Catalytic phosphorylation of polyfluoroalkanols
16.* Synthesis and stereochemistry of *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates

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Phosphorylation of α-polyfluoroalkylbenzyl alcohols by an excess of phenylphosphonic dichloride in the presence of Mg or $CaCl_2$ as the catalyst gives *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates (63—79% yield). The reaction proceeds stereoselectively, and the phosphonochloridates obtained are mixtures of two diastereomers with predominance (approximately by 10%) of one of them.

Key words: α-polyfluoroalkylbenzyl alcohols, phosphorylation, catalysis; phenylphosphonic dichloride, *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridate, stereochemistry, diastereomers.

We have previously established[2] that catalytic phosphorylation of sterically hindered tertiary α,α-dimethylpolyfluoroalkanols by an excess of phenylphosphonic dichloride (**1**) results in the formation of the corresponding phenylphosphonochloridates.

$$R_FCMe_2OH + \underset{\mathbf{1}}{PhPOCl_2} \xrightarrow{\text{Cat, }\Delta} PhP(O)(Cl)OCMe_2R_F$$

This suggests that the method of catalytic phosphorylation will also be appropriate for preparing phenylphosphonochloridates containing sterically hindered secondary polyfluoroalkyl (for example, α-polyfluoroalkylbenzyl) fragments. These acid chlorides can be of interest as intermediate products for synthesis of various types of unsymmetrical esters or amidoesters of phenylphosphonic acid.

We studied the reactions of phosphonic dichloride **1** with several α-polyfluoroalkylbenzyl alcohols (**2a—h**) in which both the position and nature of the substituent in the benzene ring and the chain length and character of the α-polyfluoroalkyl fragment were varied.

$$\underset{\mathbf{1}}{PhPOCl_2} + \underset{\mathbf{2a-h}}{RC_6H_4CHR'_FOH} \xrightarrow{\text{Cat, 140 °C}} \underset{\mathbf{3a-h}}{Ph\overset{*}{P}(O)(Cl)O\overset{*}{C}HR'_FC_6H_4R}$$

a: R = H, $R'_F = CF_3$
b: R = H, $R'_F = n\text{-}C_3F_7$
c: R = H, $R'_F = n\text{-}C_4F_9$
d: R = H, $R'_F = CF_3OCF_2CF_2$
e: R = *m*-Me, $R'_F = CF_3$
f: R = *m*-CF_3, $R'_F = CF_3$
g: R = *p*-F, $R'_F = CF_3$
h: R = *p*-Cl, $R'_F = CF_3$

Anhydrous $CaCl_2$ or Mg metal were used as catalysts. A twofold excess of the phosphorylating agent was used in all experiments to decrease the probability of the formation of by-products (the corresponding symmetrical esters), and the reaction was carried out at a possibly lower temperature (140 °C). It is established that in all cases, the catalytic phosphorylation results in the formation of *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates (**3a—h**). The conditions of the reaction and yields of the phosphonochloridates are presented in Table 1, and the main physicochemical constants of the compounds synthesized are listed in Table 2.

As follows from the data in Table 1, the rate of phosphorylation of benzyl alcohols **2** by phosphonic dichloride **1** decreases as the chain length of the α-polyfluoroalkyl radical R'_F increases and the acceptor character of the substituent R in the benzene ring of the alcohol increases.

Comparison of the catalytic activities of $CaCl_2$ and Mg shows that the efficiency of Mg metal is substantially higher than that of $CaCl_2$. A similar ratio of activities of these catalysts was observed previously for the phosphorylation of α-polyfluoroalkylbenzyl alcohols by aryl phosphodichloridates.[1]

The phosphonochloridates **3** that formed can be easily separated by distillation from an excess of the phosphorylating agent, which is regenerated in a yield close to quantitative in a state sufficiently pure to use repeatedly.

We also studied some stereochemical aspects of catalytic phosphorylation of α-polyfluoroalkylbenzyl alcohols

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* For Part 15, see Ref. 1.

[†] Deceased.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1776—1779, September, 1998.

Table 1. Catalytic phosphorylation of α-polyfluoroalkylbenzyl alcohols with an excess of phenylphosphonic dichloride

R	R′$_F$	Cat[a]	Duration of reaction/h	Yield of **3a—h** (%)	Ratio of diastereomers[b]
H	CF_3	$CaCl_2$	2.0	66	46 : 54
		Mg[c]	1.25	69	46 : 54
H	n-C_3F_7	Mg	6.0	71	46 : 54
H	n-C_4F_9	Mg	7.0	70	45 : 55
H	$CF_3OCF_2CF_2$	Mg	2.5	71	44 : 56
m-Me	CF_3	Mg	1.25	63	46 : 54
m-CF_3	CF_3	Mg	2.5	67	45 : 55
p-F	CF_3	Mg	3.0	73	46 : 54
p-Cl	CF_3	Mg	3.0	79	46 : 54[d]

