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REVIEW

Sulfur analogs of fluorinated pyrones, chromones and coumarins

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This mini-review describes the synthesis and reactions of sulfur analogs of partially fluorinated pyrones, chromones, coumarins and isocoumarins and their utility as building blocks for the synthesis of trifluoromethyl-containing heterocyclic compounds with biological interest.

1. Introduction

Published data on the synthesis and reactivity of sulfur analogs of fluorinated α- and γ-pyrones, chromones, coumarins and isocoumarins are summarized. The main attention is paid to the polyfluoroalkylated derivatives of these sulfur-containing six-membered heterocycles. Their partially hydrogenated derivatives are not discussed. The literature data clearly indicate that, although these heterocycles are less reactive than the corresponding oxygen-containing analogs, they are rather susceptible to nucleophilic attack and some of them are attractive building blocks for the synthesis of various heterocyclic compounds containing the RF group.

Keywords: sulfur analogs of pyrones, chromones, coumarins and isocoumarins; fluorine-containing heterocycles

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2. Sulfur analogs of fluorinated γ- and α-pyrones

While trifluoromethylated α- and γ-pyrones have been extensively investigated regarding their synthesis and chemical properties (1–6), little attention has been paid toward the reactivity of their sulfur analogs, probably owing to the lack of general methods for the preparation of these compounds. Only a handful of papers describing some fluorine-containing thiopyrones are present in the literature.

It was found that treatment of 6-(trifluoromethyl)comanic acid 1 with sodium hydrosulfide afforded 4-oxo-6-(trifluoromethyl)-4H-thiopyran-2-carboxylic acid or 6-(trifluoromethyl)thiocomanic acid 2. When heated or treated with H2SO4, this acid easily underwent decarboxylation leading to 2-(trifluoromethyl)-4H-thiopyran-4-one 3. As a result, both methyl and ethyl 6-(trifluoromethyl)thiocomanates 4 were obtained in low yields (7). The reaction of thiopyrone 3 with phenylhydrazine led to the formation pyrazole 5, which upon heating in MeSO3H/AcOH gave 3-(1-phenylpyrazol-5-yl)-2-(trifluoromethyl)indole 6 in good yield (8) (Scheme 1). Note that the latter products were also obtained from 2-(trifluoromethyl)-4H-pyran-4-one (8).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{F}_3\text{C} & \quad \text{F}_3\text{C} \\
1 & \quad 2 \quad (42\%) \\
\text{F}_3\text{C} & \quad \text{F}_3\text{C} \\
\text{S} & \quad \text{S} \\
2 & \quad 3 \quad (82\%) \\
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{CO}_2\text{R} \\
4a \quad (R = \text{Me, 23\%}) & \quad 4b \quad (R = \text{Et, 15\%}) \\
\end{align*}
\]


Condensation of 2H-thiopyran-4(3H)-one 7 with 4-(trifluoromethyl)benzaldehyde in the presence of 4-dimethylaminopyridine (DMAP) at room temperature for 4 h via domino aldol-rearrangement reactions gave 3-substituted thiopyran-4-one 8 in 85% yield. At higher temperature, 3-(3-fluorobenzyl)-5-[(3-fluorophenyl)hydroxymethyl]-4H-thiopyran-4-one 9 was identified as the aldol condensation–Baylis–Hillman adduct in the reaction with 3-fluorobenzaldehyde (9) (Scheme 2).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{F}_3\text{C} & \quad \text{CF}_3 \\
\text{O} & \quad \text{CO}_2\text{R} \\
\text{F}_3\text{C} & \quad \text{F}_3\text{C} \\
\text{S} & \quad \text{S} \\
\text{OH} & \quad \text{OH} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
8 \quad (85\%) & \quad 9 \\
\end{align*}
\]

Scheme 2. Synthesis of 4-thiopyrones 8 and 9.

The addition of sodium hydrosulfide hydrate to the diynone 10 under basic conditions gave 4H-thiopyran-4-one 11 in almost quantitative yield. Peracetic acid oxidation converted thiopyrone 11 to the corresponding sulfone 12 (10) (Scheme 3).
The trifluoromethylated 2H-pyran-2-thiones 13a, b were prepared by reacting the corresponding 2H-pyran-2-ones in boiling toluene with Lawesson’s reagent in 83% and 58% yields, respectively. Their reaction with nitrosobenzene led surprisingly to adducts 14a, b which proved to be isomeric with the initially expected primary Diels–Alder cycloadducts. A plausible mechanism for the formation of compounds 14 was proposed (11) (Scheme 4).

