Radical Conjugated Addition: Addition of Dialkyl Phosphonodifluoromethyl Radical onto Unsaturated Ketones

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Abstract: The free radical addition of phosphonodifluoromethyl radical is reported from iodophosphonate and sodium dithionite, triethylborane, or dilauroyl peroxide as initiator. Triethylborane promoted the radical conjugated addition onto enones.

Key words: radical reaction, fluorine, enone, phosphonate, alkene

Due to the limitation of methylenephosphonates as biological models of phosphates, difluoromethylenephosphonates have, and still arouse, interest as stable isopolar phosphate mimics.¹ It is generally assumed that the phosphate unit will be fully ionized on protein binding, and difluoromethylenephosphonates represent a new class of analogues of phosphates, which provide a powerful arsenal of biological probes for examination or perturbation of the mechanisms of phosphoryl-transfer enzymes. Their efficiency has been established through many examples of high affinity enzyme inhibitors, and difluoromethylenephosphonates emerge as excellent pyrophosphate and phosphate surrogates.

Although the addition of alkyl carbethoxydifluoromethyl free radical onto alkenes has been largely applied,² the introduction of the dialkyl phosphonodifluoromethyl group by free-radical addition has been partially studied. It has been found that Pd⁰ and Co^{II} promoted the coupling reaction from the diethyl iodo- or bromodifluoromethylphosphonates and alkenes (Scheme 1). The reaction proceeds through a radical process in the presence of catalytic amount of Pd(PPh₃)₄,³ or bromo(pyridine)cobaloxime.⁴ In the presence of Pd⁰ a group-transfer reaction was observed with alkenes affording iodoalkanes in high yields. In contrast, in the presence of Co^{III}/Zn corresponding dehalogenated phosphonates were obtained. In addition, the first method is efficient from terminal electron-rich olefins, while the second allowed the addition onto electrondeficient and -rich alkenes. This reaction could be considered as the first report of the radical-conjugated addition (RCA) of the phosphonodifluoromethyl radical onto alkenes, although this reaction involved a transition metal.

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The formal liberation of the phosphonodifluoromethyl free radical **I** has been realized from halo- and chalcogeno-phosphonates in the presence of radical initiator (Scheme 2). Tin- or light-promoted free-radical addition from O,O-dialkyl alkylsulfanyl- or alkylselanyldifluoromethylphosphonates for the preparation of secondary and primary difluoromethylphosphonates by trapping the free-radical species liberated in situ.⁵



Scheme 1 Transition-metal-promoted coupling reaction

Adducts were obtained from electron-rich alkenes, including 1,2-disustituted alkenes or alkynes. The reaction was limited by a competitive reaction due to the presence of hydrogen donor [Bu₃SnH or (Me₃Si)₃SiH]. A competitive formation of reduction product **II** or homocoupling product **III** was observed from electron-deficient alkenes as free-radical acceptors, dramatically influenced the course of the radical addition. It has been assumed that this radical presented rather an electrophilic character and better results were observed from electron-rich alkenes. Sodium hydrosulfite (or sodium dithionite) radical initiator has been largely used to generate fluorinated radicals.⁶



Scheme 2 Formal free-radical addition

Few examples concern the phosphonodifluoromethyl radical, and among them, the free-radical addition onto alkynes was noted first (Scheme 2). The reaction involved the sulfinatodehalogenation of the iododifluoromethylphosphonate,⁷ proceeding through an electron-transfer process leading to the free phosphonodifluoromethyl radical, which was then trapped by alkynes. The second radical ensured the propagation of the reaction by a radicophile attack of the iodine atom of the starting precursor, giving to this reaction a group-transfer reaction character. Recently, the method has been extended to the synthesis of γ -butyrolactones through the addition of the phosphonodifluoromethyl radical onto 4-pentenoic acids.⁸ Except this example, no general study of the addition of the phosphonodifluoromethyl radical, generated from the iodophosphonate, onto alkenes has been reported in the literature.

