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Synthesis of bis(polyfluoroalkyl)-1,3,5-triketones

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A preparative procedure was developed for the synthesis of polyfluoroalkyl-1,3,5-triketones by condensation of acetone or fluorinated methyl β-diketones with methyl perfluorocarboxylates in the presence of LiH. In the case of CF_3 substituents, the formation of triketone was accompanied by the formation of its cyclic hydrate, *viz.*, of dihydroxytetrahydropyranone.

Key words: polyfluoroalkyl-1,3,5-triketones, β-diketones, acylation, lithium hydride, keto-enol tautomerism, hydration.

Polyfluoroalkyl-1,3,5-triketones (TK) remain virtually unknown, unlike their nonfluorinated analogs for which convenient preparative synthetic procedures were developed.[1—4] There are only scarce data on metal-chelate complexes of trifluoro- and hexafluorodiacetylacetone, which were prepared from sodium salts without isolation of TK as such.[5] Syntheses of ethyl ethers of enols of some polyfluoroacylacetylacetones[6] and 4-hydroxypyridine derivatives from hexafluorodiacetylacetone[7] were also reported. Data on 1,3,5-triketones containing other fluorine-containing substituents are unavailable in the literature.

However, these compounds are of considerable theoretical and practical interest as subjects of investigation into the effect of electron-withdrawing susbtituents on the keto-enol and ring-chain tautomerism, as efficient complex-forming agents, and as intermediates in the synthesis of new fluoroalkyl-containing carbo- and heterocyclic systems.[6,8] The presence of non-equivalent reaction centers makes it possible to study competitive reactivities of these compounds in reactions with different electrophiles and nucleophiles. Both TK and their derivatives may find wide applications.[6,9]

The most common procedure for the preparation of non-fluorinated TK involves acylation of methyl β-diketones with esters under the action of KNH_2 in liquid ammonia[2] or of NaH in monoglyme.[1] Symmetrical 1,5-diaryl-substituted TK were synthesized[1] by aroylation of acetone in the presence of NaH. Sodium salts of tri- and hexafluorodiacetylacetone used in the synthesis of chelate complexes were prepared according to an analogous scheme[5] by a one-pot procedure.

Results and Discussion

Previously,[10,11] we have demonstrated that symmetrical bis(polyfluoroalkyl)-1,3,5-triketones can be prepared in satisfactory yields (30—50%) by acylation of fluorinated β-diketones with alkyl polyfluorocarboxylates (PFC) in THF using LiH as a base.

In the present study, we synthesized for the first time non-symmetrical bis(polyfluoroalkyl)-1,3,5-triketones

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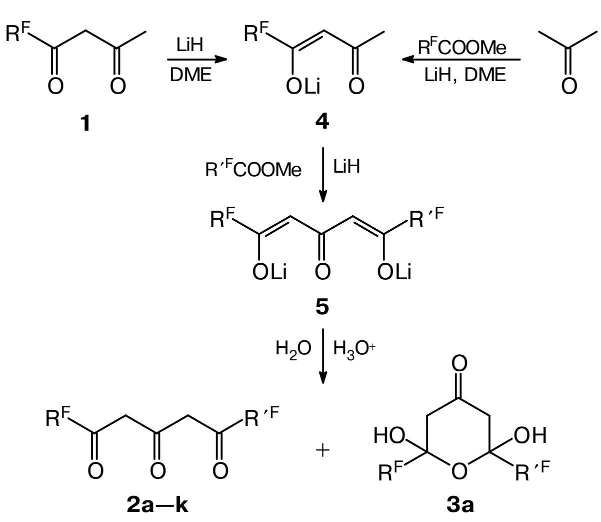
and examined the dependence of their yields on the nature of the solvent, the reagent ratio, and the fluoroalkyl chain lengths in both diketone and the acid residue.

