Synthesis of O-phosphorylated 1-substituted 2,2,2-trifluoroethanols, serine hydrolase inhibitors

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Reactivity of trifluoromethyl carbonyl compounds in a two-step reaction with dialkyl phosphites (the Abramov reaction and phosphonate—phosphate rearrangement) has been studied and the scope of this reaction for the preparation of O-phosphorylated 1-substituted 2,2,2-trifluoroethanols, serine hydrolase inhibitors, has been determined.

Key words: dialkyl phosphites, trifluoroacetone, trifluoroacetophenone, hexafluoroacetone, methyl 3,3,3-trifluoropyruvate, 1-hydroxyphosphonates, *O*,*O*-dialkyl-*O*-(2,2,2-trifluoro-1-phenylethyl) phosphates, methyl 2-(dialkoxyphosphoryl)oxy-3,3,3-trifluoropropionates, the Abramov reaction, phosphonate-phosphate rearrangement.

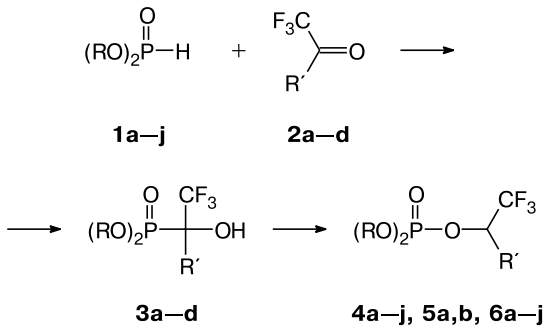
O-Phosphorylated phenols and alcohols containing electron-withdrawing substituents in the aryl and alkoxy parts of the molecule are of undoubted interest for the practical use in agrochemistry and medicine. Parathion, mercaptophos,[1] dichlophos,[2] armin[3] can serve as examples. Physiological effect of this type of compounds is first of all determined by their ability to inhibit serine esterases and considerably depends on the structure of alkoxy leaving group. Thus, it is obvious that a general approach to the molecular design of this type of esterase inhibitors consists in the variations of substituents in the leaving group.

Earlier, we have obtained the data on selective inhibitory activity of methyl 2-(dialkoxyphosphoryl)oxy-3,3,3-trifluoropropionates[4] (their synthesis has not been described so far) and *O*,*O*-dialkyl *O*-(1-trifluoromethyl-2,2,2-trifluoroethyl) phosphates,[5] possessing low acute toxicity with respect to four serine esterases, *viz.*, acetylcholinesterase, butyrylcholinesterase, carboxylesterase, and neurotoxic esterase.

The purpose of this research is the development of a convenient preparative method for the synthesis of O-phosphorylated 1-substituted 2,2,2-trifluoroethanols, serine hydrolase inhibitors, based on the Abramov reaction of dialkyl phosphites with trifluoromethyl carbonyl compounds and phosphonate-phosphate rearrangement, as well as the study of the scope of the latter reaction. Synthesis of some representatives of polyfluoroalkyl phosphates by the reaction of dialkyl phosphorochloridates with fluorinated alcohols[6,7] and by the reaction of dialkyl phosphites and polyhalogeno ketones with subsequent phosphonate—phosphate rearrangement is documented.[6,8,9] Under mild conditions,[8,9] the latter reaction led to a mixture of phosphonates and phosphates.

We studied the reactions of dialkyl phosphites **1a—j** with trifluoroacetone **2a**, trifluoroacetophenone **2b**, hexafluoroacetone **2c**, and methyl trifluoropyruvate **2d** (Scheme 1).

Scheme 1



1: R = Me (**a**), Et (**b**), Pr (**c**), Pr^i (**d**), Bu (**e**), Bu^i (**f**), Bu^s (**g**), *n*-C_5H_{11} (**h**), *i*-C_5H_{11} (**i**), *n*-C_6H_{13} (**j**);
2: R′ = Me (**a**), Ph (**b**), CF_3 (**c**), C(O)OMe (**d**);
3: R = Me; R′ = Me (**a**), Ph (**b**), CF_3 (**c**), C(O)OMe (**d**);
4: R′ = Ph; R = Me (**a**), Et (**b**), Pr (**c**), Pr^i (**d**), Bu (**e**), Bu^i (**f**), Bu^s (**g**), *n*-C_5H_{11} (**h**), *i*-C_5H_{11} (**i**), *n*-C_6H_{13} (**j**);
5: R′ = CF_3; R = Me (**a**), Et (**b**);
6: R′ = C(O)COMe; R = Me (**a**), Et (**b**), Pr (**c**), Pr^i (**d**), Bu (**e**), Bu^i (**f**), Bu^s (**g**), *n*-C_5H_{11} (**h**), *i*-C_5H_{11} (**i**), *n*-C_6H_{13} (**j**)

Compounds studied as the trifluoromethyl carbonyl components in the transformations under consideration differ in their electrophilic properties, which determined their behavior in the reactions with dialkyl phosphites.

