Synthesis of Alkenyl Fluoromethyl Ketones via a Phosphorus Ylid

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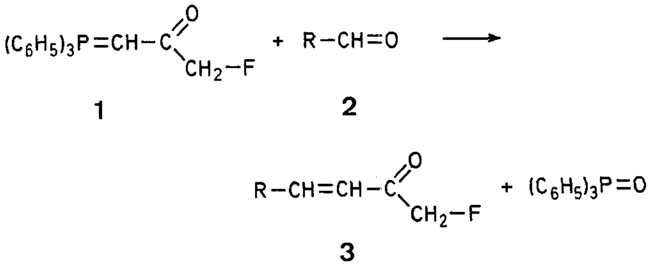
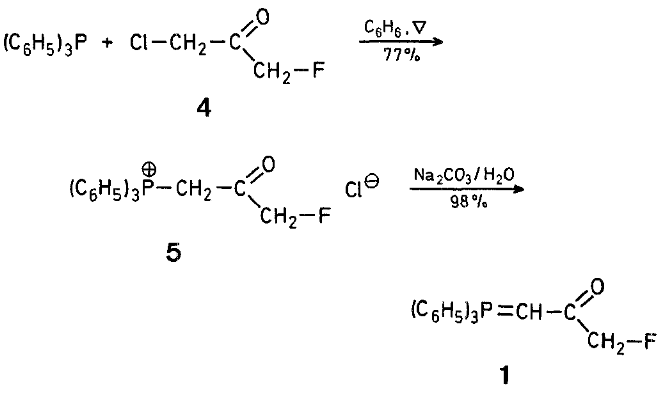
As an intermediate in the synthesis of a fluorinated analogue of a natural product, we needed a compound with the structure **3**. As yet, only the first member of the series (R = H) was obtained by a multistep sequence[1]. The Wittig reaction between the phosphorus ylid **1** and an aldehyde **2** appeared to be well-suited to the synthesis of higher homologues of **3** (R ≠ H).



The non-halogenated analogue of **1** was prepared by quaternization of triphenylphosphine with chloroacetone and subsequent treatment of the salt with an aqueous sodium carbonate solution[2]. Afterwards, chlorinated[3] and brominated[4] analogues of **1** were obtained similarly from, respectively, 1,3-dichloro- and 1,3-dibromopropanone. We applied this simple procedure to the preparation of **1** starting from 1-chloro-3-fluoropropan-2-one[5] (**4**).



The ^{19}F-N.M.R. spectrum of **1** in $CDCl_3$, at 32 °C, is normally a triplet of doublet of doublets ($^2J_{FH}=48.3$, $^4J_{FH}=5.4$, $^4J_{FP}=7.1$ Hz). Generally, only a triplet of doublets ($^2J_{FH}=48.3$, $^4J=6.2$ Hz) is recorded, the 6.2 Hz coupling constant being the mean ($^4J_{FH}+{}^4J_{FP}$)/2. In the first case, the ^{1}H-N.M.R. observed pattern for the =CH— proton is a well-resolved doublet of doublets ($^2J_{HP}=23.6$, $^4J_{HF}=5.4$ Hz) whereas in the latter case, only two unresolved humps are observed. Proton exchange between the ylid and traces of water can account for this behaviour.

Three representative examples of aldehydes **2a–c** were allowed to react with **1**, the reaction being monitored by ^{19}F-N.M.R. spectroscopy (see Tables 1 and 2). As with the brominated analogue[4] of **1** (and probably, but not described for the chlorinated one[3]), the reaction is stereospecific since only olefins of (*E*)-configuration are obtained. This assumption is based on the value of the coupling constant, close to 16 Hz, between the two vinylic protons [a lower value, close to 11 Hz, should be expected for a (*Z*)-configuration][6].

(1-Fluoroacetonyl)-triphenylphosphonium Chloride (5):

To a hot (oil-bath temperature: 90 °C), stirred solution of triphenylphosphine (26.2 g, 0.1 mol) in anhydrous benzene (110 ml) is added dropwise 1-chloro-3-fluoropropan-2-one (**4**; 11.0 g, 0.1 mol). After a while, the phosphonium chloride precipitates. At the end of the addition, stirring is continued at 90 °C for 3 h. (1-Fluoroacetonyl)-triphenylphosphonium chloride (**5**) is filtered off from the cold reaction mixture, washed with benzene, then dried under vacuum; yield: 28.7 g (77%); m.p. 187 °C (dec.).

$C_{21}H_{19}ClFOP$	calc.	C 67.66	H 5.14	Cl 9.5	F 5.01	P 8.30
(372.8)	found	67.73	5.18	9.49	5.30	8.25

^{1}H-N.M.R. (CD_3OD/TMS, 90 MHz): $\delta=4.84$ (s, P—CH_2—); 5.15 (d, $^3J_{HF}=46.7$ Hz, CH_2F); 7.8 ppm (m, —C_6H_5).

^{19}F-N.M.R. ($CD_3OD/CFCl_3$, 60 MHz): $\delta=227.1$ ppm (td, $^2J_{FH}=46.7$, $^4J_{FP}=7.1$ Hz, CH_2F).