We demonstrated (Scheme 1) that the reactions of 1,3-diketones **1** with methyl polyfluorocarboxylates in low-polar aprotic solvents (THF, monoglyme, or 1,4-dioxane) in the presence of LiH afforded (depending on the substituents in the reagents) symmetrical (**2a—d**) or non-symmetrical (**2e—k**) TK in 50—90% yields (Table 1). In the case where $R^F = R'^F = CF_3$, a mixture of TK **2a** and its cyclic hydrate **3a** was obtained (see below).

Symmetrical TK **2a—d** were also synthesized from acetone and alkyl polyfluorocarboxylates in the presence of an excess of LiH without isolation of the intermediate lithium oxoenolates **4**, *i.e.*, the reaction formally proceeded as diacylation of the starting ketone. Since the yields of TK were comparable to those obtained by acylation of the corresponding 1,3-diketones **1** under analogous conditions, this procedure is a method of choice for the preparation of symmetrical compounds.

The maximum yields were achieved where β-diketone, alkyl polyfluorocarboxylate, and LiH were taken in a ratio of 1 : 1.2 : 3 (for the synthesis from acetone, this ratio was 1 : 2.4 : 4). The yields also depended on the chain length of the perfluoroalkyl substituent. Thus the

Scheme 1



2	R^F	R'^F	**2**	R^F	R'^F
a	CF_3	CF_3	**g**	CF_3	C_4F_9
b	C_2F_4H	C_2F_4H	**h**	CF_3	C_6F_{13}
c	C_4F_9	C_4F_9	**i**	C_2F_4H	C_4F_9
d	C_6F_{13}	C_6F_{13}	**j**	C_2F_4H	C_6F_{13}
e	CF_3	C_2F_4H	**k**	C_6F_{13}	C_4F_9
f	C_3F_7	CF_3			

Table 1. Yields, physicochemical characteristics, and data from elemental analysis for compounds **2a—k** and **3a**

Compound	Yield (%)	B.p./°C (*p*/Torr)	M.p./°C	Found/Calculated (%)			Molecular formula
				C	H	F	
1,1,1,7,7,7-Hexafluoroheptane-2,4,6-trione (**2a**), 2,6-bis(trifluromethyl)-2,6-dihydroxytetrahydropyran-4-one (**3a**)[a]	50	—	—	—	—	—	—
1,1,2,2,8,8,9,9-Octafluorononane-3,5,7-trione (**2b**)	76	106—107 (14)	24—25	34.49 34.41	1.97 1.93	48.40 48.38	$C_9H_6F_8O_3$
1,1,1,2,2,3,3,4,4,10,10,11,11,12,12,13,13,13-Octadecafluorotridecane-5,7,9-trione (**2c**)	77	91—107 (8)	—	28.26 28.38	0.56 0.73	62.22 62.16	$C_{13}H_4F_{18}O_3$
1,1,1,2,2,3,3,4,4,5,5,6,6,12,12,13,13,14,14,15,15,16,16,17,17,17-Hexacosafluoroheptadecane-7,9,11-trione (**2d**)	61	112—120 (3)	36—38	27.04 27.22	0.46 0.54	65.68 65.85	$C_{17}H_4F_{26}O_3$
1,1,1,7,7,8,8-Heptafluorooctane-2,4,6-trione (**2e**)	64[b] 65[c]	55—61 (10) 75—85 (15)	55—60 58—59	33.93 34.06	1.79 1.79	47.10 47.14	$C_8H_5F_7O_3$
1,1,1,7,7,8,8,9,9,9-Decafluorononane-2,4,6-trione (**2f**)	70	69—70 (12)	72—73	30.86 30.88	1.15 1.15	54.32 54.26	$C_9H_4F_{10}O_3$
1,1,1,7,7,8,8,9,9,10,10,10-Dodecafluorodecane-2,4,6-trione (**2g**)	85[d] 90[e]	65—80 (9) 60—73 (8)	62—63 63—64	29.96 30.02	1.17 1.01	56.95 56.98	$C_{10}H_4F_{12}O_3$
1,1,1,7,7,8,8,9,9,10,10,11,11,12,12,12-Hexadecafluorododecane-2,4,6-trione (**2h**)	71[f] 68[g]	87—101 (7) 83—101 (8)	53—54 52—54	29.08 28.82	0.67 0.81	60.95 60.78	$C_{12}H_4F_{16}O_3$
1,1,2,2,8,8,9,9,10,10,11,11,11-Tridecafluoroundecane-3,5,7-trione (**2i**)	74	92—97 (9)	—	30.39 30.57	1.12 1.17	57.17 57.15	$C_{11}H_5F_{13}O_3$
1,1,2,2,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluorotridecane-3,5,7-trione (**2j**)	72	108—112 (8)	—	29.37 29.34	1.17 0.95	60.65 60.69	$C_{13}H_5F_{17}O_3$
1,1,1,2,2,3,3,4,4,10,10,11,11,12,12,13,13,14,14,15,15,15-Docosafluoropentadecane-5,7,9-trione (**2k**)	69	122—136 (13)	—	27.86 27.71	1.11 0.62	64.34 64.29	$C_{15}H_4F_{22}O_3$

