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Efficient Interconversion of α,α-Difluoromethylenephosphonates and α,α-Difluoromethylenephosphonothioates.

Serge R. Piettre.

Marion Merrell Research Institute, Strasbourg Research Center, 16 rue d'Ankara, 67080 Strasbourg, France

Dedicated with respect to Professor Ernest Wenkert

Abstract: Treatment of dialkyl 1,1-difluoromethylenephosphonates **1** with Lawesson's reagent cleanly produces the corresponding dialkyl 1,1-difluoromethylenephosphonothioates **2**. The reaction can be extended to dialkyl 1,1-difluoromethylenephosphinates and to dialkyl 1,1-difluoromethylenephosphine oxides. The reversed transformation (i.e. converting dialkyl 1,1-difluoromethylenephosphonothioates into dialkyl 1,1-difluoromethylenephosphonates) is most conveniently achieved by using dioxirane **7** or perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **8**, and produces the desired phosphonates in high yield. The synthetic interest of these transformations is discussed.

Recent years have witnessed an upsurge of interest for the 1,1-difluoromethylenephosphonate group **1**, due to its capability to act as a function isosteric to the phosphate. Blackburn's early work first demonstrated the superior electronic and structural analogy between the two functions, and this has been since then supported by X-ray crystallography data.[1,2] As a consequence, a number of papers have been devoted to the development of appropriate synthetic methodology as well as to the preparation of bioactive compounds encompassing this functional group.[3] Recently we introduced the 1,1-difluoromethylenephosphonothioates **2**, which are close analogs of **1** and whose possible applications include traditional medicinal chemistry and new therapeutic approaches such as antisense strategy.[4] In the course of a study aiming at the use of such functionalities in the design of enzyme inhibitors, it became obvious that the interconversion of 1,1-difluoromethylenephosphonates **1** and 1,1-difluoromethylenephosphonothioates **2** (Scheme 1) would provide a much greater flexibility in the access to these potentially bioactive molecules.

1 **2**

SCHEME 1

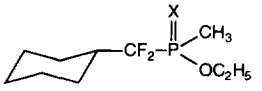
The problem of converting the phosphorous-oxygen double bond into a phosphorous-sulfur double bond was first addressed. Lawesson's reagent (**3**) was found to be well suited to achieve this transformation.[5]

TABLE 1 Conversion of 1,1-Difluorophosphonates 1 into 1,1-Difluorophosphonothioates 2

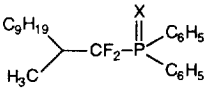
entry	R^1	R^2	Product	Yields (%) [a]	^{31}P NMR δ (ppm) [b]
1	Br	C_2H_5	**2a**	71	69.38
2	H	$CH_2C_6H_5$	**2b**	73	74.49
3	$C_{12}H_{25}$	C_2H_5	**2c**	93	77.34
4	*c*-C_6H_{11}	CH_3	**2d**	72	81.37
5	$C_9H_{19}(CH_3)CH$	C_2H_5	**2e**	90	77.47
6	*p*-$C_6H_5CH_2OC_6H_4CO$	C_2H_5	**2f**	93	72.67

a) see reference 7. b) measured downfield from H_3PO_4

Thus heating 1,1-difluoromethylenephosphonates **1** with **3** at 100°C for 90 to 120 minutes resulted in a total con-sumption of **1** and the formation of the desired 1,1-difluoromethylenephosphonothioates **2** in high yield, thereby providing a new access to this class of potentially useful compounds through the well-known chemistry of α,α-difluoromethylenephosphonates (Table 1). It is noteworthy that even in the presence of an excess of **3** and longer reaction times, the carbonyl group of starting 1,1-difluoromethylenephosphonate **1f** was left untouched as demonstrated by ^{13}C NMR spectroscopy experiment on the pure product (entry 6).[6] The transformation could be extended to 1,1-difluoromethylenephosphinate and to 1,1-difluoromethylene-phosphine oxide derivatives **4a** and **5a**, respectively, the corresponding thiocompounds **4b** and **5b** being obtained in isolated yields of 91% and 96%, respectively.



