Reactions of 2(3)-ethoxycarbonyl-5,6,7,8-tetrafluorochromones with methylamine*

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

I. Ya. Postovsky 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

2-Ethoxycarbonyl-5,6,7,8-tetrafluorochromone reacts with methylamine differently, depending on the solvent nature and the amount of the amine: in DMSO and MeCN, the fluorine atom at the C(7) atom is initially replaced and then the C(2) and/or C(9) are attacked, while in ethanol, the reaction involves the C(2) atom with opening of the pyrone ring. The reaction of 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone with methylamine results, regardless of the solvent, in opening of the chromone ring and the formation of intermediate ethyl 3-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)-2-(1-methylamino)ethylidene-3-oxopropionate, which undergoes intramolecular cyclization to give 5,6,7,8-tetrafluoro-3-(1-methylamino)ethylidene-3,4-dihydro-2*H*-benzopyran-2,4-dione.

Key words: chromone, methylamine, nucleophilic substitution, ring opening, chromone—coumarin rearrangement.

The chromone fragment is an essential structural unit of some biologically active compounds of both synthetic and natural origin, many of which are successfully used in medical practice.[1] For this reason, the synthesis of new representatives of this class and investigations of their chemical properties are of steady interest. It is known that chromones containing no fluorine atom in the aromatic ring react with amines mainly at the C(2) atom with opening of the pyrone ring to give the corresponding β-aminovinyl ketones.[2—4] Earlier, we have developed methods for the synthesis of 2(3)-ethoxycarbonyl-5,6,7,8-tetrafluorochromones and studied some of their transformations.[5—8] It has been demonstrated that 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone in the presence of ammonia and benzylamine undergoes chromone—coumarin rearrangement to give 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarins,[6] while 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone does not react with ammonia.[7] Reactions of these chromones with secondary amines (*e.g.*, morpholine) occur at the aromatic ring with displacement of the fluorine atom from position 7 (see Refs 7, 8).

In the present study, we investigated reactions of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**1**) and 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone (**2**) with a strong nucleophilic reagent (methylamine) in order to reveal the reactive sites of these chromones.

Theoretically, chromones **1** and **2** have four nonequivalent electrophilic reactive sites to be attacked by a nucleophile: the C(2) atom (in this case, the nucleophile can add to the C(2)=C(3) bond with either retention of the pyrone ring or its opening to give derivatives of 2-amino-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)-4-oxobut-2-enoic acid), the carbonyl C(4) atom, the benzene ring with the activated C(7) and C(5) atoms, and the ethoxycarbonyl group (C(9) atom).

According to the quantum-chemical calculations (Table 1) performed with the MNDO-90 program[9] for chromones **1** and **2**, the C(7) (maximum) and C(5) atoms of the benzene ring have the highest Fukui indices, while the highest positive charges are on the C(9) atom of the ethoxycarbonyl group and the carbonyl C(4) atom. Because of this, one could expect that the kinetic factors for reactions of chromones **1** and **2** with nucleophilic reagents would favor attacks on the C(9) and C(4) atoms in the case of charge control and on the C(7) and C(5) atoms in the case of orbital control, all other things being equal.

Earlier,[7] it has been shown that 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**1**) reacts with methylamine to give *N*-methyl-5,6,8-trifluoro-7-methylamino-4-oxo-4*H*-chromene-2-carboxamide (**3**) as the result of two parallel processes: aromatic substitution for the F atom bound to C(7) and transformation of the 2-ethoxycarbonyl group into a carbamoyl one. Here in the study of transformations of chromone **1** in the reaction with methylamine under different conditions, we found that the pathway of

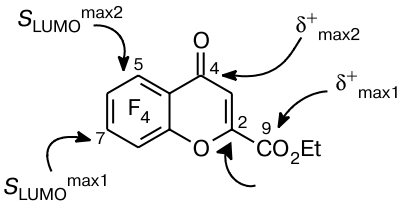
* Dedicated to Academician N. S. Zefirov on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 2093—2098, September, 2005.

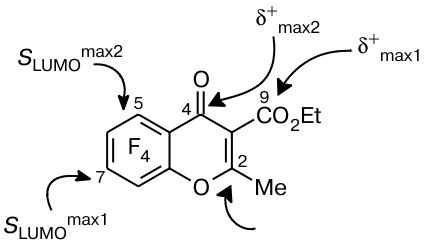
1066-5285/05/5409-2157

Table 1. Charges and the Fukui indices (LUMO) at the electrophilic centers of 2(3)-ethoxycarbonyl-5,6,7,8-tetrafluorochromones **1** and **2**

Compound	Charges, q/e (Fukui indices (LUMO))						
	C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
1	+0.056	+0.304	+0.162	–0.006	+0.102	+0.043	+0.345
	(0.197)	(0.186)	(0.312)	(0.002)	(0.365)	(0.207)	(0.041)
2	+0.158	+0.402	+0.158	–0.007	+0.090	+0.014	+0.454
	(0.030)	(0.060)	(0.155)	(0.018)	(0.271)	(0.106)	(0.066)



