Reactions of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones with N-nucleophiles

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On treatment with ammonia, primary amines, and pyrrolidine, 5,7-dimethyl-2-trifluoromethyl-8-azachromone undergoes ring opening to give β-aminovinyl ketones. The reactions with morpholine and piperidine proceed as addition to give 2-morpholino- and 2-piperidino-8-azachromanones. With ethylenediamine, diethylenetriamines, hydrazine hydrate, and hydroxylamine, this compound reacts similarly to 2-polyfluoroalkylchromones, yielding CF_3-containing dihydrodiazepines, pyrazoles, and isoxazoles with a 2-pyridone substituent.

Key words: 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones, 5,7-dimethyl-2-polyfluoroalkylchromones, amines, hydrazine hydrate, hydroxylamine, β-aminovinyl ketones, 2,3-dihydro-1*H*-1,4-diazepines, pyrazoles, isoxazoles.

The reactions of chromones with nucleophilic reagents are known[1] to involve mainly the C(2) atom, irrespective of the presence and the nature of the substituent at this atom. The introduction of a polyfluoroalkyl group into position 2 of the chromone system appreciably increases the reactivity of the pyrone ring and makes 2-polyfluoroalkylchromones highly reactive substrates in 1,4-nucleophilic addition reactions. Previously, we studied the reactions of these compounds with various amines,[2—6] hydrazines,[7] hydroxylamine,[8] and sodium azide,[9] which furnished a broad range of R^F-containing nitrogen heterocycles. It was noted[5,6] that electron-withdrawing substituents in the benzene ring promote the attack of an amine molecule on the C(2) atom, which can either stop after the nucleophilic addition or proceed further with opening of the pyrone ring to give β-aminovinyl ketones (AVK). Therefore, it appeared of interest to compare the reactivity of 5,7-dimethyl-2-polyfluoroalkylchromones[10] and 2,5,7-trimethyl-8-azachromone[11] with the reactivity of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones (5,7-dimethyl-2-polyfluoroalkyl-4*H*-pyrano[2,3-*b*]pyridin-4-ones), obtained by condensation of 3-acetyl-4,6-dimethyl-2-pyridone with R^FCO_2Et (R^F = CF_3, CF_2H, $(CF_2)_2H$) in the presence of LiH.[12]

Results and Discussion

We have studied the reactions of 5,7-dimethyl-2-trifluoromethyl-8-azachromone (**1**) with various N-nucleophiles and compared its behavior in these reactions with the behavior of 5,7-dimethyl-2-trifluoromethylchromone (**2**) and 2,5,7-trimethyl-8-azachromone (**3**). This allowed us to elucidate the influence of the N(8) atom and the CF_3 group on the reactivity of the chromone system. As expected, azachromone **1** readily reacts with ammonia, primary mono-, di-, and triamines, secondary cyclic amines, hydrazine hydrate, and hydroxylamine. These reactions involve the C(2) atom and give diverse 4,6-dimethyl-2-pyridone derivatives (the 2-pyridone form predominates in the tautomeric equilibrium with the 2-hydroxypyridine form[11,13]).

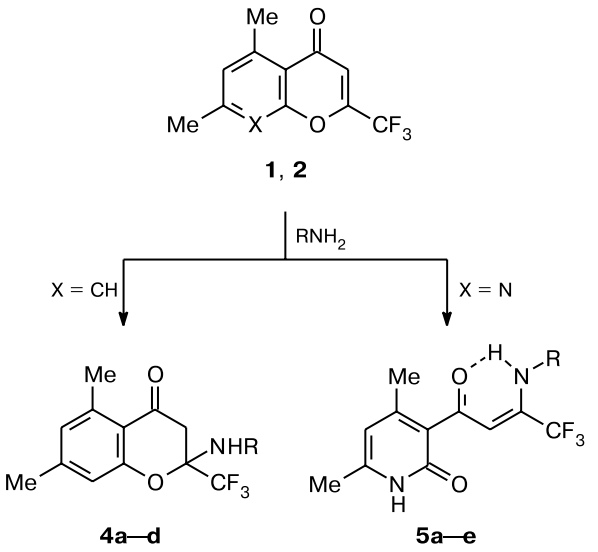
Previously,[2] it has been shown that the interaction of chromone **2** with ammonia and methyl- and benzylamines in an alcohol solution at ~20 °C stops after 1,4-addition giving rise to 2-aminochromanones **4a**—**c**. We found that chromone **2** also easily adds 2-aminoethanol to give compound **4d** but does not react with aniline. Unlike chromone **2**, azachromone **1** reacts with ammonia and primary amines at ~20 °C or with aniline in the presence of Et_3N at 75 °C with pyrone ring opening to give AVK **5a**—**e** (Scheme 1). The reaction with aniline is the second known example in which the chromone system reacts with aromatic amines at the C(2) atom (previously,[5] we reported a similar reaction of 6-nitro-2-trifluoromethylchromone).

The different structure of the products obtained in reactions of chromones **2** and **1** with primary amines is, apparently, related to the formation of a stable 2-pyridone fragment in the latter case, which shifts the ring—chain tautomeric equilibrium toward the open form **5**. The replacement of the trifluoromethyl group by a methyl group does not prevent the reaction of azachromone **3** [11] with methyl- and benzylamines at ~20 °C, which also follows a route with pyrone ring opening in AVK **5f**,**g**. However, in

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1668—1676, August, 2003.

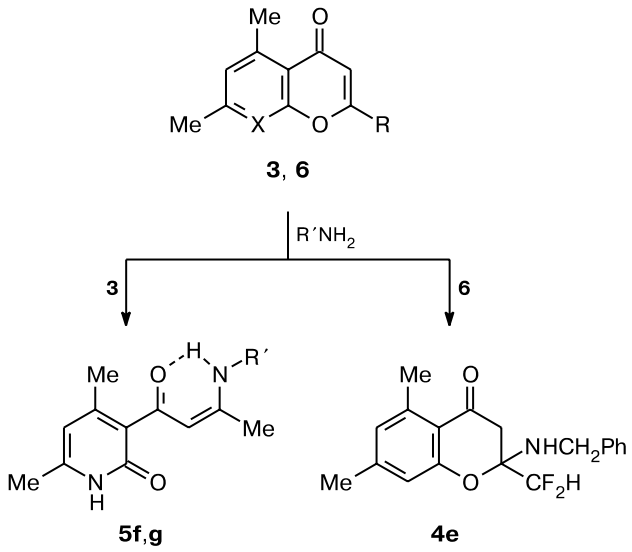
1066-5285/03/5208-1758 $25.00

Scheme 1



X = N (**1**), CH (**2**)
R = H (**a**), Me (**b**), CH_2Ph (**c**), $(CH_2)_2OH$ (**d**), Ph (**e**)

Scheme 2



X = N, R = Me (**3**);
X = CH, R = CF_2H (**6**);
R´ = Me (**5f**), CH_2Ph (**5g**)

