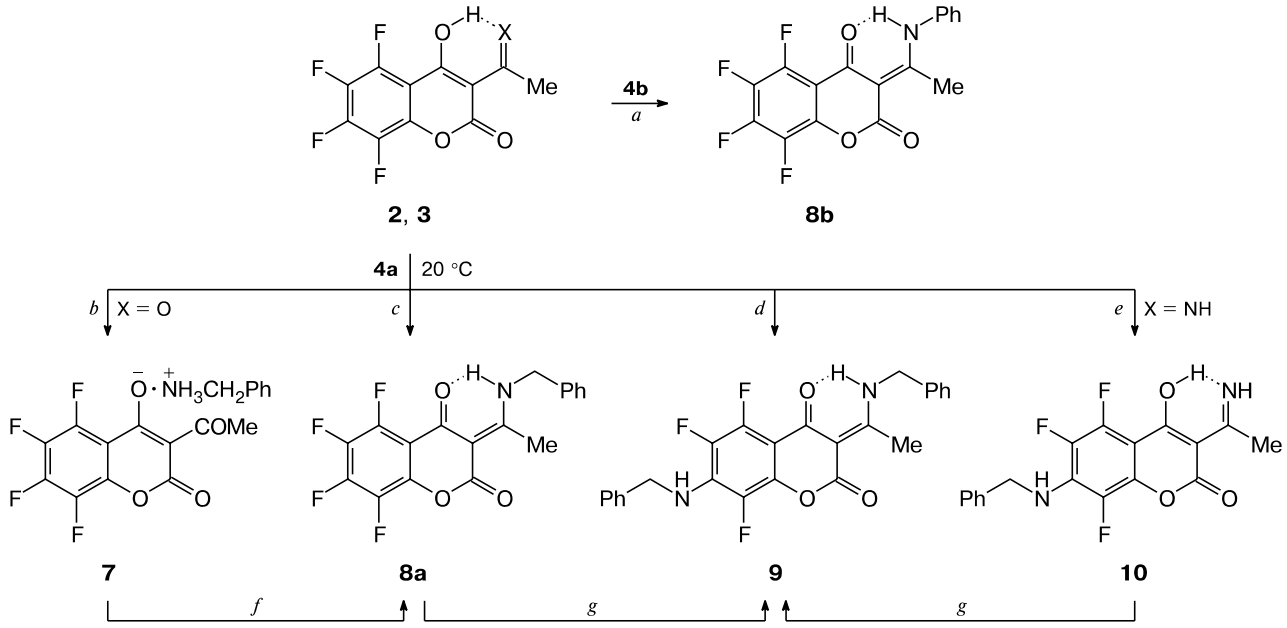
In the study of the reaction of 3-acetyl-4-hydroxycoumarin **2** with benzylamine **4a**, we found that the reaction pathway depends on the solvent nature and the reaction time. For instance, coumarin **2** reacted with benzylamine in acetonitrile at room temperature, giving salt **7** in 0.5 h (Scheme 2, path *b*), which is analogous to salt **5** (see Scheme 1). However, unlike salt **5**, compound **7** was unstable in solution and when kept in acetonitrile at room temperature for 24 h changed into 3-(1-benzylaminoethylidene)-5,6,7,8-tetrafluoro-2*H*,4*H*-benzopyran-2,4-dione (**8a**) (path *f*). The same product was obtained by the reaction of coumarin **2** with benzylamine in acetonitrile or ethanol for a day (path *c*). Note that benzopyrandione **8a** has been synthesized earlier by treatment of 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone with benzylamine *via* the chromone—coumarin rearrangement.[2,8]

The reaction of coumarin **2** with two equivalents of benzylamine **4a** in DMSO yielded 7-benzylamino-3-(1-benzylaminoethylidene)-5,6,8-trifluoro-2*H*,4*H*-benzopyran-2,4-dione (**9**) (see Scheme 2, path *d*) because of two parallel processes: condensation of one benzylamine molecule at the acetyl fragment (C(9) atom) of coumarin and nucleophilic displacement of the F atom from position 7 of the aromatic ring by a second amine molecule. Compound **9** can also be obtained by a reaction of benzopyrandione **8a** with amine **4a** in DMSO (path *g*).

