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Easy and General Access to α,α-Difluoromethylene Phosphonothioic Acids. A New Class of Compounds.

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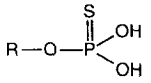
Dedicated with gratitude to Dr Christian-Johannes Jenny

Abstract: The preparation of dibenzyl α,α-difluoromethylphosphonothioate **10** from the reaction between the corresponding phosphonate **9** and Lawesson's reagent is reported. Treatment of **10** with lithium di*iso*propylamide and a variety of electrophiles demonstrate the possibility of functionalizing it. Reductive debenzylation of the adducts affords the sodium salts of α,α-difluoromethylenephosphonothioates **22** which upon acidic treatment deliver the corresponding acids **4**.

Over the past fifty years, analogs of organic phosphates in which the double-bonded oxygen is replaced by a sulfur (phosphorothioate **1**), have been the focus of increasing interest due to their considerable value as agrichemical, or because they are often powerful tools for the elucidation of enzyme mechanism and metabolic pathways.[1] For instance, phosphorothioate analogs of nucleotides are useful probes to study phosphoryl and nucleotidyl transfering enzymes. Thus, such analogs of cyclic adenosine monophosphate (cAMP) have been shown to possess agonistic or antagonistic properties on cAMP-dependent protein kinase, depending on the substitution (axial *versus* equatorial, respectively).[2] Recently, several phosphorothioate analogs of inositol polyphosphates have been synthesized and shown to be valuable probes to study recognition of *myo*-inositol 1,4,5-trisphosphate by enzymes and receptor sites.[3] Furthermore the usefulness of phosphorothioate analogs of oligonucleotides as anti-sense inhibitors has been demonstrated by their high *in vitro* and *in vivo* resistance to nuclease-promoted degradation.[4] As a result, possible therapeutic application have emerged from data such as inhibition of the cytopathic effect of HIV-1 in chronically infected H9 cells.[5] Very recently, dendrimers containing the phosphorothioate group have been described.[6]
In addition, molecules encompassing a phosphonothioate function **2** have also attracted interest because of their insecticidal properties, their potency as irreversible inhibitors of cholinesterases and their use in the preparation of nucleoside analogs.[7]
On the other hand, ever since Blackburn's seminal work in which pyrophosphate oxygens of nucleoside trisphosphates were replaced by a CF_2 group, scientists have accumulated data which demonstrate the superior electronic and structural analogy between the α,α-difluoromethylenephosphonate and the phosphate. As a result, numerous analogs **3** of biologically interesting phosphates characterized by such a functionality have been prepared. These include among others, nucleotides, glycolytic phosphates and phosphoenol pyruvate.[8]
In the light of all these data, it is reasonable to think that α,α-difluoromethylenephosphonothioates **4**, featuring the combination of a CF_2 moiety and a phosphorus-sulfur bond, should provide a class of compounds characterized by unique and useful properties. We herein report a simple preparation of these compounds and the isolation of the corresponding α,α-difluoromethylenephosphonothioic acids.



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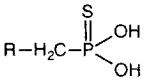

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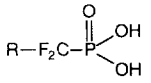

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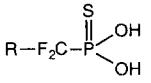
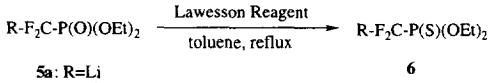


4

Our strategy parallels Kondo's work on dialkyl α–lithio-α,α-difluoromethylphosphonate **5a**.[9] It was soon realized that while treatment of dialkyl α,α-difluoromethylenephosphonate **5b** with Lawesson's reagent provided an easy access to the desired compounds **6**, conversion of the products into the corresponding α,α-difluoromethylenephosphonothioic acids **4** could not be achieved in a useful way (Scheme 1)[10]. On the other hand reaction between Lawesson's reagent and difluoromethylenephosphonic acids **3** led only to untractable mixtures.[11]
Dibenzyl α,α-difluoromethylphosphonothioate **10** would likely solve this problem as one could reasonably



