STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLVIII, 2, 2003

SYNTHESIS AND REACTIVITY OF DIFLUOROMETHYLENE BRIDGED DIPHOSPHA-DERIVATIVES

R. TÖTÖS, I. SILAGHI-DUMITRESCU*

"Babeş-Bolyai" University, Faculty of Chemistry and Chemical Engineering, Arany János Street, Nr. 11; 400028 Cluj-Napoca, Romania

INTRODUCTION

The chemistry of organophosphorus compounds has been developing very rapidly in the last four decades. This is primarily due to the considerable theoretical and especially practical importance of these compounds. The application of organophosphorus compounds as insecticides in agriculture, medicine, extractants, flotation agents in mining, plasticisers and stabilizers for polymers, antioxidants for lubricating oils, and the manufacture of non-combustible fabrics and materials are well known.[1,2,3]

Some α-fluorinated alkanephosphonic acids such as difluoromethane-diphosphonic acid[4,5,6] have already been the subjects of interest as analogues of biological phosphonyl species. There is generally a conspicuous lack of methods for the preparation of other difluoromethanephosphonates. Such compounds have been postulated to possess biologically superior properties to those of analogous nonhalogenated phosphonates. However, there are generally few synthetic methods available, which lead to other difluoromethane-phosphonates.[7]

Difluoromethylene bridged diphospha-derivatives were obtained for the first time by D. J. Burton and R.M. Flynn,[8] using the Michaelis-Arbuzov rearrangement. The same authors have obtained also the difluoromethane diphosphonic acid, which is a stable and strong acid.[5] This analogous of the pyrophosphoric acid ($H_2P_4O_7$) has a much bigger stability of the P–C–P motif toward hydrolysis in comparison with the P–O–P motif. From this reason difluoromethane diphosphonic acid can be used as chelating agent (bidentate ligand) for the modification of the properties of biological systems.

Unlike other substituents, fluorine does not introduce large steric perturbations and imparts increased hydrolytic stability as well as oxygen solubility. These properties make them useful compounds in other applications, e.g., as substitutes for additives to H_3PO_4 in fuel cell electrolytes.[9]

Inhibition of acetylcholinesterase by organophosphorus compounds is generally responsible for their acute toxicity.[10,11,12] Difluoromethylenediphosphonic acid was not found to be toxic, diphosphonates of the type P–C–P are valuable agents in the regulation of calcium metabolism in experimental laboratory animals and are potentially useful therapeutic agents for diseases involving abnormal calcification and excessive bone resorption.[4]

1. Building up the P–CF_2–P Skeleton

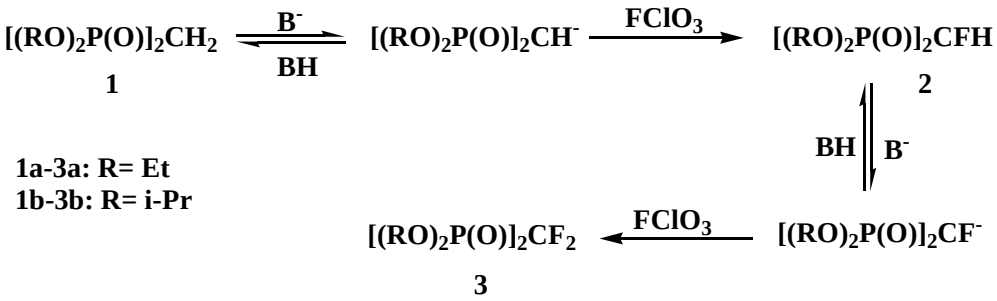
1.1. Fluorination of a methylenediphosphonate with $FClO_3$

There are just a few methods for building up the P–CF_2–P skeleton using mono- and diphosphonous compounds as starting materials. One of these methods uses the acidity of the methylene group of the tetraethyl methylenediphosphonate.

Methylenediphosphonates can be metalated with sodium, potassium, sodium hydride and n-butyllithium. The metalated methylenediphosphonates can be alkylated with active organic halides. They also can be halogenated with bromine, sodium hypochlorite[13] or perchlorylfluoride[6,14], obtaining the corresponding mono- and dihaloderivatives.

Perchloryl fluoride must have been used as an electrophylic fluorinating agent, because fluorine gas, perfluoropiperidine or perfluoro-2,6-dimethyl-piperidine each led to partial fluorine substitution of hydrogens at all possible sites in tetraethyl methylenediphosphonate.

Treatment of the sodium salt of tetraethyl methylenediphosphonate with an excess of $FClO_3$ in THF or toluene, results in the formation in good yields of tetraethyl-monofluoromethylenediphosphonate mixed with difluoromethylenediphosphonate (Scheme 1).[6,14]



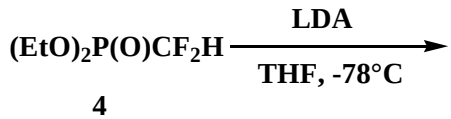
Scheme 1. *Fluorination of methanediphosphonate esters with $FClO_3$*

The fluorination reaction proceeds as a titration of base with perchloryl fluoride and shows a readily recognizable endpoint marked by a characteristic color change from dark pale to yellow. The ratio of the mono- and difluorinated products depends on the choice of conditions, and is about **2b**:**3b** = 4:1 using NaH as base and THF as solvent. By suitable adjustment of the proportion of starting materials, either product can be made to predominate. Using 1 equiv. of potassium *tert*-Butoxide as base, tetraisopropyl monofluoromethane-diphosphonate (**2b**) was obtained in 48% yield, with 2 equiv. of the base, the difluoro (**3b**) derivative could be prepared directly in 43% yield, with an increase to 73% being possible on further reaction of the monofluoroproduct.