3-Acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin (**3**) reacted with benzylamine **4a** in acetonitrile or ethanol at room temperature to give benzopyrandione **8a** (see Scheme 2, path *c*). In DMSO, this reaction started with replacement of the F atom in position 7, yielding 3-acetimidoyl-7-benzylamino-5,6,8-trifluorocoumarin (**10**) (path *e*). Use of an excess of benzylamine led to benzopyrandione **9**. This product was also obtained by a reaction of benzopyrandione **10** with benzylamine **4a** in DMSO.

Coumarins **2** and **3** reacted with less basic aniline **4b** at room temperature, regardless of the solvent nature (aceto-

Scheme 2



X = O (**2**), NH (**3**)

Reagents and conditions: *a*. DMSO or MeCN or EtOH, 20 °C; *b*. **4a** (1 equiv.), MeCN, 0.5 h; *c*. **4a** (1 equiv.), MeCN or EtOH, 24 h; *d*. **4a** (2 equiv.), DMSO, 24 h; *e*. **4a** (1 equiv.), DMSO, 24 h; *f*. MeCN, 24 h; *g*. **4a** (1 equiv.), DMSO.

nitrile, ethanol, or DMSO), at the C(9) atom to give benzopyrandione **8b** (see Scheme 2, path *a*).

In contrast to their precursors (4-hydroxycoumarins **2** and **3**), compounds **8a,b** and **9** exist as benzopyran-2,4-diones. Their ^{1}H NMR spectra show a low-field (δ 14—15) signal for the NH proton involved in intramolecular hydrogen bonding to the carbonyl group. The IR spectra of compounds **8a,b** and **9** contain characteristic bands of the hydrogen-bonded C=O group at 1641—1653 cm^{-1} and of the O—C=O group at 1699—1718 cm^{-1}. It should be noted that the structure of benzopyran-2,4-dione has also been assigned to a nonfluorinated analog of compound **8a**.[9]

To conclude, we have demonstrated that the pathway of the reactions of 5,6,7,8-tetrafluoro-4-hydroxycoumarins **1**—**3** with amines depends on the reaction conditions and the nature of the starting substrates. In contrast to analogous transformations of nonfluorinated 4-hydroxycoumarins,[4] no opening of the pyrone ring occurs. A distinctive feature of fluorine-containing 4-hydroxycoumarins **1** and **2** is that they can form stable salts in reactions with a highly basic amine (benzylamine); apparently, this is due to the increased acidity of the hydroxy H atom in these compounds because of the presence of electron-withdrawing F atoms. 3-Acetimidoyl-5,6,7,8-tetrafluorocoumarin (**3**) forms no salt, probably, because the acidity of its hydroxy H atom is diminished by the neighboring acetimidoyl substituent.

In addition, fluorine-containing coumarins **2** and **3** react with a highly basic amine (benzylamine) according to the S_NAr mechanism leading to replacement of the F atom in position 7. Apparently, the presence of the electron-withdrawing substituent at the C(3) atom in coumarins **2** and **3** favors the replacement of the F atoms; in the case of 3-acetimidoylcoumarin **3**, the only substitution product is compound **10**, in contrast to analogous transformations of coumarin **2**. This is explained by the fact that the acetyl fragment in coumarin **2** is more reactive than the acetimidoyl substituent in coumarin **3** toward monoamines.

Hence, fluorinated 4-hydroxycoumarins can be modified with primary amines at the side substituent in position 3 and at the aromatic ring (C(7) atom).

