Synthesis of 4-acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones

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4-Acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones were obtained for the first time by the reactions of fluoroalkyl-containing 1,3-diketones and 3-oxo esters with oxalyl chloride.

Key words: fluoroalkyl-containing 1,3-diketones, 3-oxo esters, oxalyl chloride, acylation, furan-2-ones.

Acylation of 1,3-dicarbonyl compounds with oxalyl chloride is used, among other methods, to synthesize substituted furan-2,3-diones.[1] The latter play an important role in organic chemistry since they can serve as convenient precursors of compounds of different classes, including acyl(aroyl)pyruvic acids, their esters and amides,[1,2] and a variety of heterocyclic derivatives.[1] Literature data on the synthesis of substituted furandiones from fluorinated 1,3-dicarbonyl compounds are lacking.

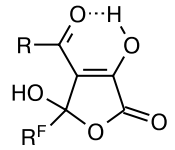
The goal of the present work was to obtain (fluoroalkyl)furandiones by reactions of 1,3-diketones and 3-oxo esters with oxalyl chloride.

Results and Discussion

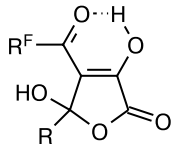
We found that the reactions of fluorine-containing 1,3-diketones **1a—c** and 3-oxo ester **2** with oxalyl chloride in anhydrous diethyl ether at room temperature do not afford expected 4-acyl-5-alkyl-2,3-dihydrofuran-2,3-diones **3**. According to the elemental analysis data, the molecular masses of products **4a—d** are higher by 18 amu (water) than those of the corresponding diones **3**. The mass spectrum of compound **4c** also shows a molecular ion peak (*m/z* 338 $[M]^+$) different from that calculated for the corresponding furan-2,3-dione **3** (*m/z* 320 $[M]^+$).

The ^{1}H NMR spectra of compounds **4** are not so informative (Table 1). The IR spectra of these compounds contain higher- and lower-frequency absorption bands of two carbonyl groups, a band of the C=C bond, and bands corresponding to the OH stretching vibrations (see Table 1).

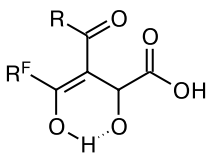
According to the elemental analysis, IR, and ^{1}H NMR data, compounds **4** can be represented by three equally probable structures, namely, 4-acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones $\mathbf{F_1}$, which are formed by *C*-acylation of a starting 1,3-dicarbonyl compound at position 2 and by *O*-acylation involving the carbonyl group at the fluoroalkyl substituent; 5-alkyl(aryl, alkoxy)-4-fluoroacyl-3,5-dihydroxyfuran-2(5*H*)-ones $\mathbf{F_2}$, which are obtained analogously except that *O*-acylation occurs at the carbonyl group bound to the nonfluorinated radical; and 3-fluoroacyl derivatives of acyl(aroyl)pyruvic acids (**A**), which are products of *C*-acylation alone.



$\mathbf{F_1}$



$\mathbf{F_2}$



A

Furanone $\mathbf{F_1}$ was preferred since a triplet ($^2J_{C-F}$ = 28.8 Hz) for the carbon atom at the C_2F_5 group in compound **4c** and a quartet ($^2J_{C-F}$ = 35.5 Hz) for the C atom at the CF_3 group in compound **4d** appear in their ^{13}C NMR spectra in a range characteristic of a quaternary rather than carbonyl C atom,[3] which would be expected for isomeric structure $\mathbf{F_2}$ or for acid **A** (Table 2).

In addition, the fluoroalkyl radicals in compounds **4b,c** are longer than a trifluoromethyl group, and signals for the fluorine atoms at the C_α atom appear as an AB system in their ^{19}F NMR spectra (see Table 1), which is characteristic of a fluoroalkyl radical bound to an asymmetric center.[4]

Hence, one can conclude that the acylation of fluoroalkyl-containing 1,3-dicarbonyl compounds **1** and **2** with oxalyl chloride yielded 4-acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones **4** ($\mathbf{F_1}$) (Scheme 1).

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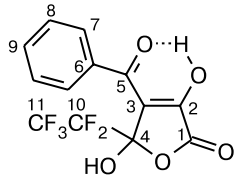
Table 1. Main physicochemical parameters of 4-acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones **4a—d**