Scheme 4. Reactions of 2H-pyran-2-thiones 13a, b with nitrosobenzene and a plausible mechanism for the formation of compound 14a.

3. Sulfur analogs of fluorinated chromones

3.1. Synthesis of fluorinated thio- and thionechromones

We found that refluxing of 2-(polyfluoroalkyl)chromones 15 with P2S5 in toluene for 4 h affords 2-(polyfluoroalkyl)thionechromones 16 in moderate to high yields. Compounds 16 are crystals...
colored from green to violet. The presence of a halogen atom in the 3-position does not prevent the reaction \((12)\) (Scheme 5).

![Scheme 5. Synthesis of 2-(polyfluoroalkyl)thionechromones 16.](image)

Tamura et al. reported that due to the high nucleophilicity of arenethiols, the reaction involving arenethiols and polyfluoroalk-2-ynoic acids could be successfully carried out in aqueous ethanol in the presence of KOH at room temperature in 0.5 h. The resulting arylthioacrylic acids 17 have the Z-configuration of the double bond; on successive treatment with PCl\(_5\) and AlCl\(_3\) in benzene at room temperature, they produce 2-(polyfluoroalkyl)thiochromones 18 in high yields \((13)\) (Scheme 6).

![Scheme 6. Synthesis of 2-(polyfluoroalkyl)thiochromones 18.](image)

The modified Baker-Venkataraman reaction of alkyl 2-mercaptophenyl ketones 20, prepared from thiosalicylic acid 19 and the corresponding alkylthiitium, with trifluoroacetic anhydride in the presence of triethylamine in boiling THF, gave 2-(trifluoromethyl)thiochromones 18a, b \((14)\) (Scheme 7).

![Scheme 7. Synthesis of 2-(trifluoromethyl)thiochromones 18a, b.](image)

3-(Polyfluoroacyl)thiochromones 22 were prepared in high yield via a chlorination-dehydrochlorination sequence by treating 3-(polyfluoroacyl)-4\(H\)-thiochroman-4-ones 21 with sulfuryl chloride \((15)\). Like 3-(polyfluoroacyl)chromones \((16, 17)\), these compounds exist as a mixture of the nonhydrate form 22 and the hydrate 22' \((3:2\) for \(RF = CF_3\) in CDCl\(_3\) and DMSO-\(d_6\)) (Scheme 8).

By anodic fluorination of thioflavone, 3-fluorothioflavone \((23a, 22\%)\) and 2,3,3-trifluorothioflavanone \((23b, 42\%)\) have been synthesized \((18, 19)\) (Scheme 9).
Scheme 8. Synthesis of 3-(polyfluoroacyl)thiochromones 22.

RF = CF₃, (CF₂)₂H, C₂F₅

Scheme 9. Synthesis of 3-fluorothioflavone (23a).

Nickel-catalyzed cycloadditions have been developed where thiophthalic anhydride reacts with alkynes to afford isothiocoumarins, benzothiophenes and thiochromones depending on the reaction conditions. Selective formation of thiochromone 24 was observed in benzene at 130°C in the presence of Ni(0)/PMe₃ (Scheme 10).

Scheme 10. Synthesis of thiochromone 24. Reaction conditions: (i) Ni(0)/PMe₃, benzene, 130°C, 5 h.

3.2. Reactions of fluorinated thio- and thionechromones

On refluxing in butanol for 4 h, thionechromones 16 react with aniline at the C-4 atom to give anils 25 in good yields (Scheme 11). When these compounds are refluxed in ethanol in the presence of concentrated HCl, they hydrolyze to 2-(polyfluoroalkyl)chromones 15, whereas in aqueous AcOH the reaction ceases at intermediate 2-hydroxy-2-(trifluoromethyl)chroman-4-ones. The reactions of aliphatic primary amines (benzylamine and 2-aminoethanol) with 16 occur ambiguously and afford a complicated mixture of substances (12). This fact is in contrast to the behavior of 2-RF-chromones 15, whose reaction with primary amines at C-2 with the formation of 3-amino-1-(2-hydroxyaryl)prop-2-en-1-ones is one of the most characteristic (21).

