Synthesis of difluorodithiopyruvic acid derivatives

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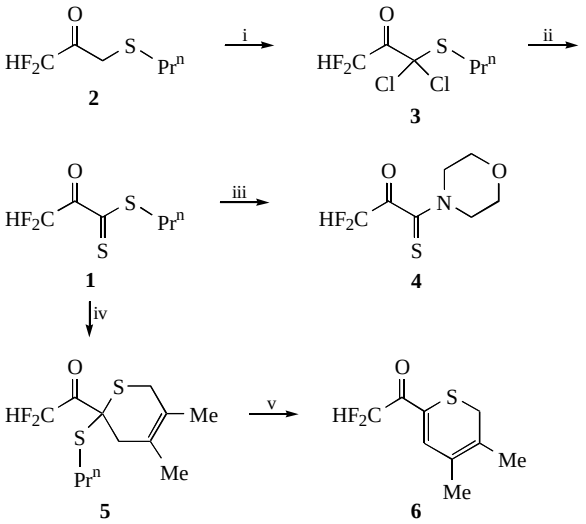
The reaction of cadmium sulfide with 1,1-dichloro-3,3-difluoro-2-oxo-1-propylthiopropane yields difluorodithiopyruvic propionate. This reacts with morpholine to give difluorodithiopyruvic morpholide; it also undergoes a cycloaddition reaction to the carbon–sulfur double bond with dimethylbutadiene to form 2-difluoroacetyl-4,5-dimethyl-2-propylthio-3*H*,6*H*-thiopyran.

Previously, when investigating polyfluoroaliphatic thioaldehydes[1] and esters of polyfluoroalkanedithiocarboxylic acids,[2] we showed that the influence of polyfluoroalkyl substituents results in an increase in the activity of the thiocarbonyl groups in the cycloaddition reactions with dienes. This has allowed us to synthesise new fluoro-containing thiopyran derivatives possessing biological activity.[3]

In continuing our research into fluoro-containing dithiocarboxylic acid derivatives we have studied the possibility of synthesising oxopolyfluoroalkanedithiocarboxylates. It is known that polyfluoro-containing ketones $R_FC(O)R$ [R = various, including sulfur-containing substituents] are effective inhibitors of many enzymes.[4] Therefore, it is possible to assume that in the case of oxopolyfluoroalkanedithiocarboxylates with dienes, new fluoro-containing ketones containing a thiopyran ring as the substituent will be formed. They may also be enzyme inhibitors.



Scheme 1 *Reagents and conditions*: i, SO_2Cl_2, CH_2Cl_2, 20 °C, 8 h, 91%; ii, CdS, MeCN, reflux, 0.5 h, 53%; iii, morpholine, benzene, 20 °C, 12 h, 36%; iv, dimethylbutadiene, diethyl ether, 20 °C, 2 h, 58%; v, $HgCl_2$, $CaCO_3$, acetone, reflux, 3 h, 63%.

It is necessary to note that among derivatives of α-oxothiocarboxylic acids, the appropriate amides $RC(=O)C(=S)NR_2$[5,6] have been investigated the most. The first representatives of the α-oxodithiocarboxylates $ArC(=O)C(=S)SR$ were synthesised in 1978,[7] and the dithiooxalates $ROC(=O)C(=S)SR$[8] are also known. Among fluoro-containing derivatives of this class only trifluoropyruvic thioamide $CF_3C(=O)C(=S)NR_2$[9,10] has been reported.

In the present work we report on the synthesis and some properties of the first representative of esters of fluoro-containing α-oxodithiocarboxylic acids, difluorodithiopyruvic propionate **1**.

For the synthesis of this compound the approach developed by us for the synthesis of polyfluoroalkanedithiocarboxylates,[2] consisting of substitution of chlorine atoms in 1,1-dichlorosulfides by sulfur by treatment with zinc or cadmium sulfides, was used. Chlorination of the ketosulfide **2**[11] with sulfuryl chloride gives 1,1-dichloro-3,3-difluoro-2-oxo-1-propylthiopropane **3**,‡ which under reflux with cadmium sulfide in acetonitrile results in compound **1** (Scheme 1).

The dithioester **1** readily reacts by nucleophilic replacement with secondary amines, in particular with morpholine, forming the difluoropyruvic thioamide **4**. Upon interaction of the dithioester **1** with dimethylbutadiene a [2 + 4] cycloaddition reaction on the C=S bond leads to formation of 2-difluoroacetyl-4,5-dimethyl-2-propylthio-2*H*,6*H*-thiopyran **5**. Under similar conditions thioamide **4** does not react with dimethylbutadiene. Upon reflux of **1** with mercury(II) chloride in acetone dethiylation occurs with formation of 2-difluoroacetyl-4,5-dimethyl-6*H*-thiopyran **6**.