In this paper we report our results in this field involving the dialkyl iododifluoromethylphosphonate and electronrich and -deficient alkenes in the presence of a variety of free-radical initiators.

The iodophosphonate **2** can be easily prepared from the dialkyl bromodifluoromethylphosphonate through the formation of the organozinc reagent and subsequent trapping with iodine,⁹ instead of the use of CF_2I_2 .⁷ Alternative preparation consists in trapping the lithiated anion prepared from the sulfide **1** with iodine (Scheme 3).¹⁰ This latter approach, based on a nucleophilic fluorination of phosphonates, is sustainable; the use of regulated chemicals such as difluorodihalomethane derivatives is not needed anymore.

	1) <i>t</i> -BuLi, THF, –78 °C	
	2) l ₂ , 1 h, -78 °C	
We301 2F (0)(0/-F1)2	010/	F 101 2F (0)(0/-F1)2
1	81%	2

Scheme 3 Iodophosphonate synthesis

Having in hand iodofluorophosphonate 2, three initiators were tested to generate the free radical for reaction with alkenes (Scheme 4). Initially, the reaction was performed from iodophosphonate 2 (1 equiv) and n-octene (1.3) equiv). The three initiator systems tested were: (A) Na₂S₂O₄/NaHCO₃ in MeCN-H₂O, (B) Et₃B in CH₂Cl₂, and (C) dilauroyl peroxide in refluxing DCE. In the presence of sodium dithionite (2 equiv) and sodium hydrogenocarbonate (1 equiv) in MeCN- $H_2O(5:3)$, the reaction was slow and required 18 hours at room temperature to be completed. Iodoalkane 3 was the exclusive product observed by analysis of the crude mixture (¹⁹F NMR) and was isolated in 75% yield by flash column chromatography. The reaction was faster with Et₃B and reached completion after 1 hour of stirring at room temperature. Best results were observed when the addition of a solution of triethylborane (0.3 equiv, 1 M in *n*-hexane) was realized in three portions to a mixture of alkene and iodophosphonate. The product was also isolated in good yield (76%), and no trace of byproduct was observed, such as the reduced radical **II** or the homodimer **III**. The last method employed dilauroyl peroxide as free-radical initiator. This later required elevated temperature (80 °C) to initiate the reaction, and was conducted by a slow addition of a solution of the initiator to a solution of alkene and iodophosphonate in refluxed DCE. The starting phosphonate was consumed within 3 hours, and the product **3** was isolated in a lower yield (45%) due probably to its moderate stability in refluxed solvent.



Scheme 4 Reagents and conditions: ^a method A: $Na_2S_2O_4$, $NaHCO_3$, $MeCN-H_2O$ (5:3), r.t, 18 h; method B: Et_3B , (0.3 equiv, 1 M in *n*-hexane), CH_2Cl_2 , r.t, 1 h; method C: dilauroyl peroxide (0.3 equiv), DCE, 80 °C, 3 h.

Table 1 Sodium Dithionite Promoted Free-Radical Addition



^a Method A: $Na_2S_2O_4$, $NaHCO_3$, $MeCN-H_2O$ (5:3), r.t.; method B: Et₃B, (0.3 equiv, 1 M in *n*-hexane), CH_2Cl_2 , r.t.

Other alkenes reacted with the radical precursor 2 under these experimental conditions (Table 1). From 1,1-disubstituted alkenes such as methylenecyclobutane the reaction reached completion after 12 hours at room temperature and lead to the iodoalkane 4 in 65%. However, a competitive elimination reaction took place from methylenecyclopentane and a mixture of alkene **5a** and iodoalkane **5b** was obtained in a 2:3 ratio, after 12 hours at room temperature.¹¹

This alkene **5a** was obtained exclusively and isolated in 47% yield when the reaction was conducted over 24 hours instead of the initial 12 hours. No success to obtain exclusively the iodoalkane **5b** was observed when using Et_3B as radical initiator (method B), and no reaction occurred with dilauroyl peroxide (method C). The reaction conditions supported the presence of other functionalities, and from the *O*-benzylallyl ether the corresponding iodoalkane **6** was isolated in good yield (74%). However, the corresponding iodohydrin cannot be obtained directly;¹² from the allylic alcohol no radical addition was observed whatever the method used.

