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A Novel Redox Reaction between 8-Aza-5,7-dimethyl-2-trifluoromethylchromone and Alkyl Mercaptoacetates

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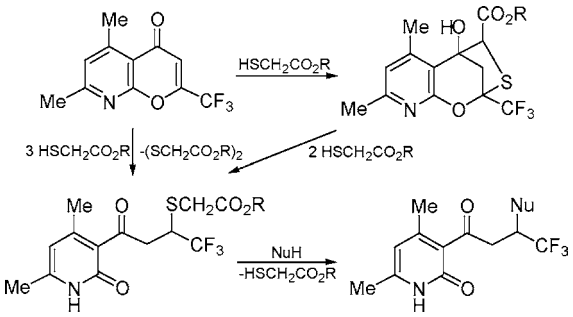
ABSTRACT



8-Aza-5,7-dimethyl-2-trifluoromethylchromone reacts with alkyl mercaptoacetates to give pyrido derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane, which undergo the reductive ring-opening to sulfanyl acetates. The latter compounds are useful CF_3-containing building blocks for the preparation of a variety of 2-pyridone derivatives.

Trifluoromethylated heterocycles continue to be of great industrial interest,[1] and therefore the development of new methods to incorporate the CF_3 group into organic compounds remains as important area of research.[2] We have shown recently[3] that the reaction of 2-trifluoromethylchromones **1** with 3 equiv of ethyl mercaptoacetate in the presence of triethylamine is a redox process, which affords dihydrothienocoumarins **2** in high yield. These compounds are the key intermediate in a novel synthesis of 3-hydrazinopyridazines,[4] which are widely used for the preparation of triazolo- and tetrazolopyridazines[5−7] and exhibit different types of biological activity as chemotherapeutics, antiinflammatory agents, CNS depressants and stimulants, and antihypertensives.[8]

The mechanism for the redox formation of coumarins **2** is not obvious, but it is most likely that, as in the cases with 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones[9] and 7-polyfluoroalkylnorkhellins,[10] the reaction initially gives benzo derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **3**, which undergo the reductive ring-opening to esters **4** under the action of ethyl mercaptoacetate (Scheme 1). Unfortunately, we were unable to isolate any intermediates in the transformation **1** → **2**.

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(3) (a) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Lork, E.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2001**, *42*, 5117. (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Röschenthaler, G.-V. *Tetrahedron* **2003**, *59*, 2625.
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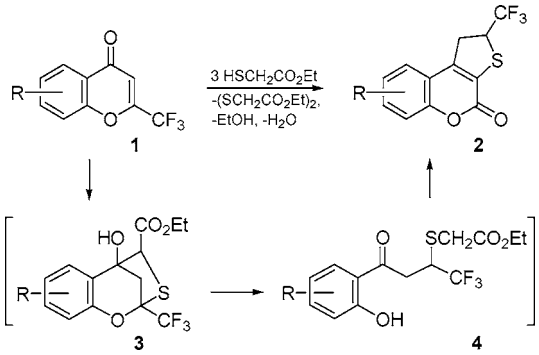
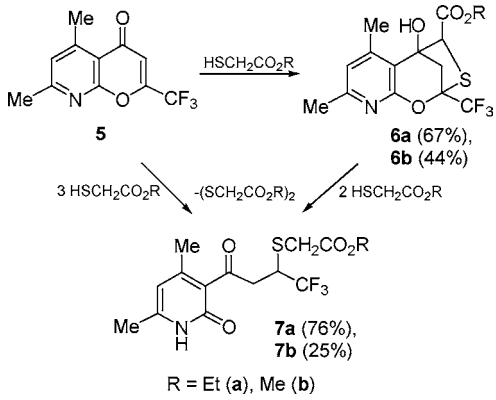
Scheme 1



Scheme 2



To verify the assumption that this useful and unusual reaction proceeds through intermediates of type **3** and/or **4** and to reveal the reaction route as a whole, we decided to extend the series of initial chromones. We hoped that drastic changes in their structure (more substantial than the simple variation of substituents in the benzene ring) would allow the process to be stopped at one of the intermediate steps. Since the key step of the transformation **1** → **2** is the formation of the coumarin system, which occurs during the interaction of phenolic hydroxyl with the ester group, it was of interest to introduce 8-azachromones into this reaction. In this case, opening of the pyrone ring results in the appearance of the oxygen atom of the amide type with decreased nucleophilic properties instead of the phenol OH group. This allows us to expect the isolation of open-chained products.