5a: R=Li
5b: R=alkyl

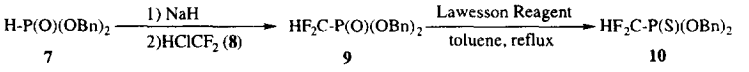
6

SCHEME 1

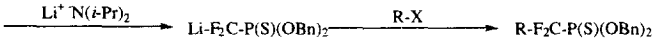
expect easy debenzylation under reductive conditions (e. g. sodium in ammonia). However work carried out in this laboratory has shown the lithium salt of **9** to be too unstable to be alkylated.[12] We envisioned that carrying out the thionylation reaction *before* the alkylation would allow an easier access to the desired dibenzyl α,α-difluoromethylenephosphonothioates **12**.

Preparation and Alkylation of Dibenzyl α,α-Difluoromethylphosphonothioate 10:

Dibenzyl α,α-difluoromethylphosphonate **9** (^{31}P NMR δ= 6.36ppm ($CDCl_3/H_3PO_4$)) was prepared in a classical way from a tetrahydrofuran (THF) solution of the sodium salt of dibenzyl phosphite **7** and chlorodifluoromethane **8** (74% yield). Refluxing **9** in toluene in the presence of one equivalent of Lawesson's reagent furnished the desired dibenzyl α,α-difluoromethylphosphonothioate **10** (^{31}P NMR δ= 74.5ppm ($CDCl_3/H_3PO_4$)) as a colorless oil, stable at 0°C for months (73% yield) (Scheme 2). We found that **10** could be conveniently deprotonated by lithium di*iso*propylamide at -78°C to give the lithiated species **11** which was reasonably stable for several hours at temperatures up to -40°C.[13] Treatment of the thereby formed nucleophilic reagent with various electrophiles delivered the desired products **12** in good yields (Scheme 2) (Table 1).[14] It is worth noting that secondary alkyl halide did not react (entry 6); this is reminiscent of what was observed with **5a**.[15]



7 **9** **10**



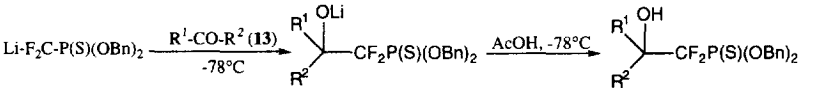
11 **12**

SCHEME 2

entry	R-X	**12**	Yield (%)	^{31}P NMR δ (ppm) [a]
1	C_2H_5-Br	a	67	78.5
2	CH_2=CH(CH_2)$_3$-Br	b	63	78.3
3	C_6H_5-CH_2Br	c	70	77.8
4	$CH_3OCH_2CH_2$-Br	d	44	77.3
5	Br(CH_2)$_4$-Br	e	56 (16)	78.0
6	*c*-C_6H_{11}-Br	f	0	-
7	(*n*-C_4H_9)$_3$Sn-Cl	g	68	81.5

Table 1: Yields of dibenzyl α,α-difluoromethylenephosphonothioate **12**. a: External reference is H_3PO_4

Lithioderivative **11** was found to react with ketones and aldehydes **13** to furnish the adducts **14** which after quenching at low temperature with glacial acetic acid, delivered the expected alcohols **15** in isolated yields ranging from 63 to 85 percents (Scheme 3).[17]

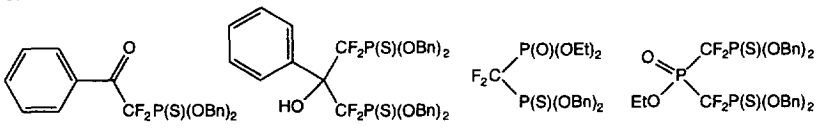


11 **14**

15a: R^1=*n*-C_5H_{11}, R^2=H, 63%
15b: R^1=*p*-$C_6H_5CH_2OC_6H_4$, R^2=H, 85%
15c: R^1=*n*-C_9H_{19}, R^2=CH_3, 76%