[a] Calculated as 0.025 moles of the catalyst per mole $RC_6H_4R'_FOH$.
[b] According to the ^{31}P-{^1H} NMR spectroscopy data.
[c] In all experiments, magnesium is dissolved during the reaction transforming into $MgCl_2$.
[d] According to the ^{19}F-{^1H} NMR spectroscopy data.

by an excess of phenylphosphonic dichloride, during which the prochiral P atom in the starting acid chloride is transformed into the chiral atom. Since the *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates that formed contain the second chiral center (benzyl α-C atom) along with the asymmetrical phosphorus atom, it can be expected that these compounds are mixtures of two diastereomers.*

In fact, the ^{31}P-{^1H} NMR spectra of the reaction mixture exhibit, along with the signal at ~35 ppm related to the phosphorylating agent taken in an excess, two closely located singlet signals. They lie in the high field region and belong to stereoisomers **A*** and **B** of the corresponding phosphonochloridates 3.

As for the **A** : **B** ratio, it deviates from the statistical one (1 : 1), and in all cases, diastereomers **B** are predominantly formed (see Table 1). The difference in contents of the isomers is relatively small (as a rule, not higher than 10%) and almost independent of the structure of the α-polyfluoroalkylbenzyl fragment of the molecule.

It should be emphasized that from the viewpoint of stereochemistry, *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates **3a—h** differ from aryl (α-polyfluoroalkylbenzyl) phosphochloridates $ArOP(O)(Cl)OCHR'_FC_6H_4R$ (4), in the synthesis of which the diastereomer ratio always coincides with the statistical one,[2] and they are similar to *O*-(α-polyfluoroalkylbenzyl) methylphosphonochloridates $MeP(O)(Cl)OCHR'_FC_6H_4R$ (5) which are also nonstatistical mixtures of diastereomers with a predominant content of isomer **B**.**

According to the ^1H, ^{19}F, and ^{31}P NMR spectra exhibiting double signals (Table 3), analytically pure phenylphosphonochloridates **3a—h** isolated from the reaction mixtures by fractional distillation *in vacuo* are

Table 2. Main physicochemical constants of *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates $PhP(O)(Cl)OCHR'_FC_6H_4R$ (**3a—h**)

Compound	R	R′$_F$	B.p./°C (p/Torr)	n_D^{20}	d_4^{20}	Found / Calculated (%) C	H	Cl	F	P	Molecular formula
3a	H	CF_3	126—127 (1)	1.5230	1.3587	50.3 50.2	3.6 3.3	10.4 10.6	16.7 17.0	9.2 9.2	$C_{14}H_{11}ClF_3O_2P$
3b	H	n-C_3F_7	128—131 (0.5)	1.4826	1.4505	44.1 44.2	2.6 2.6	8.2 8.2	30.7 30.6	7.2 7.1	$C_{16}H_{11}ClF_7O_2P$
3c	H	n-C_4F_9	151—153 (1.5)	1.4699	1.4964	42.1 42.1	2.4 2.3	7.3 7.3	35.4 35.3	6.4 6.4	$C_{17}H_{11}ClF_9O_2P$
3d	H	$CF_3OCF_2CF_2$	133—134 (0.5)	1.4740	1.4552	42.6 42.6	2.5 2.5	7.5 7.9	29.5 29.5	6.9 6.9	$C_{16}H_{11}ClF_7O_3P$
3e	m-Me	CF_3	152—153 (2)	1.5215	1.3302	51.3 51.7	3.7 3.8	10.0 10.2	16.4 16.4	8.8 8.9	$C_{15}H_{13}ClF_3O_2P$
3f	m-CF_3	CF_3	123—124 (0.5)	1.4855	1.4466	44.7 44.7	2.4 2.5	8.6 8.8	28.8 28.3	7.7 7.7	$C_{15}H_{10}ClF_6O_2P$
3g	p-F	CF_3	134—136 (1)	1.5116	1.4107	47.2 47.7	2.8 2.9	10.0 10.0	21.6 21.6	8.9 8.8	$C_{14}H_{10}ClF_4O_2P$
3h	p-Cl	CF_3	155—156 (1)	1.5325	1.4244	45.6 45.6	2.6 2.7	19.3 19.2	15.4 15.4	—	$C_{14}H_{10}Cl_2F_3O_2P$

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* Each of the diastereomers is a racemic mixture of two enantiomers.

* The diastereomer, whose signal in the ^{31}P-{^1H} NMR spectra is shifted downfield, is arbitrarily designated as **A**.

** It should be mentioned that for methylphosphonochloridates the degree of stereoselectivity is higher, and the difference in the diastereomer ratio achieves 30—35%.

