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Unexpected synthesis of dihydrothienocoumarin derivatives from 2-trifluoromethylchromones and ethyl mercaptoacetate

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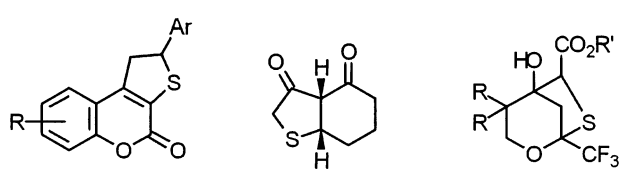
Abstract—The redox reaction of 2-trifluoromethylchromones with ethyl mercaptoacetate in the presence of triethylamine results in the formation of dihydrothienocoumarin derivatives and diethyl 3,4-dithiadipate in high yields.

It is known[1,2] that the interaction of ethyl mercaptoacetate with α,β-unsaturated ketones proceeds via nucleophilic addition of the mercapto group to an activated double bond with further cyclization at the carbonyl group leading to the corresponding tetrahydrothiophene derivatives. A similar reaction of alkyl mercaptoacetates with esters of 3-methoxy-4,4,4-trifluorocrotonic,[3] α-fluoroalkyl acetic[4] and fluoroalkyl propiolic[5] acids gives alkyl 3-hydroxy-5-fluoroalkylthiophene-2-carboxylates, and with β-chloro enones[6] and α-fluoroalkyl ketones[4] alkyl 5-fluoroalkylthiophene-2-carboxylates are formed. *o*-Hydroxychalcones[7,8] can also participate in this reaction, but owing to the *ortho*-hydroxyl group, reaction is accompanied by tandem cyclization–dehydration to 2-aryl-1,2-dihydro-4*H*-thieno[2,3-*c*]benzo[e]pyran-4-ones (dihydrothienocoumarins) **1**. When the double bond is incorporated into a ring, as in the case of cyclohex-2-enone[9] the mode of interaction with methyl mercaptoacetate is changed and the initial product of a Michael addition undergoes a spontaneous cyclization with concomitant loss of methoxide to afford the diketone **2**, existing in the enolic form. At the same time we have recently[10] studied the reactions of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with methyl and ethyl mercaptoacetates and found that in this case, the reactions occur with participation of both electrophilic centers of dihydropyrones without ring cleavage to give derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **3** (Scheme 1).

In view of the unique biological properties displayed by many fluorinated heterocyclic compounds[11] and an extension of our continuing synthetic studies concerning the reactivity of 2-polyfluoroalkylchromones,[12,13] we have started investigations of the possible use of 2-trifluoromethylchromones[14] in the reaction with ethyl mercaptoacetate. Taking into account the results of previous work,[7,8,10] it might be expected that this reaction would proceed either without opening of the pyrone ring to give benzo derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **4** or with ring opening. In the latter case, the reaction can be accompanied by cyclization and dehydration stages[7,8] to yield thieno[2,3-*c*]-coumarins **5** (Scheme 2).

Here, we describe our findings on the successful application of this reaction to the preparation of trifluoromethyl-containing compounds. Unexpectedly, the interaction of 2-trifluoromethylchromones **6a–e** with ethyl mercaptoacetate in a molar ratio of 1:3 at 80°C in the presence of Et_3N as a catalyst afforded dihydrothienocoumarins **7a–e** (in 75–85% yields) and diethyl 3,4-dithiadipate.[15] These products can be viewed as result-



Scheme 1.

Keywords: 2-trifluoromethylchromones; ethyl mercaptoacetate; redox reaction; dihydrothienocoumarins.