[a] A mixture of variable composition.

[b] From compound **1**, $R^F = CF_3$. [c] From compound **1**, $R^F = C_2F_4H$.

[d] From compound **1**, $R^F = CF_3$. [e] From compound **1**, $R^F = C_4F_9$.

[f] From compound **1**, $R^F = CF_3$. [g] From compound **1**, $R^F = C_6F_{13}$.

Table 2. Dependence of the yields of triketones **2a,c,d** and **3a** on the nature of the solvent

Solvent	Yield (%)		
	2a + **3a**	**2c**	**2d**
Et_2O	16	*	*
THF	14	46	*
1,4-Dioxane	47	75	55
Monoglyme	50	77	61
Toluene	—	50	—

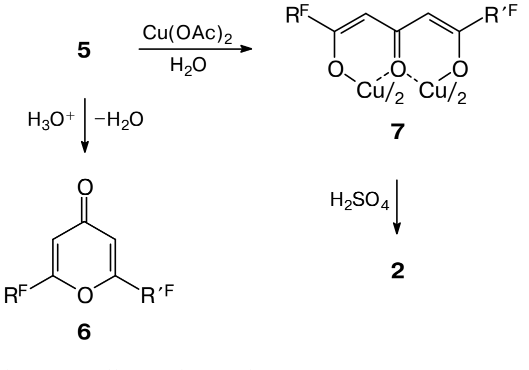
* No reaction.

yields were higher for $R^F = C_2F_4H$, C_3F_7, or C_4F_9. The yields of non-symmetrical TK **2e—k** were virtually independent of the nature of the substituents (R^F or $R'^F \neq R^F$) in diketone and alkyl PFC (see Table 1).

Monoglyme proved to be the most convenient solvent (with regard to a combination of properties, *viz.*, the boiling point, the coordinating and dissolving abilities with respect to Li salts, *etc.*) for these reactions (Table 2) although 1,4-dioxane can be used in the synthesis of TK containing $R^F \geq C_4F_9$ to reduce the reaction time. The use of THF is undesirable because of its low boiling point and noticeable resinification of the reaction mixture. Acylation of acetone proceeded also in a non-polar solvent, *viz.*, in toluene, but it afforded the product in lower yield (see Table 2, compound **2c**) and over a longer reaction time.

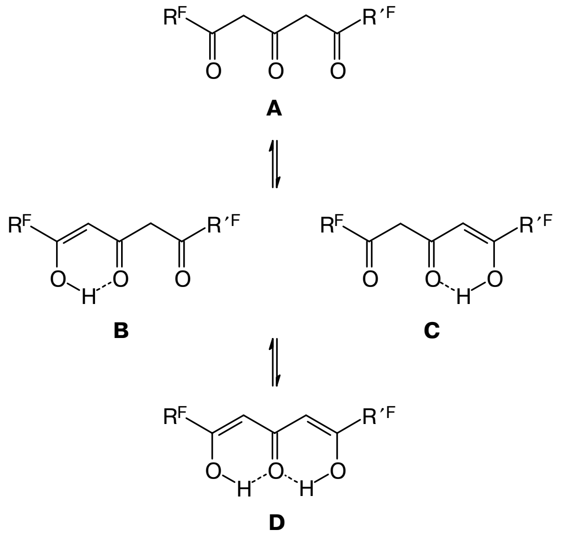
Attempts to isolate TK by treating the reaction mixture with dilute mineral acids failed because of the possible dehydration of the resulting TK to form the corresponding γ-pyrones[2] (**6**) due to the exothermic reactions of Li salts with the acid. In addition, this procedure did not allow one to completely remove the solvent from the final products. For these reasons, Li enolates **5** were first converted into copper chelates **7** followed by their decomposition to obtain triketones **2** (Scheme 2).