The less electrophilic of trifluoromethyl ketones studied, trifluoroacetone (**2a**) and trifluoroacetophenone (**2b**), are phosphorylated with dimethyl phosphite only in the

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presence of Et_3N as a catalyst, which leads to phosphonates **3a** and **3b** (it should be noted that, according to the ^{31}P NMR spectral data of the reaction mixture, no C-phosphorylated products are formed upon prolonged (20 h) reflux of an equimolar mixture of reactants in toluene if the base is absent). A possibility of the phosphonate—phosphate rearrangement is determined by electron-withdrawing properties of a substituent on the carbon atom in the α-position. Thus no phosphonate—phosphate rearrangement product **3a**, *i.e.*, the corresponding phosphate, has been detected by us after prolonged (10 h) reflux of phosphonate **3a** either in toluene with Et_3N or in DMF in the presence of CsF. Unlike **3a**, the *C*-phosphorylation product of trifluoroacetophenone **3b** upon reflux for 3 h in toluene in the presence of Et_3N in catalytic amounts was converted to phosphate **4a**, which was isolated in 69% yield (isolation by chromatography yielded 88% of **4a**).[8]

In contrast to trifluoroacetone (**2a**) and trifluoroacetophenone (**2b**), hexafluoroacetone (**2c**) and methyl trifluoropyruvate (**2d**) react exothermically with dimethyl phosphite (**1a**) in the absence of basic catalysis to form a mixture of phosphonate **3c** and phosphate **5a** (1 : 4) (in Ref. 9, this ratio was found to be 6 : 94) and phosphonate **3d** and phosphate **6a** (1 : 3), respectively. The ratio of products was determined based on the ^{31}P NMR spectra of the reaction mixtures. The signals in the ^{31}P NMR spectra of **3c** (δ 15.34 sept, $J_{P,F}$ = 3.3 Hz) and **3d** (δ 16.23 q, $J_{P,F}$ = = 3.4 Hz) are in the region characteristic of phosphonates with the corresponding spin-spin coupling constants $J_{P,F}$ = 3.3 Hz, the signals in the spectra of **5a** (δ 1.03 s) and **6a** (δ 1.02 s) indicate their phosphate structure. In the presence of Et_3N, the reaction of **1a** with **2c** and methyl trifluoropyruvate **2d** leads (according to the ^{31}P NMR spectra of the reaction mixtures) to phosphates **5a** and **6a** in virtually quantitative yields. Phosphates **5b** and **6b—j** were obtained similarly.

Phosphates **4—6**, obtained in 58—90% yields, are colorless light liquids, their composition and structures are established based on data from elemental analysis and ^1H, ^{19}F, and ^{31}P NMR spectra. Thus the ^{31}P NMR spectra exhibit signals in the region δ from −3 to 2, which confirm the phosphate nature of compounds **4—6**.

The inhibitory activity of phosphates **4—6** with respect to serine esterases enhances with the increase in the electron-withdrawing properties of α-substituents in trifluoroethoxy leaving group in the order **4** < **5** < **6**; these data will be published elsewhere. The data from biochemical studies of phosphates **4—6** are in good enough agreement with the known concepts,[10] including those published by us earlier[4,5,11,12] on the optimization of the leaving group structure in the molecules of organophosphorus serine esterase inhibitors.

In conclusion, the synthetic potential of the two-step reaction of phosphites with α-trifluoromethyl carbonyl compounds studied (the Abramov reaction and subsequent phosphonate—phosphate rearrangement) allowed broadening the synthetic scope of the method under consideration for the preparation of O-phosphorylated 1-substituted 2,2-trifluoroethanols, which is determined by electron-withdrawing properties of the α-substituent in the trifluoromethyl carbonyl component and, first of all, by the possibility of the phosphonate—phosphate rearrangement of the Abramov reaction product, *i.e.*, phosphonate. The presence of an electron-withdrawing substituent on the α-C atom of trifluoromethyl ketones is a decisive prerequisite for the phosphonate—phosphate rearrangement.