Compounds **2** and **3** cannot be separated easily by fractional distillation due to their similar boiling points. They can be readily separated by conventional or flash chromatography on silica gel using ethlyacetate/ethanol (9:1) as eluent.[6]

1.2. Reaction of dialcoxyphosphoryldifluoromethane with LDA

Another method for building a P–CF_2–P skeleton uses the action of lithium diisopropylamide (LDA) on diethyl difluoromethylphosphonate (Eq. **1**).[15,16]



Eq. 1

Addition of diethylchlorophosphate as electrophyle to the organolithium compound gave tetraethyl dilfuoromethylenediphosphonate in good yield (74%) (Eq. **2**).[16]

$$\underset{\mathbf{5}}{(EtO)_2P(O)CF_2Li} + \underset{\mathbf{6}}{(EtO)_2P(O)Cl} \xrightarrow[LiCl]{} \underset{\mathbf{3a}}{(EtO)_2P(O)CF_2P(O)(OEt)_2} \qquad \textbf{Eq. 2}$$

1.3. Direct method: Synthesis from Dialkylsodiophosphite and CF_2X_2 (X=Cl, Br)

Using the Michaelis-Becker reaction between diethyl sodiophosphite in toluene and CF_2Cl_2, tetraethyl difluoromethylenediphosphonate can be obtained with 40% yield (Eq. 3).[17]

$$\underset{\mathbf{7}}{2\,(EtO)_2P(O)Na} + \underset{\mathbf{8}}{CF_2Cl_2} \longrightarrow \underset{\mathbf{3a}}{(EtO)P(O)CF_2P(O)(EtO)_2} + 2\,NaCl \qquad \textbf{Eq. 3}$$

Using CF_2Br_2 instead of CF_2Cl_2 **3a** could be also obtained but presents difficulties by isolation due to the increased side product formation and gives low yields.[8,18,19] The advantage of using CF_2Br_2 over the CF_2Cl_2 is, the easier handling of CF_2Br_2, being a liquid.

1.4. The photochemical method

Bisphosphonates can be obtained also by a photochemical procedure.[20] The reaction of $(EtO)_2P(O)CF_2I$ and $(EtO)_2POP(OEt)_2$ under UV light (254 nm) resulted in the corresponding mixed P^{III} and P^{V} intermediate $(EtO)_2P(O)CF_2P(OEt)_2$, which affords the bisphosphonate **3a** $[(EtO)_2P(O)]_2CF_2$ upon oxidation (Eq. 4 and Eq. 5).[21]

$$\underset{\mathbf{9}}{(EtO)_2P(O)CF_2I} + \underset{\mathbf{10}}{(EtO)_2POP(OEt)_2} \xrightarrow{h\nu} \underset{\mathbf{11}}{(EtO)_2P(O)CF_2P(OEt)_2} \qquad \textbf{Eq. 4}$$

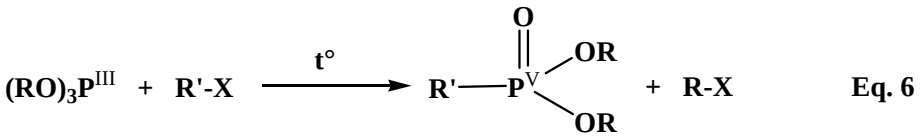
$$\underset{\mathbf{11}}{(EtO)_2P(O)CF_2P(OEt)_2} + Me_3COOH \xrightarrow{MeOH} \underset{\mathbf{3a}}{(EtO)_2P(O)CF_2P(O)(Oet)_2} \qquad \textbf{Eq. 5}$$

A disadvantage of this method is the use of the precursor **9**, which requires a multistep synthesis.[18,22]

1.5. The Michaelis-Arbuzov Reaction

The Michaelis-Arbuzov rearrangement is one of the most versatile pathways for the formation of carbon-phosphorus bonds, and involves the reaction of an ester of trivalent phosphorus with alkyl halides. This can be used as the first step for the synthesis of the CF_2 bridged diphosphorus esters and its derivatives. The reaction was discovered by Michaelis[23] in 1898 and studied in detail by Arbuzov[24] and other researchers.

The Arbuzov rearrangement is the reaction of an alkyl halide with a trialkyl phosphite, yielding a dialkyl alkylphosphonate (Eq. 6).

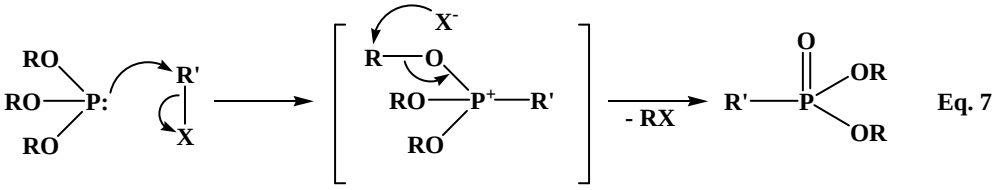


Eq. 6

R = alkyl (aryl, etc.)
R' = alkyl (aryl, etc.)
X = Cl, Br, I

Thus, during the transformation, a trivalent phosphorus (P^{III}) is converted into a pentavalent phosphorus (P^{V}). In general, the alkyl group of the halide gets attached to the phosphorus, and one alkyl group from the phosphite combines with halogen to form the new alkyl halide.[25-27]

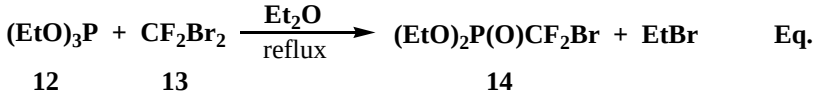
The mechanism of a normal Michaelis-Arbuzov reaction involves two S_N2 processes (Eq. **7**).



Eq. 7

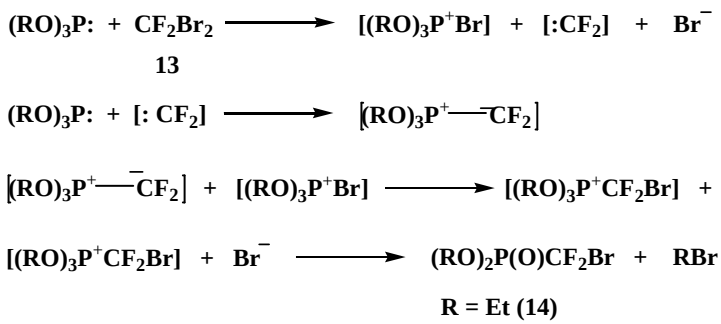
The lone pair of electrons of the phosphite attacks the alkyl group of the alkyl halide to form the addition compound in which the alkyl groups R' gets attached to the phosphorus, *i.e*. phosphorus-carbon bond forming step. At higher temperatures the quasiphosphonium cation undergoes nucleophilic attack on the alkyl rest of a P–O–R motive, through its own cation X^-, resulting in the formation of the P=O bond and the elimination of the alkyl group as the new alkyl halide. When the alkyl groups of the phosphite and the alkyl halides are identical (R=R'), the process resumes to the isomerisation of the phosphite.