Scheme 2



Theoretically, 1,3,5-triketones can exist in several tautomeric forms the most probable of which are triketo form **A**, monoenol **B** (**B** and **C** if $R^F \neq R'^F$), and bis-enol **D** (Scheme 3) (by analogy with non-fluorinated TK [12—14]).

Scheme 3



We demonstrated that the equilibrium was virtually completely shifted to dienediol structure **D** (≥95%) for all TK synthesized as evidenced by the spectroscopic data (Table 3). In the IR spectra, absorption bands characteristic of the free carbonyl group (1750—1700 cm^{-1}) are either absent or poorly pronounced. However, the spectra have bands in the region of 1660—1610 cm^{-1} corresponding to vibrations of the C=C—C=O conjugated system. The spectra of compounds **2b—d,i—k** also have no pronounced absorption maximum of the free OH group but have a broad diffuse band in the region of 3300—2600 cm^{-1} typical of stretching vibrations of the OH group involved in strong intramolecular hydrogen bonding in enols of β-diketones.[15] The ^1H NMR spectra have two-proton signals as broadened singlets at δ 11.7—13.4 corresponding to resonance of the enol OH groups of form **D** and singlets at δ 5.94—5.98 assigned to the vinyl protons of the same structure.

For all TK, except for **2a**, the signals of the methylene groups of monoenol forms **B** and **C** (the total content was ~2—4%) were observed. These signals are manifested as a quartet (for the CH_2 groups adjacent to the CF_3 substituent) and a triplet (for the CH_2 group adjacent to the R^FCF_2 substituent), which are poorly resolved (with the spin-spin coupling constant $^4J_{C,F} <$ 0.5 Hz), at δ 3.87 and 3.89, respectively. The assignment of these signals to the monoenol form was made based on the analysis and comparison of the spectra of the resulting compounds and their non-fluorinated analogs.[12—14] The signals corresponding to the vinyl protons of these tautomeric forms are masked by the signals for the protons of the bis-enol forms as can be seen

Table 3. Data from IR and ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) for the compounds synthesized

