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 , -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 d ays in the presence of a catalytic quantity of piperidine to form compounds **3**–**6**† in 64–78% yie lds. 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 Me*CH*$_2$O, 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–s pin 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 , -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.

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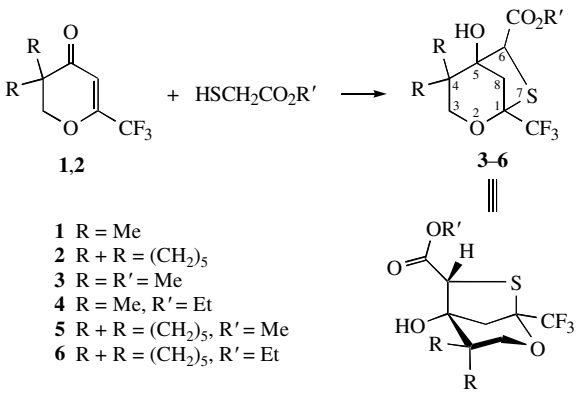

1,**2** **3**–**6**

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 l (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 92–9 3 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.01 (s, 3H, Me), 1.23 (s, 3H, Me), 2.52 [AB system, δ 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, δ 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, δ 0.27, 2H, CH_2(8), J 11.6 Hz], 3.8 (br. s, 1H, OH), 3.82 [AB system, δ 0.42, 2H, CH_2(3), J 11.9 Hz], 4.01 (s, 1H, CH), 4.23 (q, 1H, Me*CH*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 78–7 9 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.1–1.9 [m, 10H, $(CH_2)_5$], 2.52 [AB system, δ 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, δ 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 93–9 4 °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, δ 0.18, 2H, CH_2(8), J 11.6 Hz], 3.8 (br. s, 1H, OH), 4.07 [AB system, δ 0.33, 2H, CH_2(3), J 12.6 Hz], 4.08 (s, 1H, CH), 4.22 (q, 1H, Me*CH*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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