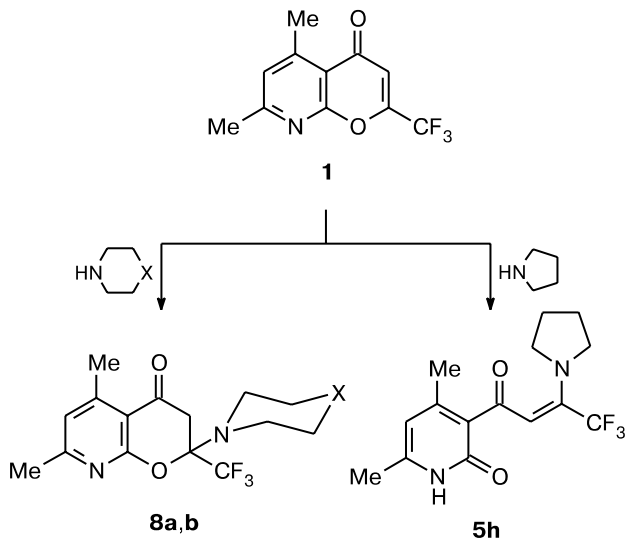
the reaction with NH_3, azachromone **3** is recovered unchanged. Judging by the chemical shift of the proton attached to the nitrogen atom (δ_{NH} = 10.4—11.5 for **5b**,**c**,**g** in $CDCl_3$), compounds **5a**—**g** have a *Z*-configuration of the double bond and occur as *s*-conformers stabilized by an intramolecular hydrogen bond (IMHB). The CF_3 group in **5c** deshields the vinylic proton of the aminoenone system compared with the Me group in **5g**; hence, its signal is shifted downfield by 0.58 ppm.

2-Difluoromethyl-5,7-dimethylchromone (**6**), like chromone **2**, adds benzylamine to afford chromanone **4e**, whereas 5,7-dimethyl-2-(1,1,2,2-tetrafluoroethyl)chromone (**7**) does not react with benzylamine, 2-aminoethanol, or ammonia under similar conditions (Scheme 2). Thus, primary amines open the pyrone ring in 5,7-dimethyl-8-azachromones, irrespective of the nature of the substituent at the C(2) atom, whereas the reactions of RNH_2 (R = H, Alk) with 5,7-dimethyl-2-R^F-chromones stop after nucleophilic 1,4-addition and are fairly sensitive to the steric factor.

Diethylamine does not react with chromones **1**—**3**, while secondary cyclic amines (morpholine, piperidine) do not react with chromones **2** or **3**, but add to the double bond of azachromone **1** in a THF solution at ~20 °C to give azachromanones **8a**,**b**, which proved to be more stable than 2-piperidino- and 2-morpholinochromanones, prepared previously[5,6] from 2-trifluoromethylchromones containing a nitro group in the benzene ring. Indeed, the piperidine derivative **8b** starts to decompose into the initial substances after storage for several months, whereas a similar adduct of piperidine with 2-trifluoromethylchromone, after storage for several days.[5] The formation of chromanones **8a**,**b** attests to a more electrophilic nature of the C(2) atom in azachromone **1** with respect to that in chromone **2** (on passing from **2** to **1**, the chemical shifts of the C(2)—C(4) atoms in the ^{13}C NMR spectra shift downfield by 0.52—0.54 ppm).[10,12]

The reaction of azachromone **1** with pyrrolidine carried out under the same conditions gave unexpectedly the *Z*-isomer of AVK **5h** (Scheme 3), *i.e.*, transition from a six- to a five-membered ring is accompanied by an in-

Scheme 3

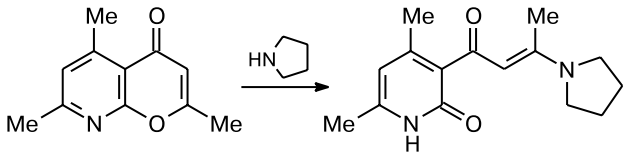


X = O (**8a**), CH_2 (**8b**)

crease in the stability of the open aminoenone form relative to the chromanone form. In this case, no IMHB is formed to stabilize the *Z*-configuration of AVK **5a**—**g**. The fact that AVK **5h** belongs to the *Z*-series was deduced from the chemical shift of the vinylic proton. For solutions **5a**—**c**,**h** in $CDCl_3$, these chemical shifts occur in a narrow range, δ 5.93—5.97.

It is noteworthy that on refluxing in methanol with pyrrolidine for 1 h, azachromone **3** is converted into AVK **5i** with *E*-configuration of the double bond (Scheme 4), as indicated by the chemical shift of the methyl group belonging to the aminoenone fragment. Unlike AVK **5g** in which the Me group is responsible for a signal at 1.99 ppm, in the case of **5i**, this group shows itself at 2.63 ppm (in the *E*-isomer prepared from 2-methyl-5,8-dimethoxychromone and pyrrolidine, δ_{Me} = 2.55 ppm[14]).

Scheme 4

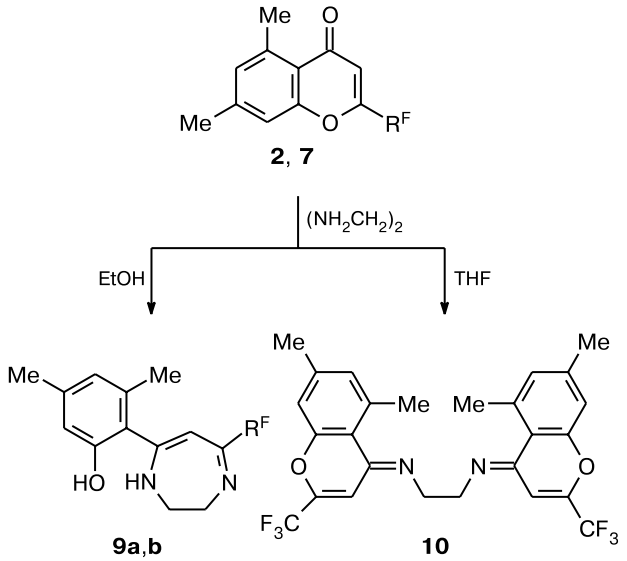


3 **5i**

The vinylic proton in compounds **5h**,**i** is manifested at 5.93 and 5.22, respectively, which implies different arrangements of the pyrrolidine residue with respect to this proton and agrees with the conclusion about the double bond configuration in AVK **5h**,**i**. Thus, on treatment with pyrrolidine, azachromone **3** is converted stereospecifically into *E*-AVK **5i**, while its trifluoromethylated analog **1** is transformed into *Z*-AVK **5h**. This outcome can be attributed to the fact that the CF_3 group has a greater van der Waals radius (2.7 Å) than the CH_3 group (2.0 Å)[15] and to unfavorable interactions between the fluorine atoms and the carbonyl oxygen atom. Due to the IMHB, azachromones **1** and **3** react with primary amines to give *Z*-AVK **5a**—**g**, while *E*-isomer was formed only for **5f** in a yield of 9% (see Table 1).