4a: X=O
b: X=S



5a: X=O
b: X=S

The reversed transformation (i.e. P=S into P=O) proved to be more difficult to achieve as most of the synthetic methods reported for the conversion of phosphorothioates into phosphates led either to the formation of the desired 1,1-difluoromethylenephosphonate in low yields and to degradation of the starting difluoromethylenephosphonothioate, or to recovery of the starting material.[8] Trichloroacetaldehyde (chloral, **6**) was found to be mildly efficient.[9] Heating a 1:20 mixture of 1,1-difluoromethylenephosphonothioate **2g** and chloral at 100°C for 21 hours, evaporating the volatiles and purifying the residue resulted in the isolation of the corresponding phosphonate **1g** in 40% yield (Table 2, entry 7, method A) and recovered starting phosphonothioate (47%). However longer heating time led to extensive decomposition and failed to improve the yield.[10]

Dimethyldioxirane **7** proved to be an efficient reagent for the conversion of **2** to **1**. Treating **2g** with one equivalent of **7** (0.1M solution in acetone) at -15°C for four hours gave a clean 2:1 mixture of phosphonate:phosphonothioate (**1g**:**2g**). Total consumption of the starting material was achieved by evaporating the solvent and repeating the procedure with an additional 0.6 equivalent of dimethyldioxirane.[11,12] This procedure followed by work-up and chromatography furnished compound **1g** in 97% isolated yield (Table 2, entry 8, method B).

A much more expeditious conversion of 1,1-difluoromethylenephosphonothioates into 1,1-difluoromethylene-phosphonates was achieved with perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **8**, a powerful yet mild reagent whose applications in organic synthesis have blossomed in the past three years.[13] Treating a chloroform solution of **2g** with a fluoroform solution of **8** (1.1 equivalent; dropwise addition) at room temperature produced cleanly the desired phosphonate **1g** in high yield (Table 2, method C). Table 2 compiles the results obtained for this conversion (entries 9 to 13).

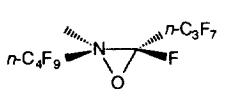
TABLE 2: Conversion of 1,1-Difluorophosphonothioates 2 into 1,1-Difluorophosphonates 1.

Entry	R^1	R^2	Method [a]	Product	Yields (%) [b]
7	$C_9H_{19}(CH_3)CH$	$C_6H_5CH_2$	A	**1g**	40
8	$C_9H_{19}(CH_3)CH$	$C_6H_5CH_2$	B	**1g**	97
9	$C_9H_{19}(CH_3)CH$	$C_6H_5CH_2$	C	**1g**	92
10	$C_9H_{19}(CH_3)CH$	C_2H_5	C	**1e**	90
11	$C_6H_5CH_2$	$C_6H_5CH_2$	C	**1h**	77
12	$C_6H_5(CH_3)CH$	C_2H_5	C	**1i**	94
13	*n*-Bu_3Sn	$C_6H_5CH_2$	C	**1j**	91

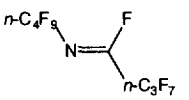
a) Method A: CCl_3CHO (20 eq), 100°C, 21 hrs; (47% recovered starting material). Method B: dimethyl dioxirane (1.6 eq), CH_2Cl_2-Et_2O, RT. Method C: perfluoro-*cis*-2-*n*-butyl-*n*-propyloxaziridine **8**. b) see reference 7.

Monitoring the reaction by ^{19}F NMR spectroscopy showed it to be complete in less than two minutes, the only other observable product being the expected perfluoroimine **9**. A precipitate was also observed. Isolation in the pure form by filtration and reaction with a CS_2 solution of triphenylphosphine (room temperature, 4 hrs)

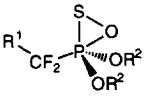
cleanly yielded triphenylphosphine sulfide (as shown by ^{31}P NMR spectroscopy)[14], thus indicating the precipitate to be elemental sulfur. In addition, this was confirmed by analysis.[15] This suggest the formation of intermediate **10** encompassing the unusual P-S-O three-membered cycle (or one of its resonance or tautomeric forms), with subsequent extrusion of sulfur *via* an electrocyclic process.[16]



