Journal of Fluorine Chemistry 131 (2010) 66–69

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of 5-(perfluoroalkylmethyl)-1,3-dioxolan-4-ones

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ARTICLE INFO

Article history:
Received 30 August 2009
Received in revised form 6 October 2009
Accepted 7 October 2009
Available online 6 November 2009

Keywords:
F-Alkyl
α-Hydroxy acid
1,3-Dioxolan-4-one
Condensation

ABSTRACT

Acid catalysed condensation of *F*-alkyl α-hydroxy acids with simple aldehydes or ketones gave *F*-alkyl 1,3-dioxolan-4-ones. When BF_3,OEt_2 was used as the catalyst, the condensation products were obtained in moderate to good yields and the "cis" isomers are largely favoured, while with HOTs/H_2SO_4 as catalyst, poor yields and lower stereoselectivities were observed.

1. Introduction

1,3-Dioxolan-4-ones are attracting a growing interest due to their use as precursors to a variety of synthetic targets. They have served as substrates for the total synthesis of (S)-oxybutynin [1], eicosanoids [2], beta lactams [3], a muscarinic receptor antagonist [4] as well as in the synthesis of substituted tetrahydrofurans [5], aldols and various kinds of alcohols [6–8]. 1,3-Dioxolan-4-ones are generally prepared by the acid or Lewis acid catalysed condensation of an α-hydroxy carboxylic acid with an aldehyde or ketone [9]. Ferrett et al. have reported the synthesis of substituted 5-phenyl-1,3-dioxolan-4-ones under microwave-assisted solvent-free conditions [10]. More recently, substituted 1,3-dioxolan-4-ones were prepared by an intramolecular cyclisation of α-methylallyloxy carboxylic acids, using $Cu(OTf)_2$ or $Al(OTf)_3$ as catalysts [11].

In a previous work, we have reported the synthesis of *F*-alkyl α-hydroxy acids by oxidative ring opening reaction of *F*-alkyl oxiranes [12]. In the present work, we describe the condensation of these acids with carbonyl compounds to obtain *F*-alkyl-1,3-dioxolan-4-ones. As for 5-alkyl-1,3-dioxolan-4-ones [13–16], the new *F*-alkylated dioxolanones may prove to be useful intermediates for the synthesis of *F*-alkylated analogues of natural dioxanones.

2. Results and discussion

The *F*-alkylated 1,3-dioxolan-4-ones have been prepared via direct acid catalysed cyclisation reaction of *F*-alkyl α-hydroxy acids with aldehydes or ketones (Scheme 1). The reaction has been performed using two methods:

- *Method A*: the acid catalyst is the mixture TsOH/H_2SO_4 and the use of solvents such as benzene, toluene or dioxane which dissolve the starting acids at high temperature (reflux) is required. As a consequence, the polymerisation reaction may be important and volatile carbonyl compounds were not appropriate for the condensation reaction.
- *Method B*: the dissolution of *F*-alkyl acids in a diethyl ether solution of BF_3,OEt_2 occurs at room temperature, the polymerisation reaction decreased considerably and the yields were better (Table 1).

Comparison of the results obtained with both methods (Table 1) shows that method B is preferred. It ensures higher selectivity and good yields. Entries 1 and 2 in Table 1 gave the highest selectivity. This may be explained, as expected, by the use of less bulky aldehydes, whilst the lowest selectivity is observed with the bulkiest groups (i.e. Ph and C_6F_{13}) which would increase the ratio of the trans isomer.

The *F*-alkyl 1,3-dioxolan-4-ones were obtained as a mixture of cis and trans isomers (see Table 1). As for non-fluorinated 1,3-dioxolan-4-ones [10,11], the cis isomer of *F*-alkyl 1,3-dioxolan-4-ones **3** was always favoured. The cis/trans ratio and assignments were determined from relative signal intensities and chemical shifts of H-(2), H-(5) or substituent signals on C-(5) and C-(2) observed in ^{1}H NMR spectra as shown in Table 2.

