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Synthesis of *cis*- and *trans*-4-Methyl-2-(trifluoromethylthio)-1,3,2-dioxaphosphinane 2-Oxide

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cis- und *trans*-4-Methyl-2-(trifluormethylthio)-1,3,2-dioxaphosphinan-2-oxid (**2**) wurden durch stereoselektive Reaktion von *cis*- und *trans*-2-Methoxy-4-methyl-1,3,2-dioxaphosphinan (**1**) mit Bis(trifluormethyl)disulfid erhalten. Die Retention der Konfiguration am P-Atom wurde aufgrund der Umsetzung mit Methanol und durch spektroskopische Daten ermittelt.

Several methods have previously been reported for the synthesis of trifluoromethylthio derivatives of organophosphorus acids $RR'P(O)SCF_3$. In the reaction of trialkyl phosphites with trifluoromethanesulfenyl chloride, according to (1), a mixture of two compounds is obtained[1].

$$(CH_3O)_3P \xrightarrow{CF_3SCl} (CH_3O)_2P(O)SCF_3 + (CH_3O)_2P(O)Cl + CH_3Cl + CH_3SCF_3 \quad (1)$$

A similar but more convenient synthesis (2) utilizes the parahalogen bis(trifluoromethyl) disulfide instead of sulfenyl chloride[2].

$$RR'P(OR) + CF_3SSCF_3 \longrightarrow RR'P(O)SCF_3 + RSCF_3 \quad (2)$$

Another route to these compounds has been provided via alcoholysis of the *S*-trifluoromethyl phosphorodichloridothioate(dithioate)[3].

$$CF_3SP(X)Cl_2 + 2\ ROH \longrightarrow CF_3SP(X)(OR)_2 + 2\ HCl \quad (3)$$

$X = O, S$

This paper describes a synthesis for model cyclic diastereoisomeric *cis*- and *trans*-4-methyl-2-(trifluoromethylthio)-1,3,2-dioxaphosphinane 2-oxide (**2**). Compounds with the 2-substituted 4-methyl-1,3,2-dioxaphosphinane 2-oxide ring system are readily available and useful in the study of dynamic phosphorus stereochemistry[4].

For the preparation of diastereoisomerically pure *cis*- and *trans*-**2**, *cis*- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphinane (**1**)[5] are used. *cis*-**1** (90%) reacts very smoothly at −80°C in dichloromethane solution with bis(trifluoromethyl) disulfide to form a mixture of the two phosphorus compounds **2**, as determined by ^{31}P and ^{19}F NMR spectroscopy.

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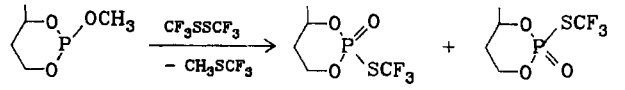


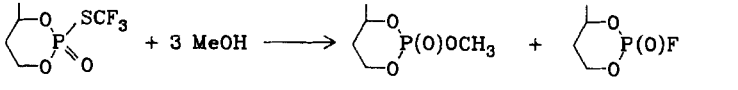
cis-**1** *trans*-**2** *cis*-**2** (4)

The major product, *trans*-**2** (89%), shows the following characteristic ^{31}P and ^{19}F NMR data: $\delta P = 3.3$ (q), $\delta F = 32.74$ (d), $^3J_{PF}$ 7.32 Hz. The minor product, *cis*-**2** (11%), shows $\delta P = 5.1$ (q), $\delta F = 34.51$ (d), $^3J_{PF}$ 8.54 Hz. While standing at -15°C, the major product slowly solidifies, thus permitting its separation from *cis*-**2** which remains liquid at this temperature.

Similarly, in the reaction of *trans*-**1** (89%) with CF_3SSCF_3 88% *cis*-**2** and 12% *trans*-**2** are formed. These results show that the Arbusov reaction between *cis*- and *trans*-**1** and CF_3SSCF_3 occurs with retention of configuration at the phosphorus atom.

Retention of configuration has previously been observed in the reaction of *cis*- and *trans*-**1** with chlorine and bromine[6], bis(phosphinyl) disulfide and other oxophosphorane-pseudohalogen compounds[7] as well as thioxophosphoranesulfenyl chloride and bromide[8].