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum One spectrometer (Nujol) in the 4000—400 cm^{-1} range. NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 (^{1}H, $SiMe_4$), 100.6 (^{13}C, $SiMe_4$), and 376.4 MHz (^{19}F, C_6F_6)). Elemental analysis was carried out on a Perkin—Elmer PE 2400 analyzer (II CHNS-O EA 1108 series). Mass spectra were recorded on a Varian MAT-311A instrument.

The starting coumarins **1**—**3** were prepared as described earlier.[2]

Reactions of coumarins 1—3 with benzylamine (4a) and aniline (4b). ***A.*** Amine **4a,b** (0.1 mmol) was added at 20 °C to a stirred

solution of coumarin **1**—**3** (0.1 mmol) in an appropriate solvent (20 mL). The course of the reaction was monitored by TLC. The solvent was removed and the solid residue was recrystallized from an appropriate solvent.

B. Amine **4a,b** (0.1 mmol) was added to a solution of coumarin **1** (0.1 mmol) in *o*-xylene (50 mL). The reaction mixture was refluxed for 18 h and concentrated. The solid residue was recrystallized from an appropriate solvent.

Benzylammonium 5,6,7,8-tetrafluoro-2-oxo-2*H*-benzo[*b*]pyran-4-olate (5) was obtained from coumarin **1** and benzylamine **4a** according to procedure ***A*** (0.5 h stirring). The yields were 29.0 mg (85%) in acetonitrile, 28.7 mg (84%) in ethanol, and 23.5 mg (69%) in DMSO. A colorless powder, m.p. 169—170 °C (from hexane). Found (%): C, 55.95; H, 3.03; F, 21.92; N, 3.76. $C_{16}H_{11}F_4NO_3$. Calculated (%): C, 56.31; H, 3.25; F, 22.27; N, 4.10. IR, ν/cm^{-1}: 3425, 3003, 2654 (NH_3^+); 1673 (OC=O); 1648 (C=C); 1577, 1523 (NH_3^+, C=C_{arom}); 1028 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 4.05 (s, 2 H, CH_2); 4.43 (s, 1 H, CH); 7.37—7.47 (m, 5 H, C_6H_5); 8.14 (br.s, 3 H, NH_3). ^{19}F NMR ($(CD_3)_2SO$), δ: −5.9, 0.94, 4.98, 13.96 (all m, 1 F each). ^{13}C NMR ($(CD_3)_2SO$), δ: 42.38 (s, C(9)); 85.03 (s, C(3)); 110.01 (m, C(4a)); 128.44 (s, C_o); 128.60 (s, C_p); 128.80 (s, C_m); 134.06 (br.s, C_{ipso}); 133.8—136.2 (dm, C(6), C(7), $^2J_{C,F}$ = 245.0 Hz); 139.8 (m, C(8a)); 139.1—141.6 (m, C(6), C(7)); 142.8—145.3 (dm, C(5), C(8), $^2J_{C,F}$ = 255.5 Hz); 161.99 (d, C(4)); 172.21 (m, C(2)).

4-Benzylamino-5,6,7,8-tetrafluorocoumarin (6a) was obtained from coumarin **1** and benzylamine **4a** according to procedure ***B***. The yield was 23.6 mg (73%), a yellow powder, m.p. 220—223 °C (from ethanol). Found (%): C, 59.12; H, 2.99; F, 23.13; N, 4.25. $C_{16}H_9F_4NO_2$. Calculated (%): C, 59.45; H, 2.81; F, 23.51; N, 4.33. IR, ν/cm^{-1}: 3374 (NH); 1693 (OC=O); 1576, 1544, 1520 (C=C_{arom}); 1014 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 4.27 (d, 2 H, NHC$\underline{H}_2$Ph, ^3J = 5.9 Hz); 5.41 (s, 1 H, CH); 7.22—7.32 (m, 5 H, Ph); 8.67 (m, 1 H, NH). ^{19}F NMR ($(CD_3)_2SO$), δ: −0.98, 4.41, 11.55, 19.28 (all m, 1 F each).