3. Experimental

F-Alkyl α-hydroxy acids were prepared from 3-*F*-alkyl-1,2-epoxypropanes [12]. IR spectra were obtained using a Perkin-

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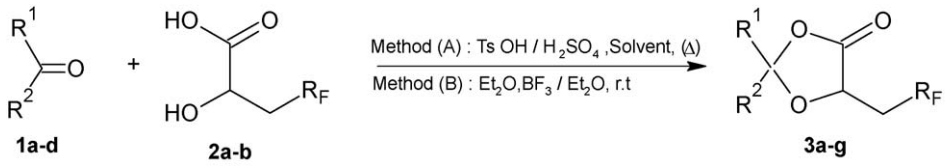
doi:10.1016/j.jfluchem.2009.10.006



3(R_F, R^1, R^2) **3a**(C_4F_9, CH_3, H) **3b**(C_6F_{13}, CH_3, H) **3c**(C_4F_9, C_6H_5, H) **3d**(C_6F_{13}, C_6H_5, H)
3e(C_6F_{13}, iPr, CH_3) **3f**(C_4F_9, iPr, H) **3g**(C_6F_{13}, iPr, H)

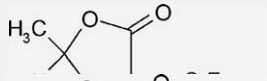
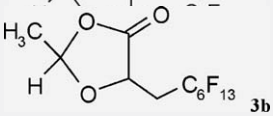
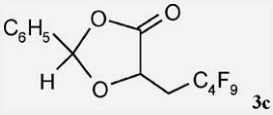
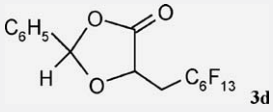
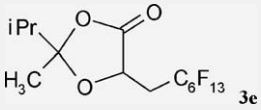
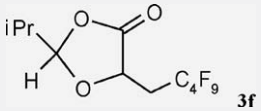
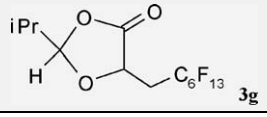
Scheme 1. Synthesis of *F*-alkyl 1,3-dioxolan-4-ones (**3**).

Elmer FT-PARAGON 1000 PC. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Brucker AC 300 instrument. Chemical shifts were reported in ppm from external C_6F_6 for ^{19}F and from internal TMS for ^{1}H and ^{13}C. HRMS spectra were obtained using MAT 95 SBE instrument. Melting points were determined using Electrothermal IA. 9000 series II and are uncorrected.

3.1. General procedure for the synthesis of F-alkyl 1,3-dioxolan-4-ones 3(c–g) by method A

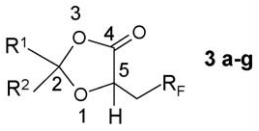
0.01 mol of the carbonyl compound **1** was added to a solution of 5 mmol of the *F*-alkyl-2-hydroxy acid **2** in 25 mL of benzene. The reaction mixture was heated under reflux, and 0.01 g of p-toluene sulfonic acid and 0.1 mL of concentrated H_2SO_4 were added. Water was removed by azeotropic distillation using a Dean-Stark apparatus. The mixture was refluxed for 12 h to complete the reaction and then cooled to room temperature. The reaction mixture was neutralised with 10% aqueous Na_2CO_3 solution. The solution was extracted three times with 30 mL portions of diethyl ether and washed several times with water. The combined organic extracts were dried over anhydrous Na_2SO_4. After the evaporation of solvent under reduced pressure, the crude product was purified by flash chromatography (SiO_2, Et_2O/petroleum ether, 30:70) and distilled under reduced pressure or recrystallised to give products **3**.

Table 1
Synthesised *F*-alkyl 1,3-dioxolan-4-ones (**3**).

Entry	Reagents	Product	Method	Time (h)	Yield (%)[a] (cis/trans)
1	**1a** + **2a**		B	1	68 (96/4)
2	**1a** + **2b**	 **3b**	B	2	65 (96/4)
					45 (54/46)
3	**1b** + **2a**	 **3c**	A	12	
					45 (52/48)
4	**1b** + **2b**	 **3d**	A	12	
			B	2	83 (66/34)
			A	12	50 (72/28)
5	**1c** + **2b**	 **3e**			
			B	1	71 (84/16)
			A	12	55 (87/13)
6	**1d** + **2a**	 **3f**			
					57 (65/35)
7	**1d** + **2b**	 **3g**	A	12	

[a] Yields obtained on isolated products.

Table 2
Chemical shifts (δH-(2) and δH-(5)) and coupling constants $^4J_{H2\ H5}$.



