# Regioselective Synthesis of Novel Perfluoroalkylated Fused Pyridines and 3-(Aminomethylene)thiochroman-4-ones from 3-(Perfluoroalkanoyl)thiochromenones and Amines

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*Received 3 September 2009; revised 26 October 2009*

Dedicated to Dr. Holger Feist on the occasion of his 50th birthday

**Abstract:** The regioselectivity of reactions of 3-(perfluoroacyl)-4*H*-thiochromen-4-ones with a range of hetaryl, aryl, and alkyl amines was examined. The reactions provide ready access to polyfluoroalkylated fused pyridines and thiochromen-4-ones.

**Key words:** heterocycles, amines, fused-ring systems, thiochromenones, perfluoroalkyl compounds

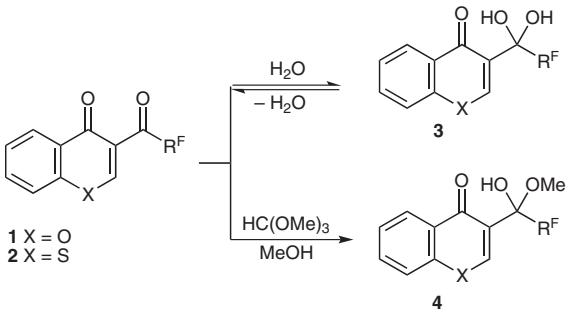
4*H*-1-Benzopyran-4-ones (chromenones) are one of the most widely distributed classes of natural compounds found in the plant kingdom.[1] Many natural and synthetic chromenone derivatives exhibit various biological activities and find use as substrates in the preparation of a variety of rearranged products and new heterocyclic systems.[1,2] Furthermore, the presence of fluorine atoms in biologically active molecules can enhance their lipophilicity and thus their in vivo uptake and transport. In particular, the trifluoromethyl group, in addition to its high electronegativity, confers increased stability and lipophilicity.[3]

Whereas the chemical properties of perfluoroalkylated chromenones have been extensively studied,[4] little attention has been paid to the synthesis and reactivity of perfluoroalkylated thiochromenones.[5] In a continuation of our studies on the synthesis and chemical properties of 3-(polyfluoroacyl)chromenones **1**, which turned out to be highly reactive toward mono- and dinucleophiles,[6] we now report the results of our studies on the reactivity of their thio analogues, the 3-(polyfluoroacyl)thiochromenones **2**. We recently reported a simple and convenient method for the synthesis of these compounds through a halogenation–dehydrohalogenation sequence, starting from commercially available thiochroman-4-one and ethyl polyfluoroalkanoates.[7] We regarded the thiochromenones **2** as desirable targets because of their relationship to naturally occurring benzopyran derivatives and their usefulness as perfluoroalkylated building blocks for the preparation of more complex partially fluorinated heterocycles and other highly functionalized biologically and medicinally important products. However, after a detailed study of the chemical behavior of **2** with various mononucleophiles and 1,3-dinucleophiles, we found that these compounds are less reactive than the corresponding 3-(perfluoroalkanoyl)chromenones **1**. Nevertheless, they react with amidines and guanidines salts to afford 5-(2-sulfanylbenzoyl)-4-(polyfluoroalkyl)pyrimidines in good yields.[8]

Here, we report on the reactions of thiochromenones **2** with some mononucleophiles, and on their applications in pyridine ring annulation with electron-rich heterocyclic amines. We recently prepared a wide range of fluorinated fused pyridines by the reaction of 3-(perfluoroalkanoyl)chromenones **1** with heterocyclic amines and, although four competitive routes were observed, the reaction pathways could be controlled with respect to the prevalent pyridine derivatives.[9] As an extension of this result, and in view of the unique biological properties displayed by many fluorinated compounds,[3] we decided to investigate whether this reaction could be applied to 3-(perfluoroalkanoyl)thiochromenones **2**.

Note that 3-(polyfluoroacyl)chromenones **1**, especially 3-(trifluoroacetyl)-4*H*-chromen-4-one, react readily with water to form stable covalent hydrates (*gem*-diols), and with alkyl orthoformates to give the corresponding hemiketals.[6a] The thio analogues **2a** ($R^F = CF_3$) and **2b** ($R^F = CF_2CF_3$), prepared by treating the corresponding 3-(perfluoroalkanoyl)-2*H*-thiochromen-4-ols with sulfuryl chloride,[7] showed analogous behavior, and they exist as a mixture of the nonhydrate form **2** and the hydrate form **3**. (In the case of **2a** in $CDCl_3$ and DMSO-$d_6$, these are

**SYNTHESIS** 2010, No. 4, pp 0671–0677
Advanced online publication: 07.12.2009
DOI: 10.1055/s-0029-1218586; Art ID: P12209SS




**Scheme 1** Reactions of chromenones **1** and thiochromenones **2** with water and methanol

present in a 3:2 ratio.) As expected, the reaction of thiochromenone **2a** with methyl orthoformate in methanol containing concentrated hydrochloric acid resulted in the formation of hemiketal **4** (X = S; $R^F = CF_3$) in a 95% yield (Scheme 1).

On extending our studies to the reaction of thiochromenones **2** with 1,3-dinucleophiles, such as electron-rich heterocyclic amines **5** (Figure 1), we found that **2a** and **2b** reacted with **5a–e** in *N*,*N*-dimethylformamide solution at 110 °C for 54–84 hours, as reported previously for the 3-(perfluoroalkanoyl)chromenones **1**.[9]

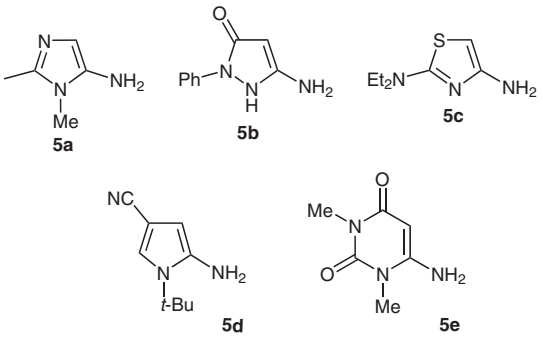
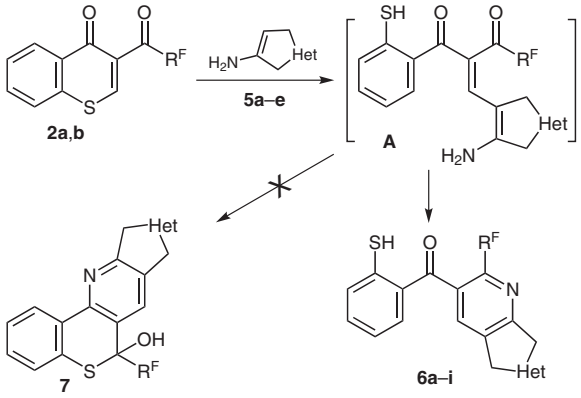



**Figure 1** Structures of the aminoheterocycles **5**

In contrast to the case of **1**, the reaction of **2** with hetarylamines **5** proceeded under harsher conditions and appeared to be more regioselective, giving the set of diverse heteroannulated pyridines **6a–i**, bearing the perfluoroalkyl substituent at the α-position of the pyridine core, as the sole isolated products in 60–92% yields (Scheme 2, Table 1).

