Reactions of ethyl 5,6,7,8-tetrafluoro-2-methylchromone-3-carboxylate and 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin with S-nucleophiles

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The reactions of ethyl 5,6,7,8-tetrafluoro-2-methylchromone-3-carboxylate with mercaptoacetic acid and 1,2-ethanedithiol afforded C(7)-substitution products. The above-mentioned chromone reacted with 2-mercaptoethanol to yield 7-mono- or 5,7,8-trisubstituted products depending on the reaction conditions. The reaction of 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin with 2-mercaptoethanol afforded a 5,7,8-trisubstituted product. The acyl-lactone rearrangement of mono- and trisubstituted chromones yielded the corresponding coumarins.

Key words: chromones, coumarins, S-nucleophiles, substitution, acyl-lactone rearrangement.

Ethyl 5,6,7,8-tetrafluoro-2-methylchromone-3-carboxylate reacts with hydrazine and hydroxylamine with the pyran ring opening to form pyrazole and isoxazole derivatives, which are converted into benzopyranopyrazole and benzopyranoisoxazole, respectively, as a result of the acyl-lactone rearrangement.[1] The reactions of this chromone with ammonia and benzylamine are also accompanied by the opening of the heterocycle followed by intramolecular cyclization[1] to form 3-carboximidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarins. In the reactions of the latter with ammonia and morpholine, the replacement of the F atom at position 7 rather than the opening of the heterocycle is the preferential process.[2] Data on the reactivities of the above-mentioned coumarins and chromone with respect to S-nucleophiles are not documented.

In the present work, we studied the reactions of ethyl 5,6,7,8-tetrafluoro-2-methylchromone-3-carboxylate (**1**) (Scheme 1) and 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin (**7**) (Scheme 2) with 2-mercaptoethanol, mercaptoacetic acid, and 1,2-ethanedithiol.

Chromone **1** reacts with mercaptoacetic acid in DMSO in the presence of Et_3N to form a 7-carboxymethylthio derivative (**2**), which is a product of nucleophilic aromatic substitution of the F atom at position 7 (see Scheme 1, Tables 1 and 2). The reaction of chromone **1** with an equimolar amount of 1,2-ethanedithiol under analogous conditions gives 7,7′-ethylenedithiodi(ethyl 5,6,8-trifluoro-2-methylchromone-3-carboxylate) (**3**). An analogous product was prepared[3] by the reaction of ethyl 5,6,7,8-tetrafluorochromone-2-carboxylate with ethylenediamine in DMSO.

The reaction of chromone **1** with 2-mercaptoethanol in DMSO in the presence of a small excess of triethylamine at 18 °C for 2 min afforded 7-(2-hydroxyethylthio)chromone (**4**) (see Scheme 1, Tables 1 and 2).

The fact that the replacement in chromone occurred at position 7 was established based on the ^{19}F NMR spectra of products **2**—**4** (see Table 2), namely, on the analysis of the signal multiplicity and the values of the spin-spin coupling constants with account of the published data.[4]

It should be noted that the conversions under consideration occurred only in the presence of a basic catalyst