R_F	R^1	R^2	δH(2) ppm		δH(5) ppm		$^4J_{H2\ H5}$ (Hz)	cis/trans (%)
			δ_{cis}	δ_{trans}	δ_{cis}	δ_{trans}		
C_4F_9	CH_3	H	5.70	5.90	4.65	4.80	1.0	96:4
C_6F_{13}	CH_3	H	5.65	5.85	4.60	4.75	0.9	96:4
C_4F_9	C_6H_5	H	6.55	6.75	4.93	4.90	1.0	54:46
C_6F_{13}	C_6H_5	H	6.75	6.60	4.65	4.50	1.0	52:48
C_6F_{13}	CH_3	iPr	–	–	4.75	4.73	–	72:28
C_4F_9	iPr	H	5.40	5.50	4.65	4.80	1.0	87:13
C_6F_{13}	iPr	H	5.40	5.50	4.65	4.70	1.0	85:15

δ_{cis}, δ_{trans}: relative to cis (major) and trans (minor) diastereomers, respectively.
^4J: relative to the cis (major) isomer.

3.2. General procedure for the synthesis of F-alkyl1,3-dioxolan-4-ones 3(a,b,d,e) by method B

To a solution of 2.5 mmol of 3-*F*-alkyl-2-hydroxy acid **2** in 3.5 mL of anhydrous diethyl ether and 23 mmol of **1** in 2.5 mL of the same solvent was added 0.5 mL (4.3 mmol) of Et_2O,BF_3 and the reaction mixture was stirred for 2 h at room temperature. The mixture was dissolved in 100 mL of diethyl ether, extracted with 50 mL of 10% CH_3COONa and washed several times with water. The ether layer was then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography (SiO_2, Et_2O/petroleum ether, 30:70) and distilled under reduced pressure or recrystallised to give products **3**.

3.2.1. 5-Perfluorobutylmethyl-2-methyl-1,3-dioxolan-4-one (3a)

Method B, Yield: 68%; colourless oil; bp: 47 °C/0.3 mmHg; IR ($CHCl_3$): ν (cm^{-1}) 1798 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.60 (d, 3H, CH_3, $^3J_{HH}$ = 5.1 Hz, (cis)), 1.63 (d, 3H, CH_3, $^3J_{HH}$ = 4.9 Hz, (trans)), 2.4–2.9 (m, 2H, CH_2), 4.65 (m, 1H, H-(5), (cis)), 4.8 (m, 1H, H-(5), (trans)), 5.70 (qd, 1H, H-(2), $^4J_{HH}$ = 1 Hz, (cis)), 5.90 (qd, 1H, H-(2), (trans)); ^{13}C NMR ($CDCl_3$): δ 171.38 (C=O, (M)), 171.20 (C=O, (m)), 125–105 (C_4F_9), 103.2 (C-(2), (m)), 102.6 (C-(2), (M)), 69.1(C-(5), (M)), 67.45 (C-(5), (m)), 32.0 (t, CH_2), 20.6(CH_3, (m)), 19.7 (CH_3, (M)); ^{19}F NMR ($CDCl_3$): 80.41 (m, 3F, CF_3), 49.9–47.48 (AB, 2F, $CF_2(\alpha)$), 37.27 (m, 2F, $CF_2(\beta)$), 35.63 (m, 2F, CF_2 (ω)); HRMS (EI): M^+ calculated 334.025, found 334.0243.

3.2.2. 5-Perfluorohexylmethyl-2-methyl-1,3-dioxolan-4-one (3b)

