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Sulfanyl- and Selanyldifluoromethylphosphonates as a Source of Phosphonodifluoromethyl Radicals and Their Addition onto Alkenes†

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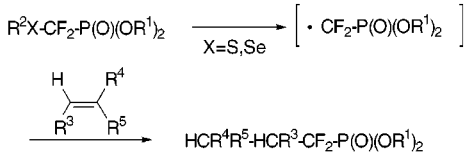
ABSTRACT



Two different strategies are shown to produce sulfanyl and selanyldifluoromethylphosphonates. Thus, treatment of sulfanyldichloromethylphosphonates by 3HF·NEt$_3$ in the presence of zinc bromide produces the corresponding sulfanyldifluoromethylphosphonates. In addition, lithiation of difluoromethylphosphonates followed by quenching with phenylsulfanyl chloride, phenylselanyl chloride, or diphenyl diselenide yields the corresponding sulfanyl- and selanyldifluorophosphonates. Generation of phosphonodifluoromethyl radicals from such precursors in the presence of alkenes produces the expected adducts.

Over the past few decades, phosphonates have emerged as valuable compounds, possessing various biological properties. Their similarity to phosphates is reinforced by the adjunction of fluorine atoms on the carbon linked to the phosphorus. Difluorophosphonates have thus become regarded as close isosteres to the corresponding phosphates, both in structural and electronic terms.[1] Several analogues of natural or unnatural phosphates, encompassing the dif-

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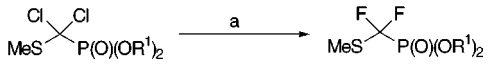
luoromethylenephosphonate moiety, have been shown to possess a better bioactivity than the corresponding nonfluorinated phosphonates.[2] As a result, recent years have witnessed the development of many new synthetic methodologies aiming at facilitating the construction of more complex structures featuring this functionnality. These methods include the reactions between metalated difluoromethylphosphonates ($MCF_2P(O)(OEt)_2$; M = Li, ZnBr, MgCl, CdCl, $CeCl_2$) and various electrophiles or the addition reaction of phosphonyl radicals onto difluoroalkenes, for example.[2a,k,3,4] We herein report novel and more practical syntheses of sulfanyl- and as yet unreported selanyldifluoromethylphosphonates and their use as precursors of phosphonodifluoromethyl radicals.

The action of $3HF{\cdot}NEt_3$ (6 equiv) on the known methylsulfanyldichloromethylphosphonates **1** and **2**[5,6] triggered no reaction. However, combining $3HF{\cdot}NEt_3$ (6 equiv) and zinc bromide (1 equiv) resulted in the formation of the desired difluorophosphonates **3** and **4** in fair yields (Scheme 1).

Scheme 1



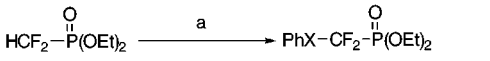
1: R^1=*i*Pr
2: R^1=Et

3: R^1=*i*Pr, 62%
4: R^1=Et , 43%

a. i. Et_3N-3HF (6 eq). ii. $ZnBr_2$ (1 eq), CH_3CN.

The corresponding phenylsulfanyl derivative **6** could also be prepared in 52% yield by reacting the lithium salt of diethyl difluoromethylphosphonate (prepared in THF from **5** and 1.5 equiv of freshly prepared LDA) with diphenyl disulfide (1.5 equiv) (Scheme 2).[7] Quenching the lithiated

Scheme 2



5

6: X=S, 52%
7: X=Se, 71-83%
(see Text)

a. i. LDA, -78°C. ii. PhXXPh or PhXCl.

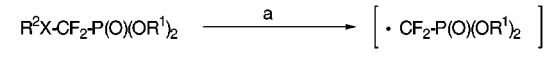
reagent with either diphenyl diselenide or *sublimed* phenylselanyl chloride produced the analogous phenylselanyl difluorophosphonate **7** in 83 and 71% isolated yields, respectively.[8]

To the best of our knowledge, only the synthesis of alkylsulfanyldifluoromethylphosphonates has been reported using electrochemical fluorination of sulfides (millimole scale). Under these conditions 4 equiv of $4HF{\cdot}FNEt_4$ was used as fluorine source to produce difluorophosphonates in about 50% yields.[9]

We next examined the potential of compounds **3** and **7** as phosphonodifluoromethyl radical precursors and their behavior in radical addition reactions. While the generation and reactivity of nonfluorinated phosphonomethyl radicals from the corresponding sulfanyl- or selanylmethylphosphonates has been well studied, the literature contains no report on the corresponding fluorinated radicals.[5b,10] These species have however been postulated as intermediates in palladium- and cobalt-mediated additions of iodo- and bromodifluoromethylphosphonates to alkenes.[11]

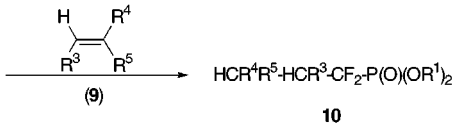
Slow addition of a toluene solution of tri-*n*-butyltin hydride and a catalytic amount of AIBN to a toluene solution of phosphonates **3** or **7** and the alkene at 90 °C resulted in the formation of adducts **10** in fair yields (Scheme 3).[12,13] Results are compiled in Table 1.

