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Simple and Efficient Synthesis of 2,2-Disubstituted--1,1-Difluorophosphonates and Phosphonothioates.

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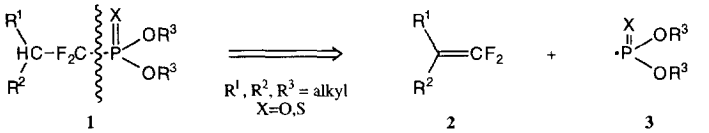
Dedicated with respect to Professor Heinz G. Viehe

Abstract: Generation of dialkyl phosphonyl and thiophosphonyl radicals in the presence of 1,1-difluoroolefins furnishes regioadducts **1**, thereby providing the first general synthesis of 2,2-disubstituted-1,1-difluorophosphonates and -phosphonothioates. Phosphinyl radicals and radicals derived from diarylphosphine oxide are shown to behave in an analogous manner. Addition of the same radicals onto a *monosubstituted* 1,1-difluoroolefin gives mainly the reverse regioadduct, thus demonstrating the complementarity of the new preparation with the synthetic methods available from the literature.

For many years, in their constant struggle to find evermore potent enzyme inhibitors, and agonist or antagonists of receptors, scientists have searched for the best isosteric function to various functional groups. Because of its importance in numerous biochemical processes, the phosphate group has induced intense work and several reports have suggested the 1,1-difluorophosphonate function to be its closest isosteric group.[1] After Blackburn's pioneering work, a wide variety of synthetic methods have been published that render compounds encompassing this function more accessible.[2] These synthetic methodologies usually rely on the reaction between metallated dialkyl difluoromethylphosphonates ($MF_2CP(O)(Oalkyl)_2$, M=Li, ZnBr, CdBr) and various electrophiles,[2a-d, 2g, 2k]. Palladium, copper and cobalt(I)-mediated reactions involving a dialkyl difluoromethylphosphonate radical as intermediate have also been described,[2f, 2i, 2j] as well as methods involving electrophilic fluorination of simple phosphonates [2e] and DAST-fluorination of ketophosphonates [2h]. An important limitation is represented by the fact that, until very recently, none of these methods allowed the simple and efficient preparation of 2,2-disubstituted-1,1-difluorophosphonates.[3,4] This paper reports on a specific preparation of compounds characterized by such a functionalization, and based on the disconnection depicted in Scheme 1.

We reasoned that such a synthesis would be possible through an addition reaction of phosphonyl and thiophosphonyl radicals **3** onto the readily available 2,2-disubstituted 1,1-difluoroolefins **2** (Scheme 1).[5] Indeed, phosphites have long been known to add onto non-fluorinated olefins through a radical-chain mechanism and several ESR studies demonstrated the involvement of phosphonyl radicals **3**.[6,7] Moreover the peroxide-catalyzed addition reaction of dialkyl phosphite to di- and tetrafluoroethylene, and chlorofluoroolefins has been described as furnishing the expected adducts. [8]

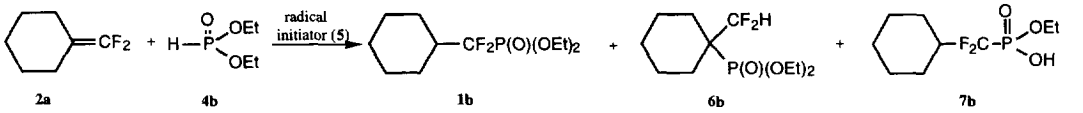


1 2 3

SCHEME 1

As a model reaction it was decided to investigate the optimal reaction conditions of **2a** with **4b** by varying the radical initiator. When a degassed benzene solution of difluoroolefin **2a** (R^1, R^2=-$(CH_2)_5$-) and diethylphosphite (**4b**) was heated at 140°C in the presence of a catalytic amount of di-*tert*-butylperoxide (**5a**) there was observed the formation of a major product, quickly identified as being the desired adduct **1b**, along with two by-products (**6b** and **7b**) and 40% of unconsumed starting material (Scheme 2). Addition of an