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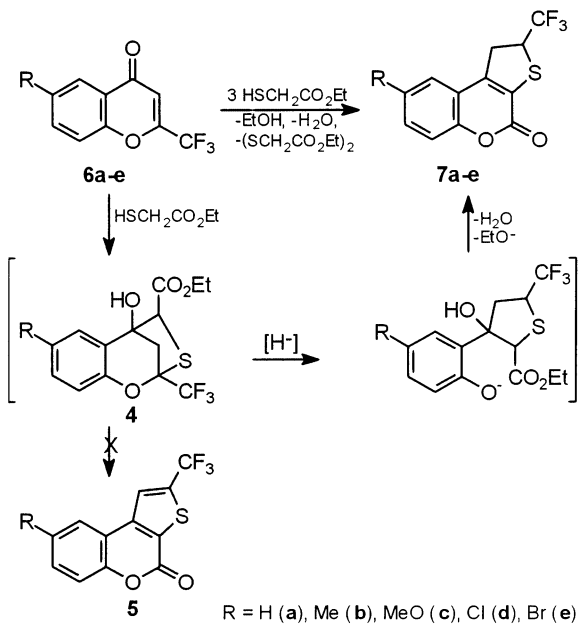

Scheme 2.

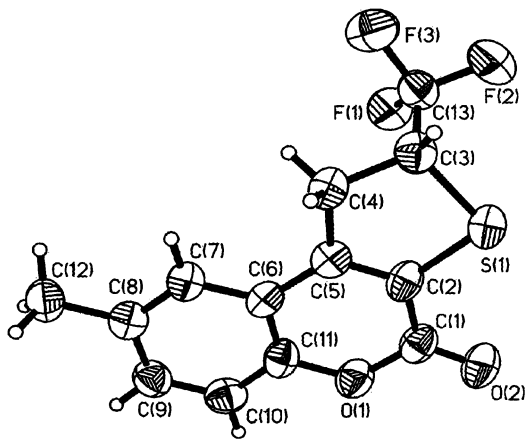

Figure 1. Molecular structure of **7b**. Selected bond lengths (pm): S(1)–C(2) 174.9(7), S(1)–C(3) 184.1(7), O(1)–C(1) 138.6(9), O(1)–C(11) 138.7(8), O(2)–C(1) 121.7(8), C(1)–C(2) 145.1 (10), C(2)–C(5) 134.5(9), C(3)–C(4) 154.6(10), C(4)–C(5) 152.0(9), C(5)–C(6) 143.2(9); selected bond angles (°): C(2)–S(1)–C(3) 90.4(3), C(1)–O(1)–C(11) 122.2(5), O(2)–C(1)–O(1) 117.5(6), O(2)–C(1)–C(2) 126.2(7), O(1)–C(1)–C(2) 116.3(6), C(5)–C(2)–C(1) 122.3(6), C(5)–C(2)–S(1) 117.3(5), C(1)–C(2)–S(1) 120.4(5), C(4)–C(3)–S(1) 108.4(5), C(5)–C(4)–C(3) 107.6(5), C(2)–C(5)–C(6) 120.8(6), C(2)–C(5)–C(4) 113.2(6), C(6)–C(5)–C(4) 125.9(6), C(11)–C(6)–C(5) 117.3(6), O(1)–C(11)–C(6) 120.9(6).

ing from a redox reaction between chromones **6** and ethyl mercaptoacetate.

The mechanism for the redox formation of coumarins **7** is not obvious. It is likely that the reaction initially gives compound **4**, which in contrast to bicycle **3** undergoes ring-opening under the action of ethyl mercaptoacetate owing to the better leaving group ability of a phenolic hydroxyl group. Further cyclization, dehydration and reduction of the intermediates give dihydrothienocoumarins **7**, while ethyl mercaptoacetate is oxidized to diethyl 3,4-dithiadipate. An addition–elimination mechanism involving Michael-adduct formation followed immediately by ring opening to a phenoxide with reformation of an α,β-unsaturated enone system is one possible starting point.

This reaction is typical only for 2-trifluoromethylchromones and does not proceed with 2-trichloromethyl- and 2-methylchromones. The structures of the compounds **7a**–**e** agree well with the results of elemental analysis, ^{1}H, ^{19}F, ^{13}C NMR and IR spectroscopy and mass-spectra. Furthermore, an X-ray diffraction analysis of the crystals of compound **7b** was performed, proving the regiochemistry of the reaction (see Fig. 1).[16]

Thus, this reaction provides a convenient one-pot process from readily available materials to the CF_3 group containing heterocycle-fused coumarins **7**, which are expected to be biologically active[17] and can be used as optical brightening agents, and as dispersed fluorescent and laser dyes.[18]

