Synthesis of 2,6-bis-polyfluoroalkyl-4*H*-pyran-4-ones

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Dedicated to Prof. Oleg N. Chupakhin on his 70th anniversary

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Abstract

A convenient synthesis is described of 2,6-bis-polyfluoroalkyl-4*H*-pyran-4-ones having symmetrical and asymmetrical structures, by dehydration of bis-polyfluoroalkyl- containing 1,3,5-triketones.

Keywords: 2,6-Bis-polyfluoroalkyl-4*H*-pyran-4-ones, bis-polyfluoroalkyl- containing 1,3,5-triketones, dehydration, synthesis

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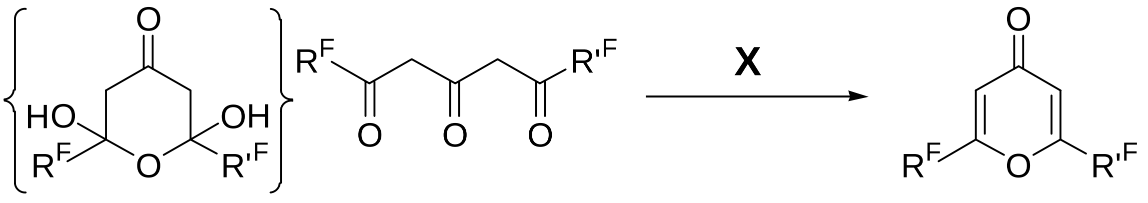
Introduction

Polyfluoroalkyl- substituted heterocyclic compounds are of particular interest owing to their biological activity, specific properties and chemical reactivity. Such compounds may have significant applications in various fields (medicinal,[1] agricultural,[2] etc.). Hence, there is a need for the development of accessible and convenient methods for the introduction of polyfluoroalkyl groups into heterocyclic systems. One of the prospective directions for investigations is the synthesis of fluoroalkyl substituted 4H-pyran-4-ones (γ-pyrones) which can be suitable precursors of polyfluoroalkylated heterocycles. In particular, recyclization of the title compounds with ammonia and primary amines can lead to 4-(1H)-pyridones or the corresponding pyridine derivatives, whose properties are widely covered in the literature.[1b,c,2c,3] On the other hand, there are only limited data concerning polyfluoroalkyl containing γ-pyrones.[4]

In the present paper the cyclization of bis-polyfluoroalkyl-1,3,5-triketones **1c–e,h–j** (or their cyclic hydrates **1a,b,f,g**)[5] to form 2,6-bis-polyfluoroalkyl-4H-pyran-4-ones by the action of various dehydrating agents has been investigated, and the selection of the optimal conditions for the dehydration has been made.

Results and Discussion

As reported earlier, the treatment of lithium salts of 1,3,5-triketones ("TK") with dilute mineral acids was accompanied by the formation of 2,6-bis-polyfluoroalkyl-4H-pyran-4-ones.[5] However, under these conditions dehydration proceeded to the end only for di- and trifluoromethyl substituted TK, whereas with the higher substituents γ-pyrones were obtained as by-products. To accomplish the conversion of TK we have examined various dehydrating agent (among them H_2SO_4, polyphosphoric acid (PPA), methanolic HCl, P_4O_{10}, trimethylsilyl phosphate $(Me_3Si)_3PO$,[6] ethyl polyphosphate $[EtOPO_2]_n$[7]) (Scheme 1).



1a,b,f,g **1c-e,h-j** **2a-j**

$\mathbf{X} = H_2SO_4$, PPA, HCl / MeOH, $(Me_3SiO)_3PO$, $(EtOPO_2)_n$ / $CHCl_3$

Scheme 1

Employment of the concentrated sulfuric acid used earlier for the cyclization of non-fluorinated TK to give γ-pyrones,[8] as well as PPA yielded unsatisfactory results – even after heating for several hours the starting TK was partially recovered (according to TLC data). Refluxing of TK with hydrochloric acid in methanol also appeared ineffective. The dehydration of TK in presence of P_4O_{10} proceeded completely by heating over a period of 10–30 min. in 50–75% yields, but was accompanied by the loss of a part of the γ-pyrones owing to adsorption on the dehydrating agent. For high-boiling compounds this problem was solved, in part, by vacuum distillation from the reaction mixture, whereas for the low-boiling ones it still led to big losses. Refluxing of TK and trimethylsilyl phosphate mixture in chloroform or without solvent led to compounds **2** in 60–70% yields. However, as ^1H- NMR data showed the γ-pyrones obtained were contaminated with silicon substances (mainly, hexamethyldisiloxane). Attempts to remove these impurities by distillation failed. Ethyl polyphosphate appeared to be the most effective dehydrating agent with regard to the isolation and yield of products formed. Thus, heating of TK in the presence of ethyl polyphosphate at reflux in chloroform during 20–60 minutes followed by workup of the reaction mixture with water resulted in the desired γ-pyrones in 75–95% yields (Table 1).