Thionechromones 16 react with phenylhydrazine readily at room temperature (12). The reaction is accompanied by vigorous H₂S evolution and affords within several minutes phenylhydrazones 26, whose non-fluorinated analogs were synthesized earlier under more drastic conditions (22, 23). On boiling in ethanol in the presence of concentrated HCl, phenylhydrazones 26 undergo ring closure to previously known 5-RF-pyrazoles 27 (24). The reaction with hydrazine hydrate occurs as easily as that of 2-RF-chromones 15 and affords pyrazole 28, whereas a similar reaction with
Scheme 11. Reactions of thionechromones 16 with N-nucleophiles.

hydroxylamine (ethanol, \(\sim 20^\circ C\), 5 min) proceeds at the thione group to give chromone oximes 29 in high yields (12) (Scheme 11).

The reduction of 2-(trifluoromethyl)-4H-chromene-4-thione 16a is impeded by the oxidative dimerization of the intermediate thiol, which affords a mixture of cis-2-(trifluoromethyl)chroman-4-thiol 30 and bis(2-trifluoromethylchroman-4-yl) disulfide 31, which were separated by simple recrystallization from hexane. Interestingly, disulfide 31 was the single product that was isolated in 23% yield from the reaction of 3-chloro-2-(trifluoromethyl)-4H-chromene-4-thione (16, \(RF = CF_3, X = Cl, R = H\)) with sodium borohydride (25) (Scheme 12).

Scheme 12. Reduction of 2-(trifluoromethyl)-4H-chromene-4-thione 16a.

Thiochromone 18a is oxidized on heating with \(H_2O_2\) in glacial acetic acid to give sulfone 32; when refluxed with excess NaBH\(_4\) in propan-2-ol, thiochromone 18a is reduced to cis-2-(trifluoromethyl)thiochroman-4-ol 33. Reduction of 18a under milder conditions (\(\sim 0^\circ C\)) with a little excess of NaBH\(_4\) can be stopped at the step of 2-(trifluoromethyl)-4H-thiochromen-4-ol 34. Treatment of 18a with hydrazine hydrate at room temperature gave pyrazole 35; when refluxed with \(P_2S_5\) in toluene for 1 h, it afforded 2-CF\(_3\)-dithiochromone 36 (26) (Scheme 13).

It was surprisingly found that thiochromone 18a reacted with Ruppert's reagent to give as a sole product 2,4-bis(trifluoromethyl)-4H-thiochromen-4-yl trimethylsilyl ether 37 in 88% isolated yield after water hydrolysis (27). This result indicated that the reaction of 18a took an entirely different course when compared with reactions of CF\(_3\)SiMe\(_3\) with 2-R\(_F\)-chromones 15, which react at C-2 (20), and exclusively proceeded as a nucleophilic 1,2-addition (Scheme 13).

The observed striking differences in reactivity between 2-CF\(_3\)-chromones 15 and 2-CF\(_3\)-thiochromones 18 appear to be connected with the difficulty met by the nucleophile in cleaving the thiopyrone S–C bond arising from the less electronegative character of the sulfur atom, which strongly reduces the electrophilicity of the 2-position, and the greater aromaticity of the thiochromone system as compared with chromones (structures 15’ and 18’, Scheme 14).
In fact, there is some double-bond character to S1–C2 (1.712 Å) and C3–C4 (1.457 Å) in 3-formylthiochromone (28), indicating a significant contribution of the resonance form 18' involving the delocalization of the lone pair on sulfur into the carbonyl (for thiophene S1–C2 (1.712 Å)) (29). This delocalization is also reflected in the IR spectra of thiochromones, which have a carbonyl band at 1610–1630 cm⁻¹, that is, considerably lower than those of chromones (1650–1670 cm⁻¹).