It is known[3] that 2-R^F-chromones readily react with ethylenediamine (EDA) in ethanol (~20 °C, 3 h) to give 2,3-dihydro-1*H*-1,4-diazepines. 5,7-Dimethyl-2-R^F-chromones **2** and **7** react with EDA in a similar way but at a lower rate, giving rise to diazepines **9a**,**b** upon refluxing in ethanol for 20 min or stirring for 24 h at ~20 °C (Scheme 5). In the case of chromone **2**, when EtOH is replaced by THF, the reaction follows a route involving the oxo group, unusual for the chromone system, to give bischromeneimine **10** in a low yield (8%). Recently,[16] we observed a similar attack on the carbonyl group in the reaction of 2-aminoethanol with 2-R^F-chromones at R^F = $(CF_2)_2H$, C_2F_5.

Scheme 5

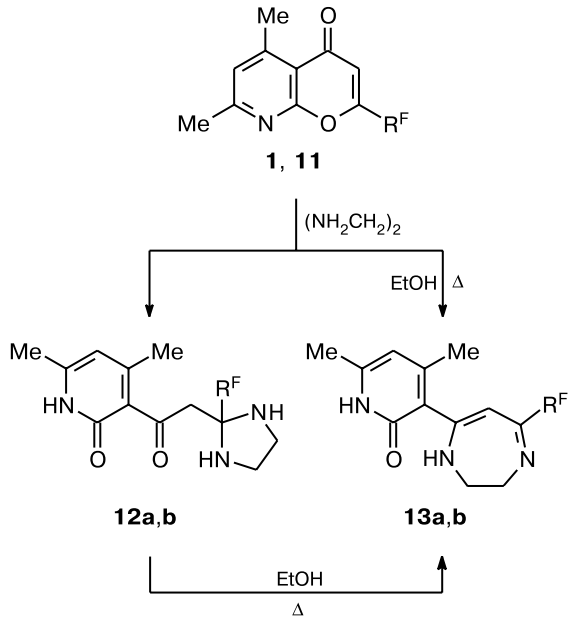


2, **7** **9a**,**b** **10**

R^F = CF_3 (**2**, **9a**), $(CF_2)_2H$ (**7**, **9b**)

The reactions of azachromones **1** and **11** with EDA, unlike those of chromones **2** and **7**, stop after the formation of AVK with a 2-aminoethyl group at the nitrogen atom, which exist in the cyclic imidazolidine form **12** (Scheme 6). Previously, compounds of this type have been synthesized by transamination of β-amino-β-trifluoromethylvinyl ketones on treatment with EDA.[17] On heating in alcohol solutions for 5 h, compounds **12a**,**b** are

Scheme 6



1, **11** **12a**,**b** **13a**,**b**

R^F = CF_3 (**1**, **12a**, **13a**), $(CF_2)_2H$ (**11**, **12b**, **13b**)

Table 1. Key characteristics of compounds **4**, **5**, **8**—**10**, **12**—**17**, and **19**—**21**

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)			^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
				C	H	N		
4d	62	119—120	$C_{14}H_{16}F_3NO_3$	55.23 55.45	5.27 5.32	4.47 4.62	$CDCl_3$: 2.32 (s, 3 H, Me(7)); 2.40 (t, 1 H, NH, *J* = 6.3); 2.59 (s, 3 H, Me(5)); 2.78 (d, 1 H, C(3)HH, *J* = 16.3); 2.80—3.05 (m, 2 H, CH_2N); 3.15 (d, 1 H, C(3)HH, *J* = 16.3); 3.48—3.60 (m, 2 H, CH_2O); 6.69 (s, 1 H, H(8)); 6.74 (s, 1 H, H(6))	3560, 3490, 3390, 3370, 1665, 1615, 1565
4e	54	93—94	$C_{19}H_{19}F_2NO_2$	68.85 68.87	5.80 5.78	4.18 4.23	$CDCl_3$: 2.31 (s, 3 H, Me(7)); 2.41 (t, 1 H, NH, *J* = 6.4); 2.59 (s, 3 H, Me(5)); 2.76 (d, 1 H, C(3)HH, *J* = 16.5); 3.09 (d, 1 H, C(3)HH, *J* = 16.5); 3.91 (AB part of an ABX-system, 2 H, CH_2, ^2J = 13.3, ^3J = 6.3); 5.89 (t, 1 H, CF_2H, $^2J_{H,F}$ = 55.1); 6.67 (s, 1 H, H(8)); 6.70 (s, 1 H, H(6)); 7.12—7.28 (m, 5 H, Ph)	3400, 1670, 1615, 1565
5a	49 [a] (86)[b]	228—230	$C_{11}H_{11}F_3N_2O_2$	50.83 50.77	4.25 4.26	10.68 10.77	$CDCl_3$: 2.29, 2.30 (both s, 3 H each, Me); 5.97 (s, 1 H, CH=); 6.20 (s, 1 H, H arom.); 6.0—9.0 (br.s, 2 H, NH_2); 12.39 (s, 1 H, NH); DMSO-d_6: 2.12, 2.15 (both s, 3 H each, Me); 5.85 (s, 1 H, CH=); 5.94 (s, 1 H, H arom.); 8.6 (br.s, 2 H, NH_2); 11.71 (s, 1 H, NH)	3420, 3325, 1645, 1615, 1550
5b	52	199—200	$C_{12}H_{13}F_3N_2O_2$	52.45 52.56	4.77 4.78	10.24 10.22	$CDCl_3$: 2.27, 2.29 (both s, 3 H each, Me); 3.08 (dq, 3 H, MeN, *J* = 5.7, $^5J_{H,F}$ = 1.1); 5.95 (s, 1 H, CH=); 6.13 (s, 1 H, H arom.); 10.38 (s, 1 H, NH); 13.03 (s, 1 H, NHCO)	1635, 1590, 1545
5c	67	186—188	$C_{18}H_{17}F_3N_2O_2$	61.76 61.71	4.91 4.89	8.17 8.00	$CDCl_3$: 2.27, 2.30 (both s, 3 H each, Me); 4.57 (d, 2 H, CH_2, *J* = 6.4); 5.96 (s, 1 H, CH=); 6.24 (s, 1 H, H arom.); 7.29—7.40 (m, 5 H, Ph); 10.62 (br.t, 1 H, NH, *J* ≈ 5.7); 12.91 (s, 1 H, NHCO)	1635, 1590, 1545
5d	57	200—202	$C_{13}H_{15}F_3N_2O_3 \cdot 0.25H_2O$	50.82 50.57	4.85 5.06	8.95 9.07	DMSO-d_6: 2.12, 2.15 (both s, 3 H each, Me); 3.39 (q, 2 H, CH_2N, *J* = 5.5); 3.58 (q, 2 H, CH_2O, *J* = 5.2); 5.06 (t, 1 H, OH, *J* = 5.0); 5.94 (s, 1 H, CH=); 5.96 (s, 1 H, H arom.); 10.32 (br.t, 1 H, NH, *J* ≈ 5.0); 11.73 (s, 1 H, NHCO)	3390, 1625, 1580
5e	38	198—200	$C_{17}H_{15}F_3N_2O_2$	60.90 60.71	4.72 4.50	8.22 8.33	DMSO-d_6: 2.17, 2.18 (both s, 3 H each, Me); 6.00 (s, 1 H, CH=); 6.38 (s, 1 H, H arom.); 7.23—7.27 (m, 3 H, arom.); 7.36—7.40 (m, 2 H, H arom.); 11.28 (s, 1 H, NH); 11.87 (s, 1 H, NHCO)	1650, 1630, 1590, 1575
5f	67	263—265 (decomp.)	$C_{12}H_{16}N_2O_2$	65.20 65.43	7.36 7.32	12.87 12.72	DMSO-d_6: (*Z* — 91%) 1.94, 2.01, 2.10 (all s, 3 H each, Me); 2.94 (d, 3 H, MeN, *J* = 5.2); 5.08 (s, 1 H, CH=); 5.81 (s, 1 H, H arom.); 10.72 (q, 1 H, NH, *J* = 5.1); 11.43 (s, 1 H, NHCO); (*E*—9%) 1.98, 2.10, 2.25 (all s, 3 H each, Me); 2.58 (d, 3 H, MeN, *J* = 4.7); 4.97 (s, 1 H, CH=); 5.80 (s, 1 H, H arom.); 7.10 (br.s, 1 H, NH); 11.43 (s, 1 H, NHCO)	1640, 1605, 1550, 1530
5g	51	198—200	$C_{18}H_{20}N_2O_2$	72.69 72.95	6.80 6.80	9.36 9.45	$CDCl_3$: 1.99, 2.22, 2.26 (all s, 3 H each, Me); 4.52 (d, 2 H, CH_2, *J* = 6.3); 5.38 (s, 1 H, CH=); 5.88 (s, 1 H, H arom.); 7.27—7.38 (m, 5 H, Ph); 11.48 (t, 1 H, NH, *J* = 6.2); 11.9 (br.s, 1 H, NHCO)	1635, 1595, 1530