In fact, we found that the reaction of 8-aza-5,7-dimethyl-2-trifluoromethylchromone (**5**) (accessible from 3-acetyl-4,6-dimethyl-2-pyridone and ethyl trifluoroacetate[11]) with alkyl mercaptoacetates at 80 °C for 4 h in the presence of Et_3N afforded bicycles **6a**,**b**. When the reaction time and the amount of Et_3N were increased, acyclic derivatives **7a**,**b**[12] were isolated instead of **6a**,**b**. Probably, they are the products of reduction of **6a**,**b** because they were formed from the latter under similar conditions (Scheme 2). To our knowledge, there are no reports on the analogous ring opening of the chromone system with reducing agents to give acyclic ketones. It is significant that we saw no reaction with known 8-aza-2,5,7-trimethylchromone[13] and ethyl mercaptoacetate under the same reaction conditions as above.

The IR spectra of compounds **6a**,**b** showed absorption bands in the two ranges 3120−3150 and 1730−1735 cm^{-1} due to the hydroxyl group and the ester carbonyl; a characteristic feature of the ^1H NMR spectra is the appearance of two AX doublets (J_{AX} = 11.8 Hz) at δ 2.63 and 3.22 ppm for the CH_2 group and two singlets at δ 4.18 and 4.45 ppm for the CH and OH protons, respectively. The IR spectra of **7a**,**b** exhibit intense absorption bands at 1725−1730 and 1660−1670 cm^{-1}, corresponding to the ester and ketone carbonyl groups. In the ^1H NMR spectra, the ABX-system of the CH_2CH fragment (J_{AB} = 17.8 Hz, J_{AX} = 10.2−10.3 Hz, J_{BX} = 3.8−3.9 Hz) and the AB-system of the CH_2S group (J_{AB} = 14.6 Hz) due to the chiral center in molecules of **7a**,**b** are observed.

On the basis of the results obtained by the study of the reaction of azachromone **5** with alkyl mercaptoacetates, we can propose a probable route of the transformation of chromones **1** into dihydrothienocoumarins **2**. The reaction begins with the addition of the mercapto group to the C(2) atom, and the resulting Michael adduct undergoes reversible cyclization to form bridged structure **3**. The reductive opening of bicycle **3** or ring opening of the Michael adduct followed by reduction under the action of an excess of ethyl mercaptoacetate led to sulfanyl acetate **4**, which undergoes two intramolecular cyclizations involving the ketone and ester carbonyl groups to produce coumarin **2**.

Hydrolysis of ester **7a** to the corresponding acid **8** can be easily performed in 87% yield by the action of HCl in aqueous ethanol at reflux for 2 h. However, cyclization of **7a** to dihydrothiophene derivative **9** under basic conditions was unsuccessful because ester **7a** easily eliminates molecule of ethyl mercaptoacetate and behaves as the masked α,β-unsaturated ketone **10**. Previously, trifluoroethylidene derivatives of acetone[14,15] and acetophenone[16,17] were prepared from trifluoroacetaldehyde, which is usually generated in situ from its hydrate, hemiacetal, or aminal, sometimes using Lewis acid catalysis.[17,18] Such fluorinated enones have attracted the

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(12) **Compound 7a:** A mixture of azachromone **5** (5.0 g, 20.6 mmol), ethyl mercaptoacetate (11.0 g, 91.2 mmol), and Et_3N (2.1 g, 20.8 mmol) was heated at 80 °C for 8 h. After dilution with aqueous ethanol and cooling, the crystalline material was isolated by filtration, washed with ethanol−water (1:1), and dried to give **7a** as colorless crystals. Yield 5.7 g (76%), mp 130−131 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, Me, J = 7.1 Hz), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 3.37 (d, 1H, C*H*HS, J = 14.6 Hz), 3.38 (dd, 1H, C*H*H, ^2J = 17.8 Hz, ^3J = 10.2 Hz), 3.48 (d, 1H, CH*H*S, J = 14.6 Hz), 3.58 (dd, 1H, CH*H*, ^2J = 17.8 Hz, ^3J = 3.9 Hz), 4.13 (m, 1H, CH), 4.22 (m, 2H, CH_2O), 6.02 (s, 1H, H arom.), 13.18 (s, 1H, NH); IR (Nujol) 1730, 1670, 1630, 1540 cm^{-1}. Anal. Calcd for $C_{15}H_{18}F_3NO_4S$: C, 49.31; H, 4.97; N, 3.83. Found: C, 49.50; H, 4.95; N, 4.04.