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15. Preparation of **7a**: a mixture of chromone **6a** (3.15 g, 15 mmol), ethyl mercaptoacetate (6.0 g, 50 mmol) and Et_3N (12 drops) without solvent was heated at 80°C for 30 h. After cooling, the reaction mixture was diluted with 10 ml of methanol and the crystalline material was isolated by filtration and washed with cold methanol to give 3.42 g (85% yield) of coumarin **7a**, mp 146–147°C. After recrystallization from ethanol, the melting point did not change. ^{1}H NMR (250.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.66–3.85 (AB-part of ABX-system, 2H, CH_2, $^2J_{AB}=18.3$; $\delta_A=3.78$, $\delta_B=3.73$, $^3J_{AX}=10.3$, $^3J_{BX}=4.5$), 4.37–4.53 (m, 1H, CH, $^3J_{H,F}=8.6$), 7.28–7.40 (m, 3H, H^6, H^8, H^9), 7.50 (ddd, 1H, H^7, $J_{H^7,H^6}=8.5$, $J_{H^7,H^8}=6.3$, $J_{H^7,H^9}=2.3$). ^{13}C NMR (50.32 MHz, $CDCl_3$, δ, ppm, J/Hz): 35.72 (q, CH_2, $^3J_{C,F}=2.3$), 47.80 (q, CH, $^2J_{C,F}=31.6$), 125.54 (q, CF_3, $^1J_{C,F}=277.9$), 144.97 (s, =C-S), 152.95 (s, =C-O), 156.08 (s, C=O), 116.92, 117.40, 123.92, 124.90, 126.34, 130.80. ^{19}F NMR (188.31 MHz, $CDCl_3$, $CFCl_3$, δ, ppm, J/Hz): −75.28 (d, CF_3, $^3J_{F,H}=8.6$). IR (Vaseline oil, ν/cm^{-1}): 1720 (C=O), 1610, 1560 (C=C, arom.). MS (70 eV, 200°C), m/z (I_{rel} (%)): 272 [M]$^+$ (100), 203 [M–CF_3]$^+$ (23), 159 [M–CO_2–CF_3]$^+$ (45), 115 [HS=CH-CF_3]$^+$ (41), 28 [CO]$^+$ (15). Found (%): C, 52.84; H, 2.64. Calcd for $C_{12}H_7F_3O_2S$ (%): C, 52.94; H, 2.59. Compounds **7b–e** also gave satisfactory analytical and spectral data.
The filtrate obtained after removal of **7a** was distilled in vacuo to give 1.5 g (43% yield) of diethyl 3,4-dithiadipate, bp 135–140°C (5 mm), n_D^{20} 1.4962 (lit.[19] bp 112–116°C (0.3 mm), n_D^{25} 1.4950). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.30 (t, 6H, 2Me, $J=7.1$), 3.58 (s, 4H, $2CH_2S$), 4.22 (q, 4H, $2CH_2$, $J=7.1$). IR (neat, cm^{-1}): 1720 (C=O).
16. Crystal data for **7b**: $C_{13}H_9F_3O_2S$, $M=286.26$, crystal size 0.5×0.4×0.2 mm^3, monoclinic, space group $P2_1/n$, $a=502.30(10)$, $b=1840.1(4)$, $c=1304.5(3)$ pm, $\beta=92.83(3)°$, $V=1.2043(5)$ nm^3, $Z=4$, $d_{calc}=1.579$ g cm^{-3}, absorption coefficient $\mu=0.301$ mm^{-1}, $F(000)=584$. The intensities of 1847 independent reflections ($R_{int}=0.16$) were measured on a STOE IPDS diffractometer with low temperature device Cryostream cooler (graphite-monochromated Mo-Kα radiation, $\lambda=71.073$ pm, $T=173$ K). The structure was solved by direct methods with the use of the SHELX-97 program package.[20] Non-hydrogen atoms were refined by the full-matrix least-squares procedures (with F^2) in an anisotropic approximation. The final discrepancy factors $R_1=0.080$, $wR_2=0.23$, GOF = 1.032. The positions of hydrogen atoms were calculated as a riding model.
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