1



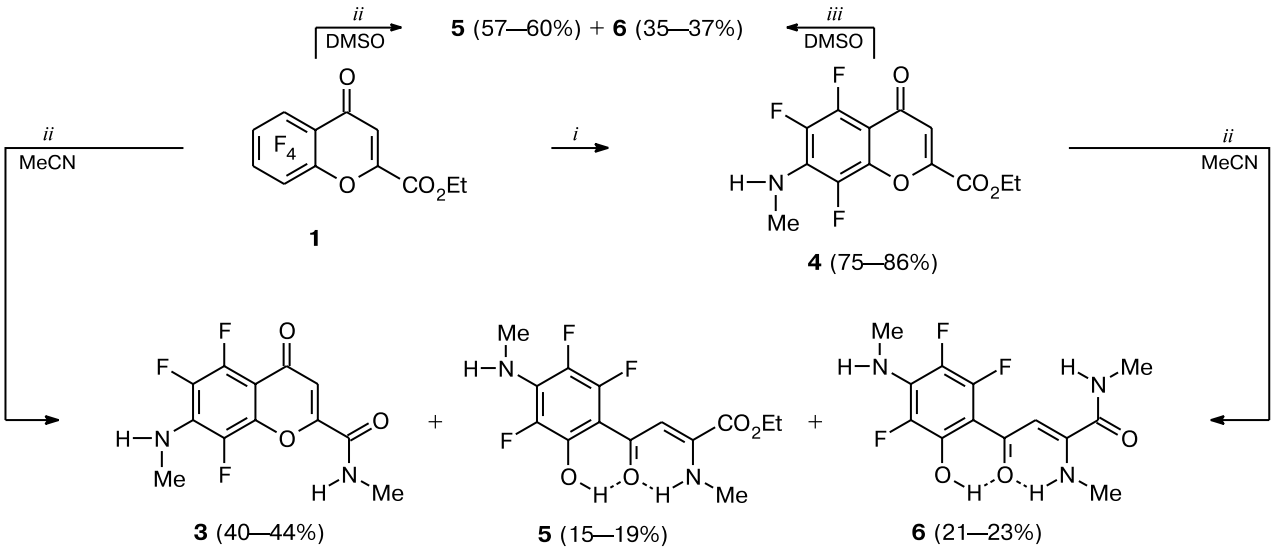
2

this reaction depends on the solvent nature and the amount of methylamine. For instance, in acetonitrile and DMSO, the room-temperature reaction with an equimolar amount of methylamine or with its excess (bubbling of gaseous methylamine for 2 h) yielded 2-ethoxycarbonyl-5,6,8-trifluoro-7-methylaminochromone (**4**) (Scheme 1) as the result of substitution of the methylamino group for the F atom in position 7 of the starting substrate.

Prolonged bubbling (6 h) of methylamine through a solution of chromone **1** in acetonitrile gave three compounds: ethyl 2-methylamino-4-oxo-4-(3,5,6-trifluoro-2-hydroxy-4-methylaminophenyl)but-2-enoate (**5**) (*via* opening of the pyrone ring in chromone **4**), chromone **3**, and *N*-methyl-2-methylamino-4-oxo-4-(3,5,6-trifluoro-2-hydroxy-4-methylaminophenyl)but-2-enamide (**6**) as the result of opening of the pyrone ring in compound **3**. The reaction in DMSO afforded only two products, **5** and **6** (see Scheme 1). Obviously, compounds **3**, **5**, and **6** are products of further transformations of chromone **4**. Indeed, when an excess of methylamine was passed through a solution of chromone **4** in acetonitrile or DMSO for 4 h, the same set of products was isolated (see Scheme 1).

In ethanol, chromone **1** reacted with an equimolar amount of methylamine at the C(2) atom to give ethyl

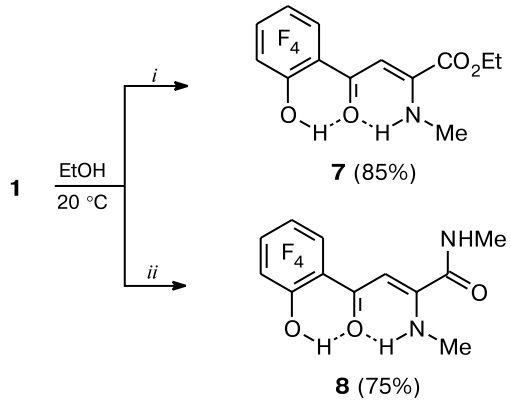
Scheme 1



i. $MeNH_2$, 20 °C, 2 h; *ii*. Excess $MeNH_2$, 20 °C, 6 h; *iii*. Excess $MeNH_2$, 20 °C, 4 h.