Full sulfur analogs of chromones (4H-thiochromene-4-thiones or dithiochromones) are poorly studied. It is only known that dithioflavones react with primary aliphatic amines to give thiochromenimines (30), while unsubstituted dithiochromone isomerizes into dithiocoumarin on heating with P₂S₅ (31). We found that 2-(trifluoromethyl)dithiochromone 36 also reacts with aniline, p-anisidine, and α-naphthylamine in boiling butanol at the thione group to give anils 38 in good yields. Treatment of dithiochromone 36 with hydrazine hydrate and phenylhydrazine gave hydrazones 39a, b and azine 40, whereas with hydroxylamine 36 reacted as easily as did thionechromones 16, giving oxime 41. When treated with acetic anhydride in the presence of catalytic amounts of concentrated H₂SO₄, oxime 41 underwent O-acetylation into compound 42 (26) (Scheme 15).

All these reactions proceed by nucleophilic 1,2-addition to give the corresponding derivatives of 2-(trifluoromethyl)thiochromone 18a without opening of the thiopyrone ring. Attempts to obtain five- and six-membered heterocycles from dithiochromone 36 and dinucleophiles, such as hydroxylamine, hydrazines and amidines under the same conditions that had previously been used for the corresponding reactions of 2-(trifluoromethyl)chromones 15, failed (26). Thus, despite the presence of the electron-withdrawing CF₃ group at the C-2 atom, thione-, thio- and dithiochromones 16, 18 and 36 react with nucleophilic agents mainly at the C-4 atom, in sharp contrast to 2-R₅-chromones 15, whose most characteristic reactions occur at C-2 and are followed by opening of the pyrone ring (21).
Although 3-RF\textsuperscript{5}CO-thiochromones 22 are less reactive than 3-RF\textsuperscript{5}CO-chromones (16, 17), they are still able to react with methyl orthoformate (methanol, HCl), amines (benzene, reflux, 5 h), and amidine and guanidine salts (DMF, 100°C, 12 h) to give good yields of the corresponding hemiketal 43, thiochromanones 44 (32) and pyrimidines 45 (33), respectively. Iaroshenko et al. reported that 3-RF\textsuperscript{5}CO-thiochromones 22 react with heterocyclic amines as reported previously for the 3-RF\textsuperscript{5}CO-chromones (34). In contrast to the case of 3-RF\textsuperscript{5}CO-chromones, reaction of 22 with heterarylamines proceeded under harsher conditions (DMF, 110°C, 54–84 h) and appeared to be more regioselective, giving the set of diverse heteroannulated pyridines 46 bearing the RF substituent at the α-position of the pyridine core as the sole isolated products in high yields (32). A somewhat unexpected result was obtained from the reaction of 22 (RF = CF\textsubscript{3}) with N-methylpyrrole. In this case, the reaction proceeded without cleavage of the thiopyrone ring to give the pyrrolyl derivative 47 in 61% yield (32) (Scheme 16).

### Scheme 16. Reactions of 3-(polyfluoroacyl)thiochromones 22.
Thus, unlike 2-(trifluoromethyl)thiochromones 18 and 36, the reactions of 3-(trifluoroacetyl)thiochromones 22 with primary amines, amidines and hetarylamines proceed as 1,4-nucleophilic addition with subsequent opening of the thiopyrone ring and cyclization with the participation of the CF₃CO group to give the corresponding heterocyclic products in good yields.

4. Sulfur analogs of fluorinated coumarins and isocoumarins

Huang et al. (35) reported that thiocoumarin reacts with perfluoroalkyl iodides in the presence of sodium hydroxymethanesulfinate (Rongalite) to give the corresponding 3-(perfluoroalkyl)thiocoumarins 48 selectively and under mild conditions. A free-radical mechanism was proposed for the reaction (Scheme 17).

\[
\begin{align*}
\text{HOCH}_2\text{SO}_2\text{Na} + \text{RF-I} & \rightarrow \text{RF-SO}_2\text{H} + \text{HOCH}_2\text{S}\text{Na} \\
\text{RF} = & \text{F(CF}_2)_6, \text{Cl(CF}_2)_4, \text{Cl(CF}_2)_6
\end{align*}
\]


The reaction of (Z)-2-fluoro-3-methoxyprop-2-enoyl chloride 49 with thiophenol in pyridine and diethyl ether at room temperature gave compound 50, which was converted into 3-fluorothiocoumarin 51 under the action of concentrated sulfuric acid in chloroform at 60°C for 1 h (36) (Scheme 18).

\[
\begin{align*}
\text{SH} + \text{Cl-CO} & \rightarrow \text{SH} + \text{FOT} \rightarrow \text{Ome} \\
\text{OMe} & \rightarrow \text{FOMe} \rightarrow \text{OMe}
\end{align*}
\]


A different mode of interaction was observed with the ester 52. In this case, the thiophenol underwent a 1,4-addition giving rise to the monothioacetal 53. When this compound was heated in the presence of potassium hydrogen sulfate to 150°C, methanol was eliminated and methyl 2-fluoro-3-(phenylthio)acrylate 54 formed (36) (Scheme 18).

