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New 4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-oxides(sulfides)

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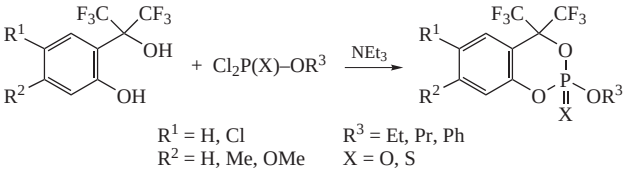
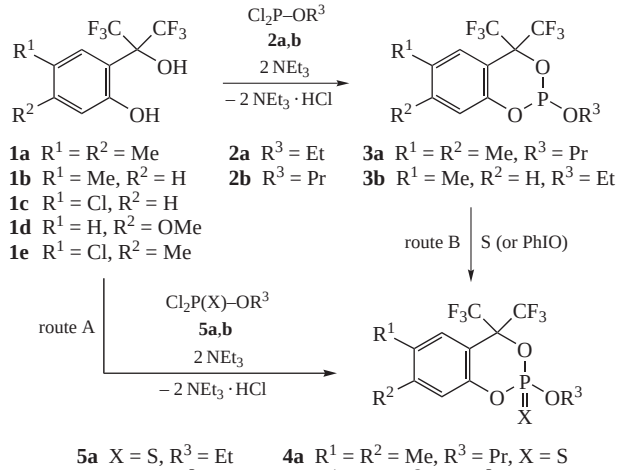
Substituted α,α-bis(trifluoromethyl)salicylic alcohols react with dichlorido(thio)phosphates in the presence of NEt_3 to afford 2-alkoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-oxide(sulfides) in high yields. The latter can be of interest as potential cholinesterase inhibitors.



Phosphoric acid esters are known to be cholinesterase inhibitors,[1] some of them having low toxicity without anticholinesterase activity.[2] This ability was the driving force to develop new medicals used nowadays in therapy and agricultural practice.[3,4] The induction of fluorine into biologically active compounds increased their lipophilicity and ability to infiltrate through the cellular membranes.[5] Additional inclusion of fluorine atoms to phosphoric acid esters can accelerate their effect due to similarity of van der Waals radii of fluorine and hydrogen atoms, and due to electronegativities of fluorine and oxygen atoms (the so-called 'masking effect').[6] In this context, the synthesis of new fluorine-containing organophosphorus compounds is of interest. Here, we present the synthesis of new compounds of this family starting form available α,α-bis(trifluoromethyl)salicylic alcohols **1a**,**b** (Scheme 1).

Previously,[7,8] fluorine-containing (thio)phosphates of type **4** were prepared by sulfur/iodosobenzene oxidation of cyclic phosphites of type **3**. In this work, thiophosphates **4a**,**b** were accessed by this protocol starting from compounds **3a**,**b** (Scheme 1, route B). In turn, compounds **3a**,**b** were prepared by reaction of alcohols **1a**,**b** with the corresponding dichloridophosphites **2a**,**b** in the presence of HCl acceptors (see Scheme 1). However, this protocol needs optimization due to insufficient availability of compounds of type **3**.



1a $R^1 = R^2 = Me$
1b $R^1 = Me$, $R^2 = H$
1c $R^1 = Cl$, $R^2 = H$
1d $R^1 = H$, $R^2 = OMe$
1e $R^1 = Cl$, $R^2 = Me$

2a $R^3 = Et$
2b $R^3 = Pr$

3a $R^1 = R^2 = Me$, $R^3 = Pr$
3b $R^1 = Me$, $R^2 = H$, $R^3 = Et$

5a X = S, $R^3 = Et$
5b X = O, $R^3 = Ph$

4a $R^1 = R^2 = Me$, $R^3 = Pr$, X = S
4b $R^1 = Me$, $R^2 = H$, $R^3 = Et$, X = S
4c $R^1 = Cl$, $R^2 = H$, $R^3 = Et$, X = S
4d $R^1 = H$, $R^2 = OMe$, $R^3 = Et$, X = S
4e $R^1 = H$, $R^2 = OMe$, $R^3 = Ph$, X = O
4f $R^1 = Cl$, $R^2 = Me$, $R^3 = Ph$, X = O

Scheme 1

Alternatively, salicylic alcohols **1c**–**e**[9,10] readily interact with dicholorido(thio)phosphates **5a**,**b** to afford new 4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinane 2-oxides(sulfides) **4c**–**f** (see Scheme 1, route A).

The reaction was carried out using equimolar amounts of substrates in aprotic solvents in the presence of NEt_3 at 20 °C for 1 h to provide full conversion of the reactants and almost quantitative yields of the products.† Important, that the full

† NMR spectra were recorded on a Bruker Avance 400 spectrometer fitted with multinuclear probe for ^1H (400.13 MHz), ^{19}F (376.5 MHz) and ^{31}P (161.97 MHz) nuclei. Spectra are reported relative to TMS, CF_3CO_2H or H_3PO_4, respectively.