2-methylamino-4-oxo-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)but-2-enoate **7** (Scheme 2). With an excess of methylamine (bubbling for 4 h), *N*-methyl-2-methylamino-4-oxo-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)but-2-enamide (**8**) was obtained (see Scheme 2).

Scheme 2



i. $MeNH_2$ (1 equiv.); *ii*. Excess $MeNH_2$.

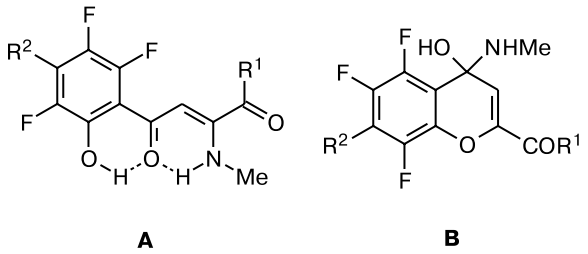
Treatment of chromone **1** with methylamine in an aprotic nonpolar solvent (toluene) gave no products.

In contrast to analogous transformations in ethanol, the initial act in the reactions of chromone **1** with methylamine in acetonitrile and DMSO is displacement of the F atom from position 7 of the chromone system, which suggests orbital control of these transformations. The formation of 7-methylaminochromone **4** under these conditions can be explained with consideration that polyfluoroarenes react with nucleophiles in bipolar aprotic solvents (DMSO: $\varepsilon = 49$, $\mu = 3.96$ D; MeCN: $\varepsilon = 36.2$, $\mu = 3.92$ D[10]) more easily than in protic ones (ethanol: $\varepsilon = 24.3$, $\mu = 1.69$ D[10]).[11]

With a large excess of methylamine in acetonitrile and DMSO, chromone **1** underwent more profound transformations. In DMSO, the major process was addition of the amine to the C(2) atom followed by opening of the pyrone ring, though addition to the C(9) atom of the ethoxycarbonyl group is also possible. In acetonitrile, the reaction mainly occurred at the C(9) atom with concomitant opening of the chromone heterocycle.

In contrast to the above transformations, the reaction of chromone **1** with methylamine in ethanol started with opening of the pyrone ring, which was evident from the formation of ester **7** in a reaction of chromone **1** with methylamine (1 equiv.). Apparently, in a protic solvent (ethanol), the carbonyl groups at the C(4) and C(9) atoms are involved in intermolecular hydrogen bonding to ethanol molecules, which decreases the charge δ+ on these atoms. As the consequence, a nucleophile attacks the C(2) atom.

Note that compounds **5**—**8** can be assigned not only open-chain form **A** but also cyclic structure **B**.

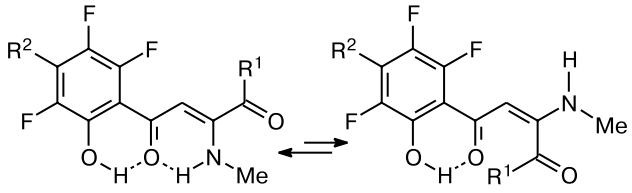


A **B**

R^1 = OEt, NHMe; R^2 = F, NHMe

However, according to the ^1H and ^{19}F NMR data, these compounds exist in solution as a mixture of the *Z*,*E*-isomers of the oxo enamine form **A** with respect to the C=C bond, the *Z*-isomer being dominant. The ^1H NMR spectra contain low-field signals (δ_H ~10—15) for the OH and NH_2 groups, which suggest their participation in intramolecular hydrogen bonding to the carbonyl group. The formation of such bonds was confirmed by the IR spectra of these compounds: the absorption bands of the carbonyl group are shifted to the lower-frequency range (~1650 cm^{-1}) compared to characteristic values of conjugated oxo groups.[12]

The *Z*- and *E*-isomers of compounds **5**—**8** can be distinguished in the ^1H NMR spectra with consideration that the amino group in the *Z*-isomer participates in intramolecular hydrogen bonding and, accordingly, its signal appears in a lower field (δ_H ~10) than the signal for the loose amino group of the *E*-isomer (δ_H ~7—8).