Scheme 3



3: R^1=*i*Pr, R^2X=MeS
7: R^1=Et, R^2X=C_6H_5Se

8



10

a. *n*-Bu_3SnH, AIBN, toluene, reflux.

Addition reactions onto electron-rich alkenes showed a complete regioselectivity. Unactivated alkenes such as *n*-octene produced the aliphatic difluoromethylphosphonate

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(7) Attempts to prepare the analogous diethyl phenylsulfanyldichloromethylphosphonate from phenylsulfanylmethylphosphonate using *N*-chlorosuccinimide were unsuccessful, giving only intractable mixtures.

(8) We found the reaction with phenylselanyl chloride to be reproducible *only* when this reagent had been purified by sublimation, leaving an unidentified, dark-brown solid residue. Yields were erratic when commercially available PhSeCl was used as such.

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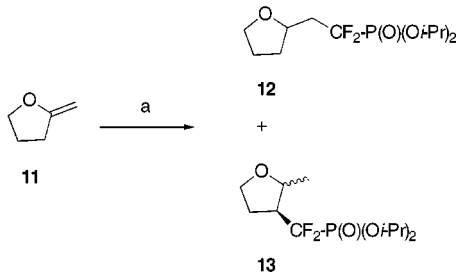
Table 1. Addition of Phosphonodifluoromethyl Radical **8** onto Alkenes

entry	radical precursor[a]	alkene (**9**)	product (**10**)[b]		yield (%)[c]
1	**3**	*n*-$C_6H_{13}CH{=}CH_2$	n-C_6H_{13}-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10a**)	56
2	**3**	$C_2H_5OCH{=}CH_2$	EtO-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10b**)	43
3	**3**	*n*-$C_4H_9OCH{=}CH_2$	n-BuO-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10c**)	54
4	**7**	*n*-$C_4H_9OCH{=}CH_2$	n-BuO-$CF_2P(O)(OEt)_2$	(**10d**)	46
5	**7**	EtOOC	$CF_2P(O)(OEt)_2$ EtOOC	(**10e**)	33[d]
6	**3**		CH_2-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10f**)	55
7	**7**		CH_2-$CF_2P(O)(OEt)_2$	(**10g**)	75
8	**3**		CH_2-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10h**)	59
9	**3**		CH_2-$CF_2P(O)(Oi\text{-}Pr)_2$	(**10i**)	45
10	**3**		$CF_2P(O)(Oi\text{-}Pr)_2$	(**10j**)	22

[a] A 1:1.4:10:0.5 ratio of radical precursor (**3** or **7**)/*n*-Bu_3SnH/alkene/AIBN. [b] All new compounds presented satisfactory analytical data. [c] Unoptimized, isolated yields. [d] Along with oligomeric material (mass spectrometry).

(entry 1). Ethyl vinyl ether (entry 2) showed a lower conversion rate (75% by ^{19}F NMR spectrometry) than *n*-butyl vinyl ether; this might be due to the lower concentration induced by its boiling point (34 °C). With less volatile ethers such as *n*-butyl vinyl ether (entries 3 and 4), no starting sulfide or selenide could be detected by ^{19}F NMR analysis of the crude mixture. The use of 10 equiv of alkene was however necessary to observe a complete consumption of **3** or **7**. In no case was the formation of dimeric phosphonate $(R^1O)_2(O)PCF_2{-}CF_2P(O)(OR^1)_2$ observed, and the amount of reduction product **5**, under these conditions, did not exceed 20%. It is to be noted that **3** and **7** behaved similarly as radical precursors (entries 3 and 4). Ethyl acrylate led to the isolation of the expected adduct along with oligomeric material. Methylene cycloalkanes smoothly added radical **8** to deliver adducts **10f** to **10i** and, not unexpectedly, cyclopentene (a 1,2-disubstituted alkene) gave adduct **10j** in lower yield. In this connection, it is interesting that the use of 2-methylenetetrahydrofuran **11** yielded a 65/35 mixture of expected adduct **12** and difluorophosphonates **13** (1:2 mixture of diastereomers), the result of sequential starting alkene isomerization and addition of radical **8** onto the thereby formed 2-methyl-3,4-dihydrofuran (Scheme 4).