The addition reaction was then extended to electron-rich alkenes such as alkylvinyl ethers. From *n*-butyl vinyl ether, the reaction afforded a mixture of products identified as the hemiacetal 9 and the corresponding aldehyde 10 in 4:6 ratio in the crude (Scheme 5). The methods B (Et₃B),¹³ or C (dilauroyl peroxide) did not allow to obtain any addition products. The presence of water seems to be necessary to convert in situ the expected unstable iodoether into the corresponding hemiacetal. Indeed, traces of hemiacetal were observed when the reaction was initiated by Et₃B in CH₂Cl₂ containing 5–10% of water. However, during the separation of 9 and 10 by flash chromatography, conversion of the acetal 9 in 10 followed by elimination of a fluorine atom from the aldehyde **10** occurred.¹⁴ In this case, only a mixture of alkene stereoisomers 11 was isolated in low yield (32%). The addition of a catalytic amount of HCl_{aq} (1%) in THF at room temperature to the crude mixture afforded exclusively the aldehyde 10 in 65% yield. This aldehyde was obtained after 1 hour under stirring followed by a short filtration on a silica pad.



Scheme 5 Vinyl ether as free-radical trap

In contrast, from cyclic vinyl ethers the hemiacetal was obtained exclusively under the method A (Table 1, entries 5 and 6). From 2,3-dihydrofurane, the *trans*-hemiacetal 7 was formed as major product in a 9:1 ratio. The mixture of isomers was isolated in excellent yield (89%). The *trans* configuration was deduced from NMR data and confirmed by ${}^{1}H{}^{19}F{}$ HOESY experiment, which showed a correlation between the hydrogen atom H2 and the two fluorine atoms of the CF₂ group. Again, no result was ob-

served when the iodophosphonate **2** and 2,3-dihydrofurane were submitted to methods B and C. The starting materials were recovered. Finally, the group-transfer reaction was attempted from 2,3-dihydropyrane. The addition proceeded smoothly and a mixture of *cis/trans* lactol isomers **8** was obtained in a 1:1 ratio. The products were isolated in a lower yield (45%). The formation of the hemiacetals from vinyl ethers as radical acceptors was issued from a substitution reaction by water of the reactive intermediate gem-iodoether.

In order to explore the limits of this group-transfer reaction, the addition was realized from electron-deficient alkenes. From ethyl acrylate no addition occurred whatever the free-radical initiator used, probably due to a competitive polymerization of the free-radical acceptor. From less sensitive to polymerization free-radical acceptors, such as enones, the reaction took place in the presence of Et₃B (0.3 equiv). However, a mixture of iodophosphonate 2 and adduct 12 was obtained after 3 hours at 20 °C. Optimization of the experimental conditions allowed to reach completion from cyclic enones and Et₃B (0.6 equiv) after 6 hours under stirring (Scheme 6). In this case, addition of 10% of the radical initiator every hour was required to observe reproducible results. From cyclohexenone and cyclopentenone, secondary difluoromethylphosphonates were obtained. The corresponding cycloalkanones $12a^{19}$ and 12b were isolated in 69% and 62% yields, respectively. Traces of 2-iodo cycloalkanone were observed in the crude mixture (19F NMR). In contrast to nonactivated alkenes, the expected α -iodoketone was presumably too reactive and gave back the intermediate radical. The reduction of this intermediate radical occurred probably through a hydrogen transfer reaction from the *n*-hexane coming from the added Et₃B solution (1 M in *n*-hexane). This kind of reduction was previously reported in the literature from xanthates.¹⁵ From alicyclic enones, such as the ethylvinyl ketone, a mixture of alkanone 13 and iodoalkanone 14 was produced in a 9:1 ratio. The corresponding phosphonate 13 was obtained in 77% yield. In all cases no reaction occurred when the alkenone and the iodophosphonate were reacted in the presence of sodium dithionite or lauroyl peroxide