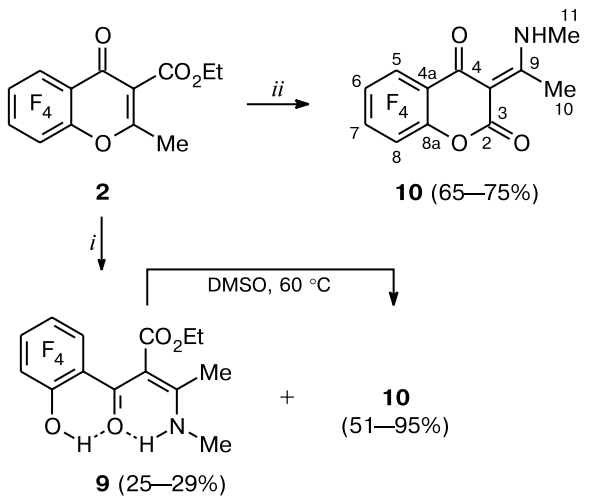
Z-**5**—**8** *E*-**5**—**8**

R^1 = OEt, NHMe; R^2 = F, NHMe

In contrast to the above transformations, the reaction of 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone **2** with an excess of methylamine yielded the only product, namely, 5,6,7,8-tetrafluoro-3-(1-methylamino)ethylidene-3,4-dihydro-2*H*-benzopyran-2,4-dione (**10**), regardless of the solvent nature (acetonitrile, ethanol, or DMSO) (Scheme 3). Its formation follows a chromone—coumarin rearrangement involving addition of the amine to the C(2)=C(3) bond, subsequent opening of the pyrone ring with the formation of intermediate ethyl 2-(1-methylamino)ethylidene-3-oxo-3-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)propionate (**9**), and final reclosure of a new pyrone ring by means of intramolecular

transesterification. In the reaction of chromone **2** with an equimolar amount of methylamine in DMSO or ethanol, a mixture of ester **9** and coumarin **10** was obtained (see Scheme 3). Intramolecular cyclization of ester **9** in DMSO gave coumarin **10** (see Scheme 3).

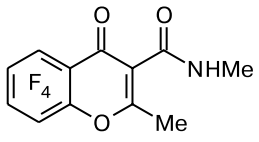
Scheme 3



Reagents and conditions: *i*. $MeNH_2$ (1 equiv.), DMSO (MeCN, EtOH), 20 °C; *ii*. Excess of $MeNH_2$, DMSO (MeCN, EtOH), 20 °C.

The presence of two low-field signals (δ_H ~11 and 12) for the OH and NH_2 groups in the ^1H NMR spectrum of compound **9** and a lower-frequency absorption band of the C=O group (1613 cm^{-1}) in its IR spectrum (Nujol) indicates that this compound exists in both solution and the solid state as an oxo enamine tautomer in which the ethoxycarbonyl group is not involved in intramolecular bonding.

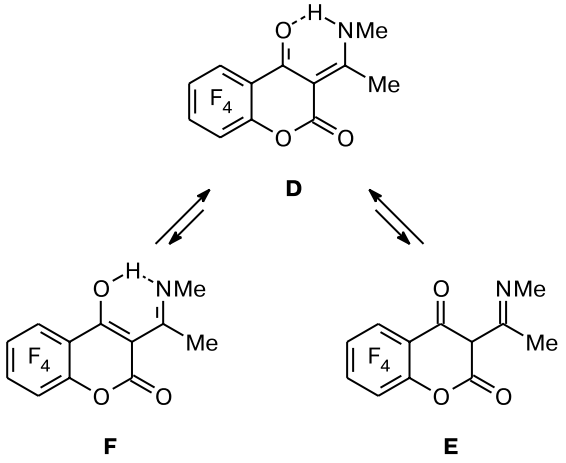
According to elemental analysis and ^1H NMR data, the structure of product **10** can be alternatively drawn as *N*-methyl-5,6,7,8-tetrafluoro-2-methylchromone-3-carboxamide **C**.



C

The choice between the two structures was based on data from IR spectroscopy and mass spectrometry. For instance, the mass spectrum of compound **10** contains, along with the molecular ion peak with *m/z* 289 (100%), intense peaks produced by fragmentation of benzopyran-2,4-dione **10** (see Experimental). In addition, its IR spectrum shows a high-frequency absorption band at 1710 cm^{-1} due to the C=O stretching vibrations in the lactone fragment, which is impossible for chromone-3-carboxamide **C**.

Benzopyran-2,4-dione **10**, for which two types of tautomerism (keto—enol and amino—enimine) are possible, can exist as one, two, or three tautomers: keto enamine (**D**), keto imine (**E**), and imino enol (**F**).



However, the ^1H, ^{19}F, and ^{13}C NMR spectra of compound **10** in DMSO-d_6 and acetone-d_6 show one set of signals corresponding to the keto enamine tautomer (**D**). For instance, a signal for methyl protons of the MeNH group in the ^1H NMR spectrum appears as a doublet (J = 5.0 Hz), which is due to their couplings with the proton at the N atom, while a signal for the MeNH proton is shifted downfield (δ ~13) because of its participation in intramolecular hydrogen bonding to the carbonyl group.

Thus, we found that the reactions of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**1**) and 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone (**2**) with methylamine occur ambiguously, depending on the reaction conditions and the structure of the starting substrate. The general feature in the behavior of chromones **1** and **2** in these reactions is opening of the chromone ring upon the addition of the amine to the C(2) atom. For chromone **2**, this is the only reaction pathway, regardless of the solvent nature; for chromone **1**, such a process occurs only in a protic solvent (ethanol). Chromone **1** has a greater reaction potential since its C(7) and C(9) atoms can be attacked in aprotic polar solvents. This difference between chromones **1** and **2** can be due to steric factors (*i.e.*, the C(2) atom in chromone **2** is more accessible than that in chromone **1**).