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)			^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
				C	H	N		
5h	90	187—188	$C_{15}H_{17}F_3N_2O_2$	57.30 57.32	5.46 5.45	8.95 8.91	$CDCl_3$: 1.96—2.00 (m, 4 H, 2 CH_2); 2.23, 2.26 (both s, 3 H each, Me); 3.48 (t, 4 H, 2 CH_2N, *J* = 6.5); 5.93 (s, 1 H, CH=); 5.97 (s, 1 H, H arom.); 10.38 (s, 1 H, NH); 12.8 (br.s, 1 H, NHCO)	1655, 1570
5i	48	254—255 (decomp.)	$C_{15}H_{20}N_2O_2$	68.89 69.20	7.72 7.74	10.78 10.76	$CDCl_3$: 1.90—1.95 (m, 4 H, 2 CH_2); 2.19 (s, 3 H, Me); 2.23 (d, 3 H, Me, *J* = 0.4); 2.63 (s, 3 H, Me); 3.26 (br.s, 2 H, CH_2N); 3.46 (br.s, 2 H, CH_2N); 5.22 (s, 1 H, CH=); 5.85 (s, 1 H, H arom.); 11.8 (br.s, 1 H, NHCO)	1640, 1610, 1530
8a	81	154—155	$C_{15}H_{17}F_3N_2O_3$	54.45 54.54	5.17 5.19	8.41 8.48	$CDCl_3$: 2.48 (s, 3 H, Me(7)); 2.63 (s, 3 H, Me(5)); 2.83—2.88, 3.00—3.05 (both m, 2 H each, CH_2N); 3.13 (AB system, Δδ = 0.09, 2 H, CH_2, *J* = 16.1); 3.34—3.39, 3.42—3.47 (both m, 2 H each, CH_2O); 6.79 (s, 1 H, H arom.)	1700, 1610, 1550
8b	65	124—126	$C_{16}H_{19}F_3N_2O_2$	58.37 58.53	5.66 5.83	8.54 8.53	$CDCl_3$: 1.15—1.41 (m, 6 H, 3 CH_2); 2.48 (s, 3 H, Me(7)); 2.63 (s, 3 H, Me(5)); 2.75—2.80, 2.97—3.02 (both m, 2 H each, CH_2N); 3.13 (s, 2 H, CH_2); 6.76 (s, 1 H, H arom.)	1695, 1605, 1550
9a	59 [c] (51) [d]	195—197	$C_{14}H_{15}F_3N_2O \cdot 0.5H_2O$	57.31 57.33	5.21 5.50	9.45 9.55	DMSO-d_6: 2.16, 2.18 (both s, 3 H each, Me); 3.31 (br.s, 2 H, C(2)H_2); 3.94 (br.s, 2 H, C(3)H_2); 4.58 (s, 1 H, CH=); 6.50,6.52 (both s, 1 H each, H arom.); 7.68 (br.s, 1 H, NH); 8.3—9.5 (br.s, 1 H, OH)	3230, 1620, 1560, 1520
9b	65	166—167	$C_{15}H_{16}F_4N_2O$	57.05 56.96	5.13 5.10	8.87 8.86	DMSO-d_6: 2.17, 2.18 (both s, 3 H each, Me); 3.30 (br.s, 2 H, C(2)H_2); 3.94 (br.s, 2 H, C(3)H_2); 4.67 (s, 1 H, CH=); 6.50, 6.52 (both s, 1 H each, H arom.); 6.64 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.6, $^3J_{H,F}$ = 6.0); 7.57 (br.s, 1 H, NH); 9.14 (br.s, 1 H, OH)	3410, 1620, 1570, 1520
10	8	205—207	$C_{26}H_{22}F_6N_2O_2$	61.37 61.42	4.34 4.36	5.52 5.51	$CDCl_3$: 2.33 (s, 3 H, Me(7)); 2.69 (s, 3 H, Me(5)); 3.89 (s, 2 H, CH_2N); 6.78 (s, 1 H, CH=); 6.87 (s, 1 H, H(6)); 6.91 (s, 1 H, H(8))	1680, 1620, 1600, 1560
12a	56	176—178	$C_{13}H_{16}F_3N_3O_2$	51.60 51.48	5.34 5.32	13.83 13.86	$CDCl_3$: 2.29, 2.40 (both s, 3 H each, Me); 3.05 (m, 4 H, 2 CH_2N); 3.35 (s, 2 H, CH_2); 3.74 (br.s, 2 H, 2 NH); 6.11 (s, 1 H, H arom.); 13.5 (br.s, 1 H, NHCO)	3355, 3325, 3300, 1695, 1640, 1545
12b	53	157—158 (subl.)	$C_{14}H_{17}F_4N_3O_2$	50.27 50.15	5.02 5.11	12.54 12.53	$CDCl_3$: 2.28, 2.39 (both s, 3 H each, Me); 2.97, 3.06 (both m, 2 H each, CH_2N); 3.32 (s, 2 H, CH_2); 3.7 (br.s, 2 H, 2 NH); 6.09 (s, 1 H, H arom.); 6.19 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.7, $^3J_{H,F}$ = 6.3); 13.2 (br.s, 1 H, NHCO)	3340, 1685, 1640, 1575, 1530
13a	65 [e] (74) [f]	255—256	$C_{13}H_{14}F_3N_3O$	54.83 54.74	4.87 4.95	14.84 14.73	DMSO-d_6: 2.08, 2.13 (both s, 3 H each, Me); 3.30 (br.s, 2 H, C(2)H_2); 3.92 (br.s, 2 H, C(3)H_2); 4.60 (s, 1 H, CH=); 5.92 (s, 1 H, H arom.); 7.75 (br.s, 1 H, NH); 11.64 (br.s, 1 H, NHCO)	3320, 3150, 1640, 1575, 1545