According to the element displacement principle, the CF_3S group is a parachlorine radical[9]. Therefore, *cis*- and *trans*-**2** should show reactions similar to the corresponding *cis*- and *trans*-2-chloro-4-methyl-1,3,2-dioxaphosphinane 2-oxides[6]. This assumption was confirmed by the methanolysis of **2**. *cis*-**2** (88%) reacts at 15 to 20°C in an NMR tube with 3 mol of methanol to give a mixture of products containing *trans*- and *cis*-2-methoxy-4-methyl-1,3,2-dioxaphosphinane 2-oxide (**3**) (rel. ratio 69:31) and *cis*- and *trans*-2-fluoro-4-methyl-1,3,2-dioxaphosphinane 2-oxide (**4**) (rel. ratio 73:27). The phosphates **3**[6] and fluoridates **4**[10,11] can be identified after 40 min at 20°C in the reaction mixture by ^{31}P NMR spectroscopy.



cis-**2** *trans*-**3** (69%) *cis*-**3** (31%) *cis*-**4** (73%) *trans*-**4** (27%) (5)

Under the same conditions, *trans*-**2** (95%) reacts slowly with methanol over a 40 min period. The resulting mixture contains only a 24% yield of a mixture of *cis*- and *trans*-**3** (rel. ratio 78:22) and *trans*- and *cis*-**4** (77:23) as observed by ^{31}P NMR spectroscopy as well as 76% unreacted **2**.

However, the reaction of *cis*- and *trans*-**2** with methanol shows relatively low selectivity. We have observed the dominating inversion of configuration at the phosphorus atom. This inversion confirms the assigned *cis*-*trans*-geometry for **2**. *cis*-**2** reacts with methanol to form *trans*-**3**, while *trans*-**2** gives *cis*-**3**.

In the ^1H NMR spectra of both isomers **2**, the protons of the methyl group at C-4 are split by the methine proton and by phosphorus with $^4J_{PH} = 2.2$ Hz for *cis*- and 2.8 Hz for *trans*-**2**. These couplings suggest an equatorial CH_3 group at C-4 in view of the lack of other splittings by a C-5 axial methylene proton[12]. In the case of an axial CH_3 at C-4, a $^4J_{PH}$ coupling with a value slightly less than 1 Hz would be expected[13].

According to *Stec*[10], the absolute value of the coupling constant between phosphorus and a magnetically active nucleus X bonded to phosphorus depends on the spatial disposition of this nucleus. Thus, the observed $J_{(PX)}$ axial coupling constant should be smaller than the

$J_{(PX)}$ equatorial value. Measured values of 8.54 Hz for *cis*-**2** and 7.32 Hz for *trans*-**2** agree with this criteria.

In addition, the IR spectrum shows ν(P=O) as a strong absorption at 1300 cm^{-1} in *trans*-**2** while it appears at 1294 cm^{-1} in *cis*-**2**. These ν(P=O) values indicate an equatorial phosphoryl group in *trans*-**2** and an axial group in *cis*-**2**, since the axial stretching vibration appears at a lower frequency than the equatorial one[14].

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Experimental Part

IR spectra: Films, Perkin-Elmer 325 spectrometer. – ^1H NMR spectra: Bruker WM 400 (TMS internal). – ^{19}F NMR: Bruker HX 60/5 (C_6F_6 internal). – ^{31}P NMR: Bruker WM 250 (85% H_3PO_4 as external standard). Positive chemical shift values are at low field relative to the standard. – Diastereoisomeric purities were determined from integrated ^{31}P and ^{19}F NMR spectra. *cis*- and *trans*-**1** were synthesized according to the literature[5].