(1-Fluoroacetyl)-methylenetriphenylphosphorane (1):

To a stirred solution of (1-fluoroacetonyl)-triphenylphosphonium chloride (**5**; 8 g, 21.5 mmol) in methanol (10.5 ml) is added rapidly a solution of sodium carbonate (1.20 g, 11.3 mmol) in water (7 ml). The mixture is then diluted with water (50 ml) and stirred for 30 min. (1-Fluoroacetyl)-methylenetriphenylphosphorane (**1**) is collected by filtration, washed with water, then dried overnight under vacuum (0.05 torr) over calcium chloride; yield: 7.1 g (98%); no m.p. (dec.).

$C_{21}H_{18}FOP$	calc.	C 74.99	H 5.39	F 5.65	P 9.20
(336.3)	found	74.72	5.28	5.50	8.91

I.R. (KBr): $\nu=1535$ cm^{-1} (C=O) (strong contribution of an oxanion form).

^{1}H-N.M.R. ($CDCl_3$/TMS, 90 MHz): $\delta=4.16$ (dd, =CH—); 4.74 (d, —CH_2F); 7.56 ppm (m, C_6H_5).

^{19}F-N.M.R. ($CDCl_3/CFCl_3$, 60 MHz): $\delta=216.7$ ppm.

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Table 1. (*E*)-Alkenyl Fluoromethyl Ketones **3a–c**

Product No.	R	Reaction Conditions solvent	equiv. of **2**	time	temperature	Yield [%]	m.p. [°C] or b.p. [°C]/torr
3a	*i*-C_3H_7	CH_2Cl_2	10	144 h	20 °C	77	50°/12
		CH_2Cl_2	10	32 h	50 °C	—[a]	
3b	2-furyl	CH_2Cl_2	10	21 h	50 °C	72	77°/0.2
3c	4-O_2N—C_6H_4	$CHCl_3$	1	72 h	70 °C	70	142.5°

[a] See procedure.

Table 2. Spectral Data for Compounds **3a–c**

Product	I.R. (CCl_4) [cm^{-1}] $\nu_{C=O}$	$\nu_{C=C}$	^{1}H-N.M.R. ($CDCl_3$/TMS, 90 MHz) δ [ppm] H-1	H-3	H-4	^{19}F-N.M.R. ($CDCl_3$/$CFCl_3$, 60 MHz) δ [ppm]
3a	1703	1625	4.98 (d, *J*=47.5 Hz)	6.31 (ddd, *J*=16.0, 2.8, and 1.1 Hz)	7.01 (dd, *J*=16.0 and 6.6 Hz)	229.2 (td, *J*=47.5 and 2.8 Hz)
3b	1695	1609	5.00 (d, *J*=47.5 Hz)	6.87 (dd, *J*= 15.9 and 3.2 Hz)	7.51 (d, *J*=15.9 Hz)	226.7 (td, *J*=47.5 and 3.2 Hz)
3c	1700[a]	1615[a]	5.30 (d, *J*=47.0 Hz)[b]	7.22 (dd, *J*=16.4 and 2.2 Hz)[b]	7.81 (d, *J*=16.4 Hz)[b]	229.6 (td, *J*=47.0 and 2.2 Hz)[b]

[a] CH_2Cl_2 solution.
[b] Acetone-d_6 solution.

(*E*)-1-Fluoro-5-methyl-3-hexene-2-one (3a; R = *i*-C_3H_7):

To a stirred solution of (1-fluoroacetyl)-methylenetriphenylphosphorane (**1**; 1.75 g, 5.2 mmol) in dichloromethane (7 ml) is added 2-methylpropanal (**2a**; 3.75 g, 52 mmol). Stirring is continued for 144 h [100% conversion is obtained within 32 h at 50 °C but purification of **3a** is difficult as polymerisation of a part of 2-methylpropanal occurs], then the solvent and the excess of 2-methylpropanal are removed under vacuum (water pump pressure). The pasty residue is stirred with hexane (10 ml) then the suspension filtered. The hexane is evaporated and the oily residue distilled bulb-to-bulb (bath temperature 80 °C/0.05 torr) to give (*E*)-1-fluoro-5-methyl-3-hexene-2-one (**3a**); yield: 0.52 g.

$C_7H_{11}FO$	calc.	C 64.59	H 8.52	F 14.60
(130.2)	found	64.52	8.59	13.96

(E)-1-Fluoro-4-(2-furyl)-3-butene-2-one (3b; R = 2-furyl):

Prepared from 2-furylaldehyde (**2b**) following the conditions indicated in Table 1. Purification is achieved by evaporation of the solvent, bulb-to-bulb distillation (bath temperature 90 °C/0.2 torr) and redistillation (Vigreux column) (Table 1).

$C_8H_7FO_2$	calc.	C 62.34	H 4.58
(154.1)	found	62.09	4.62

(*E*)-1-Fluoro-4-(*p*-nitrophenyl)-3-butene-2-one (3c; R = 4-O_2N—C_6H_4):

To a stirred solution of (1-fluoroacetyl)-methylenetriphenylphosphorane (**1**; 3.5 g, 10.4 mmol) in chloroform (15 ml) is added a solution of *p*-nitrobenzaldehyde (**2c**; 1.57 g, 10.4 mmol) in chloroform (15 ml). After reaction, a first crop of pure **3c** is obtained by filtration (1.02 g). A complement (0.5 g) is obtained by column chromatography on silica gel (chloroform as eluent); total yield: 1.52 g (70%); an analytical sample is obtained by recrystallization from benzene (Table 1).

$C_{10}H_8FNO_3$	calc.	C 57.42	H 3.85	F 9.08	N 6.70
(209.2)	found	57.57	3.77	8.93	6.71

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