Experimental

IR spectra (Nujol) were recorded on a Perkin—Elmer Spectrum One spectrometer in the 4000—400 cm^{-1} range. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400, 100.6, and 75 MHz, respectively) with $SiMe_4$ as the internal standard (C_6F_6 for ^{19}F NMR). Elemental analysis was performed on a Perkin—Elmer PE 2400 analyzer. Mass spectra were recorded on a Varian MAT-311A instrument.

Quantum-chemical MNDO computations of chromones **1** and **2** were performed with the MOPAC 6 program.[9]

The starting chromones **1** and **2** were prepared according to known procedures.[5,13]

Reactions of chromones 1 and 2 with methylamine (general procedure). Method *A*. An excess of gaseous methylamine was bubbled through a solution of chromone **1** or **2** (0.01 mol) in an appropriate solvent (20 mL) until the starting chromone was completely consumed (monitoring by TLC). The solvent was removed and the solid residue was recrystallized from the corresponding solvent.

Method *B*. A solution of chromone **1** or **2** (0.01 mol) and methylamine (0.01 mol, 0.31 g) in an appropriate solvent (20 mL) was stirred at 20 °C until the starting reagents were completely consumed (TLC). The solvent was removed and the solid residue was recrystallized from the corresponding solvent.

***N*-Methyl-5,6,8-trifluoro-7-methylamino-4-oxo-4*H*-chromene-2-carboxamide (3).** Compound **3** (1.14 g, 40%) was obtained according to method *A* by bubbling methylamine through a solution of chromone **1** in acetonitrile for 6 h. T_{subl} = 259—260 °C (ethanol).[5] Amide **3** (1.25 g, 44%) was also obtained from chromone **4** in MeCN upon the bubbling of methylamine for 4 h.

Ethyl 5,6,8-trifluoro-7-methylamino-4-oxo-4*H*-chromene-2-carboxylate (4). Compound **4** (2.56 g (85%) in acetonitrile; 2.59 g (86%) in DMSO) was obtained from chromone **1** according to method *A* by bubbling methylamine for 2 h, m.p. 207—208 °C (hexane). IR, ν/cm^{-1}: 3311, 1611 (NH); 1755 (CO_2Et); 1673 (C=O); 1647 (C=C); 1583, 1560, 1503 (C=C_{Ar}); 1093, 990 (CF_{Ar}). ^{1}H NMR (DMSO-d_6), δ: 1.34 (t, 3 H, CH_3, $^3J_{H,H}$ = 7.1 Hz); 3.08 (m, 3 H, CH_3); 4.37 (q, 2 H, CH_2, $^3J_{H,H}$ = 7.1 Hz); 6.70 (s, 1 H, =CH); 6.95 (m, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 2.13 (m, 1 F, F(8)); 3.26 (ddt, 1 F, F(6), $^3J_{F(6),F(5)}$ = 19.4 Hz, $^4J_{F(6),F(8)}$ = 10.4 Hz, $^4J_{F(6),H}$ = 2.3 Hz); 14.61 (dd, 1 F, F(5), $^3J_{F(5),F(6)}$ = 19.4 Hz; $^5J_{F(5),F(8)}$ = 9.5 Hz). Found (%): C, 52.06; H, 3.06; F, 19.20; N, 4.76. $C_{13}H_{10}F_3NO_4$. Calculated (%): C, 51.84; H, 3.35; F, 18.92; N, 4.65.

Compound **4** (2.26 g (75%) in acetonitrile; 2.43 g (79%) in DMSO) was obtained according to method *B* from chromone **1**, m.p. 207—208 °C (hexane).