8



9

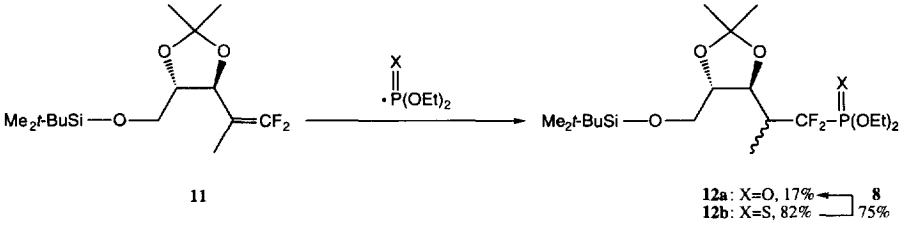


10

Amongst the synthetic implications of the present work is the following: for the first time, a simple preparation of *dibenzyl* 1,1-difluoromethylenephosphonates is available, since the corresponding dibenzyl thioderivatives can easily be prepared.[3n,4,17] As recently discussed, the problem of protecting 1,1-difluoromethylenephosphonates has proven to be accute in several cases.[18]

The present procedure also permits the preparation of compounds which can not be easily obtained otherwise. For instance compound **1i** could not be prepared by our recently published addition reaction of phosphonyl radical to 1,1-difluoroolefin.[3n] This is due jointly to the poor reactivity of the starting olefin and to the low stability of the diethylphosphonyl radical; the corresponding phosphonothioyl radical is however more stable and could be added in a useful way.[3n] Transformation of the resultant adduct **2i** by the hereabove procedure produced the target compound **1i**.

We also found that, in some cases, the use of the two-step procedure, i.e. preparation of the 1,1-difluoromethylenephosphonothioate and conversion of the P-S double bond into the P-O double bond, resulted in the isolation of the desired 1,1-difluoromethylenephosphonate in much higher yield than the direct, one-step synthesis. Thus for instance, addition of diethyl phosphonyl radical onto difluoroolefin **11** gave difluoromethylenephosphonate **12a** in 17% isolated yield while diethyl thiophosphonyl radical furnished the corresponding thioderivative **12b** in 82% yield (Scheme 2). Conversion of **12b** to **12a** using oxaziridine **8** was achieved in 75% yield, thus allowing the preparation of **12a** in an overall yield of 61%.



11

12a: X=O, 17%
12b: X=S, 82%
8
75%

SCHEME 2

Typical procedures are as follows:

P=O to P=S conversion. A toluene solution (2 mL) of diethyl 1-bromo-1,1-difluoromethylphosphonate **1a** (256 mg, 1 mmol) and Lawesson's reagent (404 mg, 1 mmol) was heated at 100°C for 120 minutes (the reaction was monitored by TLC (Heptane-AcOEt, 9:1)). The resultant mixture was cooled down, evaporated and the residue was chromatographed. Elution with heptane-AcOEt (95:15) delivered phosphonothioate **2a** (193 mg, 71% yield, colorless oil. ^1H-NMR ($CDCl_3$/ref. TMS) δ: 1.39 (t, 6H, $^3J_{H-H}$= 7.1Hz); 4.23-4.41 ppm (m, 4H). ^{19}F-NMR ($CDCl_3$/ref. C_6F_6) δ: 100.65 ppm (d, 2F, $^2J_{F-P}$=96.5 Hz). ^{31}P-NMR ($CDCl_3$/ref. H_3PO_4) δ: 69.38 ppm (t, 1P, $^2J_{F-P}$=95.6 Hz).

P=S to P=O conversion. A fluoroform solution (10 mL) of oxaziridine **8** (494 mg, 285 µL, 1.1mmol) was added dropwise to a stirring chloroform solution (10 mL) of diethyl 2-phenyl-1,1-difluoropropyl-phosphonothioate (**2i**) (309 mg, 1 mmol) at room temperature inducing a precipitate to form. After 10 minutes, the volatiles were evaporated and the residue was chromatographed on silica gel. Elution with heptane-AcOEt (8:2) and evaporation furnished 293 mg of colorless, oily product **1i** (94% yield). ^1H-NMR ($CDCl_3$/ref. TMS) δ: 1.15 (t, 3H, *J*= 7.1Hz); 1.29 (t, 3H, $^3J_{H-H}$= 7.1Hz); 1.50 (d, 3H, $^3J_{H-H}$= 7.2Hz); 3.39-3.62 (m, 1H); 3.77-4.06 (m, 2H); 4.09-4.27 (m, 2H); 7.27-7.40 ppm (m, 5H). ^{19}F-NMR ($CDCl_3$/ref. C_6F_6) δ: 46.24 (ddd, 1F, $^3J_{F-H}$= 19.2, $^2J_{F-P}$=106.7, $^2J_{F-F}$=298.7Hz); 48.97 ppm (ddd, 1F, $^3J_{F-H}$= 16.1, $^2J_{F-P}$=109.7, $^2J_{F-F}$=298.7Hz). ^{31}P-NMR ($CDCl_3$/ref. H_3PO_4) δ: 7.37 ppm (dd, 1P, $^2J_{F-P}$=107.2, 109.7Hz).