In this manner reacts triethylphosphite with dibromodifluoromethane to give bromodifluoromethylphosphonate **14** (Eq. 8).[5,8,28-30]



Eq. 8

In contrast to the normal Michaelis-Arbuzov reaction (S_N2 mechanism), the bromo-F-methylphosphonate esters are formed *via* a carbene trapping mechanism (Scheme 2).[31]



Scheme 2. *The carbene trapping mechanism*

Using triethylphosphite as reactant and diethyl ether as solvent, compound **14** could be obtained with excellent yield (Y95%).[28]

Table 1.

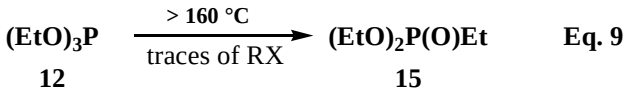
Yields of **14** as function of **R** and the solvent used

R	Solvent	$(RO)_2P(O)CF_2Br$ % 14
Me	TG	55
Et	Et_2O	95
Et	TG	55
n-Bu	Et_2O	65
i-Pr	TG	42

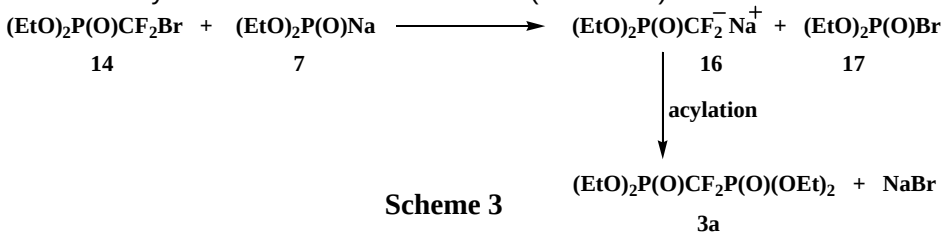
TG - tetraglyme; Et_2O – diethyl ether

Tetraethyl difluoromethylenediphosphonate **3a** cannot be obtained through another Michaelis-Arbuzov reaction between **12** and **14**.

Heating the reaction mixture at higher temperatures (>160 ℃) the triethylphosphite **12** undergoes an internal Michaelis-Arbuzov rearrangement, due to the presence of the alkyl halide rests from the former reaction, which acts as a catalyst for the internal rearrangement (Eq. **9**).[26,27]



An alternative route in order to obtain the desired difluoromethylenediphosphonate **3a** is offered by the Michaelis-Becker reaction (Scheme **3**).[5,31]



Scheme 3

The mechanism of this Michaelis-Becker type reaction (**Scheme 3**) involves not an S_N2 displacement of bromide by phosphite, but rather a positive halogen extraction of bromine followed by *in situ* acylation of the phosphate ylide **16**, to give the desired diphosphonate **3a**.

Evidence for the bromonium ion extraction in the initial step is the formation of the reduced phosphonate **4**, when the reaction is carried out in the presence of dialkyl phosphite, i.e. incomplete reaction of diethyl phosphite with Na in order to obtain **7** observed by Burton et. al.[8] (Eq. 10).

$$\underset{\mathbf{14}}{(EtO)_2P(O)CF_2Br} + \underset{\mathbf{7}}{(EtO)_2P(O)Na} \xrightarrow{(EtO)_2P(O)H \ (19)} (EtO)_2P(O)CF_2H + \underset{\mathbf{4}\quad \eta = 75\%}{\mathbf{4a}} \qquad \textbf{Eq. 10}$$

The same authors observed also a scrambling of the difluorocarbene by using bromo-difluoromethyl dibutylphosphonate and sodium diethylphosphite in order to obtain the mixed bisphosphonate, which was always accompanied by one or two symmetrical diphosphonates.[8]

There is equilibrium between compounds **7** and **16** (Eq. **11**).

$$\underset{\mathbf{16}}{(EtO)_2P(O)CF_2^-Na^+} \rightleftharpoons \underset{\mathbf{7}}{(EtO)_2PONa} + [:CF_2] \qquad \textbf{Eq. 11}$$

Despite the moderate yield,[31] the Michaelis-Becker reaction remains the best route to symmetrical bis-phosphonates.

2. Reactivity of difluoromethylene bridged diphospha-derivatives

2.1. Transesterification of difluoromethylenediphosphonates

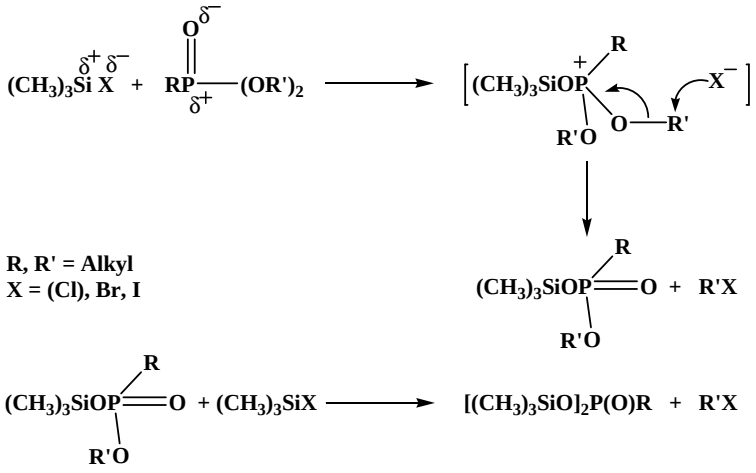
Reaction of phosphonates with PCl_5 in order to obtain halogenated phosphonates is a well-known method, but unfortunately cannot be used for the synthesis of halogenated alkylene-bisphosphonates.[1,32] The corresponding phosphonic acid cannot be chlorinated with PCl_5 because its insolubility in inert solvents suitable for chlorination, and obtaining such a phosphonic acid directly from alkylphosphonates requires an vigorous hydrolytic route resulting in the cleavage of one or more P–C bonds.[5]

A cleavage of the P–C bonds can be avoided using bis-(trimethylsilyl) phosphonates, which reacts with PCl_5 under mild and neutral conditions.[33]

Bis-(trimethylsilyl)phosphonates can be obtained through dealkylation of phosphonic acid dialkyl esters by bromotrimethylsilane.[5-7,34,35]

The mechanism of the silylation proposed by Rabinowitz[36] is shown in **Scheme 4**.