Ethyl 2-methylamino-4-oxo-4-(3,5,6-trifluoro-2-hydroxy-4-methylaminophenyl)but-2-enoate (5). Compound **5** (1.89 g (57%) in DMSO; 0.50 g (15%) in acetonitrile) was obtained according to method *A* from chromone **1** by bubbling methylamine for 6 h. The product was purified by column chromatography with chloroform as an eluent, m.p. 151—152 °C. IR, ν/cm^{-1}: 3414, 3256, 1607 (NH); 2700 (OH); 1739 (CO_2Et); 1655 (C=O); 1568, 1550, 1523 (C=C); 1002, 977 (CF_{Ar}). ^{1}H NMR ($(CD_3)_2CO$) for a mixture of the *Z*/*E*-isomers (85/15); *Z*-isomer, δ: 1.38 (t, 3 H, $OCH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1 Hz); 3.14 (m, 3 H, CH_3); 3.19 (d, 3 H, CH_3, $^3J_{H,NH}$ = 5.5 Hz); 4.39 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1 Hz); 5.72 (br.m, 1 H, NH); 6.05 (s, 1 H, =CH); 10.24 (br.s, 1 H, NH); 14.03 (br.s, 1 H, OH); *E*-isomer, δ: 1.30 (t, 3 H, $OCH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.0 Hz); 3.11 (m, 3 H, CH_3); 2.95 (d, 3 H, CH_3, $^3J_{H,NH}$ = 5.0 Hz); 4.29 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.0 Hz); 5.76 (br.m, 1 H, NH); 5.73 (s, 1 H, =CH); 7.45 (br.s, 1 H, NH); 14.46 (br.s, 1 H, OH). ^{19}F NMR ($(CD_3)_2CO$) for a mixture of the *Z*/*E*-isomers (85/15); *Z*-isomer, δ: −7.14 (ddqd, 1 F, F(5), $^3J_{F(5),F(6)}$ = 21.0 Hz, $^4J_{F(5),NH}$ = 1.3 Hz, $^5J_{F(5),CH_3}$ = 2.8 Hz, $^5J_{F(5),F(3)}$ = 0.4 Hz); −1.35 (m, 1 F, F(3)); 22.45 (dd, 1 F, F(6), $^3J_{F(6),F(5)}$ = 21.0 Hz, $^5J_{F(6),F(3)}$ = 9.0 Hz); *E*-isomer, δ: −7.45 (dm, 1 F, F(5), $^3J_{F(5),F(6)}$ = 21.0 Hz); −1.58 (m, 1 F, F(3)); 22.94 (dm, 1 F, F(6), $^3J_{F(6),F(5)}$ = 21.0 Hz). Found (%): C, 50.40; H, 4.78; F, 17.43; N, 8.23. $C_{14}H_{15}F_3N_2O_4$. Calculated (%): C, 50.61; H, 4.55; F, 17.15; N, 8.43.

Compound **5** (1.99 g (60%) in DMSO; 0.63 g (19%) in MeCN) was obtained according to method *A* from chromone **4** by bubbling methylamine for 4 h, m.p. 151—152 °C.

***N*-Methyl-2-methylamino-4-oxo-4-(3,5,6-trifluoro-2-hydroxy-4-methylaminophenyl)but-2-enamide (6).** Compound **6** (1.11 g (35%) in DMSO; 0.67 g (21%) in acetonitrile) was obtained according to method *A* from chromone **1** by bubbling methylamine for 6 h, m.p. 213—214 °C ($CHCl_3$). IR, ν/cm^{-1}: 3360, 3295, 3146, 1595 (NH); 2655 (OH); 1676 (C=O_{amide}); 1650 (C=O); 1566, 1541, 1517 (C=C); 1022, 959 (CF_{Ar}). ^{1}H NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (80/20); *Z*-isomer, δ: 2.71 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.6 Hz); 2.94 (d, 3 H, CH_3, $^3J_{H,NH}$ = 5.3 Hz); 3.0 (m, 3 H, CH_3); 5.55 (s, 1 H, =CH); 6.41 (br.m, 1 H, NH); 8.74 (br.s, 1 H, NH); 10.04 (br.s, 1 H, NH); 14.49 br.s (1 H, OH); *E*-isomer, δ: 2.67 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.6 Hz); 2.74 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.8 Hz); 2.77 (dm, 3 H, CH_3, $^3J_{H,NH}$ = 4.8 Hz); 5.50 (s, 1 H, =CH); 6.37 (br.s, 1 H, NH); 8.24 (br.s, 1 H, NH); 8.35 (br.s, 1 H, NH); 15.04 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (80/20); *Z*-isomer, δ: −7.30 (dm, 1 F, F(5), $^3J_{F(5),F(6)}$ = 23.0 Hz); −1.88 (m, 1 F, F(3)); 21.52 (dd, 1 F, F(6), $^3J_{F(6),F(5)}$ = 22.9 Hz; $^5J_{F(6),F(3)}$ = 8.5 Hz); *E*-isomer, δ: −7.70 (dm, 1 F, F(5), $^3J_{F(5),F(6)}$ = 25.0 Hz); −2.18 (m, 1 F, F(3)); 22.26 (dm, 1 F, F(6), $^3J_{F(6),F(5)}$ = 22.3 Hz; $^5J_{F(6),F(3)}$ = 8.7 Hz). Found (%): C, 49.20; H, 4.28; F, 17.73; N, 13.03. $C_{13}H_{14}F_3N_3O_3$. Calculated (%): C, 49.21; H, 4.45; F, 17.96; N, 13.25.

Compound **6** (1.17 g (37%) in DMSO; 0.73 g (21%) in MeCN) was obtained according to method *A* from chromone **4** (4 h), m.p. 213—214 °C ($CHCl_3$).