The first step of the reaction leading to **6** (Scheme 2) apparently involves an attack at the C-2 atom of **2** by the internal β-carbon of the enamine (in general, this atom is more nucleophilic than the primary amino group), with opening of the thiopyrone ring (1,4-addition; intermediate **A**). Finally, intramolecular attack by the amino group at the polyfluoroacyl group leads to fused pyridines **6**. The alternative cyclization of **A**, involving the amino group and the carbonyl carbon atom connected to the benzene ring, does not occur, and no formation of the corresponding 5*H*-thiochromeno[4,3-*b*]pyridin-5-ols **7** was detected. The reaction of 3-(polyfluoroacyl)thiochromenones **2**




**Scheme 2** Possible route for the formation of pyridines **6**

**Table 1** Isolated Yields of Heteroannulated Pyridines **6a–i**

| Thiochromenone **2** | $R^F$ | Heterocycle **5** | Product **6** | Yield (%) |
|---|---|---|---|---|
| **2a** | $CF_3$ | **5a** | **6a** | 60 |
| **2b** | $C_2F_5$ | **5a** | **6b** | 64 |
| **2a** | $CF_3$ | **5b** | **6c** | 75 |
| **2b** | $CF_2CF_3$ | **5b** | **6d** | 78 |
| **2a** | $CF_3$ | **5c** | **6e** | 92 |
| **2a** | $CF_3$ | **5d** | **6f** | 58 |
| **2b** | $CF_2CF_3$ | **5d** | **6g** | 63 |
| **2a** | $CF_3$ | **5e** | **6h** | 80 |
| **2b** | $CF_2CF_3$ | **5e** | **6i** | 82 |

with heterocyclic amines makes this class of compounds very useful for the synthesis of novel polyfluoroalkylated fused pyridines with potential biological activity.

The structures of the compounds **6** were deduced by elemental analysis; by $^1H$, $^{19}F$, and $^{13}C$ NMR spectroscopy; and by mass spectrometry. In the $^1H$ NMR spectra of **6**, a singlet corresponding to the pyridine proton appeared at δ = 7.9–8.8 ppm. In addition, all the protons of the benzene ring were shifted to a higher field, showing that opening of the thiopyrone ring took place under the action of **5**. This is in accordance with data for the salicyloyl analogues of compounds **6**, which we have described previously.[6b,9]

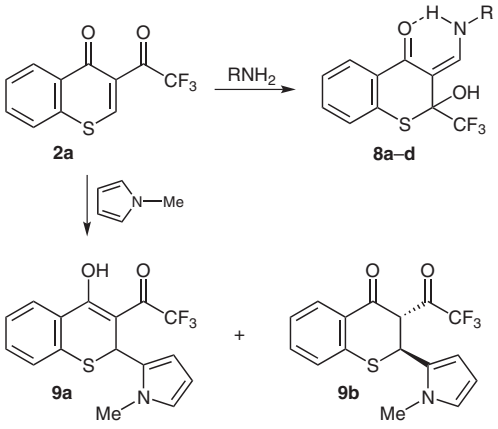
We also found that the reaction of thiochromenone **2a** with primary aromatic and aliphatic amines in refluxing benzene for five hours afforded 3-(substituted aminomethylene)-2-hydroxy-2-(trifluoromethyl)thiochromen-4-ones **8a–d** in good-to-excellent yields (Table 2). Note that only aromatic amines with electron-donating groups can be used; naphthalen-2-amine failed to react with **2a** under a range of conditions. The reaction involves the nucleophilic 1,4-addition of the amine with concomitant opening of the thiopyrone ring and subsequent intramolecular cyclization of the intermediate at the trifluoroacetyl group. The driving force for the process is the stabilization of the

enaminones **8** by a hydrogen bond between the thiopyranone carbonyl oxygen and the hydrogen of the NH group (Scheme 3). This finding is in line with some results reported for 3-(polyfluoroacyl)chromenones **1**, which react with primary aliphatic and aromatic amines under milder reaction conditions (methanol, ~20 °C) to give 3-(substituted aminomethylene)-2-hydroxy-2-(trifluoromethyl)chromen-4-ones.[6a]

**Table 2** Isolated Yields of Thiochromenones **8a–d**, **9a**, and **9b**

| R | Thiochromenone | Yield (%) |
|---|---|---|
| 4-$MeC_6H_4$ | **8a** | 91 |
| 4-$MeOC_6H_4$ | **8b** | 88 |
| Bn | **8c** | 98 |
| $PhCH_2CH_2$ | **8d** | 57 |
| –[a] | **9a + 9b** | 61 |

[a] The reactant was *N*-methylpyrrole.