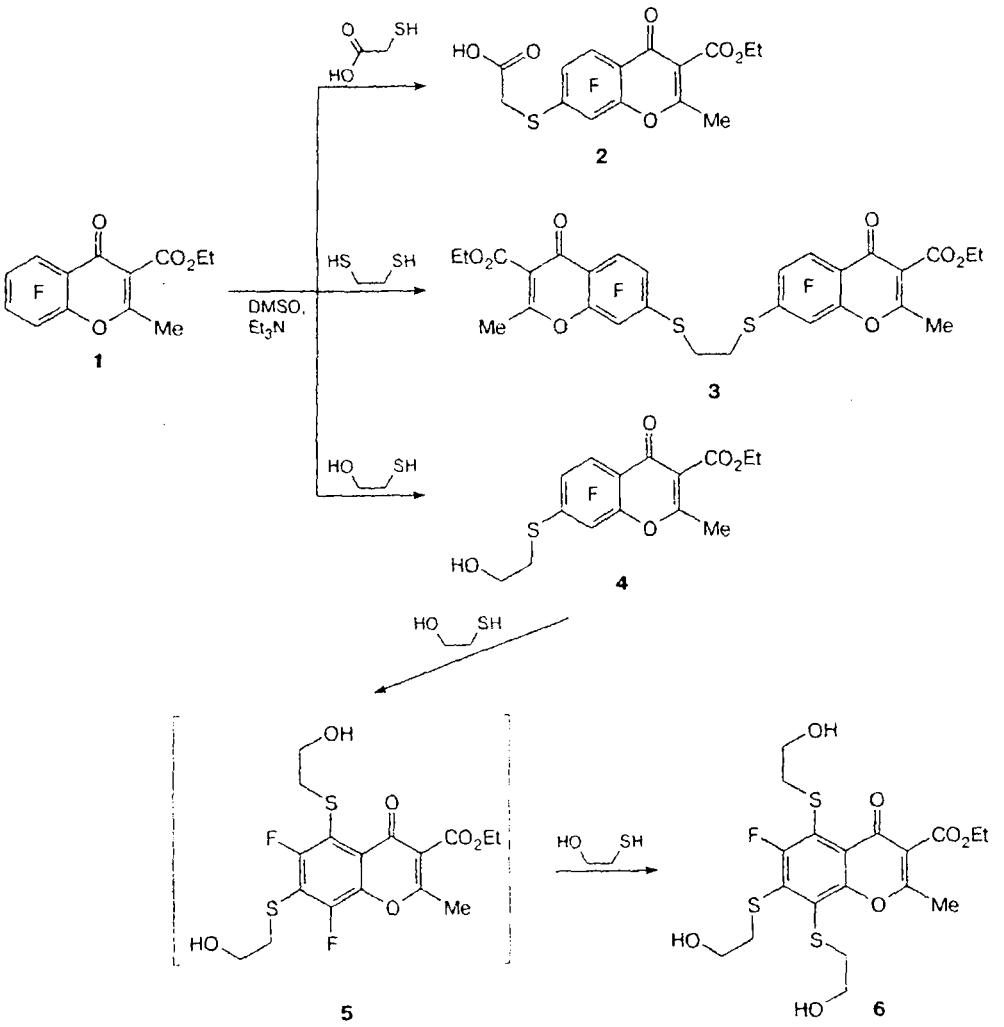
Table 1. Data of elemental analysis of compounds **2**—**4**, **6**, **8**—**10**, and **12**

Compound	Found / Calculated (%)				Molecular formula
	C	H	F	N	
2	48.04 / 47.88	2.83 / 2.95	15.01 / 15.15	—	$C_{15}H_{11}F_3O_6S$
3	50.74 / 50.76	3.06 / 3.04	17.17 / 17.21	—	$C_{28}H_{20}F_6O_8S_2$
4	49.73 / 49.73	3.71 / 3.62	15.74 / 15.73	—	$C_{15}H_{13}F_3O_5S$
6	47.90 / 47.69	4.76 / 4.84	3.84 / 3.97	—	$C_{19}H_{23}FO_7S_3$
8	45.05 / 45.42	4.63 / 4.48	3.97 / 4.23	2.85 / 3.11	$C_{17}H_{20}FNO_6S_3$
9	46.73 / 46.85	3.12 / 3.02	17.06 / 17.10	4.28 / 4.20	$C_{13}H_{10}F_3NO_4S$
10	46.74 / 46.71	2.89 / 2.71	17.16 / 17.05	—	$C_{13}H_9F_3O_5S$
12	50.41 / 50.60	3.26 / 3.34	17.26 / 17.15	—	$C_{14}H_{11}F_3O_4S$

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 8, pp. 1557—1561, August, 1999.

1066-5285/99/4808-1537 $22.00

Scheme 1



(triethylamine). Actually, heating of chromone **1** with a large excess of S-nucleophiles in DMSO at 80 °C for 10 h in the absence of a basic catalyst did not afford products **2**—**4**.

The reaction of chromone **1** with 2-mercaptoethanol over a more prolonged period yielded di- and trisubstituted products **5** and **6** (see Scheme 1). Disubstituted chromone **5** was not isolated in pure form. The formation of the latter is evidenced by the ^{19}F NMR spectrum of the reaction mixture. This spectrum has two doublet signals at δ −100.61 and −125.60 with J_{F-F} = 4 Hz, which correspond to the F atoms at the C(6) and C(8) atoms, respectively, of disubstituted chromone **5** (along with signals of the F atoms of products **4** and **6**). The value of the spin-spin coupling constant unambiguously