4-Anilino-5,6,7,8-tetrafluorocoumarin (6b) was obtained from coumarin **1** and aniline **4b** according to procedure ***B***. The yield was 24.4 mg (79%), a pale yellow powder subliming at 245—250 °C (from ethanol). Found (%): C, 58.26; H, 2.16; F, 24.47; N, 4.40. $C_{15}H_7F_4NO_2$. Calculated (%): C, 58.26; H, 2.28; F, 24.58; N, 4.53. IR, ν/cm^{-1}: 3341, 1658 (NH); 1700 (OC=O); 1571, 1514, 1463 (C=C); 1017, 1003 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 5.15 (s, 1 H, CH); 7.34—7.54 (m, 5 H, Ph); 8.98 (br.s, 1 H, NH). ^{19}F NMR ($(CD_3)_2SO$), δ: −1.55, 3.38, 10.79, 21.58 (all m, 1 F each).

Benzylammonium 3-acetyl-5,6,7,8-tetrafluoro-2-oxo-2*H*-benzo[*b*]pyran-4-olate (7) was obtained from coumarin **2** and benzylamine **4a** in acetonitrile according to procedure ***A*** (0.5 h stirring). The yield was 29.4 mg (80%), a white powder, m.p. 175—176 °C (from ethanol). Found (%): C, 55.92; H, 3.09; F, 19.46; N, 3.14. $C_{18}H_{13}F_4NO_3$. Calculated (%): C, 56.40; H, 3.42; F, 19.46; N, 3.14. IR, ν/cm^{-1}: 2972 (NH_3^+); 1664 (OC=O); 1643 (C=O); 1538, 1519, 1498 (NH_3^+, C=C); 1034 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 2.30 (s, 3 H, Me); 4.05 (s, 2 H, CH_2); 7.36—7.47 (m, 5 H, Ph); 8.17 (br.s, 3 H, NH_3). ^{19}F NMR ($(CD_3)_2SO$), δ: −2.67, 1.97, 11.91, 16.99 (all m, 1 F each).

3-(1-Benzylaminoethylidene)-5,6,7,8-tetrafluoro-2*H*,4*H*-benzo[*b*]pyran-2,4-dione (8a) was obtained from coumarin **2** and benzylamine **4a** according to procedure ***A*** (24 h stirring). The yields were 32.1 mg (88%) in acetonitrile and 31.1 mg (85%) in ethanol. A white powder, m.p. 140—142 °C (from ethanol).[2]

Compound **8a** was also obtained from coumarin **3** and benzylamine **4a** according to procedure ***A*** (24-h stirring). The yields were 30.3 mg (83%) in acetonitrile and 30.7 mg (84%) in ethanol.

Compound **8a** was also obtained by keeping compound **7** in acetonitrile for 24 h. The yield was 32.9 mg (90%).

5,6,7,8-Tetrafluoro-3-(1-phenylaminoethylidene)-2*H*,4*H*-benzo[*b*]pyran-2,4-dione (8b) was obtained from coumarin **2** and aniline **4b** according to procedure ***A*** (24 h stirring). The yields were 29.2 mg (83%) in acetonitrile, 28.1 mg (80%) in ethanol, and 23.9 mg (68%) in DMSO. A yellow powder subliming at 165 °C (from hexane). Found (%): C, 58.13; H, 2.46; F, 21.49; N, 3.79. $C_{17}H_9F_4NO_3$. Calculated (%): C, 58.13; H, 2.58; F, 21.63; N, 3.99. IR, ν/cm^{-1}: 1718 (OC=O); 1653 (C=O), 1635, 1599, 1580 (C=C, C=N); 1010, 998 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 2.58 (s, 3 H, Me); 7.44—7.58 (m, 5 H, Ph); 15.00 (br.s, 1 H, NH). ^{19}F NMR ($(CD_3)_2SO$), δ: −2.30, 2.27, 12.75, 17.57 (all m, 1 F each).