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)			^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
				C	H	N		
13b	52	241—242	$C_{14}H_{15}F_4N_3O$	53.01 53.00	4.99 4.77	12.97 13.24	DMSO-d$_6$: 2.07, 2.13 (both s, 3 H each, Me); 3.26 (br.s, 2 H, C(2)H$_2$); 3.91 (br.s, 2 H, C(3)H$_2$); 4.66 (s, 1 H, CH=); 5.91 (s, 1 H, H arom.); 6.67 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.6, $^3J_{H,F}$ = 6.0); 7.64 (br.s, 1 H, NH); 11.63 (br.s, 1 H, NHCO)	3300, 1640, 1620, 1575, 1540
14a	52	200—202 (decomp.)	$C_{15}H_{19}F_3N_4O$	54.86 54.87	5.75 5.83	16.78 17.06	$CDCl_3$: 2.17, 2.32 (both s, 3 H each, Me); 3.00 (d, 1 H, C(6)H**H**, ^2J = 16.2); 3.04—3.18 (m, 6 H, C(6)H**H**, C(2)H$_2$, C(9)H$_2$, C(10)**H**H); 3.69 (ddd, 1 H, C(3)**H**H, ^2J = 15.6, ^3J = 11.9, 3.7); 3.93—3.98 (m, 1 H, C(10)H**H**); 4.50—4.57 (m, 1 H, C(3)H**H**); 4.68 (br.s, 1 H, NH); 5.99 (s, 1 H, H arom.); 11.2—14.2 (br.s, 1 H, NHCO)	3290, 1650, 1620, 1540
14b	72	145—146	$C_{16}H_{20}F_3N_3O$	58.74 58.71	6.24 6.16	12.90 12.84	$CDCl_3$: 2.23 (s, 6 H, 2 Me); 2.28 (br.s, 1 H, NH); 3.02 (d, 1 H, C(6)H**H**, ^2J = 15.2); 3.07—3.28 (m, 5 H, C(2)H$_2$, C(9)H$_2$, C(10)**H**H); 3.41 (d, 1 H, C(6)H**H**, ^2J = 15.2); 3.59 (ddd, 1 H, C(3)**H**H, ^2J = 15.4, ^3J = 9.0, ^3J = 4.3); 3.98 (dt, 1 H, C(10)H**H**, ^2J = 17.4, ^3J = 4.5); 4.43 (ddd, 1 H, C(3)H**H**, ^2J = 15.4, ^3J = 9.0, ^3J = 4.3); 6.51, 6.54 (both s, 1 H each, H arom.)	3300, 1680, 1660, 1620, 1590
15	85 [g] (86) [h]	275—276	$C_{11}H_{10}F_3N_3O$	51.25 51.37	3.91 3.92	16.32 16.34	DMSO-d$_6$: 2.16, 2.20 (both s, 3 H each, Me); 6.08 (s, 1 H, H arom.); 6.75 (s, 1 H, CH=); 11.91 (s, 1 H, NHCO); 13.59 (s, 1 H, NH)	3350, 3160, 1640, 1580, 1535
16a,**b**	50	150—165	$C_{12}H_{12}F_3N_3O$	53.21 53.14	4.37 4.46	15.45 15.49	$CDCl_3$: **16a** (60%) 2.09, 2.31 (both s, 3 H each, Me); 3.79 (s, 3 H, MeN); 6.06 (s, 1 H, H arom.); 6.44 (s, 1 H, CH=); 12.0—14.0 (br.s, 1 H, NHCO); **16b** (40%) 2.27, 2.31 (both s, 3 H each, Me); 4.02 (s, 3 H, MeN); 6.01 (s, 1 H, H arom.); 7.02 (s, 1 H, CH=); 12.0—14.0 (br.s, 1 H, NHCO)	1650, 1590, 1555, 1515
17	68	243—244 (subl.)	$C_{11}H_{12}F_3N_3O_2$	48.07 48.00	4.45 4.39	15.30 15.27	DMSO-d$_6$: 2.14, 2.23 (both s, 3 H each, Me); 3.16 (d, 1 H, C**H**H, ^2J = 18.1); 3.47 (d, 1 H, CH**H**, ^2J = 18.1); 5.95 (s, 1 H, H arom.); 6.95 (s, 1 H, NH); 7.55 (s, 1 H, OH); 11.63 (s, 1 H, NHCO)	3320, 1635, 1610, 1555
19	74	*i*	$C_{11}H_{13}F_3N_2O_3 \cdot H_2O$	44.61 44.60	5.07 5.10	9.49 9.46	DMSO-d$_6$: 1.95, 2.08 (both s, 3 H each, Me); 5.12 (s, 1 H, CH=); 5.75 (s, 1 H, H arom.); 7.3 (br.s, 4 H, N^+H_4); 9.0—12.5 (br.s, 1 H, NHCO)	3350, 1630, 1610
20	63	223—224	$C_{11}H_{11}F_3N_2O_3$	47.70 47.83	3.86 4.01	10.04 10.14	DMSO-d$_6$: 2.12, 2.19 (both s, 3 H each, Me); 4.11 (s, 2 H, CH$_2$); 6.02 (s, 1 H, H arom.); 12.01 (s, 1 H, NHCO); 12.52 (s, 1 H, OH)	1695, 1640, 1610
21	60	255—257	$C_{11}H_9F_3N_2O_2$	51.23 51.17	3.46 3.51	10.94 10.85	DMSO-d$_6$: 2.24, 2.38 (both s, 3 H each, Me); 6.17 (s, 1 H, H arom.); 7.42 (s, 1 H, CH=); 12.19 (s, 1 H, NHCO)	3200, 1650, 1630, 1560, 1525, 1495