*6-Chloro-2-ethoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-sulfide* **4c**. A glass reactor equipped with magnetic stirring bar was charged with absolute CCl_4 (20 ml), 4-chloro-2-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenol **1c**[10] (1.47 g, 5 mmol) and NEt_3 (1.15 g, 11 mmol). Then *O*-ethyl dichloridothiophosphate **5a** (0.82 g, 5 mmol) in CCl_4 (5 ml) was added dropwise with stirring, and stirring was continued for 1 h at room temperature. Triethylammonium hydrochloride formed during the reaction was filtered off, the filtrate was concentrated and purified by silica gel chromatography. Final crystallization gave 1.72 g (90%) of product **4c**, mp 61–62 °C (pentane), R_f 0.6 (acetone–CCl_4, 1:6). ^1H NMR ($CDCl_3$) δ: 7,54 (s, 1H, Ar), 7.52 (d, 1H, Ar, $^3J_{HH}$ 12 Hz), 4.30 (q, 2H, OCH_2Me, $^3J_{HH}$ 8 Hz), 1.32 (t, 3H, OCH_2Me, $^3J_{HH}$ 8 Hz). ^{19}F NMR ($CDCl_3$) δ: 4.08 (q, 3F, CF_3, $^4J_{FF}$ 12 Hz), 1.83 (q, 3F, CF_3, $^4J_{FF}$ 12 Hz). ^{31}P NMR ($CDCl_3$) δ: 49.41 (s). Found (%): C, 32.87; H, 1.73; F, 28.11. Calc. for $C_{11}H_8ClF_6O_3SP$ (%): C, 32.96; H, 2.00; F, 28.46.

Compound **4d** was synthesized similarly from 5-methoxy-2-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenol **1d**[9] and *O*-ethyl dichloridothiophosphate **5a**; compound **4e** from **1d** and phenyl dichloridophosphate **5b**; compound **4f** from 4-chloro-5-methyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenol **1e** and **5b**.

*2-Ethoxy-7-methoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-sulfide* **4d**: yield 91%, mp 52–53 °C (pentane), R_f 0.6 (acetone–CCl_4, 1:6). ^1H NMR ($CDCl_3$) δ: 7.45 (d, 1H, Ar, $^3J_{HH}$ 12 Hz), 6.84 (dd, 1H, Ar, $^3J_{HH}$ 12 Hz, $^4J_{HH}$ 2.0 Hz), 6.67 (d, 1H, Ar, $^4J_{HH}$ 2.0 Hz), 4.31 (q, 2H, OCH_2Me, $^3J_{HH}$ 8 Hz), 3.85 (s, 3H, OMe), 1.32 (t, 3H, OCH_2Me, $^3J_{HH}$ 8 Hz). ^{19}F NMR ($CDCl_3$) δ: 3.81 (q, 3F, CF_3, $^4J_{FF}$ 12 Hz), 1.48 (q, 3F, CF_3, $^4J_{FF}$ 12 Hz). ^{31}P NMR ($CDCl_3$) δ: 51.14 (s). Found (%): C, 36.22; H, 2.79; F, 28.55. Calc. for $C_{12}H_{11}F_6O_4SP$ (%): C, 36.36; H, 2.77; F, 28.79.

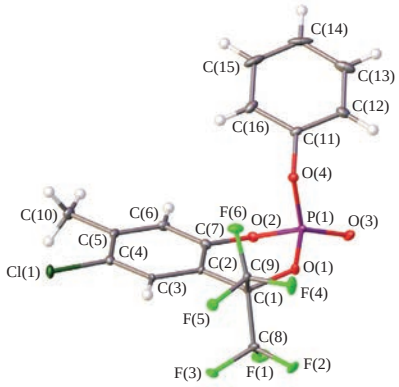


Figure 1 Molecular structure of compound **4f**. Selected bond lengths (Å) and angles (°): P(1)–O(1) 1.592(4), P(1)–O(2) 1.586(4), P(1)–O(3) 1.455(4), P(1)–O(4) 1.573(4), O(1)–C(1) 1.432(6), O(2)–C(7) 1.404(6); O(2)–P(1)–O(1) 104.3(2), O(3)–P(1)–O(1) 113.2(2), O(3)–P(1)–O(2) 112.5(2), O(3)–P(1)–O(4) 117.9(2), O(4)–P(1)–O(1) 101.3(2), O(4)–P(1)–O(2) 106.3(2), C(1)–O(1)–P(1) 125.7(3).

synthetic route was diminished by one stage. The structure of new compounds **4c**–**f** was established by ^{1}H, ^{19}F, ^{31}P NMR spectroscopy, elemental analysis and X-ray diffraction study. According to X-ray data, a phosphorus-containing six-membered cycle of **4f** adopts the distorted sofa conformation with deviation of P(1) atom from the plane formed by the rest of atoms by 0.49 Å (Figure 1).‡ Apparently, inductive effect of the Ph group bonded to the C(7) atom led to a slight elongation of the O(2)–C(7) distance up to 1.404(6) Å as compared to trivial alkoxybenzenes (1.370 Å[11]). At the same time, the O(1)–C(1) bond is elongated even greater [1.432(6) Å], apparently, due to the influence of two CF_3 groups at C(1) atom.

