Synthesis of polyfluoroalkyl-containing dienones

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Previously unknown β-fluoroalkyl-α,β,α′,β′-dienones were synthesized by dehydration of β-hydroxy-β-fluoroalkyl-α′,β′-enones.

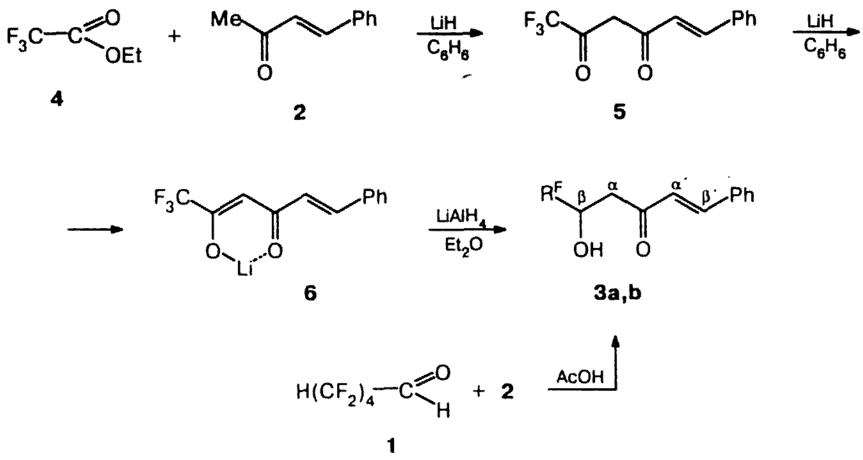
Key words: β-hydroxy-β-fluoroalkyl-α′,β′-enones, dehydration; β-fluoroalkyl-α,β,α′,β′-dienones.

Fluoroalkyl-containing β-hydroxyketones and α,β-enones contain two non-equivalent electrophilic centers and are convenient building blocks for the introduction of fluoroalkyl substituents into more complex organic and heterocyclic compounds.[1—3] In this regard β-hydroxy-β-fluoroalkyl-α′,β′-enones and β-fluoroalkyl-α,β,α′,β′-dienones containing three electrophilic centers are promising, but have not been reported yet. In this work we synthesized these compounds for the first time from fluorinated aldehydes and esters of fluorocarboxylic acids.

The synthesis of β-fluoroalkyl-α,β-enones by dehydration of β-fluoroalkyl-β-hydroxyketones with H_2SO_4 has been described.[4] The β-fluoroalkyl-β-hydroxyketones, in their turn, were obtained either by aldol condensation[4] or reduction of Li-salts of β-fluoroalkyl-β-diketones.[5]

We have found that these methods can also be used for the synthesis of β-hydroxy-β-fluoroalkyl-α′,β′-enones. Condensation of aldehyde **1** with enone **2** leads to hydroxyenone **3a** (Scheme 1). The reduction of Li-salts consists of several steps. Condensation of ethyl trifluoroacetate **4** with enone **2** in the presence of LiH yields previously unknown dione **5**, which reacts with LiH in benzene to give lithium salt **6**. It should be noted that this salt is formed at the step of condensation in the presence of LiH, however, isolation of the pure diketone is necessary to remove the by-products of condensation interfering with the reduction process. It is well known that the reduction of lithium salts of β-fluoroalkyl-β-diketones occurs smoothly if the nonfluorinated substituent is an aryl group, and that complex mixtures of products are formed in the case of alkyl substituents.[5] We found that selective reduction of the carbonyl group bound with a fluoroalkyl group, resulting in 5-hydroxyenone **3b**, occurs when Li-salt **6** (containing the nonfluorinated substituent —CH=CHPh) interacts with $LiAlH_4$ in ether.

Scheme 1



$R^F = H(CF_2)_4$ (**a**), CF_3 (**b**)

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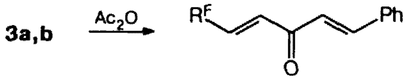
Both of the methods proposed for the synthesis of β-hydroxy-β-fluoroalkyl-α′,β′-enones can be used on a preparative scale. The aldol condensation is a one-step reaction and gives a 71% yield. However, this reaction is a lengthy process (48 h), and requires obtaining the fluorinated aldehydes (unstable under storage) prior to condensation. The reduction of Li-salts is a multistep process, but it takes less time. The yield of the reduction product is 63% on the basis of diketone **5**.