**Scheme 3** Reactions of thiochromenone **2a** with primary amines or *N*-methylpyrrole

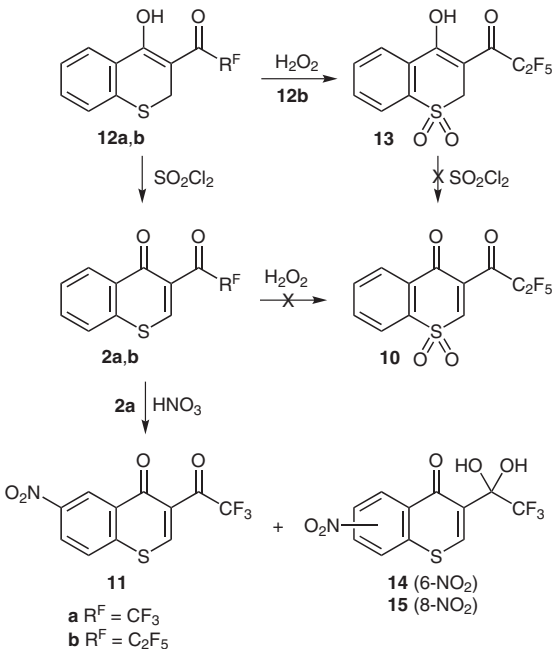
The structures of products **8a–d** were determined by comparison of their spectra with those reported for related compounds.[6a] The IR spectra of **8a–d** showed absorption bands associated with OH and NH groups of the aminoenone fragment in the ranges 3350–3200 and 1636–1587 $cm^{-1}$, respectively. A characteristic spectral feature of the $^1H$ NMR spectrum **8** is a chemical shift of the NH proton in the range δ = 11.2–12.8 ppm with a coupling constant with the olefinic proton of $^3J$ = 12.9–13.3 Hz. The doublet of the olefinic proton was observed at δ = 8.1 ppm for **8a** and **8b**, and at 7.6–7.8 ppm for **8c** and **8d**. In the $^{13}C$ NMR spectra, a signal for the carbon atom adjacent to the trifluoromethyl substituent appeared at about δ = 81.6 ppm as a distinctive quartet ($^2J_{C,F}$ = 32.3 Hz). This confirmed that the trifluoromethyl group is bonded to the $sp^3$-hybridized carbon atom. The chemical shift of the trifluoromethyl group was observed at δ = –83 ppm, and a quartet for the carbon atom was observed at δ = 125 ppm ($^1J_{C,F}$ = 285 Hz).

A somewhat unexpected result was obtained from the reaction of thiochromenone **2a** with *N*-methylpyrrole. In this case, the reaction proceeded without cleavage of the thiopyrone ring to give a 9:1 mixture of the methylpyrrolyl derivatives **9a** and **9b** in 61% yield; in other words, the major tautomer had the enolic structure (Scheme 3). Note that the starting compound **2a** was unaffected when it was heated with an excess of indole at 90 °C for 10 h. In the $^1H$ NMR spectrum, the H-2 and H-3 protons of **9b** appeared at δ = 5.63–5.73 ppm as an AB-system with a vicinal coupling constant $^3J_{H2,H3}$ = 13.0 Hz, which indicates an axial arrangement for the H-2 and H-3 atoms. Tautomer **9b** is therefore in the half-chair conformation with a *trans*-diequatorial arrangement of the substituents. Note that the reaction between 3-(perfluoroalkanoyl)chromenones and *N*-methylpyrrole resulted in the formation of the rearranged products, the 2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)-2-(polyfluoroalkyl)chromen-4-ones.[10]

All our attempts to obtain perfluoroalkylated heterocycles from thiochromenone **2a** and 1,2-dinucleophiles, such as hydroxylamine, hydrazine, or methylhydrazine, under the same conditions that had previously been used for the corresponding reactions of 3-(polyfluoroacyl)chromenones **1**[6c,11] failed to give useful results. This appears to be connected with the difficulty met by the nucleophile in cleaving the thiopyrone S–C bond. Also, in contrast with the 3-(perfluoroalkanoyl)chromenones **1**,[6d] thiochromenone **2a** did not react with enol ethers (ethyl vinyl ether, 2,3-dihydrofuran, or 3,4-dihydro-2*H*-pyran). In all cases, the starting material was recovered with a small amount of the desired adduct. The failure of the hetero-Diels–Alder reaction probably arises from the less electronegative character of the sulfur atom, which strongly reduces the electrophilicity of the C-2 atom as compared with chromenones.

It is known that the introduction of a nitro group at the 6-position of chromenones or the transformation of thiochromenones into thiochromenone 1,1-dioxides can increase the electrophilicity of the C-2 atom.[12,13] Bearing these facts in mind, we decided to prepare 3-(perfluoropropanoyl)thiochromenone 1,1-dioxide (**10**) and 6-nitro-3-(trifluoroacetyl)thiochromenone (**11**) as potentially more reactive substrates. Attempts to synthesize **10** by direct oxidation of **2** with hydrogen peroxide failed. Thiochromenol **12b**[7] was oxidized by treatment with hydrogen peroxide in glacial acetic acid to give the expected thiochromenol 1,1-dioxide **13** in 32% yield; however, all our attempts to obtain **10** by a chlorination–dehydrochlorination sequence from **13** were fruitless, and only complex reaction mixtures were obtained. We also found that nitration of **2a** with a 1:1 mixture of concentrated sulfuric acid and 98% nitric acid at 90 °C for 1 h afforded a mixture of the products **11**, **14**, and **15** in a ratio of 72:23:5 in only 18% yield (Scheme 4).

In conclusion, we have developed an easy and regioselective one-step synthesis of novel perfluoroalkylated fused pyridines starting from readily obtainable 3-(polyfluoroacyl)thiochromenones and heterocyclic amines. Because




**Scheme 4** Possible routes for the activation of thiochromenones **2**

of the presence of the 2-sulfanylbenzoyl moiety, these compounds are of considerable interest as reactive precursors for the synthesis of other useful organic materials containing polyfluoroalkyl groups.

NMR spectra were recorded on Jeol JNM-LA 400, Bruker DRX-400, Varian VXR-300, or Varian Mercury-400 spectrometers: $^1$H signals (300 or 400 MHz) and $^{13}$C-signals (100 MHz) were recorded with TMS as an internal standard; $^{19}$F signals (282 or 376 MHz) were recorded with $CFCl_3$ as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument as KBr disks. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Mass spectra were recorded on a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) with a GC inlet, or on an MX-1321 instrument (EI, 70 eV) with a direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Merck $60F_{254}$ silica gel plates were used for TLC. Melting points are uncorrected. All the solvents used were dried and distilled according to standard procedures. Satisfactory microanalyses were obtained: C ± 0.35; H ± 0.25; N ± 0.25.

**3-(Trifluoroacetyl)-4*H*-thiochromen-4-one (2a)**

Freshly distilled $SO_2Cl_2$ (3.6 g, 26.7 mmol) was added carefully to a well-stirred soln of 2,2,2-trifluoro-1-(4-hydroxy-2*H*-thiochromen-3-yl)ethanone[7] (5.7 g, 21.9 mmol) in $CHCl_3$ (200 mL), and the mixture was stirred at r.t. for 24 h. The resulting yellow soln was evaporated under reduced pressure to give a yellow solid that was purified by recrystallization (heptane) as pale yellow needles. Yield: 5.3 g (94%); mp 126–127 °C.