This work was financially supported by INTAS (grant no. 95-UA-0005).

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‡ All compounds obtained were characterised by ^1H and ^{19}F NMR and IR spectroscopy and gave satisfactory elemental analysis data.

For **1**: bp 40–43 °C (0.09 mmHg). ^1H NMR (200 MHz, C_6D_6, TMS) δ: 0.57 (t, 3H, Me, *J* 7.1 Hz), 1.27 (sextet, 2H, CH_2, *J* 7.1 Hz), 2.59 (t, 2H, SCH_2, *J* 7.1 Hz), 6.44 (t, 1H, HCF_2, J_{HF} 51.9 Hz). ^{19}F NMR (188 MHz, C_6D_6, CCl_3F) δ_F: –128.43 (d, 2F, CF_2H, J_{HF} 51.9 Hz). IR (film, ν/cm^{-1}): 1738 (s, $\nu_{C=O}$). Found (%): C 36.84; H 4.34; S 32.56. Calc. for $C_6H_8F_2OS_2$ (%): C 36.35; H 4.07; S 32.34.

For **3**: bp 110–112 °C (20 mmHg). ^1H NMR (200 MHz, $CDCl_3$, TMS) δ: 0.41 (t, 3H, Me, *J* 7.0 Hz), 1.00 (sextet, 2H, CH_2, *J* 7.0 Hz), 2.12 (t, 2H, SCH_2, *J* 7.0 Hz), 5.97 (t, 1H, HCF_2, J_{HF} 54.0 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, CCl_3F) δ_F: –121.34 (d, 2F, CF_2H, J_{HF} 54.1 Hz). Found (%): C 30.17; H 3.53; Cl 29.63; S 13.43. Calc. for $C_6H_8Cl_2F_2OS$ (%): C 30.39; H 3.40; Cl 29.91; S 13.52.

For **4**: bp 73–75 °C (0.07 mmHg), mp 47–48 °C. ^1H NMR (200 MHz, C_6D_6, TMS) δ: 3.15 (m, 4H, $2NCH_2$), 3.27 (m, 2H, OCH_2), 6.57 (t, 1H, HCF_2, J_{HF} 51.7 Hz). ^{19}F NMR (188 MHz, C_6D_6, CCl_3F) δ_F: –130.46 (d, 2F, CF_2H, J_{HF} 51.7 Hz). IR (film, ν/cm^{-1}): 1740 (s, $\nu_{C=O}$). Found (%): C 40.01; H 4.35; N 6.38; S 15.64. Calc. for $C_7H_9F_2NO_2S$ (%): C 40.18; H 4.34; N 6.70; S 15.33.

For **5**: bp 90–95 °C (0.07 mmHg). ^1H NMR (200 MHz, C_6D_6, TMS) δ: 0.57 (t, 3H, Me, *J* 7.0 Hz), 1.18 (sextet, 2H, CH_2, *J* 7.1 Hz), 1.20 (s, 3H, Me), 1.36 (s, 3H, Me), 2.10 (t, 2H, SCH_2, *J* 7.0 Hz), 2.3–2.8 (m, 4H, $2CH_2$, cyclic), 6.53 (t, 1H, HCF_2, J_{HF} 53.1 Hz). ^{19}F NMR (188 MHz, C_6D_6, CCl_3F) δ_F: –120.01 (d, 2F, CF_2H, J_{HF} 52.7 Hz). IR (film, ν/cm^{-1}): 1723 (s, $\nu_{C=O}$). Found (%): C 50.95; H 6.74; S 22.71. Calc. for $C_{12}H_{18}F_2OS_2$ (%): C 51.40; H 6.47; S 22.87.

For **7**: mp 34–35 °C (diethyl ether–hexane). ^1H NMR (200 MHz, C_6D_6, TMS) δ: 1.23 (s, 3H, Me), 1.27 (s, 3H, Me), 2.54 (s, 2H, CH_2), 5.56 (t, 1H, HCF_2, J_{HF} 52.0 Hz), 6.82 (s, 1H, CH). ^{19}F NMR (188 MHz, C_6D_6, CCl_3F) δ_F: –121.35 (d, 2F, CF_2H, J_{HF} 52.0 Hz). IR (film, ν/cm^{-1}): 1682 (s, $\nu_{C=O}$). Found (%): C 52.66; H 5.55; S 15.73. Calc. for $C_9H_{10}F_2OS$ (%): C 52.92; H 4.94; S 15.70.

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Received: Moscow, 24th April 1998
Cambridge, 23rd June 1998; Com. 8/03094D