Method B, Yield: 65%; colourless oil; bp: 70 °C/0.3 mmHg; IR ($CHCl_3$): ν (cm^{-1}) 1794 (C=O); ^{1}H NMR ($CDCl_3$):δ 1.57 (d, 3H, CH_3, $^3J_{HH}$ = 5.1 Hz, (cis)), 1.60 (d, 3H, CH_3, $^3J_{HH}$ = 4.9 Hz, isomer (trans)), 2.4–2.9 (m, 2H, CH_2), 4.60 (m, 1H, H-(5) (cis)), 4.75 (m, 1H, H-(5), (trans)), 5.65 (qd, 1H, H-(2), (cis)), 5.85 (qd, 1H, H-(2), $^4J_{HH}$ = 1 Hz, (trans)), ^{13}C NMR ($CDCl_3$): δ 171.4 (C=O, isomer (M)), 171.20 (C=O, (m)), 125–105 (C_6F_{13}), 103.24 (C-(2), (m)), 102.61 (C-(2), (M)), 69.10 (C-(5), (M)), 67.46 (C-(5), (m)), 32.24 (t, CH_2, $^3J_{CF}$ = 21.6 Hz, (M)), 20.65 (CH_3-(2), (m)), 19.75 (CH_3-(2), (M)); ^{19}F NMR ($CDCl_3$): δ 80.67 (m, 3F, CF_3), 48.8–48.24 (AB, 2F, $CF_2(\alpha)$), 39.82 (m, 2F, CF_2), 38.74 (m, 2F, CF_2), 38.17 (m, 2F, CF_2), 35.38 (m, 2F, CF_2); HRMS (EI): M^+ calculated 434.0187, found 434.0181.

3.2.3. 5-Perfluorobutylmethyl-2-phenyl-1,3-dioxolan-4-one (3c)

Method A, Yield: 45%; white solid; mp ($CHCl_3$): 89 °C; IR ($CHCl_3$): ν (cm^{-1}) 1798 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.6–3.0 (m, 2H, CH_2), 4.90 (m, 1H, H-(5), (cis)), 4.93 (m, 1H, H-(5), (trans)), 6.55 (d, 1H, H-(2), $^4J_{HH}$ = 1.06 Hz, (cis)), 6.65 (d, 1H, H-(2), (trans)), 7.51 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 170.0 (C=O), 135–125 (C_6H_5), 125–105 (C_4 F_9), 103.81 (C-(2)), 69.34 (C-(5)), 33.0 (t, CH_2, $^3J_{CF}$ = 21.6 Hz); ^{19}F NMR ($CDCl_3$): δ 83.14 (m, 3F, CF_3), 51.44–51.05 (AB, 2F, $CF_2(\alpha)$), 39.89 (m, 2F, CF_2), 38.26 (m, 2F, CF_2); HRMS (EI): M^+ calculated 396.0407, found 396.0416.

3.2.4. 5-Perfluorohexylmethyl-2-phenyl-1,3-dioxolan-4-one (3d)

Method B, Yield: 83%; white solid; mp ($CHCl_3$): 115 °C; IR ($CHCl_3$): ν (cm^{-1}) 1802 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.4–3.0 (m, 2H, CH_2), 4.65 (m, 1H, H-(5), (cis)), 4.97 (m, 1H, H-(5), (trans)), 6.57 (s, 1H, H-(2), (cis)), 6.60 (s, 1H, H-(2), (trans)), 7.56 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 170.5 (C=O); 135–125 (C_6H_5); 125–105 (C_6F_{13}); 103.85 (C-(2)); 69.36 (C-(5)), 33.15 (t, CH_2, $^3J_{CF}$ = 21.0 Hz); ^{19}F NMR ($CDCl_3$): δ 83.15 (m, 3F, CF_3), 51.52–50.70 (AB, 2F, $CF_2(\alpha)$), 42.27 (m, 2F, CF_2), 41.21 (m, 2F, CF_2), 40.50 (m, 2F, CF_2), 37.88 (m, 2F, CF_2); HRMS (EI): M^+ Calculated 496.0344, found 496.0333.

3.2.5. 5-Perfluorohexylmethyl-2-isopropyl-2-methyl-1,3-dioxolan-4-one (3e)

Method B, Yield: 71%; colourless oil; bp: 71 °C/0.2 mmHg; IR ($CHCl_3$): ν (cm^{-1}) 1797 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.02 (dd, 6H, 2 × CH_3, $^3J_{HH}$ = 6.9 Hz, (cis)), 1.03 (dd, 6H, 2 × CH_3, $^3J_{HH}$ = 6.8 Hz, (trans)), 2.03 (septuplet, 1H, H-iPr), 2.3–2.9 (m, 2H, CH_2), 4.62 (m, 1H, H-(5), (cis)), 4.73 (m, 1H, H-(5), (trans)); ^{13}C NMR ($CDCl_3$): δ 171.34 (C=O, (M)), 171.23 (C=O, (m)), 125–105 (C_4 F_9), 108.38 (C-(2), (M)), 108.08 (C-(2), (m)), 68.79 (C-(5), (M)), 67.9 (C-(5), (m)), 32.39 (t, CH_2, $^2J_{CF}$ = 21.4 Hz, (M)), 31.73 (CH_3, (M)), 15.45 (CH_3);^{19}F NMR ($CDCl_3$):δ 80.47 (m, 3F, CF_3), 48.91–48.0 (AB, 2F, CF_2 (α)), 39.76 (m, 2F, CF_2), 38.68 (m, 2F, CF_2), 38.12 (m, 2F, CF_2), 35.29 (m, 2F, CF_2); HRMS (EI): M^+ calculated 476.0656, found 476.0648.