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5. Lawesson's reagent has been reported to convert phosphonothioates and phosphorothioates into the corresponding phosphonates and phosphates, respectively; see Horner, L.; Lindel, H. *Phosphorus and Sulfur* **1982**, *12*, 259-261.
6. ^{13}C-NMR ($CDCl_3$/ref $CDCl_3$) δ: 15.97, 65.04, 70.24, 114.58, 115.6 (dt, $^2J_{C\text{-}P}$=160.0, $^2J_{C\text{-}F}$=278.7 Hz), 125.91, 127.42, 128.27, 133.11, 135.87, 163.75, 186.1 ppm (m, C=O).
7. Analytical data for all compounds (^{1}H-, ^{19}F-, ^{31}P-NMR and mass spectra) are in accordance with the structure depicted in the paper.
8. Amongst these methods were dimethyl sulfoxide-iodine at 80°C, H_2O_2-NaOH-ethanol, Me_3OBF_4 followed by *meta*-chloroperbenzoic acid, ozone-methanol-0°C, ozone-trifluoroethanol-0°C or -40°C, ozone-triphenylphosphite at -78°C and room temperature; see: a) Mikolajczyk, M.; Luczak, J. *Chem. & Ind.* **1974**, 701-702. b) Bellet, E. M.; Cassida, J. E. *J. Agr. Food Chem.*. **1974**, *22*, 207-211. c) Mikolajczyk, M.; Luczak, J. *Synthesis* **1975**, 114-115. d) Bestmann, H. J.; Kisielowski, L.; Distler, W. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 298-299. e) Skowronska, A.; Krawczyk, E. *Synthesis* **1983**, 509-510.
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10. Chloral has been reported to convert phosphorothioates into phosphates by heating at 100°C for periods of time between ten and forty minutes (reference 9b). This reaction has been speculated to involve nucleophilic addition of the sulfur atom of the P=S moiety onto the carbonyl group of chloral; in this respect, the observed poorer reactivity of the 1,1-difluoromethylenephosphonothioates may be attributed to the deactivating effect of the CF_2 group.
11. Preparation of dioxirane: Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. Dioxirane has been reported to convert phosphorothioates into the corresponding phosphates in less than 5 minutes at room temperature (see reference 12). In the case of 1,1-difluoromethylenephosphonothioates, the observed slower reaction is probably a consequence of the deactivating effect of the CF_2 group when compared to the oxygen of the phosphorothioate.
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13. a) Petrov, V. A.; Desmarteau, D. D. *J. Org. Chem.* **1993**, *58*, 4754-4755. b) Desmarteau, D. D; Donadelli, A.; Montanari, V.; Petrov, V. A.; Resnati, G. *J. Am. Chem. Soc.* **1993**, *115*, 4897-4898. c) Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511-5513. d) .Arnone, A.; Bernardi, R.; Cavicchioli, M.; Resnati, G. *J. Org. Chem.* **1995**, *60*, 2314-2315. e) Cavicchioli, M.; Mele, A; Montanari, V.; Resnati, G. *J. Chem. Soc., Chem. Commun.* **1995**, 901-902. f) Terreni, M.; Pregnolatto, M.; Resnati, G.; Benfenati, E. *Tetrahedron* **1995**, *51*, 7981-7992.
14. ^{31}P-NMR ($CDCl_3$/ref. H_3PO_4) δ: -4.79 (Ph_3P) and +43.53 ppm (Ph_3P=S).
15. The analysis was carried out by mineralisation of the sulfur with hydrogen peroxide in the presence of UV radiations and subsequent quantification as sulfate anion.
16. For convenience, these intermediates have been collectively referred to as " phosphorous oxythionate"; see reference 8b for a discussion on this subject.
17. Work carried out in this laboratory has shown the lithium salt of dibenzyl 1,1-difluoromethylphosphonate to be too unstable to be alkylated in a synthetically useful manner; Halazy, S., private communication.
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