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Unexpected synthesis of 3,5-diethoxycarbonyl-2-pentafluorophenyl-4-phenyl-7,8,9,10-tetrafluoro-4,5-dihydrobenzo[*b*]oxacin-6-one

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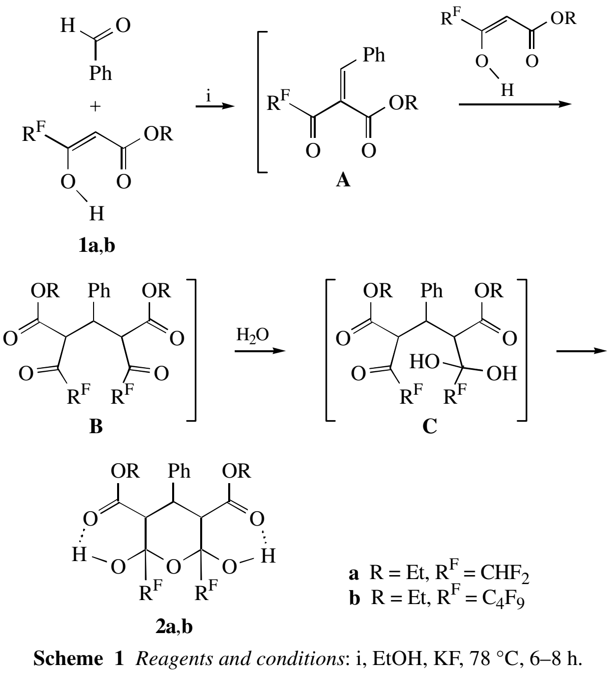
The reaction of ethyl pentafluorobenzoylacetate with benzaldehyde in the presence of a base affords 3,5-diethoxycarbonyl-2-pentafluorophenyl-4-phenyl-7,8,9,10-tetrafluoro-4,5-dihydrobenzo[*b*]oxacin-6-one in contrast to fluoroalkyl-containing 3-oxo esters yielding 3,5-dialkoxycarbonyl-2,6-dihydroxy-2,6-difluoroalkyl-4-phenyltetrahydropyranes under the same conditions.

The interaction of non-fluorinated 3-oxo esters with aldehydes (Knövenagel condensation) affords 2-alkylidene(arylidene)-3-oxo esters,[1,2] 2-alkylidene(arylidene)di(3-oxo esters)[3] or cyclohexanones[3] depending on the reaction conditions and the nature of starting reagents. Data on the reaction of fluorine-containing 3-oxo esters with aldehydes are available only for the transformations of ethyl trifluoroacetylacetate resulting in the formation of 2-arylidene-substituted ethyl trifluoroacetylacetates[4] or 4-aryl-3,5-diethoxycarbonyl-2,6-dihydroxy-2,6-di(trifluoromethyl)-tetrahydropyrans.[5]

In this work, we studied the Knövenagel condensation of fluorine-containing 3-oxo esters. We found that fluoroalkyl-containing 3-oxo esters **1a**,**b** react with benzaldehyde to form tetrahydropyrans **2a**,**b**[†,‡] (Scheme 1). These reactions were carried out in refluxing ethanol in the presence of a base (KF, piperidine) for 6–8 h providing tetrahydropyrans in moderate yields.

In principle, two isomeric structures are conceivable for these condensation products, namely, a tetrahydropyran structure like **2** or an isomeric acyclic dialkyl 2-fluoroacyl-3-phenyl-4-(1,1-dihydroxy-1-fluoroalkyl) glutarate structure like **C**. Note that an earlier report on the condensation of ethyl trifluoroacetylacetate with benzaldehyde postulated the formation of tetrahydropyran based on analytical data and IR spectroscopy.[5] We assigned the structure of tetrahydropyrans **2a**,**b** to these products based on the detailed NMR-spectroscopic characterization.

A set of resonance signals due to equivalent ester and fluoroalkyl groups in the ^{1}H and ^{19}F NMR spectra correspond to the symmetrical structure of tetrahydropyran **2**. The ^{1}H NMR spectra exhibit resonance signals of the protons H^{4} and H^{3}, H^{5} as a triplet and a doublet, respectively. This can take place only in a tetrahydropyran structure, when the two protons H^{3} and H^{5} are magnetically equivalent and interact with the third non-equivalent proton H^{4}. In the ^{19}F NMR spectra, signals of fluorine atoms at the α-carbon of the fluoroalkyl substituent are the AB system, which is typical of a fluoroalkyl radical attached to an asymmetrical centre.



Scheme 1 *Reagents and conditions*: i, EtOH, KF, 78 °C, 6–8 h.