additional catalytic amount of radical initiator **5a** after the first heating period of time and resuming heating for 20 more hours gave a 64:12:20:3 mixture of **1b/6b/7b/2a**. A search was then undertaken to provide the conditions under which i) the starting olefin would be (nearly) completely consumed and ii) the amount of desired adduct **1b** would be maximized at the expense of undesired regioadduct **6b** and by-product **7b**. It was found (Table 1) that degassing the starting solution with the freeze-thaw cycle technique and using twice[9] *tert*-butyl peroxypivalate (**5d**) furnished an 88:8:0:3 mixture (NMR spectroscopy) of **1b/6b/7b/2a**.



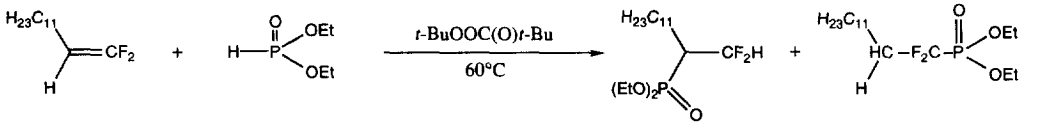
2a **4b** **1b** **6b** **7b**

SCHEME 2

Initiator[10]	Init. $t_{1/2}$ (min) at T(°C)[a]	Reaction Temp (°C)	Reaction time (hrs)	**1b**[b]	**6b**[b]	**7b**[b]	**2a**[b]
t-BuOO*t*-Bu(**5a**)	180(140)	140	29	65	12	20	3
t-BuOO*t*-Bu(**5a**)	180(140)	120	20+20	64	8	13	15
t-BuOOC(O)O*t*-Bu (**5b**)	420(100)	105	20	84	13	3	0
t-BuO$_2$C(O)C(O)O$_2$*t*-Bu (**5c**)	6.8(60)	70	1	25	0	0	75
t-BuOOC(O)*t*-Bu (**5d**)	300(60)	62	20+20	**88**	**8**	**0**	**3**

TABLE 1: a: Initiator half-life at the indicated temperature. b: ^{1}H NMR spectroscopy estimated yield.

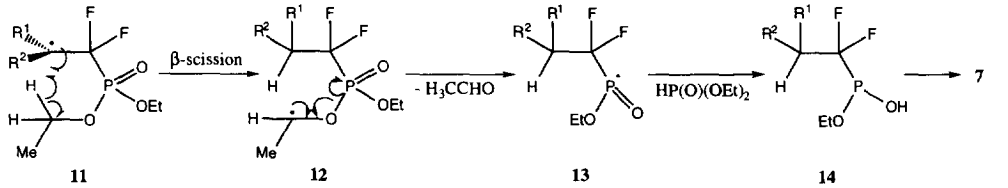
As would be expected, formation of regioisomer **6b**, resulting from addition of the phosphonyl radical onto the non-fluorinated carbon of 1,1-difluoroolefin, is clearly increased at higher temperatures. It is worth noting that the use of 2-*mono*substituted-1,1-difluoroolefin **8** as starting material provided a *reversed* regioselectivity (Scheme 3).



8 **4b** **9** (63%) **10** (18%)

SCHEME 3

By-product **7b** is probably formed through a 1,5-hydrogen atom shift involving one of the ethyl group in radical adduct **11**, followed by β-scission, loss of acetaldehyde and quenching by diethylphosphite. The thereby formed ethoxy(hydroxy)phoshine **14** would then be oxidized to give **7** (Scheme 4).