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)			^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
				C	H	N		
22	45	227—229	$C_{11}H_{11}F_3N_2O_3$	47.80 47.83	4.04 4.01	10.12 10.14	DMSO-d$_6$: 2.17, 2.22 (both s, 3 H each, Me); 3.47 (dq, 1 H, CHH, ^2J = 18.7, $^4J_{H,F}$ = 1.1); 3.85 (d, 1 H, CHH, ^2J = 18.7); 6.04 (s, 1 H, H arom.); 8.43 (s, 1 H, OH); 11.86 (s, 1 H, NHCO)	3200, 1645, 1625, 1530
23	60	250—251 (subl.)	$C_{11}H_9F_3N_2O_2$	51.42 51.17	3.56 3.51	10.89 10.85	DMSO-d$_6$: 2.21, 2.24 (both s, 3 H each, Me); 6.11 (s, 1 H, H arom.); 7.61 (q, 1 H, CH=, $^4J_{H,F}$ = 1.0); 12.02 (s, 1 H, NHCO)	1655, 1630, 1545

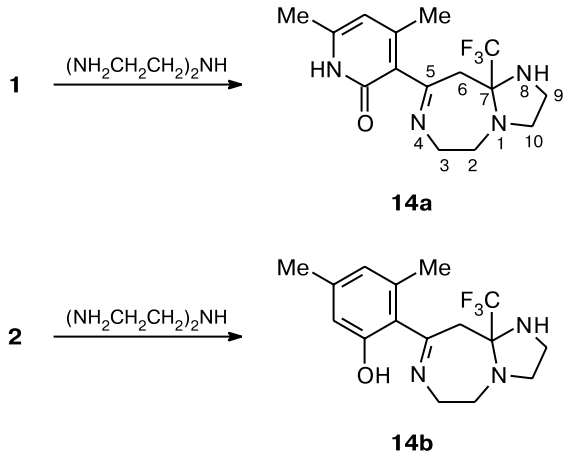
[a] From azachromone **1**.
[b] From β-diketone **18**.
[c] On heating.
[d] At ~20 °C.
[e] From azachromone **1**.
[f] From imidazolidine **12a**.
[g] From azachromone **1**.
[h] From pyrazoline **17**.
[i] Decomposes on heating to give β-diketone **18** and ammonia.

converted into dihydrodiazepines **13a**,**b**. By refluxing azachromones **1** and **11** with EDA in ethanol in the presence of concentrated HCl, one can obtain compounds **13** without the intermediate preparation of imidazolidines **12**. Under similar conditions, trimethylenediamine cleaves azachromone **1** to give 3-acetyl-4,6-dimethyl-2-pyridone. Note that the $^3J_{H,F}$ value for the $(CF_2)_2H$ group,[18] which is equal to 6.0 Hz for solutions of dihydrodiazepines **9b** and **13b** in DMSO-d$_6$, provides the conclusion that compounds **9** and **13** mainly exist in this solvent as 5-R^F-tautomers.

Recently,[4] we described a reaction with diethylenetriamine (DETA) typical of 2-R^F-chromones, which gives rise to 1,4,8-triazabicyclo[5.3.0]dec-4-enes with one of the shortest known IMHB (O—H...N=C) and a flattened fragment comprising the aromatic ring and the C(3), N(4), C(5), and C(6) atoms. It was found that compounds **1** and **2** also react with DETA to give bicyclic derivatives **14a**,**b**, despite the presence of the *o*-Me group, which disturbs the planarity of this fragment (Scheme 7).

The reaction of azachromone **1** with hydrazine hydrate at ~20 °C yields the expected pyrazole **15**, while the reaction with methylhydrazine gives a mixture of regioisomeric 3-CF$_3$- and 5-CF$_3$-pyrazoles **16a**,**b** in 3 : 2 ratio, respectively (Scheme 8). The signals in the ^{1}H NMR spectrum were assigned based on the chemical shifts of N-methyl groups, which occur at δ ≈ 3.8 for the 3-CF$_3$ isomers and at δ ≈ 4.0 for the 5-CF$_3$ isomers.[7,19,20] In addition, the singlet due to the pyrazole H(4) proton occurs in a lower field in 5-R^F pyrazoles than in the 3-R^F-pyrazoles.[7,21]

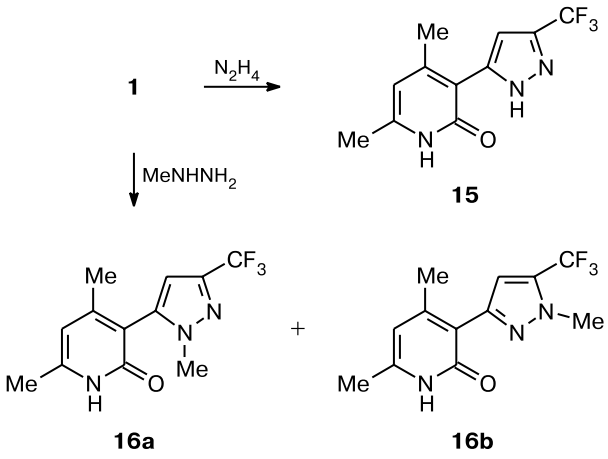
Scheme 7



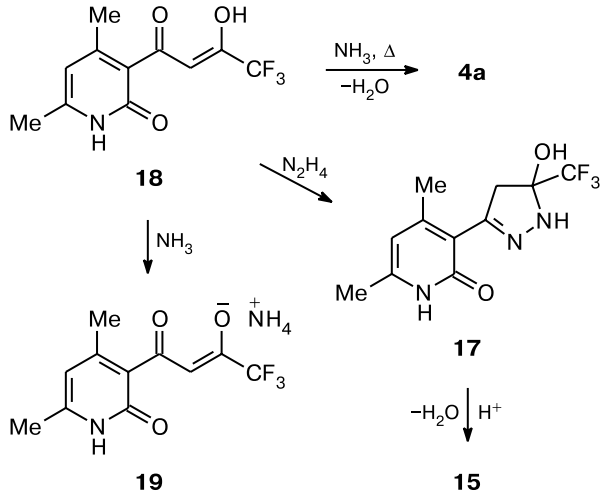
Pyrazole **15** was also obtained by dehydration of pyrazoline **17** in an acid medium, which is, in turn, formed upon the reaction of hydrazine hydrate with a precursor of azachromone **1**, namely, β-diketone **18** [12] (Scheme 9). It is noteworthy that diketone **18** reacts with NH$_3$ in aqueous ethanol at ~20 °C to give the monohydrate of salt **19** or with refluxing for 10 min to give AVK **4a**. On treatment with methylamine, diketone **18** is cleaved to give 3-acetyl-4,6-dimethyl-2-pyridone.