The structures of the obtained compounds were confirmed by IR-, ^{1}H- and ^{19}F- NMR spectroscopy, and elemental analysis. The IR spectra have bands in the region 1680–1620 cm^{-1} corresponding to vibrations of the C=C–C=O conjugated system. Also an absorption maximum in the region of 3085–3060 cm^{-1} typical of =C–H stretching vibrations is observed. The ^{1}H-NMR spectra of compounds **2a–e** have sharp singlets at δ 6.66–6.87 corresponding to the vinyl protons at C–3 and C–5. For the asymmetrically substituted γ-pyrones **2f–j** the signals of these protons are manifested as AB- systems with centers at δ 6.74–6.84 due to spin-spin coupling through the "W-conformation" [9] with the coupling constant ^{4}J H,H = 2.2–2.3 Hz.

In conclusion, a convenient method for the preparation of 2,6-bis-polyfluoroalkyl-4H-pyran-4-ones has been developed, based on the dehydration of bis-polyfluoroalkyl- containing 1,3,5-triketones by using ethyl polyphosphate.

Table 1. Dehydration of TK by action of ethyl polyphosphate

Compd.	R^F	R'^F	bp °C (mp °C)	Yield, % X = $(EtOPO_2)_n$
2a	CHF_2	CHF_2	(58 - 59)	81
2b	CF_3	CF_3	139 – 140	73
2c	C_2F_4H	C_2F_4H	194	90
2d	C_4F_9	C_4F_9	183	89
2e	C_6F_{13}	C_6F_{13}	237 (28)	87
2f	CHF_2	CF_3	177	95
2g	C_2F_4H	CF_3	180	84
2h	C_3F_7	CF_3	161	78
2i	C_4F_9	CF_3	150	79
2j	C_6F_{13}	CF_3	178	93

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were recorded on Bruker DRX 400 (400.13 MHz, ^{1}H) and Tesla BS-587A (75.3 MHz, ^{19}F) instruments in $CDCl_3$ solutions with Me_4Si (1H) and C_6F_6 (^{19}F) as internal standards. ^{19}F- NMR data are given only for CF_2H, CF_3 and C_2F_4H substituents. Infrared spectra were recorded in the 4000–400 cm^{-1} range on a Specord 75IR spectrometer. Elemental analyses (C,H,F) were measured using a Perkin Elmer Elemental Analyzer 2400.

Ethyl polyphosphate $[EtOPO_2]_n$ (Mr ≈ 432) was obtained by a literature method.[8] 2,6-Bis-polyfluoroalkyl-4H-pyran-4-ones were prepared according to the procedures given below. The course of the reaction was monitored by TLC on Silufol UV-254 plates using chloroform as eluent.

General procedure for the synthesis of compounds 2a–j

The mixture of 1,3,5-triketone (10 mmol), ethyl polyphosphate (7 mmol) and chloroform (10 ml) was heated under reflux over a period of 20–60 minutes, 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. Completion of the reaction was determined by the disappearance of a green spot of the copper triketonate (R_f = 0–0.1). Then the reaction mixture was quenched with water, extracted with chloroform (3x10 ml) and dried over Na_2SO_4. Solvent was distilled off using a fractionating column to prevent loss of δ-pyrones. The residue was distilled as usual, with the exception of compounds **2a,e** which were recrystallized from $CHCl_3$ and carbogal, respectively without distillation.

2,6-Bis-(difluoromethyl)-4*H*-pyran-4-one (2a). Pale yellow crystals from chloroform; IR (Nujol, cm^{-1}) 3085, 1680, 1640; 1H-NMR (CDCl3) δ 6.66 (s, 2H), 6.42 (t, J = 53.2 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ 38.18 (d, J = 53.5 Hz, 4F); Anal. Calcd. for $C_7H_4F_4O_2$: C, 42.87; H, 2.06; F, 38.75. Found: C, 42.56; H, 2.20; F, 39.04%.

2,6-Bis-(trifluoromethyl)-4*H*-pyran-4-one (2b). Pale yellow liquid; IR (film, cm^{-1}) 3065, 1680, 1650; ^1H-NMR ($CDCl_3$) δ 6.81 (s, 2H); ^{19}F-NMR ($CDCl_3$) δ 90.33 (s, 6F); Anal. Calcd. for $C_7H_2F_6O_2$: C, 36.23; H, 0.87; F, 49.12. Found: C, 36.60; H, 0.97; F, 48.98%.