Scheme 2

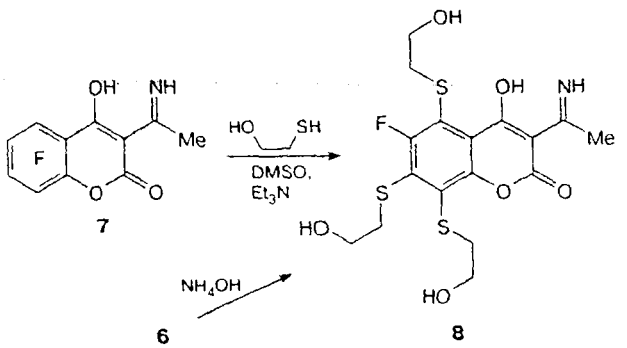


Table 2. Yields, physicochemical constants, and spectral characteristics of compounds **2**—**4**, **6**, **8**—**10**, and **12**

Compound	M.p. /°C	Yield (%)	IR, ν/cm^{-1}	NMR, δ (J/Hz)	
				^{1}H	^{19}F
2	161—163	53	3300—3000 (OH); 1720 (CO_2Et); 1670 (CO_2H); 1630 (C=O); 1550 (C=C); 990 (CF)	1.29 (t, 3 H, $OCH_2\underline{CH_3}$); 2.46 (s, 3 H, CH_3); 3.95 (s, 2 H, SCH_2); 4.31 (q, 2 H, $O\underline{CH_2}CH_3$); 13.0 (br.s, 1 H, COOH)	−146.18 (dd, 1 F, F-5); −136.07 (dd, 1 F, F-6); −130.13 (dd, 1 F, F-8, J_{5-6} = 22.0, J_{5-8} = 15.6)
3	204—206	76	1730 (CO_2Et); 1645 (C=O); 1560 (C=C); 990 (CF)	1.39 (t, 3 H, $OCH_2\underline{CH_3}$); 2.51 (s, 3 H, CH_3); 3.27 (s, 2 H, SCH_2); 4.31 (q, 2 H, $O\underline{CH_2}CH_3$)	−143.73 (dd, 1 F, F-5); −134.75 (dd, 1 F, F-6); −130.16 (dd, 1 F, F-8, J_{5-6} = 22.0, J_{5-8} = 16.6)
4	121—123	82	3510, 3450 (OH); 1720, 1710 (CO_2Et); 1640 (C=O); 1550 (C=C); 990 (CF)	1.29 (t, 3 H, $OCH_2\underline{CH_3}$); 2.46 (s, 3 H, CH_3); 3.18 (s, 2 H, SCH_2); 3.59 (m, 2 H, OCH_2); 4.31 (q, 2 H, $O\underline{CH_2}CH_3$); 4.96 (br.s, 1 H, OH)	−146.22 (dd, 1 F, F-5); −135.75 (dd, 1 F, F-6); −129.78 (dd, 1 F, F-8, J_{5-6} = 22.4, J_{5-8} = 15.5)
6	133—137	53	3500—3200 (OH); 1730 (CO_2Et); 1620 (C=O); 1540, 1500 (C=C); 990 (CF)	1.30 (t, 3 H, $OCH_2\underline{CH_3}$); 2.46 (s, 3 H, CH_3); 3.0—3.2 (m, 6 H, SCH_2); 3.5—3.62 (m, 6 H, OCH_2); 4.30 (q, 2 H, $O\underline{CH_2}CH_3$); 4.6 (br.s, 3 H, OH)	−107.9 (s, 1 F)
8*	1286—190	86[A], 71[B]	3500—3000 (OH, NH); 1680 (C=O); 1600, 1550, 1510 (C=S, C=N); 990 (CF)	2.55 (s, 3 H, CH_3); 3.03—3.16 (m, 6 H, SCH_2); 3.4—3.6 (m, 6 H, OCH_2); 4.4 (br.s, 3 H, CH_2OH); 9.98 (br.s, 1 H, NH); 11.6 (br.s, 3 H, OH)	−101.5 (s, 1 F)
9	184—191	76	3340, 3180 (NH, OH); 1680 (C=O); 1610, 1550 (C=S, C=N); 980 (CF)	2.55 (s, 3 H, CH_3); 3.12 (m, 2 H, SCH_2); 3.55 (m, 2 H, OCH_2); 4.93 (br.s, 1 H, CH_2OH); 10.15 (br.s, 1 H, NH); 11.74 (br.s, 3 H, OH)	−147.36 (dd, 1 F, F-5); −138.91 (dd, 1 F, F-6); −131.94 (dd, 1 F, F-8, J_{5-6} = 23.5, J_{5-8} = 15.0)
10*	135 (decomp.)	24[A], 86[B]	3300 (OH); 1730 (SOOH); 1630 (C=O); 1600, 1535 (C=C); 1010—990 (CF)	2.68 (s, 3 H, CH_3); 3.22 (m, 2 H, SCH_2); 3.61 (m, 2 H, OCH_2); 6.6 (br.s, 1 H, $CH_2O\underline{H}$)	−142.40 (dd, 1 F, F-5); −137.55 (dd, 1 F, F-6); −131.48 (dd, 1 F, F-8, J_{5-6} = 23.0, J_{5-8} = 15.0)
12*	87—90	67[A], 80[B]	1730 (SO_2Et); 1630 (C=O); 1600, 1535 (C=C); 1010—990 (CF)	2.03 (s, 3 H, CH_3CO); 2.40 (s, 3 H, CH_3); 3.28 (m, 2 H, SCH_2); 4.24 (m, 2 H, OCH_2); 6.1 (br.s, 1 H, $CH_2O\underline{H}$)	−143.73 (dd, 1 F, F-5); −134.75 (dd, 1 F, F-6); −130.16 (dd, 1 F, F-8, J_{5-6} = 22.0, J_{5-8} = 16.6)