Scheme 4



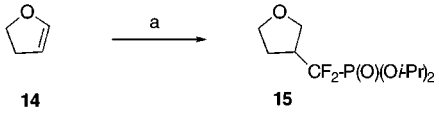
a. **3**, *n*-Bu_3SnH, AIBN, toluene, reflux.

This last result led us to consider 2,3-dihydrofuran as a possible radical acceptor; using the standard procedure, 3-(*O*,*O*-diisopropylphosphonodifluoromethyl)tetrahydrofuran **15** was isolated in 47% yield (Scheme 5). To the best of our knowledge, this is the first oxacyclopentane bearing a difluorophosphonate moiety in position 3. This result has a

(12) **Typical procedure:** To a degassed, stirring solution of diethyl phenylselanyldifluoromethylphosphonate **7** (0.205 g, 0.598 mmol) and *n*-butyl vinyl ether (0.77 mL, 5.98 mmol) in anhydrous toluene (4.7 mL) at 90 °C were added a solution of tri-*n*-butyltin hydride (0.221 mL, 0.822 mmol) and azobisisobutyronitrile (0.049 g, 0.299 mmol) in dry, degassed toluene (3.14 mL) over a period of time of 7 h. After completion of the addition, the resultant solution was heated for another 2 h, cooled to room temperature, and evaporated under reduced pressure. Chromatography of the residue on silica and elution with a 3:2 mixture of heptane/ethyl acetate led to the isolation of adduct **10d** as a colorless oil (70 mg, 46%). ^1H NMR ($CDCl_3$, 200 MHz) δ 4.29−4.15 (m, 4H, OCH_2CH_3), 3.63 (t, $^3J_{H-H} = 7.30$ Hz, 2H, $OCH_2CH_2CF_2$), 3.38 (t, $^3J_{H-H} = 6.56$ Hz, 2H, $CH_2CH_2CH_2O$), 2.48−2.15 (m, 2H, $OCH_2CH_2CF_2$), 1.60−1.15 (m, 4H, $CH_2CH_2CH_2O$), 1.32 (t, $^3J_{H-H} = 6.94$ Hz, 6H, OCH_2CH_3), 0.85 (t, $^3J_{H-H} = 6.94$ Hz, 3H, $CH_3CH_2CH_2CH_2$). ^{31}P NMR ($CDCl_3$, 81 MHz, ref H_3PO_4) δ 7.07 (t, $^2J_{P-F} = 107.41$ Hz, 1P, CF_2P). ^{19}F NMR ($CDCl_3$, 188 MHz, ref $CFCl_6$) δ −111.54 (dt, $^2J_{F-P} = 108.34$ Hz, $^3J_{F-H} = 20.32$ Hz, 2F, CF_2P). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 120.39 (dt, $^1J_{C-P} = 257.73$ Hz, $^1J_{C-F} = 215.8$ Hz, 1C, CF_2P), 71.36 (s, 1C, $CH_2CH_2CH_2O$), 64.87 (d, $^2J_{C-P} = 6.75$ Hz, 2C, OCH_2CH_3), 63.55 (m, 1C, $OCH_2CH_2CF_2$), 34.78 (dt, $^2J_{C-P} = 14.25$ Hz, $^2J_{C-F} = 20.18$ Hz, 1C, $OCH_2CH_2CF_2$), 32.08 (s, 1C, $CH_2CH_2CH_2O$), 19.93 (s, 1C, $CH_2CH_2CH_2O$), 16.77 (d, $^3J_{C-P} = 5.47$ Hz, 2C, OCH_2CH_3), 14.27 (s, 1C, $CH_3CH_2CH_2CH_2$). FTIR (film) ν (cm^{-1}) 2960, 2874, 1272, 1120, 1024, 796. MS (EI) *m*/*z* (rel int) 288 (M^+, 0.51), 231 (M^+ − Bu, 100), 203 (19), 187 (15), 175 (29), 159 (46), 138 (35), 109 (18), 93 (20), 41 (46). Exact mass (CI (isobutane), 200 eV) *m*/*z* calcd for $C_{11}H_{24}O_4PF_2$ 289.1380. Found 289.1389.

(13) We found that the use of 0.5 equiv of AIBN yields the best results at this temperature; conducting the reaction at 80 or 100 °C with the same amount of radical initiator does not affect the conversion rates and yields.

Scheme 5



14 **15**

a. **3**, *n*-Bu_3SnH, AIBN, toluene, reflux.

direct implication in the production of modified oligonucleotides and in antisense strategy.

These preliminary results indicate that generation of phosphonodifluoromethyl radicals from precursors such as **3** or **7** and their addition reactions onto alkenes represents a viable approach for the introduction of such a functional group into potentially bioactive molecules. Second-generation precursors are currently under investigation.

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Supporting Information Available: Experimental procedure and complete characterization for compounds **10a**−**10j** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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