Compound **8b** was also obtained from coumarin **3** and aniline **4b** according to procedure ***A*** (24 h stirring). The yields were 29.2 mg (84%) in acetonitrile, 29.1 mg (83%) in ethanol, and 25.3 mg (72%) in DMSO.

7-Benzylamino-3-(1-benzylaminoethylidene)-5,6,8-trifluoro-2*H*,4*H*-benzo[*b*]pyran-2,4-dione (9) was obtained from coumarin **2** and benzylamine **4a** (0.2 mmol) in DMSO according to procedure ***A*** (24 h stirring). The yield was 31.7 mg (70%), a pale yellow powder, m.p. 175—176 °C (from ethanol). Found (%): C, 66.00; H, 4.03; F, 12.76; N, 6.18. $C_{25}H_{19}F_3N_2O_3$. Calculated (%): C, 66.37; H, 4.23; F, 12.60; N, 6.19. IR, ν/cm^{-1}: 3330 (NH); 1699 (OC=O); 1641 (C=O); 1574, 1518 (C=C_{arom}); 1015 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 2.70 (s, 3 H, Me); 4.55 (br.s, 1 H, NH); 4.67 (d, 2 H, NHC$\underline{H}_2$Ph, ^3J = 6.1 Hz); 4.71 (d, 2 H, NHC$\underline{H}_2$Ph, ^3J = 5.7 Hz); 7.26—7.41 (m, 10 H, 2 Ph); 14.36 (br.s, 1 H, NH). ^{19}F NMR ($(CD_3)_2SO$), δ: −0.13, 3.66—3.70, 14.45 (all m, 1 F each). MS, *m*/*z* (I_{rel} (%)): 452 $[C_{25}H_{19}F_3N_2O_3]^+$ (30), 361 $[M - CH_2Ph]^+$ (12), 106 $[NHCH_2Ph]^+$ (11), 91 $[CH_2Ph]$ (100).

Compound **9** was also obtained from coumarin **3** and benzylamine **4a** (0.2 mmol) in DMSO according to procedure ***A*** (24-h stirring). The yield was 32.6 mg (72%).

Compound **9** was also obtained from benzopyrandione **8a** and benzylamine **4a** in DMSO according to procedure ***A*** (24-h stirring). The yield was 31.6 mg (70%).

Compound **9** was also obtained from coumarin **10** and benzylamine **4a** according to procedure ***A*** (24-h stirring). The yields were 38.9 mg (86%) in acetonitrile and 30.8 mg (68%) in DMSO.

3-Acetimidoyl-7-benzylamino-5,6,8-trifluorocoumarin (10) was obtained from coumarin **3** and benzylamine **4a** in DMSO according to procedure ***A*** (24 h stirring). The yield was 23.5 mg (65%), a gray powder, m.p. 190—191 °C (from hexane). Found (%): C, 59.95; H, 3.89; F, 15.26; N, 7.18. $C_{18}H_{13}F_3N_2O_3$. Calculated (%): C, 59.67; H, 3.62; F, 15.73; N, 7.73. IR, ν/cm^{-1}: 3371 (NH); 1710 (OC=O); 1648, 1594, 1545 (C=C, C=N); 998 (CF_{arom}). ^{1}H NMR ($(CD_3)_2SO$), δ: 2.50 (s, 3 H, Me); 4.56 (d, 2 H, NHC$\underline{H}_2$Ph, ^3J = 6.7 Hz); 7.21—7.35 (m, 5 H, Ph); 9.87

(br.s, 1 H, NH); 11.83 (br.s, 1 H, OH). ^{19}F NMR ($(CD_3)_2SO$), δ: –0.46, 3.77, 14.05 (all m, 1 F each).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 06-03-32351), the Program for State Support of Leading Scientific Schools (Grant 1766.2003.3), the Russian Science Support Foundation, and the Ural Branch of the Russian Academy of Sciences (Grant for Young Scientists and Post-Graduates).

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Received December 21, 2005;
in revised form April 26, 2006