*Reaction of cis-***1** *with* CF_3SSCF_3*: trans-4-Methyl-2-(trifluoromethylthio)-1,3,2-dioxaphosphinane 2-Oxide (trans-***2**): A solution of 3.75 g (25 mmol) of *cis*-**1** (90%) in 10 ml of CH_2Cl_2 was added dropwise between −75 and −80°C to a solution of 6.0 g (30 mmol) of CF_3SSCF_3 in 20 ml of CH_2Cl_2. The temperature of the reaction mixture was then allowed to increase to +15°C over a 30 min period. The ^{31}P NMR spectrum of the crude reaction mixture showed signals at δ = 3.3 (89%, *trans*-**2**) and 5.1 (11%, *cis*-**2**). The solvent was removed in vacuo and the residual liquid was distilled to yield 4.72 g (80%) of a pale yellow oil, b.p. 115−118°C/0.01 Torr. The oil solidified after 12 to 16 h at −15°C. Filtration of the colourless crystalline product in a closed system at −5 to −10°C gave 3.5 g of pure *trans*-**2** which exists as a liquid at room temperature. – IR (film): 533 (s), 567 (m), 590 (s), 735 (s), 757 (s), 800 (s), 895 (vs), 955, 970, 985 (vs), 1030 (vs), 1055 (vs), 1105 (vs), 1145 (vs), 1225 (m), 1245 (m), 1300 (vs), 1390 (s), 2990 cm^{-1} (m). – ^1H NMR (C_6D_6): CH_3 δ = 1.0 (dd, $^3J_{HH}$ = 6.5, $^4J_{PH}$ = 2.8 Hz). – ^{31}P NMR (CH_2Cl_2): δ = 3.3 (q, $^3J_{PF}$ = 7.32 Hz). – ^{19}F NMR (CH_2Cl_2): δ = 32.74 (d).

$C_5H_8F_3O_3PS$ (236.1) Calcd. C 25.43 H 3.41 S 13.57 Found C 25.60 H 3.50 S 13.30

*Reaction of trans-***1** *with* CF_3SSCF_3*: Synthesis of cis-***2**: A solution of 6.0 g (40 mmol) of *trans*-**1** (89%) in 10 ml of CH_2Cl_2 was added dropwise with stirring to a solution of 9.1 g (45 mmol) of CF_3SSCF_3 in 20 ml CH_2Cl_2 maintained between −75 and −80°C. Stirring was continued for 5 min after which the cooling bath was removed. The temperature of the reaction mixture increased to +20°C over a 35 min period. The ^{31}P NMR spectra with signals at δ = +5.1 and +3.3, respectively, indicated a mixture of *cis*-**2** (88%) and *trans*-**2** (12%). The solvent was removed under reduced pressure and the residual oil was purified by distillation, b.p. 122−125°C/0.35 Torr, 6.8 g (73%). In the distilled products the same *cis*/*trans*-ratio was observed. – IR (film): 535 (s), 570 (m), 595 (m), 626 (m), 706 (m), 753 (s), 790 (m), 891 (s), 960 (s), 983 (vs), 1060 (vs), 1105 (vs), 1150 (vs), 1247 (m), 1294 (vs), 1390 (w), 2990 cm^{-1} (w). – ^1H NMR (C_6D_6): CH_3 δ = 1.1 (dd, $^3J_{HH}$ = 6.5, $^4J_{PH}$ = 2.2 Hz). – ^{31}P NMR: δ = 5.1 (q, $^3J_{PF}$ = 8.54 Hz). – ^{19}F NMR (CH_2Cl_2): δ = 34.51 (d).

$C_5H_8F_3O_3PS$ (236.1) Calcd. C 25.43 H 3.41 S 13.57 Found C 25.80 H 3.20 S 13.30

*Reaction of cis-***2** *with Methanol: 2-Methoxy-* (**3**) *and 2-Fluoro-4-methyl-1,3,2-dioxaphosphinane 2-Oxide* (**4**): Into an NMR tube containing 1.2 g (5.0 mmol) of *cis*-**2** (88%), 0.48 g (15 mmol) of methanol were added at 18 to 20°C. The sample was maintained at 20°C for 40 min after which the ^{31}P NMR spectrum was recorded. In addition to ca. 12% of unreacted

cis-**2**, four new products were observed: *trans*-**3** ($\delta = -4.0$) and *cis*-**3** ($\delta = -3.2$) as well as *cis*-**4** ($\delta = -14.02$, d, $J_{PF} = 989$ Hz) and *trans*-**4** ($\delta = -14.34$, d, $J_{PF} = 997.7$ Hz) with the respective relative ratios of 69:31 and 73:27. The ^{31}P NMR data are in agreement with those in literature[6,10,11].

Reaction of trans-**2** *with Methanol:* In a manner similar to that described above 2.0 g (8.4 mmol) of *trans*-**2** (95%) and 0.80 g (25.2 mmol) of methanol yield 24% of a mixture of *cis*/*trans*-**3** (rel. ratio 78:22) and *trans*/*cis*-**4** (rel. ratio 77:23) and 76% of unreacted starting material as determined by ^{31}P NMR spectroscopy.

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