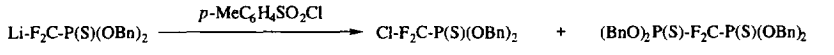
SCHEME 3

Dibenzyl α-lithio-α,α-difluoromethylphosphonothioate **11** reacted under the same conditions with one equivalent of benzoyl chloride to afford a separable mixture of monoadduct **16** and bisadduct **17** in 19 and 30 percent yield, respectively. The use of only half an equivalent of benzoyl chloride increased the yield of **17** to 54 percent. Diethyl phosphoryl chloride showed a similar behavior, giving **18** and **19** in 36 an 15 percent isolated yields.



16 **17** **18** **19**

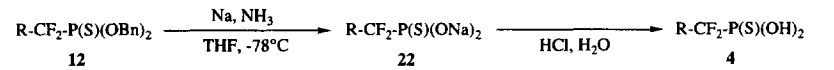
p-Toluenesulfonyl chloride produced chloride **20** (35% yield) and bisphosphonothioate **21** (40% yield). Since not a trace of *p*-toluyl difluoromethyl sulfone could be isolated or detected from the reaction mixture [18], compound **21** was presumably formed from reaction between lithiated species **11** and **20** with concomittant liberation of $LiCF_2Cl$ (Scheme 4).



11 **20** **21**

SCHEME 4

Disodium α,α-Difluoromethylenephosphonothioates 22 and Difluoromethylenephosphonic Acids 4: Dibenzyl α,α-difluoromethylenephosphonothioates **12** (0.5 mmol) were efficiently transformed into disodium α,α-difluoromethylenephosphonothioate **22** by treatment with sodium (1.2 gram-atom) in a cooled mixture (-78°C) of THF and ammonia (20mL/20mL) for 30 min. Quenching the resultant mixture at the same temperature with some acetone, warm-up and evaporation of the volatiles delivered the desired salts **22** which could be recrystallized from methanol-diethyl ether. The corresponding α,α-difluoromethylenephosphonothioic acids **4** were obtained by dissolving the sodium salts in brine, acidifying the solution with 1M aqueous HCl until pH=1 and extraction with diethyl ether (Scheme 5) (Table 2). They were obtained as colorless oils stable for months at 0°C; the second pK_a (determined by measuring the ^{31}P-NMR chemical shift as a function of the pH) was found to be 3.0, thus reflecting a much stronger acidity than the corresponding difluoromethylenephosphonoic acids. Work is in progress to fully assess the potential of this new class of compounds.[19]



12 **22** **4**

SCHEME 5

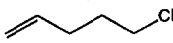
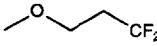
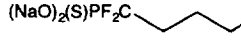
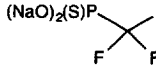
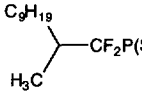
entry	**22**		Yield **22** (%)	^{31}P NMR δ (ppm)[a]	Yield **4** (%)	^{31}P NMR δ (ppm)[a]
1	$H\text{-}CF_2\text{-}P(S)(ONa)_2$	a	73	48.24	78	56.88
2	$C_2H_5\text{-}CF_2\text{-}P(S)(ONa)_2$	b	93	53.10	81	56.95
3		c	80	48.85	NA[c]	-
4		d	87	53.0	NA[c]	-
5		e	98 [b]	47.10	87	67.59
6		f	40	54.59	NA[b]	-
7		g15	73	52.44	84	53.43

Table 2: Yields of disodium α,α-difluoromethylenephosphonothioate **22** and α,α-difluoromethylenephosphonothioic acids **4**. a: CD_3OD solutions; H_3PO_4 as external reference. b: .starting material is a by-product of the reaction leading to **12e**; see footnote 16. c: N/A: not carried out.