The attack of the silicon over the phosphoryl oxygen atom (P=O) is followed by the attack of the halogene X^- on the esters alkyl group, with the formation of the alkyl-trimethylsilyl mixed ester. A second series of the above mentioned reactions lead to the formation of the bis(trimethylsilyl)phosphonate. According to this mechanism where the halogen ion is involved as nucleophile and leaving group at the same time, it's evident that the process is accelerated in function of the X as follows: $V_{Cl}<V_{Br}<V_I$, and the reaction conditions become more and more milder.[34]



Scheme 4. *Mechanism of the silylation of a phosphonate*

Using $(CH_3)_3SiBr$ as silylating agent, **19** can be obtained with high yield (Y 98%)[5,37] corresponding to **Eq. 12**:

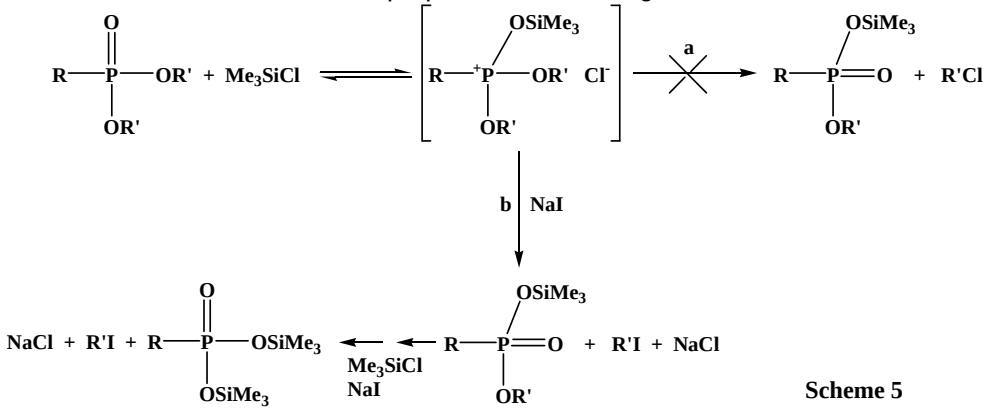
$$[(EtO)_2P(O)]_2CF_2 \;+\; 4\,Me_3SiBr \xrightarrow[2)\ 50°C/6\text{-}10h]{1)\ R.T.} [(Me_3SiO)_2P(O)]_2CF_2 \;+\; 4\,EtBr \qquad \textbf{Eq. 12}$$

3a **18** **19**

Another alternative method uses iodotrimethylsilane for dealkylation [38,39], which reacts easily with dialkylphosphonates at 10-40℃ and with a high selectivity, carboxyl and other functional groups remaining unchanged.[38] Chlorotrimethylsilane mixed with alkaline bromides or iodides.[33,40,41] is also a suitable dealkylating mixture, giving good results especially for the synthesis of phosphonic acids.

$$RP(O)(OR')_2 \;+\; 2\,Me_3SiCl \;+\; NaI \xrightarrow[r.t.]{CH_3CN} RP(O)(OSiMe_3)_2 \;+\; 2\,R'I \;+\; 2\,NaCl \qquad \textbf{Eq. 13}$$

The same authors have proposed the following reaction mechanism:[40,41]



Scheme 5

The attack of the silicon on the sp^3 oxygen atom with the formation of the phosphonium intermediate is a fast and reversible step. The second step, the attack of the X^- ion on the phosphonium intermediate is slow and irreversible. Cl^- and I^- coexists in the reaction mixture and a competition between the attack of the Cl^- and the I^-, occurs; the latter being more nucleophile way **b** will be preferred, which leads to the formation of the monosilylated compound. With the repetition of this step the bistrimethylsilylphosphonate is obtained.[40]

The trimethylsilyl esters are easily hydrolized under mild conditions to the corresponding phosphonic acids, which was the scope of the research in almost all cases.[34,35,38]

Hydrolysis of the bistrimethylsilylester **19** leads to the formation of difluoromethane-diphosphonic acid with almost 100% yield.[5]

$$\underset{\mathbf{19}}{(Me_3SiO)_2P(O)CF_2P(O)(OSiMe_3)_2} + 4\,H_2O \xrightarrow[\text{2) r.t. 20h}]{\text{1) } H_2O\ 0^\circ C} \underset{\mathbf{20}}{(HO)_2P(O)CF_2P(O)(OH)_2} + 4\,(Me_3Si)_2O \qquad \textbf{Eq. 14}$$

Compound **24** was found to be a tetrabasic acid with three points of equivalence, corresponding to the neutralization of 2, 1, 1 acid protons. The acid constants were determined by titration with NaOH.[5,6]

2.2. Synthesis of halogenated diphosphonates and diphosphonites

The chlorination of **20** can be carried out easily with PCl_5 at r.t. with an yield over 90% (Eq. **15**).[1,7,33]

$$\underset{\mathbf{19}}{[(Me_3SiO)_2P(O)]_2CF_2} + 4\,PCl_5 \longrightarrow \underset{\mathbf{21}}{[Cl_2P(O)]_2CF_2} + 4\,POCl_3 + 4\,Me_3SiCl \qquad \textbf{Eq. 15}$$

Because direct reduction of a P=O bond to P^{III} proceeds quite difficult, the next step in order to obtain difluoromethylenebis-(dichlorophosphane) is the synthesis of difluoromethylenebis-(thiophosphonic dichloride).

