2-Trifluoromethyl-4H-thiochromen-4-one and 2-trifluoromethyl-4H-thiochromene-4-thione: synthesis and reactivities

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2-Trifluoromethyl-4H-thiochromene-4-one obtained from 2-trifluoromethyl-4H-thiochromen-4-one and P2S5 reacts with aromatic amines, hydrazine hydrate, phenylhydrazine, and hydroxylamine at the C(4) atom of the chromene ring to give the corresponding anils, azine, hydrazones, and oxime of thiochromone. 2-Trifluoromethyl-4H-thiochromen-4-one is oxidized by hydrogen peroxide in AcOH into 4-oxo-2-trifluoromethyl-4H-thiochromene 1,1-dioxide and reduced by NaBH4 to 2-trifluoromethyl-4H-thiochromen-4-ol or cis-2-(trifluoromethyl)thiochroman-4-ol. When treated with hydrazine hydrate, thiochromen-4-one gives 3(5)-(2-mercaptophenyl)-5(3)-trifluoromethylpyrazole.

Key words: 2-trifluoromethyl-4H-thiochromen-4-one, oxidation, reduction, 2-trifluoromethyl-4H-thiochromene-4-thione; anils, hydrazones, azine, and oxime of thiochromone.

Chromones (4H-chromen-4-ones) belong to an important class of oxygen-containing heterocycles; many of their derivatives exhibit various kinds of biological activity and serve as the starting materials for the synthesis of novel heterocyclic systems.1,2 Chromones substantially differ in reactivity from less accessible (and, accordingly, less well studied) sulfur analogs: 4H-chromene-4-thiones (chromenethiones), 4H-thiochromen-4-ones (thiochromones), and 4H-thiochromene-4-thiones (dithiochromones). For instance, nucleophiles react with chromones mainly at the C(2) atom, regardless of the presence and nature of the substituent at this atom (1,4-addition with possible opening of the pyrone ring),2–4 while their reactions with chromenethiones and thiochromones predominantly involve the C(4) atom (1,2-addition).5–8 The presence of an RF group in position 2 of chromones makes them more reactive than their nonfluorinated analogs and facilitates reactions with various nucleophilic reagents at the C(2) atom (see Ref. 2). For this reason, it was of interest to find out how the reactivity of 2-trifluoromethylchromone (1) will change upon sequential replacement of the oxygen atoms in this compound by sulfur atoms.

Recently,9 we have described the synthesis and most important chemical properties of 2-trifluoromethyl-4H-chromene-4-thione (2); unlike chromone 1, this compound (despite the presence of the electron-withdrawing CF3 group in position 2) reacts with aniline, phenylhydrazine, and hydroxylamine at the C(4) atom, which allows regiocontrolled synthesis of the corresponding pyrazoles and isoxazoles. In the present work, we obtained 2-trifluoromethyl-4H-thiochromen-4-one (3) and 2-trifluoromethyl-4H-thiochromene-4-thione (4) and studied some of their spectroscopic and chemical properties, including reactions with a number of N-nucleophiles.

\[
\begin{align*}
1 & & 2 \\
3 & & 4
\end{align*}
\]

\[X = O \ (1, 3), \ S \ (2, 4)\]

Literature data on the chemical properties of 4H-thiochromen-4-ones that have a polyhaloalkyl group at the C(2) atom are lacking. However, it is known that thiochromones and thioflavones react with P2S5 to give 4H-thiochromene-4-thiones,10–12 are oxidized at the sulfur atom into S-oxides and S,S-dioxides,13–17 are reduced to 4H-thiochromenones and 4H-thiochromene-4-ols,16,17 are alkylated to form thiochromylum salts,18 and are halogenated and chloromethylated at position 3 (see Refs 19–22). In addition, reactions of thioflavone and 2-methylthiochromone with compounds containing an active methylene (malononitrile23 and hippuric acid24) or methyl group (2-methyl-4,6-diphenylpyrilium and 2-methyl-4,6-diphenylthiopyrilium perchlorates25) are known to occur at the carbonyl C atom. Analogously...
(i.e., according to the 1,2-addition mechanism), 2,6-dimethylthiochromone reacts with dimethylcopperlithium cuprate and 2-trifuoromethylthiochromone reacts with trimethyl(trifluoromethyl) silane. As far as we know, the nucleophilic attack of thiochromones on the C(2) atom (1,4-addition) has been found only in their reactions with the complex AlkCu—BF₃, yielding thiochromanones.

