Catalytic phosphorylation of polyfluoroalkanols
17.* Synthesis and the stereochemistry of tris(α-trifluoromethylbenzyl) phosphates

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Catalytic phosphorylation of α-trifluoromethylbenzyl alcohols with $POCl_3$ taken in a ratio of 3 : 1 under particular temperature conditions afforded predominantly symmetrical tris(α-trifluoromethylbenzyl) phosphates. The latter were obtained as mixtures of two diastereomers with a statistical ratio of the components.

Key words: α-trifluoromethylbenzyl alcohols, phosphorylation, catalysis; phosphorus oxychloride, tris(α-trifluoromethylbenzyl) phosphates, stereochemistry, diastereomers.

Previously,[2,3] we have found that catalytic phosphorylation of α-polyfluoroalkylbenzyl alcohols containing different substituents (from strong electron-withdrawing to weak electron-donating) in the aromatic nucleus with a 1.5—6.0-fold excess of $POCl_3$ is a convenient procedure for the synthesis of α-polyfluoroalkylbenzyl phosphodichloridates.

$$RC_6H_4CH(R_F)OH + POCl_3 \xrightarrow{Cat,\ \Delta} RC_6H_4CH(R_F)OPOCl_2$$

R = *m*-NO_2, *m*-CF_3, H, *m*-Me; R_F = CF_3, $C_3F_7^n$;
Cat = Mg, $CaCl_2$

It has also been demonstrated that the catalytic phosphorylation of racemic *m*-trifluoromethyl-α-trifluoromethylbenzyl alcohol (**1**) with $POCl_3$ taken in a ratio of 2 : 1 gave rise predominantly to the corresponding phosphochloridate as a statistical mixture of three diastereomers.[4]

$$\underset{\mathbf{1}}{m\text{-}CF_3C_6H_4CH(CF_3)OH} + POCl_3 \xrightarrow{Cat,\ 140—200\ ^\circ C} [m\text{-}CF_3C_6H_4CH(CF_3)O]_2POCl$$

Cat = Mg, $MgSO_4$,$CaCl_2$

The aim of the present study was to examine the possibility of extension of the catalytic phosphorylation to the synthesis of sterically hindered tris(α-trifluoromethylbenzyl) phosphates. This seemed quite possible, at least, in the case of α-polyfluoroalkylbenzyl alcohols containing strong electron-withdrawing substituents, for example, the *m*-trifluoromethyl group, in the benzene ring.

Actually, it appeared that the phosphorylation of alcohol **1** with $POCl_3$ taken in a ratio of 3 : 1 in the presence of a catalytic amount of metallic magnesium afforded tris(*m*-trifluoromethyl-α-trifluoromethylbenzyl) phosphate (**2**).

$$\mathbf{1} + POCl_3 \xrightarrow{Mg,\ 140\rightarrow200\ ^\circ C} \underset{\mathbf{2}}{[m\text{-}CF_3C_6H_4CH(CF_3)O]_3PO}$$

It is best to perform the reaction first at moderate temperature (140 °C) followed by gradual heating to 200 °C; the total reaction time is 28 h (see the Experimental section). Under these condition, the reaction was not accompanied by the formation of noticeable amounts of by-products (according to the data from GLC and ^{19}F and ^{31}P NMR spectroscopy) and phosphate **2** was isolated in high yield.

Moreover, it was found that the catalytic phosphorylation with a gradual increase in the temperature made it possible to prepare tris(α-trifluoromethylbenzyl) phosphate (**3**), which did not contain electron-withdrawing substituents in the benzene rings, from the corresponding racemic benzyl alcohol (**4**) and $POCl_3$. Taking into account the lower thermal stabilities of intermediate phosphodichloridates and phosphochloridates[5] and the ability of α-trifluoromethylbenzyl phosphodichloridate to etherify the starting benzyl alcohol,[5] we chose milder temperature conditions with the initial temperature of 120 °C; the total reaction time was 20 h.

$$\underset{\mathbf{4}}{PhCH(CF_3)OH} + POCl_3 \xrightarrow{Mg,\ 120\rightarrow200\ ^\circ C} \underset{\mathbf{3}}{[PhCH(CF_3)O]_3PO} + \underset{\mathbf{5}}{PhCH(CF_3)OCH(CF_3)Ph} + \underset{\mathbf{6}}{PhCHClCF_3}$$

According to the data from GLC-mass spectrometry and ^{19}F NMR spectroscopy, this reaction gave rise to phosphate **3** as the major product, although by-products, *viz.*, bis-α-trifluoromethylbenzyl ether (**5**) and

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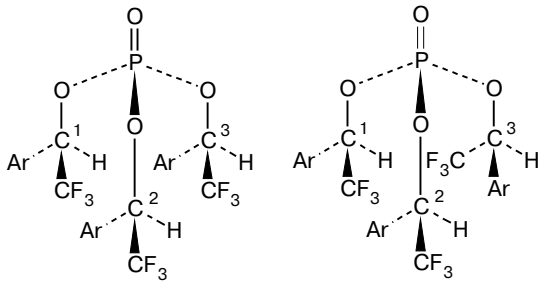
α-trifluoromethylbenzyl chloride (**6**)*[1], were also formed. Thus the **3** : **5** : **6** ratio was 76 : 20 : 4 (according to the data from GLC) or 70 : 25 : 5 (according to the data from ^{19}F NMR spectroscopy). Phosphate **3** can be separated from the ether and benzyl chloride that formed by distillation. Obviously, the corresponding side reactions led to a decrease in the yield of phosphate **3** compared to phosphate **2**.