Halogenated diphosphonates can be sulfurated with P_4S_{10} or $PSCl_3$ to bis-thiophosphonates with moderate yield.[32]

In analogous way to the synthesis of methylenebis-(thiophosphonic dichloride) by Maier[32] sulfuration of difluoromethylenebis-(phosphonic dichloride) was carried out with P_4S_{10} (Eq. **16**).

$$5\,\underset{\mathbf{21}}{[Cl_2P(O)]_2CF_2} + P_4S_{10} \longrightarrow 5\,\underset{\mathbf{22}}{[Cl_2P(S)]_2CF_2} + P_4O_{10} \qquad \textbf{Eq. 16}$$

For this process temperatures over 190 ℃ are neede d, because in the case of incomplete reaction the mixture contains **21**, **22** and the asymmetric product $Cl_2P(O)CF_2P(S)Cl_2$ which cannot be separated by distillation at reduced pressure.

Adding catalytic amounts of $AlCl_3$ to the reaction mixture the yield of the process could be raised over 60%.[42]

Through the high temperatures, cleavage of **21** and **22** occurs under the building of volatile compounds like $POCl_3$, $PSCl_3$, PCl_3, which could be identified by ^{31}P-NMR spectroscopy.

The distillation residue contains P_4S_{10}, P_4O_{10}, $P_4S_xO_{10-x}$ (x = 1-9) and a difluoromethylene bridged compound $P_4S_4O_4(CF_2)_2$.[43]

The P=S bond in thiophosphonates (**22)** can be easily reduced to P^{III} using Ph_2PCl [44,45] or $PhPCl_2$ [46] as reducing agent. (Eq. **17**).

$$\mathbf{[Cl_2P(S)]_2CF_2 + 2\ PhPCl_2 \longrightarrow Cl_2PCF_2PCl_2 + 2\ PhP(S)Cl_2} \qquad \textbf{Eq. 17}$$

22 **23**

Compounds **21**, **22**, and **23** can serve as starting materials for the synthesis of non-cyclic derivatives, and using primary amines or hydrazines aza-diphosphetidines respectively diazadiphospholidines can be obtained through ring closure reaction.

Despite the high reactivity of the three above-mentioned compounds, they are much less studied than their methylene bridged analogous.

3. Synthesis of functional derivatives of the halogenated diphosphonates and diphosphonites

3.3.1. Fluorination of bis(dichlorides) 21, 22, and 23

Organophosphorus fluorides can be obtained through halogen exchange of the corresponding chlorides (21, 22, and 23) with SbF_3, AsF_3 or alkali halides.[44,46]

$$\mathbf{3\ Cl_2PCF_2PCl_2 + 4\ SbF_3 \longrightarrow 3\ F_2PCF_2PF_2 + 4\ SbCl_3} \qquad \textbf{Eq. 18}$$

21 **24**

Pentavalent compounds can be also fluorinated, but their receptivity towards fluorination is lower than that of trivalent derivatives. Fluorination of difluoromethanebis (phosphonic dichloride) can be achieved using AsF_3 or SbF_3.

$$\mathbf{3\ [Cl_2P(O)]_2CF_2 + 4\ SbF_3 \longrightarrow 3\ [F_2P(O)]_2CF_2 + 4\ SbCl_3} \qquad \textbf{Eq. 19}$$

21 **25**

In this case the tetrafluoride **25** formed must be removed from the reaction mixture to avoid secondary reactions with the SbF_3, which lead to the decomposition of the product:

$$\mathbf{F_2P(O)CF_2P(O)F_2 + SbF_3 \longrightarrow 2\ P(O)F_3 + CF_4} \qquad \textbf{Eq. 20}$$

25

The decomposition proceeds rapidly and after short time the tetrafluorodiphosphonate is no more spectroscopically detectable.[42]

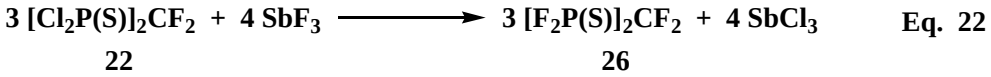
Another route to obtain the tetrafluoride **25** is the treatment of the tetrasilyl ester **19** with $PhPF_4$ (phenyltetrafluorophosphorane):[53,54]

$$\mathbf{(Me_3SiO)_2P(O)CF_2P(O)(OSiMe_3)_2} \xrightarrow{\mathbf{PhPF_4}} \mathbf{F_2P(O)CF_2P(O)F_2} \qquad \textbf{Eq. 21}$$

19 **25**

In this case the decomposition of the tetrafluorobisphosphonate **25** is inevitable, its formation was proved spectroscopically, pure **25** couldn't be isolated through distillation.

By the fluorination of difluoromethylenebis(thiophosphonic dichloride) cleavage of **22** and **26** was observed with the formation of volatile compounds. Among them F_3P and F_3PS were identified by gas IR spectroscopy.

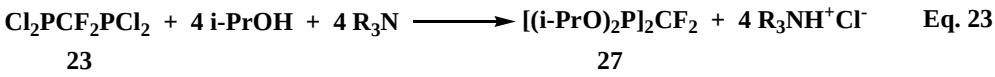


Eq. 22

Fluoride **26** has been purified by distillation and analyzed by ^{31}P and ^{19}F-NMR spectroscopy.[43]

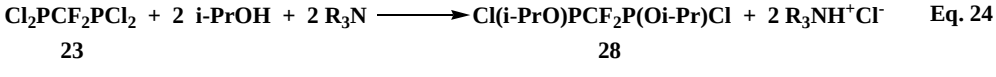
3.3.2. Alcoholysis of bis(dichlorides) 21, 22, and 23

Difluoromethylene bridged bis(phosphonic/phosphinic dichlorides) can be easily esterified with alcohols, in the presence of a base such as a tertiary amine or pyridine[46,49,51] or with alkaline alcoholates (alkoxides).[51]
This way can be obtained esters, which gives low yields using the direct way (Arbuzov reaction) (R = Me, Pr, *i*-Pr).[46]



Eq. 23

Using 1:2 molar ratios of difluoromethylenebis(dichlorophosphane): alcohol+ amine, difluoromethylenebis(phosphonochloridites) can be obtained with good yields,[50]



