Reaction of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with alkyl mercaptoacetates. Synthesis of derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane

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The reactions of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with methyl and ethyl mercaptoacetates in the presence of piperidine result in the formation of 2-oxa-7-thiabicyclo[3.2.1]octane derivatives.

We have recently[1] described the synthesis of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones **1** and **2**, which are very reactive compounds and which even at room temperature are able to add ammonia and water at the double bond to form 2-amino- and 2-hydroxy-5,5-dialkyl-2-trifluoromethyl-4-tetrahydropyrones. The reactions of dihydropyrones **1** and **2** with hydrazine hydrate occur simultaneously at two electrophilic centres to give 2-hydrazino-5,5-dialkyl-2-trifluoromethyl-4-tetrahydropyrones hydrazones.[2]

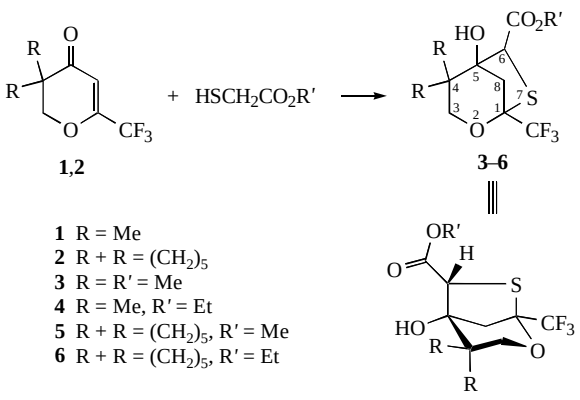
In the present work, we studied the reactions of dihydropyrones **1** and **2** with methyl and ethyl mercaptoacetates and found that in this case, the reactions occur with participation of both reaction centres of compounds **1** and **2**, while esters of thioglycolic acid act as S,C-dinucleophiles to give derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **3**–**6**.

It has previously been demonstrated[3] that interaction of alkyl mercaptoacetates 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 thiophane derivatives. A similar reaction of ethyl mercaptoacetate with 3-benzylidenechroman-4-one[4] gives ethyl 9b-hydroxy-3-phenyl-1,3,3a,9b-tetrahydro-4*H*-thieno[3,4-*c*]benzo[*e*]pyran-1-carboxylate, and with esters of aryl-[5] and polyfluoroalkyl[6] propiolic acids regioisomeric 3-hydroxythiophenes are formed.

The reactions of dihydropyrones **1** and **2** with methyl and ethyl mercaptoacetates occur at room temperature over 2–3 days in the presence of a catalytic quantity of piperidine to form compounds **3**–**6**† in 64–78% yields. According to the ^{1}H NMR data, which exhibit only one set of signals, the reaction is highly stereoselective with the product isolated as a single diastereomer featuring a *cis*-arrangement of substituents in the thiophane ring thus reducing to a minimum an unfavourable interaction between the alkoxycarbonyl and *gem*-dialkyl groups and facilitating the formation of an intramolecular hydrogen bond between hydroxyl and carbonyl. It should be noted that 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone[7] does not react with alkyl mercaptoacetates under these conditions.

A characteristic feature of the ^{1}H NMR spectra of compounds **4** and **6** is the appearance of two quartets of chemically nonequivalent protons of the methylene group MeCH_2O, indicating the presence of an asymmetric centre adjacent to the ethoxycarbonyl function. As regards compounds **5** and **6**, we observed splitting into doublets with ^4J = 1.8 Hz for each of the two signals in the high-field part of the AB system of the CH_2(3) group belonging to the axial proton (δ 3.90), which is related to its long-range spin–spin coupling with one of the nearest axial protons of the adjacent spirocyclohexane system.

Thus, we have demonstrated that dihydropyrones **1** and **2** behave similarly to α,β-unsaturated ketones[3,4] and react simultaneously with alkyl mercaptoacetates at the double bond and carbonyl group without cleavage of the pyran ring. The above reaction is simple and results in the formation of a bridged 2-oxa-7-thiabicyclo[3.2.1]octane system that has been obtained for the first time and is worthy of further investigation.