Ethyl 2-methylamino-4-oxo-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)but-2-enoate (7). Compound **7** (2.51 g, 78%) was obtained according to method *B* from chromone **1** in ethanol, m.p. 159—160 °C (EtOH). IR, ν/cm^{-1}: 3235 (NH); 2627 (OH); 1732 (CO_2Et); 1655 (C=O); 1602 (NH); 1567, 1534, 1515 (C=C); 999 (CF_{Ar}). ^{1}H NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (65/35); *Z*-isomer, δ: 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1 Hz); 2.81 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.0 Hz); 4.33 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1 Hz); 5.54 (s, 1 H, =CH); 9.0 (br.s, 1 H, NH); 13.30 (br.s, 1 H, OH); *E*-isomer, δ: 1.25 (t, 3 H, $OCH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1 Hz); 3.07 (d, 3 H, CH_3, $^3J_{H,NH}$ = 3.9 Hz); 4.33 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1 Hz); 5.74 (s, 1 H, =CH); 7.45 (br.s, 1 H, NH); 14.15 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (65/35); *Z*-isomer, δ: −7.15 (m, 1 F); −0.03 (m, 1 F); 9.16 (m, 1 F); 19.27 (m, 1 F); *E*-isomer, δ: −8.34 (m, 1 F); −1.10 (m, 1 F); 9.79 (m, 1 F); 22.75 (m, 1 F). Found (%): C, 48.54; H, 3.29; F, 23.53; N, 4.09. $C_{13}H_{11}F_4NO_4$. Calculated (%): C, 48.61; H, 3.45; F, 23.66; N, 4.36.

***N*-Methyl-2-methylamino-4-oxo-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)but-2-enamide (8).** Compound **8** (2.30 g, 75%) was obtained according to method *A* from chromone **1** in ethanol, m.p. 174—175 °C (acetone). IR, ν/cm^{-1}: 3278, 1600 (NH); 2608 (OH); 1665 (C=O_{amide}); 1650 sh (C=O); 1576, 1550, 1515 (C=C); 998 (CF_{Ar}). ^{1}H NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (80/20); *Z*-isomer, δ: 2.72 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.6 Hz); 2.99 (d, 3 H, CH_3, $^3J_{H,NH}$ = 5.3 Hz); 5.50 (s, 1 H,

=CH); 8.80 (br.q, 1 H, NH, $^3J_{NH,H}$ = 4.6 Hz); 10.38 (br.q, 1 H, NH, $^3J_{NH,H}$ = 5.3 Hz); 13.62 (br.s, 1 H, OH); *E*-isomer, δ: 2.69 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.6 Hz); 2.79 (d, 3 H, CH_3, $^3J_{H,NH}$ = 4.8 Hz); 5.48 (s, 1 H, =CH); 8.59 (br.s, 1 H, NH); 8.78 (br.s, 1 H, NH); 14.15 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6) for a mixture of the *Z*/*E*-isomers (80/20); *Z*-isomer, δ: –9.19 (m, 1 F); –1.07 (m, 1 F); 8.79 (m, 1 F); 22.54 (m, 1 F); *E*-isomer, δ: –9.89 (m, 1 F); –1.71 (m, 1 F); 8.79 (m, 1 F); 23.71 (m, 1 F). Found (%): C, 47.20; H, 3.18; F, 24.63; N, 9.03. $C_{12}H_{10}F_4N_2O_3$. Calculated (%): C, 47.07; H, 3.29; F, 24.82; N, 9.15.

Ethyl 2-(1-methylamino)ethylidene-3-oxo-3-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)propionate (9). Compound **9** (0.97 g (29%) in ethanol; 0.84 g (25%) in DMSO) was obtained according to method *B* from chromone **2**, m.p. 138—139 °C (EtOH). IR, ν/cm^{-1}: 3435, 1613 (NH); 2652 (OH); 1702 (CO_2Et); 1613 (C=O); 1549, 1513; 987 (CF_{Ar}). ^{1}H NMR (DMSO-d_6), δ: 0.82 (t, 3 H, $OCH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1 Hz); 2.72 (s, 3 H, CH_3), 3.09 (d, 3 H, CH_3, $^3J_{H,NH}$ = 5.1 Hz); 3.79 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1 Hz); 10.82 (br.s, 1 H, OH); 12.18 (br.q, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –5.39 (m, 1 F); 1.15 (m, 1 F); 8.73 (m, 1 F); 21.13 (m, 1 F). Found (%): C, 49.97; H, 3.72; F, 22.57; N, 4.05. $C_{14}H_{13}F_4NO_4$. Calculated (%): C, 50.16; H, 3.91; F, 22.67; N, 4.18.