Molecules of **4c**–**f** contain a fragment of salitione, which is an effective insecticide.[12] Therefore, one may regard these compounds as new fluorinated (thio)phospates with potential cholinesterase activity.

In summary, we developed a new synthetic scheme for 2-alkoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-oxides(sulfides). The compounds obtained can be of interest as potential cholinesterase inhibitors.

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*7-Methoxy-2-phenoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-oxide* **4e**: yield 94.5%, mp 66–67 °C (light petroleum), R_f 0.5 (acetone–CCl_4, 1:6). ^{1}H NMR ($CDCl_3$) δ: 7.50 (br.d, 1H, Ar, $^{3}J_{HH}$ 8 Hz), 7.35 (t, 2H, OPh, $^{3}J_{HH}$ 8 Hz), 7.22 (t, 1H, OPh, $^{3}J_{HH}$ 8 Hz), 7.16 (d, 2H, OPh, $^{3}J_{HH}$ 8 Hz), 6.87 (dd, 1H, Ar, $^{3}J_{HH}$ 8 Hz, $^{4}J_{HH}$ 2.5 Hz), 6,70 (dd, 1H, Ar, $^{4}J_{HH}$ 2.5 Hz), 3.86 (s, 3H, OMe). ^{19}F NMR ($CDCl_3$) δ: –1.91 (q, 3F, CF_3, $^{4}J_{FF}$ 8 Hz), –5.15 (q, 3F, CF_3, $^{4}J_{FF}$ 8 Hz). ^{31}P NMR ($CDCl_3$) δ: 23.24 (s). Found (%): C, 45.28; H, 2.66; F, 26.36. Calc. for $C_{16}H_{11}F_6O_5P$ (%): C, 44.88; H, 2.59; F, 26.62.

4-Chloro-5-methyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl) phenol **1e**: yield 93%, mp 117–118 °C (benzene) was synthesized similarly to reported procedure[10] from sodium 4-chloro-3-methylphenoxide. ^{1}H NMR ($CDCl_3$) δ: 7.38 (s, 1H, Ar), 6.81 (s, 1H, Ar), 2.33 (s, 3H, Me). ^{19}F NMR ($CDCl_3$) δ: –1.00 (s, 3F, CF_3). Found (%): C, 38.81; H, 2.07; F, 37.02. Calc. for $C_{10}H_7ClF_6O_2$ (%): C, 38.92; H, 2.29; F, 36.94.

*6-Chloro-7-methyl-2-phenoxy-4,4-bis(trifluoromethyl)-4*H*-1,3,2-benzodioxaphosphinine 2-oxide* **4f**: yield 95%, mp 70–71 °C (light petroleum). ^{1}H NMR ($CDCl_3$) δ: 7.57 (s, 1H, Ar), 7.36 (t, 2H, OPh, $^{3}J_{HH}$ 8 Hz), 7.23 (t, 1H, OPh, $^{3}J_{HH}$ 8 Hz), 7.15 (d, 2H, OPh, $^{3}J_{HH}$ 8 Hz), 7.12 (s, 1H, Ar), 2.44 (s, 3H, Me). ^{19}F NMR ($CDCl_3$) δ: –3.10 (q, 3F, CF_3, $^{4}J_{FF}$ 8 Hz), 0.05 (q, 3F, CF_3, $^{4}J_{FF}$ 8 Hz). ^{31}P NMR ($CDCl_3$) δ: 23.72 (s). Found (%): C, 42.58; H, 2.29; F, 25.03; P, 7.12. Calc. for $C_{16}H_{10}ClF_6O_4P$ (%): C, 43.02; H, 2.26; F, 25.52; P, 6.93.

‡ *Crystal data for* **4f**. Crystals of $C_{16}H_{10}ClF_6O_4P$ (M = 446.66) are tetragonal, space group $P4_12_12$, a = 8.5880(10), b = 8.5880(10) and c = = 47.180(6) Å, V = 3479.7(9) Å^3, Z = 8, d_{calc} = 1.705 g cm^{-3}, $F(000)$ = 1792. Single crystal (colorless prism-shaped, dimensions 0.27 × 0.35 × 0.38 mm) was selected and intensities of 31049 reflections were measured with a Bruker APEX-II CCD diffractometer at 120 K [ϕ and ω scans, λ(MoKα) = = 0.71073 Å, μ = 0.395 mm^{-1}, $2\theta_{max}$ = 55.754°]. Final R factors: R_1 = 0.0613 [3898 reflections with $I > \sigma(I)$], wR_2 = 0.1283 (all reflections), GOF = = 1.016. The structure was solved with the ShelXT[13] and refined with the ShelXL[14] program. Molecular graphics was drawn using OLEX2[15] program. Analysis of intensities of reflections has revealed that single crystal sample was racemic twin (Hooft parameter is ~0.5). Twinning was refined using TWIN/BASF parameters implemented in ShelXL program.

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CCDC 1851130 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.