In contrast to fluoroalkyl-containing 3-oxo esters, ethyl pentafluorobenzoyl acetate **1c** reacts with benzaldehyde under these conditions yielding product **3**[†] (Scheme 2). In the ^{19}F NMR spectrum of **3**, the resonance signals of fluorine atoms of C_6F_5 and C_6F_4 fragments are present in the ratio 1:1. The ^{1}H NMR spectrum exhibits doubled resonance signals of non-equivalent ester groups and resonance signals of two methine protons as the AB system ($J = 11.3$ Hz). From these spectral and analytical data, the structures of 5,6,7,8-tetrafluoro-4,2-(1,3-diethoxycarbonyl-2-phenyl-1,3-propylenediyl)-2-pentafluorophenylbenzo[*d*]-

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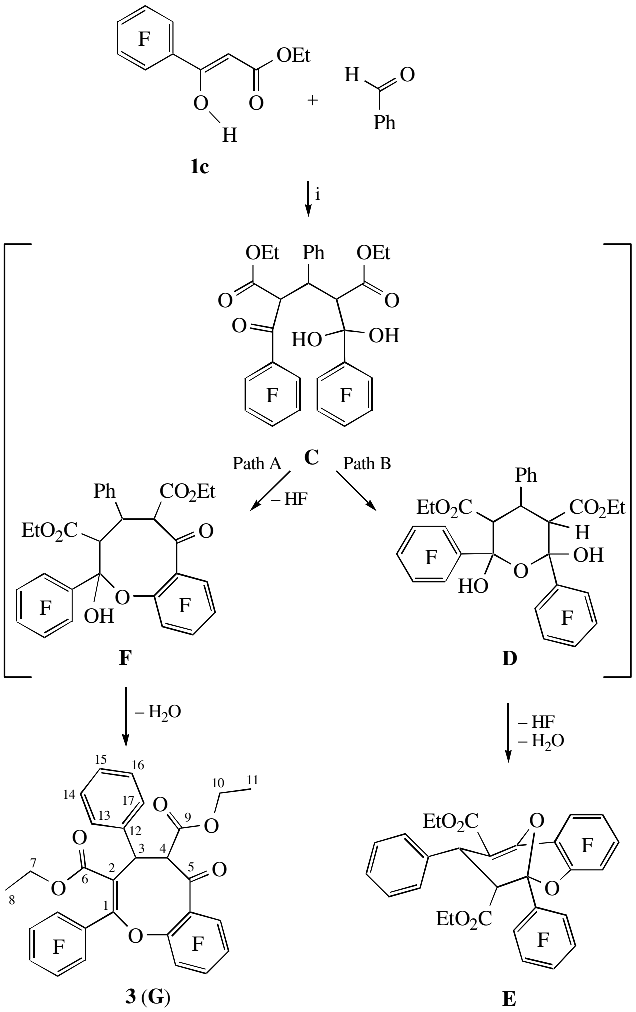
[†] All new compounds **2a**,**b**, **3** were characterised by IR (Vaseline oil), ^{19}F NMR (75.3 MHz, C_6F_6) and ^{1}H NMR (400 and 100 MHz, Me_4Si) spectroscopy; product **3** was additionally studied by ^{13}C NMR spectroscopy (100 MHz, Me_4Si).

2,6-Dihydroxy-2,6-di(difluoromethyl)-3,5-diethoxycarbonyl-4-phenyl-tetrahydropyran **2a** (typical procedure). A mixture of 3-oxo ester **1a** (16.61 g, 0.1 mol), benzaldehyde (5.31 g, 0.05 mol) and anhydrous KF (1.57 g, 0.027 mol) in ethanol (50 ml) was refluxed for 6–8 h. After cooling, the reaction mass was poured into cool water (100 ml). The organic layer was extracted with diethyl ether (2×30 ml). The ether layers were combined, shaken with an aqueous 40% $NaHSO_3$ solution and washed with water. The ether was evaporated. The residue was recrystallised from ethanol–water (~1:1) to give 8.77 g (40%) of product **2a**, mp 128–130 °C. ^{1}H NMR ([$^{2}H_6$]DMSO) δ: 0.85 (t, 3H, OCH_2Me, J 7.1 Hz), 3.11 (d, 2H, H^{3}, H^{5}, J 12.4 Hz), 3.77 (q, 2H, OCH_2Me, J 7.1 Hz), 4.05 (t, 1H, H^{4}, J 12.4 Hz), 5.76 (t, 1H, HCF_2, J_{H-F} 54.7 Hz), 7.14–7.26 (m, 5H, Ph). ^{19}F NMR ([$^{2}H_6$]DMSO) δ: 28.57 (AB system, 2F, HCF_2, J_{F-F} 278 Hz, J_{H-F} 54.7 Hz). IR (ν/cm^{-1}): 3380 (OH), 1750 (CO_2Et), 1090–1240 (CF). Found (%): C, 52.03; C, 5.29; F, 17.69. Calc. for $C_{19}H_{22}F_4O_7$ (%): C, 52.05; H, 5.06; F, 17.34.