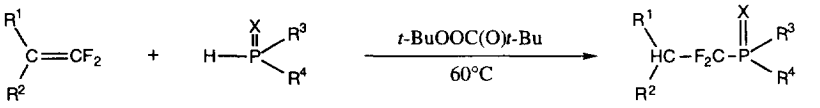


11 **12** **13** **14**

SCHEME 4

A typical procedure is as follows: 1,1-difluoromethylenecyclohexane (528 mg, 4 mmol), diethyl phosphite (2.31g, 16 mmol) and *tert*-butylperoxypivalate (174 mg, 1 mmol) in 0.5 mL of benzene were mixed in a 10 mL flask and degassed three times using the freeze-thaw cycle technique. The solution was then placed under argon in a pressure bottle and heated at 62°C for 20 hours. After cooling to room temperature an additional 44 mg portion of *tert*-butylperoxypivalate was introduced and heating resumed for 20 hours. ^{19}F-NMR spectroscopy analysis of an aliquot indicated a 97% consumption of starting material. Evaporation of the volatiles, chomatography on silica gel and elution with a 7:3 mixture of heptane-ethyl acetate afforded 717 mg (66% yield) of desired, oily product **1b** which was distilled on a Kugelrhor apparatus. More elution gave 90 mg (8% yield) of regioisomer **6b.** [11]

The generality of this preparation was investigated by reacting various 1,1-difluoroolefins and phosphorous-centered radicals together (Scheme 5). Results shown in Table 2 indicate that good yields of the desired regioadduct **1** are obtained when combining dialkyl phosphites or thiophosphites and 2,2-dialkyl-1,1-difluorolefins (entries 1 to 5). The higher yields observed for the phosphonothioates can be explained by the higher stability of the thiophosphonyl radical *versus* the phosphonyl radical.[12] Less reactive olefin such as 1,1-difluoro-2-methylstyrene provides no adduct when reacted with diethyl phosphite (entry 6); however the



2 **4** **1**

SCHEME 5

entry	2	R^1	R^2	4	X	R^3 [a]	R^4 [a]	1	Yield (%)[b], [13]
1	a	-$(CH_2)_5$-		a	O	OMe	OMe	a	66
2	a	-$(CH_2)_5$-		b	O	OEt	OEt	b	60
3	b	C_9H_{19}	CH_3	a	O	OMe	OMe	c	65
4	b	C_9H_{19}	CH_3	b	O	OEt	OEt	d	72
5	b	C_9H_{19}	CH_3	c	S	OEt	OEt	e	95
6	c	C_6H_5	CH_3	b	O	OEt	OEt	f	0[c]
7	c	C_6H_5	CH_3	c	S	OEt	OEt	g	30
8	a	-$(CH_2)_5$-		d	O	OC_6H_5	OC_6H_5	h	0[c]
9	a	-$(CH_2)_5$-		e	O	OBn	OBn	i	8[d]
10	b	C_9H_{19}	CH_3	f	S	OBn	OBn	j	65
11	a	-$(CH_2)_5$-		g	O	OEt	Me	k	71
12	b	C_9H_{19}	CH_3	h	O	C_6H_5	C_6H_5	l	72

TABLE 2: (a): Me=CH_3, Et=C_2H_5, Bn=$CH_2C_6H_5$. (b): isolated yields. (c): see text. (d): ^{1}H NMR spectroscopy estimated yield.

corresponding thiocompound is obtained in fair yield (entry 7). Diphenyl phosphite was oxidized by the initiator and no adduct was formed (entry 8). Little dibenzylphosphonate **1i** was formed under the used conditions (entry 9)[14], but dibenzylphosphonothioate **1j** was found to be formed in good yield (entry 10). The

reaction was also extended to the synthesis of 2,2-disubstituted-1,1-difluorophosphinate (entry 11), as well as to the addition of diaryl phosphine oxide (entry 12).
In conclusion, the present paper reports the first specific preparation of 2,2-disubstituted-1,1-difluorophosphonates and 2,2-disubstituted-1,1-difluorophosphonothioates.[15] The method is simple to carry out, efficient and can be extended to the synthesis of the corresponding difluoromethylenephosphinates and difluoromethylenephosphine oxide.