Scheme 6 Radical-conjugated addition

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However, this radical-conjugated addition was limited since no addition was observed, neither from (E)-cinnamaldehyde nor from (E)-4-phenyl-butenone. The substitution of the double bond appeared as a limiting parameter. These unexpected results raise the question concerning the electronic character of the phosphonodifluoromethyl radical. As speculated earlier, the electronic character of the difluoroalkyl radical should be dominated by the inductive effect of the fluorine atoms, but the influence of the fluorine lone pairs adjacent to the carbon-centered radical play a major role, giving it rather a nucleophilic character.¹⁶ Although no theoretical data are available, it might be tempting to speculate that the phosphonodifluoroalkyl radical exhibit an electrophilic/nucleophilic character. The phosphonoester function play a crucial role since traces of adduct were detected in the crude mixture when the reaction was realized from BrCF₂CO₂Et in the presence of Et₃B (18 h at 20 °C).

In conclusion, this radical-conjugated addition¹⁷ opened a new and attractive alternative to prepare secondary phosphonates taking into account that only few examples of the anionic version of this reaction are known.¹⁸ This result comes to complement the panel of addition of fluorinated free radicals onto electron-deficient alkenes reported in the literature.¹⁶ Investigations to prepare important analogues of nucleotides and cyclitols from functionalized cyclic enones are under way.

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- (19) **Typical Procedure for the Synthesis of Phosphonate 12a** To a solution of the 2-cyclohexenone (0.073 mL, 0.76 mmol) and iodo-difluoromethylphosphonate **2** (200 mg, 0.58 mmol) in CH₂Cl₂ (5 mL) at 20 °C under N₂ was slowly added a solution of Et₃B (0.058 mL, 1 M in *n*-hexane). Addition of Et₃B (5×0.058 mL) was realized every 1 h until complete consumption of the iodophosphonate. After 6 h under stirring, the solvents were evaporated under reduced pressure, and the crude mixture was purified by flash column chromatography (*n*-C₅H₁₂-EtOAc, 3:2) to afford the phosphonoketone **12a** (125 mg, 69%). ¹H NMR (250 MHz, CDCl₃): $\delta = 1.30$ (d, ³*J*_{HH} = 6.2 Hz, 12 H), 1.53–1.67 (m, 2 H), 2.05–2.61 (m, 7 H), 4.78 (dsept, ³*J*_{HH} = ³*J*_{HP} = 6.2 Hz, 2 H). ¹⁹F NMR (235 MHz, CDCl₃): $\delta = -115.7$ (ddd, ²*J*_{FF} = 299 Hz, ²*J*_{FF} = 108 Hz, ³*J*_{FH} = 13 Hz), -118.14 (ddd, ²*J*_{FF} = 299