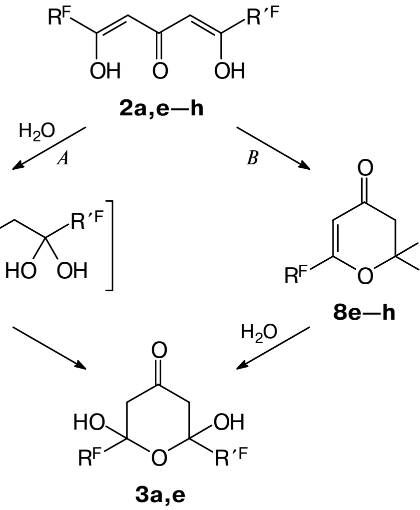
Triketone	IR, ν/cm^{-1}	^{1}H NMR, δ (J/Hz)
2a	3095 (=C—H); 1680, 1650 (C=C, C=O)	11.80 (br.s, 2 H, OH); 5.94 (s, 2 H, =CH)
3a	3500—3200 (OH); 1720 (C=O)	3.53 (d, 2 H, OH, $^4J_{H,OH}$ = 3.1); 2.97 (2 ABX systems, $\Delta\delta_{AB}$ 0.25, $^2J_{AB}$ = 17.1, $^4J_{AX}$ = 3.1, J_{BX} = 0); 2.96* (2 AB systems, $\Delta\delta_{AB}$ 0.29, $^2J_{AB}$ = 17.1)
2b**	3105 (=C—H); 1650, 1625 (C=C, C=O)	12.20 (br.s, 2 H, OH); 6.03 (tt, 2 H, CF_2H, $^2J_{H,F}$ = 53.0, $^3J_{H,F}$ = 4.7); 5.96 (s, 2 H, =CH)
2c**	3105 (=C—H); 1650, 1615 (C=C, C=O)	13.40 (br.s, 2 H, OH); 5.96 (s, 2 H, =CH)
2d**	3115 (=C—H); 1650, 1630 (C=C, C=O)	11.70 (br.s, 2 H, OH); 5.98 (s, 2 H, =CH)
2e	3080 (=C—H); 1660, 1640 (C=C, C=O)	12.60 (br.s, 2 H, OH); 6.03 (tt, 2 H, CF_2H, $^2J_{H,F}$ = 52.9, $^3J_{H,F}$ = 4.7); 5.93, 5.97 (both s, 1 H each, =CH)
2f	3088 (=C—H); 1685, 1640 (C=C, C=O)	12.50 (br.s, 2 H, OH); 5.95, 5.97 (both s, 1 H each, =CH)
2g	3072 (=C—H); 1680, 1670, 1628 (C=C, C=O)	13.30 (br.s, 2 H, OH); 5.95, 5.98 (both s, 1 H each, =CH)
2h	3095 (=C—H); 1690, 1675, 1630 (C=C, C=O)	13.20 (br.s, 2 H, OH); 5.95, 5.98 (both s, 1 H each, =CH)
2i**	3122 (=C—H); 1660, 1630 (C=C, C=O)	12.30 (br.s, 2 H, OH); 6.02 (tt, 2 H, CF_2H, $^2J_{H,F}$ = 52.9, $^3J_{H,F}$ = 4.7); 5.96, 5.97 (both s, 1 H each, =CH)
2j**	3120 (=C—H); 1660, 1630 (C=C, C=O)	12.00 (br.s, 2 H, OH); 6.02 (tt, 2 H, CF_2H, $^2J_{H,F}$ = 52.9, $^3J_{H,F}$ = 4.7); 5.96, 5.97 (both s, 1 H each, =CH)
2k**	3105 (=C—H); 1650, 1615 (C=C, C=O)	12.30 (br.s, 2 H, OH); 5.98 (s, 2 H, =CH)

* In CD_3COOD.
** 80 MHz.

from the fact that the integral intensities of these peaks are somewhat different.

It is worthy of note that TK **2a,e—h** containing the trifluoromethyl substituent underwent ring-chain conversions (Scheme 4) according to intramolecular cyclization followed by hydration (path *B*) or *vice versa* (path *A*).

Scheme 4



Isolation of compound **2a** from the chelate always afforded a mixture of TK in the bis-enol form and cyclic hydrate **3a** with a variable component ratio (from 1 : 1 to 1 : 2 with the latter predominating). Apparently, 2,6-bis(trifluoromethyl)-2,6-dihydroxytetrahydropyran-4-one (**3a**) was formed as an isomer with the 1,3-*cis*-diaxial arrangement of the OH groups. This is indirectly evidenced by splitting of only the low-field component of the AB system of the methylene groups on the protons of the OH groups with the spin-spin coupling constant $^4J_{H,OH}$ = 3.15 Hz, which disappeared when the spectrum was recorded in the presence of deuterioacetic acid.

Triketone **2g** is also prone to hydration although to a lesser degree. According to the data from ^{1}H NMR spectroscopy and elemental analysis (see Table 1), compound **2g** was isolated from the chelate in pure form and added water only upon storage. It is difficult to make the assignment of the signals in the ^{1}H NMR spectrum of hydrate **3e** because its non-equivalent protons of the methylene group give two overlapping AB systems with the centers at δ ~3. In addition, the low-field components of these AB systems are split on the OH protons for which poorly resolved doublets are observed at δ 3.53 and 3.59, respectively.