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10. Treatment of dialkyl α,α-difluorophosphonates with Lawesson reagent (1 eq) in refluxing toluene led to the formation of the corresponding phosphonothioates in yields ranging from 85 to 94 %. However all attemps ($TMSBr_t$, TMSI, acidic hydrolysis,...) to convert the products into the phosphonothioic acid **4** gave untractable mixtures (by ^{1}H-, ^{19}F- and ^{31}P-NMR spectroscopy) apparently resulting from a scrambling at the phosphorus center.
11. As determined by TLC, ^{1}H-, ^{19}F- and ^{31}P-NMR spectroscopy.
12. Gross, V.; Halazy, S. unpublished results.
13. This contrasts with diethyl α-lithio-α,α-difluoromethylenephosphonate **5a**, stable only at -78°C.
14. General procedure for compounds **12**: A solution of α,α-difluoromethylphosphonothioate **10** (1 mmol in 1mL of THF) is added dropwise to a cooled (-78°C) THF solution (4mL) of LDA (1 mmol) prepared from di*iso*propylamine and a 1.6 N hexanes solution of *n*-butyl lithium at 0°C. After 30 minutes of stirring, a solution of the halide (1 mmol in 1 mL of THF) is added dropwise and stirring continued at -41°C for four hours. The resultant mixture is then warmed up to room temperature, poured into water, and extracted three times with methylene chloride. The combined organic extract is dried over sodium sulfate and evaporated under reduced pressure. The crude residue is purified by chomatography on silica gel to furnish the desired products in yields indicated in Table 1. Eluents are as follows (A=AcOEt, H=Heptane, C=CH_2Cl_2): **10**: H-C (9:1); **12a**: H-A (98:2); **12b**: H-A (98:2); **12c**: H-C (8:2); **12d**: H-C (8:2); **12e**: H-C (85:15); **12 g**: H-A (98:2).
15. β,β-Disubstituted-α,α-difluoromethylenephosphonates and -phosphonothioates can be prepared conveniently through the addition reaction between phosphonyl or thiophosphonyl radicals and difluoroolefins; see Piettre, S. R., following paper.
16. The major product is the tetrabenzyl 6-bromo-1,1-difluoropentyl-1-phosphonothioate **12e** (56%); also isolated as a by-product is tetrabenzyl 1,1,6,6-tetrafluorohexyl-1,6-bisphosphonothioate (20%).
17. General procedure for compounds **15** to **19**: A solution of α-lithio-α,α-difluoromethylenephosphonothioate **11** (1 mmol), prepared as above, is warmed up to -41°C and stirring is continued for 30 minutes. It is then cooled down to -78°C and the reagent (1 mmol of aldehyde, ketone or acid chloride in 1 mL of THF) is added dropwise. After two hours of stirring at the same temperature, glacial acetic acid (1 mmol) is added. Warming up the solution, work-up as above and chromatography on silica gel delivered the products. Eluents (A=AcOEt, H=Heptane, C=CH_2Cl_2) and ^{31}P-NMR spectroscopy chemical shifts ($CHCl_3$; external reference=H_3PO_4) are as follows: **15a**: H-C (8:2); 76.3 ppm. **15b**: H-A (9:1); 75.7 ppm. **15c**: H-C (6:4); 74.6 ppm. **16**: H-C (8:2); 71.0 ppm. **17**: H-C (8:2); 71.0-74.0 ppm. **18**: H-A (8:2); 4.3 and 73.9 ppm. **19**: H-A (8:2); 16.5-18.6 and 71.0-73.9 ppm.
18. The analogous phenyl difluoromethyl sulfone is a known compound, reported to be stable; see Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1992**, *33*, 3101.
19. All compounds have analytical data (^{1}H, ^{19}F and ^{31}P-NMR spectroscopy, mass spectrometry, infra-red spectroscopy and combustion data) in accordance with the structures depicted in the paper.

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