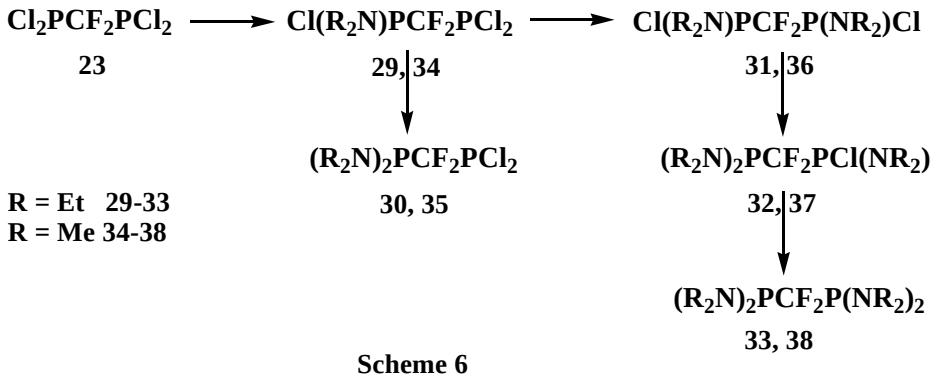
Eq. 24

which can be further reacted with alcohols, amines, organometallic compounds forming different mixed substituted derivatives in form of stereoisomers.[52]

3.3.3. Aminolysis of bis(dichlorides) 21, 22, and 23

The synthesis of $-NR_2$ substituted diphosphorus derivatives can be achieved through the substitution of one or more halogens using dialkylamines or dilakylaminotrimethylsilanes.[48]

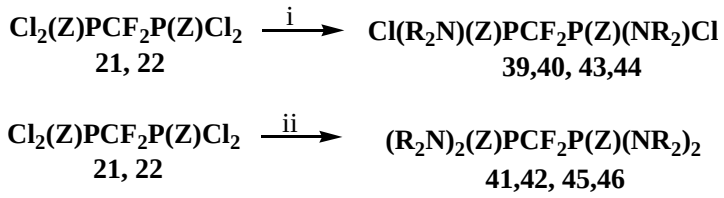
In the case of aminolysis of difluoromethylenebis-(dichlorophosphane) with dialkylamino-trimethylsilanes the reaction proceeds as in Scheme 6.



Scheme 6

Using 1:2 molar ratios of **23** and aminosilanes formation of pure **31**, and **36** was observed. No formation of the geminally disubstituted derivatives **30** and **35** was observed. Using 1:4 (or more) molar ratio of **23** and aminosilanes, pure **37** and **38** were obtained. At molar ratios under 1:2 and up to 1:4, the formation of mixtures is observed containing mono-, di-, and trisubstituted intermediates.[43]

In the case of **21** and **22** reactions with dimethyl- and diethylamino-trimethylsilane are as follows (Scheme 7):



i: 2 R_2NSiMe_3
ii: 4 R_2NSiMe_3

R = Me, 39, 41, 43, 45
R = Et , 40, 42, 44, 46
Z = O, 39, 40, 41, 42
Z = S, 43, 44, 45, 46

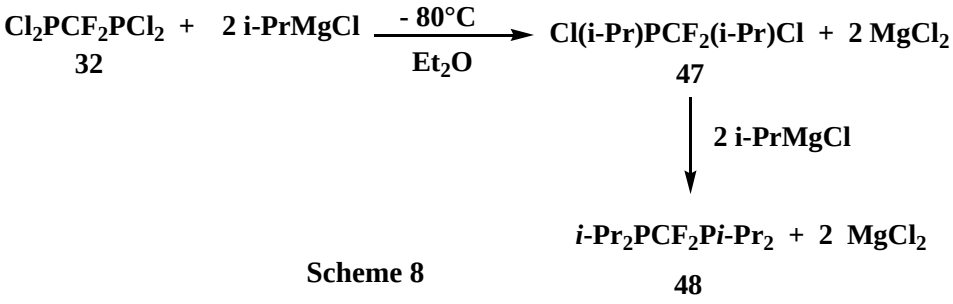
Scheme 7

Diamine **40** is formed also by a 1:0.67 ratios of **21**:aminosilane. The tetrasubsituted derivative **42** cannot be obtained using this method only by oxidation of **33** with DMSO at reduced temperatures. The substitution process stops at the stage of **40** even by the use of a 1:4 molar ratio of **21**:aminosilane. Using a molar ratio of 1:2 **21**:dimethylaminotrimethylsilane **39** can be isolated as single product. At 1:4 molar ratio **41** could be obtained in pure form in contrast to **42**. By molar ratios of **21**:aminosilanes under 1:2 and up to 1:4, formation of different mixtures is observed containing mono-, di-, and trisubstituted intermediates.[43] No formation of geminally disubsituted compounds was observed.

The aminolysis of difluoromethylenebis(thiophosphonic dichloride) (**22**) undergoes different as by **21**, only formation of mixtures are observed. The tetrasubsituted derivatives (**45**, **46**) can be obtained only by sulfuration of the corresponding trivalent compounds **33** and **38**.

3.3.4. Reactions with organometallic compounds

All difluoromethylene-bridged diphosphachlorides react easily with organometallic compounds. Reaction with *i*-PrMgCl proceeds in two steps, first the 1,3-disubstituted derivative is formed. Due to the sterical hindrance of the *i*-Pr group no geminally disubstituted derivative **47** is formed. In the second step (slow) the tetrasubstituted derivative **48** is formed, this is possible because the *i*-Pr group does not deactivate the phosphorus atoms.