3.2.6. 5-Perfluorobutylmethyl-2-isopropyl-1,3-dioxolan-4-one (3f)

Method A, Yield: 55%; colourless oil; bp: 40 °C/0.2 mmHg; IR ($CHCl_3$): ν (cm^{-1}) 1798 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 6H, 2 × CH_3, $^3J_{HH}$ = 6.7 Hz, (cis)), 1.03 (d, 6H, 2 × CH_3, $^3J_{HH}$ = 6.8 Hz, (trans)), 2.05(septuplet, 1H, CH), 2.3–2.9 (m, 2H, CH_2), 4.62 (m, 1H, H-(5), (cis)), 4.80 (m, 1H, H-(5), (trans)), 5.37 (dd, 1H, H-(2), $^4J_{HH}$ = 1.1 Hz, (cis)), 5.48 (dd, 1H, H-(2), $^4J_{HH}$ = 1.1 Hz, (trans)); ^{13}C NMR ($CDCl_3$): δ 171.34 (C=O, (M)), 171.23 (C=O, (m)), 125–105 (C_4 F_9), 108.38 (C-(2), (M)), 108.08 (C(2), (m)), 68.79 (C-(5), (M)), 67.79 (C-(5), (m)), 32.39 (t, CH_2, $^2J_{CF}$ = 21.4 Hz, (M)), 31.73 (CH), 15.45 (CH_3); ^{19}F NMR ($CDCl_3$): δ 80.61 (m, 3F, CF_3), 48.8–48.05 (AB, 2F,

CF_2 (α)), 37.35 (m, 2F, CF_2), 35.71 (m, 2F, CF_2); HRMS (EI): M^+ Calculated 362.0564, found 362.0573.

3.2.7. 5-Perfluorohexylmethyl-2-isopropyl-1,3-dioxolan-4-one (3g)

Method A, Yield: 57%; colourless oil; bp: 71 °C/0.3 mmHg; IR ($CHCl_3$): ν (cm^{-1}) 1798 (C=O); ^1H NMR ($CDCl_3$): δ 1.02 (d, 6H, 2 × CH_3, $^3J_{HH}$ = 6.8 Hz, (cis)), 1.03 (d, 6H, 2 × CH_3, $^3J_{HH}$ = 6.7 Hz, (trans)), 2.05 (septuplet, 1H, CH), 2.3–2.9 (m, 2H, CH_2), 4.63 (m, 1H, H-(5), (cis)), 4.73 (m, 1H, H-(5), (trans)), 5.36 (dd, 1H, H-(2), $^4J_{HH}$ = 1.1 Hz, (cis)), 5.48 (dd, 1H, H-(2), $^4J_{HH}$ = 1.1 Hz, (trans)); ^{13}C NMR ($CDCl_3$): 171.35 (C=O, (M)), 125–105 (C_4 F_9), 108.38 (C-(2), (M)), 108.10 (C-(2), (m)), 68.79 (C-(5), (M)), 67.79 (C-(5), (m)), 32.80 (t, CH_2, $^2J_{CF}$ = 21.3 Hz, (M)), 30.18(CH), 16.2 (CH_3); ^{19}F NMR ($CDCl_3$): δ 80.51 (m, 3F, CF_3), 48.90–48.21 (AB, 2F, CF_2 (α)), 39.73 (m, 2F, CF_2), 38.65 (m, 2F, CF_2), 38.11 (m, 2F, CF_2), 35.31 (m, 2F, CF_2); HRMS (EI): M^+ calculated 462.0500, found 462.0513.

Acknowledgment

The authors would like to thank Dr. M A Sanhoury, MRSC of the Department of Chemistry, Faculty of Sciences of Tunis for technical assistance.

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