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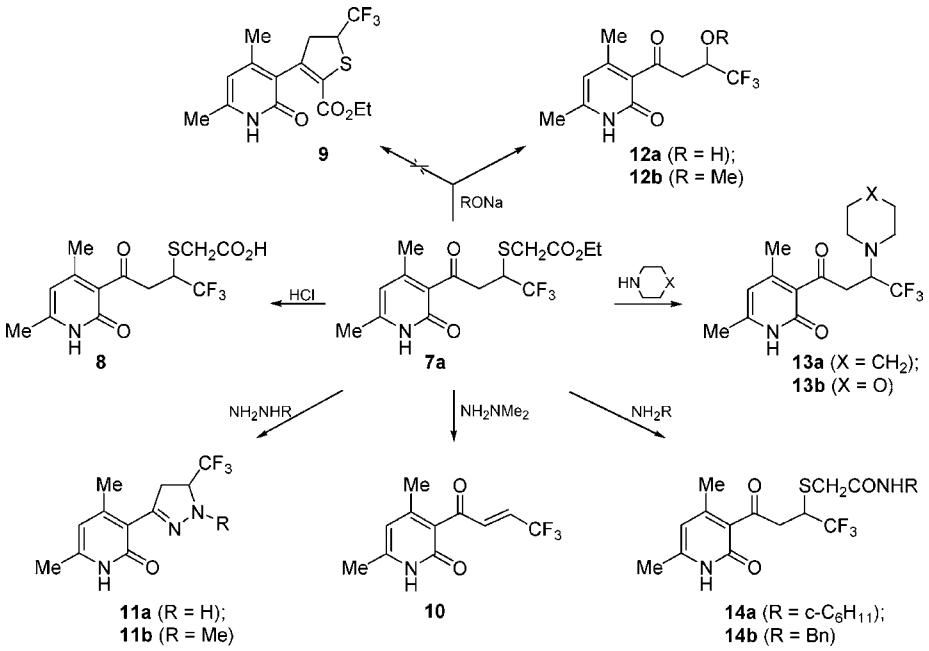
Scheme 3



attention mainly due to the possibility of using them as excellent building blocks for the preparation of a variety of CF_3-containing compounds.[14,15,19]

We found that sulfanyl acetate **7a** acts as an effective in situ source of CF_3-enone **10** in reactions with various *N*- and *O*-nucleophiles, yielding 2-pyridone derivatives **11**−**13** in good to moderate yields (Scheme 3). When ester **7a** was treated with hydrazine hydrate in ethanol for 1 day, pyrazoline **11a** was obtained in 66% yield after the usual workup. The reaction of **7a** with methylhydrazine gave only one regioisomer **11b** in 70% isolated yield (ABX-system of the CH_2CH fragment with J_{AB} = 17.4 Hz, J_{AX} = 11.6 Hz, J_{BX} = 11.1 Hz) and the other regioisomer was not detected. It is likely that the interaction of **7a** with hydrazines proceeds in the stepwise formation of enone **10** followed by further cyclocondensation at the activated double bond and the carbonyl group leading to the corresponding pyrazolines **11a**,**b**. In regard to this, a similar reaction with dimethylhydrazine gave *E*-enone **10** ($J_{CH=CH}$ = 15.7 Hz) as the only isolated product in a moderate yield (50%). In a further experiment, we observed that reactions of **7a** with sodium hydroxide, sodium methoxide, and cyclic secondary amines (piperidine, morpholine) were also accomplished by elimination of ethyl mercaptoacetate followed by addition of the nucleophile to give β-hydroxy (**12a**), β-methoxy (**12b**), and β-amino ketones (**13a**,**b**). Interestingly, the reactions of ester **7a** with primary aliphatic amines (cyclohexylamine, benzylamine) occur at the ester group to give amides **14a**,**b**.[20]

The present redox reaction could be applicable to 8-aza-2-difluoromethyl-5,7-dimethylchromone,[11] providing the corresponding difluoromethylated analogues of **6** and **7**. Further studies on the synthetic application of this methodology are now in progress.