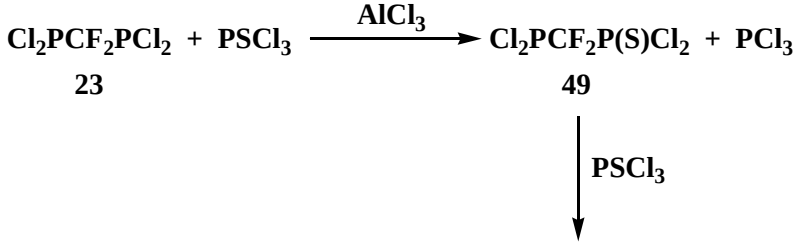


Scheme 8

The synthesis of tetrasubsituted compounds of the type $R_2P(Y)CF_2P(Y)R_2$ is limited to some cases (Y = e^- pairs, R = i-Pr, Me) the yields are low, so and indirect method is preferred which uses the reaction of esters (PhO) with RMgI.[51]

3.3.5. Oxidation and sulfuration of trivalent derivatives

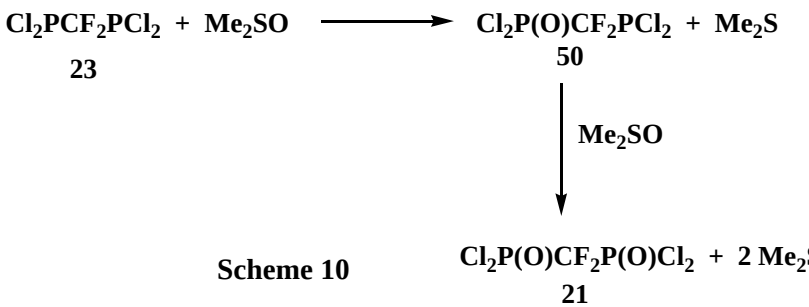
Sulfuration of the trivalent derivatives can be achieved using elementary sulfur or thiophosphoryltrichloride ($PSCl_3$), in most cases in a high boiling solvent (toluene) and using catalytic amounts of $AlCl_3$.[47]



Scheme 9

By the use of 1 equivalent of $PSCl_3$ the monosulfurated **49** is obtained, by the use of 2 equivalents or more of $PSCl_3$ only the disulfurated derivative **22** was obtained.

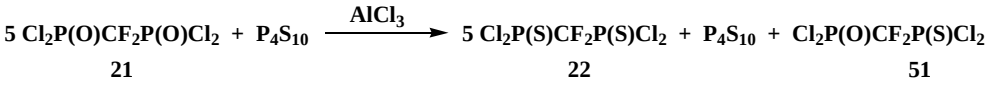
Oxidation of trivalent derivatives can be achieved using DMSO at low temperature (-80℃), the reaction is easily managea ble, mono- and dioxides are obtained depending on the molar ratio P(III):DMSO used.[49]



Scheme 10

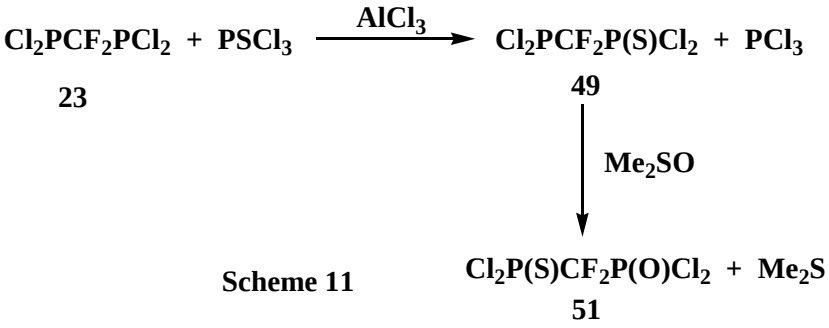
Through oxidation/sulfuration can be obtained some derivatives, which are formed as intermediates and cannot be separated from complex mixtures.

$Cl_2P(O)CF_2P(S)Cl_2$ (**51)**, is obtained as an intermediate in the following reaction (Eq. 25):



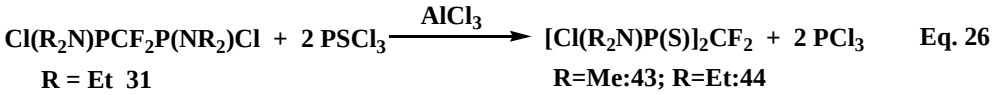
Eq. 25

Pure (**51**) can be obtained by the following procedure, using two consecutive sufluration/oxidation reactions:

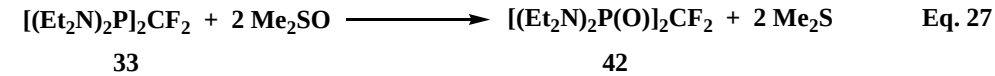


Scheme 11

Also some amines containing P(V), which cannot be obtained through direct aminolysis of the corresponding pentavalent compounds, are successfully synthesized through oxidation or sulfuration of the corresponding P(III) derivatives, e.g. Eq. 26 and Eq. 27:

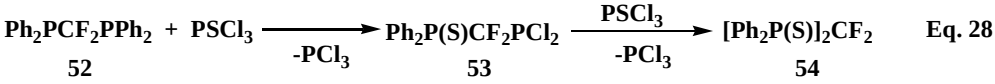


Eq. 26



Eq. 27

Must be mentioned that not only halogenides but also phosphanes can be oxidized/sulfurated, for e.g. difluoromethylenebis(diphenylphosphane):



Eq. 28

This sulfuration reaction proceeds slowly, after 7h/110 ℃ (toluene as solvent) ca. 10% of the asymmetric product **53** can be observed, for total sulfuration reflux for another 7h under the same conditions are required.

It can be concluded that the first oxidation (sulfuration) of a dilfuoromethylene bridged diphosphorus compound undergoes more rapidly, than the oxidation of the second phosphorus atom of the same molecule.[55]

CONCLUSIONS

Difluoromethylene bridged diphospha-derivatives are easily obtained through the Michaelis-Arbuzov reactions from a trialkyl phosphite using CF_2Br_2. The halogenated compounds **21**, **22** and **23** can be used for the synthesis of a wide variety of functional derivatives by halogen exchange, alcoholysis, aminolysis, alkylation, arylation and oxidation.

Through reaction of the above mentioned dichlorides (**21**, **22** and **23**) with primary amines and hydrazines lead to the formation of four-, and five-membered ring-systems are expected.