IR (KBr): 3243, 3029, 1705, 1633, 1600, 1588, 1557, 1510 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ (nonhydrate **2a**, 60%) = 7.62–7.75 (m, 3 H, H-6, H-7, H-8), 8.57–8.62 (m, 1 H, H-5), 8.68 (s, 1 H, H-2); δ (hydrate **3**, 40%) = 6.66 (br s, 2 H, 2 OH), 7.62–7.75 (m, 3 H, H-6, H-7, H-8), 8.57–8.62 (m, 1 H, H-5), 8.65 (s, 1 H, H-2).

$^1$H NMR (DMSO-$d_6$): δ (nonhydrate **2a**, 59%) = 7.71 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1 H, H-6), 7.81 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1 H, H-7), 7.91 (d, *J* = 8.1 Hz, 1 H, H-8), 8.44 (dd, *J* = 8.1, 1.4 Hz, 1 H, H-5), 9.20 (s, 1 H, H-2); δ (hydrate **3**, 41%) = 7.69 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1 H, H-6), 7.80 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1 H, H-7), 7.91 (d, *J* = 8.1 Hz, 1 H, H-8), 8.37 (s, 2 H, 2 OH), 8.51 (dd, *J* = 8.1, 1.4 Hz, 1 H, H-5), 8.90 (s, 1 H, H-2).

$^{13}$C NMR ($CDCl_3$): δ (nonhydrate **2a**) = 115.9 (q, $^1J_{C,F}$ = 289.7 Hz, $CF_3$), 126.9, 129.2, 129.4, 129.5, 132.7, 132.9, 135.0, 148.4 (C-2), 176.4 (C-4), 181.8 (q, $^2J_{C,F}$ = 38.5 Hz, C = O); δ (hydrate **3**) = 94.4 (q, $^2J_{C,F}$ = 33.9 Hz, *C*–$CF_3$), 122.9 (q, $^1J_{C,F}$ = 289.4 Hz, $CF_3$), 126.7, 127.4, 128.7, 129.1, 131.3, 132.4, 137.0, 143.6 (C-2), 180.7 (C-4).

$^{19}$F NMR ($CDCl_3$): δ (nonhydrate **2a**) = –74.50 (s, $CF_3$); (hydrate **3**) δ = –86.6 (s, $CF_3$).

Anal. Calcd for $C_{11}H_5F_3O_2S{\cdot}0.25H_2O$: C, 50.38; H, 2.11. Found: C, 50.29; H, 1.71.

**3-(2,2,2-Trifluoro-1-hydroxy-1-methoxyethyl)-4*H*-thiochromen-4-one (4)**

Concd aq HCl (0.3 mL) was added dropwise to a refluxing soln of thiochromenone **2a** (300 mg, 1.16 mmol) and $HC(OMe)_3$ (2.0 g, 18.9 mmol) in MeOH (8 mL). After the initial exothermic reaction had subsided, the mixture was allowed to stand at r.t. for 24 h. The solid that formed was filtered and washed with PE. Product **4** was isolated without recrystallization as analytically pure colorless crystals. Yield: 320 mg (95%); mp 139–140 °C.

IR (KBr): 1588, 1489 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 3.33 (s, 3 H, MeO), 7.67 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1 H, H-6), 7.77 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1 H, H-7), 7.84 (dd, *J* = 8.1, 1.0 Hz, 1 H, H-8), 8.53 (dd, *J* = 8.1, 1.4 Hz, 1 H, H-5), 8.74 (s, 1 H, H-2), 9.43 (s, 1 H, OH).

$^{19}$F NMR (DMSO-$d_6$): δ = –84.6 (s, $CF_3$).

**Compounds 6a–i; General Procedure**

A conical flask was charged with thiochromenone **2** (1 mmol), the appropriate aminoheterocycle **6** (1 mmol), and DMF (10 mL). In the case of dinucleophile hydrochlorides, NaOAc (1 mmol) was also added. The flask was fitted with a reflux condenser and the contents were heated for 54–84 h. The solvent was removed in vacuo and the product was purified by flash chromatography (silica gel) or recrystallization. The yields refer to the amounts of isolated products.

**2,3-Dimethyl-6-(2-sulfanylbenzoyl)-5-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (6a)**

Reaction conditions: DMF, 110 °C, 84 h.

Reddish solid; yield: 192 mg (60%); mp 164–167 °C; $R_f$ = 0.24 ($Et_2O$–MeOH, 5:2).

$^1$H NMR (DMSO-$d_6$): δ = 2.69 (s, 3 H), 3.85 (s, 3 H), 7.32 (t, $^3J$ = 7.7 Hz, 1 H), 7.51 (d, $^3J$ = 8.0 Hz, 1 H), 7.67 (t, $^3J$ = 7.7 Hz, 1 H), 7.86 (d, $^3J$ = 8.1 Hz, 1 H), 8.34 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 13.9, 28.5, 121.8 (q, $^1J_{C,F}$ = 275 Hz), 125.8, 125.9, 126.0, 126.1, 127.9 (q, $J_{C,F}$ = 1.2 Hz), 134.0, 134.3 (q, $J_{C,F}$ = 1 Hz), 135.6, 135.8 (q, $^2J_{C,F}$ = 34 Hz), 139.9, 147.9 (q, $J_{C,F}$ = 0.8 Hz), 159.6, 194.2.

$^{19}$F NMR (DMSO-$d_6$): δ = –59.4 (s, $CF_3$).

MS (EI, 70 eV): *m/z* (%) = 351 (22) $[M]^+$, 350 (78) $[M - 1]^+$, 336 (24), 283 (100) $[M + 1 - CF_3]^+$, 266 (15) $[M - 1 - CF_3 - CH_3]^+$, 136 (15) $[SC_6H_4CO]^+$, 109 (16) $[HSC_6H_4]^+$, 95 (22).

**2,3-Dimethyl-5-(pentafluoroethyl)-6-(2-sulfanylbenzoyl)-3*H*-imidazo[4,5-*b*]pyridine (6b)**

Reaction conditions: DMF, 110 °C, 48 h.

Light red-grey solid; yield: 234 mg (64%); mp 131–133 °C; $R_f$ = 0.18 (PE–$Et_2O$, 1:1).

