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Reactions of 7-polyfluoroalkylnorkhellins with alkyl mercaptoacetates: a simple synthesis of dihydrothienopsoralens and benzofuran derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane

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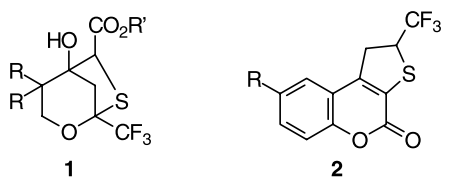
Abstract—New fluoro-containing derivatives of khellin were synthesized from 7-polyfluoroalkylnorkhellins and alkyl mercaptoacetates.

The natural furochromone khellin (4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one), obtained from the fruits and seeds of *Ammi visnaga* L. possesses a high antiatherosclerotic and lipid-altering activity[1] and is the active constituent of many modern medicines.[2] In view of the unique biological properties displayed by khellin on the one hand and by many fluorinated heterocyclic compounds[3] on the other hand, we have described recently[4] the synthesis of 7-trihalomethylnorkhellins, which are highly reactive building blocks for the preparation of new khellin derivatives with potential biological activity.

The present work is devoted to the study of the interaction of these compounds with alkyl mercaptoacetates. It is known[5] that the reaction of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with alkyl mercaptoacetates in the presence of Et_3N involves both electrophilic centers of the dihydropyrones and occurs without ring cleavage to give derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **1**. At the same time, the interaction of 2-trifluoromethylchromones with a threefold excess of ethyl mercaptoacetate is a redox process that affords dihydrothienocoumarins **2** and diethyl 3,4-dithiadipate in a high yield[6] (Scheme 1).



Scheme 1.

Taking into account the results of previous work,[5,6] we would expect that 7-polyfluoroalkylnorkhellins **3a–c**, being chromones, would react with alkyl mercaptoacetates to form dihydrothienocoumarins **2**. However, we found that, despite the structural similarly with chromones, they behave in this reaction as dihydropyrones and give compounds **4a–d** in 53–85% yields[7] (Scheme 2). It should be noted that khellin, 7-perfluorobutyl- and 7-trichloromethylnorkhellins do not react with alkyl mercaptoacetates under these conditions and we failed to isolate the individual reaction products from 7-perfluoroethyl- and 7-perfluoropropylnorkhellins.

According to the ^1H NMR data of **4a–d**, which exhibit only one set of signals, the reaction is highly stereoselective and results in the formation of only one diastereomer with the *cis*-arrangement of the substituents in the tetrahydrothiophene ring. This is most likely related to the formation of an intramolecular hydrogen bond between the hydroxyl and carbonyl groups (the IR spectra of **4a–d** in $CHCl_3$ solution had a bonded peak at 3470–3495 cm^{-1}, which were unchanged upon dilution). It seems probable that little, if any, OH···O=C intramolecular hydrogen bonding interactions can occur in *trans*-isomer.

When fluorokhellins **3a–c** were heated in a sealed ampoule at 140–150°C for 1.5 h with an excess of

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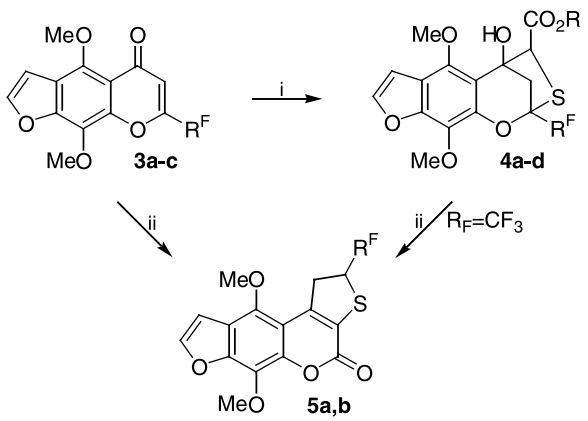

a, R^F= CF_3, R = Et; **b**, R^F= CF_2H, R = Et;
c, R^F= $(CF_2)_2H$, R = Et; **d**, R^F= CF_3, R = Me

Scheme 2. *Reaction conditions*: (i) $HSCH_2CO_2R$, Et_3N, ~20°C, 3–10 days; (ii) $HSCH_2CO_2R$, Et_3N, 140–150°C, 1.5 h.