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3. Unpublished results from this laboratory have shown that the synthetic scheme published by Martin and collaborators (reference 2g; reaction between aldehydes and 1-lithio-1,1-difluoromethylphosphonate, followed by Barton dehydroxylation reaction) can not be extended to ketones. Reference 2i describes the obtention of diethyl 1-(2-iodocyclohexyl)methyl-1,1-difluorophosphonate in 69% isolated yield from cyclohexene and diethyl iododifluoromethylphosphonate; however, it is not clear whether hydrogenolysis of the carbon-halogen bond can readily be achieved as, in the paper, this reaction is described only for compounds monosubstituted in β-position. Reference 2j reports two examples of direct obtention of β,β-disubstituted difluorophosphonates, albeit in low yields (18 and 34%).
4. After completion of this work, results obtained by Lequeux and Percy were published, that describe the addition of cerium-mediated conjugate addition of difluorophosphonate carbanion to nitroalkenes, thus resulting in the formation of difluorophosphonates disubstituted in β-position in yields ranging from 25 to 62%; see Lequeux, T. P.; Percy, J. M. *Synlett* **1995**, 361.
5. Free radical addition to olefins: see a) Tedder, J. M.; Walton, J. C. *Acc. Chem. Res.* 1976, **9**, 183. b) Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, *36*, 701.
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9. The exact amount of radical initiator depends on the starting difluoroolefin. A one-time addition of the total amount of initiator does not result in a complete consumption of the starting olefin.
10. Initiators **5a**, **5e** and **5f** are commercially available. Initiators **5b**, **5c** and **5d** were prepared according to published procedures: **5b**: Bourgeois, M.-J.; Campagnole, M.; Filliatre, Cl.; Mailard, B.; Villenave, J.-J. *Bull. Soc. Chim. Fr.*, **1982**, II-111; **5c**: Bartlett, P. D.; Hiatt, R. R. *J. Am. Chem. Soc.* **1958**, *80* 1398; Duismann, W.; Rüchardt, Ch. *Chem. Ber.* **1976**, 1834; **5d**: Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1762.
11. **1b.** B. p.: (105-110°C/0.07 Torr). ^{1}H NMR ($CDCl_3$/Me_4Si): δ 1.14-2.1 (m, 11H), 1.38 (t, 6H), 4.19-4.33 ppm (m, 4H). ^{19}F NMR ($CDCl_3$/C_6F_6): δ 45.89 ppm (dd, 2F, *J*=15.8, 11.7 Hz). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 7.83 ppm (t). IR (film): ν 1272 cm^{-1} (P=O, s). M.S. (CI, NH_3): 288 ($M+NH_4^+$), 271 ($M+H^+$). Anal. Calc. for $C_{11}H_{21}F_2O_3P$: C, 48.89; H, 7.83. Found: C, 48.88; H, 7.71. **6b.** ^{1}H NMR ($CDCl_3$/Me_4Si): δ 1.3-2.0 (m. 11H), 1.33 (t, 6H), 4.08-4.23 (m, 4H), 5.93 ppm (td, 1H, *J*=7.0, 57.0 Hz). ^{19}F NMR ($CDCl_3$/C_6F_6): δ 36.19 ppm (dd, 2F, *J*=16, 56 Hz). IR (film): ν 1272 cm^{-1} (P=O, s). M.S. (CI, NH_3): 288 ($M+NH_4^+$), 271 ($M+H^+$).
12. Viehe, H.G.; Janousek, Z.; Merényi, R. in "Substituent Effect in Radical Chemistry." *NATO ASI Series* **1986**, *189*, 301.
13. Analytical data (^{1}H-, ^{19}F-, ^{31}P-NMR, mass spectra and combustion data) for all compounds are available upon request.
14. This is probably due to the competitive formation of benzylic radicals.
15. Note added in proof: after this work had been completed, Professor W. B. Motherwell (University College, London) brought to our attention similar results obtained by his group, when reacting difluoroenol ethers of carbohydrate lactones with phosphonyl radicals.

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