Hz, ${}^{2}J_{\rm FP} = 108$ Hz, ${}^{3}J_{\rm FH} = 13$ Hz). 31 P NMR (101 MHz, CDCl₃): δ = 4.64 (t, ${}^{2}J_{\rm PF} = 108$ Hz). 13 C (63 MHz, CDCl₃): δ = 23.7 (m, *i*-Pr and CH₂), 24.0 (d, ${}^{3}J_{\rm CP} = 2.5$ Hz, *i*-Pr), 24.2 (s, CH₂), 39.8 (dt, ${}^{3}J_{\rm CF} = {}^{3}J_{\rm CP} = 4.6$ Hz, CH₂), 40.9 (s, CH₂), 42.8 (dt, ${}^{2}J_{\rm CF} = 20.6$ Hz, ${}^{2}J_{\rm CP} = 15.3$ Hz, CH), 73.8 (d, ${}^{2}J_{\rm CP} = 3.0$ Hz, *i*-Pr), 73.9 (d, ${}^{2}J_{\rm CP} = 3.0$ Hz, *i*-Pr), 121.9 (dt, ${}^{1}J_{\rm CF} = 263.0$ Hz, ${}^{1}J_{\rm CP} = 214.0$ Hz, CF₂), 208.9 (s, CO). HRMS (ESI): m/z [M + H]⁺ calcd for C₁₃H₂₄F₂O₄P: 313.1380; found: 313.1366.

Phosphonate **12b**: ¹H NMR (250 MHz, CDCl₃): δ = 1.31 (d, ³*J*_{HH} = 6.2 Hz,12 H), 1.97–2.38 (m, 6 H), 2.84–2.91 (m, 1 H), 4.80 (dsp, ³*J*_{HH} = ³*J*_{HP} = 6.2 Hz, 2 H). ¹⁹F NMR (235 MHz,

$$\begin{split} & \text{CDCl}_3): \delta = -119.04 \ (\text{ddd},^2 J_{\text{FF}} = 298 \ \text{Hz}, \,^2 J_{\text{FP}} = 101 \ \text{Hz}, \\ &^3 J_{\text{FH}} = 15 \ \text{Hz}), -117.10 \ (\text{ddd},\,^2 J_{\text{FF}} = 298 \ \text{Hz},\,^2 J_{\text{FP}} = 101 \ \text{Hz}, \\ &^3 J_{\text{FH}} = 17 \ \text{Hz}).\,\,^{31} \text{P} \ \text{NMR} \ (101 \ \text{MHz}, \ \text{CDCl}_3): \delta = 4.79 \ (\text{t}, \\ &^2 J_{\text{PF}} = 108 \ \text{Hz}).\,\,^{13} \text{C} \ (63 \ \text{MHz}, \ \text{CDCl}_3): \delta = 22.1 \ (\text{dt},\,^3 J_{\text{CF}} = \\ &^3 J_{\text{CP}} = 5.1 \ \text{Hz}, \ \text{CH}_2), \ 23.7 \ (\text{d},\,^3 J_{\text{CP}} = 4.2 \ \text{Hz},\,i\text{-}\text{Pr}), \ 24.0 \ (\text{d}, \\ &^3 J_{\text{CP}} = 3.3 \ \text{Hz},\,i\text{-}\text{Pr}), \ 37.5 \ (\text{s}, \ \text{CH}_2), \ 38.1 \ (\text{dt},\,^3 J_{\text{CF}} = \,^3 J_{\text{CP}} = 3.0 \ \text{Hz}, \ \text{CH}_2), \ 40.5 \ (\text{dt},\,^2 J_{\text{CF}} = 21.4 \ \text{Hz},\,^2 J_{\text{CP}} = 15.2 \ \text{Hz}, \ \text{CH}), \ 73.8 \ (\text{d},\,^2 J_{\text{CP}} = 7.1 \ \text{Hz},\,i\text{-}\text{Pr}), \ 119.9 \ (\text{dt},\,^1 J_{\text{CF}} = 262.0 \ \text{Hz},\,^1 J_{\text{CP}} = 217.0 \ \text{Hz}, \ \text{CF}_2), \ 215.8 \ (\text{s}, \ \text{CO}). \\ \ \text{ESI-HRMS:} \ m/z \ [\text{M} + \text{H}]^+ \ \text{calcd} \ \text{for} \ \text{C}_{12} \text{H}_{22} \text{F}_2 \text{O}_4 \text{P}: \ 299.1224; \ \text{found:} \ 299.1213. \end{split}$$