Table 3. Parameters of the ^{1}H, ^{19}F, and ^{31}P NMR spectra of *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates $PhP(O)(Cl)OCHR'_FC_6H_4R$ (**3a—h**)

Compound	R	R'_F	Diastereomer	δ ^{1}H (*J*/Hz)[a]			δ ^{19}F (*J*/Hz)[a]		δ ^{31}P-{^{1}H}[a]
				CHR'_F	R (s)	H arom. (m)	R'_F (d)	R	(s)
3a	H	CF_3	**A**	6.12 (dq, J_{H-F} = 6.4, J_{H-P} = 12.9)	—	6.80—7.91	1.26 (J_{H-F} = 6.3)	—	30.28[b]
			B	6.20 (dq, J_{H-F} = 6.3, J_{H-P} = 12.6)			0.82 (J_{H-F} = 6.3)		30.11[b]
3b	H	*n*-C_3F_7	**A**	6.14 (ddd, $^3J_{H-F}$ = 7.8, $^3J_{H-F}$ = 15.2, J_{H-P} = 12.0)	—	6.74—7.80	—	—	30.72
			B	6.31 (ddd, $^3J_{H-F}$ = 7.0, $^3J_{H-F}$ = 16.1, J_{H-P} = 11.5)	—		—	—	30.41
3c	H	*n*-C_4F_9	**A**	6.21 (ddd, $^3J_{H-F}$ = 7.9, $^3J_{H-F}$ = 14.9, J_{H-P} = 11.9)	—	6.75—7.86	—	—	30.38
			B	6.36 (ddd, $^3J_{H-F}$ = 6.9, $^3J_{H-F}$ = 15.5, J_{H-P} = 11.6)	—		—	—	29.93
3d	H	$CF_3OCF_2CF_2$	**A**	6.17 (ddd, $^3J_{H-F}$ = 8.0, $^3J_{H-F}$ = 14.8, J_{H-P} = 12.1)	—	6.80—7.88	—	—	30.39
			B	6.30 (ddd, $^3J_{H-F}$ = 7.2, $^3J_{H-F}$ = 15.9, J_{H-P} = 11.8)	—		—	—	29.88
3e	*m*-CH_3	CF_3	**A**	6.02 (dq, J_{H-F} = 6.4, J_{H-P} = 12.6)	1.83	6.69—7.88	1.47 (J_{H-F} = 6.4)	—	30.32
			B	6.11 (dq, J_{H-F} = 6.3, J_{H-P} = 12.5)	1.96		1.01 (J_{H-F} = 6.4)	—	30.24
3f	*m*-CF_3	CF_3	**A**	6.19 (dq, J_{H-F} = 6.2, J_{H-P} = 12.8)	—	6.75—7.91	1.07 (J_{H-F} = 6.2)	14.83 (s)	31.04
			B	6.31 (dq, J_{H-F} = 6.2, J_{H-P} = 12.5)	—		0.63 (J_{H-F} = 6.2)	14.93 (s)	30.95
3g	*p*-F	CF_3	**A**	5.94 (dq, J_{H-F} = 6.3, J_{H-P} = 12.9)	—	6.49—7.80	1.27 (J_{H-F} = 6.0)	−32.41 (m)	30.90
			B	6.05 (dq, J_{H-F} = 6.2, J_{H-P} = 12.4)	—		0.82 (J_{H-F} = 6.0)	−32.17 (m)	30.86
3h	*p*-Cl	CF_3	**A**	5.87 (dq, J_{H-F} = 6.3, J_{H-P} = 13.0)	—	6.78—7.78	1.41 (J_{H-F} = 6.0)	—	31.04
			B	5.98 (dq, J_{H-F} = 6.2, J_{H-P} = 12.5)	—		0.95 (J_{H-F} = 6.4)	—	30.93

[a] In C_6D_6.

[b] Without solvent.

mixtures of two diastereomers, and their ratio in the distilled product virtually coincides with the diastereomeric composition of ester-acid chlorides formed under the conditions of catalytic phosphorylation.

We have previously established that the stereochemistry of the catalytic phosphorylation of α-polyfluoroalkylbenzyl alcohols by aryl phosphodichloridates[1] and methylphosphonic dichloride[3] can be thermodynamically controlled, and the ester-acid chlorides **4** and **5** that formed are equilibrium mixtures of diastereomers. Taking into account the structural similarity of these acid monochlorides and phenylphosphonochloridates **3**, we can assume that the stereochemistry of the latter is also characterized by similar regularities.

Experimental

^{1}H and ^{31}P-{^{1}H} NMR spectra were recorded on a Bruker AMX-400 instrument, and ^{19}F NMR spectra were recorded on a Bruker WP-200SY instrument using HMDS (^{1}H NMR) as the internal standard and CF_3COOH (^{19}F NMR) and 85% H_3PO_4 (^{31}P-{^{1}H} NMR) as the external standards.

***O*-(α-Polyfluoroalkylbenzyl) phenylphosphonochloridates (3a—h) (general procedure).** A mixture of α-polyfluoroalkylbenzyl alcohol **2a—h** (0.05 mol), phenylphosphonic dichloride **1** (0.1 mol), and the corresponding catalyst (1.25 mmol) was heated at 140 °C for several hours until HCl evolution ceased. The excess of the phosphorylating agent was distilled off, and *O*-(α-polyfluoroalkylbenzyl) phenylphosphonochloridates **3a—h** were isolated from the residue by fractional distillation *in vacuo* (see Table 2).

This work was financially supported by the Russian Foundation for Basic Research (Project Nos. 94-03-08214 and 96-15-97298).

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Received December 11, 1997