

Synthesis of difluorodithiopyruvic acid derivatives

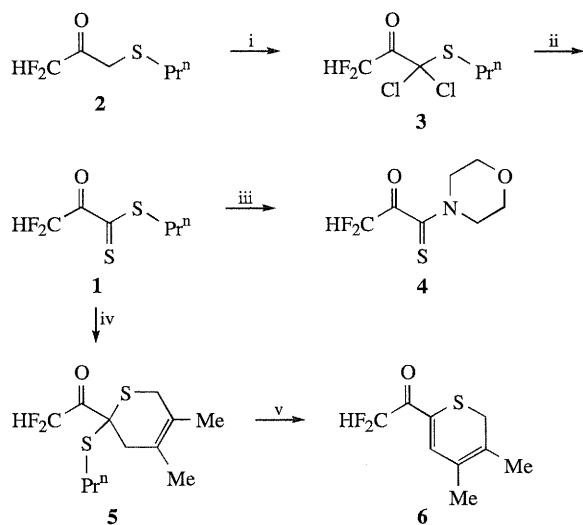
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The reaction of cadmium sulfide with 1,1-dichloro-3,3-difluoro-2-oxo-1-propylthiopropane yields difluorodithiopyruvic propionate. This reacts with morpholine to give difluorodithiopyruvic morpholide; it also undergoes a cycloaddition reaction to the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

Previously, when investigating polyfluoroaliphatic thioaldehydes¹ 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 dithio-carboxylic 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, SO₂Cl₂, CH₂Cl₂, 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, HgCl₂, CaCO₃, acetone, reflux, 3 h, 63%.

It is necessary to note that among derivatives of α-oxothio-carboxylic acids, the appropriate amides RC(=O)C(=S)NR₂^{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)SR⁸ are also known. Among fluoro-containing derivatives of this class only trifluoro-pyruvic thioamide CF₃C(=O)C(=S)NR₂^{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-dichloro-sulfides by sulfur by treatment with zinc or cadmium sulfides,

was used. Chlorination of the ketosulfide 2¹¹ 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 desethylation occurs with formation of 2-difluoroacetyl-4,5-dimethyl-6*H*-thiopyran 6.

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

For 1: bp 40–43 °C (0.09 mmHg). ¹H NMR (200 MHz, C₆D₆, TMS) δ: 0.57 (t, 3H, Me, *J* 7.1 Hz), 1.27 (sextet, 2H, CH₂, *J* 7.1 Hz), 2.59 (t, 2H, SCH₂, *J* 7.1 Hz), 6.44 (t, 1H, HCF₂, *J*_{HF} 51.9 Hz). ¹⁹F NMR (188 MHz, C₆D₆, CCl₃F) δ_F: -128.43 (d, 2F, CF₂H, *J*_{HF} 51.9 Hz). IR (film, ν/cm⁻¹): 1738 (s, ν_{C=O}). Found (%): C 36.84; H 4.34; S 32.56. Calc. for C₆H₈F₂OS₂ (%): C 36.35; H 4.07; S 32.34.

For 3: bp 110–112 °C (20 mmHg). ¹H NMR (200 MHz, CDCl₃, TMS) δ: 0.41 (t, 3H, Me, *J* 7.0 Hz), 1.00 (sextet, 2H, CH₂, *J* 7.0 Hz), 2.12 (t, 2H, SCH₂, *J* 7.0 Hz), 5.97 (t, 1H, HCF₂, *J*_{HF} 54.0 Hz). ¹⁹F NMR (188 MHz, CDCl₃, CCl₃F) δ_F: -121.34 (d, 2F, CF₂H, *J*_{HF} 54.1 Hz). Found (%): C 30.17; H 3.53; Cl 29.63; S 13.43. Calc. for C₆H₈Cl₂F₂OS (%): 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, C₆D₆, TMS) δ: 3.15 (m, 4H, 2NCH₂), 3.27 (m, 2H, OCH₂), 6.57 (t, 1H, HCF₂, *J*_{HF} 51.7 Hz). ¹⁹F NMR (188 MHz, C₆D₆, CCl₃F) δ_F: -130.46 (d, 2F, CF₂H, *J*_{HF} 51.7 Hz). IR (film, ν/cm⁻¹): 1740 (s, ν_{C=O}). Found (%): C 40.01; H 4.35; N 6.38; S 15.64. Calc. for C₇H₉F₂NO₂S (%): 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, C₆D₆, TMS) δ: 0.57 (t, 3H, Me, *J* 7.0 Hz), 1.18 (sextet, 2H, CH₂, *J* 7.1 Hz), 1.20 (s, 3H, Me), 1.36 (s, 3H, Me), 2.10 (t, 2H, SCH₂, *J* 7.0 Hz), 2.3–2.8 (m, 4H, 2CH₂, cyclic), 6.53 (t, 1H, HCF₂, *J*_{HF} 53.1 Hz). ¹⁹F NMR (188 MHz, C₆D₆, CCl₃F) δ_F: -120.01 (d, 2F, CF₂H, *J*_{HF} 52.7 Hz). IR (film, ν/cm⁻¹): 1723 (s, ν_{C=O}). Found (%): C 50.95; H 6.74; S 22.71. Calc. for C₁₂H₁₈F₂OS₂ (%): C 51.40; H 6.47; S 22.87.

For 7: mp 34–35 °C (diethyl ether–hexane). ¹H NMR (200 MHz, C₆D₆, TMS) δ: 1.23 (s, 3H, Me), 1.27 (s, 3H, Me), 2.54 (s, 2H, CH₂), 5.56 (t, 1H, HCF₂, *J*_{HF} 52.0 Hz), 6.82 (s, 1H, CH). ¹⁹F NMR (188 MHz, C₆D₆, CCl₃F) δ_F: -121.35 (d, 2F, CF₂H, *J*_{HF} 52.0 Hz). IR (film, ν/cm⁻¹): 1682 (s, ν_{C=O}). Found (%): C 52.66; H 5.55; S 15.73. Calc. for C₉H₁₀F₂OS (%): C 52.92; H 4.94; S 15.70.

† Professor Leonid N. Markovskii, a specialist in the field of macromolecular and organoelement chemistry, died on the 3rd February 1998.

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