5,6,7,8-Tetrafluoro-3-(1-methylamino)ethylidene-3,4-dihydro-2*H*-benzopyran-2,4-dione (10). Compound **10** (2.14 g (74%) in ethanol; 1.88 g (65%) in DMSO; 2.17 g (75%) in acetonitrile) was obtained according to method *A* from chromone **2**, m.p. 173—175 °C (EtOH). IR, ν/cm^{-1}: 3194, 1594 (NH); 1710 (C=O_{lact}), 1654 (C=O); 1617, 1531, 1491 (C=C); 987 (CF_{Ar}). ^{1}H NMR (DMSO-d_6), δ: 2.61 (s, 3 H, CH_3); 3.23 (d, 3 H, NCH_3, $^3J_{H,NH}$ = 5.0 Hz); 13.40 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –2.82, 1.89, 11.51, 16.74 (all m, 1 F each). ^{13}C NMR (DMSO-d_6), δ: 18.5 (s, C(10)); 31.2 (s, C(11); 95.7 (s, C(3)); 107.2 (m, C(4a)); 133.6—137.5 (m, C(5), C(8)); 138.3 (m, C(8a)); 141.2—146.2 (m, C(6), C(7)); 160.4 (d, C(2), $^4J_{C,F(8)}$ = 1.0 Hz); 176.5 (br.m, C(4)); 176.9 (m, C(9)). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 289 $[M]^+$ (100), 274 $[M - Me]^+$ (42), 272 $[M - OH]^+$ (22), 97 $[HOC{=}C{-}C(=NMe)Me]^+$ (20), 82 $[HOC{=}C{-}C(=N)Me]^+$ (20), 69 $[HOC{=}C{-}C{=}O]^+$ (30), 56 $[C(=NMe)Me]^+$ (76). Found (%): C, 49.63; H, 2.62; F, 26.51; N, 4.65. $C_{12}H_7F_4NO_3$. Calculated (%): C, 49.84; H, 2.44; F, 26.28; N, 4.84.

Compound **10** (1.47 g (51%) in ethanol; 1.62 g (56%) in DMSO) was obtained according to method *B* from chromone **2**, m.p. 173—175 °C (EtOH).

Method *C*. A solution of compound **9** (0.67 g, 0.002 mol) in DMSO (5 mL) was heated at 60 °C for 30 min. The reaction mixture was poured into water (20 mL). The precipitate that formed was filtered off. Recrystallization from ethanol gave compound **10** (0.55 g, 95%), m.p. 173—175 °C.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-33118), the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant 1766.2003.3), the Russian Foundation for Promotion of Home Science, and the Ural Branch of the Russian Academy of Sciences (Grant for young researchers and postgraduates).

References

1. G. Singh, L. Singh, and M. P. S. Ishar, *Tetrahedron*, 2002, **58**, 7883.
2. *Comprehensive Organic Chemistry*, Eds S. D. Barton and W. D. Ollis, Pergamon Press, New York, 1979.
3. *Heterocyclic Compounds*, **2**, Ed. R. C. Elderfield, New York, 1951.
4. V. Ya. Sosnovskikh, *Usp. Khim.*, 2003, **72**, 489 [*Russ. Chem. Rev.*, 2003, **72** (Engl. Transl.)].
5. V. I. Saloutin, Z. E. Skryabina, I. T. Bazyl´, and O. N. Chupakhin, *J. Fluor. Chem.*, 1993, **65**, 37.
6. V. I. Saloutin, I. T. Bazyl´, Z. E. Skryabina, and S. P. Kisil´, *Zh. Org. Khim.*, 1997, **33**, 1241 [*Russ. J. Org. Chem.*, 1997, **33** (Engl. Transl.)].
7. V. I. Saloutin, I. T. Bazyl´, Z. E. Skryabina, and O. N. Chupakhin, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 904 [*Russ. Chem. Bull.*, 1994, **43**, 849 (Engl. Transl.).
8. I. T. Bazyl´, S. P. Kisil´, Ya. V. Burgart, A. E. Sharapko, V. I. Saloutin, and O. N. Chupakhin, *Zh. Org. Khim.*, 1998, **34**, 394 [*Russ. J. Org. Chem.*, 1998, **34** (Engl. Transl.)].
9. R. Koch and V. Wiedel, *QCMP 113, QCPE Bull.*, 1992, **12**, 4.
10. A. J. Gordon and R. Ford, *The Chemist's Companion*, Wiley, New York, 1972.
11. *Reaktsionnaya sposobnost´ poliftoraromaticheskikh soedinenii* [*Reactivities of Polyfluoroarenes*], Ed. G. G. Yakobson, Nauka, Novosibirsk, 1983, 440 pp. (in Russian).
12. L. A. Kazitsina and N. B. Kupletskaya, *Primenenie UF-, IK-, YaMR- i mass-spektroskopii v organicheskoi khimii* [*Applications of UV, IR, NMR, and Mass Spectroscopy in Organic Chemistry*], Izd. Mosk. Gos. Univ., Moscow, 1979, 72 (in Russian).
13. N. N. Vorozhtsov, V. A. Barkhash, A. T. Prudchenko, and T. I. Khomenko, *Dokl. Akad. Nauk SSSR*, 1965, **164**, 1046 [*Dokl. Chem.*, 1965 (Engl. Transl.)].

Received June 24, 2005;
in revised form September 26, 2005