Experimental

^1H, ^{19}F, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DXP 200 spectrometer (200.13, 188.29, 50.32, and 81.01 MHz, respectively) with tetramethylsilane as an internal standard, and CF_3COOH and 85% aqueous H_3PO_4 as external standards.

***O,O*-Dimethyl 2,2,2-trifluoro-1-hydroxy-1-methylethylphosphonate (3a).** A solution of trifluoroacetone (**2a**) (5.0 g, 44.6 mmol), dimethyl phosphite (**1a**) (4.5 g, 40.9 mmol), and triethylamine (0.2 g) in benzene (20 mL) was kept for 1 day in a sealed tube at room temperature, benzene was evaporated, and the residue was fractionally distilled to yield phosphonate **3a** (4.2 g, 45%), b.p. 90—93 °C (3 Torr), m.p. 47—49 °C.

***O,O*-Dimethyl 2,2,2-trifluoro-1-hydroxy-1-phenylethylphosphonate (3b).** A solution of trifluoroacetophenone (**2b**) (1.0 g, 6.2 mmol), dimethyl phosphite (**1a**) (0.68 g, 6.2 mmol), and triethylamine (0.2 g) in benzene (10 mL) was kept for 1 day at room temperature, benzene was evaporated, and the residue was recrystallized from hexane to yield phosphonate **3b** (0.5 g, 30%), m.p. 138—140 °C.

The yields, boiling points, and spectral characteristics of phosphonates **3a,b** are given in Tables 1 and 2.

***O,O*-Dimethyl *O*-(2,2,2-trifluoro-1-phenylethyl) phosphate (4a).** A solution of trifluoroacetophenone (**2b**) (2 g, 11.5 mmol), dimethyl phosphite (**1a**) (1.3 g, 11.8 mmol), and triethylamine (0.2 g) in toluene (10 mL) was refluxed for 3 h, toluene was evaporated, the residue was fractionally distilled to yield phosphate **4a** (2.3 g, 69%). ^{13}C NMR ($CDCl_3$), δ: 55.00 (d, MeO, $J_{C,P}$ = 5.8 Hz); 55.79 (d, MeO, $J_{C,P}$ = 5.8 Hz); 76.68 (dq, $\underline{C}CF_3$, $J_{C,P}$ = 4.3 Hz, $J_{C,F}$ = 33.9 Hz), 123.31 (dq, CF_3, $J_{C,F}$ = 280.6 Hz, $J_{C,P}$ = 9.7 Hz); 128.27 (q, *o*-Ph, $J_{C,F}$ = 1.0 Hz); 129.11 (s, *m*-Ph); 130.63 (s, *p*-Ph); 131.55 (m, *ipso*-Ph).

***O,O*-Dialkyl *O*-(2,2,2-trifluoro-1-phenylethyl) phosphates (4b—j)** were obtained similarly to phosphate **4a** from dialkyl phosphites **1b—j** (10.5 mmol), trifluoroacetophenone **2b** (10.5 mmol), and Et_3N (0.2 g). The yields, boiling points, and spectral characteristics of phosphates **4a—j** are given in Tables 1 and 2.

***O,O*-Dimethyl *O*-(1,1,1,3,3,3-hexafluoropropan-2-yl) phosphate (5a).** A solution of dimethyl phosphite (**1a**) (3.0 g, 27.3 mmol), hexafluoroacetone (**2c**) (5.5 g, 33.1 mmol), and Et_3N (0.2 g) in THF (10 mL) was kept for 1 day in a sealed tube at room temperature, the solvent was evaporated, and the residue was fractionally distilled to obtain phosphate **5a** (6.0 g, 80%).

Table 1. Yields, boiling points, and elemental analysis data of compounds **3a,b**, **4a—j**, **5a,b**, and **6a—j**