Compound	M.p. /°C	Yield (%)	Found / Calculated (%) C	H	F	Molecular formula	IR, ν/cm^{-1}	NMR (DMSO-d$_6$, δ, J/Hz) ^{1}H	^{19}F
4a	110—112	24	37.06 37.19	2.06 2.23	25.17 25.20	$C_7H_5F_3O_5$	3180, 3090, 2700 (OH); 1810 (C=O lact.); 1670 (C=OMe); 1580 (C=C); 1230—1150 (C—F)	2.40 (s, 3 H, Me); 4.14, 9.10 (both br.s, 1 H each, OH)	81.43 (s, 3 F, CF_3)
4b	141—143	44	48.41 48.77	2.42 2.52	23.57 23.72	$C_{13}H_8F_4O_5$	3380, 3160, 2750 (OH); 1790 (C=O lact.); 1670 (C=OPh); 1600, 1580, 1540 (C=C); 1270—1100 (C—F)	6.46 (tm, 1 H, HCF_2CF_2, $^2J_{H-F}$ = 52); 7.48—7.80 (m, 5 H, Ph); 9.27 (br.s, 1 H, OH)	25.25 (m, 2 F, $HC\underline{F}_2CF_2$, AB system, $\Delta\nu$ = 214, $^2J_{F_1-F_2}$ = 298, $^2J_{F_1,F_2-H}$ = 52, $^3J_{F_1-F}$ = 8.6, $^3J_{F_2-F}$ = 3.5); 33.81 (m, 2 F, $HCF_2C\underline{F}_2$, AB system, $\Delta\nu$ = 455, $^2J_{F-F}$ = 267)
4c	124—126	30	46.32 46.17	1.89 2.08	28.12 28.09	$C_{13}H_7F_5O_5$	3400, 3200, 2700 (OH); 1800 (C=O lact.); 1670 (C=OPh); 1610, 1600, 1580, 1540 (C=C); 1220—1100 (C—F)	7.49—7.80 (m, 5 H, Ph); 3.95, 9.42 (both br.s, 1 H each, OH)	39.06 (m, 2 F, CF_2, AB system, $\Delta\nu$ = 542, $^2J_{F-F}$ = 274); 83.51 (s, 3 F, CF_3)
4d	44—45	36	37.52 37.52	2.75 2.76	22.11 22.24	$C_8H_7F_3O_6$	3460, 3170, 2700 (OH); 1760 (C=O lact.); 1690 (CO_2Et); 1640 (C=C); 1280—1170 (C—F)	1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1); 4.23 (q, 3 H, $OC\underline{H}_2CH_3$, J = 7.1); 9.21 (br.s, 1 H, OH)	81.48 (s, 3 F, CF_3)

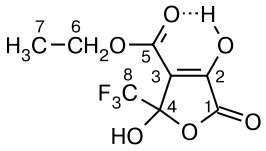
Insofar as furanones **4** contain a 1,3-dicarbonyl fragment, keto-enol tautomerism is possible for these compounds (Scheme 2).

However, the ^{1}H and ^{19}F NMR spectra of compounds **4a—d** (see Table 1) show only one set of signals, which suggests the formation of a single tautomer in each case. Almost complete enolization of these compounds is evident from a broadened low-field singlet for the OH group and from the absence of a signal for the methine proton in their ^{1}H NMR spectra. Analysis of the IR spectra of

Table 2. ^{13}C NMR spectra of furanones **4c,d** in DMSO-d$_6$



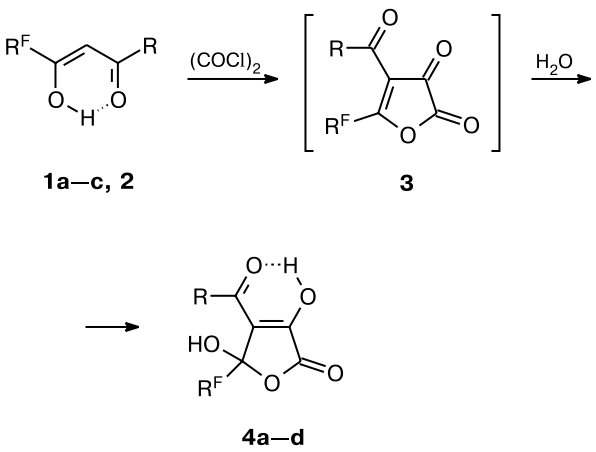
4c



4d

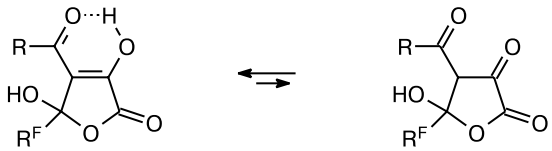
Compound	δ (J_{C-F}/Hz) C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)
4c	165.06	149.01	116.80	101.68 t ($^2J_{C-F}$ = 28)	188.21	136.75	128.62	128.80	133.52	118.42 qt ($^1J_{C-F}$ = 289, $^2J_{C-F}$ = 36)	111.00 tq ($^1J_{C-F}$ = 260; $^2J_{C-F}$ = 40)
4d	164.56	152.38	110.43	99.88 q ($^2J_{C-F}$ = 35)	160.31	60.42	14.00	121.43 q ($^1J_{C-F}$ = 286)	—	—	—