Refluxing of azachromone **1** with hydroxylamine hydrochloride (AcONa, EtOH, 1 h) affords oxime **20**, which undergoes cyclodehydration in AcOH in the presence of concentrated HCl giving rise to 3-CF$_3$-isoxazo-

Scheme 8

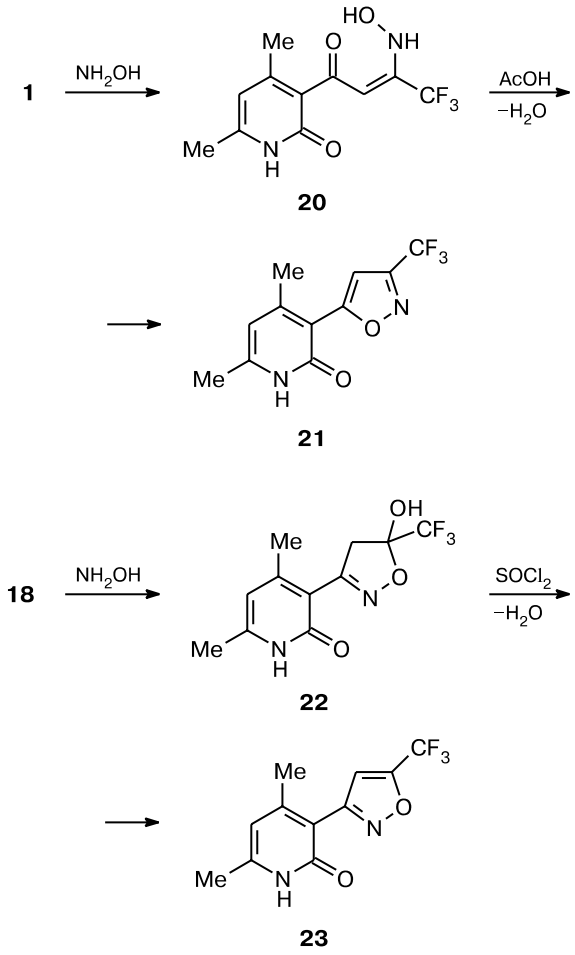


Scheme 9



le **21** (Scheme 10). Under similar conditions, β-diketone **18** furnishes isoxazoline **22**, which is dehydrated on treatment with thionyl chloride to yield 5-CF_3-isoxazole regioisomer **23**. It is worth mentioning that the reaction of azachromone **1** with $NH_2OH \cdot HCl$ without sodium acetate affords a mixture of isoxazoline **22** and isoxazole **21** in 65 : 35 ratio. Compounds **21** and **23** can be easily differentiated judging by the splitting pattern and the chemical shift of the isoxazole proton in the ^1H NMR spectrum, which shows itself as a singlet with $\delta = 7.42$ for the 3-CF_3-isomer **21** or as a lower-field quartet with $^4J_{H,F} = 1.0$ Hz and $\delta = 7.61$ (DMSO-d_6) for the 5-CF_3-isomer **23**. The same is true for the 5-(2-hydroxyaryl)-3-trifluoromethyl- and 3-(2-hydroxyaryl)-5-trifluoromethylisoxazole regioisomers.[8] These results show that the recently proposed[8] regiocontrolled synthesis of R^F-containing isoxazoles from 2-polyfluoroalkylchromones and their precursors is also applicable to the aza analogs of these compounds.

Scheme 10



Thus, as expected, 2-R^F-8-azachromones are more reactive that 2-R^F-chromones, which can be seen especially clearly in the reactions of these compounds with primary and secondary monoamines. The reactions of 8-azachromones with ethylenediamine, diethylenetriamine, hydrazine hydrate, and hydroxylamine are similar to those of chromones.

Experimental

IR spectra were obtained on an IKS-29 instrument in mineral oil. ^1H NMR spectra were recorded on a Bruker DRX-400 spectrometer in $CDCl_3$ or DMSO-d_6 operating at 400.13 MHz using Me_4Si as the internal standard. The initial chromones **2**, **6**, and **7** were described previously;[10,22] azachromones **1**, **3**, and **11** and β-diketone **18** were also reported.[11,12] Compounds **4a—c** were also described.[2] The yields, the melting points, elemental analysis data, and ^1H NMR and IR spectra of the synthesized compounds are listed in Table 1.

2-(2-Hydroxyethyl)amino-5,7-dimethyl-2-trifluoromethylchroman-4-one (4d). Chromone **2** (0.24 g, 1.0 mmol) was dissolved with heating in 5 mL of ethanol, and 2-aminoethanol (0.25 g, 4.1 mmol) was added. The resulting solution was left for 24 h at ~20 °C, concentrated, and diluted with water (10 mL); the precipitate was filtered off, dried, and recrystallized from a hexane—toluene mixture (1 : 1).

2-Benzylamino-2-difluoromethyl-5,7-dimethylchroman-4-one (4e). A mixture of chromone **6** (0.25 g, 1.1 mmol) and benzylamine (0.21 g, 2.0 mmol) was kept for 15 h at ~20 °C and for the same period at 80 °C, and cooled. Ethanol (0.5 mL), water (3 mL), and hexane (3 mL) were added and the mixture was triturated. The precipitate thus formed was filtered off, washed with water, and recrystallized from hexane.

3-[3-(Amino- or alkylamino)-4,4,4-trifluorobut-2-enoyl]-4,6-dimethylpyridin-2(1*H*)-ones (5a—d) and 3-[3-(alkylamino)but-2-enoyl]-4,6-dimethylpyridine-2(1*H*)-ones (5f,g) (general procedure). Azachromone **1** or **3** (1.0 mmol) was dissolved with heating in 5 mL of ethanol and the required amine (3 mmol) or ammonia (6 mmol) was added (ammonia and methylamine were added as 25—30% aqueous solutions). The resulting solution was allowed to stand at ~20 °C for 24 h and the resulting precipitate was filtered off, washed with aqueous ethanol (1 : 1), and dried. Compound **5a** was also obtained by refluxing a solution of β-diketone **18** (0.25 g, 0.96 mmol) in 5 mL of ethanol with 0.5 mL of 25% aqueous ammonia for 10 min using a similar procedure.

5,7-Dimethyl-2-morpholino(piperidino)-2-trifluoromethyl-8-azachroman-4-ones (8a,b) and 3-(4,4,4-trifluoro-3-pyrrolidin-1-ylbut-2-enoyl)-4,6-dimethylpyridin-2(1*H*)-one (5h) were prepared by a procedure described for AVK **5a**—**d**,**f**,**g** except that the reaction was carried out in THF and the mixture was concentrated to half its volume prior to the treatment with aqueous ethanol.

3-(3-Anilino-4,4,4-trifluorobut-2-enoyl)-4,6-dimethylpyridin-2(1*H*)-one (5e). A mixture of azachromone **1** (0.24 g, 1.0 mmol), aniline (0.30 g, 3.2 mmol), and Et_3N (3 drops) was kept at 75 °C for 20 h. After cooling, 3 mL of ethanol was added and the resulting precipitate was filtered off, recrystallized from toluene, and dried.