$^1$H NMR (DMSO-$d_6$): δ = 2.70 (s, 3 H), 3.85 (s, 3 H), 7.38 (t, $^3J$ = 7.6 Hz, 1 H), 7.54 (d, $^3J$ = 8.0 Hz, 1 H), 7.61 (t, $^3J$ = 7.6 Hz, 1 H), 7.91 (d, $^3J$ = 8.0 Hz, 1 H), 8.48 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 13.9, 28.5, 115.8 (tq, $^1J_{C,F}$ = 259 Hz, $^2J_{C,F}$ = 38 Hz), 117.0 (qt, $^1J_{C,F}$ = 287 Hz, $^2J_{C,F}$ = 38 Hz), 125.8, 126.9, 127.0, 127.3 (q, $J_{C,F}$ = 0.9 Hz), 134.1 (q, $J_{C,F}$ = 1.1 Hz), 134.4, 136.3 (q, $J_{C,F}$ = 0.8 Hz), 137.4, 139.0, 139.4 (t, $^2J_{C,F}$ = 28 Hz), 141.4, 149.7, 193.3.

MS (EI, 70 eV): *m/z* (%) = 401 (8) $[M]^+$, 385 (14) $[M - 1 - CH_3]^+$, 283 (100) $[M + 1 - C_2F_5]^+$, 265 (16) $[M - 2 - C_2F_5 - CH_3]^+$, 256 (33), 136 (27) $[SC_6H_4CO]^+$, 109 (19) $[HSC_6H_4]^+$, 95 (14), 73 (19).

**2-Phenyl-5-(2-sulfanylbenzoyl)-6-(trifluoromethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (6c)**
Reaction conditions: DMF, 110 °C, 54 h.

Pink solid; yield: 282 mg (75%); mp 179–182 °C; $R_f$ = 0.75 ($Et_2O$).

$^1$H NMR ($CDCl_3$): δ = 7.34 (t, $^3J$ = 7.8 Hz, 1 H), 7.37 (d, $^3J$ = 7.2 Hz, 1 H), 7.56 (dd, $^3J$ = 8.4, 7.2 Hz, 2 H), 7.68 (t, $^3J$ = 7.8 Hz, 1 H), 7.72 (d, $^3J$ = 7.8 Hz, 1 H), 7.88 (d, $^3J$ = 7.8 Hz, 1 H), 7.92 (d, $^3J$ = 8.4 Hz, 2 H), 8.65 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 110.8, 120.5 (2 C), 121.1 (q, $^1J_{C,F}$ = 276 Hz), 126.0 (q, $J_{C,F}$ = 1.2 Hz), 126.4, 129.2 (2 C), 133.7 (q, $J_{C,F}$ = 0.8 Hz), 134.1, 134.3, 136.3, 136.5, 139.8, 146.8 (q, $^2J_{C,F}$ = 34 Hz), 154.6, 156.8, 193.2.

$^{19}$F NMR ($CDCl_3$): δ = –66.7 (s, $CF_3$).

MS (EI, 70 eV): *m/z* (%) = 415 (26) $[M]^+$, 414 (27) $[M - 1]^+$, 413 (98) $[M - 2]^+$, 399 (25), 366 (22), 347 (66) $[M + 1 - CF_3]^+$, 346 (100) $[M - CF_3]^+$, 330 (23), 279 (37) $[M - SC_6H_4CO]^+$, 250 (16), 136 (17) $[SC_6H_4CO]^+$, 109 (15) $[HSC_6H_4]^+$, 77 (85).

**6-(Pentafluoroethyl)-2-phenyl-5-(2-sulfanylbenzoyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (6d)**
Reaction conditions: DMF, 110 °C, 54 h.

Colorless solid; yield: 330 mg (78%); mp 151–154 °C; $R_f$ = 0.65 (PE–$Et_2O$, 1:1).

$^1$H NMR ($CDCl_3$): δ = 7.07 (t, $J$ = 7.4 Hz, 1 H), 7.18 (t, $J$ = 7.4 Hz, 1 H), 7.21 (d, $J$ = 7.4 Hz, 1 H), 7.33 (t, $J$ = 7.2 Hz, 1 H), 7.41 (d, $J$ = 7.4 Hz, 1 H), 7.53 (dd, $J$ = 8.4, 7.2 Hz, 2 H), 7.88 (d, $J$ = 8.4 Hz, 2 H), 8.54 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 110.9 (tq, $^1J_{C,F}$ = 258 Hz, $^2J_{C,F}$ = 38 Hz), 112.4, 117.9 (qt, $^1J_{C,F}$ = 287 Hz, $^2J_{C,F}$ = 36 Hz), 120.5 (2 C), 126.3, 126.4 (q, $J$ = 0.9 Hz), 127.4, 129.2 (2 C), 129.5, 134.1, 134.2, 135.8, 137.9, 138.6, 144.2 (t, $^2J_{C,F}$ = 28 Hz), 154.7, 157.0, 193.1.

**2-(Diethylamino)-6-(2-sulfanylbenzoyl)-5-(trifluoromethyl)[1,3]thiazolo[4,5-*b*]pyridine (6e)**
Reaction conditions: DMF, 110 °C, 60 h.

Pale red solid; yield: 343 mg (92%); mp 141–143 °C; $R_f$ = 0.28 (PE–$Et_2O$, 1:1).

$^1$H NMR ($CDCl_3$): δ = 1.34 (t, $^3J$ = 7.1 Hz, 6 H), 3.60 (q, $^3J$ = 7.1 Hz, 4 H), 7.18 (t, $^3J$ = 7.6 Hz, 1 H), 7.42 (d, $^3J$ = 8.0 Hz, 1 H), 7.48 (t, $^3J$ = 7.6 Hz, 1 H), 7.91 (s, 1 H), 7.95 (d, $^3J$ = 8.0 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 12.6 (2 C), 46.8 (2 C), 118.3, 120.5 (q, $^1J_{C,F}$ = 275 Hz), 125.8, 128.3, 131.1, 135.7, 137.2, 140.2, 140.5, 143.8 (q, $^2J_{C,F}$ = 35 Hz), 147.7, 167.4, 173.2, 184.1.

$^{19}$F NMR ($CDCl_3$): δ = –62.6 (s, $CF_3$).

MS (EI, 70 eV): *m/z* (%) = 411 (49) $[M]^+$, 410 (17) $[M - 1]^+$, 381 (20) $[M - 1 - Et]^+$, 343 (32) $[M + 1 - CF_3]^+$, 342 (100) $[M - CF_3]^+$, 313 (44) $[M - CF_3 - Et]^+$, 270 (15), 221 (16), 146 (68), 136 (23) $[SC_6H_4CO]^+$, 109 (14) $[HSC_6H_4]^+$, 77 (63).