The ^{1}H NMR spectra of the compounds that formed upon decomposition of chelates **7e—h** have signals which can apparently be assigned to intramolecular cyclization products of TK, *viz.*, to 2-hydroxydihydropyrones **8e—h**, respectively. The signals of the methylene groups are observed as AB systems with the centers at δ 2.96—2.97 and with the close geminal spin-spin coupling constants $^2J_{H,H}$ = 16.80—17.01 Hz (for **3a,e**, $^2J_{H,H}$ = 17.13—17.25 Hz); however, these signals are characterized by the smaller difference in the chemical shifts compared with that observed for hydrates **3a,e** (~0.02 ppm instead of ~0.12 ppm). The signals for the protons of the OH groups are observed at δ 4.0—4.1. The vinyl protons give multiplets at δ 6.08—6.11 (apparently, due to splitting through the double bond on the ^{19}F nuclei of the fluoroalkyl substituent).

The existence of hydrates **3a,e** and hemiketals **8e—h** is additionally confirmed by the fact that the IR spectra of the corresponding TK have characteristic absorption bands in the regions of vibrations of the free carbonyl group (1710—1705 cm^{-1}) and of the OH group which is not involved in intramolecular hydrogen bonding (3260—3280 cm^{-1}).

Experimental

The ^{1}H NMR spectra were recorded on Tesla BS-567A (80 MHz) and Bruker DRX-400 spectrometers (400 MHz) with Me_4Si as the internal standard. The IR spectra were measured on a Specord IR-75 instrument in Nujol mulls. The data from elemental analysis, the physicochemical characteristics, and the yields of compounds **2a—k** are given in Table 1. The spectral data are listed in Table 3.

1,3,5-Triketones were prepared according to similar procedures (see below). The course of the reactions was monitored by TLC on Silufol UV-254 plates in $CHCl_3$.

Synthesis of symmetrical TK 2a—d. A solution of acetone (3.7 mL, 50 mmol) in anhydrous monoglyme (5 mL) was added dropwise with intense stirring to a suspension of LiH (1.6 g, 200 mmol) and an alkyl PFC (120 mmol)* in anhydrous monoglyme (10 mL) (in some cases, it was necessary to add several drops of methanol to initiate the reaction). Then the reaction mixture was refluxed for several hours, samples being withdrawn at intervals. The samples were treated with a solution of copper acetate and extracted with AcOEt or Et_2O. The extract was analyzed by TLC. The completion of the reaction was determined based on the disappearance of a blue spot of the diketone chelate ($R_f = 0.3—0.5$) whose mobility is substantially higher than that of the chelate of the corresponding TK ($R_f = 0—0.1$). Then the reaction mixture was treated with a solution of $Cu(OAc)_2$ (1.5 equiv.) acidified with AcOH and kept for 1—2 days. The precipitate of the chelate was filtered off, washed with hot water (until the colorless filtrate was obtained), and dried in air or in a drying chamber. Then the residue was decomposed with a 3—4-fold excess of 50% H_2SO_4 with stirring in Et_2O until the green color disappeared (the color of the organic layer was from pale-yellow to dark-brown), extracted with CH_2Cl_2 (or ether,** 4×25 mL), and dried with Na_2SO_4. The solvent was distilled off and the residue was distilled *in vacuo* or, in the case of a mixture of compounds **2a** and **3a**, recrystallized from $CHCl_3$.

Synthesis of non-symmetrical TK 2e—k. A solution of diketone (50 mmol) and anhydrous monoglyme (5 mL) was added dropwise with intense stirring and cooling to a suspension of LiH (1.2 g, 150 mmol) in anhydrous monoglyme (10 mL). Then methyl polyfluorocarboxylate (60 mmol) was rapidly added. The reaction was carried out and the products were isolated as described above.

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* In the syntheses involving methyl trifluoroacetate, a 1.5-fold (rather than 1.2-fold) excess of the latter was used due to its high volatility.

** In the isolation of TK **2a** and **2e**, Et_2O was the solvent of choice for extraction due to their high solubilities in water.