Compound	Yield (%)	B.p./°C (*p*/Torr)	Found / Calculated (%) C	H	P	Molecular formula
3a	45	90—92 (3)	27.07	4.79	13.97	$C_5H_{10}F_3O_4P$
		92 (3)	27.04	4.54	13.95	
3b	30	—	42.43	4.33	11.06	$C_{10}H_{12}F_3O_4P$
			42.27	4.26	10.90	
4a	69	97—98 (3)	42.34	4.23	11.19	$C_{10}H_{12}F_3O_4P$
			42.27	4.26	10.90	
4b	62	105—107 (3)	50.12	5.02	9.49	$C_{12}H_{16}F_3O_4P$
			49.86	5.17	9.92	
4c	58	122—124 (3)	49.69	5.55	9.32	$C_{14}H_{20}F_3O_4P$
			49.67	5.52	9.10	
4d	88	103—106 (3)	52.30	5.56	9.42	$C_{14}H_{20}F_3O_4P$
			52.17	5.92	9.10	
4e	90 (95)[8]	123—125 (4)	45.83	6.56	8.45	$C_{16}H_{24}F_3O_4P$
			45.87	6.67	8.49	
4f	89	124—126 (5)	45.77	6.46	8.35	$C_{16}H_{24}F_3O_4P$
			45.87	6.67	8.49	
4g	89	124—128 (5)	46.02	6.51	8.73	$C_{16}H_{24}F_3O_4P$
			45.87	6.67	8.49	
4h	64	152—155 (6)	54.42	7.32	7.73	$C_{18}H_{28}F_3O_4P$
			54.54	7.12	7.81	
4i	59	152—153 (3)	54.32	7.41	7.86	$C_{18}H_{28}F_3O_4P$
			54.54	7.12	7.81	
4j	50	150—154 (5)	56.93	4.88	8.14	$C_{20}H_{32}F_3O_4P$
			56.80	4.77	8.28	
5a	80	53—54 (3)	21.63	2.59	10.92	$C_5H_7F_6O_4P$
		59—60 (8)[6]	21.75	2.56	11.22	
5b	88	63—65 (5)	27.61	3.87	10.25	$C_7H_{11}F_6O_4P$
		71—72 (10)[6]	27.65	3.65	10.18	
6a	65	77—78 (1)	27.23	4.59	11.42	$C_6H_{10}F_3O_6P$
			27.08	3.79	11.64	
6b	82	88—89 (1)	32.44	4.89	9.71	$C_8H_{14}F_3O_6P$
			32.66	4.80	9.83	
6c	77	90—91 (1)	37.38	5.74	9.78	$C_{10}H_{18}F_3O_6P$
			37.28	5.63	9.61	
6d	79	88—90 (1)	37.48	5.81	9.52	$C_{10}H_{18}F_3O_6P$
			37.28	5.63	9.61	
6e	81	120—122 (1)	41.19	6.51	8.55	$C_{12}H_{22}F_3O_6P$
			41.15	6.33	8.84	
6f	76	120—122 (1)	41.31	6.57	8.65	$C_{12}H_{22}F_3O_6P$
			41.15	6.33	8.84	
6g	82	124—126 (1)	41.28	6.17	8.96	$C_{12}H_{22}F_3O_6P$
			41.15	6.33	8.84	
6h	85	135—140 (1)	44.41	6.83	8.12	$C_{14}H_{26}F_3O_6P$
			44.45	6.93	8.19	
6i	78	120—126 (1)	44.23	6.74	8.02	$C_{14}H_{26}F_3O_6P$
			44.45	6.93	8.19	
6j	71	148—149 (1)	47.54	7.83	7.41	$C_{16}H_{30}F_3O_6P$
			47.29	7.44	7.62	

Table 2. ^1H, ^{19}F, and ^{31}P NMR spectra of compounds **3a**,**b**, **4a—j**, **5a**,**b**, and **6a—j** in DMSO-d_6