$HSCH_2CO_2Et$ in the presence of Et_3N, we succeeded in obtaining dihydrothienopsoralens **5a**,**b** in 34 and 17% yields, respectively.[8] Fluorokhellin **3c** does not react under these conditions. A similar heterocyclic system with an aryl group instead of the polyfluoroalkyl substituent has recently[9] been synthesized from the corresponding *o*-hydroxychalcones and ethyl mercaptoacetate.

Treatment of compound **4a** with ethyl mercaptoacetate under similar conditions gave dihydrothienopsoralen **5a** in 64% yield, which indicates the intermediacy of compounds **4** in the transformation of khellins **3** into psoralens **5**.

Thus, as expected,[4] the replacement of the methyl group in khellin by the polyfluoroalkyl group substantially increases the reactivity of the pyrone ring of the khellin system toward nucleophiles and makes it possible to design from it new fluoro-containing heterocycles, which are of interest as biologically active compounds.

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References

1. Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672–1674.
2. Mashkovskii, M. D. *Lekarstvennye sredstva*; Vilnyus, 1993; Vol. 1, p. 396.
3. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993.
4. Sosnovskikh, V. Ya.; Kutsenko, V. A. *Mendeleev Commun.* **2000**, 238–239.
5. Sosnovskikh, V. Ya.; Mel'nikov, M. Yu. *Mendeleev Commun.* **1998**, 198–199.
6. Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Lork, E.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2001**, *42*, 5117–5119.
7. Preparation of **4a**: a mixture of fluorokhellin **3a** (0.25 g, 0.8 mmol) and ethyl mercaptoacetate (0.5 g, 4.2 mmol) in the presence of one drop of Et_3N without solvent was kept for 3 days at room temperature. Then the reaction mixture was diluted with 5 ml of ethanol and the crystalline material was isolated by filtration and washed with ethanol to give 0.25 g (72% yield) of compound **4a**, mp 148–149°C. After recrystallization from butanol, the melting point did not change. ^{1}H NMR (250 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.35 (t, 3H, $\underline{Me}CH_2$, J=7.1), 2.52 (d, 1H, $C\underline{H}H$, J_{AX}= 11.7), 3.50 (d, 1H, $CH\underline{H}$, J_{AX}=11.7), 4.01 (s, 3H, MeO), 4.23 (s, 3H, MeO), 4.28 (q, 2H, $\underline{CH_2}Me$, J=7.1), 4.29 (s, 1H, CH), 5.91 (s 1H, OH), 6.87 (d, 1H, H^3, J=2.3), 7.56 (d, 1H, H^2, J=2.3). IR (Vaseline oil, cm^{-1}): 3480 (OH), 3170, 3140 (=CH), 1740 (C=O), 1630, 1610, 1540 (arom.). Found (%): C, 49.80; H, 3.75. Calcd for $C_{18}H_{17}F_3O_7S$ (%): C, 49.77; H, 3.94.
8. Preparation of **5a**: a mixture of fluorokhellin **3a** (0.25 g, 0.8 mmol) and ethyl mercaptoacetate (0.5 g, 4.2 mmol) in the presence of one drop of Et_3N without solvent was heated in a sealed ampoule at 140–150°C for 1.5 h. After cooling, the reaction mixture was diluted with 5 ml of ethanol–water (3:1) and the crystalline material was isolated by filtration and washed with aqueous ethanol to give 0.1 g (34% yield) of compound **5a**, mp 187–188°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.96–4.17 (AB-part of ABX-system, 2H, CH_2, $^2J_{AB}$=19.3; δ_A=4.14, δ_B= 4.00, $^3J_{AX}$=4.1, $^3J_{BX}$=10.8), 4.33–4.43 (m, 1H, CH), 6.98 (d, 1H, H^3, J=2.3), 7.64 (d, 1H, H^2, J=2.3). IR (Vaseline oil, cm^{-1}): 1720 (C=O), 1610, 1580, 1550 w (arom.). Found (%): C, 51.63; H, 2.89. Calcd for $C_{16}H_{11}F_3O_5S$ (%): C, 51.62; H, 2.98.
9. Zoubir, B.; Refouvelet, B.; Aubin, F.; Humbert, P.; Xicluna, A. *J. Heterocyclic Chem.* **1999**, *36*, 509–513.