Results and Discussion

2-Trifluoromethyl-4H-thiochromen-4-one (3) was first obtained by the reaction of 4,4,4-trifluorobut-2-ynoic acid with benzenethiol in the presence of KOH followed by cyclization of phenylthioacrylic acid under the action of PCl₅ and AlCl₃ in benzene. We developed a simpler and more convenient route to 2-CF₃-thiochromone 3 (see preliminary communication) by treating 2-mercaptoacetophenone (synthesized from thiosalicylic acid and methyllithium in 66% yield (Scheme 1).

![Scheme 1](image)

The 1H and 19F NMR spectra of compounds 3 and 4 are given in Table 1. For comparison, the spectroscopic data for known chromone 1 and chromenethione 2 are also presented. On replacement of either O atom in chromone 1 by a sulfur atom (1 → 2 or 1 → 3), the signals for the H(3) and H(5) protons are substantially shifted downfield (by 0.6—0.7 and 0.3 ppm, respectively). In compound 4, because of the total deshielding effect of two S atoms, the downfield shifts of these signals are already 1.42 and 0.67, while the signals for the H(6) and H(8) protons are shifted downfield only slightly (by 0.11 ppm). Replacement of the O(1) atom by an S atom decreases the ortho-constants J₆,₇ and J₇,₈ but increases the meta-constant J₆,₈ and the constant of the spin-spin coupling between the H(3) proton and the CF₃ group (J_H,F = 0.8—0.9 Hz). In addition, this replacement substantially affects the chemical shift of the CF₃ group (δ ~ 72 for 1 and 2 and δ ~ 65 for 3 and 4).

We found that thiochromone 3 is oxidized on heating with H₂O₂ in AcOH to give sulfone 5 in 42% yield; when refluxed with excess NaBH₄ in propan-2-ol, thiochromone 3 is reduced to cis-2-(trifluoromethyl)thiochroman-4-ol (6) in 53% yield. The cis-structure of thiochromanol 6 is evident from the coupling constants. For instance, in the 1H NMR spectrum, the axial H(3a) proton manifests itself at δ 1.90 as a doublet of triplets with the geminal constant J₃a,₃e ≈ 10.6 Hz, which indicate the axial and pseudoaxial arrangement of the H(2) and H(4) atoms (see Ref. 31). Therefore, molecules of thiochromanol 6 in CDCl₃ are in the half-chair conformation with cis-equatorial and pseudoequatorial arrangements of the substituents. Note that reduction of flavones and chromones with NaBH₄/NiCl₂ in methanol also yields cis-flavan-4-ols and cis-chroman-4-ols. The formation of cis-products is due to the fact that the hydrogenation of the enone fragment proceeds on one side because of steric hindrances. Reduction of thiochromone 3 under milder conditions (~0 °C) with a smaller excess of NaBH₄ can be stopped at the step of 2-trifluoromethyl-4H-thiochromen-4-ol (7); its formation suggests that the C(4) atom in compound 3 is more reactive than the C(2) atom (Scheme 2).

<table>
<thead>
<tr>
<th>Compound</th>
<th>δ</th>
<th>J/Hz</th>
<th>19F NMR δ_CF₃ (J₁,F)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H(3)</td>
<td>H(5)</td>
<td>H(6)</td>
</tr>
<tr>
<td>1</td>
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<td>8.21</td>
<td>7.49</td>
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<td>4</td>
<td>8.16</td>
<td>8.88</td>
<td>7.60</td>
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Note. Me₄Si (1H) and CFCl₃ (19F) were used as the internal standards.