Compound	NMR, δ (*J*/Hz) ^1H	^{19}F	$\{^{31}P\}$
3a	1.64 (d, 3 H, MeC, $J_{H,P}$ = 14.7); 3.87 (d, 3 H, MeO, $J_{H,P}$ = 5.7); 3.93 (d, 3 H, MeO, $J_{H,P}$ = 5.7); 5.39 (s, 1 H, OH)	0.41 (d, $J_{F,P}$ = 3.3)	18.15 (q, $J_{P,F}$ = 3.4)
3b	3.59 (d, 3 H, MeO, $J_{H,P}$ = 10.5); 3.80 (d, 3 H, MeO, $J_{H,P}$ = 10.5); 7.38 (m, 3 H, CH_{Ar}); 7.77 (m, 2 H, CH_{Ar})	5.28 (d, $J_{F,P}$ = 3.7)	17.44 (q, $J_{P,F}$ = 3.9)
4a	3.60 (d, 3 H, MeO, $J_{H,P}$ = 11.4); 3.82 (d, 3 H, MeO, $J_{H,P}$ = 11.4); 5.64 (dq, 1 H, $J_{H,F}$ = 6.3, $J_{H,P}$ = 10.0); 7.40—7.60 (m, 5 H, CH_{Ar})	0.45 (d, $J_{F,H}$ = 6.7)	1.59 s
4b	1.17 (t, 3 H, Me, $J_{H,H}$ = 7.0); 1.34 (t, 3 H, Me, $J_{H,H}$ = 7.0); 3.94 (m, 2 H, CH_2); 4.16 (m, 2 H, CH_2); 5.63 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.51 (d, $J_{F,H}$ = 6.7)	−0.88 s
4c	0.82 (t, 3 H, $J_{H,H}$ = 7.0); 0.96 (t, 3 H, $J_{H,H}$ = 7.0); 1.54 (m, 2 H, CH_2); 1.71 (m, 2 H, CH_2); 3.82 (m, 2 H, CH_2O); 4.06 (m, 2 H, CH_2O); 5.63 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.52 (d, $J_{F,H}$ = 6.7)	−0.56 s
4d	1.07, 1.18 (both d, 3 H each, Me, $J_{H,H}$ = 6.5); 1.30, 1.37 (both d, 3 H each, Me, $J_{H,H}$ = 6.0); 4.36 (m, 1 H, CHCO); 4.62 (m, 1 H, CHCO); 5.73 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar});	0.89 (d, $J_{F,H}$ = 6.2)	−0.54 s
4e	0.85, 0.95 (both t, 3 H each, Me, $J_{H,H}$ = 7.0); 1.25, 1.66 (both m, 2 H each, CH_2); 1.46 (m, 4 H, CH_2); 3.86, 4.10 (both m, 2 H each, CH_2O); 5.63 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.53 (d, $J_{F,H}$ = 6.7)	−0.54 s
4f	0.82, 0.98 (both dm, 6 H each, Me, $J_{H,H}$ = 6.7); 1.75, 1.97 (both m, 1 H each, CH); 3.56, 3.81 (both m, 2 H each, CH_2O); 5.75 (m, 1 H, CHO), 7.40—7.60 (m, 5 H, CH_{Ar})	0.89 (d, $J_{F,H}$ = 7.2)	−0.54 s

(*to be continued*)

Table 2 (*contunued*)