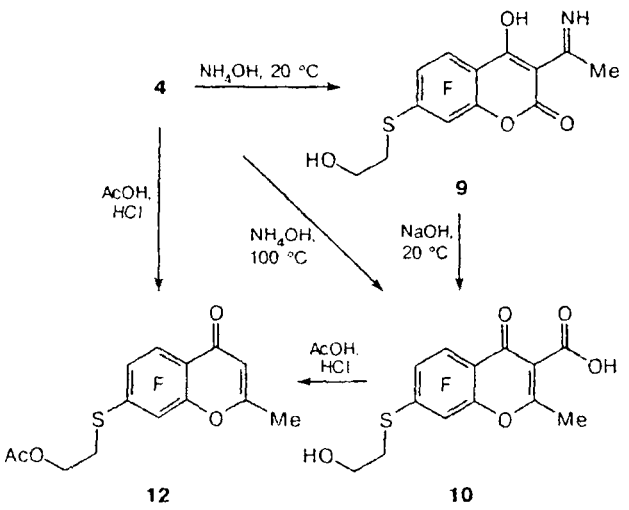
* The yields of compounds prepared according to procedures *A* and *B* are given.

indicates that the replacement of the second F atom by the 2-mercaptoethanol molecule occurs at position 5, which agrees well with the published data.[4] Evidently, compound **5** reacted with the third molecule of 2-mercaptoethanol to form trisubstituted derivative **6** rather than accumulating in the reaction mixture. Compound **6** was obtained in moderate yield as the only reaction product upon heating of chromone **1** with an excess of 2-mercaptoethanol and triethylamine for 3 h (see Tables 1 and 2).

Coumarin **7** reacted with 2-mercaptoethanol in DMSO in the presence of an excess of triethylamine at 80 °C (3 h) to form a 5,7,8-tris(2-hydroxyethylthio) derivative (**8**) (see Scheme 2, Tables 1 and 2). Compound **8** can also be synthesized by treating chromone **6** with aqueous ammonia, as a result of addition of ammonia at the C(2) atom leading to the pyran ring opening followed by intramolecular cyclization.

We failed to obtain 3-acetimidoyl-5,6,8-trifluoro-4-hydroxy-7-(2-hydroxyethylthio)coumarin (**9**) free from admixtures of the initial coumarin **7** and product **8** by treating compound **7** with 2-mercaptoethanol under conditions of the synthesis of monosubstituted derivatives **2**—**4** from chromone **1**, *i.e.*, using catalytic amounts of triethylamine. A convenient procedure for the synthesis of coumarin **9** involves the ring opening of monosubstitued chromone **4** under the action of NH_4OH and recyclization (Scheme 3, see Tables 1 and 2).