In summary, the reaction of 8-azachromone **5** with alkyl mercaptoacetates is very useful for revealing the route of the transformation **1** → **2** because, depending on the conditions, it stops at the step of product **6** or **7**. The latter may be considered as a new CF_3-containing building block for the preparation of a variety of 2-pyridone derivatives, which are of interest as biologically active compounds.

Acknowledgment. This work was financially supported by the Russian Foundation for Basic Research (grant 02-03-32706) and, in part, by the US Civilian Research and Development Foundation (grant REC-005). The authors are

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(20) **Representative Spectral and Analytical Data.** Enone **10**: ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 6H, 2Me), 6.10 (s, 1H, H arom.), 6.71 (dq, 1H, =CH, $J_{H,H}$ = 15.7 Hz, $J_{H,F}$ = 7.2 Hz), 7.38 (d, 1H, =CH, J = 15.7 Hz), 12.12 (br s, 1H, NH); IR (Nujol) 1655, 1635, 1530 cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.67; H, 4.24; N, 5.75. Pyrazoline **11a**: ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, Me), 2.15 (s, 3H, Me), 3.08 (ddd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 9.1 Hz, $^4J_{H,NH}$ = 1.4 Hz), 3.42 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 12.0 Hz), 4.35 (m, 1H, CH), 5.94 (s, 1H, H arom.), 7.48 (dd, 1H, NH, ^3J = 5.4 Hz, ^4J = 1.2 Hz), 11.61 (s, 1H, NHCO); IR (Nujol) 3280, 1660, 1630, 1545 cm^{-1}. Anal. Calcd for $C_{11}H_{12}F_3N_3O$: C, 50.97; H, 4.67; N, 16.21. Found: C, 51.00; H, 4.56; N, 16.27. β-Piperidino ketone **13a**: ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 6H, $(CH_2)_3$), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 2.50 (m, 2H, CH_2N), 2.84 (m, 2H, CH_2N), 3.31 (dd, 1H, C*H*H, ^2J = 16.0 Hz, ^3J = 10.0 Hz), 3.38 (dd, 1H, CH*H*, ^2J = 16.0 Hz, ^3J = 4.7 Hz), 3.76 (m, 1H, CH), 6.02 (s, 1H, H arom.), 13.4 (br s, 1H, NH); IR (Nujol) 1665, 1630, 1530 cm^{-1}. Anal. Calcd for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41; N, 8.48. Found: C, 58.50; H, 6.46; N, 8.14. Amide **14a**: ^{1}H NMR (DMSO-d_6) δ 1.11−1.74 (m, 10H, C_6H_{10}H), 2.16 (s, 3H, Me), 2.18 (s, 3H, Me), 3.21 (dd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 9.5 Hz), 3.27 (AB-system, $\Delta\delta$ = 0.02 ppm, 2 H, CH_2S, J_{AB} = 14.0 Hz), 3.42−3.48 (m, 1H, $C_6H_{10}H$), 3.45 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 4.5 Hz), 4.18 (quint d, 1H, CH, $J_{H,H}$ = $J_{H,F}$ = 8.9 Hz, J = 4.4 Hz), 6.02 (s, 1H, H arom.), 7.92 (d, 1H, NH, J = 7.7 Hz), 12.8 (br s, 1H, NH); IR (Nujol) 3300, 1670, 1645, 1550 cm^{-1}. Anal. Calcd for $C_{19}H_{25}F_3N_2O_3S$: C, 54.53; H, 6.02; N, 6.69. Found: C, 54.43; H, 5.99; N, 6.62.

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Supporting Information Available: ^{1}H NMR spectra for compounds **6a**, **7a**, **8**, **11b**, **12b**, **13b**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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