REFERENCES

1. J. J. Richard, K.E. Burke, J.W. O'Laughlin, C.V. Banks, *J. Am. Chem. Soc.*, **1961**, *83*, 1722.
2. M. Duc, B. Boutevin, B. Ameduri, *J. Fluorine Chem.*, **2001**, *112*, 3.
3. A.N. Pudovik, G.E.Yastrebova, *Russian Chem. Rev.*, **1970**, *39(7)*, 562.
4. T. Fonong, D. J. Burton, D. J. Pietrzyk, *Anal. Chem.*, **1983**, *55*, 1089.
5. D. J. Burton, D. J. Pietrzyk, T. Ishihara, T. Fonong, R. M. Flynn, *J. Fluorine Chem.*, **1982**, *20*, 617.
6. C. E. McKenna, Pei-de Shen, *J. Org. Chem.*, **1981**, *46*, 4573.
7. D.J. Burton, L. G. Sprague, *J. Org. Chem.*, **1988**, *53*, 1523.
8. D. J. Burton, R. M. Flynn, *J. Fluorine Chem.*, **1980**, *15*, 263.
9. T. Mahmood, J. M. Shreeve, *Inorg. Chem.*, **1986**, *25*, 3128
10. Y. Margalit, G. Amitai, Y. Ashani, *Phosphorus and Sulfur*, **1977**, *3*, 315.
11. C. Monard, J. Quinchon, *Bull. Soc. Chim. Fr.*, **1961**, 1084, 1086.
12. M. F. Sartori, *Chem. Rev.*, **1951**, *48*, 246.
13. O. T. Quimby, J. D. Curry, D. A. Nicholson, J. B. Prentice, C. H. Roy, *J. Organomet. Chem.*, **1968**, *13*, 199.
14. G. M. Blackburn, D. A. England, F. Kolkmann, *J.C.S. Chem. Comm.*, **1981**, 930.
15. L. Z. Soborovskii, N. F. Baina, *J. Gen. Chem. USSR.*, **1959**, *29*, 1115.
16. M. Obayashi, E. Ito, K. Matsui, K. Kondo, *Tetrahedron Lett.*, **1982**, *23*, 2323.
17. G. M. Blackburn, G. E. Taylor, *J. Organomet. Chem.*, **1988**, *348*, 55.
18. H. K. Nair, R. D: Guneratne, A. S. Modak, D. J. Burton, *J. Org. Chem.*, **1994**, *59*, 2393.
19. D. W. Hutchinson, D. M. Thornton, *J. Organomet. Chem.*, **1988**, *340*, 93.
20. H. K. Nair, D. J. Burton, *J. Am. Chem. Soc.*, **1994**, *116*, 6041.
21. H. K. Nair, D. J. Burton, *J. Am. Chem. Soc.*, **1997**, *119*, 9137.
22. D. J. Burton, T. Ishihara, M. Maruta, *Chem. Lett.*, **1982**, 755.
23. Michaelis, A., Kaehne, R., *Chem. Ber.*, **1898**, *31*, 1048
24. Arbuzov, A.E., *J. Russ. Phys. Chem. Soc.*, **1906**, *38*, 687
25. T. B. Brill, S. J. Landon, *Chem. Rev.* **1984**, *84*, 577.

26. A. K. Bhattacharya, G. Thyagarajan, *Chem. Rev.*, **1981**, *81*, 415.
27. H.-G. Henning, G. Hilgetag, *Z. Chem.*, **1967**, *7*, 169.
28. D. J. Burton, R. M. Flynn, *J. Fluorine Chem.*, **1977**, *10*, 329.
29. D. J. Burton, R. M. Flynn, *Synthesis*, **1979**, *8*, 615.
30. L. G. Sprague, D. J. Burton, R. D. Guneratne, W. E. Bennett, *J. Fluorine Chem.*, **1990**, *49*, 75.
31. D. J. Burton, T. Ishihara, R. M. Flynn, *J. Fluorine Chem.*, **1982**, *20*, 121.
32. L. Maier, *Helvetica Chimica Acta*, **1965**, *48*, 133.
33. T. Morita, Y. Okamoto, H. Sakurai, *Chem. Lett.*, **1980**, 435.
34. C. E. McKenna, M. T. Higa, N. H. Cheung, M.-C. McKenna, *Tetrahedron Lett.*, **1977**, 155.
35. C. E. McKenna, J. Schmidhauser, *J.C.S. Chem. Comm.*, **1979**, 739.
36. R. Rabinowitz, *J. Org. Chem.*, **1963**, *28*, 2975.
37. Gross, H., Böck, Ch., Costisella, B., Gloede, J., *Journal f. prakt. Chemie*, **1978**, *320*, 344
38. Balckburn, G.M., Ingleson, D., *J.C.S. Chem. Comm.*, **1978**, 870.
39. A. H. Schmidt, *Chem. Ztg.,* **1980**, *104*, 253.
40. T. Morita, Y. Okamoto, H. Sakurai, *Tetrahedron Lett.*, **1978**, *28*, 2523.
41. T. Morita, Y. Okamoto, H. Sakurai, *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 267.
42. K.-H. Reichert, *Diplomarbeit*, Braunschweig 1986.
43. A. Groddeck, *Dissertation*, Braunschweig 1990.
44. Fild, M., Schmutzler, R., in Kosolapoff: *Organic Phosphorous Compounds*, **1972**, *4*, 75-153
45. M. Fild, J. Heinze, W. Krüger, *Chem. Ztg.*, **1977**, *101*, 259.
46. M. Fild, K.-H. Reichert, *Chem.-Ztg.*, **1987**, *111*, 176.
47. Z. S. Novikova, A. A. Prishchenko, I. F. Lutsenko, *J. Gen. Chem. USSR*, **1977**, *47*, 707
48. Houben-Weyl **E1**, pp. 106-183 Elsevier 1982
49. Z. S. Novikova, A. A. Prishchenko, I. F. Lutsenko, *J. Gen. Chem. USSR*, **1979**, *49,* 707
50. Z. S. Novikova, A. A. Prishchenko, I. F. Lutsenko, *J. Gen. Chem. USSR*, **1979**, *49,* 616
51. H. Schmidbaur, S. Schnatterer, *Chem. Ber.*, **1986**, *119*, 2832
52. S. Hietkamp, H. Sommer, O. Stelzer, *Chem. Ber.*, **1984**, *117*, 3400
53. R. Schmutzler, *J. Chem. Soc.*, **1964**, 4551
54. R. Schmutzler, *Angew. Chem.*, **1965**, *77*, 530
55. K. Ruhnau, *Dissertation*, Braunschweig **1992**