Phosphates **2** and **3**, which were prepared for the first time, are of interest from the stereochemical standpoint because they belong to a very rare type of compounds containing three asymmetric centers. The chemical identity of the substituents at each of the asymmetric centers in the phosphates with this structure leads to the situation where only two diastereomers*[2] theoretically possible, **2** (Ar = *m*-$CF_3C_6H_4$) and **3** (Ar = Ph).



In one of them (the so-called "bisracemic"), all three asymmetric benzyl C atoms adopt an identical configuration. In another diastereomer ("meso-racemic"*[3]), the configuration of one chiral center differs from those of two other centers. It should be noted that in both cases, the tetrahedral P atom bound to the chiral centers is not asymmetric by itself. Hence, the statistical ratio between the "meso-racemic" and "bisracemic" diastereomers should be equal to 3 : 1.

The ^{31}P-{^1H} NMR spectra of phosphates **2** and **3** containing two singlet signals with the integral intensity ratio of 3 : 1 and the data from GLC for **2** indicate that the resulting compounds are actually mixtures of two diastereomers **A** and **B**,*[4] their ratio being statistical. Analysis of the ^{19}F NMR spectra confirmed this fact. In the case of the "bisracemic" diastereomer, the molecule has a threefold symmetry axis and, as a consequence, all three α-trifluoromethyl groups are magnetically equivalent. On the contrary, higher-order symmetry elements are absent in the "meso-racemic" diastereomer, which should lead to the magnetic nonequivalence of all three α-trifluoromethyl groups. In this case, the ^{19}F NMR spectra of a statistical mixture of these diastereomers would have four groups of qualitatively similar signals (doublets) with equal intensities in the region of signals of the α-CF_3 fragments. The real ^{19}F NMR spectra of phosphates **2*** and **3** are in complete agreement with those predicted theoretically for a statistical mixture of two diastereomers. Similar patterns are observed in the ^1H NMR spectra in which the methine protons of the CHR_F groups are observed as four multiplets of the AM_3X type (where M is the ^{19}F atom and X is the ^{31}P atom) with approximately equal intensities. Due to the fact that the diastereomers exist as statistical mixtures, the signals in the ^{31}P NMR spectra and the GLC peaks were unambiguously assigned to diastereomers with particular configurations. It is diastereomers **A** that have the "meso-racemic" configuration, while diastereomers **B** possess "bisracemic" configurations.

To summarize, the catalytic phosphorylation of α-polyfluoroalkylbenzyl alcohols with $POCl_3$ can selectively afford α-polyfluoroalkylbenzyl phosphodichloridates,[2,3] bis(α-polyfluoroalkylbenzyl) phosphochloridates,[4] or the corresponding triesters depending on the reaction conditions. Phosphates resulting from the replacement of two or three Cl atoms in $POCl_3$ by the α-polyfluoroalkylbenzyl fragments bearing the asymmetric center were obtained as mixtures of diastereomers with statistical component ratios regardless of the stereochemical nature of the P atom.

Experimental

The ^1H and ^{19}F NMR spectra were recorded on a Bruker WP-200SY instrument with HMDS and CF_3COOH as the internal and external standards, respectively. The proton-noise-decoupled ^{31}P NMR spectra were measured on a Bruker WP-200SY instrument in the pulsed mode with 85% H_3PO_4 as the external standard. Chromatographic separation was carried out on a Varian instrument equipped with a 15-m SE-54 capillary column and a Finnigan-MAT 800 AT ion trap as the detector using helium as the carrier gas; the samples were introduced directly into the column; the column temperature was varied from 60 to 280 °C with a rate of 4 deg min^{-1}.

Tris(*m*-trifluoromethyl-α-trifluoromethylbenzyl) phosphate (2). A mixture of alcohol **1**[2] (7.3 g, 0.03 mol), $POCl_3$ (1.5 g, 0.01 mol), and Mg (18 mg, 0.75 mg-at.) was successively heated at 140 °C for 7 h, at 160 °C for 7 h, at 180 °C for 7 h, and at 200 °C for 7 h. Then the reaction mixture was dissolved in ether (15 mL) and chromatographed on Al_2O_3 (5 g) using ether as the eluent. The solvent was removed and the residue was distilled *in vacuo*. Phosphate **2** was obtained in a yield of

*[1] Ether **5** and chloride **6** were identified by comparing with the authentic specimens, which we have synthesized and described previously.[5,6]

*[2] Each diastereomer exists as a racemic mixture of two enantiomers.