**1-*tert*-Butyl-5-(2-sulfanylbenzoyl)-6-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6f)**
Reaction conditions: DMF, 110 °C, 84 h.

Reddish solid; yield: 213 mg (58%); mp 170–172 °C; $R_f$ = 0.55 (PE–$Et_2O$, 1:1).

$^1$H NMR ($CDCl_3$): δ = 1.86 (s, 9 H), 7.35 (dd, $^3J$ = 7.8, 7.5 Hz, 1 H), 7.60 (d, $^3J$ = 7.5 Hz, 1 H), 7.71 (t, $^3J$ = 7.5 Hz, 1 H), 7.86 (d, $^3J$ = 7.8 Hz, 1 H), 8.78 (s, 1 H), 9.00 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 28.3 (3 C), 59.5, 82.2, 113.7 (q, $J_{C,F}$ = 1 Hz), 114.8 (q, $J_{C,F}$ = 2 Hz), 122.4 (q, $^1J_{C,F}$ = 275 Hz), 125.9 (2 C), 126.4 (q, $J_{C,F}$ = 2.5 Hz), 133.9, 134.2, 134.3 (q, $J_{C,F}$ = 1 Hz), 139.7, 140.8, 142.0, 143.2 (q, $^2J_{C,F}$ = 35 Hz), 147.8, 193.7.

$^{19}$F NMR ($CDCl_3$): δ = –64.9 (s, $CF_3$).

MS (EI, 70 eV): *m/z* (%) = 404 (18) $[M + 1]^+$, 403 (54) $[M]^+$, 402 (100) $[M - 1]^+$, 347 (26) $[M + 1 - C_4H_9]^+$, 346 (50) $[M - C_4H_9]^+$, 334 (23) $[M - CF_3]^+$, 326 (22), 278 (33) $[M + 1 - C_4H_9 - CF_3]^+$, 137 (13) $[HSC_6H_4CO]^+$, 136 (13) $[SC_6H_4CO]^+$, 57 (45) $[C_4H_9]^+$.

**1-*tert*-Butyl-6-(pentafluoroethyl)-5-(2-sulfanylbenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (6g)**
Reaction conditions: DMF, 110 °C, 84 h.

Reddish solid; yield: 286 mg (63%); mp 160–163 °C; $R_f$ = 85 (PE–$Et_2O$, 1:1).

$^1$H NMR ($CDCl_3$): δ = 1.89 (s, 9 H), 7.33 (dd, $^3J$ = 7.8, 7.4 Hz, 1 H), 7.62 (d, $^3J$ = 7.4 Hz, 1 H), 7.69 (t, $^3J$ = 7.4 Hz, 1 H), 7.83 (d, $^3J$ = 7.8 Hz, 1 H), 8.76 (s, 1 H), 9.07 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 28.0 (3 C), 59.9, 82.7, 114.2 (t, $J_{C,F}$ = 1.5 Hz), 115.4 (t, $J_{C,F}$ = 2.7 Hz), 115.8 (tq, $^1J_{C,F}$ = 258 Hz, $^2J_{C,F}$ = 36 Hz), 117.0 (qt, $^1J_{C,F}$ = 287 Hz, $^2J_{C,F}$ = 36 Hz), 125.9, 126.1, 126.7 (t, $J_{C,F}$ = 2.2 Hz), 133.3, 134.7, 135.5 (t, $J_{C,F}$ = 1.3 Hz), 139.2, 140.1, 142.9, 143.7 (t, $^2J_{C,F}$ = 29 Hz), 147.7, 193.0.

**1,3-Dimethyl-6-(2-sulfanylbenzoyl)-7-(trifluoromethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6h)**
Colorless solid; yield: 288 mg (80%); mp 128–131 °C; $R_f$ = 0.85 (EtOAc).

$^1$H NMR ($CDCl_3$): δ = 3.36 (s, 3 H), 3.65 (s, 3 H), 7.36 (ddd, $^3J$ = 7.8, 7.2 Hz, $^4J$ = 0.8 Hz, 1 H), 7.58 (dd, $^3J$ = 7.8 Hz, $^4J$ = 1.2 Hz, 1 H), 7.68 (ddd, $^3J$ = 8.1, 7.2 Hz, $^4J$ = 1.2 Hz, 1 H), 7.90 (dd, $^3J$ = 8.1 Hz, $^4J$ = 0.8 Hz, 1 H), 8.67 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 28.2, 29.2, 112.7, 120.4 (q, $^1J_{C,F}$ = 276 Hz), 126.1, 126.2, 127.7 (q, $^3J_{C,F}$ = 1.2 Hz), 133.7, 134.4 (2 C), 139.1, 140.1, 145.8 (q, $^2J_{C,F}$ = 35 Hz), 150.6, 150.9, 159.5, 192.3.

$^{19}$F NMR ($CDCl_3$): δ = –63.1 (s, $CF_3$).

MS (EI, 70 eV): *m/z* (%) = 395 (19) $[M]^+$, 394 (100) $[M - 1]^+$, 380 (54) $[M - CH_3]^+$, 351 (59), 326 (56) $[M - CF_3]^+$, 310 (12), 295 (19) $[M - 1 - CF_3 - 2CH_3]^+$, 136 (12) $[SC_6H_4CO]^+$, 109 (12) $[HSC_6H_4]^+$, 98 (24), 97 (19).

**1,3-Dimethyl-7-(pentafluoroethyl)-6-(2-sulfanylbenzoyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6i)**
Colorless solid; yield: 330 mg (82%); mp 113–116 °C; $R_f$ = 0.16 (PE–$Et_2O$, 1:1).

$^1$H NMR ($CDCl_3$): δ = 3.32 (s, 3 H), 3.57 (s, 3 H), 4.44 (s, 1 H, SH), 7.32 (ddd, $^3J$ = 7.8, 7.3 Hz, $^4J$ = 0.8 Hz, 1 H), 7.57 (dd, $^3J$ = 7.8 Hz, $^4J$ = 1.2 Hz, 1 H), 7.71 (ddd, $^3J$ = 7.8, 7.3 Hz, $^4J$ = 1.2 Hz, 1 H), 7.93 (dd, $^3J$ = 7.8 Hz, $^4J$ = 0.8 Hz, 1 H), 8.30 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 28.7, 29.7, 111.8 (tq, $^1J_{C,F}$ = 258 Hz, $^2J_{C,F}$ = 38 Hz), 118.5 (qt, $^1J_{C,F}$ = 287 Hz, $^2J_{C,F}$ = 36 Hz), 124.6, 130.7, 131.4 (t, $^3J_{C,F}$ = 1.6 Hz), 132.0, 133.6, 134.4, 139.2, 139.8, 137.8, 148.2 (t, $^2J_{C,F}$ = 28 Hz), 150.3, 150.9, 159.8, 192.1.