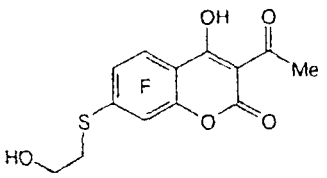
Scheme 3



Thus, we demonstrated that the acyl-lactone rearrangement is typical of mono- (**4**) and trisubstituted (**6**) chromones in a basic medium, as with the initial nonsubstituted chromone **1**.[1]

The replacement of the F atom by the 2-hydroxyethylthio group in coumarin **9** has a substantial effect on the chemical properties of the latter. Thus when treated with aqueous alkali, coumarin **9** was rearranged to chromonecarboxylic acid **10** (see Scheme 3, Tables 1 and 2). This rearrangement was not observed in the case of nonsubstituted coumarin 7.[2] Previously,[1] it has been demonstrated that the reaction of 5,6,7,8-tetrafluoro-2-methylchromone-3-carboxylic acid with NH_4OH was accompanied by the pyran ring opening and decarboxylation. Under these conditions, acid **10** is stable.

The IR and NMR spectral data do not rule out an alternative structure, *viz.*, 3-acetylcoumarin **11**.



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The structure of compound **10** was proved by chemical conversions. Thus alkaline hydrolysis of ester **4** afforded acid **10**. In addition, when treated with a mixture of acetic and hydrochloric acids, both acid **10** and its ester **4** gave the same product **12** as a result of decarboxylation and acetylation (see Scheme 3, Tables 1 and 2). Compound **12** cannot be obtained from coumarin **11**. All the above experimental data unambiguously confirm the chromone structure of heterocycle **10**.

Thus, it can be concluded that the reactions of chromone **1** with S-nucleophiles afforded products of replacement of the F atoms rather than resulting in the opening of the labile heterocycle, which was observed in the reactions of compound **1** with N-nucleophiles.[1] It is known[5,6] that the reactions of derivatives of fluoroquinoline-3-carboxylic acids with S-nucleophiles, which are the best studied reactions of this type, occur regioselectively to form 7-substituted quinolones. The reactions of 6,7-difluoro- and 6,7,8-trifluoroquinolones with 2-mercaptoethanol and *o*-aminothiophenol also afforded exclusively monosubstituted products.[7–9] The replacement of the F atoms at positions 5 and 8 occurs[10–12] if derivatives of 6,8-di- and 5,6,8-trifluoroquinolonic acids contain substituents at the C(7) atom.

The formation of trisubstituted products in reactions of fluorinated chromone and coumarin derivatives with nucleophiles was observed for the first time. We even failed to isolate monosubstituted product **9** in the reaction of coumarin **7** with 2-mercaptoethanol. This activating effect of the alkylthio group on the replacement of F atoms, which is comparable with that of strong electron-withdrawing groups (CF_3 and NO_2),[13,14] is attributable to high polarizabilty of the S—ArF bond, which is not characteristic of X—ArF bonds with other electron-donor substituents (X = OAlk, OH, NH_2, Me, *etc.*). The polarization of the S—ArF bond in DMSO is sufficient to induce additional polarization of the C—F bond.

Experimental

The IR spectra were recorded on a Specord IR-75 spectrometer in the 400–4000 cm^{-1} region (as Nujol mulls). The ^1H NMR (80 MHz, relative to Me_4Si) and ^{19}F NMR (75 MHz, relative to C_6F_6) spectra were measured on a Tesla BS-587 A spectrometer in DMSO-d_6. Elemental analysis was carried out on a Carlo Erba CHNS-O EA 1108 elemental analyzer.

Compounds **1** [15] and **7** [1] were prepared according to known procedures.

Ethyl 7-carboxymethylthio-5,6,8-trifluoro-2-methylchromone-3-carboxylate (2). Mercaptoacetic acid (3.8 g, 41.3 mmol) and triethylamine (0.3 mL) were added to a solution of chromone **1** (2 g, 6.58 mmol) in DMSO (30 mL). The reaction mixture was kept at 18 °C for 20 min and then poured into a mixture of water (150 mL) and concentrated HCl (10 mL). The precipitate that formed was filtered off, washed with water, and recrystallized from toluene. Product **2** was obtained in a yield of 1.3 g (see Tables 1 and 2).

7,7'-Ethylenedithiodi(ethyl 5,6,8-trifluoro-2-methylchromone-3-carboxylate) (3). Ethanedithiol (0.5 g, 5.32 mmol) and triethylamine (0.3 mL) were added to a solution of chromone **1** (3 g, 9.87 mmol) in DMSO (60 mL). The reaction mixture was kept for 10 min. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from CCl_4. Compound **3** was obtained in a yield of 2.5 g (see Tables 1 and 2).