2,6-Dihydroxy-2,6-di(nonafluorobutyl)-3,5-diethoxycarbonyl-4-phenyl-tetrahydropyran **2b**: yield 13.16 g (34%), mp 125–127 °C. ^{1}H NMR ($CDCl_3$) δ: 0.76 (t, 3H, OCH_2Me, J 7.2 Hz), 3.26 (d, 2H, H^{3}, H^{5}, J 12.3 Hz), 3.84 (q, 2H, OCH_2Me, J 7.2 Hz), 4.05 (t, 1H, H^{4}, J 12.3 Hz), 6.17 (br. s, 2H, 2OH), 7.30 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$) δ: 35.50 (m, 2F, CF_2), 41.29 (m, 4F, $2CF_2$), 81.03 (m, 3F, CF_3). IR (ν/cm^{-1}): 3360 (OH), 1710 (CO_2Et), 1100–1270 (CF). Found (%): C, 38.83; H, 2.62; F, 44.33. Calc. for $C_{25}H_{20}F_{18}O_7$ (%): C, 38.77; H, 2.60; F, 44.16.

*3,5-Diethoxycarbonyl-2-pentafluorophenyl-4-phenyl-7,8,9,10-tetrafluoro-4,5-dihydrobenzo[*b*]oxacin-6-one* **3**: yield 12.01 g (38%), mp 105–106 °C. ^{1}H NMR ([$^{2}H_6$]DMSO) δ: 1.09, 0.96 (2t, 6H, $2OCH_2Me$, J 7.2 Hz), 4.14–3.88 (2q, 4H, $2OCH_2Me$, J 7.2 Hz), 5.05 (AB system, 2H, H^{2}, H^{3}, $\Delta\nu$ 29.56 Hz, J 11.33 Hz), 7.6–7.28 (m, 5H, Ph). ^{13}C NMR ([$^{2}H_6$]DMSO) δ: 146.22 (C^{1}), 131.83 (C^{2}), 60.83 (C^{3}), 45.54 (C^{4}), 190.0 (C^{5}), 163.72 (C^{6}), 61.49 (C^{7}), 13.11 (C^{8}), 166.75 (C^{9}), 62.11 (C^{10}), 13.63 (C^{11}), 138.17 (C^{12}), 128.99 (C^{13}, C^{17}), 128.53 (C^{14}, C^{16}). ^{19}F NMR ([$^{2}H_6$]DMSO) δ: 23.98–20.64 (m, 2F), 19.83–19.31 (m, 1F), 16.48–15.83 (m, 1F), 12.78–12.13 (m, 1F), 8.04–7.50 (m, 1F), 5.75–5.16 (m, 1F), –0.34–1.78 (m, 2F). IR (ν/cm^{-1}): 1745 (CO_2Et), 1710 (CO_2Et, C=O), 1625, 1530 (C=C), 970 (CF). Found (%): C, 55.16; H, 2.81; F, 27.35. Calc. for $C_{29}H_{17}F_9O_6$ (%): C, 55.07; H, 2.71; F, 27.04.



Scheme 2 *Reagents and conditions*: i, EtOH, KF, 78 °C, 6–8 h.

dioxane **E** or 3,5-diethoxycarbonyl-2-pentafluorophenyl-4-phenyl-7,8,9,10-tetrafluoro-4,5-dihydrobenzo[*b*]oxacin-6-one **G** may be assigned to product **3**. A possible mechanism of the formation of compounds **G**, **E** is shown in Scheme 2. Evidently, glutarate **C** is formed as an intermediate in each case. Under reaction conditions, the latter undergoes intramolecular cyclyzation to afford heterocycle **G** (path A) or product **E** (*via* pyran **D**, path B). The cyclization occurs through the intramolecular replacement of the *ortho*-fluorine atom in the pentafluorophenyl substituent by a hydroxyl group followed by elimination of HF and H_2O (Scheme 2).

The distinction between structures **G** and **E** was made on the basis of ^{13}C NMR-spectroscopic data. The spectrum exhibited a signal at 190.0 ppm, which is typical of a carbonyl atom in structure **G**.

The formation of tetrahydropyrans in the reactions of fluoroalkyl-containing 3-oxo esters with benzaldehyde is possible because of their ability to add water to the carbonyl group bound to the fluorine-containing substituent.[6] However, non-fluorinated analogues form acyclic products of mono-[1,2] and di-condensation[2,3] of type **A** and **B** with aldehydes (Scheme 1). Apparently, when fluoroalkyl-containing 3-oxo esters react with benzaldehyde in refluxing ethanol, compounds **A**, **B** and **C** can be intermediates. Under these conditions, the end products are thermodynamically more stable tetrahydropyrans **2** (Scheme 1). The interaction of ethyl pentafluorobenzoylacetate with benzaldehyde also results in the formation of heterocyclic product. However, in contrast to the reactions of fluoroalkyl-substituted 3-oxo esters, nucleophilic aromatic substitution is the main direction of cyclization when heterocycle **3** is formed (Scheme 2).

Thus, the reactions of fluorinated 3-oxo esters with aldehydes are of interest for the synthesis of heterocycles.

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