*[3] These names have been proposed in the study[7] of an analogous compound in which the asymmetric centers are bound to the tetrahedral C atom.

*[4] Diastereomers whose ^{31}P-{^1H} NMR spectra have a signal for the P atom at lower field and which are characterized by smaller retention times in GLC are arbitrarily denoted by **A**.

* By analogy with the α-trifluoromethyl groups, the *m*-trifluoromethyl substituents in the ^{19}F NMR spectrum of a statistical mixture of the diastereomers of phosphate **2** should give (and actually give) four singlet signals with equal intensities.

6.7 g (86%), b.p. 164—165 °C (0.1 Torr), n_D^{20} 1.4275. Found (%): C, 41.8; H, 1.9; F, 43.9. $C_{27}H_{15}F_{18}O_4P$. Calculated (%): C, 41.8; H, 2.0; F, 44.0. ^{1}H NMR (C_6D_6), δ: 5.29 (dq, CH, J_{H-F} = 6.0 Hz, J_{H-P} = 10.2 Hz); 5.51 (dq, CH, J_{H-F} = 6.1 Hz, J_{H-P} = 9.8 Hz); 5.53 (dq, CH, J_{H-F} = 6.0 Hz, J_{H-P} = 10.1 Hz); 5.76 (dq, CH, J_{H-F} = 5.8 Hz, J_{H-P} = 9.8 Hz);* 6.57—7.74 (m, 12 H, C_6H_4). ^{19}F NMR (C_6D_6), δ (all signals with equal intensities): −0.24 (d, CF_3CH, J_{H-F} = 5.8 Hz); −0.17 (d, CF_3CH, J_{H-F} = 5.9 Hz); 0.08 (d, CF_3CH, J_{H-F} = 5.9 Hz); 0.19 (d, CF_3CH, J_{H-F} = 5.6 Hz); 14.62 (s, $CF_3C_6H_4$); 14.65 (s, $CF_3C_6H_4$); 14.71 (s, $CF_3C_6H_4$); 14.74 (s, $CF_3C_6H_4$). ^{31}P-{^{1}H} NMR (C_6H_6), δ: −1.85 (s), −1.67 (s) (the ratio is 25 : 75). MS, *m/z* (I_{rel} (%)): diastereomer **A**, 549 $[M - CF_3C_6H_4CHCF_3]^+$ (5), 227 $[CF_3C_6H_4CHCF_3]^+$ (100); diastereomer **B**, 549 $[M - CF_3C_6H_4CHCF_3]^+$ (4), 227 $[CF_3C_6H_4CHCF_3]^+$ (100) (according to the GLC data, **A** : **B** ratio is 74 : 26).

Tris(α-trifluoromethylbenzyl) phosphate (3). A mixture of alcohol **4** [2] (5.3 g, 0.03 mol), $POCl_3$ (1.5 g, 0.01 mol), and Mg (18 mg, 0.75 mg-at.) was successively heated at 120 °C for 4 h, at 140 °C for 4 h, at 160 °C for 4 h, at 180 °C for 4 h, and at 200 °C for 4 h. Then the reaction mixture was dissolved in ether (15 mL) and chromatographed on Al_2O_3 (5 g) using ether as the eluent. The solvent was removed and the residue was chromatographed *in vacuo*. Phosphate **3** was obtained in a yield of 2.2 g (39%), b.p. 176—178 °C (2 Torr), n_D^{20} 1.4718. Found (%): C, 50.4; H, 2.9; F, 29.8. $C_{24}H_{18}F_9O_4P$. Calculated (%): C, 50.4; H, 3.2; F, 29.9. ^{1}H NMR (C_6D_6), δ: 5.36 (dq, CH, J_{H-F} = 6.2 Hz, J_{H-P} = 10.2 Hz); 5.58 (dq, CH, J_{H-F} = 6.1 Hz, J_{H-P} = 10.1 Hz); 5.62 (dq, CH, J_{H-F} = 6.2 Hz, J_{H-P} = 10.3 Hz); 5.85 (dq, CH, J_{H-F} = 6.2 Hz, J_{H-P} = 10.0 Hz);** 6.75—7.42 (m, 15 H, Ph). ^{19}F NMR (C_6D_6), δ (all signals with equal intensities): 0.12 (d, CF_3, J_{H-F} = 6.2 Hz); 0.24 (d, CF_3, J_{H-F} = 6.2 Hz); 0.31 (d, CF_3, J_{H-F} = 6.2 Hz); 0.44 (d, CF_3, J_{H-F} = 6.2 Hz). ^{31}P-{^{1}H} NMR (C_6H_6), δ: −2.24 (s), −1.72 (s) (the ratio is 24 : 76). MS, *m/z* (I_{rel} (%)): 573 $[M + 1]^+$ (4), 413 $[M - PhCHCF_3]^+$ (3), 159 $[PhCHCF_3]^+$ (100).

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* Signals at δ 5.29—5.76 with equal intensities.
** Signals at δ 5.36—5.85 with equal intensities.

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