Compound	NMR, δ (*J*/Hz)		
	^{1}H	^{19}F	{^{31}P}
4g	0.76, 0.97 (both t, 1.5 H each, Me); 1.09 (m, 6 H, CH_2); 1.26 (m, 2 H, CH_2); 1.41 (m, 4 H, CH); 1.72 (m, 2 H); 4.23, 4.49 (both m, 1 H each, CHO_{Bu}); 5.79 (m, 1 H, CHO), 7.40—7.60 (m, 5 H, CH_{Ar})	0.91 (d, $J_{F,H}$ = 7.2); 0.97 (d, $J_{F,H}$ = 6.5)	−1.58; −1.43; −1.37; −1.19 all s
4h	0.82, 0.93 (both t, 3 H each, Me, $J_{H,H}$ = 7.0); 1.24, 1.37 (both m, 4 H each, CH_2); 1.51 (m, 2 H, CH_2); 1.68 (m, 2 H, CH_2); 3.86, 4.09 (both m, 2 H each, CH_2O); 5.63 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.54 (d, $J_{F,H}$ = 6.7)	−0.56 s
4i	0.84, 0.98 (both d, 3 H each, Me, $J_{H,H}$ = 6.4); 1.37 (m, 2 H, CH_2); 1.57 (m, 3 H); 1.77 (m, 1 H); 3.82, 4.07 (both m, 2 H each, CH_2O); 5.77 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.87 (d, $J_{F,H}$ = 6.7)	−0.36 s
4j	0.93 (m, 6 H); 1.10—1.5 (m, 16 H); 1.66 (m, 2 H); 3.78, 4.02 (both m, 2 H each, CH_2O); 5.75 (m, 1 H, CHO); 7.40—7.60 (m, 5 H, CH_{Ar})	0.89 (d, $J_{F,H}$ = 6.7)	−0.42 s
5a[a]	3.88 (d, 6 H, MeO, $J_{H,P}$ = 11.6); 5.20 (dsept, 1 H, OH, $J_{H,P}$ = $J_{H,F}$ = 6.0)	3.68 (d, $J_{F,H}$ = 6.0)	1.03 s
5b[a]	1.40 (t, 6 H, Me, $J_{H,H}$ = 7.2); 4.22 (m, 4 H, CH_2O); 5.20 (dsept, 1 H, OH, $J_{H,P}$ = $J_{H,F}$ = 6.0)	3.70 (d, $J_{F,H}$ = 6.0)	−1.23 s
6a[b]	3.93, 3.96 (both d, 3 H each, MeOP, *J* = 7.0); 3.98 (s, 3 H, MeOC(O)); 5.41 (m, 1 H, OH)	3.56 (d, $J_{F,H}$ = 6.9)	1.02 s
6b[a]	1.42 (m, 6 H, Me); 3.92 c (s, 3 H, MeOC(O)); 4.24 (m, 4 H, CH_2O); 5.27 (m, 1 H, CHO)	2.68 (d, $J_{F,H}$ = 6.9)	−2.05 s
6c[b]	0.96 (t, 6 H, Me, $J_{H,H}$ = 7.0); 1.42 (m, 4 H, $CH_3\underline{CH_2}$); 3.92 c (s, 3 H, MeOC(O)); 4.76 (m, 4 H, CH_2O); 5.34 (m, 1 H, CHO)	3.65 (d, $J_{F,H}$ = 6.9)	−2.48 s
6d[b]	1.36 (m, 12 H, Me + CH_2); 3.93 c (s, 3 H, MeOC(O)); 4.76 (m, 2 H, CH_2O); 5.38 (m, 1 H, CHO)	3.45 (d, $J_{F,H}$ = 6.9)	−2.89 s
6e	0.96 (m, 6 H, Me); 1.42 (m, 4 H, CH_2); 1.70 (m, 4 H, CH_2); 3.90 (s, 3 H, MeOC(O)); 4.14 (m, 4 H, CH_2O); 5.74 (m, 1 H, CHO)	4.02 (d, $J_{F,H}$ = 6.8)	−1.4 s
6f[a]	0.98 (m, 12 H, Me + CH_2); 1.98 (m, 2 H, CH); 3.90 (s, 3 H, MeOC(O)); 4.04 (m, 4 H, CH_2O); 5.28 (m, 1 H, CHO)	2.96 (d, $J_{F,H}$ = 6.9)	−2.76 s
6g[a]	0.96 (m, 6 H, $\underline{CH_3}CH_2$); 1.28—1.48 (m, 6 H, $\underline{CH_3}CH$); 1.56—1.88 (m, 4 H, CH_2); 3.96 (s, 3 H, MeOC(O)); 4.60 (m, 2 H, $CH_3\underline{CH}$); 5.38 (m, 1 H, CHO)	3.46 (d, $J_{F,H}$ = 6.9)	−2.05 s
6h[b]	0.96 (m, 6 H, Me); 1.44 (m, 8 H, CH_2); 1.74 (m, 4 H, CH_2); 3.94 (s, 3 H, MeOC(O)); 4.24 (m, 4 H, CH_2O); 5.44 (m, 1 H, CHO)	3.53 (d, $J_{F,H}$ = 6.9)	−1.05 s
6i[a]	1.21 (m, 12 H, Me + CH_2); 1.88 (m, 4 H, CH_2); 2.02 (m, 2 H, CH); 4.12 (s, 3 H, MeOC(O)); 4.14 (m, 4 H, CH_2); 5.42 (m, 1 H, CHO)	2.91 (d, $J_{F,H}$ = 6.9)	−2.81 s
6j[a]	0.96 (m, 6 H, Me); 1.44 (m, 12 H, CH_2); 1.74 (m, 4 H, CH_2); 3.94 (s, 3 H, MeOC(O)); 4.24 (m, 4 H, CH_2O); 5.44 (m, 1 H, CHO)	2.61 (d, $J_{F,H}$ = 6.9)	−1.81 s

[a] In $CDCl_3$.
[b] In CD_3CN.

***O*,*O*-Diethyl *O*-(1,1,1,3,3,3-hexafluoropropan-2-yl) phosphate (5b)** was obtained similarly to phosphate **5a** from diethyl phosphite (**1b**) (3.0 g, 21.7 mmol) and hexafluoroacetone (**2c**) (5.5 g, 33.1 mmol) in the presence of Et_3N (0.2 g).

Methyl 2-(dialkoxyphosphoryl)oxy-3,3,3-trifluoropropionates (6a—j) (general procedure). Methyl trifluoropyruvate **2d** (25.5 mmol) was added to a solution of dialkyl phosphite (**1a—j**) (25.0 mmol) and Et_3N (0.2 mmol) in benzene (10 mL), the mixture was stirred for 2 h at 20 °C. Benzene was evaporated and the residue was fractionally distilled. The yields, boiling points, and spectral characteristics of compounds **6a—j** are given in Tables 1 and 2.

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