MS (EI, 70 eV): *m/z* (%) = 445 (6) $[M]^+$, 327 (34) $[M + 1 - C_2F_5]^+$, 326 (100) $[M - C_2F_5]^+$, 189 (14) $[M - C_2F_5 - HSCOC_6H_4]^+$, 136 (14) $[SC_6H_4CO]^+$.

**2-Hydroxy-3-{[(4-methylphenyl)amino]methylene}-2-(trifluoromethyl)-2,3-dihydro-4*H*-thiochromen-4-one (8a)**

A mixture of thiochromenone **2a** (70 mg, 0.27 mmol) and *p*-toluidine (90 mg, 0.81 mmol) was heated at 90 °C for 3 h. The resulting mixture was cooled and diluted with MeOH (2 mL), and the solid that formed was filtered and washed with MeOH to give yellow crystals. Yield: 90 mg (91%); mp 174–175 °C.

IR (KBr): 3256, 1636, 1611, 1590, 1571, 1523 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 2.31 (s, 3 H, Me), 7.23–7.36 (m, 6 H, H-6, H-8, Ar), 7.46 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1 H, H-7), 8.01 (dd, *J* = 7.9, 1.4 Hz, 1 H, H-5), 8.12 (d, *J* = 12.9 Hz, 1 H, =CH), 8.56 (s, 1 H, OH), 12.75 (d, *J* = 12.9 Hz, 1 H, NH).

$^{19}F$ NMR (DMSO-$d_6$): δ = –82.9 (s, $CF_3$).

Anal. Calcd for $C_{18}H_{14}F_3NO_2S$: C, 59.17; H, 3.86; N, 3.83. Found: C, 59.14; H, 3.79; N, 3.83.

**2-Hydroxy-3-{[(4-methoxyphenyl)amino]methylene}-2-(trifluoromethyl)-2,3-dihydro-4*H*-thiochromen-4-one (8b)**

*Method A*. A soln of thiochromenone **2a** (100 mg, 0.39 mmol) and *p*-anisidine (130 mg, 1.04 mmol) in benzene (10 mL) was refluxed for 5 h. The resulting mixture was cooled and diluted with heptane (10 mL). The solid that formed was filtered, washed with heptane, and air-dried to give yellow crystals.

*Method B*. A soln of thiochromenone **2a** (100 mg, 0.39 mmol) and *p*-anisidine (130 mg, 1.04 mmol) in MeOH (3 mL) was refluxed for 3 h then cooled. The yellow solid that formed was filtered, washed with cooled MeOH, and air-dried to give yellow crystals.

Yield: 130 mg (88%, method A), 120 mg (81%, method B); mp 177–178 °C.

IR (KBr): 3202, 1629, 1587, 1572, 1514 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 3.77 (s, 3 H, MeO), 7.00–7.04 (m, 2 H, H-2′, H-6′), 7.29–7.38 (m, 4 H, H-6, H-8, H-3′, H-5′), 7.45 (ddd, $^3J$ = 7.9, 7.2 Hz, $^4J$ = 1.4 Hz, 1 H, H-7), 8.01 (dd, $^3J$ = 7.9 Hz, $^4J$ = 1.4 Hz, 1 H, H-5), 8.06 (d, *J* = 12.9 Hz, 1 H, =CH), 8.53 (s, 1 H, OH), 12.82 (d, *J* = 12.9 Hz, 1 H, NH).

$^{13}C$ NMR (DMSO-$d_6$): δ = 55.6, 81.6 (q, $^2J_{C,F}$ = 32.3 Hz), 101.8, 115.3, 119.2, 125.1 (q, $^1J_{C,F}$ = 285.6 Hz), 125.9, 126.1, 128.6, 129.4, 131.7, 132.2, 133.3, 135.1, 137.7, 147.7, 157.2, 183.1.

$^{19}F$ NMR (DMSO-$d_6$): δ = –83.0 (s, $CF_3$).

Anal. Calcd for $C_{18}H_{14}F_3NO_3S$: C, 56.69; H, 3.70; N, 3.67. Found: C, 56.66; H, 3.45; N, 3.70.

**3-[(Benzylamino)methylene]-2-hydroxy-2-(trifluoromethyl)-2,3-dihydro-4*H*-thiochromen-4-one (8c)**

This compound was prepared by Method A described for **8b**.

Colorless crystals; yield: 210 mg (98%); mp 128–130 °C.

IR (KBr): 3070, 1630, 1587, 1570, 1518 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 4.63 (d, AB-system, *J* = 14.8, 6.3 Hz, 2 H, $CH_2$), 7.15–7.40 (m, 8 H, H-6, H-8, H-7, Ph), 7.78 (d, *J* = 13.3 Hz, 1 H, =CH), 7.91 (d, *J* = 7.8 Hz, 1 H, H-5), 7.98 (s, 1 H, OH), 11.42 (dt, *J* = 13.3, 6.3 Hz, 1 H, NH).

$^{13}C$ NMR (DMSO-$d_6$): δ = 53.1, 81.6 (q, $^2J_{C,F}$ = 32.3 Hz), 99.3, 125.2 (q, $^1J_{C,F}$ = 285.1 Hz), 125.6, 125.9, 127.8, 128.4, 128.5, 128.9, 131.7, 132.0, 134.8, 138.4, 156.0, 182.1.

$^{19}F$ NMR (DMSO-$d_6$): δ = –83.2 (s, $CF_3$).

**2-Hydroxy-3-{[(2-phenylethyl)amino]methylene}-2-(trifluoromethyl)-2,3-dihydro-4*H*-thiochromen-4-one (8d)**

This compound was prepared in a manner analogous to that used to prepare **8c**.

Colorless crystals; yield: 250 mg (57%); mp 154–155 °C.