4,6-Dimethyl-3-(3-pyrrolidin-1-ylbut-2-enoyl)pyridin-2(1*H*)-one (5i). A solution of azachromone **3** (0.09 g, 0.48 mmol) and pyrrolidine (0.17 g, 2.4 mmol) in 1 mL of methanol was refluxed for 1 h and cooled, the precipitate was filtered off, washed with cold methanol, and dried.

7-(2-Hydroxy-3,5-dimethylphenyl)-5-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine (9a). A mixture of chromone **2** (0.24 g, 1.0 mmol) and EDA (0.27 g, 4.5 mmol) in 5 mL of EtOH was refluxed for 20 min or kept at ~20 °C for 24 h. The resulting solution was diluted with 10 mL of water and the orange-colored precipitate was filtered off, recrystallized from a toluene—hexane mixture (10 : 1), and dried. Dihydrodiazepine **9b** was prepared from chromone **7** in the same way as compound **9a**.

***N*^{1},*N*^{2}-Bis[5,7-dimethyl-2-(trifluoromethyl)-4*H*-chromen-4-ylidene]ethane-1,2-diamine (10).** Chromone **2** (0.24 g, 1.0 mmol) was dissolved in 3 mL of THF, and EDA (0.18 g, 3.0 mmol) was added. The resulting solution was allowed to stand at ~20 °C for 24 h and concentrated to dryness, the residue was dissolved in aqueous ethanol (1 : 1), and the solution was diluted with 0.5 mL of AcOH and cooled. The resulting crystals were filtered off, dried, and recrystallized from hexane.

4,6-Dimethyl-3-[2-(trifluoromethyl)imidazolidin-2-yl]acetylpyridin-2(1*H*)-one (12a). ***A.*** Azachromone **1** (0.24 g, 1.0 mmol) was dissolved in 2 mL of THF, and EDA (0.20 g, 3.3 mmol) was added. The solution was allowed to stand at ~20 °C for 24 h and the precipitate formed was filtered off, washed with THF, and dried. Under similar conditions but with trimethylenediamine instead of EDA, azachromone **1** decomposed to give 3-acetyl-4,6-dimethyl-2-pyridone.

B. A mixture of azachromone **1** (0.29 g, 1.2 mmol) and EDA (0.18 g, 3.0 mmol) in 5 mL of ethanol was refluxed for 15 min and cooled, and the precipitated crystals were filtered off, washed with aqueous ethanol (1 : 1), and dried.

4,6-Dimethyl-3-[2-(1,1,2,2-tetrafluoroethyl)imidazolidin-2-yl]acetylpyridin-2(1*H*)-one (12b) was prepared by procedure ***A*** from azachromone **11** similarly to imidazolidine **12a** except that compound **12b** was readily soluble in THF and, therefore, the crystals were isolated by concentrating the solution and washed with aqueous ethanol (1 : 1).

4,6-Dimethyl-3-[5-(polyfluoroalkyl)-2,3-dihydro-1*H*-1,4-diazepin-7-yl]pyridin-2(1*H*)-ones (13a,b). Azachromone **1** or **11** (1.0 mmol) was dissolved with heating in 3 mL of ethanol, and EDA (0.20 g, 3.3 mmol) and concentrated HCl (0.1 mL) were added. The solution was refluxed for 0.5 h, concentrated, and diluted with 5 mL of water. The precipitate formed was filtered off, dried, and recrystallized from a toluene—butanol mixture (3 : 1).

Dihydrodiazepine **13a** was also prepared by refluxing 0.3 mmol of imidazolidine **12a** in 1 mL of ethanol for 5 h.

5-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-7-trifluoromethyl-1,4,8-triazabicyclo[5.3.0]dec-4-ene (14a). Chromone **1** (0.24 g, 1.0 mmol) and diethylenetriamine (0.30 g, 2.9 mmol) were dissolved with heating in 3 mL of ethanol. The reaction mixture was allowed to stand for 24 h at ~20 °C, diluted with water, and concentrated. The precipitate was filtered off, washed with aqueous ethanol (1 : 1) and water, and dried.

Compound **14b** was prepared by a procedure reported previously.[4]

4,6-Dimethyl-3-[3(5)-(trifluoromethyl)pyrazole-5(3)-yl]pyridin-2(1*H*)-one (15). Chromone **1** (0.30 g, 1.23 mmol) was dissolved with heating in 5 mL of ethanol, and 0.5 mL of a 25% solution of hydrazine hydrate was added. The resulting mixture was allowed to stand for 2 h at ~20 °C and diluted with water. The precipitate was filtered off, washed with water, and dried.

Pyrazole **15** was also prepared by refluxing a solution of pyrazoline **17** (0.15 g, 0.55 mmol) in 1 mL of acetic acid in the presence of 3 drops of concentrated HCl for 5 h.

4,6-Dimethyl-3-[1-methyl-3-(trifluoromethyl)pyrazol-5-yl]pyridin-2(1*H*)-one (16a) and 4,6-dimethyl-3-[1-methyl-5-(trifluoromethyl)pyrazol-3-yl]pyridin-2(1*H*)-one (16b). A mixture of isomers **16a** and **16b** (3 : 2) was prepared from chromone **1** and methylhydrazine under conditions described for pyrazole **15** except that the reaction was carried out for 24 h.

3-[5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-3-yl]-4,6-dimethylpyridin-2(1*H*)-one (17). β-Diketone **18** (0.25 g, 0.96 mmol) was dissolved with gentle heating in a mixture of 4 mL of ethanol and 1 mL of dioxane, and 0.3 mL of a 25% solution of hydrazine hydrate was added. The solution was kept at ~20 °C for 2 h and cooled, and the crystals were filtered off and dried.

Ammonium 1-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-1-oxo-4,4,4-trifluorobut-2-ene-3-olate (19). β-Diketone **18**

(0.25 g, 0.96 mmol) was dissolved in 7 mL of ethanol, and 0.25 mL of 25% aqueous NH_3 was added. The solution was kept at ~20 °C for 0.5 h and cooled to give salt **19** as plate-like crystals. On heating, the salt decomposed into the initial components.

1-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-hydroxyamino-4,4,4-trifluorobut-2-ene-1-one (20), 4,6-dimethyl-3-[3-(trifluoromethyl)isoxazol-5-yl]pyridin-2(1*H*)-one (21), 3-[5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl]-4,6-dimethylpyridin-2(1*H*)-one (22), and 4,6-dimethyl-3-[5-(trifluoromethyl)isoxazol-3-yl]pyridin-2(1*H*)-one (23) were prepared by procedures reported previously.[8]

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32706) and, partially, by the US Civilian Research and Development Foundation (Grant REC-005).

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Received December 15, 2002;
in revised form May 12, 2003