It was found that H_2SO_4, a commonly used dehydrating agent for β-fluoroalkyl-β-hydroxyketones, is not efficient in the case of compounds **3a,b** because of the formation of by-products (in significant amounts). Dehydration of these compounds with Ac_2O gave good results. In this case β-fluoroalkyl-α,β,α′,β′-dienones **7a,b** were isolated (Scheme 2).

Scheme 2



7a,b

$R^F = H(CF_2)_4$ (**a**), CF_3 (**b**)

The protons at the double bond in molecules of compounds **2**, **3**, and **5** have a *trans*-orientation ($J_{CH=CH}$ = 16 Hz). It is well known that dehydration of β-fluoroalkyl-β-hydroxyketones results in *trans*-β-fluoroalkyl-α,β-enones,[4] however, in the ^1H NMR spectra of compounds **7a,b** the signals from the olefin and aryl protons overlap, which makes it impossible to determine the configuration of these compounds.

Experimental

IR spectra were recorded on a Specord 75-IR spectrophotometer (in neat liquids and in pastes in Vaseline oil for solids). ^1H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) in $CDCl_3$.

Condensation of 2,2,3,3,4,4,5,5-octafluorovaleraldehyde (1) with 4-phenyl-3-buten-2-one (2). A mixture of 2,2,3,3,4,4,5,5-octafluorovaleraldehyde (16.0 g, 70 mmol), 4-phenyl-3-buten-2-one (10.2 g, 70 mmol), and 150 mL of glacial AcOH was refluxed for 48 h, cooled, poured into water, and extracted with chloroform. The extracts were dried over $MgSO_4$, and the solvent was distilled off. The resulting residue was recrystallized from hexane to yield 18.7 g (71%) of 5-hydroxy-1-phenyl-6,6,7,7,8,8,9,9-octafluoro-1-nonen-3-one (**3a**) in the form of colorless needles, m.p. 82.5—83.0 °C. Found (%): C, 47.88; H, 3.21; F, 40.39. $C_{15}H_{12}F_8O_2$. Calculated (%): C, 47.75; H, 3.57; F, 40.52. IR, ν/cm^{-1}: 1625 (C=C); 1661 (C=O); 3395 (OH). ^1H NMR, δ: 3.06—3.13 (m, 2 H, CH_2); 3.89 (d, 1 H, OH, $J_{OH-H(\beta)}$ = 4.69 Hz); 4.81—5.00 (m, 1 H, CF_2CH); 6.09 (tt, 1 H, HCF_2, J_{H-CF_2} = 52.35 Hz, $J_{H-CF_2CF_2}$ = 5.87 Hz); 6.74 (d, 1 H, C$\underline{H}$Ph, J_{CH-CH} = 16.20 Hz); 7.40—7.60 (m, 5 H, Ph); 7.61 (d, 1 H, C$\underline{H}$CO).

6-Phenyl-1,1,1-trifluoro-5-hexene-2,4-dione (5). A suspension of LiH (6.4 g, 0.8 mol) in 300 mL of benzene was treated with a mixture of CF_3CO_2Et (99.5 g, 0.7 mol) and 4-phenyl-3-buten-2-one (90 g, 0.61 mol). After addition of the first 10 mL of the mixture, the flask was warmed until the reaction started (liberation of hydrogen), and the rest of the mixture was then added dropwise. The resulting mixture was stirred for a period of 5 h, allowed to stand overnight, and was then poured into a mixture of ice (500 g) and H_2SO_4 (100 mL), extracted with chloroform, and dried over $MgSO_4$. The solvent was distilled off, and the residue was recrystallized from hexane to yield compound **5** (96 g, 65%) in the form of yellow needles, m.p. 61.0—61.5 °C. ^1H NMR, δ: 5.99 (s, 1 H, H(α)); 6.52 (d, 1 H, CH_2Ph); 7.74 (d, 1 H, CH_2CO, J_{H-C-H} = 15.80 Hz); 7.21—7.73 (m, 5 H, Ph); 13.75 (br.s, 1 H, OH).