IR (KBr): 3350, 3270, 3060, 1630, 1590, 1571, 1535 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 2.94 (m, 2 H, $CH_2$), 3.64 (m, 2 H, $NCH_2$), 7.12–7.30 (m, 8 H, H-6, H-8, H-7, Ph), 7.60 (d, *J* = 13.1 Hz, 1 H, =CH), 7.93 (d, *J* = 7.7, 1.3 Hz, 1 H, H-5), 8.30 (br s, 1 H, OH), 11.21 (dt, *J* = 13.1, 6.3 Hz, 1 H, NH).

**2-(1-Methyl-1*H*-pyrrol-2-yl)-3-(trifluoroacetyl)-2*H*-thiochromen-4-ol (9a) and *trans*-2-(1-Methyl-1*H*-pyrrol-2-yl)-3-(trifluoroacetyl)-2,3-dihydro-4*H*-thiochromen-4-one (9b)**

A mixture of thiochromenone **2a** (100 mg, 0.39 mmol) and *N*-methylpyrrole (65 mg, 0.80 mmol) was heated at 90 °C for 40 min. The resulting mixture was treated with hexane and the solid that formed was recrystallized (toluene) as yellow crystals. Yield: 80 mg (61%); mp 194–195 °C.

IR (KBr): 1708, 1616, 1589, 1542, 1491, 1464 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ (**9a**, 88%) = 3.67 (s, 3 H, Me), 5.44 (s, 1 H, H-2), 5.47 (dd, *J* = 3.8, 1.7 Hz, 1 H, H-5′), 5.65 (dd, *J* = 3.8, 2.7 Hz, 1 H, H-4′), 6.67 (t, *J* = 2.2 Hz, 1 H, H-3′), 7.31 (dd, *J* = 7.8, 1.0 Hz, 1 H, H-8), 7.35 (td, *J* = 7.5, 1.0 Hz, 1 H, H-6), 7.47 (td, *J* = 7.5, 1.4 Hz, 1 H, H-7), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1 H, H-5); δ (**9b**, 12%) = 3.64 (s, 3 H, Me), 5.63 (d, *J* = 13.0 Hz, 1 H, H-3/2), 5.73 (d, *J* = 13.0 Hz, 1 H, H-2/3), 5.98 (dd, *J* = 3.8, 2.7 Hz, 1 H, H-4′), 6.20 (dd, *J* = 3.8, 1.7 Hz, 1 H, H-5′), 6.72 (dd, *J* = 1.7, 2.7 Hz, 1 H, H-3′), 7.41 (d, *J* = 8.0 Hz, 1 H, H-8), 7.30–7.35 (m, 1 H, H-6), 7.61 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1 H, H-7), 8.02 (dd, *J* = 8.0, 1.4 Hz, 1 H, H-5).

$^{19}F$ NMR (DMSO-$d_6$): δ (**9a**, 90%) = –71.0 (s, $CF_3$); δ (**9b**, 10%) = –78.4 (s, $CF_3$).

Anal. Calcd for $C_{16}H_{12}F_3NO_2S$: C, 56.63; H, 3.56; N, 4.13. Found: C, 56.47; H, 3.67; N, 4.14.

**6-Nitro-3-(trifluoroacetyl)-4*H*-thiochromen-4-one (11), 6-Nitro-3-(2,2,2-trifluoro-1,1-dihydroxyethyl)-4*H*-thiochromen-4-one (14), and 8-Nitro-3-(2,2,2-trifluoro-1,1-dihydroxyethyl)-4*H*-thiochromen-4-one (15)**

A mixture of thiochromenone **2a** (810 mg, 3.14 mmol), concd $H_2SO_4$ (2.5 mL), and 98% $HNO_3$ (2.5 mL) was heated at 90 °C for 1 h, then cooled and poured with stirring onto crushed ice (50 g). The solid that formed was filtered, washed with $H_2O$, dried, and recrystallized (toluene–hexane, 1:1). Yield: 170 mg (18%); mp 165–166 °C.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ (**11**, 72%) = 8.38 (dd, *J* = 8.9, 0.4 Hz, 1 H, H-8), 8.60 (dd, *J* = 8.9, 2.6 Hz, 1 H, H-7), 9.03 (dd, *J* = 2.6, 0.4 Hz, 1 H, H-5), 9.39 (s, 1 H, H-2); δ (**14**, 23%) = 8.26 (s, 2 H, 2 OH), 8.36 (dd, *J* = 8.9, 0.4 Hz, 1 H, H-8), 8.57 (dd, *J* = 8.9, 2.6 Hz, 1 H, H-7), 9.10 (dd, *J* = 2.6, 0.4 Hz, 1 H, H-5), 9.14 (s, 1 H, H-2); δ (**15 hydrate**, 5%) = 7.96 (t, *J* = 8.2 Hz, 1 H, H-6), 8.25 (s, 2 H, 2 OH), 8.87 (dd, *J* = 8.2, 1.5 Hz, 1 H, H-5/7), 8.93 (dd, *J* = 8.2, 1.5 Hz, 1 H, H-7/5), 9.09 (s, 1 H, H-2).

Anal. Calcd for $C_{11}H_4F_3NO_4S \cdot 0.25H_2O$: C, 42.94; H, 1.47; N, 4.55. Found: C, 42.67; H, 1.47; N, 4.37.

**2,2,3,3,3-Pentafluoro-1-(4-hydroxy-1,1-dioxido-2*H*-thiochromen-3-yl)propan-1-one (13)**

A 35% soln of $H_2O_2$ (1.5 g, 16 mmol) was added carefully to a well stirred soln of thiochromenol **12b** (1.0 g, 3.2 mmol) in AcOH (15 mL). The mixture was refluxed for 1 h then cooled to r.t. and poured onto $H_2O$ (100 mL). The precipitated solid was filtered and air-dried to give yellowish crystals. Yield: 0.35 g (32%); mp 135–137 °C.

IR (KBr): 1619, 1592, 1544 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 4.36 (s, 2 H, H-2), 7.79–7.90 (m, 2 H, H-6, H-7), 8.04–8.10 [m, 1 H, H-5(8)], 8.21–8.25 [m, 1 H, H-8(5)], 15.93 (s, 1 H, OH).

$^{19}F$ NMR ($CDCl_3$): δ = –116.9 (m, $CF_2$), –82.2 (t, $CF_3$, $^3J_{F,F}$ = 1.5 Hz).

Anal. Calcd for $C_{12}H_7F_5O_4S$: C, 42.11; H, 2.06. Found: 42.08; H, 2.14.

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