2,6-Bis-(1,1,2,2-tetrafluoroethyl)-4*H*-pyran-4-one (2c). Pale yellow liquid; IR (film, cm^{-1}) 3070, 1680, 1645; ^1H-NMR ($CDCl_3$) δ 6.81 (s, 2H), 6.06 (tt, 2J = 52.9 Hz, ^3J = 2.8 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ 26.58 (dt, 2J = 52.7 Hz, ^3J = 3.9 Hz, 4F, CF_2CF_2H), 40.79–40.94 (m, 4F, CF_2CF_2H); Anal. Calcd. for $C_9H_4F_8O_2$: C, 36.51; H, 1.36; F, 51.33. Found: C, 36.22; H, 1.23; F, 51.93%.

2,6-Bis-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)-4*H*-pyran-4-one (2d). Yellow liquid; IR (film, cm^{-1}) 3060, 1680, 1650, 1625; ^1H-NMR ($CDCl_3$) δ 6.87 (s, 2H); Anal. Calcd. for $C_{13}H_2F_{18}O_2$: C, 29.34; H, 0.38; F, 64.26. Found: C, 29.33; H, 0.56; F, 64.35%.

2,6-Bis-(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)-4*H*-pyran-4-one (2e). Cream-colored flake-like crystals; IR (film, cm^{-1}) 3080, 1690, 1655; ^1H-NMR ($CDCl_3$) δ 6.86 (s, 2H); Anal. Calcd. for $C_{17}H_2F_{26}O_2$: C, 27.89; H, 0.28; F, 67.47. Found: C, 27.99; H, 0.15; F, 67.12%.

2-(Difluoromethyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (2f). Pale yellow liquid; IR (film, cm^{-1}) 3070, 1680, 1640; ^1H-NMR ($CDCl_3$) δ 6.74±0.01 (AB, J = 2.2 Hz, 2H), 6.43 (t, J = 53.3 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ 90.39 (s, 3F), δ 37.92 (d, J = 53.7 Hz, 2F); Anal. Calcd. for $C_7H_3F_5O_2$: C, 39.27; H, 1.41; F, 44.37. Found: C, 39.40; H, 1.35; F, 44.32%.

2-(1,1,2,2-Tetrafluoroethyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (2g). Yellow liquid; IR (film, cm^{-1}) 3065, 1680, 1645; ^{1}H-NMR ($CDCl_3$) δ 6.80±0.01 (AB, J = 2.2 Hz, 2H), 6.0 (tt, 2J = 53.0 Hz, ^{3}J = 2.8 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ 90.16 (s, 3F); 26.62 (dt, ^{2}J = 53.7 Hz, ^{3}J = 3.9 Hz, 2F, CF_2CF_2H), 40.92–41.07 (m, 2F, CF_2CF_2H); Anal. Calcd. for $C_8H_3F_7O_2$: C, 36.38; H, 1.14; F, 50.36. Found: C, 36.50; H, 1.22; F, 50.49%.

2-(1,1,2,2,3,3,3-Heptafluoropropyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (2h). Pale yellow liquid; IR (film, cm^{-1}) 3065, 1685, 1650, 1625; ^{1}H-NMR ($CDCl_3$) δ 6.84±0.01 (AB, J = 2.2 Hz, 2H); ^{19}F-NMR (CDCl3) δ 90.12 (s, 3F); Anal. Calcd. for $C_9H_2F_{10}O_2$: C, 32.55; H, 0.61; F, 57.21. Found: C, 32.61; H, 0.70; F, 56.89%.

2-(1,1,2,2,3,3,4,4,4-Nonafluorobutyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (2i). Yellow liquid; IR (film, cm^{-1}) 3060, 1680, 1650, 1625; ^{1}H-NMR ($CDCl_3$) δ 6.84±0.01 (AB, J = 2.2 Hz, 2H); ^{19}F-NMR (CDCl3) δ 90.20 (s, 3F); Anal. Calcd. for $C_{10}H_2F_{12}O_2$: C, 31.43; H, 0.53; F, 59.66. Found: C, 31.68; H, 0.44; F, 60.01%.

2-(1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (2j). Yellow liquid; IR (film, cm^{-1}) 3060, 1680, 1650, 1620; ^{1}H-NMR ($CDCl_3$) δ 6.84±0.01 (AB, J = 2.2 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ 90.12 (s, 3F); Anal. Calcd. for $C_{12}H_2F_{16}O_2$: C, 29.90; H, 0.42; F, 63.05. Found: C, 29.47; H, 0.39; F, 62.79%.

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