1 R = Me
2 R + R = $(CH_2)_5$
3 R = R′ = Me
4 R = Me, R′ = Et
5 R + R = $(CH_2)_5$, R′ = Me
6 R + R = $(CH_2)_5$, R′ = Et

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† *5-Hydroxy-4,4-dimethyl-6-methoxycarbonyl-1-trifluoromethyl-2-oxa-7-thiabicyclo[3.2.1]octane* **3**. Dihydropyrone **1** (350 mg, 1.8 mmol) was dissolved in 300 μl (320 mg, 3.0 mmol) of methyl mercaptoacetate in the presence of one drop of piperidine, and the reaction mixture was kept for 3 days at room temperature. The resulting crystals of compound **3** were recrystallised from hexane, yield 220 mg (73%), mp 92–93 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.01 (s, 3H, Me), 1.23 (s, 3H, Me), 2.52 [AB system, Δδ 0.28, 2H, CH_2(8), *J* 11.6 Hz], 3.7 (br. s, 1H, OH), 3.78 (s, 3H, MeO), 3.81 [AB system, Δδ 0.41, 2H, CH_2(3), *J* 12.0 Hz], 4.04 (s, 1H, CH). IR (Vaseline oil, ν/cm^{-1}): 3530 (OH), 1725 (C=O). Found (%): C 44.19; H 5.25. Calc. for $C_{11}H_{15}F_3O_4S$ (%): C 44.00; H 5.03.

5-Hydroxy-4,4-dimethyl-6-ethoxycarbonyl-1-trifluoromethyl-2-oxa-7-thiabicyclo[3.2.1]octane **4**. Yield 78%, mp 89–90 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.02 (s, 3H, Me), 1.23 (s, 3H, Me), 1.31 (t, 3H, *Me*CH_2O, *J* 7.2 Hz), 2.52 [AB system, Δδ 0.27, 2H, CH_2(8), *J* 11.6 Hz], 3.8 (br. s, 1H, OH), 3.82 [AB system, Δδ 0.42, 2H, CH_2(3), *J* 11.9 Hz], 4.01 (s, 1H, CH), 4.23 (q, 1H, MeC*H*HO, *J* 7.2 Hz), 4.25 (q, 1H, MeCH*H*O, *J* 7.2 Hz). IR (Vaseline oil, ν/cm^{-1}): 3480 (OH), 1720 (C=O). Found (%): C 45.78; H 5.30. Calc. for $C_{12}H_{17}F_3O_4S$ (%): C 45.85; H 5.45.

5-Hydroxy-4,4-pentamethylene-6-methoxycarbonyl-1-trifluoromethyl-2-oxa-7-thiabicyclo[3.2.1]octane **5**. Yield 73%, mp 78–79 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.1–1.9 [m, 10H, $(CH_2)_5$], 2.52 [AB system, Δδ 0.18, 2H, CH_2(8), *J* 11.6 Hz], 3.77 (s, 3H, MeO), 3.8 (br. s, 1H, OH), 4.07 [AB system, Δδ 0.33, 2H, CH_2(3), *J* 12.2 Hz], 4.11 (s, 1H, CH). IR (Vaseline oil, ν/cm^{-1}): 3480 (OH), 1720 (C=O). Found (%): C 49.27; H 5.68. Calc. for $C_{14}H_{19}F_3O_4S$ (%): C 49.40; H 5.63.

5-Hydroxy-4,4-pentamethylene-6-ethoxycarbonyl-1-trifluoromethyl-2-oxa-7-thiabicyclo[3.2.1]octane **6**. Yield 64%, mp 93–94 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.1–1.9 [m, 10H, $(CH_2)_5$], 1.30 (t, 3H, *Me*CH_2O, *J* 7.2 Hz), 2.51 [AB system, Δδ 0.18, 2H, CH_2(8), *J* 11.6 Hz], 3.8 (br. s, 1H, OH), 4.07 [AB system, Δδ 0.33, 2H, CH_2(3), *J* 12.6 Hz], 4.08 (s, 1H, CH), 4.22 (q, 1H, MeC*H*HO, *J* 7.2 Hz), 4.24 (q, 1H, MeCH*H*O, *J* 7.2 Hz). IR (Vaseline oil, ν/cm^{-1}): 3520 (OH), 1725 (C=O). Found (%): C 50.79; H 6.00. Calc. for $C_{15}H_{21}F_3O_4S$ (%): C 50.84; H 5.97.

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