Li-salt of 6-phenyl-1,1,1-trifluoro-5-hexene-2,4-dione (6). A solution of 6-phenyl-1,1,1-trifluoro-5-hexene-2,4-dione **5** (10 g, 41 mmol) in 50 mL of dry benzene was added dropwise to a suspension of LiH (0.4 g, 50 mmol) in 100 mL of dry benzene with stirring and cooling (~10 °C) (liberation of hydrogen was kept from being too vigorous), and was stirred for 1 h. The residue was separated by filtration, washed with hexane, and dried in air to give compound **6** (8.4 g, 83%) in the form of a light yellow powder, m.p. >280 °C. IR, ν/cm^{-1}: 1570 (C=C); 1592 (C=O).

5-Hydroxy-1-phenyl-6,6,6-trifluoro-1-hexen-3-one (3b). A solution of 6-phenyl-1,1,1-trifluoro-5-hexene-2,4-dione (17 g, 70 mmol) in 50 mL of dry ether was added dropwise to a suspension of LiH (0.56 g, 70 mmol) in 50 mL of dry ether with stirring and cooling (~0 °C) (liberation of hydrogen was kept from being too vigorous). The reaction mixture was allowed to stand for 30 min, $LiAlH_4$ (1.33 g, 35 mmol) was added to it in portions, and the resulting mixture was stirred for 4 h and poured into a mixture of ice (100 g) and conc. HCl (30 mL), and extracted with chloroform. The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was recrystallized from hexane to give compound **3b** (10.8 r, 63%) in the form of colorless crystals, m.p. 69—70 °C. IR, ν/cm^{-1}: 1624 (C=C); 1660 (C=O); 3330 (OH). ^1H NMR, δ: 2.76—3.27 (m, 2 H, CH_2); 4.46—4.68 (m, 2 H, CF_3CH + OH); 6.66 (d, 1 H, $\underline{CH}$Ph, $J_{CH=CH}$ = 16.20 Hz); 7.17—7.48 (m, 5 H, Ph); 7.53 (d, 1 H, CHCO).

Dehydration of 5-hydroxy-1-phenyl-6,6,6-trifluoro-1-hexen-3-one (3b). A mixture of 5-hydroxy-1-phenyl-6,6,6-trifluoro-1-hexen-3-one (8.3 g, 34 mmol) and acetic anhydride (8.8 g, 0.1 mmol) was refluxed for 10 h (TLC monitoring), cooled, poured into water, and extracted with chloroform. The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was filtered through silica gel ($CHCl_3$ as the eluent). After the solvent was distilled off, 1-phenyl-6,6,6-trifluorohexa-1,4-diene (**7b**) (5.8 g, 76%) was obtained in the form of a light yellow oil. IR, ν/cm^{-1}: 1612 (C=CPh); 1635 (CF_3C=C); 1675 (C=O). ^1H NMR, δ: 6.83—8.02 (m, 9 H, Ph + H olefin).

Dehydration of 5-hydroxy-1-phenyl-6,6,7,7,8,8,9,9-octafluoro-1-nonen-3-one (3a). 1-Phenyl-6,6,7,7,8,8,9,9-octafluoro-1,4-nonadien-3-one (**7a**) (11.3 g, 83%) was obtained similarly from 5-hydroxy-1-phenyl-6,6,7,7,8,8,9,9-octafluoro-1-nonen-3-one (14.3 g, 38 mol) and acetic anhydride (11.3 g, 0.11 mol) in the form of a light yellow oil. Found (%): C, 50.29; H, 2.81; F, 42.43. $C_{15}H_{10}F_8O$. Calculated (%): C, 50.21; H, 3.20; F, 42.00. IR, ν/cm^{-1}: 1620 (C=CPh); 1640 (CF_2C=C); 1670 (C=O). ^1H NMR, δ: 6.13 (tt, 1 H, HCF_2, J_{H-CF_2} = 51.65 Hz, $J_{H-CF_2CF_2}$ = 5.40 Hz); 6.84—7.77 (m, 9 H, Ph + H olefin).

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