Scheme 1



R = Me, $R^F = CF_3$ (**1a**, **4a**);
R = Ph, $R^F = H(CF_2)_2$ (**1b**, **4b**), C_2F_5 (**1c**, **4c**);
R = OEt, $R^F = CF_3$ (**2**, **4d**)

Scheme 2



products **4a—d** (see Table 1) also confirms the enol structure of these heterocycles. Apparently, the enol form of furanones **4a—d** is stabilized by an intramolecular hydrogen bond between the hydroxy group and the acyl or ester CO group. The formation of this bond is confirmed by the fact that the stretching vibrations of these groups in compounds **4a—d** have somewhat lower frequencies (see Table 1) compared to the previous data.[5]

The behavior of fluoroalkyl-containing 1,3-diketones in the reactions with oxalyl chloride differs from the behavior of their nonfluorinated unsymmetrical analogs. In the case of nonfluorinated 1,3-diketones, regioselective *O*-acylation occurs at the carbonyl group in the neighborhood of the bulkier substituent,[6,7] while fluorine-containing 1,3-dicarbonyl compounds react with exclusive involvement of the fluoroacyl group. In addition, unlike nonfluorinated 1,3-diketones and 3-oxo esters, fluorinated 1,3-dicarbonyl compounds yield furan-2-ones **4** rather than furan-2,3-diones **3** as the final products. Obviously, intermediate compounds **3** are unstable in contact with atmospheric moisture. They very easily add a water molecule, probably because of the presence of a strong electron-withdrawing fluorinated group. It is known that both fluoroalkyl-containing 1,3-dicarbonyl compounds themselves and their derivatives add water to give stable *gem*-diols.[8]

Nonfluorinated furan-2,3-diones **3** also easily react with atmospheric moisture to give 3-acyl derivatives of acylpyruvic acid (**A**).[9] However, this reaction is reversible; recyclization into furan-2,3-diones occurs over P_2O_5 at 70 °C.

All attempts to dehydrate 5-fluoroalkyl-3,5-dihydroxyfuran-2-ones **4** by heating them *in vacuo* over P_2O_5 or in boiling toluene in the presence of *p*-toluenesulfonic acid with azeotropic removal of water failed.

The 4-acyl(alkoxycarbonyl)-5-fluoroalkyl-3,5-dihydroxyfuran-2(5*H*)-ones obtained can possess biological activity; in addition, these polyfunctional compounds are promising for various subsequent transformations.

Experimental

IR spectra were recorded on a Specord IR75 spectrometer in the range 4000—400 cm^{-1} (Nujol). ^1H NMR spectra were recorded on Tesla BS-567A and Bruker DRX-400 spectrometers (80 and 400 MHz, respectively) with Me_4Si as the internal standard. ^{19}F NMR spectra were obtained with a Tesla BS-587A spectrometer (75 MHz, C_6F_6). ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (100 MHz) with Me_4Si as a standard. Elemental analysis was carried out on a Carlo Erba CHNS-O EA 1108 analyzer. Mass spectra were obtained with a Varian MAT-311A instrument.

4-Acetyl-3,5-dihydroxy-5-(trifluoromethyl)furan-2(5*H*)-one (4a). A mixture of 1,3-diketone **1a** (1.54 g, 0.01 mol) and oxalyl chloride (1.27 g, 0.01 mol) in 10 mL of anhydrous Et_2O was kept at ~20 °C for 8—10 days. The solvent was evaporated, and the residue was triturated with hexane to crystallization. The crystals were washed with boiling hexane and dried *in vacuo* over P_2O_5 to give compound **4a** (0.54 g) (see Table 1).

4-Benzoyl-3,5-dihydroxy-5-(1,1,2,2-tetrafluoroethyl)furan-2(5*H*)-one (4b) was obtained analogously from 1,3-diketone **1b** (1.72 g, 0.01 mol). The yield of compound **4b** was 1.40 g (see Table 1).

4-Benzoyl-3,5-dihydroxy-5-(perfluoroethyl)furan-2(5*H*)-one (4c) was obtained analogously from 1,3-diketone **1c** (2.66 g, 0.01 mol). The yield of compound **4c** was 1.02 g (see Tables 1 and 2). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 338 $[M]^+$ (18), 294 $[M - CO_2]^+$ (4), 266 $[M - COCO_2]^+$ (22), 219 $[M - C_2F_5]^+$ (1), 191 $[M - COC_2F_5]^+$ (4), 147 $[COC_2F_5]^+$ (79), 119 $[C_2F_5]^+$ (4), 105 $[COPh]^+$ (100), 77 $[Ph]^+$ (65), 69 $[CF_3]^+$ (84), 51 $[HCF_2]^+$ (26).

4-Ethoxycarbonyl-3,5-dihydroxy-5-(trifluoromethyl)furan-2(5*H*)-one (4d) was obtained analogously from 3-oxo ester **2** (1.84 g, 0.01 mol). The yield of compound **4d** was 0.49 g (see Table 1).

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