Ethyl 7-(2-hydroxyethylthio)-5,6,8-trifluoro-2-methylchromone-3-carboxylate (4). 2-Mercaptoethanol (3.8 g, 48.7 mmol) was added to a solution of chromone **1** (3.8 g, 12.5 mmol) in DMSO (70 mL). The reaction mixture was cooled to 20 °C. Then triethylamine (2 mL) was added and the reaction mixture was kept for 2 min and poured into a mixture of concentrated HCl (70 mL) and water (130 mL). The precip-

itate that formed was filtered off, dried, and recrystallized from CCl_4. Product **4** was obtained in a yield of 3.7 g (see Tables 1 and 2).

Ethyl 6-fluoro-5,7,8-tris(2-hydroxyethylthio)-2-methylchromone-3-carboxylate (6). 2-Mercaptoethanol (16 g, 205 mmol) and triethylamine (16 mL) were added to a solution of chromone **1** (8.4 g, 27.6 mmol) in DMSO (150 mL). The reaction mixture was heated at 80 °C for 3 h, cooled, and poured into a mixture of concentrated HCl (50 mL) and water (300 mL). The precipitate that formed was filtered off, dried, and recrystallized from acetonitrile. Product **6** was obtained in a yield of 7.0 g (see Tables 1 and 2).

3-Acetimidoyl-6-fluoro-4-hydroxy-5,7,8-tris(2-hydroxyethylthio)coumarin (8). ***Method A.*** 2-Mercaptoethanol (18 g, 231 mmol) and triethylamine (18 mL) were added to a solution of coumarin **7** (5.7 g, 20.7 mmol) in DMSO (80 mL). The reaction mixture was heated at 80 °C for 3 h, cooled, and poured into a mixture of concentrated HCl (50 mL) and water (200 mL). The solution was kept at 20 °C for 24 h. The precipitate that formed was filtered off, dried, and recrystallized from acetonitrile. Product **8** was obtained in a yield of 8.0 g (see Tables 1 and 2).

Method B. A solution of chromone **6** (0.45 g, 0.94 mmol) in 25% aqueous ammonia (30 mL) was stirred at 18 °C for 48 h. The precipitate that formed was filtered off and dried. Compound **8** was obtained in a yield of 0.3 g (see Tables 1 and 2).

3-Acetimidoyl-5,6,8-trifluoro-4-hydroxy-7-(2-hydroxyethylthio)coumarin (9). A solution of chromone **4** (10 g, 27.6 mmol) in 25% aqueous ammonia (200 mL) was stirred at 20 °C for 48 h. The precipitate that formed was filtered off and dried. Product **9** was obtained in a yield of 7.0 g (see Tables 1 and 2).

7-(2-Hydroxyethylthio)-5,6,8-trifluoro-2-methylchromone-3-carboxylic acid (10). ***Method A.*** A solution of chromone **4** (0.45 g, 1.24 mmol) in 25% aqueous ammonia (40 mL) was refluxed for 2 h and acidified with concentrated HCl to pH 1—2. The precipitate that formed was filtered off, dried, and recrystallized successively from heptane and CCl_4. Product **10** was obtained in a yield of 0.1 g (see Tables 1 and 2).

Method B. A solution of coumarin **9** (6 g, 18 mmol) and NaOH (7 g, 175 mmol) in water (200 mL) was stirred at 20 °C for 2 h and acidified with concentrated HCl to pH 2—3. The precipitate that formed was filtered off, washed with water, and recrystallized from CCl_4. Compound **10** was obtained in a yield of 2.5 g (see Tables 1 and 2).

7-(2-Acetoxyethylthio)-5,6,7-trifluoro-2-methylchromone (12). ***Method A.*** A solution of compound **4** (0.65 g, 1.79 mmol) in a mixture of acetic acid (15 mL) and HCl (3 mL) was refluxed for 15 h and poured into water. The precipitate that formed was filtered off, washed with water, dried, dissolved in heptane (10 mL), and filtered from insoluble admixtures. Then the solvent was removed. Compound **12** was obtained in a yield of 0.4 g (see Tables 1 and 2).

Method B. Compound **12** was prepared as described above from acid **10** (0.40 g, 1.2 mmol) in a yield of 0.28 g (see Tables 1 and 2).

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Received December 25, 1998;
in revised form March 10, 1999