Dmowski (37) reported facile preparation of some new pyrone ring monofluorinated chromones and coumarins, including sulfur containing derivatives, by treatment of o-hydroxy-2,3,3,3-tetrafluoropropiophenone with amines and sodium sulfide. In the latter case, 3-fluoro-4-hydroxy-2-thionecoumarin 55 as a mixture of two tautomers was obtained (Scheme 19).

The methyl ester of 6-fluoro-4-hydroxy-2-oxo-2H-thiochromene-3-carboxylic acid 56 was used as the starting material for the preparation of bioactive compounds capable of decreasing HIF hydroxylase enzyme activity, thereby increasing the stability and activity of hypoxia
Scheme 19. Reaction of o-hydroxy-2,3,3,3-tetrafluoropropiophenone with sodium sulfide.

Scheme 20. Structures of compounds 56 and 57.

Inducible factor (HIF) (38). Compound 57 was suggested as an example of a novel antibacterial and anticancer agent (39) (Scheme 20).

1H-2-Benzothiopyran-1-one (isothiocoumarin 58) was prepared from thiophthalic anhydride and the corresponding tolan in the presence of Ni(0)/PPr₃ catalyst in combination with Lewis acid (MAD: methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (20) (Scheme 21).

Scheme 21. Synthesis of isothiocoumarin 58. Reaction conditions: (i) Ni(0)/PPr₃, MAD, toluene, 130°C, 3 h.

The synthetic approach to 5-(trifluoromethyl)isothiocoumarin 60 involves a bromination/dehydrobromination sequence that proceeds via thiopyranone 59 and the intermediate 4-bromoisothiochromanone as shown in Scheme 22. Irradiation (350 nm) of 60 as homogeneous solid film affords a 4:5 mixture of dimers 61a and 61b which were not separated (40) (Scheme 22).

Scheme 22. Synthesis and irradiation of 5-(trifluoromethyl)isothiocoumarin 60.
Isothionecoumarins 63 were synthesized in high yields by thionation of isocoumarins 62 by refluxing with Lawesson’s reagent in toluene for 3 h and their anticancer and antimetastatic evaluation was described (41). Alternatively, a rapid microwave-accelerated thionation of some 3-substitued isocoumarins 62 to the corresponding isothionecoumarins 63 was achieved employing Lawesson’s reagent under solventless conditions (42) (Scheme 23).


5. Conclusion

Analysis of the published data demonstrates that of the diverse fluorine-containing six-membered sulfur heterocycles, thiochromone derivatives have now been studied most comprehensively. Data on fluorinated thiopyrones and coumarins are quite scarce.

Despite the ready accessibility of trifluoromethylated thiochromones, these compounds have long remained out of sight of chemists engaged in synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that some of them, for example, 3-(trifluoroacetyl)thiochromones, are valuable substrates for the synthesis of diverse partially fluorinated heterocycles with potential biological activity. The diversity of properties of these compounds is due to the fact that, being actually highly reactive geminally activated alkenes with a good leaving group at the β-carbon atom, they acquire the ability to undergo additional reactions related to opening and transformation of the γ-thiopyrone ring. These reactions have been used to prepare various R\textsuperscript{F}-containing fused pyridines and pyrimidines.

In view of the fact that 20–30% of modern pharmaceuticals and 30–40% of agrochemical preparations contain at least one fluorine atom in the molecule (43), the research dealing with modification and study of the reactivity of fluorinated sulfur-containing heterocycles aimed at extending the synthetic scope of these compounds appear to be a topical and promising line for the future research into fluorine-containing heterocyclic compounds and search for new biologically active substances.

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